SYNTHESIS OF ADVANCED TAXOIDS AND ORGANIC FUNCTIONAL GROUP TRANSFORMATIONS USING HOMOGENEOUS AND HETEROGENEOUS CATALYSIS

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By

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Dedicated to my Parents, Teachers and Friends

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**SYNTHESIS OF ADVANCED TAXOIDS AND ORGANIC FUNCTIONAL GROUP TRANSFORMATIONS USING HOMOGENEOUS AND HETEROGENEOUS CATALYSIS**" by Mr. A. Ramani was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

Bhanu

(B. CHANDA)

Dr. (Mrs). Bhanu Chanda

Research Supervisor

PREFACE

The work presented in this thesis encompasses some aspects of Synthesis of advanced taxoids and organic functional group transformations using homogeneous and heterogeneous catalysis. **"Chemistry with a purpose"** is a theme that is greatly practiced in this research programme. Under this, development of environmentally friendly processes and technologies are focussed at. It is indeed gratifying to note that in the present thesis work, a small beginning has been made towards this goal and the results obtained are very encouraging.

Two parallel objectives are met with in this thesis work, viz. synthetic studies towards diastereoselective synthesis of taxane diterpenes and application of catalytic materials like silicalite, hydrotalcite like compounds and organometallic species for some important organic group transformations.

The work presented in this thesis is divided into three chapters. The first chapter briefly reviews some of the recent developments in taxane diterpenes. In chapter, some of the novel and newer routes to taxanes with particular emphasis on the convergent approaches are discussed.

The second chapter that presents some synthetic studies towards the advanced taxoids and protaxoids is further divided into three parts.

The first part of the second chapter, itself divided into two sections includes in the first section, synthesis of (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde and in second section, a synthetic route to (S)-(-)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde is reported. Both these compounds form the A-ring core of taxol, the former in the racemic form and the latter in optically active form.

The second part of the second chapter describes an approach to a diastereoselective synthesis of "B-*seco*-taxoids", useful intermediates to advanced taxoids. The most important

among the simplified taxol analogues are the C-aromatic taxoids. In this part of the chapter, synthesis of "B-*seco*-taxoids" *via* C2-C3 bond formation involving C-aryl metal species (cerium, lithium and magnesium) have been described.

The third and final part of the second chapter depicts attempted synthetic studies towards protaxoids. Some model studies have been carried out to study the feasibility of intramolecular carbonyl ene-reaction for the construction of the 8-membered ring.

The third chapter deals with some organic functional group transformations using homogeneous and heterogeneous catalysis. It is sub-divided into three parts. In the first part, potential of newly developed catalysts like chromium silicalite (CrS-2) and Zirconium substituted hydrotalcites in the oxidation of phenols to p-benzoquinone and catechol respectively is explored.

In the second part of the third chapter, the utility of hydrotalcites in the synthesis of coumarins is demonstrated. Application of Ni-based organometallic species for the activation of Heck-type coupling is the subject matter of the third part of the third chapter.

Replacement of stoichiometric processes by catalytic processes has resulted in development of methodologies, which are environmentally friendly with waste minimisation.

References related to the work from reviews and individual papers have been cited wherever necessary. It inadvertently any information is left out, it is just an oversight and unintentional.

ACKNOWLEDGEMENTS

It gives me great pleasure in acknowledging my deep sense of gratitude to **Dr. T. Ravindranathan,** Deputy Director and Head of Organic Chemistry: Technology Division, National Chemical Laboratory for his constant encouragement and moral support without which this work would not have attained completion.

It is a great pleasure and privilege to be associated with **Dr. (Mrs) Bhanu Chanda**, my research guide and mentor who helped me in my work with her support and expertise in the form of useful suggestions and to learn and think more about chemistry. I thank her for her excellent guidance, teaching and the feathered care during the ups and downs of my research life. I also take this opportunity to thank her for the help rendered in the preparation of this thesis.

I am thankful to the senior scientists, **Dr. H.R. Sonawane** (*Emeritus Scientist*), **Dr. S. Sivasankar, Dr (Mrs) V. Ramaswamy, Dr. A. Sudalai** and **Dr. S. Iyer** for their keen interest and involvement in my research work.

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I thank my colleagues Mr. B.S. Balaji, Mr. M.M. Jakkam, Mr. K. Saravanan, Mr. Dilip Kumar Maji and Ms. Renu Vyas for their excellent co-operation in the laboratory.

All those who have helped me directly or indirectly in many ways for the successful completion of my degree work will be remembered for a long time to come. I am grateful to one and all.

The moral support given by my brothers Sugumaran (anna), Pushparaj (thambi), Raghunath (kuttipaiyan) is like a catalyst to take research as my carrier. I would like thank my uncle **Mr.V.Eleyaperumal** (Scientist at BHEL, Trichy) for his help rendered by him for my education thoughout i.e., from H.Sc. to Ph.d.

It is a nice feeling to be amidst many friends, in their delightful and memorable company. It is a pleasure to thank them all.

Assistance rendered by analytical and spectroscopic sections (NMR, IR, GC, Mass and microanalysis) is gratefully acknowledged.

Thanks are due to Mrs. Kulkarni, Mr. Kulkarni and Mr. Bhujang for their technical assistance in the preparation of this thesis.

Thanks are due to **CSIR-New Delhi** for the financial assistance in the form of junior and senior research fellowships during the Ph.D. programme.

Finally, I am grateful to the **Director, NCL** for providing me the necessary facilities and for his permission to carry out my research work at NCL and submit the same in the form of a thesis.

A. Ramani

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Abbreviations

Ac	Acetyl
aq.	Aqueous
TBS	t-Butyl dimethyl silyl
TBDMSCl	t-Butyl dimethyl silyl chloride
n-BuLi	Butyl lithium
CAN	Ceric ammonium nitrate
$Cu(acac)_2$	Copper acetylacetonate
DBU	Diaza bicyclo undecene
DCM	Dichloro methane
Et_2O	Diethyl ether
DHP	Dihydropyran
DIBAL H	Diisobutyl aluminium hydride
DMAP	4-Dimethyl amino pyridine
$Rh_2(OAc)_4$	Dirhodium tetra acetate
gm	gram
hr.	hour
HF	Hydro fluoric acid
IR	Infra red
LAH	Lithium aluminium hydride
LDA	Lithium diisopropyl amide
MsN_3	Mesyl azide
mg	milli gram
pNBSA	p-Nitro benzene sulphonyl azide
NMR	Nuclear magnetic resonance
$Pd(OAc)_2$	Palladium acetate
$PdCl_2$	Palladium chloride
K_2CO_3	Potassium carbonate
$RhCl_3$	Rhodium chloride
$NaHCO_3$	Sodium bicarbonate
$NaBH_4$	Sodium borohydride
Na_2CO_3	Sodium carbonate
NaH	Sodium hydride
Na_2SO_4	Sodium sulphate
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
temp.	Temperature
TLC	Thin layer chromatography
pTSA	p-Toluene sulphonic acid
$VO(acac)_2$	Vanadyl acetylacetonate

ABSTRACT

The thesis entitled "**Synthesis of Advanced Taxoids and Organic Functional Group Transformations using Homogeneous and Heterogeneous Catalysis**", is divided into three main chapters. The title of the thesis clearly indicates that there are two parallel objectives *viz.* synthetic studies towards diastereoselective synthesis of taxane diterpenes and application of catalytic materials such as silicalite, hydrotalcite-like compounds and organometallic species for organic functional group transformations. The first chapter briefly reviews some of the recent developments in taxane diterpenes. The second chapter describes the synthetic studies towards the advanced taxoids and protaxoids and is further divided into three parts. The first part of second chapter is divided into two sections namely, section 1: synthesis of (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde and section 2: synthesis of (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde. The second part outlines the diastereoselective synthesis of "B-secotaxoids", useful intermediates for advanced taxoids. The third part describes attempted synthetic studies towards bicyclo(5.3.1) undecane ring systems (protaxoids). The third chapter constitutes application of the heterogenous and homogeneous catalysis for organic functional group transformations and is further divided into three parts. The first part examines the synthetic potential of two newly developed catalysts chromium silicalite (CrS-2) and Zirconium substituted hydrotalcite like compounds, for the selective oxidation of phenols to p-benzoquinones and to catechol respectively. The second part highlights the utility of hydrotalcite, the anionic clays, for the synthesis of coumarin and some of its analogues. The third part deals with the application of nickel based organometallic species, for the activation of Heck-type coupling. Each chapter except the first chapter begins with a brief overview of the latest developments in the respective areas, clearly stating the objectives, results and discussion ending with a conclusion and experimental details.

Chapter-I : Taxane diterpenes : A brief review

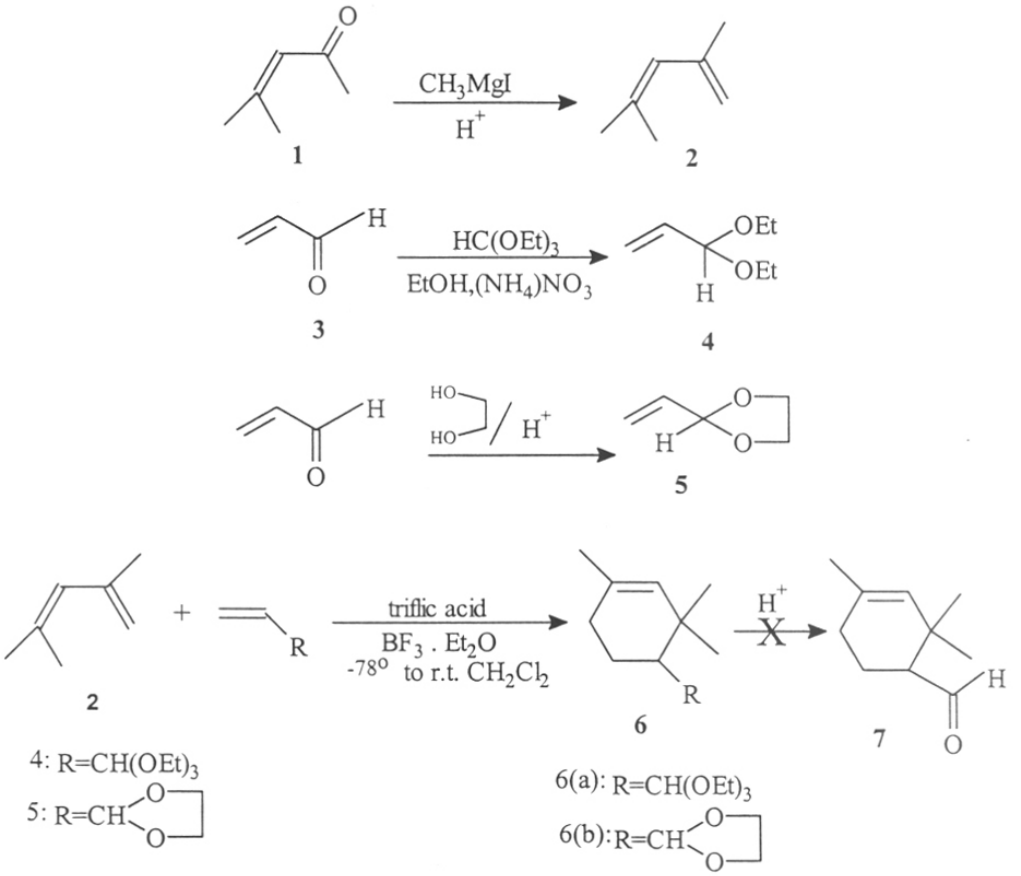
This chapter covers a general introduction to taxane diterpenes[1], along with a brief account of isolation[2], biosynthetic pathway and complexity involved in the construction of the taxane framework, pharmacological activity and some of the novel and newer routes to taxanes with particular emphasis on the convergent approach .

Chapter-II : Part-I :

Section-1: Synthesis of (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde

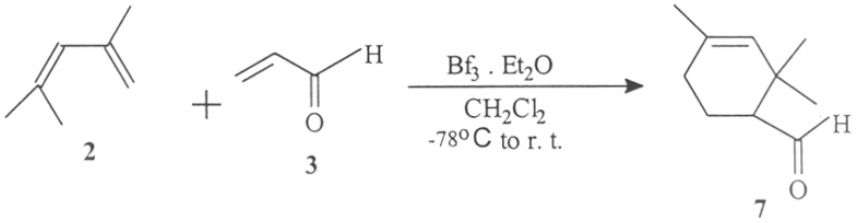
The main emphasis in this section is the development of a preparative and scalable route to (±)-A-ring system of taxol. This section also briefly reviews various approaches reported in the literature for (±)-A-ring unit of taxol. The route developed in the present work involving Diels-Alder reaction[3] of the appropriate diene and dienophile was effective in a large scale preparation of the (±)-A-ring unit. (**Scheme-1**)

SCHEME 1



The key Diels-Alder adduct (**7**) was obtained via allyl-cation mechanism[4] as depicted below: (**Scheme 2**)

SCHEME 2



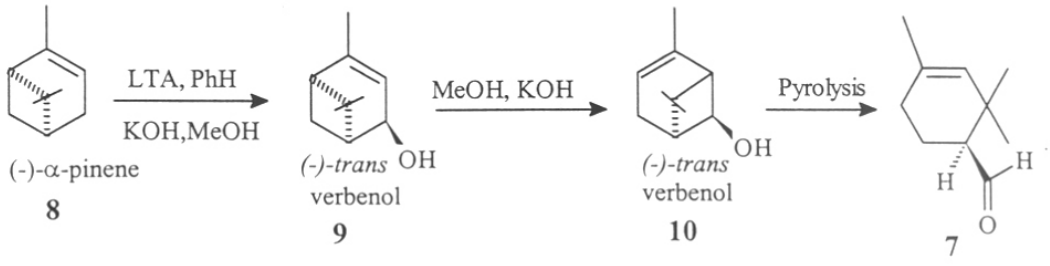
Section 2:

Synthesis of (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde

The relationship[of the structure of A-ring unit of taxol (**7**), to that of *trans*-chrysanthenol (**10**), [a, retro-ene reaction product of A-ring unit (**7**)] strongly prompted the use of readily available α-pinene (available in both enantiomeric forms), as an ideal starting material to arrive at optically active A-ring unit of taxol. This route offers a new avenue to the synthetic

studies towards the taxane diterpenes. Thus (-)-α-pinene (**8**) was converted into (-)-*trans*-verbenol (**9**) and pyrolysis of the latter led to optically active A-ring unit[8] (**7**) (**Scheme 3**)

SCHEME 3

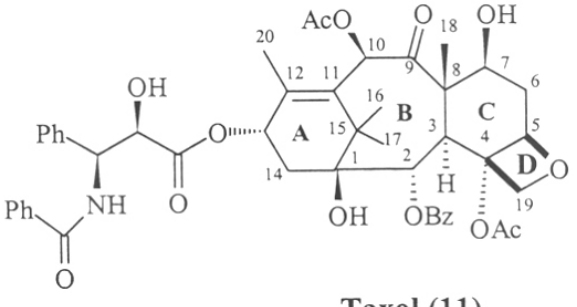


Improvement in the yields and the mechanism of the above transformation is also be discussed. The routes mentioned for racemic as well as optically active A-ring sub-unit of taxol offer good scope for their preparation in large quantities and also open up new synthetic strategies in taxane chemistry.

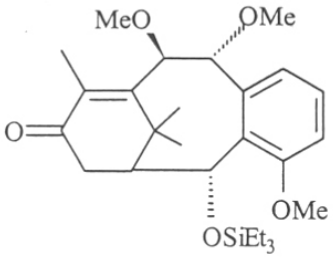
Part II

Diastereoselective synthesis of "B-seco-taxoids", versatile intermediates for advanced taxoids

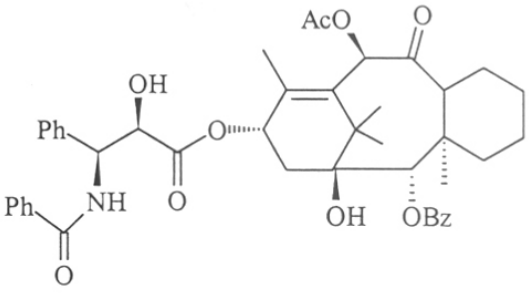
Sensitive functionalities present in natural taxol (**11**) has permitted only minor structural modifications to Structure- Activity-Relationship informations (SAR). However, simplified analogues that can be obtained *via* total synthesis can provide further an insight into the study of structure-activity relationship which can possibly enhance taxol's therapeutic activity. Several schools all over the world attempted to synthesize many simplified taxol analogues. The most important among them are C-aromatic taxoids. Such advanced taxoids possessing C-aromatic ring have been synthesized by Kuwajima[6], Nicolaou[7], Swindell[8], and Wender[9]. Some of them were found to possess activity similar to that of taxol.



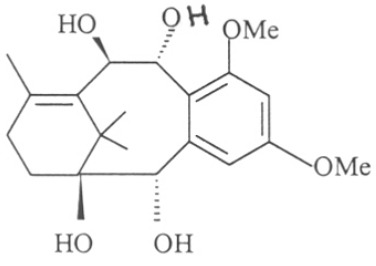
Taxol (11)



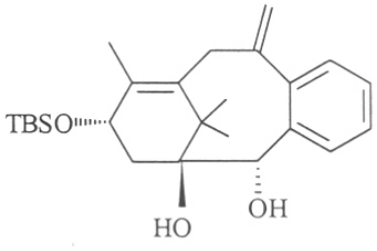
Kuwajima's taxoid (13)



Nicolaou's taxoid (14)



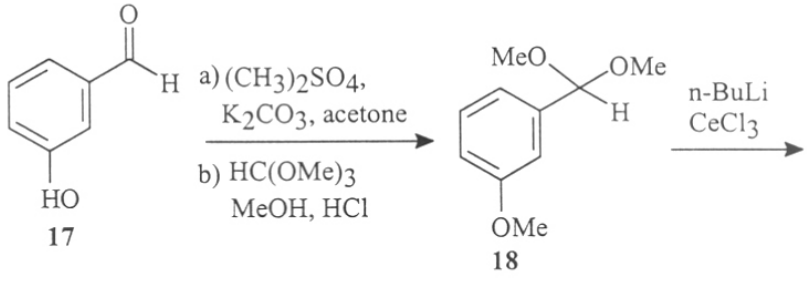
Swindell's taxoid (15)

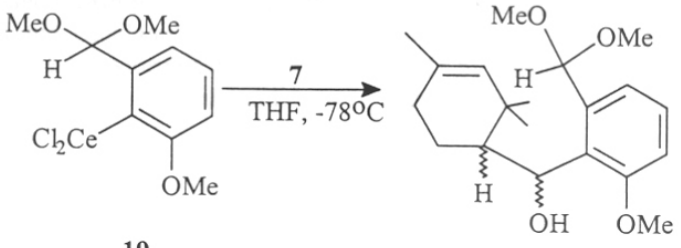


Wender's taxoid (16)

Vinylogous aldol condensation, McMurry coupling and cleavage strategies were applied in the synthesis of advanced taxoids. The present work was focussed towards the synthesis of "B-*seco*-taxoids" via C2-C3 bond formation using C-aryl metal species (Cerium, Lithium and Magnesium) and lead to them to taxane skeleton *via* intramolecular carbonyl-ene reaction. Various "B-*seco*-taxoids" have been synthesized in good chemical and optical yields following synthetic schemes are shown below.

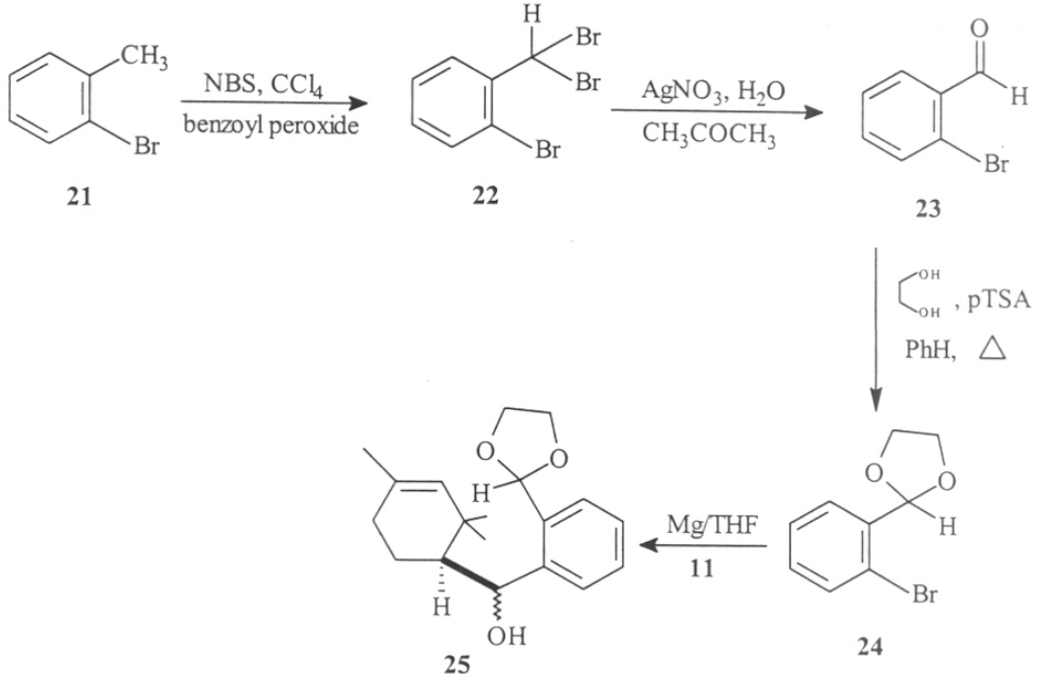
SCHEME 4





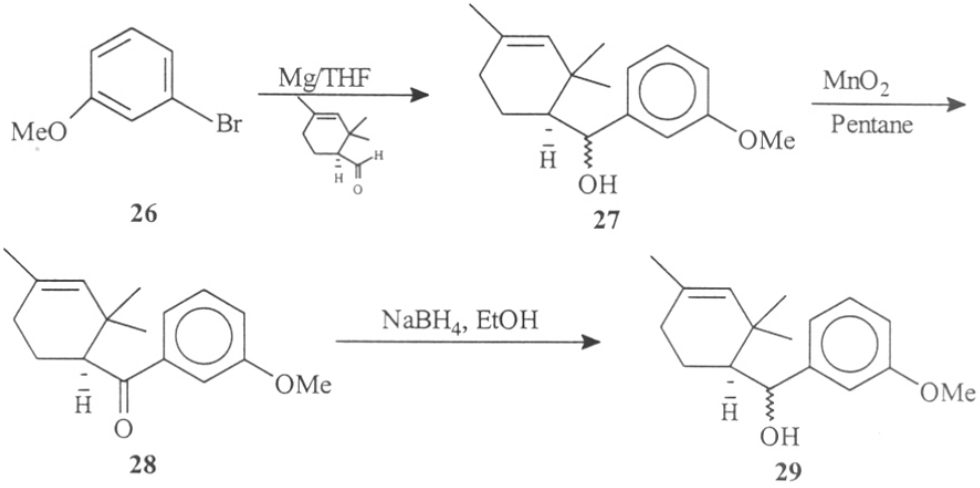
19 20

SCHEME 5



21 22 23 24 25

SCHEME 6



26 27 28 29

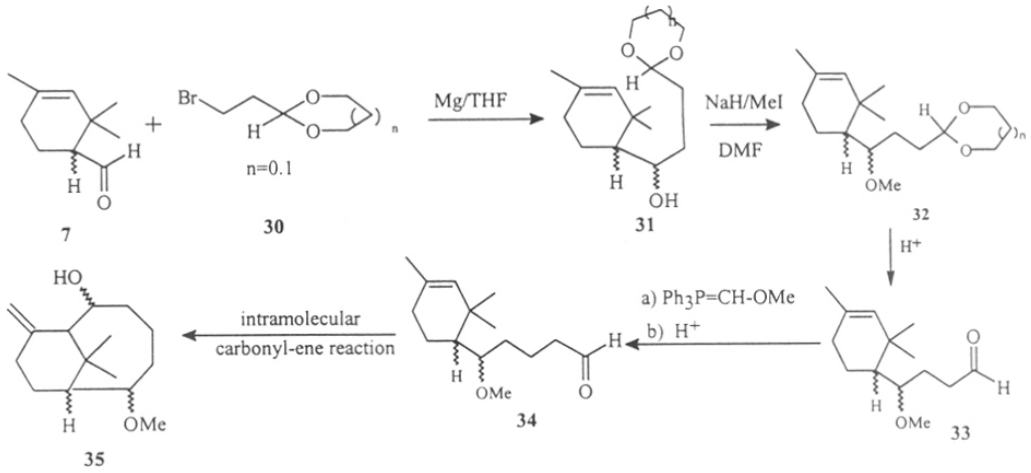
Among the "B-*seco*-taxoids" obtained, **20** and **25** are useful intermediates to obtain Kuwajima's (**12**) and Nicolaou's (**13**) Taxoids respectively. C-2-oxygenated taxoids thus obtained can also be transformed to advanced taxoids by further synthetic manipulations. Thus, **20, 25, 27-29** all are potential candidates to various advanced taxoid congeners and for the study of SAR .

Part III

Synthetic studies towards bicyclo [5.3.1] undecane ring system

Attempts were made to obtain bicyclo[5.3.1] undecane ring system (Protaxoids), from the (±)-A-ring unit of taxol. Three carbon synthons 2-(2-bromoethyl)-1,3-dioxolane and 2-(2-bromoethyl)-1,3-dioxane were prepared and coupled with A-ring unit via C2-C3 bond formation in order to study the feasibility of intramolecular carbonyl ene-reaction[10]. The various transformations are covered in the following scheme. (**Scheme-7**)

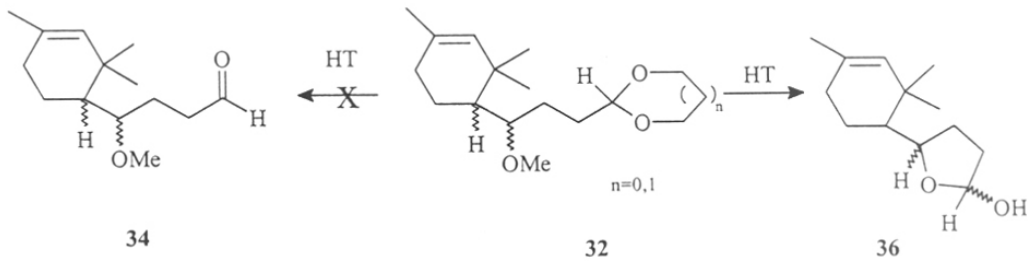
SCHEME 7



7 30 31 32 33 34 35

However, attempted deprotection of methoxyacetal (**33**) under various standard deprotection conditions yielded the lactol (**37**) exclusively with no formation of the methoxyaldehyde (**34**). (**Scheme 8**)

SCHEME 8



34 32 36

Such a lactol formation is probably unexpected and unprecedented.

Chapter III

Organic functional Group Transformations using Homogeneous and Heterogeneous Catalysis

Latest arrivals in the heterogeneous catalysis scene are Chromium silicalite[11]" (CrS-2) and Hydrotalcite-like compounds[12]. The efficiency of heterogeneous catalytic transformations, transition-state shape and site selectivity, the ability to recognize, discriminate and organize molecules at the active site, unique-properties of the framework metal-ions, e.g. acid (Lewis acid and Bronsted), base and oxidizing properties etc., coupled with the ease of operation, environmental acceptance and consequent industrial applications have brought the interface of organic synthesis and catalysis at the centre stage.

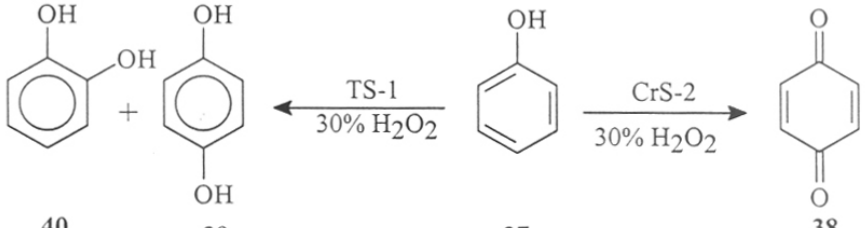
Part-I : Section 1

Selective oxidation of phenols to Quinones with hydroperoxides catalyzed by chromium silicalite CrS-2:

Various oxidizing agents bearing chromium are known for a long time in literature. These reagents generally produce toxic metallic wastes. Hence, chromium silicate has been recently synthesised and its synthetic applications for various organic functional group have been recognized[13]. It is important to note that chromium silicalite does not yield toxic metallic waste and furthermore it is required in catalytic quantity to carry out oxidative organic functional group transformations.

In this section, a method for the selective oxidation of phenols to p-benzoquinones with peroxide and catalysed by CrS-2 is demonstrated. (**Scheme 9**)

SCHEME 9



40 39 37 38

Some of the reasons for product selectivity are also discussed.

Part I: Section 2:

Selective hydroxylation of phenol to catechol with H_2O_2 using Zr^{4+} containing Zr-HT-like compounds

Hydrotalcite-like compounds are a new family of compounds having the general formula $[M(II)_{1-x}\ M(III)_x(OH)_2]^{x+}\ [A^{n-}_{x/n}\ yH_2O]^{x-}$

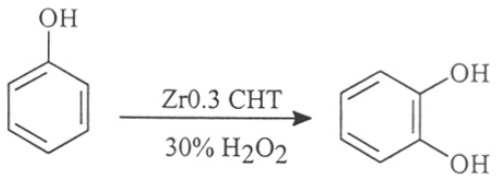
where M(II) = Cu^{2+}, NI^{2+}, CO^{2+}, Zn^{2+}, Mn^{2+} and M(III)= Al^{3+}, Fe^{3+}, Cr^{3+}, Ca^{3+}, V^{3+}, Ru^{3+}, RH^{3+} etc.

A large number of HT-like compounds with a wide variety of M(II), M(III) cation pairs have been reported in recent years[14] by the isomorphous replacement of Mg^{2+} ions. Zr^{4+} containing hydrotalcites with various Mg:Al:Zr atomic ratio were synthesized by coprecipitation method at room temperature, by adding a mixture of aqueous solutions containing $Mg(NO_3)_2$, $Al(NO_3)_3$ and $ZrO(NO_3)_2$ to a mixture of NaOH and Na_2CO_3 dropwise at constant pH (10). The presence of Zr^{4+} ion in the hydrotalcite-layers was confirmed by PXRD and UV-Vis DRS techniques.

The rationale behind the synthesis of Zr containing hydrotalcite-like compounds stems from the fact that , Zr-silicalites have been synthesized and applied as catalysts for liquid phase hydroxylation/oxidation of various organic substrates[15].

In the present study, catalytic performance of Zr containing hydrotalcite-like compound for liquid phase hydroxylation of phenol is reported. (**Scheme 10**)

SCHEME 10



37 **40**

Catechol is obtained as a product with 100% selectivity, it is found that the Zr incorporated in the HT framework plays a pivotal role for this catalytic activity. The mechanistic factor responsible for the observed o-selectivity is also discussed.

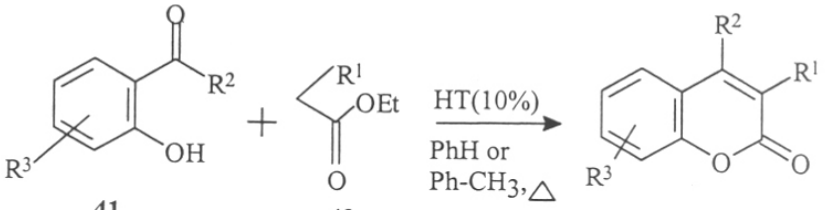
Part II

A convenient, one-pot synthesis of coumarins (2H-Benzopyran-2-ones) catalyzed by hydrotalcite-like anionic clays

Hydrotalcite, a mixed hydroxycarbonate of magnesium and aluminium, used as a basic catalyst either as such or after calcination around 723K, offers a highly active and well dispersed mixed metallic oxides with MgO-type structure. The resulting material possesses pronounced basic characters and have been used potentially, as base catalyst for aldol condensation[16], Claisen-Schmidt condensation[17] and Knoevenagel condensation[18]. The basic strength of hydrotalcite is comparable to that of piperidine and pyridine in homogenenous catalysis.

Utilizing the basicity of hydrotalcite-like anionic clays, the synthesis of coumarins [benzopyran-2(2H)-ones] from α-substituted ethylacetates and 2-acylphenols have been successfully accomplished. (**Scheme 11**)

SCHEME 11



41 **42** **43**

R^1=$COCH_3$, CO_2Et, CN, H

R^2=H, CH_3; R^3=H, OCH_3

Hydrotalcite-like compounds have been found to efficiently catalyze the synthesis of coumarin and its analogues in high yields and with almost 100% selectivity.

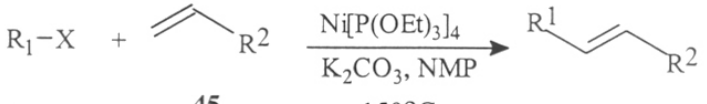
Part-III

Ni(o) catalyzed Reactions of Aryl and Vinyl halides with Alkenes and Alkynes:

Palladium-catalyzed vinylation of aryl halides (X = I, Br, Cl) provides a very powerful method for forming carbon-carbon bonds (Heck-reaction) at the unsaturated vinylic position[19]. Such reactions represent one of the most versatile tools in modern synthetic organic chemistry and has great utility for industrial applications. Although recent advances in homogeneous[20]- and heterogeneous[21] Heck catalysis have been made, the properties and activities of the existing catalysts have as yet, limited industrial applications.

It has been observed and demonstrated that $Ni[P(OEt)_3]_4$ complex efficiently catalyzes Heck-type coupling. Aryl/vinyl halides with 2-4 equiv. of alkenes/alkynes, in the presence of 2.5 equiv. of K_2CO_3 and 0.01 equiv. of $Ni[P(OEt)_3]_4$ were reacted at 150°C in degassed NMP to get vinylated products in high yields. (**Scheme 12**)

SCHEME 12



44 **45** **46**

R^1= alkyl, aryl

R^2= aryl, alkyl, CO_2R

X = I, Br

The new catalyst system $Ni[P(OEt)_3]_4$ has successfully been employed in Heck-type coupling reactions. The use of $Ni[P(OEt)_3]_4$ reveals the feasibility of a cheaper catalyst for the Heck reactions.

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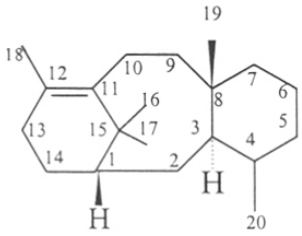
Chapter I

Taxane Diterpenoides:a brief review

In the field of cancer chemotherapy, Taxol enjoys a unique position. The discovery of taxol of ranks as one of the most significant events in the field of naturally occurring anti-cancer agents. In addition, many analogues of taxol have been isolated which possess varying degrees of oxygenation pattern. These compounds are derived from the parent taxane skeleton system (**1**) as indicated below:



(1)

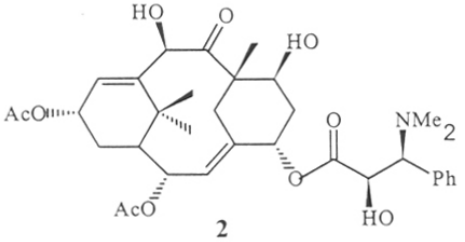
The *taxane diterpenoides* form a unique class of natural products with unusual molecular architecture or closely related skeletons and occur in various members of the genus *Taxus (taxaceae)* and closely related genera. The numbering system used for taxane skeleton is adopted by IUPAC[1] and according to the IUPAC nomenclature, the basic ring system is that of [9.3.1.$0^{3,8}$] pentadecene.

History of taxane diterpenoids:

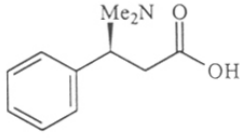
The history of *taxane diterpenoids* is highly instructive for those interested in drug development and its inherent difficulties. Initial interest in the constituents of taxus species was sparkled by the known toxicity of *Taxus baccata*, or English Yew, since human fatalities due to ingestion of this plant were recorded as long ago as the first century B.C. from Greek civilization. Julius Caesar, speaking of his wars against the Gallic tribes, writes "Catuvolcus", who was the king of half the Eburones and had joined Ambiorix in the conspiracy, was now old and weak, unable to endure the hardships of flight or fight. He solemnly cursed Ambiorix for instigating the conspiracy, and then poisoned himself with yew, a tree which is common in Gaul and Germany.[2] Then, for many centuries, the *yew* tree was regarded as the tree of death, and its toxic constituents provided a death potion in Julius Caesar's time. It is

thus ironic and encouraging that this same tree should now give cause for hope in fight against cancer.

The chemical study of a *Taxus* species was carried out by Lucas[3] who in 1856 isolated an ill-defined alkaloidal substance which he named Taxine (**2**). Although 'taxine' is almost certainly responsible for a major part of the taxocity of the yew, it proved to be a mixture of related compounds and to be very difficult to work with it, due to its instability. Early work on taxine was carried out by German, French, Italian, English, Swiss and Japanese scientists during the period of 1856-1943[4], but out of this work only that of Winterstein and his colleagues resulted in structure elucidation of a significant fragment of the mixture. These investigators obtained a nitrogeneous acid on acid hydrolysis of 'taxine' and determined its structure as 3-(dimethylamino)-3-phenyl propanoic acid (**3**); it was later named **"Winterstein's acid".**[5]

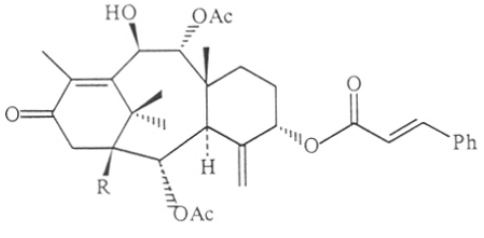


2



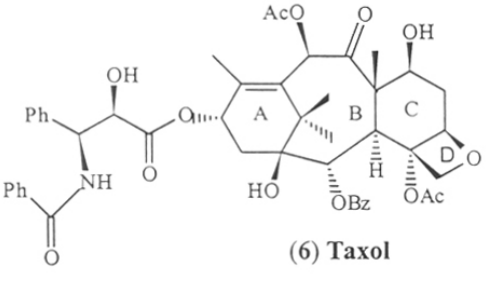
3

Later, an English group headed by Lythgoe[6] worked with material from <u>*Taxus baccata*</u> and determined the structure of its major ester as o-cinnamoyl taxicin-I-triacetate (**4**). The Japanese workers, using <u>*Taxus cuspidata*</u>, Japanese yew, as their starting material, isolated material, o-cinnamoyl-II-triacetate or taxinine (**5**) as a major component and independently determined its structure.[7]



(**4**) : R=OH
(**5**) : R=H, **taxinine**

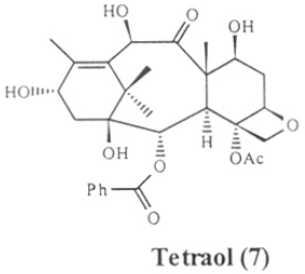
Three decades back, the bark, twigs, needles and fruits of *Taxus brevifolia,* the pacific yew tree were collected in the north-west USA for a joint project sponsored by the US department of Agriculture and National Cancer Institute to search for new sources of anti-tumour drugs. United States forest service botanist A. Borclay collected the samples of bark of pacific yew, *Taxus brevifolia Nutt*, from an Oregon forest in 1962. These samples were sent by the NCI to Wani and Wall, chemists at the Research Triangle Institute of North California. Initial screening of a crude extract of the bark showed cytotoxicity against leukaemia and inhibitory action against a variety of tumours. Investigation of this extract was made difficult by the low yields of the active compounds but its structure was finally elucidated and the compound was named Taxol[8] (**6**).



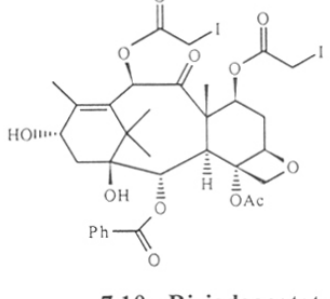
MF: $C_{47}H_{51}NO_4$
M.P. 213-216 °C
$[\alpha]_D^{20} = -49°$ (MeOH)

(6) **Taxol**

The key reaction in the structure elucidation was the cleavage of taxol by mild methonolysis[9] (base-catalyzed) to a N-benzoyl- β-phenylisoserine methyl ester ad a tetraol (**7**). The structure of tetraol was unambiguously established by X-ray crystallography of its 7,10-bisiodoacetate (**8**) at Duke University.

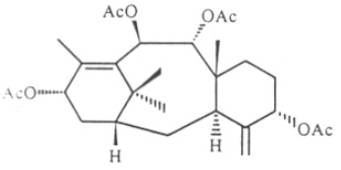


Tetraol (7)

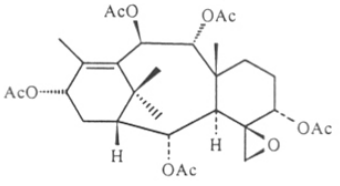


7,10 - Bisiodoacetate (8)

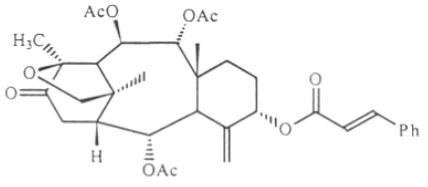
Some other taxanes are exemplified by taxusin (9)[10], baccatin III (**10**)[11], taxagifine (**11**)[12], baccatin III (**12**), 10-deacetylbaccatin (**13**), taxotere (**14**) etc.



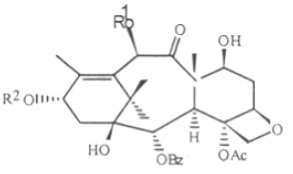
Taxusin (9)



Baccatin I (10)



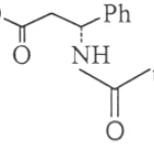
Taxagifine (11)



(**12**) R^2=H, R^1=Ac; **Baccatin-III,**

(**13**)R^2=H, R^1=H; **10-Deacetyl baccatin-III**

(**14**) R^2=

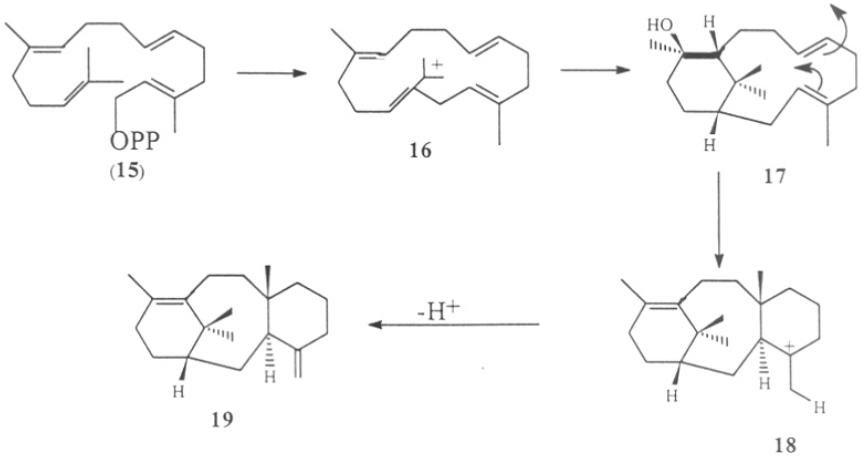


tBu,R^1,H,**Taxotere**

Biosynthesis of *taxane diterpenoids*

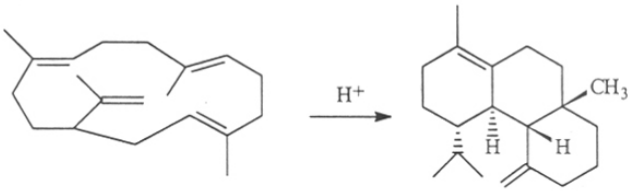
The taxane ring system itself most probably arises by electrophilic cyclization of geranylgeranyl pyrophosphate (**15**), possibly through a cationic intermediate such as (**16**). The formation of epi-verticillol (**17**) and/or epi-cembrene intermediates has been suggested[13] (**Scheme 1**).

SCHEME 1



Although the proposed biosynthetic pathway is evidently reasonable, experimental support has not been achieved so far. The treatment of cembrene (**20**) with acid yielded the tricyclic product (**21**)[14]. (**Scheme 2**)

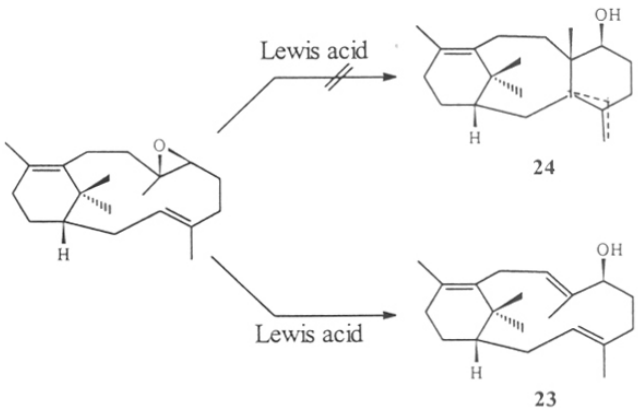
Scheme -2



20 **28**

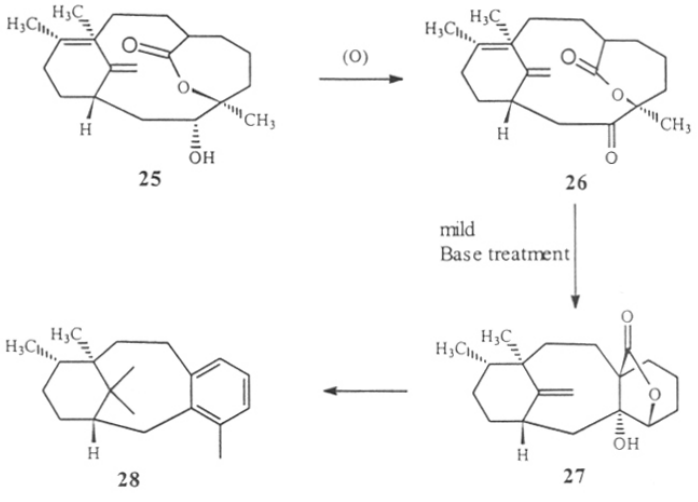
Treatment of verticillene 7,8-epoxide (**22**) with Lewis acids yielded only products resulting from rearrangements of the epoxide ring (**23**) and not the expected cyclization product (**24**) (**Scheme 3**).

Scheme -3



One experiment has yielded a skeleton related to taxane. Oxidation of clemolide (**25**) gave a ketoester (**26**), which yielded a lactone (**27**) upon treatment with mild base and the final taxane type skeleton (**28**) on more vigorous base treatment.[15] This transformation offers an interesting model for further biosynthetic work. (**Scheme 4**)

Scheme -4



25 26 27 28

Cancer and chemotherapeutic agents

The term '**Cancer**' refers to more than hundred forms of the disease. The thirty trillion cells of the normal, healthy body live in a complex, interdependent condomnium, regulating one another's proliferation. Normal cells reproduce only when instructed to do so by other cells in their vicinity. Such unceasing collaboration ensures that each tissue maintains a size and architecture appropriate to the body's needs.

Cancer cells, in stark contrast, violate this scheme; they become deaf to the usual controls on proliferation and follow their own agenda for reproduction. They also possess an even more insidious property, i.e., the ability to migrate from the site where they began to invade nearby tissues and form masses at distant sites in the body. Tumours composed of such malignant cells become more and more aggressive over time, and they become lethal. They disrupt the tissues and organs needed for survival of the organism as a whole.

Treatments for cancers

Broad categories of cancer treatments include:

Surgery to remove a tumour or diseased tissue. It is the primary mode of treatment for most solid tumours. Surgery becomes extremely difficult in the case of disseminated cancers.

Radiation to kill tumour cells. Sometimes used as a primary form of treatment, it is more often an adjunct to other therapies. The radiation may be aimed at a tumour from outside of the body, or it may be delivered by placing radioactive pellets at cancerous site. Radiation therapy besides curing cancers is accompanied by toxic-side reactions.

Biological therapies, which are based on complex substances, found in living organisms. They include immunotherapies, which attempt to turn body's immune system against cancer.

Hormone-blocking and hormone-supplementing therapies, which affect the rate at which tumour cells grow, multiply or die.

Bone marrow transplantation usually applied for blood cancer patients. It is not a therapy in itself, but is sometimes used to strengthen the depleted blood, improving the system of a patient weakened by high, potentially curative doses of radiation or chemotherapies.

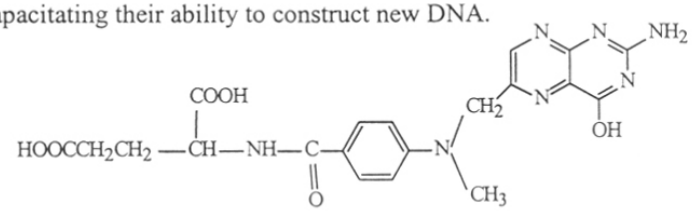
Chemotherapy, the use of drugs to kill tumour cells. It too, has a major role in most cancer treatments. Several classes of chemotherapeutic drugs act by various means, most frequently, by inhibiting the ability of tumour cells to replicate correctly. This treatment is most resorted to after all other methods of therapy have failed.

The development of an ideal cancer chemotherapeutic agent is extremely difficult, because there is little difference between the normal cells and the malignant cells, which proliferate spontaneously. The cancer cells are not really foreign to the host and they are therefore unable to elicit immunological response. Unlike anti-bacterial drugs, which may be bacteriostatic, an anti-cancer agent has to be administered until every single 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. A brief description of the families of chemotherapeutic agents and their mode of action at this jucture will be very appropriate.

Families of chemotherapeutic drugs

An antimetabolite is a chemical substance whose biological activity depends on interference in utilization of a normal metabolite in the body. Such an anti-cancer compound acts as a false substance in the biochemical reaction of a living cell. A prime example of such drug is methotreate[16], which is a chemical analogue

for the nutrient folic acid. Methotrexate functions, in part, by binding into an enzyme normally involved in the conversion of folic acid into two of the building blocks of DNA, adenine and guanine. This drug thus prevents cells from dividing by incapacitating their ability to construct new DNA.



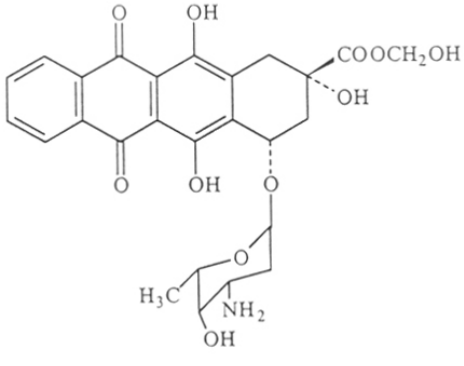
Methotrexate

(29)

Topoisomerase inhibitors

Replication of cell's genetic material requires some means to pull the DNA double helix apart into two strands. This separation is typically accomplished with the aid of a special 'topoisomerase' that temporarily cleaves one strand, posseses the other strand through the break and then reattaches the cut ends together. Drugs that inhibit the ability to topoisomerase enzymes to reattach the broken ends cause pervasive DNA strand breaks in cells that are dividing, a process that causes cells to die.[17]

e.g.: Doxorubicin



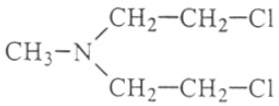
(30)

Alkylating agents

The term alkylating agents refers to alkylation of substrate by a variety of chemical agents. The substance may be any electron-rich biological system, such as amino, sulfhydryl, organic and inorganic anions. As the alkylating agents are electrophilic, they react with a variety of nucleophiles. The alkylating agents react reversibly with the biological substrate through formation of covalent bonds.

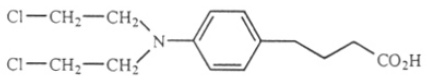
Biologically, alkylating agents form chemical bonds with particular DNA building blocks and so reproduce defects in the normal double helical structure of the DNA molecule. This disruption may take the form of breaks and inappropriate links between (or within) strands. If not mended by various DNA repair mechanisms available to the cells, the damage caused by these chemicals will trigger cellular suicide.

Compounds belonging to the class of 2-chloroethylamine are commonly known as the classical alkylating agents[11] or as nitrogen mustards. Due to their cytotoxic properties, they are used as possible anti-cancer compounds. The first nitrogen mustard derivative to be used extensively and clinically was mechlorethamine[18] (**31**).

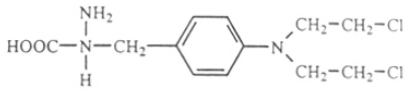


(31)

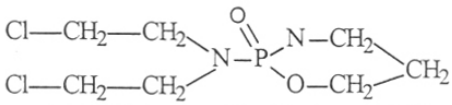
Effective nitrogen mustards, which are widespread in clinical use against tumours, are given below.[19]



Chlorambucil (32)



Phenylalanine mustard (33)



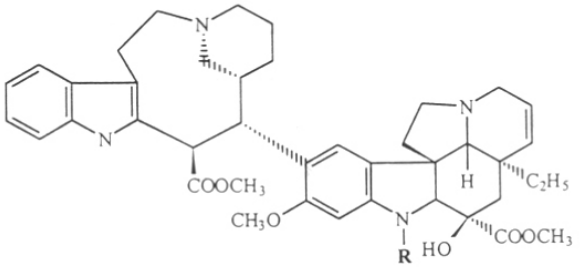
Cyclophosphamide (Endoxan) (34)

Nitrogen mustards are clinically administered as water-soluble hydrochlorides in the treatment of lymphosarcoma, leukaemia, bronchogenic carcinoma, ovarian carcinomaand other types of disseminated cancers.

Plant Alkaloids

Plant alkaloids prevent cell division by binding to the protein tubulin. Tubulin, as its name implies, forms microtubular fibres that help to orchestrate cell division. These fibres pull duplicate DNA chromosomes to either side of the parental cell, ensuring that each daughter receives a full set of genetic blueprints. Drugs that interfere with the assembly or disassembly of these tubulin fibres can prevent cells from dividing successfully. The vinca alkaloids, vincristine and

vinblastine derived from the shrub vinca rosea are widely used in cancer chemotherapy.[20]



(**36**) : R= CHO , **Vincristine**
(**37**) : R= CH_3 , **Vinblastine**

Cancer Therapeutic Activities of Taxane Diterpenoids

Among the cancer chemotherapeutic agents, taxol (one of the most important taxane diterpenoid) has a unique mode of action by inhibitng mitosis through the enhaoncement of polymerization of tubulin and consequent stabilization of microtubules. Taxol attracted pharmacologists due to its unique structure, a complex diterpenoid containing a tricyclo [9.3.1.$0^{3,8}$] pentadecane ring system and rare four-membered oxetane ring system attached with it and ester side chain, that suggested a new mechanism for an anti-tumour drug. It is an unsual mitotic inhibitor because, unlike vinca alkaloids, which inhibit microtubule assembly, it promotes the formation of discrete bundles of stable microtubules those results from the reorganization of the microtubule cytoskeleton.[21]

Microtubules are primarily composed of two subunits; α- and β-tubulin, structurally similar prolein isofamilites made up of approximately 440 aminoacids. The tubulin dimers bind two molecules of guanosine 5'-triphosphate (GTP), an event involved in the assembly of microtubules. The tubulin dimer is the building target of a number of drugs that inhibit the polymerization of tubulin. The novel characteristic of taxol is its ability to polymerize tubulin invitro in the absence of guanosine 5'-triphosphate (GTP), which is normally required for tubulin assembly.[22] It is the only drug known to bind at a specific site on the microtubule polymer.[23]

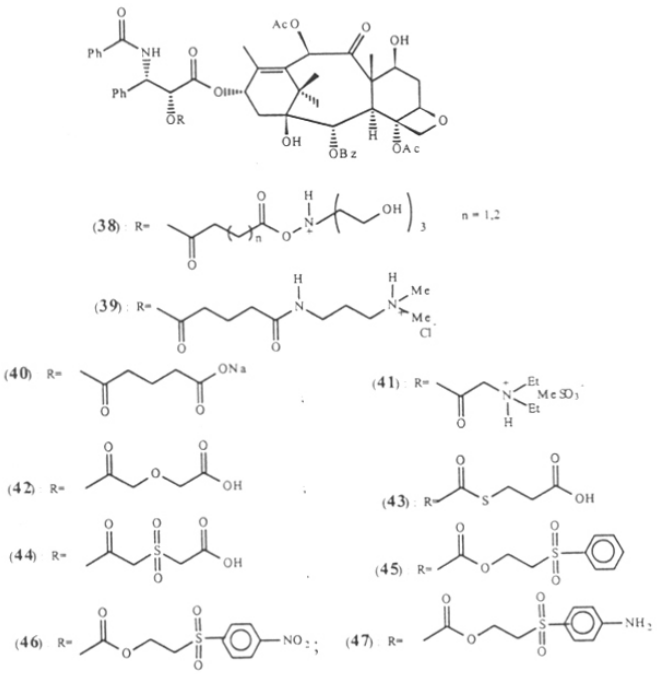
French co-workers have synthesized a highly promising analogue of taxol. Taxotere (**14**) which promotes the assembly and stability of microtubules with potency approximately twice that of taxol.[24] Taxol and taxotere (Paclitaxel^{R}) have

been shown to compete for the same binding sites[25], it appears that the microtubules are formed by taxotere induction from those formed by taxol induction.[26]

Large scale clinical trials with taxol have been hampered for a large time by relatively low supplies of the drugs.[27] Taxol entered phase I clinical trials in 1983, but immediately ran into some problems related to its formation, due to its very low-solubility in water. Hence, it was eventually formulated as an emulsion with cremophor EL^R, a polyethoxylated castor oil as a vehicle of administration. As taxol must be given at relatively high dosages, large amounts of Cremophor EL^R is known to cause histamine release.[28] Fortunately, these problems were overcome by lengthening the infusion period and premedicating patients with Glucocorticoids and anti-histamines. Phase II trials were initiated in 1985 and these proved to be very successful, taxol was found to have excellent activity agianst drug, refractory ovarian cancer[29] and against breast cancer.[30] It was approved by the US Food and Drug Administration (FDA) for the treatment of ovarian cancer in 1992. It is almost certain that taxol, and very likely taxotere, will soon be approved for the treatment of other types of cancers.

Improvement of water solubility

The C_{13} side chain is critical for maintaining the biological properties of taxol.



Deutsch *et. al,* reported a number of taxol analogues[31], exhibited improved water solubility (38-40) and they had impressive biological actions as well. Stella and collaborators[32] have reported the preparation of methanesulfonate salts of derivative of taxol (**41**). More recently, Nicolaou et. al., have successfully designed water-soluble taxol congeners[33] (**42-47**); they exhibited improved water solubility and considerable stability to neutral and ambient temperature. These profiles demonstrated the high potential for use of these compounds as water-soluble prodrugs in therapy.

Structure-Activity-Relationship (SAR) of Taxol

Extensive chemical characterization of taxol has been carried out.[34] These studies have provided a still-incomplete, but, nevertheless, substantial body of information on Structure Activity Relationships.

The sidechain

The N-benzoyl-β-phenylisoserine sidechain of taxol can be cleaved to yield baccatin (III) (**12**), which is significantly less active than taxol in both cytotoxicity assays and tubulin-assembly assays[35], indicating the importance of the sidechain for its activity. Analogues in which the side chain N-benzoyl group has been replaced with other acyl groups have also been prepared and one such analogue Taxotere^{R} (Docetaxel) has therapeutic potential. Taxotere (**14**) has an N-t-butoxy carbonyl group in place of N-benzoyl group of taxol, and also lacks the 10-acetate group[36]; it is about five times as active as taxol against taxol-resistant cells.[37]

The northern perimeter

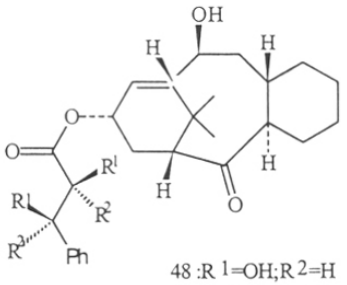
The northern perimeter portion of taxol molecule comprises carbon atoms 6-12, with oxygen functions at C_7, C9 and C_{10}. Acylation of C_7 hydroxy group[38], or its removal[39], does not significantly reduce the activity of taxol. Similarly, removal of 10-acetoxy group causes only a small reduction in activity[40], and reduction of C_9 carbonyl group to an α-OH group causes only a slight increase in activity.[41]

The southern perimeter

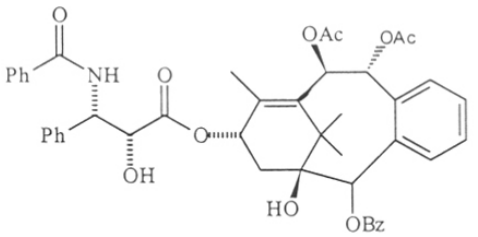
The southern perimeter portion of the molecule includes C_{14} and C_1 to C_5, and contains oxygen functions at C1 and C_2 and C_4 and the unusual oxetane ring at C_5 and C_4. This region appears to be crucial to taxol's activity.

The deoxygenation at C2 yields an inactive product.[42] Several analogues with substituted benzoyl group at C-2 have been prepared, and the interesting generalization can be made that m-substituted benzoyl derivatives are more active than taxol itself.[43] The importance of the oxetane ring is surprising, in view of its relative chemical inertness, and suggests that its role may simply be to act as lock to maintain the conformation. of the diterpenoid ring system of taxol.[44]

Synthetic Analogues



48 :R 1=OH;R 2=H
49 :R 1=H;R 2=OH

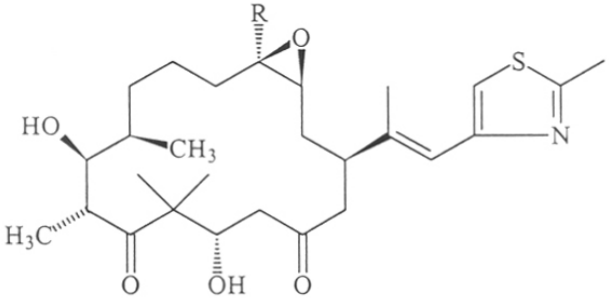


50

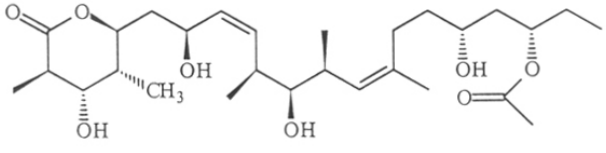
Blechert et. al.[45], and Nicolaou's group[46] have contributed to the elucidation of Structure-Activity-Relationship by chemical synthesis. Blechert et. al., found that when diastereomeric mixture of taxol analogues (**48, 49**) synthesized, and they restricted the depolymerization of tubulin and thus proved that even less functionalized taxanes can be biologically active. Nicolaou's group synthesized a bioactive taxoid (**50**), which exhibited significant cytotoxicity against a variety of tumour cell lines. These works give a much-needed driving force for synthesizing such bioactive taxoids.

Further advancements due to taxol

The clinical and commercial success of taxol in cancer chemotherapy has stimulated a worldwide search for compounds having similar mode of biological action. The epothilones[47] (**51, 52**) and discodermolide[48] (**53**) were found in the same way as taxol.



51 : R=H; **Epothilone A**
52: R=CH3, **Epothilone B**



53 :Discodermolide

Synthetic Approaches to taxane Diterpenoids

From a synthetic point of view, Taxol presents a plethora potential problems. The abundance of stereochemical details and high level of structural complexity makes the taxane diterpenoids one of the most synthetically important class of compounds. The most obvious is the challenge presented by the central B-ring, an eight-membered carbocycle. Such rings are notoriously difficult to form because of both entropic and enthalpic factors. Their synthesis is usually not possible using methods that are effective for the synthesis of smaller (3-7) and larger (10-16) ring systems.

The A-ring includes a somewhat problematic bridgehead alkene formally forbidden in a six-membered ring by Bredt's rule. However, in contrast to normal doctrine, in this case, it leads a reduction in the total strain (ca 1.5 kcal mol^{-1}), whereas the very rigid, arched structure of the entire molecule is highly strained from the steric effect of the bridgehead dimethyl groups at C_{15} (strain energy 10 kcal

mol^{-1}), in co-operation with the C_8-methyl group, which also projects outwards.[49] Thus, high transannular strain is present in taxane diterpenoids due to the presence of geminal dimethyl groups (at C_{15}) and the angular methyl group present at C_8-position.

Although the complex functionality and stereochemical issues must be dealt with, the development of a general and efficient method for the construction of a suitably substituted tricyclic carbon skeleton has often been recognized as the major task. Additionally, some of the functionalities present in taxol are quite sensitive to environmental conditions. The oxetane ring, for example will open under acidic or nucleophilic conditions and 7-hydroxyl group, if left unprotected, will epimerize under basic conditions.

Synthetic chemists, absorbed by the molecule's unique and sensitive structure and functionality, are exploring seemingly every available pathway for its synthesis. Much elegant work, however, has been reported in this area. The fruits of these endeavours include the new synthetic methodology and strategies, the synthesis of model systems, and the construction of intermediates that are projected for total and partial syntheses of the taxane diterpenoids.

The focus of most research groups has been the preparation of partial structures in an effort to explore various concepts that deal with the construction of the strained **tricyclo [9.3.1.0^{3,8}] pentadecane skeleton** equipped with functionalization suitable for further elaboration to various taxoids.

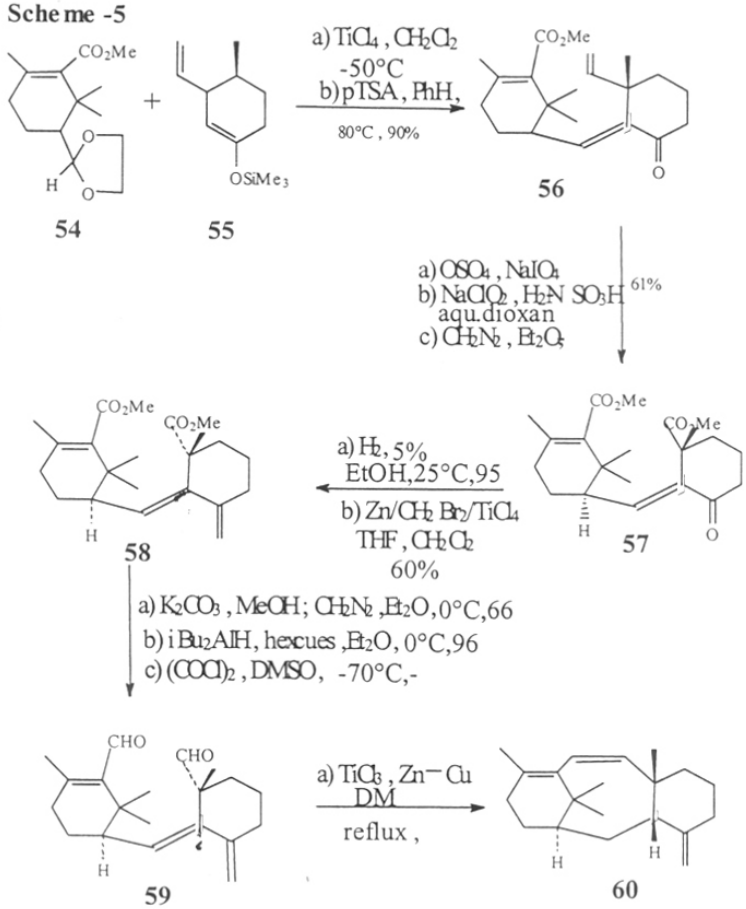
A: Convergent Approaches to Taxane Skeleton

Kende's Approach

The first convergent synthesis of a racemic taxane triene comprising the full and stereochemically correct taxane framework of natural taxusin was achieved by Kende et.al.[50]. The sterically encumbered eight-membered ring was formed via C_9-C_{10} bond formation using McMurry coupling.[51]

A and C-rings were synthesized (A-ring was synthesized according to the known literature procedure[52]) independently and coupled using directed aldol-$TiCl_4$ mediated reaction between the acetal (**54**) (A-ring) and enol-silane (**55**) (C-ring). Using standard synthetic manipulations; they arrived at the key dialdehyde (**59**) in an overall yield of 5%. The latter upon McMurry coupling furnished taxane triene (**60**) in 20% yield. It is important to mention that this methodology was later utilized by Nicolaou et. al., for the total synthesis of taxol. (**Scheme-5**).

Scheme -5

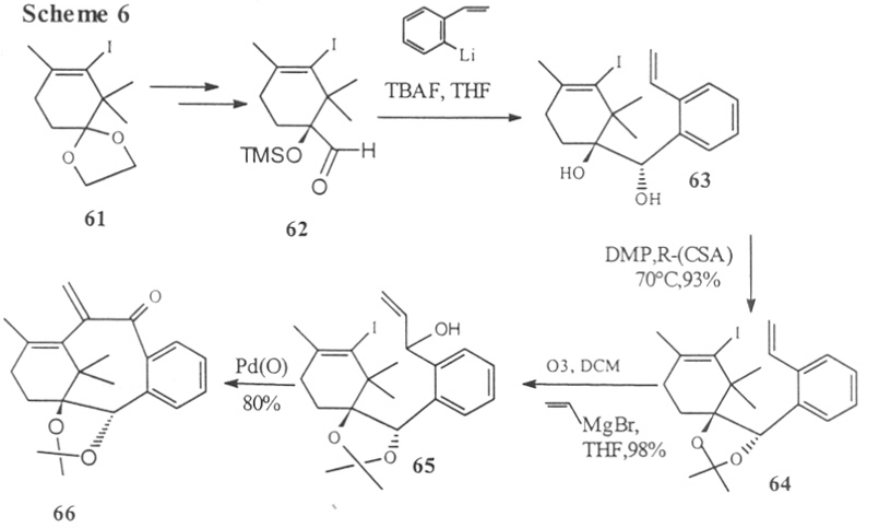


Master's Approach

Pd(0) catalyzed vinylation reaction was employed for the convergency at C10-C11 to obtain the tricyclic core of taxane (**66**) diterpenes by Master's et. al.[53] In this strategy, C-aryl taxane was constructed.

Vinyliodo ketal (**61**) was converted into vinyliodo-α-silylether aldehyde (**62**) with which 2-lithiostyrene was coupled to afford C-aryl "B-seco taxoid" (**63**). Protection of diol as acetonide and ozonolysis followed by Grignard addition gave the cyclization precurosr (**65**). Under Heck-conditions, cyclization precursor yielded the tricyclic system (**66**) in 80% yield. This methodology was also utilized for the total synthesis of taxol. It is important to mention that this is a catalytic method for tricyclic formation.

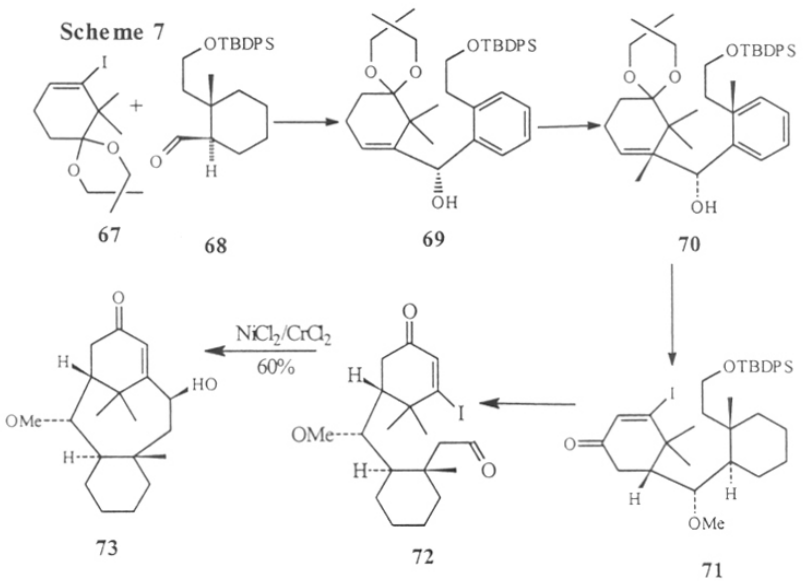
Scheme 6



Kishi's Approach

In this approach, the tricyclic enone (**73**) containing the taxane ring system was synthesized using an intramolecular Ni(II)/Cr(II)-mediated coupling of β-iodoenone aldehyde (**72**) in the key steps.[54]

Scheme 7



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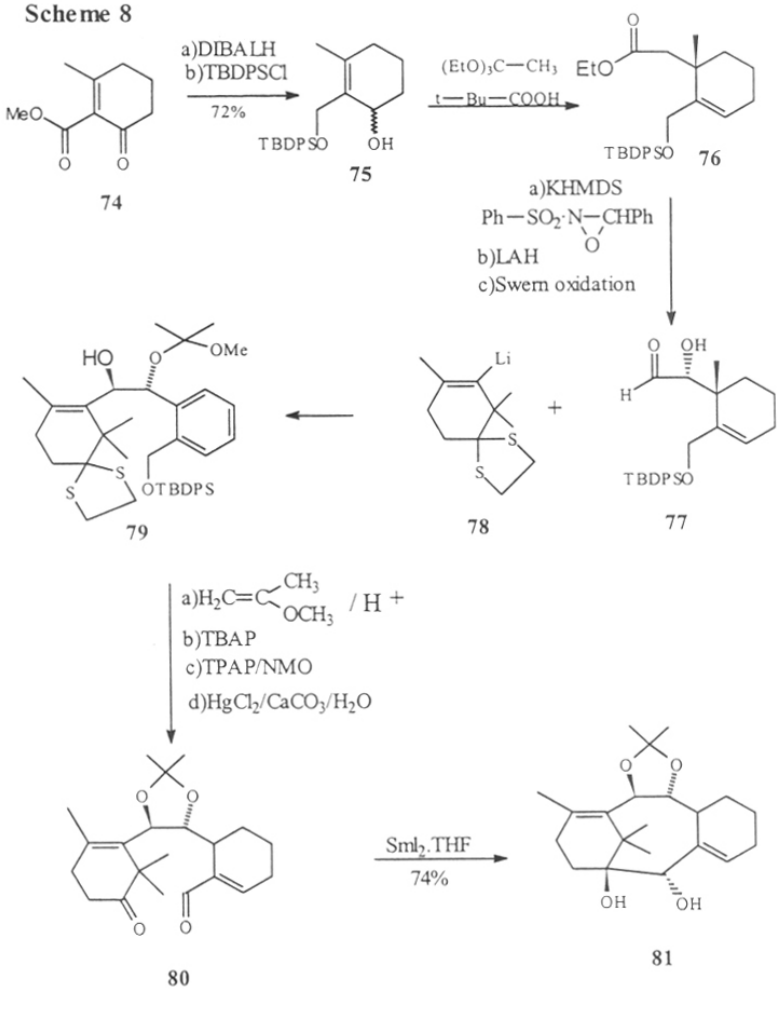
The A-ring unit (**67**) was prepared in four steps from 2,2,-dimethyl-1,3-cyclohexanedione in 47% overall yield. The C-ring unit (**68**) was reported to be synthesized in 8 steps from 2-decalone in 13% overall yield. The A and C-ring units were coupled *via* C_1 -C_2 bond formation using lithiation reaction to get C_2 hydroxy "B-seco taxane". By series of functional group transformations, cyclization

precurosr (**72**) was reached, which upon treatment with 1% $NiCl_2/CrCl_2$ at room temperature afforded the ABC-ring system of taxane diterpene in 60% yield. (**Scheme 7**).

Swindell's Approach

Here the A-ring unit (**78**) and C-ring unit (**77**) were coupled *via* C_{11} -C_{10} bond formation. Later, the tricyclic skeleton (**81**) was obtained using pinacol-coupling resulting in the bond formation at C_1 - C_2[55].

Scheme 8



The C-ring unit (**77**) was obtained from the substituted cyclohexenone moiety (**74**). The latter was reduced to substituted cyclohexene-1-ol, under Johnson's orthoester variant of Claisen ester, which upon Davis enolate oxidation procedure followed by reduction and oxidation sequences, yielded the required C-

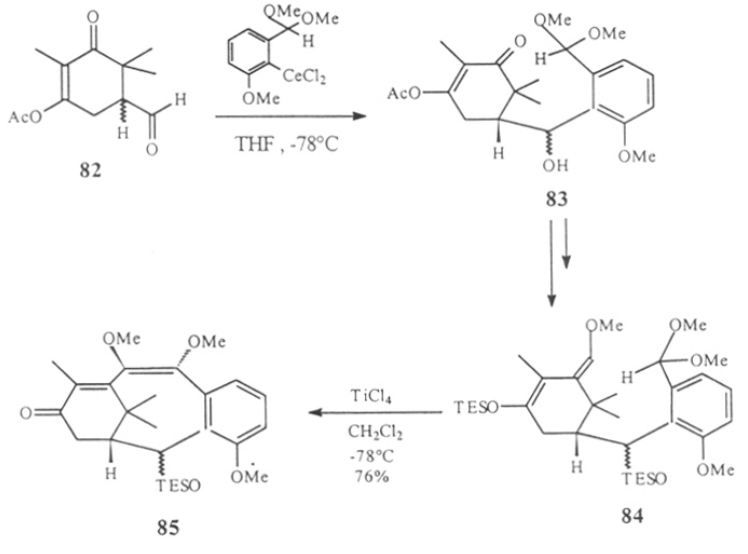
ring fragment (**77**). By lithiation process, A-ring unit was attached to it to furnish "B-seco-taxoid". This was converted into the dialdehyde (**80**), which upon treatment with SmI_2 produced the required taxane diterpenoid in 74% yield (**scheme-8**).

Kuwajima's Approach

Kuwajima's group[56+] have synthesized C-aryl taxane analogue using Lewis-acid mediated intramolecular coupling of dienylsilylether at C10 and the acetal at C9.

A-ring unit (**82**) was prepared in a straightforward manner (discussed in chapter II, part I, section 2) in 43% overall yield *via* an eight step procedure utilizing Dieckmann cyclisation in the presence of t-BuOK. C-Aryl cerium reagent derived from m-methoxybenzaldehyde dimethylacetal was reacted with the A-ring unit (**82**) to obtain "C-aryl-B-seco taxane. The cyclization precursor (**84**) was prepared from "B-seco-taxane" with subsequent transformation on the A-ring unit portion, which under the influence of $TiCl_4$ in CH_2Cl_2 at low temperature gave the tricyclic taxane in good yields (**Scheme-9**).

Scheme -9



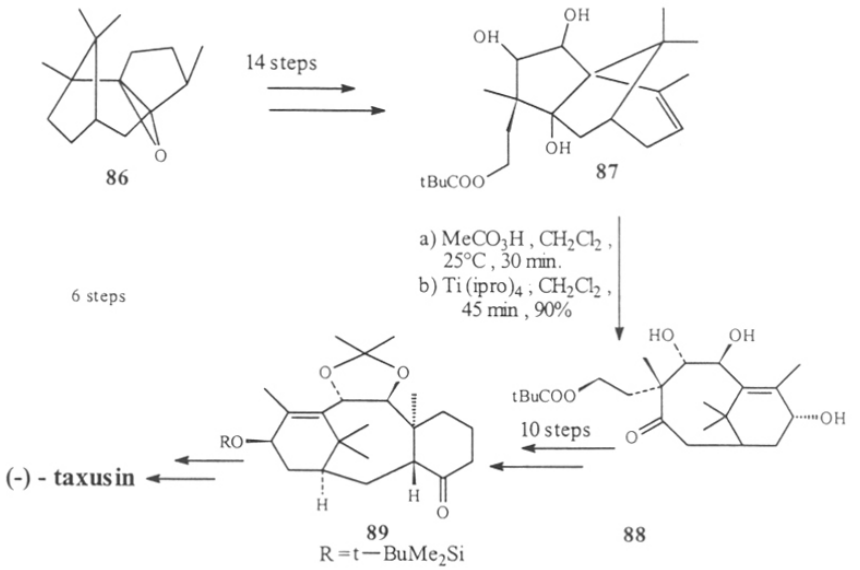
B: Total synthesis of taxane Diterpenoids

Among the taxane diterpenoids, the total synthesis of taxusin (**9**) and Taxol (**6**) have been reported. Two total syntheses to taxusin are known till now, one is based on linear strategy and the other based on convergent synthesis. Both these syntheses are described below.

Holton's Approach

The first total synthesis of Taxusin was from Holton's laboratory[75], in which they employed the naturally occurring β-patchouline oxide (**86**) as the starting material. A hydroxyepoxide fragmentation process was employed in key step to secure AB-ring system (**88**), to which C-ring was appended (**89**) using standard synthetic manipulations, and non-natural enantiomer of (-)-taxusin was prepared (**Scheme 10**).

Scheme-10



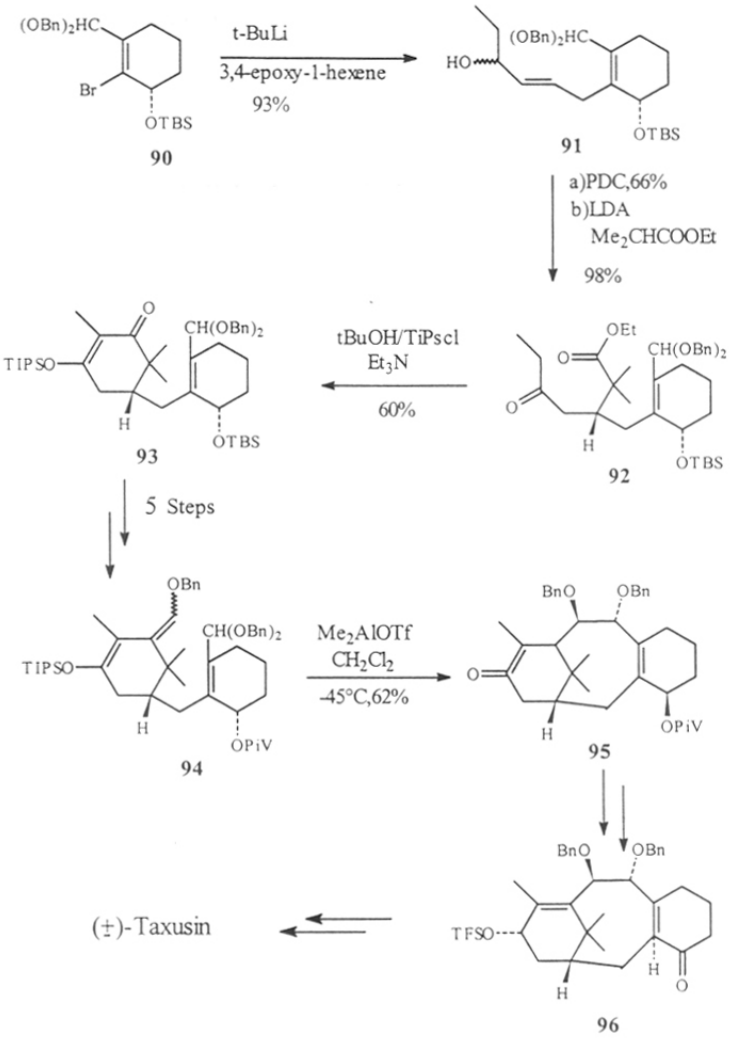
Kuwajima's Approach

The first convergent synthesis of Taxusin was achieved by Kuwajima et. al.,[58] *via* Lewis-acid mediated vinylogous aldol reaction.

A substituted cyclohexenyl bromide (**90**) system was chosen as the starting material, which corresponds to the C-ring unit of Taxusin. 3,4-Epoxy-1-hexene was attached to the C-ring *via* S_N^2 reaction employing t-BuLi to obtain an allylalcohol moiety (**91**). This was then converted into an enone from which A-ring part of taxusin was built *via* Dieckmann-type cyclization (**93**). Later, this "B-seco-taxoid" system was transformed into a cyclization precursor (**94**) and then the cyclization was induced using Me_2AlOTf to furnish the tricyclic core of taxusin ((**5**). C8-Angular methyl group was incorporated *via* cyclopropanation followed by Birch reduction (**96**). The C_5-oxygenation was introduced *via* Rubottom methodology.

Finally, methylenation of C_4 keto group resulted in the formation of (±)-taxusin (**Scheme 11**).

Scheme 11



C: Total Synthesis of Taxol

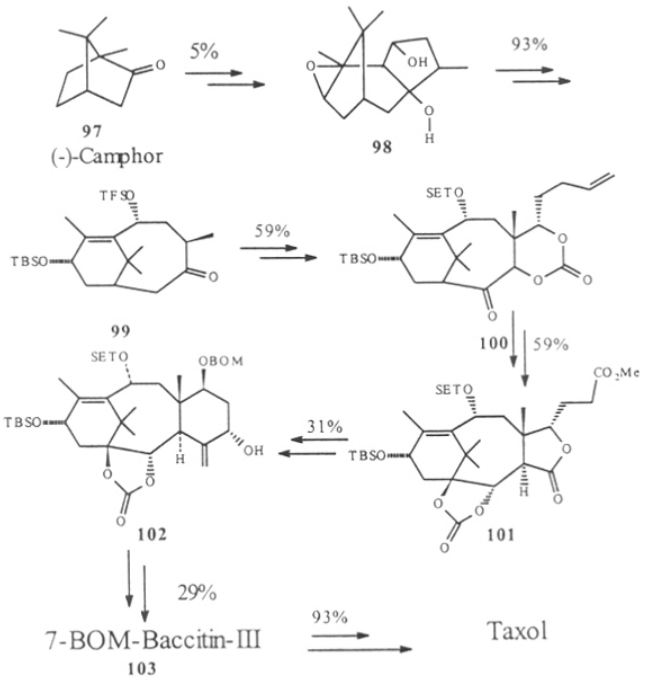
From the middle of the 1980 onwards, the number of synthetic attempts towards the construction of taxol increased considerably. Intense competition developed to complete the first total synthesis of this unusual molecule, a race which involved over forty of the best known research groups in the field of natural product synthesis.

An initial highpoint has now been reached with the first two total synthesis by the R.A. Holton et. al. , (Florida State University) and K.C. Nicolaou et. al., (Scripps

Research Institute). After the first two total syntheses, third one appeared from the laboratories of Danishefsky (Sloan-Kettering Institute for Cancer Research, New York) and the fourth one from Wender's group (Stanford University).

Holton's total synthesis of taxol

Holton et. al.,[59] first constructed the A and B rings using a linear strategy applying an elegant fragmentation of [3.3.0]-ring system (**98**) derived from β-patchoulene oxide (an international flavour and fragrance, Patchino is the trade name), which they had previously used for the synthesis of (-)-taxusine. However, to obtain the correct enantiomeric series, they had to start extravagantly, using (-)-camphor (**97**). The resulting AB-ring system (**99**) contains the complete homochiral A-ring and all the methyl groups, as well as one oxygen functional group in both the upper and lower regions for further modifications.



Scheme 12

The difficult stereocenter at C7 was constructed early, by using a diastereoselective aldol reaction with magnesium diisopropylamide and 4-pentenol. By standard synthetic manipulations, the C-ring precursor (**101**) step was then reached. The C-ring itself was constructed using Dieckmann cyclization (**102**). The keto group at C4

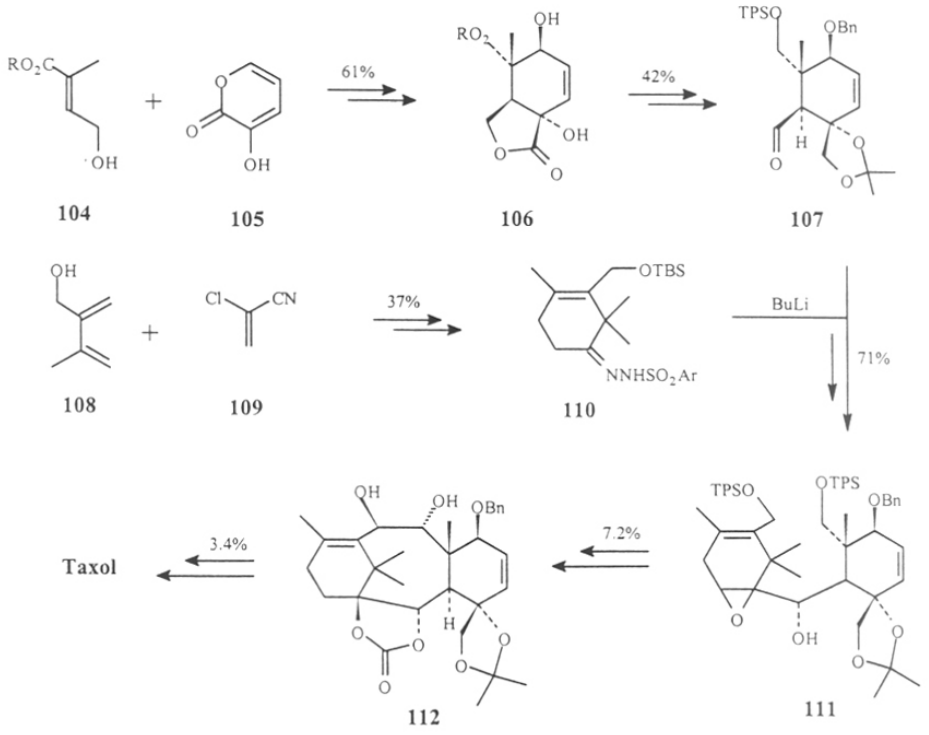
was utilized for α-hydroxylation at C5, and conversion to the methylene compound, dihydroxylation of the exo-cyclic double of C4 afforded the precursor to the oxetane. The oxetante ring was obtained by nucleophilic substitution of the secondary mesyl or tosyl group at C5, followed by acetylation of the tertiary (3°) - hydroxy group. Using C10 oxygen functionality, C9 position was also oxygenated employing a rearrangement chemistry, with benzeneselenic anhydride. The synthesis of 7-BOM-Baccatin-III was thus realized. The sidechain was synthesised at C13 position *via* Ojima's β-lactam.[60] Removal of the C_7 BOM group by hydrogenolysis furnished taxol. The overall yield of taxol from starting diol (**98**) was ca 4-5% (**Scheme12**)

Holton's synthesis shows quite good yields throughout. The synthesis starts with easily available camphor.

Nicolaou's total synthesis of taxol

Nicolaou et. al.[61], followed a much more convergent route which began with achiral precursors. The A-ring precursor (**110**) was constructed by a Diels-Alder reaction (**108** + **109**) and refunctionalized to the sulfonylhydrazone

Scheme 13



(**110**). The C-ring unit (**107**) was also prepared *via* Diels-Alder reaction, but by utilizing the principle of temporarily tethering the two reaction partners (**104** + **105**) in order to dictate the regiochemistry of the Diels-Alder product, following a Narasaka's[62] protocol. Diels-Alder product (**106**) was converted to an aldehydic functional group.

Then, theThe C2-aldehyde group of 7 (**107**) served as the electrophile and reacted very efficiently to give the A-C coupled alcohol in an excellent yield (82%). Chelation controlled epoxidation of this alcohol led to α,β-epoxy alcohol (**111**). The epoxide was selectively hydrogenated, resulting in the formation of C1-C2 diol, which was protected as carbonate.

After oxidation of C9 and C10 to the aldehyde level, the key step involved, a McMurry-Pinacol coupling to the B-ring bridge to afford the diol (**112**) in 23% yield. In order to construct the oxetane ring, the C5-C6 double bond was hydroborate and oxidized with moderate regioselectivity and yield. Oxetane ring closure and benzoate formation at C2 followed by oxidation at C13 and attaching the side chain furnished taxol in 3-4% yield (**Scheme 13**)

The regioselective synthesis of C-ring unit, McMurry-Pinacol coupling of the top B-ring bridge, for this strained molecule and benzoate formation at C2 are some of the remarkable achievements worth mentioning.

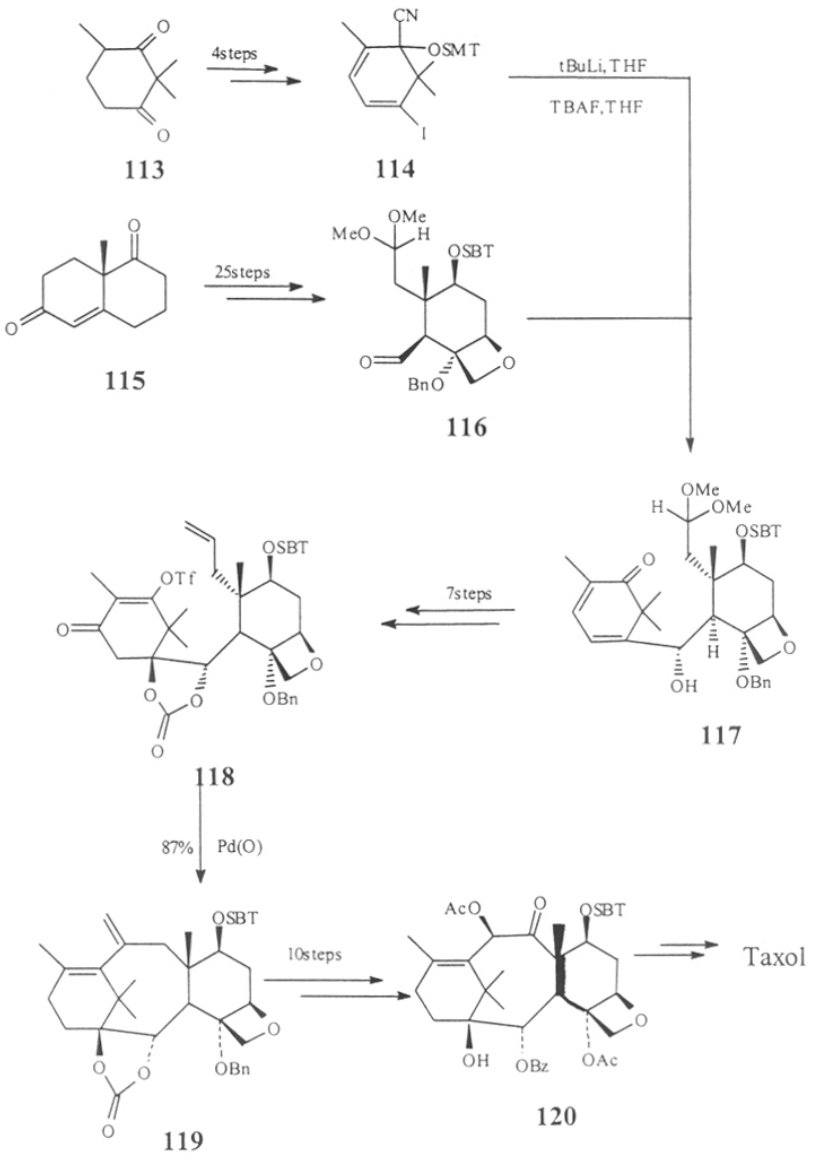
Danishefsky's synthesis of taxol

Danishefsky's[63] synthesis was also based on a convergent strategy. Here, the A-ring (**114**) and then C-ring unit's (**116**) were synthesized from trimethyl cyclohexane-1,3-dione and Wieland- and Miescher ketone (**115**) respectively.

The A-ring and C-ring thus made were coupled *via* C1 - C2 bond formation to get functionalized, "B-*seco*-taxane" skeleton (**117**). It is important to mention at this jucture that the oxetane (D) ring was built up prior to B-secotaxane formation in this methodology. From **113**, the C1 hydroxy group was obtained *via* epoxidation followed by reduction to get the C1 -C2 diol, which was protected as carbonate. The C10 dimethoxy acetal was deprotected and the aldehyde group obtained was olefinated and the C11-C12 double bond was obtained *via* triflate formation of the ketone at C11 leading to the cyclization precursor (**118**). The key cyclization was achieved *via* Heck-type coupling reaction to construct the C10 - C11 bond. After obtaining the tricyclic skeleton (**119**), the C10 exocyclic double bond was converted into C10 carbonyl functional group. The carbonyl functionality at C9 was also incorporated by standard synthetic manipulations. C7 silylprotected baccatin-III (**120**) thus obtained was

subjected to allylic oxidation which was utilized to attach the side chain to yield Taxol, following Ojima's[61] protocol. (**Scheme 14**)

Scheme 14



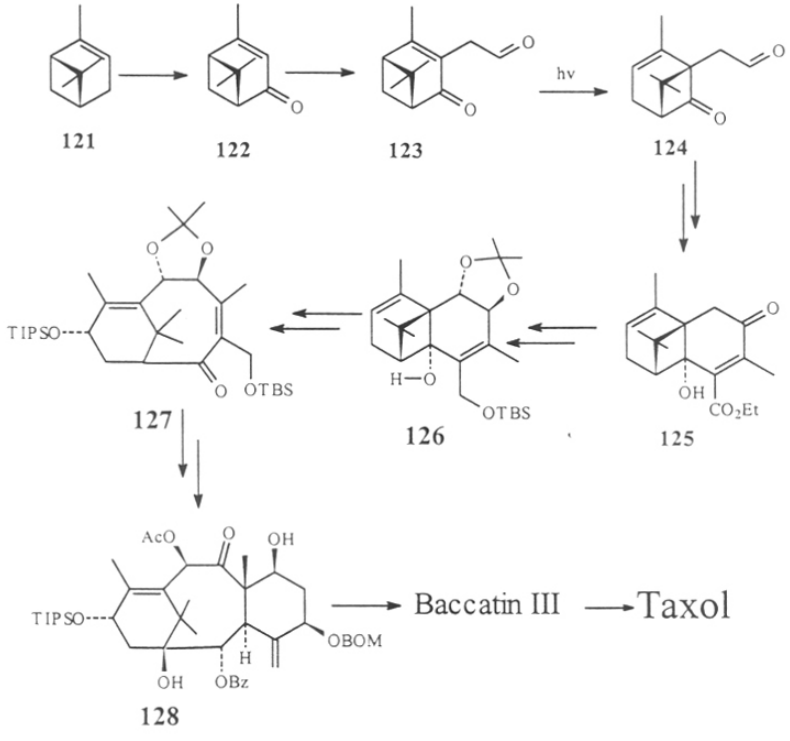
The use of Wieland-Mischler ketone and Pd(0) catalyzed cyclization to taxane skeleton makes this methodology attractive.

Wender's total synthesis of Taxol

Wender's strategy was derived from the recognition that pinene (**121**) could supply 10 of 20 carbons and the chirality of the taxol core[64]. Pinene was air oxidized to

get Verbenone[65] (**122**) and its enolate was used for C11-C10 bond formation by alkylation with 1-bromo-3-methyl-2-butene. Selective ozonolysis of more electron-rich double bond of this product provided an aldehyde (**123**). This Verbenone derivative was photorearranged to the chrystanthenone derivative[66] (**124**). The lithium salt of ethylpropiolate was added selectively to the C9 carbonyl and the C8 methyl group was then introduced by conjugate addition of $Me_2CuCNLi$, which through generation of a C3 carbanion resulted in C2 C3 bond formation. Thus the bicyclo [4.2.0] octene subunit (**125**) was obtained. This subunit was exploited selectively to obtain C9- C10 acetonide, the C4-alcoholic functionality was protected, by silylation to give the fully oxygenated bicyclo [4.2.0]-octene subunit (**126**). The latter was epoxidized and converted into AB-bicyclic system of taxol (**127**) *via* DABCO induced fragmentation. Using various organic functional group transformations, the C-ring unit was appended *via* aldol condensation (**125**). From the C-ring moiety, oxetane ring was built up (**128**). This intermediate (**129**) was converted into baccatin-III and then to taxol (**Scheme 15**)

Scheme 15



The use of pinene (**121**), an abundant component of pine trees and a major constituent of the industrial solvent turpentine and DABCO induced fragmentation leading to AB-ring system of taxol are remarkable events in this strategy.

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CHAPTER II

SYNTHESIS OF ADVANCED TAXOIDS

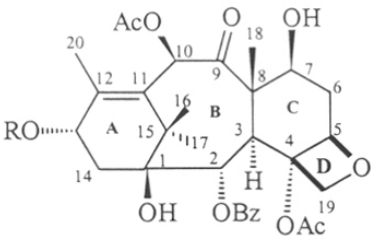
Introduction:

Synthesis of Advanced taxoids

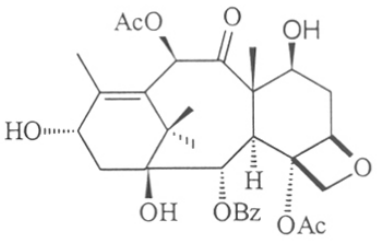
The antitumour agent Taxol (**1**) has heralded a new exciting lead for chemotherapeutic treatment of cancer.[1] Only after Horwitz's contribution concerning the mode of action[2] in 1979, organic chemists throughout the world began to address massively the synthetic challenges posed by the stereochemically complex diterpene part and the side chain part of Taxol. Indeed, clinical trials for the treatment of breast melanoma, and lung cancers have been highly encouraging; so FDA (US Food and Drug Administration) has recently approved for the treatment of breast and ovarian cancers[3] and also for marketing taxol. Consequently, an enormous amount of effort has been directed towards the total synthesis of taxol.[4] The total syntheses reported so far represent the combination of dozens of man-year expended on the benchwork with a touch of strategic overlapping. While these total syntheses are undoubtedly monumental in character, they can rarely compete effectively with the partial synthesis[5] developed from baccatin-III (**2**). The synthesis of taxane dieterpenes still remains problematic[6] because of the difficulties stemming from the high degree of strain and transannular interactions of the molecule. Thus, among the proposed routes for taxol synthesis this include direct isolation from the bark or leaves of the yew tree, biotechnology and total syntheses, the latter remains impractical as they are largely of academic interest. Despite the phenomenal success achieved from the total syntheses of taxol by various groups round the globe, much excitement still remains in the race for total syntheses, not only with respect to variability but also in yield improvement and commercial feasibility. It is noteworthy that efforts during the past fifteen years towards the synthesis of taxol have contributed greatly to the development of new synthetic methodologies and concepts. However, it would be certainly misleading to assume that industrial applicability was the prime reason for the numerous strategies that were designed and executed. Ultimately, it is very much essential to focus on the

development of simple and clinically more effective analogues of taxol that could be synthesised in a cost-effective fashion.

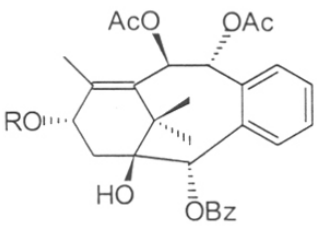
Structural synthetic modifications of taxol such as the side chain,[7] acylation of C-7 hydroxyl groups,[8] or its removal,[9] reduction of C-9 carbonyl group,[10] modification of benzoyl group at C-2[11] etc. have given substantial body of information on Structure-Activity-Relationships (**SAR**). But, the sensitive functionalities present in taxol permitted only minor structural modifications. However, simplified analogues that can only be obtained *via* total synthesis can provide further insight into the Structure-Activity-Relationships which underlie taxol's therapeutic activity. These efforts have facilitated the discovery of structurally simplified, synthetically accessible taxol congeners, which possess a comparable or superior biological profile..



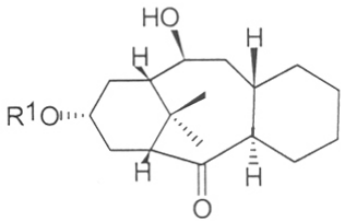
Taxol (1)



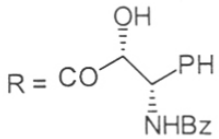
Baccatin-II (2)

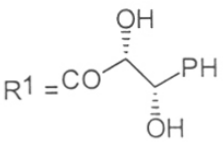


Nicolaou's Advanced Taxoid(3)



Blechert's simpilified Taxoid(4)





Accordingly, several schools all over the world have attempted to synthesize several simplified taxol congeners. It has been recently established that in certain cases,

the taxol side chain may be attached to modified taxoid systems[12,13] *viz.* (**3**) and (**4**) with retention of acceptable tubulin activity and they are christened as advanced taxoids.

Critical realization of these goals is the discovery of a concise, stereoselective synthesis of suitably functionalised taxane carbocyclic framework. Several groups have recognised the benefits of initiating the synthesis with a functionalised A-ring, then following the convergent approach. Convergent synthesis requires more or less direct ring closure of "B"-ring, which is widely used in the synthetic approaches to taxoids. Here, A and CD rings are synthesized efficiently and coupled to get "B-*seco* taxoids" followed by the 8-membered ring closure. Thus, the access to new taxane analogues was reached in the literature and the second generation of taxoids has emerged. Most of the taxane ring systems were synthesised utilising convergent synthesis by many groups involving the synthesis of a functionalised A ring, attaching the C-ring, then by ring closure either at C10-C11 (eg. Heck[14] or Kishi-Nozaki reactions[15]) or C9-C10 (eg., Pinacol[16] or vinylogous aldol reactions[17]).

It was decided to initiate work on diastereoselective synthesis of taxane ring system to obtain simple routes to taxoid congeners. The main objective of the work that is presented here revolves around the "stereoselective studies towards the construction of tricyclic taxane framework {[tricyclo ($9.3.1.0^{3,8}$) pentadecane]} system and [bicyclo (5.3.1) undecane] system of taxol core. This chapter is divided into three parts namely:

Part I **SYNTHESIS OF CYCLOHEXYL A-RING UNIT TO TAXOIDS**

Section 1 Synthesis of (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde

Section 2 Synthesis of (-)-(S)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde.

Part II **DIASTEREOSELECTIVE SYNTHESIS OF "B"-*SECO* TAXOIDS, VERSATILE INTERMEDIATES FOR ADVANCED TAXOIDS and**

Part III **SYNTHETIC STUDIES TOWARDS BICYCLO [5.3.1.] UNDECANE RING SYSTEM.**

PART - I SYNTHESIS OF CYCLOHEXYL A-RING UNIT TO TAXOIDS

Most of the synthetic studies towards taxoid system were initiated from the synthesis of A-ring unit of taxol. Synthesis of (±)-A-ring unit in large quantities is a prior requirement in the present study in order to carry out model experiments to test the feasibility of the proposed schemes. It was also proposed to synthesize the same A-ring unit in optically active form to obtain stereoselective taxoid congeners. In this regard, both the racemic as well as the chiral forms of A-ring unit was targeted and the results obtained from these studies are presented below in two sections namely:

Section 1: Synthesis of (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde

Section 2: Synthesis of (-)-(S)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde

The initial attempts were made on the racemic A-ring unit and the results obtained from these studies are presented below in the section I.

Section 1: Synthesis of (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde

Introduction:

The promising clinical performance and unique molecular architecture of taxol has evolved a vast array of synthetic options for its total synthetic studies. The most efficient of these exploits convergent strategies utilizing a functionalised ring A equivalent, upon which the remaining carbon skeleton is appended. Many laboratories have made their efforts towards the assembly of the ring "A" of taxol. The various approaches include the use of chiral terpenoids, carbohydrates, Diels-Alder adducts, isoprenoids, aldol products and other innovative annulation strategies. As our studies are focused more on the advanced taxoids (aromatic taxoids) and protaxoids (AB-ring system of taxol i.e., bicyclo [5.3.1] undecane system), an efficient synthesis of A-ring unit of taxol is crucial. Many groups have synthesized different A-ring synthons in racemic as well as in chiral forms with varying degrees of oxygenation and substitution to investigate their own B-ring annulation strategies. Some of these important approaches towards the synthesis of (±)-A ring unit of taxol are described below:

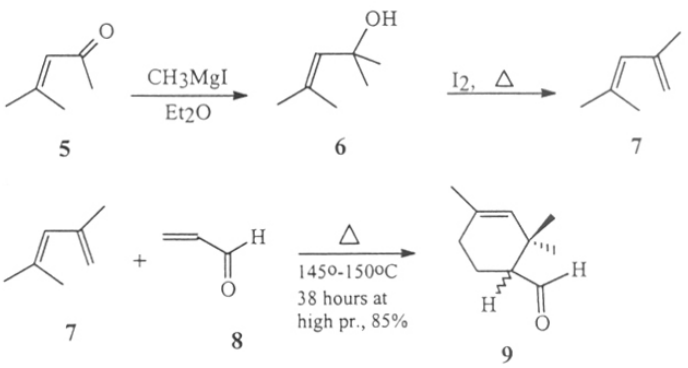
Synthesis of (±)-A-ring unit of taxol: a literature Survey

Under this subheading, various syntheses of (±)-A -ring unit of taxol available in the literature which are relevant and more in line with the present work are covered. Such syntheses involve cationic or anionic cyclisations, functionalisation of substituted cyclohexane ring systems, cycloaddition reactions and other innovative annulation strategies.

Jitkow's Approach:

One of the earliest ring-A equivalent available in the literature prior to the discovery of taxol itself was that of Jitkow et al.[18] They utilized Diels-Alder reaction to get (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde (**9**), where 2,4-dimethyl-1,3-pentadiene (**7**) was the diene and the dienophile was acrolein (**8**). The Diels-Alder adduct (**9**) was obtained via thermal Diels-Alder reaction at 150°C and at high pressure. However, no explanation was given for the observed 100% regioselectivity of the adducts obtained. They prepared this unit to test its perfumeric characteristics. (**Scheme 1**)

Scheme 1

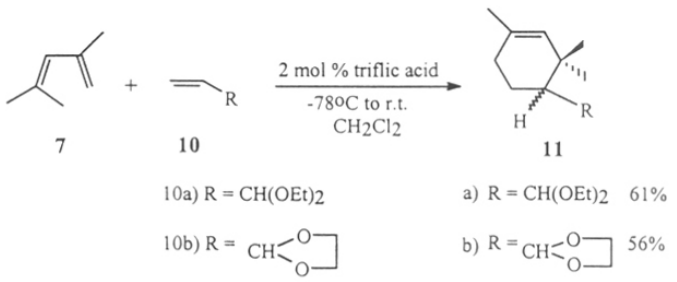


Gassmann's Approach:

In another approach[19] evolved by Gassmann, ethylene glycol acetal (**11a**) and diethylacetal (**11b**) of (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde were synthesized employing Diels-Alder strategy. Here again 2,4-dimethyl-1, 3-pentadiene (**7**) was used as the diene but either 3,3-diethoxy propene (**10a**) or 2-vinyl-1,3-dioxalane (**10b**) was used as the dienophile in place of acrolein as reported in Jitkow's approach. Mechanistically this reaction proceeds via the ionic Diels-Alder reaction involving allyl-

cation mechanism.[20] They prepared the A-ring system to study only the allyl-cation mechanism.(**Scheme 2**)

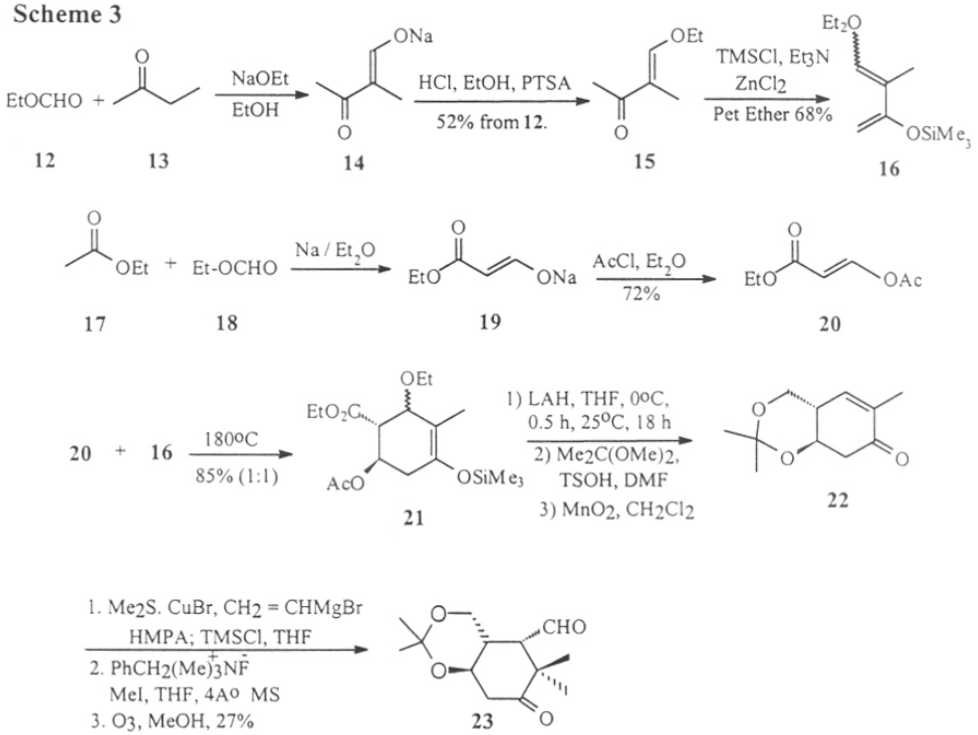
Scheme 2



Clark's Approach:

Clark's group reported[21] a synthesis of the A-ring system (**23**) based on Diels-Alder reaction as depicted below in **Scheme 3**.

Scheme 3



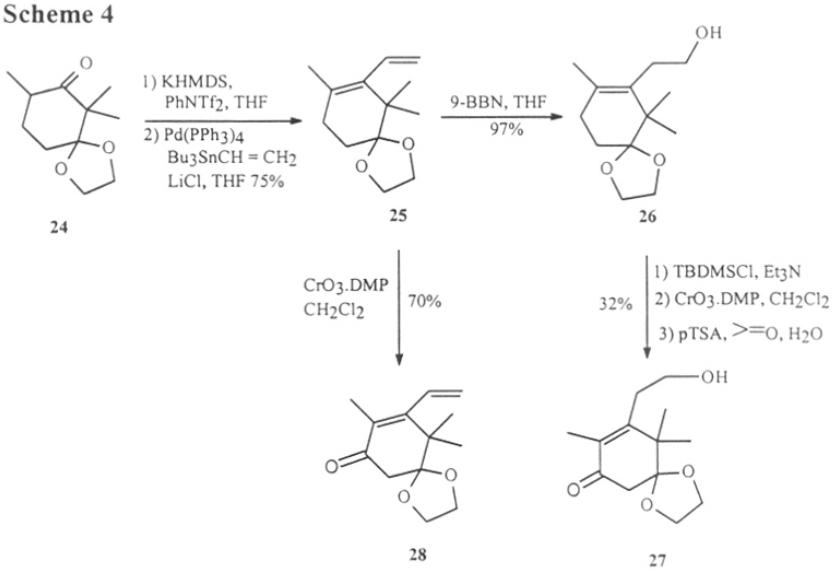
Formation of the A-ring fragment relies on the Diels-Alder reaction of 1-ethoxy-3-[(trimethylsilyl)oxy]-2-methyl-1,3-butadiene (**16**) with ethyl-E-acetoxy acrylate (**20**) to

assemble the cyclohexene ring moiety; the final carbon framework was produced through further elaboration and a carefully controlled Gilmann reaction. While this procedure had the advantage of brevity, it lacked stereocontrol and required the use of unstable starting materials.

Queneau's Approach:

In Queneau's approach[22] the known cyclohexane derivative[23] (**24**) was converted into taxol A-ring system (**27,28**) by Stile coupling and subsequent oxidation with chromium (VI) oxide and other standard synthetic manipulations. The use of toxic vinyl stannane is a drawback of this approach. (**Scheme 4**)

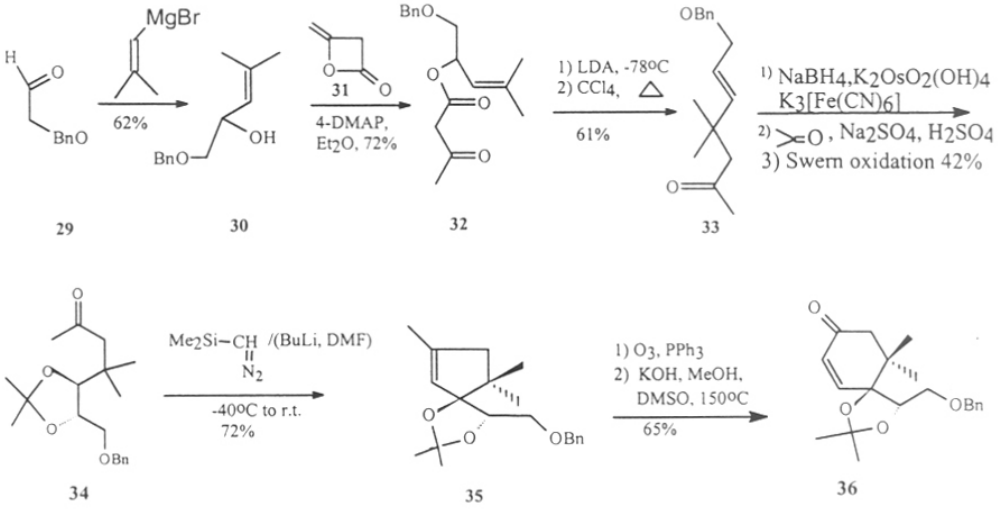
Scheme 4



Taber's Approach:

In an innovative cyclization[24] approach, Taber's group have synthesized a A-ring equivalent of taxol as a cyclohexanone derivative (**36**). Such a system was obtained *via* intramolecular C-H insertion[25] by an alkylidine carbon to get cyclopentene derivative (**35**) which was ozonolyzed and subjected to aldol condensation to give the cyclohexenone derivative. The use of expensive and toxic Osmium, LDA and butyllithium for the synthesis of A-ring system makes this approach less attractive. (**Scheme 5**)

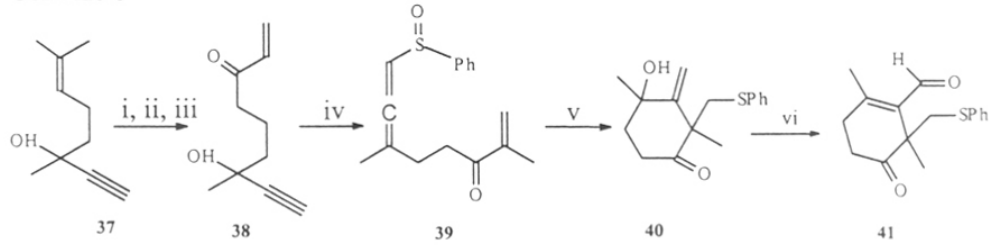
Scheme 5



Parson's Approach:

Parson's synthesis[26] of the taxol A-ring (**41**) relies on a double Michael addition of enolates derived from α,β-unsaturated ketones (**38**) to allenylsulphoxides (**39**). The allenylsulphoxide (**39**) undergoes intramolecular nucleophillic attack to form cyclohexane derivative (**40**). This synthesis involves only nucleophillic additions to form A-ring of taxol (**41**) starting from dehydrolinalool (**37**). (**Scheme 6**)

Scheme 6



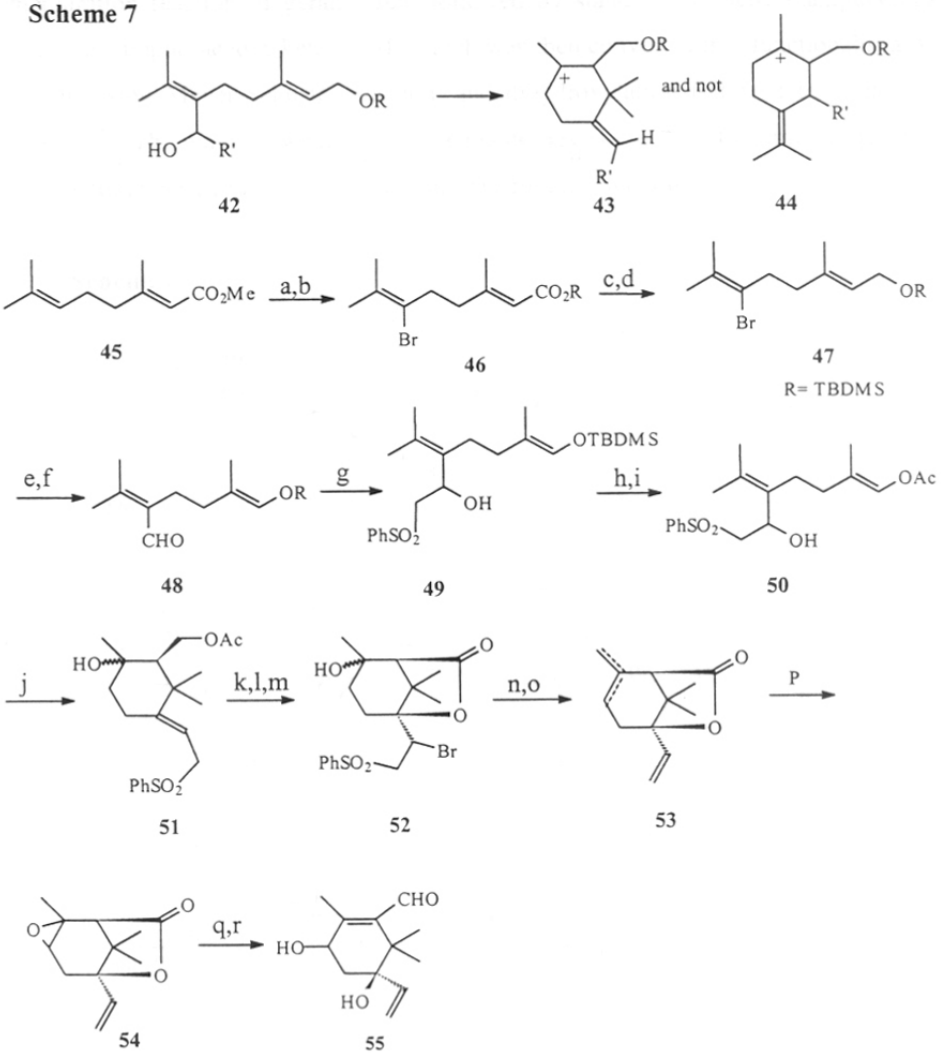
i) O_3, CH_2Cl_2, -78°C, then HOAc; (ii) 2 equ. =, MgBr, (iii) MnO_2, CH_2Cl_2; (iv) PHSCl, Et_2O Et_3N, -20°C; (v) LiSPh, THF, 0°C, then H_2O; (vi) p-DMAPCC, 1,2-dichloroethane, 100°C.

Stork's Approach:

In this approach, the readily available monoterpene geraniol was converted into a taxol A-ring system (**55**) *via* cationic cyclisation by Gilbert Stork et al.[27] Geraniol was converted into 6-(1-hydroxyalkyl) geraniol derivative (**50**), which was cyclised using Lewis acid to give regioselectively to (**43**) and not (**44**). Eventhough this methodology utilizes geraniol, (readily available material and gives fully functionalised A-ring

synthon (**55**), it involves too many synthetic operations for the required A-ring system. (**Scheme 7**)

Scheme 7

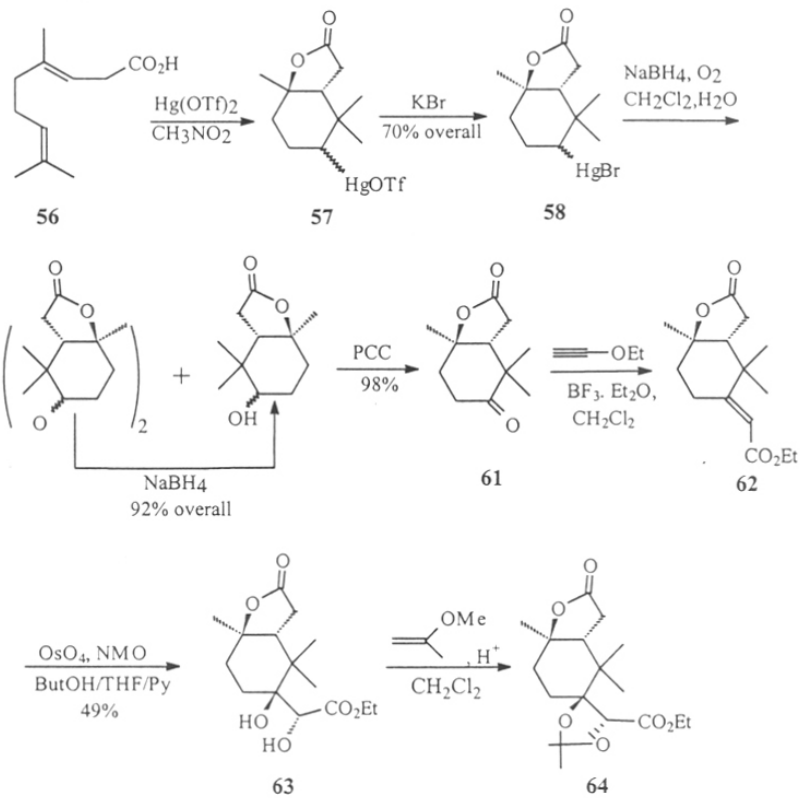


a) Br_2, CH_2Cl_2, -20°C to room temperature; (b) DBU, CH_2Cl_2, reflux, 1h; (c) AlH_3, THF, 0°C, 1 h 62% from **45**. (d) TBDMS-Cl, imidazole, CH_2Cl_2, 0°C, 12 h, 80%; (e) t-BuLi, THF, -78°C, 1h; (f) DMF, -78°C, 82%; (g) Ph-SO_2-CH_2 MgBr, 98%; (h) TBAF, THF, 0°C, 98%; (i) Ac_2O, Py, CH_2Cl_2, 97% (j) 3 equiv. of 0.5% $BF_3.Et_2O$, CH_2Cl_2, -30 to -15°C, 72%; (k) KOH, MeOH (l) Jones oxidation; (m) NBS, THF, 52% from **51**; (n) Bu_3SnH, PhH, 92%; (o) $BF_3.Et_2o$ (1.1 equiv.), CH_2Cl_2, 90% (p) mCPBA, CH_2Cl_2, 68%; (q) DIBAL, toluene ; (r) DBU, 40-50°C 40% from **54**.

Crich's approach:

Crich and Crich[28] utilized geranic acid (**56**) to arrive at the same type of cyclisation as in Stork's approach but using oxidative demercuration reaction. The oxidative demercuration reaction of geranic acid followed by standard synthetic manipulations resulted in camphoraceous ketone (**61**) which was then converted into functionalised A-ring unit using Meyer-Schuster reaction, and dihydroxylation followed by acetonide formation.[29] The main drawback of this methodology is the use of equimolar quantity of highly toxic mercuric reagents and costlier Osmium. (**Scheme 8**)

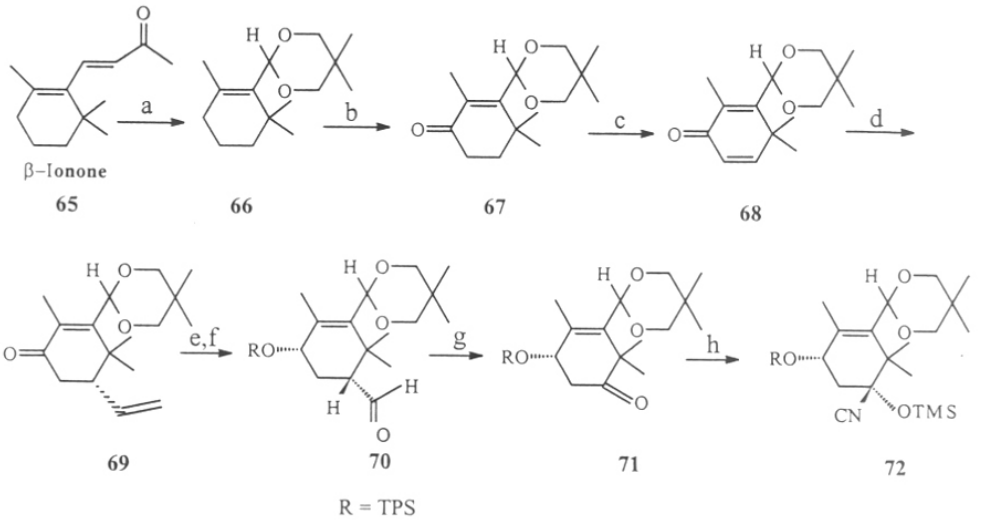
Scheme 8



Fallis's Approach:

Fallis methodology[30] involves the conversion of β-ionone (**65**) (a cyclic monoterpene) into a bis-enone (**68**), which was subjected to Michael addition followed by ozonolysis and carbonyl addition sequences to furnish fully functionalised A-ring (**72**) system of taxol. This methodology does not follow atom economy[31] in its synthetic sequence. (**Scheme 9**)

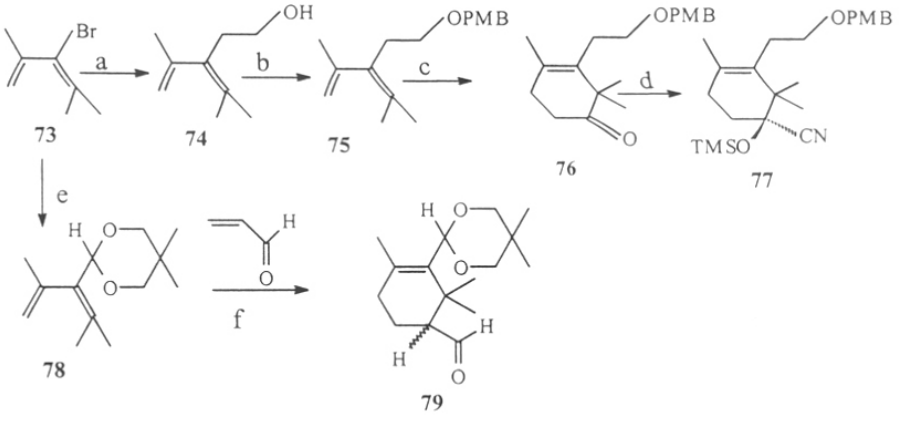
Scheme 9



a) O_3, CH_2Cl_2, -78C, Me_2S, Oxalic acid, $HOCH_2Me_2Ch_2OH$, PhH, 80C, 64%
b) SeO_2, K_2HPo4, toluene, 110°C: PCC, CH_2Cl_2, 62%; c) LDA, THF, PhSeBr, Oxone, $NaHCO_3$, MeOH, 65%; d) Vinyl magnesium bromide, THF, CuI, TMSCl, -78C, 69%; e) $NaBH_4$, MeOH, $CeCl_3.7H_2O$, 0°C, 96%; f) TPSCl, DMAP, CH_2Cl_2, 21°C, 97%; TPSOTf, Collidine, CH_2Cl_2, 21C; g) O_3, CH_2Cl_2, -78C, Me_2S, 96%; h) TMSCN, KCN, 18-C-6, 21°C, 91%

Diels-Alder strategy was also exploited by Fallis et al to synthesize a series of A-ring (**76, 77, 79**) synthons. The synthetic sequence is given below in (**Scheme 10**).

Scheme 10

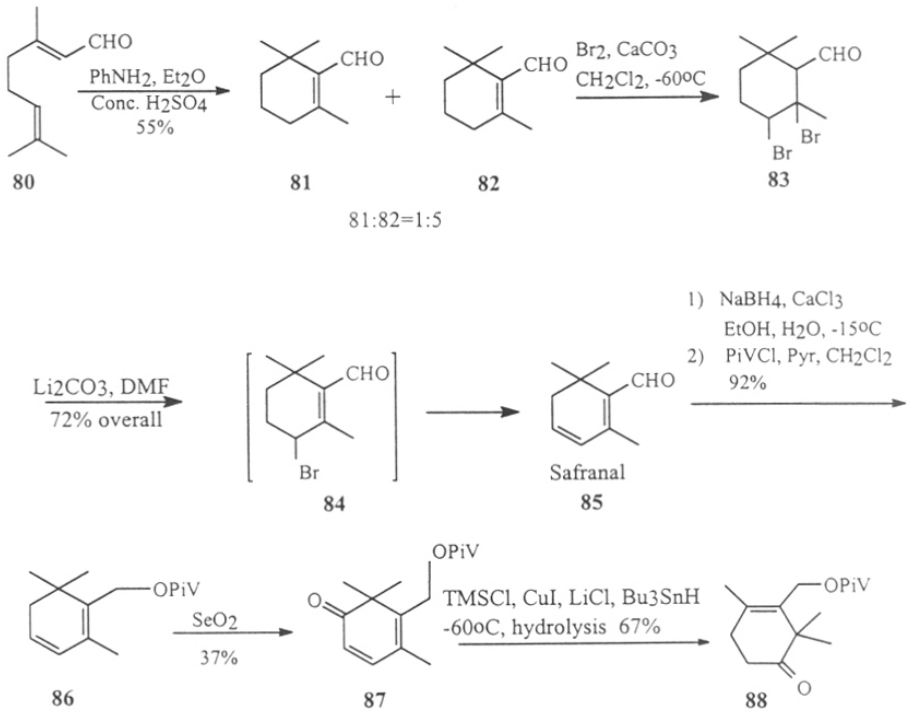


a) t-BuLi, ethylene oxide; b)Pyridine, PMBCl, c) 1,1-chloro,cyano ethylene, hydrolysis; d) TMSCN, CH_2Cl_2; e) t-BuLi, DMF, 2,2-dimethyl-1,3-propanediol, pTSA, PhH; f) Et_2AlCl, -78°C

Koskinen's Approach:

A short synthesis of the A-ring of taxol was developed from safranal (**85**) by Koskinen et al[32]. Safranol was converted into a dienone (**87**), which was reduced to get functionalised A-ring system (**88**) of taxol. Poor yields in allylic oxidation and reduction of the dienone by expensive and toxic reagents are some of the drawback of this strategy. (**Scheme 11**)

Scheme-11

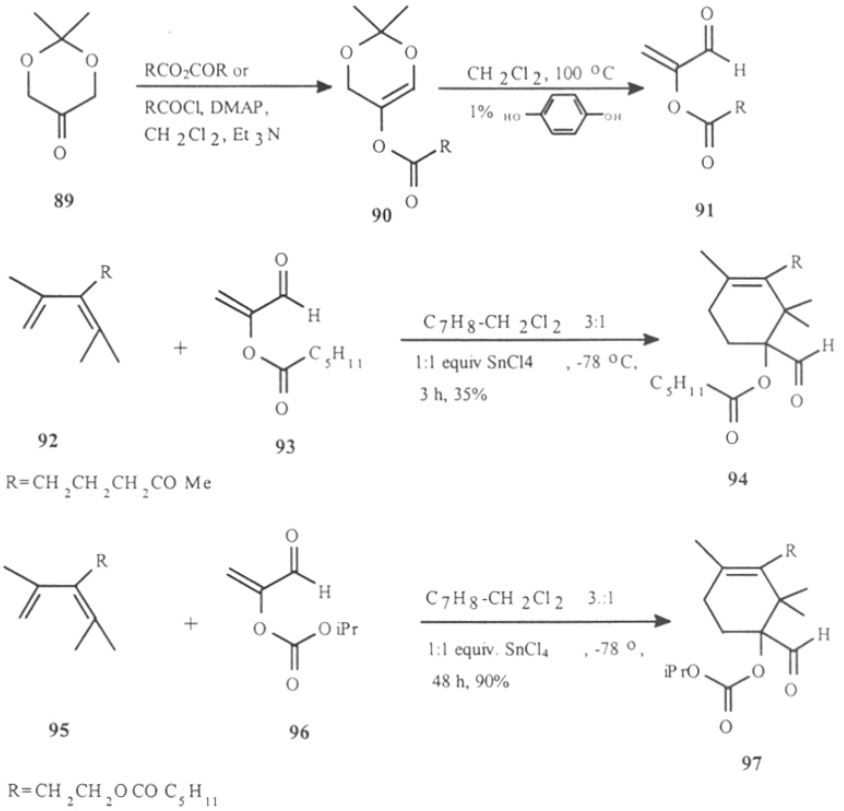


Yost's Approach:

Yost's group have developed the first general and efficient synthesis of 2-(acyloxy) acroleins (**91**)[33] and have documented the utility of these valuable reactants in Diels-Alder cycloaddition reactions. The acyloxydioxins (**90**) were prepared by o-acylation of ketone (**89**). 2-(Acyloxy) acroleins (**93, 96**) were obtained from acyloxydioxins via retrocycloaddition reaction. The 2-(acyloxy) acroleins obtained were utilized as dienophiles to furnish Diels-Alder adducts (**94, 97**) (A-ring synthons) in presence of equimolar amounts of Lewis acids. Although this method facilitates the preparation of A-ring units suitable for the elaboration of complete taxane framework,

the use of equimolar amounts of Lewis acids is environmentally hazardous and also the dienophiles employed are unstable. (**Scheme 12**)

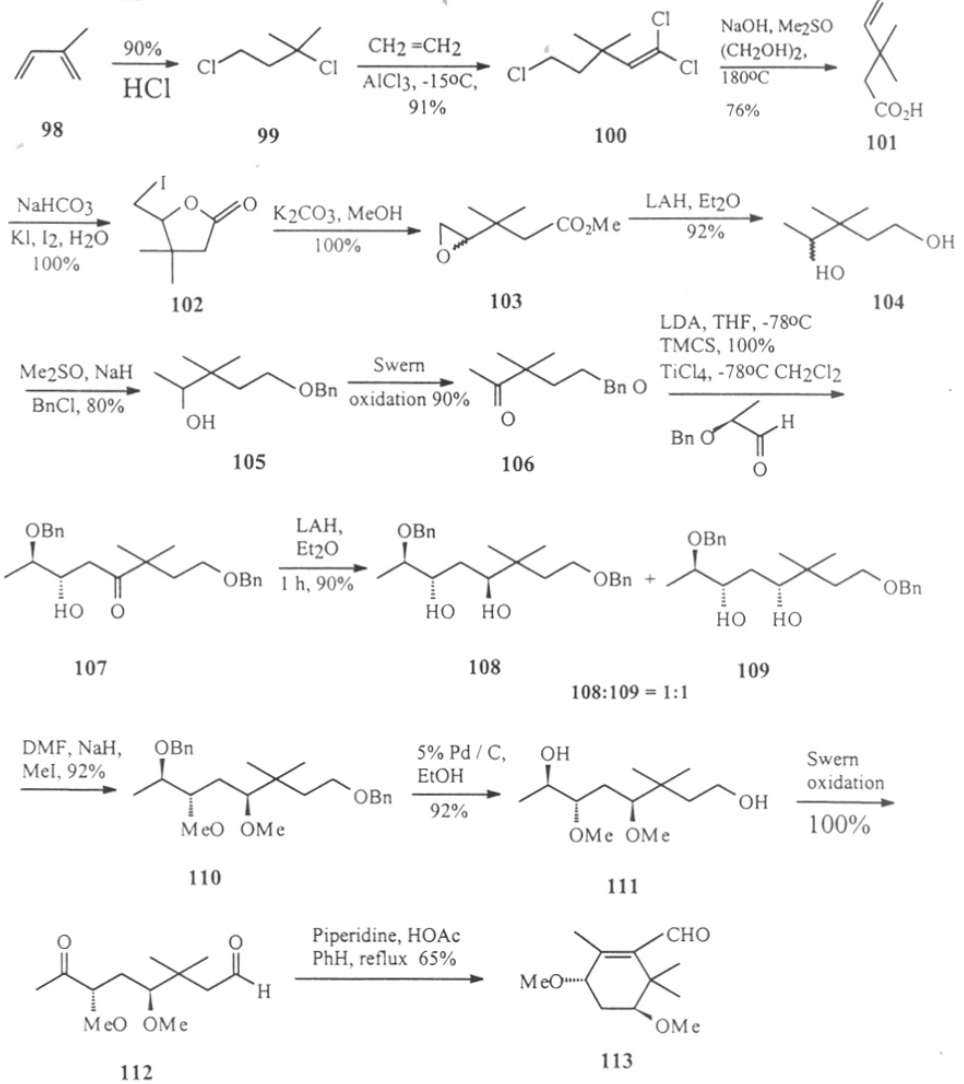
Scheme - 12



Ding's Approach:

Ding et. al.i, synthesised A-ring via an intermolecular aldol addition followed by an intramolecular aldol condensation starting from isoprene.[34] This method gives a fully functionalised A-ring synthon (**113**) over 15 steps. It is important to note that every synthetic manipulation involved in this sequence gave nearly quantitative yields. This methodology very well appeals to the synthetic audience, but, the use of gaseous ethylene, Lewis acid, expensive reagents like LDA and LAH makes the process economically less viable for the large scale preparation of A-ring. (**Scheme 13**)

Scheme - 13



Objective of the present work:

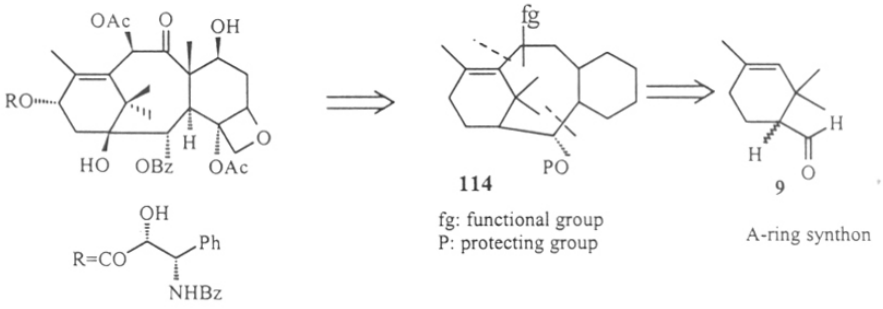
The synthetic studies towards advanced taxoids and prataxoids require a versatile A-ring synthon. A short synthesis of A-ring synthon was focused. The [(±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde] (±)-A-ring is amenable for C2-C3 bond formation (taxol numbering is used) also by a chelation controlled process after α-hydroxylation[35], such a process allows to append functionalised C-ring unit to the A-ring synthon. Later, B-ring annelation can be under taken. Thus, the aldehyde group can serve as an electrophile towards the nucleophilc species to obtain B-*seco* taxoids. In the latter, the

vinylic site can then be functionalized by Shapiro reaction,[36] for the ring closure by C9-C10 bond formation or the vinylic site as such can accept the radical or cationic species for the bond formation at C10-C11. Further, it is imperative to mention at this stage that such a functionalised A-ring synthon accommodates ten out of the twenty carbon atoms of the taxol core.

Present work:

As is evident from what has been described under "Objective", (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde (**9**) was chosen as a A-ring synthon for the present synthetic studies. Various methods for A-ring synthons reported so far in the literature involve too many steps, complicated synthetic operations, expensive reagents, toxic metallic salts and fair to poor yields in some of the steps. It was therefore, felt that a better, more efficient, shorter synthesis of A-ring synthon was necessary. This became the main objective of the present work. The retrosynthetic scheme is outlined below: (**Scheme 14**)

Scheme 14



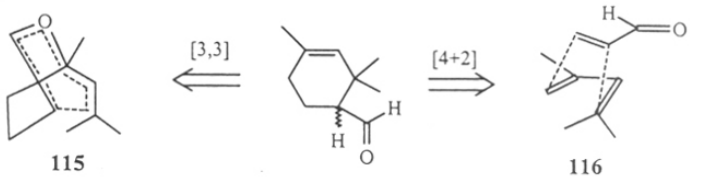
Two synthetic routes were identified and are proposed for the present work. Both of them involve concerted processes:

i) Claisen rearrangement involving [3,3-sigmatropic rearrangement]-2-vinyl-3,4-dihydro-2H-pyran (**115**).

ii) Diels-Alder reaction [(4+2)cycloaddition] involving diene and dienophile

Both the routes are shown as follows:

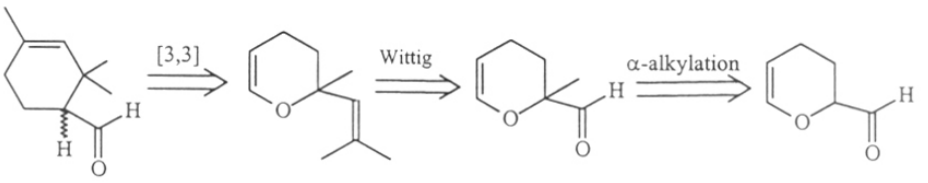
Scheme 15



115 116

Claisen-rearrangement of 3,4-dihydro-2H-pyran ethylenes provides a useful method for the synthesis of cyclohexenes.[37] It complements the method of Diels and Alder by allowing the structurally specific synthesis of cyclohexenes. (**Scheme 16**)

Scheme 16



115 117 118

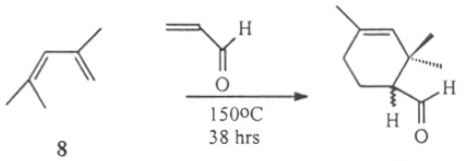
Thus, the A-ring (C-10) synthon could be prepared from the analogue of 2-vinyl-3,4-dihydro-2H-pyran (**115**). The compound **115** can then afford the desired product upon pyrolysis at 415°C in hexane solution. Such a precursor can be obtained by α-methylation followed by Wittig olefination from the acrolein dimer [Hetero-Diels-Adduct of acrolein (**118**)]. However, model studies revealed that competing reactions like Wittig reactions may interfere, hence this method was not initiated.

It was therefore, envisaged that of the various methods available for the synthesis of cyclohexene systems, those associated with the names of Diels and Alder are perhaps the most versatile. Furthermore, it gives a straightforward approach. Thus, a route to the C_{10} synthon was in turn planned via Diels-Alder reaction.

A detailed and exhaustive literature survey revealed that there are two methods available for the synthesis of the C_{10} synthon in racemic form, one involving a thermal Diels-Alder reaction[38] (Scheme 17) and the other one utilises the Ionic-Diels-Alder reaction (Scheme 18) of allyl cations.[39]

Thermal Diels-Alder reaction:

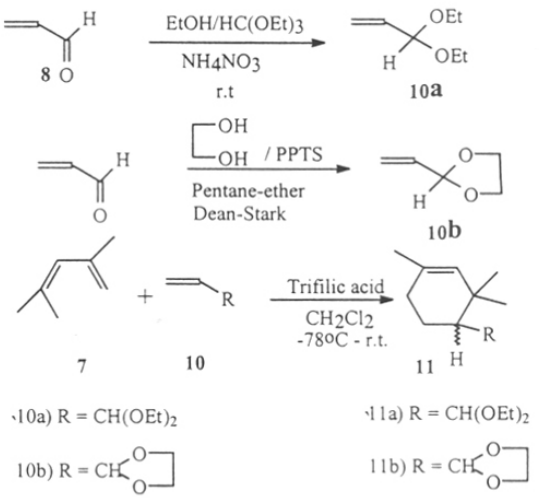
Scheme 17



8 9

Ionic Diels-Alder reaction:

Scheme 18



Both the thermal and ionic Diels-Alder reactions utilize 2,4-dimethyl-1,3-pentadiene (**7**) as the diene, which was prepared from mesityloxide over 2 steps. The cheaper and commercial availability of mesityloxide (**5**) enabled the preparation of the required diene (**7**), in large quantities for the present work. Literature proedure[40] for the preparation of diene from mesityl oxide gave (**5**) low yields. In order to improve on the reaction yields, a few modifications were carried out which resulted in improvements of yield upto 60%. (See experimental) These alterations included replacement of the dehydrating agent $KHSO_4$ with I_2. Having obtained the diene from mesityloxide via Grignard reaction methylmagnesium iodide in anhydrous ether followed by dehydration as given in experimental, the stage was now set to perform the Diels-Alder reaction. The thermal Diels-Alder reaction was first attempted to get the C_{10} synthon directly, using the 2,4-dimethyl-1,3-pentadiene (**7**) as diene and acrolein (**8**) as the dienophile. The diene (**7**) and the dienophile (**8**) were taken in 2:1 ratio in a sealed tube and heated

at 150°C for 38 hours. But, this protocol did not result in the formation of adduct (**9**); rather it had given polymerized lachrymatic products which were unidentifiable. Further modifications like the addition of hydroquinone and also use of solvents like toluene, benzene and dichloromethane or mixture of dichloromethane and benzene gave inconclusive results. Since, this thermal Jitkow's protocol was unsuccessful; the next choice was the execution of the synthesis of diethyl (**11a**) or ethylene glycol (**11b**) acetals of 2,2,4-trimethylcyclohex-3-ene-1 carbaldehyde via ionic Diels-Alder reaction.

The ionic Diels-Alder reaction required either 2-vinyl-1,3-dioxolane (**10b**) or 3,3-diethoxypropene (**10a**) as dienophile. Both the dienophiles were prepared according to the known procedures[41]. 2,4-Dimethyl-1,3-pentadiene and either 2-vinyl-1,3-dioxolane or 3,3-diethoxy propene respectively were taken in a ratio of 2:1 in dichloromethane and cooled to -78°C. A catalytic amount of trifilic acid (2 mol %) was added to the reaction mixture in dichloromethane as an alternate to 1,1,2-trichloro-1,2,2-trifluoroethane as reported in Gassmann's procedure. Usual work up followed by chromatographic purification of the product gave the expected adducts (**11a**) and (**11b**) in moderate to good yields (63-77%). The structures were confirmed by ^{1}H-NMR spectral data. (Vide experimental)

The diethylacetal product (**11a**) revealed a triplet at 0.8 δ for C(-O-CH_2-$C\underline{H}_3$)$_2$, singlets at 0.95 δ, 1.05 δ for germinal dimethyl protons, multiplet at 3.2-3.8 δ for C(-O-$C\underline{H}_2$-CH_3)$_2$ and a singlet at 5.0 δ for vinylic proton. Similarly, diethylene glycol acetal product (**11b**) revealed two singlets at 0.95 δ, 1.10 δ for germinal dimethyl protons, another singlet at 1.8 δ for vinyl methyl protons, a multiplet at 3.8-4.0 δ for -O-$C\underline{H}_2$-$C\underline{H}_2$-O- and a singlet at 5.0 δ for vinlyic proton. In this manner, the acetals of C_{10} synthon were prepared, purified and characterized.

The fully functionalised A-ring unit (9) requires the C-2 aldehydic functional group (taxol numbering is used) in its free state for further elaboration. This necessitated deprotection of diethyl and ethylene glycol acetals respectively. However, all efforts to cleave the acetal protection were unsuccessful. (e.g. acidic solvolysis[42], $PdCl_2(CH_3CN)$,[43] and DDQ, CH_3CN/H_2O[44]). Either the acetal was found to be stable to deprotection or it was destroyed during the reaction conditions. After many such unsuccessful attempts, it was decided to employ acrolein itself as the dienophile than its acetals under ionic Diels-Alder reaction conditions.

Accordingly, when the ionic Diels-Alder reaction between acrolien and diene was performed in the presence of triflic acid, also it failed to yield the desired product. However, replacement of triflic acid with Lewis acids such as $Bf_3.Et_2O$, $TiCl_4$ and $SnCl_4$ yielded the required product in excellent yields. In this manner, single batch reactions leading to 20 g of A ring synthon could be achieved.

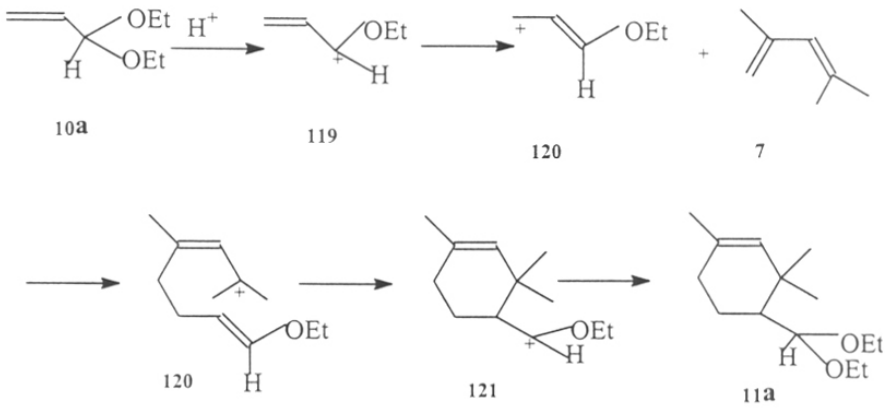
The infrared and ^1H NMR spectra confirmed the structure of the aldehydic compound with the IR absorption for the aldehyde group at 1720 cm^{-1} (due to C=O stretch), another at 2710 cm^{-1} (due to Fermi resonance[45]) and ^1H NMR chemical shift for the aldehydic function at 9.85 as doublet with J value of 2 Hz (coupling is due to the methylene proton at α-position to the aldehydic function). Further, confirmation was also obtained from its mass spectrum (M^+, 152). (see experimental section for details)

Results and Discussion:

Initial attempts to procure (±) A-ring under thermal Diels-Alder condition did not proceed to give the desired adduct; it might have been possible at high-pressure conditions. Furthermore, Diels-Alder reactions that employ acrolein as the dienophile often give undesirable results due to its ease of polymerization. In order to circumvent this problem, a variety of Lewis acids[46] and high pressures[47] conditions have been reported in literature and yet, under these conditions, yields are often less than 50%.

The acetals of the A-ring unit were obtained in moderate yields by using Gassmann's protocol (allyl cation mechanism). The mechanism by which the reaction proceeds is depicted below: **(Scheme 19)**

Scheme 19



Thus, for the first time, a low temperature process by avoiding the high-pressure conditions for the Diels-Alder reaction between acrolein and 2,4-dimethyl-1,3-pentadiene has been established. This process is amenable to scaleup.

Conclusion:

The methodology developed and described in this section for convenient preparation of (±)-A-ring synthon offers many advantages.

This A-ring unit provides ten of the twenty-carbon unit of taxol in racemic form in just three synthetic steps from commercially available starting materials.

The method developed offers an easy route to obtain A-ring synthon in multigram quantities.

It contains all the functionalities suitable for its elaboration to taxane framework and taxol analogues.

One of the scopes of the method lies in the fact that chiral A-ring unit can be obtained via asymmetric deprotonation[50], by chiral Lewis acid[51], by conversion to silylenol ether and subjecting it to α-hydroxylation either with chiral oxaziridines[52] or employing Sharpless dihydroxylation techniques.[53]

Employing triflic acid as a catalyst in the Diels-Alder reaction was not found to be a prerequisite. In fact, simple and common Lewis acids like $TiCl_4$, $SnCl_4$, $Bf_3.Et_2O$ serve the purpose equally well.

EXPERIMENTAL:

General:

All reactions requiring anhydrous conditions were performed under a positive pressure of argon nitrogen using oven-dried glassware (120°C) which were cooled under argon nitrogen in a desiccator. Solvents for anhydrous reactions were dried according to Vogel's Text Book of Practical Organic Chemistry (5th Ed., Longman group U.K. Ltd., 1989). Benzene, toluene, tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Acetonitrile, dimethylformamide, dichloromethane, and triethylamine were distilled from calcium hydride under nitrogen/argon atmosphere. All organic phases obtained from extraction were dried over anhydrous sodium sulphate. The term *in vacuo* refers to the removal of solvent on a rotary evaporator followed by evacuation (< 5mm Hg) to constant sample weight. Solvents used for chromatography were distilled prior to use Petroleum ether refers to the fraction boiling in the range of 60-80°C.

Progress of the reactions were monitored by Thin Layer Chromatography and (TLC) was visualized by ultra-violet absorption by fluorescene quenching or iodine staining or by both. Silica gel for colum chromatography refers to 60-120 mesh size, obtained from S.D. Fine Chemicals, India or SRL, India. A Buchi GKR-51 Kugelrohr distillation apparatus, vigurex column distillation apparatus and short-path distillation unit were used for distilling liquid samples.

All melting points are uncorrected in degree celsius and were recorded on a thermovik melting point apparatus or a Yanaco micromelting point apparatus. IR spectra were recorded in a Perkin-Elmer Infrared spectrometer model 599-B, model 1620 FT-IR and AIT Mattson, UK, model RS-1 FT-IR. IR bands are expressed in cm^{-1}. The spectra were recorded neat, in nujol mull or in chloroform solution. ^{1}H NMR spectra were recorded using tetramethyl silane (TMS) as an internal reference on AC-200, WH-90, Brucker FT-80A and Jeol-60 instruments using deutirated chloroform ($CDCl_3$) as solvent. Chemical shifts are expressed in delta (δ). Abbrevation used are as follows: s: singlet, d: doublet; t:triplet, dd: doublet of a doublet, m: multiplet; br: broad, dq: doublet of quartet, tdd: triplet of doublet of a doublet. ^{13}C-NMR was recorded on Bruker AC-200 instrument operating at 50 MHz. Mass spectra were recorded on a

Finnigan-Mat 1020C. Mass spectrometer and are obtained at an ionization potential of 70 eV.

Optical rotation were measured at the sodium D line on a JASCO-181 digital polarimeter at ambient temperature. Elemental analysis was performed on a carla Erba CHNS. EA1108 Elemental Analyser or by conventional combustion techniques at the microanalysis facilities at NCL, Pune.

2,4-Dimethyl-1,3-pentadiene: (7)

a) **2,4-Dimethyl-pent-2-ene-4-ol:** (6)

The Grignard reagent, methylmagnesium iodide was prepared from methyliodide (200 g, 88.0 ml, 1.4 mol), 300 ml of anhydrous ether, and activated magnesium turnings (35.0 g, 1.4 mol) in a 2 lit. round bottomed flask fitted with an overhead stirrer, dropping funnel and reflux condenser with a flow of ice-cold water. When nearly all the magnesium had dissolved the mixture was cooled to 0°C using an ice-salt bath. A solution of mesityloxide (120 g, 139.8 ml, 1.2 mol) in 300 ml of anhydrous ether was added to the Grignard reagent at such a rate that the addition did not cause a rise in temperature above 5°C. After all the addition of mesityloxide was over, the reaction mixture was refluxed for 30 minutes and allowed to stand overnight at room temperature. The total reaction mixture was poured slowly into 300 ml of ice-cold aqueous solution containing ammonium chloride (160 g). The ethereal layer was separated, the aqueous layer was extracted with diethyl ether (3 x 100 ml), the combined organic phase was washed with water (3 x 5 ml), brine (3 x 10 ml), dried over anhydrous sodium sulphate and the ether was distilled off to get 2,4-dimethylpent-2-ene-4-ol (**6**) which was found to be pure enough for further operations.

Yield	:	117.0 g; (72%)
B.P.	:	132-135°C
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 3450 (b), 3000 (b), 1450, 1380, 900.
^{1}H-NMR (60 MHz):		δ 1.3 (s, 6H, -C-($C\underline{H}_3$)$_2$) , 1.6 (s, 3H, -C=C-$C\underline{H}_3$), 1.8 (s, 3H, -C=C-$C\underline{H}_3$). 2.1 (s, 1H. -C-$\underline{O}H$), 5.2 (m, 1H, -C=C$\underline{H}$).

b) **2,4-Dimethyl-1,3-pentadiene**: (7)

In a 2-necked, 250 ml; round-bottomed flask fitted with a distillation condenser having a flow of ice-cold water and a dropping funnel was placed potassium bisulphate (30.0 g). The flask was heated to 120°C in an oil bath and the allylalcohol (2,4-dimethyl-pent-2-ene-4-ol, 117.0 g) was dropped into the flask at a rate of 5 ml per minute. The hydrocarbon (2,4-dimethyl-1,3-pentadiene) was collected in another round-bottomed flask, separated from the water by transferring into a separating funnel and dried over anhydrous sodium sulphate. It was purified by distillation over 20 g. of sodium.

Yield	:	87.0 g, (60%)
B.P.	:	92-98°C (lit[18]. 93°C)
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 3000, 16000, 1450, 1380, 900.
^{1}H NMR (60 MHz)	:	δ 1.85 (s, 9H, C=C-($C\underline{H}_3$)$_2$ and C=C-$C\underline{H}_3$), 4.6 (s, 1H, C=C-C$\underline{H}$), 4.8 (s, 1H, C=C$\underline{H}$), 5.4 (s, 1H, -C=C$\underline{H}$-).

Pyridinium-p-toluenesulfonate (10b)

In a 50 ml, round-bottomed flask pyridine (12.1 ml, 150 mmol) was taken to which p-toluenesulfonic acid monohydrate (5.7 g, 30 mmol) was added with stirring at room temperature. Upon addition of p-toluenesulfonic acid slightly exothermic reaction was observed. The reaction mixture was stirred for 20 minutes at room temperature. Pyridine was removed on a rotary evaporator to afford an almost quantitative yield of pyridinium-p-toluenesulfonate. The colourless solid obtained was recrystallized from acetone to yield the purified product.

Yield	:	6.8 g (90%)
M.P.	:	120-123°C (Lit. m.p.[54] 120°C).

2-Vinyl-1,3-dioxalane: (**10b**)

A solution of acrolein (123.0 g, 147 ml, 2.196 mol), ethylene glycol (**8**) (126.0 g, 113 ml, 2.03 mol) and pyridinium-p-toluene sulfonate (1.5 g, 6 mmol) in 300 ml of anhydrous pentane and 100 ml of anhydrous diethylether was taken in a 1 lit. round-bottomed flask and heated under reflux for 95 hours with continuous collection of water

in a Dean-Stark trap. The solvent was distilled off and the colourless residue obtained was distilled to yield 2-vinyl-1,3-dioxalane.

Yield	:	116.0 g, (57%)
B.P.	:	114-116°C (Lit.b.p.[41] 110-115°C).
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 2950, 1600, 1104, 1000.
^{1}H-NMR (200 MHz)	:	δ 3.79-4.02 (m, 4H, -O-C$\underline{H}_2$-C$\underline{H}_2$-O), 5.16 (d, 1H, J = 6 Hz, $\underline{H}$C-O), 5.40 (dd, 2H, J = 10, 7 Hz, HC=C$\underline{H}_2$), 5.79 (qd, 1H, J = 10, 7, 6 Hz, $\underline{H}$C=CH_2).

3,3-Diethoxy-1-propene: (10a)

In a 500 ml round-bottomed flask a solution containing acrolein (**8**) (44.0 g, 52.4 ml, 0.786 mol) and triethylorthoformate (144.0 g, 160 ml, 0.972 mol) was taken and the mixture was warmed gently. To this warm solution 30.0 g ammonium nitrate was introduced in one lot. A slight red coloration appeared. The mixture was stirred at room temperature for 8 hours. It was then filtered and 4.0 g of sodium carbonate was added to it. Distillation using a vigurex column yielded a major fraction boiling at 125-130°C which was collected and redistilled to get pure 3,3-diethoxy-1-propene (**10a**) as a colourless liquid.

Yield	:	80.0 g (80%).
B.P.	:	120-125°C (Lit. b.p.[41] 123-125°C).
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 2950, 1600, 1104, 1000.
^{1}H-NMR (200 MHz)	:	δ 1.2-1.25 (t,. 6H, C-OCH_2-C$\underline{H}_3$)$_2$), 3.45-3.73 (m, 4H, C-O-C$\underline{H}_2$-CH_3)$_2$), 4.85-4.92 (d, 1H, J=6 Hz, $\underline{H}$-C(OEt)$_2$), 5.2-5.4 (dd, 2H, HC=C$\underline{H}_2$), 5.8-5.9 (m, 1H, C$\underline{H}$=CH_2).

Synthesis of diethylacetal of (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde: (11a)

2,4-Dimethyl-1,3-pentadiene (**7**) (1.9 g, 2.6 ml, 20 mmol) and 3,3-diethoxy-1-propene (**10a**) (1.3 g, 1.5 ml, 10 mmol) were taken in 40 ml of anhydrous dichloromethane in a 100 ml round-bottomed flask and the mixture was cooled to -78°C (acetone - dry ice bath). To this reaction mixture a catalytic amount of triflic acid (0.1

mmol) or $BF_3.Et_2O$ (0.1 mmol) in 2 ml of dichloromethane was added with a syringe needle under N_2 atmosphere. The reaction mixture was stirred for one hour at -78°C and then allowed to warm to room temperature. It was stirred further at room temperature for 5 hours. The reaction mixture was quenched by the addition of either 0.2 ml of 40% aqueous ethylamine or 5 ml. of saturated sodium carbonate. The dichloromethane layer was separated, the aqueous layer was extracted further with dichloromethane (3 x 5 ml). The combined organic layer was dried over anhydrous sodium carbonate. The solvent was distilled off and the crude product was purified by silica gel column chromatography to yield a colourless liquid.

Yield	:	1.3 g, (61%).
B.P.	:	126-128°C at 12 mm Hg (Lit.[39] 126°C at 12 mm Hg).
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 2950, 1615 (w), 1440 (w), 1380 (w), 1100, 1060.
^{1}H-NMR (200 MHz)	:	δ 0.8 (6H, C-(O-CH_2-C$\underline{H}_3$)$_2$), 0.95, 1.05 (2s, H, C-(C$\underline{H}_3$)$_2$), 1.8 (s, 3H, C=C-C$\underline{H}_3$), 1.9-2.05 (m, 5H, 2 x C$\underline{H}_2$, 1 x C$\underline{H}$), 3.2 - 3.83 (m, 4H, C(-O-C$\underline{H}_2$-CH_{3-})$_2$), 4.82 (, 1H, $\underline{H}$-C(-OEt)$_2$), 5.01 (s, 1H, C=C$\underline{H}$).

Ethyleneglycol acetal of (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde: (**11b**)

2,4-Dimethyl-1,3-pentadiene (**7**) (1.9 g, 2.6 ml, 20 mmol) and 2-vinyl-1,3-dioxolane (**10b**) (1 g, 1.2 ml, 10 mmol) were taken in 40 ml of anhydrous dichloromethane in a 100 ml round-bottomed flask and the mixture was cooled to -78°C using an acetone dry-ice bath. To this reaction mixture a catalytic amount of (0.1 mmol) trifilic acid or $BF_3.Et_2O$ in 2 ml of dichloromethane was added with a syringe needle under N_2 atmosphere. The reaction mixture was stirred for 1 hour at -78°C and then allowed to warm to room temperature. It was stirred further at room temperature for 5 hours. Usual work up followed by column chromatography over silica gel and distillation under diminished pressure yielded ethylene glycol acetal of (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde (**11b**) as a colourless liquid.

Yield	:	1.09 g, (56%)
B.P.	:	127-131°C at 12 mm Hg (Lit.[19] 129°C at 12 mm Hg)
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 2950, 1615 (ω), 1440 (ω), 1380, 1100, 1000.

^{1}H-NMR (200 MHz) : δ 0.95, 1.10 (2s, 6H, C(-C$\underline{H}_3$)$_2$), 1.8 (s, 3H, C=C-C$\underline{H}_3$), 1.92-2.05 (m, 5H, 2 x C$\underline{H}_2$, 1 x C$\underline{H}$), 3.82-4.01 (m, 4H, -O-C$\underline{H}_2$ -C$\underline{H}_2$ -O), 4.92 (d, 1H, J = 5.6 Hz, $\underline{H}$-C(-O-CH$_2$)), 5.01 (s, 1H, C=C$\underline{H}$).

Attempted deprotection of either ethyleneglycolacetal or diethoxy acetal of (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde

In a 50 ml round-bottomed flask ethyleneglycolacetal(**11b**), (0.88 g, 4.47 mmol) or diethoxyacetal (**11a**) (1.01 g, 4.47 mmol) of (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde (**9**) was taken in 10 ml of distilled tetrahydrofuran and 5 ml of water. To this solution a catalytic amount of p-toluene sulfonic acid (10 mol %) was added and refluxed for 12-15 hours. The total reaction mixture was concentrated in vacuo and it was diluted with diethyl ether (3 x 20 ml). The ethereal layer was washed with ice-cold saturated sodium carbonate (3 x 5 ml), water (3 x 5 ml), brine (3 x 5 ml) and dried over anhydrous sodium sulphate. The solvent was distilled off on a rotary evaporator, the residue was chromatographed over silica gel to get predominantly the acetal in both the cases.

Attempted synthesis of (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde

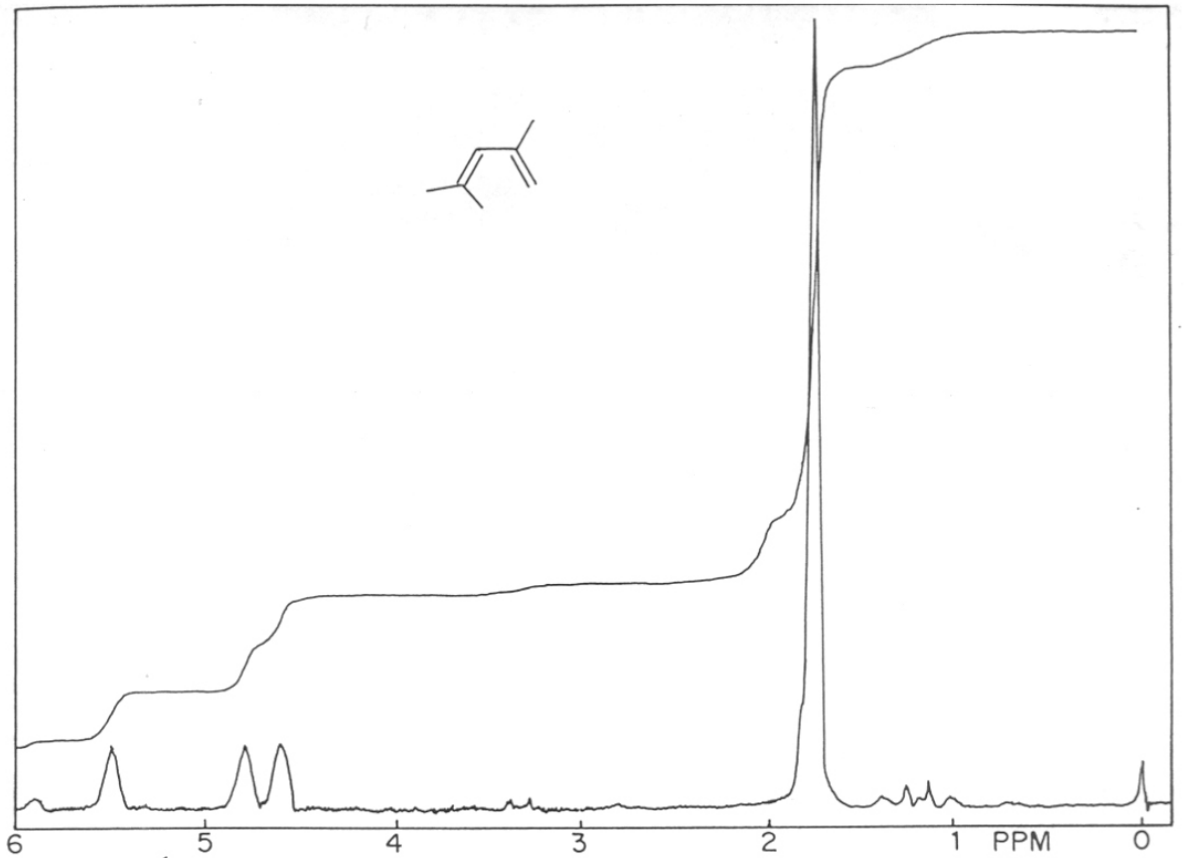
A mixture of 2,4-dimethyl-1,3-pentadiene (11 g, 115.7 mmol) and acrolein were heated in a sealed tube for 42 hours at 145-150°C. The reaction mixture was brought to room temperature. The contents of the tube was transferred into a round-bottomed flask and concentrated in vacuo. The reaction product obtained was found to polymeric and unidentifiable.

Synthesis of (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde (9)

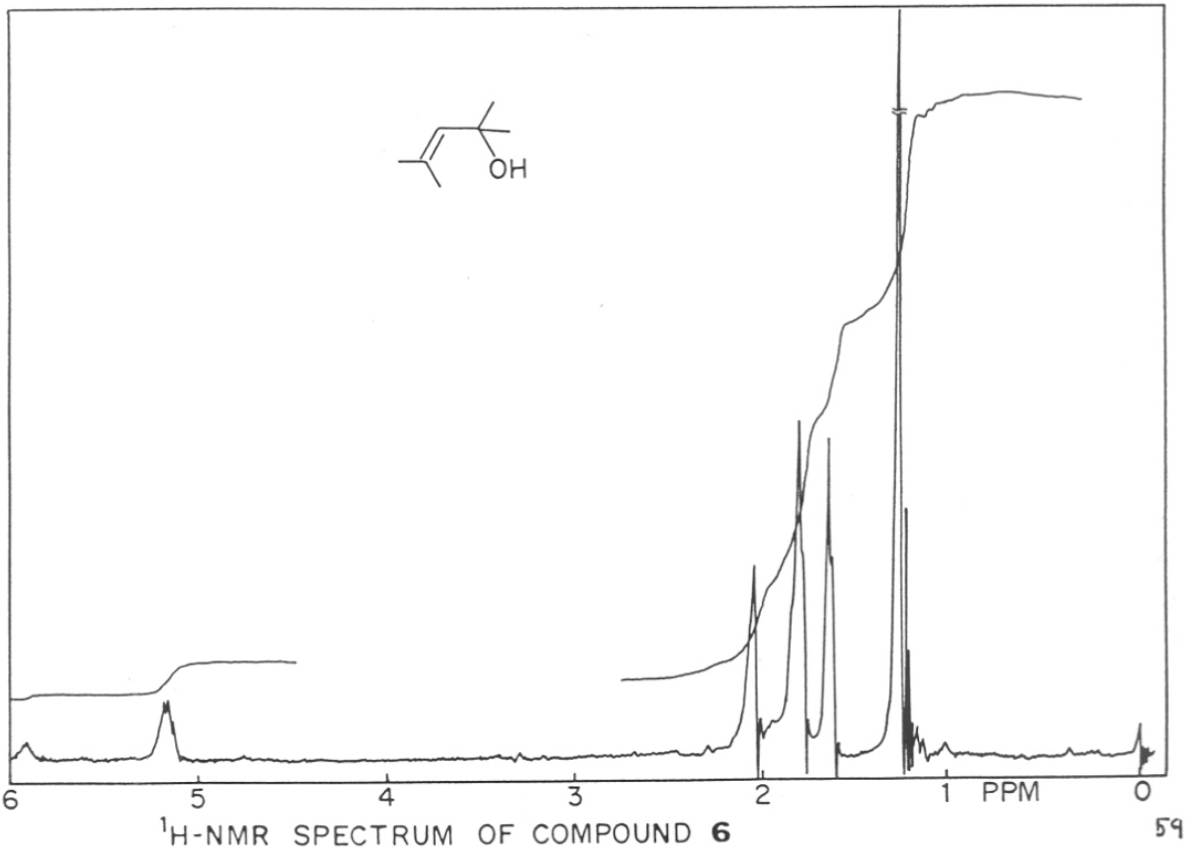
In a 250 ml round-bottomed flask 2,4-trimethyl-1,3-pentadiene (**7**), (114 g, 15.6 ml, 120 mmol) and acrolein (**8**), (3.36 g, 4.0 ml, 60 mmol) were taken in 100 ml of anhydrous dichloromethane and cooled to -78°C using an acetone-dry ice bath. To this reaction mixture a catalytic amount of $BF_3.Et_2O$ (0.85 g, 0.73 ml, 6 mmol) in 5 ml of dichloromethane was added using a syringe needle under argon atmosphere. The reaction mixture was stirred for one hour at -78°C and then allowed to warm to room temperature. It was stirred further for 5 hours at room temperature. The reaction

mixture was quenched by the addition of 15 ml of saturated sodium carbonate and stirred for 5 minutes. The dichloromethane layer was separated, the aqueous layer was extracted further with dichloromethane (3 x 20 ml), and the combined organic layer was washed with water (3 x 10 ml) brine (3 x 5 ml) and dried over anhydrous sodium carbonate. The solvent was distilled off and the residual material was purified by silica gel column chromatography and distilled at reduced pressure to furnish (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde (**9**) as a pleasant smelling liquid.

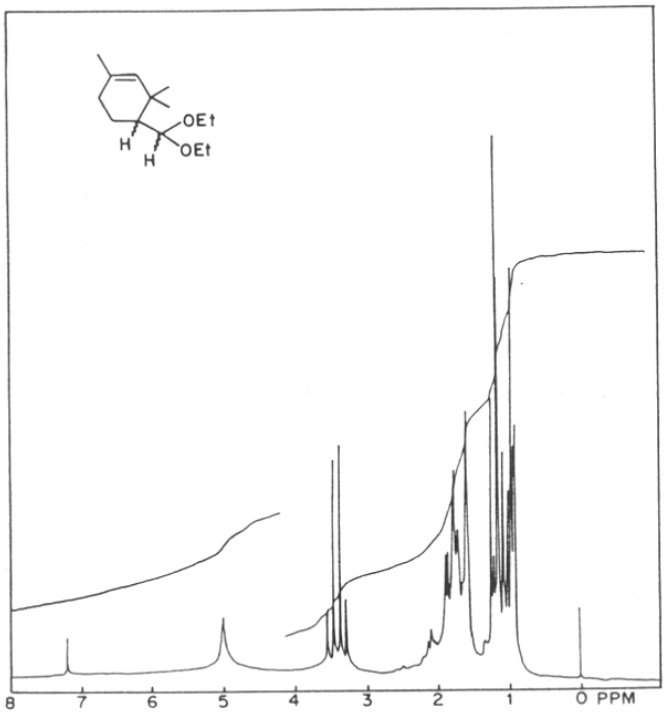
Yield	:	7.48 g, (82%)
B.P.	:	78-82°C at 18 mm Hg. (Lit.[55] 80°C at 18 mm Hg)
IR (Neat, cm^{-1}):		$\sqrt{}_{max}$ 2950, 2710 (due to fermi resonance); 1720, 1450, 1360, 1100, 1000.
^{1}H-NMR (200 MHz)	:	δ 1.2 (2s, 6H, C-($C\underline{H}_3$)$_2$), 1.63 (br.s, 3H, C=C-$C\underline{H}_3$), 1.92-2.25 (m, 5H, 2 x $C\underline{H}_2$, 1 x C$\underline{H}$), 5.05 (s, 1H, C=C$\underline{H}$), 9.85 (d, 1H, J = 2Hz, -C$\underline{H}$O).
Mass (m/z)	:	152 (41, M^+), 137 (28), 121 (55), 109 (69), 107 (56), 96 (35), 81 (100), 69 (34), 67 (45), 55 (27), 48(30), 41(47).



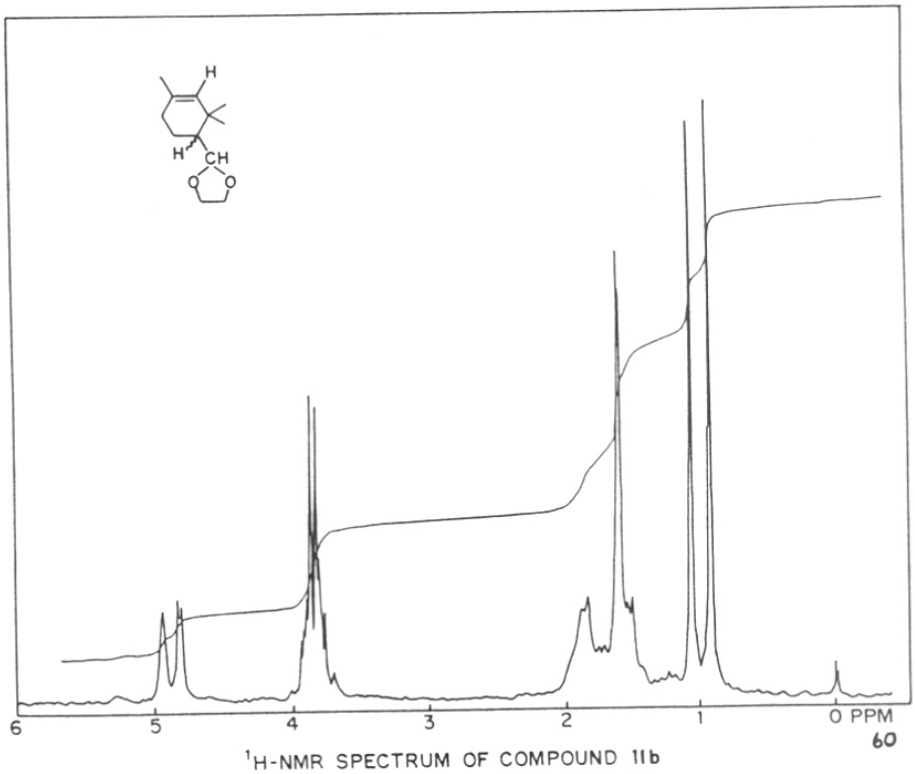
^{1}H-NMR SPECTRUM OF COMPOUND **7**



^{1}H-NMR SPECTRUM OF COMPOUND **6**



^{1}H-NMR SPECTRUM OF COMPOUND 11a



^{1}H-NMR SPECTRUM OF COMPOUND 11b

SECTION-2

Synthesis of (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde

Introduction

In the earlier section, a short, convenient, scalable synthesis of (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde (**9**) (a versatile A-ring system of taxol) was presented. This section discusses the synthesis of (S)-(-)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde from a chiral starting material.[56] Towards this goal, the above C_{10} aldehyde was synthesized from (-)-*trans*-verbenol. A flexible pyrolysis technique was employed in the key step for the conversion of (-)-*trans*-verbenol to the C_{10} aldehyde. Advantageous was the fact that (-)-*trans*-verbenol can be conveniently prepared from (-)-α-pinene, an important constituent of pine and a major component of industrial solvents like turpentine. It is noteworthy that α-pinene is available in either enantiomeric forms possessing ten of the twenty carbons of the desired taxol core. Pinene was viewed as a superb building block in a variety of synthetic routes to taxanes, which involve photochemical pathways. Such photochemical transformations hold major disadvantages such as high dilution, specialised photochemical equipments and low yields due to secondary photoproducts. The present work completely bypasses photochemical pathway by utilizing pyrolysis technique. In many ways, the present work is complementary to the photochemical pathway. Furthermore, the chiral A-ring unit obtained by this procedure serves as a starter for the stereoselective synthesis of taxanes.

When the present work was initiated in 1994, only three approaches to chiral A-ring systems were known in literature. These involved chiral starting materials like D-camphor, L-Arabinose and chiral reagent (R)-oxazaboralidine to obtain chiral A-ring systems. Later, during the course of our studies a few more approaches were reported. Some of these routes relevant to the present work are discussed briefly.

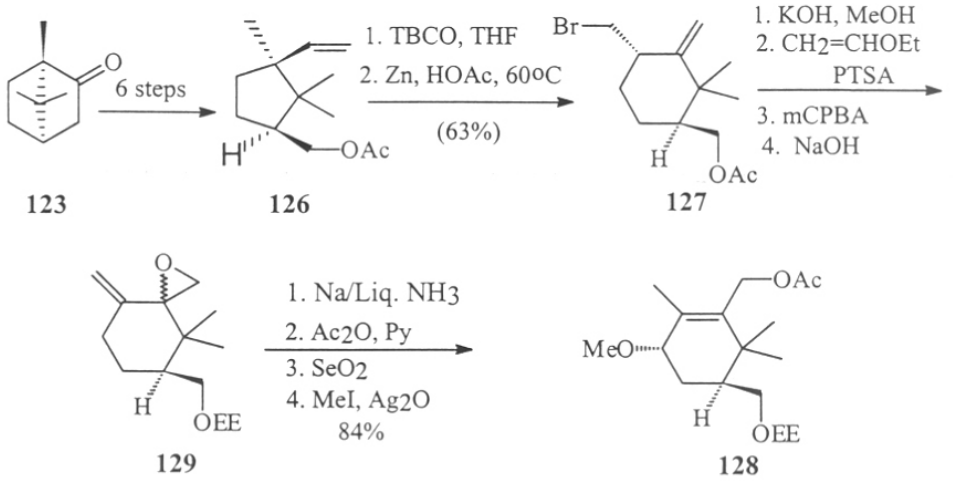
Synthesis of chiral A-ring systems: Some important approaches

1) Kitagawa's Approach:

The very first approach to taxol A-ring was by Kitagawa et al,[57], in 1980. The synthetic pathway involved a novel ring enlargement of vinylcyclopentane derivative (**126**) to cyclohexane derivative (**127**) which enlargement was achieved in the presence of TBCO (2,4,4,6-tetrabromocyclohexa-2,5-dienone) in which a Wagner-Meerwein rearrangment induced by a bromonium ion, converted cyclopentane ring into cyclohexane skeleton (**127**).

The cyclohexane skeleton obtained was transformed into the chiral A-ring (**129**) by standard functional group transformations. This methodology involved 16 steps with the use of costly reagents which are the major drawbacks of this approach (**Scheme 22**).

Scheme 22

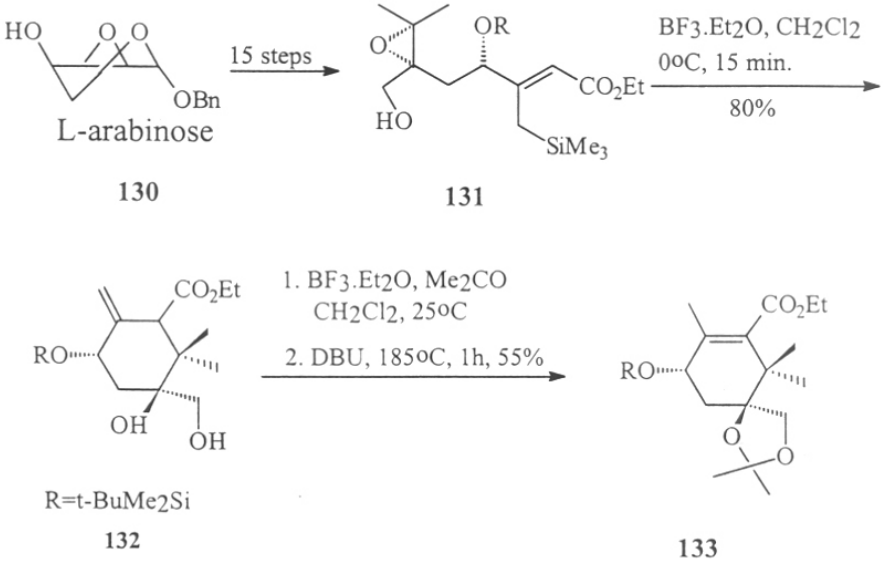


123 **126** **127** **129** **128**

Frejd's Approach:

An elegant approach to the A-ring of taxol was reported by Frejd et al[58]. The key step involved a Lewis acid promoted cyclization of epoxysilane (**131**) to assemble the cyclohexane system (**132**).

Scheme 23



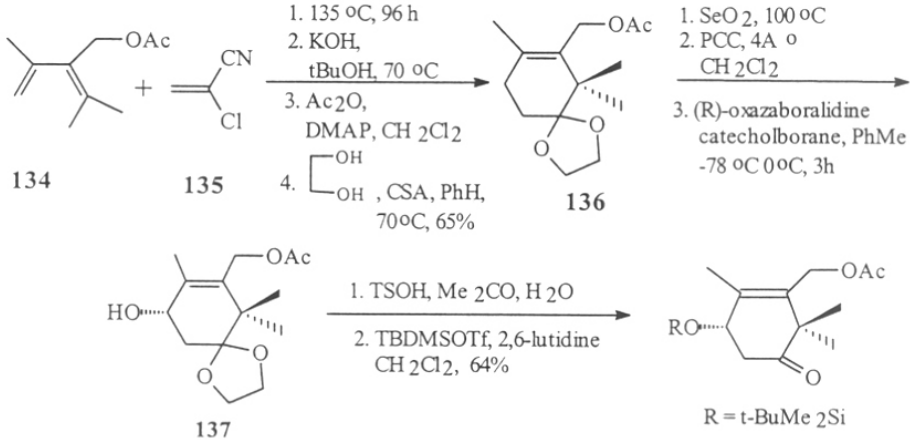
130 **131** **132** **133**

Further elaboration of this intermediate provided the required A-ring system. This synthesis starts from commercially available L-arabinose (**130**). More than twenty steps are involved in this operation and the overall yields are low. (**Scheme 23**)

Nicolaou's Approach:

Nicolaou's approach[59] applies the classic Diels-Alder cycloaddition to construct the cyclohexene derivative (**136**). In this rather simple approach, the readily available Diels-Alder partners (**134**) and (**135**) under thermal condition afforded the cyclohexene derivative (**136**) in a regiospecific manner. Thus cyclohexene derivative (**136**)

Scheme 24



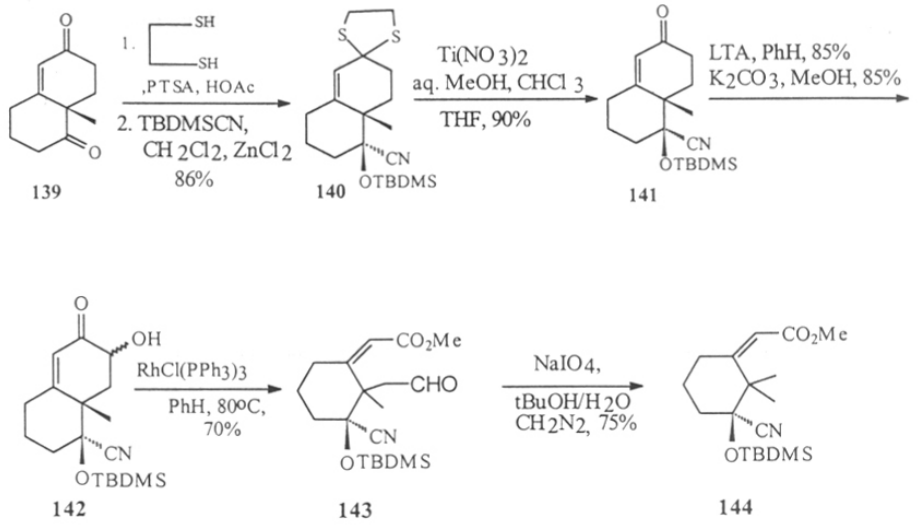
was converted into an enone derivative which was further reduced using (R)-oxazaborolidine, a chiral auxillary, to afford a chiral A-ring synthon (**137**). It is important to note that this A-ring synthon (**138**) was used in the total synthesis of taxol reported by Nicolaou and co-workers.

Watt's Approach:

An enantioselective approach to ring A of taxol (**144**) was achieved by Watt's group[66] starting from Wieland-Miescher ketone (**139**). The selective protection of (S)-(+)-enantiomer of the Wieland-Miescher ketone followed by hydrocyanation with TBDMSCN gave (**140**).

The latter was deprotected and α-hydroxylated. $NaIO_4$ cleavage, followed by esterfication and further elaborations completed the synthetic scheme. Wieland-Miescher ketone as a starting material is expensive and negates the better aspects of this approach.

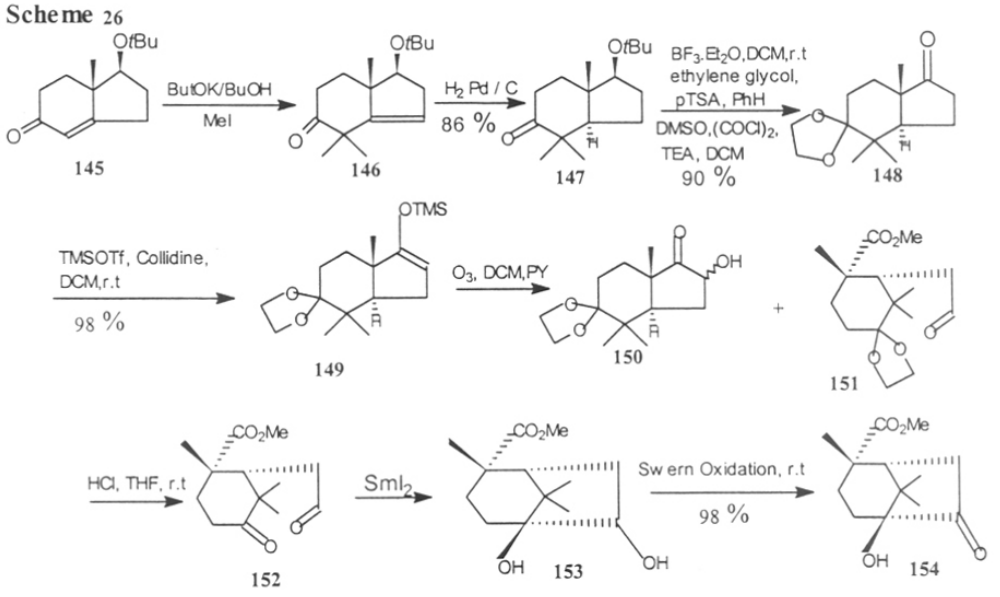
Scheme 25



Potier's Approach:

The known lower analogue of Wieland-Miescher ketone (**145**) was utilized by Potier[61] et. al, as an A-ring precursor. The five-numbered ring of this ketone was cleaved to afford the substituted cyclohexane system (**151**). Later, it was converted into optically homogeneous bridged ring system (**153**) by SmI_2 mediated reductive pinacol coupling.

Scheme 26



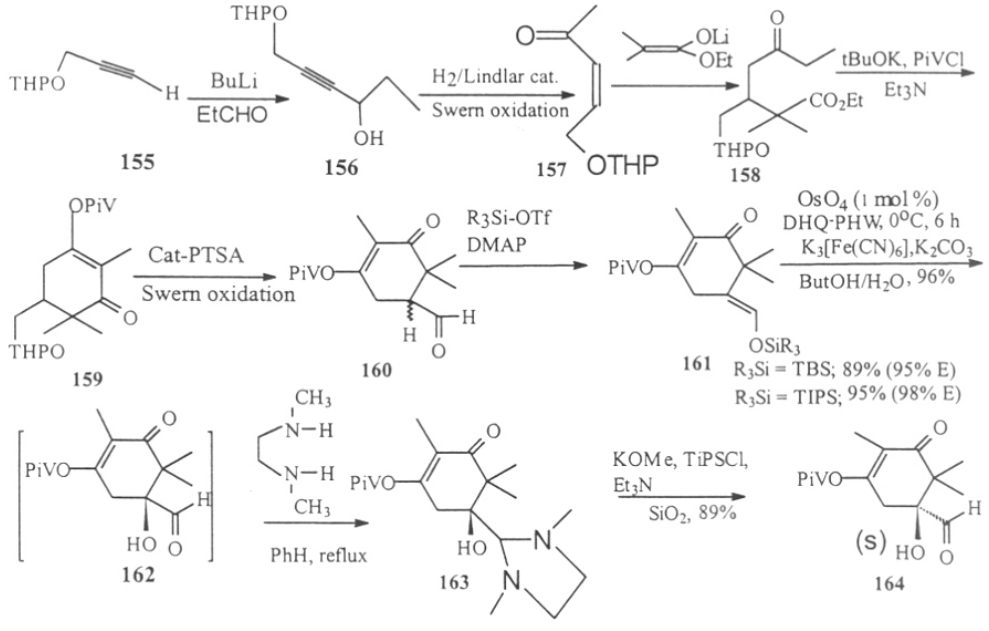
Lack of product selectivity in the ozonolysis step and the use of expensive SmI_2 are few disadvantages of this synthesis.

Kuwajima's Approach:

The A-ring system (**159**) was initially prepared in a racemic form[62] in a straightforward manner in 43% overall yield by an eight-step procedure. The key cyclization was achieved by Dieckmann cyclization to get cyclohexane ring system (**159**). Deprotection of THP-ether followed by oxidation yielded the aldehyde. The aldehyde obtained was converted into silylenol ether, owing to the sterically demanding dimethyl substituent, preferential formation of (E)-isomer was observed. The silylenol ether obtained thus was dihydroxylated using Sharpless asymmetric dihydroxylation conditions to get optically active A-ring system (**164**).[63]

Use of stoichiometric n-BuLi in the first step itself makes the process economically less viable.

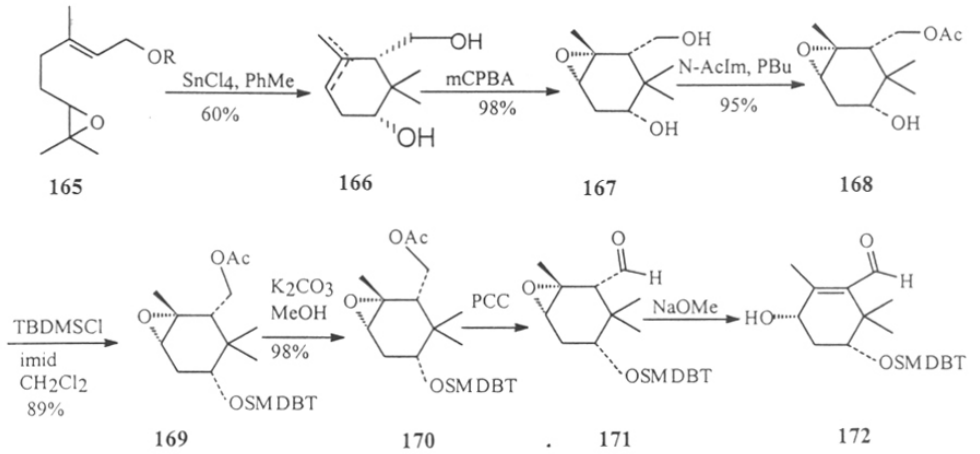
Scheme 27



Alcaraz's Approach:

The cyclohexane ring system (**166**) was efficiently prepared *via* stoichiometric cationic olefin cyclization of chiral geraniol epoxide by Alcaraz et al[64] using $SnCl_4$ in toluene. This cyclohexane ring system (**166**) was converted into fully functionalized A-ring system (**172**) by standard synthetic manipulations as shown in the scheme-28. The approach is superior to the method used by Gilbert Stork for racemic A-ring synthon (**Scheme 28**).

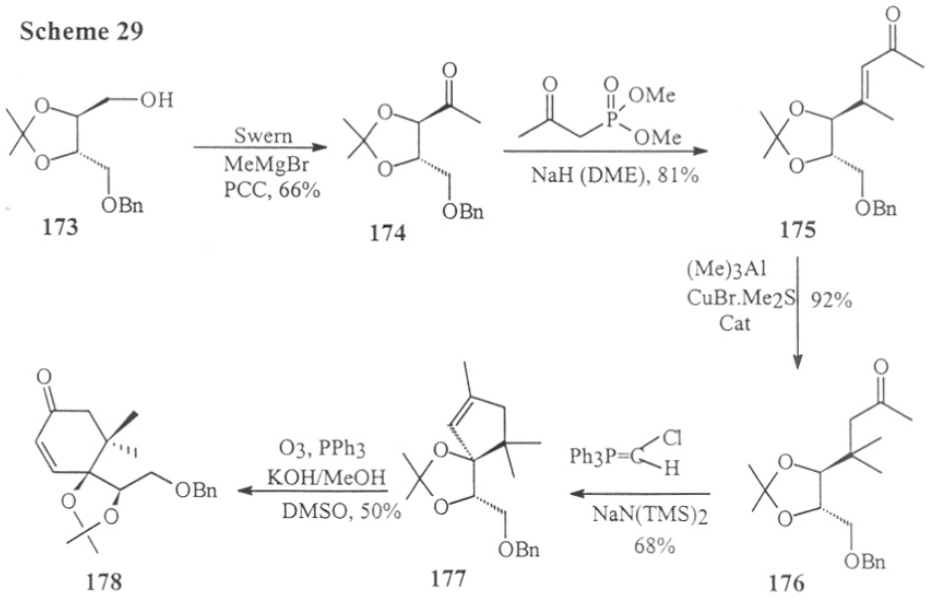
Scheme 28



Taber's Approach:

Starting from a derivative of L-tartaric acid, Taber et. al,[65] obtained an optically active cyclopentene derivative (**177**) *via* an alkylidine carbene species. The cyclopentene derivative (**177**) was ozonolyzed, then subjected to aldol condensation and dehydration to give the enantiomerically pure cyclohexenone (**178**) (**Scheme 29**).

Scheme 29

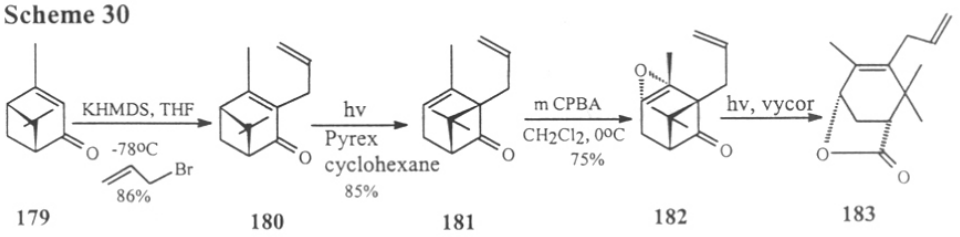


Winkler's Approach:

The cheap commercially available starting material (+)-α-pinene was converted into (+)-verbenone (**179**) which was alkylated (**180**) and then converted into chrysanthenone

derivative (**181**) by Whitham's photochemical process[66] The latter was subjected to epoxidation to obtain the β,γ-ketoepoxide (**182**) which was then transformed into the A-ring synthon (**183**) by Murray's photoprocess (**Scheme 30**).[67]

Scheme 30



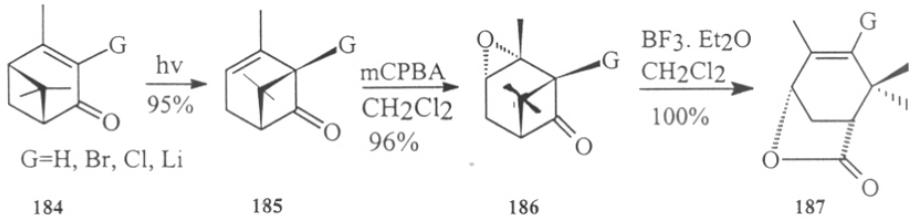
179 180 181 182 183

Thus, (+)-α-pinene was converted into an optically active A-ring system by Winkler's group.[68]

Wender's Approach:

Winkler's approach[68] and Wender's approach[69] are quite similar; both of them utilized photochemical process for the β,γ-ketoepoxide rearrangement to γ-lactone. Winkler made use of the photochemical process in two of the steps, including the γ-lactone formation whereas, Wender applied Lewis acid for the second transformation. The main disadvantage of both the strategies is the utilisation of photochemically induced transformations. (**Scheme 31**)

Scheme 31



184 185 186 187

In summary, all the reported asymmetric synthesis for A-ring systems of taxol involve numerous steps for the assembly of cyclohexane system; such strategies often require the use of expensive reagents, starting materials etc. In the present work, chiral A-ring system namely (S)-(-)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde was prepared in just three steps from easily available α-pinene.

Objective:

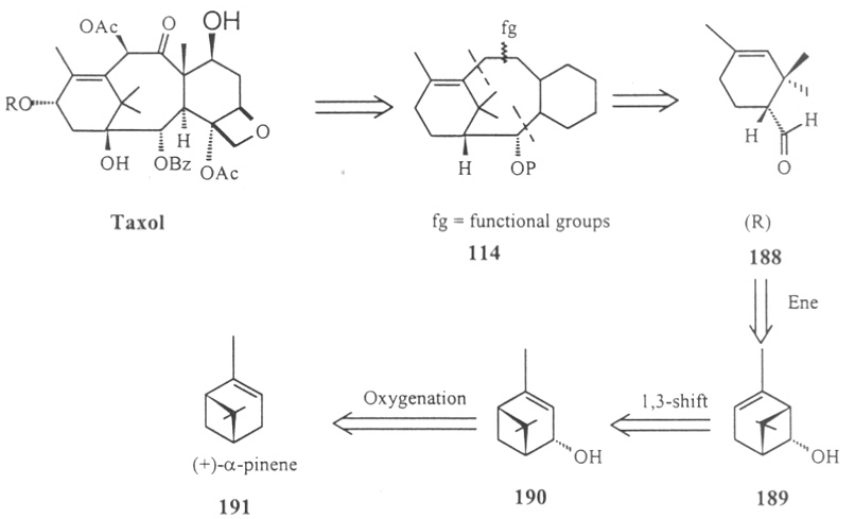
In order to synthesize advanced taxoids and protaxoids, the 2,2,4-triemthylcyclohex-3-ene-1-carbaldehyde system was chosen as the building unit, and it was first prepared in racemic form, which is described in Section 1. For the stereoselective synthesis of taxoids the, same unit was planned to be prepared in a chiral form. Utilisation of cheaply available

α-pinene in both the racemic forms was invoked. This objective and the methods employed to achieve this objective are described in this section.

Present work

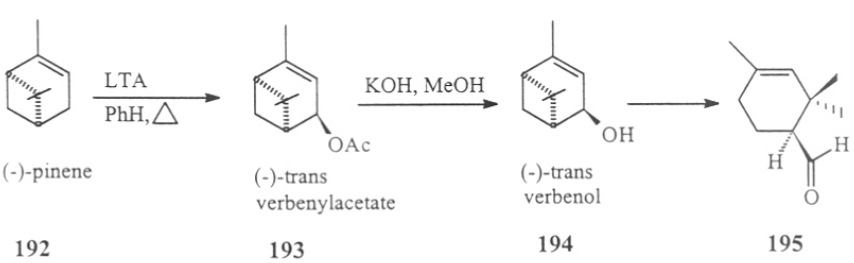
For the synthesis of chiral A-ring unit, a readily available inexpensive source of α-pinene attracted our attention as an ideal starting material, which offers ten carbon basic A-ring unit of taxol with chirality. The scheme given below represents the relationship between taxol and that of α-pinene. (**Scheme 32**)

Scheme 32



As presented in the above scheme, the (+) form of α-pinene is essential to get the absolute stereochemistry of taxol core. The desired (+)-α-pinene was however not readily accessible when the present work was initiated, therefore, (-)-α-pinene with 80% optical purity {$[\alpha]^{25}_{D}$ = -42° (neat, l=1 dm)] was used. (-)-α-Pinene is a major component of Indian terpentine oil.

Scheme 33



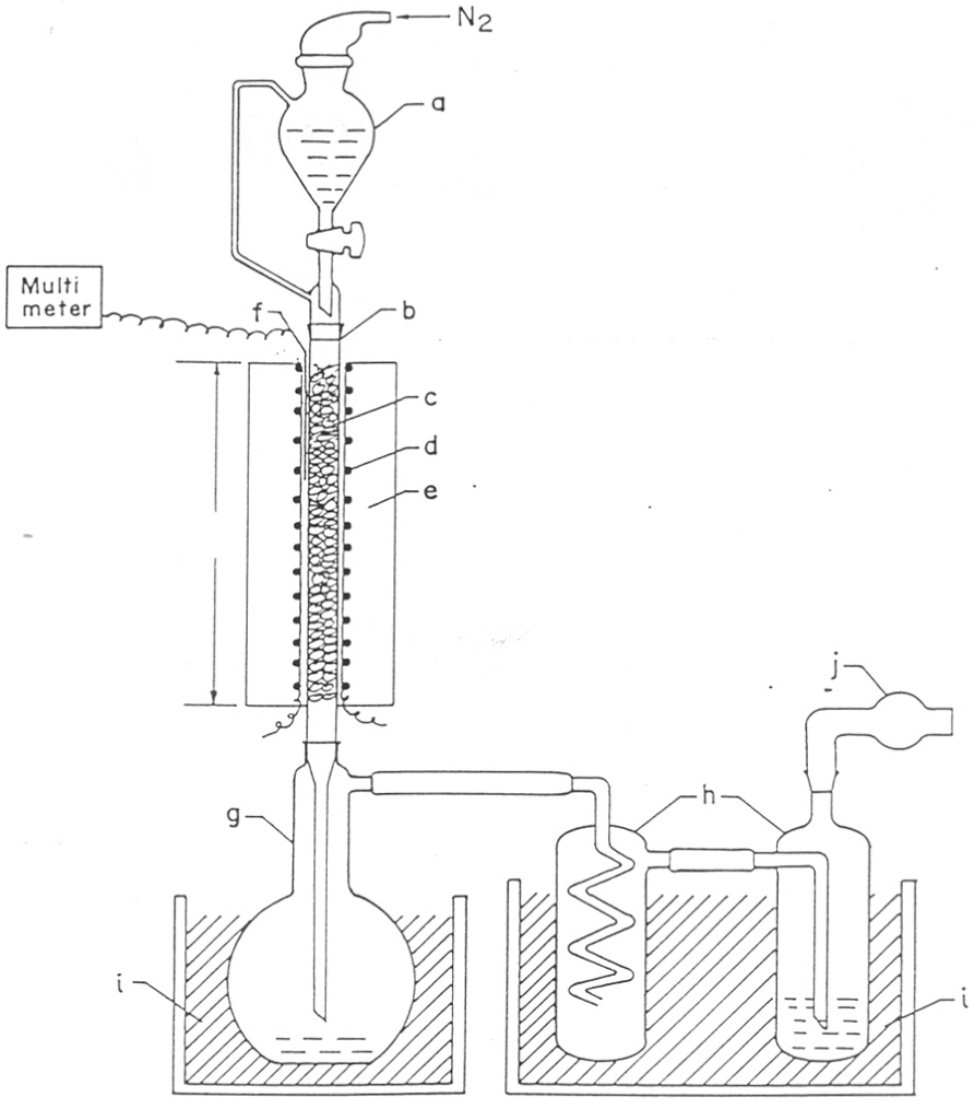
Accordingly, (-)-α-pinene (**192**) was converted into (-)-*trans*-verbenyl acetate (**193**) *via* LTA oxidation.[70] The infrared and ^{1}H NMR spectra confirmed the strcutre of (-)-*trans*-verbenylacetate (**193**) with the IR absorption for the carbonyl group at 1730 cm^{-1}, ^{1}H NMR shifts at 0.92, 1.34 δ for two singlets accounts for the geminal dimethyl protons, a singlet at 1.72 δ refers to the vinyl methyl protons, the fourth singlet at 1.93 δ indicated the presence of acetoxy methyl protons ($\underline{CH_3}$ -COO-) and a broad singlet at 5.26 δ corresponds to carbinol and vinylic protons. The compound obtained had the optical rotation $[\alpha]^{25}D$ = -123° (neat, l=1 dm).

(-)-*trans*-Verbenyl acetate (**193**) was solvolyzed in the presence of methanolic potassium hydroxide. Usual workup followed by purification furnished (-)-*trans*-verbenol (**194**) and it was fully chracterized. Its IR spectrum showed the presence of -OH group at 3400-3300 cm^{-1}, the ^{1}H NMR spectrum revealed the presence of two singlets at 0.9, 1.3 δ indicating the geminal dimethyl protons, another singlet at 1.8 δ for vinyl methyl protons and a multiplet integrating for four protons at 1.92-2.41 δ thereby confirming the structure of (-)-*trans*-verbenol (**194**). It had an optical rotation $[\alpha]^{25}_D$ = -108° (neat, l = 1 dm).

(-)-*trans*-Verbenol thus obtained was pyrolyzed in the pyrolysis unit which was designed for the present work (diagram 1).

Initially, when (-)-*trans*-verbenol (**194**) was pyrolyzed[71] (neat, according to Ohloff's procedure), the glc analysis of the pyrolyzed material revealed that the required compound (S)-2,2,4-trimethyl cyclohex-3-ene-1-carbaldehyde (**195**) was found to be present only in 24% yield along with other byproducts. The required product was characterized by peak accentuation technique in glc with that of racemic 2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde (**9**) obtained via Diels-Alder reaction (see Section I). Since, the yield of the required chiral aldehyde was only 24% it was felt necessary to improve upon the yield by carrying out some improvements in the experimental conditions.

A careful and rapid scan of the literature on α-pinene readily revealed that it was employed as a chiral synthon by two different groups to realize the intermediates (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde and its alcohol. It is noteworthy that both the groups reported their respective work much before the discovery of taxol itself. It was therefore deemed fit at this stage to offer some details of these reported transformations of α-pinene to the intermediates (-)-(S)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde and its alcohol.



a : ADDITION FUNNEL WITH SIDEARM
b : QUARTZ TUBE
c : QUARTZ RINGS
d : NICHROME WINDING
e : ASBESTOS INSULATION
f : Cr-Al THERMOCOUPLE
g : RECEIVER
h : TRAPS
i : COOLING BATH, DRY ICE-ACETONE
j : $CaCl_2$ GUARD TUBE

In the year 1981, Ohloff et. al.,[71] prepared (-)-(S)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde from (-)-*trans*-verbenol which was then converted into 2-acetoxy-β-ionone. The latter was utilized to confirm the absolute configuration of β,β-Carotene-2-ol .

Nussbaumer et al.[72], utilized its alcohol for the stereoselective synthesis of *cis*-α-Irone.

Mori[73] converted α-pinene to *trans*-verbenol; various isomers of the latter exhibit aggregating pheromone activity. The reaction involved conversion of α-pinene to *trans*-verbenylacetate *via* LTA oxidation and subsequent hydrolysis to *trans*-verbenol.

Thus, in our present work, the reported procedure of Mori[73] and G. Ohloff[71] et al. was put to use to furnish (**194**) and (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde respectively. The thermolysis of (-)*trans*-Verbenol proceeded albeit in poor yields. Several modifications in pyrolysis were carried out to realize better yields, like dilution, flow of (-)-*trans*-verbenol, varying the temperature condition etc. from these optimum conditions were set and an increase in yield from the reported 21% to 38% were achieved.

(-)-*trans*-Verbenol was subjected to pyrolysis using a 1% solution of (-)-*trans*-verbenol in hexane at various (ranging from 300°C to 370°C) temperatures in a current of N_2 at a rate of 12 ml/min. By these series of studies, it was found that the optimum temperature for pyrolysis using a 1% solution of (-)-*trans*-verbenol was 350°C, based on the maximum formation of the desired aldehyde (38%) as indicated by glc analysis of the crude pyrolyzed materials.

The glc results obtained were given in the table as below:

Table 1: Pyrolysis of 1% solution of (-)-*trans*-verbenol in hexane at various temperatures

Expt No.	Temp. in °C	% of products obtained at various retention times (min)								
		A-ring aldehyde 6.4	6.9	8.1-8.3	8.8-9.0	9.5-9.6	10.2-10.3	Beyond 10.3		
1	300	-	72.0	4.4	2.0	3.6	3.8	-	-	-
2	320	5.5	67.9	3.2	2.9	3.5	2.6	-	-	-
3	330	28.0	22.5	11.8	2.6	9.0	-	8.5	-	-
4	350	**38.0**	3.5	14.4	11.1	3.5	-	9.5	3.4	-
5	370	**37.2**	3.8	15.0	8.6	5	-	4.4	2.0	9.0

There was a decrease in the percentage conversion of the desired product at 370°C. The optimum temperature was found to be 350° for maximum conversion. Further, it has been reported by Coxon et al.,[74] that pyrolysis of *trans*-verbenol at 420°C gave isomeric aldehydes namely, 2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde and 2,2,4-trimethyl-cyclohex-4-ene-1-carbaldehyde which were difficult to separate. The other products obtained were already characterized by Coxon et. al., they were low boiling liquids, consisting of verbenol, required aldehyde and its isomer, dimethyl-3,6-octadienol, neral and limonen-5-ol. Hence the other products formed in the present pyrolysis reaction were not isolated and characterized.

The required chiral aldehyde (**195**) was isolated by column chromatography over silica gel from the pyrolyzed material and was fully characterized. Its IR spectrum showed the presence of carbonyl group (1720 cm^{-1}) , olefinic moiety (1670 cm^{-1}) while the characteristic band due to H-C=O stretching was observed at 2710 cm^{-1}. The ^{1}H-NMR spectrum exhibited three singlets at δ 0.97, 1.13 and 1.68 each integrating for three methyl protons; these are two geminal dimethyl and one vinyl methyl protons. A singlet due to the olefinic proton was observed at δ 5.08 and a doublet for aldehydic proton appeared at δ 9.80 with J value approximately 2 Hz. Thus, the chemical shift values were very well in agreement with those reported in the literature. Further confirmation was also obtained from its mass spectrum (M^+, 152). An optical rotation value of -57° (neat, l = 1 dm) was recorded for the purified product. Thus, the desired chiral C_{10}-synthon was obtained by the pyrolysis of (-)-*trans*-verbenol. Modification in the mode of pyrolysis and isolation of the desired aldehyde by column chromatography rather than isolating as bisulphite adduct helped to make improvement over the reported yield of 21% to 38%.

Results and Discussion

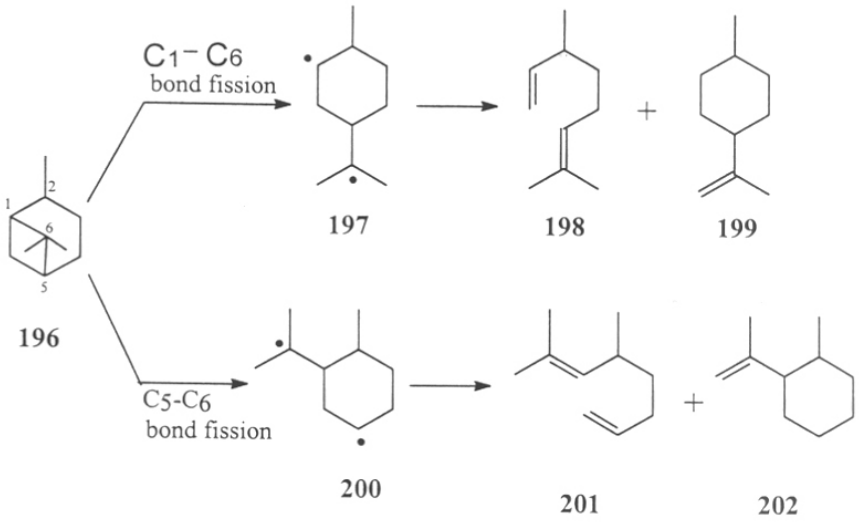
In the synthesis of (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1carbaldehyde, (-)-α-pinene was utilized as the chiral building block which offers ten of the basic A-ring unit of taxol. The unique feature of this strategy is that it offers C_{10}-aldehyde with suitably functionalised superior A-ring building unit. This strategy gives the chiral A-ring unit in just three synthetic steps.

In the present work, pyrolysis of a 1% hexane solution of (-)-*trans*-verbenol afforded the chiral A-ring unit in an improved yield of 38%. The mechanism of this transformation, i.e. conversion of (-)-*trans* verbenol to (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde is discussed below in detail.

Mechanism of the product formation

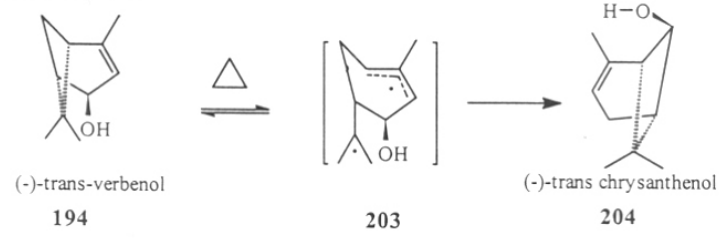
Thermolysis of cyclobutane derivatives is generally regarded as involving the intermediacy of 1,4-biradicals[75], which in turn give rise to acyclic dienes (**198, 201**) by C1-C6 or C5-C6 bond rupture as depicted below:

Scheme 34



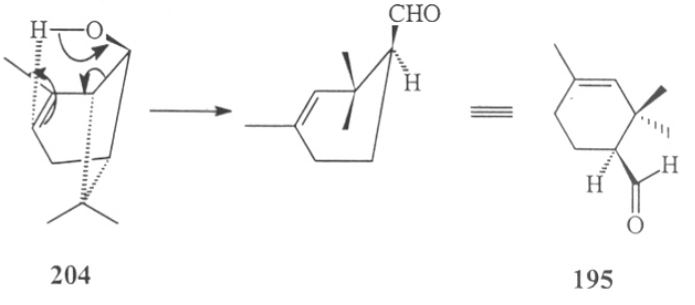
In the formation of (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde from (-)-*trans*-verbenol (**194**) C1-C6 bond fission occurs to give biradicals (**203**) allyl migration of the radical formed followed by bond formation results in a 1,3-sigmatropic shift to yield (-)-*trans*-chrysanthenol (**204**).

Scheme 34



Subsequently, (-)-*trans*-chrysanthenol undergoes the symmetry permitted process of 1,5-H sigmatropic shift.[76]

Scheme 35



Thus, mechanistically, this transformation appears to proceed *via* the formation of (-)-*trans*-chrysanthenol (**202**) involving 1,3-sigmatropic shift followed by 1,5-H shift. This rearrangement was a crucial factor in affording the desired aldehyde.

Reasons for improved yield of the chiral aldehyde from (-)-*trans*-verbenol

The comparatively high yield of the desired chiral A-ring unit could be due to the pyrolysis being conducted under high dilution. In the neat pyrolysis of *trans*-verbenol at 450°C reported by Coxon et al, 18% of the *trans*-verbenol remained unreacted. Hence, dilution ensures that almost all the *trans*-verbenol undergoes thermal process completely resulting in an increased yield. Furthermore, hexane was selected as the solvent for dilution because it does not contain any polarizable functional groups sensitive towards pyrolysis.

Ohloff et al, isolated the aldehyde as bisulphite adduct whereas in the present work the required aldehyde was chromatographed which minimizes the losses during the isolation process.

In short, modifications in the mode of pyrolysis, separation and purification using column chromatography over silica gel resulted in improved yield of chiral A-ring unit from 21% the reported 38%.

CONCLUSION

The salient features that this synthesis offers are:

1. A short synthesis of chiral A-ring of taxol has been achieved.
2. Use of readily available α-pinene to effect this synthesis in three steps resulting in the construction of ten out of the twenty carbons of taxol. This methodology offers ten of the twenty carbons of taxol core just in three steps from the cheaper and commercially available α-pinene.
3. The key step of conversion of *trans*-verbenol to A ring synthon was achieved *via* a modified pyrolysis technique.
4. This method is suitable for large-scale preparation and overcomes the disadvantages arising out of photochemical approaches reported by Winkler and Wender.
5. Improvement over the reported yield was also achieved.

EXPERIMENTAL

Preparation of Lead tetracetate:

A mixture of 550.0 g of glacial acetic acid and 185.0 g of acetic anhydride were placed in a 3-necked, round-bottomed flask provided with a thermo-well containing a thermometer and mercury-sealed overhead stirrer. The liquid was stirred and heated to 55-60°C and 300.0 g of dry red lead powder was added in portions of 15-20 g. A fresh addition was made only after the red coloration due to the preceding portion had largely disappeared. The temperature was maintained below 65°C till all the addition of red lead was over. After the addition of all the 300.0g of red lead, the flask was warmed to 80°C in order to complete the reaction.

The thick and somewhat dark solution obtained was cooled and the precipitated lead tetraacetate was filtered off and washed with glacial acetic acid. The filtered crude product was dissolved in hot glacial acetic acid containing a little acetic anhydride. The resultant solution was treated with a little decolourizing carbon and then filtered through a hot water funnel and cooled. The colourless crystalline product was filtered off and dried in a vacuum dessicator over potassium hydroxide pellets.

Yield of lead tetraacetate was 158.0 g.

A further 100.0 g of lead tetraacetate was obtained from the mother liquor by returning the mother liquor to the original flask. The contents were heated to 75°C, stirred and a stream of chloride gas was passed to it. Completion of the reaction was ensured by excess chlorine gas in the outlet. A few grams of decolourizing carbon was added and the mixture was heated at 75°C during 15 minutes. The lead tetraacetate was filtered, washed with glacial acetic acid.

A total of 250.0g of lead tetracetate obtained was stirred in a vacuum dessicator. To obtain more quantities of lead tetracetate the reaction in the same scale was repeated.

LTA oxidation of (-)-α-pinene to (-)-*trans*-verbenylacetate :(193)

Lead tetraacetate (468.0 g, 1.05 mmol) was added to a stirred solution containg (-)-α-pinene (162.0 g, 189 ml, 1.18 mmol) in anhydrous benzene at 60-70°C over a period of 15 minutes. After all the addition was over, the mixture was stirred and heated to 60-70°C for 40 minutes. The precipitate lead diacetate was filtered and washed thoroughly with benzene. Then the combined filtrate was treated with 30 ml of water to destroy the excess lead

tetraacetate present if any. The benzene layer was separated and dried over anhydrous sodium sulphate. The filtrate obtained was concentrated in vacuo to get a crude residue of *cis*-2-acetoxypin-3-ene.

The oily *cis*-2-acetoxypin-3-ene was dissolved in 600 ml of acetic acid and the solution was stirred at room temperature fo 30 minutes. The mixture was diluted with water and extracted with diethylether (3 x 150 ml). The combined ethereal extract was washed with saturated sodium carbonate till the ethereal layer became neutral, washed with water (3 x 2 ml), brine (3 x 2 ml) and dried over anhydrous sodium sulphate. Ether was distilled off and the resultant oily residue was distilled in vacuo to get *trans*-verbenylacetate.

Yield : 140.0 g (61%)

B.P. : 94-97°C at 10 mm Hg (110°C bath temperature) (Lit.[73] 88-92°C at 7 mm Hg)

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 2960, 1730, 1430, 1380, 1230, 1010, 950.

^{1}H-NMR (200 MHz) : δ 0.92, 1.34 (2 s, 6H, C-($C\underline{H}_3$)$_2$), 1.72 (s, 3H, C=C-$C\underline{H}_3$), 1.93 (s, 3H, COO-$C\underline{H}_3$), 1.95-2.35 (m, 4H, 1 x $C\underline{H}_2$, 2 x $C\underline{H}$), 5.26 (br.s, 2H, carbinol and vinylic proton).

Optical rotation : $[\alpha]^{25}_D$ = -123°C (neat, l=1 dm).

Saponification of (-)-*trans*-verbenylacetate to (-)-*trans*-verbenol: (194)

Aqueous potassium hydroxide (66.0 g in 300 ml of water) was added to solution of *trans*-verbenyl acetate (**193**) (140.0 g, 0.72 mmol) in methanol (300 ml) and the mixture was left to stand for two days in a refrigerator. Progress of the reaction was monitored by IR analysis (disappearance of the carbonyl frequency). After the complete saponification, the reaction mixture was concentrated in vacuo to remove methanol. The residual material obtained was diluted with water and extracted with diethylether (3 x 150 ml). The combined ether extract was washed with water (3 x 5 ml), brine (3 x 5 ml) and dried over anhydrous sodium sulphate. Distillation of the solvent followed by vacuum distillation of the residue furnished (-)-*trans*-verbenol (**194**) as a colourless pleasant smelling liquid.

Yield : 102.1 g, (93%)

B.P. : 92-95°C (100°C bath temperature) at 10 mm Hg (Lit.[73] 85-88°C at 8 mm Hg)

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 3400-3300 (b), 2930, 1500 (w), 1380 (w), 1040, 1020.

^{1}H-NMR (200 MHz) : δ 0.9, 1.3 (2s, 6H, C-(C$\underline{H}_3$)$_2$), 1.8 (s, 3H, C=C-C$\underline{H}_3$), 1.92-2.41 (m, 4H, 1 x C$\underline{H}_2$, 2 x C$\underline{H}$)

Optical rotation : $[\alpha]^{25}_D$ = -108°C (neat, l = 1dm)

Synthesis of (-)-(S)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde:(195)

A 1% solution of (-)-*trans*-verbenol (102.0 g, 671.1 mmol) in hexane was pyrolyzed by downward passage through a quartz tube (100 cm x 1.3 cm) at 350°C in a current of N_2 at a rate of 12 ml. per minute. The pyrolyzed material was concentrated in vacuo. The residue was chromatographed over silica gel to obtain (-)-(S)-2,2,4-trimethyl cyclohex-3-ene-1-carbaldehyde (**195**) as a light yellow pleasant smelling liquid. The chromatographed material was further purified by vacuum distillation.

Yield : 37.0 g, (36%)

B.P. : 78-82°C at 18 mm Hg (lit.[71] 80°C at 18 mm Hg)

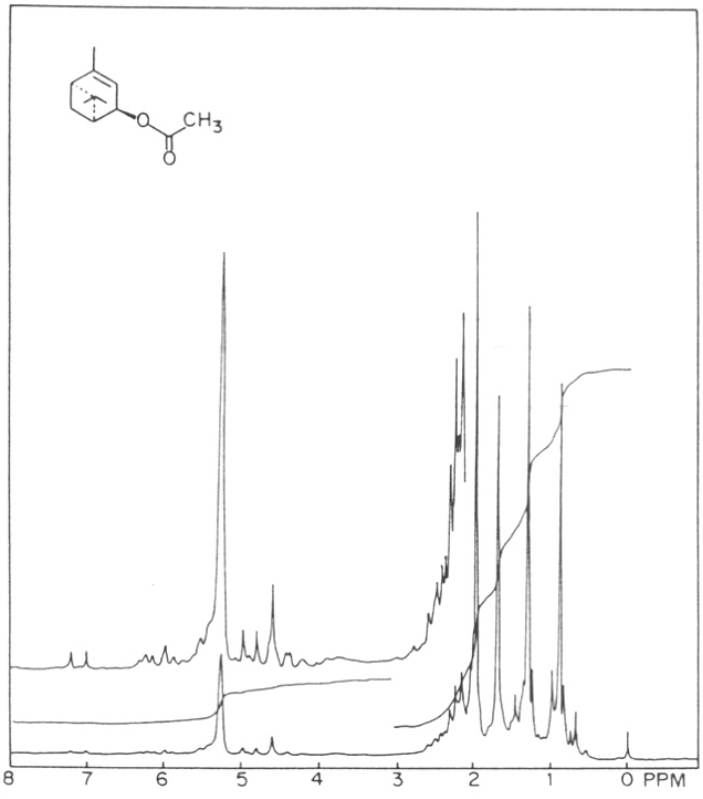
IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 2950, 2710 (due to fermi resonance), 1720, 1450, 1360, 1100, 1000.

^{1}H-NMR (200 MHz) : δ 0.96, 1.2 (2s, 6H, C(-C-C$\underline{H}_3$)$_2$), 1.62 (br.s, 3H, C=C-C$\underline{H}_3$), 1.9-2.51 (m, 5H, 2 x C$\underline{H}_2$, 1 x C$\underline{H}$), 5.05 (s, 1H, C=C$\underline{H}$), 9.85 (d, 1H, J = 2 Hz, C$\underline{H}$O).

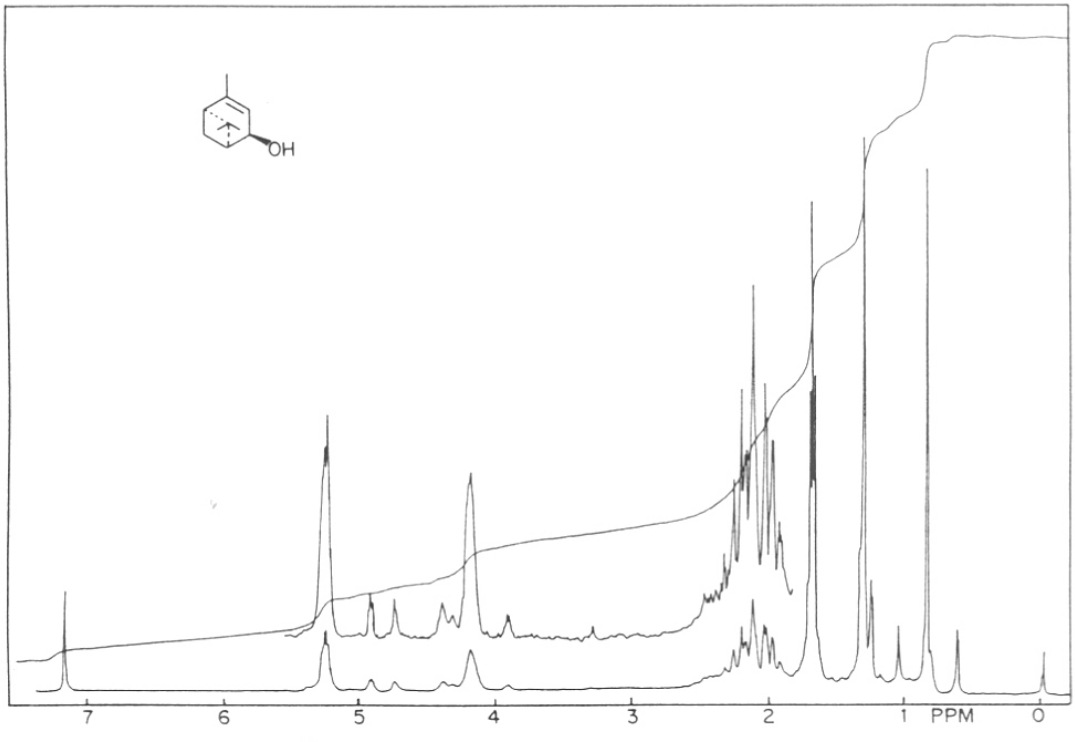
^{13}C NMR (50 MHz) : δ 19.96, 22.57, 23.48, 28.89, 29.40, 34.19, 56.33, 131.75, 132.16, 205.76.

Mass (m/z) : 152 (41, M^+), 137(28), 121(55), 109(69), 107 (56), 96(35), 81(100), 69(34), 67(45), 55(27), 43(30), 41(47).

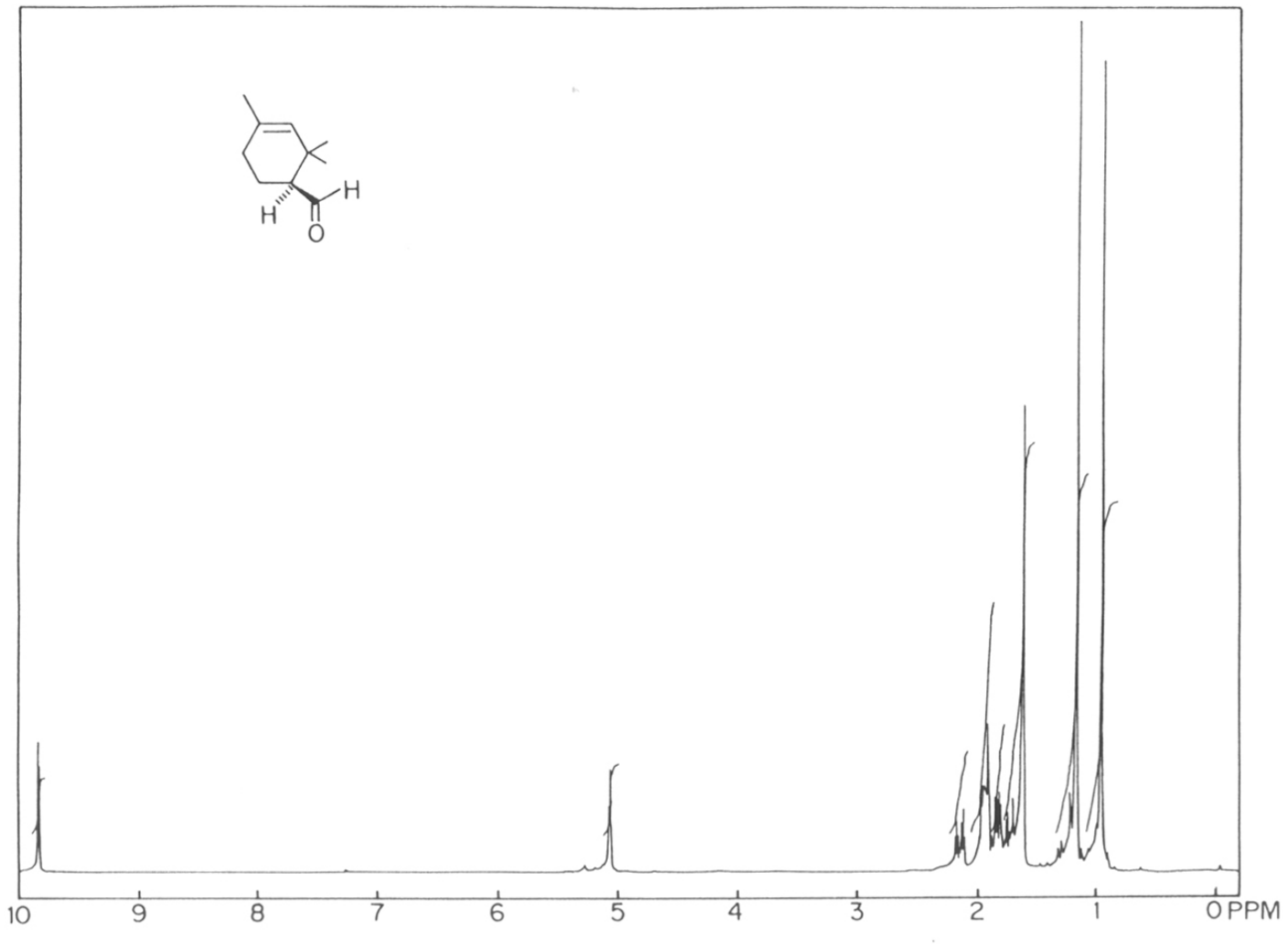
Optical rotation : $[\alpha]^{25}_D$ = -57° (neat, l= 1 dm).



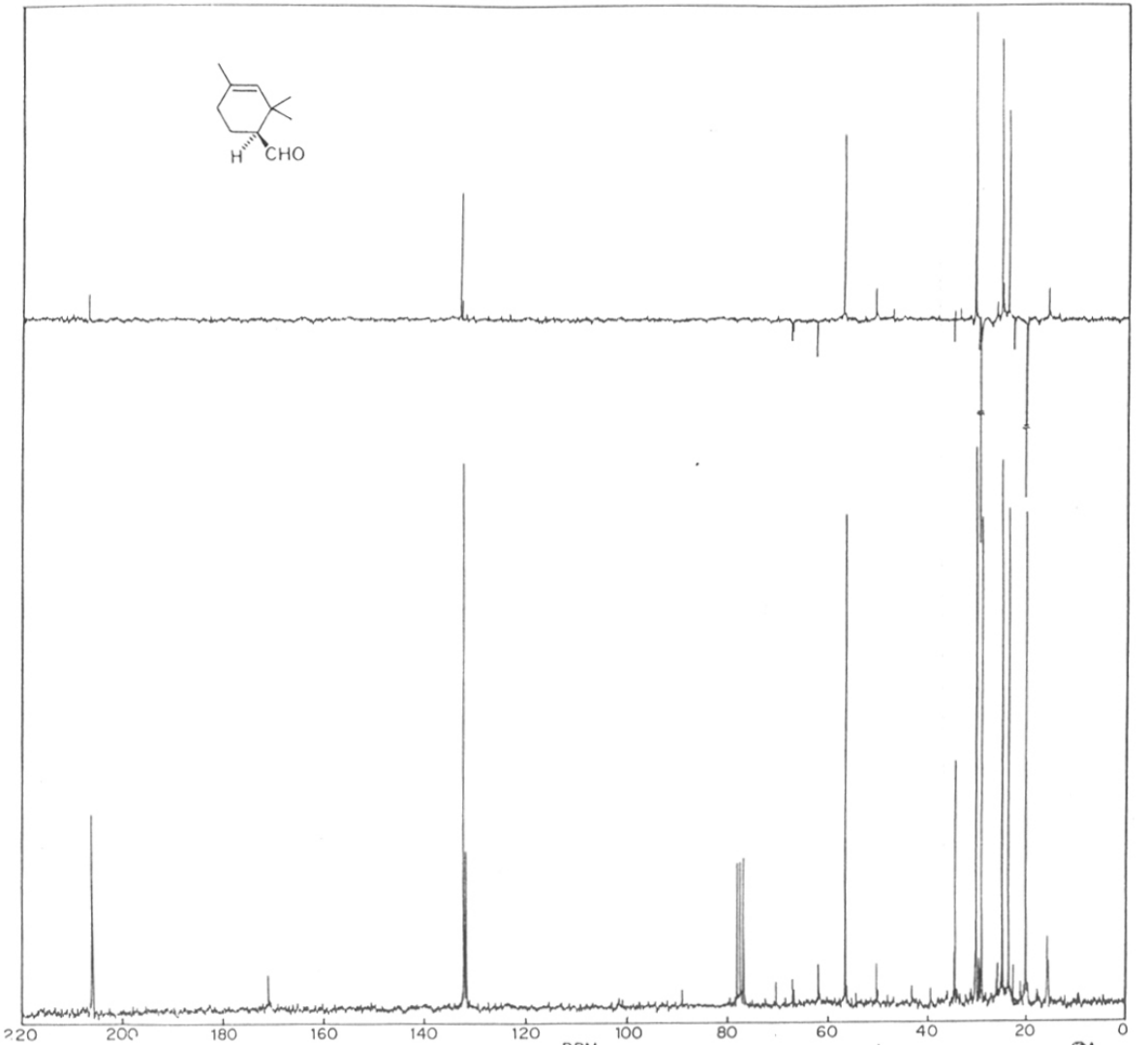
^{1}H-NMR SPECTRUM OF COMPOUND **193**



^{1}H-NMR SPECTRUM OF COMPOUND **194**



^{1}H-NMR SPECTRUM OF COMPOUND **195**



^{13}C-NMR SPECTRUM OF COMPOUND **195**

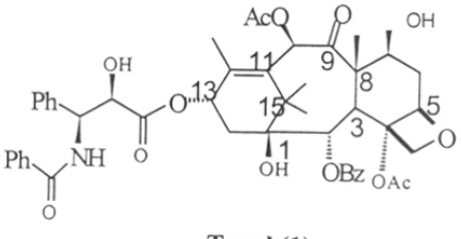
PART II

DIASTEREOSELECTIVE SYNTHESIS OF "B"-*SECO* TAXOIDS, VERSATILE INTERMEDIATES FOR ADVANCED TAXOIDS

Introduction

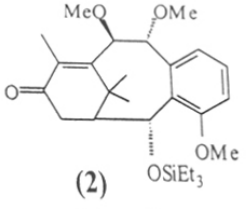
The synthesis of 2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde in racemic as well as in chiral forms was described in the earlier part of this chapter. This part of the thesis presents, the utility of these C_{10} units for the syntheses of "B-*seco* taxoids".

In search of "Second generation taxoids" and also as a new access to different taxoids, C-aromatic taxoids were chosen as the target. For taxoids to exhibit anti-cancer chemotherapeutic activity, the presence of geminal dimethyl groups, vinyl methyl group, 8-membered B-ring, 6-membered A and C rings and the phenylisoserine side chain have been found to be the minimum requirements. Accordingly, several schools all over the world attempted to synthesize simplified taxoid congeners, conforming to the above mentioned requirements. The most important among them are the C-aromatic taxoids, which were found to possess biological activity similar to taxol. Such advanced taxoids possessing C-aromatic rings were synthesized in the laboratories of Kuwajima[77], Nicolaou,[73] Masters,[78] Shea,[79] Swindell[80] and Wender[81].



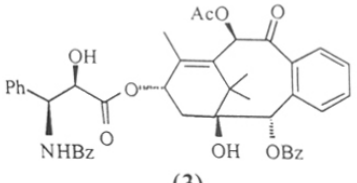
Taxol (1)

Some C- aromatic taxoids



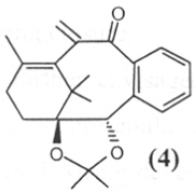
(2)

Kuwajima



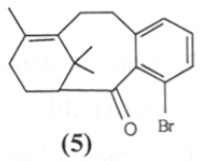
(3)

Nicolaou



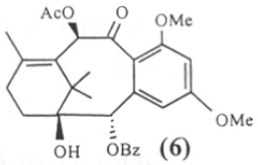
(4)

Masters



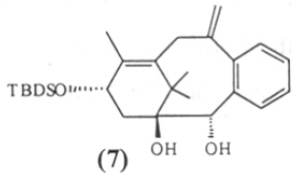
(5)

Shea



(6)

Swindell

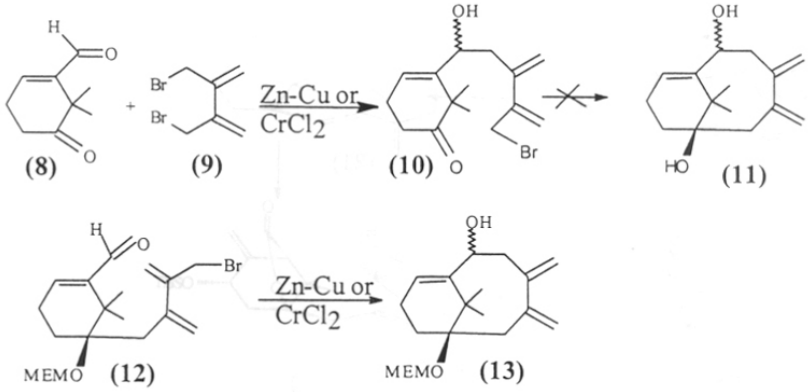


(7)

Wender

Out of these, except that of Shea's and Wender's, all the routes have adopted a convergent strategy for the "B"-ring formation. Such a convergent strategy was aimed at in the present work as well, because comparatively lesser synthetic manipulations are realised to arrive at simplified taxoids. With this view in mind, synthetic studies towards simplified taxoids via "B-*Seco* taxoids" were focused at.

When the present was planned to develop a new access to simplified advanced taxoids, the C2-C3 convergency to study the B-ring closure indicated that due to the presence of too many functional groups, transition state for ring closure may not be very conducive to such a ring closure. As an alternative, construction of "B-*seco* taxoids" by C2-C3 bond formation and subsequent ring closure studies either at C9-C10 are at C10-C11 were preferred. (**Scheme 1**)



(8) (9) (10) (11) (12) (13)

SCHEME 1

This was also evident from the work of Wang et. al.[82], who reported that ring closure at C1-C2 had failed. Subsequently, 8-membered ring formation was achieved via C10-C11 ring closure.

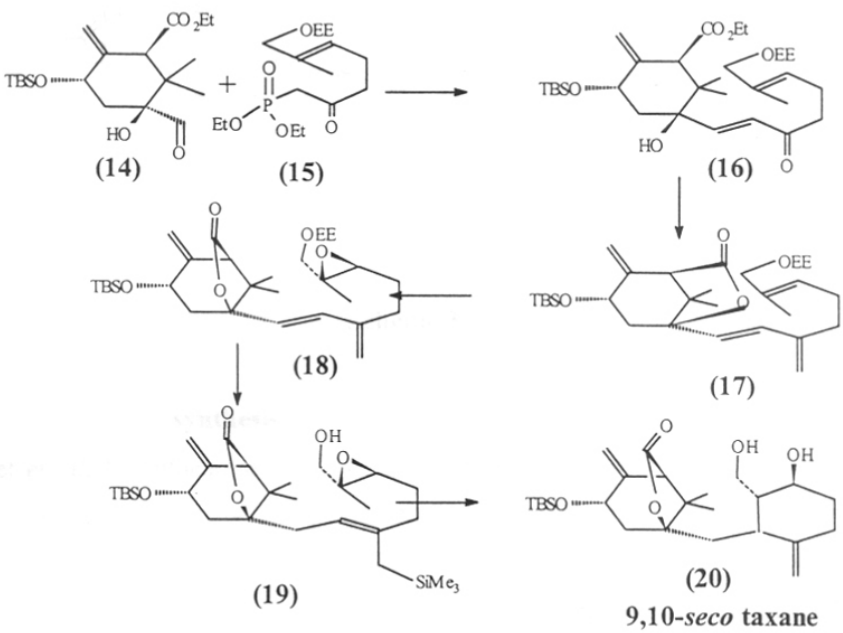
It was further envisaged that introduction of some of the stereogenic centres before the ring closure could lead to a more viable taxane synthesis. In this regard, synthesis of chiral A-ring developed and reported in Part-I of this chapter, fixes one of the stereogenic centres for the stereoselective synthesis. Some of the relevant reports available in the literature on "B-*seco*-taxoids" are worthwhile to discuss at this stage. Notable among them are the works of Queneau's, Frejd's and Genet's.

Syntheis of "B-*seco* taxoids" : Literature reports

Under this subheading, the "B-*seco*-taxoids" obtained via convergent synthesis are discussed. Starting from suitably substituted A-ring units, Queneau and Genet initiated the synthesis of "B-*seco* taxoids" through C9-C10 bond formation whereas Frejd *et. al.*, synthesized via C2-C3 bond formation.

Frejd route to "B-*seco*-taxoid"

Frejd *et. al.*,[48] synthesized a 9,10-*seco* taxane *via* an electrophilic ring closure of C-ring using an epoxy-silane moiety; this is an enantioselective synthesis of B-*seco*-taxane .

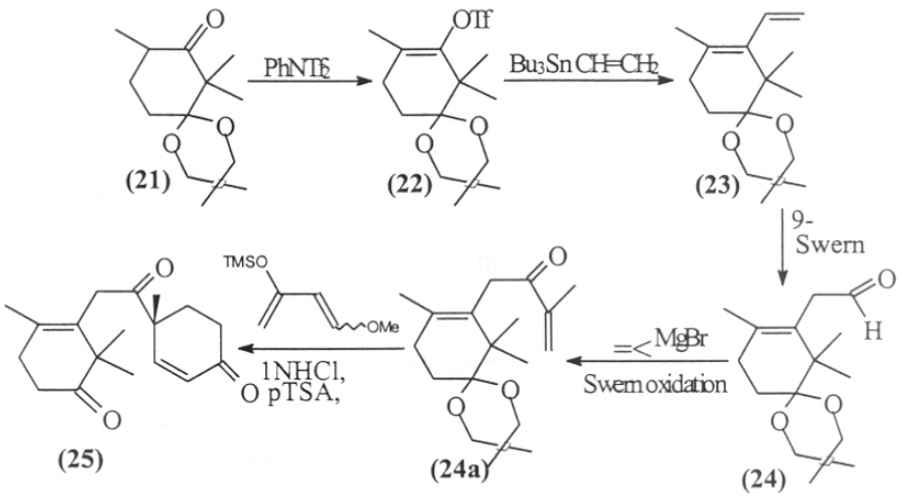


Scheme 2

The fully functionalised A-ring (already discussed in the earlier part, section 2) was directly coupled with the C-ring precursor (**15**), via C2-C3 bond formation using H-W-E reaction[83] to yield the α,β-unsaturated ketone with E-configuration (**16**). Later, by utilizing standard synthetic manipulations, epoxy-allyl silane moiety (**19**) was incorporated to the C-ring precursor, which upon treatment with $BF_3.Et_2O$ underwent C-ring closure to furnish 9,10-*seco* taxane derivative (**20**). (**Scheme 2**).

Queneau's approach to B *seco* taxane

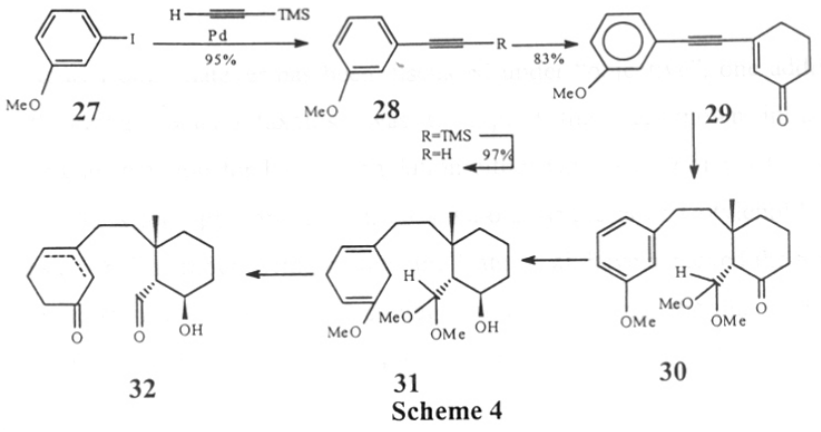
In Queneau's approach[84] A-ring ketoketal (**21**) was converted into β,γ-unsaturated aldehyde (**24**) by Stille coupling[85] and subsequent oxidation with 9-BBN, followed by Swern oxidation. The aldehyde thus obtained was transformed into a dienophile (**25**) which upon thermal Diels-Alder reaction with Danishefsky's diene[86] afforded the "B-*seco* taxoid" (**Scheme 3**).

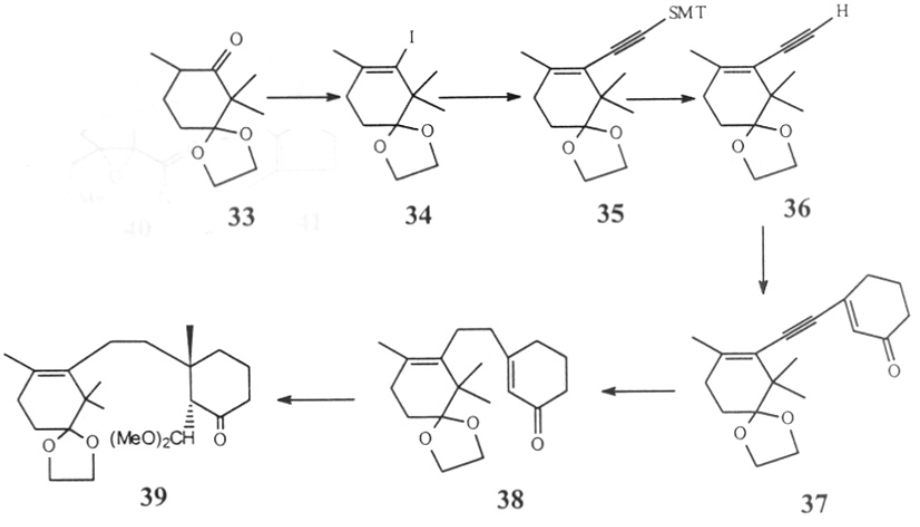


Scheme 3

Genet's B-*seco* taxoid synthesis

Genet *et. al*, [87] synthesized two "B-*seco* taxoids", one starting from m-iodoanisole and the other one from a vinyl iodide derived from keto ketal (**33**). In both the cases, A and C rings are attached to the two carbon acetylenic moiety through Sonogashira reaction. The C-ring utilized in both the cases were β-iodocyclohexanone (**Schemes 4,5**).





Scheme 5

There are no functionalizable groups at C9-C10 positions. Also low yield obtained in the three component coupling are the main drawbacks of this methodology.

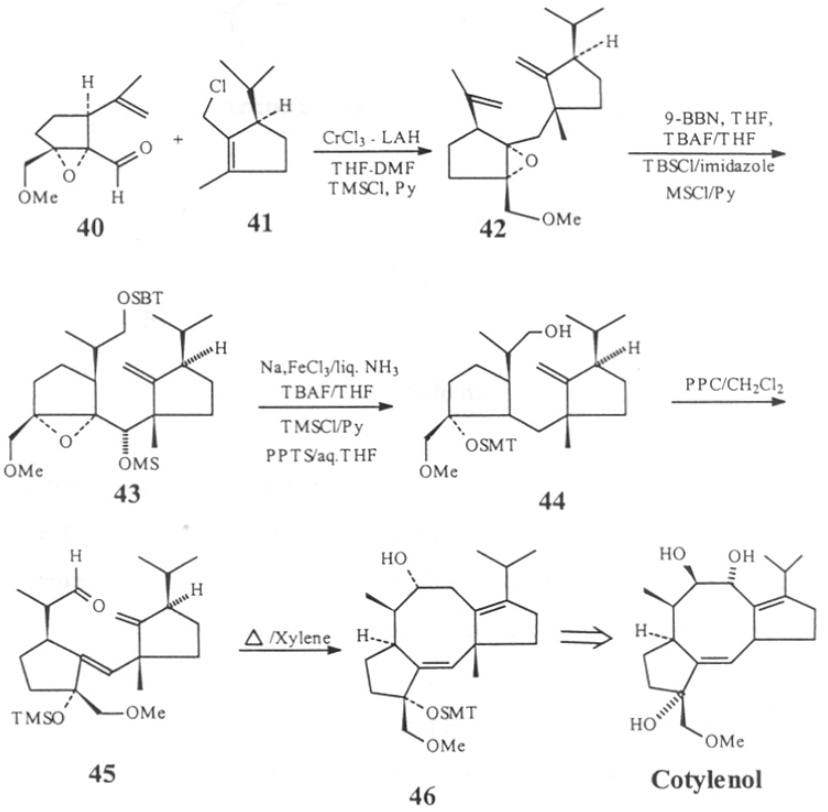
All the three approaches mentioned above for "B-*seco* taxoids" involve many synthetic operations. Except that of Frejd's approach, others are not stereoselective.

Objective

As can be surmised from the three approaches to "B-*seco* taxoids" discussed above, it was felt that there is a need to develop a synthetic route to "B-*seco* taxoids" in a stereoselective manner with comparatively fewer synthetic operations. In the present approach the main emphasis was made towards the syntheses of functionalized or functionalizable "B-*seco* taxoids" in a diastereoselective fashion.

Present work

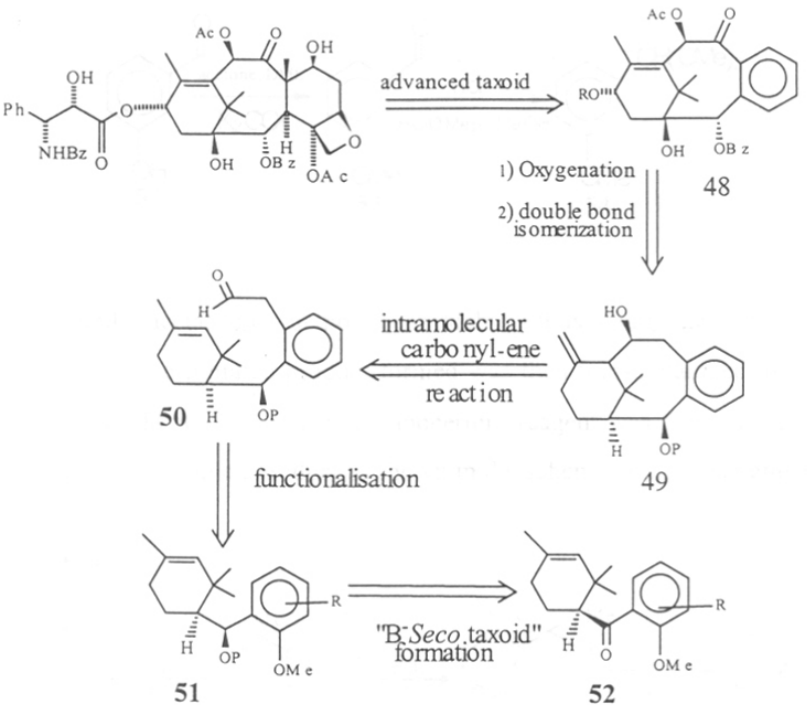
Apart from whatever has been discussed under "objective", one additional aim for synthesizing "B-*seco* taxoids" was to exploit the well-known intra-molecular "carbonyl-ene' reaction for B-ring annulation either *via* C9-C10 or *via* C10-C11 bond formation. It is felt appropriate to discuss Kato's synthesis of Cotylenol.[46] The latter possesses a 5-8-5 membered ring system and Kato et. al, have achieved the 8-membered ring formation *via* a convergent strategy and employing thermal intramolecular "carbonyl-ene" reaction. The key steps in the synthesis are depicted below. (**Scheme 6**)



Scheme 6

Our retro-synthetic analysis (see below) was based on the presumption that intramolecular "carbonyl-ene" reaction can be realised in a meta-mode of cyclization leading to advanced taxoids. The retro-synthetic plan is presented below. (Scheme 7)

Retro Synthetic plan for advanced taxoids

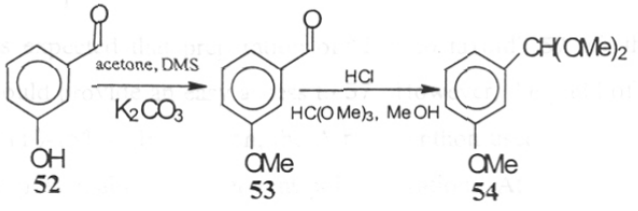


Scheme7

Dimethyl acetal of m-methoxy benzaldehyde was initially chosen as the appropriate C-ring aromatic unit. Its coupling with the A-ring unit was diligently planned keeping in mind the fact that strong basic conditions may lead to enolisation of A-ring aldehyde. It is well known that organocerium reagents are less basic than the conventional Grignard or lithium reagents and that they are strongly oxaphilic during carbonyl addition. This aspect has been amply brought out by Imamato[89] et. al., who have demonstrated that organocerium reagents do not enolise the enolizable carbonyl compounds. Thus, the organocerium reagent of dimethylacetal of m-methoxy benzaldehyde **54** was the reagent of choice for coupling with A-ring unit.

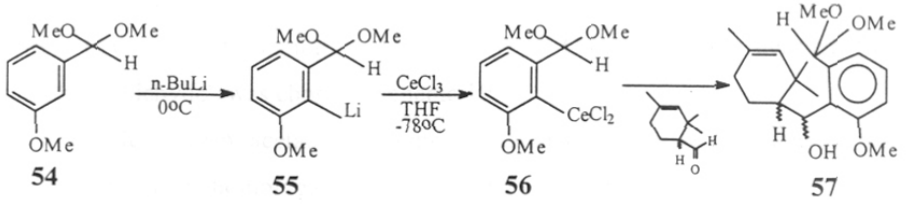
Thus, m-methoxybenzaldehyde, prepared from m-hydroxybenzaldehyde **52** by conventional methods, was reacted with trimethylorthoformate in the presence of catalytic amount of conc. HCl to furnish the desired product **54** in 85% yield. It was fully characterized by spectroscopic data (vide experimental). (**Scheme 8**)

SCHEME 8



Dimethylacetal of m-methoxybenzaldehyde thus obtained was first lithiated with n-BuLi at 0°C; the lithiated product formed was then transmetallated using anhydrous cerium trichloride at -78°C. This organocerium reagent was then added to (±)-A-ring unit to realize the coupled product as shown in the scheme below: (**Scheme 9**)

SCHEME 9



The "B-*seco* taxoid" thus obtained was purified by column chromatography and by distillation and was fully characterised by IR, NMR, Mass and elemental analysis. IR spectrum revealed the presence of -OH group at 3950 cm^{-1}. ^{1}H-NMR confirmed the presence of gem-dimethyl proton at 1.25 δ and vinyl methyl protons at 1.65δ. A multiplet centred at 1.9-2.3δ accounting for five protons corresponded to four methylene protons and one methine proton. Signal at 3.23δ and 3.38δ are integrating for six protons represented the presence of dimethylacetal and presence of a methoxy group was confirmed by a singlet at 3.8δ. A doublet (J = 4 Hz) at 4.3δ indicated the presence of carbinol proton (HC-OH) and the vinyl proton appeared at 5.15δ. Aromatic protons appeared at 6.9δ as a doublet of doublet (J = 5.7 Hz, 4.6 Hz), and as a multiplet at 7.27 - 7.31δ. Mass spectrum confirmed the mass (M^{-1} 333).

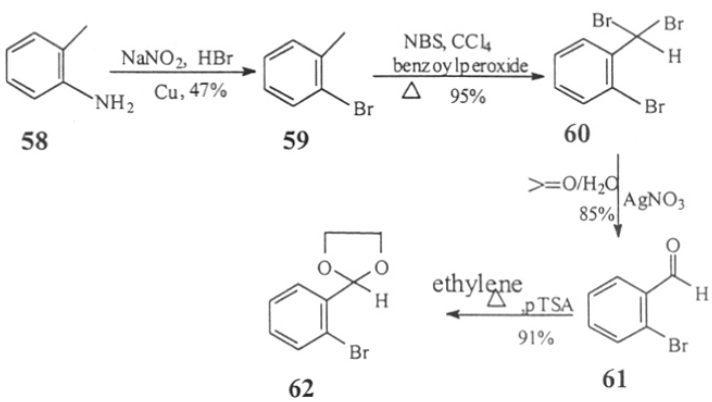
Coupling of ethylene glycol acetal of o-bromobenzaldehyde with A-ring unit via Grignard reaction

It was expected that preparation of "B-*seco* taxoid" **57** *via* the organocerium reagent **56** would provide an easy access to **57**. However, the yield of **57** was found to be very poor (10-15%). In addition, the A-ring synthon used in the reaction could not be recovered, presumably, it underwent polymerization. At the time this work was in progress, a report by Kuwajima's group[62] appeared wherein similar reaction was reported via organocerium reagent. A moderate yield was mentioned. It is assumed that the A-ring synthon used by Kuwajima reacted more efficiently with the organocerium reagent leading to better yields.

In view of the problems faced in terms of poor yields in the reaction between (**57**) and the (±)-A-ring unit; improvements in the methodology was aimed at. A very promising alternative appeared to be C-C bond formation *via* Grignard reagents, as the nucleophilic addition of Grignard reagents are known to give a good access to the desired C-C bond formation. Accordingly, a C-ring synthon derived from o-bromobenzaldehyde[90] was chosen. (Scheme 10)

Ethylene glycol acetal of o-bromobenzaldehyde possesses an aldehydic function at C-9 which can be homologated to the ene-precursor for B-ring closure.

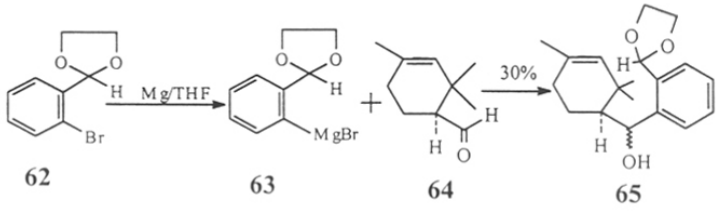
SCHEME 10



Thus o-bromobenzaldehyde (**61**) [prepared from commercially available o-toluidine, over three steps involving diazotisation[91], NBS bromination[92] followed by solvolysis[90] - (vide experimental) was converted into its ethylene glycol acetal using standard procedures (ethylene glycol/benzene/pTSA-reflux)]. Grignard reagent prepared from this protected aldehyde **62** was condensed with chiral A-ring unit **64** employing dry ether as well as dry tetrahydrofuran as the solvent. In both the cases, the product yields

were found to be only 15% and 30% respectively and these yields could not be improved further. (**Scheme 11**)

SCHEME 11

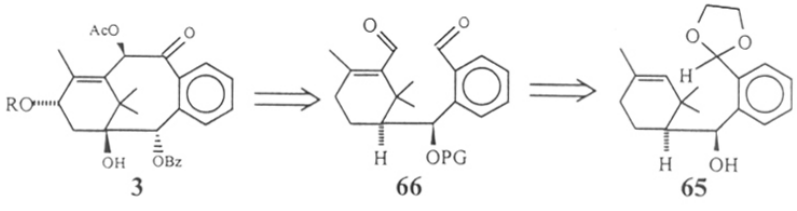


The product **65**, the required "B-*seco* taxoid" obtained as a solid was well characterized by routine analysis. Thus, the ^{1}H-NMR spectrum revealed singlets at 1.06, 1.10 and 1.65δ respectively, accounting for two geminal dimethyl protons and a vinyl methyl protons. A multiplet at 1.8-2.1δ is assigned to the presence of four methylene protons and are methine proton. A broad multiplet centred at 4.12δ confirmed the presence of acetal methylene protons (-O-C$\underline{H}_2$-C$\underline{H}_2$-O-). The carbinol proton appeared at 5.05δ as a doublet (J = 2 Hz), the vinylic proton was seen at 5.50δ as a singlet, the acetal methine proton was found as 6.05δ at a singlet. As usual, the aromatic protons were seen as a multiplet at 7.25-7.71δ accounting for four protons. Additional data from mass spectrum and from elemental analysis, also lent support to the structure.

X-ray analysis obtained from a single crystal of **65** fully confirmed the structure.

Despite unsatisfactory yields, the Grignard product **65** can be viewed as a versatile synthon to achieve a formal synthesis of Nicolaou's advanced taxoid (**3**), as shown in the following scheme. Further, work towards achieving this goal is in progress. (**Scheme 12**)

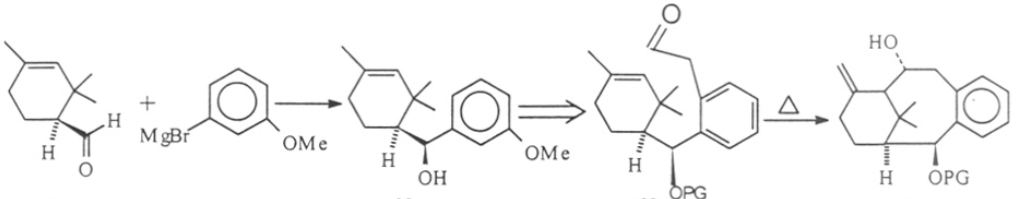
SCHEME 12



Coupling of m-bromoanisole with A-ring via Grignard reaction

Next, it was aimed to obtain "B-*seco*taxoids" by applying some improved strategy with Grignard reaction. One mode of achieving this end was to choose a different aromatic C-ring unit instead of ethylene glycol acetal of o-bromobenzaldehyde. In the case of latter, it was found that the dioxolane moiety got partially cleaved under Grignard conditions leading to moderate yield of the product. An aromatic C-ring unit like m-bromoanisole was expected to fit into our requirements favourably. (**Scheme 13**)

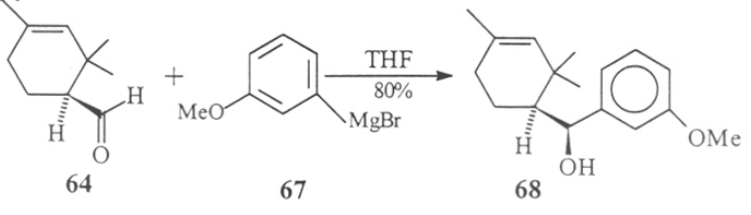
SCHEME 13



64 **67** **68** **69** **70**

Accordingly, nucleophilic addition of Grignard reagent derived from m-bromoanisole, with (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde gave the corresponding "B-*seco* taxoid" **68** in 85% isolated yield. The same sequence of reactions was repeated with (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde to furnish the optically active "B-*seco* taxoid" in more than 80% yield. (Scheme 14)

SCHEME 14



64 **67** **68**

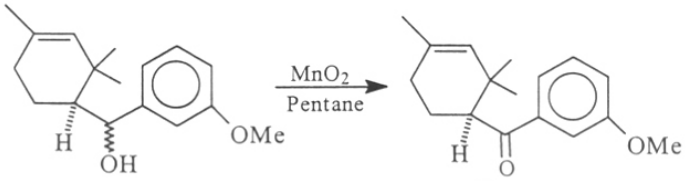
The structure of the "B-seco taxoid" **68** was confirmed by spectral data, *viz*. IR, ^{1}H NMR, ^{13}C-NMR, Mass spectrum as well as by elemental analysis. In the ^{1}H-NMR besides the peaks due to the A-ring unit, there was found a singlet at 3.8δ for -O<u>CH</u>$_3$ protons and a broad singlet at 5.05δ due to carbinol proton. The aromatic protons appeared at 6.8δ (multiplet), 6.95δ (broad singlet) and at 7.31δ (triplet, J = 7.5 Hz) respectively. In the ^{13}C-NMR spectrum, a signal at 72.55 (ppm) was assigned to the

carbon carrying the -OH functionality. For the B-*seco* taxoid **68** obtained from chiral A-ring unit, an optical rotation $[\alpha]^{25}_{D}$ = -26.4° (C=0.66, MeOH) was recorded.

At this juncture, in order to go ahead with the further synthetic operations; it was planned to carry out a sequence of reactions as shown in scheme-13 involving protection of hydroxyl function, functionalisation of C-ring double bond for 8-membered ring formation etc. Several standard methodologies and reagents like NaH-MeI/ether, NaH-MeI/THF, KOH-MeI/DMSO, MeOH-CAN etc. which were tried were unsuccessful in protection of hydroxyl function. A report by Kuwajima[62] et. al., for protection of hydroxyl function *via* silyl ether formation with TES-Cl-imidazole in dichloromethane appeared around the time that this work was in progress. However, this method also failed in the present case.

To overcome this crucial problem of protection, another route that was invoked involved oxidation of the hydroxyl function to ketone, functionalization of α-position via Davis oxaziridine[93] and Rubottom[94] α-hydroxylation of silyl enol ether followed by reduction of the resulting α-hydroxyketone to 1,2-diol. The latter can then be protected as the acetonide.

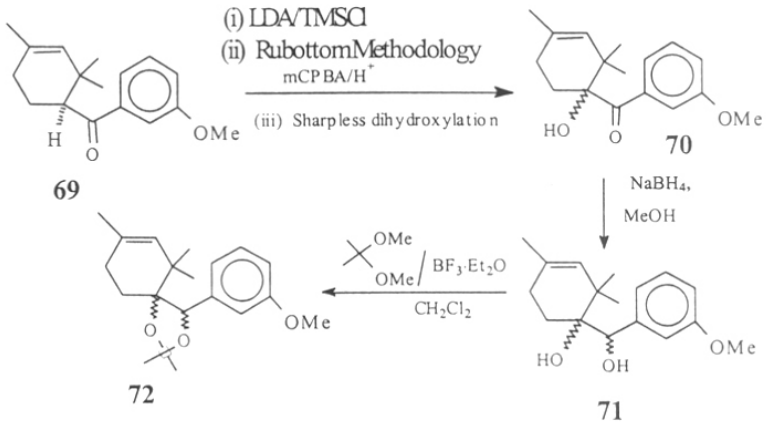
SCHEME 15



68 **69**

All the following are proposed as shown below (**Scheme 16**)

SCHEME 16



69 **70** **71** **72**

Accordingly, the benzylic alcohol **68** was oxidised to the ketone **69** with activated MnO_2 in dry pentane in nearly quantitative yield. This ketone was well characterized by IR ^{1}H-NMR, Mass and elemental analysis. In the ^{1}H-NMR, the carbinol proton which was seen earlier at 5.05δ completely disappeared. The methine proton at C-1 was observed clearly as a double doublet (J = 1.5 Hz, 10 Hz) at 3.45δ. Further support was lent from ^{13}C-NMR which revealed the presence of carbonyl carbon at 160 ppm.

α-Hydoxylation of the ketone **69** *via* Davis oxaziridine Rubottom/Sharpless methodology of the intermediate silylenol ether also met with failure, as only starting material **69** could be recovered. Thereafter, attempts were made to directly to protect the ketone **69** for further synthetic operations, but here again, the efforts were unsuccessful.

As all the possible routes to functionalise either hydroxyl function or keto group did not yield the desired results, the keto compound **69** was subjected to $NaBH_4$ reduction to obtain the alcohol back. Much to our surprise, the product of reduction **74**, was found to be different from the Grignard product in its physical properties. The alcohol obtained *via* Grignard reaction **68** was a liquid whereas $NaBH_4$ reduced product **74** turned out to be a solid. Such an observation led to the recognition that the two alcohols may be isomeric in nature.

The alcohol **74** obtained by the borohydride reduction was fully characterised by IR, ^{1}H-NMR, ^{13}C-NMR, Mass etc. Striking difference was observed in the carbinol proton which appeared as a doublet (J = 8.5 Hz) at 4.55δ. The positions of all other peaks remained more or less the same. In the mass spectrum, the molecular ion was observed at 260. The alcohol also exhibited an optical rotation $[\alpha]^{25}_D$ = -54° (c = 1.5, MeOH).

The structure of the product obtained was also confirmed by single crystal X-ray diffraction technique and the result is presented.

In conclusion, it has been demonstrated that by a convergent synthesis, some "B-*Seco* taxoids" utilising C-arylmetal species could be conveniently prepared. Although, further series of transformations did not yield encouraging results, protection of the hydroxyl group in the Grignard product **68** could be finally achieved *via* its TMS ether and its methyl ether (NaH/MeI-DMF) respectively. The same protection went with equal ease with the borohydride reduced product **74** as well. Further work in this direction is in progress.

Results and Discussion

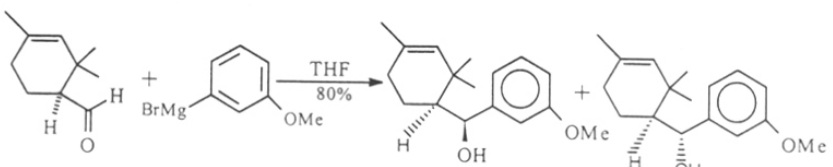
Aromatic C-ring moieties have been appended using aryl-metal species via nucleophilic addition to the C_{10}-A-ring synthon to obtain C-2 oxygenated (taxol numbering is used) "B-*Seco*-taxoids". In the present work, , "B-*seco*-taxoids" of Kuwajima (**2**) and Nicolaou (**3**) have been synthesised with few (6-8 steps) of synthetic operations. Kuwajima obtained B-*seco* taxoid in 11 steps and Nicolaou got it in 15 steps. The "B-*seco* taxoids" thus obtained are having potential utility not only for the synthesis of Kuwajima's and Nicolaou's simplified taxoids, but, perhaps also more importantly for reaching different taxoid analogues.

Of the two reagents (organocerium and organomagnesium) for nucleophilic addition reactions to the A-ring unit, Grignard reagent (organomagnesium) gave the adduct in moderate to preparative yields. Nucleophilic addition of organocerium reagent derived from m-methoxybenzaldehyde had given only poor yields. This is due to the fact that under the influence of organocerium reagent, A-ring aldehyde gets destroyed (dimerisation or polymerisation) and is not available for the adduct formation. It was also observed that there was no recovery of unreacted A-ring aldehyde from the quenched reaction mixture.

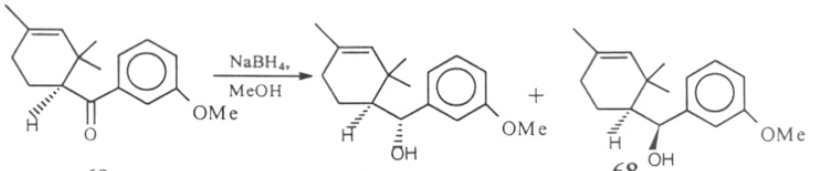
Reaction of the Grignard reagent of both ethylene glycol acetal of o-bromobenzaldehyde and m-bromoanisole when carried out using diethyl ether as solvent with C_{10}-aldehyde gave only poor yields. It was reasoned that the poor yield of product formation is due to the insoluble nature of Grignard complex in ether. However, yields were increased when THF was used as solvent instead of ether.

Even when the reaction was carried out in THF as solvent, the ethylene glycol acetal of o-bromobenzaldehyde gave only moderate yields. This is due to chelation of Mg metal with dioxalone moiety and subsequent deprotection, resulting in decreased yields. However, with m-bromoanisole as the C-ring, such a possibility does not occur; consequently the yield of Grignard product is quite high (>80%).

SCHEME 17



64 67 68 73



69 73 68

The adduct obtained *via* Grignard reaction in 80% yield comprised approximately a 3:1 mixture of diastereomers, the stereochemistry of which could not be assigned initially. On the other hand, $NaBH_4$ reduced product which was obtained in quantitative yield exhibited clearly a 1:3 mixture of the diastereomers. Both these ratios were determined by ^{1}H-NMR and HPLC.

Results from HPLC studies are given below.

The products obtained *via* Grignard reaction and sodium borohydride reduction were dissolved in methanol-water mixture (70:30) and the analysis was carried out using Waters HPLC, column employed was 5NPVPH 4μ with uv detector (232 nm). The methanol:water flow rate was 1ml/min. The Grignard product gave two peaks at a retention time of 4.48 and 4.97 minutes respectively with the area under the peaks as 120195.02 and 354239.02 respectively. The peak ratio corresponds to 25.33% and 74.66% respectively of diastereomers of C-2 hydroxylated "B-*seco* taxoids.

Similarly, sodium borohydride reduction product gave two peaks with retention times at 4.61 and 5 minute respectively with the area under the peaks as 294500.02 and 172525.03 respectively. The peak ratio comprises of 63.26% and 36.9% of diastereomers.

One of the reasons for the failure in realising α-hydroxylation of ketone (**69**), using Rubottom and Sharpless methodologies could be steric, due to the geminal dimethyls as well as the bulkier aromatic substituent (personal discussion with Prof. K.B. Sharpless at **IUPAC**-94, Hyderabad).

Conclusion

1. An efficient method for the construction of C-2 oxygenated aromatic C-ring "B-*seco* taxoids" has been developed using Grignard nucleophiles (organomagnesium reagent) for the first time.
2. These "B-*seco* taxoids" *via* B-ring closure can serve as precursors for several synthetic taxane analogues of pharmacological potential.
3. The results reported herein demonstrate the practical utility of *trans*-verbenol as a new synthetic entry point into taxane chemistry.
4. It offers a high flexibility in stereoselective construction of various functionalized key intermediates required in designing bio-active taxoids and some of these studies are currently under investigation.

Experimental

o-Bromotoluene (59)

A solution of freshly distilled o-toluidine (10.7 g, 100 mmol) in 34 ml of 40% w/w aqueous hydrobromic acid was taken in a 250 ml round-bottomed flask and cooled to 0°C in an ice-salt bath. To this a solution of sodium nitrite (73.0 g, 100 mmol) in 100 ml of water was added over a period of 30 minutes with stirring. After all the addition of sodium nitrite was over, copper powder (0.50 g) was introduced a reflux condenser was attached to the round-bottomed flask and the mixture was heated very cautiously on a boiling water bath. The vigorous nature of the reaction was controlled by removing the source of heat. When the vigorous evolution of nitrogen was moderated the flask was heated on a water bath for 30 minutes. The reaction mixture was then cooled to room temperature and it was poured into a solution of 10% sodium hydroxide. The quenched reaction mixture was extracted with diethylether (3 x 60 ml). The combined ethereal layer was washed with water (6 x 10 ml), brine (3 x 5 ml) and dried over anhydrous magnesium sulphate. The ether was distilled off on a rotary evaporator and the residue was distilled at diminished pressure to get a colourless liquid.

Yield : 8.0 g, (47%)

B.P. : 110-112°C at 20 mm Hg (Lit.[91] 58-60°C at 10 mm Hg)

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 3100 (w), 1600 (w), 1520, 1020, 725.

^{1}H NMR (60 MHz) : δ 2.38 (s, 3H, -C<u>H</u>$_3$), 7.0 (m, 1H, Ar-<u>H</u>), 7.2 (m, 2H, Ar-<u>H</u>), 7.5 (m, 1H, Ar-<u>H</u>).

o-Bromobenzylidine dibromide (60)

Finely powdered N-bromosuccinimide (22.2 g, 25.01 mmol) was added to a solution of o-bromotoluene (10.7g, 62.55 mmol) in carbontetrachloride (150 ml) containing benzoylperoxide (0.25 g) and the mixture was heated at reflux for 20 hours, while irradiating with a Hanovia 250 w mercury vapour lamp. After cooling to 0°C, the succinimide formed was removed by filtration and the solvent was evaporated in vacuo. The reddish yellow residue was distilled to give o-benzylidine dibromide as a light yellow clear liquid.

Yield : 19.4 g, (95%)

B.P. : 95-97°C at 0.5 mm Hg (Lit.[92] 96-98°C at 0.5 mm Hg)

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 3090, 3010, 1600

^{1}H-NMR (60 MHz) : δ 6.85 (s, 1H, $\underline{H}CBr_2$), 7.05-7.81 (m, 4H, Ar-$\underline{H}$).

o-Bromobenzaldehyde (61)

o-Bromobenzylidinedibromide (19.4 g, 59.0 mmol) in 180 ml of acetone was hydrolysed by adding to the stirred solution of silver nitrate (20.0g, 3.39 mmol) in 180 ml of water over a period of 15 minutes. The reaction mixture was stirred for an additional 15 minutes. The precipitated silver bromide was removed by filtration, washed with acetone (3 x 20 ml). and the combined filtrate was concentrated in vacuo. The residue obtained was diluted with diethylether (150 ml) the organic layer was washed with water (3 x 10 ml), brine (3 x 5 ml) and dried over anhydrous sodium sulphate. The residue was distilled to furnish o-bromobenzaldehyde as a colourless liquid.

Yield : 9.9 g, (85%)

B.P. : 118-121°C at 12 mm Hg (Lit.[90] 230°C).

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 3050, 3000, 1700, 1600, 1100, 1000, 780.

^{1}H-NMR (60 MHz) : δ 7.31-8.05 (m, 4H, Ar-$\underline{H}$), 10.35 (s, 1H, -C$\underline{H}$O).

Ethyleneacetal of o-bromobenzaldehyde (62)

To a solution containing o-bromobenzaldehyde (9.9 g, 54.0 mmol) in 20 ml of anhydrous benzene, ethylene glycol (4.02 g, 64-8 mmol) and p-toluene sulphonic acid (100.0 mg) were added. The resultant solution was heated to reflux in a Dean-Stark apparatus until no more water could be collected (5 hours) and then stored for 12 hours at room temperature. It was then successively washed with 2N NaOH (2 x 15 ml) , water (3 x 5 ml), brine (3 x 15 ml) and dried over potassium hydroxide pellets. The solvent was removed at reduced pressure and the crude material obtained was distilled to yield ethylene acetal of o-bromobenzaldehyde as a light yellow liquid.

Yield : 111.19 g, (91%)

B.P. : 96-100°C at 0.3 mm Hg (Lit.[90] 94-97°C at 0.3 mm Hg)

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 2950, 1600, 1000, 950, 780.

^{1}H-NMR (60 MHz): δ 3.9 (m, 4$\underline{H}$, -OC$\underline{H}_2$-C$\underline{H}_2$-O), 6.01 (s, 1H, H-C), 7.0-7.06 (m, 4H, Ar-$\underline{H}$).

Grignard reaction of ethylene acetal of o-bromobenzaldehyde with (S)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde (65)

In a 3-necked 250 ml round-bottomed flask, activated magnesium (1.8 g, 75 mmol) and traces of iodine were placed, the flask was fitted with a dropping funnel, a

reflux condenser with a guard-tube having anhydrous calcium chloride and the third neck was fitted a rubber septum. The contents were flame dried using a Bunsen burner and allowed to cool to room temperature. Under an argon atomosphere, ethylene glycol acetal of o-bromobenzaldehyde (10.0 g, 43.68 mmol) in 15 ml of anhydrous tetrahydrofuran was added and magnetically stirred for further 1 hour. The Grignard complex obtained was cooled to 0°C using an ice-salt bath. To this Grignard complex (S)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde (6.6 g, 43.42 mmol) in 15 ml of tetrahydrofuran was added using a syringe needle during 30 minutes. The reaction mixture was then warmed to room temperature and stirred for 6 hours at room temperature. The total reaction mixture was poured into a solution of saturated ammonium chloride. The tetrahydrofuran layer was separated and the aqueous layer was extracted with diethylether (3 x 100 ml). The combined organic layer was washed successively with water (3 x 2 ml), brine (3 x 5 ml) and dried over anhydrous sodium carbonate. It was then concentrated in vacuo and the residue was chromatographed over silica gel to obtain the Grignard product as crystalline solid.

Yield : 1.3 g, (25%)

B.P. : 152-155°C

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$3480 (b), 1630, 1600, 1450, 1380, 1100, 1000.

^{1}H NMR (200 MHz) : δ 1.06, 1.10 (2s, 6H, C(-CH_3)$_2$), 1.65 (s, 3H, C=C-C$\underline{H}_3$), 1.8-2.21 (m, 5H, 2 x C$\underline{H}_2$, 1 x C$\underline{H}$), 4.12 (m, 4H, -O-C$\underline{H}_2$-C$\underline{H}_2$-O-), 5.05 (d, 1H, J = 1 Hz, $\underline{H}$-C-O-CH_2-), 5.50 (s, 1H, C=C$\underline{H}$), 6.05 (s, 1H, $\underline{H}$C-OH) 7.25-7.71 (m, 4H, Ar-$\underline{H}$).

^{13}C-NMR (50 MHz) : 18.0, 23.6, 25.4, 30.4, 30.6, 35.7, 49.0, 65.6, 65.3, 68.7, 100.8, 126.3, 127.0, 127.2, 129.1, 131.9, 133.5, 144.0, 144.1.

Mass (m/z) : 302(4), 284(4), 240(45), 204(15), 179(65), 134(100), 123(38), 77(36).

Analysis **Calculated** C= 74.58% H=8.60%

Found C=74.44% H=8.62%

m-Methoxybenzaldehyde (53)

m-Hydroxybenzaldehyde (12.2 g, 100 mmol) was taken in 100 ml of acetone in a 250 ml round-bottomed flask. To this dimethylsulphate (15.0 g, 140 mmol) and potassium carbonate (6.8 g) were added and the mixture was heated to reflux for 6

hours. The inorganic salts were filtered and washed with acetone (3 x 60 ml). The combined filtrate was then concentrated in vacuo and the residue obtained was diluted with diethylether. The organic solution was washed with saturated potassium carbonate solution (3 x 20 ml), water (3 x 10 ml), brine (3 x 5 ml) and dried over anhydrous sodium sulphate. Ether was distilled off on a rotary evaporator and the residue was chromatographed over silica gel to yield m-methoxybenzaldehyde. Further purification was carried out by distillation under reduced pressure to give m-methoxybenzaldehyde as a colourless liquid.

Yield	:	13.2 g, (98%)
B.P.	:	142-146°C at 5 mm Hg (lit.[95] 143° at 50 mm Hg).
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 2950 (ω), 1720, 1620, 1540, 1300, 1120, 1100.
^{1}H-NMR (90 MHz)	:	δ 3.84 (s, 3H, -OC<u>H</u>$_3$), 7.18 (m, 1H, Ar-<u>H</u>), 7.36 - 7.45 (m, 3H, Ar-<u>H</u>), 9.8 (s, 1H, -C<u>H</u>O).

Dimethylacetal of m-methoxylbenzaldehyde (54)

In a 100 ml round-bottomed flask, m-methoxybenzaldehyde (13.2 g, 97 mmol), trimethylorthoformate (32.0 g, 33 ml, 302 mmol), anhydrous methanol (16.0 g, 20.5 ml, 500 mmol) were taken. Concentrated hydrochloric acid (5 drops) was added to the reaction mixture which was then stirred magnetically at room temperature for 48 hours. The progress of the reaction was monitored by IR spectroscopy. After the completion of the reaction, it was quenched by the addition of 10 ml. of saturated sodium carbonate solution and the total reaction mixture was concentrated in vacuo. The residue was diluted with 150 ml of diethylether the ethereal layer was then washed with water (3 x 10 ml), brine (3 x 5 ml) and dried over anhydrous sodium sulphate. Distillation of the solvent followed by concentration on a rotary evaporator gave a residual material, which was chromatographed over silica gel column. The chromatographed material thus obtained was distilled to yield dimethylacetal of m-methoxybenzaldehyde as a colourless liquid.

Yield	:	16.0 g, (89%)
B.P.	:	128-132°C at 50 mm Hg. (Lit.[95] 129°C at 50 mm Hg).
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 2950, 1600, 1450, 1350.
^{1}H-NMR (60 MHz)	:	δ 3.42 (s, 6H, C (-OC<u>H</u>$_3$)$_2$), 4.91 (s, 3H, -O-C<u>H</u>$_3$), 5.45 (s, 1H, <u>H</u>-C(OMe)$_2$), 6.9-7.12 (m, 3H, Ar-<u>H</u>).

Coupling of dimethylacetal of m-methoxybenzaldehyde with (±)-2,24-trimethylcyclohex-3-ene-1-carbaldehyde via lithiation followed by transmetallation (57)

In a 50 ml oven-dried, round-bottomed flask, fitted with a two-way stop cock and septum, hexane solution of n-BuLi (1.61 M, 6.2 ml, 10 mmol) was charged using a syringe needle under an argon atmosphere and the solution was cooled to 0°C using an ice-salt bath. To this solution dimethylacetal of m-methoxylbenzaldehyde (1.8 ml, 10 mmol) was added at 0°C via a syringe needle over a period of 5 minutes. After the addition of dimethylacetal of m-methoxybenzaldehyde was over, the reaction mixture was warmed to room temperature and stirred for 4 hours at room temperature. Anhydrous tetrahydrofuran 6 ml was added and the reaction mixture was then cooled to -78°C using an acetone-dry ice bath. This solution was added to an anhydrous tetrahydrofuran suspension containing cerium trichloride (2.8 g, 11 mmol) (which was prepared by stirring cerium trichloride in anhydrous tetrahydrofuran for 2 hours at room temperature in an oven-dried 10 ml round-bottomed flask) at -78°C and the resulting mixture was stirred for 30 minutes at -78°C. Then, the reaction mixture was poured into a vigorously stirred mixture of hexane and saturated sodium carbonate. The solid was filtered through a pad of celite. The organic layer was separated and the aqueous layer was extracted with dimethylether (3 x 100 ml). The combined organic extract was washed with water (3 x 2 ml), brine (3 x 5 ml), dried over anhydrous potassium carbonate and concentrated in vacuo. The residue was chromatographed over silica gel to furnish the coupled product as a viscous oily liquid, which was further purified by distillation.

Yield	:	0.18 g, (10.2%)
B.P.	:	162° at 0.1 mm Hg
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 3950, 3450, 1620, 1052, 780.
^{1}H-NMR (200 MHz)	:	δ 1.25 (s, 6H, C(-C$\underline{H}_3$)$_2$), 1.65 (s, 3H, C=C-C$\underline{H}_3$), 1.9-2.31 (m, 5H, 2 x C$\underline{H}_2$, 1 x C$\underline{H}$), 3.23 (s, 3H, CH-OC$\underline{H}_3$), 3.38 (s, 3H, CH-OC$\underline{H}_3$), 3.80 (s, 3H, O-C$\underline{H}_3$), 4.3 (d, 1H, J = 4 Hz, $\underline{H}$-C-OH), 5.15 (s, 1H, C=C$\underline{H}$), 5.5 (s, 1H, $\underline{H}$-C-O), 6.9 (dd, J = 5.7 Hz, 4.6 Hz, 1H, Ar-$\underline{H}$), 7.27-7.31 (m, 2H, Ar-$\underline{H}$).
Mass (m/z)	:	333(M^{-1}), 315(4), 253(45), 239(9), 225(5), 211(14), 199(10), 188(15), 179(6), 134(100), 123(38), 77(43), 63(23), 55(35).

Analysis	**Calculated**	C=71.86%; H=8.98%
	Found	C=71.63%; H=8.65%

Grignard reaction of m-bromoanisole with (-)-(S)-2,2,4-trimethylcyclohex-3-ene-1-carb-aldehyde (68)

Activated magnesium turnings (0.9 g, 38 mmol) and traces of iodine were taken in a 100 ml 3-necked, round bottomed flask fitted with a reflux condensor having a guard-tube filled with anhydrous calcium chloride, a dropping funnel and a septa was flame dried. After cooling the round-bottomed flask to room temperature 10 ml of anhydrous tetrahydrofuran was introduced, then a solution of m-bromoanisole (4.5 g, 3 ml, 24.1 mmol) in 15 ml of tetrahydrofuran was added through the dropping funnel under an argon atmosphere during 90 minutes and stirred for an additional 30 minutes at room temperature. The reaction mixture was cooled to 0°C using an ice-salt bath. Then (-)-(S)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde (3.0 g, 20.0 mmol) in 5 ml of anhydrous tetrahydrofuran was added over a period of 15 minutes using a syringe needle. The reaction mixture was then stirred at room temperature for 3 hours. The total reaction mixture was poured into a solution containing 20 ml of saturated ammonium chloride. The tetrahydrofuran layer was separated, the aqueous layer was further extracted using diethylether (3 x 100 ml). The combined organic layer was washed with water (3 x 2 ml), brine (3 x 5 ml) and dried over anhydrous sodium sulphate. The organic phase was concentrated in vacuo. The residue obtained was purified by column chromatography over silica gel to yield to Grignard product as a viscous oil, further it was distilled under diminished pressure.

Yield	:	4.4 g, (85%)
B.P.	:	180°C (200°C bath temperature at 0.1 mm Hg).
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 3400 (b), 2950 (s), 1600 (s), 1490, 1430, 1350 (ω), 1250.
^{1}H-NMR (200 MHz)	:	δ 1.12 (s, 6H, C (-C$\underline{H}_3$)$_2$), 1.6 (br.s, 3H, C=C-C$\underline{H}_3$), 1.57-1.75 (m, 2H, 1 x C$\underline{H}_2$), 1.9-2.0 (m, 3H, 1 x C$\underline{H}_2$, 1 x C$\underline{H}$), 3.85 (s, 3H, O-C$\underline{H}_3$), 5.05 (br.s, 1H, $\underline{H}$,-C-OH), 5.10 (br.s, 1H, C=C-$\underline{H}$), 6.8 (m, 2H, Ar-H), 6.95 (br.s, 1H, Ar-H), 7.31 (t, 1H, J=7.5 Hz, Ar-H).

^{13}C-NMR (50 MHz)	:	17.85, 23.57, 24.98, 29.85, 30.06, 35.09, 51.32, 55.27, 72.55, 111.68, 112.08, 118.21, 129.23, 131.76, 133.34, 147.83, 159.74.
Mass (m/z)	:	260 (8), 242(45), 227(9), 213(5), 199(10), 185(4), 173(6), 162(27), 137(70), 123(88), 109(100), 91(25), 81(92), 77(49), 67(23), 55(33).
Analysis		**Calculated** C=78.42%; H=9.29%
		Found C=78.77%; H=9.10%
Optical rotation	:	$[\alpha]_D$ = -26.4° (c=0.66, MeOH)

Manganese dioxide

In a 100 ml round-bottomed flask, potassium permanganate (19.0 g, 120.22 mmol) in 120 ml of water was taken. To this a solution of manganese (II) sulphate (22.3 g, 147.68 mmol) in 30 ml of water and 24 ml of 40% aqueous sodium hydroxide solution were added simultaneously by keeping the round-bottomed flask in a boiling water bath during one hour. Later, the reaction mixture was stirred at room temperature for an additional one hour. The brown precipitate of manganese dioxide was isolated by filtration on a Buckner funnel using water aspirator. The precipitate was washed thoroughly using distilled and demineralized water until the washings were colourless. The brownish cake was dried at 100-120°C for 9 hours and was ground into a fine powder using a pestle and mortar. The powder obtained was transferred into a 100 ml round-bottomed flask and stored in a desiccator.

Benzylic oxidation of (68) with manganese dioxide (69)

In a oven-dried, 250 ml round-bottomed flask, activated manganese dioxide (6.0 g) was placed to which anhydrous pentane (100 ml), Grignard alcohol (**68**) (1.3 g, 5.0 mmol) was added via a syringe needle under an argon atmosphere. The reaction mixture was stirred magnetically for 6 hours during which time the progress of the reaction was monitored by TLC. The reaction mixture was filtered and the solid was washed several times with hot petroleum ether. The combined filtrate was concentrated in vacuo. The viscous oily residue was chromatographed on silica gel then distilled to afford the oxidised product.

Yield	:	1.25 g (97%).
B.P.	:	170°C at 0.1 mm Hg

IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 3000 (s), 1680 (s), 1600 (s), 1480 1460, 1420, 1350 (w), 1250, 1200, 1150, 1000.
^{1}H-NMR (200 MHz)	:	δ 0.95 (s, 6H, C (-C<u>H</u>$_3$)$_2$), 1.67 (s, 3H, C=C-C<u>H</u>$_3$), 1.82 (m, 2H, 1 x C<u>H</u>$_2$), 2.05 (m, 2H, 1 x C<u>H</u>$_2$), 3.45 (dd, 1H, J = 1.5, 10 Hz, <u>H</u>-C-CO-), 3.8 (s, 3H, -O-C<u>H</u>), 5.15 (s, 1H, C=C<u>H</u>), 7.1 (m, 1H, Ar-<u>H</u>), 7.35 (t, 1H, J= 7.5 Hz, Ar-<u>H</u>), 7.55 (m, 2H, Ar-<u>H</u>).
^{13}C-NMR (50 MHz)	:	23.34, 23.57, 24.88, 29.73, 31.22, 35.24, 50.47, 55.54, 112.8, 119.21, 121.09, 129.55, 131.19, 132.9, 14.7, 160, 204.09.
Mass (m/z)	:	258(6), 243(4), 225(1), 214(15), 201(3), 184(3), 153(4), 150(7), 135(100), 128(4), 123(5), 115(2), 107(24), 96(16), 92(12), 81(18), 77(22), 64(7), 55(15).
Analysis		**Calculated** : C=79.0% ; H=8.53%
		Found : C=79.28%; H=8.42%
Optical rotation	:	$[\alpha]^{25}_{D}$ = +7° (c=0.6, $CHCl_3$).

Reduction of arylketone (69) with sodiumborohydride (73)

In a two-necked, 50 ml round bottomed flask, the arylketone (**69**) (0.13 g, 0.04 mmol) was taken in 5 ml of ethanol. To this reaction mixture sodiumborohydride (0.025 g, 0.6 mmol) was added at 0°C. The reaction mixture was then allowed to stir at room temperature for 6 hours. Progress of the reaction was monitored by TLC. After the completion of the reaction, the solvent ethanol was removed on the rotary evaporator and 5 ml of saturated ammonium chloride was added to the residue. The aqueous reaction mixture was extracted with diethylether (3 x 50 ml), the combined extract was washed with dil. HCl (3 x 3 ml), water (3 x 5 ml), brine (3 x 2 ml) and dried over anhydrous sodium sulphate. The solvent was removed on a rotary evaporator and the residue was chromatographed over silica gel to yield the crude alcohol as a solid. Further distillation under diminished pressure to furnish the pure alcohol in almost quantitative yield as a colourless solid. This was recrystallized with petroleum ether to yield a fine crystalline material.

Yield	:	0.12 g, (98%)
B.P.	:	180°C at 0.1 mm Hg (200°C bath temperature).
IR (Neat, cm^{-1})	:	$\sqrt{}_{max}$ 3400 (b), 2950 (s), 1600 (s), 1490, 1250, 880.

^{1}H-NMR (200 MHz)	:	δ 1.05 (s, 3H, C-C$\underline{H}_3$), 1.32 (s, 3H, C-C$\underline{H}_3$), 1.65 (br.s, 3H, C=C-C$\underline{H}_3$), 1.57-1.65 (m, 2H, 1 x C$\underline{H}_3$), 1.71-2.0 (m, 3H, 1 x C$\underline{H}_2$, 1 x C$\underline{H}$), 3.9 (s, 3H, C-C$\underline{H}_3$), 4.55 (d, 1H, J = 8.5 Hz, $\underline{H}$-C-OH), 5.05 (s, 1H, C=C$\underline{H}$), 6.9 (m, 2H, Ar-$\underline{H}$), 6.95 (br.s, 1H, Ar-$\underline{H}$), 7.31 (t, 1H, J = 7.5 Hz, Ar-$\underline{H}$).
^{13}C-NMR (50 MHz)	:	23.51, 23.81, 30.36, 32.43, 35.56, 49.63, 55.41, 78.39, 112.85, 113.29, 119.78, 129.61, 130.60, 135, 147.18, 159.97, 168.27.
Mass (m/z)	:	260(15), 245(15), 227(4), 214(4), 199(3), 185(2), 171(2), 162(10), 147(4), 137(86), 123(100), 115(4), 109(97), 91(25), 81(87), 77(50), 67(23), 55(32).
Optical rotation	:	$[\alpha]^{25}_{D}$ = -54° (c=1.5, MeOH)
Analysed		**Calculated** C= 78.42%; H=9.29%
		Found C= 79.07%; H=9.23%

N-Benzylidenedenzyenesulfonamide

A 1 lit., three necked round bottomed flask was equipped with a mechanical stirrer, Dean-stark water separator, double-walled condensor attached to an argon gas inlet and outlet needle connectors through a mineral oil bubbler. Into the flask were placed 5A° powdered molecular sieves (30.0 g), Amberlyst 15 ion exchange resin (0.40 g), benzenesulfonamide (32.3 g; 205.48 mmol) 330 ml of anhydrous toluene and freshly distilled benzaldehyde (21.5 g, 202.60 mmol). The reaction mixture was stirred and heated under reflux in an argon atmosphere. Water which separated during the reaction was periodically removed and refluxing was continued until water separation ceased (approximately 18 hours). The reaction mixture was cooled to room temperature without stirring and the insoluble materials were filtered through a 500 ml capacity sintened-glass funnel of medium porosity. The residue in the filter funnel was washed thoroughly with toluene (3 x 125 ml). The collected filtrate was concentrated on a rotary evaporator to furnish a thick yellow oily residue which solidified upon standing. The residue obtained was triturated with 300 ml of pentane and the solid obtained was broken into a powder with the aid of flat-ended flass rod. The solid was separated by filtration through a 500 ml. Sintered glass funnel of medium porosity, washed with distilled pet.ether (2 x 50 ml) and air dried.

Yield	:	42.8 g (87%)
B.P.	:	78-82°C (Lit.[96] 76-80°C)

^{1}H-NMR (60 MHz) : δ 7.6 (m, 6H, Ar-H), 8.0 (m, 4H, Ar-H), 9.06 (s, 1H, -N=CH).

(±)-*Trans*-2-(phenylsulfonyl)-3-phenyl oxaziridine

A 1 lit., 3 necked flask was equipped with a mechanical stirrer and 250 ml pressure-equalizing addition funnel. Into the flask were placed 100 ml of saturated aqueous sodium carbonate solution, benzyltriethylammonium chloride (2.5 g, 10.97 mmol) and N-benzylidene benzenesulfonamide (24.5 g, 100.0 mmol) distilled in 70 ml of chloroform. The reaction mixture was stirred vigorously at 0-5°C (ice bath) while a solution of 85% m-chloroperbenzoic acid (22.1 g, 128.5 mmol) was added dropwise over a period of 1 hr. at 0-5°C. The total reaction mixture was transferred into a separatory funnel to separate the chloroform layer and the chloroform layer was washed with ice-cold water (6 x 20 ml), aqueous sodium sulphite (10%, 6 x 20 ml), water (3 x 50 ml) and brine (3 x 20 ml). The chloroform solution was dried over anhydrous potassium carbonate for 2 hours, it was filtered and the solvent was removed using a rotary evaporator by taking due care to maintain the bath temperature below 40°C. The resulting white solid was washed with a small portion of pentane and then dissolved in 320 ml of ethylacetate without heating, and filtered through a fluted filler paper; 180 ml of pentane was added to the filtrate and cooled in a refrigerator overnight (12 hours). The white crystalline oxaziridine obtained was separated by filtration, washed with pentane (80 ml) and air-dried for 1 hour.

Yield : 15.8 g (72%)

B.P. : 93-96°C (lit.[96] 92-94°C)

^{1}H-NMR (200 MHz) : δ 5.5 (s, 1H, N-C-Ar-H), 7.4 (s, 5H, Ar-H), 7.6-7.8 (m, 3H, Ar-H), 8.05 (br.d, 2H, J=7.1, Ar-H).

Attempted-α-Hydroxylation of the ketone

In a 50 ml oven-dried two-necked, round-bottomed flask fitted with an argon gas bubbler, rubber septum and a magnetic bar was placed 3 ml of freshly distilled anhydrous tetrahydrofuran. The reaction mixture was cooled to -78°C and 0.6 ml of 1molar solution of NaHMDS in tetrahydrofuran was added. A solution of (±)-trans-2-(phenylsulfonyl)-3-phenyloxaziridine (187 mg, 0.75 mmol) in 3 ml of anhydrous tetrahydrofuran was added over a period of 15 minutes. The reaction mixture was allowed to come to 0°C over a period of 2 hours and then stirred at 0°C for 2 hours. It was quenched by the addition of 3 ml of saturated ammonium chloride and diluted with

10 ml of diethylether. The ethereal layer was separated and the aqueous layer was extracted twice with diethylether. The combined organic extract was successively washed with saturated aqueous sodium thiosulphate (3 x 10 ml), brine (2 x 5 ml) and dried over anhydrous sodium sulphate. The ethereal extract was concentrated on a rotary evaporator, the residue was found to identical in all respect the starting material by routine analyses like ir, glc, nmr.

Silylation of Grignard alcohol

In 50 ml, oven-dried, round bottomed flask, a dihloromethane (20 ml) solution of Grignard alcohol (**68**) (0.82 g, 12.5 mmol), imidazole (0.825 g, 12.5 mmol) and trimethylsilylchloride (0.68 g, 6.27 mmol) was stirred at room temperature for 12 hours. Progress of the reaction was monitored by TLC. After the completion of the reaction, it was quenched by the addition of 6 ml of saturated sodium carbonate. The total reaction mixture extracted using dichloromethane (3 x 60 ml), the combined dichloromethane layer was washed with water (3 x 5 ml), brine (3 x 5 ml) and dried over anhydrous sodium carbonate. It was then concentrated on a rotary evaporator and the residue obtained was chromatographed over neutral alumina using 0.5% ethylacetone/hexane including 0.25% triethylamine to get the C-2 silylated product as an oil. Further it was purified by distillation under reduced pressure.

Yield : 1.0 g, (96%)

B.P. : 150°C at 0.1 mm Hg

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 2950, 1600, 1065, 835, 780, 740.

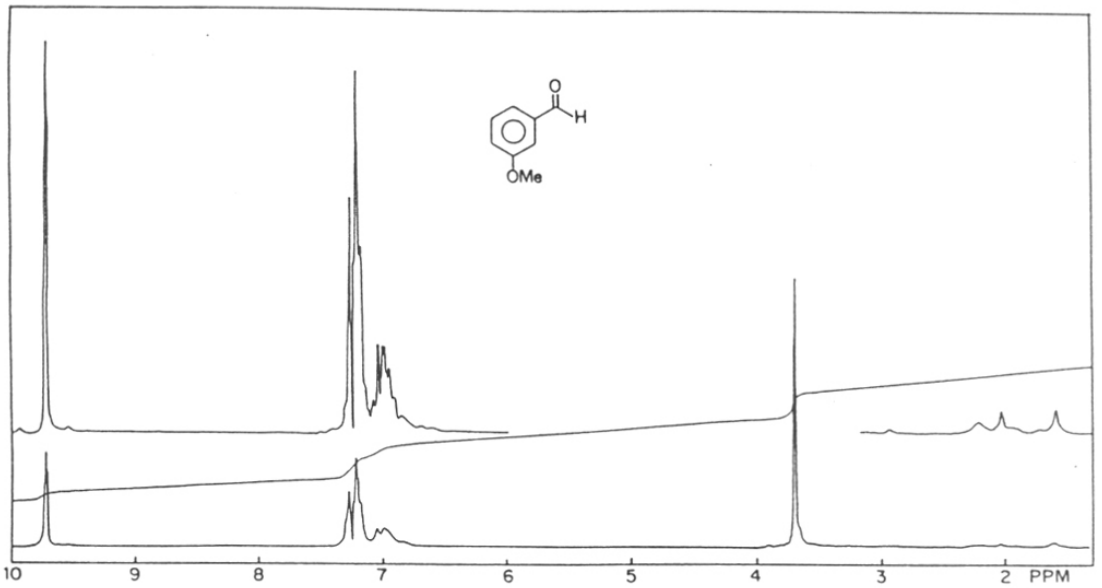
^{1}H NMR (200 MHz) : δ 0.1 (s, 3H, -Si-C$\underline{H}_3$), 0.05 (s, 6H, Si(-C$\underline{H}_3$)$_2$), 1.0 (s, 6H, C-(C$\underline{H}_3$)$_2$), 1.6 (br.s, 3H, C=C-C$\underline{H}_3$), 1.4-1.82 (m, 5H, 2 x C$\underline{H}_2$, 1 x C$\underline{H}_2$, 1 x C$\underline{H}$), 3.9 (s, 3H, -O-C$\underline{H}_3$), 4.95 (d, 1H, J = 1.5 Hz, $\underline{H}$-C-Si-O), 5.02 (br.s, 1H, C=C$\underline{H}$), 6.8-6.91 (m, 2H, Ar-$\underline{H}$), 6.92 (br.s, 1H Ar-$\underline{H}$), 7.25 (t, 1H, J = 7.5 Hz, Ar-$\underline{H}$).

^{13}C-NMR (50 MHz) : 0.80, 18.48, 23.28, 23.56, 24.75, 31.01, 35.66, 52.71, 55.37, 112.41, 112.95, 119.02, 129.12, 131.42, 133.91, 148.59, 159.53.

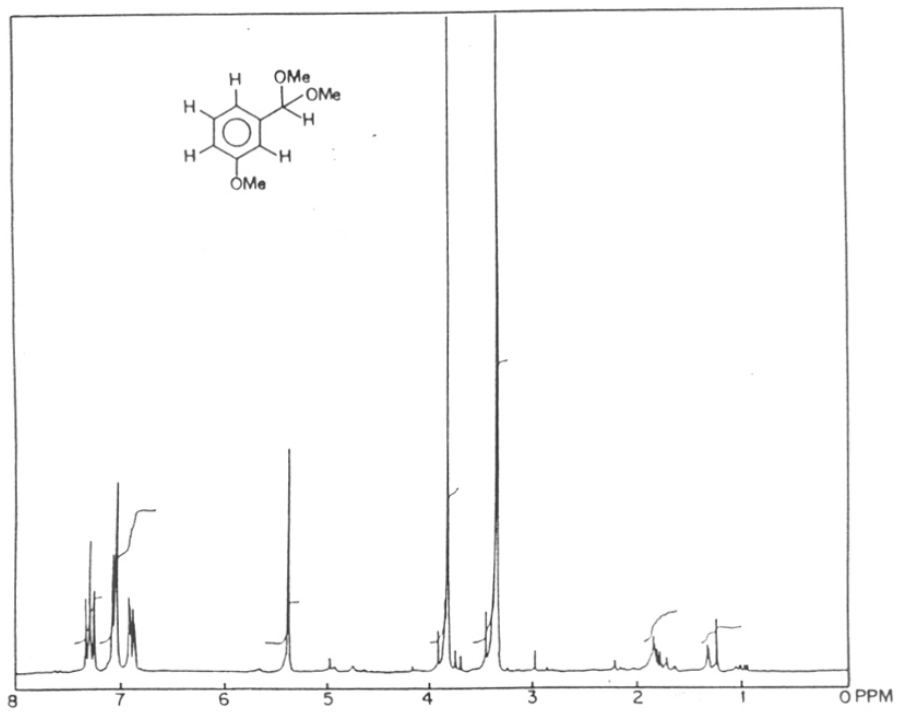
Mass (m/z) : 332(1), 315(2), 242(45), 227(9), 213(6), 199(15), 137(85), 123(80), 109 (100), 91(25), 81(92), 77(49), 67(23), 55(33).

Analysis **Calculated** : C=72.24%; H=9.62%

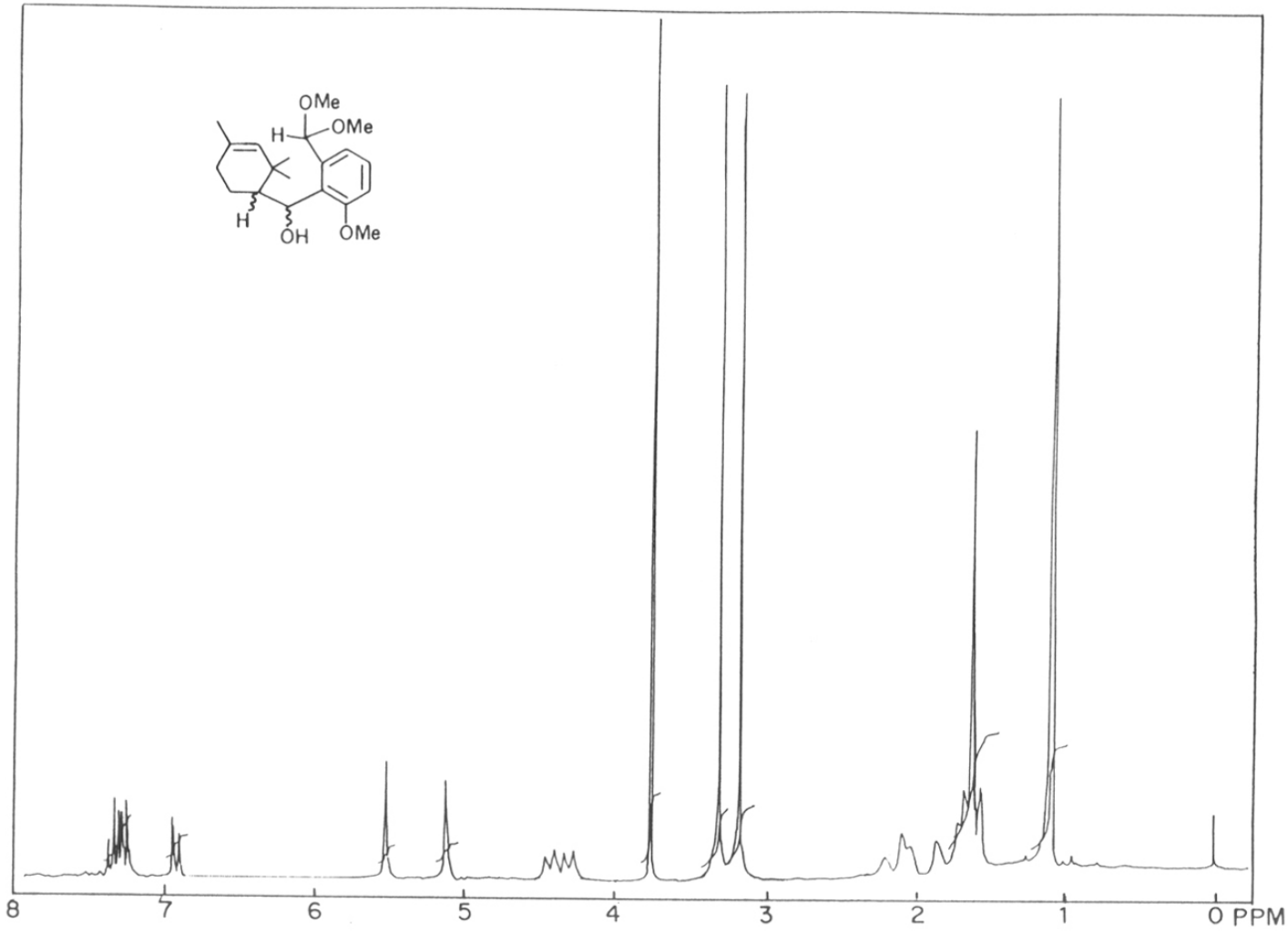
Found : C=72.01%; H=9.58%



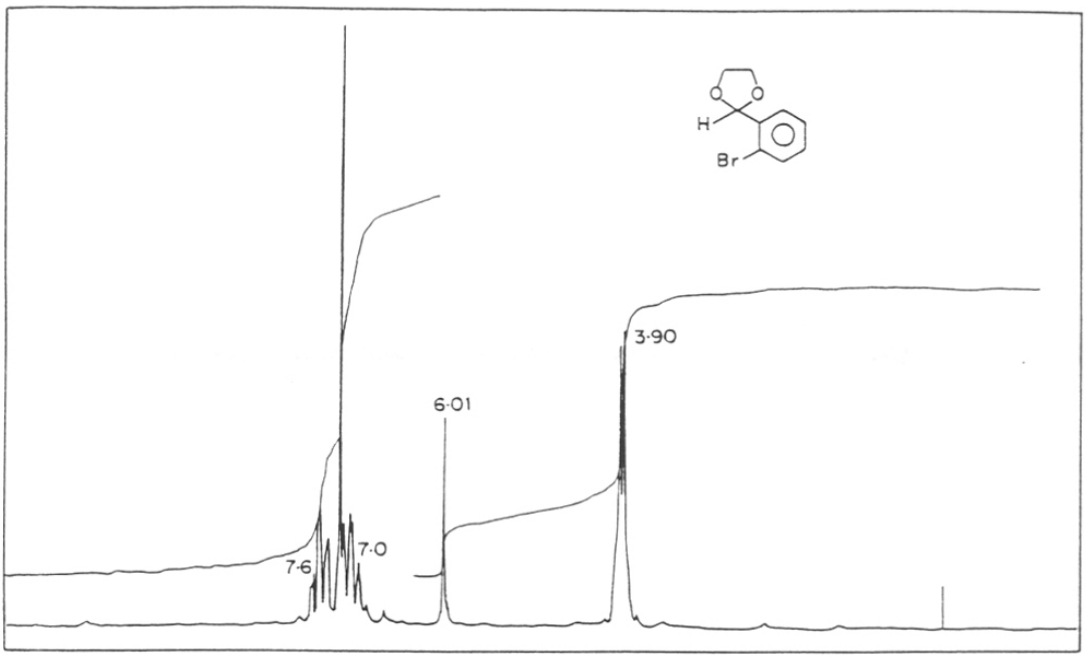
^{1}H-NMR SPECTRUM OF COMPOUND **53**



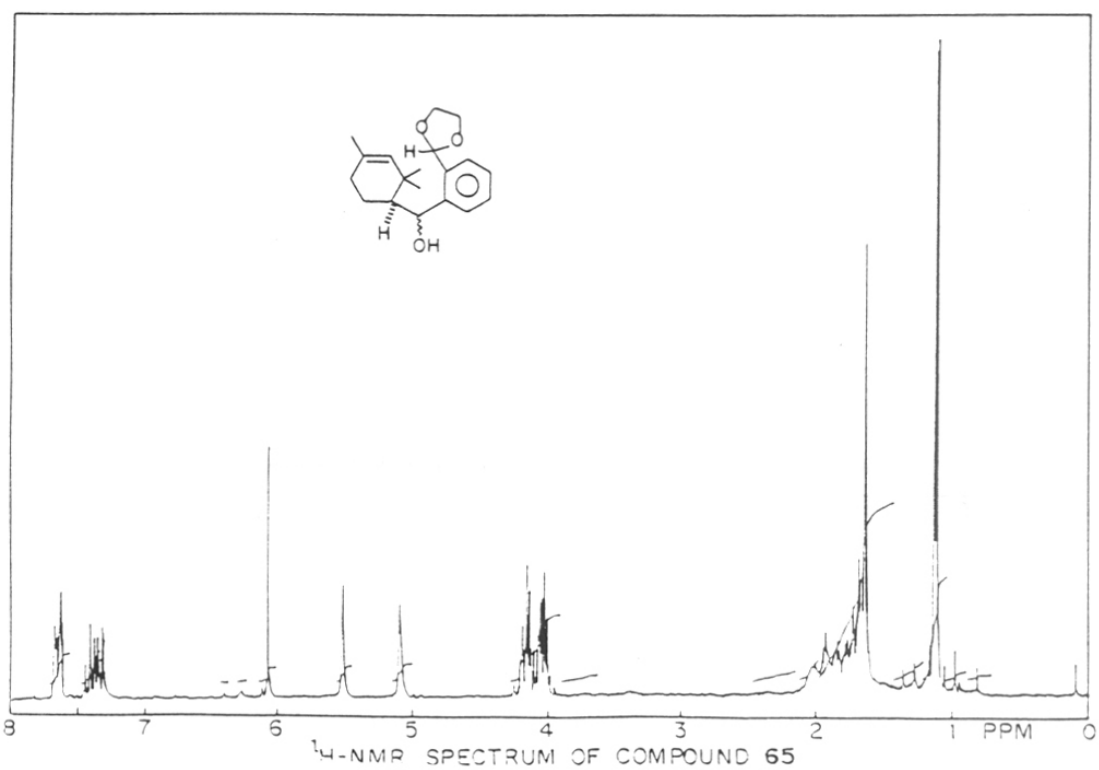
^{1}H-NMR SPECTRUM OF COMPOUND **54**



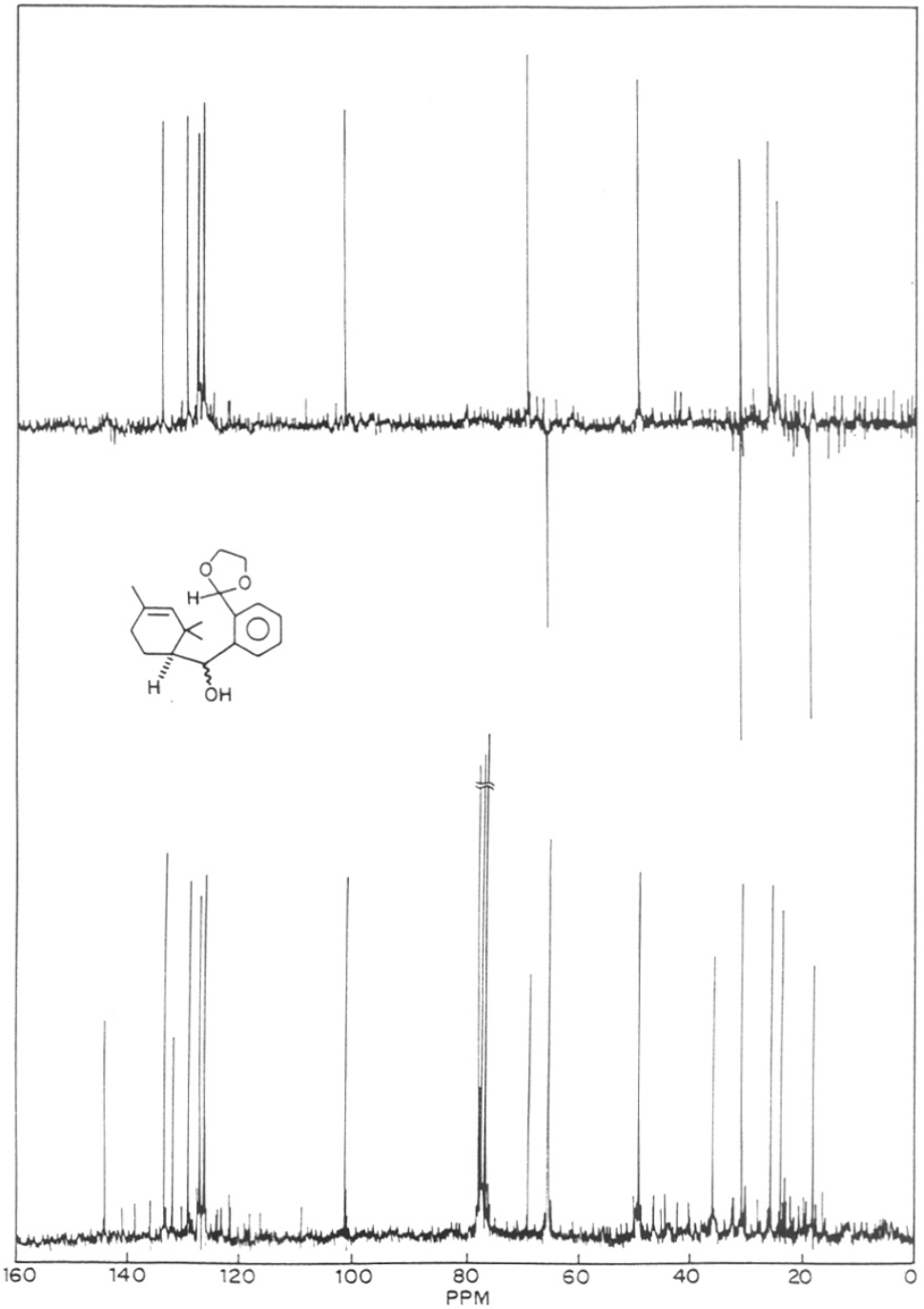
H-NMR SPECTRUM OF COMPOUND **57**



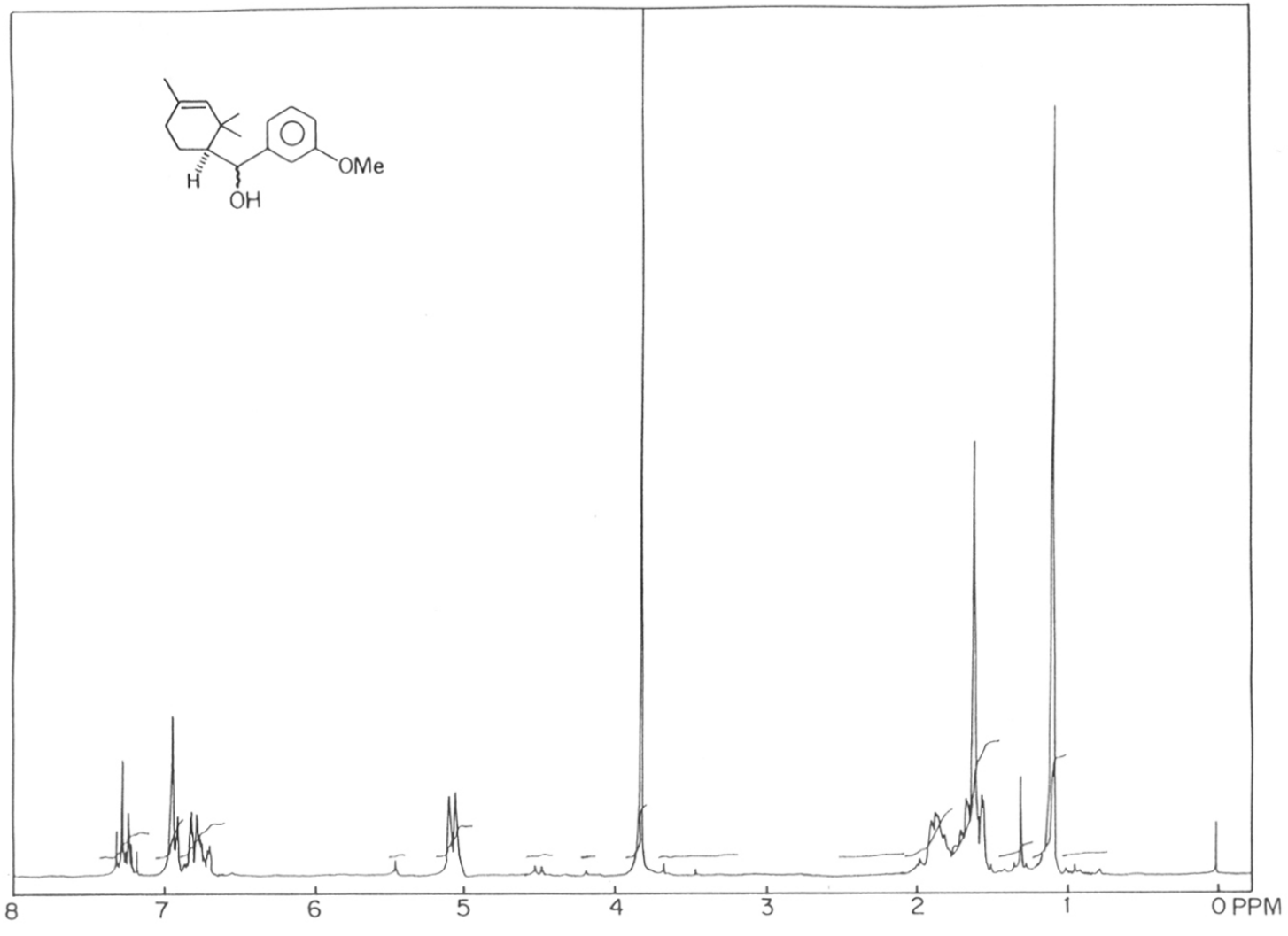
^{1}H-NMR SPECTRUM OF COMPOUND **62**



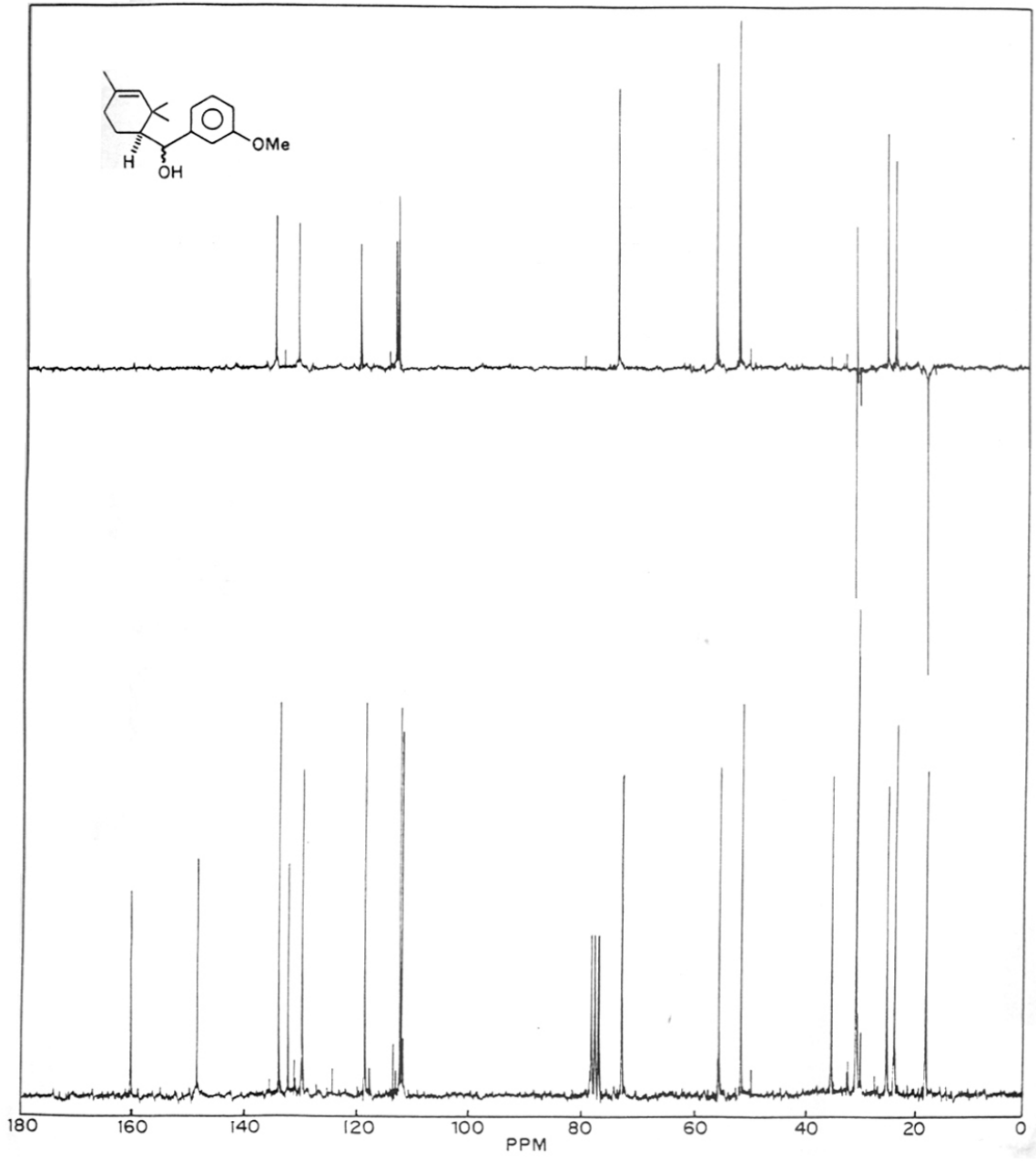
^{1}H-NMR SPECTRUM OF COMPOUND **65**



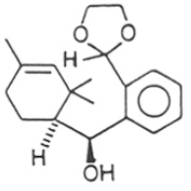
^{13}C-NMR SPECTRUM OF COMPOUND **65**

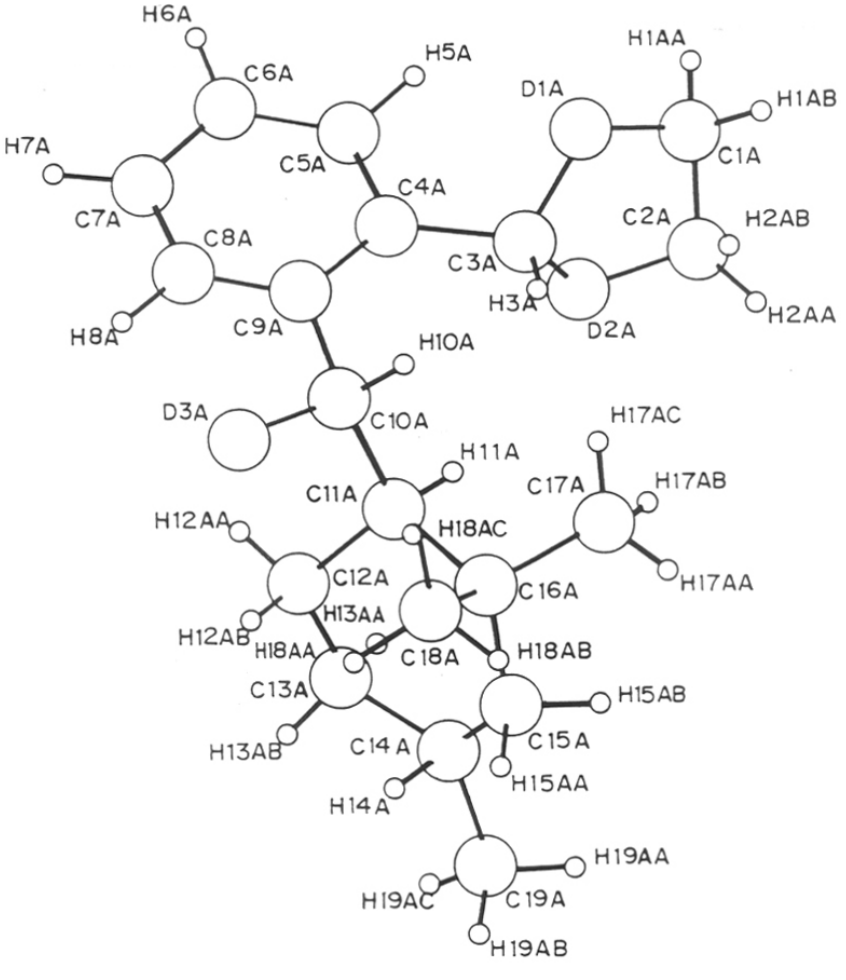


^{1}H-NMR SPECTRUM OF COMPOUND **68** (Grignard product)

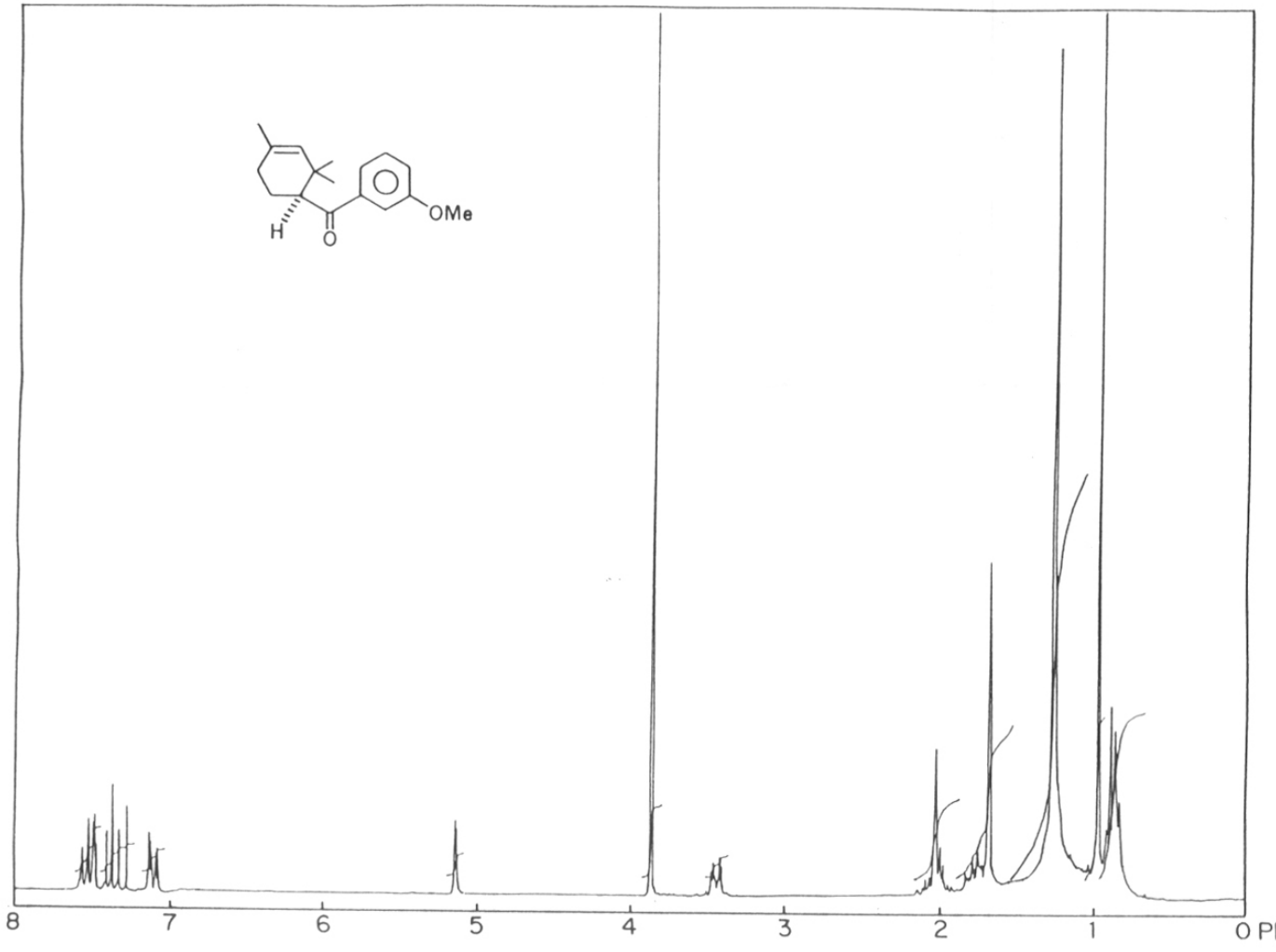


^{13}C-NMR SPECTRUM OF COMPOUND 68

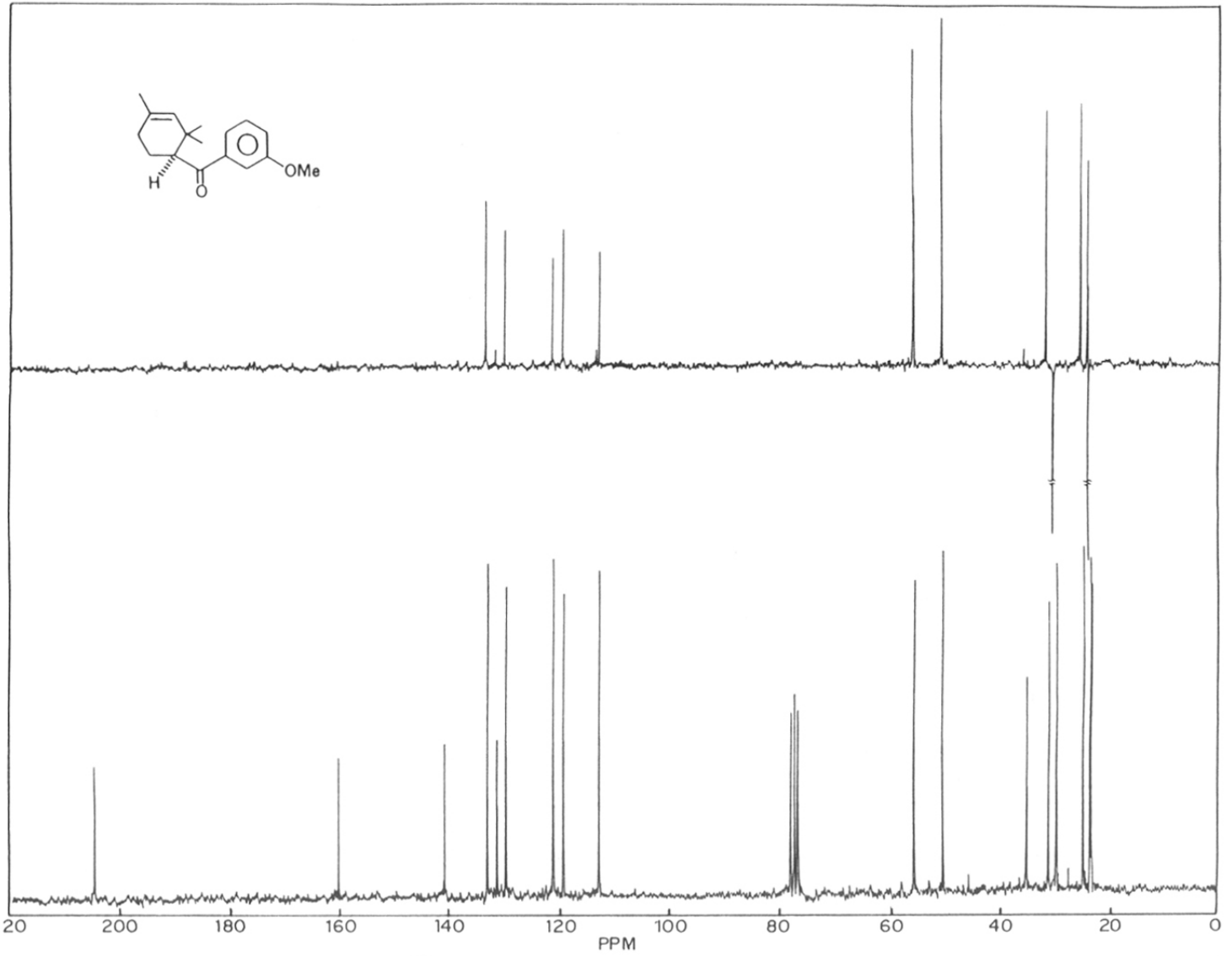




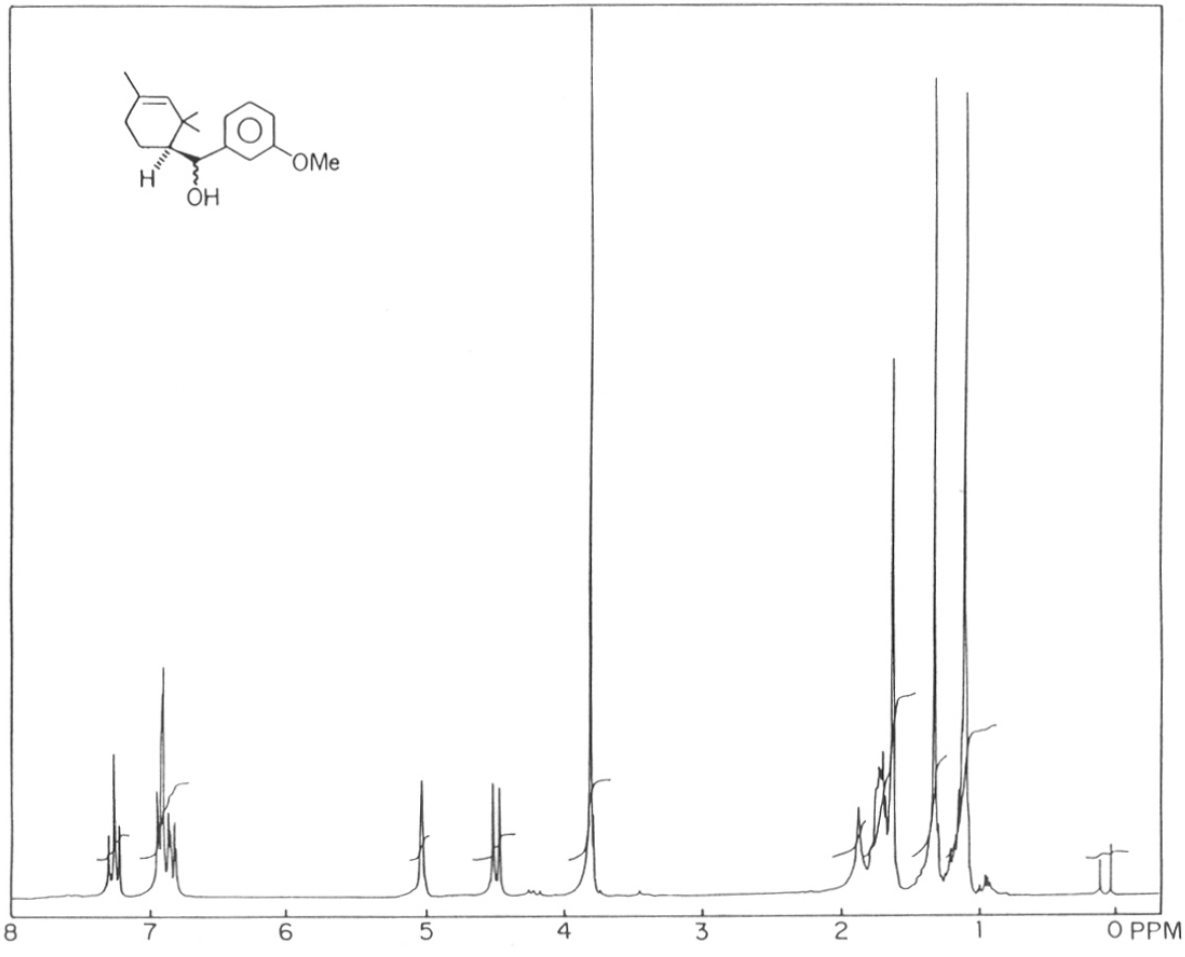
X-RAY STRUCTURE OF COMPOUND **65**



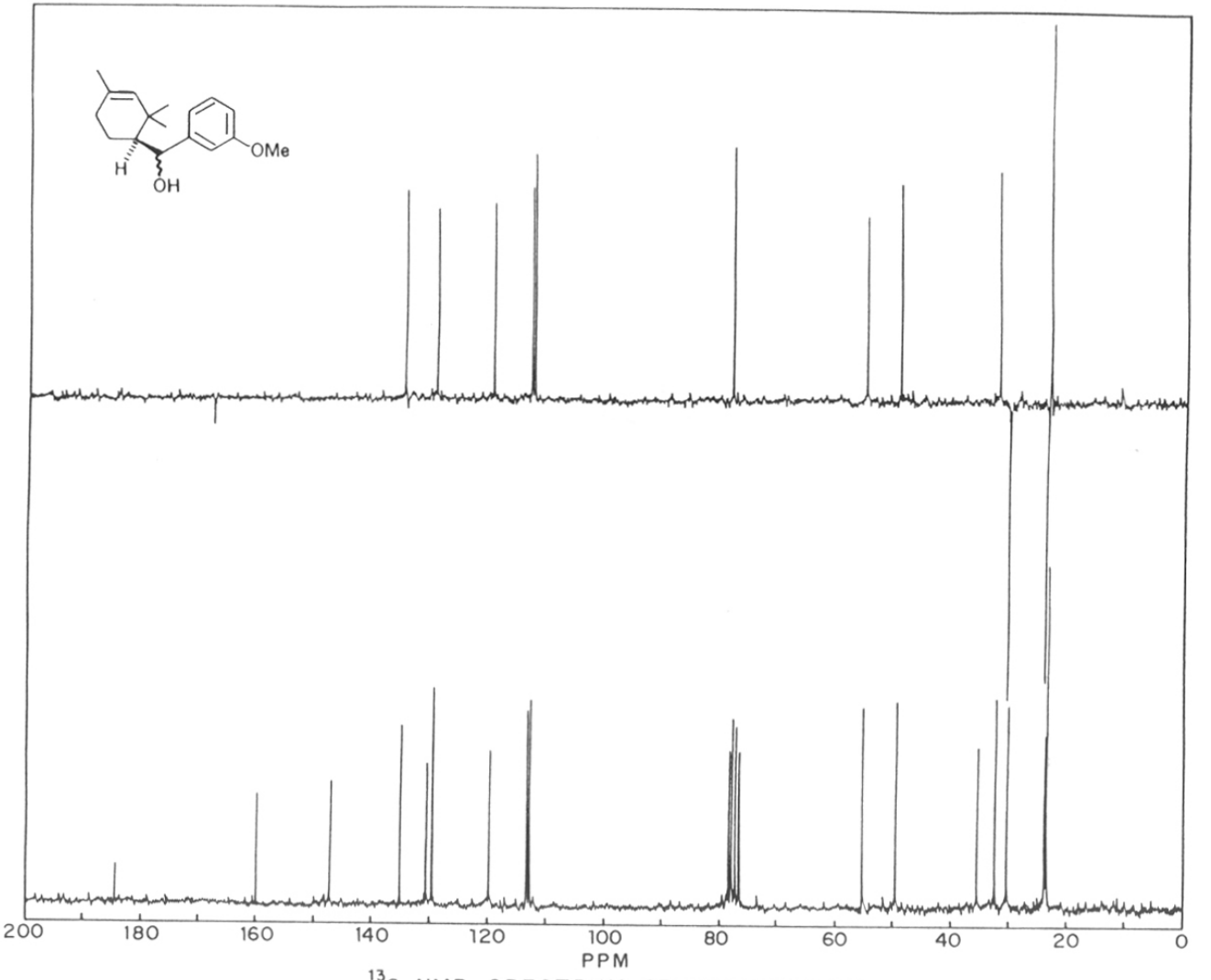
^{1}H-NMR SPECTRUM OF COMPOUND **69**



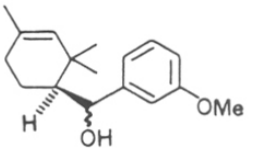
^{13}C-NMR SPECTRUM OF COMPOUND **69**

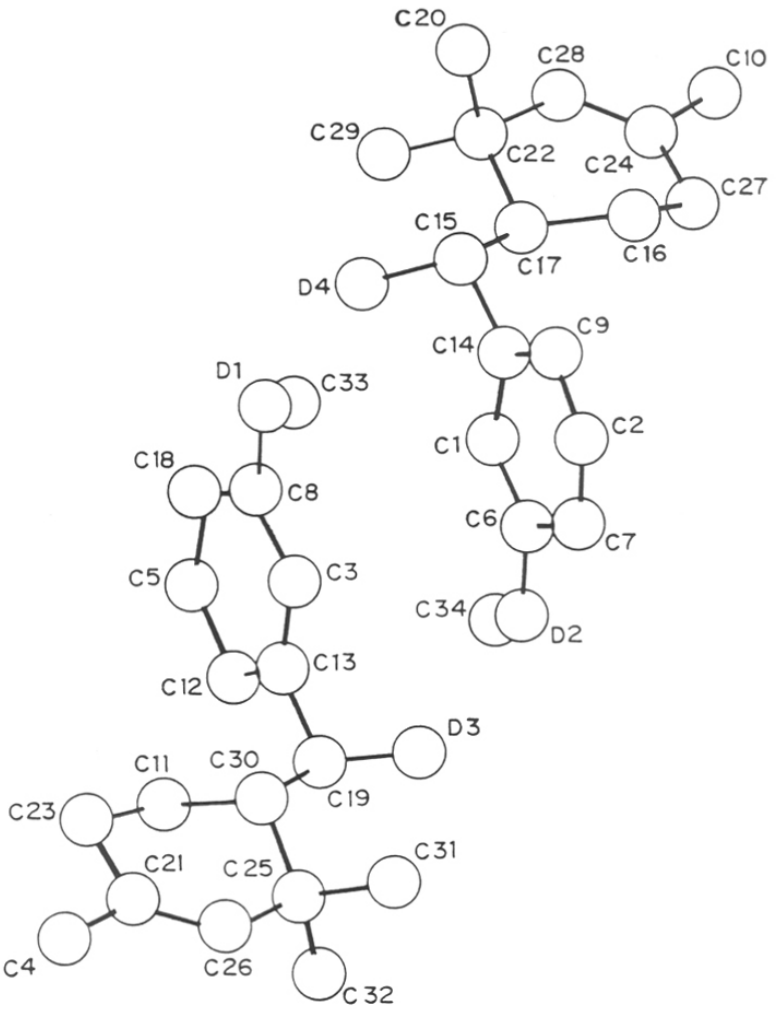


^{1}H-NMR SPECTRUM OF COMPOUND **73** ($NaBH_4$ reduced pdt.)

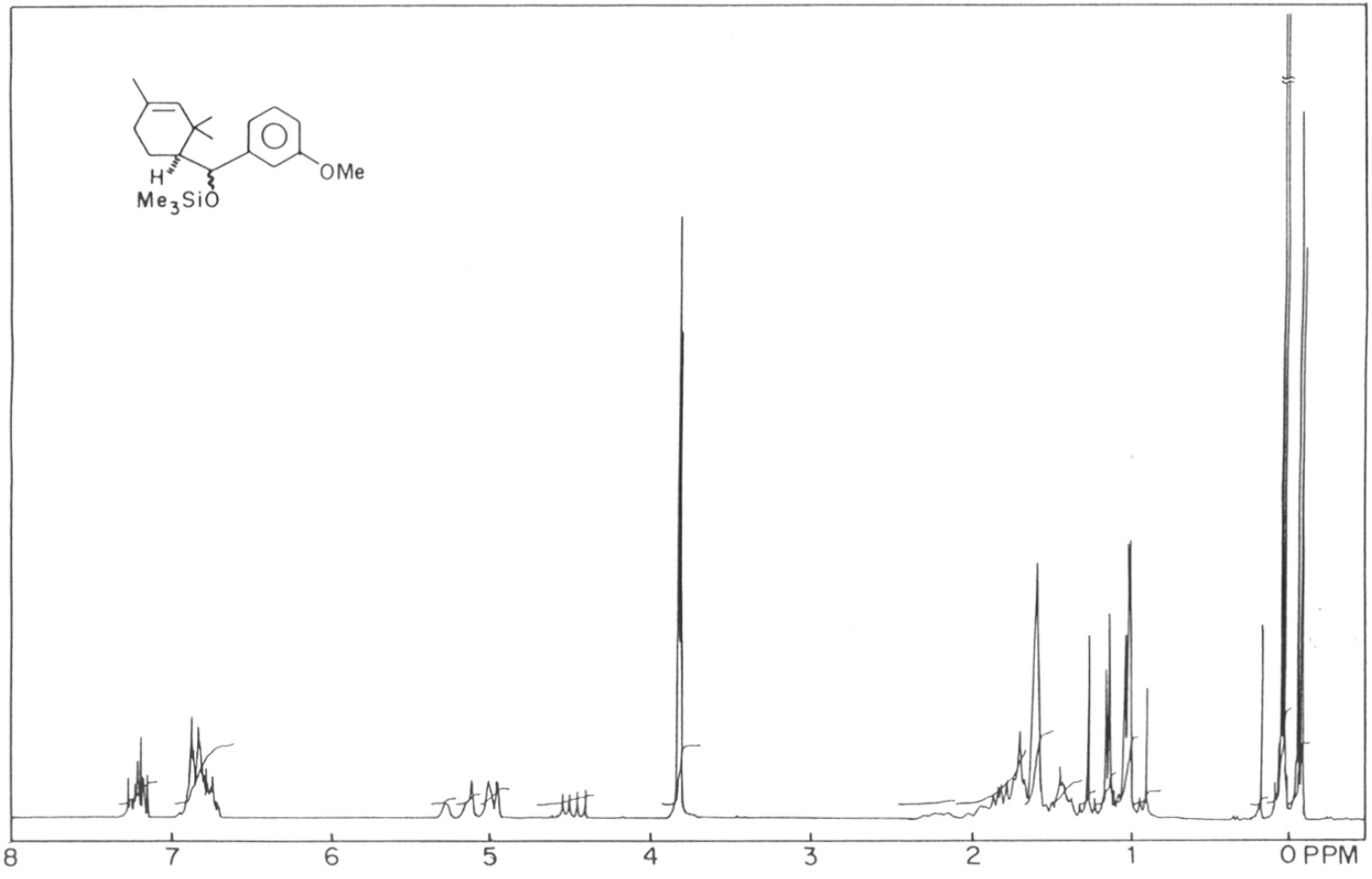


^{13}C-NMR SPECTRUM OF COMPOUND **73**

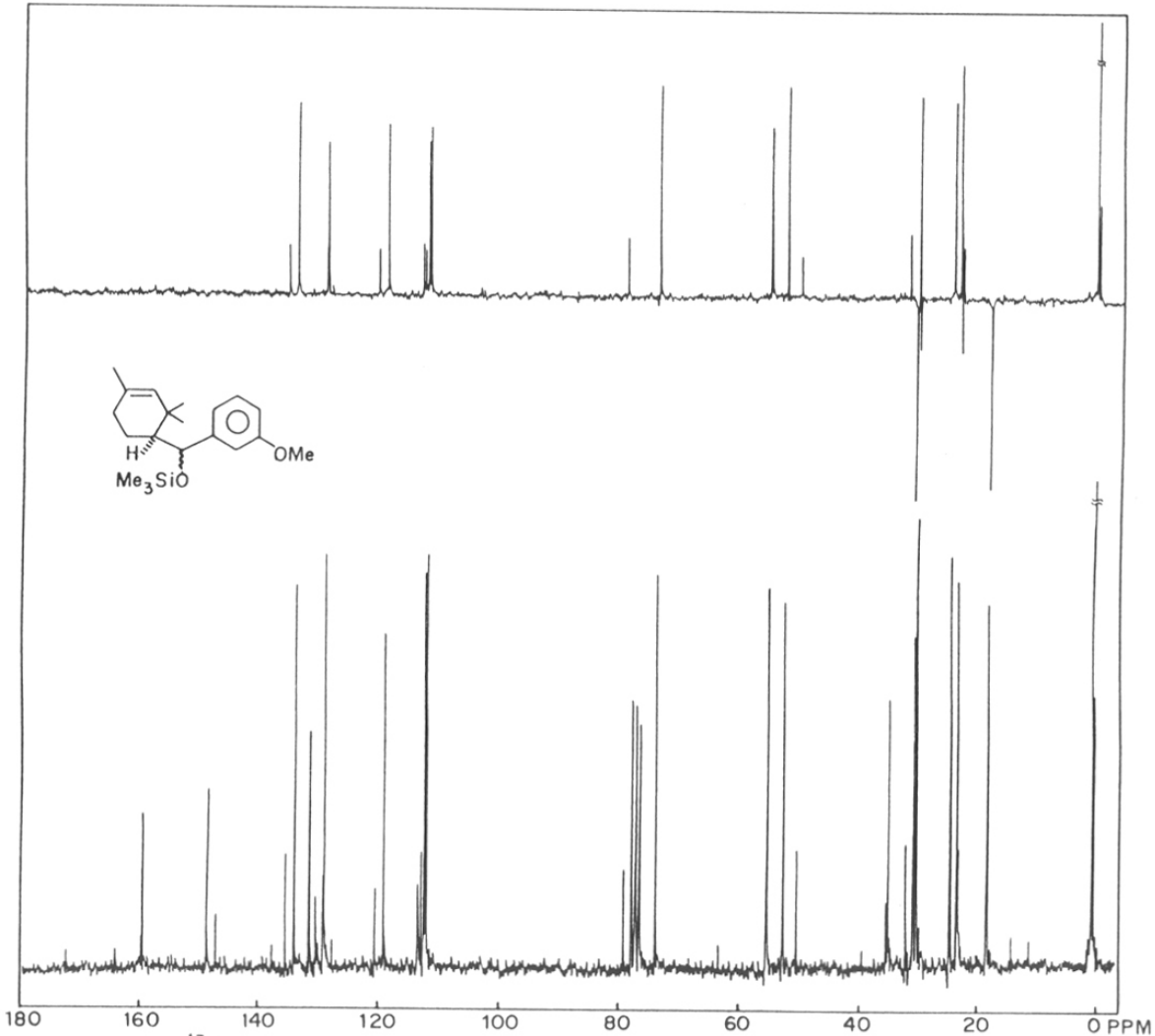




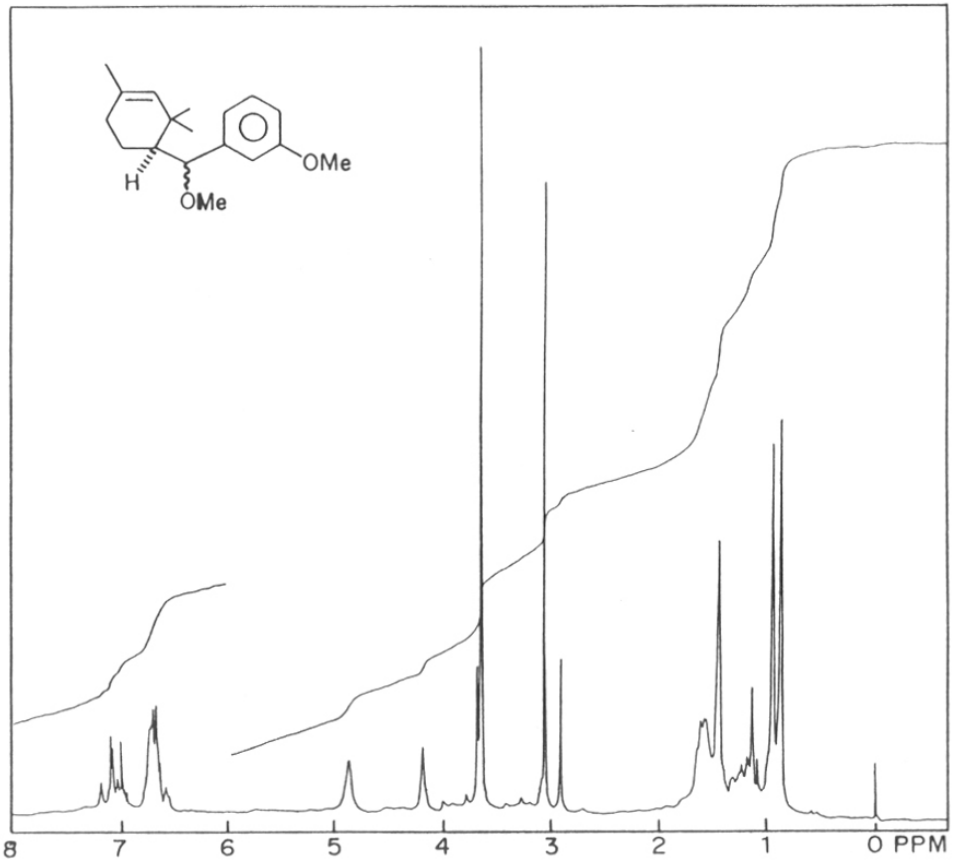
X-RAY STRUCTUR OF COMPOUND **73**



^{1}H-NMR SPECTRUM OF SILYL ETHER OF COMPOUND (**68**)



^{13}C-NMR SPECTRUM OF SILYL ETHER OF COMPOUND (**68**)



^{1}H-NMR SPECTRUM OF METHYLETHER OF COMPOUND (68)

PART III

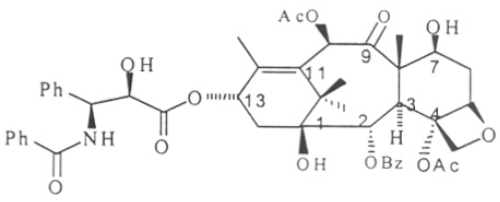
SYNTHETIC STUDIES TOWARDS BICYCLO [5.3.1.] UNDECANE RING SYSTEM.

Introduction

The two parts of this chapter discussed earlier (part I and part II) encompassed the synthesis of 2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde (both in racemic and chiral forms) and their utility in the diastereoselective synthesis of C-2 oxygenated "B-seco taxoids". This part deals with the attempted synthetic studies towards the bicyclo [5.3.1] undecane ring system starting from (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde.

The bicyclo [5.3.1] undecane ring system (**1**) is a key substructure of taxane natural products including taxol (**2**).

(1)



(2)

From this substructure, by suitable synthetic manipulations it should be possible to construct the taxane skeleton and thereby carry out a synthesis of taxol itself. Indeed many leading groups of organic chemists attempted to synthesize this bicyclo [5.3.1] undecane ring system. More in relevance with the contents of this chapter, Holton's three approaches will be discussed briefly. It is of importance to note at this stage that from bicyclo [5.3.1] undecane ring system,[97] Holton's group synthesized two of the most important taxane diterpenes, viz. taxusin[98] and taxol[4a] itself.

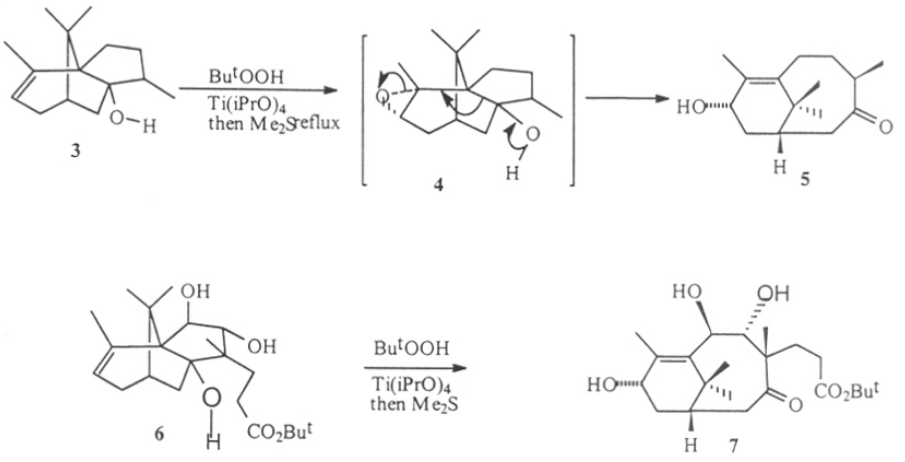
Wender et. al[4d] have reported very recently, a strategy based on the cleavage of strained psuedofunctional group (four-membered ring system) to furnish this bicyclic system and have extended this bicyclic system to the synthesis of taxol.

A convergent approach towards AB-ring system of taxol has been reported by Crich and Natarajan[99] via an efficient 8-exo-tet-alkylation of-α-sulfonyl anion.

One more convergent synthesis of AB-ring system is by Prange et al.[100], who made use of the synthon of Queneau (Chapter II, part I, section.1).

For the sake of brevity, other approaches will not be included or discussed here.

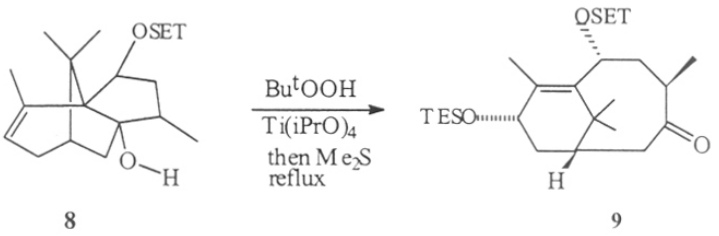
SCHEME-1



Holton's Approach to bicyclo [5.3.1] undecane ring system

In this approach, the key step is a rearrangement process involving a variant of Wharton fragmentation. In a model study, it was demonstrated that a hydroxyl epoxide intermediate (**4**) could undergo a fragmentation providing the bicyclo [5.3.1] undecane ring system. The same approach was further extended to the first total synthesis of taxusin and taxol.

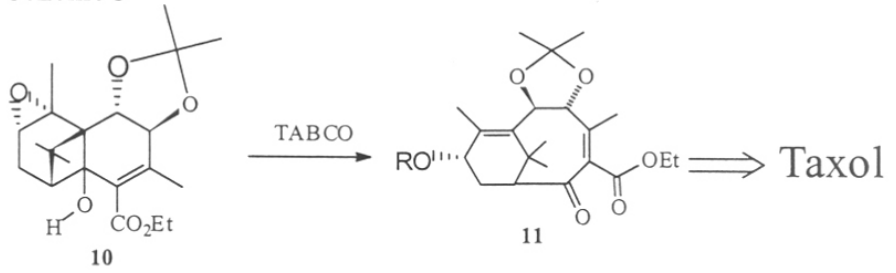
Scheme 2



Wender's Approach

Wender et. al have reported very recently, a strategy based on cleavage of strained four-membered ring using TABCO to furnish an eight-8-membered ring and extended this bicyclic system to the synthesis of taxol.

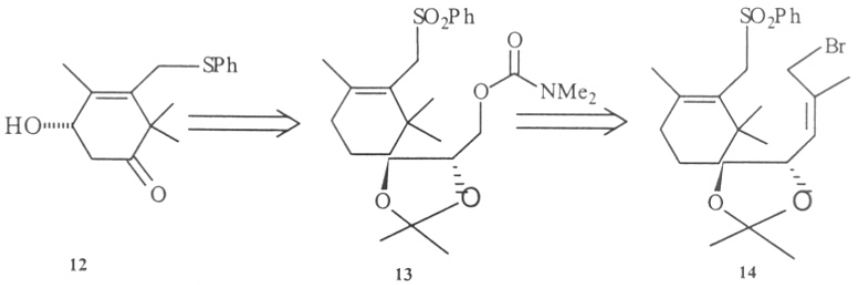
Scheme 3



Crich[99] et. al's convergent approach

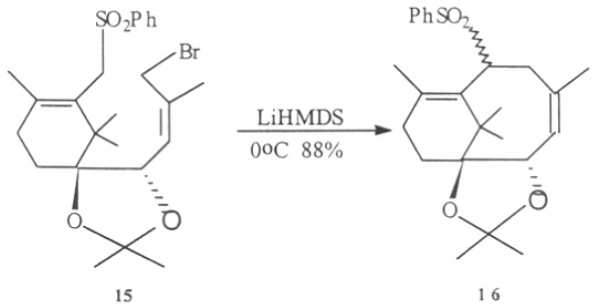
The required A-ring unit was synthesized on lines similar to Nicolaou's and the ring closure was effected at C9-C10.

Scheme 4



The crucial ring closure of (**15**) to give (**16**) was achieved with LiHMDS at 0°C to afford an 88% yield of (**16**). The cyclization was achieved via 8-exo-tet-alkylation of α-sulfonyl anion generated using LiHMDS.

Scheme 5



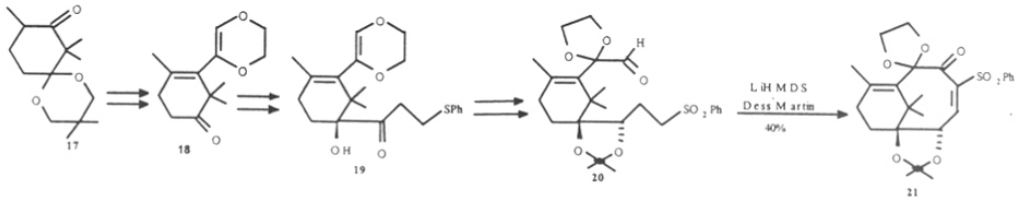
Prange's Approach

As mentioned earlier, the known A-ring synthon of Queneau was utilized in this approach and the B-ring closure was achieved at C8-C9. The bond between C10-C11 was effected using Pd cross coupling of dioxenyl-tri-n-butyl stannane to yield the

dienone (**18**). Michael addition of (**18**) with thiophenol yielded the phenylsulfide (**19**). The remaining sequence of reactions are shown in scheme (**6**).

The cyclization precursor (**20**) was cyclized to give (**21**) in moderate yields in the presence of LiHMDS.

Scheme 6

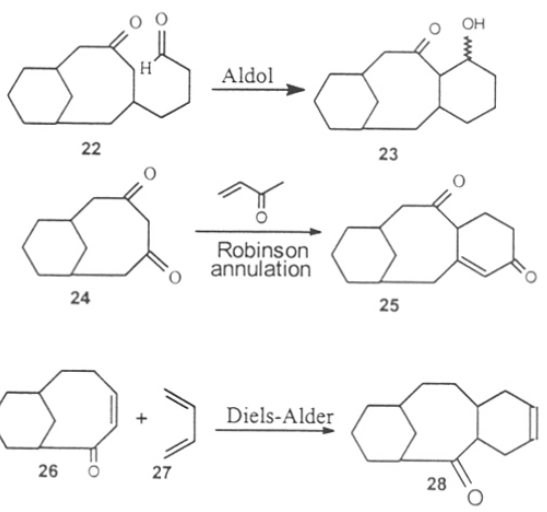


This approach has a number of synthetic manipulations as compared to Crich's approach with poorer yields. Crich's approach also suffers from the use of expensive reagents.

Objective

It is the objective of this present work to develop a method for the construction of 8-membered ring and utilise this in the form of AB-ring synthon (protaxoid) to construct taxane structure. The latter can be realised by appending the C-ring *via* aldol condensation, Robinson's annulation, Diels-Alder reaction etc.

Scheme 7



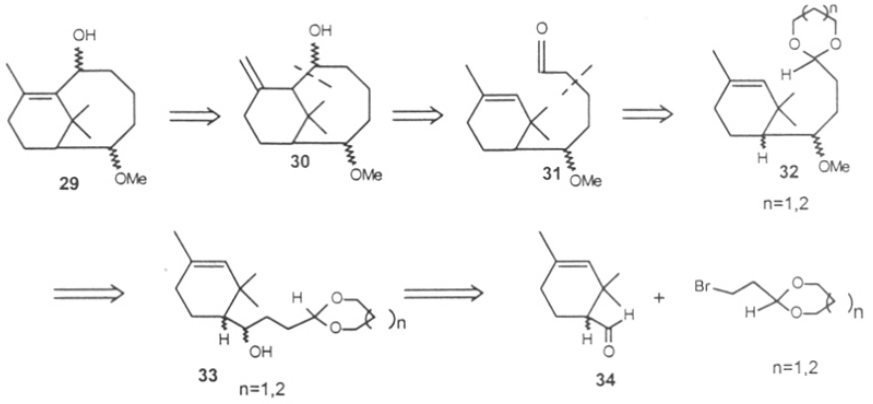
It was thus proposed to carry out the above transformation involving the construction of 8-membered ring as depicted below. The reactions involved would encompass Heck, carbonyl-ene and radical modes of cyclisation at C9-C10 and C10-

C11. However this method after construction of AB-ring, would be suitable for construction of alicyclic C-ring only and not of the aromatic C-ring. The model experiments thus designed would serve to study the feasibility of Heck reaction,[101] carbonyl-ene reaction[102] and radical modes of cyclisation[103] reactions.

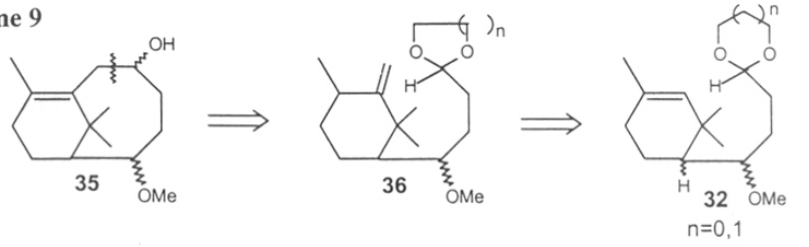
Experimental Design

Intramolecular carbonyl-ene reaction

Scheme 8

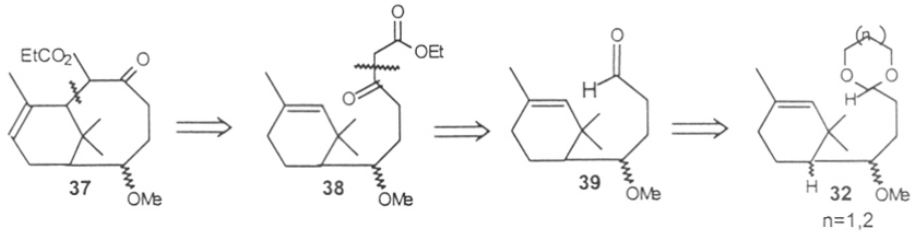


Scheme 9



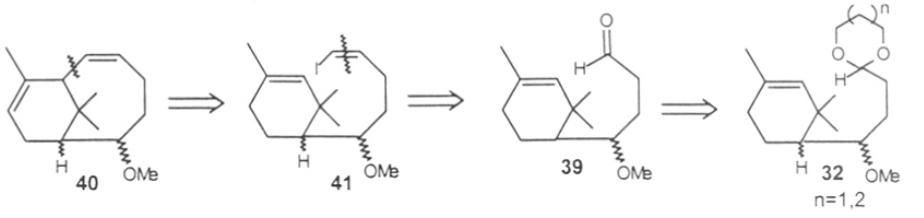
Radical mode of cyclization

Scheme 10

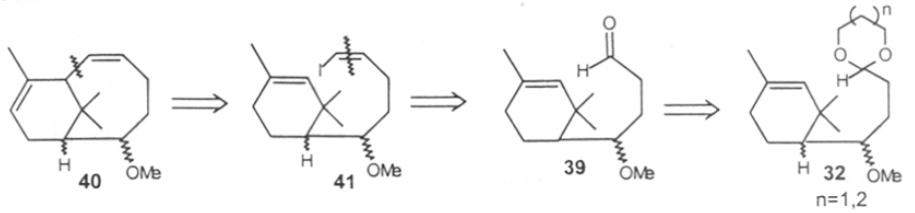


Heck-mode of cyclization

Scheme 11

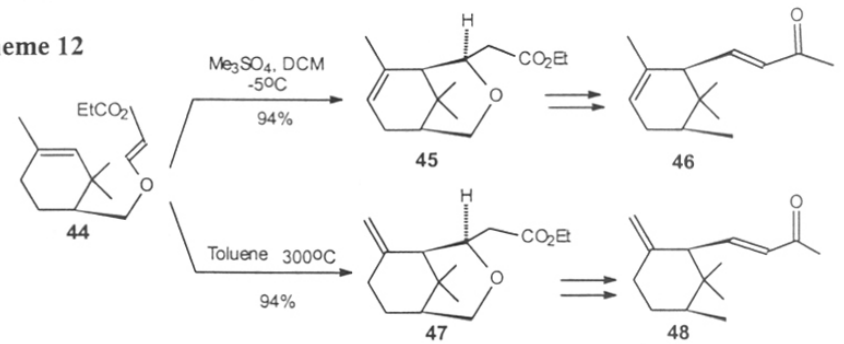


Scheme 11



The schemes that are shown using various approaches, derives further support from reactions already reported in literature. for e.g. Kato's synthesis of Cotylenol to realise 8 membered ring system (already discussed in part II), meta-mode of cyclization using ene-type reaction by Nussbaucer[104] et al. utilizing the same A-ring unit obtain cis-Irones.

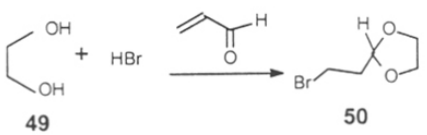
Scheme 12

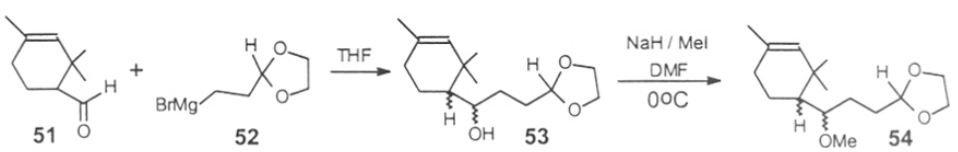


Present work

After clearly bringing out the objective of the work, it was thus decided to put the ideas to practice. The key intermediate which would effectively be utilized for all these types of reaction is (**39**). Accordingly, preparation of this compound was undertaken first.

Scheme 13





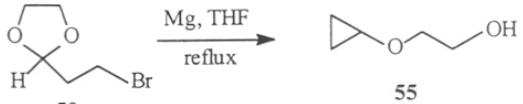
2-(2-Bromoethyl)-1,3-dioxolane[105] was prepared following the literature procedures by passing anhydrous hydrobromic acid to ethylene glycol followed by the

addition of acrolein. Usual workup and purification by distillation afforded the required three carbon synthon which was fully characterized.

2-(2-Bromoethyl)-1,3-dioxalane was then converted into a Grignard complex with Mg in THF, then it was reacted with (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde to yield the adduct (**53**). The adduct thus obtained had the following spectral values. IR spectrum showed an absorption at 3500 cm^{-1} for -OH group. ^{1}H-NMR spectrum revealed a singlet at 0.95 δ for geminal dimethyl protons, a broad singlet at 1.5-1.7 δ accounted for vinylmethyl protons and methylene protons, at 1.73 - 2.13 δ a multiplet appeared for six methylene protons and two methine protons, acetal methylene protons appeared as multiplet at 3.82 - 4.00 δ, acetal methine proton was found at 4.9 δ as a triplet and the vinylic proton was observed as a broad singlet at 5.05 δ.

Although 2-(2-bromoethyl)-1,3-dioxolane reacted with the C_{10}-aldehyde to afford the adduct in good yields, many a times the reaction failed and yielded a heterogeneous mass. A search through the literature revealed that, this could be due to the formation of cyclopropyl-(2-hyroxyethyl)-ether.[106]

Scheme 14

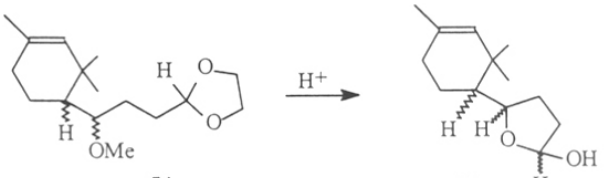


50 **55**

Hence, the reaction conditions were altered (slow addition of bromocompound and by controlling reaction condition by judicious heating and cooling) to obtain the required Grignard adduct (**53**) without any side-products.

The Grignard alcohol thus obtained was converted into its methyl ether (NaH-MeI/DMF) as shown in scheme **13**. This methylether (**54**) was fully characterized in the usual manner (vide experimental). It thus remained to deprotect the dioxolane moiety in (**54**), for further elaboration. Standard deprotection conditions (See part I, section 1) failed to yield the required aldehyde (**39**), instead, a compound was obtained in almost quantitatiave yields which was characterized as the lactol.

Scheme 15

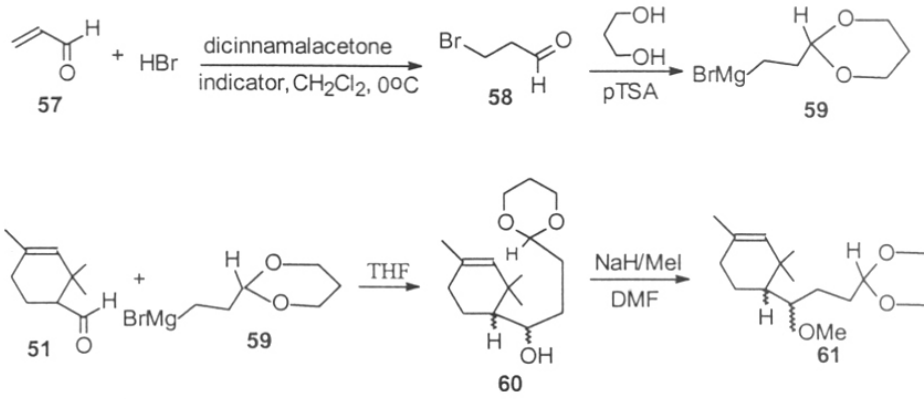


54 **56**

The IR and NMR spectral data of the lactol formed were in full agreement with the structure. IR spectrum confirmed the presence of -OH group at 3500 cm^{-1}. In ^{1}H-NMR two singlets at 0.87 and 0.92 δ were assigned to gem-dimethyl protons, a singlet at 1.65 δ integrated for five protons (vinyl methyl and two methylene protons), a multiplet at 1.72 - 2.23 δ accounted for seven protons comprising of six methylene proton and one methine proton. C-2 methine proton (taxol numbering is used) appeared as a multiplet at 4.15 δ, the vinylic proton appeared as a broad singlet at 5.05 δ and the carbinol proton as a broad double doublet at 5.45 δ (J = 8 Hz, 10 Hz).

Since the 2-(2-bromomethyl)-1,3-dioxolane was found to be thermal unstable under Grignard conditions, 2-(2-brmoethyl)-1,3-dioxane[107] was also prepared to furnish its Grignard adduct. The 2-(2-bromoethyl)-1,3-dioxane was prepared using Stowell's procedure (vide experimental).

Scheme 16

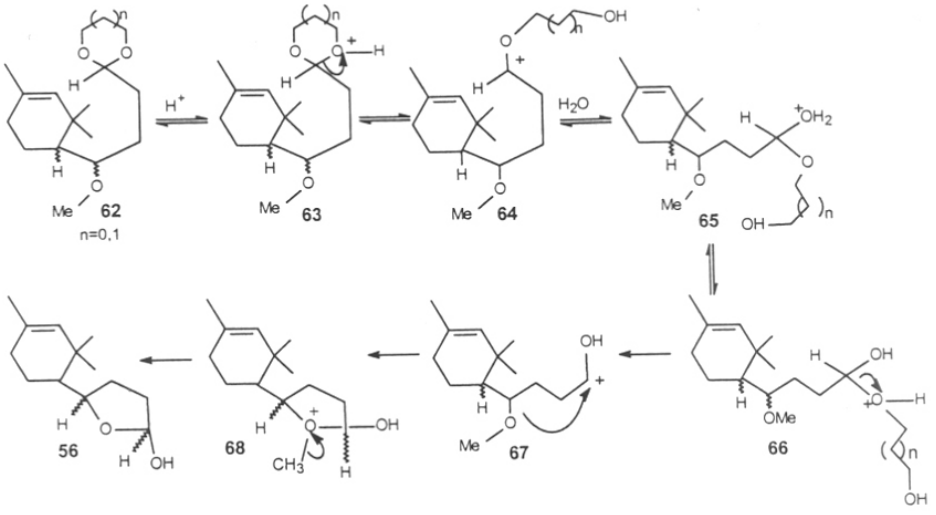


The bromo compound thus obtained was subjected to adduct formation with (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde under Grignard condition. The reaction underwent smoothly to furnish Grignard adduct in excellent yields; the adduct was well-characterized (vide. experimental). This Grignard adduct (**60**) was then converted into its methyl ether (**61**) under NaH-DMF/MeI conditions at 0°C (vide experimental) .

Attempted deprotection of dioxane moiety too furnished the unwanted lactol (**56**) whose structure was confirmed beyond doubt by spectral means..

The mechanism of lactol formation is represented below.

Scheme 17



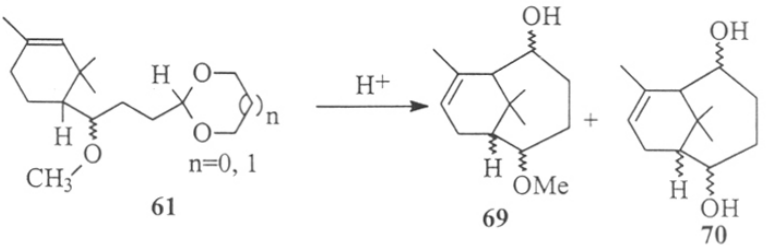
Results and Discussion

Several modes of cyclisation for the syntheses of 8-membered rings are reported in literature. Chief among them are Kato's, employing carbonyl-ene reaction[88], Pattenden's radical based method[108] Master's Heck-coupling based synthesis[78], White's synthesis of bicyclo [4.3.1] system[109] etc. Some of these methods prompted the initiation of the proposed synthesis of bicyclo[5.3.1] ring system of taxol *via* carbonyl-ene reaction, radical modes of cyclisation, Heck-coupling etc.

Efforts in these lines to achieve the target in the present work have been described in detail in this part of the chapter (Present work). Although the Grignard adducts from 2-(2-bromoethyl)-1,3-dioxolane and 2-(2-bromoethyl)-1,3-dioxane were obtained in excellent yields, they could not be carried over for further for synthetic manipulations, as the major product during deprotection of both (**54**) and (**61**) turned out to be lactol (**56**), resulting in unsuccessful attempts towards the expected goal.

In fact, at one stage during the deprotection, it was almost felt that a product like (**69, 70**) was obtained, but it turned out to be a wishful thinking only! From the IR spectral data, it appeared that the required deprotection followed by intramolecular carbonyl-ene reaction had occurred. Due to the complete absence of -OCH_3 protons in the ^{1}H-NMR and due to the fact that the mass spectral data were not in conformity with the structure (**69, 70**), occurrence of a reaction a shown below was proposed.

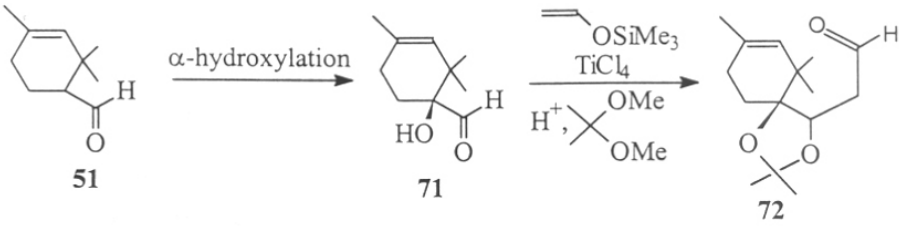
Scheme 18



All the spectra data were in full conformity with the structure proposed (vide experimental). Generally it is expected that a methoxy group is one of the most stable protecting groups of a hydroxyl functionality. Therefore, the results obtained were unexpected, which thwarted further efforts in proceeding with the proposed scheme.

Currently, work on functionalisation at C-1 (taxol numbering is used) followed by other synthetic manipulations to furnish an intermediate like (**72**) is in progress. On this, intermediate various reactions like Heck, ene, radical cyclisations etc can be carried out to effect the desired cyclisation to give a 8-membered ring.

Scheme 19



Conclusion

Some valuable educative hints have been obtained during the unsuccessful exercise mentioned in this part. A lot of hard work and many experiments that were carried out, led to plenty of disappointments and disillusions. Yet a feeling of inner satisfaction remains, mainly due to that behind every success, there is a big story of failure! The knowledge derived from these failures will hopefully go a long way in preparing one towards future endeavors of similar type.

It is hoped that some of these results will serve as a beacon of light for future successes.

Experimental

Synthesis of 2-(2-bromoethyl)-1,3-dioxalone (50)

In a 500 ml, round-bottomed flask fitted with a gas-inlet and outlet (having guard-tube filled with anhydrous calcium chloride) was taken 200.0 g of ethylene glycol, (3.25 mol), to which anhydrous hydrogen bromide (generated by the addition of bromine on tetralin) was passed at 0°C till the weight of the contents were reached 320.0 g. The amount of anhydrous hydrogen bromide passed was 120.0 g (1.5 mol). After the addition of 1.5 mol of hydrogen bromide was over, 56.0 g of acrolein (1 mol) was added rapidly via a syringe needle. The reaction mixture was then allowed to stir for 1 hour at room temperature.

The total reaction mixture was extracted diethylether (3 x 150 ml), the combined organic layer was washed with 5% aqueous $NaHCO_3$ (3 x 50 ml), washed with (3 x 10 ml), brine (3 x 5 ml) and dried over anhydrous sodium sulphate. The extract was concentrated on a rotatory evaporator and the residue was distilled under reduced pressure to afford pure 2-(2-bromoethyl)-1,3-dioxolane.

Yield	:	109.5g (61%)
B.P.	:	68-70°C (at 8 mm Hg) (Lit.[105] 68-70°C at 8 mm Hg)
IR (Neat, cm^{-1})	:	2870, 1250, 1150, 1140, 1015.

^{1}H-NMR (200 MHz) : δ 2.13 (d of t, 2H, J = 4.5, 7 Hz, -$\underline{CH_2}$-); 3.43 (t, 2H, J = 7 Hz, -$\underline{CH_2}$-Br); 3.83 (m, 4H, -O-$\underline{CH_2}$-$\underline{CH_2}$-O)); 4.88 (t, 1H, J = 4.5, -O-$\underline{CH}$-O-).

Grignard reaction of 2-(2-bromoethyl)-1,3-dioxolane with (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde (53)

The Grignard complex was prepared from 2-(2-bromoethyl)-1,3-dioxolane (4.0 g, 2.6 ml, 22.1 mmol) in an anhydrous tetrahydrofuran (15 ml) by reacting it with activated magnesium turnings (0.70 g, 29.2 mmol) and by taking due care that the reaction mixture did not reflux. The resultant mixture was stirred for an additional one hour at room temperature, then cooled to 0°C using an ice-salt bath. To this cooled solution, (±)-2,2,4-trimethyl cyclohex-3-ene-1-carbaldehyde (3.0 g, 19.9 mmol) in 15 ml of anhydrous tetrahydrofuran was added during 10 minutes while maintaining the temperature at 0°C. The reaction mixture was then stirred at room temperature for 6 hours. Progress of the reaction was monitored by thin layer chromatography. The total reaction mixture was then poured into an ice-cold solution of 50 ml of saturated ammonium chloride. The tetrahydrofuran layer was separated and the aqueous layer was immediately extracted with diethylether (3 x 100 ml). The combined organic layer was washed with water (3 x 2 ml), brine (3 x 5 ml) and dried over anhydrous sodium carbonate. Distillation of the solvent and concentration on rotary evaporator gave a thick yellowish residue which was purified by column chromatography. Distillation at diminished pressure yielded the pure alcohol as a light coloured liquid.

Yield : 4.6 g (91%)

B.P. : 150°C-152°C at 0.1 mm Hg

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 3500(b), 2900 (b), 1400, 1150, 1000.

^{1}H-NMR (200 MHz) : δ 0.95 (s, 6H, C-($\underline{CH_3}$)$_2$); 1.5-1.71 (br.s, 5H, C=$\underline{CH_3}$ and 1 x $\underline{CH_2}$); 1.73-2.13 (m, 8H, 3 x $\underline{CH_2}$, 2 x $\underline{CH}$); 3.82-4.0 (m, 4H, -O-$\underline{CH_2}$-$\underline{CH_2}$-O-); 4.9 (t, 1H, -O-C$\underline{H}$-O-); 5.05 (s, 1H, C=C-$\underline{H}$).

Mass (m/z) : 253 (M^{-1},2); 236(4), 221(2); 208(2); 192(40); 185(2); 177(6); 168(4); 159(38); 148(35); 131(29); 121(45); 109(42); 96(42); 96(75); 87(42); 81(95); 73(89); 69(100); 55(52).

Analysis : Calculated: C: 70.83%; H: 10.30%

Found : C: 70.51%: H: 10.15%

Synthesis of methyl ether from the Grignard alcohol obtained by the reaction between 2(2-bromoethyl-1,3-dioxolane and (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde (54)

In a 50 ml round-bottomed flamed flask fitted with a reflux condenser, septa and equipped with a magnetic bar was placed 60 per cent sodium hydride (0.826 g, 20.66 mmol) dispersed in mineral oil. The sodium hydride was washed with anhydrous petroleum ether (5 x 2ml). To the washed sodium hydride 6 ml of anhydrous dimethylformamide was charged via a syringe needle. The contents were cooled to 0°C with ice-salt bath. A 2 ml solution of the Grignard alcohol (**52**) (2.5 g, 9.8 mmol) in DMF was added to sodium in dimethyl formamide over a period of ten minutes. Then, the reaction mixture was warmed to room temperature and stirred for 30 minutes. It was again cooled to 0°C and iodomethane (4.2 g, 29.5 mmol) was introduced at 0°C. The reaction mixture was warmed for six hours at 60°C during which time ice-cold water was circulated in the condenser and the progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled to 0°C, 20 ml of saturated ammonium chloride was added and then the resultant mixture was stirred for 10 minutes. The contents were extracted with diethylether (3 x 30 ml), washed with water (3 x 2 ml), brine (3 x 2 ml) and dried over anhydrous sodium carbonate. The solvent was distilled off on a rotatory evaporator and the residual material was chromatographed over silica gel. The product material thus obtained was further purified by distillation under diminished pressure to furnish a light yellow coloured viscous oily liquid.

Yield : 2.52g, (96%)

B.P. : 130°C-132°C at 0.1 mm Hg

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 2950, 1450(s), 1380, 1250, 1200.

^{1}H NMR (200 MHz) : δ 1.92 (s, 3H, C-$\underline{CH_3}$); 1.98 (s, 3H, C-$\underline{CH_3}$); 1.52-1.77 (m, 5H, C=C-$\underline{CH_3}$, 1 x $\underline{CH_2}$); 1.87-1.95 (m, 8H, 3 x $\underline{CH_3}$, 2 x $\underline{CH}$); 3.4 (s, 3H, -C-O-$\underline{CH_3}$); 3.75-4.02 (m, 4H, -O-$\underline{CH_2}$-$\underline{CH_2}$-O-); 4.85 (t, 1H, acetal methine proton); 5.05 (s, 1H, C=C-$\underline{H}$).

Mass (m/z) : 267 (2); 253(1); 236(16); 231(1; 221(3); 206(4); 92(6); 174(14); 167(7); 159(28); 145(47); 133(24); 121(23); 113(100); 107(13); 96(33); 86(24); 81(33); 77(22); 73(69); 59(30); 55(31).

Analysis : **Calculated** C= 71.61%; H = 10.44%

Found C=71.42%; H= 10.31%

Attempted deprotection of dioxolane moiety from the methoxydioxolane compound (56)

In a 50 ml round-bottomed flask, the methoxy dioxolane compound (**54**) (1.2g, 4.47 mmol) dissolved in 10 ml of distilled tetrahydrofuran and 5 ml of distilled water was taken. To this p-toluene sulfonic acid (0.08 g) was added and the reaction mixture was heated to reflux for 3 hours. The contents were concentrated in vacuo and the residue obtained was extracted with diethylether (3 x 25 ml).

The combined organic layer was washed with saturated sodium carbonate (3 x 2ml), water (3 x 2 ml) and brine (3 x 2 ml). The dried (over anhydrous sodium carbonate) ether solution was concentrated on a rotatory evaporator and the residue obtained was chromatographed over silica gel. Distillation of the product obtained from chromatography yielded the lactol (**56**) as a colourless liquid.

Yield : 0.77 g, (87%)

B.P. : 140°C-142°C at 0.1 mm Hg.

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 3500 (b); 2980; 1440; 1320, 1180.

^{1}H-NMR (200 MHz) : δ 0.87 (br.s, 3H, C-$\underline{CH_3}$);0.92 (br.s, 3H-C-$\underline{CH_3}$); 1.6 (br.s, 5H, C=C-$\underline{CH_3}$, 1 x $\underline{CH_2}$); 1.72-2.23 (m, 7H, 3 x $\underline{CH_2}$, 1 x $\underline{CH}$); 4.15 (m, 1H, $\underline{H}$-C-O-CH-OH); 5.05 (br.s, 1H, C=C-$\underline{H}$); 5.45 (br.dd, 1H, J = 8 Hz, 10 Hz, -O-C$\underline{H}$-OH).

Mass (m/z) : 209 (M^+,2); 193(10); 176(7); 149(8); 148(10); 133(29); 121(48); 107(39); 92(50); 81(32); 107(39); 92(50); 81(32); 71(100); 55(52).

Preparation of dicinnamalacetone indicator

A solution of 5 g of sodium hydroxide in 50 ml of water and 40 ml of ethanol was prepared at 0°C in a 250 ml. Erlenmeyer flask. To this mixture was added a solution of 1.84 ml of (0.025 mmol, 1.45 g) of acetone in 6.3 ml (0.050 mol, 6.6 g) of freshly distilled cinnamaldehyde. This mixture was stirred thoroughly at room temperature for 30 minutes.

The resulting voluminous yellow precipitate was filtered with suction, washed with 100 ml of water and dried to furnish 6.5 g of 1,9-diphenylnona-1,3,6,8-tetraen-5-

one (dicinnamalacetone). The material thus obtained was recrystallized from 200 ml of hot 95% ethanol to yield 3.5 g of yellow crystals.

M.P. : 142-143°C (lit.[110] m.p. 142°C).

Synthesis of 2-(2-bromoethyl)-1,3-dioxane (59)

In a one litre, three-necked round bottomed flask equipped with a mechanical stirrer, thermometer and gas inlet tube were placed 375 ml of anhydrous dichloromethane, 56.0 g, (1.0 mmol) of freshly distilled acrolein, and 0.05 g of dicinnamalacetone indicator, under nitrogen. The resulting yellow solution was cooled to 0°C in an ice-salt bath. To this reaction mixture, anhydrous hydrogen bromide (generated by the addition of bromine on tetralin) was bubbled until the indicator showed deep-red coloration.

The ice-bath was removed and 0.05 g of p-toluene sulfonic acid monohydrate and 76.0 g, (1.00 mol, 72 ml) of 1,3-propanediol were added. The yellow solution was stirred at room temperature for 8 hours.

The total reaction mixture was concentrated in a rotatory evaporator. The residual oil thus obtained was diluted with 250 ml of diethylether, washed with saturated aqueous sodium bicarbonate (2 x 125 ml) and dried over anhydrous potassium carbonate. The ethereal layer was concentrated on a rotary evaporator and the residual oil was distilled in vacuo through a Vigreux column to afford 2-(2-bromoethyl)-1,3-dioxane as a colourless liquid.

Yield : 126.0g; 65%

B.P. : 73-77°C at 2.0 mm Hg (Lit.[107] b.p. 72-75°C at 2.0 mm Hg).

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 2980; 2870; 1250; 1150; 1140; 1015.

^{1}H NMR (200 MHz) : δ 1.38 (d of m, 1H, one 5-position on dioxane ring); 1.8-2.4 (m, the other 5 position on the dioxane ring); 2.14 (d of t, 2H, $\underline{CH_2}$-C-Br); 3.45 (t, 2H, $\underline{H_2}$C-Br); 3.80 (d of t, 2H, 4 and 6-positions on ring); 4.15 (d of double d, 2H, 4 and 6-positions on ring); 4.71 (t, 1H, 2-position on ring).

Grignard reaction between 2-(2-bromoethyl)-1,3-dioxane and (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde (60)

The Grignard complex was prepared under an argon atmosphere from 2-(2-bromoethyl)-1,3-dioxane (4.31 g, 22.1 mmol) and activated magnesium turnings (0.70

g, 29.2 mmol) in 20 ml of anhydrous tetrahydrofuran. The Grignard complex mixture thus obtained was cooled to 0°C and to this mixture (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde (3.0 g, 19.9 mmol) in 20 ml of tetrahydrofuran was added at 0°C and the resultant mixture was stirred at room temperature for 6 hours. Usual workup followed by chromatographic purification and distillation under reduced pressure afforded the alcohol (**60**) as a colourless oil.

Yield : 4.86 g, (92%).

B.P. : 160-163°C at 0.1 mm Hg

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 3500 (b); 2900(b); 1400, 1150, 1000.

^{1}H NMR (200 MHz) : δ 0.9 (s, 6H, C-($\underline{CH_3}$)$_2$); 1.3 (m, 2H, -$\underline{CH_2}$-from dioxolane ring); 1.65 (br.s, 5H, C=C-$\underline{CH_3}$; 1 x $\underline{CH_2}$); 1.75-2.24 (m, 7H, 3 x CH_2, 1 x $\underline{CH}$); 3.75 (m, 2H, -$\underline{CH_2}$-from dioxane ring); 4.05-4.11 (m, 2H, -$\underline{CH_2}$-from dioxane ring); 4.50 (t, 1H acetal methine proton); 5.01 (s, 1H, C=C-$\underline{H}$).

Mass (m/z) : 267 (M^{+1}, 2); 239(10), 229(1); 218(1); 207(1); 192(4); 177(3); 159(8); 148(5); 133(4); 120(7); 107(10); 96(13); 87(87); 81(40); 77(37); 71(100); 59(52).

Analysis : **Calculated** C=71.60%; H=10.52%

Found C=71.23%; H=10.45%.

Methylation of Grignard product (60) obtained from 2-(2-bromoethyl)-1,3-dioxane with (±)-2,2,4-trimethylcyclohex-3-ene-1-carbaldehyde (61)

In a 50 ml round-bottomed flask was taken 60 per cent sodium hydride (0.432 g, 10.33 mmol) dispersed in mineral oil under an argon atmosphere. The sodium hydride was washed with anhydrous petroleum ether and 6 ml of dry dimethylformamide was added and cooled to 0°C. A 6 ml anhydrous dimethylformamide solution of Grignard alcohol (60) (2.65 g, 6.9 mmol) was added to the sodium hydride at 0°C and the mixture was stirred at room temperature for 30 minutes. The contents were cooled again to 0°C to which iodomethane (2.1g, 14.7 mmol) was added and the reaction mixture was stirred under reflux for 6 hours. Usual up followed by chromatographic purification and distillation of the product obtained afforded the methylated product was a colourless oil.

Yield : 2.7 g, (96%)

B.P. : 142-146°C at 0.1 mm Hg.

IR (Neat, cm^{-1}) : $\sqrt{}_{max}$ 2950, 1450 (s), 1380, 1250, 1000.

^{1}H NMR (200 MHz) : δ 0.88 (s, 3H, C-$\underline{CH_3}$); 0.93 (s, 3H, C-$\underline{CH_3}$); 1.25 (s, 2H, -$\underline{CH_2}$-from the dioxane ring); 1.5-1.72 (m, 5H, C=C-$\underline{CH_3}$, 1 x $\underline{CH_2}$); 1.81-2.2 (m, 7H, 3 x $\underline{CH_2}$, 1 x $\underline{CH}$); 3.24 (s, 3H, -O-$\underline{CH_3}$); 3.45 (m, 1H, $\underline{H}$-C-O-CH_3); 3.72 (t, 2H, J = 6.2 Hz, -$\underline{CH_2}$- from the dioxane ring); 4.1 (m, 2H,-$\underline{CH_2}$-from the dioxane ring); 4.62 (t, 1H, J=4.5Hz, acetal methine proton);

Mass (m/z) : 281(M^{-1}, 2); 267(1); 250(6); 206(3); 192(14); 174(8); 167(4); 159(52); 148(32); 133(23); 121(32); 107(20); 96(34); 91(36); 87(27); 81(47); 71(100); 55(26).

Analysis : **Calculated** C=72.29%; H=10.76%
Found C=71.98%; H=10.78%

Attempted deprotection of the dioxane moiety from methoxy dioxane compound (56)

In a 50 ml round-bottomed flask, the methoxydioxane compound (**61**) (1.25 g, 4.47 mmol) dissolved in 10 ml of tetrahydrofuran and 5 ml of water was taken. To mixture this p-toluene sulfonic acid (0.08g) was added and the resultant mixture was heated to reflux for 3 hours. The contents were concentrated in vacuo and the residue obtained was extracted with diethylether (3 x 20 ml). The combined organic layer was washed with sodium bicarbonate (3 x 2ml), water (3 x 2 ml), brine (3 x 2 ml) and dried over anhydrous sodium carbonate.

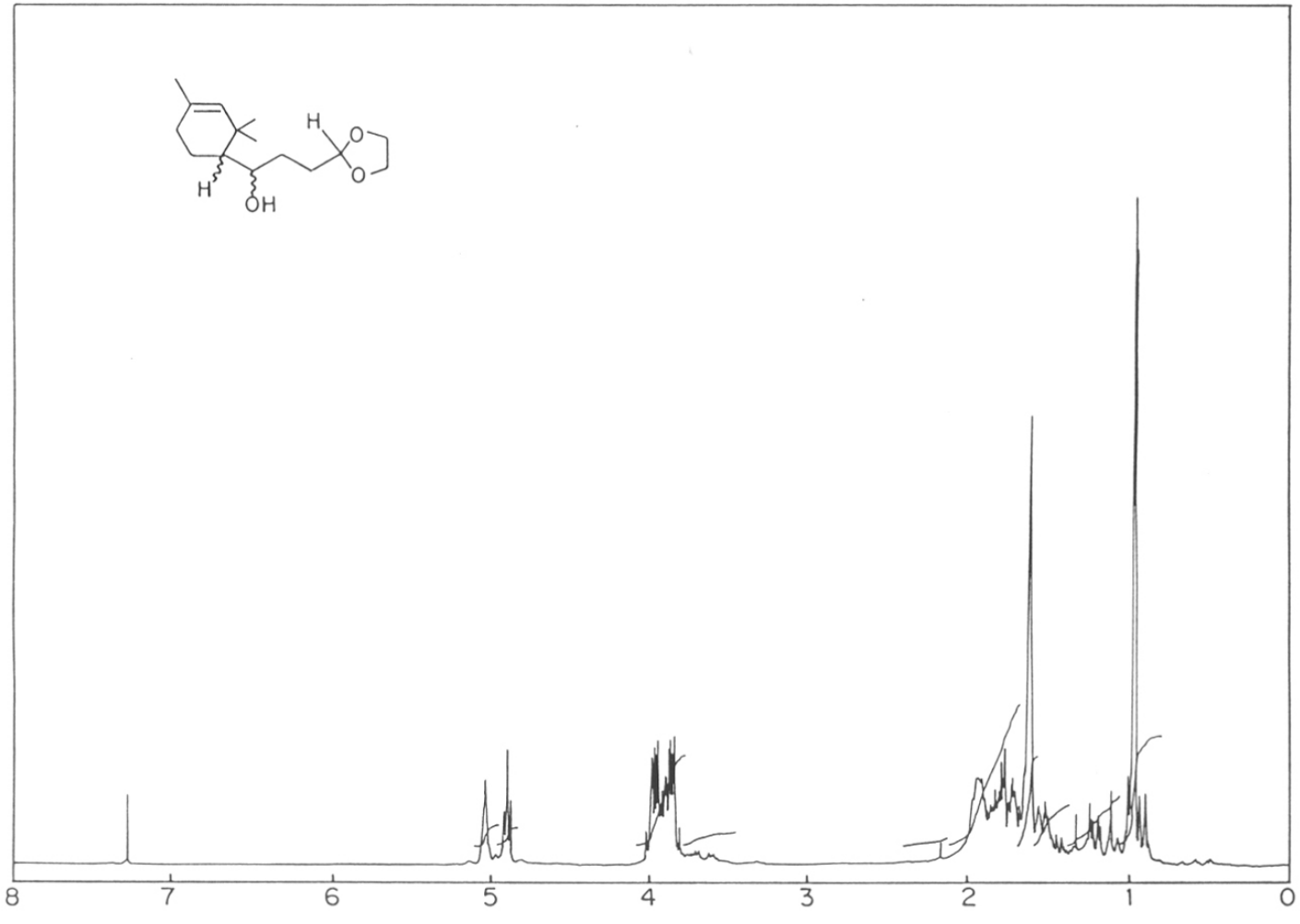
The ether extract was concentrated on a rotary evaporator and the residue obtained was chromatographed over silica gel. Distillation of the product obtained from chromatography yielded the lactol (**56**) as a colourless oily liquid.

Yield : 0.77g (87%)

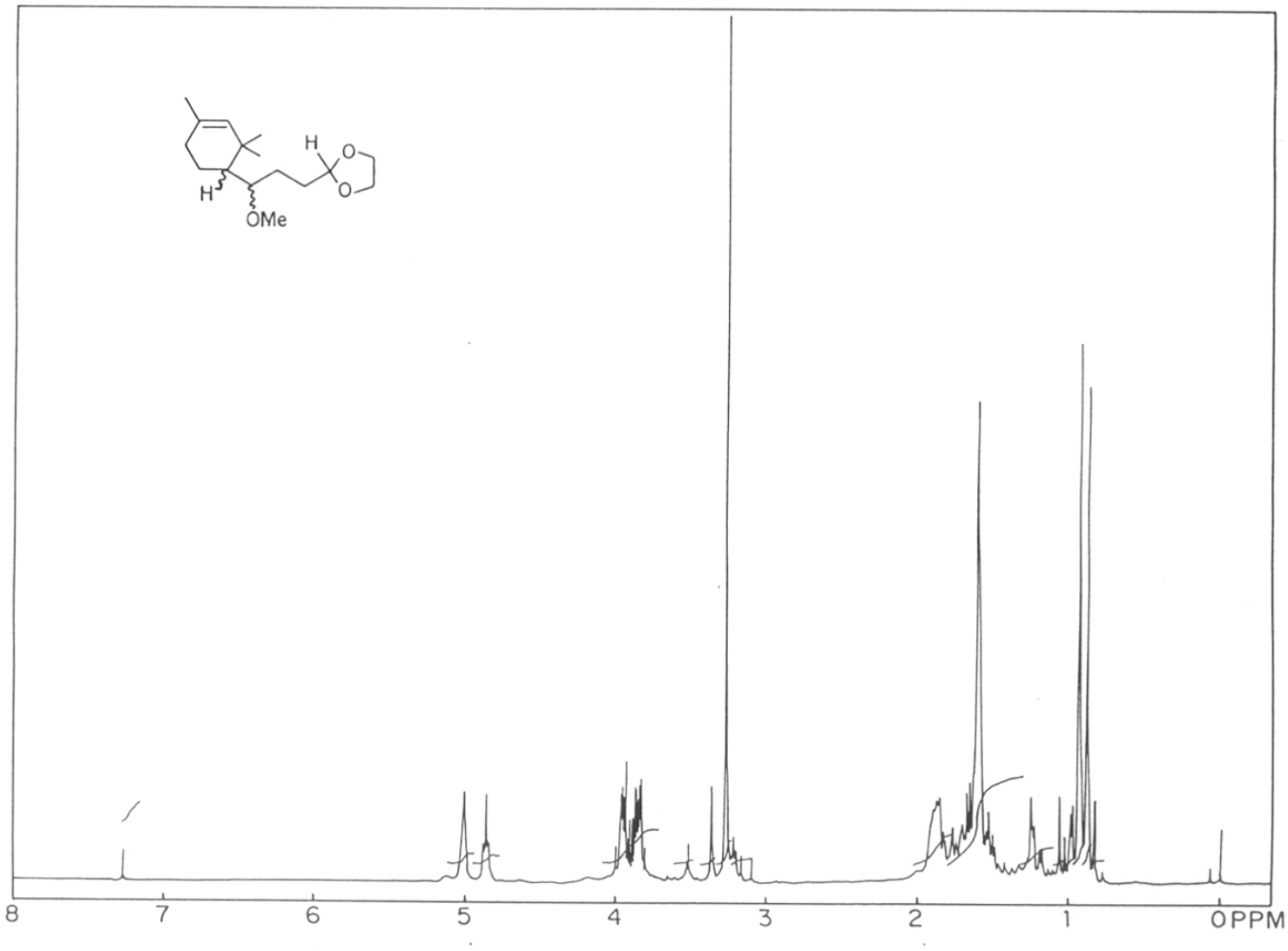
B.P. : 140°C-142°C at 0.1 mm Hg.

IR (Neat, cm^{-1}) : $\sqrt{_{max}}$ 3500 (b); 2980; 1440; 1320, 1180.

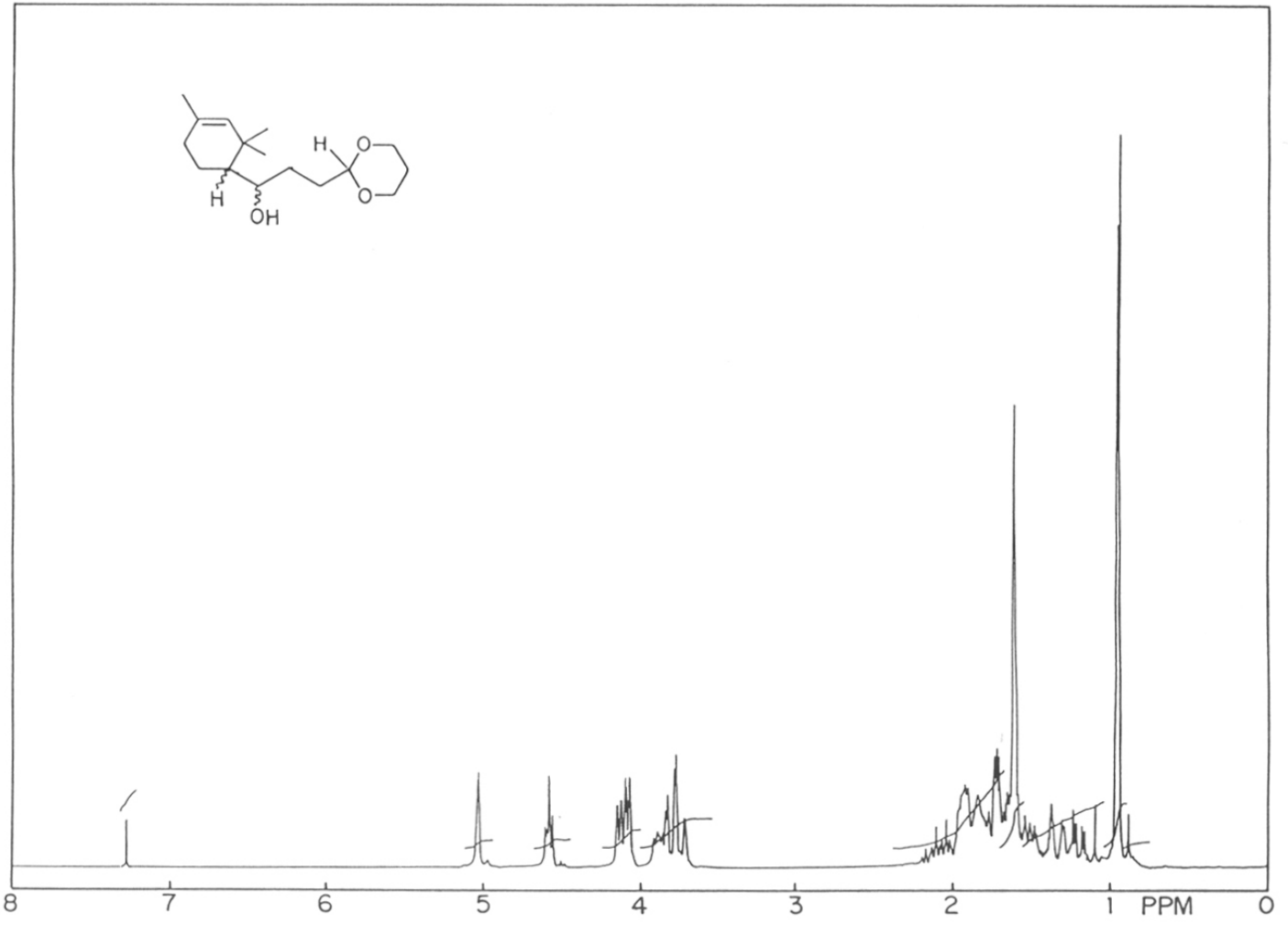
^{1}H-NMR (200 MHz) : δ 0.87 (br.s, 3H, C-$\underline{CH_3}$);0.92 (br.s, 3H-C-$\underline{CH_3}$); 1.6 (br.s, 5H, C=C-$\underline{CH_3}$, 1 x $\underline{CH_2}$); 1.72-2.23 (m, 7H, 3 x $\underline{CH_2}$, 1 x $\underline{CH}$); 4.15 (m, 1H, $\underline{H}$-C-O-CH-OH); 5.05 (br.s, 1H, C=C-$\underline{H}$); 5.45 (br.dd, 1H, J = 8 Hz, 10 Hz, -O-C$\underline{H}$-OH).



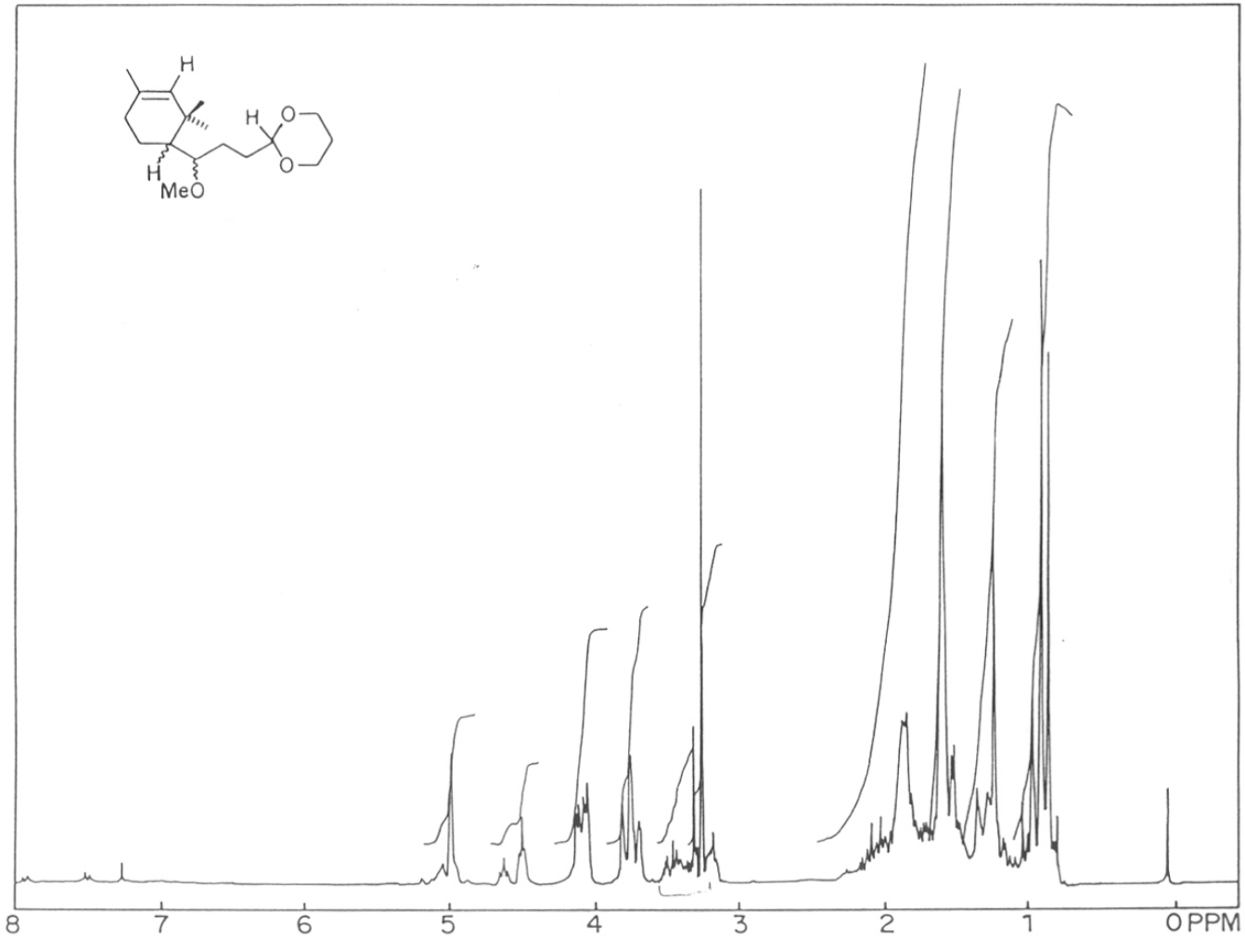
^{1}H-NMR SPECTRUM OF COMPOUND **53**



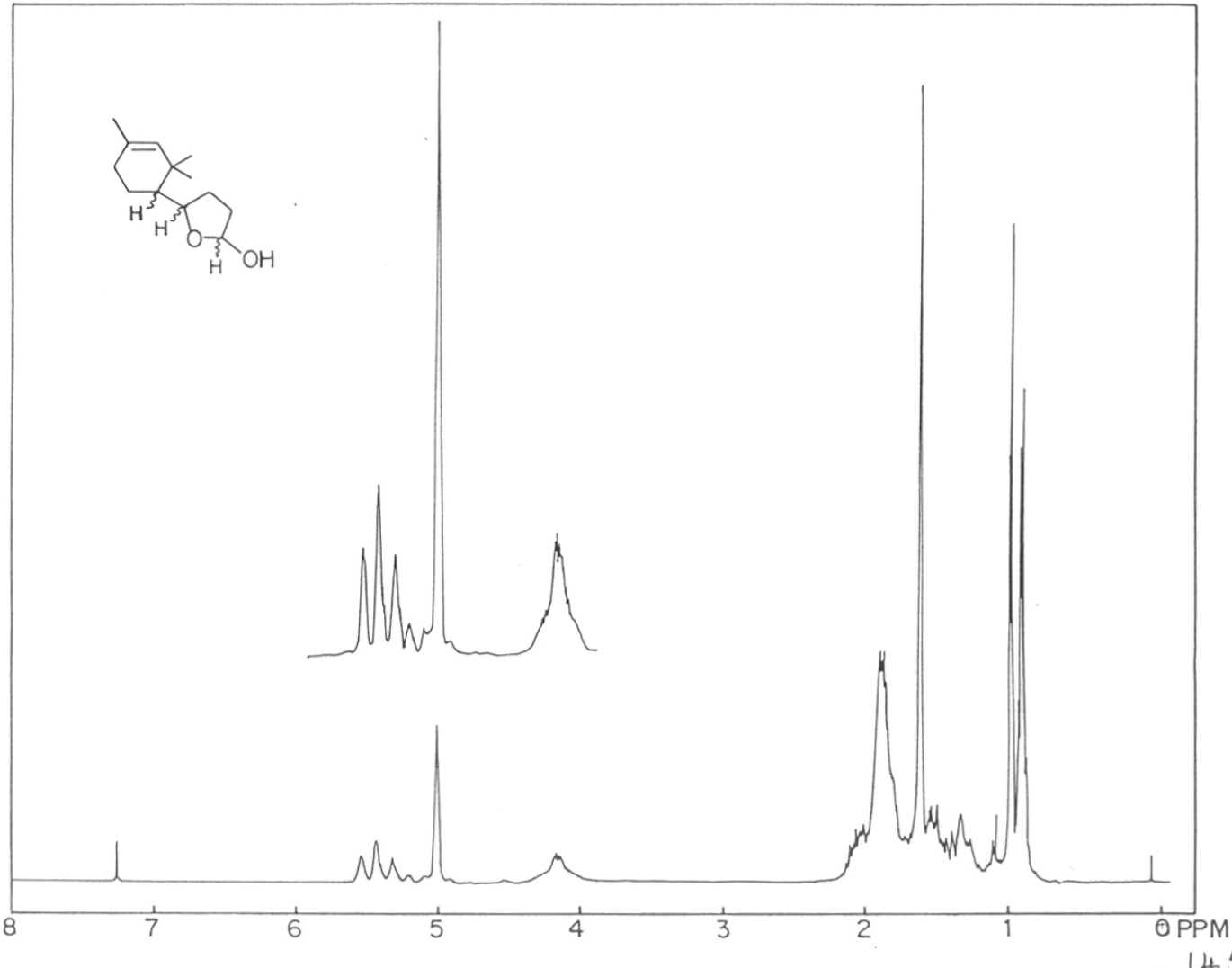
^{1}H-NMR SPECTRUM OF COMPOUND **54**



^{1}H-NMR SPECTRUM OF COMPOUND **60**



^{1}H-NMR SPECTRUM OF METHYL ETHER OF COMPOUND **60**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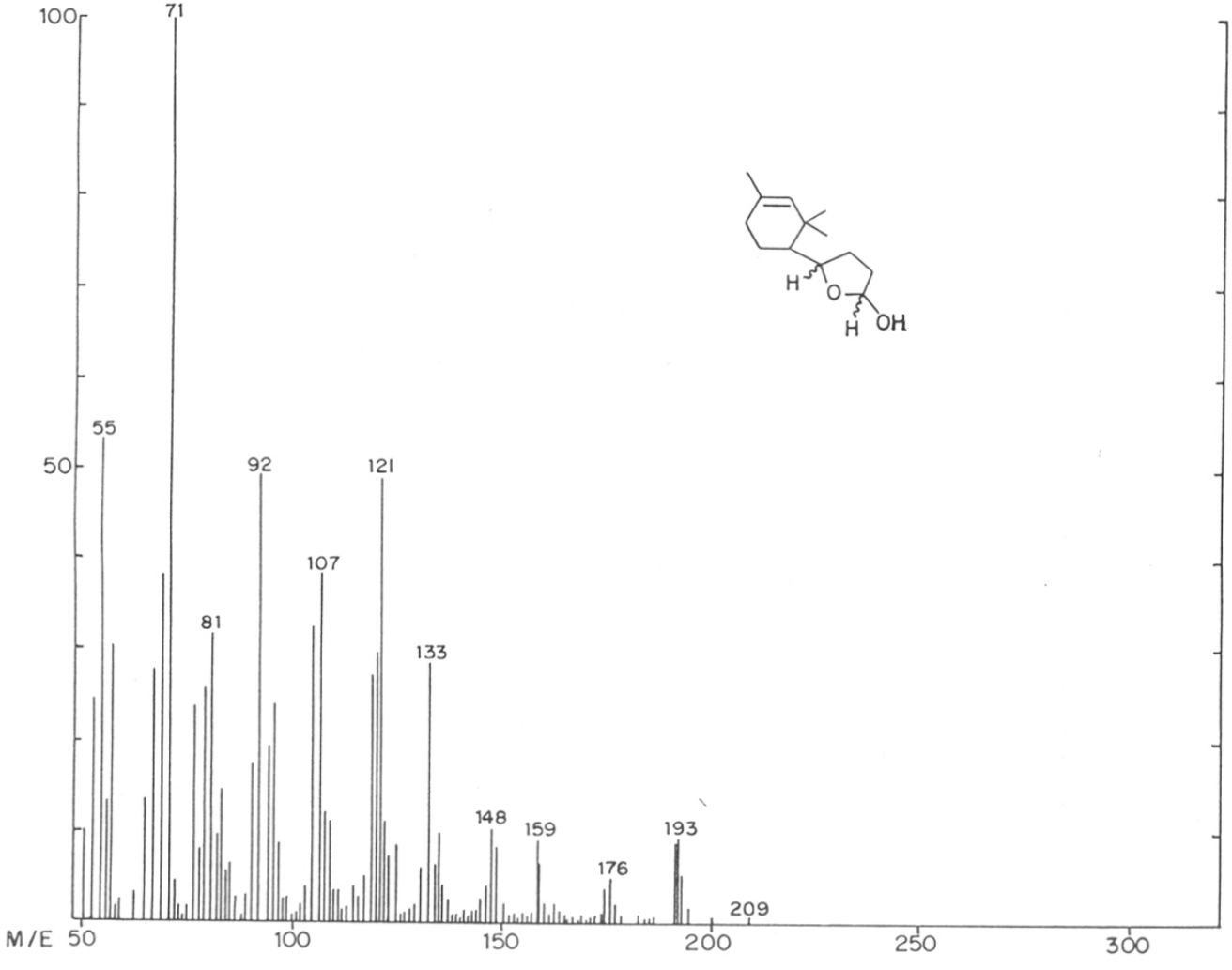

MASS SPECTRUM OF LACTAL

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CHAPTER III

ORGANIC FUNCTIONAL GROUP TRANSFORMATION USING HOMOGENEOUS AND HETEROGENEOUS CATALYSIS

This chapter deals with the "**Organic Functional Group Transformations using homogeneous and heterogeneous catalysis**", and it is divided into three parts of the three parts. The first two parts are focussed on heterogeneous catalysis. The first part of this chapter is divided into two sections and both the sections highlight the oxidation of phenol to p-benzoquinone and catechol using chromium silicalite (Section-1) and Zr^{4+}- containing hydrotalcite-like anionic clays (Section-2) respectively. The second part utilizes hydrotalcite-like anionic clays for the synthesis of coumarins. The third part employs organonickel complexes for the Heck-type coupling reactions.

PART-I

SECTION-1: SELECTIVE OXIDATION OF PHENOLS TO QUINONES WITH HYDROPEROXIDES CATALYSED BY CrS-2:

Introduction

The interface of synthetic organic chemistry and zeolite induced transformations has acquired an enhanced degree of attention and activity in recent times.[1] Zeolites are endowed with unique physical and chemical characteristics, which offer opportunities to manipulate active site micro-environment, similar to catalytic antibodies[2] and metalloenzymes.[3] Zeolites encapsulated with metal complex act as biomimics. Some of the prominent physical characteristics of zeolites are their ruggedness to temperature, high surface area and pressure and their ability to recognise, discriminate and organise molecules with less than an angstrom level precision at the active site. It is noteworthy that the chemical characteristics can be manipulated by changing the metal ions in the framework e.g, acidic and basic (either Lewis or Bronsted), oxidizing and reducing properties etc. Indeed, these highly useful and versatile properties make zeolite as a superb candidate for developing highly desirable environmentally benign and cost effective heterogeneous catalytic technologies. The two most important areas where zeolite catalysts are extensively used are in the petroleum refinery/petrochemical industry and in organic fine chemicals. Technologically, in recent years, the major incentives for inventions in catalytic technologies have been the replacement of environmentally unsafe and hazardous process and waste reduction, prompted mainly by Governmental mandates all over the world. Chemical process licensors and the

chemical R&D in general are focussing their attention on developing enviro-catalysts. In this respect, technologically, zeolites offer increased selectivity of the desired product, easy work up, regeneration of the catalyst and most importantly they are environmentally acceptable.

Zeolites are porous crystalline, hydrated aluminosilicates, having highly ordered rigid three dimensional framework structure, with cavities and channels of molecular dimensions. These highly porous crystals are constructed from tetrahedral building units of $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$, which are arranged into various framework structures by sharing common oxygen atoms and are represented by the general empirical unit cell formula[4] $Mx/n[(AlO_2)_x\ (SiO_2)_y].\ ZH_2O$, where M is a cation of valence n, Z is the number of water molecules, the sum of (x+y) is total number of tetrahedra in the unit cell. The net negative charge of the framework generated by alumina is compensated by cations (M), which are often from group I or II or rare earth ions, or organic species. Moreover, the cations are mobile and may usually be exchanged, when M is a proton the Bronsted acidity is generated in the zeolites. The Si/Al molar ratio decides the number of acidic sites in the zeolites. Si/Al ratio is always greater or equal to one, because Al^{3+} does not occupy adjacent tetrahedral sites, according to Loewenstein's rule.[5]

Classification of zeolites

Zeolites have been traditionally classified as small, medium are large pore types, based on the ring size of the largest pore system. Small pore zeolites consists of 8MR (8 membered ring) pore system with ≈4Å diameter. All medium pore having a ten atom ring system with a diameter of 5.6Å. The third category is the large pore zeolites having 12 atom rings of cavities with a diameter of 7.4Å. Recently, a very large pore zeolite aluminophosphate molecular sieve (UPI-5), containing a 18-membered ring has been synthesized.[6] An extra large 20-membered ring pore openings called cloverite and a mesoporous chromium silicate (pore diameter 20-100Å) MCM-41 have also been discovered[7]. The following table gives a general classification of zeolites based on their pore diameter.

Figure 1 : Zeolite structures

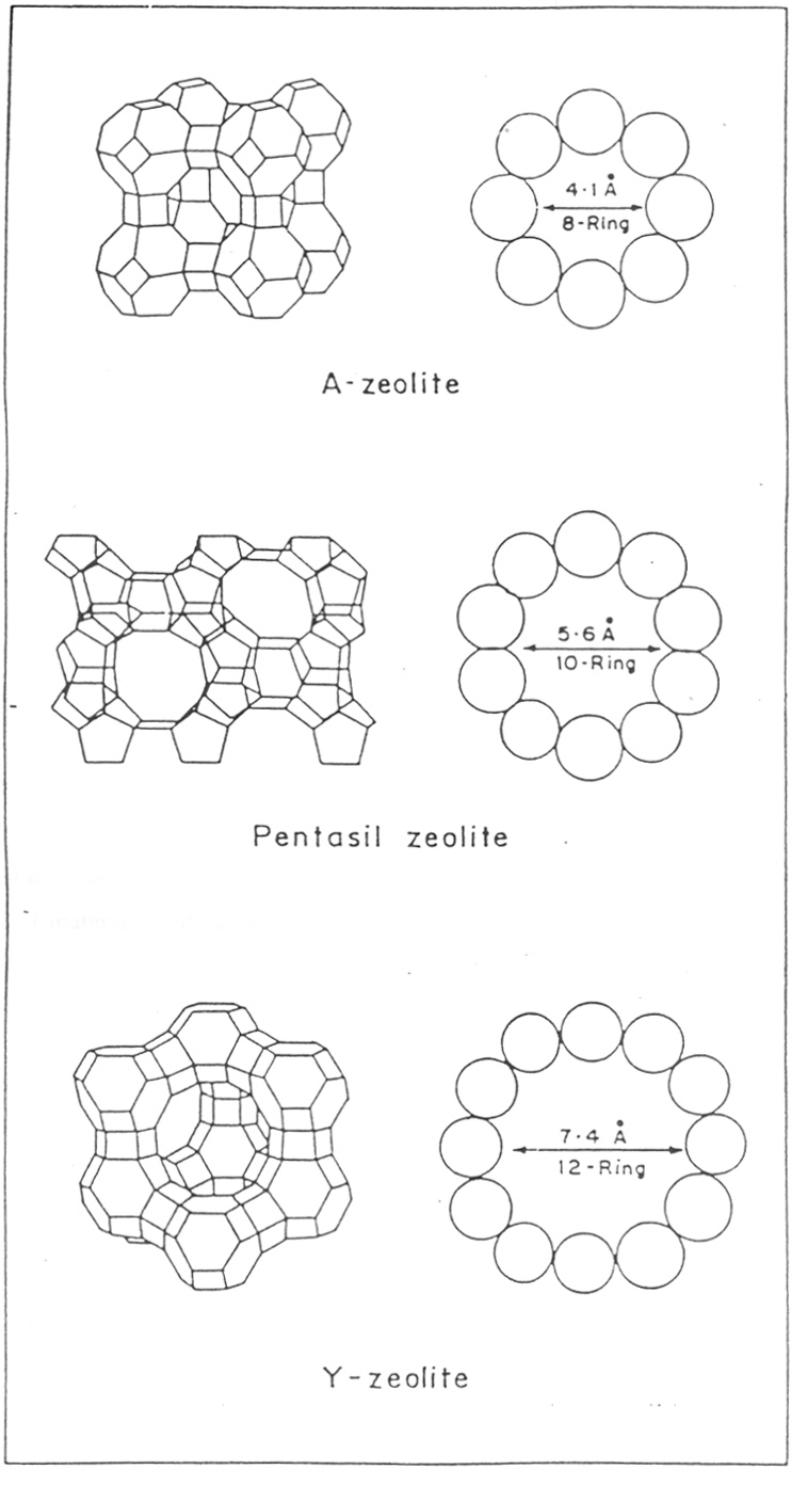


Table-1: Classification of zeolites based on their pore-diameter

Small pore	Medium pore	Large pore
A	ZSM-5	Faujasite
Erionite	ZSM-11	X-/Y- zeolite
Chabazite	ZSM-22	Mordenite
RhO	ZSM-23	L
	ZSM-48	Omega
	TS-1, VS-1	ZSM-12
	TS-2, VS-2	Offretite
	Silicalite	MCM-41
	Theta-1	

Nomenclature of zeolites

The International Zeolite Association Structure Commission (IZASC) and IUPAC have assigned structural codes for natural and synthetic zeolites[8].

Designations consisting of three capital letters have been used to identify structure types. These mnemonic codes are generally derived from the names of the type of materials and do not include numbers and characters other than Roman letters. These codes do not depend on the composition as well as on the distribution of various possible atoms such as Si, Al, P, Ga and Ti etc. Some examples are given in Table 2.

Table 2: IUPAC Nomenclature of zeolites

Name	Code
Mordenite	MOR
Faujastite	FAU
Sodalite	SOD
Erionite	ERI

Some of the zeolites are named after their inventors or the institution from where they are originally synthesized. e.g, Zeolite Socony Mobil (ZSM) and Virginia Polytechnic Institute (VPI).

A large body of structure related literature exists on these zeolite materials, including excellent reviews on the topochemistry of zeolites by Smith[9] and zeolite crystallography by McCusker[10]. An invaluable reference for the study of zeolite frameworks and materials is compiled by Meier and Olsor's Atlas of zeolite structure types.[11] A comprehensive handbook of zeolite nomenclature, synthesis and characterization data, with extensive references to the journals and patent literature has recently been compiled by Szostack.[12]

Application of zeolites in organic synthesis

Utilizing the Bronsted and Lewis acidities of zeolite materials, various types of reactions have been catalysed. The most important application of zeolites is in reaction catalyzed by proton acids and Lewis acids where, the change from a homogeneous to heterogeneous procedure bring advantages in respect of easy separation, recycliability of the catalyst, environmental friendliness etc. As it is evident by the number of reviews,[13] the application of zeolites in organic synthesis is a blossoming field and there is enormous scope for employing them for organic functional group transformations. In relevance to the present work, application of zeolites in the field of oxidation of organic functional groups is discussed below.

Oxidation Reactions catalyzed by zeolite materials

When the Al-ions are replaced by Ti-ions, porous titanosilicate molecular sieves result. The first useful titanosilicate discovered is TS-1[14], a titanosilicate with ZSM-5 (MFI) structure. Many other titanosilicalites have also been synthesized subsequently, two of them being TS-2[15] with a MEL structure of Ti-β with BEA structure.[16]

Titanium silicalite is a remarkable microporous catalyst for the selective oxidation of a variety of organic substrates by aqueous hydrogen peroxide under mild conditions. The discovery of this material is considered to be one of the landmarks in 40 years of catalysis research and has great potential for the future, from environmental consideration and for production of fine chemicals.

Hydrogen peroxide is the oxidant of choice, which does not pose handling problems associated with concentrated peroxides and the by-product is water. Because of simpler work up (ease of separation, regeneration and handling) and reduced environmental problems compared to homogeneous or phase transfer catalysis systems, many heterogeneous processes involving TS-1 have been developed.

The various reactions catalysed by TS-1 and presented in Table 3.

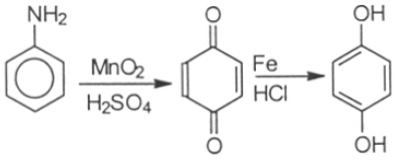
Table-3: Reactions catalyzed by TS-1

Reactions	Products
1. Benzene + H_2O_2	Phenol + H_2O
2. Phenol + H_2O_2	Dihydroxybenzene + H_2O
3. Olefins + H_2O_2	Epoxides + H_2O
4. Cyclohexanol + H_2O_2	Cyclohexanone + H_2O
5. Alkanes + H_2O_2	Alcohols + H_2O
6. Alcohols + H_2O_2	Aldehydes and ketones + H_2O
7. Sulfides + H_2O_2	Sulfoxides + H_2O
8. Ketones + NH_3 + H_2O_2	Oximes + H_2O

Two applications of TS-1 have already been commercialized very recently by Enichem, Italy. (**Scheme 1**)

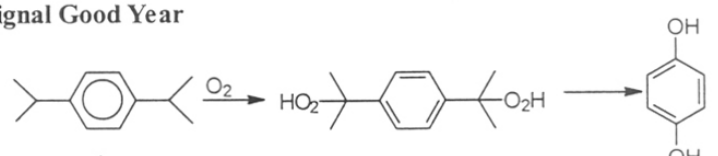
Scheme 1

Eastman Kodak



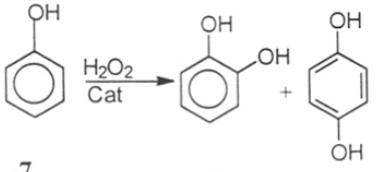
1 2 3

Signal Good Year



4 5 3

Rhone Poulenc, Brichima, Enichem



7 8 3

Hydroxylation of phenol to catechol and hydroquinone

The above three are important processes for the production of catechol and hydroquinone.

The Eastman Kodak process has nearly been abandoned for economic and environmental reasons. The Signal-Goodyear process produces only hydroquinone, while the processes based on hydroxylation of phenol with H_2O_2 produce both catechol and hydroquinone. At present, more than 50% of the total world production (of about 60,000 tpa) is based on the H_2O_2 processes. In the presence of various catalysts, phenol is oxidized by hydrogen peroxide to form hydroquinone and catechol. The catalysts used are typically Co^{2+}/Fe^{2+} salts/Fe-complexes (Brichimia), $HClO_4/H_3PO_4$ additives (Rhone Poulenc), metal chelates (ubc) and TS-1 (Enichem). Except the Enichem process, which uses a solid catalyst, the other processes are based on solution phase catalysis. The use of solid catalyst enables its easy separation, thereby lowering product recovery costs and reducing waste (and treatment costs). Another important benefit is, the production of less tar even at high phenol conversion. Thus, the Enichem process was commercialized (15,000 tpa) in Italy recently. More recently, the National Chemical Laboratory, Pune (NCL) has also developed an improved process for the hydroxylation of phenol using a solid microporous titanosilicate catalyst and hydrogen peroxide[17].

Ammoximation of cyclohexanone

Another commercial application of TS-1 is in the ammoximation of cyclohexanone in a single step into cyclohexanone oxime, used in the production of caprolactam for Nylon-6 manufacture, in the presence of H_2O_2 and NH_3.

Raschig Process:

$3NH_3 + CO_2 + 2H_2O \rightarrow (NH_4)_2CO_3 + (NH)_4HCO_3$

$(NH_4)_2CO_3$ or $(NH_4)HCO_3 + NOx \rightarrow (NH_4)_2NO_2 + CO_2$

$(NH_4)_2NO_2 + 2SO_2 + NH_3 + H_2O \rightarrow HON(SO_3NH_4)_2$

$HON(SO_3NH_4)_2 + 2H_2O \rightarrow NH_2OH\ H_2SO_4 + (NH_4)_2SO_4$

cyclohexanone + $H_2NOH.H_2SO_4 + NH_3$ ---> cyclohexanone oxime + $(NH_4)_2SO_4 + H_2O$.

BASF Process

$NH_3 + 1.5\ H_2SO_4$ (dil) + $2NO + 1.5\ H_2 \rightarrow NH_2OH.H_2SO_4 + 0.5\ (NH_4)_2SO_4$

Cyclohexanone + $NH_2OH.\ H_2SO_4 + 2NH_3 \rightarrow$ cyclohexanone oxime + $(NH_4)_2SO_4 + H_2O$

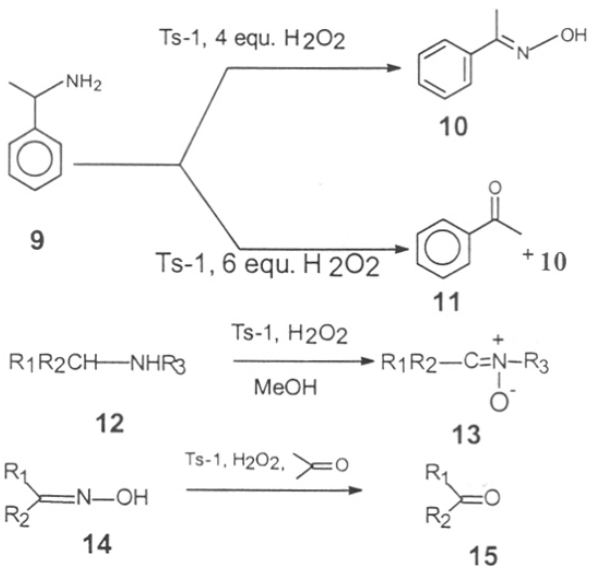
Enichem process

Cyclohexanone + NH_3 + H_2O_2 -------> cyclohexanone oxime + H_2O

The commercially used Raschig and BASF process convert cyclohexanone into the oxime using hydroxylamine sulphate, the hydroxylamine sulphate itself being obtained in many steps involving SO_2, NO_2 and NH_3 in the Raschig Process and in one or two steps in the BASF process using NO,H_2 and H_2SO_4. The above processes involve the use of corrosive and enviormentally undesirable raw materials. Enichem has recently commercialized (at Porta Maghera, Italy; 15,000 tpa) a novel single step process based on TS-1. The reactants are cyclohexanone, ammonia and hydrogen peroxide. The process besides less polluting, avoids, the production of the undesirable (in the west) ammonium sulphate as a byproduct.

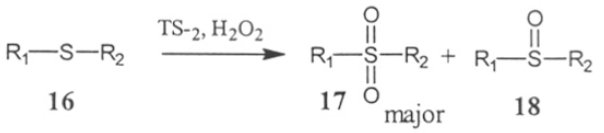
Of late, a new catalytic method for the selective oxidation of benzylic and allylic amines into the corresponding oximes[18] (**10**), secondary amines (**12**) to nitrones[19] (**13**) and oxidative cleavage of oximes (**14**) to carbonyl compounds[20] (**15**) catalyzed by TS-1 and H_2O_2 have been reported.

Scheme 2



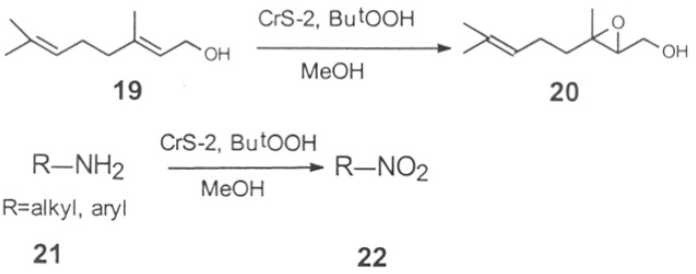
Oxidation of various thioethers selectively to sulfoxides[21] (**17**) using TS-2 and H_2O_2 has also been achieved.

Scheme 3



Similar to that of TS-1 and TS-2, of late, a newly synthesized chromium silicalite[22] has shown excellent catalytic activities. A chemoselective epoxidation of various olefins (**19**) to the corresponding epoxides (**20**), direct oxidation of various primary amines (**21**) to the corresponding nitro compounds[23] (**22**) using 70% tert-butyl hydroperoxide as the oxidant are some of the transformations that are carried out with this versatile catalyst.

Scheme 4



Oxidation of Phenols to Quinones

Oxidative transformation of phenol is of biological[24] and synthetic [25] importance. Quinones have found extensive use in electron transfer reactions in biological systems, particularly as dehydrogenating agents in steroid chemistry[26] and as far as biology is concerned, their reversible reduction to the corresponding hydroquinones is considered to be a reaction of prime importance.[27] Quinones constitute an important class of compounds by virtue of their wide spectrum of biological activity[28], and their utility as synthetic intermediates.[29] Numerous published papers reflect the current interest in quinones as oxidants and some selected quinones with high oxidation potentials have gained acceptance as reagents in organic chemistry.[30]

Synthetic approaches to Quinones: an overview

A large number of oxidizing agents have been used for the preparation of quinones, including sodium dichromate,[31] CrO_3[32], chromic acid[33], nitric acid[34], iodic acid[35], thallium triacetate[36], ferric chloride[37], silver oxide[38], Ag_2CO_3/celite[39], sodium

chlorate[40], MnO_2[41], N-chlorosuccimide/(Et_3N[42], CAN[43], ceric sulfate[44], benzeneselenic anhydride[45], lead dioxide[46] and Fremy's salt.[47]

Ganeshpure et. al.[48], oxidized phenols to quinones with molecular oxygen employing aqua [N,N'-bis(2'-pyridinecarboxamido)-1,2-benzene]cobalt II, [Co(bpd)H_2O][49] as a catalyst. Transition metals, such as Fe, Cu and Mo are well known to catalyse oxidation of phenols with hydrogen peroxide.[50] $RuCl_3$ catalysed oxidation of trimethylphenol with 30% H_2O_2 in acid medium to the corresponding p-benzoquinones was developed by Matsumoto[51] et.al.

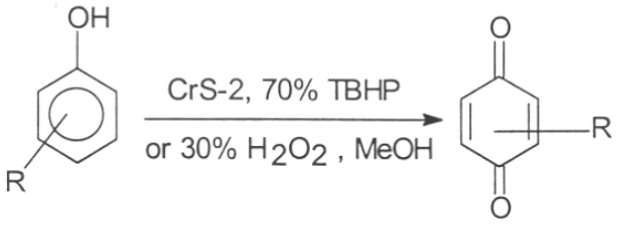
Objective

Oxidation is a basic and indispensable method in organic synthesis, and a number of stoichiometric[52] and catalytic[53] reactions have been reported. Oxidation of phenols to quinones is an importance area of synthetic organic chemistry. The resulting oxidized product, quinone, has greater importance in industry (e.g., anthraquinone dyestuffs), in organic synthesis, as dienophiles in Diels-Alder reactions and in nature, where they play a vital role in electron transport in the respiratory and photosynthetic elements of biological systems.[54] Most of the known methods involve reactions using stoichiometric homogeneous conditions. Tedius work up and the generation of toxic metallic residues resulting from the use of large excess of metallic reagents are, the main disadvantages often encountered in the literature reported methods. Hence, there is a need for cleaner, catalytic alternatives which do not generate excessive amounts of inorganic salts as by-products.

A heterogeneous catalytic method without these disadvantages is considered to be desirable. In this part of this chapter therefore, a newly developed chromium silicalite (CrS-2) as a catalyst for selective oxidation of various phenols to the corresponding p-quinones with 30% H_2O_2 or 70% (TBHP) tert-butylhydroperoxide as the oxidant is described. Chromium containing medium pore molecular sieve (Si/Cr > H_2O) having MEL (CrS-2) topology efficiently catalyses the oxidation of various phenols.

The following (Scheme 5) gives an account of the synthesis and characterization of Cr-ZSM-11 (CrS-2) and its unique selectivity in the oxidation of phenols.

Scheme 5



23 **24**

R = alkyl

Results and Discussion

Three chromium silicalites with Si:Cr input ratios of 40,80 and 150:1 were prepared and characterized by X-ray powder diffraction (XRD), IR, ESR spectral techniques and cyclic voltagram. Finally, the output in the zeolite was determined by wet chemical analysis.

The oxidation results are summarized in Table 4.

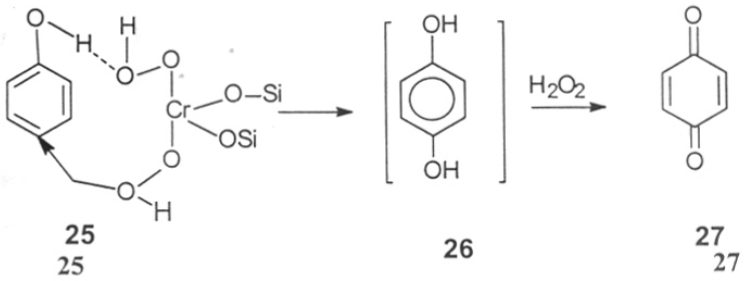
Table 4: Oxidation of phenols with 70% TBHP or 30% H_2O_2 catalysed by Cr-S-2

Entry	Substrate	Product	Yield (%)
1.	Phenol	1,4-Benzoquinone	36
2.	3-Methlyphenol	2-Methyl-1,4-benzoquinone	30
3.	2,6-Dimethylphenol	2,6-Dimethyl-1,4-benzoquinone	38
4.	3,5-Dimethylphenol	2,6-Dimethyl-1,4-benzoquinone	35
5.	2,5-Dimethylphenol	2,5-Dimethyl-1,4-benzoquinone	42
6.	2-Naphthol	1,4-Naphthoquinone	30*
7.	1,4-Hydroquinone	1,4-Benzoquinone	35

***Reaction carried out for 12 hours, for rest of the substrates for 4 hours.**

Evidently, selective formation of p-benzoquinone (entries 1 and 7) was observed and no ortho-isomer was isolated. However, the product yields were only moderate, the remaining was essentially starting material in each case studied. The selectivity of the product formation can be explained by the following probable mechanism.

Scheme 6



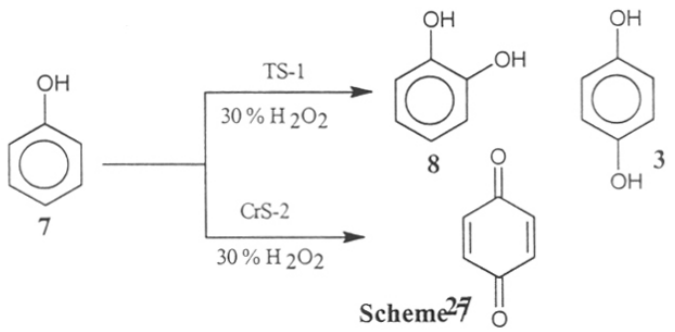
25 **26** **27**

25 27

Scheme 6

The influence of solvents on the reaction rate and product formation was also observed; in pet-ether (60-80°C) and the chloroform as a solvent, although the reaction proceeded at room temperature, it took comparatively longer reaction time than in methanol. The shorter reaction time in methanol with improved yield may be due to soluble nature of both the reagent and the substrate.

2-Amino, 2-nitro, 2,4,6-trichlorophenols failed to undergo oxidation under the reaction conditions employed here. 2-Amino, 2-nitrophenols, did not undergo oxidation probably, due to hydrogen bonding. In the case of 2,4,6-trichlorophenol since all the o-,p-positions are blocked the oxidation did not proceed. It is interesting to note that the alkylphenols underwent smooth oxidation without fail to give moderate yields of quinones. The quinones thus obtained could serve as dienophiles. The known oxidation of aniline to p-benzoquinone when tried with chromium silicalite yielded only nitrobenzene and not the quinone.



Scheme 7

Titanium silicalite TS-1 has been reported to catalyze phenol to catechol and hydroquinone whereas in the present case, CrS-2 yielded selectively the p-benzoquinones. No o-quinone is formed. The selectively differences between titanium and chromium silicalites towards the oxidation of phenols can be explained by the higher redox potential[55] of the Cr^{5+}/Cr^{4+} couple (0.50 V) as compared to the Ti^{4+}/Ti^{3+}

couple (0.06V); the larger the redox potential, the greater its reducibility. The more easily reducible ions are more potent in decomposing ROOH.

o-Nitrophenol, o-aminophenol failed to yield the corresponding p-benzoquinones. This could probably be due to the hydrogen bonding of phenolic functional group with the nitro, amino functional groups. 2,4,6-Trichlorophenol too failed to undergo oxidation under the reaction conditions employed here. This may be due to the presence of chlorine atom para to -OH group which resists the oxidation of this substrate.

The results given in table 4 gives the information that more number of alkyl groups makes the oxidation easier. p-Benzoquinones, xyloquinones and 1,4-naphthoquinones thus obtained from the corresponding phenols are useful as dienophiles in the Diels-Alder reactions.

Conclusion

1. Selective oxidation of phenols to p-quinones was achieved in a heterogeneous fashion, employing CrS-2 as a catalyst and 30% H_2O_2 or 70% TBHP as oxidant.
2. CrS-2 is a new, stable, recyclable solid heterogeneous catalyst for selective oxidation of phenols to quinones.
3. This heterogeneous catalyst is advantageous with respect to easy separation and is environmentally benign.
4. CrS-2 induced catalytic methodology presented in this section should serve as a model for planning oxidation reactions and should be a useful addition to synthetic organic chemistry.
5. The catalyst was recovered and reused three times without loss of activity and selectivity.
6. The present methodology does not give toxic waste materials which are usually obtained in the case of stoichiometric metal oxidants.
7. p-Benzoquinone is obtained as the sole product with 100% selectivity without the formation of any intermediate phenols.

Experimental:

Synthesis of Chromium Silicalite:

The hydrothermal synthesis of chromium silicate was carried out using silica gel of the following composition: SiO_2: 0.012 Cr_2O_3: 0.4NBu_4OH: 30H_2O with tetrabutylammonium hydroxide as the organic template.

In a typical synthesis NBu_4OH (Aldrich, 20% methanolic solution) was added slowly to an ice-cold solution of tetraethylsilicate (22.0 g, Aldrich 99.9% pure) under vigorous stirring. The mixture was stirred at room temperature for 2 hours and then $Cr(NO_3)_3$. $9H_2O$ (1.0g, Aldrich 99% pure) in water (10 ml) was added dropwise. The mixture was stirred at 343K for 1 hour and then the remaining water was added. The resultant homogeneous reaction mixture (pH=11.80) was charged into a stainless steel autoclave and heated at 443K for 90 hours under static condition to induce crystallization. After crystallization, the light green product was filtered, washed with deionized water, dried at 383K and calcined at 773K under air or nitrogen. The yield of the product was between 70 and 80 mass%. The chromium silicalite thus obtained was characterized by X-ray powder diffraction (XFD), IR and ESR spectral techniques.

IR (self-supported wafer, cm^{-1}): $\sqrt{}_{max}$, 963, 790, 550, 410.

963 cm^{-1} Si-O-Cr stretching , 790, 550, 460 MEL framework stretching.

General procedure for the oxidation of phenols with 30% H_2O_2 or 70% TBHP catalyzed by Chromium Silicalite (CrS-2):

In a typical experimental 30% H_2O_2 (1.25 ml, 11 mmol) or 70% TBHP (1.5 ml, 11 mmol) was added dropwise to a stirred mixture of phenol (5 mmol) and the catalyst (10% w/w) in methanol (20 ml) and the reaction mixture was refluxed for 4 hours. The catalyst was then filtered off and the reaction mixture was diluted with diethylether (50 ml) and water (20 ml). The excess peroxide present in the mixture was decomposed by treating the ethereal layer with sodium bisulphite solution (4 x 10 ml); progress of peroxide decomposition was monitored using starch-iodide reagent. The organic layer was successively washed with ice-cold 5% sodium hydroxide solution to remove the unreacted phenol present in the reaction mixture. The organic layer was then washed with water, brine and dried over anhydrous sodium sulphate. The ether was evaporated and the residue was further purified by flash chromatography.

1,4-Benzoquinone:

Yield : 0.19 g; 36%

M.P. : 116-119°c (Lit.[56] 113-115°c)

IR (Nujol, cm^{-1}) : $\sqrt{}_{max}$ 1660 (b); 1500, 1370, 1320, 1200.

^{1}H NMR (90 MHz) : δ 6.8 (s, 4H, vinyl protons).

2-Methyl-1,4-benzoquinone:

Yield : 0.3 g, 30%

M.P. : 67-69°C (lit.[57] 69°C).

IR (Nujol, cm^{-1}) : 2980, 1600 (b), 1500, 1360, 1320, 1200, 1000.

^{1}H NMR (90 MHz) : δ 2.0 (s, H, vinylmethyl protons); 6.7 (m, 3H, vinyl protons).

2,5-Dimethy-l-,4-benzoquinone:

Yield : 0.26 g; 38%

M.P. : 123-126°C (Lit.[58] 125°C).

IR (Nujol, cm^{-1}) : $\sqrt{}_{max}$ 2900, 1650 (b), 1340, 1250.

^{1}H NMR (90 MHz) : δ 2.05 (s, 6H, vinylmethyl protons); 6.55 (s, 2H, vinyl proton)

2,6-Dimethyl-1,4-benzoquinone:

Yield: : 0.26 g; 38%

M.P. : 72-75°C (lit.[59] 71-73°C)

IR (Nujol, cm^{-1}) : $\sqrt{}_{max}$ 3000, 1650 (b), 1340, 1250.

^{1}H NMR (90 MHz) : δ 2.0 (s, 6H, vinylmethyl protons); 6.55 (s, 2H, vinyl protons).

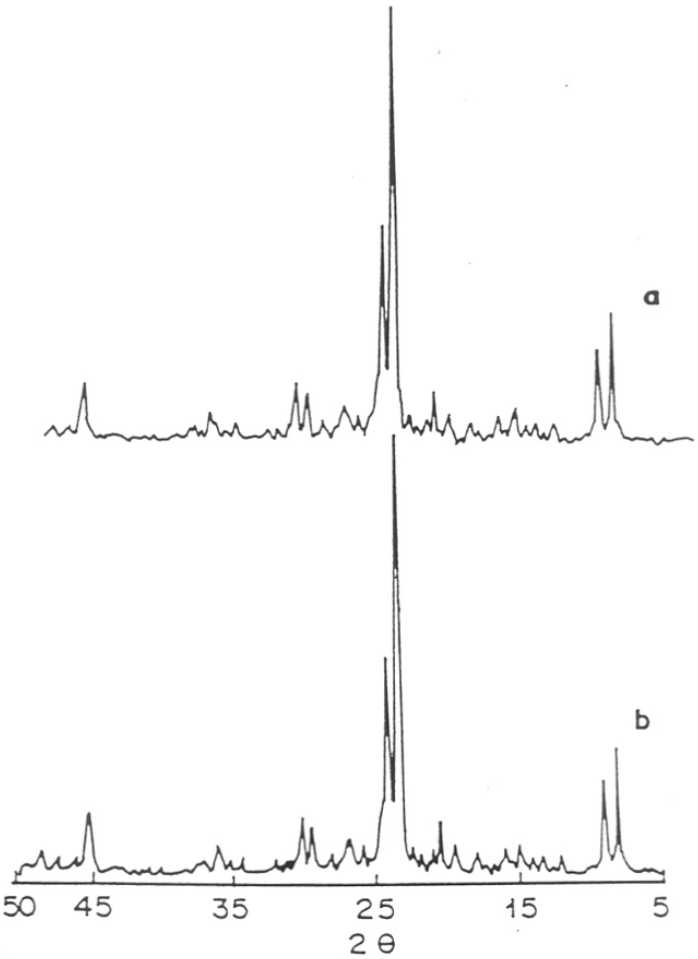
1,4-Naphthoquinone:

Yield: : 0.24 g; 30%

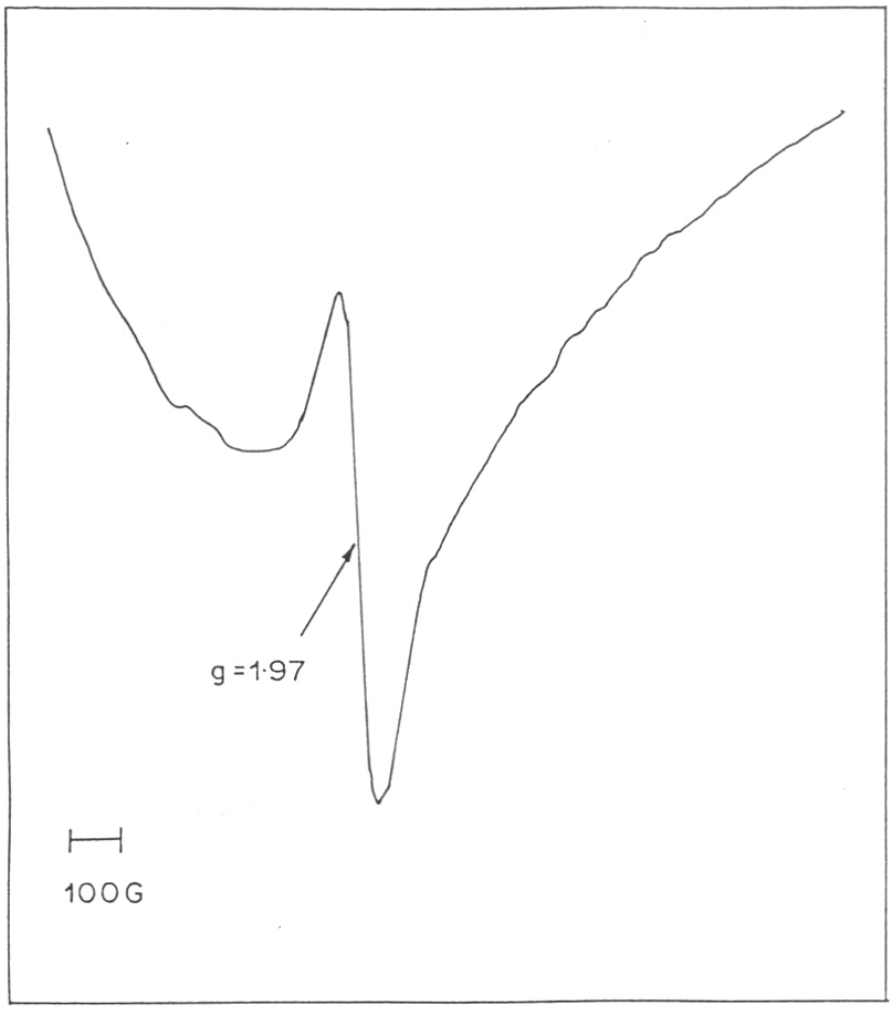
M.P. : 124-127°C (lit.[60] 125°C).

IR (Nujol, cm^{-1}) : $\sqrt{}_{max}$ 3000, 1750, 1620, 1500, 1400, 1350.

^{1}H NMR (90 MHz) : δ 7.03 (s, 2H, vinyl protons); 7.65-8.2 (m, 4H, Ar-H).



X-Ray powder diffraction profiles of
a) silica polymorph of ZSM-11 and
b) Cr-ZSM-11 ; data collected on a Rigaku Max III VC instrument using Ni-filtered Cu-$K\alpha$ radiation.



ESR Spectrum of calcined Cr-ZSM-11(Spectrum recorded on a Bruker ER 200 D spectrometer at room temperature).

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SECTION 2

SELECTIVE HYDROXYLATION OF PHENOL TO CATECHOL WITH H_2O_2 USING Zr^{4+}- CONTAINING Zr-HT-LIKE COMPOUNDS

Introduction

The selective oxidation of phenols to quinones with CrS-2 was described in section-1 of this chapter. This section deals with the application of a new hydrotalcite-like anionic clays containing Zr^{4+} in the brucite -like layers as catalysts in the liquid-phase hydroxylation of phenol with H_2O_2.

Clays are among the most common minerals on the earth's surface and they are indispensable to our existence. They are widely employed as industrial adsorbents, ion-exchangers, acid scavengers, ceramics and certain building materials. In addition, clays are highly versatile, affording both industrial and laboratory catalysts with excellent regio and stereoselectivity.[1] Besides their use as catalysts and reactive supports, it has also been suggested that clays may been have involved in the formation of the original proteins and generic materials.[2] Clay catalysts have distinct advantages over homogeneous catalysts as the work up of the reaction mixture is often followed by simple filtration to remove the clay. Pillaring the clay gives a more clearly defined reaction space and can produce catalysts which begin to rival the zeolites in stability and shape selectivity.[3]

Based on the structure and charges of layers and interlayers, clays can be classified broadly into two categories:

I Cationic or Smectite type clays having layer lattice structure in which two dimensional oxyanions are separated by layers of hydrated cations and

II Hydrotalcite-like anionic clays wherein the charges on the layer and gallery anions are reversed complimentary, to the smectite type clays.

The latter mentioned compounds are receiving considerable interest in recent years owing to their wide industrial applications. In relevance to the present work, hydrotalcite-like anionic clays are discussed in detail.

Hydrotalcite-like Anoinic clays

Anionic clays (natural and synthetic) are less diffuse in nature than cationic clays, but relatively inexpensive to prepare in the laboratory. Synthetic anionic clays, either as such or under controlled thermal decomposition have many industrial

applications and more will probably be found in new and unexpected areas, complimentary to those of cationic clays.

Hydrotalcite (HT), a mixed hydroxycarbonate of magnesium and aluminium was first discovered in Sweden around 1842 and its name derives from the fact that, it can be easily crushed into a white powder similar to talc. It occurs in nature in foliated and controlled plates. The first exact formula for hydrotalcite [$Mg_6Al_2(OH)_{16}CO_3.4H_2O$] and of the other isomorphous minerals was presented by E. Manasse.[4] At the sametime, Mg-Fe hydroxycarbonate (called pyroaurite due to its likeness to gold upon heating) was also found. Pyroaurite was later recognized to be isostructural with hydrotalcite. Later, in 1942, Feitknecht synthesized a large number of compounds having hydrotalcite-like structures, to which he gave the name "doppelschicht struktren" (double sheet structures). Feitknecht assigned them a structure with intercalacted hydroxide layers.[5] This hypothesis was refuted only on the basis of single-crystal XRD analysis[6] which showed that the cations are localized in the same layers, while the anions and water molecules are located in the interlayer region. However, the terms "Feitknect's compounds" and "mixed hydroxides" are still used. Thus, for a longtime the anionic clays were mainly the obejct of mineralogical studies.

After 1970 hydrotalcite-like anionic clays appeared in the patent and in open literature in connection with various industrial applications. The first patent by Brocker and Marosi claimed hydrotalcite-like materials as very good precursors for hydrogenation catalyst.[7] The first paper in the open literature[8] and technical review[9] probably went unnoticed because of the language in which it was written. A recent review[10] and a monograph[11], by Trifiro et. al., furnishes a complete understanding of the nature and physiochemical properties of hydrotalcite-like materials.

Nomenclature

Many names are used as a function of the composition and nature of the polytype forms (hydrotalcite, manasseite, Sjorgenite, Stitchite etc.,) and Drits et al.[12] have proposed a systematic nomenclature in order to limit the number of new mineral names.

Hydrotalcite-like anionic clays may be defined by their chemical composition namely, $[M^{2+}_{(1-x)}M^{3+}_{x}(OH)_2]^{x+}$ $(A^{n-}_{(x/n)}]\cdot m\ H_2O$, by the basal spacing and the stacking sequence;

where

M^{2+} and M^{3+} are the divalent and trivalent ions respectively,

A is the interlayer anion,

x is the ratio of trivalent metal,

m is the sum of water molecules located in the interlayer region.

Structural properties of Hydrotalcite like anionic clays

The structures and the different methods for the synthesis of HT compounds have been carefully reviewed.[13]

The structure of HT-like compounds can be best visualized by starting with the structure of the brucite [$Mg(OH)_2$], wherein each Mg^{2+} ions are octahedrally surrounded by hydroxyl groups (6 fold coordinated to OH^-). Each octahedra shares edges to form an infinite sheet like structure.[14] If the part of Mg^{2+} ions are replaced by cations[15] with higher charge, but with similar radius (such as Al^{3+} in hydrotalcite, Fe^{3+} in pyroaurite and Cr^{3+} in Stichite), the brucite-like sheets (layers) gain positive charge and the electroneutrality is maintained by anions located in disordered interlayer domains, also containing water molecules. (Fig.1). The anions and water molecules are randomly located in the interlayer region, being free to move by breaking and making bonds (as in liquid water). The oxygen atoms of the water molecules and $(CO_3)^{2-}$ groups are distributed approximately closely around the symmetry axes through the hydroxy groups (0.56 A° apart) of the adjacent brucite-like sheets (Fig.2). These hydroxyls are tied to the $(CO_3)^{2-}$ groups directly or via an intermediate H_2O through hydrogen bridges.[16] $OH^-....CO_3^{2-}$ HO^- or $HO^-....H_2O^-$ $.....CO_3^{2-}$ $.....OH^-$. The $(CO_3)^{2-}$ groups are situated flat in the interlayer and H_2O is loosely bound; they can be eliminated without destroying the structure. The HT structure can accomodate wide variations in the M^{2+}/M^{3+} ratio and the nature of cations, as well as different types of anions; however, only a few type of variations appear in nature and carbonate is the preferred anion.

Properties of hydrotalcite-like anionic clays

The anionic clays based on hydrotalcite-like compounds have found many practical applications. These hydrotalcites have been used as such or (mainly) after calcination.

The most interesting properties of the oxides obtained by calcination are the following:

1. High surface area
2. Basic properties

Hydrotalcite-like Anionic Clays (Layered Double Hydroxides)

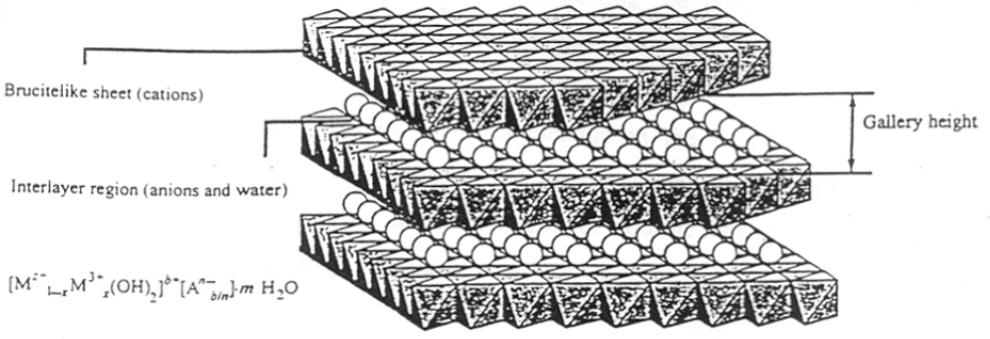


Fig.1 Schematic representation of the hydrotalcite-like structure

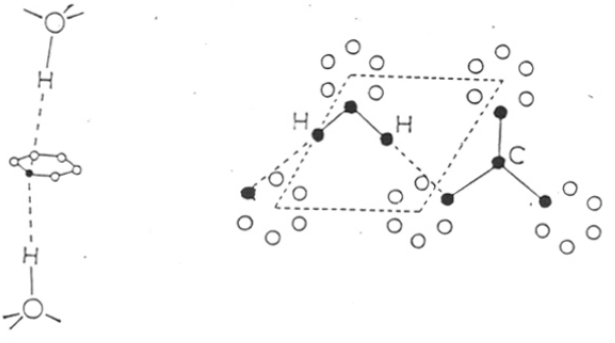


Fig.2 Position of interstitial atoms between the brucite-like sheets

3. Formation of homogeneous mixture of oxides with very small crystal size, stable to thermal treatments, which by reduction form small and thermally stable metal crystallites.
4. "Memory Effect" which allows the reconstruction under mild conditions of the original hydrotalcite structure when contacting the product of the thermal treatment with water solutions containing various anions.

Properties 1,2 and 3 have found application in the field of heterogeneous catalysis (hydrogenation, reforming, basic catalysts and as supports). Properties 1,2 and 4 are utilized in applications such as the scavenging of chloride ions and the purification of water containing waste anions (Organic as well as inorganic).

Although the available literature on anionic clays is significantly less abundant, hydrotalcite-like anionic clays can open up new and unexpected areas of applications complimentary to those of cationic clays. From this point of view, it is important to note that all the knowledge acquired for all the cationic clays, can also be applied to the anionic clays with necessary adaptations. The nature of basic properties of the anionic clays are discussed below.

Basic properties

Thermal calcination of hydrotalcite-like materials around 723K offers a highly active and well-dispersed mixed metallic oxides with high surface area and high thermal stability. Thermal treatments induce dehydration, dehydroxylation and loss of the charge compensating anions, resulting in mixed oxides with MgO-type structures.[17] The resulting material possesses pronounced basic characters and are used potentially as base catalyst. Hydrotalcites are thus consequently a class of precursors useful for the preparation of catalytically active oxides showing basic properties.

Upon calcination, the hydrotalcite is transformed with simultaneous elimination of water and carbon dioxide. This can be achieved without phase segregation upto 673K. Above this temperature, a Mg(Al)O mixed oxide appears, CO_2 and water are released without modification of the nature of the neighbouring carbonate entities. A spinel-like phase $MgAl_2O_4$ is observed at 1073K with the presence of some carbonate species occluded in the structure. The catalytic activity regularly increased with the decomposition of the least stable carbonates, and goes through a maximum at a calcination temperature of 773K where the more stable carbonate species are not totally eliminated as shown by the TG and IR analysis data. Thus, Figueras[18] et. al found that

these thermally stable carbonates are rather comparable to those found by King and Graces[19] in K-X, Rb-X and Cs-X zeolites calcined at 720K and thus may similarly be attributed to high basic strength of these species. Dehydroxylation begins well before the formation of spinel phase and results in a decrease of activity. This suggests that the basic sites are essentially the hydroxyl groups rather than O^{2-} species.

Reichle[20] et. al. argues that in the case of calcined hydrotalcites, the active surface includes hydroxyl groups and a range of O^{2-}-Mg^{2+} acid-base pairs. The Lewis sites associated with the oxygen framework located in corners of the crystal should have a stronger basicity than the oxygens located either on edges or on crystal faces.

It is suggested by Trifiro[10] et. al, that the basic properties of calcined hydrotalcite depend upon the Al/(Al + Mg) ratio. When the amount of Al increases, the total number of basic sites decreases[21], but the proportion of the stronger ones increases. Thus, for any base-catalyzed reaction, a maximum in activity should occur for an optimum Al/(Al + Mg) ratio. The optimum will depend on the base strength needed to activate the particular reactant. It was found out by Corma[22] et. al., that in the condensation between acetophenone and benzaldehyde, a maximum activity occurs for Al/(Al + Mg) ratio between 0.25 to 0.30. It was also viewed that smaller crystallites are more active than large crystals, indicating that the stronger basic sites, probably those occupied by oxygens at corners, play an important role in basic catalysis. Furthermore, Corma et.al. determined the basic strength and number of basic sites in calcined hydrotalcite (CHT) by carrying out the condensation of benzaldehyde with compounds having active methylene groups. It has been found that the Mg-Al calcined hydrotalcite possesses basic sites with pK upto 16.5, most of the basic sites exhibit pK values in the range of 10.7-13.3. These authors have also compared the catalytic activity of CHT with other base catalysts such as alkali exchanged zeolites and sepiolites. It has been found that catalysts derived from hydrotalcites are most active for condensation reactions. Thus, it is clear that hydrotalcite-like anionic clays are superior in basic properties than alkali exchanged Y-zeolites and sepiolites.

Hydrotalcite-like materials in organic synthesis

The high surface area and the basic properties of hydrotalcite-like anionic clays coupled with thermal stability helps to utilize such materials as catalysts. The isomorphous replacement of Mg^{2+} by trivalent ions enables preparation of a large number of HT-like compounds. Many HT-like compounds with a wide variety of M(II)

M(III) cation pairs have been reported in recent years and utilized in the field of heterogeneous catalysis. Some of important catalytic transformations are discussed below:

Polymerization reactions: Kohijiya[23] et. al., have investigated the polymerization of propylene oxide using synthetic hydrotalcites. Polymerization at 293K (88 hours) gave a conversion of 83% of polypropylene oxide (PPO). Nakatsuka[29] et. al. realised the polymerization of β-propiolactone employing calcined HT with MgO/Al_2O_3 molar ratio 17.6 to furnish 100% conversion of propiolactone.

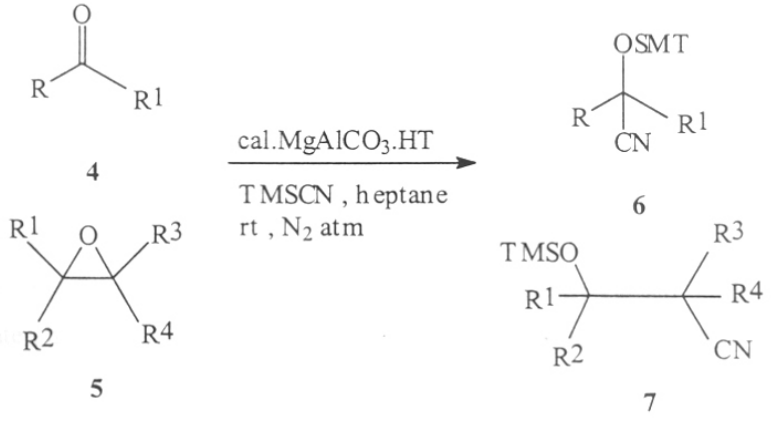
C-Alkylation (Scheme 1): Catalytic activity of hydrotalcite (Mg/Al = 2.8) for the selective C-monoalkylation of 2,4-pentadione (**1**) with reactive alkylating agents (**2**) was executed by Figueras et. al.[25].

Scheme 1

1 2 3

Cyanosilylation (Scheme 2): The use of basic oxides obtained from hydrotalcite precursors for the cyanosilylation of carbonyl compounds (**4**) and nucleophilic ring opening of oxiranes (**5**) using TMSCl was demonstrated by Choudary's group.[26]

Scheme 2



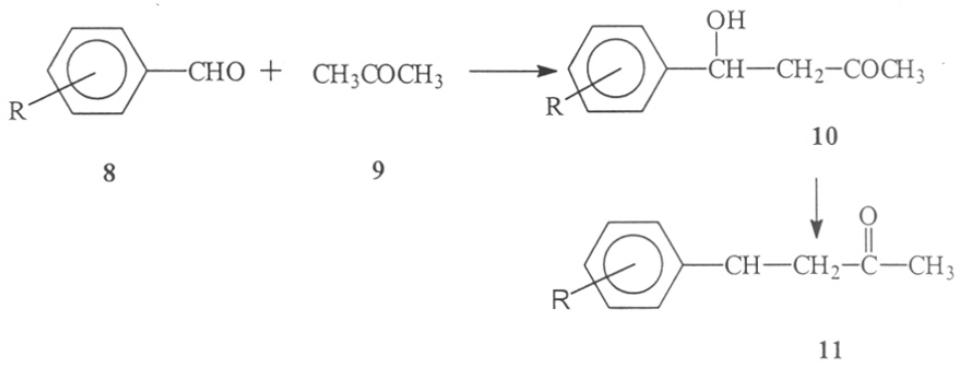
4 5 6 7

Condensation reaction (Scheme 3)

Condensation reaction (aldol) between acetone and different substituted benzaldehydes (**8**) were executed by Figueras et. al.[18] using hydrotalcite as solid catalysts. The nucleophilic strength of the substituents were also studied and the order was found to be as follows.

$$p\text{-}NO_2 > m\text{-}Cl > p\text{-}Cl > Me > p\text{-}OMe$$

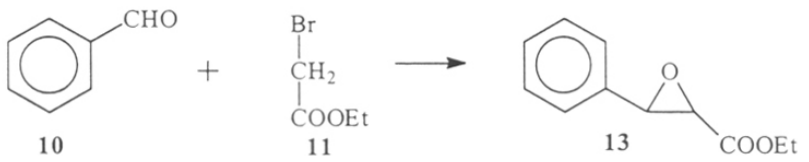
Scheme 3



Darzen's Glycidic ester condensation (Scheme 4)

It was found by Corma's group that Darzen's glycidic ester condensation reaction was favoured when the reaction was carried out between benzaldehyde (**10**) and ethyl-bromoacetate (**11**).

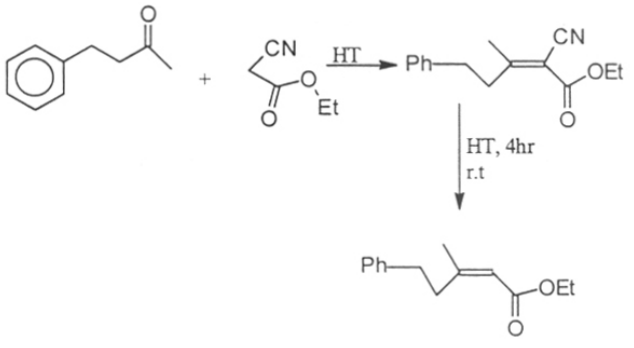
Scheme 4



Synthesis of citronitril (Scheme 5)

The first step for the production of citronitril, i.e. the condensation benzylacetone (**14**) with ethylcyanoacetate (**15**) was efficiently carried out by Figueras group.[28] Later, hydrolysis of the ester led to the synthesis of citronitril (**17**).

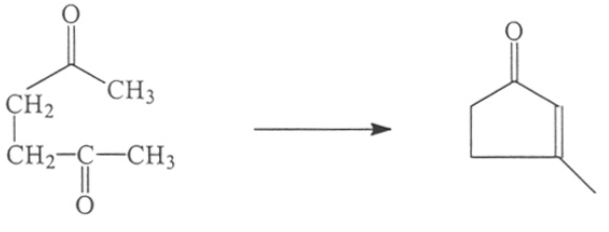
Scheme 5



Synthesis of 3-methyl-cyclopent-2-ene-1-one (Scheme 6)

An intramolecular condensation of acetonylacetone[29] (**18**) using calcined hydrotalcite in MeOH was found to give 3-methyl-cyclopent-2-ene-1-one (**19**).

Scheme 6

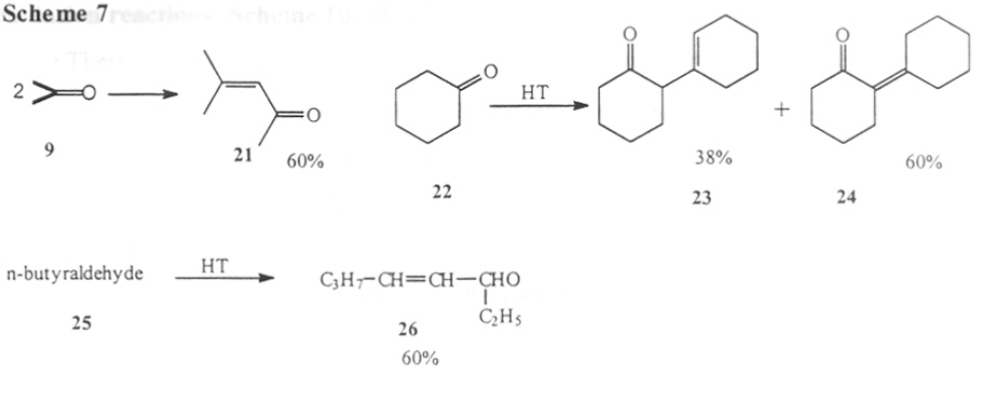


18 **19**

Aldol condensation (scheme 7)

Aldol condensation of acetone (**9**), cyclohexanone (**22**), n-butyraldehyde (**25**) were experimented using HT by Reechle[30] and it has given moderate yields of α,β-unsaturated carbonyl compounds (**21,23,26**).

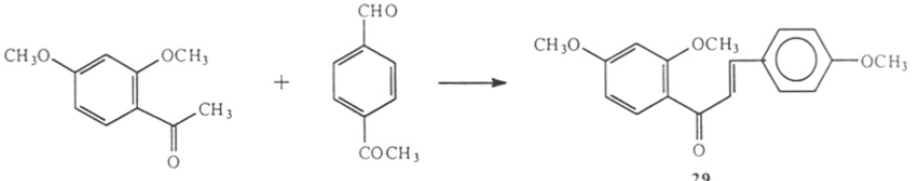
Scheme 7



Claisen-Schmidt condensation (Scheme 8)

Biologically active natural product chalcones were synthesized by Corma[18] et al via Claisen-Schmidt condensation between substituted 2-hydroxyacetophenones (**27**) and substituted benzaldehyde (**28**) to furnish 2'-hydroxychalcone. Furthermore, the synthesis of pharmacologically interesting (owing to its diuretic and choleretic properties) synthesis of Vesidryl (2', 4,4'-trimethoxychalcone) (**29**) was also achieved for the first time.

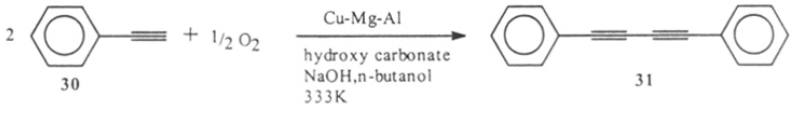
Scheme 8



Coupling of phenylethyne (Scheme 9)

Cu-Mg-Al hydroxycarbonate, derived from Cu-Mg-Al hydrotalcite afforded the coupling of phenylethyne (**30**) to 1,4-diphenylbuta-1,3-diyne (**31**) in the presence of sodium hydroxide and oxygen.[31] This method offers a heterogeneous alternative to the conventional homogeneous reaction such as Glaser and Eglington reaction and Cadiot-Chodkiemicz reaction.[32]

Scheme 9

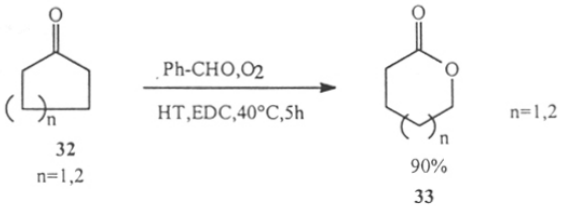


Oxidation reactions (Scheme 10, 11, 12)

There are few examples for the oxidation reactions utilizing hydrotalcites. These include Baeyer-Villiger oxidation[33] of ketones (**Scheme 10**), epoxidation of electron-deficient alkenes,[34] (**Scheme 11**) epoxidation of alkenes[35] (**Scheme 12**) etc.

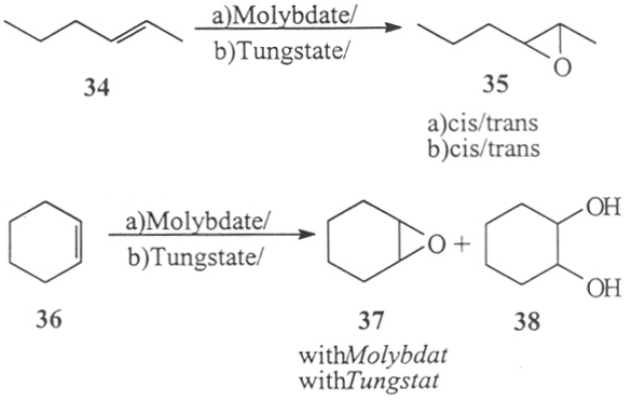
Baeyer-Villiger oxidation of ketones was achieved using a combination of oxidant systems containing molecular oxygen and benzaldehyde in the presence of hydrotalcites using EDC as a solvent to afford high yields of lactones (**33**) and esters at 40°C.

Scheme 10



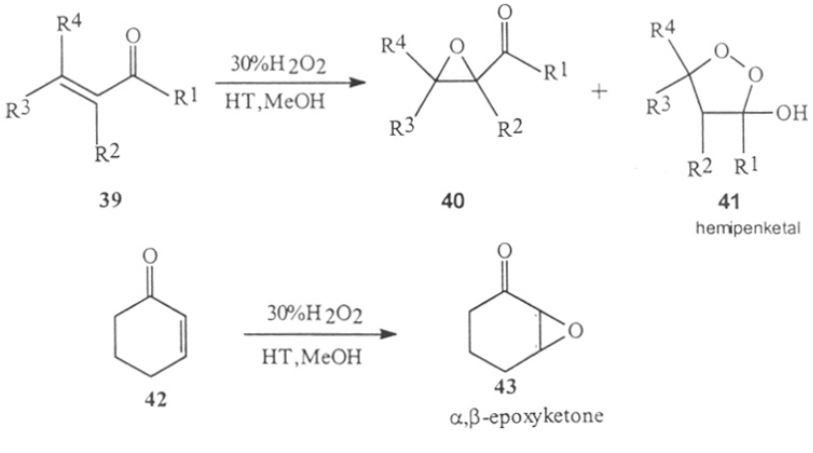
Hydrotalcite pillared with polyoxometalates of Mo and W were found to catalyze epoxidation of alkenes with H_2O_2. Epoxidation of 2-hexene (**34**) was favoured than that of cyclohexene (**36**) as the latter, underwent subsequent hydrolyses of epoxides to form diols.

Scheme 11



Hydrotalcite (Mg/Al = 2-5) promoted epoxidation of electron-deficient alkenes with H_2O_2 were studied by Figueras et. al. With the most open chain substrates, the epoxide is not the only product but 3-hydroxy-1,2-dioxolanes (**41**) (hemiperkeals) was also obtained, whereas cyclic ketones gave exclusively α,β-epoxyketones (**43**).

Scheme 12



In summary, HT-like anionic clays are versatile catalysts for polymerization, condensation reaction and oxidation reaction etc. In the present study utility of Zr-containing hydrotalcite-like compounds for oxidation of phenols is discussed.

Objective

Hydrotalcite like compounds have the general formula:

$[M(II)_{1-x}\ M(III)_x(OH)_2]^{x+}\ [A^{n-}{}_{x/n}]^x\ .\ yH_2O$

where

M(II) = Cu^{2+}, NI^{2+}, CO^{2+}, Zn^{2+}, Mn^{2+} and

M(III)= Al^{3+}, Fe^{3+}, Cr^{3+}, Ca^{3+}, V^{3+},[36,37] and more recently Ru^{3+} and Rh^{3+} were synthesized[38] and reported. However no attempts have been made so far on the synthesis of HT-like compounds containing Zr^{4+} ion. The importance of Zr containing HT-like compounds stem from the fact that they could be similar to zeolites containing Zr-silicalites which have been used as catalysts for liquid phase hydroxylation of phenols.[39] In the light of the above facts, preliminary studies on the synthesis of new Zr containing anionic clays and their catalytic ability in the liquid-phase hydroxylation of phenol were focussed at.

Present work

The hydroxylation of phenol to catechol and hydroquinone was expected in the present study. Akin to Cr species, Zr^{4+} species do not have high redox potential. The synthesis of polyhydroxy phenols are important because the conventional chemical methods include usually very harsh conditions such as sulphonation followed by sodium hydroxide fusion thereby generating inorganic waste materials. Additionally, they lack atom economy. Furthermore, the disposal of waste materials may cause environmental pollution. The synthesis of polyhydroxy phenols from phenol with the use of heterogeneous catalysts using H_2O_2 as oxidant is considered as environmentally safer process. Moreover, oxidations involving HT-like anionic clays are not studied in detail, only fewer oxidation methods were studied such as Baeyer-Villiger oxidation, epoxidation of alkenes and epoxidation of electron-deficient alkenes. Only in the case of epoxidation reaction, H_2O_2 was employed as an oxidant whereas in the Baeyer-Villiger oxidation, O_2 is used. Hence to explore the possibility of hydroxylation of phenols new Zr^{4+} containing HT-like materials were synthesized and their catalytic performance in the liquid-phase hydroxylation of phenols were studied.

Zr containing hydrotalcite like anionic materials were synthesized by co-precipitation method in an alkaline medium at room temperature. To an aqueous solution containing a mixture of $Mg(NO_3)_2$, $Al(NO_3)_3$ and $ZrO(NO_3)_2$, a mixture of NaOH and Na_2CO_3 was added dropwise at constant pH (around 10) by reading the pH with a pH meter. After all the addition was over, the resulting precipitate was filtered, washed with demineralized and double distilled water several times till the pH of the filtrate was extractly 7; the precipitate thus obtained was then dried at 373K overnight. The presence of Zr in the brucite like-layer was confirmed by powder X-ray diffraction uv-visible diffuse reflectance spectroscopic techniques.

XRD - studies

All the materials obtained by the precipitation methods were purified and dried at 373K overnight and then these materials obtained were powdered. The materials thus synthesized as per precipitation method include various MgAl-Zr-HT with Mg:Al:Zr atomic ratio ranging from 3:1:0 to 3:0:1 and these were subjected PXRD analysis separately.

The PXRD analysis of Zr 0.0HT to Zr 0.6HT are given in table alongwith the elemental analysis.

Sample	[1]Mg:Al:Zr Atomic ratio	[2]Carbon Content	[3]Lattice Parameter		
			a(A°)	c(A°)	v(A°)^3
Zr0.0HT	3:0.96:0.00	2.44	3.0584	23.1811	187.8
Zr0.1HT	3.0.85:0.07	-	3.0643	23.4570	190.8
Zr0.2HT	3:0.78:0.14	2.71	3.0688	23.5305	191.9
Zr0.3HT	3:0.68:0.21	2.91	3.0687	23.7243	193.5
Zr0.4HT	3.0.67:0.33	3.01	3.0732	23.7681	194.4
Zr0.5HT	3:0.57:0.37	-	3.0773	23.9383	196.3
Zr0.6HT	3:0.52:0.50	3.51	3.0780	24.1184	197.9

[1]Determined by X-ray fluorescene spectroscopy
[2]Determined by elemental analysis
[3]Refined using least sequence fitting method for hexagonal crystal system

From the table, it is evident that the increase in lattice parameters "a" and "c" with corresponding increase in the unit cell volume "v" with the increase in Zr content clearly demonstrates the effective incorporation of Zr^{4+} in the HT framework. The increase in "a" parameter is attributed to the isomorphous substitution of Al^{3+} by Zr^{4+} in HT matrix. The constant increase in "c" paramter over the increase of Zr^{4+} content may be due to the weakening of the interaction between brucite-like layer and inter-layer anions. Although a single phase corresponding to HT is obtained for all the samples, the crystallinity of the samples decreased with increase in Zr content. A binary Zr containing HT without Al forms a poorly crystalline ZrO_2 phase (spinel) rather than a HT phase, indicating that the presence of Al favours the formation of pure HT-like phase. Since, the Al^{3+} is isomorphously replaced by Zr^{4+}, the electroneutrality should be compensated by the incorporation of more amount of carbonate anions $(CO_3)^{2-}$. This fact is supported by an increase in carbon content from 2.44% to 3.51% for Zr0.0HT to Zr0.6HT.

UV-vis diffuse reflectance spectroscopic studies

All the synthesized samples were subjected uv-vis reflectance spectroscopic studies and the uv spectra are given in the Fig.3.

All these samples, including the one calcined at 723K (Fig 3d), exhibited a single narrow band in uv region (210 nm). This absorption band is attributed to the LMCT spectra (arises from $p\pi$-$d\pi^*$ electronic charge transfer due to ligand metal interaction). Pure ZrO_2 and physical mixture of Zr0.0HT and ZrO_2 exhibited bands at 240 and 320 nm (near uv region). These results confirm the absence of ZrO_2 species within the sample and indicate that the Zr^{4+} cations are well dispersed in the HT matrix, similar to that of Zr-Silicalites[40,41].

Hydroxylation of phenol

Initial study was conducted using Zr0.3HT (having Mg:Al:Zr = 3:0:68:0.21) on the hydroxylation of phenol using H_2O_2/phenol molar ratio 7.0 in solvents such as water, carbon tetrachloride and methanol. Those solvents did not show any catalytic activity. However, appreciable activity was observed when petroleum ether was used as solvent. The TLC studies revealed that the products obtained were not o-quinone or p-quinone but they are catechol and hydroquinone (solvent system 20% ethylacetate in pet.ether). The phenol had more Rf value than catechol and catechol had more Rf value than that of hydroquinone. Later, the percentage of product formation was analyzed by GLC

studies. Later some of Zr containing hydrotalcites have been tested as catalysts in the hydroxylation of phenol using H_2O_2 as oxidant (H_2O_2/Phenol molar ration 3.5-7.0). The results obtained in hydroxylation of phenol over various Zr containing hydrotalcites are presented in Table below.

Table 2 Hydroxylation of phenol with H_2O_2 over MgAlZr-HT

Catalyst	H_2O_2/phenol molar ration	TON[a]	Product selectivity (mass %)	
			Catechol	Hydroquinone
Zr0.0-HT	5.0	-	-	-
Zr0.1-HT	5.0	1.4	100	-
Zr0.3-HT	5.0	1.0	100	-
Zr0.3-HT[b]	5.0	3.8	100	-
Zr0.3-CHT[c]	5.0	1.9	100	-
Zr0.3-HT	7.0	29.1	73.8	26.2
Zr0.3-HT	10.0	40.5	65.1	34.9
ZrS-1	5.0	-	-	-
ZrO_2	5.0	-	-	-

[a]TON = Turnover number (mole of phenol converted per mole of Zr atom). [b] H_2O_2 was added dropwise using a syringe pump at a rate of 0.5 ml h^{-1} . [c]Sample calcined at 723 K/5 h. Reaction conditions: solvent light petroleum (bp 60-80°C) 30 ml; phenol, 1g; catalyst, 100 mg; temperature 353 K; time 8 h.

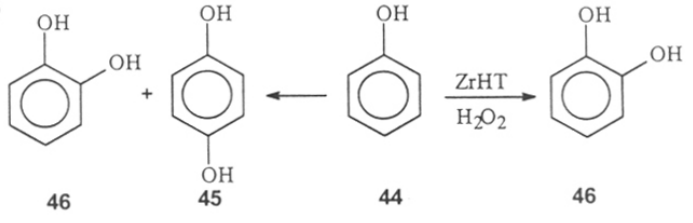
It is interesting to note from the table that the turnover number [TON=Turnover number (mole of phenol converted per mole of Zr atom)] increases four fold (1.0 to 3.8) when H_2O_2 was added dropwise using a syringe pump rather than adding it in one lot. Similarly, a two fold increase (1.0 to 1.9) in catalytic activity is noticed if the sample is calcined at 723K for 5 hours. The most important point to mention is that, in all these cases catechol is obtained as a unique product with 100% selectivity with glc studies with 10% conversion of phenol. However, with the increase in H_2O_2/phenol molar ratio from 3.5 to 5.2 and 7.0, eventhough the TON is increased the selectivity to catechol decreased at the cost of hydroquinone. The pure MgAl-HT does not possesses any catalytic activity under the same conditions; this was also true in the case of ZrO_2 and ZrS-1 whereas Zr^{4+} containing hydrotalcites show the catalytic activity for the hydroxylation of phenol to catechol clearly indicates that the Zr^{4+} present in the HT framework plays a pivotal role in catalytic activity.

Results and Discussion

The Zr-HT compounds were synthesised and characterized and the data obtained confirms the presence of Zr^{4+} in brucite-like layers.

The Zr^{4+} present in the HT framework was found to be active in the hydroxylation of phenol using H_2O_2 as an oxidant. Akin to that of TS-1 in the hydroxylation of phenol, Zr HT-like compounds gave 100% selectivity and furnished only catechol (**45**).

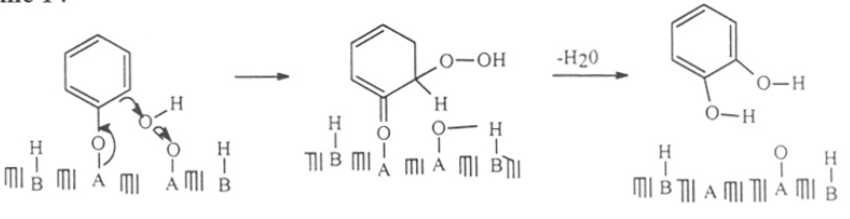
Scheme 13



Both phenol and H_2O_2 are dissociatively adsorbed as proton, phenoxide ion and peroxide ion. The protons bind to the surface basic sites while the phenoxide ion and peroxide ion are attached to the neighbouring Lewis acidic sites. Nucleophilic attack of by C-2 of the adsorbed phenoxide group onto the adsorbed peroxide ion takes place to furnish the catechol selectively. Thus the Zr-HT framework directs the ortho-hydroxylation of phenol.

The selectivity can be due to the following fact.[42] (**Scheme 14**)

Scheme 14



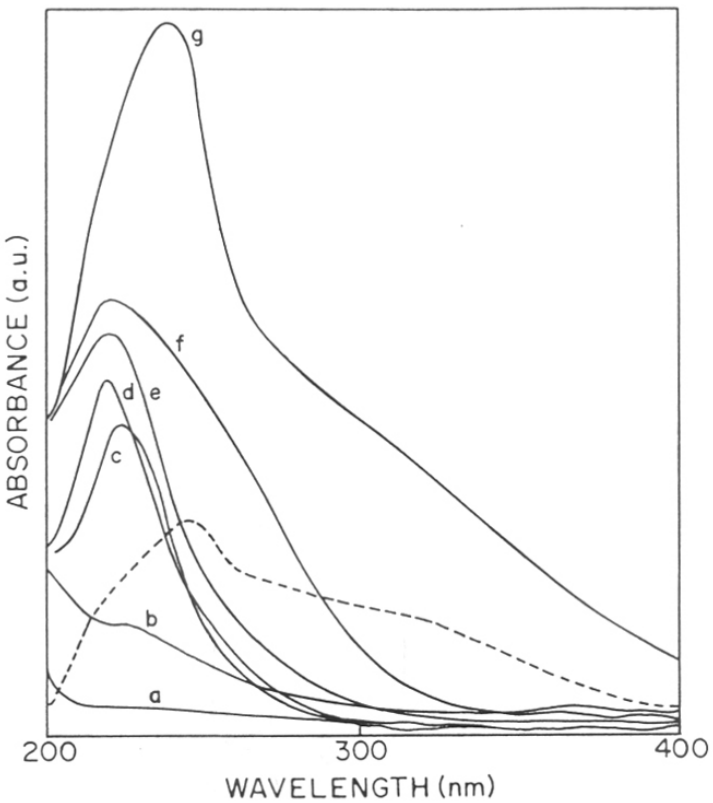
Mechanism of alkylation of phenol to catechol over Zr-HT-like compounds (A) acidic sites B basic sites:

Thus, the preferential ortho-hydroxylation over these catalysts may be due to proximity of the adsorbed peroxide fragment to the ortho position of the surface of the phenoxide ion, where the phenoxide ion may be held by Zr^{4+} species, present in the Zr-HT like compounds.

Further work is in progress to improve the catalytic performance of these anionic clays.

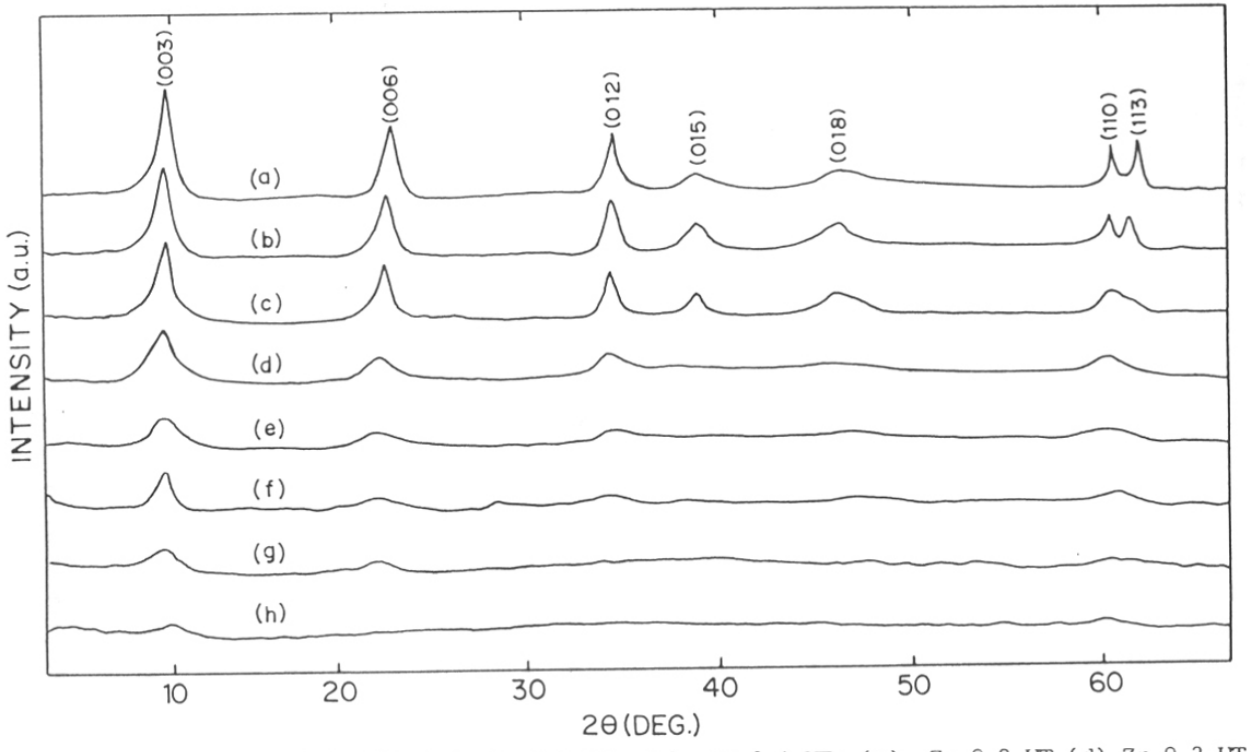
Conclusion

1. Liquid phase hydroxylation of phenol was studied using a new catalytic system.
2. It found that the Zr incorporated in the HT framework plays a pivotal role for catalytic activity.
3. These anionic clays exhibit ortho-selectivity to furnish catechol in the hydoxylation of phenol. Further more it was found superior to TS-1 with respect to 100% ortho-selectivity.
4. Pure and crystalline Zr containing HT-like compounds have been synthesized easily by a simple co-precipitation method and their catalytic hydroxylation of phenol to catechol was evaluated.
5. The catalyst was recycled and reused atleast three times without loss of activity and selectivity.



UV-Vis DR spectra of MgAlZr-HT

(a) Zr 0.0-HT; (b) Zr 0.1-HT; (c) Zr 0.3-HT;
(d) Zr 0.3-CHT; (e) Zr 0.5-HT; (f) Zr 0.8-HT;
(g) ZrO_2 (.....) Zr 0.0-HT + ZrO_2 (physical mixture)



PXRD patterns of MgAlZr-HT: (a) Zr 0.0-HT; (b) Zr 0.1-HT; (c) Zr 0.2-HT (d) Zr 0.3-HT (e) Zr 0.4-HT; (f) Zr 0.5-Ht (g) Zr 0.6-HT (h) Zr 0.7-HT

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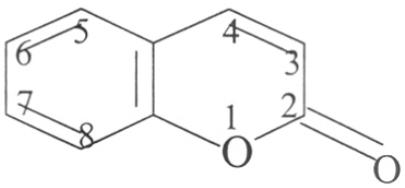
PART II

A CONVENIENT, ONE-POT SYNTHESIS OF COUMARINS (2H-BENZOPYRAN-2-ONES) CATALYSED BY HYDROTALCITE-LIKE ANIONIC CLAYS

Introduction

Earlier part (part I) of this chapter described the oxidation of phenols to p-benzoquinones and catechol using chromium silicate (CrS-2) and synthesis of a new Zr^{4+} containing hyrotalcite-like anionic clays and its application in the oxidation of phenol. This part of the thesis highlights the utility of hydrotalcite-like anoinic clays for the synthesis of coumarin and its analogues.

Coumarin, 2H-1-benzopyrano-2-one (**1**) is the odoriferous principle of the tonka bean (Dipteryx odorata), sweet clover (Melilotus officinalis and alba), and woodruff (Asperula odorata); widely distributed in the plant kingdom, it occurs in oil of lavender, oil of cassia, citrus oils, balsalm peru and in some 60 other species of plants.[1]



1

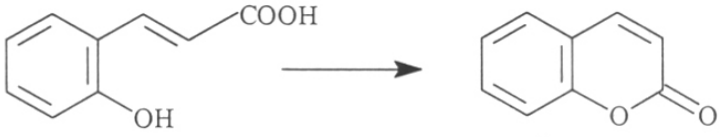
Coumarin is widely used in perfumery, cosmetic, and related industries owing to its pleasant bitter-sweet and characteristic odour. Large quantities of coumarin were earlier used in the food industry mostly associated with vanillin for flavoring chocolates, candies, confections, and baked goods.

Coumarin was first isolated by Vogel[2] 1820 by extraction from tonka beans (Dipteryx odorata), which contains 1.5% coumarin. This method remained the source of coumarin until the synthetic methods, pioneered by Perkin in 1868, largely displaced coumarin from natural sources.

Bio-synthesis of coumarin (Scheme 1)

Structurally, the benzopyrone nucleus can be regarded as a derivative of 2'-hydroxycinnamic acid (**2**), formed by lactonization of the carboxyl and 2'-hydroxy functions.

Scheme 1



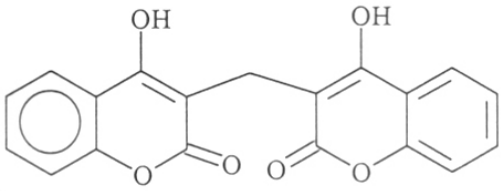
2 **1**

As such, the simple coumarin nucleus is phenyl propanoid, having a C_6 benzene ring linked to a C_3-aliphatic side chain. It has long been recognised[3] that phenyl propanoids are most commonly derived via the Shikimate-chorismate biosynthetic pathway.

Biological activity of coumarins

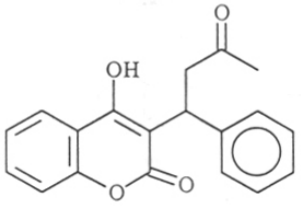
Coumarins occupy a special role in the realm of natural and synthetic organic chemistry because many products which contain this subunit exhibit useful and diverse biological activity. A large number of coumarin derivatives have been identified in plants and many of them have been synthesized and studied for their physiological activity. Only a few are mentioned because of their economic significance.

Dicumarol (**3**) is prepared synthetically by reaction of 4-hydroxycoumarin with formaldehyde[4].

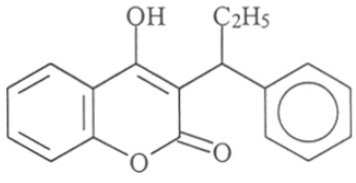


3

Warfarin (**4**) is related to dicumarol and also all 3-substituted 4-hydroxycoumarins, also possess hemorrhogic properties.[5] Of these, warfarin, 3-α-acetonylbenzyl-4-hydroxycoumarin, is a highly effective rodenticide. It is prepared by the Michael condensation of benzylidine acetone with 4-hydroxycoumarin.[6] Phenprocoumaron (**5**), similar in structure to warfarin, usually maintains the anticoagulant effect established by other anticoagulants.[7]

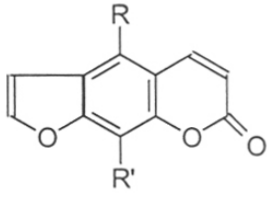


4



5

Among the furanocoumarins (**6,7,8,9**) which Psoralen (**6**) to exhibits anti-tumour activities[8], whereas bergapten (**7**), isopimpinillin (**8**), xanthotoxin (**9**) are known for their malluscidal activity.[9]



6 R=R'=H psoralen,

7 R=OCH_3, R'=H, bergapten

8 R=R'=OCH_3, isopimpinillin

9 R'=OCH_3, R=H, xanthotoxin

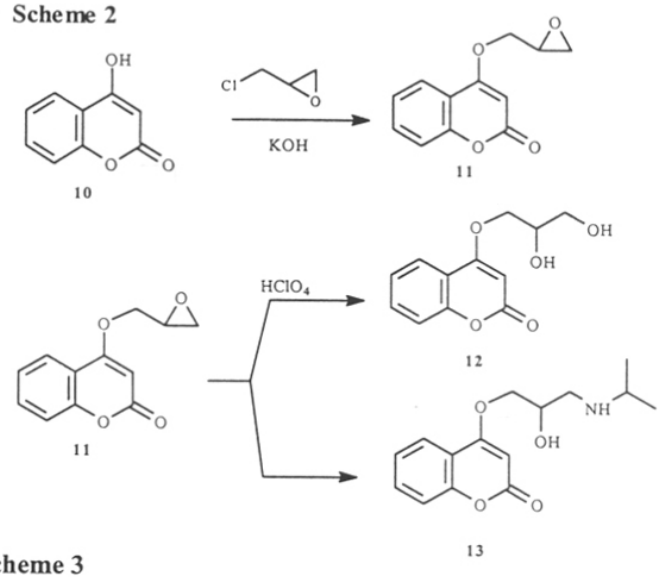
Several 3-substituted 7-hydroxycoumarins rank among the most efficient photostable laser dyes emitting in the blue-green region of the visible spectrum. The lasing range covered by coumarin dyes is appreciably extended when the 3-substituent is a heterocyclic moiety.[10] These were also found to exhibit variable antibacterial activities against Gram positive, Gram negative and acid fast bacteria.

3-Alkyl coumarins are reported to have anthelmintic, hypnotic and insecticidal properties[11] and 3-phenyl coumarins are reported to possesses anti-coagulant and coronary-constricting properties[12]

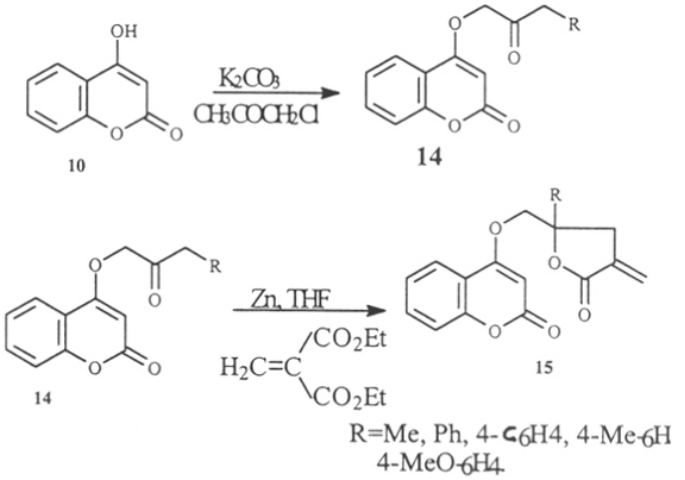
Recent advances in the field of coumarins for biological activities (Scheme 2,3,4)

Of late, there have been some interest in the preparation of several 4-hydroxycoumarin derivatives[11, 12, 13] as well as 7-hydroxycoumarin derivatives[14] with various functional groups, such as 2-hydroxy-3-isopropylaminopropyl, (**13**) 2-3-epoxypropyl (**12**), 2,3-dihydroxypropyl (**12**) and α-methylene-√-butyrolactone moieties (**15**) and they have been found to be best for antiplatelet activity over other clinically useful antiplatelet drugs such as aspirin, eicosapentanoic acid, dipyridomole and ticlopidine.

Scheme 2

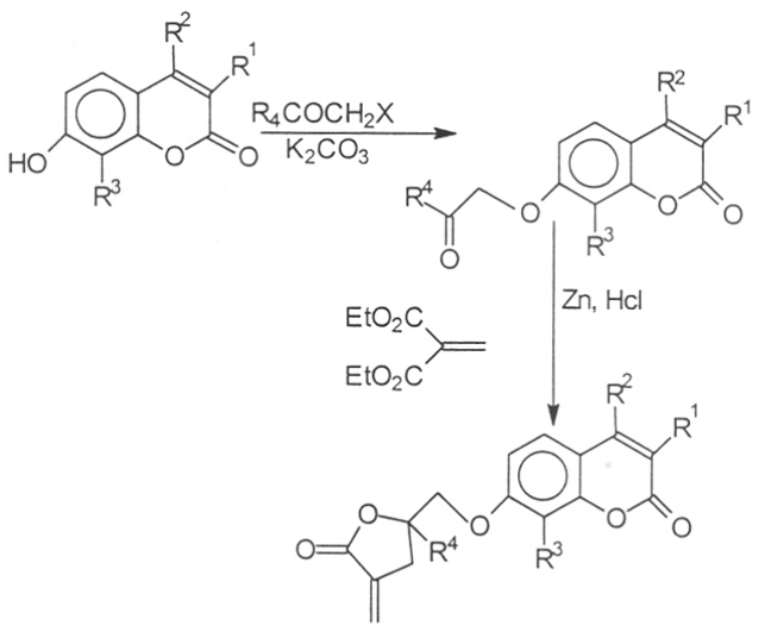


Scheme 3



R=Me, Ph, 4-C6H4, 4-Me-6H
4-MeO-6H4.

Scheme 4



	R^1	R^2	R^3	R^4
a	H	H	H	CH_3
b	H	CH_3	H	CH_3
c	CH_3	CH_3	CH_3	CH_3
d	H	H	H	C_6H_5
e	H	CH_3	H	C_6H_5
f	CH_3	CH_3	CH_3	C_6H_5
g	H	H	H	p-C_6H_4f
h	H	H	H	p-C_6H_4Cl
i	H	H	H	p-C_6H_4Br
j	H	H	H	p-$C_6H_4C_6H_5$
k	H	H	H	p-C_6H_4-OCH_3

The SAR studies have also been evaluated in detail.

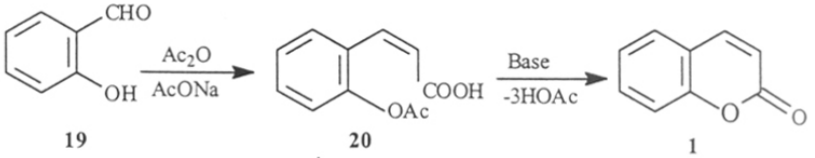
Methods of preparation of coumarins

There are many synthetic routes to the coumarins[15] including Perkin Raschig method, Pechmann, Knoevenagel and Wittig reactions. The practical methods for the synthesis of coumarins use as starting materials, either salicylaldehyde or phenol, from which the pyrone ring is elaborated. Some of the methods described below give poor yields of coumarin itself but often excellent yields of certain substituted coumarins.

Perkin reaction (Scheme 5)

William H. Perkin synthesized coumarin (**1**) in 1868[16] by heating the sodium salt of salicylaldehyde with acetic anhydride. Perkin later found that sodium acetate could serve as the base catalyst in stead of sodium salicylaldehyde.

Scheme 5



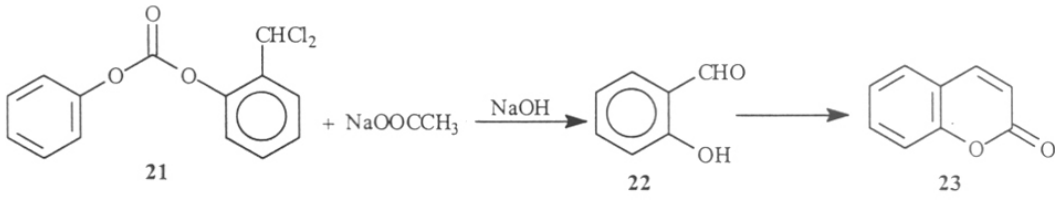
19 **20** **1**

cis-o-acetoxy cinnamic acid

Raschig Method (Scheme 6)

Rachig method[17] is a practical method for the preparation of coumarin. It involves the conversion of benzalchloride (**21**) intermediate from o-cresol directly to coumarin by heating with anhydrous sodium acetate.

Scheme 6

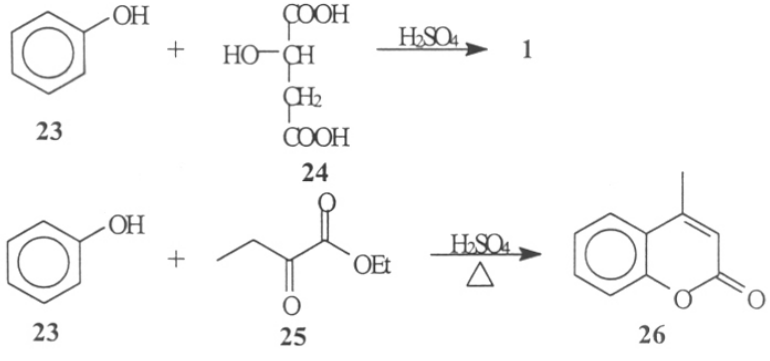


21 22 23

Pechmann condensation (Scheme 7)

Coumarins have been synthesized by the Pechmann condensation[18], i.e. by condensation of substituted phenols (**23**) with β-ketoesters (**25**), malic acid[19], maleic or furmaric acids[20] in the presence of conc. H_2SO_4.

Scheme 7



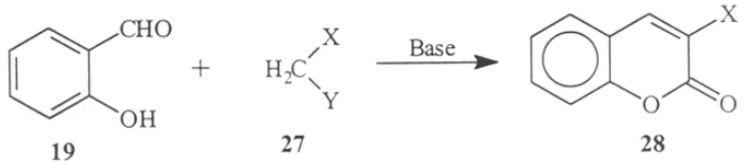
23 24 23 25 26

Various reagents have been used for this reaction e.g. P_2O_5, H_2SO_4, $POCl_3$, H_3PO_4 and $ZnCl_2$.[21] In all these methods mixtures of substituted phenols, β-ketoesters and the acidic catalysts were allowed to stand overnight for a number of days depending on their reactivity or were heated above 150°C[22]. Recently, cation exchange resins[23] and solid support catalysts[24] have also been used. G.L. Kad et. al., of late, accelarated Pechmann reaction by microwave irradiations.[25]

Knoevenagel reaction (Scheme 8)

The Knoevenagel reaction[26], in which a benzaldehyde is reacted with an activated methylene compound to form a cinnamic acid derivative, is readily adapted to coumarin synthesis by incorporation of a hydroxy group ortho to the aldehydic function. This methodology constitute a significant and widely used route to coumarins which has been adapted to incorporate alternative approaches both to the salicylaldehyde (**19**) and to the cinnamate components.

Scheme 8

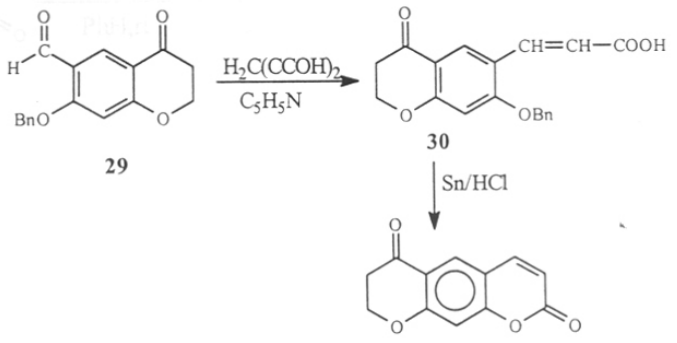


19 **27** **28**

Various bases like pyridine[27], piperidine[28], dimethylamine[29] have also been for Knoevenagel condensation .

Utilizing this conventional procedure, some of the naturally occurring compounds, viz. Gravelone[30] (**31**) and Xanthyletin[31] (**33**) have been synthesised (Schemes 9,10).

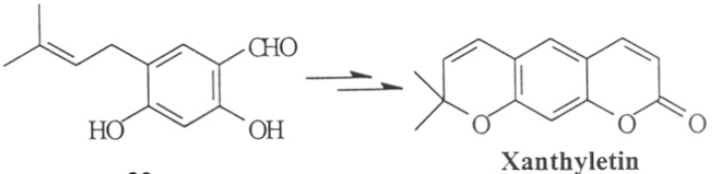
Scheme 9



29 **30**

31
Graveolane

Scheme 10



32 **Xanthyletin**
33

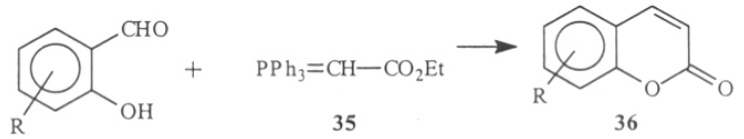
Elaboration of the side chain of the salicycaldehyde coupled with Knoevenagel condensation enabled the synthesis of xanthyletin (**33**).

Wittig methodologies to coumarins (Schemes 11,12, 13, 14)

Phosphorous ylides can function as the carbanionic species in Knoevenagel like reactions.

Substituted salicylaldehydes (**34**) react with $PH_3P{=}CH\text{-}CO_2Et$ (**35**) in boiling N,N-diethylaniline to give good yields of coumarins (**36**)[32] (**Scheme 11**).

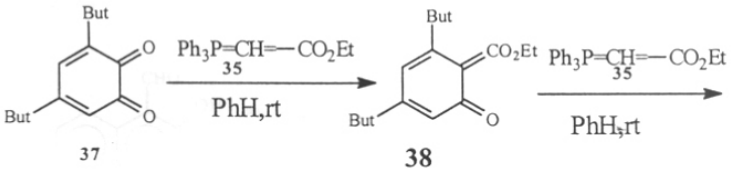
Scheme 11



34 **35** **36**

3,5-Di-t-butyl-1,2-benzoquinone afforded a -4-substituted coumarin (**40**).[33]

Scheme 12



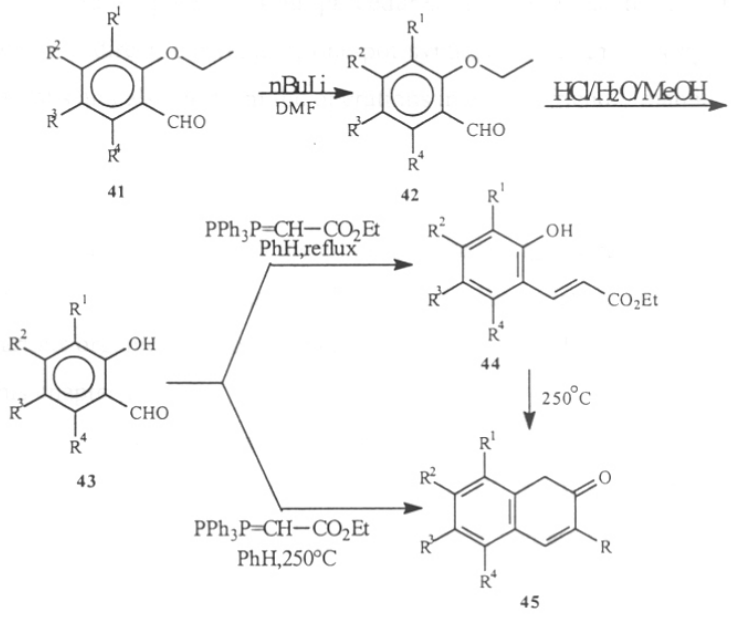
37 **38**

39 **40**

In a similar manner, 2-hydroxyacetophenone[34] and benzophenone[35] yield a 4-substituted coumarins.

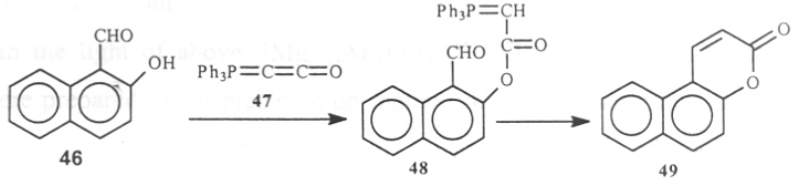
Directed lithiation of phenolic ethers and dealkylation followed by Wittig reaction of ethoxycarbonyl methylene triphenylphosphoranes afforded o-hydroxycinnamates (**44**) and coumarins (**45**). On heating, the o-hydroxycinnamic esters are converted into the coumarins[36] (**Scheme 13**).

Scheme 13



The addition of cumulated ylide[37] to salicylaldehyde also leads to coumarin (**49**) (**Scheme 14**).

Scheme 14



In summary, coumarins are prepared from phenol (**23**), salicylaldehyde (**19**), using various methodologies. Each synthesis mentioned has comparatively advantages and disadvantages. Many more methods are available, since they do not come under the purview of the present work, they are not discussed here.

Objective

Coumarins are of biological, pharmacological, industrial and economically important class of compounds. They have been utilized for the preparation other natural products such as coumarino-α-pyrones, coumarino-√-pyrones, furanocoumarins,

chromenes, coumarones and α-acylresorcinols. The synthesis of coumarins and their analogues suffer from, drastic acidic or basic conditions, multiple steps, complicated synthetic operations and lengthier work-up procedures. Hence, it was felt a worthwhile exercise to establish a direct, convenient, one-pot synthesis of coumarins by avoiding such harsh conditions and also perform the operations in an eco-friendly manner.

Present work

Recently, various types of clays have been utilized as heterogeneous catalysts in the field of synthetic organic chemistry. Hydrotalcite-like anionic clays have been employed for various organic functional group transformations (already discussed in the earlier part of this chapter).

Hydrotalcites can be represented by the general formula $Mg_6Al_2(OH)_{16}.4H_2O$. These compounds upon thermal calcination around 723K result in the formation of highly active mixed metallic oxides with high surface area, and are used potentially as a catalyst for various base catalysed condensation reactions owing to their basic properties. The Claisen-Schmidt condensation was catalyzed by hydrotalcite-like anionic compounds to furnish Vesidryl[38], (a pharmacologically interesting chalcone) and the Knoevenagel condensation to arrive at citronitril[39] by Corma et. al. prompted the synthetic studies towards coumarin *via* Knoevenagel condensation utilizing hydrotalcite-like anionic clays.

In the light of above, $[Mg_{(1-x)}Al_x(OH)_2]^{x+}\ CO_3^{2-}.mH_2O$ with Mg/Al rations of 2,3,4 were prepared by co-precipitation method under low supersaturation conditions[40] by adding simultaneously a mixture of aqueous solutions of NaOH (2-3M) and Na_2CO_2(0.2-0.35 M) at room temperature, with vigorous stirring and by maintaining the pH 9-10. The resulting heavy slurry was aged at 65°C for 30 min. with vigorous stirring. The precipitate was filtered, washed several times with distilled and demineralised water and dried in an air oven at 110°C overnight.

The FT-IR spectra of uncalcined samples reveal characteristic bands around 3500 cm^{-1}, 1640 cm^{-1} and 1380 cm^{-1} assigned to hydroxyl stretching (√ OH str.), hydroxyl bending (√-OH bend) and asymmetric stretching (√3) of carbonate respectively.

The XRD of the synthesized samples show sharp and symmetric peaks for (003), (006), (110) and (113) planes and broad and asymmetric peaks for (102), (105) and (108) planes which are characteristic of clay minerals possessing layered structure.[41]

The Table-1 below represents the typical XRD patterns of Mg-Al-HT with an Mg/Al atomic ratio of 3.

Table 1: XRD data of Mg-Al-HT with Mg/Al atomic ratio=3

Hkl	d(obs) (A°)	I/I max (%)
003	7.841	100
006	3.945	47
012	2.588	41
018	1.975	18
110	1.532	18
113	1.510	17

For calcination, about 3 g of the sample was placed in a 20 ml pyrex tube and calcined in air at 450°C and kept at this temperature for 8 h and then cooled to room temperature. The powder XRD patterns of calcined hydratalcites offer a highly disordered MgO phase with $d_{(200)}$ of the resulting MgO being less than that of pure MgO due to the dissolution part Al^{3+} in the MgO lattice to form solid solutions.

As the aim of present work is to check the activity and selectivity of calcined hydrotalcites with various Mg/Al atomic ratios for the synthesis of coumarins, salicylaldehyde and ethylacetatoacetate were taken in anhydrous EtOH with 10% w/w of the catalyst and the mixture was refluxed for 24 hours. There was no product formation. Similar was the case when anhydrous THF, dioxane and MeOH were used as the solvent.

The required product was formed in almost quantitative yield when benzene or toluene was used as solvent. Due to the carcinogenic nature of benzene, all the remaining experiments were carried out using toluene only.

The results obtained with various α-acylphenol and 2-substituted ethylaceate have been tabulated below and the products obtained were characterized by routine analyses (vide experimental).

Table 2: Synthesis of coumarins catalysed by $MgAl_3$.O CHT

Substrate	Reagent	Yield of the product (%)
Salicylaldehyde	Ethylacetoacetate	83
Salicylaldehyde	diethylmalonate	87
Salicylaldehyde	cyanoethylaceate	93
Salicylaldehyde	ethylacetate	24
o-Hydroxyacetophenone	cyanoethylacetate	92
o-Hydroxyacetophenone	ethylacetoacetate	87
o-Vanillin	ethylacetoacetate	85
o-Vanillin	cyanoethylacetate	92

Reaction conditions: 10.00 mmole of substrate + 11.00 mmole of reagent; solvent: Toluene (30 ml); Reaction temperature 353K, Time 4h; catalyst 10 wt% * Reaction time: 48 h.

The order of the reactivity of reagents was found to be: cyanoethylacetate>diethyl-malonate>ethylacetoacetate>ethylacetate.

Screening experiments were also carried out to find our the activity of hydrotalcites using various ratios of hydrotalcites and also with other catalytic materials and the results obtained are tabulated as below:

Table 3: Knoevenogel condensation of salicylaldehyde with diethylmalonate/ethylcyanoacetate catalyzed by hydrotalcite-like anionic clays

Catalyst	Reagent used	
	Diethylmalonate % of yield of product	Ethylcyano acetate % of yield of product
MgAl 2.0-CHT	40	48
MgAl3.0-CHT	83	95
[1]MgAl 3.0-HT	15	60
[2]MgAl 3.0-HT	45	95
MgAl 4.0-CHT	35	60
[3]MgO	12	23
[4]Al_2O_3	-	-
CS-X-Zeolite	-	-
HZSM-5	-	-

Reaction conditions 10.00 mmole of salicylaldehyde + 11.00 mmole of diethylmalonate/ethylcyanoacetate; solvent: Toluene (30 ml): Reaction temperature; 353K; Time; 4H; catalyst 10 wt.%.

[1]Uncalcined hydrotalcite [2]Catalyst 50 wt%
[3]MgO obtained from decomposition of co-precipitated $Mg(OH)_2$.
[4]Al_2O_3 obtained from decomposition of co-precipitate $Al(OH)_3$.

No reaction was observed with HZSM-5 which indicated that the acidic catalyst is not very much active for this reaction. The CS-X zeolite too was not found to be active. Pure MgO was slightly active whereas Al_2O_3 was not at all active but the reaction proceeded with hydrotalcite which indicated that the calcined hydrotalcites were more basic and catalyzed the reaction. In this study, MgAl 3.0CHT was found to be active the most active when MgAl 4.0 CHT was used activity was less as was the case with MgAl 2.0 CHT. Thus, the optimum catalyst is MgAl 3.0 CHT for the selective formation of coumarins.

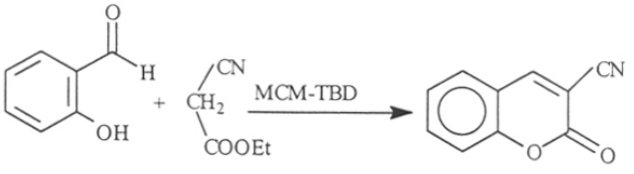
Unlike the conventional Knoevenagel condensation, in the present case, malonic acid does not participate in the reaction to yield 3-substituted coumarin. Ethylbromoacetate and ethylchloroacetate totally failed to give the 3-substituted coumarin.

Results and Discussion

An efficient, one-pot synthesis of coumarins have been achieved effectively in good yields using a heterogeneous hydrotalcite-like anionic clays.

It is noteworthy that, recently Jacob's et.al[42], have reported the synthesise of 3-cyanocoumarin using 1,5,7-triazabicyclo [4.4.0] dec-5-ene-immobilized in MCM-41, in moderate yields (58% yields) only.

Scheme 15



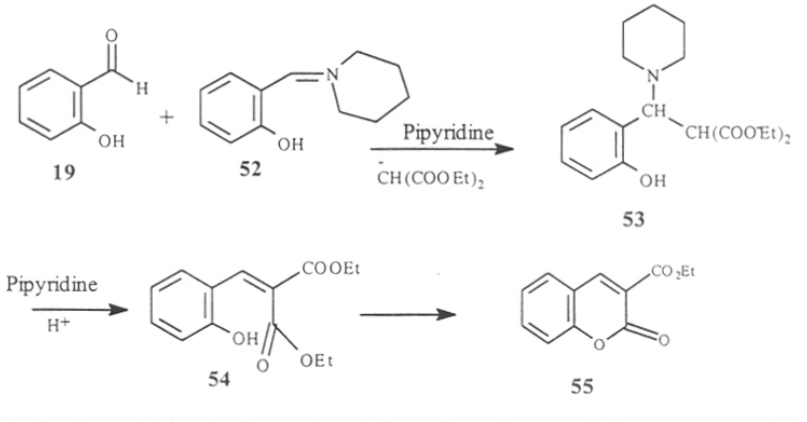
19 50 51

In the present work, the yields of the products obtained is almost nearly quantitative, which is indicative that the hydrotalcite-like anionic clays are superior to the other catalytic materials in such transformations.

Two mechanisms have been proposed for the Knoevenagel reaction. When piperidine is used as a base, it forms an imine or iminium salt (**52**) which subsequently reacts with the enolate of the active methylene compound.

Due to the presence of o-hydroxygroup, intramolecular ring closure to the coumarin can occur in a facile manner.

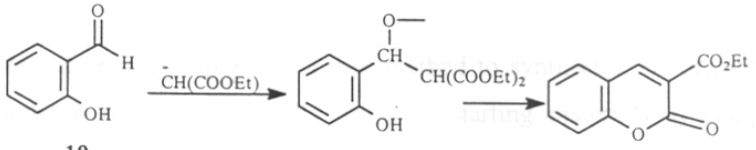
Scheme 16



19 52 53 54 55

In the other mechanism, the carbanion derived from the active methylene compound by deprotonation by the amine is considered to attack the carbonyl group without further intervention by the base, to give rise to coumarins.

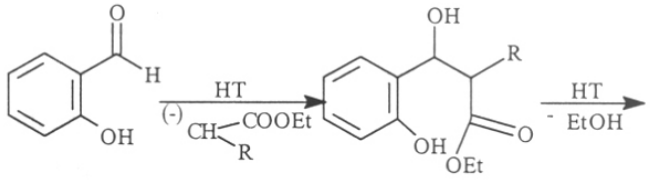
Scheme 17



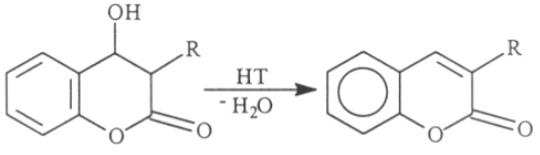
19 56 55

In the present work, the basic property of the catalyst is considered to be responsible for the deprotonation of active methylene compounds; the carbanionic species thus generated undergoes 1,2-addition with the carbonyl group of the substrate, followed by intramolecular esterification and elimination of water to furnish the coumarin.

Scheme 18



19 37



58 59

The role of hydrotalcite-like anionic clays is important, as this avoids the formation of Schiff bases, which is a major problem with the familiar immobilized primary and secondary amines.[43]

Malonic acid does not yield the coumarin; this may probably due to the poisoning nature of basic sites of the catalyst by protons of the reagent. Ethylbromoacetate and ethylchloroacetate too failed to furnish the respective coumarins, the reason for this could not be speculated at present.

In summary, the results obtained prove that it is feasible to synthesize various coumarins using hydrotalcite-like anionic clays as the catalytic systems. The thermal and mechanical stability of the catalyst ensures easy separation of the solid catalyst and the liquid phase, which is a serious problem for organic polymer supported catalysts.[44]

Conclusion

1. The present reaction represents a new method to synthesize 2H-benzopyran-2-one skeleton from commercially available starting materials in one-pot and under mild conditions.
2. In general, the hydrotalcite-like anionic clays worked better than MCM-TBD in terms of reaction conditions and yield.
3. This method is advantageous because of easy separation of product materials, quantitative yield, minimal environmental effects and recyclability of the catalytic materials.
4. The catalyst Mg.Al 3.0 CHT could be reused for many times without significant loss of activity and selectivity, catalyst was easily regenerated by washing with ethanol, followed by calcination.
5. Under the reaction conditions that were operative the product selectivity remained essentially 100%.
6. This is the first report that the hydrotalcite-like anoinic clays are able to catalyze the formation of coumarin under Knoevenagel condensation conditions.

EXPERIMENTAL:

Preparation of Mg:Al hydrotalcite:

The hydrotalcite clay with the composition of Mg/Al=3 was prepared by Co-precipitation method as follows:

Magnesium nitrate (115.38 g., 0.45 mole) and aluminium nitrate (56.27 g, 0.15 mole) were dissolved in 300 ml. of distilled and demineralized water. The magnesium nitrate and aluminium nitrate mixture was labeled as solution B. Sodium hydroxide (25.0g, 0.63 mole) and sodium carbonate (15.0 g, 0.53 mole) were dissolved in 150 ml of distilled and demineralized water and labeled as solution A.

Solution A and solution B were added simultaneously by means of a burette into a 100 ml beaker containing about 300 ml of double distilled water at a rate of about 60 ml of solution A per hour with constant stirring. Till the addition of solution A was over the pH of the reaction mixture was maintained at about 10 by adjusting the flow of solution B.

After the addition of all of solution A was complete, the precipitate obtained was aged at 65°C for 30 minutes. Then the solution was cooled to room temperature. The precipitate was filtered and the filtrate was washed several times with distilled water till the pH of the filtrate remained neutral. Finally, the precipitate was dried at 100°C in an air oven for 8 hours. The lumps were crushed into powder and stored in a dessicator.

General Procedure for the synthesis of coumarin:

Salicylaldehyde, o-hydroxyacetophenone, ethylacetate and 2-substituted ethylacetates were purified by distillation and o-vanillin was purified by recrystallization.

Into a flame dried 50 ml round-bottomed flask fitted with a reflux condenser containing a solution of o-acylphenol (10.0 mmol), 2-substituted ethylacetate (11.0 mmol) in anhydrous toluene/benzene 30 ml was introduced calcined hydrotalcite (10% w/w with respect to the weight of 2-substituted ethylacetate). There appeared an yellow coloration upon the addition of the catalyst. The reaction mixture was refluxed for 3-4 hours under an inert (nitrogen or argon) atmosphere. It was then allowed to cool to room temperature and the catalyst was filtered off using whatmann filter paper and further washed several times with toluene, the combined filtrate was concentrated *in vacuo* and brought to room temperature when the required product solidified. Recrystallization from petroleum ether yielded the pure coumarins.

Coumarin 2H-1-Benzopyran-2-one.

Yield: 0.36 g, 24%

M.P. 71-73°C (lit.[45] m.p. 69-73°C)

IR (nujol cm^{-1}): $\sqrt{}_{max}$ 3000, 1700, 1600

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 6.4 (d, J = 6.1 Hz, =C-C, 1H); 7.2-7.3 (m, Ar-H, 2H); 7.4-7.55 (m, Ar-H, 2H); 7.7 (d, J=6.1 Hz, H-C=C-C=O; 1H) .

3-acetylcoumarin; 3-acetyl-2H-1-benzopyran-1-one:

Yield: 1.7 g, 93%

M.P.: 120-126°C (lit.[46] m.p 124°C).

IR (Nujol, cm-^{1}): $\sqrt{}_{max}$ 3100, 1720, 1700, 1650, 1600.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.7 (S, -C-CH_3, 3H); 7.3-7.45 (m, Ar-H, 2H); 7.55-7.7 (m, Ar-H, 2H), 8.55 (s, 1H).

3-Ethyl carboxylate-2H-1-benzopyran-1-one; ethyl-3-coumarin carboxylate.

Yield: 1.9 g, 89%

M.P.: 92-94°C (lit.[47] mp. 94°C).

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.45 (t, J = 7.3 Hz, -C-CH_2-CH_3, 3H); 4.4 (q, J=7.3 Hz, -C-CH_2-CH_3, 2H); 7.3-7.4 (m, Ar-H, 2H); 7.6-7.7 (m, Ar-H, 2H); 8.5 (s, -H-C=C=CO, 1H).

3-Acetyl-4-methyl-coumarin:

Yield 1.7 g, 84%

M.P. 102-105°C (Lit.[48] m.p. 103°C)

IR (Nujol, cm^{-1}): $\sqrt{}_{max}$ 2900, 1690, 1600.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.5 (s, -C=C-CH_3, 3H); 2.65 (s, -CO-CH_3, 3H); 7.35-7.45 (m, Ar-H, 2H); 7.55-7.65 (m, Ar-H, 1H); 7.8 (m, Ar-H, 1H).

4-methyl-3-ethylcoumarin carboxylate:

Yield : 1.83 g, 79%

M.P. : 94-97°C (Lit.[49] 95-96°C)

IR (Nujol, cm^{-1}): : $\sqrt{}_{max}$ 2900, 1720, 1650, 1600.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.45 (t, J = 7.3 Hz, -O-C(O)-CH_2-$\underline{CH_3}$, 3H); 2.7 (s, -CH=C-$\underline{CH_3}$, 3H); 4.45 (q, J = 7.3 Hz, -O-C(O)-$\underline{CH_2}$-CH_3, 2H); 7.4-7.45 (m, Ar-$\underline{H}$, 2H); 7.55-7.65 (m, Ar-$\underline{H}$, 1H); 7.8 (m, Ar-$\underline{H}$, 1H).

3-Acetyl-8-methoxycoumarin:

Yield: 1.76 g, 81%

M.P. 198-201°C

IR (Nujol, cm^{-1}): $\sqrt{}_{max}$ 2880, 1720, 1650, 1600.

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 2.75 (s, O-C(O)-$\underline{CH_3}$, 3H); 4.00 (s, -O$\underline{CH_3}$, 3H); 7.2-7.3 (m, Ar-$\underline{H}$, 3H); 8.5 (s, $\underline{H}$-C=C=O, 1H).

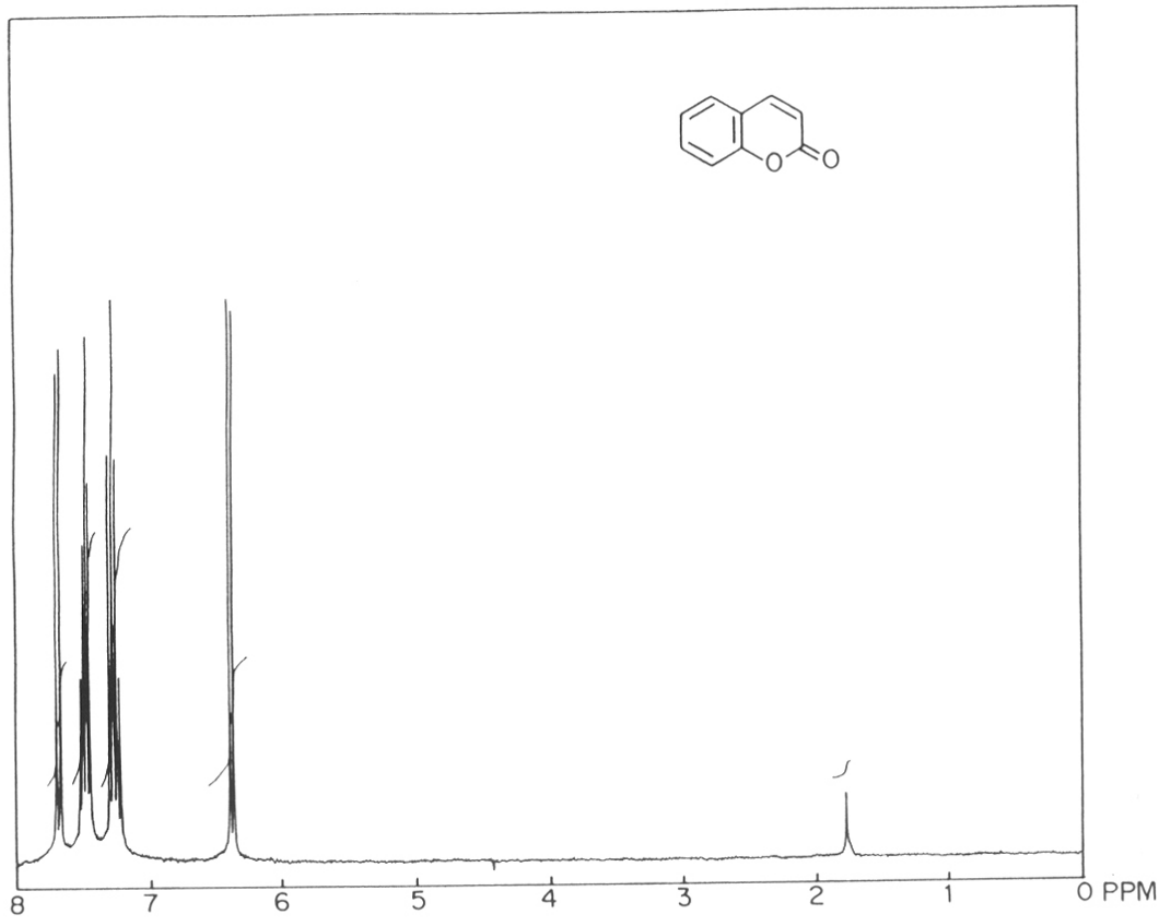
8-Methoxy-3-ethylcoumarin carboxylate:

Yield 1.97; 82%

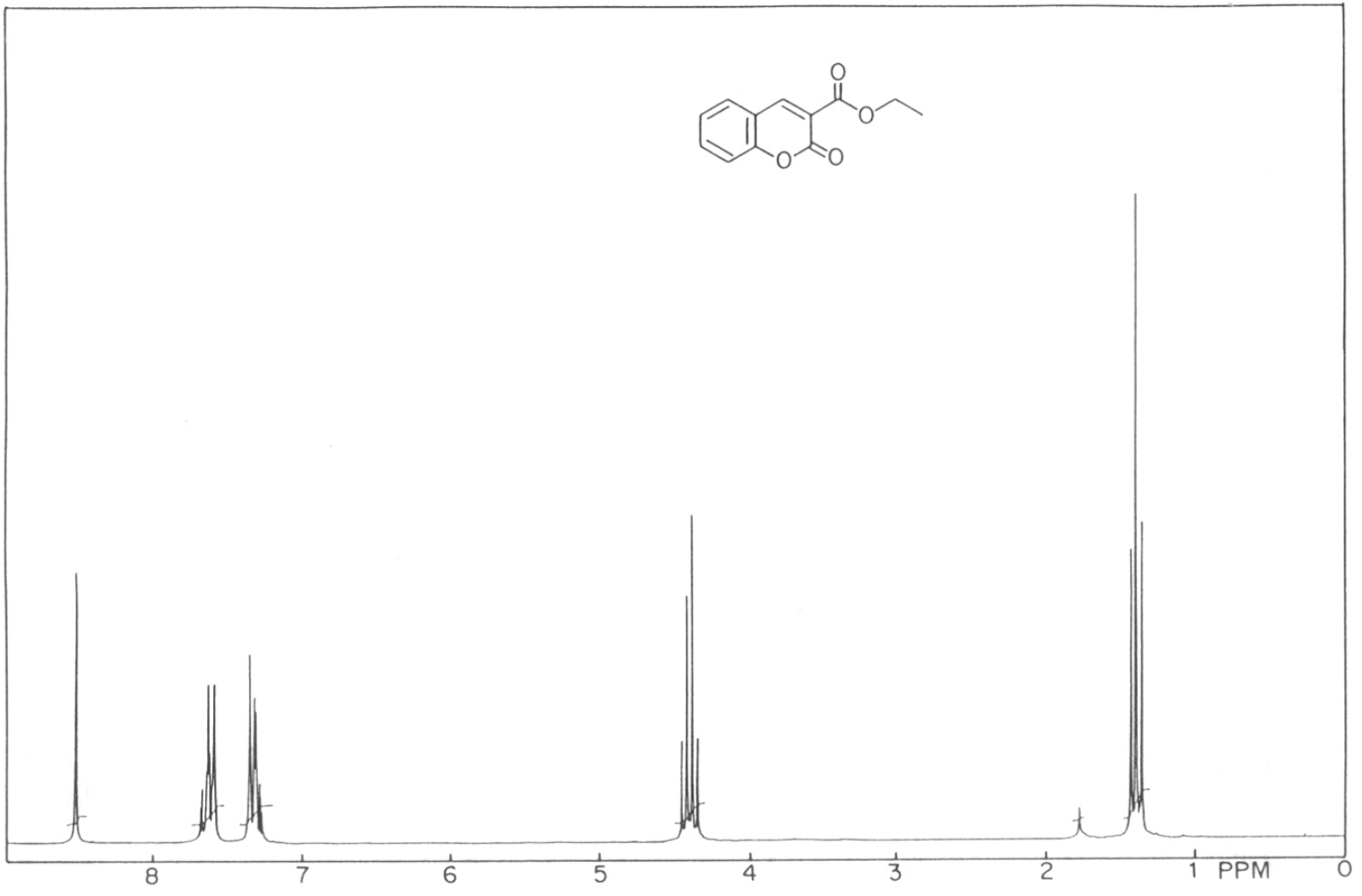
M.P. 185-189°C

IR (Nujol, cm^{-1}) $\sqrt{}_{max}$ 2900, 1740, 1600.

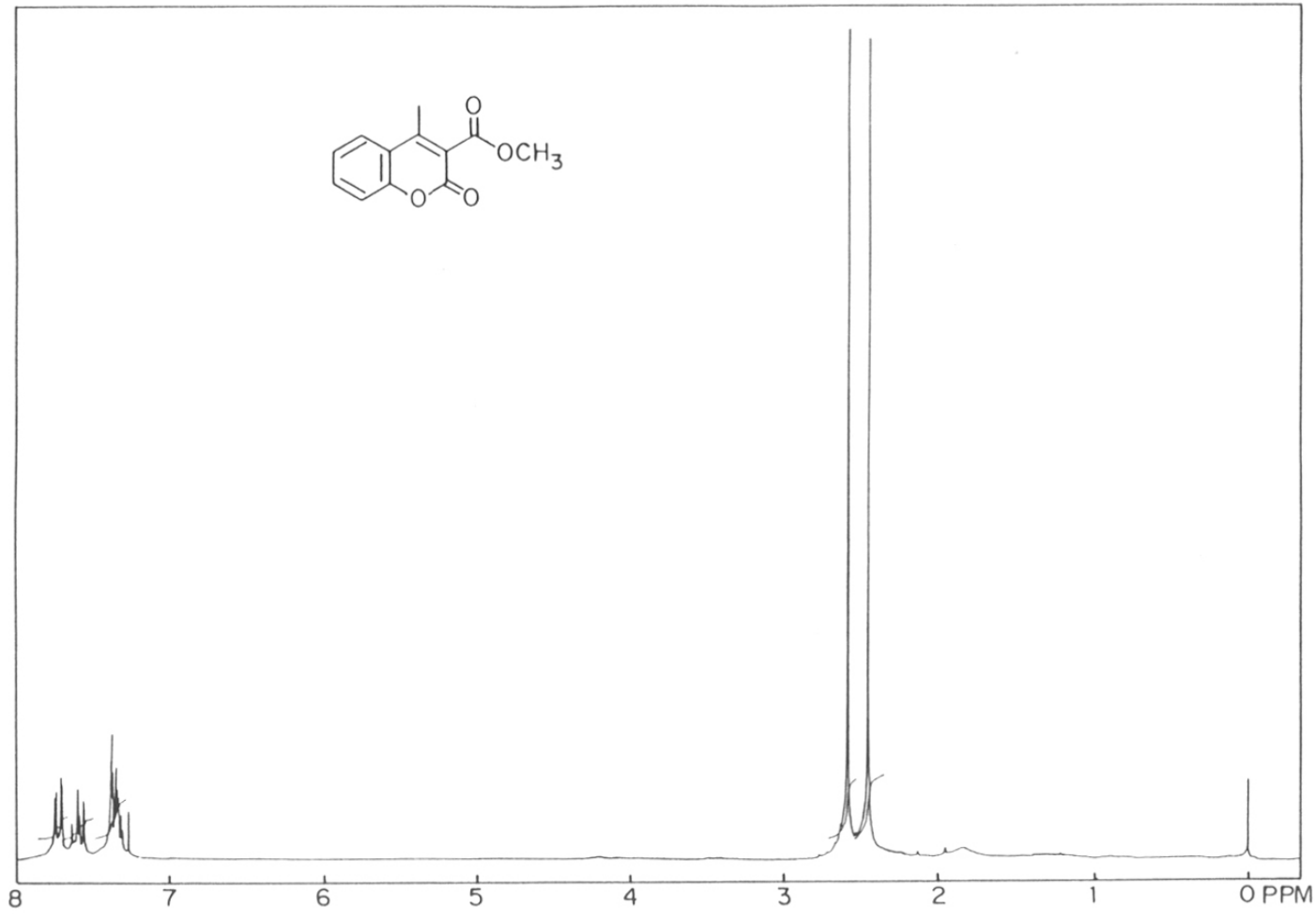
^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.4 (t, t, 7.3 Hz, -C-$\underline{CH_3}$, 3H); 4.0 (s, -O$\underline{CH_3}$, 3H); 4.4 (q, J=7.3 Hz, -C-$\underline{CH_2}$-CH_3, 2H); 7.2-7.35 (m, Ar-$\underline{H}$, 3H); 8.5 (s, $\underline{H}$-C=C=O, 1H).



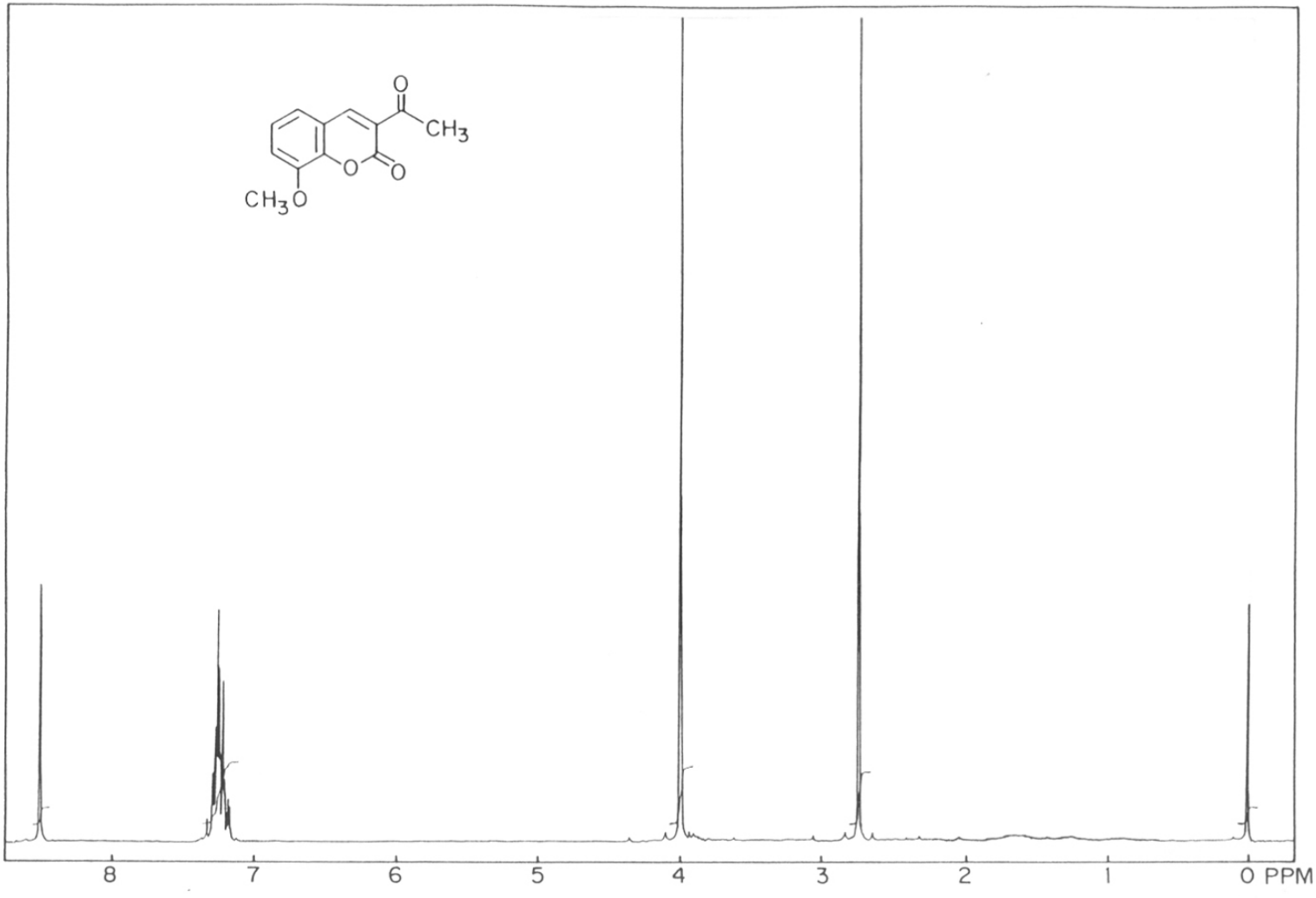
^{1}H-NMR SPECTRUM OF COUMARIN



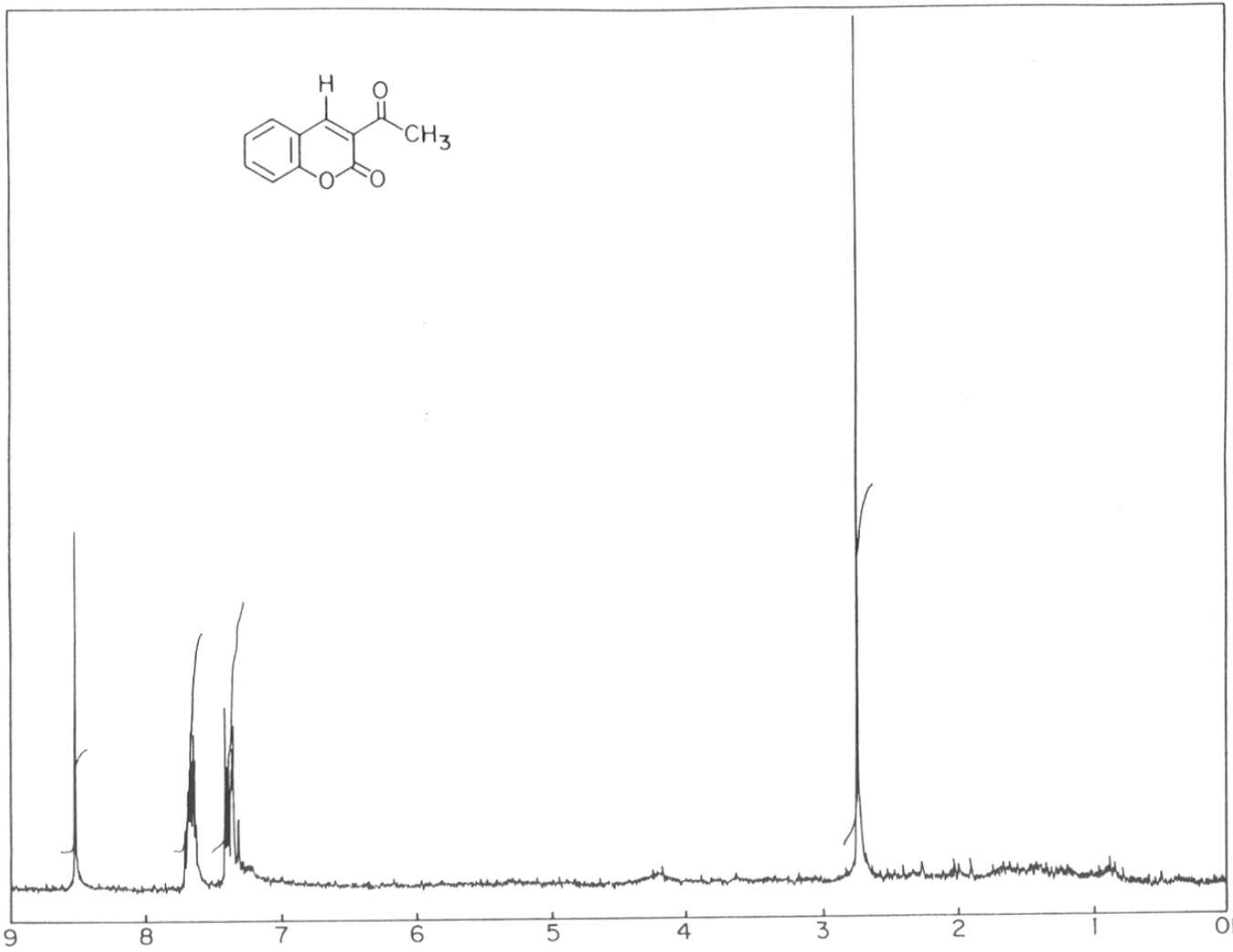
^{1}H - NMR SPECTRUM OF COUMARIN - 3 - ETHYLCARBOXYLATE



H-NMR SPECTRUM OF 4-METHYL-3-ACETYL COUMARIN



H-NMR SPECTRUM OF 8-METHOXY-3-ACETYL COUMARIN



^{1}H-NMR SPECTRUM OF 3-ACETYL COUMARIN

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Ni (0) catalyzed reaction of aryl and vinyl halides with alkenes and alkynes

Introduction

This part of chapter III describes the utility of Ni (0) catalysts for the Heck-type coupling reaction.

One of the most important topics in synthetic organic chemistry is the development of new, highly efficient synthetic methodologies which generate minimal waste, thereby saving resources as well as our environment. In this respect, the Heck-reaction[1] has in recent years become one of the most important methods for C-C bond formations, since it allows the synthesis of a wide variety of compounds such as carbocycles and heterocycles using catalytic amount of Pd. Furthermore, the methodologies involving Pd complexes are compatible with almost all sorts of functional groups.

Heck-reaction is the palladium-catalyzed coupling of haloarenes and haloalkenes with alkenes. Although, this reaction was discovered by Richard F. Heck[2] as early as the late sixties, it was not applied and developed till the seventies and eighties to the extent that important synthetic reactions are. Later, palladium (0)-catalyzed coupling of aryl and vinyl halides and triflates with main group organometallics *via* oxidative-addition, trans- metallation, and reductive elimination sequences have been very broadly developed and has an over whelming amount of literature associated with it. However, relatively few fundamental principles are involved, the understanding of which made the area both approachable and usable.

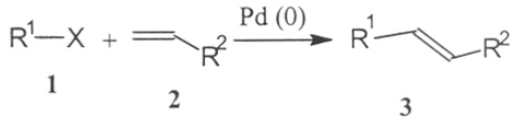
Palladium complexes have a very rich organic chemistry and are among the most readily available easily prepared and easily handled of transition metal complexes. Most often $Pd(PPh_3)_4$, Pd(dba) + PPh_3 are used. Even Pd(II) catalyst precursors such as $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$ or $PdCl_2(CH_3CN)_2$ are efficient as, they are readily reduced to the catalytically active Pd(0) in the reaction medium. Thus, Pd enjoys two stable oxidation states, the +2 state and zerovalent state, and it is the facile redox interchange between these two oxidation states which is responsible for the rich reaction chemistry that palladium complexes display. Each oxidation state has its own chemistry.

Mechanism of Heck-reaction

One can get enough educated on the concepts of oxidative addition, olefin insertion and reductive elimination while understanding the mechanism of Heck-reaction.

During its infancy, reasonable concepts for mechanism has emerged, which serves as a working hypothesis. The common mode of Heck-type coupling reaction can be depicted as below:

Scheme 1



1 2 3

where

R^1 = alkenyl(vinyl), aryl

R^2= alkenyl,aryl, alkyl, CO_2R etc.

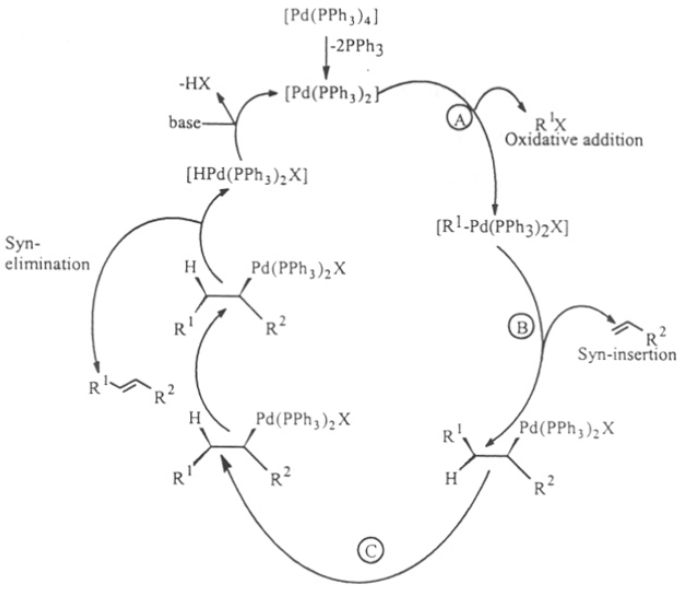
X= halide, triflate, mesylate etc.

A co-ordinatively, unsaturated $14e^-$ palladium (0) species is assumed to be the catalytically active complex. The palladium (0) complexes are electron-rich, nucleophilic species, prone to oxidation. Hence, oxidative addition occurs at the catalytic cycle as the first step, where haloalkenes or haloarenes are assumed to oxidatively add to Pd(0) species (step A), generating a σ-alkenyl or σ-aryl palladium (II) complex. This step is "Oxidative addition" because the metal is formally oxidized from Pd(0) to Pd(II) and the oxidizing from Pd(0) to Pd(II) and the oxidizing agent, R^1-X to the metal.

The oxidative addition process has a number of general features. The order of reactivity[3] is I > OTf > Br >> Cl such that chlorides are rarely useful in this reaction. The nature of the leaving group X also affects the oxidative addition of haloarenes or haloalkenes is the rate-determining step.[4]

In the next step, an alkene molecule is co-ordinated, probably *via* a four-centered transition state (step B). Thirdly, internal rotation (Step C) occurs to get the *syn*-orientation between σ-palladium bond and hydrogen which would be eliminated. The reaction gets terminated (Step D) by β-hydride elimination. The catalyst is regenerated after the elimination of HX in presence of the base.[5] The mechanistic pathway is depicted below.

Scheme 2



Although a reasonable working hypothesis has been established for the mechanism of the palladium-catalyzed arylation and alkenylation of alkenes, the individual steps are far from being completely understood. Nevertheless, an insight into the factors determining these reactions has contributed to the further development and improvement of these methods. Furthermore, numerous other metallic σ-alkenyl or σ-aryl species have emerged *via* oxidation. Those procedures too follow σ-alkenyl or σ-aryl metallic species via oxidative addition reactions employing Co, Rh, Ir, Pt, and Ni(0) complexes. Many groups have investigated the use of other metal catalysts for this reaction, based on the known mechanism of Pd catalyzed vinylation reaction and reported.

Vinylation reaction of aryl and alkenyl halides by metal catalysts other than Pd: Literature reports

Oxidative addition reactions of organic halides by many metal complexes are well known. Hence, it is better to discuss the factors determining the oxidative reactions.

a) The transition metal must be in a low valent state, behaving either as nucleophile or a reductant in which electrons are removed from the electron-rich metal center.

b) Unlike the group 1 and 2 metals that readily react in bulk, group 8 metals must be in the atomic state, usually through complexation by ligands.

c) Reactivity of group 8 metals towards oxidative addition increases from right to left in the periodic table.

d) The co-ordination number of the metal and the type of the ligand is also important. eg., M $(PPh_3)_4$ where M=Ni(0), Pd(0), Pt(0) having the d^{10} configuration are co-ordinated compounds which are reactive towards oxidative addition (dissociative mechanism).

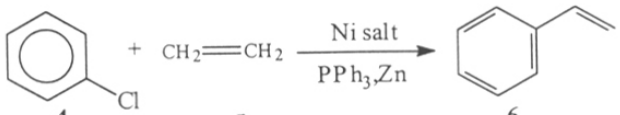
e) The phosphine ligands are σ-donors (lone-pair donations) which increase the electron density of the central metal atom and makes the metal a good nucleophile, at the same time increases the tendency of the phosphine to dissociate.

f) Steric effects are much more important than electronic effects in determining the dissociation of phosphine ligands from transition-metal complexes. The greater the size of the ligand, the greater is the tendency for dissociation.

Based on the above rationale various metal catalysts have been employed for the Heck-type coupling and they are discussed below.

Styrene was prepared from chlorobenzene and ethylene in the presence of a nickel salt, triarylphosphine, and zinc.[6]

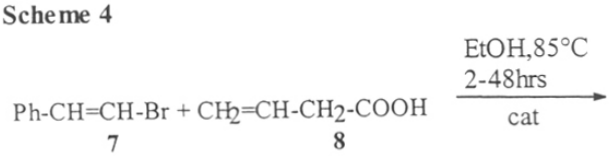
Scheme 3



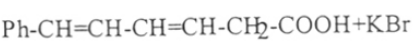
4 5 6

$RhCl(PPh_3)_3$, $Ni(PPh_3)_3$, $[Rh(COD)(PPh_3)_2]PF_6$ were employed[7] for reaction of vinylic halides with alkali salts of 3-butenoic acids to furnish dienoic acids, containing 3,5-conjugated double bonds. The reaction is exemplified as follows, for the reaction between the β-bromostyrene and the potassium salt of 3-butenoic acid.

Scheme 4



7 8

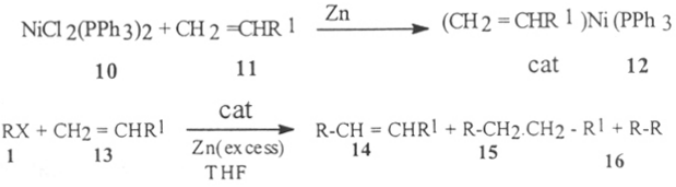


9

Boldrini et. al.[8], reported that coupling of activated olefins with aryl and vinylhalides can be brought about by using a catalytic amount of dichlorobis-

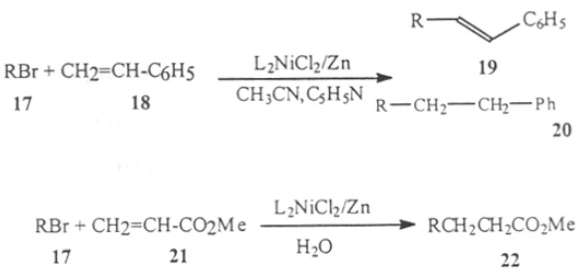
(triphenylphosphine) nickel $[NiCl_2(PPh_3)_2]$ and an excess of zinc powder in tetrahydrofuran. The active catalyst was found to be (n^2-alkene)bis (triphenylphosphine) nickel complex (**12**) which then reacts with organic halides to give substitution product (vinylated product), saturated product (1,4-addition product) and homo coupling of product of the organic halide.

Scheme 5



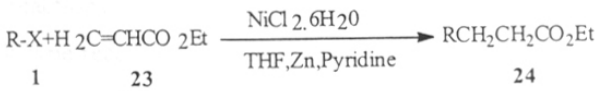
The catalytic system $(Ph_3P)_2NiCl_2$/Zinc/pyridine in acetonitrile was reported[9] to be effective for reactions of aryl and alkyl bromides with styrene and methylacrylate. With styrene, the reaction yields stilbenes and β-alkyl styrenes. Methyl acrylates reacts to give conjugate addition products.

Scheme 6



Various organic halides ranging from aromatic and vinylic to saturated aliphatic halides with electron deficient olefins under the influence of $NiCl_2.6H_2O$ in the presence of zinc and pyridine in THF leads to conjugate addition products according to Sustmann et. al.[10]

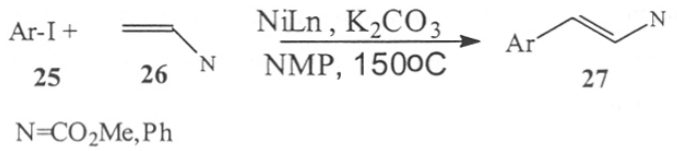
Scheme 7



R=Alkyl,aryl and vinyl.

$CoCl(PPh_3)_3$, $RhCl(PPh_3)_3$ and $IrClCO(PPh_3)_2$ catalyzed vinylation of aryl iodides were reported[11] to yield cinnamates and stilbenes in high yields by using K_2CO_3 as the base and NMP as solvent at 150°C.

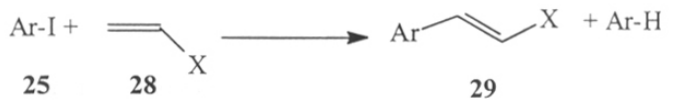
Scheme 8



N=CO_2Me, Ph

Vinylation of aryl iodides using $Pt(COD)Cl_2/PPh_3$ as a catalyst system was studied by Kelkar[12] and it was found that dehalogenated products were formed in the presence of organic bases.

Scheme 9



The vinylation of 4-bromo-4'-hydroxybiphenyl and ethylacrylate was studied[13] by Kelkar et. al using the catalyst $NiCl_2.6H_2O/PPh_3$ in the presence of a organic base. Ethyl 4-(4'-hydroxyphenyl)cinnamate was formed as vinylation product with a selectivity as high as 98%.

Scheme 10

In summary, Ni, Rh, Pt, Co, Ir metal catalysts have been studied for the Heck-type coupling reactions. In the present work, cheaply available Ni metal was chosen to study the Heck-type reactions. It was viewed that the replacement of Pd catalyst by Ni catalyst could make the Heck-type coupling more cost-effective.

Objective

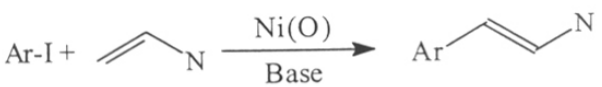
Although zero-valent Nickel complexes readily undergo oxidative addition with organic halides[14], very few examples of nickel catalyzed vinylation have been described in the literature[8,9]. In both the references, zinc metal was used for the reaction of the Ni(II) complex to Ni(0) complex, *in situ* which in turn gave complex mixture of products, resulting in poor selectivity in the vinylation. The catalyst system $NiCl_2/PPh_3/Zn$ was not found to be very useful for Heck-type reaction because it gave different types of products with ethylacrylate (addition product) and styrene (substitution product). A highly active and air sensitive complex, $Ni(PPh_3)_4$, generated *in situ* by the action of Et_3Al on $Ni(acac)_2$ has been used for the intramolecular reaction of aryl halides with olefins to form indoles.[15] $NiCl_2.6H_2O/PPh_3$ was used as a catalyst system but, it is studied for the special case 'i.e.' (4-bromo-4'-hydroxy biphenyl and ethylacrylate). $Ni[P(OPh_3)]_4$ and $Ni[P(OEt)_3]_4$ are stable metal complexes of Ni(O) and are well known to undergo ligand dissociation, oxidative addition and reductive elimination reactions and have been used to catalyze the reaction of allylacetates with nucleophiles.[16]

$Ni[P(OPh_3)]_4$ and $Ni[P(OEt)_3]_4$ were found to be stable, easy to prepare, therefore, it was planned to study their activity in the reaction between aryl halides and olefins (Heck reaction) and alkynes.

Present work

Studying the feasibility of Ni catalyzed vinyl reaction using $Ni[P(OEt)_3]_4$ and $Ni[P(OPh)_3]_4$ became our objective for the present work.

Scheme 11



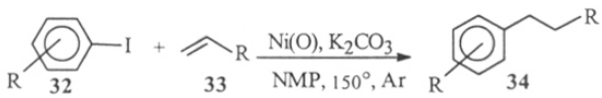
25 **26** **27**

N: CO_2Me, CO_2Et, Ph, etc.

From the preliminary experiments, it was observed that reaction did not proceed with solvents like THF, CH_3CN toluene, dioxane, DMF, EtOH etc. Such an observation demanded that certain minimum temperature is required for catalytic activity. Hence, 1-methylpyrroli-dinone was selected as solvent. Using 1-methylpyrrolidinone as solvent, the effect of temperature on the activity was studied in the range of 120-180°C.

Reaction did not take place at 120°C indicating that a certain minimum temperature above 145°C was required for the catalysis. The catalytic activity was good at 150°C itself, when K_2CO_3 is used the base. The experimental condition thus optimized is depicted below.

Scheme 12



R=CO 2Me, CO2Me, Ph
Reaction conditions: ArI/Olefin/K 2CO3/Cat.
=1/2-4/2.5/01; NMP, 150°, 24 h, Ar.

The Heck reaction of aryl iodide with styrene and ethylacrylate in the presence of $Ni[P(OPh_3)]_4$ and $Ni[P(OEt)_3]_4$ gave high yields of the corresponding *trans* cinnamates selectively. The *trans* product obtained (E-configuration) was confirmed by its J value in the NMR spectroscopy of the products (above 12 Hz).

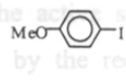
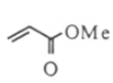
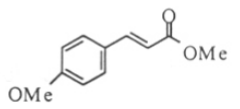
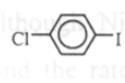
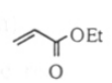
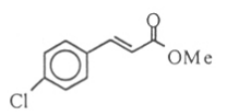
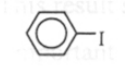
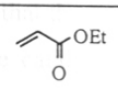
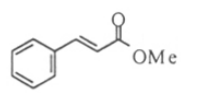
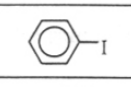
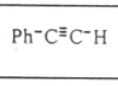
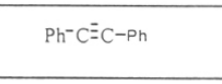
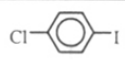
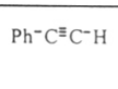
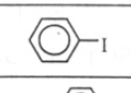
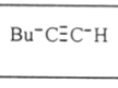
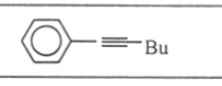
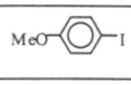
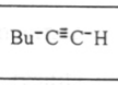
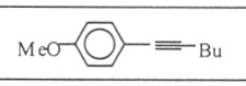
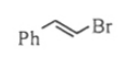
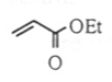
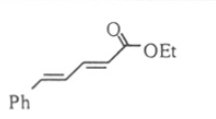
To examine the applicability of nickel catalyzed vinylation of organic halides, reaction with alkenes aryl halides as well as vinyl halides were examined. Various aryl iodides and styryl bromide undergo vinylation very easily. Arylbromides and chloroarenes do not undergo the vinylation reaction. Alkyl halides too resist under the reaction conditions. The aryl iodides and styryl bromide underwent reaction, also to give terminal alkynes such as phenylacetylene, n-hexyne and diphenylacetylenes in moderate yields (55-69% of yield).

Thus, reaction with terminal alkynes gave moderate yields of the substitution product, but no reaction was observed with ethylcyanoacetate and diethyl malonate under different conditions similar was the case with succinimide.

The use of organic base did not show any reactivity, however, K_2CO_3 as the base gave good activity and selectivity to the vinyl product.

The rate of reaction was faster when $Ni[P(OEt)_3]_4$ was used as the catalyst, and it was observed that, when PPh_3 was used as the ligand the rate of the reaction increased further. Reaction of p-chloroiodobenzene with ethylacerylate took 24 hours when $Ni[P(OPh_3)_4]$ was used and the reaction was over within 11-12 hours with $Ni[P(OEt)_3]_4$ when PPh_3 was added to the reaction mixture, the reaction was over in 3-5 hours.

The results obtained in the present work were tabulated below.

No	Aryl/Vinyl halide	Olefin/Alkyne	Time, h	Product	Yield
1			12 h		89%
2			12 h		85%
3			12 h		92%
4					69%
5			12 h		61%
6					65%
7					68%
8					76%

Reaction conditions: ArI/Olefin or alkyne/$K_2CO_3$6/cat=1/2.4/2.5/0.1; NMP, 150°C, 12h; All products have been characterized by IR and NMR.

Results and Discussion

The present catalytic activity of the reported Ni catalysts have given the vinylated products in high selectivity. Usually dehalogenated, saturated and homocoupling products accompany the vinylated product when metal catalysts other than Pd are used. In the present system, vinylated product is obtained with E-configuration as the sole reaction product and in high yields.

K_2CO_3 as a base was found to be highly efficient as compared to the organic bases. High efficiency of K_2CO_3 may be due to facile removal of hydrogen iodide formed during the reaction. The reduction of aryl iodide did not occur because K_2CO_3 has no reasonable hydrogen source.

The reaction mechanism for nickel catalyzed vinylation is probably similar to Pd-catalyzed vinylation reaction. The possible mechanism involves the dissociation of

ligands to form Ni(0) complex, the oxidative addition of arylhalide to the Ni(0) complex, the insertion of olefin, the elimination of the vinylated product and the regeneration of the Ni(0) complex by the removal of hydrogen iodide with K_2CO_3.

The active species of the nickel complex described by Boldreni et. al was produced by the reduction with reducing agents such as zinc metal. There is no reducing metal necessary in the present system.

Although $Ni[P(OPh)_3]_4$ or $Ni[P(OEt)_3]_4$ itself was active for vinylation, the activity and the rate of the reaction was enhanced in the presence of arylphosphine ligands. This result shows that the co-ordination of triphenylphosphine and substrates to nickel is important for the catalysis with nickel complexes. In other words, in the presence of PPh_3 a new catalyst system may be formed which is more active and increases the rate of the reaction.

Furthermore, the catalyst is not only active for vinylation but also for the substitution at the sp-carbon (i.e., with phenyl acetylene and 1-hexyne).

Among the two catalyst systems in comparison $Ni[P(OEt)_3]_4$ was found to be active than $Ni[P(OPh_3)]_4$. This may be due to the dissociative mechanism, which is more operative with the concerned catalyst.

In the light of the results obtained, the present work demonstrates that both $Ni[P(OEt)_3]_4$ and $Ni[P(OPh)_3]_4$ are potential catalysts for vinylation and alkenylation of aryl iodide and styryl bromide exhibiting high selectivity in their performances. The competitive reductive elimination reaction was avoided with the use of K_2CO_3 as the base. The catalyst is selective only for aryl iodides, styryl bromides and aliphatic halides did not undergo vinylation with this new catalytic system for Heck-type reactions. The product obtained in this reaction was also selective (vinylated product).

Conclusion

1. Novel and stable Ni(0) catalysts have been effective for the activation of aryl/vinyl halides.
2. The vinylated products can be obtained without other competing reactions under the present conditions in a better and cleaner fashion.
3. The use of $Ni[P(OEt)_3]_4$ and $Ni[P(OPh)_3]_4$ reveals the feasibility of a cheaper catalyst for Heck reaction.
4. Vinylation was successful with $Ni[P(OPh_3)]_4$ and $Ni[P(OEt)_3]_4$ as catalysts and the rate of reaction was found to be faster with $Ni[P(OEt)_3]_4$.
5. Presently, work on development of heterogeneous process involving Ni for Heck-type coupling is in progress, aided by the knowledge acquired through this homogeneous catalysis.

Experimental:

Tetrakis(triethylphosphite)nickel (0):

Methanol and diethylamine were distilled for the reaction, triethylphosphite used in the preparation was distilled under vacuum prior to use, (b.p. 50-52°C at 13 mm Hg). The preparation was carried out in air; an inert atmosphere was not necessary.

Nickel (II) chloride hexahydrate (10.0 g ; 0.04 mol) was dissolved in 100 ml of methanol contained in a 250 ml round bottomed flask. A stirring bar was placed in the flask and the mixture was stirred with cooling (ice-salt bath). Stirring at 0°C was continued for further period of ten minutes after which 18 ml of triethylphosphite was added over a period of one minute by maintaining the temperature at 0°C.

Upon the addition of triethylphosphite, the colour of the solution turned dark red. Further cooling (at 0°C) and vigorous stirring was continued and diethylamine was added dropwise from a syringe over a period of 10 minutes. After the addition of about 5 ml of diethylamine, there appeared white crystals of tetrakis(triethylphosphite)nickel (0).[16] Addition of diethylamine was stopped when the color of the liquid had faded to pink. The reaction mixture was allowed to stand at 0°C without stirring.

The crystals were collected on a glass frit by means of suction filter and washed with ice-cold methanol. The washing was continued until the product remained colourless. The product was transferred quickly to a 50 ml round-bottomed flask which was connected to a liquid nitrogen cooled trap and a vacuum pump and dried for 5 hours at room temperature.

Yield:12.2 g (40%).

Iodobenzene: PhI

Aniline (10.0 g, 107 mmol) was dissolved in a mixture of 28 ml of concentrated hydrochloric acid and 28 ml of water contained in a 250 ml round-bottomed flask. The flask was immersed in a bath of crushed ice and cooled until the temperature of the contents reached below 5°C. Sodium nitrite (8.0 g, 114.3 mmol) dissolved in 37 ml of water and chilled to 0°C was added in small volumes to the cold aniline hydrochloride solution. The temperature of the contents was maintained so as not to exceed above 10°C.

To the solution of phenyldiazonium chloride as obtained above, a solution containing potassium iodide (13.0 g 108 mmol) in 20 ml of water was added slowly and with constant stirring. Evolution of nitrogen was observed. The mixture was allowed to stand at 0°C for few hours. The flask was fitted with an air condenser and the mixture was heated continuously in a boiling water bath until the evolution of gases ceased. The reaction mixture was allowed to cool to room temperature and then it was neutralized with 10% sodium hydroxide solution.

The above mixture was extracted with diethylether (3 x 100 ml), the combined organic extracts was washed with sodium bisulphite (3 x 20 ml), water (3 x 20 ml), brine (3 x 20 ml) and dried over anhydrous sodium sulphate. It was then concentrated in vacuo and distilled to yield iodobenzene as colourless liquid.

Yield:	10.73 g (49%)
B.P.	186-190°C (lit.[17] b.p. 188°C)
IR (Neat) cm^{-1}:	$\sqrt{}_{max}$ 2950 (w), 1600, 1550 (w), 1020, 840, 770, 700.
^{1}H-NMR (60 MHz) :	δ 7.15-7.3 (m, 5H, Ar-H).

4-Methoxyiodobenzene:

4-Methoxyaniline (13.1 g, 107 mmol) was diazotized using of sodium nitrite (8.0 g, 114.3 mmol) to which potassium iodide (18.0 g, 108 mmol), solution was added. Usual work up followed by recrystallization afforded 4-methoxyiodobenzene as colourless solid.

Yield:	13.7 g (55%)
M.P.	52-55°C (Lit.[18] m.p. 51-52°C)
IR (Nujol) cm^{-1}:	$\sqrt{}_{max}$ 3000 (CO), 1600, 1300, 1050, 870.
^{1}H-NMR (90 MHz) :	δ 3.8 (s, 3H, O-$\underline{CH_3}$); 6.65 (d, J=8.5 Hz, Ar-$\underline{H}$, 2H); 7.65 (d, 2H, J= 8.5 Hz, Ar-$\underline{H}$).

4-Chloroiodobenzene:

4-Chloroaniline (13.7 g, 107 mmol) was diazotized using a sodium nitrite (8.0 g, 114.3 mmol) to which potassium iodide was introduced. Usual work up followed by recrystallization furnished 4-Chloroiodobenzene.

Yield:	12.2 g; (48%)
M.P.	56-58°C (Lit.[19] 57°C)

IR (Nujol) cm^{-1}: $\sqrt{}_{max}$ 2950, 1600, 1550, 1190, 1000, 850.

^{1}H-NMR (60 MHz) : δ 7.1 (d, 2H, J = 8Hz, Ar-H); 7.5 (d, 2H, J=8 Hz, Ar-H).

β-Bromostyrene:

Cinnamic acid (37.0 g, 0.25 mmol) was dissolved in a 250 ml round bottomed flask and cooled in an ice-bath with constant stirring. A solution of 40.09 g (13 ml, 0.25 mol.) of bromine dissolved in 25 ml of chloroform was added rapidly in three portions with vigorous stirring and cooling (0°C). The contents were allowed to stand in an ice-bath for 30 minutes for the complete crystallization of the brominated product. The product was separated by filtration. The bulk of the brominated product was refluxed with 375 ml of 10% aqueous sodium carbonate solution for 2 hours. The reaction mixture was allowed to cool to room temperature and was then extracted with diethylether (3 x 75 ml). The combined ethereal layer was washed with water (3 x 5 ml), brine (3 x 5 ml) and dried over anhydrous calcium chloride. Ether was removed on a rotary evaporator and the residue was chromatographed to obtain pure β-bromostyrene, which was further purified by distillation.

Yield: 35.2 g (77%)

B.P. 110-112°C at 20 mm Hg (Lit.[20] 55-56° at 2 mm Hg).

IR (Neat) cm^{-1}: $\sqrt{}_{max}$ 3100, 1600, 1460, 1230, 950, 750.

^{1}H-NMR (200 MHz) : δ 6.85 (d, 1H, J=10 Hz, C= CHBr); 7.15 (d, 1H, J = 10 Hz, Ar-CH= C-); 7.35-7.65 (m, 5H, Ar-H).

Phenylacetylene:

Potassium hydroxide pellets (25.0 g) was placed in a 50 ml round-bottomed flask and moistened with few drops of water. The flask was fitted with a still-head carrying a dropping funnel and a condenser set for downward distillation. The flask was heated to 200°C in an oil bath and β-bromostyrene (18.0g) was added dropwise to the molten alkali at a rate of about one drop per second. The phenylacetylene began to distill over; later the oil bath was maintained at 230°C until no more product distilled over. The upper layer of the distillate was separated, dried over potassium hydroxide pellets and distilled to give phenylacetylene as a colorless liquid.

Yield: 6.42 g (49%)

B.P. 142-144°C (Lit.[21] 142°C)

IR (Neat) cm^{-1}: $\sqrt{}_{max}$ 3310, 2950, 2150, 1600, 120, 630.

^{1}H-NMR (200 MHz) : δ 3.05 (s, 1H, ≡C-H,); 7.2 - 7.3 (m, 3H, Ar-H); 7.4-7.5 (m, 3H, Ar-H).

General procedure for the reaction between aryl/vinyl iodides with alkenes/alkynes in the presence of tetrakis (triethylphosphite) nickel (0):

1-Methylpyrrolidinone was degassed, the iodo, bromo compounds, acrylates, alkynes were purified either by distillation or by recrystallization prior to use.

Into a flame dried 50 ml round-bottomed flask fitted with a reflux condenser was charged, a mixture of tetrakis (triethylphosphite) nickel (0) (0.1 mmol), aryl/vinyl halide (1.0 mol), alkene/alkyne (2-4 mmol), potassium carbonate (2.5 mmol) and 5 ml of degassed 1-methyl pyrrolidinone and the mixture was heated at 150°C for 12 hours. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and was poured into 20 ml of 10% hydrochloric acid solution.

The quenched reaction mixture was extracted with ethylacetate (3 x 20 ml). The combined organic layer was washed with water till pH of the extract became neutral, then with brine (3 x 5 ml) and dried over anhydrous sodium sulphate. It was then concentrated in vacuo. The residual material was purified by column chromatography on silica gel to obtain the coupled products.

3-(4-Methoxyphenyl)-2-propenoic acid methylester:

Yield: 0.17 g (89%)

M.P. 95-97°C (Lit.[22] 94-95°C)

IR (Nujol) cm^{-1}: $\sqrt{}_{max}$ 2950, 1720, 1630, 1600

^{1}H-NMR (200 MHz) : δ 3.75 (s, 3H, $COOCH_3$); 3.8 (s, 3H, OCH_3); 6.3 (d, 1H, J= 12 Hz, -CH= CH-COO-); 6.9 (d, 2H, J= 8 Hz, Ar-H); 7.45 (d, J = 8 Hz, Ar-H, 2H); 7.65 (d, 1H, J = 12 Hz, Ar-CH=CH).

3-(4-Chlorophenyl)-2-propenoic acid ethylester:

Yield: 0.18 g, (85%)

M.P. 113-113°C (Lit.[23] 110.5°C)

IR (Nujol) cm^{-1}: $\sqrt{}_{max}$ 3000, 1720, 1650, 1600.

^{1}H NMR (200 MHz) : δ 1.32 (t, 3H, J=6.5 Hz, $COOCH_2\underline{CH_3}$); 4.25 (q, 2H, J = 6.5 Hz, $COO\underline{CH_2}CH_3$); 6.4 (d, 1H, J = 10 Hz, CH= C<u>H</u>-COO-); 7.3 (d, 2H, J = 8 Hz, Ar-<u>H</u>); 7.45 (d, 2H, J= 8Hz, Ar-<u>H</u>); 7.6 (d, 1H, J= 10 Hz, Ar-C<u>H</u>=CH-).

3-Phenyl-2-propenoic acid ethyl ester:

Yield: 0.15 g; (92%)

M.P. low melting solid, (lit.[24] 6.5-7.5°C, b.p. 271°C).

IR ($CHCl_3$) cm^{-1}: $\sqrt{}_{max}$ 3100 (CO), 1760, 1740, 1600.

^{1}H-NMR (200 MHz) : δ 1.4 (t, 3H, J=6.4 Hz, $COOCH_2\underline{CH_3}$); 4.24 (q, 2H, J = 6.4 Hz, $COO\underline{CH_2}CH_3$); 6.4 (d, 1H, J =14 Hz, -CH=C<u>H</u>-COO-) 7.6 (d, J = 14 Hz, 1H, Ar-CH=CH-).

^{13}C-NMR (50 MHz): δ 17.03; 60, 119.43, 127.5, 128.31, 130, 140.02, 168.23

Diphenylacetylene:

Yield: 0.13 g (69%)

M.P. 61-63° (lit.[25] m.p. 62-65°C).

IR ($CHCl_3$) cm^{-1}: $\sqrt{}_{max}$ 3950 (CO), 1600 (s).

^{1}H-NMR (60 MHz) : δ 7.2-7.7 (m, 10H, Ar-<u>H</u>).

1-(4-chlorophenyl)-2-phenylacetylene:

Yield: 0.13 g (61%)

M.P. -72°C

IR (Nujol) cm^{-1}: $\sqrt{}_{max}$ 3950, 1600, 1500, 1100, 1000, 780.

^{1}H-NMR (60 MHz) : δ 6.5-7.9 (m, 10H, Ar-<u>H</u>)

1-(4-Methoxyphenyl)-1-hexyne:

Yield: 0.10 g, (65%)

M.P. 120°C at 20 mm Hg (Lit. b.p., 229-232°C)

IR (Nujol) cm^{-1}: $\sqrt{}_{max}$3950, 1600, 1500, 1450, 1100, 1000, 780.

^{1}H-NMR (200 MHz) : δ 0.95 (t, 3H, J=6.5 Hz, CH_2-$C\underline{H_3}$); 1.5 (m, 4H, -$C\underline{H_2}$.$C\underline{H_2}$-CH_3); 2.4 (t, 2H, J = 6.5 Hz, C≡C-$C\underline{H_2}$-CH_2); 3.85 (s, 3H,

O-C<u>H</u>$_3$); 6.65 (d, 2H, J= 8Hz, Ar-<u>H</u>); 7.65 (d, 2H, J = 8 Hz, Ar-<u>H</u>).

2,4-Dienyl-5-phenylpentanoic acid ethyl ester:

Yield: 0.15 g (76%)

M.P. 111-113°C

IR (Nujol) cm^{-1}: $\sqrt{}_{max}$ 2950, 1720, 1600.

^{1}H-NMR (200 MHz) : δ 1.25 (t, 3H, J = 7.5 Hz, -COOCH$_2$C<u>H</u>$_3$); 4.1 (q, 2H, J=7.5 Hz, COOC<u>H</u>$_2$CH$_3$); 6.0 (d, 1H, J = 14 Hz, -C<u>H</u>=CH-COO- , 1H); 6.95 (dd, J = 12 Hz, 7 Hz, 2H, -CCO-); 7.1 - 7.6 (m, 6H, 5 aryl protons and one vinyl proton).

1-Phenyl-1-hexyne:

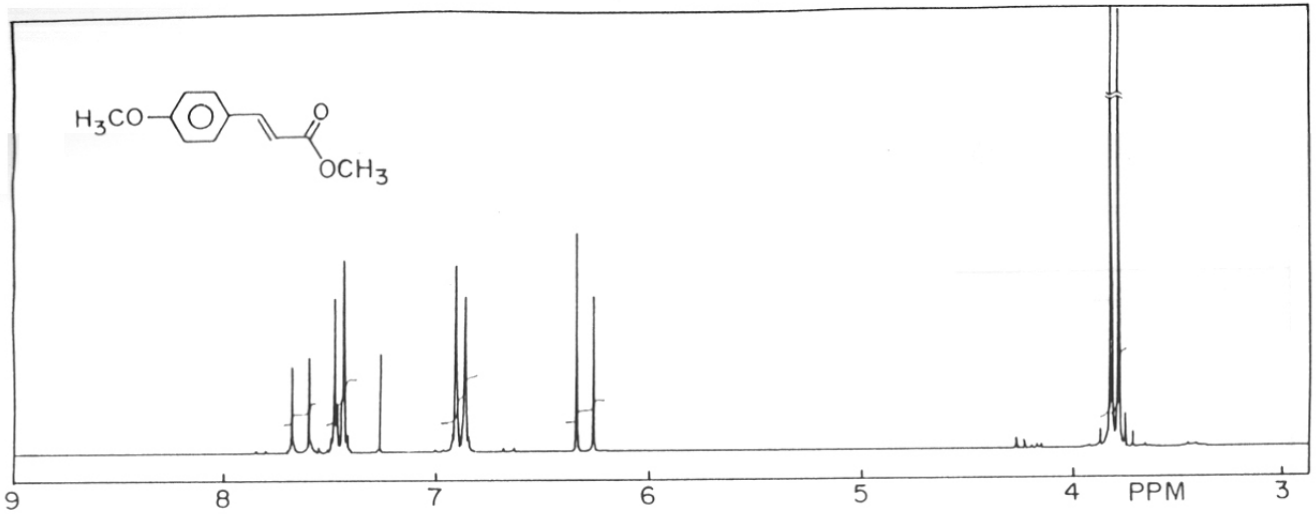
Yield : 0.10 g (65%)

B.P. : 120°C at 20 mm Hg (lit[26]. B.P., 229-232°C)

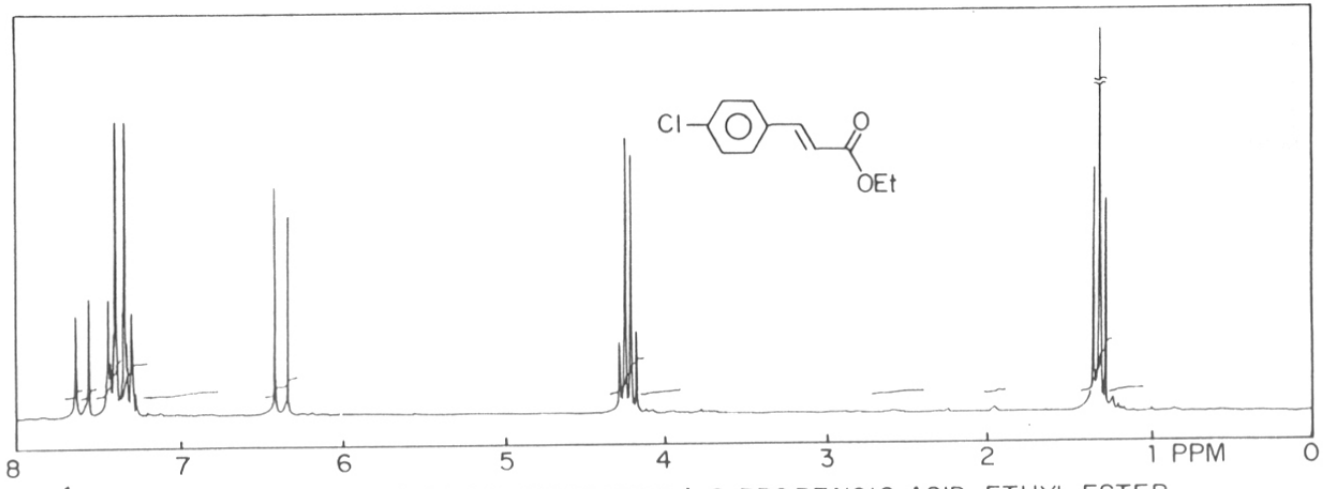
IR ($CHCl_3$) cm^{-1} : $\sqrt{}_{max}$ 3950, 1600, 1500, 1450, 1100, 1000, 780.

^{1}H-NMR (200 MHz): δ 0.95 (t, 3H, J= 6.5 Hz, -CH$_2$-C<u>H</u>$_3$); 1.5 (m, 4H, -<u>CH$_2$</u>-<u>CH$_2$</u>.CH$_3$); 2.4 (t, 2H, J = 6.5 Hz, C≡C-C<u>H</u>$_2$-CH$_2$); 7.25-7.3 (m, 3H, Ar-<u>H</u>); 7.38-7.41 (m, 3H, Ar-<u>H</u>).

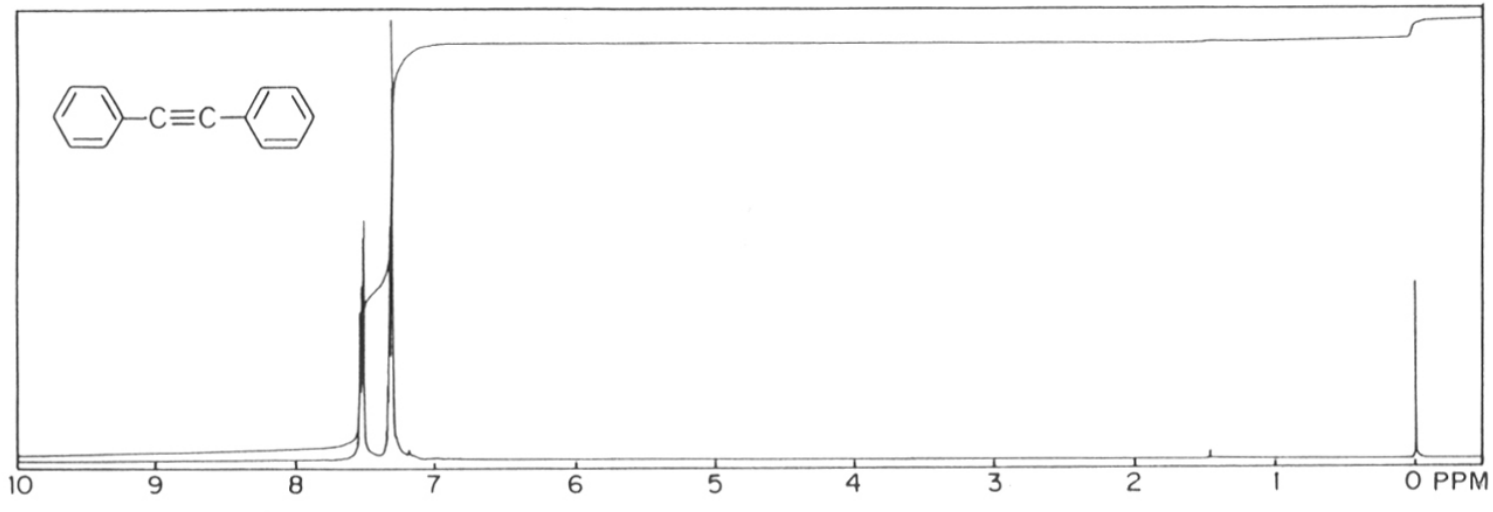
^{13}C-NMR (50 MHz): 12.03, 19.21.52, 31.41, 80.51, 90, 128.05, 130, 134.16.



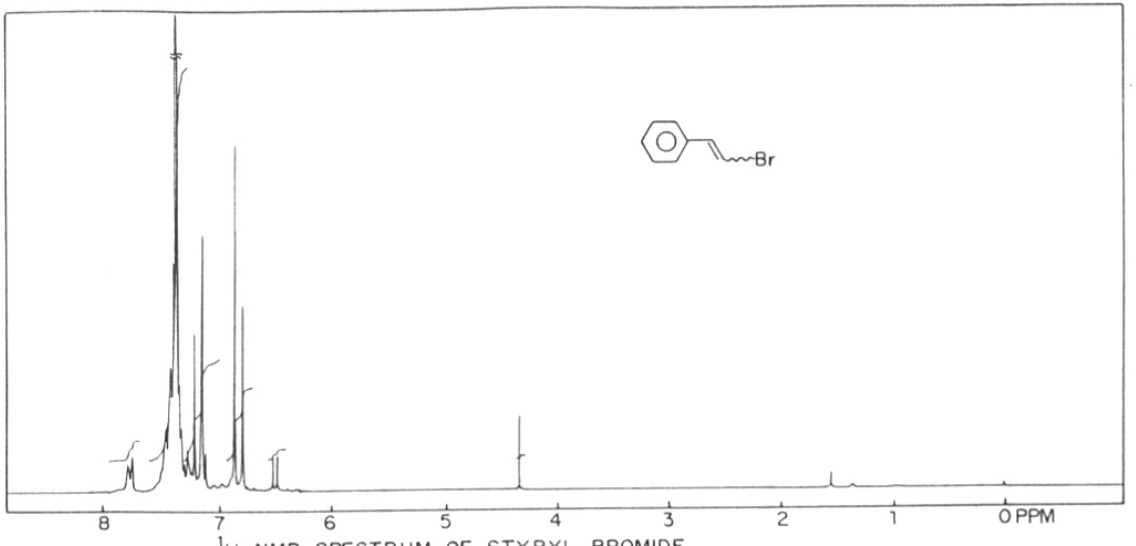
^{1}H-NMR SPECTRUM OF 3-(4-METHOXYPHENYL)-2-PROPENOIC ACID METHYL ESTER



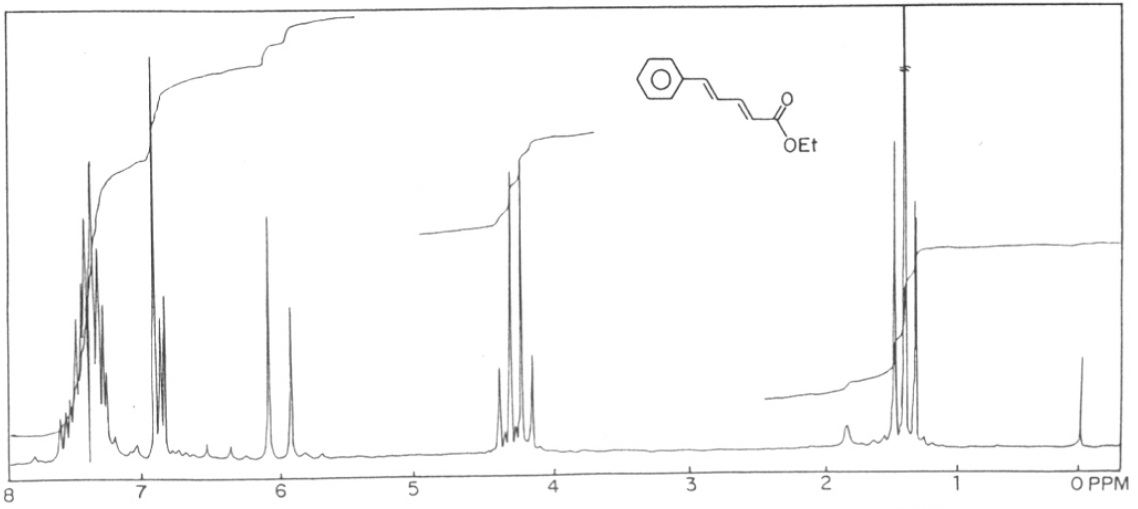
^{1}H-NMR SPECTRUM OF 3-(4-CHLOROPHENYL)-2-PROPENOIC ACID ETHYL ESTER



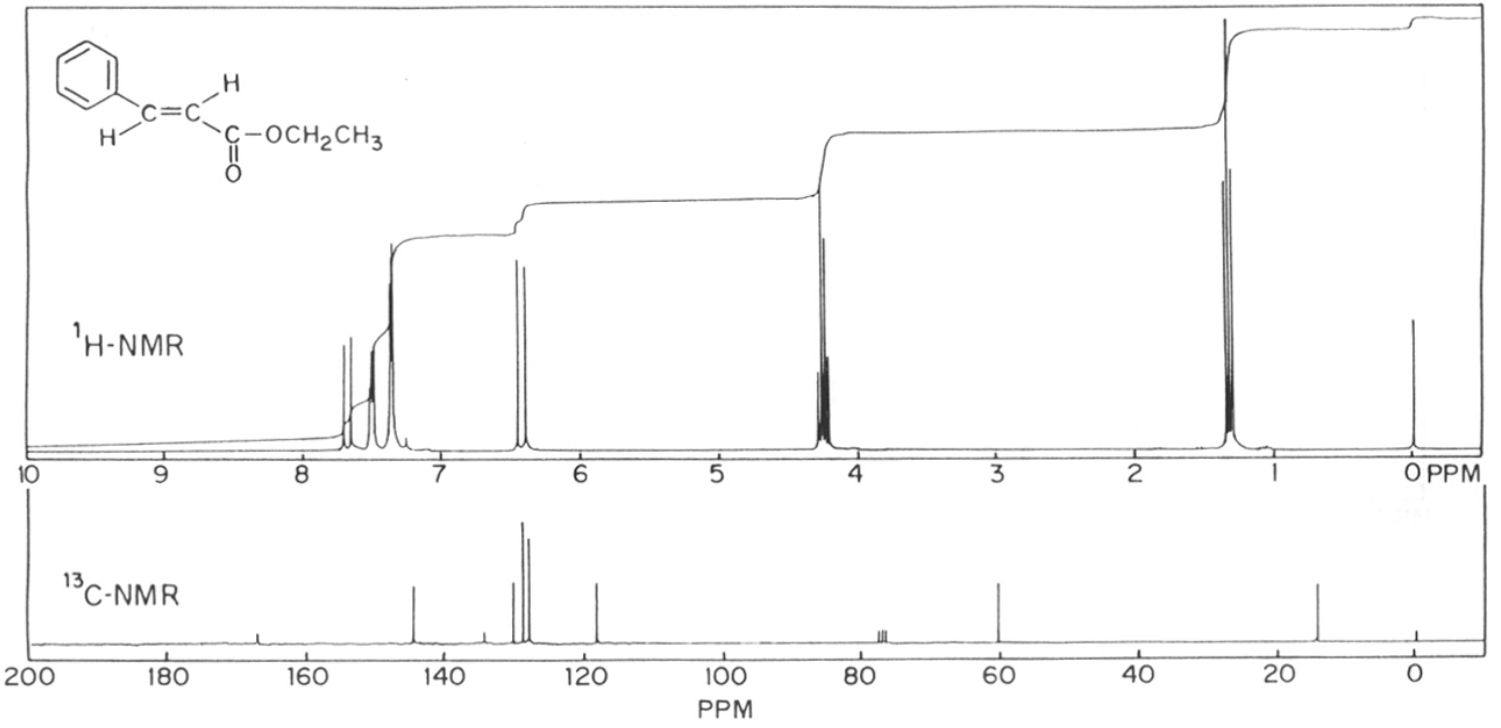
^{1}H-NMR SPECTRUM OF DIPHENYLACETYLENE



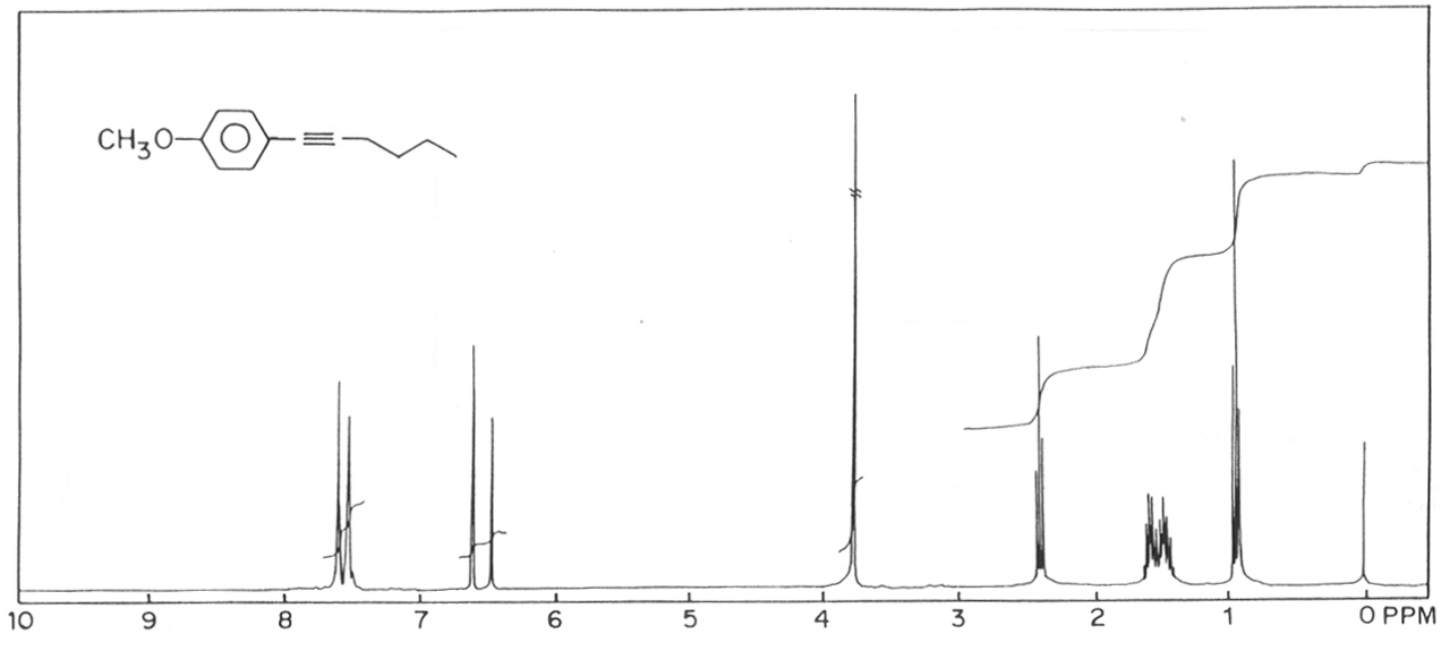
^{1}H-NMR SPECTRUM OF STYRYL BROMIDE



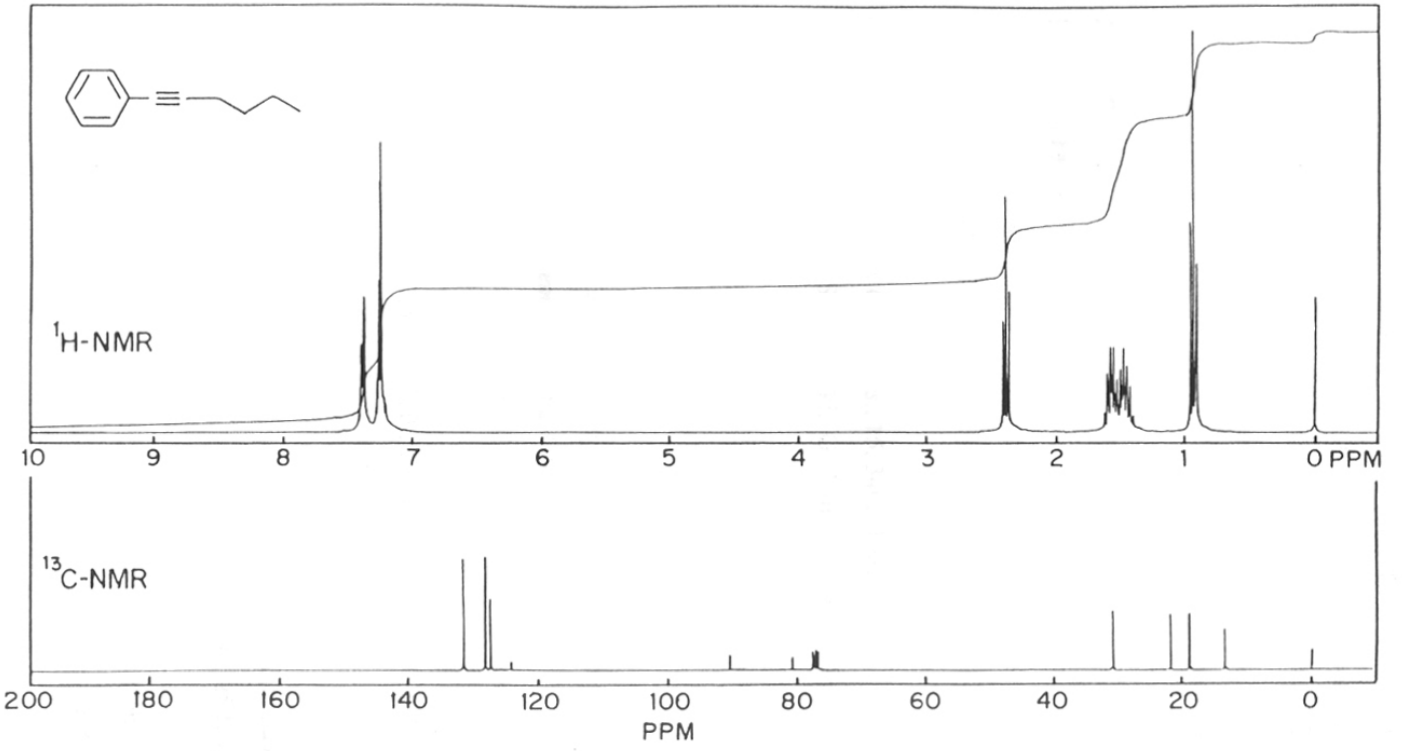
^{1}H-NMR SPECTRUM OF 2,4-DIENYL-5-PHENYL PENTANOIC ACID ETHYL ESTER



^{1}H-NMR & ^{13}C-NMR SPECTRUM OF 3-PHENYL-2-PROPENOIC ACID ETHYL ESTER



^{1}H-NMR SPECTRUM OF 1-(4-METHOXYPHENYL)-1-HEXYNE



^{1}H-NMR & ^{13}C-NMR SPECTRUM OF 1-PHENYL-1-HEXYNE

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7. Synthesis of bicyclo [5.3.1] undecane skeleton *via* vinyl cyclopropane cyclopentene rearrangement
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8. Some studies on Michael addition of β-ketoesters with benzylidene ketones catalyzed by hydrotalcites
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2. An improved process for the preparation of (±)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde: Taxol A-ring unit.
A. Ramani, Bhanu M. Chanda, HR. Sonawane, T. Ravindranathan
(Indian Patent to be filed)

3. An improved process for the preparation of (-)-(S)-2,2,4-trimethyl-cyclohex-3-ene-1-carbaldehyde: Chiral A-ring unit of taxol
A. Ramani, S.G. Sudrik, Bhanu M. Chanda, H.R. Sonawane
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A. Ramani, S. Velu, Bhanu M. Chanda, S. Sivasankar
(Indian Patent to be filed).