# SYNTHETIC STUDIES ON RESORTHIOMYCIN, CAMPTOTHECIN AND APPLICATION OF HETEROGENEOUS CATALYSTS IN ORGANIC TRANSFORMATIONS

**A THESIS**
SUBMITTED TO THE
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(IN CHEMISTRY)

BY

**D.E. PONDE**

DIVISION OF ORGANIC CHEMISTRY : TECHNOLOGY
NATIONAL CHEMICAL LABORATORY
PUNE-411 008

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# CERTIFICATE

Certified that the work incorporated in the thesis entitled *'Synthetic Studies on **Resorthiomycin, Camptothecin and Application of Heterogeneous Catalysts in Organic Transformations"*** by ***D.E. Ponde*** was carried out by the candidate under my supervision. Such material as had been obtained from sources has been duly acknowledged in the thesis.

V.H. Deshpande

August 1998

(V.H. Deshpande)

RESEARCH GUIDE

**DEDICATED TO THE FOND MEMORY OF MY MOTHER**

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*At this juncture my mind is travelling fast and I remember my brothers and sisters, who have been a constant source of encouragement to me and blessed me throughout. I am particularly very much thankful to my brother Mr. Vishvanath Ponde and brother-in-law Mr. Sureshrao Bhalsing for their financial support. My special thanks and love go to my wife, Manisha, for her much needed moral support and constant encouragement.*

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*August 1998* ***(D. E. PONDE)***

*National Chemical Laboratory*
*Pune 411 008 (India)*

## GENERAL REMARKS

1. All the temperatures are in °C. All the melting points and boiling points are in °C and are uncorrected.

2. PMR spectra were recorded either on Varian T-60, FT-80A, Brucker WH-90, WH-200 or MSL 300 MHz instruments in $CDCl_3$ solution containing TMS as in internal standard with chemical shift ($\delta$) expressed in ppm downfield from TMS. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad.

3. Infra-red spectra ($\nu$ max in $cm^{-1}$) were recorded as either thin film or nujol mull on Perkin-Elmer Infra-red 683B or 160S FT IR spectrometer with sodium chloride optics.

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

5. All solvents and reagents were purified and dried by standard procedures. All evaporations were carried out under reduced pressure on Buchi rotary evaporator.

6. TLC was carried out on silica gel plates prepared by spreading the slurry (in $CCl_4$) and drying at room temperature. The plates were analysed by keeping in iodine chamber.

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

8. GLC was carried out on Hewlett Packard 5890.

9. Column chromatography was performed on silica gel (60-120 mesh) or on neutral alumina. Petroleum ether refers to the fraction boiling in the range 60-80°C.

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

# ABBREVIATIONS

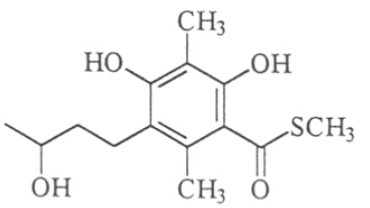
| | | |
|---|---|---|
| Ac | : | Acetyl |
| Ar | : | Aryl |
| Bn | : | Benzyl |
| bp | : | Boiling point |
| *t*-Bu | : | *tert*-Butyl |
| $CDCl_3$ | : | Deutrated chloroform |
| DCC | : | N,N-Dicyclohexylcarbodiimide |
| DEGS | : | Diethylene glycol succinate |
| DIBAL-H | : | Diisobutylaluminium hydride |
| DMAP | : | 4-(Dimethylamino)pyridine |
| DME | : | 1,2-Dimethoxyethane |
| DMF | : | Dimethylformamide |
| DMSO | : | Dimethylsulphoxide |
| IR | : | Infra-red |
| LAH | : | Lithium aluminium hydride |
| Me | : | Methyl |
| min | : | Minute(s) |
| mp | : | Melting point |
| Ms | : | Methanesulphonyl (mesyl) |
| nm | : | Nanometer |
| NBS | : | N-bromosuccinamide |
| NMR | : | Nuclear Magnetic Resonance |
| PCC | : | Pyridinium chlorochromate |
| Ph | : | Phenyl |
| p-TSA | : | p-Toluenesulphonic acid |
| $Et_3SiH$ | : | Triethylsilane |
| $Bu_3SnH$ | : | Tributyltinhydride |

# ABSTRACT

The thesis entitled "**Synthetic Studies on Resorthiomycin, Camptothecin and Application of Heterogeneous Catalysts in Organic Transformations**" is divided into three chapters.

## CHAPTER I: SYNTHETIC STUDIES ON RESORTHIOMYCIN

Resorthiomycin **1**, a novel antitumor antibiotic was isolated from the fermentation broth of a strain of *Streptomyces collinus*.[1] Resorthiomycin exhibited *in vitro* cytotoxic activity against mouse leukemia L5178 Y cells. Its novel hexasubstituted skeleton coupled with biological activity prompted us to take up its synthesis. The efforts directed towards the total synthesis of resorthiomycin are discussed in Section A and B. Section C describes mild and efficient method for thiol-esterification.



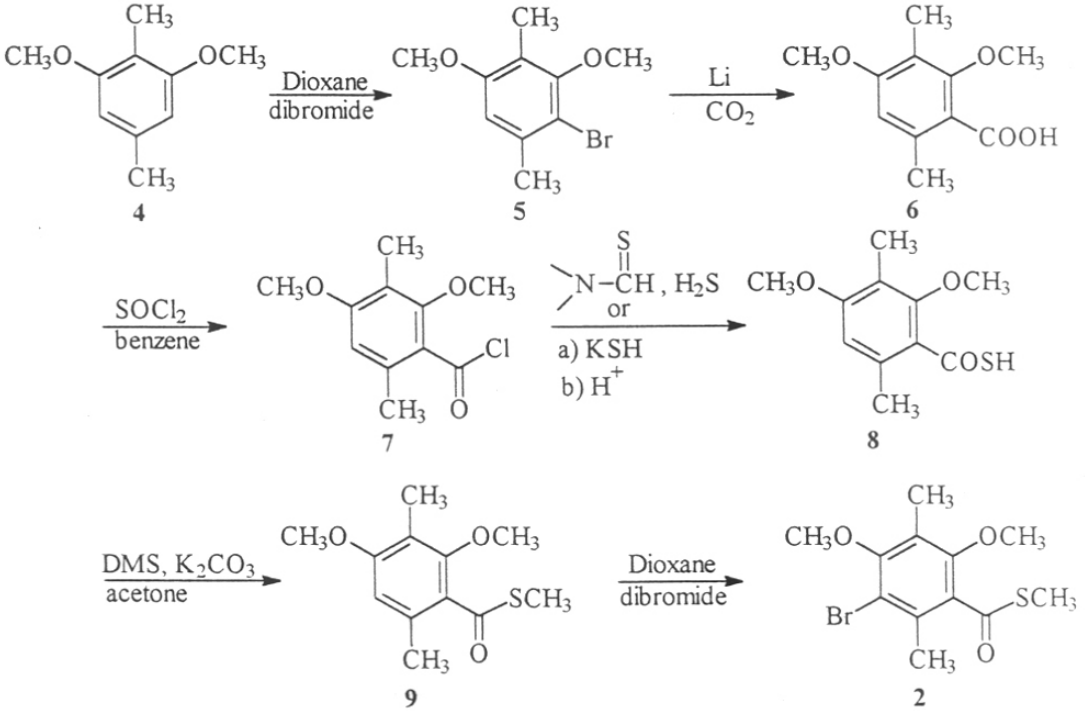

**1**

### Section A: Attempted synthesis of resorthiomycin

The synthesis of resorthiomycin by the carbon-carbon bond formation through Wurtz-Fittig or Heck coupling reaction of the substituted methyl thiobenzoate **2** with 3-(1,3-dithiolane)-1-bromobutane (**3**) or methyl vinyl ketone attracted us because of the ability of this approach to produce resorthiomycin by convergent synthesis, which if successful could be elaborated to asymmetric synthesis of resorthiomycin. The key intermediate **2** could be obtained from 1,3-dimethoxy-2,5-dimethylbenzene (**4**) while the protected butanone **3** could be obtained from methyl acetoacetate.

The substituted methyl thiolbenzoate **2** was prepared as shown in Scheme-1. 1,3-Dimethoxy-2,5-dimethylbenzene (**4**) prepared by known method[2] was subjected to bromination by dioxane-dibromide in ether to afford bromo derivative **5**. Lithiation of **5** followed by quenching it with dry ice gave resorcillinic acid **6**. The acid **6** was subjected to reaction with thionyl chloride followed by treatment with potassium hydrogen sulfide to yield the corresponding thiol acid **8** which was esterified using dimethyl sulfate and potassium carbonate to furnish the thiol ester **9**. The thiol ester **9** was brominated using dioxane-dibromide to give required substituted methyl thiolbenzoate **2.**

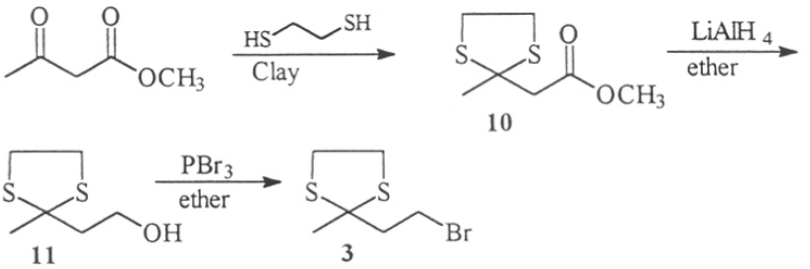
**Scheme 1**



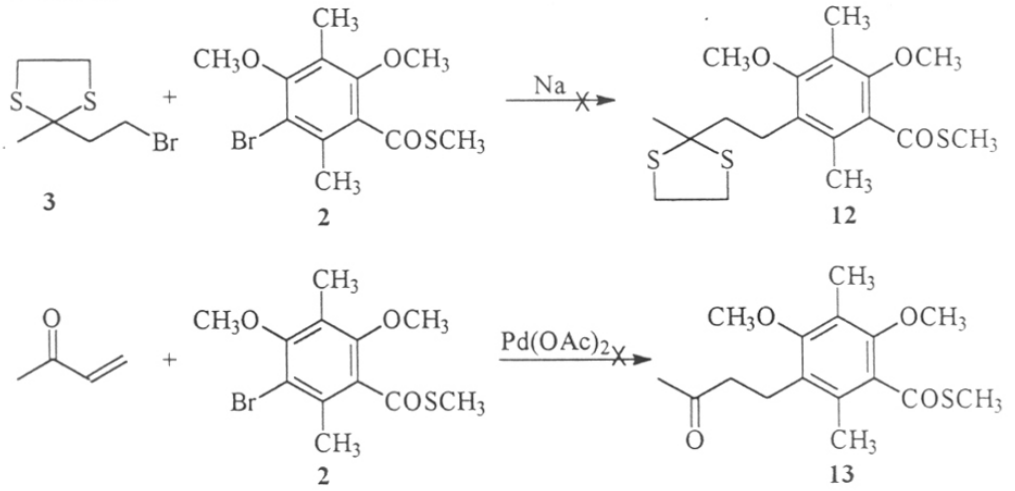

The protected butanone **3**, the other required synthon for Wurtz reaction was prepared as shown in Scheme 2. Methyl acetoacetate was protected using ethanedithiol over natural kaolinitic clay which underwent lithium aluminium hydride reduction to afford alcohol **11**. The alcohol **11** was converted into 3-(1,3-dithiolane)-1-bromobutane (**3**) using phosphorous tribromide.

The coupling of the two bromo derivatives **2** and **3** was attempted with sodium. However the desired alkylated product **12** could not be obtained. Heck coupling reaction between methyl vinyl ketone and substituted methyl thiolbenzoate **2** was found to be unsuccessful (Scheme-3).

**Scheme 2**




**Scheme 3**

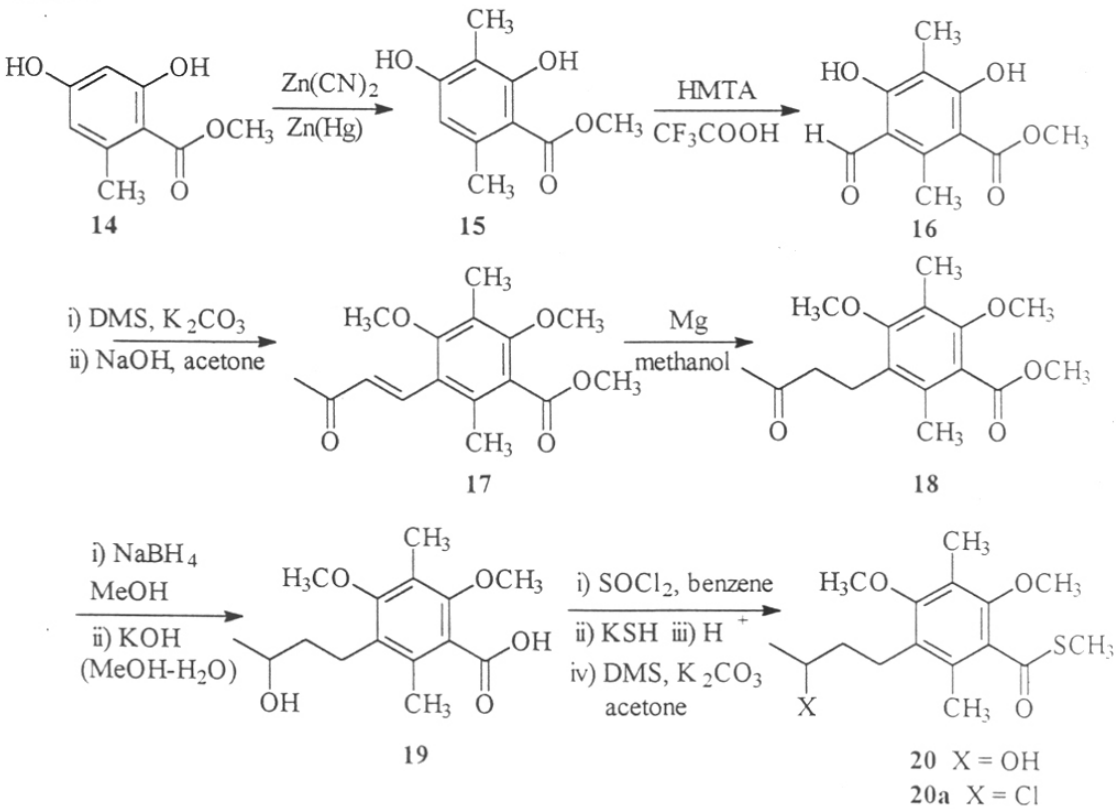



**Section B: Total synthesis of resorthiomycin**

This section describes the successful synthesis of (±) resorthiomycin. Methyl orsellinate (**14**) was prepared by known methods[3] and subjected to modified Gatterman condition to afford an intermediate aldehyde which on Clemmensen reduction gave β-orcinolcarboxylate (**15**) (Scheme-4). It was further formylated by hexamethylene tetramine to afford hexasubstituted benzaldehyde **16**. The aldehyde **16** was subjected to methylation using dimethyl sulfate-potassium carbonate followed by condensation with

acetone in the presence of sodium hydroxide to afford α,β-unsaturated ketone **17**. Reduction of **17** with magnesium in methanol furnished keto-ester **18**. Sodium borohydride reduction of **18** followed by hydrolysis resulted in the formation of acid **19**. In an attempt to prepare resorthiomycin dimethyl ether, the acid **19** was first treated with thionyl chloride followed by potassium hydrogen sulfide. The acidic product obtained was esterified with dimethyl sulfate and potassium carbonate to yield thiol ester. The spectroscopic and analytical data of the thiol ester showed that the chloroderivative **20a** was formed instead of the required hydroxy compound **20.**

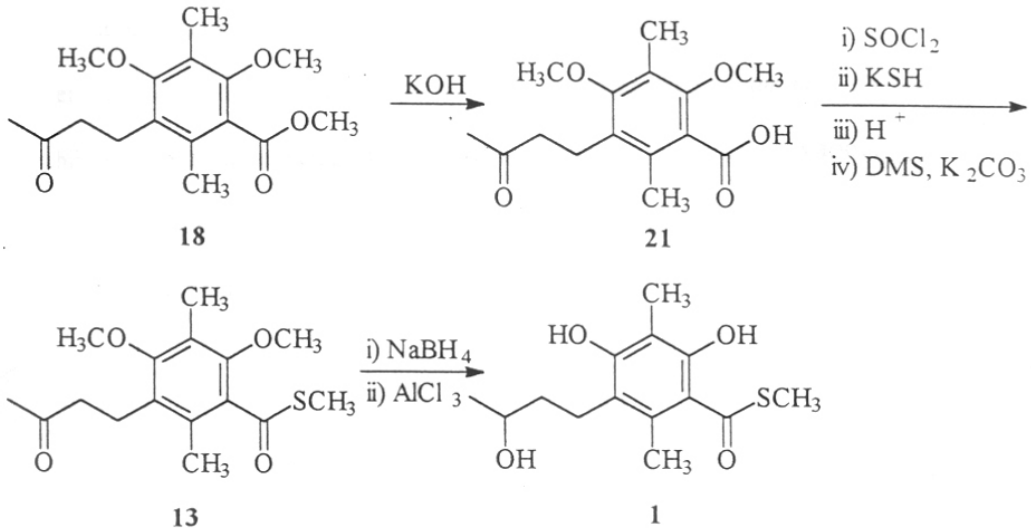
**Scheme 4**




In order to circumvent this problem, the ketoester **18** was hydrolysed to afford the corresponding keto-acid **21** (Scheme-5) which was converted into keto-thiol ester **13** by sequential reactions with thionyl chloride followed by treatment with potassium hydrogen sulfide and esterification with dimethyl sulphate and potassium carbonate. The

keto-thiol ester **13** was subsequently reduced with sodium borohydride and demethylated with $AlCl_3$ to afford (±) resorthiomycin **1**.

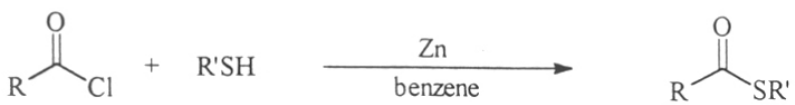
**Scheme 5**




**Section C: Mild and efficient method for thiol esterification**

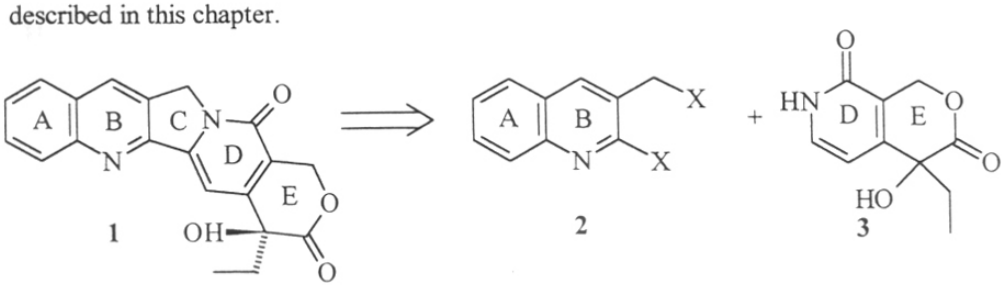
In search of a new method for thiol esterification during the synthesis of resorthiomycin it was observed that acid chloride in presence of zinc undergoes reaction with thiol to afford the corresponding thiol esterified product. Aromatic, aliphatic and heteroaromatic acids undergo thiol esterification with various thiols in almost quantitative yield. Another important feature of this methodology is that even unsaturated acids undergo thiol esterification without isomerisation of double bond.

**Scheme 6**



# CHAPTER -II : SYNTHETIC STUDIES ON CAMPTOTHECIN AND ITS INTERMEDIATES

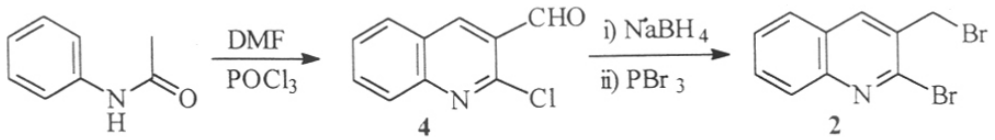
Camptothecin (**1**), a pentacyclic antitumor alkaloid, was isolated by Wall and co-workers[4] in 1966 from the stem wood of the tree *Camptotheca acuminata* (Nyssaceae). It exhibits potent antileukemic and antitumor activities in animals. Various synthetic approaches attempted for the preparation of camptothecin and its intermediates are described in this chapter.




**Route A: Photochemical reaction approach**

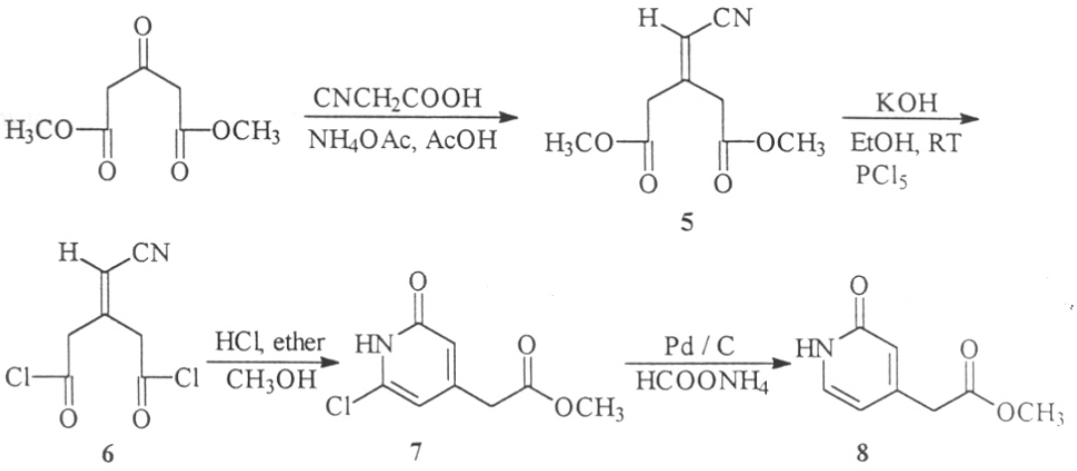
This approach is centered on the construction of ABCD ring synthon of camptothecin *via* C-N and C-C bonds formation between AB and D ring synthons (Scheme-3).The AB ring synthon **2,** prepared from 2-chloro-3-quinolinecarboxaldehyde (**4**) (Scheme 1) which in turn was obtained by reaction of acetanilide with N,N-dimethyl formamide in phosphorous oxychloride. Thus the aldehyde **4** was reduced with sodium borohydride to afford the corresponding alcohol which was converted to the dibromoquinoline derivative **2** using phosphorous tribromide.

**Scheme 1**



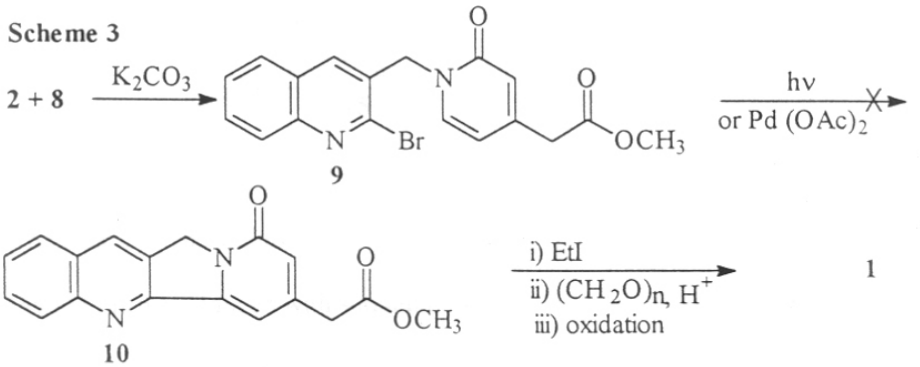
The D ring precursor pyridone derivative **8** was prepared as shown in Scheme 2. Condensation of dimethyl acetonedicarboxylate with cyanoacetic acid afforded the diester **5** which underwent hydrolysis followed by phosphorous pentachloride reaction to yield the diacid chloride **6**. Addition of HCl gas followed by cyclisation gave the chloropyridone **7**. It was dehalogenated to furnish the desired pyridone derivative **8**.

**Scheme 2**




The condensation of pyridone **8** with 2-bromo-3-bromomethylquinoline (**2**) in presence of potassium carbonate in acetonitrile gave the N-alkylated pyridone **9** in good yield (Scheme 3). Attempts were made to construct the ABCD rings of camptothecin by photochemical as well as intramolecular Heck cyclisation of the intermediate **9** to obtain **10** from which the total synthesis of camptothecin is known.

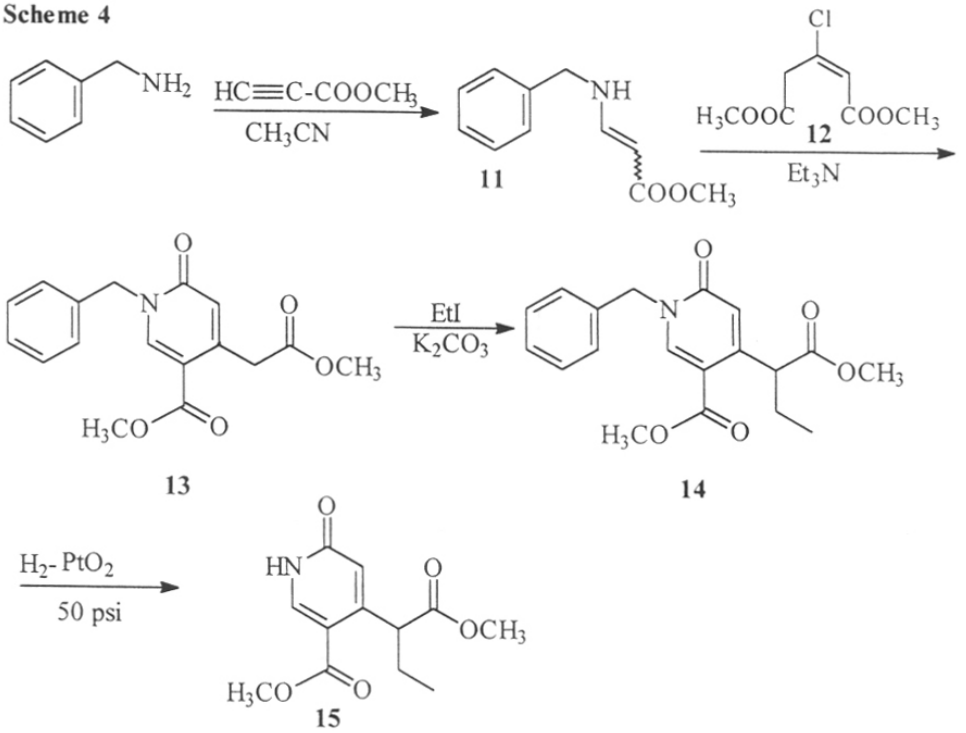
**Scheme 3**



**Route B: Intramolecular Heck reaction approach**

The key step of this approach is Heck reaction to couple AB ring synthon with D ring. Pyridone derivative **15**, the D ring synthon, was prepared from benzyl amine as shown in Scheme 4. Benzyl amine on Michael type addition with methyl propiolate afforded an adduct **11**. This underwent crucial cyclisation with dimethyl 3-chloro-2-pentenedioate (**12**) to afford an intermediate cyclised product **13**. It was ethylated using ethyl iodide and potassium carbonate to furnish **14**, which was debenzylated by hydrogenolysis with platinum dioxide at 50 psi in acetic acid to afford pyridone **15**.

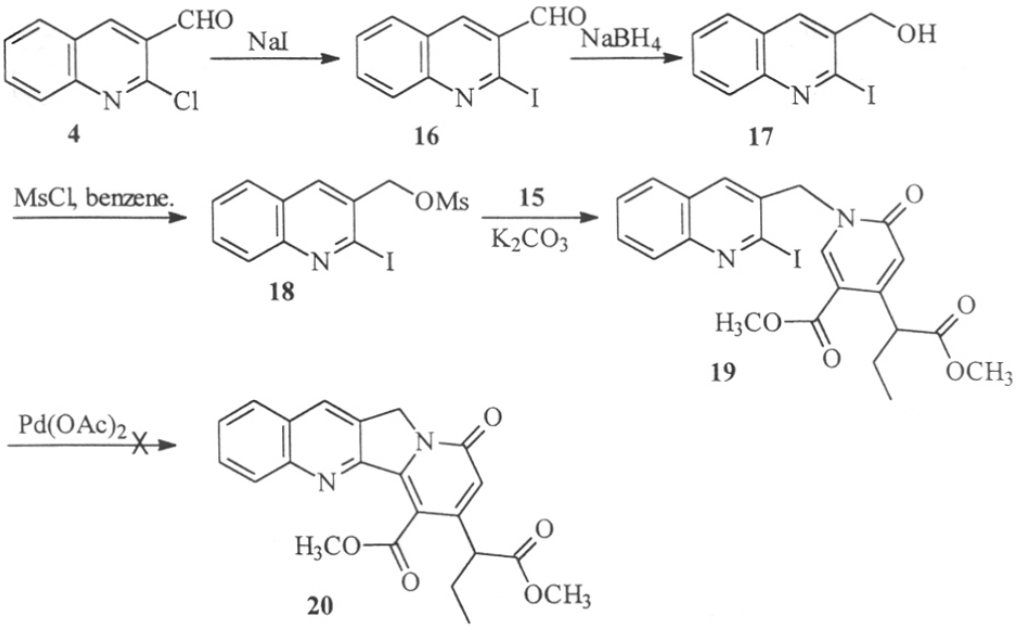
**Scheme 4**




The AB ring synthon **18** was prepared from 2-chloro-3-quinolinecarbaldehyde (**4**) (Scheme-5). The Chloroaldehyde **4** was converted into iodo-aldehyde **16** using sodium iodide. It was reduced with sodium borohydride to furnish the corresponding alcohol **17** which was subjected to reaction with methane sulfonyl chloride to afford mesyl derivative **18**. It was condensed with the pyridone **15** using potassium carbonate in

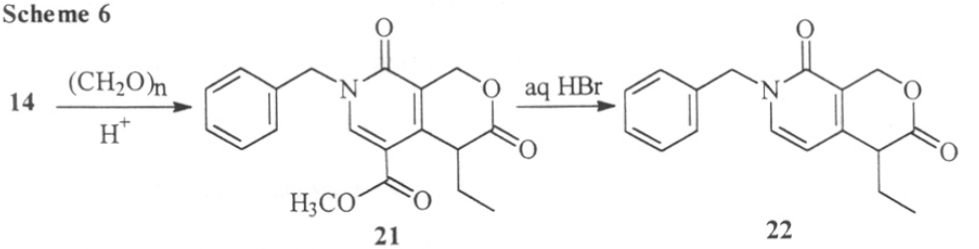
furnish N-alkylated product **19**. Various reaction conditions including catalysts, bases, solvents for intramolecular Heck reaction were tried, however, all efforts failed to give desired product **20**.

**Scheme 5**



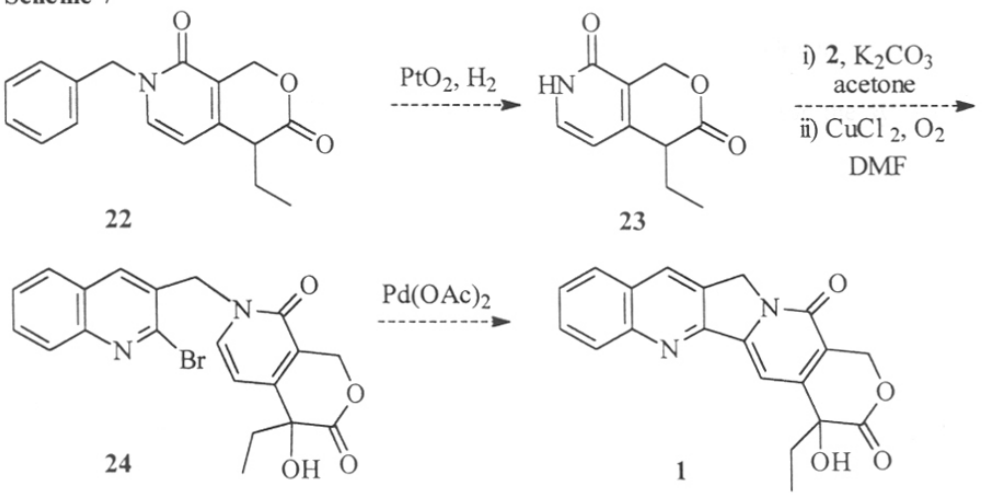

Comins et al.[5] used intramolecular Heck reaction for converting an intermediate **24** into **1**. In order to obtain the intermediate **24**, the ethylated product **14** was hydroxymethylated using paraformaldehyde to afford lactone **21** as shown in Scheme 6. Lactone **21** was decarbomethoxylated using aq. hydrobromic acid to yield decarbomethoxylated product **22**.

**Scheme 6**



Debenzylation of compund **22** and further N-alkylation with dibromo derivative **2** using potassium carbonate followed by oxidation and intramolecular Heck reaction would yield camptothecin (Scheme-7).

**Scheme 7**




## CHAPTER III: APPLICATION OF HETEROGENEOUS CATALYSTS IN ORGANIC TRANSFORMATIONS

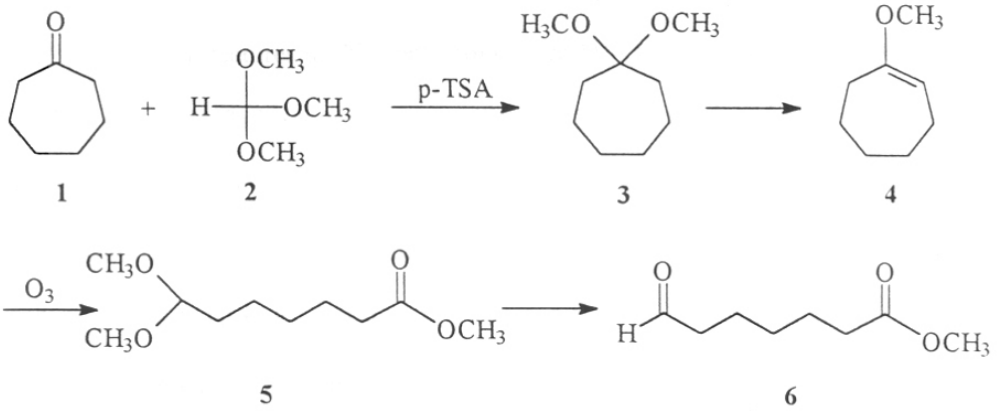
Clay catalyzed reactions in organic chemistry have been attracting considerable attention in recent years. Clays are aluminosilicates.[6] Kaolinitic clays are 1:1 clays associating one tetrahedral and one octahedral layers. They have many advantages such as ease of handling, non-corrosiveness, low cost and regeneration. Due to their Bronsted and Lewis acidity, clays both in ion exchanged form and natural form function as efficient catalysts for various organic transformations.[7]

This chapter is divided into two sections. Section A deals with protection of carbonyl compounds catalyzed by natural kaolinitic clay and Section B deals with transesterification and transthiolesterification reactions catalyzed by clay.

**Section A: Protection of carbonyl compounds catalysed by natural kaolinitic clay**

During the course of our studies on prostaglandin synthesis, the required intermediate methyl 7-oxoheptanoate (**6**) was prepared by ozonolysis of 1-methoxy-1-cycloheptene (**4**) (Scheme 1) which in turn was prepared from cycloheptanone (**1**) and trimethyl orthoformate. Wohl[8] reported a single step procedure for the synthesis of cyclic enol ethers via intermediate acetals, for which no suitable method was available to monitor the reaction by GC and also the GC condition for separating a mixture of cycloheptanone, trimethyl orthoformate, 1,1-dimethoxy cycloheptane and 1-methoxy-1-cycloheptene simultaneously, was not available. In this work a good GC separation condition was developed for the quantitative estimation of the reaction mixture. Based on GC analysis, the reaction was optimized to obtain maximum yield of **6**.

**Scheme 1**




1 2 3 4

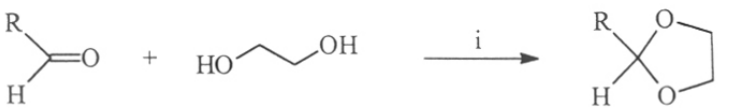
5 6

For the conversion of **1** to **3** various heterogeneous catalysts were employed and it was found that naturally occuring kaolinitic clay efficiently catalyzed this conversion. From this observation, a general methodology for the preparation of acyclic acetals, ketals, thioacetals and thioketals has been developed by using kaolinitic clay as a catalyst.

Subsequent study revealed that the variety of carbonyl groups (aliphatic, aromatic, heteroaromatic, α,β-unsaturated, sterically hindered) could be protected with

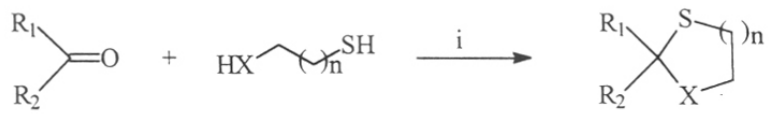
different protecting groups such as ethylene glycol, ethaneoxathiol, ethanedithiol and 1,3-propanedithiol over natural kaolinitic clay to afford 1,3-dioxolane (**7**), 1,3-oxathiolane (**8**), 1,3-dithiolane (**9**) and 1,3-dithiane (**10**) respectively with high yield (Scheme-2).

**Scheme 2**



R = alkyl, aryl

**7**



$R_1$ = H, alkyl, aryl  n = 1, 2
$R_2$ = alkyl, aryl  X = O, S
i = Clay (10% wt/wt), benzene, △, 2hr.

**7** 1,3-Dioxolane
**8** 1,3-Oxathiolane X = O, n = 1
**9** 1,3-Dithiolane X = S, n = 1
**10** 1,3-Dithiane X = S, n = 2

The salient features of this methodology are 1) A wide range of carbonyl groups could be protected. 2) Various protecting groups could be employed. 3) The sterically hindered ketones such as camphor could be easily thioacetalized with 1,2-ethanedithiol and 1,3-propanedithiol. 4) α,β-Unsaturated ketones underwent protection without the shift of double bond to β, γ-position. 5) Chemoselective protection of aldehydes in the presence of ketones could be possible.

**Section B: Transesterification and transthiolesterification over natural kaolinitic clay**

In our continuing interest in the application of clay to organic transformations, when methyl acetoacetate was reacted with primary alcohol over clay, the product obtained was characterized as a transesterified moiety. Based on this observation, a variety of primary alcohols were studied for transesterifiction of β-keto esters and a

general methodology for transesterification of β-keto esters has been developed (Scheme 3).

**Scheme 3**


Salient features of the methodology are as follows:

1) Methyl acetoacetate is successfully transformed into synthetically useful esters.

2) A variety of primary alcohols containing sensitive functional groups can be employed in this transformation. 3) A special feature of this method is that, unsaturated alcohols, like crotyl, cinnamyl, propargyl and allyl underwent transesterification affording unsaturated esters in high yields, however, it should be noted that transesterification with allylic alcohols is generally difficult with other catalysts. 4) Industrially important long carbon chain esters could be synthesised.5) No isomerization of double bond occurred during transesterification.6) Reaction is possible even with phenols and aniline. 7) Reaction fails in the case of secondary and tertiary alcohols, and it is selective only for primary alcohols.8) Reaction appears to be specific only for transesterification of β-keto esters. 9) The clay catalyst was recovered and reused at least three times.

The conversion of β-keto ester moiety to its thiol analogue is problematic, as it always undergoes facile decarboxylation upon its hydrolysis. However, this synthetic problem can now be conveniently solved by one to one exchange of thiols with β-keto ester to yield transthiolesterified product catalyzed by natural kaolinitic clay. (Scheme-4). A number of thiols were employed and a general methodology for transthiol esterification has been developed.

**Scheme 4**

Since the catalyst is active towards transesterification, and transthiolesterification under the same catalytic condition, it is of interest to study the reactivity pattern of different kinds of diols, amino alcohols and mercapto alcohols towards β-keto ester over natural kaolinitic clay and such selectivity study was carried out.

This section also describes the selectivity study of reaction of ethylene glycol, ethaneoxathiol and ethanedithiol with β-keto esters over natural kaolinitic clay.

## References


1) Tahara, M.; Okabe, T.; Furihata, K.; Tanaka, N.; Yamaguchi, H.; Nishimura, T. and Suzuki, H. *J. Antibiotics*, **1991**, *44*, 255.

2) Azzena, U.; Denurra, T.; Melloni, G. and Piroddi, A. M. *J. Org. Chem.* **1990**, *55*, 5386.

3) Sargent, M. V.; Vogel, P. and Elix, J. A. *J. Chem. Soc. Perkin Trans 1*, **1975**, 1986.

4) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T. and Sim, G. A. *J. Am. Chem. Soc.*, **1966**, *88*, 3888.

5) Comins, D. L.; Baevsky, M. F. and Hong, H. *J. Am. Chem. Soc.*, **1992**, *114*, 10971.

6) Laszlo, P. *Pure and Applied Chem.*, **1990**, *62*, 2027.

7) Cornelis, A. and Laszlo, P. *Synlett*, **1994**, 155.

8) Wohl, R. A. *Synthesis*, **1974**, 38.

# CHAPTER I

# SYNTHETIC STUDIES ON RESORTHIOMYCIN

## Introduction

Cancer is occuring with dismaying frequency around the world. In India, cancer is regarded as the third leading cause of death, the other two being heart diseases and tuberculosis. The definition of cancer or malignancy is very difficult, but it can be defined[1] as the state in which a family of cells grow progressively with permanent impairment of normal growth control. Tumor is a general term indicating any normal mass or growth of tissue that is not necessarily life-threatening. A "Cancerous tumor" is a malignant neoplasm of potential danger.

Cancer can arise in any organ of the body even though some sites are more prone than others. The most dangerous property of cancer cells, which normal cells lack, is their ability to enter other body organs through blood and lymph vessels. This disease has attracted worldwide attention and search for reliable methods to cure it is continuously going on.

Radiation, surgery and chemotherapy are some of the methods used at present in the treatment of cancer, out of which the former two can be used only in the early stages of disease when it is localised. But in many cases the disease is not detected in primary stages and often spreads into the whole body. Then radiotherapy or surgery cannot help to stop this disease being fatal. In these cases, the only tool in oncologist's hand to fight against cancer to save the patient is chemotherapy alone or in combination with radiation and surgery.

Cancer chemotherapy involves the use of chemicals ordinarily foreign to the body, which when administered to the host bearing tumor, will adversely affect the tumor without destroying the host. This treatment is mostly resorted to after all other methods of therapy have failed. The main disadvantage of cancer chemotherapy is the toxicity of the drugs used.

So far nearly 3,00,000 different compounds have been documented, either obtained from natural sources or synthesis, as potential anticancer agents. Out of these only about 40 are, today, considered useful in varying degrees, in the treatment of more than 100 types of human cancers.[2]

The development of ideal chemotherapeutic agent for cancer is extremely difficult because anti-cancer agent has to be administered until every single cancer cell is completely destroyed. Such an agent has, therefore, to be non-toxic to the host cell during its prolonged administration and at the same time it has to be sufficiently toxic to the cancer cell. Hence the quest to find a better drug goes on.

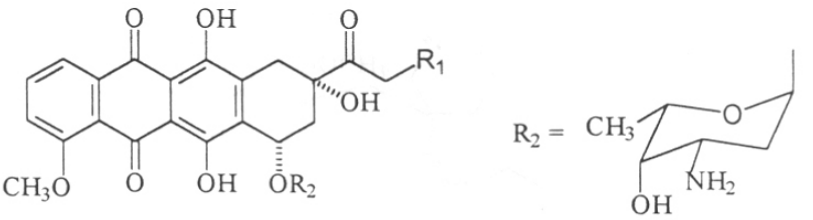
A large number of anticancer drugs, now being used in medical practice, have been approved by National Cancer Institute, USA. Further, many are undergoing clinical trials. All the antineoplastic agents can be classified into five categories namely (1) Alkylating agents (2) Antimetabolites (3) Anthracycline antibiotics (4) Natural products and (5) Miscellaneous agents.

1. **Alkylating agents:** Busulfan and chlorambucil are the examples of the alkylating agents used in the treatment of cancer.

2. **Antimetabolites:** Antimetabolites like 5-fluorouracil and methotrexate are helpful to cure some types of cancer.

3. **Anthracyclines**

The anthracyclines are a group of structurally related antitumor antibiotics. The two prototype anthracyclines are adriamycin and daunomycin produced from streptomyces species.[3] Their potent activity was discovered in 1963, when adriamycin[3] and daunomycin,[4] first isolated by Di Marco et al. were found to be effective as antileukemic agents.



Adriamycin $R_1 = OH$, $R_2 =$ Daunosaminyl
Daunomycin $R_1 = H$, $R_2 =$ Daunosaminyl

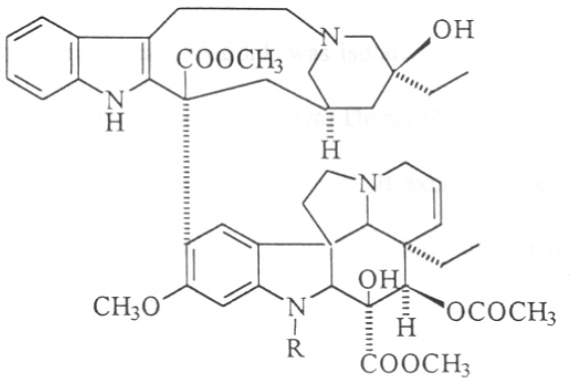
The tumor cell growth inhibiting property of the anthracyclines has generally been attributed to the interaction of these drugs with DNA. Adriamycin has shown promising results in solid tumors also.

**4. Natural products : Drugs derived from plant sources**

To acquire new anticancer agents a variety of sources have been explored including synthetic compounds, microbial and plant extracts etc. Consequently numerous plant extracts are being screened leading to the discovery of new natural products showing promising anticancer activity.

**Vinca alkaloids**

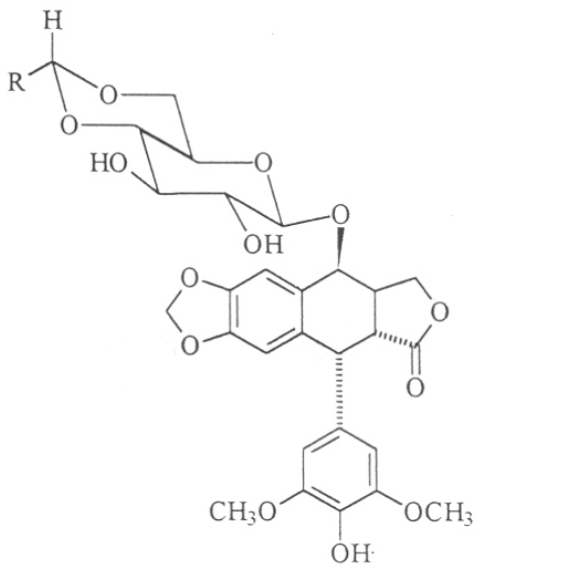
The most important development in the investigation of plant products as potential anticancer agents is the discovery of the dimeric alkaloids of *Vinca rosea L.*[5] Two of the alkaloids, vinblastine and vincristine (VCR) have demonstrated remarkable antitumor activity. They have been the first examples of antitumor agents isolated from plant sources.

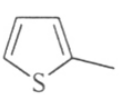


Vinblastine R = $CH_3$
Vincristine R = CHO

**Etoposide**

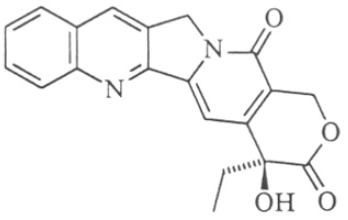
Etoposide is a semisynthetic compound prepared from podophyllotoxin which was isolated from the May Apple or *Podophyllum pellatum*.[6] Sandoz group prepared a number of synthetic analogues of podophyllotoxin, water soluble analogues like etoposide and teneposide and these are available in the market as anticancer agents.



Etoposide R = $CH_3$ , Teneposide R = 

**Camptothecin**

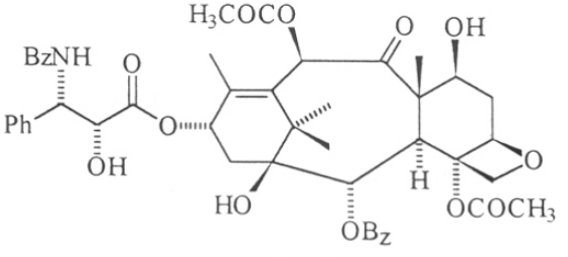
Camptothecin, a pentacyclic alkaloid, was isolated by Wall et al.[7] in 1966 from the stem wood of the tree *camptotheca acuminata* Decne (Nyssaceae), a tree distributed widely and abundantly in the southern part of China. It exhibits potent antileukemic and antitumor activities in animals and hence it continues to be one of the most important lead compounds among the anticancer natural products.




20 (S)-Camptothecin

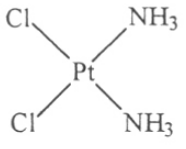
**Taxol**

Taxol, a complex polyoxygenated diterpene isolated from the Pacific Yew, *Taxus brevifolia* was discovered by Wani and co-workers. It is the most important member of the taxane class of compounds and has been the focus of much attention because of its anticancer properties and effectiveness against a number of leukemias and solid tumors.[8]



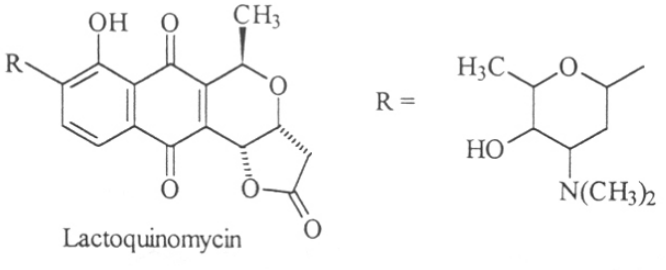

Taxol

*cis*-Diammineplatinum(II)dichloride (cisplatin) demonstrated significant activity in carcinomas of the urinary bladder.[9]




Cisplatin

One of the major problems in the treatment of cancer is the development of resistance to anticancer agents. In the course of screening programme for new antitumor antibiotics, using drug resistant neoplastic cells, Tanaka et al.[10] found that a soil *Streptomyces* strain IM 8442T produces a novel antibiotic which inhibits antibiotic-resistant cell sublines of L5178Y murine lymphoma more markedly than the parental cells. The new agent was named as lactoquinomycin. Lactoquinomycin displayed inhibitory activity against bacteria, particularly Gram-positive organisms, but no significant activity was observed against fungi.

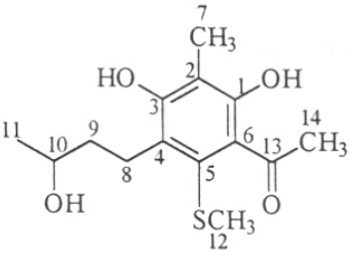



Lactoquinomycin

In the course of a similar screening programme using the multidrug resistant tumor cell line, Tanaka and co-workers discovered resorthiomycin,[11a] a novel antitumor antibiotic, from the culture broth of a strain of *Streptomyces collinus* by ethyl acetate extraction, silica gel chromatography and HPLC.

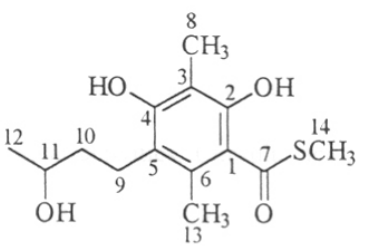
Resorthiomycin was obtained as a pale yellow oil which was miscible with methanol, ethanol, chloroform and ethyl acetate but hardly miscible with water. Tanaka

and co-workers reported structure of resorthiomycin to be 6-acetyl-4-(3-hydroxybutyl)-2-methyl-5-methylthioresorcinol (**1**) on the basis of spectral studies[11b] and elemental analysis.

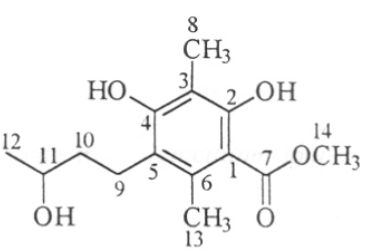


**1**

Professor Haruo Seto, University of Tokyo, suggested that the $SCH_3$ group should not directly bind to the benzene ring, and instead, forms a methylthio ester at C-6 carbon. Mass spectral fragmentation peak (M-$SCH_3$) of **1** and long range $^{13}C$-$^{1}H$ couplings observed between a methyl proton and three carbons (C-4, C-5 and C-6) were not compatible with the proposed structure. To confirm the structure, Tanaka and co-workers[12] stirred a mixture of resorthiomycin **1** and sodium methoxide in dry methanol overnight. It was acidified with dilute hydrochloric acid and extracted with ethyl acetate. Column chromatographic purification gave **3** which showed that structure of resorthiomycin should be **2** and not **1**.



**2**



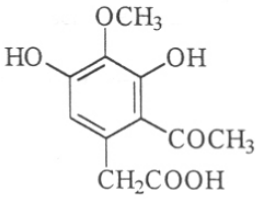
**3**

In $^{13}$C-NMR spectrum, the signal of C-7 in **2** appeared at an extremely low field (198.2 ppm) which is characteristic of the carbonyl carbon in a thiol ester. In **3**, this signal was shifted to higher field (172.4 ppm), also suggesting the formation of carboxylate. The PMR spectrum of **3** indicated that the signal of 14-$CH_3$ had shifted from 2.45 ppm to 3.93 ppm. This change suggested that the -$SCH_3$ group was replaced by $OCH_3$ group in **3**.

All the data described above indicate that the correct structure of resorthiomycin is S-methyl 2,4-dihydroxy-3,6-dimethyl-5-(3-hydroxybutyl) thiobenzoate (**2**). However, the absolute configuration at C-11 has not been determined. The antitumor antibiotic was named resorthiomycin because it is a derivative of resorcinol and is unique in having a methylthio group.

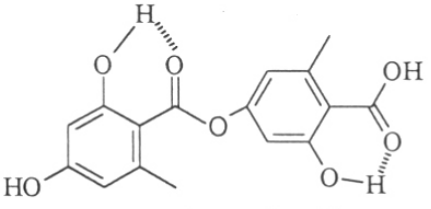
The effect of several clinically useful antitumor drugs on colony formation by V 79/s cells was examined in the presence or absence of resorthiomycin.[13] The inhibitory activity of actinomycin D was significantly enhanced by the addition of resorthiomycin. Similarly resorthiomycin also exhibited enhanced activity when combined with vincristine but the antibiotic had no effect on the cytocidal activity of doxorubicin, methotrexate or 5-fluorouracil. On the other hand this antibiotic does not possess any antibacterial or antifungal activity.

Numerous resorcinol derivatives occur in nature and many of them exhibit various biological activities. Curvulic acid, a metabolite from *Penicillium janthinellum* C-268, was found to have antimicrobial activity[14] on a defined medium.



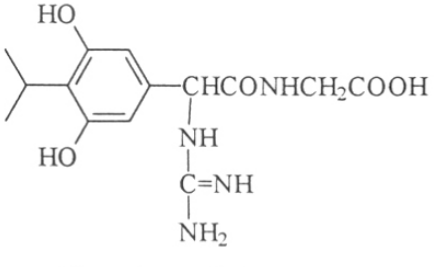
Curvulic acid

Lecanoric acid which was first isolated from lichen[15] by Fischer and Fischer and from fungi[16] by Umezawa et al., was reported to inhibit histidine decarboxylase. The inhibition by lecanoric acid was competitive with histidine and noncompetitive with pyridoxal phosphate. Lecanoric acid did not inhibit aromatic amino acid decarboxylase.



Lecanoric acid

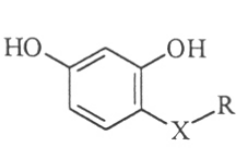
Resorcinomycin A, a new antibiotic produced by *Streptoverticillium reseoverticillatum*, was found to show antibacterial activities against various species of mycobacteria.[17]



Resorcinomycin A

The antifungal activity of the synthetic 2,4-dihydroxyacylophenones and 2,4-dihydroxyalkylbenzenes, against *Trichophyten spp.* and other fungi was investigated. Some compounds tested showed potent antifungal activity against *Trichophyton spp.*[18] and other fungi and some were more active than amphotericin B. The activity of these

compounds was found to be closely related to the length of the aryl and alkyl substituents attached to the resorcinol moiety.




$X = -\overset{O}{\overset{\|}{C}}-$ , $R = -(CH_2)n-CH_3$

$X = CH_2$ , $R = -(CH_2)n-CH_3$

$n = 1\text{-}9$

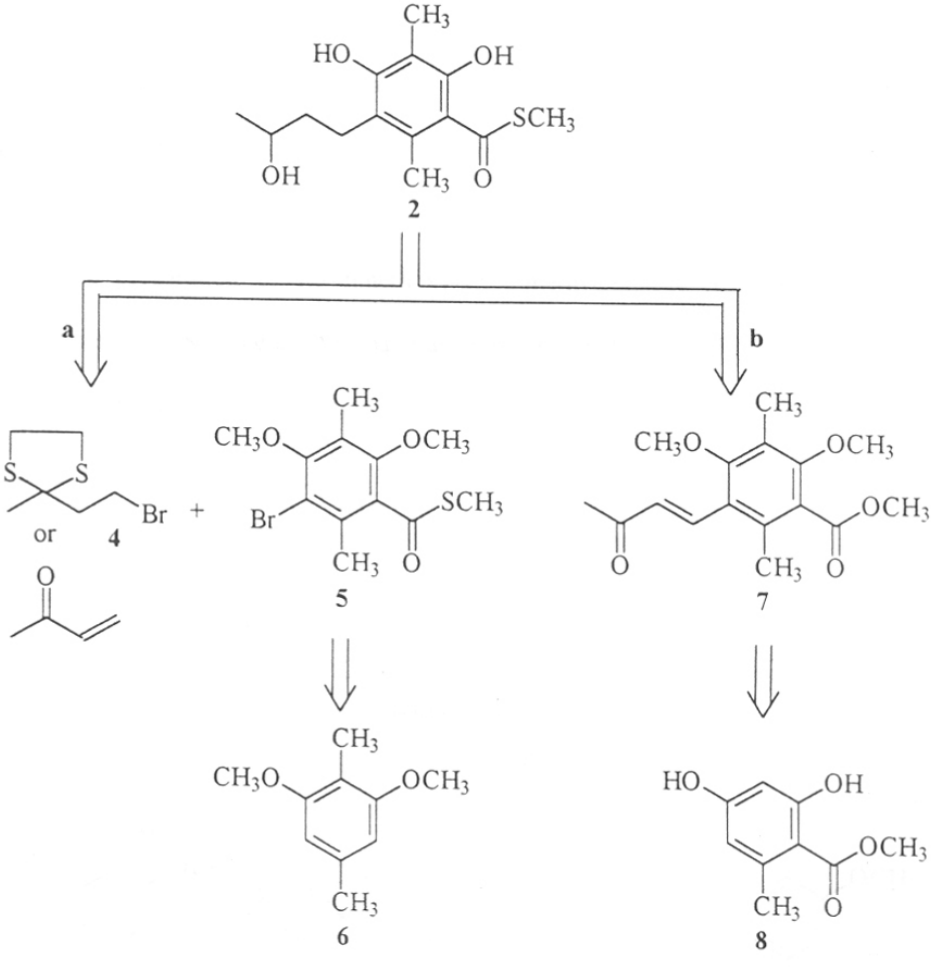
Eventhough the resorcinol derivatives show various biological activities, none of them show antitumor activity. Resorthiomycin is found to be an exception for this class of compounds. It is also having a different identity as it contains methyl thiol ester moiety.

## PRESENT WORK

The novel hexasubstituted skeleton of resorthiomycin (**2**) having methyl thiol ester moiety coupled with its antitumor activity prompted us to take up its total synthesis and also to confirm the proposed structure of resorthiomycin by attempting its total synthesis.

The retrosynthetic analysis of resorthiomycin revealed two distinct approaches for its synthesis (Scheme-1).

**Scheme 1**



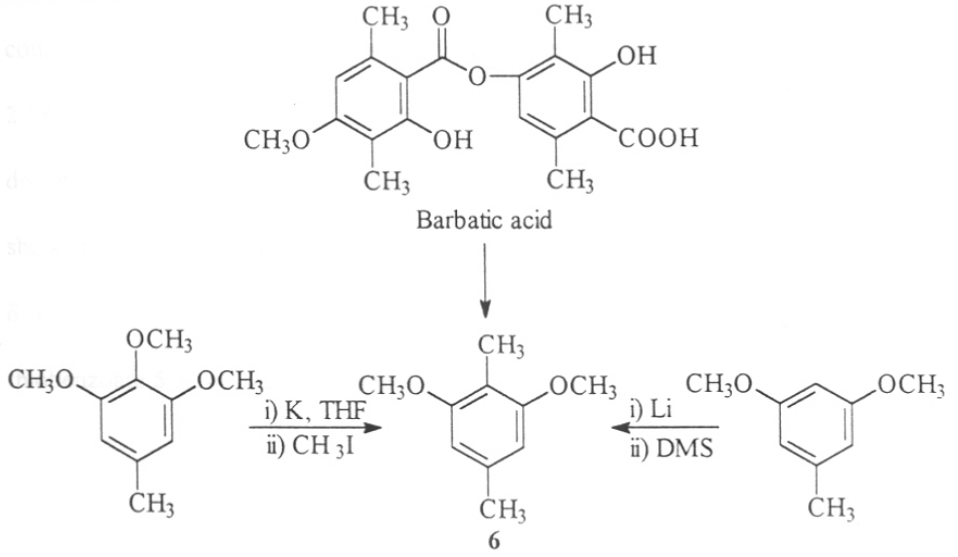
The approach "a" utilises the carbon-carbon bond formation between two units **4** and **5**. Efforts directed towards this condensation are described in Section A. The Section B describes the total synthesis of (±)-resorthiomycin (**2**) making use of approach b. A mild and efficient method for thiol esterification has been described in Section C.

**Section A: Attempted synthesis of resorthiomycin**

The synthesis of resorthiomycin by the carbon-carbon bond formation through Wurtz-Fittig or Heck coupling reaction of the substituted methyl thiobenzoate **5** with 3-(1,3-dithiolane) 1-bromobutane (**4**) or methyl vinyl ketone attracted us because of the ability of this approach to produce resorthiomycin by convergent synthesis, which if successful could be elaborated to asymmetric synthesis of resorthiomycin. The key intermediate **5** could be obtained from 1,3-dimethoxy 2,5-dimethylbenzene (**6**) while the protected bromo derivative **4** could be obtained from methyl acetoacetate.

The preparation of 1,3-dimethoxy-2,5-dimethylbenzene (**6**) was reported by different methods (Scheme 2). Azzena et al.[19] reported metalation of 1,2,3-trimethoxy-5-methylbenzene followed by quenching with methyl iodide to give **6** in good yield, while

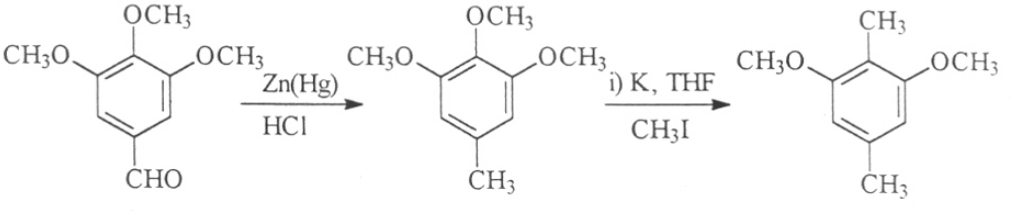
**Scheme 2**



the lithiation of 3,5-dimethoxytoluene followed by treatment with dimethyl sulfate was reported by Ridley et al.[20] One more method reported was based on alkaline hydrolysis of barbatic acid,[21] followed by decarboxylation and methylation of isolated product to give **6**.

In the present work 1,3-dimethoxy-2,5-dimethylbenzene was prepared by known method[19] as shown in Scheme 3.

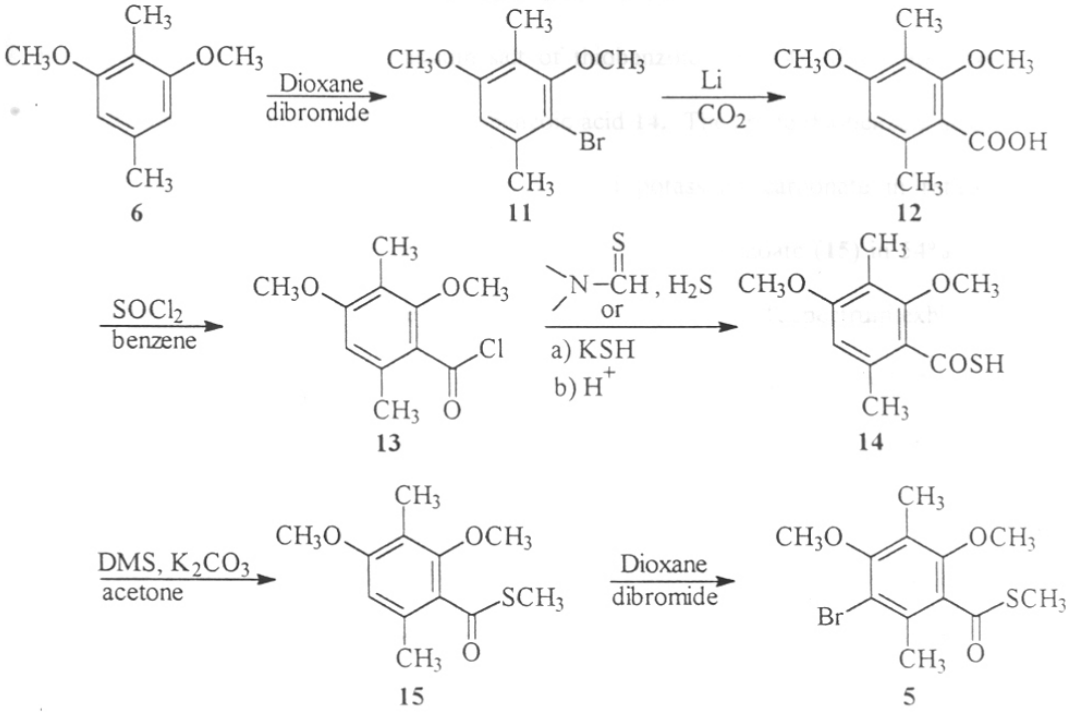
**Scheme 3**




**9** **10** **6**

Clemmensen reduction of 3,4,5-trimethoxybenzaldehyde (**9**) gave 1,2,3-trimethoxy-5-methylbenzene (**10**) in 70.4% yield. The disappearance of carbonyl peak in the IR spectrum, as well as singlet corresponding to a proton at δ 9.90 in the PMR spectrum proved that carbonyl group in **9** was reduced. The structure of **10** was further confirmed by its PMR spectrum which showed a methyl group appearing as a singlet at δ 2.38. 1,3-Dimethoxy-2,5-dimethylbenzene (**6**) was obtained by reductive demethoxylation of **10** followed by quenching it with methyl iodide. Its PMR spectrum showed newly formed methyl group at δ 2.11 and a singlet corresponding to 6 protons at δ 3.79. 1,3-Dimethoxy-2,5-dimethylbenzene (**6**) was then converted into substituted thiobenzoate **5** as shown in Scheme 4.

**Scheme 4**




1,3-Dimethoxy-2,5-dimethylbenzene (**6**) was monobrominated using dioxane dibromide in ether to give bromo derivative **11** in 76% yield. Its structure was confirmed on the basis of PMR spectrum. The aromatic region showed singlet corresponding to only one proton at δ 6.40. The substituted resorcillinic acid **12** was obtained in moderate yield after lithiation of bromo derivative **11** followed by quenching it with dry ice.[22a] The structure of acid **12** was confirmed on the basis of its physical and spectral data reported in the literature.[22b] Treatment of **12** with thionyl chloride in benzene in presence of catalytic amount of DMF under reflux afforded its acid chloride derivative **13**. The crude acid chloride was converted to thiol ester **15** by two different methods.

In method A the acid chloride **13** was treated with N,N-dimethylthioformamide[23] at room temperature for 4 hr and then hydrogen sulfide gas was bubbled through the solution to afford the corresponding thiobenzoic acid **14**, which was esterified using dimethyl sulfate and potassium carbonate in acetone to yield **15** in 39.8% yield.

Alternatively (method B) the acid chloride **13** was treated with potassium hydrogen sulfide[24] to afford potassium salt of thiobenzoic acid **14**. Acidification with dilute hydrochloric acid afforded the thiobenzoic acid **14.** The crude thiobenzoic acid **14** was as such esterified using dimethyl sulfate and potassium carbonate in refluxing acetone to afford S-methyl 2,4-dimethoxy-3,6-dimethyl thiobenzoate (**15**) in 54% yield. Its structure was confirmed on the basis of its spectral data. The IR spectrum exhibited a peak for ester carbonyl at 1670 $cm^{-1}$ while PMR spectrum showed a singlet corresponding to three protons at δ 2.45 which was a characteristic signal for methyl thiol ester. The intermediate **5** was obtained in 38% yield by monobromination of methyl thiol ester **15** using dioxane dibromide in ether. Its PMR spectrum showed the absence of aromatic proton which confirmed its hexasubstituted benzene skeleton (FIG. I).

As thiol esters in general are not very stable under acidic or basic conditions it was decided to carry out demethylation study at this stage, so that necessary changes could be made in the synthetic strategy. In view of this, a model study of demethylation reactions was carried out as shown in Scheme 5 and Scheme 6.

Salicylic acid (**16**) was methylated using dimethyl sulfate and potassium carbonate in acetone under reflux to give **17** which was hydrolysed using potassium hydroxide in methanol-water (1:1) to afford the corresponding acid **18**. The acid **18** was converted to the corresponding thiol ester **19** in 42% yield using the same reaction sequence employed for conversion of **12** to **15** (method B; Scheme 4). Demethylation of **19** was achieved using anhydrous aluminium chloride in dichloromethane at 0°C to afford the compound **20**. The demethylation experiment showed that the thiol methyl ester group was stable under the reaction conditions. The thiol methyl ester group appeared as a singlet at δ 2.45 in the PMR spectrum while the chelated hydroxyl group

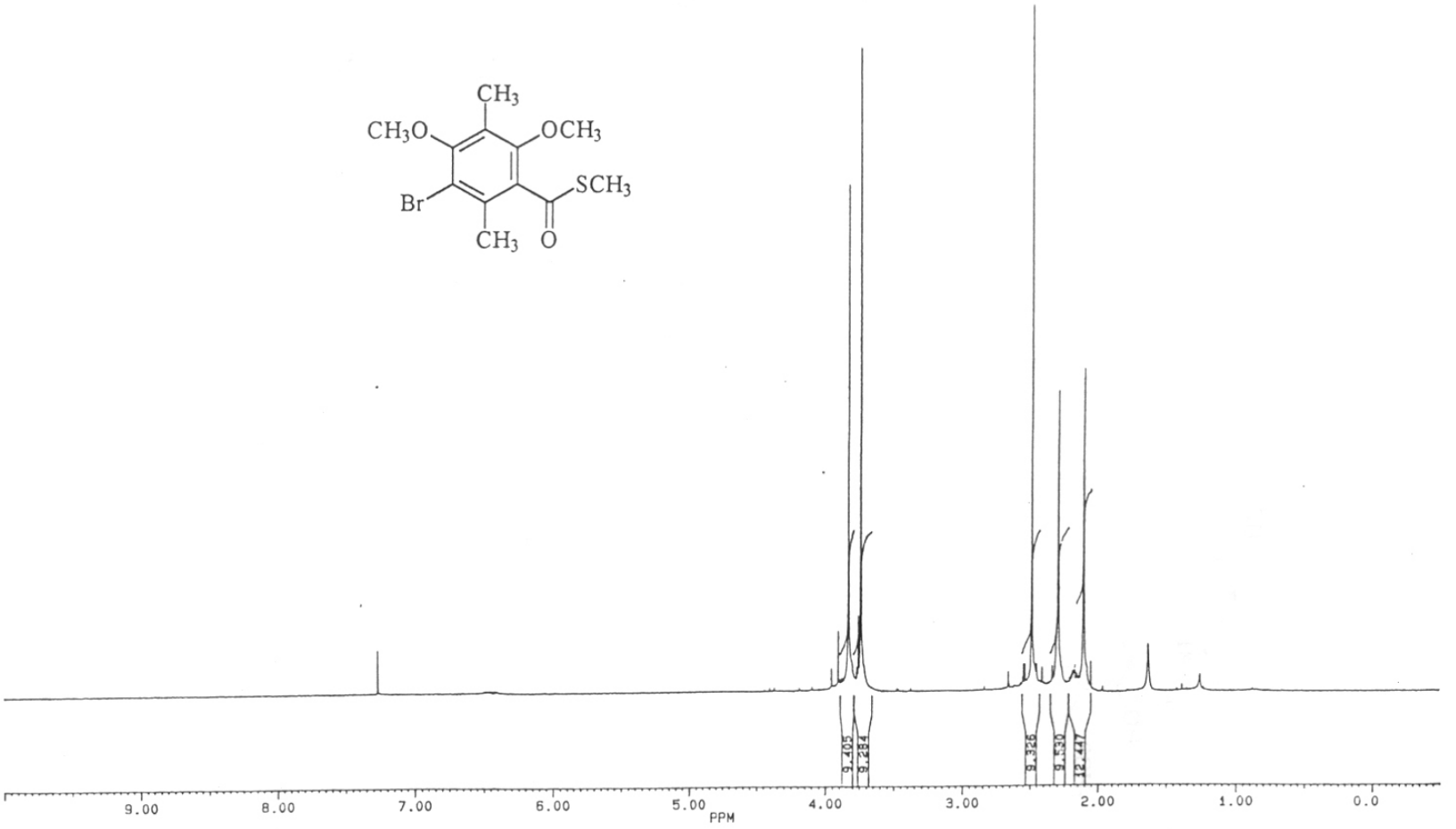
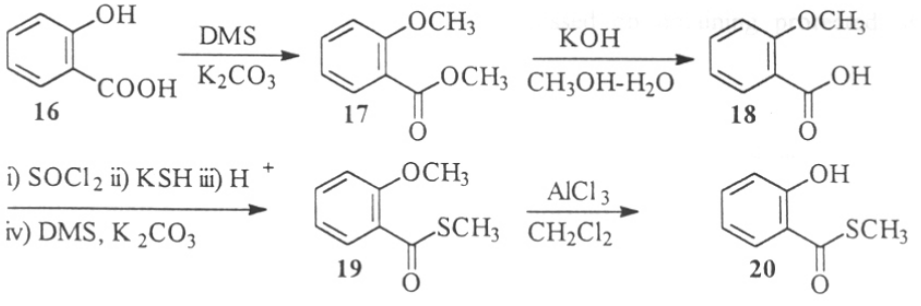



FIG I : PMR SPECTRUM OF THE COMPOUND 5 IN CDC13

appeared as a singlet at δ 10.80 which supported the structure of methyl 2-hydroxy thiobenzoate (**20**).

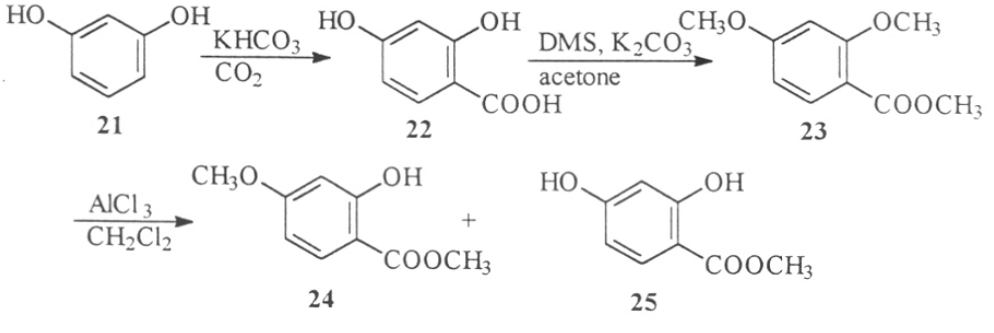


**Scheme 5**




Further, this study was extended for the demethylation of chelated and non-chelated methoxyl groups also. For this purpose reaction sequence was carried out as shown in Scheme 6.

**Scheme 6**

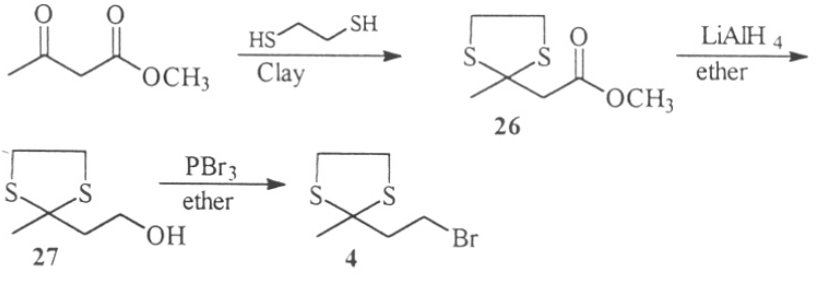



Resorcinol (**21**) was subjected to Kolbe reaction[25] to afford resorcylic acid (**22**). Dimethoxy ester **23** was obtained after methylation of **22** by dimethyl sulfate and potassium carbonate in acetone under reflux. A sample of methyl 2,4-dihydroxybenzoate (**25**), to be used as an authentic sample in the demethylation study of **23**, was prepared from **22** by reaction with methanol containing a few drops of sulfuric acid. Dimethoxy ester **23** was demethylated using aluminium chloride to afford a mixture of **24** and **25**. When it was stirred for longer time, the TLC showed complete conversion of **24** to **25**.

Results of the demethylation of **19** and **23** under the same reaction conditions i.e. aluminium chloride in dichloromethane, suggested that intermediate **5** was the right choice for coupling reaction as shown in the retrosynthetic Scheme 1. Having prepared the bromo derivative **5**, the attention was focussed on obtaining protected bromo butanone **4**.

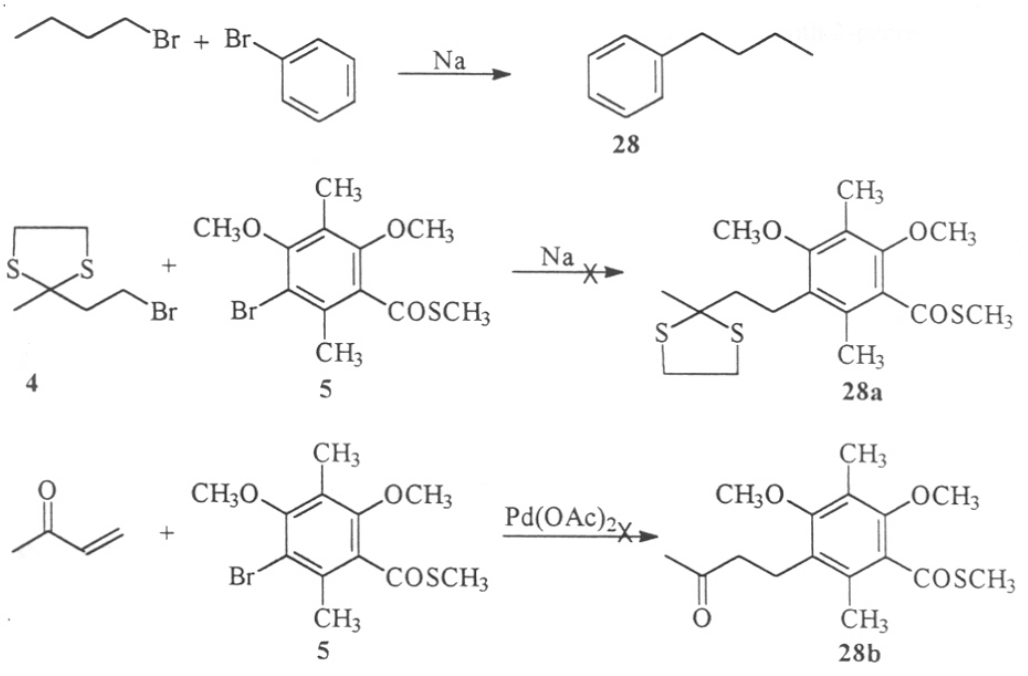
Methyl acetoacetate was protected (Scheme-7) with 1,2-ethanedithiol using natural kaolinitic clay to afford methyl 3-(1,3-dithiolane) butanoate (**26**) in 80% yield. It was reduced with lithium aluminium hydride in ether to afford **27.** The structure of alcohol **27** was confirmed on the basis of spectral means. The PMR spectrum showed disappearance of ester peak and formation of two triplets at δ 2.20 and at δ 3.85. The alcohol **27** on further treatment with phosphorous tribromide in dry ether at 0°C gave 3-(dithiolane)-1-bromobutane (**4**) in 68.4% yield. Its PMR spectrum showed two triplets, at δ 2.50 and δ 3.50. The structure of **4** was further confirmed by mass spectrum which showed m/z. at 226 ($M^+$) and 228 ($M^+$+2).

**Scheme 7**



Having obtained the key intermediates **4** and **5**, the next aim was to couple the two moieties to get the side chain protected thiol ester **28a**. In this regard, Wurtz-Fittig[26] coupling of bromobenzene and bromobutane using sodium metal in benzene was carried out successfully as a model experiment.

**Scheme 8**




The hexasubstituted thiol ester **5** and protected bromo derivative **4** were heated with sodium metal in benzene (Scheme 8) at 80°C for 4 hr in the first instance. It was found that the reaction mixture failed to produce desired product **28a** and only the starting materials were recovered even after continuing the reaction for a longer time.

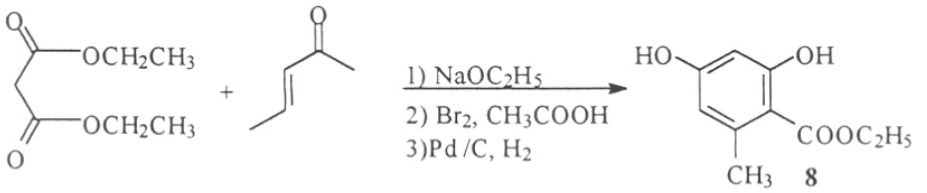
Subsequently, the bromo derivative **5** was treated with methyl vinyl ketone in presence of palladium acetate. However, the desired product **28b** could not be obtained.

These unsuccessful results in both the coupling reactions may be due to steric factors. As this convergent route to resorthiomycin failed, the alternative linear route was attempted which is described in Section B.

**Section B: Synthesis of Resorthiomycin**

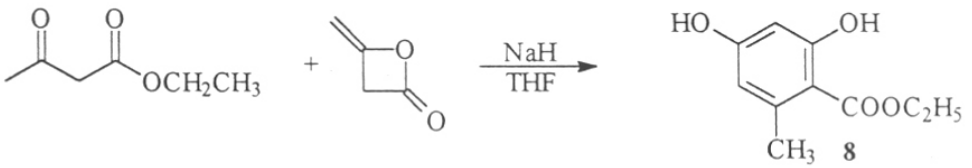
Methyl or ethyl orsellinate (**8**) is an ideal starting material for the synthesis of resorthiomycin utilizing the approach b as shown in Scheme 1. The successful efforts to achieve the goal of synthesis of resorthiomycin are described in this section.

Some of the methods reported for the preparation of methyl orsellinate are as follows. Bartlett et al.[27] found that condensation of diethyl malonate with 3-penten-2-one under base catalysed reaction condition afforded an intermediate dihydroresorcylic ester which was then dehydrogenated with bromine to furnish dibromo compound followed by hydrogenolysis in the presence of 10% palladium-carbon to give ethyl orsellinate.



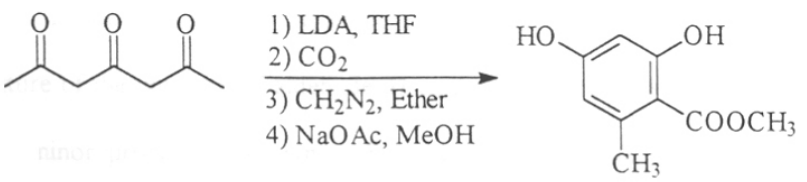

**8**

The reactivity of diketene towards the active methylene of β-keto ester was studied by Kato and Hozumi.[28]



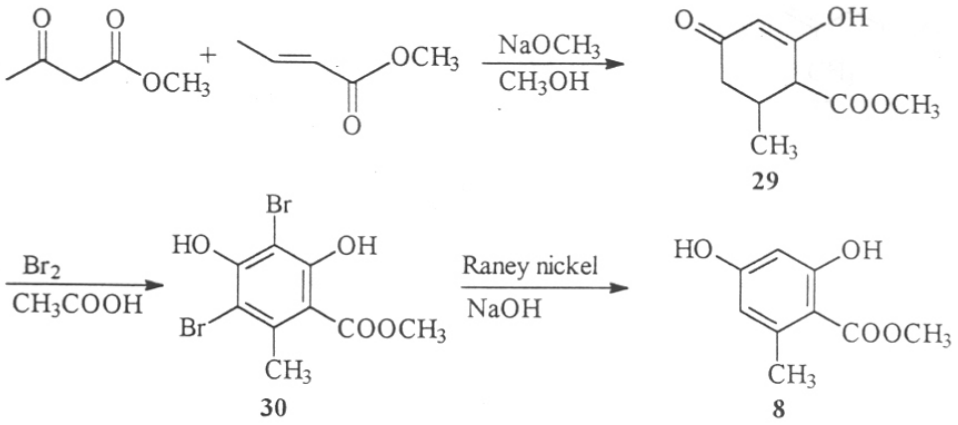

**8**

Howarth et al.[29] found that treatment of diacetylacetone with 4 equiv. of lithium diisopropylamide in tetrahydrofuran under nitrogen and carboxylation of the soluble, yellow trilithium salt with carbon dioxide gave tetraacetic acid as an oil in 47% yield. This acid was esterified using diazomethane in ether which on treatment with 1M methanolic sodium acetate gave methyl orsellinate in 50% yield.



Methyl orsellinate (**8**) was also prepared by Sargent et al.[30] starting from methyl acetoacetate and methyl crotonate as shown in Scheme 9. In the present work the same sequence of reactions was followed.

**Scheme 9**



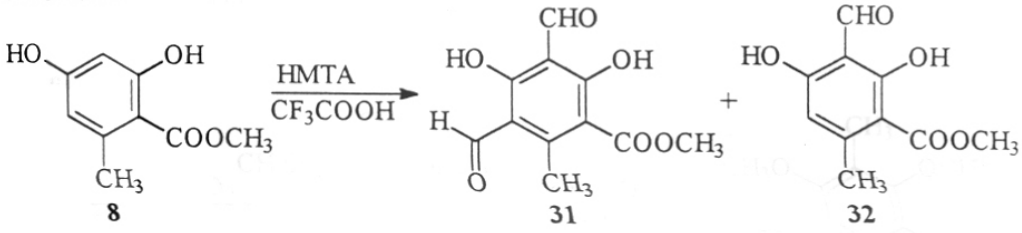

Initially methyl crotonate was prepared by esterification of crotonic acid with methanol using catalytic amount of sulfuric acid. However, yield obtained by this method was very low. Then an alternate method[31] was employed for its preparation in which thionyl chloride was added dropwise to a cold solution of crotonic acid in methanol affording the desired product in 70% yield.

Michael-Aldol type addition of methyl acetoacetate with methyl crotonate in the presence of sodium methoxide in methanol afforded methyl dihydro-orsellinate (**29**) in 65% yield as a yellow solid. It was brominated in glacial acetic acid to furnish methyl 3, 5-dibromo-2, 4-dimethoxy-6-methyl benzoate (**30**) in 95% yield. Methyl orsellinate (**8**) was obtained in 82% yield by Raney nickel reduction[32] of **30** in the presence of sodium hydroxide.

In order to obtain **32** from **8**, it was subjected to Duff [33] reaction, but it gave a mixture of the unwanted dialdehyde **31** as a major product and the desired aldehyde **32** as a minor product as shown in Scheme 10. Both the aldehydes **31** and **32** were characterized by spectral methods. Dialdehyde **31** was characterized from its PMR

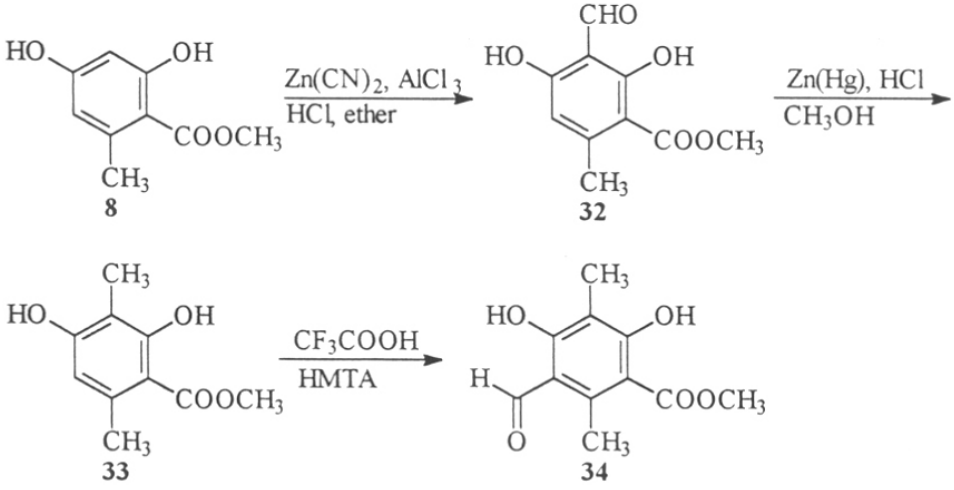
spectrum as it showed no aromatic proton and two aldehydic protons at δ 9.90 and δ 10.10.

**Scheme 10**




To overcome this problem, methyl orsellinate (**8**) was formylated by modified Gatterman reaction[34] as shown in Scheme 11.

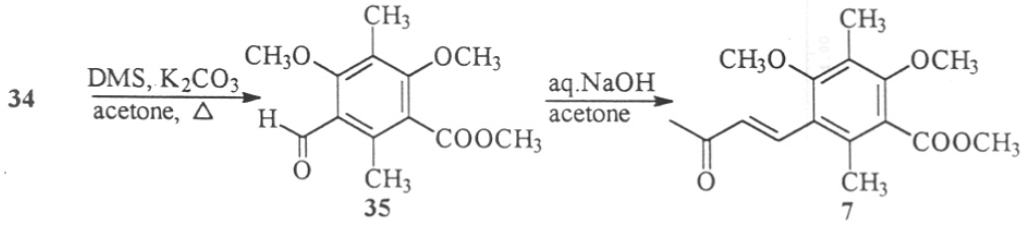
**Scheme 11**




Methyl orsellinate (**8**) was formylated using aluminium chloride and zinc cyanide in ether to afford methyl 2,4-dihydroxy-3-formyl-6-methylbenzoate (**32**) in 80% yield as colourless needles. No other isomer was formed. PMR spectrum of **32** showed two single proton peaks at δ 10.20 and 6.40 for aldehyde and aromatic proton respectively. The compound **32** was reduced under Clemmensen reaction condition[34] to yield methyl β-orcinolcarboxylate (**33**) in 78% yield which had physical and spectral characteristics same as those reported in literature. Hexasubstituted aldehyde ester **34** was obtained by reaction of compound **33** with trifluoroacetic acid and hexamethylenetetramine.[35] A

singlet at δ 10.30 in PMR spectrum for aldehydic proton, two singlets for chelated hydroxyls at δ 12.25 and δ 13.10 and molecular ion peak at m/z. 224 in the mass spectrum confirmed the structure.

**Scheme 12**




The aldehyde ester **34** was methylated using dimethyl sulfate and potassium carbonate in refluxing acetone (Scheme-12) to afford methylated ester **35** in 89% yield. Its PMR spectrum showed two singlets corresponding to 3 protons each at δ 3.80 and 3.85 for newly formed methoxyl groups. The molecular ion peak at m/z 252 in the mass spectrum further supported the structure. Aromatic aldehydes undergo condensation with acetone in presence of sodium hydroxide to form α,β-unsaturated ketones.[36] When compound **35** was subjected to the above condensation at 0°C, it gave condensed ester 7 as an oil in 71% yield. Its structure was fully confirmed using spectral methods. The PMR spectrum (FIG. II) of condensed ester 7 showed a singlet at δ 2.20 for side chain methyl group, two singlets at δ 2.30 and 2.40 for aromatic methyl groups, a singlet at δ 3.65 for ester group, two singlets at δ 3.75 and 3.90 for methoxy groups and two doublets at δ 6.65 (J = 17 Hz) and δ 7.65 (J = 17 Hz) for trans olefinic protons. The ester 7 was proposed to be converted into resorthiomycin **2** as shown in Scheme 13.

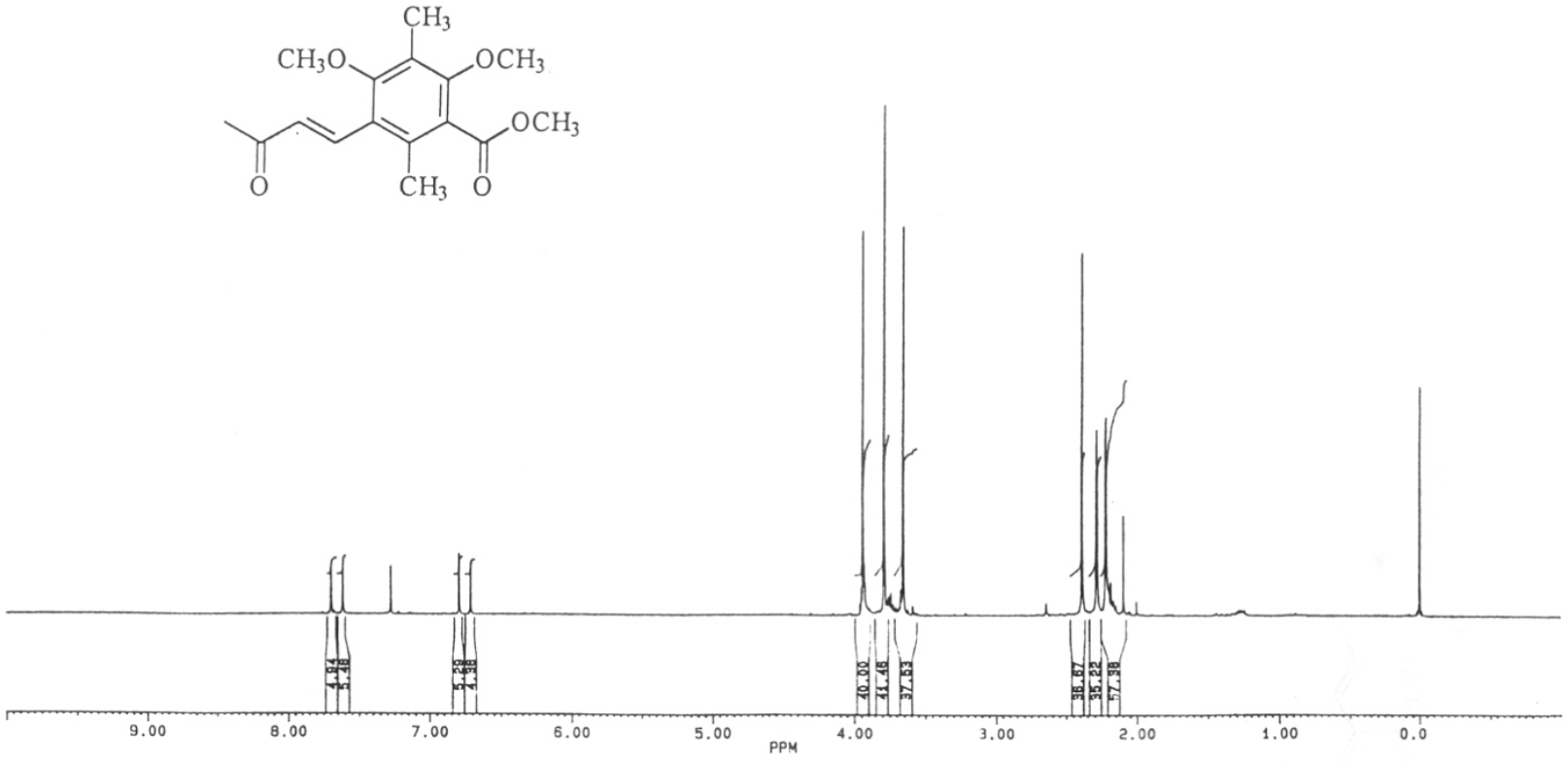
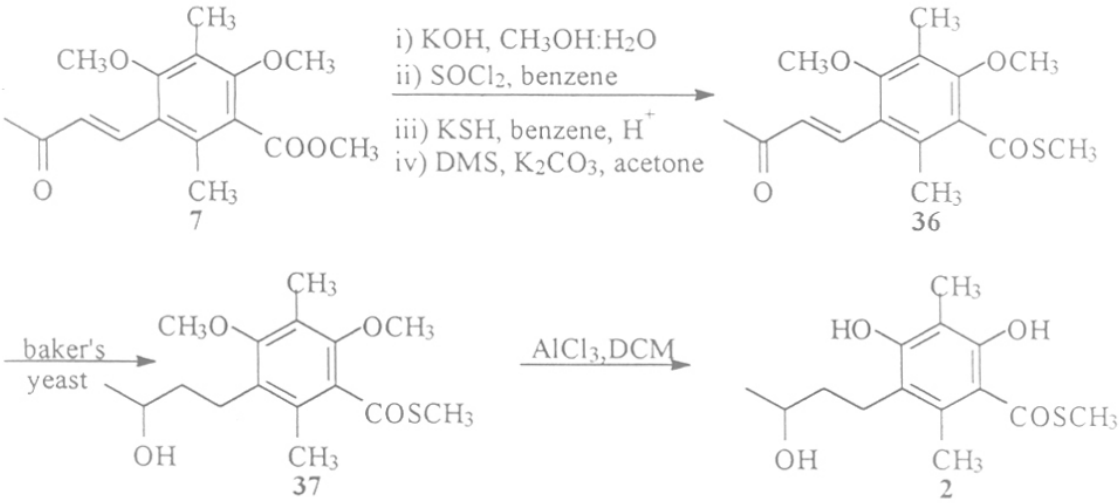


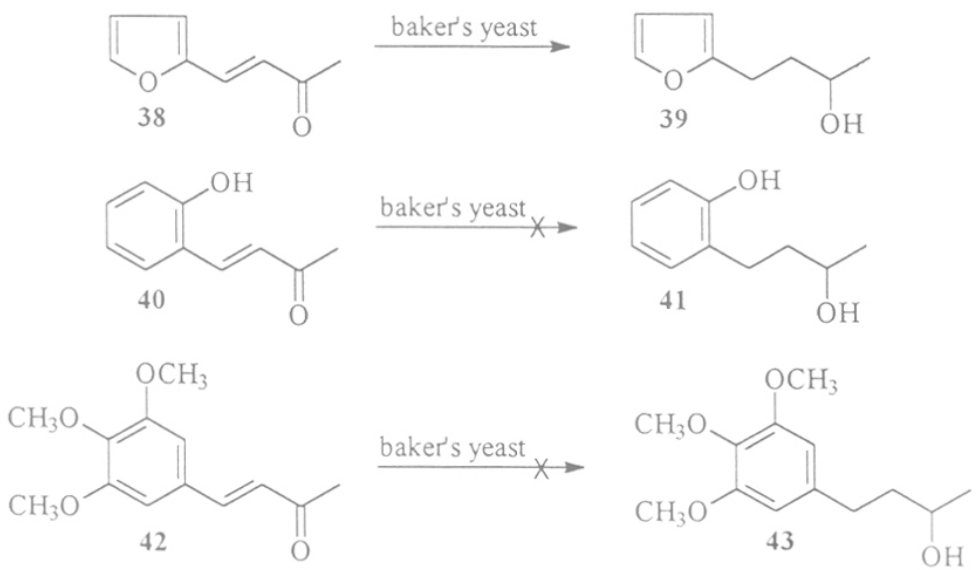

FIG II : PMR SPECTRUM OF THE COMPOUND 7 IN $CDCl_3$

**Scheme 13**




In this context, model reactions for reduction of α,β-unsaturated ketones by baker's yeast were tried as shown in Scheme 14.

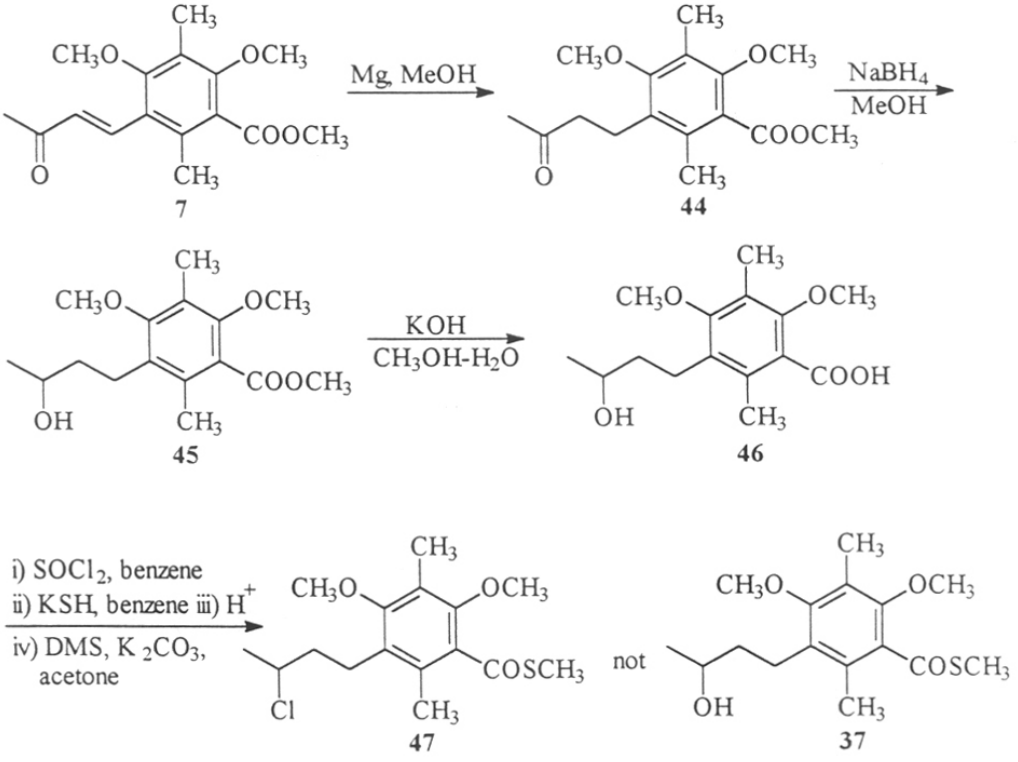
**Scheme 14**




It has been reported[37 a,b] that an α,β-unsaturated keto compound such as **38** on reduction with baker's yeast affords the alcohol **39** showing that the baker's yeast not only reduces double bond but also reduces the keto group. The similar reduction with baker's yeast on compounds **40** and **42** failed to give the desired alcohols **41** and **43**

respectively and the reaction gave a complex mixture of products. The starting α,β-unsaturated ketones **40** and **42** were prepared from salicylaldehyde and 3,4,5-trimethoxy benzaldehyde respectively. Thus, these model experiments suggested that the conversion of compound **36** to **37** by baker's yeast mediated reduction may pose some problems. Hence route for the synthesis of resorthiomycin as proposed in Scheme 13 was discontinued. An alternate approach attempted for the synthesis of resorthiomycin is shown in Scheme 15.

**Scheme 15**




When the condensed ester **7** was reduced with magnesium in methanol[38] it gave a mixture of compounds **44** and **45**. Silica gel chromatographic separation of the mixture afforded ketone **44**, m.p. 81°C, in 88% yield and the alcohol **45** in 7% yield. The structure of **44** was confirmed on the basis of its spectral data. Its PMR spectrum (FIG-III) showed disappearance of olefinic protons of α,β-unsaturated ketone and formation

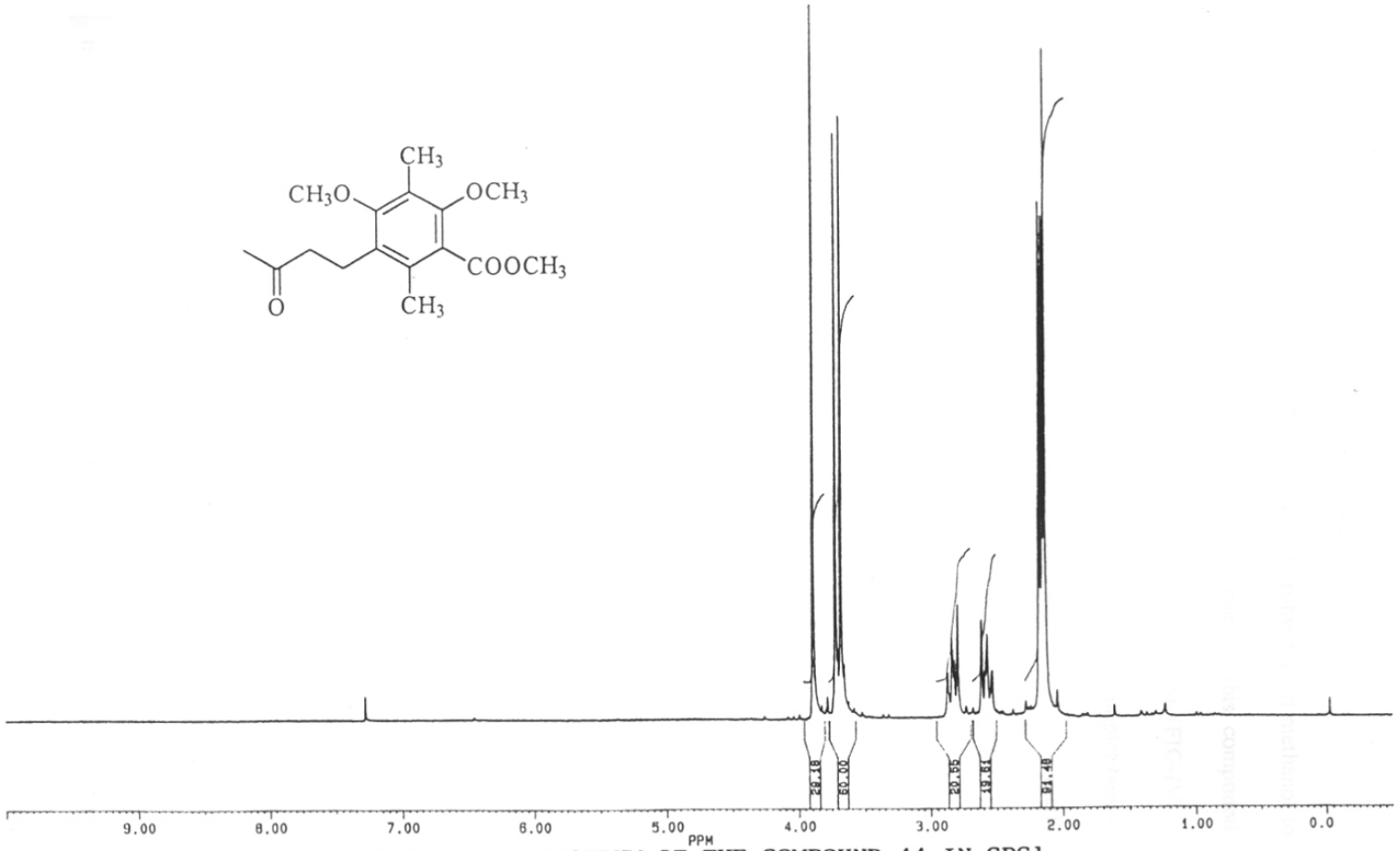



FIG III : PMR SPECTRUM OF THE COMPOUND 44 IN $CDCl_3$

of two multiplets between δ 2.52 - 2.65 and δ 2.75-2.85 for the methylene groups. Its structure was further confirmed by its mass spectrum (m/z 294).

The keto ester **44** was reduced with sodium borohydride in methanol to give **45** as an exclusive product in 90.12% yield. IR spectrum of this compound showed absorption bands at 1720 and 3400 $cm^{-1}$; while PMR spectrum (FIG-IV) showed a doublet corresponding to three protons at δ 1.15 (J = 7 Hz), a multiplet between δ 1.57 and 1.70 for the side chain methylene protons, singlet at 2.30 for the methyl groups attached to aromatic ring, a multiplet between δ 2.65-2.75 for benzylic methylene protons, a singlet at δ 3.75 for methyl ester group and a methine proton showed a multiplet between δ 3.60 and 3.70. Hydroxy acid **46** was obtained by hydrolysis of **45** by potassium hydroxide in aqueous methanol under reflux in 80% yield. Its PMR spectrum showed disappearance of ester peak.

The acid **46** was treated with thionyl chloride in benzene to afford the corresponding acid chloride derivative, which was used as such for further reaction. This was stirred with potassium hydrogen sulfide for 12 hr at room temperature. Acidification of the reaction mixture with dilute hydrochloric acid and extraction with chloroform afforded thiobenzoic acid which was esterified as such using dimethyl sulfate and potassium carbonate in acetone. However, the expected product **37** was not obtained, instead the chloro derivative **47** was obtained. The structure of **47** was established by its spectral analysis. IR spectrum showed disappearance of absorption band corresponding to hydroxyl group. Its PMR spectrum showed doublet (J=7 Hz) at δ 1.55 corresponding to side chain methyl protons, a multiplet between δ 1.78 and 1.92 for methylene protons, a singlet at δ 2.20 for two methyl groups attached to aromatic ring, a singlet at δ 2.48 for the methyl thiol ester group, a multiplet between δ 2.65 and 2.90 for the side chain benzylic methylene protons, a singlet at δ 3.72 for the methoxyl group and

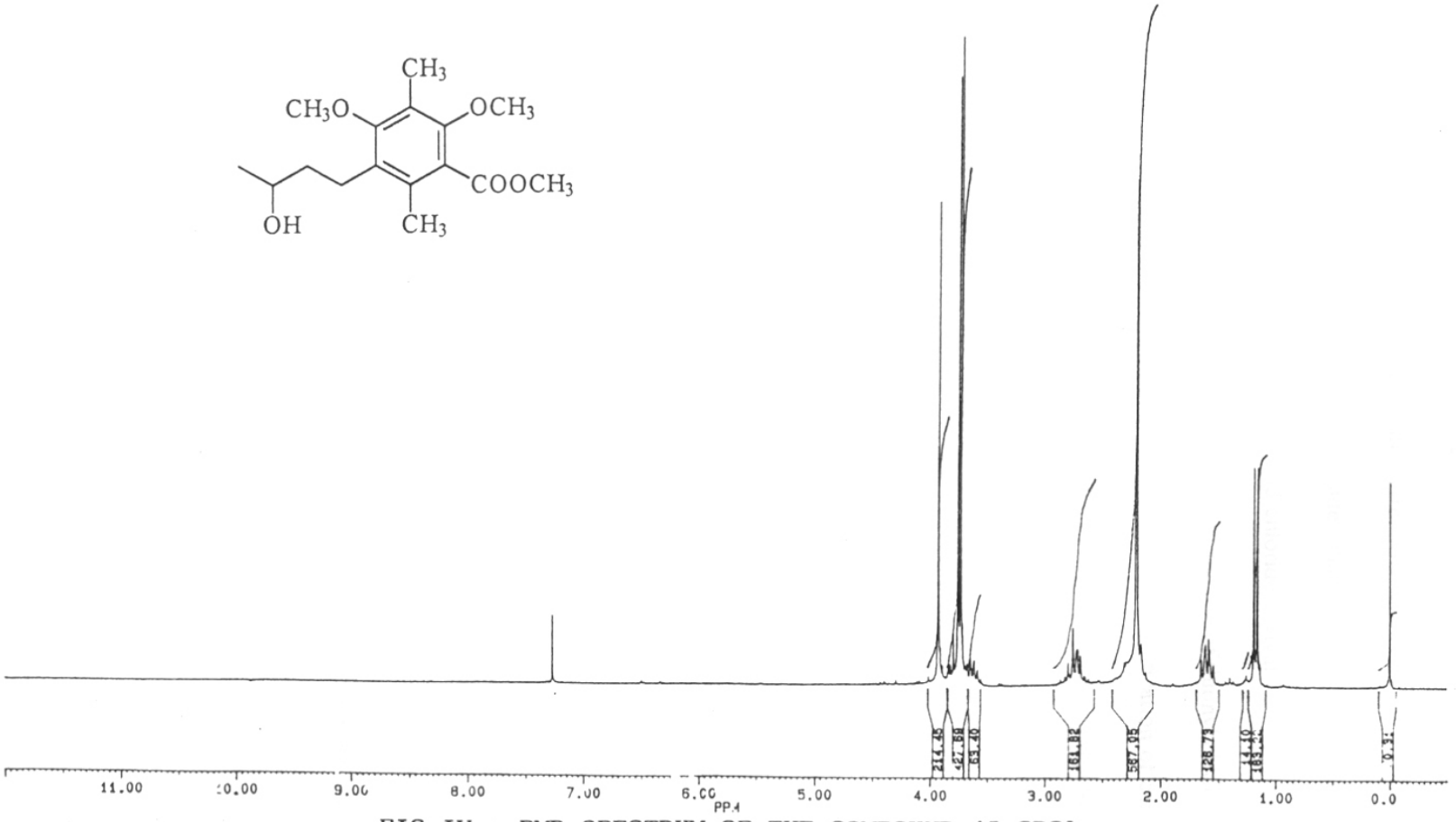



FIG IV : PMR SPECTRUM OF THE COMPOUND 45 $CDCl_3$

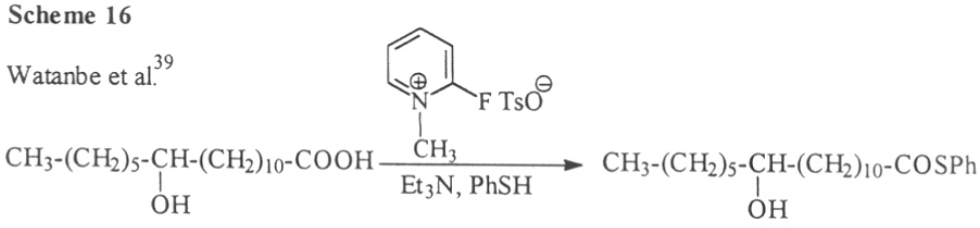
a multiplet between δ 4.05 and 4.15 for the methine proton. The molecular ion peak at m/z. 330 in the mass spectrum confirmed the structure.

Thionyl chloride must have converted side chain hydroxyl into its chloro derivative during conversion of acid **46** into its acid chloride derivative. This suggested that acid **46** has to be converted to thiol ester **37** without the use of thionyl chloride.

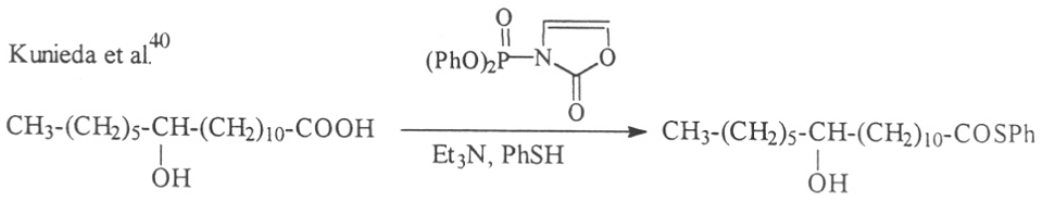
Two more methods reported in the literature for thiol esterification of carboxylic acid in presence of secondary hydroxyl group are shown in Scheme 16. It would require addition of methane thiol for preparation of corresponding methyl thiol ester. These methods could not be tried due to difficulty of addition of low boiling thiol.

**Scheme 16**

Watanbe et al.[39]

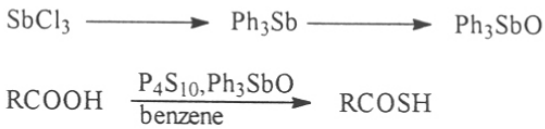



Kunieda et al.[40]




Treatment of carboxylic acid in benzene with phosphorous pentasulfide and triphenylantimony oxide at 40°C to afford thiobenzoic acid is a known reaction[41] (Scheme 17).

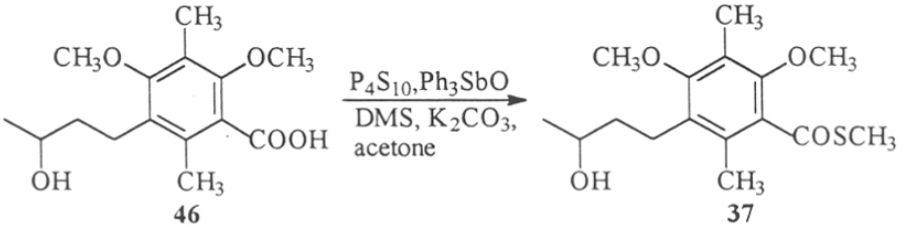
**Scheme 17**



Accordingly, triphenylantimony was obtained by Grignard reaction[42] of trichloroantimony and phenylmagnesium bromide in 16.1% yield. Triphenylantimony was oxidised using *tert*-butylhydroperoxide[43] to furnish triphenylantimony oxide in 90% yield.

When acid **46** was treated with triphenylantimony oxide and phosphorous pentasulfide (Scheme 18) in benzene at 40°C for 1 hr it afforded the respective thiobenzoic acid which was esterified with dimethyl sulfate and potassium carbonate in acetone to furnish dimethyl ether of resorthiomycin **37** in overall 5% yield.

**Scheme 18**




**46** **37**

The IR spectrum revealed absorption bands at 1673 and 3447 $cm^{-1}$ for methyl thiol ester group and hydroxyl group respectively. Its PMR spectrum (FIG. V) showed a singlet corresponding to three protons at δ 2.45, which suggested the presence of newly formed methyl thiol ester. The structure was further confirmed by its $^{13}C$ NMR spectrum (FIG. VI) and mass spectrum (m/z 312). Though our problem of converting acid to thiol ester keeping side chain hydroxy group intact was solved, the poor yield obtained prompted us to modify the route and the results are shown in Scheme 19.

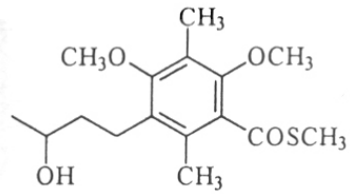






FIG V : PMR SPECTRUM OF THE COMPOUND 37 IN $CDCl_3$

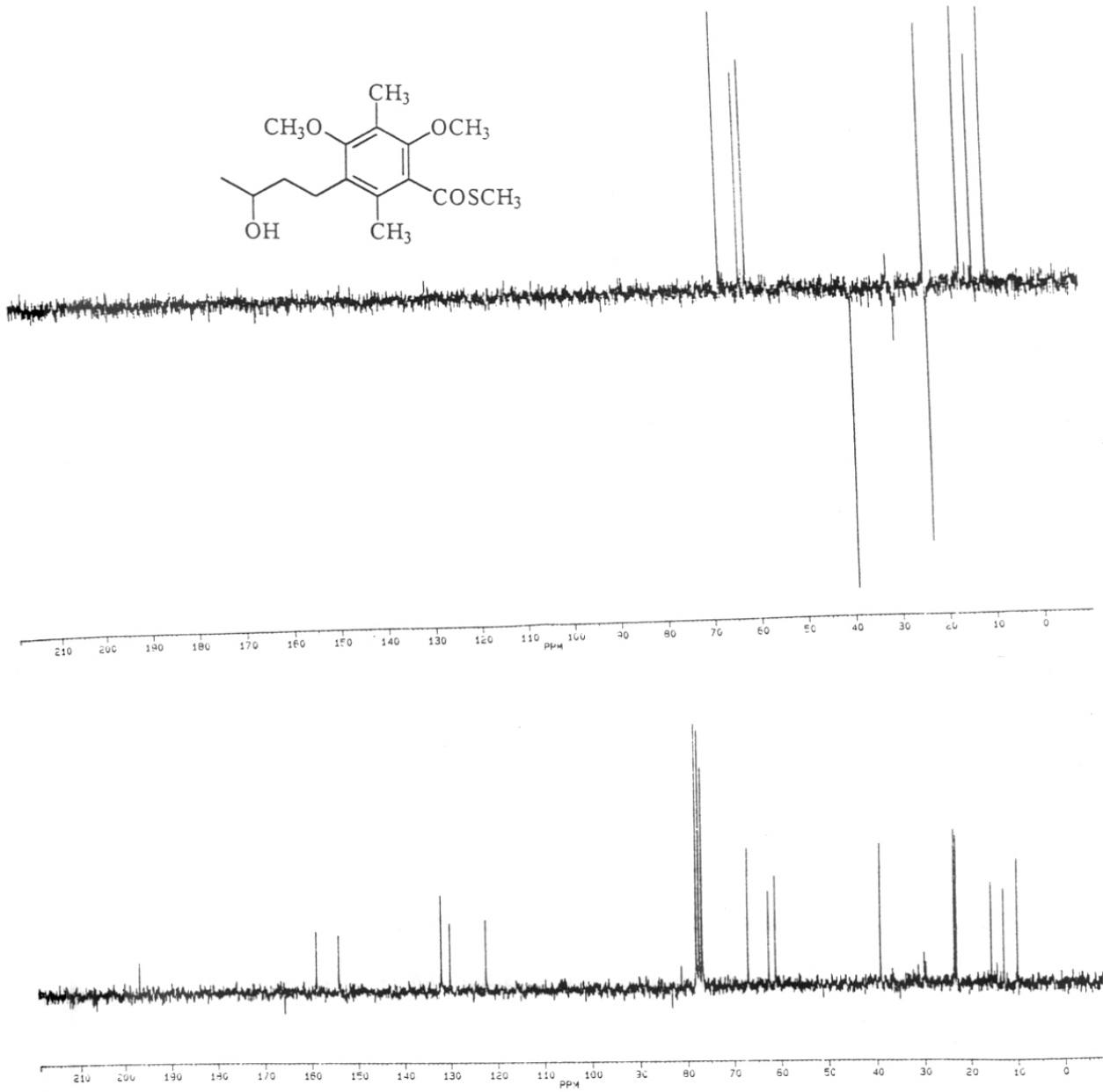
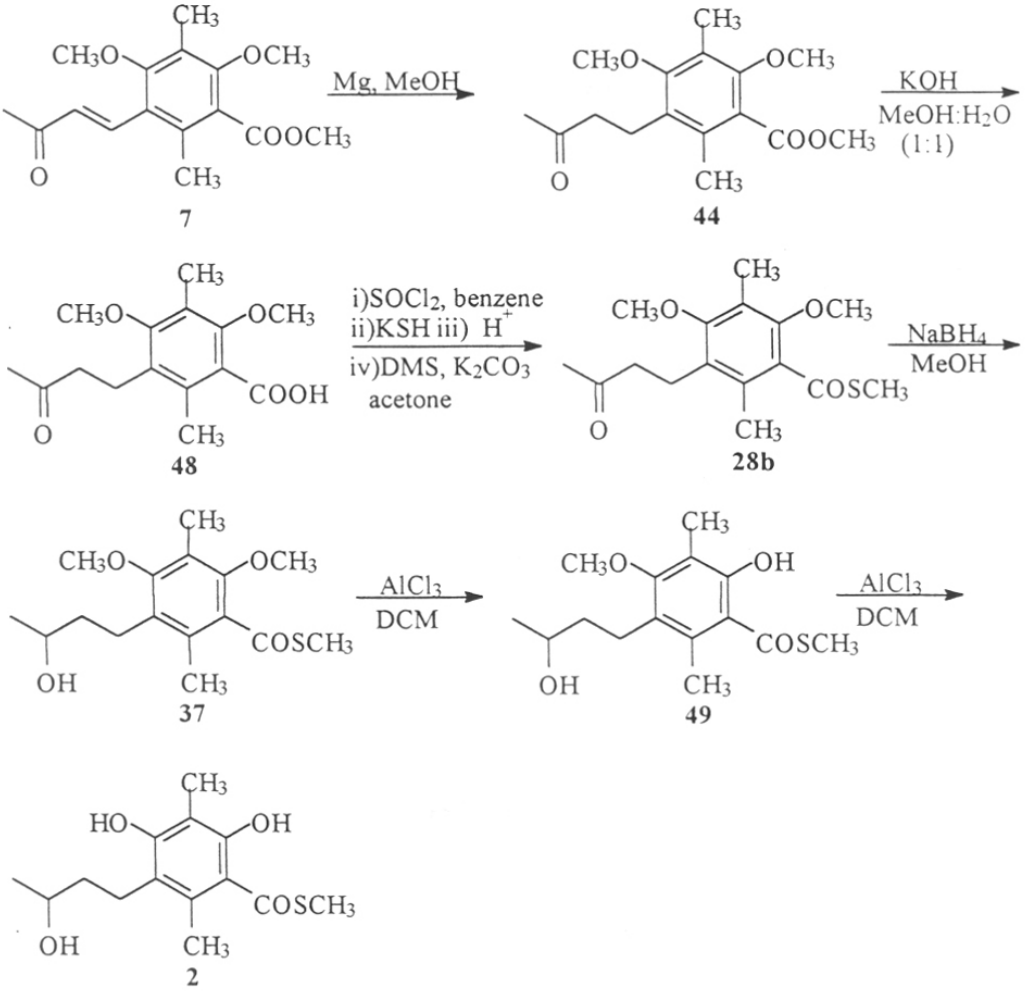



FIG VI: $^{13}C$ NMR SPECTRUM OF THE COMPOUND 37 IN $CDCl_3$

**Scheme 19**




In order to reduce the double bond in **7** selectively, it was treated with magnesium and methanol, but it gave a mixture of required keto ester **44** and the over reduced hydroxy ester **45**. Hydrogenation over Pd/C afforded similar results. The desired keto ester **44** was isolated in pure form from the reaction mixture by column chromatography. It was hydrolysed using potassium hydroxide in methanol-water (1:1) to afford acid **48** in 79% yield. It was fully characterized using spectral means. The IR spectrum showed a broad band in the region 3000 $cm^{-1}$ and also a carbonyl absorption band at 1710 $cm^{-1}$. The disappearance of ester peak at δ 3.65 in the PMR spectrum proved that ester group in **44** was hydrolysed. All other protons in the PMR spectrum

resonated at their respective chemical shifts. The mass spectrum exhibited the molecular ion peak at m/z. 280.

The acid **48** was converted to thiol ester **28b** by reaction of acid with thionyl chloride followed by reaction with potassium hydrogen sulfide and methylation using dimethyl sulfate and potassium carbonate to afford desired S-methyl ester **28b** in 39% yield. The structure of methyl thiol ester **28b** was established with the help of its spectral data. The disappearance of broad band in the region 3000 $cm^{-1}$ as well as the formation of sharp absorption band at 1670 $cm^{-1}$ for the methyl thiol ester group in the IR spectrum of **28b** supported the structure. Its structure was confirmed on the basis of PMR spectrum (FIG. VII) which showed a singlet at δ 2.18 for the side chain methyl protons, two singlets at δ 2.19 and 2.20 for two aromatic methyl protons, a singlet at 2.48 for thiol methyl ester protons, a multiplet between δ 2.55 and 2.65 for methylene protons, a multiplet between δ 2.80 and 2.92 for the benzylic protons and a singlet at δ 3.72 for the methoxyl groups. The $^{13}C$ NMR spectrum (FIG. VIII) as well as the presence of molecular ion peak at m/z. 310 in the mass spectrum further confirmed the structure.

The ketone functionality in thiol ester **28b** was reduced with sodium borohydride to provide resorthiomycin dimethyl ether **37** in 90% yield. It was fully characterized using IR, PMR, $^{13}C$ NMR and MS spectra. The IR spectrum showed disappearance of absorption band at 1710 $cm^{-1}$ and appearance of a broad band in the region 3447 $cm^{-1}$. The PMR spectrum showed a doublet at δ 1.15 (J = 7 Hz) for the side chain methyl group, multiplet between δ 1.52 and 1.68 for the methylene protons, a singlet at δ 2.2 for two methyl protons, a singlet at δ 2.50 for thiol methyl ester protons, a multiplet between δ 2.68 and 2.78 for benzylic protons, a multiplet between δ 3.60 and 3.70 for methine proton and a singlet at δ 3.72 for two methoxyl groups. The presence of molecular ion peak at m/z. 312 in the mass spectrum further proved the structure.

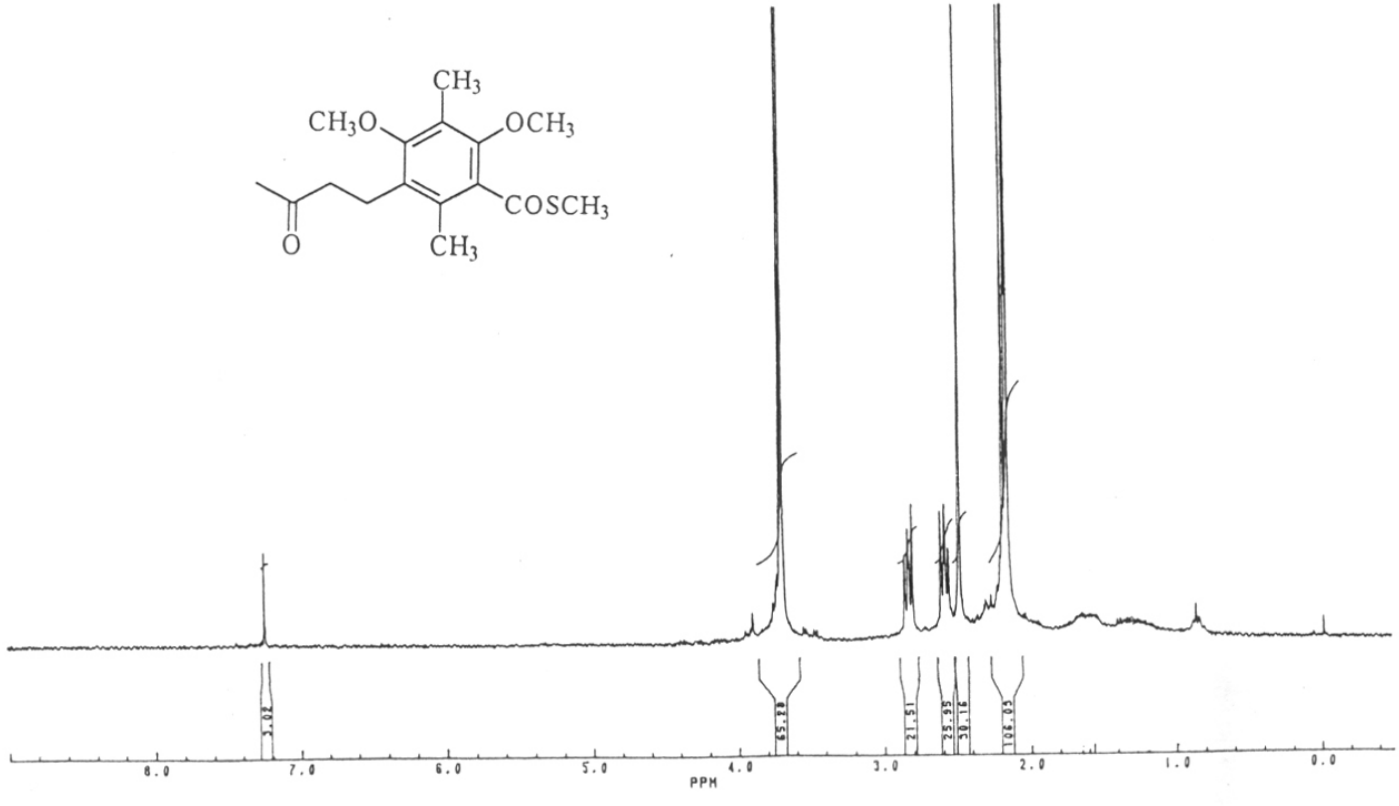



FIG VII : PMR SPECTRUM OF THE COMPOUND 28b IN $CDCl_3$

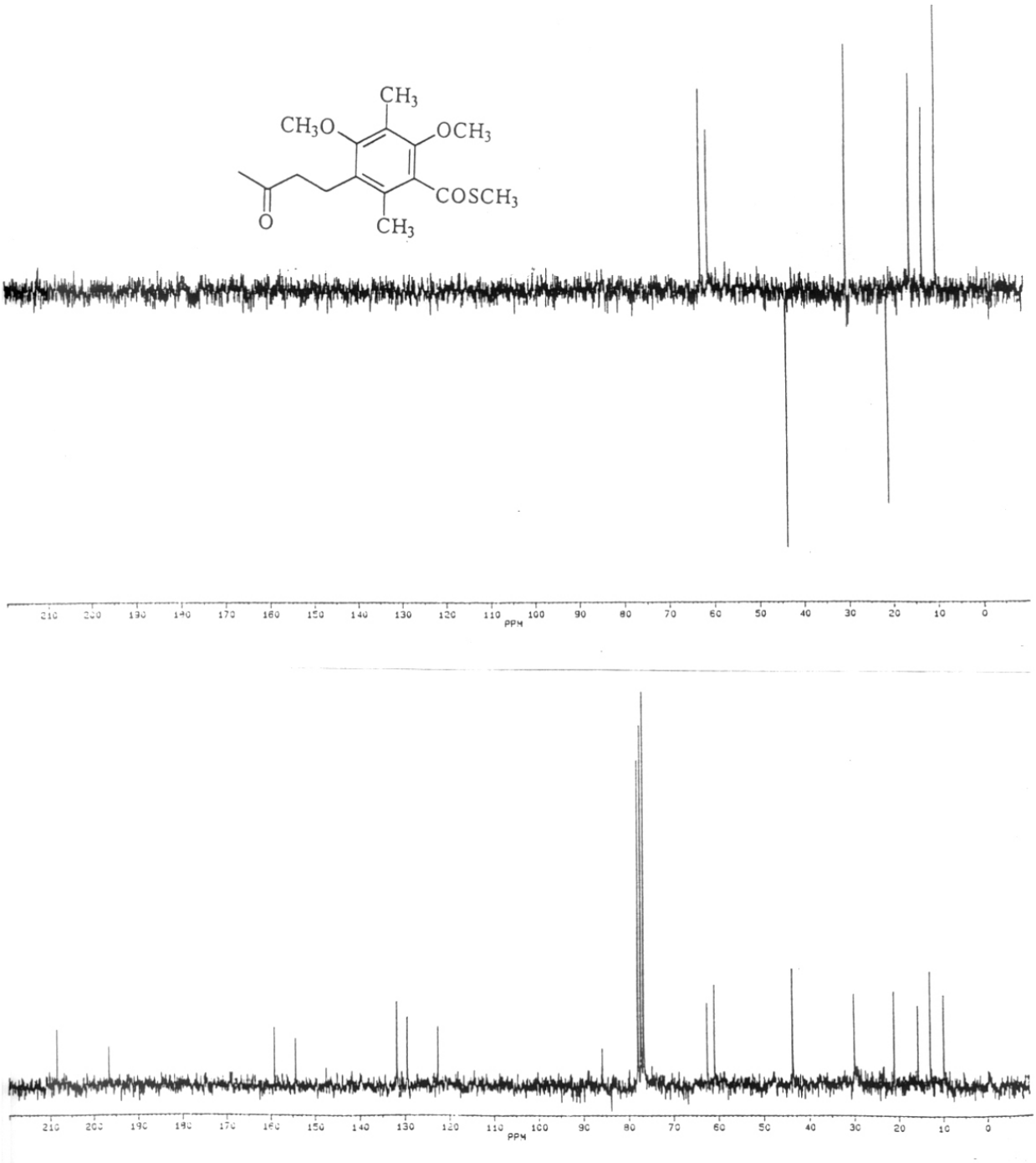



FIG VIII : $^{13}C$ NMR SPECTRUM OF THE COMPOUND 28b IN $CDCl_3$

The methyl thiol ester **37** was treated with anhydrous aluminium chloride in dichloromethane at 0°C to afford monomethyl ether of resorthiomycin **49**. The compound **49** was fully characterized by IR, PMR and MS spectra. In comparison with dimethyl ether of resorthiomycin **37**, PMR spectrum of **49** showed only one singlet corresponding to three protons at δ 3.75 and appearance of chelated hydroxyl peak at δ 8.8 (br s) and thus confirmed the structure.

Monomethyl ether of resorthiomycin **49** was further demethylated using anhydrous aluminium chloride in dichloromethane under reflux for 4 hr to yield resorthiomycin in 60% yield. It was fully characterized by IR, PMR (FIG. IX) and mass spectra (FIG. X) and found to be identical to that reported in the literature. This constitutes the first total synthesis of resorthiomycin.

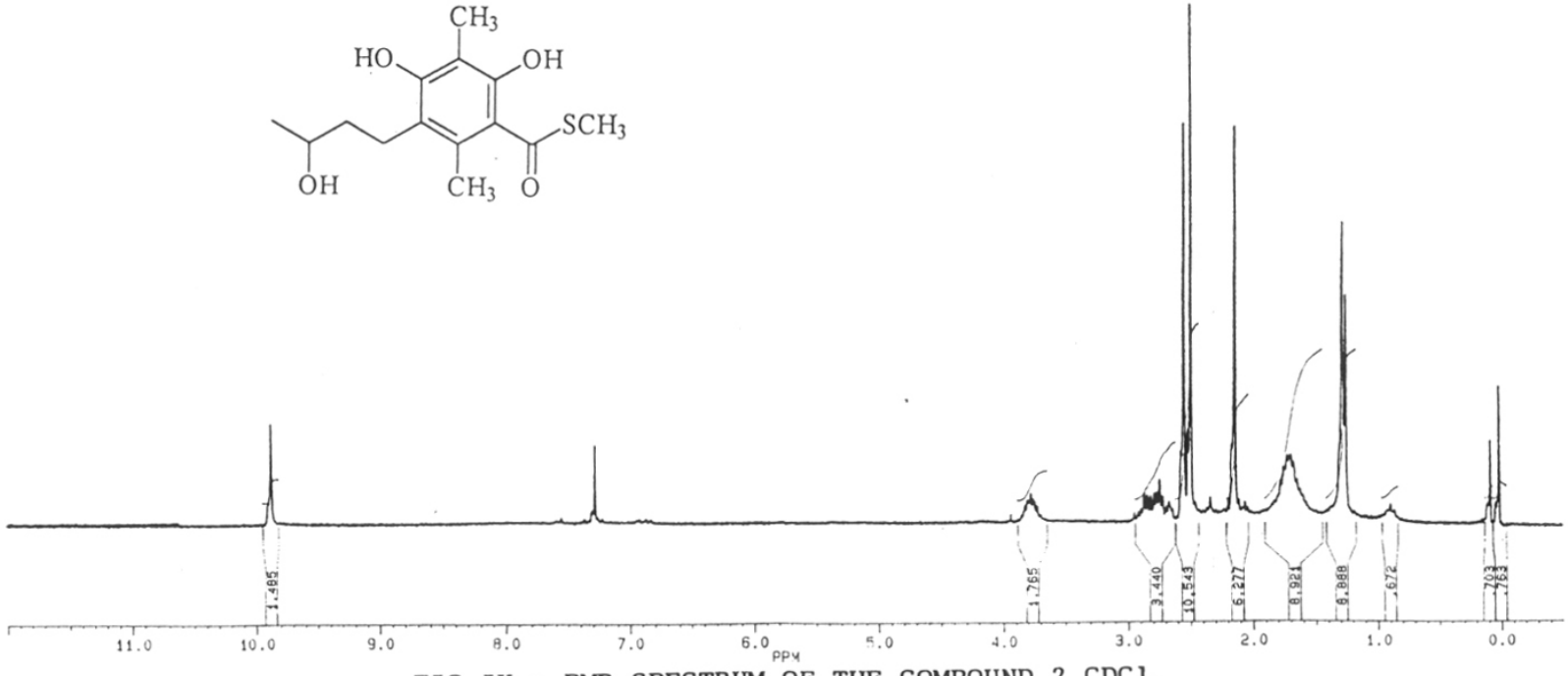



FIG IX : PMR SPECTRUM OF THE COMPOUND 2 $CDCl_3$

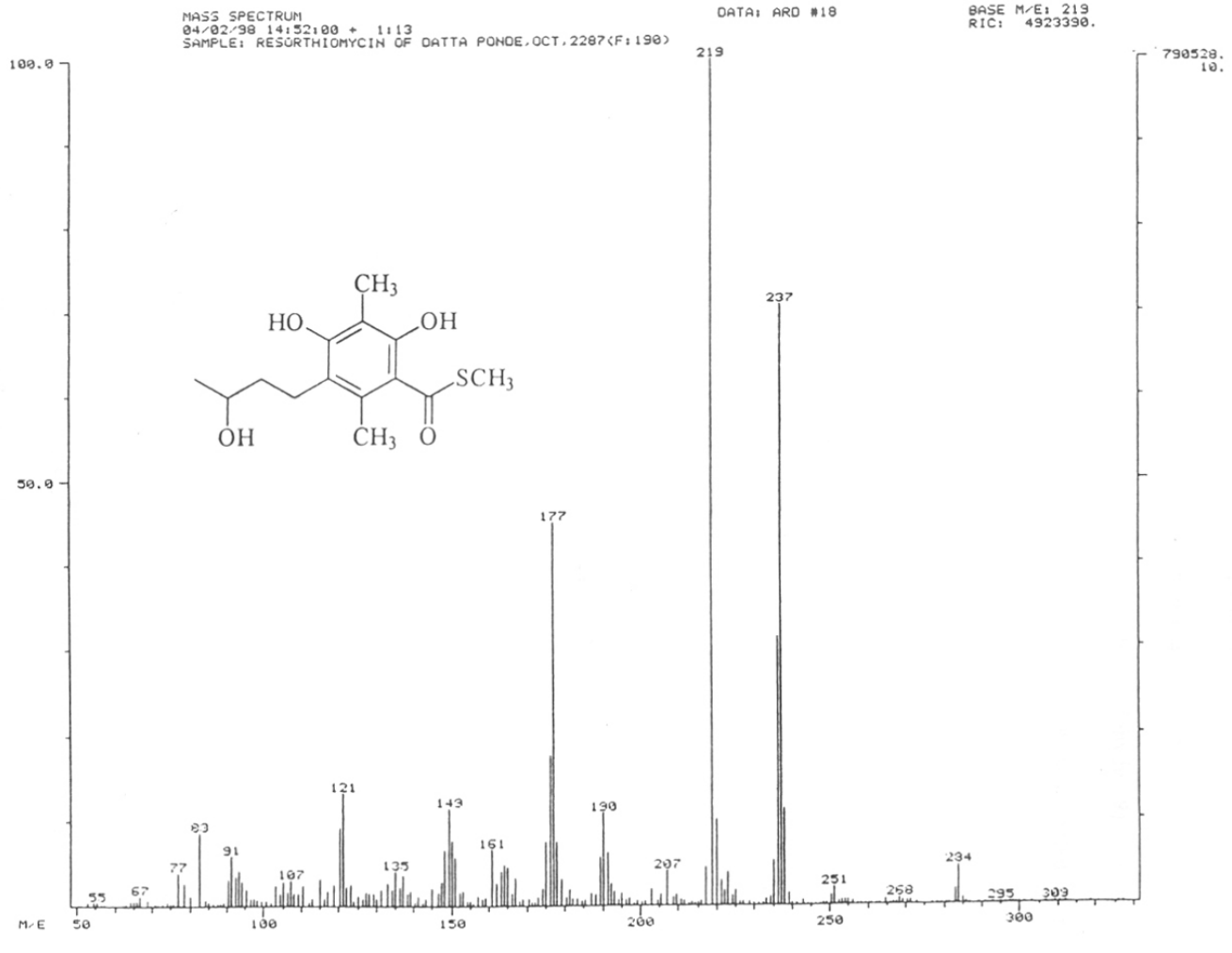



FIG X : MASS SPECTRUM OF THE COMPOUND 2

## Experimental

**1,2,3-Trimethoxy-5-methylbenzene (10)**

To a mixture of amalgamated zinc [prepared from zinc wool (20.9 g) and mercuric chloride (2.61 g)], concentrated hydrochloric acid (78.5 ml) and water (78.5 ml), an ethanolic solution (55 ml) of 3,4,5-trimethxoybenzaldehyde (**9**) (7.84 g, 0.04 mol) was added and refluxed for 8 hr. The reaction mixture was cooled to room temperature, diluted with water and extracted with chloroform. The chloroform extract was washed with water, dried ($Na_2SO_4$) and concentrated under vacuum to give the crude product which was distilled under reduced pressure to afford colourless liquid which solidified immediately and was characterized as 1,2,3-trimethoxy-5-methylbenzene (**10**) by physical and spectral means.

**Yield :** 5.12 g (70.4%)

**B.P.:** 115°C/ 5mm [Lit.[44] b.p. 253°C]

**PMR ($CDCl_3$, 90 MHz):** δ 2.38 (s, 3H, Ar$\underline{CH_3}$); 3.85 (s, 9H, 3 x ArO$\underline{CH_3}$); 6.30 (s, 2H, 2 x Ar$\underline{H}$).

**1,3-Dimethoxy-2, 5-dimethylbenzene (6)**

A solution of 1,2,3-trimethoxy-5-methylbenzene (**10**) (5.096 g, 28 mmol) in anhydrous THF (5 ml) was added dropwise to a mixture of the freshly cut potassium (3.27 g, 0.084 g atom) in anhydrous THF (20 ml) and vigorously stirred at room temperature. The mixture was stirred for 24 hr at room temperature and then chilled to 0°C, methyl iodide (5.96 g, 42 mmol) dissolved in anhydrous THF (5 ml) was slowly added and the resulting mixture was stirred for 4 hr. The reaction was quenched by slow dropwise addition of water (10 ml) and extracted with ether (3 x 50 ml). The organic phase was collected, washed with water, dried ($Na_2SO_4$) and evaporated to afford the crude product which was purified by silica gel column chromatography using

pet. ether- acetone as an eluent to afford 1,3-dimethoxy-2,5-dimethylbenzene (**6**) as a solid.

**Yield :** 2.44 g (52.6%)

**M.P.:** 49°C (Lit.[45] m.p. 49-50°C)

**PMR ($CDCl_3$, 200 MHz):** δ 2.11 (s, 3H, Ar$\underline{CH_3}$); 2.38 (s, 3H, Ar$\underline{CH_3}$); 3.79 (s, 6H, 2 x ArO$\underline{CH_3}$); 6.34 (s, 2H, 2 x Ar$\underline{H}$).

**1,3-Dimethoxy-2, 5-dimethyl-4-bromobenzene (11)**

To a stirred solution of 1,3-dimethoxy-2, 5-dimethylbenzene (**6**) (2.16 g, 13.01 mmol) in ether (15 ml) was added dioxane dibromide (3.22 g, 13.01 mmol) in ether (15 ml). This solution was stirred for 30 min. Then it was washed with water ( 2 x 25 ml), aqueous sodium bicarbonate and again with water (25 ml). The solvent ether was dried ($Na_2SO_4$) and removed on rotavapor. Chromatographic purification of the crude bromo residue afforded 1,3-dimethoxy-2,5-dimethyl-4-bromobenzene (**11**).

**Yield:** 2.42 g (76%)

**PMR ($CDCl_3$, 200 MHz):** δ 2.15 (s, 3H, Ar$\underline{CH_3}$); 2.35 (s, 3H, Ar$\underline{CH_3}$); 3.85 (s, 3H, ArO$\underline{CH_3}$); 3.90 (s, 3H, ArO$\underline{CH_3}$); 6.40 (s, 1H, Ar$\underline{H}$).

**2,4-Dimethoxy-3, 6-dimethylbenzoic acid (12)**

Over a period of 30 min, a solution of 1,3-dimethoxy-2,5-dimethyl-4-bromo benzene (**11**) (2.40 g, 9.8 mmol) in dry ether (15 ml) was added dropwise to a well stirred mixture of lithium (150 mg, 21.4 mmol) in the form of fine shaving in ether (10 ml) in such a way to maintain a gentle reflux of the solvent continuously under $N_2$ atmosphere. After the complete addition it was refluxed for further 30 min. The reaction mixture was cooled by ice-water and diluted by adding more ether (15 ml). It was then cooled to -50°C and poured into a beaker containing crushed cardice (20 g) in

the form of slurry with dry ether (20 ml). The cardice was allowed to evaporate overnight. The reaction mixture was warmed to evaporate ether. It was acidified with hydrochloric acid. The crude solid acid was collected by suction filtration. 2,4-Dimethoxy-3,6-dimethylbenzoic acid (**12**) was obtained as a white crystalline solid, crystallized from ethyl acetate.

**Yield:** 1.33 g (65%)

**M. P.:** 103°C (Lit.[22] m.p. 104-105°C)

**IR ($CHCl_3$):** 910, 1080, 1250, 1590, 1700 and 3000 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 2.18 (s, 3H, Ar$\underline{CH_3}$); 2.55 (s, 3H, Ar$\underline{CH_3}$); 3.85 (s, 3H, ArO$\underline{CH_3}$); 3.87 (s, 3H, ArO$\underline{CH_3}$); 6.55 (s, 1H, Ar$\underline{H}$).

**MS (m/z):** 210 ($M^+$, 58); 192 (100); 177 (28); 163 (23); 149 (30); 134 (16); 91 (28); 77 (27); 65 (15).

**S-Methyl-2,4-dimethoxy-3,6-dimethyl thiobenzoate (15)**

**Method A**

To an ice-cold mixture of 2,4-dimethoxy-3, 6-dimethylbenzoic acid (**12**) (650 mg, 3.09 mmol) and thionyl chloride (550 mg, 4.66 mmol) in benzene (25 ml) was added two drops of N, N-dimethylformamide. The reaction mixture was refluxed for 6 hr. The benzene was distilled off. The crude acid chloride **13** thus formed was diluted with benzene (25 ml) and dimethylthioformamide (275 mg, 3.09 mmol) was added. The reaction mixture was stirred at room temperature for 4 hr and $H_2S$ gas was passed into the reaction mixture at a moderate rate. Water (25 ml) was added and the organic layer was separated, dried ($Na_2SO_4$) and concentrated under vacuum. The corresponding thiobenzoic acid **14** obtained was esterified as such using dimethyl sulfate and potassium carbonate to afford a viscous oil which was characterized as S-methyl-2,4-dimethoxy-3,6-dimethyl thiobenzoate (**15**).

**Yield:** 294 mg (39.8%)

**IR (Neat):** 1500, 1590 and 1670 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.15 (s, 3H, Ar$\underline{CH_3}$); 2.35 (s, 3H, Ar$\underline{CH_3}$); 2.45 (s, 3H, ArCOS$\underline{CH_3}$); 3.85 (s, 3H, ArO$\underline{CH_3}$); 3.90 (s, 3H, ArO$\underline{CH_3}$); 6.30 (s, 1H, Ar$\underline{H}$).

**Method B**

To an ice-cold mixture of 2,4-dimethoxy-3,6-dimethylbenzoic acid (**12**) (650 mg, 3.09 mmol) and thionyl chloride (550 mg, 4.66 mmol) in benzene (25 ml) was added two drops of dimethylformamide. The reaction mixture was refluxed for 6 hr. The benzene was distilled off from the reaction mixture. Additional benzene (10 ml) was added and again distilled off. The reaction mixture was allowed to come to room temperature. Again benzene (25 ml) was added. Potassium hydrogen sulfide (444 mg, 6.1 mmol) was added and allowed to stirr at room temperature overnight and then diluted with water (25 ml). The reaction mixture was acidified with cold dil. hydrochloric acid. The organic layer was separated, dried ($Na_2SO_4$) and concentrated under vacuum. The residue obtained was esterified as such using dimethyl sulfate and potassium carbonate in acetone to afford the crude ester which on silica gel column chromatography using pet.ether-acetone as an eluent gave a viscous oil which was characterized as S-methyl-2,4-dimethoxy-3,6-dimethylthiobenzoate (**15**) by spectral methods.

**Yield:** 401 mg (54%)

Spectral data was identical to the product obtained by method A.

**S-Methyl-2,4-dimethoxy-3,6-dimethyl-5-bromo thiobenzoate (5)**

To a stirred solution of S-methyl-2, 4-dimethoxy-3,6-dimethyl thiobenzoate (**15**) (120 mg, 0.5 mmol) in ether (10 ml) was added dioxane dibromide (124 mg, 0.5 mmol)

in ether (5 ml). This solution was stirred for 30 min and then it was washed with water (25 ml). The solvent ether was dried ($Na_2SO_4$) and removed on rotavapor. The residue was chromatographed on silica gel column using 2% acetone in pet-ether to give a pale yellow viscous oil which was characterized as S-methyl-2,4-dimethoxy-3,6-dimethyl-5-bromo-thiobenzoate (**5**) on the basis of its spectral data.

**Yield:** 60 mg (38%)

**IR ($CHCl_3$):** 1490, 1610 and 1660 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.15 (s, 3H, Ar$\underline{CH_3}$); 2.30 (s, 3H, Ar$\underline{CH_3}$); 2.45 (s, 3H, ArCOS$\underline{CH_3}$); 3.75 (s, 3H, ArO$\underline{CH_3}$); 3.88 (s, 3H, ArO$\underline{CH_3}$).

**Methyl 2-methoxybenzoate (17)**

A mixture of salicylic acid (**16**) (4.14 g, 0.03 mol), dimethyl sulphate (8.5 ml, 0.09 mol) and anhydrous potassium carbonate (10 g) in dry acetone (100 ml) was refluxed with occasional shaking for 8 hr. Usual work up and chromatographic purification afforded **17** as a colourless liquid.

**Yield:** 3.58 g (72%)

**IR (Neat):** 1020, 1490, 1600 and 1730 $cm^{-1}$.

**PMR ($CDCl_3$, 90 MHz):** δ 3.90 (s, 6H, 2 x -$\underline{OCH_3}$); 6.90 - 7.0 (m, 2H, 2 x Ar$\underline{H}$); 7.42 - 7.50 (m, 1H, Ar$\underline{H}$); 7.80 (m, 1H, Ar$\underline{H}$).

**2-Methoxybenzoic acid (18)**

A solution of sodium hydroxide (1.6 g, 0.04 mol) in water (15 ml) was added to the solution of ester **17** (3.50 g, 0.02 mol) in methanol (15 ml). After the addition, the reaction mixture was refluxed for 6 hr. The methanol was distilled off and the aqueous part was acidified with cold dilute hydrochloric acid. It was extracted with ethyl acetate

and the ethyl acetate extract was washed with water, dried ($Na_2SO_4$) and concentrated on rotavapor. Chromatographic purification of the residue afforded a solid which was characterized as 2-methoxybenzoic acid (**18**) by spectral methods.

**Yield:** 2.17 g (68%)

**M.P.:** 101°C (lit.[46] m.p. 101.5°C)

**PMR ($CDCl_3$ + DMSO-$d_6$):** δ 3.85 (s, 3H, ArO$\underline{CH_3}$); 6.95-7.05 (m, 2H, 2 x Ar$\underline{H}$); 7.42 - 7.50 (m, 1H, Ar$\underline{H}$); 7.65 - 7.70 (m, 1H, Ar$\underline{H}$).

**S-Methyl-2-methoxythiobenzoate (19)**

Compound **18** (2 g, 13.1 mmol) was converted to compound **19** by using the same procedure as that for converting **12** to **15** (method B).

**Yield:** 1.0 g (42%)

**IR (Neat):** 750, 900, 1030, 1120, 1500, 1590 and 1640 $cm^{-1}$.

**PMR ($CDCl_3$, 90 MHz):** δ 2.45 (s, 3H, COS$\underline{CH_3}$); 3.85 (s, 3H, ArO$\underline{CH_3}$); 6.80-7.75 (m, 4H, 4 x Ar$\underline{H}$).

**S-Methyl 2-hydroxythiobenzoate (20)**

To the solution of ester **19** (800 mg, 4.3 mmol) in dichloromethane (20 ml) was added anhydrous aluminium chloride (1.16 g, 8.6 mmol) at 0°C. It was stirred for 1 hr and then allowed to come to room temperature. It was stirred at room temperature for 4 hr and then poured into cold dilute hydrochloric acid, and warmed on water bath for 20 min. It was extracted with dichloromethane, dried ($Na_2SO_4$) and concentrated on rotavapor. Chromatographic purification of the residue afforded **20** as a creamish solid.

**Yield:** 487 mg (66%)

**M. P.:** 33-35°C

**I.R. ($CHCl_3$):** 1590, 1665 and 3350 $cm^{-1}$

**PMR ($CDCl_3$, 90 MHz):** δ 2.45 (s, 3H, $COSCH_3$); 6.60 - 7.75 (m, 4H, 4 x ArH); 10.80 (s, 1H, ArOH).

**MS (m/z):** 168 ($M^+$, 18), 149 (12), 121 (100), 93 (32), 65 (62), 57 (32), 53 (20), 43 (36).

**β-Resorcylic acid (22)**

To a solution of resorcinol (4.0 g, 36.3 mmol) in water (40 ml) was added potassium hydrogen carbonate (20.0 g). The reaction mixture was heated on steam bath for 4 hr. Then it was refluxed vigorously for 30 min. on flame and a rapid stream of carbon dioxide was passed through the solution. In the same hot condition, reaction mixture was acidified with concentrated hydrochloric acid (18 ml). The reaction mixture was allowed to cool to room temperature and then it was chilled in an ice bath. Crude β-resorcylic acid (**22**) was obtained by filtration. It was recrystallized from water.

**Yield :** 3.28 g (58.6%)

**M.P.:** 215°C (Lit.[25] m.p. 216-217°C).

**Methyl 2,4-dimethoxybenzoate (23)**

A mixture of β-resorcylic acid (**22**) (3.0 g, 19.4 mmol), dimethyl sulfate (7.35 ml, 77.6 mmol) and anhydrous potassium carbonate (10.0 g) in acetone (25 ml) was refluxed for 8 hr. Usual work up followed by column chromatography afforded **23** as a colourless liquid.

**Yield :** 3.43 g (90%)

**PMR ($CDCl_3$, 90 MHz):** δ 3.75 (s, 3H, $ArOCH_3$); 3.85 (s, 6H, 2 x $ArOCH_3$); 6.30-6.45 (m, 2H, 2 x ArH); 7.68 - 7.80 (m, 1H, ArH).

**MS (m/z):** 196 ($M^+$, 57); 179 (5); 165 (100); 150 (15); 135 (30); 122 (42); 107 (52); 92 (29); 79 (62); 63 (80).

**Methyl 2,4-dihydroxybenzoate (25)**

To an ice cold solution of ester **23** (3.0 g, 15.3 mmol) in dichloromethane (30 ml) was added anhydrous aluminium chloride (6.10 g, 45.9 mmol) at 0°C. The reaction mixture was allowed to come to room temperature. It was stirred at room temperature for 12 hr. It was then poured slowly into a cold dilute hydrochloric acid and warmed on water bath for 20 min. After cooling to room temperature, a colourless crystalline solid separated was filtered, washed with water and dried. This crude solid on column chromatography gave pure methyl 2-hydroxy-4-methoxybenzoate (**24**)

[PMR ($CDCl_3$, 90 MHz): δ 3.75 (s, 3H, $COOCH_3$); 3.85 (s, 3H, $ArOCH_3$); 6.25 - 6.40 (m, 2H, 2 x ArH); 7.55 - 7.70 (m, 1H, ArH); 10.8 (s, 1H, ArOH).]. When the reaction was further continued for 12 hr without isolating **24,** usual work up afforded a solid which was characterized as methyl 2, 4-dihydroxybenzoate (**25**).

**Yield:** 1.59 g (62%)

**M. P.:** 120°C ( Lit.[47] m.p. 120°C )

**PMR (90 MHz, $CDCl_3$):** δ 3.85 (s, 3H, $ArCOOCH_3$); 6.25 - 6.40 (m, 2H, 2 x ArH); 7.50-7.60 (m, 1H, ArH); 11.1 (br s, 1H, ArOH)

**MS (m/z):** 168 ($M^+$, 48); 136 (100); 125 (5); 108 (95); 95 (12); 80 (40); 69 (38); 63 (12); 52 (38).

**Methyl 3-(1,3-dithiolane) butanoate (26)**

A mixture of methyl acetoacetate (11.6 g, 0.1 mol), 1,2-ethanedithiol (10.34 g, 0.11 mol) and natural kaolinitic clay (1.16 g, 10% wt/wt) in toluene (150 ml) was refluxed for 8 hr under Dean Stark condition to remove water. The clay catalyst was

filtered out. The toluene was concentrated and the product distilled at reduced pressure to afford methyl 3-(1,3-dithiolane) butanoate (**26**) as a colourless liquid.

**Yield:** 15.36 (80%)

**B.P.:** 123-125°C/10 mm (Lit.[48] b.p. 94-97°C/2 mm)

**IR (Neat):** 1020 and 1740 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 1.90 (s, 3H, $\underline{CH_3}$); 3.0 (s, 2H, $\underline{CH_2}COOCH_3$); 3.35 (s, 4H, -S$\underline{CH_2CH_2}$S-); 3.70 (s, 3H, -COO$\underline{CH_3}$).

**$^{13}$C-NMR ($CDCl_3$, 50 MHz):** δ 31.43, 39.77, 49.97, 51.51, 62.09, 170.30

**MS (m/z):** 192 ($M^+$, 15); 132 (2); 119 (100); 111 (18); 100 (25); 77 (22); 67 (26).

**3-( 1, 3-Dithiolane ) butane-1-ol (27)**

To a slurry of lithium aluminium hydride (1.97 g, 52 mmol) in dry ether (50 ml) at 0°C a solution of protected butanone **26** (10 g, 52 mmol) in dry ether (50 ml) was added dropwise over a period of 1 hr. The reaction mixture was then stirred at room temperature for 18 hr. Usual work up using aqueous ammonium chloride solution afforded 3-(1,3-dithiolane) butane-1-ol (**27**).

**Yield:** 6.23 g (73%)

**IR ($CHCl_3$):** 3400 $cm^{-1}$

**PMR ($CDCl_3$, 90 MHz):** δ 1.80 (s, 3H, $\underline{CH_3}$); 2.20 (t, J= 7 Hz, 2H, $\underline{CH_2}CH_2OH$); 3.35 (s, 4H, -S$\underline{CH_2CH_2}$S-); 3.85 (t, J= 7 Hz, 2H, $\underline{CH_2}OH$)

**MS (m/z):** 164 ($M^{+\cdot}$ 25); 149 (5); 119 (100); 105 (10); 86 (8); 71 (28); 59 (49).

**3-(1,3-Dithiolane)-1-bromobutane (4)**

Over a period of 1 hr, a solution of phosphorous tribromide (1.64 g, 6 mmol) in dry ether (25 ml) was added dropwise to a well stirred mixture of 3-(1,3-dithiolane) butane-1-ol (**27**) (1.0 g, 6 mmol) and pyridine (474 mg) in dry ether (50 ml) at 0°C. After the addition, the reaction mixture was stirred at room temperature for 1 hr. The reaction was quenched with water and extracted with ether. The ether layer was washed with water, dried ($Na_2SO_4$) and concentrated under reduced pressure. Chromatographic purification of the residue afforded a pale yellow semisolid which was characterized as 3-(1,3-dithiolane)-1-bromobutane (**4**) by spectral methods.

**Yield:** 946 mg (68.4%)

**PMR ($CDCl_3$, 200 MHz):** δ 1.80 (s, 3H, $\underline{CH_3}$); 2.5 (t, J=7 Hz, 2H, -$\underline{CH_2}CH_2Br$); 3.35 (s, 4H, -S$\underline{CH_2}\underline{CH_2}$S-); 3.50 (t, J=7 Hz, 2H, $CH_2\underline{CH_2}Br$)

**MS (m/z):** 228 ($M^+$+2); 226 ($M^+$,15); 211 (7); 146 (10), 131 (9); 119 (100); 103 (5); 87 (22); 71 (13); 58 (72).

**Butylbenzene (28)**

To a vigorously stirred mixture of sodium (1.125 g, 48.9 g atom) in dry benzene (25 ml) was added a mixture of bromobenzene (2.6 g, 16.5 mmol) and bromobutane (2.55 gm, 18.6 mmol) in dry benzene (15 ml) dropwise over 35 min. at room temperature. After the addition, reaction mixture was refluxed for 3 hr. The reaction mixture was allowed to cool down and methanol (10 ml) was added to destroy the excess of sodium followed by addition of methanol-water (1:1). The benzene extract was washed with water, dried ($Na_2SO_4$) and concentrated in vacuum. Chromatographic purification of the residue afforded butylbenzene as a colourless liquid.

**Yield:** 635 mg (28.52%)

**PMR ($CDCl_3$, 200 MHz):** δ 1.0 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$); 1.40-1.50 (m, 2H, $CH_2CH_2\,\underline{CH_2}CH_3$); 1.70 - 1.80 (m, 2H, $CH_2\underline{CH_2}CH_2CH_3$); 2.70 (t, J = 7 Hz, 2H, $Ar\underline{CH_2}$); 7.25 - 7.40 (m, 5H, 5 x Ar<u>H</u>

**Methyl crotonate**

To an ice cold stirred solution of crotonic acid (100 g, 1.16 mol) in dry methanol (1000 ml) was added dropwise thionyl chloride (127 ml, 1.74 mol) over a period of 90 min at 0-5°C. It was stirred overnight at room temperature. The reaction mixture was poured on crushed ice and extracted with ether (5 x 100 ml). The combined ether layer was washed with sodium bicarbonate solution, followed by 1% hydrochloric acid, water, dried ($Na_2SO_4$) and concentrated. It was distilled at normal pressure to afford methyl crotonate as colourless liquid.

**Yield:** 81.39 g (70%)

**B.P.:** 121°C (Lit.[31] b.p. 121°C)

**Methyl dihydro-orsellinate (29)**

To a well stirred solution of sodium methoxide, prepared from sodium (17.25 g) in dry methanol (250 ml), were added methyl acetoacetate (87 g, 0.75 mol) and methyl crotonate (75 g, 0.75 mol) in turn. It was refluxed for 44 hr. The methanol was removed by distillation. The residue was cooled and ether (400 ml) was added to it. The precipitated salt was filtered and dissolved in water (100 ml). It was cooled to 5°C and acidified with ice cold concentrated hydrochloric acid. Precipitated compound was filtered off and washed with water and dried. Crystallization of the solid from ethyl acetate furnished the corresponding methyl dihydro-orsellinate (**29**).

**Yield:** 89.7 g (65%)

**M.P.:** 122° (Lit.[30] m.p. 122-124°C).

**Methyl 3, 5-dibromo-2,4-dihydroxy-6-methylbenzoate (30)**

Bromine (63.2 ml, 1.22 mol) in glacial acetic acid (75 ml) was added to a stirred solution of methyl dihydro-orsellinate (**29**) (75 g, 0.4 mol ) in glacial acetic acid (240 ml) in such a controlled rate that the temperature of the reaction mixture did not exceed 40-45°C. The mixture was then stirred for 1 hr and set aside for 18 hr. Water was added and the product was separated by filtration, washed with water and dried. Then it was crystallized from hexane-ethyl acetate (7:3) to afford methyl 3,5-dibromo-2,4-dihydroxy-6-methyl benzoate (**30**) as a pale yellow solid.

**Yield:** 130 g (95%)

**M.P.** 105-107°C (Lit.[30] m.p. 105-106°C)

**IR (nujol):** 1030, 1720 and 3300 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.50 (s, 3H, Ar$\underline{CH_3}$); 3.82 (s, 3H, ArCOO$\underline{CH_3}$); 6.50 (br s, 1H, Ar$\underline{OH}$); 12.10 (s, 1H, Ar$\underline{OH}$).

**Methyl orsellinate (8)**

Methyl 3, 5-dibromo-2, 4-dihydroxy-6-methyl benzoate (**30**) (65 g, 0.19 mol) was dissolved in 2N sodium hydroxide solution (1285 ml) at 0°C. Nickel-aluminium alloy (55.0 g) was added with stirring to it in small portions as rapidly as possible. The Raney nickel was removed by filtration. The filtrate was strongly acidified by concentrated hydrochloric acid at ice-cold condition. The aqueous solution was extracted with diethyl ether. The organic layer was washed with water, brine, dried ($Na_2SO_4$) and concentrated to obtain a residue which was recrystallized from ethyl acetate to give methyl orsellinate (**8**).

**Yield:** 28.73 g (82%)

**M.P.:** 138°C (Lit.[30] m.p. 138-140°C)

**IR (nujol):** 1040, 1720 and 3300 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.50 (s, 3H, Ar$\underline{CH_3}$); 3.80 (s, 3H, ArCOO$\underline{CH_3}$); 6.4 (br s, 3H, 2 x Ar$\underline{H}$ + Ar$\underline{OH}$); 12.40 (s, 1H, Ar$\underline{OH}$).

**MS (m/z):** 182 ($M^+$, 40); 150 (100); 122 (53), 94 (18); 69 (22).

**Methyl 2,4-dihydroxy-3-formyl-6-methylbenzoate (32): Method A**

To an ice-cold solution of methyl orsellinate (**8**) (1.39 g, 7.63 mmol) in trifluoro acetic acid (30 ml) was added hexamethylenetetramine (1.28 g, 9.15 mmol). It was refluxed for 12 hr. Trifluoroacetic acid was distilled out. Then water (30 ml) was added and heated at 60°C for 6 hr. The aqueous solution was extracted with ethyl acetate. The organic layer was washed with water, brine, dried ($Na_2SO_4$) and concentrated to obtain a residue which was purified over silica gel column using pet.ether-acetone for elution, to afford methyl 3,5-diformyl-2,4-dihydroxy-6-methylbenzoate (**31**) as a yellow solid.

**Yield:** 549 mg (30%)

**M.P.:** 157°C (Lit.[49] m.p. 159°C)

**PMR ($CDCl_3$, 90 MHz):** δ 2.45 (s, 3H, Ar$\underline{CH_3}$); 3.80 (s, 3H, ArCOO$\underline{CH_3}$); 9.90 (s, 1H, Ar$\underline{CHO}$); 10.1 (s, 1H, Ar$\underline{CHO}$); 12.85 (br s, 1H, Ar$\underline{OH}$); 13.4 (s, 1H, Ar$\underline{OH}$).

Further elution afforded methyl 2, 4-dihydroxy-3-formyl-6-methylbenzoate (**32**) as a crystalline solid.

**Yield:** 224 mg (14%)

**M.P.:** 147°C (Lit.[34] m.p. 146°C)

**IR (nujol):** 1020, 1610, 1730 and 3400 (br) $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.52 (s, 3H, Ar$\underline{CH_3}$); 3.85 (s, 3H, ArCOO$\underline{CH_3}$); 6.40 (s,1H, $\underline{ArH}$); 10.20 (s, 1H, Ar$\underline{CHO}$); 12.1 (s, 1H, Ar$\underline{OH}$).

**MS (m/z):** 210 ($M^+$, 52); 178 (32); 150 (100); 122 (25); 94 (19); 66 (18); 53 (18).

**Methyl 2,4-dihydroxy-3-formyl -6-methylbenzoate (32): Method B**

To a mixture of methyl orsellinate (**8**) (28 g, 0.15 mol) and zinc cyanide (51.5 g, 0.43 mol) in dry ether (550 ml) was added anhydrous aluminium chloride (58.9 g, 0.44 mol ) dissolved in ether (500 ml) at 0°C. The cooled mixture was saturated with HCl gas. After 24 hr the etheral layer was decanted from a viscous oil, which was hydrolysed by heating on a steam bath for 20 min with water (500 ml). The reaction mixture was cooled and the solid product separated was filtered, washed with water and air dried. It was recrystallized from methanol to afford **32** as a crystalline solid.

**Yield:** 25.84 g (80%)

Spectral data was identical as mentioned above.

**Methyl, β-orcinolcarboxylate (33)**

To a mixture of amalgamated zinc [prepared from zinc wool (133.3 g) and mercuric chloride (10.13 g)], concentrated hydrochloric acid (480 ml) and water (240 ml) a methanolic solution (960 ml) of aldehyde **32** (24.0 g, 0.114 mol) was added and refluxed for 6 hr. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried ($Na_2SO_4$) and concentrated under vacuum to give a solid. It was crystallized from methanol to afford colourless needles of methyl β-orcinolcarboxylate (**33**).

**Yield:** 17.4 g (78%)

**M.P.:** 145°C (Lit.[34] m.p. 145-146°C)

**IR (nujol):** 1030, 1720 and 3300 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.12 (s, 3H, Ar$\underline{CH_3}$); 2.45 (s, 3H, Ar$\underline{CH_3}$); 3.85 (s, 3H, ArCOO$\underline{CH_3}$); 6.20 (s, 1H, Ar$\underline{H}$); 12.0 (s, 1H, Ar$\underline{OH}$).

**MS (m/z):** 196 ($M^+$, 42); 164 (95); 136 (100); 107 (22); 79 (28).

**Methyl 2,4-dihydroxy-3,6-dimethyl-5-formyl benzoate (34)**

To a mixture of methyl β-orcinolcarboxylate (**33**) (17 g, 86.7 mmol) and hexamethylenetetramine (14.45 g, 103 mmol) was added at 0°C trifluoroacetic acid (250 ml). The reaction mixture was refluxed for 12 hr and the solvent was distilled under reduced pressure. Water (600 ml) was added and heated at 60°C for 6 hr. Orange coloured solid obtained was filtered under suction, washed with water (100 ml) and dried to give orange solid which was characterized as methyl 2,4-dihydroxy-3,6-dimethyl-5-formyl benzoate (**34**) by spectral methods.

**Yield:** 17.48 g (90%)

**M.P.:** 112-113°C (Lit.[35] m.p. 113-114°C)

**IR (nujol):** 1030, 1100, 1490, 1600, 1720 and 3300 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.10 (s, 3H, Ar$\underline{CH_3}$); 2.85 (s, 3H, Ar$\underline{CH_3}$); 3.85 (s, 3H, ArCOO$\underline{CH_3}$); 10.30 (s, 1H, Ar$\underline{CHO}$); 12.25 (s, 1H, Ar$\underline{OH}$); 13.10 (s, 1H, Ar$\underline{OH}$).

**MS (m/z):** 224 ($M^+$, 60); 192 (100); 164 (92); 136 (40); 107 (38); 83 (52); 77 (61).

**Methyl 2,4-dimethoxy-3, 6-dimethyl-5-formyl benzoate (35)**

A mixture of aldehyde-ester **34** (17.4 g, 0.077 mol), dimethyl sulfate (21.8 ml, 0.231 mol) and anhydrous potassium carbonate (40 g) in dry acetone (150 ml) was refluxed with occasional shaking for 8 hr. Potassium carbonate was filtered off and washed with acetone. Combined acetone was distilled off, water (300 ml) was added and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried ($Na_2SO_4$) and concentrated. This residue on silica gel column chromatography gave methyl 2,4-dimethoxy-3, 6-dimethyl-5-formyl benzoate (**35**) as a viscous liquid.

**Yield:** 17.42 g (89%)

**PMR ($CDCl_3$, 90 MHz):** δ 2.18 (s, 3H, Ar$\underline{CH_3}$); 2.40 (s, 3H, Ar$\underline{CH_3}$); 3.75 (s, 3H, ArCOO$\underline{CH_3}$); 3.80 (s, 3H, Ar$\underline{OCH_3}$); 3.85 (s, 3H, Ar$\underline{OCH_3}$); 10.35 (s, 1H, Ar$\underline{CHO}$).

**MS (m/z):** 252 ($M^+$, 85); 237 (50); 221 (100); 205 (55); 191 (22); 177 (28); 163 (32); 105 (20); 91 (50); 77 (61); 65 (38); 51 (41); 43 (58).

**Methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-oxo-1-butenyl) benzoate (7)**

A solution of sodium hydroxide (0.50 g) in water (3 ml) was added at 0°C to the solution of methylated compound **35** (5.84 g, 23.1 mmol) in acetone (50 ml). After the addition, the reaction mixture was stirred at room temperature overnight. It was then diluted with water and extracted with ethyl acetate. The ethyl acetate extract was washed with water, dried ($Na_2SO_4$) and concentrated under vacuum. Chromatographic purification of the residue afforded methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-oxo-1-butenyl)benzoate (7) as a viscous oil.

**Yield:** 4.80 g (71%)

**IR (Neat):** 840, 1020, 1200, 1570, 1650, 1720 and 2910 $cm^{-1}$.

**Yield:** 1.91 g (81.1%)

**IR ($CHCl_3$):** 735, 910, 1500, 1600, 1720 and 2960 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.38 (s, 3H, $\underline{CH_3}CO$); 3.90 (s, 9H, $ArO\underline{CH_3}$); 6.20 (s, 2H, 2 x Ar$\underline{H}$); 6.60 (d, J = 17 Hz, 1H, CH=$\underline{CH}$-C=O); 7.44 (d, J = 17 Hz, 1H, $\underline{CH}$=CH-C=O).

**Methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-oxobutyl) benzoate (44)**

To an ice-cold solution of the α,β-unsaturated keto ester **7** (5.0 g, 17.1 mmol) in dry methanol (50 ml) was added freshly activated magnesium (4.15 g, 71 gm atom) and stirred at that temperature for 1 hr. The reaction mixture was allowed to come to room temperature and stirred for 12 hr. The solvent methanol was removed under vacuum and the residue was treated with 3N dilute hydrochloric acid (100 ml). It was then extracted with chloroform (3 x 50 ml), washed with brine and dried ($Na_2SO_4$). The combined chloroform extract was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography to furnish **44** as a crystalline white solid.

**Yield:** 4.43 g (88%)

**M.P.:** 81°C

**IR (nujol):** 1030, 1510, 1600 and 1720 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.12 (s, 3H, $\underline{CH_3}CO$); 2.15 (s, 3H, $Ar\underline{CH_3}$); 2.18 (s, 3H, $Ar\underline{CH_3}$); 2.52-2.65 (m, 2H, $ArCH_2\underline{CH_2}$); 2.75-2.85 (m, 2H, $Ar\underline{CH_2}CH_2$); 3.65 (s, 3H, $ArCOO\underline{CH_3}$); 3.70 (s, 3H, $ArO\underline{CH_3}$); 3.85 (s, 3H, $ArO\underline{CH_3}$).

**MS (m/z):** 294 ($M^+$, 62); 276 (38); 263 (50); 237 (100); 229 (23); 207 (35); 192 (30); 91 (21).

**Anal.** Cal for $C_{16}H_{22}O_5$ C, 65.30%; H, 7.48%

Found C, 65.34%; H, 7.41%

Further elution afforded methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-hydroxybutyl) benzoate (**45**) as a viscous oil.

**Yield:** 35 mg (7%)

**IR (Neat):** 1050, 1720 and 3400 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 1.15 (d, J = 7 Hz, 3H, $\underline{CH_3}CH$); 1.57-1.70 (m, 2H, $ArCH_2\underline{CH_2}$); 2.30 (s, 6H, 2 x $Ar\underline{CH_3}$); 2.65-2.75 (m, 2H, $Ar\underline{CH_2}CH_2$); 3.60-3.70 (m, 1H, -$\underline{CH}$-OH); 3.75 (s, 3H, $ArCOO\underline{CH_3}$); 3.80 (s, 3H, $ArO\underline{CH_3}$); 3.90 (s, 3H, $ArO\underline{CH_3}$).

**Methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-hydroxybutyl) benzoate (45)**

To a cold (0°C) solution of keto ester **44** (4.78 g, 16.2 mmol) in dry methanol (50 ml) was added sodium borohydride (673 mg, 17.8 mmol), slowly with constant stirring. The reaction mixture was then stirred at room temperature for 3 hr. The methanol was distilled off, water (50 ml) was added and it was acidified with dilute hydrochloric acid. The reaction mixture was extracted with ethyl acetate, the ethyl acetate extract was washed with brine, dried ($Na_2SO_4$) and concentrated to leave a residue which after column chromatographic purification on silica gel with 5% acetone-pet.ether afforded methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-hydroxybutyl) benzoate (**45**) as a viscous oil.

**Yield:** 4.30 g (90.12%)

Spectral data was identical to that mentioned above.

**2,4-Dimethoxy-3,6-dimethyl-5-(3-hydroxybutyl) benzoic acid (46)**

A solution of potassium hydroxide (2.16 g, 38.5 mmol) in water (20 ml) was added to the solution of ester **45** (4.0 g, 13.5 mmol) in methanol (20 ml). After the addition, the reaction mixture was refluxed for 10 hr. The methanol was distilled off and the reaction mixture was acidified with cold dilute hydrochloric acid. It was extracted with ethyl acetate and the ethyl acetate extract was washed with brine, dried ($Na_2SO_4$) and concentrated on rotavapor. Chromatographic purification of the residue afforded a solid which was characterized as 2,4-dimethxoy-3,6-dimethyl-5-(3-hydroxybutyl) benzoic acid (**46**) by spectroscopic methods.

**Yield:** 3.04 g (80%)

**IR (nujol):** 910, 1100, 1580, 1700, 2900 and 3400 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 1.18 (d, J = 7 Hz, 3H, $\underline{CH_3}CH$); 1.55-1.70 (m, 2H, $ArCH_2\underline{CH_2}$); 2.25 (s, 3H, $Ar\underline{CH_3}$); 2.35 (s, 3H, $Ar\underline{CH_3}$); 2.70-2.80 (m, 2H, $Ar\underline{CH_2}CH_2$); 3.70 (m, 1H, -$\underline{CH}$-OH); 3.75 (s, 3H, $ArO\underline{CH_3}$); 3.80 (s, 3H, $ArO\underline{CH_3}$).

**MS (m/z):** 282 ($M^+$, 41); 249 (30); 223 (72); 193 (88); 163 (30); 91 (41); 84 (100); 77 (32).

**Preparation of triphenylantimony**

To a well stirred mixture of bromobenzene (2.0 g) and magnesium (300 mg) in dry ether (30 ml) was added antimony trichloride (900 mg). The reaction mixture was refluxed for 2 hr. It was cooled and added to water in small portions. The organic layer was separated, dried ($Na_2SO_4$) and concentrated to afford colourless crystals of triphenylantimony.

**Yield :** 500 mg (16.1%)

**M.P.:** 46-47$^0$C (Lit. [42] m.p. 46$^0$C)

**Preparation of triphenylantimony oxide**

To a solution of triphenylantimony (450 mg, 1.27 mmol) in benzene (5 ml) under $N_2$, was added *tert*.butylhydroperoxide (114 mg). The temperature of the reaction mixture was increased immediately to 40-45$^0$C . The reaction mixture was kept as such for 20 min. and then benzene was evaporated. Crude residue was washed with ether to afford crystalline powder of triphenylantimony oxide.

**Yield :** 416 mg (90%)

**M.P.:** 218$^0$C ( Lit.[43] m.p. 219$^0$C)

**S-Methyl 2,4-dimethoxy-3, 6-dimethyl-5-(3-hydroxybutyl) thiobenzoate (37)**

To a suspension of phosphorous pentasulfide (44 mg, 0.01 mmol) and triphenylantimony oxide (18 mg, 0.05 mmol) in dry benzene (5 ml) was added acid **46** (282 mg, 1mmol). The reaction mixture was heated upto 40$^0$C and kept at that temperature for 1 hr. The precipitated salt was filtered off. The benzene part was dried ($Na_2SO_4$) and concentrated to afford a residue which was esterified as such using dimethyl sulfate and potassium carbonate in refluxing acetone to afford crude thiol ester. Chromatographic purification of the crude thiol ester gave a viscous oil which was characterized as S-methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-hydroxybutyl) thiobenzoate (**37**).

**Yield:** 15.6 mg (5%)

**IR (Neat):** 1570, 1673, 2928 and 3447 (br) cm$^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 1.15 (d, J = 7 Hz, 3H, $\underline{CH_3}CH$); 1.52-1.68 (m, 2H, $ArCH_2\underline{CH_2}$); 2.20 (s, 6H, 2 x $Ar\underline{CH_3}$); 2.50 (s, 3H, $COS\underline{CH_3}$); 2.68-2.78 (m, 2H, $Ar\underline{CH_2}CH_2$); 3.60-3.70 (m, 1H, $\underline{CH}$-OH); 3.72 (s, 6H, 2 x $Ar\underline{OCH_3}$).

**$^{13}$C-NMR ($CDCl_3$, 50 MHz):** δ 9.90; 12.76; 15.51; 22.84; 23.28; 29.85; 39.0; 60.98; 62.45; 66.90; 122.25; 129.99; 131.91; 153.98; 158.81; 196.56.

**MS (m/z):** 312 ($M^+$, 5); 265 (9); 138 (7); 120 (7); 107 (91); 91 (57); 77 (100); 65 (15).

**2,4-Dimethoxy-3, 6-dimethyl-5-(3-oxobutyl) benzoic acid (48)**

A solution of sodium hydroxide (1.36 g, 34.0 mmol) in water (15 ml) was added to a solution of the ester **44** (2.5 g, 8.5 mmol) in methanol (15 ml). After the addition, the reaction mixture was refluxed for 10 hr. The methanol was distilled off and aqueous part was acidified with cold dilute hydrochloric acid. It was then extracted with ethyl acetate and the ethyl acetate extract was washed with brine, dried ($Na_2SO_4$) and concentrated to obtain 2,4-dimethoxy-3,6-dimethyl-5-(3-oxobutyl) benzoic acid (**48**) as a white solid.

**Yield:** 1.85 g (79%)

**M.P.:** 128°C

**IR (nujol):** 1710 and 3000 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.17 (s, 3H, $\underline{CH_3}CO$); 2.22 (s, 3H, $Ar\underline{CH_3}$); 2.30 (s, 3H, $Ar\underline{CH_3}$); 2.55-2.65 (m, 2H, $ArCH_2\underline{CH_2}$); 2.85-2.95 (m, 2H, $Ar\underline{CH_2}CH_2$); 3.70 (s, 3H, $ArO\underline{CH_3}$); 3.80 (s, 3H, $ArO\underline{CH_3}$).

**MS (m/z):** 280 ($M^+$, 12), 262 (12); 223 (23); 205 (12); 193 (16); 163 (13); 91 (35); 83 (40); 69 (56); 57 (100).

**S-Methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-oxobutyl)-thiobenzoate (28b)**

Compound **48** (1.0 g) was converted to compound **28b** by using the same procedure as that for converting **12** to **15** (Method B).

**Yield:** 431 mg (39%)

**IR ($CHCl_3$):** 1490, 1600, 1670 and 1710 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 2.18 (s, 3H, $\underline{CH_3}CO$); 2.19 (s, 3H, $Ar\underline{CH_3}$); 2.20 (s, 3H, $Ar\underline{CH_3}$); 2.48 (s, 3H, $COS\underline{CH_3}$): 2.55-2.65 (m, 2H, $ArCH_2\underline{CH_2}$); 2.80-2.92 (m, 2H, $Ar\underline{CH_2}CH_2$); 3.72 (s, 6H, 2 x $ArO\underline{CH_3}$).

**$^{13}C$ NMR ($CDCl_3$, 50 MHz):** δ 9.87; 12.80; 15.66; 21.08; 29.99; 43.75; 60.85; 62.48; 122.62; 129.42; 131.69; 155, 159.12; 197.2, 208.35.

**MS (m/z):** 310 ($M^+$, 38); 292 (5); 278 (10); 265 (58); 237 (22); 231 (18); 217 (15); 205 (38); 193 (100); 175 (18); 161 (18); 149 (15); 133 (17); 91 (25); 77 (14).

**S-Methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-hydroxybutyl) thiobenzoate (37)**

To a cold solution of keto-thiol ester **28b** (400 mg, 1.2 mmol) in dry methanol (5 ml) was added sodium borohydride (50 mg, 1.32 mmol), slowly with constant stirring. It was stirred at that temperature for 2 hr. The methanol was distilled off, water (10 ml) was added and acidified with dilute hydrochloric acid. The aqueous part was extracted with chloroform, the combined chloroform extract was washed with water, brine, dried ($Na_2SO_4$) and concentrated to leave a residue which after column chromatographic purification on silica gel with 5% acetone-pet. ether afforded a viscous oil which was characterized as S-methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-hydroxybutyl) thiobenzoate (**37**).

**Yield:** 362 mg (90%)

Spectral data was identical to the product obtained by using triphenylantimony oxide and phosphorous pentasulfide.

**S-Methyl 2,4-dimethoxy-3,6-dimethyl-5-(3-chlorobutyl) thiobenzoate (47)**

Compound **47** was obtained when acid **46** was treated with thionyl chloride, followed by potassium hydrogen sulfide and esterfication in a hope to get **37**.

**IR (neat):** 1680 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 1.55 (d, J=7 Hz, 3H, $\underline{CH_3}CH$); 1.78-1.92 (m, 2H, $ArCH_2\underline{CH_2}$); 2.20 (s, 6H, 2 x $Ar\underline{CH_3}$); 2.48 (s, 3H, $COS\underline{CH_3}$); 2.65-2.90 (m, 2H, $Ar\underline{CH_2}CH_2$); 3.72 (s, 6H, 2 x $ArO\underline{CH_3}$); 4.05-4.15 (m, 1H, -$\underline{CH}$Cl).

**MS (m/z):** 330 ($M^+$, 10); 283 (100); 264 (25); 247 (48); 237 (30); 233 (55); 205 (15); 191 (20); 177 (20); 163 (60); 149 (50); 105 (30); 91 (60).

**S-Methyl 3,6-dimethyl-2-hydroxy-5-(3-hydroxybutyl)-4-methoxy thiobenzoate (49)**

To the solution of resorthiomycin dimethyl ether (**37**) (300 mg, 0.96 mmol) in dichloromethane (15 ml) was added anhydrous aluminium chloride (0.25 g, 1.92 mmol) at 0°C. It was stirred for 2 hr and allowed to come to room temperature. The reaction mixture was stirred at room temperature for 12 hr. It was then poured slowly into cold dilute hydrochloric acid and warmed on water bath for 20 min. After cooling to room temperature, it was extracted with dichloromethane (3 x 10 ml). The combined dichloromethane part was dried ($Na_2SO_4$) and concentrated to afford a residue, which on column chromatographic purification gave **49** as a viscous oil.

**Yield:** 177 mg (62.1%)

**IR (Neat):** 1660 and 3300 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 1.20 (d, J = 7 Hz, 3H, $\underline{CH_3}CH$); 1.53-1.66 (m, 2H, $ArCH_2\underline{CH_2}$); 2.18 (s, 3H, $Ar\underline{CH_3}$); 2.45 (s, 3H, $COS\underline{CH_3}$); 2.50 (s, 3H, $Ar\underline{CH_3}$); 2.68-2.78 (m, 2H, $Ar\underline{CH_2}CH_2$); 3.60-3.70 (m, 1H, -CH-OH); 3.75 (s, 3H, $ArO\underline{CH_3}$); 8.80 (br s, 1H, ArOH)

**S-Methyl 2,4-dihydroxy-3,6-dimethyl-5-(3-hydroxybutyl) thiobenzoate (2)**

To an ice cold solution of resorthiomycin monomethyl ether **49** (100 mg, 0.33 mmol) in dichloromethane (10 ml) was added anhydrous aluminium chloride (87 mg, 0.66 mmol) at 0°C. It was stirred for 1 hr and allowed to come to room temperature. It was refluxed for 4 hr. It was then poured slowly into cold dilute hydrochloric acid and warmed on water bath for 20 min. After cooling to room temperature, it was extracted with dichloromethane (3 x 10 ml). The combined dichloromethane part was dried ($Na_2SO_4$) and concentrated. This residue on silica gel column chromatography gave resorthiomycin **2** as a viscous oil.

**Yield:** 58 mg (60%)

**IR ($CHCl_3$):** 1150, 1600 and 3300 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 1.25 (d, J = 7 Hz, 3H, $\underline{CH_3}CH$); 1.63-1.73 (m, 2H, $ArCH_2\underline{CH_2}$); 2.14 (s, 3H, $Ar\underline{CH_3}$); 2.45 (s, 3H, $ArCOS\underline{CH_3}$); 2.55 (s, 3H, $Ar\underline{CH_3}$); 2.65-2.85 (m, 2H, $Ar\underline{CH_2}CH_2$); 3.75 (m, 1H, -CHOH); 9.80 (br s, 1H, ArOH).

**MS (m/z):** 284 ($M^+$, 4); 237 (70); 219 (100); 207 (5); 190 (11); 177 (48); 149 (11); 121 (12).

# Section C

# Mild and Efficient method for Thiol Esterification

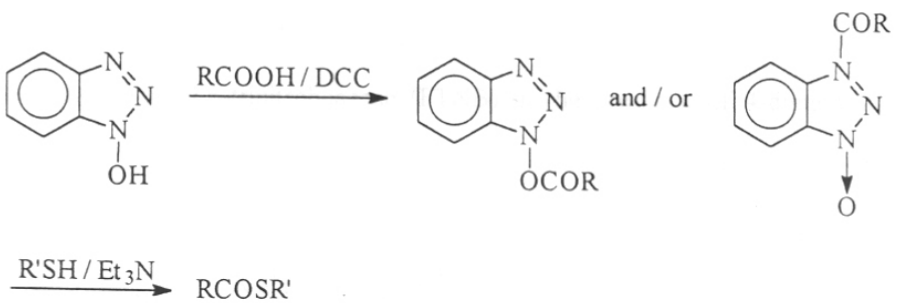
## Introduction

Thiol esters have attracted a great deal of attention in recent years as active acylating agents, especially in the synthesis of macrocyclic lactones and peptides.[50] They are activated derivatives of carboxylic acids and show higher reactivity and selectivity towards nucleophiles than the corresponding oxygen analogues.[51] The thiol ester is a versatile functional group which facilitates the formation of carbon-carbon bond. Synthesis of macrocyclic natural products and the asymmetric carbon-carbon bond formation[51] through the metal enolates derived from thiol esters, have added a new dimension to the utility of these esters.

A wide variety of thiol esterification methods have been reported for the conversion of carboxylic acid or its derivative to thiol ester *via* a single step procedure. Most of these methods are based on the strategy of activation of carboxylic group followed by addition of thiol. These regularly used methodologies along with a few more recently reported developments in this field are presented here.

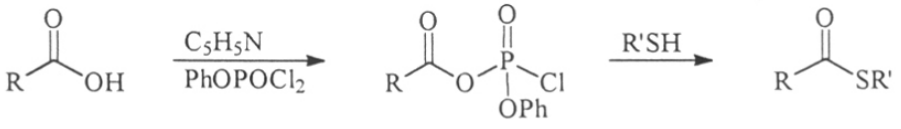
**Kusuo Horiki**[52]

This method of esterification consists of two stages (i) reaction of carboxylic acid with 1-hydroxybenzotriazole in presence of dicyclohexylcarbodiimide followed by addition of thiol.



**Hsing-Jang Liu and Subramaniam Iyer Sabesan**[53]

The condensation of carboxylic acids and thiols is greatly facilitated by the use of phenyl dichlorophosphate as an activating agent giving thiol esters in good yields. Broad spectrum of thiols including 1°, 2°, 3°, phenyl, benzyl etc. undergo esterification, even sterically hindered *t*-butyl mercaptan gave good yields.




**Liu et al.**[54]

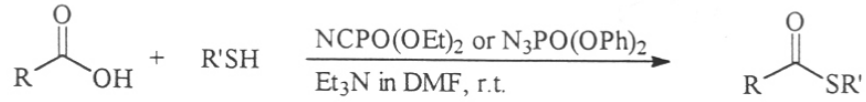
Acid or base sensitive compounds undergo smooth transformation to thiol esters at room temperature under near neutral conditions using N,N-dimethylphosphoramidic dichloride (DMPADC) as a carboxylic acid activator. Special feature of this method is that even penicillins V and G undergo smooth transformation to the corresponding thiol esters.


**Kim and Yang**[55]

Thiol esters can be conveniently prepared by the reaction of carboxylic acid with thiol and 1-fluoro-2,4,6-trinitrobenzene (FTNB) in the presence of 4-dimethylamino-pyridine.

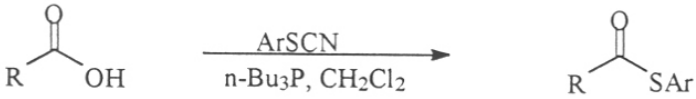
**Yamada et al.**[56]

In this method diethyl phosphorocyanidate or diphenyl phosphorazidate were used as activating agents. This method can be applied to thiol esterification of α-amino acid derivatives.



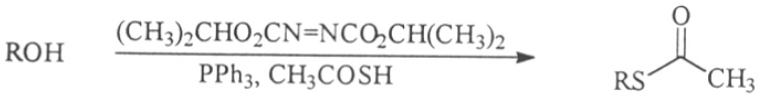

**Grieco et al.**[57]

Benzenethiol esters can be synthesized in good to excellent yields by treating carboxylic acids with phenyl thiocyanate in the presence of tri-n-butylphosphine.



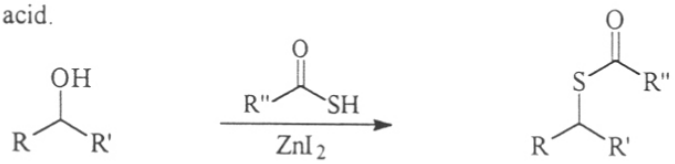

**Volante et al.**[58]

Various alcohols were converted to the corresponding thiolacetates by treatment with triphenylphosphine and diisopropyl azodicarboxylate in the presence of thiolacetic acid.




**Gauthier et al.**[59]

Numerous functionally diverse thiol esters are prepared in high yields in a mild "one-pot" synthesis from activated alcohols and thiolacids under Lewis acid catalysis and in particular zinc iodide. Benzylic, allylic and tertiary alcohols can be activated with Lewis acid.

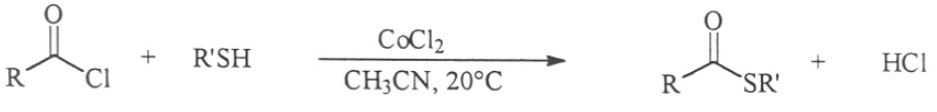


**ReiBig and Scherer**[60]

Treatment of acyl chlorides with copper (I) mercaptides provides an excellent method for thiol esterification.


**Ahmed and Iqbal**[61]

Cobalt (II) chloride was used in place of toxic thallium and copper (I) mercaptides in a one-pot synthesis of thiol esters.



## Present work

As is evident from the literature survey of thiol esterification, most of the methods employ reagents which activate carboxylic acid group. Difficulty associated in the preparation of the reagent becomes mandatory which certainly limits the scope of these reactions. The disposal of the side products becomes a problem and is environmentally unacceptable in the present context of heightened global awareness.

Some of the existing methods for the conversion of acid into thiol esters are generally applicable but search for more efficient and convenient methods which use inexpensive reagents is still worthwhile. Heterogeneous catalysts may play a major role in this case. Heterogeneous catalysis is fast developing into an important field in its own right basically on account of the inherent and obvious advantages of insoluble catalysts over soluble ones.

While the synthesis of resorthiomycin was in progress, it was decided to prepare thiol ester derivatives of resorthiomycin. Various heterogeneous catalysts and reagents were tried as depicted in Table 1, however, all the efforts remained unsuccessful for converting carboxylic acid to thiol ester.

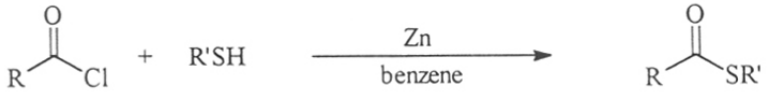
**Table 1**

| Acid | Thiol | Reagent/Catalyst |
|---|---|---|
| Benzoic | Benzyl mercaptan | Natural Kaolinitic clay |
| Acetic | Thiophenol | Montmorillonite $K_{10}$ |
| Benzoic | Benzyl mercaptan | Hβ |
| Benzoic | Benzyl mercaptan | Ts-1 |
| Acetic | Benzyl mercaptan | HZSM-5 |
| Acetic | Thiophenol | HY |
| Benzoic | Benzyl mercaptan | Camphor sulfonic acid |
| Benzoic | Benzyl mercaptan | DMAP |

While the work on thiol-esterification was in progress Yadav et al.[62] found that stoichiometric amount of zinc in benzene enhances esterification of acid chlorides with a variety of functionalized alcohols. They claimed that transition metal possesses a peculiar property of enhancing the media oriented reaction through their coordination capabilities and zinc should be one of such elements to facilitate a reaction particularly esterification type.

Our recent interest in the chemistry of thiol esters has led us to test synthetic applicability of zinc towards thiol esterification and preliminary results are reported here. It was found that zinc is an efficient catalyst for thiol esterification of various functionalized acid chlorides and thiols under a mild reaction condition offering good to excellent yield. Several examples illustrating this novel and rapid procedure for the conversion of carboxylic acid chlorides to thiol esters are illustrated in Scheme 20 and Table 2.

**Scheme 20**




**50** **51 a - l** **52 a - l**

**Table 2**

| Entry | R | $R^1$ | Time (min) | Yield (%) |
|---|---|---|---|---|
| a | $C_6H_5$ | $C_6H_5CH_2$ | 30 | 94 |
| b | $CH_3$ | $C_6H_5CH_2$ | 20 | 95.5 |
| c | 4-$ClC_6H_4$ | $C_6H_5CH_2$ | 60 | 73.2 |
| d | 4-$NO_2C_6H_4$ | $C_6H_5CH_2$ | 90 | 61 |
| e | $CH_3CH$=CH | $C_6H_5CH_2$ | 120 | 82 |
| f | $C_6H_5$-CH=CH | $C_6H_5CH_2$ | 120 | 89.8 |
| g | 4-$C_5H_4N$ | $C_6H_5CH_2$ | 90 | 92 |
| h | $CH_3(CH_2)_4$ | $C_6H_5CH_2$ | 30 | 68.5 |
| i | $CH_3$ | $C_6H_5$ | 30 | 71 |
| j | $C_6H_5$ | $C_6H_5$ | 45 | 81 |
| k | $CH_3$ | $C_2H_5$ | 30 | 87.6 |
| l | $C_6H_5$ | $C_2H_5$ | 30 | 79.9 |

As evident from Table-2, this method appears to be general as a variety of acid chlorides (aliphatic, aromatic, heteroaromatic, α,β-unsaturated) and thiols can be employed efficiently.

As shown in Table 2, benzoyl chloride (**50a**) underwent thiolesterification with benzyl mercaptan (**51a**) in the presence of zinc to furnish thiol esterified compound **52a**. Its structure was confirmed by spectral analysis. The IR spectrum showed absorption band at 1665 $cm^{-1}$. The PMR spectrum exhibited a characteristic singlet at δ 4.20 for the methylene protons. The mass spectrum showed molecular ion peak at m/z 228, thus confirming the structure. The PMR spectrum of the thiol ester **52b** showed benzylic protons resonating as a singlet at δ 4.0 and methyl protons resonating as a singlet at δ 2.25. The presence of molecular ion peak at m/z 166 in the mass spectrum confirmed the structure. The PMR spectrum of **52c** showed a singlet at δ 4.05 for the methylene

protons, a multiplet at δ 7.27-7.50 and two doublets at δ 7.90 and δ 8.08 for the aromatic protons. The thiol ester **52d** showed physical properties consistent to that reported in literature.[63] The PMR spectrum exhibited a characteristic singlet at δ 4.05 for the methylene protons, a multiplet at δ 7.20 - 7.38 for five aromatic protons and two doublets at δ 8.30 (J = 8 Hz) and δ 8.37 (J = 8 Hz) for aromatic protons. The structure of the ester **52e** was confirmed by its PMR spectrum (FIG. XI) in which methyl protons resonated as doublet at δ 1.90 (J = 7 Hz), singlet at δ 4.20 for benzylic protons, a doublet at δ 6.15 (J = 16 Hz) for an olefinic proton adjacent to carbonyl functionality, a multiplet at δ 6.85-7.05 for olefinic proton and a singlet at δ 7.30 for aromatic protons. The mass spectrum showed molecular ion peak at m/z 192, thus confirming the structure. The PMR spectrum (FIG. XII) of thiol ester **52f** showed a singlet at δ 4.30 for the benzylic protons, a doublet at δ 6.75 (J = 16 Hz) for the olefinic proton adjacent to carbonyl group, two multiplets at δ 7.25-7.45 (8 protons) and 7.52-7.60 (2 protons) corresponding to aromatic protons and a doublet at δ 7.70 (J = 16 Hz) for the olefinic proton. The mass spectrum (m/z 254), further proved the structure. The PMR spectrum of thiol ester **52g** exhibited a singlet at δ 4.35 for the benzylic protons, a multiplet at δ 7.25-7.40 for the aromatic protons and two doublets in the region of δ 7.75 (J = 8 Hz) and δ 8.80 (J = 8 Hz) for the AB system aromatic protons. The mass spectrum showed molecular ion peak at m/z. 229, thus confirming the structure. The structure of thiol ester **52h** was confirmed by its PMR spectrum (FIG. XIII) in which methyl protons resonated as multiplet at δ 0.82 - 0.93, multiplet at δ 1.28-1.38 for four methylene protons adjacent to methyl group, a multiplet at δ 1.62-1.70 for two methylene protons, a triplet at δ 2.55 (J = 7 Hz) for methylene protons adjacent to carbonyl group, a singlet at δ 4.10 for benzylic protons and a multiplet at δ 7.20-7.35 for five aromatic protons.

Salient features of the newly developed methodology are as follows:

(i) Various functionalized acid chlorides (aliphatic, aromatic, heteroaromatic, α,β-unsaturated) were transformed into synthetically useful thiol esters.

(ii) No isomerization occured in the case of α,β-unsaturated acid chloride, whereas the reaction carried out in the presence of bases such as triethylamine or pyridine required more time and also led to double bond isomerized product.

The present procedure for the preparation of thiol esters from carboxylic acid chlorides and thiols is advantageous with regards to the mildness of reaction conditions and easy work-up for the isolation. Also this method has other environmentally benign features and no inorganic wastes are produced. The thiol ester synthesis described above may be a valuable alternative for all processes where direct transformation of a carboxylic acid to the corresponding thiol ester is not required.

## Experimental

**General procedure for the activation of zinc**

A mixture of zinc powder (40 g) and 10% hydrochloric acid (15 ml) was stirred for 2 min. It was filtered and washed with distilled water (30 ml) followed by acetone (20 ml). It was then dried in oven and used immediately.

**Typical procedure for thiol esterification**

The acid chloride (11 mmol) was dissolved in dry benzene (30 ml) and the activated zinc (1 eq.) was added to it with stirring. It was cooled to 0°C and thiol (10 mmol) was added into the reaction dropwise, and allowed to come to room temperature for the requisite period of time (20 min-2 hr). The reaction was monitored by TLC. After completion of reaction, the zinc was filtered off. The filtrate was dried ($Na_2SO_4$) and concentrated under vacuum to furnish a residue which after chromatographic purification afforded pure thiol ester which was characterized by PMR, IR, and mass spectroscopy.

**S-Benzyl thiobenzoate (52a)**

| | |
|---|---|
| **Nature:** | Viscous pale yellow oil |
| **Yield:** | 94% |
| **IR (Neat):** | 1665 $cm^{-1}$ |
| **PMR ($CDCl_3$, 90 MHz):** | δ 4.20 (s, 2H, Ar$\underline{CH_2}$); 7.05-7.35 (m, 8H, $\underline{ArH}$); 7.75 - 7.90 (m, 2H, $\underline{ArH}$). |
| **MS (m/z):** | 228 ($M^+$, 42); 122 (10); 105 (100). |

**S-Benzyl thioacetate (52b)**

| | |
|---|---|
| **Nature:** | Colourless viscous liquid |
| **Yield:** | 95.5% |

**IR (Neat):** 1672 $cm^{-1}$

**PMR ($CDCl_3$, 90 MHz):** δ 2.25 (s, 3H, $\underline{CH_3}$); 4.0 (s, 2H, Ar$\underline{CH_2}$); 7.08 (s, 5H, Ar$\underline{H}$).

**MS (m/z):** 166 ($M^+$, 10); 123 (22); 91 (100); 65 (18).

**S-Benzyl-4-chlorothiobenzoate (52c)**

**Yield:** 73.2%

**IR ($CHCl_3$):** 830, 1030, 1590, 1665 and 2900 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 4.05 (s, 2H, Ar$\underline{CH_2}$); 7.27-7.50 (m, 5H, Ar$\underline{H}$); 7.90 (d, J = 8 Hz, 2H, Ar$\underline{H}$); 8.08 (d, J = 8 Hz, 2H, Ar$\underline{H}$).

**MS (m/z):** 262 ($M^+$, 8); 139 (83); 111 (38); 91 (100); 75 (18); 65 (32).

**S-Benzyl-4-nitrothiobenzoate (52d)**

**Nature:** Solid

**M.P.:** 62 °C (Lit.[63] m.p. 62 °C)

**Yield:** 61%

**PMR ($CDCl_3$, 300 MHz):** δ 4.05 (s, 2H, Ar$\underline{CH_2}$); 7.20-7.38 (m, 5H, Ar$\underline{H}$); 8.30 (d, J = 8 Hz, 2H, Ar$\underline{H}$); 8.37 (d, J = 8 Hz, 2H, Ar$\underline{H}$).

**S-Benzyl thiocrotonate (52e)**

**Nature:** Pale yellow oil

**Yield:** 82%

**IR (Neat):** 1495, 1608 and 1665 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 1.90 (d, J= 7 Hz, 3H, $\underline{CH_3}CH$); 4.20 (s, 2H, $Ar\underline{CH_2}$); 6.15 (d, J = 16 Hz, 1H, CH=$\underline{CH}$-CO); 6.85-7.05 (m, 1H, $CH_3$-$\underline{CH}$=CH); 7.30 (s, 5H, Ar$\underline{H}$)

**MS (m/z):** 192 ($M^+$, 58); 177 (7); 91 (58); 69 (100).

**S-Benzyl thiocinnamate (52f)**

**Nature:** Viscous liquid

**Yield:** 89.8%

**PMR ($CDCl_3$, 200 MHz):** δ 4.30 (s, 2H, $Ar\underline{CH_2}$); 6.75 (d, J= 16 Hz, 1H, ArCH=$\underline{CH}$); 7.25-7.45 (m, 8H, Ar$\underline{H}$); 7.52-7.60 (m, 2H, Ar$\underline{H}$); 7.70 (d, J = 16 Hz, 1H, Ar$\underline{CH}$=CH).

**MS (m/z):** 254 ($M^+$, 19); 162 (12); 130 (100); 103 (22); 91 (24); 77 (18).

**S-Benzyl-thioisonicotinate (52g)**

**Yield:** 92%

**IR (Neat):** 1670 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 4.35 (s, 2H, $Ar\underline{CH_2}$); 7.25-7.40 (m, 5H, Ar$\underline{H}$); 7.75 (d, J = 8 Hz, 2H, Ar$\underline{H}$); 8.80 (d, J = 8 Hz, 2H, Ar$\underline{H}$).

**MS (m/z)** 229 ($M^+$, 19); 169 (6); 123 (13); 106 (75); 91 (100); 78 (63); 65 (28).

**S-Benzyl thiohexanoate (52h)**

**Nature:** Pale yellow oil

**IR (Neat):** 1650 $cm^{-1}$

**Yield:** 68.5%

**PMR ($CDCl_3$, 300 MHz):** δ 0.82-0.93 (m, 3H, $\underline{CH_3}CH_2$); 1.28-1.38 (m, 4H, 2 x $\underline{CH_2}$); 1.62-1.70 (m, 2H, $\underline{CH_2}CH_2CO$); 2.55 (t, J= 7 Hz, $CO\underline{CH_2}CH_2$); 4.10 (s, 2H, $Ar\underline{CH_2}$); 7.20-7.35 (m, 5H, Ar$\underline{H}$).

**S-Phenyl thioacetate (52i)**

**Nature:** Viscous liquid

**Yield:** 71%

**PMR ($CDCl_3$, 90 MHz):** δ 2.37 (s, 3H, $\underline{CH_3}CO$); 7.30 (s, 5H, Ar$\underline{H}$).

**S-Phenyl thiobenzoate (52j)**

**Yield:** 81%

**IR (nujol):** 1490, 1605 and 1660 $cm^{-1}$.

**PMR ($CDCl_3$, 90 MHz):** δ 7.20-7.60 (m, 8H, Ar$\underline{H}$); 7.80-8.10 (m, 2H, Ar$\underline{H}$).

**S-Ethyl thioacetate (52k)**

**Nature:** Colourless liquid

**Yield:** 87.6%

**PMR ($CDCl_3$, 90 MHz):** δ 1.25 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$); 2.31 (s, 3H, $\underline{CH_3}CO$); 2.87 (q, J = 7 Hz, 2H, $\underline{CH_2}CH_3$).

**S-Ethyl thiobenzoate (52l)**

**Nature:** Colourless liquid

**Yield:** 79.9%

**PMR ($CDCl_3$, 90 MHz):** δ 1.30 (t, J = 7Hz, 3H, $CH_2\underline{CH_3}$); 3.08 (q, J = 7 Hz, 2H, $\underline{CH_2}CH_3$); 7.30 -8.10 (m, 5H, Ar$\underline{H}$)

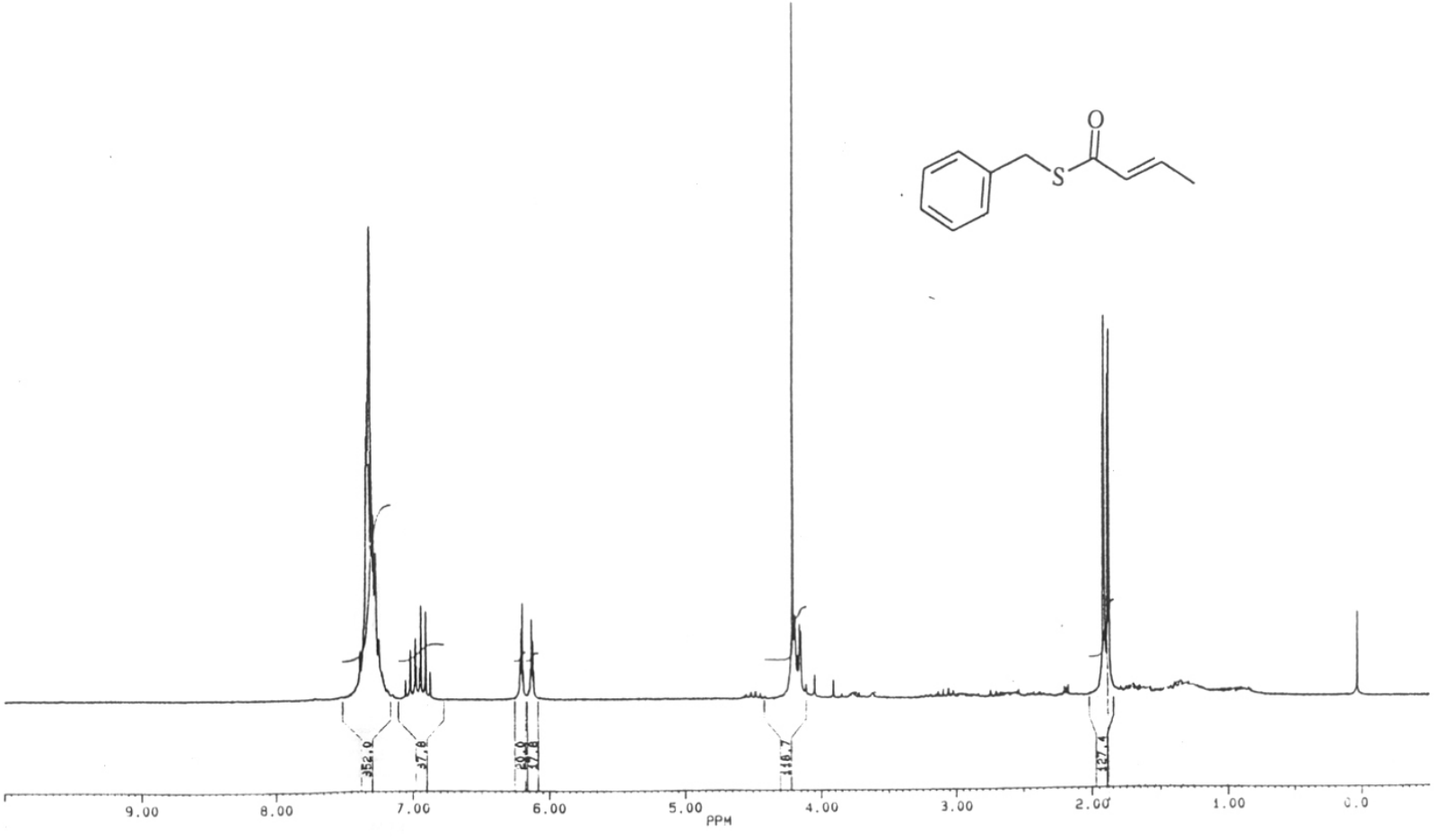



FIG XI : PMR SPECTRUM OF THE COMPOUND 52e IN $CDCl_3$

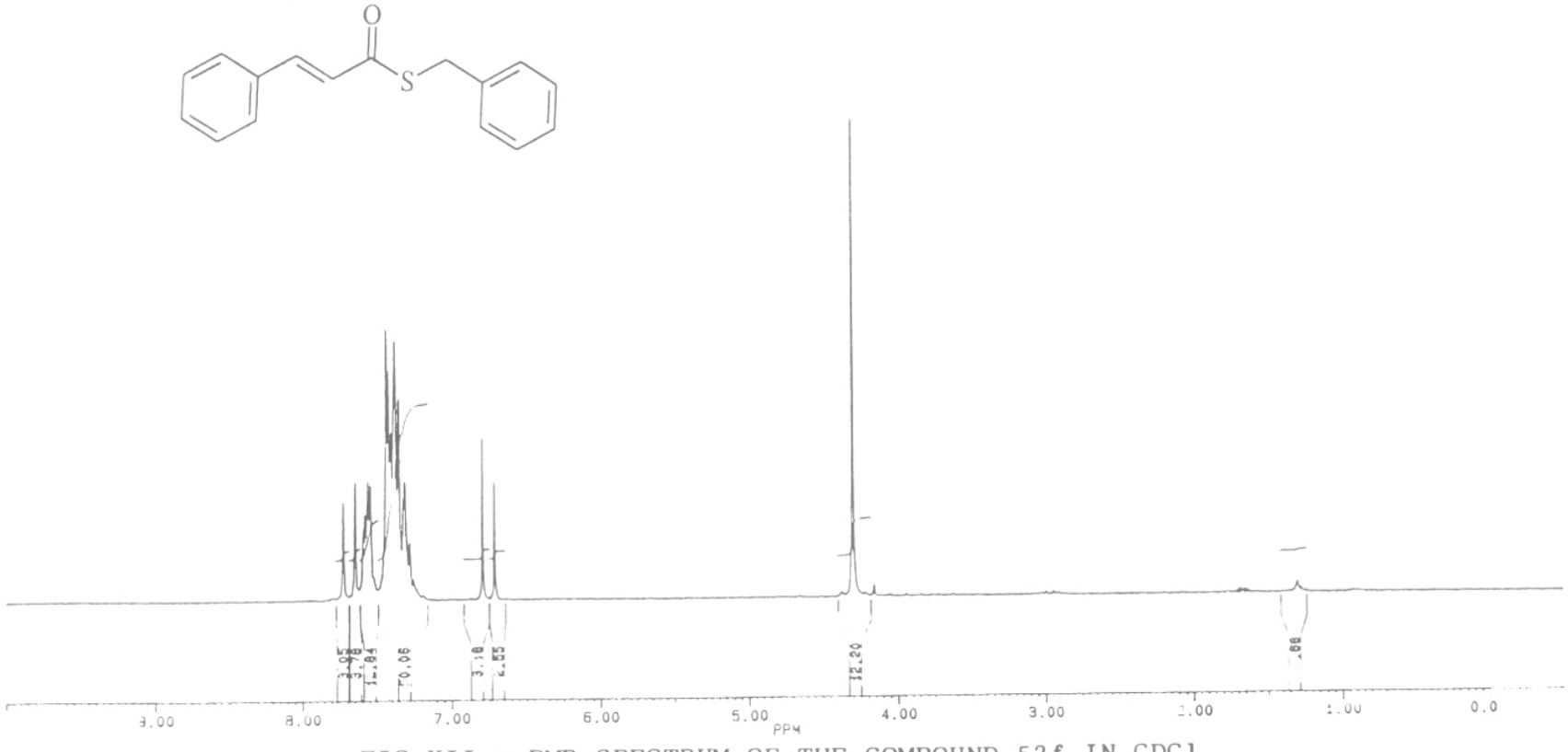



FIG XII : PMR SPECTRUM OF THE COMPOUND 52f IN $CDCl_3$

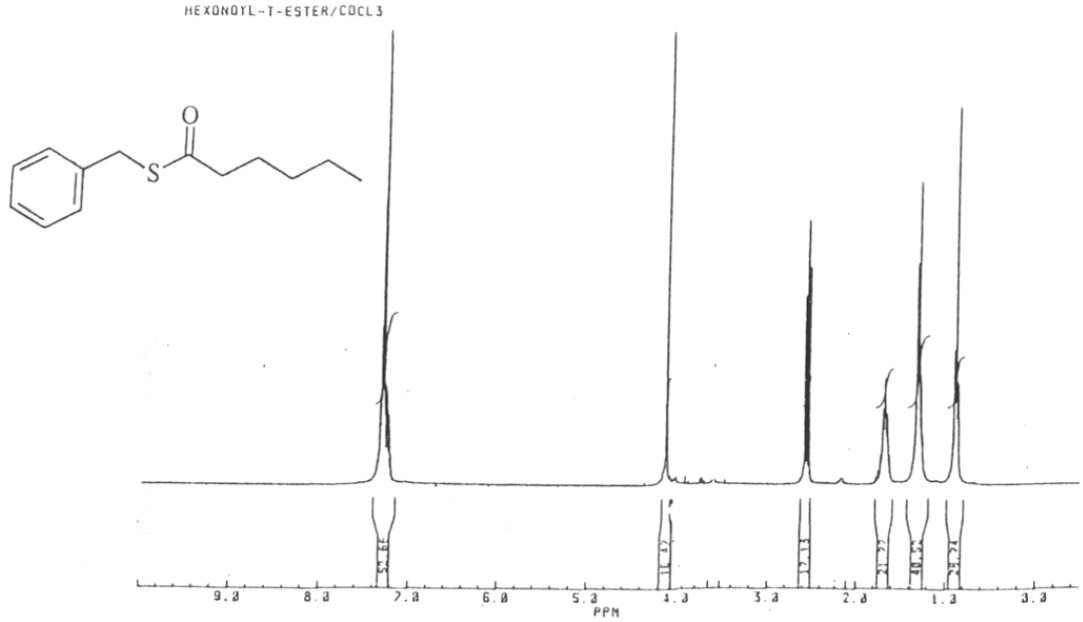



FIG XIII : PMR SPECTRUM OF THE COMPOUND 52h IN $CDCl_3$

## References


1) Pettit, G.R.; Cragg, G.M. and Herald, C.L. Biosynthetic Products for Cancer Chemotherapy, Vol.4, Elsevier, Amsterdam (**1984**).

2) Neuss, N.; Gorman, M. and Johnson, I. S. Methods in Cancer Research Vol.III, Academic Press, N.Y.(**1967**).

3) Arcamone, F.; Franceschi, G.; Penco, S. and Selva, A. *Tetrahedron Lett.*, **1969**, 1007-1010.

4 a) Grein, A.; Spalla, C.; Di Marco, A. and Canevazzi, G. *G. Microbiology*, **1963**, 109.

4 b) Arcamone, F.; Franceschi, G.; Orezzi, P.; Cassinelli, G.; Barbieri, W. and Mondelli, R.J. *J.Am. Chem. Soc.* **1964**, *86*, 5334-5335.

5) Cutts, C.T.; Beer, C.T. and Noble, R. L. *Cancer Res*, **1960**, *20*, 1023.

6) Cassady, J.M. and Dourous, J.D. Anticancer agents based on natural product models. Academic Press (**1980**).

7) Wall, M. E.; Wani, M.C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T. and Sim, G. A. *J. Am. Chem. Soc.*, **1966**, 88, 3888.

8) Nicolaou, K. C.; Wei-Min Dai and Guy, R. K. *Angew Chem Int. Ed. Eng.*, **1994**, *33*, 15.

9) Rosenberg, B.; VanCamp, L.; Trosko, J. E. and Mansour, V. H. *Nature*, **1969**, *222*, 385-386.

10) Tanaka, N.; Okabe, T.; Isono, F.; Kashiwagi, M.; Nomoto, K.; Takahashi, M.; Shimazu, A. and Nishimura, T. *J. Antibiotics*, **1985**, *38*, 1327-1332.

11) a) Suzuki, H.; Tahara, M.; Takahashi, M.; Matsumura, F.; Okabe, T.; Shimazu, A.; Hirata, A.; Yamaki, H.; Yamaguchi, H.; Tanaka, N. and Nishimura, T. *J. Antibiotics*, **1990**, *43*, 129-134.

11) b) Tahara, M.; Okabe, T.; Furihata, K.; Tanaka, N.; Yamaguchi, H.; Nishimura, T. and Suzuki, H. *J. Antibiotics*, **1990**, *43*, 135-137.

12) Tahara, M.; Okabe, T.; Furihata, K.; Tanaka, N.; Yamaguchi, H.; Nishimura, T. and Suzuki, H. *J. Antibiotics*, **1991**, *44*, 255.

13) Tahara, M.; Tomida, A.; Nishimura, T.; Yamaguchi, H. and Suzuki, H. *J. Antibiotics*, **1990**, *43*, 138-142.

14) Nakakita, Y.; Shima, S. and Sakai, H. *Agric. Biol. Chem.*, **1984**, *48(7)*, 1899-1900.

15) Fischer, E. and Fischer, H.O.L. *Chem. Ber.* **1913**, *46*, 1138-1139.

16) Umezawa, H.; Shibamoto, N.; Naganawa, H.; Ayukawa, S.; Matsuzaki, M. and Takeuchi, T. *J. Antibiotics*, **1974**, *27*, 587-596.

17) Masaki, S.; Konishi, T.; Tsuji, N. and Shoji, J. *J. Antibiotics*, **1989**, *42*, 463-466.

18) Mizobuchi, S. and Sato, Y. *Agric. Biol. Chem.* **1985**, *49*, 1327-33.

19) Azzena, U.; Denurra, T.; Melloni, G. and Piroddi, A. M., *J. Org. Chem.*, **1990**, *55*, 5386-5390.

20) Ridley, D. D.; Ritchie, E. and Taylor, W. C. *Aust. J. Chem.* **1968**, *21*, 2979-2988.

21) Cresp, T. M.; Djura, P.; Sargent, M. V.; Elix, J. A.; Engkaninan, U. and Murphy, D. P. H. *Aust. J. Chem.*, **1975**, *28*, 2417-34.

22) a) Vogel's Textbook of Practical Organic Chemistry, Longman group UK Ltd., fifth edition, 1069, **1989**.

b) Elix, J. A. and Norfolk, S. *Aust. J. Chem.* **1975**, *28*, 1113-1124.

23) Kobayashi, Y. and Itabashi, K. *Synthesis*, **1985**, 671-672.

24) Noble, P. and Tarbell, D. S. Org. Syn. **1952**, *32*, 101.

25) Vogel's Textbook of Practical Organic Chemistry, Longman Group UK Ltd., fifth edition, 1068, **1989**.

26) Vogel's Textbook of Practical Organic Chemistry, Longman Group UK Ltd., third edition, 512, **1956**.

27) Bartlett, A. J.; Holker, J. S. E.; O' Brien and Simpson, T. J. *J. Chem. Soc. Perkin Trans. 1*, **1983**, 667-670.

28) Howarth, T. T.; Murphy, G. P. and Harris, T. M. *J. Am. Chem. Soc.*, **1969**, *91*, 517-518.

29) Kato, T. and Hozumi, T. *Chem. Pharm. Bull.*, **1972**, *20*, 1574-1578.

30) Sargent, M. V.; Vogel, P. and Elix, J. A. *J. Chem. Soc. Perkin Trans. 1*, **1975**, 1986-91.

31) Kumar, B. and Verma, R. K. *Syn. Commun.* **1984**, *14*, 1359-1363.

32) Santesson, J. *Acta. Chem. Scand.* **1970**, *24*, 3373-3378.

33) Ogata, Y.; Kawasaki, A. and Sugiura, F. *Tetrahedron*, **1968**, *24*, 5001-5010.

34) Whalley, W. B. *J. Chem. Soc.* **1949**, 3278.

35) par C'esar Pulgarin, Gunzinger, J. and Tabacchi, R. *Helvetica Chimica Acta.* **1985**, *68*, 1948-1951.

36) Porter, W. R. and Trager, W. F. *J. Heterocycl. Chem.* **1977**, *14*, 319-320.

37 a) Fuganti, C.; Grasselli, P.; Servi, S. and Hogberg, H. E. *J. Chem. Soc. Perkin Trans. 1*, **1988**, 3061-3065.

37 b) Gu Jian Xin, Li Zu-Yi and Lin Guo-Qiang, *Tetrahedron*, **1993**, *49*, 5805-5816.

38) Hudlicky, T.; Zingde, G. S. and Natchus, M. G. *Tetrahedron Lett.*, **1987**, *28*, 5287-5290.

39) Watanabe, Y.; Shoda, S. and Mukaiyama, T. *Chemistry Letters*, **1976**, 741-742.

40) Kunieda, T.; Abe, Y. and Hirobe, M. *Chemistry Letters*, **1981**, 1427-1428.

41) Nomura, R.; Miyazaki, S. I.; Nakano, T. and Matsuda, H. *Chem. Ber.* **1990**, *123*, 2081-2082.

42) Heiffer and Heller, *Ber.* **1904**, *37*, 4621.

43) Razuvaev, G. A.; Brilkina, T. G.; Krasilnikova, E. V.; Zinovjeva, T. and Filimonov, A. I. *J. Organometal. Chem.* **1972**, *40*, 151-157.

44) Kindlar, K. and Luehrs, K. *Chem. Ber.* **1966**, *99*, 227-32 (CA: 1966; 64:7988g).

45) Ridley, D. D.; Ritchie, E. and Taylor, W. C. *Aust. J. Chem.* **1968**, *21*, 2979.

46) Dippy, J. F. J. and Lewis, R. H. *J. Chem. Soc.* **1937**, 1426-29.

47) Takeya, K. and Itokawa, H. *Chem. Pharm. Bull.* **1982**, *30*, 1496-99.

48) Tanimoto, S.; Matsumura, Y.; Sugimoto, T. and Okano, M. *Bull.Chem. Soc.Jpn*, **1978**, *51*, 665-666.

49) Elix, J. A.; Wilkins, A. L. and Wardlaw, J. H. *Aust. J. Chem.* **1987**, *40*, 2023-29.

50) For review a) Masamune, S.; Bates, G. S. and Corcoran, J. W. *Angew, Chem. Int. Ed.*, **1977**, *16*, 585. B) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. c) Back, T. G. *Tetrahedron*, **1977**, *33*, 3041.

51) Hirama M.; Garvey, D. S.; Lu, L. D.-L and Masamune, S. *Tetrahedron Lett.*, **1979**, 3937.

52) Horiki, K. *Syn. Commun.* **1977**, *7*, 251-259.

53) Liu, H- J. and Sabesan S. I. *Can. J. Chem.* **1980**, *58*, 2645-48.

54) Liu, H- J.; Lee, S. P. and Chan, W. H. *Syn. Commun.* **1979**, *9*, 91-96.

55) Kim, S. and Yang, S. *Chem. Lett.* **1981**, 133-134.

56) Yamada, S.; Yokoyama, Y. and Shioiri, T. *J. Org. Chem.* **1974**, *39*, 3302-03.

57) Grieco, P. A.; Yokoyama, Y. and Williams, E., *J. Org. Chem.* **1978**, *43*, 1283-85.

58) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119-22.

59) Gauthier, J. Y.; Bourdon, F. and Young, R.N. *Tetrahedron Lett.* **1986**, *27*, 15-18.

60) ReiBig H. U and Scherer, B. *Tetrahedron Lett.* **1980**, *21*, 4259-4262.

61) Ahmed, S. and Iqbal, J. *Tetrahedron Lett.* **1986**, *27*, 3791-3794.

62) Yadav, J. S.; Reddy, G. R.; Reddy, M. M.; Meshram H. M. *Tetrahedron Lett.* **1998**, *39*, 3259-62.

63) Hibbert, H. and Sturrock, M. G. *J. Am. Chem. Soc.*, **1928**, *50*, 3374-76.

# CHAPTER II

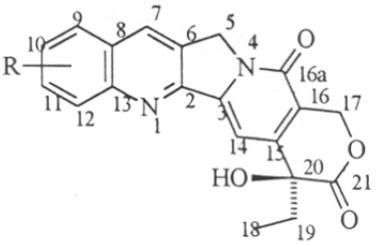
# SYNTHETIC STUDIES ON CAMPTOTHECIN AND ITS INTERMEDIATES

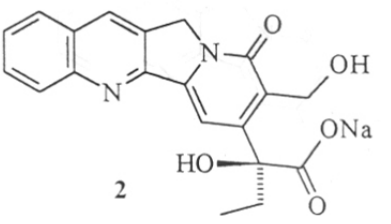
## Introduction

Camptothecin (**1**), a pentacyclic alkaloid, was isolated by Wall et al.[1] in 1966 from the stem wood of *Camptotheca acuminata* Decne (Nyssaceae), a tree distributed widely and abundantly in the southern part of China. It exhibits potent antileukemic and antitumor activities in animals and hence has become molecule of choice for studies for both synthetic chemists as well as medicinal chemists.

Camptothecin is a potent inhibitor of the growth of leukemia cells *in vitro* and shows good antitumor activity against murine L1210 and P 388 leukemia and B16 melanocarcinoma *in vitro*. Because of the low solubility of camptothecin (**1**), the sodium salt (**2**) was tested and was found to be active against solid tumors of the gastro-intestinal tract.

Wani and Wall isolated 10-hydroxycamptothecin (**1a**) and 10-methoxycamptothecin (**1b**) from the stem wood of *Camptotheca acuminata*.[2] Compounds **1** and **1b** were isolated from *Ophiorrhiza mungos* Linn (Rubiaceae)[3] also. Gunasekera et al. isolated **1** and **1c** from *Ervatamia heyneana* (Wall) T. Cooke (Apocynaceae).[4] Govindachari et al.[5] isolated camptothecin (**1**), 9-methoxycamptothecin (**1c**) and other related alkaloid mappicine (**3**) from Indian plant *Nothapodytes foetida* (Wight) Sleumer (Icacinaceae).



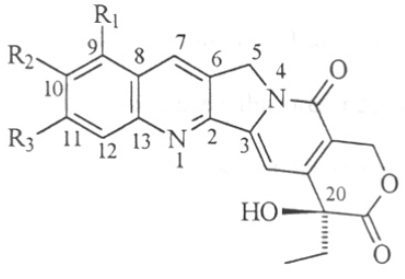

**2**

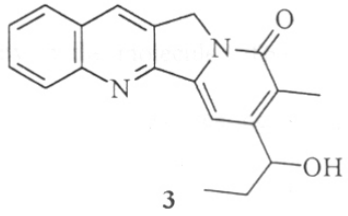
**1** R = H **1b** R = 10-$OCH_3$ **1d** R = 11-OH
**1a** R = 10-OH **1c** R = 9-$OCH_3$ **1e** R = 11-$OCH_3$

In addition to **1**, **1a** and **1b**, 11-hydroxycamptothecin (**1d**) and 11-methoxycamptothecin (**1e**) were isolated from the fruits of *C. acuminata.*[6]

Camptothecin was also isolated from *Merrilliodendron megacarpum* (Helmsl) Sleum (Icacinaceae).[7] The content of camptothecin in *Nothapodytes foetida* was found to be more than that of other plants.[5] The content of camptothecin in different parts of *Camptotheca acuminata* was examined and it was found that it is higher in fruits than in other parts of the tree.[6]

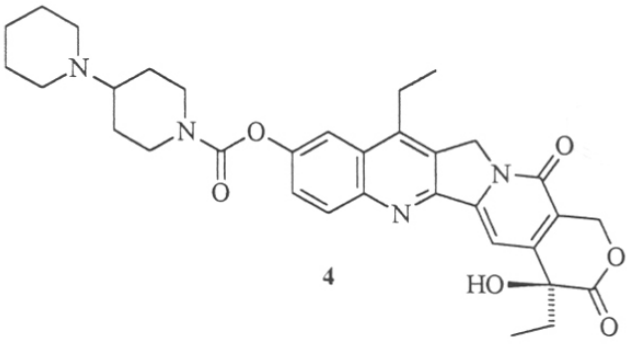
Eventhough camptothecin (**1**) showed high antitumor activity, the initial excitement slowed down due to severe toxicity and solubility problems hence it attracted only marginal attention at clinical or chemical levels between 1973 to 1985. However, a number of promising analogues have now been prepared that show improved solubility, low overall toxicity and impressive *in vitro* activity against certain solid tumors. These derivatives include 20(S)-9-[(dimethylamino)methyl]-10-hydroxycamptothecin (Topotecan)[8] (**1f**), 9-aminocamptothecin[9] (**1g**), 10,11-(methylenedioxy) camptothecin (**1h**), Irinotecan[10] (**4**), 10,11-(methylenedioxy)-7-[(N-methylpiperazino) methyl]-20(S)-camptothecin trifluoroacetate (**5**) and 10,11-(ethylenedioxy)-7-[(N-methylpiperazino) methyl]-20(S)-camptothecin trifluoroacetate (**6**) (GI-147211C).[11]



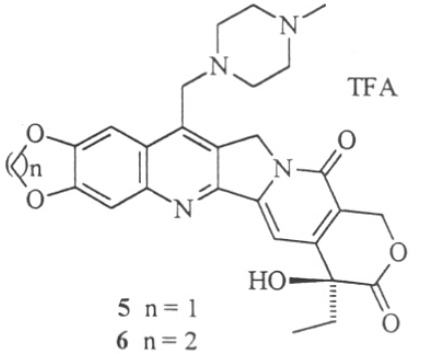




3

1f $R_1 = CH_2NMe_2$, $R_2 = OH$, $R_3 = H$
1g $R_1 = NH_2$, $R_2 = R_3 = H$
1h $R_1 = H$, $R_2,R_3 = -OCH_2O-$



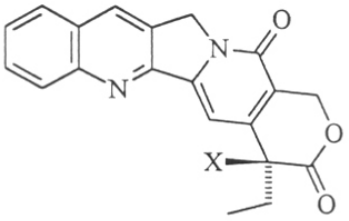
4



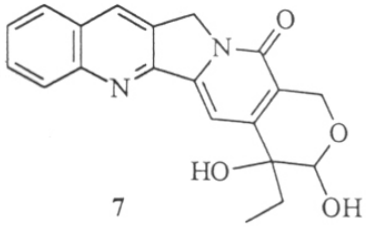
5 n = 1
6 n = 2

## STRUCTURE AND CHEMICAL PROPERTIES

The structure of 20 (S)-camptothecin (**1**) was deduced from its spectral properties (UV, IR, PMR, MS) and certain chemical properties. Formation of chloroacetate (**1i**), mono-O-acetate (**1j**) as well as reaction with thionyl chloride in the presence of pyridine to give 20-chlorocamptothecin (**1k**) suggested the presence of hydroxyl group. Camptothecin undergoes rapid saponification to give sodium salt **2** which on acidification gives **1** and lactol (**7**) formation with sodium borohydride at room temperature suggested the presence of a lactone moiety in the molecule.[1] The X-ray crystallographic analysis of its iodoacetate **1l** which was formed by treating **1i** with sodium iodide in acetone[1] helped to deduce the structure.



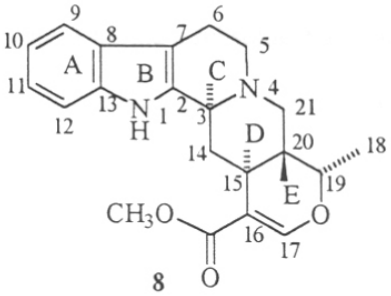
1 X = OH, 1i X = $OCOCH_2Cl$
1j X = $OCOCH_3$, 1k X = Cl
1l X = $OCOCH_2I$



7

Shamma et al.[12] suggested the Le Men-Taylor numbering system[13] for numbering of camptothecin (**1**). The choice of this nomenclature was based on the probable biogenetic relationship between camptothecin and the indole alkaloids, especially ajmalicine (**8**). The pyridone carbonyl carbon in camptothecin was assigned the number 16a as it was not assigned by the above nomenclature.

Camptothecin (**1**) unlike other alkaloids does not form a stable salt with mineral acids. Thus, it is not an alkaloid in the usual sense of definition. The hydroxyl group imparts an unusual electrophilic character to the lactone carbonyl due to strong intramolecular hydrogen bonding, thus making it highly reactive towards nucleophiles such as amines, aqueous alkali and sodium borohydride.



**8**

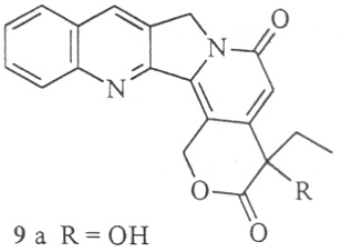
## STRUCTURE ACTIVITY RELATIONSHIP

1. The 20(S)-enantiomeric configuration found in the natural camptothecin is a prerequisite for antitumor activity.[14] The 20(R)-isomer showed one-tenth the cytotoxic activity and was marginally active *in vivo*.[15]

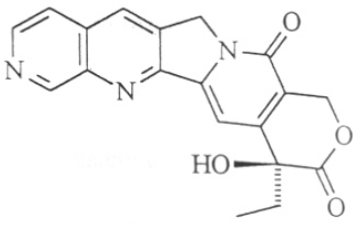
2. Eventhough the sodium salt of camptothecin **2** was found to be active in clinical trials, its activity was only one tenth of **1** when administered intravenously.[16]

3. The lactol **7** formed by sodium borohydride reduction showed no antitumor activity.[6] These results might have led to the conclusion that the lactone ring is essential for activity. Camptothecin acetate **1j**, 20-chlorocamptothecin **1k** and 20 deoxycamptothecin were inactive. The substitution of 20-ethyl group by allyl, benzyl or propargyl resulted in retention of activity.[17]

4. Danishefsky et al.[18] prepared isocamptothecin (**9a**) and isohomocamptothecin (**9b**). Compound **9a** showed a slight activity *in vitro* in the inhibition of nucleic acid synthesis. Compound **9b** was inactive in the same bioassay.



9 a R = OH
b R = $CH_2OH$

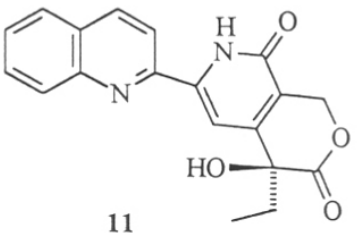


**10**

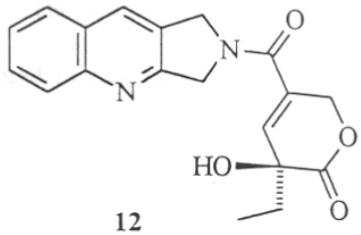
5. Modification in ring A having a substituent at **9** or **10** is compatible with activity. 10-Hydroxy and 10-methoxycamptothecins (**1a**) and (**1b**) were found to be active.[17,19] Modification in ring A having substituent at position 11 leads to compounds of relatively low activity while a substitution at position 12 results in inactivation.[20] The 11-azacamptothecin analogue **10** showed good activity.[21]

6. Substitution in ring B having groups at 7 position leads to compounds having variable activity.

7. Modification in the ring C leads to inactivation. Due to lack of planarity **11** showed inactivity.[22]

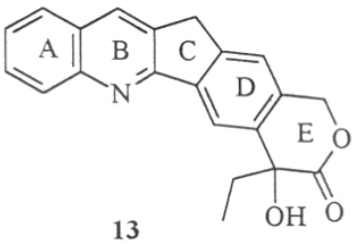


**11**

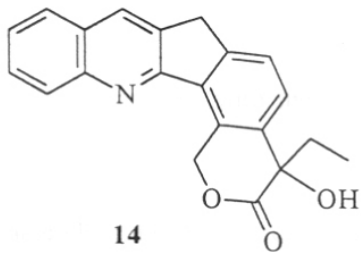


**12**

8 Compounds such as **12** in which the D ring of camptothecin has been deleted are biologically inactive.[22] The compound **13** which has same spatial identity with camptothecin showed at least 40-60 fold decrease in activity, while **14** was inactive.[15]

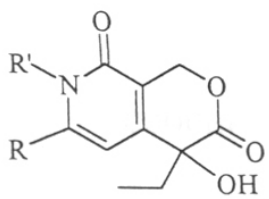



**13**

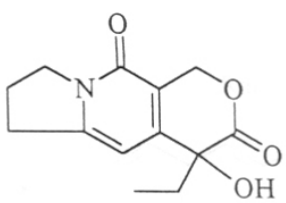


**14**

9 As an α-hydroxy-δ-lactone in camptothecin was thought to be responsible for the antitumor activity of camptothecin, a number of ring DE (**15**) and ring CDE analogues (**16**) were prepared but these were found to be inactive.[23,24]



**15**



**16**

**Total Synthesis**

This section describes the various synthetic approaches towards camptothecin. The synthetic work was reviewed[25] from time to time. The synthetic methodes towards camptothecin reported since 1992 are briefly presented in this part which are mainly classified into

1. Construction of ABC and E rings
2. Construction of CDE rings
3. Construction of AB and DE rings.
4. Miscellaneous methods

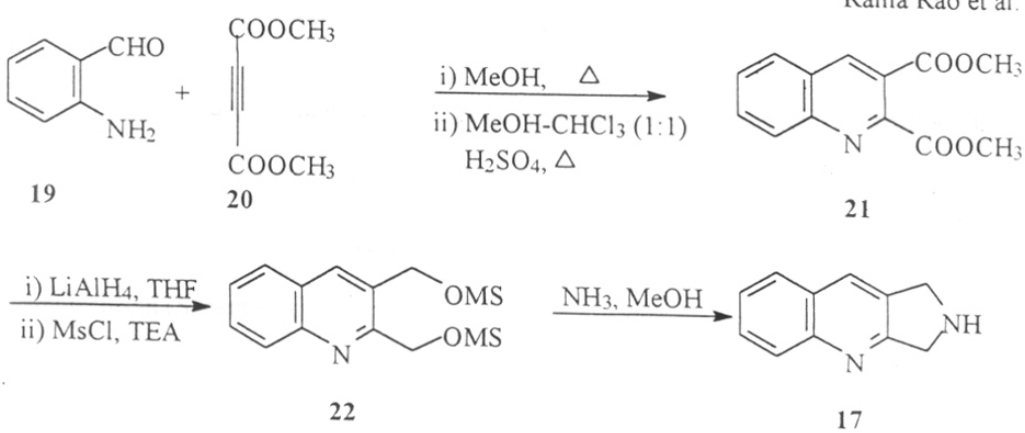
**1. Synthesis of camptothecin by constructing ABC and E rings.**

Rama Rao et al.[26] reported a regioselective and convergent approach to (±)-camptothecin which involved the reaction of the tricyclic diamine **17** with the pseudo acid chloride **18**.

This synthesis was aimed at obtaining pseudo acid chloride **18** in a regiospecific manner and to overcome the problem of mixture of pseudo acid chlorides obtained by Corey et al.[26a] in his synthesis, employing a tandem Diels-Alder, retro Diels-Alder cycloaddition methodology. The compound **17** was prepared from 2-aminobenzaldehyde (**19**) as shown in Scheme-1.

**Scheme 1**

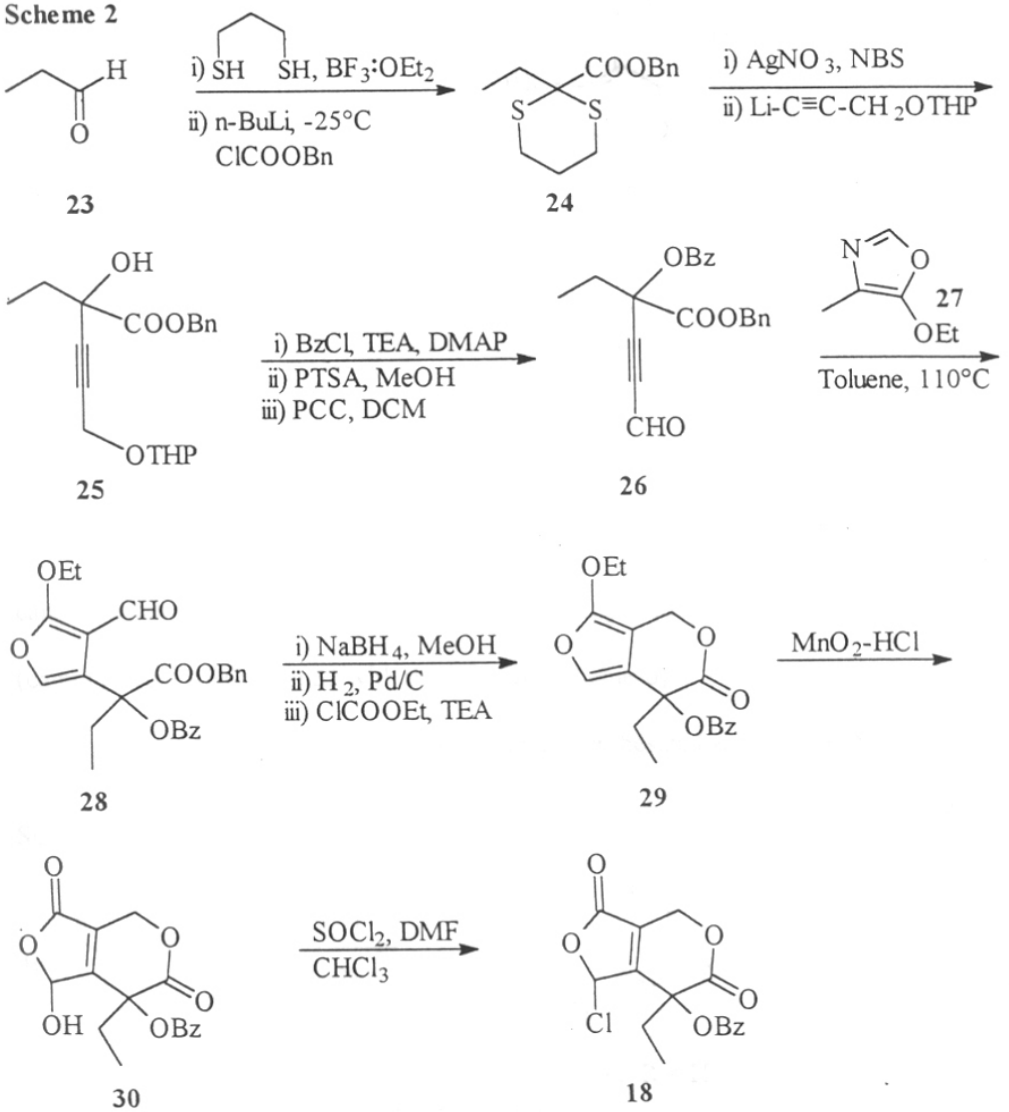
Rama Rao et al.[26]




19 20 21 22 17

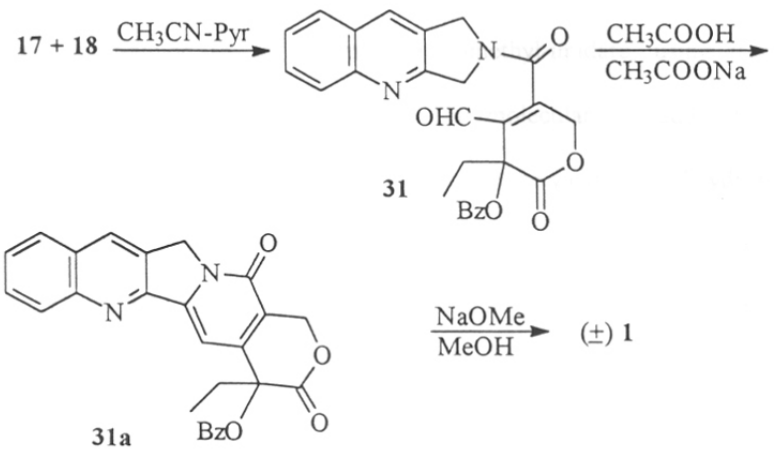
The pseudo acid chloride **18** was prepared from propionaldehyde (**23**) as shown in Scheme-2.

**Scheme 2**




Aldehyde **31**, obtained by the reaction of pseudo acid chloride **18** with **17** in acetonitrile-pyridine, underwent intramolecular cyclization to give the pentacyclic system. Hydrolysis of benzoate ester using sodium methoxide in methanol gave (±)-camptothecin (Scheme-3).

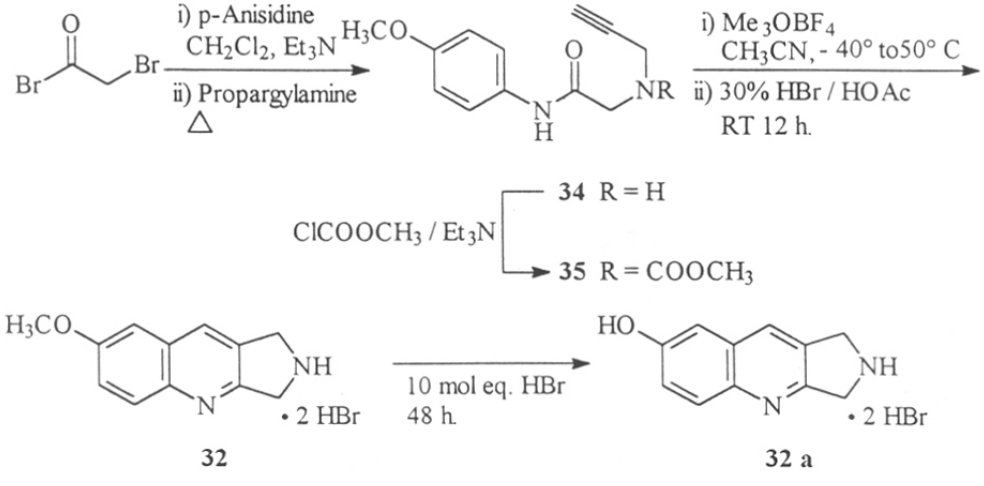
**Scheme 3**




Fortunak et al.[27] reported a 9 step convergent total synthesis of (S)-10-methoxy camptothecin which involved the reaction of the pyrrolo [3,4-b] quinoline ring system (camptothecin ABC ring) **32** with the acid **33** (Scheme-6).

Pyrrolo [3,4-b]quinoline ring system was synthesized as shown in Scheme-4.

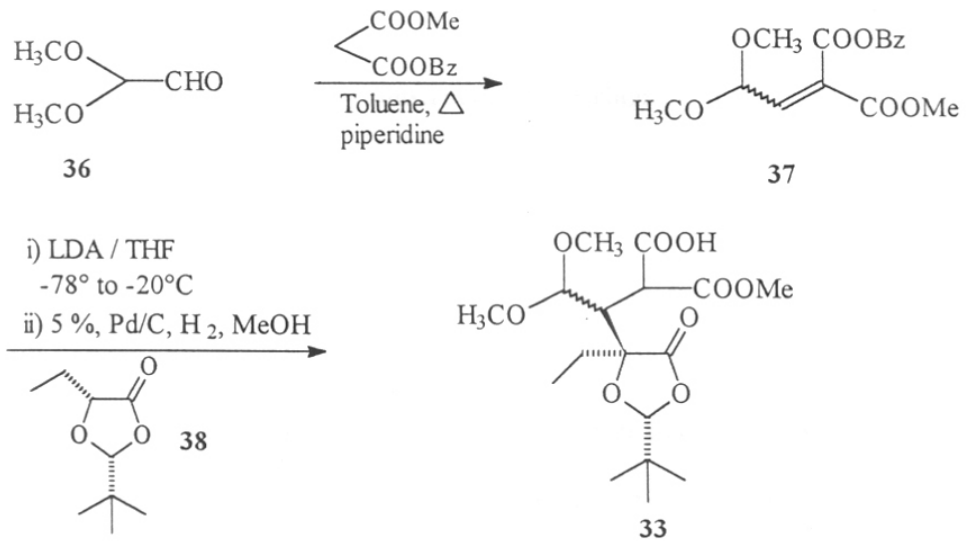
**Scheme 4** Fortunak et al.[27]



Condensation of α-bromo acetyl bromide with p-anisidine, furnished the amine **34**. Protection of the amine as its methyl carbamate **35** followed by careful conversion of the N-aryl-amide to an intermediate O-methyl-imidate, using trimethyloxonium tetrafluoroborate in acetonitrile at -45° C. Intramolecular cycloaddition and elimination of methanol followed by removal of methyl carbamate yielded the dihydrobromide salt of pyrrolo [3,4-b] quinoline (**32**).

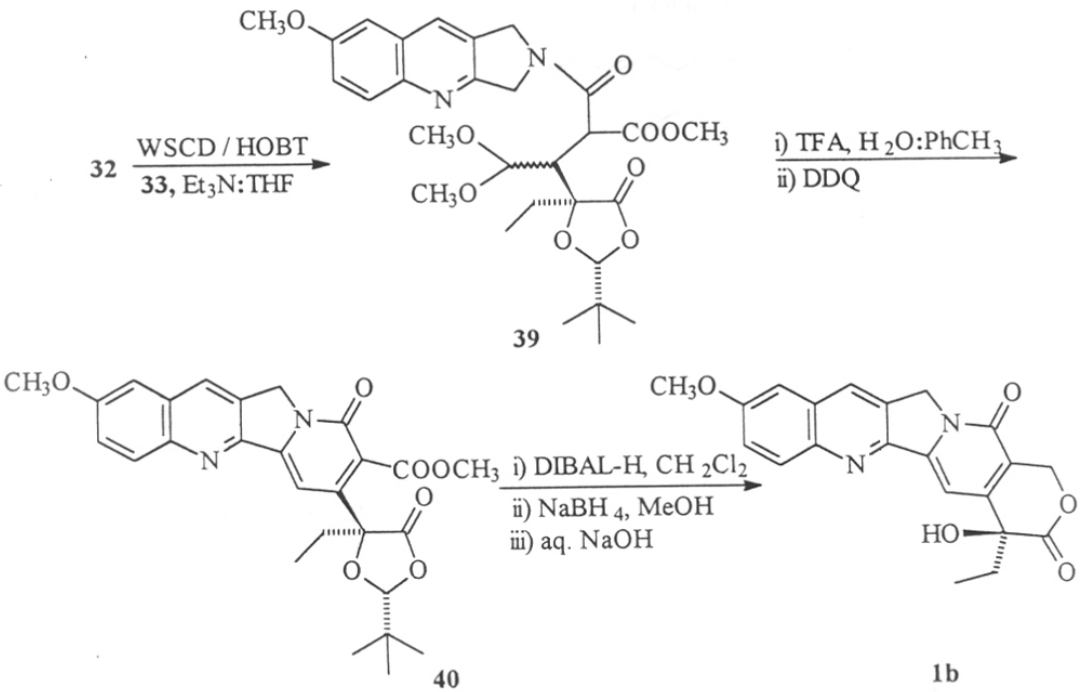
The acid **33** was prepared in three steps from glyoxal-1,1-dimethyl acetal (**36**) as depicted in Scheme-5. Glyoxal-dimethylacetal (**36**) on condensation with benzylmethyl malonate furnished ester **37** in 82% yield. Michael addition of chiral dioxolan-4-one **38** using LDA as the base provided an intermediate ester which on hydrogenation furnished half acid **33**.

**Scheme 5**




Both **32** and **32a** reacted with **33** to yield (S)-10-methoxy (**1b**) and (S)-10-hydroxy camptothecin (**1a**) respectively as shown in Scheme-6.

**Scheme 6**

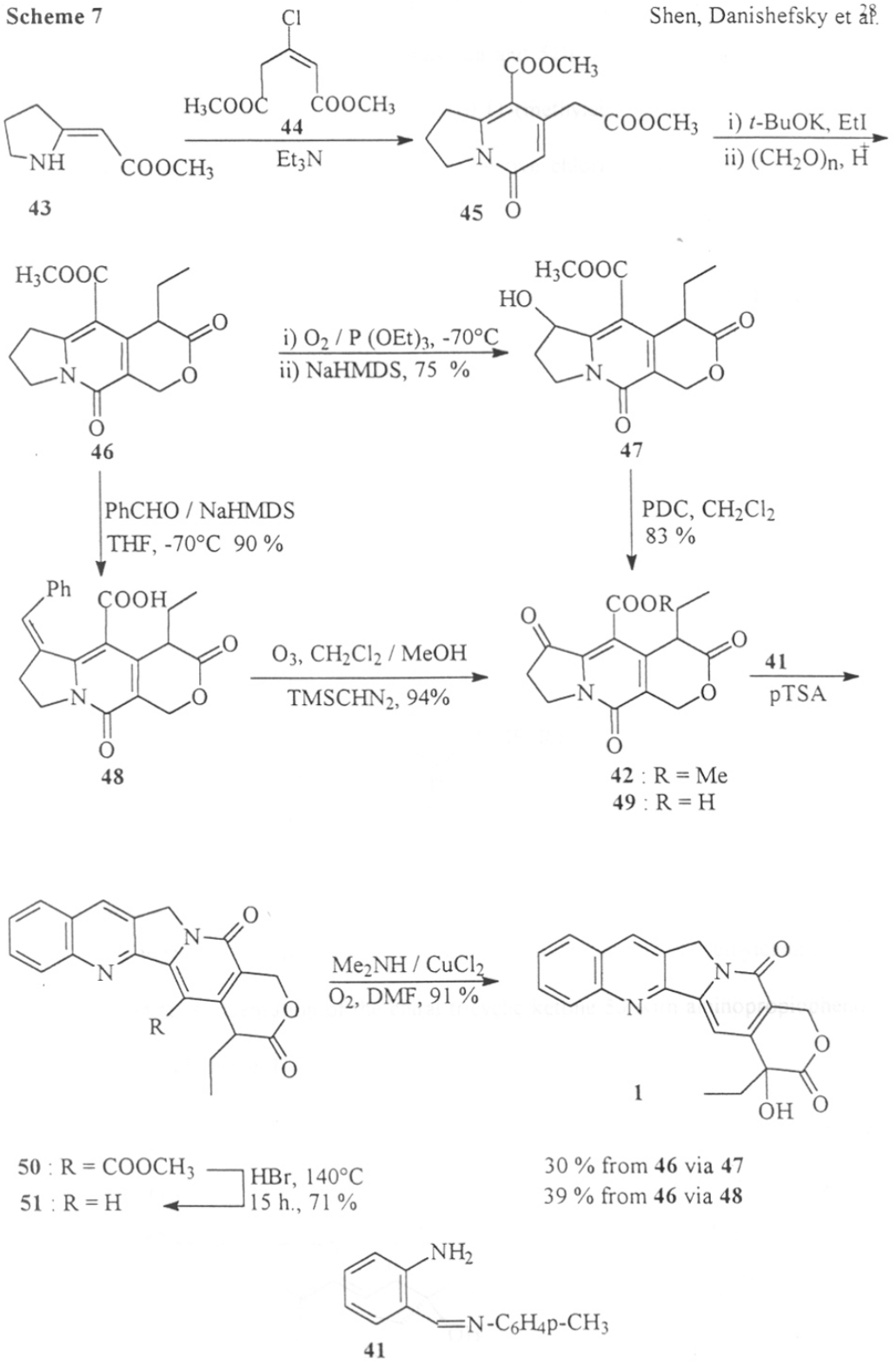



**Synthesis of camptothecin by constructing CDE rings.**

Shen, Danishefsky and group[28] reported in 1993 a relatively high yielding synthesis of (±)-camptothecin (**1**). In this synthesis Danishefsky employed his earlier methodology incorporating certain changes to overcome the drawbacks of his earlier synthesis. The formation of regioisomers during hydroxymethylation in previous synthesis has been avoided by delaying hydrolysis of the ester to the last but one step.

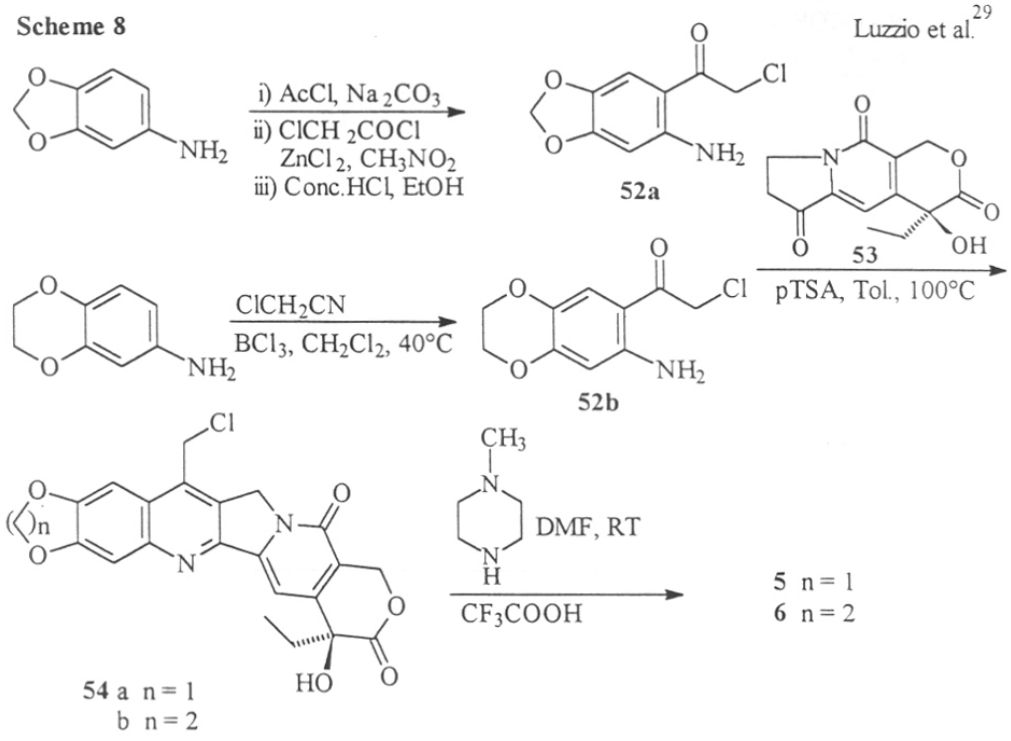
Friedlander condensation of Schiff base **41** with **42** gave **50** in 75% yield, which was converted to dl-20-desoxycamptothecin (**51**) by reaction with HBr. The compound **51** was converted to **1**. Thus addition of enamine **43** to **44** gave pyridone **45** in 92% yield (Scheme 7). Ethylation and hydroxymethylation yielded the tricyclic compound **46**. Camptothecin was synthesized from **46** by two routes. First route *via* **47** yielded camptothecin in 30% yield, while the second *via* **48** yielded **1** in 39% yield.

**Scheme 7** Shen, Danishefsky et al.[28]



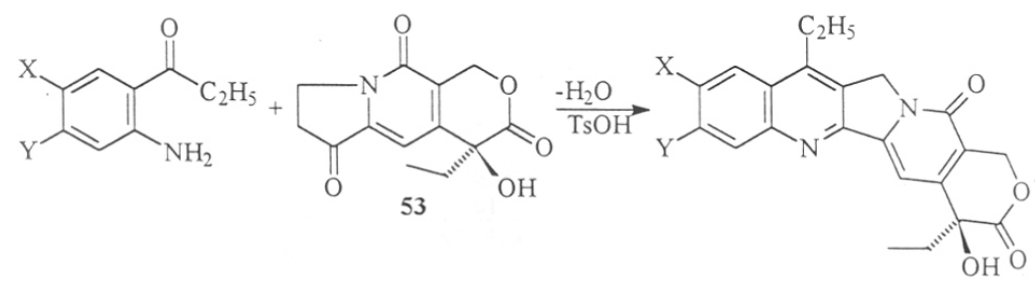
Luzzio et al.[29] synthesized camptothecin derivatives **5** and **6** using Friedlander condensation of substituted acetophenones **52a** and **52b** with the tricyclic ketone **53** to yield the corresponding 7-(chloromethyl)-10,11-(methylene or ethylenedioxy)-20(S)-camptothecins (**54a,b**) (Scheme-8). The respective chlorides were displaced with N-methylpiperazine to provide the corresponding camptothecin derivative **5** and **6**.

**Scheme 8** Luzzio et al.[29]




Yaegashi et al.[30] reported twenty six novel A-ring modified 7-ethylcamptothecins by Friedlander condensation of the chiral tricyclic ketone **53** with aminopropiophenones as depicted in Scheme-9.

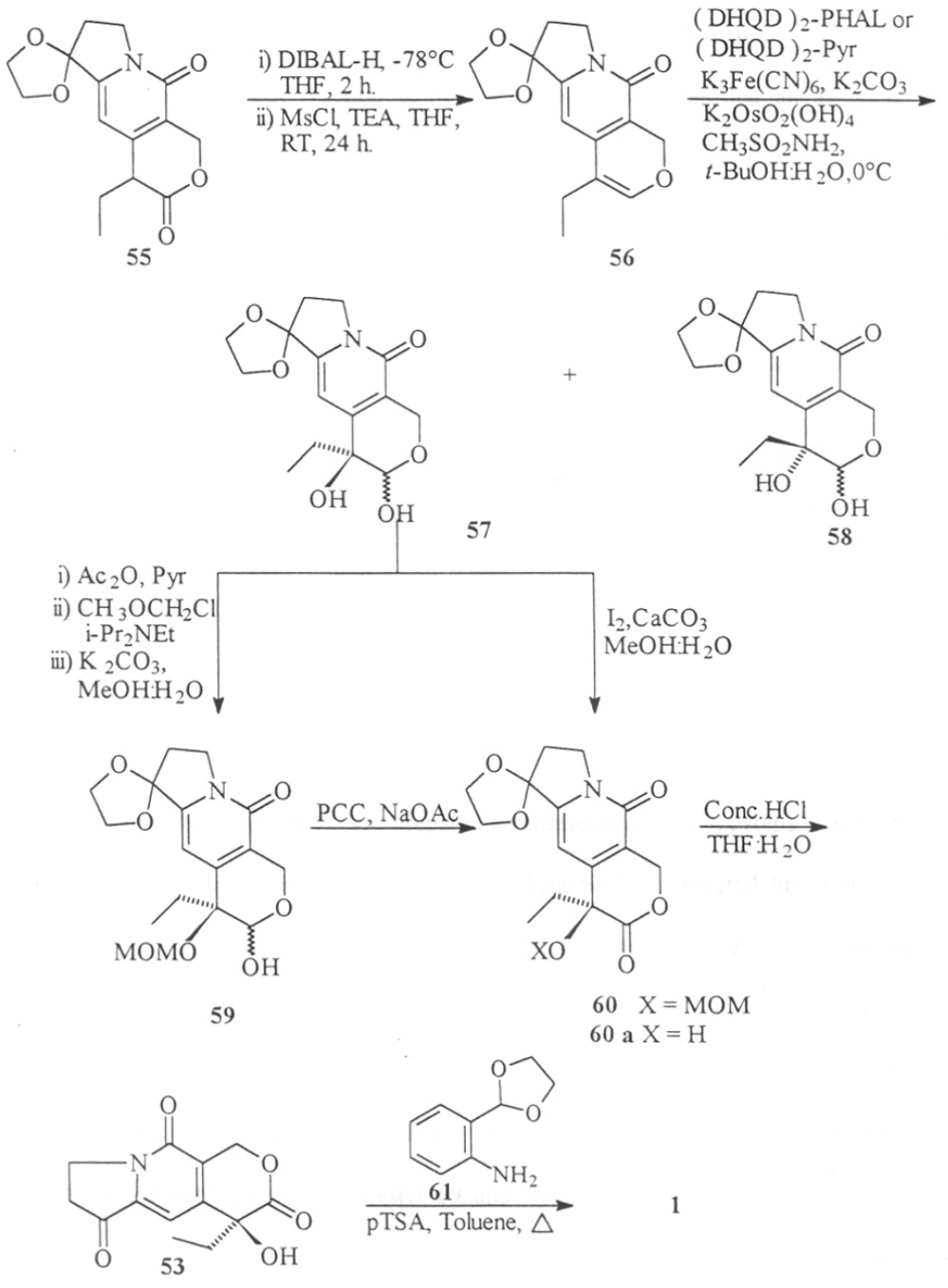
**Scheme 9** Yaegashi et al.[30]



Enantioselective synthesis of tricyclic ketone **53** was achieved by Jew et al. in 1995, using Sharpless catalytic asymmetric dihydroxylation (AD).[31] The substrate for the AD reaction, the endocyclic enol ether **56** was prepared from lactone **55** in two steps, as shown in Scheme-10.

Jew et.al[31]

**Scheme 10**

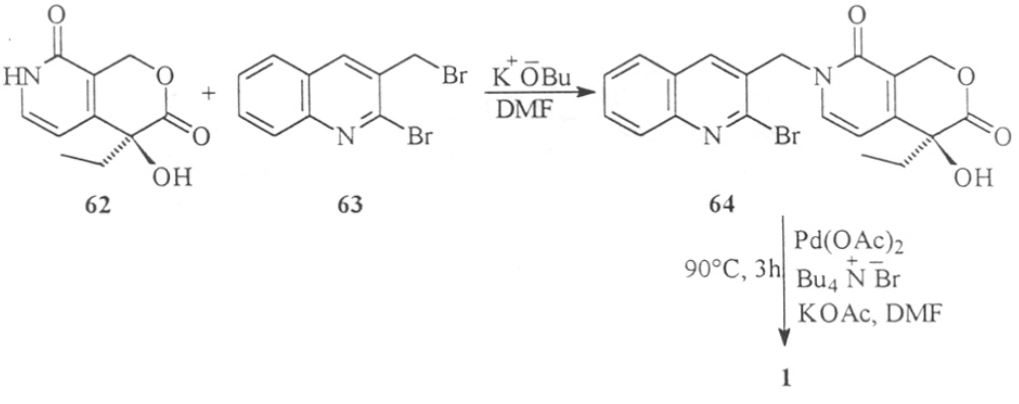


Asymmetric dihydroxylation under Sharpless' conditions provided diols **57** and **58**. The diol **57** on oxidation using Corey's conditions of $I_2/CaCO_3$ furnished ∝ hydroxy lactone **60a** in 48% yield. Deprotection of acetal was effected using concentrated HCl in THF: $H_2O$ system to furnish ketone **53**. Friedlander condensation with amino acetal **61** in refluxing toluene furnished **1** in 69% yield.

**Synthesis of camptothecin by construction of AB rings and DE rings.**

Based on Heck reaction strategy Comins et al.[32] reported an asymmetric synthesis of (S)-camptothecin in which N-alkylation of the pyridone **62** with the bromoquinoline **63** provided the intermediate **64** which on Heck reaction affordd **1** (Scheme 11).

**Scheme 11** Comins et al.[32]

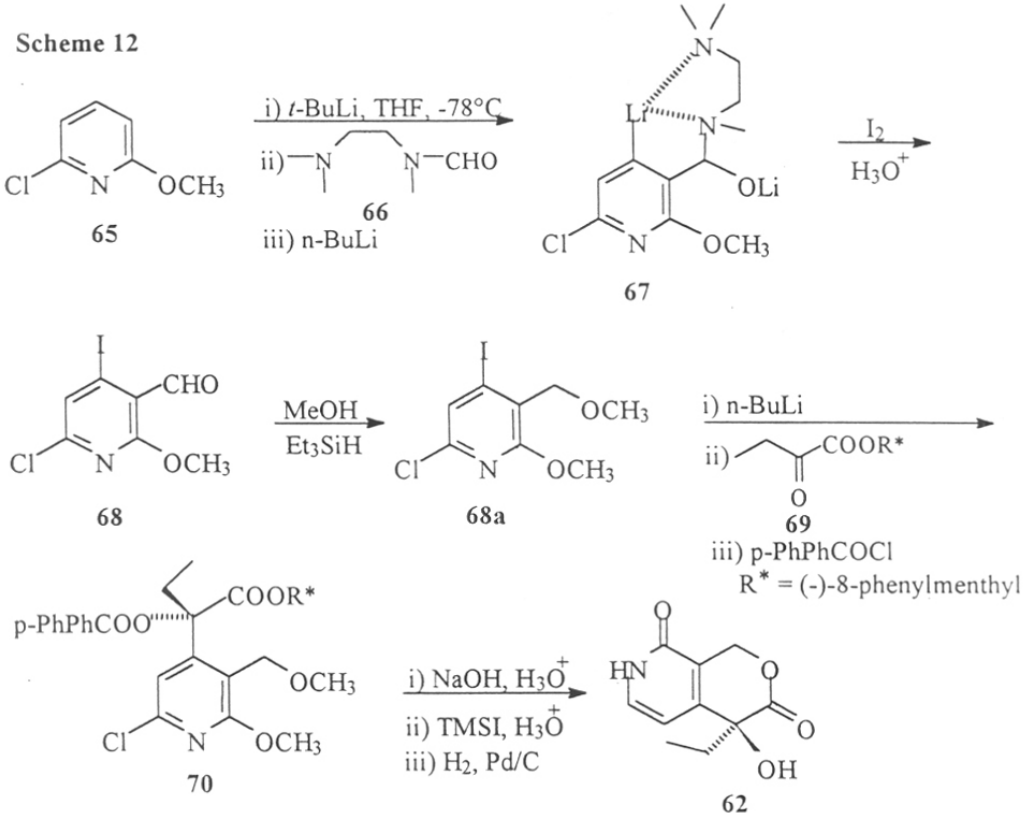



**62** **63** **64** **1**

The hydroxylactone **62** was prepared enantioselectively in six steps starting from 2-chloro-6-methoxypyridine (**65**) as shown in Scheme-12. Directed lithiation on **65** followed by trapping with formamide **66** gave α-amino alkoxide *in situ*, which on further treatment with n-BuLi and quenching with iodine gave the iodo derivative **68** in 78% yield. Methyl ether **68a** was prepared in 92% yield from **68** in one step on treatment with MeOH, triethylsilane and TFA. Lithium halogen exchange followed by condensation with chiral α-keto ester **69** and trapping with 4-phenylbenzoyl chloride

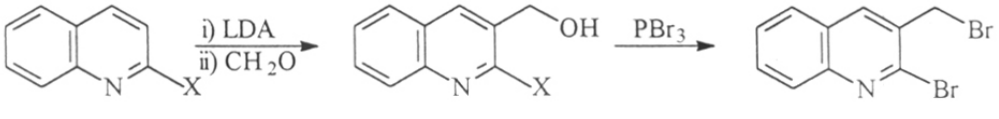
gave **70**. Saponification to the hydroxyacid, cyclization using TMSCl/NaI followed by hydrolysis and catalytic hydrogenation yielded the desired intermediate **62**.

**Scheme 12**




The bromoquinoline **63** was prepared in two steps from 2-chloroquinoline (**71a**). Hydroxymethylation using LDA and paraformaldehyde yielded **72a** which was converted to **63** using $PBr_3$ (Scheme-13).

**Scheme 13**




**71 a** X = Cl
**b** X = Br

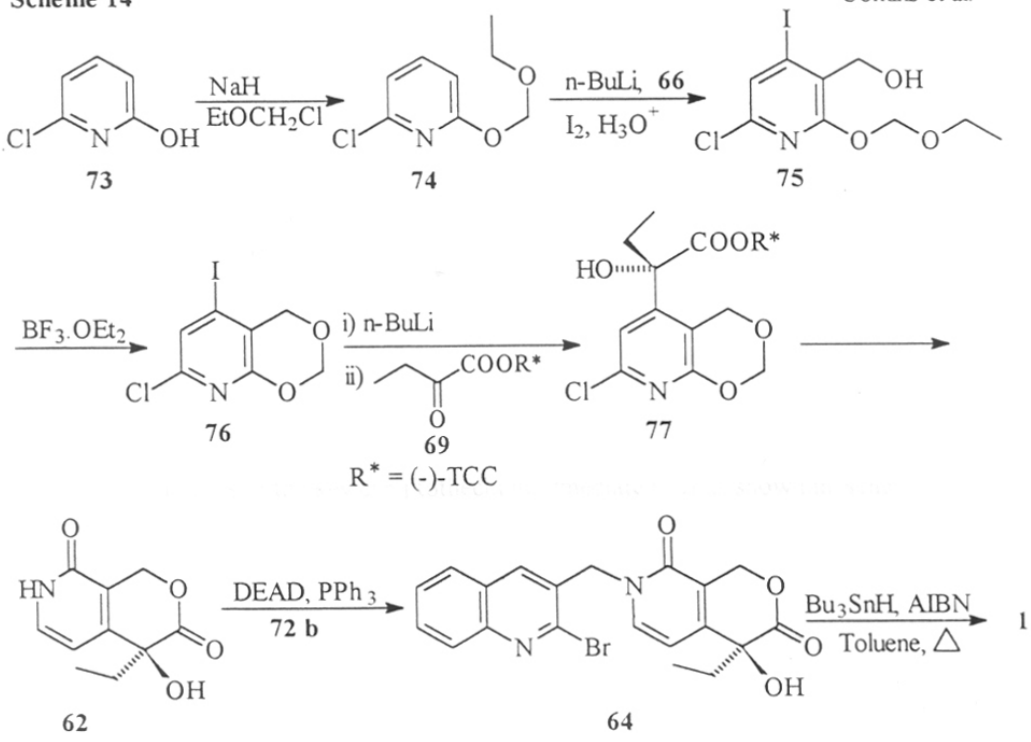
**72 a** X = Cl
**b** X = Br

**63**

N-alkylation of pyridone **62** with **63** using *t*-BuOK/DME to furnish intermediate **64** followed by intramolecular Heck reaction provided (S)-camptothecin in 59% yield. This methodology is flexible for the synthesis of camptothecin derivatives. The most important features of this methodology are the directed lithiation reaction which fixes the aldehyde functionality to furnish lactone as a single regioisomer and optically active synthesis of pyridone (DE ring unit).

In an another similar approach towards camptothecin Comins et al.[33] N-alkylated pyridone **62** under Mitsunobu reaction condition with **72b** to yield **64**. Treatment of **64** with tributyltin hydride and AIBN in toluene gave S-camptothecin (**1**) in 55% yield as depicted in Scheme 14.

**Scheme 14** Comins et al.[33]

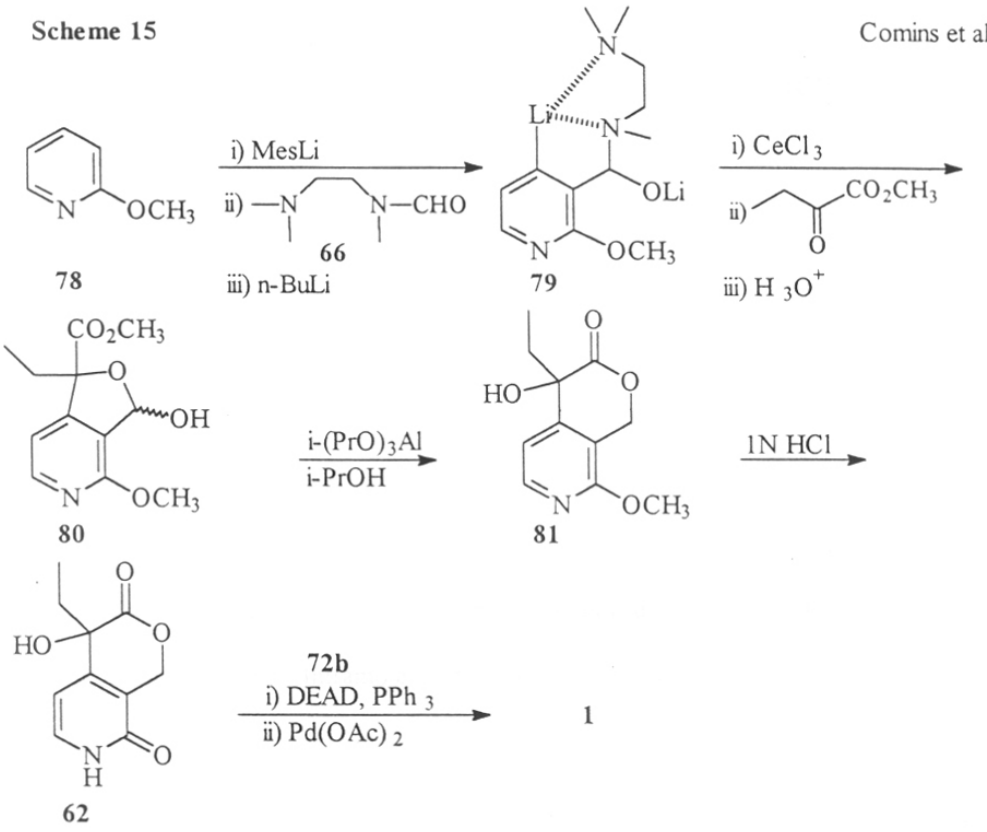



**73** **74** **75** **76** **69** **77** **62** **64**

By employing the Mitsunobu conditions for coupling **62** and **72b** the authors have achieved coupling at room temperature compared to refluxing DME required for alkylating the dibromo compound in the previous synthesis.

In 1994 Comins et al.[34] reported a synthesis of camptothecin (Scheme 15) using similar strategy. By taking 2-methoxy pyridine (**78**) as the starting material the authors have avoided the reduction step necessary to remove the chlorine in the previous synthesis.

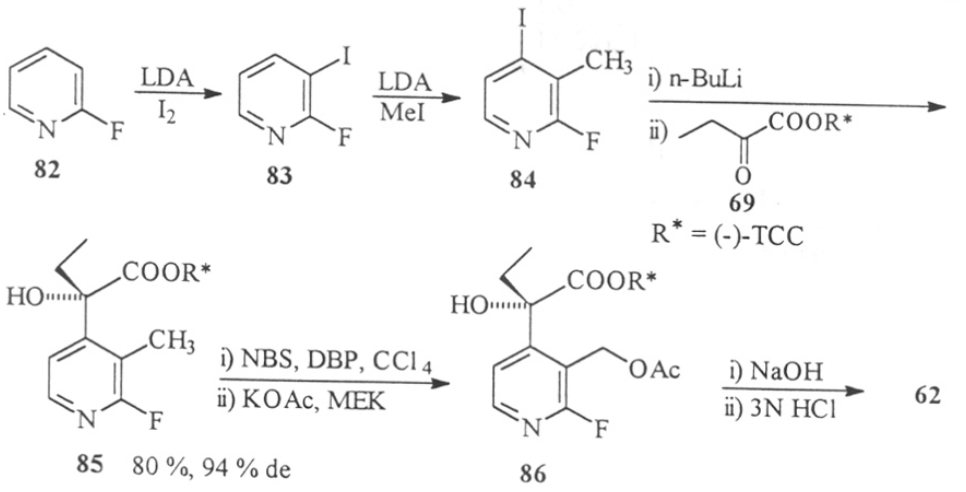
**Scheme 15** Comins et al.[34]




Starting from 2-fluoropyridine (**82**), Comins and Saha[35] in 1995, reported an asymmetric synthesis of the key camptothecin intermediate (**62**) as shown in Scheme 16.

**Scheme 16**

Comins and Saha[35]

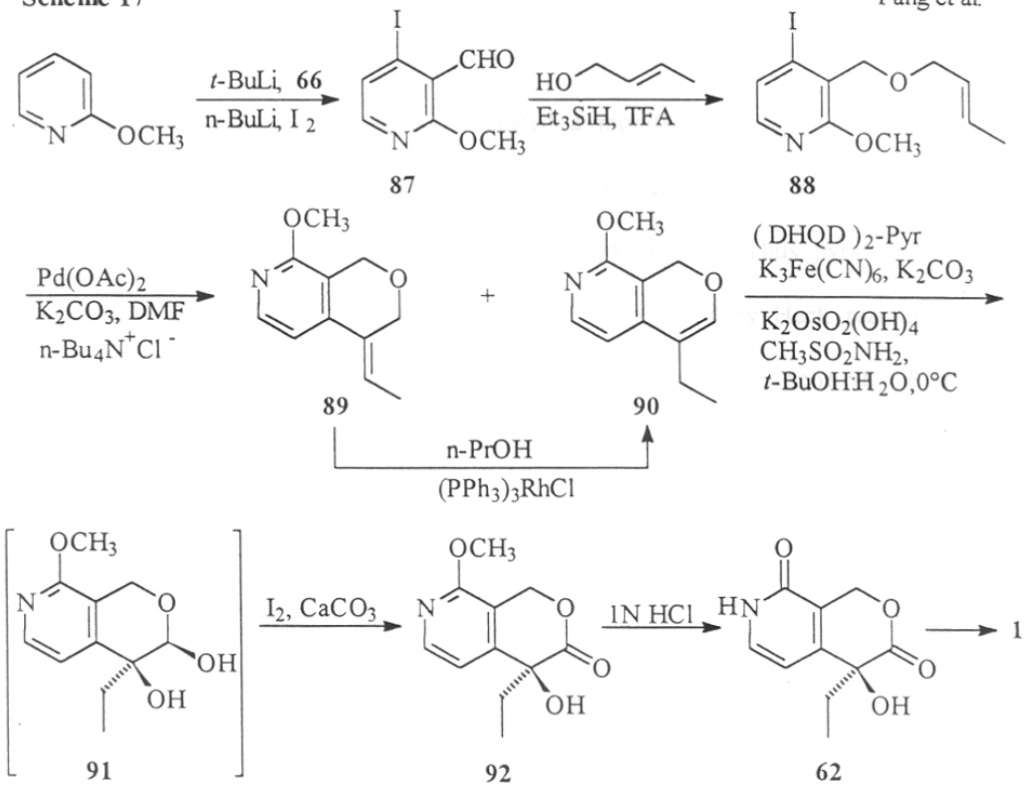



**82** **83** **84** **69** **85** 80 %, 94 % de **86**

Fang et al.[36] reported (Scheme 17) the first catalytic asymmetric route to 20(S)-camptothecin using Sharpless asymmetric dihydroxylation (AD) reaction. The 2-methoxy pyridine when subjected to Comins' conditions of lithiation, furnished iodo aldehyde **87**. Treatment of **87** with crotyl alcohol and triethyl silyl hydride furnished ether **88** in 63% yield. Intramolecular Heck reaction furnished the desired enol ether **90** along with the isomeric allyl ether **89**. The allyl ether **89** was isomerized to enol ether **90** using Wilkinson's catalyst. AD reaction on enol ether **90** using $(DHQD)_2$-PYR ligand yielded **92** in 94% ee. The reaction of **92** with 1N HCl afforded the pyridone **62**.

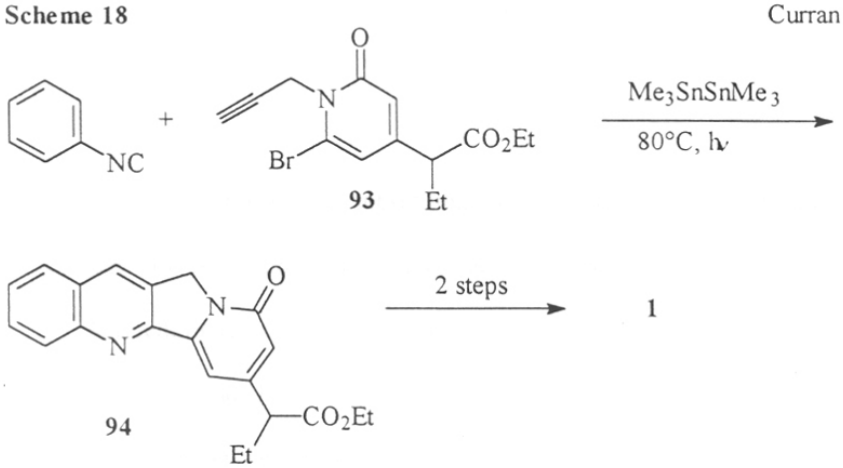
As Comins had previously reported[32] the two step conversion of **62** to camptothecin (**1**), it constituted a formal total synthesis of **1**.

**Scheme 17** Fang et al.[36]




Curran[37] employed a novel 4 + 1 radical annulation methodology for the construction of the quinoline part of the molecule (Scheme 18).

**Scheme 18** Curran and Liu[37]

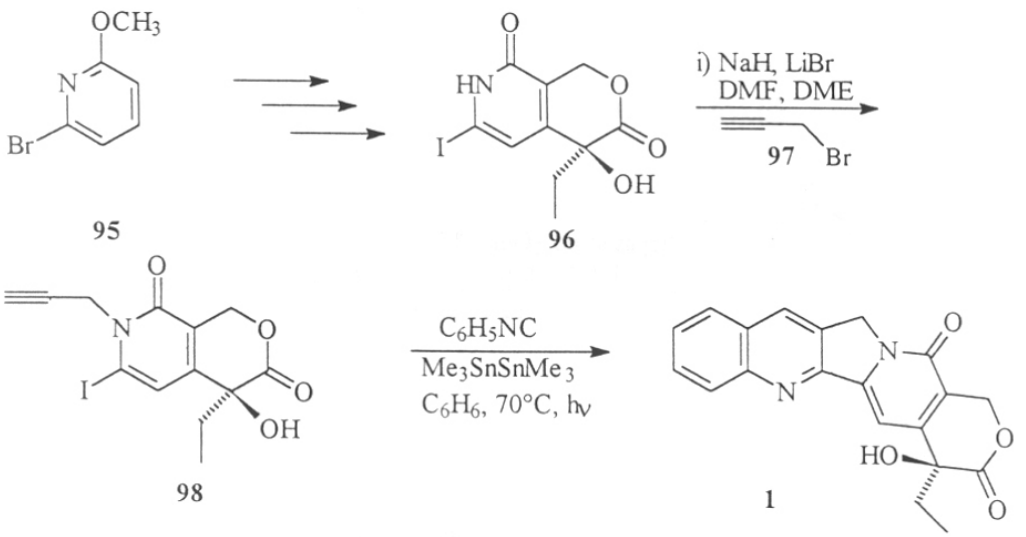



Radical annulation using phenyl isocyanide and **93** in presence of bistrimethyl tin gave tetracyclic intermediate **94** which was converted to camptothecin in

2 steps. Major drawback of this synthesis is that, the reaction conditions were not tolerant of substituents on the A and B rings.

Later in 1995 Curran et al.[38] reported a modified synthesis of asymmetric camptothecin. In this synthesis authors avoided the problem experienced by them in the previous synthesis during construction of E-ring of camptothecin. Thus, pyridine **95** was converted to pyridone **96** using Comins' condition followed by Heck reaction and Sharpless' asymmetric dihydroxylation. N-propargylation gave pyridone **98**. Radical annulation using phenyl isocyanide and hexamethyldistannane gave camptothecin in optically pure form (Scheme 19).

**Scheme 19** Curran et al.[38]



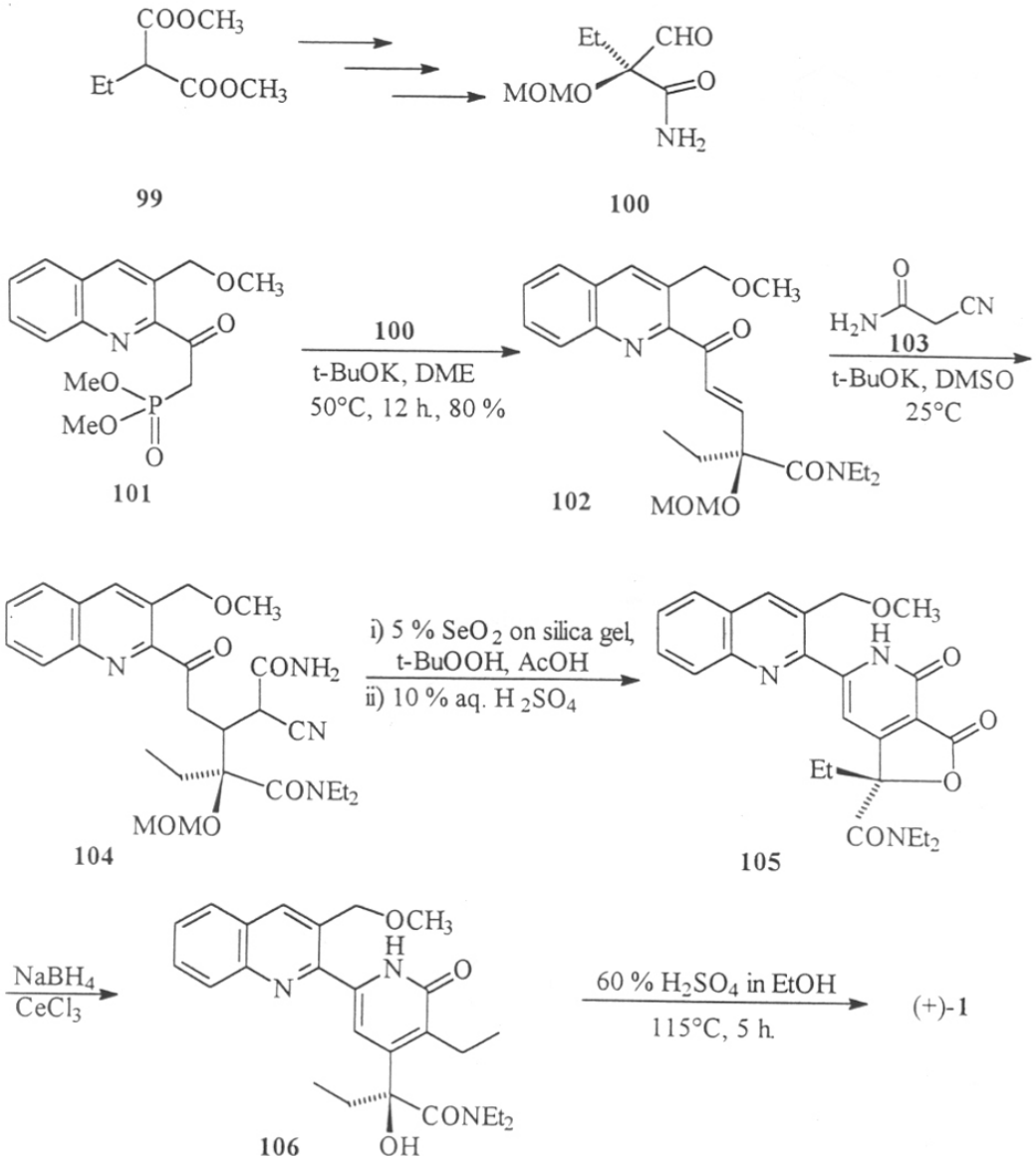

By taking appropriate substituted phenyl isocyanide and propargyl bromides various derivatives of camptothecin have been accessed.

**Miscellaneous synthetic methods**

Ciufolini and Roschangar[39] reported the best enantioselective synthesis of camptothecin (**1**) in ten linear steps in 30%, overall yield starting from dimethyl 2-ethylmalonate (**99**) as depicted in Scheme 20. The compound **99** was converted to the aldehyde **100,** which on condensation with phosphonate **101** afforded the enone **102**. Michael addition with cyanoacetic amide (**103**) followed by cyclization and oxidation

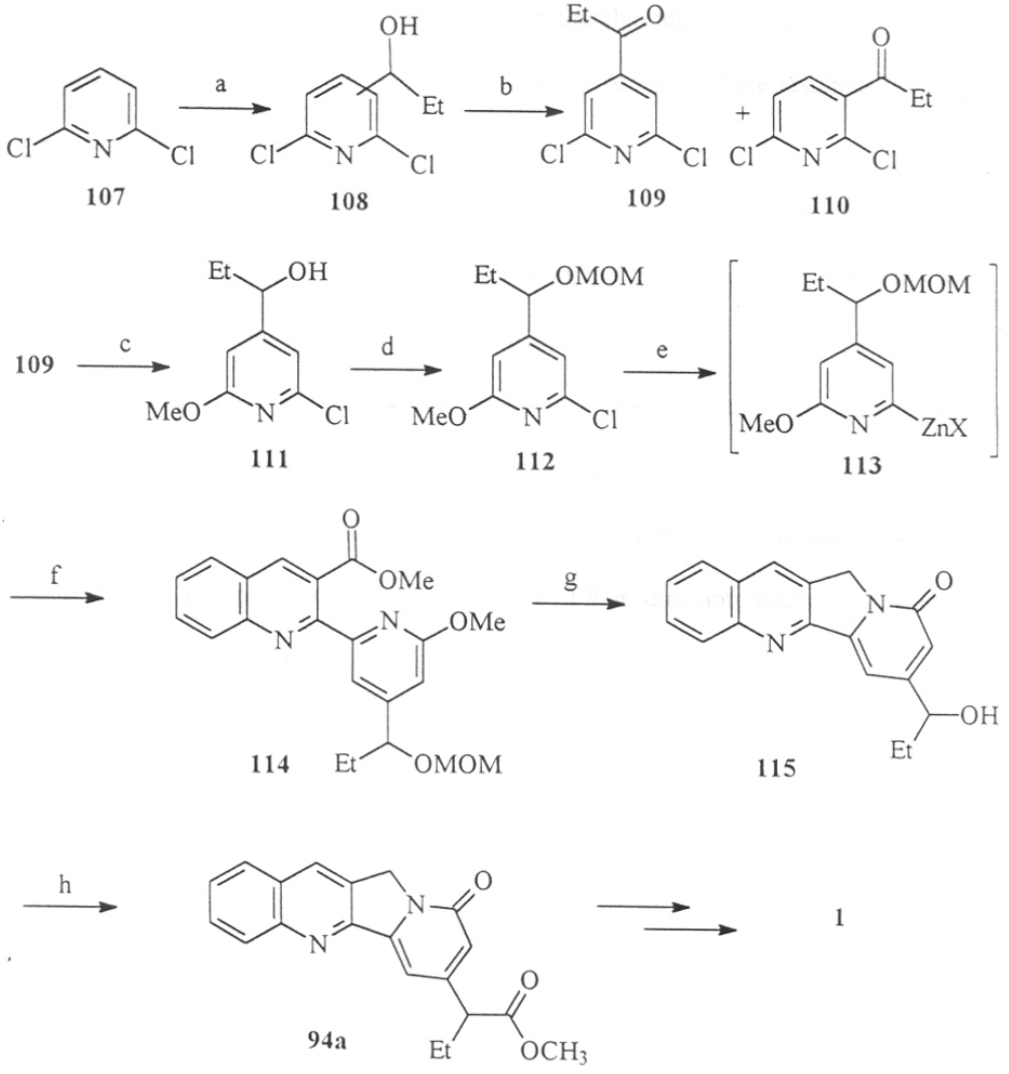
furnished pyridone **105** which on reduction by borohydride in the presence of cerium chloride furnished alcohol **106.** It was lactonized with sulfuric acid in ethanol to give camptothecin in 94% yield.

**Scheme 20** Ciufolini and Roschangar[39]



In 1997, Murata et al.[40] achieved formal total synthesis of camptothecin via two types of lithiation reactions of pyridine derivative and a Pd-catalyzed carbonylation of pyridylmethyl methanesulfonates (Scheme-21).

**Scheme 21** Murata et al.[40]




a] i) *t*-BuLi, THF, -85°C ii) EtCHO, -85° to 25°C
b] i)PCC, $CH_2Cl_2$, 25°C
c] i) NaOMe, MeOH, reflux ii) $NaBH_4$, MeOH, 25°C
d] i) NaH, THF, 25°C ii) MOMCl, 25°C
e] i) Lithium naphthalenide, THF, -90° to -78°C ii) $ZnCl_2$, THF, -78 to 25°C
f] i) Methyl 2-chloroquinoline-3-carboxylate $(Ph_3P)_4Pd$ ( 5 mol %), THF
g] i)$LiAlH_4$, ether, 0°C, ii) $CBr_4$, $Ph_3P$ iii) 3N HCl
h] i) MesCl, $Et_3N$, $CH_2Cl_2$ ii) CO (10atm), $(Ph_3P)_2PdCl_2$, $Et_3N$, MeOH

Lithiation of 2,6-dichloropyridine (**107**) and trapping it with propanal gave **108** in 69% yield as a mixtures of regioisomers. After the oxidation of **108**, the isomers **109** and **110** were easily separated by silica gel column chromatography. The ketone **109** was transformed into **112** through the substitution of the chloride on the pyridine ring with the methoxide, reduction of the ketone moiety and protection of the resulting hydroxyl group as the MOM group.

The 2-chloropyridine derivative **112** was treated with lithium naphthalenide complex in THF at -90°C and transmetalated to the zinc derivative **113**. This was subjected to the Pd-catalyzed cross coupling with the methyl 2-chloro-3-quinolinecarboxylate to afford **114**. The compound **114** was converted to tetracyclic compound **115** by reduction of the ester moiety, followed by bromination, hydrolysis and cyclization. Pd-catalyzed carbonylation gave the known intermediate **94a**. As Danishefsky et al. reported the 2 step conversion of **94a** to camptothecin , it constituted formal total synthesis of **1**.

## Present work

Plant kingdom is an exceptionally viable, renewable resource of biologically active natural products many of which were used in treatment of different diseases and some have provided lead structures for the development of modified derivatives with enhanced activity and/or reduced toxicity. Continued search for isolation of new compounds from plants to fight against deadly diseases like cancer resulted in the isolation of camptothecin by Wall and coworkers[1] from *Camptotheca acuminata*. It exhibits antitumor and antileukemic properties. In 1985 Hsiang and coworkers[42] found that camptothecin inhibited topoisomerase-I which stimulated efforts to find new analogues with improved biological activity as well as sustained the interest in synthesizing camptothecin itself to make it available in larger quantities.

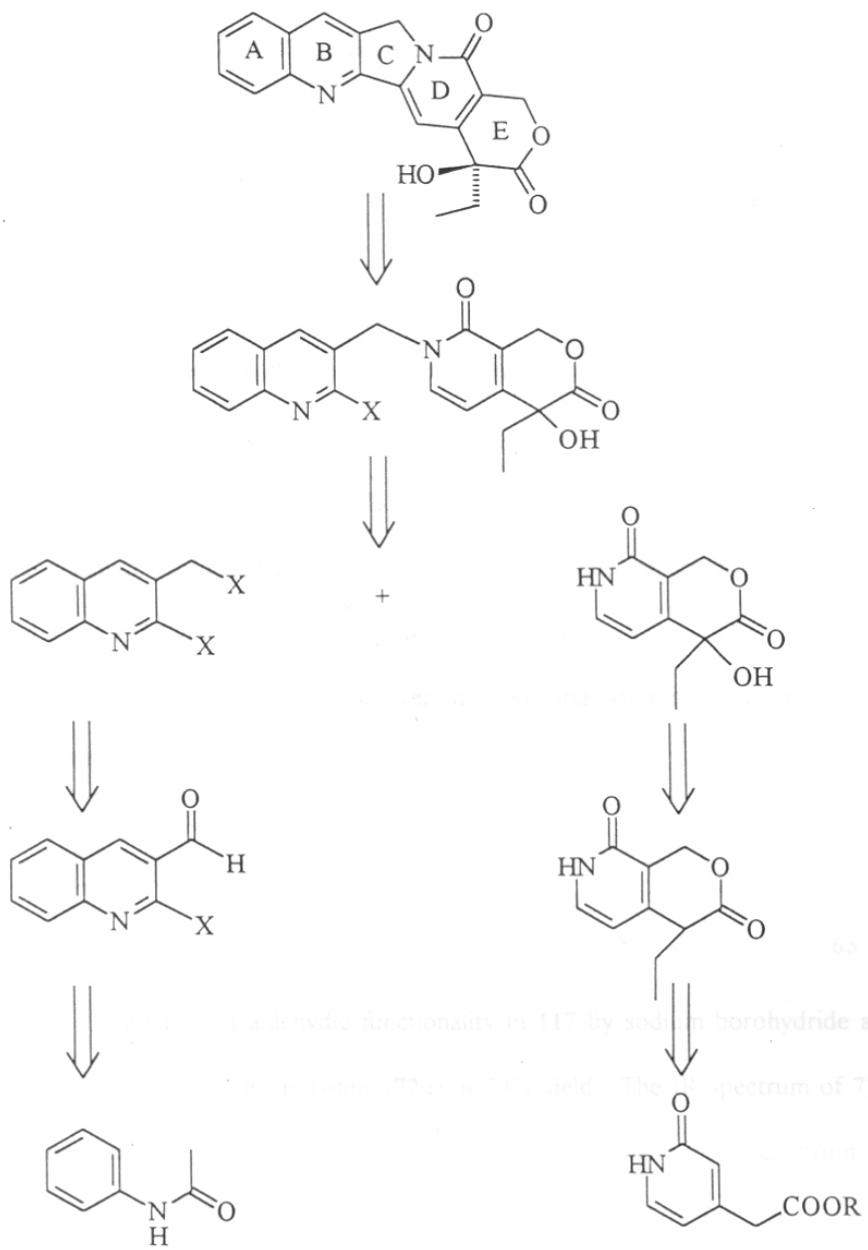
Some of the analogues of camptothecin like topotecan (**1f**), irinotecan (**4**) etc. are under clinical trials against various types of cancer and several additional ones like 9-aminocamptothecin (**1c**) are being prepared for clinical trials.

The present work was undertaken in view to develop synthetic strategies for camptothecin which could be used for the preparation of its analogues as well. The synthetic strategy for assembly of camptothecin skeleton is shown in the retrosynthetic scheme.

**Route A: Photochemical reaction approach**

This approach is centered on the construction of ABCD ring synthon of camptothecin *via* C-N and C-C bond formation between AB and D ring synthons. The AB ring synthon could be prepared from acetanilide whereas D ring synthon could be prepared from dimethyl acetone-1,3-dicarboxylate (**116**).

**Retrosynthetic Scheme**

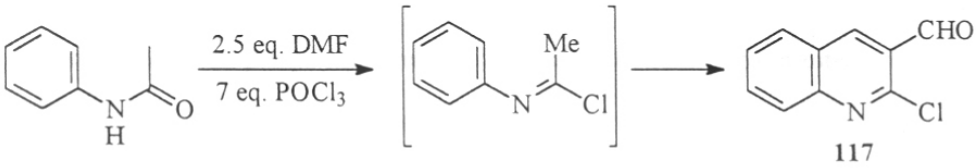



X = Br or I

**Synthesis of AB ring synthon**

Vilsmeier-Haack formylation of acetanilide in one step with 2.5 equivalents of dimethylformamide and seven equivalents of phosphoryl chloride[43] gave 2-chloro-3-formylquinoline (**117**) in 80% yield (Scheme 22).

**Scheme 22**

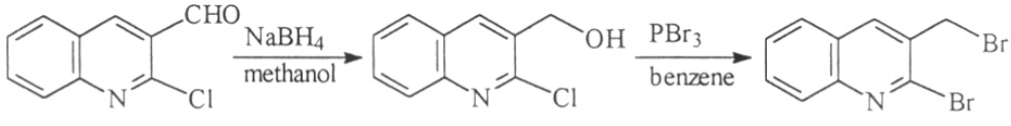



**117**

Its IR spectrum showed absorption band at 1700 $cm^{-1}$ for the aldehyde carbonyl group. The PMR spectrum showed a doublet of doublet at δ 7.52, a multiplet between δ 7.60-8.07 and a singlet at δ 8.73 for the aromatic protons and a singlet at δ 10.56 for the aldehyde proton. The mass spectrum exhibited the molecular ion peak at m/z. 191 ($M^+$) and 193 ($M^+$+2) further supported the structure.

The compound **117** was converted to AB ring synthon as shown in Scheme 23.

**Scheme 23**




**117** **72a** **63**

Reduction of aldehydic functionality in **117** by sodium borohydride afforded 2-chloro-3-hydroxymethylquinoline (**72a**) in 70% yield. The IR spectrum of **72a** showed absorption band at 3480 $cm^{-1}$ for the hydroxyl group. The PMR spectrum exhibited a singlet at δ 4.70 for oxymethylene, a multiplet at δ 7.49-8.08 and a singlet at δ 8.45 for the aromatic protons. The presence of molecular ion peak at m/z. 193 and 195 ($M^+$+2) further proved the structure. 2-Bromo-3-bromomethylquinoline (**63**) was obtained in 67.7% yield when alcohol **72a** was reacted with phosphorous tribromide. The PMR spectrum of **63** revealed a singlet at δ 4.75 for methylene protons, a multiplet at δ 7.55-

8.11 and singlet at δ 8.30 for aromatic protons. The mass spectrum revealed the molecular ion peak at m/z. 299 ($M^+$) and 301 ($M^+$ +2) which confirmed the structure of **63**.

**Synthesis of D ring synthon**

The 'D'-ring synthon can be prepared from dimethyl acetone-1,3-dicarboxylate. Non-cyclic esters of β-keto acids react with cyanoacetic acid to form esters of *cis* and *trans* β-γ-unsaturated-γ-cyano carboxylic acids.[44] Thus, the reaction of dimethyl acetone-1,3-dicarboxylate (**116**) [ prepared from citric acid[45] ] with cyanoacetic acid[46] in the presence of ammonium acetate and glacial acetic acid yielded dimethyl-3-cyanomethylene glutarate (**118**) in 92% yield (Scheme 24). The IR spectrum of **118** showed absorption bands at 2230 and 1730 $cm^{-1}$ for the nitrile and ester carbonyl groups respectively. Hydrolysis of ester **118** was carried out using sodium hydroxide in ethanol-water at room temperature to affod the acid **119.** 4-Cyano-3-butenoic acid (**119**) on treatment with phosphorous pentachloride in dry ether gave the acid chloride **120,** which was not isolated and carried out further reaction as such. HCl gas was passed through the acid chloride **120** in ether at 0°C to give the desired pyridone **121** in 60% yield. The IR spectrum of **121** showed absorption band at 1660 $cm^{-1}$ for lactam carbonyl group. Its PMR (FIG. I) spectrum showed a singlet at δ 3.55 for the methylene protons, a singlet at δ 3.75 for methyl ester and two singlets at δ 6.65 and δ 6.80 for olefinic protons.

The chloropyridone **121** was dechlorinated by transferhydrogenolysis using ammonium formate and 10% Pd/C in methanol at room temperature to yield 4-carbomethoxymethyl 2-pyridone (**122**) in 70% yield. Its PMR spectrum (FIG. II) showed a singlet at δ 3.50 for methylene protons, a singlet at δ 3.72 for methyl ester group, a doublet (J=7 Hz) at δ 6.30, a singlet at δ 6.45 and a doublet (J = 7 Hz) at δ 7.33 for the olefinic protons.

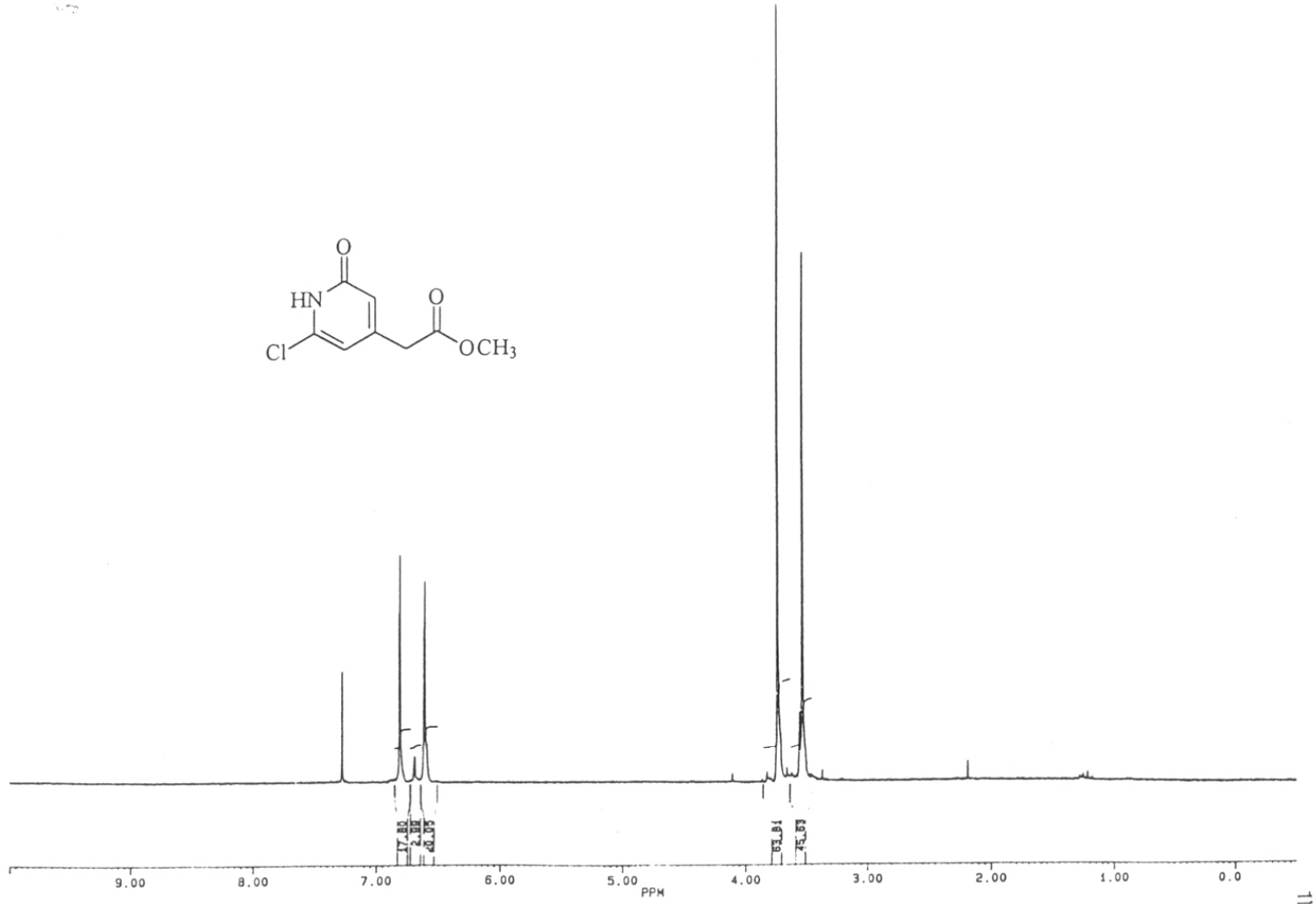



FIG I: PMR SPECTRUM OF THE COMPOUND 121 IN $CDCl_3$

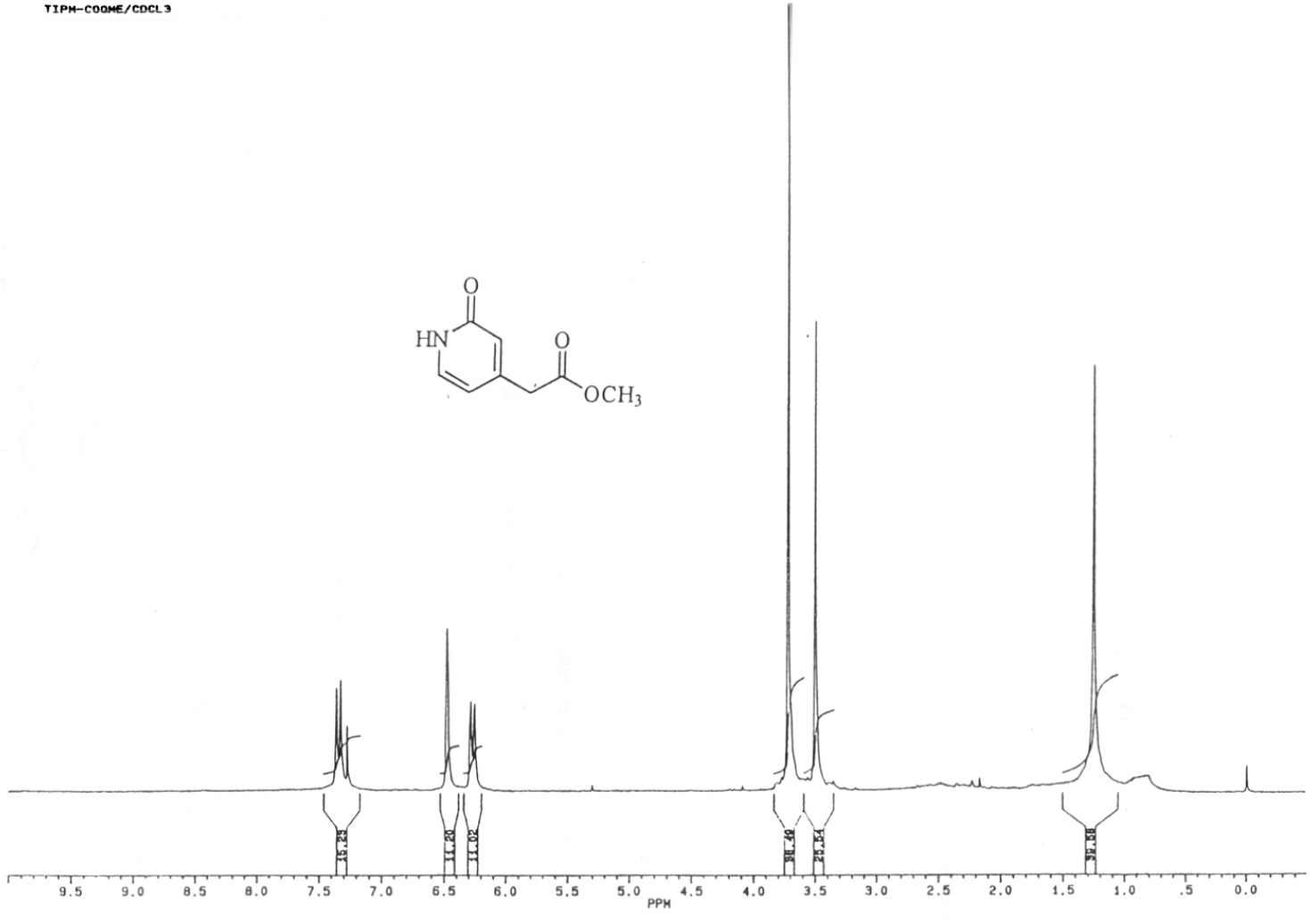
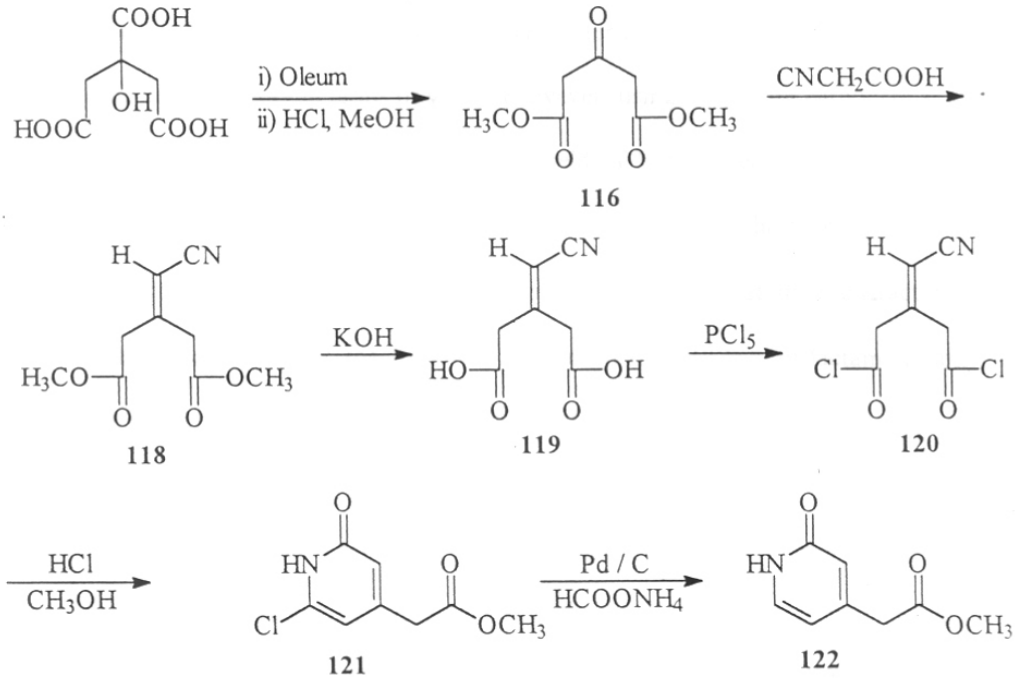


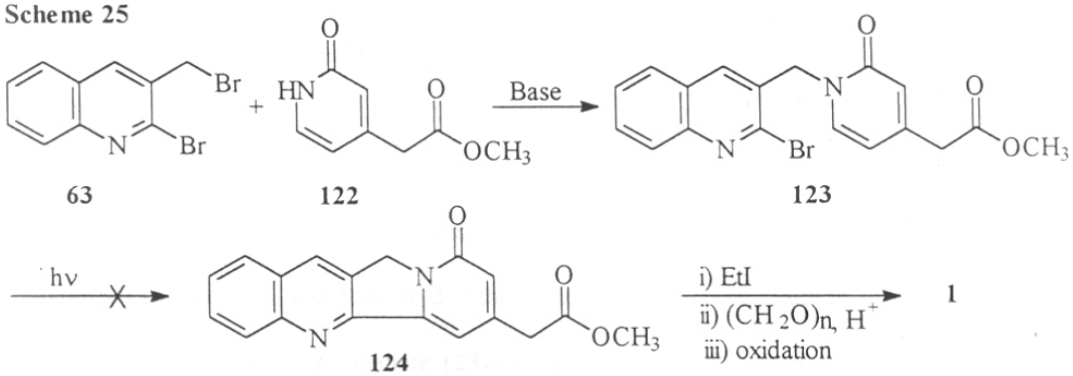

FIG II: PMR SPECTRUM OF THE COMPOUND 122 IN $CDCl_3$

**Scheme 24**




Having thus obtained the key intermediates **63** and **122**, the next aim was to couple the two moieties to get the tetracyclic intermediates of camptothecin. It was proposed that the N-alkylation of the pyridone **122** with **63** in the presence of base could give the N-alkylated compound **123**, which on photochemical cyclization could give the desired tetracyclic compound **124**. The compound **124** could then be converted by three known steps[41] to (±)-camptothecin (**1**) (Scheme 25).

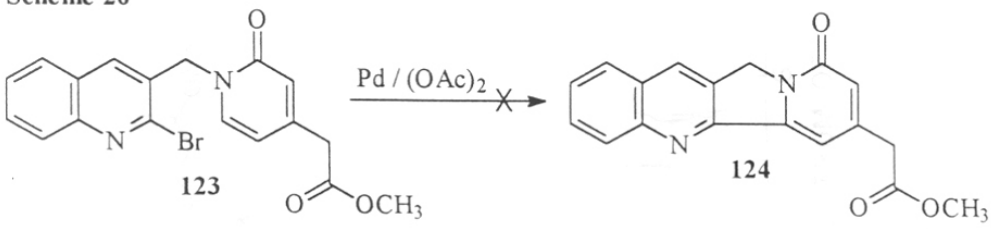
**Scheme 25**



Thus, the pyridone **122** was N-alkylated with diboromo compound **63** using reported methods like sodium hydride, potassium tertiary butoxide etc. which were found to be unsatisfactory in terms of yield. However, using potassium carbonate as the base and acetonitrile as the solvent gave 65% yield of N-alkylated product **123**. The structure of **123** was confirmed by PMR spectrum (FIG. III) which showed the N-methylene group at δ 5.15. The remaining protons resonated at their characteristic chemical shift values. The IR spectrum of **123** showed the presence of lactam carbonyl band at 1670 $cm^{-1}$ which ruled out the possibility of O-alkylation.

Initially intramolecular radical cyclization method was used for C-C bond formation. When N-alkylated product **123** was irradiated at 300 nm in acetonitrile-water as solvent and using propylene oxide as a acid scavanger for 3 hrs at first instant, it showed a complex pattern on TLC. Various attempts were made using different reaction conditions, but failed to give the desired product **124**. When all attempts for photoinduced radical intramolecular cyclisation of **123** to **124** failed, intramolecular Heck reaction was carried using Pd $(OAc)_2$, KOAc, DMF, $Bu_4N^+Br^-$ at 90°C and stirred for 3 hrs, however, it also met with failure (Scheme 26).

**Scheme 26**




Thus, it was decided to convert the intermediate **123** into Comins' intermediate **64** by hydroxymethylation and oxidation reactions. Comins and coworkers[32] have reported (Scheme 11 and Scheme 27) the intramolecular Heck reaction of **64** into dl-camptothecin (**1**). The intermediate **123** was heated at 110°C with paraformaldehyde in presence of sulphuric acid in dioxane for 18 hr. Usual work-up of the reaction showed

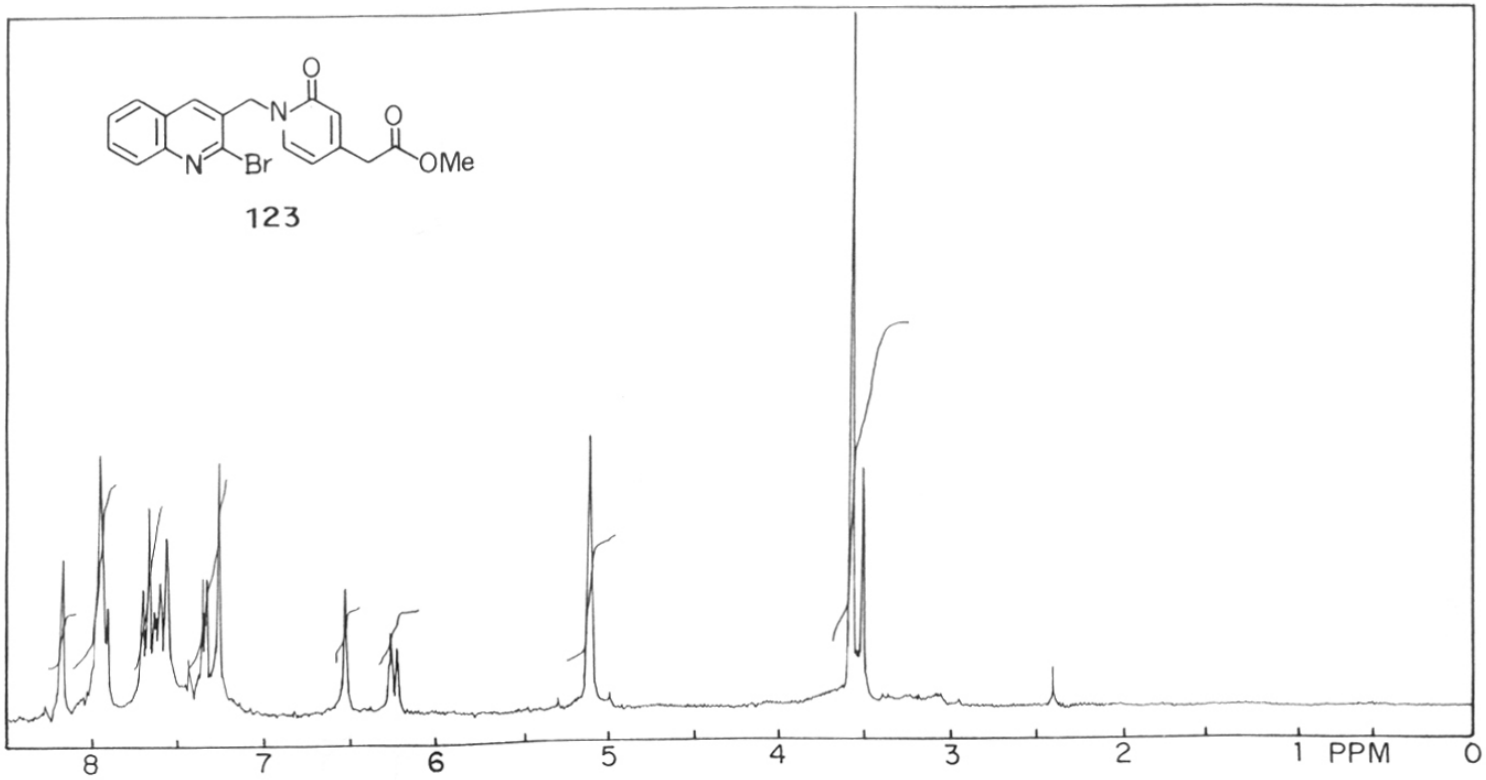
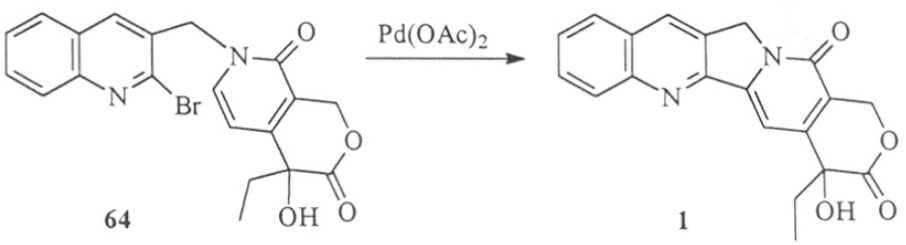



FIG. III: $^{1}H$ NMR SPECTRUM OF THE COMPOUND **123** IN $CDCl_3$

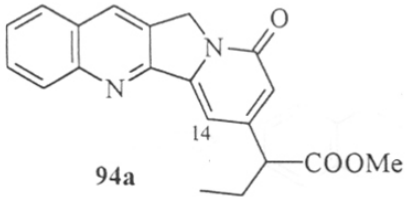
formation of a number of products (TLC) from which the desired lactone could not be isolated. It was observed by Danishefsky and coworkers[41] that similar hydroxymethylation reaction in their synthesis of camptothecin yielded a mixture of deoxycamptothecin and isodeoxycamptothecin (Scheme 28) since the C-14 position of camptothecin was not blocked. Therefore this work was discontinued.

**Scheme 27**



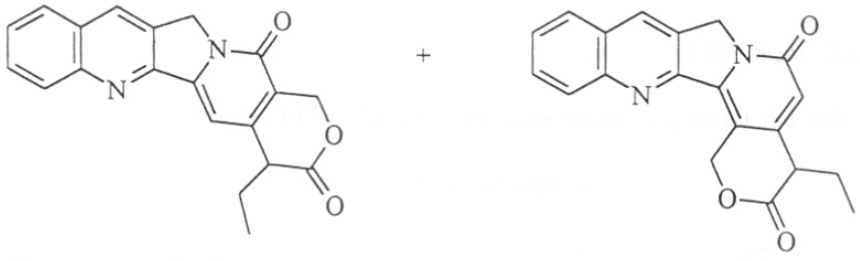

64 1

**Scheme 28**




94a

HCHO, $H_2SO_4$, Dioxane
100°C, 16 hr

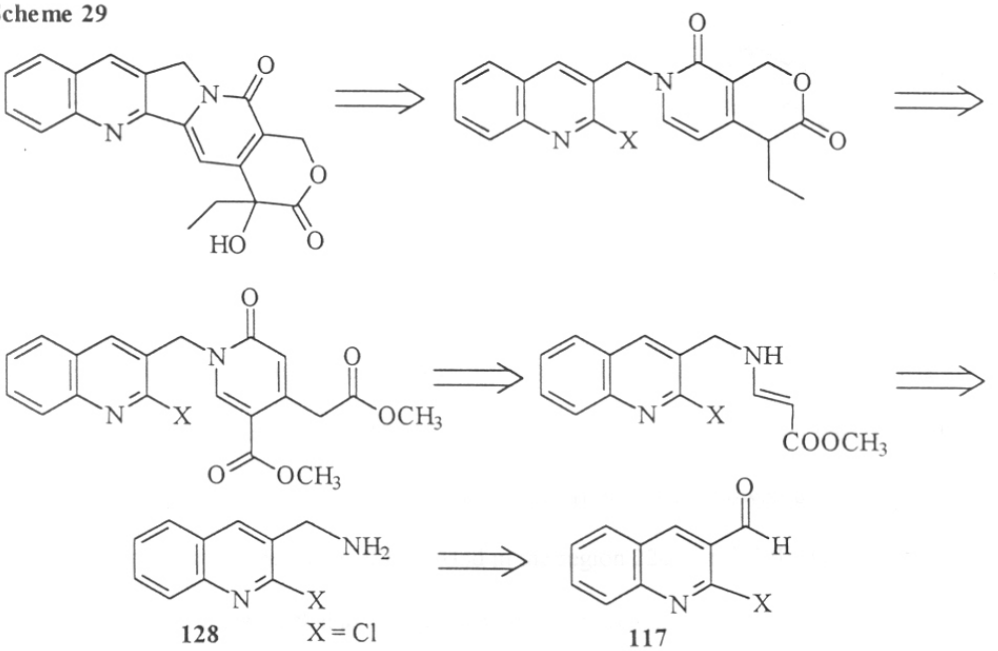


Deoxycamptothecin + Isodeoxycamptothecin

**Route B: Intramolecular Heck reaction approach**

In another approach it was proposed to synthesize camptothecin by using intramolecular Heck reaction in linear or convergent way. Based on this strategy, a following retrosynthetic scheme was proposed (Scheme 29).

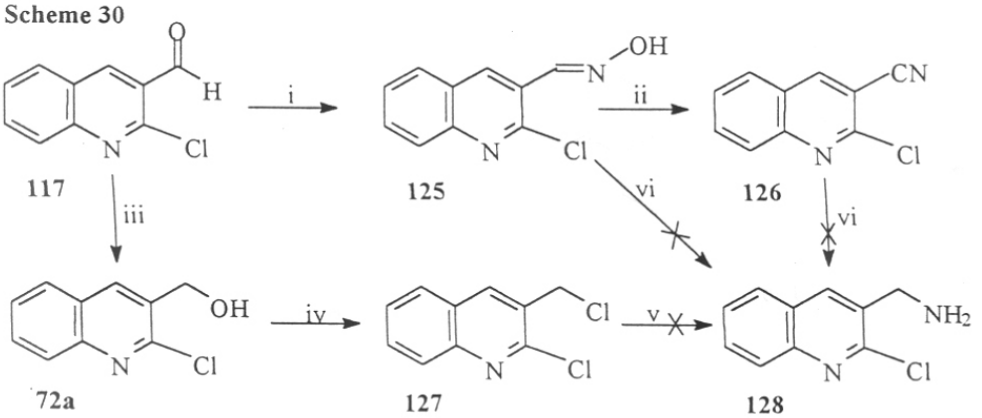
**Scheme 29**




The amine **128** (X = Cl) which is a key intermediate in this scheme was not reported in the literature. It was planned to prepare **128** from 2-chloro-3-quinolinecarboxylaldehyde (**117**). The attempts were made to convert the aldehyde **117** into the required amine **128** as summarized in Scheme 30.

Aldehyde **117** was converted into oxime **125** by treatment with hydroxylamine hydrochloride.[47] The IR spectrum of **125** showed absorption band at 3250 $cm^{-1}$ for the hydroxyl group. Its PMR spectrum showed disappearance of signal corresponding to aldehydic proton. The structure of oxime **125** was further confirmed by converting it into ethyl ether by reaction with ethyl iodide in the presence of potassium carbonate.[47]

**Scheme 30**




i) $HOH_2N{\bullet}HCl$ iv) $PCl_5$, benzene

ii) $SOCl_2$, benzene v) Hexamethylenetetramine

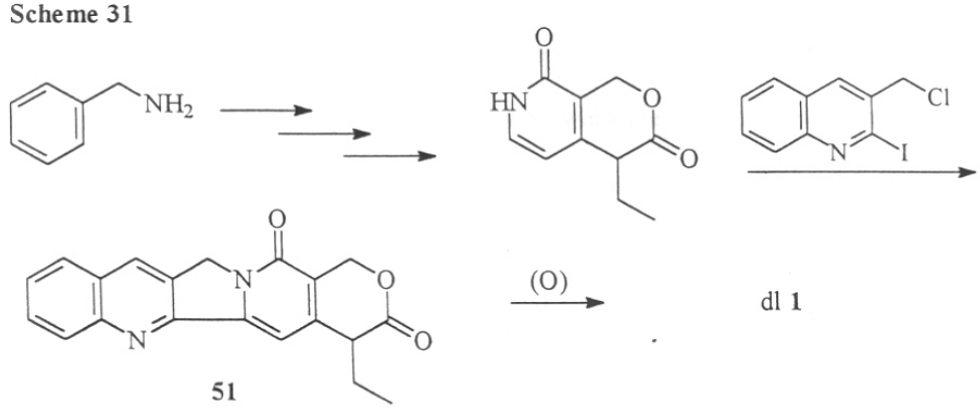
iii) $NaBH_4$, MeOH vi) Raney nickel, 10% Pd / C, $H_2$

Reduction of the oxime **125** with Raney nickel as well as catalytic hydrogenation failed to give the desired amine **128**. The oxime **125** was then converted into nitrile **126** by treatment with thionyl chloride.[47] The IR spectrum of **126** showed disappearance of hydroxyl peak and appearance of new band in the region 2200 $cm^{-1}$. Efforts to reduce the nitrile **126** with Raney nickel as well as catalytic hydrogenation were unsuccessful.

The aldehyde **117** was then converted into the dichloro quinoline derivative **127** *via* the alcohol **72a** with a hope to get the required amine **128** from the chloride by reaction with hexamethylenetetramine.[48] Unfortunately, this reaction also failed to give the desired amine **128**. To our surprise, every reaction, leading to amine **128,** gave a complex mixture of products. This might be due to unstability of the amine **128.** As all attempts to get the amine **128** were unsuccessful, the linear strategy towards the synthesis of camptothecin was abandoned.

Here again the convergent approach is based on construction of AB and DE ring synthons. The key steps in this approach is the construction of C ring of camptothecin by employing intramolecular Heck reaction ( Scheme-31).

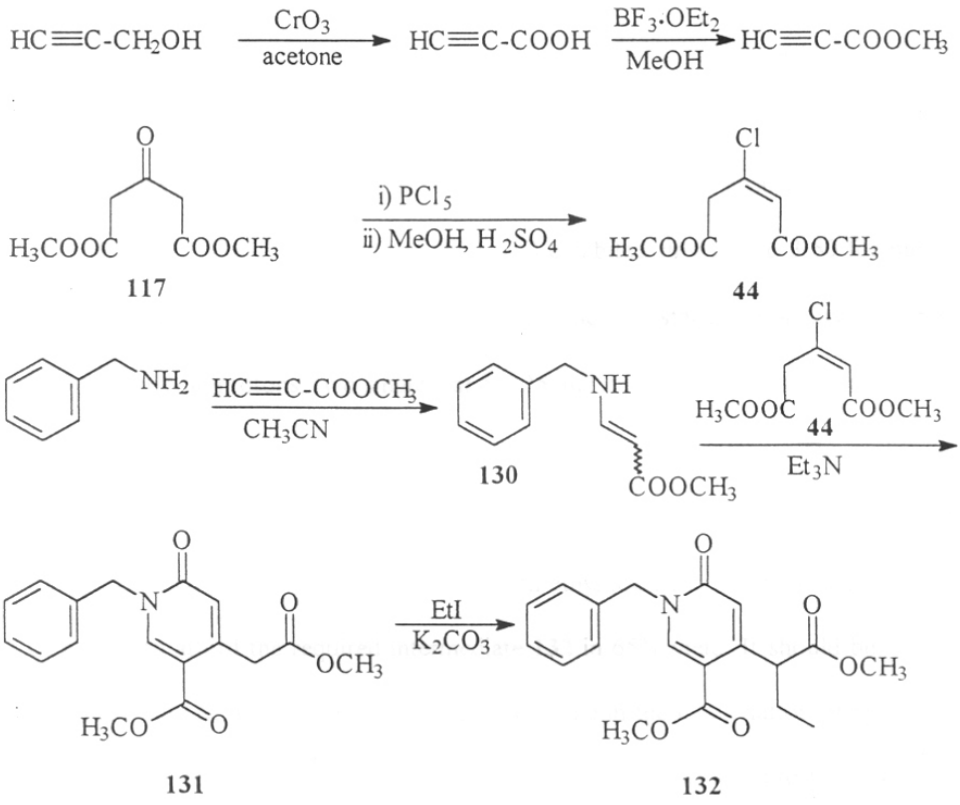
**Scheme 31**




**51**

An alternate synthetic sequence for camptothecin is shown in Scheme 32.

**Scheme 32**




Here, the pyridone skeleton was built on the nitrogen of benzyl amine. The methyl propiolate (**129**) required in this strategy was prepared from propargyl alcohol by oxidation with chromic acid[49] followed by esterification using borontrifluoride-etherate[50] in methanol. Michael addition[51] reaction of **129** with benzylamine in acetonitrile at room

temperature gave the Michael adduct **130** in 67% yield. Its PMR spectrum showed mixture of *cis* and *trans* isomers. In case of *cis* isomer, olefinic proton adjacent to ester group appeared as a doublet (J=7.5 Hz) at δ 4.65 while the same proton in *trans* isomer appeared as a doublet (J=13.5 Hz) at δ 4.80. In case of *cis* isomer olefinic proton adjacent to nitrogen showed doublet of doublet (J=7.5 Hz and J=13.5 Hz) at δ 6.70 while the same proton in *trans* isomer showed doublet of doublet (J=7.5 Hz and J=13.5 Hz) at δ 7.60. This isomeric mixture was used as such for further reactions.

The Michael adduct **130** underwent crucial cyclisation with dimethyl 3-chloro-2-pentenedioate **44** ( prepared from reaction of dimethyl 1,3-acetone dicarboxylate with phosphorous pentachloride followed by esterification using sulfuric acid in methanol )[52] in the presence of triethylamine to give the desired pyridone **131**. The structure of **131** was confirmed by spectral analysis. The IR spectrum showed absorption band at 1670 and 1720 $cm^{-1}$. The PMR spectrum (FIG. IV) exhibited singlet at δ 3.60 for methylene protons, two singlets at δ 3.66 and δ 3.72 for the methyl ester functionality, a singlet at δ 5.05 for benzylic protons, two singlets at δ 6.35 and δ 8.15 corresponding to one proton each for pyridone and a singlet at δ 7.25 for five aromatic protons. The molecular ion peak at m/z. 315 in the mass spectrum confirmed the structure.

The pyridone **131** was C-alkylated with ethyl iodide in the presence of potassium carbonate to afford the required intermediate **132** in 65% yield. It should be noted here that potassium carbonate was used for the first time in the C-alkylation of pyridone **131**. It is evident from the reported methods[53] on synthesis of camptothecin that earlier workers have used NaH or $KOBu^t$ as a base for C- alkylation with ethyl iodide. The PMR spectrum (FIG. V) showed a triplet at δ 0.87 (J=7 Hz) for methyl protons, a multiplet between δ 1.6-2.21 for methylene protons and a triplet (J=7 Hz) at δ 4.30 for methine proton. The remaining protons resonated at their characteristic chemical shift

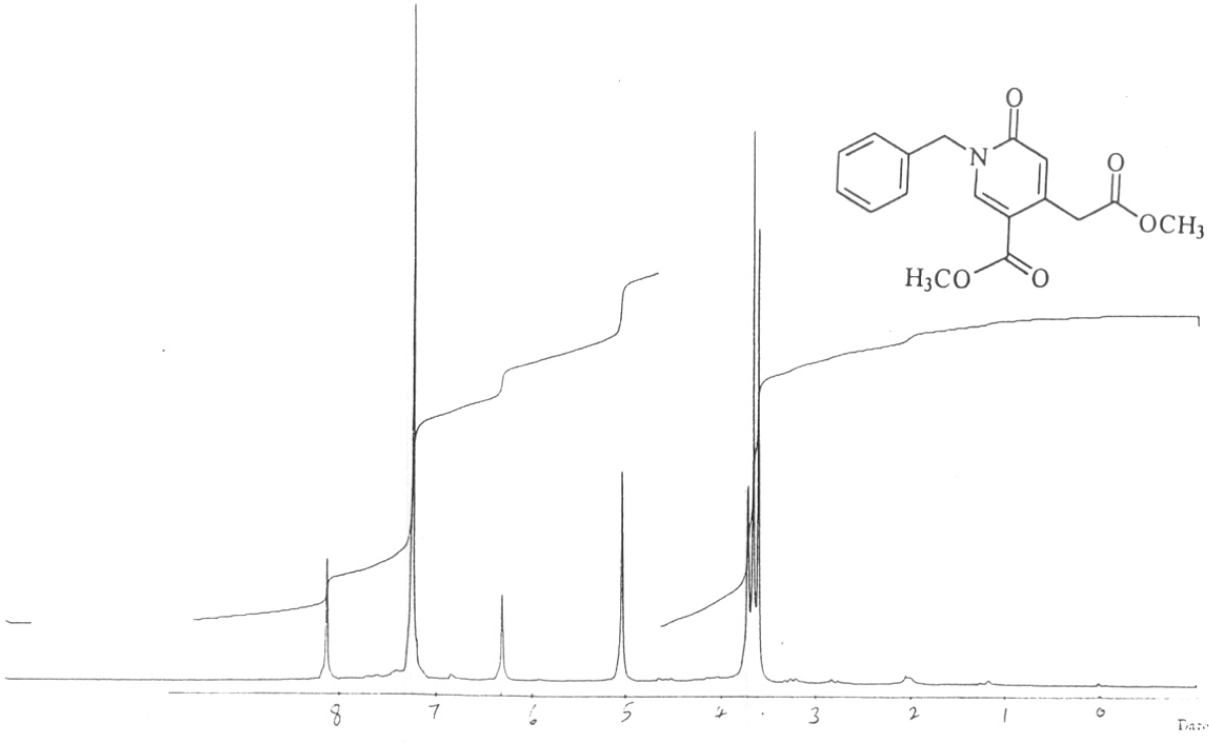



FIG IV: PMR SPECTRUM OF THE COMPOUND 131 IN $CDCl_3$

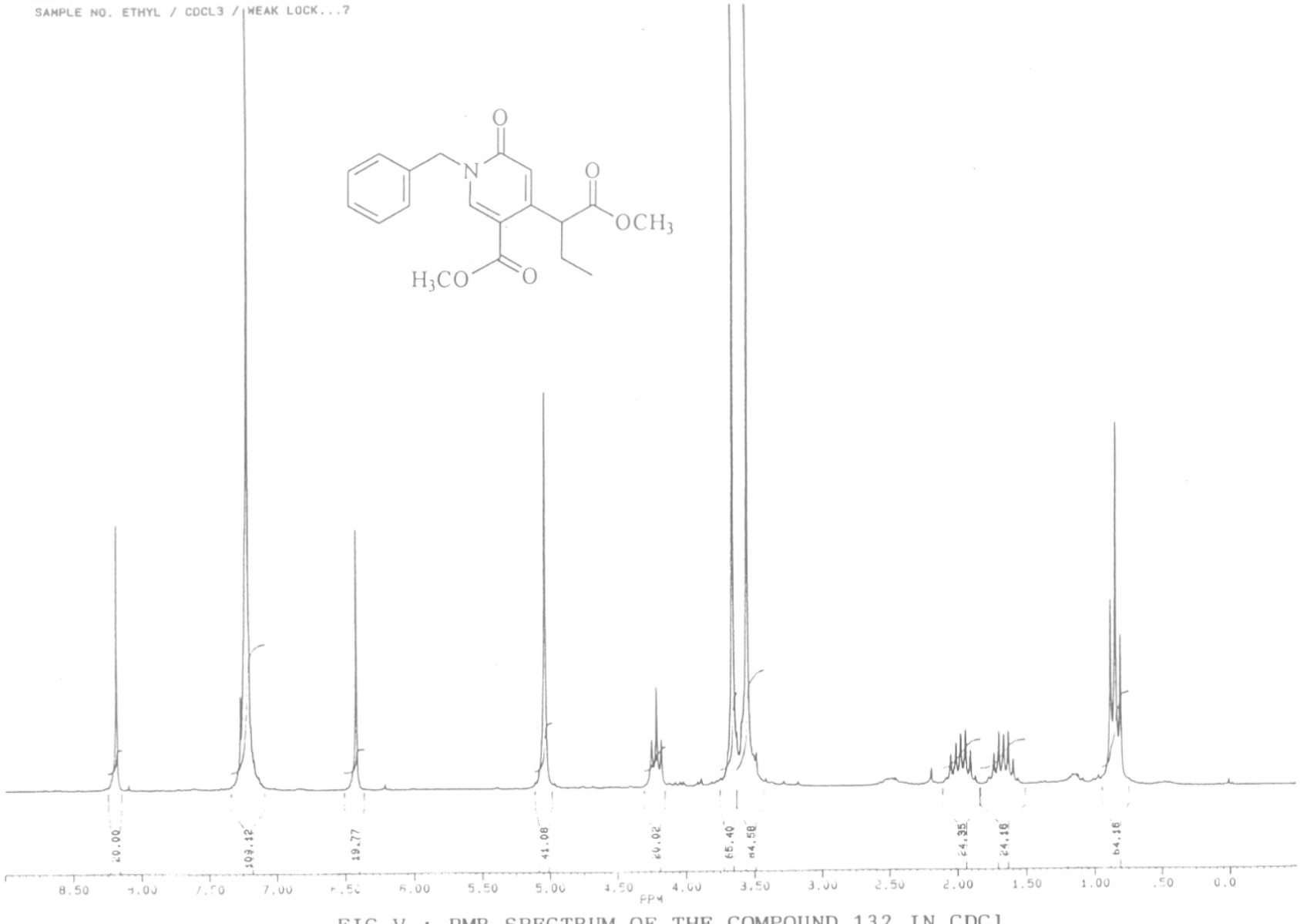
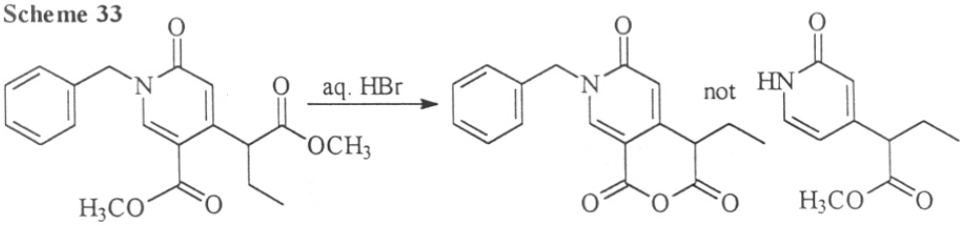



FIG V : PMR SPECTRUM OF THE COMPOUND 132 IN $CDCl_3$

positions. The structure was further confirmed by $^{13}C$ NMR spectrum (FIG. VI) and by the presence of molecular ion peak at m/z 343 in the mass spectrum.

Simultaneous N-debenzylation and decarbomethoxylation are reported[54] by heating with aqueous hydrobromic acid (48%). It was decided to carry debenzylation and decarbomethoxylation of ethylated compound **132** in one step using aq. hydrobromic acid, so as to get required pyridone **133**. When ethylated compound **132** was refluxed with 48% aq. hydrobromic acid initially for 5 hrs, TLC showed a polar spot which may be corresponding to acid, so reaction was continued for 18 hrs with the follow up of TLC and found that the spot having nearby same $R_f$ as that of starting **132** became more and more intense. When the product was isolated and characterized, it was found to be anhydride**133a** instead of formation of the required compounmd **133** (Scheme 33).

**Scheme 33**




**132** **133a** **133**

The structure of anhydride **133a** was confirmed on the basis of its PMR spectrum which showed disappearance of both ester peaks. All the remaining protons resonated at their characteristic chemical shifts. The IR spectrum of **133a** showed absorption bands at 1670 and 1730 $cm^{-1}$ for the lactam carbonyl and anhydride carbonyl group, thus supporting the structure.

It was decided to carry out first debenzylation of **132**. Hydrogenolysis of **132** with 10% Pd/C in ethyl acetate as well as in methanol failed to debenzylate **132**. The unreacted **132** was recovered.

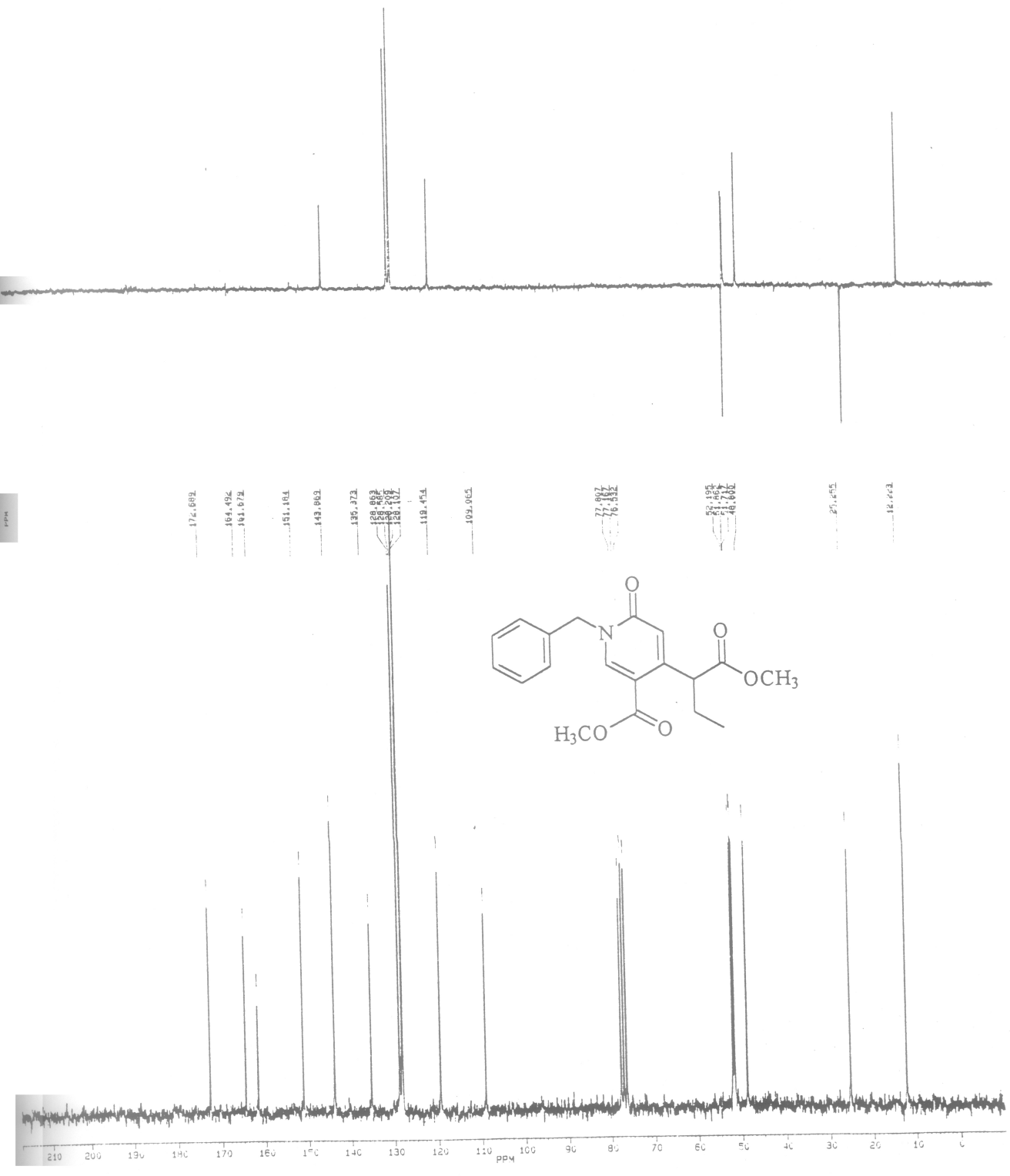
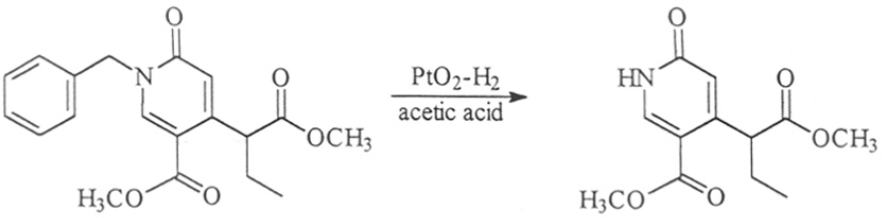



FIG VI: $^{13}C$ NMR SPECTRUM OF THE COMPOUND 132 IN $CDCl_3$

Debenzylation of the intermediate **132** was finally accomplished by subjecting it to hydrogenolysis with 10% $PtO_2$ at 50 psi in glacial acetic acid[55] to afford the pyridone **134** in 50% yield (Scheme 34).

**Scheme 34**



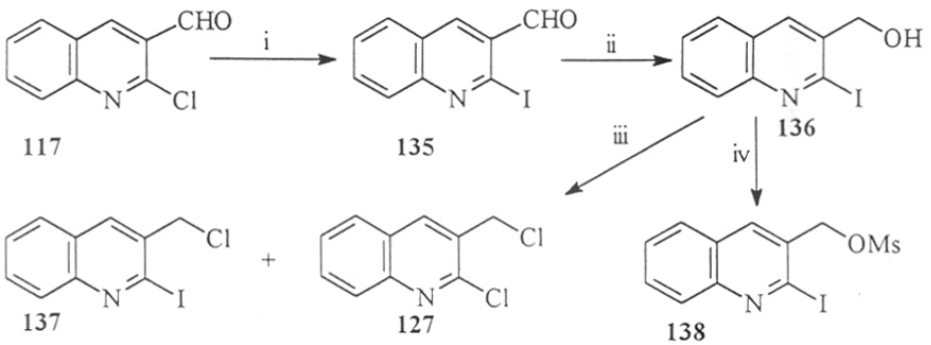

**132** **134**

The structure of **134** was confirmed by spectral analysis. Its PMR spectrum (FIG. VII) showed disappearance of signal at δ 5.05 for benzylic protons and singlet at δ 7.25 for aromatic protons. The structure was further confirmed by $^{13}C$ NMR spectrum (FIG. VIII) and presence of molecular ion peak at m/z. 253 in the mass spectrum.

**Synthesis of AB ring synthon required for intramolecular Heck reaction.**

The AB ring synthon **63** prepared from 2-chloro-3-formyl quinoline **117** (see scheme 23) can be used. However as the iodo compounds are known as good leaving groups, it was planned to prepare a iodo derivative **138** as a AB ring synthon (Scheme 35).

**Scheme 35**




i) NaI, $CH_3CN$ ii) $NaBH_4$, MeOH iii) $PCl_5$, benzene iv) MsCl, benzene.

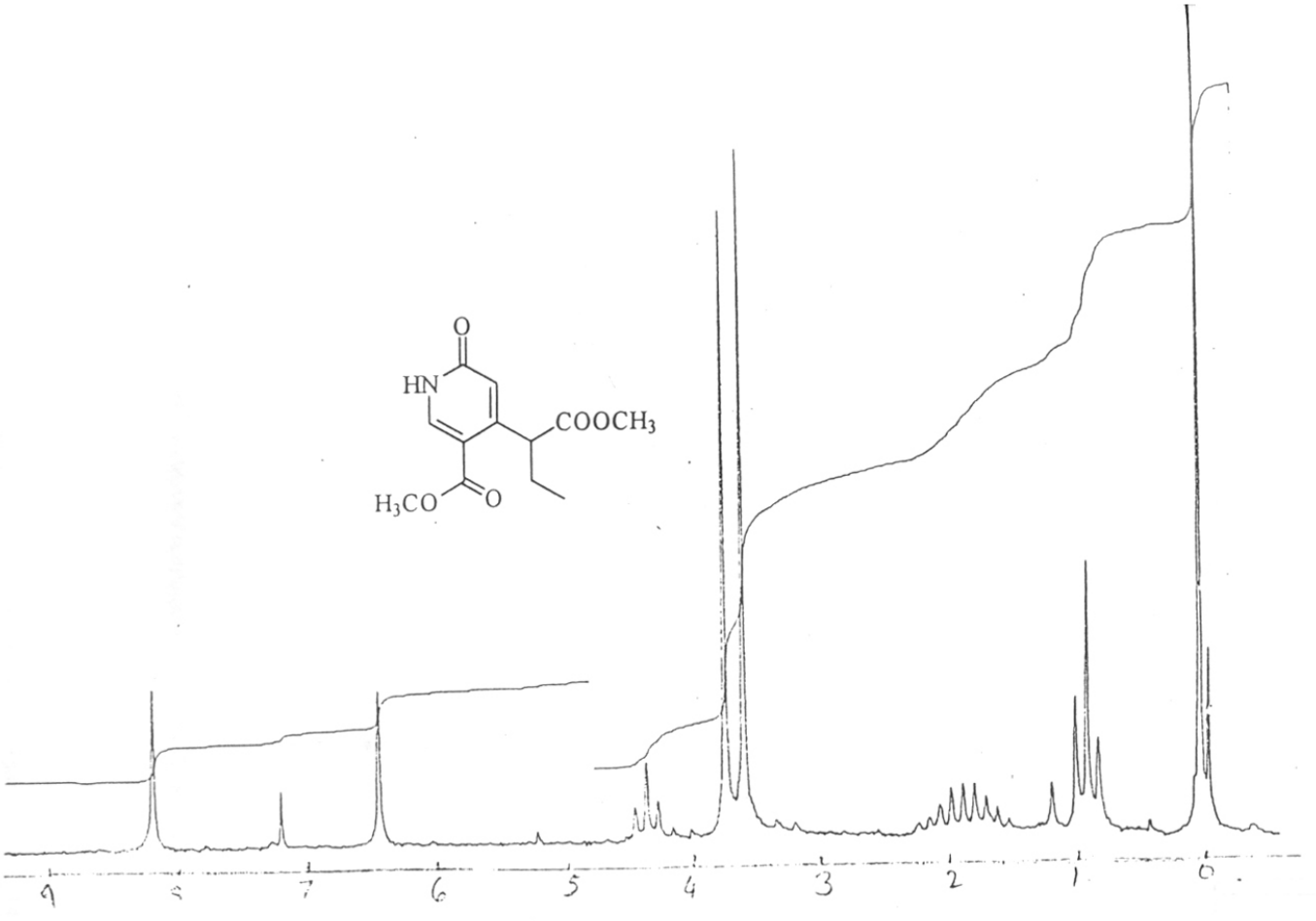



FIG VII: PMR SPECTRUM OF THE COMPOUND 134 IN $CDCl_3$

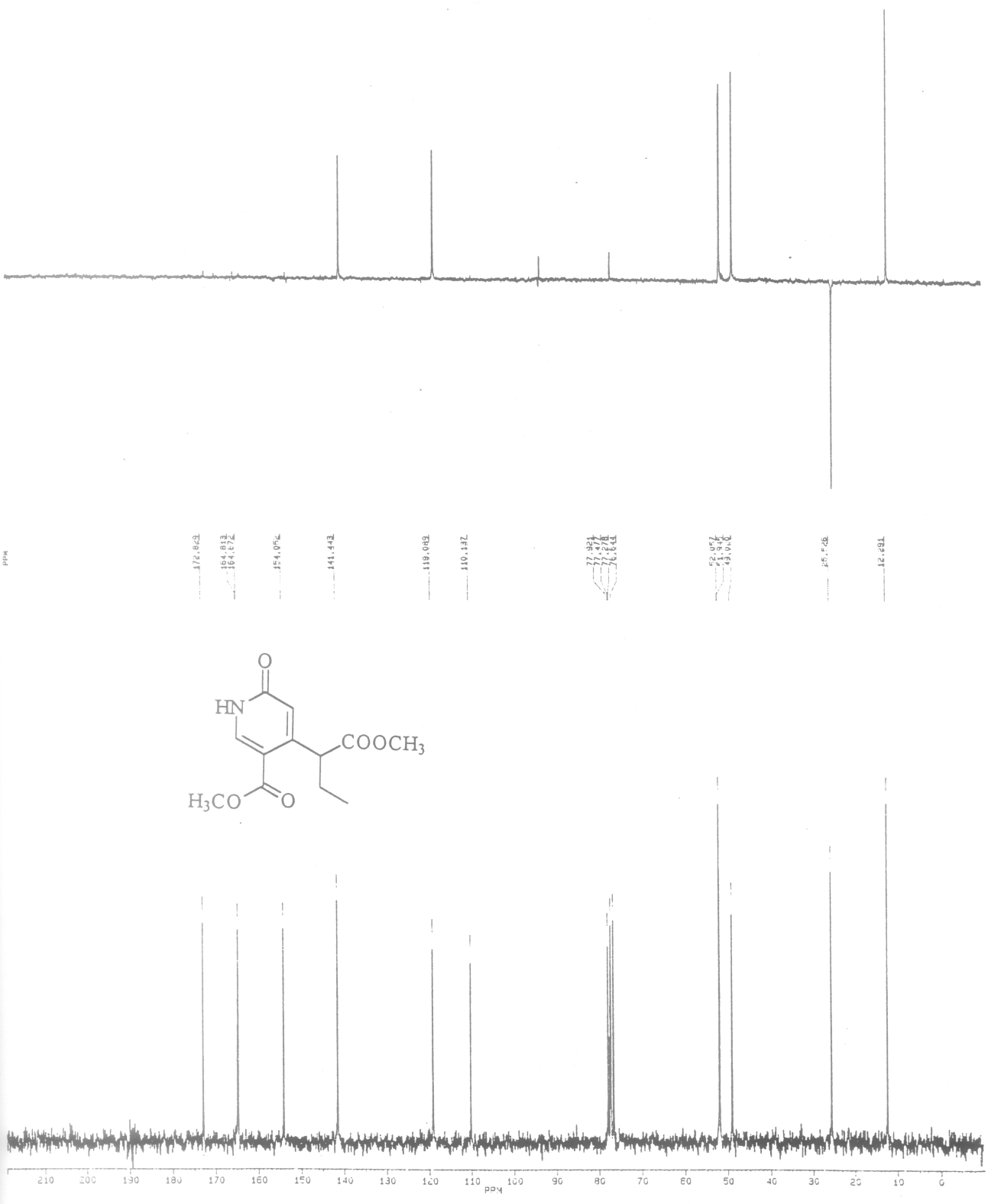
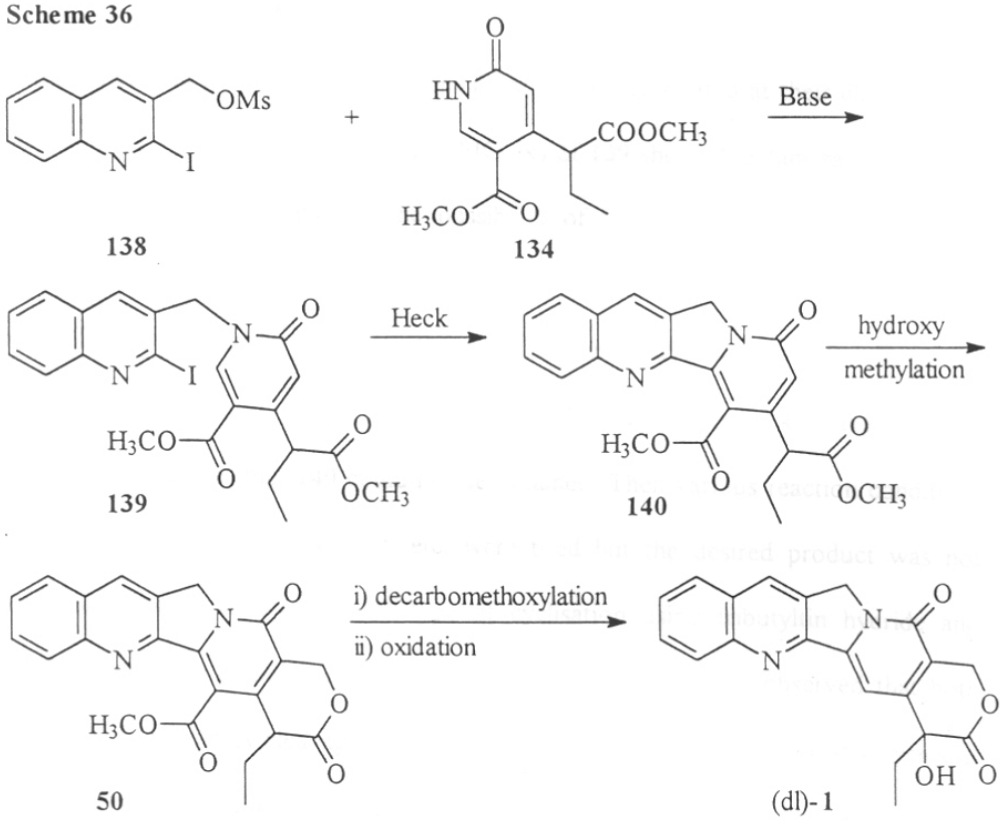



FIG VIII : $^{13}C$ NMR SPECTRUM OF THE COMPOUND 134 IN $CDCl_3$

The chloro aldehyde **117** was converted into iodo aldehyde **135** using sodium iodide under acidic conditions.[56] The reduction of **135** using sodium borohydride to the alcohol **136** followed by reaction with phosphorous pentachloride afforded a mixture of 2-iodo-3-chloromethylquinoline (**137**) and 2-chloro-3-chloromethylquinoline (**127**), which could not be seperated by column chromatography. But mass spectrum of the mixture showed that both the compounds are formed. The mixture of the both compounds showed almost identical PMR spectra. Then mesyl derivative **138** was prepared from **136** using methane sulfonyl chloride in benzene. With both the components i.e. the AB ring synthon **138** and D ring synthon **134** in hand, it was proposed to synthesize camptothecin according to Scheme 36.

**Scheme 36**



The N-alkylation of the pyridone **134** with iodomesylated derivative **138** using a base could give the N-alkylated compound **139**. The cyclisation of **139** under Heck reaction condition could give the desired tetracyclic compound **140**. The compound **140** could then be converted by the known steps to camptothecin. Thus ethylation, lactonisation and decarbomethoxylation could give deoxycamptothecin which on oxidation would give camptothecin (**1**).

Accordingly, pyridone **134** was N-alkylated with 2-iodo-3-mesylquinoline (**138**) using potassium carbonate as base in acetonitrile to furnish N-alkylated product **139** in 71.8% yield. The structure of **139** was fully confirmed by spectral means. The IR spectrum of the compound **139** showed absorption bands of 1720 and 1660 $cm^{-1}$ for the ester and lactam carbonyl groups respectively. The PMR spectrum (FIG. IX) showed the N-methylene group at δ 5.30. It also showed disappearance of singlet at δ 3.15 for the methyl protons of mesyl group. The remaining protons resonated at their characteristic chemical shift. The $^{13}$C-NMR spectrum (FIG. X) of **139** showed lactam carbonyl signal at 164.37 ppm which ruled out the possibility of O-alkylated product. The mass spectrum exhibited the molecular ion peak at m/z. 520.

The intramolecular Heck reaction on compound **139** (Scheme 37) was carried out using 1 mole% Pd $(OAc)_2$, 1.5 eq $Et_3N$, $CH_3CN$ under reflux for 4 hr. However the desired tetracyclic product **140** could not be obtained. Then various reaction conditions such as temperature, time, solvent, etc. were tried but the desired product was not obtained. Comins reported[33] such type of cyclisation using tributyltin hydride and AIBN, however, in present case it also met with failure. It was observed that both debenzylated product by cleavage of C-N bond and deiodo products are mostly formed if reaction was continued for a longer time or starting material remained as such when it was continued for a shorter time or less amount of catalyst was used. The failure of the

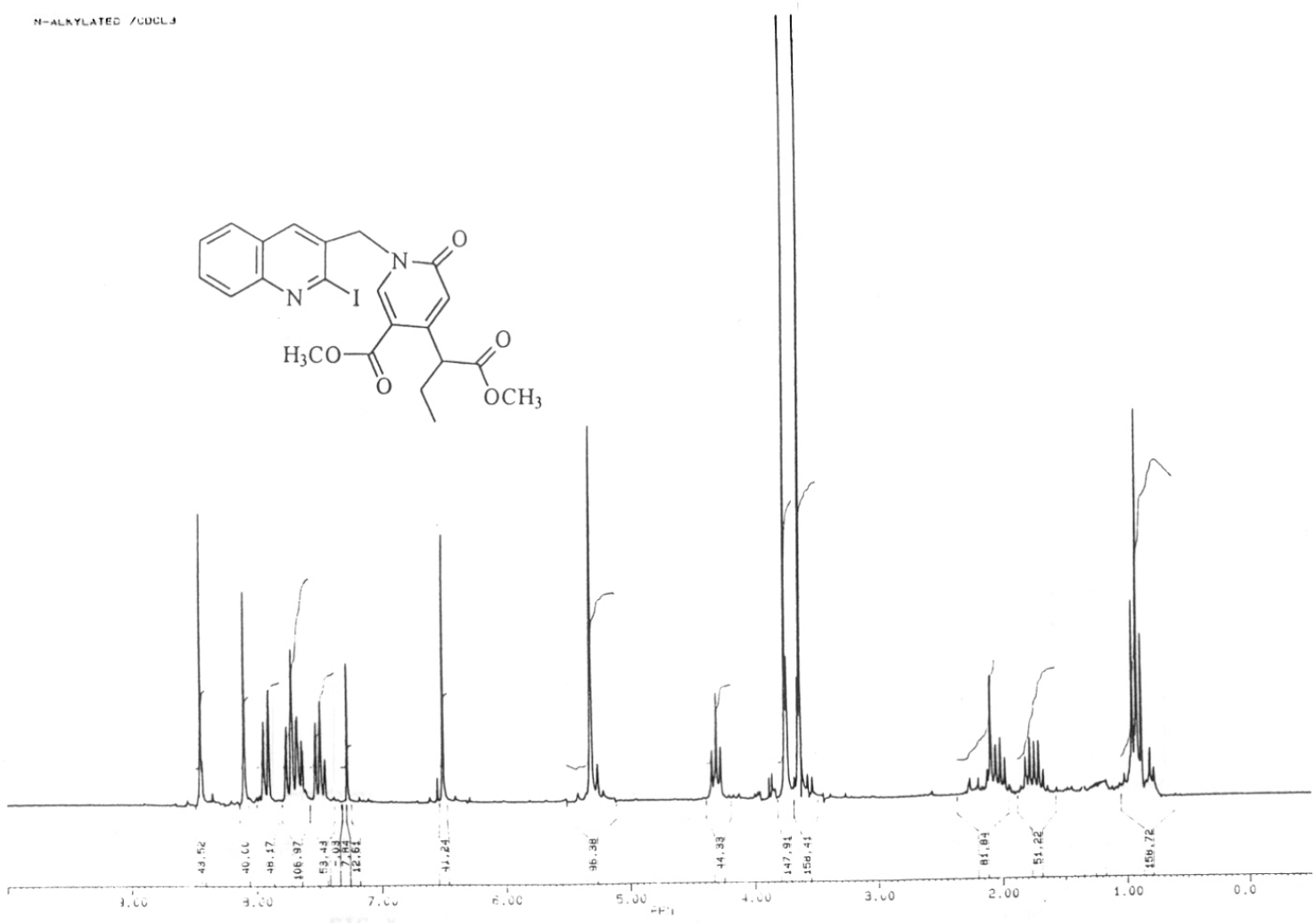



FIG IX : PMR SPECTRUM OF THE COMPOUND 139 IN $CDCl_3$

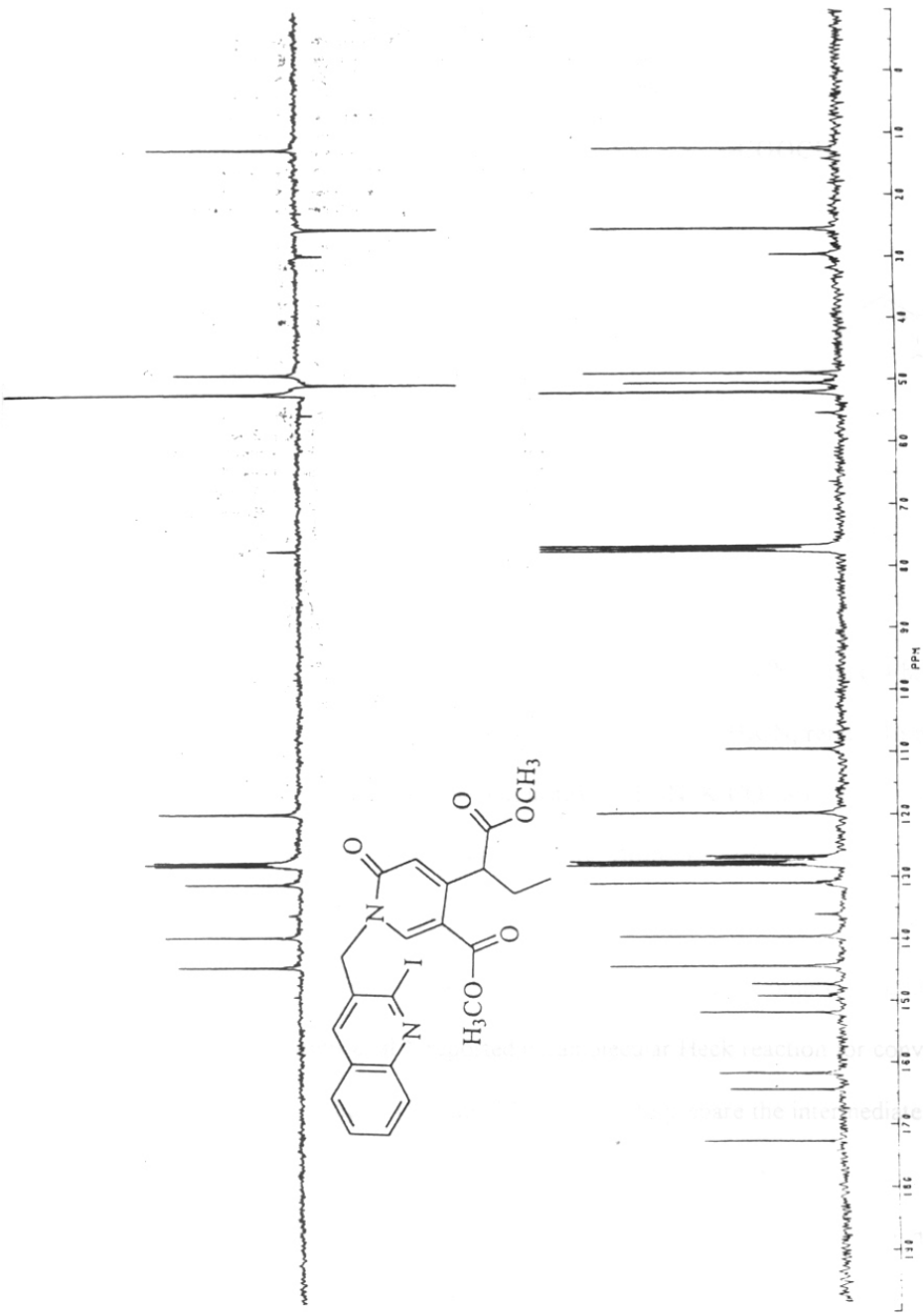
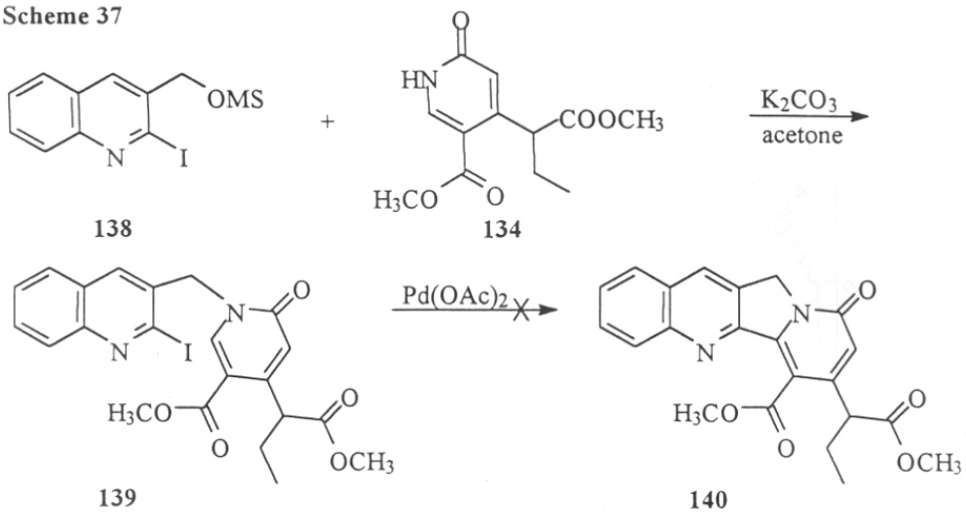



FIG X : $^{13}C$ NMR SPECTRUM OF THE COMPOUND 139 IN $CDCl_3$

intramolecular Heck reaction might be due to electron withdrawing ester group present in **139**.

**Scheme 37**




**138** **134** **139** **140**

Attempted reaction conditions for conversion of **139** into **140**

i) 1 mole% Pd $(OAc)_2$, 1.5 eq. $Et_3N$, $CH_3CN$, reflux, 4 hr.

ii) 3 mole% Pd $(OAc)_2$, 1.5 eq. $Et_3N$, $CH_3CN$, reflux, 16 hr.

iii) Similar as ii), but instead of $Et_3N$, $K_2CO_3$ was used as a base.

iv) Pd $(OAc)_2$, KOAc, DMF, $Bu_4N^+ Br^-$, 90°C, 3hr (Comins' condition).

v) Pd $(OAc)_2$, $Et_3N$, $CH_3CN$ in sealed tube at 90°C for 15 hr.

vi) $Bu_3SnH$, AIBN, Toluene, reflux, 8 hr (Comins' condition).

Comins et al[32]. reported intramolecular Heck reaction for converting intermediate **64** to camptothecin (Scheme 27). In order to prepare the intermediate **64**, from **132,** the reaction sequence was modified as shown in Scheme 38.

Ethylated product **132** underwent hydroxymethylation and cyclisation using paraformaldehyde in dioxane with a catalytic amount of sulfuric acid in sealed tube to afford lactone **141** in 68.5% yield. The IR spectrum of the compound **141** showed absorption bands at 1722 and 1660 $cm^{-1}$ for the lactone and lactam carbonyl functionalities. Its PMR spectrum (FIG. XI) showed a doublet of doublet from δ 5.40 to

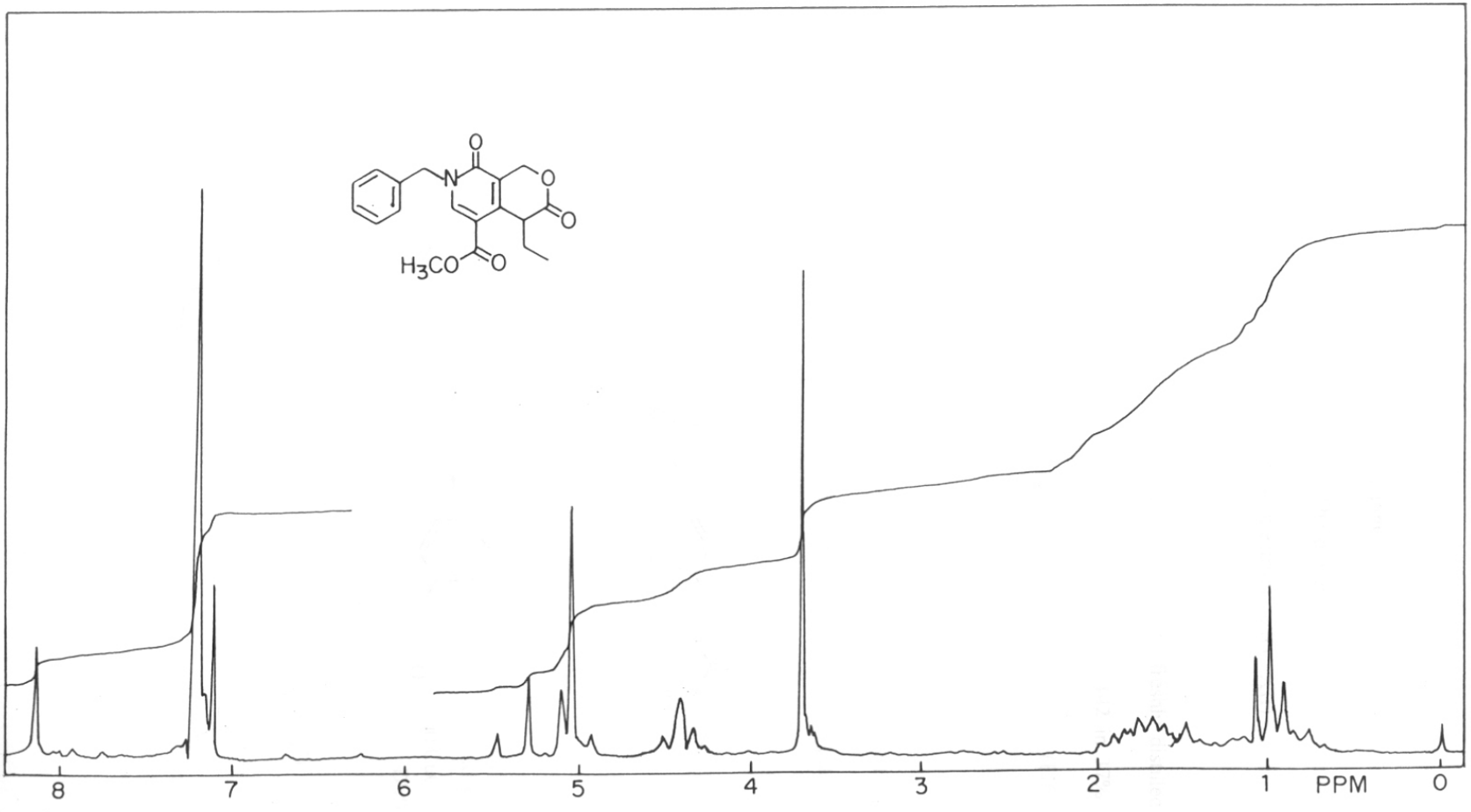
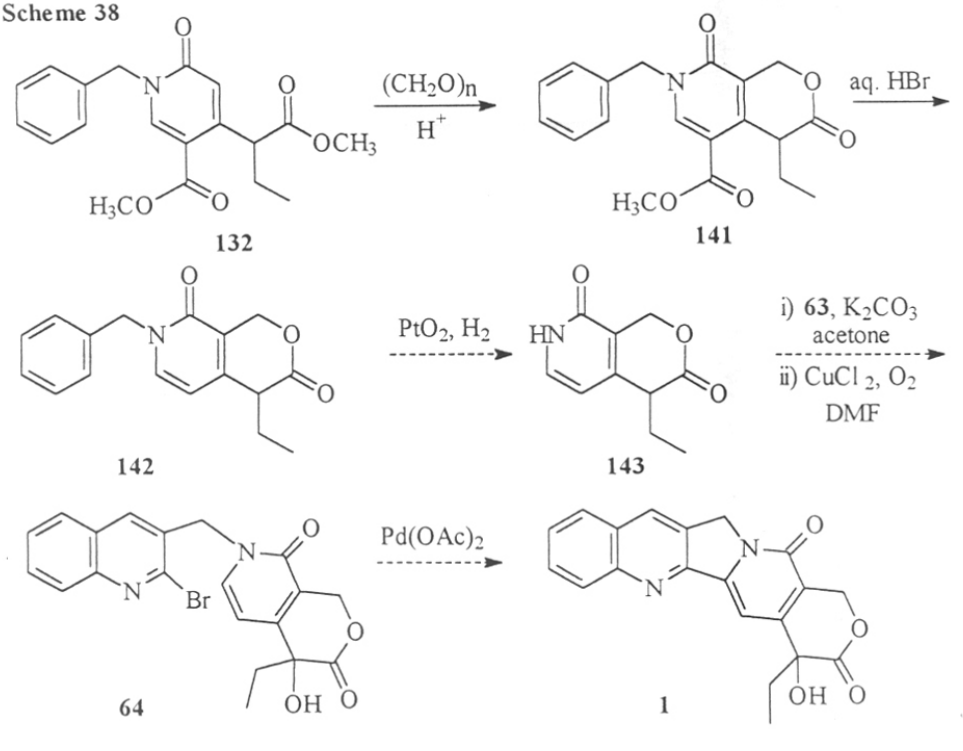



FIG. 11 : PMR SPECTRUM OF THE COMPOUND 141 IN $CDCl_3$

5.00 for oxymethylene group. It also showed disappearance of one methyl ester peak indicating formation of a lactone. A proton resonating at δ 6.43 adjucent to the carbonyl functionality of pyridone **132** also disappeared. The presence of molecular ion peak at m/z 341 in the mass spectrum and $^{13}C$ NMR spectrum (FIG. XII) confirmed the structure.

The lactone **141** was decarbomethoxylated using freshly distilled 48% hydrobromic acid to furnish N-benzyl protected DE ring synthon **142** in 37%. The structure of **142** was confirmed by spectral analysis. The PMR spectrum (FIG. XIII) showed disappearance of methyl ester peak and appearance of a doublet at δ 6.05 (J=8 Hz). All remaining protons resonated at their characteristic chemical shifts. The mass spectrum exhibited the molecular ion peak at m/z. 283. In order to achieve the synthesis of Comins intermediate **64**, a reaction sequence as shown in Scheme 38 was planned.

**Scheme 38**




**132** **141** **142** **143** **64** **1**

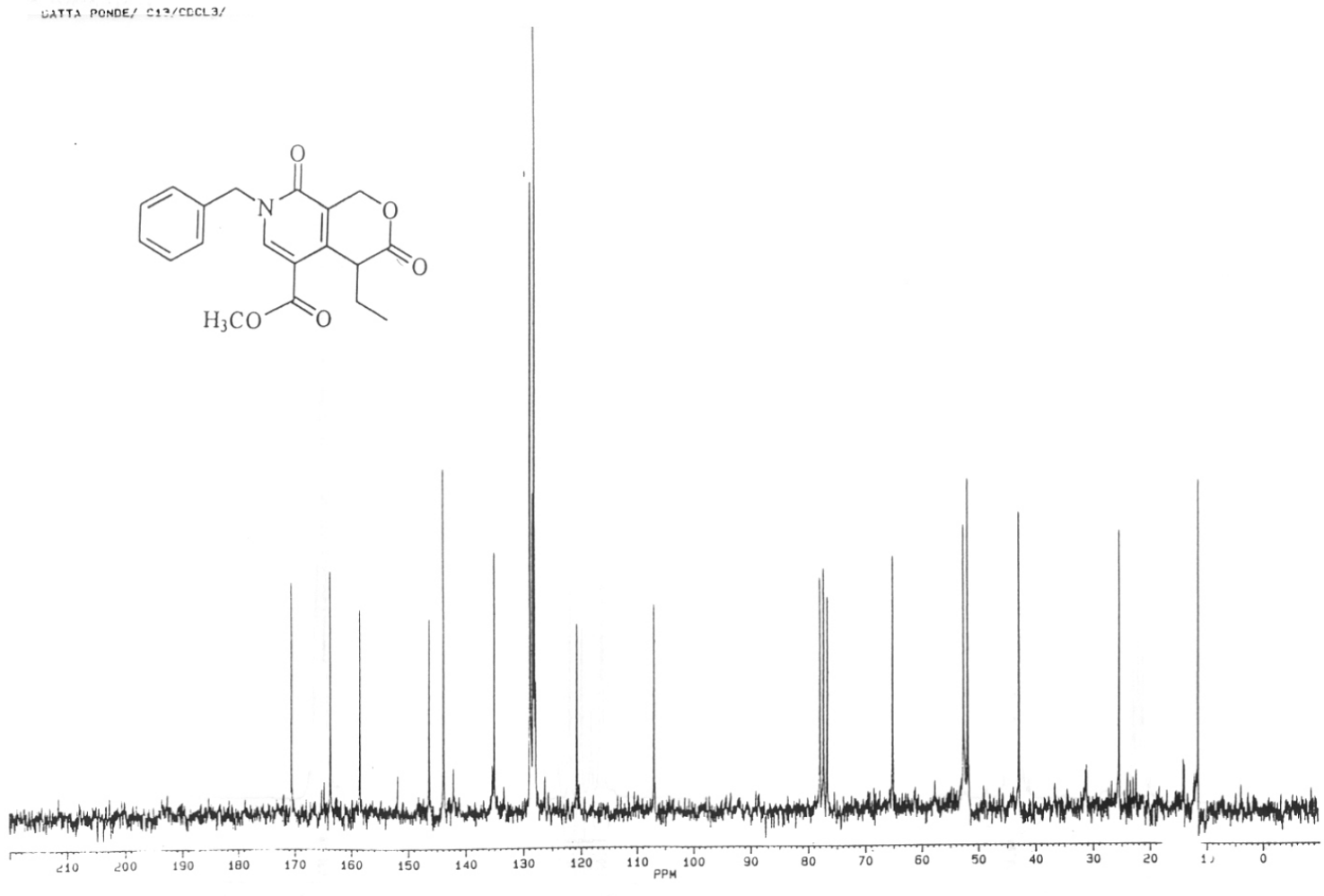



FIG XII : $^{13}C$ NMR SPECTRUM OF THE COMPOUND 141 IN $CDCl_3$

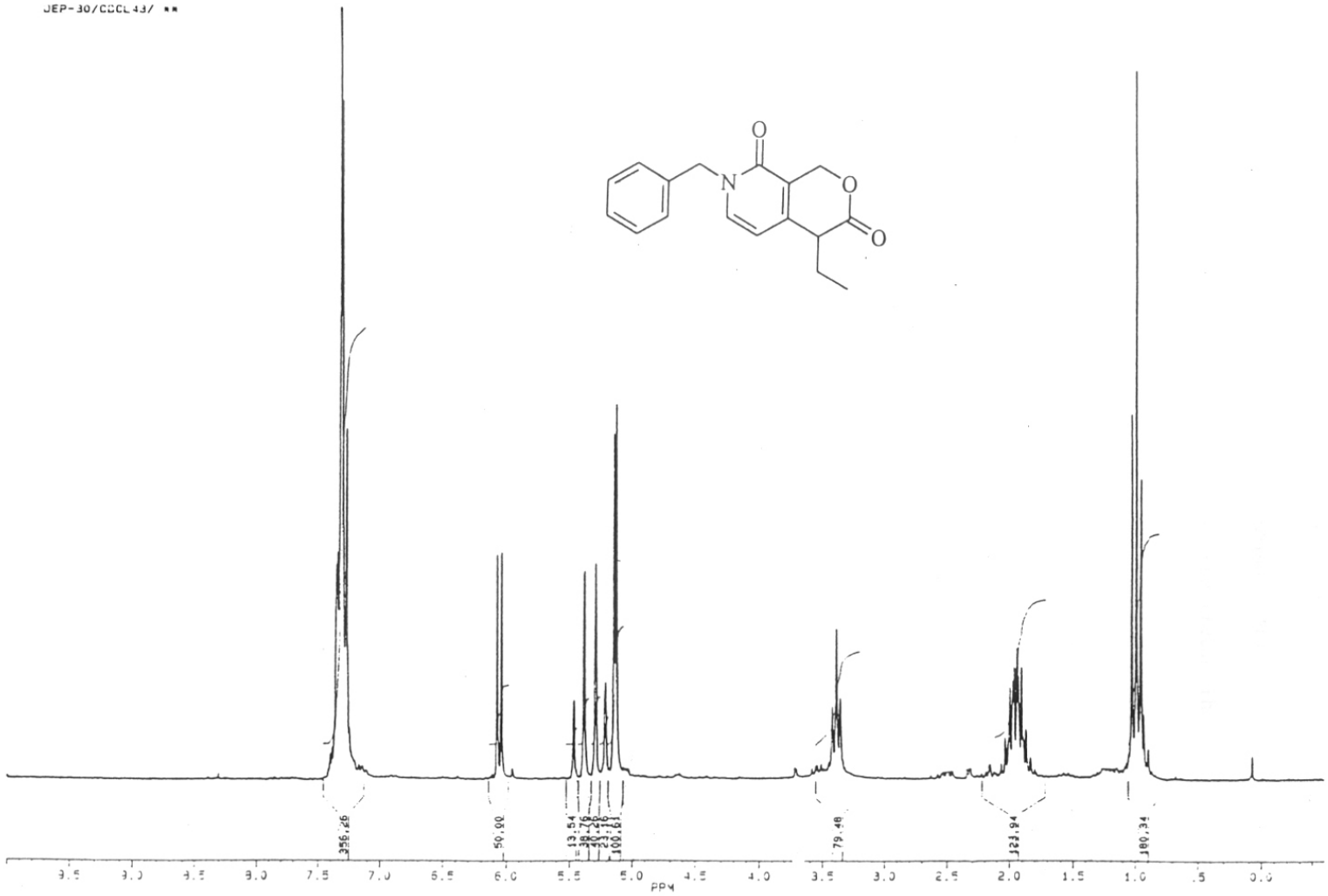



FIG XIII: PMR SPECTRUM OF THE COMPOUND 142 IN $CDCl_3$

The debenzylation of compound **142** by hydrogenation over platinum dioxide and further N-alkylation with **63** using potassium carbonate followed by oxidation and intramolecular Heck reaction would yield camptothecin. This work is in progress in our laboratory.

## Experimental

### 2-Chloro-3-quinolinecarbaldehyde (117)

N, N- Dimethylformamide (54.31 g, 0.744 mol, 57.6 ml) was cooled to 0°C and to it was added $POCl_3$ (319.8 g, 2.083 mol, 194.4 ml) dropwise with stirring. After the addition was complete, acetanilide (40.2 g, 0.297 mol) was added in small portions with stirring at room temperature. The reaction mixture was then heated at 75°C for 18 hr. It was then poured into ice-water and stirred for 30 min at 0-10°C. The solid thus separated was filtered, washed thoroughly with water and dried. It was characterized as 2-chloro-3-quinolinecarbaldehyde (**117**).

**Nature:** Yellow solid

**Yield:** 46.17 g (80%)

**M. P.:** 149°C (Lit.[43] m.p. 148-149°C)

**IR (Nujol):** 1060, 1470, 1500, 1590, 1630, 1700 and 2850 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 7.52 (dd, 1H, J=8 Hz and J=2 Hz, ArH); 7.60-8.07 (m, 3H, 3 x ArH); 8.73 (s, 1H, ArH); 10.56 (s, 1H, CHO).

**MS (m/z):** 191 ($M^+$), 193 ($M^+$+2), 192, 190, 164, 155, 127, 101.

### 2-Chloro-3-hydroxymethylquinoline (72a)

A solution of 2-chloro-3-quinolinecarbaldehyde (**117**) (36.0 g, 187.9 mmol) in methanol (300 ml) was cooled to 10°C. Sodium borohydride (7.20 g, 190 mmol) was then added in small lots over a period of five min. After the addition was complete, the reaction mixture was stirred at room temperature for 1 hr. Then it was slowly poured onto 500 g of crushed ice with good agitation. The solid thus separated was filtered, dried and crystallized from ethyl acetate to obtain 2-chloro-3-hydroxymethylquinoline (**72a**).

| | |
|---|---|
| **Nature:** | Pale yellow solid |
| **Yield:** | 25.4 g (70%) |
| **M. P.:** | 163°C (Lit.[57]m.p. 162-163°C) |
| **IR (Nujol) :** | 1088, 1350, 1470, 1500, 1590, 3360, 3400 and 3480 $cm^{-1}$ |
| **PMR ($CDCl_3$, 200 MHz):** | δ 4.70 (s, 2H, $\underline{CH_2}$); 7.49-8.08 (m, 4H, 4 x Ar$\underline{H}$); 8.45 (s, 1H, Ar$\underline{H}$). |
| **MS (m/z):** | 193 ($M^+$), 195 ($M^+$+2), 194, 192, 176, 164, 158, 140, 128. |

**2-Bromo-3-bromomethylquinoline (63)**

A solution of 2-chloro-3-hydroxymethylquinoline (**72a**) (1.5 g, 7.75 mmol) in benzene (15 ml) was cooled to 5°C in an ice bath and to it a solution of $PBr_3$ (4.2 g, 15.45 mmol) in benzene (5.0 ml) was added dropwise along with stirring. After the addition was complete, the reaction mixture was stirred at 5°C for 15 min and then at room temperature for 30 min. The reaction mixture was then treated with aqueous ammonia until alkaline. The organic layer was separated, washed with water, dried and evaporated to obtain 2-bromo-3-bromomethylquinoline (**63**).

| | |
|---|---|
| **Nature:** | White needles |
| **Yield:** | 1.57 g (67.7%) |
| **M. P.:** | 135-138°C (Lit.[58]m.p. 136-138°C) |
| **IR (Nujol):** | 760, 1450, 1500 and 1620 $cm^{-1}$ |
| **PMR ($CDCl_3$, 200 MHz):** | δ 4.75 (s, 2H, $\underline{CH_2}$); 7.55-8.11 (m, 4H, 4 x Ar$\underline{H}$), 8.30 (s, 1H, Ar$\underline{H}$ ). |
| **MS (m/z)** | 299 ($M^+$), 301 ($M^+$+2), 303, 257, 222, 220, 177, 140, 113, 88, 57. |

**Dimethyl acetonedicarboxylate (116)**

Fuming sulfuric acid (20% free $SO_3$) (77.7 ml) was cooled to -5°C and finely powdered citric acid (35 g) was added in four to five hrs in such a way that temperature of the reaction did not increase above 0°C for half amount of citric acid. Remaining half amount of citric acid was added in such a way that temperature of the reaction mixture did not rise above 10°C. After citric acid had gone completely into the solution the temperature of the reaction mixture was allowed to rise gradually until a vigorous evolution of gas commenced. After the more vigorous foaming had ceased, the temperature of the reaction mixture was raised to about 30°C and kept there until no more foaming occurred. The reaction mixture was cooled down again to 0°C and crushed ice (250 g) was added in small portions at such a rate that the temperature did not rise above 10°C. The addition of ice required 3 hrs. The reaction mixture was again cooled to 0°C and filtered as rapidly as possible. The acetonedicarboxylic acid is light gray to white in color and esterified immediately as it is unstable. The acetonedicarboxylic acid was added to a solution of methanol saturated with hydrogen chloride and refluxed for 4 hrs. The reaction was cooled to room tempetarure and kept as such for 12 hrs. The contents of the flask were poured into 1 Kg of ice in a beaker. The aqueous part was extracted with diethyl ether (5 x 125 ml). The combined organic layer was washed with 10% $Na_2CO_3$ solution (200 ml), then once with dilute sulfuric acid, water and dried ($Na_2SO_4$). Ether was distilled off. The crude product was distilled under vacuum to afford dimethyl acetonedicarboxylate (**116**) as a colourless liquid.

| | |
|---|---|
| **Nature:** | Colourless liquid |
| **Yield:** | 9.5 g (30%) |
| **B.P.:** | 131-133°C/ 9 mm (Lit.[45] b.p. 131-136°C/ 9 mm) |

**Dimethyl-3-cyanomethyleneglutarate (118)**

To a solution of dimethyl acetonedicarboxylate (**116**) (19.35 g, 111.3 mmol) in benzene (250 ml) was added cyanoacetic acid (10.4 g, 122.7 mmol), ammonium acetate (1.71 g, 22.3 mmol) and glacial acetic acid (3.0 g, 50.2 mmol) and the reaction mixture was refluxed in an oil bath at 140°C for 24 hr while removing the water formed in the reaction using a Dean Stark apparatus. The reaction mixture was then cooled and was washed with saturated $NaHCO_3$, brine, dried ($Na_2SO_4$) and concentrated to obtain dimethyl-3-cyanomethyleneglutarate (**118**).

**Nature:** Colourless liquid

**Yield:** 20.07 g (92%)

**IR (Neat):** 890, 1040, 1645, 1730, 2230 and 2900 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 3.35 (d, J=1.5 Hz, 2H, $\underline{CH_2}$); 3.59 (s, 2H, $\underline{CH_2}$); 3.67 (s, 3H, $COO\underline{CH_3}$); 3.70 (s, 3H, $COO\underline{CH_3}$); 5.47 (s, 1H $\underline{CH}$).

**3-Cyanomethyleneglutaric acid (119)**

A solution of the diester **118** (19.7 g, 0.1 mol) in ethanol (50 ml) was cooled in an ice-bath. To this solution was added sodium hydroxide (1.0 g, 0.025 mol) slowly with stirring. After the addition was complete, the reaction mixture was stirred with cooling for 2 hr. The ethanol was removed under reduced pressure and the residue was cooled in ice. To it 50 ml ice-water was added and then it was acidified with an ice-cold 4 N $H_2SO_4$ solution to pH 2. The reaction mixture was then extracted with ethyl acetate. The organic layer was washed once with brine, dried ($Na_2SO_4$) and concentrated to obtain the diacid **119**.

**Yield:** 15.2 g (90%)

**4-carbomethoxymethyl-6-chloro-2-pyridone (121)**

To a solution of the diacid **119** (3.6 g, 21.3 mmol) in dry ether (40.0 ml) was added $PCl_5$ (11.16 g, 53.52 mmol) slowly with stirring at room temperature. After the addition of $PCl_5$ was complete, the reaction mixture was stirred for 1 hr. HCl gas generated by addition of sulfuric acid to NaCl was dried by passinng through a concentrated sulfuric acid trap and it was then bubbled into the above acid chloride solution in dry ether at 0°C for 1 hr. The ether was removed by distillation and to the residue methanol was added and it was stirred for 3 hr. The methanol was removed by distillation and to the residue aqueous $NaHCO_3$ was added and it was extracted with ethyl acetate. Work up as usual yielded a residue which was purified over a silica gel column using pet.ether – acetone as an eluent to yield 4-carbomethoxymethyl-6-chloro-2-pyridone (**121**).

**Nature:** White crystalline solid

**Yield:** 2.91 (60%)

**IR (Nujol):** 1660, 1730 and 3300 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 3.55 (s, 2H, $CO\underline{CH_2}$); 3.75 (s, 3H, $COO\underline{CH_3}$); 6.65 (s, 1H); 6.80 (s, 1H).

**4-Carbomethoxymethyl-2-pyridone (122)**

To a solution of 4-carbomethoxymethyl -6-chloro- -2-pyridone (**121**) (2.0 g, 8.14 mmol) in methanol (25 ml) was added ammonium formate (2.56 g, 40.64 mmol) and 10% Pd/C (0.5 g) and the reaction mixture was stirred at room temperature for 20 hr. The catalyst was removed by filtration and the residue was washed with methanol. The filtrate along with the washings was concentrated to obtain a residue which was purified over a silicagel column using pet.ether-acetone for elution to obtain 4-carbomethoxymethyl-2-pyridone (**122**).

**Nature:** Colourless solid

**Yield:** 960 mg (70.0%)

**M.P.:** 109°C

**IR (Nujol):** 1660 and 1720 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 3.50 (s, 2H, $\underline{CH_2}$); 3.72 (s, 3H, $COO\underline{CH_3}$); 6.3 (d, J=7 Hz, 1H); 6.45 (s, 1H); 7.33 (d, 1H, J=7 Hz).

**MS (m/z):** 167 ($M^+$), 136, 123, 109, 91, 69, 59, 53.

**Alkylation of the pyridone 122 with quinoline 63**

To a solution of the pyridone **122** (475 mg, 2.84 mmol) in dry acetonitrile (20 ml) was added anhydrous potassium carbonate (785 mg, 5.67 mmol ) and the reaction mixture was refluxed for 10 min. Then a solution of 2-bromo-3-bromomethylquinoline (**63**) (850 mg, 2.84 mmol) in dry acetonitrile (20 ml) was added to the reaction mixture and refluxed for 3 hr. The acetonitrile was removed by distillation, water was added and it was extracted with chloroform (5 x 20 ml). The combined organic layer was washed with water, brine, dried ($Na_2SO_4$) and concentrated to obtain a residue which was purified over a silica gel column to yield N-alkylated product **123**.

**Yield:** 713 mg (65%)

**IR ($CHCl_3$):** 1585, 1670 and 1730 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 3.50 (s, 2H, $\underline{CH_2}COOCH_3$); 3.60 (s, 3H, $COO\underline{CH_3}$); 5.15 (s, 2H, $Ar\underline{CH_2}$); 6.20 (d, J=7 Hz, 1H); 6.55 (s, 1H), 7.34 (d, J=7 Hz, 1H); 7.55-7.92 (m, 4H, 4 x $Ar\underline{H}$); 8.17 (s, 1H, $Ar\underline{H}$).

**2-Chloro-3-quinolinecarboxaldehyde oxime (125)**

To the aldehyde **117** (1.9 g, 10 mmol) in methanol (25 ml) was added hydroxylamine hydrochloride (1.04 g, 15 mmol) and sodium acetate (1.2 g, 15 mmol) and the reaction mixture was allowed to stirr at 35°C for 20 min. It was diluted with water (25 ml) and the solid separated was filtered, washed with water, dried and crystallized from methanol to yield the oxime **125** as a white solid.

**Yield:** 1.6 g (77.6%)

**M. P.:** 194-6°C (Lit.[47] m.p. 194°C)

**IR (Nujol):** 1630 and 3250 $cm^{-1}$

**2- Chloro-3-cyanoquinoline (126)**

A mixture of 2-chloro-3-quinoline carboxaldehyde oxime (**125**) (2.0 g, 10 mmol) and thionyl chloride (2.4 g, 20 mmol) was refluxed with stirring in benzene (10 ml) for 3 hr. The solvent was removed under vacuum to afford crude product which was purified by short band of silicagel using chloroform as an eluent to afford 2-chloro-3-cyanoquinoline (**126**).

**Yield:** 1.09 (77.7%)

**IR (Nujol):** 1650 and 2200 $cm^{-1}$

**PMR ($CDCl_3$, 80 MHz):** δ 7.41-8.30 (m, 4H, 4 x ArH), 8.85 (s, 1H, ArH).

**2-Chloro-3-chloromethylquinoline (127)**

To a solution of 2-chloro-3-hydroxymethylquinoline (**72a**) (7.0 g, 36.17 mmol) in chloroform (60 ml) was added $PCl_5$ (9.05 g, 43.41 mmol) slowly at room temperature with stirring. After the addition was complete, the reaction mixture was stirred at room temperature for 4 hr. The chloroform was distilled off and to the residue cold water was

added and it was then neutralized with dil. $NaHCO_3$, and concentrated to obtain a solid which was characterized as 2-chloro-3-chloromethylquinoline (**127**).

**Nature:** White solid

**Yield:** 7.41 g (96.6%)

**M. P.** 114-116°C

**IR (Nujol):** 1320, 1460 1600 and 3030 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 4.78 (s, 2H, $\underline{CH_2}Cl$); 7.47–8.10 (m, 4H, 4 x Ar$\underline{H}$); 8.31 (s, 1H, Ar$\underline{H}$).

**MS (m/z):** 211 ($M^+$), 213 ($M^+$+2), 178, 176, 149, 140, 113, 87.

**Propiolic acid**

To propargyl alcohol (30 g, 535 mmol) in acetone (250 ml) was added dropwise with stirring and ice- cooling a solution of chromium trioxide (98 g, 720 mmol) and sulphuric acid (115 g) which was diluted to 360 ml with water, during 5 hr. in such a way that temperature of reaction mixture did not rise above 20°C. The reaction mixture was allowed to warm to room temperature and stirred further for 14 hr at room temperature. The acetone layer was separated and distilled on water bath at normal pressure till the b. p. of the distillate was 76-8°C. The residue was extracted with methylene chloride (5 x 200 ml). The dark yellow extract was dried and concentrated at normal pressure. The residue was fractionated under vacuum to afford propiolic acid as a colourless liquid.

**Yield:** 15 g (40%)

**B. P.:** 52.4°C/ 12 mm (Lit.[49] b. p. 52.5-54°C/ 9 mm)

**PMR ($CDCl_3$, 90 MHz):** δ 3.1 (s, 1H, C$\underline{H}$), 10.3 (s, 1H, COO$\underline{H}$).

**Methyl propiolate (129)**

To a solution of propiolic acid (12 g, 168 mmol) in dry methanol (25 ml) was added via syringe freshly distilled boron trifluoride etherate (44 ml, 356 mmol). The solution was refluxed for 1.5 hr and further stirred at room temperature for 4 hr. Water (25 ml) was added and the mixture was extracted with methylene chloride (5 x 100 ml). The organic layer was washed with water followed by brine and dried ($Na_2SO_4$). The solvent was removed and the residue was distilled at normal pressure to afford pure methyl propiolate (**129**).

**Nature:** Colourless liquid

**Yield:** 4 g (25%)

**B. P.:** 103°C (Lit.[50] b. p. 103°C)

**PMR ($CDCl_3$, 90 MHz):** δ 3.10 (s, 1H, C<u>H</u>), 3.75 (s, 3H, COO<u>CH</u>$_3$).

**Methyl 3-benzylamino-2-propionate (130)**

To a solution of benzyl amine (10.7 g, 0.1mol) in acetonitrile (50 ml) was added dropwise under ice-cooling and stirring at 5-10°C, methyl propiolate (8.4 g, 0.1 mol) and stirred for 1 hr at room temperature. Concentration under reduced pressure afforded yellow semisolid which was characterized as methyl 3- benzylamino-2-propionate (**130**) by spectral means.

**Yield:** 12.73 (67%)

**PMR ($CDCl_3$, 200 MHz):** *cis* isomer δ 3.75 (s, 3H, COO<u>CH</u>$_3$); 4.25 (d, J=5 Hz, 2H, N<u>CH</u>$_2$), 4.65 (d, J=7.5 Hz, 1H, <u>CH</u>COOCH$_3$); 6.70 (dd, J=7.5 Hz and J= 13.5 Hz, 1H, NH-<u>CH</u>=CH); 7.30 (m, 5H, 5 x Ar<u>H</u>); 8.15 (br s, 1H, <u>NH</u>). *Trans* isomer δ 3.75 (s, 3H, COO<u>CH</u>$_3$); 4.37 (d, J=6 Hz, 2H, N<u>CH</u>$_2$), 4.80 (d, J=13.5 Hz, 1H, <u>CH</u>COOCH$_3$); 5.05 (br s, 1H, <u>NH</u>), 7.30

(m, 5H, 5 x ArH), 7.60 (dd, J=7.5 Hz and J=13.5 Hz, 1H, NH-CH=CH).

**Dimethyl 3-chloro-2-pentenedioate (44)**

Dimethyl 1,3-acetonedicarboxylate (**116**) (6 g, 54 mmol) was taken in a 3 necked round botton flask equipped with a reflux condensor and $CaCl_2$ guard tube, inlet for bubbling nitrogen and a stopper. A gentle flow of nitrogen was started and phosphorous pentachloride (6 g, 34 mmol) was added in portions (thirteen equal parts at the interval of 3 min) with vigorous stirring. After the addition was over, it was stirred at 40°C for 30 min. The resulting red solution was cooled with ice and poured into ice-water (100 ml). It was stirred for 15 min. and extracted with methylene chloride (3 x 50 ml). The red oil (5.80 g) obtained after removal of the solvent was refluxed with a mixture of methanol (30 ml) and concentrated sulfuric acid (2 ml) for 18 hr. Excess methanol was distilled out and the residual yellow solution was poured into water (50 ml). The aqueous solution was saturated with sodium chloride and extracted with methylene chloride (8 x 50 ml). The organic layer was washed with aqueous saturated sodium bicarbonate (25 ml) and brine (25 ml) and dried ($Na_2SO_4$). Concentration and distillation at reduced pressure afforded a colourless liquid which was characterized as dimethyl 3-chloro-2-pentenedioate (**44**).

**Yield:** 3.97 g (60%)

**B. P.:** 55-60°C/0.02 mm (Lit.[52] b.p. 50-58°C/0.02 mm)

**PMR ($CDCl_3$, 90 MHz);** δ 3.70 (s, 6H, 2 x $COOCH_3$), 4.11 (s, 2H, $CH_2$), 6.20 (s, 1H, CH).

**1-Benzylamino-5-carbomethoxy-4-carbomethoxymethyl-2-pyridone (131)**

To a solution of enamine **130** (5 g, 26.3 mmol) in absolute methanol (50 ml) was added **44** (5.55 g, 28.93 mmol) and triethylamine (5.32 g, 52.6 mmol). The resultant mixture was stirred at room temperature for 66 hr after which the reaction mixture was concentrated to dryness. It was purified by column chromatography (eluent 5% acetone in pet. ether) to yield 1-benzylamino-5-carbomethoxy-4-carbomethoxymethyl-2-pyridone (**131**) as a semisolid

**Yield:** 5.37 g (64.8%)

**IR ($CHCl_3$):** 912, 1060, 1496, 1608, 1670, 1720 and 2952 $cm^{-1}$

**PMR ($CDCl_3$, 80 MHz):** δ 3.60 (s, 2H, $\underline{CH_2}COOCH_2$); 3.66 (s, 3H, $COO\underline{CH_3}$); 3.72 (s, 3H, $CH_2COO\underline{CH_3}$); 5.05 (s, 2H, $Ar\underline{CH_2}$); 6.35 (s, 1H); 7.25 (s, 5H, 5 x Ar$\underline{H}$); 8.15 (s, 1H).

**MS (m/z):** 315 ($M^+$, 29), 284 (7), 209 (9), 177 (91), 65 (15).

**1-Benzylamino-5-carbomethoxy-4-(1-carbomethoxypropyl)-2-pyridone (132)**

To a solution of 1-benzylamino-5-carbomethoxy-4-carbomethoxymethyl-pyridone **(131)** (3.15 g, 10 mmol) in acetonitrile (50 ml), potassium carbonate (2.66 g, 20 mmol) and ethyl iodide (2.35 g, 15 mmol) were added and the mixture was refluxed for 10 hr. The reaction mixture was filtered. The filtrate was concentrated to afford a residue which was characterized as 1-benzylamino-5-carbomethoxy-4-(1-carbomethoxypropyl) 2- pyridone (**132**) by spectral means.

**Nature:** Pale yellow viscous oil

**Yield:** 2.22 g (65%)

**IR ($CHCl_3$):** 910, 1452, 1670, 1728 and 2932 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 0.87 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$); 1.60-2.21 (m, 2H, $CH\underline{CH_2}CH_3$); 3.55 (s, 3H, $COO\underline{CH_3}$); 3.65 (s, 3H,

$COOCH_3$); 4.30 (t, J=7 Hz, 1H, $CHCH_2$); 5.05 (s, 2H, $ArCH_2$); 6.43 (s, 1H); 7.25 (s, 5H, 5 x ArH); 8.20 (s, 1H).

**$^{13}C$ NMR ($CDCl_3$, 50 MHz):** δ 12.22, 25.25, 48.80, 51.71, 51.86; 52.19, 109.05, 119.45, 128.1, 128.58, 128.86, 135.37, 143.86, 151.18, 161.67, 164.49, 172.68.

**MS (m/z):** 343 ($M^+$+13), 283 (13), 268 (9), 252 (4), 91 (100), 59 (8).

**5-Carbomethoxy- 4-(1-carbomethoxypropyl)- 2-pyridone (134)**

To a solution of 1-benzylamino-5-carbomethoxy-4-(1-carbomethoxypropyl)-2-pyridone (**132**) (3.43 g, 0.01 mol) in glacial acetic acid (20 ml) was added platinum dioxide (40 mg) and hydrogenolysis was carried out at 50 psi for 8 hrs. Completion of reaction was confirmed by TLC. The catalyst was filtered off and the reaction mixture was neutralized with sodium bicarbonate solution. The aqueous part was extracted with chloroform (3 x 100 ml). The combined organic part was dried ($Na_2SO_4$) and concentrated on rotavapour to afford a residue which on purification using silica gel column chromatography using pet. ether-acetone as an eluent afforded a semisolid which was characterized as debenzylated pyridone **134** on the basis of spectral means.

**Yield:** 1.26 g (50%)

**IR ($CHCl_3$):** 1106, 1661, 1727 and 3020 $cm^{-1}$

**PMR ($CDCl_3$, 80 MHz):** 0.90 (t, J=7 Hz, $CH_2CH_3$); 1.65-2.15 (m, 2H, $CH_2CH_3$); 3.65 (s, 3H, $COOCH_3$); 3.75 (s, 3H, $COOCH_3$); 4.4 (t, J=7 Hz, $CHCH_2$); 6.45 (s, 1H); 8.2 (s, 1H).

**$^{13}C$ NMR (50 MHz, $CDCl_3$):** 12.29, 25.52, 49.02, 51.94, 52.05, 110.13, 119.08, 141.44, 154.05, 164.67, 164.81, 172.82.

**MS (m/z):** 253 ($M^+$, 10), 221 (50), 193 (93), 178 (100), 162 (58), 150 (20), 134 (40), 106 (25).

**2-Iodo-3-quinolinecarbaldehyde (135)**

To a solution of 2-chloro-3-quinolinecarbaldehyde (**117**) (6.0 g, 31.32 mmol) in acetonitrile (90 ml) was added a 35% HCl solution (1.5 ml). Sodium iodide (14.1 g, 93.99 mmol) was then added and the reaction mixture was refluxed for 7 hr. The acetonitrile was then distilled out and the residue was allowed to cool. Water (125 ml) was added and the reaction mixture was rendered alkaline using saturated aqueous sodium carbonate. A solid product thus separated was filtered, washed with water and dried in air. 2-Iodo-3-quinolinecarbaldehyde (**135**) thus obtained was crystallized from ethanol.

**Nature:** Pale yellow solid

**Yield:** 6.49 g (73%)

**M.P.:** 148°C (Lit. [56] m.p. 150-152°C)

**IR ($CHCl_3$):** 910, 1450, 1575, 1615 1700 and 2940 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz):** δ 7.5-8.04 (m, 4H, 4 x ArH); 8.42 (s, 1H, ArH); 10.22 (s, 1H, CHO).

**MS (m/z):** 283 ($M^+$), 254, 191, 162, 156, 128, 101, 75.

**3-Hydroxymethyl-2-iodoquinoline (136)**

A solution of 2-iodo-3-quinolinecarbaldehyde (**135**) (3.15 g, 11.12 mmol) in methanol (25 ml) was cooled to 10°C. Sodium borohydride (42 mg, 11.35 mmol) was then added in small lots over a period of five min. After the addition was complete, the reaction mixture was stirred at room temperature for 1 hr. Then it was slowly poured onto 50 g of crushed ice with good agitation. The solid thus separated was filtered, dried and crystallized from ethyl acetate to obtain 3-hydroxymethyl-2-iodoquinoline (**136**).

**Nature:** White solid

**Yield:** 2.59 g (81.8%)

**M. P.:** 188°C (Lit.[57] m.p. 189°C).

**IR (Nujol):** 1088, 1350, 1470, 1500, 1590, 3360, 3400 and 3480 $cm^{-1}$

**PMR ($CDCl_3$+ DMSO-$d_6$):** δ 4.62 (s, 2H, $\underline{CH_2}$); 7.49-8.08 (m, 4H, 4 x Ar$\underline{H}$); 8.45 (s, 1H, Ar$\underline{H}$ ).

**MS (m/z):** 285 ($M^+$), 159, 158, 140, 131, 129, 128, 115, 103, 77.

**3-Chloromethyl-2-iodoquinoline (137)**

To a solution of 3-hydroxymethyl-2-iodoquinoline (**136**) (2.24 g, 7.82 mmol) in benzene (30 ml) was added $PCl_5$ (1.96 g, 9.43 mmol) and the reaction mixture was stirred at room temperature for 1 hr. Work up as for **127** afforded a mixture of 3-chloromethyl-2-iodo-quinoline (**137**) and 2-chloro-3-chloromethylquinoline (**127**) which could not be separated by column chromatography but mass spectrum showed formation of both the products.

**Compound 138**

To a solution of 3-hydroxymethyl-2-iodoquinoline (**136**) (0.895 g, 3.14 mmol) in dry benzene (20 ml) at 5°C containing triethylamine (0.636 g, 6.28 mmol) was added a solution of methanesulfonyl chloride (0.719 g, 6.28 mmol) in dry benzene (10 ml). After the addition was complete, the reaction mixture was stirred at 5°C for 2 hr. Water was added to the reaction mixture and the organic phase was separated. It was then washed with water, brine, dried ($Na_2SO_4$) and concentrated to obtain a residue which was purified over a silica gel column to yield the mesylate **138**.

**Nature:** White crystalline solid

**M.P.:** 109°C

**Yield:** 1.07 g (87.7%)

**PMR ($CDCl_3$, 200 MHz):** δ 3.15 (s, 3H, S-$\underline{CH_3}$); 5.40 (s, 2H, O$\underline{CH_2}$); 7.64 (m, 1H, Ar$\underline{H}$); 7.82-8.12 (m, 4H, 4 x Ar$\underline{H}$).

**MS (m/z):** 363 ($M^+$), 362, 268, 236, 192, 176, 158, 140, 128, 114

**Alkylation of the pyridone 134 with quinoline 138**

To a solution of the pyridone **134** (253 mg, 1 mmol) in dry acetonitrile (10 ml) was added anhydrous potassium carbonate (0.133 g, 1.0 mmol) and the reaction mixture was refluxed for 10 min. Then a solution of mesyl derivative (**138**) (399 mg, 1.1 mmol ) in dry acetonitrile (20 ml) was added to the reaction mixture and it was refluxed for 3 hr. The acetonitrile was removed by distillation, water was added and it was extracted with chloroform (5 x 20 ml). The combined organic layer was washed with water, brine, dried ($Na_2SO_4$) and concentrated to obtain a residue which was purified by silica gel column chromatography to give **139**.

**Yield:** 373.36 mg (71.8%)

**IR (Nujol):** 1660 and 1720 $cm^{-1}$

**PMR ($CDCl_3$, 200 MHz ):** δ 0.92 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$); 1.70-2.21 (m, 2H, $\underline{CH_2}CH_3$); 3.65 (s, 3H, COO$\underline{CH_3}$); 3.75 (s, 3H, COO$\underline{CH_3}$); 4.30 (t, J=7 Hz, 1H, $\underline{CH}CH_2$); 5.30 (s, 2H, N$\underline{CH_2}$); 6.50 (s, 1H); 7.40-7.95 (m, 4H, 4 x Ar$\underline{H}$); 8.10 (s, 1H); 8.45 (s, 1H, Ar$\underline{H}$).

**$^{13}C$ NMR ($CDCl_3$, 200 MHz):** δ 12.25, 25.29, 29.51, 48.83, 50.43, 51.93, 109.43, 119.63, 126.52, 126.88, 127.37, 127.70, 128.05, 130.91, 139.37, 144.29, 147.17, 149.14, 151.79, 161.67, 164.37, 172.66.

**MS (m/z):** 520 ($M^+$), 393 (68%), 192 (12), 176 (50), 140 (55), 128 (20), 111 (25), 97 (40), 83 (60), 69 (65), 57 (100).

**Synthesis of lactone (141)**

A mixture of 1-benzylamino-5-carbomethoxy-4-(1-carbomethoxypropyl)-2-pyridone (**132**) (343 mg, 1 mmol), paraformaldehyde (2.0 g), concentrated sulfuric acid (0.2 ml) and water (0.2 ml) in dioxane (4 ml) in a sealed thick wall tube was heated at 107°C for 24 hr. The reaction miture was then poured into brine (25 ml) and extracted with dichloromethane (3 x 25 ml). The combined extracts were dried ($Na_2SO_4$) and concentrated to afford a pale yellow oil which after chromatographic purification gave lactone **141**.

**Nature:** Pale yellow viscous oil

**Yield:** 233.5 (68.5%)

**IR ($CHCl_3$):** 1217, 1307, 1456, 1616, 1660, 1722 and 3018 $cm^{-1}$

**PMR ($CDCl_3$, 90 MHz):** δ 0.98 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$); 1.54-1.92 (m, 2H, $CH\underline{CH_2}CH_3$); 3.68 (s, 3H, $COOCH_3$); 4.25-4.54 (t, J=7 Hz, 1H, $\underline{CH}$); 5.00 (distorted d, J=16 Hz, 1H, $\underline{CH_2}O$); 5.05 (s, 2H, N-$CH_2$); 5.38 (distorted d, J=16 Hz, 1H, $\underline{CH_2}O$); 7.26 (s, 5H, 5 x Ar$\underline{H}$); 8.15 (s, 1H).

**$^{13}C$ NMR ($CDCl_3$, 50 MHz):** δ 11.49, 25.33, 42.83, 51.85, 52.58, 65.15, 106.9, 120.6,128.3, 128.78, 128.92, 134.98, 143.83, 146.29, 158.46, 163.64, 170.51.

**MS (m/z):** 341 ($M^+$, 15), 257 (5), 222 (5), 91 (100), 65 (20).

**Decarbomethoxylation of lactone 141**

A mixture of lactone **141** (170 mg, 0.49 mmol) and freshly distilled aq.HBr (5 ml) was heated under reflux under nitrogen for 18 hrs. Completion of reaction was confirmed by TLC. The reaction mixture was poured into 25 ml of water and aqueous part was extracted with chloroform (3 x 25 ml). The combined organic layer was washed with brine, dried ($Na_2SO_4$) and concentrated to afford a crude residue which after silica gel column chromatographic purification gave N-benzyl protected DE ring synthon **142**.

**Nature:** Pale yellow viscous oil

**Yield:** 52.35 mg (37%)

**PMR ($CDCl_3$, 200 MHz):** δ 0.95 (t, J=7 Hz, 3H, $CH_2\underline{CH_3}$); 1.90-2.05 (m, 2H, $\underline{CH_2}CH_3$); 3.40 (t, J=7 Hz, $\underline{CH}CH_2$); 5.15 (d, 2H, $\underline{NCH_2}$); 5.25 (distorted d, J=16 Hz, 1H, $\underline{CH_2}$); 5.45 (distorted d, J=16 Hz, 1H, $\underline{CH_2}$); 6.05 (d, J=8 Hz, 1H); 7.26 (m, 6H, 5 x Ar$\underline{H}$+$\underline{CH}$).

**MS (m/z):** 283 ($M^+$, 31%), 237 (5), 212 (7), 192 (10), 107 (12), 91 (100), 65 (13).

## *References*


1. Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T. and Sim, G. A. *J. Am. Chem. Soc.*, **1966**, *88*, 3888.
2. Wani, M. C. and Wall, M. E. *J. Org. Chem.*, **1969**, *34*, 1364.
3. Tafur, S.; Nelson, J. D.; DeLong, D. C. and Svoboda, G. H. *Lloydia*, **1976**, *39*, 261.
4. Gunasekera, S. P.; Badwa, M. M.; Cordell, G. A.; Farnsworth, N. R. and Chitnis, M. *J. Nat. Prod.*, **1979**, *42*, 475.
5. a) Govindachari, T. R. and Viswanathan, N. *Indian J. Chem.* **1972**, *10*, 435.
   b) Agarwal, J. S. and Rastogi, R. P. *Indian J. Chem.*, **1973**, *11*, 969.
6. Cai, J.-C. and Hutchinson, C. R. The Alkaloids: Chemistry and Pharmacology, Ed. A. Brossi, Academic Press, New York, **1983**, *21*, 101.
7. Arisawa, M.; Gunasekera, S. P.; Cordell, G. A. and Farnsworth, N. R. *Planta Med.*, **1981**, *43*, 404.
8. Kingsbury, W. D.; Boehm, J. C.; Jakas, D. R.; Holden, K. G.; Hecht, S. M.; Gallagher, G.; Caranfa, M. J.; McCabe, F. L.; Faucette, L. F.; Johnson, R. K. and Hertzberg, R. P. *J. Med. Chem.* **1991**, *34*, 98.
9. a) Giovanella, B. C.; Stehlin, J. S.; Wall, M. E.; Wani, M. C.; Nicholas, A.; Liu, L. F.; Silber, R. and Potmesil, M. *Science*, **1989**, *246*, 1046.
   b) Kharbanda, E.; Rubin, H.; Gungi, H.; Hinz, B.; Giovanella, P.P. and Kufe, D. *Cancer Res.*, **1991**, *51*, 6836.
10. Sawada, S.; Okajima, S.; Aiyama, R.; Nokata, K.; Faruka, T.; Yokokura, T.; Sugino, E.; Yamaguchi, K. and Miyasaka, T. *Chem. Pharm. Bull.*, **1991**, *39*, 1446.

11. Sawada, S.; Nokata, K.; Furuta, T.; Yokokura, T. and Miyasaka, T. *Chem. Pharm. Bull.* **1991**, *39*, 2574.

12. Shamma, M. *Experientia*, **1968**, *24*, 107.

13. Le Men, J. and Taylor, W. I. *Experientia*, **1965**, *21*, 508.

14. Wani, M. C.; Nicholas, A. W. and Wall, M. E. *J. Med. Chem.*, **1987**, *30*, 2317.

15. Nicholas, A. W.; Wani, M. C.; Manikumar, G.; Wall, M. E.; Kohn, K. W. and Pommier, Y. *J. Med. Chem.*, **1990**, *33*, 972.

16. Sheriha, G. M. and Rapoport, H. *Phytochemistry*, **1976**, *15*, 505.

17. Wani, M, C.; Ronman, P. E.; Lindley, J. T. and Wall, M. E. *J. Med. Chem.* **1980**, *23*, 554.

18. Danishefsky, S.; Volkmann, R. and Horwitz, S. B. *Tetrahedron Lett.*, **1973**, 2521.

19. Wani, M. C.; Nicholas, A. W. and Wall, M. E. *J. Med. Chem.* **1986**, *29*, 2358.

20. Wani, M. C.; Nicholas, A. W.; Manikumar, G. and Wall, M. E. *J. Med. Chem.* **1987**, *30*, 1774.

21. Uehling, D. E.; Nanthakumar, S. S.; Croom, D.; Emerson, D. L.; Leitner, P. L. Luzzio, M. J.; McIntyre, G.; Morton, B.; Profeta, S.; Sisco, J. M.; Sternbach, D. D.; Tong, W. Q.; Vuong, A.; Yates, J. and Besterman, J. M. *J. Med. Chem.* **1995**, *38*, 1106.

22. Kurihara, T.; Tanno, H.; Takemura, S.; Harusawa, S. and Yoneda, R. *J. Heterocycl. Chem.* **1993**, *30*, 643.

23. Lackey, K.; Besterman, J. M.; Fletcher, W.; Leitner, P.; Morton, B. and Sternbach, D. D. *J. Med. Chem.*, **1995**, *38*, 906.

24. Danishefsky, S.; Quick, J. and Horwitz, S. B. *Tetrahedron Lett.* **1973**, 2525.

25. a) Schultz, A. G. *Chem. Rev.*, **1973**, *73*, 385.

b) Hutchinson, C. R. *Tetrahedron*, **1981**, *37*, 1047.

c) J.-C. Cai, C. R. Hutchinson, *Chem. Heterocycl. Compound*, **1983**, *25*, 753.

d) Suffiness, M.; Cordell, G. A. in The alkaloids, Vol. 25, (Ed. A. Brossi), Academic Press, Orlando (1985), Ch.1 and p.75.

e) Wall, M. E.; Wani, M. C.; Nicholas, A. W.; Manikumar, G.; Tele, C.; Moore, L.; Truesdale, A.; Leitner, P. and Besterman, J.M. *J. Chem. Med.* **1993**, *36*, 2689.

26. Rama Rao, A. V.; Yadav, J. S. and Valluri, M. *Tetrahedron Lett.*, **1994**, *35*, 3613.

26a.Corey, E. J.; Crouse, D. E.; Anderson, J. E. *J. Org. Chem.* **1975**, *40*, 2140.

27. Fortunak, J. M. D.; Kitteringham, J.; Mastrocola, A. R.; Mellinger, M.; Sisti, N. J.; Wood, J. L. and Zhuang, Z.-P. *Tetrahedron Lett.*, **1996**, *37*, 5683.

28. Shen, W.; Coburn, C. A.; Bornamann, W. G. and Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 611.

29. Luzzio, M. J.; Besterman, J. M.; Emerson, D. L.; Evans, M. G.; Lackey, K.; Leitner, P. L.; McIntyre, G.; Morton, B.; Myers, P. L.; Peel, M.; Sisco, J. M.; Sternbach, D. D.; Tong, W.-Q.; Truesdale, A.; Uehling, D. E.; Vuong, A.; and Yates, J. *J. Med. Chem.* **1995**, *38*, 395.

30. Yaegashi, T.; Sawada, S.; Nagata, H.; Furuta, T.; Yokokura, T. and Miyasaka, T. *Chem. Pharm. Bull.* **1994**, *42*, 2518.

31. Jew, S. -S.; Ok, K. D.; Kim, H. J.; Kim, M. G.; Kim, J. M.; Hah, J. M. and Cho, Y. S. *Tetrahedron Asymmetry*, **1995**, *6*, 1245.

32. Comins, D. L.; Baevsky, M. F. and Hong, H. *J. Am. Chem. Soc.*, **1992**, *114*, 10971.

33. Comins, D. L.; Hong, H. and Jianhua, G. *Tetrahedron Lett.*, **1994**, *35*, 5331.

34. Comins, D. L.; Hong, H.; Saha, J. K. and Jianhua, G. *J. Org. Chem.*, **1994**, *59*, 5120.

35. Comins, D. L. and Saha, J. K. *Tetrahedron Lett.*, **1995**, *36*, 7995.

36. Fang, F. G.; Xie, S. and Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142.

37. Curran, D. P. and Liu, H. *J. Am. Chem. Soc.*, **1992**, *114*, 5863.

38. Curran D. P.; Ko, S. B. and Josien, H. *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 2683.

39. Ciufolini, M. A. and Roschangar, F. *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 1692.

40. Murata, N.; Sugihara, T.; Kondo, Y. and Sakamoto, T. *Synlett.*, **1997**, 298.

41. Volkmann, R.; Danishefsky, S.; Egglser, J. and Solomon, D. M. *J. Am. Chem. Soc.*, **1971**, *93*, 5576.

42. Hsiang, Y. M.; Hertzberg, R.; Hecht, S. and Liu, L. F. *J. Biol. Chem.*, **1985**, *260*, 14873.

43. Cohn, O. M.; Narine, B. and Tarnowski, B. *J. Chem. Soc. Perkin Trans 1*, **1981**, 1520.

44. Simchen, G. *Chem. Ber.*, **1970**, *103*, 389.

45. a) Adams, R.; Chiles, H. M. and Rassweiler, C. F. *Org. Syn.*, **1982**, Coll. Vol. *1*, 10.

b) Adams, R. and Chiles, H. M. *Org. Syn.*, **1982**, Coll. Vol. *1*, 237.

46. Inglis, J. K. H. *Org. Syn.*, **1967**, Coll. Vol.*1*, 254.

47. Bhat, N. B. and Bhaduri, A. P. *Ind. J. Chem.*, **1984**, *23B*, 431.

48. Galat, A. and Elion, G. *J. Am. Chem. Soc.*, **1939**, *61*, 3585.

49. Wolf, V. *Chem. Ber.*, **1953**, *86*, 735.

50. Kadaba, P. K. *Synthesis*, **1971**, 316.

51. Grohe, K. and Heitzer, H, *Liebigs Ann. Chem.*, **1987**, 29.

52. Bryson, T. A. and Dolak, T. M. *Org. Syn.*, **1988**, Coll. Vol. *6*, 505.

53. a) Quick, J. *Tetrahedron Lett.*, **1977**, 327.

b) Kametani, T.; Onasawa, T. and Ihara, M, *J. Chem. Soc. Perkin Trans 1*, **1981**, 1563.

54. Danishefsky, S. and Etherdge, S. J. *J. Org. Chem.* **1974**, *39*, 3430.

55. King, H. and Work, T. S. *J. Chem. Soc.*, **1940**, 1307.

56. Cohn, O. M.; Narine, B. and Tarnowski, B. *J. Chem. Soc. Perkin Trans 1*, **1981**, 1520.

57. Narasimhan, N. S.; Sunder, N. M.; Ammanamanchi, R. and Bonde, B. V. *J. Am. Chem. Soc.*, **1990**, *112*, 4431.

58. Lyle, R. E.; Portlock, D. E.; Kane, M. J. and Bristol, J. A. *J. Org. Chem.*, **1972**, *37*, 3967.

# CHAPTER III

# APPLICATION OF HETEROGENEOUS CATALYSTS IN ORGANIC TRANSFORMATIONS

## Introduction

The term "Catalysis" was coined by Berzelius[1] in 1835 according to whom the definition of catalyst is: physiological and chemical reactions proceed in the presence of a substance which does not itself get altered during the course of the reaction. In other words, Berzelius catalyst is a substance which by its mere presence evokes chemical actions which could not take place in its absence. Examples (i) oxidation of ethyl alcohol to acetic acid (ii) combustion of hydrogen, both in the presence of platinum at room temperature, etc.

A new definition of catalysis after Berzelius was given by W. Ostwald,[2] based on the knowledge of chemical equilibrium, that all chemical reactions proceed via a number of more or less stable intermediates. According to Ostwald the phenomenon catalysis can be understood as an acceleration of a thermodynamically feasible reaction through the presence of a substance, the catalyst, which itself is neither essentially altered nor consumed by this chemical action.

The basic concept of a catalyst is that, a substance in a small amount causes a large change. A more precise and perhaps better definition states that "a catalyst is a substance which increases the rate of attainment of equilibrium of a reacting system without causing any great alteration in the free energy change involved."

It is incorrect to say that the catalyst should remain unchanged at the end of a catalyzed reaction. In practice the catalysts are sintered, eroded, etched or covered with residues left behind by the interacting molecules.

Another important aspect of catalysts behaviour is that, it determines the path of a reaction. e.g. the decomposition of ethanol over alumina catalysts yields ethylene and water. While over copper or silver catalysts, acetaldehyde and hydrogen are the products.

Similarly, the nickel-catalyzed reaction between benzaldehyde and hydrogen gives toluene as the major products, whereas benzyl alcohol is produced when copper-chromite catalysts are used.

**Classification**

The catalysts are classified into two main types (1) Homogeneous catalysts and, (2) Heterogeneous catalysts.

It is interesting to note that, in the beginning industrial catalytic processes (alcohol fermentation and soap making, known since ancient times) used homogeneous catalysts or enzymes without knowing anything of catalysis. The first "modern" process also used a homogeneous catalyst, nitric oxide to oxidize $SO_2$ to $SO_3$ in the earlier ("lead chamber") sulfuric acid manufacture.

1. **Homogeneous catalysis**

In its widest sense homogeneous catalysis occurs when the catalyst and the reactants, both are in the same phase, either gas or liquid. In more recent years the term has come to be applied more specifically to the use of a solution of certain organometallic compounds in which a central metal atom is surrounded by a regular pattern of atoms or molecules, known as ligands, with which it is co-ordinated. Depending on the nature of the ligands, the metal atom may be in a low positive, zero or low negative state.

A special feature of homogeneous catalytic transition metal complex reactions is the enhanced selectivity compared with heterogeneous catalytic reactions.

In homogeneous catalytic reactions the catalysts and reactants are present in one phase and from an engineering view point, a major disadvantage of this arises from the difficulty in separating the product from the catalysts; this is a peculiar problem in large scale conversions with open reaction systems.

The reactions of industrial importance are primarily hydroformylation (oxo synthesis), carbonylation, addition of HCN and olefin polymerization.

2. **Heterogeneous catalysis**

In heterogeneous catalysis the reaction takes place at the interface between the catalysts and the less dense phase. In other words heterogeneous catalysis describes the enhancement in the rate of a chemical reaction brought about by the presence of an interface between two phases.

In general much higher temperatures, are used in heterogeneous catalytic reactions than in homogeneous catalytic ones.

Heterogeneous catalysts may be divided naturally into two distinct groups. (1) metals and (2) non-metals.

The former group comprised largely of the metals of groups VIII and IB, the latter of metal oxides and sulfides, salts and acids; the first mentioned are the most important. The non-metal catalysts may be further subdivided according to their electrical conductivity into (a) semiconductors and (b) insulators. Thus metals are, in general, good catalysts for reactions involving hydrogen atom addition or removal of oxygen atoms. Conversely, semiconductor catalysts are poor hydrogenation catalysts. Insulators, of which alumina and silica are the most important, are good dehydration catalysts, but they possess very little ability to catalyze hydrogenation or oxidation.

**Clays as heterogeneous catalyst**

Clays are aluminosilicates[3] in which aluminium (III) cations are bonded to an octahedral arrangement of oxygen anions. Repetition of these aluminate units in two dimensions forms an octahedral layer. Likewise a tetrahedral layer is formed from silicate units.

Clays are classified according to the relative number of tetrahedral and octahedral layers. Montmorillonite clays, which have been used in synthetic organic chemistry have

an octahedral layer sandwiched between two tetrahedral layers. Kaolinites[4] i.e. clays from which china ware is made are 1:1 clays associating one tetrahedral and one octahedral layer. The resulting sheets are planar. The planar clay platelets stack on top of one another (Fig-1).

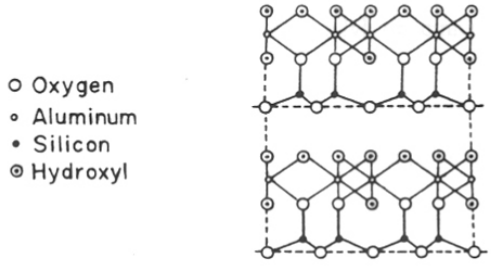
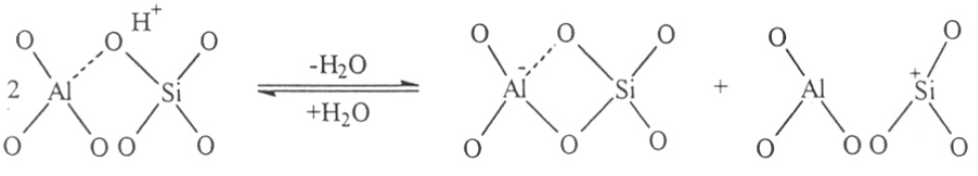



FIG. 1

The surface acidity (using the Hammett Ho acidity function) for natural clays with $Na^+$ or $NH_4^+$ as interstitial cations ranges from +1.5 to -3.[5] Washing of the clay with mineral acid, such as HCl, brings $H_O$ down to -6 to -8, which is between the $H_O$ for concentrated nitric acid ($H_O$= -5) and that for sulfuric acid ($H_O$= -12).

The Bronsted acidity of clays stems from the terminal hydroxyl groups and from the bridging oxygens. At the edges of platelets which break off, particularly in the octahedral layer, coordinatively unstaturated Al (III), Fe (II) and Fe (III) centers arise which act as a Lewis acid centers (Fig.2).

Generation of Lewis acid site on heating




Bronsted site Lewis site

**Fig. 2**

Clays have many advantages over conventional homogeneous catalysts such as ease of handling, non-corrosiveness, low-cost and regeneration. Due to their Bronsted

and Lewis acidities, clays both in their natural and ion-exchanged forms, function as efficient catalyst for various organic transformations.[6] We have recently reported the catalytic property of natural kaolinitic clay for transdithioacetalization of acetals, ketals, oximes, enamines and tosylhydrazones[7], tetrahydropyranylation[8], selective regeneration of carboxylic acids from their corresponding allyl or cinnamyl esters[9], and for the preparation of oxazolines.[10]

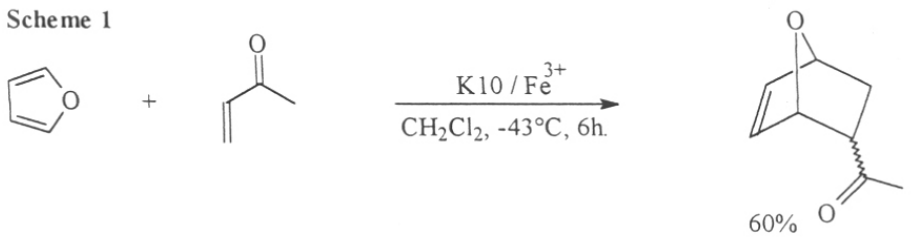
The kaolinitic clay was procured from the Padappakara mine of Quilon District, Kerala, India and it was subsequently purified and characterized by FT- IR, XRD, UV, ESR, SEM, EDX and chemical analysis by AAS. The composition of the clay has been determined by wet chemical analysis (in %): $SiO_2$=67.45, $Al_2O_3$=22.2, $Fe_2O_3$=6.1, $TiO_2$=3.45 and K=0.8.

**Reactions catalyzed by clay**

Diels-Alder cycloadditions:

Lewis acid catalysis is a mainstay for Diels-Alder cycloadditions. With normal electron demand in Diels-Alder reaction the Lewis acid lowers the LUMO for the dienophile thus narrowing the HOMO-LUMO gap, hence the catalysis. This key reaction of organic synthesis has also been catalyzed successfully using doped clays.[11a-c] Furans are dienes notorious for their reticence toward undergoing Diels-Alder cycloadditions, since they have to shed their aromaticity as the reaction proceeds (Scheme 1). Earlier 15 Kbars of pressure was used to carry out reaction, however, with doped clays reaction can be run at ambient temperature and pressure.[12]

**Scheme 1**



Friedel-Crafts reaction:

Olah[13] has surveyed the Lewis acids used as catalysts in the Friedel-Crafts reaction. However, use of standard Lewis acid catalysts is associated with problems such as their handling, the necessity of using large amounts and also the isomerization which they often trigger.

Pierre Laszlo[14] and co-workers used improved heterogeneous clay catalyst for Friedel-Crafts reaction. It was found to be advantageous from environmental point of view by vastly reducing the amount of catalyst as compared to the standard procedures using aluminium chloride.

Benzoylation of aromatics by benzoyl chloride and K10-Fe (III) catalyst was studied and the yields were found to be very good (Table 1)

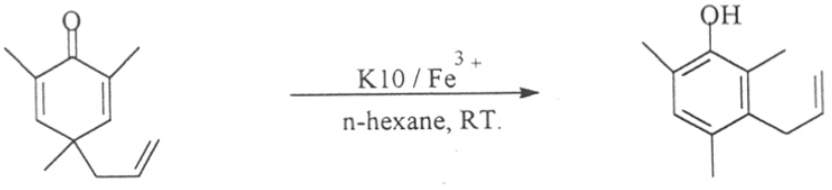
**Table 1:** Benzoylation of aromatic substrates by benzoyl chloride and K10-Fe (III) catalysts

| Substrates | Time | Temperature °C | Yield % |
|---|---|---|---|
| Anisole | 5 min. | 160 | 100 |
| Mesitylene | 15 min. | 160 | 98 |
| p-Xylene | 3 hr. | 140 | 100 |

Cyclohexadienone-phenol rearrangement:

Crawford and Curtin had determined kinetics of cyclohexadienone-phenol rearrangement in hydrocarbon solvent with sulfuric acid as the homogeneous catalyst, and found that the half-life was five hours at 80°C.[15] When they replaced the homogeneous catalyst with the K10 montmorillonite the half-life remained the same, but the reaction could be carried out at room temperature. Upon drying carefully this clay catalyst in an oven prior to use, in order to benefit from maximum Bronsted acidity, the half-life decreased to five minutes, the reaction could be carried out still at room temperature. If the acidity is yet heightened by exchanging Fe (III) ( Scheme-2 ) into the clay, the half-life is again decreased, to five seconds, still at room temperature.[16]

**Scheme 2**



# Section A

# Protection of Carbonyl Compounds Catalyzed by Natural Kaolinitic Clay

## Introduction: Protecting groups in organic synthesis

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. For the last hundred years, great efforts have been made by researchers to develop new protecting groups for organic functionalities and deprotection methods were also developed after Fischer's pioneering work in the field of carbohydrate[17] and peptide chemistry.[18]

A protective group must fulfill a number of requirements. It must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group. The protective group should have a minimum of additional functionality to avoid further sites of reaction.

The introduction of isopropylidene acetal as blocking group for diols in carbohydrate synthesis and chloroacetyl group as well as urethane as N-terminal blocking group in the selective synthesis of peptides was the beginning in this field.

### Protection for the carbonyl group

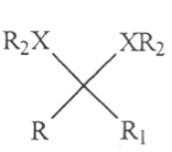
During a synthetic sequence a carbonyl group may have to be protected against attack by various reagents such as strong or moderately strong nucleophiles including organometallic reagents, acidic, basic, catalytic or hydride reducing agents and some oxidants.[19]

The most useful protective groups are the acyclic and cyclic acetals or ketals, and the acyclic or cyclic thio acetals or ketals. The carbonyl group forms a number of other very stable derivatives. They are less used as protective groups because of the greater difficulty involved in their removal. Such derivatives include oximes, imines, cyanohydrins, hydrazones and semicarbazones.[19]

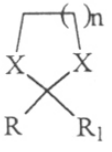
Cyclic and acyclic acetals and thioacetals are stable to aqueous and non-aqueous bases, nucleophiles including organometallic reagents and to hydride reduction. The oxygen derivatives are stable to neutral and basic catalytic reduction. At the same time, they are readily cleaved by acid hydrolysis. In contrast, thioacetals are very labile to the neutral and basic catalytic reduction, oxidation and cleavage by heavy metal salts like Hg (II), Ag (I), Fe (IV) or Cu (II) salts but they are resistant to acid hydrolysis.

The order of reactivity of the carbonyl group in general is aldehydes (aliphatic > aromatic) > acyclic ketones and cyclohexanones > cyclopentanones > α,β-unsaturated ketones >> aromatic ketones. Due to the pronounced difference in reactivity between the different carbonyl groups, in many cases a reactive carbonyl group may be protected selectively in the presence of less reactive one.

Acetals or ketals take two general forms viz. (a) acyclic; (b) cyclic where R can




a




b

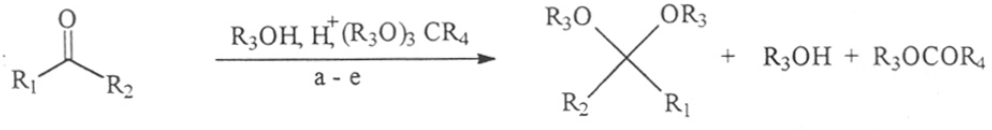
be H, aryl or alkyl and $R_1$ can be alkyl, aryl; X can be O and S. $R_2$ can be aryl or alkyl and n=1 or 2.

A wide range of protic acids, Lewis acids and heterogeneous catalysts have been employed for the acetalization and thioacetalization of aldehydes and ketones. Aldehydes in general can be acetalized in the presence of weaker acids such as ammonium chloride,[20] ammonium nitrate,[21a] calcium chloride,[21b] alumina[22] and lanthanide halides.[23] Ketones require stronger acids and mineral acids such as hydrochloric acid or sulfuric acid or sulfonic acids such as toluene-p-sulfonic acid.[24]

**Preparation of acyclic acetals ketals, thioacetals and thioketals :**

For the preparation of acyclic acetals, ketals, thioacetals and thioketals water may be removed with dehydrating reagents such as molecular sieves,[25] calcium sulfate,[26] copper sulfate[27] and alumina. Although this approach often allows acetalization to be carried out at room temperature, it appears to give high yields with only more reactive aldehydes or ketones. Ortho esters are the most widely used reagents for this purpose, and react with the water to form an ester and an alcohol (Scheme-3).

**Scheme 3**




a: Montmorillonite clay K10 Ref: *Synthesis*, **1977**, 467.

b: $NH_4Cl$ Ref: *Synthesis*, **1990**, 313.

c: $NH_4NO_3$, RT Ref: *Org. Syn. Coll.Vol.*, 1963,**4**, 101.

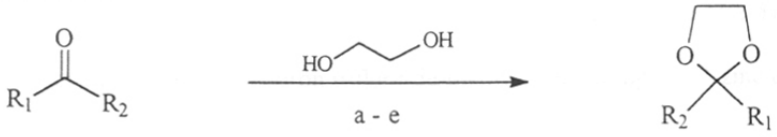
d: pTSA Ref: *Synth. Commun.*, **1977**, *7*, 409.

e: HCl, RT Ref: *J. Org. Chem.*, **1970**, *35*, 3375.

**Preparation of 1,3-dioxolanes**:

The most commonly employed method for acetal formation involves heating an aldehyde or ketone with an alcohol or diol in an inert solvent such as benzene, toluene or xylene, which allows removal of water by continuous azeotropic distillation with a Dean-Stark apparatus (Scheme-4).

**Scheme 4**



a : ppts, benzene, 1hr Ref: *Synthesis*, **1979**, 724.

b: $BF_3 \cdot OEt_2$ Ref: *J. Am. Chem. Soc.*, **1954**, *76*, 1728.

c: pTSA, benzene Ref: *J. Am. Chem. Soc.*, **1948**, *70*, 2827.

d: Oxalic acid, $CH_3CN$ Ref: *Synth. Commun.*, **1973**, *3*, 725.

e: $SeO_2$, $CHCl_3$, 28°, 4hr Ref: *J. Am. Chem. Soc.*, **1955**, *77*, 2224.

Most commonly used method is addition of pTSA to equimolar mixture of carbonyl compound and ethylene glycol in an inert solvent, under reflux. Pyridinium p-toluenesulfonate (ppts) is a particularly mild catalyst which has been used on acid-sensitive substrates and is often employed when toluene-p-sulfonic acid is unsuitable. [28] The extent of double bond isomerization during acetalization of enones is dependent on the pKa of the acid catalyst, and acetalization of cyclic enones can be carried out without double bond migration with fumaric acid.[29] Adipic acid[30] has been used for the same purpose with steroidal enones. Diaryl ketones are particularly difficult to acetalize under standard conditions, but triflic acid[31] in nitromethane appears to overcome this long-standing problem.

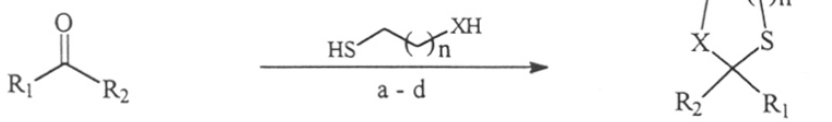
**Preparation of 1,3-oxathiolanes, 1,3-dithiolanes and 1,3-dithianes**

Apart from the use as protecting groups, thioacetals have gained prominence in organic transformations because of the ease with which they act as acyl anion equivalent.[32] Synthetic chemists have used this protocol widely to metallate thioacetals and later unmasked the carbonyl compound, in chain extension reactions. This marked reversal of the reactivity of carbonyl group was developed and introduced by Corey and Seebach[33] and was termed as "Umpolung of the reactivity".

In general, dithioacetals have been prepared by protic acid or Lewis acid catalysed condensations of carbonyl compounds with thiols (Scheme-5).[19] Lewis acids used for this purpose are boron trifluoride-diethyl ether complex,[34a] zinc chloride or

aluminium chloride.[34b] More recently, Nafion-H catalyst,[34c] silica gel treated with thionyl chloride,[35] anhydrous lanthanum chloride[23], anhydrous iron (III) chloride dispersed on silica gel,[36] HY zeolite,[37] Mg-ZnTF[38] and modified clays such as Mont-KSH[39] and Ce-Mont[40] have been developed for such synthetic transformations. We envisioned that natural kaolinitic clay could also be used for acetalization and thioacetalization and this section describes some of our observations.

**Scheme 5**




X = O, S n = 1, 2

a: HY-zeolite Ref: *Tetrahedron Lett.*, **1972**, *33*, 825.

b: Mg-ZnTF Ref: *Tetrahedron Lett.*, **1983**, *24*, 169

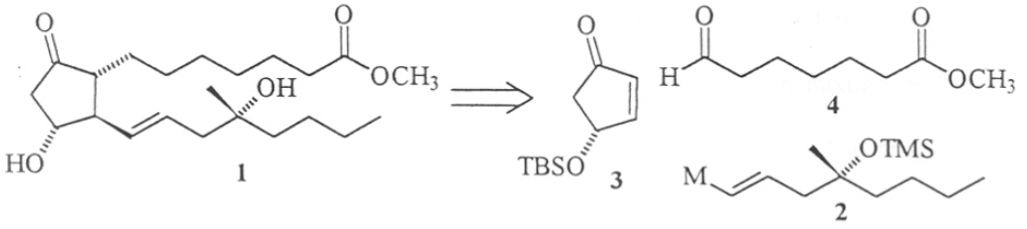
c: Mont-KSH Ref: *J. Chem. Soc. Chem. Commun.*, **1992**, 1192

d: Ce-Mont Ref: *J. Org. Chem.*, **1995**, *60*, 403

## Present work

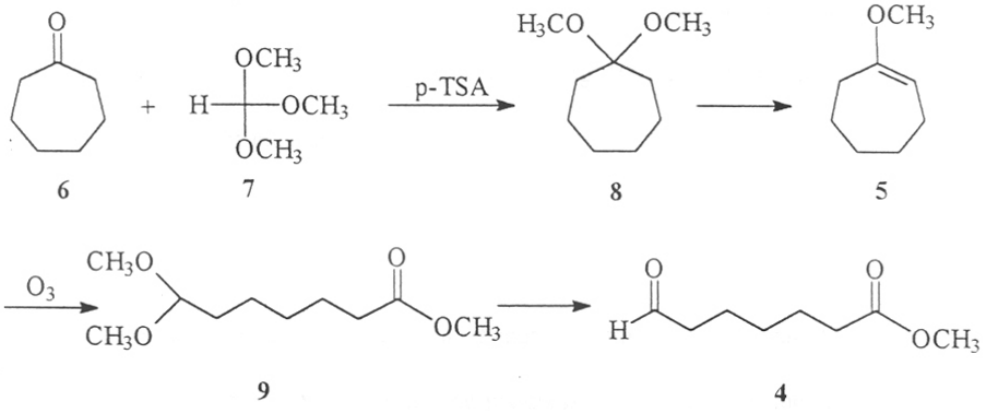
As a part of the ongoing programme for the total synthesis of misoprostol[41a,b] (Scheme 6), we needed one of the fragments **4** for further synthetic work.

**Scheme 6**




It was decided to prepare methyl 7-oxoheptanoate (**4**) by ozonolysis of 1-methoxy-1-cycloheptene (**5**), which in turn can be prepared from cycloheptanone (**6**) and trimethyl orthoformate (**7**) as shown in Scheme 7.

**Scheme 7**




Wohl[42] reported a one step procedure for the synthesis of cyclic enol ethers via intermediate acetals in which the acetal content could not be judged by GC analysis.[43] No suitable methods were available to monitor these reactions by GC and to our knowledge, there is no report giving conditions for separating a mixture of cycloheptanone (**6**), trimethyl orthoformate (**7**), 1,1-dimethoxycycloheptane (**8**) and 1-methoxy-1-cycloheptene (**5**) simultaneously. In the present work, a baseline separation

was achieved by developing GC conditions for the quantitative analysis of the reaction mixture so that these reactions could be optimized for the maximum yield of **4** or **5**.[44]

In a typical procedure cycloheptanone was subjected to Wohl's conditions for the preparation of **5**, i.e. a mixture of trimethyl orthoformate, cycloheptanone and p-toluenesulphonic acid was stirred at room temperature for 24 hr and then heated to remove the methanol liberated. It was observed that the reaction mixture could be directly heated under reflux for 8 hr to achieve complete conversion. The progress of this reaction was monitored by GC analysis as described. Further, the **5** thus obtained (after distillation) was subjected to ozonolysis in methanol at -75°C to give **4**. The methanolic solution was analyzed directly by GC.

The separation of a mixture of trimethyl orthoformate (**7**), cycloheptanone (6), 1,1-dimethoxycycloheptane (**8**) and 1-methoxy-1-cycloheptene (**5**) was initially tried on 5% OV-101 at 100°C but **5** and **8** were eluted at nearly the same retention time. A baseline separation was successfully achieved using 10% DEGS at 90°C, as shown in Fig.3. The order of elution was **7** ($t_R$= 0.97), **5** ($t_R$=2.05), **8** ($t_R$=4.42) and **6** ($t_R$=7.20 min). The total time required for the separation of all the components was less than 8 min.

In order to estimate the amount of methyl formate and methanol formed during the preparation of **5** and **8**, indicating the progress of the reaction, the reaction mixture was analyzed at 60°C on the same column and the order of elution was methyl formate ($t_R$=0.67), methanol ($t_R$=0.96) and trimethyl orthoformate ($t_R$=2.19 min). The progress of the conversion of **6** to **5** using different reaction conditions was monitored by GC as described and the results are given in Table-2.

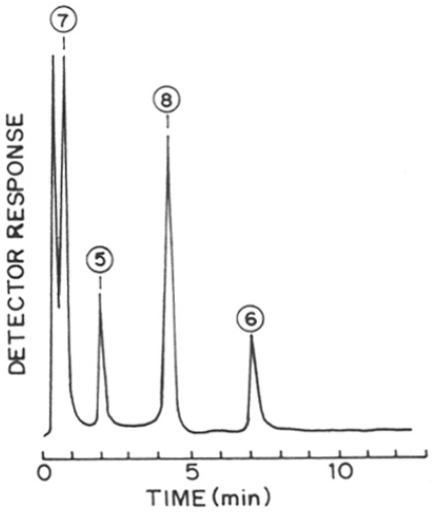



FIG.3

Gas chromatogram showing separation of reaction mixtures during the conversion of **6** into **5** obtained using a 10% DEGS column at 90°C. Peak: 7= trimethyl orthoformate (**7**) ($t_R$=0.97 min), 5= 1-methoxy-1-cycloheptene (**5**) ($t_R$=2.05 min), **8**= 1,1-dimethoxycycloheptane (**8**) ($t_R$=4.42 min), 6= cycloheptanone (**6**) ($t_R$=7.20 min).

**Table 2:** Progress of the reaction monitored by gas chromatography

| Reaction conditions | Concentration (%) | | |
|---|---|---|---|
| | **6** | **5** | **8** |
| Stirred at room temperature for 24 hr | 12.43 | 37.64 | 40.56 |
| Room temperature for 24 hr then | | | |
| 120°C for 6 hr | - | 92 | 5 |
| 120°C for 4 hr | 1.36 | 18.00 | 72.37 |
| 120°C for 8 hr | - | 94.07 | 2.37 |

For quantitative analysis, mixtures of compound **5** and **6** of different compositions ranging from 1:9 to 10:0 (5:6) were prepared in dichloromethane, e.g., 10

mg of **6**, 90 mg of **5** were dissolved in 10 ml of dichloromethane. With an injection volume of 2 µl, GC analysis of all the solutions was carried out; calibration graphs for 5 and **6** were plotted separately and were found to be linear. Aliquots of the reaction mixture to be monitored were analyzed by GC directly at different intervals.

Compound **5** was subjected to ozonolysis using the reported conditions and the reaction was monitored by GC. The column temperature was programmed for 90° to 150°C at 20°C/min. The chromatogram (Fig.4) showed the separation between **6, 9** and **4** with the retention times being 7.20, 12.26 and 13.81 min. respectively (during the reaction a small amount of **5** was converted into the more stable keto form, cycloheptanone). It was assumed that the peak at $t_R$=12.26 min. was due to the intermediate methyl 7,7-dimethoxyheptanoate (**9**) as the peak disappeared after acid hydrolysis with increase in the amount of **4** present ($t_R$=13.81 min).

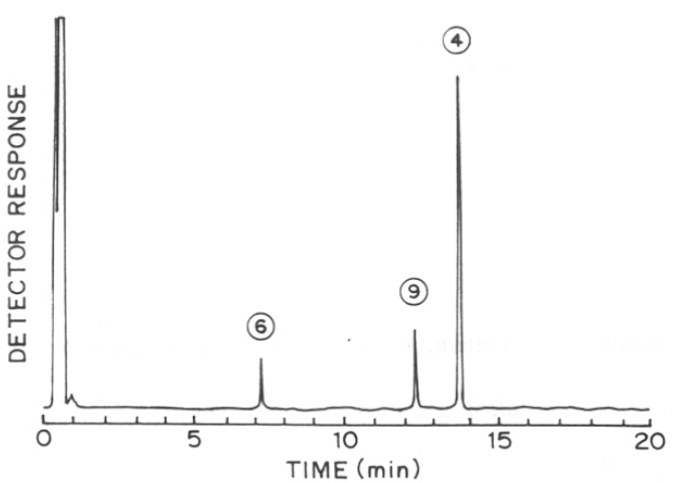
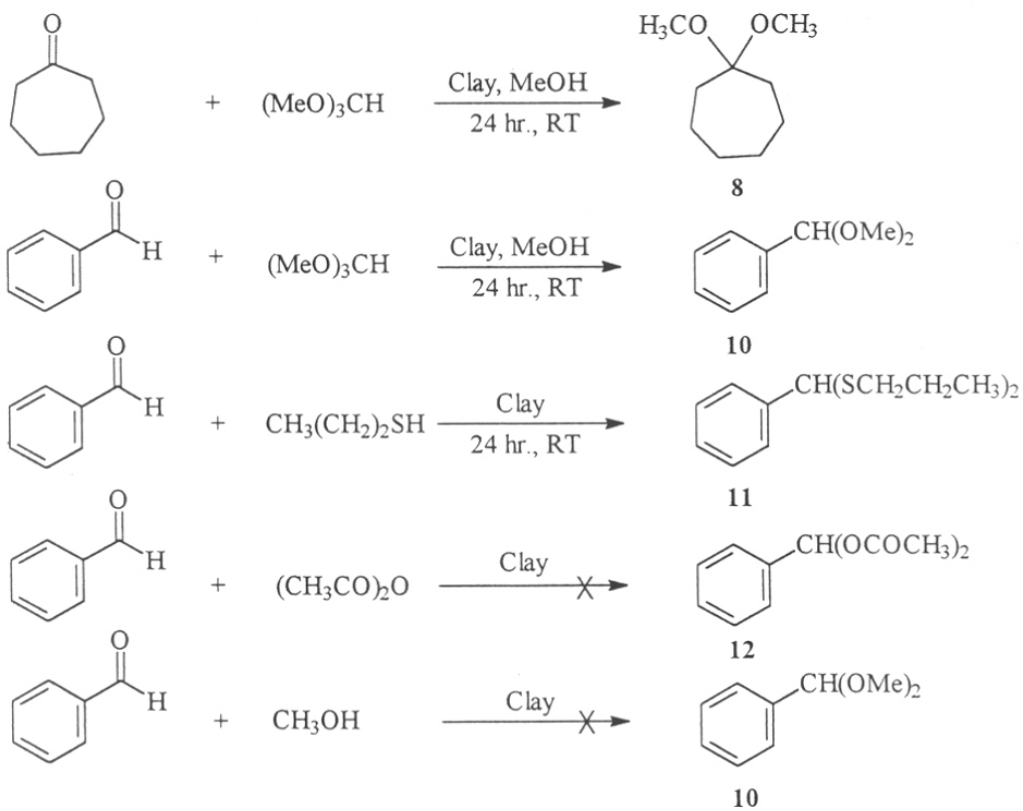



FIG. **4**

Gas chromatogram showing the separation of the products after ozonolysis of **5** to **4**. Column, 10% DEGS; temperature, programmed from 90°C (7.5 min) to 150°C at 20°C/min. Peaks **6**=cycloheptanone (**6**) ($t_R$=7.20 min); **9**= methyl 7,7-dimethoxyheptanoate (**9**) ($t_R$=12.26 min); **4**= methyl 7-oxoheptanoate (**4**) ($t_R$=13.81 min)

When conversion of cycloheptanone (**6**) to 1,1-dimethoxycycloheptane (**8**) was tried using natural kaolinitic clay instead of pTSA, it gave acetal **8** in good yields. This result prompted us to study the preparation of acyclic acetals and thioacetals by using natural kaolinitic clay and the results are as shown in Scheme 8.

**Scheme 8**

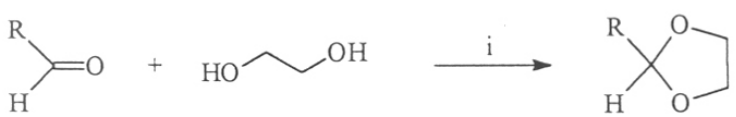



When benzaldehyde was stirred with trimethyl orthoformate in the presence of natural kaolinitic clay, it gave the corresponding acetal in 96% yield and treatment of benzaldehyde with 1-propanethiol in the presence of natural kaolinitic clay afforded the corresponding thioacetal in 94% yield. However, reaction of benzaldehyde with acetic anhydride or methanol in the presence of natural kaolinitic clay met with failure. When ethylene glycol was treated with benzaldehyde in the presence of natural kaolinitic clay it gave 2-phenyl-1,3-dioxolane in good yield. Considering all these observations a general

methodology for acetalization and thioacetalization has been developed and the results are summarized as depicted in Scheme 9.

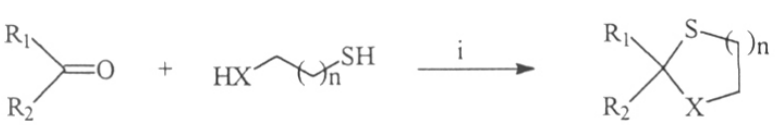
To a stirred solution of one equivalent of carbonyl compound in benzene, were added successively natural kaolinitic clay (10% mass by wt.) and one equivalent of ethylene glycol or ethane-1,2-dithiol or ethane-1,2-oxathiol or propane 1,3-dithiol and the mixture was refluxed with stirring. The progress of the reaction was monitored by TLC. Then the clay catalyst was filtered and the filtrate was washed with water. The solvent was dried ($Na_2SO_4$) and removed under reduced pressure. The purification was achieved by flash chromatography to yield 1,3-dioxolane, 1,3-dithiolane, 1,3-oxathiolane and 1,3-dithiane when ethylene glycol, ethane 1,2-dithiol, ethane 1,2-oxathiol and propane 1,3-dithiol were used as respectively.

**Scheme 9**




R = alkyl, aryl

**13**




$R_1$ = H, alkyl, aryl  n = 1, 2
$R_2$ = alkyl, aryl  X = O, S
i = Clay (10% wt/wt), benzene, △, 2hr.

**13** 1,3-Dioxolane
**14** 1,3-Oxathiolane X = O, n = 1
**15** 1,3-Dithiolane X = S, n = 1
**16** 1,3-Dithiane X = S, n = 2

**Table-3**: Protection of carbonyl functions with ethane 1,2-diol, Hydrothiol, Dithiol and Propane 1,3- dithiol over natural kaolinitic clay[a].

| Entry | Substrate | 1,3-Dioxolane (**13**) 1,3-Oxathiolane (**14**) Yield (%)[b] | | 1,3-Dithiolane (**15**) 1,3-Dithiane (**16**) Yield (%)[b] | |
|---|---|---|---|---|---|
| | | **13** | **14** | **15** | **16** |
| a. | 1- Butanal | 91 | - | 92 | - |
| b. | 1- Hexanal | 90 | - | - | - |
| c. | Crotonaldehyde | 92 | - | 70 | - |
| d. | 3-Methylcyclohex-2-ene-1-one | 0 | - | 90 | - |
| e. | (R)- Carvone | 0 | - | 72 | - |
| f. | (R)- Camphor | 0 | - | 85 | 68 |
| g. | Cyclohexanone | 0 | - | 80 | - |
| h. | Menthone | 0 | - | 65 | 60 |
| i. | Benzaldehyde | 95 | 95 | 98 | 95 |
| j. | 4-Methoxybenzaldehyde | 92 | 86 | - | - |
| k. | 4-Chlorobenzaldehyde | 81 | - | - | - |
| l. | 4-Nitrobenzaldehyde | 75 | - | - | - |
| m. | 1,4-Benzenedicarboxaldehyde | 92[c] | 94[c] | 88[c] | - |
| n. | 3,4,5-Trimethoxybenzaldehyde | 86 | - | - | - |
| o. | Furan-2-carboxaldehyde | 93 | - | 85 | 64 |
| p. | Cinnamaldehyde | 93 | - | - | - |
| q. | Acetophenone | 0 | 89 | 97 | 72 |
| r. | Benzophenone | 0 | 81 | 75 | 65 |

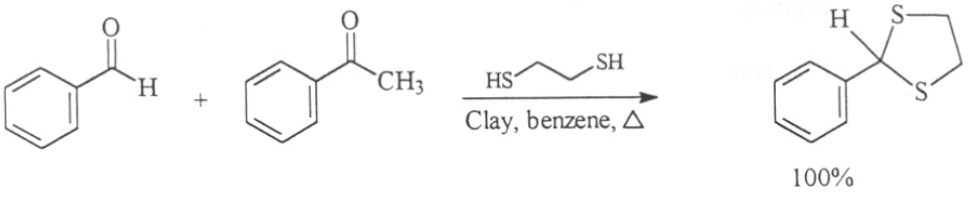
a: Catalyst was reused three times without loss of activity; b: Isolated yield; characterized by IR, $^{1}H$ and $^{13}C$ NMR and MS; c: Underwent diprotection with 2 moles of reagent.

Formation of cyclic acetals, ketals, thioacetals and thioketals were confirmed by the absence of carbonyl band corresponding to aldehyde or ketone in their IR spectra. Further confirmation of the products was carried out with physical properties and spectral properties including PMR and mass spectra and by comparison with the literature data.

**Selectivity**

In order to examine the selectivity of the present thioacetalization with use of the clay, an equimolar mixture of benzaldehyde, acetophenone, ethane-1, 2-dithiol and 10% (wt/wt) clay in benzene was refluxed for 2 hr and it was found that perfect chemoselectivity was observed ( Scheme-10).

**Scheme 10**




100%

**Conclusion**

1 Evidently, under clay catalyzed reaction conditions various protecting groups such as ethylene glycol, ethane oxathiol, ethane 1,2-dithiol and propane 1,3-dithiol were used for the protection of carbonyl compounds.

2. The clay catalyses the protection of variety of aldehydes (aliphatic, aromatic, heteroaromatic, α,β-unsaturated) with ethane-1, 2-diol. Ketones, however, failed to undergo protection under such reaction conditions.

3. In contrast, both aldehydes and ketones could be thioacetalised with ethane-1,2-oxathiol, ethane-1,2-dithiol and propane-1,3-dithiol producing corresponding derivatives in excellent yield.

4. Even the sterically hindered ketones eg. camphor could be thioacetalized with ethane-1,2-dithiol and propane-1,3-dithiol.

5. A special feature of this catalytic process is that α,β-unsaturated carbonyl compounds underwent protections without the shift of the double bond to β,γ-position or without 1,4-addition.
6. Cyclic ketone like cycloheptanone and benzaldehyde could be acetalized with trimethyl orthoformate and benzaldehyde could be thioacetalized with 1-propanethiol in very high yield.
7. This method exhibits high chemoselectivity for selective protection of aldehydes in the presence of keto carbonyl functions.
8. The catalyst can be reused, recycled and is non-polluting and available at low cost.
9. Reaction condition is very simple. It does not give any side products.
10. Reaction does not require elevated temperature and longer time.

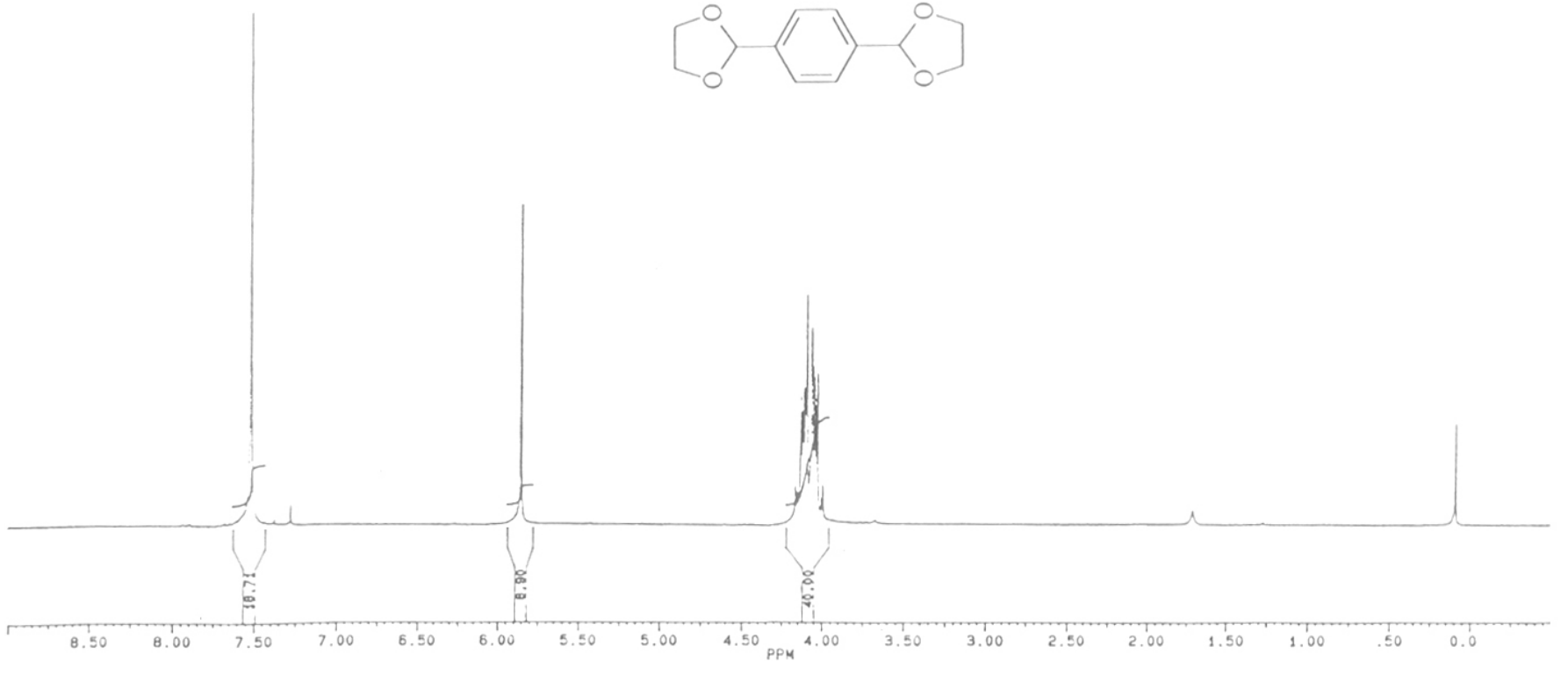



FIG I : PMR SPECTRUM OF THE COMPOUND 13m IN $CDCl_3$

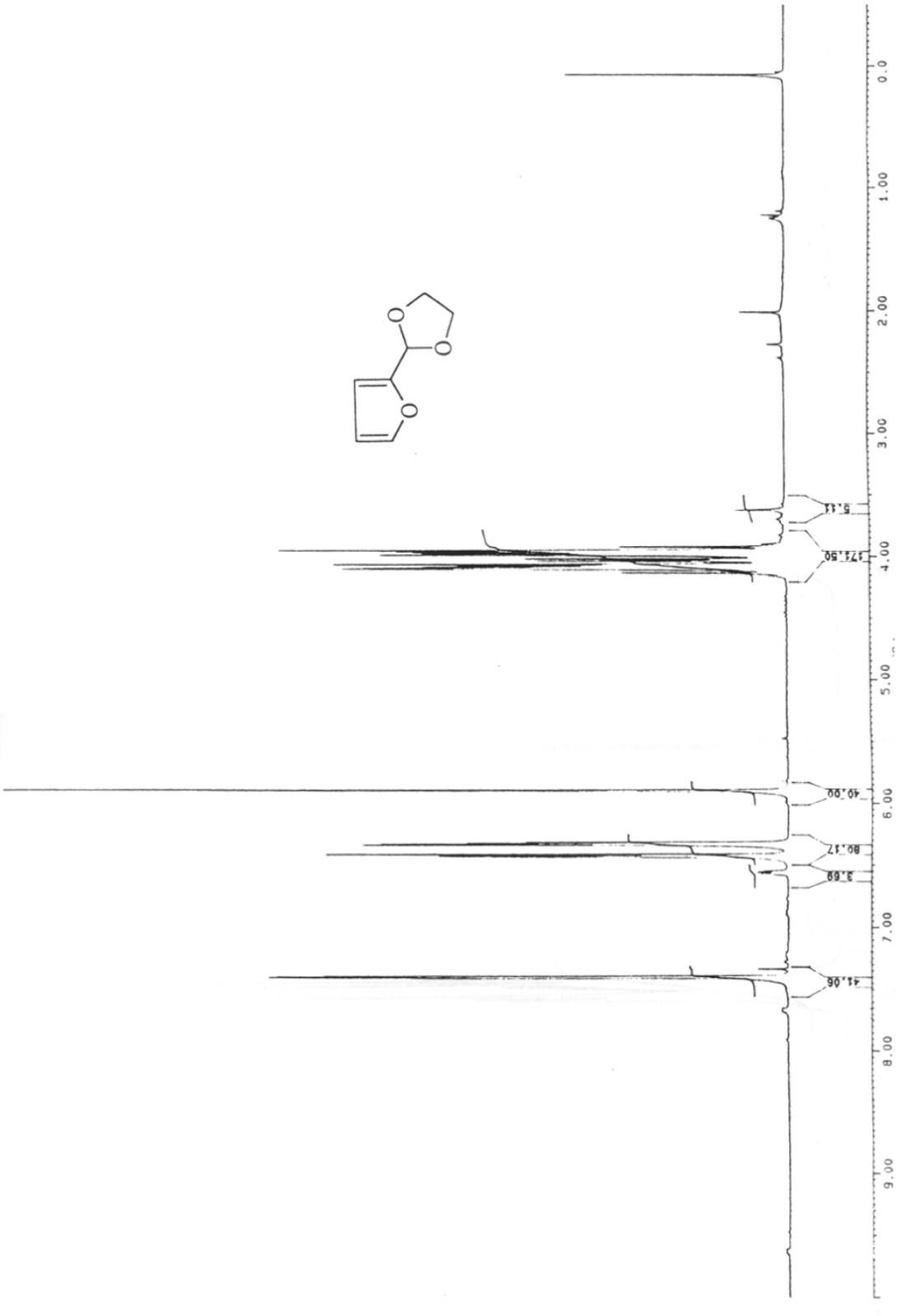



FIG II : PMR SPECTRUM OF THE COMPOUND 13O IN $CDCl_3$

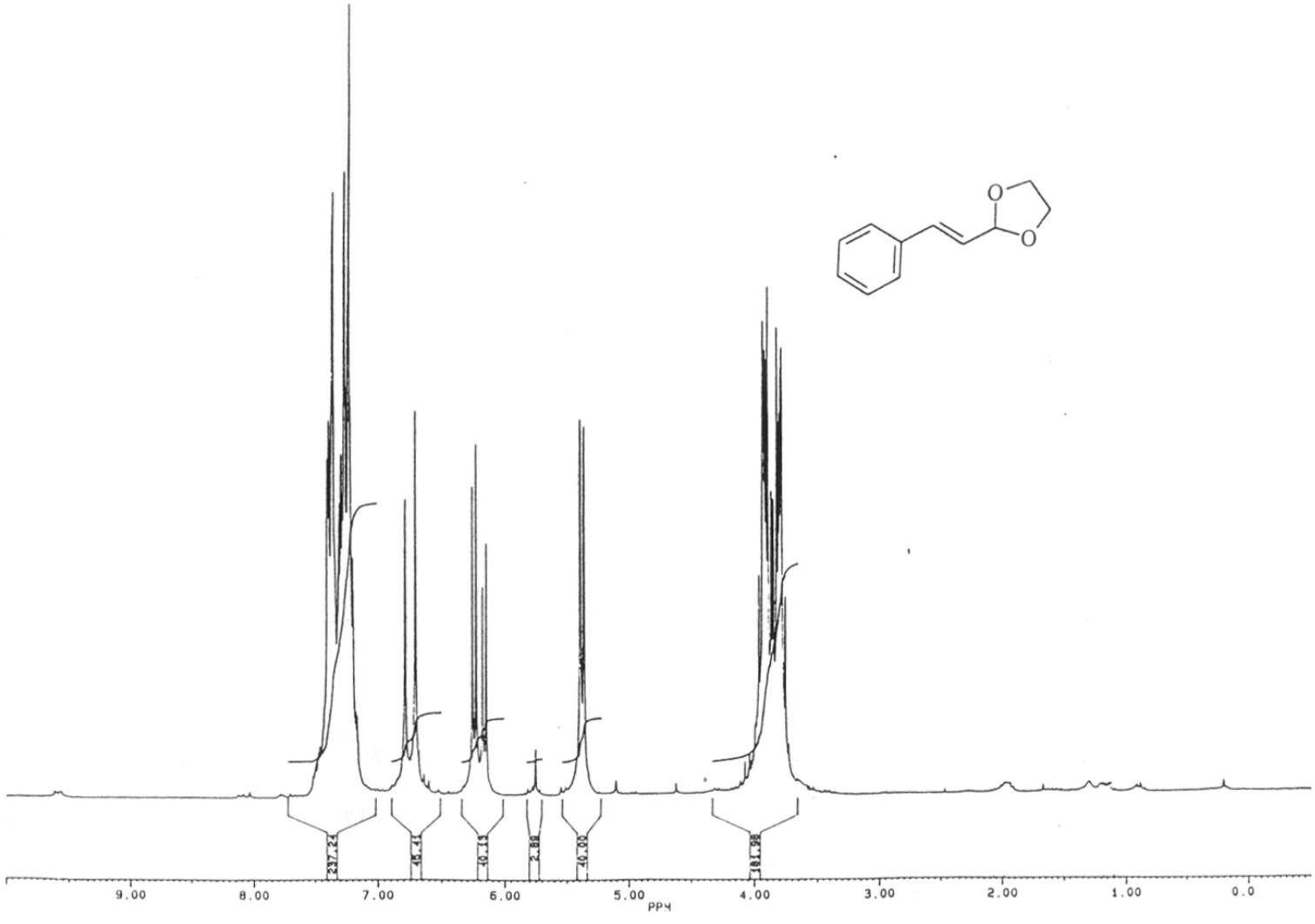



FIG III: PMR SPECTRUM OF THE COMPOUND 13p IN $CDCl_3$

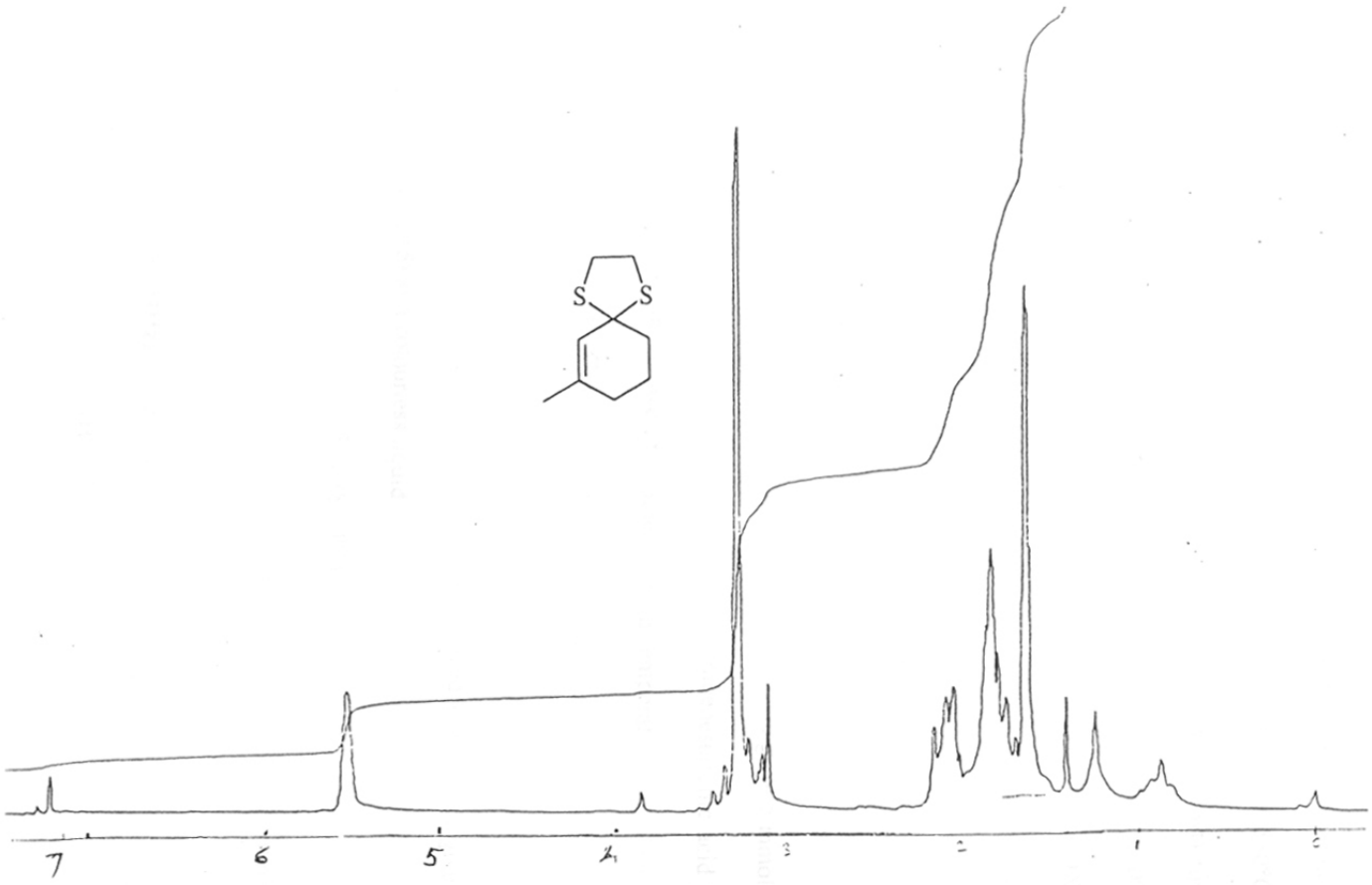



FIG IV: PMR SPECTRUM OF THE COMPOUND 15d IN $CDCl_3$

# 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 characterized 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.

**1-methoxy-1-cycloheptene (5)**

To a well stirred mixture of cycloheptanone (**6**) (5.0 g, 44.5 mmol) and trimethyl orthoformate (**7**) (9.44 g, 89 mmol) was added p-toluenesulfonic acid (46 mg, 0.245 mmol) at 0°C. It was allowed to come to room temperature and then directly heated under reflux for 8 hr. Gas chromatographic analysis on 10% DEGS at 90°C showed complete disappearance of the ketone **6**. Initially, methanol and methyl formate were distilled off. The residue was distilled under reduced pressure to give 1-methoxy-1-cycloheptene (**5**) as a colourless liquid.

**Yield :** 4.57 g (81.4%)

**B.P. :** 52-55°C/20 mm (Lit.[42] b.p.90-91°C/87 mm)

**IR (Neat) :** 910 and 1655 $cm^{-1}$.

**PMR ($CDCl_3$, 90 MHz):** δ 1.30-2.30 (m, 10H, -$\underline{CH_2}$-); 3.35 (s, 3H, -$\underline{OCH_3}$); 4.60 (t, 1H, J=7 Hz, -$\underline{CH}$).

**Methyl 7-oxoheptanoate (4)**

To a solution of 1-methoxy-1-cycloheptene (**5**) (5.0 g, 39.6 mmol) in dry methanol (50 ml) at -78°C, ozone was introduced for 3 hr. Excess of ozone dissolved in the solution was excluded by introducing argon into the mixture for 10 min. at the same temperature. To this solution was added dimethyl sulfide (5 ml) at -78°C and then the mixture was slowly warmed up to room temperature over a period of 2 hr. After stirring for 2 days at room temperature, the mixture was concentrated under reduced pressure and the residual oil was dissolved in a 1:1 mixture of diethyl ether and petroleum ether (100 ml) and the mixture was washed with water and dried ($Na_2SO_4$). After evaporation of the solvent using a rotary evaporator, the residual oil was distilled under reduced pressure to give methyl 7-oxoheptanoate (**4**) as a colourless oil.

**Yield :** 3.76 g (60%).

**B.P. :** 80-82°C/5 mm of Hg (Lit.[44] 82-86°C/5 mm of Hg).

**IR (Neat) :** 1020, 1720 and 2830 $cm^{-1}$.

**PMR ($CDCl_3$, 90 MHz):** δ 1.30-1.90 (m, 6H, 3 x $\underline{CH_2}$); 2.20-2.60 (m, 4H, 2 x $\underline{CH_2}CO$); 3.60 (s, 3H, $COO\underline{CH_3}$); 9.65 (br s, 1H, $\underline{CH}O$).

**1, 1-Dimethoxy cycloheptane (8)**

To a mixture of cycloheptanone (4 g, 35.6mmol) and trimethyl orthoformate (11.3 g, 106.8 mmol) was added clay (400 mg, 10% wt/wt) and it was stirred at room temperature for 12 hr. Completion of reaction was confirmed by GLC. Clay catalyst was filtered off, excess orthoformate was distilled off under reduced pressure, and the residue was distilled under vacuum to give 1, 1-dimethoxy cycloheptane (**8**) as a colourless liquid.

**Yield:** 4.17 g, (80%)

**B. P.:** 70°C/10 mm (Lit.[45] b.p. 73°C/10 mm)

**Benzaldehyde dimethyl acetal (10)**

To a mixture of benzaldehyde (5.3 g, 50 mmol) and trimethyl orthoformate (15.9 g, 0.15 mol) was added clay (530 mg 10% wt/wt) and it was stirred at room temperature for 3 hr. Completion of reaction was confirmed by GLC. Clay catalyst was filtered off, excess orthoformate was distilled off under reduced pressure, and the residue was distilled under vacuum to give benzaldehyde dimethyl acetal (**10**) as a colourless liquid.

**Yield :** 7.29 g (96%)

**B. P.:** 84-86°C/18 mm (Lit.[46] b.p. 194-6°C)

**PMR ($CDCl_3$, 90 MHz):** δ 3.30 (s, 6H, 2 x -O$\underline{CH_3}$); 5.40 (s, 1H, $\underline{CH}$); 7.30-7.45 (m, 5H, Ar$\underline{H}$).

**Benzaldehyde dipropyl thioacetal (11)**

To a mixture of benzaldehyde (1.06 g, 0.01 mol) and 1-propanethiol (2.28 g, 0.03 mol) was added clay (100 mg) and it was stirred for 4 hr at room temperature. Completion of the reaction was confirmed by GLC. The clay catalyst was filtered off and the filtrate was washed with water and dried ($Na_2SO_4$). After evaporation of the solvent using a rotatory evaporator, the residual oil was chromatographed using pet.ether -acetone as eluent to afford benzaldehyde dipropyl thioacetal (**11**) as a pale yellow viscous liquid.

**Yield :** 2.25 g (94%)

**PMR ($CDCl_3$, 90 MHz):** δ 0.90 (t, J = 8 Hz, 6H, 2 x $CH_2\underline{CH_3}$); 1.50 (m, 4H, 2 x $CH_2\underline{CH_2}CH_3$); 2.45 (t, J = 8 Hz, 4H, 2 x -S$\underline{CH_2}$); 4.75 (s, 1H, $\underline{CH}$); 7.0-7.35 (m, 5H, 5 x Ar$\underline{H}$).

**General procedure for acetalization and thioacetalization of carbonyl compounds**

In a general reaction procedure, a mixture of carbonyl compound (10 mmol), and ethane-1,2-diol or 1-hydroxyethane-2-thiol or ethane-1,2-dithiol or propane-1,3-dithiol (11 mmol) and clay 10% (wt/wt) in benzene (25 ml) was refluxed for 2 hr. After the reaction was complete (TLC), the clay was filtered off and the product was purified by flash chromatography to afford 1,3-dioxolane, 1,3-oxathiolane, 1,3-dithiolane or 1,3-dithiane respectively.

**1,3-Dioxolane, 2-propyl (13a)**

**Yield:** 91%

**PMR ($CDCl_3$, 90 MHz):** δ 0.85 (br t, 3H, $CH_2\underline{CH_3}$); 1.20-1.50 (m, 4H, $CH_3\underline{CH_2}$ $\underline{CH_2}$); 3.80-3.95 (m, 4H, -O$\underline{CH_2CH_2}$O-); 4.70 (t, J=7 Hz, 1H, -$\underline{CH}$).

**1,3-Dioxolane, 2-pentyl (13b)**

**Yield:** 90%

**PMR ($CDCl_3$, 200 MHz):** δ 0.80 (br t, 3H, $CH_2\underline{CH_3}$); 1.15-1.40 (m, 8H, $CH_3$-$(\underline{CH_2})_4$-); 3.70-3.90 (m, 4H, -O$\underline{CH_2CH_2}$O); 4.72 (t, J=7 Hz, 1H, -$\underline{CH}$).

**1,3-Dioxolane, 2-(1-propenyl) (13c)**

**Yield:** 92%

**PMR ($CDCl_3$, 90 MHz):** δ 1.70 (d, 3H, J = 7 Hz, $\underline{CH_3}$); 3.50-4.0 (m, 4H, O$\underline{CH_2}$ $\underline{CH_2}$O); 4.90-5.90 (m, 3H, $\underline{CH}$=$\underline{CH}$-$\underline{CH}$).

**1,3-Dioxolane, 2-phenyl (13i)**

**Nature:** Colourless liquid

**Yield:** 95%

**PMR ($CDCl_3$, 200 MHz):** δ 4.05-4.20 (m, 4H, O$\underline{CH_2}\underline{CH_2}$O-); 5.85 (s, 1H, -$\underline{CH}$); 7.40-7.60 (m, 5H, 5 x Ar$\underline{H}$).

**1,3-Dioxolane, 2-(4-methoxyphenyl) (13j)**

**Yield:** 92%

**IR (Neat):** 830, 1490 and 1600 $cm^{-1}$

**PMR ($CDCl_3$, 90 MHz):** δ 3.75 (s, 3H, ArO$\underline{CH_3}$); 3.90-4.00 (m, 4H, O$\underline{CH_2}\underline{CH_2}$O-); 5.70 (s, 1H, $\underline{CH}$); 6.70 (d, J = 8 Hz, 2H, 2 x Ar$\underline{H}$); 7.20 (d, J = 8 Hz, 2H, 2 x Ar$\underline{H}$).

**1,3-Dioxolane, 2-(4-chlorophenyl) (13k)**

**Yield:** 81%

**PMR ($CDCl_3$, 90 MHz):** δ 3.90-4.00 (m, 4H, O$\underline{CH_2}\underline{CH_2}$O-); 5.60 (s, 1H, $\underline{CH}$); 7.25 (d, J = 8 Hz, 2H, 2 x Ar$\underline{H}$); 7.45 (d, J = 8 Hz, 2H, 2 x Ar$\underline{H}$).

**1,3-Dioxolane, 2-(4-nitrophenyl) (13l)**

**Nature:** Solid

**Yield :** 75%

**M.P. :** 88-90°C (Lit.[47] m.p. 90.5°C )

**PMR ($CDCl_3$, 90 MHz):** δ 3.90 - 4.0 (m, 4H, -O$\underline{CH_2}\underline{CH_2}$O-); 5.80 (s, 1H, $\underline{CH}$); 7.67 (d, J = 8.5 Hz, 2H, 2 x Ar$\underline{H}$); 8.1 (d, J = 8.5 Hz, 2H, 2 x Ar$\underline{H}$).

**1,3-Dioxolane, 2,2'-p-phenylenebis (13m)**

**Nature:** White solid

**Yield :** 92%

**M.P. :** 87°C (Lit[48] m.p. 89-90°C)

**PMR ($CDCl_3$, 90 MHz):** δ 4.0-4.20 (m, 8H, -O$\underline{CH_2CH_2}$O-); 5.80 (s, 2H, -$\underline{CH}$), 7.50 (s, 4H, 4 x Ar$\underline{H}$).

**MS (m/z):** 222 ($M^+$, 15); 177 (70); 149 (20); 133 (100); 105 (45).

**1,3-Dioxolane, 2-(3,4,5-trimethoxyphenyl) (13n)**

**Nature:** Viscous oil

**Yield :** 86%

**PMR ($CDCl_3$, 90 MHz):** δ 3.60 (s, 3H, ArO$\underline{CH_3}$); 3.70 (s, 6H, 2 x ArO$\underline{CH_3}$); 3.80-4.0 (m, 4H, -O$\underline{CH_2CH_2}$O); 5.60 (s, 1H, $\underline{CH}$); 6.60 (s, 2H, 2 x Ar$\underline{H}$).

**1,3-Dioxolane, 2-(2 -furfuryl) (13o)**

**Nature:** Yellowish viscous liquid

**Yield :** 93%

**PMR ($CDCl_3$, 200 MHz):** δ 3.95-4.15 (m, 4H, -O$\underline{CH_2CH_2}$O-); 5.90 (s, 1H, $\underline{CH}$); 6.34 (m, 1H, Ar$\underline{H}$); 6.44 (m, 1H, Ar$\underline{H}$); 7.41 (m, 1H, Ar$\underline{H}$).

**1,3-Dioxolane, 2-styryl (13p)**

**Yield :** 93%

**PMR ($CDCl_3$, 200 MHz):** δ 3.80-4.05 (m, 4H, -O$\underline{CH_2CH_2}$O-); 5.40 (d, J = 7.5 Hz 1H, $\underline{CH}$); 6.20-6.30 (dd, J = 7.5 Hz, J = 7.5 Hz, 1H, -

CH=CH-CH); 6.8 (d, J = 17 Hz, 1H, -CH=CH-CH); 7.3-7.5 (m, 5H, 5 x ArH).

**$^{13}$C-NMR ($CDCl_3$, 50 MHz):** 63.23; 103.41; 125.18; 126.59; 128.26; 128.65; 134.17; 135.55.

**1,3-Oxathiolane, 2-phenyl (14i)**

**Nature:** Colourless liquid

**Yield :** 95%

**PMR ($CDCl_3$, 200 MHz):** δ 3.0-3.25 (m, 2H, -S$CH_2$); 4.10-4.50 (m, 2H, -O$CH_2$); 6.1 (s, 1H, CH); 7.57-7.80 (m, 5H, 5 x ArH).

**1,3-Oxathiolane, 2-(4-methoxyphenyl) (14j)**

**Nature:** Viscous liquid

**Yield :** 86%

**PMR ($CDCl_3$, 90 MHz):** δ 3.10-3.15 (m, 2H, S$CH_2$); 3.75 (s, 3H, -O$CH_3$); 3.8-4.2 (m, 2H, -O$CH_2$); 5.90 (s, 1H, CH); 6.70-6.80 (m, 2H, 2 x ArH); 7.20-7.25 (m, 2H, 2 x ArH).

**1,3-Oxathiolane, 2,2'-p-phenylenebis (14 m)**

**Nature:** Yellow solid

**Yield :** 94%

**M.P.:** 123°C

**PMR ($CDCl_3$, 200 MHz):** δ 2.95-3.12 (m, 4H, -S$CH_2$); 4.10-4.40 (m, 4H, -O$CH_2$); 6.10 (s, 2H, 2 x -CH); 7.5-7.8 (m, 4H, 4 x ArH).

**Acetopheonone oxathiolane (14q)**

**Nature:** Colourless liquid

**Yield:** 89%

**PMR ($CDCl_3$, 90 MHz):** 1.88 (s, 3H, $\underline{CH_3}$); 2.85-3.3 (m, 2H, -S$\underline{CH_2}$); 3.7-4.5 (m, 2H, -O$\underline{CH_2}$); 7.15-7.55 (m, 5H, 5 x Ar$\underline{H}$).

**Benzophenone oxathiolane (14r)**

**Yield :** 81%

**PMR ($CDCl_3$, 200 MHz):** δ 3.10 (t, J = 7 Hz, 2H, S$\underline{CH_2}$); 4.10 (t, J = 7 Hz, 2H, O$\underline{CH_2}$); 7.20-7.60 (m, 10H, 10 x Ar$\underline{H}$).

**1,3-Dithiolane, 2-propyl (15a)**

**Nature:** Pale yellow viscous liquid

**Yield :** 92%

**PMR ($CDCl_3$, 90 MHz):** δ 0.80-1.10 (br t, 3H, $\underline{CH_3}$); 1.20-2.0 (m, 4H, $\underline{CH_2CH_2}$); 3.20 (s, 4H, S$\underline{CH_2CH_2}$S); 4.40 (t, J = 7 Hz, 1H, -$\underline{CH}$).

**1,3-Dithiolane, 2-(1-propenyl) (15c)**

**Nature:** Pale yellow viscous liquid

**Yield :** 70%

**PMR ($CDCl_3$, 90 MHz):** δ 1.65 (d, J = 7 Hz, 3H, $\underline{CH_3}$); 3.15 (s, 4H, S$\underline{CH_2CH_2}$S); 4.85 (d, J=7 Hz, 1H, $\underline{CH}$); 5.30-5.70 (m, 2H, $\underline{CH}$=$\underline{CH}$).

**3-Methyl-2-cyclohexene-1-one-thioketal (15d)**

**Yield :** 90%

**PMR ($CDCl_3$, 90 MHz):** δ 1.70 (s, 3H, $\underline{CH_3}$); 1.75-2.15 (m, 6H, 3 x $\underline{CH_2}$); 3.3 (s, 4H, $S\underline{CH_2CH_2}S$); 5.50 (s, 1H, $\underline{CH}$).

**MS (m/z):** 186 ($M^+$, 42); 158 (80); 130 (20); 126 (79); 111 (41); 98 (42); 93 (100); 77 (52); 65 (22); 58 (32).

**5-Isopropenyl-2-methyl-2-cyclohexen-1-spiro-2'-(1,3-dithiolane) or carvone ethylenethioketal (15e)**

**Nature:** Viscous oil

**Yield :** 72%

**IR (Neat) :** 1630 $cm^{-1}$.

**PMR ($CDCl_3$, 200 MHz):** δ 1.76 (s, 3H, $\underline{CH_3}$); 1.92 (s, 3H, $\underline{CH_3}$); 1.70-2.50 (m, 5H, 2 x $\underline{CH_2}$ + $\underline{CH}$); 3.29 (s, 4H, $S\underline{CH_2CH_2}S$); 4.72 (s, 2H, $=\underline{CH_2}$); 5.40-5.60 (m, 1H, $=\underline{CH}$).

**MS (m/z):** 226 ($M^+$, 28); 166 (65); 133 (100); 105 (57); 91 (70).

**Camphor ethylenethioketal (15f)**

**Nature:** Colourless oil

**Yield :** 85%

**PMR ($CDCl_3$, 90 MHz):** δ 0.90 (s, 3H, $\underline{CH_3}$); 1.03 (s, 6H, 2 x $\underline{CH_3}$); 1.10-2.70 (m, 7H, $3\underline{CH_2}$ + $\underline{CH}$), 2.90-3.40 (m, 4H, $S\underline{CH_2CH_2}S$).

**MS (m/z)** 228 ($M^+$, 35); 200 (100); 185 (15); 118 (90).

**Cyclohexanone ethylenethioketal (15g)**

**Nature:** Colourless viscous liquid

**Yield :** 80%

**PMR ($CDCl_3$, 300 MHz):** δ 1.33-1.40 (m, 2H, $\underline{CH_2}$); 1.57-1.65 (m, 4H, 2 x $\underline{CH_2}$); 1.95-2.01 (m, 4H, 2 x $\underline{CH_2}$); 3.25 (s, 4H, $S\underline{CH_2}\underline{CH_2}S$).

**$^{13}$C-NMR ($CDCl_3$, 50 MHz):** δ 23.16; 24.81; 25.96; 28.34; 31.73; 38.12; 42.68; 68.60.

**MS (m/z):** 174 ($M^+$, 50); 146 (52); 131 (100); 118 (17); 114 (22).

**Menthone ethylenethioketal (15h)**

**Nature:** Colourless oil

**Yield :** 65%

**PMR ($CDCl_3$, 90 MHz):** δ 0.75-1.0 (m, 9H, 3 x $\underline{CH_3}$); 1.15-1.90 (m, 7H, 3 x $\underline{CH_2}$ + $\underline{CH}$); 2.05-2.60 (m, 2H, 2 x $\underline{CH}$); 3.25 (s, 4H, $S\underline{CH_2}\underline{CH_2}S$).

**1,3-Dithiolane, 2-phenyl (15i)**

**Nature:** Colourless liquid

**Yield :** 98%

**PMR ($CDCl_3$, 200 MHz):** δ 3.10-3.40 (m, 4H, $S\underline{CH_2}\underline{CH_2}S$); 5.50 (s, 1H, $\underline{CH}$); 7.0-7.50 (m, 5H, 5 x Ar$\underline{H}$).

**MS (m/z):** 182 ($M^+$, 68); 153 (79); 121 (100); 77(30).

**1,3-Dithiolane, 2,2'-phenylenebis (15m)**

**Nature:** Solid

**Yield :** 88%

**M.P. :** 198°C (Lit.[35] m.p. 198°C).

**PMR ($CDCl_3$, 200 MHz):** δ 3.35 (m, 8H, 2 x $S\underline{CH_2CH_2}S$); 5.48 (s, 2H, 2 x $\underline{CH}$); 7.30 (s, 4H, 4 x Ar$\underline{H}$).

**1,3-Dithiolane, 2-(2 -furfuryl) (15o)**

**Nature:** Pale yellow viscous liquid

**Yield :** 85%

**PMR ($CDCl_3$, 90 MHz):** δ 3.30 (s, 4H, $S\underline{CH_2CH_2}S$); 5.50 (s, 1H, $\underline{CH}$); 6.13-6.15 (m, 2H, 2 x Ar$\underline{H}$); 7.22-7.24 (m, 1H, Ar$\underline{H}$).

**1,3-Dithiolane, 2-phenyl-2-methyl (15q)**

**Nature:** Viscous colourless oil

**Yield :** 97%

**PMR ($CDCl_3$, 90 MHz):** δ 2.05 (s, 3H, $\underline{CH_3}$); 3.30 (s, 4H, $S\underline{CH_2CH_2}S$); 7.05-7.30 (m, 3H, 3 x Ar$\underline{H}$); 7.55-7.70 (m, 2H, 2 x Ar$\underline{H}$).

**MS (m/z):** 196 ($M^+$, 15); 181(21); 167(20); 105 (100); 77 (82); 60 (90).

**1,3-Dithiolane, 2,2-diphenyl (15r)**

**Nature:** Solid

**Yield :** 75%

**M.P. :** 103-105°C (Lit.[49] m.p. 105°C)

**PMR ($CDCl_3$, 90 MHz):** δ 3.40 (s, 4H, $S\underline{CH_2CH_2}S$); 7.14-7.35 (m, 6H, 6 x Ar$\underline{H}$); 7.45-7.65 (m, 4H, 4 x Ar$\underline{H}$).

**MS (m/z):** 258 ($M^+$,30), 229 (95); 165 (100).

**Camphor trimethylenemercaptol (16f)**

**Yield :** 68%

**PMR ($CDCl_3$, 90 MHz):** δ 0.9 (s, 3H, $\underline{CH_3}$); 1.05 (s, 3H, $\underline{CH_3}$); 1.15 (s, 3H, $\underline{CH_3}$); 1.25-2.25 (m, 9H, 4 x $\underline{CH_2}$ + $\underline{CH}$); 2.40-3.10 (m, 4H, $S\underline{CH_2}CH_2\underline{CH_2}S$).

**Menthone trimethylenemercaptol (16h)**

**Nature:** Solid

**Yield :** 60%

**M.P. :** 41°C (Lit.[50] m.p. 42°C)

**PMR ($CDCl_3$, 90 MHz):** δ 0.75 - 1.05 (m 9H, 3 x $\underline{CH_3}$); 1.85-2.25 (m, 11H, 4 x $\underline{CH_2}$ + 3 x $\underline{CH}$); 2.35-3.35 (m, 4H, -$S\underline{CH_2}CH_2\underline{CH_2}$).

**MS (m/z):** 244 ($M^+$, 22); 95 (100), 81 (90); 71 (80).

**1,3-Dithiane, 2-Phenyl (16i)**

**Nature:** Solid

**Yield :** 95%

**M.P. :** 73°C (Lit.[51] m.p. 73°C)

**PMR ($CDCl_3$, 90 MHz):** δ 1.65-2.35 (m, 2H, $CH_2\underline{CH_2}CH_2$); 2.75-3.40 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}$); 5.15 (s, 1H, $\underline{CH}$); 7.15-7.60 (m, 5H, 5 x Ar$\underline{H}$).

**1,3-Dithiane, 2-(2 -furfuryl) (16o)**

**Nature:** Solid

**Yield :** 64%

**M.P. :** 42°C (lit.[52] m.p. 43°C)

**PMR ($CDCl_3$, 90 MHz):** δ 1.85- 2.25 (m, 2H, $CH_2\underline{CH_2}CH_2$); 2.80-3.05 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}$); 5.20 (s, 1H, $\underline{CH}$); 6.20-6.40 (m, 2H, 2 x Ar$\underline{H}$); 7.25-7.40 (m, 1H, Ar$\underline{H}$).

**1,3-Dithiane, 2-phenyl-2-methyl (16q)**

**Nature:** Solid

**Yield :** 72%

**M.P. :** 33°C (Lit.[51] m.p. 34°C)

**PMR ($CDCl_3$, 90 MHz):** δ 1.75 (s, 3H, $\underline{CH_3}$); 1.82-2.05 (m, 2H, $CH_2\underline{CH_2}CH_2$); 2.65-2.75 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}$); 7.18-7.50 (m, 3H, 3 x Ar$\underline{H}$); 7.85-8.0 (m, 2H, 2 x Ar$\underline{H}$).

**1,3-Dithiane, 2,2'-diphenyl (16r)**

**Nature:** Solid

**Yield :** 65%

**M.P. :** 114°C (lit.[53] m.p. 114°C)

**PMR ($CDCl_3$, 90 MHz):** δ 1.86-2.15 (m, 2H, $CH_2\underline{CH_2}CH_2$); 2.65-2.90 (m, 4H, $\underline{CH_2}CH_2\underline{CH_2}$); 7.24-7.80 (m, 10H, 10 x Ar$\underline{H}$).

**MS (m/z):** 272 ($M^+$, 40); 198 (95); 165 (100)

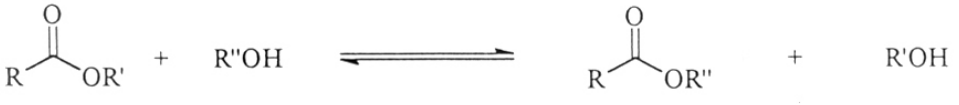
# Section B

# Transesterification and Transthiolesterification over Natural Kaolinitic Clay

## Introduction

Transesterification is a process where an ester is transformed into another ester through interchange of the alkoxy moiety (Scheme-11).[54] Since the reaction is an equilibrium process, the transformation occurs essentially by simply mixing two components. However, it has been shown that the reaction is accelerated by Lewis acid catalysts (such as boron tribromide,[55] anhydrous aluminium trichloride embedded in polystryene-divinyl benzene[56]), Bronsted acid catalysts (such as hydrochloric, phosphoric, sulfonic, sulfuric or p-toluenesulfonic acid[57]), or basic catalysts (such as metal alkoxides[58], metal carbonates[59]).

**Scheme 11**



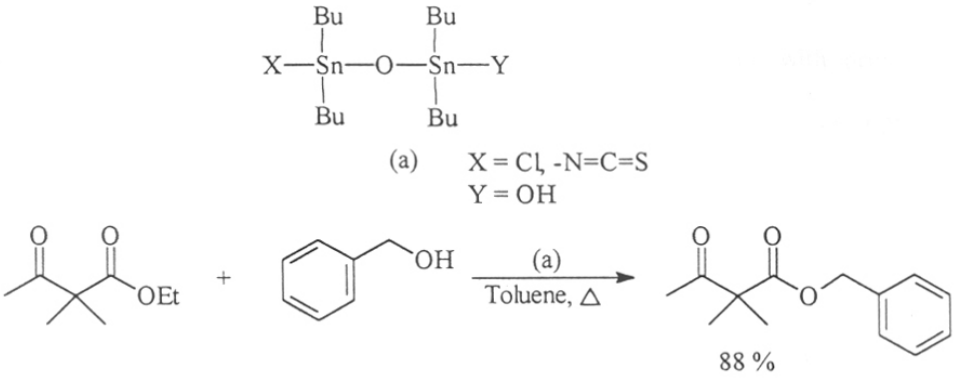

Transesterification is more advantageous than the ester synthesis from carboxylic acid and alcohol, due to poor solubility of some of the acids in organic solvents, whereas the esters are commonly soluble in most of the solvents. Some esters especially methyl or ethyl esters are readily or commercially available and thus serve as starting materials for transesterification. Transesterification is applicable in paint industry. It has long history in industry as well as production of esters of oils and fats. It also plays an important role in polymerization.[54]

However, it is apparent that the reaction under the acidic or basic conditions does not meet the requirements of modern synthetic chemistry, which needs the highly efficient and selective reaction conditions. Also, efforts are being continued to make the reaction catalytic, milder and more selective.

Recently Otera et al.[60] reported a very convenient and efficient method for transesterification. It was found that transesterification could be carried out under practically neutral conditions using 1,3-disubstituted tetrabutyldistannoxane (a). It was

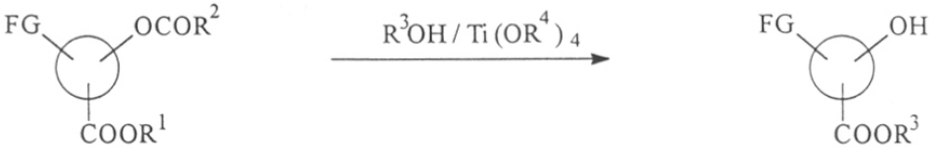
shown that various type of esters were synthesized under very mild conditions and this methodology was applied to the stereo and regioselective synthesis of trisubstituted α,β-unsaturated carboxylic acids. Transesterifications of non-enolizable β-ketoesters were also achieved by this catalyst (Scheme-12).

**Scheme 12** Otera et al.[60]




Titanium (IV) alkoxides[61] were found to be useful for carrying out transesterification of various functionalized substrates (Scheme-13).

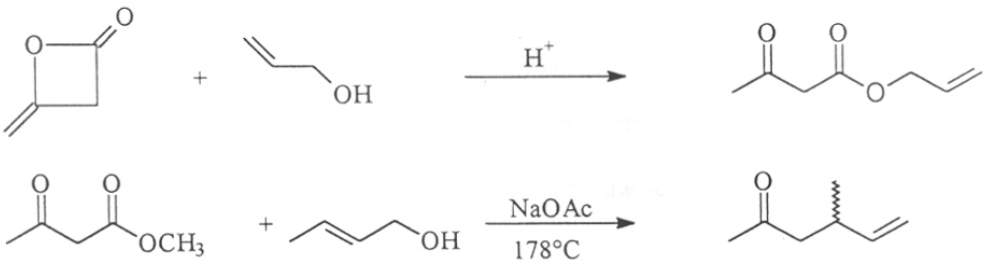
**Scheme 13** Seebach et al.[61]




FG = Functional groups such as- Si $(CH_3)_3$, $NO_2$, CN, Br, OH

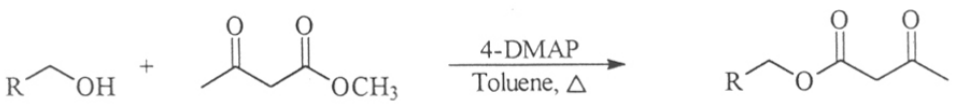
Titanate mediated transesterification is extremely mild but is found to be unsuccessful to give allyl ester from an ethyl ester. Previous methods for the formation of the allylic acetoacetate that are based on the acid catalyzed opening of diketene limits the range of available compounds to esters of acetoacetic acids. Potentially more general methods that rely on basic catalysis at higher temperature either failed or led to decarboxylated rearrangement product [ Carroll rearrangement] [62] (Scheme-14).

**Scheme 14**



Taber et al.[63] found that reaction of methyl acetoacetate with primary or secondary alcohol in the presence of a catalytic amount of 4-(dimethylamino) pyridine (4-DMAP) in toluene solution at reflux gave respective acetoacetates (Scheme-15).

**Scheme 15** Taber et al.[63]

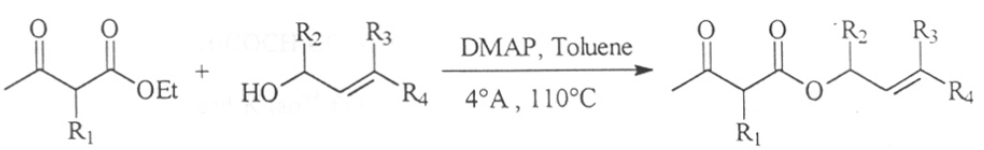


8 examples

Although Taber's DMAP promoted method is effective for transesterification of primary and secondary alcohols, it fails in the case of long chain alcohols due to decomposition of the acetoacetate. Only enolizable β-keto esters react and tertiary alcohols do not participate in the reaction.

Transesterification of β-keto ester with allylic alcohol was attempted by Gilbert et al.[64] using DMAP as catalyst but it led to decarboxylative rearrangement. They solved this problem by using molecular sieves (4 $^{0}$A) as it removed ethanol formed during transesterification and shifted the equilibrium in favour of the allylic ester (Scheme-16).

**Scheme 16** Gilbert et al.[64]



Chavan et al.[65a] reported a tin-based superacid for the transesterification of β-keto esters. This catalyst is effective for primary, secondary and tertiary alcohols but failed with aromatic β-keto esters. Even though aromatic β-keto esters could be transesterified with Hβ-zeolite,[65b] it fails to transesterify primary alcohols chemoselectively in the presence of secondary ones.

Thus, development of a new catalytic method, which can effectively overcome problems experienced in the transesterification reaction, should heighten the synthetic scope of the reaction. In this connection, the use of heterogeneous catalysts in the liquid phase offers several advantages compared with their homogeneous counterparts, including ease of recovery, recycling and enhanced stability.

## **β-Keto thiol ester**: Literature review

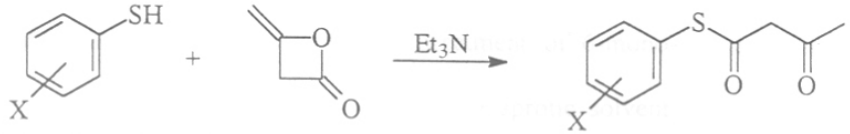
The role of thiol esters as acylating agents in biochemical processes and their high reactivity with various nucleophiles has made them attractive synthetic intermediates in a variety of chemical transformations. [66]

The known process of getting β-keto thiol ester is the reaction of thiol with diketene.[67] But it suffers from many disadvantages due to low stability, high volatility and toxicity of diketene, and also to the fact that it is not readily transformed into its substituted derivatives.

Baker et al.[68] reported a Claisen condensation method for the synthesis of S-alkyl-β-keto thiol ester. Ethyl thiolacetate, $CH_3COSC_2H_5$ in the presence of sodium metal condenses in a similar way like ethyl acetate, and forms a sulfur analog of acetoacetic ester $CH_3COCH_2COSCH_2CH_3$.

Nakazumi and Kitao[69] found that reaction of benzenethiols and diketene in the presence of triethylamine gave β-keto thiol esters (Scheme-17).

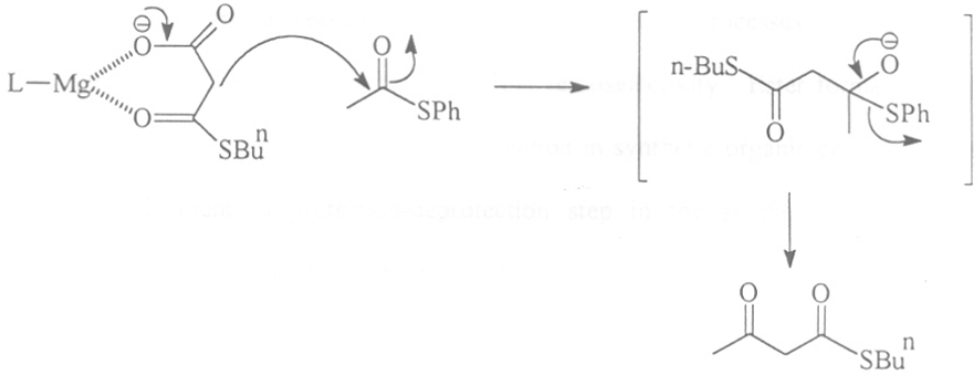
**Scheme 17** Nokazumi and Kitao[69]




X = H, p-$CH_3$, p-$OCH_3$

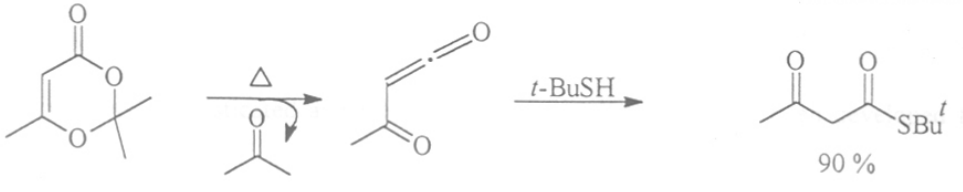
Kobuke and Yoshida[70] reported a new method for the preparation of S-n-butyl acetothiolacetate. They carried out intermolecular acetyl transfer reaction in thiolmalonate-thiolacetate system under much milder conditions. Thus, n-butyl thiolmalonate was reacted with 1 equiv. of phenyl thiolacetate in the presence of magnesium acetate and imidazole in THF at room temperature for 80 hr, to yield 60% of S-n-butyl acetothiolacetate (Scheme-18).

**Scheme 18** Kobuke and Yoshida[70]




Alvarado et al.[71] replaced the diketene by 1,3-dioxin-4-ones as acetoacetylating reagent and found that treatment of *t*-butyl thiol with 2,2,6-trimethyl-*4H*-1,3-dioxin-4-one, gave 90% yield of S-*tert*butyl acetothiolacetate (Scheme-19).

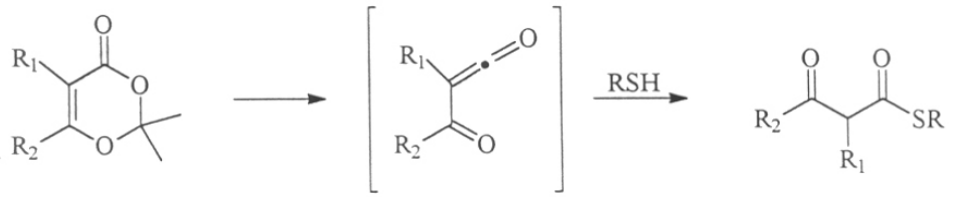
**Scheme 19** Alvarado et al.[71]



The best synthesis of S-alkyl-β-keto thiol ester was reported by Sakaki et al.[72] In this methodology they showed that treatment of 6-mono-and 5,6-disubstituted 1,3-dioxin-4-ones and thiols in an appropriate aprotic solvent gave S-alkyl β-keto thiol esters in high yields. An important feature of this methodology is the introduction of a variety of substituents at desired position.

**Scheme 20**

Sakaki et al.



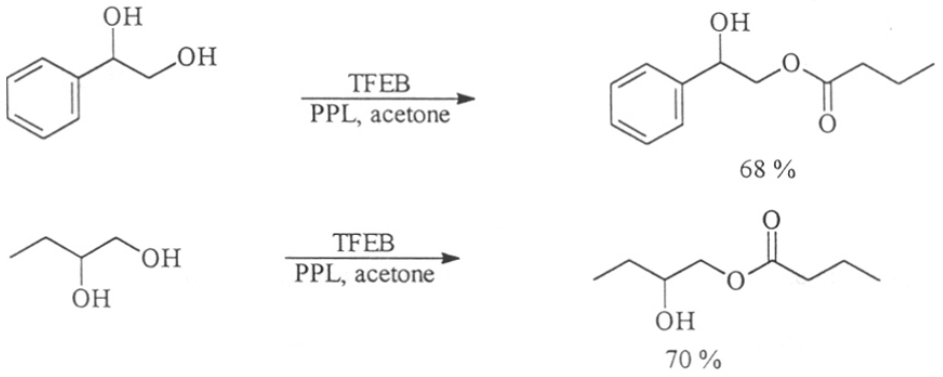

## Selectivity study in transesterification

There is an increasing demand for efficient processes in chemical transformations with high degree of stereo- and regioselectivity. Ester formation and hydrolysis reactions are getting increasing attention in synthetic organic chemistry due to their involvement in protection-deprotection step in the synthesis of complex molecules. Special care is, however required in order to carry out these reactions in regio-and chemoselective manner.

Acylation of alcohols is one of the most fundamental transformations in organic chemistry. In general acylations of alcohols are carried out using hyper-reactive acylating reagents such as acyl chlorides or acid anhydrides. However, it is considerably difficult to conduct chemoselective acylation of alcohols containing polyfunctional groups by use of such reactive acylating reagents. Often chemoselective acylation of the primary hydroxyl group of a primary-secondary diol is required, and several biocatalysts, sophisticated and relatively expensive reagents have been developed for this purpose.

Parmar et al.[73] found that Lipases from *Porcine pancreas* (PPL) and *Candida cylindracea* (CCL) (Scheme-21) in different organic solvents allow discrimination of the primary and secondary hydroxyl groups, and also between two primary hydroxyl groups towards acylation with 2,2,2-trifluoroethyl butyrate (TFEB) in diols and triols with high regioselectivity.

**Scheme 21** Parmar et al.[73]

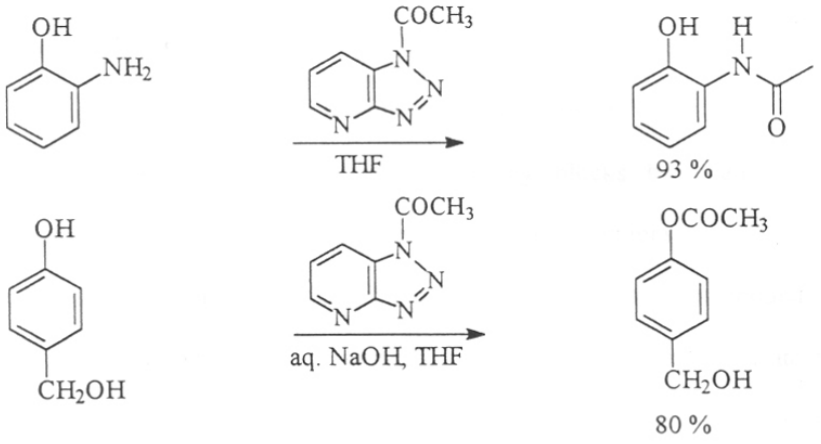



Mukaiyama et al.[74] found that selective acylation of a primary carbinol group of diols containing primary and secondary carbinol or exclusive O-acylation of aromatic amino alcohols, can be achieved using 2,2-bipyridyl-6-yl carboxylates and cesium fluoride (Scheme-22).

**Scheme 22** Mukaiyama et al.[74]

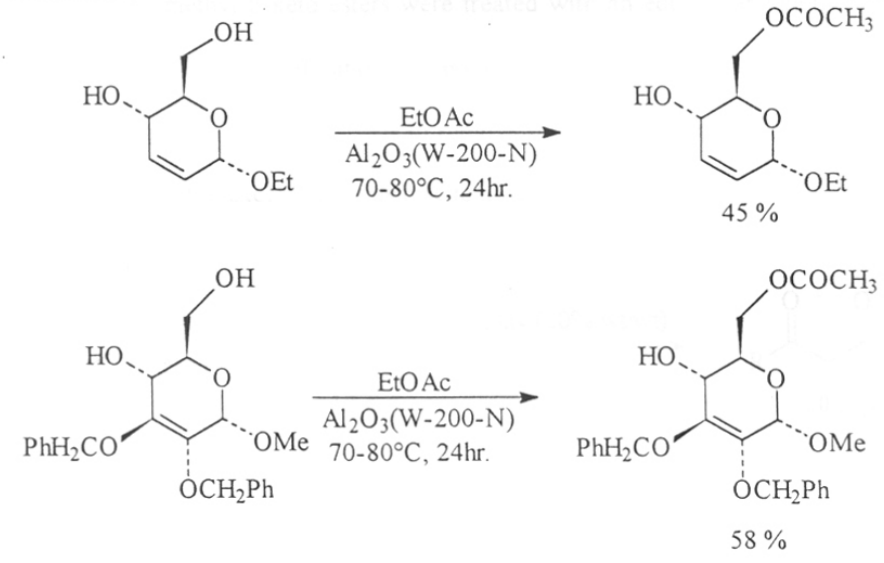

Chemoselective acylation of aminophenols and hydroxyalkylphenols was achieved by Paradisi et al.[75] using 1-acetyl-v-triazolo [4,5-b] pyridine (Scheme-23).

**Scheme 23** Paradisi et al.[75]




Posner et al.[76] reported a neutral, mild, simple and extremely convenient new method for effective acetylation of primary alcohols even in the presence of some base-sensitive (e.g. chlorohydrin) and acid sensitive (e.g. ethylenic, pyridyl) primary alcohols using commercially available Woelm-200-neutral chromatographic alumina at room temperature (Scheme -24 ).

**Scheme 24** Posner et al.[76]



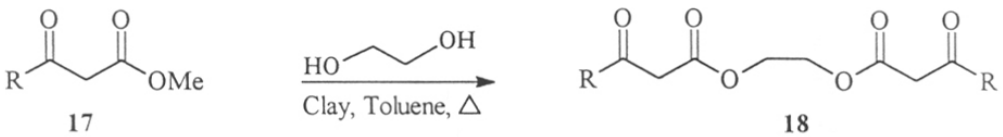
## Present work

### Transesterification of β-keto esters

β-Keto esters[77] serve as important synthons by virtue of the ease with which they can be transformed to chiral building blocks by chemical or enzymatic transformations as well as a tool for chain extension reactions.

During our initial work on protection of carbonyl compounds over natural kaolinitc clay, when it was attempted to protect methyl acetoacetate with ethylene glycol, it was quite surprising to note that instead of protection transesterification took place (Scheme-25). This reaction suggested that this catalyst can be useful for transesterification reaction.

**Scheme 25**



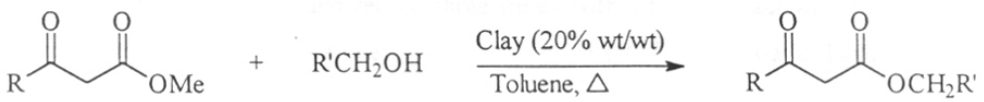

**17**

$R = CH_3$

**18**

When methyl β-keto esters were treated with an equimolar amount of primary alcohols in the presence of catalytic amount of natural kaolinitic clay under reflux in toluene using Dean-Stark apparatus to remove methanol, the corresponding esters were obtained in good to excellent yields ( Scheme-26 ).

**Scheme 26**




**19 a-p**

**20 a-p**

**Table-4:** Transesterification of β-keto esters with different alcohols catalysed by natural kaolinitica and montmorillonite K10 clays.

| Entry | Substrate **17** R | Alcohol **19 a-p** $R^1$ | t(h) | Product (**20 a-p**)[b] Yield(%)[c] | |
|---|---|---|---|---|---|
| | | | | Kaolinitic | Mont.K10 |
| a | Me | Benzyl | 3 | 85 | 86 |
| b | Me | 2-Phenylethyl | 3 | 87 | 80 |
| c | Me | Furfuryl | 4 | 84 | 85 |
| d | Me | Cinnamyl | 6 | 80 | 72 |
| e | Me | Allyl | 6 | 75 | - |
| f | Me | Cyclohexyl | 12 | 0d | - |
| g | Me | Geranyl | 8 | 70 | - |
| h | Me | Crotyl | 8 | 80 | 75 |
| i | Me | Propargyl | 7 | 79 | 80 |
| j | Me | Dodecyl | 10 | 75 | 70 |
| k | Me | Menthyl | 12 | 0d | 0d |
| l | Me | t-Butyl | 12 | 0d | 0d |
| m | Me | Octadecyl | 11 | 71 | 70 |
| n | Me | Tetrahydrofurfuryl | 4 | 90 | 84 |
| o | Me | 2-Chloroethyl | 4 | 84 | 75 |
| p | Ph | Propargyl | 9 | 51 | - |

a: Catalyst was recovered and reused three times without loss of activity; b: Reaction was monitored on TLC and all new compounds gave satisfactory data; c: Isolated yield; d: No reaction.

Table-4 attests the present method to be applicable for a wide range of compounds. Salient features of the methodology are as follows:

(i) Methyl acetoacetate is successfully transformed into synthetically useful esters.

(ii) A variety of primary alcohols containing sensitive functional groups can be employed in this transformation.

(iii) When β-keto esters with an aliphatic moiety were transesterified with alcohols, the corresponding transesterified products were obtained in high yields. However, for an aromatic moiety of β-keto ester, the corresponding transesterified product was obtained in moderate yield (entry-p).

(iv) A special feature of this method is that unsaturated alcohols like crotyl, cinnamyl, propargyl and allyl underwent transesterification affording unsaturated esters in high yields, although it should be noted that transesterification with allylic alcohols is generally difficult with other catalysts.

(v) Table-4 shows the preparation of long carbon chain esters which are often a starting material for the polymer industry (entry j & m).

(vi) Reaction fails in the case of secondary and tertiary alcohols, (entries f, k, l) and is selective only for primary alcohols.

(vii) In agreement with Mori's procedure[78] in which KCN was employed, no isomerization of double bond has occurred during transesterification (entry g).

(viii) It is important to mention that the reaction appears to be specific only for transesterification of β-keto ester. Other esters like normal esters, unsaturated esters, α-keto esters as well as γ-keto esters fail to undergo the reaction which is a limitation of the present method. This procedure works particularly well on multigram scale.

In order to gauge the scope and generality of the method, the following experiments were carried out as shown in Scheme-27.

One of the most important features of the methodology is that even phenols could be used to transesterify β-keto esters efficiently. In a similar manner aniline underwent reaction to give the corresponding amidation product. When the keto group at the β-position is protected, then transesterification fails. In the case of α-methyl-β-keto ester

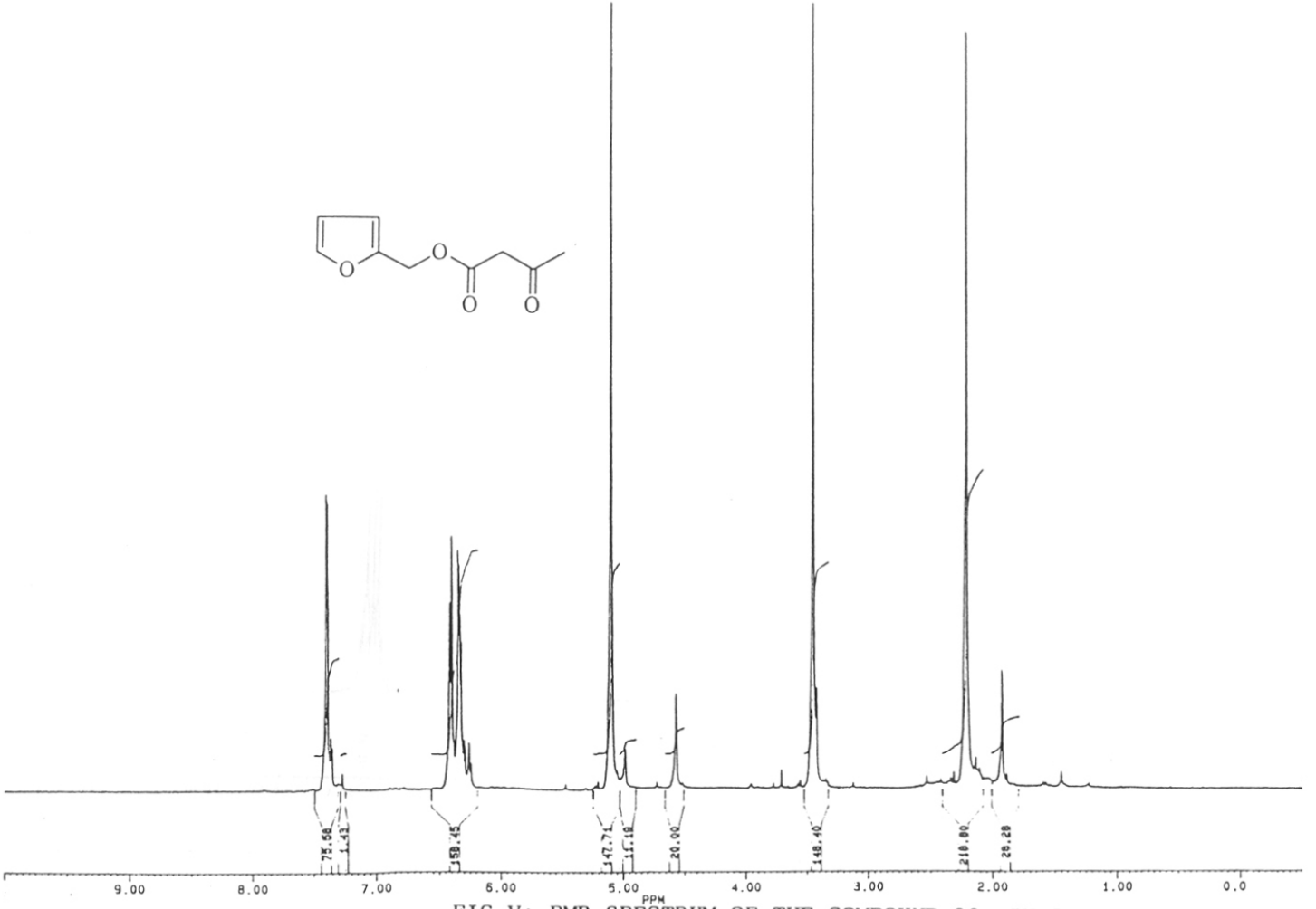



FIG V: PMR SPECTRUM OF THE COMPOUND 20c IN CDC13

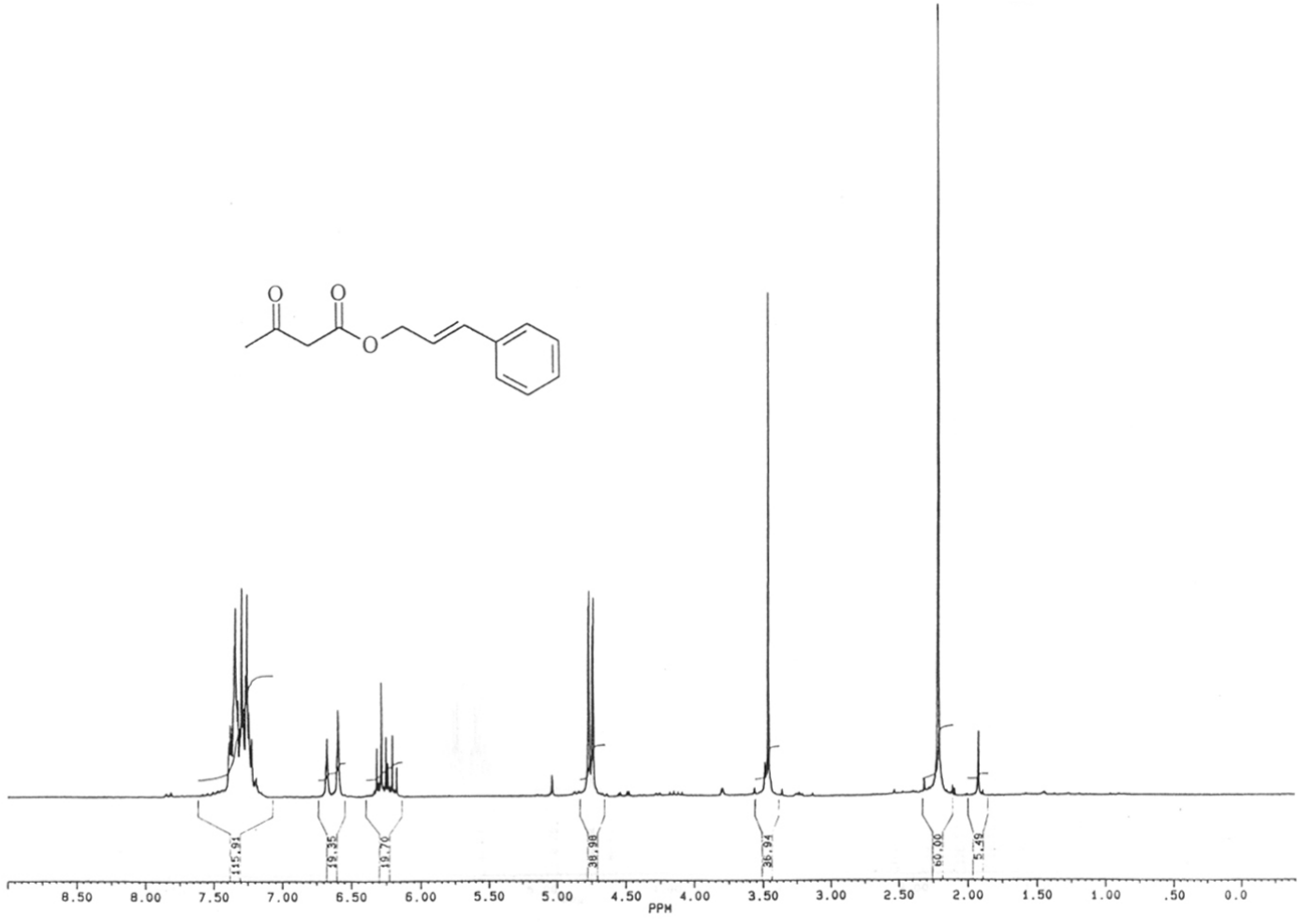



FIG VI: PMR SPECTRUM OF THE COMPOUND 20d IN $CDCl_3$

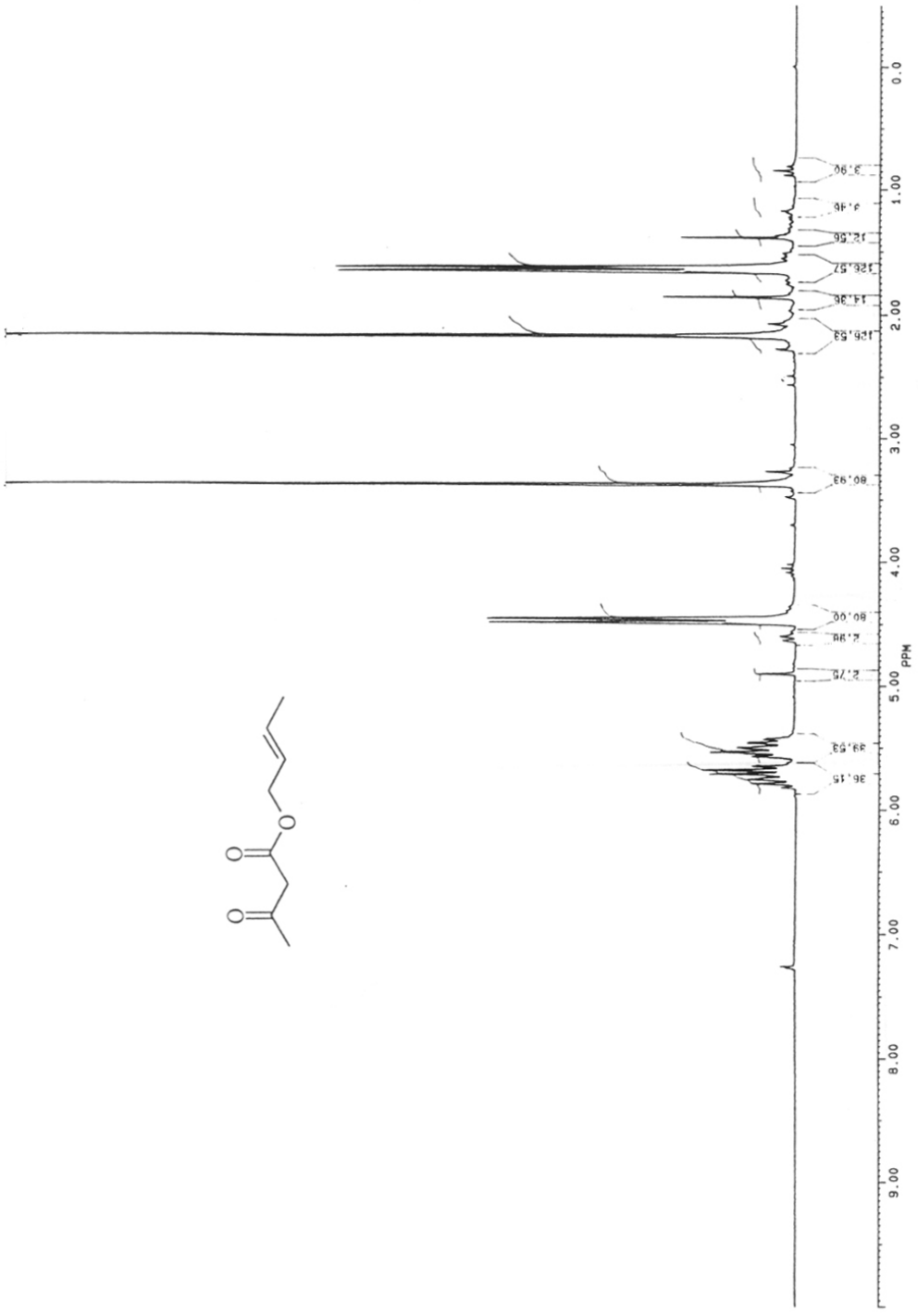



FIG VII: PMR SPECTRUM OF THE COMPOUND 20h IN $CDCl_3$

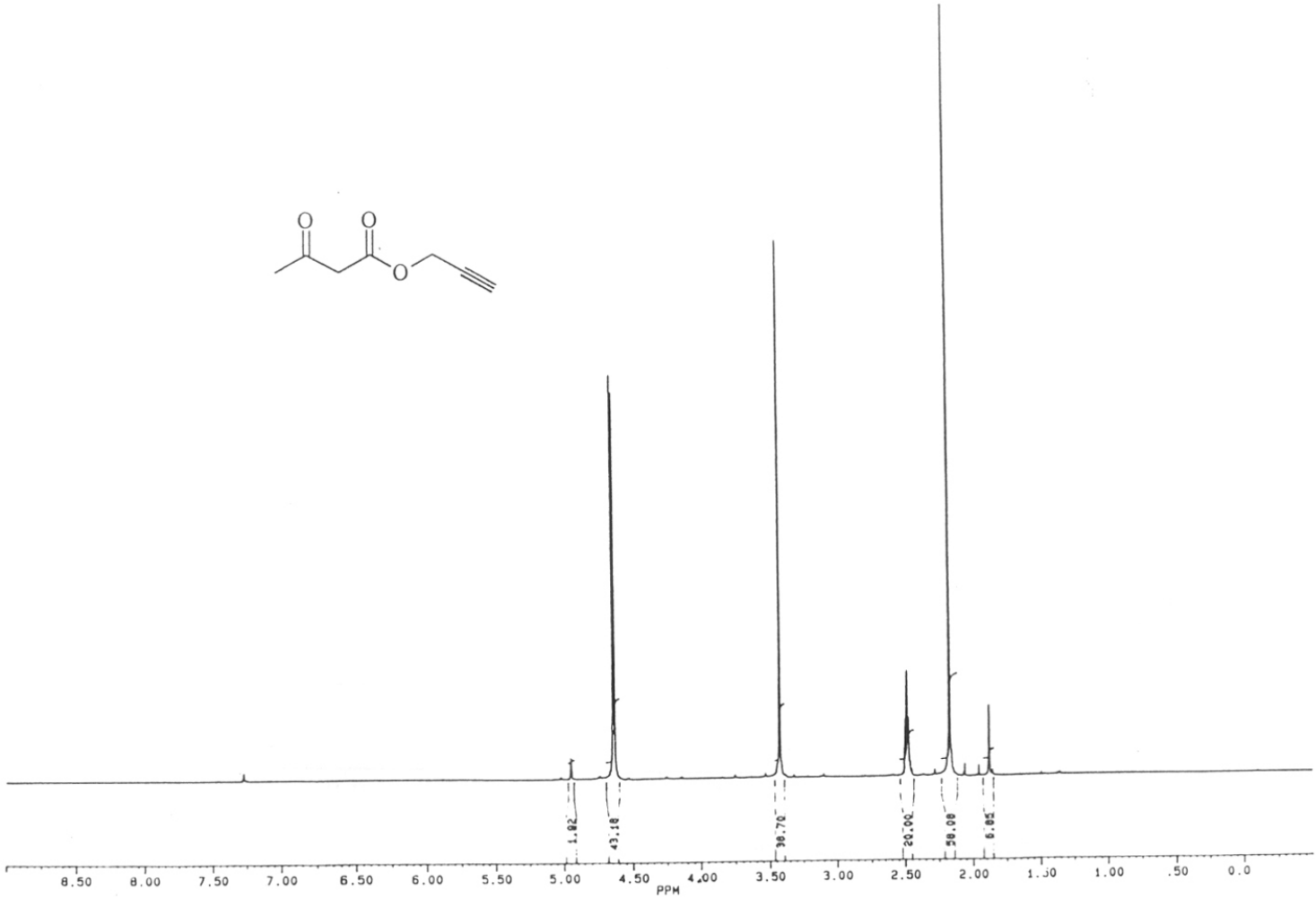



FIG VIII: PMR SPECTRUM OF THE COMPOUND 20i IN CDCl3

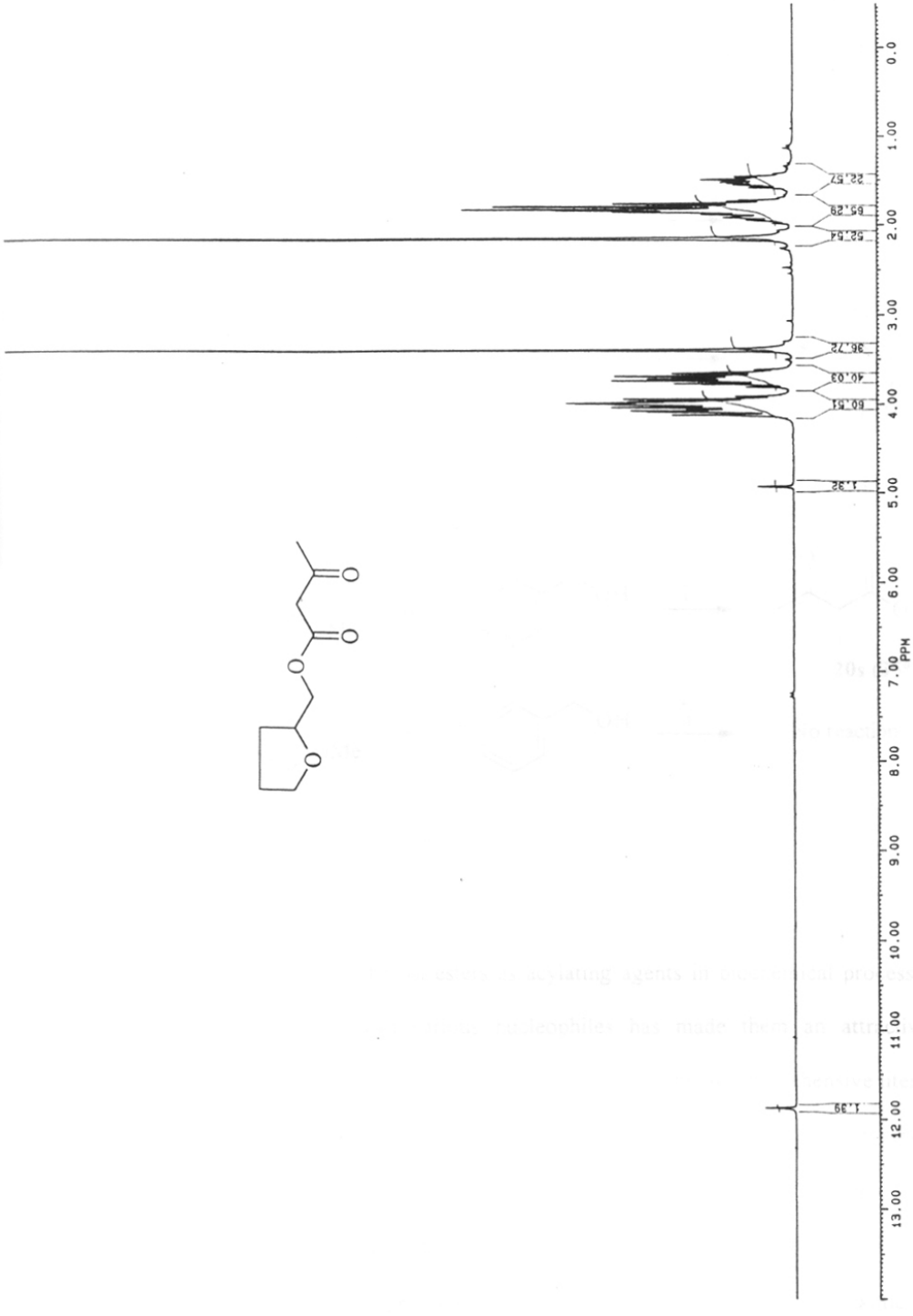
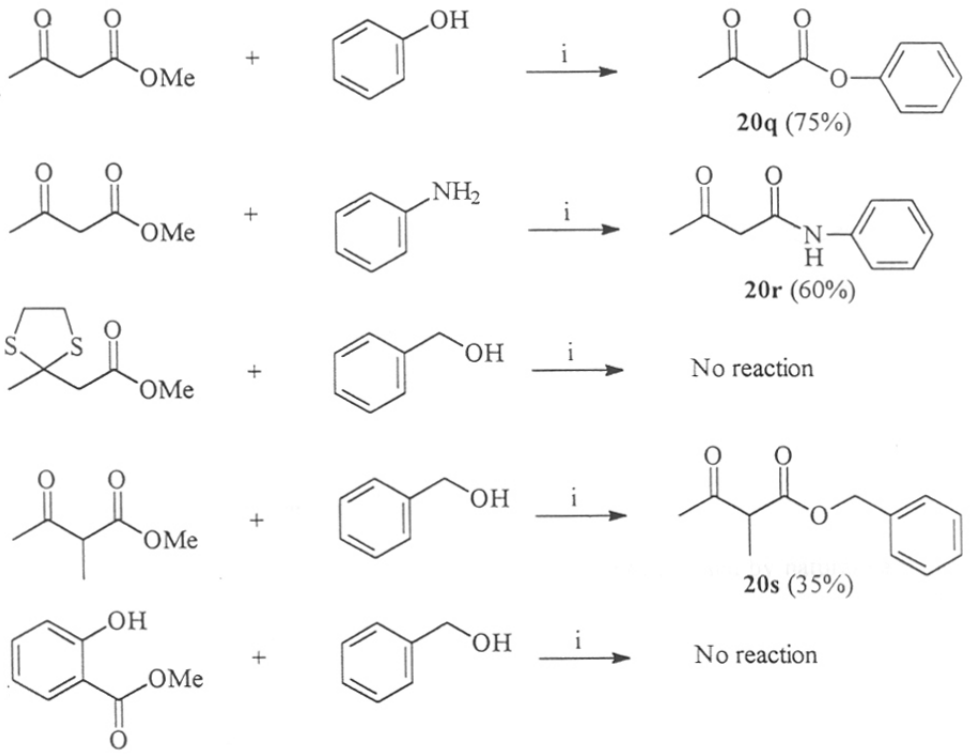



FIG IX : PMR SPECTRUM OF THE COMPOUND 20n IN $CDCl_3$

the transesterification proceeds to give the product in low yield. Methyl salicylate failed to undergo transesterification.

**Scheme 27**



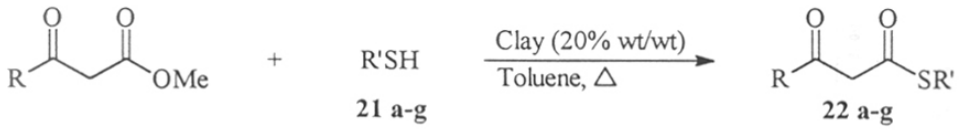

i) Clay (20% wt/wt.), Toluene, Δ

**Transthiolesterification of β-keto esters**

The role of thiol esters as acylating agents in biochemical processes and their high reactivity with various nucleophiles has made them an attractive synthetic intermediate in a variety of chemical transformations. A comprehensive literature search has revealed that the exchange of normal ester with thiols is not reported in the literature. The conversion of a β-keto ester moiety to its thiol- analogue is problematic as it always undergoes facile decarboxylation upon hydrolysis. Further, the preparation of such thiol esters generally requires multi-step synthesis utilizing exotic reagents and drastic reaction conditions. However, this synthetic problem can now be conveniently

solved by one to one exchange of thiols with β-keto esters to yield transthiolesterified products catalyzed by natural kaolinitic clay. In our continuing interest in the application of natural kaolinitic clay in synthetic transformations, we have subjected a variety of thiols for transthiolesterification with β-keto esters, and the results are presented in Scheme-28 and Table-5.

**Scheme 28**




As evident from Table-5, this method appears to be quite general as a variety of thiols can be employed. The yields of the transthiolesterified products are moderate, and the reaction time ranges from 6-12 hr.

**Table-5:** Transthiolesterification of various β-keto esters catalysed by natural kaolinitic clay with different thiols[a]

| Entry | Substrate **17** R | Thiol (**21 a-g**) $R^1$ | t(h) | Product(**22 a-g**)[b] Yield (%)[c] |
|---|---|---|---|---|
| a. | Me | Phenyl | 8 | 70 |
| b. | Me | 4-Chlorophenyl | 6 | 75 |
| c. | Me | 2-Ethoxyphenyl | 8 | 64 |
| d. | Me | Benzyl | 6 | 71 (53)[d] |
| e. | Me | 4-Methoxyphenyl | 8 | 69 |
| f. | Ph | Benzyl | 12 | 42 (26)[d] |
| g. | Ph | Furfuryl | 12 | 51 |

a: Catalyst was recovered and reused three times without loss of activity; b: All new compounds gave satisfactory spectral data; c: Isolated yield; d: Numbers in parentheses refer to yields using montmorillonite K10 clay as catalyst.


FIG X : PMR SPECTRUM OF THE COMPOUND 22a IN $CDCl_3$

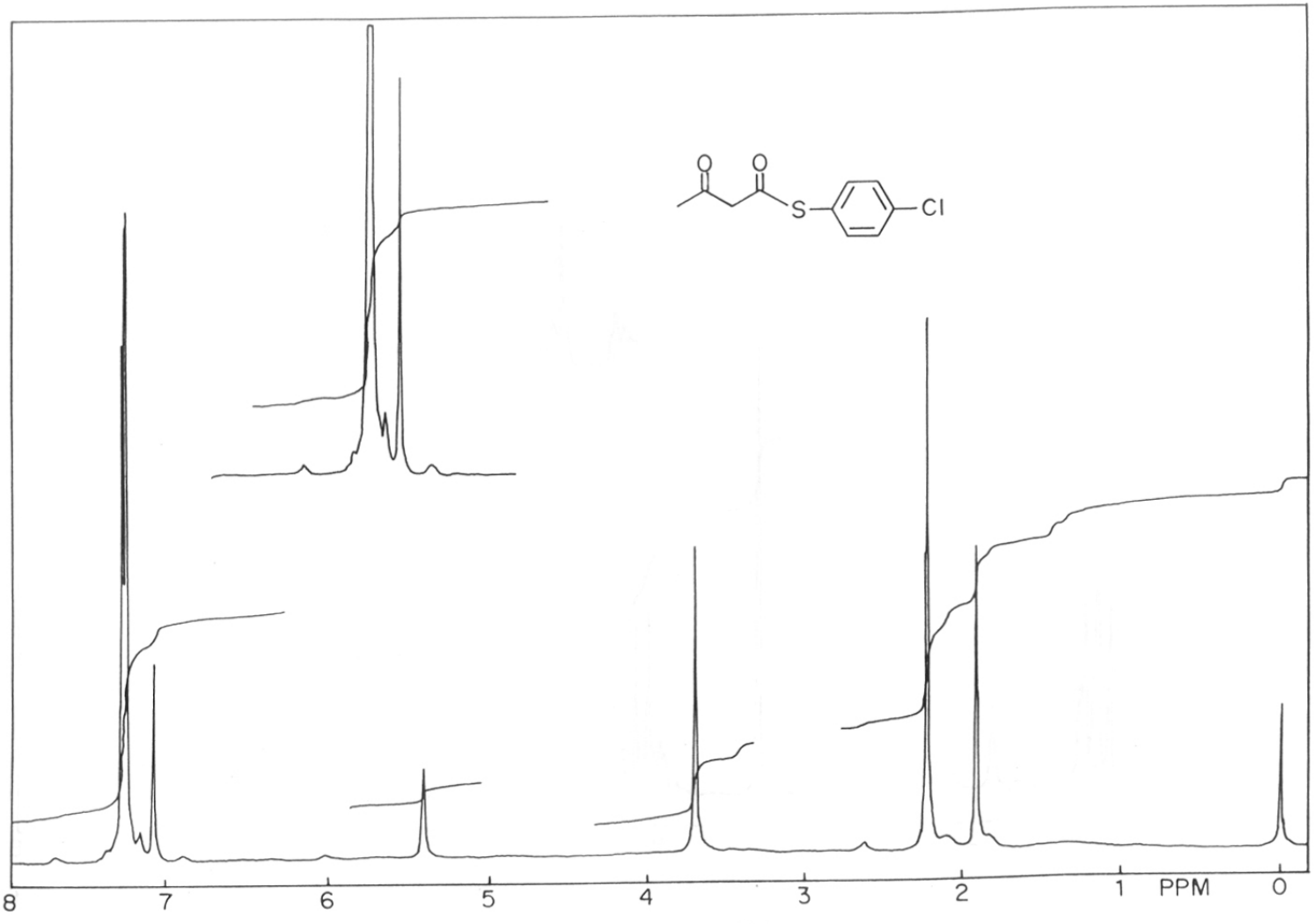



FIG. XI : PMR SPECTRUM OF THE COMPOUND **22b** IN $CDCl_3$

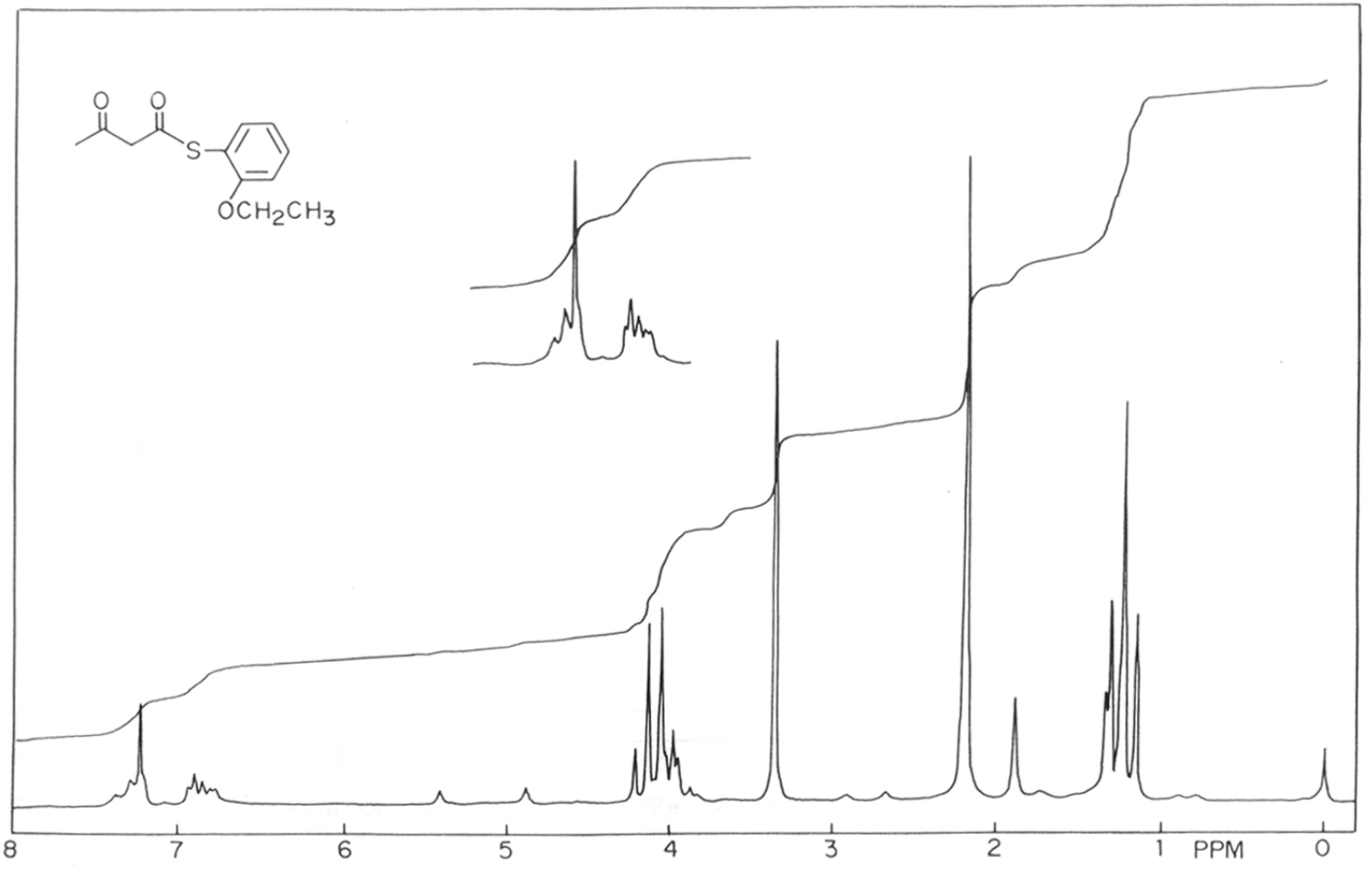



FIG. XII : PMR SPECTRUM OF THE COMPOUND **22c** IN $CDCl_3$

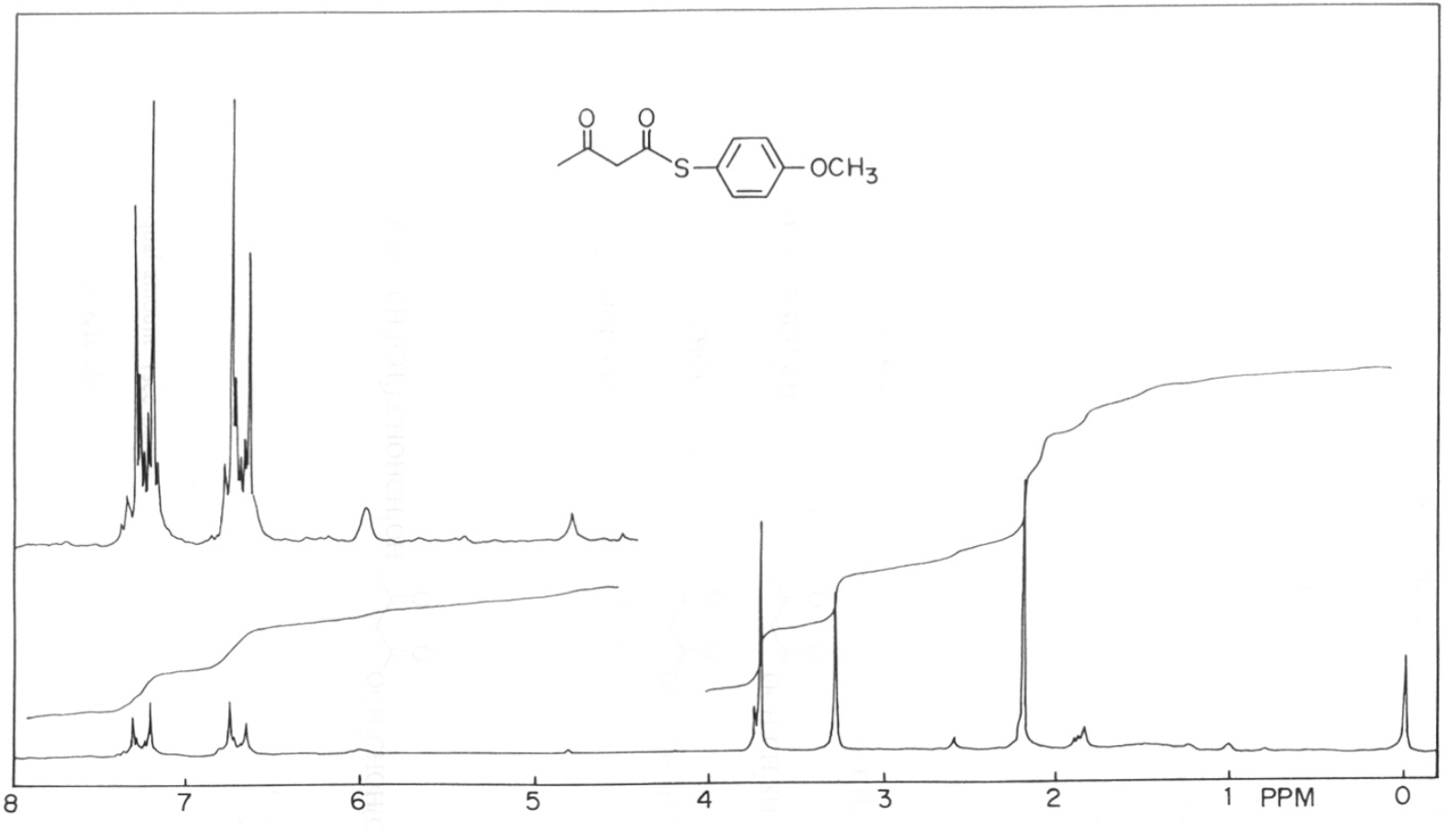
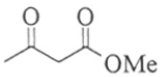
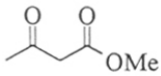
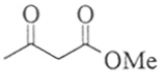
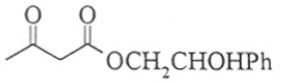
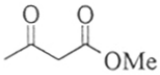
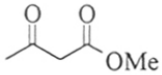
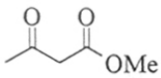



FIG. XIII : PMR SPECTRUM OF THE COMPOUND **22e** IN $CDCl_3$

Selectivity study of transesterification with alcohols, thiols and amines

Since the catalyst is active towards transesterification and trans-thiolesterification under the same catalytic condition, it is of interest to study the reactivity pattern of different kinds of diols, amino alcohols and mercapto alcohols towards β-keto ester over natural kaolinitic clay and the results of such study are presented in Table-6.

Table 6: Selective transesterification of β keto esters with amino alcohol, mercapto alcohol and diols catalyzed by natural kaolinitic clay.a

| Entry | β- Keto ester 17 | Substrate | Product[b] 23 | Yield (%)[c,e] |
|---|---|---|---|---|
| a |  | $H_2NCMe_2CH_2OH$ |  | 61 (58) |
| b |  | $HSCH_2CH_2OH$ |  [d] | 49 (48) |
| c |  | $PhCHOHCH_2OH$ |  | 48 |
| d |  | $HOCH(CH_2OH)_2$ |  | 55 |
| e |  | $CH_3CH_2CHOHCH_2OH$ |  | 60 (54) |
| f |  | $CH_3(CH_2)_7CHOHCH_2OH$ |  | 55 (53) |

a: Catalyst was reused three times without loss of activity; b: all compounds gave satisfactory spectral data; c: isolated yield; d: ketone protected product 24 also formed with almost equal amount (see Scheme 29); e: numbers in parentheses refer to yields using montmorillonite K10 clay as catalyst.

Major features are enumerated as follows.

In the case of aliphatic amino alcohols, amine being more nucleophilic than alcohol, it reacts faster with ester giving the corresponding amidation product (entry a), which is in agreement with Mukaiyama's [74] procedure.

It has been observed that the hydroxyl group of 2-mercapto ethanol (entry b) reacts preferentially over thiol.

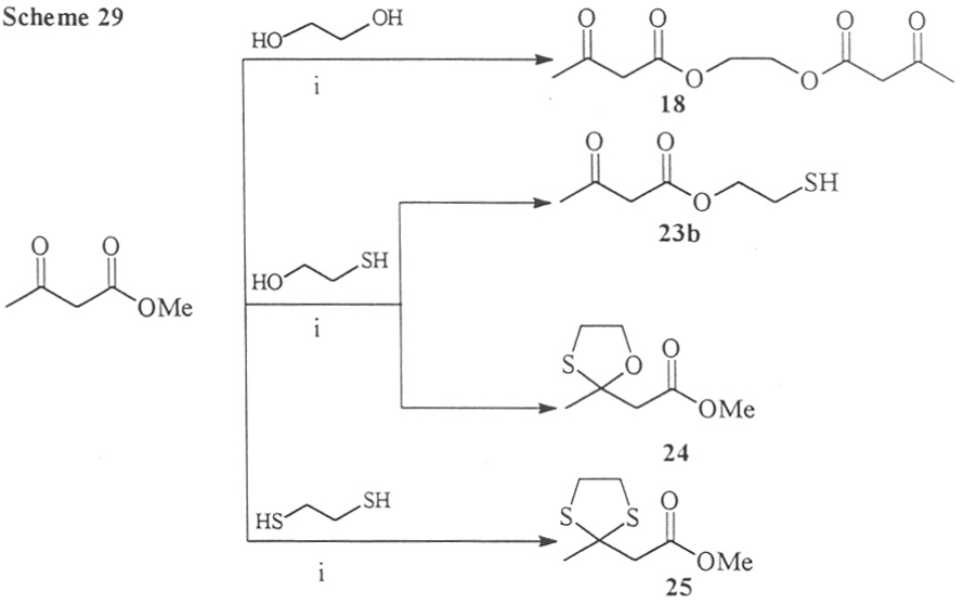
In the case of glycerol, the only product obtained was the ditransesterified product, however excess of either the catalyst or the β-keto ester is used (entry-d).

Another important feature of the present methodology is that, unlike Posner's procedure which fails to selectively acylate 1,2 or 1,3 diols, the clay catalyst efficiently transesterifies primary alcohols of 1,2 diols as shown in Table-6 (entry c, e & f)

When a β-keto ester is treated with ethylene glycol, ethane oxathiol and ethane 1,2- dithiol, both transesterification and ketone protection could be possible. The results are as shown in Scheme-29.

From Scheme-29, it is evident that thiol being more nucleophilic than alcohol, dithiol under the clay condition undergoes selective protection with the ketone carbonyl while diol gets selectively transesterified with the β-keto ester to produce the ditransesterified product. In the case of oxathiol, a mixture of both protected **23b** as well as transesterified products **24** are obtained in almost equal proportions (see Table-6, entry b).

**Scheme 29**




i = Clay (kaolinitic or montmorillonite K10) 20% (wt/wt), toluene, reflux

It has been observed that commercially available Montmorillonite K10 clay has also been found to be effective for transesterification, transthiolesterification and thus exhibiting the same selectivity and reactivity pattern of kaolinitic clay (Tables- 4,5 and 6).

**Mechanism**

Natural kaolinitic clay has a surface acidity measuring between 1.5 to -3 in the Hammett Ho acidity function scale. By simple washing of the clay with mineral acid such as 0.1 M HCl, brings down Ho between -6 and -8. i.e. to values intermediate of conc. $HNO_3$ and oleum.[5] We believe that the enhanced catalytic activity of the acid activated clay could be attributed to the significant amount of both Lewis acidity derived from Al remaining in the edges of the platelets and Bronsted acidity of co-ordinated hydroxyl groups of $Al^{3+}$, $Fe^{3+}$ and and $Ti^{4+}$ ions relocated in the interlamellar space of the clay.

The fact that both transesterification and transthiolesterification are successful only for β-keto esters leads us to propose the following transition state model which

of the β-keto ester forms a stable enolate complex with $Al^{3+}$ present in the clay by the way of coordination so that the acyl oxygen bond of the β-keto ester is weakened, thereby the incoming nucleophile attacks the ester carbonyl leading to transesterified product. In the case of protection of the carbonyl compounds the Lewis acid center in the clay activates the carbonyl compounds by way of coordination so that the nucleophiles could approach the carbonyl group effectively to give the corresponding product (Fig-6).

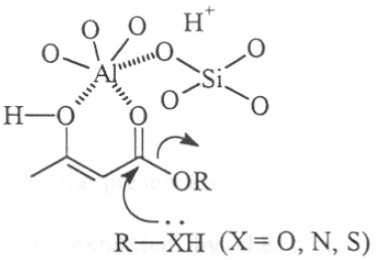
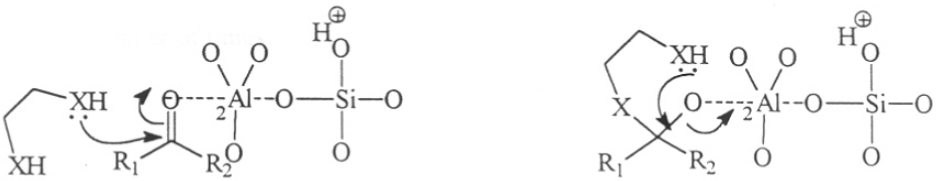



**Fig. 5**




$R_1$, $R_2$ = H, alkyl, aryl
X = O, N, S

**Fig. 6**

# CHAPTER 3

**Conclusion :**

In summary, it has been shown that naturally occurring kaolinitic as well as Montmorillonite K10 clay could efficiently catalyze transesterification of β-keto ester by a variety of alcohols, especially unsaturated alcohols and long chain alcohols. For the first time, transthiolesterifications of β-keto esters with various thiols have been studied. The reactivity of nucleophiles like alcohols, thiols and amines towards transesterification reaction was systematically studied. Natural clay is an effective and convenient catalyst for acetalization and thioacetalization of carbonyl compounds and high chemoselectivity exhibited by the clay-catalyzed reaction should be useful for selective protection of aldehydes in the presence of keto carbonyl functions. Besides the high selectivity and reactivity exhibited by the clay, the method has other environmentally benign features: no inorganic wastes are produced and the catalyst can be reused a number of times.

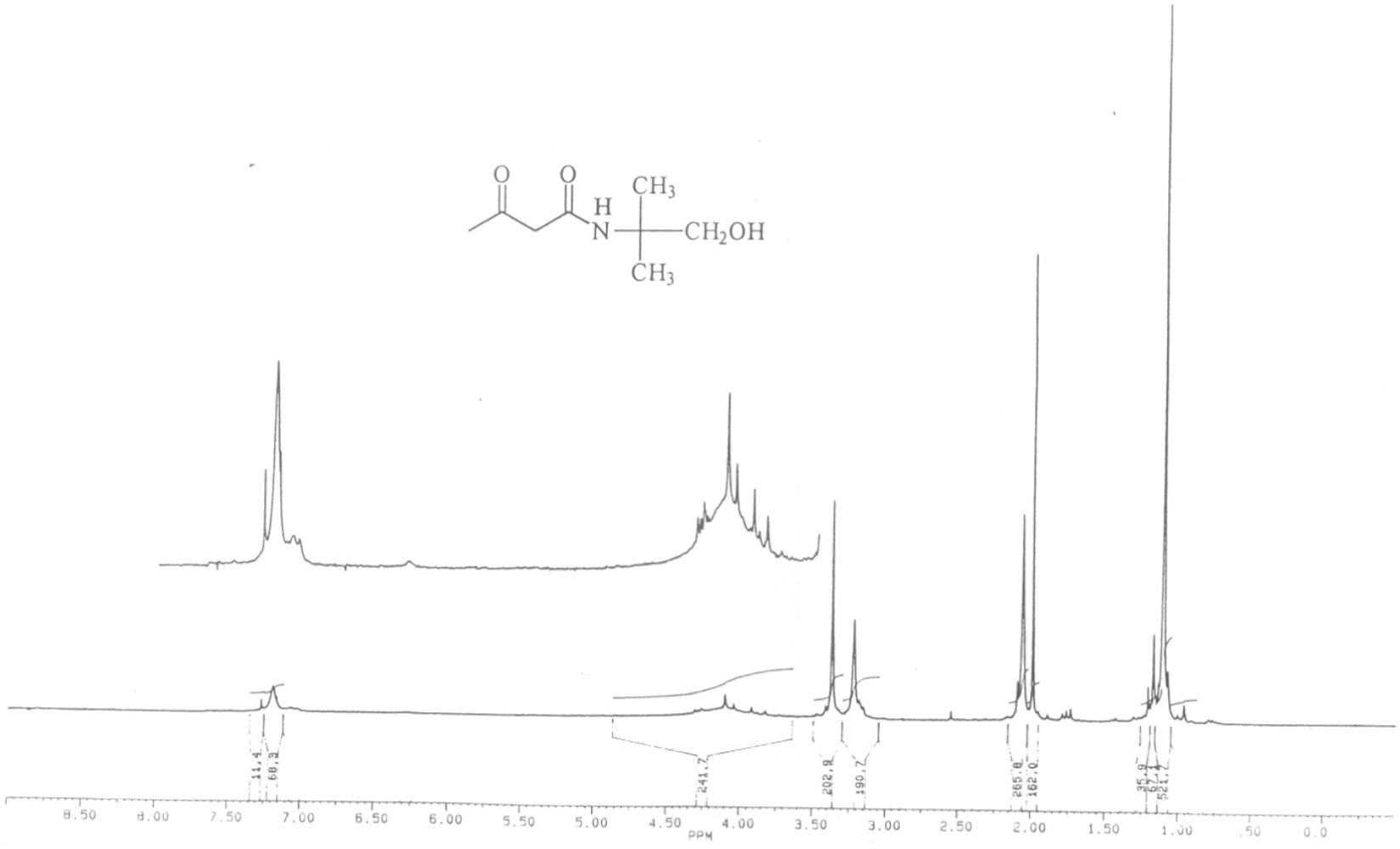



FIG XIV : PMR SPECTRUM OF THE COMPOUND 23a IN $CDCl_3$

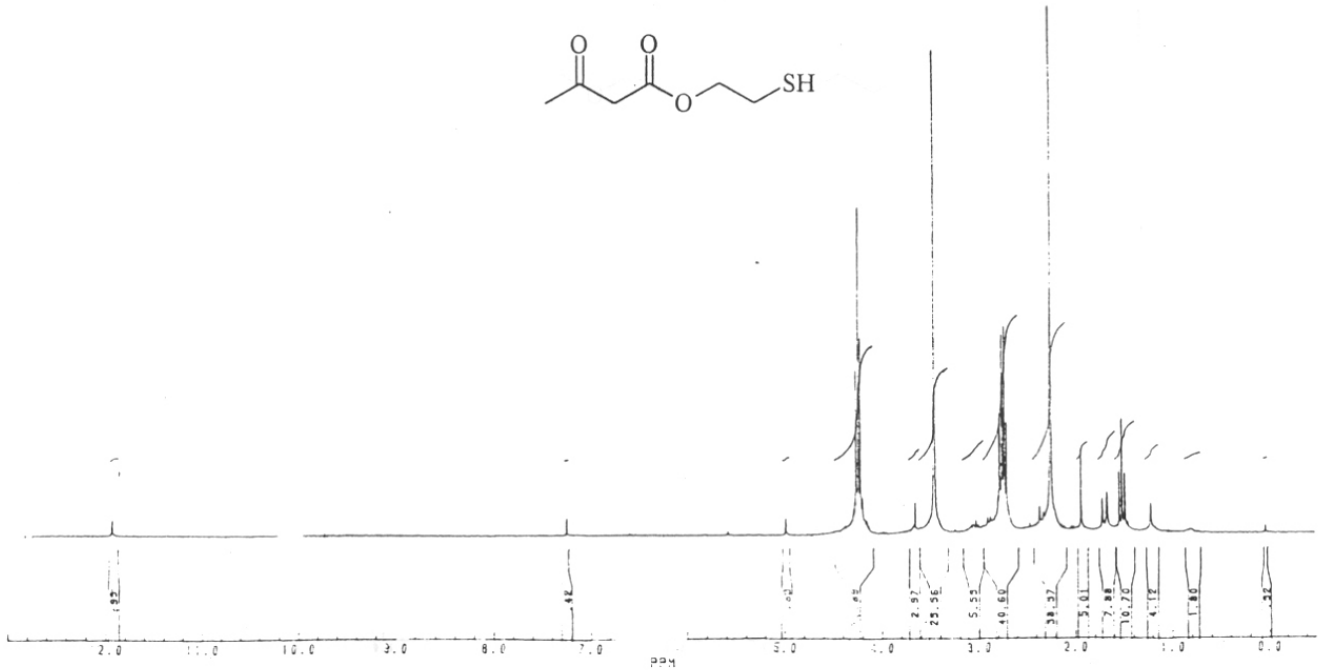



FIG XV : PMR SPECTRUM OF THE COMPOUND 23B IN $CDCl_3$

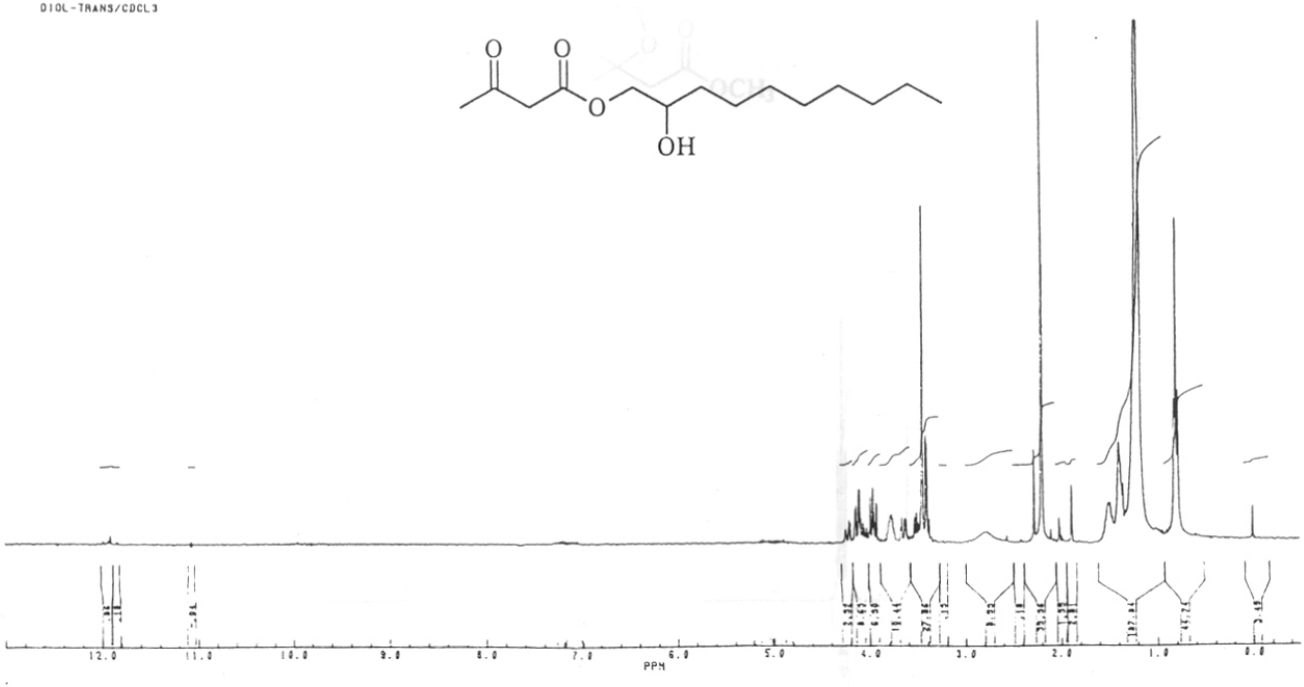



FIG XVI: PMR SPECTRUM OF THE COMPOUND 23f IN $CDCl_3$

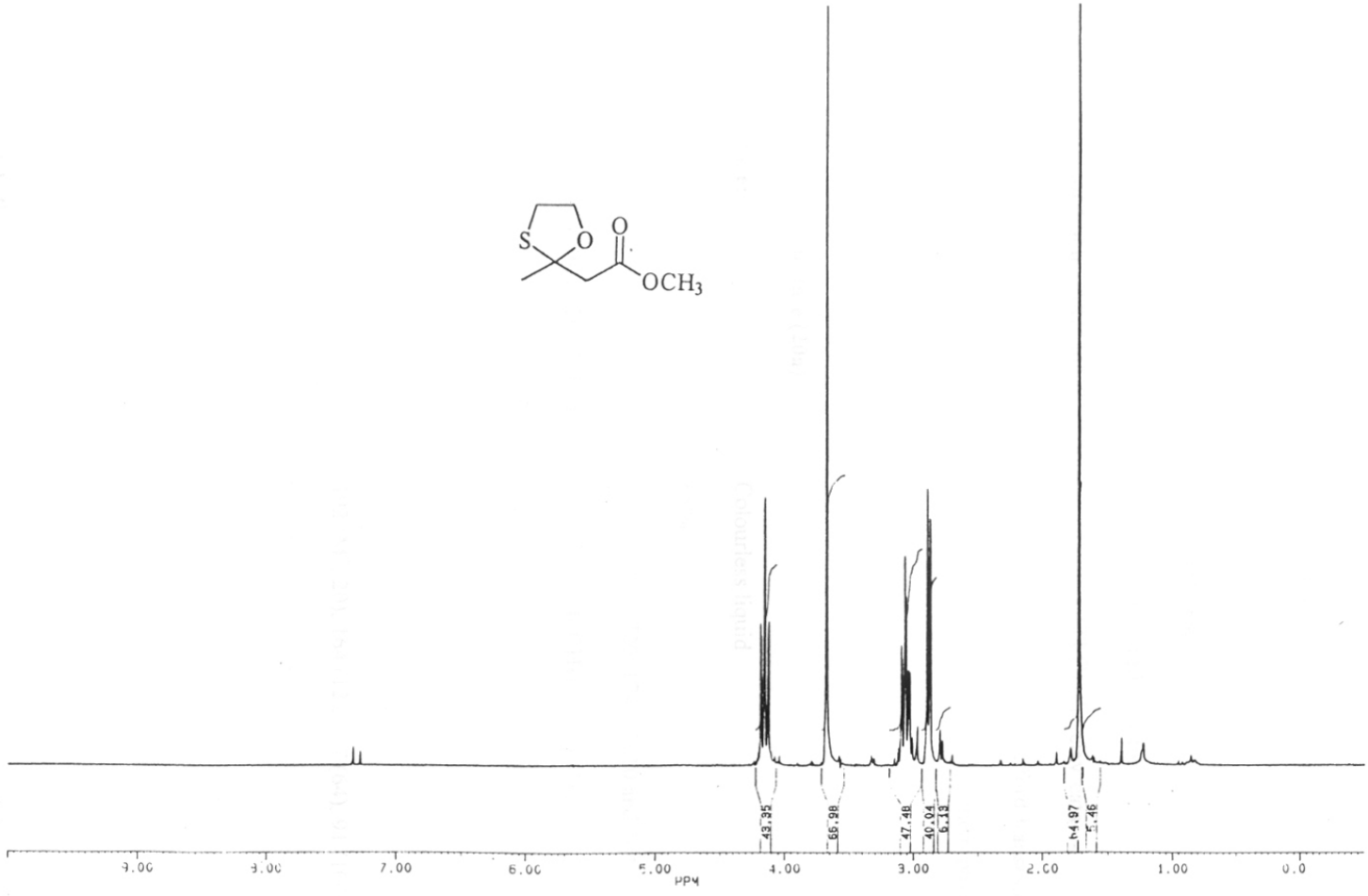



FIG XVII : PMR SPECTRUM OF THE COMPOUND 24 IN $CDCl_3$

## Experimental

**General procedure for the transesterification and transthiolesterification of β-keto esters**

In a general reaction, a mixture of β-keto ester (10 mmol), alcohol or thiol (11 mmol) and clay 20% (wt/wt) in toluene (25 ml) was refluxed for 4-12 hr under Dean-Stark condition. After the reaction was complete (TLC), the clay catalyst was filtered off and the product was purified by column chromatography to afford transesterified or transthiolesterified product respectively. They were identified by their physical and spectral properties and by comparison with the reported values.

**Benzyl acetoacetate (20a)**

| | |
|---|---|
| **Nature:** | Colourless liquid |
| **Yield:** | 85% |
| **IR (Neat):** | 1030, 1620, 1720, 1740, 2910 and 3040 $cm^{-1}$ |
| **$^1$H NMR ($CDCl_3$, 200 MHz):** | δ 2.25 (s, 3H, $\underline{CH_3}$); 3.5 (s, 2H, $\underline{CH_2}$); 5.2 (s, 2H, Ar$\underline{CH_2}$); 7.25 (s, 5H, 5 x Ar$\underline{H}$). |
| **$^{13}$C NMR ($CDCl_3$, 50 MHz):** | δ 29.81, 49.70, 66.82, 126.71, 128.29, 128.43, 135.23, 166.84, 200.50. |
| **MS (m/z):** | 192 ($M^+$, 20), 164 (12), 107 (64), 91 (100), 85 (9), 79 (45), 65 (22), 58 (12). |

**2-Phenyl ethyl acetoacetate (20b)**

| | |
|---|---|
| **Nature**: | Liquid |
| **Yield:** | 87% |
| **IR (Neat)**: | 1060, 1610, 1720, 1750, 3000 and 3060 $cm^{-1}$ |

**$^1$H NMR ($CDCl_3$, 200 MHz)** : δ 2.2 (s, 3H, $\underline{CH_3}$); 3.0 (t, J=7 Hz, 2H, Ar$\underline{CH_2}$); 3.4 (s, 2H, CO$\underline{CH_2}$); 4.4 (t, J=7 Hz, 2H, O$\underline{CH_2}$); 7.3 (s, 5H, 5 x Ar$\underline{H}$) (enolic acetoacetyl resonances were observed at δ 1.95, 5.05 and 12.5).

**$^{13}$C NMR ($CDCl_3$, 50 MHz)**: δ 30.04, 35.03, 50.04, 63.63, 126.44, 128.61, 128.94, 137.54, 166.13, 200.58.

**MS (m/z):** 206($M^+$, 18), 108 (15), 91 (100), 81 (45), 77 (10), 67 (30), 58 (90).

**Furfuryl acetoacetate (20c)**

**Nature**: Colourless liquid

**Yield:** 84%

**IR (Neat)** : 1030, 1620, 1720, 1740 and 2900 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz)** : δ 2.25 (s, 3H, $\underline{CH_3}$); 3.45 (s, 2H, $\underline{CH_2}$CO); 5.15 (s, 2H, Ar$\underline{CH_2}$ ); 6.3-6.4 (m, 2H, 2 x Ar$\underline{H}$); 7.45 (m, 1H, Ar$\underline{H}$) (enolic acetoacetyl resonances were observed at δ 1.95, 4.90 and 12.0).

**$^{13}$C NMR ($CDCl_3$, 50 MHz)** : δ 30.12, 49.94, 57.46, 110.78, 111.19, 142.57, 149.04, 166.92, 200.42.

**MS (m/z):** 182 ($M^+$, 8), 154 (2), 97 (25), 85 (5), 81 (100), 69 (8), 58 (5), 53 (22).

**Cinnamyl acetoacetate (20d)**

**Nature**: Colourlss liquid

**Yield:** 80%

**IR (Neat)** : 1048, 1610, 1720, 1740, 2920 and 3020 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz)** : δ 2.25 (s, 3H, $\underline{CH_3}$); 3.45 (s, 2H, $\underline{CH_2}$); 4.75 (d, J=7 Hz, 2H, $O\underline{CH_2}$); 6.2-6.35 (m, 1H, $CH=\underline{CH}-CH_2$); 6.65 (d, J=19.0 Hz, 1H, $\underline{CH}=CH-CH_2$); 7.25-7.4 (m, 5H, 5 x Ar$\underline{H}$) (enolic acetoacetyl resonances were observed at δ 1.95, 5.1 and 12.7).

**$^{13}$C NMR ($CDCl_3$, 50 MHz)**: δ 30.0, 49.85, 65.70, 122.5, 126.62, 128.13, 128.58, 134.57, 136.04, 166.87, 200.40.

**Allyl acetoacetate (20e)**

**Nature**: Liquid

**Yield:** 75%

**IR (Neat)** : 1030, 1650, 1720, 1740 and 2960 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz)** : δ 2.25 (s, 3H, $\underline{CH_3}$); 3.5 (s, 2H, $\underline{CH_2}$); 4.6 (d, 2H, $C=\underline{CH_2}$); 5.25 (d, 2H, $O\underline{CH_2}$); 5.85 (m, 1H, $\underline{CH}$) (enolic acetoacetyl resonances were observed at δ 1.95, 5.0 and 12.5).

**MS (m/z)**: 142 ($M^+$,15) 124 (15), 114 (20), 100 (32), 85 (100), 69 (25), 58 (90).

**Geranyl acetoacetate (20g)**

**Nature**: Viscous liquid

**Yield:** 70%

**$^1$H NMR ($CDCl_3$, 200 MHz)** : δ 1.6 (s, 3H, $\underline{CH_3}$); 1.7 (s, 6H, 2 x $\underline{CH_3}$); 1.95-2.1 (m, 4H, 2 x $\underline{CH_2}$); 2.25 (s, 3H, $CO\underline{CH_3}$); 3.35 (s, 2H, $CO\underline{CH_2}$); 4.6 (d, J=7 Hz, 2H, $O\underline{CH_2}$); 5.05 (br t, 1H, $C=\underline{CH}CH_2CH_2$); 5.25 (br t, 1H, $C=\underline{CH}CH_2O$).

**Crotyl acetoacetate (20h)**

| | |
|---|---|
| **Nature**: | Colourless liquid |
| **Yield:** | 80% |
| **IR (Neat)** : | 1040, 1620, 1720, 1740 and 2960 $cm^{-1}$ |
| **$^1$H NMR ($CDCl_3$, 200 MHz)** | δ 1.6 (d, J=7Hz, 3H, $CHCH_3$); 2.2 (s, 3H, $COCH_3$); 3.4 (s, 2H, $COCH_2$); 4.45 (d, J=7Hz, 2H, $OCH_2$ ); 5.4-5.55 (m, 1H, CH); 5.65-5.8 (m, 1H, CH) (enolic acetoacetyl resonances were observed at δ 1.9, 4.95 and 12.0). |
| **$^{13}$C NMR ($CDCl_3$, 200 MHz)** : | δ 17.65, 30.03, 49.97, 65.91, 89.62 (enolic), 124.61, 131.90, 166.90, 200.44. |
| **MS (m/z)**: | 156 ($M^+$, 2), 138 (2), 128 (2), 102 (13), 85 (15), 71 (31), 55 (100). |

**Propargyl acetoacetate (20i)**

| | |
|---|---|
| **Nature**: | Colourless liquid |
| **Yield:** | 79% |
| **IR (Neat)** : | 1040, 1720, 1740, 2260 and 2950 $cm^{-1}$ |
| **$^1$H NMR ($CDCl_3$, 200 MHz)** : | δ 2.2 (s, 3H, $CH_3$); 2.5 (t, J=2Hz, 1H, CH); 3.45 (s, 2H, $COCH_2$); 4.65 (d, J=2Hz, 2H, $CH_2$) (enolic acetoacetyl resonances were observed at δ 1.9, 4.9 and 12.0). |
| **$^{13}$C NMR ($CDCl_3$, 50 MHz)** : | δ 30.09, 49.63, 52.68, 75.51, 77.25, 89.14 (enolic), 166.36, 200.06. |
| **MS (m/z)**: | 140 ($M^+$, 5), 125 (5), 98 (88), 85 (100), 69 (72), 67 (9), 57 (9), 55 (52), 53 (49). |

**Dodecyl acetoacetate (20j)**

**Nature**: Viscous oil

**Yield:** 75%

**IR (Neat)** : 1030, 1720, 1740 and 2970 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz)** : δ 0.8 (br t, 3H, $CH_2\underline{CH_3}$); 1.25 (br s, 20H,10 x $\underline{CH_2}$); 2.25 (s, 3H, $\underline{CH_3}$); 3.45 (s, 2H, $CO\underline{CH_2}$); 4.1(t, J=7 Hz, 2H, $\underline{CH_2}CH_3$) (enolic acetoacetyl resonances were observed at δ 1.90, 4.95 and 12.15).

**MS (m/z)**: 271 ($M^+$ +1, 27), 168 (7), 140 (7), 125 (6), 111 (12), 103 (100), 97 (22), 85 (40), 69 (42), 56 (35).

**Octadecyl acetoacetate (20m)**

**Nature**: Solid

**Yield:** 71%

**M.P.**: $41^0$C ( Lit.[79] m.p. 39°C)

**IR ($CHCl_3$)** : 1030, 1720, 1740 and 2910 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz)** : δ 0.9 (br t, 3H, $\underline{CH_3}$); 1.25 (br s, 32H, 16 x $\underline{CH_2}$); 2.25 (s, 3H, $CO\underline{CH_3}$); 3.5 (s, 2H, $CO\underline{CH_2}$); 4.1 (t, J=7 Hz, 2H, $\underline{CH_2}O$) (enolic acetoacetyl resonances were observed at δ 1.95, 5.0 and 12.15).

**MS (m/z)**: 355 ($M^+$+1, 35), 336 (5), 224 (5), 125 (8), 111 (15), 103 (100), 97 (27), 85 (35), 69 (36), 56 (55).

**$^1$H NMR ($CDCl_3$, 200 MHz)** : δ 2.5 (t, J=6Hz, 1H, CH); 4.0 (S, 2H, $COCH_2$); 4.75 (d, J=6Hz, 2H, $CH_2$); 7.3-7.85 (m, 5H, 5 x ArH) (enolic resonances were observed at δ 5.65 and 12.15)

**MS (m/z)**: 202 ($M^+$, 10), 192 (10), 147 (12), 120 (10), 105 (100), 91 (10), 77 (65), 69 (25).

**Phenyl acetoacetate (20q)**

**Nature:** Colourless liquid

**Yield:** 75%

**B.P.:** 130°C/4 mm (Lit.[80] b.p.80-82°C/0.2 mm)

**Acetoacetanalide (20r)**

**Nature:** Solid

**M.P.:** 82°C (Lit.[81] m.p. 84-85°C)

**$^1$H NMR ($CDCl_3$, 90 MHz):** 2.25 (s, 3H, $CH_3$); 3.60 (s, 2H, $CH_2$); 7.12 –7.55 (m, 5 x ArH); 9.30 (br s, NH).

**2-Methyl benzyl acetoacetate (20s)**

**Nature**: Viscous liquid

**Yield:** 35%

**$^1$H NMR ($CDCl_3$, 200 MHz)**: δ 1.25 (d, J=10 Hz, 3H, $CH_3$); 2.25 (s, 3H, $COCH_3$); 3.4-3.5 (q, J= 10 Hz, 1H, CH); 5.15 (s, 2H, $CH_2$); 7.3 (s, 5H, 5 x ArH).

**S-Phenyl-acetothioacetate (22a)**

| | |
|---|---|
| **Nature**: | Viscous liquid |
| **Yield:** | 70% |
| **IR (Neat)**: | 1095, 1610, 1672, 1720 and 3062 $cm^{-1}$ |
| **$^1$H NMR ($CDCl_3$, 200 MHz)**: | δ 2.25 (s, 3H, $CO\underline{CH_3}$); 3.7 (s, 2H, $CO\underline{CH_2}$); 7.4(s,5H, 5 x Ar$\underline{H}$) (enolic acetoacetyl resonances were observed at δ 1.90, 5.5 and 12.75). |
| **$^{13}$C NMR ($CDCl_3$, 50 MHz)**: | δ 30.23, 57.55, 127.07, 129.34, 129.57, 134.38, 174.81, 199.52. |
| **MS (m/z)**: | 94 ($M^+$,5), 130 (3), 110 (100), 85 (60), 77 (12), 69 (13), 66 (16). |
| **Analysis** | calculated for $C_{10}H_{10}O_2S$: C, 61.85; H,5.15<br>Found: C, 61.77; H, 5.19. |

**S-4-Chlorophenyl-acetothioacetate (22b)**

| | |
|---|---|
| **Yield:** | 75% |
| **IR ($CHCl_3$):** | 825, 1090, 1600, 1680, 1720 and 3020 $cm^{-1}$ |
| **$^1$H NMR ($CDCl_3$, 90 MHz)**: | δ 2.25 (s,3H, $CO\underline{CH_3}$); 3.7 (s,2H, $CO\underline{CH_2}$); 7.25 (d, J=2Hz, 4H, 4 x Ar$\underline{H}$) (enolic acetoacetyl resonances were observed at δ 1.95, 5.4 and 12.0). |

**S-2-Ethoxyphenyl-acetothioacetate (22c)**

| | |
|---|---|
| **Nature**: | Viscous liquid |
| **Yield:** | 64% |
| **IR (Neat)**: | 1020, 1680, 1720 and 3010 and $cm^{-1}$ |
| **$^1$H NMR ($CDCl_3$, 90 MHz)**: | δ 1.3 (t, J = 8Hz, 3H, $\underline{CH_3}$); 2.2 (s, 3H, $CO\underline{CH_3}$); |

3.45 (s,2H, $CO\underline{CH_2}$); 4.2 (q, J = 8Hz, 2H, $\underline{CH_2}CH_3$); 6.8-7.4 (m, 4H, 4 x Ar$\underline{H}$) (enolic acetoacetyl resonances were observed at δ 1.95, 4.9 and 12.0).

**MS (m/z)**: 238 ($M^+$,5), 154 (100), 126 (90), 97 (55), 85 (35), 69 (12).

**S-Benzyl-acetothioacetate (22d)**

**Nature**: Viscous liquid

**Yield:** 71%

**IR (Neat)**: 1030, 1675 and 1720 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 90 MHz)**: δ 2.25 (s, 3H, $CO\underline{CH_3}$); 3.6 (s,2H, $CO\underline{CH_2}$); 4.1(s,2H, $\underline{CH_2}S$); 7.2(s,5H, 5 x Ar$\underline{H}$) (enolic acetoacetyl resonances were observed at δ 1.95, 5.35 and 12.0).

**$^{13}$C NMR ($CDCl_3$, 50 MHz)**: δ 29.83, 49.81, 65.54, 89.5 (enolic), 126.55, 128.44, 128.79, 137.44, 166.91, 200.32.

**MS (m/z)**: 208 ($M^+$,8), 150 (4), 123 (30), 103 (7), 91 (100), 85 (75), 82 (8), 77 (10), 65 (15).

**Anal.** calculated for $C_{11}H_{12}O_2S$: C, 63.96; H, 5.76.

Found: C, 63.40; H, 5.72.

**S-4-Methoxyphenyl-acetothioacetate (22e)**

**Yield:** 69%

**IR ($CHCl_3$)**: 820, 1090, 1680, 1720 and 3010 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 90 MHz)**: δ 2.25 (s, 3H, $CO\underline{CH_3}$); 3.35 (s, 2H, $CO\underline{CH_2}$); 3.7 (s, 3H, $\underline{OCH_3}$); 6.8 (d, J = 10 Hz, 2H, 2 x Ar$\underline{H}$); 7.25 (d, J = 10 Hz, 2H, 2 x Ar$\underline{H}$).

**MS (m/z)**: 224 ($M^+$, 13), 168 (8), 153 (5), 140 (100), 125 (20), 96 (9), 85 (8), 69 (6).

**Analysis** calculated for $C_{11}H_{12}SO_3$: C, 58.92; H, 5.25.

Found: C, 58.81; H, 5.30.

**S-Benzyl-benzoylthioacetate (22f)**

**Nature**: Viscous liquid

**Yield:** 42%

**IR (Neat)**: 1020, 1680, 1720 and 3030 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz)**: δ 4.0 (s,2H, $CO\underline{CH_2}$); 4.15 (s,2H, $\underline{CH_2}S$); 7.25-8.0 (m, 10H, 10 x Ar$\underline{H}$) (enolic acetoacetyl resonances were observed at δ 6.1 and 13.25).

**MS (m/z)**: 270 ($M^+$,10), 233 (8), 228 (10), 192 (97), 147 (100), 129 (15), 124 (55), 120 (48), 115 (8).

**S-Furfuryl-benzoylthioacetate (22g)**

**Nature**: Viscous liquid

**Yield:** 51%

**$^1$H NMR ($CDCl_3$, 200 MHz)**: δ 4.0 (s,2H, $CO\underline{CH_2}$); 4.15 (s,2H, $\underline{CH_2}S$); 6.2-6.4 (m,2H, 2 x Ar$\underline{H}$); 7.3-7.8 (m, 6H, 6 x Ar$\underline{H}$); (enolic acetoacetyl resonances were observed at δ 6.1 and 13.15).

**MS (m/z)**: 260 ($M^+$, 12), 226 (5), 192 (30), 147 (40), 122

(25), 113 (18), 106 (100), 91 (22), 81 (58), 77 (65), 69 (45), 65 (25).

**N-2-(2,2-dimethyl ethane-1-ol)-acetoacetamide (23a)**

**Nature**: Viscous liquid

**Yield:** 61%

**IR (Neat)**: 1620, 1680, 1720 and 3300 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz)**: δ 1.1 (s,6H, 2 x $\underline{CH_3}$); 2.25 (s,3H, CO$\underline{CH_3}$); 3.3 (s,2H, CO$\underline{CH_2}$); 3.45 (s,2H, $\underline{CH_2}$OH).

**2-Mercaptoethyl-acetoacetate (23b)**

**Nature**: Liquid

**IR (Neat)**: 1020, 1710, 1740 and 3300 cm-1

**$^1$H NMR ($CDCl_3$, 200 MHz)**: δ 1.5 (t, 1H, $\underline{SH}$); 2.25 (s,3H, CO$\underline{CH_3}$); 2.7 (dt, J=2Hz, J=2Hz, 2H, $\underline{CH_2}$SH); 3.5 (s,2H, CO$\underline{CH_2}$); 4.3 (t,2H, $\underline{CH_2}$O).

**MS (m/z)**: 162 ($M^+$,20), 139, 103, 85, 60, 43.

**1-Phenyl-1, 2-ethanediol,2-acetoacetate (23c)**

**Nature**: Viscous oil

**Yield:** 48%

**IR (Neat)**: 1020, 1450, 1600, 1720, 1740 and 3350 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz)**: δ 2.25 (s, 3H, CO$\underline{CH_3}$); 2.88 (br s, 1H, CH$\underline{OH}$); 3.5 (s, 2H, CO$\underline{CH_2}$); 4.25-4.4 (m, 2H, $\underline{CH_2}$OH); 4.95(m, 1H, $\underline{CH}$OH); 7.3 (s, 5H, 5 x Ar$\underline{H}$).

**Glycerol 1,3-diacetoacetate (23d)**

**Nature:** Viscous oil

**Yield:** 55%

**IR (Neat):** 1050, 1240, 1720, 1740 and 3450 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz):** δ 2.25 (s, 6H, 2 x $CO\underline{CH_3}$); 3.2 (br,1H, $CH\underline{OH}$); 3.5 (s, 4H, 2 x $CO\underline{CH_2}$); 3.7-3.8 (m,1H, $\underline{CH}OH$), 4.05-4.35 (m,4H, 2 x $\underline{CH_2}OH$).

**1, 2-Butanediol 1-acetoacetate (23e)**

**Nature:** Viscous oil

**Yield:** 60%

**IR (Neat):** 1030, 1380, 1460, 1720, 1740 and 3400 $cm^{-1}$

**$^1$H NMR ($CDCl_3$, 200 MHz):** δ 0.92 (br t,3H, $CH_2\underline{CH_3}$); 1.40-1.47 (m,2H, $\underline{CH_2}$); 2.25 (s,3H, $CO\underline{CH_3}$); 3.5 (s,2H, $CO\underline{CH_2}$); 3.8-3.9 (m,1H, $C\underline{H}OH$); 4.0-4.25 (m,2H, $\underline{CH_2}OH$).

**1, 2-Decanediol 1-acetoacetate (23f)**

**Nature:** Viscous oil

**Yield:** 55%

**IR (Neat):** 1030, 1380, 1460, 1720, 1740 and 3400 $cm^{-1}$

**PMR (CDCl3, 200 MHz):** δ 0.9 (br t, 3H, $CH_2\underline{CH_3}$); 1.3 (br s, 14H, 7 x $\underline{CH_2}$); 2.25 (s, 3H, $\underline{CH_3}CO$); 2.6 (br, 1H, $\underline{OH}$); 3.5 (s, 2H, $\underline{CH_2}CO$); 3.75-3.85 (m, 1H, $\underline{CH}OH$); 4.0-4.25 (m, 2H, $\underline{CH_2}O$).

**Ethylene glycol diacetoacetate (18)**

| | |
|---|---|
| **Nature**: | Viscous oil |
| **Yield:** | 35% |
| **IR (Neat)**: | 1040, 1720 and 1740 $cm^{-1}$ |
| **$^1$H NMR ($CDCl_3$, 200 MHz)**: | δ 2.2 (s, 6H, 2 x $\underline{CH_3}$); 3.4 (s, 4H, 2 x $\underline{CH_2}$); 4.3 (s, 4H, 2 x O$\underline{CH_2}$). |
| **MS (m/z)**: | 231 ($M^+$+1, 22), 188 (28), 147 (5), 129 (85), 85 (100), 69 (22), 57 (5). |

**Methyl-3- (1,3-oxathiolane) butanoate (24)**

| | |
|---|---|
| **Nature**: | Liquid |
| **Yield:** | 79.5% |
| **IR (Neat)**: | 1040 and 1730 $cm^{-1}$ |
| **$^1$H NMR ($CDCl_3$, 200 MHz)**: | δ 1.75 (s,3H, $\underline{CH_3}$); 2.9 (d, J = 5 Hz, 2H, CO$\underline{CH_2}$); 3.05 (t, J = 5Hz, 2H, S$\underline{CH_2}$); 3.65 (s,3H, O$\underline{CH_3}$); 4.15 (t, J = 5Hz, 2H, O$\underline{CH_2}$). |
| **MS (m/z)**: | 176 ($M^+$,5), 161 (3), 117 (20), 103 (46), 85 (8), 69 (4), 59 (100). |

**Methyl-3- (1,3-dithiolane) butanoate (25)**

| | |
|---|---|
| **Nature**: | Colourless liquid |
| **Yield:** | 85% |
| **$^1$H NMR ($CDCl_3$, 200 MHz)**: | δ 1.9 (s,3H, $\underline{CH_3}$); 3.0 (s,2H, CO$\underline{CH_2}$); 3.35 (s,4H, S$\underline{CH_2}\underline{CH_2}$S); 3.7 (s,3H, O$\underline{CH_3}$). |
| **$^{13}$C NMR ($CDCl_3$, 50 MHz)**: | δ 31.43, 39.77, 49.97, 51.51, 62.09, 170.30. |
| **MS (m/z)**: | 192 ($M^+$,15), 132 (3), 119 (100), 111 (18). |

## References


1. Perspectives in catalysis " Proceeding of the 12th Swedish Symposium on Catalysis Lund October 11th 1979", Ed. Ragnar Larsson, publication of Liber Laromedel Lund, CWK Gleer Up, 1981.
2. Heterogeneous Catalysis, Ed. Davis, B. H. and Hettinger, Jr., W. P. Publication of American Chemical Society, ACS Symposium Series, Washington, D.C. 1983.
3. Laszlo, P. *Pure & Applied Chem.*, **1990,** *62*, 2027-2030.
4. Laszlo, P. *Science*, **1987**, *235*, 1473-1477.
5. Sabu, K.R., Sukumar, R.and Lalithambika, M. *Bull. Chem. Soc. Jpn.*, **1993**, *66*, 3535-3541.
6. Cornelis, A. and Laszlo, P. *Syn. Lett.*, **1994**, 155-161.
7. Jnaneshwara, G. K.; Barhate, N. B.; Sudalai, A.; Deshpande, V.H.; Wakharkar, R. D.; Gajare, A. S.; Shingare, M. S. and Sukumar, R. *J. Chem. Soc. Perkin Trans.1*, **1988**, 965-968.
8. Upadhya, T.T.; Daniel, T.; Sudalai, A.; Ravindranathan, T. and Sabu, K.R. *Syn. Commun.*, **1996**, *26*, 4539-4544.
9. Gajare, A.S.; Kulkarni V.R.; Barhate, N.B.; Shingare, M.S. and Wakharkar, R.D. *Syn. Commun.*, **1998**, *28*, 25-33.
10. Jnaneshwara, G.K.; Deshpande, V.H.; Lalithambika, M.; Ravindranathan, T. and Bedekar, A.V. *Tetrahedron Lett.*, **1998**, *39*, 459-462.
11. a) Laszlo, P. and Lucchetti, J. *Tetrahedron Lett.*, **1984**, *25*, 1567-1570.
    b) Laszlo, P. and Lucchetti, J. *Tetrahedron Lett.*, **1984**, *25*, 2147-2150.
    c) Laszlo, P. and Moison, H. *Chem. Lett.*, **1989**, 1031-1034.
12. Laszlo, P and Moison, H, Lucchetti, J. *Tetrahedron Lett.*, **1984**, *25*, 4387-4388.

13. Olah, G.A. Friedel-Crafts Chemistry; Wiley, New York, **1973**.

14. Laszole, P. and Mathy, A. *Helv. Chim. Acta.*, **1987**, *70*, 577-586.

15. Curtin, D.Y. and Crawford, R.J. *J. Am. Chem. Soc.*, **1957**, *79*, 3156-3159.

16. Chalais, S.; Laszlo, P. and Mathy, A. *Tetrahedron Lett.*, **1986**, *27*, 2627-2630.

17. Fischer, E. Ber. *Dutsch. Chem. Ges*, **1895**, *28*, 1145.

18. Fischer, E. and Otto, E. *Ber. Dtsch. Chem. Ges.*, **1903**, *36*, 2106.

19. a) Lowenthal, H.J.E. In Protective Groups in Organic Chemistry; McOmie, J.F.W. Ed., Plenum Press: New York, **1973**.

    b) Greene, T.W. "Protective Groups in Organic Synthesis", John Wiley, New York, **1981**.

20. Azzena, U.; Cossu, S.; Denurra, T.; Melloni, B. and Piroddi, A.M. *Synthesis*, **1990**, 313.

21. VanAllan, J.A. *Org. Synth.*, Coll. Vol. 4, **1963**, 21.

22. Schill, G.; Doerjer, G.; Logemann, E. and Fritz, H. *Chem. Ber.*, **1979**, *112*, 3603.

23. Garlaschelli, L. and Vidari, G. *Tetrahedron Lett.*, **1990**, *31*, 5815-5816.

24. Wenkert, E. and Goodwin, T.E. *Synth. Commun*, **1977**, *7*, 409.

25. Roelofson, D.P. and Bekkum, H. *Synthesis*, **1972**, 419.

26. Stenberg, V.I. and Kubik, D.A. *J. Org. Chem.*, **1974**, *39*, 2815.

27. Hanzlik, R.P. and Leinwetter, M. *J. Org. Chem.*, **1978**, *43*, 438.

28. Sterzycki, R. *Synthesis*, **1979**, 724.

29. De Leeuw, J. W.; De Waard, E.R.; Beetz, T. and Huisman, H.O. *Recl. Trav. Chim. Pays. Bgs.*, **1973**, *92*, 1047.

30. Brown, J.J.; Lenhard, R.H. and Bernstein, S. *J. Am. Chem. Soc.*, **1964**, *86*, 2183.

31. Thurkauf, A.; Jacobson, A.E. and Rice, K.C. *Synthesis*, **1988**, 233.

32. Seebach, D. *Synthesis*, **1969**, 17.

33. Corey, E.J. and Seebach, D. *J. Org. Chem.*, **1975**, *40*, 231.

34. Olah, E.A.; Narang, S.C.; Meidar, D.; Salem, G.F. *Synthesis*, **1981**, 282.

35. Kamitori, Y.; Hojo, M.; Masuda, R.; Kimura, T.; and Yoshida, T. *J. Org. Chem.*, **1986**, *51*, 1427.

36. Patney, H.K. *Tetrahedron Lett.*, **1991**, *32*, 2259-2260.

37. Kumar, P.; Reddy; R.S.; Singh, A.P. and Pandey, B. *Tetrahedron Lett.*, **1992**, *33*, 825-826.

38. Corey, E.J. and Shimoji, K. *Tetrahedron Lett.*, **1983**, *24*, 169-172.

39. Villemin, D.; Labiad, B. and Hamadi, M. *J. Chem. Soc. Chem. Commun.*, **1992**, 1192.

40. Tateiwa, J.; Horiuchi, H. and Uemura, S. *J. Org. Chem.*, **1995**, *60*, 4039.

41. a) Chen, S. L.; Schaub, R. E. and Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3450-3454.

b) Suzuki, M.; Kawagishi, T.; Suzuki, T. and Noyori, R. *Tetrahedron Lett.*, **1982**, *23*, 4057-4060.

42. Wohl, R.A. *Synthesis*, **1974**, 38-40.

43. a) Verzele, M.; Acke, M. and M. Anteunis, *J. Chem. Soc.*, **1963**, 5598.

b) Schank, K. and Pack, W. *Chem. Ber.*, **1969**, *102*, 1892.

c) House, H.O.; Czula, L.J.; Gall, M. and Olmstead, H.D. *J. Org. Chem.*, **1969**, *34*, 2324.

44. Suzuki, M.; Kawagishi, T.; Yanagisawa, A.; Suzuki, T.; Okamura, N. and Noyori, R. *Bull. Chem. Soc., Jpn.*, **1988**, *61*, 1299-1312.

45. Zajac, W. W. $J_R$. and Byrne, K. *J. Org. Chem.* **1970**, *35*, 3375-3377.

46. Mamedov, S. and Avanesynan, M. A. Zh. Obshch. Khim. 1962, 32, 2834-8. (CA: 1963, 58:9005f).

47. Hibbert, H. and Sturrock, M.G. *J. Am. Chem. Soc.*, **1928**, *50*, 3374-76.

48. Venkataramu, S.D.; Cleveland, J.H. and Pearson, D.E. *J. Org. Chem.*, **1979**, *44*, 3082-84.

49. Fasbender, H. *Ber.*, **1888**, *21*, 1473.

50. Hauptmann, H. and Moura Campos, M. *J. Am. Chem. Soc.*, **1950**, *72*, 1405.

51. Hoppmann, A.; Weyerstahl, P. and Zummack, W. *Liebigs Ann. Chem.*,**1977**, *9*, 1547-1556.

52. Taschner, M.J. and Kraus, G.A. *J. Org. Chem.*, **1978**, *43*, 4235.

53. Autenrieth, W. and Wolf, K. *Ber. Dtsch. Chem. Ges.*, **1899**, *32*, 1375.

54. Otera, J. *Chem. Rev.***1993**, *93*, 1449-1470.

55. Yazawa, H.; Tanaka, K. and Kariyone, K. *Tetrahedron Lett.* **1974**, 3995-3996.

56. Blossey, E.C.; Turner, L.M. and Neckers, D.C. *Tetrahedron Lett.* **1973**, 1823-26.

57. (a) Rehberg, C.E. and Fisher, C.H. *J. Am. Chem. Soc.* **1944**, *66*, 1203-1207. (b) Rehberg, C.E.; Faucette, W.A. and Fisher, C.H. *J. Am. Chem. Soc.* **1944**, *66*, 1723-1724. (c) Rehberg, C.E. *Organic Synthesis; Wiley; New York,* **1955**; *Collect Vol.3,* pp.146-148. (d) Haken, J.K. *J. Appl. Chem.* **1963**, *13*, 168-171.

58. (a) Taft, R.W., Jr.; Newman, M.S. and Verhoek, F.H. *J. Am. Chem. Soc.* **1950**, *72*, 4511-4519. (b) Billman, J.H.; Smith, W.T., Jr. and Rendall, J.L. *J. Am. Chem. Soc.* **1947**, *69*, 2058-2059.

59. (a) Osipow, L.; Snell, F.D.; York, W.C. and Finchler, A. *Ind. Eng. Chem.* **1956**, *48*, 1459-1462. (b) Osipow, L.; Snell, F.D. and Finchler, A. *J. Am. Oil. Chem.*

*Soc.* **1957**, *34*, 185-188. (c) Komori, S.; Okahara, M. and Okamoto, K. *J. Am. Oil. Chem. Soc.* **1960**, *37*, 468-473.

60. Otera, J.; Yano, T.; Kawabata, A. and Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383-2386.

61. Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B. and Zuger, M. *Synthesis* **1982**, 138-141.

62. a) Carroll, M. F. J. Chem. Soc. **1940**, 704.

b) Carroll, M. F. J. Chem. Soc. **1940**, 1266.

c) Carroll, M. F. J. Chem. Soc. **1941**, 507.

63. Taber, D.F.; Amedio, J. Jr. and Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618-3619.

64. Gilbert, J. C. and Kelly, T. A. *J. Org. Chem.* **1988**, *53*, 449-450.

65. a) Chavan, S.P.; Zubaida, P.K.; Dantale, S.W.; Keshavaraja, A.; Ramaswamy, A.V. and Ravindranathan, *T. Tetrahedron Lett.* **1996**, *37*, 233-236.

65. b) Balaji, B.S.; Sasidharan, M.; Kumar, R. and Chanda, B. *J. Chem. Soc, Chem.Commun.* **1996**, 707-708.

66. Ahmed, S. and Iqbal, J. *Tetrahedron Lett.*, **1986**, *27*, 3791-3794,

67. Yaggi, N. F. and Douglas, K. T. *J. Chem. Soc.Chem. Commun.* **1977**, 609-610.

68. Baker, R. B. and Reid, E. E. *J. Am. Chem. Soc.* **1929**, *51*, 1567-70.

69. Nakazumi, H. and Kitao, T. *Chem. Lett.* **1978**, 929-930.

70. Kobuke, Y. and Yoshida, J. *Tetrahedron Lett.* **1978**, 367-370.

71. Lopez-Alvarado, P.; Avendano, C. and Menendez, J.C. *Syn. Commun.* **1992**, *22*, 2329-2333.

72. Sakaki, J.; Kobayashi, S.; Sato, M. and Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 2262-2264.

73. Parmar, V. S.; Sinha, R.; Bisht, K. S.; Gupta, S.; Prasad, A. K.and Taneja, P. *Tetrahedron*, **1993**, *49*, 4107-4116.

74. Mukaiyama, T.; Pai, F.C.; Onaka, M. and Narasaka, K. *Chem. Lett.* **1980**, 563-566.

75. Paradisi, M. P.; Zecchini, G. P. and Torrini, I. *Tetrahedron Lett.* **1986**, *27*, 5029-5032.

76. (a) Posner G.H. and Oda, M. *Tetrahedron Lett.* **1981**, *22*, 5003-5006. (b) Rana, S.S.; Barlow, J.J. and Matta, K.L. *Tetrahedron Lett.*, **1981**, *22*, 5007-5010. (c) Posner, G.H.; Okada, S.S.; Babiak, K.A.; Miura, K. and Rose, K.K. *Synthesis.* **1981**, *11*, 789-790.

77. Benetti, S.; Ramagnoli, R.; Dekisi, C.; Spalluto, G. and Zanirato, U. *Chem. Rev.* **1995**, *95*, 1065-1114.

78, Mori, K.; Tominaga, M.; Takigawa, T. and Matsui, M. *Syn. Comm.*, **1973**,*3*, 790-791.

79. Korte, von F. and Wusten F. *Ann. Der Chemie*, **1961**, *647*, 18-22.

80. Clemens, R. J. and Hyatt, J. A. *J. Org. Chem.*; **1985**, *50*, 2431-35.

81. Williams, J. W. and Krynitsky, J. A. *Org. Syn.*; **1955**, Coll. Vol. *3*, 10.

# PUBLICATIONS

1. Monitoring the conversion of methyl 7-oxoheptanoate by gas chromatography.
   Wakharkar, R. D.; Biswas, S. S.; Borate, H. B. and **Ponde, D. E.**
   *J. Chromatography A*, **1994**, *662*, 420-423.
2. Natural Kaolinitic Clay: A Remarkable Reusable Solid Catalyst for the selective Functional Protection of Aldehydes and Ketones.
   **Ponde, D. E.**; Borate H. B.; Sudalai, A.; Ravindranathan T. and Deshpande V. H.
   *Tetrahedron Lett.*, **1996**, *37*, 4605-4608.
3. Selective Catalytic Transesterification, Transthiolesterification and Protection of Carbonyl Compounds over Natural Kaolinitic Clay.
   **Ponde, D. E.**; Deshpande, V. H.; Bulbule, V. J.; Sudalai, A. and Gajare, A. S.
   *J. Org. Chem.*, **1998**, *63*, 1058-1063.
4. Synthesis of antitumor antibiotic Resorthiomycin-
   **Ponde, D. E.**; Ramalingam, S.; Borate, H. B. and Deshpande, V. H.
   (To be communicated).
5. A mild and efficient methodology for thiol esterification-
   **Ponde, D. E.**; Ramalingam, S.; Borate, H. B. and Deshpande, V. H.
   (To be communicated).
6. Synthetic approaches directed towards camptothecin.
   **Ponde, D. E.**; Gokhale, N. J.; Jnaneshware, G. K.; Borate, H. B. and Deshpande, V. H. 10$^{th}$ IUPAC International Conference on Organic Synthesis, Bangalore (India), Dec. 11-15 (1994).