“SYNTHETIC STUDIES IN HETEROCYCLIC COMPOUNDS”

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“SYNTHETIC STUDIES IN HETEROCYCLIC COMPOUNDS”

Thesis submitted for the degree of

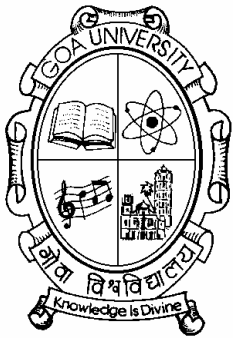
DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

By

Ms. Sonia G. Naik

To



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CERTIFICATE

Certified that the research work embodied in this thesis entitled "**Synthetic Studies in Heterocyclic Compounds**" has been carried out under my supervision and is bonafied work of **Ms. Sonia G. Naik**. This work is original and has not been submitted for any other degree of this or any other University.

(Prof. S. G. Tilve)
Goa University
Signature of Guiding Teacher

Date:

DECLARATION

I hereby declare that the research work incorporated in this thesis entitled "**Synthetic Studies in Heterocyclic Compounds**" is the result of investigations carried out by me at Department of Chemistry, Goa University, Goa-India, under the supervision of **Prof. S. G. Tilve**.

This work is original and has not been submitted for degree to this or any other University.

Date:

Ms. Sonia G. Naik
Goa University

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I have worked with a great number of people whose contribution in assorted ways to the research and the making of this thesis deserved special mention. It is a pleasure to convey my gratitude to them all in my humble acknowledgement.

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Ms. Sonia G. Naik

GENERAL REMARKS

1. Nuclear Magnetic Resonance spectra were recorded on a Bruker-300 MHz instrument using tetramethylsilane (TMS) as the internal standard. Chemical shifts have been expressed in δ ppm units downfield from TMS. Selected data are reported as follows. Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. s. = broad singlet, dd = doublet by doublet, dt = doublet by triplet and skewd t = skewd triplet), coupling constant (*J* in Hz), relative proton ratio and assignments. NMR spectra were obtained in deuterated chloroform unless otherwise stated. Multiplicities of carbon signals were obtained from DEPT experiment.
2. High Resolution Mass spectra (HRMS) were recorded on a MicroMass ES-QTOF Mass spectrometer.
3. IR spectra were recorded on a Shimadzu FT-IR spectrophotometer, (solids-KBr pellet/liquid-neat).
4. All melting and boiling points were measured by normal Thiels tube method and are uncorrected.
5. Distilled solvents used in all cases.
6. Commercial reagents were used without further purification.
7. All reagents were prepared using literature methods.
8. Hexanes or pet ether refers to petroleum fraction boiling between 60-80 ^{o}C.
9. All solvents and reagents were purified and dried by standard techniques.
10. All the reactions were monitored by thin layer chromatography (TLC) on silica gel (13% $CaSO_4$ as binder).
11. Column chromatography was performed on silica gel 60-120 mesh size.
12. Room temperature = 25-27 °C.

ABBREVIATIONS

General Abbreviations

anhyd.	:	anhydrous
b.p.	:	boiling point
cat.	:	catalytic
Equiv.	:	Equivalent
Expt.	:	Experiment
Fig.	:	Figure
FGI	:	Functional group interconversion
g	:	gram
glac.	:	Glacial
lit.	:	literature
mins.	:	minutes
mmol	:	millimole
m.p.	:	melting point
R.T./r.t.	:	room temperature
sat.	:	saturated
TLC	:	Thin layer chromatography
%	:	percentage
^{o}C	:	degree celcius
MW/M.W.	:	Microwave
mL	:	milliliter
o	:	Ortho
m	:	Meta
p	:	Para
conc.	:	concentrated
hr/hrs	:	hour/hours
MPa	:	Megapascals
aq.	:	aqueous
dil.	:	dilute
et al.	:	Et alia (and others)
mmHg	:	Millimeters of mercury

E	:	Eentegegen (opposite)
Z	:	Zissamen (together)

Compound abbreviations

Ac_2O	:	Acetic anhydride
AcOH	:	Acetic acid
9-BBN	:	9-Borabicyclo[3.3.1]nonane
DBU	:	Diazabicycloundecene
BIMs	:	Bis(indolyl)methanes
Boc_2O	:	Di-tert-butyl dicarbonate
n-BuLi	:	*n*-Butyl lithium
t-BuLi	:	*tert*-Butyl lithium
CAN	:	Cerric ammonium nitrate
m-CPBA	:	*m*-Chloroperbenzoic acid
DCE	:	Dichloroethane
DCM	:	Dichloromethane
DIBAL-H	:	Diisobutylaluminium hydride
DMAP	:	4-Dimethyl amino pyridine
DMF	:	*N*,*N*-Dimethylformamide
DMS	:	Dimethyl sulphate
DMSO	:	Dimethyl sulfoxide
EDC	:	Ethylene dichloride
Et	:	Ethyl
Et_2O	:	Diethyl ether
EtOAc	:	Ethyl acetate
EtOH	:	Ethanol
HCl	:	Hydrochloric acid
HNO_3	:	Nitric acid
H_2SO_4	:	Sulphuric acid
K_2CO_3	:	Potassium carbonate
LAH	:	Lithium aluminium hydride
LDA	:	Lithium diisopropylamide
Me	:	Methyl

MeCN	:	Acetonitrile
MeOH	:	Methanol
NaOAc	:	Sodium acetate
NaOH	:	Sodium hydroxide
NaOMe	:	Sodium methoxide
Na_2SO_4	:	Sodium sulphate
NBS	:	*N*-Bromosuccinimide
PBr_3	:	Phosphorous tribromide
PCC	:	Pyridinium chlorochromate
PCy_3	:	Tricyclohexylphosphine
Pet ether	:	Petroleum ether
Ph_2O	:	Diphenyl ether
PMA	:	Phosphomolybdic acid
PPA	:	Polyphosphoric acid
PPh_3	:	Triphenyl phosphine
PTSA	:	*p*-Toluenesulfonic acid
TBAB	:	Tetra butyl ammonium bromide
TFA	:	Trifluoro acetic acid
THF	:	Tetrahydrofuran

Spectroscopic abbreviations

IR	:	Infra Red
PMR (^{1}H-NMR)	:	Proton Magnetic Resonance
Calcd	:	Calculated
$CDCl_3$	:	Deuterated chloroform
CMR (^{13}C-NMR)	:	Carbon-13 Magnetic Resonance
cm^{-1}	:	Frequency in wavenumber
δ	:	Delta (Chemical shift in ppm)
DEPT	:	Distortionless Enhancement by Polarisation Transfer
DMSO-d_6	:	Deuterated dimethyl sulfoxide
GC-MS	:	Gas chromatography-Mass spectrometry
Hz	:	Hertz
J	:	Coupling constant

MHz	:	Megahertz
ppm	:	Parts per million
br.s	:	Broad singlet
d	:	Doublet
t	:	Triplet
q	:	Quartet
m	:	Multiplet
dd	:	Doublet of doublet
M^+	:	Molecular ion
m/z	:	Mass to charge ratio

Papers published in Journals:

1) An efficient synthesis of α-(alkylidene)-5,5-dimethyl-δ-lactones, **Parsekar, S. B.**; Amonkar, C. P.; Nadkarni, V. S.; Tilve, S. G. *Indian J. Chem. B* **2009,** *48B,* 1333.
2) Convenient synthesis of 2,2-Dimethyl-3,4-dihydro-2H-pyrano[2,3-*b*] quinoline, **Parsekar, S. B.**; Amonkar, C. P.; Parameswaran, P. S.; Tilve, S. G. *Synth.Commun.* **2010**, *40*, 3251-3258.
3) Convenient synthesis of Mukonine, **Parsekar, S. B.**; Tilve, S. G. (manuscript under preparation).
4) Graphite catalyzed conjugate addition of indole and 2-methyl indole to electron deficient olefins, **Parsekar, S. B.**; Tilve, S. G. (manuscript under preparation).

Conferences attended:

1) Poster presented at Advances in Organic chemistry and chemical biology, conference held in Jan **2006**, at IICT Hyderabad (selected for best poster award).
2) Poster presented at International conference on Advances in Drug Discovery Research, held in Feb **2007**, Aurangabad.
3) Royal Society of Chemistry, West India Section-Research Scholars symposium held in October **2008** at Goa University.
4) Chemical Research Society of India meeting held in February **2009** at NCL Pune.

Dedicated

to

My Mother

Late Mrs. Usha G. Naik

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CHAPTER 1

CHAPTER 1

Synthesis of α-(alkylidene)-5,5-dimethyl-δ-lactones

Introduction

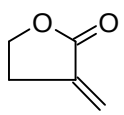
A lactone is a cyclic ester which can be seen as the condensation product of an alcohol group –OH and a carboxylic acid group –COOH in the same molecule. The most stable structure for lactones is the 5-membered lactones (gamma lactones) and 6-membered lactones (delta-lactones) because of the minimal angle strain in such structures. A large number of naturally occurring gamma lactones and delta lactones contain an exocyclic double bond with substitution on it, and are known as α-(alkylidene substituted) γ lactones **1** and α-(alkylidene substituted) δ lactones **2** respectively (**Fig. 1**).

1 **2**

Fig. 1

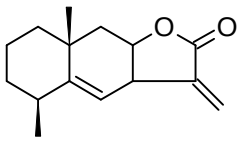
These α-(alkylidene substituted) lactones constitute an important group of natural products,[1] especially as insect pheromones,[2] flavor components, and essential oils.[3] In addition, these molecules have been used as synthetic precursors for cyclopentanones, butenolides, furans,[4] and natural lignans.[5,6]

The representative members shown below exemplify the structural diversity found within this class of natural products (**Fig. 2**).



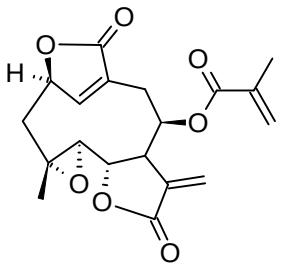
Tulipalin A

3



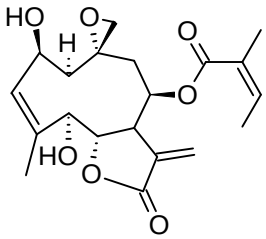
Alantolactone

4



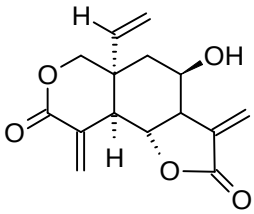
Elephantopin

5



Euparotin

6



Vernolepin

7

Fig. 2

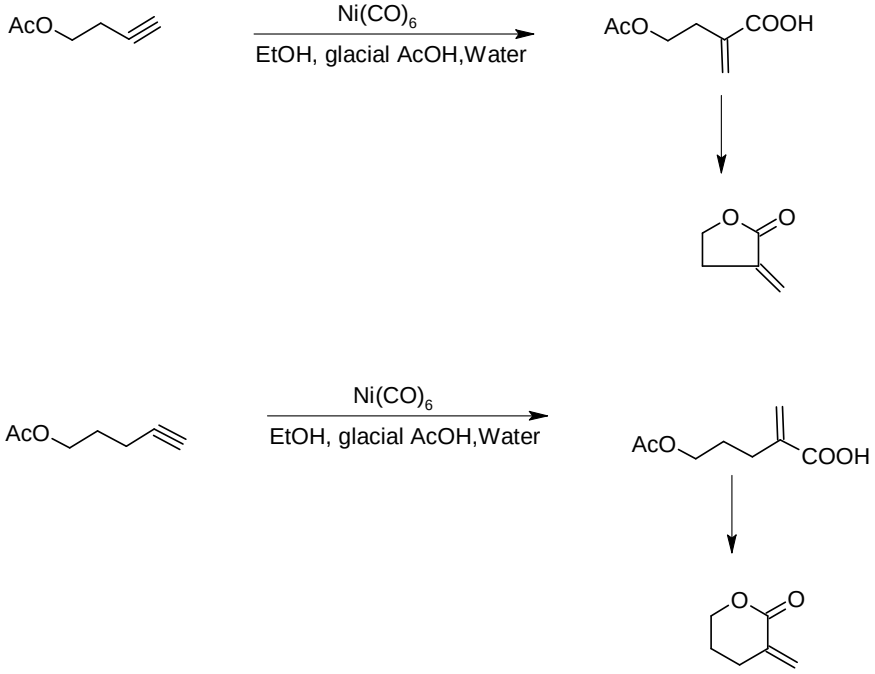
These include α-methylene-γ-butyrolactone, tulipalin A **3**,[7] the simplest member of this class of natural products and alantolactone **4**,[8] vernolepin **7**,[9] a sesquiterpene tumor inhibitor, possesses in addition to the α-methylene-γ-lactone structural feature, an α-methylene-δ-lactone function. Further structural diversity is exemplified by euparotin **6**[10] which possesses an α-methylene-γ-lactone unit trans-fused to a cycloheptane ring and by elephantopin **5**[11] which possesses the same structural unit trans-fused to a ten membered ring.

These compounds have received much attention due to the biological activities associated with them, such as cytotoxicity,[12] antitumor,[13] antibacterial,[14] plant growth inhibition,[15] antifungal[16] and antiallergic properties.[17] These activities are mainly attributed to the presence of unsaturation which acts as (Michael acceptor) alkylating agent.

Literature Review

α-(Alkylidene substituted)-lactones are a target for developing synthetic methodologies due to their widespread occurrence in a variety of biologically active natural products.

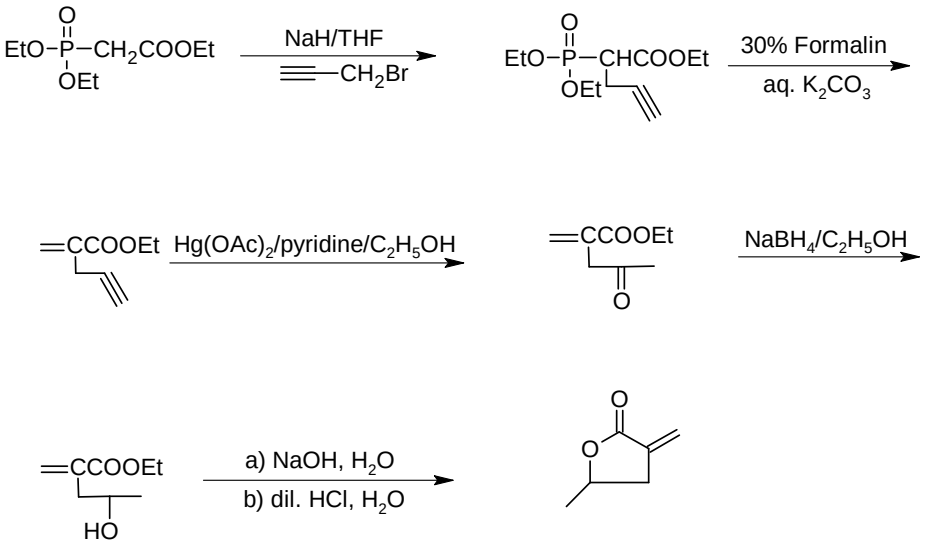
Although there are various methods[18-26] available for the synthesis of α-(alkylidene substituted)-γ-lactones, for the corresponding δ-lactones there are only a few reports. One of the earliest syntheses of α-methylene lactone is reported by Jones *et al*.[27] They have reacted acetate of but-3-yn-1-ol in ethanol containing glacial acetic acid in presence of water with nickel carbonyl to get the α-methylene-γ-lactone. The same strategy was also extended for the preparation of the α-methylene-δ-lactone (**Scheme I**).



Scheme I

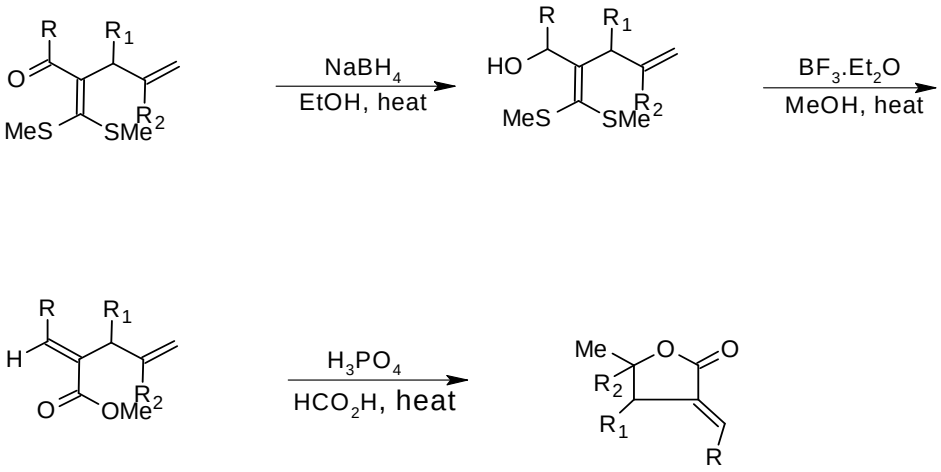
Some of the recent methods for the synthesis of α-(alkylidene) lactones are mentioned below –

Rajgopalan *et al*.[28] reported the synthesis of γ-methyl-α-methylene butyrolactone via alkylation of phosphonate, followed by Wittig-Horner reaction, hydration, reduction and lactonisation (**Scheme II**).



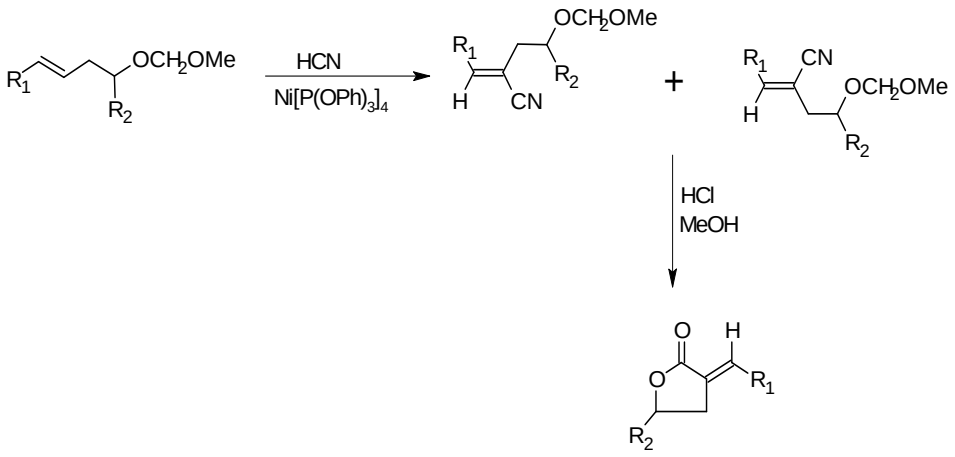
Scheme II

Junjappa *et al.*[29] describes the synthesis of α-(alkylidene)-γ-butyrolactones which involves reduction of keto group of dithioacetals to alcohol with sodium borohydride in refluxing ethanol, followed by methanolysis with borontrifluoride etherate, and heating with a mixture of phosphoric and formic acid (1:1) (**Scheme III**).



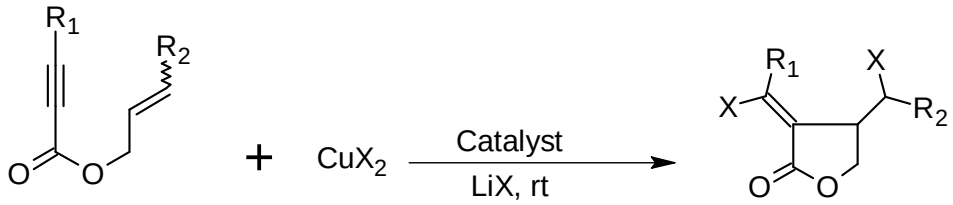
Scheme III

Smallridge *et al.* [30] have carried out hydrocyanation of protected β-hydroxyalkenes to give unsaturated nitriles which on treatment with HCl underwent cyclization to α-alkylidene-γ-lactones (**Scheme IV**).



Scheme IV

Jiang *et al*. [31] have reported a synthesis of the α-alkylidene-γ-butyrolactones from acyclic ester precursor, 2'-alkenyl 2-alkynoates using $CuCl_2$ or $CuBr_2$ in presence of $PdCl_2(PhCN)_2$ in acetonitrile or $Pd_2(dba)_3.CHCl_3$ in acetic acid and LiCl or LiBr at room temperature (**Scheme V**).



Z or *E*

R_1=H, alkyl; R_2=H, alkyl; X=Cl, Br

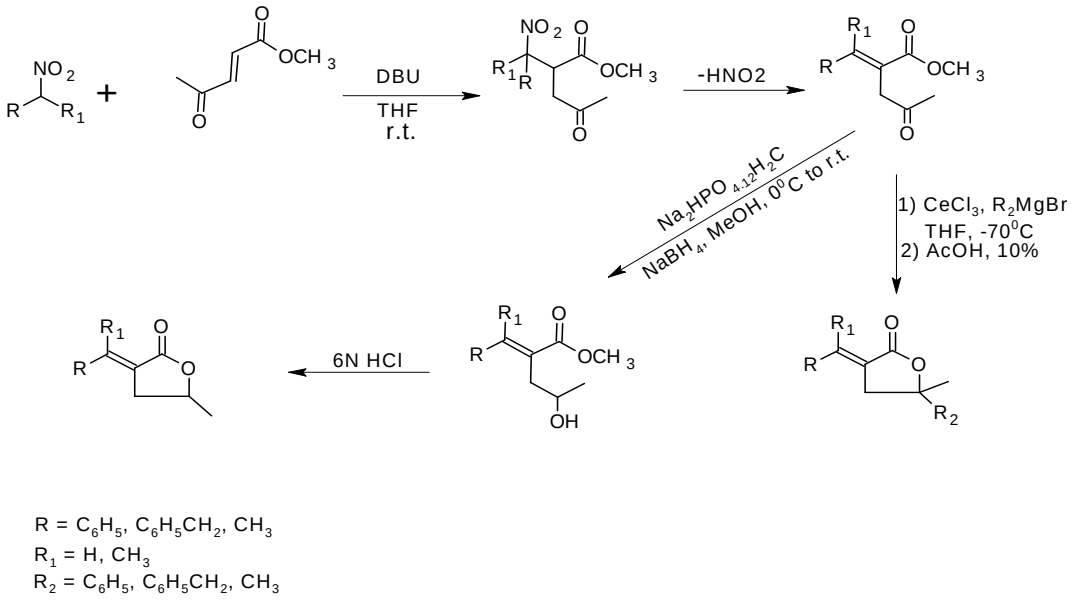
Catalyst- $PdCl_2(PhCN)_2$ in acetonitrile (X=Cl)

$Pd_2(dba)_3.CHCl_3$ in acetic acid (X=Br)

Scheme V

Ballini *et al*.[32] have developed a simple methodology for the synthesis of various γ-substituted-α-(alkylmethylene)-γ-butyrolactones. In this method the steps involved are Michael addition of nitroalkanes to enones, base mediated elimination, reduction of keto function, and followed by acid mediated lactonisation. Selective addition of

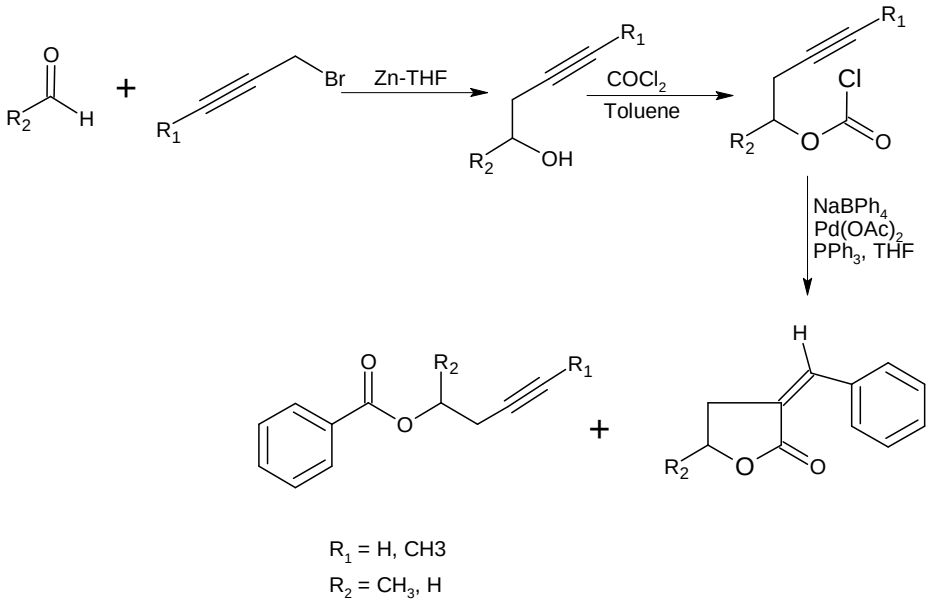
Grignard reagent to keto group of the unsaturated ester furnished γ,γ-disubstituted lactones (**Scheme VI**).



R = C_6H_5, $C_6H_5CH_2$, CH_3
R_1 = H, CH_3
R_2 = C_6H_5, $C_6H_5CH_2$, CH_3

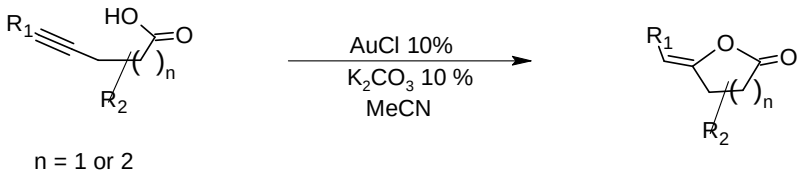
Scheme VI

Grigg *et al.*'s[33] synthesis involves preparation of appropriate chloroformates from homopropargylic alcohols with $COCl_2$ in toluene followed by cyclisation in presence of $NaBPh_4$ as the anion capture reagent in THF at 65-70 ^oC in the presence of $Pd(OAc)_2$ (10 mol %) and PPh_3 (20 mol %), to give the α-methylene-γ-butyrolactones (**Scheme VII**).



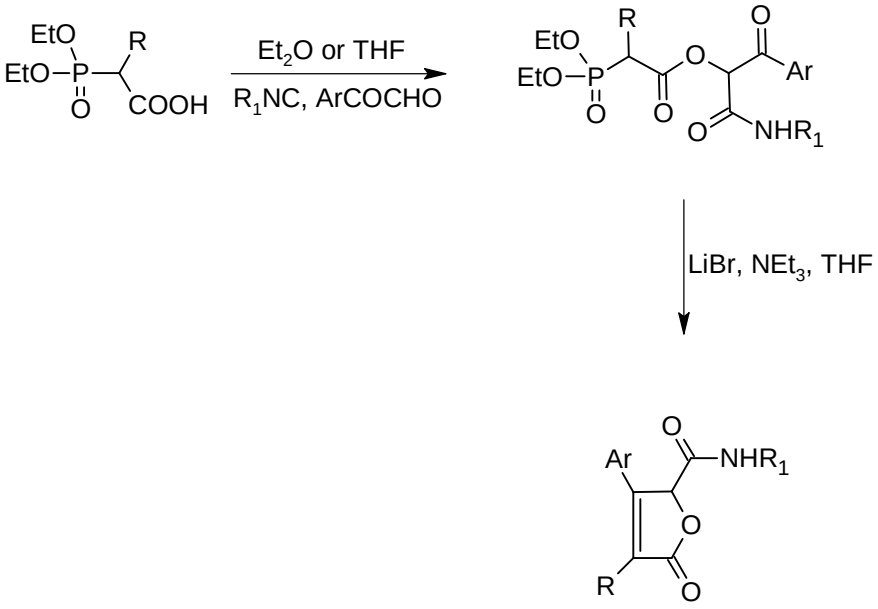
Scheme VII

Patrick *et al.*[34] have developed a method for the synthesis of both γ- and δ- alkylidene lactones by intramolecular cyclisation of ω-acetylenic acids catalysed by AuCl in acetonitrile at room temperature (**Scheme VIII**).



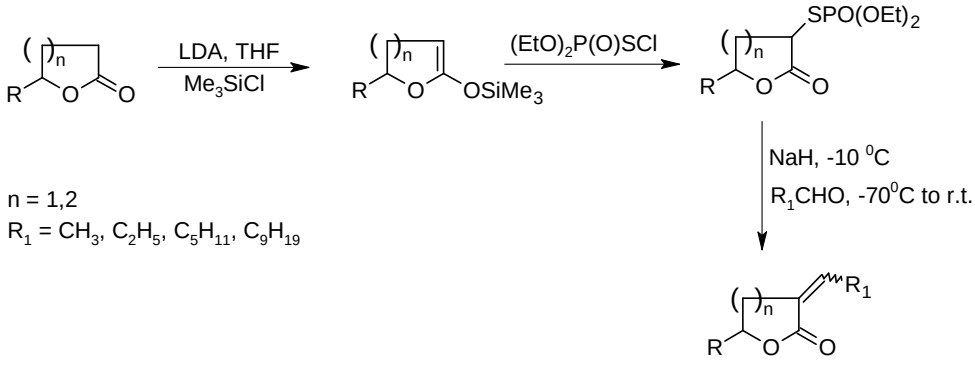
Scheme VIII

Sweeney *et al.* [35] have synthesized γ-lactones via a Passerni-like three component condensation. The first step is the combination of an aryl glyoxal with an aryl isonitrile and a 2-substituted –2-(diethoxyphosphoryl) acetic acid. The product of this reaction 2-[2-(phosphoryl) acetoxy]ketoamide is then cyclised by H.W.E. reaction upon exposure to LiBr and NEt_3 in THF, to give α-alkylidene lactones (**Scheme IX**).



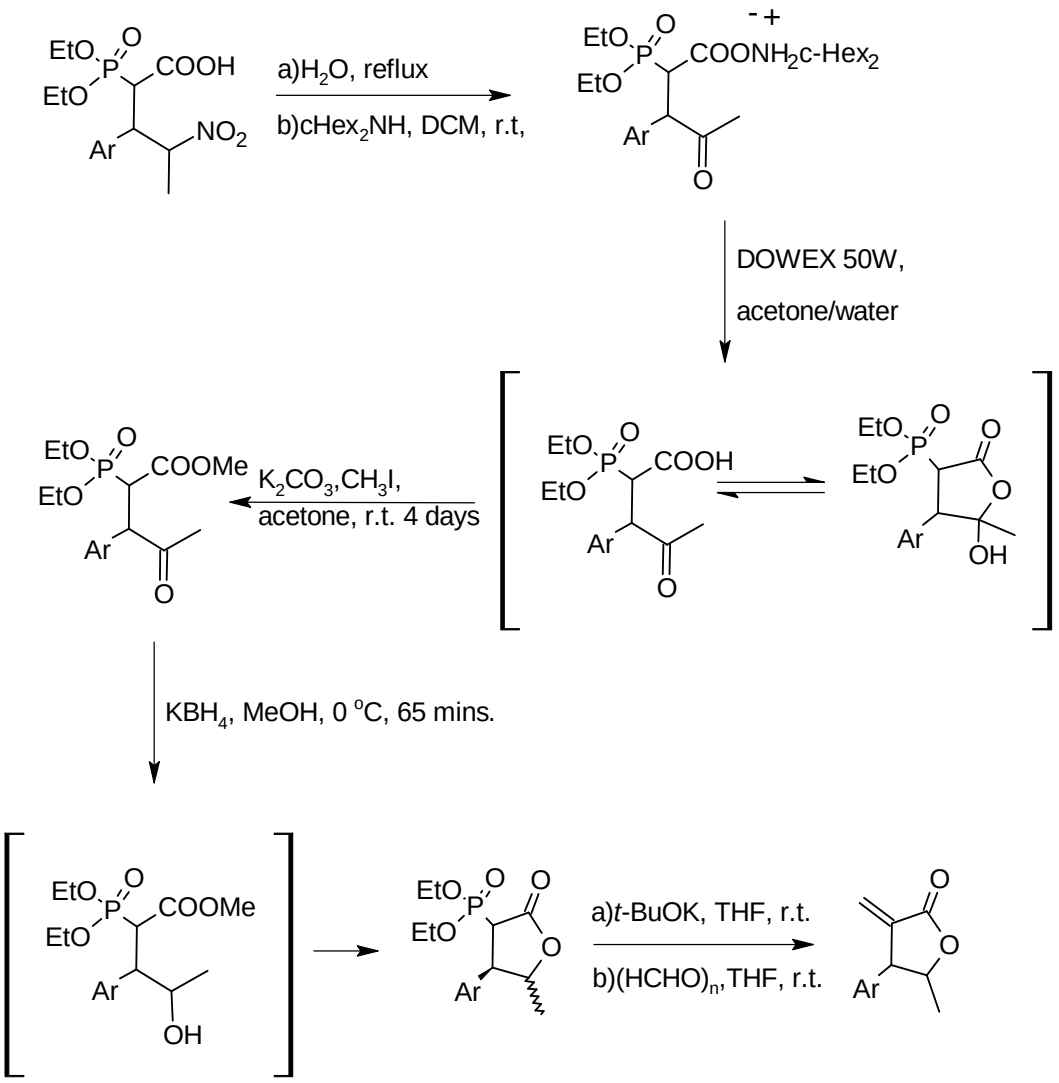
Scheme IX

Krawczyk *et al*.[36] have developed methodology for the synthesis of α-alkylidene γ- and δ-lactones. For this purpose they prepared *O*-silylated lactones from the appropriate lactones using LDA, THF and Me_3SiCl, followed by thiophosphorylation with *O,O*-diethyl chlorothiophosphonate. Next, the thiophosphate anions were generated by the action of sodium hydride and were reacted with various aldehydes to get the α-alkylidene lactones (**Scheme X**).



Scheme X

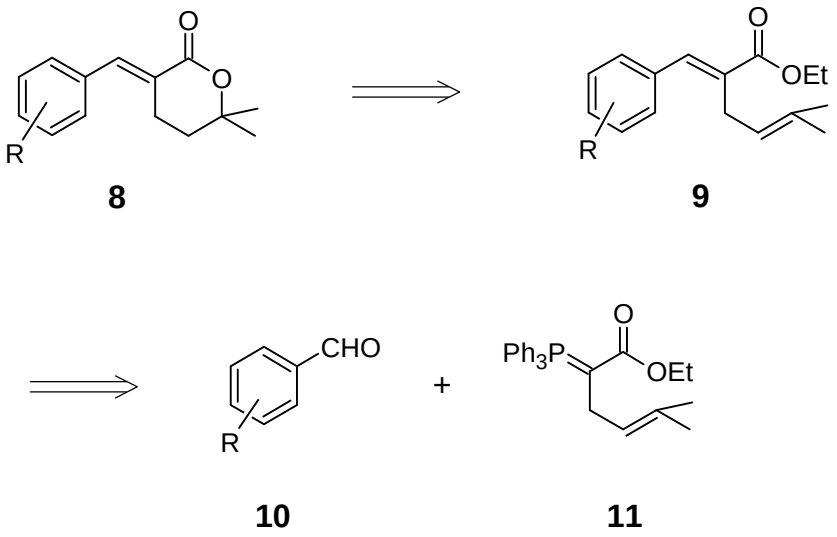
Albrecht *et al*.[37] reported the synthesis of α-methylene butyrolactone from 3-aryl-2-diethoxyphosphoryl-4-nitroalkanoic acid. The first step was the Nef reaction followed by esterification. Further, they reduced this ester to afford the corresponding γ-hydroxyalkanoates which spontaneously got lactonized to α-diethoxyphosphoryl-γ-lactone. This lactone was then converted to α-methylene butyrolactone using Horner-Wadsworth-Emmons olefination (**Scheme XI**).



Scheme XI

Present Work

From above literature survey it is evident that there are number of methods available for the synthesis of α-alkylidene-γ-butyrolactones. However, there are few methods available for the synthesis of corresponding δ-lactones. So, we were interested in synthesizing δ-lactones having α-alkylidene groups. Our retrosynthesis for such α-(alkylidene)-5,5-dimethyl-δ-lactones is shown below (**Scheme XII**).

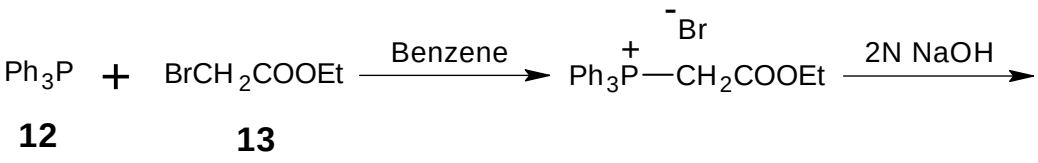


8 **9** **10** **11**

Scheme XII

Thus phosphorane **11** could react with aldehydes (**10**) to give unsaturated esters (**9**) which then could be cyclized to give targeted compounds **8.**

The prenyl phosphorane **11** was prepared by literature method[38] involving two steps. In the first step triphenyl phosphine (**12**) was reacted with ethylbromoacetate (**13**) to get a salt, which after basic workup furnished a stable carboethoxymethylenetriphenyl phosphorane (**14**) (**Scheme XIII**).



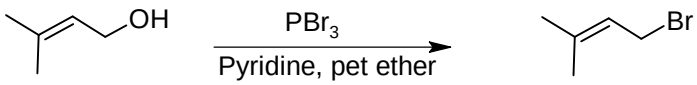
12 **13**

$Ph_3P{=}CHCOOEt$

14

Scheme XIII

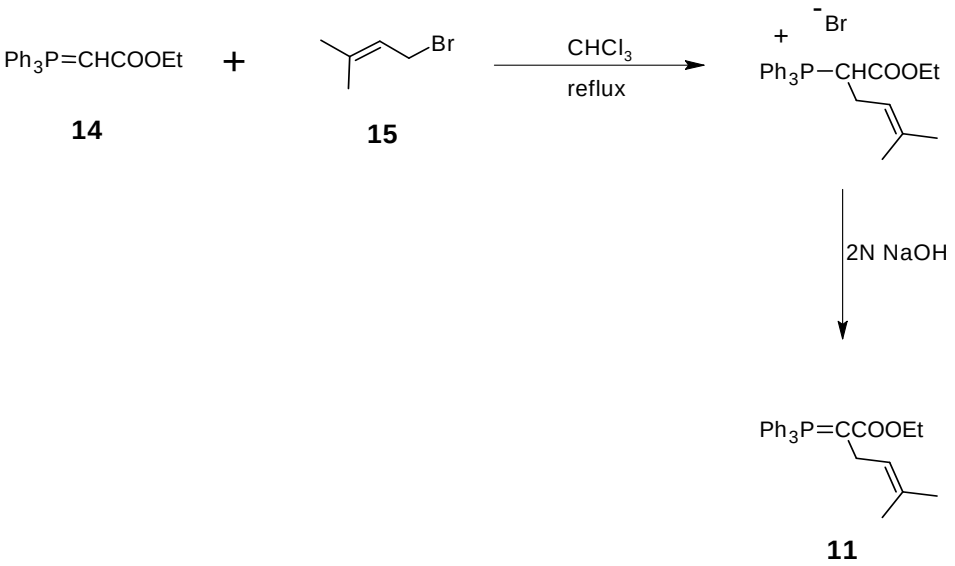
Prenyl bromide was prepared by reaction of 3-methyl-2-buten-1-ol with PBr_3 in presence of pyridine in petroleum ether (**Scheme XIV**).



15

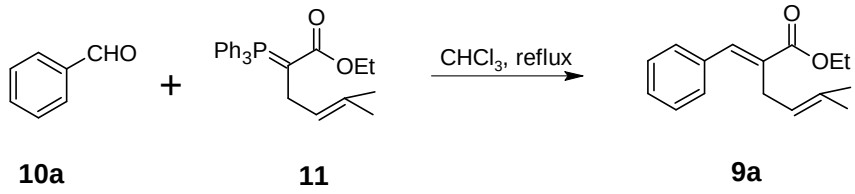
Scheme XIV

In the next step alkylation of stable phosphorane **14** was carried out with prenyl bromide (**15**) to get a salt, which after the usual basic workup gave the required prenyl phosphorane **11** (**Scheme XV**).



Scheme XV

Our next step was to condense this prenyl phosphorane **11** with benzaldehyde (**10a**), (**Scheme XVI**).



Scheme XVI

This was accomplished by refluxing benzaldehyde (**10a)** with prenyl phosphorane **11** in chloroform for 3.0 hours. TLC of the reaction mixture showed disappearence of the starting benzaldehyde (**10a**) and appearence of a new spot along with the lower spot of triphenyl phosphine oxide. The solvent was evaporated and the crude product was purified by column chromatography over silica gel using hexanes: EtOAc (9:1) as an eluent to obtain a pleasant smelling viscous liquid.

Its IR spectrum exhibited a strong band at 1709 cm^{-1} which indicated the presence of a conjugated ester carbonyl bond.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz, δ ppm) (**Fig. I**) showed signal at δ 1.35 (t, *J* = 6.9 Hz, 3H) and δ 4.30 (q, *J* = 6.9 Hz, 2H) which was attributed to $–OCH_2CH_3$ group of ester moiety. The peaks observed at δ 1.67 (s, 3H) and δ 1.75 (s, 3H) were assigned to the protons on allylic methyl groups. The peaks seen at δ 3.24 (d, *J* = 6.3 Hz, 2H) and δ 5.18 (m, 1H) was due to the methylene protons and CH of prenyl group ($-CH_2CH=C<$). The signal observed at δ 7.38 (m, 5H) was attributed to aromatic protons of phenyl ring while the peak seen at δ 7.71 (s, 1H) was assigned to the benzylic proton. The downfield shift of this proton indicated it to be *cis* to the $–COOCH_2CH_3$ group (*E* geometry).

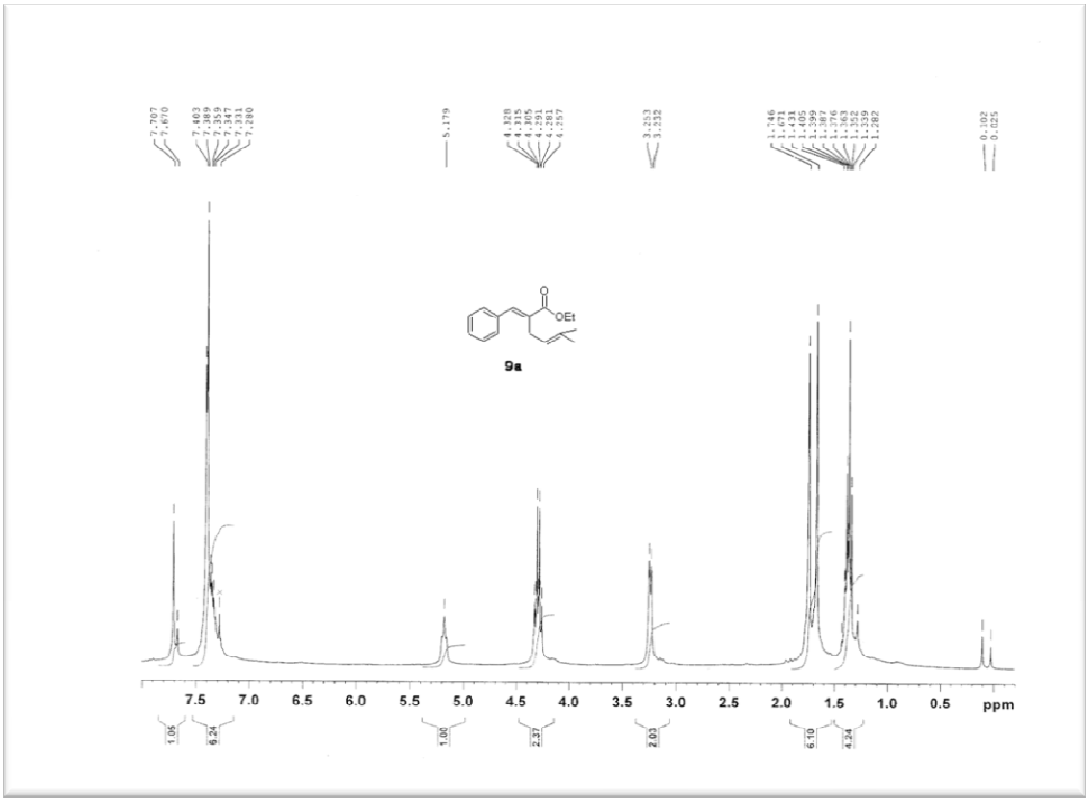


Fig. I : ^{1}H-NMR spectrum of Compound **9a**

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz, δ ppm) (**Fig. II**) showed peaks at δ 14.29 (CH_3), 17.95 (CH_3), 25.74 (CH_3), 26.84 (CH_2), 60.77 (OCH_2), 121.68 (CH), 128.26 (CH), 128.36 (2 X CH), 129.35 (2 X CH), 132.62 (CH), 132.93 (C), 135.81 (C), 138.74 (CH), 168.34 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

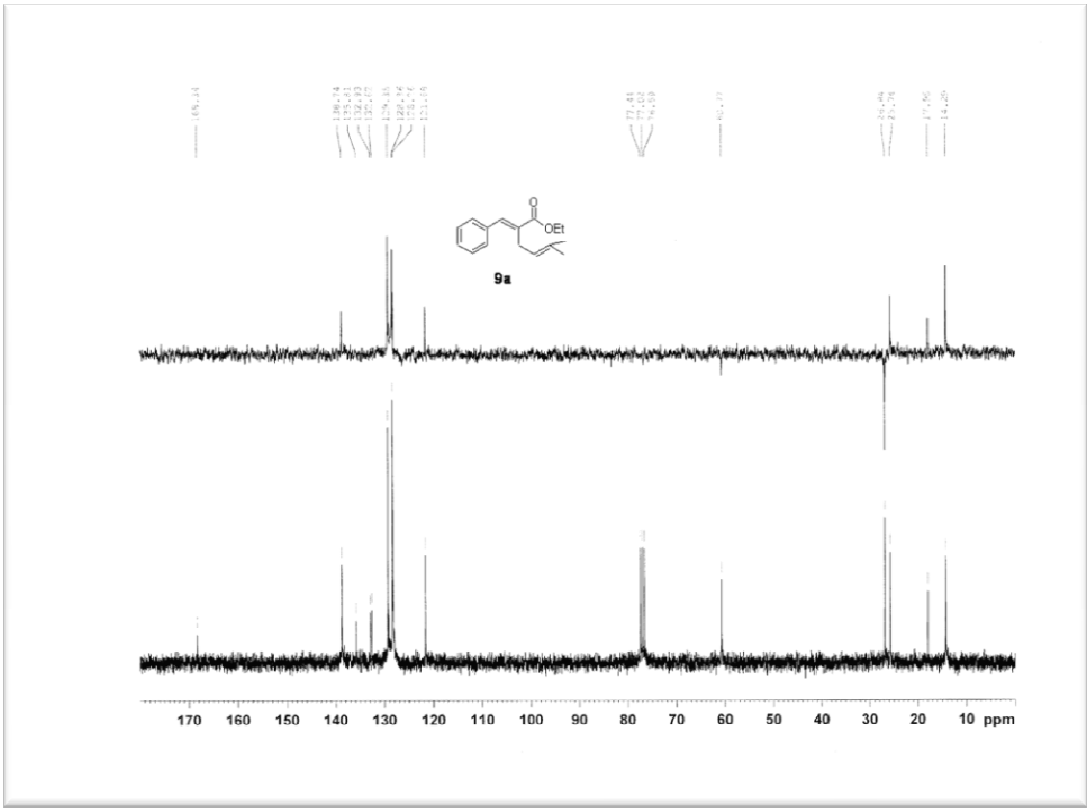
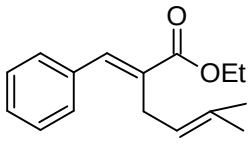


Fig. II : ^{13}C-NMR spectrum of Compound **9a**

The GC-MS of this compound showed peak at *m/z* 244 (M^+).

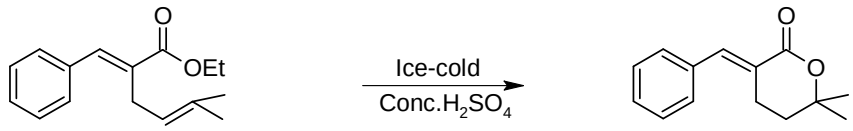
The boiling point of this compound was 134-39 ^oC/0.06 mmHg (Bath temperature).

Hence, based on the mode of formation and spectral data, the ester should have structure **9a**. The yield of the product ester from **10a** was found to be 92%.



9a

Our next aim was to carry out the cyclisation of the α,β-unsaturated ester (**9a**), and we thought to explore sulphuric acid catalysed cyclisation for this purpose (**Scheme XVII**).



9a **8a**

Scheme XVII

The pleasant smelling viscous ester **9a** was subjected to conc. sulphuric acid in an ice-cold condition for one hour, after which there was seen a new spot on TLC and absence of the reactant spot. The crude liquid obtained after workup was purified by column chromatography over silica gel using hexane-EtOAc (9:1) as an eluent to obtain a viscous liquid.

The IR spectrum of this compound showed strong band at 1703 cm^{-1} which was attributed to the carbonyl group of α,β-unsaturated six membered lactone.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz, δ ppm) showed peaks at δ 1.46 (s, 6H), δ 1.90 (t, *J* = 6.9 Hz, 2H) and δ 2.92 (dt, *J* = 6.9 Hz & 2.1 Hz, 2H) which were attributed to the two methyl groups and two methylene groups ($-CH_2-CH_2-$) of the six membered lactone respectively. The peaks observed at δ 7.38-δ 7.51 (m, 5H) were assigned to aromatic ring protons. While the signal at δ 7.96 (br.s, 1H) was attributed to the benzylic proton.

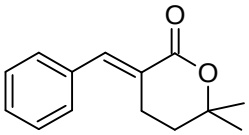
The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz, δ ppm) showed peaks at δ 22.69 (CH_2), 27.80 (2 X CH_3), 33.16 (CH_2), 80.19 (C), 124.42 (C), 128.55 (2 X CH), 129.14 (CH), 130.33 (2 X CH), 135.13 (C), 141.51 (CH), 167.10 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

The high resolution mass spectrum of the compound displayed strong peak at *m/z* 239.1049 presumably due to $[M+Na]^+$ pseudo ions. The elemental composition of which was determined to be $C_{14}H_{16}O_2$. HRMS *m/z* calculated for $C_{14}H_{16}O_2Na[(M+Na)^+]$ was 239.1048, found : 239.1049.

The boiling point of this compound was found to be 140-45 ^{o}C/0.09 mmHg (Bath temperature).

Based on the above spectral data and mode of formation, structure **8a** was assigned to the expected lactone having *E* geometry indicating that there is no change in stereochemistry occurred during cyclisation. The yield of the product was found to be 57%.



8a

Thus, successfully we were able to get the expected δ lactone **8a**, but we were not satisfied with the yield obtained in the final cyclisation step. Hence, more efforts were put to improve the yield in this step.

Our second attempt was to use polyphosphoric acid as a cyclising agent (**Scheme XVIII**).

9a **8a**

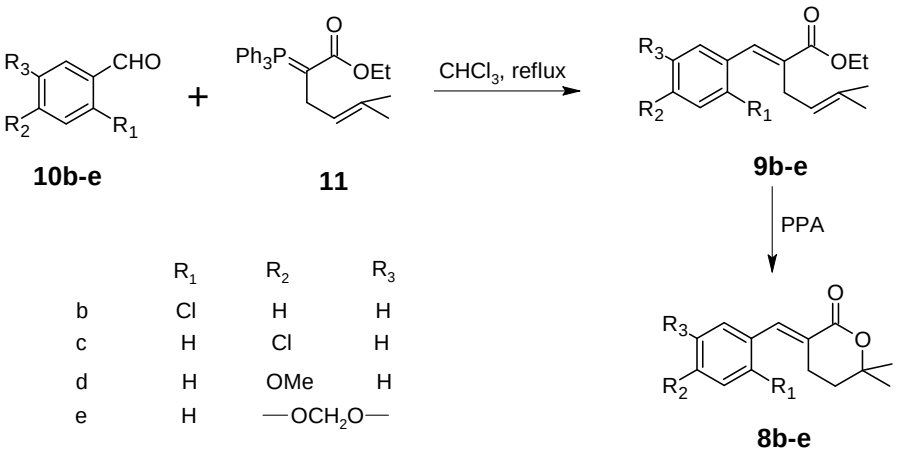
Scheme XVIII

Accordingly, the α,β-unsaturated ester **9a** was subjected to PPA cyclisation, where it was warmed with PPA for 5 minutes to get the product. The progress of the reaction was monitored by TLC. The crude product obtained after the workup was purified by column chromatography over silica gel using hexane-EtOAc (9:1) as an eluent to furnish a viscous liquid.

This viscous liquid was found to be the same δ lactone **8a** which was obtained in previous sulphuric acid cyclisation protocol as indicated by its appearence on TLC and other spectroscopic analysis. The yield of the product was found to be 96%.

Hence, gratifyingly we succeeded in increasing the yield from 57% to 96%.

After this success, we thought to generalise this protocol to prepare series of δ lactones which could be tested for their biological activities. Hence, the strategy was extended for the aromatic aldehydes having both electron withdrawing as well as electron donating groups as shown in **Scheme XIX**.



	R_1	R_2	R_3
b	Cl	H	H
c	H	Cl	H
d	H	OMe	H
e	H	—OCH_2O—	

Scheme XIX

The Wittig reaction of *o*-chlorobenzaldehyde (**10b**) which has electron withdrawing group at *ortho* position was done in refluxing chloroform for 2 hrs and 45 mins. The progress of the reaction was monitored by TLC. After the reaction was complete the column chromatographic purification of the crude product over silica gel using hexanes-EtOAc (9:1) as eluent gave a pleasant smelling viscous liquid.

IR (KBr) : 1713 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm):

δ 1.28	t	3 H (*J* = 7.2 Hz)	- $OCH_2\underline{CH_3}$
δ 1.54	s	3 H	- CH_3
δ 1.64	s	3 H	- CH_3
δ 3.03	d	2 H (*J* = 6.6 Hz)	- $\underline{CH_2}$-CH =
δ 4.23	q	2 H (*J* = 7.2 Hz)	- $O\underline{CH_2}CH_3$
δ 5.07	m	1 H	- CH_2-$\underline{CH}$ =
δ 7.23	m	3 H	ArH
δ 7.36	m	1 H	ArH
δ 7.68	s	1 H	Ar-$\underline{CH}$ = C

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

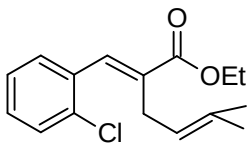
δ 14.24 (CH_3), 17.79 (CH_3), 25.70 (CH_3), 27.04 (CH_2), 60.88 (OCH_2), 121.32 (CH), 126.44 (CH), 129.35 (CH), 129.45 (CH), 130.33 (CH), 132.87 (C), 134.02 (C), 134.35 (C), 134.51 (C), 135.79 (CH), 163.73 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

GC-MS: *m/z* 278 (M^+).

The boiling point of the compound was found to be 180-85 ^{o}C/0.07 mmHg (Bath temperature).

Based on the mode of formation and above spectral data, structure **9b** was assigned to the product. The yield of the product ester from **10b** was found to be 93%.



9b

This α,β-unsaturated ester **9b** was then subjected to PPA cyclisation for 5 minutes, after which the reaction was found to be complete as indicated by TLC technique. The usual workup followed by column chromatographic purification over silica gel using hexanes-EtOAc (9:1) as an eluent afforded a white solid.

IR (KBr) : 1691 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.41	s	6 H	2 X - CH_3
δ 1.80	t	2 H (*J* = 6.9 Hz)	= C-CH_2-$\underline{CH_2}$-
δ 2.66	dt	2 H (*J* = 6.9 & 2.4 Hz)	= C-$\underline{CH_2}$-CH_2-
δ 7.24	m	3 H	ArH
δ 7.38	m	1 H	ArH
δ 8.00	br.s.	1 H	-$\underline{CH}$ = C -

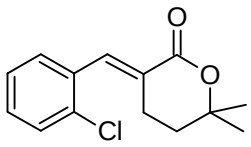
^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :
δ 21.98 (CH_2), 27.93 (2 X CH_3), 33.24 (CH_2), 80.60 (C), 126.31 (CH), 126.98 (C), 129.79 (2 X CH), 129.82 (CH), 133.62 (C), 134.48 (C), 138.31 (CH), 166.12 (C=O).

The multiplicities of carbon signals mentioned above were obtained from DEPT experiments.

HRMS : *m/z* found 251.0821. Calcd for $C_{14}H_{15}O_2Cl$, $(M+H)^+$ 251.0839.

The melting point of the compound was found to be 104-09 ^{o}C.

Based on the mode of formation and above spectral data structure **8b** was assigned to the product. The yield of the product was found to be 83%.



8b

Similarly, the Wittig olefination reaction of *p*-chlorobenzaldehyde (**10c**) was carried out with prenyl phosphorane **11** in refluxing chloroform for 2 hrs and 30 mins. After the reaction was complete as indicated by TLC, the column chromatographic purification of the product was done over silica gel using hexanes-EtOAc (9:1) as an eluent to afford the viscous liquid.

IR (KBr) : 1725 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.35	t	3 H (*J* = 7.2 Hz)	- $OCH_2\underline{CH_3}$
δ 1.62	s	3 H	- CH_3
δ 1.72	s	3 H	- CH_3
δ 3.18	d	2 H (*J* = 6.6 Hz)	- $\underline{CH_2}$-CH =
δ 4.23	q	2 H (*J* = 7.2 Hz)	- $O\underline{CH_2}CH_3$
δ 5.12	t	1 H (*J* = 7.2 Hz)	- CH_2-$\underline{CH}$ =
δ 7.34	m	4 H	ArH
δ 7.61	s	1 H	Ar-$\underline{CH}$ = C

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

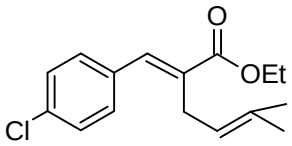
δ 14.26 (CH_3), 17.97 (CH_3), 25.70 (CH_3), 26.81 (CH_2), 60.87 (OCH_2), 121.33 (CH), 128.60 (2 X CH), 130.41 (C), 130.64 (2 X CH), 133.20 (C), 134.21 (C), 136.87 (C), 137.35 (CH), 168.03 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

GC-MS : *m/z* 278 (M^+).

The boiling point of the compound was found to be 205-10 ^{o}C/0.11 mmHg (Bath temperature).

Based on the mode of formation and above spectral data, structure **9c** was assigned to the product. The yield of the product ester from **10c** was found to be 90%.



9c

This α,β-unsaturated ester **9c** was then subjected to PPA cyclisation. After 5 minutes, when the reaction was complete as indicated by TLC technique, workup of reaction mixture was carried out, and the crude product was then purified by column chromatography over silica gel using hexanes-EtOAc (9:1) as an eluent to get a white solid.

IR (KBr) : 1698 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.40	s	6 H	2 X - CH_3
δ 1.84	t	2 H (*J* = 6.9 Hz)	= C-CH_2-$\underline{CH_2}$-
δ 2.81	dt	2 H (*J* = 6.9 & 2.1 Hz)	= C-$\underline{CH_2}$-CH_2-
δ 7.30	s	4 H	ArH
δ 7.83	br.s	1 H	-$\underline{CH}$ = C -

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

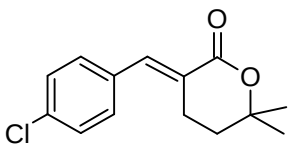
δ 22.62 (CH_2), 27.72 (2 X CH_3), 33.02 (CH_2), 80.11 (C), 124.95 (C), 128.77 (2 X CH), 131.43 (2 X CH), 133.50 (C), 135.07 (C), 139.07 (C), 139.97 (CH), 166.62 (C=O).

The multiplicities of carbon signals mentioned above were obtained from DEPT experiments.

HRMS : *m/z* found 273.0673. Calcd for $C_{14}H_{15}O_2Cl$, $(M+Na)^+$ 273.0658.

The melting point of the compound was found to be 103-07 ^oC.

Hence, based on the mode of formation and above spectral data structure **8c** was assigned to the product. The yield of the product was found to be 79%.



8c

Our next aim was to condense benzaldehyde having electron donating group on the benzene ring. Hence, anisaldehyde (**10d**) was condensed with phosphorane **11** in refluxing chloroform for 3.0 hrs. When the reaction was complete, as indicated by TLC technique, the column chromatographic purification of the product was carried out over silica gel using hexanes-EtOAc (9:1) as an eluent to furnish the viscous liquid.

IR (KBr) : 1711 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.30	t	3 H (*J* = 7.2 Hz)	- $OCH_2C\underline{H}_3$
δ 1.64	s	3 H	- CH_3
δ 1.68	s	3 H	- CH_3
δ 3.19	d	2 H (*J* = 6.3 Hz)	- $C\underline{H}_2$-CH =
δ 3.78	s	3 H	- OCH_3
δ 4.21	q	2 H (*J* = 7.2 Hz)	- $OC\underline{H}_2CH_3$
δ 5.1	m	1 H	- CH_2-C<u>H</u> =
δ 6.84	d	2 H (*J* = 8.7 Hz)	ArH
δ 7.31	d	2 H (*J* = 8.7 Hz)	ArH
δ 7.59	s	1 H	Ar-C<u>H</u> = C

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

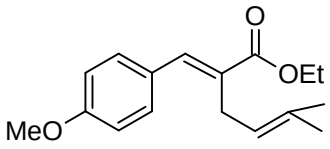
δ 14.31 (CH_3), 18.01 (CH_3), 25.73 (CH_3), 26.80 (CH_2), 55.26 (OCH_3), 60.65 (OCH_2), 113.86 (2 X CH), 121.84 (CH), 128.30 (C), 130.41 (C), 130.51 (C), 131.16 (2 X CH), 132.90 (C), 138.50 (CH), 159.73 (C), 168.58 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

GC-MS : *m/z* 278 (M^+).

The boiling point of the compound was found to be 188-95 ^oC/0.07 mmHg (Bath temperature).

Based on the mode of formation and above spectral data, structure **9d** was assigned to the product. The yield of the product ester from **10d** was found to be 88%.



9d

The resulting α,β-unsaturated ester **9d** was then subjected to PPA cyclisation for 5 minutes. The progress of the reaction was monitored by TLC. When the reaction was complete, the usual workup was carried out, followed by column chromatographic purification over silica gel using hexanes-EtOAc (9:1) as an eluent to afford a white solid.

IR (KBr) -1695 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) (**Fig. III**):

δ 1.39	s	6 H	2 X - CH_3
δ 1.84	t	2 H (*J* = 6.9 Hz)	= C-CH_2-C<u>H</u>$_2$-
δ 2.83	dt	2 H (*J* = 6.9 & 2.4 Hz)	= C-C<u>H</u>$_2$-CH_2-
δ 3.79	s	3 H	-OCH_3
δ 6.89	d	2 H (*J* = 9 Hz)	ArH
δ 7.41	d	2 H (*J* = 9 Hz)	ArH
δ 7.84	br.s	1 H	-C<u>H</u> = C -

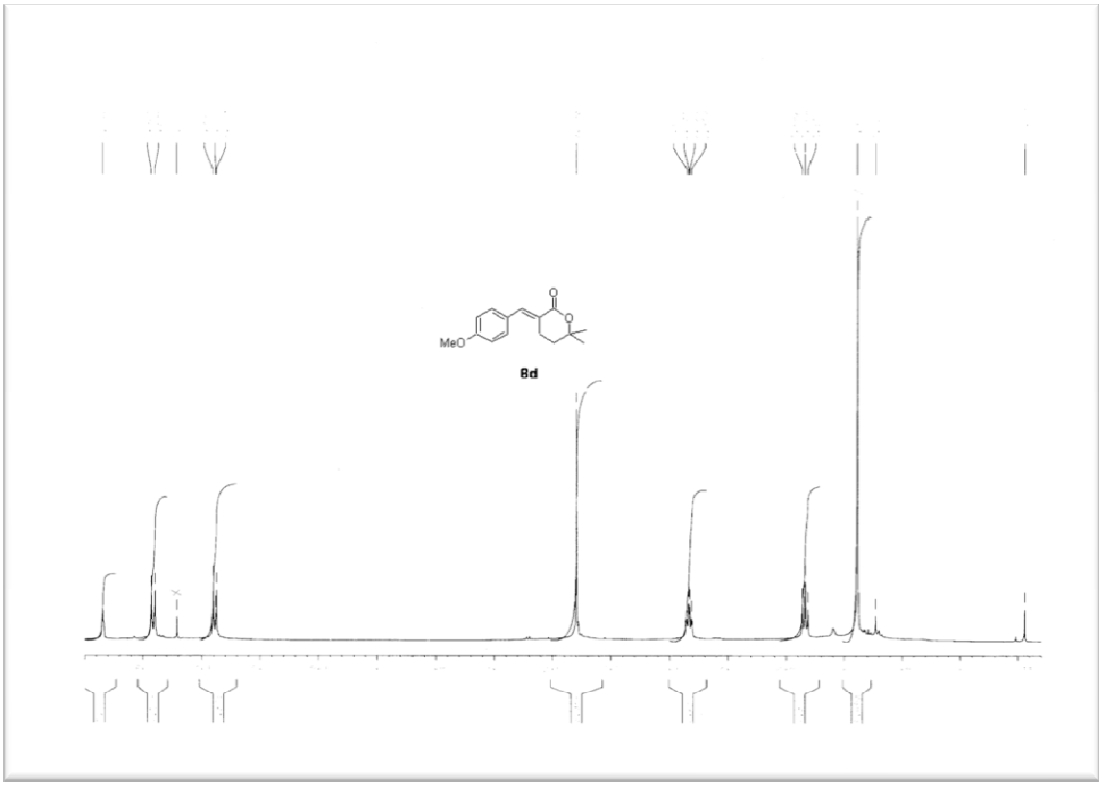


Fig. III : ^{1}H-NMR spectrum of Compound **8d**

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) (**Fig. IV**):

δ 22.78 (CH_2), 27.67 (2 X CH_3), 33.08 (CH_2), 55.27 (OCH_3), 79.71 (C), 113.99 (2 X CH), 121.72 (C), 127.87 (C), 132.26 (2 X CH), 141.16 (CH), 160.27 (C), 167.32 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

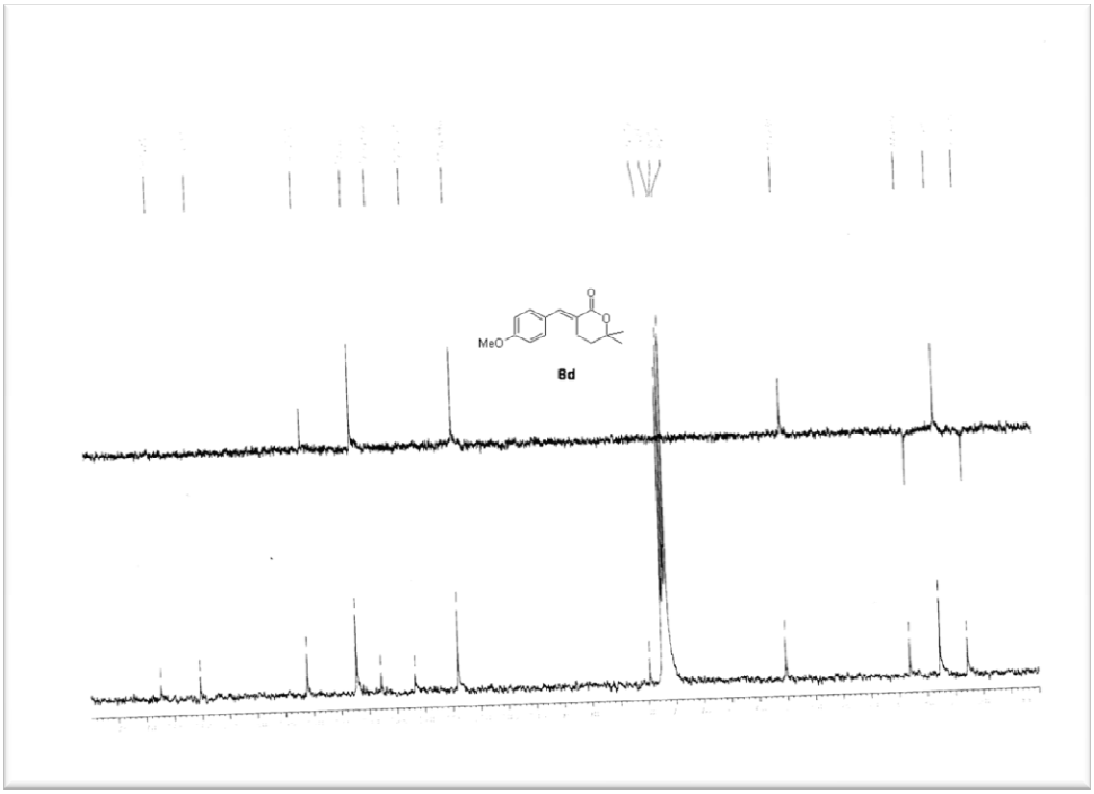


Fig. IV : ^{13}C-NMR spectrum of Compound **8d**

HRMS (**Fig. V**) : *m/z* found 269.1146. Calcd for $C_{15}H_{18}O_3$, $(M+Na)^+$ 269.1154.

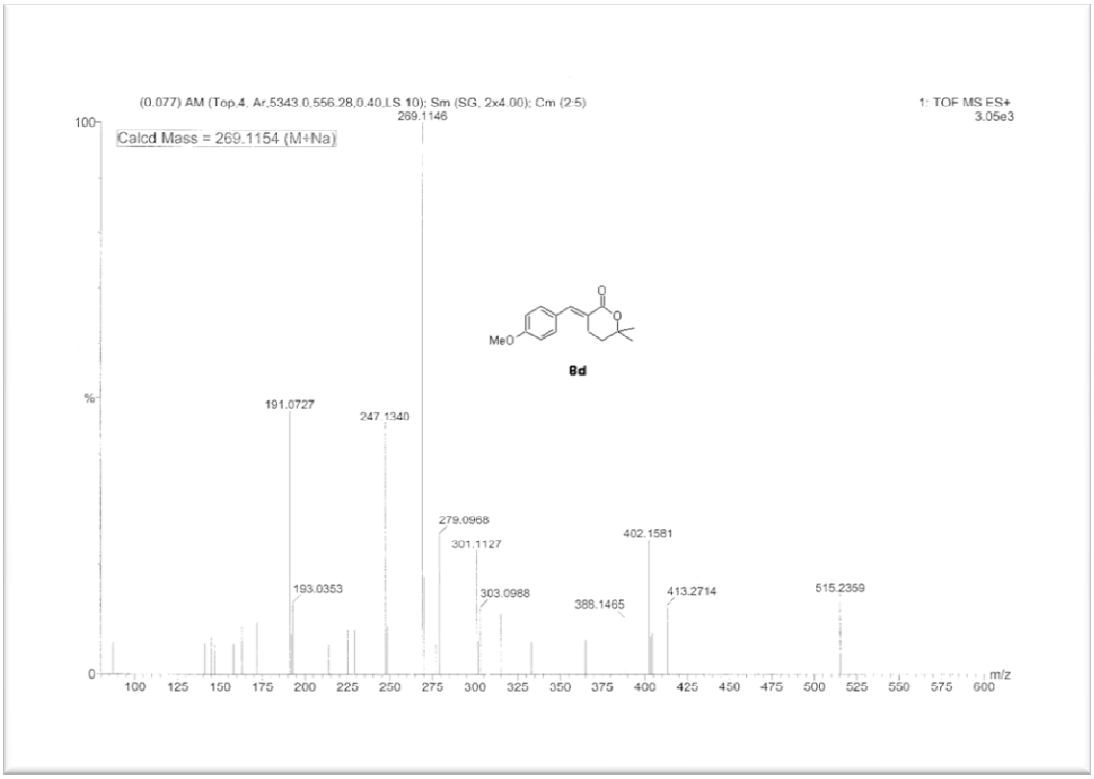
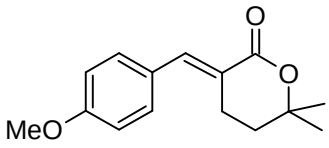


Fig. V : HRMS of Compound **8d**

The melting point of the compound was found to be 75-79 ^{o}C.

Hence, based on the above spectral data and mode of formation, structure **8d** was assigned to the product. The yield of the product was found to be 91%.



8d

Similarly, Wittig olefination reaction was performed on 3,4-methylenedioxybenzaldehyde having electron donating group (**10e**) in refluxing chloroform for 3.0 hrs. After the reaction was complete, as indicated by the TLC technique, the column chromatographic purification of the product was performed over silica gel using hexanes-EtOAc (9:1) as an eluent to furnish a viscous liquid.

IR (KBr) : 1705 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.33	t	3 H (*J* = 7.2 Hz)	- $OCH_2\underline{CH_3}$
δ 1.70	s	3 H	- CH_3
δ 1.75	s	3 H	- CH_3
δ 3.23	br.d	2 H (*J* = 6.0 Hz)	- $\underline{CH_2}$-CH =
δ 4.27	q	2 H (*J* = 7.2 Hz)	- $O\underline{CH_2}CH_3$
δ 5.15	m	1 H	- CH_2-$\underline{CH}$ =
δ 6.00	s	2 H	-OCH_2O-
δ 6.81-6.92	m	3 H	ArH
δ 7.60	s	1 H	Ar-$\underline{CH}$ = C

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

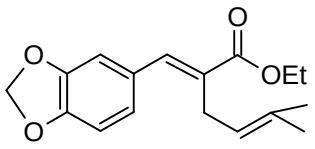
δ 14.29 (CH_3), 17.98 (CH_3), 25.71 (CH_3), 26.84 (CH_2), 60.72 (OCH_2), 101.24 (CH_2), 108.31 (CH), 109.4 (CH), 121.67 (CH), 124.34 (CH), 129.77 (C), 131.01 (C), 132.97 (C), 147.72 (2 X C), 168.43 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

GC-MS : *m/z* 288 (M^+).

The boiling point of the compound was found to be 175-80 ^oC/0.06 mmHg (Bath temperature).

Based on the mode of formation and above spectral data structure **9e** was assigned to the product formed. The yield of the product ester from **10e** was found to be 84%.



9e

In the next step, α,β-unsaturated ester **9e** was subjected to PPA cyclisation for 5 minutes. The progress of the reaction was monitored by TLC. After completion of the reaction, the usual workup was carried out, followed by column chromatographic purification over silica gel using hexanes-EtOAc (9:1) as an eluent to afford a white solid.

IR (KBr) : 1686 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.46	s	6 H	2 X - CH_3
δ 1.91	t	2 H (*J* = 6.6 Hz)	= C-CH_2-$C\underline{H}_2$-
δ 2.88	dt	2 H (*J* = 6.6 & 2.1 Hz)	= C-$C\underline{H}_2$-CH_2-
δ 6.02	s	2 H	-OCH_2O-
δ 6.88	d	1 H (*J* = 8.4 Hz)	ArH
δ 7.03-7.09	m	2 H	ArH
δ 7.87	br.s.	1 H	-C$\underline{H}$ = C -

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

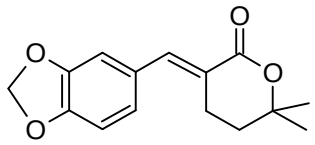
δ 22.86 (CH_2), 27.76 (2 X CH_3), 33.13 (CH_2), 79.85 (C), 101.5 (OCH_2O), 108.53 (CH), 109.87 (CH), 126.17 (CH), 141.29 (CH), 122.35 (C), 129.39 (C), 147.88 (C), 148.45 (C), 167.25 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

HRMS : *m/z* found 283.0945. Calcd for $C_{15}H_{16}O_4$, $(M+Na)^+$ 283.0946.

The melting point of the compound was found to be 129-33 ^oC.

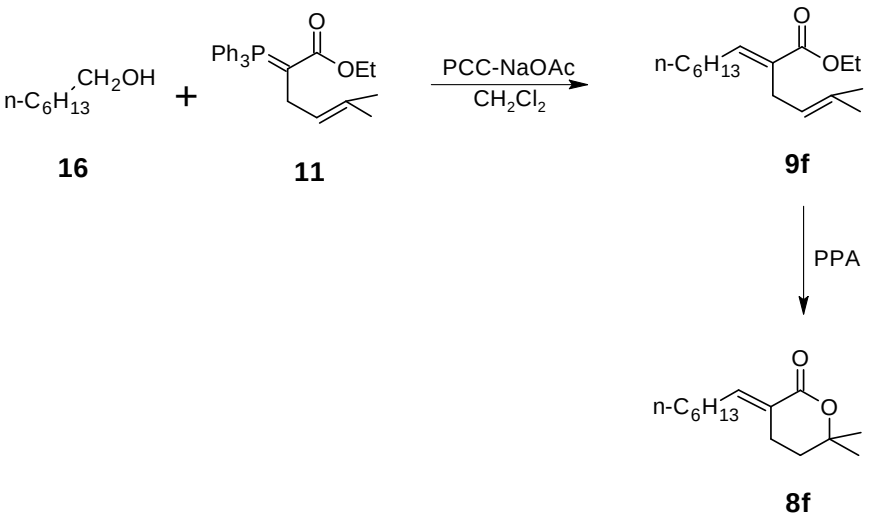
Hence, on the basis of spectral data and mode of formation, structure **8e** was assigned to the product. The yield of the product was found to be 78%.



8e

After successfully synthesising various α-benzylidene-δ-dimethyl-δ-lactones (**8a-e**), we thought to check the feasibility of this method for the synthesis of α-alkylidene-δ-dimethyl-δ-lactones.

To make our scheme more concise, it was visualised to explore domino oxidation-Wittig reaction approach[39] reported from our laboratory on aliphatic alcohol, and the aliphatic alcohol selected for this purpose was *n*-heptanol as depicted in **Scheme XX**.



Scheme XX

It was planned to treat the alcohol **16** with PCC in presence of sodium acetate and prenyl phosphorane **11** in dichloromethane to get the α,β-unsaturated ester, which can inturn be converted to δ-lactone using PPA.

So as per planned procedure, we took PCC and sodium acetate in anhyd. CH_2Cl_2. To this then *n*-heptanol **16** and phosphorane **11** were added, and the reaction mixture was allowed to stir under normal PCC oxidation conditions. After 3.0 hrs TLC showed dissappearence of starting materials and appearence of a new spot. To the reaction mixture then ether was added and it was filtered on celite. The residue obtained was purified by column chromatography over silica gel using hexanes-EtOAc (9:1) as an eluent to afford a thick viscous liquid.

IR (KBr) : 1715 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 0.91	Skewd t	3 H (*J* = 7.1 Hz)	- $OCH_2C\underline{H}_3$
δ 1.28-1.71	m	17 H	- $(CH_2)_4CH_3$, 2XCH_3
δ 2.21	m	2 H	- CH-C$\underline{H}_2$-CH_2-
δ 3.02	d	2 H (*J* = 6.6 Hz)	- C$\underline{H}_2$-CH =
δ 4.20	q	2 H (*J* = 7.1 Hz)	- OC$\underline{H}_2CH_3$
δ 5.03	m	1 H	- CH_2-C$\underline{H}$ =
δ 6.76	t	1 H (*J* = 7.5 Hz)	-C$\underline{H}$ = C

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

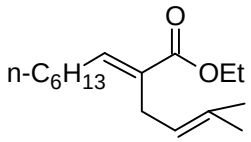
δ 14.01 (2XCH_3), 14.23 (CH_3), 22.53 (CH_2), 23.98 (CH_3), 28.59 (CH_2), 28.71 (CH_2), 28.78 (CH_2), 28.97 (CH_2), 31.62 (CH_2), 60.35 (OCH_2), 121.95 (CH), 131.58 (C), 131.79(C), 142.63 (CH), 168.05 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

GC-MS : *m/z* 252 (M^+).

The boiling point of the compound was found to be 178-85 ^oC/0.07 mmHg (Bath temperature).

On the basis of above spectral data and mode of formation structure **9f** was assigned to the product formed. The yield of the product was found to be 95%.



9f

In the next step, α,β-unsaturated ester **9f** was subjected to PPA cyclisation for 5 minutes. After completion of the reaction, which was indicated by TLC technique, the usual workup was carried out. Finally, the crude product was purified by column chromatography over silica gel using hexanes-EtOAc (9:1) as an eluent to afford a thick colourless viscous liquid.

IR (KBr) : 1722 cm^{-1}

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 0.90	Sckewd t	3 H (*J* = 6.6 Hz)	- $CH_2\underline{CH_3}$
δ 1.31-1.58	m	14 H	- $(CH_2)_4$-, 2XCH_3
δ 1.85	t	2 H (*J* = 6.9 Hz)	-$\underline{CH_2}$-CH_2-
δ 2.17	q	2 H (*J* = 7.2 Hz)	= CH-$\underline{CH_2}$-
δ 2.54	br.t.	2 H (*J* = 6.9 Hz)	-CH_2-$\underline{CH_2}$-
δ 7.00	t	1 H (*J* = 7.5 Hz)	-$\underline{CH}$ = C

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

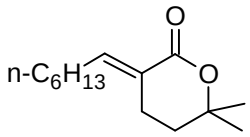
δ 13.98 (CH_3), 22.42 (CH_2), 24.63 (CH_2), 27.58 (CH_3), 27.71 (CH_3), 28.69 (CH_2), 29.37 (CH_2), 30.28 (CH_2), 33.80 (CH_2), 34.66 (CH_2), 80.4 (C), 126 (C), 138 (CH), 178.61 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

HRMS : *m/z* found 225.1850. Calcd for $C_{14}H_{24}O_2$, $(M+H)^+$ 225.1854.

The boiling point of the compound was found to be 210-12 ^{o}C/0.07 mmHg (Bath temperature).

Based on the mode of formation and above spectral data, structure **8f** was assigned to the product. The yield of the product was found to be 81%.



8f

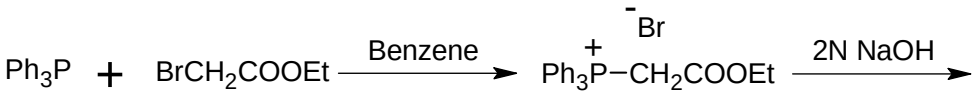
After utilizing the reaction sequence for aliphatic aldehyde, we thought of checking the feasibility of this method with ketones. The ketones tried were acetone, ethyl methyl ketone and acetophenone. In none of the cases we could get the condensation product. With acetophenone the reaction was attempted at its boiling point also, all we could get in this case was triphenyl phosphine oxide and acetophenone.

Conclusion

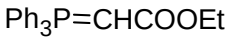
A convenient and efficient method has been developed using Wittig reaction for the synthesis of α-(alkylidene)-5,5-dimethyl-δ-lactones. The reaction works well with alkyl as well as aryl aldehydes. The presence of electron donating or withdrawing groups on aromatic ring did not affect the Wittig product yields. In situ oxidation of primary alcohol Wittig reaction methodology developed in our laboratory worked well for the preparation of the intermediate ester. PPA cyclisation process was found to be better yielding compared to H_2SO_4 cyclisation. However, the present method could not be extended to ketones to get α,α-disubstituted alkylidene lactones.

Experimental

1.1 Preparation of Triphenyl-α-ethoxycarbonyl methylene-phosphorane (**14**)



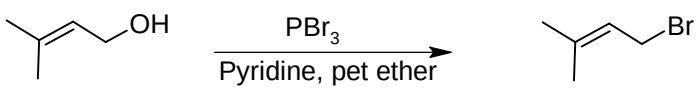
12 **13**



14

To the solution of triphenyl phosphine (**12**) (15.0 g, 57 mmol) in dry benzene (25 mL) was added a solution of ethylbromoacetate (**13**) (9.55 g, 57 mmol) in dry benzene (10 mL). The reaction mixture was vigorously shaken and left overnight at room temperature. The solid observed in the reaction mixture was filtered, washed with dry benzene and dried. This solid was then dissolved in water (150 mL) and benzene (100 mL) was added to it. It was neutralised with 2N sodium hydroxide using phenolphthalein as indicator. The benzene layer was separated, dried over anhyd. sodium sulphate and concentrated under reduced pressure. Addition of hexanes (40-60 ^{o}C) resulted in the separation of the crystalline product, which was filtered and dried to afford triphenyl-α-ethoxycarbonyl methylene phosphorane (**14**) (16.4g, 82%, m.p. 125-126 ^{o}C)

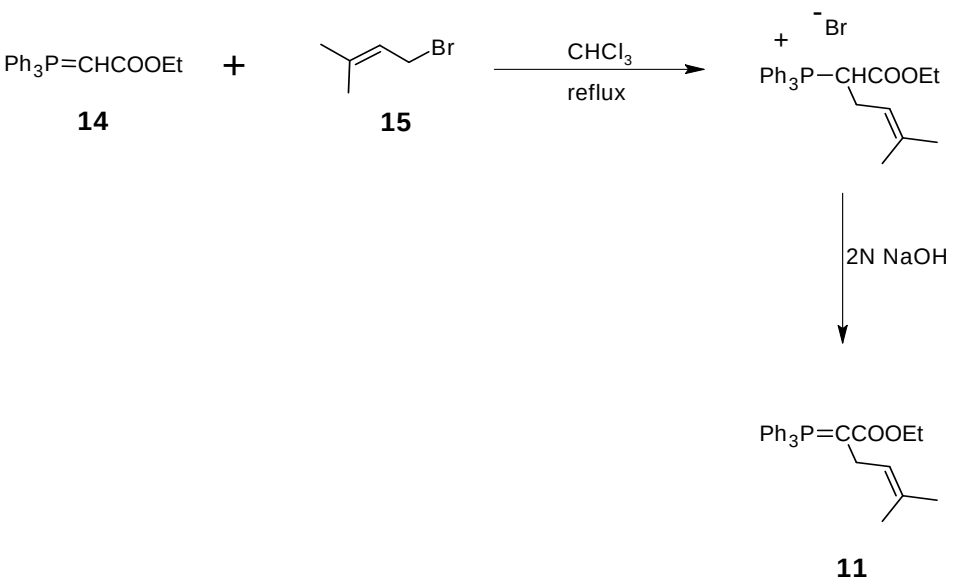
1.2 Preparation of 1-Bromo-3-methyl-but-2-ene (prenyl bromide) (**15**)



15

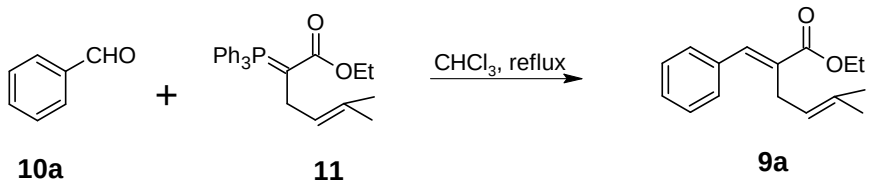
A solution of phosphorus tribromide (15.4 g, 57 mmol) in light petroleum (20 mL) was added slowly to a stirred mixture of 3-methyl-2-buten-1-ol (12.94 g, 0.15 mol) and dry pyridine (2.04 g, 26 mmol) in light petroleum (50 mL) at 0 ^{o}C. After 1 hr, ice water was added and the organic layer was separated. The organic layer was washed first with sodium bicarbonate solution and then with water. Drying over anhyd. sodium sulphate and evaporation of solvent under reduced pressure afforded a colourless prenyl bromide (**15**) (13.15g, 59%).

1.3 Preparation of Carboethoxy-(α-prenyl)-methylenetriphenyl phosphorane (**11**)



A mixture of prenyl bromide (**15**) (3.5 mL, 0.028 mol) and carboethoxymethylenetriphenyl phosphorane (**14**) (5 g, 0.014 mol) was refluxed in chloroform (25 mL) for 5 hrs and kept overnight at room temperature. Removal of chloroform resulted in a thick transparent semisolid which was taken in water (60 mL) and washed twice with benzene (2 X 10 mL). Benzene (30 mL) was added to it, followed by addition of two drops of phenolphthalein indicator. Sodium hydroxide solution (2N) was added to it with stirring till pink colour persisted. The benzene layer was separated and washings were given to the aqueous layer with benzene (2 X 10 mL). The combined benzene layer was dried over anhyd. sodium sulphate and the solvent was removed under reduced pressure to furnish carboethoxy-(α-prenyl)-methylenetriphenyl phosphorane (**11**) (3.9 g, 65%).

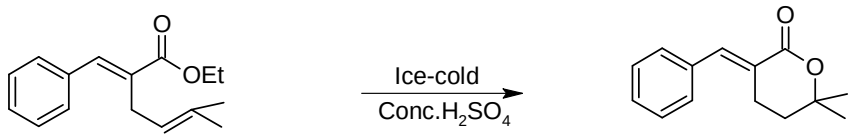
1.4 Preparation of (*E*)-Ethyl-(α-prenyl)cinnamate (**9a**)



10a **11** **9a**

A solution of benzaldehyde (**10a**) (0.106 g, 1 mmol), prenyl phosphorane (**11**) (0.417 g, 1 mmol) in chloroform (10 mL) was refluxed for 3.0 hrs. The TLC of the reaction mixture showed appearance of a new spot. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to furnish a thick viscous liquid (**9a**) (0.225g, 92%) b.p. 134-139 ^{o}C/0.06 mmHg (Bath temperature).

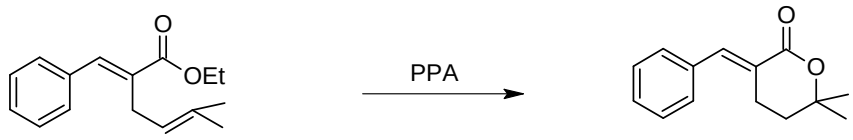
1.5 Preparation of (*E*)-α-Benzylidene-δ-dimethyl-δ-lactone (**8a**) using sulphuric acid



9a **8a**

To a flask containing ice cold ester (**9a**) (0.245g, 1 mmol) was added ice cold conc. sulphuric acid (2 mL) and the reaction mixture was stirred in an ice bath for 1 hr. After the completion of reaction, sufficient crushed ice was added to the reaction mixture, and was extracted in diethyl ether (2 X 5 mL). The combined organic extract was dried over anhyd. sodium sulphate and the solvent was evaporated to dryness. The crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to yield a thick colourless viscous liquid (**8a**) (0.123g, 57%), b.p. 140-145 ^{o}C/0.09 mmHg (Bath temperature).

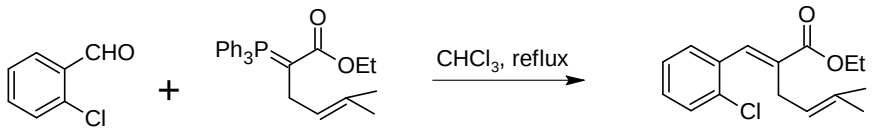
1.6 Preparation of (*E*)-α-Benzylidene-δ-dimethyl-δ-lactone (**8a**) using PPA



9a **8a**

To a flask containing ester (**9a)** (0.245g, 1 mmol) was added polyphosphoric acid (2 mL). The reaction mixture was warmed on water bath for 5 mins. Chilled water (15 mL) was added to the reaction mixture and it was subsequently extracted with diethyl ether (3 X 10 mL). The diethyl ether layer was washed twice with sat. sodium bicarbonate solution and dried over anhyd. sodium sulphate. The solvent was removed and the residue was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a thick colourless viscous liquid (**8a)** (0.208 g, 96%), b.p. 140-145 ^{o}C/0.09 mmHg (Bath temperature).

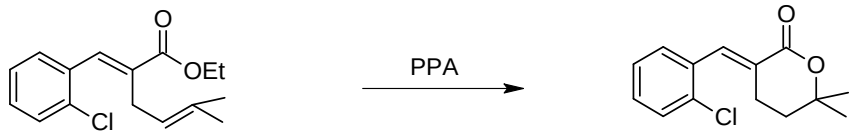
1.7 Preparation of (*E*)-Ethyl-(α-prenyl)-2-chlorocinnamate (**9b**)



10b **11** **9b**

Followed the same procedure as in Expt. 1.4. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a thick viscous liquid (**9b**) (93%), b.p. 180-185 ^{o}C/0.07 mmHg (Bath temperature).

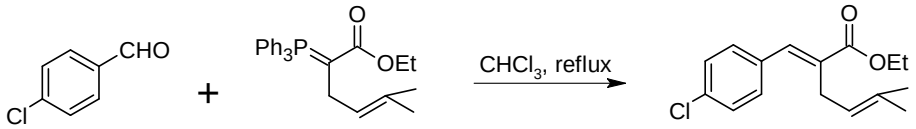
1.8 Preparation of (*E*)-α-(2-Chlorobenzylidene)-δ-dimethyl-δ-lactone (**8b**)



9b **8b**

Followed the same procedure as in Expt. 1.6. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to yield a white solid (**8b)** (83%), m.p. 104-109 ^{o}C.

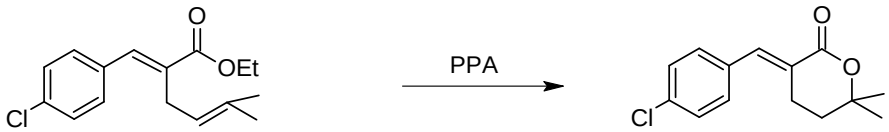
1.9 Preparation of (*E*)-Ethyl-(α-prenyl)-4-chlorocinnamate (**9c**)



10c **11** **9c**

Followed the same procedure as in Expt. 1.4. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a thick viscous liquid (**9c)** (90%), b.p. 205-210 ^{o}C/0.11 mmHg (Bath temperature).

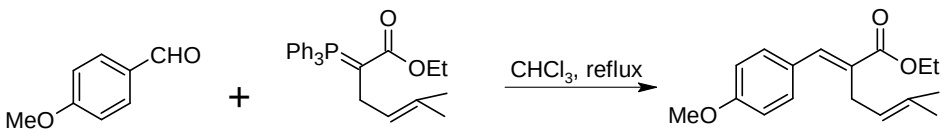
1.10 Preparation of (*E*)-α-(4-Chlorobenzylidene)-δ-dimethyl-δ-lactone (**8c**)



9c **8c**

Followed the same procedure as in Expt. 1.6. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to yield a white solid (**8c)** (79%), m.p. 103-107 ^{o}C.

1.11 Preparation of (*E*)-Ethyl-(α-prenyl)-4-methoxycinnamate (**9d**)



10d **11** **9d**

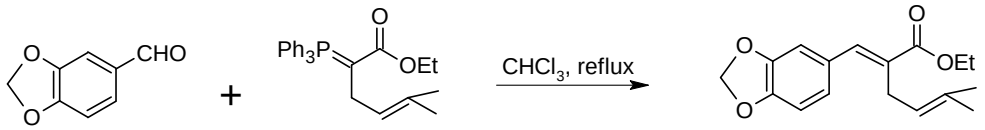
Followed the same procedure as in Expt. 1.4. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as eluent to furnish a thick viscous liquid (**9d**) (88%), b.p. 188-195 ^{o}C/0.07 mmHg (Bath temperature).

1.12 Preparation of (*E*)-α-(4-Methoxybenzylidene)-δ-dimethyl-δ-lactone (**8d**)

9d **8d**

Followed the same procedure as in Expt. 1.6. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to yield a white solid (**8d**) (91%), m.p. 75-79 ^{o}C.

1.13 Preparation of (*E*)-Ethyl-(α-prenyl)-3,4-methylenedioxycinnamate (**9e**)



10e **11** **9e**

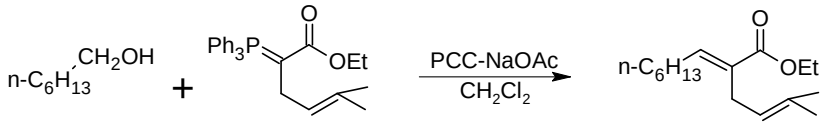
Followed the same procedure as in Expt. 1.4. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to furnish a thick viscous liquid (**9e**) (84%), b.p. 175-180 ^{o}C/0.06 mmHg (Bath temperature).

1.14 Preparation of (*E*)-α-(3,4-Methylenedioxybenzylidene)-δ-dimethyl-δ-lactone (**8e**)

9e **8e**

Followed the same procedure as in Expt. 1.6. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to yield a white solid (**8e)** (78%), m.p. 129-133 ^{o}C.

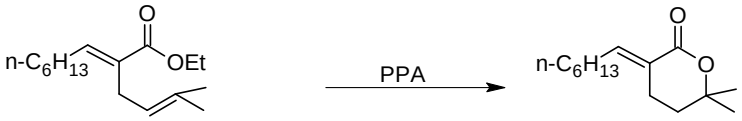
1.15 Preparation of (*E*)-Ethyl-2-(3-methylbut-2-enyl)non-2-enoate (**9f**)



16 **11** **9f**

To a magnetically stirred suspension of PCC (0.32 g, 1.5 mmol) and NaOAc (0.12 g, 1.5 mmol) in anhyd. dichloromethane (10 mL), alcohol (**16)** (0.12 g, 1 mmol) in anhyd. dichloromethane (5 mL) was added followed by prenyl phosphorane (**11)** (0.42 g, 1 mmol) in one portion. After 3.0 hrs, diethyl ether (5 mL) was added and the supernatant solution was decanted from the black granular solid. The combined organic layers were filtered through a short pad of celite. The residue obtained after evaporation of the solvent was further purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to afford a thick viscous liquid, (**9f**) (0.247 g, 95%), b.p. 178-185 ^{o}C/0.07 mmHg (Bath temperature).

1.14 Preparation of (*E*)-α-Heptylidene-δ-dimethyl-δ-lactone (**8f**)



9f **8f**

Followed the same procedure as in Expt. 1.6. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as eluent to furnish a thick colourless viscous liquid (**8f)** (81%), b.p. 210-212 ^{o}C/0.07 mmHg (Bath temperature).

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CHAPTER 2

CHAPTER 2

Synthesis of 2, 2-Dimethyl-3,4-dihydro-2*H*-pyrano [2,3-*b*]quinolines

Introduction

Quinoline derivatives represent the major class of heterocycles and a number of preparations have been known since the late 1800s. These are important compounds for synthetic and biological chemists.[1] The quinoline ring system occurs in various natural products especially in alkaloids, and its skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties, being used as anti-malarial, anti-inflammatory, antiasthamatic, antibacterial, antihypertensive and tyrosine kinase inhibiting agents.[2] In addition, quinolines are valuable synthons used for the preparation of nano and mesostructures with enhanced electronic and photonic properties.[3]

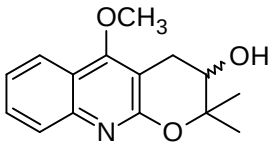
Alkaloids containing the pyranoquinoline and furoquinoline core constitute a significant group of the quinoline alkaloids. In the case of furo[2,3-*b*]quinoline alkaloids, the furan ring is fused to *b* bond of quinoline (**I**) and in case of pyrano[2,3-*b*]quinoline alkaloids, pyran ring is fused to the *b* bond of quinoline (**II**) (**Fig.1**).

I **II**

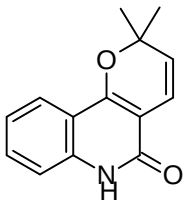
Fig. 1

The plant family *rutaceae* especially *Balfourodendron riedelianum* a small Brazilian tree is known[4,5] to be a prolific source of pyranoquinoline and furoquinoline alkaloids. These class of natural products have been reported[6,7] to be associate with interesting pharmacological as well as biological activities such as antiallergic, anti-inflammatory, antipyretic, analgesic, antiplatelet, psychotropic and estrogenic activity.[8]

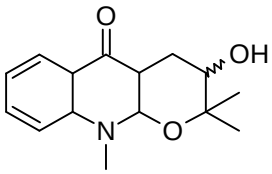
Some examples of natural products containing the pyranoquinoline and furoquinoline core structures[9] are shown in **Fig. 2**:-



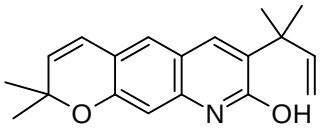
Geibalansine **1**



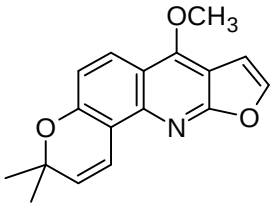
Flindersin **2**



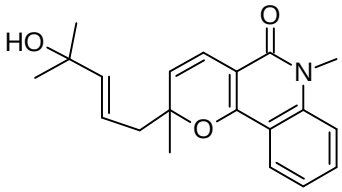
Ribalinine **3**



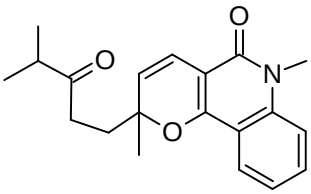
Helietidine **4**



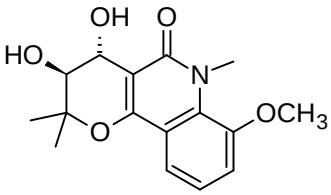
Dutadrupine **5**



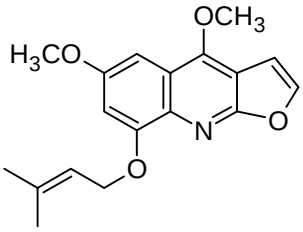
Simulenoline **6**



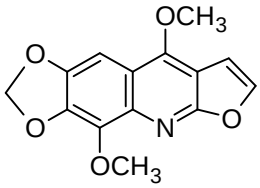
Huajiaosimuline **7**



Zanthodioline **8**



Teclealbine **9**

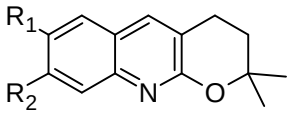


Flindersiamine **10**

Fig. 2

The development of efficient synthesis of pyranoquinolines and furoquinolines has been the focus of much research for several decades and continues to be an active and rewarding research area.

In this section, we have directed our efforts towards developing a general synthesis of 2,2-dimethyl pyranoquinoline skeleton **11** (**Fig. 3**).



11

Fig. 3

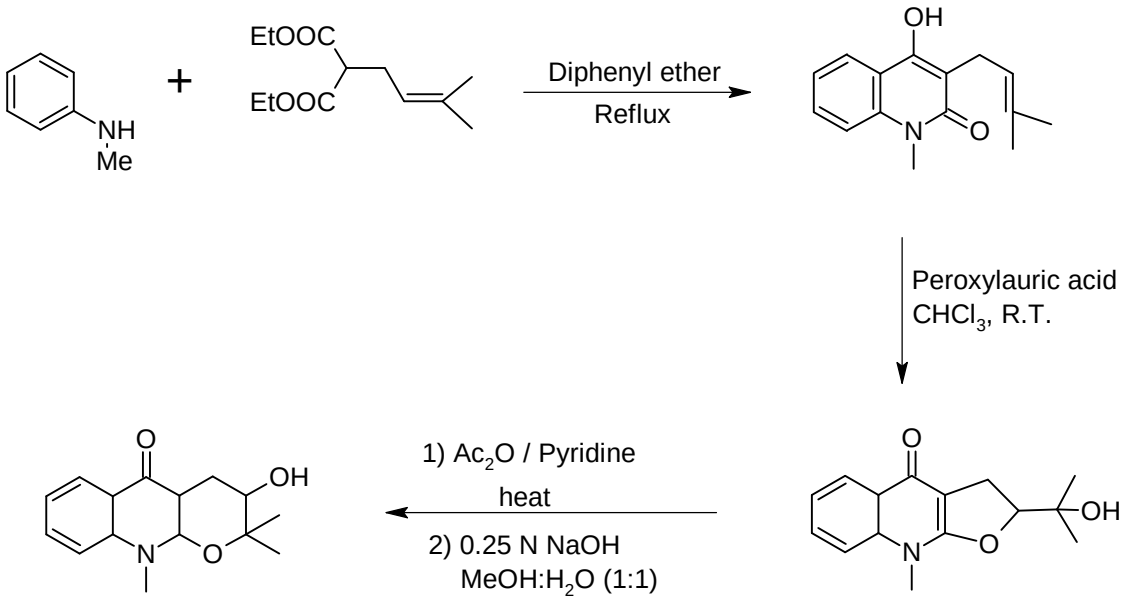
Literature Review

Owing to the potent biological activities of these pyranoquinoline and furoquinoline alkaloids, numerous methods have been developed for their synthesis. The synthetic method for the preparation of pyranoquinoline system is based on either oxidative cyclization of 4-hydroxy-3-(3'-methylbut-1'-enyl)-2-quinolinones **12** with DDQ[10] or the Prevost reaction of 3-prenyl-2-quinolones **13**[11] (**Fig. 4**). Though these methods have proven to be fairly satisfactory, the overall yield of the alkaloids was only 15-35 % because the routes to obtain the precursor prenylquinolines gave low yields (21-35 %)[12,13] and often were attended by undesired side reactions (such as the formation of unwanted 3-(3'-methylbut-1'-enyl)-2-quinolinones as the major product).[14]

12 **13**

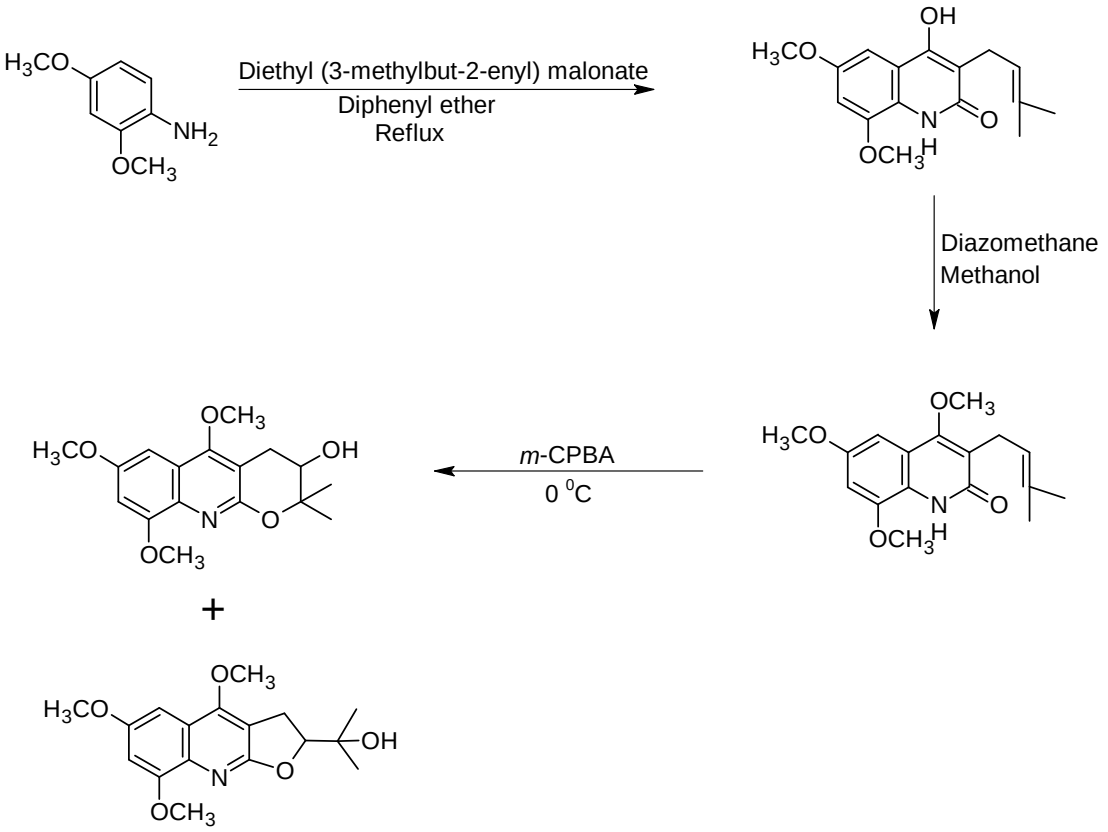
Fig. 4

Corral *et al.*[15] have reacted *N*-methyl aniline with diethyl-(3-methybut-2-enyl)-malonate to obtain the prenylquinoline which they have further treated with peroxylauric acid to give furoquinolone. They have also prepared pyranoquinolone from furoquinolone using acetic anhydride and base (**Scheme I**).



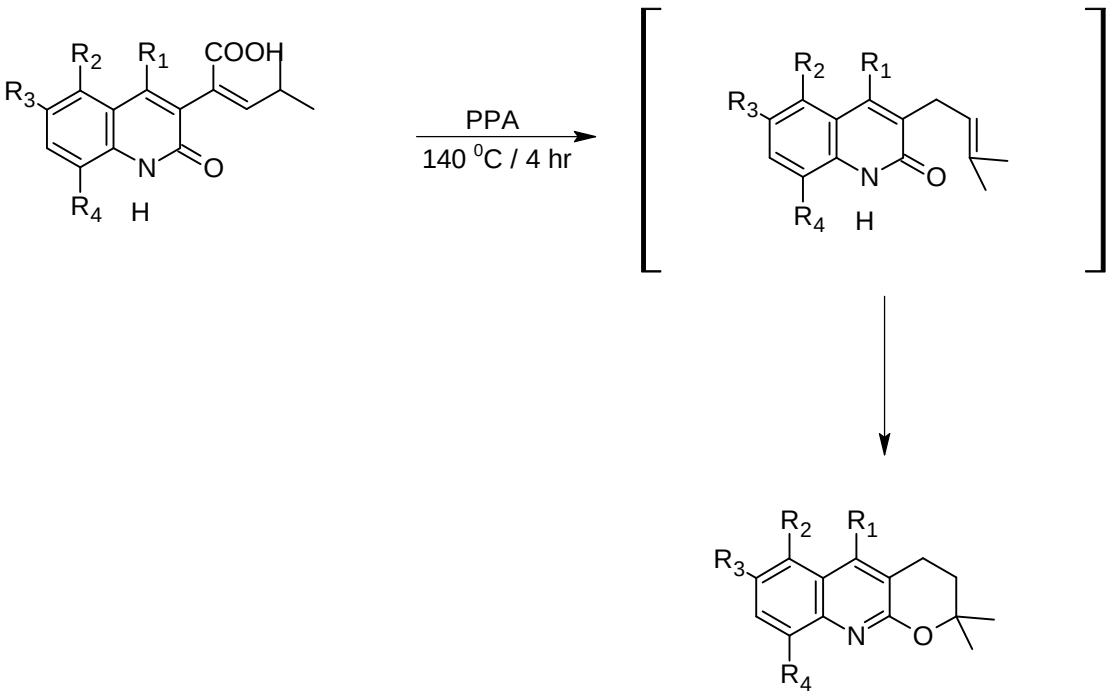
Scheme I

Grundon *et al*.[16] have treated 2,4-dimethoxyaniline with diethyl (3-methylbut-2-enyl) malonate in boiling diphenyl ether to get 4-hydroxyl-2-quinolone. Subsequently they treated this 4-hydroxy-2-quinolone with ethereal solution of diazomethane in methanol followed by oxidation with *m*-chloroperoxybenzoic acid in chloroform at 0 ^{o}C to give a mixture of pyranoquinoline and furoquinoline products (**Scheme II**).



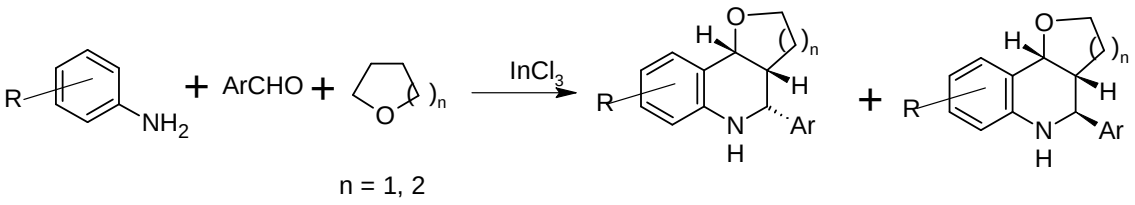
Scheme II

Rajendra Prasad *et al.*[17] have synthesized pyranoquinolines by treating carboxy derivative of the 2-quinolinone with polyphosphoric acid at 140 °C (**Scheme III**).



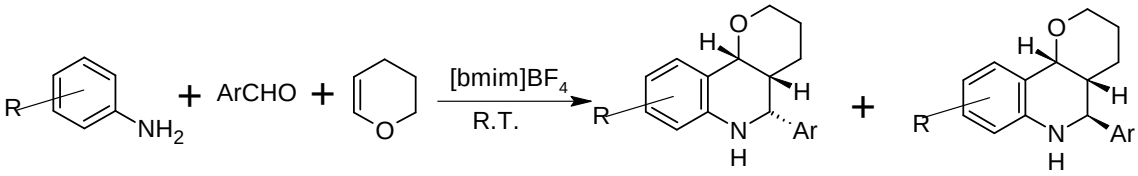
Scheme III

Kametani *et al.*[18] reported indium chloride catalysed cycloaddition of aldimines with various enol ethers to afford the corresponding pyranoquinoline derivatives (**Scheme IV**).



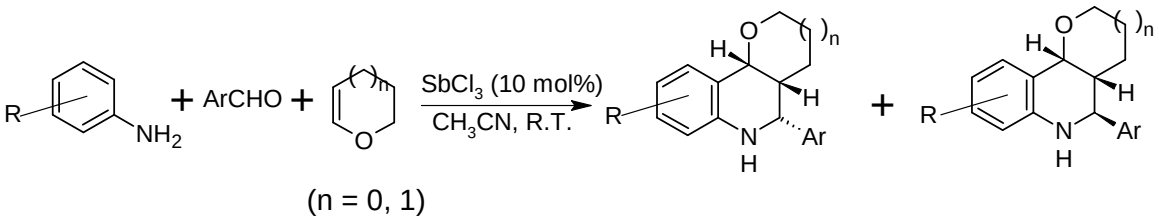
Scheme IV

Yadav *et al.*[19] have described that ionic liquids are found to catalyse efficiently the three component-coupling reactions of aldehydes, amines and cyclic enol ethers such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran under mild and convenient condition to afford corresponding pyranoquinolines (**Scheme V**).



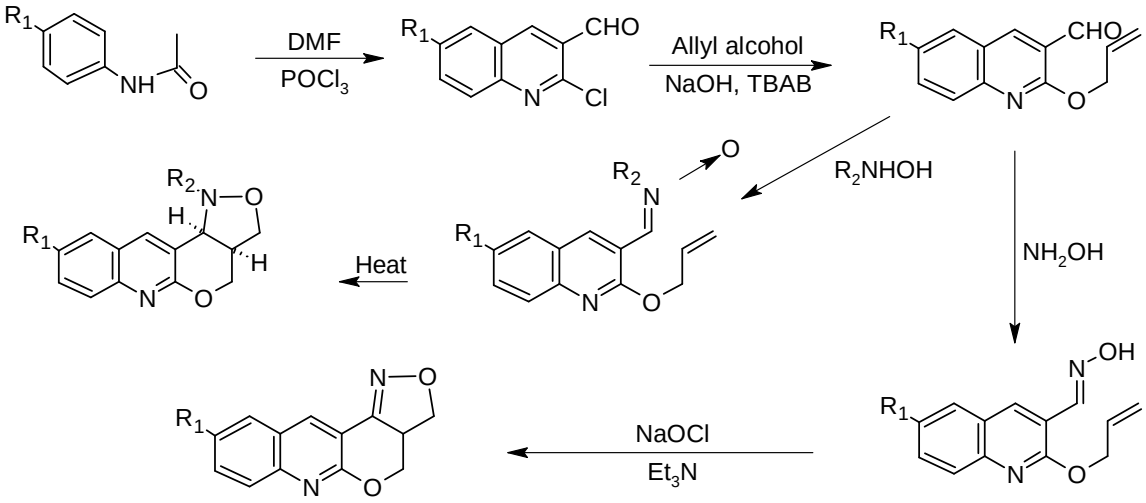
Scheme V

Maiti & Kundu[20] have reported the synthesis of substituted pyrano and furoquinolines via an imino Diels-Alder reaction using antimony trichloride ($SbCl_3$) as a catalyst (**Scheme VI**).



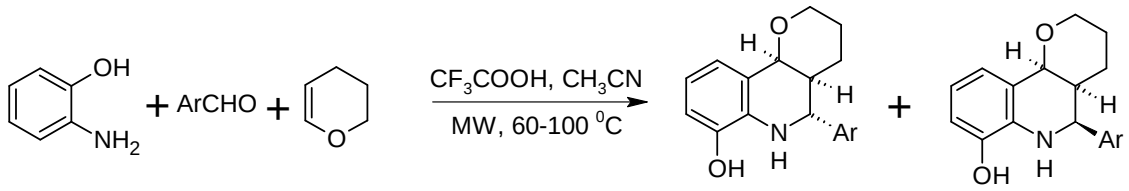
Scheme VI

Kalita *et al.*[21] have prepared tetrahydroisoxazolo-, dihydroisoxazolo-, and dihydropyrazolo-pyrano[2-3-*b*]quinolines from acetanilides via intramolecular 1,3-dipolar cycloaddition reactions involving nitrones, nitrile oxides and nitrile imines as 1,3-dipoles (**Scheme VII**).



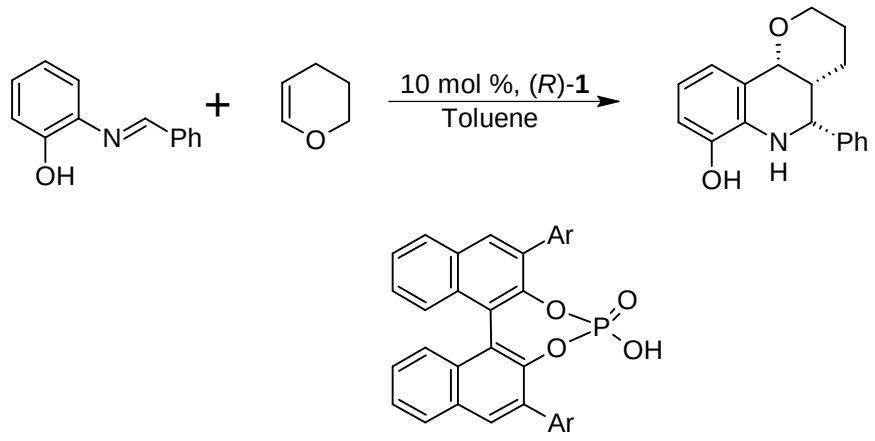
Scheme VII

Wei-Min and co-workers[22] have reported the aza-Diels Alder reaction of 2-aminophenol in combination with substituted benzaldehyde and electron rich cyclic alkenes under controlled microwave heating in presence of catalytic amount of CF_3COOH to afford corresponding pyranoquinolines (**Scheme VIII**).



Scheme VIII

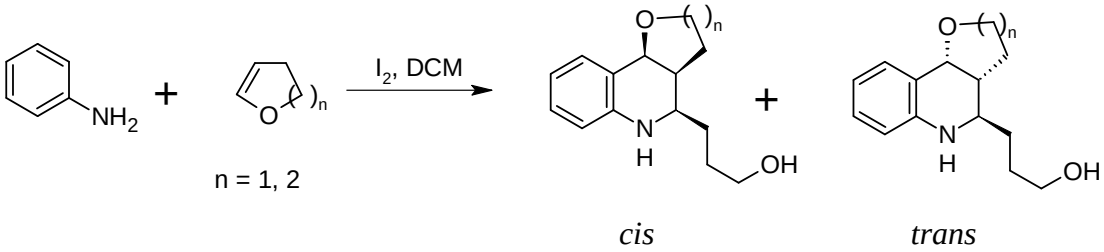
Akiyama *et al.*[23] have reported enantioselective aza Diels-Alder reactions by using chiral phosphoric acid derived from chiral BINOL and demonstrated its catalytic activity as chiral bronsted acid catalyst (**Scheme IX**).



(*R*) - **1** Ar = 9 anthryl

Scheme IX

Lin *et al.*[24] have developed highly efficient method for the synthesis of pyranoquinoline and furoquinoline derivatives via a molecular iodine catalyzed domino reactions of anilines with cyclic enol ethers, such as 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran (**Scheme X**).

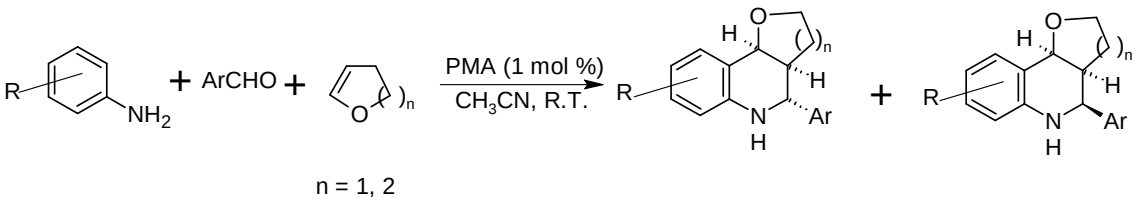


cis *trans*

Scheme X

Various other reagents are also reported for this sequence. Yadav *et al.*[25] have reported montmorillonite-clay as a catalyst. Lakshmikantham *et al.*[26] reported polyaniline supported indium trichloride as a reusable catalyst, Zang *et al.*,[27a] Chen *et al.*,[27b] extensively studied cycloaddition reaction of anilines with various enol ethers to afford corresponding pyranoquinolines.

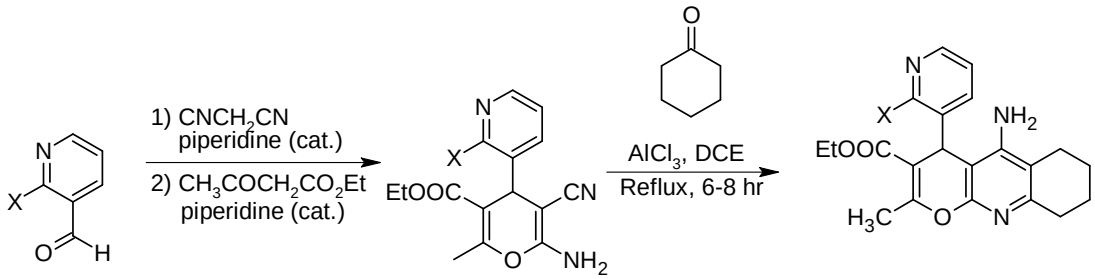
Yadav *et al.*[28] have described a synthesis of pyrano and furoquinoline derivatives via aza-Diels Alder reaction using 1 mol % of phosphomolybdic acid (PMA, F.W.: $H_3PMO_{12}0_{40}$) as a catalyst (**Scheme XI**).



n = 1, 2

Scheme XI

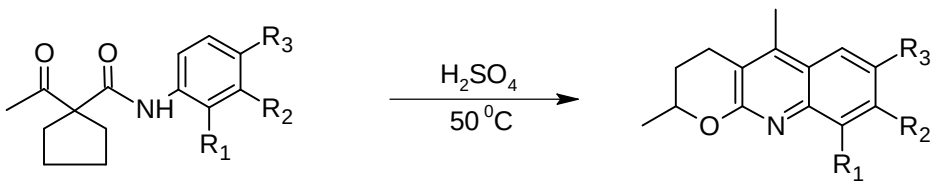
Marco-Contelles *et al.*[29], have described synthesis of pyranoquinolines from 3-pyridine carboxaldehydes. They treated 3-pyridine carboxaldehydes with malononitrile and ethyl acetoacetate in presence of piperidine to get 4*H*-pyran units, which were further reacted with cyclohexanone in presence of aluminium trichloride to afford the corresponding pyranoquinolines (**Scheme XII**).



X = OMe, Br, Cl

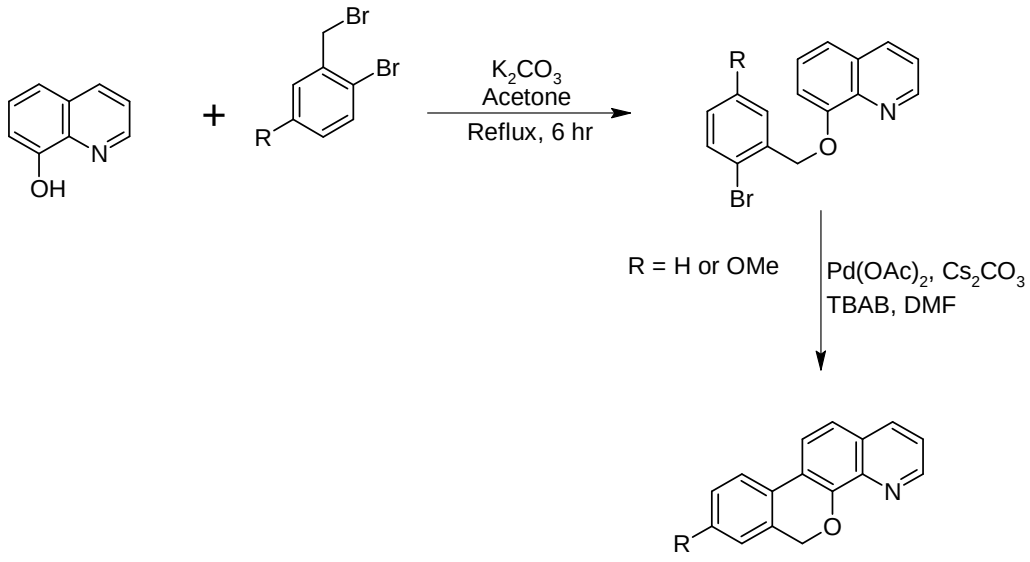
Scheme XII

Zhang *et al.*[30] have prepared pyranoquinolines from 1-acetyl-*N*-aryl cyclopentanecarboxamides via tandem cyclization/ring-opening/recyclization reaction using sulphuric acid at 50 ^{o}C (**Scheme XIII**).



Scheme XIII

Majumdar *et al.*[31] have carried out alkylation of hydroxylquinolines with substituted benzyl bromide followed by palladium-catalyzed cyclization to give benzannulated pyranoquinolines (**Scheme XIV**).

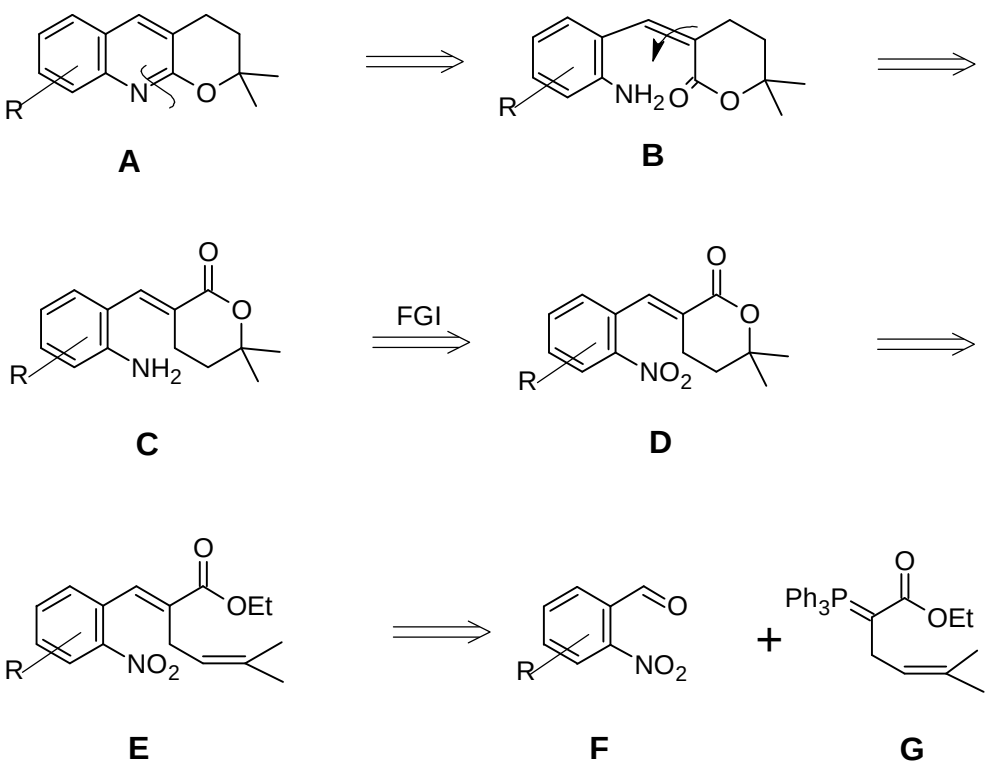


Scheme XIV

Present Work

Retrosynthesis

In view of the importance of pyranoquinoline ring system for various biological activities and very few synthetic methods being available we found it interesting to use our experience in phsophorane chemistry to develop a convenient method for the synthesis of pyranoquinolines. Our simple four step disconnection approach towards pyranoquinoline is shown in **Scheme XV**.

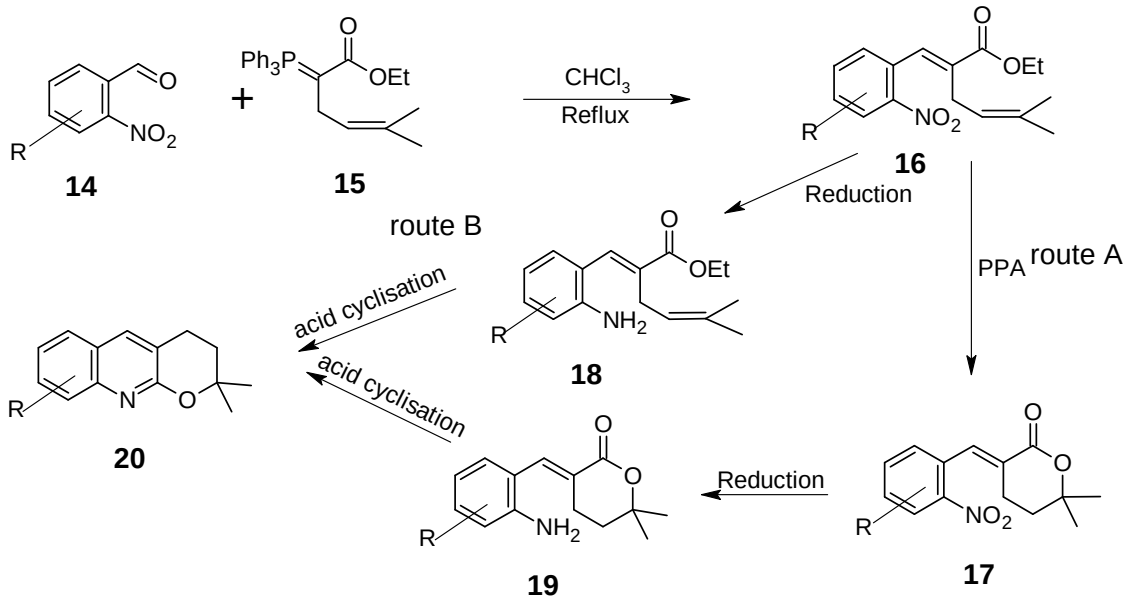


Scheme XV

The pyranoquinoline (**A**) could be obtained from the corresponding amino lactone (**B**). The amino lactone (**B**) has a *Z* geometry which is difficult to obtain but if the corresponding *E* compound (**C**) is obtained during cyclization, it can be converted to (**B**). The compound (**C**) can be obtained from corresponding nitro compound (**D**) which inturn can be obtained from uncyclised (**E**). Compound (**E**) could easily be prepared from *o*-nitrobenzaldehyde (**F**) by condensing it with Wittig reagent (**G**).

Synthetic plan

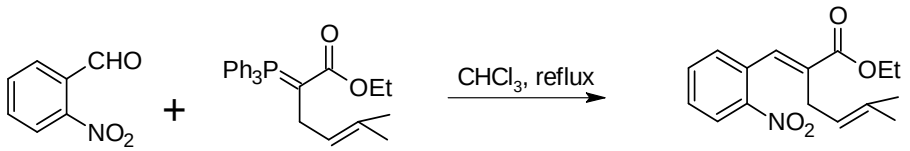
The synthetic plan envisaged by us is depicted in **Scheme XVI**. We envisaged that *o*-nitrobenzaldehyde (**14**) on condensation with Wittig reagent **15** will give the key intermediate ester **16**. It was thought that the *o*-nitrocinnamate ester **16** on lactonisation followed by reduction could form **19** via intermediate **17** which on acid cyclisation should provide **20**. The other slightly shorter route was ester **16** to be reduced first to give **18** which then on acid cyclisation would provide directly **20**.



Scheme XVI

The first step in our projected synthesis was Wittig reaction for which we required the corresponding prenyl phosphorane **15**. The preparation of this is already described in the first chapter.

To start with we took *o*-nitrobenzaldehyde (**14a**) and it was refluxed with prenyl phosphorane **15** in chloroform for 3.0 hrs (**Scheme XVII**).



14a **15** **16a**

Scheme XVII

TLC of the reaction mixture showed the disappearance of the starting aldehyde and appearance of a new spot along with triphenylphosphine oxide. The crude product was purified by column chromatography over silica gel using hexanes-EtOAc (9:1) as an eluent to obtain a pleasant smelling viscous liquid.

As expected the IR spectrum of the compound exhibited strong band at 1713 cm^{-1} due to the carbonyl bond of α,β-unsaturated ester group.

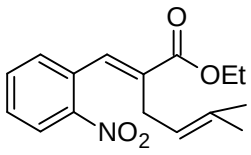
The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz, δ ppm) showed peaks at δ 1.35 (t, 3H, *J* = 7.2 Hz) δ 4.30 (q, 2H, *J* = 7.2 Hz) which were attributed to the ester group (-OCH_2CH_3) while the signal at δ 1.42 (s, 3H) and δ 1.64 (s, 3H) were assigned to the two methyl groups of the prenyl moiety. The peaks observed at δ 2.98 (d, 2H, *J* = 6.3 Hz) and at δ 5.03 (m, 1H) were assigned to the prenyl moiety (-CH_2CH=C<). The peaks observed at δ 7.37 (d, *J* = 7.5 Hz, 1H), δ 7.51 (t, *J* = 7.5 Hz, 1H), δ 7.65 (t, *J* = 7.8 Hz, 1H) and at δ 8.13 (d, *J* = 8.1 Hz, 1H) were attributed to aromatic protons, while the signal at δ 7.9 (s, 1H) was assigned to the benzylic proton.

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz, δ ppm) showed peaks at δ 14.23 (CH_3), δ 17.64 (CH_3), δ 25.66 (CH_3), δ 27.06 (CH_2), δ 61.04 (OCH_2), δ 120.97 (CH), δ 124.72 (CH), δ 128.90 (CH), δ 131.18 (CH), δ 132.07 (C), δ 132.81 (C), δ 133.28 (CH), δ 133.91 (C), δ135.59 (CH), δ 147.71 (C), δ 167.28 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

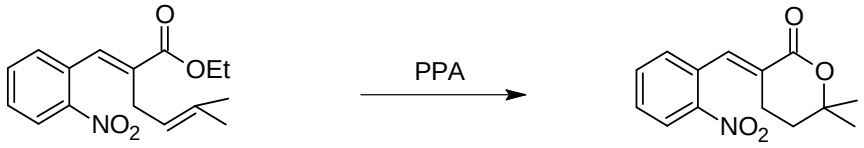
In GC/MS molecular ion peak was shown at *m/z* 289.

Thus on the basis of mode of formation and above spectral analysis, structure **16a** (*E*-isomer) was assigned to the product formed. The yield of the product was found to be 90 %.



16a

We thought to exploit first route A from our projected synthesis. Accordingly, the pleasant smelling α,β-unsaturated ester **16a** was subjected to the PPA cyclization for 5 minutes to furnish δ lactone (**Scheme XVIII**).



16a **17a**

Scheme XVIII

The progress of the reaction was monitored by TLC. The crude product obtained after workup was then purified by column chromatography over silica gel using hexanes-EtOAc (9:1) as an eluent to obtain a white solid.

The IR spectrum of this compound showed strong band at 1774 cm^{-1} which was attributed to the carbonyl group of α,β-unsaturated six membered lactone.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz, δ ppm) showed peaks at δ 1.46 (s, 6H), δ 1.85 (t, *J* = 6.9 Hz, 2H) and δ 2.56 (dt, *J* = 6.9 Hz & 2.4 Hz, 2H) were attributed to the two methyl groups (2 X CH_3) and two methylene groups (-CH_2-CH_2-) of the six membered lactone respectively. The peaks observed at δ 7.39 (d, *J* = 7.5 Hz, 1H), δ 7.55 (t, *J* = 7.5 Hz, 1H), δ 7.69 (t, *J* = 7.5 Hz, 1H) and at δ 8.17 (d, *J* = 8.1 Hz, 1H)

were assigned to aromatic ring protons. While the signal at δ 8.11 (br.s, 1H) was attributed to the benzylic proton.

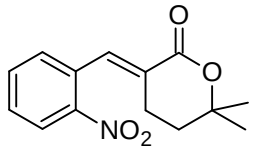
The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz, δ ppm) showed peaks at δ 21.66 (CH_2), δ 27.96 (2 X CH_3), δ 33.13 (CH_2), δ 80.94 (C), δ 125 (CH), δ 127.04 (C), δ 129.41 (CH), δ 130.66 (CH), δ 131.21 (C), δ 133.43 (CH), δ 138.15 (CH), δ 147.72 (C), δ 165.79 (C=O).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

The high resolution mass spectrum of the compound displayed strong peak at *m/z* 284.0893 presumably due to $[M+Na]^+$ pseudo ions. The elemental composition of which was determined to be $C_{14}H_{15}NO_4$. HRMS *m/z* calculated for $C_{14}H_{15}NO_4Na[(M+Na)^+]$ was 284.0899, found : 284.0893.

The melting point of the compound was found to be 96-98 ^oC.

Based on the above spectral data and mode of formation structure **17a** was assigned to the expected lactone having *E* geometry. The yield of the product was found to be 85%.

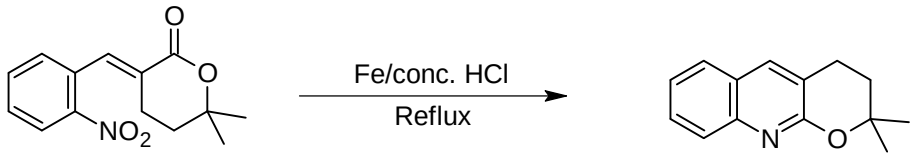


17a

Since reduction and cyclisation are the next two consecutive steps leading to pyranoquinoline core structure, we thought to exploit domino approach wherein both reduction and cyclisation can take place in one pot.

In this regard we planned to use a method[32] which was published by our group wherein Fe and conc. HCl were used for reductive cyclisation. The nitrolactone **17a**

was treated with Fe and conc. HCl and was refluxed on water bath, till the starting material disappeared as indicated by TLC (**Scheme XIX).**



17a **20a**

Scheme XIX

The usual basic workup followed by column chromatographic purification over silica gel using hexanes-EtOAc (8:2) as an eluent afforded a white solid.

The IR spectrum of this compound showed bands at 1622, 1562, 1492 and 1415 cm^{-1}.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz, δ ppm) (**Fig. I**) showed peaks at δ 1.50 (s, 6H), δ 1.96 (t, *J* = 6.6 Hz, 2H) and δ 3.04 (t, *J* = 6.3 Hz, 2H) which were attributed to the two methyl groups (2 X CH_3) and two methylene groups (-CH_2-CH_2-) of the pyran ring respectively. The peaks at δ 7.36 (t, *J* = 7.8 & 7.2 Hz, 1H), δ 7.58 (t, *J* = 8.1 & 7.2 Hz, 1H), δ 7.68 (d, *J* = 7.5 Hz, 1H), δ 7.85 (d, *J* = 8.7 Hz, 1H) and δ 7.88 (s, 1H) were assigned to the five aromatic protons of quinoline ring.

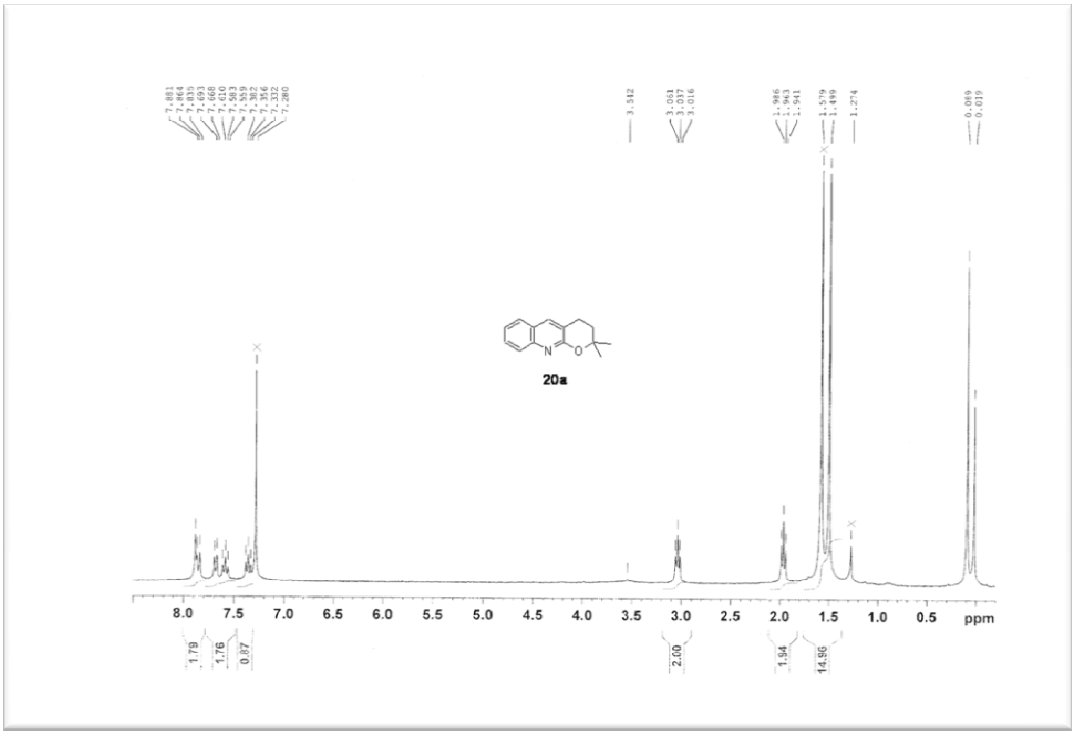


Fig. I : ^{1}H-NMR spectrum of Compound **20a**

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz, δ ppm) (**Fig. II**) showed peaks at δ 22.62 (CH_2), δ 27.36 (2 X CH_3), δ 32.41 (CH_2), δ 77.08 (C), δ 117.66 (C), δ 123.88 (CH), δ 125.19 (C), δ 126.56 (CH), δ 127.22 (CH), δ 129.02 (CH), δ 137.51 (CH), δ 146.42 (C), δ 159.72 (C).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

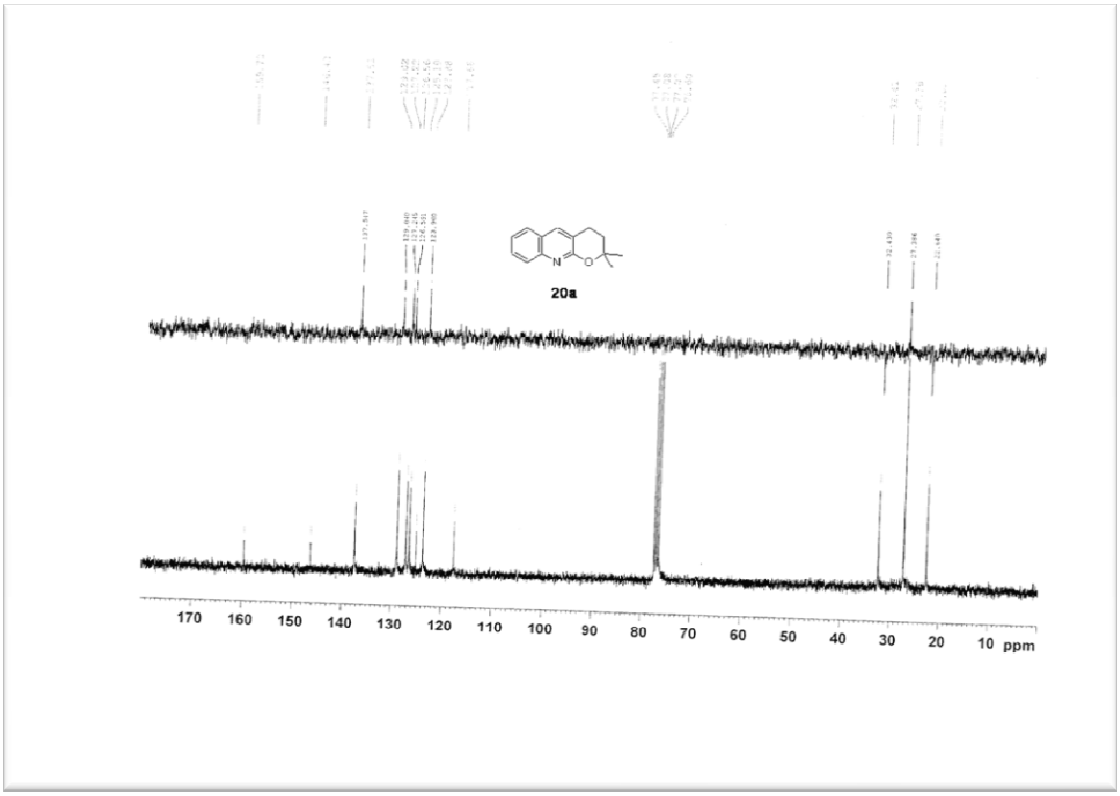
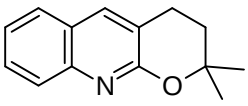


Fig. II : ^{13}C-NMR spectrum of Compound **20a**

The high resolution mass spectrum (HRMS) of the compound showed strong peak at *m/z* 236.1049 presumably due to $[M+Na]^+$ pseudo ions. The elemental composition of which was determined to be $C_{14}H_{15}NO$. HRMS, *m/z* calculated for $C_{14}H_{15}NONa$ $[(M+Na)^+]$ was 236.1051, found : 236.1049.

Melting point of the compound was found to be 103-105 ^oC.

Based on the spectral data and mode of formation structure **20a** was assigned to the pyranoquinoline core structure. The yield of the product was found to be 54%.



20a

Here, the reduction of nitro to amino, isomerisation of *E* to *Z* lactone and cyclisation took place in one pot in a domino fashion. Thus, we succeeded in getting the 3,4-dihydro-pyranoquinoline compound in good yield.

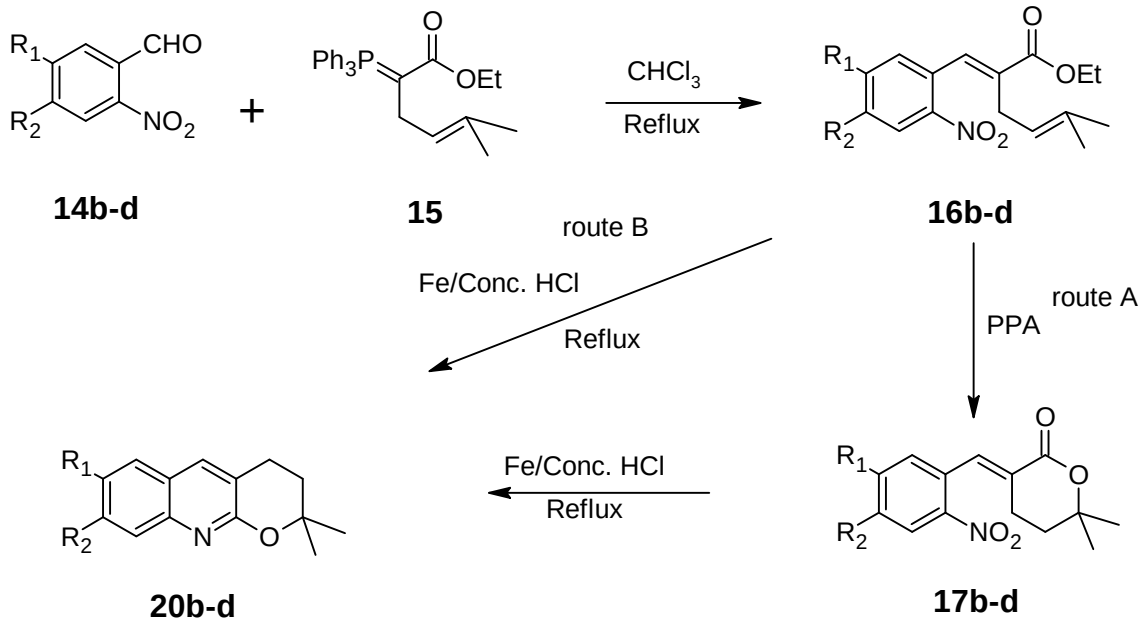
Furthermore, in order to make our synthesis more concise an alternate method i.e. route B was attempted, wherein Wittig product (**16a**) was directly subjected to reductive cyclisation employing Fe and conc. HCl to get the corresponding dihydropyranoquinoline (**20a**) without isolating the lactone intermediate.

Thus, the α,β-unsaturated ester **16a** was subjected to Fe and conc. HCl and was heated on boiling water bath till the starting material disappeared as indicated by TLC. The usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent afforded a white solid.

The appearance of this compound on TLC and its spectral analysis such as IR, ^{1}H-NMR, ^{13}C-NMR and HRMS were matching with that of the 3,4-dihydropyranoquinoline (**20a**) prepared by the previous route A. Hence formation of it was confirmed.

However, the yield of isolated product during this one-pot concurrent reduction/ isomerisation/ cyclisation was found to be only 19%.

Once establishing a protocol for the synthesis of pyranoquinoline **20a**, we decided to generalize the method to make more such analogues of pyranoquinolines. For this purpose, we selected three nitrobenzaldehydes namely 5-substituted-2-nitrobenzaldehyde (**14b**), 3,4-dimethoxy-6-nitrobenzaldehyde (**14c**) and 3,4-methylenedioxy-6-nitrobenzaldehyde (**14d**) as depicted in **Scheme XX**.

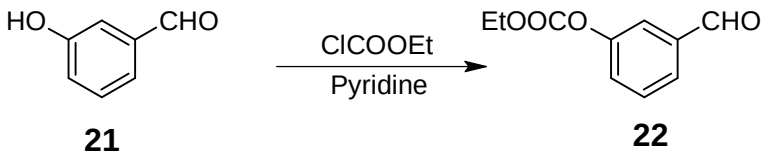


	R_1	R_2
b	OCOOEt	H
c	OCH_3	OCH_3
d	—— OCH_2O ——	

Scheme XX

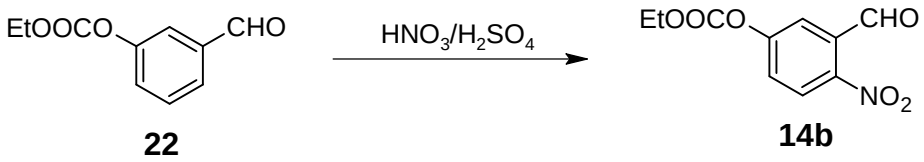
We thought to start with 5-substituted-2-nitrobenzaldehyde (**14b**). It was prepared by referring literature method from 3-hydroxy benzaldehyde (**21**).

Thus, hydroxyl group protection of 3-hydroxybenzaldehyde (**21**) was carried out with ethylchloroformate in presence of pyridine as per reported procedure (**Scheme XXI)**. The spectral data of the product was found to be identical with that of the reported in literature.[33]



Scheme XXI

The nitration on *O*-protected benzaldehyde (**22**) was carried out by subjecting it to sulphuric acid/ nitric acid mixture. After usual workup the crude product was recrystallized from hexanes to get pale yellow needles of ethyl-3-formyl-4-nitrophenylcarbonate (**14b**). The crystallized product was melted at 61 ^{o}C (Lit.[34] m.p.-60-61 ^{o}C) (**Scheme XXII**)



22 **14b**

Scheme XXII

The Wittig olefination reaction of this 5-substituted-2-nitrobenzaldehyde (**14b**) with prenyl phosphorane (**15**) was done in refluxing chloroform for 3.0 hrs. The product was obtained as a pleasant smelling viscous liquid after column chromatographic purification.

IR (KBr): 1770 cm^{-1} (C=O of carbonate group), 1712 cm^{-1} (C=O of ester group)

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.26-1.43	m	6 H	2 X - $OCH_2C\underline{H}_3$
δ 1.64	s	6 H	2 X- CH_3
δ 2.93	d	2 H (*J* = 6.6 Hz)	- $C\underline{H}_2$-CH =
δ 4.19-4.33	m	4 H	2 X - $OC\underline{H}_2CH_3$
δ 4.95	br. s.	1 H	- CH_2-C<u>H</u> =
δ 7.15	d	1 H (*J* = 2.4 Hz)	ArH
δ 8.14	d	1 H (*J* = 9.0 Hz)	ArH
δ 7.29	dd	1 H (*J* = 9.0 & 2.4 Hz)	ArH
δ 7.79	s	1H	Ar-C<u>H</u> = C

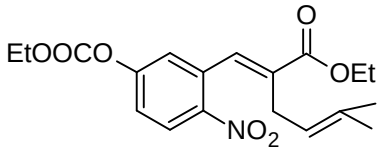
^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

δ 14.11 (CH_3), δ 14.20 (CH_3), δ 17.54 (CH_3), δ 25.61 (CH_3), δ 26.99 (CH_2), δ 61.11 (OCH_2), δ 65.56 (OCH_2), δ 120.65 (CH), δ 121.23 (CH), δ 123.52 (CH), δ 126.56 (CH), δ 133 (C), δ 134.11 (C), δ 134.40 (C), δ 134.72 (CH), δ 144.71 (C), δ 152.32 (C), δ 154.06 (C), δ 167.03 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

In GC/MS molecular ion peak was shown at *m/z* 377.

Thus, on the basis of mode of formation and spectral data structure **16b** was assigned to the product formed. The yield of the product was found to be 82%.



16b

This α,β-unsaturated ester **16b** was then subjected to PPA cyclisation followed by usual workup. After column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent, a white solid was obtained.

IR (KBr): 1774 cm^{-1} (C=O of carbonate group), 1717 cm^{-1} (C=O of lactone group)

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.34	t	3 H (*J* = 7.2 Hz)	- $OCH_2\underline{CH_3}$
δ 1.40	s	6 H	2 X- CH_3
δ 1.78	t	2 H (*J* = 6.9 Hz)	-$\underline{CH_2}$-CH_2-
δ 2.53	t	2 H (*J* = 6.9 Hz)	-$\underline{CH_2}$-$C(CH_3)_2$
δ 4.30	q	2 H (*J* = 7.2 Hz)	- $O\underline{CH_2}CH_3$
δ 7.18	d	1 H (*J* = 2.4 Hz)	ArH
δ 8.17	d	1 H (*J* = 9.0 Hz)	ArH
δ 7.32	dd	1 H (*J* = 9.0 & 2.4 Hz)	ArH
δ 8.03	s	1H	Ar-$\underline{CH}$ = C

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm):

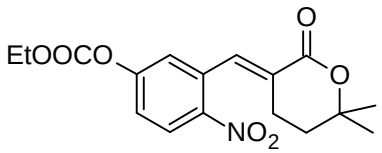
δ 14.11 (CH_3), δ 21.60 (CH_2), δ 27.95 (2 X CH_3), δ 33.08 (CH_2), δ 65.68 (CH_2), δ 81.00 (C), δ 121.56 (CH), δ 123.08 (CH), δ 126.89 (CH), δ 127.63 (C), δ 133.22 (C), δ 137.22 (CH), δ 144.66 (C), δ 152.31 (C), δ 154.10 (C), δ 165.48 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

HRMS: *m/z* $[M + Na]^+$ Calcd for $C_{17}H_{19}NO_7Na$: 372.1059; found: 372.1059.

The melting point of the compound was found to be 104-106 ^{o}C.

Based on the mode of formation and spectral data, structure **17b** was assigned to the product formed. The yield of the product was found to be 95%.



17b

Final step was reductive cyclisation. Here, both the routes of reductive cyclisation i.e. from δ-lactones as well as from α,β-unsaturated ester were attempted to get 3,4-dihydropyranoquinoline.

Route A

In this method δ lactone (**17b)** was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent furnished a white solid product in 85 % yield.

Route B

In this method the corresponding α,β-unsaturated ester **16b** was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent furnished a white solid product in 36 % yield.

The two compounds obtained by these two methods were found to be identical which was indicated by TLC and other spectroscopic analysis.

IR (KBr): 3300 (OH), 1612, 1517, 1434, 1367 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) (**Fig. III**):

δ 1.46	s	6 H	2 X- CH_3
δ 1.93	t	2 H (*J* = 6.9 Hz)	-$\underline{CH_2}$-CH_2-
δ 2.99	t	2 H (*J* = 6.9 Hz)	-$\underline{CH_2}$-$C(CH_3)_2$
δ 5.58	br.s.	1 H	Ar-O$\underline{H}$
δ 7.03	d	1 H (*J* = 2.7 Hz)	ArH
δ 7.21	dd	1 H (*J* = 9.0 & 2.7 Hz)	ArH
δ 7.73	s	1 H	ArH
δ 7.76	s	1 H	ArH

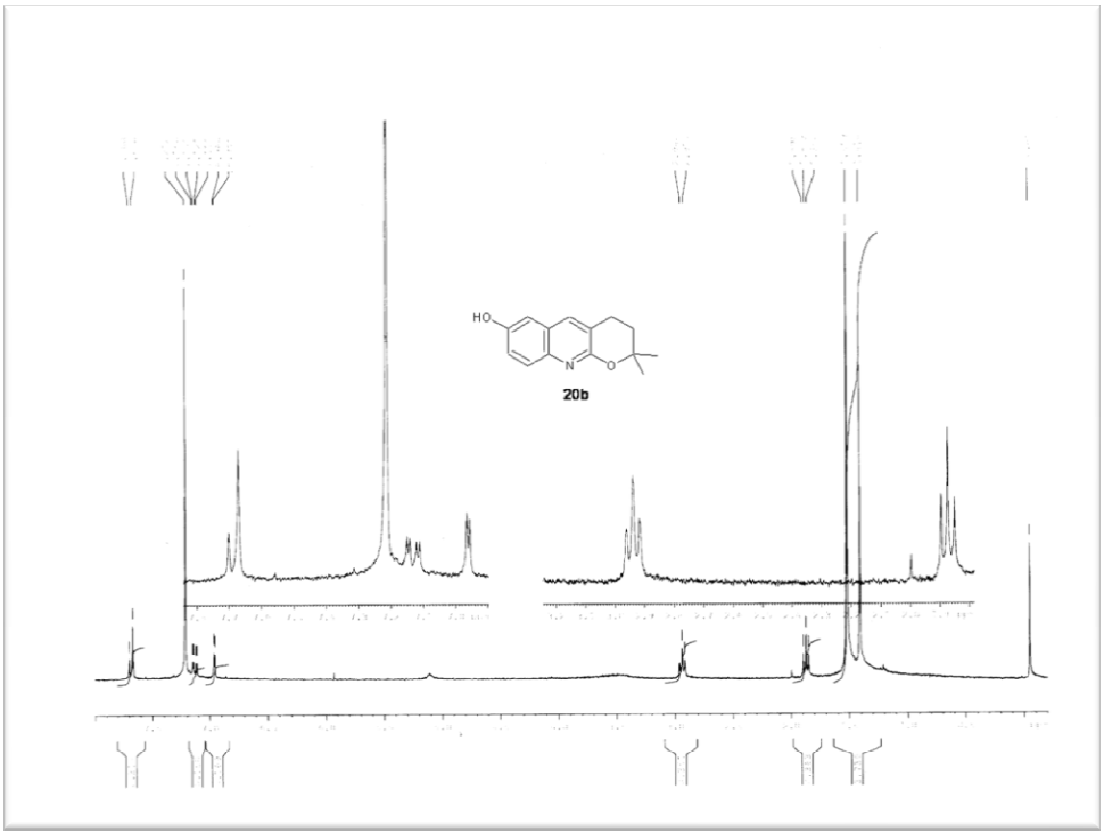


Fig. III : ^{1}H-NMR spectrum of Compound **20b**

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

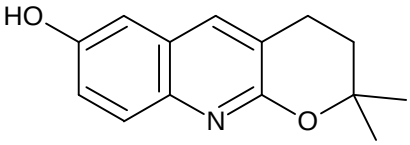
δ 22.59 (CH_2), δ 27.28 (2 X CH_3), δ 32.39 (CH_2), δ 70.19 (C), δ 108.46 (CH), δ 118.06 (CH), δ 120.69 (CH), δ 125.83 (CH), δ 128.52 (C), δ 136.16 (C), δ 141.62 (C), δ 152.02 (C), δ 158.20 (C).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

HRMS: *m/z* $[M + Na]^+$ Calcd for $C_{14}H_{15}NO_2Na$: 252.1; found: 252.0999.

The melting point of the compound was found to be 223-225 ^{o}C.

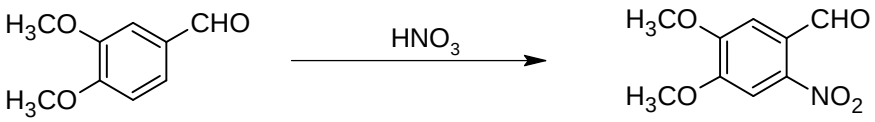
Based on the mode of formation and spectral data, structure **20b** was assigned to the product formed.



20b

Interestingly during the reductive cyclisation the carbonate group was also cleaved.

Third aromatic nitroaldehyde which was used was 3,4-dimethoxy-6-nitrobenzaldehyde (**14c**). 3,4-dimethoxy-6-nitrobenzaldehyde (**14c**) was prepared from 3,4-dimethoxybenzaldehyde (**23**) by treating it with nitric acid. After usual workup, the crude product was recrystallized from ethanol to afford pale yellow needles of 3,4-dimethoxy-6-nitrobenzaldehyde (**14c**). The crystallized product was melted at 132 ^{o}C (Lit.[34] m.p. 133^{o}C) (**Scheme XXIII**).



23 **14c**

Scheme XXIII

Condensation of this 3,4-dimethoxy-6-nitrobenzaldehyde (**14c**) with phosphorane **15** was carried out in refluxing chloroform for 3.0 hrs. After column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent, the product was obtained as a thick viscous yellow liquid.

IR (KBr): 1709 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) (**Fig. IV**):

δ 1.37	t	3H (*J* =7.2 Hz)	- $OCH_2C\underline{H}_3$
δ 1.49	s	3 H	- CH_3
δ 1.67	s	3 H	- CH_3
δ 3.00	d	2 H (*J* = 6.0 Hz)	- $C\underline{H}_2$-CH =
δ 3.92	s	3 H	- OCH_3
δ 4.00	s	3 H	- OCH_3
δ 4.31	q	2 H (*J* = 7.2 Hz)	- $OC\underline{H}_2CH_3$
δ 5.1	m	1 H	- CH_2-C$\underline{H}$ =
δ 6.77	s	1 H	ArH
δ 7.75	s	1 H	ArH
δ 7.94	s	1 H	Ar-C$\underline{H}$ = C

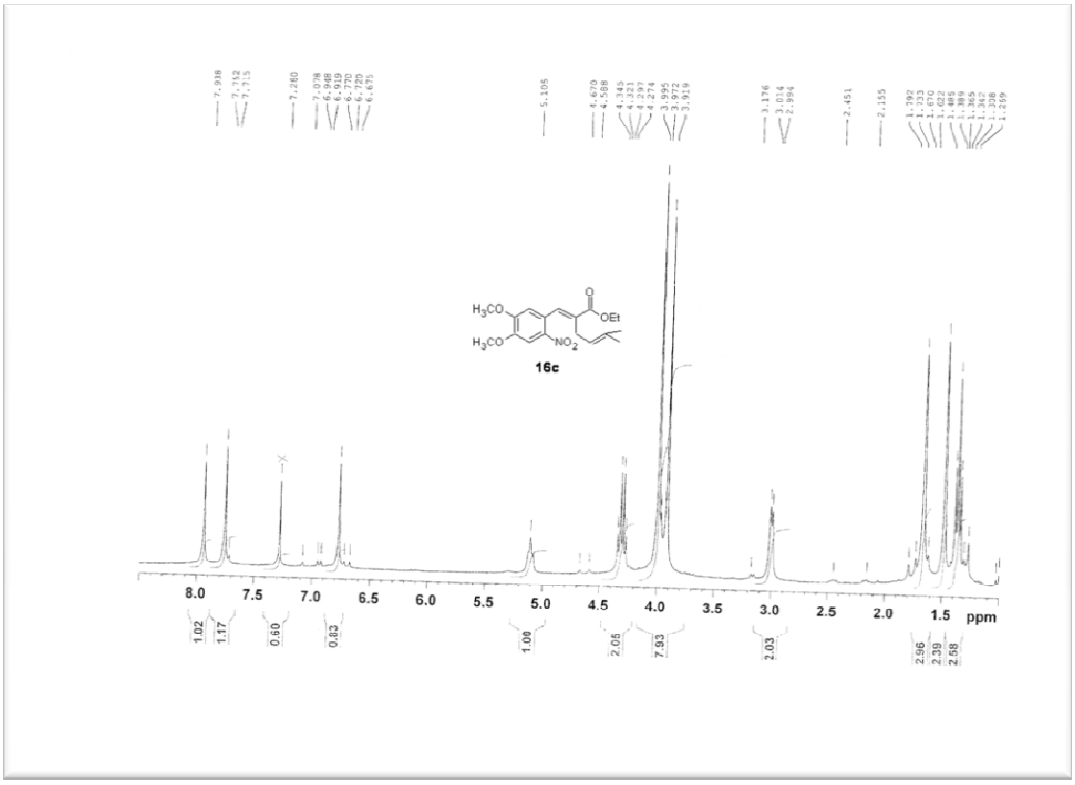


Fig. IV : ^{1}H-NMR spectrum of Compound **16c**

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) (**Fig. V**):

δ 14.24 (CH_3), δ 17.85 (CH_3), δ 25.62 (CH_3), δ 27.28 (CH_2), δ 56.33 (OCH_3), δ 56.40 (OCH_3), δ 60.99 (OCH_2), δ 107.70 (CH), δ 112.42 (CH), δ 121.77 (CH), δ 126.66 (C), δ 132.75 (C), δ 132.83 (C), δ 136.82 (CH), δ 140.15 (C), δ 148.55 (C), δ 152.97 (C), δ 167.41 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

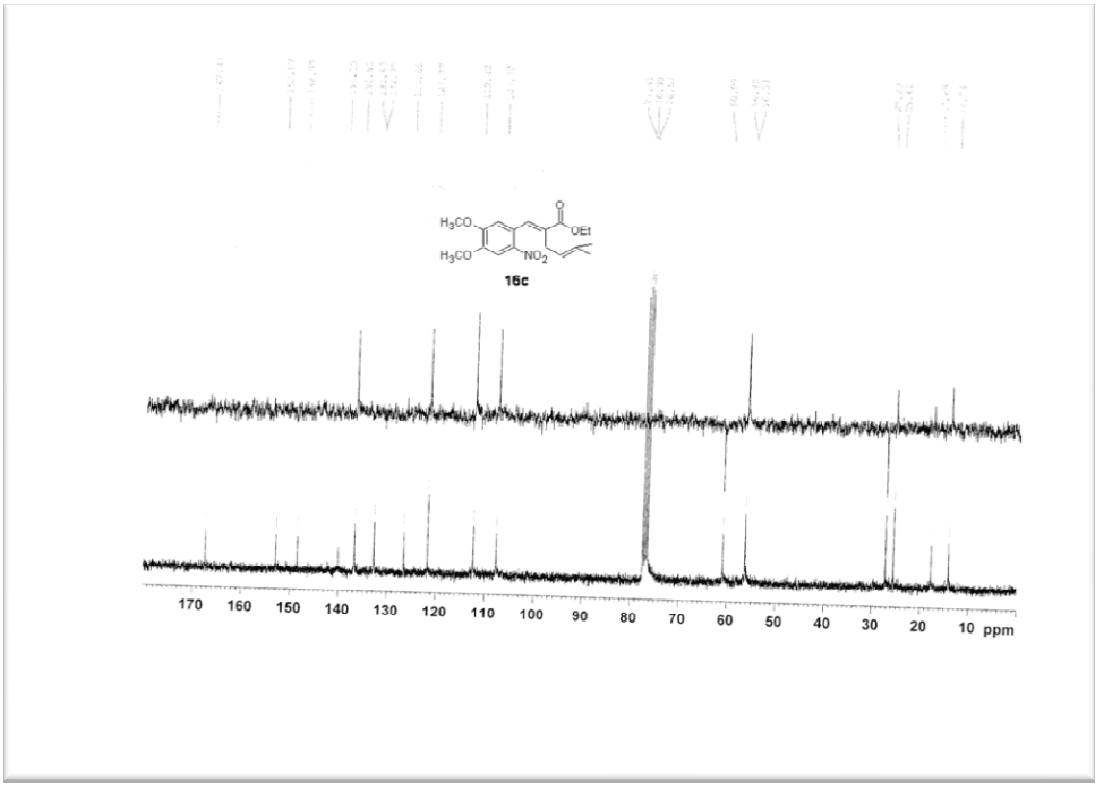
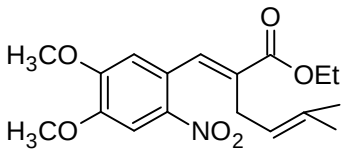


Fig. V : ^{13}C-NMR spectrum of Compound **16c**

In GC/MS, molecular ion peak was shown at *m/z* 349.

On the basis of mode of formation and spectral data, structure **16c** was assigned to the product formed. The yield of the product was found to be 66%.



16c

The α,β-unsaturated ester **16c** was further subjected to PPA cyclisation. The usual work up followed by column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent gave a yellow solid.

IR (KBr): 1692 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) (**Fig. VI**):

δ 1.46	s	6 H	2 X- CH_3
δ 1.85	t	2 H (*J* = 6.9 Hz)	-$\underline{CH_2}$-CH_2-
δ 2.55	dt	2 H (*J* = 6.6 & 2.1 Hz)	-$\underline{CH_2}$-$C(CH_3)_2$
δ 3.98	s	3 H	- OCH_3
δ 4.00	s	3 H	- OCH_3
δ 6.73	s	1 H	ArH
δ 7.76	s	1 H	ArH
δ 8.11	br.s.	1 H	Ar-$\underline{CH}$ = C

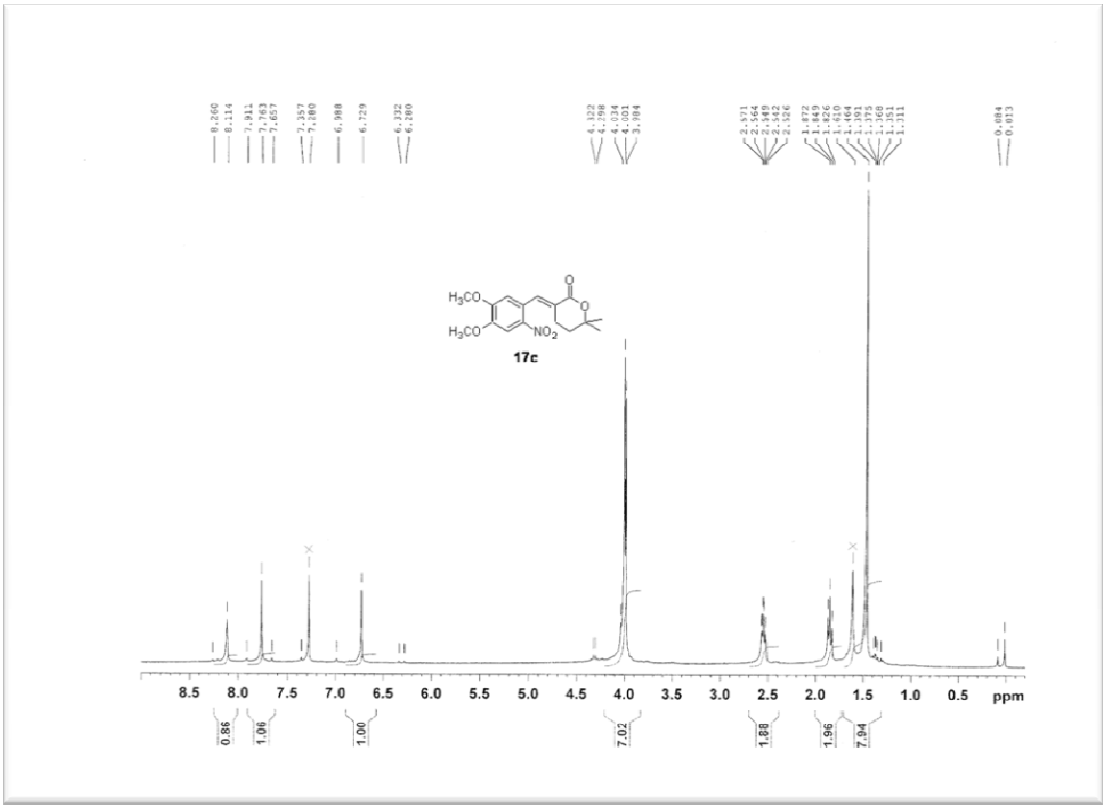


Fig. VI : ^{1}H-NMR spectrum of Compound **17c**

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) (**Fig. VII**):

δ 21.75 (CH_2), δ 27.98 (2 X CH_3), δ 33.20 (CH_2), δ 56.47 (OCH_3), δ 56.62 (OCH_3), δ 80.83 (C), δ 107.97 (CH), δ 111.63 (CH), δ 125.75 (C), δ 126.16 (C), δ 139.17 (CH), δ 140.33 (C), δ 148.88 (C), δ 153.14 (C), δ 166.02 (C=O).

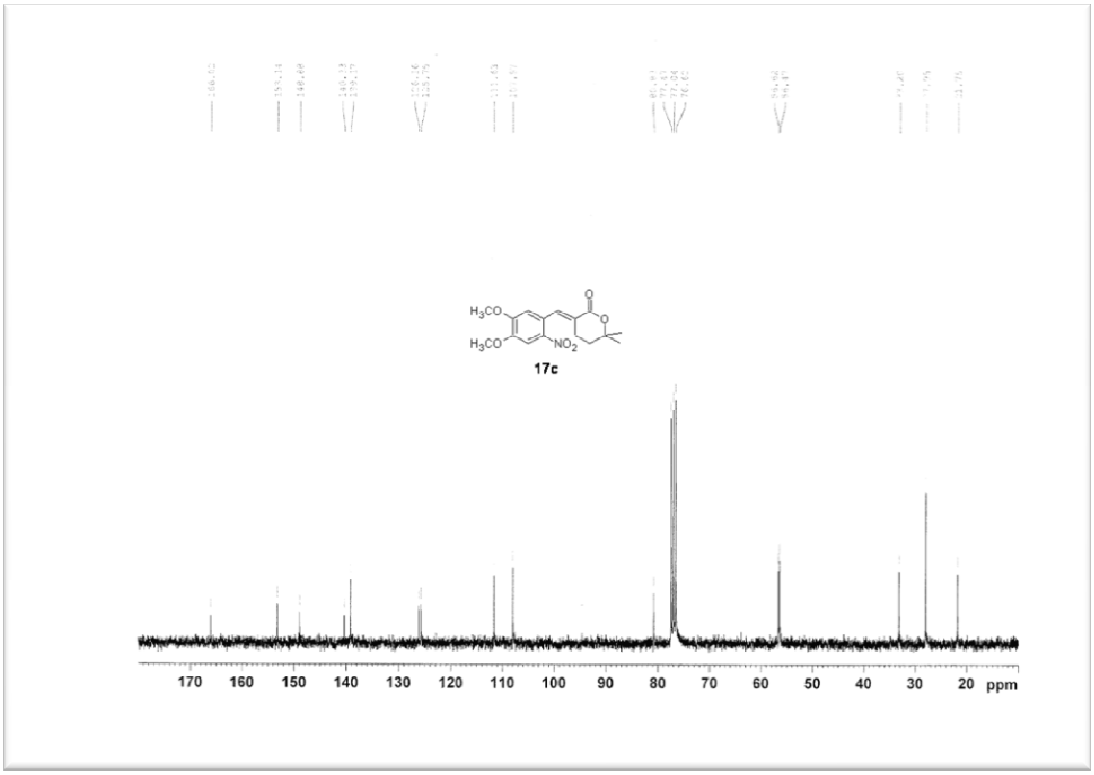
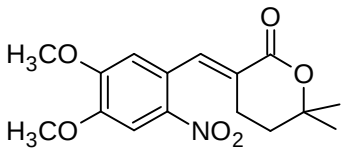


Fig. VII : ^{13}C-NMR spectrum of Compound **17c**

HRMS: *m/z* $[M + Na]^+$ Calcd for $C_{16}H_{19}NO_6Na$: 344.1110; found:344.1113.

The melting point of the compound was found to be 181-182 ^oC.

Based on the spectral data and mode of formation structure **17c** was assigned to the product. The yield of the product was found to be 80%.



17c

For further reductive cyclisation both routes were attempted.

Route A

Corresponding δ lactone **17c** was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent gave a white solid in 76 % yield.

Route B

The α,β-unsaturated ester **16c** was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent furnished a white solid in 25 % yield.

The two compounds obtained by both these routes were found to be identical which was indicated by TLC and other spectroscopic analysis.

IR (KBr): 1612, 1496, 1458, 1381 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) (**Fig. VIII**):

δ 1.47	s	6 H	2 X- CH_3
δ 1.93	t	2 H (*J* = 6.6 Hz)	-$\underline{CH_2}$-CH_2-
δ 2.97	t	2 H (*J* = 6.6 Hz)	-$\underline{CH_2}$-$C(CH_3)_2$
δ 3.98	s	3 H	- OCH_3
δ 3.99	s	3 H	- OCH_3
δ 6.95	s	1 H	ArH
δ 7.2	s	1 H	ArH
δ 7.7	s	1 H	ArH

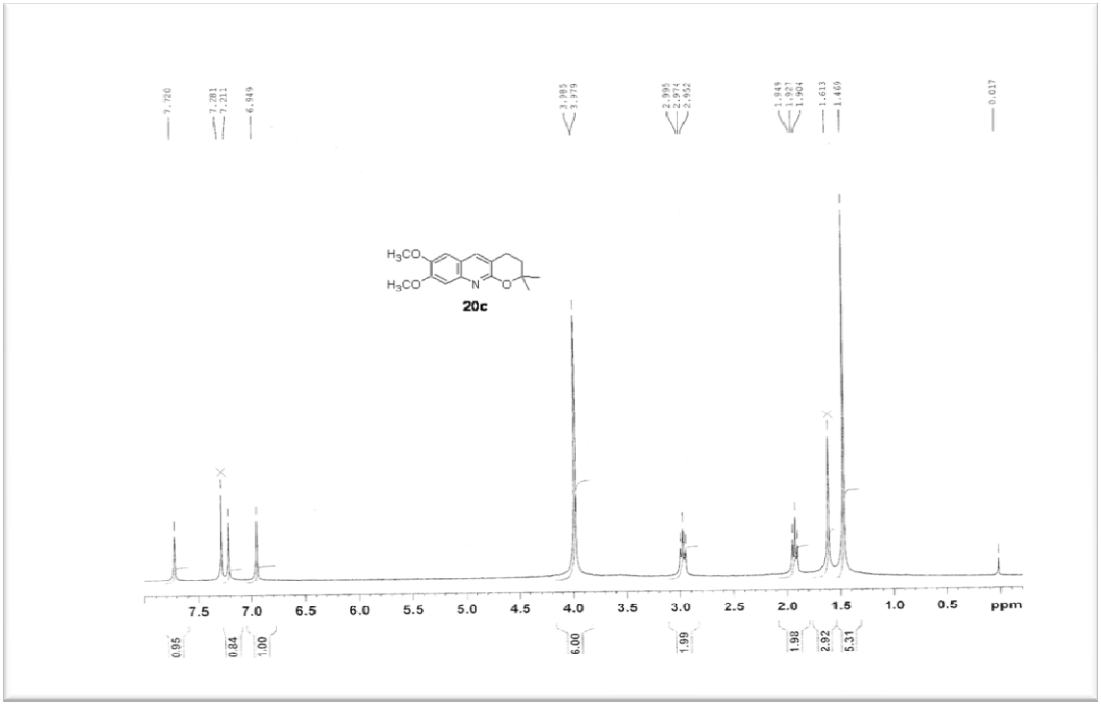


Fig. VIII : ^{1}H-NMR spectrum of Compound **20c**

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) (**Fig. IX**):

δ 22.43 (CH_2), δ 27.28 (2 X CH_3), δ 32.51 (CH_2), δ 55.87 (2 X CH_3), δ 76.53 (C), δ 104.69 (CH), δ 106.62 (CH), δ 114.85 (C), δ 119.92 (C), δ 136 (CH), δ 143.05 (C), δ 147.81 (C), δ 152.07 (C), δ 158.66 (C).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

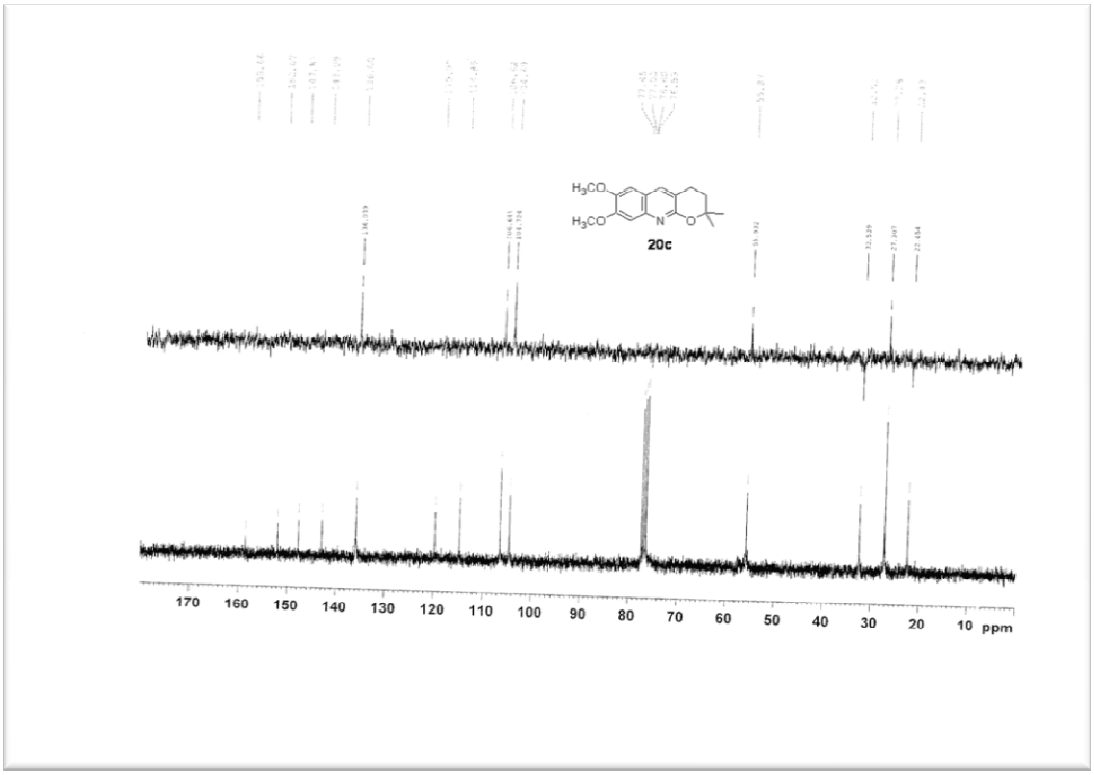
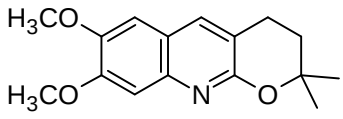


Fig. IX : ^{13}C-NMR spectrum of Compound **20c**

HRMS: *m/z* $[M + Na]^+$ Calcd for $C_{16}H_{19}NO_3Na$: 296.1263; found: 296.1263.

The melting point of the compound was found to be 156-158 ^oC.

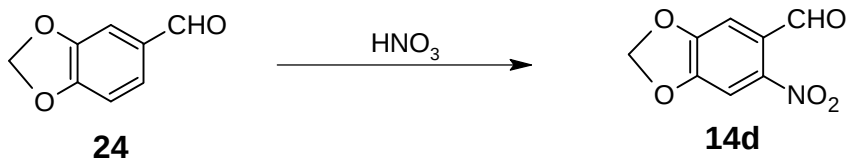
Based on the mode of formation and spectral data structure **20c** was assigned to the product formed.



20c

Another nitrobenzaldehyde chosen for this purpose was 3,4-methylenedioxy-6-nitrobenzaldehyde (**14d**). 3,4-methylenedioxy-6-nitrobenzaldehyde (**14d**) was obtained from 3,4-methylenedioxybenzaldehyde (**24**) by treating it with nitric acid. After usual workup the crude product was recrystallized from ethanol to furnish pale

yellow needles of 3,4-methylenedioxy-6-nitrobenzaldehyde (**14d**). The crystallised product was melted at 87^{o}C (lit.[34] m.p. 88 ^{o}C) (**Scheme XXIV**).



24 **14d**

Scheme XXIV

The Wittig olefination reaction of 3,4-methylenedioxy-6-nitrobenzaldehyde (**14d**) with phosphorane **15** was performed in refluxing chloroform for 3.0 hrs. After column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent the product was obtained as a yellow viscous liquid.

IR (KBr): 1713 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.35	t	3H (*J* =7.2 Hz)	- $OCH_2\underline{CH_3}$
δ 1.51	s	3 H	- CH_3
δ 1.67	s	3 H	- CH_3
δ 3.00	d	2 H (*J* = 6.6 Hz)	- $\underline{CH_2}$-CH =
δ 4.29	q	2 H (*J* = 7.2 Hz)	- $O\underline{CH_2}CH_3$
δ 5.06	m	1 H	- CH_2-$\underline{CH}$ =
δ 6.17	s	2 H	- OCH_2O-
δ 6.74	s	1 H	ArH
δ 7.65	s	1 H	ArH
δ 7.83	s	1 H	Ar-$\underline{CH}$ = C

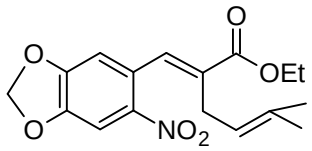
^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

δ 14.21 (CH_3), δ 17.68 (CH_3), δ 25.66 (CH_3), δ 27.15 (CH_2), δ 60.99 (OCH_2), δ 103.20 (CH_2), δ 105.50 (CH), δ 109.74 (CH), δ 121.02 (CH), δ 128.74 (C), δ 132.74 (C), δ 133.05 (C), δ 136.22 (CH), δ 141.87 (C), δ 147.78 (C), δ 151.77 (C), δ 167.30 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

GC/MS: *m/z* 333 [M^+].

On the basis of mode of formation and spectral data, structure **16d** was assigned to the product formed. The yield of the product was found to be 68%.



16d

The resulting α,β-unsaturated ester **16d** was then subjected to PPA cyclisation. The usual workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (9:1) as an eluent gave a yellow solid.

IR (KBr): 1697 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) :

δ 1.45	s	6 H	2 X- CH_3
δ 1.85	t	2 H (*J* = 6.9 Hz)	-$\underline{CH_2}$-CH_2-
δ 2.56	dt	2 H (*J* = 6.9 & 2.4 Hz)	-$\underline{CH_2}$-$C(CH_3)_2$
δ 6.18	s	2 H	- OCH_2O-
δ 6.73	s	1 H	ArH
δ 7.67	s	1 H	ArH
δ 8.04	br.s.	1 H	Ar-$\underline{CH}$ = C

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) :

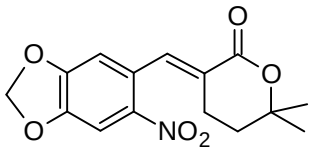
δ 21.65 (CH_2), δ 27.94 (2 X CH_3), δ 33.11 (CH_2), δ 80.83 (C), δ 103.38 (OCH_2O), δ 105.79 (CH), δ 109.00 (CH), δ 126.14 (C), δ 127.84 (C), δ 138.91 (CH), δ 142 (C), δ 148.13 (C), δ 151.94 (C), δ 165.9 (C=O).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

HRMS: *m/z* $[M + Na]^+$ Calcd for $C_{15}H_{15}N\,O_6Na$: 328.0797; found 328.0800.

The melting point of the compound was found to be 176-177 ^oC.

Based on the mode of formation and spectral data structure **17d** was assigned to the product. The yield of the product was found to be 82%.



17d

Further reductive cyclisation was done using both the routes.

Route A

In this method the δ lactone **17d** was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent gave a white solid in 83% yield.

Route B

In this method the corresponding α,β-unsaturated ester **16d** was subjected to Fe and conc. HCl reflux. Usual basic workup followed by column chromatographic purification over silica gel using hexanes:EtOAc (8:2) as an eluent furnished a white solid in 33% yield.

The two compounds obtained by both these routes were found to be identical which was indicated by TLC and other spectroscopic analysis.

IR (KBr): 1620, 1480, 1465, 1388 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) (**Fig. X**):

δ 1.44	s	6 H	2 X- CH_3
δ 1.89	t	2 H (*J* = 6.6 Hz)	-$\underline{CH_2}$-CH_2-
δ 2.92	t	2 H (*J* = 6.6 Hz)	-$\underline{CH_2}$-$C(CH_3)_2$
δ 6.02	s	2 H	- OCH_2O-
δ 6.91	s	1 H	ArH
δ 7.15	s	1 H	ArH
δ 7.65	s	1 H	ArH

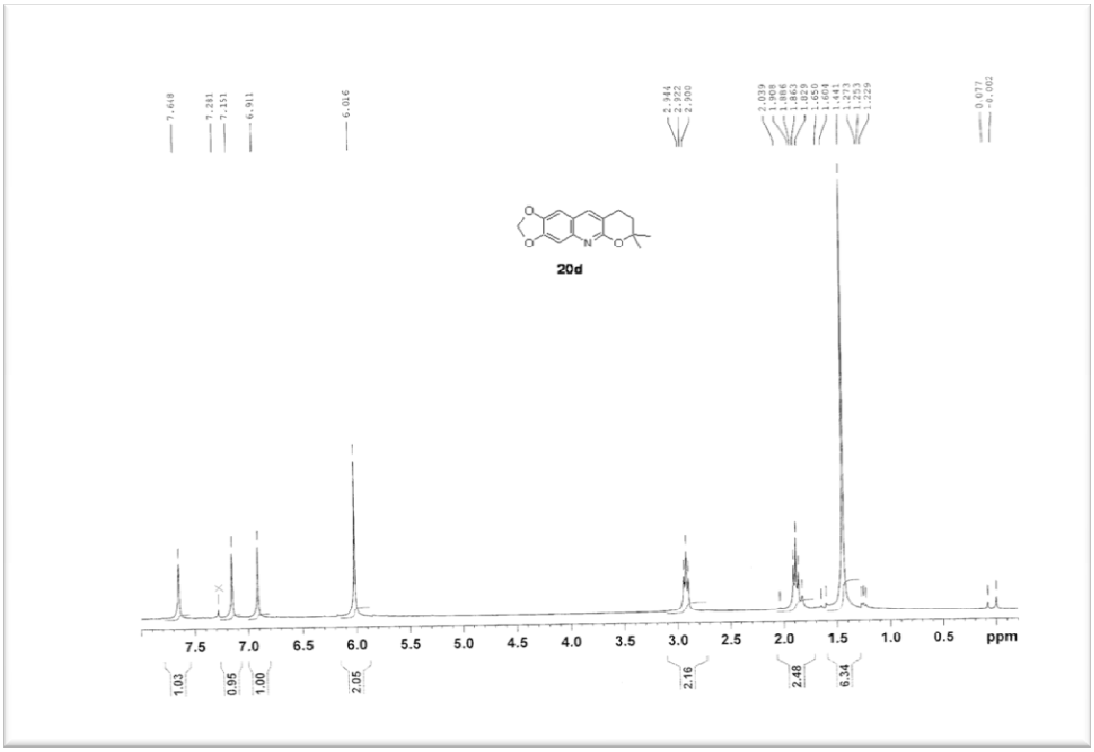


Fig. X : ^{1}H-NMR spectrum of Compound **20d**

^{13}C-NMR ($CDCl_3$, 75 MHz, δ ppm) (**Fig. XI**):

δ 22.32 (CH_2), δ 27.26 (2 X CH_3), δ 32.44 (CH_2), δ 76.65 (C), δ 101.26 (CH_2), δ 102.08 (CH), δ 104.40 (CH), δ 114.78 (C), δ 121.10 (C), δ 136.57 (CH), δ 144.24 (C), δ 145.83 (C), δ 150.21 (C), δ 158.60 (C).

The multiplicities of the carbon signals mentioned were obtained from DEPT experiments.

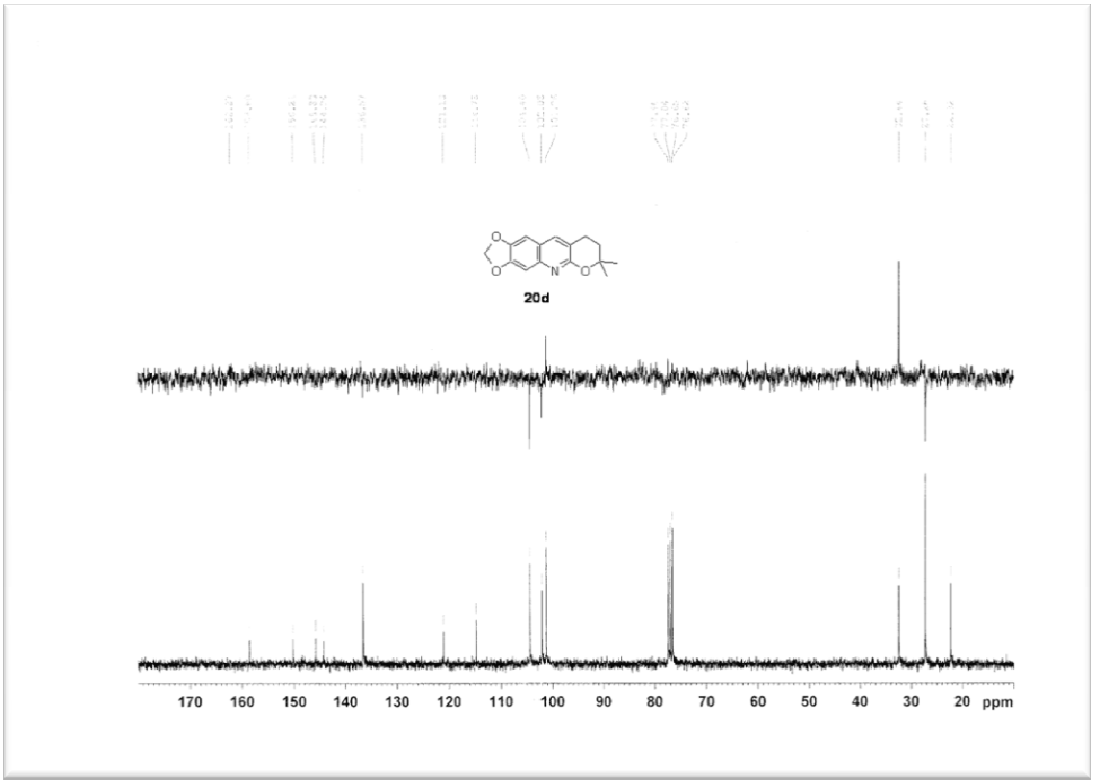
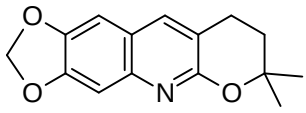


Fig. XI : ^{13}C-NMR spectrum of Compound **20d**

HRMS: *m/z* $[M + Na]^+$ Calcd for $C_{15}H_{15}N\,O_3Na$: 280.0950; found: 280.0958.
The melting point of the compound was found to be 177-179 ^oC.

Based on the mode of formation and spectral data structure **20d** was assigned to the product formed.



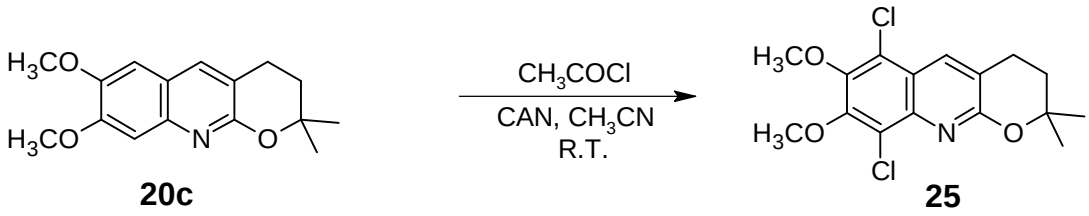
20d

Thus, we have successfully completed the synthesis of four 3,4-dihydropyranoquinoline molecules (**20a-d**).

Some of the chlorinated compounds containing quinoline ring structure, such as chloroquine and quinine exhibit good antimalarial activity. Owing to the importance of these compounds, we thought to chlorinate our 3,4-dihydropyranoquinoline compounds in order to study the biological activity (if any) associated with it.

At this point the literature search on the chlorinating agents was performed and we found out that the acetyl chloride in presence of CAN in acetonitrile acts as an efficient chlorinating agent for activated aromatic system.[35]

The 3,4-dihydropyranoquinoline compound selected for this purpose was 7,8-dimethoxy-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (**20c**). The substrate **20c** was treated with acetyl chloride in acetonitrile in presence of CAN for 8.0 hrs, till the disappearance of the starting material (monitored by TLC) (**Scheme XXV**).



Scheme XXV

After workup the residue was purified by column chromatography over silica gel using hexanes:EtOAc (7:3) to furnish a pale yellow solid.

IR spectrum of this compound showed absorptions at 1593.20 cm^{-1}, 1556.55 cm^{-1}, 1485.19 cm^{-1}, 1454.33 cm^{-1} and 1263.37 cm^{-1}.

The ^{1}H-NMR ($CDCl_3$, 300 MHz, δ ppm) (**Fig. XII**) showed strong peak at δ 1.48 (s, 6H) which was assigned to the two methyl groups 2 X ($-CH_3$) on the pyran ring. The signal at δ 1.94 (t, *J* = 6.6 Hz, 2H) and at δ 3.04 (t, *J* = 6.6 Hz, 2H) was attributed to $-CH_2-CH_2-$ group of pyran ring moiety. Whereas the signal at δ 3.97 (s, 3H) and δ 4.00

(s, 3H) was assigned to the two methyl groups 2 X (-CH_3) of two methoxy moieties on the benzene ring. The signal due to one aromatic proton was observed at δ 8.20 (s, 1H).

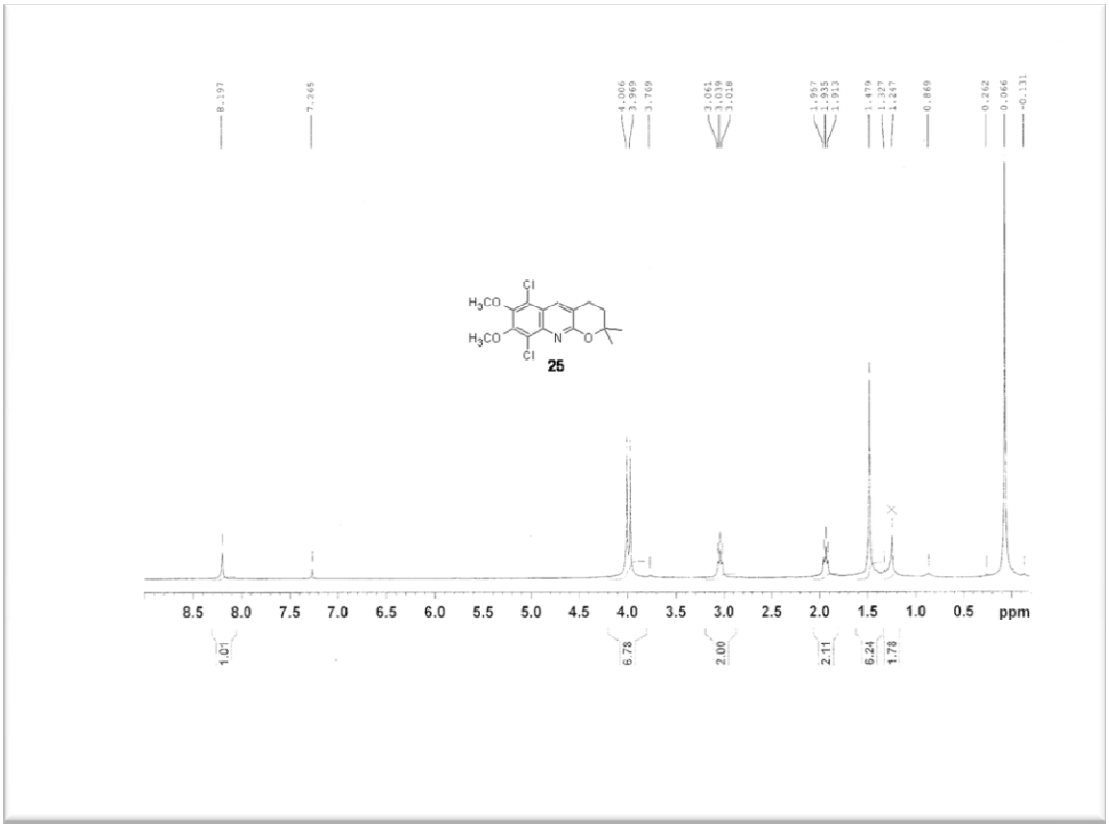


Fig. XII : ^{1}H-NMR spectrum of Compound **25**

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz, δ ppm) (**Fig. XIII**) showed peaks at δ 22.64 (CH_2), δ 27.28 (2 X CH_3), δ 32.32 (CH_2), δ 61.27 (CH_3), δ 61.38 (CH_3), δ 77.96 (C), δ 118.58 (C), δ 120.58 (C), δ 121.32 (C), δ 122.79 (C), δ 134.76 (CH), δ 140.82 (C), δ 147.50 (C), δ 152.02 (C), δ 160.46 (C).

The multiplicities of the carbon signals mentioned above were obtained from DEPT experiments.

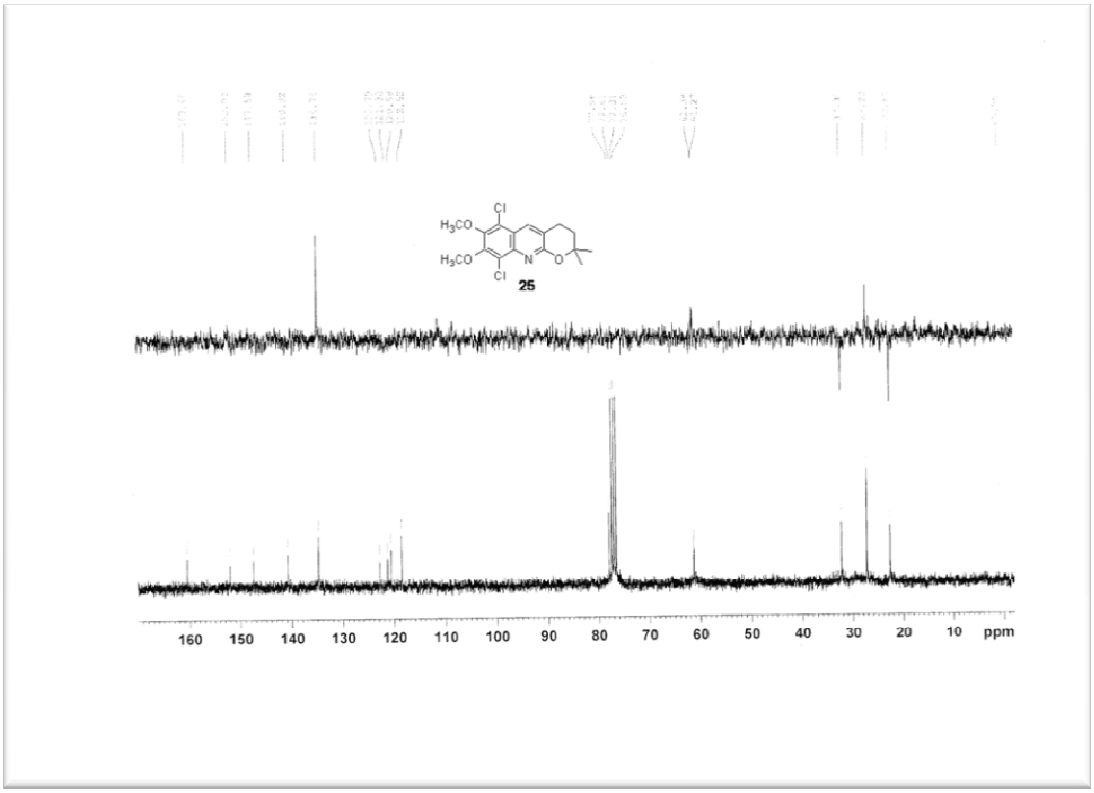


Fig. XIII : ^{13}C-NMR spectrum of Compound **25**

The high resolution mass spectrum (**Fig. XIV**) of the compound displayed strong peak at *m/z* 342.0662 presumably due to $[M+H]^+$ pseudo ions. The elemental composition of which was determined to be $C_{14}H_{17}NO_3Cl_2$. HRMS *m/z* calculated for $C_{14}H_{17}NO_3Cl_2H[(M+H)^+]$ was 342.0663, found : 342.0662.

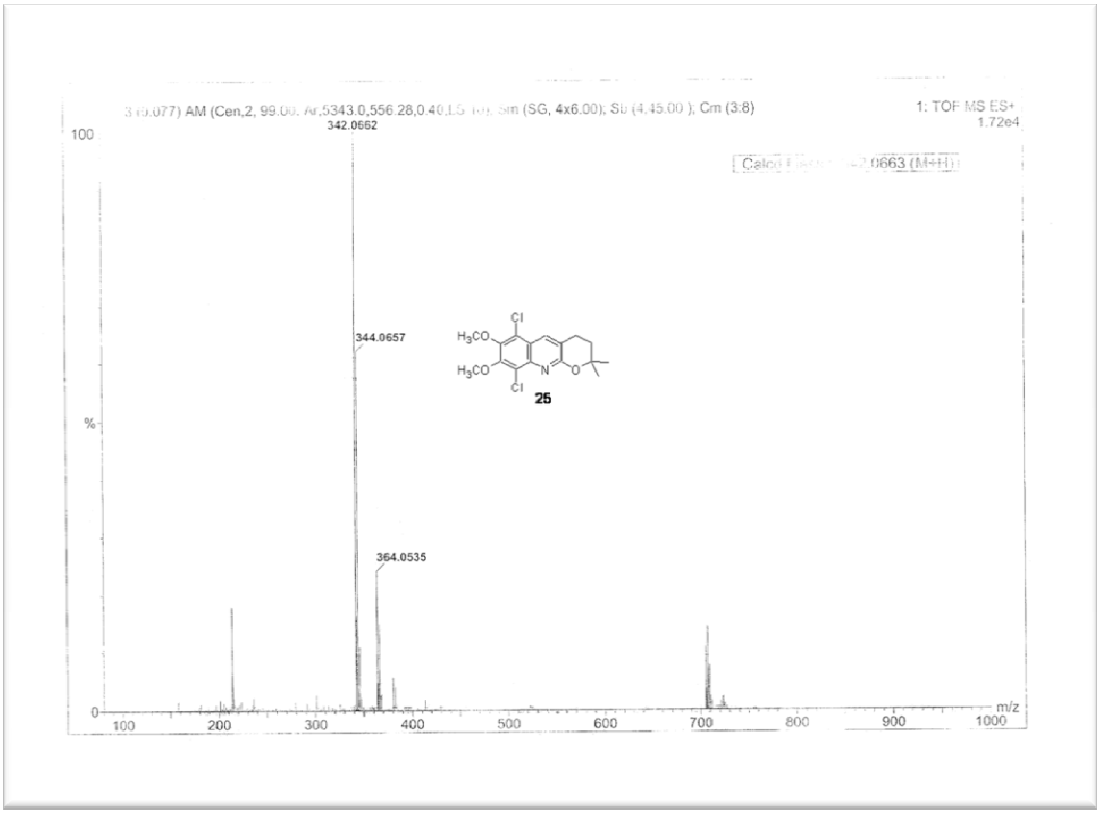
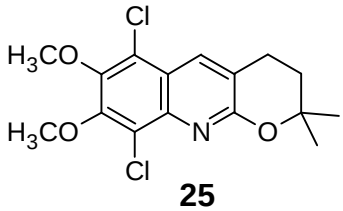


Fig. XIV : HRMS spectrum of Compound **25**

The melting point of the compound was found to be 98-100 ^{o}C.

Thus on the basis of mode of formation and spectral data the formation of dichlorinated compound **25** was confirmed. The yield of the product was found to be 73%.



25

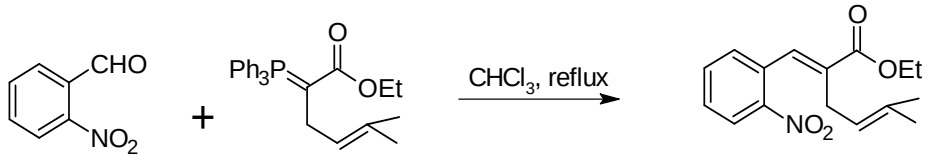
Thus, we have prepared chlorinated 3,4-dihydropyranoquinoline molecule **(25)** which could be tested for its biological activity.

Conclusion

We have developed a convenient synthesis of 2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines from *o*-nitrobenzaldehydes using Wittig reaction as a key reaction. The Wittig condensation product was converted to 2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolines by two routes. The first route involve lactonisation using PPA followed by reductive cyclisation of the lactone. The overall yield of this two step approach was found to be good. While the direct reductive cyclisation to target compounds gave low overall yield. We also demonstrated the chlorination of pyranoquinoline (**20c)** takes place in the benzene nucleus of the quinoline ring which could be useful to make biologically active molecules.

Experimental

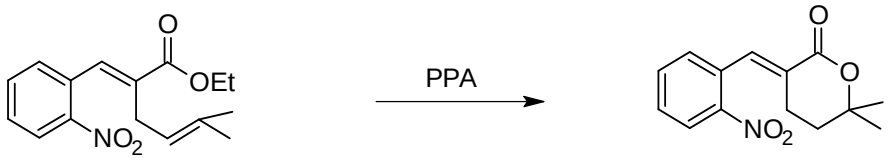
2.1 Preparation of Ethyl (2*E*)-5-Methyl-2[(2-nitrophenyl)methylidene)hex-4-enoate (**16a**)



14a **15** **16a**

A solution of *o*-nitrobenzaldehyde (**14a**) (0.151 g, 1 mmol), phosphorane **15** (0.417 g, 1.0 mmol) in chloroform (10 mL) was refluxed for 3 hrs. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to furnish a thick viscous yellow liquid (**16a**) (0.260 g, 90%).

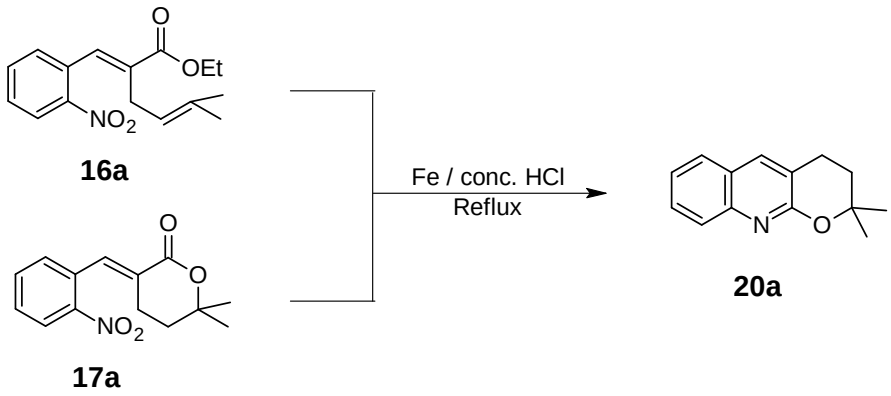
2.2 Preparation of (3*E*)-6,6-Dimethyl-3-[(2-nitrophenyl)methylidene]tetrahydro-2*H*-pyran-2-one (**17a**)



16a **17a**

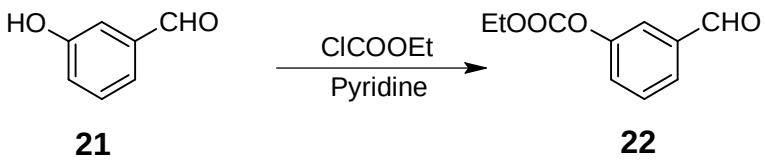
To a flask containing compound **16a** (0.289 g, 1 mmol) was added polyphosphoric acid (2 mL). The reaction mixture was warmed on water bath for 5 min. Chilled water (15 mL) was added to the reaction mixture and it was subsequently extracted with diethyl ether (3 X 10 mL). The diethyl ether layer was washed twice with sat. $NaHCO_3$ solution and then dried over anhyd. sodium sulphate. The solvent was removed under vacuum pump and the residue was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a white solid (**17a**) (0.222 g, 85%), m.p. 96-98 ^{o}C.

2.3 Preparation of 2,2-Dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (**20a**)



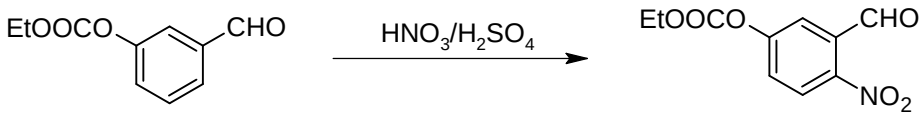
Concentrated HCl (8 mL) was added to a magnetically stirred mixture of esters **16a** (0.289 g, 1 mmol) or **17a** (0.261 g, 1 mmol) and Fe powder (0.838 g, 15 mmol). The reaction mixture was allowed to stir for 15 mins. and was subsequently refluxed on a water bath. After completion of the reaction (the progress of the reaction was monitored by thin TLC), the reaction mixture was filtered and the residue was washed with water (3 X 5 mL). This combined filtrate was washed with diethyl ether (2 X 10 mL) and filtered on celite. The filtrate was basified with solid NaOH pellets and the compound was subsequently extracted in diethyl ether (3 X 15 mL). The combined organic extracts were dried over anhyd. Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give a white solid (**20a**) [0.040 g, (19 % from **16a**), 0.115 g, (54 % from **17a**)] m.p. 103-105 ^{o}C.

2.4 Preparation of Ethyl-3-Formylphenyl carbonate (**22**)



3-Hydroxybenzaldehyde (**21**) (15.0 g, 0.123 mol) was dissolved in dry pyridine (100 mL). The solution was cooled in an ice bath and ethyl chloroformate (20 mL) was added dropwise over a period of 30 mins. The resulting solution was stirred for 2 hrs at room temperature. The product was extracted into diethyl ether (3 X 25 mL), and the ether extract was washed consecutively with water, 5% HCl, 5% cold NaOH and again with water. The dried organic extract was evaporated to give the product (**22**) as yellow syrup (23 g, 97%) which was directly nitrated.

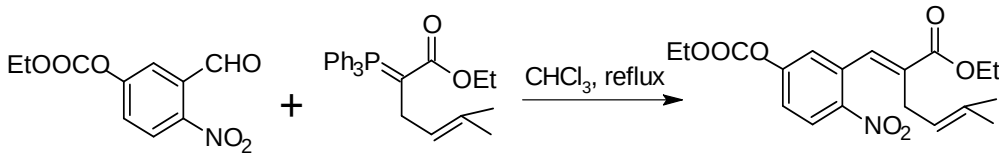
2.5 Preparation of Ethyl 3-Formyl 4-nitrophenyl carbonate (**14b**)



22 **14b**

Ethyl 3-formyl phenyl carbonate (**22**) (14.0 g, 0.0072 mol) was dissolved in conc. H_2SO_4 (135 m L). The solution was cooled to -5 ^oC and a solution 67.5 mL of fuming nitric acid (3.44 ml, sp.g. 1.49, 0.0814 mol) in 25 mL of conc. H_2SO_4 was added dropwise over 15 mins. at -5 to 0 ^oC. Stirring was continued at -5 to 0 ^oC for 1 hr. Water (500 mL) was added dropwise at -10 ^oC and the product was extracted into chloroform (3 X 50 mL). Evaporation of the dried solvent gave a gum which was crystallized from hexanes to give product (**14b**) as pale yellow needles (13 g, 76%, m.p. 60-61 ^oC).

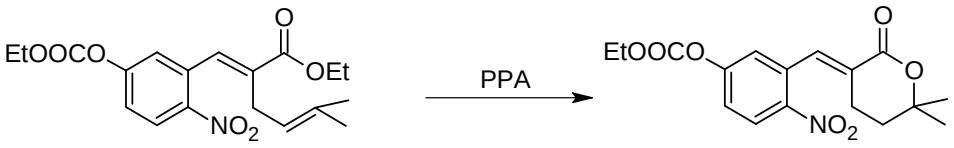
2.6 Preparation of Ethyl (2*E*)-2-({5-[(ethoxycarbonyl)oxy]-2-nitrophenyl} methylidene)-5-methylhex-4-enoate (**16b**)



14b **15** **16b**

Followed the same procedure as in Expt. 2.1. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to furnish a thick viscous yellow liquid (**16b**) (82%).

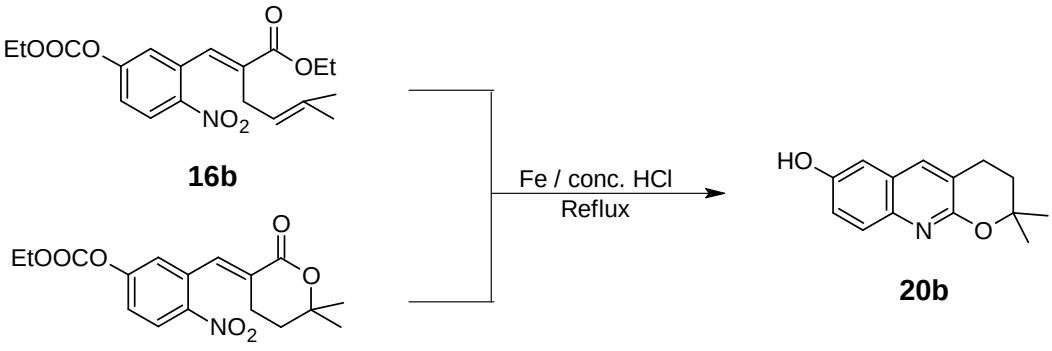
2.7 Preparation of 3-[(*E*)-(6,6-Dimethyl-2-oxodihydro-2*H*-pyran-3(4*H*)-ylidene) methyl]-4-nitrophenyl ethyl carbonate (**17b**)



16b **17b**

Followed the same procedure as in Expt. 2.2. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a white solid (**17b**) (95%) m.p. 104-106 ^{o}C.

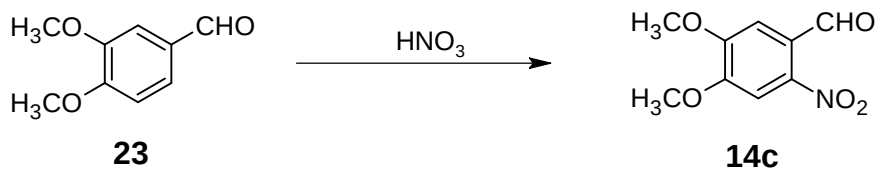
2.8 Preparation of 2,2-Dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-ol (**20b**)



16b **17b** **20b**

Followed the same procedure as in Expt. 2.3, except the basification was carried out using liquid ammonia instead of solid NaOH pellets. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give a white solid (**20b**) (36% from **16b**, 85% from **17b**) m.p. 223-225 ^{o}C.

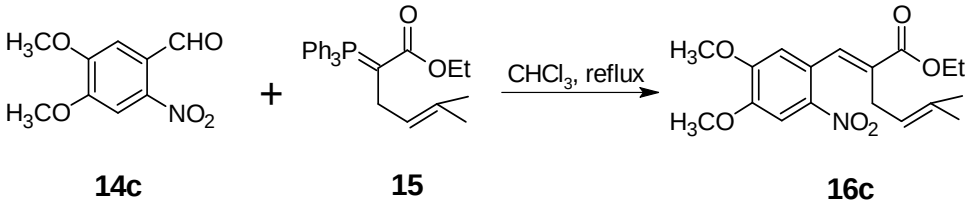
2.9 Preparation of 3,4-Dimethoxy-6-nitrobenzaldehyde (**14c**)



23 **14c**

Nitric acid (35 mL, 1.4 d) was cooled to 0 ^{o}C and 3,4-dimethoxybenzaldehyde (**23**) (5 g) was added to it in lots with constant stirring. The addition was complete in about 10 mins. During the addition the temperature of the reaction mixture was kept below 0^{o} C. The ice bath was removed and the reaction mixture was stirred for 5 mins. It was then warmed on water bath to get a clear reddish brown solution. This solution was kept in ice bath and stirred vigorously till the solid product separated out. The reaction mixture was then poured into ice cold water. The pale yellow solid thus obtained was filtered, washed with water and dried. It was recrystallized from ethanol to furnish 3,4-dimethoxy-6-nitrobenzaldehyde (**14c**) (5.2 g, 82%) m.p. 133 ^{o}C.

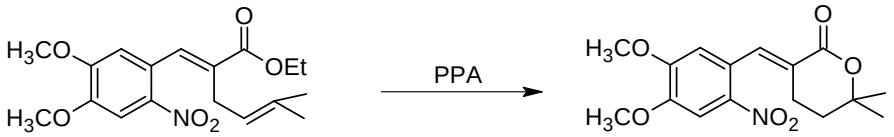
2.10 Preparation of Ethyl (2*E*)-2-[(4,5-dimethoxy-2-nitrophenyl)methylidene]-5-methylhex-4-enoate (**16c**)



14c **15** **16c**

Followed the same procedure as in Expt. 2.1. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a thick viscous yellow liquid (**16c**) (66%).

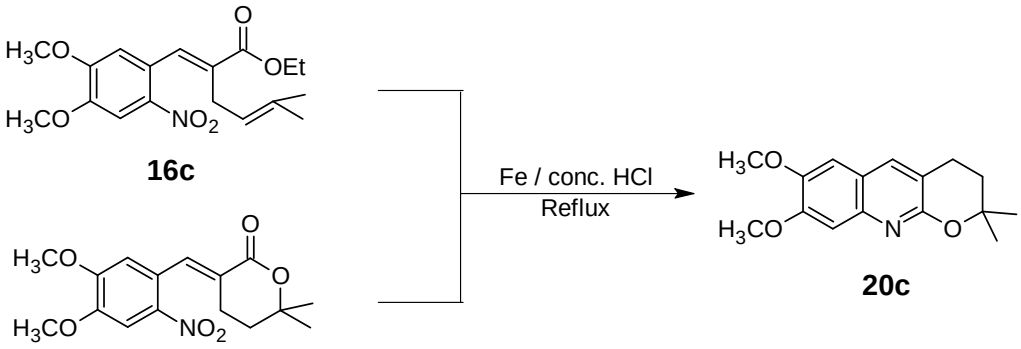
2.11 Preparation of (3*E*)-3-[(4,5-Dimethoxy-2-nitrophenyl)methylidene]-6,6-dimethyltetrahydro-2*H*-pyran-2-one (**17c**)



16c **17c**

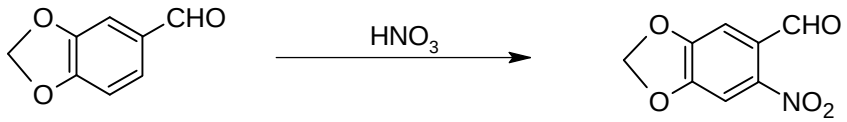
Followed the same procedure as in Expt. 2.2. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a yellow solid (**17c**) (80%) m.p. 181-182 ^{o}C.

2.12 Preparation of 7,8-Dimethoxy-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (**20c**)



Followed the same procedure as in Expt. 2.3. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give a white solid (**20c**) (25% from **16c**, 76% from **17c**), m.p. 156-158 ^{o}C.

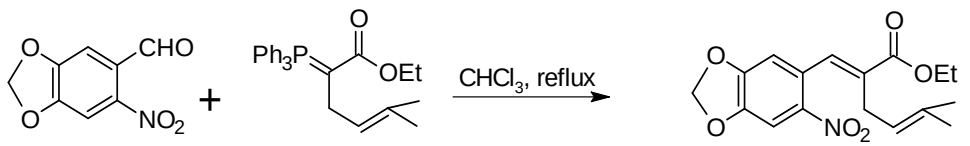
2.13 Preparation of 3,4-Methylenedioxy-6-nitrobenzaldehyde (**14d**)



24 **14d**

Nitric acid (35 mL, 1.4 d) was cooled to 0 ^{o}C and 3,4-methylenedioxybenzaldehyde (**24**) (5 g) was added to it in lots with constant stirring. The addition was complete in about 10 mins. During the addition the temperature of the reaction mixture was kept below 0 ^{o}C. The ice bath was removed and the reaction mixture was stirred for 5 mins. It was then warmed on water bath to get a clear reddish brown solution. This solution was kept in ice bath and stirred vigorously till the solid product separated out. The reaction mixture was then poured into ice cold water. The pale yellow solid thus obtained was filtered, washed with water and dried. It was recrystallized from ethanol to furnish 3,4-methylenedioxy-6-nitrobenzaldehyde (**14d**) (5.5 g, 97%) m.p. 87 ^{o}C.

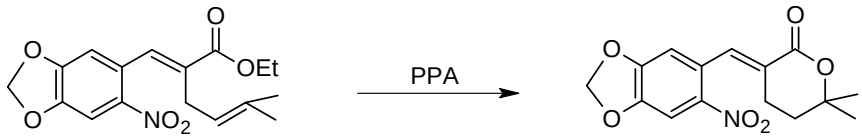
2.14 Preparation of Ethyl (2*E*)-5-methyl-2-[(6-nitro-1,3-benzodioxol-5-yl) methylidene]hex-4-enoate (**16d**)



14d **15** **16d**

Followed the same procedure as in Expt. 2.1. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a thick viscous yellow liquid (**16d**) (68%).

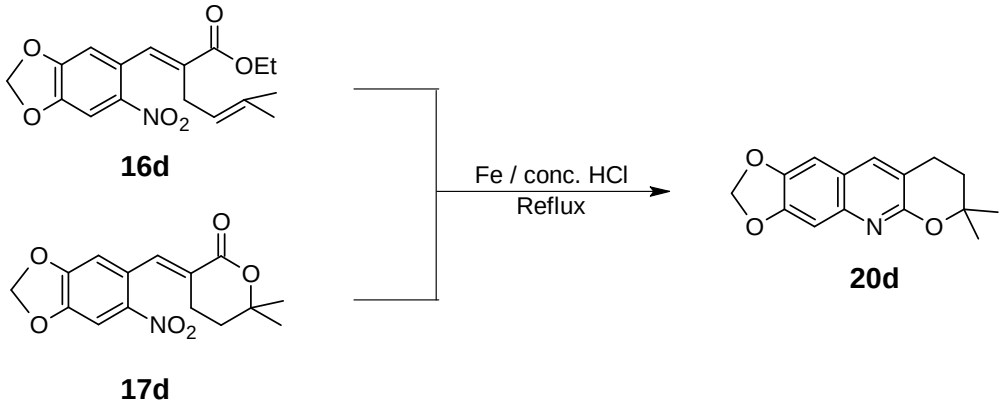
2.15 Preparation of (3*E*)-6,6-Dimethyl-3-[(6-nitro-1,3-benzodioxol-5-yl) methylidene]tetrahydro-2*H*-pyran-2-one (**17d**)



16d **17d**

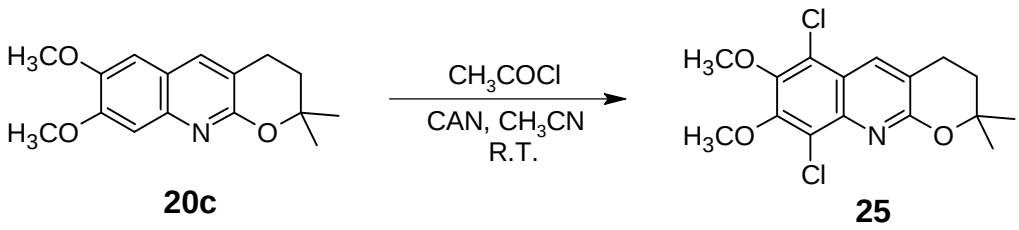
Followed the same procedure as in Expt. 2.2. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to give a yellow solid (**17d**) (82%) m.p. 176-177 ^{o}C.

2.16 Preparation of 7,8-Methylenedioxy-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (**20d**)



Followed the same procedure as in Expt. 2.3. Crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give a white solid (**20d**) (33% from **16d**, 83% from **17d**) m.p. 177-179 ^{o}C.

2.17 Preparation of 6,9-Dichloro-7,8-dimethoxy-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*] quinoline (**25**)



To a stirred mixture of the 7,8-dimethoxy-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[2,3-*b*]quinoline (**20c**) (0.200 g, 0.73 mmol) and freshly distilled acetylchloride (0.056 g, 0.73 mmol) in acetonitrile (5 mL) was added ceric ammonium nitrate (0.040 g, 0.073 mmol) in one portion under N_2 at room temperature. The reaction mixture was allowed to stir for 8 hrs. After completion of the reaction (the progress of the reaction was monitored by TLC), the reaction mixture was diluted with diethyl ether (15 mL) and washed thoroughly with sat. aqueous $NaHCO_3$ solution (3 X 5 mL), brine (3 X 5 mL) and dried over anhyd. Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel using hexanes:EtOAc (7:3) as an eluent to give a pale yellow solid (**25**) (0.180 g, 73%), m.p. 98-100 ^{o}C.

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CHAPTER 3
Section A

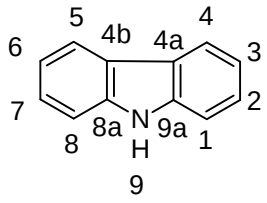
CHAPTER 3

SECTION A

Synthesis of Mukonine

Introduction

Carbazoles are a series of natural products which are widely distributed in higher plants. Although carbazole (**1**) (**Fig. 1**) itself is a natural product isolated from coal tar in 1872 by Graebe and Glaser, the first simple carbazole from plant sources was not discovered until the 1960s.[1]



1

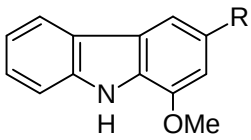
Fig. 1

A large number of biologically active carbazole alkaloids have been isolated from natural sources.[2-10] Many of these natural products display biological properties such as antitumor, psychotropic, anti-inflammatory, anti-histaminic, antibiotic and antioxidative activities.[11-18] As synthetic materials, many carbazole derivatives exhibit photoreactive, photo conductive and light emitting properties.[19-20] Carbazoles have also been recognized as useful scaffold in anion binding studies.[21] Their useful bioactivities and their interesting structural features attracted the attention of synthetic chemists and led to the development of many different synthetic stategies. Since 1979, new highly substituted carbazole alkaloids have been found by several groups in different terrestrial plants.

The first carbazole alkaloid to be isolated from plant source was murrayanine (**2**) extracted from the stembark of the small tree Murraya Koenigii (*Fam. Rutaceae*)[22] an Indian medicinal plant commonly known as “curry-leaf tree” and used externally to cure eruptions.[23] Since then, the field has expanded enormously large due to the promising biological activities of many of the carbazole alkaloids.

The carbazole alkaloids have primarily been isolated from plants of the genus Murraya, Glycosmis and Clausena from the family *Rutaceae*, particularly 1-oxygenated carbazole alkaloids like murrayanine (**2**), mukoeic acid (**3**) and mukonine (**6**). Extracts of the leaves and bark of this tree have been used as a folk medicine for analgesia and local anesthesia, as well as for the treatment of eczema, rheumatism and dropsy. The shrub *clausena excavata* is traditionally used in China for the treatment of snakebites, abdominal pain and as a detoxification agent. Extensive studies of the *clausena* genus have resulted in several compounds with interesting biological activities.

The isolation of several 3-methyl carbazole derivatives from higher plants[5] and of carbazole (**1**) from Glycosmis pentaphylla[24] shows that the aromatic methyl group can be eliminated oxidatively from the key intermediate 3-methyl carbazole via -CH_2OH, -CHO and -COOH functionalities. [3] The isolation of 3-methyl carbazole from the genus *clausena*,[25] the co-occurrence of murrayanine (**2**), mukoeic acid (**3**), murrayafoline A (**4**), koenoline (**5**) in *M.Koenigii*, as well as the subsequent isolation of mukonine (**6**) (**Fig. 2**) support the hypothesis of biomimetic hydroxylation of 3-methyl carbazole.[26] Congeners that differ in the oxidation state of the C-3 methyl group, i.e -CH_2OH, -CHO, -COOH and -COOMe, were found for various alkaloids, a fact which indicates an *in vivo* oxidation of carbazole alkaloids.



2. Murrayanine
R = CHO

3. Mukoeic acid
R = COOH

4. Murrayafoline A
R = Me

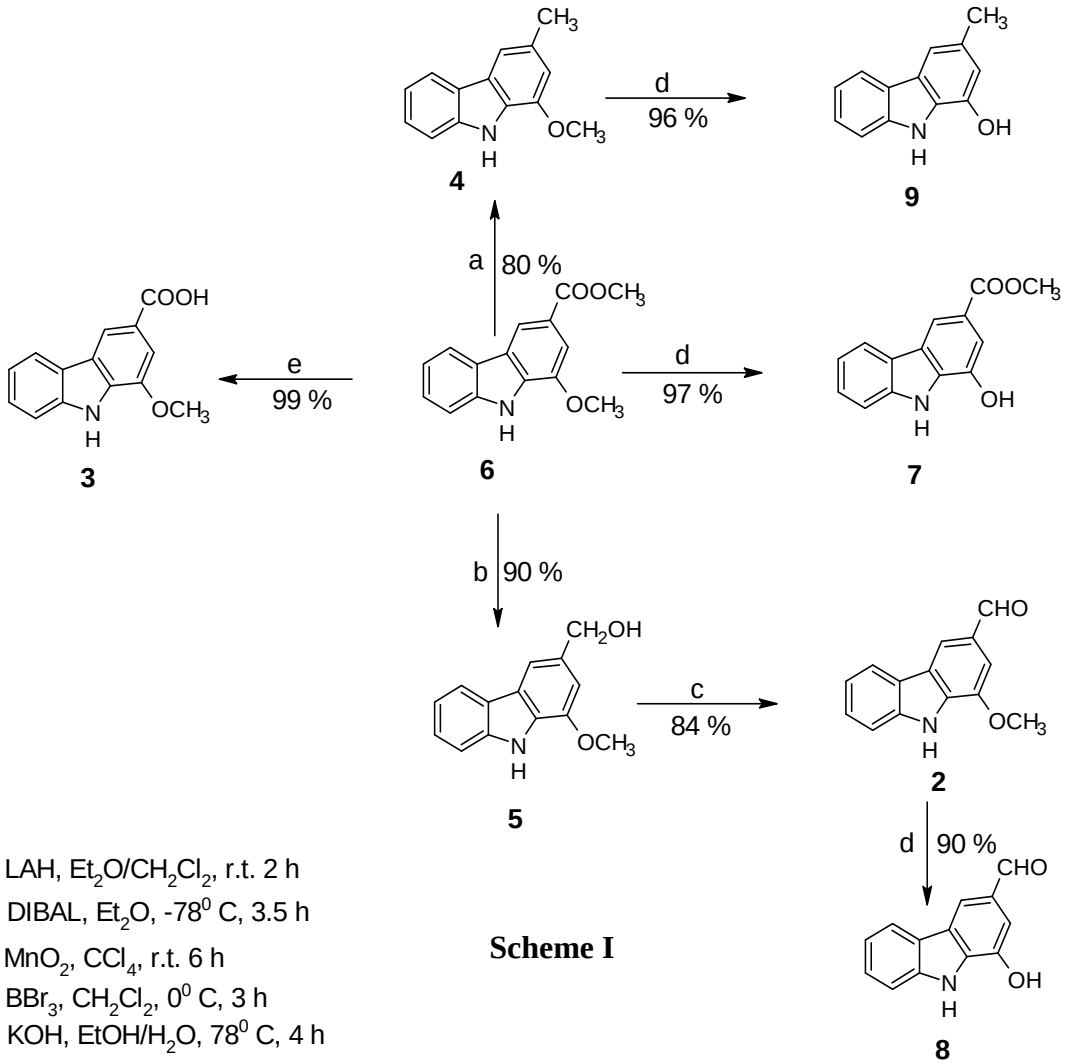
5. Koenoline
R = CH_2OH

6. Mukonine
R = COOMe

Fig. 2

Thus a systematic classification of tricyclic carbazole alkaloids has been suggested based on their oxygenation pattern.[27]

Bringmann *et al.*[28] have successfully transformed mukonine(**6**) to seven further 1-oxygenated carbazole alkaloids like murrayanine (**2**), mukoeic acid (**3**), murrayafoline A (**4**), koenoline (**5**), clausine E (**7**), *o*-demethyl murrayanine (**8**) and 1-hydroxy-3-methyl carbazole (**9**) (**Scheme I**). Some of them show antibiotic,[29] antifungal[30] and cytotoxic[31] properties and neoplasm inhibitory effects on mitosis[32] as well as a good activity against the malaria parasite Plasmodium falciparum also exhibited by some dimeric carbazoles.[33]



a LAH, Et_2O/CH_2Cl_2, r.t. 2 h
b DIBAL, Et_2O, -78^0 C, 3.5 h
c MnO_2, CCl_4, r.t. 6 h
d BBr_3, CH_2Cl_2, 0^0 C, 3 h
e KOH, $EtOH/H_2O$, 78^0 C, 4 h

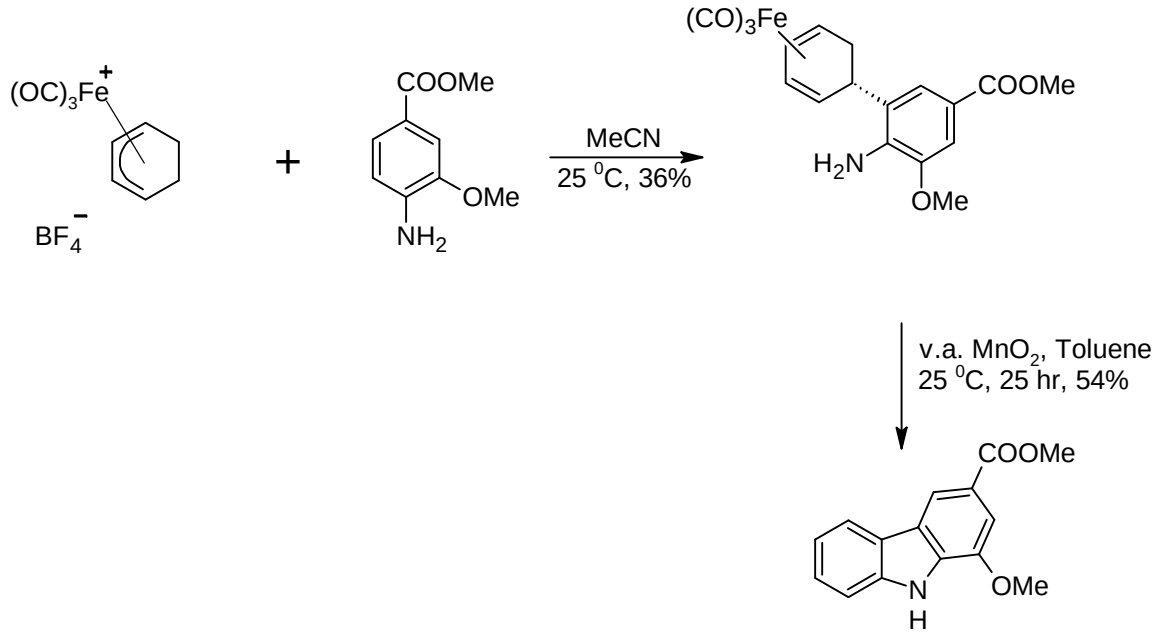
Scheme I

A Literature Review

Given the biological importance of natural carbazole alkaloids, an intensive effort has been directed towards their total synthesis. Widely used methods for synthesis of 1-oxygenated carbazoles include the classical Fischer indolisation with appropriate phenylhydrazones,[34] intramolecular cyclisation of indoles,[35] and oxidative cyclisation of diarylamines.[36] Increasingly important are transition metal-mediated and -catalyzed processes for preparation of carbazoles.[8]

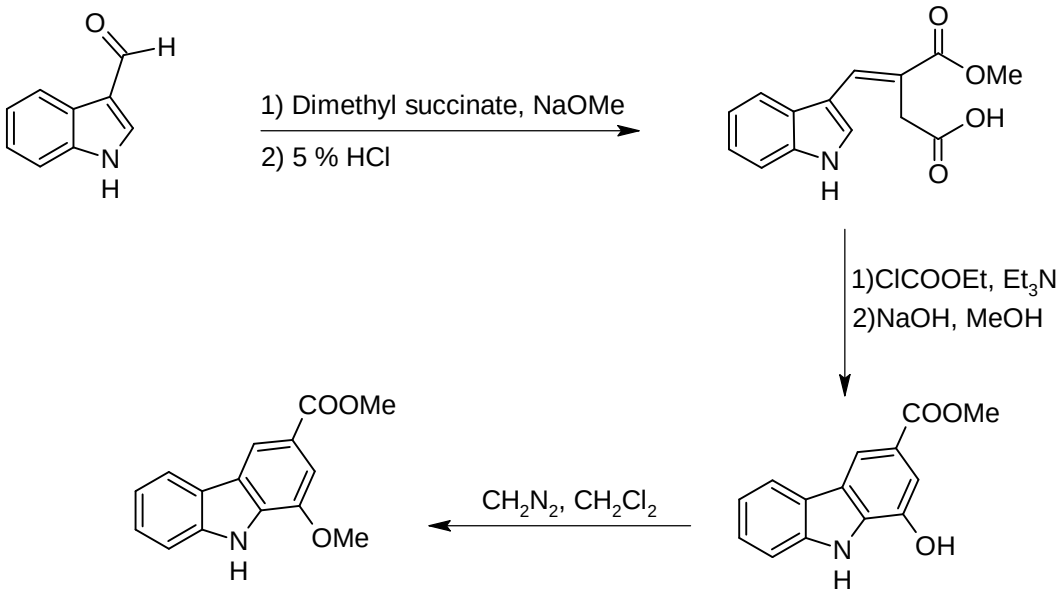
Literature methods for the synthesis of mukonine (**6**) are mentioned below-

Knolker *et al.*[37] have prepared mukonine based on iron-mediated construction of the carbazole ring system. They carried out electrophilic substitution of the commercial arylamine using iron-complex cation in acetonitrile at room temperature to get the corresponding iron complex regio and stereoselectively in 36% yield. Oxidative cyclisation of this complex with very active manganese dioxide (v.a. MnO_2) at room temperature in toluene afforded mukonine in 54% yield (**Scheme II**).



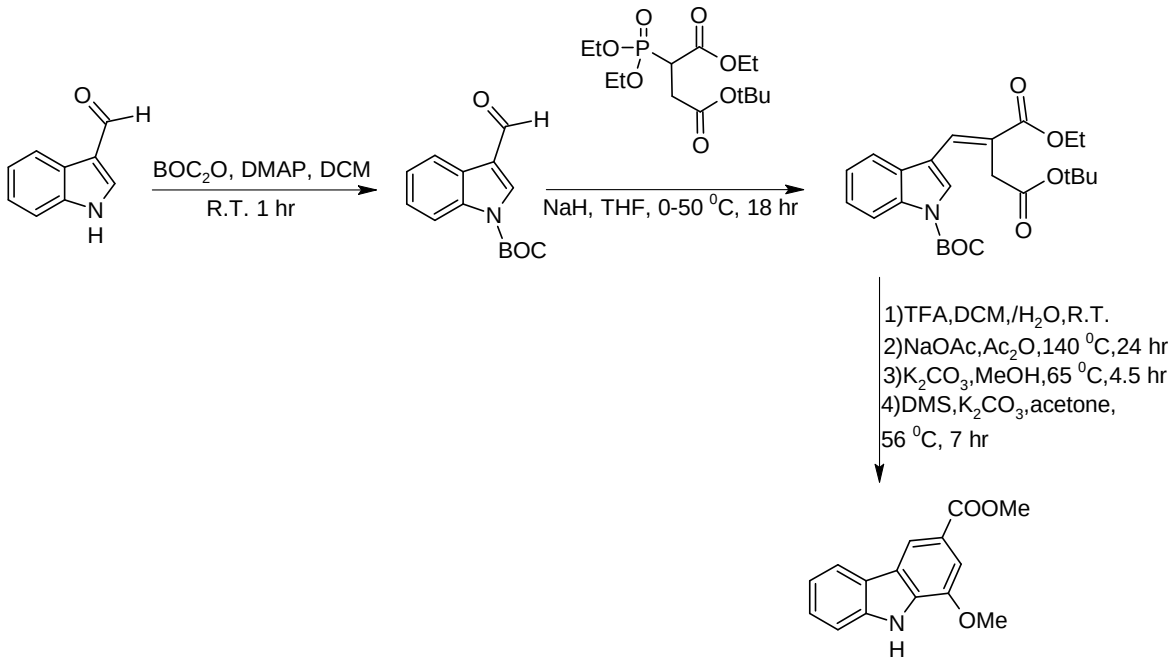
Scheme II

Brenna *et al.*[35b] reported the synthesis of mukonine starting from 3-formylindole via a base promoted cyclization. They carried out reaction of 3-formylindole with dimethyl succinate and sodium methylate in methanol to afford corresponding product through a Stobbe condensation. In a one-pot operation this product was then transformed to the aromatic derivative by reacting with ethyl chloroformate in the presence of triethylamine. After deacetylation of the aromatic derivative, the corresponding hydroxy derivative was methylated to give mukonine (**Scheme III**).



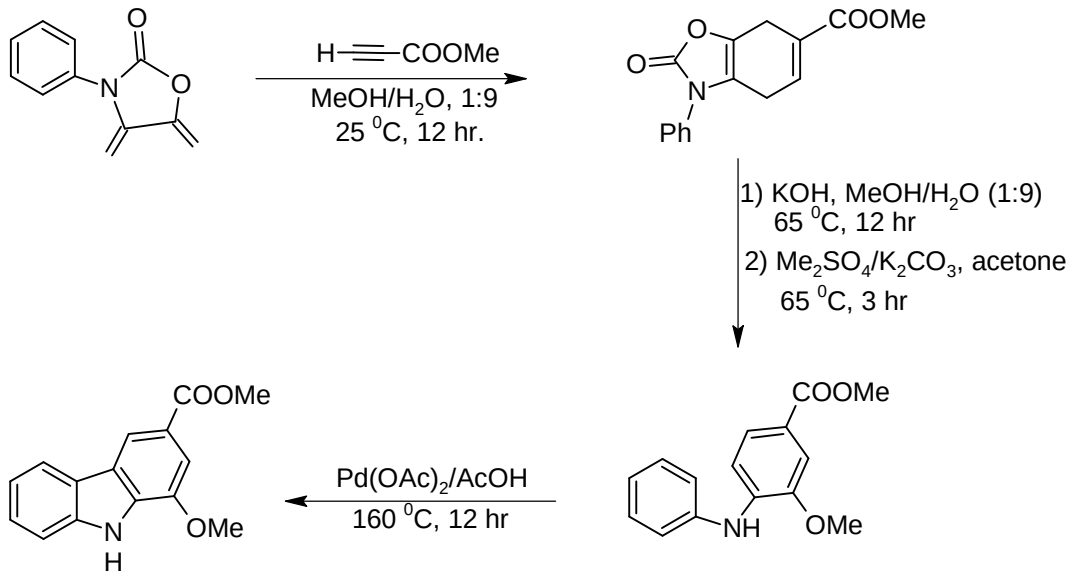
Scheme III

Bringmann *et al.*[28] started the synthesis from N-protected indole-3-carbaldehyde. The key steps in their synthesis are Horner-Emmons reaction, cyclization with sodium acetate in acetic anhydride followed by methanolysis and o-methylation with dimethyl sulphate in acetone to yield mukonine (**Scheme IV**).



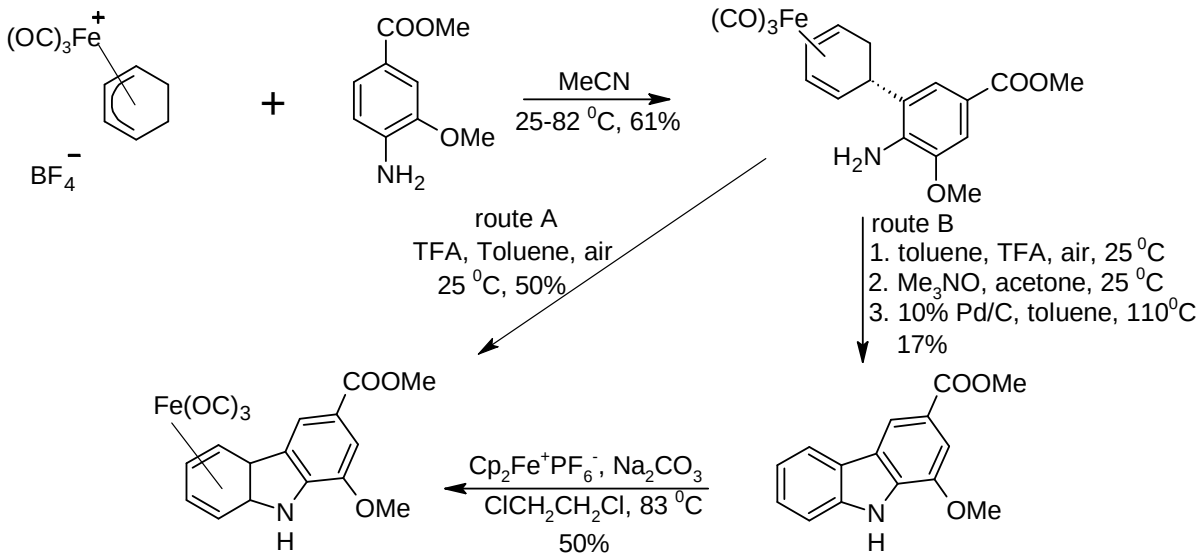
Scheme IV

Zempoalteca *et al.*[38] have described synthesis of mukonine based on a regioselective Diels-Alder reaction of *N*-phenyl-4,5-dimethylidene-2-oxazolidinone with methyl propiolate. Successive transformation of the cycloadduct in one step to the corresponding phenyl aryl amine and palladium promoted cyclisation of the latter provided mukonine (**Scheme V**).



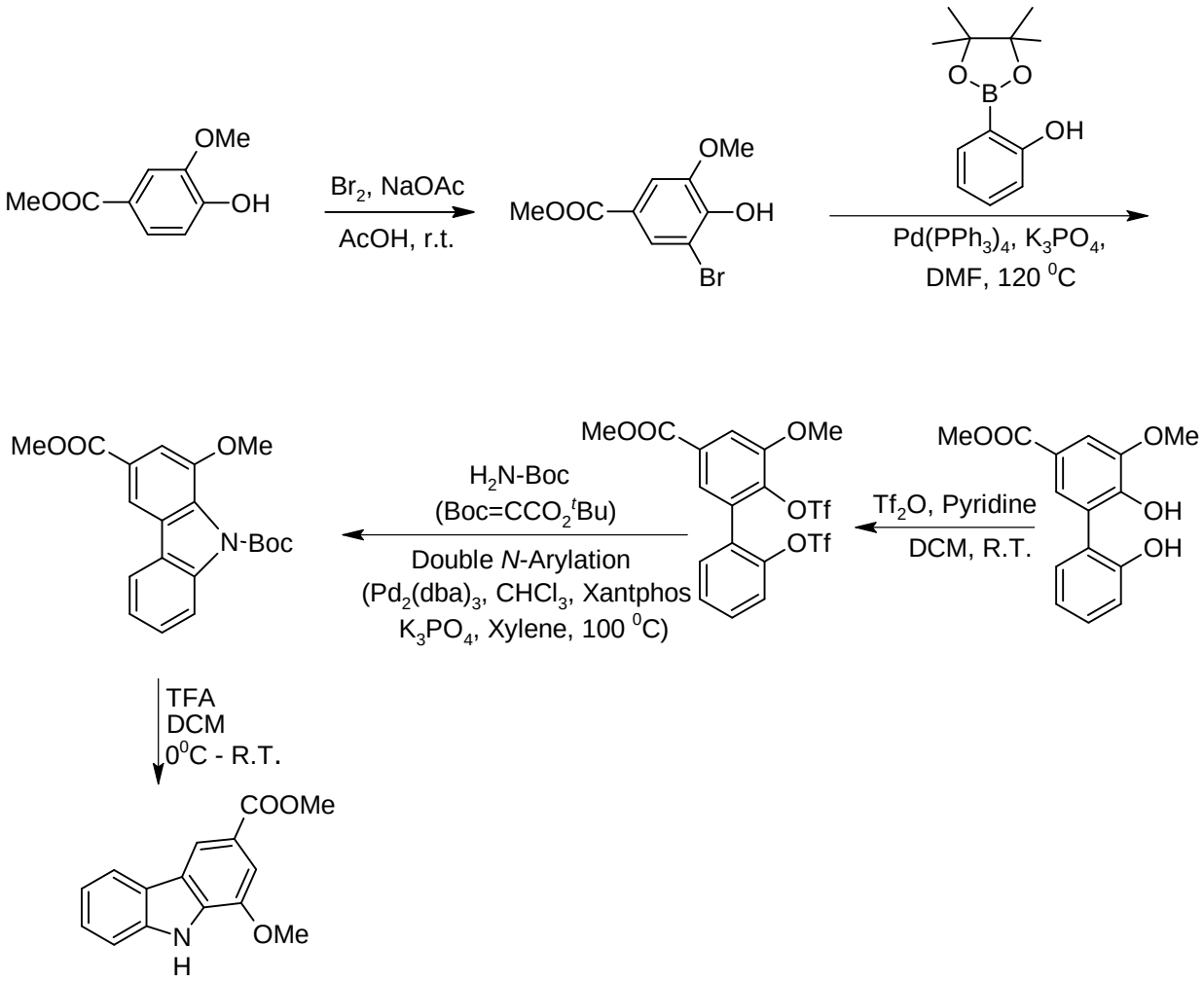
Scheme V

Knolker *et al.*[39] started synthesis of mukonine from arylamine. Reaction of the iron complex cation with the arylamine by refluxing in acetonitrile gave the corresponding iron complex. The iron complex is subjected to smooth cyclodehydrogenation by reacting with air in trifluoroacetic acid to afford the 4a, 9a-dihydro-9*H*-carbazole complex. Aromatization of this complex with concomitant demetalation by using ferricenium hexafluorophosphate in the presence of sodium carbonate provided mukonine in 50% yield (route A: three steps, 15% overall yield). An alternative method was also attempted wherein they carried out demetalation and subsequent catalytic dehydrogenation to get mukonine (route B: three steps, 17% overall yield) (**Scheme VI**).



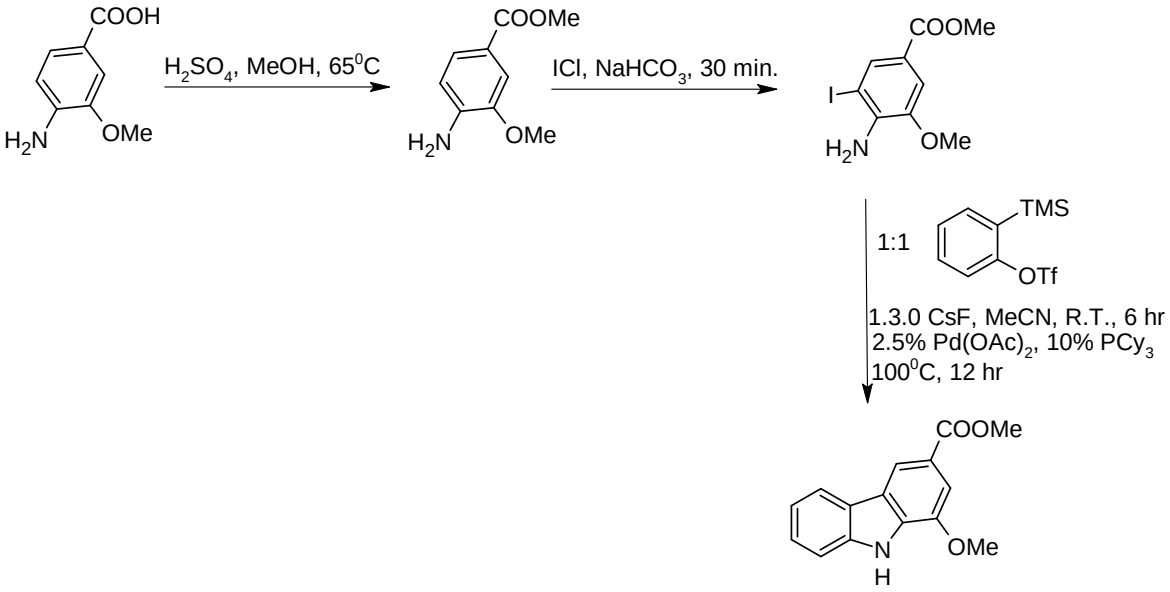
Scheme VI

Kuwahara *et al.*[40] synthesized mukonine via the double *N*-arylation starting from methyl vanillate and the pinacol ester of 2-hydroxyphenylboronic acid. Bromination of methyl vanillate followed by the Suzuki-Miyaura coupling with the pinacol ester of 2-hydroxyphenylboronic acid gave biphenyldiol. Biphenyldiol was converted to the corresponding ditriflate, which was subjected to the double *N*-arylation with *o*-tert-butyl carbamate. Using xantphos as the ligand, the desired product was obtained in 70% yield, which was then deprotected using TFA to get mukonine quantitatively (**Scheme VII**).



Scheme VII

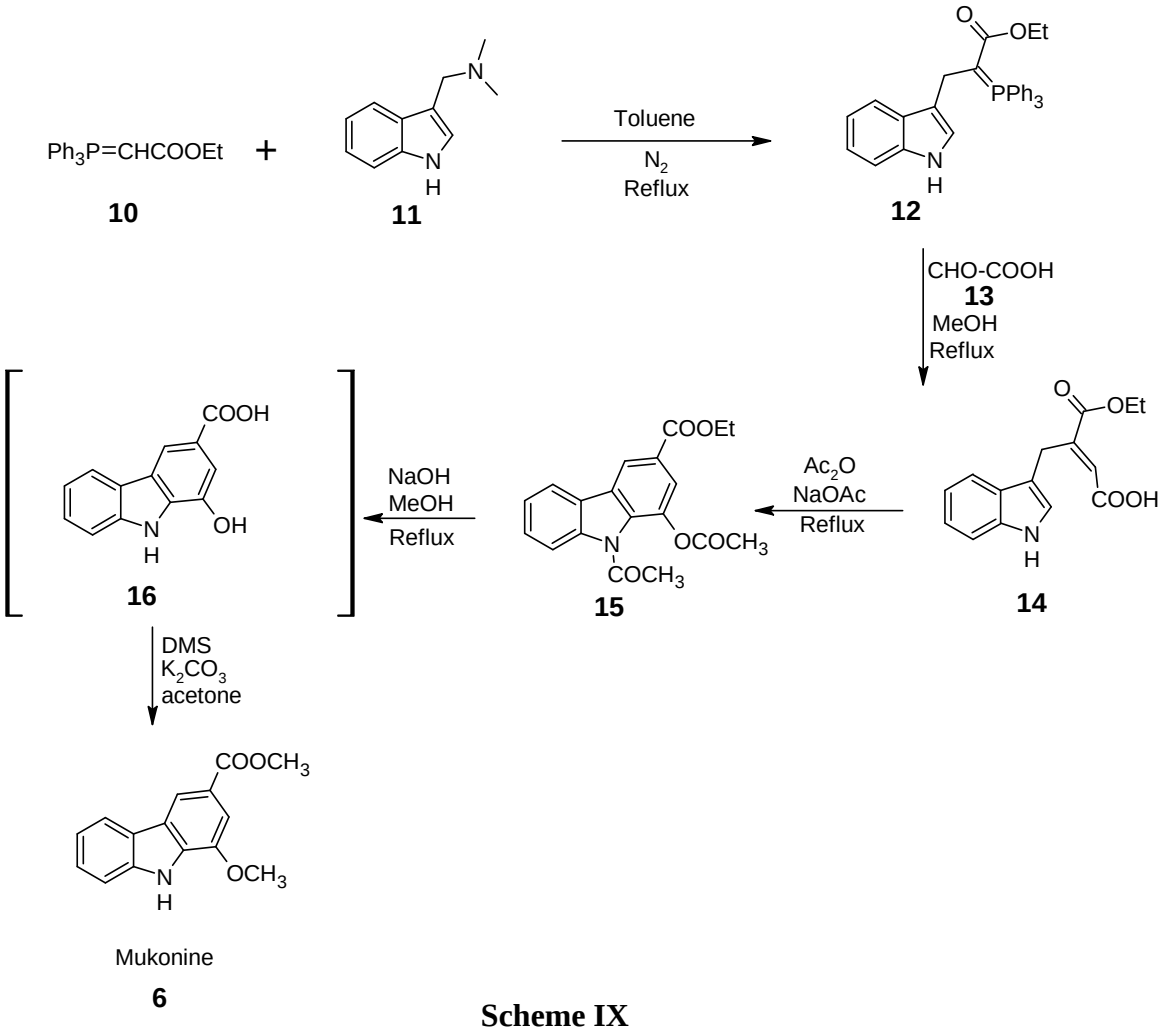
Liu *et al.*[41] prepared mukonine in three steps from commercially available 4-amino-3-methoxybenzoic acid. 3-Methoxy-4-amino benzoic acid was reacted with methanol to afford methyl 3-methoxy-4-aminobenzoate in 98% yield. Iodination using ICl in dichloromethane afforded methyl 4-amino-3-iodo-5-methoxybenzoate in 82% yield. Methyl 4-amino-3-iodo-5- methoxybenzoate was allowed to react with silylaryltriflate and CsF at room temperature in acetonitrile. Then $Pd(OAc)_2$ and PCy_3 were added and the reaction was heated to 100 ^{o}C for 12 hr under argon to get mukonine (**Scheme VIII**).


COOH
H2N
OMe
H2SO4, MeOH, 65°C
COOMe
H2N
OMe
ICl, NaHCO3, 30 min.
COOMe
I
H2N
OMe
1:1
TMS
OTf
1.3.0 CsF, MeCN, R.T., 6 hr
2.5% Pd(OAc)2, 10% PCy3
100°C, 12 hr
COOMe
N
H
OMe

Scheme VIII

Present Work

Our continued interest in the application of Wittig reaction prompted us to investigate the usage of phosphorane chemistry towards the synthesis of carbazole alkaloid mukonine **6**. The essential elements of our simple approach to the mukonine ring system is shown in **Scheme IX**.

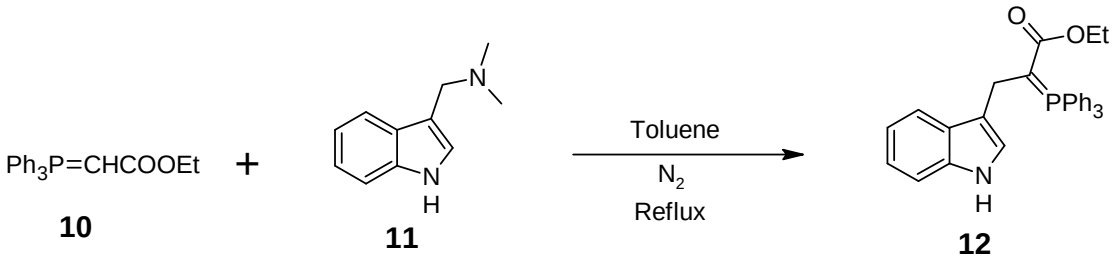


Scheme IX

As depicted in **Scheme IX**, first is preparation of homoskatolidene phosphorane **12**. This preparation of homoskatolidene phosphorane **12** by alkylation of stable carboethoxymethylenetriphenyl phosphorane **10** is reported in literature.[42] In the next step, glyoxylic acid (**13**) on condensation with homoskatolidene phosphorane **12** could give the product **14** having both the acid and the ester group. Subsequent cyclisation of this product **14** with sodium acetate in acetic anhydride could give the

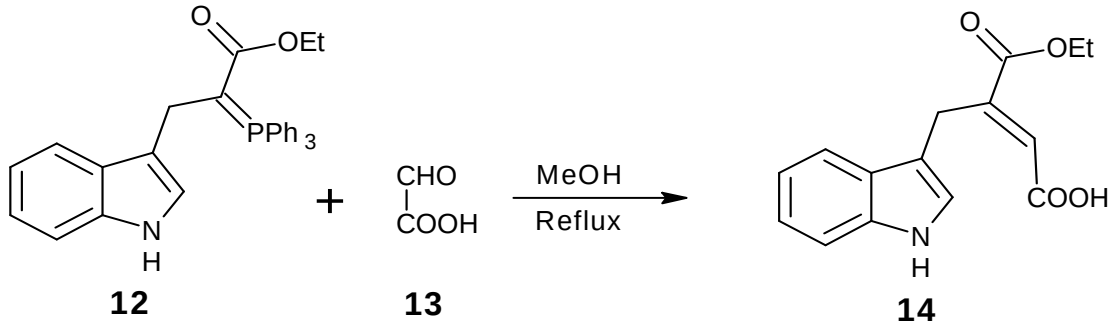
carbazole framework (**15**). Subsequent methanolysis and o-methylation with dimethyl sulphate in acetone could give the target molecule mukonine (**6**).

Accordingly, we started with the synthesis. The homoskatolidene phosphorane **12** was prepared in two steps. The first step was preparation of stable carboethoxymethylenetriphenyl phosphorane **10** which is already been discussed in chapter 1. In the second step, this stable phosphorane **10** was alkylated with gramine (**11**) in toluene under nitrogen atmosphere to get white solid of homoskatolidene phosphorane **12** in 93% yield (**Scheme X**).



Scheme X

The homoskatolidene phosphorane **12** was then refluxed with 50% aqueous solution of glyoxylic acid (**13**) in methanol for 10.0 hrs (**Scheme XI**).



Scheme XI

TLC of the reaction mixture showed appearence of new spot along with triphenylphosphine oxide spot. The solvent was evaporated followed by the corresponding workup for acid. The crude product obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to obtain a white solid.

Its IR spectrum showed two strong bands one at δ 1681 cm^{-1} and another at δ 1724 cm^{-1} indicating the presence of two carbonyl groups. The broad band due to hydroxyl group of acid was observed at 3053 cm^{-1}. In addition to this, the absorption due to N-H bond of indole ring was observed at 3394 cm^{-1}.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz , δ ppm) (**Fig. I**) showed signals at δ 1.24 (t, *J* = 7.2 Hz, 3H) and δ 4.20 (q, *J* = 7.2 Hz, 2H) which was attributed to -OCH_2CH_3 group of ester moiety. The peak observed at δ 4.38 (s, 2H) was due to -CH_2- attached to the third position of indole ring. The vinylic proton was observed at δ 7.05 (s, 1H). The downfield shift of this proton indicated it to be *cis* to the -$COOCH_2CH_3$ group (*E* geometry). Peaks due to aromatic protons were observed at δ 6.82 (s, 1H), δ 7.12 (t, *J* = 7.2 Hz, 1H), δ 7.19 (t, *J* = 6.9 Hz, 1H), δ 7.33 (d, *J* = 7.8 Hz, 1H), δ 7.72 (d, *J* = 7.5 Hz, 1H) and proton attached to nitrogen was observed at δ 8.03 (br.s., 1H).

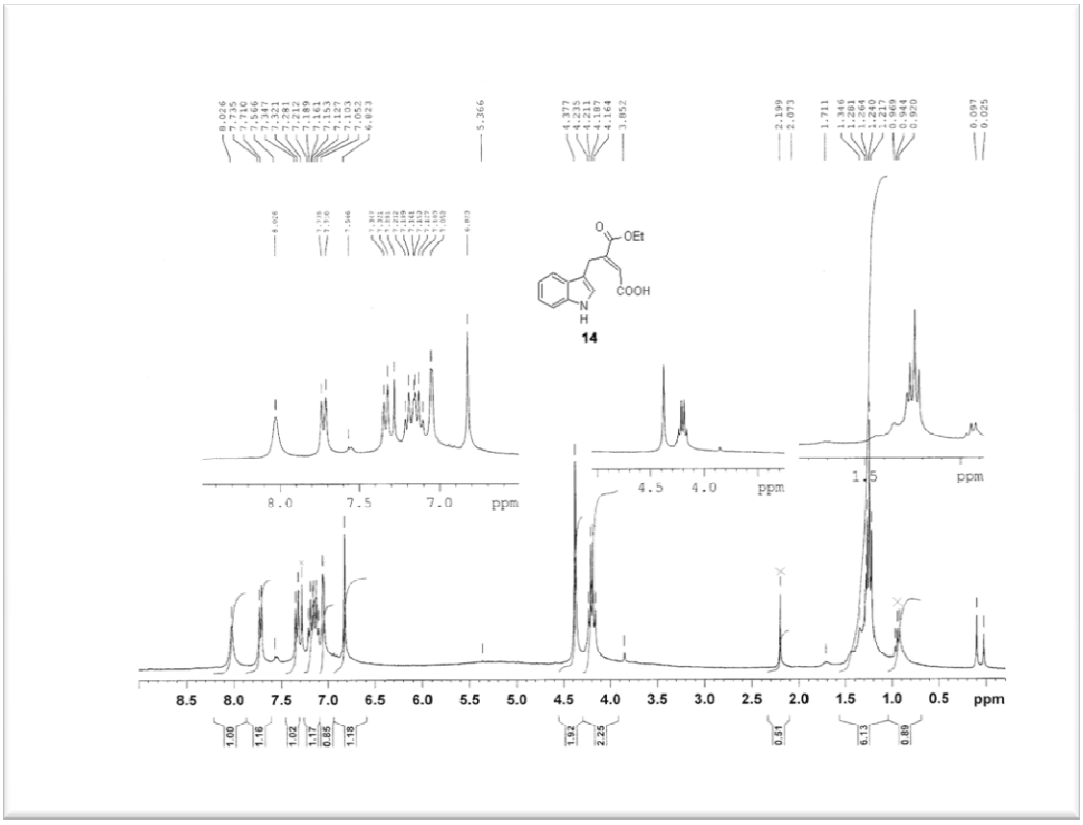


Fig. I : ^{1}H-NMR spectrum of Compound **14**

The ^{13}C-NMR spectrum ($CDCl_3$, 75 MHz, δ ppm) (**Fig. II**) spectrum showed peaks at δ 13.96 (CH_3), δ 29.66 (CH_2), δ 61.74 (OCH_2), δ 109.96 (C), δ 113.57 (CH), δ 119.68 (CH), δ 120.47 (CH), δ 122.63 (CH), δ 124.76 (2 X CH), δ 128.70 (C), δ 136.03 (C), δ 148.62 (C), δ 166.60 (C=O), δ 166.98 (C=O).

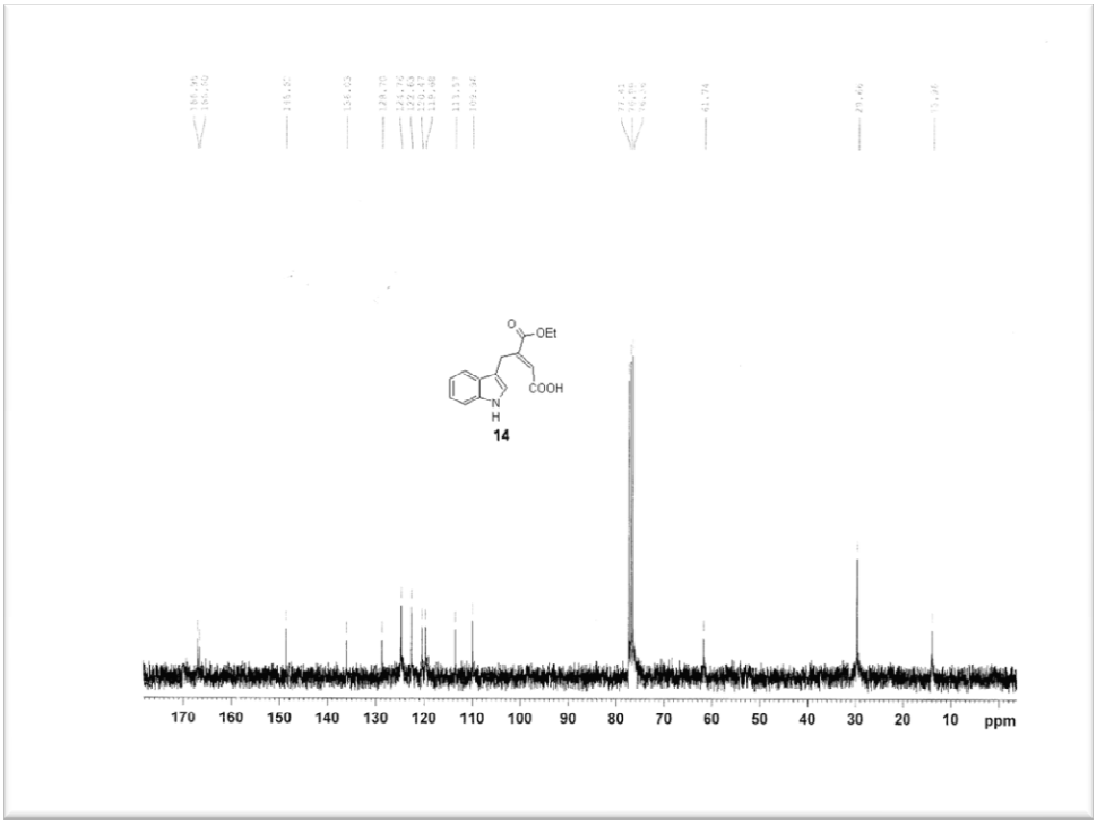
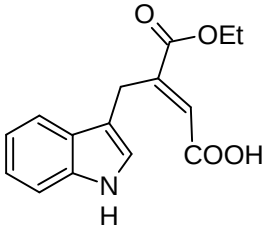


Fig. II : ^{13}C-NMR spectrum of Compound **14**

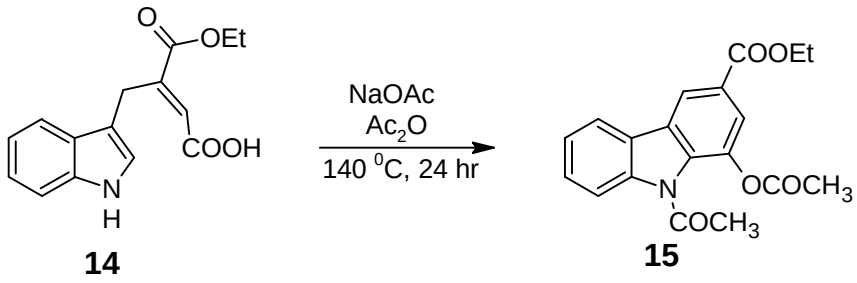
The high resolution mass spectrum of the compound displayed strong peak at *m/z* 296.0887 presumably due to $[M+Na]^+$ pseudo ions. The elemental composition of which was determined to be $C_{15}H_{15}NO_4$. HRMS *m/z* calculated for $C_{15}H_{15}NO_4$ Na $[(M+Na)^+]$ was 296.0899, found : 296.0887. The melting point of this compound was found to be 108-111 ^oC.



14

Hence, based on the mode of formation and spectral data, compound **14** was confirmed to be the predicted one. The yield of the product was found to be 80%.

Our next aim was to carry out the cyclisation to get the carbazole framework **Scheme XII**.



14 **15**

Scheme XII

To achieve this we refluxed compound **14** with sodium acetate in acetic anhydride for 24 hrs, after which there was seen disappearance of the starting materials on TLC. Evaporation of the solvent followed by column chromatographic purification over silica gel using hexanes:ethyl acetate(7:3) as an eluent furnished a white solid.

The IR spectrum of this compound showed absence of band due to N-H stretching and presence of three bands at 1712 cm^{-1}, 1718 cm^{-1} and 1774 cm^{-1} indicating the presence of three carbonyl groups.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz , δ ppm) (**Fig. III**) showed signals at δ 1.38 (t, *J* = 7.2 Hz, 3H) and δ 4.40 (q, *J* = 7.2 Hz, 2H) which was due to -OCH_2CH_3 group of ester moeity. The peak observed at δ 2.38 (s, 3H) was attributed to -CH_3 group of -OAc moeity, and another peak at δ 2.80 (s, 3H) was attributed to -CH_3 group of -NAc moeity. The signals due to remaining aromatic protons were observed at δ 7.46 (t, *J* = 7.2 Hz, 1H, H-6), δ 7.60 (t, *J* = 7.2 Hz, 1H, H-7), δ 7.85 (s, 1H, H-2), δ 8.00 (d, *J* = 8.4 Hz, 1H, H-8), δ 8.38 (d, *J* = 7.8 Hz, 1H, H-5), δ 8.70 (s, 1H, H-4).

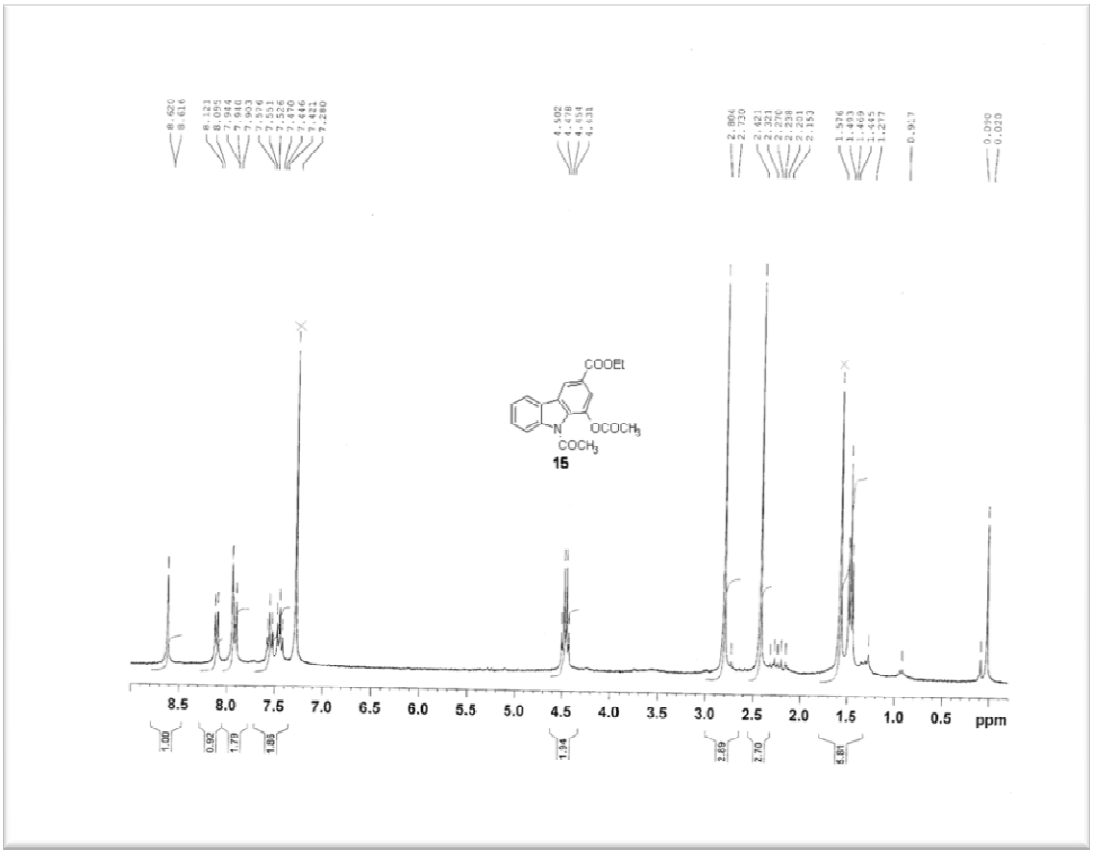


Fig. III : ^{1}H-NMR spectrum of Compound **15**

The ^{13}C-NMR spectrum (DMSO-d6, 75 MHz, δ ppm) spectrum (**Fig. IV**)) showed peaks at δ 14.67, δ 21.16, δ 27.15, δ 61.51, δ 114.84, δ 119.38, δ 121.55, δ 122.99, δ 124.16, δ 124.74, δ 126.32, δ 128.92, δ 129.07, δ 133.20, δ 137.87, δ 139.27, δ 165.46, δ 168.67, δ 170.91.

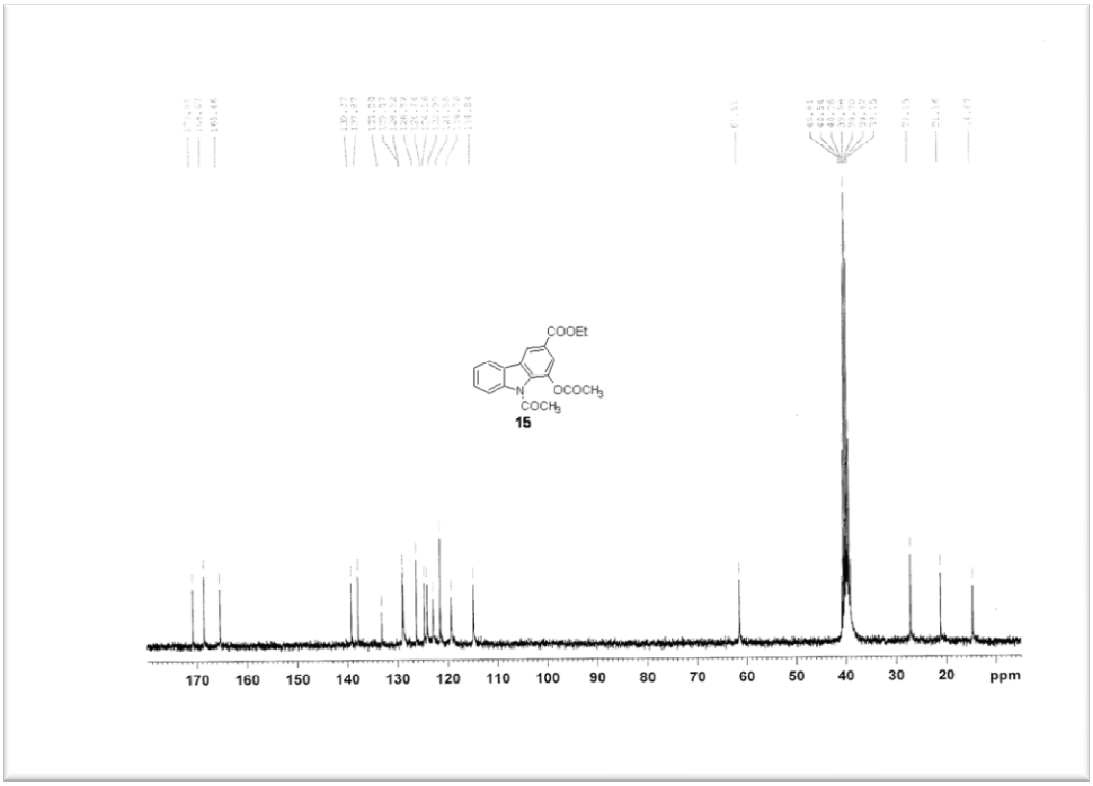
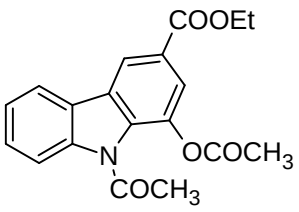


Fig. IV : ^{13}C-NMR spectrum of Compound **15**

The high resolution mass spectrum of this compound displayed strong peak at *m/z* 362.1003 presumably due to $[M+Na]^+$ pseudo ions. The elemental composition of which was determined to be $C_{19}H_{17}NO_5$. HRMS *m/z* calculated for $C_{19}H_{17}NO_5Na[(M + Na)^+]$ was 362.1004, found : 362.1003.

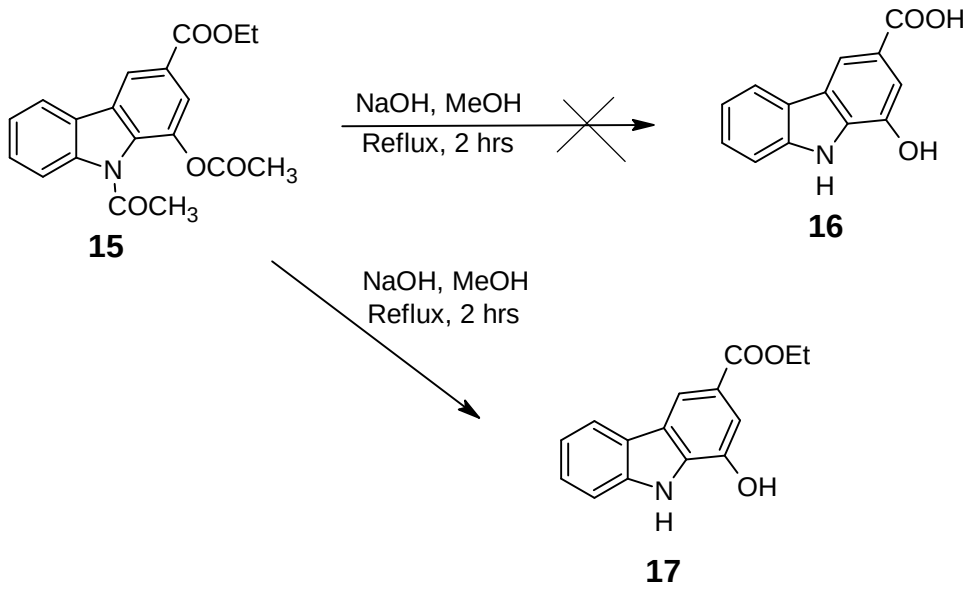
The melting point of the compound was found to be 118-121 ^oC.

Hence, based on the mode of formation and spectral data structure (**15**) was assigned to the compound. The yield of the product was found to be 65%.



15

Now, as we obtained the required moeity in hand, there was a need to knock off both the acetyl groups followed by hydrolysis of ester to get the acid which is our next target compound. Hence, the compound **15** was refluxed with NaOH in methanol for 2 hrs (**Scheme XIII**).



Scheme XIII

TLC indicated disappearance of starting material and appearance of a new spot. The reaction was neutralized with 1:1 HCl solution. It was then extracted in diethyl ether. The solvent was evaporated followed by column chromatographic purification over silica gel using hexanes:ethyl acetate (8:2) as an eluent to obtain a white solid.

This solid in its IR spectrum showed strong peaks at 3350 cm^{-1} and 3300 cm^{-1} due to N-H stretching and O-H stretching, and peak at 1653 cm^{-1} indicating the presence of carbonyl group.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz , δ ppm) (**Fig. V**) showed signals at δ 1.48 (t, *J* = 7.2 Hz, 3H) and δ 4.47 (q, *J* = 7.2 Hz, 2H) which was due to presence of -CH_2CH_3 group of ester moiety, which indicated that the ester group did not hydrolyse to acid. Another broad signal was observed at δ 6.17 (br.s., 1H) indicating the presence of -OH group. The aromatic protons were observed at δ 7.30 (t, *J* = 7.8 Hz, 1H, H-6), δ 7.46-δ 7.50 (m, 2H, H-7 & H-8), δ 7.72 (s, 1H, H-2), δ 8.13 (d, *J* = 7.8

Hz, 1H, H-5), δ 8.47 (s, 1H, H-4) and signal due to proton on nitrogen was observed at δ 8.54 (br.s., 1H, NH).

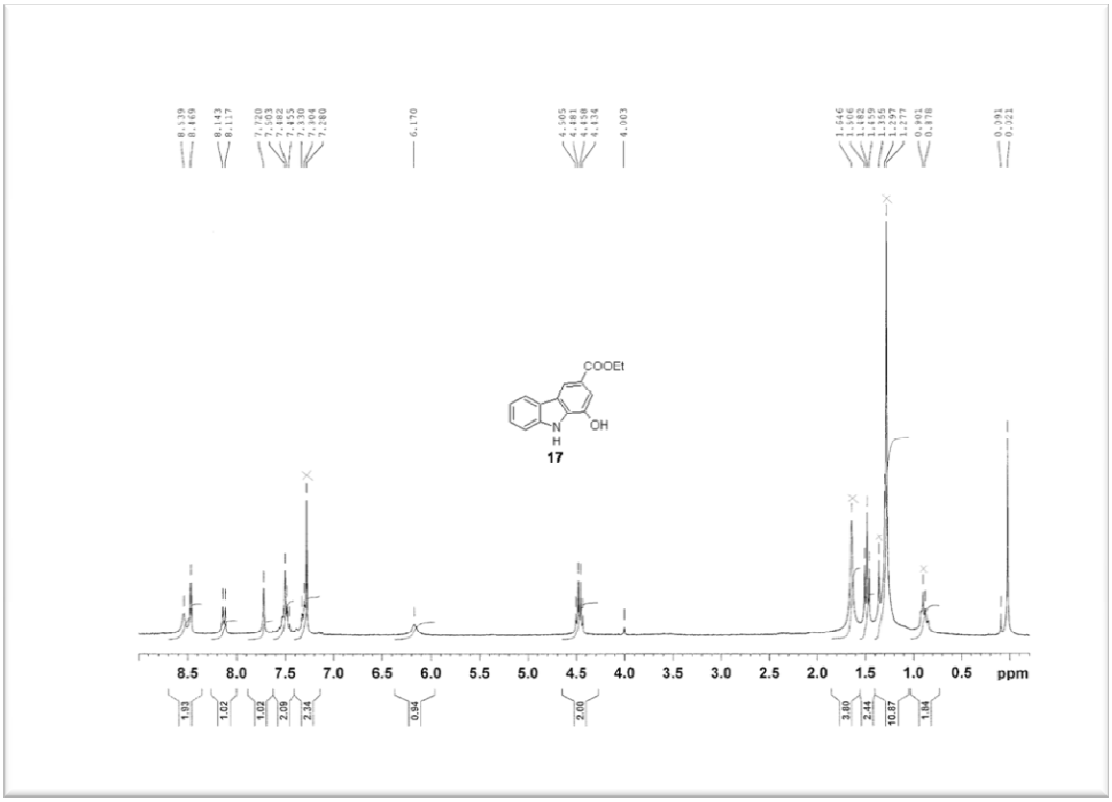
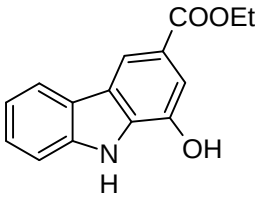


Fig. V : ^{1}H-NMR spectrum of Compound **17**

The high resolution mass spectrum of this compound displayed a strong peak at m/z 278.0792 presumably due to $[M+Na]^{+}$ pseudo ions. The elemental composition of which was determined to be $C_{15}H_{13}NO_3$. HRMS *m/z* calculated for $C_{15}H_{13}NO_3Na[(M+Na)^{+}]$ was 278.0793, found:278.0792.

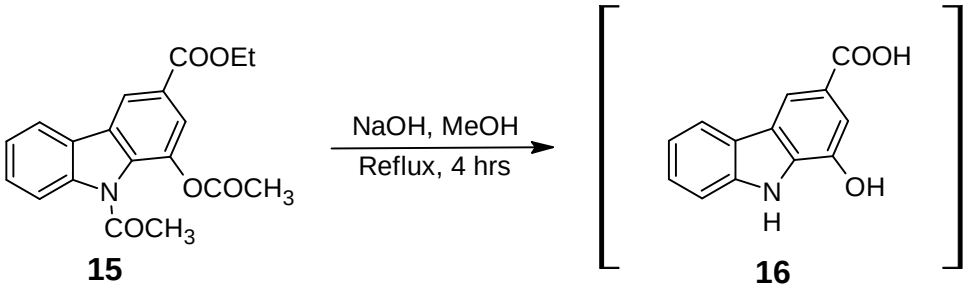
The melting point of the compound was found to be 165-167 ^{o}C.

Hence, based on the mode of formation and spectral data, the compound should have structure **17**. The yield of the product was found to be 98%.



17

Hence, we succeeded to knock off both the acetyl groups but failed to hydrolyse the ester. In order to achieve both our aims, i.e. to knock off the acetyl groups as well as to hydrolyse the ester we thought to reflux the reaction mixture for longer duration (**Scheme XIV**).



15 **16**

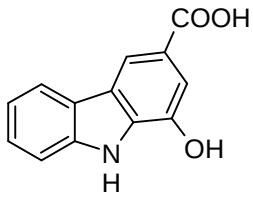
Scheme XIV

The compound **15** was refluxed with NaOH in methanol for 4 hrs. TLC of the reaction mixture showed disappearence of both, the starting compound **15** as well as the compound **17**, and there was seen one new spot on TLC. The reaction was neutralized with 1:1 HCl solution. It was then extracted in diethyl ether. The solvent was evaporated and the residue obtained was analyzed by IR spectroscopic technique, as it was difficult to purify this residue.

The IR spectrum of this residue showed strong band at 1703 cm^{-1} due to carbonyl group of acid moiety. The broad band was observed at 3250 cm^{-1} due to hydroxyl group.

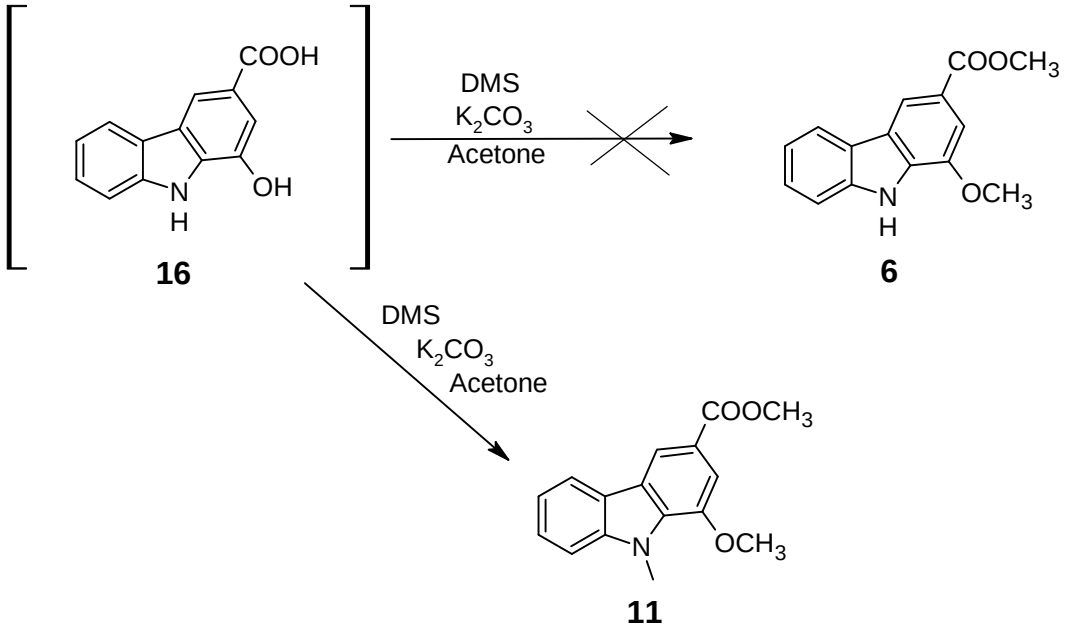
The high resolution mass spectrum of this residue displayed strong peak at *m/z* 250.0454 presumably due to $[M+Na]^+$ pseudo ions. The elemental composition of which was determined to be $C_{13}H_{19}NO_3$. HRMS *m/z* calculated for $C_{13}H_{19}NO_3Na[(M+Na)^+]$ was 250.0480, found:250.0454.

Hence, based on the mode of formation and above spectral data formation of compound **16** was confirmed.



16

To get our target molecule mukonine, the crude compound **16** without further purification (as it was difficult to purify) was treated with K_2CO_3 and dimethyl sulphate in dry acetone **(Scheme XV**).



Scheme XV

The reaction mixture was refluxed for 8 hrs, after which there was seen appearance of a new spot on TLC. The solvent was evaporated and the residue was purified by column chromatography over silica gel using hexanes:EtOAc (7:3) as an eluent to obtain a white solid.

The IR spectrum of this compound showed presence of a band at 1697 cm^{-1}, which was attributed to the presence of the carbonyl group of ester. There was seen dissappearence of N-H and O-H peaks.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz , δ ppm) (**Fig. VI**) showed signals at δ 3.99 (s, 3H), δ 4.07 (s, 3H) and δ 4.22 (s, 3H) which were attributed to -NCH_3, -OCH_3 and -$COOCH_3$ group. Aromatic protons were observed at δ 7.30-δ 7.57 (m, 3H, H-6, H-7, H-8), δ 7.61 (s, 1H, H-2), δ 8.12 (d, *J* = 8.1 Hz, 1H, H-5), δ 8.49 (s, 1H, H-4).

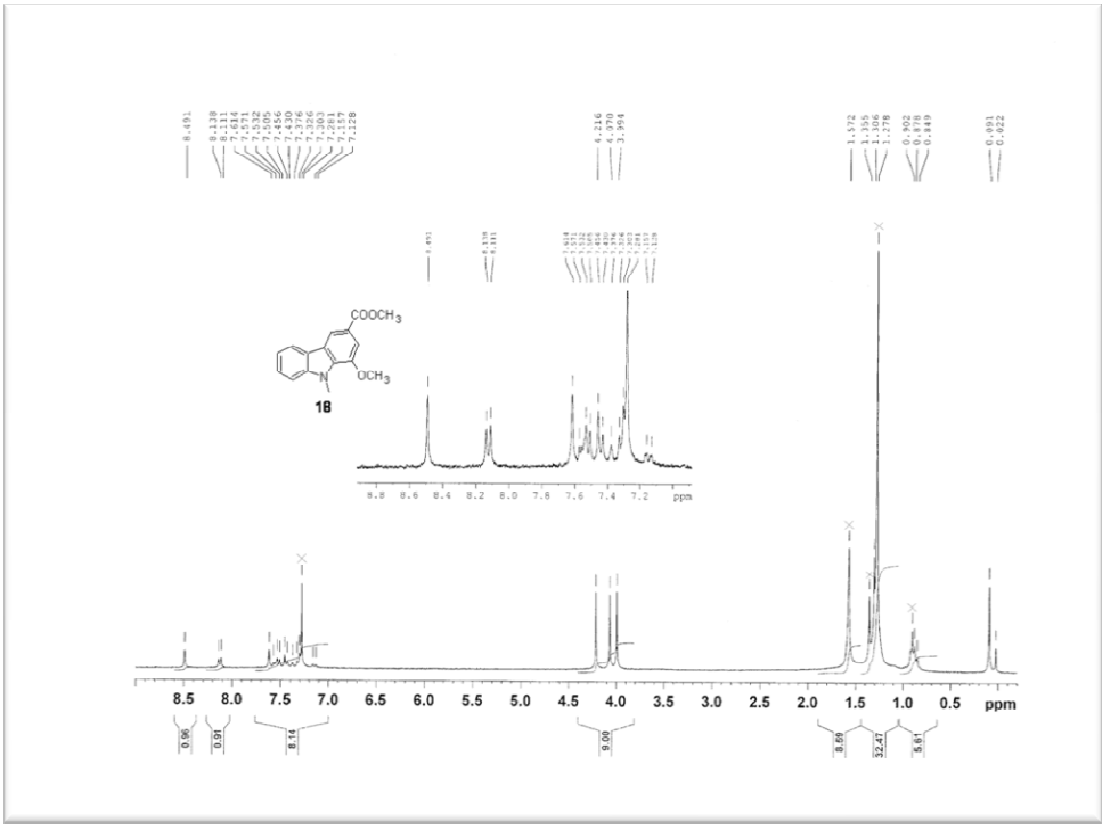
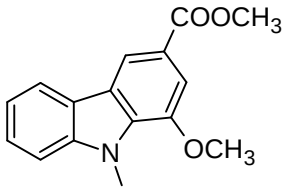


Fig. VI : ^{1}H-NMR spectrum of Compound **18**

The high resolution mass spectrum of this compound displayed strong peak at *m/z* 292.0947, presumably due to $[M+Na]^+$ pseudo ions. The elemental composition of which was determined to be $C_{16}H_{15}NO_3$. HRMS *m/z* calculated for $C_{16}H_{15}NO_3Na[(M+Na)^+]$: 292.0950, found: 292.0947.

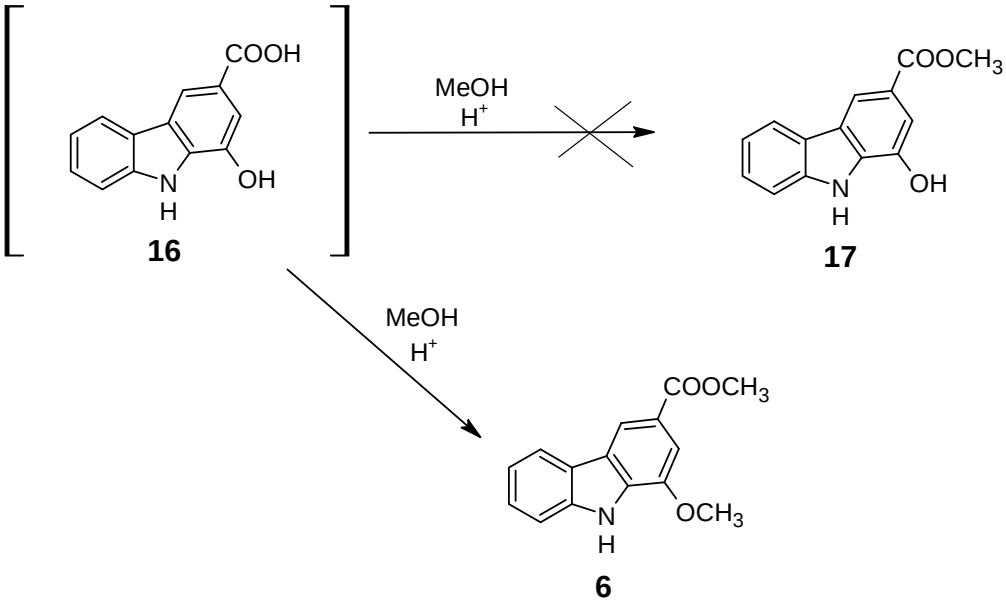
The melting point of the compound was found to be 122-125 ^{o}C.

Hence, based on the mode of formation and above spectral data the formation of *N*-methylated compound **18** was confirmed. The yield of the product was found to be 58%.



18

Since, we did not succeed to get the mukonine molecule in hand, we thought of an alternate approach for it. The crude compound **16** was refluxed with a few drops of sulphuric acid in methanol for 10.0 hrs (**Scheme XVI**).



Scheme XVI

The solvent was evaporated and the residue obtained was dissolved in ether. The ether layer was dried over sodium sulphate, ether was evaporated and the residue was purified by column chromatography over silica gel using hexanes:ethyl acetate (9:1) as an eluent to get a white solid. In IR spectrum of this compound there was seen a strong band at 1703 cm^{-1} indicating the presence of carbonyl group of ester. There was also seen a strong band at 3392 cm^{-1} due to N-H stretching.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz , δ ppm) (**Fig. VII**) showed signals at δ 3.51 (s, 3H) and δ 3.98 (s, 3H) which was attributed to -OCH_3 and -$COOCH_3$ group. Aromatic protons were observed at δ 7.28-7.50 (m, 3H, H-6, H-7 & H-8), δ 7.62 (s, 1H, H-2), δ 8.11 (d, *J* = 7.5 Hz, 1H, H-5), δ 8.45 (s, 1H, H-4) and signal due to proton on nitrogen was observed at δ 8.68 (br.s., 1H, NH).

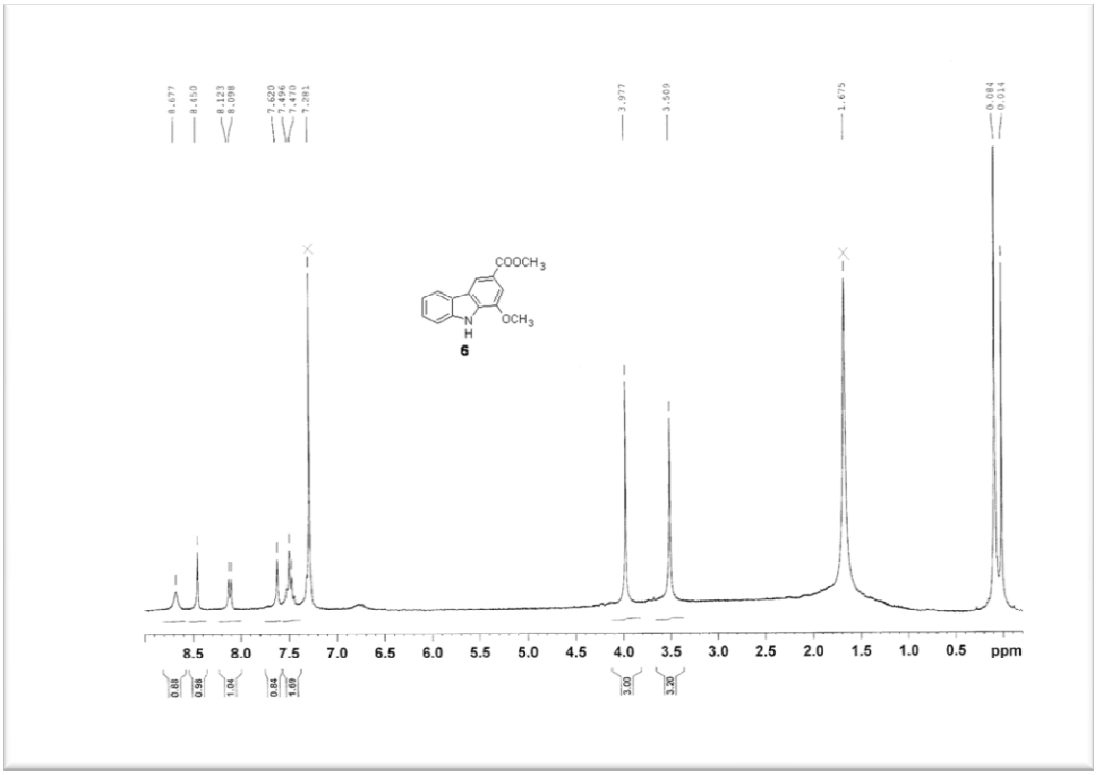
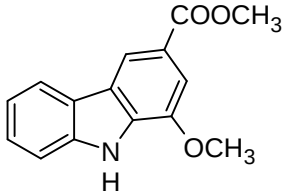


Fig. VII : ^{1}H-NMR spectrum of Compound **6**

The melting point of the compound was found to be 198-200 ^{o}C.

Hence, based on the above spectral data, structure **6** was assigned to the product. The yield of the product was found to be 41%.



6

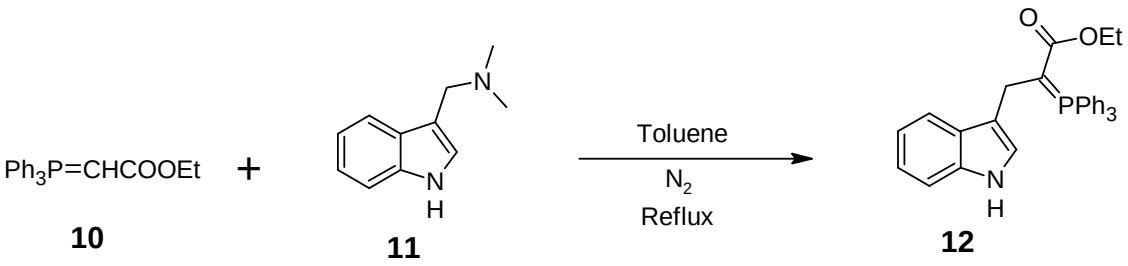
This completed the synthesis of carbazole alkaloid mukonine (**6**), which also constitute the formal synthesis of alkaloids murrayanine (**2**), mukoeic acid (**3**), murrayafoline A (**4**) and koenoline (**5**).

Conclusion

We have developed a convenient synthesis of carbazole alkaloid mukonine using Wittig reaction and cyclisation with sodium acetate in acetic anhydride as key steps.

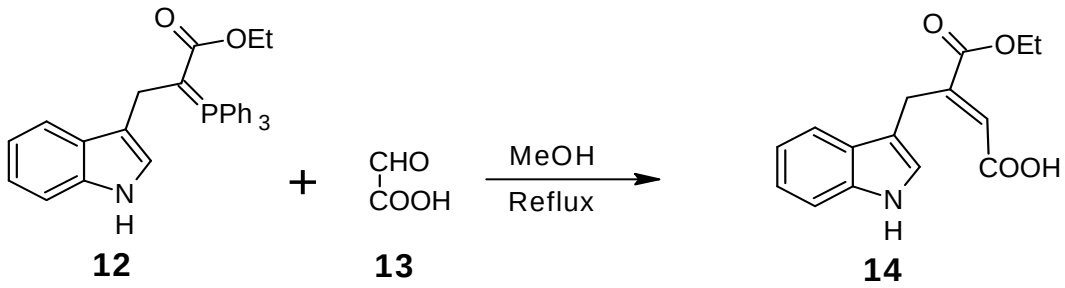
Experimental

3.1 Preparation of Triphenyl-α-ethoxycarbonylhomoskatolidene phosphorane (**12**)



A solution of gramine (**11**) (2.5 g, 0.014 moles) in toluene (20 mL) was added to a solution of carboethoxymethylenetriphenyl phosphorane (**10**) (5.0 g ,0.014 moles) in toluene (50 mL). The reaction mixture was refluxed for 12 hrs under nitrogen atmosphere. The mixture was chilled, the precipitate was filtered off and consecutively washed with cold toluene and petroleum ether. It was recrystallized from ethyl acetate to get the white solid of triphenyl-α-ethoxycarbonylhomoskatolidene phosphorane **12** (6.37 g, 93%); m.p. 189-190 ^{o}C.

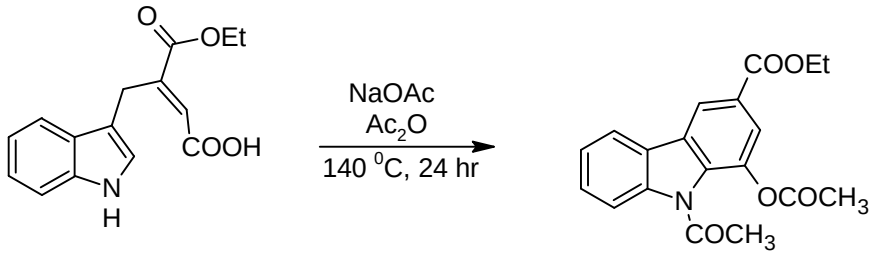
3.2 Preparation of (2*E*)-4-Ethoxy-3-(1*H*-indol-3-ylmethyl)-4-oxobut-2-enoic acid (**14**)



A mixture of glyoxylic acid (50% solution in water) (3.19 g, 0.022 moles), homoskatolidene phosphorane (6.85 g, 0.014 moles) was refluxed in methanol (25 mL) for 10.0 hrs. Methanol was evaporated, and the residue was dissolved in ethyl acetate (30 mL). The ethyl acetate layer was extracted with sat. sodium carbonate (3 X 30 mL). The sodium carbonate extract was then cooled, acidified using 1:1 HCl solution to pH- 2-3 and extracted with diethyl ether (3 X 30 mL). The diethyl ether

layer was dried over anhydrous sodium sulphate, the solvent was evaporated and the residue obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to furnish a white solid (**14**) (3.13 g, 80%); m.p. 108-111 ^{o}C.

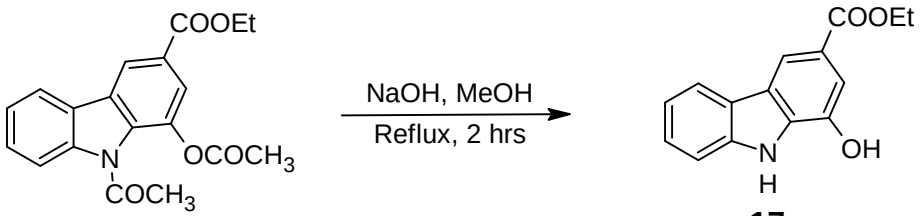
3.3 Preparation of 1-Acetoxy-9-acetyl-3-ethoxycarbonylcarbazole (**15**)



14 **15**

The compound **14** (2.5 g, 9.15 mmol) was refluxed with sodium acetate (1.62 g , 20 mmol) in acetic anhydride (33 mL) for 24.0 hrs. The acetic anhydride was removed under vacuum pump and purification of the remaining residue by column chromatography over silica gel using hexanes:EtOAc (7:3) as an eluent gave a white solid (**15**) (2.0 g, 65%); m.p. 118-121 ^{o}C.

3.4 Preparation of Ethyl 1-hydroxy-9*H*-carbazole-3-carboxylate (**16**)

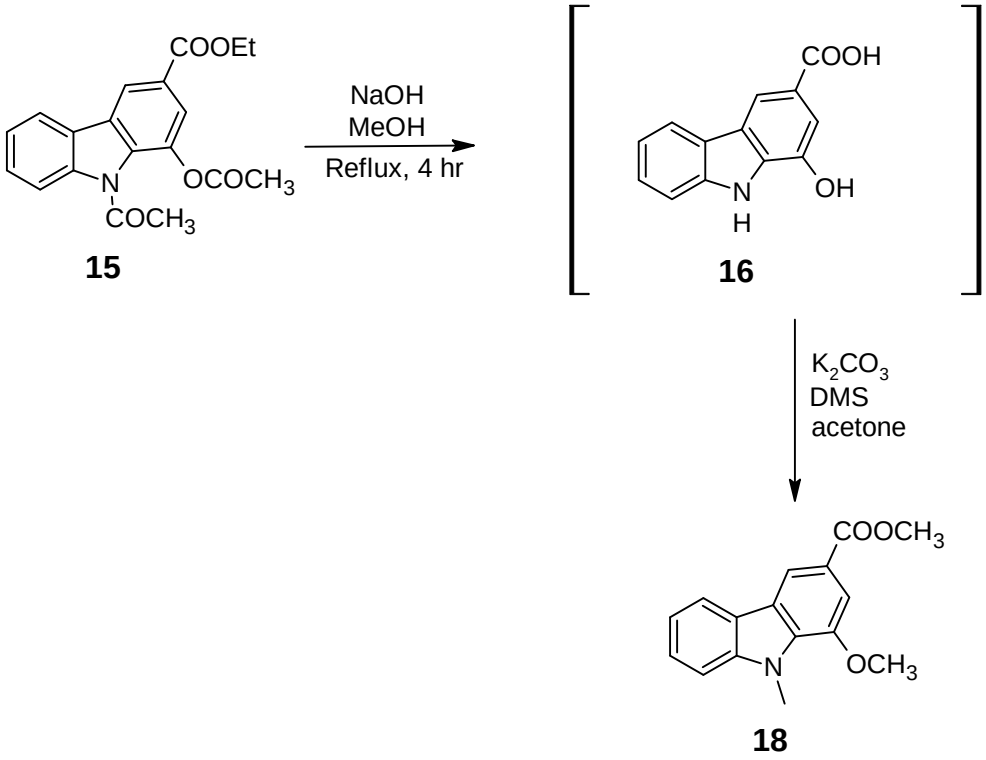


15 **17**

A mixture of compound **15** (0.64 g, 1.89 mmol) in methanol (8 mL) was refluxed with solution of sodium hydroxide (0.15 g, 3.75 mmol) in water (7 mL) for 2 hrs. The reaction mixture was cooled to room temperature, acidified with 1:1 HCl solution and extracted in diethyl ether (3 X 10 mL). The diethyl ether layer was dried over anhydrous sodium sulphate, and the solvent was evaporated to dryness. The residue obtained was purified by column chromatography over silica gel using

hexanes:EtOAc (8:2) as an eluent to get a white solid (**17**) (0.47 g, 98%); m.p. 165-167 ^{o}C.

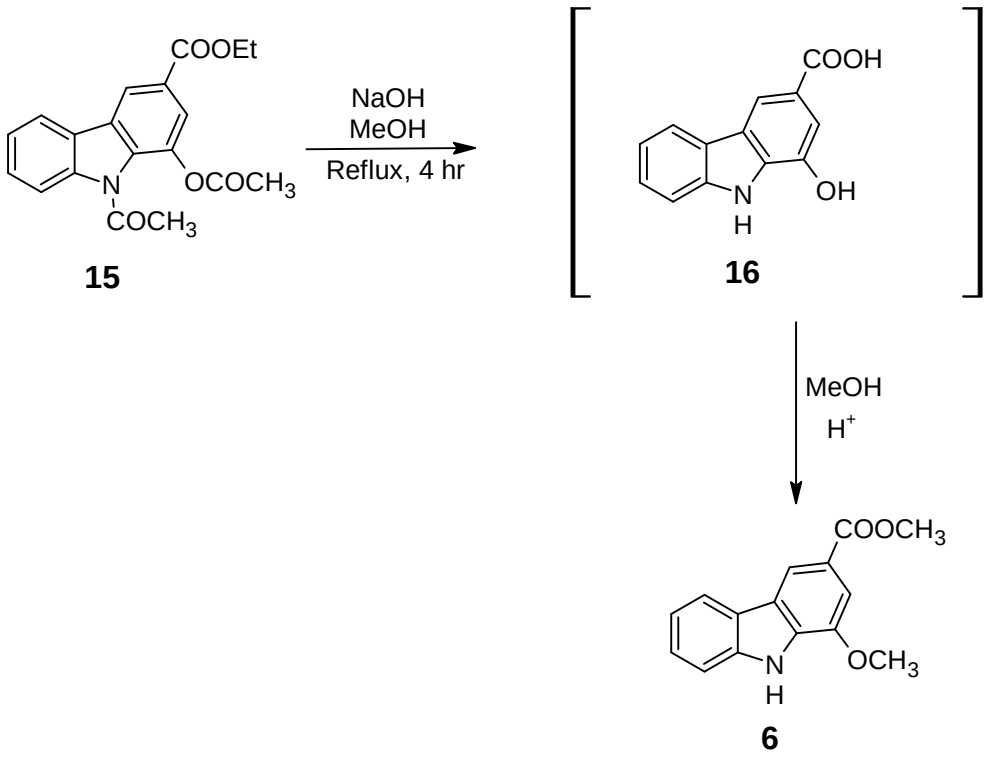
3.5 Preparation of Methyl 1-methoxy-9-methyl-9*H*-carbazole-3-carboxylate (**18**)



15 **16** **18**

A mixture of compound **15** (0.5 g, 1.47 mmol) in methanol (6 mL) was refluxed with solution of sodium hydroxide (0.15 g, 3.75 mmol) in water (7 mL) for 4 hrs. The reaction mixture was cooled to room temperature, acidified with 1:1 HCl solution and extracted in diethyl ether (3 X 10 mL). The diethyl ether layer was dried over anhydrous sodium sulphate, and the solvent was evaporated to dryness. The residue obtained without further purification was dissolved in dry acetone (6 mL) and to it K_2CO_3 (0.2 g, 1.47 mmol) and dimethylsulphate (0.19 g, 1.47 mmol) were added. The reaction mixture was refluxed for 8.0 h and solvent was evaporated to dryness. The residue obtained was purified by column chromatography over silica gel using hexanes:EtOAc (7:3) as an eluent to afford a white solid (**18**) (0.22 g, 58%); m.p. 122-125 ^{o}C.

3.6 Preparation of Methyl 1-methoxy-9*H*-carbazole-3-carboxylate (**6**)



A mixture of compound **15** (0.5 g, 1.47 mmol) in methanol (6 mL) was refluxed with solution of sodium hydroxide (0.15 g, 3.75 mmol) in water (7 mL) for 4 hrs. The reaction mixture was cooled to room temperature, acidified with 1:1 HCl solution and extracted in diethyl ether (3 X 10 mL). The diethyl ether layer was dried over anhydrous sodium sulphate, and the solvent was evaporated to dryness. The residue obtained without further purification was refluxed with conc. H_2SO_4 (1 mL) in methanol (10 mL) for 10.0 hrs. The solvent was evaporated under vacuum, and the residue obtained was dissolved in ether (10 mL). The ether layer was dried over sodium sulphate, ether was evaporated and the residue obtained was purified by column chromatography over silica gel using hexanes: EtOAc (9:1) as an eluent to get a white solid (**6**) (0.23 g, 41%); m.p. 198-200 ^{o}C.

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CHAPTER 3
Section B

CHAPTER 3

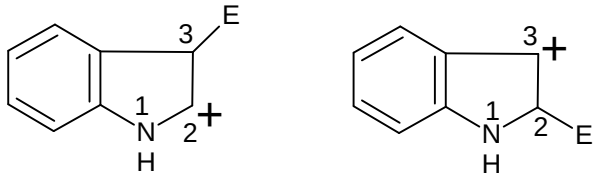
SECTION B

An unusual synthesis of indole 2-carboxylates

Introduction

Indoles are known to possess various biological properties including antibacterial, cytotoxic, antioxidative and insecticidal activities.[1] Some indole derivatives are used as antibiotics in pharmaceuticals.[1b] The preparation of different indole compounds and evaluation of their bioactivity is of great interest. We have attempted the synthesis of 2-prenyl indole and 2,3'-bis(indolyl)methane derivative in this section which eventually lead to the synthesis of ethyl indole 2-carboxylates. These ethyl indole-2-carboxylates are valuable starting materials for the synthesis of various alkaloids,[2] heterocyclic compounds[3] and biologically active compounds.[4]

The chemistry of indole is dominated by electrophilic substitution reaction.The heterocyclic ring of indole is very electron rich in comparison with its benzene counterpart, hence, there is a strong preference for electrophilic substitution in the 5-membered ring. Attack on the nitrogen would destroy the aromaticity of pyrrole ring, hence the two other positions C-2 and C-3 are only the alternatives. When considering the stability of the two generalised cations, **A** and **B**, it is realised that the intermediate **B** cannot derive further resonance stabilisation without disrupting the aromatic ring, whereas **A** can derive contribution from the lone pair of nitrogen (**Fig. 1**). Due to the higher resonance stabilization of Wheland intermediate **A** the preference for electrophilic position is at 3-position rather than at 2-position.



A **B**

Fig. 1

I) An attempt towards the synthesis of 2,3'-bis(indolyl)methane (BIM):

Introduction

The indole unit forms the basis for general BIM structures. BIMs are molecules containing two indolyl moieties connected to the same carbon atom (**Fig. 2**).

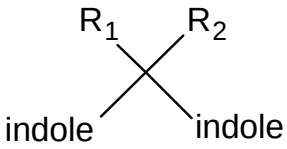


Fig. 2

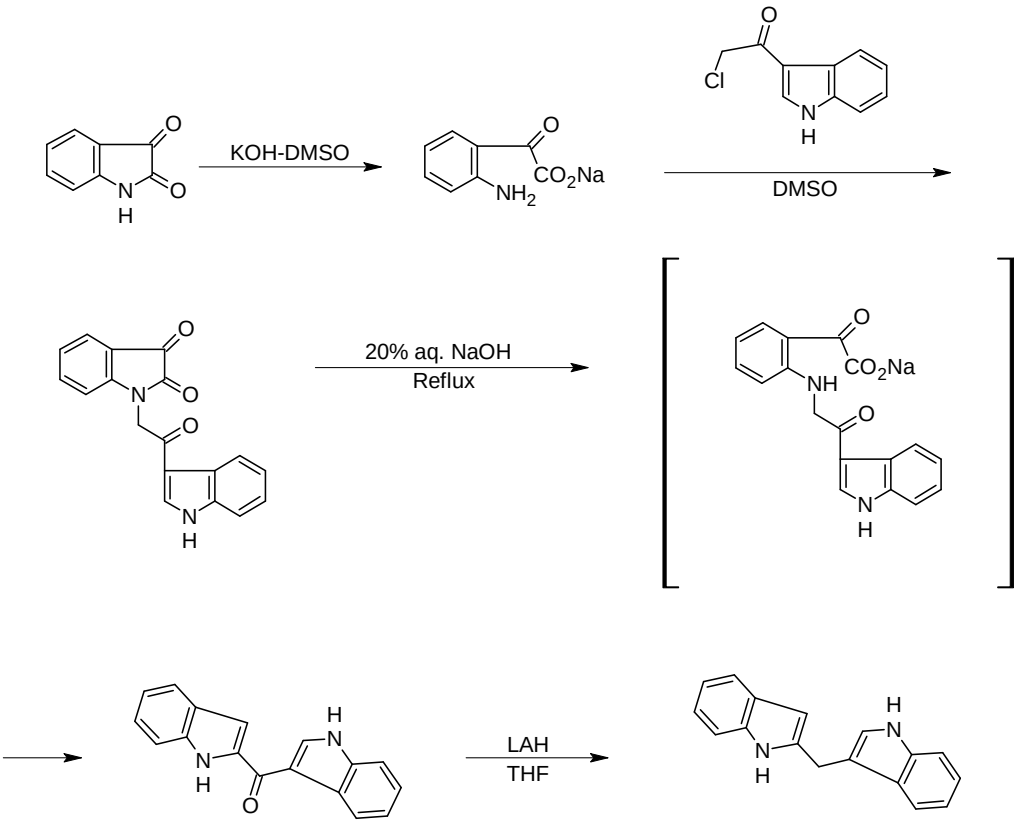
Bis(indolyl)methanes and their derivatives are known to be important intermediates in organic synthesis and pharmaceutical chemistry and exhibit various physiological properties.[5] Bis(indolyl)methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism,[6] and induce apoptosis in human cancer cells.[7] Therefore, there is great interest in the synthesis of these compounds. The indole ring is more reactive at 3-position, and therefore the majority of BIMs found in literature are 3,3'-BIMs.

A Literature Review

Usually the synthesis of 2,3'-BIMs is quite difficult due to the higher reactivity of the indole ring at position 3 as discussed before, and controlling this is not possible. To overcome the lack of nucleophilic reactivity at position 2 of the indole ring a completely different mechanism is required.

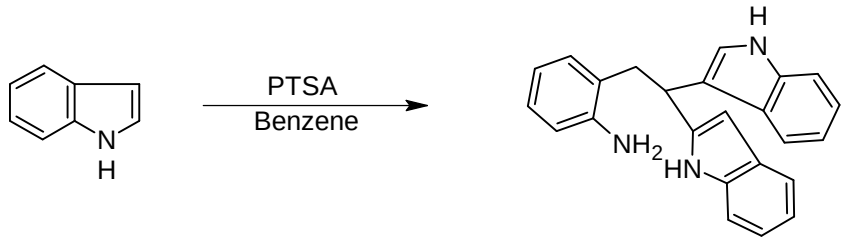
Some of the recent methods for the synthesis of 2,3'-BIMs are mentioned below –

Jackson *et al.*[8] prepared 2,3'-bisindolyl methane derivative from indoline-2,3-dione. The ring-opening of *isatin* undergoing alkaline hydrolysis in DMSO produced the amine. Reaction of the amine with 2-chloro-1-(1*H*-indol-3-yl)-ethanone followed by ring closure and ring opening yielded the corresponding methanone. Reduction of this methanone with LAH produced the 2,3'-bisindolyl methane derivative (**Scheme I**).



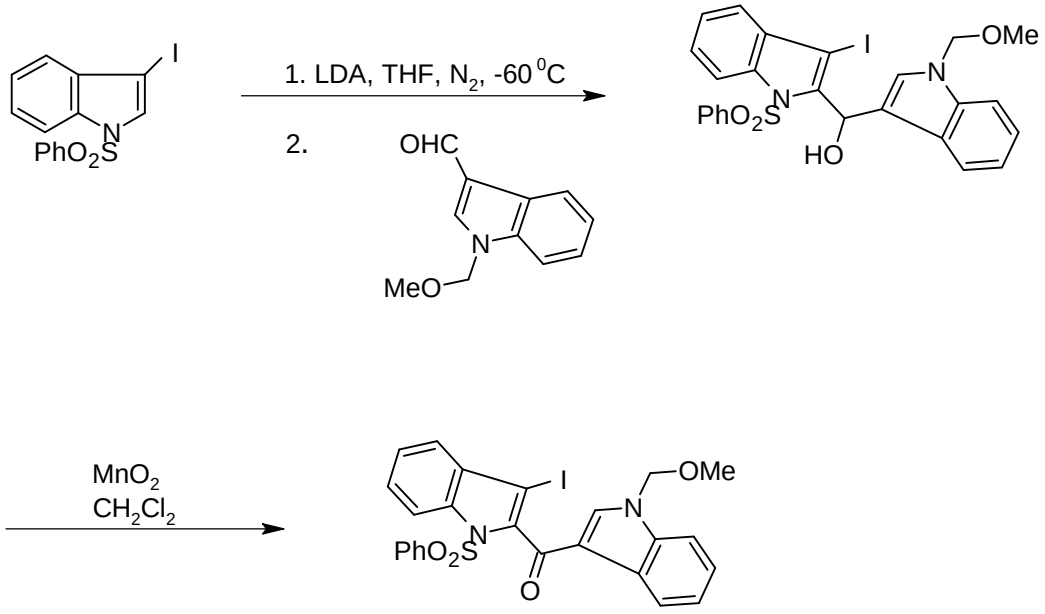
Scheme I

Murakami *et al.*[9] treated indole with PTSA in benzene to afford 2,3'-bisindolyl methane derivative (**Scheme II**).



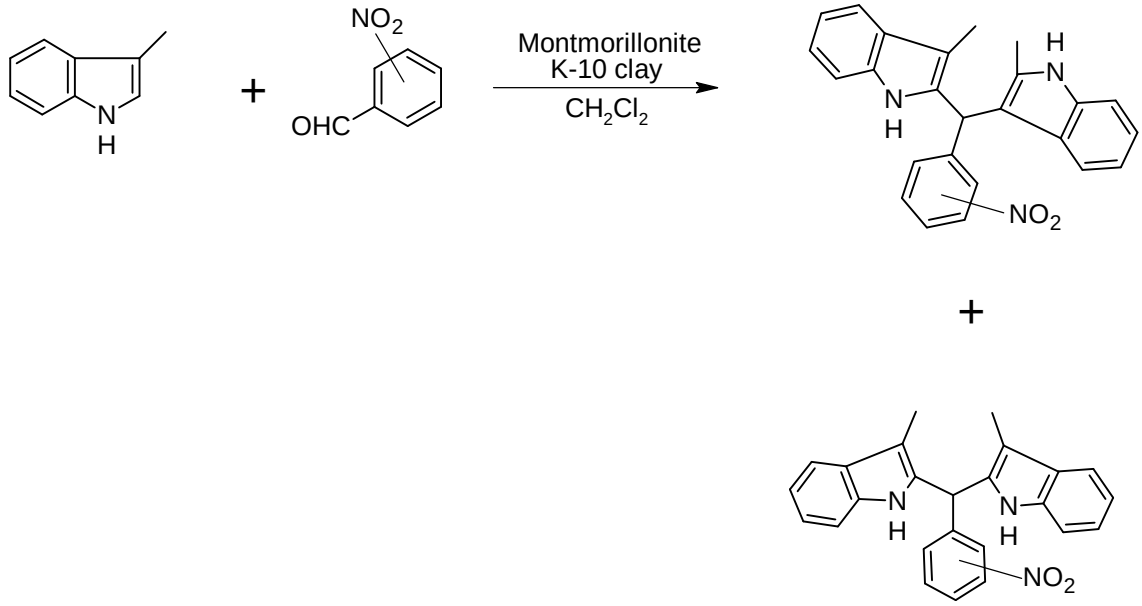
Scheme II

Rossi *et al.*[10] have reacted lithium derivative of 3-iodo-1-(phenylsulphonyl)-1*H*-indole with 1-methoxymethyl-1*H*-indole-3-carbaldehyde to get the corresponding alcohol which was then oxidised with active manganese dioxide to (1-benzenesulfonyl-3-iodo-1*H*-indol-2-yl)(1-methoxymethyl-1*H*-indol-3-yl)methanone (**Scheme III**).



Scheme III

Harigaya *et al.*[11] reacted 3-methylindole with *ortho*- or *meta*-nitrobenzaldehyde in presence of Montmorillonite K-10 clay to yield 2,3'- and also 2,2'-bisindolyl methane derivatives (**Scheme IV**).

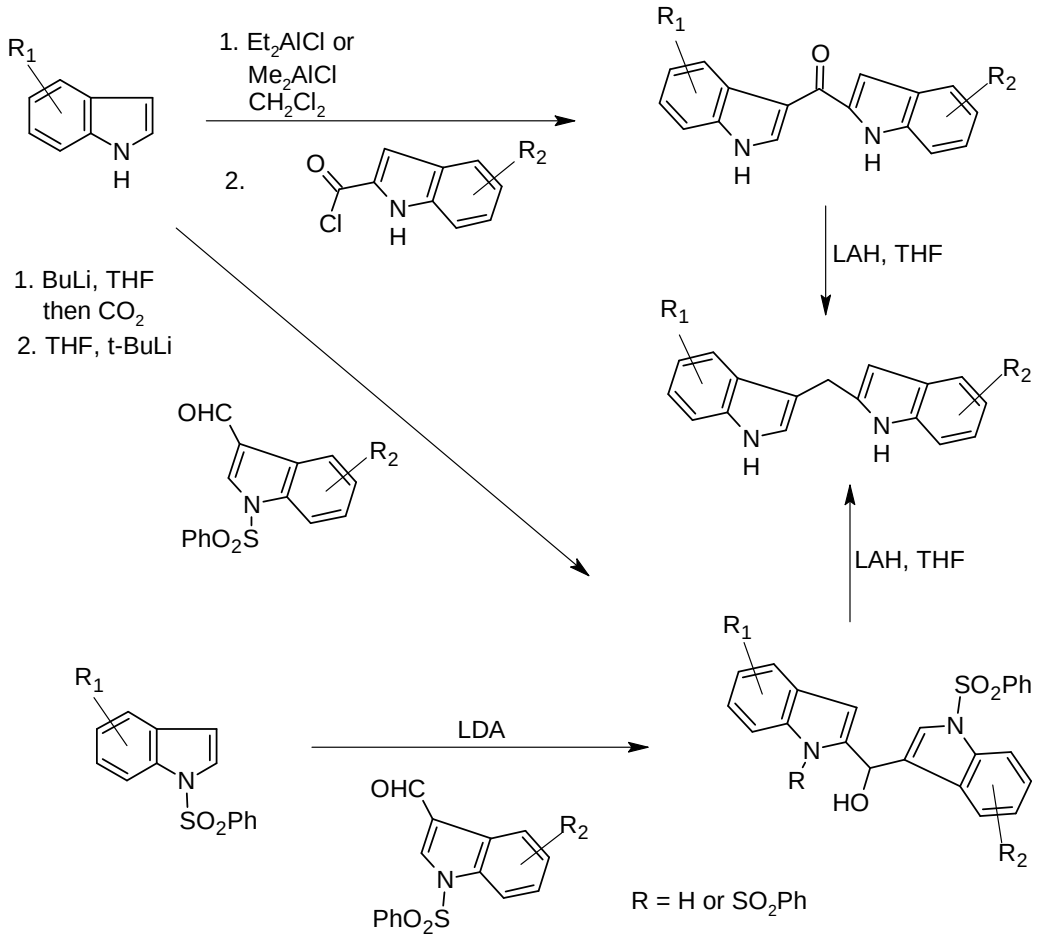


Scheme IV

Bergman *et al.*[12] have provided three different routes for the synthesis of 2,3'-BIMs as depicted in **Scheme V**. In the first route, Lewis acid-assisted acylation of the substituted indoles is used to produce the corresponding ketones, followed by reduction with LAH to yield corresponding 2,3'-BIM.

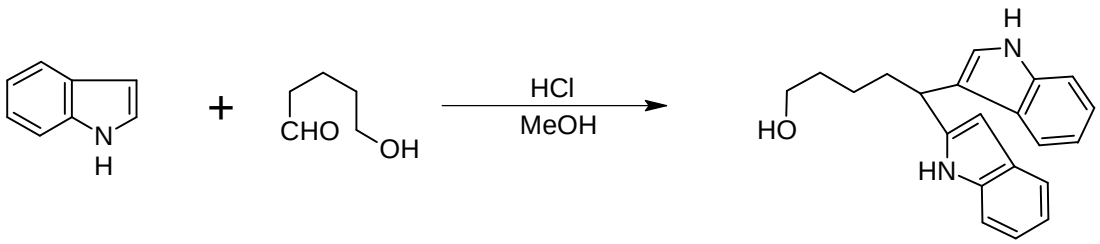
In the second approach, position 2 of *N*-protected indole is lithiated, followed by reaction with 1-benzenesulfonylindole-3-carboxaldehydes to give the alcohol; the latter in turn was reduced to 2,3'- bisindolyl methane derivative.

In the third route, the indole derivative was treated with LDA in THF followed by addition of 1-benzenesulfonylindole-3-carboxaldehydes the alcohol, obtained was then reduced with LAH yielding corresponding 2,3'- bisindolyl methane derivative.[13]



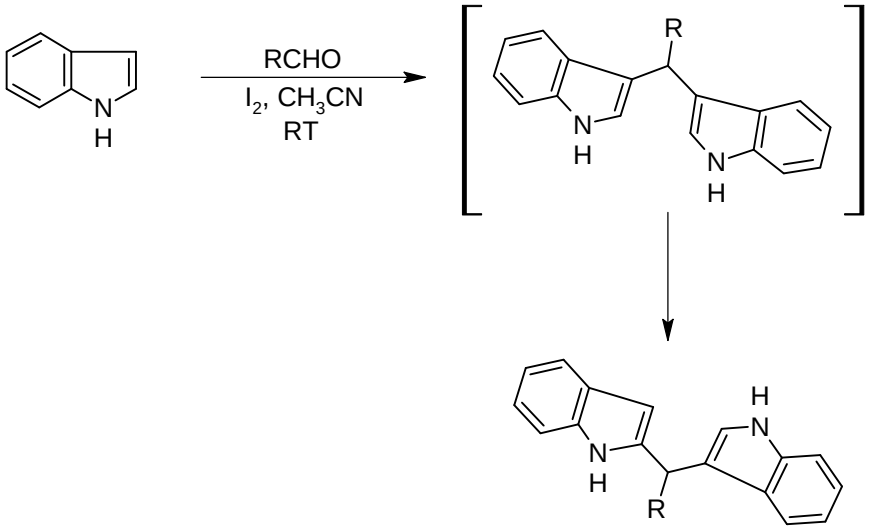
Scheme V

Giannini *et al.*[14] have reported the synthesis of 2,3'-bisindolyl methane derivative by treating indole and 5-hydroxy-pentanal in methanolic hydrochloric acid (**Scheme VI**).



Scheme VI

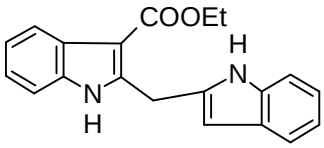
Gu *et al.*[15] condensed indole and aldehyde in presence of iodine in acetonitrile at room temperature to afford 3,3'-bisindolyl methane derivative which after isomerisation gave 2,3'-bisindolyl methane derivative (**Scheme VII**).



Scheme VII

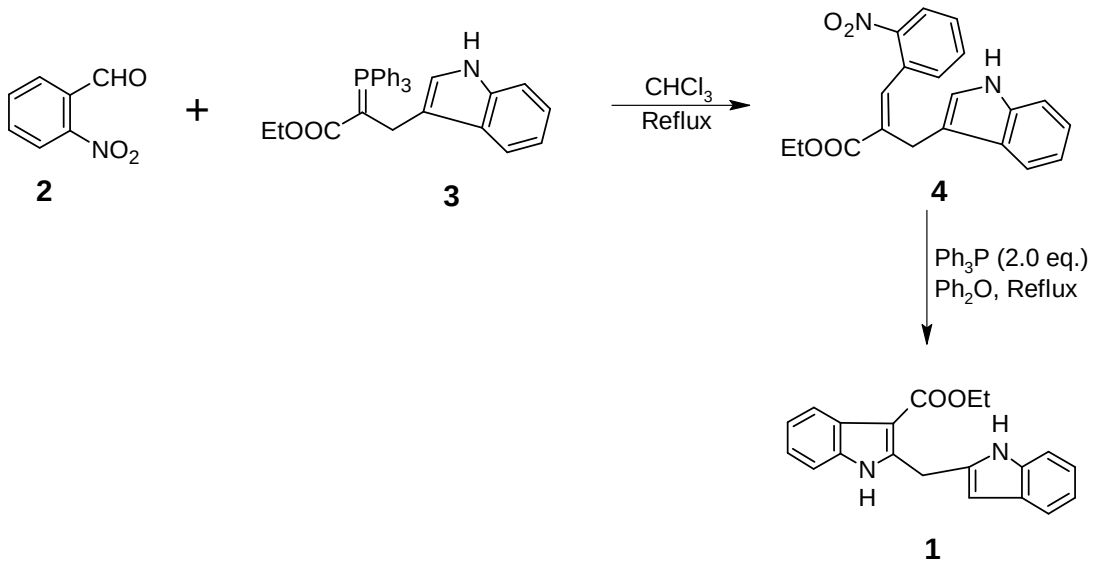
Present Work

Our aim was to synthesize 2,3'-bisindolyl methane derivative having structure **1** which could be tested for its biological activity. Again we were interested to use phosphorane chemistry for this purpose.



1

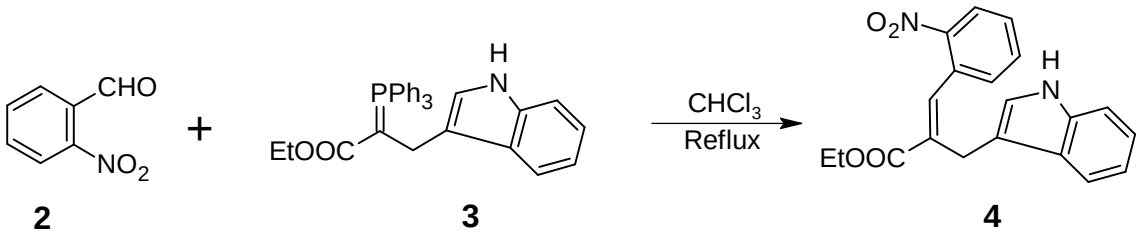
The methodology envisaged by us (**Scheme VIII**) is based on the literature method reported to synthesize 2-vinyl indoles.[15] The steps involved are Wittig reaction followed by reductive cyclisation.



2 **3** **4** **1**

Scheme VIII

The first step in our projected synthesis was Wittig reaction of *o*-nitrobenzaldehyde **(2)** with homoskatolidene phosphorane (**3**) (**Scheme IX**).



2 **3** **4**

Scheme IX

The preparation of homoskatolidene phosphorane (**3**) is discussed in section 1 of this chapter. This homoskatolidene phosphorane (**3**) was refluxed with *o*-nitrobenzaldehyde (**2**) in chloroform for 2.5 hrs. TLC of the reaction mixture showed the dissappearence of the aldehyde and appearence of new spot along with triphenyl phosphine oxide. The crude product was purified by column chromatography over silica gel using hexanes-EtOAc (9:1) as an eluent to obtain a yellow viscous liquid.

The IR spectrum of the compound exhibited strong band at 3412 cm^{-1} which was due to N-H stretching of indole ring structure. Strong band at 1714 cm^{-1} was due to carbonyl bond of α,β-unsaturated ester moiety.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz, δ ppm) (**Fig. I**) showed peaks at δ 1.28 (t, *J* = 6.9 Hz, 3H) and δ 4.27 (q, *J* = 6.9 Hz, 2H) were attributed to the ester group (-OCH_2CH_3). The peaks observed at δ 3.83 (s, 2H) was attributed to methylene group attached to third position of indole ring. Signal at δ 6.91 (s, 1H) was assigned to proton on 2-position of indole ring. The remaining aromatic protons were observed at δ 7.08 (t, *J* = 6.9 Hz, 1H), δ 7.19 (t, *J* = 7.2 Hz, 1H), δ 7.34 (d, *J* = 8.1 Hz, 1H), δ 7.42 (t, *J* = 7.5 Hz, 1H), δ 7.44- δ 7.56 (m, 3H) and δ 8.13 (d, *J* = 7.8 Hz, 1H). The broad signal at δ 7.97 (br.s., 1H) was attributed to the proton on nitrogen of indole ring. While the signal exhibited at δ 8.07 (s, 1H) was assigned to the benzylic proton. The downfield shift of this proton indicated it to be *cis* to the –COOEt group (*E* geometry).

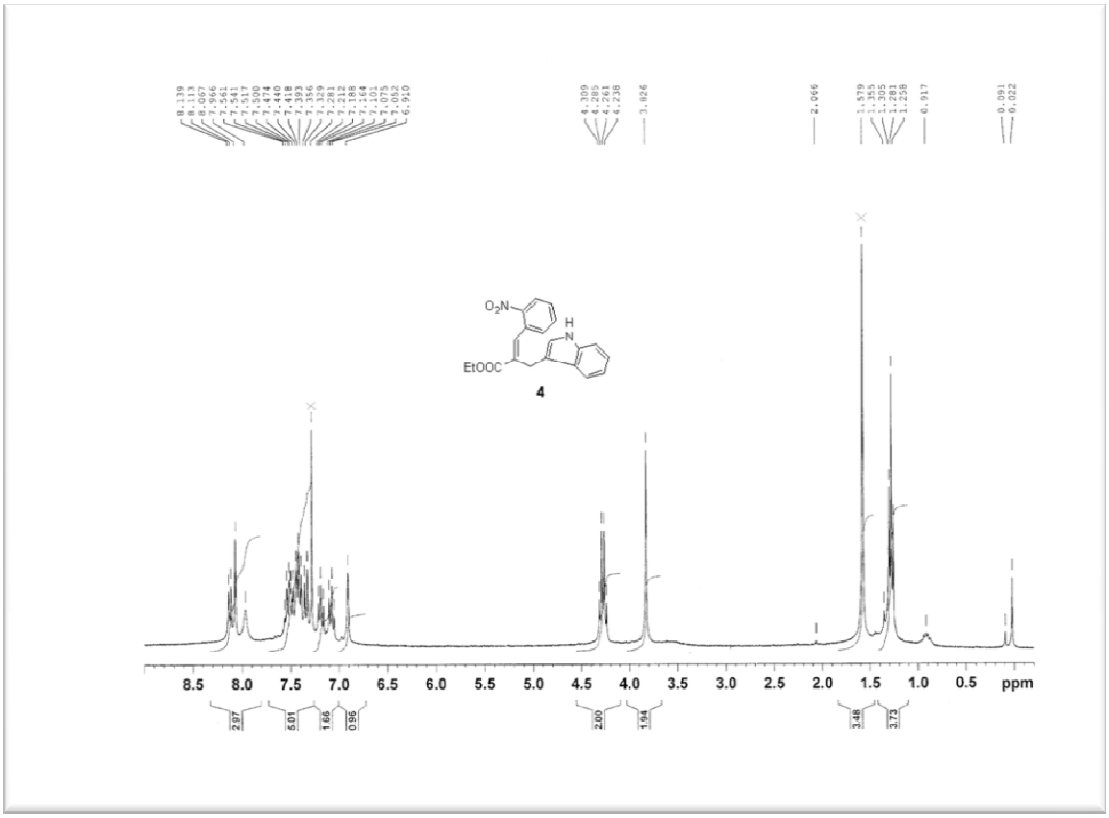


Fig. I : ^{1}H-NMR spectrum of Compound **4**

^{13}C-NMR spectrum ($CDCl_3$, 75 MHz, δ ppm) (**Fig. II**) showed peaks at δ 14.18 (CH_3), 23.52 (CH_2), 61.19 (OCH_2), 111.11 (CH), 113.76 (C), 118.62 (CH), 119.23 (CH), 121.76 (CH), 122.07 (CH), 124.82 (CH), 126.95 (C), 129.09 (CH), 130.95 (CH), 131.67 (C), 133.34 (C), 133.47 (CH), 136.08 (CH), 136.27 (C), 147.68 (C), 167.71 (C=O).

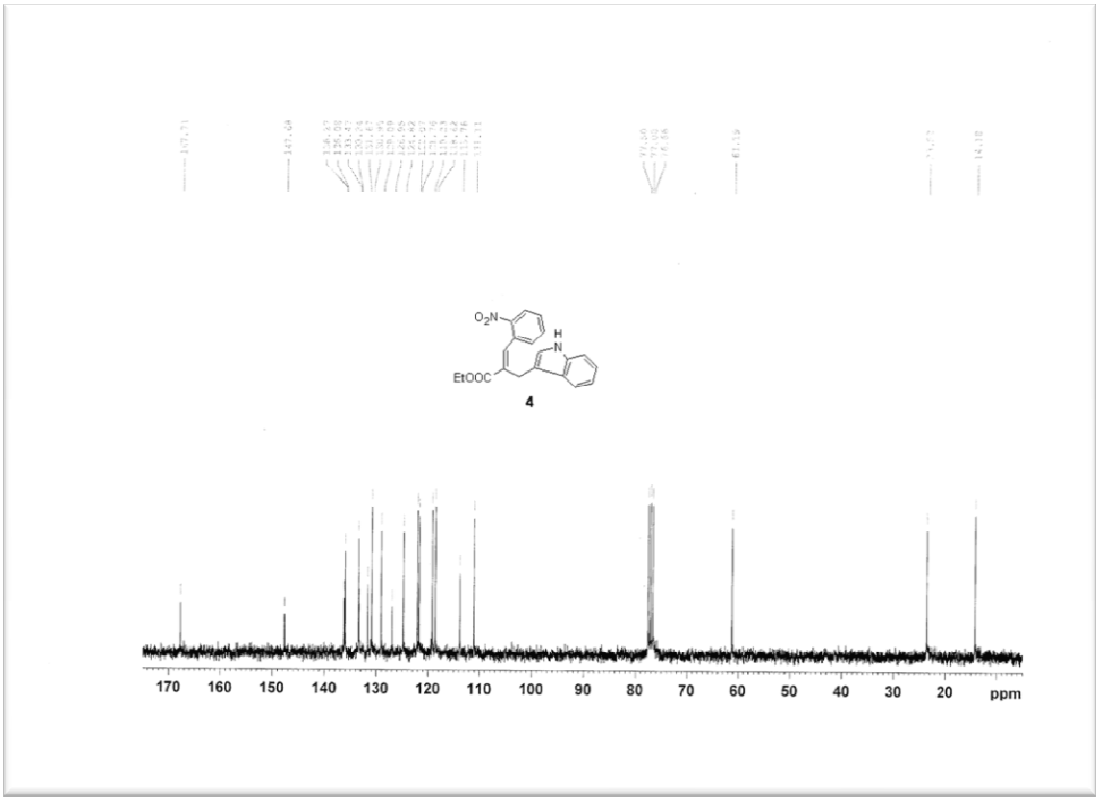
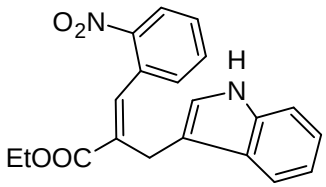


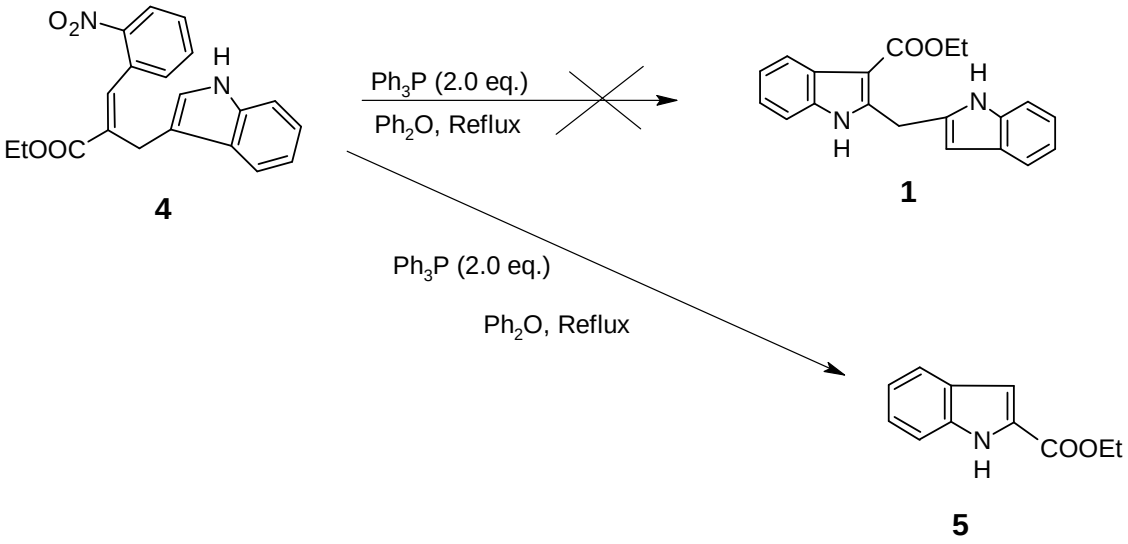
Fig. II : ^{13}C-NMR spectrum of Compound **4**

Based on the mode of formation and above spectral data structure **4** was assigned to the product formed. The yield of the product was found to be 93%.



4

In the next step compound **4** was refluxed with triphenyl phosphine in diphenyl ether for 5.0 hrs (**Scheme X**), after which there was seen dissappearence of compound **4** on TLC and appearence of a new spot.



Scheme X

The crude product was then purified by column chromatography over silica gel using hexanes-EtOAc (8:2) as an eluent to get a white solid.

The IR spectrum of the compound exhibited strong band at 3311 cm^{-1} which was due to N-H stretching of indole ring moiety. Strong band at 1693 cm^{-1} was due to carbonyl group of ethyl ester.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz, δ ppm) (**Fig. III**) showed peaks at δ 1.44 (t, *J* = 7.2 Hz, 3H) and δ 4.44 (q, *J* = 7.2 Hz, 2H) which was attributed to the ester group -OCH_2CH_3. The aromatic protons were observed at δ 7.18 (t, *J* = 7.2 Hz, 1H), δ 7.26 (s, 1H), δ 7.35 (t, *J* = 7.5 Hz, 1H), δ 7.45 (d, *J* = 8.4 Hz, 1H) and 7.72 (d, *J* = 7.8 Hz, 1H). The peak observed at δ 8.92 (br.s., 1H) was attributed to the proton on nitrogen of indole structure.

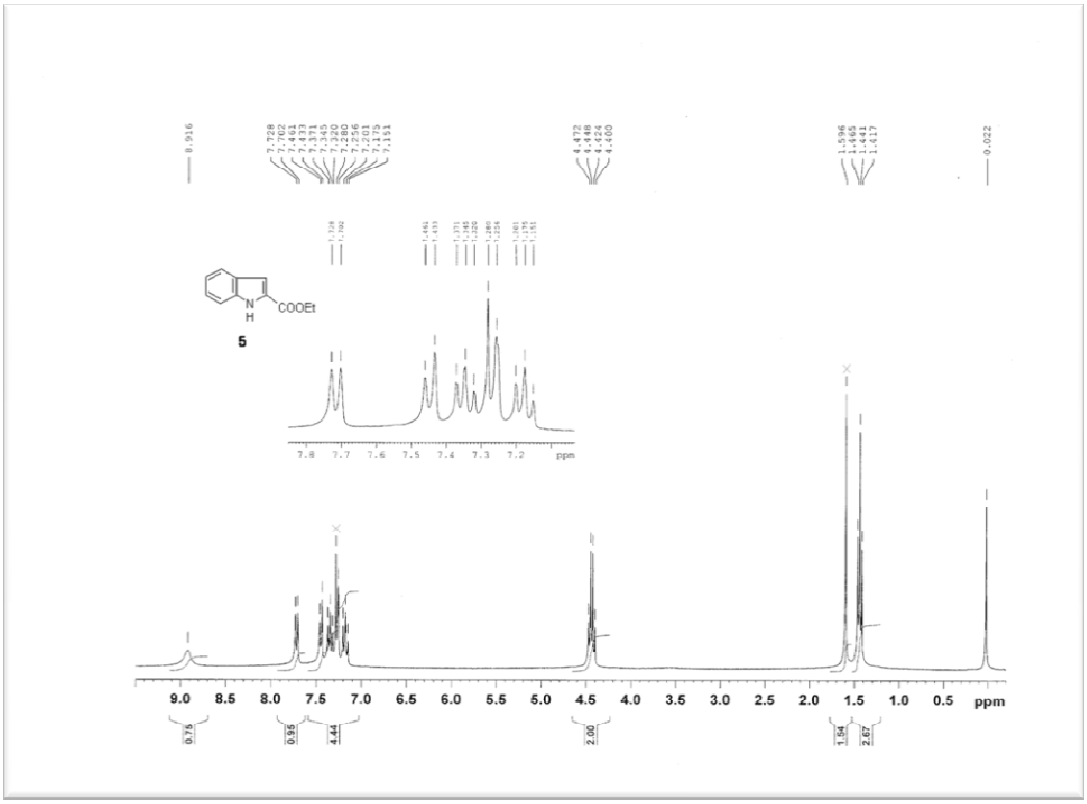
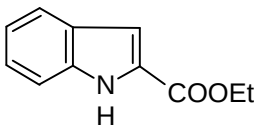


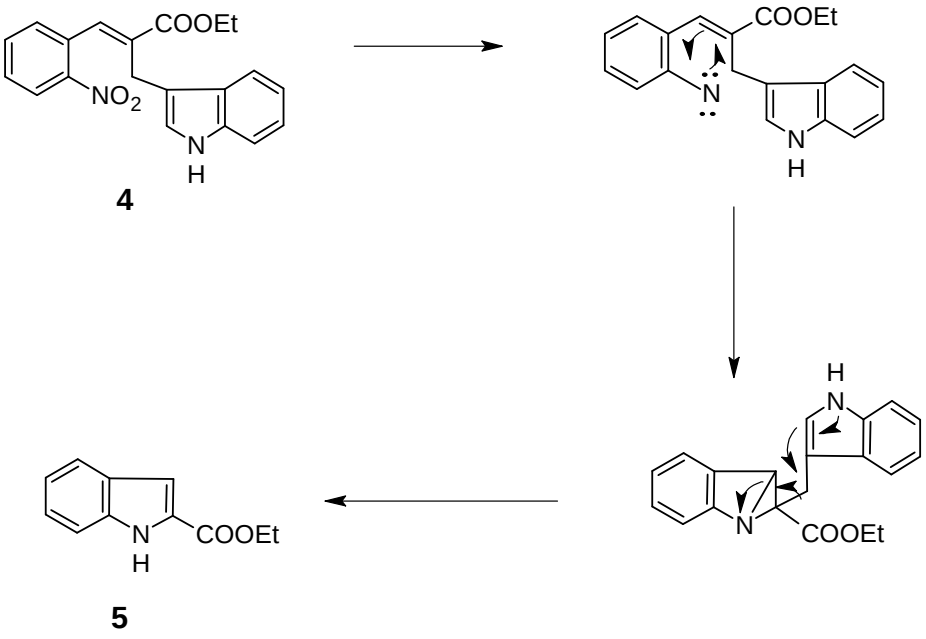
Fig. III : ^{1}H-NMR spectrum of Compound **5**

Looking at the above spectral data, it is confirmed that we could not synthesize the expected 3,3'-BIM molecule, but the product which actually we got in our hand was ethyl indole-2-carboxylate (**5)**. It was further confirmed by its similarity with lit.[16] m.p. 110-112 ^{o}C, found 109-111 ^{o}C. The yield of the product was found to be 35%.



5

A probable mechanism is postulated for this unusual formation of ethyl indole-2-carboxylate is depicted in **Scheme XI.** However, we did not isolated 3-methyl indole probably due to its oligomerisation under the reaction conditions.



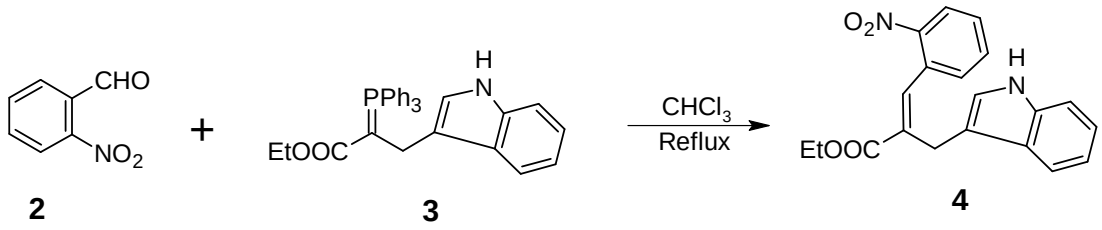
Scheme XI

Conclusion

An unsuccessful attempt has been made to synthesize 2,3’-BIM molecule, actually leading to the synthesis of ethyl indole-3-carboxylates. A probable mechanism for its formation is also postulated.

Experimental

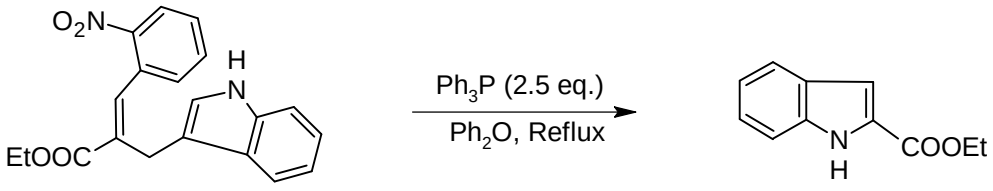
3.7 Preparation of Compound **4**



2 **3** **4**

A solution of *o*-nitrobenzaldehyde (**2**) (0.302 g, 2 mmol) and homoskatolidene phosphorane (**3**) (0.954 g, 2 mmol) in chloroform (15 mL) was refluxed for 2.5 hrs. The TLC of reaction mixture showed appearence of a new spot. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography over silica gel using hexanes:EtOAc (9:1) as an eluent to furnish a yellow viscous liquid (**4)** (0.651 g, 93%).

3.8 Preparation of Ethyl indole-3-carboxylate (**5**)



4 **5**

A mixture of compound **4** (0.350 g, 1 mmol) and triphenyl phosphine (0.524 g, 2.0 mmol) in diphenyl ether (10 mL) was heated under reflux for 5.0 hrs. The progress of the reaction was monitored by TLC. Diphenyl ether was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give solid ethyl indole-2-carboxylate (**5**) (0.066 g, 35%), m.p. 109-111 ^{o}C.

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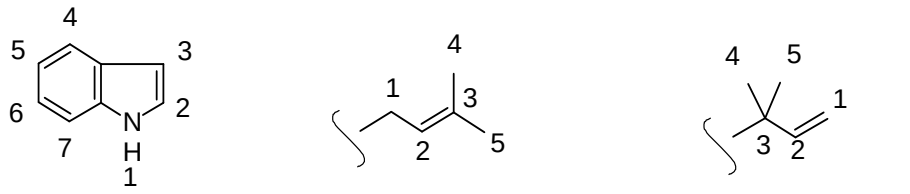
II) An attempt towards the synthesis of 2-prenyl indole:

Introduction

Prenylated indole alkaloids are hybrid natural products containing indole/indoline and isoprenoid moieties or structures derived thereof. They are widely distributed in terrestrial and marine organisms, especially in the genera *Penicillium* and *Aspergillus* of ascomycota, and display broad structure diversity. These compounds often carry biological and pharmacological activities distinct from their non-prenylated aromatic precursors.[1–3]

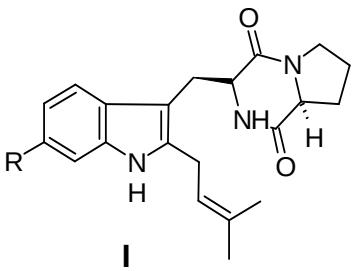
In the structures of prenylated indole alkaloids, the prenyl moieties can be connected via its C-1 or C-3 to an aromatic nucleus which are referred to as regular or reverse prenyl moieties respectively (**Fig. 1**).



Indole/Indoline Regular prenyl moiety Reverse prenyl moiety

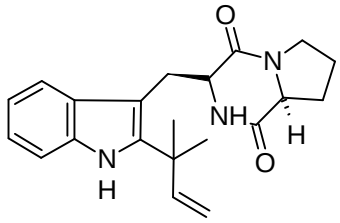
Fig. 1

These are some of the prenylated indole alkaloids having γ,γ-dimethyl allyl and α,α-dimethyl allyl system attached to C-2 of indole ring[4] (**Fig. 2**).



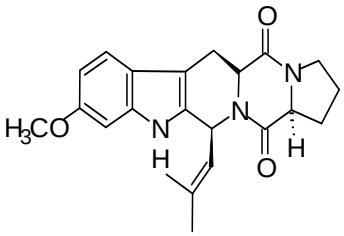
I

Tryprostatin A, R = OCH_3
Tryprostatin B, R = H



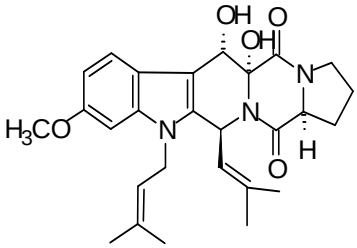
II

Deoxybrevianamide E



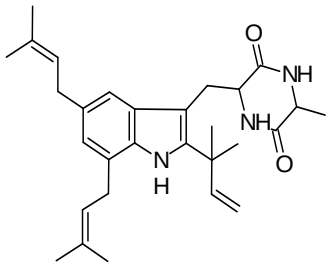
III

Fumitremorgin C



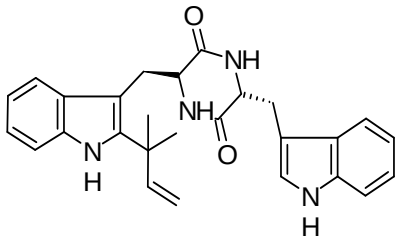
IV

Fumitremorgin B



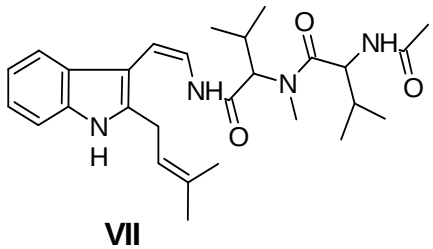
V

Echinulin



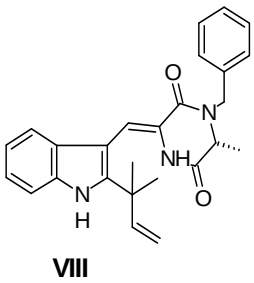
VI

Fellutanine B



VII

Terpeptin



VIII

Neoechinulin A

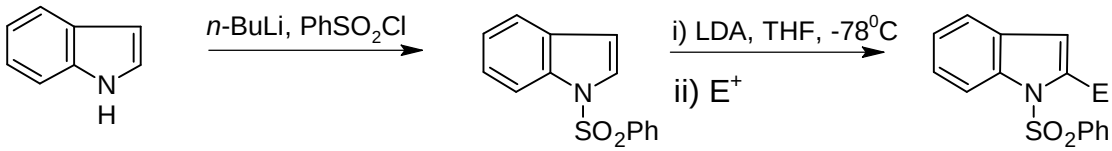
Fig. 2

In order to lay groundwork for the synthesis of these complex prenylated indole alkaloids, an attempt was made to synthesise the α-prenyl indole nucleus.

A Literature Review

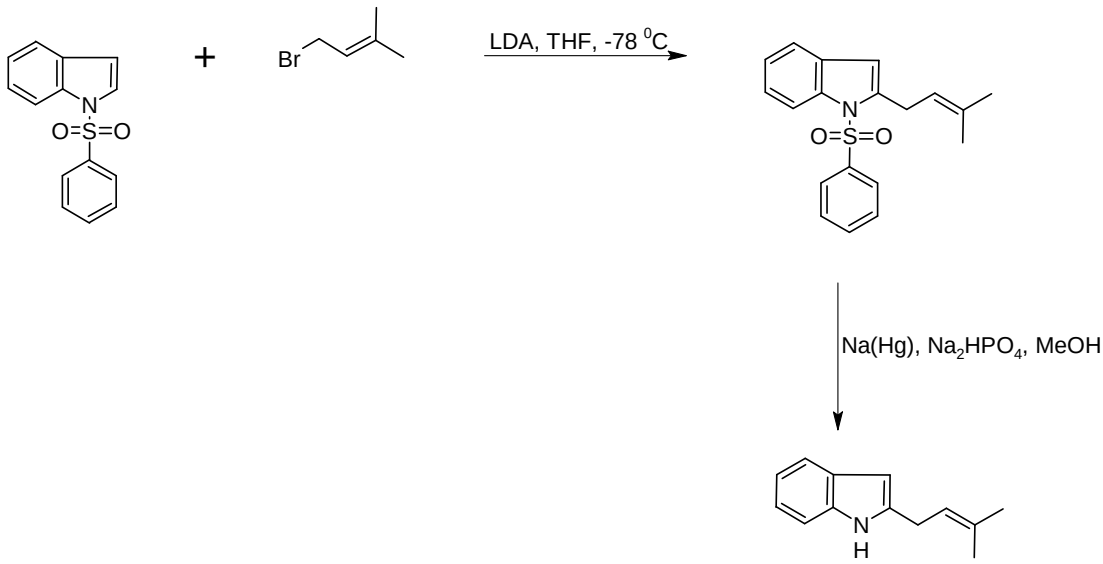
Usually the regiospecific metallation of *N*-protected indoles is exploited for the synthesis of 2-substituted indoles. Nitrogen-protected 2-lithioindoles have been widely used in synthesis since the pioneering work of Sundberg and Russel,[5] with phenylsulfonyl protecting group.[6] From *N*-protected indoles, deprotonation (lithiation) can be effected at C-2, which can result in various C-2 substituted indoles that subsequently act as precursors in the synthesis of biological active compounds.

Thus, 1-(phenylsulfonyl)indole is prepared from indole with *n*-butyllithium and benzenesulfonyl chloride. This is then lithiated at C-2 with lithium diisopropylamide (LDA), and the resulting 2-lithiospecies treated with various electrophiles to afford C-2 substituted indoles[7] (**Scheme I**).



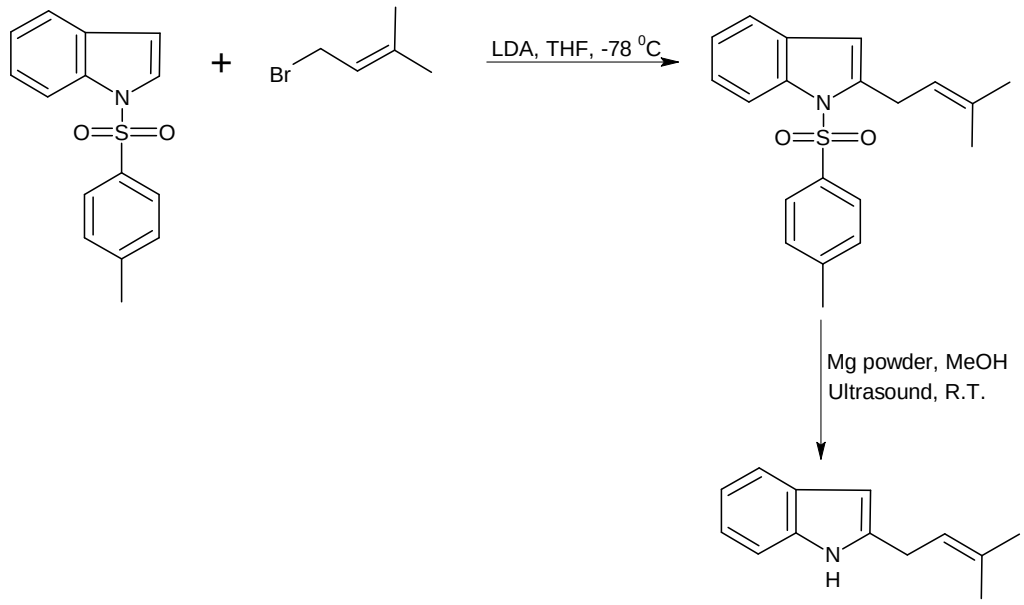
Scheme I

Swindell *et al.*[8] metalated *N*-(benzene-sulfonyl) indole with lithium diisopropylamide. The resultant α-lithio compound was treated with prenyl bromide to get the α-prenylated derivative which was then reduced with sodium amalgam to liberate α-prenyl indole (**Scheme II)**.



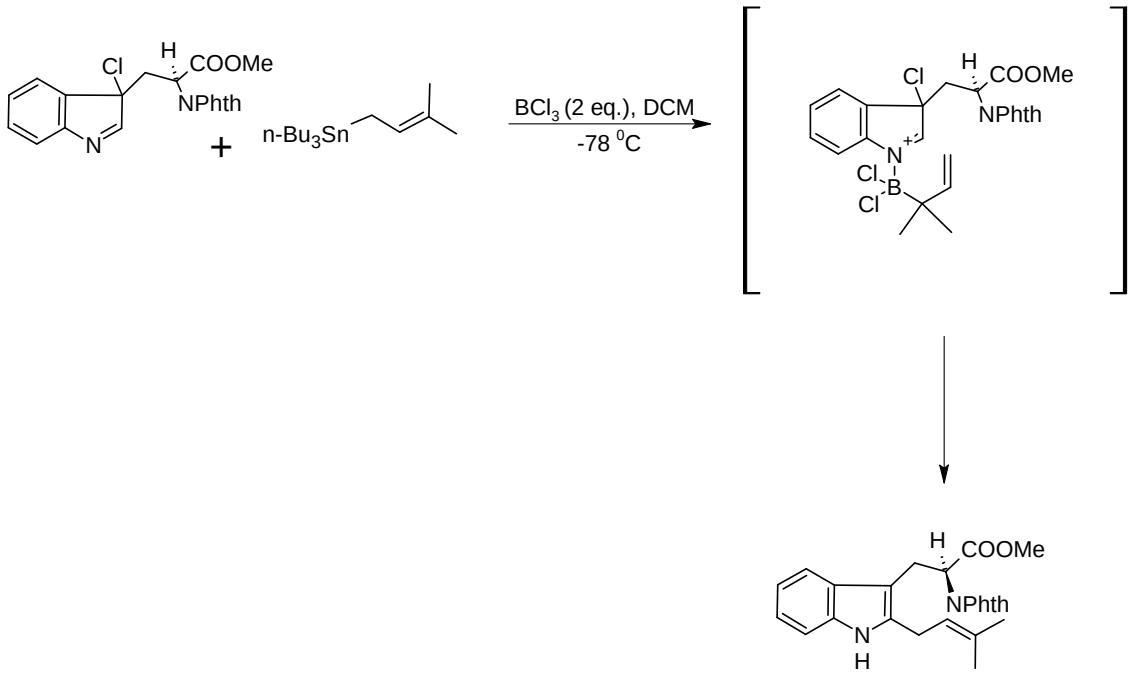
Scheme II

Stanovnik *et al.*[9] modified the procedure of Swindell *et al.*[8], wherein instead of benzene sulfonyl protecting group, they used tosyl protecting group. The protecting group was knocked off by magnesium powder in methanol under ultrasonic condition (**Scheme III**).



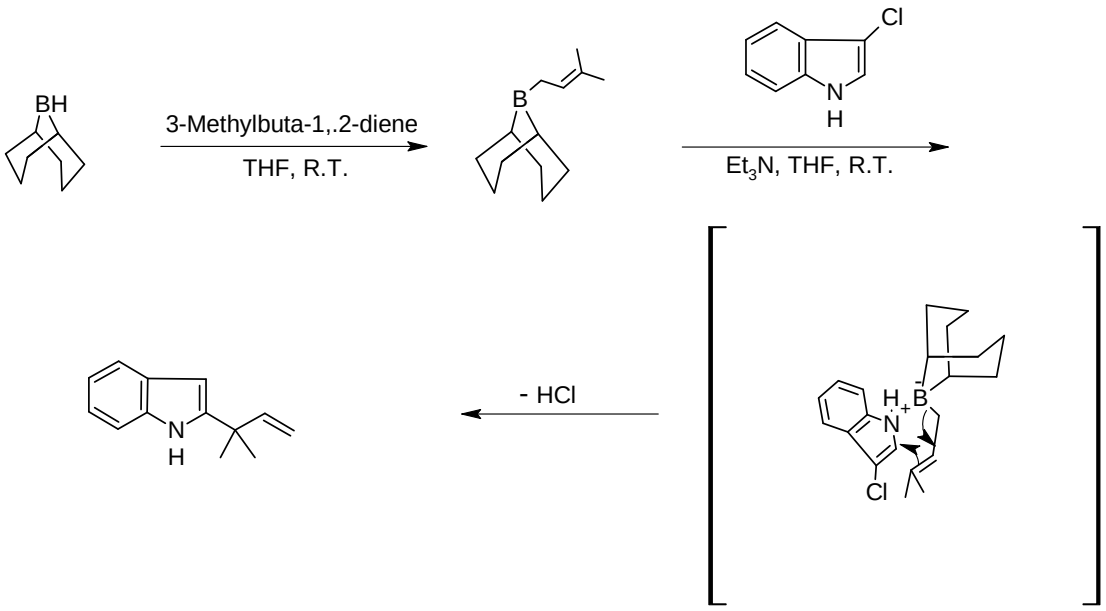
Scheme III

Danishefsky *et al.*[10] treated the solution of 3-chloroindolenine in dichloromethane with stannane in presence of 2 equiv. of BCl_3 at -78^{0}C to get the α-prenylated indole derivative (**Scheme IV**).



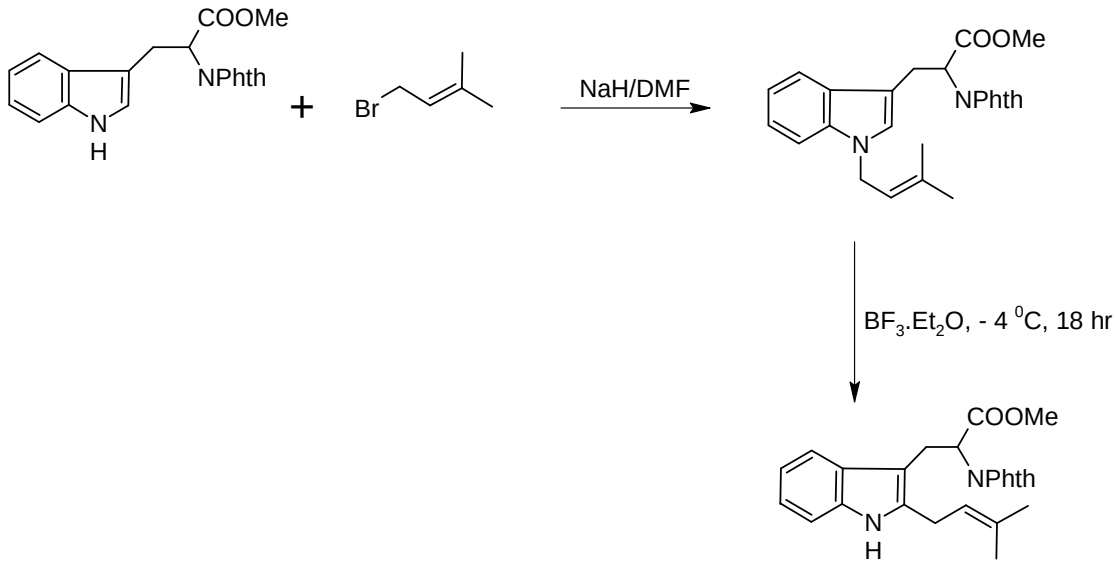
Scheme IV

Stanovnik *et al.*[11] prepared α-isoprenylindole using 9-BBN. They converted 9-BBN first to 9-(3-methylbut-2-enyl)-9-borabicyclo[3.3.1]nonane using 3-methylbuta-1,2-diene in THF at room temperature. This was then reacted with 3-chloroindole in THF in presence of triethyl amine at room temperature (**Scheme V)**.



Scheme V

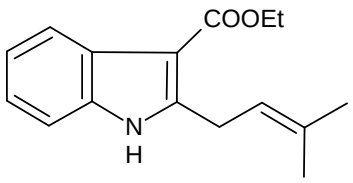
Prabhakar *et al.*[12] started theie synthesis from N^a-acetyltryptamine. They converted first it to a N^a-prenyl-N^b-acetyl tryptamine derivative with prenyl bromide in presence of NaH in DMF. Further, the N^a-prenylated derivative was treated with $BF_3.Et_2O$ at – 4 ^oC for 18 hrs. to yield 2-prenylated tryptamine nucleus (**Scheme VI**).



Scheme VI

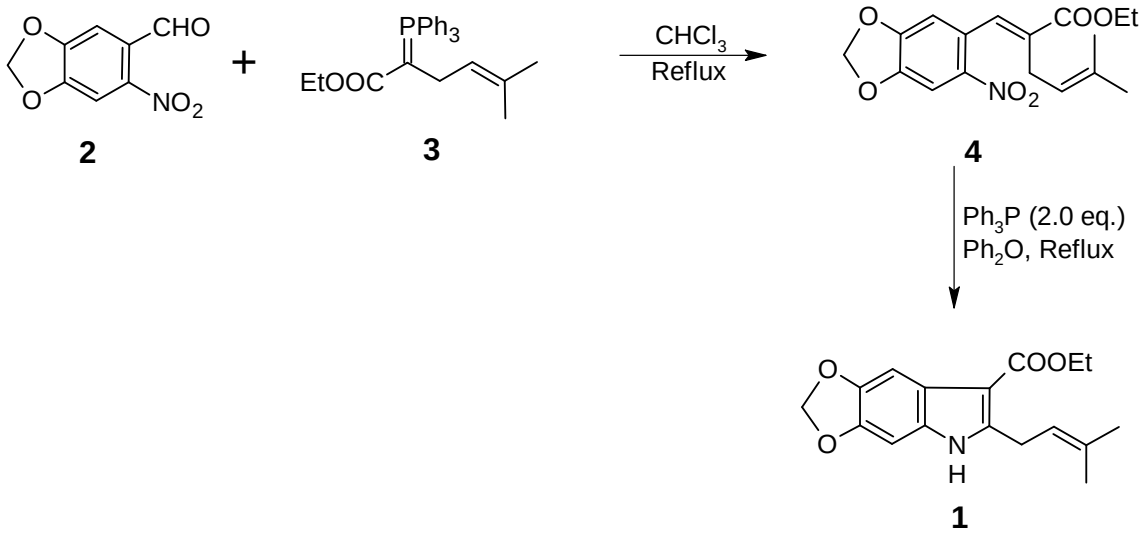
Present Work

Most of the reported methods for the synthesis of α-prenyl indole make use of preformed indoles, however we have attempted the synthesis which need not require preformed indoles. Our intention was to prepare α-prenyl indole derivative having structure **1** which could be further converted to bioactive prenylated indole alkaloids having complex structural framework.



1

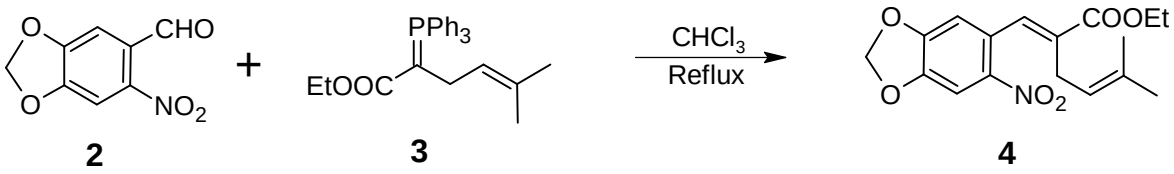
The methodology envisaged by us (**Scheme VII**) is based on the literature method reported to synthesise 2-vinyl indoles[13] wherein the steps involved are Wittig reaction and reductive cyclisation.



2 **3** **4** **1**

Scheme VII

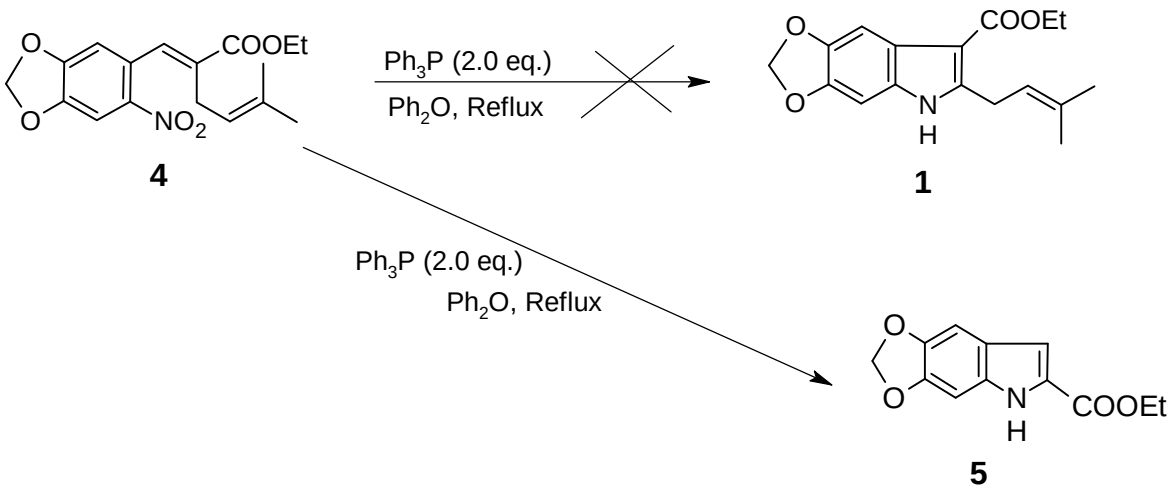
The Wittig reaction of 3,4-methylenedioxy benzaldehyde (**2**) with prenyl phosphorane (**3**) was performed in refluxing chloroform for 3.0 hrs to get the α,β-unsaturated ester **4** (**Scheme VIII**). This α,β-unsaturated ester **4** is synthesised and characterised in Chapter 2.



2 **3** **4**

Scheme VIII

As per planned methodology compound **4** was then refluxed with triphenyl phosphine in diphenyl ether for 4.0 hrs, after which there was seen dissappearence of compound **4** on TLC and appearence of new spot (**Scheme IX)**.



4 **1** **5**

Scheme IX

The crude product was then purified by column chromatography over silica gel using hexanes-EtOAc (8:2) as an eluent to get the white solid.

The IR spectrum of the compound exhibited strong band at 3307 cm^{-1} which was due to N-H stretching of indole ring moiety. Strong band at 1687 cm^{-1} was due to carbonyl group of ethyl ester.

The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz, δ ppm) (**Fig. I**) showed peaks at δ 1.41 (t, *J* = 7.2 Hz, 3H) and δ 4.39 (q, *J* = 7.2 Hz, 2H) which was attributed to the ester group -OCH_2CH_3. The signal due to methylene proton was observed at δ 5.99 (s, 2H). The aromatic protons were observed at δ 6.84 (s, 1H), δ 7.01 (s, 1H) and δ 7.12 (s, 1H). The peak observed at δ 8.79 (br.s., 1H) was attributed to the proton on nitrogen of indole ring structure.

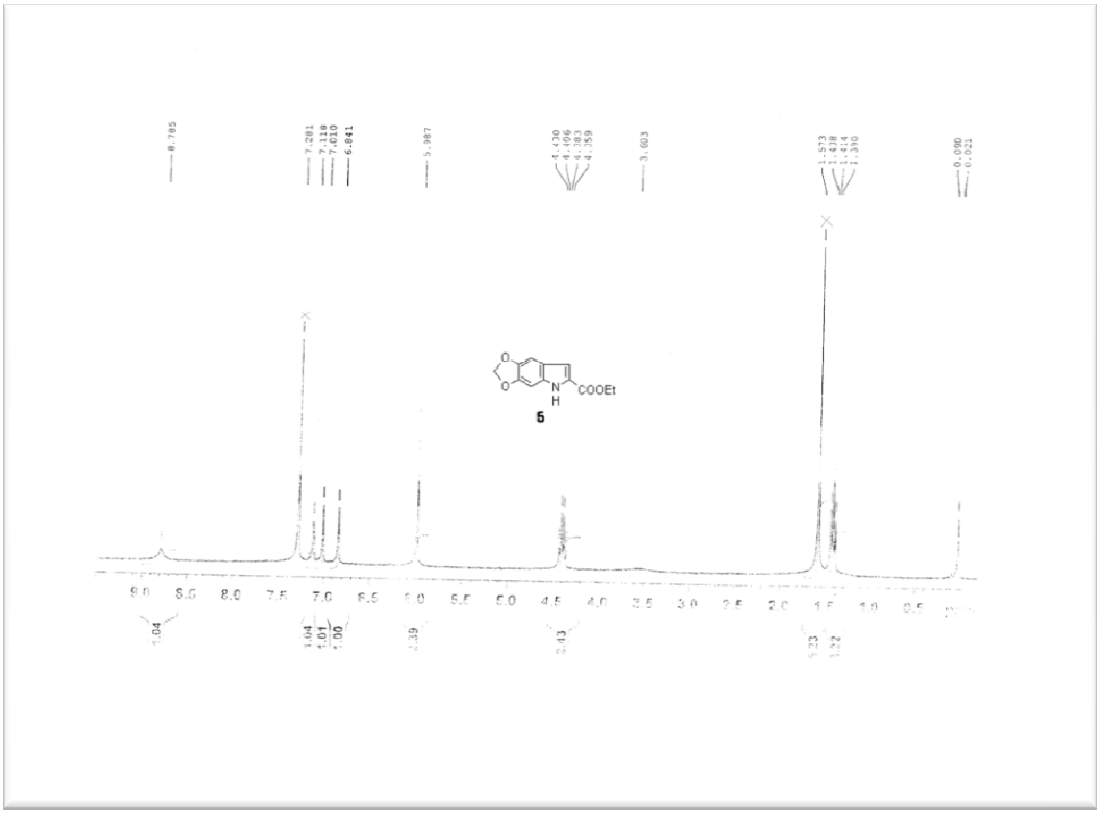
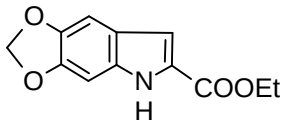


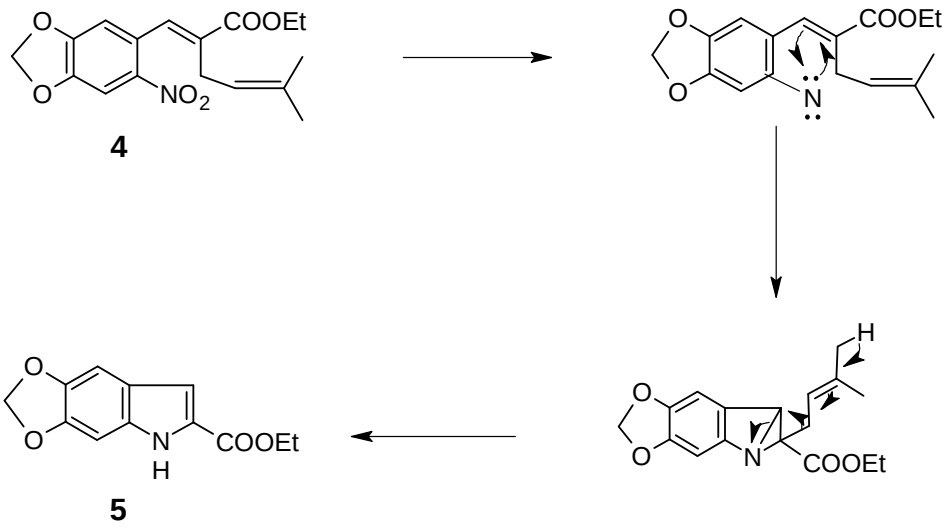
Fig. I : ^{1}H-NMR spectrum of Compound **5**

Looking at the above spectral data, we can say that we failed to synthesize the expected α-prenyl indole nucleus, but the product formed was ethyl-5,6-methylenedioxyindole-2-carboxylate (**5**). It was further confirmed by its similarity with lit.[14] m.p. 175-178 ^{o}C, found 174-176 ^{o}C. The yield of the product was found to be 32%.



5

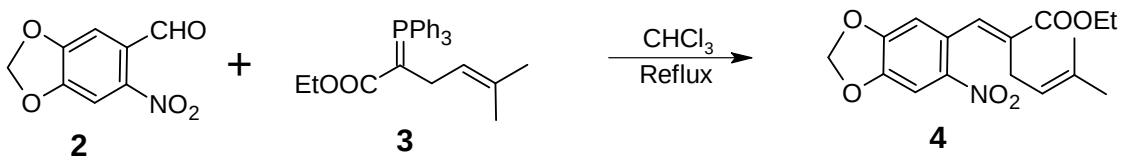
A probable mechanism is postulated for this unusual formation of ethyl-5,6-methylenedioxyindole-2-carboxylate (**5**) is depicted in **Scheme X.**



Scheme X

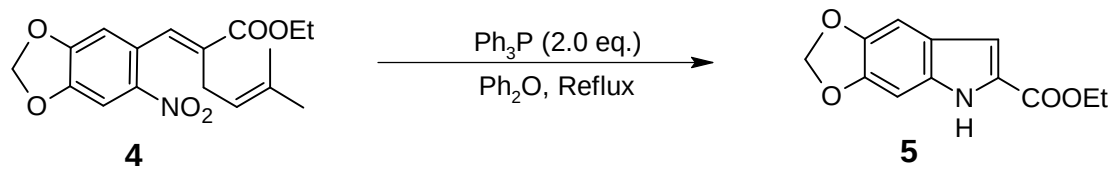
Experimental

3.9 Preparation of Compound **4**



Please refer Chapter 2, Expt. No. 2.3.

3.10 Preparation of Ethyl-5,6-methylenedioxyindole-2-carboxylate (**5**)



A mixture of compound **4** (0.333 g, 1 mmol) and triphenyl phosphine (0.524 g, 2.0 mmol) in diphenyl ether (10 mL) was heated under reflux for 4.0 hrs. The progress of the reaction was monitored by TLC. Diphenyl ether was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel using hexanes:EtOAc (8:2) as an eluent to give ethyl-5,6-methylenedioxyindole-2-carboxylate (**5**) (0.075 g, 32%), m.p. 174-176 ^{o}C.

Conclusion

An attempt has been made to synthesise α-prenyl indole nucleus, which actually lead to the synthesis of ethyl-5,6-methylenedioxyindole-2-carboxylate.

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CHAPTER 4

CHAPTER 4

Graphite catalyzed conjugate addition of indole and 2-methyl indole to electron deficient olefins

Introduction

Indole and many of its derivatives are present in many substances commonly found in nature,[1] as well as in many compounds that show pharmacological and biological activities.[2] Because of this, indoles and their derivatives have great importance in synthetic organic chemistry. The 3-position of indole is the preferred site for the electrophillic substitution reaction as discussed in chapter 3, section B. The resultant products 3-alkyl or acyl indoles are versatile intermediates for the synthesis of a wide range of indole derivatives.[3]

In recent years, catalytic Michael-type additions of indoles to nitro olefins have emerged as a powerful method for the formation of new C-C bonds in organic synthesis. Nitro olefins are very attractive Michael acceptors because the nitro group is the strongest electron-withdrawing group known[4] and can serve as a masked functionality. This *synthetic chameleon* can be transformed in to different functionalities after the Michael addition has taken place.[5] Hence, 2-indolyl-1-nitroalkanes are the highly versatile intermediates[6] for the preparation of several classes of biologically active compounds such as melatonin analogues,[7] 1,2,3,4-tetrahydro-β-carbolines (THBCs)[8] and triptans[9] (**Fig. 1**).

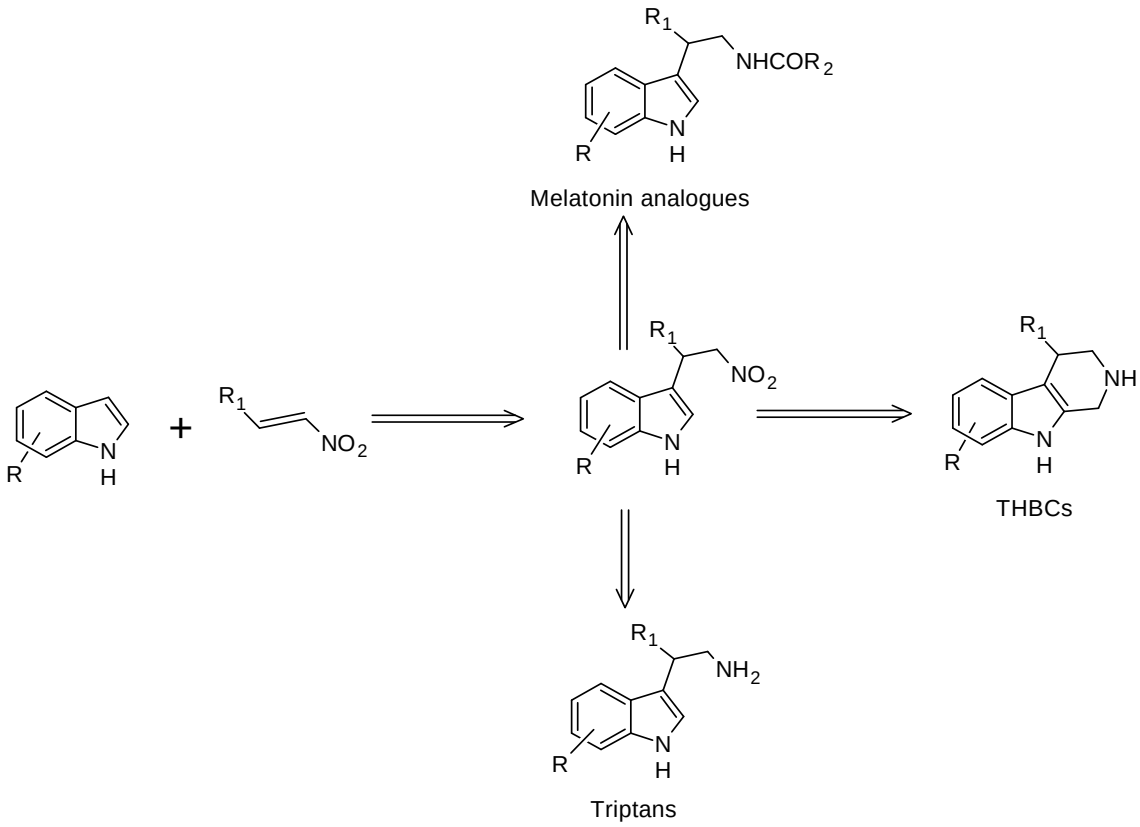
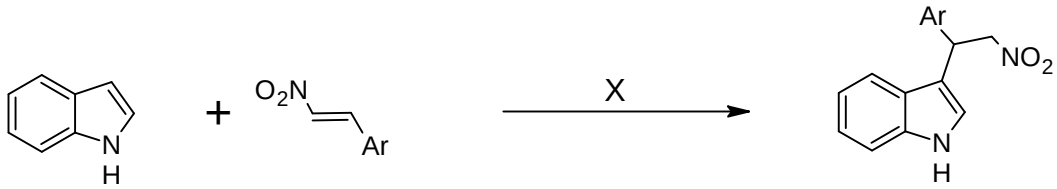

R1
NHCOR2
N
H
R
Melatonin analogues
R1
NO2
R
N
H
R1
NO2
R
N
H
R1
NH
R
N
H
THBCs
R1
NH2
R
N
H
Triptans

Fig. 1

A Literature Review

Some literature pertaining to the conjugate addition of indole to nitrostyrenes is reviewed below (**Scheme I** and **Table 1**). However, many of these reported procedures involve strongly acidic conditions, expensive reagents and laborious isolation of the target products. Furthermore, acid catalyzed conjugate addition of indoles requires careful control of the acidity to prevent side reactions, such as dimerization or polymerisation.



Scheme I

Table 1

Sr. No.	X	Reference
1	$Yb(OTf)_3$ (2.5 mol%), CH_3CN	10
2	$InCl_3$, CH_2Cl_2, r.t.	11
3	$InBr_3$ (5 mol%), THF/H_2O	12
4	$Sc(OTf)_3$ (5 mol%), 1-Dodecyloxy-4-heptadecafluorooctyl benzene (4g/L), CO_2, 50 ^oC, 15 MPa	13
5	*Bis*-arylureas or bis-arylthiourease, r.t., toluene or solventless	14
6	10 mol% SmI_3, CH_3CN, Reflux	15
7	Chiral *bis*-sulfonamide (2 mol%), $CHCl_3$	16
8	10 mol% SmI_3, M.W., silica gel support	17
9	Chiral [Salen AlCl] complex, pyridine, DCM	18
10	$[Al(DS)_3].3H_2O$, water, r.t.	19
11	$CeCl_3.7H_2O$, NaI, SiO_2, r.t.	20,21
12	I_2, ether, r.t.	22
13	Thiourea-based organocatalyst (20 mol%), CH_2Cl_2, -24 ^oC	23
14	M.W., 800 W, Silica gel	24,25
15	$H_3PW_{12}O_{40}$, water, r.t.	26

Sr. No.	X	Reference
16	10 mol% $Zn(OTf)_2$, 12 mol% (*s*)-Ph-bisoxazoline, Toluene, 0 ^oC	27
17	Basic Al_2O_3, 60 ^oC	28
18	10 mol% sulfamic acid, 60 ^oC	29
19	Carbohydrate-Based Tolylsulfonyl Hydrazine (10 mol%), water, r.t.	30
20	Silica sulfuric acid, EDC, r.t.	31
21	Water, 100 ^oC	32
22	Tetrabutylammonium hydrogen sulphate (TBAHS) (50 mol%), water	33
23	NBS (10 mol %), CH_2Cl_2, 40 ^oC	34
24	MW, Water	35

Present work

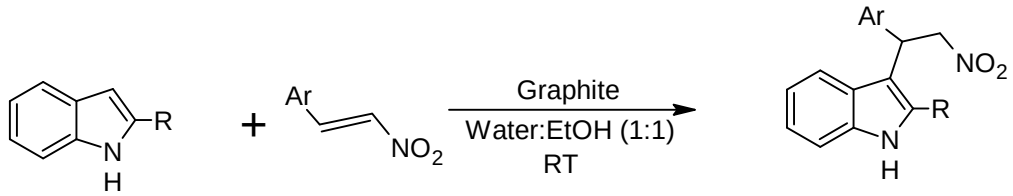
Although the Michael addition of nucleophilic indoles to nitroalkenes has been well studied, the area is far from fully explored. Environmental concerns in research and industry are increasing with the increasing pressure to reduce the amount of pollutants produced, including organic solvents whose recovery is mandated by ever more strict laws. Hence the challenge for a sustainable environment calls for the use of clean procedures to avoid the use of harmful reagents and solvents.

In recent years graphite has found its use in organic transformations. It is found to be an effective catalyst for Friedel-Craft alkylation[36] & acylation[37] reactions, Diels Alder reaction,[38] and conversion of aldehydes into nitriles[39]. It is also reported for hydrogenation of olefins using potassium graphite intercalates.[40] Taking into consideration its ability to act as a catalyst (Lewis acid), we thought to exploit it for the above Michael-type additions of indoles to electron deficient olefins.

To start with we first mixed indole and nitrostyrene (1:1 mole) in ethanol as a solvent. Checking (TLC) that no reaction takes place by stirring the reaction mixture we added 100 mg of graphite (flakes, Aldrich chemicals) and continued stirring the reaction mixture further. However after prolonged stirring we could not notice (TLC) any product formation. Next, we tried the reaction other solvents like dioxane, dichloromethane, chloroform, toluene, THF and methanol. In none of these cases we could observe (TLC) any product formation. Further, we attempted the reaction in water (universal solvent) where we found that reaction does take place (TLC). However, reaction could not go to completion as reaction mass was sticking to the stirring needle as reactants and product are insoluble in the medium. The observation of formation of product suggested that indeed graphite is acting as a catalyst. To further confirm this observation one reaction in water without graphite was repeated where after prolonged stirring we could observe trace amount product formation. This suggested that for the reaction to take place water is essential and graphite is accelerating the reaction. So, we tried different combination in different ratio of water miscible solvents (THF-water, dioxane-water, methanol-water and ethanol-water). The ideal solvent water combination ratio was found to be 1:1 where the reaction mixture remained homogenous and the reaction could go to completion (TLC, after

consumption of nitrostyrene) in a shorter time. Of the solvent combination considering the toxicity and the price we chose ethanol-water combination for further study. Next, the effect of catalyst loading was also investigated. For 0.67 mmol of indole and 0.56 mmol of nitrostyrene, when 25 mg of graphite was used reaction took 15.0 hrs for completion. But when graphite quantity was increased to ≥ 50 mg, the reaction got completed in 12.0 hrs.

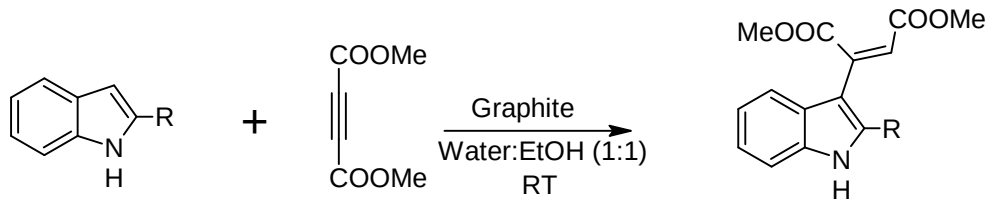
In a typical experiment, indole/2-methyl indole (0.56 mmol) was stirred with nitrostyrene (0.67 mmol) in presence of graphite (0.05 g) at room temperature in water:EtOH (1:1) (6 mL) mixture till completion of the reaction (monitored by TLC for consumption of nitrostyrene) (**Scheme II & III**). Using this methodology indole/2-methyl indole (**1a-b**) and various substituted nitrostyrenes/acetylene dicarboxylate (**2a-g**) were reacted smoothly to afford the corresponding 3-alkylated product (**3a-n**). The structure of these products was confirmed by its IR, ^{1}H-NMR and ^{13}C-NMR spectra. The results are summarized in **Table 2**. Overall it is observed that the 2-methyl indole reacts faster and gives comparatively better yield than the parent indole.



1a-b **2a-f** **3a-l**

R = H, CH_3

Scheme II

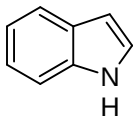
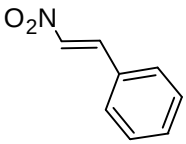
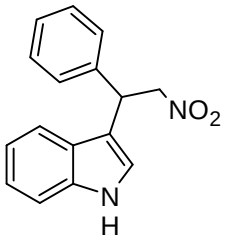
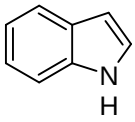
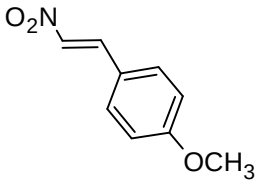
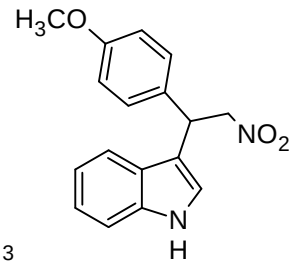
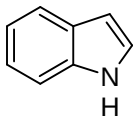
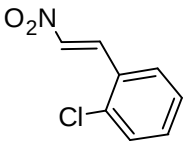
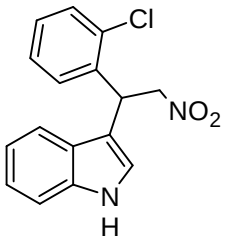
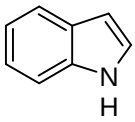
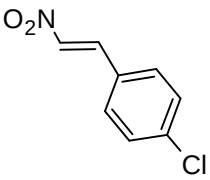
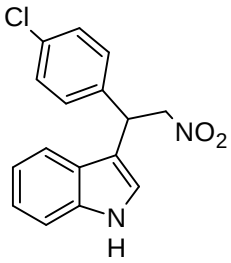
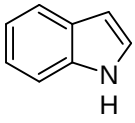
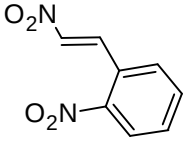
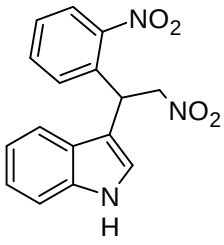


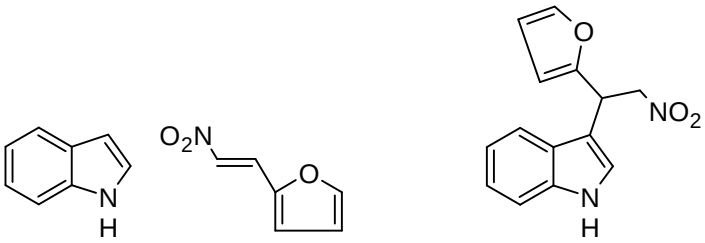
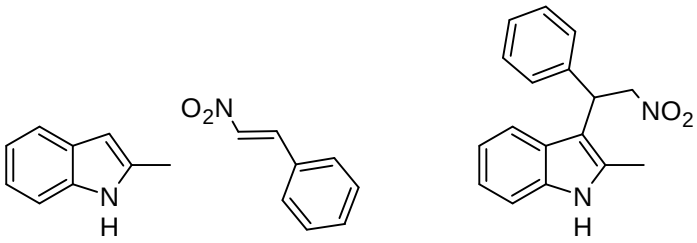
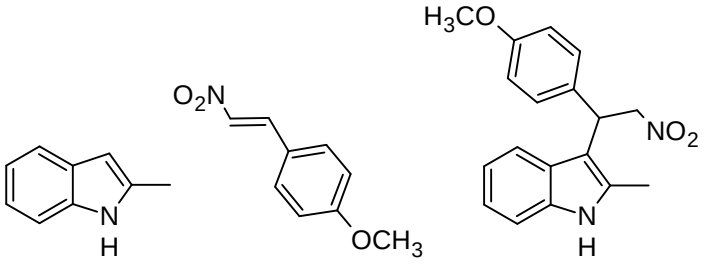
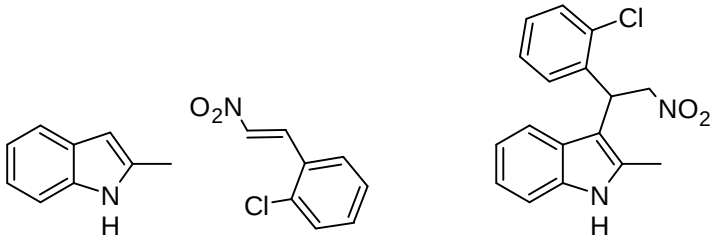
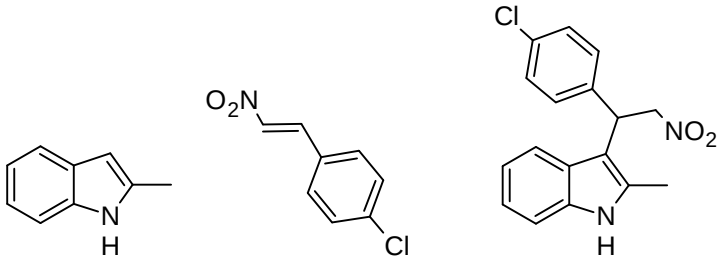
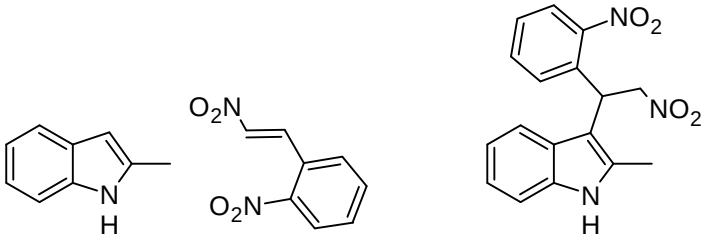
1a-b **2g** **3m-n**

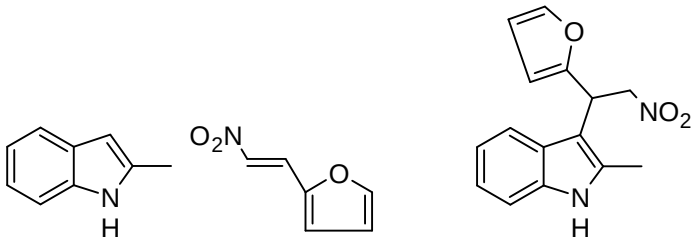
R = H, CH_3

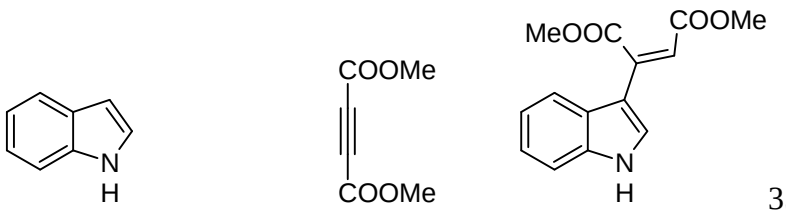
Scheme III

Table 2

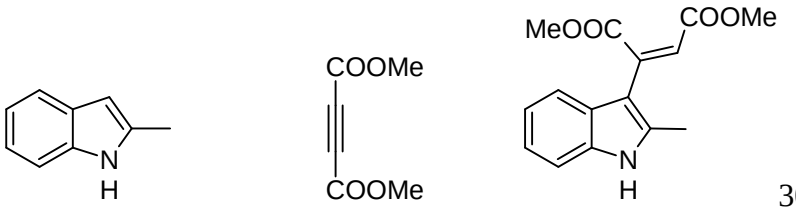
Entry	Nucleophile (**1**)	Electrophile (**2**)	Product (**3**)	Time	Yield (%)
a				7.0 hrs	41%
b				12.0 hrs	42%
c				10.0 hrs	37%
d				9.0 hrs	62%
e				8.0 hrs	40%

f		12.0 hrs	38%
g		8.0 hrs	65%
h		40 mins.	54%
i		50 min.	59%
j		35 min.	46%
k		30 min.	42.5%

l  30 min. 35%

m  35 min.

51.5%

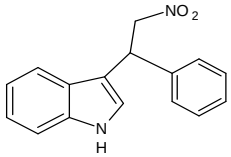
n  30 min.

90%

The yield of the product is based on nitrostyrene consumed. The most of the nitrostyrene probably gets polymerized (a spot at the base of TLC noticed which we were never able to get in a pure form from column). The unreacted indole was recovered in all experiments. Based on recovered indole the yields are always above 80%. Nitrostyrene in absence of indole do not get polymerised under the experimental conditions. This suggest that indole first adds to nitrostyrene and then the inertmediate goes on adding in a conjugate manner leading to polymerization. We have also recycled the graphite for five cycles. However, the low yields of the product makes our route unattractive *vis-à-vis* other literature methods though the method is attractive in terms of green chemistry principles. Further studies are required to know the exact fate of nitrostyrene and to make the route attractive. We also tried addition reaction of indole with other electron deficient elcrophiles like methyl vinyl ketone, chalcone, cinnamaldehyde, coumarin, methyl cinnamate, acrylonitrile, phenyl propynoic acid, methyl(2*E*)-3-(2-nitrophenyl)acrylate, (2*E*)-3-(4-methoxyphenyl) acrylic acid and diethyl fumarate without any success.

Spectral Data

Compound **3a**



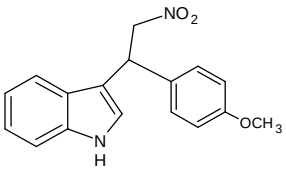
Colourless viscous liquid.

IR (KBr): 3427, 1556, 1379 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.97 (dd, *J* = 8.1 & 12.3 Hz, 1H), 5.10 (dd, *J* = 7.8 & 12.3 Hz, 1H), 5.22 (dd, *J* = 7.8 & 8.1 Hz, 1H), 7.07-7.48 (m, 10H), 8.12 (br.s., 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 41.57, 79.54, 111.37, 114.49, 118.93, 119.97, 121.61, 122.70, 126.13, 127.55, 127.76, 128.05, 128.55, 128.91, 136.53, 139.23.

Compound **3b**



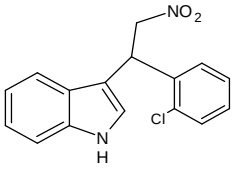
White solid; mp 148-150 ^{o}C.

IR (KBr): 3379, 1546, 1377 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.80 (s, 3H), 4.92 (dd, *J* = 7.5 & 12.0 Hz, 1H), 5.07 (dd, *J* = 7.5 & 12.0 Hz, 1H), 5.16 (dd, *J* = 7.5 & 8.4 Hz, 1H), 6.86-7.47 (m, 9H), 8.11 (br.s., 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ = 40.45, 55.41, 79.83, 111.92, 114.24, 118.87, 119.04, 121.74, 122.52, 126.42, 129.30, 133.02, 136.10, 136.64, 158.56.

Compound **3c**



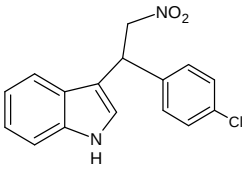
Pale pink solid; mp 104-106 ^{o}C.

IR (KBr): 3412, 1541, 1379 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.98-5.08 (m, 2H), 5.77 (dd, *J* = 7.5 Hz, 1H), 7.08-7.25 (m, 7H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 8.15 (br.s., 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 37.97, 77.70, 111.36, 113.28, 118.92, 120.03, 121.94, 122.78, 126.18, 127.26, 128.82, 128.96, 130.14, 133.85, 136.48.

Compound **3d**



Pale pink solid; mp 102-104 ^{o}C.

IR (KBr): 3408, 1543, 1381 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) (**Fig. I**) : δ = 4.93 (dd, *J* = 8.4 & 12.45 Hz, 1H), 5.08 (dd, *J* = 7.5 & 12.45 Hz, 1H), 5.2 (t, *J* = 7.8 Hz, 1H), 7.05 (d, *J* = 2.1 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.20-7.30 (m, 5H), 7.41 (t, *J* = 7.5 Hz, 2H), 8.14 (br.s., 1H).

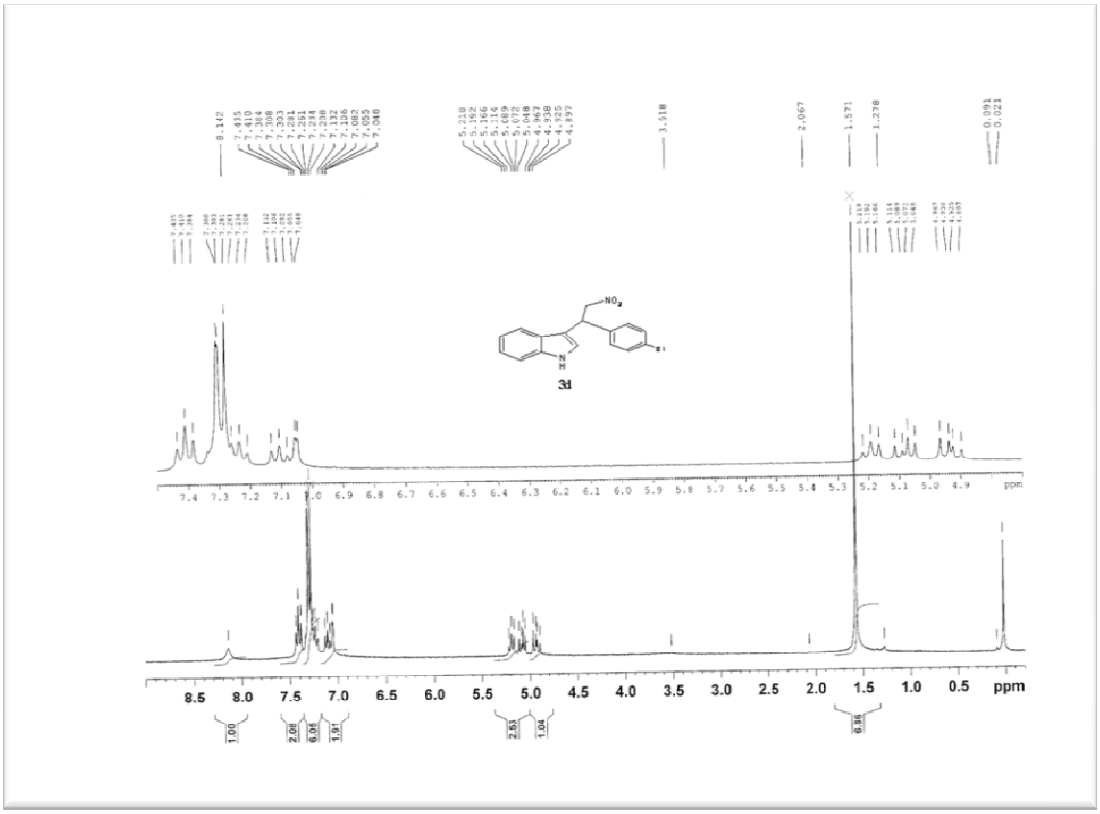


Fig. I : ^{1}H-NMR spectrum of Compound **3d**

^{13}C-NMR (100 MHz, $CDCl_3$) (**Fig. II**) : δ = 40.94, 79.26, 111.46, 113.93, 118.77, 120.08, 121.50, 122.85, 125.88, 129.08, 129.11, 133.40, 136.49, 137.73.

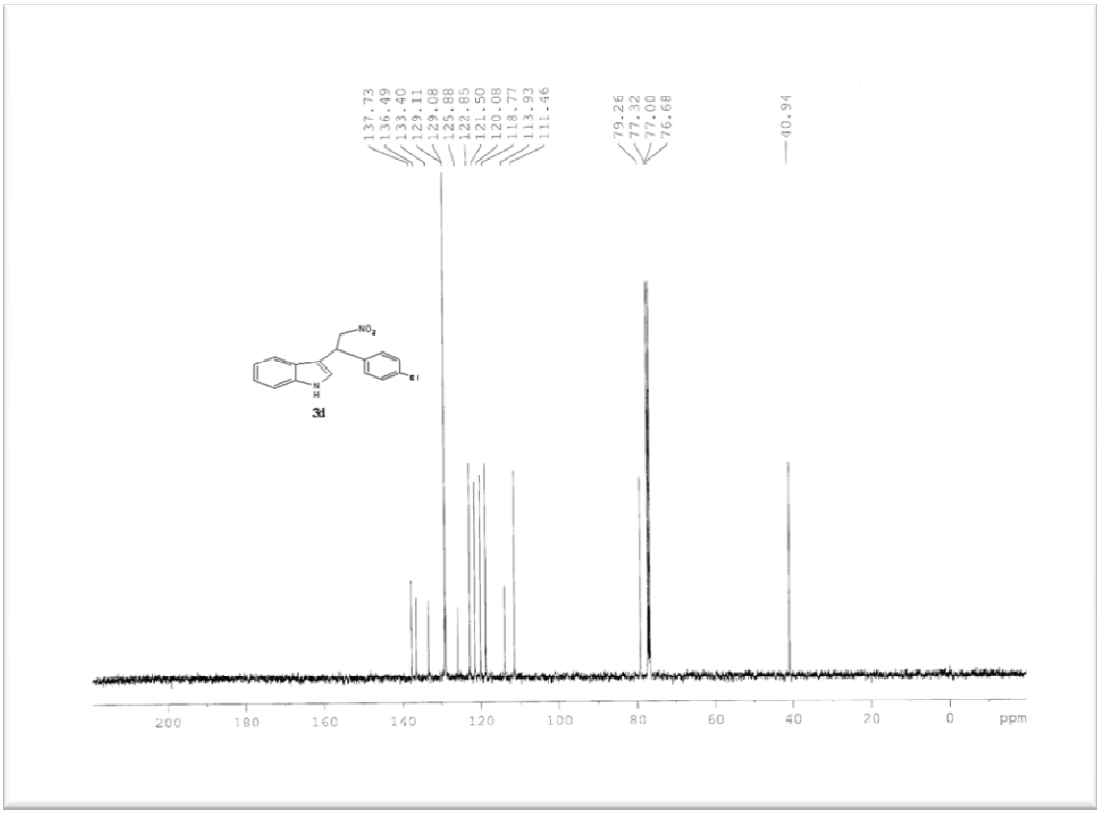
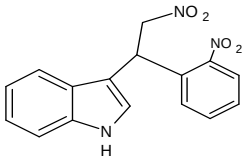


Fig. II : ^{13}C-NMR spectrum of Compound **3d**

Compound **3e**



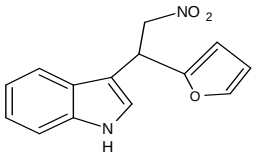
Pale pink solid; mp 115-117 ^{o}C.

IR (KBr): 3419, 1556, 1373 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.06-5.20 (m, 2H), 5.90 (dd, *J* = 6.6 & 7.8 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.18-7.55 (m, 7H), 7.93 (d, *J* = 7.5 Hz, 1H), 8.19 (br.s., 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 36.42, 78.12, 111.46, 112.74, 118.62, 120.21, 122.04, 122.93, 125.05, 125.86, 128.57, 129.91, 133.17, 133.72, 136.44, 149.61.

Compound **3f**



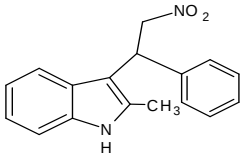
Yield: 85%; white solid; mp 96-98 ^{o}C.

IR (KBr): 3417, 1556, 1377 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.94 (dd, *J* = 7.5 & 12.3 Hz, 1H), 5.08 (dd, *J* = 8.1 & 12.6 Hz, 1H), 5.28 (t, *J* = 7.5 Hz, 1H), 6.19 (d, *J* = 3.0 Hz, 1H), 6.33 (m, 1H), 7.13-7.41 (m, 5H), 7.58 (d, *J* = 7.8 Hz, 1H), 8.23 (br.s., 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 35.75, 77.91, 107.41, 110.49, 111.53, 111.79, 118.75, 120.14, 122.71, 125.76, 136.37, 142.28, 152.24.

Compound **3g**



Pale yellow solid; mp 90-92 ^{o}C.

IR (KBr): 3396, 1546, 1377 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) (**Fig. III**) : δ = 2.39 (s, 3H), 5.10 (dd, *J* = 6.8 & 10.0 Hz, 1H), 5.17-5.25 (m, 2H), 7.02 (dt, *J* = 1.2 & 7.6 Hz, 1H), 7.10 (dt, *J* = 1.2 & 8.0 Hz, 1H), 7.22-7.32 (m, 6H), 7.36 (dd, *J* = 7.6 & 7.2 Hz, 1H), 7.86 (br.s., 1H).

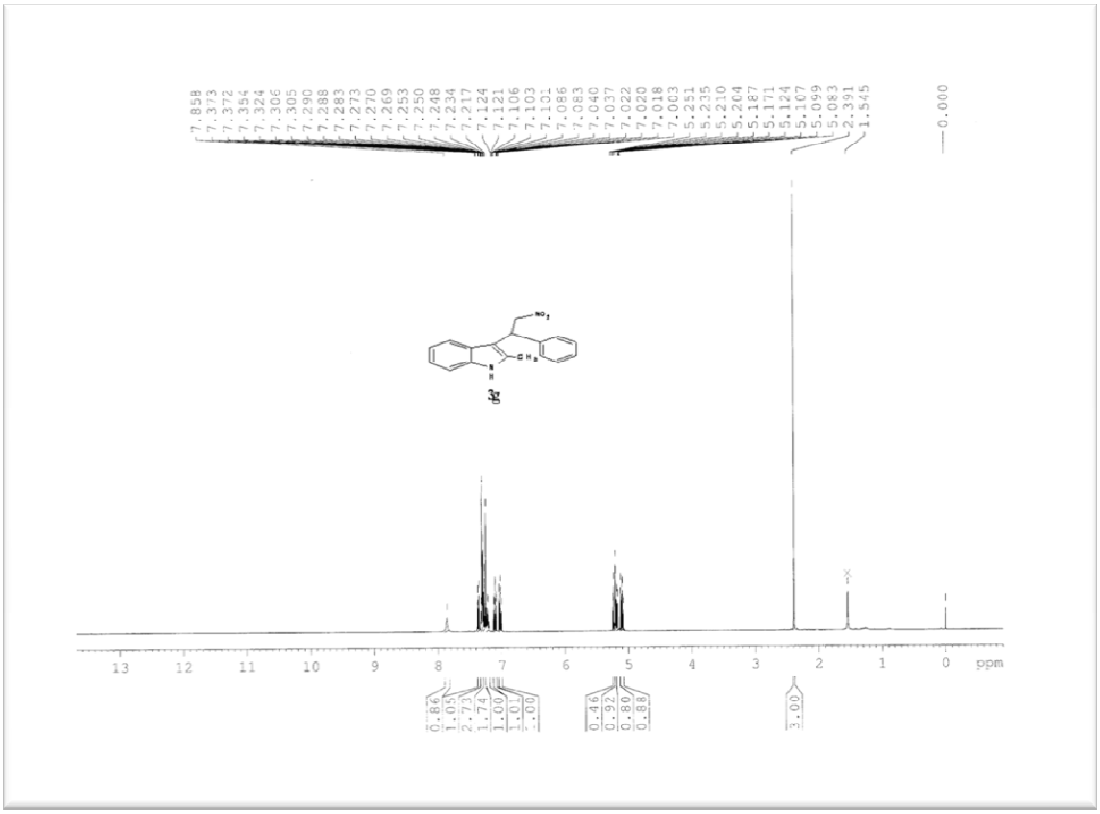


Fig. III : ^{1}H-NMR spectrum of Compound **3g**

^{13}C-NMR (100 MHz, $CDCl_3$) (**Fig. IV**) : δ = 12.03, 40.43, 78.61, 108.95, 110.65, 118.60, 119.76, 121.36, 126.88, 127.06, 127.29, 128.76, 132.78, 135.41, 139.50.

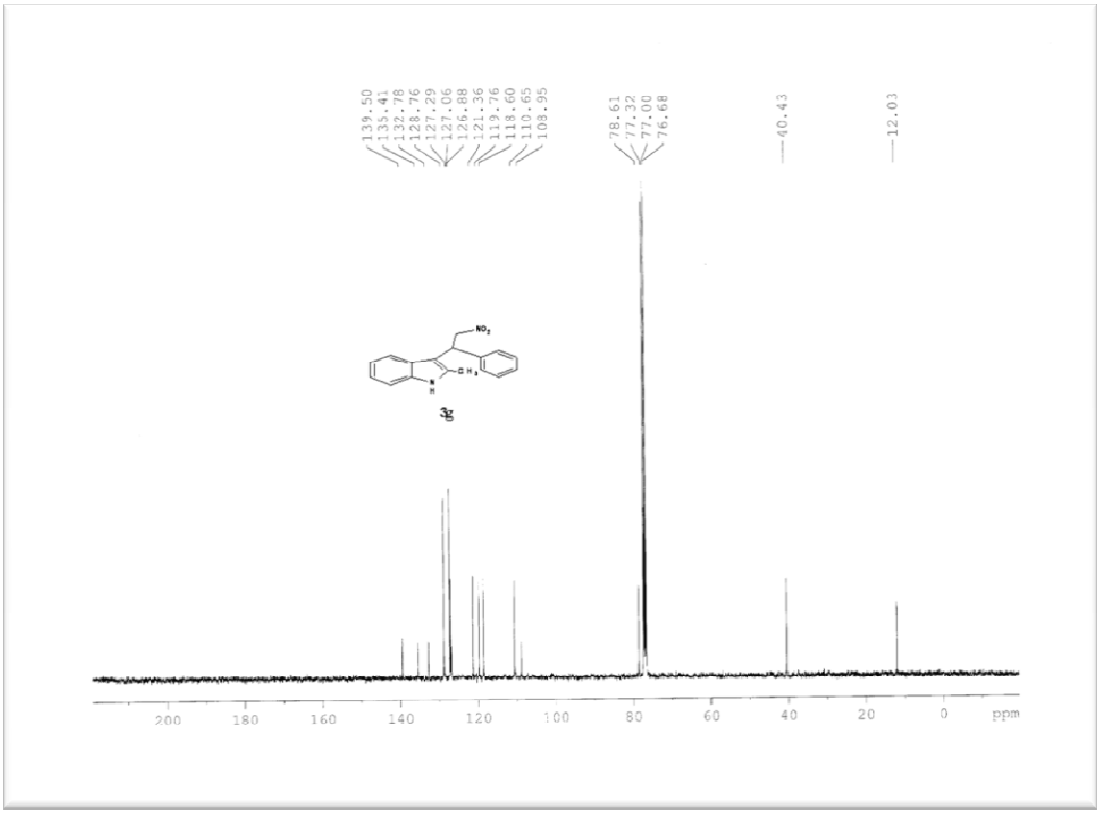
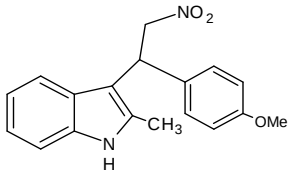


Fig. IV : ^{13}C-NMR spectrum of Compound **3g**

Compound **3h**



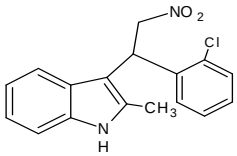
Pale pink solid; mp 114-116 ^{o}C.

IR (KBr): 3425, 1544, 1382 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.75 (s, 3H), 5.07 (dd, *J* = 6.8 & 8.8 Hz, 1H), 5.13 (dd, *J* = 6.4 Hz, 1H), 5.18 (dd, *J* = 5.6 & 8.8 Hz, 1H), 6.80-7.37 (m, 8H), 7.86 (br.s., 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.97, 39.75, 55.20, 78.83, 109.04, 110.63, 114.07, 118.60, 119.67, 121.26, 126.81, 128.32, 131.45, 132.66, 135.36, 158.46, 176.47.

Compound **3i**



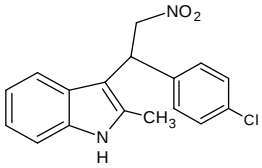
Pale yellow solid; mp 147-149 ^{o}C.

IR (KBr): 3375, 1544, 1377 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 5.13 (d, *J* = 2.4 Hz, 1H), 5.15 (s, 1H), 5.48-5.52 (m, 1H), 7.04 (dt, *J* = 1.2 & 8.0 Hz, 1H), 7.10 (dt, *J* = 1.2 & 8.0 Hz, 1H), 7.16-7.26 (m, 3H), 7.37 (dd, *J* = 1.6 & 7.2 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.53 (dd, *J* = 2.0 & 7.2 Hz, 1H), 7.87 (br.s., 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 12.23, 38.40, 77.13, 106.95, 110.73, 110.78, 118.45, 119.81, 121.26, 127.02, 127.05, 128.60, 130.32, 133.57, 133.99, 135.37, 136.60.

Compound **3j**



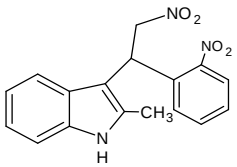
Pale yellow solid; mp 152-154 ^{o}C.

IR (KBr): 3415, 1543, 1386 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 5.06 (dd, *J* = 7.2 & 10.4 Hz, 1H), 5.14 (d, *J* = 6.8 & 7.2 Hz, 1H), 5.19 (dd, *J* = 6.8 & 10.4 Hz, 1H), 7.03 (dt, *J* = 1.2 & 7.6 Hz, 1H), 7.11 (dt, *J* = 1.2 & 7.6 Hz, 1H), 7.22-7.28 (m, 5H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.91 (br.s., 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.99, 39.88, 78.39, 108.45, 110.77, 118.38, 119.89, 121.51, 126.62, 128.66, 128.89, 132.84, 132.92, 135.40, 138.03.

Compound **3k**



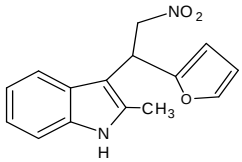
Yellow solid; mp 162-165 ^{o}C.

IR (KBr): 3387, 1550, 1369 cm^{-1} (C=O).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 5.10 (q, *J* = 8.8 Hz, 1H), 5.23 (q, *J* = 7.2 Hz, 1H), 5.92 (t, *J* = 8.4 Hz, 1H), 6.99-7.79 (m, 8H), 7.90 (br.s., 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.91, 36.13, 106.87, 110.85, 117.88, 120.04, 121.49, 125.31, 126.73, 128.28, 128.47, 132.72, 133.91, 134.04, 135.36, 149.71.

Compound **3l**



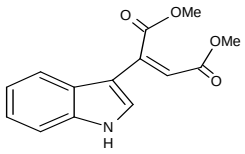
White solid; mp 82-84 ^{o}C.

IR (KBr): 3396, 1546, 1381 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 4.89-4.96 (m, 1H), 5.16-5.22 (m, 2H), 6.07-7.37 (m, 7H), 7.88 (br.s., 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 11.79, 35.27, 106.55, 107.24, 110.45, 110.64, 118.55, 119.75, 121.47, 126.60, 133.10, 135.38, 141.97, 152.28.

Compound **3m**



Yellow solid; mp 86-88 ^{o}C.

IR (KBr): 3388, 1732, 1714 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) (**Fig. V**) : δ = 3.64 (s, 3H), 3.86 (s, 3H), 6.95 (s, 1H), 7.12-7.23 (m, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.56 (d, *J* = 2.7 Hz, 1H), 8.50 (br.s., 1H).

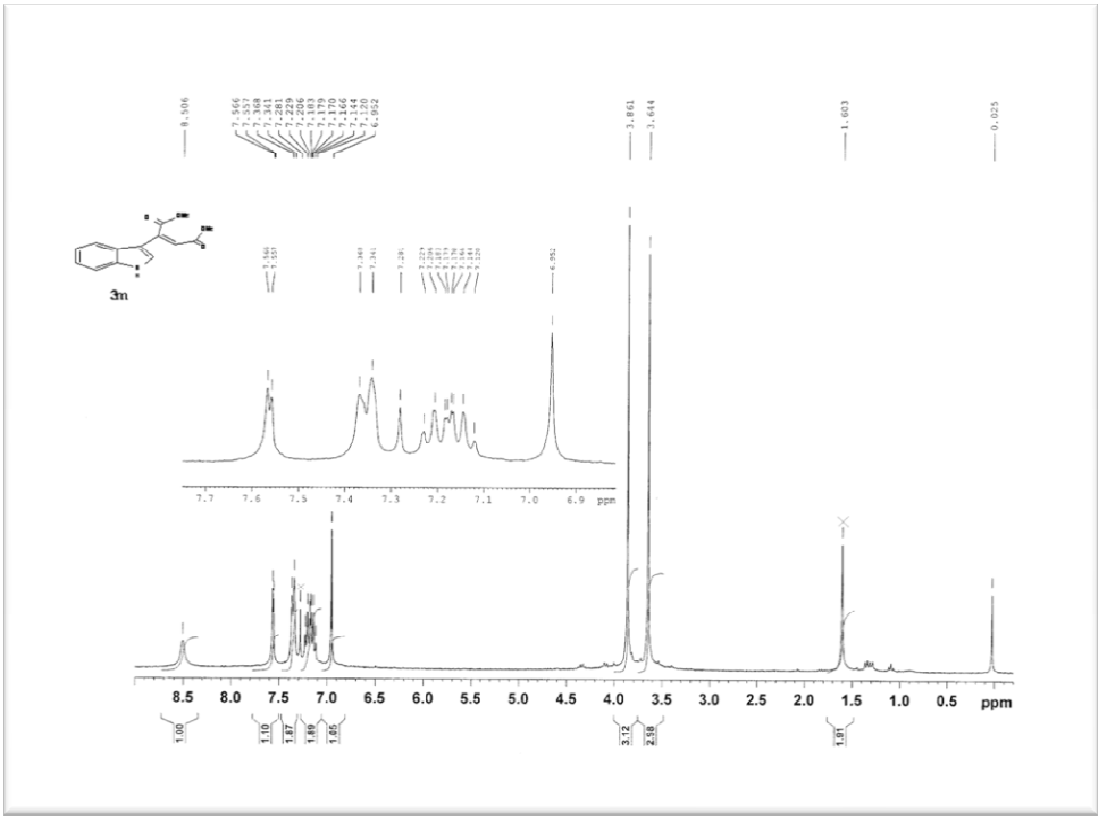


Fig. V : ^{1}H-NMR spectrum of Compound **3m**

^{13}C-NMR (100 MHz, $CDCl_3$) (**Fig. VI**) : δ = 51.83, 52.79, 108.82, 111.61, 119.39, 120.44, 122.27, 124.71, 126.32, 127.56, 135.63, 137.77, 166.48, 167.97.

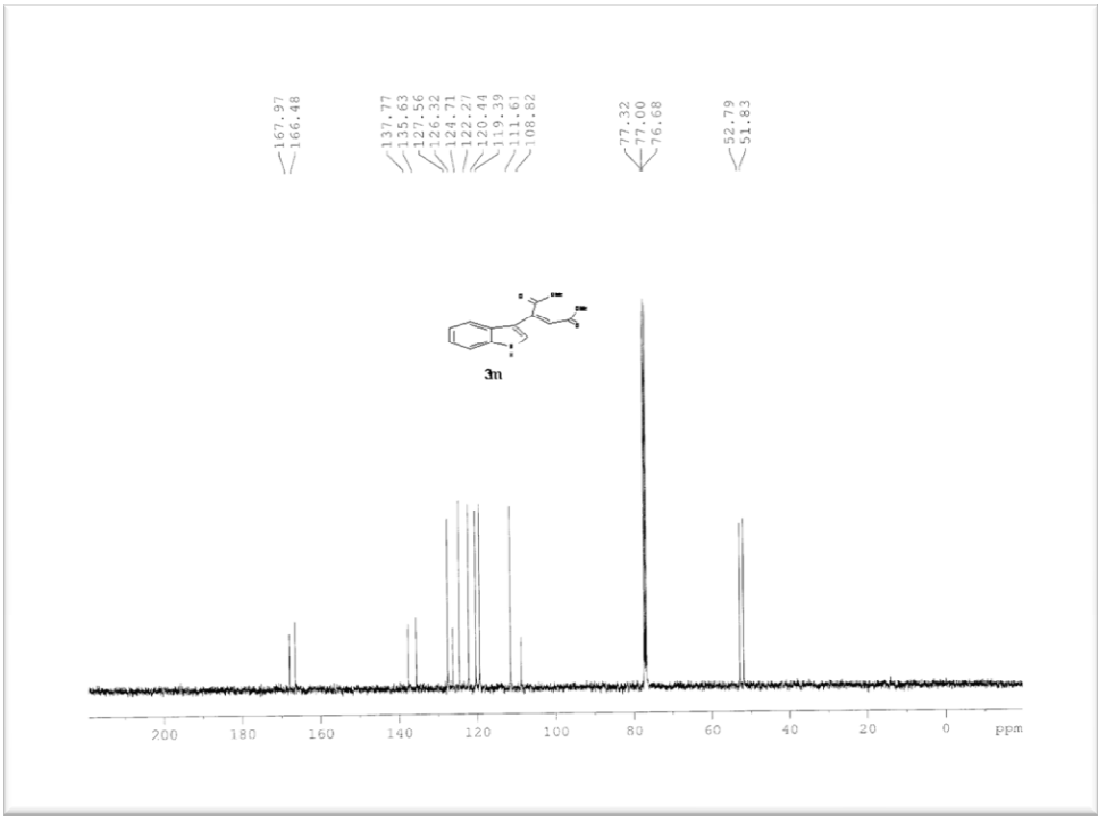


Fig. VI : ^{13}C-NMR spectrum of Compound **3m**

HRMS (**Fig. VII**) : *m/z* found 282.0744. Calcd for $C_{14}H_{13}NO_4$, $(M+Na)^+$ 282.0742.

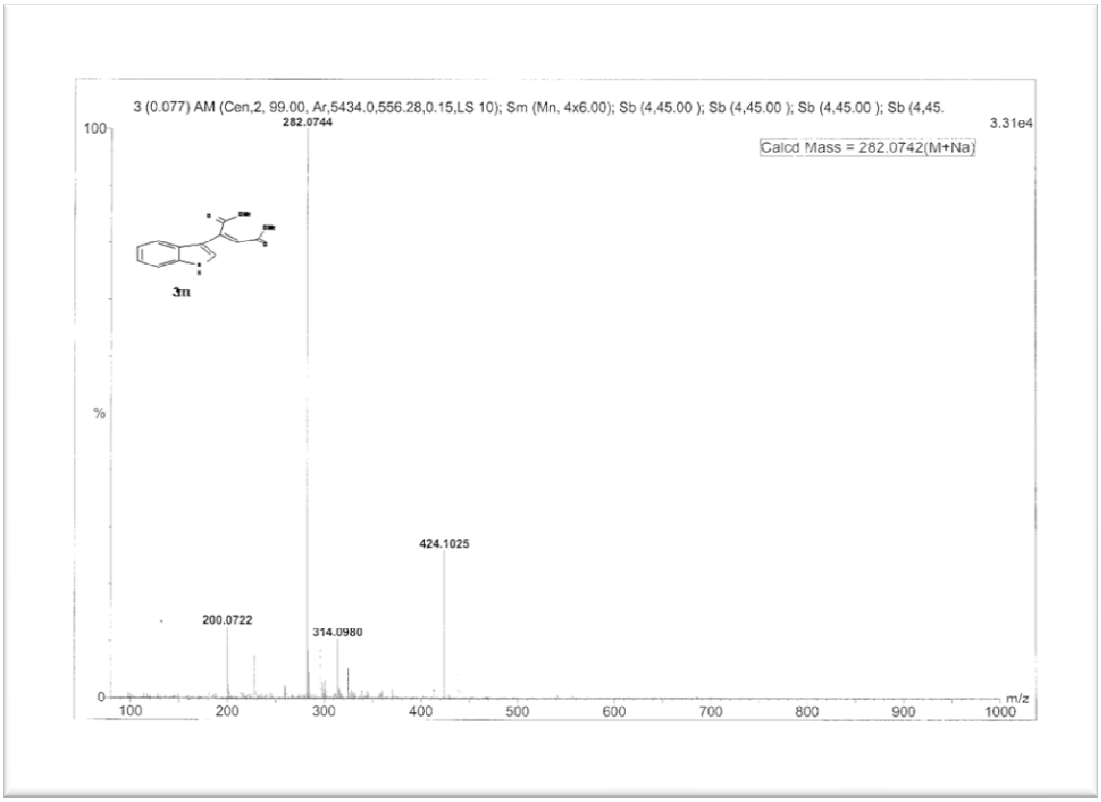
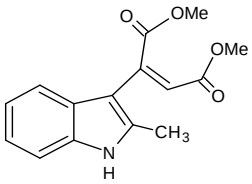


Fig. VII : HRMS spectrum of Compound **3m**

Compound **3n**



Yellow solid; mp 116-118 ^{o}C.

IR (KBr): 3371, 1720 cm^{-1}.

^{1}H-NMR (400 MHz, $CDCl_3$) (**Fig. VIII**) : δ = 2.12 (s, 3H), 3.61 (s, 3H), 3.78 (s, 3H), 7.02-7.25 (m, 5H), 8.24 (br.s., 1H).

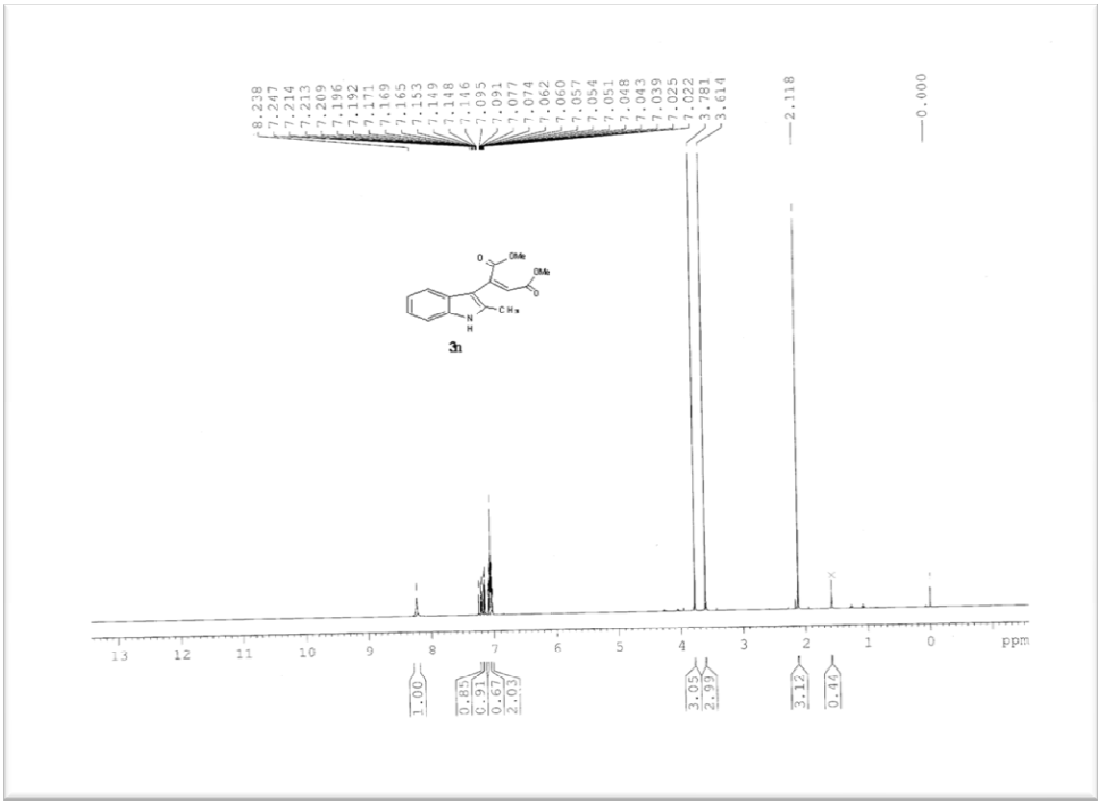


Fig. VIII : ^{1}H-NMR spectrum of Compound **3n**

^{13}C-NMR (100 MHz, $CDCl_3$) (**Fig. IX**) : δ = 12.73, 51.80, 52.76, 106.60, 110.65, 118.54, 120.03, 121.38, 127.36, 127.79, 135.10, 135.57, 138.53, 165.86, 167.86.

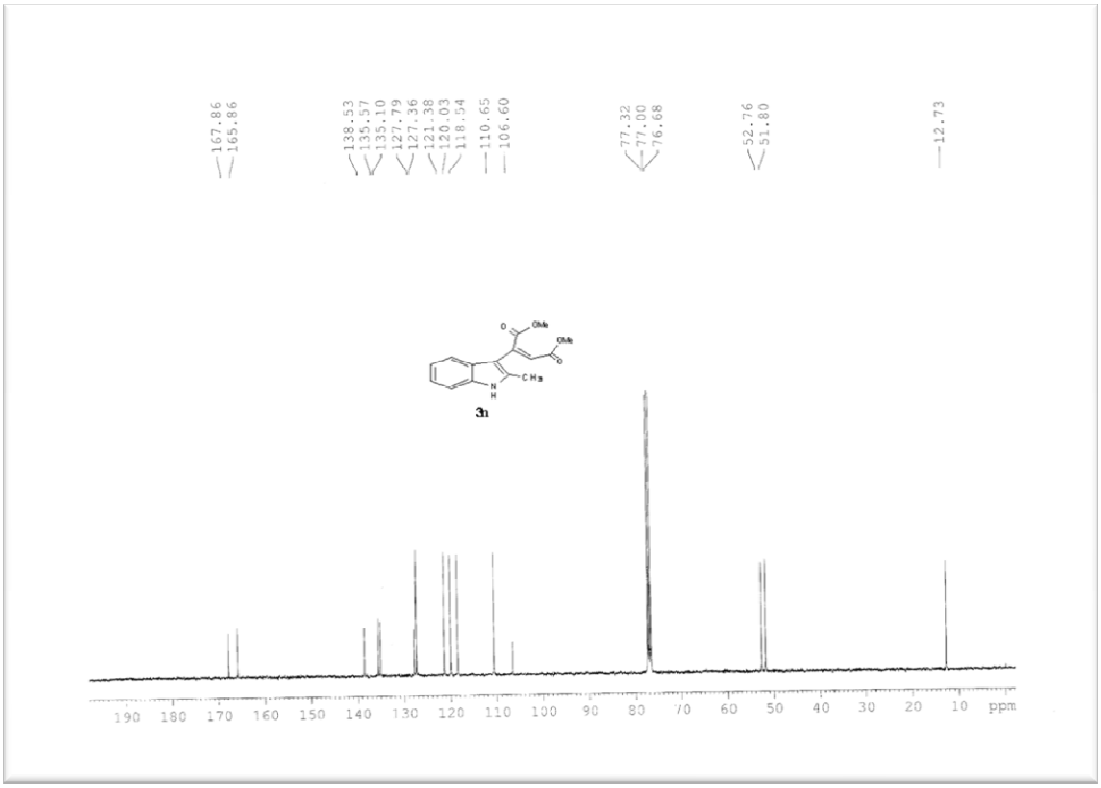


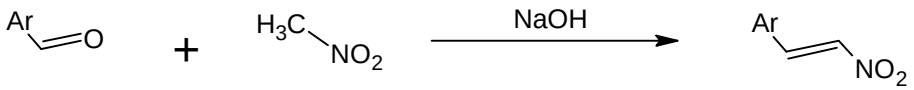
Fig. IX : ^{13}C-NMR spectrum of Compound **3n**

Conclusion

We have developed a graphite catalysed green methodology for the conjugate addition of indole and 2-methyl indole to nitrostyrenes in Water:EtOH (1:1) solvent at room temperature

Experimental

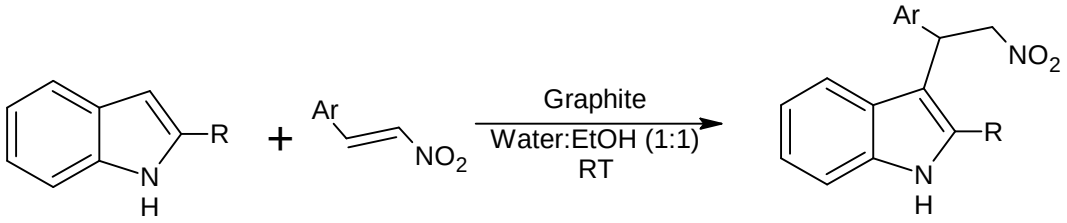
4.1 General procedure for the preparation of Nitrostyrenes (**2a-f**)



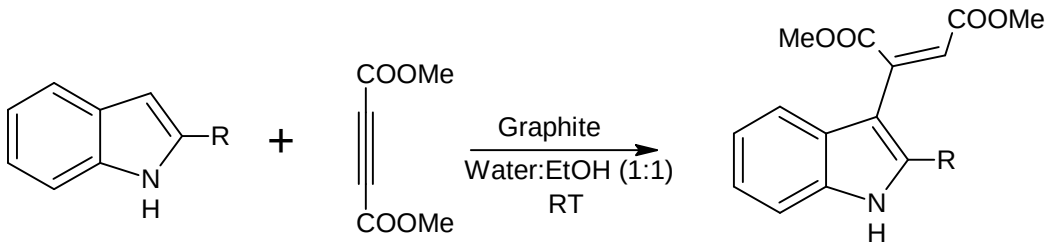
2a-f

A mixture of aldehyde (0.014 moles), nitromethane (0.014 moles) and methanol (3 mL) was cooled to -10 ^{o}C. To this cold NaOH solution (20%, 2 mL) was added dropwise with vigorous stirring maintaining the temperature at 10-15 ^{o}C. After 15 mins., a bulky white/pale yellow precipitate was observed. Temperature of the reaction mixture was decreased to -5 ^{o}C with ice cold water. It was then slowly poured in 4N HCl (7 mL). The resulting precipitate was filtered, washed with ice cold water, dried and the product obtained was weighed.

4.2 General procedure for the addition of indoles to electron deficient olefins (**3a-n**)



R	Ar	R	Ar
H	phenyl	Me	phenyl
H	p-methoxyphenyl	Me	p-methoxyphenyl
H	o-nitrophenyl	Me	o-nitrophenyl
H	o-chlorophenyl	Me	o-chlorophenyl
H	p-chlorophenyl	Me	p-chlorophenyl
H	2-furyl	Me	2-furyl



R = H, CH_3

A mixture of indole/2-methyl indole (**1a-b**) (0.67 mmol) (in case of acetylene dicarboxylate 0.56 mmol indole/2-methyl indole was used) and β-nitrostyrene/acetylene dicarboxylate (**2a-g**) (0.56 mmol) was dissolved in water:EtOH (1:1) (6 mL). To this 0.05 g graphite flakes were added and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, water (5 mL) was added. It was then filtered and extracted with diethyl ether (3 X 5 mL). The combined organic layer was dried over anhydrous sodium sulpate and concentrated to obtain the crude product. Further purification was achieved using column chromatography/flash chromatography using ethyl acetate and petroleum ether as an eluent. The % yield of the products obtained was found to be in between 35-90%.

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