STUDIES ON SYNTHESIS OF NITROGEN CONTAINING NATURAL AND UNNATURAL PRODUCTS FROM CYCLIC ANHYDRIDES

THESIS

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by

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Dedicated to my Parents &

Dinumama....

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "***Studies on Synthesis of Nitrogen Containing Natural and Unnatural Products from Cyclic Anhydrides***" which is being submitted to the ***University of Pune*** for the award of ***Doctor of Philosophy*** in ***Chemistry*** by ***Mr. Prasad B. Wakchaure*** was carried out by him under my supervision at the National Chemical Laboratory, Pune. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

July 2011
Pune

Dr. N. P. Argade
(Research Guide)

Candidate's Declaration

I hereby declare that the research work incorporated in the thesis entitled "***Studies on Synthesis of Nitrogen Containing Natural and Unnatural Products from Cyclic Anhydrides***" submitted for the degree of ***Doctor of Philosophy*** in ***Chemistry*** to the ***University of Pune***, has been carried out by me at the Division of Organic Chemistry, National Chemical Laboratory, Pune, India, from February 2006 to June 2011 under the supervision of Dr. Narshinha P. Argade. This work has not been submitted in part or full by me for a degree or diploma to this or any other University or Institution.

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This Ph. D. thesis is the result of the extraordinary efforts, affection and sacrifices of my parents. No word would suffice to express my gratitude and love to all my family members and relatives for their continuous showering of boundless affection on me and supporting me in whatever I choose or did. I would like to dedicate this moment of joy to my parents and family. I can't find the right words for my beloved wife Prajakta, for her patience and love.

Finally, my acknowledgement would not be complete without thanking the God, for giving me the strength and courage to fulfil my dreams.

….Prasad

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General Remarks

- All the solvents used were purified using the known literature procedures.
- Petroleum ether used was of 60-80 °C boiling range.
- Silica gel column chromatographic separations were carried out by gradient elution with light petroleum ether-ethyl acetate mixture, unless otherwise mentioned (silica gel, 60-120 mesh/100-200 mesh/230-400 mesh).
- TLC was performed on E-Merck pre-coated 60 F_{254} plates and the spots were rendered visible by exposing to UV light, iodine, *p*-anisaldehyde (in ethanol), bromocresol green (in ethanol) and ninhydrin (in ethanol).
- IR spectra were recorded on Shimadzu FTIR instrument, for solid either as nujol mull or in chloroform solution (concentration 0.05 to 10%) and neat in case of liquid compounds.
- NMR spectra were recorded on Brucker ACF 200 (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR), ACF 400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) and DRX 500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometers. Chemical shifts (δ) reported are referred to internal reference tetramethyl silane.
- Mass spectra were taken on MS-TOF mass spectrometer.
- HRMS were taken using EI method on MSI-UK AUTOCONCEPT DIP-EI and ESI method on MS-TOF mass spectrometer.
- Microanalysis data were obtained using Flash EA 1112 series and Elementar Vario EL analyser.
- All the melting points reported are uncorrected and were recorded using an electro-thermal melting point apparatus.
- All the compounds previously known in the literature were characterized by comparison of IR and NMR spectra as well as melting point with authentic samples.
- All the new experiments were repeated two or more times.
- Starting materials were obtained from commercial sources or prepared using known procedures.

Abbreviations

Å	Angstrom
AcCl	Acetyl chloride
AIBN	2,2'-Azobisisobutyronitrile
Aq	Aqueous
BINAP	2,2'bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Boc	t-Butoxycarbonyl
cat	Catalytic
CCDC	Cambridge crystallographic data centre
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexyldicarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarization transfer
DFT	Density Functional Theory
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	*N*,*N*-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
EDCI	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride
ee	Enantiomeric excess
EI	Electron impact
eq	Equation
equiv	Equivalent
ESI	Electro spray ionization
h	Hour(s)
HMDS	1,1,1,3,3,3-hexamethydisilazane
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectra
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IC	Inhibitory concentration
IPA	Isopropyl alcohol
IR	Infra Red
KHMDS	Potassium bis(trimethylsilyl)amide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamine
LiTMP	Lithium tetramethylpiperidide

m-CPBA	*m*-Chloroperbenzoic acid
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
Mp	Melting point
MS	Mass Spectrum
MsCl	Methanesulfonyl chloride
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
ORTEP	Orthogonal thermal ellipsoid plots
PCC	Pyridinium chlorochromate
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium
PPA	Polyphosphoric acid
p-TSCl	p-Toluenesulphonyl chloride
p-TSOH	*p*-Toluenesulfonic acid
Py	Pyridine
rac	Racemic
rt	Room temperature
TBAF	Tetrabutylammonium floride
TBSCl	*tert*-Butyldimethylsilyl chloride
TEA	Triethylamine
TES	Triethylsilyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMSCl	Trimethylchlorosilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TPP	Triphenylphosphine
UV	Ultraviolet

Abstract

The present dissertation entitled "**Studies on Synthesis of Nitrogen Containing Natural and Unnatural Products from Cyclic Anhydrides**" is divided into two chapters. The first chapter portrays a contemporary literature account on the applications of the homophthalic anhydrides and their derivatives in organic synthesis. In second chapter, concise and efficient approaches employing cyclic anhydrides as the precursors for the synthesis of various natural and unnatural products have been described by implementing the novel synthetic routes (Figure).

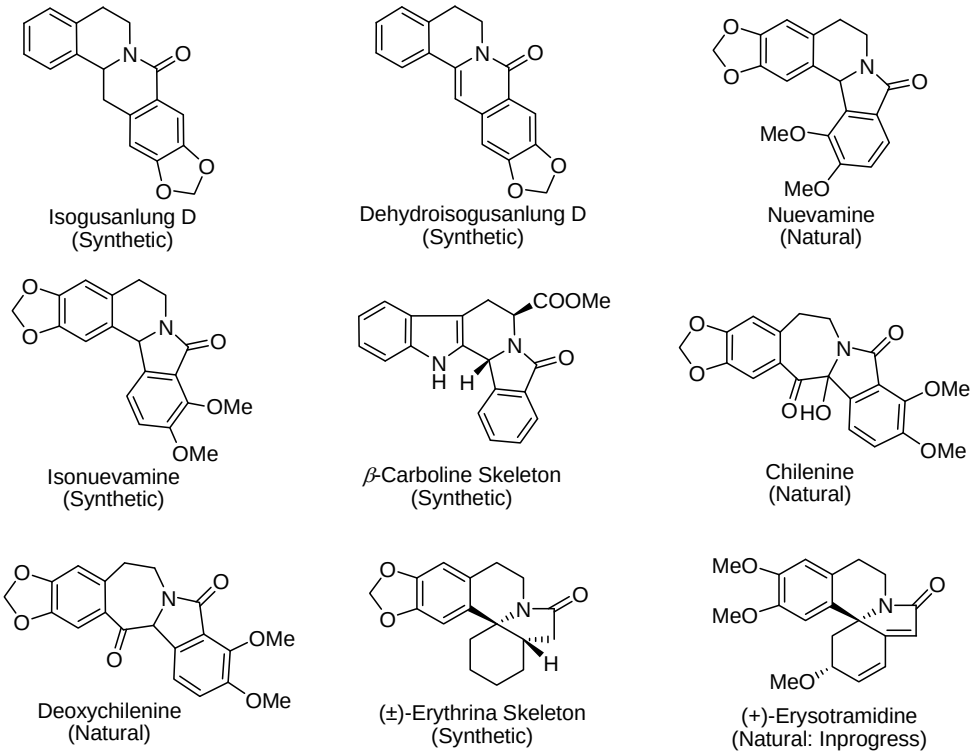
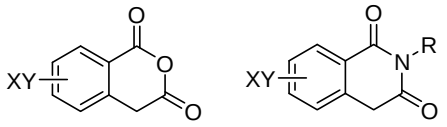


Figure. Nitrogen containing bioactive natural and unnatural products synthesized using cyclic anhydrides as the potential precursors

<u>Chapter 1</u>: A Concise Literature Account on the Applications of Homophthalic Anhydrides and their Derivatives in Organic Synthesis

Homophthalic anhydrides and their derivatives have been known for more than a century and are widely used in the organic synthesis (Figure 1). They are used as starting materials in the synthesis of variety of heterocyclic compounds, especially the isoquinolines via cycloaddition reactions. This chapter presents summary of various reports on applications of homophthalic anhydrides and their derivatives in organic synthesis.



XY = Me, OH, OMe, -OCH_2O-

R = Alkyl/Aryl

Figure 1. Homophthalic anhydrides and homophthalimides

Chapter 2: Synthetic Studies Towards Nitrogen Containing Natural and Unnatural Products Using Cyclic Anhydrides and their Derivatives

This chapter is divided into three sections. Section A presents our general approaches towards the isogusanlung D and dehydroisogusanlung D starting from the 3,4-methylenedioxyhomophthalic acid. The section B presents our synthetic studies on total synthesis of natural products nuevamine, chilenine and deoxychilenine and unnatural products isonuevamine and (+)-*β*-carboline, utilizing the serendipitously witnessed facile air-oxidation of the active methylene group in the corresponding homophthalimides and intramolecular cyclizations as the key steps. In the last section C, our synthetic studies towards the synthesis of erythrina alkaloid architecture and erysotramidine have been presented. The detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been also appropriately included at the end of each section.

Section A: Synthetic Studies Towards Isogusanlung D and Dehydroisogusanlung D

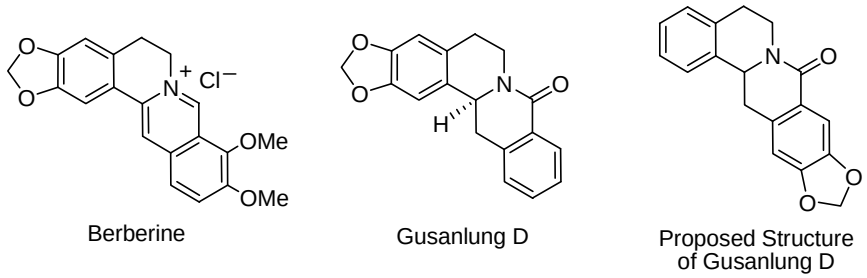
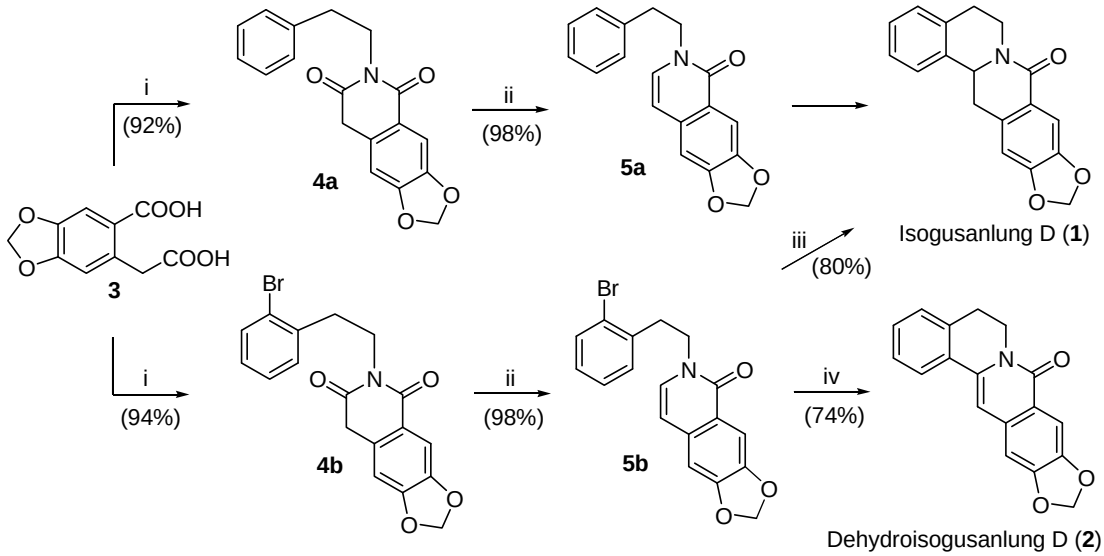


Figure 1. Reported and proposed structures of gusanlung D

Protoberberine alkaloids are an important class of natural products containing a tetracyclic ring skeleton with an isoquinoline core possessing antiinflammatory, antimicrobial, antileukemic and antitumor activities. Many elegant achiral and chiral synthetic routes to protoberberines have been reported in the literature.

Gusanlung D was isolated in 1995 and was claimed as the first protoberberine alkaloid unoxygenated at ring D (Figure 1). Kesser et al. from India reported the synthesis of gusanlung D well before its isolation. In all four racemic and one asymmetric syntheses of gusanlung D are

known. In our research group total synthesis of gusanlung D was completed by using homophthalic anhydride as the starting material. Unfortunately, the analytical and spectral data reported for the natural and synthetic gusanlung D were not in agreement with each other. In the ^{1}H NMR data of isolated gusanlung D one of the downfield singlet at δ 7.35 indicated the possible *peri*-interaction between the D-ring aromatic proton and lactam carbonyl. Therefore we proposed an alternate structure in which the ring D has been oxygenated.



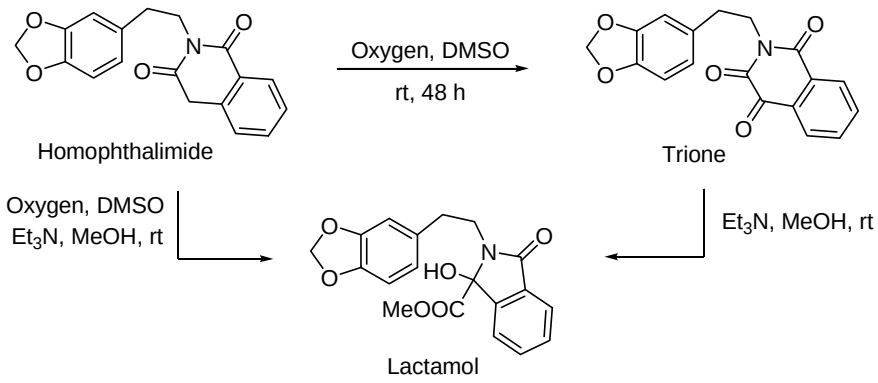
Scheme 1. *Reagents, conditions and yields*: (i) Homobenzylamine/*o*-bromohomobenzylamine, *o*-dichlorobenzene, 180 ^{o}C, 3 h (92/94%); (ii) (a) $NaBH_4$, EtOH, 0 ^{o}C, 6 h, (b) H^+/HCl, rt, 12 h (98%); (iii) AIBN, Bu_3SnH, benzene, reflux, 2 h (80%); (iv) $Pd(OAc)_2$, (n-Bu)$_4$NBr, K_2CO_3, DMF, 120 ^{o}C, 24 h (74%).

Synthesis of our proposed isogusanlung D (**1**) started with an efficient regioselective reductive dehydration of unconjugated imide carbonyl groups of the homophthalimides **4a**/**b** to respectively obtain the enamides **5a**/**b** in excellent yields. The enamide **5a** was subjected for various acid induced intramolecular cyclization conditions but none of them worked well to furnish the proposed isogusanlung D (**1**). The radical induced intramolecular cyclization of enamide **5b** well served the purpose and resulted into the formation of isogusanlung D (**1**). Similarly, the synthesis of the corresponding dehydroisogusanlung D (**2**) was accomplished by taking the advantage of promising intramolecular Heck-coupling reaction of enamide **5b** (Scheme 1).

Unfortunately the spectral data obtained for our proposed structure was also differing from the isolated natural product. At this point, we feel that revision in the reported structural assignment of gusanlung D is must and it would be more appropriate to re-establish the actual structure of the natural product on the basis of X-ray crystallographic analysis.

Section B: Studies Towards the Total Synthesis of Nuevamine, (+)-Isoindolo-*β*-carboline, Chilenine and Deoxychilenine

Recently we witnessed serendipitous facile benzylic air-oxidation of homophthalimide to the corresponding trione and its alcoholysis to ring contraction product the lactamol (Scheme 1). We have successfully utilized these two precursors to complete the total synthesis of above specified natural and unnatural products. The details of all these studies have been discussed in the present section in three parts.



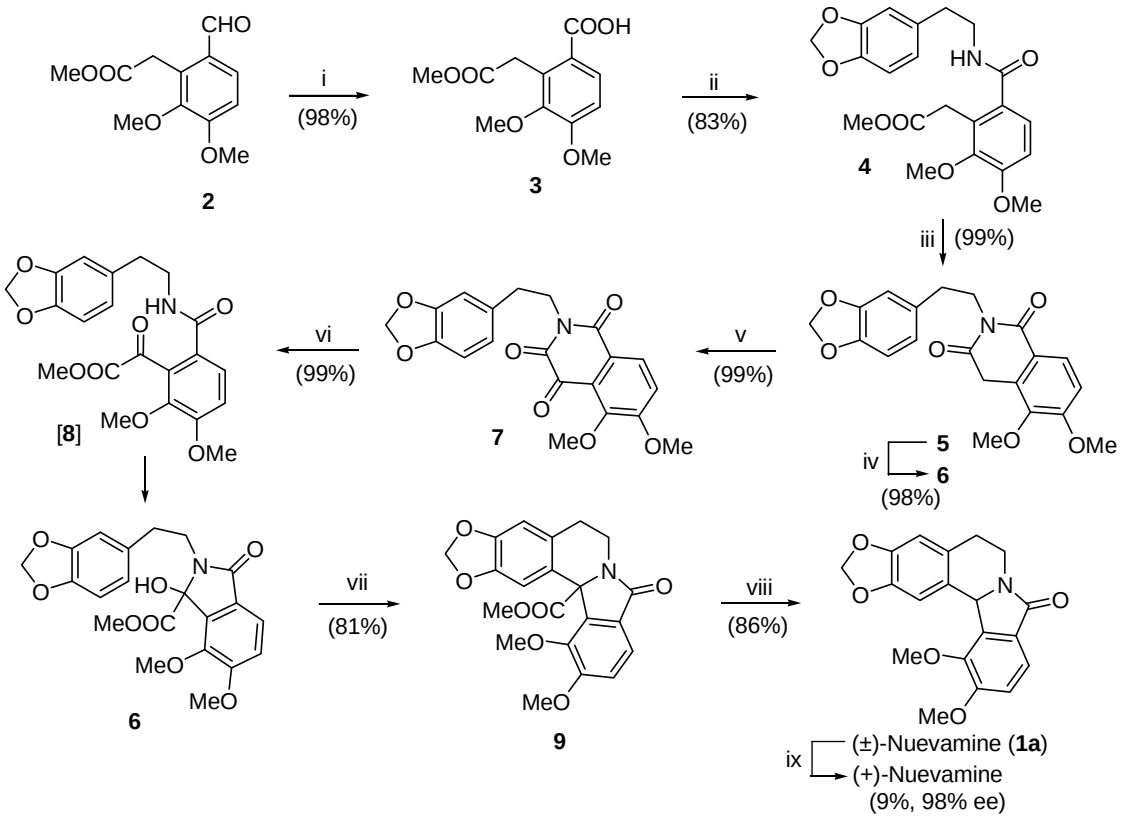
Scheme 1. Serendipitous air-oxidation of homophthalimide and alcoholysis

Section B: 1. Syntheses of Nuevamine

[A] Synthesis of Nuevamine via Facile Air-oxidation of Homophthalimide

The naturally occurring (±)-nuevamine isolated from the *Berberis darwini* Hook species is the first and sole representative of the isoindolo[1,2-*a*]isoquinoline family till date. Three synthetic approaches for nuevamine are known in the literature. This part illustrates our efforts towards the total synthesis of nuevamine in two segments. The first segment presents an application of homophthalimide towards the synthesis of nuevamine via remarkable benzylic air-oxidation. Second segment details our concise approach to nuevamine by using the regioselective reduction of suitably substituted phthalimide.

Our approach towards nuevamine started with the preparation of aldehyde **2**, which was obtained by using the known procedure in good yield (Scheme 2). Jones oxidation of aldehyde **2** furnished mono-methyl ester of 3,4-dimethoxyhomophthalic acid **3** in excellent yield. Dehydrative coupling of acid **3** with homopiperonyl amine resulted into the formation of methyl ester of homophthalamic acid **4**, which upon treatment with Et_3N readily furnished the desired precursor homophthalimide **5**. The solution of homophthalimide **5** in DMSO and MeOH (4:1) on treatment with Et_3N under oxygen atmosphere provided the expected lactamol **6**.



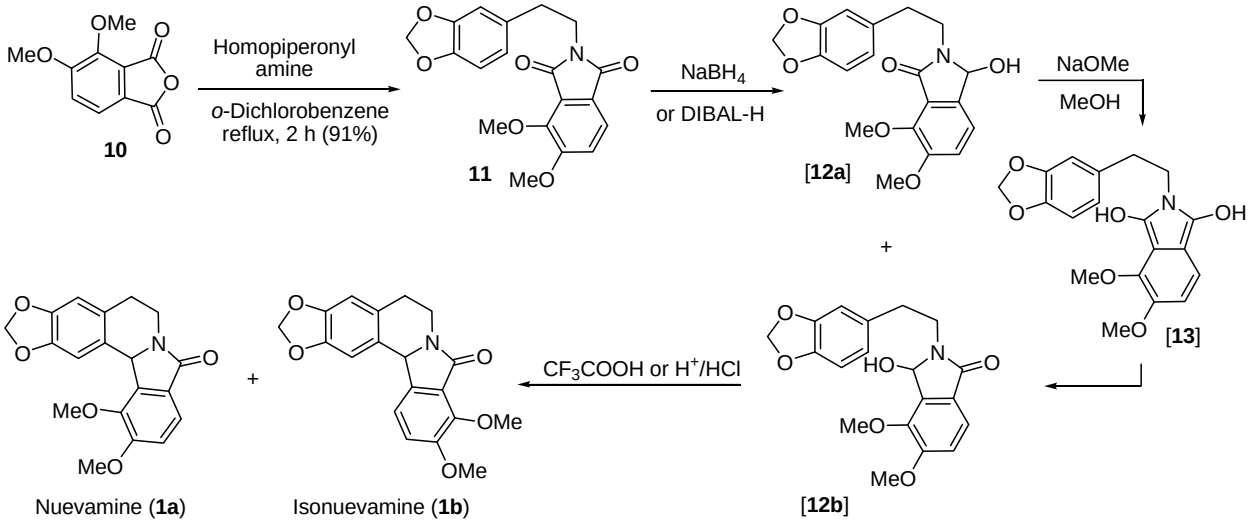
Scheme 2. *Reagents, conditions and yields*: (i) Jones reagent, acetone, rt, 5 h (98%); (ii) *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI), HOBt, DMF, homopiperonyl amine, rt, 3 h (83%); (iii) MeOH, Et_3N, rt, 20 min (99%); (iv) DMSO + MeOH (4:1), Et_3N, oxygen atmosphere, rt, 24 h (98%); (v) DMSO, oxygen atmosphere, rt, 48 h (99%); (vi) MeOH, Et_3N, rt, 3 h (99%); (vii) TFA, rt, 2 h (81%); (viii) NaCl, DMSO, H_2O, 185 ^oC, 30 min (86%); (ix) $CHCl_3$ + EtOAc (1:3), four recrystalisations of conglomerate, each 24 h (9%, 98% ee).

The lactamol **6** on treatment with trifluoroacetic acid, underwent organized intramolecular dehydrative cyclization to yield compound **9** possessing a core structure of natural nuevamine. The demethoxycarbonylation of the angular carbmethoxy function of compound **9** in the complete absence of oxygen furnished the desired natural product nuevamine (**1a**) in 86% yield. We were also successful in isolating an intermediate trione **7** by using a neutral oxidizing condition, which provided a concrete proof for the hypothetically proposed reaction pathway. The single crystal X-ray data revealed that the crystalline nuevamine racemate is a rare conglomerate. As expected, the four successive recrystalizations of (±)-**1a** from chloroform plus ethyl acetate mixture (1:3) led to the spontaneous resolution to furnish the enantiomerically pure (+)-nuevamine in 9% recrystalization yield with 98% ee (by chiral HPLC). Starting from aldehyde **2**, (±)-nuevamine (**1a**) was obtained with 55% overall yield in 6-steps.

[B] Synthesis of Nuevamine via Regioselective Reduction of 3,4-Dimethoxyhomopiperonylphthalimide

This part comprises of an efficient regioselective reductions of the 3,4-dimethoxyhomopiperonylphthalimide (**11**) for the steric, electronic and thermodynamic reasons to accomplish the simple one-pot synthesis of both nuevamine (**1a**) and isonuevamine (**1b**) (Table 1). 3,4-Dimethoxyhomopiperonylphthalimide (**11**) was synthesized in 91% yield by the dehydrative condensation of homopiperonyl amine and 3,4-dimethoxylphthalic anhydride (**10**).

Table 1. Regioselective reductions of 3,4-dimethoxyhomopiperonylphthalimide



Sr. No.	Reducing agent	Solvent	Temp. °C	Reaction time†	Cyclization Conditions	% Yield (1a:1b, by ^{1}H NMR#/HPLC)
1	$NaBH_4$ (5.00 equiv.)	Et_2O	rt	96 h	TFA, rt, 1 h	90 (95:5)
2	″	″	Reflux	48 h	″	92 (95:5)
3	**″**	**THF**	**rt**	**96 h**	**″**	**92 (100:0)/(99.9:0.01)**
4	″	″	Reflux	1 h	″	94 (94:6)
5	″	MeOH	rt	2 h	″	90 (80:20)
6	$NaBH_4$ (20.00 equiv.)	″	Reflux	5 min.	″	93 (93:7)
7	**″**	**″**	**″**	**30 min.**	**″**	**90 (99:1)/(99:1)**
8	DIBAL-H (1.10 equiv.)	DCM	0 °C	1 h	H^+/HCl, rt, 2 h	84 (14:86)
9	″	″	–78 °C	2 h	″	80 (8:92)/(9:91)

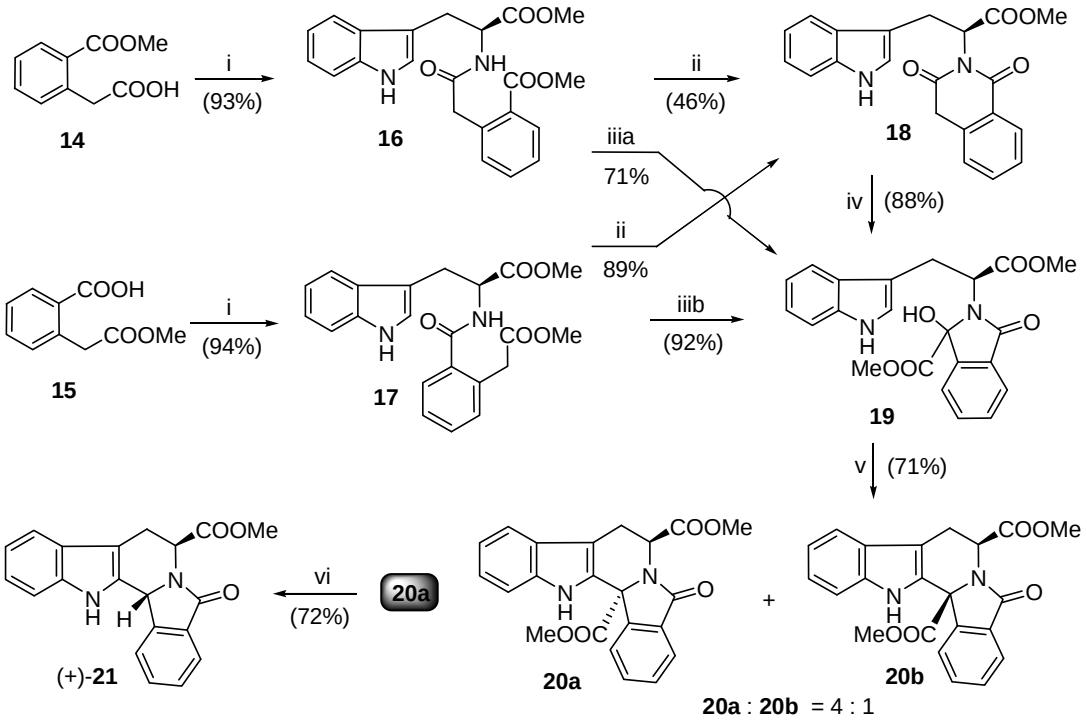
† On completion of the reaction (by TLC) the solvent was removed in vacuo and as such the obtained residue was further subjected for an acid catalyzed intramolecular dehydrative cyclization conditions. # The ratio of **1a**:**1b** was determined from the integral values of methine proton of isonuevamine and nuevamine.

Various reaction conditions like temperature and solvents were screened for the regioselective reduction of unsymmetrical phthalimide (**11**) using $NaBH_4$ and DIBAL-H as the readily available reducing agents. The complete gain in regioselectivity was observed by using THF as

the solvent at room temperature and methanol at reflux to exclusively form the nuevamine (**1a**). The use of DIBAL-H as the reducing agent, we could get the opposite regioselectivity for steric reasons, which provided isonuevamine (**1b**) as the major product.

Section B: 2. Stereoselective Synthesis of (+)-Isoindolo-*β*-carboline

The *β*-carboline is an important structural motif observed in many structurally interesting historic natural products such as reserpine, yohimbine, rutacarpine and ajmalicine. The natural and unnatural *β*-carbolines as well as their analogues and congeners are of high synthetic interest as an important hypotensive agents.



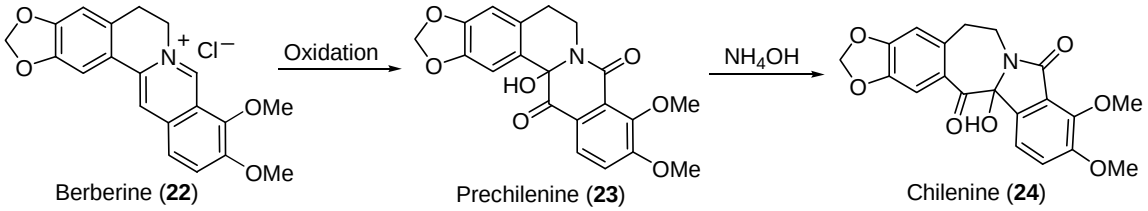
Scheme 3. *Reagents, conditions and yields*: (i) **14**/**15**, *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI), (*S*)-tryptophan methyl ester hydrochloride, DMAP, DCM, Et_3N, rt, 6 h (93/94%); (ii) **16**/**17**, Et_3N, MeOH, rt, 24/4 h (46/89%); (iii) (a) Et_3N, MeOH, rt, 48 h, (71%), (b) Et_3N, MeOH, oxygen atmosphere, rt, 18 h, (92%); (iv) Et_3N, MeOH, rt, 12 h, (88%); (v) AcOH, cat. H^+/H_2SO_4, rt, 6 h (**20a**: 57%, ~100% ee, **20b**: 14%); (vi) **20a**, NaCl, DMSO, H_2O, AcOH, 210 ^oC, 2 h (72%, 98% ee).

Further generalization of air-oxidation propensity of homophthalimide to desired isoindole with the completion of (+)-isoindolo-*β*-carboline synthesis has been described in this part. The required imide precursors **16**/**17** obtained respectively from monoesters of homophthalic acids **14**/**15** were subjected for the formation of desired imide **18** followed by air-oxidation in the same pot (Scheme 3). The excellent reaction rate and yield for the formation of air-oxidation product **19** was observed from the compound **17** as compared to **16**. This is probably due to the

aliphatic ester group in compound **17** which permits the higher rate for the intramolecular cyclization to form imide **18**. Thus the obtained lactamol **19** on acid catalyzed intramolecular dehydrative cyclization gave diastereomeric mixture of isoindolo-*β*-carbolines **20a**/**b** with 71% yield in 4:1 ratio. The major product **20a** was further transformed to (+)-isoindolo-*β*-carboline (**21**) by using Krapcho demethoxycarbonylation conditions. Highly stereoselective demethoxycarbonylation in the present approach at higher temperature is noteworthy. The relative stereochemistry in both compound **20a** and (+)-**21** was unambiguously confirmed by using the X-ray crystallographic data.

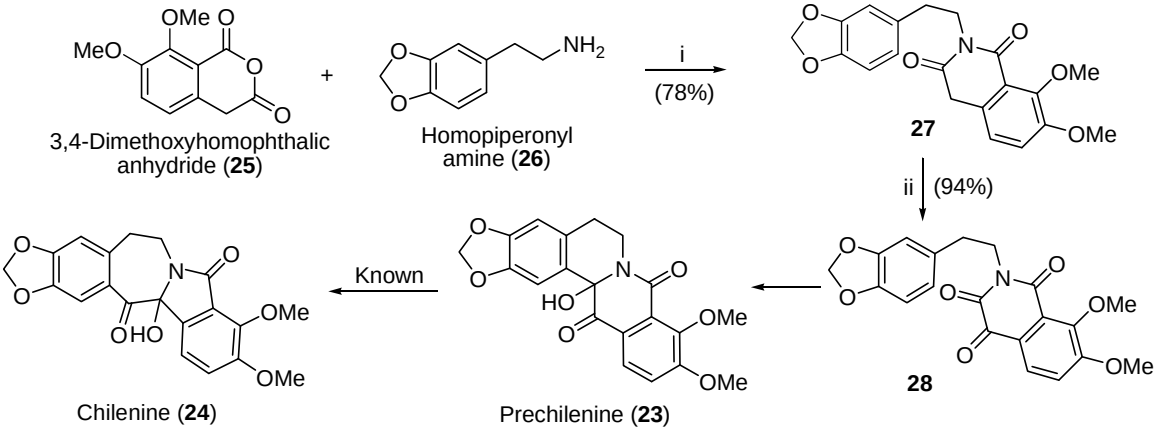
Section B: 3. Synthetic Studies Towards Chilenine, Deoxychilenine and Lennoxamine

Chilenine (**24**), deoxychilenine (**39**) and lennoxamine (**33**) are the isoindolobenzazepine class of alkaloids and are of Chilean genesis. The biogenesis of chilenine (**24**) was postulated to proceed via oxidation of quaternary salt of berberine (**22**) to prechilenine (**23**) which then undergoes skeleton rearrangement to chilenine (**24**) (Scheme 1). Large number of elegant synthesis for these three natural products has been reported till date.



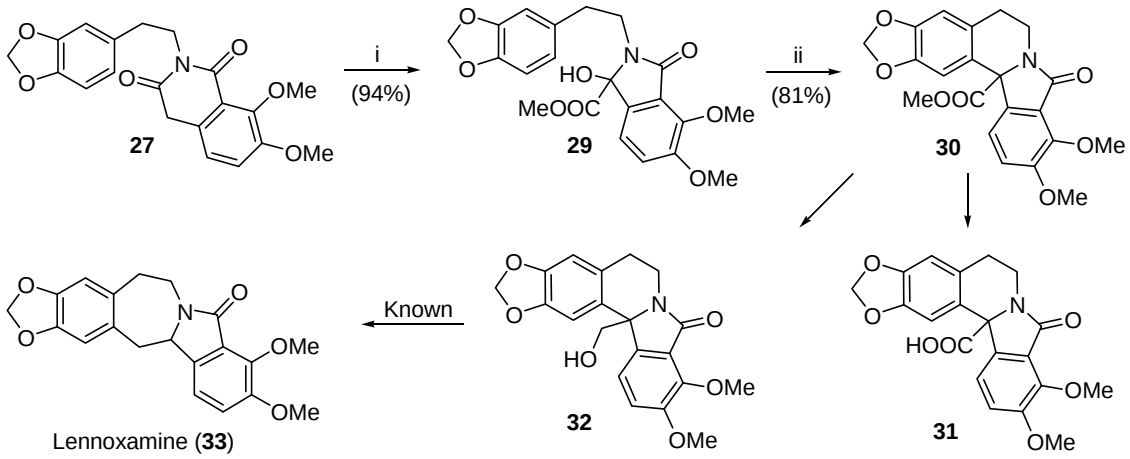
Scheme 4. Proposed biogenetic type route to chilenine

Present part describes our approaches towards these natural products by using the chemoselective intramolecular acylation of lactamol that delivered the core benzazepine unit.



Scheme 5. *Reagents, conditions and yields*: (i) Homopiperonyl amine, *o*-dichlorobenzene, 190 ^{o}C, 3 h (78%); (ii) DMSO, O_2, rt, 24 h (94%).

In our initial synthetic studies we sought for intramolecular Friedel-Crafts acylation of trione **28** to furnish chilenine (**24**) (Scheme 5). The potential precursor, imide **27** was synthesized from 3,4-dimethoxyhomophthalic anhydride (**25**) and homopiperonyl amine (**26**), which upon our well established air-oxidation resulted into the formation of trione **28** in an excellent yield. All our attempts to transform the trione **28** to chilenine (**24**) utilizing acid catalyzed (TFA, H_2SO_4/AcOH, *p*-TSA/xylene), Lewis acid catalyzed ($BF_3.OEt_2$, $AlCl_3$, $AuCl_3$, TMSOTf) and thermal cyclization (DMSO reflux, neat heating 200 °C) conditions were unsuccessful and always ended up with either the unreacted starting material or excessive decomposition.

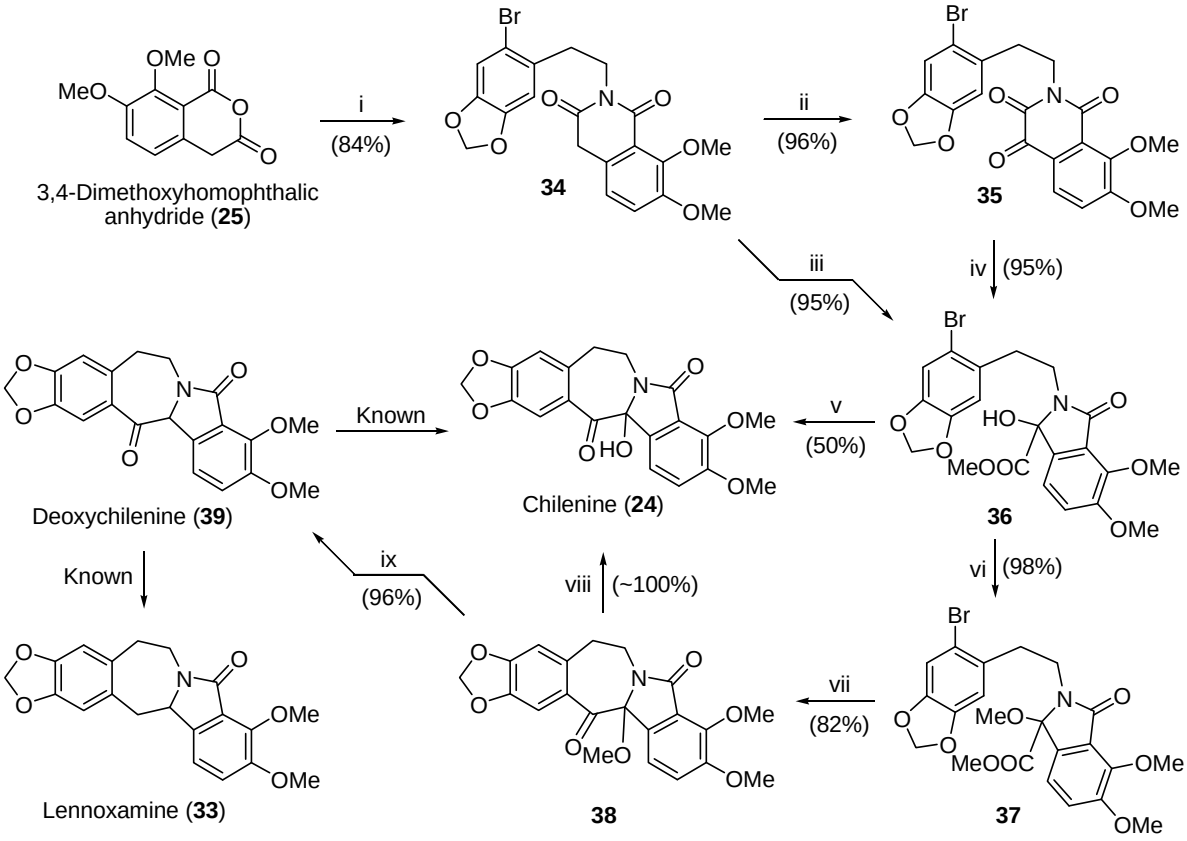


Scheme 6. *Reagents, conditions and yields*: (i) DMSO, MeOH, Et_3N, O_2, rt, 24 h (94%); (ii) TFA, rt 2 h (81%).

As depicted in scheme 6 yet another strategy was planned for the synthesis of lennoxamine (**33**). The compound **30** was readily synthesized in good yield via the air-oxidation of imide **27** to form lactamol **29**, followed by its acid catalyzed intramolecular dehydrative cyclization. The compound **30** was subjected to various reduction conditions by using the reducing agents like $LiAlH_4$, DIBAL, $LiBH_4$, $NaBH_4$ etc. We were unable to reduce the doubly benzylic ester functionality in compound **30** to obtain the alcohol **32**. In our efforts to hydrolyze the ester functionality to carboxylic acid, we noticed the decarboxylation. Hence we were unable to complete the formal synthesis of lennoxamine using known alcohol **32**.

Finally we planned a lithiation strategy for the chemoselective intramolecular cyclization of trione/lactamol to form seven membered benzazepine ring (Scheme 7). The bromo-imide **34** was obtained by condensation of 3,4-dimethoxyphthalic anhydride (**25**) and *o*-bromohomopiperonyl amine, which upon air-oxidation provided the expected bromo-trione **35**. Again, the trione **35** on treatment with *t*-BuLi in THF at −78 °C and −100 °C, with or without HMPA, underwent instantaneous complete decomposition. Pleasantly, the lithiation of bromo-lactamol **36** in THF

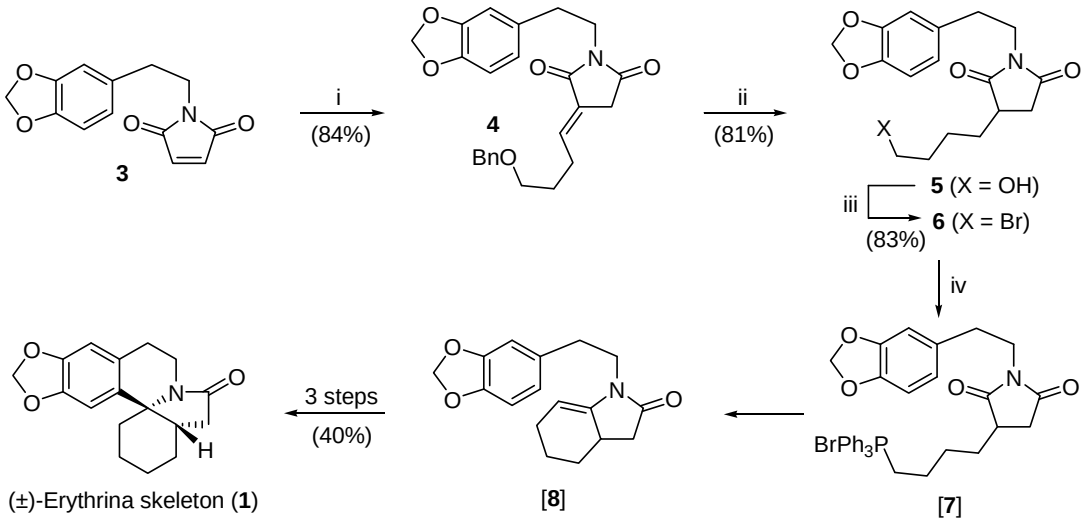
and HMPA mixture by using *t*-BuLi resulted into the desired intramolecular cyclization to furnish chilenine (**24**) in 50% yield. We could improve the yield upto 82% by conversion of lactamol to its methyl ether derivative and again by employing the same set of cyclization reaction conditions. Acid catalyzed hydrolysis of thus obtained compound **38** provided the desired chilenine (**24**) in quantitative yield. The compound **38** on treatment with $BF_3.OEt_2$ and triethylsilane furnished deoxychilenine (**39**) in excellent yield. The conversions of deoxychilenine (**39**) to chilenine (**24**) and lennoxamine (**33**) are well known in the literature. Thus finally we were successful in utilizing the air oxidation propensity of homophthalimide for the total synthesis of chilenine and deoxychilenine.



Scheme 7. *Reagents, conditions and yields*: (i) *o*-Bromohomopiperonyl amine, *o*-dichlorobenzene, 190 °C, 3 h (84%); (ii) DMSO, O_2, rt, 24 h (96%); (iii) DMSO + MeOH (4:1), Et_3N, O_2, rt, 24 h (95%); (iv) MeOH, Et_3N, rt, 6 h (95%); (v) THF + HMPA (4:1), *t*-BuLi, –78 °C to rt (50%); (vi) H^+/H_2SO_4, MeOH, rt (98%); (vii) THF + HMPA (4:1), *t*-BuLi, –78 °C to rt (82%); (viii) TFA, H_2O, rt, 2 h (~100%); (ix) Et_3SiH, $BF_3.OEt_2$, DCM, 0 °C, 20 min (96%).

Section C: Synthetic Studies Towards Erythrina Alkaloids

Erythrina alkaloids containing the fused spirocyclic skeleton comprises a widespread class of bioactive natural products. They show a wide range of pharmacological properties including sedative, hypotensive, anticonvulsive, CNS depressing and curare-like properties. This section describes the total synthesis of erythrina alkaloid skeleton and in progress synthesis of (+)-erysotramidine.

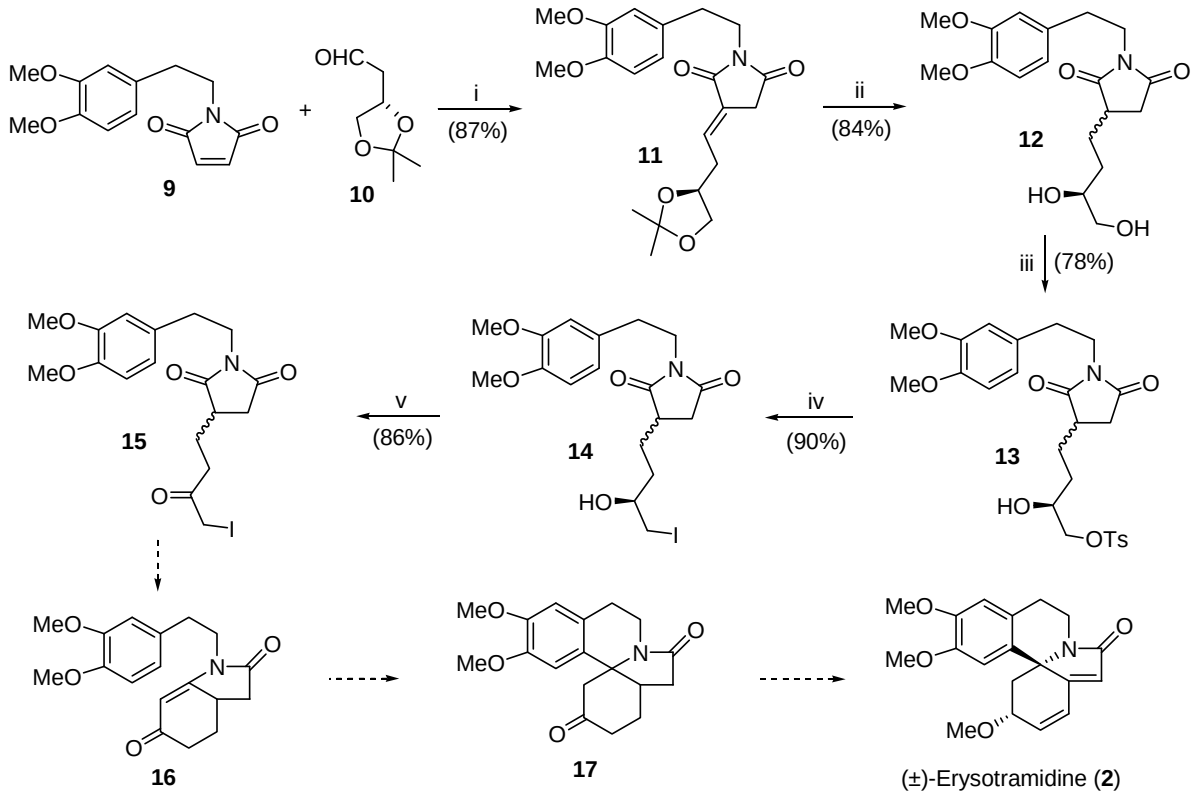


Scheme 1. *Reagents, conditions and yields*: (i) $BnOCH_2CH_2CH_2CHO$, TPP, THF, reflux, 24 h (84%); (ii) $H_2/Pd(OH)_2$, ethanol, 60 ^oC, 3 h (81%); (iii) CBr_4, TPP, DMF, rt, 12 h (83%); (iv) (a) TPP, 140 ^oC, 3 h, (b) *n*-BuLi, THF, –78 ^oC to rt, (c) TFA, rt, 2 h (40% for 3 steps).

The total synthesis of erythrina alkaloid skeleton has been completed starting from imide **3** (Scheme 1). Wittig reaction of imide **3** with *γ*-benzyloxybutyraldehyde provided the product **4**. The simultaneous hydrogenation of double bond and hydrogenolysis of *O*-benzyl group in compound **4** yielded an alcohol **5** which was further transformed to the corresponding bromo compound **6** in good yield. The imide **6** was subjected for intra-molecular non-classical Wittig reaction which formed unisolable intermediate **8** and it on in situ acid catalyzed Pictet-Spengler type of cyclization diastereoselectively provided the desired erythrina skeleton **1** in good yield.

This section also includes application of the above discussed protocol for the actual synthesis of natural product (+)-erysotramidine (**2**) (Scheme 2). Thus the Wittig reaction of aldehyde **10** with imide **9** yielded the product **11**, which upon hydrogenation provided reduced acetonide deprotected product **12** in 84% yield. The selective conversion of primary alcohol to iodo compound was achieved via standard tosylation followed by nucleophillic displacement. The obtained product **14** was oxidized to ketone **15** by using IBX. Further studies on intramolecular

Wittig reaction to obtain the spiro compound **17** and its transformation to the natural product erysotramidine are in progress in our laboratory (Scheme 2).



Scheme 2. *Reagents, conditions and yields*: (i) TPP, THF, reflux, 24 h (87%); (ii) $H_2/Pd(OH)_2$, ethanol, 60 ^oC, 12 h (84%); (iii) TsCl, DMAP, Et_3N, DCM, rt, 6 h (78%); (iv) NaI, acetone, 70 ^oC, 6 h (90%); (v) IBX, EtOAc, 80 ^oC, 8 h (86%).

Note: Compound, scheme and figure numbers in the abstract are different from those in the thesis.

Chapter 1

A Concise Literature Account on the Applications of Homophthalic Anhydrides and their Derivatives in Organic Synthesis

This Chapter Features the Following Topics:

1.1 Introduction

Homophthalic anhydride has been known for more than a century and is widely used as a building block for the synthesis of alkaloids, dyes and a variety of medicinally important compounds. According to IUPAC nomenclature, the homophthalic anhydrides **1** are named as 1*H*-2-benzopyran-1,3(4*H*)-diones. Positions of substitution in the benzene nucleus are usually indicated by the numbering system for the respective 2-carboxy phenylacetic acids **2** and substitution at the methylene position is called α-substitution. Homophthalimides **3**, an important derivative of homophthalic anhydrides/acids are also known for more than a century and have wide applications in organic synthesis (Figure 1).

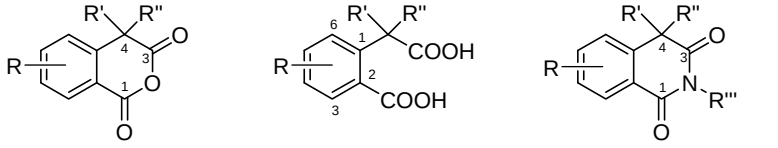


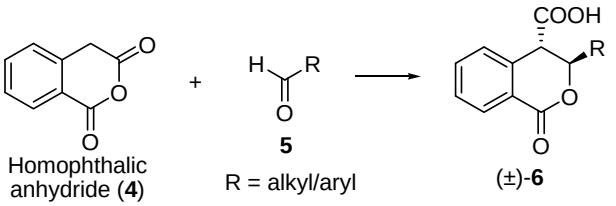
Figure 1. Homophthalic acids and derivatives

Homophthalic anhydrides/acids are frequently being used in the organic synthesis, interest in their chemistry has grown after sixties, mainly due to their successful applications in the form of Diels-Alder-type cycloaddition reaction in the synthesis of a variety of natural and synthetic compounds. Comprehensive reviews on homophthalic anhydrides and their applications in organic synthesis are published by Stanoeva et al. in 1984[1] and by Gonzalez-Lopez et al. in 2009.[2] Recently a Ph. D. dissertation from our group reported a concise literature account on the applications of homophthalic anhydrides and their derivatives in organic synthesis.[3] To avoid repetition, the contents of earlier dissertation from our group have not been listed here. This chapter summarizes various reports on syntheses and applications of homophthalic anhydrides/acids and homophthalimides in synthetic organic chemistry. Total synthesis of natural products occupies a keystone position in organic chemistry and hence an attempt has been made to focus more on natural product synthesis reports involving homophthalic anhydrides/acids and homophthalimides in the synthetic scheme. A short overview of synthesis of homophthalic anhydrides/acids and homophthalimides has been presented prior to their applications in organic synthesis; however, no pretension of completeness has been claimed.

1.2 Background

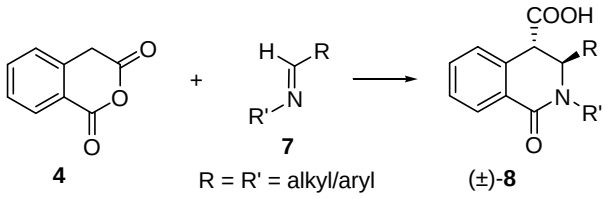
Prior to discussion on the synthesis and applications, we wish to reason why homophthalic anhydrides are such useful synthons in organic chemistry. Few properties which attributes to this versatile molecule have been discussed in brief. The α-methylene protons of homophthalic anhydrides are highly acidic and exchangeable with deuterated methanol. Hence, number of α-substituted derivatives of homophthalic anhydrides and homophthalimides are reported in literature. Also, both the carbonyl groups present are in different chemical environment with respect to the benzene ring. This results in a highly regioselective anhydride ring opening by nucleophiles attacking the non-conjugated carbonyl group. Apart from these general properties, the following three reactions have made homophthalic anhydrides truly useful synthons in organic synthesis.

The reaction of homophthalic anhydride (**4**) with an aldehyde **5** using strong base to form annulation product **6** was observed for the first time by Muller in 1931[4] and later it was studied in details by Pinder & co-workers[5] in 1958 (Scheme 1). The reaction involves nucleophilic attack on the aldehyde carbonyl by an anhydride-derived enolate. More importantly, for the first time this demonstrated the ability of homophthalic anhydride to undergo annulation reaction.



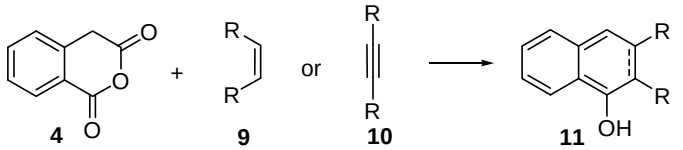
Scheme 1. Muller/Pinder cycloaddition reaction

Cushman et al.[6] and Haimova et al.[7] in 1977 observed the similar annulation reaction of homophthalic anhydride with imine **7** to form isoquinoline moiety **8**. This reaction laid the foundation for much of the subsequent work on isoquinoline chemistry (Scheme 2).



Scheme 2. Cushman/Haimova isoquinoline synthesis

Thirdly, Tamura et al.[8] in 1981 reported a Diels-Alder-type cycloaddition of homophthalic anhydride with alkenes **9** or alkynes **10** to produce fused products **11** (Scheme 3).



Scheme 3. Tamura cycloaddition reaction

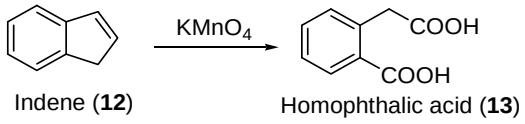
Much of the synthetic chemistry evolved subsequent to discovery of these three reactions, which made homophthalic anhydrides the versatile synthons. This resulted in the development of large numbers of methods for the synthesis of various substituted homophthalic anhydrides/acids as they needed; by known, modified or new methods. A few general methods have been discussed in the following section.

1.3 Synthesis of Homophthalic Acids/Anhydrides

1.3.1 General Methods for the Synthesis of Homophthalic Acids/Anhydrides

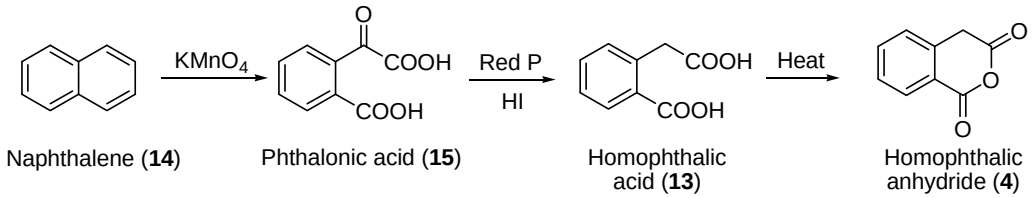
Homophthalic anhydrides are generally synthesized from the corresponding homophthalic acids by using dehydrating agents like acetyl chloride, acetic anhydride or trimethylsilylethoxyacetylene.

Homophthalic acid (**13**) was first synthesized in 1890 by Miller[9] from the fraction of coal-tar oil which is rich in indene. Oxidation of indene (**12**) with chromate or permanganate resulted into the formation of homophthalic acid (**13**) (Scheme 4).[10]



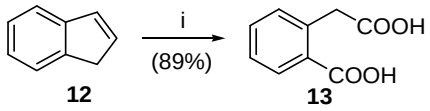
Scheme 4. First report on homophthalic acid synthesis

Homophthalic anhydride (**4**) was synthesized first by Graebe and Trumpy[11] in 1898 (Scheme 5). Oxidation of naphthalene (**14**) by permanganate formed phthalonic acid (**15**). Phthalonic acid (**15**) was reduced to homophthalic acid (**13**) by using the red phosphorus and hydroiodic acid. Further heating of homophthalic acid furnished homophthalic anhydride (**4**).



Scheme 5. First report on homophthalic anhydride synthesis

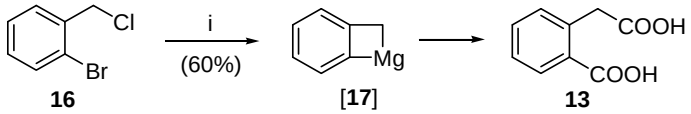
Weinreb and co-workers[12] used a combination of osmium tetraoxide (OsO_4) and Jones reagent in acetone at room temperature for the oxidative cleavage of various types of alkenes into acids and/or ketones. The above mentioned reaction works well even in presence of basic nitrogen functionality (Scheme 6).



12 **13**

Scheme 6. *Reagents*, *conditions and yields*: (i) OsO_4 (cat.), Jones reagent, acetone, rt, 20 h (89%).

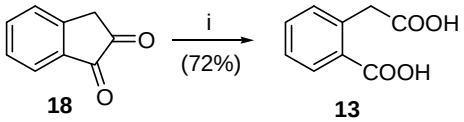
De Boer et al.[13] reported the synthesis of homophthalic acid (**13**) by using 1,3-divalent organomagnesium reagent **17**. The reaction involves slow addition of a dilute solution of *o*-bromobenzyl chloride (**16**) in THF to magnesium metal (which has been sublimed, powdered and activated with a little 1,2-dibromoethane) (Scheme 7).



16 [**17**] **13**

Scheme 7. *Reagents*, *conditions and yields*: (i) (a) Mg, THF, rt, 7 h, (b) dry ice (60%).

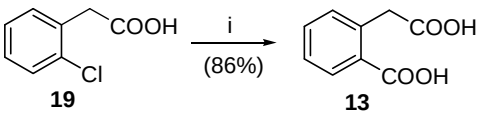
Homophthalic acid (**13**) has been also synthesized by hydrogen peroxide oxidation of 1,2-indanediones (**18**) (Scheme 8).[14,15]



18 **13**

Scheme 8. *Reagents*, *conditions and yields*: (i) H_2O_2, AcOH, rt, 15 min (72%).

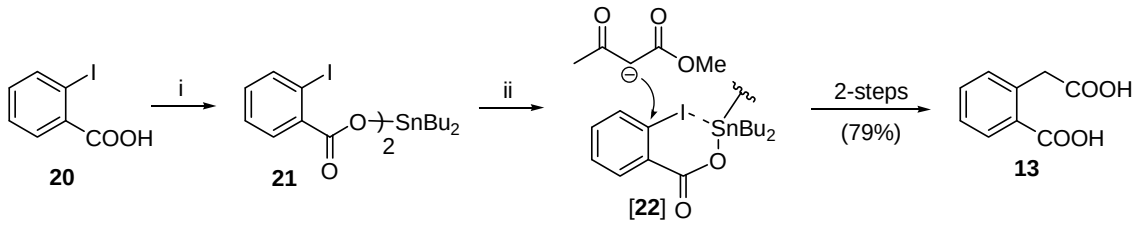
They are also synthesized by cobalt carbonyl catalyzed carbonylation[16] of *o*-chlorophenylacetic acid (**19**) under photostimulation in aqueous sodium hydroxide (Scheme 9).



19 **13**

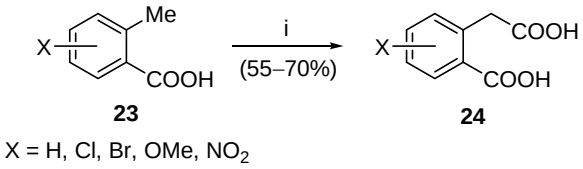
Scheme 9. *Reagents*, *conditions and yields*: (i) $Co_2(CO)_8$, CO, aq. NaOH, *hv*, 65 ^oC (86%).

Maitra and co-workers[17] reported di-*n*-butyltin dichloride (DBTDC) induced nucleophilic substitution of 2-iodobenzoates in water to provide homophthalic acid (**13**) in good yield. Toxic organo-tin compound used was only about 0.75 equivalent (Scheme 10). This is the advantage over their previous method in which 1 to 3 equivalents of organo-tin reagent was required.[18]



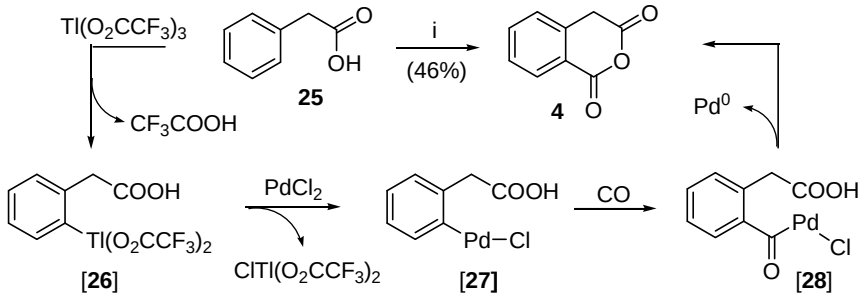
Scheme 10. *Reagents*, *conditions and yields*: (i) Bu_2SnCl_2, $EtN(Pr\text{-}i)_2$, toluene, 40 °C, 12 h; (ii) Methyl acetoacetate, Na_2CO_3, H_2O, 88–90 °C, 24 h (79%).

The another reported method for synthesis of homophthalic acids is by the deprotonation of the methyl group of *o*-toluic acids (**23**) and carboxylation of the resulting dianion (Scheme 11).[19]



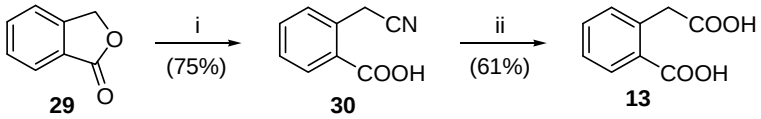
Scheme 11. *Reagents*, *conditions and yields*: (i) LDA, $(MeO)_2CO$, THF, –78 °C to rt, 4 h (55–70%).

Larock et al.[20] synthesized homophthalic anhydride (**4**) by metallization of the aromatic nucleus with thallium(III) trifluoroacetate followed by carbonylation reaction (Scheme 12).



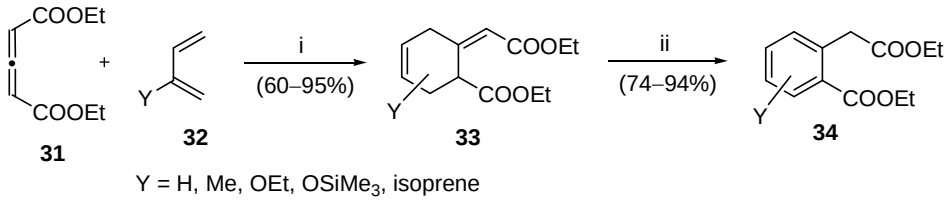
Scheme 12. *Reagents*, *conditions and yields*: (i) $Tl(O_2CCF_3)_3$, TFA, $PdCl_2$, CO, 25 °C, 2 days (46%).

Two-step procedure for the preparation of homophthalic acid (**13**) is by the treatment of phthalide (**29**) with potassium cyanide to obtain the ring-opened 2-carboxybenzyl nitrile (**30**) followed by hydrolysis using sulfuric acid (Scheme 13).[21]



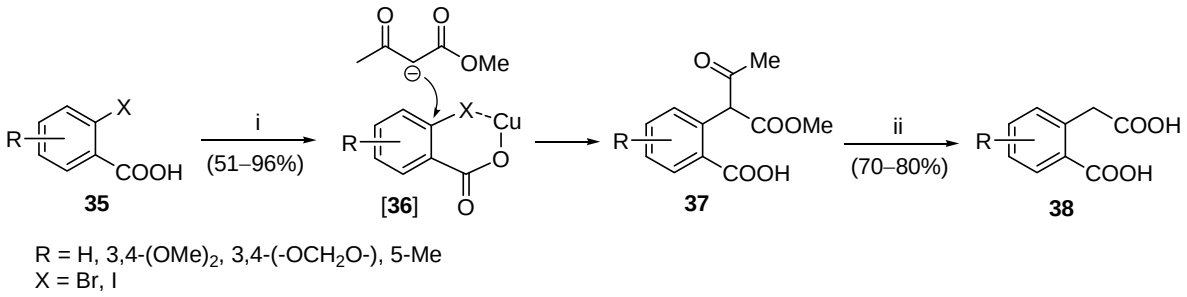
Scheme 13. *Reagents*, *conditions and yields*: (i) KCN, 180 °C, 4 h (75%); (ii) H^+/H_2SO_4, 100 °C, 10 h (61%).

Kozikowski et al.[22] portrayed an elegant preparation of homophthalic acids from nonaromatic compounds by employing a Diels-Alder reaction. Thus, Diels-Alder reaction of allene **31** with various substituted butadienes **32** yielded the cycloadducts **33** in high yields, which easily transformed further to the desired compounds by a sulfur-mediated dehydrogenation (Scheme 14). If the dienes bearing functional groups have weak electronic effects, the mixtures of regioisomeric homophthalates were obtained after dehydrogenation e.g. methyl, isoprene.



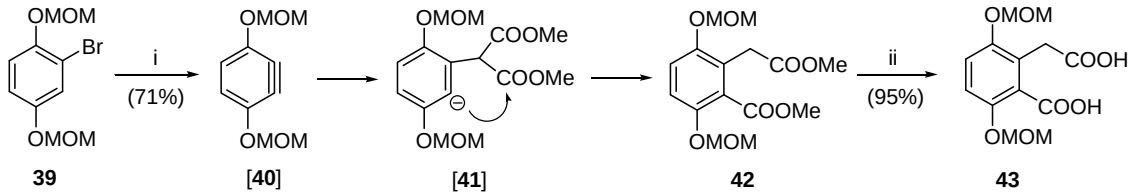
Scheme 14. *Reagents*, *conditions and yields*: (i) Benzene, reflux, 6–18 h (60–95%); (ii) Sulfur, decaline, 195–200 ^{o}C, 2.5 h (74–94%).

Mckillop and co-workers[23] synthesized homophthalic acids by direct arylation of β-dicarbonyl compounds with *o*-halobenzoic acids **35** in the presence of a strong base and a copper (I) halide. This follows the retro-Claisen condensation of the intermediate α-aryl-β-dicarbonyl compounds **37** to form homophthalic acids. This method has wide applicability as various substituted homophthalic acids have been synthesized by using this protocol (Scheme 15).



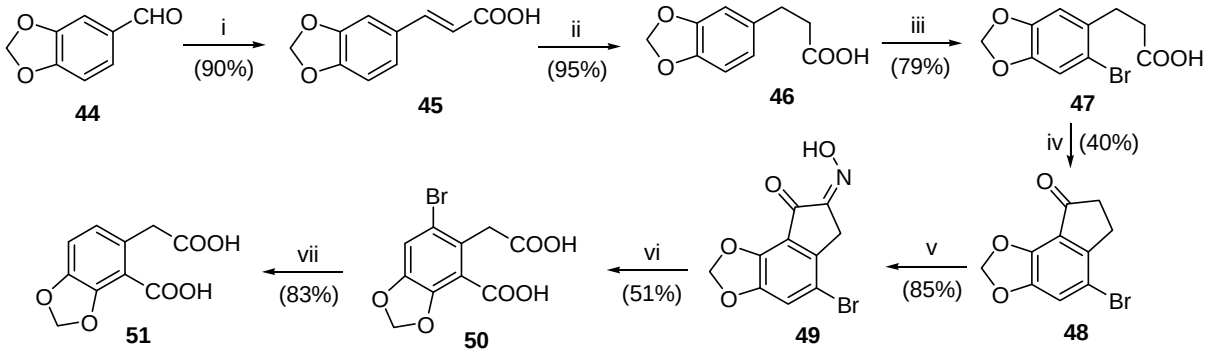
Scheme 15. *Reagents*, *conditions and yields*: (i) Methyl acetoacetate, NaH, CuBr, 60–80 ^{o}C, 5–7 h (51–96%); (ii) 2 N aq. NaOH, rt, 30 min (70–80%).

Guyot et al.[24] reported the arylation of malonic ester with aryne in the presence of a strong base to provide homophthalic acids. Danishefsky and co-workers[25] optimized the reaction condition to obtain the various substituted homophthalic acids in good yields and utilized the same for the synthesis of various natural products. One representative example has been depicted in Scheme 16.



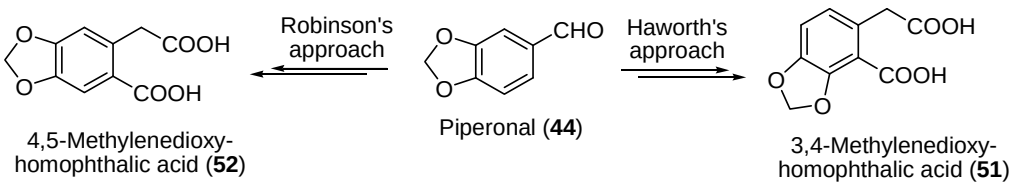
Scheme 16. *Reagents, conditions and yields*: (i) $LiCH(CO_2Me)_2$, LiTMP, THF, –78 °C (71%); (ii) (a) KOH, MeOH, H_2O, reflux, 2 h, (b) 1 N HCl (95%).

Shamma et al.[26] developed an eight step sequence for the synthesis of 3,4-methylenedioxyhomophthalic acid (**51**) (Scheme 17). Thus, the condensation reaction between piperonal (**44**) and malonic acid formed cinnamic acid **45** which upon catalytic hydrogenation furnished the acid **46**. The reactive position of aromatic ring in acid **46** was blocked by bromination, which permits the regioselective hydrindone **48** formation from acid **46**. Second order Beckmann rearrangement of oxime **49** yielded bromo-homophthalic acid **50**, which was then debrominated to form 3,4-methylenedioxyhomophthalic acid (**51**).



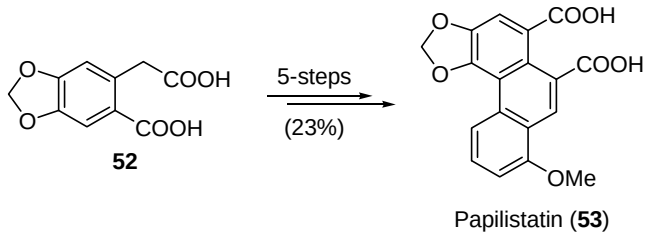
Scheme 17. *Reagents, conditions and yields*: (i) Malonic acid, pyridine, reflux, 6 h (90%); (ii) H_2/Pd–C, water (95%); (iii) Br_2, AcOH, rt, 6 h (79%); (iv) P_2O_5, chlorobenzene, reflux, 2 h (40%); (v) Isoamyl nitrite, conc. HCl, benzene, 50 °C, 2 h (85%); (vi) (a) *p*-TsCl, aq. NaOH, 12 h (51%); (vii) Na–Hg, water, 90 °C, 16 h (83%).

The above discussed strategy was originally developed by Sir Robert Robinson[27] in 1907 for the synthesis of 4,5-methylenedioxyhomophthalic acid (**52**) during their studies towards natural product brazilin and haematoxylin. Later, in 1926 Haworth et al.[28] modified this strategy and used for the synthesis of 3,4-methylenedioxyhomophthalic acid (**51**) (Scheme 18).



Scheme 18. Synthesis of 3,4-methylenedioxyhomophthalic acid (**51**) and 4,5-methylenedioxyhomophthalic acid (**52**)

All the three routes utilize piperonal (**44**) as the precursor for hydrindone synthesis followed by Beckmann rearrangement. Shamma et al. claimed some advantage with respect to yield and work-up procedures over the Robinson's and Haworth's approaches. Protection of the reactive position in aromatic ring by bromination has been used successfully to get selectivity in hydrindone formation. Thus the selectivity in the homophthalic acid preparation was controlled. Very recently, Wu et al.[29] completed the first total synthesis of papilistatin (**53**) by synthesizing required 4,5-methylenedioxyhomophthalic acid (**52**) with further refinements in the process (Scheme 19).



52 Papilistatin (**53**)

Scheme 19. Total synthesis of papilistatin

1.3.2 Synthesis of Homophthalic Anhydrides from Homophthalic Acids

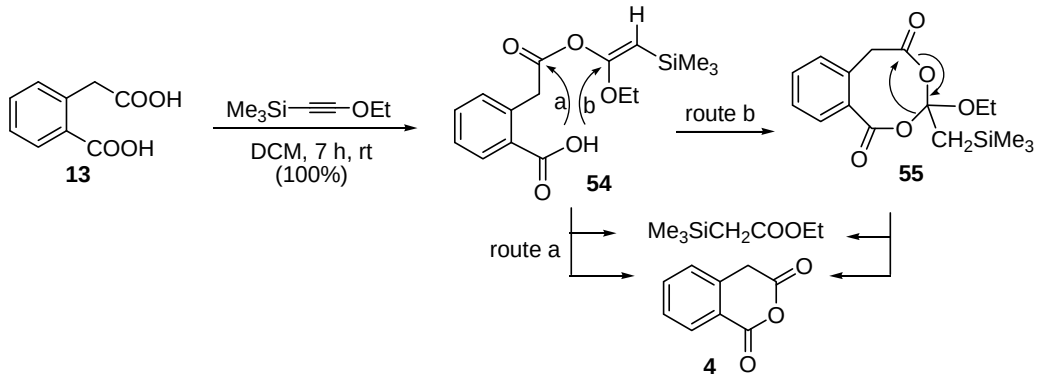
Homophthalic anhydrides are generally synthesized by dehydration of respective homophthalic acids by using dehydrating agents such as acid chloride and acetic anhydride.[30] These methods are not always effective with respect to yield. Acetic anhydride in some cases causes acylation of active methylene group of homophthalic acid and requires aqueous work-up.

Initially acetylene based reagent, ethoxyacetylene was used for this purpose.[31] However, it is unstable and highly volatile. Analogous to ethoxyacetylene, Kita et al.[32] discovered trimethylsilylethoxyacetylene to circumvent those disadvantages. It can be readily prepared by the trimethylsilylation of the commercially available ethoxyacetylene. A typical dehydration procedure involves addition of trimethylsilylethoxyacetylene to the suspension of dicarboxylic acid in dichloromethane or 1,2-dichloroethane and stirring the reaction mixture at room temperature until the acid dissolves in the solution.

The reaction usually proceeds to completion at room temperature within few hours to give the desired anhydrides accompanied by the volatile ethyl trimethylsilylacetate as the only side product. This is the most powerful dehydrating agent for the formation of wide range of anhydrides in almost quantitative yields.

The plausible mechanism involves the addition of carboxylic acid across the triple bond to form the acetal intermediate **54**, which directly transforms to the anhydride (route a) (Scheme 20).

Second possibility involves the formation of orthoester intermediate **55** followed by rapid ring contraction to yield the anhydride with the elimination of ethyl trimethylsilyl acetate (route b).



Scheme 20. Dehydrative cyclization of homophthalic acid

1.4 Applications of Homophthalic Anhydrides

Large number of bioactive natural products has been synthesized by using homophthalic anhydrides as the convergent building blocks. Cycloaddition of homophthalic anhydride and imine provided an easy access to protoberberine as well as benzo[*c*]phenanthridine family alkaloids. Cycloaddition with quinones also proved efficient to access many complex anthracycline antibiotics. This section portrays the synthesis of above mentioned classes of natural products, along with the mention of synthesis of requisite homophthalic anhydrides at the end of description.

1.4.1 Synthesis of Protoberberine Alkaloids

Protoberberines **56** are a large class of alkaloids characterized by tetracyclic ring skeleton with an isoquinoline core (Figure 2).[33] The 13-methyltetrahydroprotoberberines **57** constitute a small family of fused polycyclic alkaloids isolated from various species of the herb *corydalis*.[34] Cushman et al.[6] and Haimova et al.[7] for the first time, independently carried out the cycloaddition reaction of dihydroisoquinoline **58** with 4,5-dimethoxyhomophtalic anhydride (**59**) (Scheme 21). Mixture of both *anti*-**60** and *syn*-**61** diastereomers was obtained from which *anti*-**60** precipitated as the major product (90% yield). The thermodynamically more stable *syn*-diastereomer **61** could be accessed via epimerization in >95:5 diastereoselectivity by refluxing the *anti*-diastereomer **60** in acetic acid. Both the *anti*-**60**

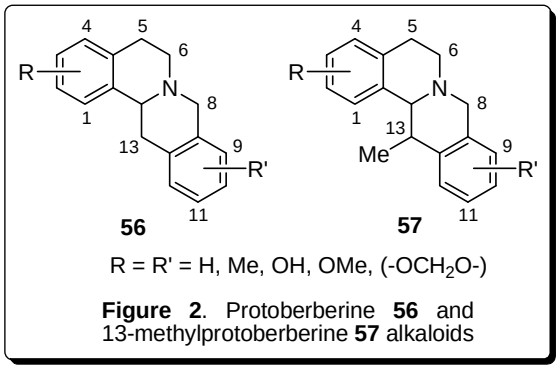
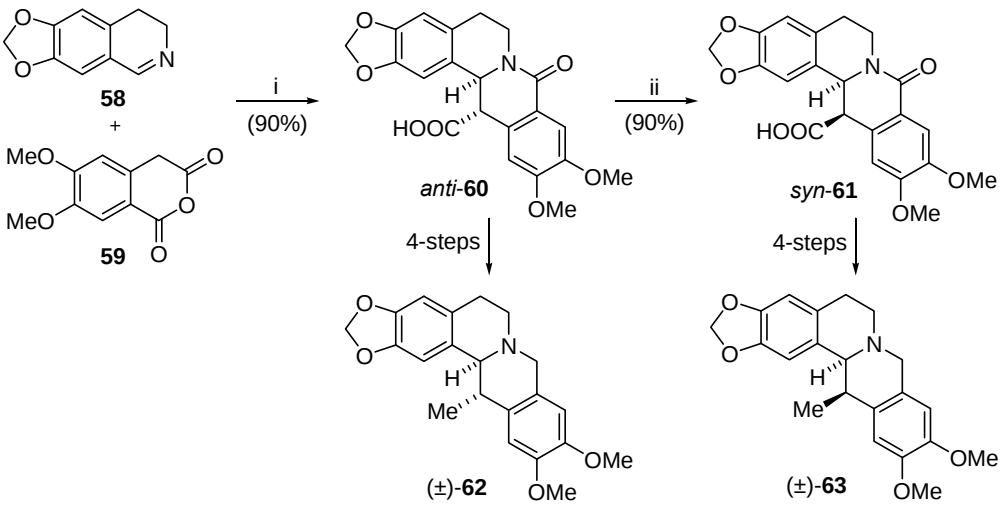


Figure 2. Protoberberine **56** and 13-methylprotoberberine **57** alkaloids

and *syn*-**61** thus obtained were converted into *anti*- and *syn*-13-methyltetrahydroprotoberberine alkaloids (**62** and **63**) respectively by converting the carboxylic acid unit to a methyl group in four steps.

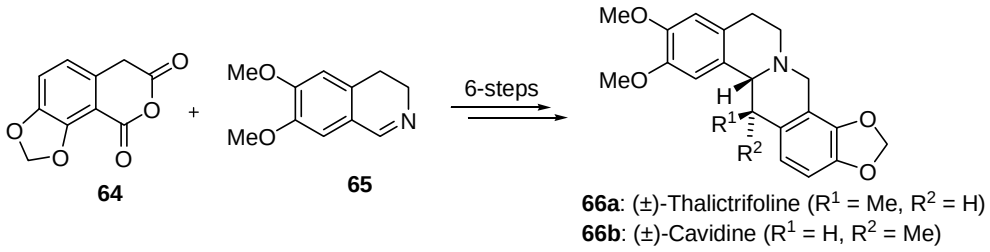


Scheme 21. *Reagents*, *conditions and yields*: (i) $CHCl_3$, rt, 30 min (90%); (ii) AcOH, reflux, 12 h (90%).

This approach was proved to be a general method for the synthesis of 13-methyltetrahydroprotoberberine family alkaloids. Synthesis of few members of this family have been explained in this part in brief along with the synthesis of required homophthalic anhydride.

(i) *Synthesis of Thalictrifoline and Cavidine*

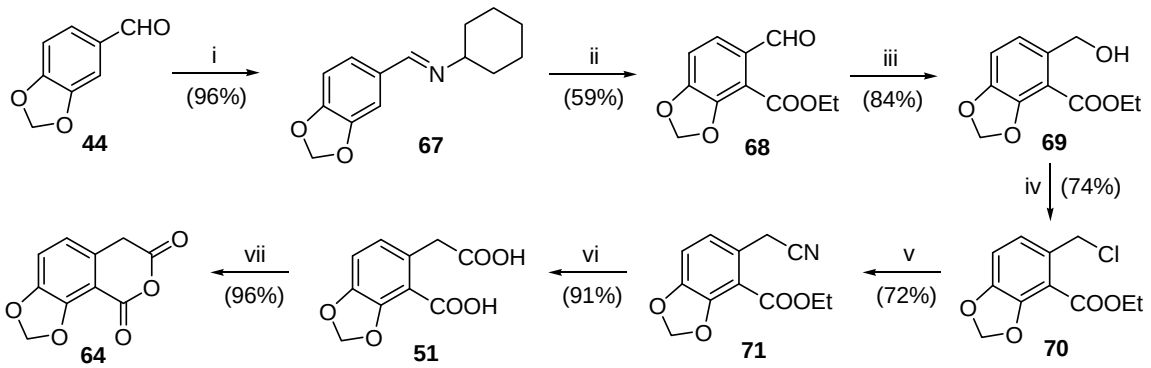
Cushman and co-workers[35] used the above discussed protocol to synthesize thalictrifoline (**66a**) and cavidine (**66b**) by cycloaddition of 3,4-methylenedioxyhomophthalic anhydride (**64**) and dihydroisoquinoline **65** (Scheme 22).



Scheme 22. Synthesis of thalictrifoline and cavidine

The synthesis of required 3,4-methylenedioxyhomophthalic anhydride (**64**) is depicted in scheme 23.[36] Piperonylidenecyclohexylamine (**67**) upon *ortho*-lithiation and reaction with ethyl chloroformate followed by acidic work-up provided aldehyde **68**. The catalytic hydrogenation of the aldehyde **68** to the benzyl alcohol **69** proceeded with excellent yield. The conversion of the benzyl alcohol **69** to the benzyl chloride **70** was achieved by treatment with thionyl chloride.

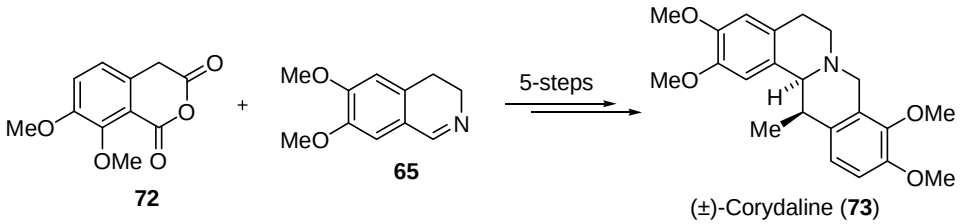
The synthesis of 3,4-methylenedioxyhomophthalic anhydride (**64**) was accomplished by displacement of the chloride of **70** with cyanide, basic hydrolysis followed by cyclodehydration of the diacid **51**.



Scheme 23. *Reagents*, *conditions and yields*: (i) Cyclohexylamine, benzene, reflux, 12 h (96%); (ii) (a) *n*-BuLi, THF, –78 ^{o}C, 3 h, (b) EtOOCC1, –78 to 23 ^{o}C, 4 h (59%); (iii) H_2, 10% Pd/C, EtOH (84%); (iv) $SOCl_2$, DCM, 23 ^{o}C, 2 h (74%); (v) KCN, DMSO, 23 ^{o}C, 12 h (72%); (vi) Aq. KOH, reflux, 3 h (91%); (vii) AcCl, reflux, 6 h (96%).

(ii) *Synthesis of (±)-Corydaline*

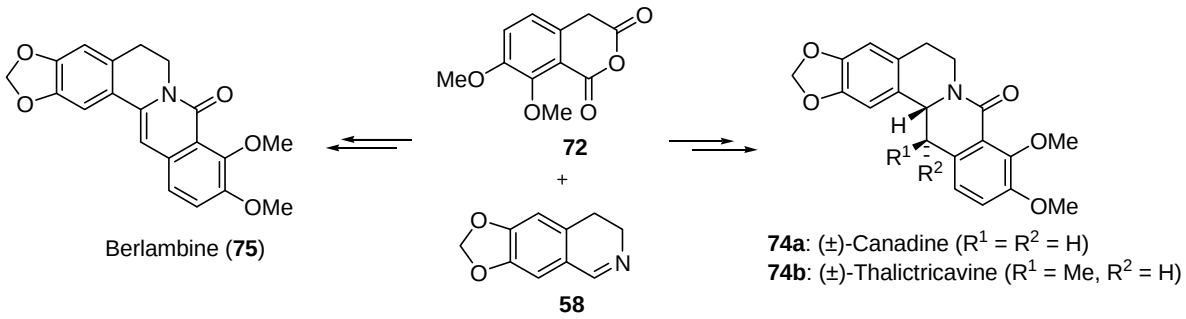
Corydaline (**73**) was first isolated in 1826 by Wackenroder from *Corydalis tuberose*.[37] Cushman and co-workers[38] completed the total synthesis of (±)-corydaline (**73**) in 5 steps by condensing 3,4-dimethoxyhomophthalic anhydride (**72**) and dihydroisoquinoline **65** (Scheme 24).



Scheme 24. Synthesis of (±)-corydaline

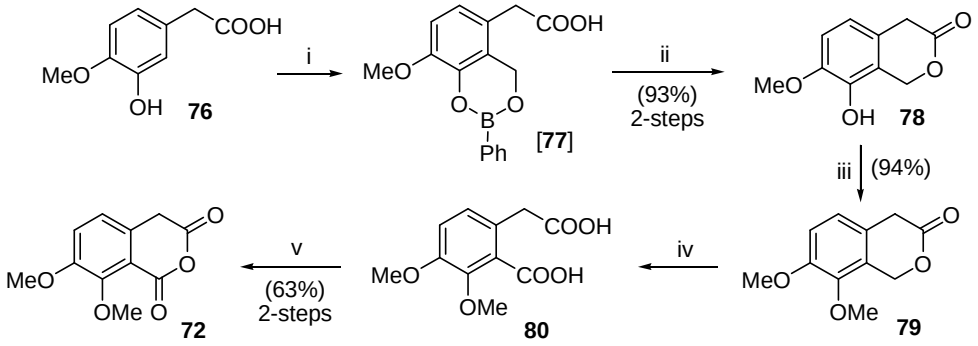
(iii) *Syntheses of (±)-Canadine, (±)-Thalictricavine and Berlambine*

Syntheses of (±)-canadine (**74a**), (±)-thalictricavine (**74b**) and berlambine (**75**) were achieved by Cushman and co-workers using the same cycloaddition propensity of 3,4-dimethoxyhomophthalic anhydride (**72**) and dihydroisoquinoline **58**[39] (Scheme 25).



Scheme 25. Synthesis of (±)-canadine, (±)-thalictricavine and berlambine

3,4-Dimethoxyhomophthalic anhydride (**72**)[39] was synthesized by using anchimerically assisted hydroxymethylation of the homoisovanillic acid (**76**) (Scheme 26). Thus the obtained intermediate **77** was hydrolyzed without isolation to the lactone **78**. The corresponding methyl ether **79** upon oxidation with potassium permanganate provided the crude 3,4-dimethoxyhomophthalic acid (**80**), which was further dehydrated to the desired anhydride **72**.



Scheme 26. *Reagents*, *conditions and yields*: (i) (a) $PhB(OH)_2$, toluene, reflux 1 h, (b) paraformaldehyde, 3 Å molecular sieves, 100 ^oC, 46 h; (ii) H_2O, reflux, 2 h (93%); (iii) Dimethyl sulfate, acetone, K_2CO_3, reflux, 2 h (94%); (iv) $KMnO_4$, aq. KOH, rt, 16 h; (v) AcCl, reflux, 2 h (63%).

1.4.2 Synthesis of Benzo[*c*]phenanthridine Alkaloids

Among the isoquinoline alkaloids, benzo[*c*]phenanthridine alkaloid[40] contains a tetracyclic core with different substitution patterns in ring A and D (Figure 3). More than 80 different alkaloids have been isolated and characterized in this class[41] and are considered as biosynthetic products of protoberberine alkaloids.[42] Numbers of benzophenanthridine class of alkaloids have been synthesized by using the cycloaddition propensity of homophthalic anhydrides, a few of them have been discussed in brief in the following section.

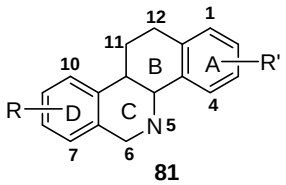
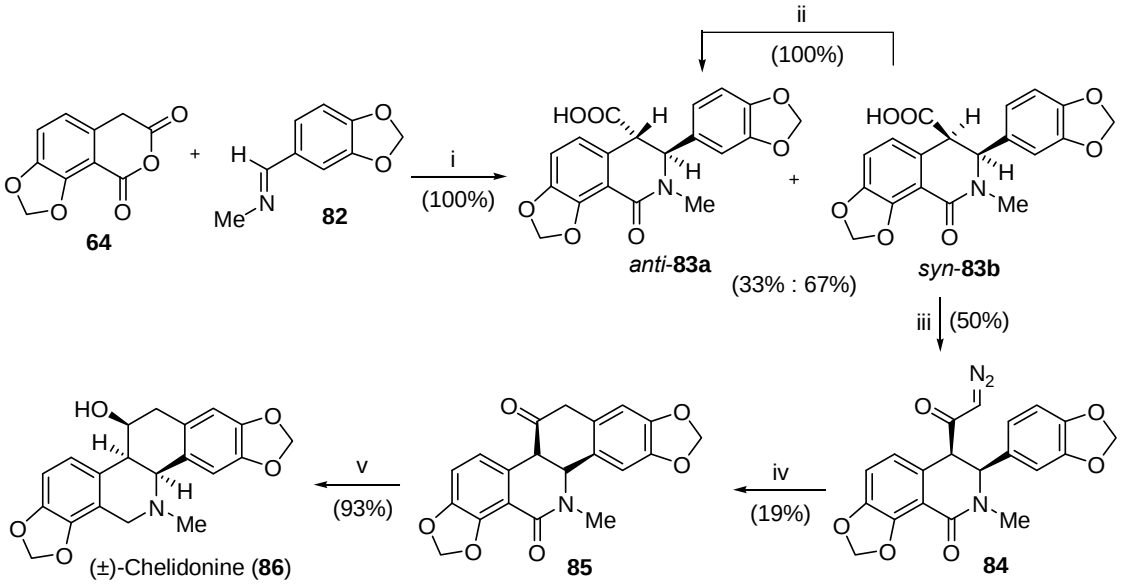


Figure 3. Benzo[*c*]phenanthridine skeleton

(i) *Total Synthesis of (±)-Chelidonine*

Condensation of 3,4-methylenedioxyhomophthalic anhydride (**64**) and Schiff base **82** has enabled Cushman and co-workers[36] to synthesize (±)-chelidonine (**86**) (Scheme 27). This results into the formation of 33% *anti*-**83a** (thermodynamic product) and 67% *syn*-**83b** (kinetic product). Extensive optimization of reaction conditions like temperature and solvent has enabled them to form the less favored *syn*-diastereomer. *Syn*-diastereomer **83b** could be converted to *anti*-product **83a** by refluxing in acetic acid. Acid chloride of *syn*-diastereomer **83b** was converted to diazo ketone **84**, which upon brief exposure to strong acid resulted in the formation of cyclic ketone **85** but in low yield. Finally $LiAlH_4$ reduction of **85** furnished (±)-chelidonine (**86**) in high yield.



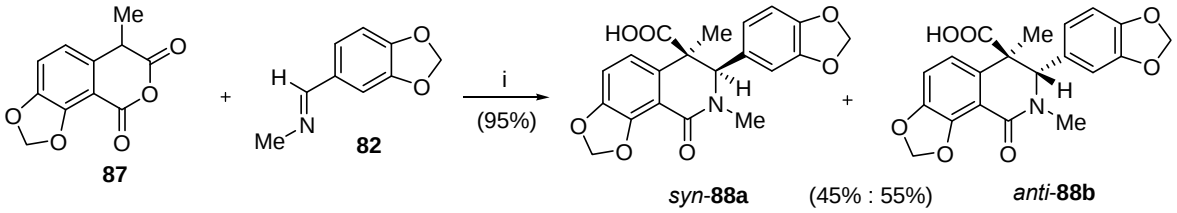
Scheme 27. *Reagents*, *conditions and yields*: (i) CH_3CN, reflux, 1 h (100%); (ii) AcOH, reflux, 13 h (100%); (iii) (a) Et_3N, benzene-DCM (2:1), (b) $SOCl_2$, CH_2Cl_2, 0 to 23 ^oC, 2 h, (c) CH_2N_2, Et_2O, (50%); (iv) TFA, 0 ^oC, 1 min (19%); (v) $LiAlH_4$, THF, 23 ^oC, 18 h (93%).

(ii) *Synthesis of (±)-Corynoline, (±)-6-Oxocorynoline and (±)-Isocorynoline*

(±)-Corynoline (**91**),[43] (±)-6-oxocorynoline (**92**)[44] and (±)-isocorynoline (**94**)[45] are the members of 13-methylbenzo[*c*]phenanthridine class of alkaloids isolated from *Corydalis incisa*. Cushman and co-workers[46] used 7-methylhomophthalic anhydride **87** and piperonylidenemethylamine (**82**) to construct both *cis* and *anti* B-C ring fusion as well as the quaternary stereogenic center by cycloaddition approach.

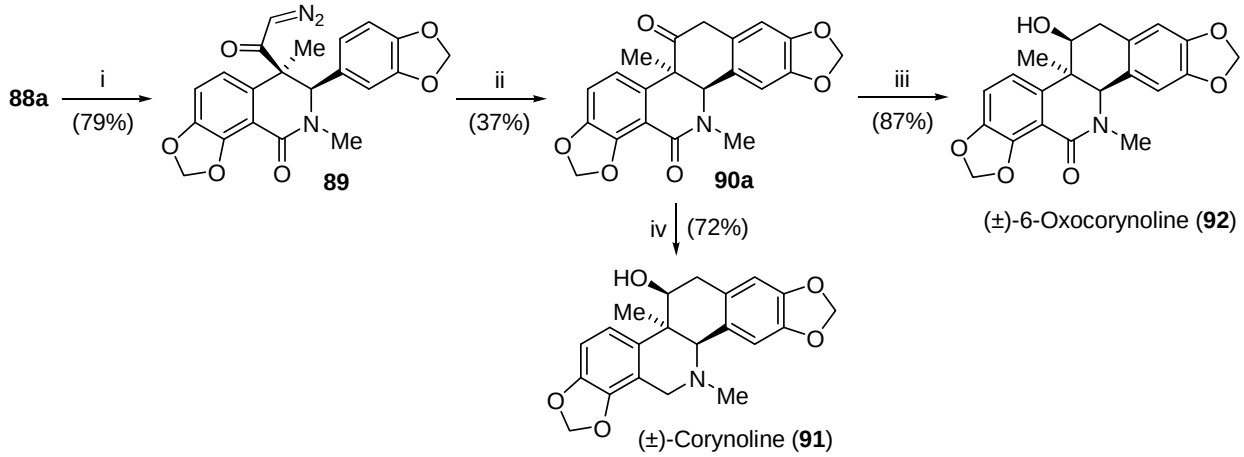
The reaction exhibited solvent dependent diastereoselectivity (Scheme 28). Very low diastereoselectivity (*syn*:*anti* = 45:55) was observed in methanol, while in benzene highest (*syn*:*anti* = 8:92) diastereoselectivity was obtained. The *syn*- and *anti*-diastereomers were readily

separable by chromatography, but unlike the analogous reaction of 7-unsubstituted homophthalic anhydrides, epimerization was not possible due to the lack of benzylic proton.



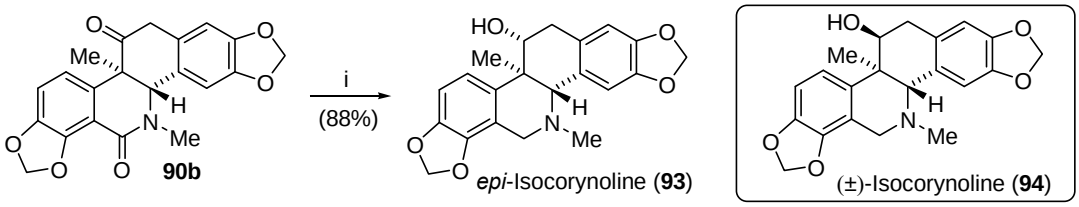
Scheme 28. *Reagents*, *conditions and yields*: (i) Methanol, rt, 1.5 h (95%).

cis-Fused (±)-corynoline (**91**) and (±)-6-oxocorynoline (**92**) were synthesized from *syn*-diastereomer **88a** via the formation of diazo ketone **89** (Scheme 29). Reduction of the two carbonyl groups present in compound **90a** using $LiAlH_4$ yielded the tricyclic alkaloid corynoline (**91**) while diastereoselective reduction of ketone **90a** with $NaBH_4$ yielded the natural alkaloid 6-oxocorynoline (**92**).



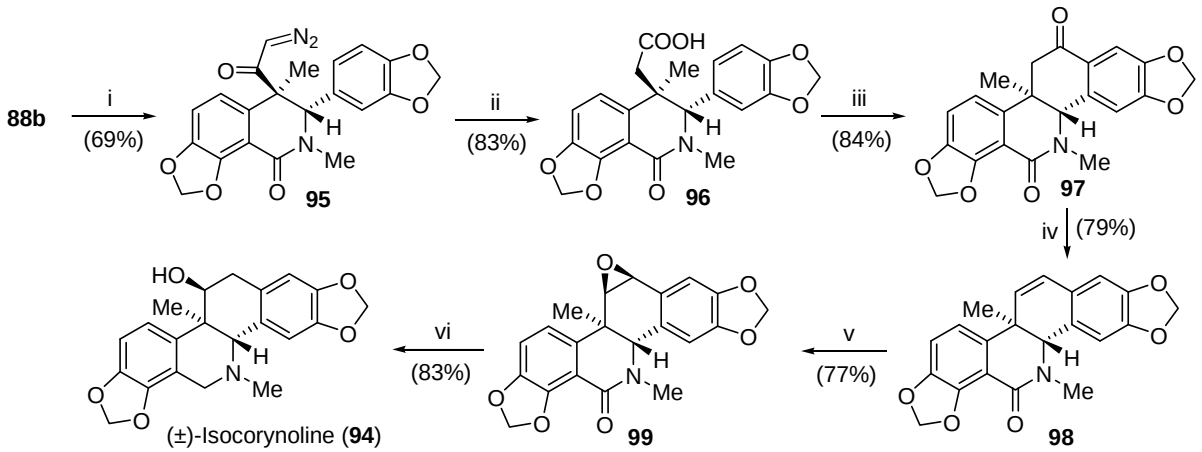
Scheme 29. *Reagents*, *conditions and yields*: (i) (a) $SOCl_2$, 12 h, rt, (b) CH_2N_2, benzene, Et_2O, 0 ^oC (79%); (ii) TFA, 0 ^oC, 10 min (37%); (iii) $NaBH_4$, MeOH, reflux, 1 h (87%); (iv) $LiAlH_4$, THF, reflux, 17 h (72%).

A straightforward reduction of *anti*-diastereomer **88b** synthesized from compound **88b** was not possible, instead it furnished *epi*-isocorynoline (**93**) (Scheme 30). In case of its *syn*-diastereomer **90a**, due to cis fused B-C ring, hydride delivery took place from convex/α-side to result into β-alcohol. In case of *trans*-fused compound **90b**, axial methyl group directed hydride delivery from β-face to form α-alcohol **93**.



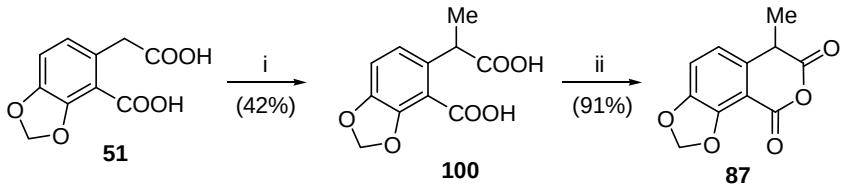
Scheme 30. *Reagents*, *conditions and yields*: (i) $LiAlH_4$, dioxane, reflux, 16 h (88%).

Many attempts made by author for inversion at the stereo center in *epi*-isocorynoline (**93**) were unsuccessful. This resulted in devising of slightly different strategy for construction of *trans*-fused B-C ring system from *anti*-**88b** in seven steps (Scheme 31). The B ring of this natural product was assembled by the homologation of *anti*-cycloadduct **88b**, followed by Friedel-Crafts cyclization reaction. The reduction of the thus formed ketone **97** followed by elimination of the resulting carbinol under acidic conditions, formed olefin **98**. The epoxidation of olefin **98** followed by its diaxial opening by using $LiAlH_4$ as the hydride source gave access to the final product (±)-isocorynoline (**94**).



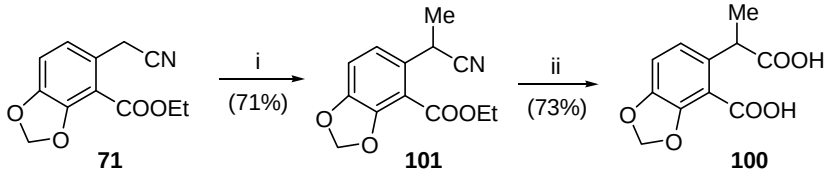
Scheme 31. *Reagents*, *conditions and yields*: (i) (a) $SOCl_2$, 12 h, rt, (b) CH_2N_2, benzene, Et_2O, 0 ^oC, 2 h (69%); (ii) (a) Ag_2O, MeOH, reflux, 2 h, (b) KOH, EtOH, reflux, 4 h (83%); (iii) P_2O_5, CH_3SO_3H, 45 ^oC, 30 min (84%); (iv) (a) $NaBH_4$, isopropyl alcohol, rt, 16 h, (b) *p*-TSA, benzene, reflux, 16 h (79%); (v) *m*-CPBA, DCM, rt, 1 h (77%); (vi) $LiAlH_4$, THF, reflux, 4 h (83%).

7-Methylhomophthalic anhydride **87**[46] was initially synthesized by alkylation of tri-anion of 3,4-methylenedioxyhomophthalic acid (**51**) (Scheme 32).



Scheme 32. *Reagents*, *conditions and yields*: (i) LDA (3 equiv.), THF-HMPA (4:1), 0 ^{o}C, 15 min then MeI (42%); (ii) AcCl, reflux, 6 h (91%).

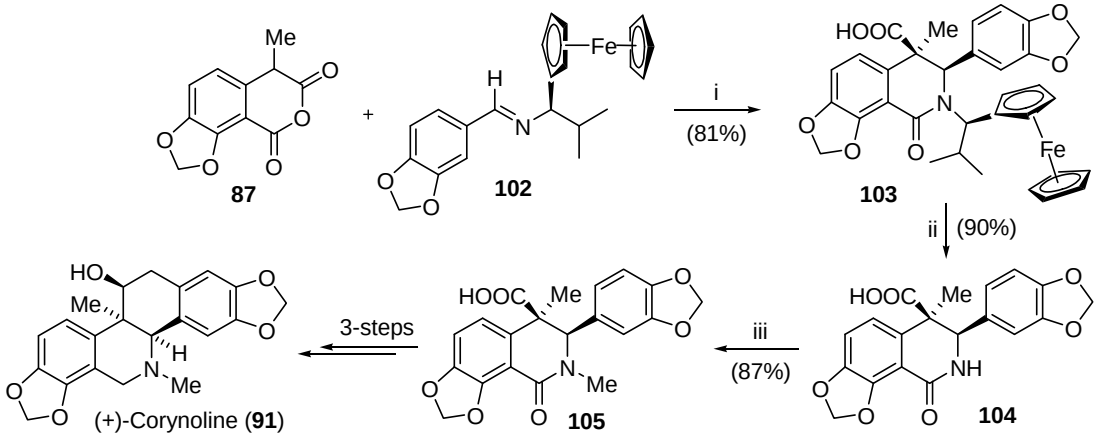
Due to low yield, alkylation of nitrile **71**[36] was carried out to obtain compound **101**, which was hydrolyzed to furnish the 7-methylhomophthalic acid **100** (Scheme 33).



Scheme 33. *Reagents*, *conditions and yields*: (i) LDA, –78 ^{o}C, MeI (71%); (ii) Aq. KOH, reflux, 3 h (73%).

(iii) *Asymmetric Synthesis of (+)/(–)-Corynoline*

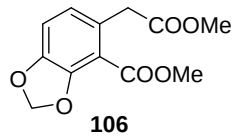
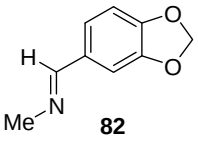
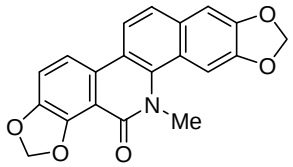
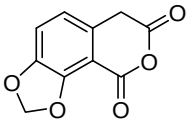
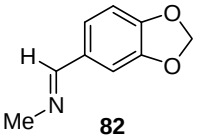
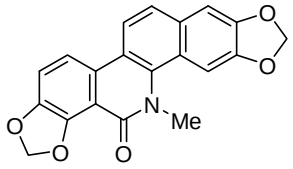
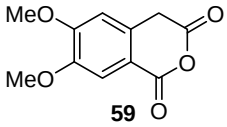
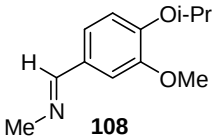
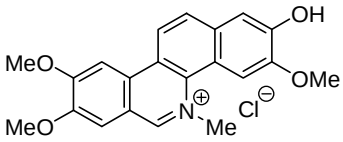
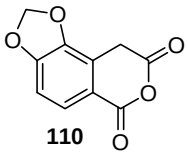
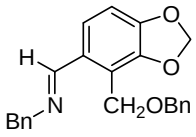
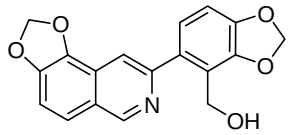
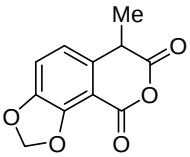
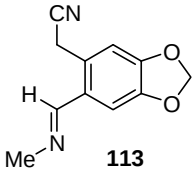
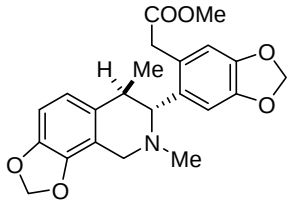
After the racemic total synthesis, Cushman and co-workers[47] reported an asymmetric synthesis of (+)/(–)-corynoline using cycloaddition of chiral imine **102** and racemic homophthalic anhydride **87** (Scheme 34). The chiral induction using the ferrocenyl chiral auxiliary effectively resulted in the *syn*-cycloadduct **103** with 89:11 diastereoselection. Optically pure enantiomer **103** was obtained after crystallization of the crude product. The removal of the chiral auxiliary, methylation of the lactam **104**, followed by the hydrolysis of the thus formed methyl ester gave the carboxylic acid **105**, which was further transformed to (+)-corynoline (**91**) by employing similar set of reaction conditions as depicted for the racemic synthesis in Scheme 29.



Scheme 34. *Reagents*, *conditions and yields*: (i) Benzene, reflux, 84 h (81%, 89:11 dr); (ii) TFA, $HSCH_2COOH$, rt, 72 h (90%); (iii) (a) KOH, Me_2SO_4, acetone, rt, 1.5 h, (b) KOH, methanol, H_2O, reflux, 2 h (87%).

A few more alkaloids of benzophenanthridine and isoquinoline class synthesized by cycloaddition of various substituted homophthalic anhydrides and imine have been listed in Table 1.

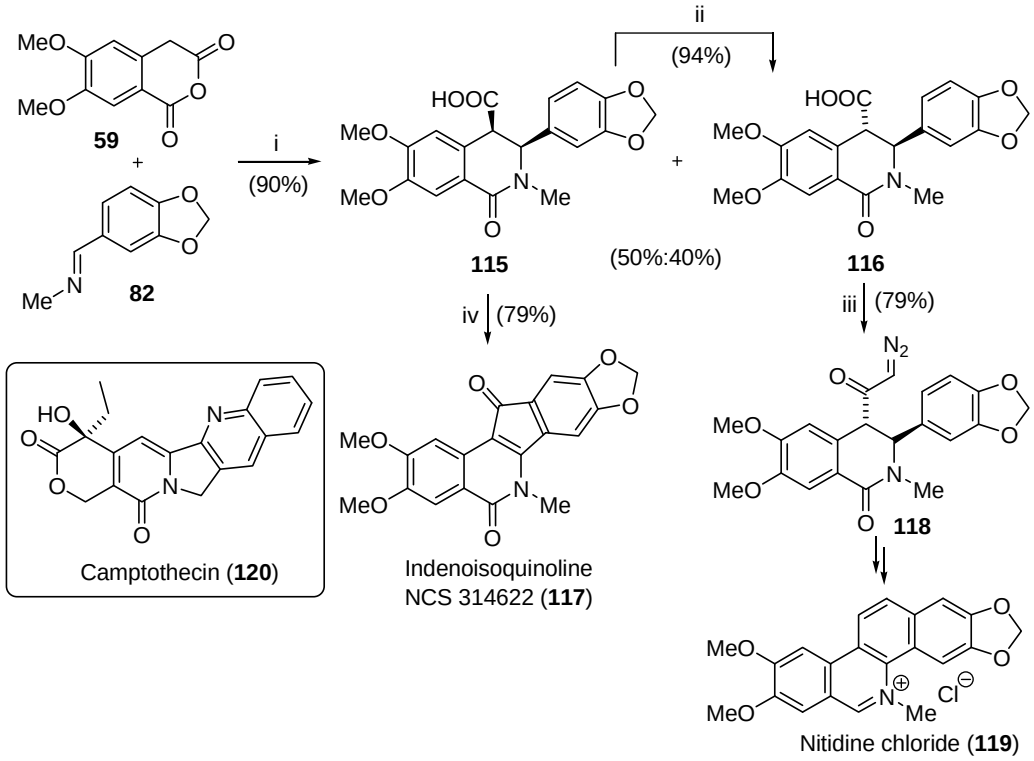
Table 1. Synthesis of benzo[*c*]phenanthridine alkaloids by using imine cycloaddition

 **106** Shamma et al. (1978)[26]	 **82**	 Oxysanguinarine (**107**) (nematicide)[48]
 **64** Smidrkal et al. (1984)[49]	 **82**	 Oxysanguinarine (**107**)
 **59** Cushman et al. (1985)[50]	 **108**	 Fagaronine chloride (**109**) (antitumor)[51]
 **110** Xu & co-workers (1998)[52]	 **111**	 Decumbenine B (**112**)
 **87** Cushman & co-workers (1984)[53]	 **113**	 Corydalic acid methyl ester (**114**)

(iv) ***Synthesis of Indenoisoquinoline Topoisomerase I Inhibitors***

Cushman & co-workers[54] in 1978 coincidently, observed the formation of indenoisoquinoline **117** from the *cis*-cycloadduct **115** (Scheme 35). At the same time *trans*-cycloadduct **116** was transformed via diazo-compound **118** to nitidine chloride (**119**), [55] a potent hepatitis B virus inhibitor.[56] Twenty years later in 1998 during *in vitro* screening, author reported moderate

cytotoxicity for indenoisoquinoline **117** parallel to camptothecin (**120**).[57] As camptothecins are the only class of topoisomerase I inhibitors approved for cancer treatment, indenoisoquinoline **117** showed certain advantages over camptothecins (**120**).[58] First, in contrast to the camptothecins, which are inactivated by lactone hydrolysis at physiological pH, the indenoisoquinolines are chemically stable. Second, the enzyme-DNA cleavage complexes stabilized by indenoisoquinoline **117** are more persistent than those induced by camptothecin (**120**). Long camptothecin infusion times are necessary to compensate for the reversibility of the camptothecin cleavage complexes during chemotherapy to achieve maximal activity. Third, the indenoisoquinolines induce a unique pattern of DNA cleavage sites relative to the camptothecins, indicating that they may target the human genome differently and therefore potentially exhibit a different spectrum of anticancer activity from the camptothecins.



Scheme 35. *Reagents*, *conditions and yields*: (i) $CHCl_3$, 25 °C, 30 min (90%); (ii) AcOH, reflux, 16 h (94%); (iii) (a) $SOCl_2$, benzene, reflux, 15 min, (b) CH_2N_2, Et_2O, rt, 30 min (79%); (iv) $SOCl_2$, 4 h, rt (79%).

However, the potential clinical utility of the lead compound indenoisoquinoline **117** itself is limited by its moderate activity, both as a cytotoxic agent in cancer cell cultures and as a topoisomerase I poison. Still after considerable success with indenoisoquinoline **117**, >400 different indenoisoquinolines were synthesized by Cushman & co-workers using differently substituted homophthalic anhydrides. Few of them were found more potent than

indenoisoquinoline **117**. Out of which three have been identified and screened as the leads for clinical development (Figure 4).[59]

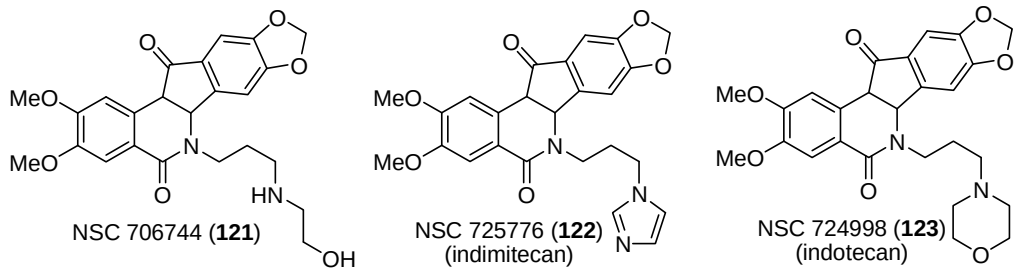


Figure 4. Potential drug leads of indenoisoquinoline class in development stages

1.4.3 Synthesis of Anthracycline Antibiotics

Anthracycline antibiotics are a class of drugs used in cancer chemotherapy and are the most effective anticancer agents ever developed.[60] The first anthracyclines discovered[61] from *Streptomyces peucetius* bacteria in 1960 were daunorubicin (**124**) and doxorubicin (**125**) (Figure 5). They are effective against different types of cancer than any other class of chemotherapy agents with proven clinical effectiveness against leukemias, lymphomas, breast carcinomas, and sarcomas.[62] Still, usefulness of these drugs was considerably limited due to their cardiotoxicity, acquired resistance and vomiting.

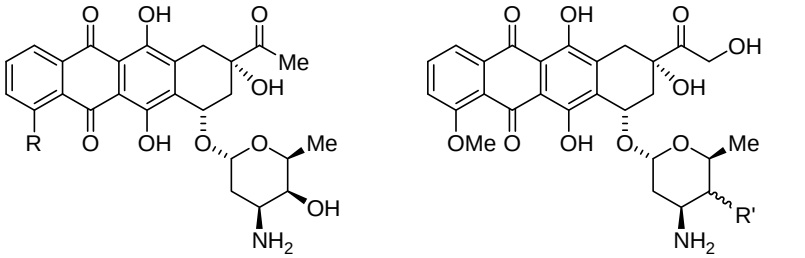


Figure 5: Anthracycline antibiotic drugs currently in clinical practice

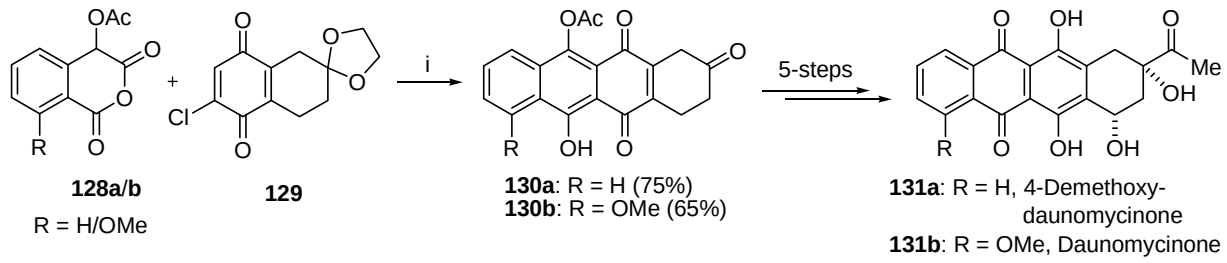
This has prompted the synthesis of many (>2000) synthetic anthracycline antibiotics, of which only a few reached the status of a drug e.g. idarubicin (**126**) and epirubicin (**127**), the structural analogues of daunorubicin (**124**) and doxorubicin (**125**) respectively. The absence of a methoxy group in idarubicin (**126**) lowers toxicity, increases fat solubility and hence cellular uptake. This improves its antineoplastic activity. Epirubicin (**127**) has a different spatial orientation of the hydroxyl group at the 4' carbon of the sugar, which may account for its faster elimination to result in the reduced toxicity. Hence epirubicin (**127**) is favored over doxorubicin (**125**) for the treatment against breast, ovarian, gastric, lung cancer and lymphomas. Since anthracyclines are

antibiotics, they can kill or inhibit the growth of bacteria, but due to their high toxicity to humans, they were never used to treat infections.

Homophthalic anhydride and their derivatives proved efficient as the precursors in the synthesis of quite a few members of anthracycline antibiotics in a convergent manner. Two representative examples are discussed here in brief and few examples are listed in Table 2.

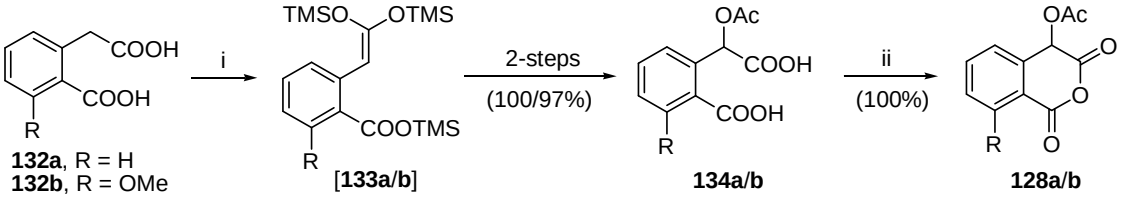
[A] ***Synthesis of 4-Demethoxydaunomycinone and Daunomycinone by Tamura et al.***

'Anionically mediated' Diels-Alder cycloaddition between the enolate generated from homophthalic anhydride **128a**/**b** and the highly reactive chloroquinone **129** as the dienophile to form tetracyclic compound **130a**/**b** was the basis of the Tamura's total synthesis[63] (Scheme 36). Daunomycinone (**131b**) and 4-demethoxydaunomycinone (**131a**) are the corresponding aglycone of daunorubicin (**124**) and idarubicin (**126**). The presence of a chlorine atom in quinone **129** controls the regiochemistry of the cycloaddition and facilitates aromatization of the formed cycloadducts via elimination of HCl. Additional five steps were required further to complete the highly convergent total synthesis of 4-demethoxydaunomycinone and daunomycinone.



Scheme 36. *Reagents*, *conditions and yields*: (i) (a) NaH, THF, rt, (b) 80% aq. TFA, 50 ^{o}C, 2 h (75/65%).

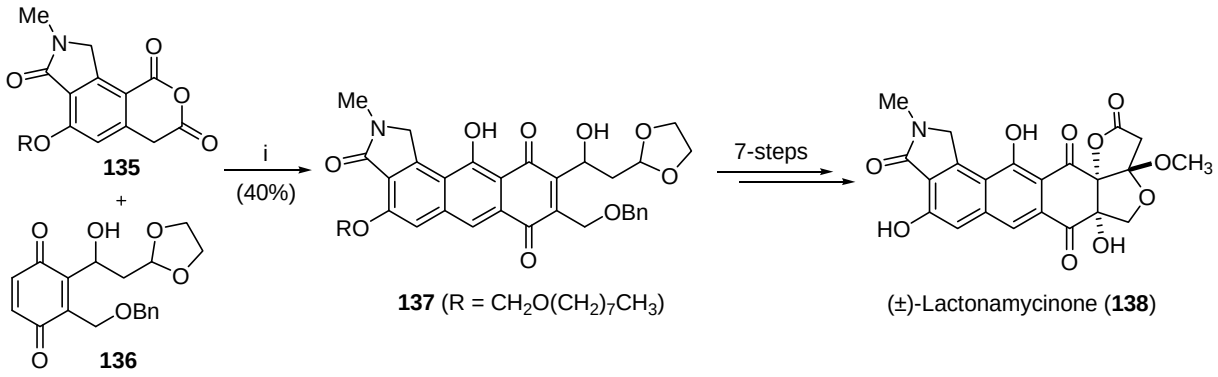
Acetoxyhomophthalic anhydrides **128a**/**b** were synthesized from corresponding trimethylsilyl derivatives **133a**/**b** of homophthalic acid **132a**/**b** followed by their Rubottom oxidation and dehydrative cyclization (Scheme 37).



Scheme 37. *Reagents*, *conditions and yields*: (i) (a) LDA (3.2 equiv.), TMSCl, THF, –78 ^{o}C to rt, (b) $Pb(OAc)_4$, benzene, rt, 2 h (100/97%); (ii) Trimethylsilylethoxyacetylene, DCM, rt, 4 h (100%).

[B] ***First Total Synthesis of Lactonamycinone by Danishefsky et al***.

Tamura cycloaddition reaction has been successfully applied by Danishefsky and co-workers[64] in the construction of the C-ring of the natural product lactonamycinone in a convergent fashion (Scheme 38). The reaction of homophthalic anhydride **135** with quinone **136**, in the presence of sodium hydride, afforded the tetracyclic intermediate **137** with complete control of the regioselectivity. Additional seven steps were required further to complete the total synthesis of natural product lactonamycinone (**138**).



Scheme 38. *Reagents*, *conditions and yields*: (i) NaH, THF, –78 to 0 ^{o}C (40%).

Regioselective cycloaddition was performed by taking the advantage of unprotected hydroxyl group present in the side chain of quinone **136**. This is the first example of regioselective Tamura cycloaddition by intramolecular catalysis through an alkoxide-based metal bridge. The possible transition states involved are predicted in Figure 6.

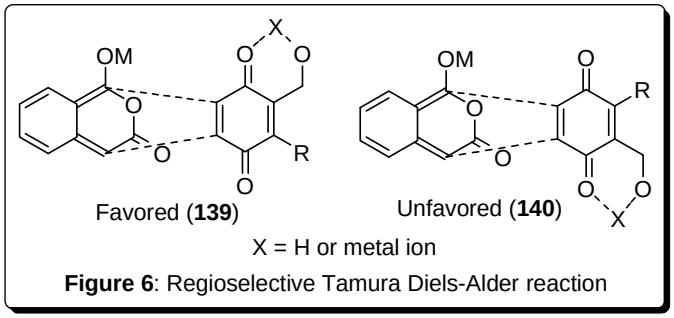
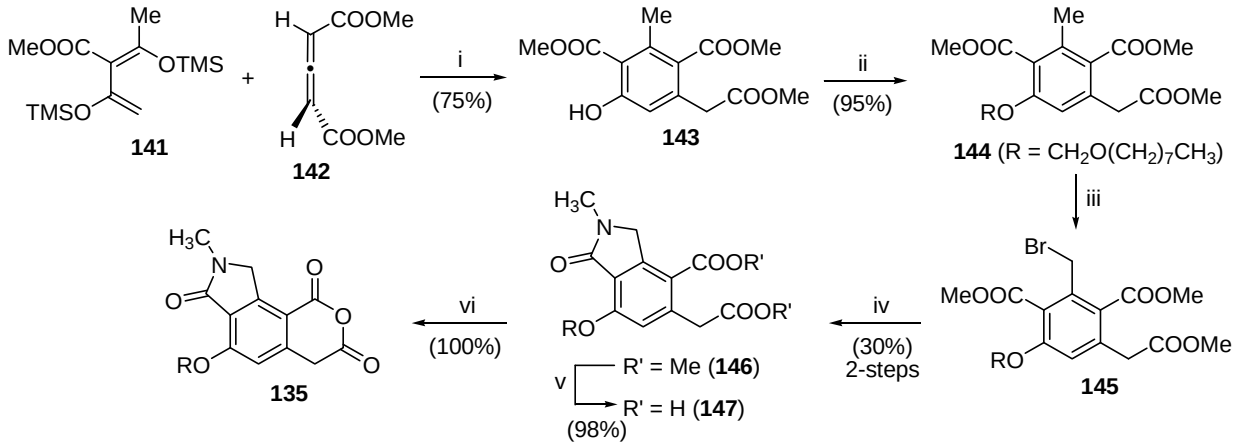


Figure 6: Regioselective Tamura Diels-Alder reaction

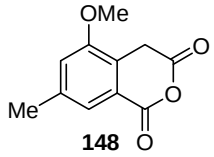
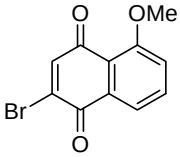
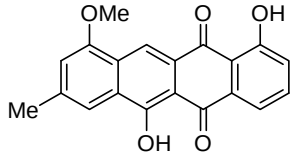
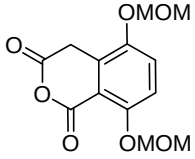
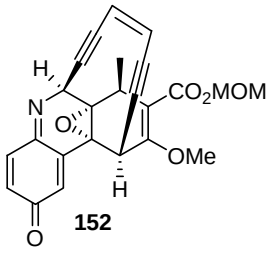
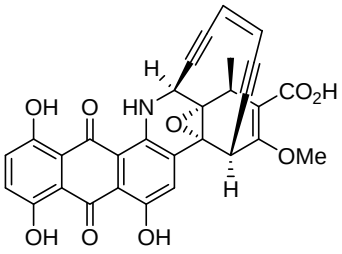
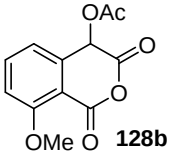
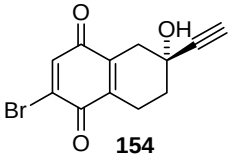
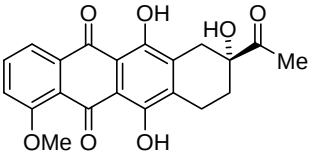
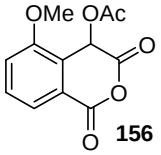
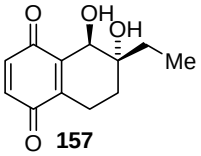
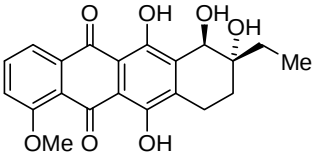
The route for homophthalic anhydride **135** starts with the diene **141** (Scheme 39). Cycloaddition of diene **141** and the 1,3-dicarbomethoxyallene (**142**) furnishes dimethyl homophthalate **143** in 75% yield. To overcome issues of solubility in the later stages of synthesis, the phenolic function of compound **143** was protected as an unconventional octyloxymethyl ether derivative. The benzylic methyl group of compound **144** was selectively brominated with *N*-bromosuccinimide and benzoyl peroxide to obtain the compound **145** but in low yield. Treatment of the resulting compound with methylamine formed lactam **146** along with the isomeric isoindolinone. Hydrolysis of the diester followed by dehydrative cyclization of resulting diacid produced the homophthalic anhydride **135**.

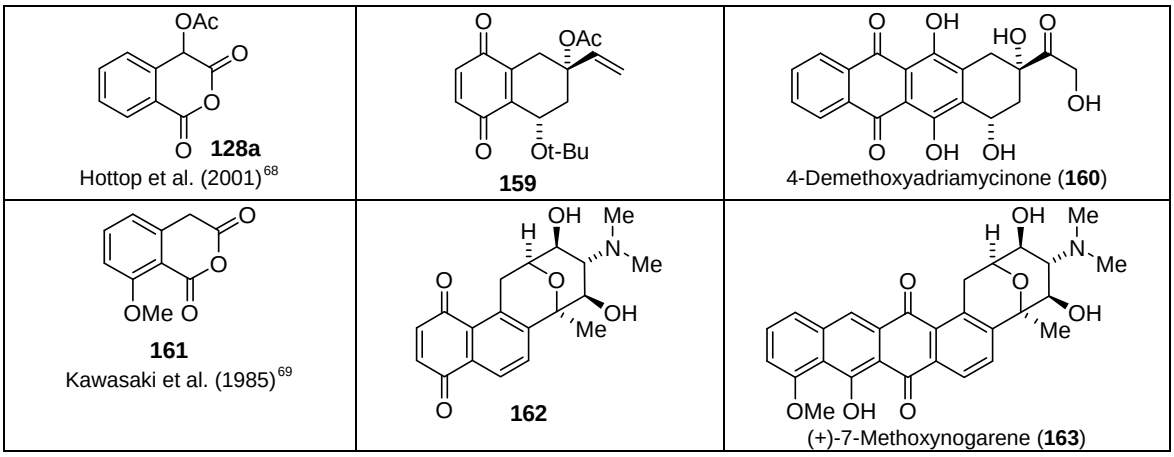


Scheme 39. *Reagents*, *conditions and yields*: (i) (a) Neat, 105 ^{o}C, (b) NH_4F, MeOH (75%); (ii) $CH_3(CH_2)_7OCH_2Cl$, DIPEA, DMF (95%); (iii) NBS, benzoyl peroxide (cat.), UV, benzene; (iv) K_2CO_3, NH_2Me, MeOH-CH_3CN (1:2) (30%); (v) KOH, MeOH (98%); (vi) Trimethylsilylethoxyacetylene, CH_3CN-CH_2Cl_2 (100%).

Quite a few anthracyclines and related natural and synthetic products have been synthesized by cycloaddition of homophthalic anhydrides and quinones. They are listed along with their respective anhydride and quinone precursors in Table 2.

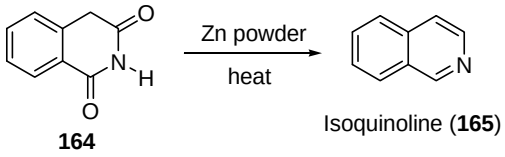
Table 2: Synthesis of anthracycline antibiotics and related natural products from various homophthalic anhydrides

 **148** Tamura et al. (1986)[65]	 **149**	 SS-228R (**150**)
 **151** Danishefsky & co-workers (1996)[25]	 **152**	 Dynemicin A (**153**)
 **128b** Kita & co-workers (1985)[66]	 **154**	 (–)-7-Deoxydaunomycinone (**155**)
 **156** Kita & co-workers (1989)[67]	 **157**	 (–)-γ- Rhodomycinone (**158**)



1.5 Homophthalimides: An Overview

Homophthalimide (**164**), an important derivative of homophthalic acid is known for more than a century. Formation of isoquinoline (**165**) through vigorous heating with zinc powder was first described by Le Blanc in 1888 (Scheme 40).[70]

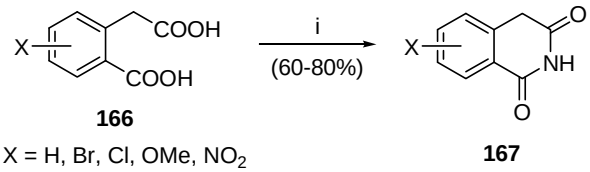


Scheme 40. Isoquinoline synthesis

Homophthalimides are generally synthesized by the condensation of homophthalic anhydrides/acids and various substituted amines. We have made considerable efforts for the synthesis of various natural and synthetic products by using homophthalimides and will be discussed in the subsequent part. Few other methods of homophthalimides synthesis have been briefly summarized in this part.

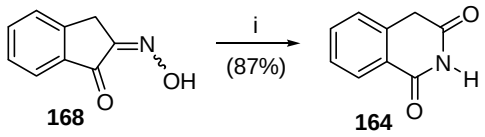
1.5.1 Synthesis of Homophthalimide

Crockett et al.[71] and Tsou et al.[19] have reported the synthesis of homophthalimide by condensation of urea and homophthalic anhydrides/acids **166** (Scheme 41).



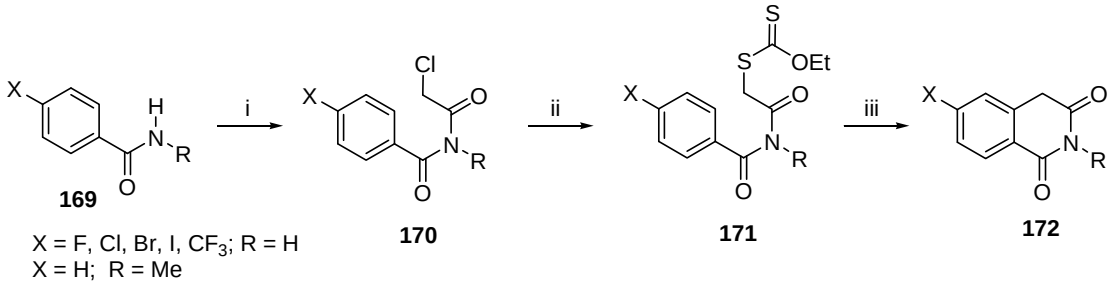
Scheme 41. *Reagents*, *conditions and yields*: (i) Urea, with or without *o*-dichlorobenzene, 150–180 ^{o}C, 2–3 h (60–80%).

Dongare and co-workers[72] developed silica supported molybdenum oxide catalyst for Beckmann rearrangement of various oximes. The reaction condition is tolerable for various acid sensitive protecting groups are the advantage of this methodology (Scheme 42).



Scheme 42. *Reagents*, *conditions and yields*: (i) MoO_3, SiO_2, EtOH, reflux, 18 h (87%).

Synthesis of homophthalimides based on a radical cyclization of xanthates **171** to homophthalimides **172** has been reported by Zard & co-workers[73] (Scheme 43). Heating xanthates **171** in refluxing *o*-dichlorobenzene with slow addition of stoichiometric amount of di-*tert*-butyl peroxide yields the desired homophthalimides **172**. The products very often precipitated upon cooling of the reaction mixture or after partial evaporation of the solvent under vacuum, hence could be isolated by mere filtration. The formation of regioisomers with unsymmetrical substrates is the limitation of this methodology.

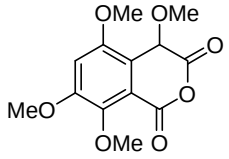
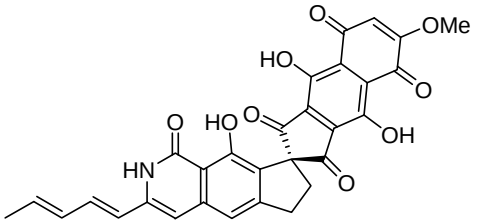
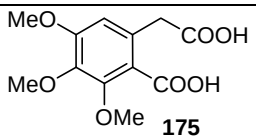
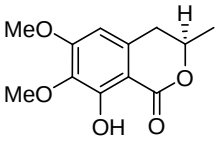
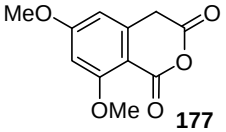
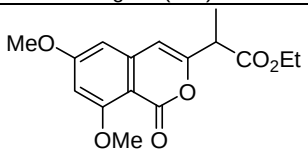
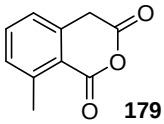
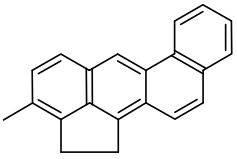
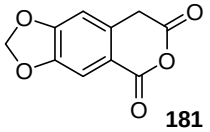
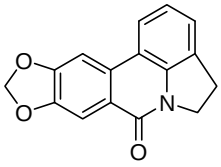
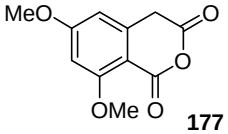
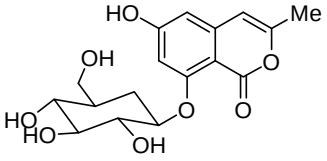
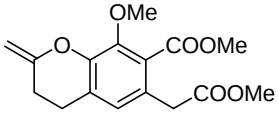
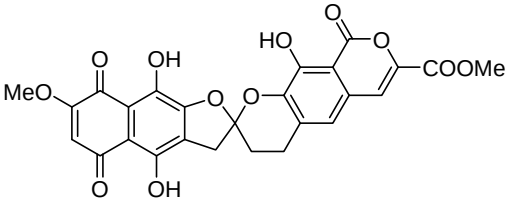


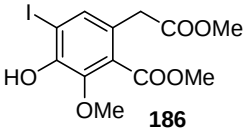
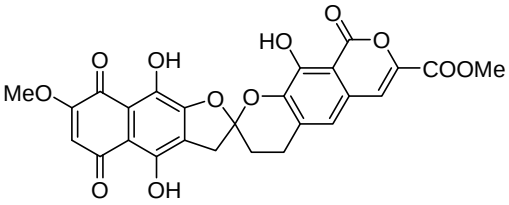
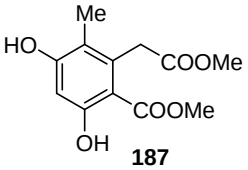
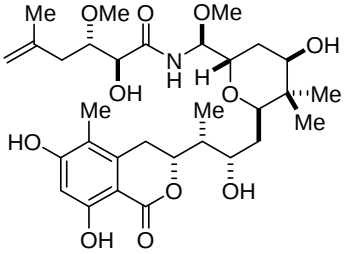
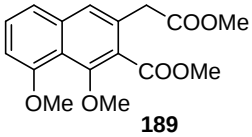
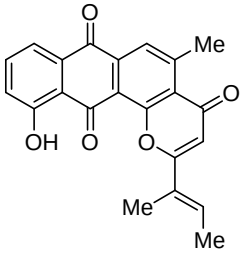
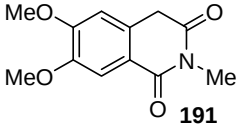
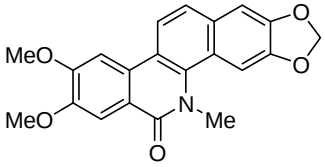
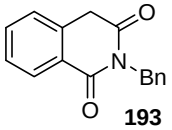
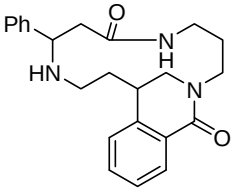
Scheme 43. *Reagents*, *conditions and yields*: (i) $ClCH_2COCl$, toluene, reflux; (ii) KSCSOEt, CH_3CN (80–95% over 2-steps); (iii) $(t\text{-}BuO)_2$, $o\text{-}C_6H_4Cl_2$, reflux, 1–1.5 h (40-65%).

Few other natural products of different types have been also synthesized by using homophthalic anhydrides as the precursors (Table 3). Various novel strategies were used to synthesize these natural products as well as differently substituted homophthalic acids/anhydrides. This has not just provided the access to the complex natural products but the efforts towards these targets also served as the principle driving force for the discovery of new chemistry. Fredericamycin A (**174**), γ-rubromycin (**185**) are the two complex spiro-cycles synthesized by using diester of homophthalic acid as the key precursors. Three different syntheses appeared recently for (+)-psymberin (**188**) starting from same precursor dimethyl homophthalate **187**. In few cases homophthalimides were used for the synthesis of natural products like oxynitidine (**192**) and isocyclocelabenzine (**194**) in which isocyclocelabenzine (**194**) is the 13-membered macrocycle.

Schematic synthetic strategies towards all these natural products have been well reviewed by Shaw et al.[2] and discussed in brief in a Ph. D. dissertation[3] from our research group, these natural products have been only listed in Table 3 along with the precursor homophthalic anhydrides.

Table 3: Different types of natural products synthesized from homophthalic anhydrides and their derivatives

 **173** Kita et al. (2001)[74]	 Fredericamycin A (**174**)
 **175** Saeed et al. (2005)[75]	 Kigelin (**176**)
 **177** Bauta et al. (2003)[76]	 NM-3 (**178**) (angiogenesis inhibitor)
 **179** Koreeda & co-workers (1993)[77]	 3-Methylcholanthrene (**180**)
 **181** Castedo & co-workers (1996)[78]	 Lycorines (**182**)
 **177** Saeed et al. (2005)[79]	 Delphoside (**183**)
 **184** Kita & co-workers (2007)[80]	 *γ*-Rubromycin (**185**)

 **186** Brimble & co-workers (2009)[81]	 *γ*-Rubromycin (**185**)
 **187** Crimmins et al. (2009)[82] Smith & co-worker (2008)[83] Floreancig & co-worker (2005)[84]	 (+)-Psymberin (**188**)
 **189** McDonald & co-worker (2005)[85]	 Kidamycinone (**190**)
 **191** Parez et al. (1992)[86]	 Oxynitidine (**192**)
 **193** Iida et al. (1986)[87]	 Isocyclocelabenzine (**194**)

1.6 Summary

The above discussion reveals that homophthalic anhydrides/acids are a versatile synthons in organic synthesis. After first report in 1890, interest in their chemistry has grown consistently, particularly in the natural products synthesis. This small molecule with multiple functionalities has proven its efficacy through building the backbones of many structurally complex and medicinally important molecules in a convergent manner. The syntheses of these creatures would have become difficult otherwise. This has been exemplified by the laboratory access to large number of protoberberine, benzophenanthridine and anthracycline class of natural and synthetic products by using homophthalic anhydrides. Many bioactive indenoisoquinolines as well as anthracyclines have been synthesized by the use of homophthalic anhydrides, few of them are in clinical practice and few are in development stages. This ascertains the utility of homophthalic anhydrides and their derivatives in the organic synthesis and medicinal chemistry.

Since many years, our research group is using cyclic anhydrides as the starting materials for the natural product synthesis; the considerable attempts have been made here by using homophthalic anhydrides for the synthesis of natural and synthetic products. In this context, our synthetic studies towards protoberberine alkaloids starting from homophthalic anhydrides have been presented in the following part. We have been successful in the total synthesis of nuevamine, β-carboline, chilenine and deoxychilenine using the facile air-oxidation of homophthalimide. We have also successfully constructed erythrina alkaloid frame-work through a novel synthetic route. These studies have been discussed in details in chapter 2.

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Chapter 2

Synthetic Studies Towards Nitrogen Containing Natural and Unnatural Products Using Cyclic Anhydrides and their Derivatives

This Chapter Features the Following Topics:

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

This chapter is divided into three sections. Section A presents our general approach towards the isogusanlung D and dehydroisogusanlung D starting from the 4,5-methylenedioxyhomophthalic acid (Figure). The section B presents our synthetic studies on total synthesis of natural products nuevamine, chilenine and deoxychilenine and unnatural products isonuevamine and (+)-*β*-carboline, utilizing the serendipitously witnessed facile air-oxidation of the active methylene group in the corresponding homophthalimides and intramolecular cyclizations as the key steps. In the last section C, our synthetic studies towards the synthesis of erythrina alkaloid architecture and erysotramidine have been presented. The detailed experimental procedures, complete tabulated analytical and spectral data and some selected NMR spectra have been also appropriately included at the end of each section.

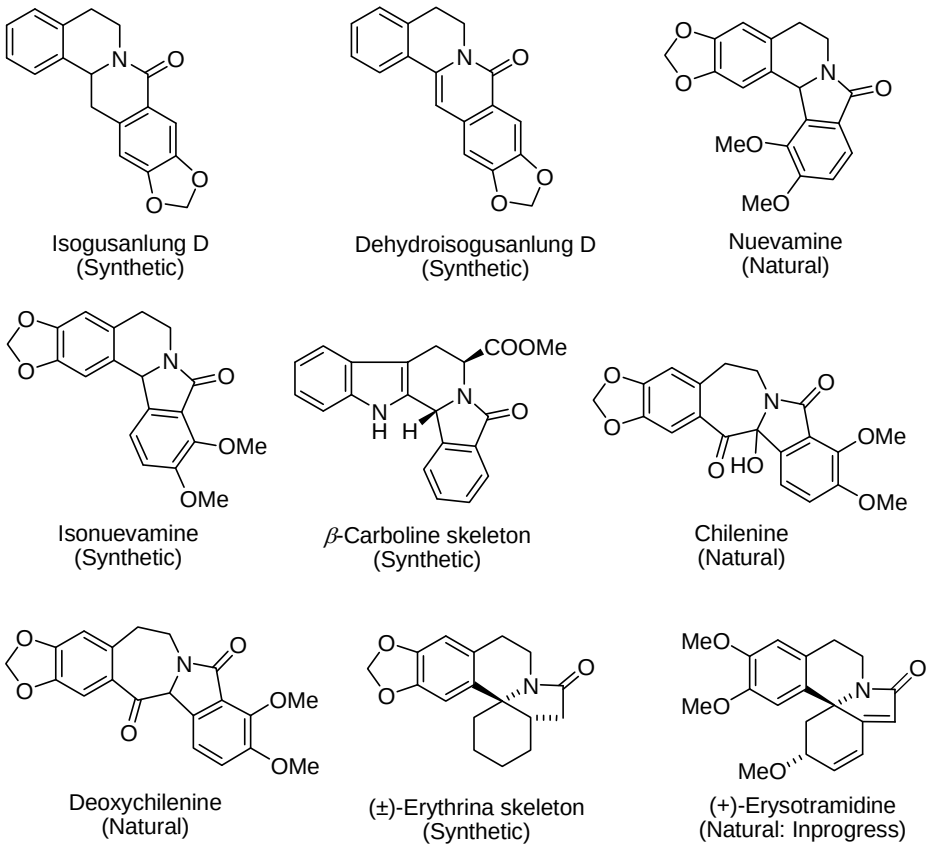


Figure. Nitrogen containing bioactive natural and unnatural products synthesized using cyclic anhydrides as the potential precursors

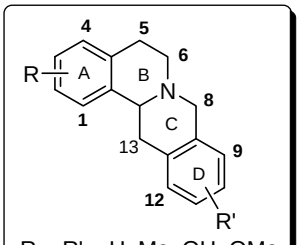
Chapter 2: Section A

Synthetic Studies Towards Isogusanlung D and Dehydroisogusanlung D

This Section A of Chapter 2 Features the Following Topics:

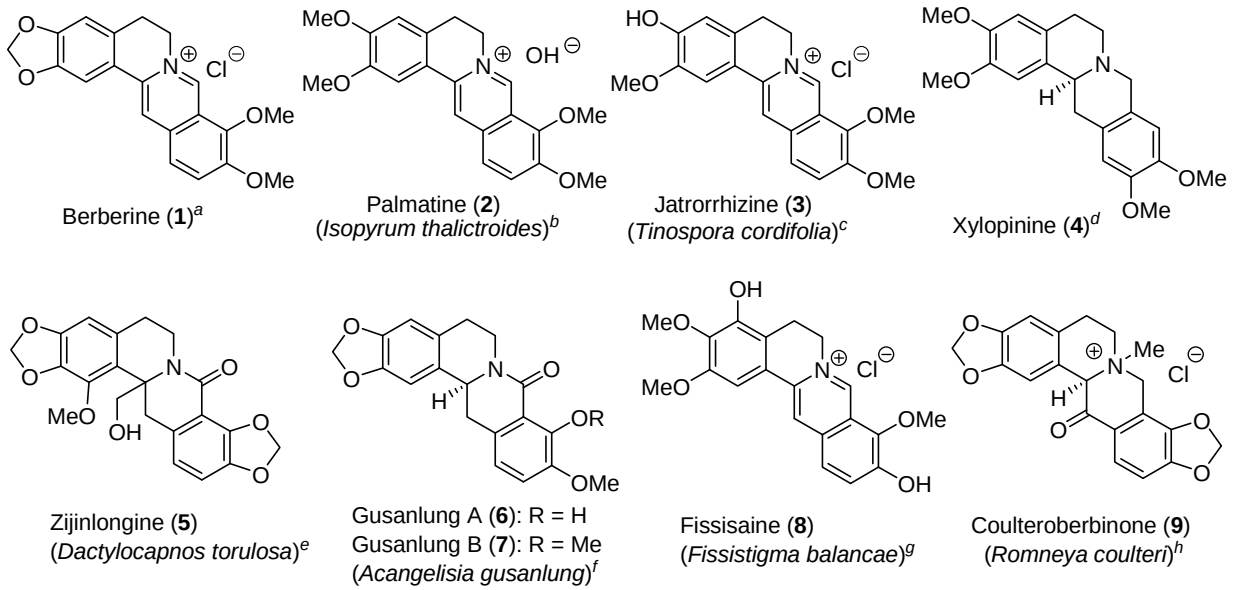
2A.1 Background

Protoberberines are widely distributed in plant families like Papaveraceae, Berberidaceae, Fumariaceae, Menispermaceae, Ranunculaceae, Rutaceae, Annonaceae etc. They are the largest class of natural products containing a tetracyclic ring skeleton with an isoquinoline core[1] (Figure 1) and are considered as biogenetically derived from tyrosine.[2,3] Various biological properties have been attributed to this class including antiinflammatory, antimicrobial, antileukemic and antitumor activities.[4] Large numbers of these alkaloids have been isolated from various plant species with different substitution pattern in ring A and D. Few of the representative examples of this class are presented in Figure 2.



R = R' = H, Me, OH, OMe, (-OCH_2O-)

Figure 1. Protoberberine skeleton



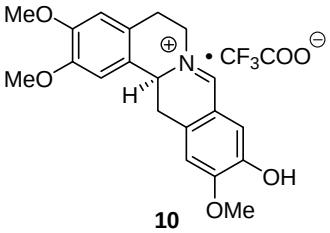
[a] Reference 5. [b] Reference 6. [c] Reference 7. [d] Reference 4.

[e] Reference 8. [f] Reference 9. [g] Reference 10. [h] Reference 11.

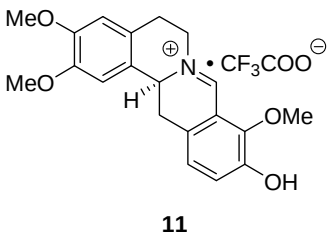
Figure 2. Protoberberine family alkaloids

Many elegant achiral and chiral synthetic routes to protoberberines have been reported in the literature.[4,12] Among the variety of strategies developed for the asymmetric synthesis of protoberberines, two classical procedures, the Pictet–Spengler[13] and the Bischler–Napieralski[14] cyclization have been most frequently used for the construction of the tetrahydroisoquinoline nucleus. The quaternary protoberberine alkaloids (QPA) represent approximately 25% of all currently known protoberberine skeletons isolated from natural sources.[2] Although

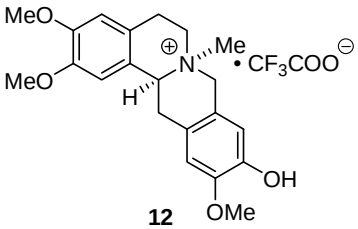
protoberberine alkaloids differ in the number and position of oxygen functions on the aromatic rings A and D, two oxygenation patterns most frequently occurred are at carbons 2,3,9,10 and 2,3,10,11. The former group occurs most commonly, while the latter has been labeled "pseudoprotoberberine" as the prefix and it is less widespread.[15] Some 2,3,10,11-oxygenated alkaloids display higher activity in biological assays (e.g. antimalarial activity) than the corresponding 2,3,9,10-substituted analogues.[16] As mentioned above, protoberberines are the largest class of isoquinoline alkaloids, newer and structurally interesting members of this family are still being isolated. Few examples of recently isolated members are listed in Figure 3.



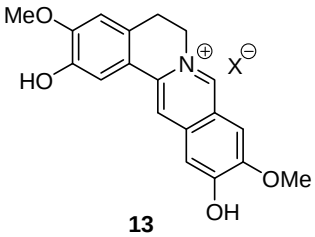
10
(*Annoan glabra*)[a]



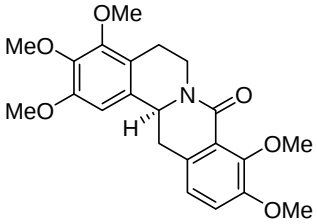
11
(*Annoan glabra*)[a]



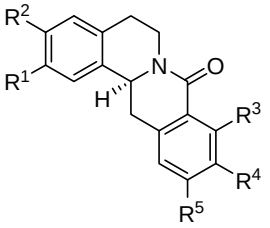
12
(*Annoan glabra*)[a]



13
(*Xylopia parviflora*)[b]



(–)-4-Methoxy-13,14-dihydrooxypalmatine (**14**)
(*Cocculus orbiculatus*)[c]



15 ($R^1 = R^2 = R^3 = OMe$, $R^4 = OH$, $R^5 = H$)
16 ($R^1 = R^5 = OH$, $R^2 = R^4 = OMe$, $R^3 = H$)
17 ($R^1 = R^2 = R^3 = R^4 = OMe$, $R^5 = OH$)
18 ($R^1 = R^4 = OH$, $R^2 = R^3 = R^5 = OMe$)
(*Polyalthia longifolia*)[d]

[a] Reference 17. [b] Reference 18. [c] Reference 19. [d] Reference 20.

Figure 3. Recently isolated protoberberine family alkaloids

(–)-Gusanlung D (**19**) is the simplest member of the protoberberine family and is claimed as the first protoberberine which is unoxygenated in ring D (Figure 4). Zhang et al.[21] isolated this natural product from the stem of the *Acangelisia gusanlung* which is a small shrub distributed in Hainan Island of southern China (its whole stem is used in folk medicine). There are five racemic and one asymmetric synthesis reported for gusanlung D. Among them one recent synthesis has been discussed in the following part along with the total synthesis from our research group.

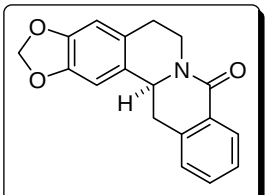
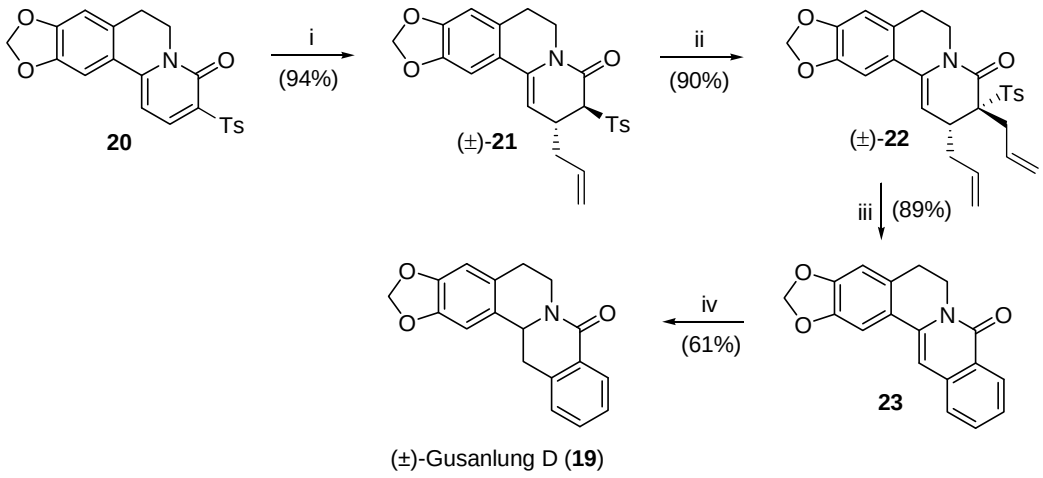


Figure 4.
(–)-Gusanlung D (**19**)

2A.1.1 Synthetic Approaches Towards Gusanlung D

Before the isolation of gusanlung D in 1995, Kesser et al.[22] from India in 1992 reported its racemic synthesis via the generation and trapping of *α*-oxo-*o*-quinodimethanes. Unfortunately, the analytical and spectral data reported for the natural and synthetic gusanlung D were not in agreement with each other. Padwa and Waterson reported a neat approach to (±)-gusanlung frame work by taking advantage of Pummerer/Mannich induced cyclization cascade.[23] Recently, Reimann et al.[24] reported the synthesis of (±)-gusanlung D from the *Reissert*-compounds. Chrzanowska et al.[25] reported the first asymmetric synthesis of both (+)/(–)-gusanlung D indicating the possibility of considerable amount of contamination of dehydrogusanlung D (**23**) with the natural product.

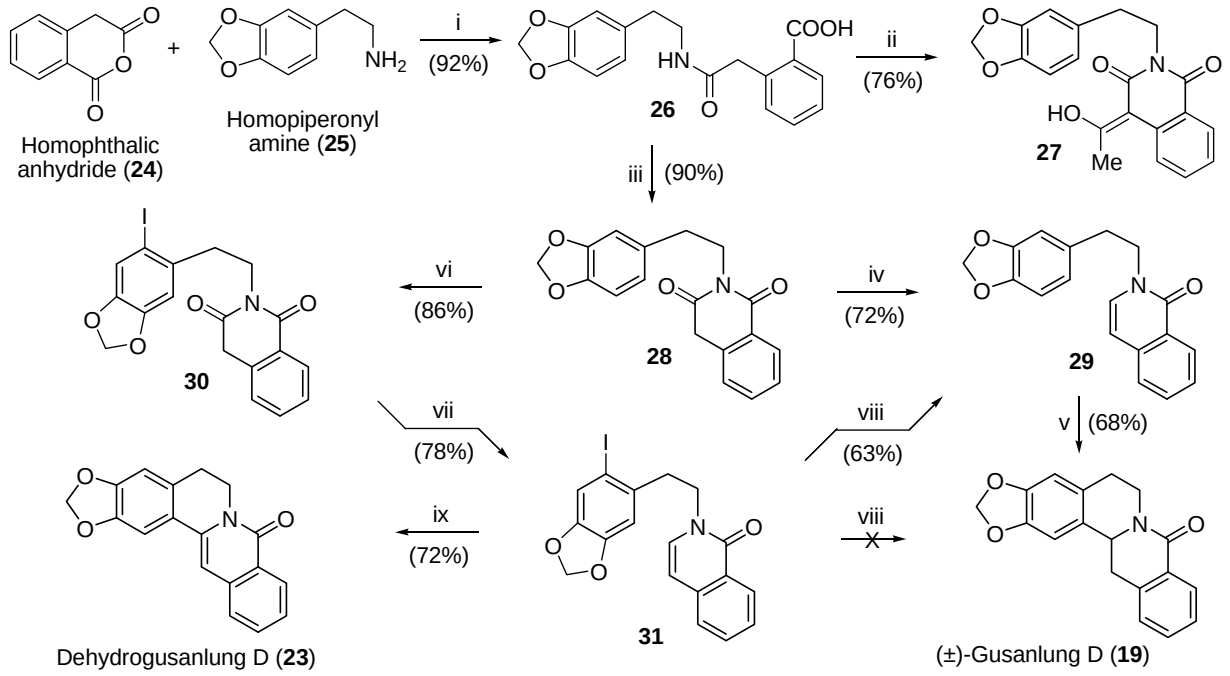
Recently, Chang et al.[26] reported the synthesis of (±)-gusanlung D (**19**) via dehydrogusanlung D (**23**), by taking the advantage of ring-closing metathesis (RCM) (Scheme 1). The key intermediate **20** (synthesized in 5 steps) was subjected for sequential double allylation to give RCM precursor **22**. Grubb's first generation catalyst was used for the construction of D ring of natural product to give dehydrogusanlung D (**23**). Finally, reduction of the dehydrogusanlung D (**23**) furnished gusanlung D (**19**).



Scheme 1. *Reagents*, *conditions and yields*: (i) AllylMgBr, THF, rt, 1.5 h (94%); (ii) Allyl bromide, NaH, THF, rt, 12 h (90%); (iii) (a) Grubbs 1st Gen. catalyst, DCM, rt, 12 h, (b) *t*-BuOK, *t*-BuOH, reflux, 24 h (89%); (iv) Pd/C, $HCOONH_4$, MeOH, reflux, 5 h (61%).

Very recently Argade and co-workers[27] completed the synthesis of (±)-gusanlung D (**19**) using homophthalic anhydride as the potential precursor. As the unconjugated carbonyl group in the homophthalic anhydride/imide can be regioselectively explored, homophthalic anhydride/imide

turned out be the most appropriate building block for the synthesis of (±)-Gusanlung D (**19**) (Scheme 2).



Scheme 2. *Reagents, conditions and yields*: (i) Ether-THF (4:1), rt, 2 h (92%); (ii) Ac_2O, AcONa, 60 ^oC, 3 h (76%); (iii) HMDS, $ZnCl_2$, benzene, 2.5 h (90%); (iv) (a) $NaBH_4$, EtOH, 0 ^oC, 6 h, (b) H^+/HCl, rt, 12 h (72%); (v) Conc. HCl, rt, 48 h (68%); (vi) I_2, CF_3COOAg, $CHCl_3$, rt, 8 h (86%); (vii) (a) $NaBH_4$, EtOH, 0 ^oC, 6 h, (b) H^+/HCl, rt, 12 h (78%); (viii) AIBN, Bu_3SnH, benzene, reflux, 6 h (63%); (ix) $Pd(OAc)_2$, tetramethylguanidine (TMG), AcONa, DMF, 110 ^oC, 20 h (72%).

The regioselective ring opening of homophthalic anhydride (**24**) at the more reactive unconjugated carbonyl with homopiperonyl amine (**25**) in an ether-THF mixture at room temperature exclusively furnished the *N*-homopiperonylhomophthalamic acid (**26**) in 92% yield. An attempted preparation of the corresponding homophthalimide **28** using an acetic anhydride-sodium acetate induced dehydration of **26** resulted instead in the formation of a homophthalimide **27** bearing an α-acyl substitution in 76% yield (formed due to the highly acidic nature of the α-methylene protons of such systems). A singlet signal at δ 11.05 and the corresponding absence of a methylene proton signal in the ^{1}H NMR spectrum of the above product clearly revealed that the product existed exclusively as the enol **27** which is stabilized by conjugation of the double bond with the carbonyl group and the phenyl ring as well as by six-membered intramolecular hydrogen bonding. Ultimately, the acid **26** on treatment with hexamethyldisilazane (HMDS)-$ZnCl_2$[28] gave the desired *N*-homopiperonylhomophthalimide

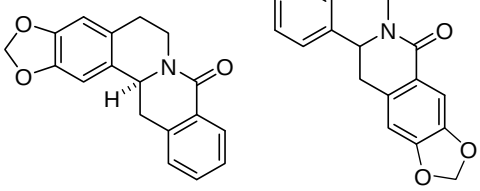
(**28**) in 90% yield. Regioselective reduction of the unconjugated carbonyl in imide **28** was envisaged to provide the corresponding hydroxylactam, which upon intramolecular cyclization would provide the desired racemic protoberberine (±)-**19**. Interestingly, when the sodium borohydride reduction of **28** was carried out using the conditions reported by Speckamp et al.[29] the expected hydroxylactam formed as an intermediate, directly furnished the *N*-homopiperonylisoquinolinone (**29**) in 72% yield via an in situ dehydration. The formation of **29** constitutes a formal synthesis of (±)-gusanlung D (**19**), since **29** is a known precursor that can be easily transformed to the gusanlung D as demonstrated by Padwa and Waterson.[23] This acid catalyzed cyclization condition was used to convert the enamide **29** to (±)-gusanlung D (**19**) in 68% yield.

However, the analytical and spectral data obtained for the compound **19** did not match with those reported for the isolated natural product but were in full agreement with those reported in the earlier syntheses.[22-25] Chrzanowska et al. had opined that the discrepancy could have arisen due to a possible contamination of the isolated natural product with a considerable amount of the formed corresponding oxidized product dehydrogusanlung D (**23**),[26] during the isolation process. Therefore, the synthesis of dehydrolactam **23** was planed via a route that had the potential to deliver (±)-gusanlung D (**19**) as well. Towards this end, selective iodination of the imide **28** using iodine-silver trifluoroacetate afforded the *N*-(*o*-iodohomopiperonyl)homophthalimide (**30**) in 86% yield. As expected, the $NaBH_4$ reduction of **30** using Speckamp et al. conditions as before, furnished the *N*-(*o*-iodohomopiperonyl)isoquinolinone (**31**) in 78% yield. The compound **31** could potentially serve as a precursor to both (±)-gusanlung D (**19**) through an intramolecular radical cyclization as well as dehydrogusanlung D (**23**) via an intramolecular Heck-coupling reaction.[30] Unfortunately, attempts at intramolecular radical cyclization of **31** using the standard conditions-azoisobutyronitrile/tributyltin hydride (AIBN/Bu_3SnH) failed to deliver the protoberberine (±)-**19**; instead dehalogenated product **29** was obtained in 63% yield. Nevertheless, $Pd(OAc)_2$-TMG induced[31] intramolecular Heck-coupling of iodoisoquinolinone **31** was successful and provided the desired dehydrogusanlung D (**23**) in 72% yield. The obtained analytical and spectral data for **23** were in complete agreement with the reported data.[26] However, a comparison of the analytical and spectral data of compound **23** with those of gusanlung D (**19**) and those reported for the isolated natural product ruled out the possibility that the isolated product could have been contaminated with a considerable amount of **23**.

2A.2 Rational for present work

As discussed above, before the isolation of gusanlung D in 1995, Kesser et al.[22] from India in 1992 reported its racemic synthesis; unfortunately the analytical and spectral data reported for the natural and synthetic gusanlung D were not in agreement with each other. All the four earlier approaches synthesized gusanlung D as proposed by Zhang et al.[21] Therefore it was necessary to correct the structure of this natural product.

In the reported structure **19**, ring A is electron rich due to presence of methylenedioxy group and hence two aromatic singlets must be upfield (Figure 5). This is observed in all four earlier syntheses including the synthesis from our group in which the two singlets are close to δ 6.67 and 6.72 ppm. ^{1}H NMR data reported during isolation by Zhang et al. contains one of the aromatic singlet at δ 7.35 ppm. This is an additional downfield shift. For such downfield shift, some electron withdrawing group/*peri*-interaction in the aromatic ring is required. This clicked the new structure in our mind. We felt that the isolated natural product could be the isomeric compound **35** in which due to *peri*-interaction with the carbonyl group one of the hydrogen would show downfield shift and other at its normal upfield position. Therefore we proposed the new structure **35**, and planned the synthesis by following the similar strategy developed earlier in our research group as described above in Scheme 2. The synthesis of the proposed structure **35** was the beginning of the actual work of this dissertation which has been described in the following part.



Reported Gusanlung D [(–)-**19**]

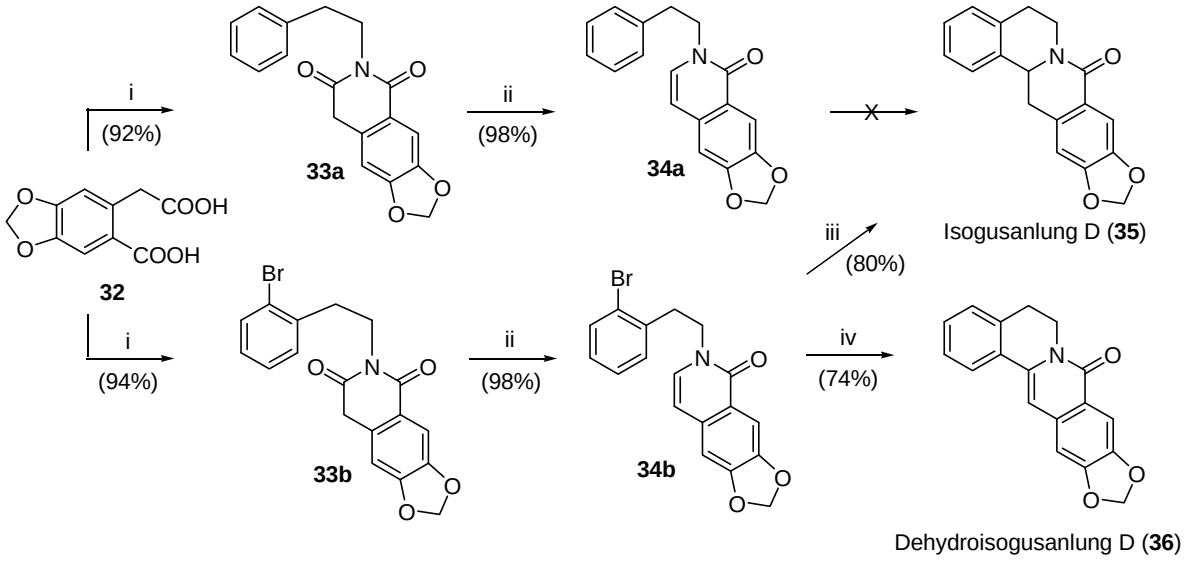
Our proposed structure (**35**)

Figure 5.

2A.3 Results and discussion

The synthesis of our proposed structure begins with the preparation of required 4,5-methylenedioxyhomophthalic acid (**32**) by using Mckillop's protocol.[32] The thermal double dehydrative condensation of homobenzylamine/*o*-bromohomobenzylamine with 4,5-methylenedioxyhomophthalic acid (**32**) respectively gave the corresponding imides **33a**/**33b** in high yields (Scheme 3). The regioselective reductive-dehydration of both the imides **33a**/**33b** respectively provided the required isoquinolinone derivatives **34a**/**34b** in 98% yields. All our attempts to induce acid catalyzed intramolecular cyclization of **34a** to (±)-isogusanlung D (**35**) met with failure, probably due to the absence of any activating group on phenyl ring, required to

force such type of cyclizations. However, treatment of the aryl bromide **34b** with azoisobutyronitrile-tributyltin hydride (AIBN-Bu_3SnH) induced intramolecular radical cyclization[33] to the desired (±)-isogusanlung D (**35**) in 80% yield and **34b** on Heck-coupling reaction[34] gave the corresponding dehydroisogusanlung D (**36**) in 74% yield.



Scheme 3. *Reagents, conditions and yields*: (i) Homobenzylamine/*o*-bromohomobenzylamine, *o*-dichlorobenzene, 180 ^oC, 3 h (92/94%); (ii) (a) $NaBH_4$, EtOH, 0 ^oC, 6 h, (b) H^+/HCl, rt, 12 h (98%); (iii) AIBN, Bu_3SnH, benzene, reflux, 2 h (80%); (iv) $Pd(OAc)_2$, $(n\text{-}Bu)_4NBr$, K_2CO_3, DMF, 120 ^oC, 24 h (74%).

Unfortunately the spectral data obtained for our proposed structure was also differing from the isolated natural product. Indeed, one of the aromatic singlet obtained for our proposed compounds was having the expected downfield shift (δ 7.59 ppm) and other one was at upfield region (δ 6.69 ppm) but still differ from the isolated one (7.35 & 6.80 ppm).

At this point, we feel that revision in the reported structural assignment of gusanlung D is must and it would be more appropriate to re-establish the actual structure of the natural product on the basis of X-ray crystallographic analysis.

^1H NMR data for isolated and synthetic gusanlung D is compiled in Table 1 along with the data obtained for our newly proposed structure.

Table 1. Comparison of the ^{1}H NMR spectral data for isolated and synthetic gusanlung D along with the our proposed structure

Proton No.[a]	^{1}H NMR Spectral Data (δ value in ppm)		
	Gusanlung D (Zhang et al.)[21]	**Gusanlung D (Argade & co-workers)**[27]	**Isogusanlung D (Present Dissertation)27**[27]
1	7.35 (s)	6.72 (s)	7.59 (s)
4	6.80 (s)	6.67 (s)	6.69 (s)
5	2.70 – 3.40 (m)	2.70 – 2.80 (m) 2.85 – 3.05 (m)	2.80 – 3.07 (m)
6	2.70 – 3.40 (m) 4.80 (m)	2.85 – 3.05 (m) 4.90 – 5.00 (m)	2.80 – 3.07 (m)
9	8.07 (d, 8.0)	8.13 (d, 8)	7.15 – 7.35 (m)
10	7.29 – 7.41 (m)	7.39 (t, 8)	"
11	7.29 – 7.41 (m)	7.46 (t, 8)	"
12	7.29 – 7.41 (m)	7.24 (d, 8)	"
13	2.70 – 3.40 (m)	2.85 – 3.05 (m) 3.18 (dd, 16, 4)	3.14 (dd) 4.84 – 5.00 (m)
13a	3.95 (m)	4.83 (dd, 13, 4)	4.84 – 5.00 (m)
-OCH_2O-	6.06, 6.20 (2s)	5.96 (s)	6.02 (d)

[a] Proton No. indicates the proton present at the corresponding carbon whose numbering pattern is same as shown in Figure 1.

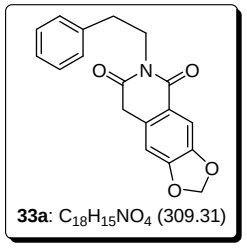
2A.4 Summary

We have attempted for the structure revision of the reported natural product gusanlung D by using a general approach developed earlier in our group starting from homophthalic anhydride to synthesize claimed gusanlung D. The synthesis of isogusanlung D and dehydroisogusanlung D have been completed by taking the advantage of intramolecular radical induced cyclizations and Heck-coupling reaction, respectively. Unfortunately, the analytical and spectral data obtained for our proposed berberine analogues did not concur with the reported data of the natural product. Revision in the reported structural assignment of gusanlung D is a must and it would be more appropriate to re-establish the actual structure of the natural product gusanlung D on the basis of X-ray crystallographic analysis.

2A.5 Experimental section

Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard on 200 and 400 MHz spectrometers. ^{13}C NMR spectra were recorded on 200, 400 and 500 NMR spectrometers (50, 100 & 125 MHz respectively). IR spectra were recorded on a FT-IR spectrometer. Elemental analyses were obtained by using Elementar Vario EL analyzer. Column chromatographic separations were done on silica gel (60-120, 230-300 mesh). Commercially available homophthalic anhydride, 2-bromophenylethylamine, hexamethyldisilazane (HMDS), zinc chloride, silver trifluoroacetate, tributyltin hydride and palladium (II) acetate were used.

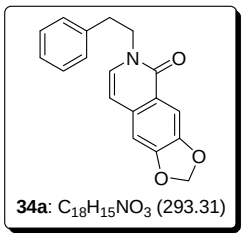
6-Phenethyl-[1,3]dioxolo[4,5-*g*]isoquinoline-5,7(6*H*,8*H*)-dione (33a). A stirring solution of homobenzylamine (108 mg, 0.89 mmol) and 4,5-methylenedioxyhomophthalic acid (**32**, 200 mg, 0.89 mmol) in *o*-dichlorobenzene (10 mL) was refluxed at 180 ^{o}C for 3 h. After cooling the reaction mixture to room temperature it was loaded on silica gel column and initially eluted with petroleum ether for the removal of *o*-dichlorobenzene. The column was further eluted with petroleum ether–ethyl acetate (4:1) as an eluent to furnish compound **33a** as yellow crystalline solid (253 mg, 92%). **Mp** 110–112 ^{o}C. **IR** ($CHCl_3$) ν_{max} 1711, 1665, 1622 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.84–2.96 (m, 2H), 3.91 (s, 2H), 4.12–4.23 (m, 2H), 6.07 (s, 2H), 6.65 (s, 1H), 7.16–7.34 (m, 5H), 7.59 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 34.0, 36.4, 41.4,



33a: $C_{18}H_{15}NO_4$ (309.31)

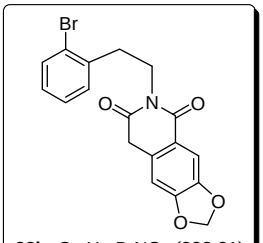
102.0, 106.3, 107.8, 119.4, 126.4, 128.4, 128.9, 130.3, 138.6, 147.7, 152.5, 164.0, 169.7. **Anal**. **Calcd** for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 70.02; H, 4.63; N, 4.40.

6-Phenethyl-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (34a). To a solution of the homophthalimide **33a** (150 mg, 0.49 mmol) in EtOH (10 mL) at 0 °C was added an excess of $NaBH_4$ (304 mg, 8.00 mmol) with stirring. The reaction mixture was stirred under inert atmosphere for 6 h at 0 °C with addition of 2-3 drops of 2 N HCl in EtOH at intervals of 20 min. The excess of $NaBH_4$ was then quenched at 0 °C by addition of 2 N HCl in EtOH until acidic (pH = 3). The reaction mixture was allowed to warm to room temperature and stirred for further 12 h. The EtOH was distilled off under reduced pressure and the residue was diluted with water (20 mL) and extracted with ethyl acetate (25 mL × 3). The combined organic layer was washed with water, 5% aqueous $NaHCO_3$ solution, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate (4:1) as an eluent gave **34a** (139 mg, 98%). **Mp** 107–109 ºC. **IR** ($CHCl_3$) ν_{max} 1657, 1620, 1606 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.07 (t, J = 8 Hz, 2H), 4.18 (t, J = 8 Hz, 2H), 6.07 (s, 2H), 6.25 (d, J = 8 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 6.82 (s, 1H), 7.14–7.34 (m, 5H), 7.80 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 35.3, 51.5, 101.6, 103.6, 105.5, 105.6, 121.7, 126.5, 128.6, 128.9, 130.7, 134.3, 138.3, 147.8, 151.7, 161.2. **Anal**. **Calcd** for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.68; H, 5.11; N, 4.97.



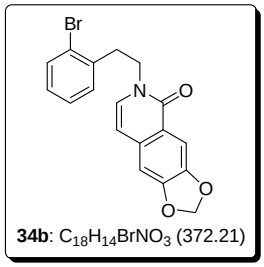
34a: $C_{18}H_{15}NO_3$ (293.31)

6-(2-Bromophenethyl)-[1,3]dioxolo[4,5-*g*]isoquinoline-5,7(6*H*,8*H*)-dione (33b). It was prepared from *o*-bromohomobenzylamine (446 mg, 2.23 mmol) and 3,4-methylenedioxy-homophthalic acid (**32**, 500 mg, 2.23 mmol) in 94% yield (814 mg) using the same procedure as described for compound **33a** above. **Mp** 134–136 ºC. **IR** ($CHCl_3$) ν_{max} 1709, 1665, 1657, 1649, 1618 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.00–3.15 (m, 2H), 3.90 (s, 2H), 4.15–4.30 (m, 2H), 6.06 (s, 2H), 6.65 (s, 1H), 7.00–7.32 (m, 3H), 7.53 (dd, J = 8 and 2 Hz, 1H), 7.58 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 34.1, 36.4, 39.6, 102.0, 106.3, 107.7, 119.3, 124.6, 127.4, 128.1, 130.2, 130.9, 132.7, 138.2, 147.6, 152.4, 163.9, 169.7. **Anal**. **Calcd** for $C_{18}H_{14}BrNO_4$: C, 55.69; H, 3.63; N, 3.61. Found: C, 55.55; H, 3.47; N, 3.80.



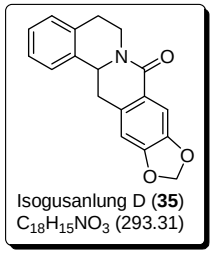
33b: $C_{18}H_{14}BrNO_4$ (388.21)

6-(2-Bromophenethyl)-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (34b). It was prepared from **33b** (600 mg, 1.54 mmol) in 98% yield (563 mg) using the same procedure as described for compound **34a** above. **Mp** 153–155 ºC. **IR** ($CHCl_3$) ν_{max} 1655, 1618, 1605 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.23 (t, J = 8 Hz, 2H), 4.22 (t, J = 8 Hz, 2H), 6.08 (s, 2H), 6.27 (d, J = 6 Hz, 1H), 6.76 (d, J = 6 Hz, 1H), 6.83 (s, 1H), 7.04–7.21 (m, 3H), 7.56 (d, J = 8 Hz, 1H), 7.81 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 35.3, 49.2, 101.5, 103.5, 105.3, 105.5, 121.5, 124.3, 127.6, 128.3, 130.5, 131.3, 132.7, 134.2, 137.4, 147.6, 151.5, 161.1. **Anal**. **Calcd** for $C_{18}H_{14}BrNO_3$: C, 58.08; H, 3.79; N, 3.76. Found: C, 57.94; H, 3.65; N, 3.69.



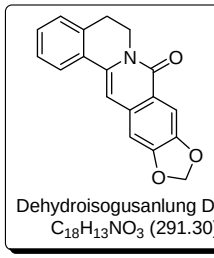
34b: $C_{18}H_{14}BrNO_3$ (372.21)

(±)-Isogusanlung D (35). To a refluxing solution of compound **34b** (200 mg, 0.53 mmol) in benzene (10 mL), was added a solution of tributyltin hydride (0.3 mL, 1.07 mmol) and AIBN (9 mg, 0.05 mmol) in benzene (5 mL) with constant stirring in a dropwise fashion over a period of 5 min. under nitrogen atmosphere. The reaction mixture was refluxed for an additional 2 h. Then the reaction mixture was cooled to room temperature and the solvent benzene was removed in vacuo. The obtained residue was then dissolved in acetonitrile (20 mL) and washed with *n*-hexane (25 mL x 3). Concentration of the acetonitrile layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate (7:3) as an eluent furnished pure compound **35** as a white crystalline solid (116 mg, 74%). **Mp** 157–159 ºC. **IR** ($CHCl_3$) ν_{max} 1639, 1611 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 2.80–3.07 (m, 4H), 3.14 (dd, J = 12 and 4 Hz, 1H), 4.84–5.00 (m, 2H), 6.02 (d, J = 4 Hz, 2H), 6.69 (s, 1H), 7.15–7.35 (m, 4H), 7.59 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 29.6, 37.7, 38.5, 55.1, 101.4, 106.7, 108.3, 123.1, 125.8, 126.6, 126.7, 128.9, 132.8, 134.9, 135.7, 146.9, 150.4, 164.1. **Anal**. **Calcd** for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.57; H, 5.05; N, 4.66.



Isogusanlung D (**35**)
$C_{18}H_{15}NO_3$ (293.31)

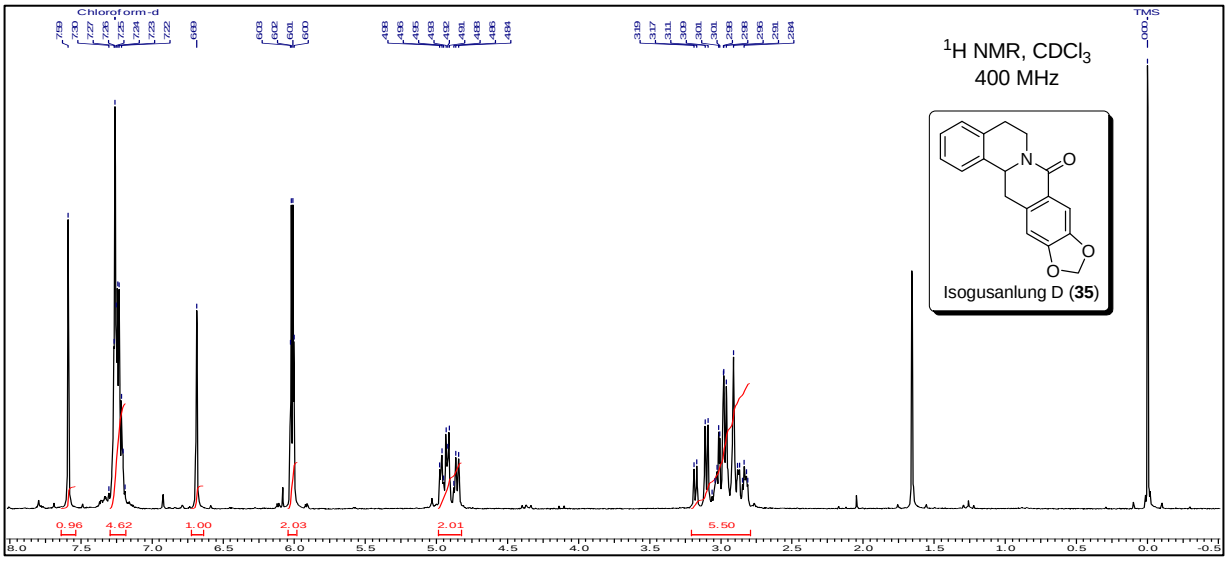
Dehydroisogusanlung D (36). To a stirred solution of compound **34b** (200 mg, 0.53 mmol) in DMF (10 mL) was added K_2CO_3 (438 mg, 3.18 mmol), tetrabutylammonium bromide (346 mg, 1.07 mmol), $Pd(OAc)_2$ (11 mg, 10 mol%) at room temperature under nitrogen atmosphere. Then the reaction mixture was heated at 120 ^{o}C for 24 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (20 mL),

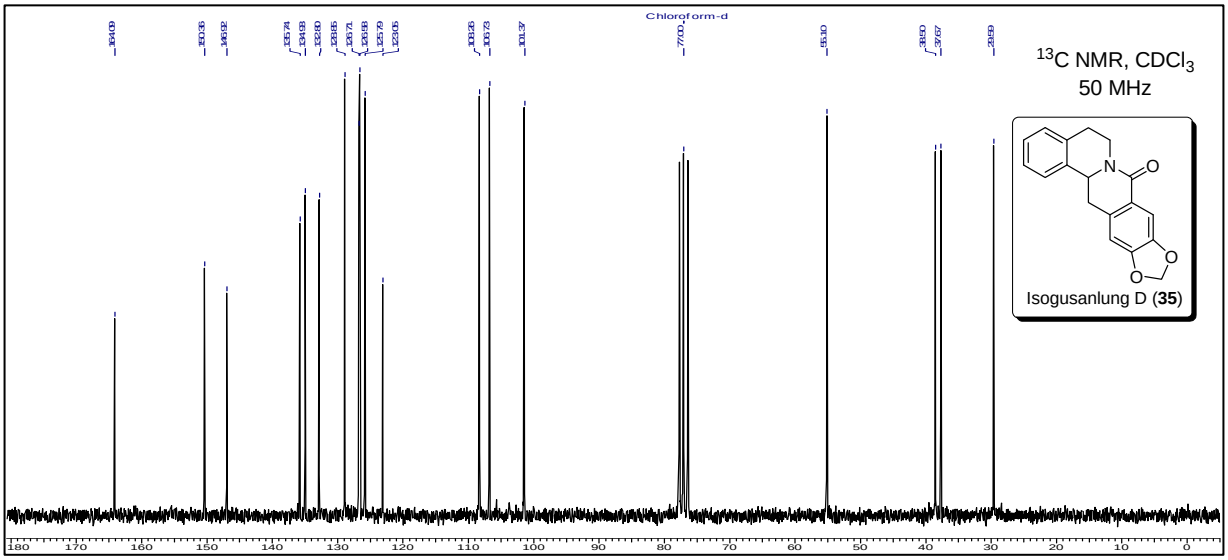


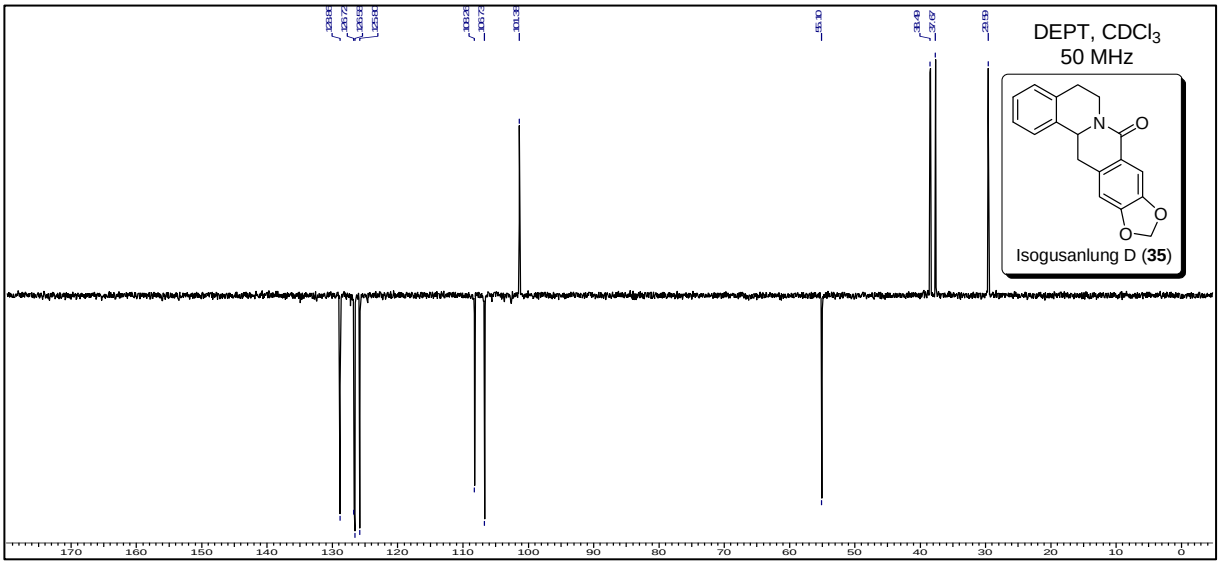
Dehydroisogusanlung D (**36**)
$C_{18}H_{13}NO_3$ (291.30)

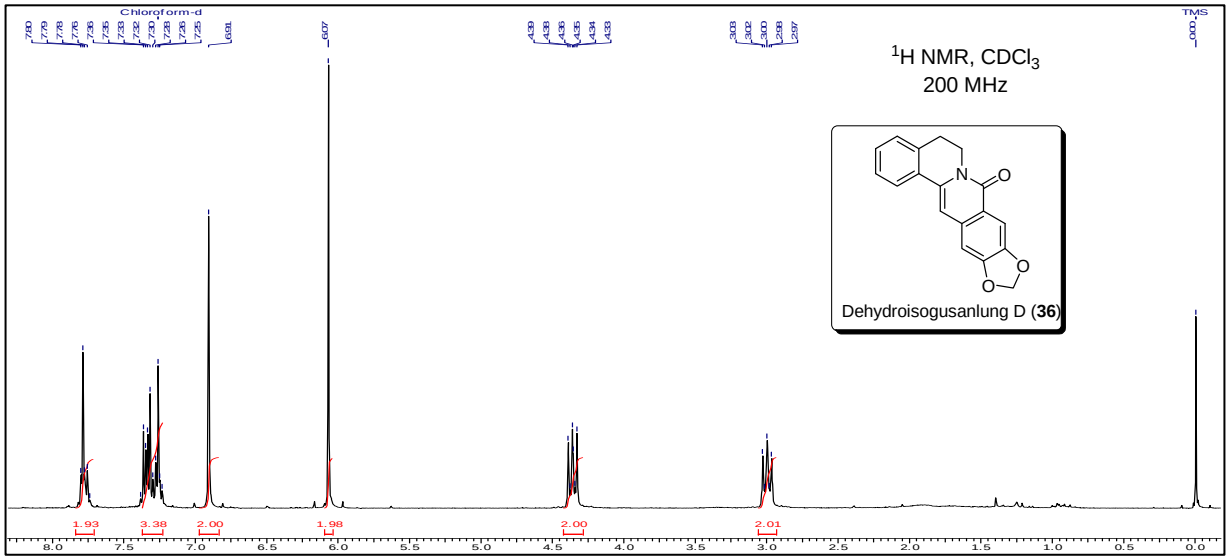
washed with brine and finally dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate (7:3) as an eluent furnished compound **36** as yellow crystalline solid (125 mg, 80%). **Mp** 174–175 ºC. **IR** ($CHCl_3$) ν_{max} 1649, 1605 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.95–3.05 (m, 2H), 4.30–4.40 (m, 2H), 6.07 (s, 2H), 6.91 (s, 2H), 7.20–7.40 (m, 3H), 7.70–7.80 (m, 1H), 7.79 (s, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 28.2, 39.3, 101.4, 102.5, 103.5, 105.3, 120.2, 124.4, 127.1, 127.7, 128.8, 129.8, 133.5, 134.8, 135.8, 147.4, 151.5, 160.9. **Anal**. **Calcd** for $C_{18}H_{13}NO_3$: C, 74.22; H, 4.50; N, 4.81. Found: C, 74.37; H, 4.42; N, 4.89.

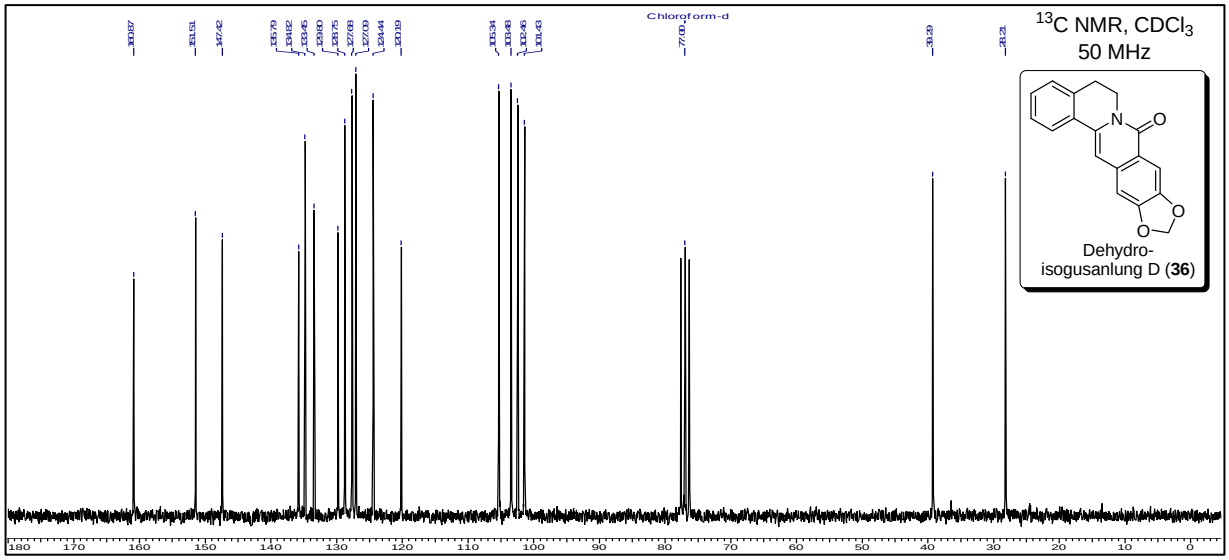
2A.6 Selected spectra

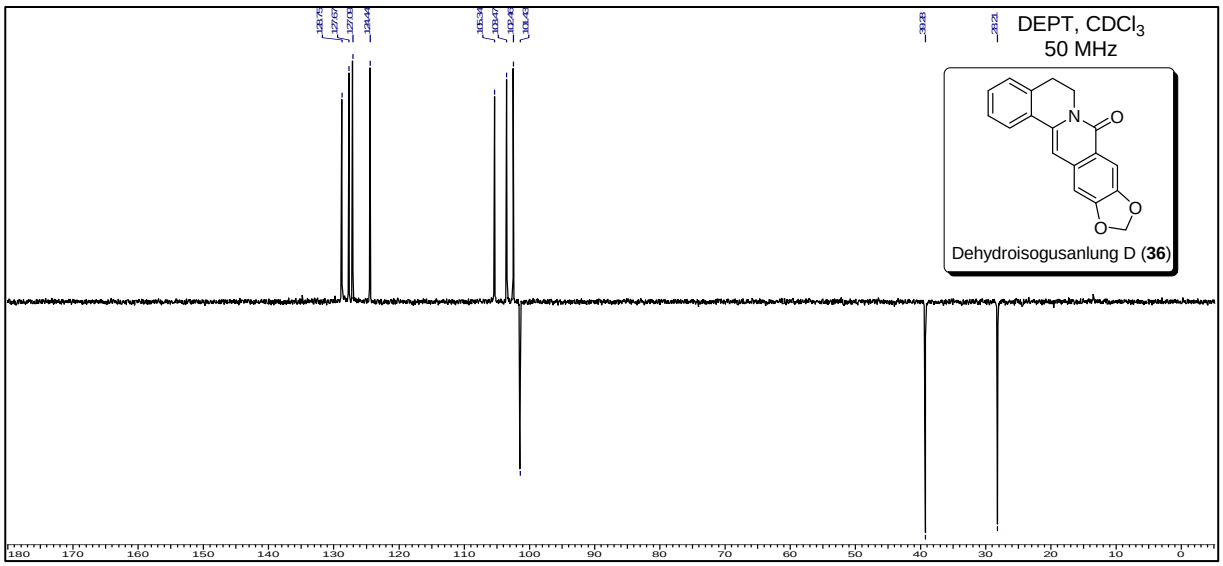

Chloroform-d
TMS
^{1}H NMR, CDCl$_3$
400 MHz
Isogusanlung D (**35**)
0.96
4.62
1.00
2.03
2.01
5.50


Chloroform-d
^{13}C NMR, CDCl$_3$
50 MHz
Isogusanlung D (**35**)


DEPT, CDCl$_3$
50 MHz
Isogusanlung D (**35**)


Chloroform-d
TMS
^{1}H NMR, CDCl$_3$
200 MHz
Dehydroisogusanlung D (**36**)
1.93
3.38
2.00
1.98
2.00
2.01


Chloroform-d
^{13}C NMR, CDCl$_3$
50 MHz
Dehydro-
isogusanlung D (**36**)


DEPT, CDCl$_3$
50 MHz
Dehydroisogusanlung D (**36**)

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(14) (a) Venkov, A. P.; Ivanov, I. I. *Tetrahedron* **1996**, *52*, 12299. (b) Larsen, R. D.; Reamer, R. A.; Corley, E. G.; Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem*. **1991**, *56*, 6034. (c) Pai, B. R.; Natarajan, S.; Manikumar, G.; Rajaraman, R.; Suguna, H. *J. Org. Chem*. **1978**, *43*, 1992.

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(30) (a) Comins, D. L.; Joseph, S. P.; Zhang, Y.-M. *Tetrahedron Lett*. **1996**, *37*, 793. (b) Kirschbaum, S.; Waldmann, H. *J*. *Org*. *Chem*. **1998**, *63*, 4936. (c) Crisp, G. T. *Chem*. *Soc*. *Rev*. **1998**, *27*, 427.

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Chapter 2: Section B

Studies Towards the Total Synthesis of Nuevamine, (+)-Isoindolo-*β*-carboline, Chilenine and Deoxychilenine

This Section B of Chapter 2 Features the Following Topics:

2B.1 Syntheses of Nuevamine

2B.1.1 Background

The naturally occurring (±)-nuevamine (**1a**)[1,2] from the *Berberis darwini* Hook species[1] is the first and sole representative of the isoindolo[1,2-*a*]isoquinoline family, biogenetically related to protoberberines (Figure 1).[2] Bioactivity of this promising natural product has not been reported till date. On the basis of synthesis, the structure of nuevamine (**1a**) has been re-established by Alonso et al.[2] with the alteration in the positions of two methoxy groups (Scheme 1). The reaction sequence involves the treatment of chilenine (**2**) an isoindolobenzazepine class of natural product, with methanolic sodium hydroxide to form phthalimidol **4**. Subsequent acidification of thus formed **4** furnished nuevamine (**1a**).

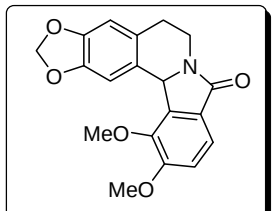
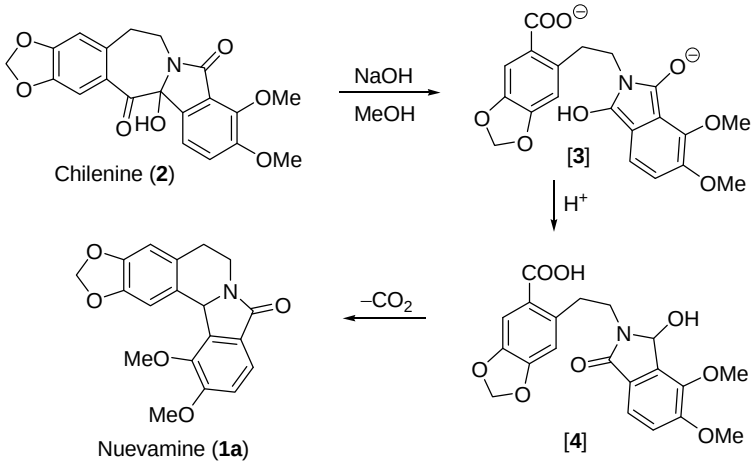


Figure 1. Nuevamine (**1a**)



Scheme 1. Structure revision of nuevamine

This part illustrates our efforts towards the total synthesis of nuevamine in two segments. The first segment presents an application of homophthalimide towards the synthesis of nuevamine. In the course of our studies towards the total synthesis of gusanlung D,[3] we observed the facile air-oxidation of the benzylic methylene groups of homophthalimides which encouraged us to report simple and efficient access to the nuevamine. Second segment details our concise approach towards nuevamine by using the regioselective reduction of suitably substituted phthalimide. Three synthetic approaches for nuevamine are known in the literature, which have been discussed in the subsequent part.

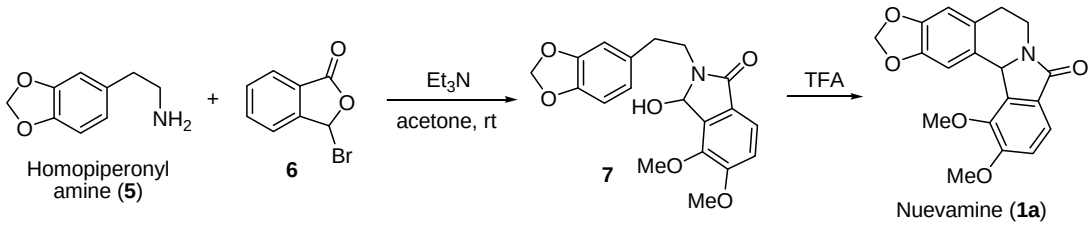
2B.1.2 Synthetic Approaches Towards Nuevamine

Several general approaches for the synthesis of isoindoloisoquinoline skeleton are known in the literature.[4] Very recently, Couture and co-workers have reported two elegant approaches to

nuevamine (**1a**) by using an aryne-mediated intramolecular cyclization and a Parham cyclization as the key reactions. These two syntheses are discussed here in brief along with the first synthetic approach by Alonso et al.

[A] ***Acid-mediated cyclization of phthalimidol***[2]

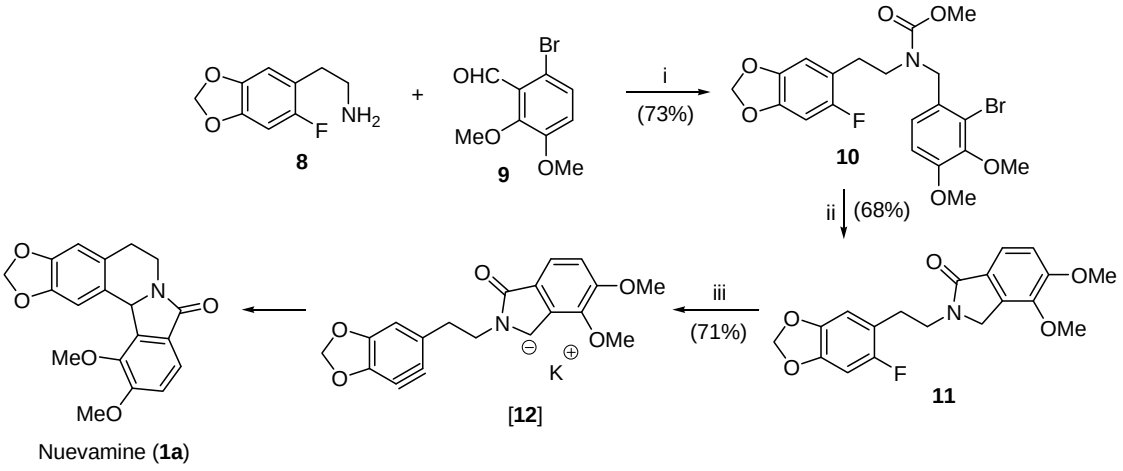
Alonso et al. reported the first synthesis of natural product nuevamine (**1a**) by condensation of homopiperonyl amine (**5**) with 3-bromophthalide (**6**). Thus, the formed phthalimidol **7** upon acid treatment furnished nuevamine (**1a**) (Scheme 2).



Scheme 2. First synthesis of nuevamine

[B] ***Aryne-mediated cyclization***[5]

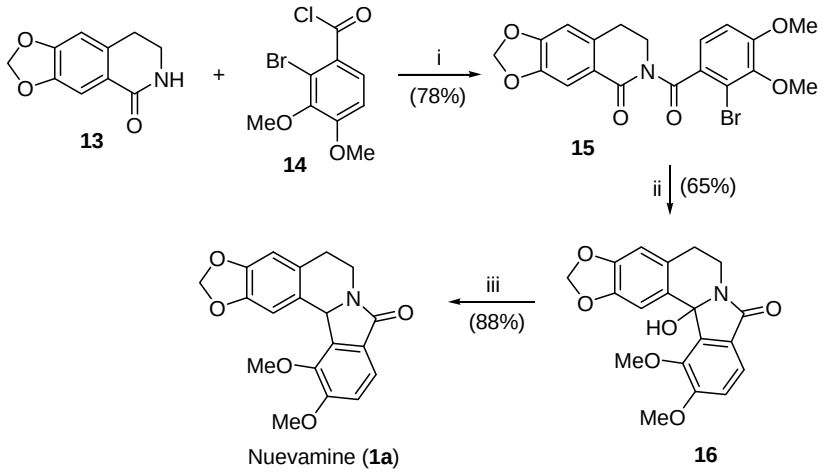
Couture and co-workers developed a novel approach, wherein, the key strategy was the choice of the halides. The metal-halogen exchange in **10** occurs preferentially with bromides over fluorides to form **11** in the first key step (Scheme 3). Whereas an aryl fluoride **11**, on treatment with KHMDS generates the aryne intermediate **12**; which undergoes an immediate intramolecular cyclization to deliver the required natural product in the second key step.



Scheme 3. *Reagents, conditions and yields*: (i) (a) $PhCH_3$, *p*-TSA, reflux, 3 h, (b) $NaBH_4$, MeOH, rt, 1 h, (c) ClCOOMe, CH_2Cl_2, Et_3N, 0 °C to rt, 3 h (73%); (ii) *t*-BuLi, THF, –100 °C to rt, 30 min (68%); (iii) KHMDS (2 equiv.), THF, –78 °C to rt, 2 h (71%).

[C] *Parham cyclization*[6]

Couture and co-workers developed another efficient methodology for the synthesis of the isoindolinone template based on Parham cyclization. Thus, application of the Parham protocol with diacylamine precursors **15** lead to regiospecific construction of the isoindolo[1,2-*a*]isoquinolinone framework **16** (Scheme 4). The formed 12*b*-hydroxy isoindolo[1,2-*a*]isoquinolinone **16** was reduced using triethylsilane to deliver the natural product nuevamine (**1a**).



Scheme 4. *Reagents, conditions and yields*: (i) THF, *n*-BuLi, –78 °C to rt, 2.5 h (78%); (ii) *t*-BuLi, THF, –100 °C to rt, 30 min (65%); (iii) Et_3SiH (2 equiv.), TFA (1 equiv.), CH_2Cl_2, rt, 2 h (88%).

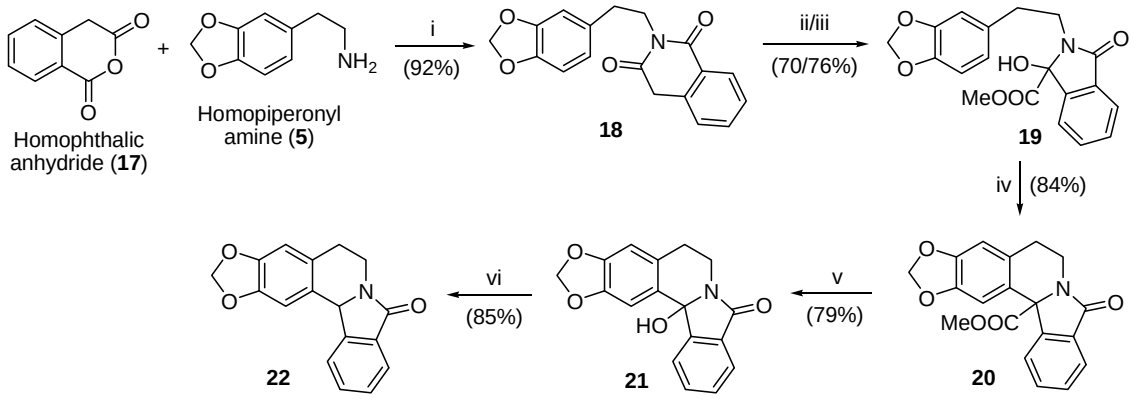
2B.1.3 Synthesis of Nuevamine via Facile Air-oxidation of Homophthalimide

2B.1.3.1 Rational for Present Work

Since our group is continuously utilizing cyclic anhydrides as the synthons in the natural product synthesis,[7] considerable efforts have been made here to utilize homophthalic anhydrides and their derivatives in the synthesis of natural and synthetic products. Recently we witnessed serendipitous facile benzylic air-oxidation of homophthalimide **18** to the lactamol **19** (Scheme 5). We have successfully utilized this serendipitous result to complete the total synthesis of nuevamine (**1a**). The corresponding homophthalimide **18**[8] was synthesized by the condensation of homophthalic anhydride (**17**) and homopiperonyl amine (**5**).[9]

We were carrying out the $NaBH_4$ reduction of homophthalimide **18** in methanol with the aim of regioselective reduction of the more reactive unconjugated imide carbonyl group for the further enzymatic resolution and synthesis of gusanlung D. In the above reaction condition, we observed the formation of a new product in 70% yield but to our surprise, the ^{1}H NMR spectrum of the product revealed the absence of both the benzylic protons from the starting material **18**.

Careful analysis of both the analytical and spectral data of the product indicated the formation of an isoindole **19** with a net oxidative ring contraction.



Scheme 5. *Reagents, conditions and yields*: (i) *o*-Dichlorobenzene, reflux, 3 h (92%); (ii) $NaBH_4$, MeOH, rt, 20 h (70%); (iii) MeOH, Et_3N, rt, 12 h (76%); (iv) 6 M H_2SO_4 + AcOH (1:2), rt, 2 h (84%); (v) NaCl, H_2O, DMSO, 175 ^oC, 30 min (79%); (vi) $NaBH_4$, TFA, rt, 5 h (85%).

We presumed that a catalytic amount of $NaBH_4$ got converted into sodium methoxide in situ. This base generates benzylic carbanion in homophthalimide **18** which reacts further with the dissolved oxygen. Thus, we proposed a facile air-oxidation of the benzylic carbon in the imide **18**, followed by very fast regioselective methanolysis (catalyzed by the methoxide) and an intramolecular ring closure pathway for the formation of α-hydroxy ester **19**. Our hypothesis was justified when we carried out the reaction of imide **18** in methanol using triethylamine as the base catalyst and obtained the same α-hydroxy ester **19** in 76% yield.

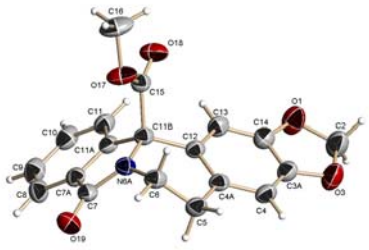
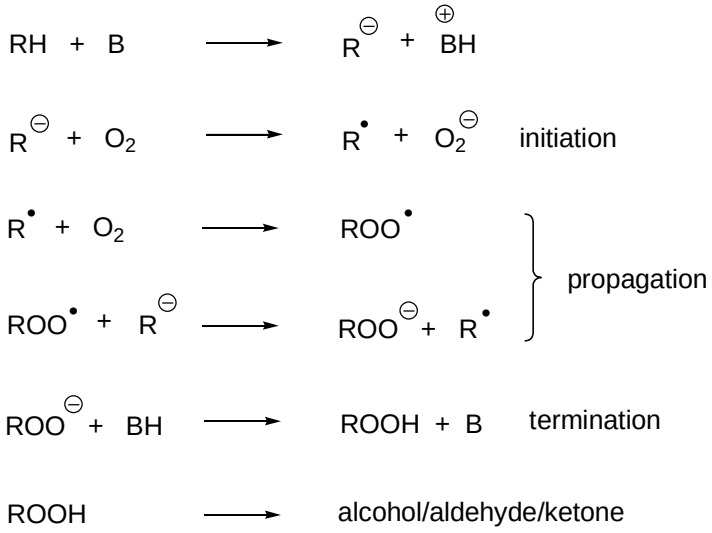


Figure 2. ORTEP Diagram of **20**

The lactamol **19** on treatment with catalytic amount of sulfuric acid in acetic acid at room temperature underwent an expeditious intramolecular dehydrative ring closure to yield the isoindoloisoquinoline **20** with an angular carbmethoxy function in 84% yield. Finally, the structure of compound **20** was confirmed by using X-ray crystallographic analysis (Figure 2). The compound **20** on decarboxylation furnished the isoindoloisoquinoline **21** in 79% yield, with an angular hydroxyl function, as a result of the reaction of the formed stable doubly benzylic intermediate carbanionic species with the dissolved oxygen. The compound **21** on $NaBH_4$-TFA reduction furnished the desired isoindoloisoquinoline **22** via the corresponding iminium intermediate in 85% yield.

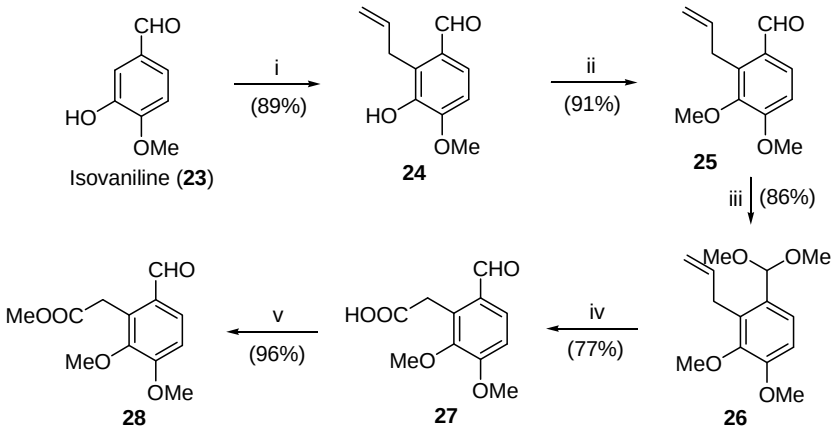
Our literature search revealed that such type of air-oxidation of methylated homophthalimide, under the basic conditions, to the corresponding tertiary alcohol intermediate is known.[10,11] Such autoxidation phenomenon has been studied in details and found general in nature. On the basis of reaction kinetics and other parameters, the plausible mechanism is proposed by Gersmann and co-workers[12] (Scheme 6). Oxygen itself is not reactive enough to abstract the acidic hydrogen. Therefore, such autoxidation proceeds faster in presence of base. In basic medium hydroperoxides formation proceeds via generation of carbanion, its oxidation (by O_2) to form alkyl radicals followed by its further reaction with oxygen. Thus the hydroperoxides formed often react further to give alcohols, ketones, and sometimes more complicated products.[13]



Scheme 6. General mechanism of air-oxidation reaction

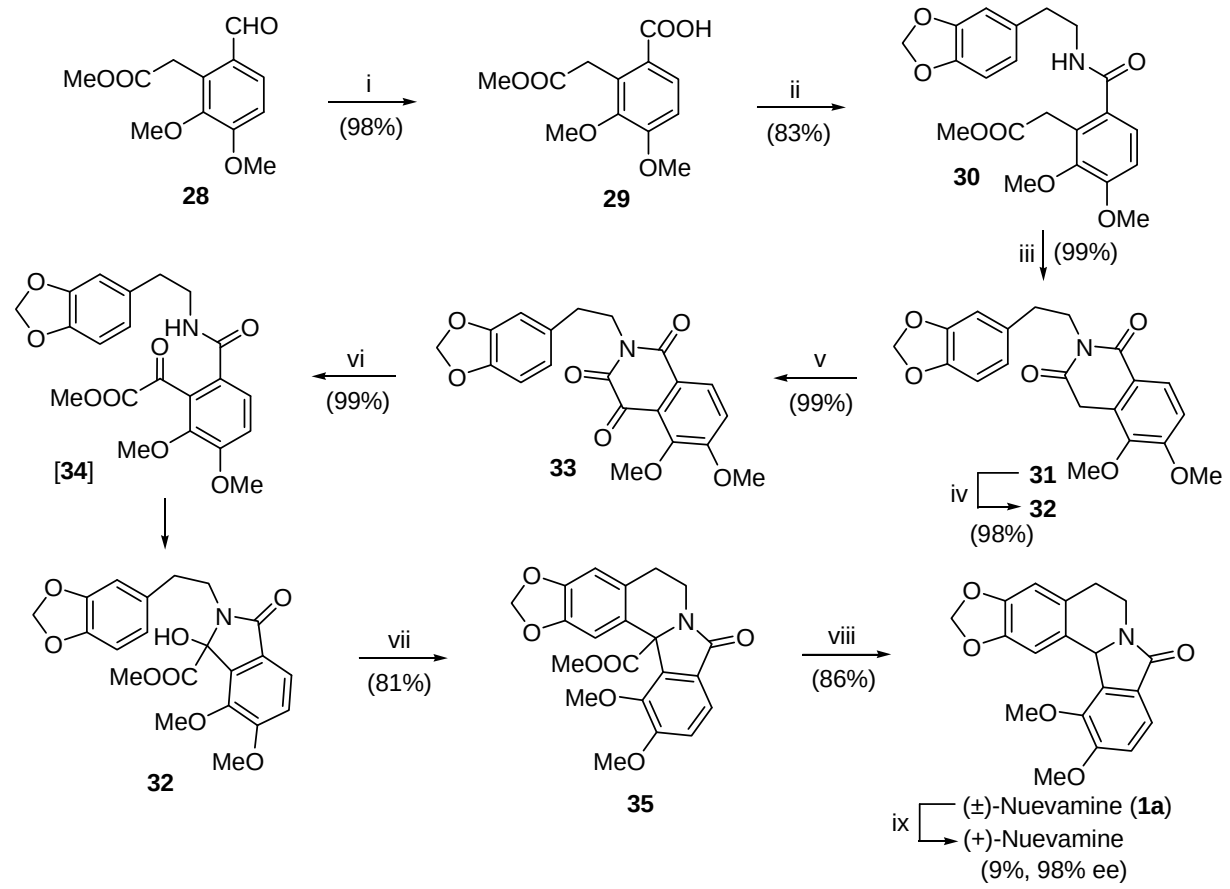
2B.1.3.2 Results and Discussion

All the results summarized in Scheme 5, prompted us to launch a program towards the synthesis of nuevamine (**1a**). We synthesized the required 5,6-dimethoxyhomophthalic acid from the isovanillin (**23**) and obtained the corresponding methyl 2-(6-formyl-2,3-dimethoxyphenyl)acetate (**28**) in six steps using the known procedure (Scheme 7).[14] The reaction sequence involves *o*-allylation of isovanillin (**23**) followed by its Claisen rearrangement in dimethylacetamide to form **24**. After methylation of the phenol in **24** and the protection of the formyl group by trimethyl orthoformate furnished **26**. Oxidative cleavage of allyl chain led to the acid **27**. The dimethylacetal gets hydrolyzed during the acidic work-up. Finally acid **27** was converted into its methyl ester to give **28**.



Scheme 7. *Reagents, conditions and yields*: (i) (a) Allyl bromide, K_2CO_3, acetone, reflux, 3 h, (b) Dimethylacetamide, reflux, 10 h (89%); (ii) MeI, K_2CO_3, DMF, rt, 10 h (91%); (iii) $HC(OMe)_3$, MeOH, NH_4Cl, reflux, 2 h (86%); (iv) $KMnO_4$, $NaIO_4$, K_2CO_3, *t*-BuOH-H_2O, rt, 4 h (77%); (v) $SOCl_2$, MeOH, 0 ^oC, 1.5 h (96%).

The aldehyde **28** on Jones oxidation gave the desired 5,6-dimethoxyhomophthalic acid mono-ester **29** in 98% yield (Scheme 8). The *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI) induced intermolecular dehydrative coupling reaction of acid **29** with homopiperonyl amine gave the homophthalamic acid methyl ester **30** in 83% yield. The solution of ester **30** in methanol, on treatment with catalytic amount of triethylamine at room temperature immediately furnished the white precipitate of homophthalimide **31** in quantitative yield. Herein, the homophthalimide **31** was insoluble in methanol and we did not observe formation of any further air-oxidized product. However, the solution of imide **31** in DMSO + MeOH mixture (4:1), on treatment with catalytic amount of triethylamine under the oxygen atmosphere at room temperature for 24 hours furnished the desired product **32** in 98% yield via the requisite facile air-oxidation pathway. At this stage, we decided to isolate and characterize the proposed intermediate trione **33**. In a control experiment, we stirred the solution of imide **31** in DMSO under the oxygen atmosphere for 48 hours at the room temperature, specifically under the neutral conditions and noticed the facile air-oxidation of methylene group in **31** to the corresponding carbonyl group to form the trione **33** [both by the change in color of the reaction mixture (colorless to yellow) and thin layer chromatography (tlc)]. We could actually isolate the reactive trione **33** in 99% yield and its structure was established on the basis of analytical and spectral data. The isolated pure trione **33** was fairly stable at room temperature for 48 hours plus time and then started undergoing the slow decomposition. The freshly isolated trione **33** on treatment with methanol-triethylamine at room temperature again furnished the expected product **32** in quantitative yield via the unisolable keto-ester **34** intermediate.



Scheme 8. *Reagents, conditions and yields*: (i) Jones reagent, acetone, rt, 5 h (98%); (ii) *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI), HOBt, DMF, homopiperonyl amine, rt, 3 h (83%); (iii) MeOH, Et_3N, rt, 20 min (99%); (iv) DMSO + MeOH (4:1), Et_3N, oxygen atmosphere, rt, 24 h (98%); (v) DMSO, oxygen atmosphere, rt, 48 h (99%); (vi) MeOH, Et_3N, rt, 3 h (99%); (vii) TFA, rt, 2 h (81%); (viii) NaCl, DMSO, H_2O, 185 ^oC, 30 min (86%); (ix) $CHCl_3$ + EtOAc (1:3), four recrystalisations, each 24 h (9%, 98% ee).

As expected, the lactamol **32** on acid catalyzed intramolecular dehydrative cyclization furnished the isoindoloisoquinoline **35** in 81% yield. Finally, the decarboxylation of the angular carbmethoxy function in **35** in the complete absence of oxygen, gave the desired natural product (±)-nuevamine (**1a**) in 86% yield. Starting from aldehyde **28**, the nuevamine was obtained in six steps with 55% overall yield. The obtained analytical and spectral data for **1a** were in complete agreement with the reported data and the structure of nuevamine was further confirmed on the basis of X-ray crystallographic analysis (Figure 3).

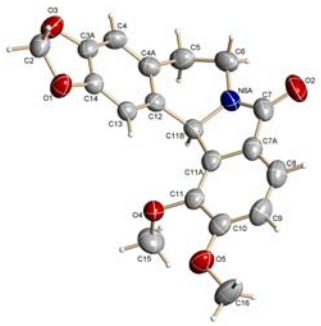


Figure 3. ORTEP Diagram of **1a**

The single crystal X-ray data indicated that the crystalline nuevamine racemate is a rare conglomerate. As expected, the four successive recrystalisations of

(±)-**1a** from chloroform plus ethyl acetate mixture (1:3) led to the spontaneous resolution to furnish the enantiomerically pure (+)-nuevamine in 9% recrystalisation yield with 98% ee (by chiral HPLC).

In summary, we have demonstrated a noteworthy total synthesis of nuevamine by taking the advantage of facile air-oxidation propensity of the active methylene group in homophthalimide to the corresponding carbonyl group. The observed present air-oxidation process is general in nature and would be useful to design the congeners of nuevamine and several other types of natural and unnatural carbocycles and heterocycles.

2B.1.4 Synthesis of Nuevamine via Regioselective Reduction of 3,4-Dimethoxyhomopiperonylphthalimide

2B.1.4.1 Rational for Present Work

The demand for ready access to natural products and natural product like molecular systems has been always on increasing trend. Atom economy and selectivity are the real keys for the synthetic efficiencies.[15] In continuation of our studies on cyclic anhydrides chemistry,[7] very recently we have reported the total synthesis of nuevamine with the complete control on regioselectivity, by taking the advantage of a facile air-oxidation of *N*-homopiperonyl-5,6-dimethoxyhomophthalimide.[16] We reasoned that the straight forward regioselective reduction of the corresponding simple starting material, the 3,4-dimethoxyhomopiperonylphthalimide would be feasible for the steric, electronic and thermodynamic reasons and which in turn can constitute simple one-pot approach to both nuevamine (**1a**) and isonuevamine (**1b**) (Figure 4). In this context, we herein report our studies towards the regioselective reductions of unsymmetrical imide and the synthesis of target compounds in the subsequent part of this section.

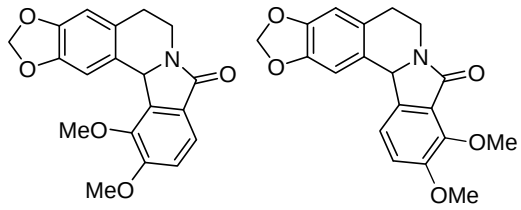


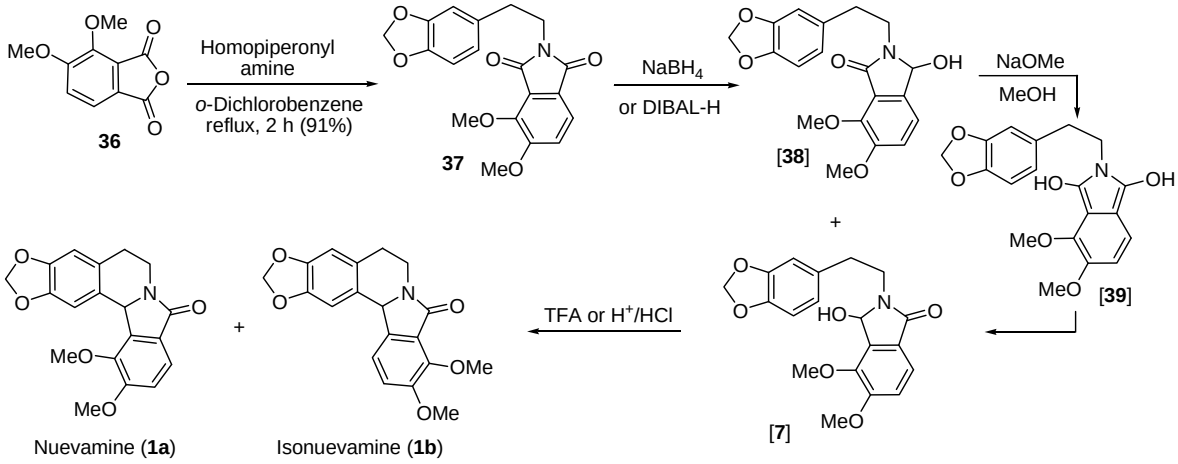
Figure 4. Nuevamine (**1a**) and Isonuevamine (**1b**)

2B.1.4.2 Results and Discussion

The synthesis starts with the condensation of homopiperonyl amine[9] with 3,4-dimethoxyphthalic anhydride **36**[17] in refluxing *o*-dichlorobenzene to furnish the desired imide **37** in 91% yield (Table 1). To address the issue of regioselective reduction of unsymmetrical imide **37**, sodium borohydride was chosen as the reducing agent.[18] On careful scrutiny of the structure of unsymmetrical imide **37**, it was realized that the regioselective reduction of **37** to the corresponding lactamol **7** would be possible for the following reasons, *viz*. (i) as per the Constantino protocol[19] the affinity/weak complex formation of $NaBH_4$ with an adjacent methoxy group will preferentially reduce the "C-1" carbonyl group, (ii) the electron withdrawing inductive effect of two adjacent methoxy group will make the "C-1" carbonyl more reactive, (iii) the extended para-conjugation of the four position methoxy group with the "C-2" carbonyl will make it relatively less reactive as per the principle of least motion[20] and (iv) the formed reduced product **7** would be thermodynamically more stable than the corresponding **38** for the possible six-membered intramolecular hydrogen bonding with the adjacent oxygen atom from the 3-position methoxy group. Hence we decided to systematically study the $NaBH_4$

reduction of imide **37** under the different reaction conditions and the results obtained are summarized in Table 1. The sodium borohydride reduction of imide **37** in diethyl ether at room temperature/reflux conditions gave the mixture of known[1,2] lactamols **38** plus **7** in 80% plus yield with 6:94 ratio (by ^{1}H NMR). It was noticed that the lactamols **38** and **7** were not stable to silica gel column chromatographic purification conditions and even at room temperature they showed some indications of decomposition. Hence it was decided to immediately transform them to the desired products without any purification.

Table 1. Regioselective reductions of 3,4-dimethoxyhomopiperonylphthalimide



Sr. No.	Reducing agent	Solvent	Temp. °C	Reaction time†	Cyclization Conditions	% Yield (1a:1b, by ^{1}H NMR#/HPLC¶)
1	$NaBH_4$ (5.00 equiv.)	Et_2O	rt	96 h	TFA, rt, 1 h	90 (95:5)
2	″	″	Reflux	48 h	″	92 (95:5)
3	**″**	**THF**	**rt**	**96 h**	**″**	**92 (100:0)/(99.9:0.01)**
4	″	″	Reflux	1 h	″	94 (94:6)
5	″	MeOH	rt	2 h	″	90 (80:20)
6	$NaBH_4$ (20.00 equiv.)	″	Reflux	5 min.	″	93 (93:7)
7	**″**	**″**	**″**	**30 min.**	**″**	**90 (99:1)/(99:1)**
8	DIBAL-H (1.10 equiv.)	DCM	0 °C	1 h	H^+/HCl, rt, 2 h	84 (14:86)
9	″	″	–78 °C	2 h	″	80 (8:92)/(9:91)

† On completion of the reaction (by TLC) the solvent was removed in vacuo and as such the obtained residue was further subjected for an acid catalyzed intramolecular dehydrative cyclization conditions. # The ratio of **1a**:**1b** was determined from the integral values of methine proton of isonuevamine and nuevamine. ¶HPLC details: Column- Grace Denali RP-18 (250 × 4.6 mm), mobile phase-MeOH:H_2O (70:30), wavelength- 254 nm, flow rate- 1.0 mL/min, retension times- 4.55 min (isonuevamine)/6.96 min (nuevamine).

Thus the obtained mixture of **38** and **7**, on acid catalyzed intramolecular dehydrative cyclization provided the mixture of **1a** and **1b** in the ratio 95:5 with 90% yield (Table 1, entries 1 and 2). The reduction of imide **37** in THF at room temperature for 96 hours followed by acid catalyzed cyclization exclusively furnished the desired product **1a** in 92% yield (Table 1, entry 3). As per our above mentioned postulations the $NaBH_4$ reduction reaction of **37** turned out to be

completely regioselective for the steric and electronic reasons. The same reaction under reflux for 1 hour time was equally efficient but it was not completely regioselective and after the acid catalyzed cyclization, the mixture of **1a** and **1b** in 94:6 ratio (Table 1, entry 4) were obtained. The reaction of imide **37** in methanol at room temperature was very fast but the selectivity in the final products turned out to be very low (**1a**:**1b** = 80:20) (Table 1, entry 5). In the above reaction, an increase in the reaction temperature to reflux conditions is expected to further decline the reduction region-selectivity. Fortunately our hypothesis about the higher thermodynamic stability of **7** over **38** turned out to be correct, when we performed the $NaBH_4$ reduction of **37** in refluxing methanol for 30 min time followed by the acid catalyzed cyclization, the product **1a** was obtained in 90% yield (**1a**:**1b** = 99:1) (Table 1, entry 7). The complete gain in regionselectivity at the higher temperature clearly revealed that, in the presence of requisite amount of sodium methoxide formed *in situ* from the reaction of $NaBH_4$ and methanol, under the reflux conditions completely transforms the thermodynamically less stable **38** to more stable **7** *via* the plausible unisolable intermediate **39** with the formation and delocalization of benzylic carbanion on **38**. Alternatively, the possibility of formation of an oxy-anion on **38** followed by its delocalization with an intramolecular hydride shift to form the more stable product **7** also appears sound. Herein the observed base catalyzed transformation of **38** to **7** under the reflux condition is noteworthy and for thermodynamic reasons it results in ~100% regioselectivity with high yields in a short time duration. As expected,[21] the DIBAL-H reduction of imide **37** at –78 °C was chiefly controlled by steric factors and the mixture of products **38** and **7** was obtained. The above mixture of **38** and **7** on treatment with conc. HCl at room temperature furnished the column separable mixture of **1a** and **1b** in the ratio 9:91 with 80% yield (Table 1, entry 9). In the above mentioned DIBAL-H reduction of imide **37**, all attempts to further refine the regioselectivity by lowering the temperature up to –100 °C failed. The analytical and spectral data obtained for nuevamine and isonuevamine were in complete agreement with the reported data.[1,2,16]

In summary, starting from 3,4-dimethoxyhomopiperonylphthalimide, an efficient one-pot two-step synthesis of nuevamine and isonuevamine by respectively taking the advantage of highly regioselective electronically and thermodynamically favoured sodium borohydride reductions and sterically favoured DIBAL-H reduction reactions have been demonstrated. The observed base catalyzed reversal in regioselectivity *via* the conversion of kinetically favoured product to the thermodynamically favoured product is noteworthy.

2B.2 Stereoselective Synthesis of (+)-Isoindolo-*β*-carboline

2B.2.1 Background

The *β*-carboline nucleus (**40**) is present in very important bioactive natural products, such as rutaecarpine (**41**), ajmalicine (**42**) and yohimbine (**43**) (Figure 5).[22] This group of indole alkaloids is of widespread distribution being found in 23 angiosperm plant families, 3 fungi genera, and in a variety of animal tissues.[23] Both natural and unnatural *β*-carboline compounds, as well as their analogues and congeners, are of high synthetic interest as important hypotensive agents.[22,24]

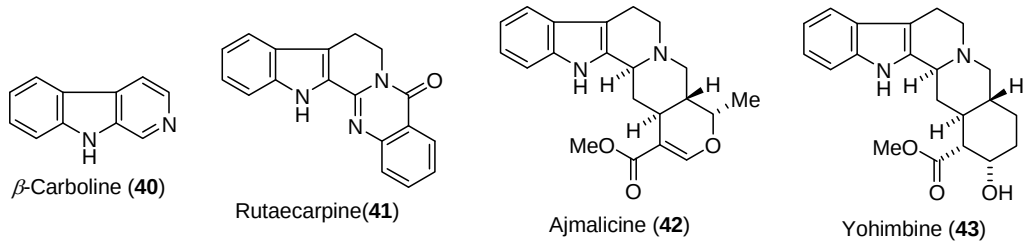
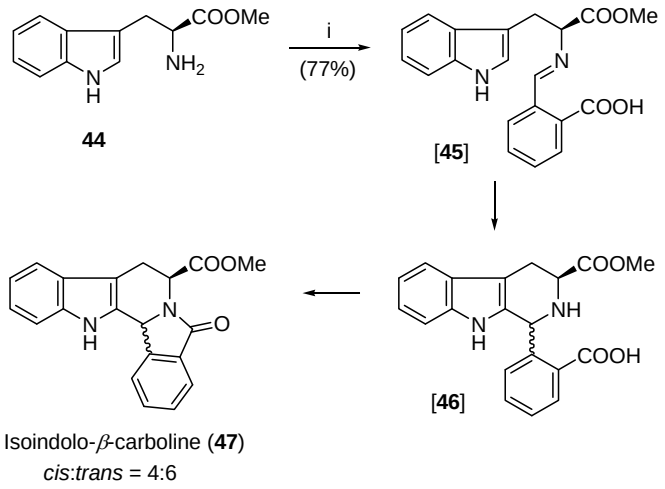


Figure 5. Bioactive natural products containing *β*-carboline frame-work

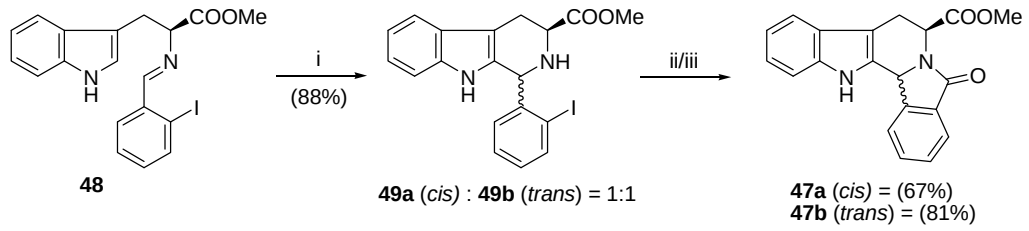
2B.2.2 Synthetic Approaches Towards (+)-Isoindolo-*β*-carboline

Isoindolo-*β*-carboline (**47**) system is an important target, for which several racemic syntheses, starting from 3-hydroxyphthalide or phthalimide derivatives are known.[25] Bailey and co-workers[26] reported stereoselective approach affording a 20% diastereomeric excess (Scheme 9). The reaction of (*S*)-tryptophan methyl ester (**44**) and 2-carboxybenzaldehyde in toluene under reflux furnished isoindolo-*β*-carboline (**47**) via the formation of imine **45** followed by its Pictate–Spengler cyclization to **46** and lactamization of thus formed **46** in one pot.



Scheme 9. *Reagents, conditions and yields*: (i) 2-Carboxybenzaldehyde, toluene, reflux (77%).

Another stereoselective approach to isoindolo-*β*-carboline (**47**) has been reported by Grigg and co-workers,[27] which takes advantage of a palladium-catalyzed carbonylation process, but with an observed partial racemization (Scheme 10). The equimolar ratio of *cis* and *trans* diastereomers (**49a** and **49b**) obtained were separated by flash column chromatography and subjected for carbonylation reaction to furnish isoindolo-*β*-carboline (**47a**/**b**).



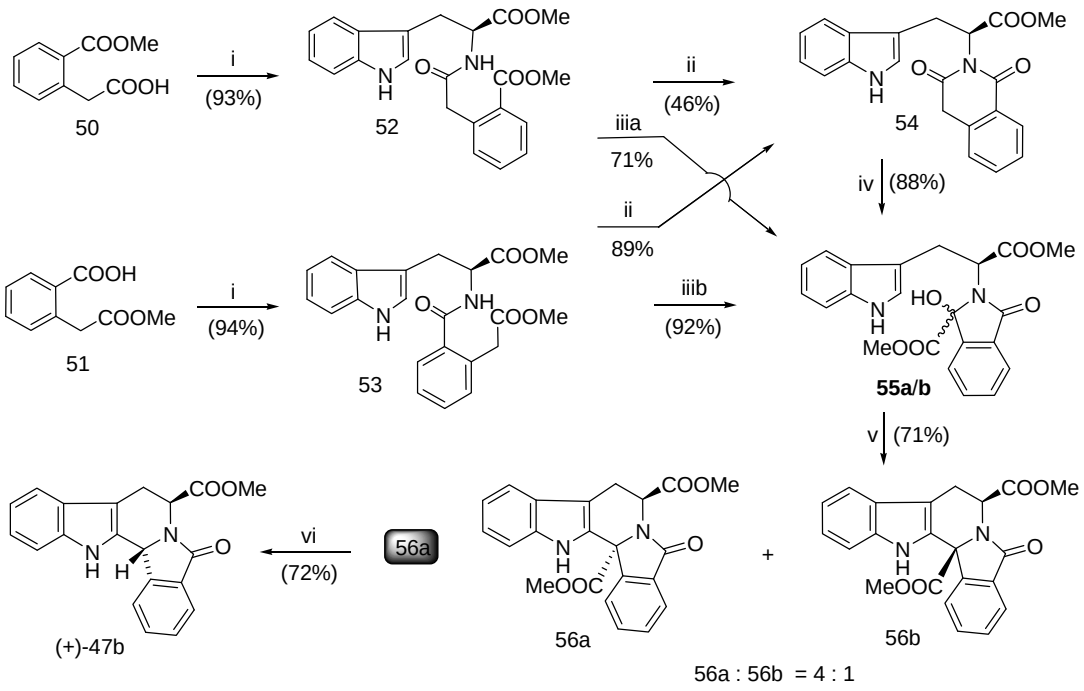
Scheme 10. *Reagents, conditions and yields*: (i) *p*-TSA, toluene, reflux, 8 h (88%); (ii) **49a**, $Pd(OAc)_2$, PPh_3, Et_3N, CO (1 atm), toluene, 110 ^oC, 16 h (67%); (iii) **49b**, $Pd(OAc)_2$, PPh_3, Et_3N, CO (1 atm), toluene, 110 ^oC, 16 h (81%).

2B.2.3 Rational for Present Work

The above-mentioned studies revealed that starting from the (*S*)-tryptophan and pre-reduced 3-hydroxyphthalide, the stereoselectivity obtained during the course of intramolecular cyclization was weak. During our extensive studies on cyclic anhydrides and their use in the construction of structurally interesting and biologically important natural/unnatural products,[7] we have recently witnessed a facile air-oxidation of the active methylene group in homophthalimide to the corresponding carbonyl group; this strategy was successfully used for the synthesis of the natural product nuevamine.[16] Hence, we envisaged homophthalic anhydride and (*S*)-tryptophan as suitable building blocks for the synthesis of enantiomerically and diastereomerically pure isoindolo-*β*-carbolines. Herein, we report another application of such propensity of homophthalimides to undergo air-oxidation to complete the stereoselective synthesis of isoindolo-*β*-carboline with high enantiomeric excess.

2B.2.4 Results and Discussion

We started the synthesis of (+)-**47b** from the isomeric acids **50**/**51** and (*S*)-tryptophan via the requisite precursor, imide **54**. Homophthalic anhydride upon treatment with methanol in the presence of boron trifluoride diethyl etherate ($BF_3{\cdot}Et_2O$) underwent a highly regioselective methanolysis at the more reactive unconjugated carbonyl group and furnished the mono-ester **51**[28] in quantitative yield (Scheme 11). On the other hand, the reaction of homophthalic acid with one equivalent of diazomethane in diethyl ether furnished the opposite mono-ester **50**[29] in 95% yield via the reaction of the more acidic aromatic carboxylic group.



Scheme 11. *Reagents, conditions and yields*: (i) **50**/**51**, *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI), (*S*)-tryptophan methyl ester hydrochloride, DMAP, DCM, Et_3N, rt, 6 h (93/94%); (ii) **52**/**53**, Et_3N, MeOH, rt, 24/4 h (46/89%); (iii) (a) Et_3N, MeOH, rt, 48 h, (71%), (b) Et_3N, MeOH, oxygen atmosphere, rt, 18 h, (92%); (iv) Et_3N, MeOH, rt, 12 h, (88%); (v) AcOH, cat. H^+/H_2SO_4, rt, 6 h (**56a**: 57%, ~100% ee, **56b**: 14%); (vi) **56a**, NaCl, DMSO, H_2O, AcOH, 210 ^oC, 2 h (72%, 98% ee).

The *N*-ethyl-*N*'-(3-dimethylaminopropyl) carbodimide hydrochloride (EDCI) induced dehydrative coupling reactions of isomeric acids **50** and **51** with (*S*)-tryptophan furnished the corresponding homophthalamic esters **52** and **53**, respectively, in high yields. Both **52** and **53** upon treatment with triethylamine furnished the corresponding imide **54**. As anticipated, the intramolecular cyclization of **53**, involving the non-conjugated ester unit, to form **54** was faster and more efficient (89% yield) than the cyclization of **52** to **54** involving an aromatic ester unit (46% yield). Treatment of any of the three precursors **52**/**53**/**54** with triethylamine in methanol furnished directly a mixture of diastereomeric lactamols **55a**/**b**, not separable by silica-gel column chromatography, in a 2:3 ratio (by ^1H NMR) with 71%/92%/88% yields, respectively. In the case of **52**/**53**, the entire transformation occurs in one-pot. The sequence consists of an initial conversion of **52**/**53** to the imide **54**, followed by a facile in situ chemoselective air-oxidation of the methylene group in homophthalimide **54** to the corresponding reactive trione intermediate. This subsequently undergoes regioselective methanolysis at the unconjugated imide carbonyl group and then an intramolecular ring closure to yield the oxidative ring-contracted product. We could also enhance the rates of these air-oxidation reactions by carrying them out under an

oxygen atmosphere. The ^{1}H NMR spectrum of the mixture of **55a**/**b** (2:3) revealed that in **55b**, the signal for the methyl ester of the tryptophan subunit was shielded due to the intramolecular influence of the free β-hydroxyl group, present on the same face, on an ester moiety. Initially, we were unhappy with the 20% diastereomeric excess obtained in the formation of **55a**/**b**; however, in the next transformation of **55a**/**b** to **56a**/**b**, it was possible to gain some diastereoselectivity. The above mixture of **55a**/**b** on treatment with trifluoroacetic acid at room temperature furnished **56a** exclusively, but with only 21% yield. When a catalytic amount of sulfuric acid in acetic acid was used to carry out the same reaction, a separable mixture of intramolecular dehydrative cyclization products **56a**/**b** was obtained in a 4:1 ratio (by ^{1}H NMR) with an improved yield of 71%. We presume that the present acid-catalyzed cyclization takes place via an SN^1 mechanism, and in the conversion of **55a**/**b** (20% de) to **56a**/**b** (60% de), the cyclization of a transient *N*-acyliminium ion[30] takes place with the predominant formation of the trans-isomer **56a**. In the event of an SN^2 mechanism being in operation, we feel that a dynamic kinetic resolution of the substrate **55a** could be occurring via the partial racemization of **55b** through the ring-chain tautomerism. Unfortunately, all our attempts to further improve the diastereomeric excess met with failure, as the rate of cyclization was plausibly faster than the rate of formation of *N*-acyliminium ion/racemization of **55b**. We separated the diastereomeric mixture of **56a** and **56b** by silica-gel column chromatography and further confirmed the structure as well as the enantiomeric purity of the major isomer **56a** from X-ray crystallographic data and chiral HPLC (100% ee), respectively (Figure 6). In the ^{1}H NMR spectrum of **56a**, we noticed a considerable geometry-dependent shielding of the α-methine proton. In **56a**/**b**, the angular carbomethoxy group is attached to the carbon, which is both allylic and benzylic with an adjacent tertiary amide nitrogen atom. Hence, we systematically studied the demethoxycarbonylation of both **56a** and **56b** under the Krapcho and Lovey conditions, suitable for germinal diesters, β-ketoesters, and α-cyano esters.[31] The reaction of the major isomer **56a** with sodium chloride in moist dimethyl sulfoxide at 210 ^{o}C furnished 100% diastereomerically pure **47b** in 72% yield. Plausibly, this proceeds via the regioselective demethoxycarbonylation of the angular α-ester moiety, followed by inversion of the formed α-carbanion to the β-carbanion and subsequent abstraction of a proton from the same β-face. At this stage, we felt that the possible escaping of methyl chloroformate/hydrochloric acid formed during the course of the

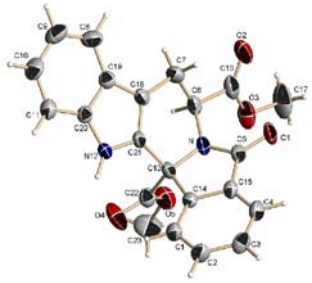


Figure 6. ORTEP diagram of **56a**

reaction at 210 ^{o}C can result in in situ formation of sodium hydroxide, causing the excessive racemization of the asymmetric center present in the tryptophan subunit. The synthesis of (±)-**47** and the comparison of chiral HPLC data of the racemic mixture with (+)-**47a** revealed that our concern about the racemization of (+)-**47a** was indeed correct and it was obtained with only 66% ee. We reasoned that, it would be possible to stop such a racemization of (+)-**47a** by carrying out the demethoxycarbonylation in the presence of acetic acid, which would then generate only the weak base sodium acetate in situ. Thus, we repeated the demethoxycarbonylation of (–)-**56a** in the presence of acetic acid and obtained (+)-**47a** with a similar yield of 72%, but this time with 98% ee (by chiral HPLC). Thus, starting from homophthalic anhydride, enantiomerically pure (+)-isoindolo-*β*-carboline (**47a**) was obtained in five steps with 35% overall yield. The analytical and spectroscopic data obtained for (+)-**47a** were in complete agreement with the reported data.[27] The structure of (+)-**47a** was also confirmed from the X-ray crystallographic data (Figure 7). Pure **56b** or **56b** in the mixture of **56a**/**b** (4:1) on treatment with sodium chloride in moist dimethyl sulfoxide at 210 ^{o}C remained completely unreacted, and we were unable to force the demethoxycarbonylation of the angular ester moiety in **56b**. On the basis of a manually prepared flexible molecular model, we feel that in the case of compound **52b**, the negatively charged chloride ion is unable to access the carbonyl group of the angular ester moiety because of the internal steric crowding and also repulsive *p*-cloud interactions reasons. Further, demethoxycarbonylation of the second carbomethoxy group on compounds of the type (+)-**47a**, without any racemization at the asymmetric angular position, is already known in the literature.[32]

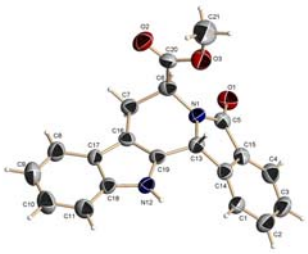


Figure 7. ORTEP diagram of (+)-**47a**

In summary, we have demonstrated the first stereoselective approach to enantiomerically pure (+)-isoindolo-*β*-carboline by taking advantage of a facile chemoselective air-oxidation of homophthalimide and gain in the diastereoselectivity during the intramolecular dehydrative cyclization process. We feel that the highly stereoselective geometry-dependent demethoxycarbonylation in the present approach is also noteworthy.

2B.3 Synthetic Studies Towards Chilenine, Deoxychilenine and Lennoxamine

2B.3.1 Background

(±)-Chilenine (**57**), (±)-deoxychilenine (**58**) and (±)-lennoxamine (**59**) were respectively isolated from *Berbelis empetrifolia*, *Berbelis actinacantha* and *Berbelis darwinii*[1,33] and they belong to isoindolobenzazepine class of alkaloids (Figure 8).[34]

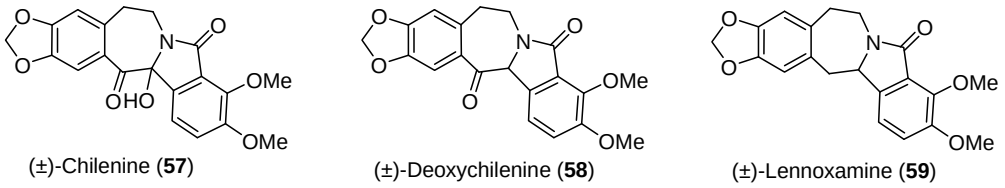
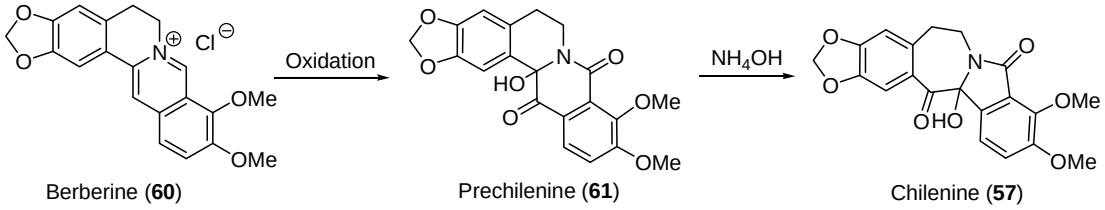


Figure 8. Chilean berberis products

These natural products are biogenetically related to protoberberines; hence their ring systems are accessible by oxidation of berberine alkaloids (Scheme 12).[35,4c]



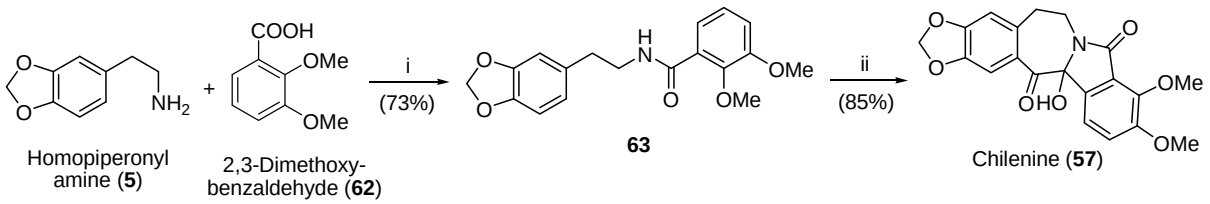
Scheme 12. Biogenetic pathway for chilenine

Although there are no reports about any important pharmacological effects shown by these three natural products, various heterocyclic compounds containing the isoindolinone skeleton have important biological activities. Many of these have been prepared and examined as antihypertensive,[36] antipsychotic,[37] antiinflammatory,[38] anesthetic,[39] antiulcer[40] and vasodilatory agents.[41] Unique structure of these three natural products made them popular in the community of synthetic organic chemists. Due to various biological properties known for benzazepine class of heterocycles, they were important target for the medicinal chemists too.

2B.3.2 Synthetic Approaches Towards Chilenine, Deoxychilenine and Lennoxamine

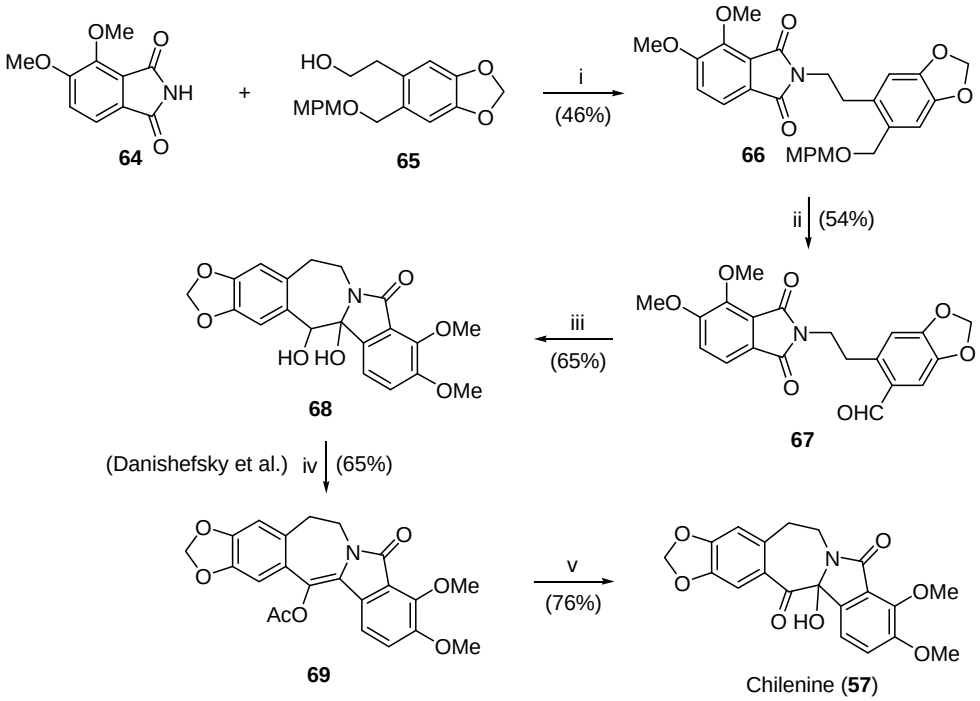
On the basis of important biological properties conferred on berberine class of compounds and the intriguing structural features of these three natural products, several syntheses of chilenine (**57**)[42] and lennoxamine (**59**)[43] have been accomplished with elegance. Few representative syntheses of each of these natural products are discussed here in brief.

Kim and co-workers[42a] reported a short two step procedure for the synthesis of chilenine (**57**). Thus, treatment of amide **63** with oxalyl chloride and $AlCl_3$ in DCM furnished chilenine (**57**) in high yield (Scheme 13).



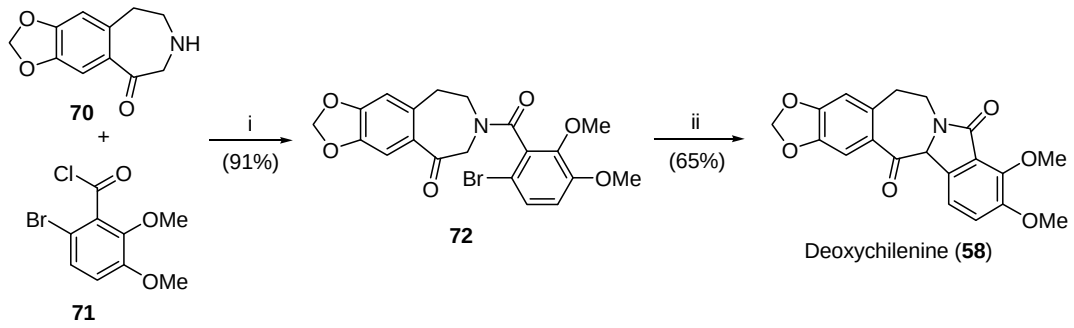
Scheme 13. *Reagents, conditions and yields*: (i) *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI) (73%); (ii) $AlCl_3$, DCM, rt, 4 h (85%).

Yoda et al.[42e] synthesized diol intermediate **68** to accomplish the formal synthesis of chilenine, as this diol **68** has been successfully converted by Danishefsky et al.[42(l)] to chilenine in two steps (Scheme 14). Coupling of phthalimide **64** and alcohol **65** using Mitsunobu condition formed a coupling product **66** in moderate yield. Deprotection of MPM-group in **66** by DDQ took place to form the desired aldehyde **67** in the same pot. Finally, SmI_2 mediated intramolecular pinacol coupling in **67** furnished diol **68** in 65% yield. This diol **68** has been converted to chilenine (**57**) by Danishefsky et al. in high yield. The reaction sequence involves formation of enol acetate **69** and its osmylation to yield chilenine (**57**).



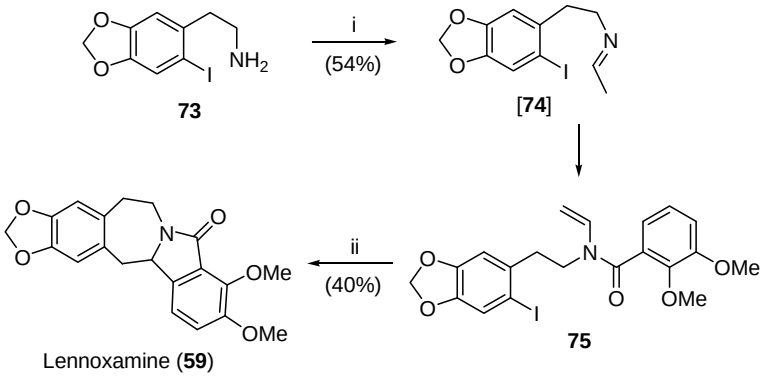
Scheme 14. *Reagents, conditions and yields*: (i) DEAD, PPh_3, THF (46%); (ii) DDQ, CH_2Cl_2-H_2O (10:1), −10 °C (54%); (iii) SmI_2, THF (65%); (iv) Ac_2O, pyridine, 60 ^oC (65%); (v) (a) OsO_4, pyridine, (b) H_2S, MeOH (76%).

Recently, Honda and Sakamaki[42c] have reported the first synthesis of deoxychilenine (**58**) employing novel palladium-catalyzed intramolecular arylation (Scheme 15). Acylation of benzazepinone **70** by benzoyl chloride **71** furnished amide **72** in 91% yield which was further subjected for palladium catalyzed intramolecular arylation to produce deoxychilenine (**58**) in 65% yield.



Scheme 15. *Reagents, conditions and yields*: (i) Aq. $NaHCO_3$, Et_2O, 0 ^oC (91%); (ii) $Pd_2(dba)_3/CHCl_3$, BINAP, KO*t*-Bu, dioxane, reflux (65%).

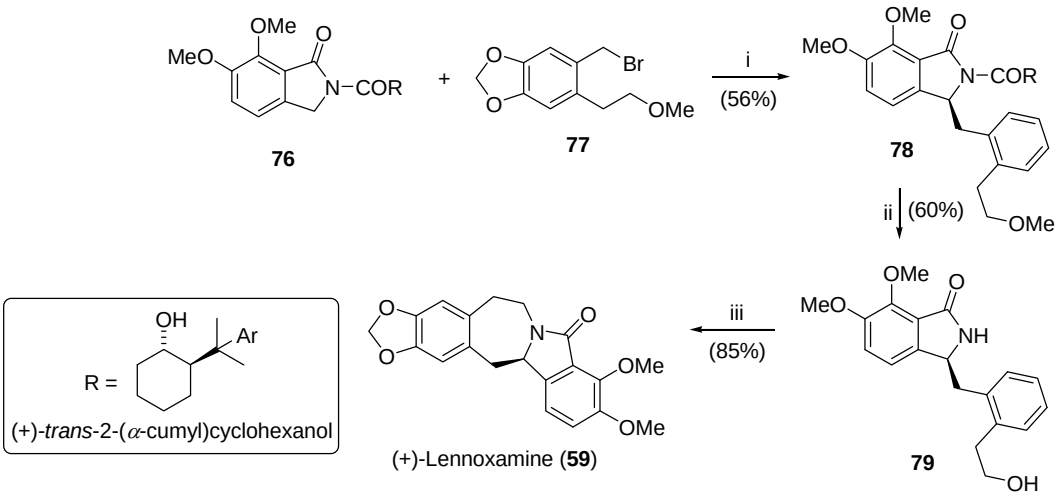
Ishibashi and co-workers[43f] reported a short synthesis of lennoxamine (**59**) by using a radical cascade (Scheme 16). The synthesis starts with the formation of Schiff base **74** by condensation of *o*-Iodohomopiperonyl amine (**73**) and acetaldehyde. Schiff base **74** upon acylation by 2,3-dimethoxybenzoyl chloride produced **75**. Treatment of **75** with hexa-*n*-butyldistannane (Bu_6Sn_2) in boiling *o*-dichlorobenzene resulted into the formation of aryl radical which further undergoes two sequential cyclizations to form lennoxamine (**59**).



Scheme 16. *Reagents, conditions and yields*: (i) (a) Acetaldehyde, THF, 4 Å MS, 10 ^oC, 5 h, (b) 2,3-dimethoxybenzoyl chloride, Et_3N, 30 min (54%); (ii) Bu_6Sn_2, *hv*, *o*-dichlorobenzene, reflux, 4 h (40%).

Comins and co-workers[43g] reported first asymmetric synthesis of (+)-lennoxamine (**59**) by using (+)-*trans*-2-(α-cumyl)cyclohexanol (TCC) as a chiral auxiliary (Scheme 17). Thus, alkylation of isoindole **76** by benzyl bromide **77** forms **78**. Removal of chiral auxiliary and deprotection of

methyl ether by $AlCl_3$ gave alcohol **79** in 60% yield. Finally, mesylation and cyclization provided enantiopure (+)-lennoxamine (**59**).



Scheme 17. *Reagents, conditions and yields*: (i) NaHMDS, THF, −78 °C (56%); (ii) $AlCl_3$, NaI (60%); (iii) (a) MsCl, Et_3N (86%), (b) NaH, THF (99%).

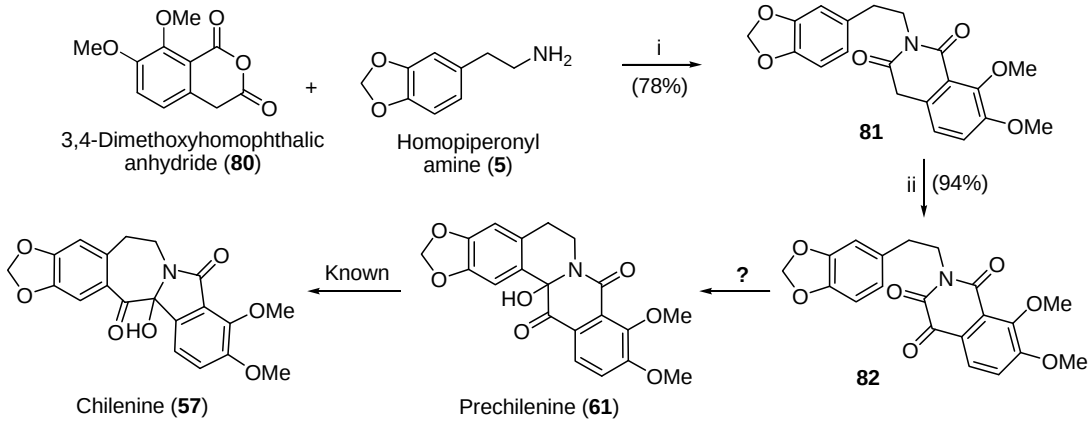
2B.3.3 Rational for Present Work

In continuation of our comprehensive studies on cyclic anhydrides and their derivatives to bioactive natural and unnatural products,[7] recently we serendipitously witnessed a facile air-oxidation of homophthalimides and utilized it for the synthesis of nuevamine and isoindolo-*β*-carboline.[16,44] Those two examples involve Pictate-Spengler cyclization of the formed isoindole to result into the formation of six-membered B-ring of the target compound. We planned here to construct seven membered B-ring of the isoindolobenzazepine family natural products by using the observed facile air-oxidation protocol. The isoindole product formed due to serendipitous air-oxidation of homophthalimide provided us the template in which we thought, isoindolobenzazepine family natural products would fit well if one takes the right substitution pattern in the precursors. In this context, we herein reports the results towards total synthesis of chilenine and deoxychilenine from 3,4-dimethoxyhomophthalic anhydride via partially separate routes utilizing intramolecular acylation as the decisive step.[45]

2B.3.4 Results and Discussion

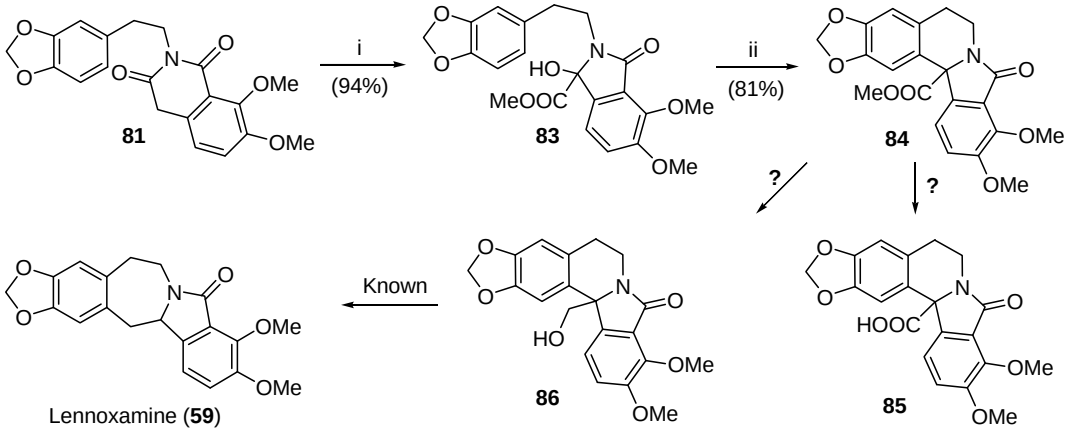
The actual work towards the target molecules started with the synthesis of homophthalimide **81**. The reaction of 3,4-dimethoxyhomophthalic anhydride (**80**)[46] and homopiperonyl amine (**5**) in refluxing *o*-dichlorobenzene furnished the required homophthalimide **81** in 78% yield (Scheme 18). As expected, the homophthalimide **81** underwent the facile air-oxidation at an activated

benzylic position and provided the prospective precursor trione **82** in 94% yield. In principle the selective Friedel-Crafts type intramolecular acylation of trione **82** should provide the direct access to chilenine (**57**) via the ring expansion and recyclization mechanism or via prechilenine (**61**). All attempts to transform the trione **82** to **57** utilizing acid catalyzed (TFA, H_2SO_4/AcOH, *p*-TSA/xylene), Lewis acid catalyzed ($BF_3.OEt_2$, $AlCl_3$, $AuCl_3$, TMSOTf) and thermal cyclization (DMSO reflux, neat heating 200 °C) conditions were unsuccessful and always ended up with either the unreacted starting material or excessive decomposition.



Scheme 18. *Reagents, conditions and yields*: (i) *o*-Dichlorobenzene, 190 °C, 3 h (78%); (ii) DMSO, O_2, rt, 24 h (94%).

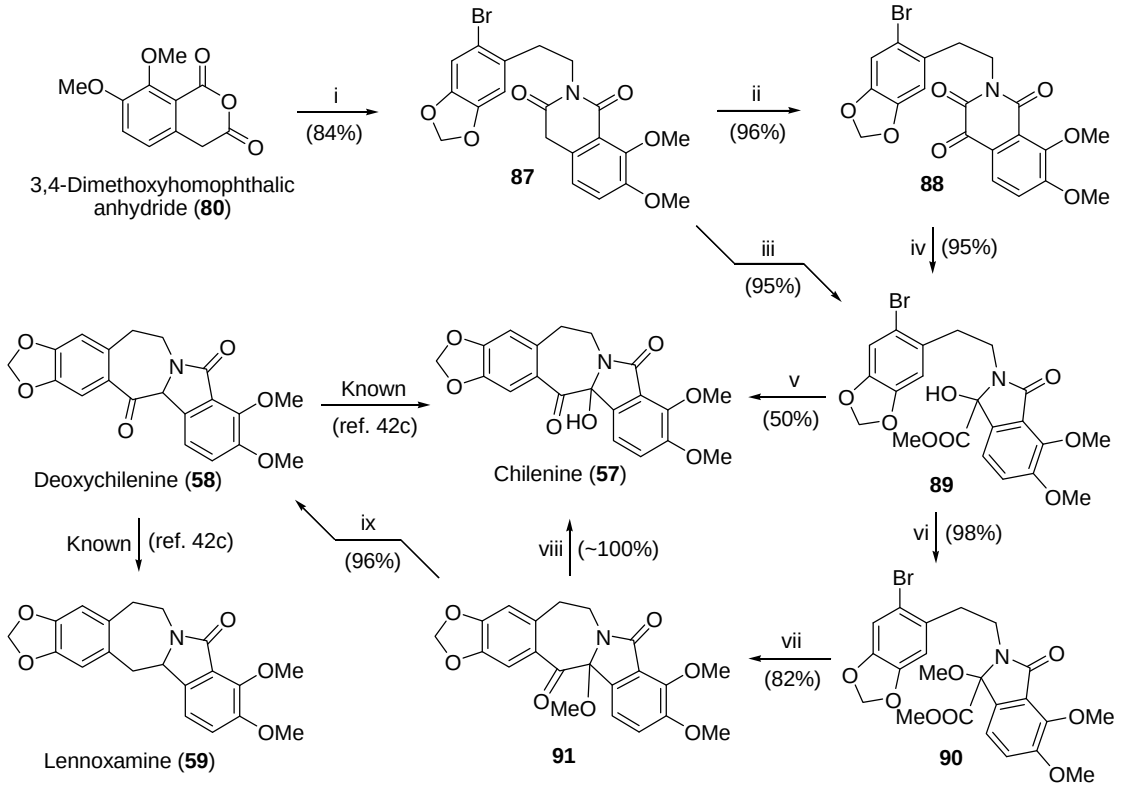
Yet another strategy was planned for the synthesis of lennoxamine (**59**) (Scheme 19). The isoindole **84** was readily synthesized in good yield via the air-oxidation of imide **81** to form lactamol **83**, followed by its acid catalyzed intramolecular dehydrative cyclization. The compound **84** was subjected to various reduction conditions by using the reducing agents like $LiAlH_4$, DIBAL, $LiBH_4$, $NaBH_4$ etc.



Scheme 19. *Reagents, conditions and yields*: (i) DMSO, MeOH, Et_3N, O_2, rt, 24 h (94%); (ii) TFA, rt, 2 h (81%).

We were unable to reduce the doubly benzylic ester functionality in compound **84** to obtain the alcohol **86**. In our efforts to hydrolyze the ester functionality to carboxylic acid **85**, we noticed the decarboxylation. Hence we were unable to complete the formal synthesis of lennoxamine using known alcohol **86**.[42f] Hence all initial attempts to directly transform the trione **82** and lactamol **83** to chilenine (**57**) and lennoxamine (**59**) were not successful.

In the second segment of studies, starting from 3,4-dimethoxyhomophthalic anhydride (**80**) and *ortho*-bromohomopiperonyl amine, we similarly synthesized the *ortho*-bromotrione **88** and *ortho*-bromolactamol **89** in 96% and 95% yields respectively, for the lithium-halogen exchange to induce the essential intramolecular cyclizations (Scheme 20).



Scheme 20. *Reagents, conditions and yields*: (i) *o*-Bromohomopiperonyl amine, *o*-dichlorobenzene, 190 ^{o}C, 3 h (84%); (ii) DMSO, O_2, rt, 24 h (96%); (iii) DMSO + MeOH (4:1), Et_3N, O_2, rt, 24 h (95%); (iv) MeOH, Et_3N, rt, 6 h (95%); (v) THF + HMPA (4:1), *t*-BuLi, –78 ^{o}C to rt (50%); (vi) H^+/H_2SO_4, MeOH, rt (98%); (vii) THF + HMPA (4:1), *t*-BuLi, –78 ^{o}C to rt (82%); (viii) TFA, H_2O, rt, 2 h (~100%); (ix) Et_3SiH, $BF_3.OEt_2$, DCM, 0 ^{o}C, 20 min (96%).

Again, the trione **88** on treatment with *t*-BuLi in THF at −78 °C and −100 °C, with or without HMPA, underwent instantaneous complete decomposition. Pleasantly, the *ortho*-bromolactamol **89** on treatment with *t*-BuLi (2.20 equiv.) in THF at −78 °C underwent intramolecular chemoselective acylation to form the crucial seven membered benzazepine core and furnished

the target compound chilenine (**57**) in 15–20% yields along with large amount of debrominated staring material (45% of **83**). In the above mentioned reaction the use of HMPA as a co-solvent improved the yield to 45–50%.

In the conversion of **89** to **57**, the instability of in situ generated oxyanionic species from compound **89** and/or its display of ring chain tautomerism might be plausibly affecting on the efficiency of intramolecular acylation reaction. Hence the free tertiary –OH group in compound **89** was transformed to –OMe by treating it with excess of methanol and concentrated sulfuric acid to obtain lactamolmethyl ether **90** in quantitative yield. The above specified hypothesis turned out to be reasonable and finally the compound **90** in THF and HMPA mixture, on *t*-BuLi (1.10 equiv.) induced intramolecular acylation furnished the corresponding desired cyclized product **91** in 82% yield. Herein the intramolecular chemoselective demethoxylative acylation to form the seven membered benzazepine ring system over the possible nucleophilic substitution of an angular –OMe group to furnish the corresponding six membered piperidine unit is remarkable. The compound **91** on usual acid catalyzed hydrolysis furnished the chilenine (**57**) in quantitative yield, while the same on treatment with triethylsilane underwent Lewis acid catalyzed displacement of an angular –OMe group with the hydride ion and provided the deoxychilenine (**58**) in 96% yield. In the ^{1}H NMR spectrum of deoxychilenine (**58**) the methine proton appeared as singlet at δ 5.15 and it was not exchangeable with deuterium, indicating the absence of any associated keto-enol tautomerism. The analytical and spectral data obtained for both chilenine and deoxychilenine were in agreement with the reported data.[1,33,42f] The conversions of deoxychilenine (**58**) to chilenine (**57**) and lennoxamine (**59**) are well known in the literature.[42c]

In summary, starting with the unsymmetrical cyclic anhydride we have accomplished five steps total synthesis of berberis natural products chilenine and deoxychilenine in decent overall yields via the penultimate stage common intermediate. In the present approach, the involved critical *t*-BuLi induced intramolecular chemoselective acylation that delivered the benzazepine core is noteworthy.

2B.4 Summary

Homophthalic anhydrides, as already mentioned offer remarkable advantages in the organic synthesis due to the presence of different reaction sites available on them to explore. Homophthalimides, an important derivative of homophthalic anhydrides, has wide applications in the organic synthesis. Due to presence of two carbonyl groups in different chemical environment, it provides an added advantage of their regioselective reactivity.

Serendipity has got its own significance in organic synthesis. Many interesting chemical reactivities have been unveiled serendipitously. We came across one of the case in which we observed a serendipitous base catalyzed benzylic air-oxidation of homophthalimides during our synthetic studies towards protoberberine family natural product gusanlung D and used it for the synthesis of different natural and synthetic products. Thus, overall, in the present section, we have seen the utility of differently substituted homophthalimides for the simple and efficient total synthesis of natural and synthetic products. We have achieved a noteworthy total synthesis of nuevamine by using the facile air-oxidation of homophthalimide. We could isolate the reactive intermediate trione under neutral condition, which is responsible for the formation of final product isoindole from homophthalimide. The second application of this air-oxidation propensity of homophthalimide was the stereoselective synthesis of (+)-isoindolo-β-carboline with high enantiomeric excess. Geometry-dependent demethoxycarbonylation, gain in the diastereoselectivity during the intramolecular dehydrative cyclization step and preservation of high enantiomeric excess at high temperature is worth mentioning in this approach. Third application of the air-oxidation propensity was the five steps total synthesis of berberis natural products chilenine and deoxychilenine in decent overall yields. The above mentioned syntheses proved the generality of the air-oxidation process.

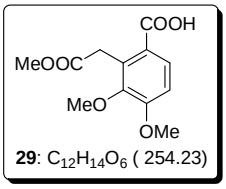
We have also completed an efficient one-pot two-step synthesis of nuevamine and isonuevamine by taking the advantage of highly regioselective electronically and thermodynamically favored sodium borohydride reductions and sterically favored DIBAL-H reduction of 3,4-dimethoxyhomopiperonylphthalimide. This provides a short access to these carbocycles using simple starting material over the all earlier approaches including our approach.

In addition, we feel that there is a huge scope for exploring the hidden reactivities of these small molecules with ample functionality *viz*. homophthalic anhydrides/imides. It can be said with assurance that homophthalic anhydrides/imides will be continuously explored and utilized in the field of organic and medicinal chemistry in future.

2B.5 Experimental section

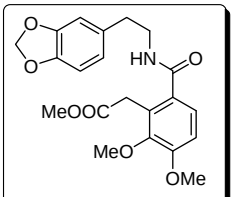
Melting points are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard on NMR spectrometers operating at 200, 400 and 500 MHz. ^{13}C NMR spectra were recorded on 200, 400 and 500 NMR spectrometers (50, 100 & 125 MHz respectively). IR spectra were recorded on FT-IR spectrometer. Elemental analyses were obtained by using Elementar Vario EL analyzer. Mass spectra and HRMS were taken on ESIMS mass spectrometer and HRMS (ESI) respectively. Column chromatographic separations were done on silica gel (60–120, 230–400 mesh). Commercially available $NaBH_4$, Jones reagent, *N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt), piperonal, 2,3-dimethoxybenzaldehyde, isovanillin, homophthalic anhydride, acetic anhydride, (*S*)-tryptophan, *t*-BuLi, $BF_3.OEt_2$ and Et_3SiH and nitromethane were used.

3,4-Dimethoxy-2-(2-methoxy-2-oxoethyl)benzoic acid (29). To a stirred solution of compound **28** (700 mg, 2.94 mmol) in acetone (20 mL) was added Jones reagent (6 mL) in dropwise fashion at room temperature and the reaction mixture was stirred for 4 h. The excess of reagent was quenched by addition of *i*-PrOH. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (25 mL x 3). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo gave pure compound **29** as a crystalline solid (732 mg, 98% yield). **Mp** 128–130 ºC. **IR** ($CHCl_3$) ν_{max} 1734, 1686, 1597 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.70 (s, 3H), 3.81 (s, 3H), 3.94 (s, 3H), 4.18 (s, 2H), 6.91 (d, J = 8 Hz, 1H), 7.96 (d, J = 10 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 32.5, 51.8, 55.8, 60.8, 110.2, 121.0, 129.0, 131.7, 147.8, 156.8, 172.0, 172.3. **Anal. Calcd** for $C_{12}H_{14}O_6$: C, 56.69; H, 5.54. Found: C, 56.64; H, 5.55.



29: $C_{12}H_{14}O_6$ (254.23)

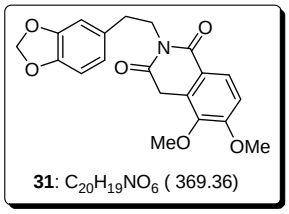
Methyl 2-(6-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl carbamoyl)-2,3-dimethoxyphenyl)acetate (30). To a stirred solution of compound **29** (650 mg, 2.55 mmol) in DMF (15 mL) at 0 ºC was slowly added HOBt (413 mg, 3.06 mmol) and *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI, 535 mg, 2.80 mmol). The reaction mixture was stirred under inert atmosphere for 20 min. Homopiperonyl amine (420 mg, 2.55 mmol) in DMF (7 mL) was added to the above reaction mixture in a dropwise fashion over 10 min and it was further stirred for 4 h at room temperature. The reaction mixture was diluted with water (50 mL) and



30: $C_{21}H_{23}NO_7$ (401.40)

extracted with ethyl acetate (25 mL x 3). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether-ethyl acetate mixture (4:6) as an eluent gave **30** as a white crystalline solid (851 mg, 83% yield). **Mp** 120–121 ^oC. **IR** ($CHCl_3$) ν_{max} 1734, 1710, 1630 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.81 (t, J = 8 Hz, 2H), 3.62 (q, J = 6 Hz, 2H), 3.70 (s, 3H), 3.78 (s, 3H), 3.83 (s, 2H), 3.87 (s, 3H), 5.93 (s, 2H), 6.43 (t, J = 6 Hz, 1H), 6.62–6.78 (m, 3H), 6.83 (d, J = 8 Hz, 1H), 7.17 (d, J = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 32.4, 35.2, 41.1, 52.1, 55.7, 60.5, 100.8, 108.3, 109.0, 110.9, 121.6, 123.6, 127.0, 130.0, 132.6, 146.1, 147.6, 147.8, 153.9, 168.9, 173.7. **Anal. Calcd** for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.77; N, 3.49. Found: C, 63.02; H, 5.80; N, 3.61.

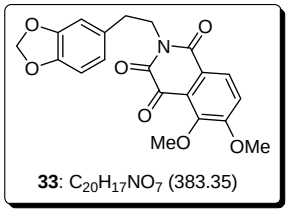
2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-5,6-dimeth-oxyisoquinoline-1,3(2*H*,4*H*)-dione (31). To a stirred solution of compound **30** (750 mg, 2.03 mmol) in MeOH (20 mL) at room temperature



31: $C_{20}H_{19}NO_6$ (369.36)

was added catalytic amount of Et_3N (1 drop) and the reaction mixture was stirred for 30 min. The obtained white precipitate was filtered out and washed with MeOH (5 mL) and dried in vacuo to provide pure compound **31** as a snow-white crystalline solid (683 mg, 99% yield). **Mp** 216–217 ºC. **IR** (Nujol) ν_{max} 1705, 1666, 1597 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.76–2.81 (m, 2H), 3.88 (s, 3H), 3.96 (s, 5H), 4.07–4.19 (m, 2H), 5.93 (s, 2H), 6.74 (s, 2H), 6.82 (s, 1H), 7.02 (d, J = 8 Hz, 1H), 7.99 (d, J = 10 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 32.0, 33.9, 41.5, 55.9, 60.3, 100.8, 108.2, 109.4, 111.5, 118.4, 121.8, 125.9, 128.2, 132.5, 144.6, 146.1, 147.6, 156.6, 164.3, 169.9. **Anal. Calcd** for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found: C, 64.90; H, 5.01; N, 3.53.

2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-5,6-dimethoxyisoquinoline-1,3,4(2*H*)-trione (33). The solution of compound **31** (100 mg, 0.27 mmol) in DMSO (5 mL) was stirred under the oxygen

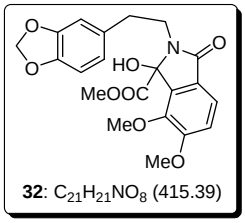


33: $C_{20}H_{17}NO_7$ (383.35)

atmosphere for 48 h at room temperature. To the formed yellow colored reaction mixture was added ethyl acetate (20 mL) and the total organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo gave pure compound **33** as a yellow solid (102 mg, 99% yield). **Mp** 155–157 ºC. **IR** ($CHCl_3$) ν_{max} 1724, 1707, 1676 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.81–2.93 (m, 2H), 3.97 (s, 3H), 4.01 (s, 3H), 4.12–4.23 (m, 2H), 5.93 (s, 2H), 6.73 (s, 2H), 6.80 (s, 1H), 7.35 (d, J = 10 Hz, 1H), 8.15 (d, J = 10 Hz, 1H). **^{13}C**

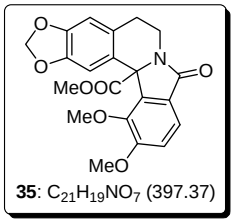
NMR ($CDCl_3$, 100 MHz) δ 33.1, 41.8, 56.7, 60.8, 101.0, 108.5, 109.2, 118.1, 121.7, 122.5, 124.8, 126.4, 132.6, 145.9, 147.5, 149.3, 157.5, 157.9, 162.2, 173.0. **Anal. Calcd** for $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65. Found: C, 62.57; H, 4.61; N, 3.58.

Methyl 2-(2-(benzo[*d*][1,3]dioxyl-5-yl)ethyl)-1-hydroxy-6,7-dimethoxy-3-oxoisoindoline-1-carboxylate (32). *Method A*: To the stirred solution of compound **33** (50 mg, 0.13 mmol) in MeOH (5 mL) was added catalytic amount of Et_3N (1 drop) at room temperature and the reaction mixture was further stirred for 3 h. Concentration of the reaction mixture in vacuo directly furnished compound **32** as a faint brown solid (53 mg, 99% yield). *Method B*: To the solution of compound **31** (500 mg, 1.35 mmol) in mixture of DMSO (20 mL) and MeOH (5 mL) was added Et_3N (0.5 mL) and the reaction mixture was stirred under the oxygen atmosphere at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether-ethyl acetate mixture (4:6) as an eluent furnished compound **32** as a faint brown solid (548 mg, 98% yield). **Mp** 145–146 ºC. **IR** ($CHCl_3$) ν_{max} 3483, 1742, 1701, 1618 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.68–2.97 (m, 2H), 3.30–3.48 (m, 1H), 3.51–3.70 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 4.81 (s, 1H), 5.92 (s, 2H), 6.65–6.78 (m, 3H), 7.04 (d, J = 8 Hz, 1H), 7.53 (d, J = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 34.6, 41.3, 53.9, 56.1, 61.0, 86.3, 100.8, 108.2, 109.2, 114.1, 119.6, 121.6, 124.4, 132.5, 136.1, 143.6, 146.0, 147.5, 156.1, 167.5, 171.5. **Anal. Calcd** for $C_{21}H_{21}NO_8$: C, 60.71; H, 5.09; N, 3.37. Found: C, 60.52; H, 5.00; N, 3.44.



32: $C_{21}H_{21}NO_8$ (415.39)

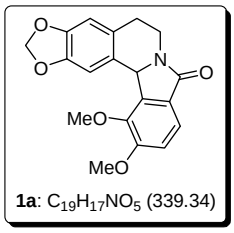
10,11-Dimethoxy-7-oxo-5,6-dihydro-7*H*-1,3-dioxa-6*a*-aza-indeno[5,6-*c*]fluorene-11*b*-carboxylic acid methyl ester (35). The solution of compound **32** (400 mg, 0.96 mmol) in TFA (10 mL) was stirred at room temperature for 2 h. To the reaction mixture was added ethyl acetate (30 mL) and organic layer was washed with 5% aqueous solution of $NaHCO_3$, water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether-ethyl acetate mixture (3:7) as an eluent gave compound **35** as a crystalline solid (309 mg, 81% yield). **Mp** 233–235 ºC. **IR** ($CHCl_3$) ν_{max} 1742, 1686, 1612 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ



35: $C_{21}H_{19}NO_7$ (397.37)

2.71 (dt, J = 16 & 6 Hz, 1H), 3.01 (ddd, J = 16, 8 & 6 Hz, 1H), 3.40 (ddd, J = 14, 9 & 6 Hz, 1H), 3.73 (s, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 4.30 (ddd, J = 12, 7 & 4 Hz, 1H), 5.90 (dd, J = 9 & 2 Hz, 2H), 6.58 (s, 1H), 7.08 (d, J = 8 Hz, 1H), 7.58 (d, J = 10 Hz, 1H), 7.67 (s, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 28.5, 37.0, 53.3, 56.2, 60.2, 70.0, 101.0, 108.4, 109.4, 113.8, 119.8, 125.2, 127.6, 128.3, 137.3, 143.9, 146.3, 147.3, 156.1, 167.7, 170.6. **Anal. Calcd** for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.81; N, 3.54. Found: C, 63.32; H, 4.71; N, 3.59.

10,11-Dimethoxy-5,11*b*-dihydro-6*H*-1,3-dioxa-6*a*-aza-indeno[5,6-*c*]fluoren-7-one [Nuevamine (±)-1a]. To the stirred solution of compound **35** (200 mg, 0.50 mmol) in the mixture of DMSO (7 mL) and H_2O (1 mL) was added NaCl (32 mg, 0.55 mmol). The reaction mixture was deoxygenated by bubbling excess of nitrogen gas for 3 h and it was heated for 30 min at 185 ^oC. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue by using petroleum ether-ethyl acetate mixture (3:7) as an eluent furnished the desired compound **1a** as a crystalline solid (146 mg, 86% yield). **Mp** 214–215 ºC (ethyl acetate), (Lit.[1] 212 ºC). **IR** ($CHCl_3$) ν_{max} 1680, 1651, 1620 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.78–3.12 (m, 2H), 3.57 (dt, J = 12 & 6 Hz, 1H), 3.98 (s, 3H), 4.00 (s, 3H), 3.95–4.15 (m, 1H), 5.63 (s, 1H), 5.90 (dd, J = 12 & 2 Hz, 2H), 6.67 (s, 1H), 7.07 (d, J = 8 Hz, 1H), 7.32 (s, 1H), 7.59 (d, J = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 28.8, 38.7, 56.2, 58.3, 60.5, 100.9, 107.4, 108.4, 113.2, 119.7, 126.6, 128.4, 128.8, 136.1, 144.3, 146.4, 146.7, 155.4, 167.5. **Anal. Calcd** for $C_{19}H_{17}NO_5$: C, 67.24; H, 5.04; N, 4.12. Found: C, 67.09; H, 5.11; N, 4.15.

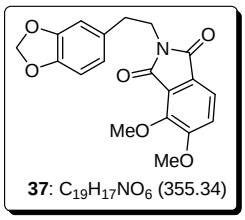


1a: $C_{19}H_{17}NO_5$ (339.34)

(+)-Nuevamine. Four successive recrystalisations of conglomerate (±)-nuevamine (120 mg) from the chloroform plus ethyl acetate mixture (1:3, 1 mL/20 mg) with 24 h as the each recrystalisation time furnished the enantiomerically pure (+)-nuevamine (11 mg, 9% recrystalisations yield, 98% ee by chiral HPLC). Mp 215 ºC; $[\alpha]^{20}_D$ = + 185 (c 1.0, $CHCl_3$). ***HPLC details*.** Column: chiralcel OD (250 x 4.6 mm), mobile phase: isopropyl alcohol:hexane (20:80), wavelength: 254 nm, flow rate: 1 mL/min, retention time: 17.6 min (+)-isomer, 23.4 min (–)-isomer.

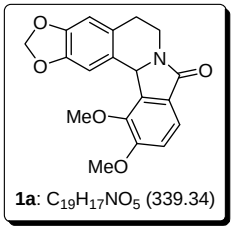
2-(2-(Benzo[d][1,3]dioxol-5-yl)ethyl)-4,5-dimethoxyisoindoline-1,3-dione (37). A stirred solution of homopiperonyl amine (793 mg, 4.80 mmol) and 3,4-dimethoxyphthalic anhydride

(**36**, 1.00 g, 4.80 mmol) was heated at reflux in *o*-dichlorobenzene (20 mL) for 2 h. After cooling the reaction mixture, it was loaded on silica gel column and initially the column was eluted with pet. ether for the removal of *o*-dichlorobenzene and then it was eluted with pet. ether and ethyl acetate mixture (7:3) to obtain pure compound **37** as a white crystalline solid 1.55 g (91%). **Mp** 155–157 °C. **IR** ($CHCl_3$) ν_{max} 1765, 1711 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.82–2.93 (m, 2H), 3.76–3.87 (m, 2H), 3.95 (s, 3H), 4.13 (s, 3H), 5.92 (s, 2H), 6.60–6.75 (m, 3H), 7.10 (d, J = 8 Hz, 1H), 7.53 (d, J = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 34.2, 39.4, 56.5, 62.5, 100.8, 108.2, 109.2, 115.6, 119.3, 121.7, 121.8, 124.5, 131.8, 146.1, 147.1, 147.6, 157.6, 166.1, 167.4. **Anal. Calcd** for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.00; H, 4.76; N, 3.71%.



37: $C_{19}H_{17}NO_6$ (355.34)

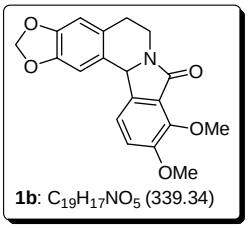
10,11-Dimethoxy-5,11b-dihydro-6H-1,3-dioxa-6a-aza-indeno[5,6-c]fluoren-7-one (Nuevamine, 1a). *Method A*: To a solution of imide **37** (50 mg, 0.14 mmol) in THF (5 mL) was added $NaBH_4$ (26 mg, 0.70 mmol) and the reaction mixture was stirred at room temperature for 96 h. The reaction mixture was concentrated in vacuo and further stirred with trifluoroacetic acid (2 mL) at room temperature for 1 h. Reaction mixture was then neutralized with 5% aqueous solution of $NaHCO_3$ and extracted to the ethyl acetate (10 mL × 3). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using pet. ether and ethyl acetate mixture (4:6) as an eluent gave compound **1a** as a white crystalline solid 44 mg (92%). *Method B*: To a refluxing solution of imide **37** (50 mg, 0.14 mmol) in methanol (4 mL) was added $NaBH_4$ (104 mg, 2.80 mmol) and the reaction mixture was further refluxed for 30 min under stirring. The reaction mixture was concentrated in vacuo and further stirred with trifluoroacetic acid (2 mL) at room temperature for 1 h. Repetition of above work-up and column chromatographic purification procedures provided compound **1a** as a white crystalline solid 43 mg (90%).



1a: $C_{19}H_{17}NO_5$ (339.34)

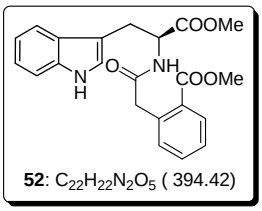
8,9-Dimethoxy-5,11b-dihydro-6H-1,3-dioxa-6a-aza-indeno[5,6-c]fluoren-7-one (Isonuevamine, 1b). To a stirred solution of imide **37** (100 mg, 0.28 mmol) in DCM (5 mL) at –78 °C was added the solution of DIBAL-H (1.00 M, 0.30 mL) in toluene in a drop-wise fashion. After stirring the reaction mixture at the same temperature for 2 h, it was allowed to reach room temperature. The reaction mixture was concentrated in vacuo and further stirred with conc. HCl

(2 mL) at room temperature for 1 h. Repetition of above work-up procedure followed by flash column chromatographic purification of the obtained residue provided major compound **1b** as a white crystalline solid 80 mg (75%) and minor compound **1a** (8 mg, 5%). **Mp** 193–194 °C (ethyl acetate), (Lit.[2] 195–196 °C). **IR** ($CHCl_3$) ν_{max} 1688, 1680 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.68–2.83 (m, 1H), 2.89–3.07 (m, 1H), 3.39 (ddd, J = 14, 8 and 4 Hz, 1H), 3.91 (s, 3H), 4.07 (s, 3H), 4.25−4.39 (m, 1H), 5.46 (s, 1H), 5.93 (dd, J = 12 and 2 Hz, 2H), 6.66 (s, 1H), 7.04 (s, 1H), 7.15 (d, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 29.2, 38.2, 56.7, 58.0, 62.5, 101.0, 105.4, 109.0, 116.1, 118.4, 125.0, 127.8, 128.3, 137.6, 146.5, 146.7, 147.2, 152.7, 166.1. **LC-MS** m/z 340.07 [$(M+1)^+$].



1b: $C_{19}H_{17}NO_5$ (339.34)

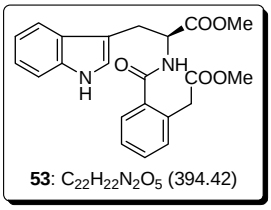
(*S*)-Methyl 2-(2-(3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-ylamino)-2-oxoethyl)benzoate (52). To a stirred slurry of acid **50** (300 mg, 1.54 mmol) in DCM (20 mL) was added *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodimide hydrochloride (EDCI, 590 mg, 3.09 mmol), (*S*)-tryptophan methyl ester hydrochloride (391 mg, 1.54 mmol) and cat. DMAP under a nitrogen atmosphere. The reaction mixture was cooled to 0 ^oC and Et_3N (0.20 mL, 1.54 mmol) was added slowly and the reaction mixture was stirred at room temperature for further 6 h. DCM was removed in vacuo and to the reaction mixture was added water (30 mL) and then it was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with 1 N HCl, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate (2:3) as an eluent gave compound **52** as a thick oil (566 mg, 93%). $[\alpha]^{20}_D$ +29.6 (c 2.8, $CHCl_3$). **IR** ($CHCl_3$) ν_{max} 3477, 3422, 1740, 1717, 1665 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.24 (d, J = 4 Hz, 2H), 3.62 (s, 3H), 3.74 (s, 3H), 3.82 (d, J = 16 Hz, 1H), 3.92 (d, J = 16 Hz, 1H), 4.83–4.91 (m, 1H), 6.77 (d, J = 4 Hz, 1H), 6.84 (bd, J = 8 Hz, 1H), 7.05 (t, J = 8 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 7.28–7.38 (m, 3H), 7.42–7.48 (m, 2H), 7.91 (d, J = 8 Hz, 1H), 8.02 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 27.3, 41.8, 51.9, 52.0, 52.9, 109.1, 111.2, 118.1, 119.1, 121.5, 122.9, 127.1, 127.2, 129.0, 130.8, 131.9, 132.4, 136.0, 136.2, 167.7, 170.7, 172.2. **Anal. Calcd** for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.09; H, 5.53; N, 7.22.



52: $C_{22}H_{22}N_2O_5$ (394.42)

(*S*)-Methyl 3-(1*H*-indol-3-yl)-2-(2-(2-methoxy-2-oxoethyl)benzamido)propanoate (53). To a stirred slurry of acid **51** (1.50 g, 7.73 mmol) in DCM (50 mL) was added *N*-ethyl-*N*'-(3-

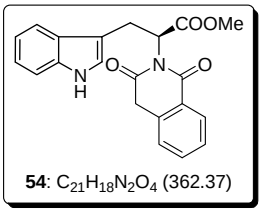
dimethylaminopropyl)carbodimide hydrochloride (EDCI, 2.95 g, 15.46 mmol), (*S*)-tryptophan methyl ester hydrochloride (1.96 g, 7.73 mmol) and cat. DMAP under a nitrogen atmosphere.



53: $C_{22}H_{22}N_2O_5$ (394.42)

The reaction mixture was cooled to 0 ^oC and Et_3N (1.10 mL, 7.78 mmol) was added slowly and the reaction mixture was stirred at room temperature for further 6 h. DCM was removed in vacuo and to the reaction mixture was added water (50 mL) and then it was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with 1 N HCl, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether-ethyl acetate (2:3) as an eluent provided compound **53** as a thick oil (2.86 g, 94%). $[\alpha]^{20}_D$ +41.1 (*c* 2.0, $CHCl_3$). **IR** ($CHCl_3$) ν_{max} 3477, 3422, 1736, 1655 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.33–3.45 (m, 2H), 3.59 (s, 3H), 3.72 (s, 3H), 3.81 (d, *J* = 16 Hz, 1H), 3.88 (d, *J* = 16 Hz, 1H), 5.07–5.14 (m, 1H), 7.02 (bd, *J* = 8 Hz, 1H), 7.07 (bs, 1H), 7.10 (d, *J* = 8 Hz, 1H), 7.17 (t, *J* = 8 Hz, 1H), 7.20–7.28 (m, 2H), 7.31–7.42 (m, 3H), 7.56 (d, *J* = 8 Hz, 1H), 8.19 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 27.5, 38.6, 52.0, 52.3, 53.2, 109.5, 111.3, 118.3, 119.3, 121.9, 123.1, 127.3, 127.4, 127.8, 130.4, 131.2, 132.4, 135.7, 136.1, 168.9, 172.4, 172.7. **Anal. Calcd** for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.11; H, 5.54; N, 7.17.

(*S*)-Methyl 2-(1,3-dioxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-3-(1*H*-indol-3-yl)propanoate (54). *Method A*: To a stirred solution of compound **53** 300 mg, 0.76 mmol) in methanol (20 mL) at room temperature was added Et_3N (2 drops) and the reaction mixture was stirred for further 4 h

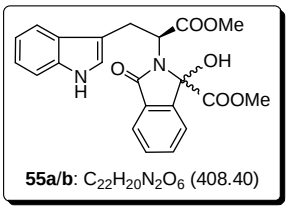


54: $C_{21}H_{18}N_2O_4$ (362.37)

under argon atmosphere. The reaction mixture was concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (3:2) as an eluent to obtain compound **54** as a thick oil (245 mg, 89%). $[\alpha]^{20}_D$ –131.0 (*c* 2.0, $CHCl_3$). **IR** ($CHCl_3$) ν_{max} 3477, 1744, 1720, 1674 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 3.53–3.79 (m, 3H), 3.74 (s, 3H), 3.85 (d, *J* = 24 Hz, 1H), 5.87 (dd, *J* = 8 and 8 Hz, 1H), 6.99 (t, *J* = 8 Hz, 1H), 7.03 (s, 1H), 7.09 (t, *J* = 8 Hz, 1H), 7.15 (d, *J* = 8 Hz, 1H), 7.25 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8 Hz, 1H), 7.54 (t, *J* = 8 Hz, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.97 (bs, 1H), 8.12 (d, *J* = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 24.3, 36.0, 52.3, 53.7, 111.0, 111.1, 118.3, 119.1, 121.6, 123.0, 124.7, 126.9, 127.3, 127.5, 128.9, 133.6, 133.9, 135.9, 164.4, 169.5, 170.3. **Anal. Calcd** for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.47; H, 4.94; N, 7.74.

Method B: To a stirred solution of compound **52** (400 mg, 1.01 mmol) in methanol (15 mL) at room temperature was added Et_3N (2 drops) and the reaction mixture was stirred for further 24 h under argon atmosphere. The reaction mixture was concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (3:2) as an eluent to obtain compound **54** as a thick oil (170 mg, 46%).

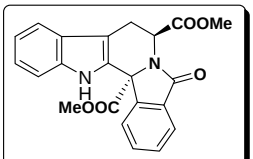
(*R*)-Methyl 2-((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)-1-hydroxy-3-oxoisoindoline-1-carboxylate (55a) and (*S*)-Methyl 2-((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)-1-hydroxy-3-oxoisoindoline-1-carboxylate (55b). *Method A*: To a stirred solution of amide **53** (2.00 g, 5.07 mmol) in methanol (50 mL) at room temperature was added Et_3N (1 mL) and the reaction mixture was stirred for further 6 h at room temperature. The reaction mixture was oxygenated by bubbling excess of oxygen gas for 6 h and stirred for further 6 h. The reaction mixture was concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (1:1) as an eluent to obtain the mixture of compounds **55a**/**b** inseparable by column chromatography (2:3, 1.90 g, 92%). *Method B*: To a stirred solution of amide **52** (100 mg, 0.253 mmol) in methanol (10 mL) at room temperature was added Et_3N (2 drops) and the reaction mixture was stirred for 48 h under atmospheric conditions. The reaction mixture was concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (1:1) as an eluent to obtain mixture of compounds **55a**/**b** (2:3, 73 mg, 71%). *Method C*: To a stirred solution of imide **54** (200 mg, 0.55 mmol) in methanol (15 mL) at room temperature was added Et_3N (2 drops) and the reaction mixture was stirred for 12 h under atmospheric conditions. The reaction mixture was concentrated in vacuo and the obtained residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (1:1) as an eluent to obtain mixture of compounds **55a**/**b** (2:3, 198 mg, 88%). **Mp** 72–74 ^{o}C. $[\alpha]^{20}_{D}$ –98.0 (*c* 0.2, $CHCl_3$). **IR** ($CHCl_3$) ν_{max} 3476, 3398, 1744, 1736, 1709, 1701 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.78 (s, 1.80H), 3.38 (s, 1.20H), 3.44–3.75 (m, 1.40H), 3.69 (s, 1.20H), 3.75 (s, 1.80H), 3.96 (dd, *J* = 14 and 10 Hz, 0.60H), 4.09 (bs, 0.40H), 4.49 (bs, 0.60H), 4.71 (dd, *J* = 10 and 6 Hz, 0.60H), 4.93 (dd, *J* = 10 and 6 Hz, 0.40H), 7.04–7.21 (m, 3H), 7.27–7.43 (m, 2H), 7.50–7.58 (m, 2H), 7.59–7.70 (m, 1H), 7.77–7.90 (m, 1H), 8.08 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 125 MHz) δ 24.70, 25.63, 52.47, 52.69, 52.97, 53.47, 54.13, 56.40, 87.53, 88.69, 110.70, 110.92, 111.16, 111.23, 118.31, 118.35, 119.30, 119.32, 121.67, 121.82, 121.93, 122.21, 123.09, 123.55 (2 carbons), 124.00,



55a/b: $C_{22}H_{20}N_2O_6$ (408.40)

126.95, 127.04, 130.26 (2 carbons), 130.76, 130.81, 132.76 (2 carbons), 135.96, 136.09, 143.74, 143.93, 167.88, 168.65, 169.18, 170.26, 171.17, 171.86. **Anal. Calcd** for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.57; H, 5.06; N, 6.99.

(*S*)-Methyl 5,7,8,13b-tetrahydro-5-oxo-13*H*-13*b*-methoxycarbonyl-(*S*)-indolo[2,3-*c*]isoindolo[2,1-*a*] pyridine-7-carboxylate (56a) and (*R*)-Methyl 5,7,8,13b-tetrahydro-5-oxo-13*H*-13*b*-methoxycarbonyl-(*S*)-indolo[2,3-*c*]isoindolo[2,1-*a*] pyridine-7-carboxylate (56b). To a stirred solution of mixture of **55a**/**b** (1.70 g, 4.16 mmol) in AcOH (15 mL) at 10 °C was added conc. H_2SO_4 (2 drops) and the reaction mixture was stirred at room temperature for 6 h.

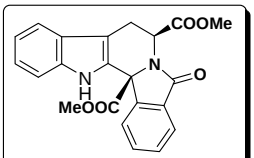


56a: $C_{22}H_{18}N_2O_5$ (390.38)

The reaction mixture was diluted with ethyl acetate (30 mL) and the organic layer was washed with 5% aqueous $NaHCO_3$ solution, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (230–400 mesh) column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate (7:3) as an eluent furnished compound **55a** (920 mg, 57%) and **55b** (230 mg, 14%) as crystalline solids with the total yield 71%.

55a: Mp 189–191 °C. $[\alpha]^{20}_D$ –43.6 (*c* 1.0, $CHCl_3$). ~100% ee by chiral HPLC. IR ($CHCl_3$) ν_{max} 3248, 1755, 1749, 1684 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.16 (dd, *J* = 16 and 4 Hz, 1H), 3.36 (dd, *J* = 16 and 8 Hz, 1H), 3.89 (s, 3H), 3.97 (s, 3H), 4.54 (dd, *J* = 12 and 4 Hz, 1H), 7.11 (dt, *J* = 8 and 2 Hz, 1H), 7.22 (dt, *J* = 8 and 2 Hz, 1H), 7.38 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.52 (dt, *J* = 8 and 2 Hz, 1H), 7.66 (dt, *J* = 8 and 2 Hz, 1H), 7.82 (dd, *J* = 8 Hz, 1H), 8.07 (d, *J* = 8 Hz, 1H), 8.68 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 23.3, 52.2, 53.3, 53.9, 68.8, 108.5, 111.9, 118.9, 119.5, 122.7, 123.8, 124.2, 125.5, 129.5, 130.1, 130.3, 133.3, 137.1, 143.1, 167.7, 168.3, 169.6. **Anal. Calcd** for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.65; H, 4.80; N, 7.12. **HPLC details:** Column: chiralcel ODH (250 x 4.6 mm), mobile phase: Ethanol: *n*-Hexane (15:85), wavelength: 240 nm, flow rate: 0.5 mL/min, retention time: 25.4 min (–)-isomer, 27.5 min (+)-isomer.

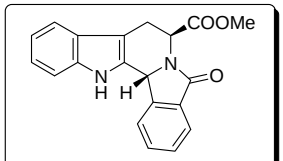
56b: Mp 120–122 °C. $[\alpha]^{20}_D$ +63.5 (*c* 2.4, $CHCl_3$). **IR** ($CHCl_3$) ν_{max} 3454, 1742, 1740, 1701 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.17 (dd, *J* = 16 and 6 Hz, 1H), 3.31 (dd, *J* = 16 and 2 Hz, 1H), 3.67 (s, 3H), 3.73 (s, 3H), 5.86 (dd, *J* = 8 and 2 Hz, 1H), 7.04–7.24 (m, 2H), 7.36–7.66 (m, 4H), 7.80–7.95 (m, 2H), 9.06 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 24.9, 51.0, 52.4, 53.3, 66.9, 107.7,



56b: $C_{22}H_{18}N_2O_5$ (390.38)

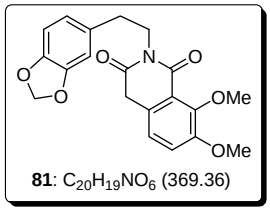
111.5, 118.7, 119.9, 121.9, 123.0, 124.8, 126.1, 128.2, 129.7, 130.2, 133.0, 137.3, 144.7, 170.1, 170.8, 171.0. **Anal. Calcd** for $C_{22}H_{18}N_2O_5$: C, 67.69; H, 4.65; N, 7.18. Found: C, 67.72; H, 4.56; N, 7.07.

(*S*)-7-Oxo-6,7,11b,12-tetrahydro-5*H*-6a,12-diaza-(*R*)-indeno[1,2-*a*]fluorene-6-carboxylic acid methyl ester (47b). To a stirred solution of compound **56a** (700 mg, 1.79 mmol) in a mixture of DMSO (20 mL), water (1 mL) and acetic acid (1 mL) was added NaCl (100 mg, 1.79 mmol). The reaction mixture was deoxygenated by bubbling excess of nitrogen gas for 12 h. Then it was heated at 210 °C for 2 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (25 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel (100–200 mesh) column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate (4:1) as an eluent gave compound **47b** as a white crystalline solid (429 mg, 72%). **Mp** 238–240 °C (ethyl acetate) (Lit.[27] 166–168 ºC). $[\alpha]^{20}_D$ +101.6 (c 1.0, $CHCl_3$), 98% ee by chiral HPLC; **IR** ($CHCl_3$) ν_{max} 3470, 1742, 1739, 1686 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 3.20 (ddd, J = 16, 8 and 2 Hz, 1H), 3.47 (td, J = 16 and 2 Hz, 1H), 3.72 (s, 3H), 5.78 (d, J = 6 Hz, 1H), 6.24 (s, 1H), 7.06–7.23 (m, 2H), 7.36 (dd, J = 8 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 7.51 (t, J = 8 and 2 Hz, 1H), 7.64 (dt, J = 8 and 2 Hz, 1H), 7.85 (d, J = 8 Hz, 1H), 7.92 (d, J = 8 Hz, 1H), 8.53 (bs, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ24.5, 50.3, 52.6, 55.5, 106.2, 111.2, 118.4, 119.8, 122.5, 122.7, 124.3, 126.4, 128.8, 129.3, 131.2, 132.4, 136.7, 143.6, 168.7, 171.6. **Anal. Calcd** for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.09; H, 4.68; N, 8.43. **HPLC details**. Column: chiralcel ODH (250 x 4.6 mm), mobile phase: isopropyl alcohol: Pet Ether (30:70), wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 11.2 min (+)-isomer, 12.7 min (–)-isomer.



(+)-**47b**: $C_{20}H_{16}N_2O_3$ (332.35)

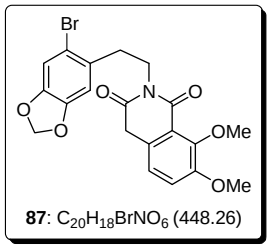
2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-7,8-dimethoxyisoquinoline-1,3(2*H*, 4*H*)-dione (81). A stirring solution of 3,4-dimethoxyhomophthalic anhydride[46] (**80**, 500 mg, 2.25 mmol) and homopiperonyl amine (**5**, 371 mg, 2.25 mmol) was refluxed in *o*-dichlorobenzene (10 mL) for 3 h. The reaction mixture was allowed to cool down to room temperature and then it was loaded on silica gel column. Initially the column was eluted with excess of petroleum ether for the removal of *o*-dichlorobenzene and then it was further eluted with petroleum ether–ethyl acetate mixture (6:4) to obtain pure compound **81** as a yellow solid (648 mg, 78%). **Mp**



81: $C_{20}H_{19}NO_6$ (369.36)

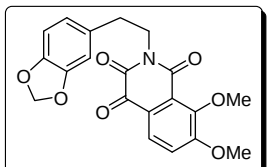
155–157 ºC. **IR** ($CHCl_3$) ν_{max} 1717, 1673 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.77–2.89 (m, 2H), 3.90 (s, 3H), 3.92 (br s, 2H), 3.94 (s, 3H), 4.07–4.18 (m, 2H), 5.92 (s, 2H), 6.74 (s, 2H), 6.82 (s, 1H), 6.97 (d, J = 8 Hz, 1H), 7.15 (d, J = 8 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 33.7, 36.1, 41.6, 56.2, 61.2, 100.7, 108.0, 109.3, 117.4, 119.3, 121.7, 122.6, 126.4, 132.3, 145.9, 147.4, 150.9, 152.9, 162.5, 169.6. **ESIMS** (m/z) 392 $[M + Na]^+$. **Anal. Calcd** for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79. Found C, 64.79; H, 4.97; N, 3.67.

2-(2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)ethyl)-7,8-dimethoxyisoquinoline-1,3(2*H*, 4*H*)-dione (87). It was obtained from 3,4-dimethoxyhomophthalic anhydride[46] (**80**, 1.00 g, 4.50 mmol) and *o*-bromohomopiperonyl amine (1.09 g, 4.50 mmol) using the same procedure as described above for **81**, as a yellow solid (1.69 g, 84%). **Mp** 172–174 ºC. **IR** ($CHCl_3$) ν_{max} 1717, 1673 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.00 (dd, J = 10 and 8 Hz, 2H), 3.90 (s, 3H), 3.91 (s, 2H), 3.92 (s, 3H), 4.18 (dd, J = 10 and 8 Hz, 2H), 5.94 (s, 2H), 6.82 (s, 1H), 6.96 (s, 1H), 6.96 (d, J = 8 Hz, 1H), 7.15 (d, J = 8 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 34.1, 36.3, 39.9, 56.4, 61.3, 101.6, 110.4, 112.6, 114.7, 117.6, 119.4, 122.7, 126.5, 131.4, 147.0, 147.3, 151.1, 153.0, 162.6, 169.7. **ESIMS** (*m*/*z*) 470 and 472 $[M + Na]^+$. **HRMS** (ESI) calcd for $C_{20}H_{19}BrNO_6$ 448.0396, found 448.0394.



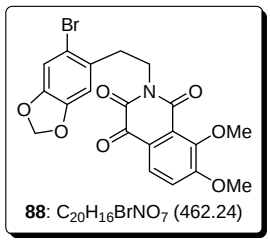
87: $C_{20}H_{18}BrNO_6$ (448.26)

2-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-7,8-dimethoxyisoquinoline-1,3,4(2 *H*)-trione (82). To a stirring solution of compound **81** (300 mg, 0.813 mmol) in DMSO (10 mL) at room temperature was bubbled excess of oxygen gas for 12 h and then it was further stirred for 12 h. To the formed yellow colored reaction mixture was added ethyl acetate (30 mL) and the combined organic layer was washed three times with brine (15 mL) to remove DMSO and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (1:1) as an eluent furnished compound **82** as a yellow solid (292 mg, 94%). **Mp** 186–188 ºC. **IR** ($CHCl_3$) ν_{max} 1681 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.85–2.92 (m, 2H), 3.97 (s, 3H), 4.04 (s, 3H), 4.17–4.24 (m, 2H), 5.93 (s, 2H), 6.72 (s, 2H), 6.83 (s, 1H), 7.29 (d, J = 8 Hz, 1H), 8.09 (d, J = 8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 33.7, 42.5, 56.6, 61.5, 100.9, 108.3, 109.4, 116.3, 121.9, 122.6, 123.9, 126.5, 131.8, 146.2, 147.7, 151.2, 157.1, 160.0, 161.1, 173.8. **ESIMS** (*m*/*z*) 406 $[M + Na]^+$. **HRMS** (ESI) calcd for $C_{20}H_{18}NO_7$ 384.1083, found 384.1083.



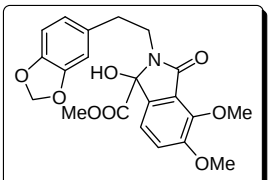
82: $C_{20}H_{17}NO_7$ (383.35)

2-(2-(6-Bromobenzo[*d*][1,3]dioxol-5-yl)ethyl)-7,8-dimethoxyisoquinoline-1,3,4(2*H*)-trione (88). It was obtained from compound **87** (200 mg, 0.446 mmol) by using the same procedure as described above for **82**, as a yellow solid (198 mg, 96%). **Mp** 192–194 ºC. **IR** ($CHCl_3$) ν_{max} 1727, 1685 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.97 (t, J = 8 Hz, 2H), 3.87 (s, 3H), 3.96 (s, 3H), 4.19 (t, J = 8 Hz, 2H), 5.87 (s, 2H), 6.75 (s, 1H), 6.88 (s, 1H), 7.22 (d, J = 8 Hz, 1H), 8.01 (d, J = 8 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 33.9, 40.7, 56.6, 61.4, 101.6, 110.4, 112.6, 114.6, 116.2, 122.5, 123.9, 126.4, 130.8, 147.2, 147.4, 151.1, 157.1, 159.9, 161.0, 173.7. **ESIMS** (m/z) 484 and 486 $[M + Na]^+$. **Anal. Calcd** for $C_{20}H_{16}BrNO_7$: C, 51.97; H, 3.49; N, 3.03. Found C, 52.05; H, 3.64; N, 3.32.



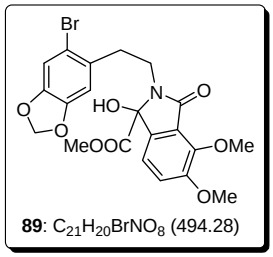
88: $C_{20}H_{16}BrNO_7$ (462.24)

Methyl 2-(2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)-1-hydroxy-4,5-dimethoxy-3-oxoisoindoline-1-carboxylate (83). *Method A*: To the solution of compound **81** (300 mg, 0.813 mmol) in mixture of DMSO (20 mL) and MeOH (5 mL) at room temperature was added Et_3N (0.50 mL) and to the reaction mixture was bubbled excess of oxygen gas for 6 h and then it was further stirred for 18 h. To the formed dark blue colored reaction mixture was added ethyl acetate (30 mL) and the combined organic layer was washed three times with brine (15 mL) to remove DMSO and then by 2 N HCl (10 mL), brine (15 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (4:6) as an eluent furnished compound **83** as a brown solid (317 mg, 94% yield). *Method B*: To the stirred solution of compound **82** (200 mg, 0.522 mmol) in MeOH (5 mL) was added catalytic amount of Et_3N (1 drop) at room temperature and the reaction mixture was stirred for 3 h. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (4:6) as an eluent furnished compound **83** as a brown solid (208 mg, 96%). **Mp** 138–140 ºC. **IR** ($CHCl_3$) ν_{max} 3501, 1737, 1705 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.74–3.01 (m, 2H), 3.20–3.38 (m, 1H), 3.61–3.79 (m, 1H), 3.72 (s, 3H), 3.88 (s, 3H), 4.09 (s, 3H), 4.65 (br s, 1H), 5.92 (s, 2H), 6.68–6.78 (m, 3H), 7.04 (d, J = 8 Hz, 1H), 7.12 (d, J = 8 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 34.3, 41.9, 53.8, 56.3, 62.3, 87.4, 100.7, 108.1, 109.1, 116.0, 117.1, 121.5, 122.8, 132.6, 136.0, 145.9, 146.5, 147.5, 154.0, 165.8, 171.1. **ESIMS** (m/z) 438 $[M + Na]^+$. **HRMS** (ESI) calcd for $C_{21}H_{22}NO_8$ 416.1345, found 416.1343.



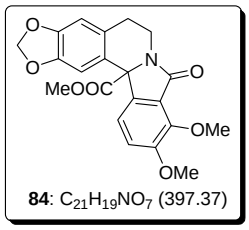
83: $C_{21}H_{21}NO_8$ (415.39)

Methyl 2-(2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)ethyl)-1-hydroxy-4,5-dimethoxy-3-oxoisoindoline-1-carboxylate (89). *Method A*: It was obtained from compound **87** (1.40 g, 3.12 mmol) by using the same procedure as described above for **83**, as a brown solid (1.46 g, 95% yield). *Method B*: It was obtained from compound **88** (150 mg, 0.324 mmol) by using the same procedure as described above for **83**, above as a brown solid (152 mg, 95%). **Mp** 178–180 ºC. **IR** ($CHCl_3$) ν_{max} 3503, 1737, 1706 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.85–3.19 (m, 2H), 3.23–3.41 (m, 1H), 3.59–3.74 (m, 1H), 3.76 (s, 3H), 3.90 (s, 3H), 4.12 (s, 3H), 4.61 (br s, 1H), 5.95 (s, 2H), 6.84 (s, 1H), 6.99 (s, 1H), 7.09 (br s, 2H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ 34.9, 39.9, 54.2, 56.5, 62.5, 87.3, 101.6, 110.5, 112.7, 114.5, 116.1, 117.0, 123.0, 131.7, 136.0, 146.9, 147.1, 147.4, 154.3, 166.0, 171.8. **ESIMS** (*m*/*z*) 516 and 518 $[M + Na]^+$. **Anal. Calcd** for $C_{21}H_{20}BrNO_8$: C, 51.03; H, 4.08; N, 2.83. Found C, 50.64; H, 3.87; N, 2.48.



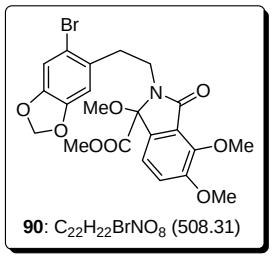
89: $C_{21}H_{20}BrNO_8$ (494.28)

Methyl 9,10-dimethoxy-8-oxo-5,6,8,12*b*-tetrahydro-[1,3]dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinoline-12*b*-carboxylate (84). The solution of compound **83** (900 mg, 2.16 mmol) in TFA (10 mL) was stirred at room temperature for 2 h. To the reaction mixture was added ethyl acetate (60 mL) and organic layer was washed with 5% aqueous solution of $NaHCO_3$, water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (1:1) as an eluent gave compound **84** as a crystalline solid (700 mg, 81% yield). Thick oil; **IR** ($CHCl_3$) ν_{max} 1737, 1694 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.67–3.08 (m, 2H), 3.52–3.71 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3 H), 4.06 (s, 3H), 4.31–4.45 (m, 1H), 5.91 (d, J = 2 Hz, 1H), 5.96 (d, J = 2 Hz, 1H), 6.60 (s, 1H), 7.15 (d, J = 8 Hz, 1H), 7.39 (s, 1H), 7.68 (d, J = 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 28.5, 36.9, 53.3, 56.6, 62.5, 68.1, 101.2, 107.3, 108.7, 116.1, 119.4, 123.9, 126.9, 128.5, 136.3, 146.4, 147.0, 147.5, 153.5, 165.7, 170.5; **Anal. Calcd** for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.81; H, 5.18; N, 3.20.



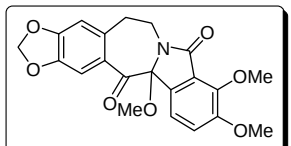
84: $C_{21}H_{19}NO_7$ (397.37)

Methyl 2-(2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)ethyl)-1,4,5-trimethoxy-3-oxoisoindoline-1-carboxylate (90). To a stirring solution of compound **89** (1.00 g, 2.02 mmol) in methanol (30 mL) was added conc. H_2SO_4 (2 mL) in a drop-wise fashion at 0 °C. The reaction mixture was stirred for 8 h at room temperature and then methanol was distilled off under the reduced pressure. The obtained residue was dissolved in ethyl acetate (60 mL) and the organic layer was washed with saturated aq. $NaHCO_3$ (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (1:1) as an eluent furnished compound **90** as a off-white solid (1.00 g, 98%). **Mp** 124–126 ºC. **IR** ($CHCl_3$) ν_{max} 1753, 1706 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.95 (s, 3H), 3.00–3.22 (m, 2H), 3.30–3.69 (m, 2H), 3.76 (s, 3H), 3.91 (s, 3H), 4.13 (s, 3H), 5.95 (s, 2H), 6.87 (s, 1H), 6.99 (s, 1H), 7.09 (d, J = 8 Hz, 1H), 7.19 (d, J = 8 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 34.1, 40.6, 50.4, 53.4, 56.5, 62.5, 92.6, 101.6, 110.5, 112.7, 114.5, 116.0, 118.0, 124.0, 131.3, 132.2, 147.1, 147.2, 147.5, 154.5, 166.6, 168.2. **ESIMS** (*m*/*z*) 530 and 532 $[M + Na]^+$. **HRMS** (ESI) calcd for $C_{22}H_{22}BrNO_8$ 508.0607, found 508.0630.



90: $C_{22}H_{22}BrNO_8$ (508.31)

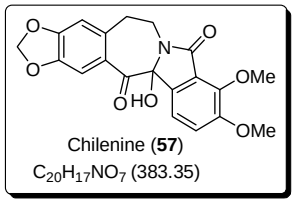
9,10,12*b*-Trimethoxy-5*H*-[1,3]dioxolo 4'',5'':4',5']benzo 1',2':4,5] zepino[2,1-*a*]isoindole-8,13(6*H*,12*bH*)-dione (91). To a stirring solution of compound **90** (500 mg, 0.984 mmol) in THF plus HMPA mixture (15 mL, 4:1) was added *t*-BuLi (0.90 mL, 1.18 mmol, 1.30 M) at –78 °C in a drop-wise fashion. The reaction mixture was further stirred for 30 min at the same temperature and then it was allowed to reach room temperature. The reaction was quenched by adding few drops of saturated aq. NH_4Cl. After removal of THF in vacuo, ethyl acetate (50 mL) was added to the reaction mixture and the organic layer was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (6:4) as an eluent furnished compound **91** as a off-white solid (0.32 g, 82%). **Mp** 150–152 ºC. [Lit.[42(o)] 146–147 ºC]. **IR** ($CHCl_3$) ν_{max} 1701, 1685 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 2.80–3.00 (m, 1H), 3.06 (s, 3H), 3.36–3.60 (m, 2H), 3.91 (s, 3H), 4.03 (s, 3H), 4.14–4.40 (m, 1H), 5.97 (s, 2H), 6.67 (s, 1H), 6.82 (s, 1H), 7.13 (d, J = 8 Hz, 1H), 7.51 (d, J = 8 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 30.5, 38.7, 51.1, 56.4, 62.3, 94.7, 101.8, 109.0, 109.2, 116.2,



91: $C_{21}H_{19}NO_7$ (397.37)

120.4, 123.9, 130.5, 131.6, 133.5, 146.6, 146.9, 151.4, 154.3, 166.4, 199.4. **ESIMS** (*m*/*z*) 420 $[M + Na]^+$.

12*b*-Hydroxy-9,10-dimethoxy-5*H*-[1,3]dioxolo[4'',5'':4',5']benzo[1',2':4, 5]azepino [2,1-*a*]isoindole-8,13(6*H*,12*bH*)-dione (Chilenine, 57). *Method A*: To a stirring solution of compound **89** (200 mg, 0.40 mmol) in THF plus HMPA mixture (10 mL, 4:1) was added *t*-BuLi

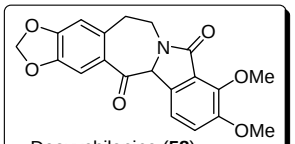


Chilenine (**57**)
$C_{20}H_{17}NO_7$ (383.35)

(0.68 mL, 0.89 mmol, 1.30 M) at –78 °C in a drop-wise fashion. The reaction mixture was further stirred for 30 min at the same temperature and then allowed to warm to room temperature. The reaction was quenched by adding few drops of saturated aq. NH_4Cl. After removing THF in vacuo, ethyl acetate (30 mL) was added to the reaction mixture and the organic layer was further washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (4:6) as an eluent furnished compound **57** as a faint yellow solid (78 mg, 50% yield). *Method B*: The compound **91** (100 mg, 0.25 mmol) was stirred in 50% aqueous TFA (4 mL) at room temperature for 2 h. After quenching the reaction by saturated aq. $NaHCO_3$ it was extracted to ethyl acetate (20 mL) and the organic layer was washed with brine (10 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (4:6) as an eluent furnished compound **57** as a faint yellow solid (97 mg, 100%). **Mp** 115–116 ºC [Lit.[42n] 114–116 ºC]. **IR** ($CHCl_3$) ν_{max} 3402, 1704 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.04 (ddd, J = 15, 6 and 4 Hz, 1H), 3.38 (ddd, J = 14, 11 and 6 Hz, 1H), 3.59 (ddd, J = 14, 6 and 4 Hz, 1H), 3.84 (s, 3H), 3.95 (s, 3H), 4.18 (ddd, J = 14, 10 and 4 Hz, 1H), 4.56 (br s, 1H), 5.94 (d, J = 2 Hz, 1H), 5.96 (d, J = 2 Hz, 1H), 6.66 (s, 1H), 6.74 (s, 1H), 7.01 (d, J = 10 Hz, 1H), 7.40 (d, J = 8 Hz, 1H). **^{13}C NMR** (50 MHz, $CDCl_3$) δ 31.0, 37.8, 56.4, 62.3, 90.4, 101.8, 108.6, 109.5, 116.3, 119.2, 122.6, 129.8, 133.7, 135.6, 146.0, 146.8, 151.4, 154.0, 166.1, 202.4. **ESIMS** (*m*/*z*) 406 $[M + Na]^+$.

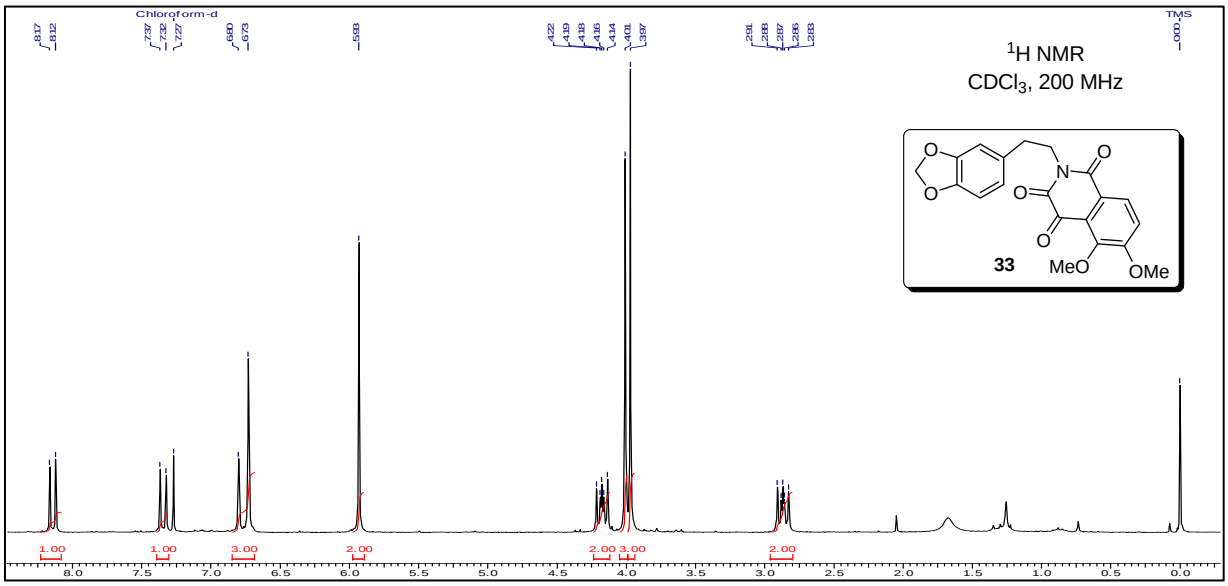
9,10-Dimethoxy-5*H*-[1,3]dioxolo[4'',5'':4',5']benzo [1',2':4,5] azepino [2,1-*a*]isoindole-8,13(6*H*,12*bH*)-dione (Deoxychilenine, 58). To a stirring solution of compound **91** (100 mg, 0.25 mmol) and Et_3SiH (0.12 mL, 0.75 mmol) in DCM (5 mL) was added $BF_3.OEt_2$ (0.10 mL) at –10 °C in a drop-wise fashion. The reaction mixture was further stirred for 20 min at the same temperature and then quenched by adding few drops of saturated aq. $NaHCO_3$. Ethyl acetate (20 mL) was added to the reaction mixture and the organic layer was washed with water (10 mL),

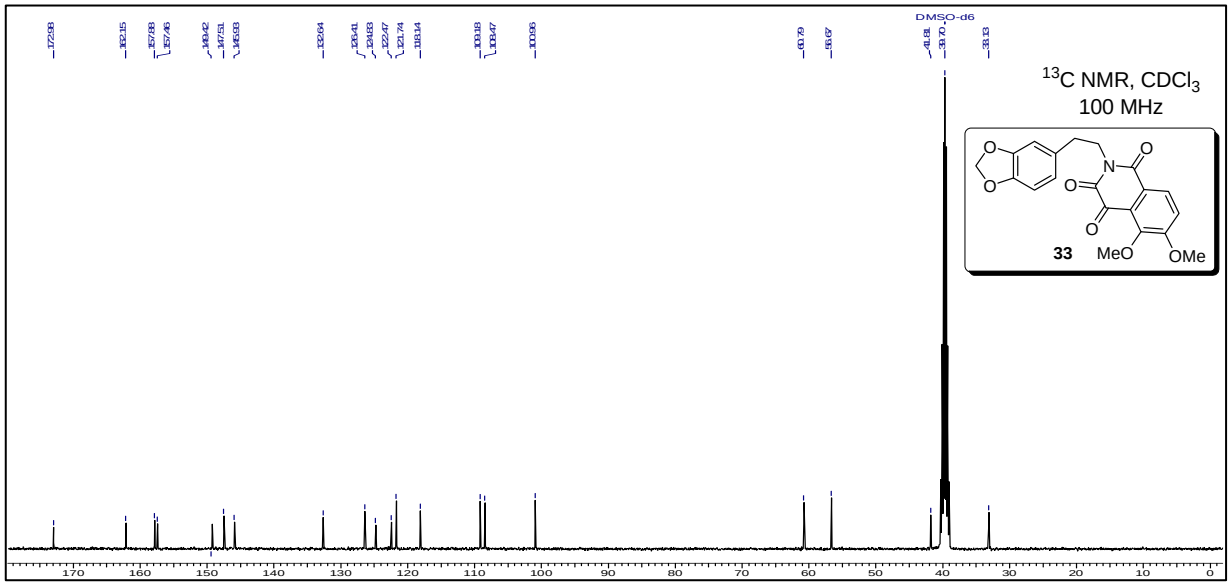
brine (10 mL) and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue using petroleum ether–ethyl acetate mixture (4:6) as an eluent furnished compound **58** as a white solid (89 mg, 96%). **Mp** 155 ºC. [Lit.[42c] 156–157 ºC]. **IR** ($CHCl_3$) ν_{max} 1694, 1613 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) δ 3.01 (ddd, J = 15, 4 and 2 Hz, 1H), 3.25 (dt, J = 14 and 4 Hz, 1H), 3.59 (ddd, J = 14, 6 and 2 Hz, 1H), 3.90 (s, 3H), 4.02 (s, 3H), 4.27 (dt, J = 14 and 4 Hz, 1H), 5.15 (s, 1H, not exchangeable with D_2O), 6.00 (d, J = 2 Hz, 2H), 6.71 (s, 1H), 6.90 (s, 1H), 7.18 (d, J = 8 Hz, 1H), 7.58 (d, J = 8 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 31.5, 41.3, 56.6, 62.5, 65.9, 101.9, 108.6, 109.3, 116.5, 120.1, 124.1, 31.2, 132.3, 133.8, 146.5, 147.2, 151.6, 153.1, 167.4, 201.0. **ESIMS** (m/z) 390 $[M + Na]^+$.

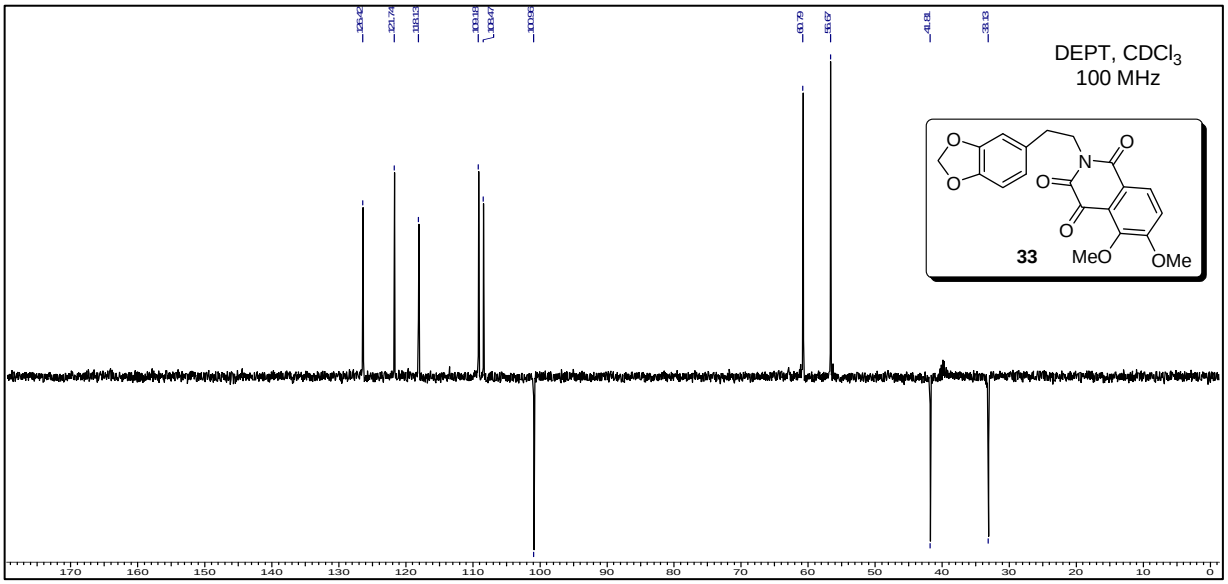


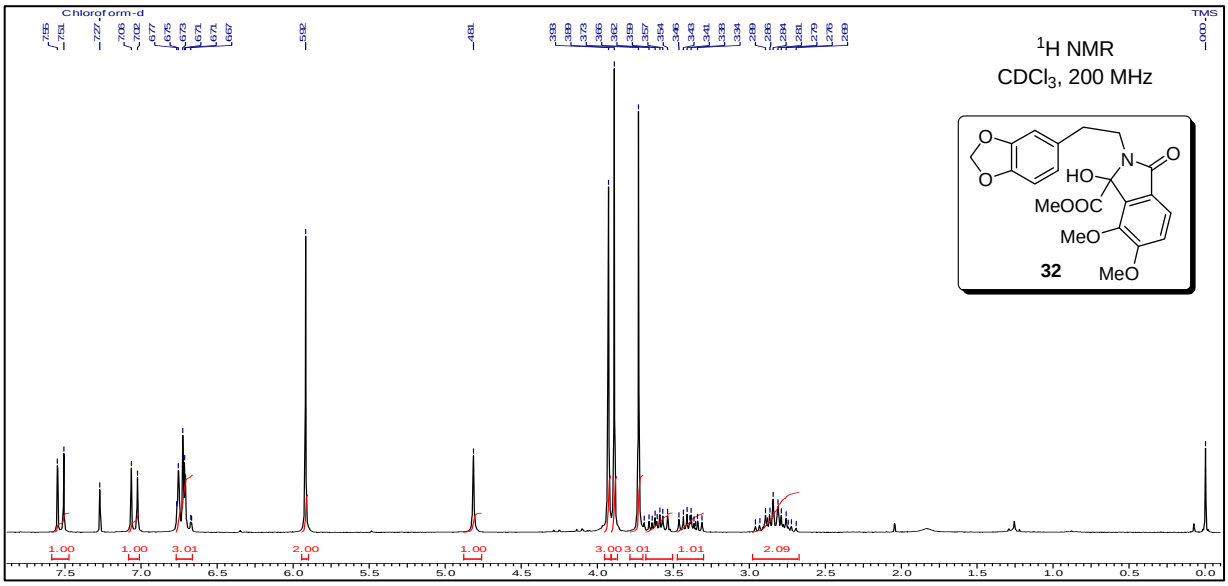
Deoxychilenine (**58**)
$C_{20}H_{17}NO_6$ (367.35)

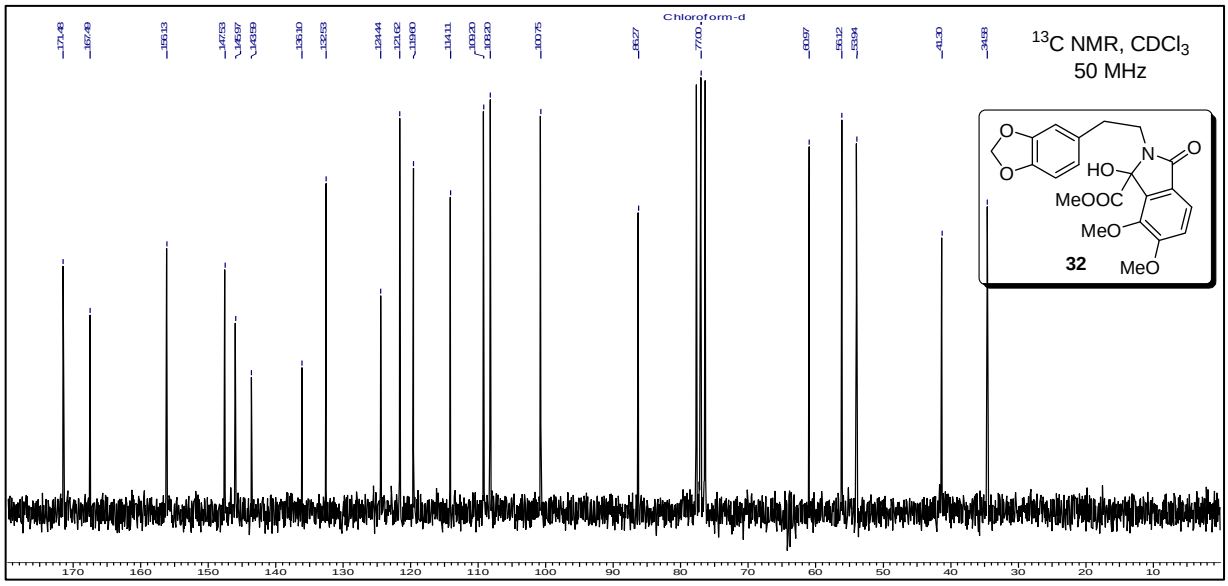
2B.6 Selected spectra

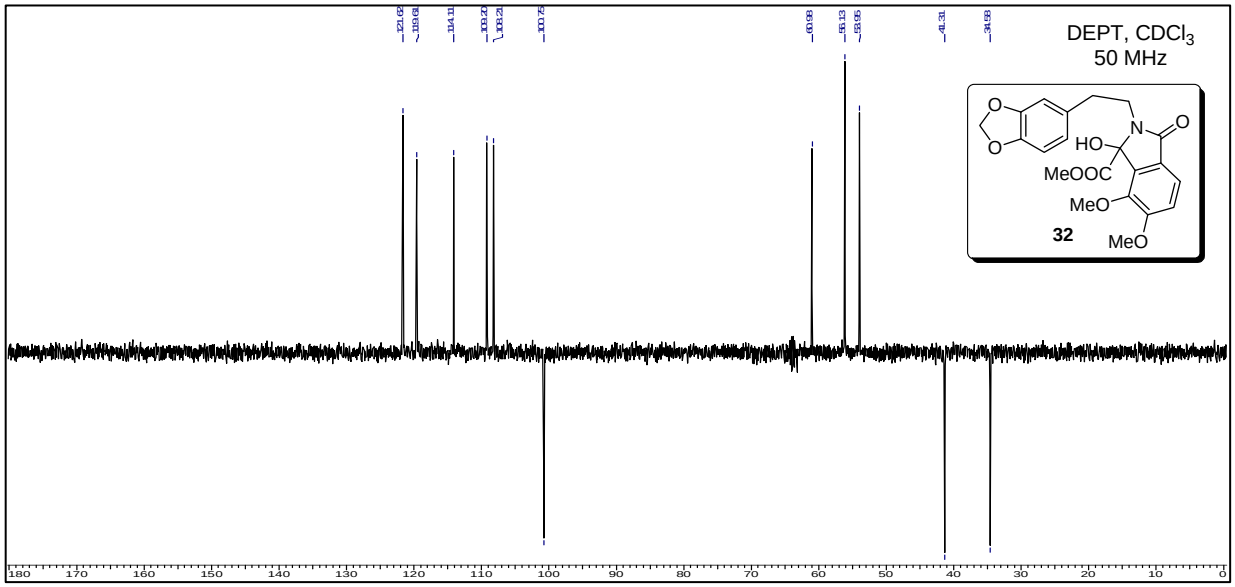

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
33
MeO
OMe

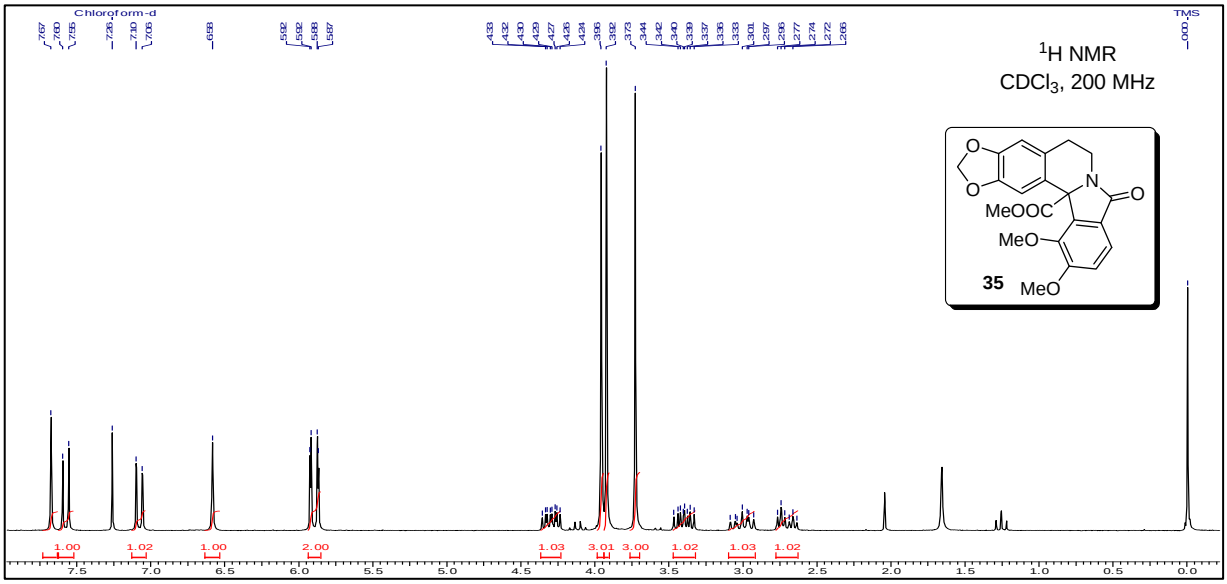

DMSO-d6
^{13}C NMR, $CDCl_3$
100 MHz
33
MeO
OMe

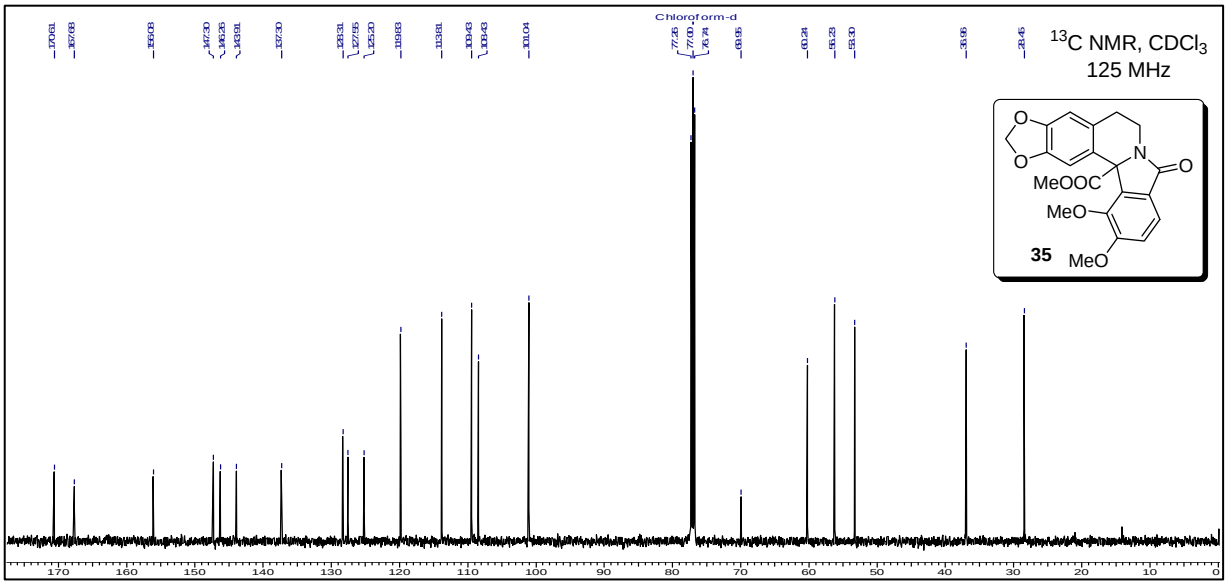

DEPT, $CDCl_3$
100 MHz
33
MeO
OMe

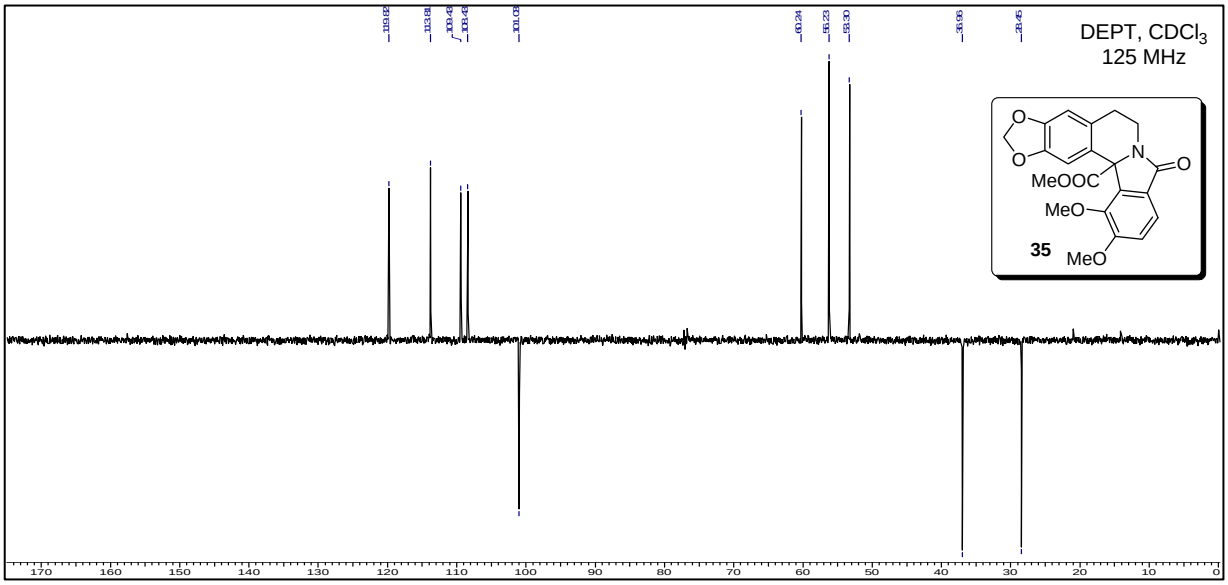

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
HO
MeOOC
MeO
MeO
32

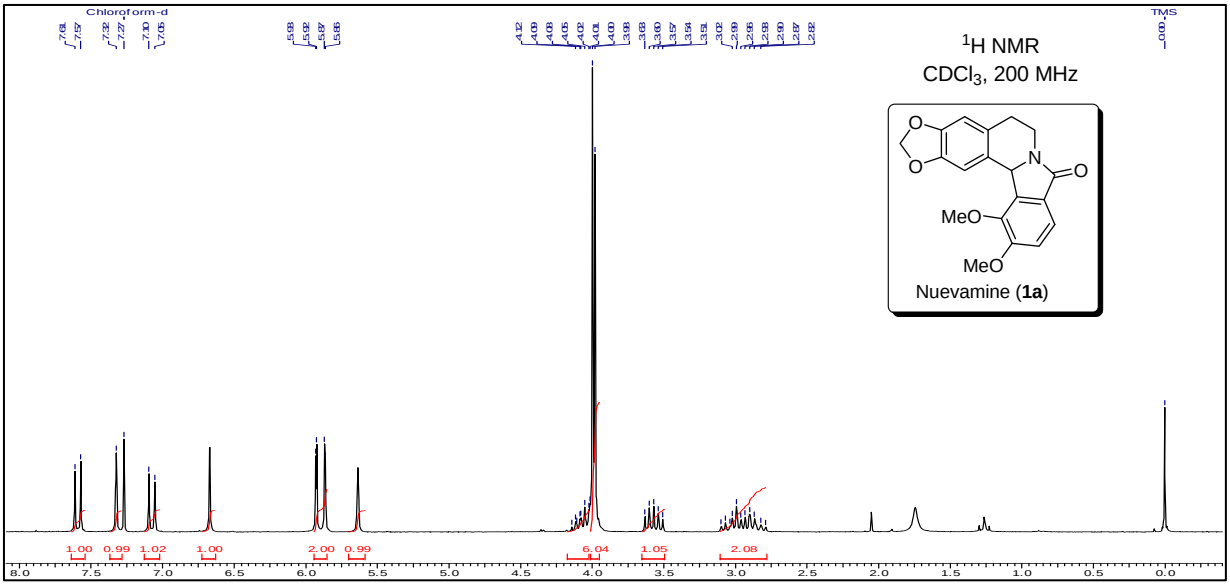

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
HO
MeOOC
MeO
MeO
32

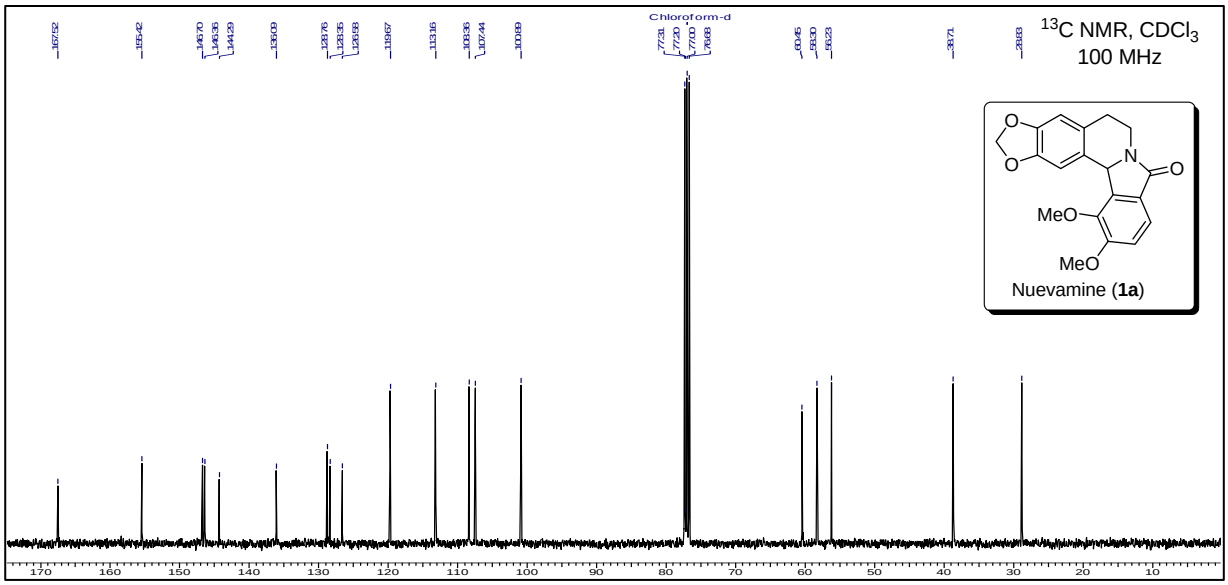

DEPT, $CDCl_3$
50 MHz
HO
MeOOC
MeO
MeO
32

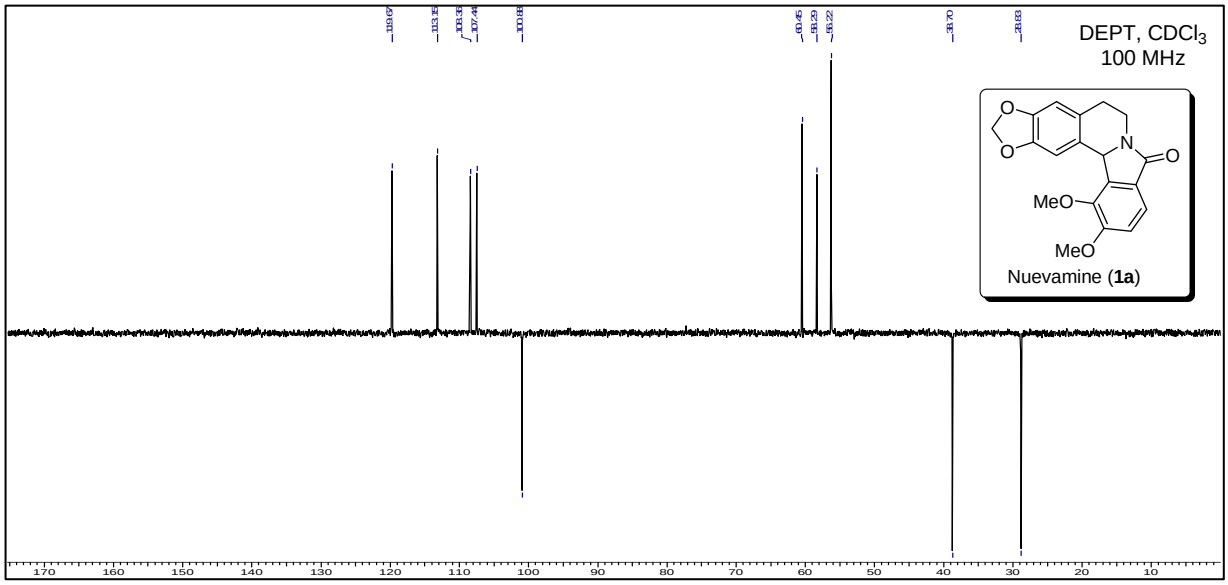

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
MeOOC
MeO
35
MeO

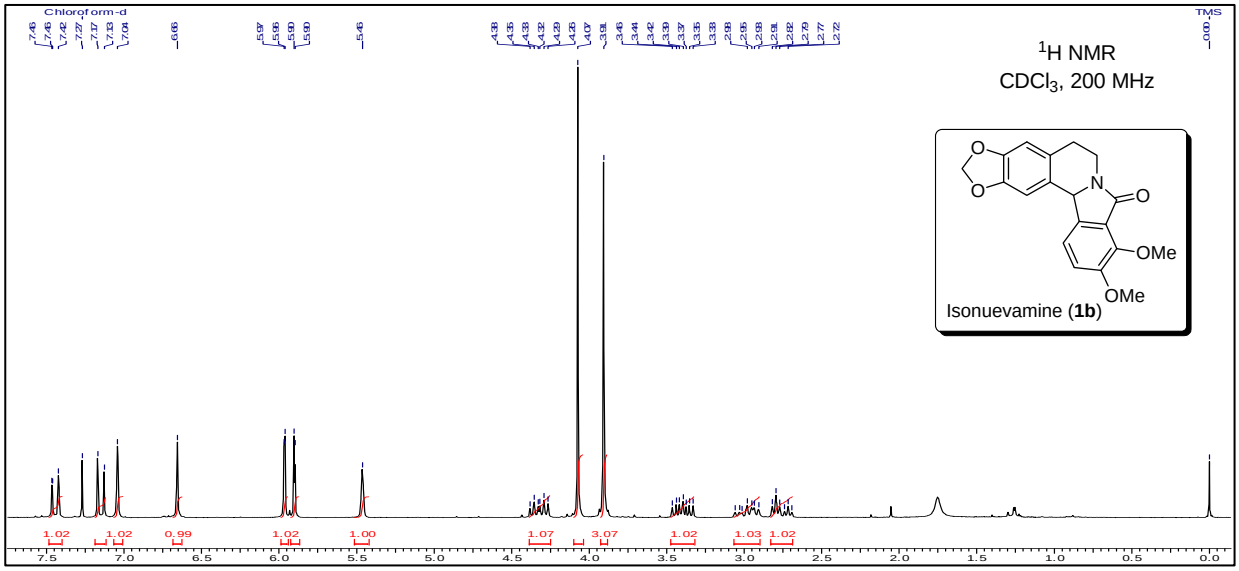

Chloroform-d
^{13}C NMR, $CDCl_3$
125 MHz
MeOOC
MeO
35
MeO

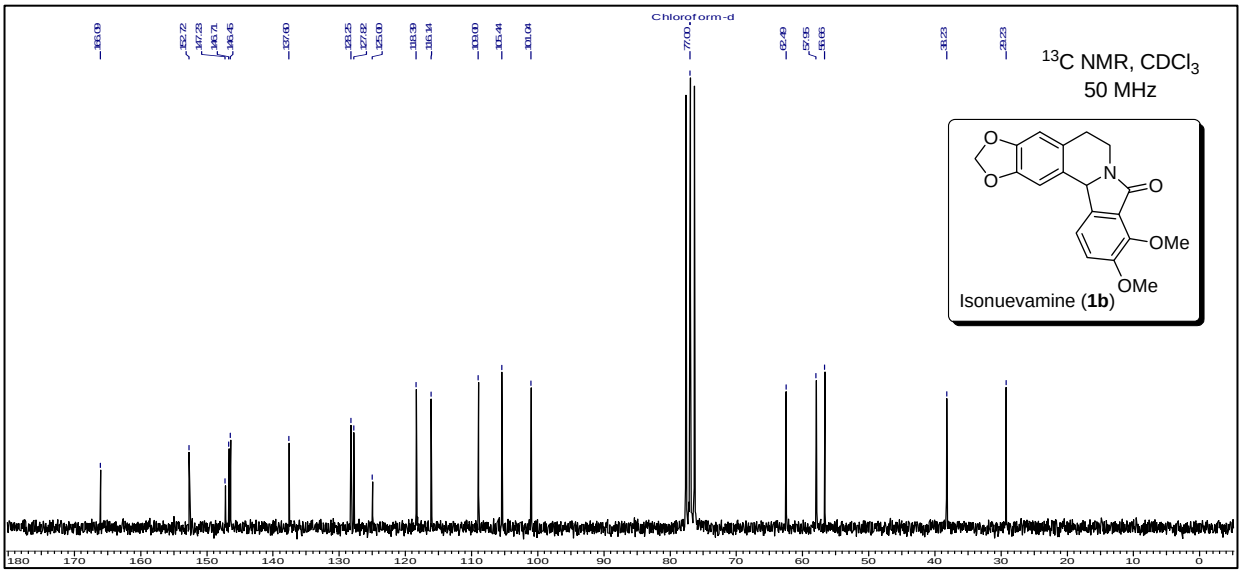

DEPT, $CDCl_3$
125 MHz
MeOOC
MeO
35
MeO

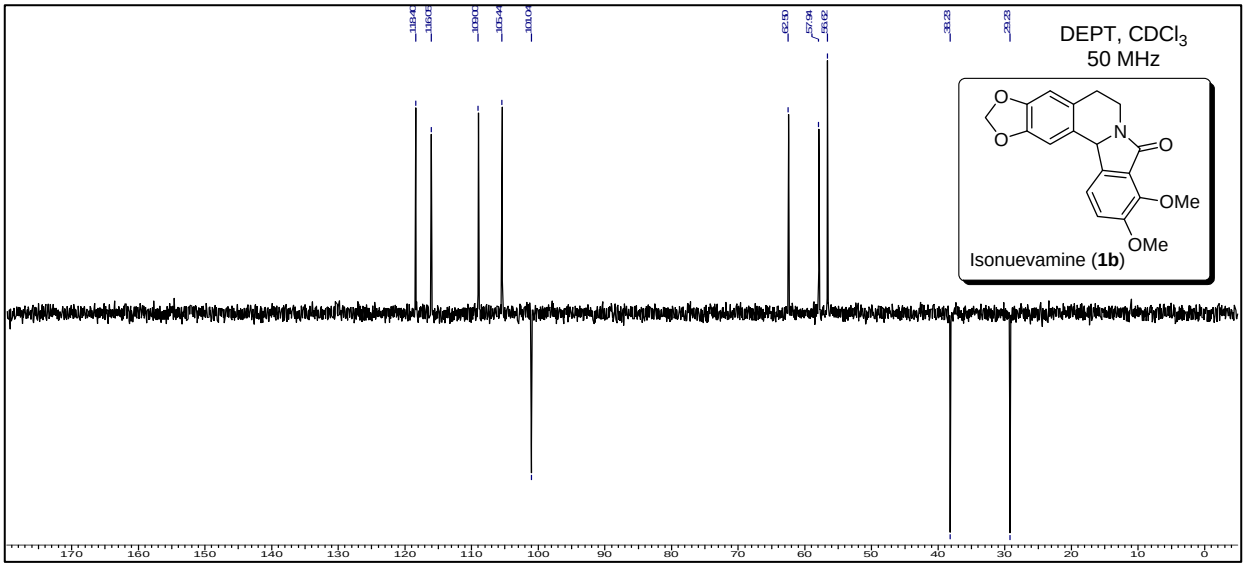

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
O
O
N
O
MeO
MeO
Nuevamine (**1a**)
1.00 0.99 1.02 1.00 2.00 0.99 6.04 1.05 2.08

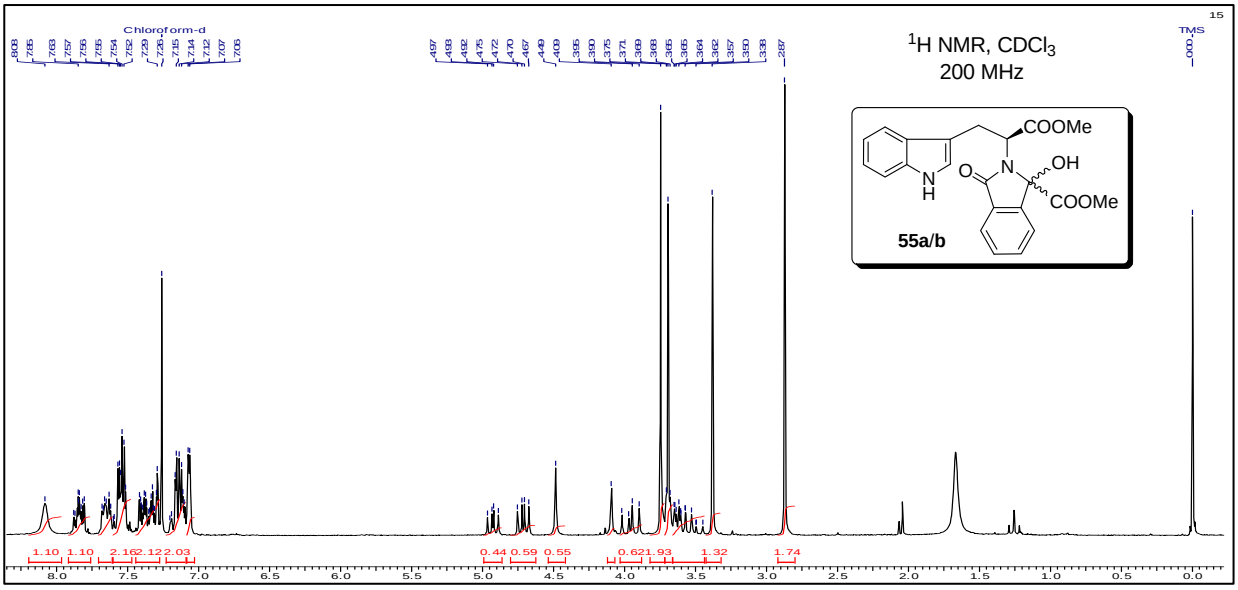

Chloroform-d
^{13}C NMR, $CDCl_3$
100 MHz
O
O
N
O
MeO
MeO
Nuevamine (**1a**)

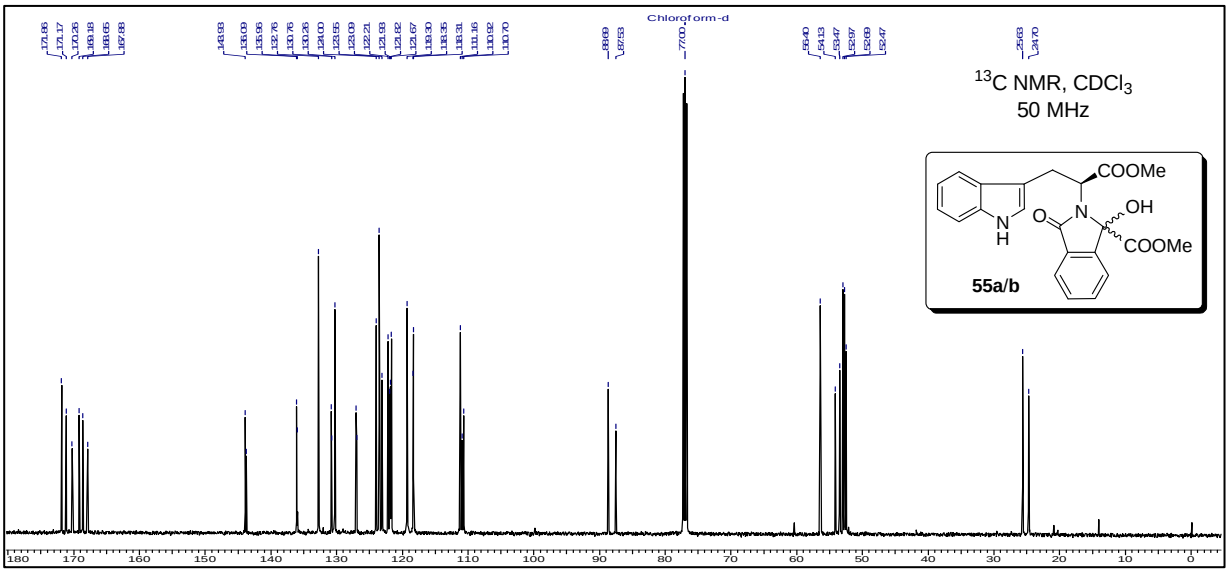

DEPT, $CDCl_3$
100 MHz
O
O
N
O
MeO
MeO
Nuevamine (**1a**)

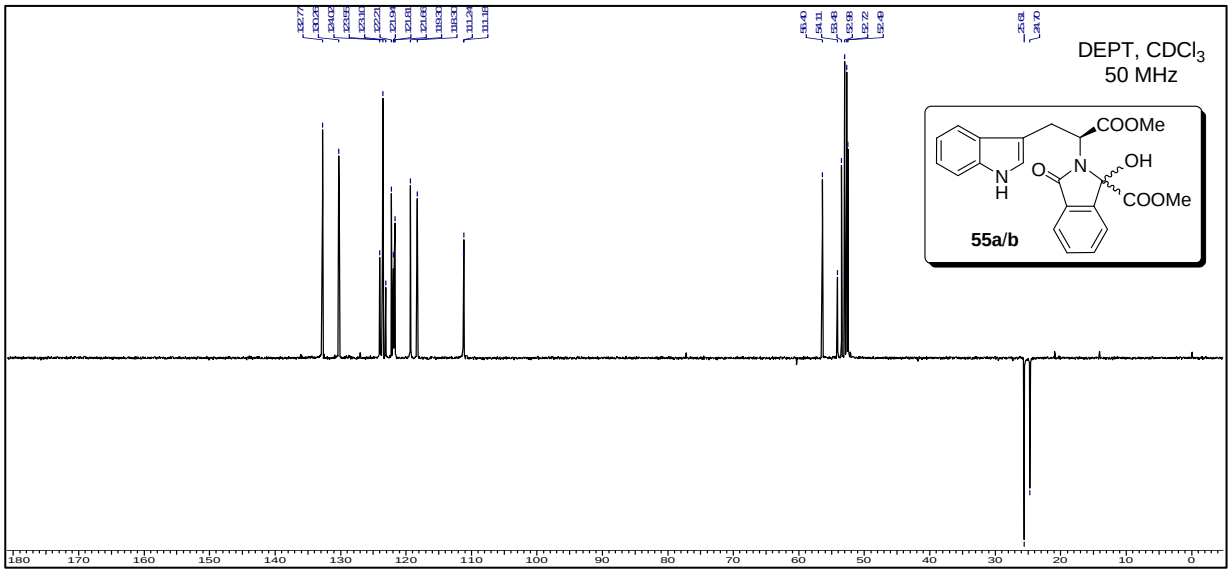

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
Isonuevamine (**1b**)

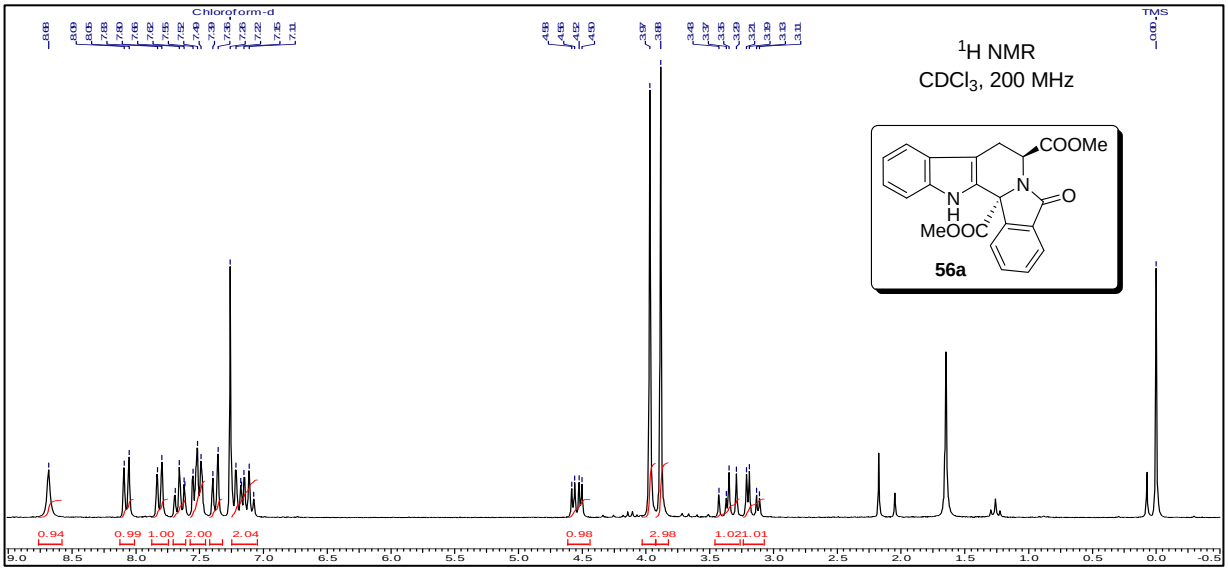

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
Isonuevamine (**1b**)

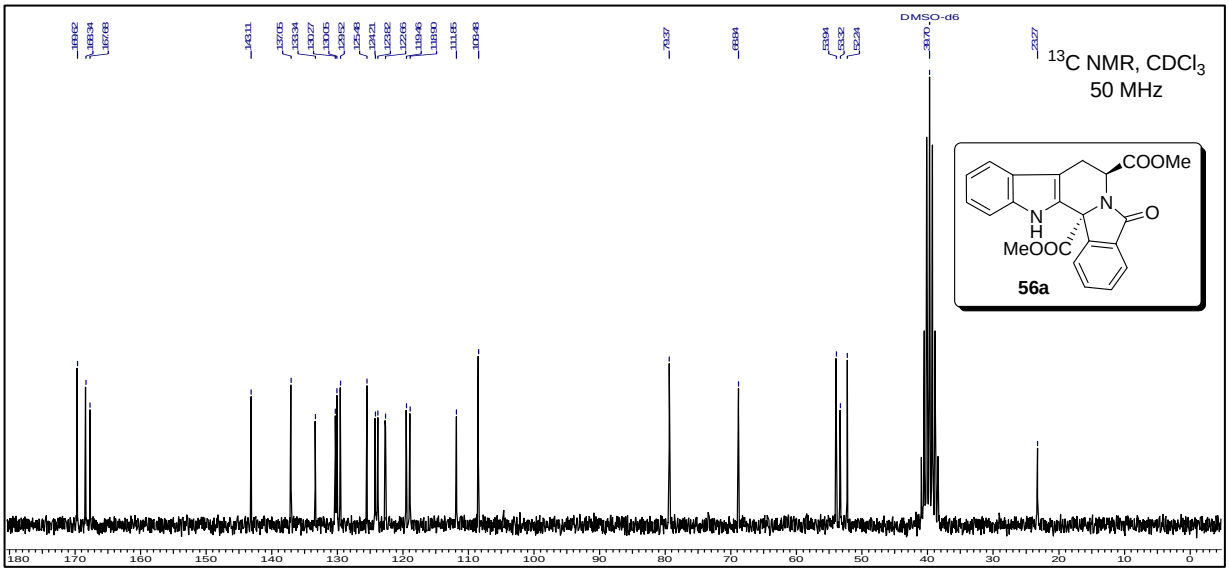

DEPT, $CDCl_3$
50 MHz
Isonuevamine (**1b**)

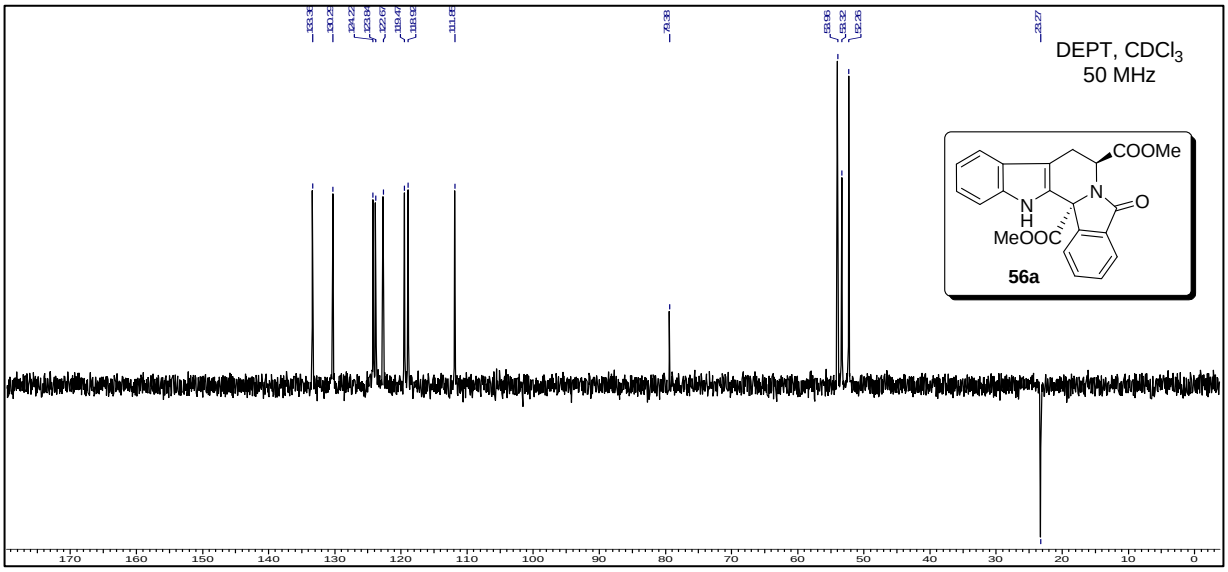

Chloroform-d
TMS
^{1}H NMR, CDCl$_3$
200 MHz
COOMe
OH
COOMe
55a/b

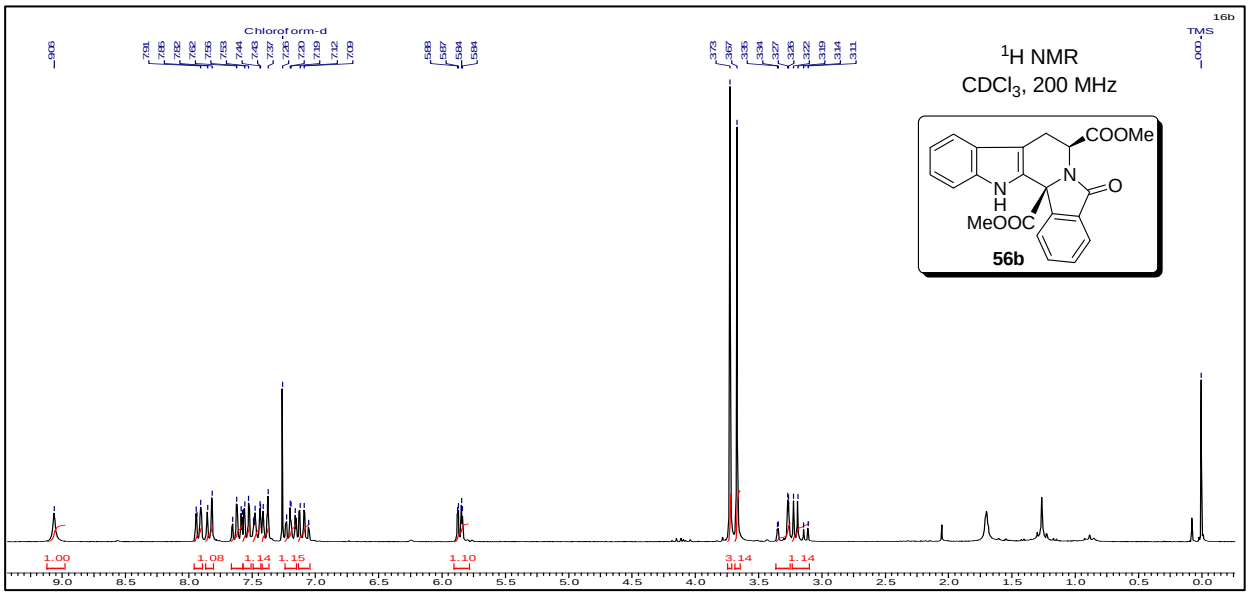

Chloroform-d
^{13}C NMR, CDCl$_3$
50 MHz
COOMe
OH
COOMe
55a/b

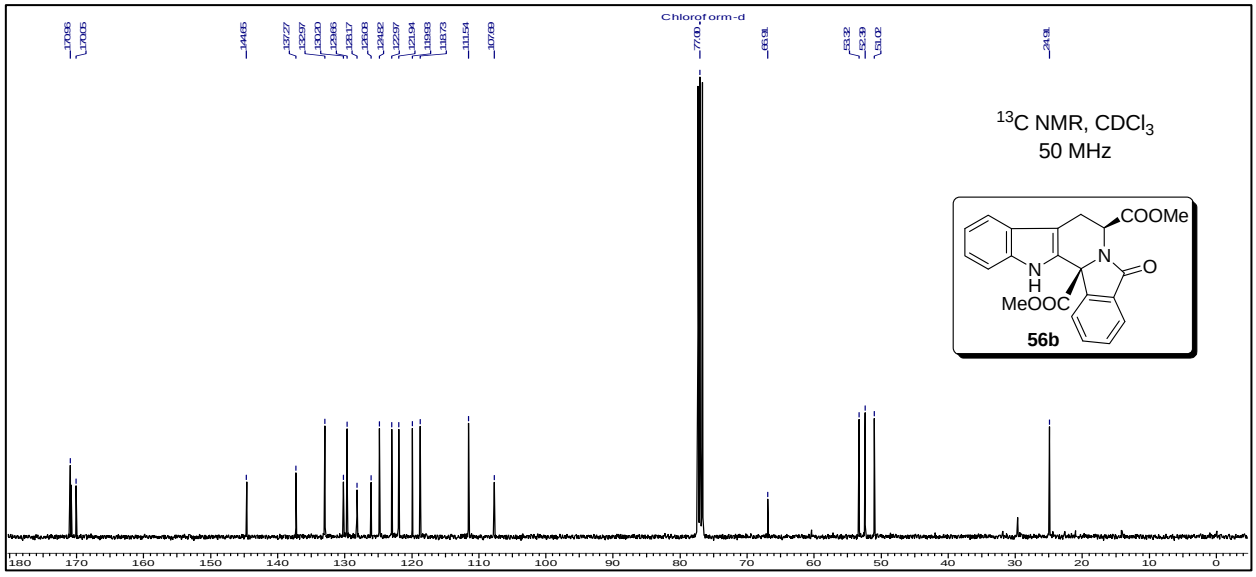

DEPT, CDCl$_3$
50 MHz
COOMe
OH
COOMe
55a/b

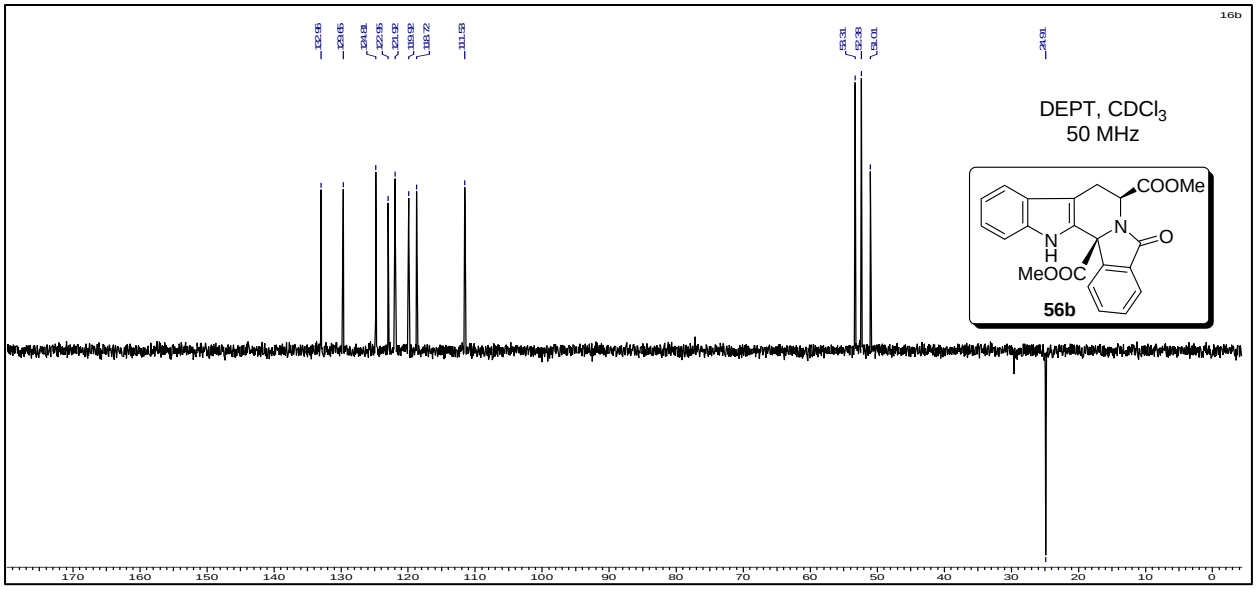

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
COOMe
N
H
MeOOC
N
O
56a
0.94
0.99
1.00
2.00
2.04
0.98
2.98
1.021.01

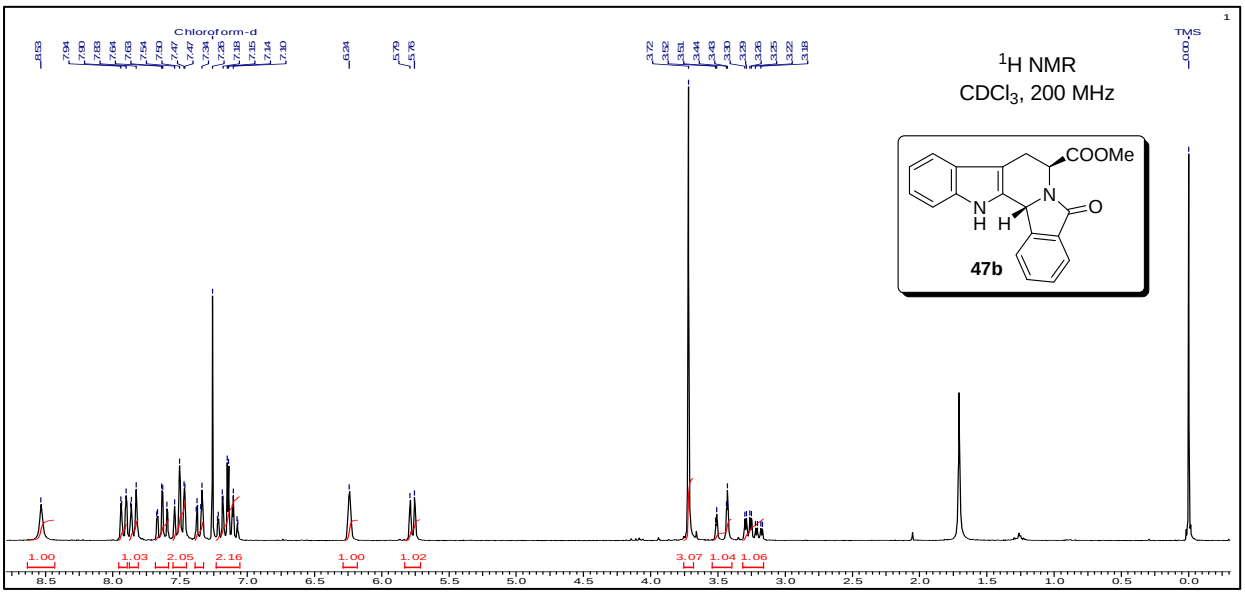

DMSO-d6
^{13}C NMR, $CDCl_3$
50 MHz
COOMe
N
H
MeOOC
N
O
56a

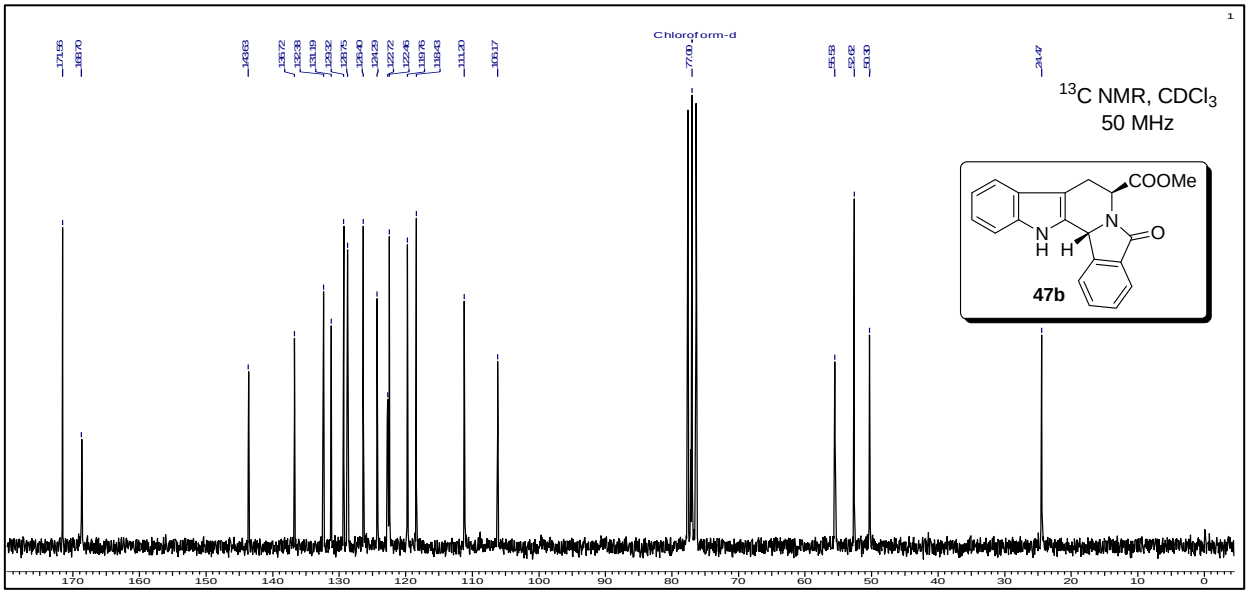

DEPT, $CDCl_3$
50 MHz
COOMe
N
H
MeOOC
N
O
56a

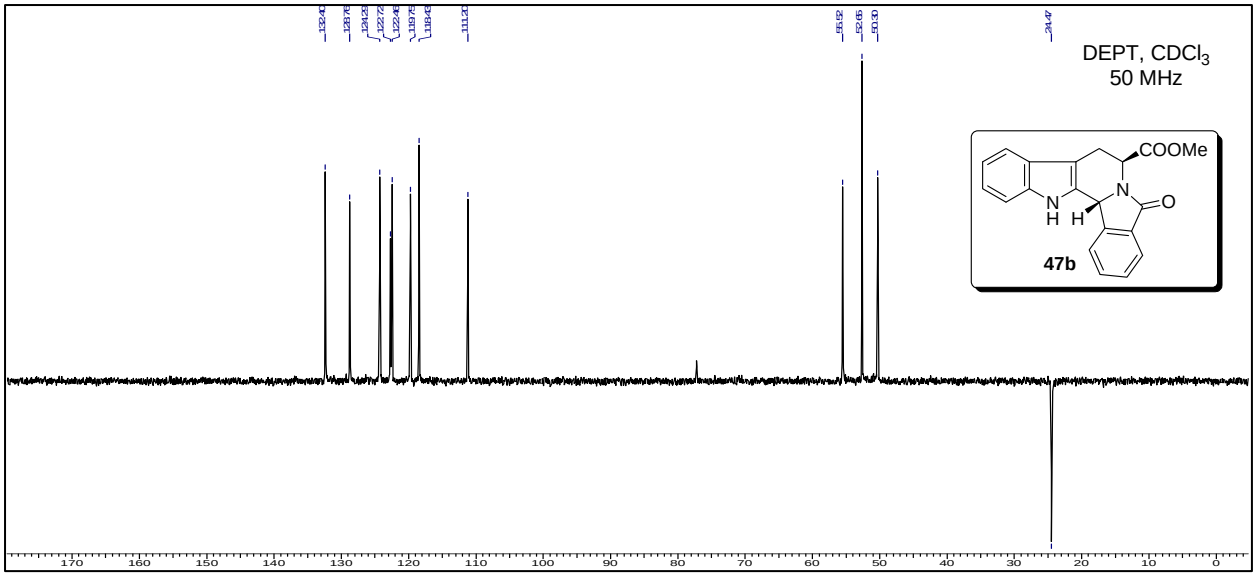

16b
Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
COOMe
N
H
MeOOC
N
O
56b

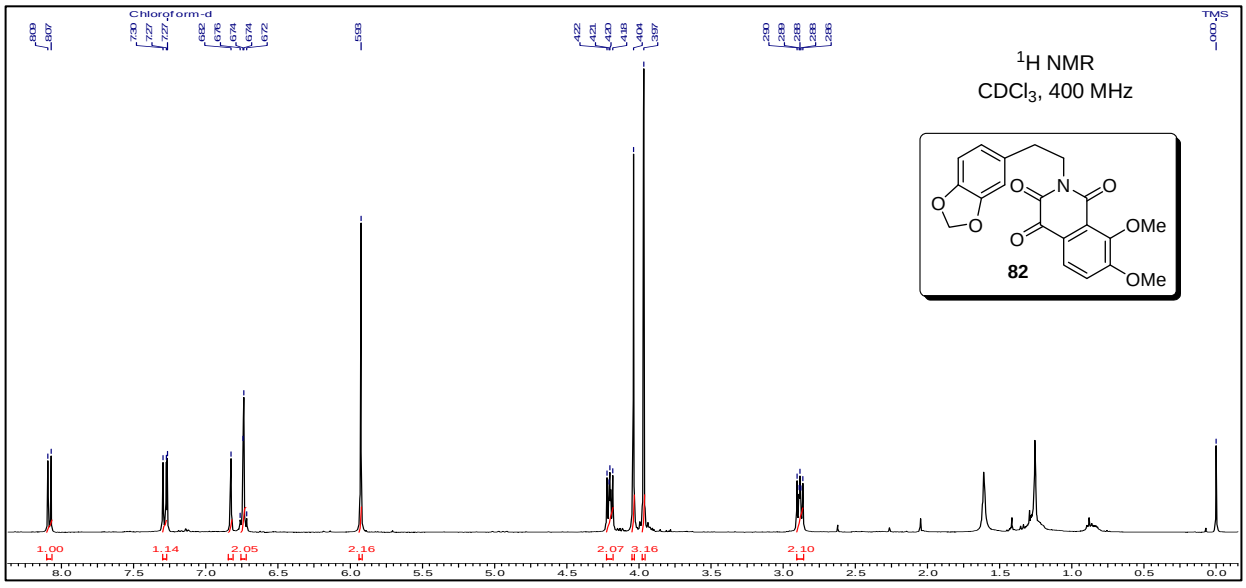

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
COOMe
N
H
MeOOC
N
O
56b

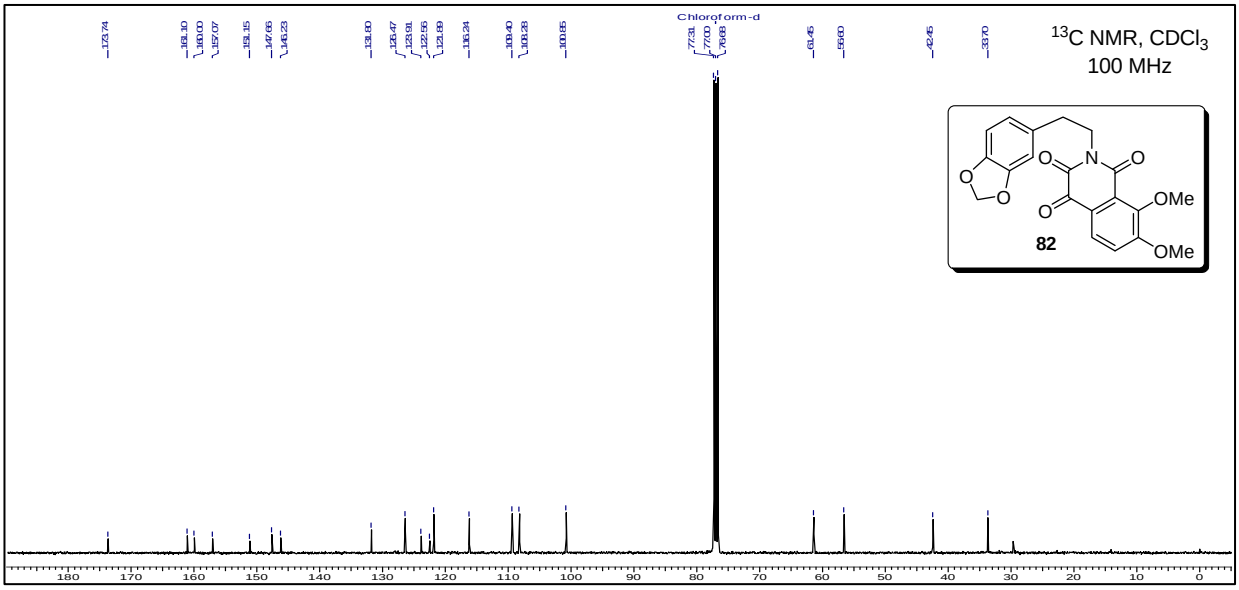

16b
DEPT, $CDCl_3$
50 MHz
COOMe
N
H
MeOOC
N
O
56b

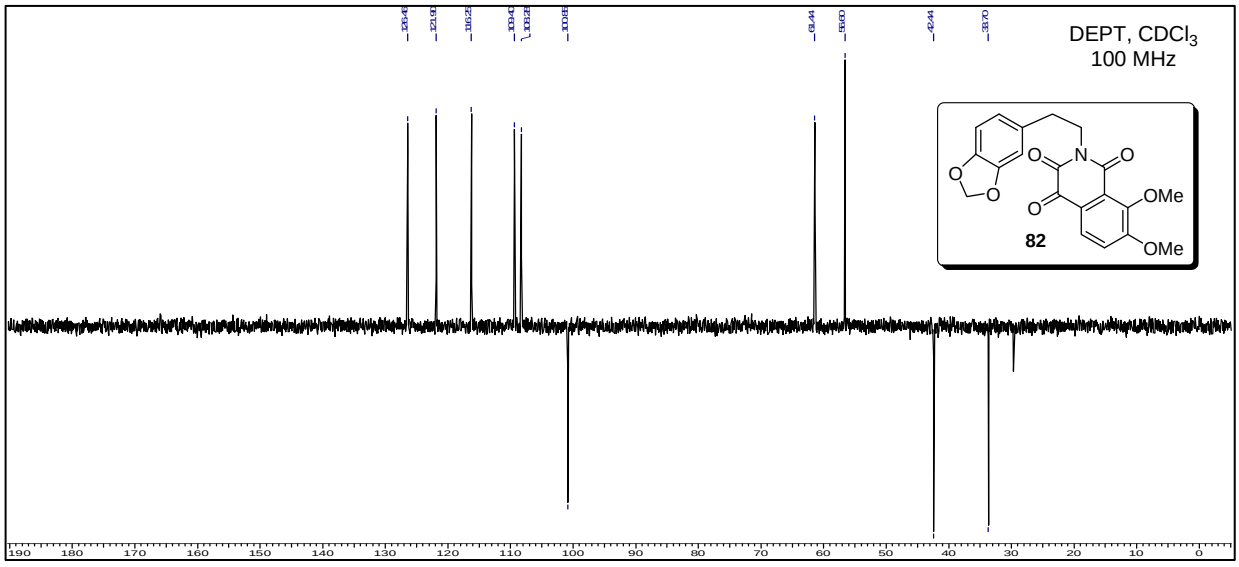

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
COOMe
N
H H
O
47b

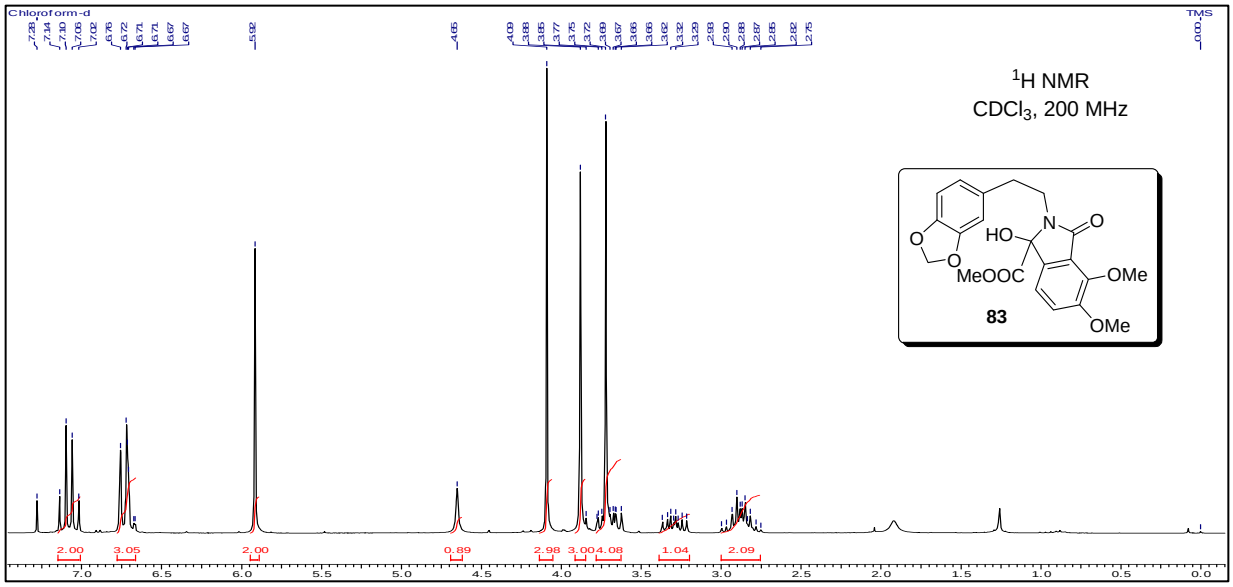

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
COOMe
N
H H
O
47b

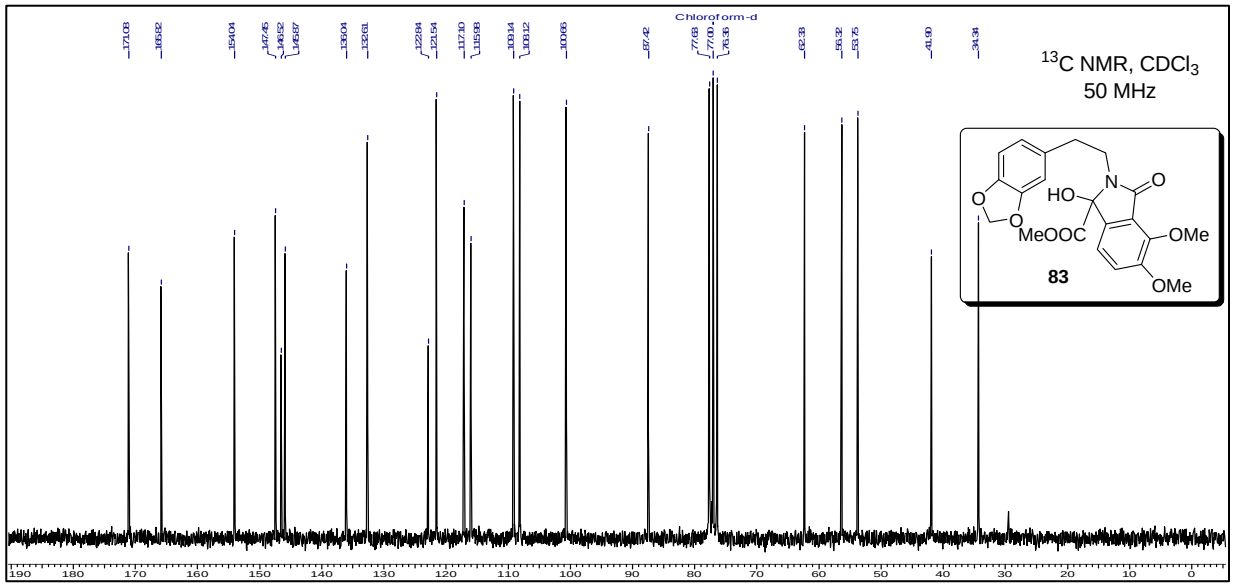

DEPT, $CDCl_3$
50 MHz
COOMe
N
H H
O
47b

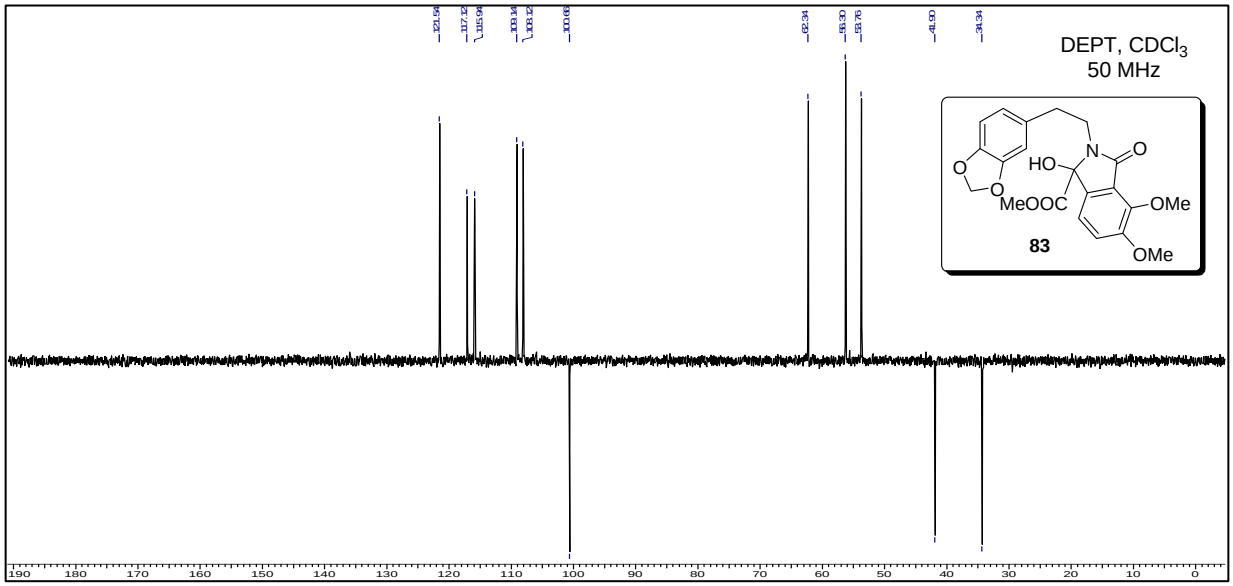

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 400 MHz
82
OMe
OMe

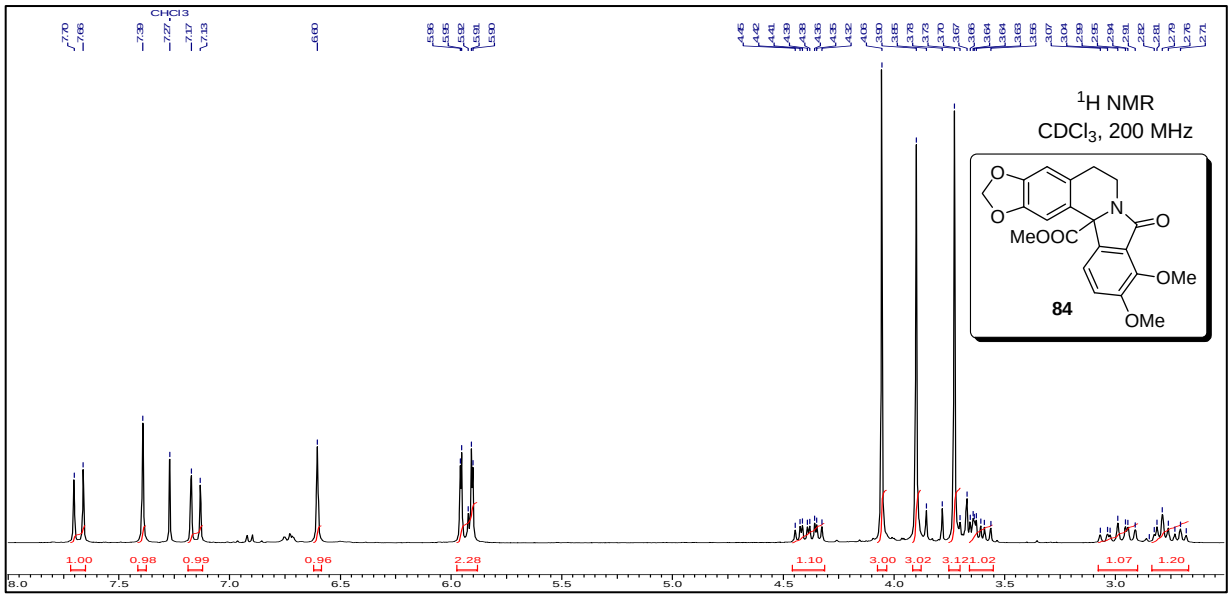

Chloroform-d
^{13}C NMR, $CDCl_3$
100 MHz
82
OMe
OMe

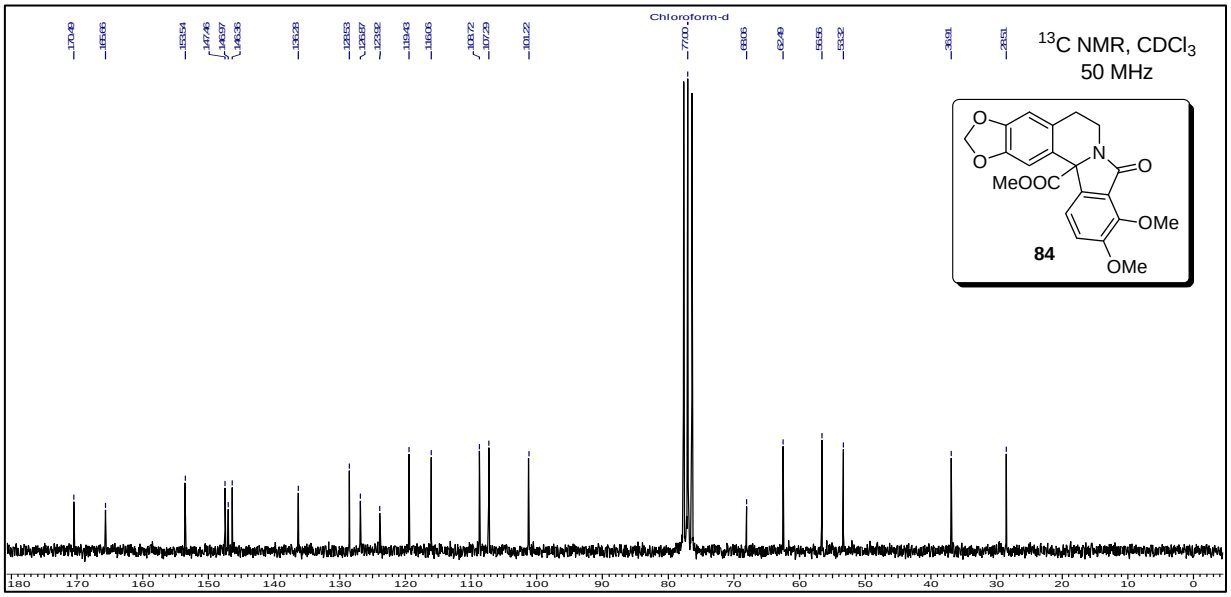

DEPT, $CDCl_3$
100 MHz
82
OMe
OMe

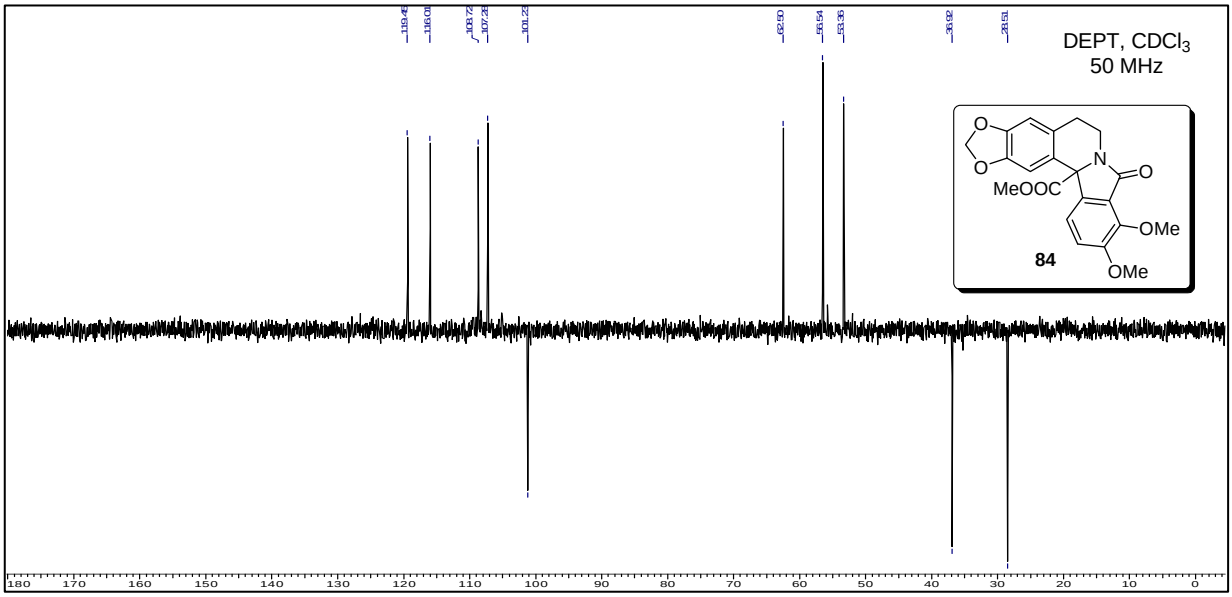

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
HO
N
O
O
O
MeOOC
OMe
OMe
83

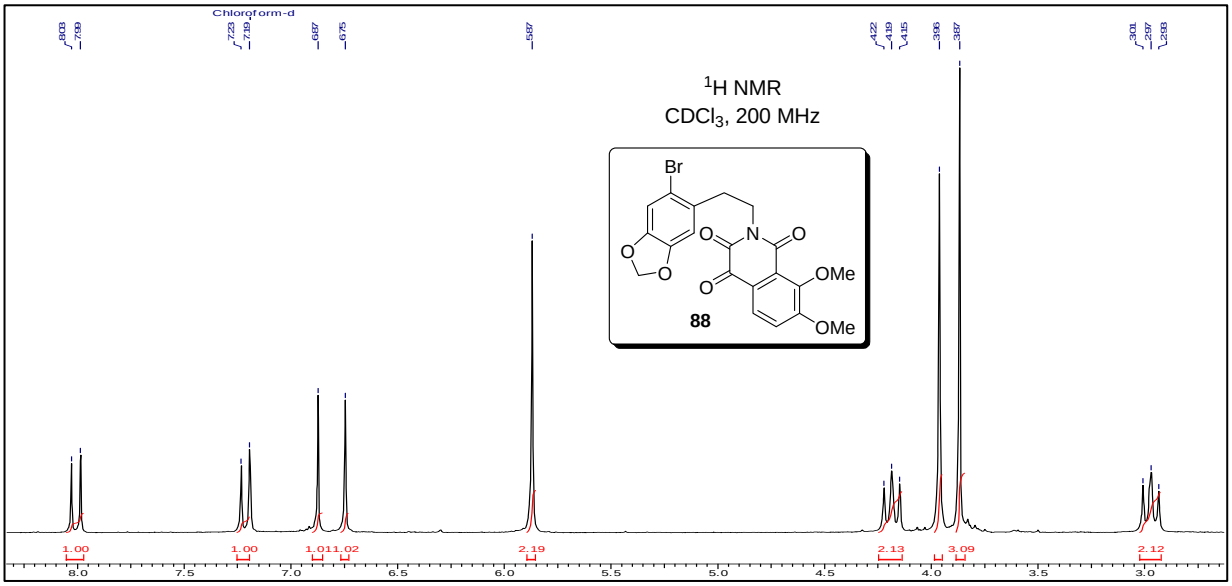

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
HO
N
O
O
O
MeOOC
OMe
OMe
83

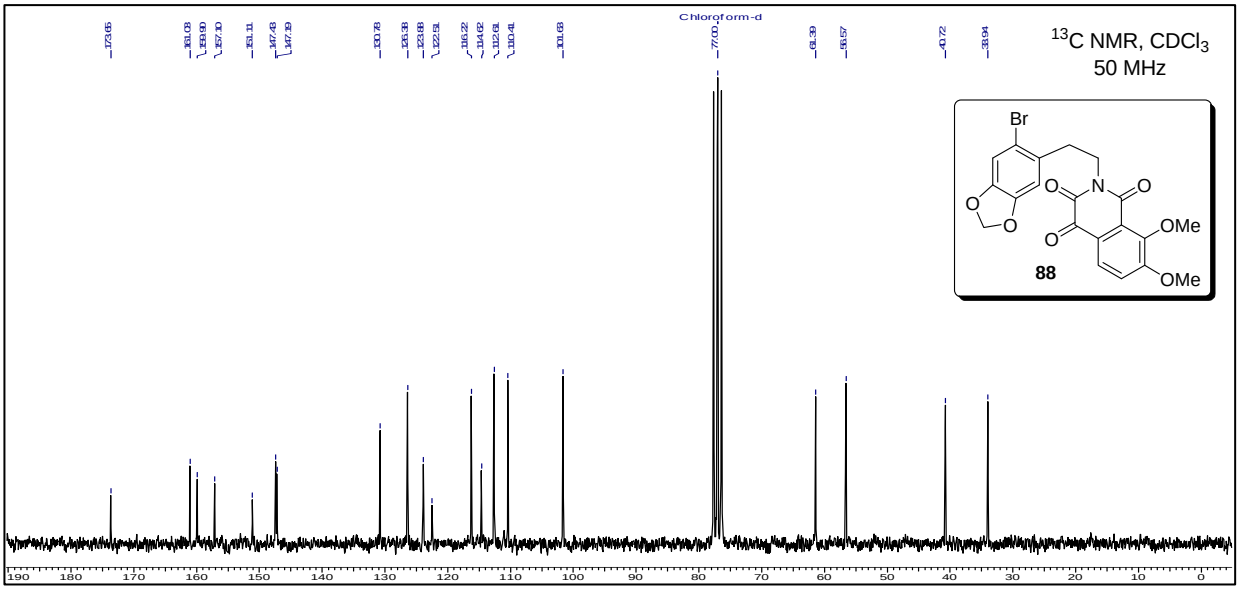

DEPT, $CDCl_3$
50 MHz
HO
N
O
O
O
MeOOC
OMe
OMe
83

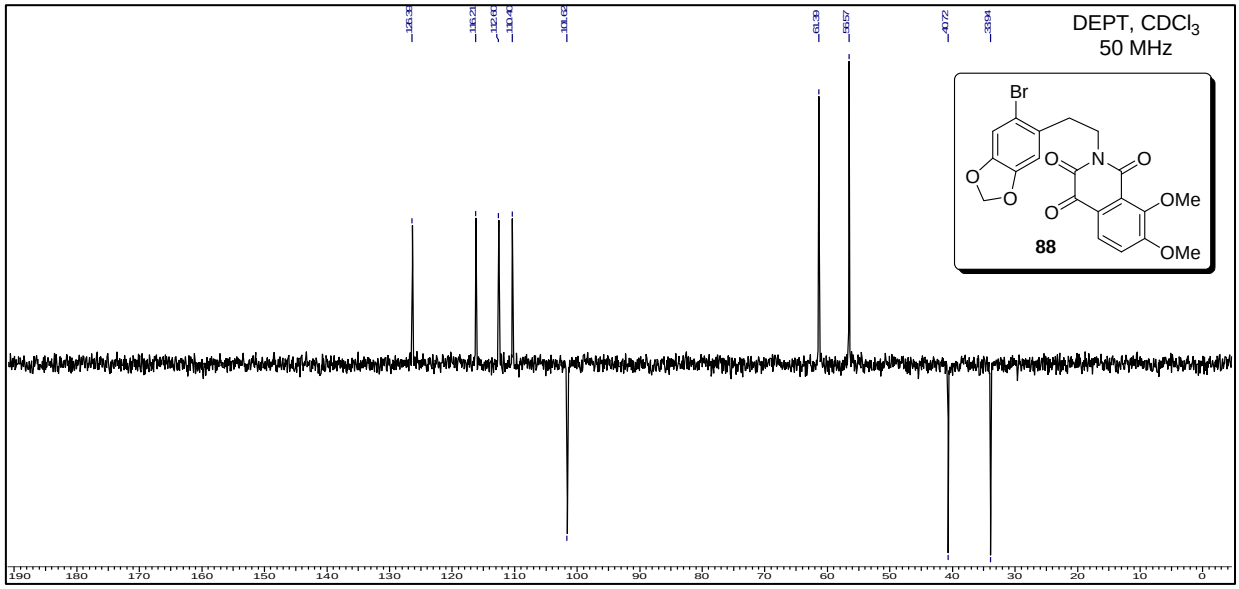

CHCl3
^{1}H NMR
$CDCl_3$, 200 MHz
MeOOC
OMe
OMe
84

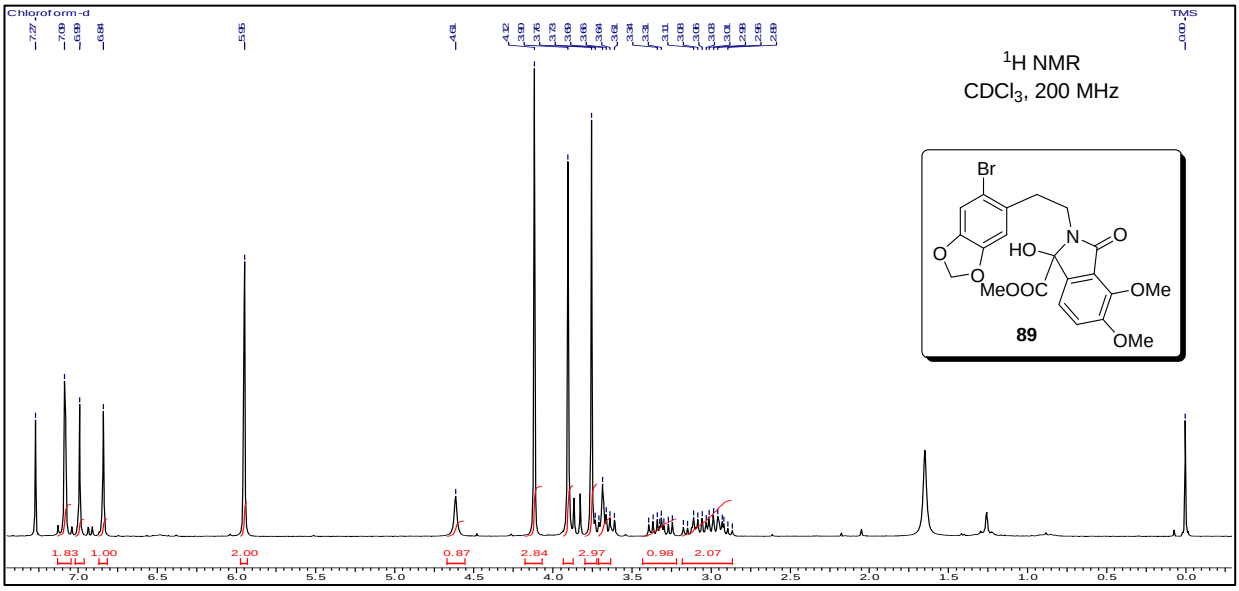

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
MeOOC
OMe
OMe
84

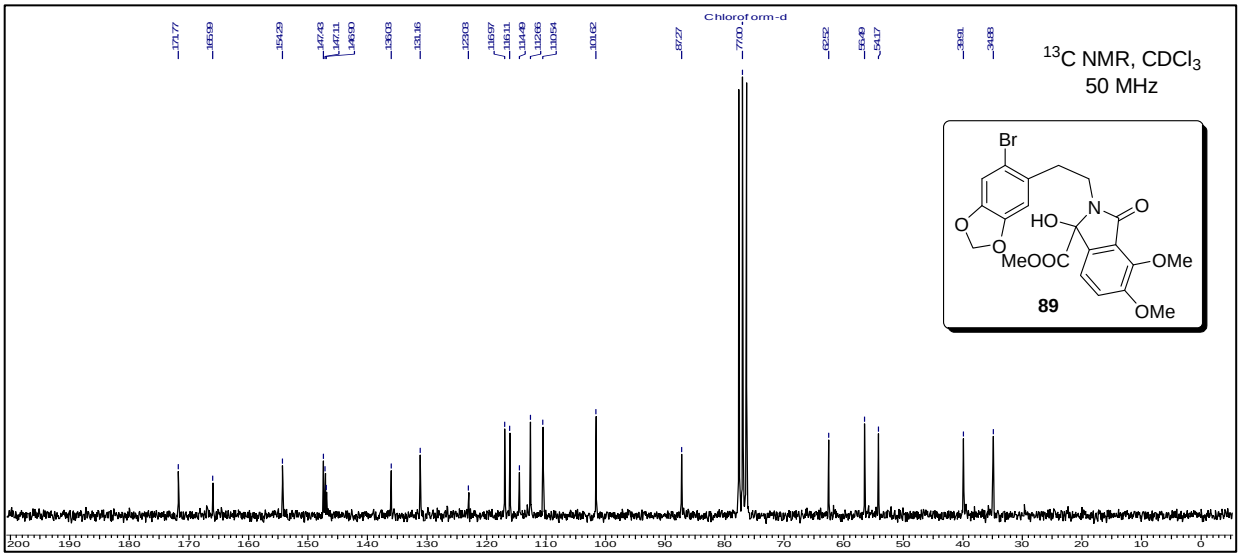

DEPT, $CDCl_3$
50 MHz
MeOOC
OMe
OMe
84

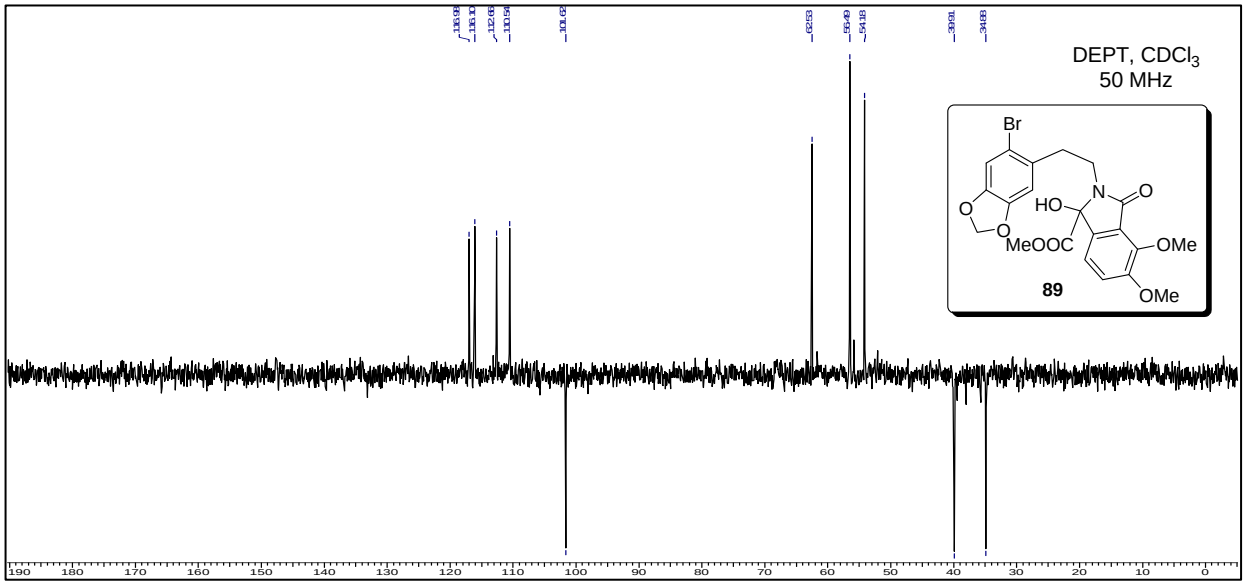

Chloroform-d
^{1}H NMR
$CDCl_3$, 200 MHz
Br
O
N
O
O
O
O
OMe
OMe
88

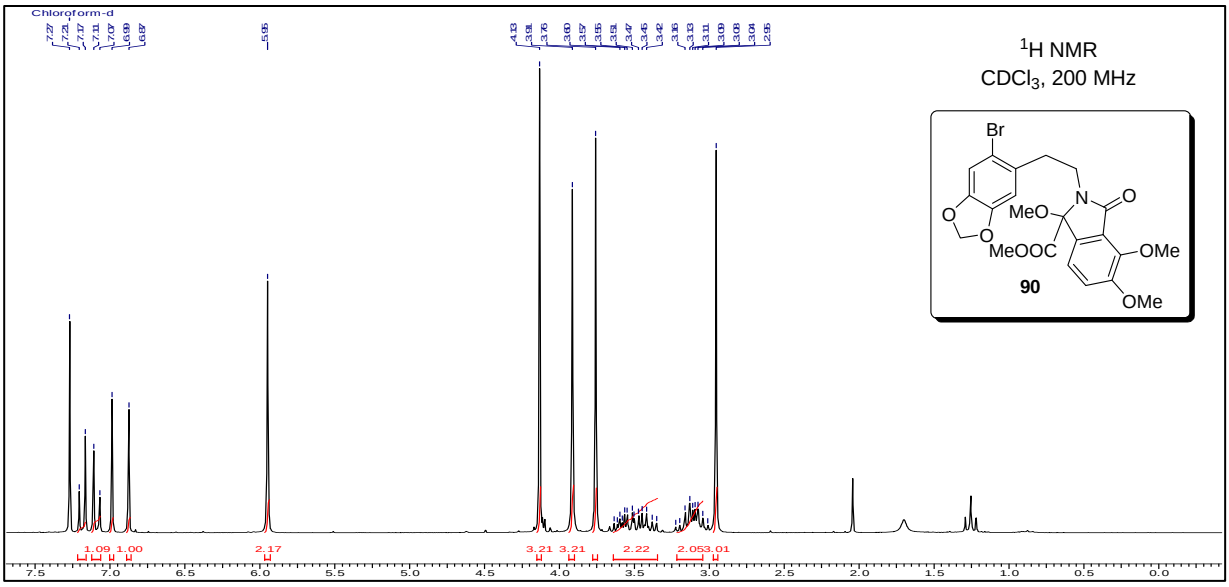

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
Br
O
N
O
O
O
O
OMe
OMe
88

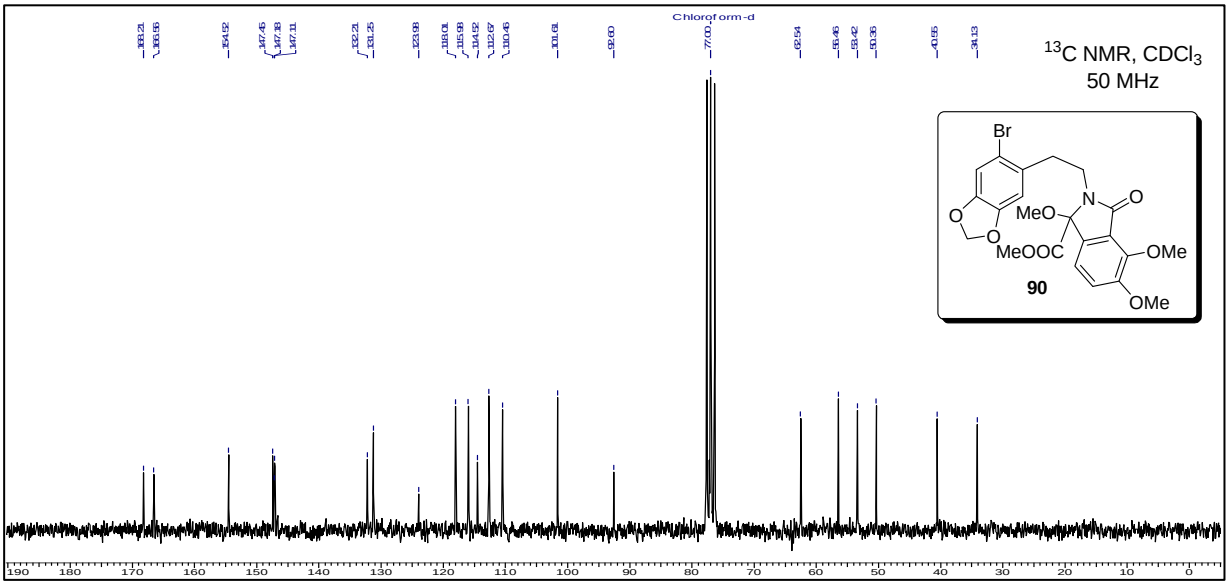

DEPT, $CDCl_3$
50 MHz
Br
O
N
O
O
O
O
OMe
OMe
88

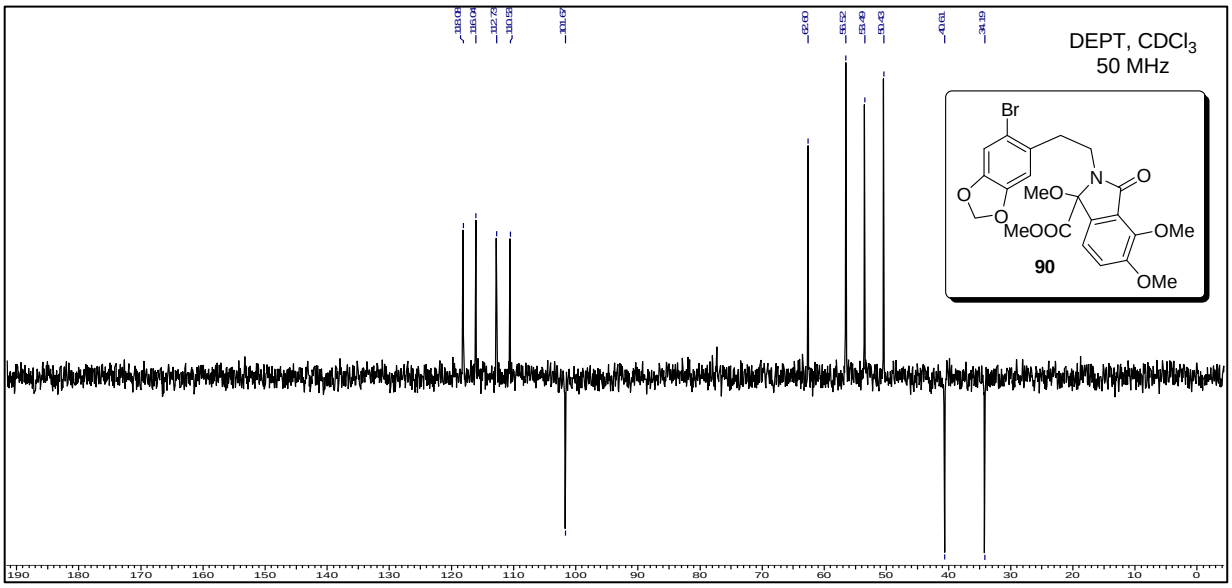

Chloroform-d
TMS
^{1}H NMR
$CDCl_3$, 200 MHz
Br
O
N
O
HO
O
MeOOC
OMe
OMe
89
1.83
1.00
2.00
0.87
2.84
2.97
0.98
2.07

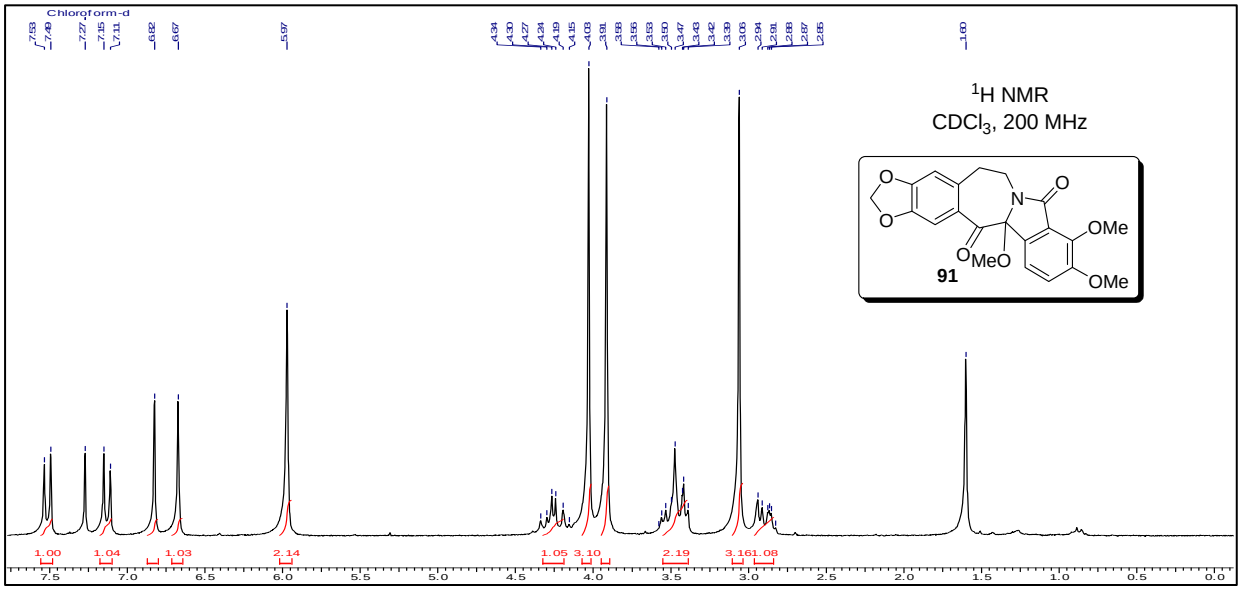

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
Br
O
N
O
HO
O
MeOOC
OMe
OMe
89

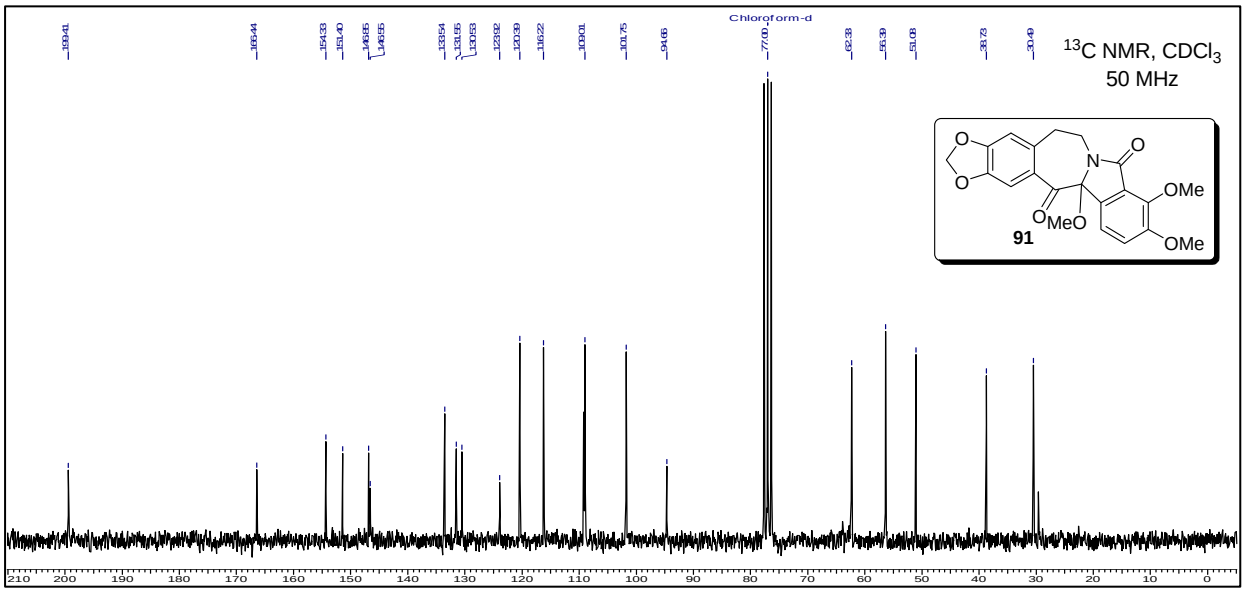

DEPT, $CDCl_3$
50 MHz
Br
O
N
O
HO
O
MeOOC
OMe
OMe
89

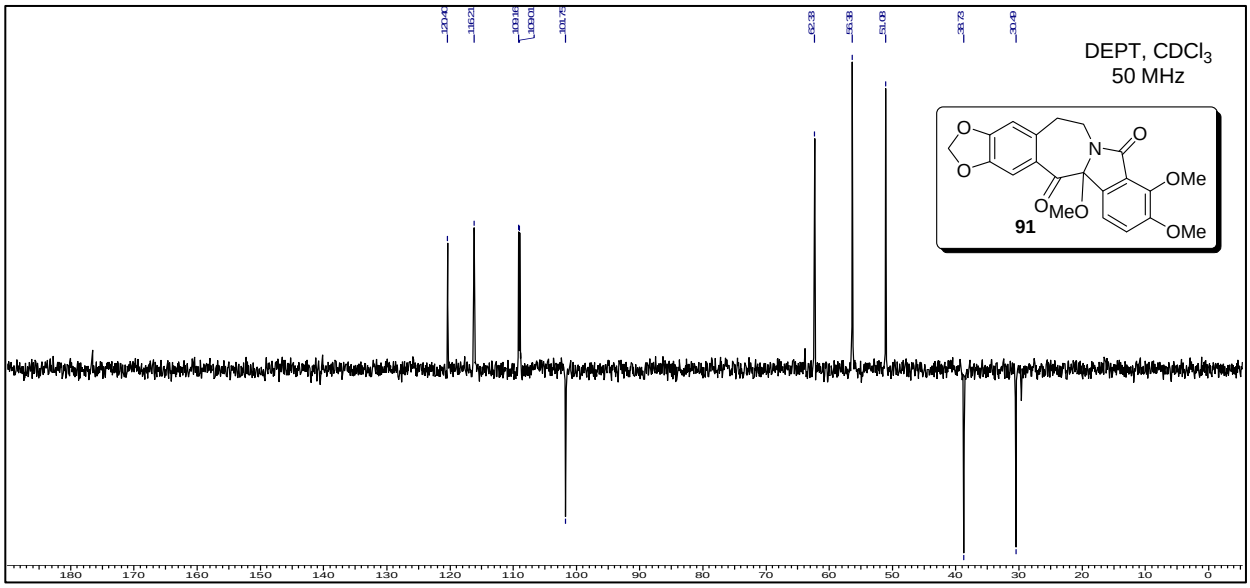

Chloroform-d
^{1}H NMR
$CDCl_3$, 200 MHz
Br
MeO
N
O
O
O
MeOOC
OMe
OMe
90

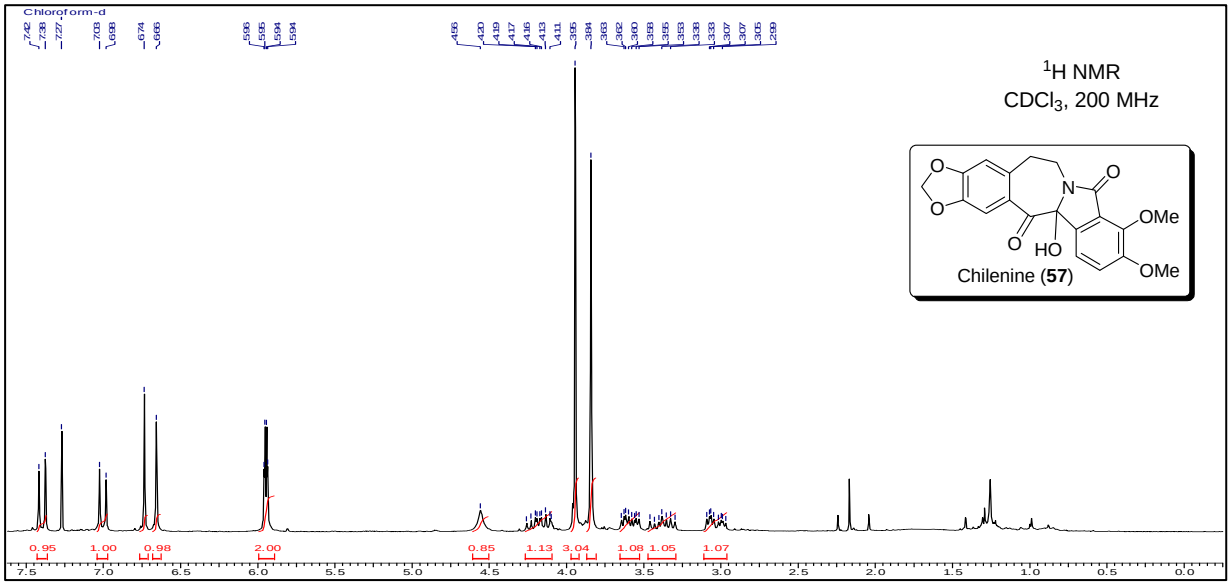

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
Br
MeO
N
O
O
O
MeOOC
OMe
OMe
90

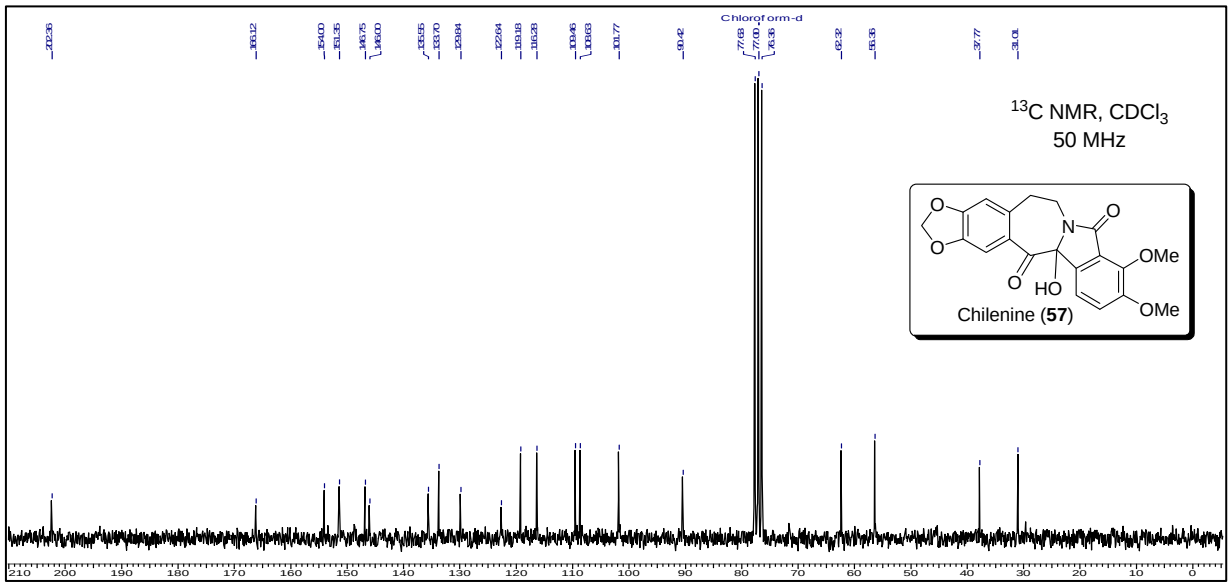

DEPT, $CDCl_3$
50 MHz
Br
MeO
N
O
O
O
MeOOC
OMe
OMe
90

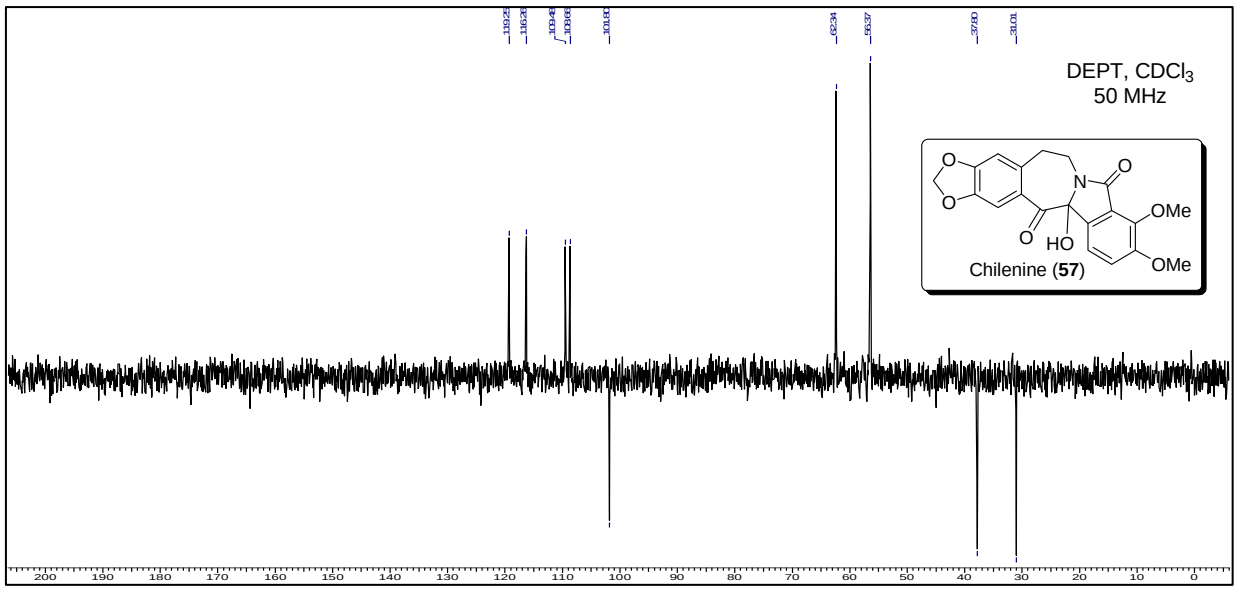

Chloroform-d
^{1}H NMR
$CDCl_3$, 200 MHz
91

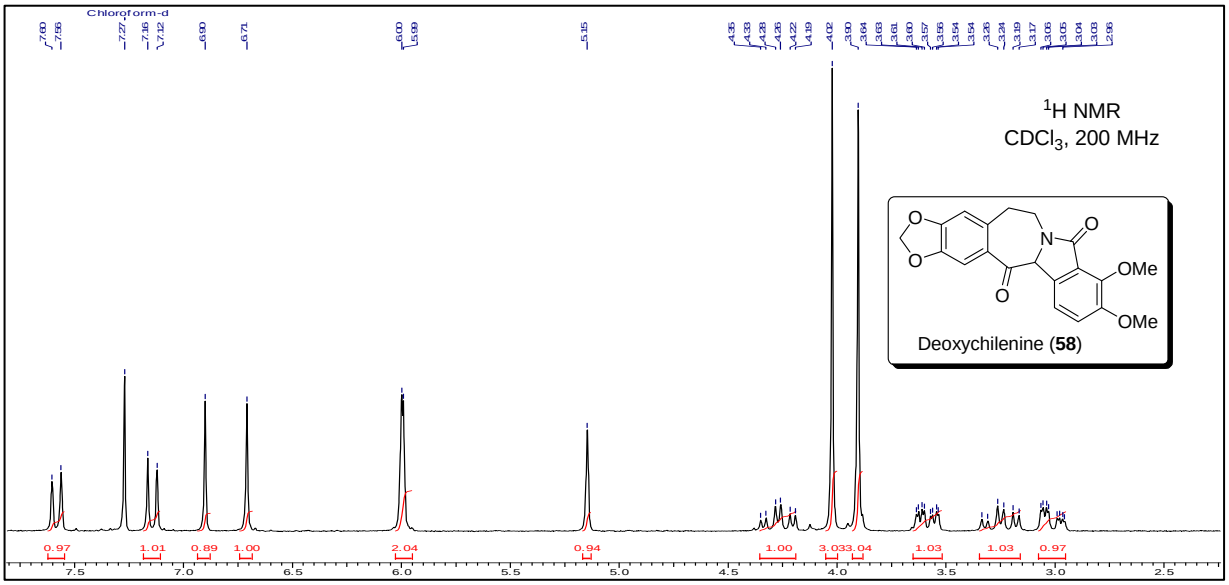

Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
91

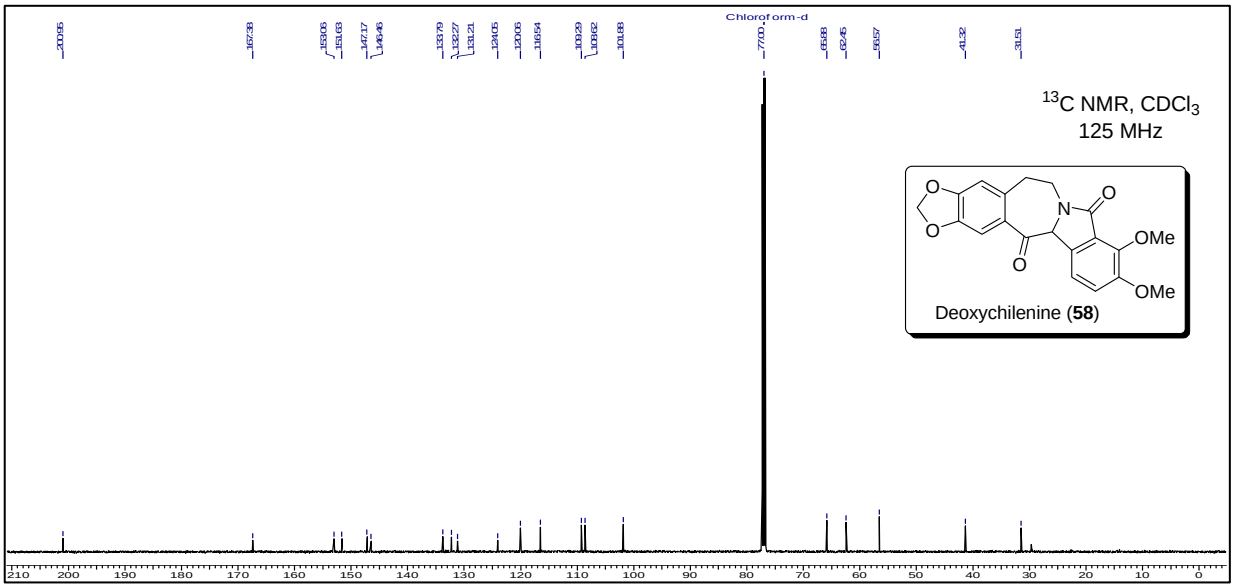

DEPT, $CDCl_3$
50 MHz
91

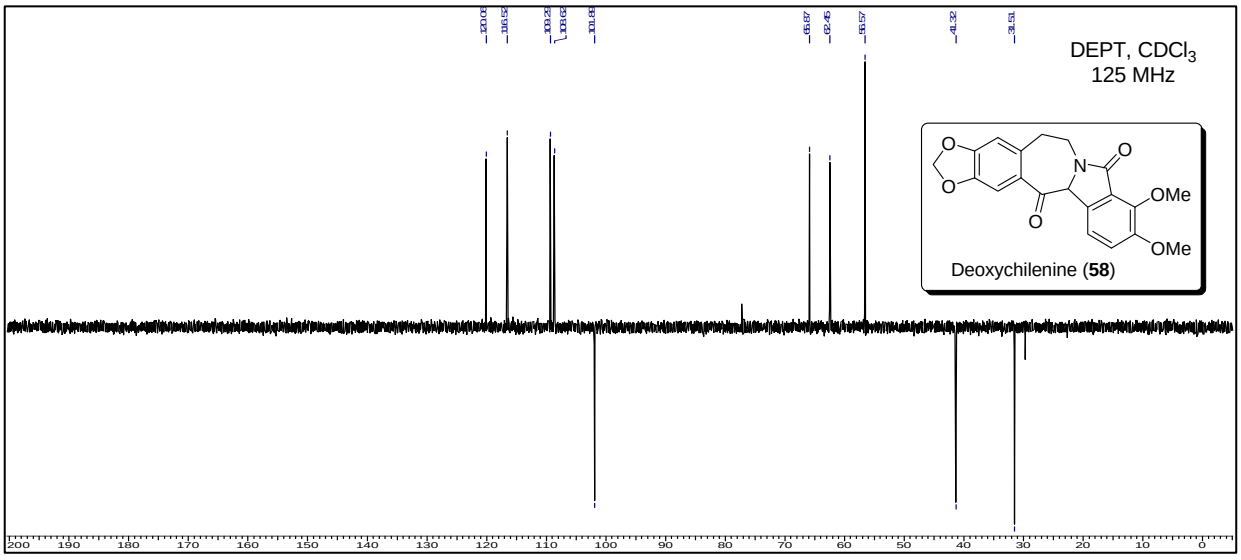

Chloroform-d
^{1}H NMR
$CDCl_3$, 200 MHz
Chilenine (**57**)


Chloroform-d
^{13}C NMR, $CDCl_3$
50 MHz
Chilenine (**57**)


DEPT, $CDCl_3$
50 MHz
Chilenine (**57**)


Chloroform-d
^{1}H NMR
$CDCl_3$, 200 MHz
OMe
OMe
Deoxychilenine (**58**)


Chloroform-d
^{13}C NMR, $CDCl_3$
125 MHz
OMe
OMe
Deoxychilenine (**58**)


DEPT, $CDCl_3$
125 MHz
OMe
OMe
Deoxychilenine (**58**)

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Chapter 2: Section C

Synthetic Studies Towards Erythrina Alkaloids

This Section C of Chapter 2 Features the Following Topics:

2C.1 Background

Erythrina alkaloids (Figure 1), a large class of natural products found in tropical and subtropical regions, represent attractive synthetic targets to the organic chemists due to their use in indigenous medicine.[1] The name erythrina has been derived from the Greek word erythros, meaning "red," referring to the flower color of certain species. Members of the Erythrina family, as exemplified in Figure 2, display curare-like and hypnotic activity and a variety of pharmacological effects are associated with the erythrina class of natural product including sedative, hypotensive, neuromuscular blocking and CNS activity.[2] Many nice approaches have been employed for the synthesis of this class of natural products.[3] These molecules display a wide range of substitution pattern surrounding the ring skeleton particularly in the A- and D-rings (these are usually methoxy or methylenedioxy). Few members have been isolated which contain substitution pattern in the C-ring in the form of hydroxy, methoxy or carbonyl group. New members of this family are still being isolated.[4]

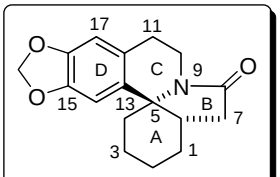
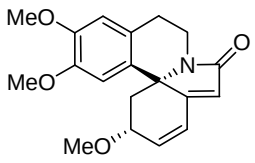
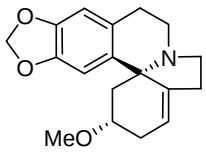


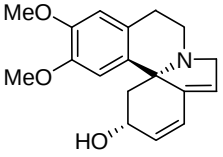
Figure 1. Erythrina Skeleton (**1**)



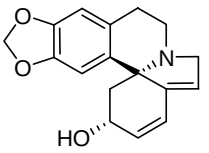
Erysotramidine (**2**)
(*Erythrina arborescens*)[a]



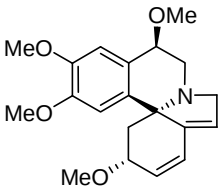
Erythramine (**3**)
(*Erythrina sandwicensis*)[b]



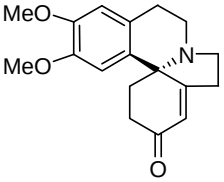
Erythravine (**4**)
(*Erythrina mulungu*)[c]



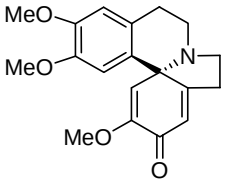
Erythrocarine[d] (**5**)



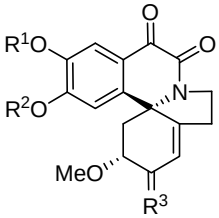
Erythristemine (**6**)
(*Erythrina lysistemon*)[e]



13-Demethoxyerythratidienone (**7**)
(*Erythrina lithosperma*)[f]



o-Erysodienone (**8**)
(*Erythrina lithosperma*)[g]



(*Erythrina subumbrans*)[h]

9: $R^1 + R^2 = CH_2$, $R^3 = \beta$-OH, H
10: $R^1 = R^2 = CH_3$, $R^3 = \beta$-OH, H
11: $R^1 = R^2 = CH_3$, $R^3 = O$

[a] Reference 5. [b] Reference 6. [c] Reference 7. [d] Reference 8.
[e] Reference 9. [f] Reference 10. [g] Reference 11. [h] Reference 4.

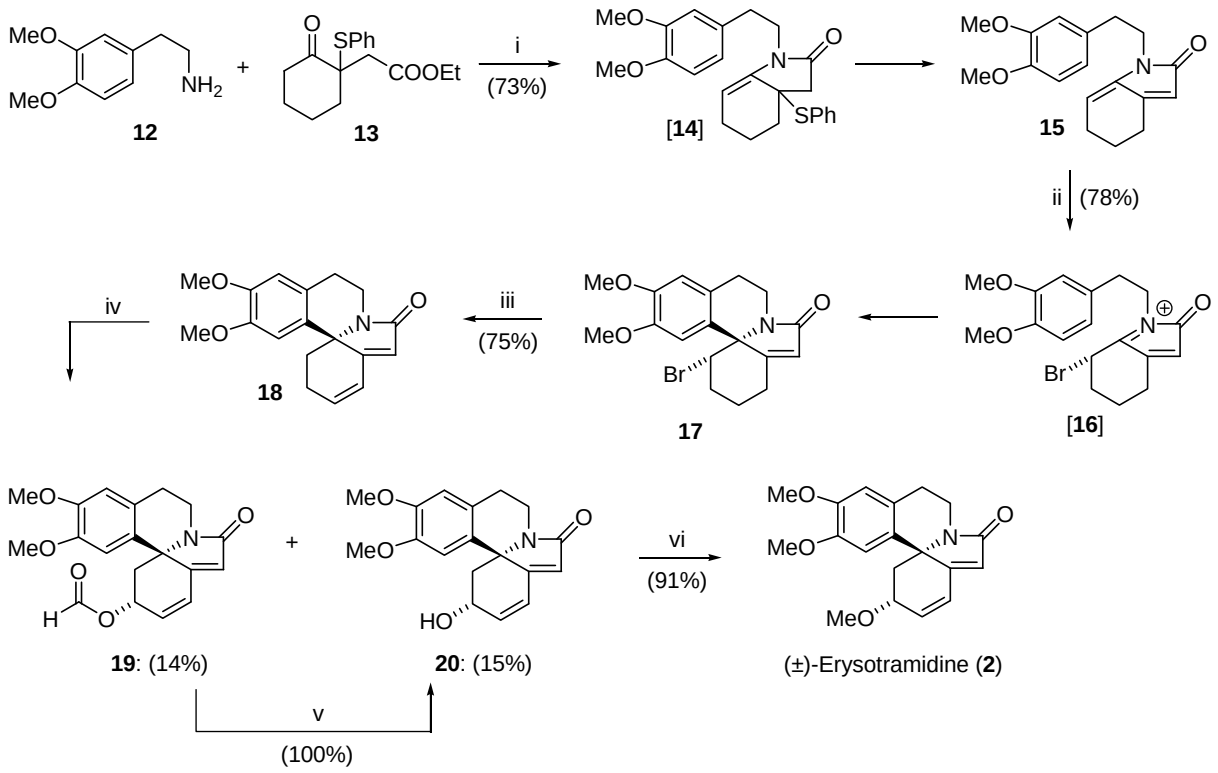
Figure 2. Erythrina family alkaloids

Some of the recent strategies on the construction of the core spirocyclic structure include intramolecular cyclization reactions such as radical cyclizations, electrophilic substitution, cyclizations on *N*-acyliminium intermediates or Pummerer-induced cyclizations, Heck reactions and anionic substitution reactions. The above mentioned examples in Figure 2 reveal that there are slight variations in the structures from each other with respect to the position of double bond and substitution pattern in A- and D-rings. We were interested in the total synthesis of (+)-erysotramidine (**2**) which was isolated by Ito et al.[5] in 1973 from *Erythrina arborescens* for which several synthetic approaches have been reported in the literature.[12] Out of them, only four recent approaches have been discussed in the following part.

2C.1.1 Synthetic Approaches Towards (+)-Erysotramidine

[A] NBS-Promoted Cyclization of a Hexahydroindolinone Derivative by Padwa and co-workers[12d]

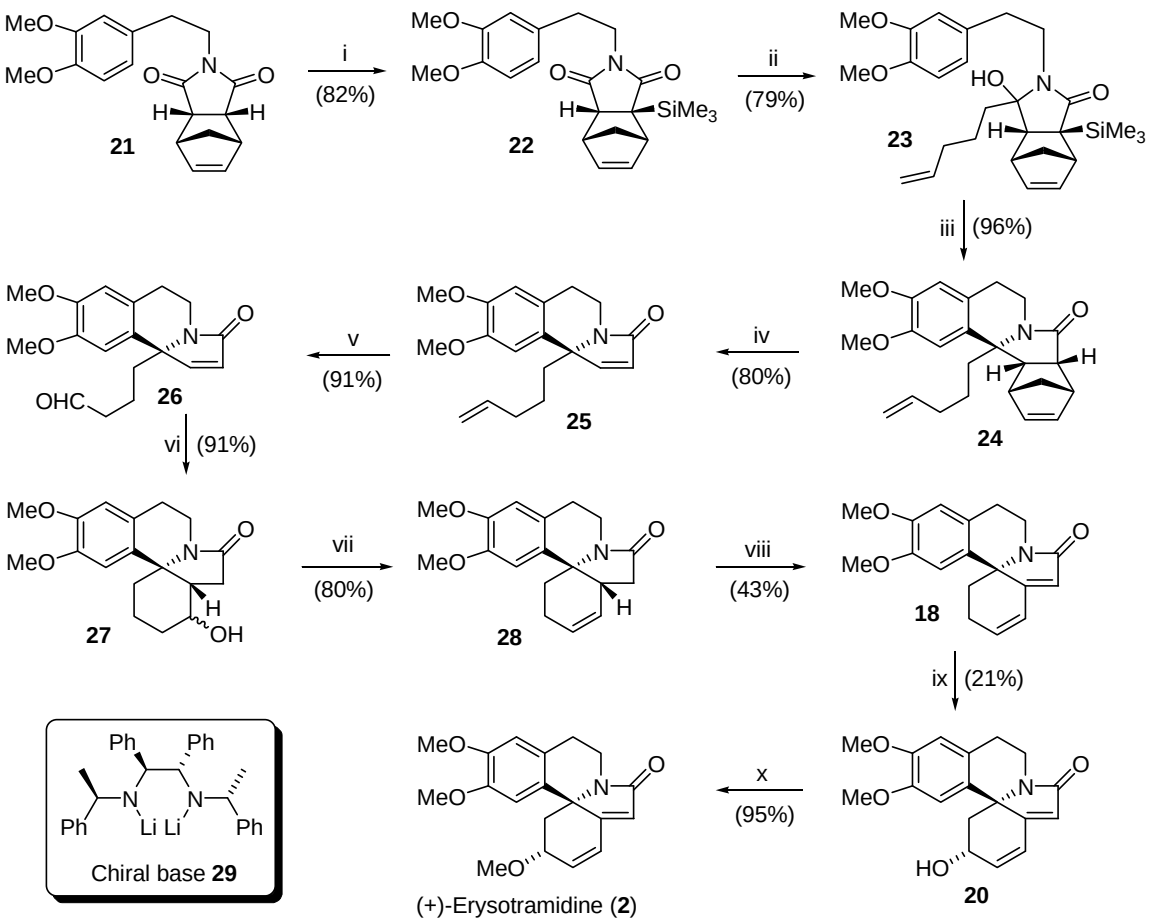
Padwa's research group reported an elegant synthesis of (±)-erysotramidine (**2**) by using NBS catalyzed cyclization of hexahydroindolinone. The approach starts with the synthesis of bicyclic lactam **15** (Scheme 1). Condensation of homoveratrylamine (**12**) with ketoester **13** followed by treatment with TFA yielded **15**. The reaction sequence involves initial generation of the expected hexahydroindolinone **14** followed by an acid-catalyzed elimination of the phenyl sulfanyl group. All the efforts using acid-promoted cyclization of **15** failed, perhaps as a consequence of the anti-aromatic character of the resulting five membered cationic ring intermediate. However bicyclic lactam **15** underwent an extremely smooth cyclization to the desired erythrinan skeleton **17** in 78% yield when it was treated with NBS in acetonitrile. The reaction was dependent on the nature of the solvent and acetonitrile was the only solvent found favorable for cyclization. Subjection of **17** to DBU in refluxing xylene furnished the diene-lactam **18** in 75% yield. This product was presumably formed by an initial dehydrobromination followed by isomerization of the π-bond into the thermodynamically most stable position. Stereoselective allylic oxidation with selenium dioxide in the presence of formic acid gave a 1:1 mixture of formate **19** and alcohol **20** as the single diastereomers. The stereochemical outcome of the oxidation involves attack by the oxidant from the least hindered *α*-position. Formate **19** was quantitatively transformed into alcohol **20** by treatment with acetyl chloride in ethanol. Finally, compound **20** was converted into (±)-erysotramidine (**2**) in 91% yield by *o*-methylation using KOH/MeI in THF.



Scheme 1. *Reagents*, *conditions and yields*: (i) (a) Toluene, reflux, 3 h, (b) TFA, reflux, 48 h (73%); (ii) CH_3CN, NBS, rt, 3 h (78%); (iii) Xylene, DBU, reflux, 48 h (75%); (iv) 1,4-Dioxane, SeO_2, HCOOH, reflux, 7 days (**19**: 14%, **20**: 15%); (v) Acetyl chloride, EtOH, rt, 1 h (100%); (vi) MeI, THF, NaOH, TBAB, rt, 36 h (91%).

[B] Asymmetric Synthesis by Simpkins and co-workers[12e]

Simpkins and co-workers reported chiral base **29** induced asymmetric desymmetrization approach to accomplish the total synthesis of (+)-erysotramidine (**2**) (Scheme 2). The synthesis starts with the treatment of bridged imide **21** with bis-lithium amide base **29** to give the *C*-silylated imide product **22** in 82% yield and 92–94% ee. Grignard addition reaction with imide **22** took place with complete regiocontrol at the carbonyl carbon away from the silicon function. Thus, the use of a pent-4-enyl Grignard reagent gave adduct **23** in good yield. Desilylation of this compound using TBAF, followed by *N*-acyliminium mediated ring closure gave **24** in excellent yield and as a single diastereomer. Very high yield was obtained for retro-Diels–Alder reaction of **24** to form the desired unsaturated lactam **25**. The oxidative cleavage of olefin **25** furnished aldehyde **26** in excellent yield. The exposure of **26** to tributyltin hydride led efficiently to the desired hydroxylactam **27** as a mixture of diastereomers at the newly formed carbinol centre in the 3:1 ratio. Dehydration of **27** using Burgess reagent proved high yielding and highly regioselective to provide lactam **28**, which was dehydrogenated to give **18**.



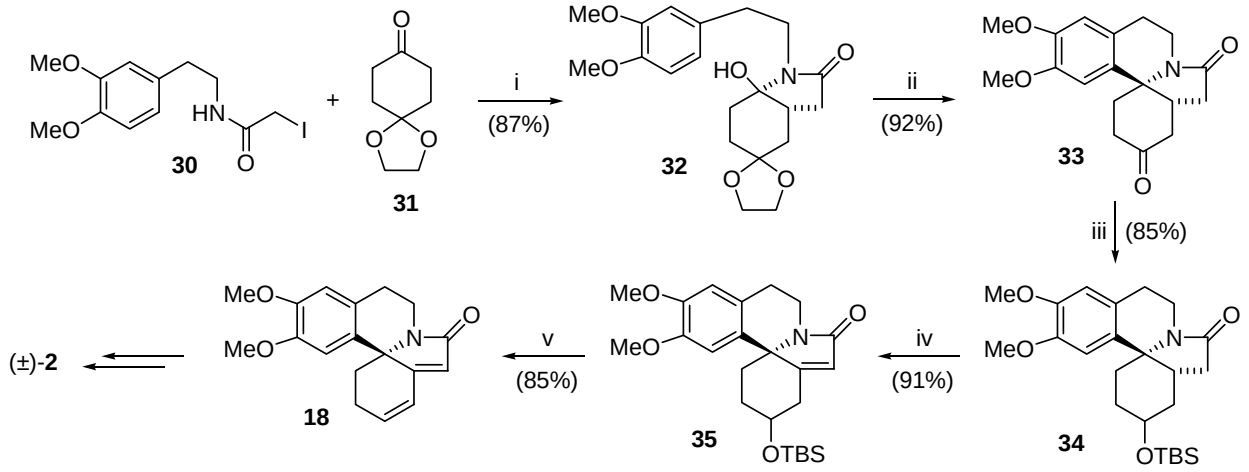
Scheme 2. *Reagents*, *conditions and yields*: (i) Base **29**, THF, Me_3SiCl, −78 °C, 3 h then rt, 12 h (82%); (ii) $H_2C{=}CH(CH_2)_3MgBr$ (5 equiv.), THF, −78 °C to rt, 12 h (79%); (iii) (a) TBAF, THF, rt, 12 h (b) TFA, CH_2Cl_2, 0 °C to rt, 2 d (96%); (iv) Heat, in vacuo, 50 sec. (80%); (v) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane-H_2O (91%); (vi) Bu_3SnH, AIBN, toluene-benzene (2:1), reflux, 12 h (91%); (vii) Burgess reagent, benzene, reflux, 6 h (80%); (viii) (a) LDA, −78 °C, PhSeSePh, THF, 1.5 h, (b) $NaIO_4$, MeOH-H_2O, 4 h (43%); (ix) SeO_2, HCO_2H, reflux, 4 d (21%); (x) MeI, Et_4NBr, KOH, THF, 36 h (95%).

The diene-lactam **18** was previously prepared by Padwa and co-workers[12d] in their studies towards a synthesis of (±)-erysotramidine (**2**) (Scheme 1). Those conditions enabled conversion of **18** into the alcohol **20**. The reaction was clean but slow, giving high yield based on recovered starting diene (79%) and only low levels of conversion (20–25%) could be achieved. Methylation of **20** under the established conditions gave the (+)-erysotramidine **2**.

[C] General and Efficient Synthesis by Tu and co-workers[12f]

Tu and co-workers achieved a highly efficient route to (±)-erysotramidine (**2**) as depicted in Scheme 3. The synthesis commenced by the condensation of the lithium enolate of ketone **31** with **30** to furnish the alkylation product **32** in 87% yield as a single diastereoisomer. This diastereomer **32** was smoothly converted to the cis-fused tetracyclic skeleton **33** via *N*-

acyliminium ion cyclization. Reduction of ketone in **33** by $NaBH_4$ and the protection of thus formed alcohol as TBS ether furnished **34**. Oxidative elimination of the corresponding phenylselenylation product of **34** with $NaIO_4$ resulted in the desired unsaturated amide **35**. Unsaturated diene amide **18**, which was the known intermediate for the synthesis of **2**, was obtained from **35** in 85% overall yield via three steps involving TBS deprotection, mesylation of thus formed alcohol and its DBU promoted elimination. Finally, the total synthesis of **2** was accomplished according to the reported sequence through stereoselective allylic oxidation and the final methylation.

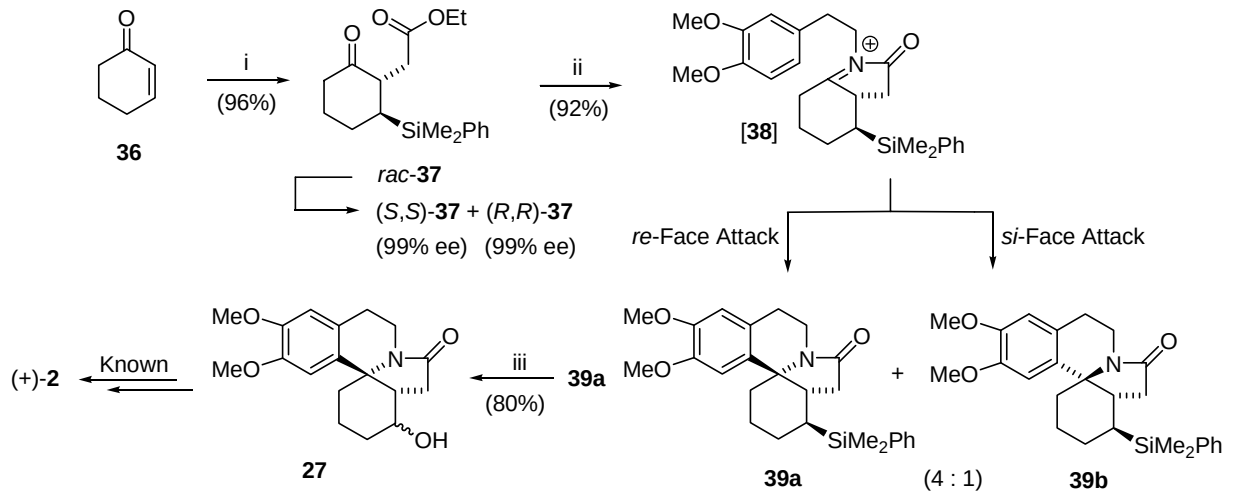


Scheme 3. *Reagents*, *conditions and yields*: (i) LDA, THF, −78 °C, 1 h (87%); (ii) (a) TFA, CH_2Cl_2, 0 °C, 5 h, (b) TsOH, acetone, reflux, 3 h (92%); (iii) (a) $NaBH_4$, methanol, 0 °C, 30 min, (b) TBSCl, imidazole, DMF, rt, 1 h (85%); (iv) LDA, THF, PhSeCl, −78 °C, 1 h, (b) $NaIO_4$, methanol, rt, 1 h (91%); (v) (a) TBAF, THF, rt, 5 h, (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, (c) DBU, THF, reflux, 3 h (85%).

[D] Domino Process by Tietze and co-workers[12g]

Domino reaction involves intramolecular multiple transformations of functional groups in one pot. The substrates containing many functional groups take part in chemical transformations one at the time. This enables short synthesis of complex molecules and hence is the popular concept in the organic synthesis. Tietze and co-workers very recently applied this domino reaction strategy successfully for the synthesis of (+)-erysotramidine (**2**) with reduced number of steps. The necessary cyclohexanone derivative **37** was prepared by a conjugate addition of the silyl zincate to cyclohexenone (**36**) in the presence of catalytic amounts of CuI (Scheme 4). The in situ generated enolate was then quenched with ethyl bromoacetate to give the ketoester **37** in 96% yield as a single diastereomer with a 2,3-*trans*-orientation. Resolution of *rac*-**37** on a chiral stationary phase enabled authors to obtain (*S*,*S*)-**37** and (*R*,*R*)-**37** with >99% ee. Reaction of the ketoester (*S*,*S*)-**37** and the homoveratrylamine with two equivalents of $AlMe_3$ in the presence of

15 mol% of indium triflate followed by treatment with triflic acid led to a 4:1 mixture of the desired spirocyclic compounds **39a** and **39b** in 92% yield. The two diastereomers were easily separated by chromatography on silica gel.



Scheme 4. *Reagents*, *conditions and yields*: (i) $Zn(SiMe_2Ph)$, CuI, THF, −78 °C, 2 h then $BrCH_2COOEt$, −78 °C to −20 °C, 3.5 h (96%); (ii) (a) Homoveratrylamine, $AlMe_3$, $In(OTf)_3$, CH_3CN, rt, 24 h, (b) TfOH, 80 °C, 4 h (92%); (iii) (a) $BF_4H{\cdot}OEt_2$, 1,2-dichloroethane, 80 °C, 10 h, (b) H_2O_2, KF, K_2CO_3, MeOH-THF (1:1), rt, 36 h (80%).

As the final step for the synthesis of the alcohol **27**, a Tamao-Fleming oxidation of the silane **39a** was performed. The use of tetrafluoroboronic acid-diethyletherate at 80 °C under microwave irradiation followed by oxidation of the formed fluorosilane with H_2O_2 in the presence of KF formed alcohol **27** (α:β = 9:1). The **27** was an intermediate in the synthesis of (+)-erysothramidine (**2**) by Simpkins et al.[12e] its preparation constitutes a formal synthesis of **2** with reduced number of steps.

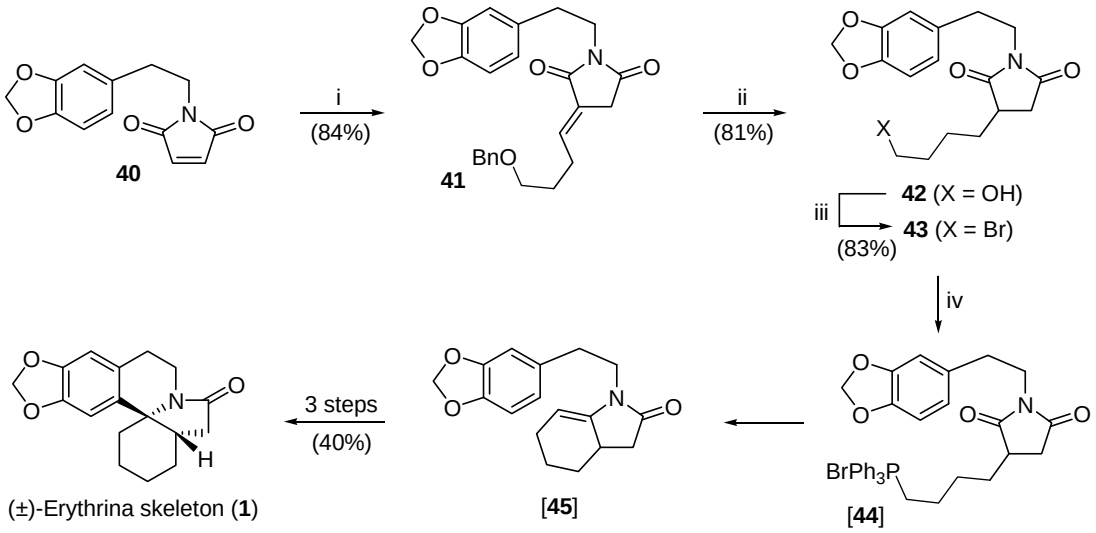
2C.2 Rational for present work

Non-classical Wittig reaction (on carbonyl carbon other than aldehyde and ketone) is well explored in the literature on various carbonyl compounds like esters, lactones, thio-esters, anhydrides, imides, amides etc. A comprehensive review on this important aspect has been published by Murphy and co-workers.[13] Our research group has been continuously utilizing cyclic anhydrides as the synthons in the synthesis of natural and synthetic products.[14] Since various substituted imide compounds could be easily synthesized from different cyclic anhydrides, we were interested here to perform the above mentioned non-classical Wittig reaction on imide carbonyl and use the obtained enamide precursors for the Pictet-Spengler type of cyclization for the generation of quaternary centre of erythrina skeleton. The following part

describes the total synthesis of erythrina alkaloid skeleton and in progress synthesis of natural product (+)-erysotramidine.

2C.3 Results and discussion

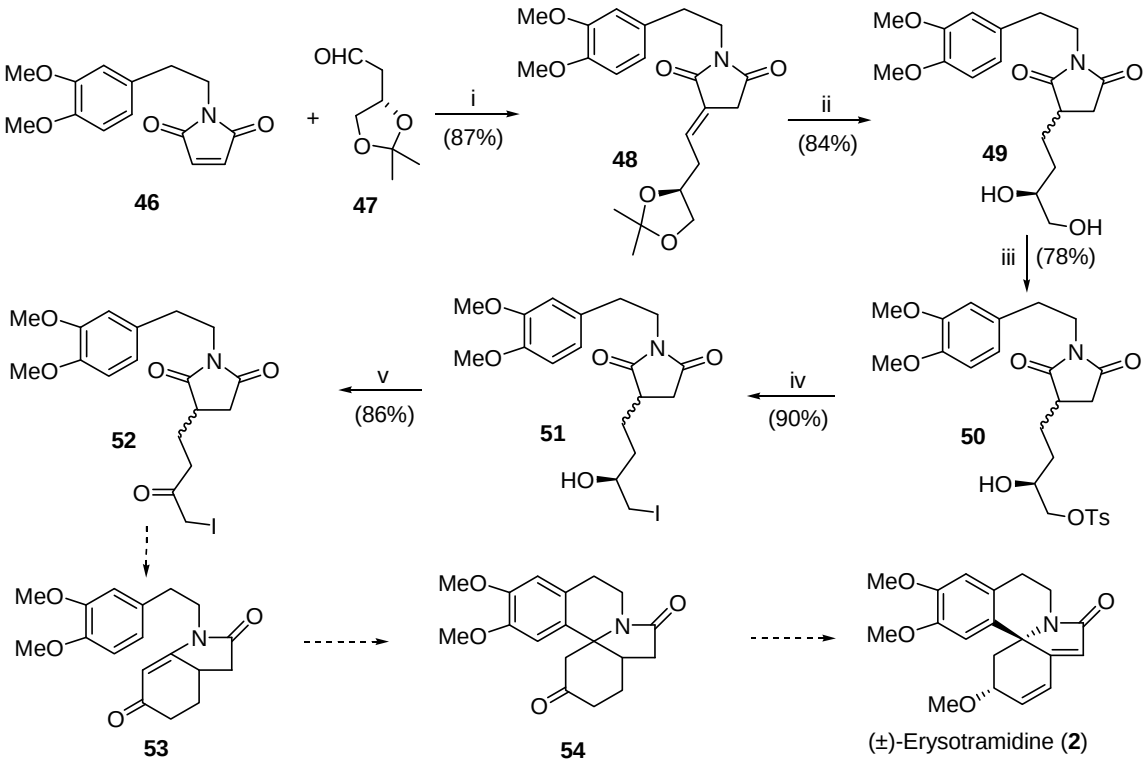
Basic erythrina skeleton (**1**) has been synthesized by Tietze and co-workers[15] by using domino reaction with the reduced number of steps. We have recently developed four-step pathway for the synthesis of (±)-erythrina skeleton (**1**) which involves intramolecular non-classical witting reaction as the key step (Scheme 5). The synthesis starts from known imide **40**.[16] Wittig reaction of imide **40** with *γ*-benzyloxybutyraldehyde provided the product **41**. The simultaneous hydrogenation of double bond and hydrogenolysis of *o*-benzyl group in compound **41** yielded an alcohol **42** which was further transformed to the corresponding bromo-compound **43** in good yield. Thus the obtained **43** was heated with triphenylphosphine (TPP) at 140 ^{o}C for 3 hours to furnish the corresponding salt **44**. The salt was found to be moisture sensitive, hence after cooling the reaction to room temperature, dry THF was added to it and the reaction mixture was stirred at room temperature under nitrogen atmosphere to dissolve the salt **44**.



Scheme 5. *Reagents, conditions and yields*: (i) $BnOCH_2CH_2CH_2CHO$, TPP, THF, reflux, 24 h (84%); (ii) $H_2/Pd(OH)_2$, ethanol, 60 ^{o}C, 3 h (81%); (iii) CBr_4, TPP, DMF, rt, 12 h (83%); (iv) (a) TPP, 140 ^{o}C, 3 h, (b) *n*-BuLi, THF, –78 ^{o}C to rt, (c) TFA, rt, 2 h (40% for 3 steps).

The solubility of the salt in THF was less. We thought the solubility would increase in next step during the formation of ylide from the salt **44**. Thus, treatment of partially soluble salt **44** in dry THF with *n*-BuLi at –78 ^{o}C formed unstable intermediate **45**. During the above step we did not observe any increase in the solubility of salt **44**. After quenching the reaction and aqueous work-up, the obtained product was passed quickly through silica gel column as the enamide **45** was

found unstable. Finally, enamide **45** was subjected for the acid catalyzed Pictet-Spengler type of cyclization to furnish erythrina skeleton (**1**) in 40% yield over three steps. The analytical and spectral data was found in accordance with the reported data.[17] We feel that there is scope for increasing the yield of the Wittig reaction by using different solvents, temperature and bases, since the yield can be improved by increasing the solubility of the salt **44**. Work is in progress to optimize the yield of the reaction to prove the synthetic utility of our strategy.



Scheme 6. *Reagents, conditions and yields*: (i) TPP, THF, reflux, 24 h (87%); (ii) $H_2/Pd(OH)_2$, ethanol, 60 ^oC, 12 h (84%); (iii) TsCl, DMAP, Et_3N, DCM, rt, 6 h (78%); (iv) NaI, acetone, 70 ^oC, 6 h (90%); (v) IBX, EtOAc, 80 ^oC, 8 h (86%).

After implementation of the above discussed non-classical Wittig reaction on succinimide frame work for the synthesis of erythrina skeleton, we planned the synthetic studies towards natural product (+)-erysotramidine (**2**) (Scheme 6). The strategy was similar to our earlier developed approach for erythrina skeleton (**1**) except oxygen functionality on the aldehyde coupling partner (**47**). The purpose of this precursor was to have oxygen functionality in A-ring in order to have right substitution pattern for the synthesis of natural product. The second reason was to synthesize stable ylide for the purpose of making it completely soluble and hence improve the yield of the reaction. Having these thoughts in mind we synthesized α-iodoketo-compound **52**. The synthesis started with preparation of known aldehyde **47** from (*L*)-malic acid.[18] The Wittig

reaction of known imide **46**[16] with aldehyde **47** yielded the adduct **48**. Treatment of **48** with $Pd(OH)_2$ under hydrogen atmosphere provided double bond reduced as well as acetonide deprotected product **49** in 84% yield. The selective conversion of primary alcohol in **49** to iodo compound **51** was achieved via tosylation at primary alcohol to furnish **50** followed by its nucleophillic displacement by sodium iodide. The obtained alcohol **51** was oxidized to ketone **52** by using IBX in excellent yield. Further studies on intramolecular Wittig reaction to obtain the spiro-compound **54** and its transformation to the natural product (±)-erysotramidine (**2**) is in active progress in our laboratory.

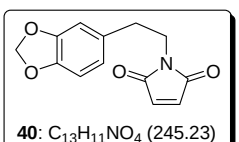
2C.4 Summary

A short four steps access to (±)-erythrina skeleton has been described by taking the advantage of two sequential Wittig reactions. The developed protocol for the synthesis of this skeleton will be utilized for the synthesis of natural product (±)-erysotramidine. The work is in active progress towards the target molecule by taking in account the oxygenation pattern in A-ring of natural product. The developed strategy after the yield optimization in the non-classical Wittig reaction would be highly useful to develop natural and synthetic analogs as well as other natural products of erythrina family.

2C.5 Experimental section

Melting points are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on 200 and 400 MHz spectrometers. ^{13}C NMR spectra were recorded on 200 and 400 NMR spectrometers (50 & 100 MHz respectively). IR spectra were recorded on a FT-IR spectrometer. Column chromatographic separations were done on silica gel (60-120 mesh). Commercially available maleic anhydride, *n*-BuLi, $Pd(OH)_2$, trifluoroacetic acid, homoveratrylamine were used.

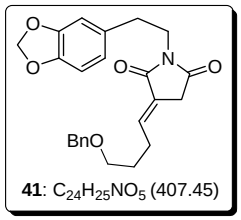
1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-1*H*-pyrrole-2,5-dione (40). To a stirring solution of maleic anhydride (1.78 g, 18.16 mmol) in dry acetic acid (50 mL) was added homopiperonyl amine (3.00 g, 18.16 mmol) at room temperature and reaction mixture was refluxed for 16 hours. After cooling the reaction mixture, acetic acid was removed in vacuo. Ethyl acetate (60 mL) was added to the obtained crude residue and the organic layer was washed three times with water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue by using petroleum ether-ethyl acetate mixture (7:3) as an



40: $C_{13}H_{11}NO_4$ (245.23)

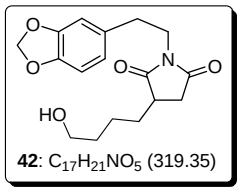
eluent furnished compound **40** as a yellow solid (3.16 g, 71% yield). **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 2.82 (dd, J = 8 & 8 Hz, 2H), 3.71 (dd, J = 8 & 8 Hz, 2H), 5.93 (s, 2H), 6.55−6.75 (m, 5H).

(*E*)-1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-(4-(benzyloxy)butylidene)pyrrolidine-2,5-dione (41). To a stirring solution of imide **40** (2.80 g, 11.4 mmol) in THF (60 mL) was added triphenylphosphine (3.29 g, 12.57 mmol) and the reaction mixture was stirred at room temperature for 15 min. Then the solution of γ-benzyloxybutyraldehyde (2.23 g, 12.57 mmol) in THF (10 mL) was added to the reaction mixture and further refluxed for 24 hours. After cooling the reaction mixture, THF was removed in vacuo. The obtained crude residue was purified by silica gel column chromatography by using petroleum ether-ethyl acetate mixture (6:4) as an eluent to furnish compound **41** as thick oil (3.90 g, 84% yield). **IR** ($CHCl_3$) ν_{max} 1768, 1705, 1678 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.80 (qt, J = 6 Hz, 2H), 2.29 (q, J = 8 Hz, 2H), 2.82 (dd, J = 9 & 8 Hz, 2H), 3.15 (d, J = 2 Hz, 2H), 3.48 (t, J = 6 Hz, 2H), 3.75 (dd, J = 9 & 8 Hz, 2H), 4.49 (s, 2H), 5.92 (s, 2H), 6.60−6.85 (m, 4H), 7.25−7.40 (m, 5H); **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 26.4, 28.0, 31.6, 33.2, 39.8, 68.7, 72.8, 100.7, 108.1, 109.0, 121.5, 125.8, 127.4, 127.5, 128.2, 131.5, 137.8, 138.0, 146.1, 147.5, 169.4, 173.7.



41: $C_{24}H_{25}NO_5$ (407.45)

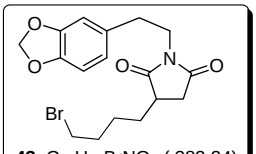
1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-(4-hydroxybutyl)pyrrolidine-2,5-dione (42). To a stirring solution of compound **41** (3.80 g, 9.33 mmol) in ethanol (80 mL) was added cat. $Pd(OH)_2$ at room temperature and the reaction mixture was further heated at 60 ^oC under hydrogen atmosphere for 3 hours. After cooling the reaction mixture, it was filtered to remove catalyst. The crude product obtained after the removal of ethanol in vacuo was further purified by silica gel common chromatography by using petroleum ether-ethyl acetate mixture (1:1) as an eluent to furnish the compound **42** as thick oil (2.41 g, 81% yield). **IR** ($CHCl_3$) ν_{max} 3456, 1772, 1701 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.25−1.95 (m, 7H), 2.20−2.45 (m, 1H), 2.65−2.88 (m, 4H), 3.55−3.80 (m, 4H), 5.92 (s, 2H), 6.57−6.75 (m, 3H); **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 22.9, 31.0, 32.2, 33.1, 34.2, 39.7, 39.9, 62.3, 100.9, 108.2, 109.2, 121.8, 131.4, 146.2, 147.6, 176.4, 179.7.



42: $C_{17}H_{21}NO_5$ (319.35)

1-(2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl)-3-(4-bromobutyl)pyrrolidine-2,5-dione (43). To a stirring solution of compound **42** (2.30 g, 7.21 mmol) in dry DMF (30 mL) was added triphenylphosphine (TPP, 3.77 g, 14.42 mmol) and tetrabromomethane (CBr_4, 4.78 g, 14.42

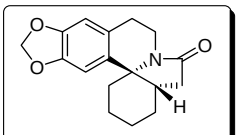
mmol) at 0 °C. After stirring the reaction mixture at room temperature for 12 hours, ethyl acetate (50 mL) was added and it was washed three times with water, brine and dried over Na_2SO_4.



43: $C_{17}H_{20}BrNO_4$ (382.24)

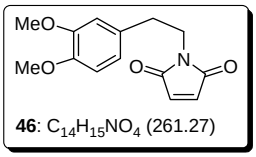
Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue by using petroleum ether-ethyl acetate mixture (7:3) as an eluent furnished compound **43** as thick oil (2.28 g, 83% yield). **IR** ($CHCl_3$) ν_{max} 1774, 1703 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.34−1.60 (m, 3H), 1.70−1.98 (m, 3H), 2.20−2.45 (m, 1H), 2.65−2.90 (m, 4H), 3.42 (t, J = 8 Hz, 2H), 3.70 (dd, J = 8 & 6 Hz, 2H), 5.93 (s, 2H), 6.57−6.77 (m, 3H); **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 25.2, 30.4, 32.1, 33.1 (2 carbons), 34.1, 39.5, 39.9, 100.9, 108.2, 109.2, 121.8, 131.3, 146.2, 147.6, 176.2, 179.4.

15,16-Methylenedioxy-*cis*-erythrinan-8-one (1). To the DCM (5 mL) solution of compound **43** (200 mg, 0.52 mmol) was added triphenylphosphine (137 mg, 0.50 mmol) at room temperature and the reaction mixture was further stirred for 10 min till it gets dissolve. DCM was removed in vacuo and the obtained thick oil was heated neat at 140 °C for 3 hours. After cooling the reaction mixture, dry THF (10 mL) was added to dissolve the reaction mass under nitrogen atmosphere. Reaction was cooled to –78 °C and *n*-BuLi (0.40 mL, 0.62 mmol, 1.60 M in hexane) was added. Reaction mixture was stirred at the same temperature for 30 min and then allowed to reach room temperature slowly. Reaction was quenched by adding 2-3 drops of saturated solution of aq. ammonium chloride. THF was removed in vacuo and the obtained crude residue was passed quickly through a pad of silica gel by using petroleum ether-ethyl acetate mixture (7:3) as an eluent. The pure fraction obtained was concentrated in vacuo and trifluoroacetic acid (4 mL) was added to it. After stirring the reaction mixture for 2 hours at room temperature, diethyl ether (30 mL) was added to it and the organic layer was washed three times by 10% aq. $NaHCO_3$, water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue by using petroleum ether-ethyl acetate mixture (6:4) as an eluent furnished compound **1** as thick oil (59 mg, 40% yield). **IR** ($CHCl_3$) ν_{max} 1671 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 1.45−1.55 (m, 2H), 1.57−1.74 (m, 3H), 1.80−1.86 (m, 2H), 1.95−2.08 (m, 1H), 2.34 (dd, J = 8 & 4 Hz, 2H), 2.50−2.58 (m, 1H), 2.64−2.73 (m, 1H), 2.88−3.00 (m, 1H), 3.18−3.28 (m, 1H), 3.97−4.07 (m, 1H), 5.92 (s, 2H), 6.56 (s, 1H), 6.86 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 20.2, 20.7, 27.0, 27.6, 35.0, 36.0, 36.5, 37.8, 62.7, 101.0, 105.0, 109.1, 126.9, 136.0, 146.1, 146.2, 174.2.



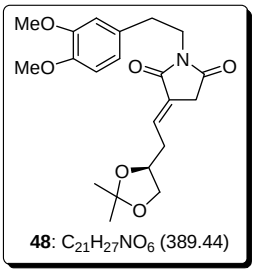
(±)-Erythrina skeleton (**1**)
$C_{17}H_{19}NO_3$ (285.33)

1-(3,4-Dimethoxyphenethyl)-1*H*-pyrrole-2,5-dione (46). It was prepared from maleic anhydride (2.70 g, 27.62 mmol) and homoveratrylamine (5.00 g, 27.62 mmol) in 74% yield (5.32 g) using same procedure as described for **40** above.



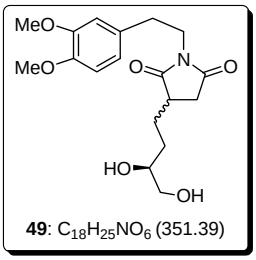
46: $C_{14}H_{15}NO_4$ (261.27)

(*E*)-1-(3,4-Dimethoxyphenethyl)-3-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethylidene)pyrrolidine-2,5-dione (48). It was prepared from imide **46** (5.00 g, 19.15 mmol) and aldehyde **47** (4.13 g, 28.72 mmol) in 87% yield (6.48 g) using the same procedure as described for compound **41** above. **IR** ($CHCl_3$) ν_{max} 1770, 1708, 1682 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.35 (s, 3H), 1.42 (s, 3H), 2.44 (t, J = 8 Hz, 2H), 2.80−2.92 (m, 2H), 3.22 (d, J = 2 Hz, 2H), 3.60 (dd, J = 8 & 6 Hz, 1H), 3.74−3.85 (m, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 4.10 (dd, J = 6 & 6 Hz, 1H), 4.26 (qt, J = 6 Hz, 1H), 6.73−6.88 (m, 4H); **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 25.3, 26.8, 32.0, 33.1, 34.1, 39.9, 55.8 (2 carbon), 68.8, 74.0, 109.5, 111.1, 111.8, 120.7, 127.9, 130.2, 133.2, 147.6, 148.8, 169.3, 173.6.



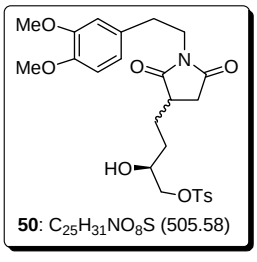
48: $C_{21}H_{27}NO_6$ (389.44)

3-(3,4-Dihydroxybutyl)-1-(3,4-dimethoxyphenethyl)pyrrolidine-2,5-dione (49) (Diastereomeric mixture). It was prepared from **48** (6.00 g, 15.42 mmol) in 84% yield (4.54 g) using the same procedure as described for compound **42** above. **IR** ($CHCl_3$) ν_{max} 1352, 1773, 1701 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.35−2.00 (m, 4H), 2.13 (bs, 2H), 2.32 (dq, J = 14 & 4 Hz, 1H), 2.70−2.90 (m, 4H), 3.35−3.50 (m, 1H), 3.58−3.80 (m, 4H), 3.85 (s, 3H), 3.88 (s, 3H), 6.70−6.84 (m, 3H); **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 27.3, 27.4, 29.6, 29.8, 32.8, 34.07, 34.12, 39.3, 39.4, 39.6, 55.77, 55.79, 66.3, 66.4, 71.4, 71.6, 111.1, 111.9, 120.9, 130.0, 147.6, 148.6, 176.4, 176.5, 179.9, 180.0.



49: $C_{18}H_{25}NO_6$ (351.39)

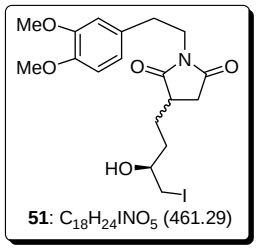
4-(1-(3,4-Dimethoxyphenethyl)-2,5-dioxopyrrolidin-3-yl)-2-hydroxybutyl 4-methylbenzenesulfonate (50) (Diastereomeric mixture). To a stirring solution of compound **49** (4.00 g, 11.39 mmol) in DCM (40 mL) was added tosyl chloride (2.61 g, 13.67 mmol), Et_3N (4.80 mL, 34.17 mmol) and cat. DMAP. After stirring the reaction mixture at room temperature for 6 hours, DCM was removed in vacuo. The obtained crude residue was purified by silica gel column chromatography by using petroleum ether-ethyl acetate mixture (4:6) as an eluent to furnish compound **50** as thick oil (4.48 g, 78% yield). **IR** ($CHCl_3$) ν_{max}



50: $C_{25}H_{31}NO_8S$ (505.58)

3421, 1701 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.35−2.05 (m, 5H), 2.15−2.40 (m, 1H), 2.46 (s, 3H), 2.60−2.90 (m, 4H), 3.65−3.78 (m, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 3.85−4.05 (m, 3H), 6.67−6.83 (m, 3H), 7.37 (d, J = 8 Hz, 2H), 7.80 (d, J = 8 Hz, 2H); **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 21.6, 27.1, 27.4, 29.3, 29.6, 29.8, 32.8, 34.2, 34.3, 39.17, 39.24, 39.7, 55.8 (2 carbon), 68.78, 68.82, 73.5, 111.1, 111.9, 120.9, 127.9, 129.9, 130.0, 132.3, 154.1, 147.6, 148.7, 176.18, 176.21, 179.4, 179.5.

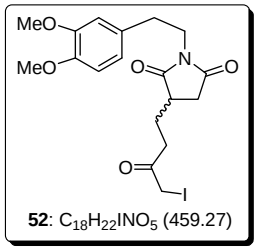
1-(3,4-Dimethoxyphenethyl)-3-(3-hydroxy-4-iodobutyl)pyrrolidine-2,5-dione (51)



51: $C_{18}H_{24}INO_5$ (461.29)

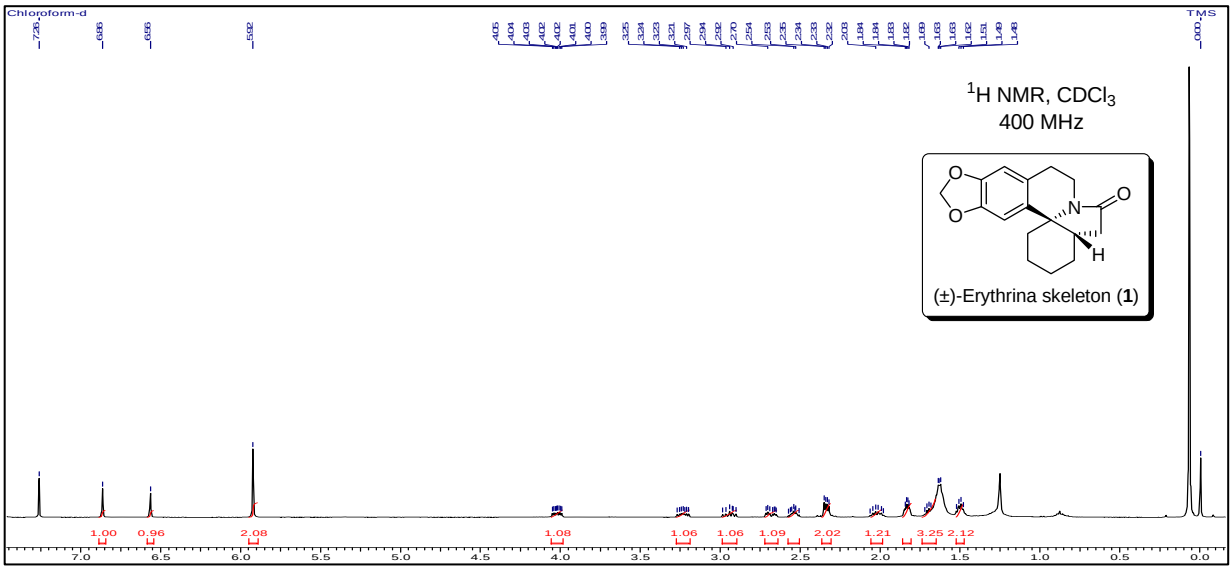
(Diastereomeric mixture). To a stirring solution of compound **50** (4.00 g, 7.92 mmol) in acetone (50 ml) was added NaI (2.37 g, 15.8 mmol) and the reaction mixture was stirred further for 6 hours at 70 ^oC. After cooling the reaction mixture to room temperature, acetone was removed in vacuo. Ethyl acetate (50 mL) was added to the obtained residue and the organic layer was washed by water, brine and dried over Na_2SO_4. Concentration of organic layer in vacuo followed by silica gel column chromatographic purification of the obtained residue by using petroleum ether-ethyl acetate mixture (1:1) as an eluent furnished compound **51** as a thick oil (3.28 g, 90% yield). **IR** ($CHCl_3$) ν_{max} 1773, 1701 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.40−2.00 (m, 5H), 2.20−2.42 (m, 1H), 2.67−2.92 (m, 4H), 3.14−3.27 (m, 1H), 3.28−3.40 (m, 1H), 3.45−3.62 (m, 1H), 3.68−3.80 (m, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 6.70−6.85 (m, 3H); **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 15.2, 15.4, 27.4, 27.7, 32.8, 33.1, 33.3, 34.16, 34.24, 39.2, 39.6, 55.80, 55.81, 70.35, 70.38, 111.0, 111.9, 120.9, 129.9, 147.6, 148.8, 176.2, 176.24, 179.4, 179.5.

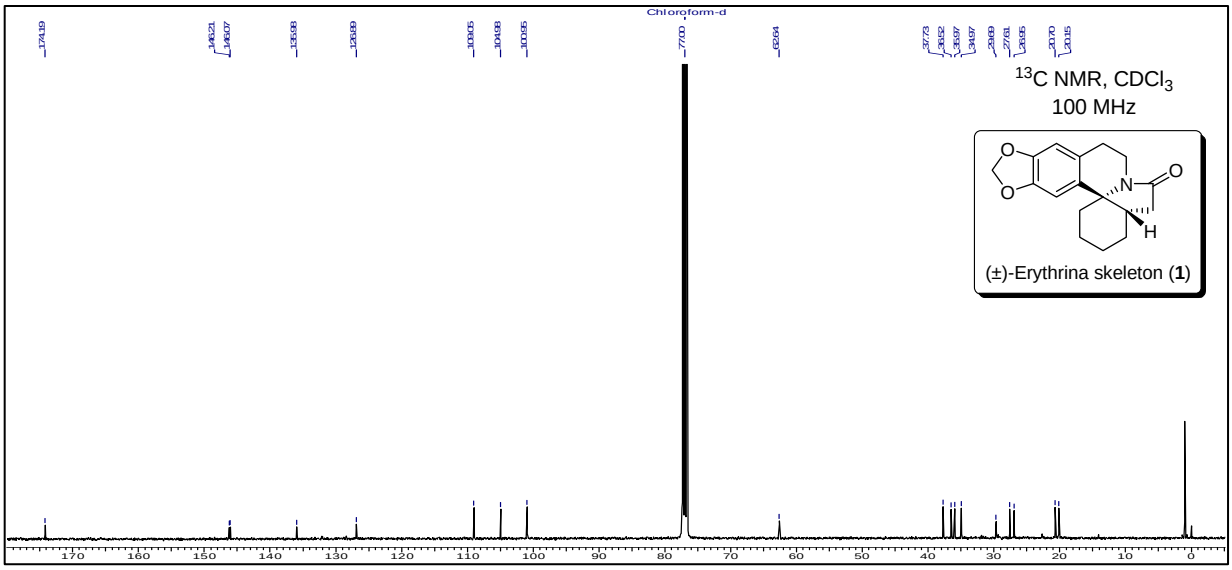
1-(3,4-Dimethoxyphenethyl)-3-(4-iodo-3-oxobutyl)pyrrolidine-2,5-dione (52). To a stirring solution of compound **51** (1.00 g, 2.16 mmol) in ethyl acetate (20 mL) was added IBX (668 mg, 2.38 mmol) and the reaction mixture was refluxed for 8 hours. After cooling the reaction mixture to room temperature, it was filtered and the obtained filtrate was concentrated in vacuo. The crude product obtained was further purified by silica gel column chromatography by using petroleum ether-ethyl acetate mixture (1:1) as an eluent to furnish the compound **52** as thick oil (856 mg, 86% yield). **IR** ($CHCl_3$) ν_{max} 00 cm^{-1}; **^{1}H NMR** ($CDCl_3$, 200 MHz) δ 1.90 (dq, J = 8 & 2 Hz, 2H), 2.28 (dd, J = 16 & 2 Hz, 1H), 2.65−2.92 (m, 6H), 3.37−3.80 (m, 2H), 3.83 (s, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 6.68−6.82 (m, 3H); **^{13}C NMR** ($CDCl_3$, 50 MHz) δ 5.8, 25.9, 32.8, 34.5, 35.8, 38.2, 39.6, 55.8 (2 carbon), 111.0, 111.9, 120.9, 129.9, 147.7, 148.7, 175.9, 179.1, 201.8.

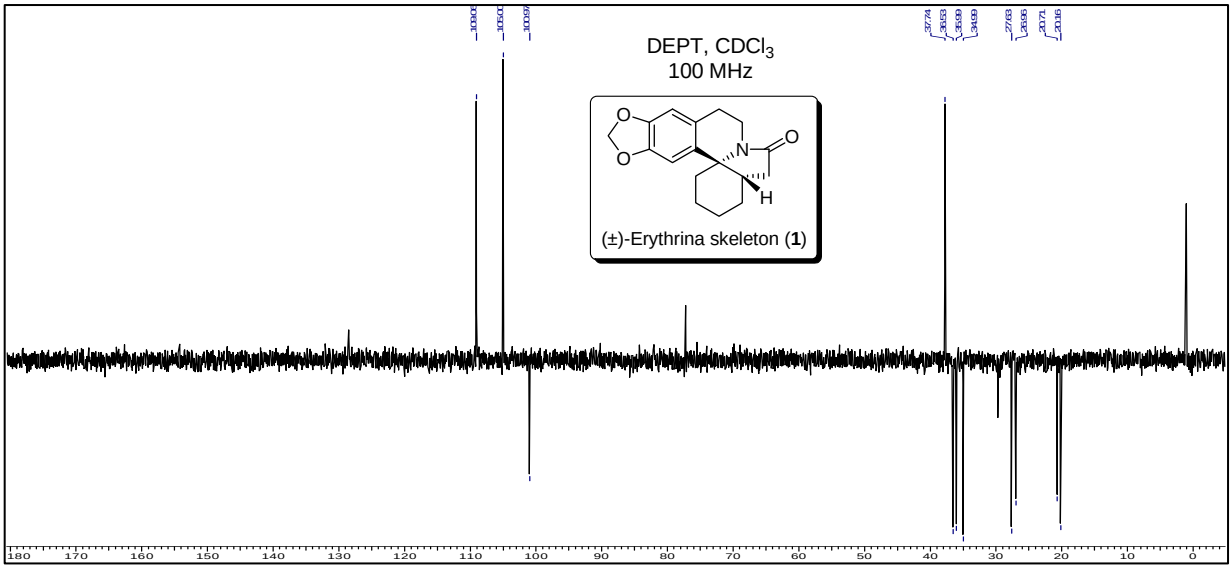


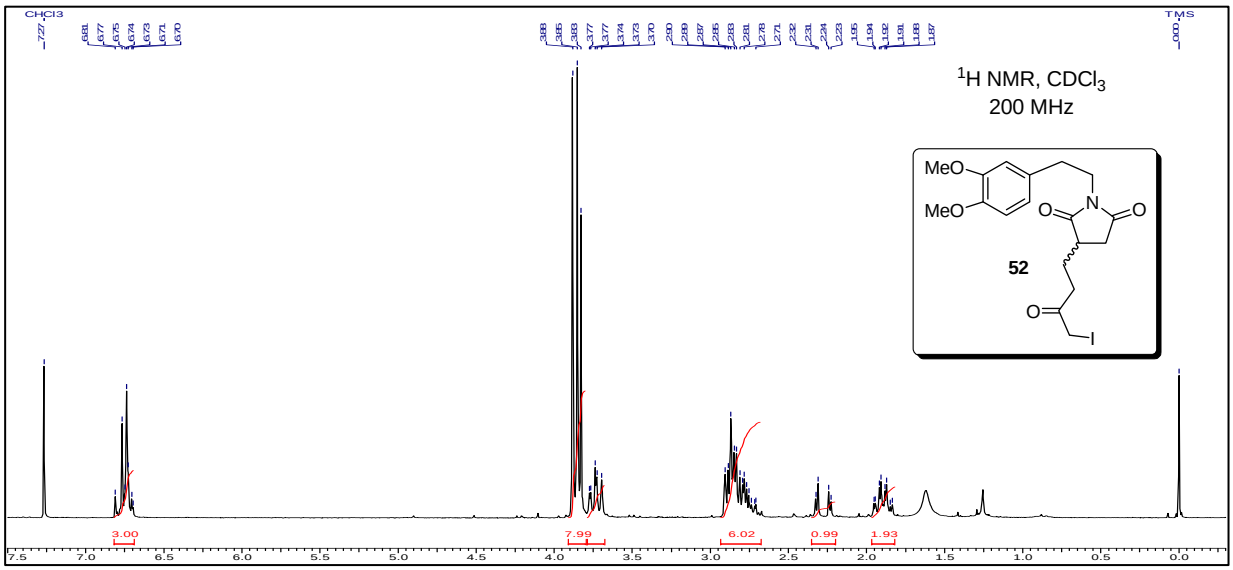
52: $C_{18}H_{22}INO_5$ (459.27)

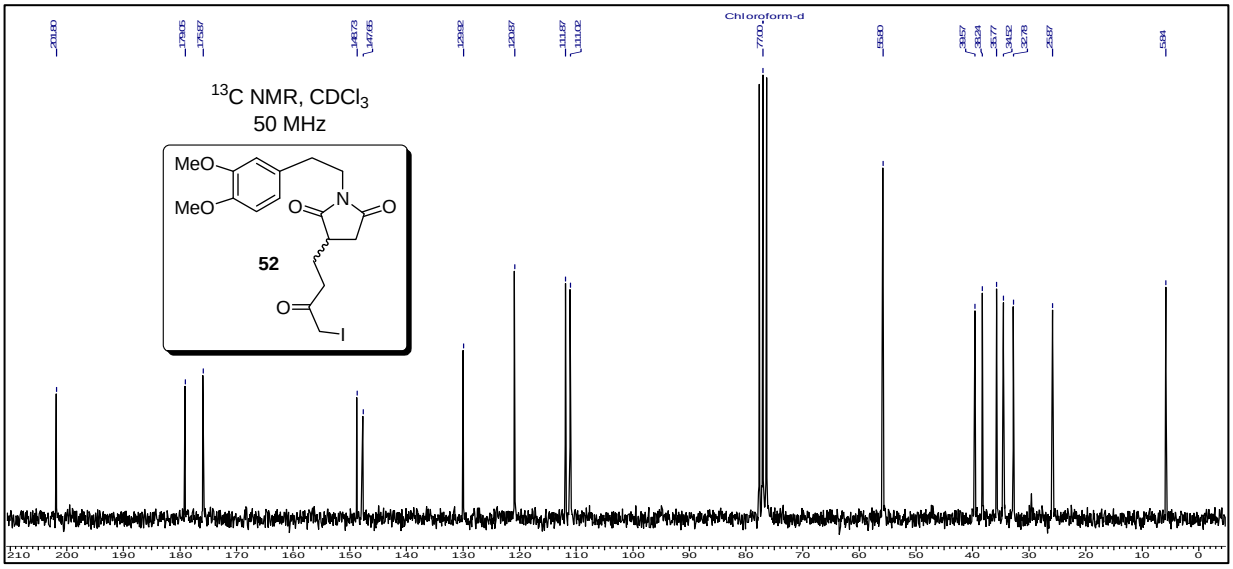
2C.6 Selected spectra

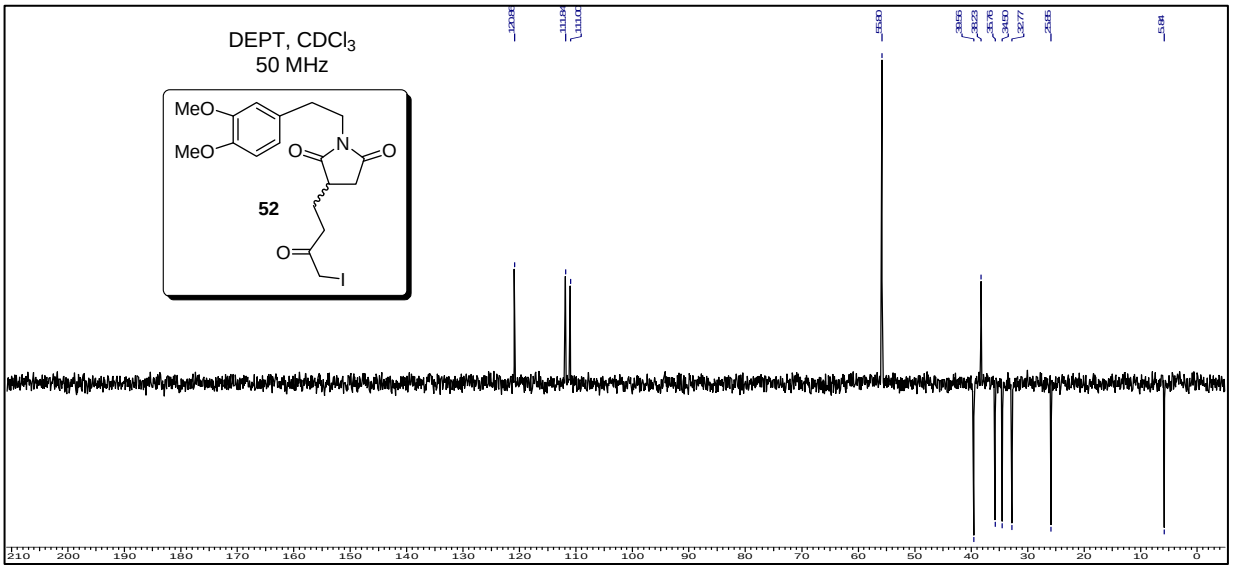

Chloroform-d
TMS
^{1}H NMR, CDCl$_3$
400 MHz
(±)-Erythrina skeleton (**1**)


Chloroform-d
^{13}C NMR, CDCl$_3$
100 MHz
(±)-Erythrina skeleton (**1**)


DEPT, CDCl$_3$
100 MHz
(±)-Erythrina skeleton (**1**)


^{1}H NMR, $CDCl_3$
200 MHz
MeO
MeO
O
N
O
52
O
I


^{13}C NMR, $CDCl_3$
50 MHz
MeO
MeO
O
N
O
52
O
I


DEPT, $CDCl_3$
50 MHz
MeO
MeO
O
N
O
52
O
I

2C.7 References

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Overall Conclusion

Development of novel carbon–carbon and carbon–heteroatom bond forming reaction for the synthesis of complex bioactive natural and synthetic products has been foremost area of research in synthetic organic chemistry. Present dissertation describes our studies towards the development of novel carbon–carbon and carbon–heteroatom bond forming reactions with the cyclic anhydride derivatives, and their applications for the facile synthesis of structurally interesting bioactive natural and synthetic products along with the concise account of the chemistry of homophthalic anhydrides and their derivatives. Homophthalic anhydrides/acids are a versatile synthons in organic synthesis. This small molecule with multiple functionalities has been efficiently utilized for building the backbones of many structurally complex and medicinally important molecules in a convergent manner.

Since many years, our research group is using cyclic anhydrides as the starting materials for the natural product synthesis; the considerable attempts have been made by us using homophthalic anhydrides for the synthesis of natural and synthetic products. We have attempted for the structure revision of the proposed natural product gusanlung D by using a general approach developed earlier in our group starting from homophthalic anhydride to synthesize claimed gusanlung D. The synthesis of isogusanlung D and dehydroisogusanlung D have been completed by taking the advantage of intramolecular radical induced cyclizations and Heck-coupling reaction, respectively. Unfortunately, the analytical and spectral data obtained for our proposed berberine analogues did not concur with the reported data of the natural product.

We have demonstrated the applications of serendipitously observed air-oxidation of homophthalimide for the synthesis of different natural and synthetic products. We have achieved a noteworthy total synthesis of nuevamine by using the facile air-oxidation of homophthalimide. We could isolate the reactive intermediate trione under neutral condition, which is responsible for the formation of final product isoindole from homophthalimide. The second application of air-oxidation propensity of homophthalimide was the stereoselective synthesis of (+)-isoindolo-*β*-carboline with high enantiomeric excess. Geometry-dependent demethoxycarbonylation, gain in the diastereoselectivity during the intramolecular dehydrative cyclization step and preservation of high enantiomeric excess at high temperature have been worth mentioning in this approach. Third application of the air-oxidation propensity was the five steps total synthesis of berberis natural products chilenine and deoxychilenine in decent overall yields. The use of

Parham cyclization for the construction of seven membered ring was the key feature of this approach.

We have also completed an efficient one-pot two-step synthesis of nuevamine and isonuevamine by taking the advantage of highly regioselective electronically and thermodynamically favored sodium borohydride reductions and sterically favored DIBAL-H reduction reactions. This provides a short access to these architectures using simple starting material over the all earlier approaches including our approach.

A short four steps access to (±)-erythrina skeleton has been described by taking the advantage of two sequential Wittig reactions. The developed protocol for the synthesis of this skeleton will be utilized for the synthesis of natural product (±)-erysotramidine. The work is in active progress towards the target molecule by taking in account the oxygenation pattern in A-ring of natural product. The developed strategy after the optimization of the non-classical Wittig reaction would be highly useful to develop natural and synthetic analogs as well as other natural products of erythrina family.

Perspective

Natural products are the secondary metabolites isolated from tissues of plants and fermentation broth of microorganisms. In recent years, there has been a great surge in finding lead compounds from marine sources as well. These substances have pharmacological effects, hence are used to cure various diseases, but the natural occurrence in very minute quantities limits their usefulness. Isolation of the natural products therefore becomes a difficult, slow, expensive and inefficient process. The laboratory synthesis has made it possible to access these substances in large quantities.

Organic chemistry is fascinating science which deals with the isolation, structure elucidation and laboratory synthesis of these secondary metabolites with the similar properties, chemical composition and structural arrangement of atoms in the space. In other words, it's a replication of Nature by making artificial molecules for well being of mankind. Although, it is not always easy to construct these metabolites in the laboratory, the huge efforts put in by large number of organic chemists have made it possible to synthesize any molecule in the laboratory routinely. Organic chemist is therefore an architect of constructing molecules of Nature.

Isolation of natural product is a continuous process and novel molecules are being isolated everyday and many more will be isolated in future. Each of these metabolites has different functionalities and structural architecture. Therefore, lots of new strategies, methodologies, reagents and chemical reactivities are needed to be continuously explored for synthesizing natural products and their analogues.

I feel extreme satisfaction and overwhelming happiness for being the student of such fascinating science. During the research tenure, we, in our research group could study the small part of organic synthesis, which provided us a nice opportunity for learning a lot of basic and applied chemistry, not only from our work but also from the vast literature. Our research group has successfully utilized cyclic anhydrides as the precursors in the organic synthesis, wherein, I used homophthalic anhydride and their derivatives for the synthesis of few natural and synthetic products. I feel that the novel carbon–carbon and carbon–heteroatom bond forming approaches, which we have developed, are quite general in nature and would be useful in designing several important natural products and their hybrids for structure activity relationship studies. On the basis of literature and our contribution in this field, it can be said with assurance that cyclic anhydrides will spread their wings still wider over the field of organic and pharmaceutical chemistry in near future.

List of Publications

(1) Facile air-oxidation of *N*-homopiperonyl-5,6-dimethoxyhomophthalimide: simple and efficient access to nuevamine
P. B. Wakchaure, S. Easwar, V. G. Puranik and N. P. Argade
Tetrahedron **2008**, *64*, 1786.

(2) A facile biogenetic synthesis of pulcheotine A
P. B. Wakchaure and N. P. Argade
Synthesis **2008**, 2321.

(3) Stereoselective synthesis of (+)-isoindolo-*β*-carboline
P. B. Wakchaure, V. G. Puranik and N. P. Argade
Tetrahedron: *Asymmetry* **2009**, *20,* 220.

(4) Syntheses of reported protoberberine gusanlung D
P. B. Wakchaure, S. Easwar and N. P. Argade
Synthesis **2009**, 1667.

(5) Regioselective $NaBH_4$ and DIBAL-H reductions of 3,4-dimethoxyhomopiperonyl-phthalimide: concise and efficient synthesis of nuevamine and isonuevamine
P. B. Wakchaure, S. S. Kunte and N. P. Argade
Indian J. Chem. **2011**, *50B*, 868.

(6) Intramolecular chemoselective acylation of suitably substituted isoindole: synthesis of chilenine and deoxychilenine
P. B. Wakchaure and N. P. Argade
Synthesis **2011**, in press.

(7) Synthetic studies towards erythrina alkaloids
P. B. Wakchaure and N. P. Argade
Unpublished results.

Erratum