SYNTHETIC STUDIES TOWARDS BIOACTIVE MOLECULES AND CATALYTIC CHEMICAL TRANSFORMATIONS

THESIS
SUBMITTED TO THE
UNIVERSITY OF PUNE
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

BY

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NOVEMBER 1998

Dedicated

To my dear Family Members

Form-A

CERTIFICATE

Certified that the work incorporated in the thesis entitled ***"Synthetic studies towards bioactive molecules and catalytic chemical transformations"*** *by* ***Mr. G.K. Jnaneshwara*** was carried out by him under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

V.H. Deshpande

18 Nov 1998
PUNE

V.H. Deshpande
Research Guide

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CHAPTER III :

Catalytic chemical transformations.

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Bhushan, G.Ravi, Ramesh, Raghavan, Phukan, Godwin, Dinesh, V.R. Hegde, Upadyaya, Milind, Gurunath, Shivshankar, Shivappa, Vincent, Sharmaji, Renu, Ethiraj, Manoj, Ghote, Bennur, Ms. Tripura, Gopal, Mrs. Chitra, Dr. Vijay Dhondge, Dr. (Ms.) P. K. Zubaidha, Dr. (Ms.) Shubhada, Sampaji for being an integral part of my student days, from whom I received help and support, fun and excitement in various ways, during the entire course of the investigation work presented in this thesis.

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Jnaneshwar G.K

JNANESHWAR. G.K

November, 1998

NCL, Pune.

General Remarks:

1. All melting points and boiling points are uncorrected and the temperatures are in the centigrade scale.

2. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.

3. Organic layers were dried over anhydrous sodium sulfate. All evaporations were carried out under reduced pressure on Buchi rotary evaporator.

4. TLC analysis was carried out on glass plates using silica gel GF-254 and the plates were analyzed by keeping in iodine or under UV light.

5. In cases where chromatographic purification was done, silica gel (60-120 mesh) was used as the stationary phase.

6. IR spectra were recorded on Perkin-Elmer Infrared Spectrophotometer Model 68B or on Perkin-Elmer 1615 FT Infrared spectrophotometer.

7. ^{1}H NMR and ^{13}C NMR were recorded on **Varian FT-80A** (20 MHz), **Bruker WH-90** (22.63 MHz), **Bruker AC-200** (50 MHz) or **Bruker MSL-300** (75 MHz). Figures in parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard.The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and bs = broad singlet.

8. Mass spectra were recorded at an ionization energy of 70eV on Finnigan MAT-1020, automated GC/MS instrument.

9. Microanalysis was carried out in the microanalytical section of NCL.

10. GLC was carried out Hewlett Packard 5890.

11. The compound numbers, scheme numbers and references given in each chapter refer to that particular chapter only.

Abbreviations

Ac	Acetyl
acac	acetoacetate
Ar	Aryl
Bu	Butyl
^{t}Bu	*tert*-Butyl
DBDMH	1,3-Dibromo-5,5'-dimethyl hydrontoin
NBS	*N*-Bromosuccinamide
DMAP	*N,N*-Dimethyl amino pyridine
DMF	*N,N*-Dimethyl formamide
DMS	Dimethyl Sulphate
DMSO	Dimethyl sulfoxide
EDC	Ethylene Dichloride
Et	Ethyl
FBAC	Floridian bryozan *amathia convoluta*
gm	Gram
hr	Hour
LAH	Lithium aluminium hydride
Me	Methyl
Ms	Methane sulfonyl
MS	Mass spectrum
Mg	Milli gram
MW	Microwave
M.P.	Melting point
Pd/C	Palladized Carbon
Ph	Phenyl
NaH	Sodium hydride
PPh_3	Triphenylphosphine
o- PPh_3	$_{o}$-Tolylphosphine
p-TSA	p-Toluene sulfonic acid
^{i}Pr	Isopropyl
Py	Pyridine
TBAB	Tetrabutylammonium bromide
TFA	Trifluoroacetic acid
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
Ts	Tosyl
TEA	Triethylamine

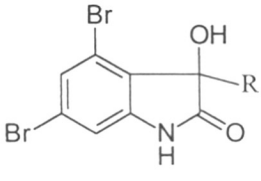
ABSTRACT

The Thesis entitled **"Synthetic studies towards Bioactive molecules and catalytic Chemical transformations"** is divided into three chapters.

CHAPTER I:

Synthesis of convolutamydine A, Microwave-assisted preparation of isatins:

Pettit and co-workers[1] isolated a new series of alkaloids convolutamydineA-D (1a-d) from the bryozoan *Amathia convoluta*, collected from Gulf of Mexico in Florida. It was extracted with EtOH and elaborate fractionation and chromatographic separation of the extract gave convolutamycine A[1] (**1a**, 8.6 x 10^{-6} %), B (**1b**, 10.7 x 10^{-6} %), C (**1c**, 6.0 x 10^{-7} %) and D (**1d**, 3 x 10^{-7} %) yield. These compound contains novel 4,6-dibromo-3-hydroxyoxindole unit with various substituents at C-3. The alkaloids exhibit a potent activity in the differentiation of HL-60 human promyetocytic leukemia cells. Synthesis of convolutamydineA **(1a)**. and micro-wave assisted general method for preparation of isatins are described.



1a R= CH_2COCH_3 A
1b = CH_2CH_2Cl B
1c = CH_3 C
1d = $CH=CH_2$ D

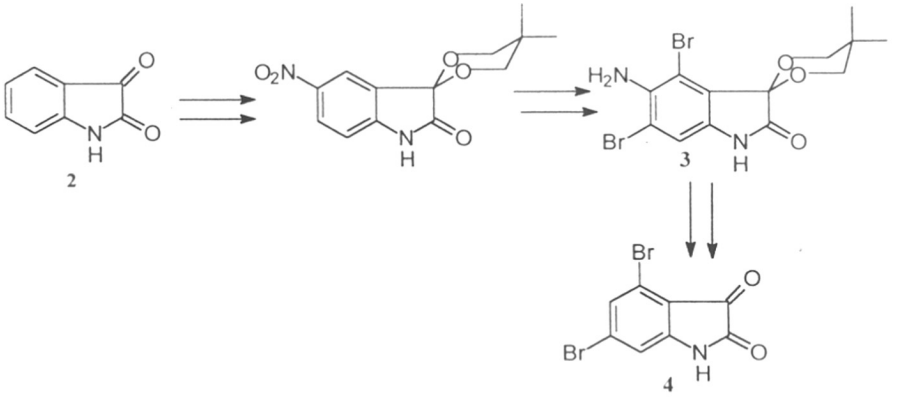
Section I:

Preparation of 4,6 -dibromoisatin :

Part I: Preparation of 4,6 -dibromoisatin (4) starting from Isatin

4, 6-Dibromoisatin is a key intermediate for the synthesis of convlutamydine A. Direct bromination of isatin gives undesired 5, 7-dibromoisatin. An approach to prepare 4, 6-dibromoisatin starting from isatin is described.

Scheme - 1:

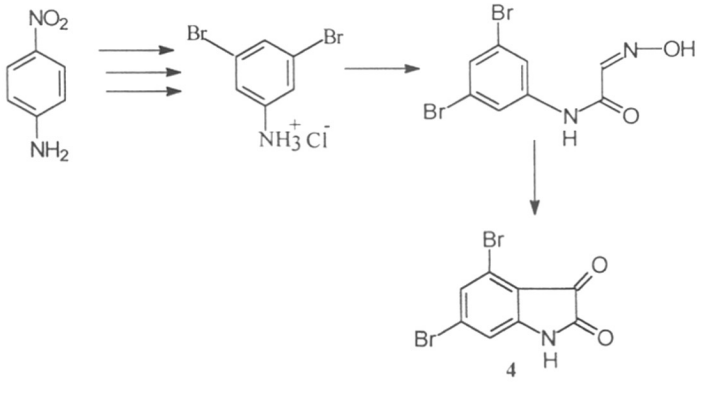


Isatin **(2)** was converted into 5- nitroisatin. Its protection followed by reduction and then bromination gave dibromoderivative **3** which was further converted into 4,6-dibromoisatin **(4)** by deamination and deprotection. **(Scheme-1)**

Part II: Preparation of 4,6 –dibromoisatin (4) from *p* –nitroaniline by microwave assisted method

p-Nitroaniline was converted into to 3,5-bromo-4–aminonitrobenzene. Its deamination followed by Raney nickel reduction gave 3,5 - dibromoaniline. Its isonitrosoacetanilide derivative was cyclised with sulfuric acid under microwave condition to give 4,6-dibromoisatin in good yield in 15-20 seconds. **(Scheme-2)**

Scheme-2:

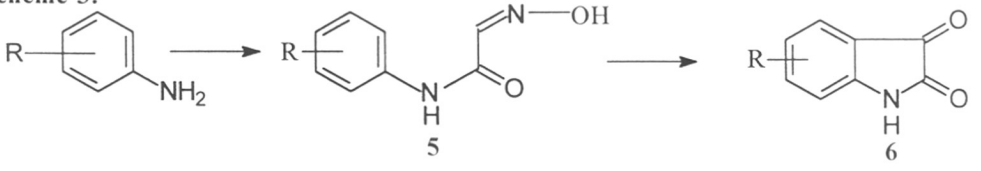


Section 2: Microwave assisted method for preparation of isonitrosoacetanilide 5 and isatin derivaties 6

Part-1: Preparation of isonitrosoacetanilide 5 and isatin 6

Different anilines were converted into intermediate isonitrosoacetanilides using micro- wave conditions in 15-25 seconds. Thus a mixture of aniline, chloral, hydroxylamine hydrochloride, sodium sulfate and catalytic amount of conc. HCl was irradiated in micro- wave oven for 15 seconds. The intermediates were cyclised with sulfuric acid either under microwave conditions or by heating, to give isatins.[2] **(Scheme-3)**

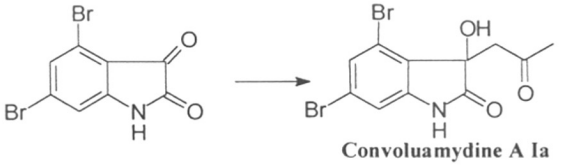
Scheme-3:



Part-II: Synthesis of convolutamydine A and its Fluoroderivative

The 4,6-dibromoisatin was subjected to aldol codensation with acetone in presence of different **(Scheme-4)** bases to give dl- convolutamydine A. **(1a)**

Scheme-4



Convoluamydine A Ia

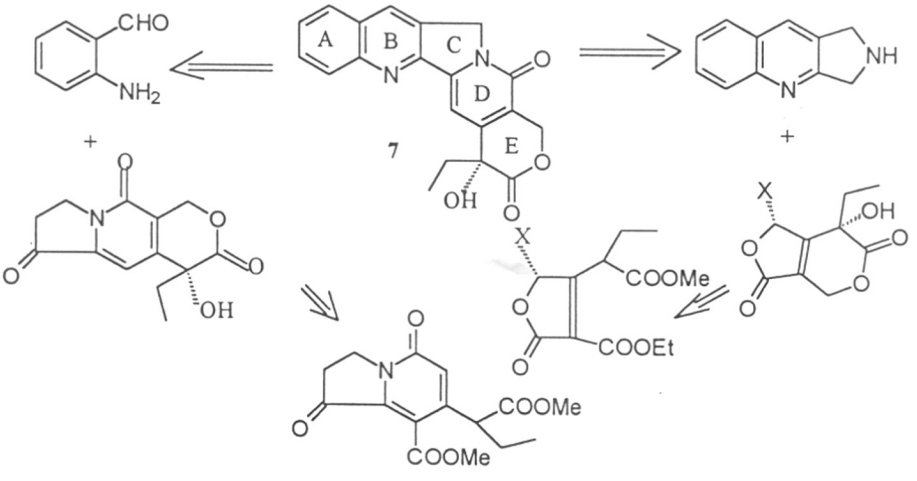
Triethylammoniumbenzyl hydroxide was found to be the best reagent in the present case of aldol condensation.

Chapter II: Synthetic approaches to Camptothecin 7

Camptothecin **(7)**, a pentacyclic alkaloid was isolated from the steam wood of the tree *Camptotheca accuminata* by wall et al.[3] in 1966. It exhibits antileukemic and antitumor activity in animals. Its derivatives like irinotecan, topotecan showed marked

synthesis of camptothecin, which are described in this chapter. The retrosynthetic analysis of camptothecin is shown in **Scheme-5**.

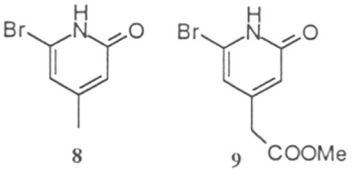
Scheme-5



Section I : CD ring synthon of camptothecin :

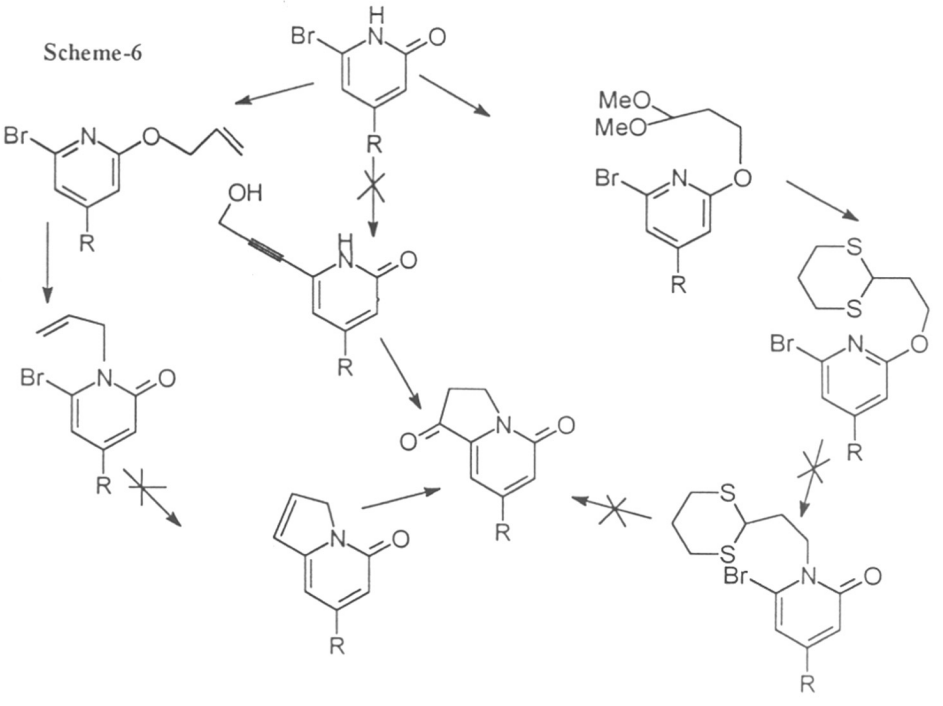
Part I Approaches towards CD ring from pyridone 8 and 9:

Pyridone **8** and **9** were prepared from ethylacetoacetate and dimethyl acetonedicarboxylate in 5 steps respectively.



Various approaches to construct CD ring synthon from the pyridones were tried including Heck, umplong and Michael addition as shown in **Scheme-6** are described here.

Scheme-6

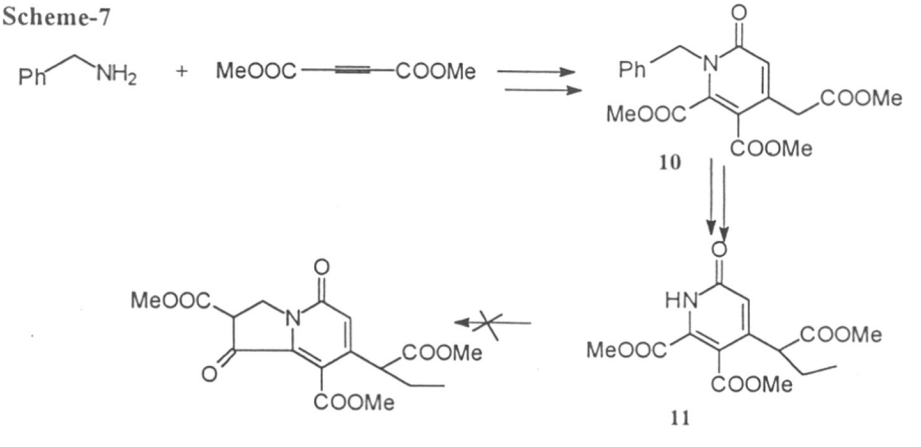


R=CH_2COOMe Or Me

Part II: Synthetic efforts towards CD ring synthon from benzyl amine

Attempts were made to construct the CD rings from benzylamine, which was first converted to N-benzyl pyridone**10** in three steps **(Scheme7)**. Ethylation followed by debenzylation gave pyridone**11**. Further efforts were made to convert **11** into CD ring synthon.

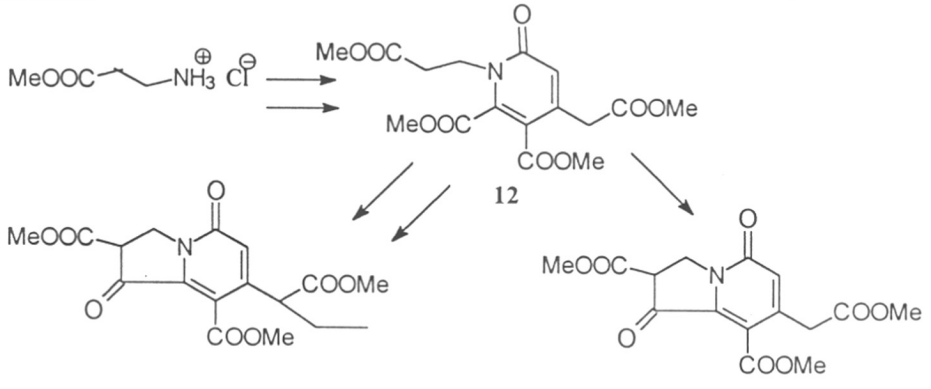
Scheme-7



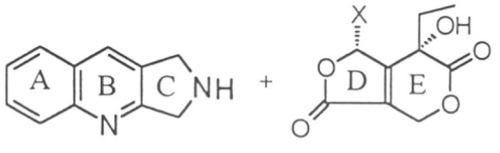
Part-III: From β–Alanine methyl ester hydrochloride

β–Alanine was converted into its methyl ester hydrochloride **(Scheme-8),** which on reaction with dimethylacetylenedicarboxylate followed by cyclisation with dimethyl-3-chloroglutaconate gave pyridone **12**. Ethylation followed by Dieckmann condensation gave the required CD rings from which synthesis of camptothecin is known[4].

Scheme-8



Section II: ABC and D ring synthons of camptothecin

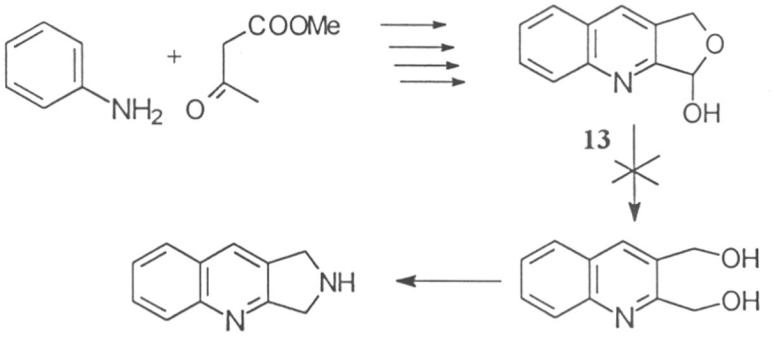


In the literature[5] condensation of ABC and DE rings to camptothecin is known. Attempts were made to synthesise ABC and DE rings from aniline and methylacetoacetate respectively.

Part I : Synthetic efforts directed towards ABC rings

The synthetic efforts were made from both known methods and new methods which are described here. Aniline was converted to lactal **13** in four steps. Attempts were made to convert it into ABC rings synthon as shown in **Scheme 9**.

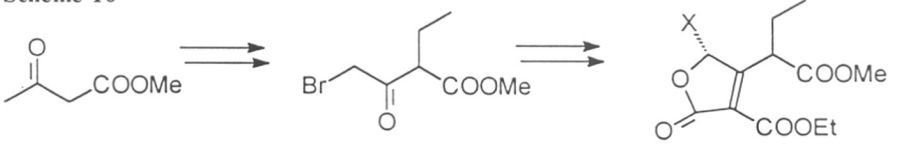
Scheme-9



Part II: Synthetic approaches towards DE ring synthon

Methylacetoacetate was converted into desired lactone**14**in 3 steps. Its bromination with NBS gave **15**. **(Scheme-10)**

Scheme-10



14, X=H

15, X=Br

CHAPTER III : Catalytic Chemical Transformations

Section 1: Transfer hydrogenation[6]

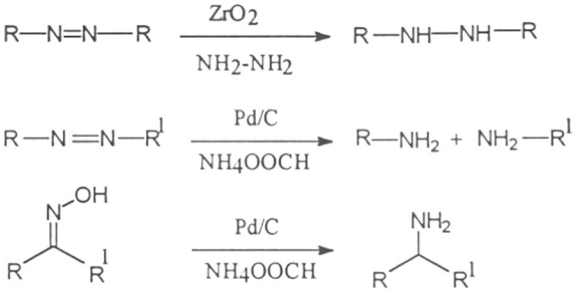
Aromatic hydrazo compounds are very important intermediates in dying fabrics, i.e in textile industries and their usefulness are also known in preparative and analytical chemistry. Several different methods were known in literature to convert azo derivative into hyrdazo or amines. To avoid hazardous chemicals and to develop new reduction method ZrO_2 and Pd/C were found very good catalysts with hydrogen donors in the reduction of azo compounds.

Part - I : Catalytic transfer hydrogenation of oxime, azo compounds using Pd/C with ammonium formate as hydrogen donor

Azo and oximes were reduced to corresponding amines using (ammonium formate) as a hydrogen donor in presence of Pd/C. α–Amino acids were also prepared which are very useful building blocks in peptide synthesis. Selective reduction is also described in the **part 1**

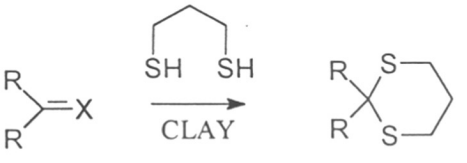
Part II Selective reduction of azobenzenes over Hydrated Zirconia

In the **part 2** azo compounds were selectively reduced at hydrazo stage. Generally azo compound reduction suffer drawback such as cleavage into amines.



Section II: Transdithioacetalization of acetals, ketals and oximes catalyzed by natural Kaolinitic Clay [7]

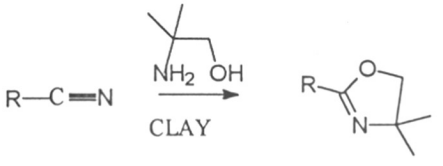
Clays and modified clays are used for several synthetic conversions. Since their reusability, heterogeneous, environmentally safe nature attracted several chemists. In this section a study of transdithioacetalisation of ketals, oximes and other functional groups are described. Oximes, tosylhydrazones are important in the purification of carbonyl compounds were also transdithioacetalated using Kaolinitic clay.



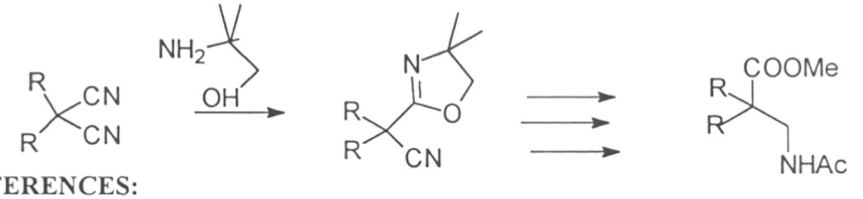
X = $(OMe)_2$, N—OH , N—NH—Ts

Section III: Natural Kaolinitic clay Catalyzed conversion of Nitriles to 2-Oxazolines

Oxazolines have been extensively used as protecting groups.[8] The recemic and chiral oxazolines have attracted much attention in asymmetric synthesis. The utility of Kaolinitic clay as a lewis acid for the preparation of several oxazolines is described in this section.



The use of clay was further extended to prepare amino acids. Malanonitrile derivatives were selectively protected and converted to unnatural amino acids, which are also important intermediates for β lactams.



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CHAPTER I

Synthesis of convolutamydine A, Microwave-assisted preparation of isatins

Introduction

The World Health Organisation estimated that the cancer kills roughly six millions peoples annually. Scientists initiated war against cancer but still not succeeded completely to cure the disease effectively. Cancer[1] is actually referred to more than hundred forms of the disease. Almost every tissue in the body can spawn malignancies. In a normal healthy body 30 trillion cells co-operatively work together regulating one another's proliferation and follow their own internal agenda for reproduction in maintaining health. When cancer struck the cells, the affected cell will ignore the others instructions and starts replication leading to malligent cells (tumors). They also possess even more insidious properties, i.e. their ability to migrate from the site where the cancer began and invades nearby tissue and forms masses at distinct sites in the body. A surgeon can remove a primary tumor relatively easily, but when the cancer became lethal or the tumors formed at distinct place then it is difficult to remove.

Though the cancer is a little older disease, has changed its grasp due to advanced technologies, industries, environmental pollutions, smoking, exposure to dangerous chemicals, chewing tobacco, high intake of fatty food, consumption of large amount of alcoholic beverages, exposures to different light radiation and the signals of cellular phones etc.. Though it is difficult to cure cancer, one can prevent oneself from this giant disease. Controlled diet, eating vegetables, non-smoking, controlled exercise, chemoprevention by in taking vitamin A, C and E etc. Tea extracts, cabbage, fruits etc. also help in cancer prevention.

Treatment of cancers

The cancer treatment can be divided into four types based on the therapy used.

(1) **Surgery**: Surgical excision of the tumor is both quick and safe. But removal of the tumor from the affected site are some times critical and surgeon may need to

cut large amount of healthy tissuse may damage patient. When the cancer is at the primary stage this is the best method.

(2) **Radiation**: Radiation therapy is preferable to surgery in many instances. Though effective, in this method, powerful X-rays or γ-rays may inflict genetic damages and may kill healthy cells. The radiation therapy some times fails when the cancer is found at different sites (widespread).

(3) **Chemotherapy**: In early 1940 chemotherapetic drugs have been developed and physician found that combination of drugs may cure leukemias, lymphomas and testicular cancers etc., unfortunately the majority of the most common cancer like breast, lung, colorectal and prostate cancers are not yet curable with chemotherapy alone. The drug compounds, which attack on topoisomerase enzymes are responsible in replication of cells in tumor site. The available chemotheraphetic drugs often fails on patients because they kill many healthy cells and thus brings serious side effects.

(4) **Combined modality therapy**: This therapy requires the efforts of a wide assortment of specialists-oncologists, surgeons, pathologists and radiologists etc. Breast cancer can be cured by the combination of surgery and radiotherapy, followed by chemotherapy. A new mode of combined modality therapy-induction chemotherapy-applies chemotherapy first and surgery or radiotherapy afterward.

Anticancer drugs used in chemotherapy and combined modality therapy:

The effective chemotherapy can be achieved by understanding the machenism of anticancer drugs and type of cancer cells. Though selective tumor cell killing drugs are unknown, a method developed to selective binding of topoisomerase enzymes I and II which are present in larger amount in tumor cells than in normal cells which are responsible for growth of tumor cells (replication). So these drugs are allowed to bind to topoisomerase enzymes in cancer cells and then treated with radiation to remove tumors.

The other factor is that cancer cells produces some chemicals which coagulate the platelets and become safer themselves by coating platelets on surface. These coated cancer cells will grow by consuming growth factors from platelets. So experiments showed some anticancer drugs developed which interfere with the platelet function and prevent blood coating near cancer cells and cures the cancer.

The anticancer drugs can be classified based on action of break and repair mechanism of DNA double helix. The classification is briefly described here.

(1) **Antimetabolites**: These compounds act as false substances in the biochemical reactions of the living cells. A prime example, methotrexate, which is a chemical analogue for the nutrient folic acid. Methotrexate functions, in part by binding to an enzyme normally involved in the conversion of folic acid into two of the building blocks of DNA, adenine and guanine. This drug prevents cells from dividing by incapacitating their ability to construct new DNA, other examples are 5-florouracil, gemcitabine

(2) **Topoisomerase inhibitors**: Replication of a cells genetic material requires separation of DNA double helix. After separation these two strands separately form new DNA double helix. The separation of double helix generally requires special aid from special "topoisomerase" enzyme. Anticancer drugs have the ability to inhibit these enzymes and causes the cells to die, example for such drugs are. Doxorubicine,Adriamtcin, CPT-11.

(3) **Alkylating agents**: Certain compounds form chemical bonds with particular DNA building blocks and produce defect in the normal double helix structure of DNA molecule. This disruption may take the form of breaks and inappropriate links between strands. If not mended by the various DNA repair mechanisms available to the cell, the damage caused by these chemicals will trigger cellular suicide. Cyclophosphamide, chlorambucial are examples of this category.

4. **Plant alkaloids**: Some of the plant derived compounds can prevent cell division by binding to the proteintubulin (a fiber helps in orchestrate cell division). The fiber pulls duplicate DNA chromosomes to either side of the parent cell, ensuring that each daughter cell receives a full set of genetic blueprints. Drugs interfere with the assembly or dissemble of these tubule fibers can prevent cells from dividing successfully e.g. vinblastine, vinorelbine, paclitaxel, docetaxel etc.

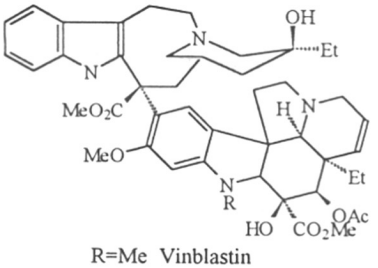
based on the origin The anticancer drugs[2] are classified into two categories:

a) Plant origin

b) Microbial origin

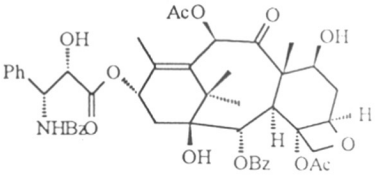
a) **Plant origin**: Many anticancer drugs have been isolated from plants. Some of the important examples are given below:

Plant Origin

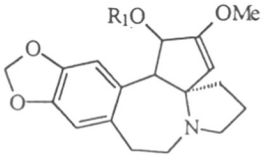


R=Me Vinblastin

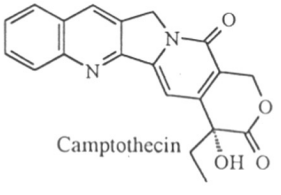
R=CHO Vincristin



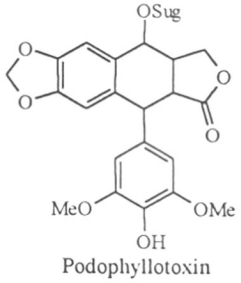
Bz = PhCO- Taxol



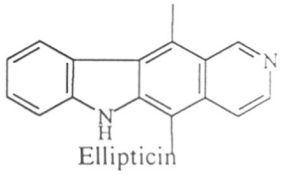
Heringtonia



Camptothecin



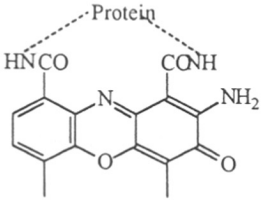
Podophyllotoxin



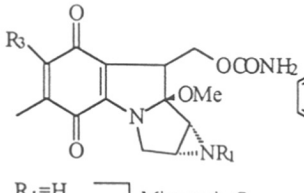
Ellipticin

b) **Microbial origin**: These are originally isolated from bacteria's, fungi's, marine sources (algae) etc. The some examples are given below:

Microbial Origin

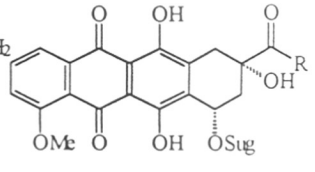


Actinomycin



R_1=H, R_3=NH_2 — Mitomycin C

R_3=OMe — Mitomycin A



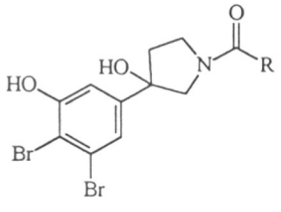
R=Me, Daunomycin

R= CH_2OH, Adriamycin

The sea is a rich source for marine natural products, some of which exhibit biological activity. Many of these natural products carry unique structure marking them distinct from other natural products[3] e.g. halogenated compounds. Several halogenated products with simple structure were isolated from marine bacterial, fungal and algae products, where as complex molecules were isolated from marine animals (snails, sponges and bryozans etc). Isolation and characterization of several marine natural products have been published and reviewed.[3] A brief account of the natural products isolated from Floridian bryozoan *Amathia convoluta (FBAC)* is given here.

Bryostatins[4] represent one of the medically most promising series of marine animal constituents. Pettit et al.[4] extracted these complex microlides from FBAC species. These compounds exhibited exceptional antineoplastic activity (100% life extension) against the lymphocytic leukemia.

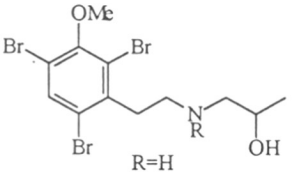
Convolutamides A-F

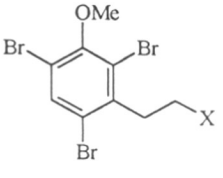


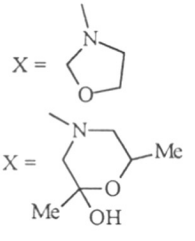
R=12~28 carbon atoms

R=12-30 where unsaturation at 18 or 19 position

ConvolutamainesA-E



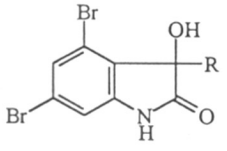




Pettit et al.[5] also isolated convolutamides A-F natural products[6] and convolutmaines A-E (tested positive to cytotoxic activity) from FBAC species where convolutamide contains an N-acyl β-lactam moiety with a dibromo phenol group and convolutamines A-E contains secondary amine group.

Recently Pettit and co-workers isolated a new series of alkaloids from FBAC containing a dibromohydrooxindole moiety and named them as Convolutamydines A-D.[7]

Convolutamidine A-D



A R =  1a

B R =  1b

C R = —Me 1c

D R =  1d

These compounds have been showed to exhibit a biological activity in differentiation of HL-60 cells.

Isolation and characterization of convolutamydines A-D:

From 100 kg of the bryozoan *Amathia convoluta*, collected from Gulf of Mexico in Florida, extraction with EtOH and elaborative fractionation and chromatographic separation of the extract gave convolutamycine A[8] (**1a**, 8.6 x 10^{-6} %), B (**1b**, 10.7 x 10^{-6} %), C (**1c**, 6.0 x 10^{-7} %) and D (**1d**, 3 x 10^{-7} %). The structure of convolutamydineA was first determined to be 4,6-dibromo-3-hydroxy-3-(2-oxypropyl)-2-indoline by extensive spectroscopic techniques. In comparison with the spectral data of **1a**, convolutamydines B-D (**1b-1d**) were inferred to be related analogs of **1a**. Thus convolutamydines A-D (**1a-1d**) belong to a new class of alkaloids, in which a dibromohydroxy oxindole nucleus is having a variety of substitutents at C-3 from marine natural origin. These compounds showed a negative Cotton effect in their CD spectra. The stereochemistries of these compounds have not been determined so far. Convolutamydine A and B exhibit the bioactivity in differentiation of HL-60 cells. However, the biological evaluation of convolutamydines C and D could not be achieved because both were isolated only in minute quantities.

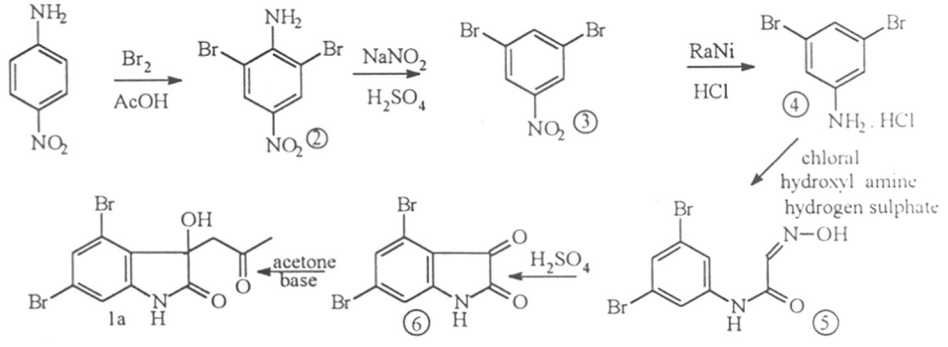
Synthesis:

The convolutamydines A-D contain the novel 4,6-dibromo-3-hydroxyoxindoline structure and they only differ from each other in the nature of the substituents at C-3. Recently the syntheses of convolutamydines A and C have been reported.

Synthesis of convolutamydine A:

This compound exhibits a potent activity in the differential of HL-60 human promiocytic leukemia cells. Its first synthesis was reported by Garden et al.[9] starting from p-nitroaniline with modified Sandmeyer methodology as shown in **Scheme-I**.

Scheme-1



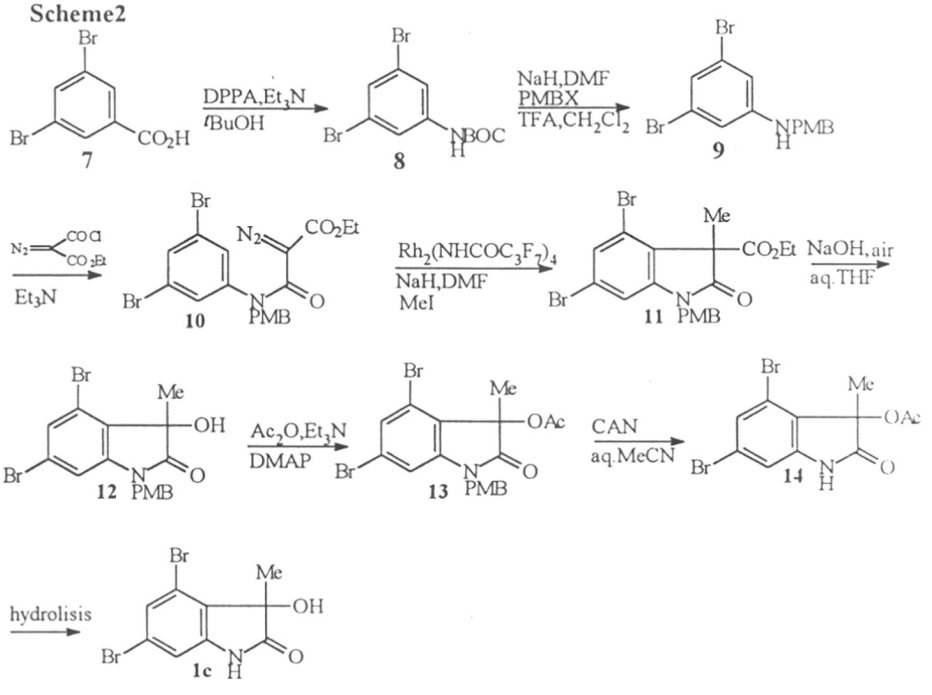
For the synthesis of convolutamydine A an obvious precursors is 4,6-dibromoisatin **6**. In the literature[10] the yield of **6** from 3,5-dibromoaniline was disappointing i.e. 10%. The low yield was ascribed to inefficient formation of the intermediate α-isonitrosoacetanilide (11%). Garden and co-workers[9] modified some steps to constitute good yield of 4,6-dibromoisatin (**6**).

3,5-Dibromoaniline hydrochloride (**4**) was prepared starting from p-nitroaniline by initial bromination in glacial acetic acid followed by reductive deamination using sodium nitrite in acidified ethanol to form 3,5-dibromonitrobenzene (**3**). The Raney nickel hydrogenation of **3** gave excellent yield of 3,5-dibromoaniline, which was subsequently precipitated and recrystallised as its hydrochloride salt **4**.

A modified Sandmyer methodology used to prepare isonitrosoacetanilide (5) involves a mixture of the aniline hydrochloride **4**, chloral, hydroxyl amine hydrogen sulfate, sodium sulfate in water and ethanol stirring at 60° to 80°C for 3-4 hrs. The resulted isonitroacetanilide **5** was then cyclised to dibromoisatin **6** with 86% H_2SO_4 at 60 to 110°C in 82% yield. The condensation of the isatin **6** with acetone was carried out using catalytic amount of Et_2NH in 77% yield of (±)-convolutamydine A (**1a**) with overall yield of 52.07%. The authors have studied a model reaction of isatin and acetone using varying quantities of S(-)-proline and it was observed that no asymmetric induction in the product.

Synthesis of Convolutamydine C (1c):

Scheme2



Convolutamydine C (**1c**) was isolated from the FBAC and has a similar structural framework of convolutamydine A. The first synthesis of the Convolutamydine (**1c**) was reported by Moody et al.[11] starting from 3,5-dibromobenzoic acid (**7**). The 7 was converted into N-*tert*-butoxy carbonyl 3,5-dibromoaniline (**8**) by the reaction of diphenyl phosphoridazide and Et_3N in *tert*-butylalcohol by a modified Curtiues rearrangement. The BOC protected compound **8** was then converted to N-p-methoxybenzyldiazoamide **10** in few steps as shown in **Scheme-2**. Treatment of diazoamide **10** with a catalytic amount of rhodium (II) perfluorobutyramide gave oxindoline, which was subsequently *C*-methylated using NaH and methyl iodide to give ester **11**. The ester **11** on refluxing in aqueous alkali in presence of air gave hydroxy compound **12**. The compound **12** was protected as its acetate using acetic anhydride to give acetyl compound **13**. Oxidative removal of the PMB from the acetyl compound **13** with CAN in acetonitrile gave acetyl convolutamidine C **14**. The final hydrolysis of acetate **14** with aqueous NaOH gave (±) convolutamydine (**1c**) in overall 19.9% yield.

Present work

Section I: Preparation of 4,6-dibromoisatin:

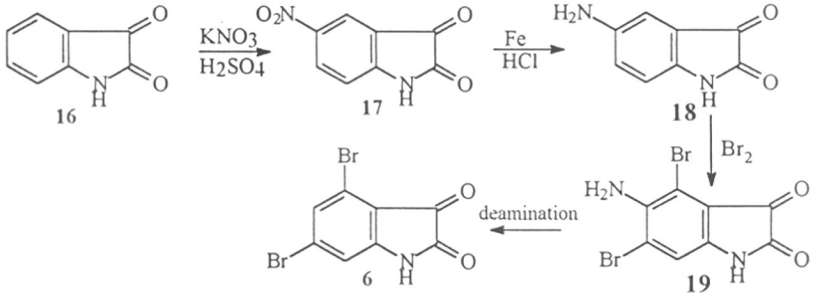
Marine bryozoans have proved to be a rich source of compounds having intriguing structures and interesting biological activity. The isolation of convolutamydine A-D from FBAC led new discovery to dibromohydroxyoxindole alkaloids. Convolutamydine A and B were found to exhibit a potent activity in the differentiation of HL-60 human promycolicytic leukemia cells. These compounds differ in the substitution at C-3 position of dibromohydroxyoxindole.

Part I: Preparation of 4,6-dibromoisatin (6) starting from isatin:

4,6-Dibromoisatin (6) is a key intermediate for the syntheses of convolutamydine A. For the preparation of 4,6-dibromoisatin mainly two methods are known in the literature starting from p-nitroaniline. The previously described method yielded only 10% yield of 4,6-dibromoisatin.[10] Recently a similar sequential reaction by improving the formation isonitrosoacetanilide using a modified Sandmeyer[9] reaction gave 4,6-dibromoisatin in overall 67.62% yield.

The proposed synthesis of 4,6-dibromoisatin is shown in **Scheme-3** starting from isatin (**17**).

scheme 3:

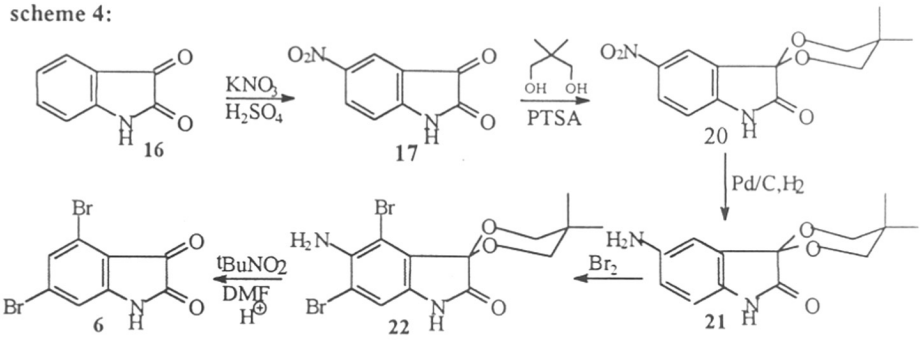


The nitration of isatin is known to give 5-nitroisatin (**17**). Its selective reduction to 5-aminoisatin **18** followed by bromination would give 4,6-dibromo-5-aminoisatin (19). Its deamination should furnish 4,6-dibromoisatin (**6**).

The commercially available isatin was converted to 5-nitroisatin (**17**) in 70% yield using KNO_3 in conc. H_2SO_4 at 0°C. The selective reduction of 5-nitroisatin to 5-aminoisatin using Fe/conc. HCl or Pd/C, H_2 catalysed reduction failed to give the desired aminoproduct **18**.

A modified approach was proposed which is given in **Scheme-4**.

scheme 4:



Isatin was converted to 5-nitroisatin **17** in 70% yield. Its protection with 2,2'-dimethyl-1,3-propanediol in presence of p-TSA in cyclohexane under azeotropic removal of water formed, furnished protected compound **20**. The ^{1}H NMR spectrum of **20** showed two singlets for methyl groups at δ 0.90 and 1.45 and two doublets at δ 3.28 and 4.58 for two methylene groups. The aromatic protons appeared at δ 7.05, 8.15 and 8.38 while the mass spectrum showed M^+ 278.

The reduction of nitrocompound **20** with Pd/C under H_2 atmosphere. in methanol gave amino compound **21**. Its ^{1}H NMR showed two methyl singlets at δ 0.9 and 1.44 and two methylene protons at δ 3.29 and 4.60 as two doublets. The aromatic protons were shifted to δ 6.5 and 6.80. The Mass spectrum has molecular ion peak at M^+ 248. The bromination of **21** gave a mixture of products. After careful chromatograpic separtions the major product was separated and characterised as the desired dibromo compound **22** by spectral data. Its ^{1}H NMR spectrum showed two methyl singlets at δ 0.95 and 1.40 and methylene groups at δ 3.45 and 4.55 as doublet. The single aromatic proton appeared at δ 6.95 as a singlet. The mass spectrum has M^+ 404. The deprotection and deamination of the amine **22** by $NaNO_2$ and H_2SO_4 in ethanol[12] failed to give dibromoisatin **6**.

The reagent of choice for the deamination of aromatic amine is *t*-butyl nitrate and was prepared according to the literature procedure.[12] The amine **22** was stirred with *t*-butyl nitrate in dry DMF at 60°C to furnish diaminodibromocompound which was subsequently deprotected with aq. oxalic acid solution to give 23% of the desired 4,6-

dibromoisatin (**6**) m.p. 250°C (lit[9]. m.p. 252°C). The structure of the product was confirmed by its spectral data. As the overall yield of 4,6-dibromoisatin (49 %) was not satisfactory, an alternative modified method was developed which is described in Part II.

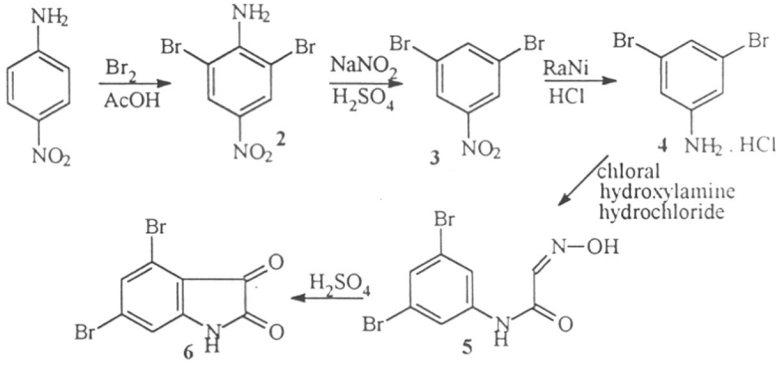
Part II

Preparation of 4,6-dibromoisatin from p-nitroaniline by microwave-assisted method:

Earlier Baker et al.[10] prepared 4,6-dibromoisatin (**6**) in very low yield (11%). The low yield is due to inefficient formation of the intermediate α-isonitrosoacetanilide while the following cyclisation to **6** proceeded smoothly (80%). Garden et al.[9] prepared α-isonitrosoacetanilide in good yield (82%) using a modified Sandmeyer methodology. A mixture of 3,5-dibromoaniline, chloral, hydroxylamine hydrogen sulfate, sodium sulfate in aqueous ethanol was stirred at 60-80°C for 2-6 hrs to give isonitrosoacetanilide **5** in 80% yield which on cyclisation with 86% H_2SO_4 afforded 4,6-dibromoisatin in 86% yield.

In the present work a microwave-assisted methodology for the preparation of isonitrosoacetanilide **5** as well as for isatin **6** has been developed.

scheme 5



The p-nitroaniline was brominated in acetic acid with 2 eq. of bromine to furnish 2,6-dibromo-4-nitroaniline (**2**) m.p. 204°C (yield 95%). The compound **2** was deaminated using $NaNO_2$, H_2SO_4 in ethanol to give 3,5-dibromonitrobenzene (**3**) m.p. 106 °C. The nitro group of **3** was reduced using Raney nickel under H_2 atmosphere to give 3,5-dibromoaniline and subsequently precipitated as its hydrochloride **4**.

The amine hydrochloride **4** was then taken in a test tube mixed with hydroxylamine hydrochloride, chloral and sodium sulfate in 3 ml of water and one drop of Conc. HCl and irradiated in microwave oven for 1-2 min with occasional shaking. After 2 min the water layer was decanted from Na_2SO_4 and filtered to give isonitrosoacetanilide **5** in 85% yield m.p. 190°C (lit[9] m.p. 191°C). The isonitrosoacetonilide **5** was converted into the corresponding isatin **6** under microwave with 85% H_2SO_4 in 80% yield. The product **6** was characterised by spectral analysis.

Thus the microwave-assisted method was found to be effective for preparation of the desired isatin derivatives in high yield in short time. Based on this microwave-assisted study a general method for the preparation of various substituted isonitrosoacetanilide and isatins has been developed which is described in **Section 2** of this chapter.

Section 2

Microwave assisted method for preparation of isonitrosoacetanilide and isatin derivaties.

Microwave oven was introduced early as domestic oven for rapid cooking in kitchens. Latter its use was extended to synthetic organic chemistry. Microwaves generate rapid intense heating of polar substances with consequent significant reductions in reaction times and give cleaner reactions,[13] that are easier to work-up than those from conventional heating. In the early days of microwave-irradiation reactions were performed in domestic ovens. Latter the development of new equipment, allowed the focused irradiation resulting in better control on power and temperature, now allow more efficient reactions. The microwaves create heating in the interior of the sample and then radiated outward which is contrast to conventional heating where the heat is generated in the outer region then it is directs towards the center, unlike other non-conventional energy sources (such as ultrasound, high pressure and vacuum flask thermolysis). Most of the reactions carried out on supported media or in the absence of solvent constitute an environmentally cleaner and safer technique. High yields of products can be obtained in short time and reduced energy costs.

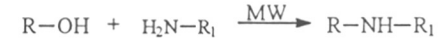
The beneficial effects of microwave radiation can be utilized to improve processes, specially if classical methods require harsh conditions, prolonged reaction

times or high temperatures and where the processes consist of sensitive reagents or increases in reaction temperature could cause product decomposition can be easily handled in microwave.

Several articles and reviews[13] are published in the literature mentioning the use of microwaves for organic syntheses. Some of the important microwave-assisted reactions are give below:

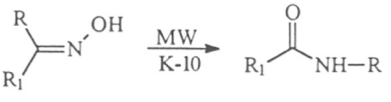
Linders et al.[14] examined the cycloaddition of 6-demethoxy-β-dihydrothebaine with methylvinyl ketone. The classical heating causes the extensive polymerisation of the dinophile which has been eliminated using microwave.

Jiang et al.[15] carried out N-alkylation of aniline with propanol and catalytic amount of Raney nickel under microwave irradiation conditions in excellent yield (90%).

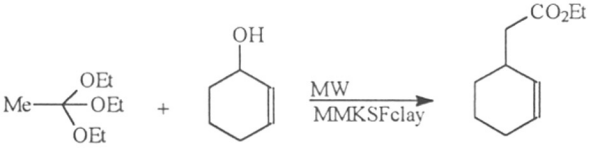


The microwave method is useful with solid supported reactions using clay, alumina, silica gel etc.

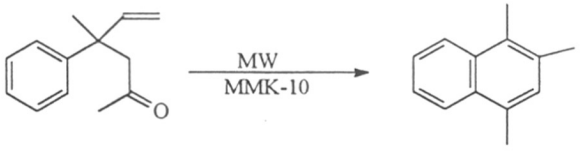
The use of montmorillonite clay under microwave has several advantages. Boschet al.[16] showed poorly reactive oximes which did not react under classical conditions to give Beckmann product.



Huber et al.[17] used MMKSF clay under microwave for Claisen rearrangement reaction where under normal conditions this reaction does not take place.



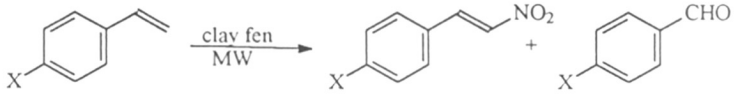
Srikrishna et al.[18] showed enones gives naphthalenes under microwave condition.



Kad et al.[19] converted benzylalcohols to benzyl iodides under microwave condition with NaI.

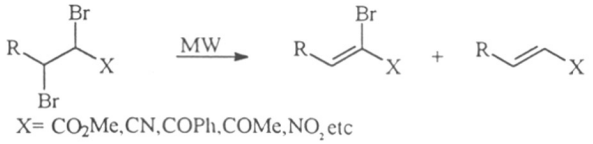
$$ArC\,H_2OH + NaI \longrightarrow ArCH_2I$$

Varma et al.[20] used dry microwave technology for several types of reactions, one of them is nitrostyrenes preparation, under solvent free condition styrene and its derivatives gave β-nittrostyrene in good yields under microwave.



X = Cl,H,OMe,Me

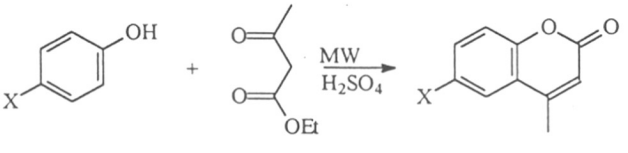
Saoudi et al.[21] used microwave for functionalisation of alkenes.



X= CO_2Me,CN,COPh,COMe,NO_2 etc

Ortiz et al.[22]used the microwave condition for the Heck reaction. The conventional methods takes 20-22 hrs.

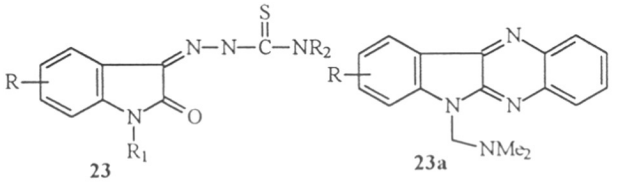
Singh et al.[23] used microwave for Pechman reaction where several substituted coumarines were prepared.



Baruah et al.[24] used microwave for deoxamination and detosylation with $BiCl_3$ where other heating reactions takes longer time.

X= NHTs, OH

In connection with our work on convolutamydine A, an antitumor alkaloid, the microwave method has been exploited for rapid preparation of 4,6-dibromoisatin (6). The isatins are also important intermediates for the syntheses of several biological active compounds some of them are isatin-3-thiosemicarbazone **23** (used in tonic convolutions as antiviral agent), N,N-dimethylamino indoplenazin **23a** (antimicrobial activity) etc.

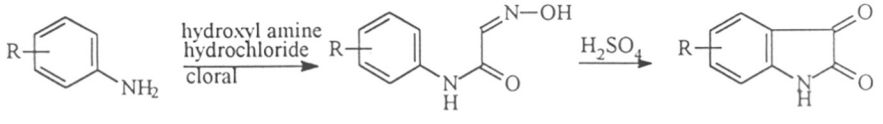


23 **23a**

Isatins are also used in dyes.[25,26] Some of the literature procedures for the syntheses of isatin are listed below.

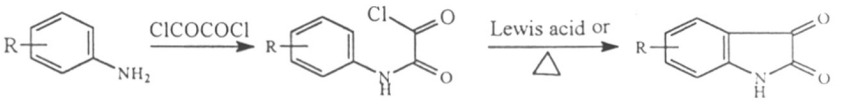
Sandmeyer procedure:

This is a most frequently used method[26] for the synthesis of isatins which involves the formation of an isonitrosoacetanilide from aniline, chloral hydrate and hydroxylamine hydrochloride. The isonitrosoacetanilide further cyclised into isatin with sulphuric acid.



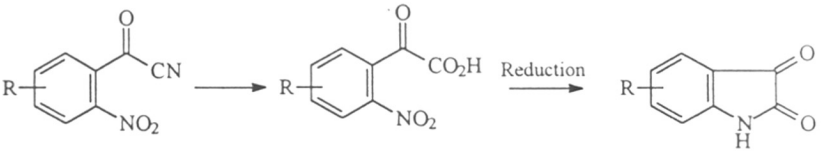
Stolle procedure:

Treatment of aniline with oxalylchloride[26] followed by cyclisation of the

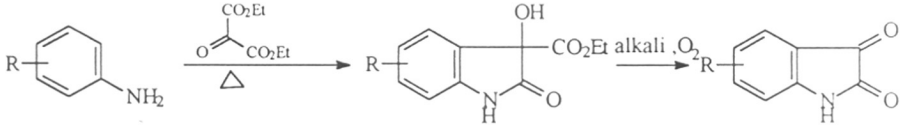


intermediate is an another useful method for isatin synthesis. Generally Lewis acid is used for cyclisation.

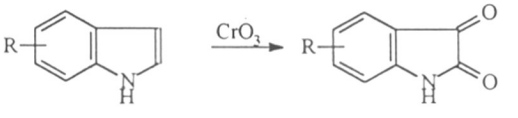
The reductive cyclisation[26] as the key step also be usefull for isatin preparation.



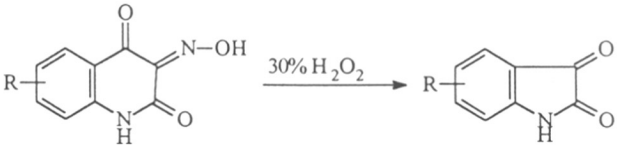
Martinet reaction[26] involves the use of aniline and oxamalonic ester, which gives the hydroxy intermediate which on alkaline hydrolysis furnishes isatin.



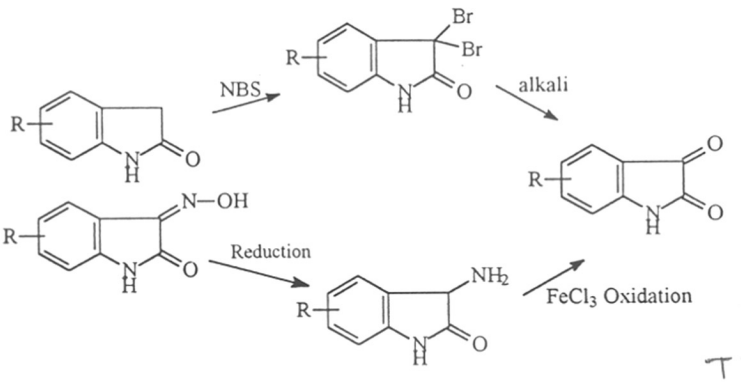
Oxidation of a variety of indoles[26] with chromic acid directly gives isatins.



The oxime derivatives of quinolines[26] were also directly converted to isatin using oxidative hydrogenperoxide conditions.

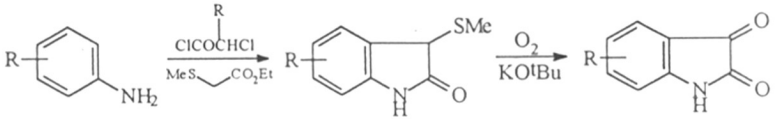


The oxindoles were converted to isatin[26] by oxidation using NBS or $FeCl_3$.



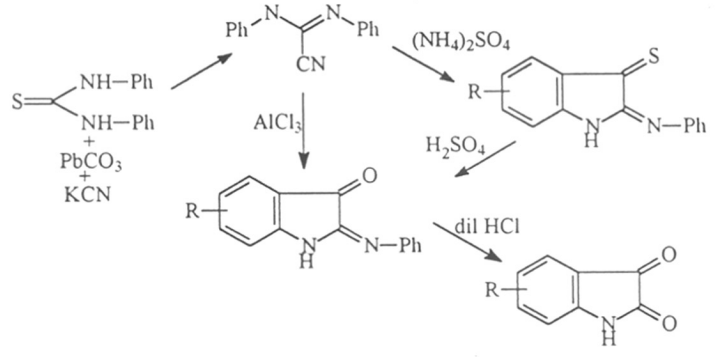
Gassman synthesis[25]

Various aromatic amines on treatment with chloroacetylchloride and methylthioacetic ester in triethylamine gave an intermediate which was further oxidised



to isatins.

Thioureas[26] were also cyclised with $PbCO_3$ and KCN to give isatins.



Present work

Part1: Preparation of isonitrosoacetanilide and isatin[27]

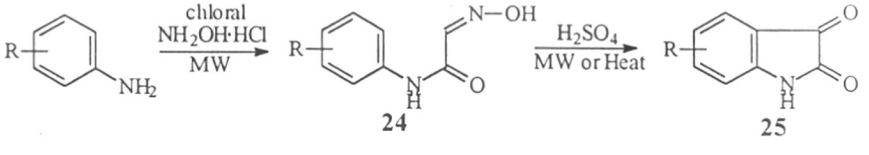
Derivatives of isatin are key intermediates in the synthesis of natural products. An alkaloid, (±)-convolutamydine-A, isolated recently[8] from marine bryozoan *Amathia*

convoluta was found to show a potent activity in the differentiation of HL-60 human promyelocytic leukemia cells. The synthetic precursors to this type of alkaloids are also isatin derivatives.

The microwave assisted chemical transformations have become important due to several advantages over the conventional thermal reactions. A number of applications in synthetic organic chemistry have been regularly reported over the last few years.[13] In this **chapter I** we wish to present microwave-assisted preparation of isatin derivatives and an efficient synthesis of (±)-convolutamydine-A.

The derivatives of isatin are reportedly synthesized from the corresponding aromatic amines by Sandmeyer method. The standard reaction conditions involve heating a mixture of aromatic amine, chloral and hydroxylamine hydrochloride resulting in the intermediate isonitrosoacetanilide **24**, which can be cyclised to isatin **25** under the acidic conditions. This procedure often results in the formation of resinous material with loss of yields. In order to find superior protocol for the synthesis of isatin we investigated this reaction under microwave conditions. A mixture of aromatic amine, chloral and hydroxylamine hydrochloride was exposed to microwave irradiation in a domestic microwave oven (**Scheme-6**). The careful analysis of the reaction mixture indicated the formation of isonitrosoacetanilide **24** in two to three minutes in most cases. This intermediate was smoothly cyclised to the isatin **25** with 86 % H_2SO_4 under microwave conditions or by heating the reaction mixture.

Scheme-6



A number of derivatives of isatin were prepared by the modified procedure and the results are summarized in Table-1. The reactions are general and both the steps gave good yields.

Table-1: Preparation of isonitrosoacetanilide **24** and isatin **25** from aromatic amines.

No.	Aromatic amine	Yield (%)[a,b] of isonitrosoacetanilide, **24**	Yield (%)[a] of Isatin, **25** (from **24**)
1.	Aniline	89	75[b]
2.	Toluidine	82	70[c]
3.	Anisidine	77	65[c]
4.	*p*-Flouroaniline	91	61[b]
5.	*p*-Nitroaniline	88	-
6.	Benzylamine	50	-
7.	Anthranilic acid	94	-
8.	3,5-Dibromoaniline	80	85[b]

[a]Isolated; [b]microwave method; [c]thermal method.[ref. 6]

Synthesis of convolutamydine A:

Part II: Convolutamydine A, a metabolite isolated from the marine FBAC, presents an interesting 4,6-dibromo-3-hydroxyoxyindole nucleus. This compound exhibits a potent activity in the differentiation of HL-human promyclocytic leukemia cells. The obvious precursor to the synthesis of this compound is 4,6-dibromoisatin (**6**). The condensation of 4,6-dibromoisatin (**6**) with acetone in presence of base gave convolutamidine A.Various bases have been used to improve the yield of Convolutomydine A and the results are presented in **Table-2**

Scheme 7

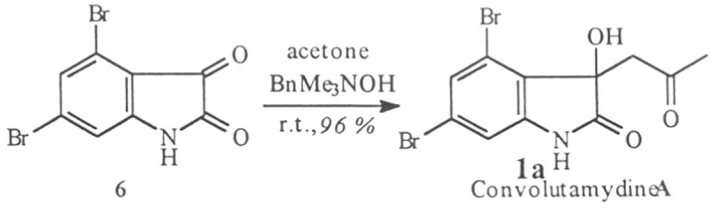


Table-2 The yield of Convolutamydine A(**1a**) obtained with different bases.

Quantity of base used	Base	Yield Of **1a**
50mg	Et_2NH	75%
50mg	15cc of 60% EtOH containing 0.16% KOH	79%
50mg	15 cc of NH_3 in ethanol 10 ml	72%
50mg	Piperidine	68%
50mg	Morpholine	65%
50mg	Benzyltrimethylammoniumhydroxide (40%solution in water)	98%

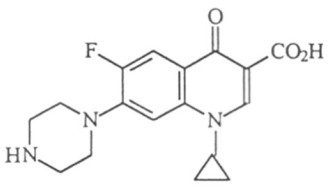
The Convolutalmidine A (**1a**) obtained was fully characterized with the help of spectral and analytical methods.

Fluoro derivative of convolutamydine A:

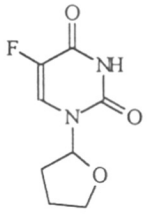
Organofluorine[28] compounds are found to have some interesting stemming properties, conferred upon a molecule by the presence of fluorine. These properties made them to conquer the area of agrochemicals, dyes and pharmaceuticals. Several interesting organofluoro compounds have been used in agrochemicals, dyes, surfactants, polymers and pharmaceuticals.

Majority of fluorine containing organic drugs are being used for a wide range of diseases They are being used as antimicrobial,[29] antihypertensive, antimalarial[29], antiinflammatory and anticancer. Fluoroquinolone derivatives are used as antimicrobials, examples of this class are norfloxacin ciprofloxacin, florofur etc. Florofur a drug which releases 5-fluorouracil *in vivo* used for treatment of cancer.[30] The malaria which is

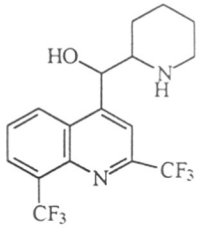
resistance to the other drugs can be cured by fluorine containing drug mefloquine. Some of the important fluorine containing compounds are given below.



ciprofloxin

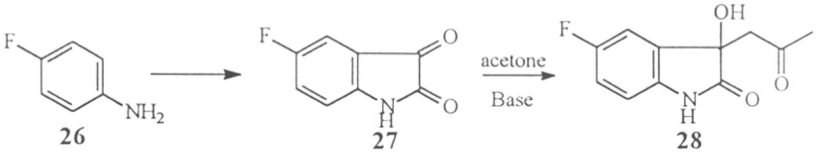


florofur



mefloquine

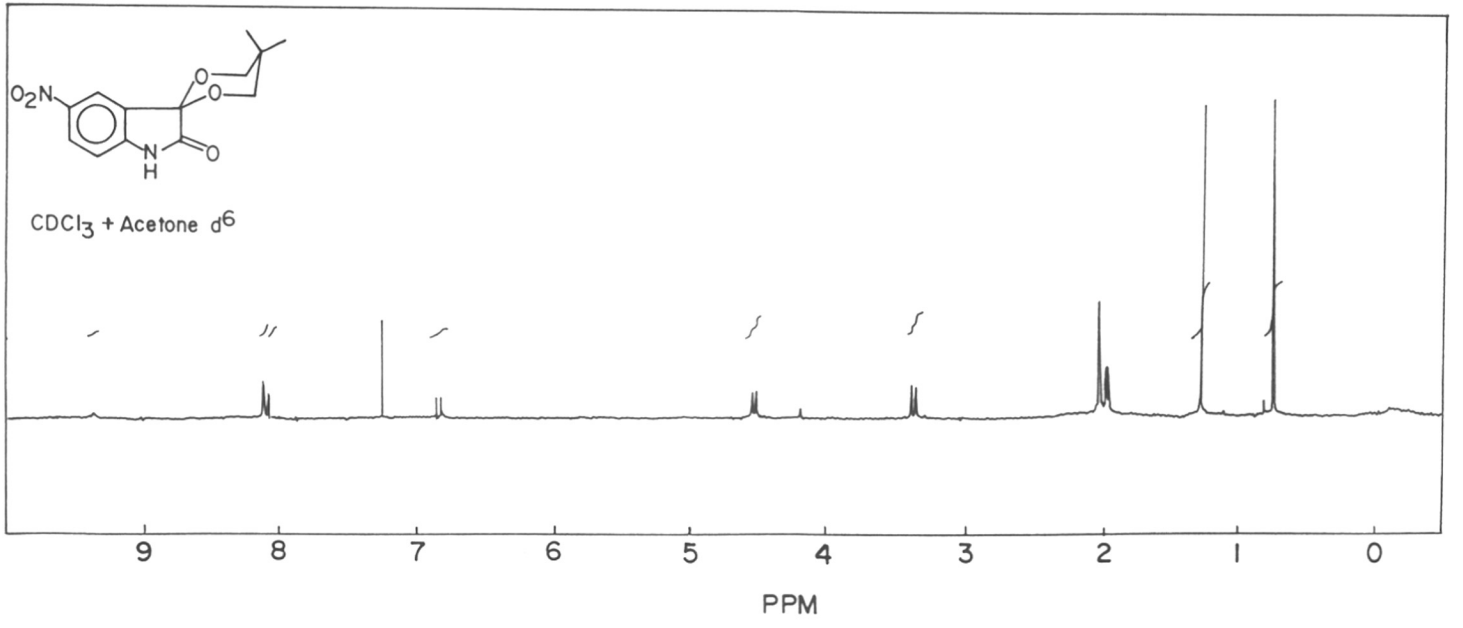
Based on the above discussion it was decided to prepare fluoro derivative of convolutamydine A. The 5-fluoroisatin (**27**) was prepared from 4-fluoroaniline (26 by microwave methodology was treated with catalytic diethylamine in acetone to give the corresponding fluoro derivative **28** in 72% yield.

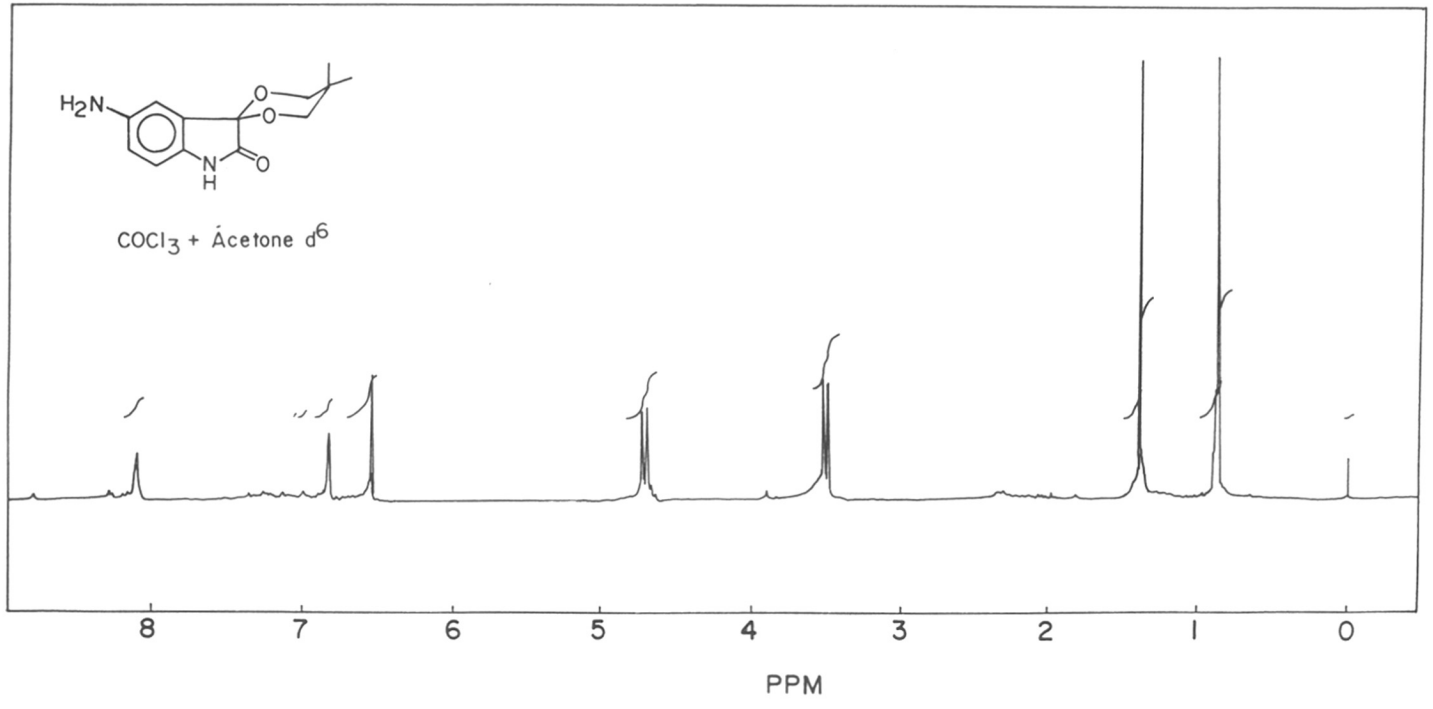


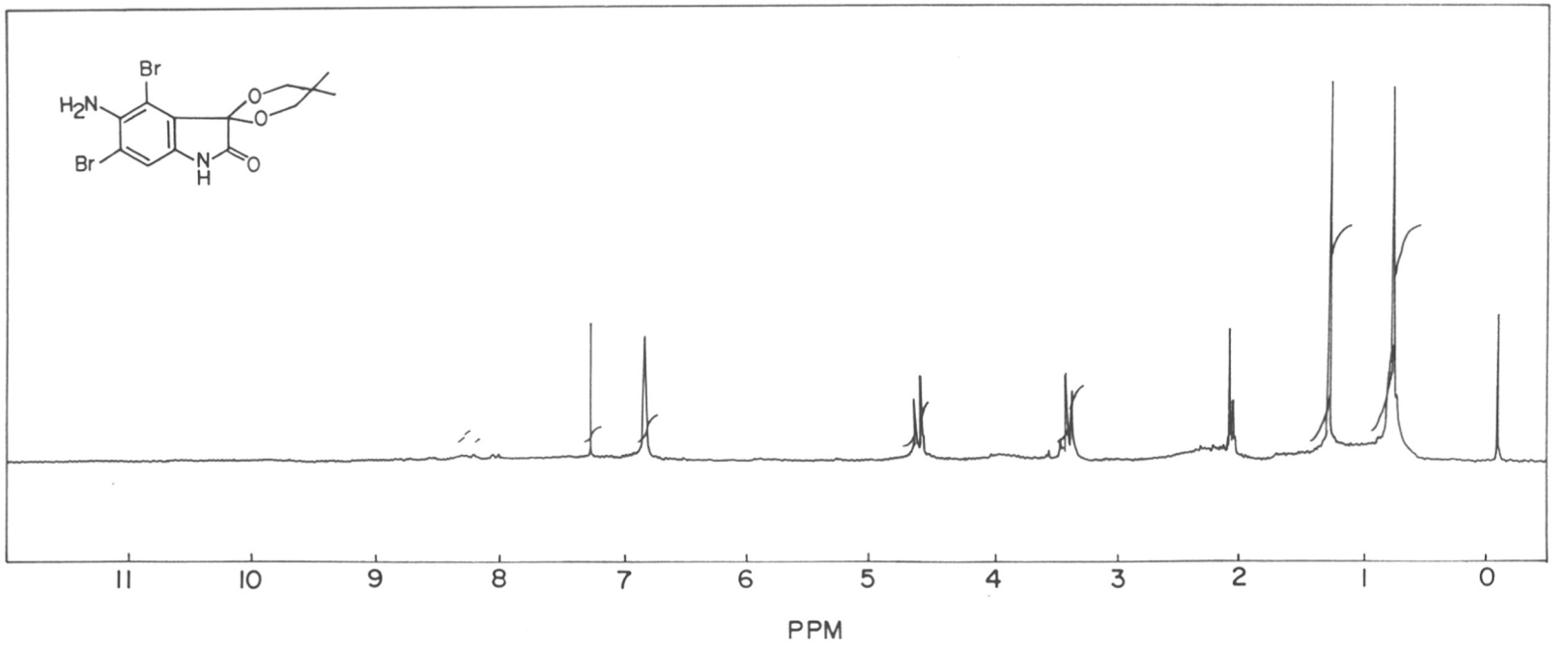
26 **27** **28**

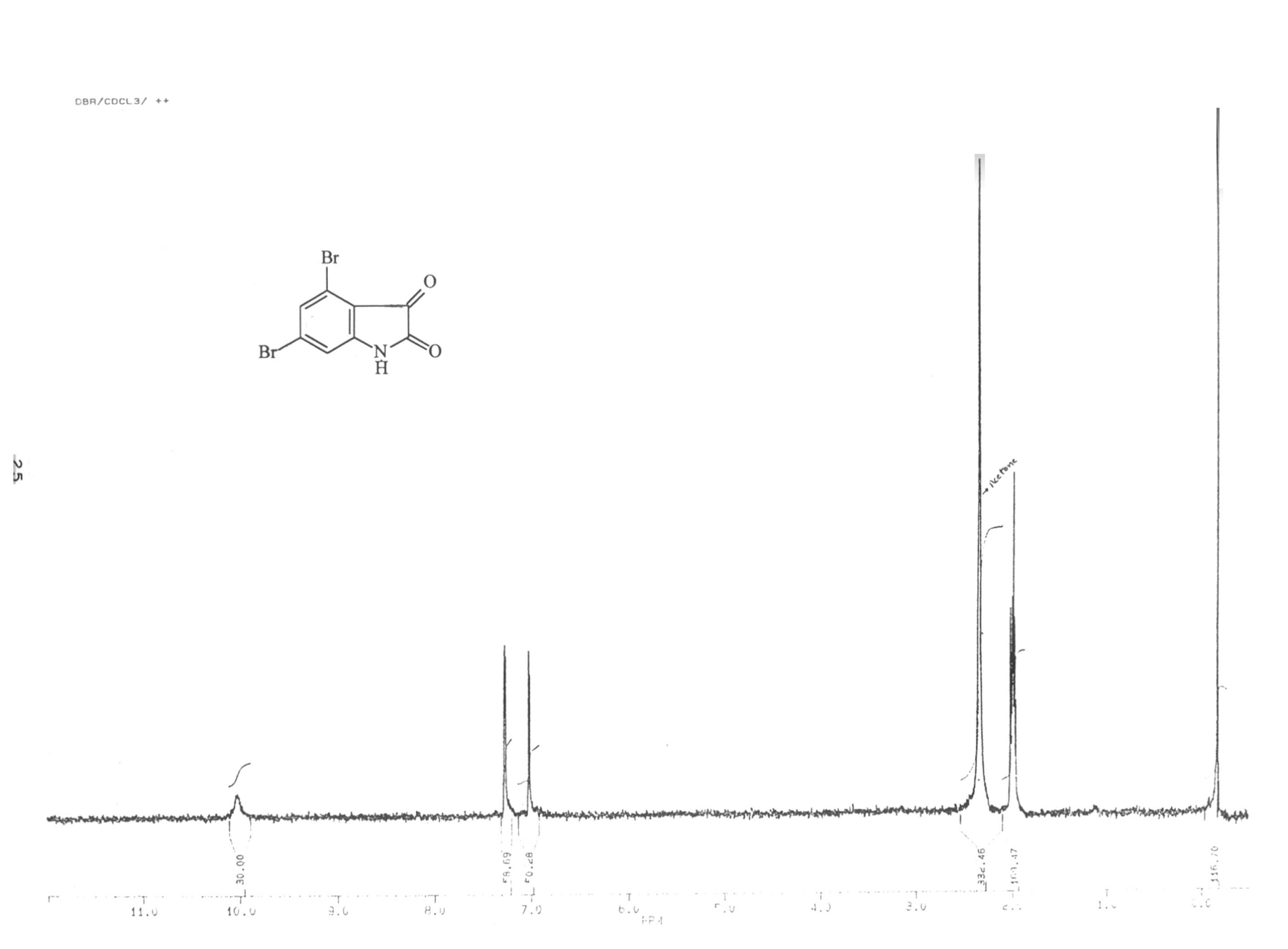
The structure of **28** was confirmed by its ^{1}H NMR where ^{1}H NMR showed singlet at 1.98 for methyl and doublet of dublet at δ 2.85 and 3.10 for methylene protons of acetone moiety while IR had carbonyl peak at 1740 cm^{-1}.

In conclusion we achieved the total synthesis of convolutamidiene A, using rapid micro-wave methodology in excellent yield. We also prepared fluoro analogue of convolutamidine, which we hope may show enhanced biological activity.

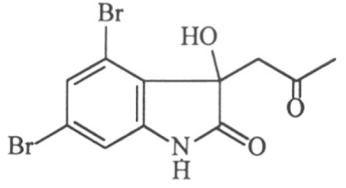

O_2N
O
O
N
H
O
$CDCl_3$ + Acetone d^6
9
8
7
6
5
4
3
2
1
0
PPM

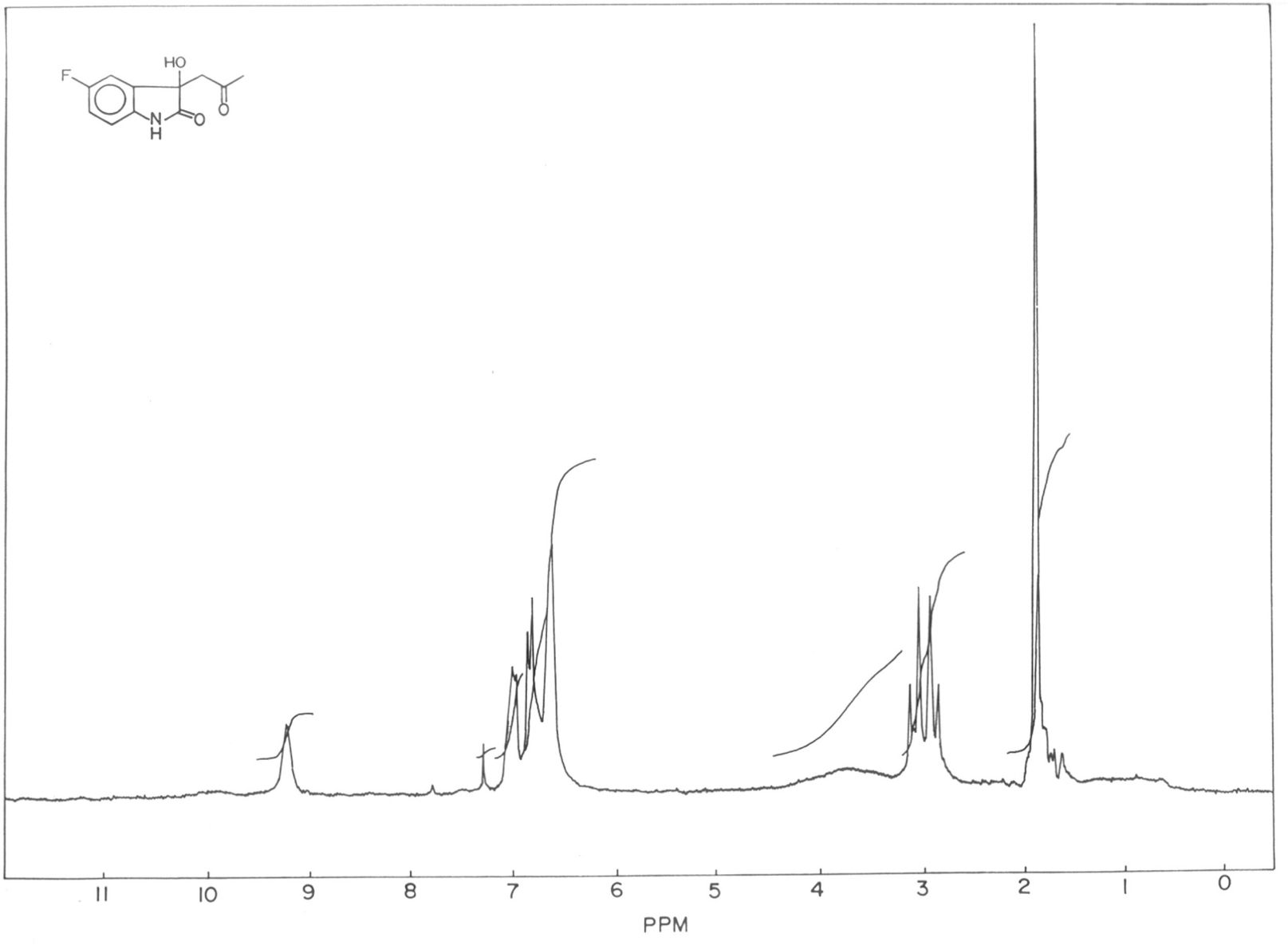

H2N
O
O
N
H
O
COCl3 + Ácetone d6
8
7
6
5
4
3
2
1
0
PPM


Br
H2N
Br
O
O
N
H
O
11
10
9
8
7
6
5
4
3
2
1
0
PPM


DBR/CDCL3/ ++
Br
O
Br
N
H
O
Acetone
30.00
F0.69
F0.68
336.46
103.47
116.70
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

AE/CDCL3+ACETONE D6




HO
F
O
N
H
O
11
10
9
8
7
6
5
4
3
2
1
0
PPM

Experimental

5-Nitroisatin (18)

In a 100 ml round bottom flask containing conc. sulfuric acid (12ml) was cooled to -5°C using ice salt mixture. Isatin (6 gm, 0.0408 mole) was added in portion-wise with stirring in 15 min. The mixture was stirred half an hour more and then added KNO_3 (4.10 gm, 0.041 mole) in portions, during this period mixture turns to brown which was stirred at O°C for 1 hr. Then to the reaction mixture, ice pieces were added at O°C and the precipitated yellow solid was filtered, washed several times with cold water and then air dried.

M.P. : 253°C (lit[12] mp 252°C)

Yield : (5.48 gm; 70%)

IR (Nujol) : 3600, 1740, 1600 cm^{-1}.

^{1}H NMR (200MHz,DMSOd^6):δ 7.0-7.05 (m, 1H); 8.20-8.25 (m, 1H); 8.40-8.45 (m, 1H).

MS (m/z) : 192M^+ (30), 164 (100), 90 (80), 63 (79).

5-Nitroisatin acetal (20)

The mixture of nitro compound **17** (3 gm, 0.021 mole), 2,2'-dimethyl-1,3-propandiol (1.625 gm, 0.02 mole) was suspended in cyclohexane (20ml) with catalytic amount of p-TSA and was refluxed with azeotropic removal of water using Dean Stark apparatus. The reaction mixture was cooled to room temperature and the light greenish solid separated was filtered and washed with dilute sodium bicarbonate solution water and air dried to give **20**.

M.P. : 198°C

Yield : (4.72 gm, 82%)

IR (Nujol) : 3600, 1720, 1600 cm^{-1}

^{1}H NMR (200MHz,DMSOd^6): δ 0.90 (s, 3H); 1.45 (s, 3H); 3.28 (d, J = 12.9 Hz, 2H); 4.55 (d, J = 12.9 Hz, 2H); 7.70-7.05 (m, 1H); 8.10- 8.15 (m, 1H); 8.30-8.35 (m, 1H).

MS (m/z) : 278 M^+ (5), 250 (100), 164 (90), 90 (40).

5-Amino isatin acetal 21

The nitro compound **20** (2.76 gm, 0.01 mole) in 20 ml of methanol was stirred with 10% Pd/C (100 mg) under H_2 atmosphere for 12 hr. The mixture was then filtered to remove the catalyst and the methanol layer was concentrated to give solid residue which was purified by column chromatography over silica gel to give **21**.

M.P. : 135°C

Yield : (1.69gm, 69%)

IR (Nujol) : 3560, 1720, 1600 cm^{-1}

^{1}H NMR (200MHz,Acetone d_6): δ 0.90 (s, 3H); 1.44 (s, 3H); 3.29 (d, J = 12.9 Hz, 2H); 4.70 (d, J = 12.9 Hz, 2H); 6.50 (s, 2H); 6.80 (s, 2H).

MS (m/z) : 248 M^+ (45), 220 (100), 134 (60), 106 (43).

4,6-Dibromo-5-amino isatin acetal 22

Amino compound **21** (0.580, 2.8 mmol) in rectified spirit (5 ml) was cooled to 0°C, a solution of bromine in chloroform (1ml, 5.6mmol) [1ml Br_2 dissolved in 50 ml $CHCl_3$] was added slowly and the reaction mixture was stirred for 3 hr. The ethanol was removed and the residue was washed with water, dried and recrystallized from ethanol to give **22**.

M.P. : 240°C

Yield : (0.74gm, 78%)

IR (Nujol) : 3600, 1720, 1600 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 0.95 (s, 3H); 1.45 (s, 3H); 3.45 (d, J = 12.9 Hz, 2H); 4.55 (d, J = 12.9 Hz, 2H); 6.95 (s, 1H).

Ms(m/z) : 406 (M+2), 404 (M^+), 202, 141, 97.

4,6-Dibromoisatin 6

A mixture of compound **22** (0.220 gm, 0.65 mmol), t-butyl nitrite (1 ml) were stirred in DMF (5ml) for 10 hr at 60°C. After the reaction was over (TLC), the mixture was diluted with ethyl acetate and organic layer was washed several times with water then brine solution and concentrated. The residue obtained was directly stirred with saturated oxalic acid solution at 50°C overnight and cooled. The mixture was diluted

with water, a solid was separated filtered and was recrystallised from ethanol to obtain 6.

M.P. : 256°C (lit[9]. 254°C)

Yield : (0.040 gm, 23%)

^{1}H NMR (200MHz, $CDCl_3$) : δ 7.05 (s, 1H); 7.30 (s, 1H); 10 (bs, 1H).

MS (m/z) : M^+, 305.

2,6-Dibromo-4-nitroaniline (2)

A solution of p-nitroaniline (20 gm , 0.45 mole) in glacial acetic acid (100 ml) at 65°C was stirred during addition of bromine (23.18 gm, 14.8 ml, 0.290 mole) in 20 ml of acetic acid within 4 hrs.. The reaction was then poured into a slurry of ice and water. The yellow solid separated was filtered, washed several times with water and air dried to give **2**.

Yield : (40.75 gm, 95%)

M.P. : 204°C

^{1}H NMR (200MHz,$CDCl_3$) : δ 6.8 (s, 2H); 8.25 (s, 2H).

MS (m/z) : 296 (M^+).

3,5-Dibromonitrobenzene (3)

A three neck round bottom flask containing compound **2** (9.6 gm, 0.031 mole) and rectified spirit (100 ml) was arranged a mechanical stirrer on a water bath and to the boiling reaction mixture was added approximately 2 ml H_2SO_4. Slowly then pulverised $NaNO_2$ (2.139gm, 0.031 mole) was added in portions, boiling was continued for a half hour, after the $NaNO_2$ addition was complete. The mixture was allowed to cool, the solids were collected by filtration and washed with water. The 3,5-dibromonitrobenzene (**3**) was separated from remaining inorganic salts by dissolving it in boiling ethanol and filtering the hot solution and concentration.

Yield : (6.3 gm, 71%)

M.P. : 106°C

MS (m/z) : 281 (M^+).

3,5-Dibromoaniline•Hydrobromide (4)

A thick slurry **3** (1.41 gm , 5.0 mmol) and Raney Nickel catalyst (100mg) in absolute ethanol (3 ml) was stirred under hydrogen for 6 hrs. After filtration of the solution and addition of equal volume of water caused crystallisation of the amine which was then taken in chloroform (5ml), Conc.HCl was added, the resultant precipitated hydrochloride was filtered and air dried to give **4**.

Yield : (0.812 gm, 61%)

M.P. : free amine mp 56°C

MS (m/z) : 251 (M^+)

3,5-Dibromoisonitroacetanilide (5)

A mixture of compound **4** (0.100gm, 3 mmol), chloral (0.07 gm, 3 mmol), hydroxyl ammonium hydrochloride (0.07 gm, 0.0003 mole) and sodium sulphate (0.56 gm, 30 mmol) in 3ml of water and 2 drop of conc. HCl was irradiated in micro-wave oven for 5-10 min. with occasional shaking After the reaction ice was added. The solid separated was filtered and recrystallised from ethyl acetate.

Yield : (0.108 gm, 85%)

M.P. : 191°C

MS (m/z) : 324 (M^+), 322.

4,6-Dibromoisatin (6)

Compound **5** (0.200gm, 6 mmol) in 0.86% H_2SO_4 (1ml) was irradiated in micro-wave oven cautiously for 5-10 min. The reaction mixture was then cooled and poured over ice. The precipitate formed was filtered and recrystallised with ethanol to give the desired **6**.

Yield : (0.16 gm, 85%)

M.P. : 256°C (lit[9]. 254°C)

General procedure for isonitrosoacetanilide:

A mixture of aromatic amine (1.70 mmol), chloral (2.00 mmol), hydroxylamine hydrochloride (2.55 mmol) and sodium sulphate (2 g) in water (4 ml) was irradiated in microwave oven for three minutes. The completion of the reaction was monitored by tlc. The reaction mixture was then added to crushed ice and precipitated product **24** was filtered, washed with water and dried (77-94% yield). The product was found to be pure by spectral analysis and by melting point. This general method was followed for the preparation of all isonitrosoacetanilides 24 (**Table-1**).

General procedure to prepare isatin :

Method A

Isonitrosoacetanilide (1.9mmol) dissolved in 1 ml of 85% sulfuric acid irradiated in microwave-oven, after reaction mixture was cooled and poured into ice, the solid separated is filtered and air dried.

Method B

Isonitrosoacetanilide (1.9 mmol) dissolved in 1 ml of 85% sulfuric acid heated on water bath (80°C) for one hr. reaction mixture then cooled and poured into ice, the solid separated was filtered and air dried.

Table-1: Comparison of experimental data of isonitrosoacetanilide 24 and isatin 25 from aromatic amines.

No.	Aromatic amine	mp of isonitrosoacetanilide, in ° C		Litrature mp of Isatin, in ° C	
		Lit mp	Obs mp	Lit mp	Obs mp
1.	**Aniline**	**175**[26]	**173**	**195**[26]	**196**
2.	***p*-Toluidine**	**162**[26]	**161**	**180**[26]	**182**
3.	***p*-Anisidine**	**121**[26]	**119**	**201**[26]	**203**
4.	***p*-Flouroaniline**	**160**[30]	**159**	**224**[30]	**227**
5.	***p*-Nitroaniline**	**204**[26]	**202**	--	-
6.	**Benzylamine**	**142**[26]	**141**	--	-
7.	**Anthranilic acid**	**208**[26]	**207**	--	-
8.	**3,5-dibromoaniline**	**198**[9]	**199**	**254**[9]	**259**

Convolutamidine A 1a

4,6-Dibromoisatin **6** (0.200 gm, 0.65 mmol) in acetone (5 ml) was stirred with catalytic triethylbenzylammonium hydroxide, overnight. The acetone was removed from the reaction and white solid was recrystallised from pet ether:ethyl acetate. Yield (210 mg, 98%).

M.P. : 196°C (lit[9] mp195°C)

^{1}H NMR (200MHz,$CDCl_3$) : δ 2.05 (s, 3H); 3.3 (d, J = 21.6 Hz, 1H); 3.9 (d, J = 21.6 Hz, 1H); 7.02 (s, 1H); 7.22 (s, 1H).

5-Fluoro derivative of Convolutamidine A 28:

Fluoroisatin **(26)** (0.324 gm,1.96 mmol) in acetone (5ml) stirred with catalytic Et_2NH (1 drop) over night. After the reaction (TLC), the acetone was removed and the residue recrystallised with ethyl acetate:pet ether to give **28** .

Yield : (0.31 gm, 71%)

M.P. : 196-198°C.

IR : 3500, 1740, 1600 cm^{-1}

^{1}H NMR (200MHz, $CDCl_3$) : δ 1.9 (s, 3H); 2.85 (d, J = 20.2 Hz, 2H); 3.1 (d, J = 20.2 Hz, 2H); 3.8 (bs, 1H); 6.6-7.1 (m, 3H); 10 (s, 2H).

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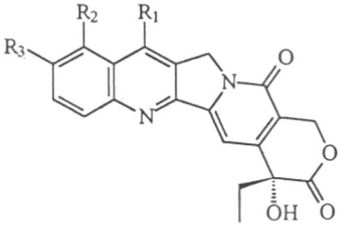
Chapter II:

Synthetic approaches to Camptothecin

Introduction

Camptothecin (**1**) is a novel, plant origin antitumor agent that was isolated from *Camptotheca accuminata* decene by Wall *et al.*[1] Unfortunately camptothecin had toxic effect on human hence research on it got initial set back and it commanded only marginal attention at clinical or chemical levels between 1973 to 1985. A number of promising analogues have now been prepared that show improved solubility, low overall toxicity and impressive *in vivo* activity against certain solid tumors. Some of the more active derivatives are irrnotecan **(2),** topotecan **(3)** etc..



(1) $R_1=R_2=R_3=H$

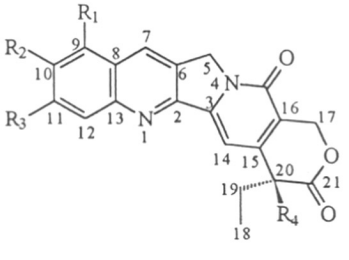
(2) $R_1=Et$, $R_2=H$

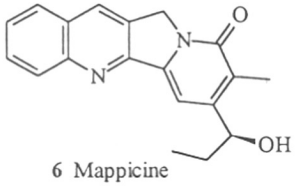
$R_3=$ —OCO—N⟨ ⟩N⟨ ⟩

(3) $R_1=H$ $R_2=CH_2NMe_2.HCl$ $R_3=OH$

Naturally occurring derivatives of camptothecin

10-Hydroxycamptothecin (**4**) and 10-methoxycamptothecin (**5**) were some of the other derivatives isolated by Wall *et al.*[2] from *Camptotheca accuminata*. Govindachari *et al.* isolated mappicine (**6**) and 9-methoxycamptothecin (**7**) from an Indian plant *Nathapodytes fotida*[3]. Hsu isolated 11-hydroxycamptothecin[3b] (**8**) and 11-methoxycamptothecin (**9**) from the fruits of *Camptotheca accuminata*. Deoxycamptothecin (**10**) was isolated from the same tree by Hutchinson and co-workers.[4]



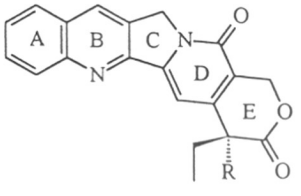


6 Mappicine

Derivatives	R_1	R_2	R_3	R_4
4	H	OH	H	OH
5	H	OMe	H	OH
7	OMe	H	H	OH
8	H	H	OH	OH
9	H	H	OMe	OH
10	H	H	H	H

Structure and characterization

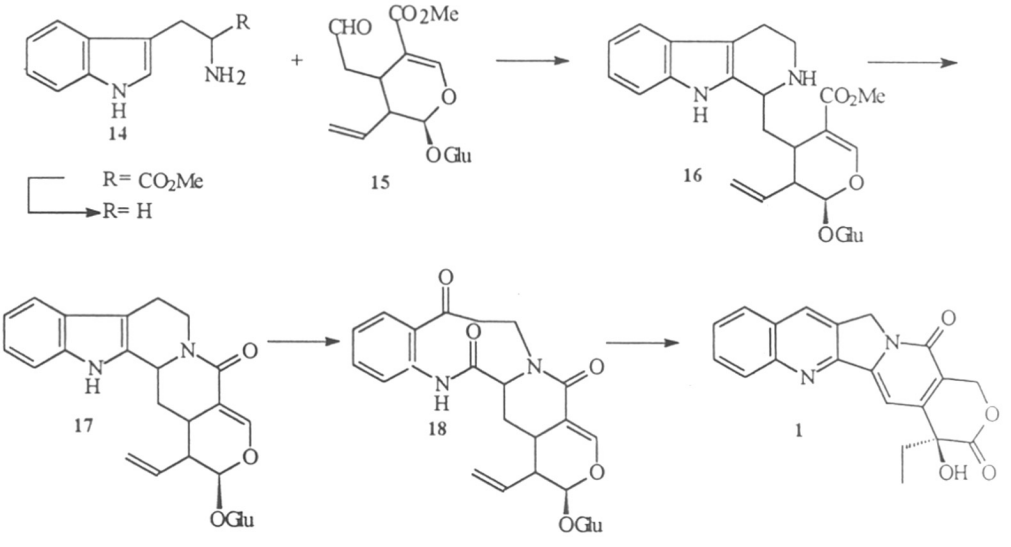
Based on the spectral properties of camptothecin like UV, IR, ^{1}H NMR, MS its structure was proved to be **1**. X-ray crystallography structure of its iodoacetate[5] **11** showed that the rings ABCD of camptothecin are coplanar. The formation of monoacetate **12** with acetic anhydride and chloro compound **13** with thionyl chloride proved the presence of a tertiary hydroxyl group. Formation of its sodium salt with sodium hydroxide and regeneration to **1** on acidification, proved the presence of a lactone structure. Lactal formation on reduction with $NaBH_4$ further gave a proof for lactone moiety.



11: R = $OCOCH_2I$
12: R = OAc
13: R = Cl

Biogenesis

Hutchinson *et al.*[5] by radioactive labeling experiments proved tryptophan (**14**) and secologanin (**15**) are the biogenetic intermediates. These combine to form stricosidine (**16**). The stricosidine (**16**) was lactamized to the lactam strictosamide (**17**) which *via* reduction and oxidation gives keto lactam **18**. The intramolecular cyclisation of **18** produces a pyrroloquinoline derivative; which in turn through a sequence of oxidation-reduction steps, transformed into camptothecin (**1**).



Structural requirements for antitumor activity in camptothecin and related compounds

Camptothecin itself is found to be very active against variety of leukemias and solid tumors. It has been found that structural variation[7] in camptothecin skeleton changes the antitumor activity. Such variations in the structure are summarized in **Table 1.**

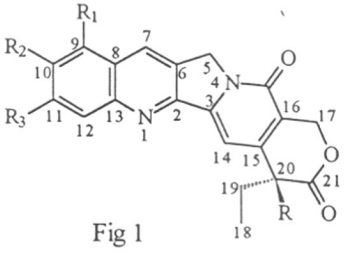


Fig 1

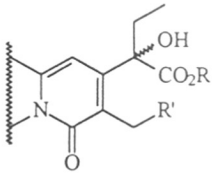


Fig 2

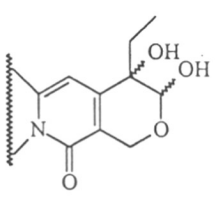
Table 1

Fig 1

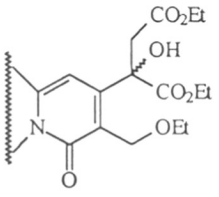
R	R_1	R_2	R_3	Activity
OH	H	H	H	Active
OH	OH	H	H	Highly active
OH	H	OMe	H	Active
OH	OMe	H	H	Active
OAc	H	H	H	Inactive
Cl	H	H	H	Inactive
H	H	H	H	Less active
OH	H	H	H	Less active
OH	H	H	OCH_2CH_2Na	Inactive
OH	H	H	OCH_2CH_2N	Active
OH	H	H	NH_2	Active
OH	H	H	Cl	Active
OH	H	H	OH	Active
OH	H	H	OMe	Active

Fig 2

R	R^1	Activity
NHMe	OH	Less active
Me_2CHNH	OH	Less active
Me_2CHNH	OAc	Less active
Me_2CHNH	C_4H_8N	inactive
ONa	OH	Active



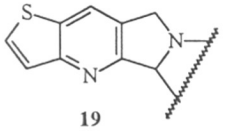
less active



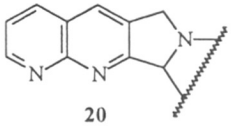
inactive

Modification of ABC rings

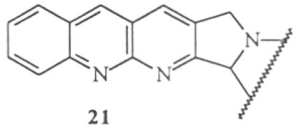
Introduction of hydroxy, methoxy, functionality at 10 position in the A ring of camptothecin has less effect on antitumor activity, where as 9-methoxy, 11-hydroxy or methoxy showed improved activity. Substitution at 12 position with Cl, OH, OMe also exhibit improved activity. 10-Chloro, fluoro, OCH_2CO_2H, sodium salts were more active than sodium salt of camptothecin whereas 11-fluoro, sodium salt of camptothecin is inactive. Heteroaromatic analogues like **19** and **20** showed decreased activity while ring modification *viz.* (**21**) showed comparable activity.



19



20



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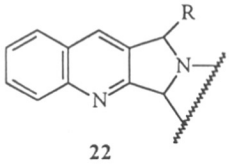
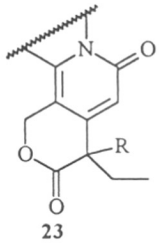


22

R = OH, OAc, Et

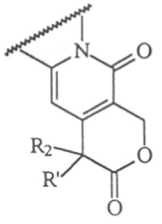


23

7-Chloro, acetoxy, or methoxy, camptothecin showed decreased activity. The N-oxide has same effect. Substitution at 5 position **22** with OH, or OAc, Et showed decreased activity. So ABC planner rings with free nitrogen may be responsible for biological activity of camptothecin.

Modification in DE ring

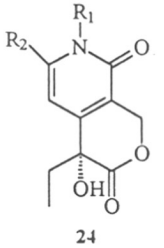
Isocamptothecin (**23**) showed reduced activity. Hydroxy group replacement in E ring with Cl, allyl, ethyl and CH_2OH showed no activity.



R^1	R_2	Activity
Allyl	Ethyl	Inactive
Et	Et	Inactive
CH_2OH	Et	Inactive
OH	Allyl	Active
OH	Propargyl	Active

Replacement of ethyl group of camptothecin by allyl, propargyl, benzyl, isopropyl methoxy, ethyl showed no marked charge in activity.

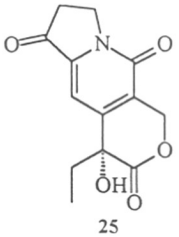
The reduced activity of sodium salt of camptothecin compared to **1** believed to be due to pH 7.0 in human blood. The lack of regeneration of **1** in this pH is effecting factor. The lactal obtained by reduction with $NaBH_4$ showed reduced activity. So hydroxy lactone is essential for biological activity of camptothecin (**1**).



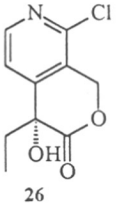
24

R_1 = H or Me

R_2 = Hor CO_2Me



25



26

Synthetic intermediates **24**, **25** and **26** are found to be inactive. ABC ring in conjugation with DE ring and pyridone moiety is required for biological activity of (**1**).

Action of camptothecin

Camptothecin interferes with the DNA-breakage - reunion reaction catalyzed by topoisomerase I by trapping a covalent enzyme DNA. This enzyme is found higher in leukemia cells than in normal cells.

Synthesis

Various synthetic approaches towards camptothecin are reported and reviewed in the literature.[8] For convenience these synthetic routes are classified based on ring constructions and are briefly described in this part.

a. A + CDE ring synthon b. ABC + D + E ring synthon

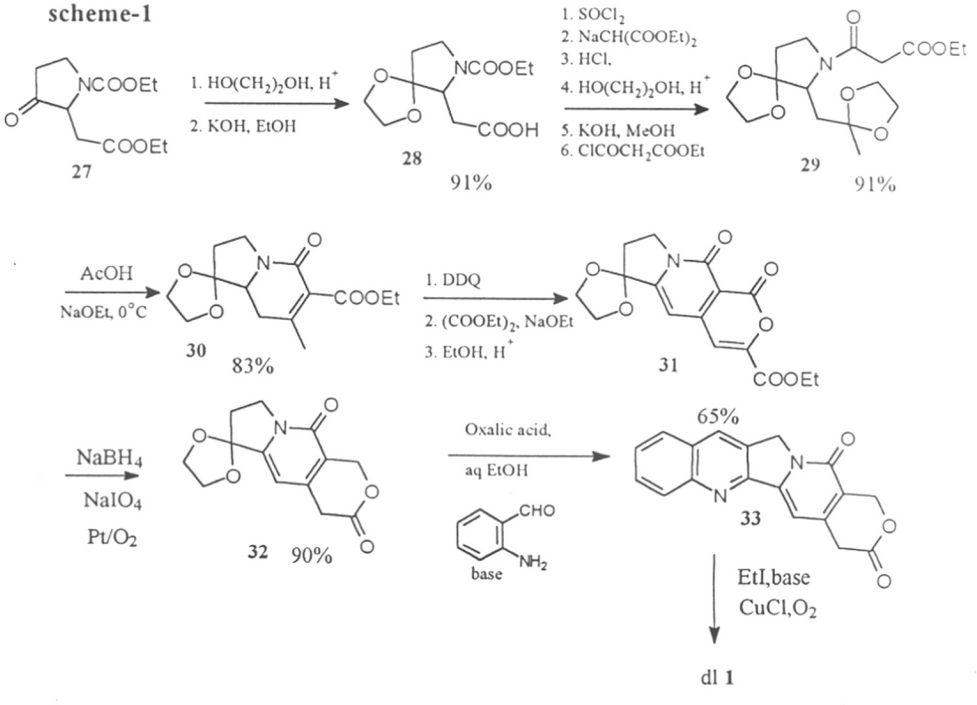
c. ABC + DE ring synthon d. AB + DE ring synthon

e. miscellaneous.

a. A + CDE ring synthons (Friedlander condensation is the key step)

Shamma's approach (Tetrahedron 1973, **29**, 1949)

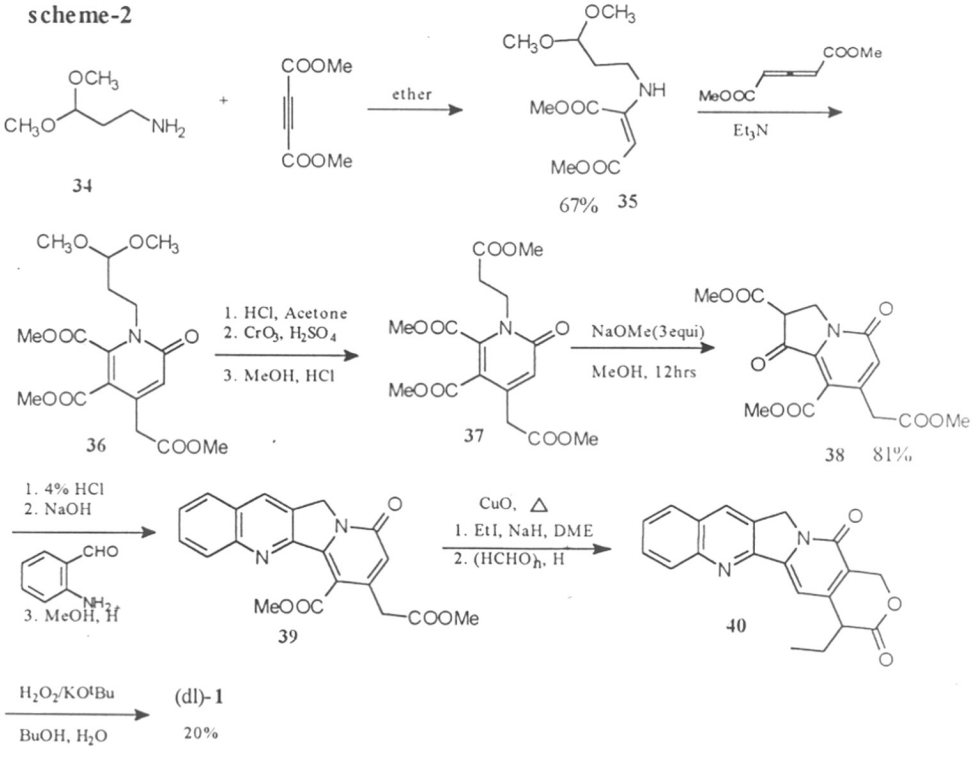
scheme-1



Pyrrolidone **27** was protected and saponified with KOH to give acid **28** in 91% yield. The acid **28** was converted into methyl ketone by sequential reactions as shown in **Scheme-1**. Selective deprotection of **29** with acetic acid at 60°C followed by cyclisation using sodium ethoxide furnished dihydropyridone **31** in 83% yield. Oxidation with DDQ followed by condensation with diethyloxalate gave pyridone **31** in 65% yield. Borohydride reduction of the pyridone **31** followed by periodate oxidation provided lactal, which was oxidized with Pt/O_2 to give lactone **32**. Deprotection of acetal **32** with oxalic acid followed by Friedlander condensation with o-aminobenzaldehyde gave quinoline **33** which was converted to (±)-camptothecin by ethylation and oxidation in overall 6.5% yield.

Danishefky approach (J. Am. Chem. Soc.1971, **93**, 5571)

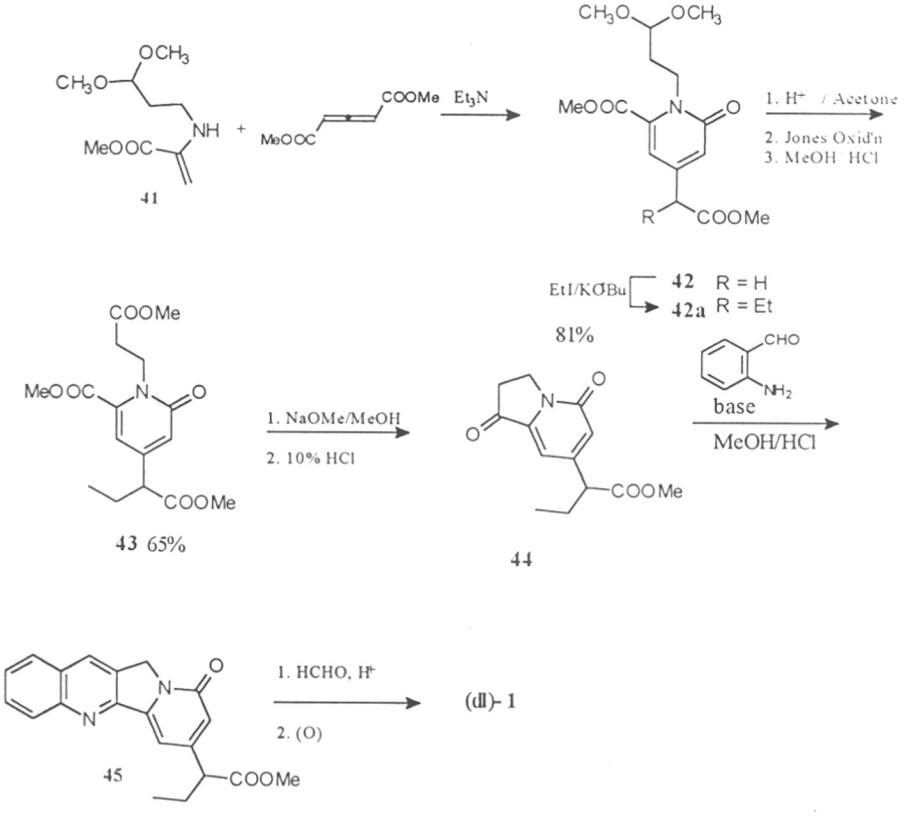
scheme-2



Enamine ester **35** **(Scheme-2)** was prepared from β-aminopropionaldehydedimethyl acetal **(34)** and dimethylacetylenedicarboxylate. The enamine ester **35** was treated with allene at RT to give pyridone **36** in 45% yield. Its deprotection, oxidation and esterification gave compound **37**. The Dieckmann cyclisation of **37** using sodium methoxide in methanol gave **38**. Its decarboxylation under acidic condition followed by Friedlander condensation gave quinoline **39**. Copper catalyzed decarboxylation of **39** followed by ethylation and hydroxy methylation gave lactone **40** which was oxidized to (±)-**1** in overall 1.2 % yield.

Quick's approach (Tetrahedron Lett 1977, **4**, 327)

Scheme-3:

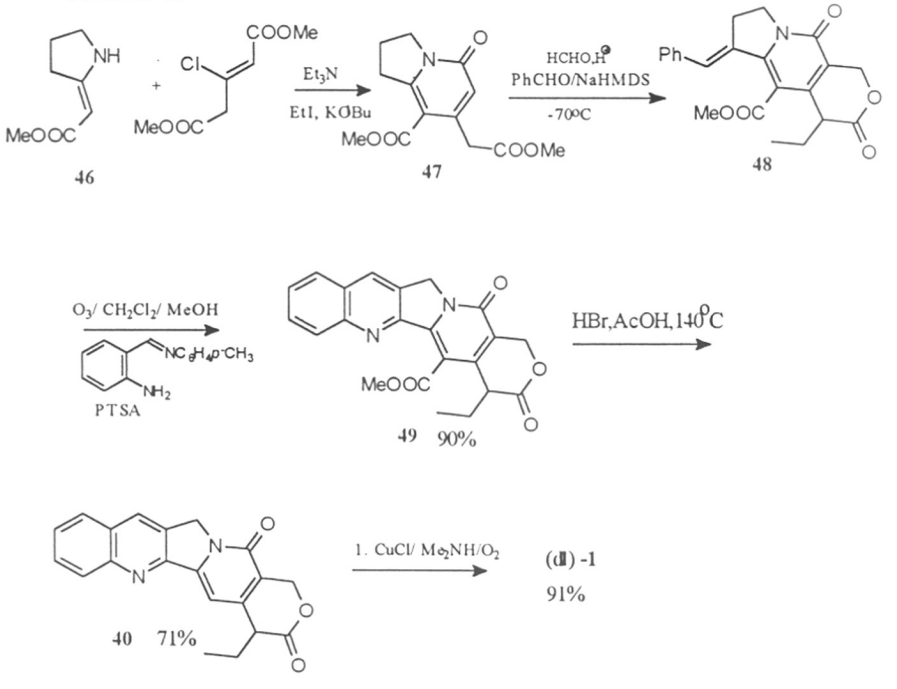


Enamine of methylpyruvate **41** **(Scheme-3)** was cyclised with allene to give pyridone **42** This pyridone **42** was ethylated using EtI, KO^{t}Bu/DME in 63% yield. Further deprotection of the resulting pyridone **42a** was oxidized and esterified to give triester **43** in 65% yield. Dieckmann condensation of **43** followed by decarboxylation

gave ketone **44**, which under Friedlander condensation and subsequent esterification gave ester **45**. The ester **45** was then converted to (dl)-1 by hydroxy methylation and oxidation in overall 1.8 % yield.

Danishfsky's 2nd approach (J. Org. Chem. 1995, **60**, 611)

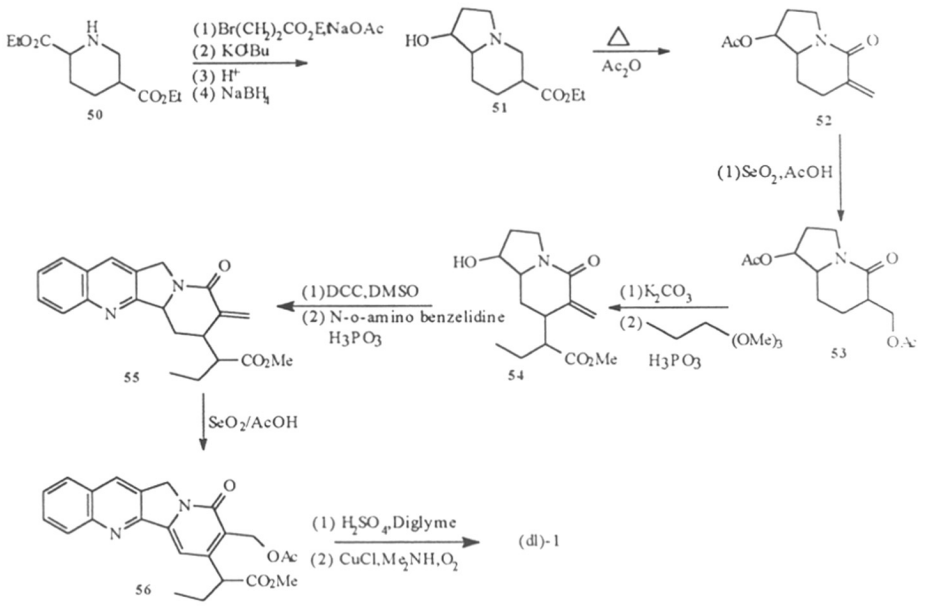
Scheme-4:



Enamine **46** was reacted with allene to give pyridone **47** in 92% yield (**Scheme-4**). Its ethylation using ethyl iodide, KO^{t}Bu, followed by hydroxy formylation and treatment with benzaldehyde using NaHMDS gave olefinic lactone **48**. Ozonolysis of the olefinic lactone **48** gave ketone. The ketone formed was condensed with N (o-amino benzilidine) p-toluidine to give pentacyhclic lactone **49**. The hydrolysis and decarboxyltion (HBr) of this lactone **49** gave deoxycamptothecin **40**. The oxidation of **40** gave (dl)-**1** in 30% overall yield.

Rapoport's approach (J. Am. Chem. Soc., 1972, **94**, 3631)

Scheme-5:



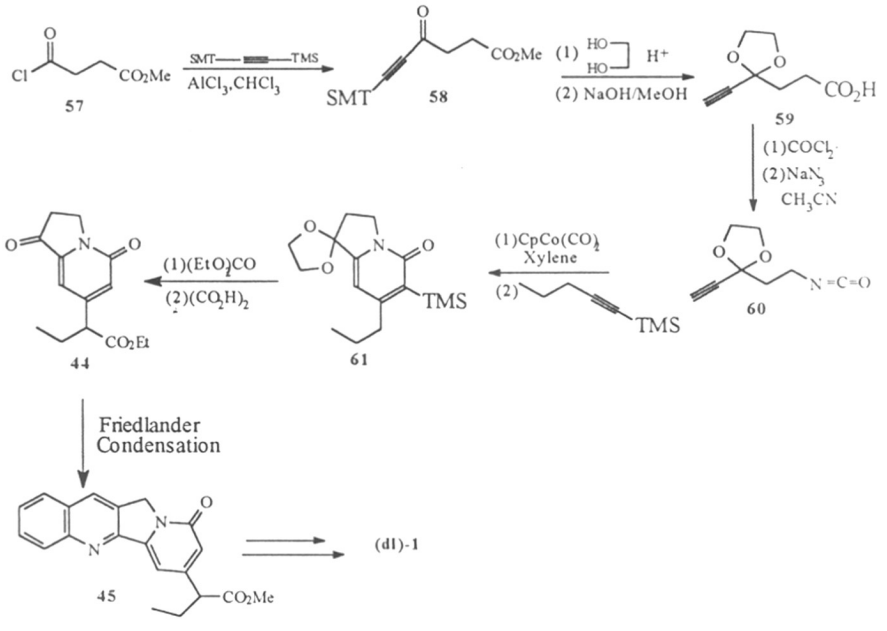
Bicyclic alcohol **51** was prepared from diethylpiperidine **50** in four steps (N-alkylation, Dieckmann condensation, decarboxylation and reduction as shown in **Scheme-5**. When the bicyclic alcohol **51** was refluxed with acetic anhydride, a novel rearrangement takes place with the formation of α-methylene lactam piperidone acetate **52** which was further oxidized with SeO_2 in acetic acid to diacetate **53**. Hydrolysis of the acetate **53** followed by Claisen ortho-ester rearrangement reaction with trimethyl orthobutyrate furnished **54** in 100% yield. Oxidation of the **54** [DCC, DMSO] followed by Friedlander condensation gave quinoline **55**, which was aromatized with SeO_2 in acetic acid to **56**. Hydrolysis of **56** followed by oxidation gave (dl)-1 in 15% overall yield.

Vallhardt's approach (J. Org. Chem. 1984, **49**, 4786)

1,2-Bistrimethylsilyl acetylene was acylated with 3-carbomethoxy propanoyl chloride to give ketoester **58** in 83% yield. Protection of the ketone **58 (Scheme-6)** with ethylene glycol in benzene provided ketal in 97% yield. Its hydrolysis with NaOH in

MeOH gave acid **59** which was then converted into acid chloride (oxalyl chloride) and further Curtiues rearrangement with NaN_3 in acetonitrile gave isocyanate **60** in 84%

Scheme-6:

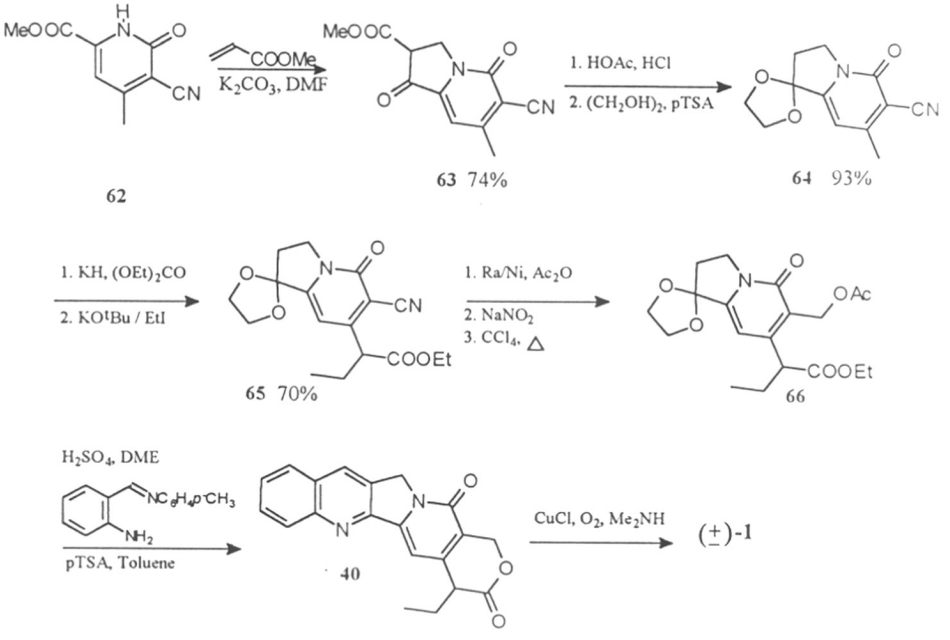


yield. Cobalt mediated cyclisation with trimethylsilyl-1-pentene with the isocyanate 60 gave pyridone **61** in 60% yield. Treatment of **61** with diethyl carbonate in presence of KH gave ester, which was deprotected with oxalic acid in ethanol to give ketone **44** in 54% yield. Friedlander condensation provided quinoline **45** in 78% yield, which was further, converted to (dl)-1 in 2 steps. The overall yield was 8.7%.

Wani's approach. (J. Med. Chem., 1980, **23**, 554)

Tandem Michael Dieckmann condensation (**Scheme-7**) of pyridone **62** with methyl acrylate gave keto ester **63** in 74% yield. Its hydrolysis, decarboxylation followed by protection furnished **64** in 93% yield. The ethyl ester group in **64** was introduced by using KH and diethyl carbonate, which was further, ethylated using EtI, KO^{t}Bu to give **65**. Raney Ni reduction of **65** followed by treatment with $NaNO_2$ gave ketal 66. Lactonisation of **66** using sulfuric acid gave lactone which under Friedlander condensation gave deoxycamptothecin **40**, which on oxidation with CuCl gave (dl)-1 in overall 28%, yield.

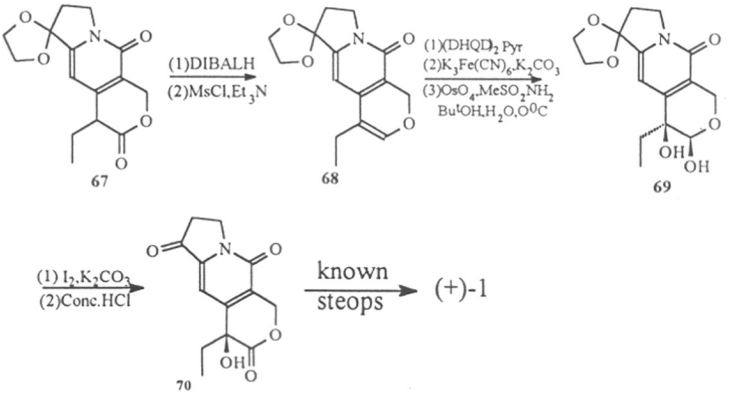
Scheme-7:



Similar procedure was adopted to get chiral (+)-1 using prolinol as a chiral agent.

Jew's approach (Tetrahedron: Assym., 1995, **6**, 1245)

Scheme-8:

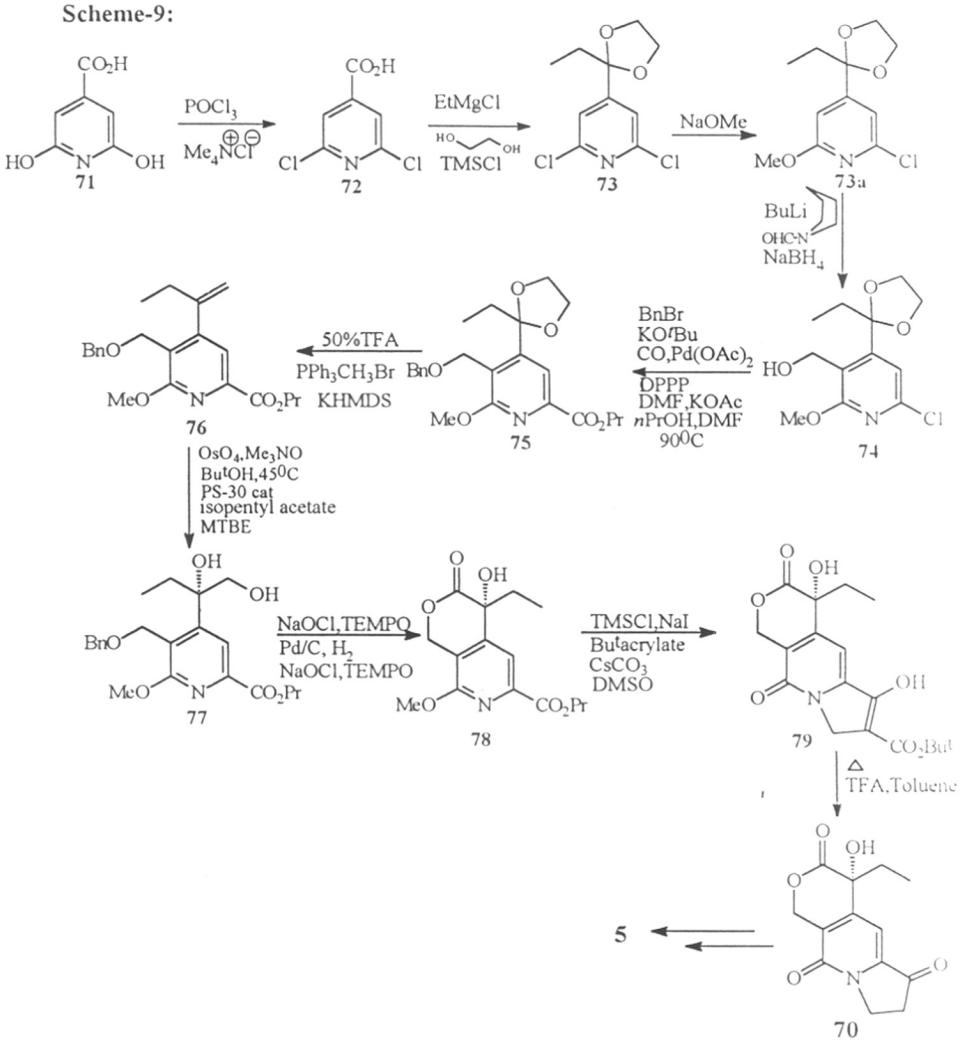


The synthesis consists of asymmetric dihydroxylation using Sharpless asymmetric procedure $(DHQD)_2$ PHAL or $(DHQD)_2$ pyridine of olefinic ether **68 (Scheme-8)**. Thus diol **69** formed was further oxidized to lactone **70** using $CaCO_3$ in presence of iodine. Hydrolysis of the ketal gave chiral intermediate **70** from which (+)-1 was prepared by known Friedlander method.

Henegar's approach (J. Org. Chem., 1997, **62**, 6585)

Commercially available citrazinic acid **71** was first converted to 2,6, dichloro isonicotonic acid **72 (Scheme-9)** with $POCl_3$ in 78% yield. Conversion of the acid 72 into ethyl ketone was achieved in 84% yield by reaction of ethylmagnesium chloride at -40°C. This was further converted to crystalline ketal **73** in 99% yield using ethylene glycol and TMSCl. The ketal **73** was treated with NaOMe in refluxing methanol to give methoxy compound **73a** in 89% yield. Further it was then converted into alcohol **74** by using Comins procedure in 99% yield.

Scheme-9:



Protection of the alcohol **74** as benzyl ether (BnBr, t-BuOK) followed by carbonylation and esterification gave propyl ester **75** in 89% yield. Deketalisation of the **75** with 50% TFA gave 98% yield of ketone which on treatment with Wittig reagent. (PPh_3PCH_3Br, KHMDS DMF) gave olefin **76**. Dihydroxylation of the compound **76** with OsO_4, Me_3NO, $2H_2O$, tBuOH, 45°C followed by resolution gave asymmetric diol **77** in 38% yield (PS-30 cat isopentyl acetate MTBE resolving catalyst).

The primary alcohol of diol **77** was oxidized to aldehyde in 95% yield using sodium hypochlorite and TEMPO. Hydrogenalysis of benzyl ether gave lactol, which on second TEMPO oxidation gave lactone **78**. Reaction of the lactone **78** with TMSI gave pyridone in 89% yield. Annulation of cyclopentanone ring was done with t-butyl acrylate

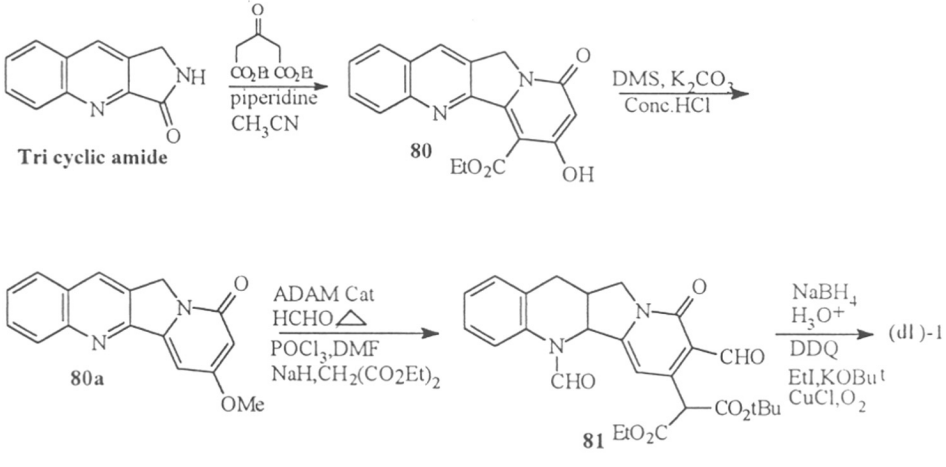
(10 eq) and $CsCO_3$ (2 eq.) in DMSO at 50°C to give **79** in 75% yield. Decarboxylation of β-keto ester **79** was carried out using TFA in toluene to give **70** in 95% yield. The intermediate CDE ring synthon **70** was obtained in 6.4 % overall yield with ee > 99.6%.

b. ABC + D + E ring synthon

Sugasawa's approach (Tetrahedron Lett. 1972, **50**, 5109)

Tricyclicamide was condensed with diethyl acetonedicarboxylate at 60°C, which underwent intramolecular cyclisation in presence of piperidine in acetonitrile to give pyridone **80**. The decarboxylation of **80** followed by methylation gave quinoline **80a**. The quinoline **80a** on hydrogenation followed by formylation and then alkylation gave compound **81** as shown in **scheme-10**. The reduction of this aldehyde **81** followed by decarboxylation and aromatisation with DDQ gave intermediate lactone which was further ethylated (EtI, $KOBu^t$) and oxidized to give (dl)-**1**, in overall 8.4% yield.

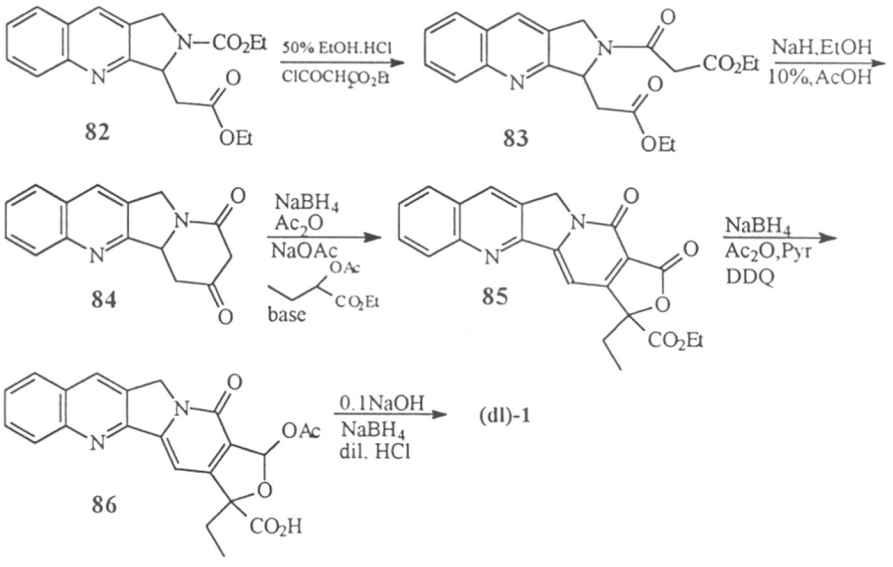
Scheme-10:



Strok's approach (J. Am. Chem. Soc., 1971, **93**, 4074)

N-Carboethoxy group in diester **82** was hydrolyzed and decarboxylated with ethanolic HCl to get amine which was treated with acid chloride of ethyl malonate to give amide ester **83** as shown in **Scheme-11**.

Scheme-11

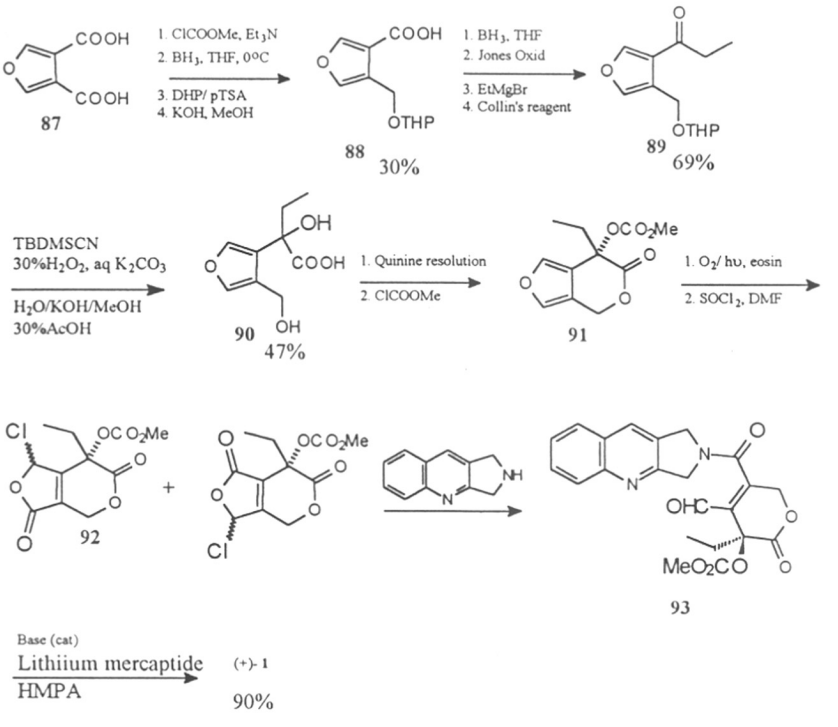


The Dieckmann cyclisation of amide ester **83** using NaH and further decarboxylation furnished keto amide **84**. Reduction of the keto amide **84** followed its conversion to acetate and its nucleophilic exchange of acetate with anion of diester with base gave lactone **85**. The lactone **85** was reduced, acetylated then aromatized with DDQ oxidation to furnished acetyl derivative **86**. This acetyl derivative **86** was then hydrolyzed with 0.1 N NaOH and reductively opened to an intermediate which on cyclisation with dil. HCl gave (±)-**1** in overall 29% yield.

Corey's approach (J. Org. Chem. 1975, **40**, 2140)

Corey and co-workers reported the first asymmetric synthesis of camptothecin (**1**). 3,4-Furan dicarboxylic acid **87** was selectively reduced to alcohol, as shown in **Scheme-12**. Further, the intermediate alcohol was protected as THP ether **88**. The carboxylic acid group of THP ether **88** was reduced with diborane to alcohol, which on Jones oxidation furnished aldehyde.

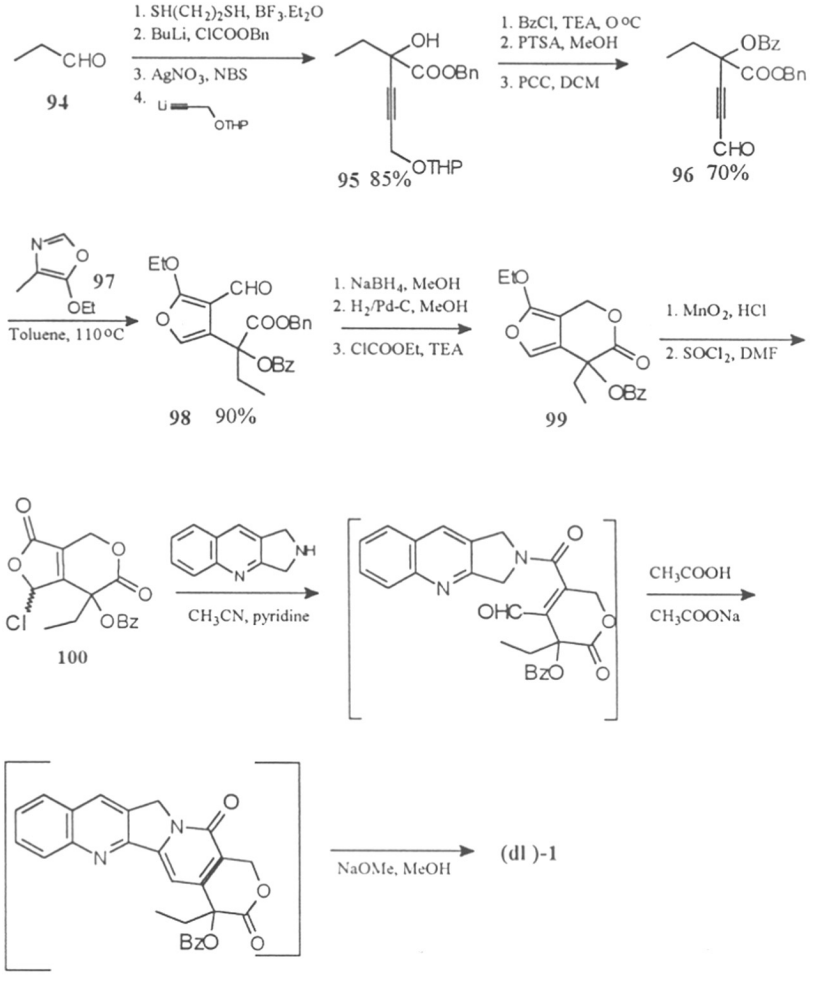
Scheme-12:



The intermediate aldehyde was further treated with ethyl magnesium bromide followed by oxidation using Collins reagent to afford ketone **89**. This ketone **89** was further reacted with TBDMSCN to give cyano hydrin, which was further, hydrolyzed to acid. The THP ether of the intermediate acid was deprotected in acetic acid to furnish the corresponding alcohol **90**. The racemic alcohol **90** was resolved by using quinine and the resolved tertiary alcohol **90** was protected with chloromethylformate to give lactone **91**. Photooxidation of the chloroformate ester **91** followed by thionyl chloride reaction gave pseudochloride **92**. This pseudochloride **92** was reacted with tricyclic amine to give intermediate aldehyde **93**, which on cyclisation with base gave quinoline lactone. This lactone was converted to (+)-**1** by hydrolysis of ester group in overall 4.6% yield.

Rama Rao's approach. (Tetrahedron Lett. 1994, **35**, 3613)

Scheme-13:

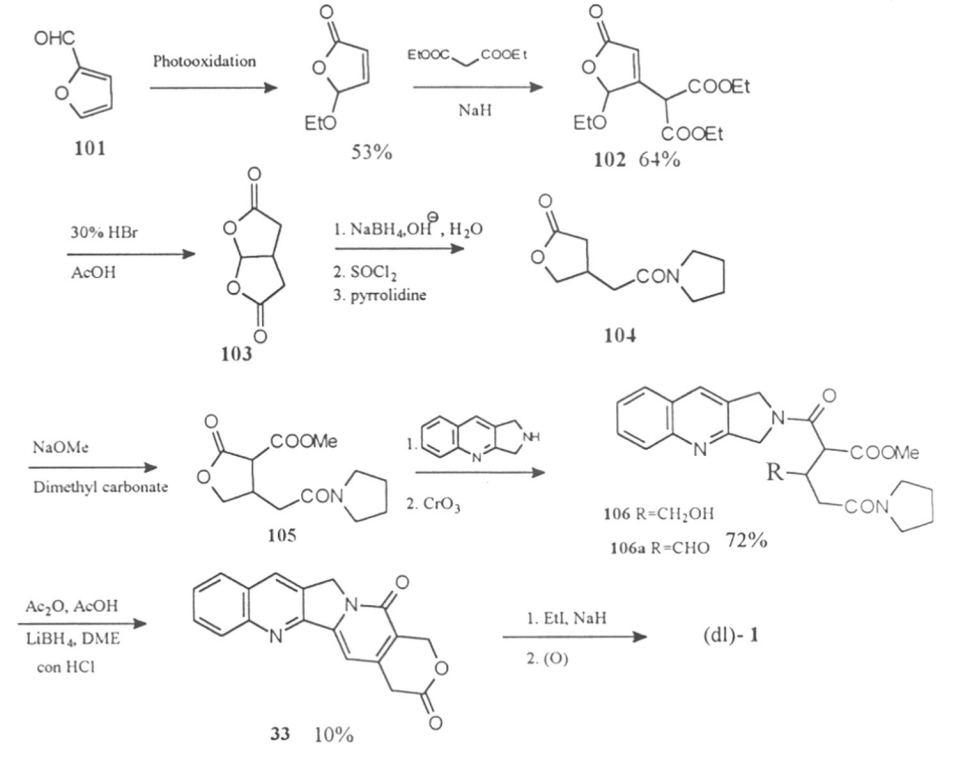


Propionaldehyde (**94**) was converted to alcohol **95** by sequential reaction of protection, introduction of benzyl ester, deprotection of dithiane and nuclcoprilic attack of lithio derivative of THP ether of propargyl alcohol as shown in the **Scheme-13**. This alcohol **95** was protected as benzyl ether and further converted to aldehyde **96** by deprotection and PCC oxidation. The aldehyde **96** was subjected to Diels Alder reaction with **97** followed by reduction of aldehyde function, hydrogenalysis of benzyl group and

cyclisation to give lactone **99**. This lactone **99** was oxidized with MnO_2 and treated with thionyl chloride to give pseudochloride **100**. The pseudochloride **100** was then treated with tricyclicamine and an intermediate aldehyde formed was cyclised to give (±)-**1** in overall 40% yield.

Pandit's approach (Tetrahedron, 1981, **37**, 371)

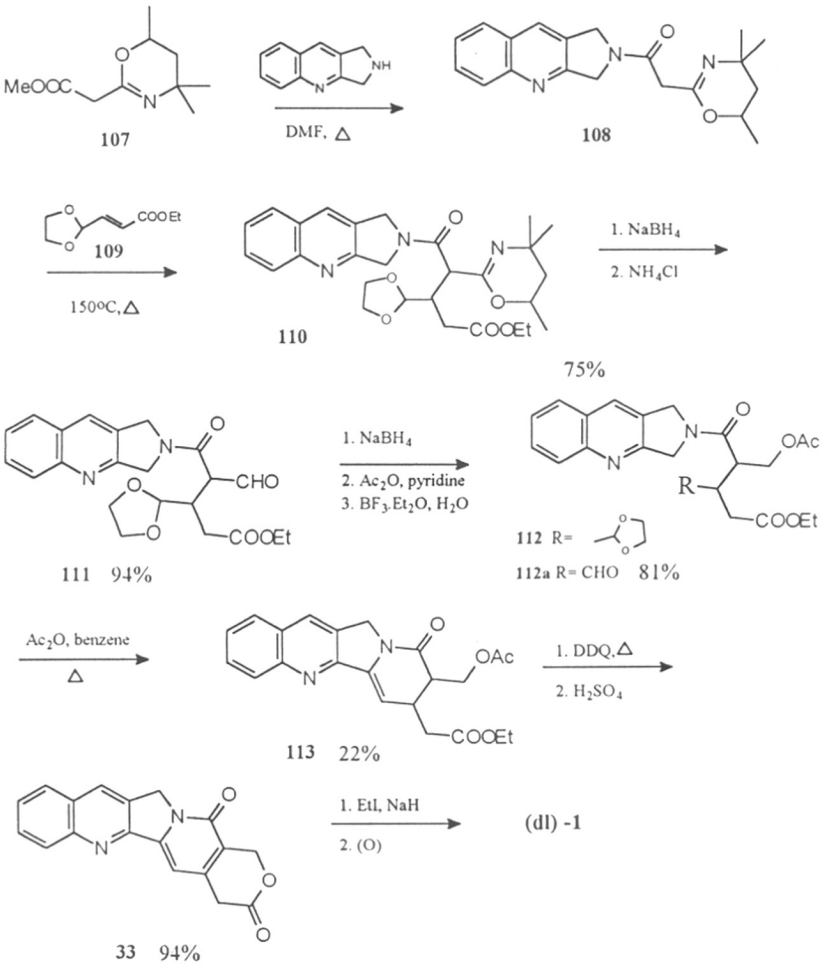
Scheme-14:



Furfuraldehyde **101** was first converted to hemiacetal **102** by photooxidation and Michael addition of diethyl malonate. The decarboxylation and *in situ* cyclisation of the hemiacetal **102** gave lactone **103**. The lactone **103** on reduction followed by reactions with thionyl chloride and pyrrolidone gave amido lactone **104**. The amido lactone **104** on treatment with dimethyl carbonate and sodium methoxide gave ester amide **105**. This ester amide **105** was reacted with tricyclic amine, methoxide and the resultant alcohol **106** was further oxidized with CrO_3 to aldehyde **106a**. Cyclisation of the aldehyde **106a** with acetic anhydride followed by lithium borohydride reduction gave lactone **33**. Further it was converted into (±)-**1** in two steps with overall 0.05% yield. (**Scheme-14**).

Meyer's approach (J. Org. Chem., 1973, **38**, 1974)

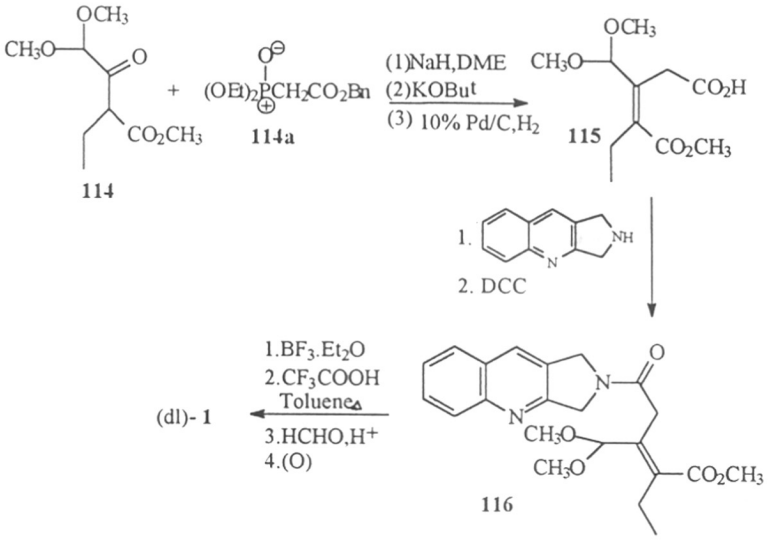
Scheme- 15:



Tricyclic amine was condensed with oxazoline ester **107** to give amide **108**. When the amide **108** was subjected to Michael addition with acetal **109**, it gave ester acetal **110**. The reduction of oxazoline **110** followed by deprotection gave aldehyde **111** which was further converted to acetate **112** as shown in **Scheme-15**. The acetal group in **112** was deprotected with $BF_3.Et_2O$ to give intermediate aldehyde **112a**, which was then cyclised with acetic anhydride to give ester **113**. The ester **113** was then oxidized with DDQ and lactonised with H_2SO_4 to give lactone **33** which was converted to (±)-**1** by known method in overall 8.2% yield.

Buchi's approach (J. Org. Chem.1976, **41**, 699)

Scheme-16:

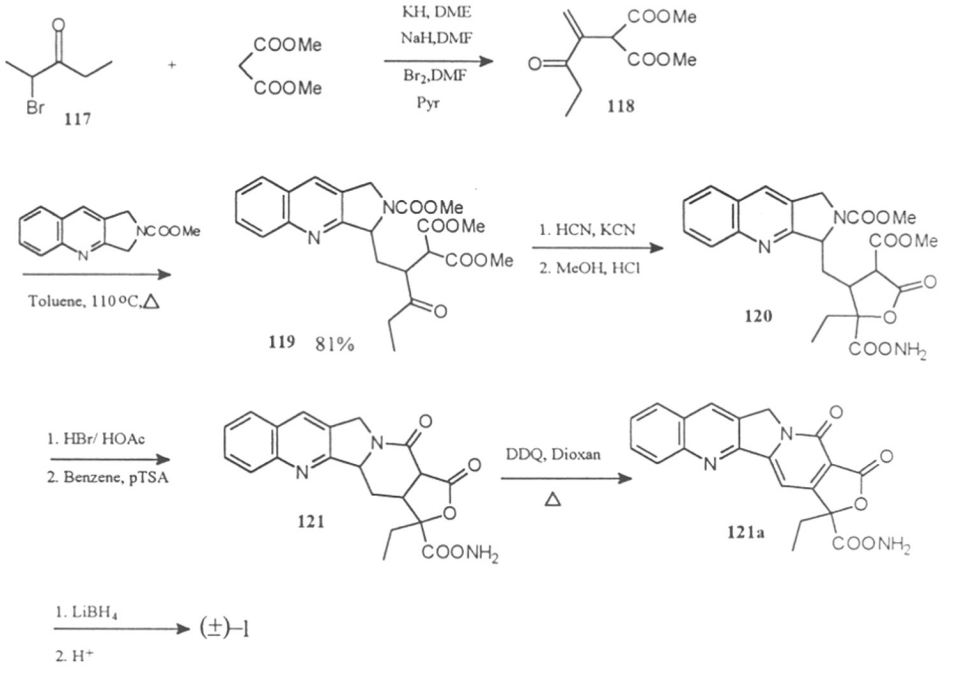


The acid **115** was prepared starting from dimethyl acetal **114** by Wittig-Horner reaction with phosphonate ylide **114a**, followed by isomerization of double bond and hydrogenalysis with Pd/C. The acid **115** was condensed with tricyclicamine to give acetal **116**. The acetal **116** was then converted to (±)-**1** by sequential reactions as shown in the **Scheme-16** in overall 10.8% yield.

Wall's approach (J. Am. Chem . Soc., 1972, **94**, 3631)

The olefinic ketone **118** was prepared from bromo ketone **117** and diethylmalonate in four steps as shown in **Scheme-17**. The ketone **118** undergoes Michael addition with tricyclic amine ester to give triester **119**. The triester **119** was further converted to lactone **120** in two steps by treating it with HCN/KCN followed by methanolic HCl. Cyclisation of the lactone **120** gave quinoline lactamide **121** which was further converted to (dl)-**1** in three steps, oxidation, reduction and hydrolysis, in overall 24% yield.

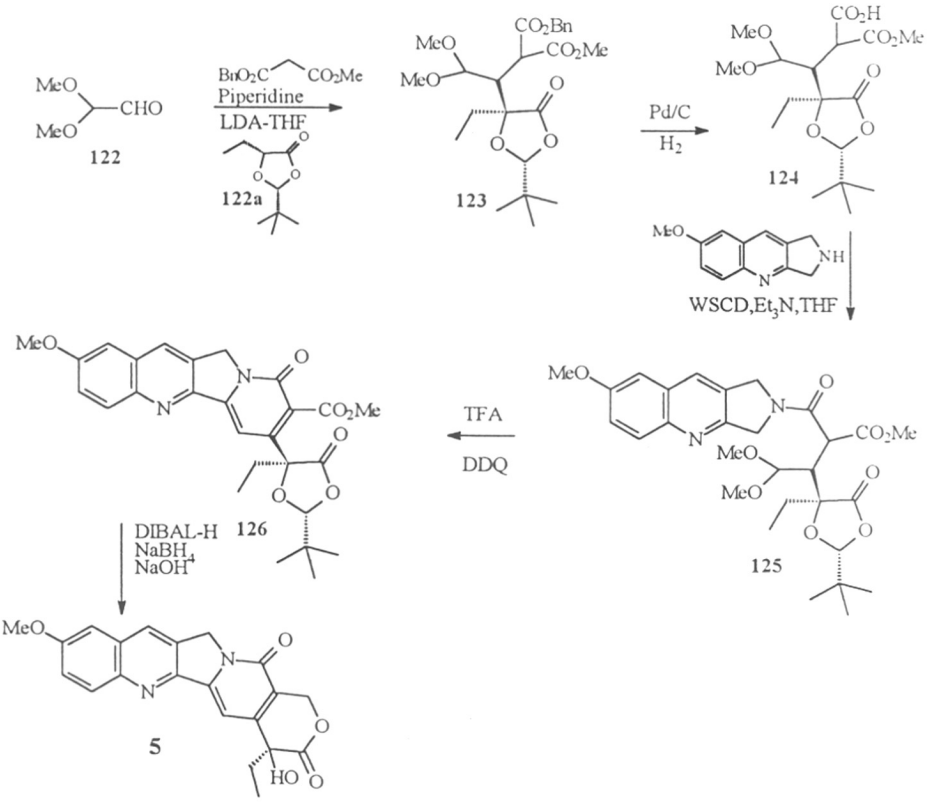
Scheme-17:



Fortunak's approach (Tetrahedron Lett., 1996, **37**, 5683)

Glyoxal-1,1-dimethyl acetal **122** was condensed with benzyl methyl malonate to yield an olefin which was utilized as a Michael acceptor in reaction with the enolate of **122a** to give an adduct (**Scheme-18**) **123**. Hydrogenanysis with Pd/C of the benzyl group of the adduct **123** gave acid **124**. The acid **124** was then condensed with tricyclic amine to give acetal **125**. Acidic cyclisation of the acetal **125** and subsequent DDQ oxidation gave ester **126**. Reduction of the methyl ester **126** with DIBAL-H followed by $NaBH_4$ reduction and alkaline hydrolysis yielded (S)-10-methoxycamptothecin (**5**) in overall 25% yield.

Scheme-18:

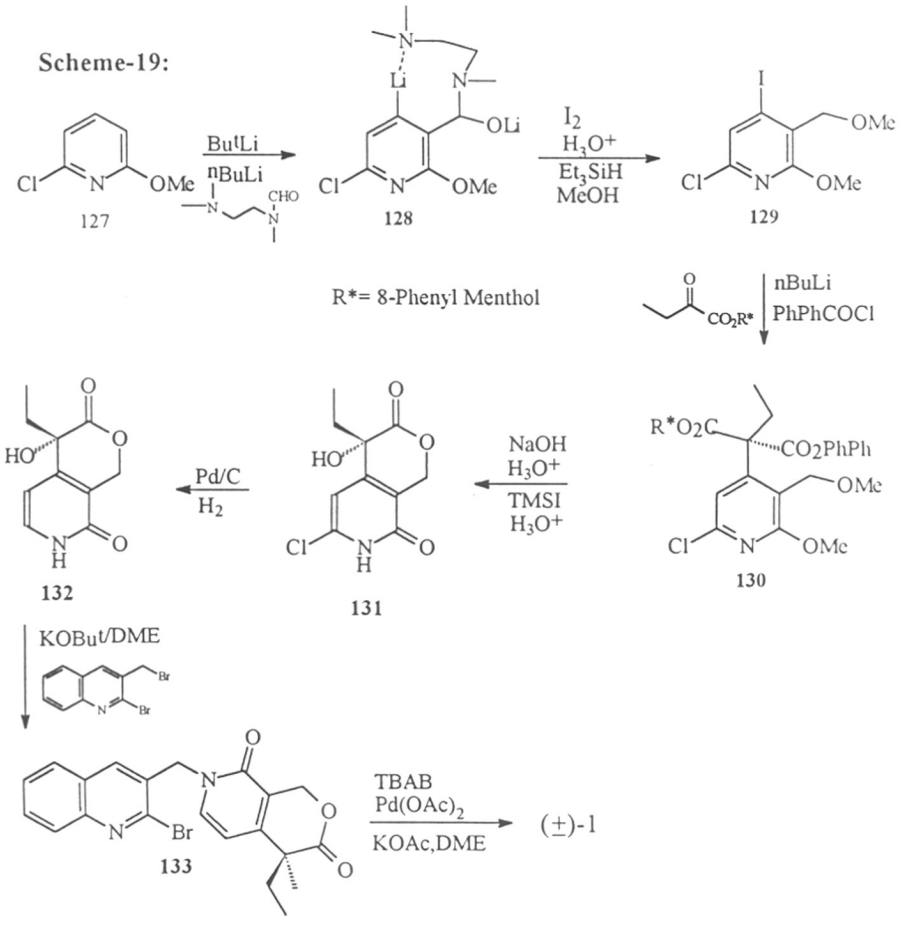


c. AB + DE ring synthon

Comins's approach (J.Am.Chem. Soc., 1992, **114**, 10971)

Comins et al. employed 2-chloro-6-methoxypyridine (**127**) as starting material. This pyridine **127** was converted to iodo methyl ether **129** in a sequence of six steps as depicted in **Scheme-19**. The ether **129** was then subjected to lithium halide exchange and then condensed with chiral α-ketoester to give an intermediate alcohol, which was trapped with 4-phenyllbenzoyl chloride to give ester **130**. Hydrolysis of ester **130** followed by demethylation with TMSI gave compound **131**. The dechlorination of compound **131** with Pd/C furnished compound **132**. N-alkylation of **132** with 2-bromo-3-bromomethylquinoline gave lactone **133** which was further cyclised under Heck condition to give (±)-**1** in overall 12.2% yield.

Scheme-19:

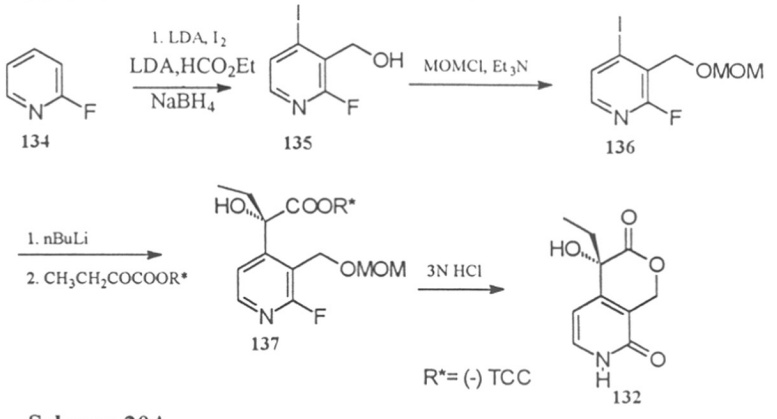


Comins and co-workers[10,11] reported two more similar approaches to (±)-1 in 1994 .

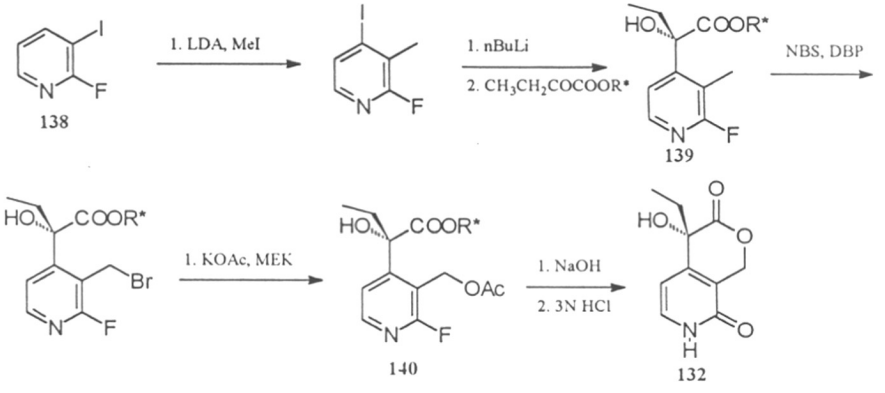
Comins's 4th approach (Tetrahedron Lett., 1995, **36**, 7795)

2-Fluoropyridine (**134**) was converted to iodo alcohol **135** in three steps *viz.* iodination formylation and reduction as shown in **Scheme-20**. MOM chloride protection of the alcohol **135** gave MOM ether **136**. The ether **136** on lithium iodo exchange and quenching it with chiral α-ketaester gave alcohol **137**. The alcohol **137** was then lactonised to the DE ring synthon **132** of camptothecin.

Scheme-20



Scheme-20A

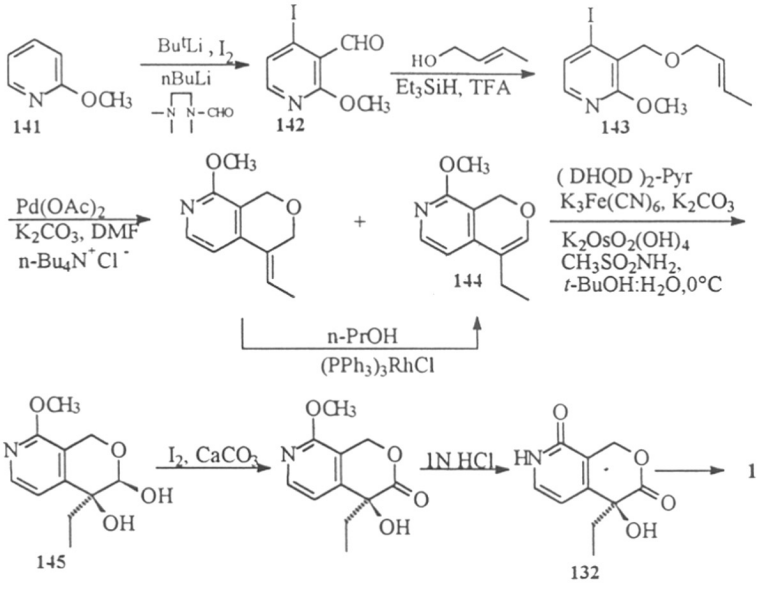


In another approach the same lactone **132** was prepared starting from iodo fluoro pyridine **138** as shown in **Scheme-20A**. Nuclear methylation using LDA, MeI, and lithium iodo exchange of the compound **138** with α-ketoester gave alcohol **139**. The alcohol **139** was then treated with NBS and converted to acetate **140**. Hydrolysis of the acetate **140** using sodium hydroxide followed by lactonisation with 3N HCl gave the DE ring synthon **132** of (±)-camptothecin.

Fang approach (J. Org. Chem., 1994, **59**, 6142)

2-Methoxypyridine **141** was converted to aldehyde **142** according to the Comins's approach. Further reductive etherification of the aldehyde **142** with crotylalcohol gave iodo ether **143**. Cyclisation of the iodo ether **143** with $Pd(OAc)_2$ gave olefin **144**.

Scheme- 21:



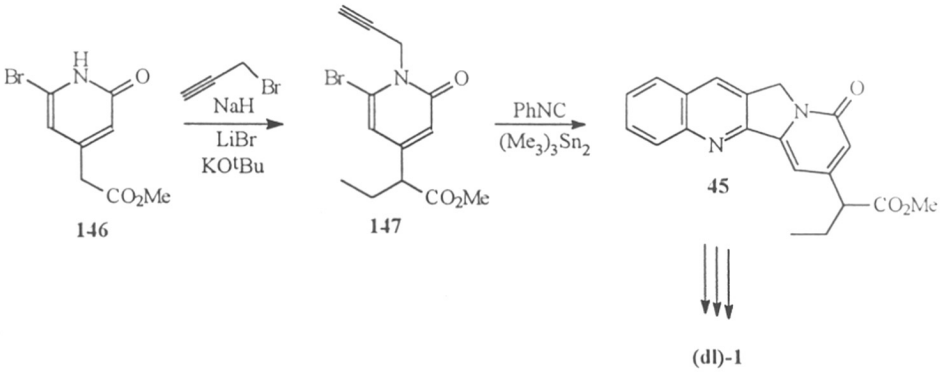
The olefin **144** under Sharpless asymmetric dihydroxylation gave diol **145**. The diol **145** on oxidation with I_2 and $CaCO_3$ gave an intermediate methoxy lactone which was converted to the DE ring synthon **132** of (±)-**1** by HCl hydrolysis (**Scheme-21**).

d. Miscellaneous approach

Curran's1st approach (J. Am. Chem. Soc., 1992, **114**, 5863)

The bromopyridone **146** was prepared from dimethyl acetonedicarboxylate and cyanoacetic acid in five steps. The pyridone **146** was first N-alkylated with propargyl bromide followed by ethylation with EtI gave acetylinic ester **147** The radical cyclisation of acetylinic ester **147** with phenyl isocyanate using bis-trimethylditin furnished quinoline **45**. The quinoline **45** was then converted to (±)-**1** by known methods in overall 3% yield (**Scheme-22**).

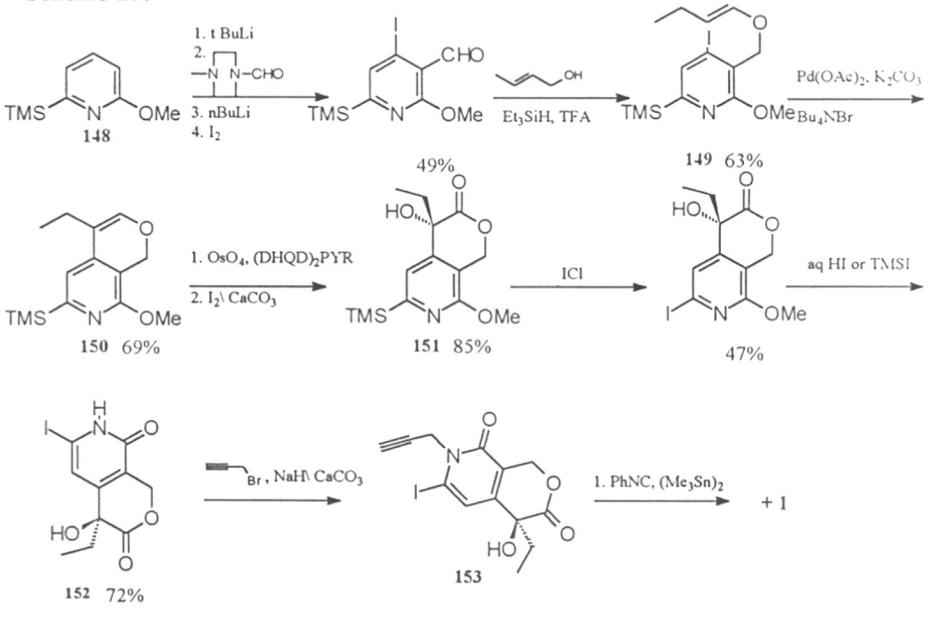
Scheme-22:



Curran's 2nd approach (Angew. Chem. Int. Ed. Engl., 1995, **34**, 2683)

An intermediate lactone **151** similar to Fang's approach[12] (see **scheme-21**) was prepared from 2 silyl-6-methoxy pyridine by employing six steps as shown in **Scheme-23**.

Scheme-23:



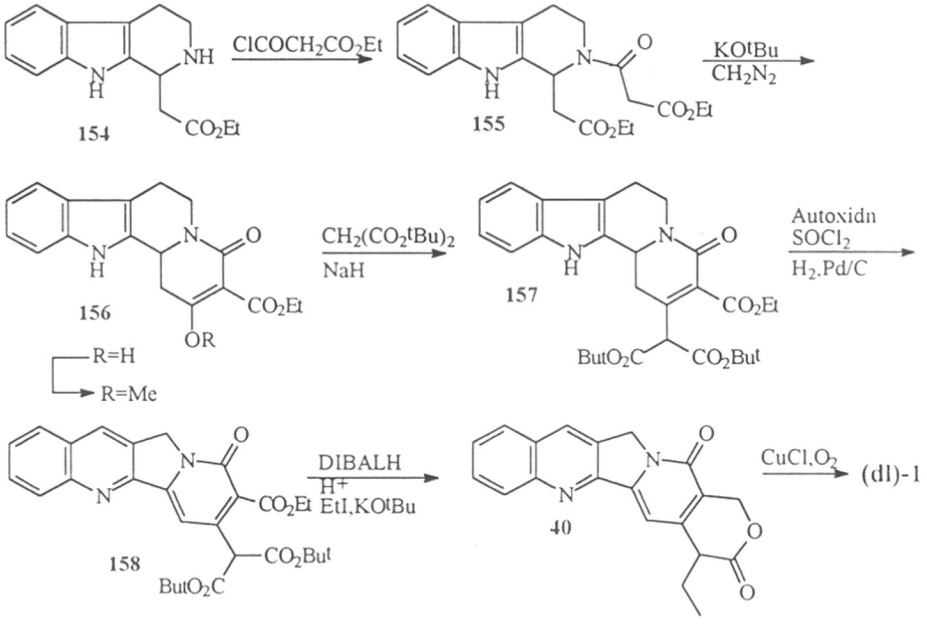
The TMS in the lactone **151** was exchanged with ICl and the resultant iodo lactone was treated with TMSI to give iodopyridone **152**. N-Alkylation of iodopyridone **152** with propargyl bromide gave acetylinicpyridone **153**. Radical cyclisation of the

acetylinicpyridone **153** with phenyl isocyanate using bistributylditin gave (+)-**1** in 4.8% yield.

Winterfeldt's approach (Angew. Chem. Int. Ed. Engl., 1972, **11**, 289)

The reaction of amino ester **154** with carbethoxyacetyl chloride gave amide 155. The amide **155** was then converted to triester **157** by sequential reactions as shown in **Scheme-24**.

Scheme-24



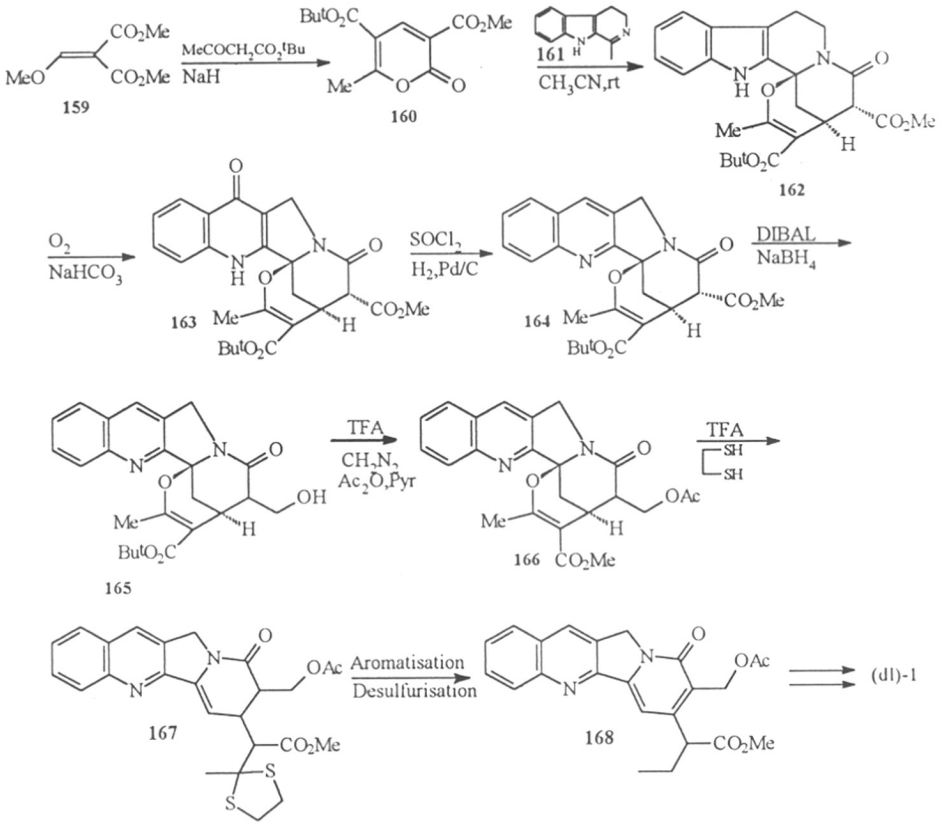
The triester **157** was autoxidised to give intermediate keto amide, which was then cyclised and further reacted with thionyl chloride to give chloro compound. This chloro compound was dehalogenated with Pd/C, H_2 to give quinoline **158**. The ethyl ester of quinoline **158** was reduced with DIBAL-H to alcohol which was hydrolyzed, decarboxylated and then ethylated to give **40** which was oxidized to give (±)-**1** in overall 21% yield.

Kametani's approach (J. Org. Chem., 1983, **48**, 3150)

Dihydro β-carbonine **161** was condensed with pyrone **160** to give pentacyclic ester **162**. The ester **162** on singlet oxygen mediated rearrangement and using similar

procedure of Winterfeldt method[13] gave diester **164**. Diester **164** was then converted to acetate **166** in five steps as shown in **Scheme-25**.

Scheme-25:



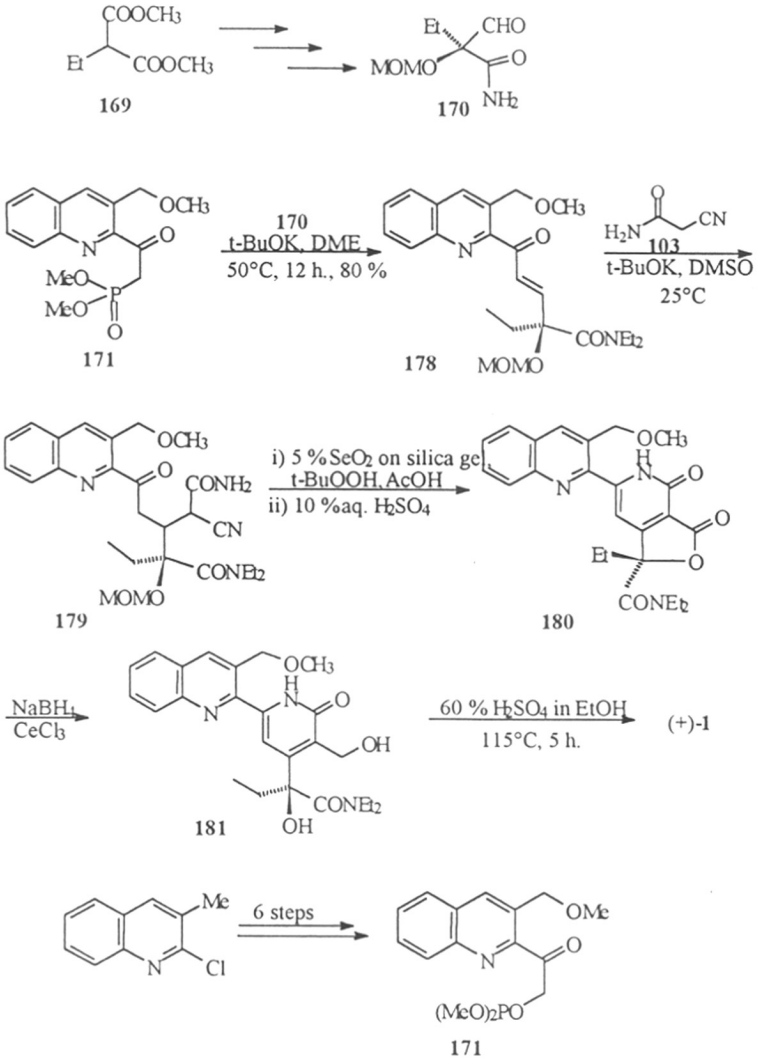
This acetate **166** was protected as thioketal to give compound **167** using ethanedithiol. Its further conversion of (±)-**1** was achieved in three steps, Raney nickel reduction, DDQ aromatisation, oxidation, in overall 40% yield.

Kametanis 2nd approach similar to this (±)-**1** prepared in overall 0.73% yield.

Ciufolini's approach (Angew. Chem. Int. Ed. Engl., 1996, **35**, 1692)

Dimethyl 2-ethyl-2-malonate **169** was converted to chiral amide aldehyde **170** in four steps as shown in **Scheme-26**.

[1] Scheme- 26:



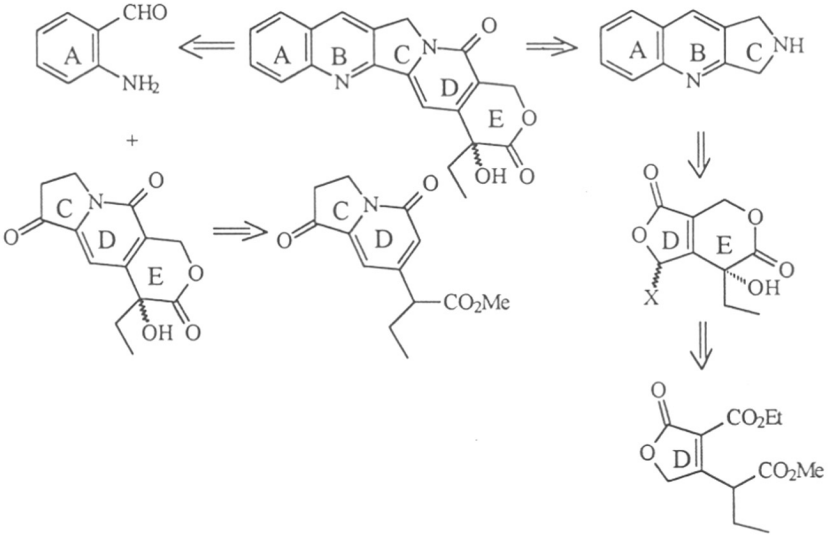
The condensations of the aldehyde **170** with ylide **171** under Wittig Horner condition gave olefin **178**. The olefin **178** underwent Michael addition with cyanoacetamide to give ketamide **179**, and then oxidative amortization of the ketoamide **179** with SeO_2 followed by cyclisation with aqueous H_2SO_4 gave lactone **180**. The lactone **180** was further reduced with $NaBH_4$ to give alcohol **181**. The alcohol **181** was then lactonised with sulfuric acid to give (+)-**1** in overall 30% yield.

Present work

As described earlier (S)-camptothecin (**1**) a pentacyclic alkaloid isolated from *Camptotheca acuminata*[1] in 1966 continues to be one of the most important lead compounds among the anticancer natural products. A number of promising analogs have been prepared that show-improved solubility, low toxicity and impressive activity against certain solid tumors. Recently camptothecin has showed potent antiviral activity and it may be useful in AIDS chemotheraphy. Several interesting synthetic methods have been developed in last decade and many syntheses rely on Friedlander quinoline synthesis to construct the ring B of camptothecin.

Various synthetic approaches towards campthethecin[8] and its intermediates were made which are described in this chapter. For convenience the chapter has been divided into two sections. The **section I** deals with the synthesis of CD ring synthon while the **section II** deals with the synthesis of ABC + DE ring synthons of camptothecin. The retro synthetic analysis of camptothecin is shown in **Scheme-27**.

Scheme-27:



Section I

CD ring synthon of camptothecin

For the synthesis of camptothecin (**1**), the CD ring synthon is a key intermediate as the synthon on condensation (Friedlander reaction)[14] with o-amino benzaldehyde or its derivative directly gives a tetracyclic intermediate which could be then converted into 1. This method is useful especially for the preparation of camptothecin derivatives, having various substituents in A ring. Attempts have been made to synthesize CD ring synthon, which is presented in three parts.

CD ring synthon

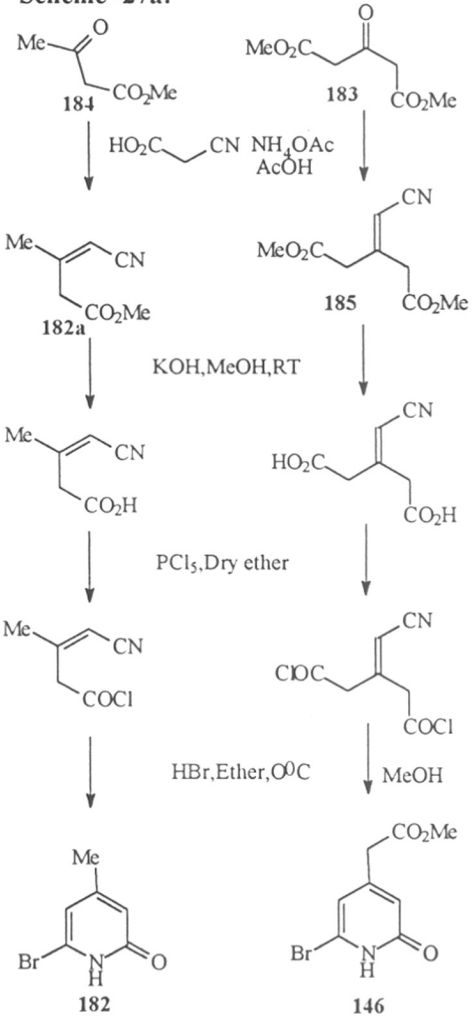
Part I: Approaches towards CD ring from pyridone 182 and 146.

The synthetic efforts toward CD ring synthon starting from pyridones **182** and **146** are given in **Scheme-28**. In order to carry out few model reactions for N-alkylation of 2-pyridone system, 6 bromo-4-methyl-2-pyridone **182** was prepared from easily available methyl acetoacetate (**184**). Non-cyclic ester of β-ketoacids reacts with cyanoacetic acid to form esters of *cis* and *trans* β-γ-unsaturated-γ-cyanocarboxylic acids[15]. Thus the reaction of **184** with cyanoacetic acid in presence of ammonium acetate and glacial acetic acid yielded methyl-4-cyano-3-methyl ester **182a** in 79.1% yield (**Scheme-27a**). The IR spectrum of **182a** showed absorption bands at 2220 and 1750 cm^{-1} for the nitrile and carbonyl groups respectively. Hydrolysis of **182a** to the acid followed by its reaction with PCl_5 yielded the acid chloride. Addition of gaseous HBr at 0°C afforded the desired pyridone **182** in 62.8% yield. The IR spectrum showed absorption band at 1652 cm^{-1} for lactam carbonyl group. The ^1H NMR spectrum exhibited a singlet at δ 2.20 for the methyl protons, two doublets at δ 6.46 and 6.60 for olefinic protons. The mass spectrum (M^+ 187) further proved its structure.

Similar reaction sequence was carried out on dimethylacetone 1,3-dicarboxylate **183** to get the required pyridone **146**.[15,16] Thus the reaction of **183** with cyanoacetic acid yielded cyano ester **185**. Its hydrolysis to diacid followed by PCl_5 gave acid chloride. This subsequent cyclised with gaseous HBr at 0°C in dry ether and quenching the reaction with methanol afforded the desired pyridone **146**. The IR spectrum of the compound **146** showed absorption bands at 1730 (ester C=O) and 1660 cm^{-1} (lactam

C=O). The ^{1}H NMR spectrum revealed a singlet at δ 3.47 for the methylene protons, a singlet at δ 3.67 for the methoxy and two doublets at δ 6.57 and 6.78 for the olefinic protons. The mass spectrum exhibited the molecular ion peak at m/z. 245 (M^+) 247 (M^+ + 2).

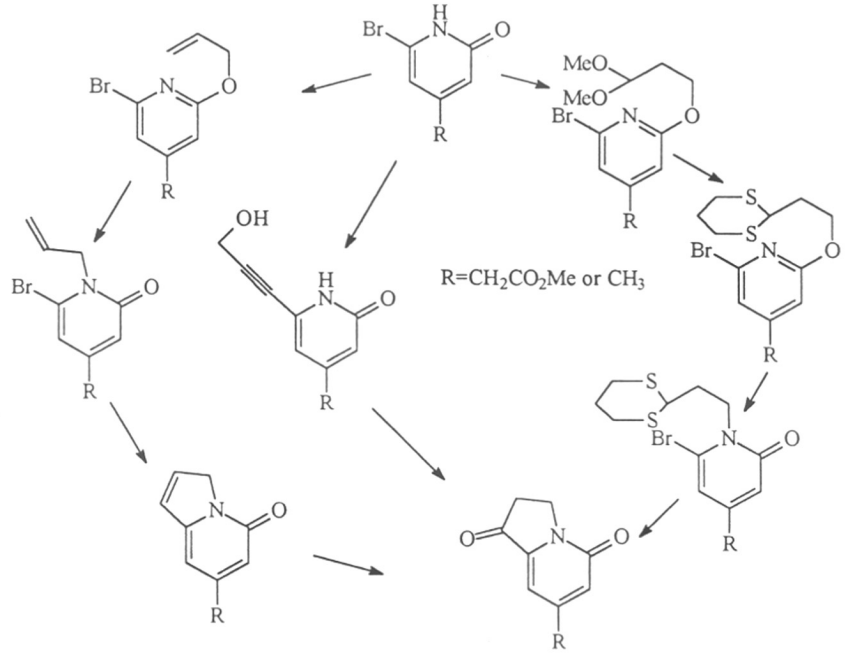
Scheme -27a:



After obtaining both the pyridones, the following approaches as shown in **Scheme-28** was attempted to prepare CD ring synthon.

1. Umpolung and radical approach
2. Heck approach (allyl)
3. Heck approach (propargyl)

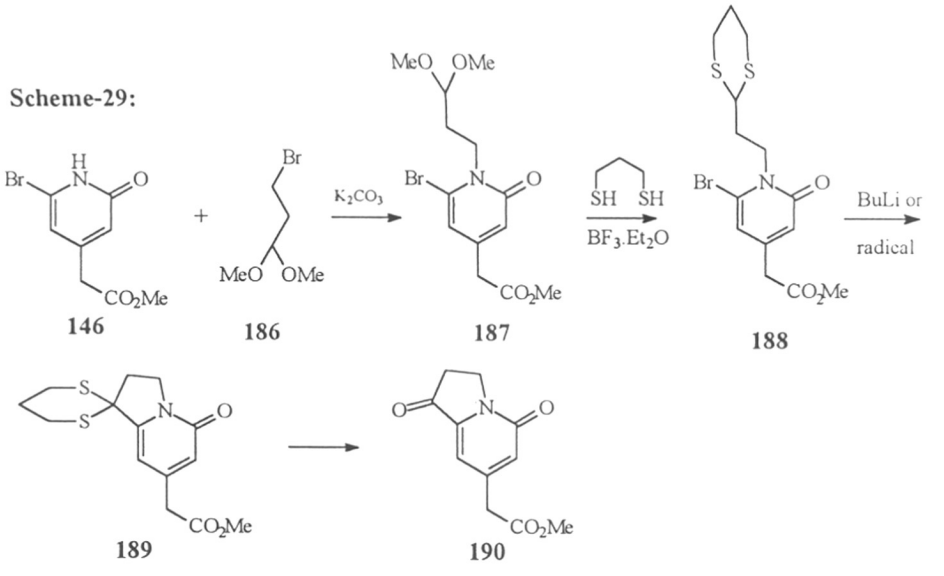
Scheme -28:



1. **Umpolung and radical approach**

Intramolecular umpolung[17] as well as radical reaction[18] were attempted as shown in **Scheme-29**, starting from the pyridone **146**. *N*-alkylation of pyridone **146** with bromoacetal **186** followed by trans dithioacetylation would give dithiane derivative **188**, which under Umpolung reaction condition should cyclise to give **189**. Oxidative dethioketalisation of the cyclised pyridone **189** would provide CD ring synthon **190** of camptothecin.

Scheme-29:



Acetal of 3-bromopropionaldehyde **186** was prepared according to the known procedure[17b] reported for the corresponding chloro acetal. The methanolic solution of HBr was cooled to 0°C, and acrolein was added dropwise. Usual work up gave the desired bromo acetal **186**, which was confirmed by its NMR and b.p.

The bromo pyridone **146** when subjected to alkylation with bromo acetal **186** in acetonitrile with K_2CO_3 gave the expected *N*-alkylated product in very low yield. The *N*-alkylation product **187** obtained in 8% yield after chromatography separation,was confirmed by its NMR, MS and IR. ^{1}H NMR of *N*-alkylated product showed triplet at δ 4.0 for methylene protons and IR showed 1660 cm^{-1} peak where as major *O*-alkylated **187a** obtained during alkylation showed in its ^{1}H NMR a triplet at δ 4.2 for methylene proton. IR had aromatic pyridine peak at 1600 cm.$^{-1}$

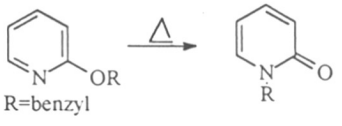
In order to study the formation of *O* and *N* alkylated products in the presence of K_2CO_3 in acetonitrile a series of experiments were carried out with different alkylating agents and methyl bromo pyridone **182**. The reaction with allyl and propargyl bromides gave major *N*-alkylated products and the results obtained are given in **Table 1**.

Table-1: Reaction of alkyl halide with pyridone 182 and K_2CO_3 in acetinitrile

Alkyl halide	N-alkyl	O-alkyl
Allyl bromide	60% **194**	35% **196**
Propargyl bromide	70% **182b**	28% **196a**
Bromoacetal **186**	7% **191**	87% **191a**

The structures of *N*-alkyl and *O*-alkyl products were confirmed by their corresponding NMR , IR and mass spectral values which are given in experimental part.

Peter Beak[19] reported that when *O*-alkyl imidate was heated to 300°C, a thermal rearrangement takes place to give N-alkyl product (amide).



Based on this observation, the alkoxy pyridine **187a** which was obtained as a major product during the alkylation of pyridone**146** with bromo acetal **186** was thought to be useful to construct CD ring synthon **190** as shown in **Scheme-30**.

Thus the *O*-alkylated product **191** was transdithiolated using either propane dithiol or 1,3-ethane dithiol in presence of BF_3 etherate[20] in chloroform to give **192** or **192a** respectively which were characterised by their spectroscopic analysis.

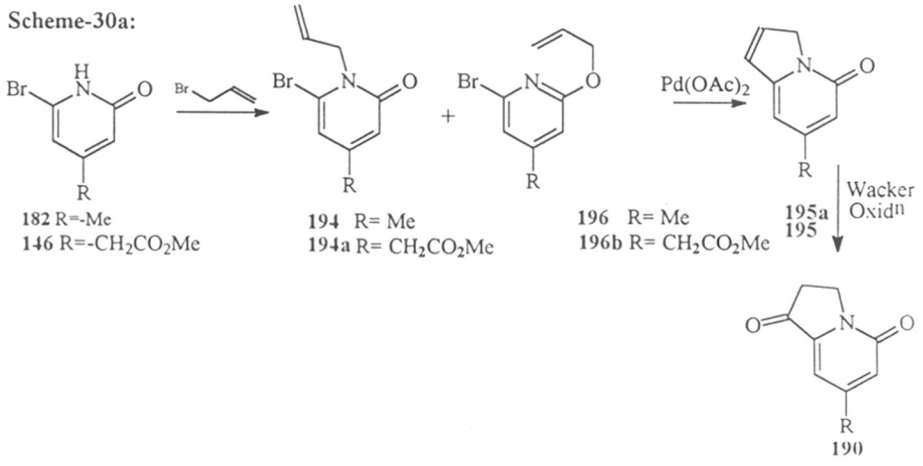
In order to obtain *N*-alkylated product **193**, the *O*-alkylated dithiane derivative **192** was heated neat at 300°C under N_2 atmosphere for 30 min. However, the product obtained was a complex mixture of compounds (TLC) from which the desired compound **193** could not be obtained. Further to carry out radical cyclisation, [18] the *O*-alkylated derivatives **192a** was similarly heated but the reaction again failed to give desired product **193**.

Further, efforts were made to improve the yield of *N*-alkylated pyridones by changing bases like Et_3N, sodium carbonate, sodium hydride etc. and in both polar and non polar solvents. However, the yield of *N*-alkylated pyridones could not be improved.

Heck reactions

The proposed approach towards CD rings synthon by Heck reaction is showed in **Scheme-30a**. The *N*-alkylation of **146** with allyl bromide followed by intramolecular Heck reaction would provide olefin **195**. This olefin can be converted into **190** using $PdCl_2/O_2$ to give CD ring synthon **190** of **1**, **Scheme-30a**.

Scheme-30a:



182 R=-Me
146 R=-CH_2CO_2Me

194 R= Me
194a R= CH_2CO_2Me

196 R= Me
196b R= CH_2CO_2Me

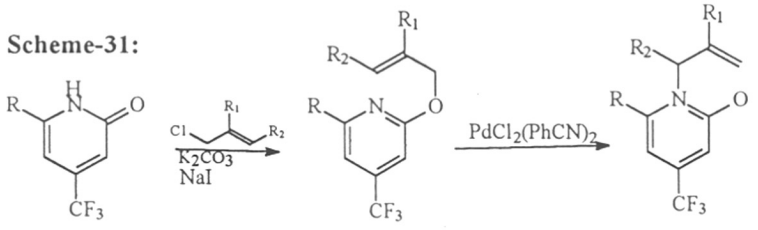
195a
195

190

So the pyridone **146** was subjected to alkylation with allyl bromide in presence of K_2CO_3 in acetonitrile to give 62% yield of *N*-alkylated product **194a**. The ^1H NMR spectrum of **194a** displayed two singlets at δ 6.40 and 6.85 and multiplet between δ 5.7 - 6.0. The IR showed the presence of carbonyl group at 1700 cm^{-1} peak. The desired *N*-alkylated product was then subjected to the Heck reaction with $Pd(OAc)_2$ PPh_3 in DMF. The product obtained showed disappearance of the protons in olefinic region, in its NMR spectrum and was characterized as the starting pyridone **146** based on the spectroscopic data. When the 2-*O*-alkylated pyridine **196b** was subjected to the similar Heck condition ($Pd(OAc)_2$ Et_3N in dry CH_3CN) gave a slower moving (by TLC) product than the starting pyridine **194a**. The IR spectrum showed the presence of amide group at 1660 cm^{-1} and ester 1700 cm^{-1} and absence of aromatic peak at 1600 $cm.^{-1}$ This was characterized as *N*-akylated pyridone **194a** and concluded that *O*-alkylated pyridone

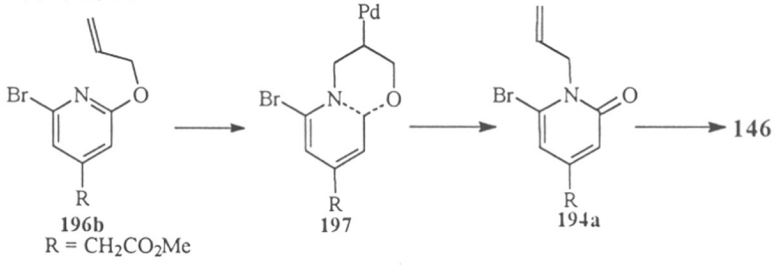
196b gets converted into *N*-alkylated pyridone under Heck condition. Venkataraman *et al.*[22] reported that when 6-aryl-4-trifluoro methyl 2(1H) pyridones **198** undergoes conversion to *N*-allylated product when Pd (II) used as catalyst (given in **Scheme-31**).

Scheme-31:



Based on these observation mechanism is proposed which is given in (**Scheme-32**).

Scheme-32

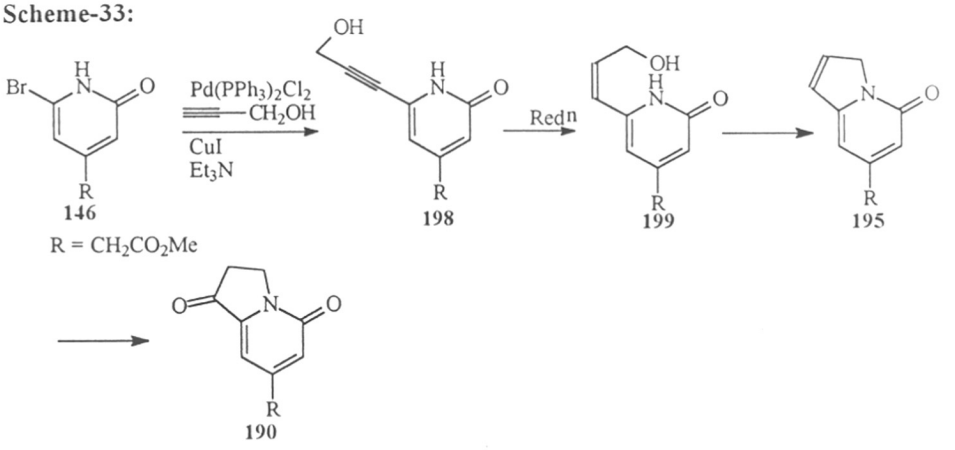


Palladium helps in formation and stabilization of Claisen rearrangement intermediate **197 (Scheme-32)** which normally requires harsh condition (300°C). The equilibrium then shifts to give product **194a**. The longer reflux time gives pyridone (**146**) the identical results were obtained when PPh_3 replaced by *O*-tolyl phosphine.

Heck reaction with propargyl alcohol :

In another approach towards CD ring the following **Scheme-33** was proposed.

Scheme-33:



Bromo pyridone **146** under Heck reaction with propargyl alcohol[23] would give alcohol **198**. The hydrogenation using Lindlar catalyst would give allylic alcohol **199** and subsequent cyclization using Mitsunobo condition and oxidation would lead to CD ring synthon of (**1**).

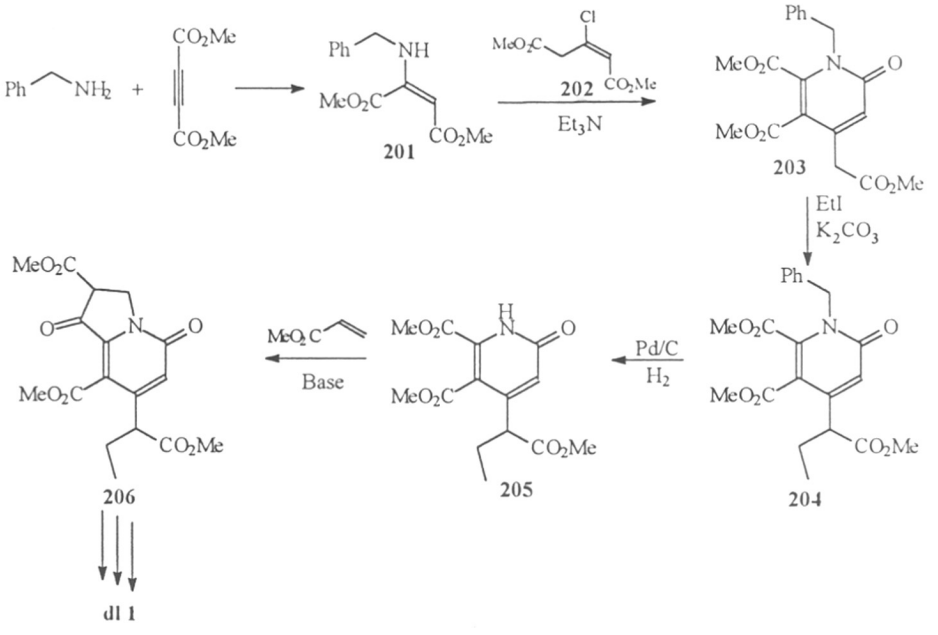
The attempted reaction on bromopyridone **146** with propargyl alcohol under Heck condition using $Pd(PPh_3)_2Cl_2$, CuI and Et_3N gave a mixture of products. Therefore this route was abandoned.

Part-II: Synthetic efforts towards CD ring synthon from benzyl amine:

The synthetic approach starting from benzyl amine was proposed as shown in the **scheme-34.**

Benzylamine (**200**) under Michael addition with dimethylacetylenedicarboxylate would give imine **201**, which can be further converted to benzyl pyridone **203**. Ethylation followed by debenzylation would give pyridone **205**, which could be then converted into CD ring synthon of camptothecin.

Scheme-34:-



Benzylamine (**200**) was treated with dimethylacetylenedicarboxylate at 0°C[24] in acetonitrile to give benzyl imine **201** in 98% yield. Its ^{1}H-NMR showed two singlets for methyl esters at δ 3.6 and 3.7 and a olefinic proton at δ 5.1 as a singlet. The benzylic protons showed a doublet J=5.9 Hz at δ 4.5. Aromatic protons appeared as a singlet at δ 7.3. The IR showed the ester carbonyl groups in the region 1700 cm.$^{-1}$

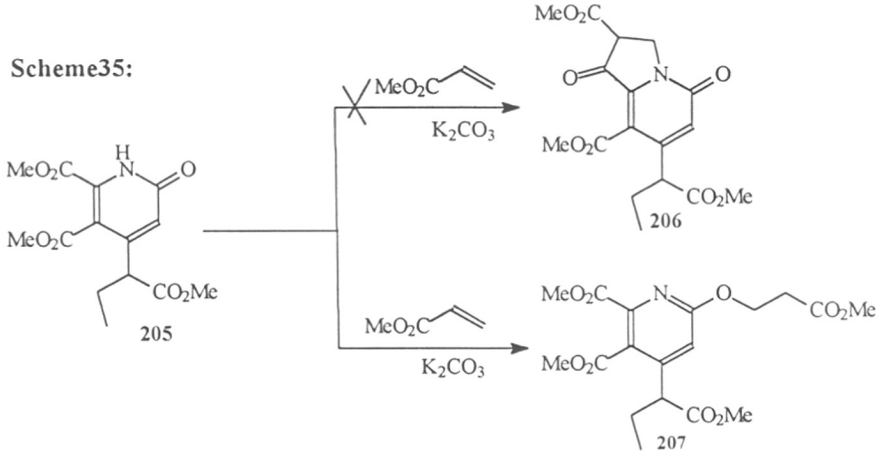
The imine **201** was further treated with 3-chlorodimethylglutoconate in presence of Et_3N in MeOH and stirred at room temperature for 64 hr. After usual workup and a careful chromatographic separation gave the product **203** in 43% yield. The formation of **203** was confirmed by its ^{1}H NMR, IR and mass spectrum values. Where ^{1}H NMR showed the peak corresponding olefinic proton at δ 6.45, benzylic protons at δ 5.2, aromatic protons multiplet at δ 7.12 to δ 7.15 and for methylene at δ 3.72. Ethylation of the pyridone **203** was carried out using one mole of dry K_2CO_3 with excess of EtI in dry acetonitrile at 80°C for 16 hrs. Workup of the reaction and chromatographic purification gave pyridone **204** in 82% yield. The formation of **204** was confirmed by its ^{1}H NMR spectrum, which showed disappearance of a singlet at 3.72 due to methylene protons and appearance of a multiplet in the region δ 1.65-2.28, a triplet at δ 3.90 indicated the formation of mono ethylated product. The mass spectrum showed molecular ion peak at

M^+ 401, which further supported its structure. Debenzylation of the pyridone **204** was carried out by hydrogenation at 50°C under 60 psi in the presence of catalytic amount of $HClO_4$ with 10% Pd/C. The formation of the debenzylated product, **205** was confirmed by its ^1H NMR and IR. Where ^1H NMR showed, absence of benzylic methylene and aromatic protons. The IR showed disappearance of 1600 cm^{-1} peak and mass spectrum had M^+ at 311.

After getting the pyridone **205** our next aim was to carry out tandem Michael Dieckmann addition with methyl acrylate.

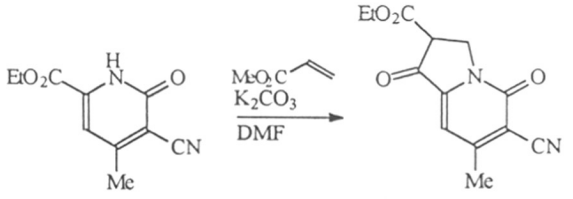
Attempted tandem Michael, Dieckmann reaction of pyridone **205** with methyl acrylate failed to give the desired keto ester pyridone **206** but it gave an *O*-alkylated product.

Scheme35:



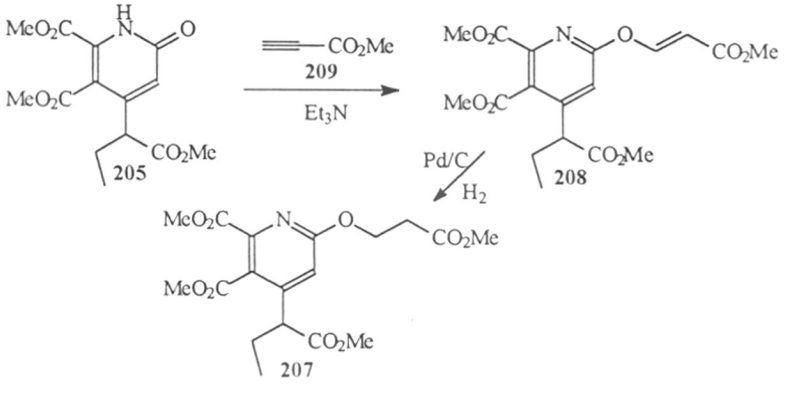
Michael reaction addition product **207, (Scheme-35)** was confirmed by its ^1H NMR, IR and MS analysis. Its ^1H NMR showed two triplets at δ 2.81 and 4.67 assigned for addition of methyl acrylate. The IR spectrum of **207** showed a peak at 1600 cm^{-1} for aromatic ring.

Wall *et. al.*[25] showed that cyano pyridone on treatment with methyl acrylate using K_2CO_3 as a base in DMF gives ketoester in good yield.



In another attempt (**scheme-36**) an alkylation of **205** was carried out using methyl propargylate (**209**) in methanol using Et_3N as a base. The ^1H NMR of the product showed two doublets (J = 14.6 Hz) at δ 5.7 and 7.6 for *trans* olefinic protons and rest of the peaks at expected region which confirmed the formation of Michael adduct **208**. Its mass spectrum showed molecular ion at 395.

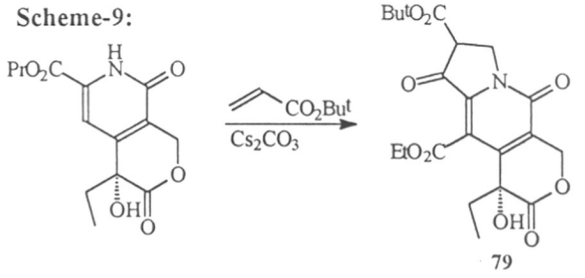
Scheme-36:



Further, reduction of the pyridine derivative **208** with 5% Pd/C and H_2 gave a reduced product which was found to be identical in all respect with **207.** The spectral values were identical to product obtained from methyl acrylate addition product with pyridone **205**.

Recently Henger *et al.*[26] reported the CDE ring synthon (**Scheme-9**).
by Michael Dieckmann reaction on pyridone **79** with butyl acrylate using $CsCO_3$ in DMSO.

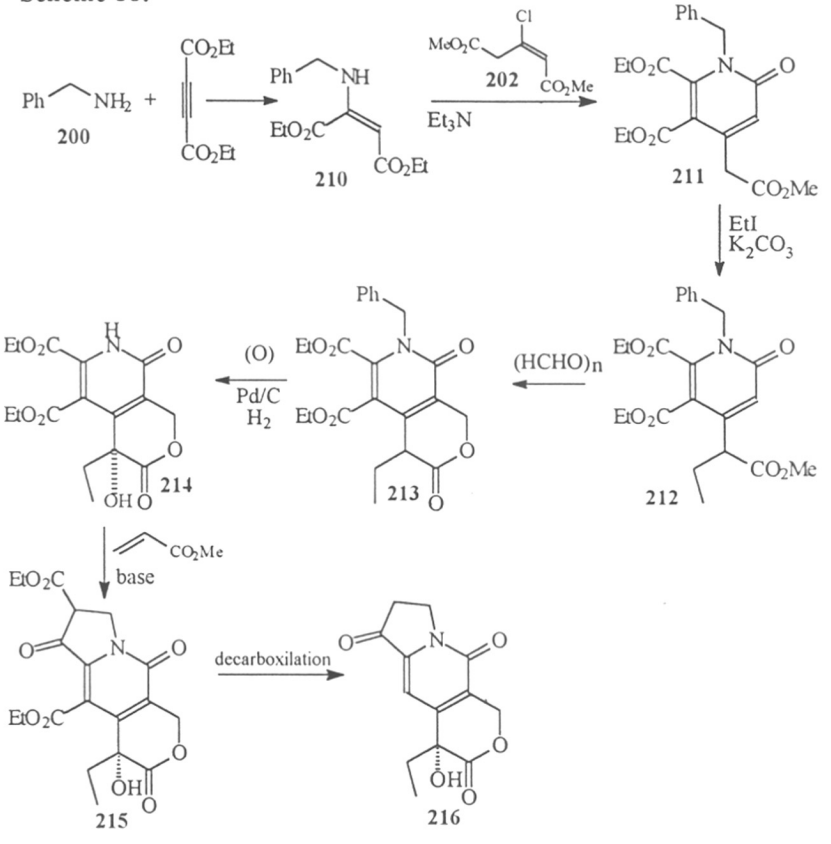
Scheme-9:



79

Thus modified **Scheme-38** was proposed starting from benzyl amine.

Scheme-38:



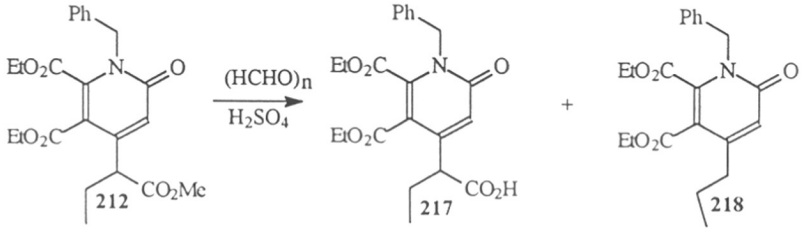
The benzylamine(**200**) was treated with diethylacetylenedicarboxylate to give imine **210** as yellow oil in 98% yield. The imine **210** was characterized by its ^{1}H NMR, that showed an olefinic proton at 5.15 and two benzylic methylene protons at 4.55. Aromatic protons appeared as a multiplet in the region δ 7.25 to 7.35.

The imine **210** was the cyclised to benzyl pyridone **211** with 3-chlorodimethyl glutoconate (**202**) in presence of Et_3N. The product formation was confirmed by its ^{1}H

NMR and IR spectra. The NMR showed an olefinic proton as a singlet at δ 6.52 and aromatic protons at 7.2 to 7.3 as a multiplet. The molecular ion peak at 397 in the mass spectrum confirmed the structure. Ethylation of the pyridone **211** was been carried out using K_2CO_3 in acetonitrile with excess EtI. The formation of the ethylated pyridone **212** was confirmed by the disappearance of methylene protons as a singlet at δ 3.72 and appearance of a multiplet in the region δ 1.7 to 2.15 for methylene protons, a triplet at δ 3.98 for methine confirmed the monoethylated product **212**.

Further, lactonisation[27] of **212** was attempted using paraformaldehyde in presence of H_2SO_4 in dioxane. However, instead of the formation of lactone **213,** the products formed in the reaction were separated and characterized as acid **217** and its decarboxylated product **218** as shown in **Scheme-39**.

Scheme-39:

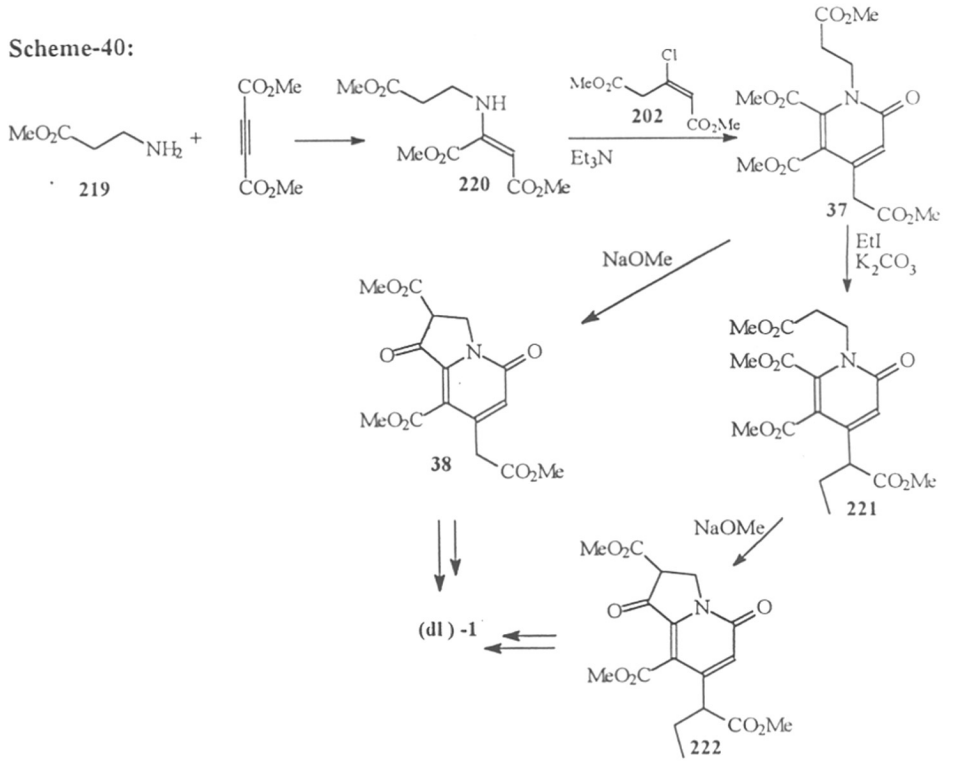


The structure of the products **217** and **218** were confirmed by their NMR, MS and IR values. This method also failed to give desired CD ring synthon.

Part III: From β-alanine methyl ester hydrochloride:

Based on the above observation it was thought that the *N*-alkylated propyl ester moiety should be present from beginning and a **Scheme-40** was proposed and attempted. Commercially available β-alanine was esterified using dry methanol and HCl gas to give methyl ester of β-alanine hydrochloride (**219**). The hydrochloride of β-alanine **219** was suspended in acetonitrile and treated with 2 eq. of NEt_3 at 0°C. Dimethylacetylenedicarboxylate in acetonitrile was added and stirred for 5 hr to give an imine **220** as an oil in 94% yield. The imine **220** showed characteristic olefinic proton at 5.15 δ in NMR. The imine **220** was then dissolved in dry methanol and treated with 3-chlorodimethylglutaconate (**202**) in presence of Et_3N.

Scheme-40:



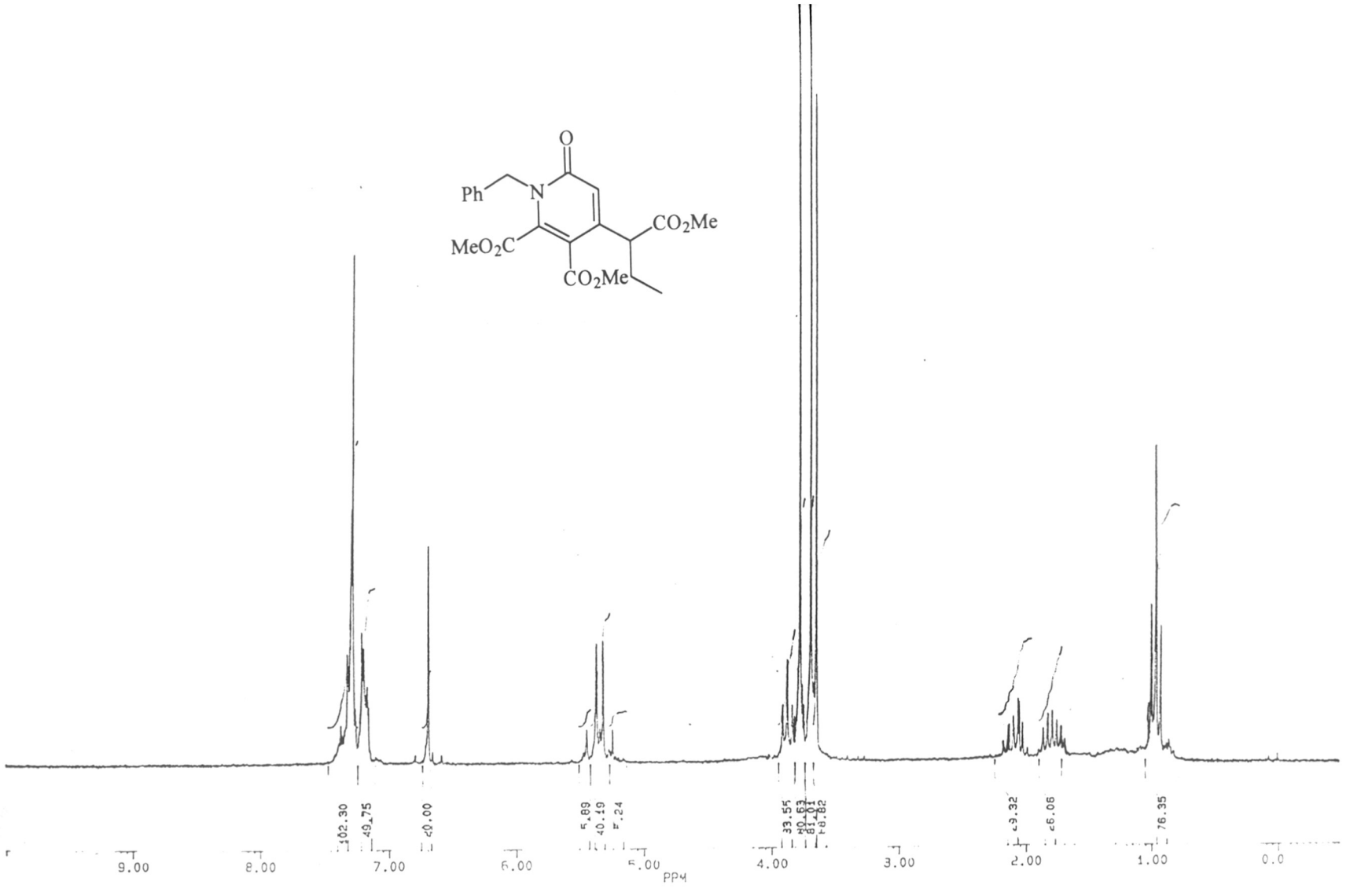
The reaction mixture was stirred at room temperature for 65hr. Usual workup and chromatographic purification gave pyridone **37** in 42% yield. Its structure ^{1}H NMR showed two triplets with J=7.1 Hz at δ 2.8 and 4.12 showing presence of propyl moiety. IR showed 1750 cm^{-1} and 1660 cm^{-1} for ester and amide (C=O) respectively. The ethylation of pyridone **37** with ethyl iodide in presence of K_2CO_3 with acetonitrile under reflux condition gave the ethylated pyridone **221**. The structure of **221,** was confirmed by its ^{1}H-NMR, MS and IR analysis. The ^{1}H NMR showed a multiplet at δ 1.65-2.25 for methylene protons and a triplet at δ 3.8 for methine proton. Its mass spectrum showed M^+ at 397. The Dieckmann cyclisation using NaOMe gave keto ester **222**. Its NMR showed in disappearance of triplet at δ 2.8 for two protons and appearance of a triplet at δ 3.80 for one proton. Mass spectrum showed M^+ at 367.

Similarly the Dieckman condensation of pyridone **37** with NaOMe gave ketoester pyridone **38** which is a reported intermediate of camptothecin (**1**).[28]

As the synthesis of (±)-**1** from pyridons **222** and **38** are known (see **Scheme's 2** and **3**). This method constitutes the formal synthesis of camptothecin.

Conclusion

Partial synthon of (**1**) was achieved from commercially available β-alanine.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Ph
N
MeO2C
CO2Me
CO2Me
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49.75
20.00
5.89
40.19
7.24
33.55
10.63
81.01
10.82
9.32
6.06
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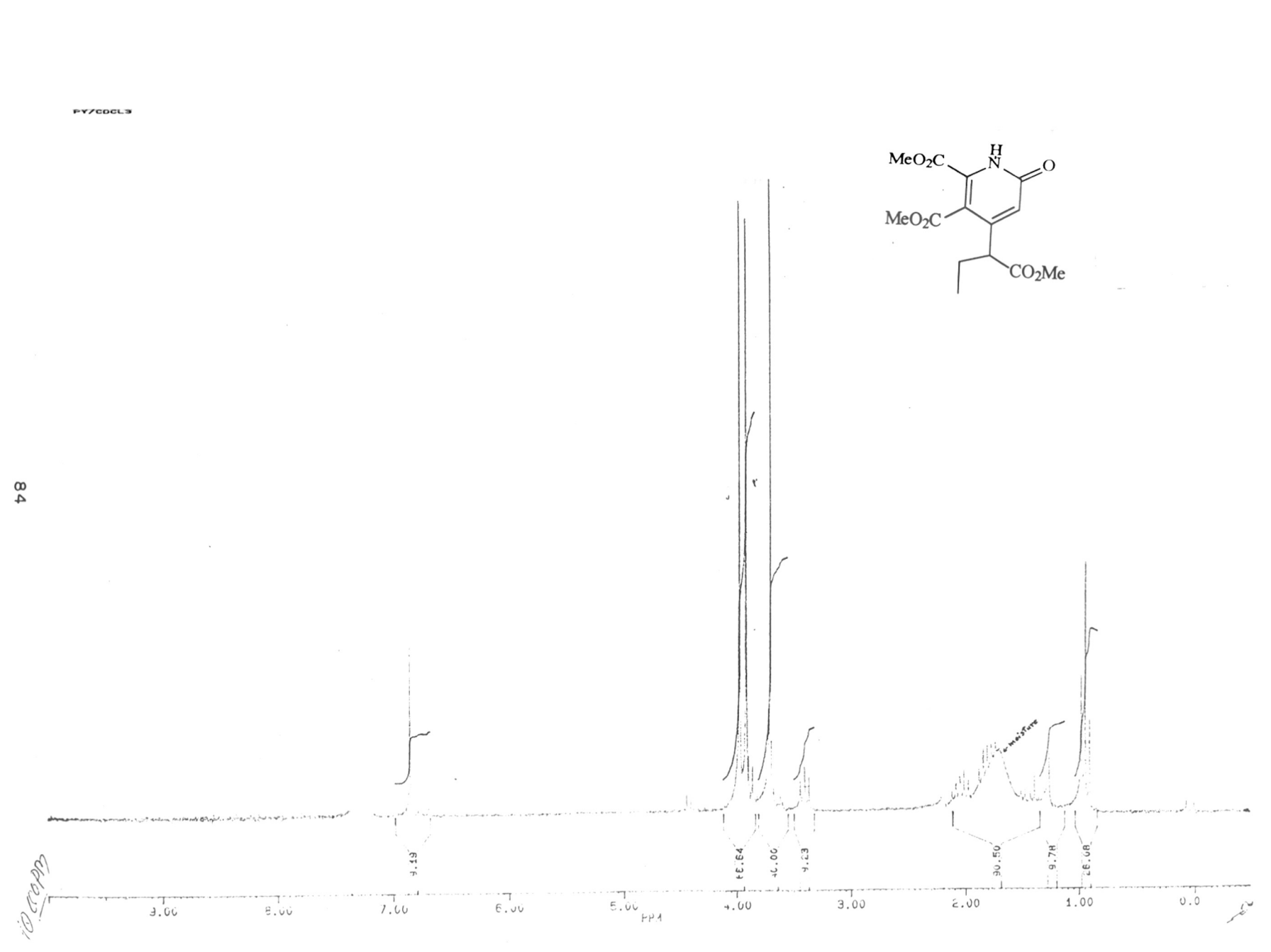
4.00
3.00
2.00
1.00
0.0
PPM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H
N
O
MeO2C
CO2Me
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44.64
40.00
9.23
30.50
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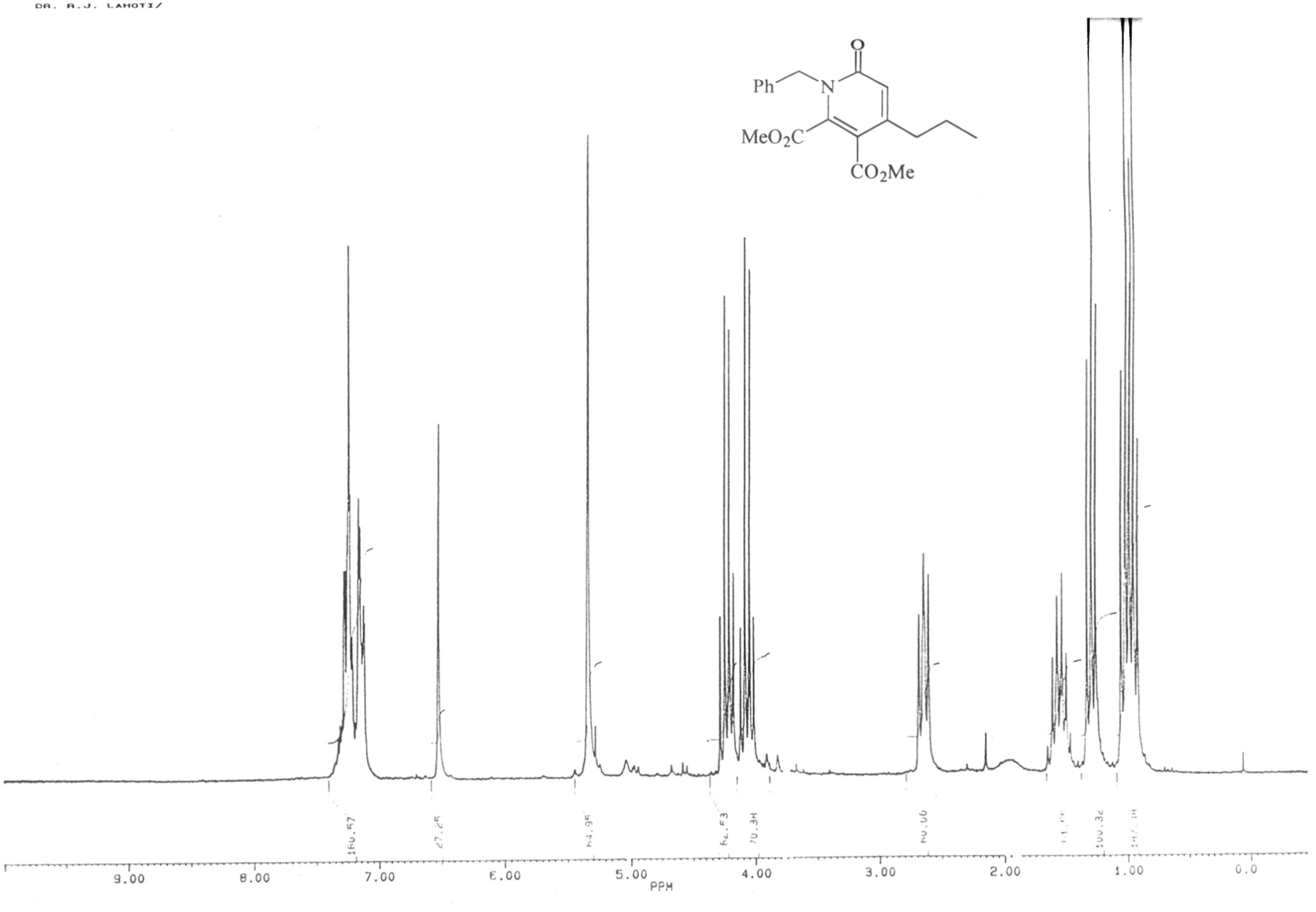
4.00
3.00
2.00
1.00
0.0
PPM


DR. R.J. LAMOTTE
Ph
N
O
MeO2C
CO2Me
9.00
8.00
7.00
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5.00
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2.00
1.00
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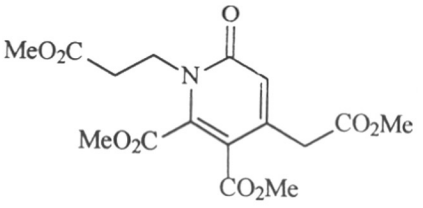
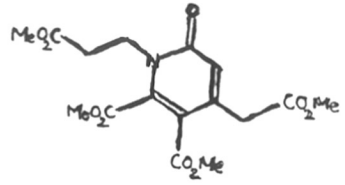
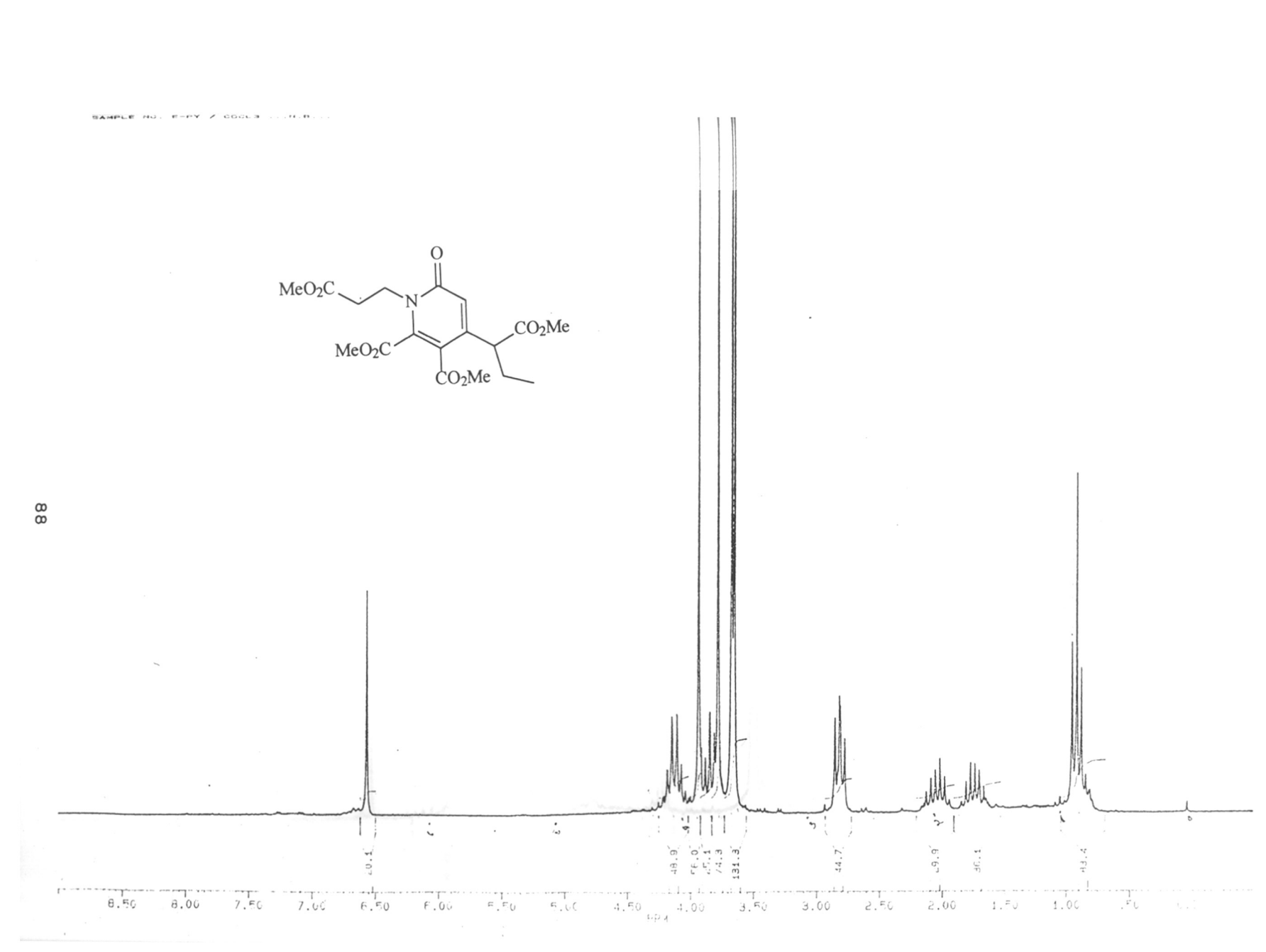
PPM

SAMPLE NO. PY / CDCL3



PYRIDONE

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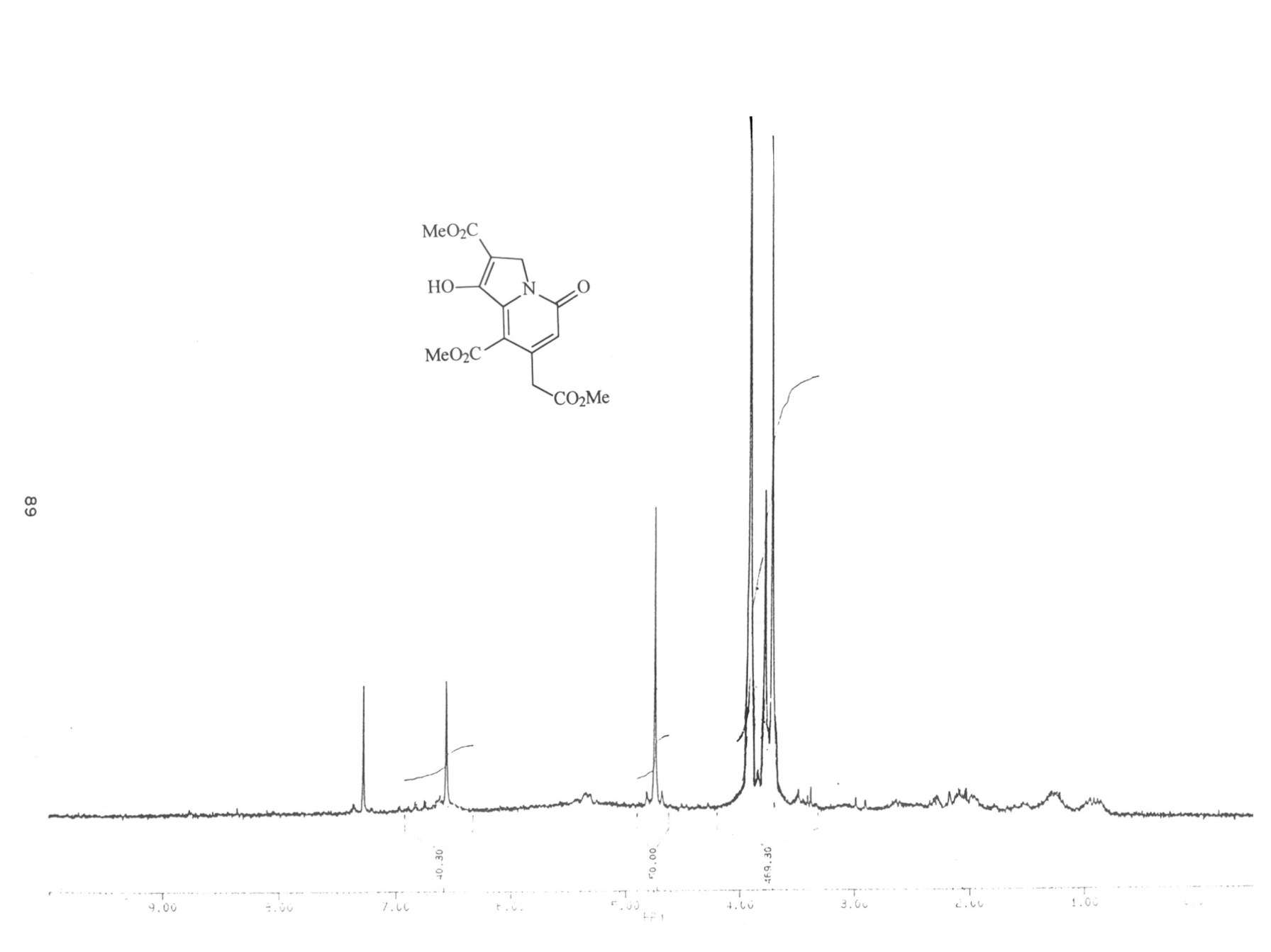
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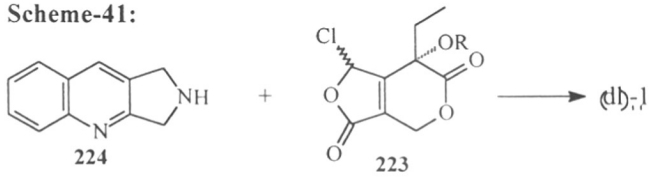
Section II:

ABC and D ring synthons of camptothecin

Camptothecin, due to its novel antitumor activity followed by low existence in natural sources, made many groups of scientists to develop commercial synthetic methods. Keeping this view in mind efforts were directed towards the development of a synthetic method to camptothecin starting from aniline and methyl acetoacetate.

Scheme-41:



Corey, Rama Rao and others prepared camptothecin by condensing pseudochloride half ester **223** with tricyclic amine **224** using base catalysed cyclisation of the intermediate aldehyde as shown in **Scheme-41** (for more detail see **Schemes-12** and **13**.)

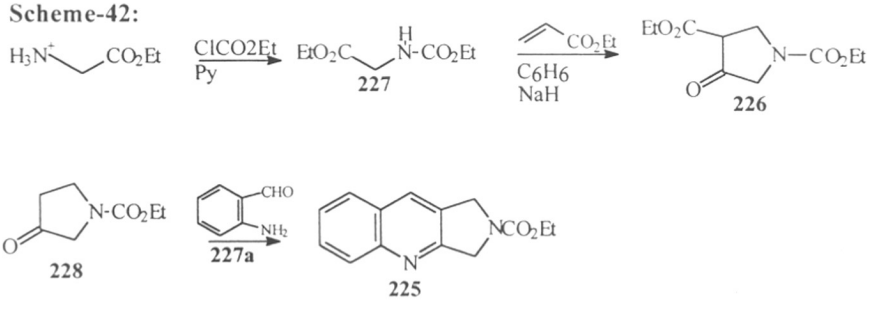
Part I

Synthetic efforts directed towards ABC rings :

The known synthetic methods for the preparation of tricyclic amine are briefly summarised below:

a) Starting from glycin ethyl ester [29]:

Scheme-42:

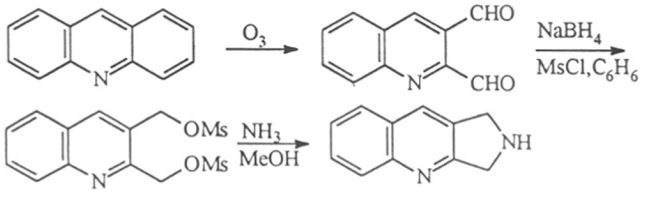


Glycin ethyl ester hydrochloride was converted to its urethane derivative **227** which under Michael addition with ethyl acrylate followed by Dieckmann condensation gave β-keto ester, **226**. It was easily decarboxylated to corresponding ketone **228** in

89% yield (**scheme-42**). The acid catalysed condensation of the ketone (**228**) with catalytic p-TSA at 90° (neat) with o-amino benzaldehyde gave tricyclic amine ethyl ester **225** in 86% yield.

Corey's Method [34a]

Scheme-43:

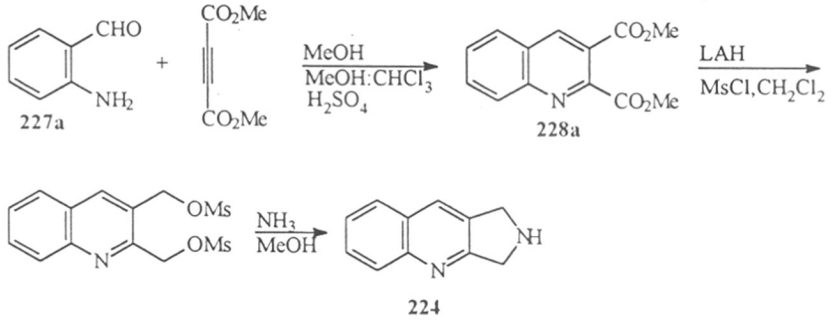


224

Acridine on ozonalysis gave quinoline dialdehyde (**Scheme-43**). Its reduction ($NaBH_4$) to diol followed by protection with mesyl chloride gave dimesylate. The cyclisation of dimesylate with methanolic ammonia gave tricyclic amine **224** in 19% yield.

Rama Rao's method [34b]

Scheme-44:



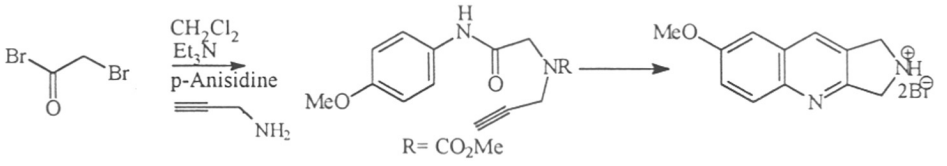
227a **228a** **224**

The o-aminobenzaldehyde **227a** was subjected to Michael addition with dimethylacetylene dicarboxylate followed by sulfuric acid cyclisation gave quinoline diester **228a.** This diester on reduction with LAH gave diol (**scheme-44**) which was protected as mesylate and cyclised with methanolic ammonia to tricyclic amine **224**.

Fortunak's method[42]

In this approach α-Bromoacetylbromide was condensed with p-anisidine to give bromo amide which on N-alkylation with propargyl amine gave compound **226a**.

scheme -45



226a

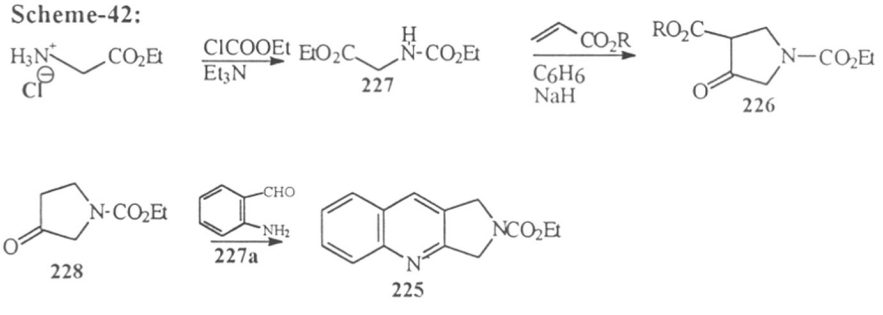
This was further cyclised to give substituted tricyclic amine hydrobromide as shown in **scheme-45**.

Synthesis of ABC rings synthon

Present work

The method reported[29] from glycine ethyl ester was attempted to get the tricyclic amine **225**. Thus glycine ethyl ester hydrochloride was converted to its urethane **227** in 97% yield.

Scheme-42:

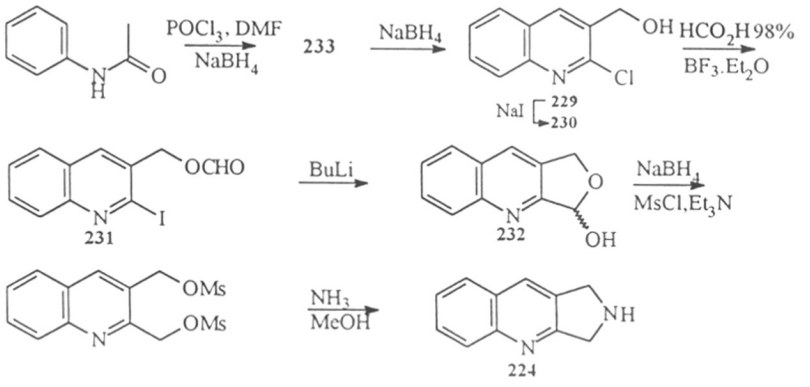


This urethane **227** formed was condensed with methyl acrylate using NaH. First Michael adduct was formed (TLC) which *in situ* underwent Dieckmann cyclisation to give β-ketoester in 68% yield. The β-ketoester **226** was decarboxylated with 10% HCl to give N-carboxyethyl-3-pyrrolidone **228** in 89% yield. The product formation was conformed by its ^{1}H NMR. 3-Pyrrolidoneester **228** was condensed with o-

aminobenzaldehyde in presence of p-TSA[29] in the ratio 1:2:0.02 at 190°C for 5 min. to give required product **225** in 24% yield. Its conversion to **224**.hydrobromide salt with distilled HBr gave poor yield of tricyclic amine hydrobromide.

A synthetic approach for the preparation of tricyclic amine was proposed starting from acetanilide.

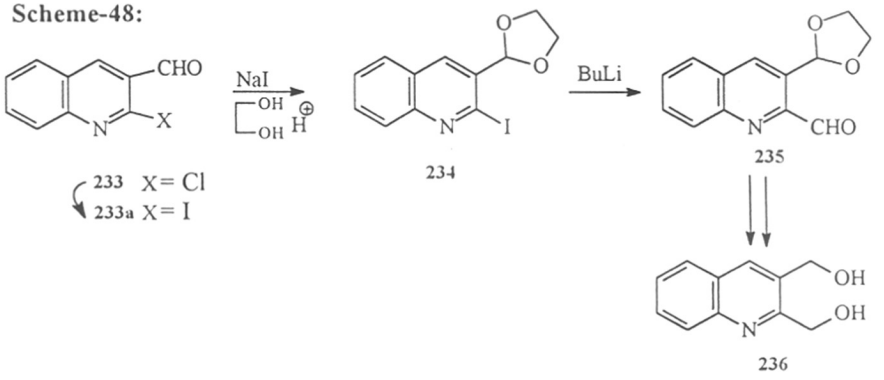
Scheme-47:



Acetanilide was converted to 2-chloro-3-formylquinoline (**233**)[30,40] in 80% yield. Reduction of the quinolinealdehyde **233** with $NaBH_4$ in MeOH gave 2-chloro-3-hydroxymethylquinoline **229** in 85% yield. The structure of **229** was confirmed by NMR, MS, and IR analyses. In the NMR spectrum, aldehyde peak at δ 10.56 as a singlet had disappeared and a new benzylic methylene peak appeared at δ 4.67 as a singlet. Conversion of chloro **229** to iodo **230** was carried out according to the literature procedure by refluxing the chloro compound **229** with NaI in acetonitrile for 36 hours.[30] The formation of the iodo compound was confirmed by its m.p. and MS (M^+ 285). ^1H NMR showed a shift of the benzylic protons from δ 4.60 to 4.80 and the B ring of quinoline proton got shifted from δ 8.32 to 8.40 confirmed its structure. Formate ester **231** was prepared by treating 2-iodo-alcohol **230** and formic acid (98%) with $BF_3.OEt_2$. The formation of the formate ester **231** was confirmed by its ^1H NMR and IR analyses. ^1H NMR showed ester peak of formate at δ 8.31 as a singlet. It has been reported[30] that when formate ester **231** is treated with BuLi it gives lactal **232**. However in the present case the ester failed to give the desired lactal **232**.

In another approach 2-chloro-quinolinealdehyde (**233**) was converted to 2-iodoaldehyde **233a** by refluxing chloro aldehyde **233** with NaI in acetonitrile (**Scheme-48**).

Scheme-48:



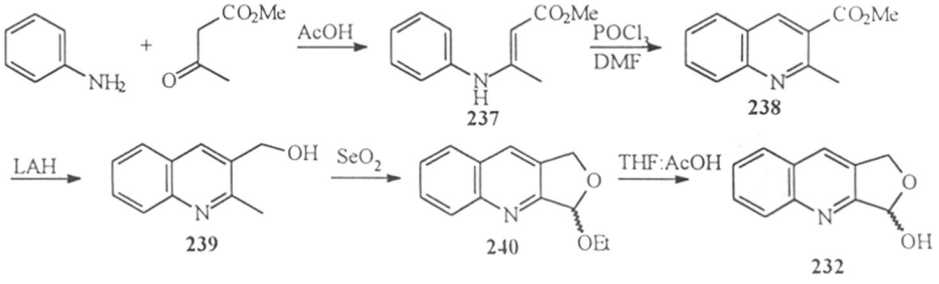
The iodoaldehyde **233a** was characterised by its MS, NMR and m.p. The aldehyde peak of chloroaldehyde **233** was shifted from δ 10.56 to 10.22 and the B ring of quinoline proton was shifted from δ 8.73 to δ 8.42. It was protected using ethylene glycol by refluxing in benzene with catalytic amount of p-TSA. The formation of product **234** was confirmed by its ^{1}H NMR and MS analysis. ^{1}H NMR showed the disappearence of aldehyde peak and appearance of multiplet between δ 4.10 and 4.25 of the four protons of acetal and methine singlet appeared at δ 6.05. The mass spectrum of acetal has M^+ 327 which conformed the strcuture **234**.

When the acetal protected iodoquinoline **234** was reacted with BuLi[31] (15% in hexane) followed by treatment with DMF gave a mixture of products and the desired product **235** could not be isolated and this synthetic method was abandoned.

Synthetic approach starting from aniline

An alternate approach for the synthesis of tricyclic amine was proposed starting from aniline (**Scheme-49**).

Scheme-49:

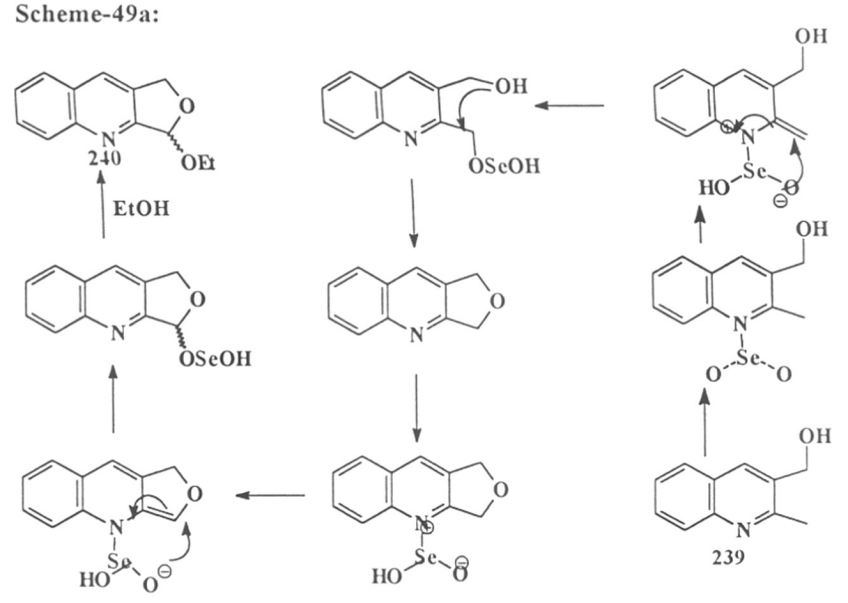


The aniline was converted to imine **237** in 94.8 % yield by refluxing aniline with methyl acetoacetate in cyclohexane using catalytic amount of acetic acid and removing the water azeotropically (Dean Stark). The formation of the product was confirmed by its ^{1}H NMR analysis, showed methyl ester protons at δ 3.60 and methyl peak at δ 1.95. The imine **237** was then subjected to Vilsmeir-Heck reaction conditions[32] ($POCl_3$, DMF) to give methyl 2-methyl-3- quinolinecarboxylate **238** in 62% yield. The structure of the ester **238** was confirmed by its NMR and MS (M^+, 201). The ^{1}H NMR showed the quinoline B ring proton at δ 8.75 as a singlet and methyl ester peak at δ 3.95 and the methyl now appeared at δ 2.95 as a singlet confirmed the formation of product. The reduction of the ester **238** with LAH gave alcohol **239**. The ^{1}H NMR showed disappearance of methoxy peak at δ 3.95 and appearence of a peak at δ 4.80 as singlet for benzylic protons. The SeO_2 oxidation of 2,3-dimethyl quinoline is reported to give quinoline-3-methyl-2-carboaldehyde in 50% yield.[33] Thus the alcohol **239** was subjected to oxidation with SeO_2 in xylene to give tricycliclactal **232** in poor yield. However, when a mixture of the alcohol **239**, ethanol and cyclohexane was refluxed with SeO_2, a product obtained was characterised as acetal **240**. Its ^{1}H NMR showed a triplet at δ 1.35, a multiplet at δ 4.05 (-O$\underline{CH_2}$CH$_3$) and a singlet at δ 6.20 (-CH-).

The probable mechanism for the formation of **240** is shown in the **Scheme-49a**. The selenic acid reacts with quinoline nitrogen and cation generated was neutralised by olefin formation, subsequently migration of selenide group and further nucleophilic

replacement gives ether. The second equivalent of SeO_2 helps in formation of acetal as per mechanism.

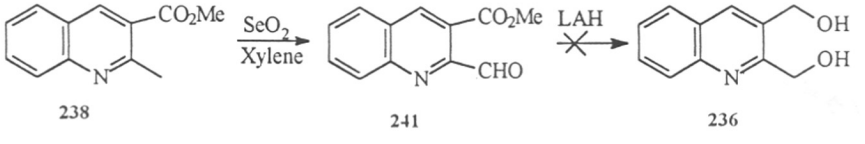
Scheme-49a:



The acetal **240** was hydrolysed with acetic acid in THF (1:1) to give lactal **232**. The lactal (**232**) formation was confirmed by ^1H NMR where the peaks of ethoxy of acetal, **240** which appeared at δ 1.35 and 4.05, have now disappeared and ring lactal proton appeared at δ 6.60 as singlet. This lactal **232** was then subjected to $NaBH_4$ reduction but it failed to give required diol **236** from which the preparation of tricyclic amine is already known.[34]

In another alternate route 2-methyl-3-carboxylatemethylester **238** was converted to aldehyde **241** with SeO_2 in xylene. The formation of **241** was confirmed by ^1H NMR spectra. Which showed the disapperance of methyl protons at δ 2.95 and appearance of aldehyde proton at δ 10.9. Further more reduction of the aldehyde **241** with LAH failed to give desired diol **236.**

Scheme-50a:

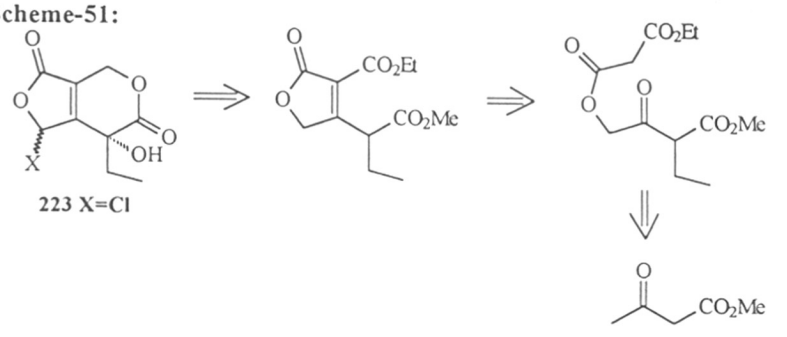


Part II: Synthetic approaches towards DE ring synthon:

Corey et al.[34a] reported preparation of pseudochloride **223** starting from 3,4-furandicarboxylic acid (see **Scheme-10**). Rama Rao and coworkers[34b] reported DE ring synthon **223** starting from propanaldehyde (see **Scheme-11**).

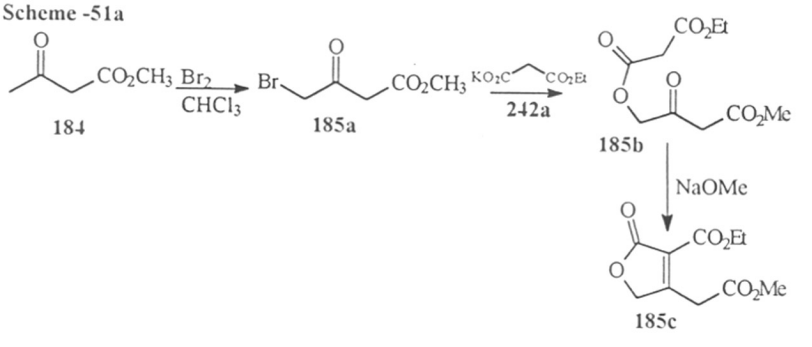
Our retrosynthetic analysis to pesudochloride**223** is given in **scheme-51**.

Scheme-51:



To see the fecibility of the method a model reaction has been carried out starting from methylacetateacetate (**184**) as shown in **scheme-51a**.

Scheme -51a

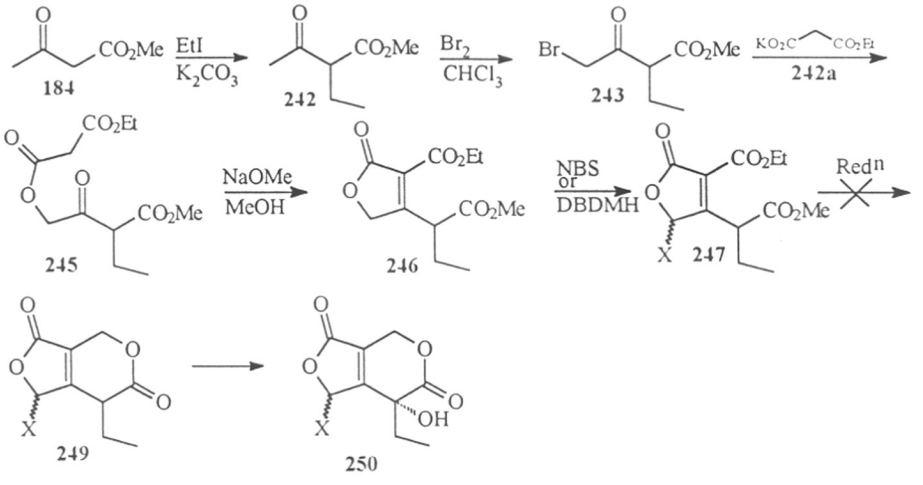


184 185a 185b 185c

On successful standardisation of this methodology was extended to the required moiety. Based on the retrosynthetic analysis of the psuedochloride **223**, our approach starts from easily available methyl acetoacetate, which can be ethylated, brominated and further esterified with monopotassium salt of ethyl malonate to give triester. This triester on Aldol type condensation followed by bromination would give pseudochloride like synthon that can be converted to DE ring synthon.

Methylacetoacetate (**184**) was ethylated using K_2CO_3, EtI and acetonitrile in 92% yield. The ethylated product **242** was characterised by its NMR.

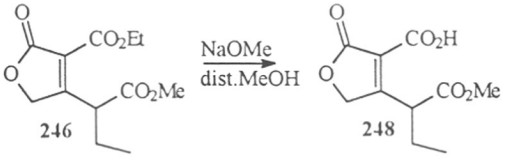
Scheme-52:



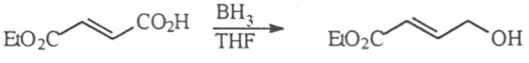
Bromination of the ethylated product **242** was carried out by using bromine in chloroform.[35] The crude bromo product **243** was used as such for esterifiation with mono potassium salt of ethylmalonate[36] **242a** at room temperature in presence of triethylbenzylammonium chloride as PTC. The ester **245** formation was confirmed by its NMR, MS (M^+ 276) and IR. Its ^1H NMR showed the presence of two singlets of methylene groups appeared at δ 4.85 and δ 3.55, methyl ester protons as a singlet at δ 3.65. The treatment[37] of **245** was carried out using NaOMe in dry MeOH to give cyclised product **246** in 60% yield. The formation of **246** was confirmed by its ^1H NMR study, which showed the presence of ethoxy group. Triplet at δ 1.05 and a quartet at δ 4.35 of ester ethyl group protons was observed for **246**. Other ethyl group gave a triplet at δ 1.35 with a multiplet at δ 1.70 - 2.10, and a triplet of methine proton at δ 4.45. Methyl ester protons at δ 3.75 as a singlet and the lactone methylene (CH_2-O) at δ 5.0. The ring halogenation was carried out using the procedure reported[38] for butanolides. Bromination of the lactone **246** with dibromohydrontoin[38] gave bromolactone **247** in 73% yield. The product formation was confirmed by its ^1H NMR. ^1H NMR showed disappearance of a singlet at δ 5.00 (-OCH_2-; 2H) and showed a peak at δ 6.90 as a singlet for one proton. Further selective reduction of the bromolactone **247** with excess of $NaBH_4$ failed to give the desired DE ring synthon **225**.

In another approach the intermediate **246** was selectively hydrolysed to acid **248** using NaOMe in methanol. The acid **248** obtained after acidic work up was characterised by its NMR and MS spectral analyses. The ^{1}H NMR spectrum clearly showed the absence of peaks corresponding to ethyl ester (**Scheme-53**).

Scheme53

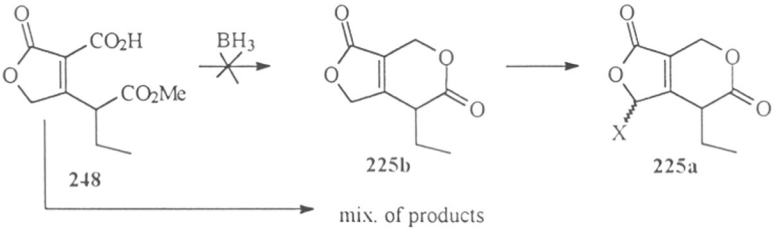


The selective reduction of α,β-unsaturated acid in presence of ester with diborane is known.[39]

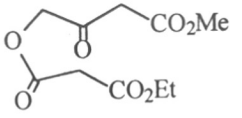


An attempt was made to convert the acid **248** to dilactone with diborane, but reaction gave a mixture of unseparable products (**Scheme-54**).

Scheme-54

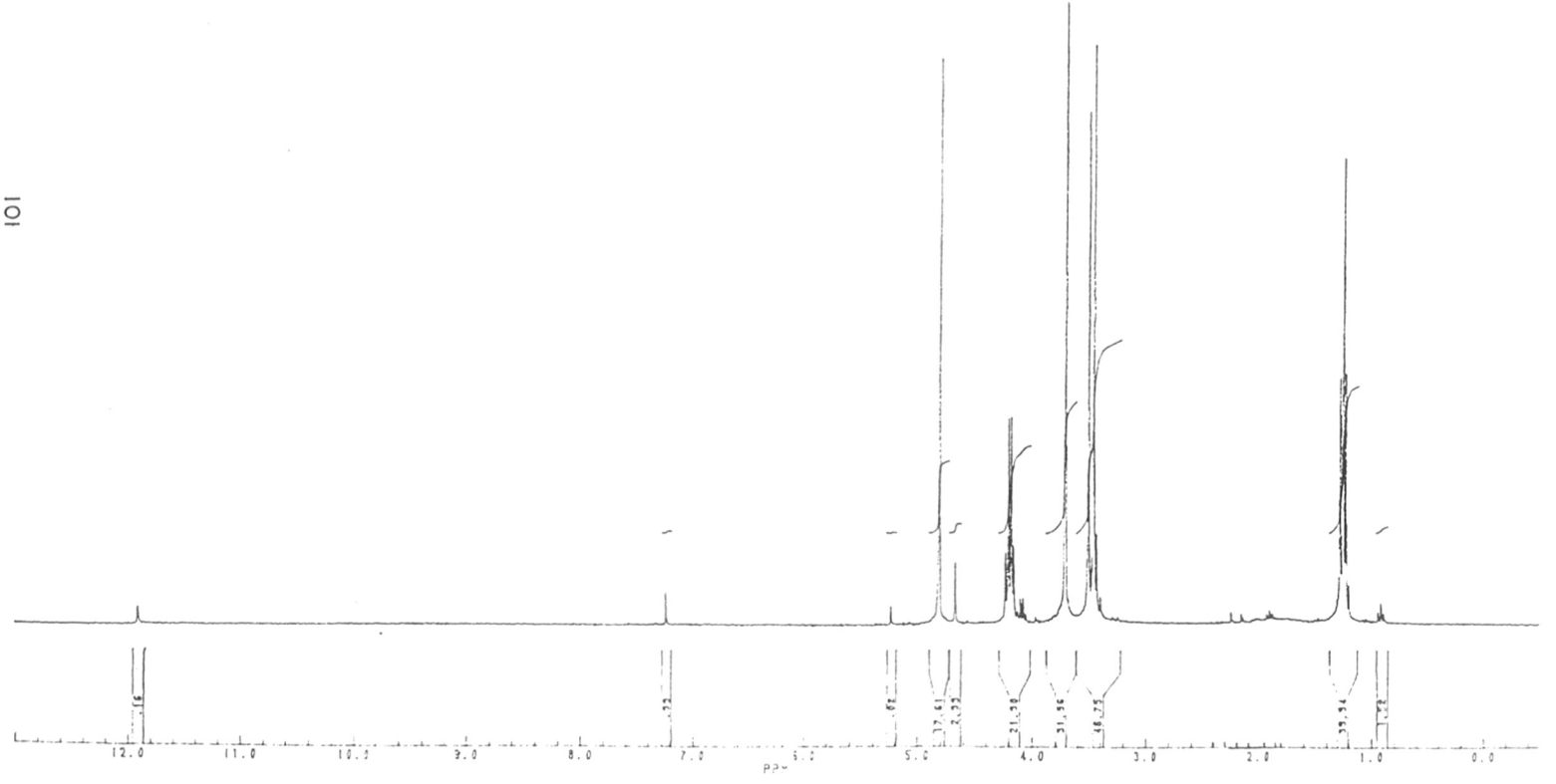


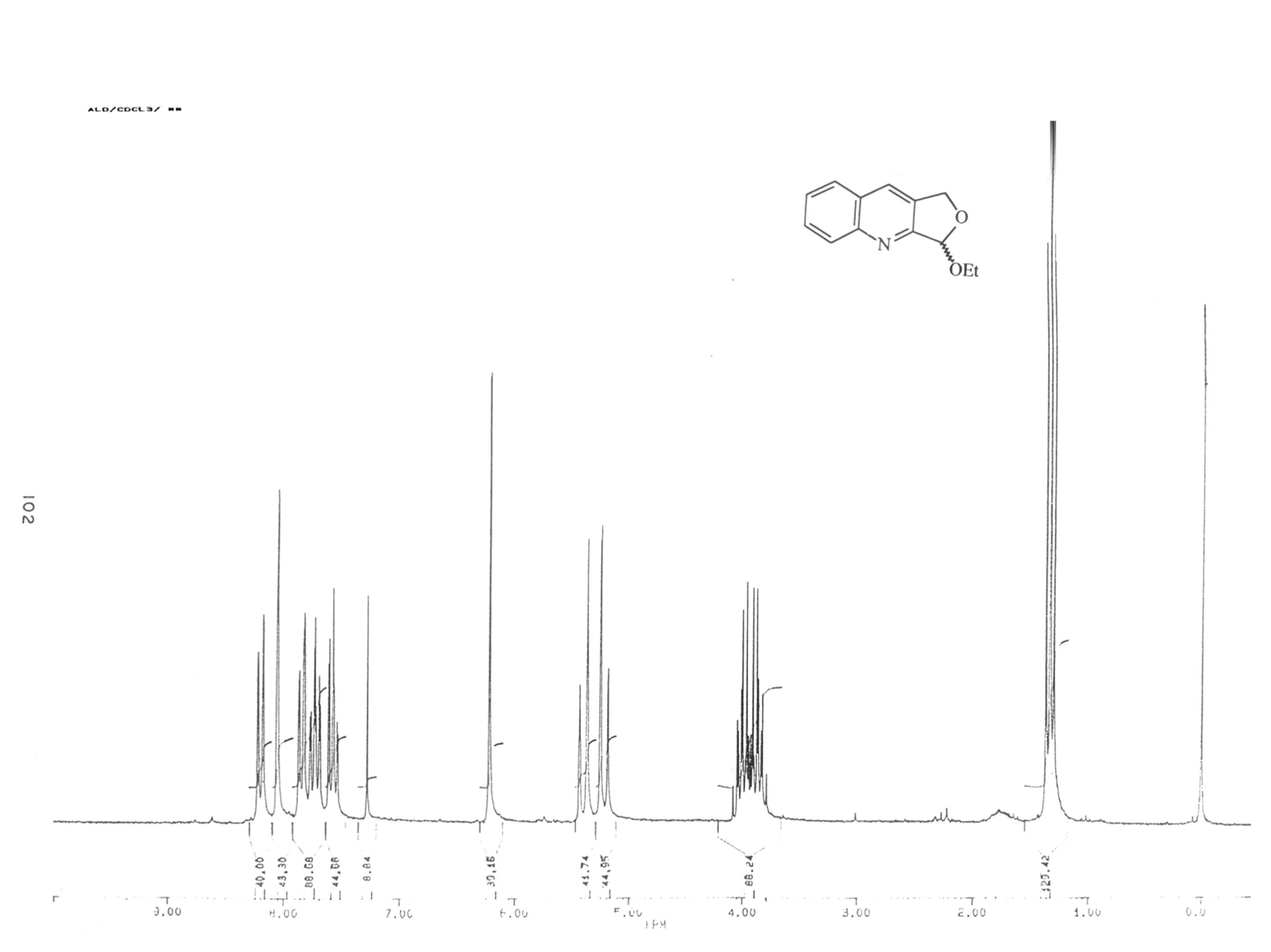
Thus the various efforts towards the preparation of tricyclic amine and pseodochloride are presented in this section.



B-3/CDCL3

~~NK-8081/CDCL3~~

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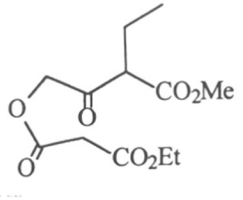
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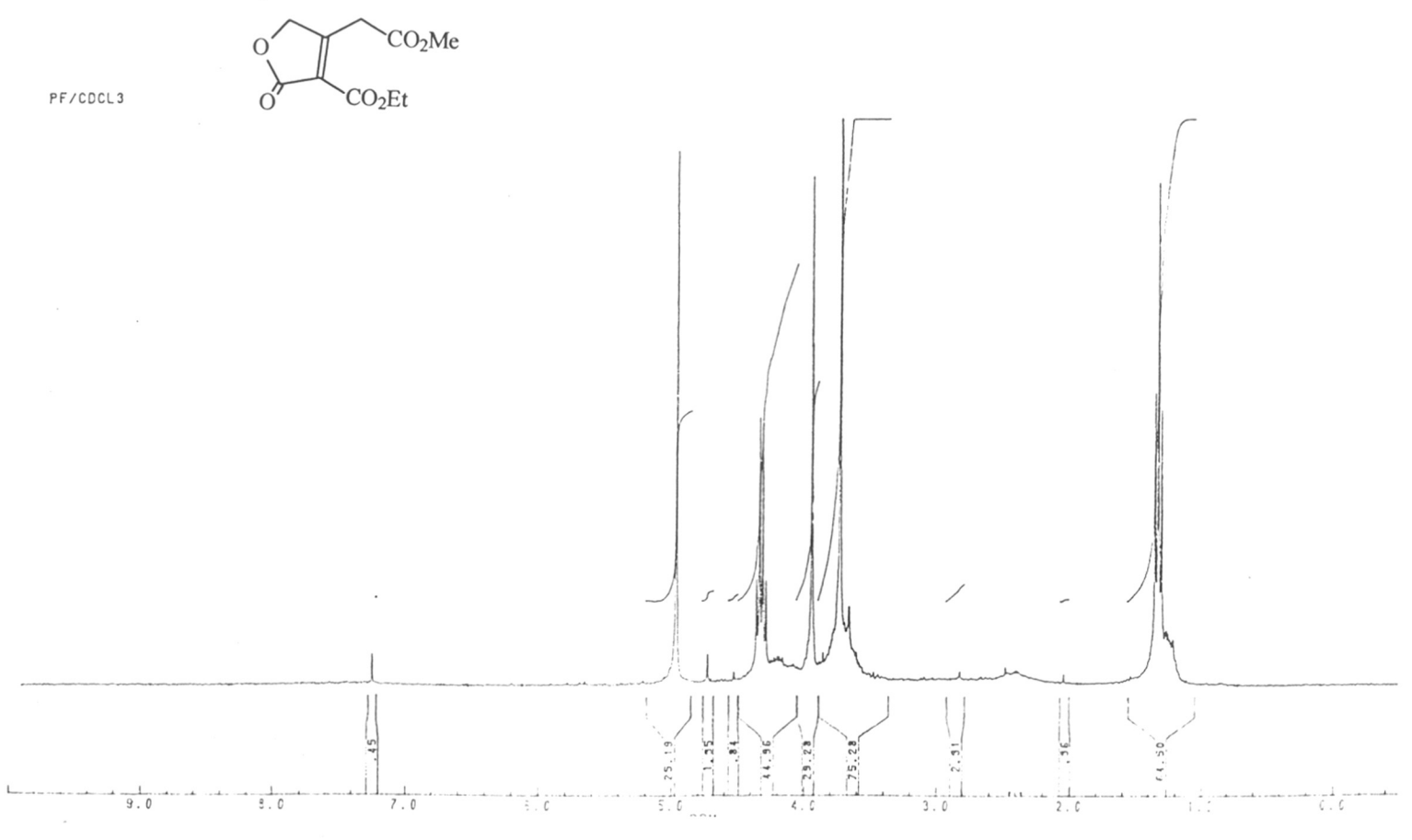
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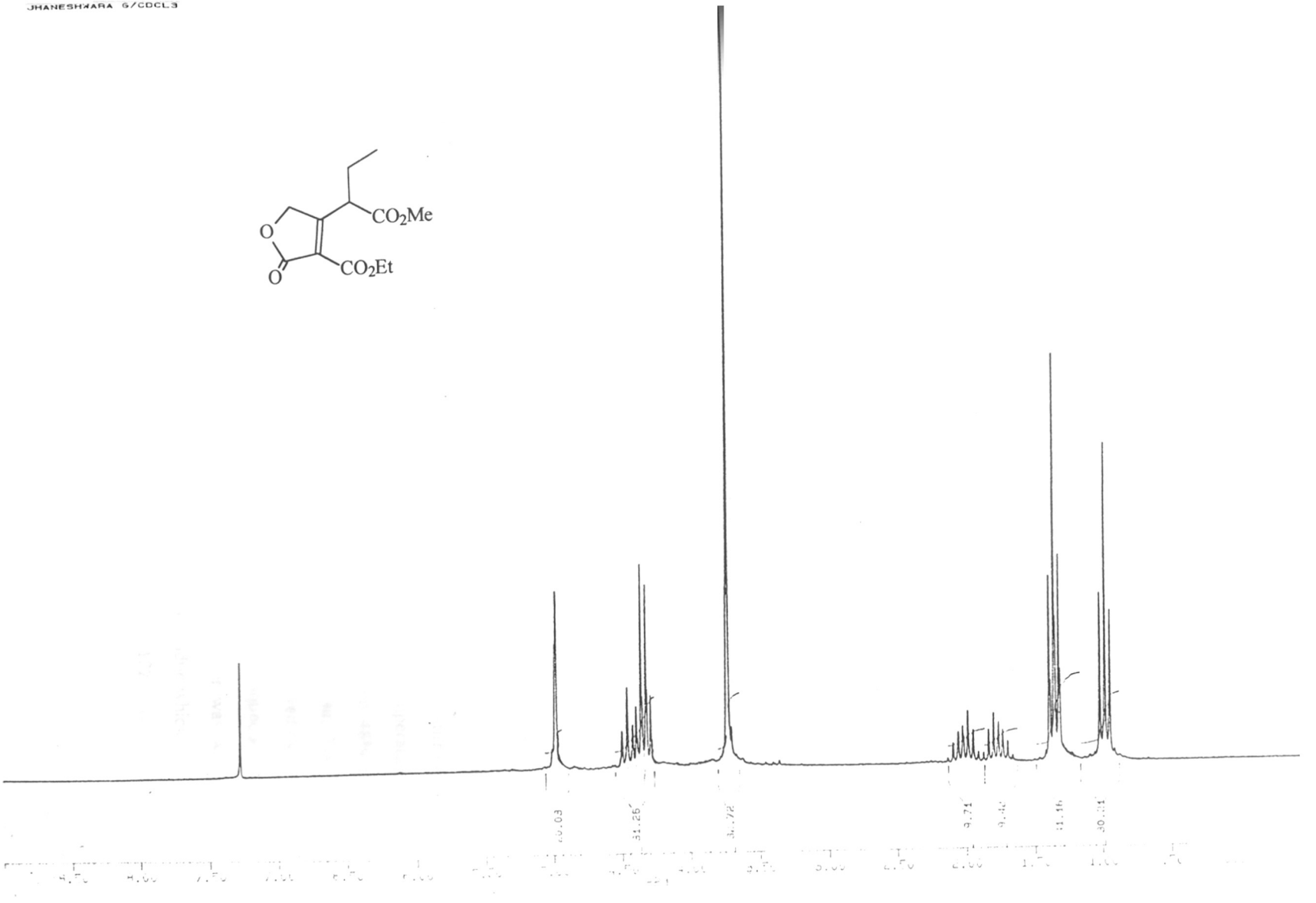
JHANESHWARA G/CDCL3
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CO2Me
CO2Et

EXPERIMENTAL

Methyl-4-cyano-3-methyl-3-butenoate (182a)

To a solution of methylacetoacetate **184** (27.52 gm; 237 mmol) in benzene (60 ml) was added cyanoacetic acid (22 gm, 258.8 mmol), ammonium acetate (3.6 gm, 46.75 mmol), and glacial acetic acid (6.1 ml) and the reaction mixture was stirred and refluxed for 8 hr using Dean Stark apparatus. The solvent was removed by distillation under reduced pressure and cold water was added to the residue followed by extraction with chloroform, then the organic layer was washed with water, brine then dried over Na_2SO_4 and concentrated to give a mixture of *cis* and *trans* isomers of **182a.**

Yield : (25.9 gm, 79.1%)

6-Bromo-4-methyl-2-pyridone (182)

To the above crude ester **182a** (25.43 gm, 183 mmol) in methanol (80 ml) was added potassium hydroxide (25.6 gm, 457 mmol) slowly at 0°C, with stirring then allowed to reach room temperature over 3 hr. The methanol was removed under reduced pressure. Ice was added to the residue and it was extracted with dichloromethane (2 x 50 ml) The aqueous layer was acidified with 4N H_2SO_4 under ice cooling. The residue was extracted with chloroform (6 x 80 ml). The combined organic layer was dried over Na_2SO_4. On concentration it gave crude liquid of the corresponding acid (15.7 gm, 68.6%). The crude acid (15.7gm, 126 mmol) was then taken in dry ether (160 ml) was added PCl_5 (35.03 gm, 168 mmol) in small portions with stirring at 0°C. After addition was complete the reaction mixture was stirred at room temperature for 1.5 hr.. Then this solution was cooled to 0°C. HBr gas (generated from 48% HBr and concentrated H_2SO_4) was passed through the cooled solution for 2 hr. The reaction mixture was stirred at room temperature for 1 hr. The ether was removed by distillation and to the residue aqueous $NaHCO_3$ was added cautiously. The aqueous layer was extracted with ethylacetate(3×50 ml). The combined organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated to obtain a residue which was purified by column- chromatography on silica gel to give bromopyridone **182** as white solid.

Yield : (14.85 gm, 62.8%)

M.P. :152°C (Lit. 149°C)

IR (Nujol) : 3300, 1652, 1620, 850 $cm.^{-1}$

^{1}H NMR (60MHz; $CDCl_3$) :δ 2.20 (s, 3H); 6.46 (d, J=1Hz, 1H); 6.60 (d, J = 1Hz, 1H); 9.75 (bs, 1H, ex. D_2O).

MS (m/z) :189 (M+2); 187 (M^+); 161; 159; 143; 108; 80; 64; 53.

Dimethylacetonedicarboxylate (183)

In a 3 neck round bottomed flask (3 lit.) fitted with mechanical stirrer was placed 320 ml of oleum (20%). Then the flask was cooled efficiently with ice salt mixture, (internal temperature of the acid was maintained between -5°C to -10°C) stirred and finely powdered 140 gm citric acid was added in portions. The temperature of the reaction was not allowed to increase more than 0°C until half of the citric acid was added.

The remaining half of citric acid was added at internal temperature 5°C (addition takes 4 to 5 hr.). Then the solution was stirred at ice salt mixture until all citric acid dissolves. The reaction mixture was slowly allowed to reach room temperature, taking care to avoid much foaming (by cooling sometimes with ice water) when gas evolution stops (2 to 3 hr) the reaction mixture was again cooled with ice salt mixture to -5°C and 480 gm of ice pieces in portions were added so that the internal temperature of the mixture should not rise more than 10°C, (which took 2 hr)then cooled to 0°C and the separated precipitate was filtered through sintered funnel and the acetonedicarboxylic acid collected was pressed to dry.

In a three neck, r.b flask, containing methanolic HCl (prepared from 200 ml of dry methanol in which HCl gas (130gm) generated from NaCl and H_2SO_4 was passed) was fitted with two stoppers, a condenser with $CaCl_2$ guard tube. The flask was heated to 45°C on water bath, and the above acid was added in portions and shaken to dissolve. Then the solution was allowed to cooled to room temperature and kept overnight for (12 hr). The contents were then poured into ice water and the aqueous layer was extracted with dichloromethane (3×50ml) The combined dichloromethane layer was washed with 10% Na_2CO_3 solution. The dichloromethane layer was dried over Na_2SO_4 on concentration followed by vacuum distillation gave the required product **183**.

B.p. : 127 to 130°C/12mm Hg

Overall yield : (40 gm, 30%)

^{1}H NMR (90 MHz; $CDCl_3$) δ 3.55 (s, 4H), 3.65 (s, 6H).

Dimethyl-3-cyanoethylene glutarate (185)

A mixture of dimethylacetonedicarboxylate **183** (21.5 gm, 123.7 mmol), cyanoacetic acid (11.6 gm, 136.4 mmol), ammonium acetate (1.91 gm, 24.8 mmol) and glacial acetic acid (3.340 gm, 55.9 mmol, 3.2 ml) in benzene (250 ml) was refluxed in an oil bath for 24 h with continuos removal of water using Dean -Stark apparatus.

The reaction mixture was then cooled and was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to obtain (22.30 gm, 92%) of **185** as a liquid.

IR (neat) : 2990, 2230, 1735, 1640, 850 cm^{-1}

^{1}H NMR (60 MHz; $CDCl_3$) : δ 3.35 (d, J = 1.5 Hz, 2H); 3.59 (s, 2H); 3.67 (s, 3H); 3.70 (s, 3H); 5.47 (s, 1H).

6-Bromo-4-carbomethoxymethyl-2-pyridone (146)

A solution of the diester (**185**) (23 gm, 116 mole) in methanol (100 ml) was cooled in an ice bath. To this KOH (16 gm, 0.36 mole) was added slowly with stirring. After the addition was over the reaction mixture was stirred with cooling for 2 hr. The methanol was removed under reduced pressure. To this ice pieces (50 gm) were added, followed by acidification with cold 4N H_2SO_4 solution and extracted with ethylacetate. The organic layer was dried over Na_2SO_4 and concentrated to get crude diacid. The crude acid (23 gm, 0.136 mole) in dry ether (300 ml) was stirred and cooled to 0°C, PCl_5(56.75 gm, 0.272 mole) was added in portions, then was stirred for 1 hr. HBr gas (generated from 48% HBr and concentrated H_2SO_4) was passed through the ether solution and then stirred overnight. The ether was removed and the residue was cooled and 60 ml of dry methanol was added slowly. After 3 hr the methanol was removed and the residue was diluted with water and extracted with ethylacetate (3×50 ml). The combined ethylacetate layer was washed with saturated $NaHCO_3$, the ethylacetate layer was dried over Na_2SO_4, concentration followed by column chromatography on silica gel to give the product **146** as a pale yellow solid.

Yield: : (19 gm, 57%)

MP :140-141°C

IR (nujol) : 3300, 1730, 1660, 1510, 1470, 1200 cm^{-1}

^{1}H NMR (80 MHz; $CDCl_3$,) : δ 3.47 (s, 2H); 3.67 (s, 3H) ; 6.57 (d, J = 1 Hz, 1H); 6.78 (d, J= 1Hz, 1H).

MS (m/z) : 247 (M+2); 245 (M^+); 217; 188; 166; 133; 78; 59.

3-Bromopropionaldehyde dimethylacetal (186)

Saturated methanolic HBr was prepared from of dry MeOH (37 ml) (HBr gas generated using 48% HBr and H_2SO_4) by passing HBr gas while cooling with ice salt mixture. Acrolein (30.01 gm; 0.565 mol) was added dropwise into the cooled methanolic HBr solution The reaction mixture was then diluted with $CHCl_3$ and solid $NaHCO_3$ was added until effervescence ceases, filtered and $NaHCO_3$ solid washed with $CHCl_3$. The combined $CHCl_3$ was dried over Na_2SO_4, concentrated and distilled under reduced pressure to give the required product **186** as a colourless liquid.

Yield **: (72.2 gm, 73%)**

^{1}H NMR (60 MHz; CCl_4,) : δ 2.05 (q, J = 8 Hz, 2H); 3.32 (s, 6H); 3.4 (t, J = 8Hz, 2H); 4.5 (t, J = 8Hz, 1H).

BP : 58 °C / 17 mm.

N-Alkylation of pyridone 146 with 3-bromo propionaldehyde dimethylacetal (186)

A mixture of bromopyridone **146** (245 mg, 1 mmol), 3-bromopropionaldehyde dimethyl acetal **186** (183 mg, 1 mmol) and potassium carbonate (207 mg, 1.5 mmol) in dry acetonitrile (25ml) was refluxed on water bath for 6 hr. After the reaction was over, the acetonitrile was removed under vacuum. Water (10 ml) was added to the residue and extracted with chloroform. Removal of the chloroform gave crude product, which was purified by column chromatography to give pure product **187a** and **187**.

6-Bromo-4-carbomethoxy-methyl-2-pyridyl-3,3-dimethoxy propyl ether (187a)

Yield : (247 mg, 87%)

IR (neat) : 1600, 1700, 1200, 750 $cm.^{-1}$

^{1}H NMR (90 MHz; $CDCl_3$,): δ 2.00 (q, J = 7 Hz, 2H); 3.40 (s, 2H); 3.60 (s, 3H); 3.60 (s, 6H); 4.2 (t, J = 7 Hz, 2H); 4.50 (t, J = 7 Hz); 6.40 (s, 2H); 6.9 (s, 1H, CH)

MS (m/z) : 349 (M+2), 347 (M^+).

6-Bromo-4-carbomethoxymethyl-N-3,3'-dimethoxypropyl -2-pyridone (187)

Yield : (0.02gm, 8 %)

IR (neat) : 1740,1700, 1660 1200, 750 $cm.^{-1}$

^{1}H NMR (90 MHz; $CDCl_3$,) : δ 2.00 (q, J = 7 Hz, 2H); 3.40 (s, 2H); 3.60 (s, 3H); 3.60 (s, 6H); 4.0 (t, J = 7Hz, 2H); 4.50 (t, J = 7 Hz); 6.20 (s, 2H); 6.7 (s, 1H, CH).

MS (m/z) : 349 (M+2), 347 (M^+), 224, 153, 75

6-Bromo-4-carbomethoxy methyl-2-pyridyl-3(1,3-dithian)propyl ether (192)

A mixture of $BF_3.Et_2O$ (0.06 ml), AcOH (0.12 ml) in $CHCl_3$ (5 ml) was kept at 70°C. A solution of dimethoxy acetal **187a** (0.174 gm, 0.5 mmol) and 1,3-propane dithiol (0.05 gm, 0.5 mmol) in $CHCl_3$ (5ml) was added through a syringe and refluxed for 3 hr. After the reaction, $CHCl_3$ layer was washed with brine solution and purified by column chromatography over silica gel to give product **192**.

Yield : (0.190 gm, 96%)

IR (nujol) : 3000, 1600, 1700, 1100, 850 $cm.^{-1}$

^{1}H NMR (80 MHz; $CDCl_3$) : δ 1.2-1.5 (m, 4H); 1.7-1.9 (m, 4H); 3.4 (s, 2H); 3.6 (s, 3H); 4.1 (t, J = 8 Hz, 2H); 4.35 (t, J = 6.5 Hz, 1H); 6.5 (s, 1H); 6.9 (s, 1H).

MS (m/z) : 395 (M+2); 391 (M^+); 368; 301; 206; 146.

N-Alkylation of pyridone 182 with 3-bromodimethyl acetal (186)

A mixture of bromo pyridone **182** (0.87 gm, 0.0046 mole) bromo acetal 186 (0.842 gm, 0.0046 mole) and K_2CO_3 (0.953 gm 0.0092 mole) in acetonitrile (30 ml) was refluxed on water bath for 7-8 hr. After the reaction was over, acetonitrile was removed under vacuum. The residue was dissolved in water extracted with Chloroform. The crude product obtained after removal of $CHCl_3$ was purified by column chromatography, to give of product **191a** and **191**.

6-Bromo-4-methyl-2-pyridyl-3,3'-dimethoxypropyl ether (191a)

Yield : (0.89 gm, 87%)

IR (nujol) : 3000, 1600, 1550, 1300, 1110 $cm.^{-1}$

^{1}H NMR (90 MHz; $CDCl_3$,): δ 2.6 (q, J = 5.3 Hz, 2H); 2.8 (s, 3H); 3.7 (s, 6H); 4.6 (t, J = 5.3 Hz, 2H); 4.8 (t, J = 5.3 Hz, 1H); 6.4 (s, 1H); 6.7 (s, 1H).

MS (m/z) : 293 (M+2); 291 (M^+); 214, 185, 91.

6-Bromo-4-methyl-N-3,3'-dimethoxypropyl -2-pyridone (191)

Yield : (0.019gm, 7 %)

IR (nujol) : 3000, 1740, 1550, 1300, 1110 $cm.^{-1}$

^{1}H NMR (90 MHz; $CDCl_3$,) : δ 2.60 (q, J = 5.3 Hz, 2H); 2.8 (s, 3H); 3.7 (s, 6H); 4.2 (t, J = 5.3 Hz, 2H); 4.75 (t, J = 5.3 Hz, 1H); 6.2 (s, 1H); 6.5 (s, 1H).

MS (m/z) : 293 (M+2); 291 (M^+); 212, 183, 95.

6-Bromo-4-methyl-2-pyridyl-3-(1,3-dithiolane) (192a)

A mixture of acetic acid (0.24 ml), $BF_3 \cdot Et_2O$ (0.12 ml) in chloroform (7 ml) was kept at 70°C. A solution of dimethoxy acetal **191a** (0.290 gm, 1 mmol) and 1,2-ethane dithiol (0.094 gm, 1 mmol) in chloroform (5ml) was added through syringe at 70°C and the reaction was stirred with reflux for 6 hr.. The reaction mixture was cooled and the organic layer was washed with $NaHCO_3$ solution, brine and purified by column chromatography to give compound **192a**.

Yield : (0.253 mg, 80%)

IR (neat) : 3200, 1600, 1400, 1210 $cm.^{-1}$

^{1}H NMR (80 MHz; $CDCl_3$) : δ 2.2 (q, J = 6.6 Hz, 2H); 2.25 (s, 3H); 3.2 (s, 4H); 4.3 (t, J = 6.6 Hz, 2 H); 4.65 (t, J = 6.6 Hz, 1H); 6.5 (s, 1H); 6.9 (s, 1H).

MS (m/z) : 323 (M+2); 321 (M^+); 224 , 181, 98.

6-Bromo-4-methyl-2-pyridyl-3-(1,3-dithiane)propyl ether (192b)

A mixture of $BF_3 \cdot Et_2O$ (0.06 ml), AcOH (0.12 ml), in $CHCl_3$ (5ml) was kept at 70°C. A solution of acetal **191a** (0.1465 gm, 0.5 mmol) and 1,3-propane dithiol (0.05 gm, 0.5 mmol) in $CHCl_3$ (3 ml) was added dropwise and then stirred for 4-5 hr. Then the organic layer was washed with 5% NaOH solution and organic layer was separated, dried over Na_2SO_4 followed by purification gave the dithiane product **192b**.

Yield : (0.155 gm, 92%)

^{1}H NMR (80 MHz; $CDCl_3$) : δ 1.85-2.1 (m, 2H); 2.2 (s, 3H); 2.75-2.9 (m, 4H); 4.2 (t, J = 6 Hz, 2H); 4.35 (t, J = 6 Hz, 1H); 6.4 (s, 1H); 6.5 (s, 1H).

General procedure for alkylation

A mixture of bromopyridone **182** or **146** (1 mmol) alkyl halide (1 mmol) and K_2CO_3 (2 mmol) in acetonitrile (10 ml) was refluxed on water bath for 5-6 hr. The acetonitrile was removed under reduced pressure to give a residue, which was then dissolved in water (20 ml) and extracted with chloroform. The organic layer was then washed with brine solution (20 ml) dried over Na_2SO_4, concentrated and purified by column chromatography using silica gel.

6-Bromo-4-methyl-2-pyridyl allyl ether (196)

Yield : (0.078 gm, 35%)

IR (neat) : 3300, 2400, 2100, 1650, 1600, 1300 cm.$^{-1}$

^{1}H NMR (80 MHz; $CDCl_3$,) : δ 2.2 (s, 3H); 4.7-4.8 (m, 2H); 5.10 (m, 2H); 5.9-6.3 (m, 1H); 6.5 (s, 7H); 6.9 (s, 1H).

MS (m/z) : 213 (M^{+2}); 211 M^+; 173; 132; 92.

6-Bromo-4-methyl-N-allyl-2-pyridone (194)

Yield : (0.12 gm, 60%)

IR (neat) : 3300, 1700, 1650, 1500, 100 cm.$^{-1}$

^{1}H NMR (80 MHz; $CDCl_3$,) : δ 2.2 (s, 3H); 4.75-4.8 (m, 2H); 5.1-5.2 (m, 2H); 5.7-6.3 (m, 1H); 6.2 (s, 2H).

MS (m/z) : 213 (M+2); 211 (M^+); 171; 133; 88.

6-Bromo-4-methyl-2-pyridyl propargyl ether (196a)

Yield : (0.063gm, 28%)

IR (neat) : 3100, 2900, 2210, 1650, 1600, 1300 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$,): δ 2.2 (s, 3H); 2.40 (t, 1H, ≡-H); 4.9 (d, J = 4.7 Hz, 2H); 6.5 (s, 1H); 6.75 (s, 1H).

MS (m/z) : 227 (M^{+2}); 225 (M^+); 188, 146, 107.

6-Bromo-4-methyl-N-propargyl-2-pyridone (182b)

Yield : (0.16 gm, 70%)

IR (neat) : 300, 2900, 2200, 1700, 1500, 900 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$,): δ 2.5 (s, 3H); 2.3 (t, J = 4.7 Hz, 1H); 4.95 (d, J = 4.7 Hz, 2H); 6.2 (s, 1H); 6.35 (s, 1H).

MS (m/z) : 227 (M+2); 225 (M^+); 185, 143, 105.

6-Bromo-4-(carbomethoxy methyl)-2-pyridyl allyl ether (196b)

Yield : (0.162 gm, 28%)

IR (neat) : 3900, 3522, 3299, 1718, 1654, 1600, 900 $cm.^{-1}$

^{1}H NMR (80 MHz; $CDCl_3$,):δ 3.51 (s, 2H); 3.70 (s, 3H); 4.7-4.80 (m, 2H); 5.1-5.5 (m, 2H); 5.7-6.2 (m, 1H); 6.6 (s, 1H); 7.0 (s, 1H).

MS (m/z) : 287 (M+2); 285 (M^+); 247; 167; 127.

6-Bromo-4-carbomethoxy methyl-N-allyl-2-pyridone (194a)

Yield : (0.210 gm , 62%)

IR (neat) : 3900, 3522, 1720, 1440, 1200 $cm.^{-1}$

^{1}H NMR (80 MHz; $CDCl_3$,) :δ 3.4 (s, 2H); 3.70 (s, 3H); 4.95-5.2 (m, 2H); 5.6-5.65 (m, 2H); 5.7-6.0 (m, 1H); 6.4 (s, 1H); 6.85 (s, 1H).

MS (m/z) : 287 (M+2); 285 (M^+); 256; 167; 91.

3-Chlorodimethylglutaconate (202)

Concentrated H_2SO_4 (200 ml) was stirred at room temperature using mechanical stirrer, citric acid (55 gm) was added in portions and allowed to stir for 10-12 h. The reaction mixture was cooled to 0 °C. Distilled MeOH (100 ml) was added slowly, stirred overnight then kept at RT for 2 days. Then the reaction mixture was poured into crushed ice and extracted with dichloromethane, dried over Na_2SO_4, evaporation of organic layer gave the crude product (30gm) which was directly used for next step.

Dimethylacetonedicarboxylate (**183**) (10 gm) was stirred at room temperature, to which PCl_5 (12.62 gm) was added slowly in portions. After the addition was over, the reaction was warmed with hot water (80°C) for one hr. This mixture was then poured into ice and extracted with dichloromethane, organic layer was dried over Na_2SO_4 and evaporation of dichloromethane gave crude product which was then dissolved in methanol (25 ml), sulfuric acid (5 ml) and refluxed for 48 hr. The reaction mixture was cooled and poured into ice. The mixture was then extracted with dichloromethane, evaporation of dichloromethane followed by distillation under reduced pressure, [120°C at 5 mm Hg] gave 3-chlorodimethyl glutoconate (4.96 gm, 45%).

(N-benzyl) amine-2-dimethyl-butenoate (201)

Benzyl amine (2.33 gm, 0.0218 mole) in acetonitrile (50 ml) was cooled to -5°C using ice salt mixture. To this a solution of dimethylacetylenedicarboxylate (3.095 gm, 0.0218 mole) in acetonitrile (20 ml) was added. The resultant solution was then stirred for 1 hr at room temperature. The acetonitrile was removed under reduced pressure to give yellow oil.

Yield : (5.42 gm , 98%)

^{1}H NMR (, 80 MHz; $CDCl_3$,):δ 3.6 (s, 3H); 3.7 (s, 3H); 4.5 (d, J = 5.9 Hz, 2H); 5.1 (s, 1H); 7.3 (s, 5H); 8.5 (Bs, 1H).

(N-benzyl) amine-2-diethyl-butenoate (210)

The above procedure was used to prepare imine **210** from diethylcarboxylate (2.02 gm, 0.0122 mole) and benzylamine (1.30 gm, 0.012 mole).

Yield : (3.23 gm, 98%)

^{1}H NMR (200 MHz; $CDCl_3$): δ 1.16-1.35 (m, 6H); 4.05-4.25 (m, 4H); 4.55 (d, J = 7.3 Hz, 2H); 5.15 (s, 2H); 7.25-7.35 (m, 5H); 8.45 (bs, 1H).

4-(carbomethoxymethyl)-5,6-dicarbomethoxy-N-benzyl-2-pyridone (203)

To the solution of imine **201** (5.42 gm, 0.02 mole) in dry methanol (40 ml) was added dimethyl 3-chlorodimethylglutoconate (6.28 gm, 0.0327 mole). To this stirred solution triethyl amine (3.3 gm, 4.54 ml, 0.0327 mole) was added and then stirred at room temperature for 65 hr. Reaction mixture was the concentrated to near dryness. Column purification over silica gel gave **203** as yellow solid

Yield : (3.55 gm, 43%)

IR : 3500, 1710, 1660,1600, 1300 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 3.65 (s, 3H); 3.68 (s, 3H); 3.7 (s, 3H); 3.72 (s, 2H); 5.2 (s, 2H); 6.45 (s, 1H); 7.12-7.15 (m, 5H).

MS (m/z) : 373 (M^+); 342; 252; 220; 91; 65.

Analysis : **Cal.** C 61.12%, H 5.09%, N 3.75%.
Observed: C 61.22%, H 5.12%, N 3.92%.

4-Carbomethoxy methyl-5,6-dicarboethoxy-N-benzyl-2-pyridone (211)

The same above experimental procedure was followed by taking imine **210** (3.23 gm, 0.0116 mole), chlorodimethylglutamate (3.456 gm, 0.018 mole) and TEA (1.94gm, 0.018 mole).

Yield : (2.31 gm, 41%)

IR (neat) : 3500, 1720, 1660,1600, 1210 cm^{-1}

^{1}H NMR (200 MHz; $CDCl_3$): δ 1.05 (t, J = 7.1 Hz, 3H); 1.30 (t, J = 7.1 Hz, 3H); 3.65 (s, 3H); 3.75 (s, 2H); 4.10 (q, J = 7.1 Hz, 2H); 4.20 (q, J = 7.1 Hz, 2H); 5.3 (s, 2H); 6.52 (s, 1H); 7.2-7.3 (m, 5H).

MS (m/z) : 397 (M^+); 365; 118; 62.

Analysis	: Cal	C 63.476%,	H 5.79%,	N 3.526%.
	Observed	C 63.686%,	H 5.88%,	N 3.62%.

4-(1-Carbomethoxypropyl)-5,6-dicarbomethoxy-N-benzyl-2-pyridone (204)

A mixture of pyridone **203** (1.15 gm, 0.003 mole) potassium carbonate (0.45 gm, 0.0032 mole), excess ethyl iodide and catalytic amount of TBAB in acetonitrile (20 ml) was refluxed for 16 hr with occasional addition of ethyl iodide. After the reaction was over (TLC) the acetonitrile was removed under vacuum and the residue was treated with excess of water. The aqueous layer was then extracted with $CHCl_3$ (3 x 25 ml) combined organic layer was dried over Na_2SO_4 concentrated and the residue was purified using silica gel column chromatography to obtain **204**.

Yield : (1.23 gm, 82%)

IR (neat) : 3200, 3100, 1760,1660, 1600, 1200 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.95 (t, J = 7.1 Hz, 3H); 1.65-1.85 (m, 1H); 2.05-2.2 (m, 1H); 3.70 (s, 3H); 3.75 (s, 3H); 3.8 (s, 3H); 3.9 (t, J = 7.1 Hz, 1H); 5.32 (s, 1H); 5.65 (s, 1H); 6.70 (s, 1H); 7.1-7.35 (m, 5H).

MS (m/z) : 401 (M^+); 370; 280; 220; 142; 91.

4-(1-Carbomethoxypropyl)-5,6-dicarboethoxy-N-benzyl-2-pyridone (212)

Same above procedure was adopted where pyridone **211** (0.85 gm, 2.14 mmol) K_2CO_3 (0.30gm; 2.25 ml) and TBAB catalyst were used.

Yield : (0.77 gm, 85%).

IR (neat) : 3500, 2900, 1730, 1650 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$,): δ 0.95 (t, J = 7.1 Hz, 3H); 1.00 (t, J = 7.1 Hz, 3H); 1.25 (t, J = 7.1 Hz, 3H); 1.7-1.82 (m, 1H); 1.8 -2.15 (m, 1H); 3.70 (s, 3H); 3.9 (t, J = 7.1 Hz, 1H); 4.10 (q, J = 7.1 Hz, 2H); 4.20 (q, J = 7.2 Hz, 2H); 5.50 (s, 1H); 5.55 (s, 1H); 6.65 (s, 1H); 7.15-7.4 (m, 5H).

MS (m/z) : 421 (M^+); 391; 358; 93.

4-(1-Carbomethoxypropyl)-5,6-dicarbomethoxy-2-pyridone (205)

Ethyl pyridone **204** (1.4 gm, 3.49 mmol), 10% Pd/C catalyst (550 mg) and $HClO_4$ (0.3 ml) in acetic acid (25 ml) were stirred at 50°C and 60 psi pressure of hydrogen for 5 hr. After reaction was over (TLC) Pd/C was filtered off and acetic acid was removed by distillation. The residue was then treated with water and extracted with chloroform. Chloroform layer was dried over Na_2SO_4 and purified by column chromatography over silica gel to give **205**.

Yield : (1.085 gm, 76.85%)

IR (neat) : 3100, 1730, 1660,1600, 1220 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.95 (t, J = 7.1 Hz, 3H); 1.70-1.85 (m, 1H); 1.9-2.10 (m, 1H); 3.40 (t, J = 7.2 Hz, 1H); 3.75 (s, 3H); 3.9 (s, 3H); 3.95 (s, 3H); 6.85 (s, 1H); 8.05 (Bs, 1H).

MS (m/z) : 311 (M^+); 279, 264, 236, 91.

Analysis : **Cal.** C 54.01% H 5.46% N 4.5%

Observed C 54.32% H 5.51% N 4.7%

4-(1-Carbomethoxy propyl)-5,6-dicarbomethoxy 2-pyridyl (208)

Compound **205** (0.155 gm, 0. 49 mmol) in acetonitrile (5 ml), was cooled to 0°C. A solution of TEA (0.07 ml) in acetonitrile (1 ml) was added dropwise and stirred for 15 min. A solution of methylpropargylate (0.04gm, 0. 49 mmol) in acetonitrile (5 ml) was then added and stirred for 1 hr, at room temperature. The acetonitrile and Et_3N were removed under reduced pressure and the residue was purified by column chromatography over silica gel to give **208**.

Yield : (0.162gm, 82%)

IR (neat) : 3420, 1650, 1600 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.85 (t, J = 7.3 Hz, 3H, 1.7-1.9 (m, 1H); 1.95-2.1 (m, 1H); 3.6 (t, J = 7.3 Hz, 1H); 3.8 (s, 3H); 3.85 (s, 3H); 3.9 (s, 3H); 3.95 (s, H); 5.7 (d, J = 14.6 Hz, 1H); 6.85 (s, 2H); 7.6 (d, J = 14.6 Hz, 1H).

MS (m/z) : 395 (M^+); 336; 312; 284; 213; 157.

4 (1-Carbomethoxypropyl)-5,6-dicarboethoxy-2-pyridyl-3-methylpropionate (207)

A Compound **205** (0.260 mg, 0.836 mmol), K_2CO_3 (0.125 gm, 0. 92 mmol) and methyl acrylate (0.085 gm, 0. 9 mmol) were stirred in DMF (5 ml) at 45°C for 24 hr. Then the reaction mixture was partitioned between ethylacetate and water. The ethylacetate layer was washed with water (3 times) followed by brine and dried over Na_2SO_4 column chromatography gave pure product **207**(0.266 gm, 80%).

B Compound **208** (0.050 mg, 0.12 mmole) in distilled methanol (5 ml) with Pd/C (20 mg) catalyst were stirred under H_2 balloon at room temperature overnight, the catalyst was filtered and methanol was evaporated to give product **207** in (0.051 mg, 92%) yield.

IR (neat) : 3420, 3300, 1650, 1600 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.95 (t, J = 7.5 Hz, 3H); 1.71-1.89 (m, 1H); 1.95-2.12 (m, 2H); 2.81 (t, J = 7.1 Hz, 2H); 3.68 (s, 3H); 3.7 (s, 3H); 3.88 (t, J = 7.1 Hz, 1H); 3.91 (s, 3H); 3.95 (s, 3H); 4.67 (t, J = 7.1 Hz, 2H); 6.95 (s, 1H).

^{13}C NMR (50 MHz) : 12.08 (q); 26.54 (t); 34.762 (t); 49.53 (q); 52.69 (q); 53.48 (q); 58.72 (q); 67.8 (d); 120.6 (d); 123.05 (s); 133 (s); 152 (s); 163.7 (s); 164 (s); 165.7 (s); 171.7 (s); 176.5 (s).

MS (m/z) : 387 (M^+); 357; 327; 301; 297; 92.

Attempted lactonisation of 212:

A mixture of compound **212** (0.35 gm, 0.8 mmol), paraformaldehyde (350 mg) H_2SO_4 (0.1 ml) in dioxane (2 ml) and water (0.1 ml) was heated in a thick glass tube (seal) at 107°C for 24 hr. The reaction mixture was then cooled and the product was partitioned between water and dichloromethane. The organic layer was separated and dried over Na_2SO_4 and purified by column chromatography over silica gel to give acid **217** and decarboxylated product **218**.

4(1-carboxalic propyl acid) 5,6-carbomethoxy N-benzyl-2-pyridone (217)

Yield : (0.15 gm, 22%)

IR (nujol) : 3500, 1720, 1660 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.95 (t, J = 7.1 Hz, 3H); 1.05 (t, J = 7.1 Hz, 3H); 1.25 (t, J = 7.1 Hz, 3H); 1.75-1.9 (m, 1H); 1.95-2.11 (m, 1H); 3.90 (t, J = 7.2 Hz, 1H); 4.05 (q, J = 7 Hz, 2H); 4.20 (q, J = 7.1 Hz, 2H); 5.35 (s, 2H); 6.5 (bs, 1H, CO_2H,); 6.8 (s, 1H); 7.1-7.3 (m, 5H).

MS (m/z) : 415 (M^+); 280; 91.

4-Propyl-5,6-dicarboethoxy N-benzyl 2-pyridone (218)

Yield : (0.183 gm, 52%)

IR (neat) : 3200, 1710, 1660, 1400, 1220 $cm.^{-1}$

^{1}H-NMR (200 MHz; $CDCl_3$): δ 0.95 (t, J = 7.1 Hz, 3H); 1.05 (t, J = 7.1 Hz, 3H); 1.25 (t, J = 7.1 Hz, 3H); 1.5-1.60 (m, 2H); 2.55-2.6 (m, 2H); 4.05 (q, J = 7.1 Hz, 2H); 4.15 (q, J = 7.1 Hz, 2H); 5.35 (s, 2H); 6.55 (s, 1H); 7.2-7.3 (m, 5H).

MS (m/z) : 371 (M^+); 338; 91; 64.

Analysis : **Cal**: C 67.9%, H 6.73%, N 3.77%

Observed: C 67.73%, H 6.52%, N 3.71%

β-Alaninemethyl ester hydrochloride (219)

β-Alanine (8.0 gm, 0.1 mole) was suspended in dry MeOH (50 ml) in a three neck flask, equipped with $CaCl_2$ guard tube, stopper and bubbler. Dry HCl [generated from NaCl and H_2SO_4] was passed through H_2SO_4 trap and then to the reaction mixture at 0°C for 4 h and kept for stirring (overnight). Removal of MeOH under reduced pressure gave **219** as a white solid (12.24 gm, 98%).

N-(2-methylpropionate)-2,dimethyl butanoate (220)

β-Alaninemethyl ester hydrochloride (**219**) (3.74 gm, 0.034 mole) in acetonitrile (50 ml) cooled to 0°C. $NaHCO_3$ (2.856 gm) was added in portion followed by

dimethylacetylenedicarboxylate (4.72 gm, 0.034 mole) in acetonitrile (20 ml) and solution was stirred for 5 hr. at room temperature. After the reaction acetonitrile was removed under reduced pressure, to the residue water was added and extracted with chloroform. The organic layer was dried over Na_2SO_4 and evaporation of chloroform gave product **220**.

Yield : (9.30 gm, 94%).

^{1}H NMR (200 MHz; $CDCl_3$): δ 2.5 (t, J = 7.2 Hz, 2H); 3.2 (s, 3H); 3.6 (s, 3H); 3.7 (s, 3H); 4.2 (t, J = 7.2 Hz, 2H); 5.15 (s, 1H); 8.5 (bs, 1H).

4-(1-Carbomethoxymethyl)-5,6-dicarbomethoxy-N-(1-methylpropanoate)-2-pyridone (37)

A mixture of compound **220** (7.2 gm, 0.033 mole), 3-chlorodimethylglutanoate (9.7 gm, 0.0507 mole) and triethylamine (5.74 ml, 0.04125 mole) in dry methanol (50 ml) was stirred at room temperature for 65 h. The reaction mixture was concentrated to dryness under vacuum and the crude product was purified by column chromatography over silica gel to give compound **37**.

Yield : (4.28 gm, 42.8%)

IR (nujol) : 3200, 1750,1660, 1200, 720 $cm.^{-1}$

^{1}H NMR ($CDCl_3$; 200 MHz): δ 2.8 (t, J = 7.1 Hz, 2H); 3.62 (s, 6H); 3.7 (s, 2H); 3.72 (s, 3H); 3.99 (s, 3H); 4.12 (t, J = 7.1 Hz, 2H); 6.42 (s, 1H).

MS (m/z): 369 (M^+); 338; 310; 223; 87; 59; 55.

Analysis : **Cal**: C 52.03%, H 5.14%, N 3.79%.
Observed: C 52.25%, H 5.25%, N 3.82%.

4-(Carbomethoxypropyl)-5,6-dicarbomethoxy-N-(-1-methylpropionate)-2-pyridone (221)

Compound **37** (1 gm, 2.7 mmol) ethyl iodide (4 ml), K_2CO_3 (0.374 gm, 2.7 mmol) with catalytic amount of TBAB in dry acetonitrile (5 ml) were refluxed for 9 hr. on water bath, with occasional addition of ethyl iodide. After the completion of reaction, acetonitrile was removed under vacuum and the residue dissolved in water and extracted

with chloroform, concentration and purification by column chromatography over silica gel gave product **221**.

Yield : (0.88 gm, 82%)

IR (nujol) : 3200, 1710, 1440,1660, 1210, 870 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.85 (t, J = 7.1 Hz, 3H); 1.65-1.8 (m, 1H); 1.85-2.25 (m, 1H); 2.77 (t, J = 7.2 Hz, 2H); 3.6 (s, 3H); 3.65 (s, 3H); 3.75 (s, 3H); 3.8 (t, J = 7.1 Hz, 1H); 3.9 (s, 3H); 4.05 (t, J = 7.2 Hz, 2H); 6.50 (s, 1H).

MS (m/z) : 397 (M^+); 366; 338; 264; 236; 220; 55.

4-(1-carbomethoxypropyl)-1,6-[8-carbomethoxy-9(7H)oxo-cyclopentano-2-pyridone (222)

To the compound **221** (0.225gm, 0.56 mmol) in dry benzene was added freshly prepared NaOMe (50 mg, 0.68 mmol) at 10°C and the reaction mixture was refluxed for 6 h. The reaction mixture was acidified with cold dil. HCl and extracted with ethylacetate. The organic layer was dried over Na_2SO_4 concentrated and purified by column chromatography to give product **222**.

Yield : (100 mg, 48%)

IR (nujol) : 3500, 1700, 1440, 1210 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.85 (t, J = 7.1 Hz, 3H); 1.65-1.8 (m, 1H); 1.8-2.05 (m, 1H); 2.6 (t, 1H); 3.65 (s, 3H); 3.70 (s, 3H) 3.8 (t, J = 7.1 Hz; 1H) 3.86 (s, 3H); 4.10 (d, J = 7.1Hz, 2H); 6.85 (s, 1H); 10.1 (bs, 1H).

MS (m/z) : 367 (M^+); 295; 265; 237; 206; 134.

4-(1-carbomethoxy methyl) 1,6-[8-carbomethoxy 9-(7H)oxo] cyclopentanone pyridone (38)

To the compound **37** (0.246 gm, 6.6 mmol) in dry benzene (5 ml) was added freshly prepared NaOMe (0.108 gm, 2 mmol) at 10°C and reaction was stirred for 1/2 hr and then refluxed for 6 hr. The reaction mixture was cooled to 0°C and acidified

cautiously with cold dil. HCl and extracted with chloroform (3 x 25 ml) and dried over Na_2SO_4 The chloroform was removed and the residue was purified to give **38**.

Yield : (0.14 gm, 63%)

IR (nujol) : 3500, 1720, 1100, 720 cm^{-1}

^{1}H NMR (200 MHz; $CDCl_3$): δ 2.10 (bs, 1H); 3.65 (s, 3H); 3.8 (s, 2H); 3.9 (s, 6H); 4.75 (s, 2H); 6.55 (s, 1H).

MS (m/z) :337 (M^+); 283; 223; 136; 59.

Ethyl N (carboethoxy) glycinate (227)

To the glycine ethyl ester hydrochloride (15 gm, 0.107 mole) in acetonitrile (50 ml) Et_3N (11.55 gm, 15.9 ml, 0.107 mole) was added at 0°C, followed by addition of ethyl chloroformate (11.5 gm, 12.78 ml, 0.108 mole) dropwise over 30min. The mixture was then stirred further at room temperature for 3 hr. After the reaction was over (TLC), the acetonitrile was removed under reduced pressure and water was added and extracted with dichloromethane to give product **227** as an oil.

Yield : (18.5 gm, 97%)

^{1}H NMR (60MHz; CCl_4) :δ 1.25 (t, J = 7.1 Hz, 6H); 3.8 (d, 2H); 4.25 (q, J = 7.1 Hz, 4H); 5.85 (s, 1H).

Methyl-(1-ethoxy)carboxyl-4-oxo-3-pyrrolidine carboxylate (226)

To NaH (1.5 gm, 0.085 mole 60% suspension in oil), prewashed with pet ether (60ml) the ester **227** was added (10 gm, 0.045 mole) in dry benzene (20 ml) under N_2, and the mixture was stirred at room temperature for 5 min. To this distilled methyl acrylate (3.77gm, 0.045mole) was added at room temperature in dry benzene (15 ml) and stirred for 1/2 hr. The reaction mixture was then refluxed for 2 h, quenched with saturated ammonium chloride solution and benzene (50 ml) layer was separated. The aqueous layer was extracted with ethylacetate (3×25 ml) and combined organic layer was dried over Na_2SO_4 and concentrated to give ester **226**.

Yield : (7.7 gm, 68%).

^{1}H NMR (200 MHz; $CDCl_3$): δ 1.25 (t, J = 7.1 Hz, 3H); 3.75 (s, 3H); 4.0-4.35 (m, 6H); 7.85 (bs, 1H).

1-Carboethoxyethyl-3-pyrrolidone (228)

To the above keto ester **226** (5 gm, 0.025 mole) 10% HCl solution was added and refluxed for 4 hr. The reaction mixture was then cooled and extracted with dichloromethane. The combined organic phase was dried over Na_2SO_4 and concentrated and then distilled in Kugelrohr apparatus.

Yield : 3.7 gm

BP : 140°C (5 mm, Hg)

^{1}H NMR (60MHz; CCl_4) : δ 1.3 (t, J = 7.4 Hz, 3H); 2.6 (t, J = 7.9 Hz, 2H); 3.65 (t, J = 4.5 Hz, 2H); 3.7 (s, 2H); 4.2 (q, J = 7.9 Hz, 2H).

N-(Carbethoxy)-2,3-dihydro-1H-pyrolo(3,4b) quinolines (225)

A mixture of o-Aminobenzaldehyde (**227a**) (1.83 gm, 15mmol), keto ester **228** (1.199 gm, 7.6 mmol) and p-TSA (0.38 gm) were heated at 190°C for 5 min then the reaction mixture was cooled and agitated with NaOH (14 ml of 85% solution) for 18 hr. The aqueous layer was extracted with $CHCl_3$ to give crude product, which was purified by column chromatography to give **225**.

Yield : (0.88 gm, 24%).

M.P. : 134°C (lit.[29] 133-135°C)

IR (nujol) : 1700, 1625 cm.$^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 1.35 (t, J = 7Hz, 3H); 4.28 (q, J = 7 Hz, 2H); 5.83 (s, 4H) 7.50-8.17 (m, 5H).

MS (m/z) : 242 (M^+); 214, 186, 91.

2- Chloro-3-quinoline carbaldehyde (233)

N,N-Dimethylformamide (22.63 gm, 24 ml, 0.31 mole) was stirred and cooled to -5°C with ice salt mixture, $POCl_3$ (133 gm, 81 ml, 0.868 mole) was then added dropwise (white solid formed). To the mixture, acetanilide (18.7 gm, 0.124 mole) was then added in portions at room temperature. The reaction mixture was then kept stirring at 78°C for 18 hr. After reaction mixture was cooled and then poured into ice with stirring. The yellow solid separated after half an hour was filtered, then thoroughly washed with water and dried, and the product was recrystallised from rectified spirit.

Yield : (19.0 gm, 80%)

M.P. : 148°C (Lit.[40] 149°C)

IR (nujol) : 1700, 1600, 1060 cm^{-1}

^{1}H NMR (200 MHz; $CDCl_3$: δ 7.52-8.07 (m, 4H); 8.73 (s, 1H); 10.56 (s, 1H).

MS (m/z) : 191 (M^+); 193(M+2); 127; 101

2-Chloro-3-hydroxymethylquinoline (229)

A solution of 2-chloro-3-formylquinoline (**233**) (11.49 gm, 60 mmol) in distilled methanol (100 ml) was cooled to 0°C. $NaBH_4$ (2.4 gm, 60 mmol) was then added in small portions, over a period of 20 min. The reaction mixture was then allowed to reach room temperature and stirred for 5 hr. Then the reaction mixture was poured into ice water, filtered, dried and the product **229** was recrystallised from ethanol.

Yield : (9.82 gm, 85%)

M.P : 162°C (Lit.[30] 163°C)

IR (nujol) : 3480, 3360, 1600, 1085 $cm.^{-1}$

^{1}H NMR (200 MHz; $DMSOd_6$): δ 4.60 (s, 2H); 5.55 (bs, 1H) 7.4-8..0 (m, 4H); 8.32 (s, 1H).

MS (m/z) : 195 (M+2); 193(M^+); 164; 140; 101.

2-Iodo-3-hydroxymethylquinoline (230)

A solution of 2-chloro-3-hydroxymethylquinoline (**229**) (6 gm, 31.2 mmol) NaI (5 gm, 31.2 mmol) in acetonitrile (50ml) was refluxed for 36 hr. The acetonitrile was removed under reduced pressure and treated with water to give a precipitate, which was filtered dried and recrystallised from ethanol

Yield of 230 : (6.5 gm, 73%)

M.P. : 189°C (lit.[30] 180°C)

IR (nujol) : 3480, 1600, 1500, 1340 $cm.^{-1}$

^{1}H NMR (200 MHz; $DMSOd^6$): δ 4.80 (s, 2H); 8.3 - 7.50 (m, 4H); 8.4 (s, 1H); 10.10 (bs, 1H).

MS (m/z) : 285 (M^+); 158; 130; 103; 63.

2-Iodo-3-hydroxymethylquinolineformyl ester (231)

A solution of 2-iodo-3-hydroxymethylquinoline (**231**) (2.52 gm, 9 mmol) formic acid (6ml, 98%) and $BF_3.Et_2O$ (3 ml) were stirred at room temperature for 8 hr. The mixture was basified with cold saturated $NaHCO_3$ solution and the solid separated was filtered, dried in air and recrystalised from pet.ether-ethylacetate.

Yield : (2.4gm, 90%)

M.P. : 95°C (Lit.[30] 94°C)

^{1}H NMR (200 MHz; $CDCl_3$): δ 5.43 (s, 2H); 7.5-8.23 (m, 5H) 8.31 (s, 1H).

2-Iodo-3-quinolinecarbaldehyde (233a)

A solution of 2-chloro-3 quinolinecarboxyaldehyde (**233**) (5 gm, 26.1 mmol) and NaI (11.75 gm, 78.33 mmol) in dry acetonitrile (20 ml) was refluxed on water bath for 36 hr. The acetonitrile was removed under reduced pressure, and the reaction mixture was diluted with ice water. The solid was then filtered dried and crystalysed from ethanol togive **233a**.

Yield : (5.22 gm, 72%)

M.P. : 153°C (Lit.[41] 152°C)

IR (nujol) : 2940, 1730, 1454, 1165 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 7.51-8.04 (m, 4H); 8.42 (s, 1H); 10.22 (s, 1H).

MS (m/z) : 283 (M^+); 254; 156; 101; 75.

2-Iodo 3-(1,3 dioxalane) quinoline (234)

The iodo compound **233a** (5 gm, 0.017 mole) ethylene glycol (1.09 gm, 0.017 mole) in cyclohexane (50 ml) and p-TSA (0.523 gm) were refluxed with azeotropic removal of water using Dean Stark apparatus. After 12 hr. the reaction mixture was cooled and poured into $NaHCO_3$ solution. Cyclohexane layer was separated, the aqueous layer was extracted with ethylacetate and combined organic layer (cyclohexane and ethylacetate) was dried over Na_2SO_4 followed by concentration to give solid which was purified by column chromatography over silica gel.

Yield of 234 : (5.67 gm, 96.4%)

IR (nujol) : 3000, 1600, 1450 cm

^{1}H NMR (200 MHz; $CDCl_3$,): δ 4.1-4.25 (m, 4H); 6.05 (s, 1H); 7.50-8.05 (m, 4H); 8.25 (s, 1H).

MS (m/z) : 327 (M^+); 283; 200; 156; 128; 101; 73.

3-(N-Phenyl)amine 2-butenoic acid methyl ester (237)

In a 250 ml flask fitted with a reflux condenser and a Dean Stark constant water separator, aniline (19.0 gm, 0.204 mole), methylacetoacetateate (29.6 gm, 0.024 mmol) **184**, benzene (100 ml) and glacial acetic acid (29.6 gm, 0.024 mmol) were heated to reflux for 8 hr. Then the reaction mixture was cooled and benzene layer washed with $NaHCO_3$ solution and the benzene layer was concentrated to give ester **237** in 37.02 gm, 94.8% yield.

^{1}H NMR (90 MHz; $CDCl_3$): δ 1.95 (s, 3H); 3.6 (s, 3H); 4.6 (s, 2H); 6.8-7.1 (m, 5H).

2-Methylquinoline-3-methyl carboxylate (238)

Anhydrous DMF (15.76 ml, 0.22 mole) was cooled at -5°C with a ice salt mixture, $POCl_3$ (58.79 gm, 0.65 mole) was added dropwise (white solid formed). A solution of emine **237** (39.02 gm, 0.20 mole), in chloroform (40 ml) was then added in 2 hr. The reaction mixture was stirred at 60°C for 5 hr. Cool the reaction mixture and pour into saturated $NaHCO_3$ solution. The organic layer was separated and aqueous layer was extracted with chloroform (2 x 50 ml). The combined organic layers were dried over Na_2SO_4 and concentrated to give the product **238** (25.4 gm, 62%).

IR (nujol) : 3200; 1700; 1600 $cm.^{-1}$

^{1}H NMR (200 MHz;$CDCl_3$): δ2.95 (s, 3H); 3.95 (s, 3H); 7.35-7.72 (m, 4H),8.75(s,1H)

MS (m/z) : 201 (M^+); 169; 142; 75

2-Carboxaldehyde 3-quinoline methyl carboxylate (241)

To the compound **238** (2.48 gm, 0.012 mole) was added SeO_2 (1.36 gm; 0.012 mole) refluxed in xylene (25 ml). After 8 hr., the xylene was removed under reduced pressure and the residue was purified by column chromatography to give aldehyde **241** (1.85 gm, 69%).

IR (nujol) : 1750, 1600, 1210 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 4.05 (s, 3H); 7.8-8.3 (m, , 4H); 8.6 (s, 1H); 10.9 (s, 1H).

MS (m/z) : 215 (M^+); 187; 156; 128; 75

2-Methyl-3-hydroxymethylquinoline (239)

The ester **238** (5.3 gm, 0.0275 mole) in dry THF (25 ml) was added slowly at 0°C to the suspension of LAH (1 gm, 0.0275mole) in dry THF (10 ml). The reaction mixture was stirred overnight and quenched with ethylacetate then poured into ice, excess ethylacetate was added and precipitate was filtered. The precipitate was washed with ethylacetate, the combined ethylacetate layer was dried over Na_2SO_4 and solvent was evaporated.The residue was purified by column chromatography to give product **239**.

Yield : (2.2 gm, 48%)

IR (nujol) : 3500, 1600, 720 $cm.^{-1}$

^{1}H NMR (200 MHz; Acetoned[6]): δ 2.6 (s, 3H,); 2.90 (bs, 1H, OH) 4.8 (s, 2H); 7.35-7.9 (m, 4H); 8.05 (s, 1H);.

MS (m/z): 173 (M^+); 155; 144; 115; 77.

Analysis : **Cal**: C: 76.52% H 6.22% N 8.21%

Observed: C: 76.3% H 6.35% N 8.09%

Tricyclic ethoxy lactal (240)

To the mixture of alcohol **239** (2.0 gm, 0.0115 mole) and SeO_2 (1.28, 0.0115 mole) in rectified spirit (15 ml) cyclohexane was added and refluxed for 8 hr. After reaction was over the solvent was removed and crude product was purified by column chromatography over silica gel to give product **240**.

Yield : (1.30 gm, 52%)

IR (nujol) : 3000, 1600, 780 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 1.35 (t, J = 7.1 Hz, 3H); 3.80-4.05 (m, 2H); 5.2 (d, J = 7.3Hz, 1H); 5.4 (d, J = 7.3 Hz, 1H); 6.2 (s, 1H); 7.60-8.25 (m, 5H).

MS (m/z): 215 (M^+), 187, 171, 92.

Analysis	: **Cal**:	C 72.75%	H 6.15%	N 6.82%
	Observed:	C 72.55%	H 6.04%	N 6.51%

Hydrolysis of ethoxy lactal (240)

Compound **240** (1.5 gm, 6 mmol) in THF:H_2O:CH_3CO_2H (2 ml : 2ml : 2 ml) was refluxed on water bath for 24 h. The reaction mixture then cooled and neutralized with $NaHCO_3$. The solid separated was filtered, dried and recrystalysed from ethanol to give **232**.

Yield : (1.25 gm, 96%)

M.P : 153°C

IR (nujol) : 3500, 1600, 1100 $cm.^{-1}$

^{1}H NMR (200 MHz; Acetone d^6): δ 5.2 (d, J = 7.3 Hz, 2H); 5.40 (d, J = 7.3 Hz, 1H); 6.50 (bs, 2H 6.6 (s, 1H); 7.7-8.25 (m, 5H);

MS (m/z): 187 (M^+); 171; 169; 113; 59.

Analysis	: **Cal**:	C: 71.00%	H: 4.61%	N: 7.456%
	Observed:	C: 70.58%	H: 4.81%	N: 7.486%

Methyl 4-bromoacetoacetate (185a)

To methylacetoacetate (**184**) (5.8 gm, 0.0499 mole) in chloroform (25 ml). Bromine (7.982 gm, 2.56 ml, 0.0499 mole) in chloroform (25 ml) was added dropwise. The reaction mixture was stirred for 24 hr. then air was bubbled to remove HBr gas and the reaction mixture was poured into ice. The organic layer was separated and aqueous layer was extracted, with chloroform (3×25 ml) The combined organic layer was dried over Na_2SO_4 concentrated to give product **185a**.

Yield : (6.04 gm, 60%)

IR (neat) : 1720, 1700 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 3.67 (s, 2H); 3.74 (s, 3H); 4.05 (s, 2H).

Methyl-4-(ethyl malonate)- acetoacetate 185b

A mixture of bromo ketone **185a** (11.5 gm, 0.05 mole), and ethyl potassium malonate salt **242a** (9.12 gm, 0.05 mole) was stirred at room temperature in benzene (10 ml) with TBAB (0.35 gm) for 10 hr. After that the reaction mixture was poured into ice, the benzene layer was separated and dried over Na_2SO_4, concentrated followed by column chromatography purification gave product **185b**.

Yield : (2 gm, 14%)

IR (neat) : 1760, 1720, 1200 cm.$^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 1.2 (t, J = 7.0 Hz, 3H); 3.4 (s, 2H); 3.45 (s, 2H); 3.6 (s, ^{1}3H); 4.42 (q, J = 7 Hz, 2H); 4.8 (s, 2H).

3-Carboethoxy 4 (carbomethoxy)-2(5H)furanone (185c)

To the ester **185b** (200 mg, 0.40 mmol) in dry MeOH (5 ml), NaOMe (65 mg, 1.2 mmol) was added in portions and then the mixture was stirred for 15 hr, and refluxed for 1/2 hr. at 70°C. The reaction mixture was then cooled and poured into cold dilute HCl (5%), and extracted with ethylacetate. The organic layer was dried over Na_2SO_4, concentrated and the residue was purified by column chromatography to give product **185c**.

Yield : (0.15 gm, 81%).

IR (nujol) : 1720, 1620, 1450, 760 cm.$^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 1.30 (t, J = 7.1 Hz, 3H); 3.7 (s, 3H); 4.0 (s, 2H); 4.4 (q, J = 7.1 Hz, 2H); 5.0 (s, 1H).

Methyl-2-ethylacetoacetate (242)

To a mixture of methylacetoacetate (**184**) (22 gm, 0.189 mole), K_2CO_3, (53 gm) and TBAB (100mg) in dry acetonitrile (50 ml) was added a solution of ethyl iodide (26.18 gm , 18.75 ml, 0.189 mole) in acetonitrile (20 ml) The reaction mixture was then stirred overnight at room temperature. After reaction acetonitrile was removed under vacuum and the residue was dissolved in water and extracted with ethylacetate. The

combined ethylacetate layer was dried over Na_2SO_4. Concentration of the ethyacetate gave ethylated product **242**.

Yield : (25.2 gm, 92%)

IR (neat) : 1740, 1720 $cm.^{-1}$

^1H NMR (200 MHz; $CDCl_3$): δ 0.95 (t, J = 7.1 Hz, 3H); 1.8-1.95 (m, 2H); 2.23 (s, 3H); 3.74 (s, 3H); 3.35 (t,J = 7 Hz, 1H); 3.74 (s, 3H).

Methyl-4-bromo-2-ethylacetoacetate (243)

A solution of compound **242** (13.46 gm, 0.093 mole) in chloroform (35 ml) was cooled to 0°C and bromine (14.93, 4.8 ml, 0.093 mole) in chloroform (20 ml) was added dropwise. The reaction mixture was then stirred for 10 hr. at room temperature and HBr gas was removed by passing air. The mixture was then poured into aqueous solution of $NaHCO_3$. The chloroform layer was separated and the aqueous layer was then extracted with chloroform and combined organic layer was dried over Na_2SO_4 and concentrated to give product **243** as a liquid.

Yield : (19.31 gm, 82%)

IR (nujol) : 1740, 1720 $cm.^{-1}$

^1H NMR (200 MHz; $CDCl_3$): δ 0.95 (t, J = 7.1 Hz, 3H); 1.8-1.95 (m, 2H); 3.4 (t, J = 7.1 Hz, 2H); 3.75 (s, 3H); 4.85 (s, 2H).

Potassium salt of ethyl malonate 242a.

A solution of diethyl malonate (100 gm, 0.625 mole) in rectified spirit (500 ml) was cooled to 0°C. To this KOH (35 gm, 0.625 mole) was added in portions and stirred overnight then reaction mixture was refluxed on water bath for 1/2 hr. Partial distillation of the ethanol (400 ml) gave a colourless solid which was filtered and dried to give **242a**.

Yield : 50 gm

Methyl-4-(ethyl malonate)-2-ethyl acetoacetate 245b

A mixture of, bromo compound **243**, (37.17 gm, 0.166 mole) and monopotassium salt of ethylmalanoate (**242a**) (31.16 gm, 0.166 mole) in distilled benzene (250 ml) with triethylbenzylamine hydrochloride (350 gm) was stirred overnight.

The mixture was poured into water and the benzene layer was separated and dried over Na_2SO_4, organic layer then. then concentration and purification of the benzene layer over silica gel column gave the required product. **185b**.

Yield : (6 gm, 13.13%)

IR (nujol) : 1760, 1720, 1100 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 0.95 (t, J = 7.1 Hz, 3H); 1.3 (t, J = 7.1Hz, 3H); 1.8-1.9 (m, 2H); 3.55 (s, 2H); 3.65 (s, 3H); 4.25 (q, J = 7.1 Hz, 2H); 4.85 (s, 2H).

MS (m/z) : 275 (M^+); 246; 146; 126; 115; 58.

3(carboethoxy) 4-(2 carbomethoxy propane) 2(5H) furanone (246)

To the compound **245b** (0.274 gm, 1 mmol) in dry methanol (10 ml), NaOMe (0.162 gm, 3 mmol) was added in portions and stirred for 1/2 hr. and then the mixture was refluxed for 1 hr and poured into cold dil. HCl (5%). The mixture was extracted with ethylacetate and combined organic layer was dried over Na_2SO_4, concentrated, and purified over silica gel column to give products **246** and **248**.

Yield of 246 : (0.128 gm, 51%)

IR (nujol) : 1720, 1100 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 1.05 (t, J = 7.1 Hz, 3H); 1.35 (t, J = 7.1Hz, 3H); 1.7-1.8 (m, 1H); 1.90 - 2.1 (m, 1H); 3.75 (s, 3H); 4.35 (q, J = 7.1 Hz, 2H); 4.45 (t, J = 8.1 Hz, 1H); 5.0 (s, 2H).

MS (m/z) : 256 (M^+); 224; 210; 178; 150; 55.

3 (carboxylic acid) 4-(2 carbomethoxy propane) 2-(5H)furanone 248.

Yield of 248 : (0.0512 gm, 22%)

IR (nujol) : 3400, 1720, 1100 $cm.^{-1}$

^{1}H NMR ($CDCl_3$; 200 MHz): δ 1.00 (t, J = 7.0 Hz, 3H); 1.5-1.7 (m, 2H); 2.85 (t, J = 7.00 Hz, 1H); 3.85 (s, 3H); 4.75 (s, 2H).

MS (m/z) : 228 (M^+); 184; 152; 113; 55.

5-Bromo-3(carboethoxy)4-(2 carbomethoxy propane) 2-(5H)furanone 247

A mixture of the lactone (0.274 mg, 1.07 mmol) and 1,3-dibromo-5,5'-dimethyl hydantoin (0.157 gm, 0.55 mmol) in dry carbon tetrachloride (10ml) was stirred at room temperature. The solid separated was filtered off and the organic layer was separated, concentrated and the residue was purified by flash column chromatography to give product **247**.

Yield : (0.265 gm, 73%)

IR (nujol) : 1720, 1450 $cm.^{-1}$

^{1}H NMR (200 MHz; $CDCl_3$): δ 1.05 (t, J = 7.1 Hz, 3H); 1.35 (t, J = 7.1 Hz, 3H); 1.65-1.70 (m, 1H); 2.15-2.4 (m, 1H); 3.75 (s, 3H); 4.1 (q, J = 7.1 Hz, 2H; 6.9 (s, 1H).

MS (m/z) : 335 (M^+); 333; 304; 224; 255, 91.

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CHAPTER-III

Catalytic Chemical Transformations:

Introduction:

A catalyst is substance that accelerates a rate of chemical reaction but is not consumed in the reaction. Catalysts can be recycled, which play a key role in biochemical processes and most of industrial and chemical processes. The catalysts may be of different types, acids, bases, organometallics, enzymes, polymer supported, molecular sieves, zeolites, clays, phase transfer catalysts, metals and metal oxides, transition metal complexes etc. They have the ability to catalyse variety of chemical reactions such as (1) Decomposition (2) Hydration (3) Dehydration (4) Reduction (5) Oxidation (6) Hydrogenation (7) Dehydrogenation (8) Halogenation (F, Cl, Br, I) (9) Sulfurization (10) Desulfurization (11) Alkylation (12) Condensation (13) Polymerization (14) Isomerization etc.

A catalyst may control a chemical reaction (1) by increasing the reactivity between molecules brought into play in the reaction and (2) by facilitating the interaction between the reacting molecules by loosening certain linkages or bonds within them. For example in oxidation reaction catalyst activate oxygen and help the reactant to absorb oxygen. In catalytic hydration or dehydration, catalyst helps either addition of water or in removal of water during reaction process. In catalytic hydrogenation catalyst helps the addition of hydrogen to substance by ionising hydrogen gas. In dehydrogenation reaction catalyst helps in the removal of hydrogen gas which is liberated during process. In catalytic halogenation or dehalogenation catalyst helps addition or removal of halogens by radical or ionic mechanism. In alkylation or acylation reactions catalyst assists in formation of cation as well as stabilizing it in the process. In condensation process catalyst helps either removal of water or other eliminated products. In polymerisation, catalyst polarizes the double bonds or initiates the formation of free radicals. In catalytic isomerisation reactions catalyst helps in rearrangement of groups within interacting molecules to form isomeric compounds.

Catalytic reactions can either take place in solutions or on surfaces. Most of metal ions or hydrogen ions are functions as acid-base catalysts or in electron transfer reactions. Several organometallic complexes were used as acid-base polarizes or single-

electron transfer catalysts. In olefin hydrogenation where Wilkinson's catalyst is used to carry out catalytic hydrogenation reaction under very mild conditions of atmospheric pressure at ambient temperature. Wilkinson and co-workers[1c] applied phosphine complexes of ruthenium and iridium for several hydrogenation reactions. The novel phosphine ligand based catalysts (Wilkinson) inspired Knowles and co-workers[1c] to apply it in asymmetric hydrogenation reactions. One of the most important industrial process involving transition metal complex, as a catalyst is the hydroformylation of olefins. The CO and H_2 which are produced from coal or natural gas are directly used as industrial feedstocks for organic chemical preparations. Catalysts are also useful in olefin polymerisation (Ziegler catalyst), partial oxidations i.e. incorporating -CHO, $-CO_2H$, oxirane etc. into the products. C-H Bond activations in hydrocarbons are also carried out using organometalic catalysts.

Enzymes are separate class of catalysts without them the process of life will not take place. Enzymes, which possess complex polymeric structure catalyze biological reactions efficiently and functions only at relatively mild temperatures. For example (1) Breakdown of proteins and carbohydrates; (2) Biosynthetic process that leads to growth and replacement of living organisms; (3) Photo-synthesis; (4) Catalyses oxidation processes that convert food into CO_2, H_2O and energy etc.

The incorporation of catalytic groups into the solid polymers gives a reusable catalyst. For example sulfonic acid groups are incorporated by direct sulfonation of cross-linked polystyrene gives sulphoneted polymers which act as acidic catalysts. Various amines, quinones, phosphine ligands incorporated on polymers are also used in catalytic reactions.

Several aluminosilicates like zeolites, clays and molecular sieves are used as heterogeneous catalysts. Zeolites, bear catalytic sites having microscopic cavities and are comparable to enzymes. Zeolites catalyse several type of reactions like oxidation, halogenation, alkylation or acylation and isomerisation reactions. Molecular sieves, which are similar in structure to the zeolites, are also used in acid catalysed reactions. Clays and other layered materials are also used in acid catalysed reactions.

Metals, metal oxides and metal sulfides some times used in combination with each other are important as industrial catalysts. Palladium, Nickel and Platinum as powders or on supports are used in olefin hydrogenation in food industries. Copper,

Nickel, Platinum are used in carbonyl reductions. Several other application of metal and metaloxids are given in the literature.[1e]

Catalytic reactions can take place in different phases. If the catalysis is in single phase then it is called a homogeneous catalysis. If the catalysis is occuring in the presence of more than one phase is called heterogeneous catalysis.

The activity of a catalyst depends mainly in respet of atom position and neighbouring atoms. The unsaturated valence forces on catalyst capable of effecting a distortion among the reacting molecules. The residual forces are smallest in the case of molecules situated in the middle of crystal surfaces and most for atoms at the edges and corners. So activity of finely divided metals used as catalysts not only increases specific surface but also physical efficiency for catalytic activity by increasing edges and corners.

Section I:

Transfer Hydrogenation:

The catalytic reduction using molecular hydrogen is well known in literature which is important synthetically both in laboratory and industry. The hydrogenation can be carried out with homogeneous catalyst as well as heterogeneous catalyst. Olefins, ketones, nitriles, nitro groups and other functional groups are reduced using catalytic hydrogenation method. Since hydrogen is a gas of high diffusibility and is easily ignited and presents considerable hazards. Brude[3] tried to replace it by hydrogen donors. Recent discovery of new and efficient hydrogen donors like ammonium formate, have almost successfully replaced elemental hydrogen. The recent pioneering work by Niyori[1a,1b] in asymmetric transfer hydrogenation of carbonyl, olefins and imines using chiral phosphine based rhodium and iridium complexes are evidences for development of catalytic transfer hydrogenation.

Homogeneous transfer hydrogenation:

The phosphine complexes of rhodium, iridium along with hydrogen donors like isopropanol, hydrazine, formic acid, formates and cyclohexene are used in reductions. Here all the participants of a reaction including the catalyzing agent are in one and the same state of aggregation and in the same phase. The complexes with chiral ligands are used in asymmetric reduction of ketones to alcohols.

Heterogeneous transfer Hydrogenation:

The most useful catalysts for heterogeneous transfer reduction are based on palladium metal. Catalysts may be bulk metal, finely divided or dispersed on various carriers like carbon, $CaCO_3$, $BaSO_4$, asbestos etc. Generally heterogeneous catalysts need lower reaction temperature and can be used in aqueous media. Often a heterogeneous catalyst can be recycled several times for the same type of reaction before its activity is noticeably diminished. The vapor-phase transfer hydrogenation of ketones with heterogeneous catalysts using alcohol as hydrogen donors appeared to be good industrial use.

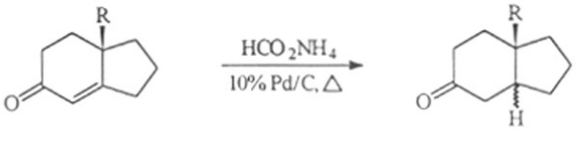
Part - I : Catalytic transfer hydrogenation of oxime, azo compounds using Pd/C with ammonium formate as hydrogen donor.

Transfer hydrogenation of oxime and azo groups using Pd/C Ammonium formate:

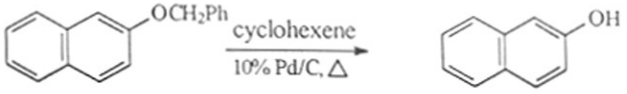
Palladium adsorbed on carbon is the versatile catalyst for reduction of olefins. On going current interest to use Pd/C with different hydrogen donors, developed new chemistry for reduction of different functional groups. In 1974 Brieger et al.[1f] reviewed the use of Pd/C with hydrogen donors. Later in 1985 Johnstone's[3] review where the Pd/C used as heterogeneous catalyst which been compared with homogeneous catalysts in transfer hydrogenation reactions. In 1988 Ram and Ehrenkaufer[2] reviewed the use of ammonium formate and their salts in transfer reduction with Pd/C. The review contains reduction of azides to amine, nitro to amine, α-nitroester to α-aminoester, nitriles to methyl, dehalogenation, hydrogenolysis of protecting groups, reduction of triple bonds etc.

Application of Pd/C in transfer hydrogenation system appeared in the literature after 1988 is briefly described here.

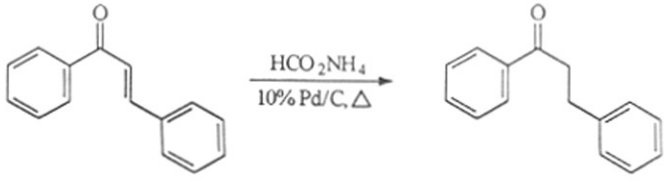
Rao et al.[4] carried out some palladium assisted transfer hydrogenation of cyclic α,β-unsaturated ketones by ammonium formate, They found that double bond can be selectively reduced without effecting carbonyl functions.



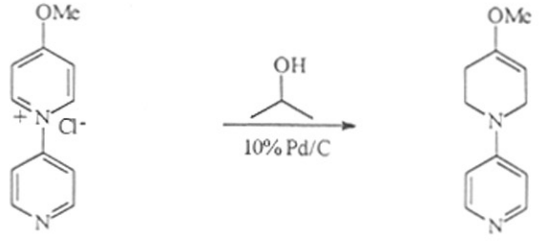
Sansanwal and Krishnamurthy[5] observed that the transfer hydrogenation could be applied for deprotection of *O*-benzyl derivatives with Pd/C, cyclohexene system.



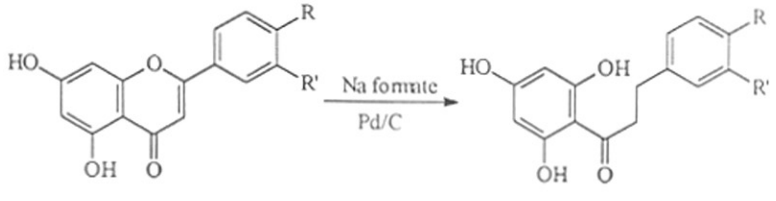
Vimal et al.[6] converted chalcone to dihydrochalcones. The carbonyl function remains uneffective in both cyclohexene or in ammonium formate when used as hydrogen donors.



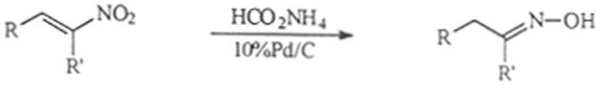
Sathe and Kulkarni[7] studied Pd/C in reduction of heterocyclic compounds. Cyclohexanol or isopropanol was used as a solvent.



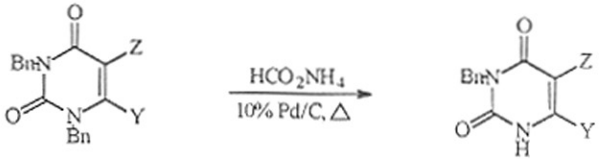
Krishnamurthy and Sathyanarayana[8] found catalytic transfer hydrogenation is useful in facile conversion of hydroxy flavones in to hydroxy dihydro chalcones.



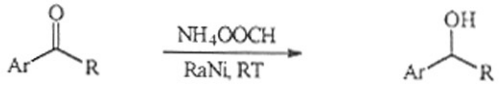
Kabalka et al.[9] reported that Pd/C can assist transfer hydrogenation of α,β-unsaturated nitroalkenes to oximes using ammonium formate at room temperature.



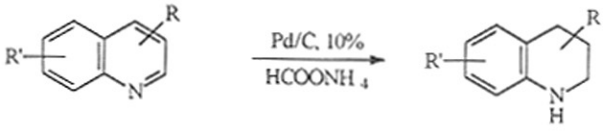
Botta et al.[10] used catalytic hydrogen transformation to regioselective deprotection of 1,3-dibenzyl uracils.



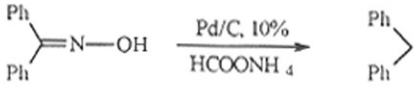
Chen et al.[11] reduced alkyl aryl ketones to alcohols by using Raney Nickel and ammonium formate combination.



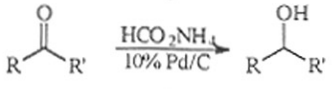
Balczewski and Joule[12] found that Pd/C and ammoniun formate combination is applicable for selective reduction of heterocyclic ring in quinolines and isoquinoline.



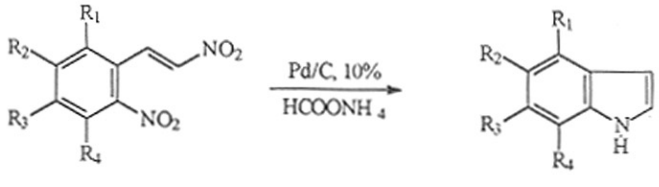
Balicki[13] failed to convert oximes into amines but he got hydrocarbons using ammonium formate Pd/C combination.



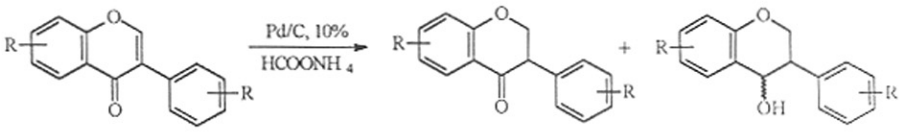
Singh[14] reduced ketones to alcohols using Pd/C and ammonium formate



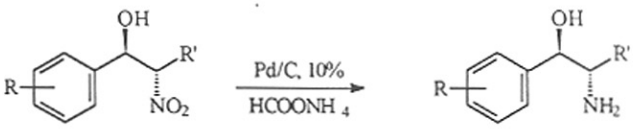
Rajeswari et al.[15] conveniently used in the preparation of indoles from 2-nitro, β-nitro styrenes which were reductively cyclised using Pd/C and ammonium formate.



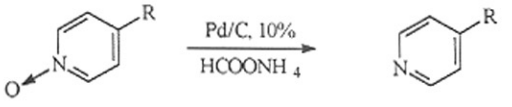
Wahala and Hasa[16] reduced isoflavones to oxyisoflavonones and isoflavan-4-ols .



Barrett and Spilling[17] used Pd/C and ammonium formate system to reduce stereospecifically β- nitro alcohols into hydroxy amines.



Balicki[18] efficiently deoxygenated heteroaromatic N-oxides with ammonium formate as a catalytic hydrogen transfer agent.



Present work

The reduction of aromatic azo and azoxy compounds has received a good deal of attention, both preparatively and analytically.[19] It proceeds via the hydrazo derivative to the amine or a mixture of two amines when the original azo compounds is unsymmetric. Azobenzene undergoes reductive cleavage to aniline with a number of reagents such as metal-acid combinations and on transfer hydrogenation over Pd.[20] Reductive cleavage of azo and azoxybenzene continues to be used in connection with structural determination of azo dyes. More recently Cp_2TiBH_4 has been reported to reduce azobenzenes to the corresponding amines.[21]

Catalytic transfer hydrogenation with Pd/C as catalyst and ammonium formate as hydrogen source has found widespread use in the reduction of various functionalities.[21] This forms a safe alternative to use hydrogen gas.

Recently the regiospecific reductive ring opening of epoxide and glycidic ester under transfer hydrogenation using Pd/C ammonium formate was reported.[22] The

present work deals with the reductive cleavage of various azobenzenes as well as the reduction of various oximes to the corresponding amines in moderate yields using ammonium formate as H_2 source. The results of the reductive cleavage of the N=N of azobenzene to give the corresponding amines, using four equivalent of ammonium formate at ambient temperature are summarised in Table 1.

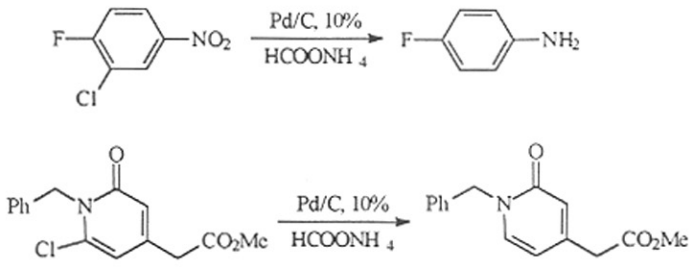
Table-1: Pd-catalysed transfer hydrogenation of azobenzenes using ammonium formate as H_2 source:

$$Ar{-}N{=}N{-}Ar' \xrightarrow[HCOONH_4\ MeOH]{Pd/C,\ 10\%} Ar{-}NH_2 \quad + \quad H_2N{-}Ar'$$

Entry	Substrate	Product[a] (%) yield[b] (Method A)
1	Azobenzene	Aniline (63)
2	4-Aminoazobenzene	Aniline (31) + 1,4-diaminobenzene (64)
3	4-Hydroxyazobenzene	Aniline (29) + 4-aminophenol (54)
4	4-Methyl-4'-hydroxyazobenzene	p-Toluidine (31) + 4-aminophenol (47)
5	4-Chloro-4'-hydroxyazobenzene	Aniline (25) + 4-aminophenol (48)
6	4-Nitro-4'-hydroxyazobenzene	1,4-Diaminobenzene (49) + 4-aminophenol (34)
7	2-Methoxy-4'-hydroxyazobenzene	o-Anisidine (30) + 4-aminophenol (64)
8	2-Nitro-4-methoxy-4'-hydroxy-azobenzene	3,4-Diaminoanisole (21) + 4-aminophenol (55)
9	Acetophenone azine	α-Methylbenzylamine (30)

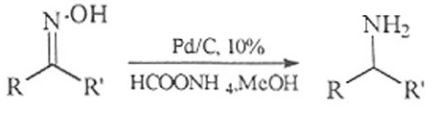
[a]Characterised by spectral data. [b]Isolated after chromatograhic purification

The reducible groups such as chloro and nitro also underwent facile reduction under the reaction conditions. Selective reduction of C-Cl[26] bond over a C-F bond or C-N (debenzylation)[23] has been achieved with present system.



The reduction of various carbon-nitrogen systems to saturated derivatives with different reducing agents provides highly useful process for the preparation of amines and related functionalities.[24] The reduction of oximes and subsequent cleavage of the N-O bond to afford primary amines occurs with a variety of potent hydride reagents, including LAH.[25] **Table 2** gives the various oximes that underwent reduction with two equivalent of ammonium formate at reflux temperature to produce the corresponding amines in moderate yields.

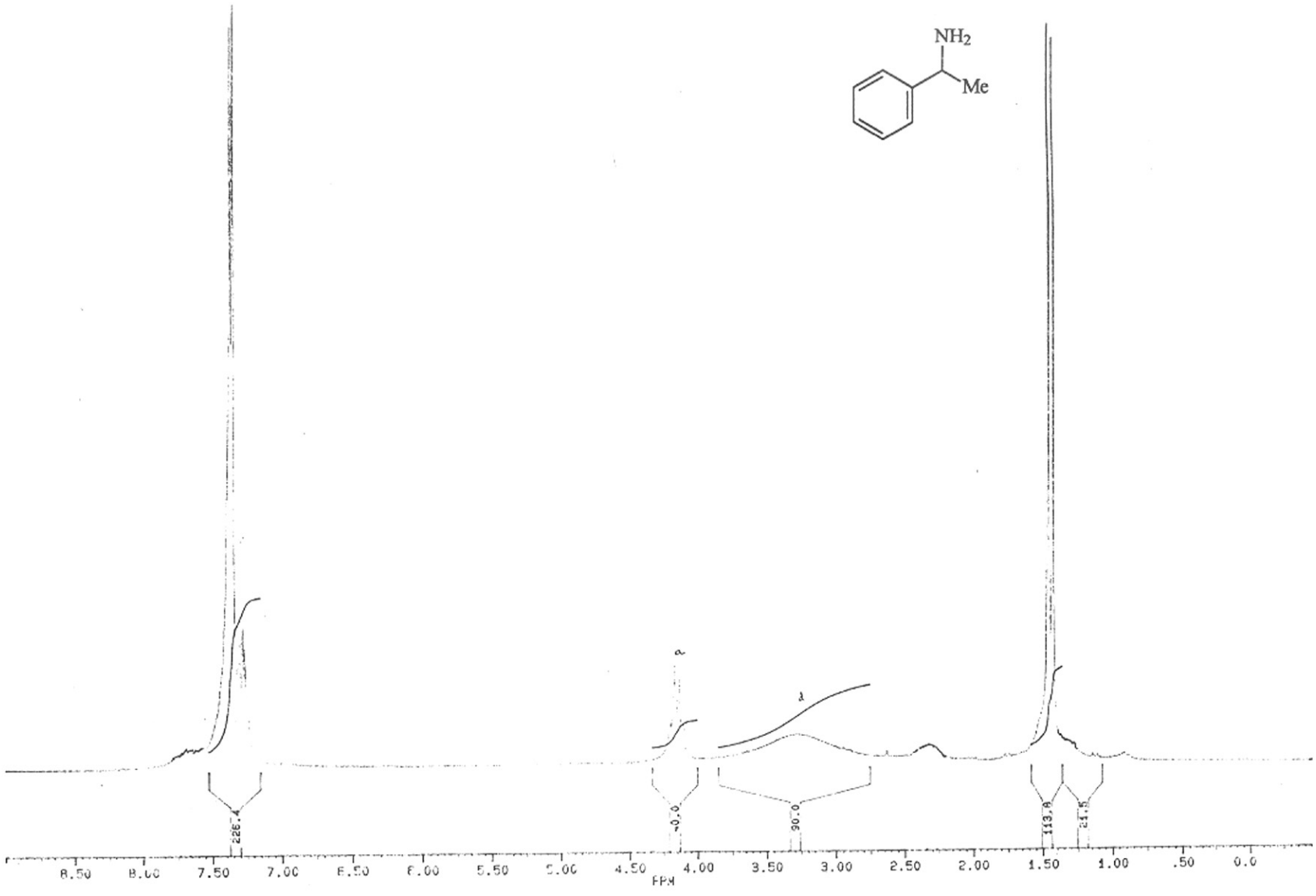
Table 2: Pd-catalysed transfer hydrogenation of oximes using ammonium formate:

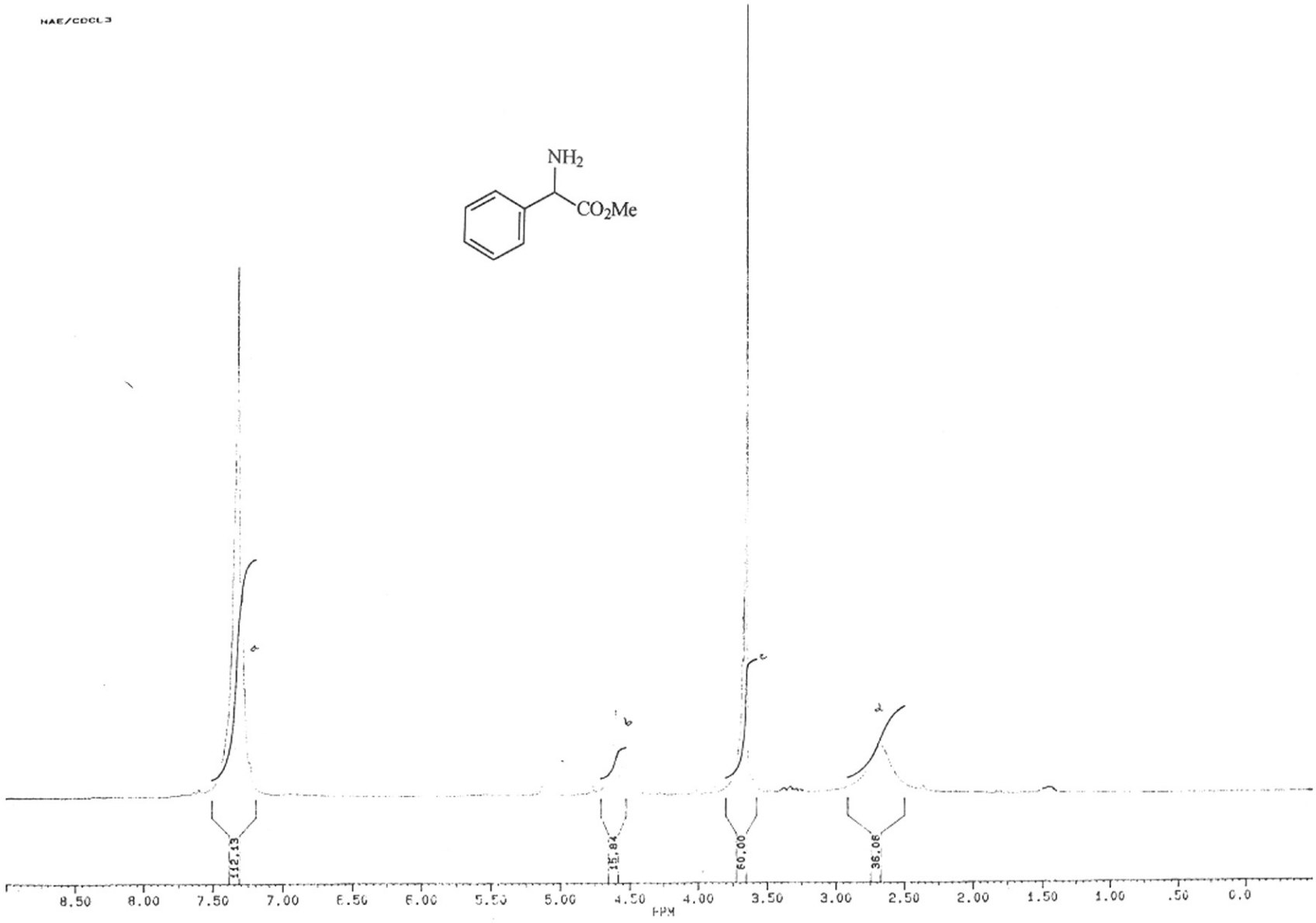


Entry	Oxime	Amine (Method B)	Yield
1	Benzaldoxime	Benzylamine	42
2	Acetophenone oxime	α-Methylbenzylamine	41
3	Cyclohexanone oxime	Cyclohexylamine	42
4	β-Ionone oxime	2-Amino-4-(2,6,6-trimethylcyclohex-1-en-1-yl) but-3-ene	29
5	Carvone oxime	1-Amino-2-methyl-5-(1-methylethenyl) cyclohex-2-ene	22
6	Methylphenylglyoxalate oxime	2-Phenylglycine methyl ester	45
7	Ethyl (4-methoxyphenyl) glyoxalate oxime	4-Methoxyphenylglycine ethyl ester	55

[a]characterised by spectral data. [b]Isolated after chromatographic purification

SAMPLE NO. MEAP / CDCL3




HAE/CDCL3
NH2
CO2Me
112.13
15.84
60.00
36.06
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
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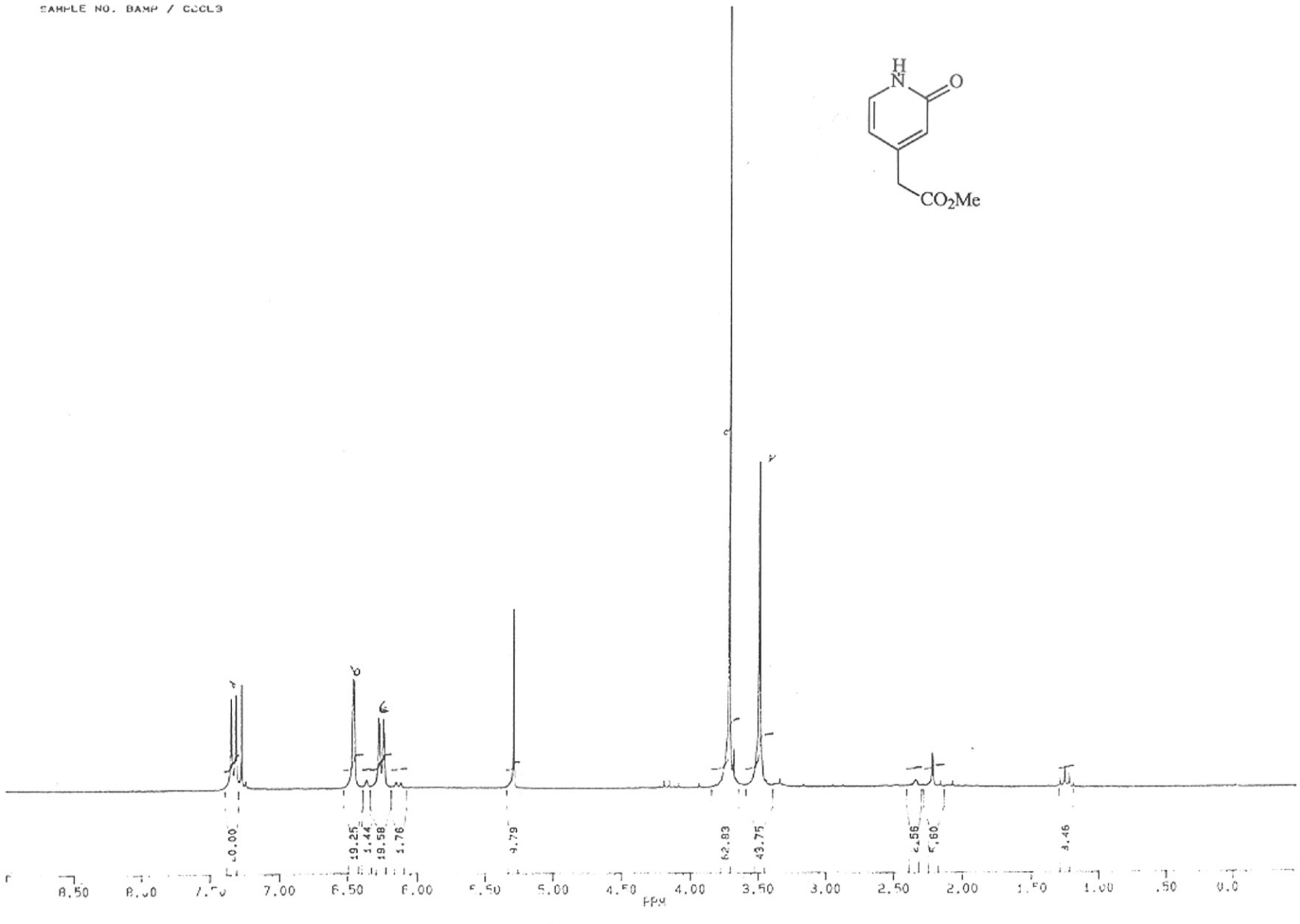
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM


SAMPLE NO. BAMP / CDCL3
H
N
O
CO2Me
10.00
19.25
3.44
19.58
3.76
9.79
62.83
43.75
6.56
6.60
3.46
8.50
7.00
6.50
6.00
5.50
5.00
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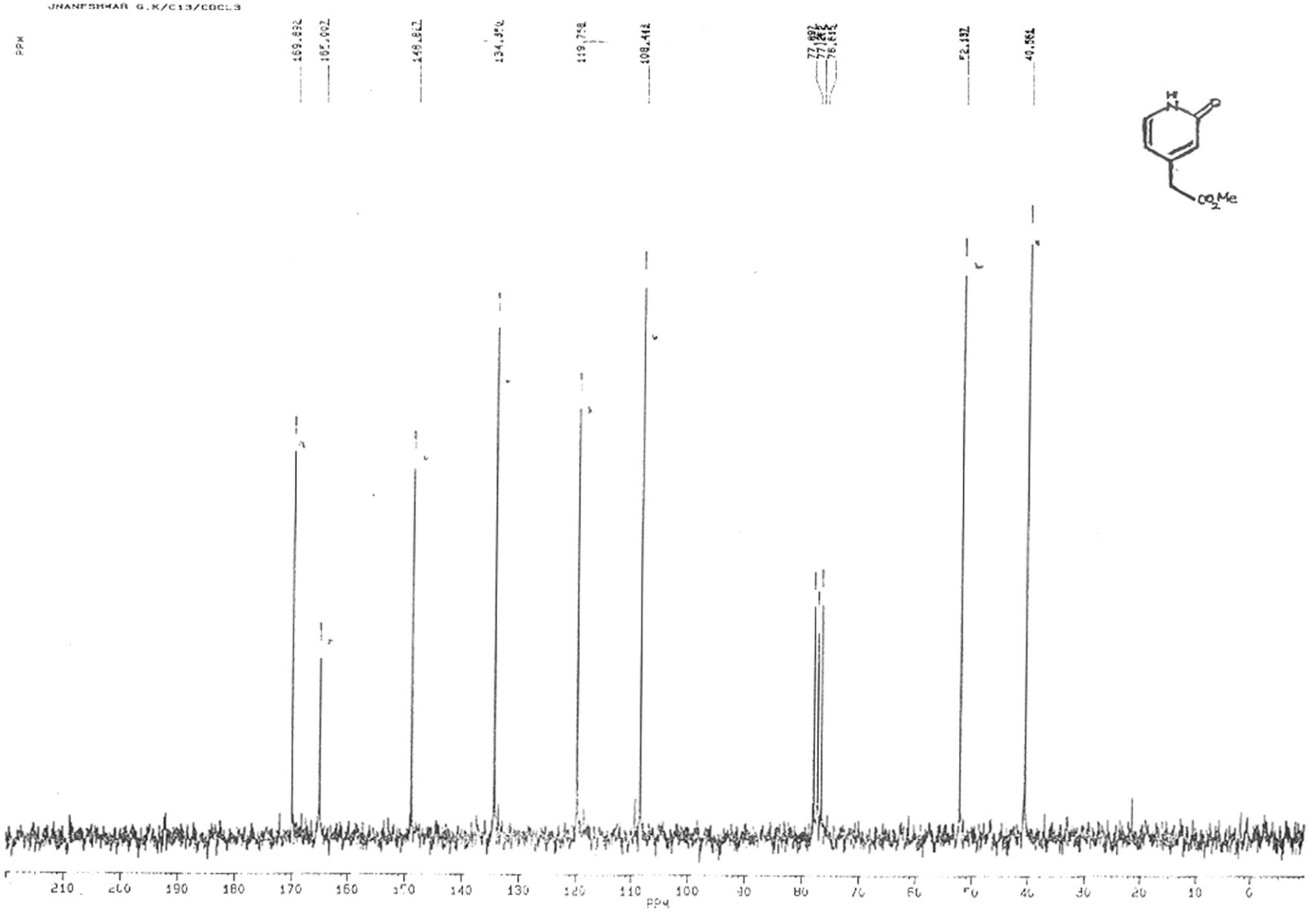
4.00
3.50
3.00
2.50
2.00
1.50
1.00
.50
0.0
PPM


JNANESHWAR G.K/C13/CDCL3
PPM
169.838
165.092
149.862
134.850
119.758
108.448
77.682
77.166
76.650
52.182
40.564
CO2Me
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM

Further it is to be noted that C=N has been reduced preferentially over C=C (entries 4 & 5 Table 2). The yields in the case of oxime reduction are moderate owing to the instability of the amines under the reaction conditions.

Pd/C catalyses the decomposition of ammonium formate into CO_2 and H_2 at low temperature and which is efficiently transfered to organic -N=N- or -C=N-R groups.

Conclusion:

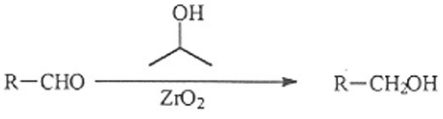
It has been shown that the ammonium formate Pd/C is versatile, selective and rapid method for catalytic hydrogenation of N=N and C=N functionalities. This forms a safe alternative to the use of hydrogen gas and also the oximes are also reduced to amines by this method.

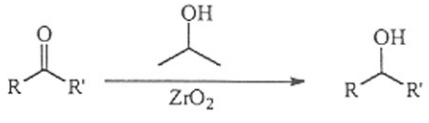
Part-II

Selective reduction of azobenzenes over Hydrated Zirconia:

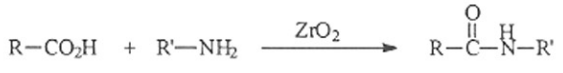
Heterogeneous, reusable commercially available catalysts are always preferred over homogeneous catalysts. A dual nature catalysts like acidic and reductive are very rare in nature. Hydrous ZrO_2 is one of them. Hydrous Zirconium (IV) oxide is an amorphous hard solid stable in air at room temperature for more than seven years. The catalyst was easily prepared by a simple method[28] by the treatment of an aqueous solution of zirconium oxychloride with aqueous sodium hydroxide at room temperature. The precipitated Zirconium hydroxide was filtered and was heated at 300°C for 5 hr. Several applications of hydrated ZrO_2 are known in the literature.

Shibagaki et al.[39] used ZrO_2 with isopropanol in reduction of aldehydes and ketones.

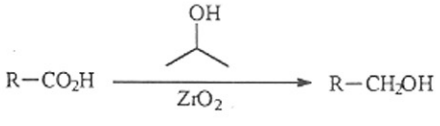




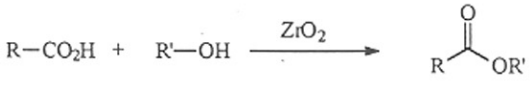
Takahashi et al.[30] reported that amidation of carboxylic acids with amines can be carried out with ZrO_2.



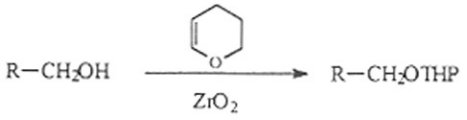
Takahashi et al.[31] reported ZrO_2 with isopropanol as an effective catalyst in reduction of carboxylic acids to alcohols.



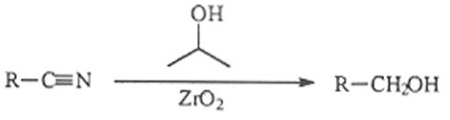
Takahashi et al.[32] used ZrO_2 as a mild acid catalyst to esterify the carboxylic acid with alcohol.



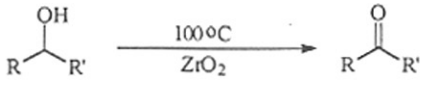
Gajare[33] used ZrO_2 as a acidic catalyst in protection of alcohols with dihydropyran.



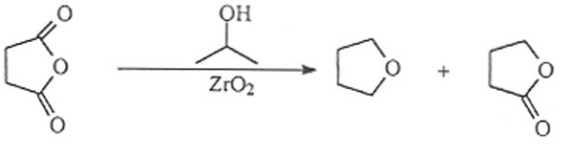
Takahashi et al.[34] also reported that ZrO_2 is a very good catalyst in converting nitriles to alcohols with isopropanol.



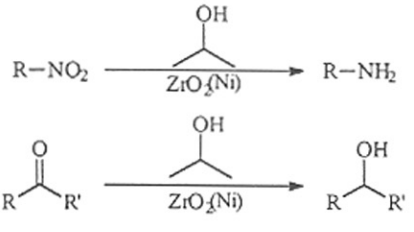
Kuno et al.[28] used ZrO_2 in oxidation of secondary alcohols which shows duel nature of catalyst.



Takahashi et al.[35] also reported dicarboxylic anhydrides can reduce over ZrO_2 with isopropanol.



Sudalai et al.[36] reported nickel stabilized ZrO_2 a useful catalyst in reduction of nitro arenes and carbonyl groups.



Thus, ZrO_2 was found to be a useful catalyst in oxidation, reduction and acid catalysed reactions in organic transformations.

Present work

In view of the current interest in catalytic processes and to develop a catalytic reduction of azo compounds to hydrazo compounds using inexpensive hydrogen donors like hydrazine hydrate and reusable zirconia catalyst, this study was under taken. The catalytic reduction with hydrated ZrO_2 is known for different functional groups using isopropanol as hydrogen donor. In the present work the use of ZrO_2 catalyst in reduction of azo compounds to hydrazo derivatives was studied.

The selective reduction of azo compounds to hydrazo derivatives assures importance because the hydrazo generally suffers a facile reductive cleavage of -NH-NH- bond to amines under reaction conditions.[37] A variety of reagents such as diimide, $NaBH_4$ in the presence of metal catalysts, LAH, cobalt boride with hydrazine hydrate, SmI_2 hydrogen telluride etc. have been used. These reagents which ere reported[38] to accomplish azo to hydrazo transfer suffers the lack of reuseability of catalyst. Catalytic hydrogenation[39] with Pd/C or Raney Ni were also used in presence of hydrogen gas. Zinc and other metals were used in the reduction but due to strongly acidic conditions which have to be avoided to prevent the benzidine rearrangement of the hydrazo benzene.

The preparation of ZrO_2 catalyst is easy. A various substituted azobenzenes (CH_3, Cl, CO_2H, NH_2) underwent selective reduction with hydrazine hydrate to form hydrazo derivative in high yields. However it is to be noted that hydroxy azobenzene underwent reductive cleavage smoothly to produce the corresponding aniline in excellent yields. Surprisingly, no reaction took place in the absence of base. Sodium carbonate or at least two molar equivalent of $NaHCO_3$ was required to achieve the complete reduction of azo group. Several examples illustrating this novel and efficient procedure for the reduction of azo to hydrazo compounds are given in the **Table 1**.

Table1: Hydrated ZrO_2 catalysed transfer hydrogenation of azobenzenes using hydrazine hydrate - $NaHCO_3$[a]

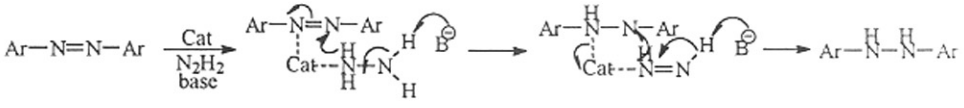
Entry	Substrate	Time in h	Product[b] (% Yield)[c] (Method C)
1.	Azobenzene	10	Hydrazobenzene (86)
2.	4,4'-Dimethylazobenzene	10	4,4'-Dimethylhydrazobenzene (78)
3.	4,4'-Dimethoxyazobenzene	10	4,4'-Dimethoxyhydrazobenzene (80)
4.	4,4'-Dichloroazobenzene	10	4,4'Dichlorohydrazobenzene (90)
5.	4-Aminoazobenzene	10	4-Aminohydrazobenzene (75)
6.	Azobenzene-4,4'-dicarboxylic acid	10	Hydrazobenzene-4,4'-dicarboxylic acid (81)[d]
7.	4-Hydroxyazobenzene	12	Aniline (64) + 4-Aminophenol (36)
8.	2-Methoxy-4-hydroxyazo benzene	12	o-Anisidine (62) + 4-Aminophenol (32)
9.	1-Phenylazo-2-naphthol	5	Aniline (65) + 1-Amino-2-naphthol (20)
10.	1-(4-Methylphenylazo)-2-naphthol	5	p-Toluidine (70) + 1-Amino-2-naphthol (15)
11.	1-(4-Methoxyphenylazo)-2-naphthol	5	p-Anisidine (55) + 1-Amino-2-naphthol (33)
12.	1(4-chlorophenylazo)-2-naphthol	5	4-Chloroaniline (72) + 1-Amino-2-naphthol (23)

[a]In the absence of $NaHCO_3$, no reaction takes place. [b]Characterized by IR, ^1H and ^{13}C NMR and MS and compared with authentic samples. [c]Isolated after chromatographic purification. [d]The product isolated after acidifying the reaction mixture with acetic acid.

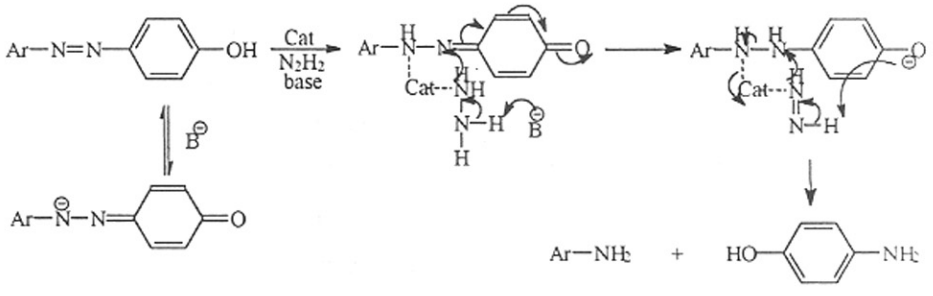
Mechanism

Based on the above observed result of the reduction of symmetrical and unsymmetrical azobenzenes containing hydroxy group the following probable mechanisms have been proposed which are dipicted in **scheme-1** and **scheme-2** respectively.

Scheme-1: For symmetrical Azobenzenes



scheme- 2: For unsymmetrical Azobenzenes:



In conclusion ZrO_2 in a very good catalyst with hydrogen donors like hydrazine hydrate to reduce azo to hydrazobenzene.

Section-II

Transdithioacetalization of acetals, ketals and oximes catalyzed by natural Kaolinitic Clay

Introduction

Kaolinite clays contain one tetrahedral and one octahedral layer as shown in **figure 1**. Alumina (III) cations[40] are bonded in an octahedral arrangement with oxygen anions and repetition of these AlO_6, units in two-dimension forms an octahedral layer. Likewise, a tetrahedral layer is formed from SiO_4 silicate units. Clays are used as effeicient catalysts. They have capacity to stabilize high energy intermediates formed during organic reaction and efficiently stores energy in their lattice structures which then release in the form of chemical energy, Low cost, easy handling, noncorrosive nature, reusable and environmentally friendly nature are clays additional feutures, Due to the presence of both Bronsted and Lewis acid characters clays are useful as ion exchange catalysts. These properties made clays as a versatile catalyst for various organic transformations.

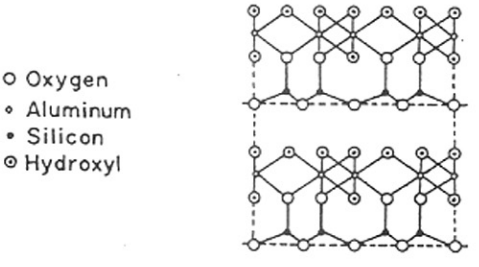


FIG. 1

Several applications of clay in various transformations like selective functional protection of carbonyl groups, hydroxyl groups, transesterification and transdithioesterification of β-ketoester have been reported in the literature[41].

Natural kaolinitic clay (procured from the Padappara mines of quilon District, Kerala, India) has surface acidify measuring between 1.5 to -3 in the Hammett Ho acidity function scale. By just the treatment with aqueous HCl (0.1 M) the surface acidity of the clay can be brought in the range of conc. HNO_3 or oleum (i.e. -6 to -8). Enhanced catalytic activity of clay is believed to be due to Lewis acidity derived from Al remaining

on the edges of the platelets and Bronsted acidity of coordinated hydroxyl groups by Al^{3+}, Fe^{3+} and Ti^{2+} ions relocated in the intralameller space of the clay.

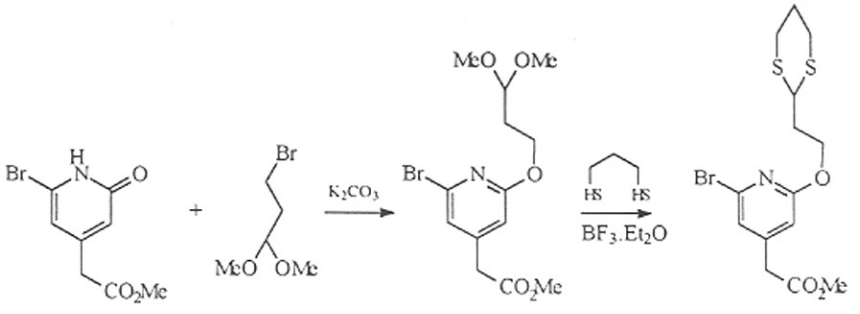
Untreated natural clays or modified clays can be used as catalysts for organic transformations. The main aspects of the heterogeneous catalysts are lameller swelling properties and large specific surfaces availability of both Bronsted and Lewis acidic catalytic sites and their low costs. They are be useful in anionic reactions, Diels-Alder reaction, acid-catalysed reactions,[41-57] aromatic chlorination, Friedel Craft reactions, Clay doped metallic nitrates for Friedel Craft reactions are also useful for 1,3-dithane protection.

The protection of carbonyl groups as acetals or dithioacetals is often necessary during the multistep synthesis of many useful compounds.[58] More particularly, 1,3-dithianes have found wide synthetic uses as precursor of acyl anion displaying a reactivity equivalent of unpolung.[59] For example 1,3-dithianes can be metallated with BuLi and the resultant anions are sufficiently stable to serve as effective nucleophiles in C-C bond forming reactions. Smith (III) et al.[58c] used this method to build complex molecules like cyclosporin A, (-) FK 506, capamycin, demethoxycapamycin etc. Although thioacetals have been prepared by protic acids,[60] solid acid,[61] or Lewis acid catalysed condensation of carbonyl compounds with thiols,[60] of late, transdithioacetylation of acetals has gained favour as the method of choice in which catalysts such as $BF_3.OEt_2$,[62] $Bu_2^iAlS(CH_2)_2SalBu_2$,[63] and $CoCl_2$ Me_3SiCl[64] and Tungsten hexachloride[65] have been employed. However since such catalysts are either expensive or ineffective with hindered ketones, a reusable and solid clay catalyst would have advantages over classical acids because of its strong acidity (H=-9 to -11), non-corrosive nature, high selectivity and ease of subsequent product work-up.[66]

Aldehyde and ketones are generally purified and characterised *via* their oximes or tosylhydrazones since they form crystalline products which may be employed as versatile synthetic intermediates and used in other reactions,[67] they can also be prepared from non-carbonyl compounds.[68] The optical purity of chiral carbonyl compounds is often determined by analysis of their acetal with chiral diols. Since many useful reactions have been developed to prepare oximes from non-carbonyl compounds (e.g. the Barton reaction)[68] an efficient catalytic transdithioacetalization of oximes is of importance since it leads to a novel and direct method for thioacetal preparation.

Present work

In connection with our work on the synthesis of camptothecin we attempted to alkylate the bromopyridone, prepared by a known method,[69] as described in **chapter II** with 3-bromo propionaldehyde dimethylacetal[70] to obtain the *N*-alkylated product; However, the *O*-alkylated product was produced exclusively instead. Although latter product was of no use in the synthesis of camptothecin, we decided to study its transdithioacetyltion in the presence of clay. Accordingly the *O*-alkylated pyridine was subjected to transdithioacetylization with propane-1,3-dithiol in the presence of clay when it gave the corresponding 1,3-dithiane derivatives in high yield.



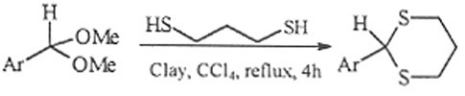
Clays have many useful properties, e.g. they are easy to handle, non-corrosive, inexpensive and may be regenerated. Further, their acidity, both Bronsted and Lewis, in their natural and ion-exchanged forms, enables them to function as efficient catalysts for various organic transformations.[66] To the best of our knowledge, the direct transformation of oximes, to dithianes has not been reported in the literature.

Recently, our group has reported the catalytic application of natural kaolinitic clay for the selective protection of carbonyl compounds,[41h] hydroxy compounds[41c] and selective regeneration of carboxylic acids from their corresponding allyl and cinnamyl esters.[41k] Natural kaolinitic clay efficiently catalyses transdithioacetalization of acetals, ketals, oximes, high yields, thereby constituting an important synthetic method for dithioacetalization of carbonyl compounds.

The kaolinitic clay, procured from the Padappakara mine of Quilon District, Kerala, India, after purification and characterisation,[41j] had the following composition as determined by wet chemical analysis: SiO_2=67.45%, Al_2O_3=22.2%, Fe_2O_3=6.1%, TiO_2=3.45%, and K=0.8%.

The **Table 2** shows the transdithioacetylation of arylacetals using clay and other catalysts. It was observed that other acidic catalysts such as silica gel, sulfated ZrO_2 Hβ-zeolite and montmorillonite clay are also efficient in catalyzing transdithioacetylization, although Al_2O_3 was to be found inactive. A variety of aryl acetals having substitutents such as NO_2, CO_2H, OH, Cl etc. including unsaturated acetals were successfully transformed into 1,3-dithianes in high yield.

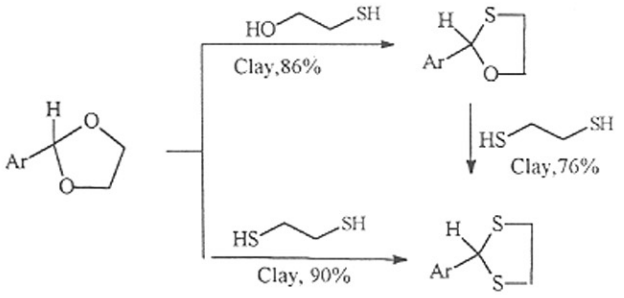
Table-2: Transdithioacetalization of aryl acetals with propane-1,3-dithiol catalysed by clay



Entry	Substitution's on Ar (or acetal used)	Catalyst	Yield (%)*
1	4-OMe	Clay	88[b]
		Al_2O_3	0
		SiO_2	60
		Sulfated ZrO_2	72
		Hβ-zeolite	76
		Montmorillonite	80
2	4-Cl	Clay	80
3	2-NO_2	Clay	82
4	2-OH	Clay	94
5	2-CO_2H	Clay	90
6	3,4,5-$(OMe)_3$	Clay	90
7	3-OMe, 4-OH, 5-NO_2	Clay	87
8	3,5-$(OMe)_2$, 4-OH	Clay	92
9	(Cinnamaldehyde)	Clay	79
10	(Furan-2-carbaldehyde)	Clay	69

[a]Isolated yield, characterized on the basis of IR, ^{1}H-NMR and ^{13}C NMR and MS spectral evidence. [b]Catalyst recovered and re-used at least 3 times without any loss of activity.

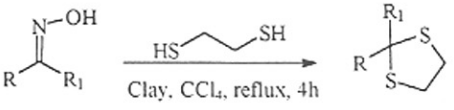
Table 3 summarises the transdithioacetylization of a variety of aliphatic acetals and ketals catalysed by kaolinitic clay.



The 1,3-dioxolanes when refluxed with either ethane-1,2-dithiol or marcaptoethanol in the presence of kaolinitic clay gave the 1,3-oxodithiolane or the 1,3-dithiolane. Similarly the 1,3-oxothiolane gave the 1,3-dithiolane.

Table 1 lists a variety of aldoximes and ketoximes which underwent transdithioacetalization with ethane-1,2-dithiol in the presence of the clay to produce their corresponding 1,3-dithianes in excellent yields. However, aromatic ketoximes failed to undergo the reaction (entries 10 and 11). The clay catalyst was recovered and re-used at least three times with no loss of activity.

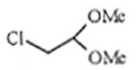
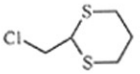
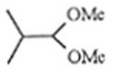
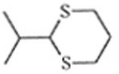
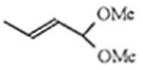
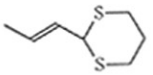
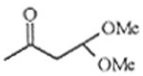
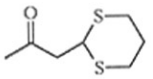
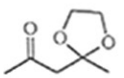
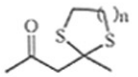
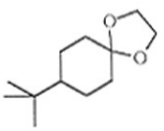
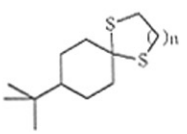
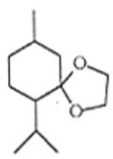
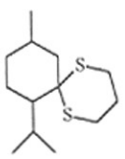
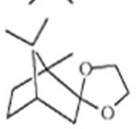
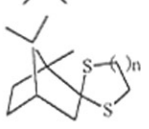
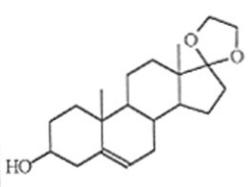
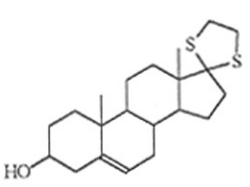
Table 1: Transdithioacetalization of aldoximes and ketoximes



Entry	R (entry 1-5) aromatic ring substitution, (or oxime used)	Yield %
1	H	94
2	4-OMe	85 (87[b])
3	4-Cl	80
4	4-NO_2	82
5	3-NO_3	84
6	(Cinnamaldehyde)	94
7	(Butyraldehyde)	79
8	(Cyclohexanone)	91
9	(3-Methylcyclohexenone)	75
10	(Acetophenone)	0
11	(Benzophenone)	0

[a]All products were characterised on the basis of IR, NMR, mass and ^{13}C NMR spectral results; yields are those isolated after column chromatography. [b]Yield corresponds to 1,3-dithiane.

Table-3: Transdithioacetalisation of aliphatic acetals and ketals catalysed by clay

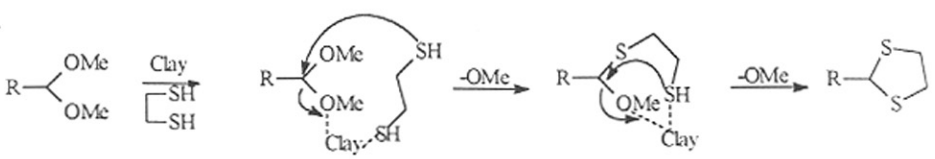
Entry	Substrate	Product	Yield
1			86
2			89
3			81
4			50
5			78
6			78
7			67
8			80
9			76
10			81

n=1or2

A remarkable feature observed was that keto acetals underwent chemoselective transdithioacetalization in preference to ketone in excellent yields. Even sterically hindered ketones α-halogenated acetals and unsaturated acetals were successfully transformed into dithianes and dithiolanes in high yields.

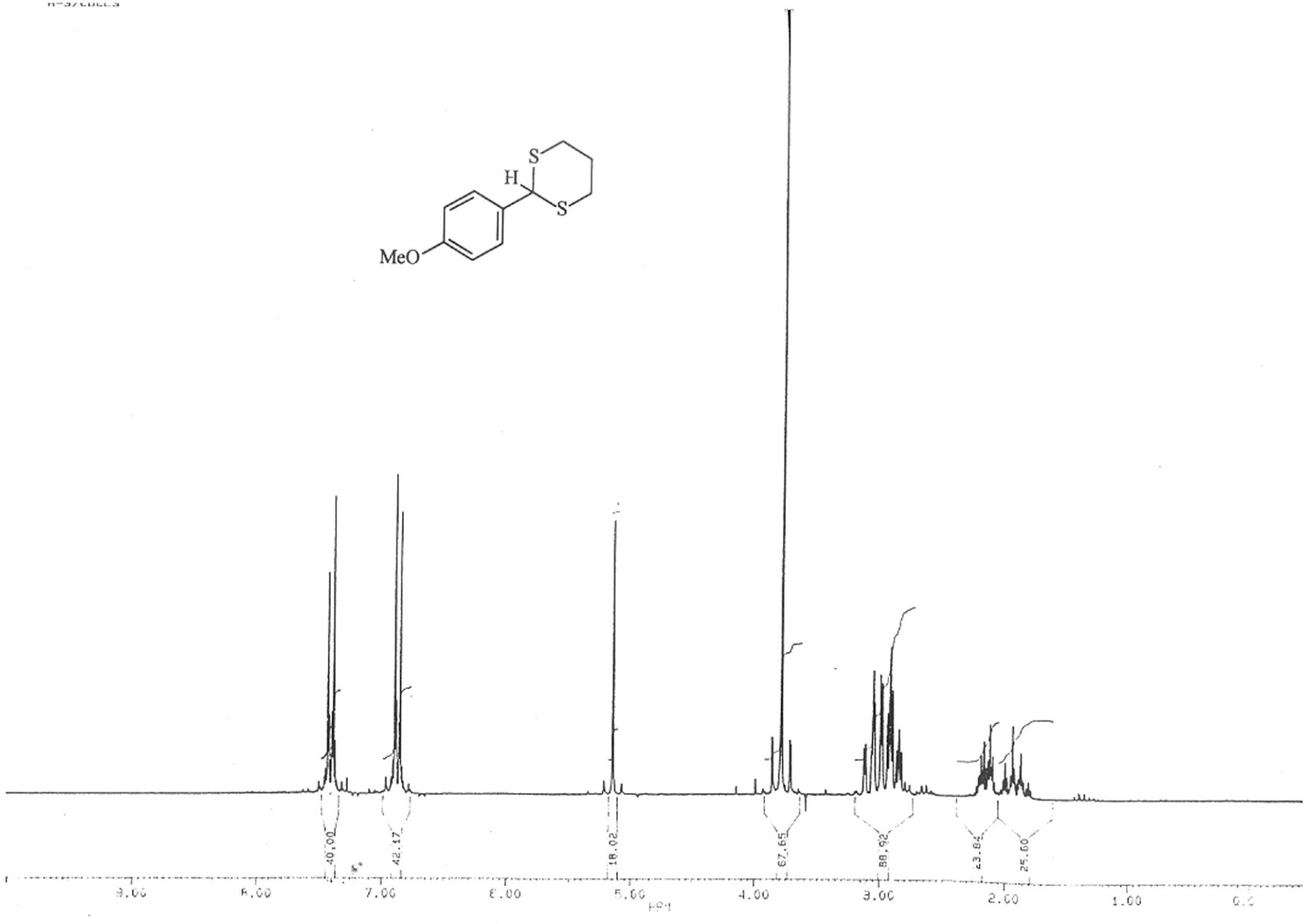
The enhanced catalytic activity of the acid activated clay may be attributed to a significant level of Lewis acidity derived from Al remaining in the platelet edges and the Bronsted acidity of coordinated hydroxy groups of Al^{3+}, Fe^{3+} and Ti^{4+} ions relocated in the interlamellar space of the clay.[40]

Mechanism



Conclusion

Natural clay is an effective and convenient catalyst for transdithioacetalization of acetals, ketals and oximes.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H
S
MeO
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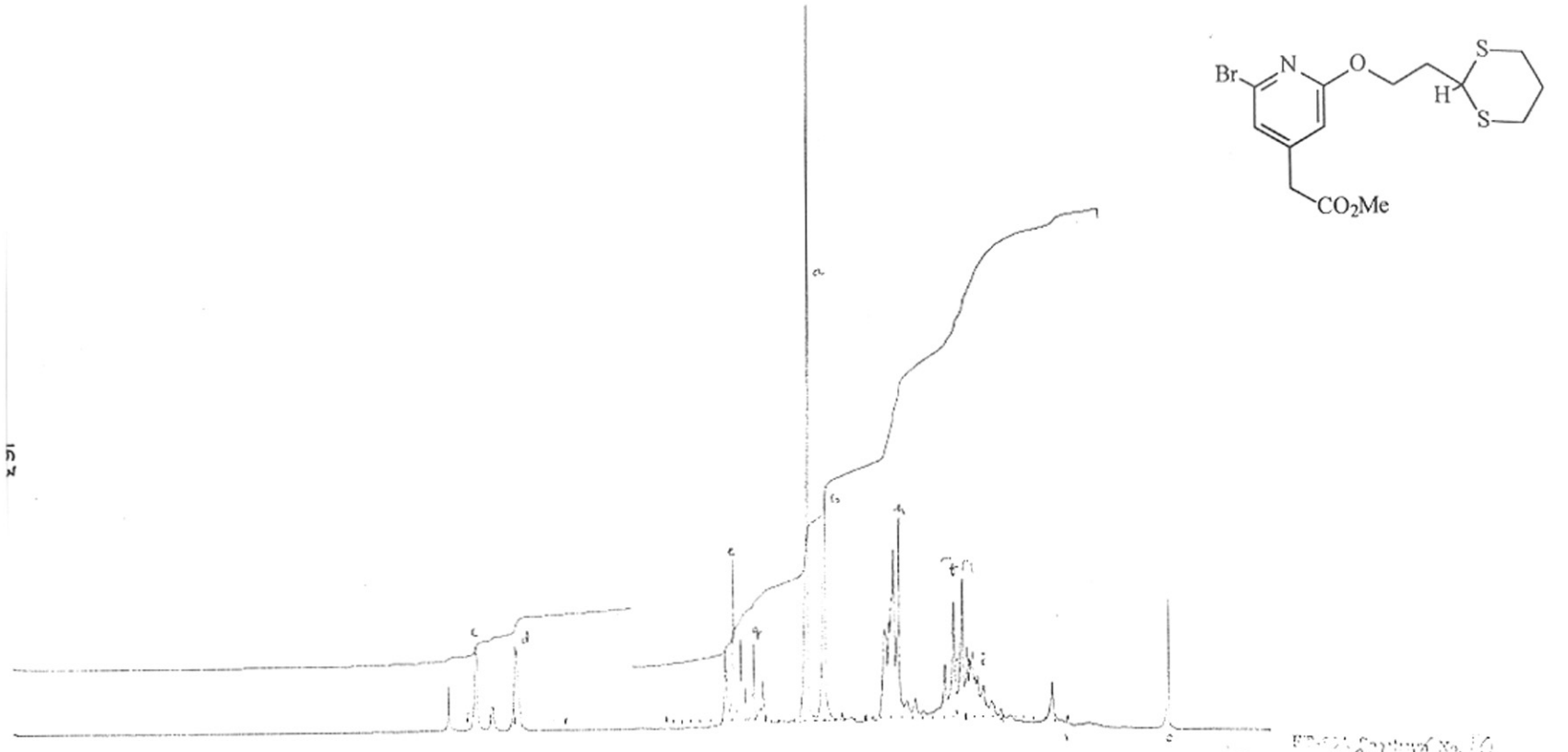
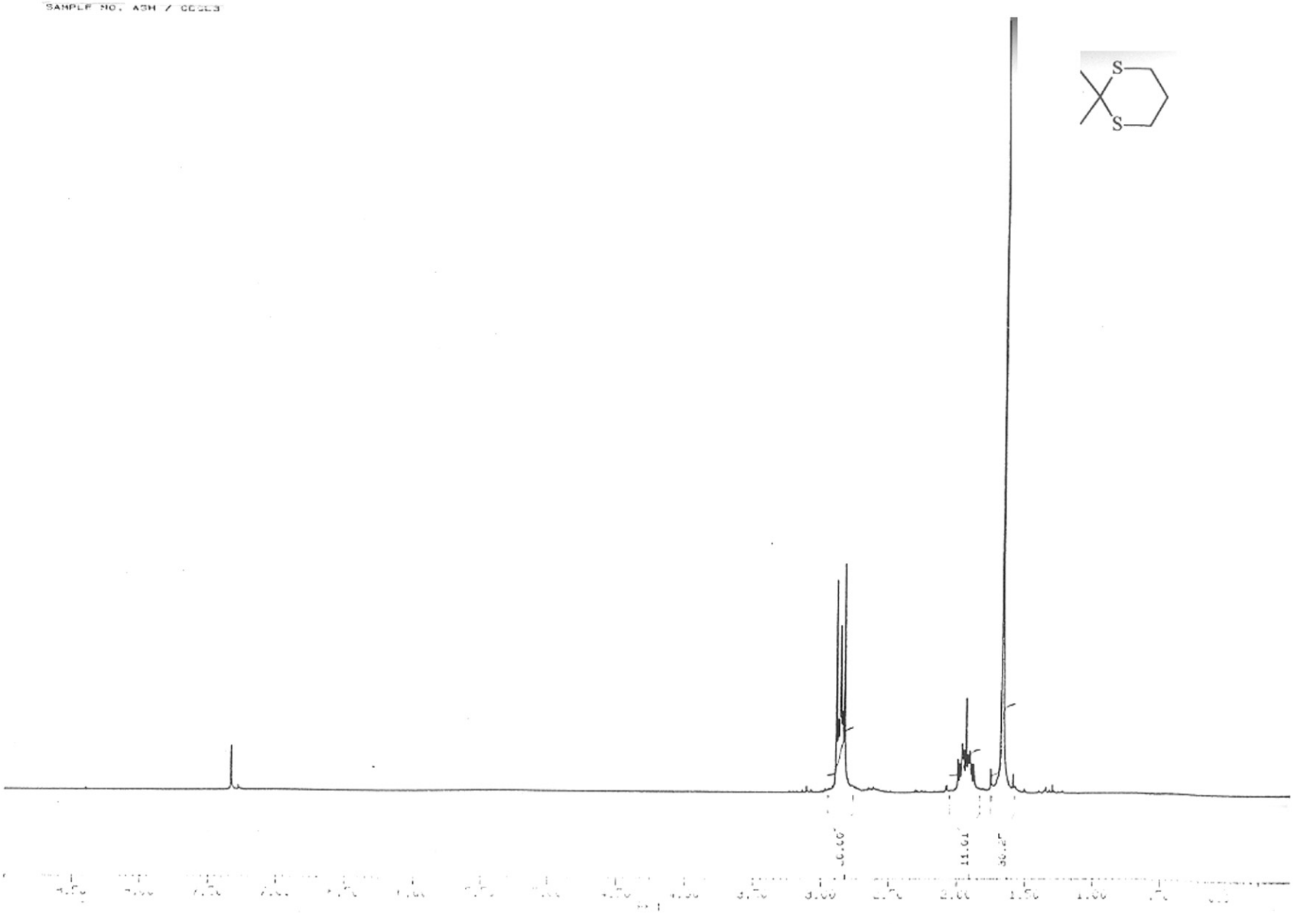
42.17
18.02
67.65
88.92
43.84
25.60
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM


Br
N
O
S
H
S
CO2Me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S
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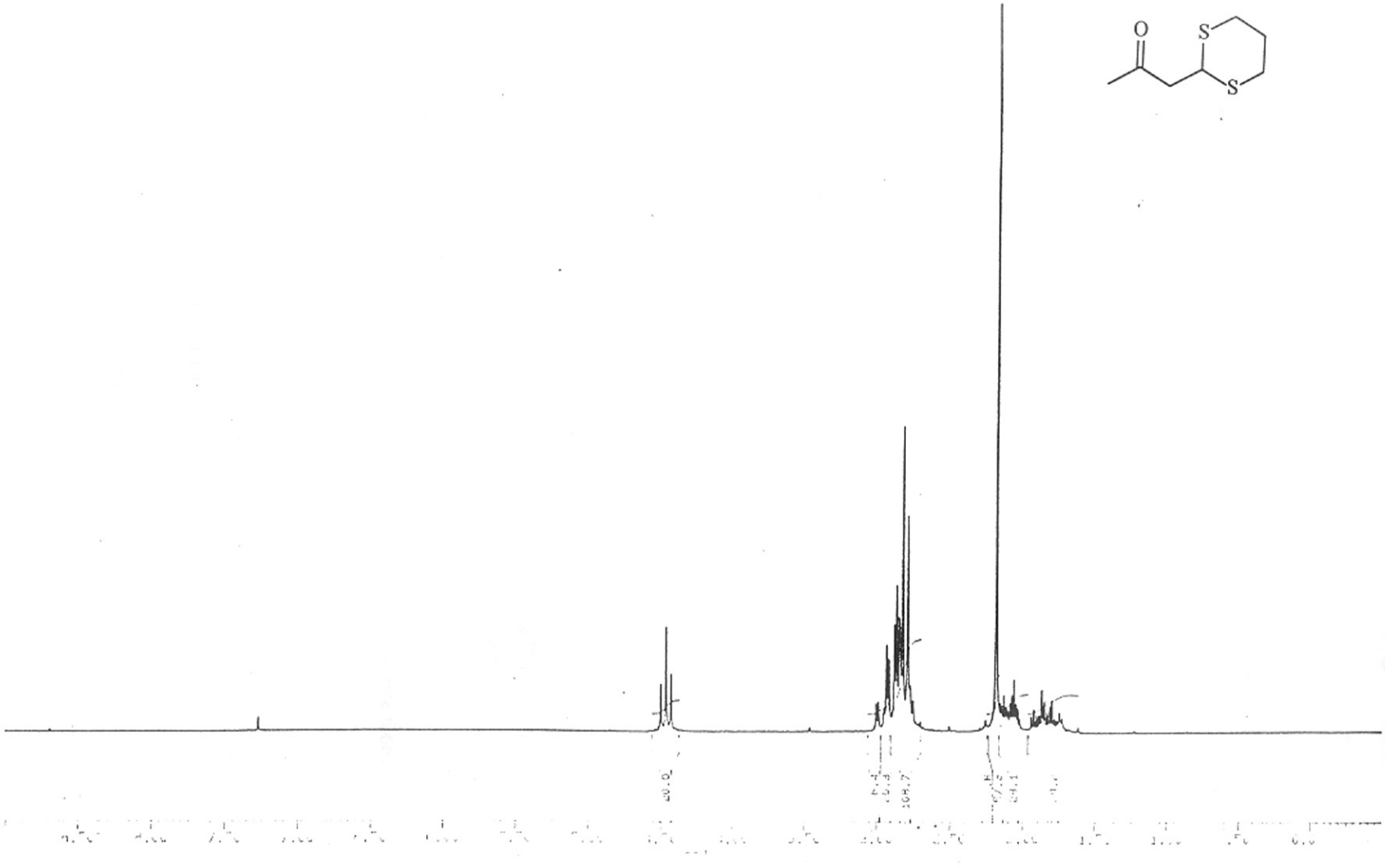
11.04
30.45

SAMPLE NO. A1 / CDCL3



Section III

Natural Kaolinitic clay Catalyzed conversion of Nitriles to 2-Oxazolines

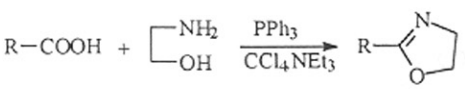
Introduction

Racemic and non-racemic oxazolines continues to be important functionality in synthetic organic chemistry. Oxazoline has been used extensively as protecting group,[71,60] while its optically active analogue has gained importance as valuable auxiliary in asymmetric synthesis.[72] Several chiral oxazolinyl ligand systems developed in the past few years include semicorrin[73] aryl mono-oxazolines as well as C_2 symmetric bis-oxazoline[73,74] and Pybox[75] have proved extremely efficient for a whole range of transition metal catalyzed enantioselective transformations.

The 2-oxazoline, a cyclic iminoamide, was also found in many natural products, such as cidiacyclamide[76] iron chelating parabactin[76] ect. Several methods are known to prepare oxazolines in the literature from carboxylic acid,[77] carboxylic ester,[74,77] nitrile[78] aldehyde[79] and amido alcohols.[80] Most of the methods utilize complex reagent, strongly acidic conditions and stringent reaction parameters with occasionally low yields of the reaction products Some of the recent methods are briefly presented here.

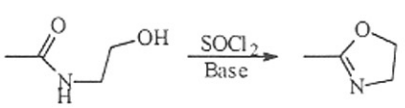
1. **Carboxylic acids**

   Traditional and modified appeal reaction conditions[72e] are effective in preparation of oxazolines,



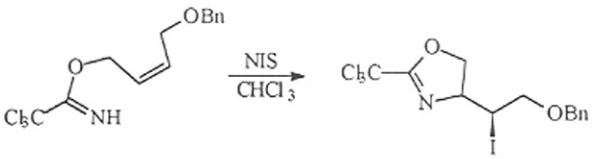
2. **Hydroxyamides-Hydroxyl activation**:

   Activation of hydroxyl group of hydroxyamide with thionyl chloride followed by cyclisation using a base gives oxazoline.[72e]



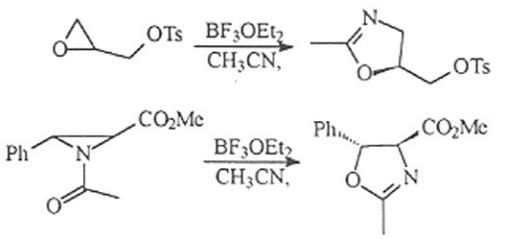
3. **Enamides - Alkene activation**

   N-(Allyl)amides can be cyclised using conc. H_2SO_4 or $Mn(OAc)_3$,TFA, RSSR, PhSeBr, NIS[72e] etc to form oxazolines.



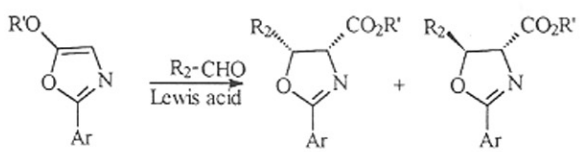
4. **Epoxide/aziridine ring opening**

Epoxide or aziridine ring opening reaction is a useful method in the preparation of racemic and non racemic oxazoline[72e].



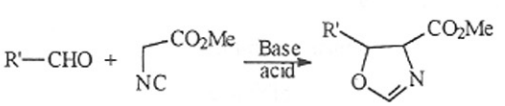
5. **Electro cyclic reactions**[72e]

Addition reaction (3+2) of 5-alkoxyoxazoles with aldehydes gives cis/trans mixture of oxazoline.



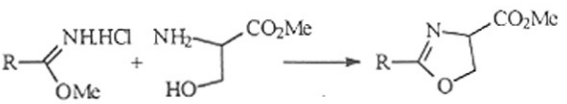
6. **Schollkpf method**[72e]

Aldehydes on condensation with isocyanides produce oxazolines in presence of basic as well as acidic catalysts in high yields.

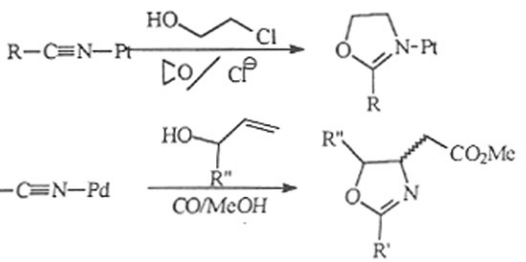


7. **Other methods**

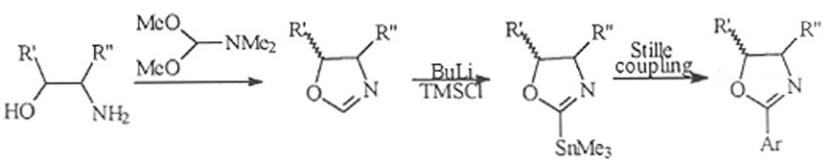
Iminoethers hydrochlorides[72e] on condensation with amino alcohols give oxazolines in high yields.



Platinum and palladium complexe[s2e] of nitriles are effective in the preparation of oxazolines.



Lithiation followed by Stille[72e] coupling is a suitable method for laboratory preparation oxazoline.

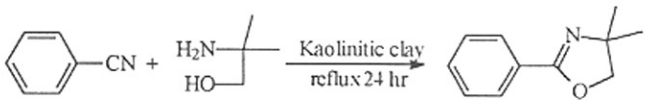


Present work

The applications of inorganic solids such as natural clays as efficient catalysts in organic transformations have been studied recently.[40] The natural clays have several advantages as they are inexpensive, environment friendly, non-toxic, recoverable, reusable and also used as mild catalysts. The acidic properties[41e] of natural clays have been exploited in several synthetic applications.[41i-h] Since oxazoline formation is catalyzed by Lewis and Bronsted acids, we thought that Kaolinitic clay might be an

efficient and mild catalyst for the conversion of aromatic and aliphatic nitriles into 2-substituted oxazoline. Hence a mixture of nitrile 20% kaolinitic clay was refluxed with

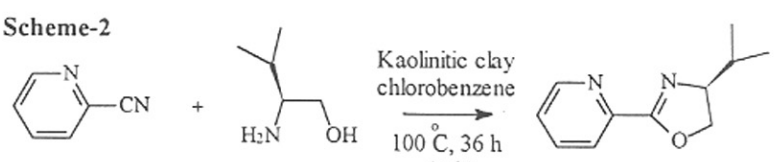
Scheme-1



2-amino-2-methylpropanol for 12-24 hr (**Scheme-1**) to afford very good yield of oxazoline (**Table1** Method A).However,when the reaction was performed with 1.5eq. of aminoalcohol in refluxing o-dichlorobenzene, the product was isolated in slightly lower yield.(**Table1**,Method B) Several different substituted aromatic, aliphatic and heterocyclic nitriles were converted to 2-oxazolines. The nitriles attached to pyridyl nucleus were converted to oxazolines in excellent yields. Moreover, aromatic nitriles with electron withdrawing or electron releasing functional group were converted to oxazolines with same efficiency with an exception of p-chlorobenzonitrile, which gave the oxazoline in lower yield. The other examples include 2 cyanofuran and 1,2-dicyanobenzene furnished the corresponding oxazolines with 90 and 85% isolated yield respectively. Different functional groups could tolerate this reaction condition and no cleavage of methoxy group was observed as reported by Clark and Wood[84] under microwave irradiation, catalyzed by $ZnCl_2$. Aliphatic nitriles were also converted to oxazolines in good yield as demonstrated for the reaction of malononitrile with 4 chlorobutyronitrile. The reusability of the catalyst was studied for the reaction of benzonitrile. The catalyst from the reaction of benzonitrile in o-dichlorobenzene was separated by filtration, reactivated by treatment of 1 M HCl and was found to be equally efficient in the next cycle of the same reaction giving the oxazoline in 69% yield. When 10% w/w clay catalyst was used instead of 20%, similar results were obtained.

The reaction of 2-cyanopyridine (**Scheme-2**) with L-valinol gave S-(-)-4-isopropyl-2-(2-pyridyl) oxazoline with >98% optical purity as determined by comparison of optical rotation with literature value.[84]

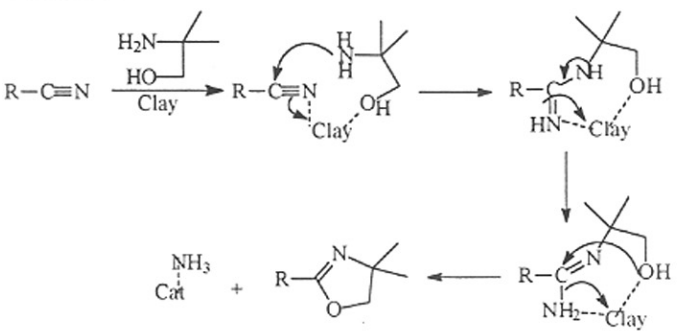
Scheme-2



Chiral pyridinyloxazoline of this type are used as efficient ligands in several asymmetric transformations.[85]

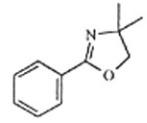
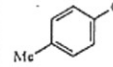
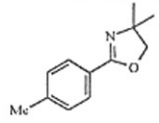
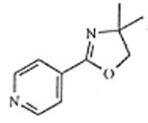
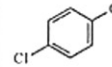
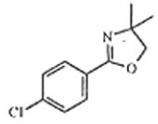
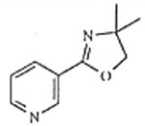
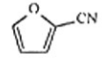
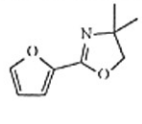
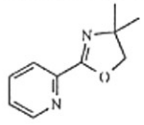
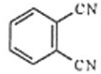
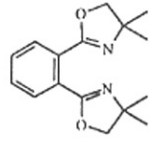
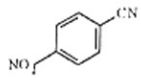
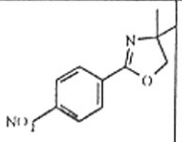
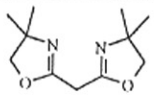
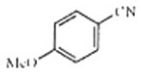
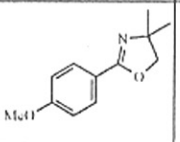
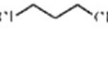
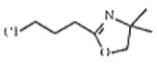
Mechanism: The probable mechanism for the formation of 2-oxazoline is shown in **Scheme-3.**

Scheme-3:



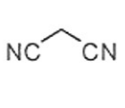
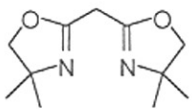
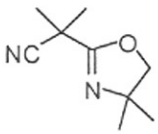
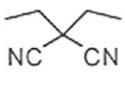
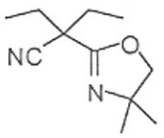
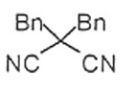
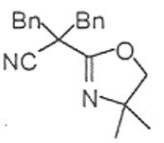
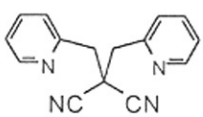
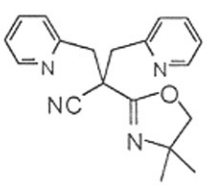
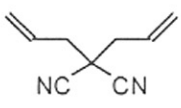
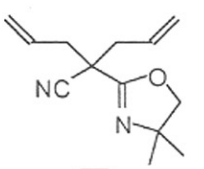
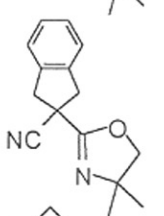
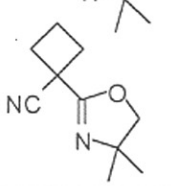
The reaction of malononitrile with excess of 1,2-aminoalcohol and 20% Kaolinitic clay gave the bis oxazoline in high yield. Since the chiral bis-oxazolines are very important in asymmetric synthesis it was thought to extent the clay methodology for the preparation of bis-oxazolines. The required substituted malononitriles were prepared by alkylation of malononitrile with excess K_2CO_3 and alkyl halides in acetonitrile. When diethyl malononitrile was refluxed with excess aminoalcohol and clay, it was found that only mono oxazolines had formed in high yield. Even under strong reaction conditions and with high catalyst loadings gave only mono-oxazoline and no trace of bis-oxazoline was obtained. In order to test the generality of this observation, a range of 2,2-dialkyl malononitrile were investigated for this reaction and results are presented in **Table 2**.

Table-1: Conversion of Nitriles to 4,4-Dimethyl 2-oxazolines with 2-amino-2-methylpropanol catalyzed by Koalinitic clay.[a]

Entry	Nitrile	Oxazoline	Method[15] (% Yield[b])	Entry	Nitrile	Oxazoline	Method[15] (% Yield[b])
1			A (86) B (71)	7			A (82)
2			A (96) B (80)	8			A (75) B (66)
3			A (95)	9			A (90)
4			A (95)	10			A (85)
5			A (93)	11			A (90)
6			A (87) B (70)	12			A (56)

[a]All the oxazolines show satisfactory spectral data. [b]Isolated yield.

Table 2. Conversion of malononitriles to 2-Oxazolines.[a]

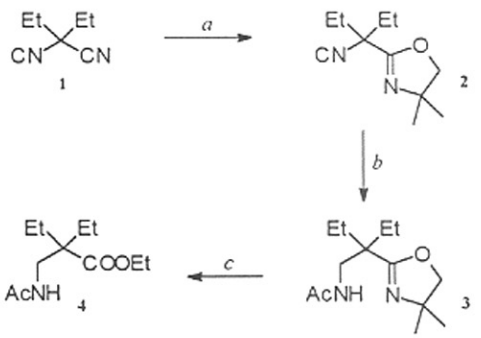
Entry	Malononitrile	Oxazoline	Yield[b] in %
1			90
2			76
3			90 92[c]
4			92 90[c] 92[d]
5			80
6			91
7			78 93[d]
8			82

[a]Malononitrile was treated with excess of 2-amino-2-methylpropanol (6-7 eq.) and catalyst (20 % w/w) at 160-65 °C for 16 h. All the products are characterised by usual spectral and analytical methods: [b]isolated yield; [c]with Montmorillonite clay; [d]under microwave irradiation (8-10 min.) with kaolinitic clay.

The reaction with disubstituted malononitrle furnished the bis-oxazoline in excellent yield as also observed by Bolm[84] in his $ZnCl_2$ catalysed conversion of nitrile to 2-oxazolines. Reaction of 2,2-disubstituted malononitrles under the identical condition resulted in the formation of mono-oxazolines with no detectable amount of bis-oxazoline. It was interesting to note that the reaction of 2,2-dimethylmalononitrile with excess of aminoalcohol catalyzed by $ZnCl_2$ also furnished exclusively mono-oxazoline. The same transformation was also investigated with commercially available montmornolite K-10 clay as the catalyst. Selective formation of mono-oxazolines with this catalyst was observed with equal efficiency under more powerful microwave irradiation. The formation of mono-oxazolines in all these cases could be due to steric hindrance of the neopentyl type center of the substituted malononitrile derivatives as observed by Davis.[81]

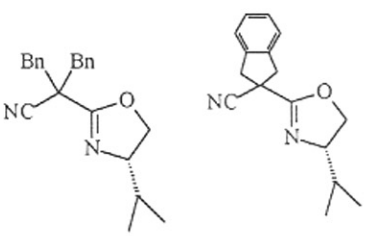
This methodology was then extended to prepare unnatural amino acids. Since these amino acids have found importance in synthetic organic chemistry due to the recent development in peptide science and new drug research. Non α-amino acids make an important part of unnatural amino acids and their chemistry has been reviewed recently.[82]A simple strategy for the general synthesis of 2,2-dialkyl-3-amino propionic acids was developed as an extention of the present findings. These types of compounds have been known[83] to be used as intermediate to β-lactams and other biologically useful compounds. Protected 2,2-diethyl-3-amino propionic acid was synthesised as an example starting from 2,2-diethyl malononitrile. The mono oxazoline prepared by Kaolinitic clay catalyzed reaction was hydrogenated with Ra/Ni catalyst at 50 psi pressure with base NaOAc at room temperature followed by acidic cleavage of oxazoline to furnish the amino acid ester (**Scheme-4**).

Scheme-4:



Scheme-4: a) 2-amino-2-methylpropanol, Kaolinitic clay, 160-65 °C, 90 %; b) RaNi, Ac_2O, 50 psi, r.t., 80 %; c) H_2SO_4, EtOH, Δ, 55 %.

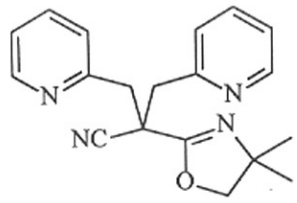
The mono-oxazolines of chiral amino alcohol (L)-valinol were also prepared. Dibenzyl and cyclobenzyl derivatives of malononitrile with (L)-valinol gave mono-oxazoline derivatives in 65% and 40% yield.

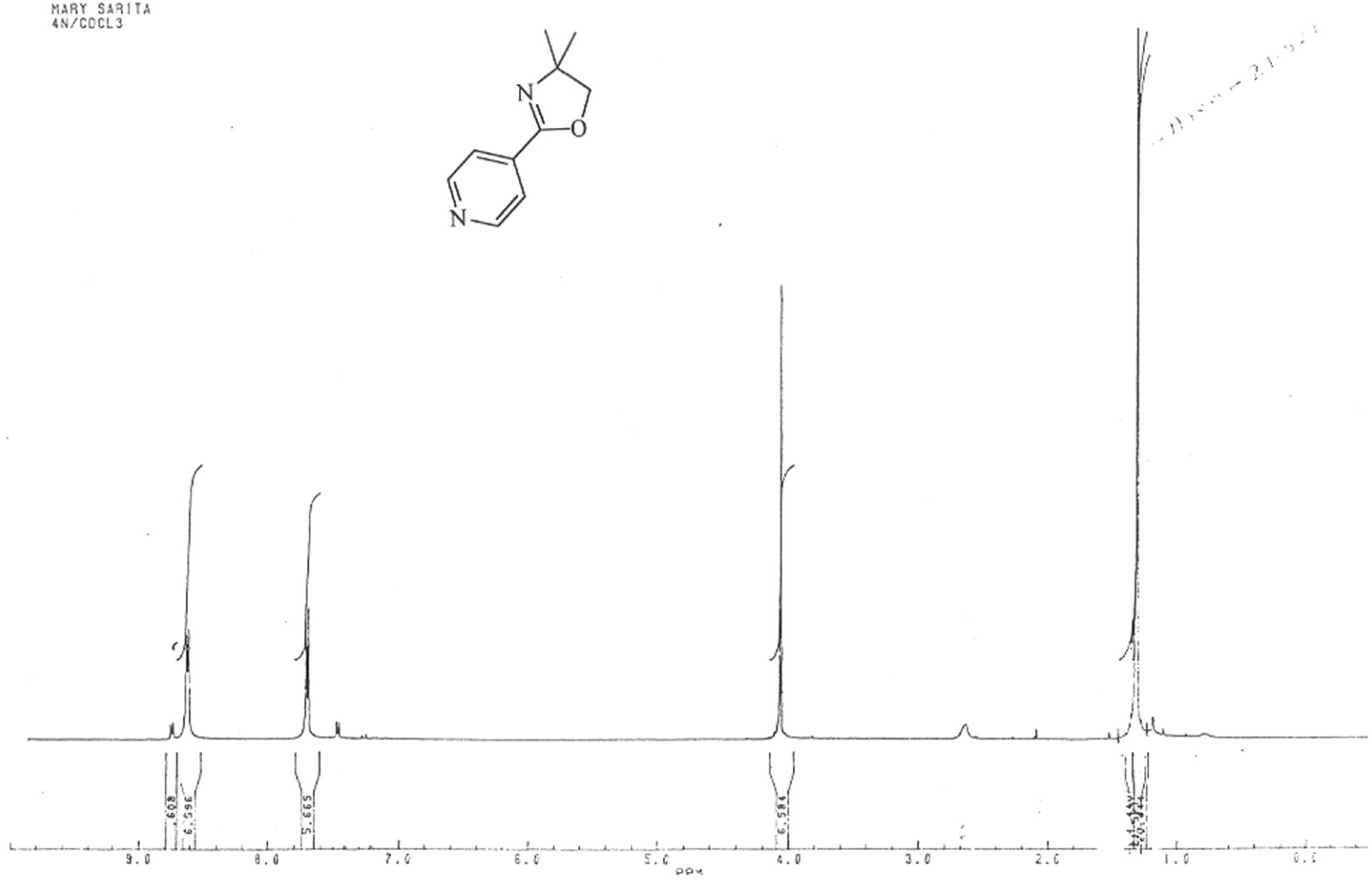


Conclusion

1. The Kaolinitic clay was effectively used as a catalyst which converts aromatic, heterocyclic and aliphatic nitriles to 2-oxazolines.
2. Disubstituted malononitriles form mono-oxazolines instead of bisoxazolines in presence of catalytic amount of the clay.
3. The mono-oxazolines formed from substituted malononitriles are converted to α-unnatural amino acids, which are synthetically useful in peptide chemistry.

NP/CDCL3




MARY SARITA
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O
N
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8.0
7.0
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3.0
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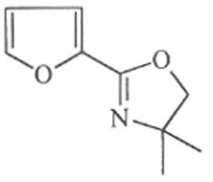
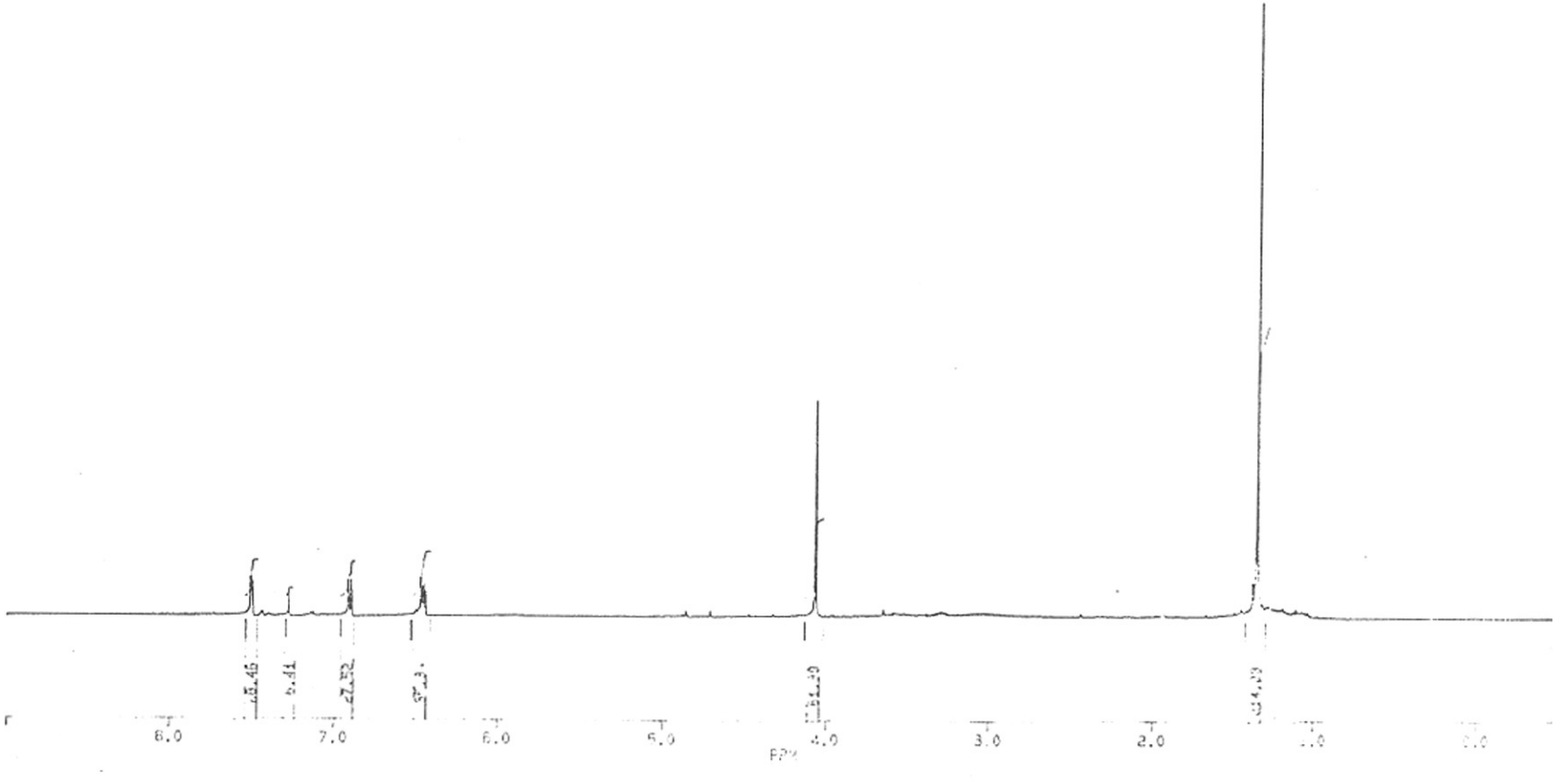
PPM

FP/CDCL3





177

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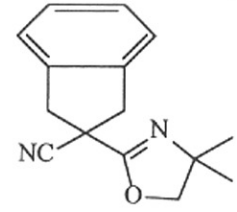

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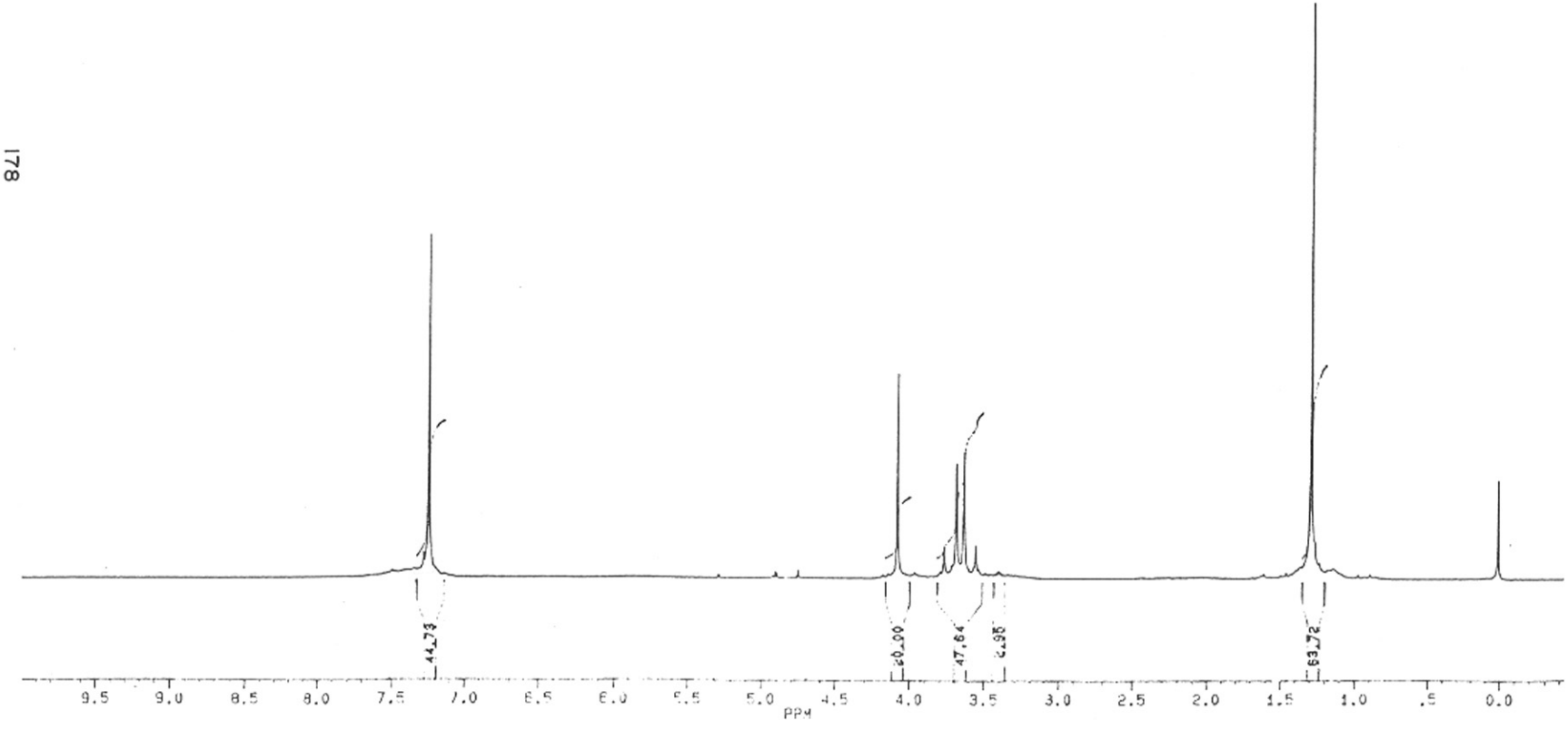
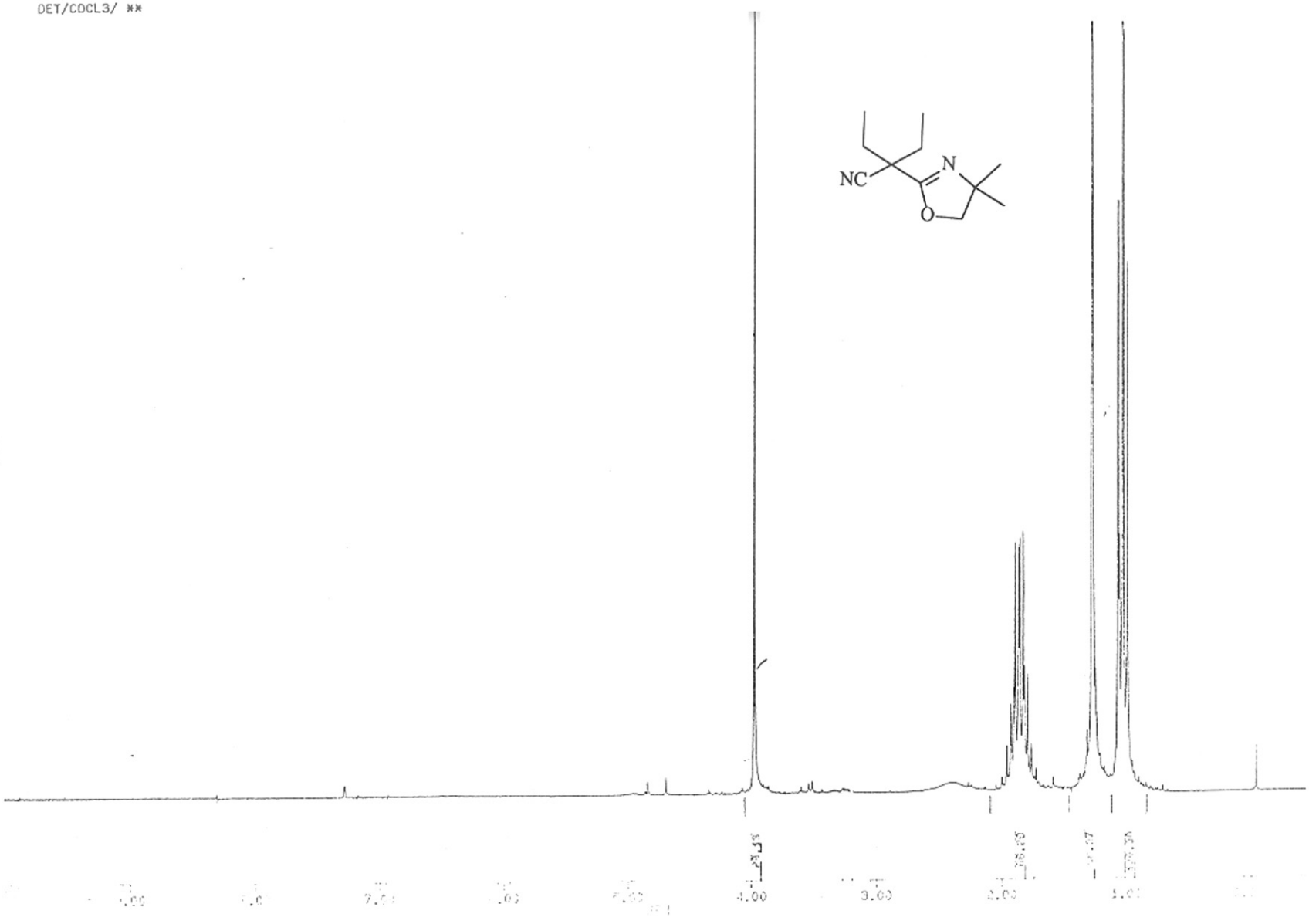
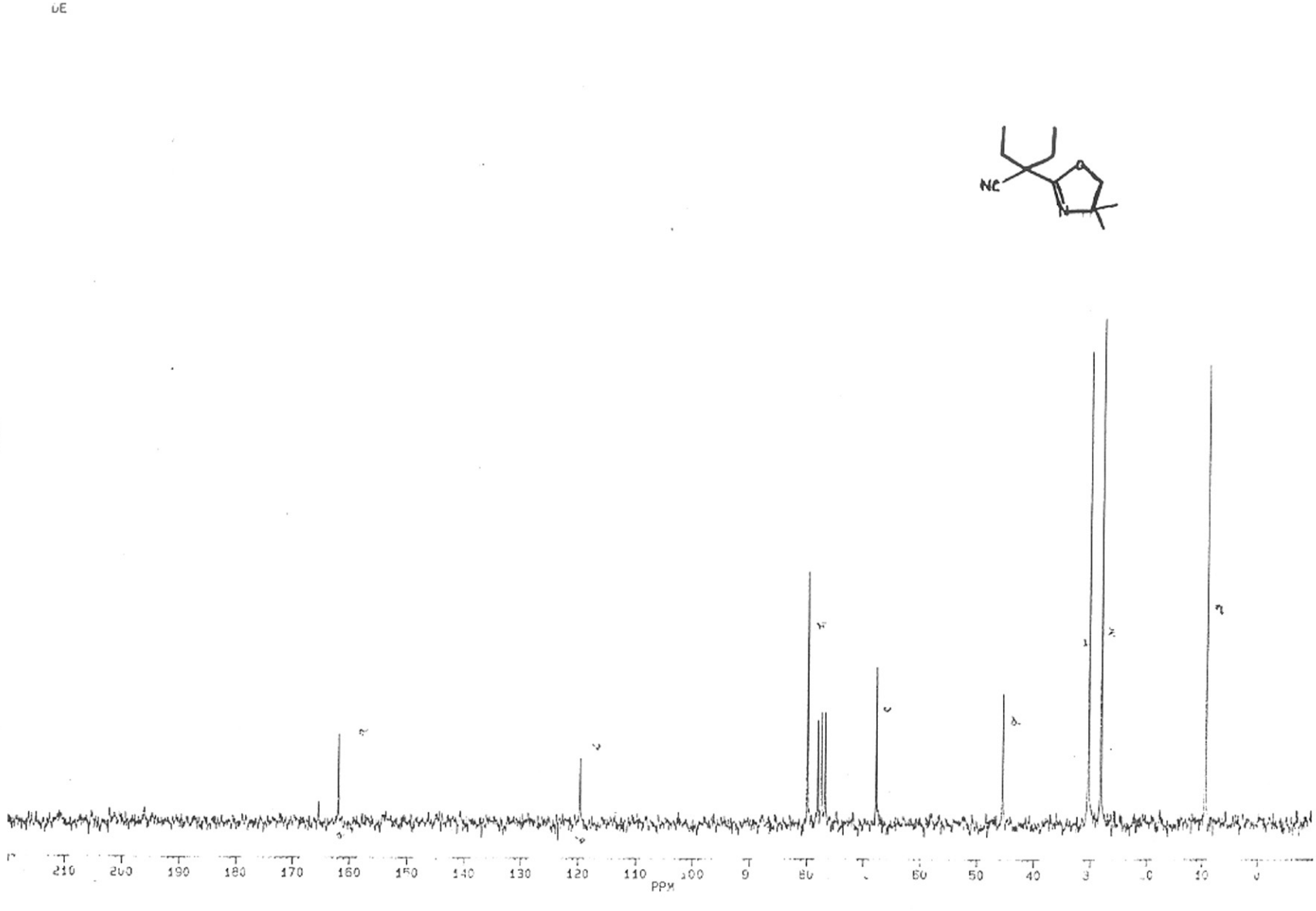


DET/CDCL3/ **

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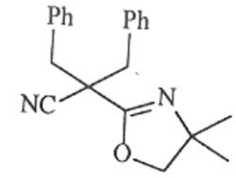
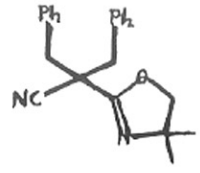
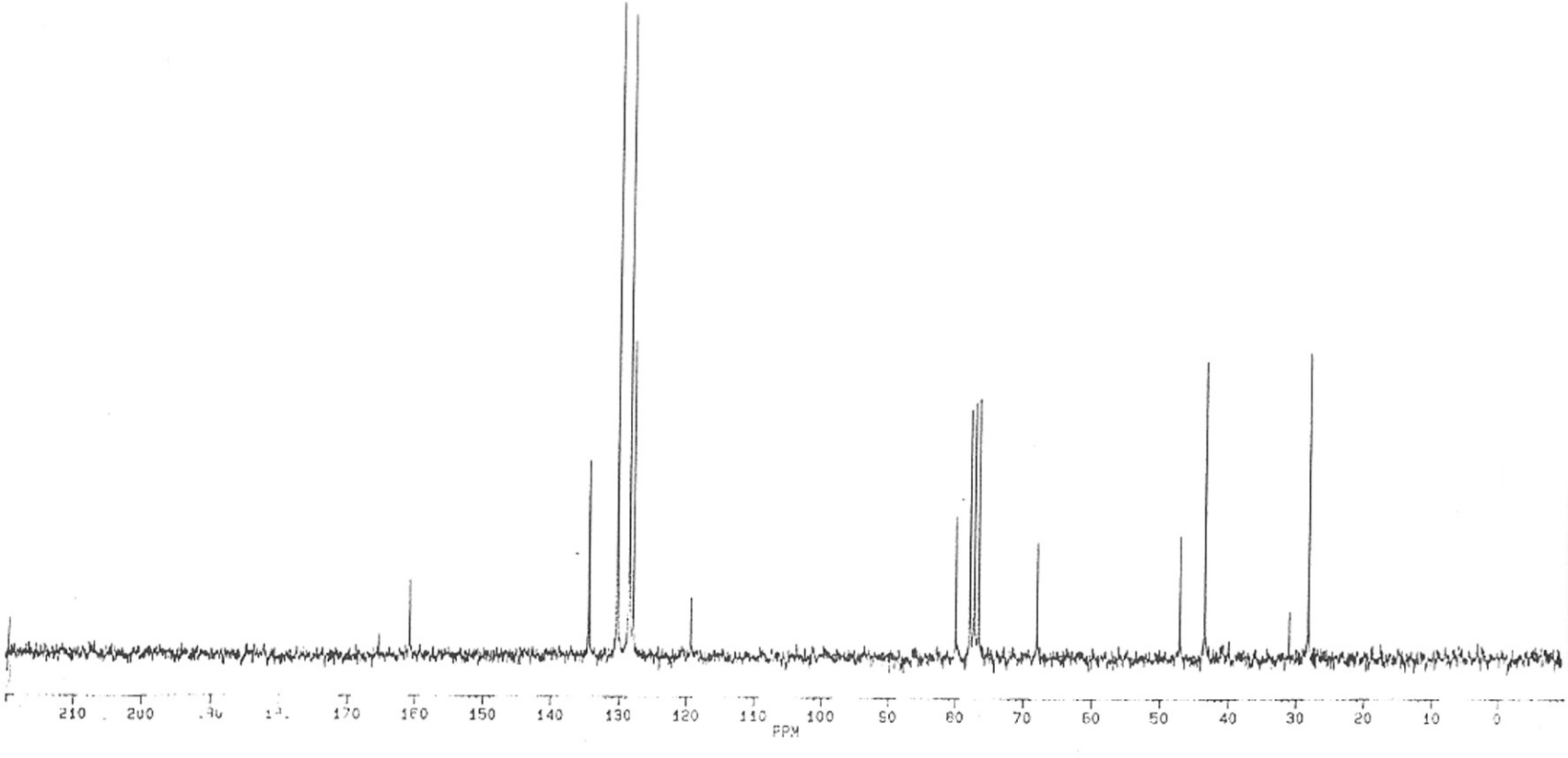
O
N
PPM

A.V. BEDEKAR/CDCL3



β2


Ph
Ph
NC
O
N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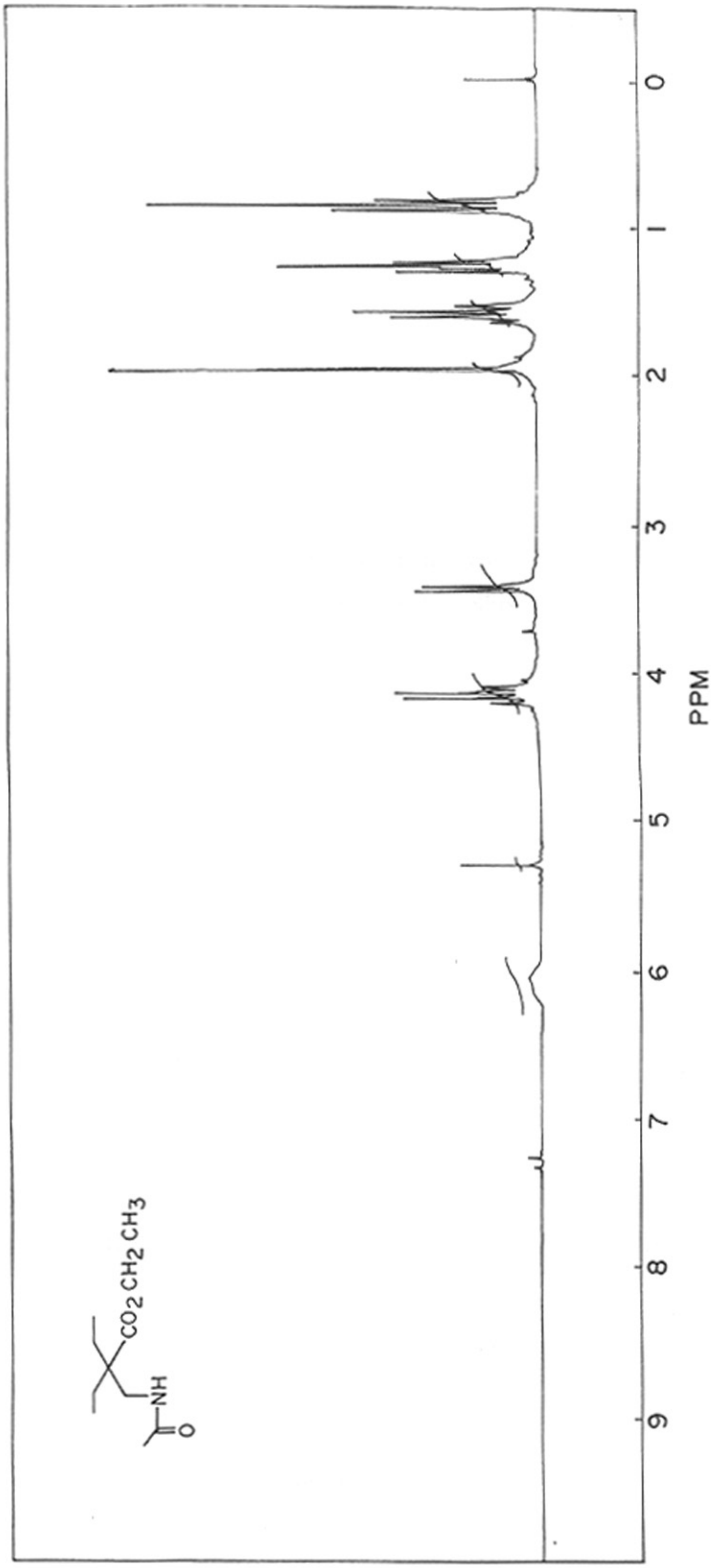
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Experimental

Transfer Hydrogenation

Method A

A mixture of azobenzene (0.01 mole), ammonium formate (0.04 mole) and 10% Pd/C (180 mg) in methanol 20 ml was stirred at room temperature for 5 hr. The progress of the reaction was monitored by TLC. After the reaction was complete the catalyst was filtered off and the crude product was purified by flash chromatography (yields are given in the tables)

Method B

A mixture of oxime (0.01 mole), ammonium formate (0.02 mole) and 10% Pd/C (135 mg) in MeOH (20 ml) was boiled under reflux for 5 hr. The reaction was monitored by TLC. After the reaction was complete the catalyst was filtered off and the crude product was purified by flash chromatography.

Method C

A mixture of azobenzene (5 mmol), hydrazine hydrate (5 mmol), $NaHCO_3$ (10 mmol) and hydrate zirconia (125 mg, 10% wt.) in ethanol (20 ml) was refluxed for 10 hr. After the reaction was complete (TLC) the catalyst was filtered off, the reaction mixture concentrated and the product was purified by flash chromatography to afford the hydroazobenzene.

Aniline

IR ($CHCl_3$) : 3500, 3000, 1600 $cm.^{-1}$

^1H NMR (200MHz,$CDCl_3$) : δ 3.2 (s, 2H); 6.2-6.5 (m, 3H); 6.7-6.9 (m, 2H).

O-Anisidine

IR ($CHCl_3$) : 3600, 1600, 1520 $cm.^{-1}$

^1H NMR (200MHz,$CDCl_3$) : δ 3.55 (bs, 2H); 3.8 (s, 3H); 6.65-6.8 (m, 4H)

4-Amino-2-naphthol

M.P.	: 272°C
^{1}H NMR (200MHz,$CDCl_3$)	: δ 6.9-8.4 (m, 6H); 9.5 (bs, 1H).
MS (m/z)	: 159 (M^+), 158, 157, 119, 40.

p-Toluidine

M.P.	: 41°C
IR ($CHCl_3$)	: 3500, 3100, 1600 $cm.^{-1}$
^{1}H NMR (200MHz,$CDCl_3$)	: δ 2.2 (s, 3H); 3.2 (bs, 2H); 6.55 (d, J = 9 Hz, 2H); 6.95 (d, J = 9 Hz, 2H).

p-Anisidine

M.P.	: 57°C
IR ($CHCl_3$)	: 3600, 1600, 1400 $cm.^{-1}$
^{1}H NMR (200MHz,$CDCl_3$)	: δ 3.5 (bs, 2H); 3.7 (s, 3H); 6.55 (d, J = 9 Hz, 2H); 6.8 (d, J = 9 Hz, 7H)

4-Chloroaniline

M.P.	: 68°C
IR ($CHCl_3$)	: 3600, 1600, 1500 $cm.^{-1}$
^{1}H NMR (200MHz,$CDCl_3$)	: δ 3.5 (bs, 2H); 6.55 (d, J = 9 Hz, 2H); 7.58 (d, J = 9 Hz, 2H)

1,4-Diaminobenzene

M.P.	: 143°C
IR ($CHCl_3$)	: 3600, 1600 $cm.^{-1}$
^{1}H NMR (200MHz,$CDCl_3$)	: δ 3.50 (bs, 4H); 6.35 (s, 4H).

4-Aminophenol

M.P.	: 188°C
IR ($CHCl_3$)	: 3500, 1600 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 4.30 (bs, 2H); 6.40-6.50 (q, J = 9 Hz, 4H); 8.4 (bs, 1H)

3,4-Diaminoanisole

M.P.	: 206°C
IR ($CHCl_3$)	: 3500, 1600, 1440 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 3.6 (bs, 4H); 3.555 (s, 3H); 6.1-7.1 (m, 3H)

4-Fluoroaniline

IR ($CHCl_3$)	: 3600, 1600 $m.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	; δ 3.55 (bs, 2H); 6.55-6.6 (m, 2H); 6.8-6.85 (m, 2H)

2-Phenylglycine methyl ester

Yield	: (0.74 gm , 45%)
IR ($CHCl_3$)	: 3500-3300, 1740, 1600, 1450, 1400, 1250, 1180, 1100, 1000, 740 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 2.7 (bs, 2H); 3.70 (s, 3H); 4.6 (s, 1H); 7.35 (s, 5H)
MS (m/z)	: 165 (M^+), 150, 135, 121, 105, 91, 77.

α-Methylbenzylamine

Yield	: (0.496 gm, 41%)
IR ($CHCl_3$)	: 3500,2500, 1600, 1450, 1300, 1000, 700 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.45 (d,J=7Hz, 3H); 3.1-3.5 (bs, 2H); 4.10-4.25 (q, J = 3.5 Hz, 1H); 7.40 (s, 5H).
MS (m/z)	: 121 (M^+), 120, 106, 79, 66.

4-Methoxyphenylglycine ethyl ester

Yield	: (1.149 gm , 55%)
IR ($CHCl_3$)	: 3500-3300, 1740, 1600,1250, 1050, 820 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.3-1.4 (t, J = 3 Hz, 3H); 4.3 (s, 3H); 4.2-4.4 (q, J = 4 Hz, 2H); 4.45 (s, 1H); 6.9-6.95 (d, J = 8 Hz, 2H); 7.3 - 7.35 (d, J = 8 Hz, 2H).
MS (m/z)	: 209(M^+), 208, 164, 145, 136, 111, 97, 83, 77, 57.

1-Amino-2-methyl-5-(1-methylethenyl)cyclo-hex-2-ene

Yield	: (0.33gm; 22%)
IR ($CHCl_3$)	: 3500,2500, 1610, 1450, 1390, 950, 500 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.2-1.35 (m, 1H); 1.75 (s, 3H); 1.90 (s, 3H); 2.05-2.40 (m, 4H); 3.2-3.3 (dd, J = 3 & 5 Hz, 1H); 4.65 (m, 2H); 6.0-6.1 (m, 1H); 10.1 (bs, 2H).
MS (m/z)	: 151 (M^+), 150, 135, 124, 109, 99, 93, 84, 69 cm^{-1}.

2-Amino-4-(2,6,6-trimethylcyclohex-1-en-yl)but-3-ene

Yield	: (0.55gm; 29%)
IR ($CHCl_3$)	: 3500,3000, 1600, 1450, 940, 500 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 0.7-0.85 (m, 4H); 1.6-1.7 (s, 9H); 2-2.1 (m, 3H); 2.3-2.9 (m, 3H); 4.6 (s, 2H); 5.8 (dd, J = 3 & 5 Hz, 2H); 8.9-9.0 (brs, 2H).
MS (m/z)	: 193 (M^+), 192, 160, 146, 134, 120, 105, 91, 77.

Hydrazobenzene

Yield	: (0.79 gm; 86%)
M.P	: 126°C
IR ($CHCl_3$)	: 3400, 2900, 1600, 1450 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 5.60 (bs, 2H); 6.7-6.8 (m, 4H); 7.05-7.15 (m, 4H); 7.7- 7.65 (m, 2H).

MS (m/z) : 184(M^+), 183, 182, 152, 105, 92, 81, 77, 65.

4,4'-Dimethylhydrazobenzene

Yield : (0.826 gm, 78%)

M.P. : 129.0°C

IR ($CHCl_3$) : 3600, 2900, 1600, 1500 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 2.3 (s, 6H); 6.8 (bs, 2H); 7.4 (d, J = 9 Hz, 4H); 7.65 (d, J = 9 Hz, 4H).

MS (m/z) : 212(M^+), 211, 210, 181, 165, 152, 119, 91, 65.

4,4'-Dimethoxyhydrazobenzene

Yield : (0.976 gm; 80%)

M.P. : 140°C

IR ($CHCl_3$) : 3600, 2900, 1600, 1450 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 3.5 (bs, 2H); 3.6 (s, 6H); 6.85 (d, J = 9 Hz, 4H); 7.22 (d, J = 9 Hz, 4H).

MS (m/z) : 244(M^+), 243, 242, 229, 145, 137, 108.

4,4'-Dichlorohydrazobenzene

Yield : (1.15 gm; 90%).

M.P. : 130°C

IR ($CHCl_3$) : 3550, 2900, 1600, 1500 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 4.00 (bs, 2H); 7.0 (d, J = 9 Hz, 4H); 7.95 (d, J = 9 Hz, 4H).

MS (m/z) : 252(M^+), 251, 250, 217, 182, 127, 99, 73, 64.

4-Aminohydrazobenzene

Yield	: (0.746gm, 75%)
M.P.	: 158°C
IR ($CHCl_3$)	: 3600, 1600, 1450 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 6.8 (bs, 2H); 6.75-6.90 (m, 2H); 7.2-7.3 (m, 1H); 7.4-7.6 (m, 4H); 7.75-7.95 (m, 4H).
MS (m/z)	: 199 (M^+), 198, 197, 167, 120, 92, 77, 65.

Hydrazobenzene 4,4'-dicarboxylic acid

Yield	: (1.10 gm; 81%)
M.P.	: 298°C
IR ($CHCl_3$)	: 3550, 1600, 1420 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 3.5 (bs, 2H); 6.95 (d, J = 9 Hz, 2H); 8.10 (d, J = 9 Hz, 2H).
MS (m/z)	: 272 (M^+), 271, 270, 226, 149, 137, 120, 42, 65.

TRANSDITHIOACETALISATION

EXPERIMENTAL

Purification of Natural Kaolinitic Clay

The kaolinitic clay was procured from the padappakara mine of Quilon District, Kerala, India and it was subsequently purified by separating coarser mineral impurities from clay particles followed by drying and calcination. The 550°C calcined clay samples (1 part by wt) were boiled with 2M HCl (4 parts by wt) for 45 min. The leached samples were then washed free of chloride ions and dried at 110°C for 12 hr.

It was characterised by FT IR, XRD, UV, ESR, SEM, EDX and chemical analysis by AAS. The composition of the clay was determined by wet chemical analysis (in%): SiO_2 = 67.45, Al_2O_3 = 22.2,Fe_2O_3 = 6.1,TiO_2 = 3.45 and K = 0.8.

General procedure for transdithioacetalisation of acetals, ketals and oximes.

A mixture of acetal, ketal or oxime (0.005 mole) ethane or propane dithiol (0.005 mole) and clay (10% by wt of starting material) in either benzene or CCl_4 was refluxed for 4 to 6 hr. After completion of the reaction (TLC) the clay catalyst was filtered off. The filtrate was evaporated to give crude product then purified over silica gel by flash chromatography.

2-(4-Methoxyphenyl)-1,3 dithiane

Clay yield	: (0.99 gm 88%)
SiO_2	: (0.67 gm, 60%)
ZrO_2	: (0.81 gm 72%)
Hβ	: (0.85 gm, 76%)
M.M. Clay	: (0.90 gm, 80%)
IR ($CHCl_3$)	: 2925, 1600, 1500, 1250, 1050 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.82-2.00 (m, 1H); 2.10-2.25 (m, 1H); 2.80-3.15 (m, 4H); 3.80 (s, 3H); 5.15 (s, 1H); 6.83 (d, J = 9 Hz, 2H); 7.43 (d, J = 9 Hz, 2H)
MS (m/z)	: 226 (M^+), 151, 121.

2-(4-Chlorophenyl)-1,3-dithiane

Yield	: (0.92 gm, 80%)
IR ($CHCl_3$)	: 2950, 160, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.80-1.85 (m, 2H); 1.80-3.30 (m, 4H), 5.40 (s, 1H); 7.70 (d, J= 9 Hz, 2H); 7.80 (d, J = 9 Hz, 2H).
MS (m/z)	: 230 (M^+), 155, 74.

2-(2-Nitrophenyl)-1,3-dithiane

Yield	: (0.98 gm, 82%.)
IR ($CHCl_3$)	: 2120, 1210, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.85 -2.30 (m, 2H); 2.70-3.40 (m, 4H); 5.80 (s, 1H); 7.00-7.80 (m, 4H).
MS (m/z)	: 241 (M^+), 166, 106.

2-(2-hydro oxyphenyl)-1,3-dithaine

Yield	: (0.99 gm, 94%)
IR ($CHCl_3$)	: 3200, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.85-2.25 (m, 2H); 2.85-3.15 (m, 4H); 5.25 (s, 1H); 6.80-6.95 (bs, 1H), 7.30-7.40 (m, 4H).
MS (m/z)	: 212 (M^+); 138, 77.

2-(2-Carboxyphenyl)-1,3-dithiane

Yield	: (1.08 gm, 90%)
IR ($CHCl_3$)	: 3500, 1700, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.82-2.15 (m, 2H); 2.80-3.00 (m, 4H); 5.20 (s, 1H); 6.0 (bs, 1H); 7.00-7.95 (m, 4H).
MS (m/z)	: 240 (M^+), 212, 196, 83, 74.

2-(3,4,5-Trimethoxyphenyl)-1,3-dithiane

Yield	: (1.28gm, 90%)
IR ($CHCl_3$)	: 1600, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.80-2.10 (m, 2H); 2.80-3.20 (m, 4H); 3.80 (s, 6H); 3.85 (s, 3H); 5.10 (s, 1H); 6.60 (s, 1H); 7.15 (s, 1H).
MS (m/z)	: 286 (M^+); 196, 125, 78.

2-(3-Methoxy-4-hydroxy-5-nitrophenyl)-1,3-dithiane

Yield	: (1.24 gm, 87%)
IR ($CHCl_3$)	: 3250, 1250, 760 $cm.^{-1}$
^1H NMR (90MHz,$CDCl_3$)	: δ 1.85-2.10 (m 2H); 2.87-3.00 (m, 4H); 3.15 (s, 3H); 5.16 (s, 1H); 6.50 (s, 1H).
MS (m/z)	: 287 (M^+), 213, 37.

2-(3,5-Dimethoxy-4-hydroxyphenyl)-1,3-dithiane

Yield	: (1.26 gm, 92%)
IR ($CHCl_3$)	: 3450, 1600, 760 $cm.^{-1}$
^1H NMR (90MHz,$CDCl_3$)	: δ 1.80-2.10 (m, 2H); 2.80-3.20 (m, 4H); 3.75 (s, 6H); 5.16 (s, 1H); 6.62 (s, 1H); 7.00 (s, 1H).
MS (m/z)	: 276 (M^+), 198, 154, 83, 55.

2-(2-phenylethylidene)-1,3-dithiane

Yield	: (0.87 gm, 79%)
IR ($CHCl_3$)	: 2560, 760 $cm.^{-1}$
^1H NMR (90MHz,$CDCl_3$)	: δ 1.90-2.10 (m, 2H); 2.8-3.00 (m, 4H); 4.76 (d, J = 8 Hz, 1H); 6.10-6.92 (m, 2H); 7.40-7.80 (m, 5H).
MS (m/z)	: 222 (M^+), 147, 131, 77.

2-(-1,3-dithian-2-yl)furan

Yield	: (0.64 gm, 69%)
IR ($CHCl_3$)	: 2900, 1250, 1050, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.85-2.10 (m, 2H); 2.9-3.00 (m, 4H); 5.25 (s, 1H); 6.36 (m, 2H); 7.45 (br, 1H).
MS (m/z)	: 186 (M^+); 121, 112, 84.

2,2-Dimethyl-1,3-dithiane

Yield	: (0.63 gm, 86%)
IR ($CHCl_3$)	: 3100, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.65 (s, 3H); 1.90-2.0 (m, 2H); 2.85-2.90 (m, 4H).
MS (m/z)	: 148 (M^+), 133, 115, 74, 59.

2-(1-Chloromethyl)-1,3-dithiane

Yield	: (0.74 gm, 89%)
IR ($CHCl_3$)	: 3100, 1520, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.85-2.20 (m, 2H); 2.82-2.87 (m, 4H); 3.87 (d, J=7 Hz, 2H); 4.17 (t, J = 7 Hz, 1H).
MS (m/z)	: 168 (M^+), 134, 119, 74.

2-Isopropyl-1,3-dithiane

Yield	: (0.65 gm, 81%)
IR ($CHCl_3$)	: 2560, 1220, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.55 (d, J = 7 Hz, 6H); 2.10-2.50 (m, 2H); 3.10-3.30 (m, 5H); 4.48 (d, J = 7 Hz, 1H).
MS (m/z)	: 162 (M^+), 119, 55.

2- (1-Propenyl)-1,3-dithiane

Yield	: (0.40 gm, 50%)
IR ($CHCl_3$)	: 3150, 1220, 760 $cm.^{-1}$
^1H NMR (90MHz,$CDCl_3$)	: δ 1.70 (d, J = 7 Hz, 3H); 1.75 (m, 2H); 2.80-3.40 (m, 4H); 4.35 (d, J = 7 Hz, 1H); 6.20-6.50 (m, 2H).
MS (m/z)	: 160 (M^+), 85.

1-(1,3-Dithain-2-yl)-propan-2-one

Yield	: (0.68 gm, 75%)
IR ($CHCl_3$)	: 3150,2900,1710,1410,1360,1160 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.70-2.15 (m, 2H); 2.21(s,3H); 2.80-2.95(m,8H); 4.47 (d, J = 9 Hz, 1H);.
MS (m/z)	: 176 (M^+), 133, 119, 91, 73, 59.

4-^{t}Butylcyclohexanone thioketal

Yield	: (0.81 gm, 67%)
IR ($CHCl_3$)	: 3150, 2910, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 0.85 (s, 6H); 0.95 (s, 3H); 0.95-1.92 (m, 6H); 1.95-2.25 (m, 2H); 2.25-2.40 (m, 3H); 2.70-2.90 (m, 4H).
MS (m/z)	: 244 (M^+).

1-(2-Methyl-1,3-dithian-2yl)-propane-2-one

Yield	: (0.74gm, 78%)
IR ($CHCl_3$)	: 3150, 2905, 1715, 750 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.60 (s, 3H); 2.15 (s, 3H); 1.80-2.20 (m, 2H); 2.85-3.00 (m, 4H); 3.1 (s, 2H).
MS (m/z)	: 190 (M^+),147, 133,107, 87, 59.

2-Menthone thioketal

Yield	: (0.97gm, 80%.)
IR ($CHCl_3$)	: 3000, 1410, 1220, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ0.80-1.10 (m, 9H); 1.15-1.60 (m, 5H); 1.65-2.20 (m, 5H); 2.50-3.00 (m, 4H).
MS (m/z)	: 244 (M^+), 159, 137, 81.

Camphor-2-thioketal

Yield	: (0.97gm, 76%)
IR ($CHCl_3$)	: 3150, 760 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 0.90-1.00 (m, 4H); 1.25 (s, 9H); 1.50-1.80 (m, 5H); 1.82 (m, 4H).
MS (m/z)	: 256 (M^+), 217, 69, 55.

Cyclohexanone thioketal

Yield	: (0.79 gm, 91%)
IR ($CHCl_3$)	: 3100, 1100, 910 $cm.^{-1}$
^1H NMR (200MHz,$CDCl_3$)	: δ 1.35-1.45 (m, 2H); 1.55-1.70 (m, 4H); 2.00 (t, J = 6 Hz, 4H); 3.25 (s, 4H).
MS (m/z)	: 174 (M^+), 146, 131.

3-Methylcyclohex-2-enone thioketal

Yield	: (0.69 gm, 75%)
^1H NMR (200MHz,$CDCl_3$)	: δ 1.7 (s, 3H); 1.75-2.00 (m, 4H); 2.1-2.2 (m, 2H); 3.25-3.45 (m, 4H); 5.6 (s, 1H).
MS (m/z)	: 186 (M^+), 158, 126, 111.

2-Phenyl-1,3-dithiolane

Yield : (0.85 gm, 94%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 3.35-3.60 (m, 4H); 5.65 (s, 1H); 7.25-7.40 (m, 3H); 7.45-7.60 (m, 2H).

MS (m/z) : 182 (M^+), 153, 121, 77.

2-(4-Methoxyphenyl)-1,3-dithiolane

Yield : (0.90, 85%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 3.30-3.45 (m, 4H); 3.8 (s, 3H); 5.6 (s, 1H); 6.87 (d, J = 9 Hz, 2H); 7.47 (d, J = 9 Hz, 2H).

MS (m/z) : 212 (M^+), 168, 135.

2-(4-Chlorophenyl)-1,3-dithiolane

Yield : (0.86 gm, 80%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 3.30-3.60 (m, 4H); 5.60 (s, 1H); 7.30 (d, J = 9 Hz, 2H); 7.5 (d, J = 9 Hz, 2H).

MS (m/z) : 216 (M^+), 188, 155, 137.

2-(4-Nitrophenyl)-1,3-dithiolane

Yield : (0.93 gm, 82%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 3.35-3.60 (m, 4H); 5.60 (s, 1H); 7.67 (d, J = 9 Hz, 2H); 8.15 (d, J = 9 Hz, 1H).

MS (m/z) : 227 (M^+); 199, 182, 166,152, 77.

2-(3-Nitrophenyl)-1,3-dithiolane

Yield : (0.95 gm, 84%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 3.3-3.60 (m, 4H); 5.6 (s, 1H); 7.60-8.00 (m, 4H).

MS (m/z) : 208 (M^+), 178, 134, 121, 115, 89.

2-(2-Phenylethylidene)-1,3-dithiolane

Yield : (0.97 gm, 94%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 3.20-3.45 (m, 2H); 5.23 (d, J = 9 Hz, 1H); 6.15-6.25 (d, J = 9 Hz, 1H); 6.50 (d, J = 18 Hz, 1H); 7.20-7.40 (m, 5H).

MS (m/z) : 208 (M^+), 179, 147, 115.

Butyl-1,3-dithiolane

Yield : (0.58 gm, 79%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 0.7-1.5 (t, 3H); 1.2-1.75 (m, 4H); 2.2-2.35 (m, 1H); 2.85-2.95 (t, 4H).

MS (m/z) : 148 (M^+), 134, 120, 111, 105, 85.

2-Phenyl-1,3-oxadithiolane

Yield : (0.74 gm, 76%)

IR ($CHCl_3$) : 2950, 1600, 1050, 820, 720 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 3.3 (m, 2H); 3.80 (s, 3H); 4.0-4.5 (m, 2H); 6.1 (s, 1H); 6.83 (d, J = 9 Hz, 2H); 7.43 (d, J = 9 Hz, 2H)

MS (m/z) : 196 (M^+), 168, 154, 92.

Experimental

Preparation of 2-oxazolines

Method A A mixture of aromatic nitrile (0.005 mole), 2-amino methyl propanol (0.04 mole) and 20 mg (10% wt of starting material)of clay catalyst were refluxed for 24 hr. After the complition of reaction, the mixture was diluted with dichloromethane and clay catalyst was filtered off. The dichloromethane layer then washed with water followed by brain solution and then dried over Na_2SO_4. concentrate the dichloromethane layer and purified the residue over nutral alumina by flash column chromatography.

Method B A mixture of aromatic nitrile (0.005 mole) , 2-amino methyl propanol(0.04 mole) and 20 mg(10% wt of starting material) of clay catalyst in o-dichlorobenzene (10ml) refluxed for 24 hr. After reaction (TLC) the reaction mixture poured into dichloromethane and clay catalyst was filtered off and washed with dichloromethane (3 x 20 ml) the combined dichloromethane layer washed with water followed by brain solution and dried over Na_2SO_4 the organic layer then concentrated and purified by column chromatography.

Phenyl (4,4'-dimethyl)-2-oxazoline

Yield : (0.73 gm; 86%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.40 (s, 6H); 4.1 (s, 2H); 7.10-7.4 (m, 3H); 7.8-7.9 (m, 2H).

MS (m/z) : 175 (M^+), 160, 104, 76.

4-Pyridinyl-(4,4'-dimethyl)-2-oxazoline

Yield : (0.84 gm; 96%) dichlorobenzene (0.70 gm; 80%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.40 (s, 6H); 4.1 (s, 2H); 7.45 (d, J = 8 Hz, 2H); 8.62 (d, J = 8 Hz, 2H).

MS (m/z) : 176 (M^+), 161, 105

3-Pyridinyl (4,4'-dimethyl)-2-oxazoline

Yield : (0.83 gm, 95%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.40 (s, 6H); 4.05 (s, 2H); 7.2-7.4 (m, 1H); 8.02-8.2 (m, 1H); 8.6-8.65 (m, 1H); 9.0-9.1 (m, 1H).

MS (m/z) ; 176 (M^+), 161, 133, 105.

2-Pyridinyl (4,4'-dimethyl)-2-oxazoline

Yield : (0.83 gm, 95%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.40 (s, 6H); 4.05 (s, 2H); 7.2-7.4 (m, 1H); 7.6-7.8 (m, 1H); 7.85-8.0 (m, 2H); 8.6-8.65 (m, 1H).

MS (m/z) : 176 (M^+), 161, 144, 133, 105, 78.

4-Nitrophenyl (4,4'-dimethyl)-2-oxazoline

Yield : (1.02 gm, 93%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.40 (s, 6H); 4.05 (s, 2H); 8.15 (d, J = 9 Hz, 2H); 8.35 (d, J = 9 Hz, 2H).

MS (m/z) : 220 (M^+), 205, 190, 149.

4-Methoxylphenyl (4,4'-dimethyl)-2-oxazoline

Yield : (0.890 gm, 87%) dichlorobenzene (0.7175 gm, 70%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.4 (s, 6H); 3.8 (s, 3H); 4.1 (s, 2H); 6.8 (d, J = 9 Hz, 2H); 7.8 (d, J = 9 Hz, 2H).

MS (m/z) : 205 (M^+), 190, 162, 134.

4-Methylphenyl (4,4'-dimethyl)-2-oxazoline

Yield	: (0.77 gm, 82%)
^{1}H NMR (200MHz,$CDCl_3$)	: δ 1.4 (s, 6H); 2.6 (s, 3H); 4.1 (s, 2H); 7.3 (d, J = 8.5 Hz, 2H); 7.7 (d, J = 8.5 Hz, 2H).
MS (m/z)	: 189 (M^+), 190, 136, 76.

4-Chloro-(4,4'-dimethyl)-2-oxazoline

Yield	: (0.78 gm, 75%) in dichlorobenzene (0.68 gm, 66%)
^{1}H NMR (200MHz,$CDCl_3$)	: δ 1.4 (s, 6H); 4.1 (s, 2H); 7.25 (d, J = 9 Hz, 2H); 7.75 (d, J = 9 Hz, 2H).
MS (m/z)	: 209 (M^+), 194, 138, 111.

Furyl-(4,4'-dimethyl)-oxazoline

Yield	: (0.74 gm, 90%)
^{1}H NMR (200MHz,$CDCl_3$)	: δ 1.40 (s, 6H); 4.1 (s, 2H); 6.41-6.45 (m, 2H); 6.9-6.92 (m, 1H); 7.45-7.46 (m, 1H).
MS (m/z)	: 165(M^+), 149, 135, 121, 94.

1,2-Bis-(4,4'-dimethyloxazoline 2yl)-benzene

Yield	: (1.15 gm, 85%)
^{1}H NMR (200MHz,$CDCl_3$)	: δ 1.4 (s, 12 H); 4.1 (s, 4H); 7.4-7.45 (m, 2H); 7.65-7.7 (m, 2H).
MS (m/z)	: 272(M^+), 257, 216, 185, 130, 102.

1,2-Bis-(4,4'-diemthyl-2-oxazoline-2-yl)-propane

Yield	: (0.945 gm, 90%)
^{1}H NMR (200MHz,$CDCl_3$)	: δ 1.30 (s, 6H); 3.6 (s, 2H); 4.0 (s, 2H).

MS (m/z) : 210(M^+), 208, 193, 137.

4-Chlorobutyl-2-oxazoline

Yield : (0.49 gm, 56%)

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.29 (s, 6H); 1.9-2.1 (m, 2H); 2.4 (t, J = 7 Hz, 2H); 3.45 (t, J = 7 Hz, 2H); 4.1 (s, 2H).

MS (m/z) : 175(M^+), 139, 126, 86, 58.

(4S-4-Isopropyl-2(2-pyridinyl)-2-oxazoline

Yield : (0.60 gm, 64%) $[\alpha]_D$ = (-)105° (C = 5 , $CHCl_3$)

^{1}H NMR (200MHz,$CDCl_3$) : δ 0.88 (d, J = 3 Hz, 3H); 0.99 (d, J = 3Hz, 3H); 1.8 - 1.9 (m, 7H); 4.02-4.1 (m, 2H); 4.4-4.50 (m, 1H); 7.25-7.30 (m, 1H); 7.6 - 7.8 (m, 2H); 7.9-8.0 m, 1H); 8.6-8.65 (m, 1H).

MS (m/z) : 190(M^+), 147, 119, 104, 92, 77.

2-Methyl-2'(4,4'-dimethyl-2'-oxazoline) propionitrile

Yield : (0.63gm,76%)

IR ($CHCl_3$) : 1550, 2100 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.25 (s, 6H); 1.55 (s, 6H); 3.95 (s, 2H).

MS (m/z) ; 166 (M^+), 151, 136, 121, 98.

Analysis :Cal C; 65.06; H, 8.4; N, 16.86

Obs C, 65.32; H, 8.8; N, 16.92

2-Ethyl-2'-(4,4'-dimethyl-2'-oxazoline)butyronitrile

Yield : (0.87gm,90%)

IR ($CHCl_3$) : 2110, 1560 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.0-1.1 (m, 6H); 1.3 (s, 6H); 1.8-1.95 (m, 4H); 4.0 (s, 2H).

MS (m/z) : 194(M^+), 179, 166, 121, 84.

^{13}C NMR : 162 (s), 119 (s), 80(t), 66(s), 45 (s), 30(t), 28(q), 10(q).

Cyano-1'-(4,4'-dimethyl-2-oxazoline) cyclobutane

Yield : (0.75gm, 82%)

IR ($CHCl_3$) : 2150, 1550 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.65 (s, 6H); 2.4-2.65 (m, 2H); 2.9-3.1 (m, 4H); 4.39 (s, 2H).

MS (m/z) : 181(M^+), 165, 137, 80.

2-Allyl-2'(4,4'-dimethyl-2-oxazoline) pent-4-en-nitrile

Yield : (0.98 gm,91%)

IR ($CHCl_3$) : 2220, 1520$cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.2 (s, 6H); 2.5-2.65 (m, 4H); 3.95 (s, 2H); 5.1-5.25 (m, 4H); 5.65-5.9 (m, 2H).

MS (m/z) : 218(M^+), 203, 178, 123.

2-Benzyl-3-phenyl-2'(4,4'-dimethyl-2-oxazoline) propionitrile

Yield : (1.46 gm, 92%) microwave (1.43 gm, 90%) heat

IR ($CHCl_3$) : 2100, 1600 $cm.^{-1}$

M.P. : 110°C

^{1}H NMR (200MHz,$CDCl_3$) : δ 1.5 (s, 6H); 3.2 (dd, J =12.0 and16.2 Hz, 4H); 3.85 (s, 2H); 7.2-7.45 (m, 10H).

^{13}C NMR : 160.6 (s), 134(s), 130.13(d), 128.35 (d), 127.72 (d), 119.15 (d), 76.43 (t), 6.81 (s), 47.09 (s), 43.4 (t), 28.04 (q).

MS (m/z) : 318(M^+), 227, 173, 156, 91.

Analysis :**Cal.** C, 79.24; H, 6.92; N, 8.085

Obs. C, 79.75; H, 7.12; N, 8.80

2-(2-Methylenepyridyl)-[2'-(4,4'-dimethyl-2-oxazoline)-3-(2-pyridyl)]propionitrile

Yield	: (1.25 gm, 80%)
IR ($CHCl_3$)	: 2100, 1600 $cm.^{-1}$
M.P.	: 63°C
^1H NMR (200MHz,$CDCl_3$)	: δ 1.1 (s, 6H); 3.45 (dd, J = 13.5Hz and 16.2Hz, 4H); 3.95 (s, 2H); 7.1-7.2 (m, 2H); 7.35-7.4 (m, 2H); 7.6-7.7 (m, 2H); 8.5-8.6 (m, 2H).
MS (m/z)	: 320(M^+), 305, 228, 95, 15.

2-Cyano-2'(4,4'-Dimethyl-2-oxazoline) indane

Yield	: (0.94gm,78%) under microwave (1.1gm, 93%)
IR ($CHCl_3$)	: 2180, 1600 $cm.^{-1}$
M.P.	: 83°C
^1H NMR (200MHz,$CDCl_3$)	: δ 1.3 (s, 6H); 3.8 (dd, J = 10.8 and 16.5 Hz, 4H); 4.1 (s, 2H); 7.2-7.3 (m, 4H).
MS (m/z)	: 240(M^+), 141, 115, 92.

Cyclic benzyl mono isopropyl oxazoline:

^1H NMR (200MHz,$CDCl_3$)	:δ0.85(d, J = 5.4Hz, 3H) ; 0.90 (d, J=5.4Hz, 3H) ; 1.70-1.90 (m, 1H), 3.7 (dd, J=18.8 and 23.5 Hz, 4H);4.0-4.1 (m, 1H); 4.1-4.2 (m,1H) 4.3-4.4 (m,1H)7.2-7.3 (m, 4H).

Benztl mono isopropyl oxazoline:

^1H NMR (200MHz,$CDCl_3$)	: δ 0.75 (d, J = 5.4Hz, 3H); 0.85 (d, J = 5.4Hz, 3H);1.5-1.65 (m, 1H) 3.2 (dd, J = 13.5 and 14 Hz, 4H); 3.7-3.8 (m, 1H); 3.85-3.95 (m, 1H); 4.2-4.3 (m, 1H); 7.35 (s, 10H).

1. ***2-[3-Cyano-3-pentyl]-4,4-dimethyl-1,3-oxazoline, 2:*** A mixture of 2,2-diethylmalononitrile (0.20 g; 1.64 mmol), 2-amino-2-methyl propanol (1.20 g; 12.8 mmol) and kaolinitic clay (0.04 g; 20 % w/w) was stirred at 160-65 °C for 16 h. The reaction mixture was diluted with dichloromethane (30 mL), the catalyst was filtered and washed with same solvent and the combined organic extract was washed with water, brine and dried on Na_2SO_4. The residue was purified by column chromatography on neutral alumina to afford the pure oxazoline 2 as oil

Yield : (0.25 g; 90% yield).

^{1}H NMR (200MHz,$CDCl_3$) : δ^H 1.00 (t, J = 7.0 Hz, 6H), 1.25 (s, 6H), 1.75 – 1.95 (m, 4H), 3.95 (s, 2H).

MS (m/z) : 195 (M^++1, 3), 179 (65), 166 (75), 151 (100), 135 (25), 121 (39), 96 (45).

2. ***2-[3-(N-Acetylaminomethyl)-3-pentyl]-4,4-dimethyl-1,3-oxazoline,3:*** Compound 2 (0.15 g; 0.77 mmol) Raney nickel catalyst (0.05 g) were stirred in acetic anhydride (5 mL) and sodium acetate(63mg, 0.77mmol) at 50 psi pressure of hydrogen gas for 7 h at ambient temperature. The reaction mixture was taken up in chloroform (20 mL), the catalyst was filtered and the product was isolated by usual work up to afforded pure 3 after chromatography over neutral alumina.

Yield : (0.14 g; 80 % yield)

IR (Nujol) : ν 3383, 1654, 1561, 1218 $cm.^{-1}$

^{1}H NMR (200MHz,$CDCl_3$) : δ^H 0.85 (t, J = 7.0 Hz, 6H), 1.30 (s, 6H), 1.55 – 1.65 : (m, 4H), 2.00 (s, 3H), 3.40 (d, J = 7.1 Hz, 2H), 3.95 (s, 2H), 6.65 (b s, 1H).

MS (m/z) : 241 (M^++1, 2), 240 (M^+, 1), 225 (5), 169 (30), 154 (100).

3. ***2,2-Diethyl-3-N-acetylamino propionic acid ethyl ester, 4:*** A mixture of compound 3 (0.10 g; 0.41 mmol) and catalytic amount of concentrated sulfuric acid

in ethanol (5 mL) was refluxed for 8 h. After the reaction was over the solvent was evaporated and product isolated by usual procedure and purified by column chromatography to give 4

Yield	: (0.05 g; 55 % yield).
IR (Nujol)	: ν 3300, 1700, 1650, 1420 $cm.^{-1}$
^{1}H NMR (200MHz,$CDCl_3$)	: δ^H 0.85 (t, J = 7.0 Hz, 6H), 1.25 (t, J = 7.1 Hz, 3H), 1.50 - 1.65 (m, 4H), 1.98 (s, 3H), 3.42 (d, J = 7.1 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 5.95 (b s, 2H)
MS (m/z)	: 215 (M^+,5), 186(12), 170(12), 144(100), 129(5), 101(60), 21 (45).

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Publications

1. "Regiospecific acylation of aromatic compounds and selective reduction of azobenzenes over hydratedzirconia"
   M.L.Patil, **G.K.Jnaneshwar**, D.P.Sabde, M.K.Dongre, A.Sudalai and V.H.Deshpande *Tetrahedron Lett*,**1997**,*38*,2137.
2. "Palladium catalysed transfer hydrogenation of azobenzenes and oximes using Ammoniumformate"
   G.K.Jnaneshwar, A.Sudalai and V.H.Deshpande *J.Chem.Research(s)*, **1998**,160
3. "Transdithioacetilation of acetals,ketals,oximes,enamines and tosylhydrazones catalyzed by Natural Kaolinitic Clay"
   G.K.Jnaneshwar, N.B.Bharate, A.Sudalai and V.H.Deshpande R.D.Wakharkar, A.S.Gajare, M.S.Shingare, R.Sukumar *J.Chem.Soc. Perkin Trans 1*, **1998**,965.
4. "Natural Kaolinitic Clay catalyzed conversion of nitriles to 2-oxazolines"
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5. Clay catalyzed conversion of 2,2 disubstituted malononitriles to 2-oxazolines:towards unnatural aminoacids
   G.K.Jnaneshwar, V.H.Deshpande and A.V.Bedekar *J.Chem.Research*(s) (communicated).
6. Rapid microwave methadology to prepare isatin and synthesis of convolutamydine A.
   G.K.Jnaneshwar, A.V.Bedekar,and V.H.Deshpande *Synthetic communication* (accepted).
7. Convolutamydine A starting from isatin
   G.K.Jnaneshwar, and V.H.Deshpande (manuscript under preparation).
8. Preparation of CD ring of camptothiceine starting from commercial β-alanine.
   G.K.Jnaneshwar, and V.H.Deshpande (manuscript under preparation).

Poster Presented:

1. International conference on Organic Synthesis(IUPAC),Bangalore,India.Dec.11-16,1994.page no.181 (P-THU-8)
   "Synthetic approaches directed towards Camptothecein" by D.E Ponde,N.J Ghokale,**G.K Jnaneshwara**,H.B Borate and V.H Deshpande.

2. International conference on Organic Synthesis(IUPAC),Bangalore,India.Dec.11-16,1994. Page no.181 (P-THU-7)
   "Regiospecific Synthesis of Saintopin" by **G.K Jnaneshwara**,Beena Rai,H.B Borate and V.H Deshpande.