SYNTHESES OF β-KETO ESTER SYNTHONS AND THEIR APPLICATIONS IN THE SYNTHESES OF NATURAL PRODUCTS

A Thesis

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By

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MAY 1998

என் பெற்றோருக்கு சமர்ப்பணம்.....

Dedicated to my Parents.....

राष्ट्रीय रासायनिक प्रयोगशाला (वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद) पुणे - 411 008

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "**SYNTHESES OF β-KETO ESTER SYNTHONS AND THEIR APPLICATIONS IN THE SYNTHESES OF NATURAL PRODUCTS**" by Mr B. S. Balaji 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)

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Chemweb.com, beilstein.com, yahoo.com, acs.org, chemfiner.camsoft.com

Indeed it is my pleasure to mention that I have spent unforgettable days of my life with my friends..... It is very difficult to mention everybody's name. Friends like Dattu, mama (மாமா), Srirajan, கோயான் Ravi, தலைவர் Selva, Chottu Saravanan, Janu, Ramani, Patils, ஜோள்ளு Ramesh and of course Ethiraj (who always kept me in a light mood) are hard to come by.

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I thank Director, NCL for allowing me to work in NCL and permitting me to submit the work in the form of a thesis.

It has never been my intention to hurt anyone's feelings knowingly or unknowingly. In spite of my efforts, if I have caused any inconvenience to anyone, my apologies for the same.

(B. S. Balaji)

CONTENTS

CHAPTER II

Some synthetic studies directed towards the construction of lactone ring present in naturally occurring lignan lactones

CHAPTER III

Total synthesis of Diplodialide A

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

GENERAL REMARKS

1. All melting points and boiling points temperatures are in centigrade scale.
2. The compound numbers, scheme numbers and reference numbers given in each chapter refers to that particular chapter only.
3. All solvents were distilled prior to use. Petroleum ether refers to the fraction collected in the boiling range 60-80°C.
4. Organic layers were dried over anhydrous sodium sulfate (Na_2SO_4)
5. TLC analysis were carried out on glass plates using silica gel; GF-254 and the plates were developed by iodine stain.
6. In cases where chromatographic separations were done, SiO_2 (60-120 mesh) was used as the stationary phase.
7. Flash chromatography refers to coloumn chromatography performed using 230-400 mesh silica gel obtained from SRL India.
8. The IR spectra were recorded on Perkin-Elmer spectrophotometer model 683B or 1605 FT-IR and absorptions are expressed in cm^{-1}.
9. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker WH-90 or Bruker AC-200 or MSL 300 MHz instruments using tetramethylsilane as the internal standard using $CDCl_3$ as solvent. The following abbreviations were used. s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, dd = doublet of doublet, dt =doublet of triplet.
10. The mass spectra were recorded on Finnigan MAT-1020-B-70eV mass spectrometer.
11. Slow addition of the compounds were performed using syringe addition pump Orion make model 341B SAGE PUMPS.
12. Microwave reactions were carried out in Batliboi Eddy make domestic microwave oven model no. ER 5054D operating at 2450 MHz.
13. Chemical names for most of the compounds were generated using Autonam (Beilstein Commander Ver 2.3).

Abstract

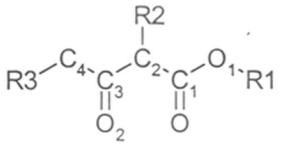
The thesis entitled "**Syntheses of β-Keto Ester Synthons and their Applications in the Syntheses of Natural Products**" is divided into three chapters.

Chapter I Simple and high yielding methods for β-keto ester syntheses

This chapter is divided into three sections, each of which is dealing with novel methods for the syntheses of β-keto esters.

Section A: Efficient syntheses of β-keto esters by condensation of aldehydes and ethyl diazoacetate in the presence of zeolites

A general introduction deals with the various reported methods available for the formation of β-keto ester. β Keto esters[1] represent an important class of compounds, which are multi-coupling reagents with electrophilic and nucleophilic sites. They can generally be represented as



Though several methods are available for the formation of β keto esters, the main idea of this work was to utilise easily accessible aldehydes as substrates for the preparation of β-keto esters. Lewis acid catalysed[2] condensation of ethyldiazoacetate and aldehydes is known; still there was an ample need to develop much simpler and efficient method. New synthetic avenues using commercially available solid catalysts including zeolites was explored for this purpose. It was shown that use of H-β as the catalyst gave good yields of corresponding β-keto esters with aromatic aldehydes and excellent yields with aliphatic aldehydes.

The reaction can be represented as follows

$$RCHO + N_2CHCO_2Et \xrightarrow[\Delta]{\text{H-β,EDC}} RCOCH_2CO_2Et + N_2\uparrow$$

where R = Et, Pentyl, Phenyl, p-methylphenyl,3,4-methylenedioxyphenyl etc.

The advantages of this method are

(i) good to excellent yield of β keto esters are obtained.

(ii) reaction provides clean conversion and scale up is very easy.

(iii) avoids use of strong bases, which are used in the conventional methods.

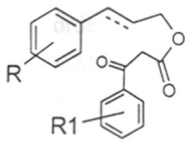
(iv) catalyst is easy to separate, is recyclable and has minimal environmental hazards.

Section B:

Part I Synthesis of β–keto esters *via* transesterification in the presence of heterogeneous catalysts.

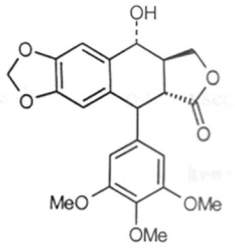
Although the method explained in Section A Chapter I worked well for the syntheses of ethyl or methyl β keto esters, there was difficulty in preparing alkyl or aryl esters. This is attributed to the difficulties encountered in preparing the corresponding diazo esters. To circumvent the problem, a new method was developed, which makes use of transesterification reaction[3].

As part of the ongoing programme for the syntheses of antitumour lignan lactones like podophyllotoxin[4], several intermediate β keto esters of the type, shown below were required.



R = R1 = H
R = H, R1 = 3,4,5-trimethoxy
R = 3,4-methylenedioxy, R1 = 3,4,5-trimethoxy

These are key intermediates, which are used in the present synthetic methodology for podophyllotoxin, details of which is discussed in Chapter II.



Podophyllotoxin

1

Generally, transesterification of allylic alcohol is very difficult because it undergoes decarboxylative Carroll rearrangement[5]. In this regard, an efficient method for transesterification of β keto ester has now been developed with various alcohols, viz, primary, secondary, allylic, benzylic etc. as depicted in the scheme below.

$$RCOCH_2CO_2Et + R^1OH \xrightarrow[\Delta]{\text{H-}\beta\text{/ Toluene}} RCOCH_2CO_2R^1 + EtOH$$

The advantages of the present method are summarised as follows.

(i) In the case of transesterification of primary and secondary alcohols with alkyl acetoacetates excellent yields have been obtained (>90 %)

(ii) Aromatic β keto esters gave moderate yields (50 - 60 %) which may be attributed to their bulkiness.

(iii) Transesterification has been found to be very selective for β keto esters. Other esters like α- keto, γ keto, α halo and unsaturated were not transesterified.

(iv) Catalyst is very easily filtered off and removal of solvents yielded practically pure products.

(v) It is a non-hazardous environmentally friendly method.

Part II Microwave assisted synthesis of β-keto esters via transesterification in the presence of catalysts

Microwave assisted organic reactions[6] have attracted considerable attention in the past few years. "Dry reaction conditions" or "solvent free conditions" is offers several advantages. Hazardous solvents like benzene, toluene etc., which are commonly used in transesterification reactions. Additionally this method dispenses away with drying of the solvents.

In the case of transesterification of aroyl β keto esters, yields were only moderate. In order to improve on the yields as well as on the reaction time, reaction conditions etc. MW assisted transesterification was resorted to. The results obtained indicated improvement in the yields from ≈50 % to ≈70-75 %; the reaction time was also considerably reduced (from 8 hrs to a mere 10-15 min.) and primary alcohols were quantitatively transesterified even in the absence of catalyst.

Chapter II

Some synthetic studies directed towards the construction of lactone ring present in naturally occurring lignan lactones.

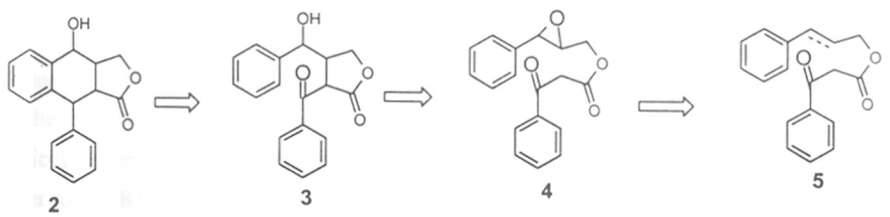
This Chapter is divided into three sections.

Section A:

Attempted cyclisation of 3-oxo-3-phenylpropanoic acid 3-phenyl-2-propenyl ester (E) using ionic methods

Part-I Epoxidation methods

Epoxidation[7] and site selective opening of oxiranes is a well-established method for the construction of different natural products. The retro scheme for podophyllotoxin[4], an anti tumour lignan lactone can be depicted as follows.



The β-keto ester **5** (prepared according to Chapter-I Section B) was subjected to epoxidation. Several classical and non-classical methods were attempted like,

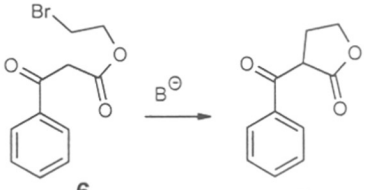
$VO(acac)_2$/ TBHP, $Ti(iPrO)_4$/DET, mCPBA etc. for epoxidation and the results obtained are described in this section.

Part II: Michael addition methods

The attempted cyclisation of the intermediate **5** under Michael addition reaction conditions like NaH/benzene, K_2CO_3/THF *etc.* also did not led to the required lactone **3**.

Part III: Attempted cyclisation of 3-oxo-3-phenylpropionic acid 2-bromo-ethyl ester

Properly positioned bromine atom in the molecule can be displaced by a nucleophile to yield lactone as depicted below.



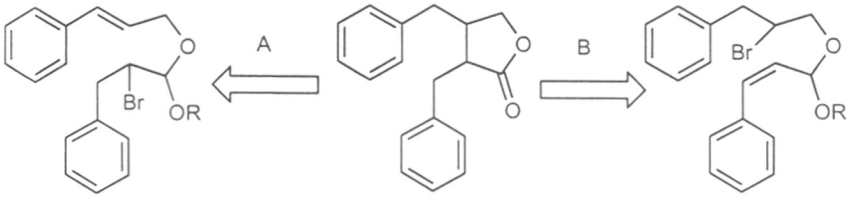
6 **7**

However, the various studies based on extension of the same with substituted bromoesters which are described in this section did not furnish the lactone **7**.

<u>Section B:</u> Construction of lactone ring employing radical cyclisation methods: Some approaches

Part I: **Free radical reactions in organic chemistry**

An attempted method, based on radical cyclisation of bromo acetals **9, 10** are

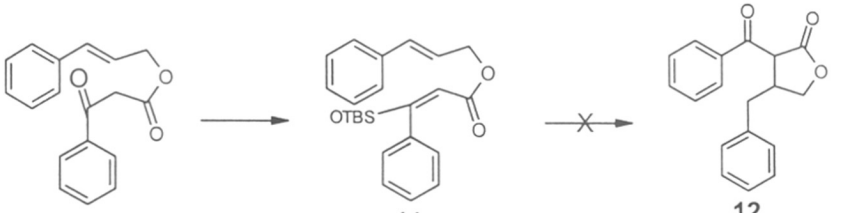


10 **8** **9**

discussed in this section. Due to the poor yield associated with the preparation of one of the intermediates (**10**), work in this route (**A**) could not pursued. Similarly, the difficulties encountered with the protection of α,β unsaturated aldehyde made the other route (**B**) a mirage.

Part II: Cation radical cyclisation of unsaturated silyl enol ethers

The pioneering work by Snider[8] based on oxidative cyclisation of unsaturated silylenolethers for the construction of tricyclic systems is well known and the same methodology was applied in the present case. This part deals with various methods employed for the preparation of the intermediates required for the lactonisation. (details are given in the thesis). Similarly, the intermediate **5** was converted to the corresponding silyl enol ether using TBDMSOTf. All attempts to effect cyclisation of the intermediate **11** with Pd (II) or Ce (IV) species to yield the lactone **12** failed.



Part III: Attempted photo-chemical cyclisation of α chloro ester

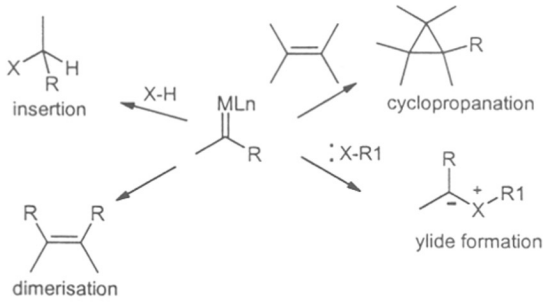
A study of the photochemical decomposition of α halo esters is also explained in this section. Though the required cyclisation did not take place under photo-chemical conditions, a new synthetic route for the deprotection of chloro acetyl esters has been achieved.

Section C

Studies on the application of Carbene intermediates for the construction of lactone ring

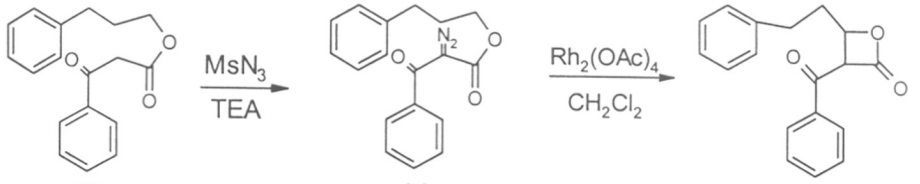
Part I C-H insertion reactions

Due to the versatile utility of catalytic methods for the generation of metallo carbenes[9], several schemes have been reported for the synthesis of various natural products.



Typical reactions of metallocarbenes. R = alkyl, aryl, carbonyl.

A detailed study on the C-H insertion reaction of the intermediate **14** was undertaken. The required diazo ester was prepared from **13** by diazo transfer reaction using mesyl azide. The intermediate **14** when subjected to C-H insertion using $Rh_2(OAc)_4$ in refluxing CH_2Cl_2 resulted in clean conversion (55%) and the product formed was found to be a 4 membered β lactone **15** rather than the expected γ lactone. Several catalysts having different ligands on Rh metal were prepared viz acetate, octanoate, trimethylacetate, trifluoroacetate, MEPY. Except the trifluoroacetate which did not yield any cyclic product all the other catalysts gave β lactone **11** as the major product.

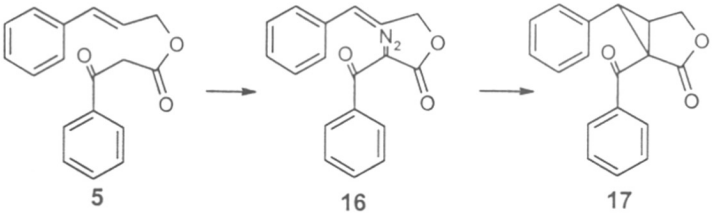


13 **14** **15**

The unusual formation of β lactone **15** as a major product can be explained due to the conformational preferences, which placed the reacting C-H bond in close proximity to the carbenoid centre. In this part a detailed study of various α diazo β keto esters has been carried out, and the results indicate that, in all probabilities, the site selectivity in C-H insertion reaction depends on steric bulk of the reacting metallo carbene.

Part II Cu (II) catalysed cyclopropanation of intermediate (16)

As mentioned in the previous section various attempts were made to prepare the required γ lactone were unsuccessful. Studies were directed towards an alternate route involving construction of the intermediate cyclopropyl lactone **17** and the same is mentioned in the following scheme.



5 **16** **17**

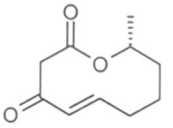
Though $Rh_2(OAc)_4$ catalysed cyclopropanation was successful, it resulted in poor yield of the required cyclopropyl lactone **17**. The use of $Cu(acac)_2$ in refluxing

benzene yielded the required product **17** in more than 70 % yield. Different conditions employed to cleave the cyclopropyl ring are also described in this section.

Chapter III

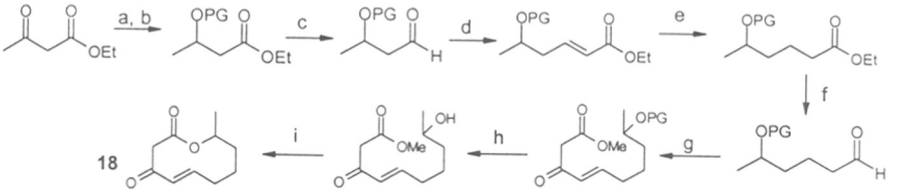
Total synthesis of Diplodialide A

In 1975 Wada[10] *etal* isolated an open-chain pentaketide named Diplodialide A **18** from the culture filtrate of *Diplodia Pinea* (IFO 6472). It exhibited inhibition of steroid 11 α hydroxylase in *Rhizopus Stolonifer* (IFO 5781).



Diplodialide - A

After the successful demonstration of intermolecular transesterification (Chapter I Section B) application of intramolecular transesterification is demonstrated in this work. In this section, a short and efficient synthesis diplodialide A involving intramolecular transesterification as the key step is described.



a) $NaBH_4$/ EtOH. b)TBDMSiCl/imidazole. c) Dibal-H /-78°C. d) $Ph_3P{=}CHCO_2Et$ e)Pd/C H_2. f)Dibal-H / -78°C. g) $NaH/(OEt)_2(O)PCH_2COCH_2CO_2Me$. h) HF. i)H-β/ Toluene/ reflux.

Commercially available ethylacetoacetate was reduced with $NaBH_4$ and the hydroxyl group was protected. DIBAL H reduction followed by Wittig olefination of the latter provided the required C_6 ester unit. Pd/C reduction followed by Dibal H reduction gave the C_6 aldehyde unit. Horner Emmons olefination with phosphonoester of γ bromo methylacetoacetate, followed by deprotection gave the hydroxy ester. This was transesterified to furnish diplodialide A.

References.

1. Benetti, R.Romagnoli, C. De Risi, G.Spalluto and V. Zanarito, *Chem. Rev.*, 1995, **95**, 1065.
2. C. R. Holmquist and E. J. Roskamp, *J. Org. Chem.*, 1989, **54**, 3258.b) Davale, P. N. Patil and R. S. Mali, J. Chem. Res (S), 1994, 152.
3. Otera, *Chem. Rev.*, 1993, **93**, 1449.
4. Ward, R. S, *Synthesis*, 1992, 719.

5. Carrol, M. F. *J. Chem. Soc.*, 1940, 704.
6. Abramovich, R. A., *Org. Prep. Proced. Int.*, 1991, **23**, 683. b) Caddick S., *Tetrahedron*, 1995, **51**, 10403.
7. Sharpless, K. B., *etal. J. Am. Chem. Soc.*, 1987, **109**, 5765. b) Alvarez, E., Nunez, M. T. and Martin, V. S., *J. Org. Chem.*, 1990, **55**, 3429.
8. Snider, B.B., and Kwon,T., *J. Org. Chem.*, 1992, **57**, 2399.
9. Padwa,A. and Austin, D. J., *Angew. Chem.Int.Ed.Engl.*, 1994,**33**,1797. b) Taber, D. F., and Yu,K. K., *J. Am. Chem. Soc.*, 1995, **117**,5757. c) Doyle,M. P. *etal J. Org. Chem.*, 1996, **61**, 9146.
10. Ishida, T and Wada, K, *J.C.S. Chem. Comm.*, 1975, 209.

CHAPTER I

SIMPLE AND HIGH YIELDING METHODS FOR β-KETO ESTER SYNTHESES

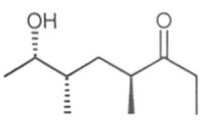
அவனன்றி ஓரணுவும் அசையாது

Nothing will move without His consent

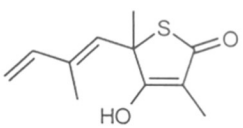
Chapter I

General introduction

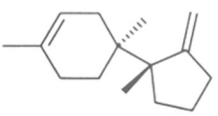
β–Keto esters[1] are multicoupling reagents having electrophilic carbonyl and nucleophilic carbon which make them a valuable tool for the synthesis of complex molecules. They are one of the basic building blocks in the total synthesis of sex pheromones like serricornine[2] (**1**) and various natural products like thiolactomycin[3] (**2**), trichodiene[4] (**3**), polyoximic acid[5] (**4**), chokol[6] (**5**) prostaglandin $PGF_{2\alpha}$[7] (6), *ar* - pseudotsugonoxide[8] (**7**) and syncarpic acid[9] (**8**) and diplodialide[10] (**9**)



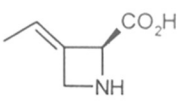
Serricornine (**1**)



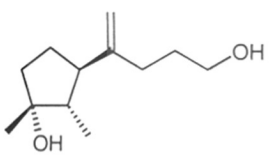
Thiolactomycin (**2**)



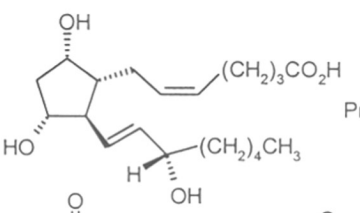
Tricodiene (**3**)



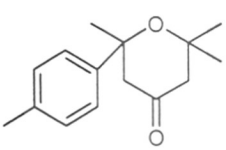
Polyoximic acid (**4**)



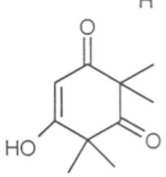
Chokol A (**5**)



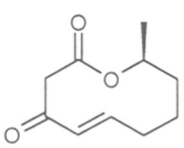
Prostaglandin PGF_{2a} (**6**)



ar Pseudotsugonoxide (**7**)



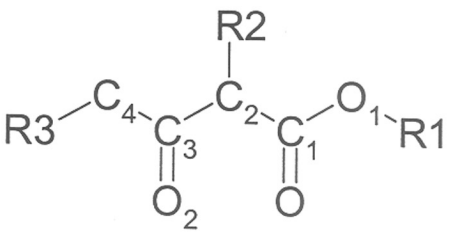
Syncarpic acid (**8**)



Diplodialide A (**9**)

Generally β–keto esters are found as keto-enol tautomers. The amount of enol content depends on the substituents, which stabilise the tautomers. Solvents like $CHCl_3$,[11] DCM which form weak hydrogen bonding disfavour the enol formation whereas nonpolar solvents like benzene, toluene etc. generally favour the enol form. In the case of aroyl β–keto esters even at room temp., the enol content is appreciable.

β–Keto esters can generally be represented as follows.

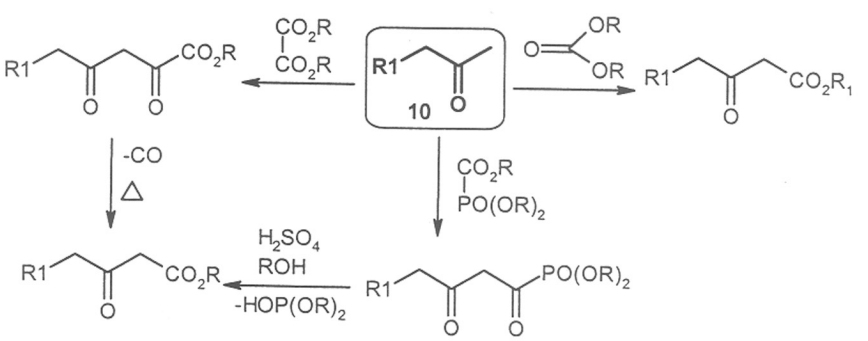


A brief account of the various methods for the formation of β–keto esters based on the following strategies of bond formation is presented below.

a) formation of C_1-C_2 bond
b) formation of C_2-R2 bond
c) formation of C_2-C_3 bond
d) formation of C_3-O_2 bond
e) formation of C_3-C_4 bond
f) formation of C_4-R3 bond
g) formation of C_1-O_1 bond

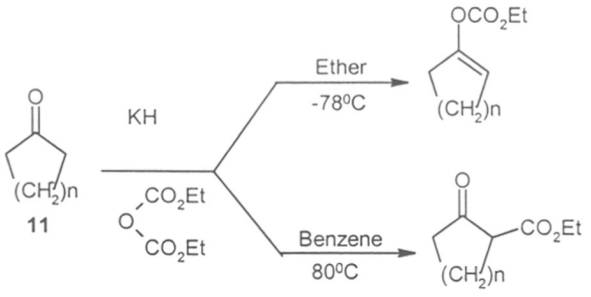
Formation of C_1-C_2 bond

This bond is formed by the regiospecific C-acylation of unsymmetrical ketones **10**. The usual procedures involve reaction on enolate with dialkyl carbonates,[12] dialkyl oxalates[13] and (diethoxyphosphinyl) formates.[14] Generally, unsymmetrical ketones are preferentially acylated at the less substituted α–carbon atom with poor regioselectivity. [**Scheme 1**]



Scheme 1

Winkler *et.al*[15] employed anisylcyanoformate as the acylating agent as it allows ester hydrolysis without decarboxylation. The advantage of this method lies in the fact that here the acylation-alkylation sequence is reversed. Based on safety aspects, stability and cost, cyanoformates are not preferred as the acylating agent. Diethyldicarbonate[16] as the acylating agent has a unique advantage; by varying the experimental conditions either O-acylation or C-acylation of the cycloalkanone **11** can be achieved as depicted in **[Scheme 2].** C-alkylation product as the major one is realised when aminosulphoxonium tetraphenylborate[17] is employed.



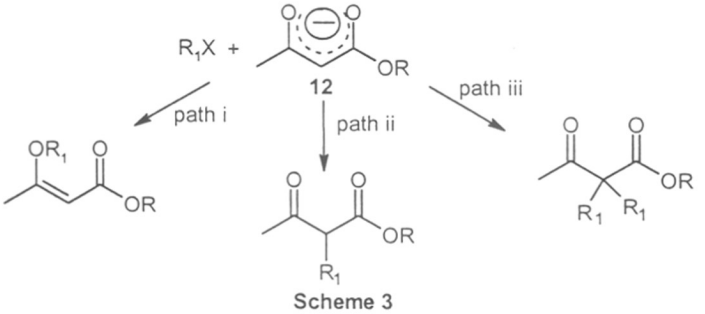
Scheme 2

b) Formation of C_2-R2 bond

Several alkylations, like alkylation under normal conditions, alkylation via Michael reaction, Lewis-acid catalysed alkylation, metal catalysed alkylation, alkylation via diazoacetates, insertion reaction with diazoacetates, heteroatoms-C_2 bond formation, alkylation through rearrangements, acylation *etc.* are known. Some of the salient features of these alkylations are briefly described.

(i) Normal alkylation

C_2-R2 bond is formed by the alkylation of a β–keto ester. Due to the bidentate nature of the anion **12**, the enolate can react at the oxygen center (path i)[18] or at the carbon centre (path ii),[19] together with the possibility of bis alkylation also occurring (path iii)[20] as illustrated in **[Scheme 3]**

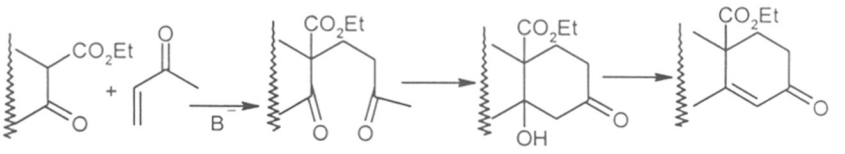


Scheme 3

A polar aprotic medium, a large counter ion, low concentration of the anion, a hard leaving group and an alkylating agent of low SN_2 reactivity usually are expected to favour O-alkylation (path i); the C-alkylation requires opposite conditions. Ion pair extraction and phase-transfer catalysis favour exclusive C-alkylation.

ii) Alkylation using Michael Reaction

The well known "Robinson annulation" which is a widely cited method for building of cyclic compounds belongs to this category.**[Scheme 4]**

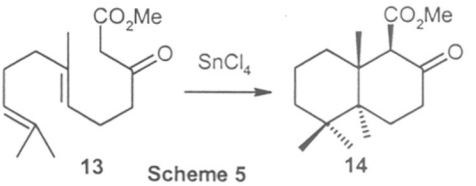


Scheme 4

Intramolecular Michael reaction normally leads to a single stereochemical product. But a careful investigation by Stork *et.al.*[21] revealed that the Michael addition was not selective in polar medium (Bu^tOH or MeOH) and a mixture of *cis* and *trans* adducts were obtained. Following Stork's method, Barco *et.al.*[22] developed an elegant route to an advanced intermediate for the synthesis of 9(0) methanoprostacyclin and a total synthesis of (±) isoclovene has also been achieved.

(iii) Lewis-acid catalysed alkylation

Lewis-acids like $SnCl_4$,[23] $Hg(CF_3COO)_2$[24] catalyse alkylations of β–keto esters, leading to cyclic products especially cyclohexanone derivatives. **13 →14. [Scheme 5]**

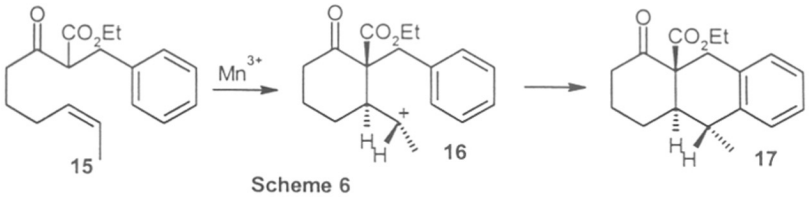


13 **Scheme 5** 14

(iv) Metal-catalysed alkylation

Allylic halides, allylic ethers etc. whcih are sources for allyl palladium complexes are utilised in allylation of nucleophiles. Metal-catalysed intramolecular reaction studied by Tsuji *et.al.*[25] reports that the formation of 5, 6,or 7-membered cyclic β–keto ester by the Pd catalysed alkylation of active methylene compounds with allylic ether moiety is dependant on several factors like substrates, ligands and solvents.

According to Snider *et.al.*[26] the oxidative cyclisation of **15** catalysed by Mn (III) proceeds through generation of a C_2 radical that adds to the olefinic bond followed by radical oxidation to a carbocation **16** subsequent electrophilic attack of the carbocation to an aromatic ring and proton elimination affords **17**, as depicted below **[Scheme 6].**



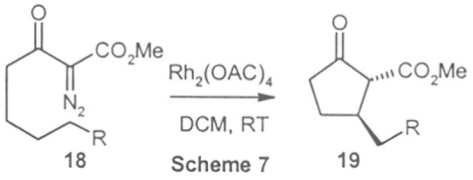
Scheme 6

(v) Alkylation *via* diazoacetates

C_2-R2 bond is also formed by the insertion of carbene generated from diazoacetate to a properly positioned olefinic bond to form a cyclopropane ring. The latter undergoes regioselctive opening with nucleophiles resulting in the formation of alkylated β–keto ester. An examination of the molecular model clearly reveals that the observed bond scission involves the bond that overlaps well with the carbonyl system.[27]

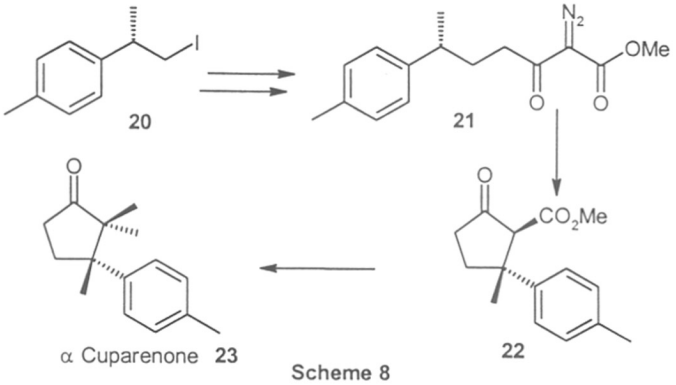
(vi) Insertion reaction with diazoacetates

Rhodium catalysed C-H insertion[28] of α diazo β–keto ester gives cyclised product **18→ 19 [Scheme 7].**



18 Scheme 7 19

Of the two possible modes of cyclisation, the one giving 5-membered ring is the sole product of this reaction. The efficiency of C-H insertion decreases from methine to methylene to methyl. If the chiral center is the site of insertion then retention in configuration is observed. This concept is well utilised in the total synthesis of α cuparenone (**23**)[29] and the route is outlined below **20→ 23 [Scheme 8]**.



Scheme 8

Insertions into an aromatic C-H bond, X-H bond where X= nitrogen are also known.[30]

(vii) Heteroatoms – C_2 bond formation

There are two methods available for this bond formation when oxygen is the heteroatom. One method for the formation of α hydroxy β ketoester is by the treatment of ester enolate with oxidising agents[31] (H_2O_2 or mCPBA). The other concept demonstrates the utility of fluoride ions in proton abstraction, followed by photo oxidation of the intermediate with singlet oxygen.[32] Generation of an enolate with lithioenamine and quenching with benzoyl peroxide leading to tertiary alcohol is also reported recently.[33]

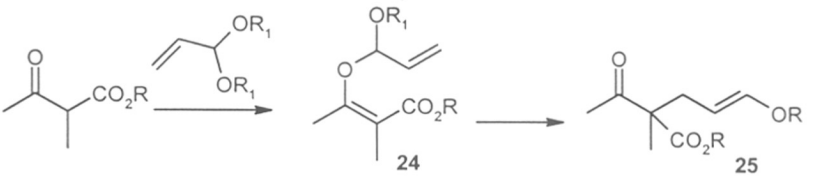
Ester enolate upon treatment with either methyl thiotosylate[34] or phenyl selenenyl chloride[35] leads to C-S and C-Se bond formation respectively. Cyclopentanones have been prepared from the latter compounds *via* oxidation and elimination.

To obtain halogen as the hetero atom, sulphuryl chloride[36] for the chlorine atom, magnesium bromide etherate / H_2O_2[37] for the bromine atom and acetyl hypofluorite[38] for fluorine are often the reagents of choice.

(viii) Alkylation through rearrangements

Several rearrangements are known but Claisen rearrangement of allyl vinyl ethers is a widely accepted method in this category. The reaction of β–keto ester with diethyl acetal of α,β enals[39] leads to the corresponding ethoxylated product **24**. The latter undergoes Claisen rearrangement to give a product which is equivalent to a Michael adduct **24□25**. Chief advantages of this method are: (i) use of mild acidic

conditions that will minimise aldol cyclisation (ii) synthesis of the products in a protected form **[Scheme 9].**



Scheme 9

Other reported methods involve Cu (I) catalysed arylation of β–keto esters[40] or Pd (II) catalysed diazo insertion.[41]

(ix) Acylation

Conversion of one β–keto ester into another β–keto ester by acylation and deacylation is a widely accepted alternative to cross Claisen condensation. The choice of the base for acylation step is crucial. In addition, Lewis acids like $SnCl_4$[42] can also be used when nitrile is used as the acylating agent. In the case of cyclic β–keto esters, either direct acylation by acid chlorides in the presence of Lewis acids[43] or Fries rearrangement of O-acylated derivatives catalysed by $TiCl_4$[44] or formation of the ester enolate by LDA followed by condensation with acid chlorides or esters have been employed.[45]

Formation of C_2-C_3 bond

Acetate anions, carboxylic acid dianions, ketene acetals, malonate anions and other procedures constitute the formation of C_2-C_3 bond.

Acetate anions

The classical acetoacetic ester synthesis or Claisen like condensation *i.e.* acylation of an ester enolate with another ester functionality makes an easy access to β–keto esters. The use of relatively weak bases like NaOMe or NaH leads to exclusive self-condensation products. An important breakthrough in this regard was made by Rathke *et.al.*[46] who found out that "*solutions of ester enolates prepared at low temp. using lithium amides are stable and can be allowed to reach room temp. without the production of condensation product*".

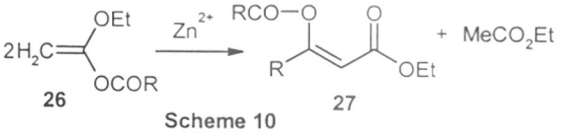
Ester enolates can also be generated from halo esters involving metals like Mg, Zn, Pd. Various acylating agents like thiomethyl ester,[47] N-methoxy-N-methyl amides[48] are also encountered besides acid chlorides.

Carboxylic acid dianions

Generation of dianions of carboxylic acids with strong non-nucleophilic bases[49] or ion radical system followed by condensation with esters or acid chlorides[49] result in the formation of β keto acids.

Ketene acetals

Treatment of O acyl ketene **26** with Zn salt produced enol acylated β–keto esters **27**[50] as shown below **[Scheme 10].** O-silyl ketenes,[51] 1,1-diaminoethens, 1,1-dimorpholinoethenes[52] etc. have also been reported as other sources of ketene acetals.



26 **27**

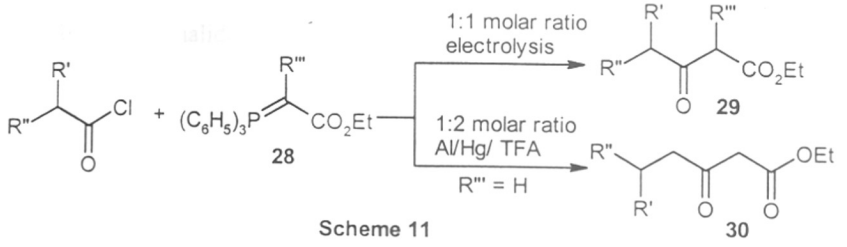
Scheme 10

Malonate anions

The basic draw back of the classical acetoacetic ester synthesis is that when two different esters having α hydrogen are employed, all the four possible products are obtained. To circumvent this problem, carboxylic acid moieties possessing different electronic properties have been employed. The reaction of diethyl malonate anion[53] as nucleophile with irreversible acylating agents like acid chlorides leads to β–keto esters. Yet another example is offered by Meldrum's acid (2,2-dimethyl-1,3-dioxane-1,6dione)[54] which also yields β–keto esters upon reaction with acid chlorides.

Other methods

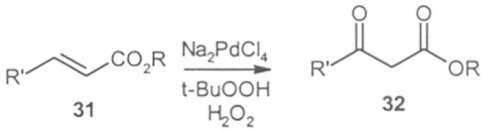
Reaction of acyl chlorides with [1-(alkyloxycarbonyl)-alkylidine]triphenyl phosphorane (**28**)[55] followed by the electrolysis of phosphonium chloride gave β substituted acetoacetates **29**. The reductive elimination by aluminum amalgam catalysed by trifluoroacetic acid[56] produced the β–keto ester **30 [Scheme 11]**. Sulphur extrusion from thioepoxides or base catalysed rearrangement of epoxycyclobutenols[57] are some of the other methods for β–keto esters.



Scheme 11

C_3-O_2 bond formation

The simplest method is the oxidation of a β hydroxy ester. Other methods include direct hydration of acetylenic esters,[58] hydrolysis of enamino esters,[59] oxidation

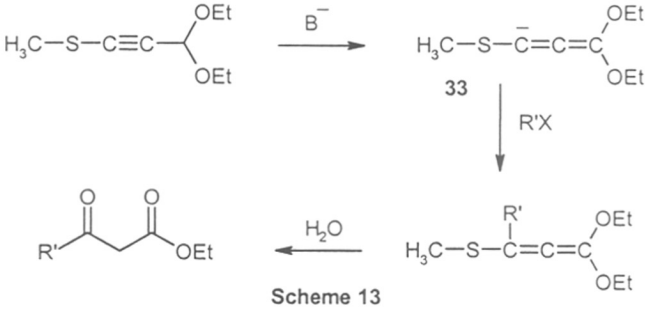


Scheme 12

of a conjugate double bond by $KMnO_4$ and a variant of Wacker process[60] *i.e.* the oxidation of α,β unsaturated ester by TBHP or H_2O_2 in the presence of Pd catalyst **31** **32 [Scheme 12]**.

C_3-C_4 bond formation

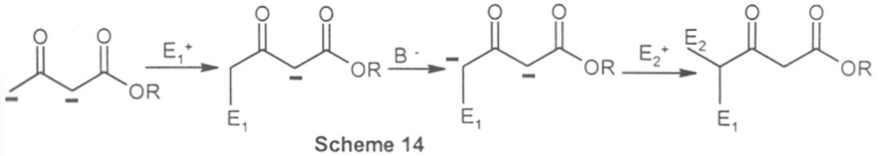
Formation of this bond is the most difficult and the least studied. The attack of a carbanion to a carbonyl is the basic reaction and as there are two carbonyls selectivity is often unpredictable. The addition of lithium dimethylcopper to disubstituted ethyl malonyl chloride,[61] or alkylation of allenic carbanion **33** with alkyl halides followed by hydrolysis[62] are some of the methods available for C_3-C_4 bond formation **[Scheme 13]**.



Scheme 13

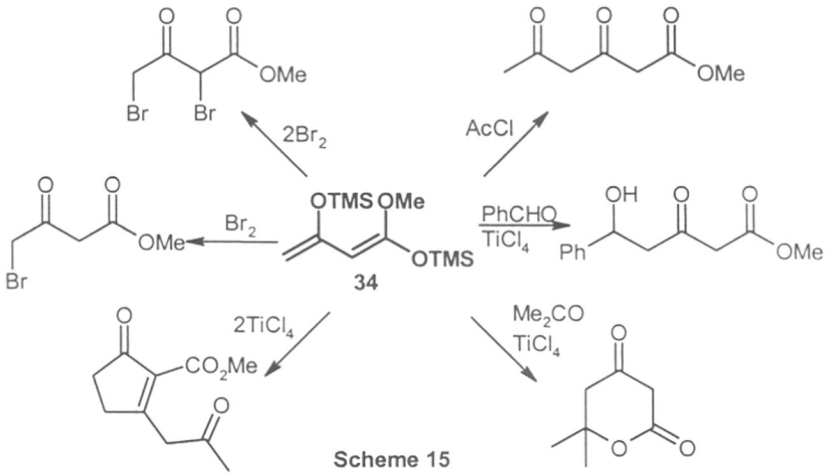
C_4-R3 bond formation

In C_4-R3 bond formation, γ alkylation of a β–keto ester occurs. The dianion generation in stages can be effected with NaH, then with n-BuLi, followed by alkylation using different alkyl halides **[Scheme 14]**



Scheme 14

Due to the well-known difference in reactivity between enolates and silyl enol ethers[63] application of the latter in the above reaction is more diverse than the former. The various transformations of silyl enol ethers **34** can be represented as shown below **[Scheme 15]**



Scheme 15

For the preparation of alkylidene derivatives, aldol condensation or Wittig olefination of the phosphorylated derivatives are the accepted methods.[64]

C_1-O_1bond formation

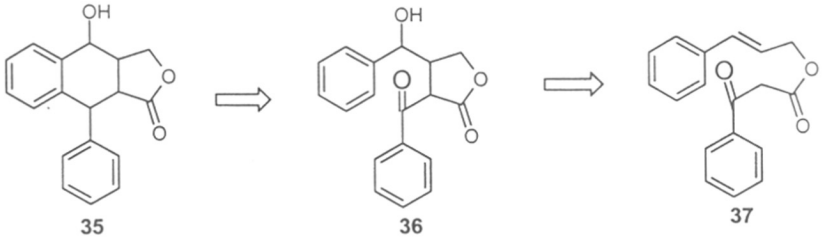
Esterification of β keto acids is one of the simplest methods that can be envisaged in C_1-O_1 bond formation. However, facile decarboxylation is one of the drawbacks of this method. The preferred method therefore is the acetoacetylation of alcohols which can be efficiently carried out with diketene[65] or with 2,2,6-trimethyl-4H-1,3-dioxin-4-one.[66] A synthetically useful method is the transesterification[67] of β–keto esters with corresponding alcohols.

Section A

Efficient synthesis of β–keto esters by the condensation of aldehydes with ethyldiazoacetate in the presence of zeolites

Objective:

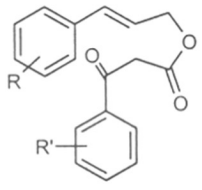
It is clear from what has been discussed under "General introduction" that there are several methods available for β–keto ester synthesis. However a retro synthetic scheme leading to an aryl lignan via a key β–keto ester synthon (please refer to Chapter II) would require development of methods to synthesise the crucial intermediates of the type **37** **[scheme 16]**.



35 **36** **37**

Scheme 16

A thorough literature search indicated that no satisfactory preparative methods are available for the synthesis of compounds of the type **37**.



37 R = R1 = H
38 R = H, R1 = 3,4,5-trimethoxy
39 R = 3,4-methylenedioxy, R1 = 3,4,5-trimethoxy

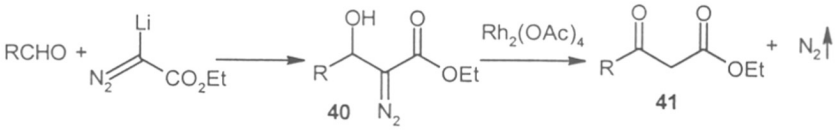
Taliawi *et.al.*[68] are reported to have utilised compounds of the type **37** in their studies, but no details of preparation of **37** are available.

In view of the above observations, it was felt imperative to develop a practical method for the facile preparation of such compounds. This in effect constitutes the subject matter of the present work in this section.

Present work:

As has been described in the earlier part of this chapter, several methods are reported (for C_2-C_3 bond formation) for β–keto ester synthesis. In respect of utilisation of cheaper and easily accessible starting materials, mention may be made of condensation of aldehydes with ethyldiazoacetate to give rise to β–keto esters. The

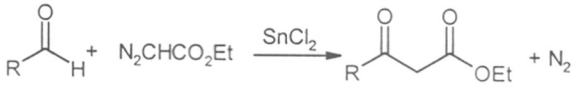
method developed by Pellicciari *et.al.*[69] incorporates expensive $Rh_2(OAc)_4$ as the catalyst and the air sensitive lithiodiazoacetate as the condensing agent **[Scheme 17]**.



Scheme 17

Prior to Pellicciari's method, conversion of **40** to **41** was possible by refluxing **40** with HCl or subjecting **40** to vacuum thermolysis. The drawback of the latter method was that it gave *unsatisfactory results* when *sensitive groups* were present and in some cases possible rearrangements were also observed. It was also observed that the presence of a hydroxyl group α to the diazo functionality altered the general reactivity of alkyl diazo ketones. Reductive removal of diazo functionality, manipulative alteration to various products like α amino compounds or α amino β hydroxy esters or to α amino alcohols *etc.* resulted in the formation of β–keto ester only.

The above transformations under thermal conditions to yield β–keto ester do not appear to be general in nature. In 1978 Fernandez *et.al.*[70] had demonstrated that $BF_3.Et_2O$ can also effect the condensation of aldehydes with ethyldiazoacetate. In 1989, Roskamp and Holmquist[71] reported an efficient and direct method for β–keto esters by reaction of aldehydes with ethyldiazoacetate catalysed by Sn (II) chloride. For the first time, Lewis acid as a catalyst in such operations was invoked. With the aim to generate alkylidene- type reagent by reacting ethyldiazoacetate with low valent main group metal like tin and utilising this reagent to convert an aldehyde to an alkene *via* a pseudo-Wittig type reaction, the authors have found that only β–keto ester was formed as the main product. The reaction sequence is given below **[Scheme 18]**



Scheme 18

Several Lewis-acids like BF_3, $ZnCl_2$, $ZnBr_2$, $AlCl_3$, $SnCl_2$, $GeCl_2$, $SnCl_4$ etc. were found to catalyse the above reaction; however, best results were obtained with BF_3, $GeCl_2$ and $SnCl_2$. Two of the striking features of the reaction are its selectivity and mild conditions. It is note worthy to mention that aromatic aldehydes had lower reaction rates. Nitro group in a substrate did not undergo reduction at an appreciable rate although tin metal was present. Known *toxicity of tin* compounds is one of the limitations of this method.

Closely following Roskamp's report was a disclosure by Mali *et.al.*[72] for a simple route to β–keto esters *via* activated alumina promoted reaction of aldehydes with ethyldiazoacetate **[Scheme 19]**.

Scheme 19

The role of activated alumina in a large number of surface-mediated solid phase reactions was put to good application in this method. The reaction was found to be general for both aliphatic and aromatic aldehydes. Although this method provides convenient and straight-forward route to the synthesis of β–keto ester, it utilises a large excess (ten times the weight of aldehyde) of alumina and hence is *not catalytic*.

A comparative study of Roskamp's and Mali's route to β–keto ester suggests that a judicious combination of Lewis-acid activity with surface activity in a catalyst would be an ideal route for β–keto ester synthesis. Such catalytic properties are found widely in microporous materials, especially zeolites. At this juncture, a brief introduction to heterogeneous catalysts with special reference to zeolites is apt. The exploration of the utility of solid heterogeneous catalysts possessing acidity equivalent to $BF_3.Et_2O$ has been made in the present study.

From the acidity point of view zeolites have been shown to replace the following catalysts in several acid catalysed reactions.

(a) Homogeneous Lewis acid catalysts like $AlCl_3$, $FeCl_3$ (b) Conventional acidic catalysts like Al_2O_3, SiO_2 (c) Mineral acids and organic acids

Zeolites: A brief introduction

Zeolites[73] are hydrated, crystalline, microporous aluminosilicates. The general formula of zeolites can be represented as

$$M_{x/n}[(AlO_2)_x(SiO_2)_y]zH_2O$$

The net negative charge on the framework is same as the number of aluminum atoms and is balanced by exchangeable charge compensating cations. x+y represents the total number of tetrahedra in the unit cell of zeolite. The ratio of $y/x > 1$ controls the acidity and the morphology of the zeolites.

Based on the morphological characteristics[73-75], crystal structure, chemical composition, effective pore diameter and natural occurrences, zeolites have been classified into several groups. According to IUPAC nomenclature system[76] the naming is based on their framework density and number of T atoms per 1000Å, irrespective of

their composition, distribution of T-atoms, cell dimensions or symmetry parameters. Based on the pore size they can be classified as follows.

Pore Size	Number of T in pore opening	Max. Free diameter Å	Example
Small	6 and 8	4.3	Erionite
Medium	10	6.3	ZSM – 5
Large	12	7.5	Y, βeta, ZSM – 12
Extra large	18	12	VPI – 5

Zeolites[77] and related microporous materials have attracted considerable international importance due to their versatility. After the development of molecular modeling of zeolites structures, the depth of understanding the catalytic chemistry and structure activity relationship has shown a dramatic growth.

Application of zeolites in the synthesis of organic fine chemicals is a relatively underdeveloped area,[78] when compared to the successful use of zeolites in hydrocarbon processing or petroleum refining. Some of the reasons may be:

- Many of the target organic molecules to be synthesised are too bulky to be built in or to desorb from the zeolite pore systems
- The average synthetic organic chemist is not acquainted with zeolites and their potentials other than their use as drying agents

Various reasons due to which zeolites are considered as a superior catalyst over conventional homogeneous catalyst[79] are listed below:

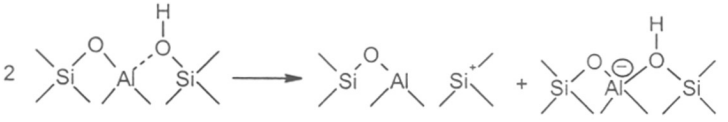
- Improvement of existing process by simple exchange of conventional catalysts
- Introduction of commercially viable reactions into industry, which are previously unsuccessful owing to catalyst problems like insufficient activity, selectivity and catalyst life
- Change over from homogeneous catalysts to heterogeneous catalysts due to the environmental problems, technical problems such as separation of the catalyst *etc.*
- Heterogenisation – immobilisation of homogeneous catalyst to avoid separation problems
- Combination of several individual reactions into one step synthesis
- *Opening up previously unknown synthetic routes*
- Time saving *i.e.* catalyst development by computer aided catalyst design

- Contribution to environmental protection, energy saving and waste minimisation

Acidity:

The presence of aluminum in tetrahedrally coordinated silicon structure in zeolite generates a net negative charge that requires the presence of compensating cations that are located in the porous system of the structure. When the cations are exchanged with $NH_4^{\square}$, thermal decomposition of NH_4^+ in air results in loss of ammonia and causes acidity to zeolites. Several of the well known acidic zeolites are H-ZSM5, HY, Hβ, ReY etc.

Brönsted acid sites can be transformed into Lewis acid sites as shown below, *via* loss of water molecules



Brönsted acid site Lewis acid site

Applications using small pore zeolites have attracted rather little attention but with the large pore molecular sieves (12 ring and larger) applications have expanded greatly. It is the discovery and utilisation of medium pore zeolites notably the ZSM - 5 family and other 10 ring zeolites that had the greatest impact in the area of microporous materials. The use of ZSM-5 and related materials have enabled a revolution in shape-selective control of reaction selectivity. Based on isomorphous substitution, remarkable shape selective oxidations with H_2O_2 using TS-1 and related zeolites have been achieved.

Zeolites are not only superior to homogeneous catalysts but also are superior to conventional proton catalysts. The various advantages are

- Thermal stability of zeolites enable the reactions to be performed at elevated temp. as compared with conc.H_2SO_4 catalysed reactions
- Reduces corrosion problems
- Shape selectivity [allowing reactants to enter and products to desorb for a given molecular diameter] is governed by the zeolite geometry
- Possibility to reactivate the catalyst
- Easy preparation of bifunctional catalysts by joining Brönsted acidity to metals or metal ions inside the zeolite

Zeolites have gained importance in not only in the field of organic or inorganic synthesis but also in the pharmaceutical field. [80] It is worthy of mention that natural

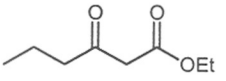
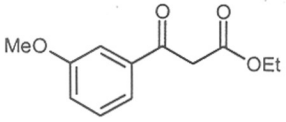
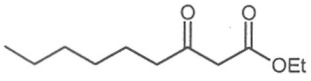
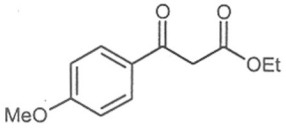
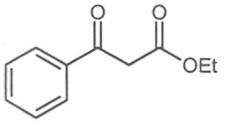
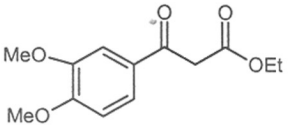
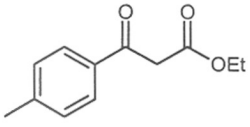
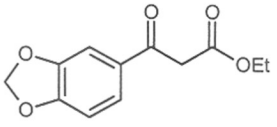
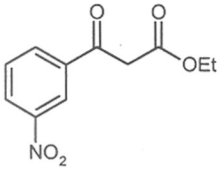
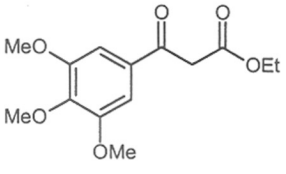
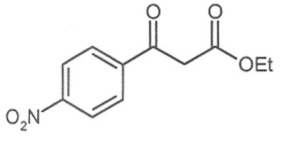
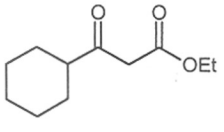
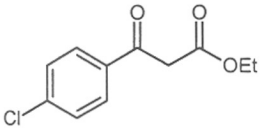
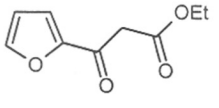
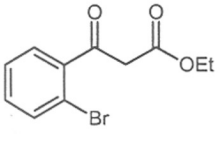
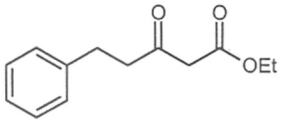
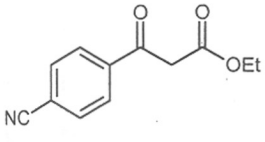
zeolites cure gastrointestinal problems. For example, a number of non-fibrous natural zeolites like *clinoptilolite* and *phillipsite* were tested in humans and were found to be promising. ZSM – 5 which is also non fibrous, can be synthesised at desired silica alumina ratio, particle size, having good acid stability, minimum change in structure during passage through the stomach, with reproducible sorptive properties, exhibiting high selectivity for amines, ammonia and more precisely N-nitrosodimethyl amine (a known carcinogen) absorption. All these properties made ZSM –5 an excellent candidate as a pharmaceutical drug.

Results and discussion

Due to the simple manipulative operations with zeolite the reaction of aromatic aldehydes with ethyldiazoacetate catalysed by zeolite was attempted first. All the previously described methods gave low yields of β–keto esters with aromatic aldehydes; it was thus felt worth-wile to study this reaction with heterogeneous catalysts, especially zeolites. Thus, the condensation of ethyldiazoacetate with benzaldehyde in the presence of H-ZSM-5 gave a product in 55% yield, which in IR showed peaks at 3340, 1735 and 1690 cm^{-1}, characteristic of keto esters. The analysis of the ^{1}H NMR spectrum showed peak at 4.1 δ (2H) corresponding to the methylene proton flanked by two carbonyls, invariably confirmed the formation of β–keto ester. Additionally the appearance of two singlets for the enolic form at 5.7 δ and 12.3 δ, the disappearance of C*H*O proton at 8.5 δ in the ^{1}H NMR spectrum further confirmed the product formation. The presence of singlet carbonyl resonances at 192.25 ppm and at 167.17 ppm in ^{13}C NMR spectrum (for ketone and ester functionality respectively) finally confirmed the assigned structure.

Encouraged by this modest yield with H-ZSM-5, other acidic zeolite like HY, Hβ *etc.* were tried with a view to increase the yield of the β–keto ester formed. Whereas an yield of 70% was obtained with HY, Hβ was found to be the ideal catalyst yielding more than 75% of the β–keto ester. Study of the reaction in the presence of various solvents suggested that ethylene dichloride is ideal for the transformation. Thus several aromatic aldehydes were subjected to condensation with ethyldiazoacetate and the results obtained are presented in table. In order to test generality of the reaction and the efficacy of the catalyst, a few reactions of aliphatic aldehydes with ethyldiazoacetate were also carried out. (**Table I**)

Table I: Condensation of ethyl diazoacetate with various aldehydes

Entry	β–keto ester	Yield %	Entry	β–keto ester	Yield %
a		>90	j		62
b		>90	k		61
c		72	l		60
d		76	m		68
e		85	n		56
f		71	o		79
g		74	p		52
h		81	q		77
i		84			

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Explanation of the product formation

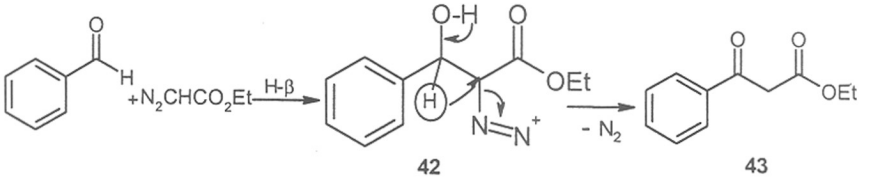
Progress in the knowledge of the mechanism of action of most solid catalyst still remains limited,[81] due to the fact that the nature of the *catalyst-reactant interactions* are still uncertain. The elemental steps are not precisely known. The major drawback encountered is "*surfaces of solid catalysts are extremely complicated*". The number of "*active sites*" can be very small with respect to the overall surface and consequently their structure is almost unknown at an atomic level.

Let us consider during a catalytic cycle, the molecules that interact with the surface have at least during one elementary step, one or many chemical bonds with one or several surface atoms. Therefore the so-called "*active site*" during the catalytic process is a kind of supramolecule which includes both the molecule and one or few atoms from the surface. If the substrate is an organic molecule, the *working site* has a *surface organometallic character* and the rules of organometallic chemistry can be applied to this supramolecule. On surfaces it is really difficult to accurately predict the surface structure and structure reactivity.

A detailed study on the synthesis of molecular models of these supramolecules constitutes an important step towards a molecular approach to surface catalysis.

The only reliable approach to this problem is to really study the elemental step of surface reactions on real surfaces. A possible experimental approach may be to prepare well-defined surface organometallic entities and then to study the reactivity of the well-defined organometallic entity.

Such a theoretical study is beyond the scope of the present work; it was therefore decided not to really probe the exact mechanism of the reaction. However the mechanism of the present reaction can be represented as follows **[Scheme 20]**.

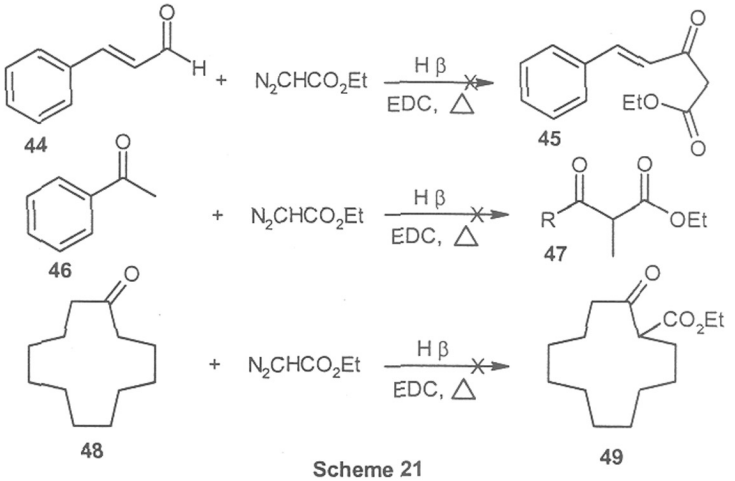


42 43

Scheme 20

Mechanistically it appears that the formation of β–keto ester **43** proceeds via α diazo β hydroxy ester type of intermediate **42** generated by the electrophilic attack of the species formed by the complexation of aldehyde with the acid sites of the catalyst on ethyldiazoacetate. The loss of nitrogen followed by *1,2- hydride shift* is expected to lead to the observed β–keto ester formation.

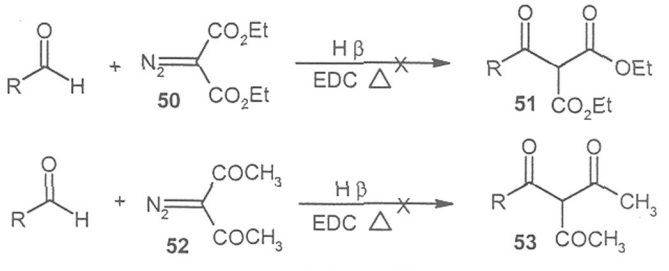
Contrary to our expectations, the reaction with saturated aliphatic aldehyde was over within a short period (<2 hrs.) to provide quantitative yield of the corresponding β–keto ester. However neither α,β unsaturated aldehydes like cinnamaldehyde, hexadienal nor the ketones like acetophenone, cyclododecanone underwent condensation **[Scheme 21]**.



Scheme 21

A plausible explanation may be 'in the case of unsaturated aldehyde **44** due to the delocalisation, the carbonyl carbon is slightly electropositive in nature. Hence it cannot form a complex with the acid sites of the catalyst and that makes the compound unreactive for condensation'. In the case of ketones (**46, 48**) a *1,2-hydride shift* is not possible. Hence they also did not undergo condensation.

Similarly, attempted condensation of either diazo malonate (**50**) or diazo acetylacetone (**52**) did not yield any condensed product **[Scheme 22]**.



Scheme 22

The observed experimental results are in good agreement with the proposed mechanism. Acidity of the catalyst is not sufficient enough to bring about the condensation as the electron with drawing groups present in the diazo compounds stabilise the latter to a greater extent.

Conclusion

A new convenient synthesis of β–keto esters from commercially available aldehydes has been achieved. The various advantages of this methodology are summarised as below

- A facile and efficient preparation of β–keto ester by the condensation of ethyldiazoacetate with aldehydes using zeolite as the catalyst has been achieved
- For the first time zeolite have been demonstrated to catalyse condensation of ethyldiazoacetate with aldehydes efficiently
- With lesser reactive aromatic aldehydes, this method has been shown to improve the yields of the corresponding β–keto ester considerably
- The methodology avoids use of strong bases that are normally employed in conventional methods
- The catalysts are easy to separate by simple filtration and are recycled at least three times without much loss in their activity.
- The catalysts are associated with minimum environmental hazards.
- It has been demonstrated that acidic zeolites like Hβ, HY are excellent alternatives to Lewis acids like $SnCl_4$, $BF_3.Et_2O$.

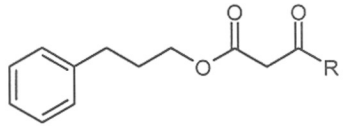
Section B

Part I

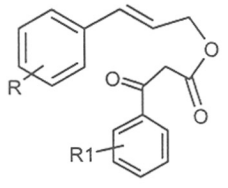
Synthesis of β–keto esters *via* transesterification in the presence of heterogeneous catalysts.

Introduction

In the earlier section of this Chapter, several methods for the synthesis of β–keto esters that are available in literature have been described in detail. Additionally, a facile, preparative, zeolite-mediated condensation of aldehydes with ethyldiazoacetate to give β–keto ester[82] developed during the present work has also been described. However, this method has some limitations for ready preparation of intermediates of the type **37-39, 54, 55**. This is due to the fact that the corresponding diazoacetates with which the aldehyde is to be condensed is neither available nor accessed easily.

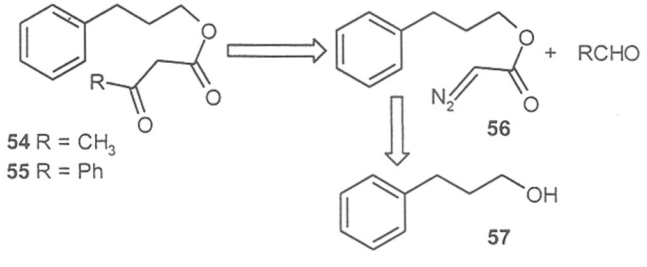


54 R = CH_3
55 R = Ph



37 R = R1 = H
38 R = H, R1 = 3,4,5-trimethoxy
39 R = 3,4-methylenedioxy, R1 = 3,4,5-trimethoxy

None of the intermediates **37-39, 54, 55** are reported in literature. These intermediates were required in connection with some synthetic schemes proposed for aryl lignans (see Chapter II for details). As there was no direct method available for the synthesis of such intermediates, a convenient route employing the condensation of corresponding diazo ester with aldehydes was considered. The following retro scheme clearly spells out the requirements.



54 R = CH_3
55 R = Ph

56

57

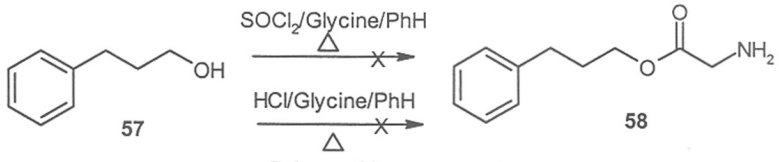
Scheme 22

The above retro synthetic scheme **[Scheme 22]** appears to be a short method comprising preparation of the required diazo ester followed by its condensation with

different aldehydes. Various methods that are reported in the literature for the conversion of alcohols to the corresponding diazo ester were attempted with the alcohol **57**, in order to convert it to the diazo ester **56**. Some of these approaches are described below.

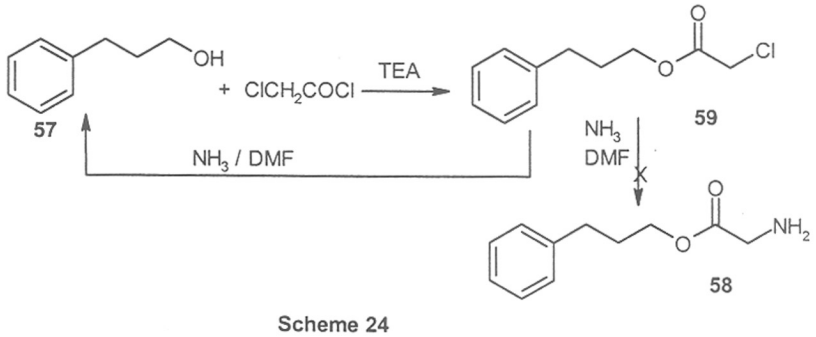
Present work

A general method for the preparation of ethyldiazoacetate consists of diazotisation of glycine ethyl ester with $NaNO_2$. On these lines, it was a straightforward and indeed a convenient exercise to consider application of the same reaction for the formation of the required diazoester. As a simple case, initially the alcohol **57** was subjected to condensation with glycine. However all the conventional methods that are reported (as shown below) **[Scheme 23]** for this particular transformation were unsuccessful.



Scheme 23

An alternate two-step synthesis involving the conversion of chloro ester **59** to amino ester **58** was attempted next. Conversion of menthol to the corresponding glycinate ester using the same protocol has been reported in literature. Using standard procedure, alcohol **57** was converted to the corresponding chloroacetyl ester **59** employing TEA as the base.[83] The amination using NH_3/DMF did not yield the required glycinate ester; instead, it gave back the starting material **[Scheme 24]**.

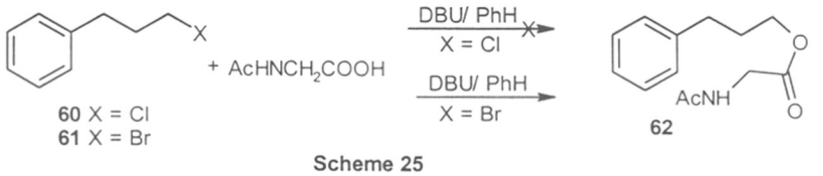


Scheme 24

It was indeed on a disappointing note that the required nucleophilic displacement did not occur; instead, deprotection of the chloroacetyl group had taken place. In order to determine whether the deprotection was due to any moisture present in

the ammonia, two control experiments were carried out. One reaction in which the chloroacetyl ester was stirred with a mixture of water and DMF for 2 days, and in other experiment dry NH_3 (distilled from Na) and DMF were used. From the results of the two control experiments, it was clear that only in the NH_3 reaction the observed cleavage occurred (see "Results and discussion" for more details).

Some detailed studies on the deprotection of chloroacetyl group and a plausible explanation are discussed in chapter II.



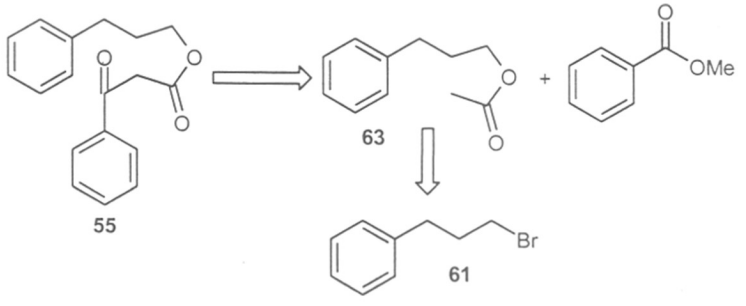
60 X = Cl
61 X = Br

62

Scheme 25

An entirely different route with protected glycine was considered **[Scheme 25]** in which the alcohol **57** was first converted to the halo derivative by standard procedures and the later was then condensed with N-acetyl glycine.[84] With chloro derivative **60** the condensation with N-acetyl glycine did not proceed, but with the bromo derivative **61** the required product **62** was obtained, albeit in poor yields. Starting from the alcohol (**57**), the N-acetyl glycine derivative **62** via the bromo derivative **61** was obtained in low yields. Hence this method was found to be impractical and was not pursued further. All the methods described above failed to provide the desired diazo ester **56**.

It was envisaged that if the bromo compound **61** could be conveniently converted to **63**,[85] then the required ester **55** could be achieved by condensation of **63** with methyl benzoate (see retro scheme) **[Scheme 26]**.



Scheme 26

However, Claisen condensation of **63** with methyl benzoate gave a complex mixture from which the required product could not be isolated.

Yet another method to obtain the β–keto ester **55** could be via transesterification of a suitable β–keto ester with alcohols. The field of transesterification is of immense

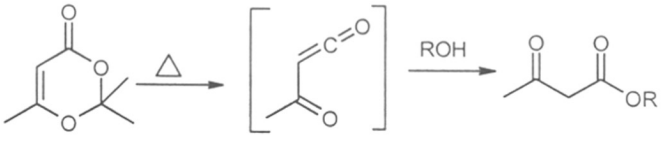
importance in Organic Chemistry; a brief introduction to this is given below, with special emphasis to transesterification of β–keto esters.

Transesterification of β–keto esters

Transesterification is an important reaction, widely used for the synthesis of fatty acid esters in industry. It can be acid catalysed or base catalysed. It has an added advantage over the conventional esterification of acids; in the case of β–keto ester the esterification of the β keto acid often leads to decarboxylation. Even vinyl ether formation has often been observed. A combination of DBN as the base and alkyl sulphates as alkylating agents[86] avoids such possible decarboxylation, since the esterification can be conducted at room temp. and no heating is required

A new era in the preparation of β–keto ester from alcohol was opened up by Boese[65] who first introduced diketene for the preparation of acetoaceticester in the presence of pTSA. Later, basic catalysts like alcoholates,[87a] 4-DMAP[87b] *etc.* for the preparation allylic, primary, secondary and tertiary acetoacetates were used. Though this method enjoyed widespread acceptance and support, the intrinsic problem associated with this method was the lachrymatic and toxic nature of diketene that posed safety problems and difficulties were encountered in large-scale preparations.

It was only in the past decade or so, that an alternative to "diketene free" acetoacetylation of alcohols with 2,2,6-trimathyl-4H-dioxin-4-one (**64**) was developed[66] **[Scheme 27]**.



64

Scheme 27

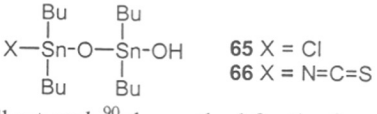
Some of the advantages of this method include: avoiding the use of acid catalysts, transesterification of hindered tertiary alcohols and polyhydroxylated alcohols. Moreover, the method gives better yield than the direct transesterification of methylacetoacetate.

A practical method for transesterification of methylacetoacetate was developed by Taber *etal.*,[88] wherein 4-DMAP was used as the catalyst **[Scheme 28]**.

Scheme 28

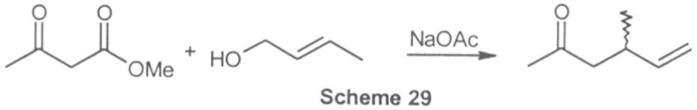
This method found widespread industrial application as well. However, an important drawback of this method is that transesterification of non-enolisable β–keto esters is not possible. Similarly tertiary alcohols are also not transesterified. The expensive 4-DMAP as the catalyst has been substituted with 4-Å molecular sieves for the shifting of the equilibrium towards the products; yet, the drawbacks as described above persisted.

Otera *etal.*[89] could overcome some of these problems of transesterification employing 1,3 disubstituted tetrabutyl distannoxanes (**65, 66**) as the catalyst under neutral conditions.



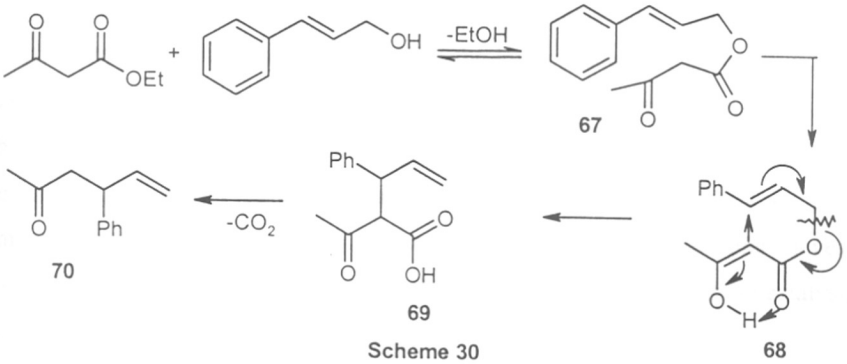
According to Gilbert *etal.*,[90] the method for the formation of allylic acetoacetates that are based on the acid catalysed opening of diketene limits the range of available compounds to esters of acetoacetic acid. Basic catalysts at higher temp. either fail or lead to decarboxylattive rearranged product.

At this juncture, it is very relevant to mention decarboxylative rearrangement of allylic esters. *i.e* Carroll rearrangement[87a] **[Scheme 29]**.



Scheme 29

Previous findings on the transesterification of cinnamyl alcohol with β–keto esters clearly indicate that only Carroll rearrangement had occurred and no transesterification product was formed **[Scheme 30]**.



Scheme 30

It was evident from the Carroll rearrangement that esters of allyl alcohols are rather difficult to isolate. In the above sequence of reactions, the first step is the re-esterificaion **67**, which is catalysed by the alkaline catalyst, the second step is the rearrangement of the resulting ester to a β keto acid **69**, which then readily decarboxylates to give the observed unsaturated ketone **70**.

In the Taber's procedure, problems associated with slow rate of equilibrium and competitive entrainment of the allylic alcohol reduced its practical utility. Gilbert's method was the first successful one for the transesterification of allylic alcohols. In this method, the yield decreases from primary to secondary allylic alcohols for which an explanation was provided based on the steric constranits.

Later, Witzeman *etal.*[91] introduced transesterification based on thermal reaction of *tert*-butyl acetoacetates with various alcohols. A detailed study was conducted and it was demonstrated that the thermal decomposition of *tert*-butyl acetoacetate generates acylketene which upon attack by nucleophiles produced β–keto esters, β keto amides etc.

Recently, highly efficient method for transesterification of acetoacetic esters with various alcohols in the presence of sulphated super acids[92] have been reported. However, the method was unsuccessful in the transesterification of benzoyl derivatives.

Development of new method for transesterification

A detailed description of the literature methods as mentioned above clearly indicates that there is no efficient method for the preparation of intermediates of the type **55**. The feasibility of application of the general methods to **55** also does not seem to exist. Due to these constraints and limitations, it became necessary to develop a mild and efficient method for **55** via transesterification. Compounds of the type **55** are reckoned to serve as crucial intermediates in the synthesis of various aryl lignan lactones.

Transesterification being an equilibrium process can be effected in the presence of acid catalysts, with efficient removal of the lower alcohol by azeotropic distillation. Use of solid heterogeneous catalysts like zeolites was invoked in the present work for this purpose, as our experience with such catalysts in β–keto ester synthesis was very rewarding (see part I of this chapter). Additionally, zeolites which are essentially microporous aluminosilicates can be used as substitutes for molecular sieves in the effective removal of water, lower alcohols etc. Hence the utility of these catalysts in the present study has been explored in detail.

It is reported in literature that liquid phase hydrogenation of methylacetoacetate in the presence of Ni exchanged Y-zeolite proceeds with transesterification[93] with the solvent n-butanol at the acid sites of the catalyst. However in this case, the transesterification occuring as a side reaction could be suppressed by treatment of the catalyst with NH_3 or with pyridine. Thus the area of transesterification with zeolite remained relatively unexplored.

As a model experiment, ethylacetoacetate and compound **43** were subjected to transesterification with different alcohols in toluene in the presence 5- 10% of the zeolite **[Scheme 31]**.

R = CH_3, R' =Et R" = primary,
43 R = Ph, R' = Et secondary, benzyl etc.

Scheme 31

Analysis of the product showed the formation of the transesterified product in good to excellent yields. Encouraged by this initial positive result, several zeolite catalysts were screened for this purpose and several transesterification reactions were successfully carried out. Details of these results are presented under "Results and discussions".

Results and discussions

Dihydro cinnamyl alcohol was prepared by the reduction of cinnamyl alcohol. The structure of dihydro cinnamyl alcohol (**57**,) was confirmed by its ^{1}H NMR which revealed appearance of triplets at 3.7 δ (2H, O*CH*$_2$), 2.8 δ (2H, benzylic), a multiplet at 2.1-1.9 δ (2H) and the disappearance of olefinic protons at 6.65 δ and 6.4-6.3 δ. This alcohol was then converted to its chloroacetyl ester **59** according to standard procedures. The IR peaks at 1740 and 800 cm^{-1} for ester carbonyl and C-Cl stretching respectively and a singlet at 3.9 δ (2H, *CH2*-Cl) and a triplet at 4.2 δ (2H, O*CH2*) in ^{1}H NMR further confirmed the structure. In order to prepare the amino compound **58** from this chloro compound, a well-established method[83] for the conversion of Cl to NH_2 was attempted, *viz* NH_3/DMF. When this chloroester was subjected to amination using this combination reagent, a clean conversion took place and a slower moving product was isolated by column chromatography. However, analysis of the compound by IR (a band at 3320 cm^{-1}) and ^{1}H NMR proved the compound to be dihydro cinnamyl alcohol (**57**)

rather than the required amino compound, indicating that hydrolysis of the chloro ester **59** to give back the starting alcohol had occurred during the course of the reaction.

In order to confirm whether basic hydrolysis of the ester group took place or the cleavage took place in the presence of moisture, two control experiments were carried out. It was observed that, cleavage took place only with NH_3/DMF and not with water/DMF. This observation ruled out the possibility of the presence of moisture which might have facilitated hydrolysis. The results obtained did not appear to be in conformity with what is reported for menthol glycinate preparation. Since in the present case, deprotection occured, attempts to prepare the glycinate ester of dihydro cinnamyl alcohol could not be realised by this method.

As an alternative, a different route employing protected glycinate **[Scheme 27]** was considered. Here dihydrocinnamyl alcohol was converted into its chloro derivative **60** which showed ^{1}H NMR resonances at 3.4 δ (t, 2H, CH_2-Cl)and 2.8 δ (t, 2H, benzylic). But condensation of this chloro derivative with N-acetyl glycine in the presence of DBU did not proceed at all. It may be attributed to the low reactivity of the chloro compound. This was indeed found to be the case, because, instead of **60**, when **61** was used, the corresponding condensed product **62** was obtained in less than 40 %. The product showed IR peaks at 3300, 1740 cm^{-1} for the NH and ester functionality's and ^{1}H NMR peaks at 6.3-6.4 δ (br, N*H*), 4.2 δ (t, 2H, OCH_2), 4.0 δ (d, 2H, CH_2NH), 2.65 δ (t, 2H, benzylic) and 2.1 δ (s, 3H, CH_3CO). Although the required product **63** was obtained, the overall yield starting from alcohol **57** was <20 % and so this method could not be applied as a preparative method.

Attention was then directed towards a simpler and well-established method **[Scheme 28]** ie. Claisen condensation to prepare the required β–keto ester, which would avoid the preparation of the corresponding diazo ester. In this regard, the bromo compound **61** was converted into acetate **63**. The formation of acetate **63** was confirmed by the presence of ester carbonyl at 1730 cm^{-1} in IR and a singlet at 2.0 δ (3H) for methyl group in ^{1}H NMR. However, when this acetate was subjected to Claisen condensation under usual conditions, it resulted in a complex mixture which could not be separated. Due to faliure to condense the acetate, a one to one exchange of ester to alcohol, namely, transesterification was considered as the next rational approach.

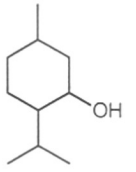
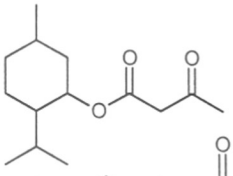
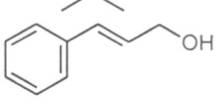
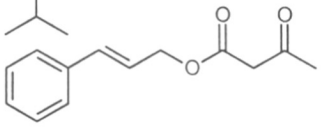
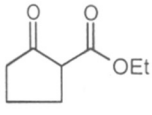
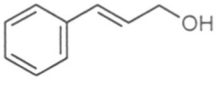
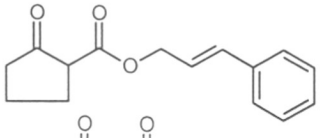
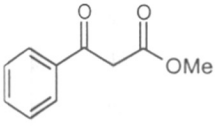
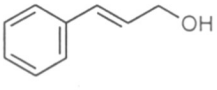
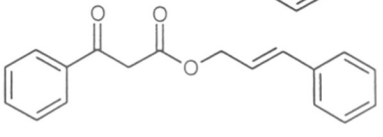
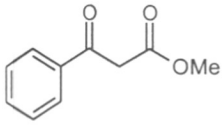
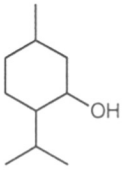
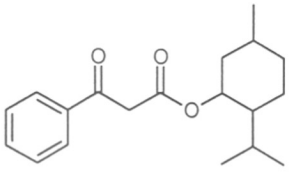
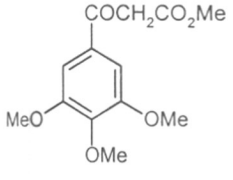
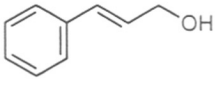
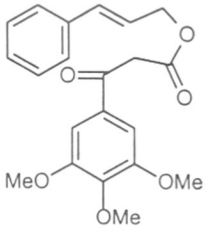
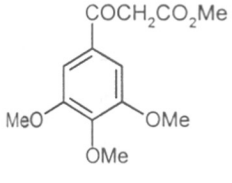
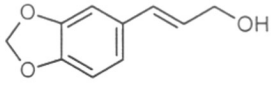
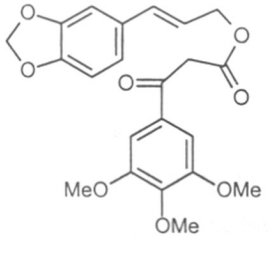
As a simple case, ethylacetoacetate was mixed with phenethyl alcohol and the zeolite catalyst H-ZSM-5 (10% wt/wt) in toluene and refluxed, the ethyl alcohol formed was azeotropically removed using Dean-Stark apparatus **[Scheme 31]**. The formation of turbidity in the toluene distillate clearly showed that transesterification was taking place.

Even after several hours of reflux, the reaction did not go to completion. The reaction was stopped tentatively after refluxing for 10 hrs. Removal of the catalyst by filtration and distillation of the solvent at reduced pressure followed by purification of the product obtained resulted in a compound (85 %), which was different from ethylacetoacetate and phenethyl alcohol. The compound showed 1735 (ester carbonyl), 1700 (ketone carbonyl)cm-^{1} in IR and a peak at 3.2 δ (s, 2H, $COCH_2CO_2$) in ^{1}H NMR spectrum clearly proved the formation of the transesterification product. The disappearance of a quartet at 4.2 δ (2H, OCH_2) and a triplet at 1.25 δ (t, 3H, CH_3) in ^{1}H NMR further confirmed the product formation. Additionally, the ^{13}C NMR showed resonances at 200.38 ppm (ketone) and 166.91 ppm (ester), thereby confirming the structure of the product. In order to demonstrate the generality of the reaction and also to improve the yield further, catalysts having varying acidity were screened. Catalysts like H-Y, H-β, Fe-Y, Fe-β, Sn based Y, H-ZSM-12, Rare earth-Y were tried for this purpose and all these catalysts were found to be effective for the transformation giving yields varying from 55 –95 %. In the present study, H-β was found to be superior as it produced >95 % of the transesterification product.

It was therefore decided to check the feasibility of the newly developed method with allyl alcohols, in particular cinnamyl alcohol, as the reports suggest that these products *via* Carroll rearrangement **[Scheme 30]** are difficult to isolate. When the same reaction was tried by the presently developed zeolite catalysed method, it was found to be successful. Although the reaction did not go to completion, the maximum, yield (95 %) was obtained after 8 hrs. of reaction. Analysis of the product showed IR peaks at 3340, 1735, 1690 cm^{-1} corresponding to β–keto ester, the ^{1}H NMR spectrum showed peaks at 8.0 δ (2H) typical of aromatic protons ortho to the carbonyl, 6.7 δ (1H) and 6.35-6.45 δ (1H) for the cinnamyl protons 4.1,5.75,12.6 δ (2H, $COCH_2CO_2$) for the methylene and enolic protons confirmed the structure **67**. The peak at 4.1 δ corresponds to the ketone form and 5.75, 12.5 δ peaks corresponds to enolic form. ^{13}C NMR showed resonances at 192.39 (ketone carbonyl) (s), 167.32 (ester carbonyl) (s), 87.12 (enolic) (d), 45.89 ($COCH_2CO_2$) (t) and the mass peak at 280 and the base peak at 105 further confirmed the structure.

After successfully applying the new method for the preparation of cinnamyl esters, the generality of the present method was put to test. Thus methylacetoacetate/ ethylacetoacetate was transesterified with various alcohols like primary (dodecyl), secondary (menthol), benzyl etc. All the reaction gave excellent yields of the corresponding transesterified products (see **Table II**).

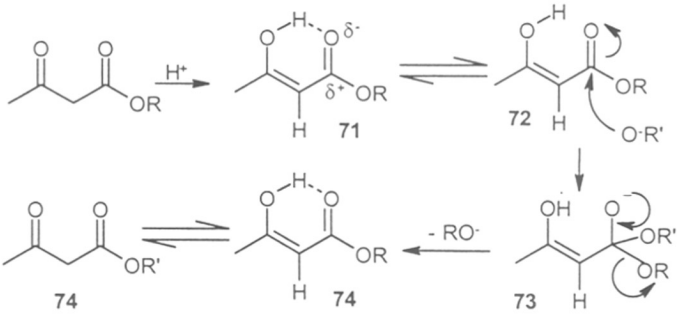
Table II Transesterification of various β-keto esters with alcohols

	Substrate	Alcohol	Product	Yield %
a	$CH_3COCH_2CO_2C_2H_5$	$C_6H_5(CH_2)_2OH$	$CH_3COCH_2CO_2(CH_2)_2C_6H_5$	96
b	$CH_3COCH_2CO_2C_2H_5$	$C_{12}H_{25}OH$	$CH_3COCH_2CO_2C_{12}H_{25}$	86
c	$CH_3COCH_2CO_2C_2H_5$	$C_6H_5CH_2OH$	$CH_3COCH_2CO_2CH_2C_6H_5$	81
d	$CH_3COCH_2CO_2C_2H_5$			95
e	$CH_3COCH_2CO_2C_2H_5$			95
f				84
g				66
h	$C_6H_5COCH_2CO_2CH_3$	$C_6H_5(CH_2)_3OH$	$C_6H_5COCH_2CO_2(CH_2)_3C_6H_5$	64
i	$C_6H_5COCH_2CO_2CH_3$	$C_{12}H_{25}OH$	$C_6H_5COCH_2CO_2C_{12}H_{25}$	71
j				69
k				62
l				59

Similarly, cyclic β–keto ester (see **Table II** entry f) was also successfully transesterified with cinnamyl alcohol. Finally the crucial intermediates **37-39** required for the proposed synthetic plan leading to various natural products (see Chapter II) were also successfully transesterified. The yields of the products obtained from benzoyl acetates are moderate only; this may be attributed to the bulkiness of the substrate. Higher acid strength of Hβ (*vis-a-vis* Y type zeolite) coupled with large pore openings and void space (*vis-a-vis* ZSM-5, ZSM-12) may be responsible for its better activity.

In order to understand and attribute the reasons for low yields associated with the transesterification of benzoyl acetate, the basic principles underlying the acidity[94] of zeolite could be considered. The Brönsted acidity of solid acid is the ability to donate or at least partially transfer a proton which comes in contact with the surface anions.

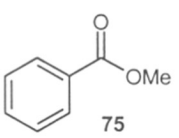
In a catalytic reaction " *diffusion of reactant through the zeolite micropores to reach an active site, adsorption of the reactants on the active sites, chemical reaction to give the adsorbed product, desorption of the product and finally diffusion of the product through the zeolite channels"* takes place. It is therefore the bulkiness of the product, which makes it unable to come out through the pores, resulting in moderate yield of the reactions of benzoyl acetates. Due to the presence of Lewis and Brönsted acidity, it is still not clear whether transesterification is a surface catalysed reaction or a pore selective reaction. A probable mechanism for the transesterification is proposed which can be represented as below.



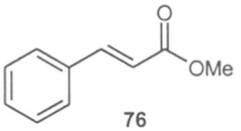
Scheme 32

In the first step the β–keto ester complexes with the acid sites of the catalyst leading to the shifting of the equilibrium towards the enol form. Due to this, slight positive charge is generated at the carbon of ester carbonyl **71**. The nucleophilic alkoxide moiety then attacks the carbon of ester carbonyl leading to the complete electron transfer to the ester oxygen **72**. In the charge reversal step, the lower alcohol is displaced **73** which is then protonated to form the corresponding alcohol whose azeotropic removal led to the transesterified product **74 [Scheme 32]**.

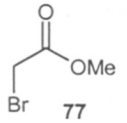
In support of the postulated mechanism, attempts were made to transesterify various esters with alcohols. Esters like aromatic **75**, α,β unsaturated **76**, α halo **77**, saturated **78**, α keto **79** and γ keto **80** were selected. However, none of these esters could be transesterified. The various esters chosen are given below.



75



76



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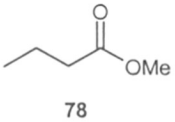
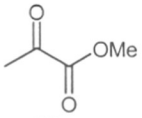


78



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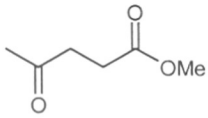


80

The difference in reactivity of β–keto ester from that of the other esters in transesterification may, probably be, due to the formation of an acyl ketene intermediate in the former.[95] None of the other esters have the possibility of forming a 6 membered intermediate which can stabilise the charge polarisation. It is therefore the typical keto enol form of the β–keto ester which enables it to undergo facile and efficient transesterification with various alcohols.

Conclusion

A facile synthesis of β–keto ester has been developed *via* transesterification catalysed by zeolites.[96] This method offers several advantages over the existing methods:

1. In the case of transesterification of primary and secondary alcohols with alkyl acetoacetates, excellent yields have been obtained (>90 %).
2. For the first time, aromatic β–keto esters **37-39, 55** have been prepared *via* transesterification. The yields are however only moderate (50-60 %), this may be attributed to their steric bulk.
3. Transesterification has been found to be very selective for β-keto esters. Other esters like α- keto, γ-keto, α–halo and saturated and unsaturated esters were not transesterified. A rational explanation has been offered.
4. Several catalysts with Lewis-acid acidity like H-Y, Hβ, H-ZSM-5, H-ZSM-12, Re-Y were screened and Hβ was found to be the best catalyst for the present work.
5. The reactions are easy to work-up which involve filtration of the catalyst and purification of the products.
6. This is the first detailed study of transesterification catalysed by zeolites.
7. The catalysts can be recycled several times (at least three times) without much loss in the activity.
8. The method offers a non-hazardous, environment-friendly (pollution free) process for transesterification of β–keto esters.

Section B

Part II

Microwave assisted synthesis of β–keto ester *via* transesterification in the presence of catalysts

Introduction

In Section B Part I, a facile and efficient synthesis of β–keto ester *via* zeolite catalysed transesterification has been reported for the first time.[96] Though this method was efficient, some of the intermediates which are reported for the first time **37-39, 55** could be obtained only in moderate yields. In order to improve the yields of transesterification of alkyl benzoyl acetates, it was felt a worthwhile exercise to explore the field of microwave irradiation for this purpose. At this juncture, a brief look into microwave assisted organic reactions would be helpful.

Microwave assisted organic reactions have attracted much attention in the past few years. Knowledge of basic principles of microwave[97a-c] may help to understand and appreciate its usefulness as an important tool in organic reactions.

The wave-length of microwave is from 1 cm to 1 meter and the frequency is from 30 GHz to 300 MHz. Generally domestic microwave oven operates at 2,450 MHz corresponding to a wave length of 12.2 cm. Like conventional heating, the energy transfer is not by conduction or convection but it is by dielectric loss. The efficacy of heat production by this mode depends on the characteristic dielectric relaxation of the sample i.e. the temp. and viscosity of the sample.

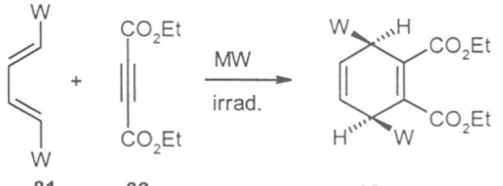
MORE (Microwave-induced Organic Reaction Enhancement) chemistry was developed by Bose *etal.*[97d] and several applications are recorded in literature. They are suitable for a variety of preparative reactions on small scale to medium size scale. These reactions are conducted in a few min. with complete safety in open vessels at ambient pressure in domestic microwave oven. The strategy is to heat rapidly the reactants with minimal vaporisation. When the reaction cannot be performed neat, a high boiling solvent with high dielectric constant is employed. Generally, hydrocarbon solvents are not preferred since they are not suitable for the absorption of microwave energy efficiently.

Microwave irradiation can be used as an efficient source for thermal energy. Performing reactions under this condition would lead to faster and cleaner reactions which may be attributed to less thermal decomposition of product and minimisation of secondary process (unwanted side reactions). "*Dry reaction condition*"[98] often used in microwave has several advantages. Using reagents supported on inorganic solid

materials in the absence of solvent or the "*dry media conditions*" together with microwave irradiation leads to good results under very simple and safe conditions. Since solvents are not used at all, the waste disposal is minimum. Moreover, drying of organic solvents can be avoided. The term "dry reaction conditions" used in microwave should not be confused with the "dry reaction conditions" of organic reactions. In the latter, it is the rigorous purification of solvents to exclude moisture and in the former it is the complete absence of solvent itself.

Various reactions like Diels-Alder,[99] Claisen, "ene" reaction etc. can be carried out under microwave irradiation conditions. Some of the examples are given below.

Diels-Alder reaction under microwave condition furnishes better yield of the adduct. Not only the yields are improved, but the time required for the transformation is drastically reduced from a few hrs. to a few min.

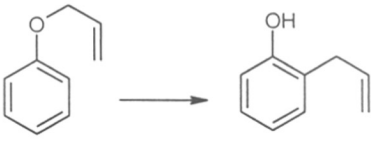


81 **82** **83**

Diels - Alder reaction

Scheme 33

Similarly, the crucial interplay of reaction time, temp. and solvent is illustrated in the Claisen rearrangement of allyl ether[99] as shown below.

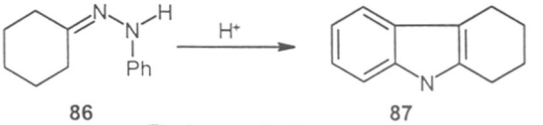


84 **85**

Claisen rearrangement

Scheme 34

Abramovitch *etal.*[100] demonstrated that the application of microwave irradiation resulted in [3,3] sigmatropic rearrangement **86**⇌**87** involved in Fischer cyclisations as shown below **[Scheme 35]**.

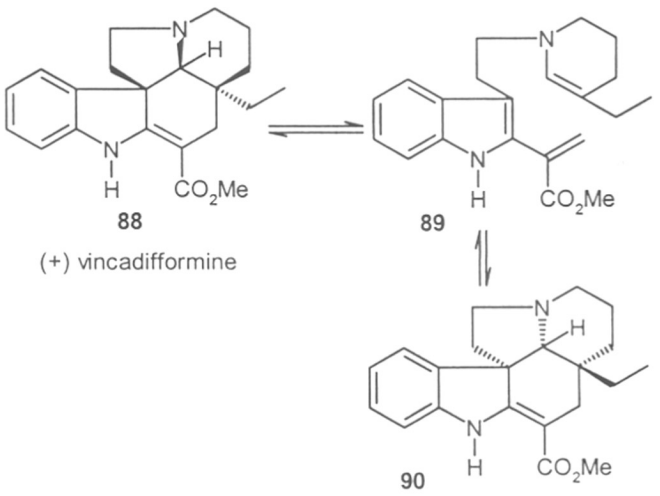


86 **87**

Fischer cyclisation

Scheme 35

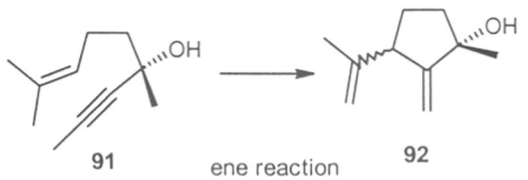
An efficient racemisation in DMF was reported by Takano *etal.*[101] under microwave conditions *i.e.* the cycloconversion of (+) Vincadifformine (**88**) to the (-) isomer **90** via [4+2] cycloaddition as given below **[Scheme 36]**.



Natural product racemisation

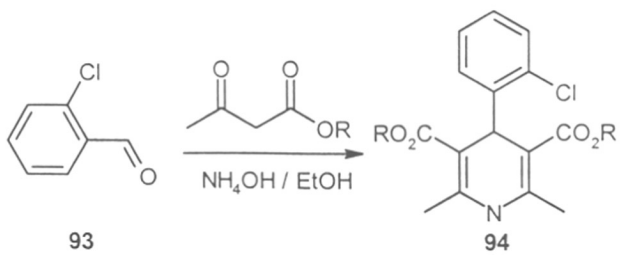
Scheme 36

The "ene" cyclisation[99] of the acetylenic compoud **91** to give the compound **92** was successfully performed under microwave irradiation **[Scheme 37]**.



Scheme 37

Microwave irradiation is also efficiently applied in other types of cyclisation reactions like Hantsch-1,4-dihydropyridine synthesis[102] **[Scheme 38]**.



Hantsch-1,4-dihydro pyridine synthesis

Scheme 38

Recently Bose *et.al.*[97d] have successfully synthesised α amino β lactams utilising their MORE technology.

Apart from what has been discussed, various other reactions have also been successfully carried out using microwave. The rapid and high yielding synthesis of radiopharmaceuticals labeled with short lived radio nuclei remains an important challenge to the synthetic chemist. Microwave assisted syntheses are much faster than the corresponding thermal syntheses. The shorter microwave treatment[103] relative to conventional heating not only leads to less decay of the radio active product, but also causes less degradation of the reagents and reduces the generation of side products which makes isolation of the desired labeled compound easy.

Present study

Given the vast utility of microwave assisted organic reactions for the improvement on the yields of the reactions, reduction in reaction time, avoiding use of hazardous solvents, it was decided to carry out the transesterification reactions in the present study, under microwave irradiation. In the case of transesterification of aroyl β-keto esters **37-39, 55** yields obtained were only moderate giving thereby a good scope for improvement under microwave irradiation conditions.

Results and discussion

The transesterification reactions, which gave only moderate yields of ~55-60 % of β–keto esters, with solid catalysts were attempted first, with a view to improve their yields. It was gratifying to note that the reaction furnished more than 70-80 % of the corresponding products in a short span of 10 min. as compared to a time span of 8 hrs. for thermal reactions. Further, it was observed that as in thermal reactions, primary alcohols underwent transesterification faster than secondary alcohols. With a few primary alcohols the reaction proceeded even in the absence of the catalyst (bromoethanol, chloroethanol) (**Table III** entry 5,6).

Table III. Transesterification of β–keto esters under microwave irradiation conditions.

Entry	β–Keto ester	Alcohol	Yield %
1	Methylacetoacetate	3-Phenyl propanol	95
2	Ethylbenzoylacetate	Cinnamyl alcohol	78
3	Ethylbenzoylacetate	3-Phenyl propanol	80
4	Ethylbenzoylacetate	Ethoxyethanol	72

5	Ethylbenzoylacetate	2-Chloroethanol	70
6	Ethyl benzoylacetate	2-Bromoethanol	73
7	Ethylbenzoylacetate	Phenethyl alcohol	80
8	Ethyl-3,4,5-trimethoxy benzoylacetate	3-Phenylpropanol	69

A specific microwave effect in rate acceleration is still under discussion. Few detailed studies by Pollington *etal.*[104] have proved that there is no specific microwave effect for rate enhancement of organic reactions. The reduction in time for various reactions can be attributed to the increased temp. of the reaction.

Hazardous solvents like benzene, toluene *etc.* which are commonly encountered in thermal transesterification reactions are mostly avoided under microwave conditions.

When organic molecules are converted within zeolite micropores under a specified set of reaction conditions, the interactions often lead to dramatically different patterns of selectivity, reactivity etc. Enhanced reactivity of surfaces under microwave irradiation may be one of the reasons for the improvement of yields of the products. Moreover, temp. effects are also significant; they not only affect the thermodynamic potentials and kinetic mechanisms but also often profoundly alter the adsorption/desorption equilibria. It is therefore clear from the above facts, that, the increased yields obtained on microwave irradiation may be attributed to a temp. effect which forces the transesterification equilibrium in an irreversible manner *i.e.* the complete removal of the lower alcohol by evaporation.

Conclusion

It has been demonstrated that under microwave irradiation conditions, transesterification of β–keto esters with different alcohols proceed with higher yields, in a very short reaction span and avoids the use of any aromatic solvents that are generally employed in thermal reactions. This ideal situation of "dry reaction conditions" enables minimum waste and offers an environment friendly procedure. Moreover, for the first time it has been demonstrated that transesterification (an industrially important reaction) can be performed with greater efficiency using microwave. Unlike the "conventional heating in solvent media", where a considerable amount of heat applied is always lost due to (*i.e.* 100 % quantum efficiency) dissipation, here, in microwave assisted method use of "dry reaction conditions" has a lot of potential for an industrially viable route to transesterification. Considerable reduction in reaction time as compared to conventional methods is also an important point to note.

Experimental

Preparation of ethyldiazoacetate

Preparation of glycine ethyl ester hydrochloride[105]

Thionyl chloride (60 gm, 36.8 ml, 50.4 mmol) was added gradually to a stirred and cooled (0°C) suspension of glycine (25.2 gm, 33.6 mmol) in absolute ethanol (125ml). The mixture was allowed to warm to room temp. and stirred for 30 min. and then refluxed until the solution became clear (4½ hrs). The solvent was removed under vacuum to afford glycine ethyl ester hydrochloride as a white solid which was used as such for the next step.

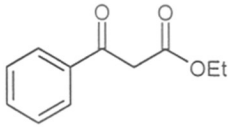
Preparation of ethyldiazoacetate[106]

Glycine ethyl ester hydrochloride (46.0 gm, 33.0 mmol) obtained from the previous step was taken in 200 ml of DCM. The suspension was then cooled with ice and salt mixture and NaOAc/HOAc buffer was added to maintain a neutral pH. A solution of $NaNO_2$ (22.8gm, 33.0 mmol) in water (30ml) was added slowly and the resultant yellow mixture was stirred at room temp. for ½ hour and at room temp. for 2 hrs. The yellow solution thus obtained was transferred to a separating funnel and the organic layer was washed with sodium carbonate solution till the washings became neutral. The DCM solution thus obtained was passed through a short column of silica gel and stored as such in the fridge over sodium sulphate.

General procedure for condensation of ethyldiazoacetate with aldehydes

A solution of the aldehyde (5.0mmol) and ethyldiazoacetate (7.5 mmol) in EDC (10ml) containing zeolite H-β (50 mg, 10 % wt/wt) was refluxed for 8 hrs. under an inert (N_2) atm. The catalyst was recovered by filtration and distillation of solvent under reduced pressure furnished the crude material. It was purified by silicagel column chromatography.

3-Oxo-3-phenylpropanoic acid ethyl ester[107]



Yield : 691 mg (72 %).

IR (neat) cm^{-1}

3340, 1735, 1690, 1590

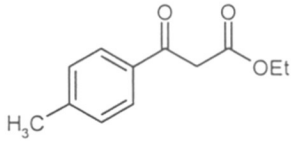
^{1}H NMR δ (200 MHz, $CDCl_3$)

8.1-8.0 (m, 2H), 7.8-7.4 (m, 3H), 4.23-4.15 (m, 2H), [4.0,5.7,12.3] (s, 2H), 1.3-1.15 (m, 3H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

192.25 (s), 167.17 (s), 135.79 (s), 133.29 (d), 128.67 (d), 128.40 (d), 125.68 (d), 87.05 (enolic), 60.85 (t), 45.48 (t), 13.66 (q)

Benzenepropanoic acid, -4-methyl-β-oxo-, ethyl ester[107]



Yield : 783 mg (76 %).

IR (neat) cm^{-1}

3320, 1735, 1700, 1595

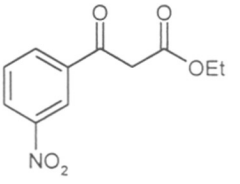
^{1}H NMR δ (90 MHz, $CDCl_3$)

7.9-7.2 (m, 4H), 4.20-4.1 (m, 2H), [4.0,5.6,12.6] (s, 2H), 2.40 (s, 3H), 1.26-1.15 (m, 3H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

191.64 (s), 167.16 (s), 144.09 (s), 133.62 (s), 128.06 (d), 126.29 (d), 86.32 (enolic), 60.74 (t), 60.54 (t), 45.42 (t), 21.05 (q), 13.68 (q), 13.50 (q)

Benzenepropanoic acid, -3-nitro-β-oxo-, ethyl ester



Yield : 1.007 gm (85 %).

M.Pt : 78-80°C (Lit.[108] 78-79°C)

IR (nujol) cm^{-1}

3310, 1740, 1700, 1595, 1540

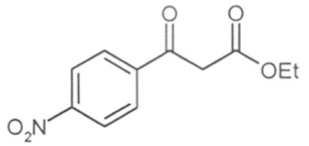
^{1}H NMR δ (90 MHz, $CDCl_3$)

8.1-7.9 (m, 2H), 7.6-7.3 (m, 2H), 4.1 (q, J=7Hz, 2H), [3.9,5.7,12.6] (s, 2H), 1.1 (t, J=7Hz, 2H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

190.55 (s), 165.78 (s), 147.70 (s), 135.09 (s), 132.80 (d), 128.89 (d), 123.85 (d), 121.74 (d), 88.99 (enolic), 61.25 (t), 45.64 (t), 13.58 (q).

Benzenepropanoic acid, -4-nitro-β-oxo-, ethyl ester



Yield : 841 mg (71 %).

M.Pt. : 70-72°C (Lit.[108]. 70-73°C)

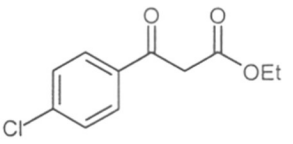
IR (nujol) cm^{-1}

3315, 1735, 1710, 1590, 1530

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

8.4-7.9 (m, 4H), 4.25-4.1 (m, 2H), [4.0,5.7,12.6] (s, 2H), 1.28-1.1 (m, 3H)

Benzenepropanoic acid, -4-chloro -β-oxo-, ethyl ester[109a]



Yield : 839 mg (74 %).

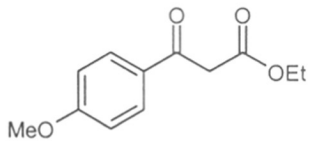
IR (neat) cm^{-1}

1750, 1715, 1590, 810

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.9-7.3 (m, 4H), 4.2-4.1 (m, 2H), [4.0,5.6,12.5] (s, 2H), 1.35-1.2 (m, 3H)

Benzenepropanoic acid, -4-methoxy -β-oxo-, ethyl ester[107]



Yield : 677 mg (61 %).

IR (neat) cm^{-1}

3300, 1725, 1695, 1590, 1420

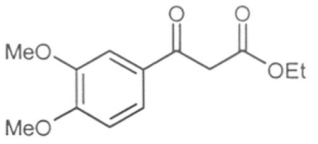
^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.4-6.9 (m, 4H), 4.1-4.0 (m, 2H), [3.9,5.6,12.6] (s, 2H), 3.8 (s, 3H), 1.2-1.0 (m, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

190.92 (s), 167.65 (s), 163.90 (s), 131.8 (s), 130.9 (d), 130.75 (d), 114.21 (d), 113.81 (d), 61.11 (t), 55.34 (q), 45.55 (t), 13.91 (q)

Benzenepropanoic acid, -3,4-dimethoxy-β-oxo-, ethyl ester



Yield : 756 mg (60 %).

IR (neat) cm^{-1}

3310, 1730, 1695, 1595

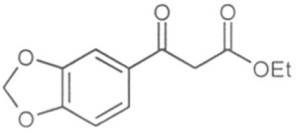
^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.3-7.2 (m, 2H), 6.9 (d, J=8Hz, 1H), 4.1 (q, J=8Hz, 2H), 3.9 (s, 8H), 1.0 (t, J=8Hz, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

191.03 (s), 167.71 (s), 153.87 (s), 149.19 (s), 129.30 (s), 126.70 (d), 123.51 (d), 110.50 (d), 61.32 (t), 56.10 (q), 55.92 (q), 45.64 (t), 14.06 (q)

Benzenepropanoic acid, -3,4-methylenedioxy -β-oxo-, ethylester[72]



Yield : 802 mg (68 %).

M.Pt. :41°C (Lit.[72] 41°C)

IR (nujol) cm^{-1}

1740, 1680, 1635

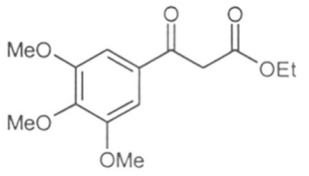
^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.60-7.55 (m, 1H), 7.45 (d, J=7Hz, 1H), 6.95 (d, J=7Hz, 1H), 6.05 (s, 2H), 4.25 (q, J=7.4Hz, 2H), [3.95,5.6,12.6] (s, 2H), 1.24 (t, J=7.4Hz, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

190.61 (s), 167.66 (s), 152.40 (s), 148.43 (s), 130.97 (s), 125.19 (d), 108.05 (d), 108.00 (d), 102.12 (t), 61.40 (t), 45.82 (t), 14.09 (q)

Benzenepropanoic acid, -3,4,5-trimethoxy-β-oxo-, ethyl ester



Yield : 790 mg (56 %).

IR (neat) cm^{-1}

3315, 1735, 1700, 1590

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.0 (s, 2H), 4.1 (q, J=8Hz, 2H), 3.8 (s, 9H), [3.75,5.5,12.4] (s, 2H), 1.3 (t, J= 8Hz, 3H)

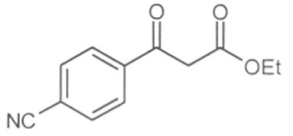
^{13}**C** NMR δ (50 MHz, $CDCl_3$)

191.31 (s), 167.58 (s), 153.21 (s), 143.39 (s), 131.26 (s), 106.90 (d), 106.31 (d), 61.48 (t), 60.90 (q), 56.33 (q), 46.04 (t), 14.11 (q)

Mass (70 eV)

m/z 282 (M^+), 283 (M+1), 267, 253, 236, 221, 209, 195 (base peak), 181, 167, 152, 137, 122, 107, 95, 77

Benzenepropanoic acid, -4-cyano-β-oxo-, ethyl ester[109b]



Yield : 911 mg (84 %).

M.Pt : 63°C (Lit.[109b] 63-64°C)

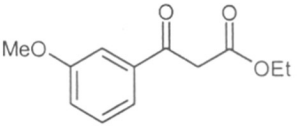
IR (nujol) cm^{-1}

2240, 1740, 1700, 1260

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.2 (s, 4H), 4.1 (q, J=8Hz, 2H), [3.9,5.4,12.1] (s, 2H), 1.0 (t, J=8Hz, 3H)

Benzenepropanoic acid, -3-methoxy-β-oxo-, ethyl ester



Yield : 679 mg (62 %).

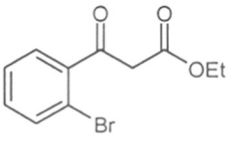
IR (neat) cm^{-1}

3320, 1730, 1695, 1590

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.4-6.8 (m, 4H), 4.1 (q, J=7Hz, 2H), 3.75 (s, 3H), [3.9,5.5,12.3] (s, 2H), 1.2 (t, J=7Hz, 3H)

Benzenepropanoic acid, -2-bromo-β-oxo-, ethyl ester



Yield : 1.098 gm (81 %).

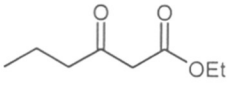
IR (neat) cm^{-1}

3310, 1730, 1710, 1030, 900

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.4-7.0 (m, 3H), 4.05 (q, J=7.4Hz, 2H), [3.9,5.2,12.1] (s, 2H), 1.0 (t, J=7.4Hz, 3H)

Hexanoic acid, -3-oxo-, ethyl ester[109c]



Yield : 742 mg (94 %).

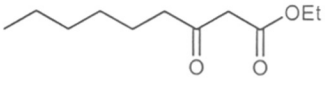
IR (neat) cm^{-1}

1730, 1700, 1470

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

4.2 (q, J=7Hz, 2H), 3.3 (s, 2H), 2.4-2.1 (m, 4H), 1.2-1.0 (m, 6H)

Nonanoicacid, -3-oxo-, ethyl ester[109d]



Yield : 930 mg (93 %).

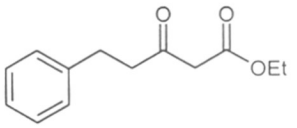
IR (neat) cm^{-1}

1735, 1695, 1450

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

4.15 (q, J=7Hz, 2H), 3.27 (s, 2H), 2.45 (t, J=7Hz, 2H), 1.4-1.1 (br, 11H), 0.9-0.8 (m, 3H)

Pentanoic acid, -3-oxo-5-phenyl, ethyl ester[71]



Yield : 814 mg (74 %).

IR (neat) cm^{-1}

3300, 1735, 1695

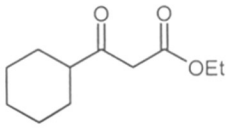
^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.3-7.1 (m, 5H), 4.2 (q, J=7Hz, 2H), [3.6,5.5,12.4], (s, 2H), 3.2-3.0 (m, 2H), 2.8-2.6 (m, 2H), 1.2 (t, J=7Hz, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

202.60 (s), 168.05 (s), 141.74 (s), 128.58 (d), 127.98 (d), 123.93 (d), 82.60 (enolic), 62.13 (t), 47.35 (t), 37.58 (t), 29.01 (t), 13.98 (q)

Propanoic acid, -3-cyclohexyl-3-oxo, ethyl ester[71]



Yield : 703 mg (71 %).

IR (neat) cm^{-1}

1730, 1700, 1450, 1000

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

4.2 (q, J=7Hz, 2H), 3.45 (s, 2H), 2.7-2.6 (m, 1H), 1.9-1.7 (m, 4H), 1.6-1.1 (m, 6H), 1.0 (t, J=7Hz, 3H)

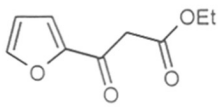
^{13}**C** NMR δ (50 MHz, $CDCl_3$)

205.66 (s), 167.39 (s), 61.10 (t), 50.77 (d), 47.28 (t), 28.17 (t), 25.14 (t), 25.30 (t), 14.06 (q)

Mass (70 eV)

m/z 198 (M^+), 180, 151, 143, 130, 125, 111, 105, 95, 87, 81, 67, 55 (base peak)

Propanoic acid, 3-furan-2-yl-3-oxo, ethyl ester



Yield : 473 mg (52 %).

IR (neat) cm^{-1}

3315, 1742, 1695

^{1}H NMR δ (90 MHz, $CDCl_3$)

7.6-7.5 (m, 1H), 6.6-6.5 (m, 2H), 4.15 (q, J=6Hz, 2H), [3.8-5.4-12.4] (s, 2H), 1.3 (t, J=6Hz, 3H)

Preparation of diazo diethyl malonate[110]

A solution of mesyl azide (1.45 gm, 12 mmol) in dry DCM (15ml) was added drop wise over 10 min. to a stirred solution containing diethyl malonate (1.60 gm, 10 mmol) and TEA (1.15 gm, 11.5 mmol) in 10 ml of dry DCM. The resulting yellow solution was stirred over night at room temp. After the completion of the reaction (as monitored by TLC) the reaction mixture was transferred to a separating funnel. The reaction flask was rinsed with more DCM (10-15 ml). The combined organic layer was washed successively with water, aq. NaOH (5%), water and finally with brine. It was dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded the crude diazo malonate which was purified further by column chromatography using DCM as the eluent.

Yield : 1.60 gm (86 %).

IR (neat) cm^{-1} : 2150, 1720, 1600

^{1}H NMR δ (60 MHz, CCl_4) 4.18 (q, J=6Hz, 4H), 1.32 (t, J=6Hz, 6H)

Preparation of diazo acetylacetone[110]

A solution of mesyl azide (1.45 gm, 12 mmol) in dry DCM (15ml) was added drop wise over 10 min. to a stirred solution containing acetylacetone (1.00 gm. 10 mmol) and TEA (1.15 gm, 11.5 mmol) in 15 ml of dry DCM. The resulting yellow solution was stirred over night at room temp. After the completion of the reaction (as monitored by TLC) the reaction mixture was transferred to a separating funnel. The reaction flask was rinsed with more DCM (10-15 ml). The combined organic layer was washed successively with water, aq. NaOH (5%), water and finally with brine. It was dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded the crude diazo acetylacetone which was purified further by column chromatography using DCM as the eluent.

Yield : 1.046 gm (83 %).

IR (neat) cm^{-1} : 2140, 1670

^{1}H NMR δ (60 MHz, CCl_4) : 2.37 (s)

Preparation of chloro-acetic acid 3-phenyl-propyl ester (59)

Preparation of 3-phenyl-propan-1-ol (57)

Cinnamyl alcohol (13.4 gm, 0.10 mol) was dissolved in 75 ml of dry ethanol. 5% Pd/C (1.35 gm, 10% wt/wt) was added to this and the mixture was hydrogenated under pressure (50 psi) in a hydrogenation flask for 4 hrs. After the reaction was over [as analysed by TLC] the catalyst was filtered through celite and it was washed further with 15 ml of ethanol. The solvent was removed under reduced pressure to yield 13.5 gm (99%) of almost pure 3-phenyl-propan-1-ol which was used as such without further purification.

IR (neat) cm^{-1}

3320, 1595

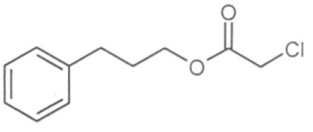
^{1}**H** NMR δ (60 MHz, $CDCl_3$)

7.4-7.2 (m, 5H), 3.7 (t, J=6Hz, 2H), 2.75 (t, J=6Hz, 2H), 2.5 (br, OH), 2.1-1.9 (m, 2H)

Condensation of 3-phenyl-propan-1-ol with chloroacetyl chloride

3-Phenyl-propan-1-ol (1.36 gm, 10 mmol) was mixed with TEA (1.2 gm, 12 mmol) in 20 ml dry DCM at 0°C. To this reaction mixture, chloroacetyl chloride (1.134 gm, 0.8 ml, 10.04 mmol) in 6 ml of dry DCM was added slowly. The resultant mixture was stirred at 0°C for ½ hr. and at room temp. for 2 hrs. A white solid of TEA.HCl was filtered and washed with 5 ml of dry DCM. The combined organic layer was washed with 2N HCl, saturated $NaHCO_3$, water, brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded the chloro-acetic acid 3-phenyl-propyl ester as a colourless liquid.

Chloro-acetic acid 3-phenyl-propyl ester (59)



Yield : 1.744 gm (82 %).

IR (neat) cm^{-1}

1740, 1600, 1000, 800

^{1}**H** NMR δ (80 MHz, $CDCl_3$)

7.2 (s, 5H), 4.2 (t, J=7.5Hz, 2H), 3.9 (s, 2H), 2.5 (t, J=7.5Hz, 2H), 2.1-1.9 (m, 2H)

Preparation of diazo-acetic acid 3-phenyl-propyl ester

Attempted preparation of amino-acetic acid 3-phenyl-propyl ester (58)

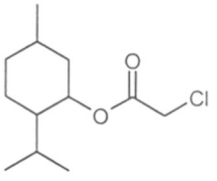
The chloro-acetic acid 3-phenyl-propyl ester (425 mg, 2.0 mmol) in a mixture of DMF (8ml) and 25% NH_3 (aq. 4.5ml) was stirred for 24 hrs. at room temp. The mixture was then extracted with Et_2O. The ether extract was washed with saturated $NaHCO_3$, followed by water and finally with brine. It was dried over Na_2SO_4. Removal of the solvent under reduced pressure provided (250 mg, 92 %) of a product that was identified as 3-phenyl-propan-1-ol (**57**).

Preparation of amino-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester[83]

Preparation of chloro-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester

A solution of chloroacetyl chloride (226 mg, 2.0 mmol) in 5 ml of dry Et_2O was slowly added over a period of ½ hr. to a stirred mixture containing (2-isopropyl-5-methyl-cyclohexanol (menthol) (312 mg, 2.0 mmol) and pyridine (158 mg, 2.0 mmol) in 10 ml of dry Et_2O at 0°C. After warming to 23°C the yellow suspension was stirred for 4 hrs. more. The precipitate was removed by filtration and the filtrate was washed with 2N HCl, saturated $NaHCO_3$, water, and brine and then dried over Na_2SO_4. The solvent was distilled off under reduced pressure to yield (450 mg, 97%) the chloro-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester as a colourless oil.

Chloro-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester



IR (neat) cm^{-1}

1740, 1550, 1290, 970, 810

^1H NMR δ (90 MHz, $CDCl_3$)

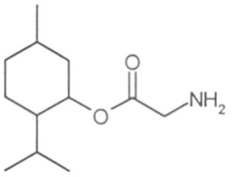
4.8-4.7 (m, 1H), 4.0 (s, 2H), 2.1-1.9 (m, 1H), 1.8-1.6 (m, 7H), 1.2-0.9 (m, 9H)

Preparation of amino-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester

The chloro-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester (233 mg, 1.0 mmol) obtained as above was mixed with DMF (6 ml) and 25 % NH_3 (aq. 3 ml) and the solution was stirred at room temp. for 24 hrs. It was then diluted with Et_2O, the organic layer was washed successively with $NaHCO_3$, water, brine dried over Na_2SO_4. Removal

of the solvent under reduced pressure yielded the crude amino-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester which was purified by column chromatography.

Amino-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester



Yield : 187 mg (88 %).

IR (neat) cm^{-1}

3310, 1730, 1450, 1350

^{1}H NMR δ (60 MHz, CCl_4)

4.6 (br, 1H), 3.4 (s, 2H), 2.2-0.9 (m, 11H), 0.8-0.7 (m, 9H)

Condensation of *N*-acetyl glycine with (3-halo-propyl)-benzene

Preparation of *N*-acetyl glycine[111]

In a 100 ml Erlenmeyer flask 3.75 gm (5.0 mmol) of glycine in 15 ml of water was taken and this mixture was shaken vigorously until all the glycine dissolved (~20 min.). Acetic anhydride (95%, 10.75 gm, 10.0 mmol) was added in one portion and the resultant mixture was shaken vigorously for 5 min. The flask was then stoppered and kept in refrigerator over night. The precipitate formed was filtered, washed with ice cold water and dried at 110°C (4 hr). Recrystallisation from boiling water furnished the pure product.

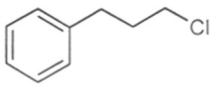
M.Pt. : 208°C (Lit.[111] 207-208°C)

IR (nujol) cm^{-1} : 3310, 1700, 1220

Preparation of (3-chloro-propyl)-benzene[112] **(60)**

3-Phenylpropan-1-ol (544 mg, 4.0 mmol) and triphenylphosphine (1.572 gm, 6.0 mmol) were taken in 100 ml two necked round bottomed flask. MeCN (12 ml) and CCl_4 (3 ml) were added to the flask. After the exothermic formation of the intermediate is complete, the reaction mixture was refluxed for 3 hrs. and the mixture was cooled, 10 ml of water and 7 ml of DCM were added. The organic layer was separated. The aqueous layer was extracted with DCM, the combined organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded the 1-chloro-3-phenyl propane (580 mg, 94%).

(3-Chloropropyl)-benzene (60)



IR (neat) cm^{-1}

1600, 1490, 1440, 1290, 970, 790

^{1}H NMR δ (60 MHz, $CDCl_3$)

7.1-7.0 (m, 5H), 3.5 (t, J=6Hz, 2H), 2.8 (t, J=6Hz, 2H), 2.1-1.9 (m, 2H)

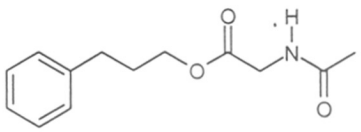
Preparation of (3-bromo-propyl)-benzene (61)

To 48 % HBr (6.5 gm) in a 100 ml round bottomed flask were added Con. H_2SO_4 (1.9 gm, 0.82 ml) in portions with shaking. 3-Phenyl propan-1-ol (3.4 gm, 25.0 mmol) was added slowly followed by 1.5 ml of Con. H_2SO_4. The mixture was gently refluxed for one hr, after which it was cooled. Distillation of the reaction mixture afforded the product along with HBr. The lower layer was removed and the upper layer was extracted with DCM. The organic layer was mixed with the lower layer and washed with water, saturated $NaHCO_3$, and finally with brine. The organic layer was dried over Na_2SO_4 and removal of the solvent under reduced pressure yielded (3-bromo-propyl)-benzene (3.75 gm, 75 %) which was used as such for the next step.

Condensation of *N*-acetyl glycine with (3-bromo-propyl)-benzene[84]

(3-Bromo-propyl)-benzene obtained from the previous step (199 mg, 1.0 mmol) in 1 ml of benzene was added to a solution of N-acetyl glycine (109 mg, 0.85 mmol) and DBU (129 mg, 085 mmol) in benzene (3 ml). The reaction mixture was refluxed with stirring for 3 hrs. after which it was cooled and diluted with Et_2O (10 ml). The precipitate obtained was filtered off and was washed with Et_2O (5 ml). The organic layer was washed with water, 1 M HCl, saturated $NaHCO_3$ and finally with brine and then dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded the crude product that was purified by column chromatography to afford 108 mg (46 %) of the condensed product.

Acetylamino-acetic acid 3-phenyl propyl ester (62)



IR (neat) cm^{-1}

3300, 1740, 1650, 1200

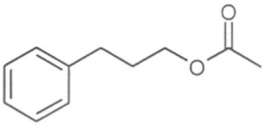
^{1}H NMR δ (80 MHz, $CDCl_3$)

7.2-7.1 (m, 5H), 6.2 (br, 1H), 4.2 (t, J=6.4Hz, 2H), 4.0 (d, J=4.8Hz, 2H), 2.65 (t, J=6.4Hz, 2H), 2.1 (s, 3H), 2.2-1.9 (m, 2H)

Condensation of (3-bromo-propyl)-benzene (62) with acetic acid[85]

(3-Bromo-propyl)-benzene (1.0 gm, 5.0 mmol) was mixed with acetic acid (600 mg, 10 mmol). To this reaction mixture TEA (500 mg, 5.0 mmol) was added slowly and the resultant mixture was refluxed for 2 hrs. at 145°C. The reaction mixture was cooled, and was poured into excess of hexane. The TEA.HCl complex formed was filtered and washed with hexane. The organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded the acetylated product (710 mg, 80%).

Acetic acid 3-phenyl-propyl ester (63)



IR (neat) cm^{-1}

1730, 1600, 1250

^{1}H NMR δ (80 MHz, $CDCl_3$)

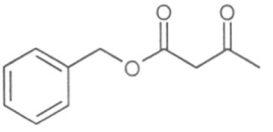
7.2-7.1 (m, 5H), 4.0 (t, J=7Hz, 2H), 2.8 (t, J=7Hz), 2.0 (s, 3H), 1.9-1.8 (m, 2H)

Transesterification of β–keto ester with various alcohols

General procedure:

In a typical experiment 5 mmol of the β–keto ester and 5 mmol of the alcohol were dissolved in dry toluene (25 ml) to which 10 % (wt/wt of β–keto ester) of the catalyst was added. The resultant mixture was heated to 110°C (bath temp.) with azeotropic removal of ethanol/methanol. After 8 hr. the reaction mixture was cooled, the catalyst was filtered off and washed with more solvent (10 ml). The combined organic solvent was removed under reduced pressure. Purification by column chromatography yielded the product.

Butanoic acid, 3-oxo-, phenyl methyl ester



Yield : 778 mg (81 %).

IR (neat) cm^{-1}

3320,1738,1695

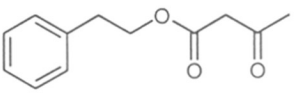
^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.3-7.1 (m, 5H), 5.1 (s, 2H), 3.45 (s, 2H), 2.2 (s, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

200.19(s), 166.81 (s), 135.37 (s), 128.43 (d), 128.22 (d), 128.14 (d), 66.76 (t), 49.70 (t), 29.73 (q)

Butanoic acid, 3-oxo-, 2-phenyl ethyl ester



Yield : 989 mg (96 %).

IR (neat) cm^{-1}

3310,1729,1690

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.3-7.2 (m, 5H), 4.3 (t, J=7Hz, 2H), [3.2, 4.9, 12.5] (s, 2H), 2.9 (t, J=7Hz), 2.2 (s, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

200.38(s), 166.91 (s), 137.40 (s), 128.73 (d), 128.39 (d), 126.49 (d), 89.2 (enolic), 65.48 (t), 49.71 (t), 34.72 (t), 29.75 (q)

Mass (70 eV)

m/z 220 (M^+), 136, 117 (base peak), 104, 91, 85, 77, 65, 57

Butanoic acid, 3-oxo-, dodecyl ester

$CH_3COCH_2CO_2C_{12}H_{25}$

Yield : 1.161 gm (86 %).

IR (neat) cm^{-1}

3300,1740,1700

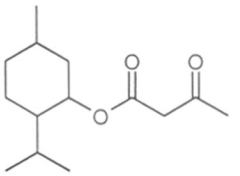
^{1}**H** NMR δ (90 MHz, $CDCl_3$)

4.0 (t, J=6.8Hz, 2H), [3.4, 4.9, 12.2] (s, 2H), 2.2 (s, 3H), 1.3-1.1 (m, 20H), 0.85-0.75 (m, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

199.80(s), 166.83 (s), 89.39 (enolic), 64.99 (t), 49.64 (t), 31.74 (t), 29.49 (t), 29.18 (t), 29.06 (t), 28.35 (t), 25.65 (t), 22.47 (t), 20.68 (q), 13.80 (q)

Butanoic acid, 3-oxo-, 5-methyl-2-(1-methyl ethyl) cyclohexyl ester



Yield : 1.140 gm (95 %).

IR (neat) cm^{-1}

3320,1738,1695

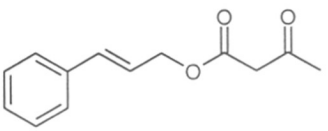
^{1}**H** NMR δ (200 MHz, $CDCl_3$)

4.75 (dt, J=12Hz, J=6Hz, 1H), [3.45, 4.9, 12.2] (s, 2H), 2.25 (s, 3H), 2.1-1.9 (m, 3H), 1.75-1.65 (m, 2H), 1.5-1.4 (m, 2H), 1.2-0.9 (m, 10H), 0.85 (d, J=6Hz, 3H)

^{13}**C** NMR (50 MHz, $CDCl_3$)

199.70 (s), 166.22 (s), 89.49 (enolic), 74.60 (d), 49.86 (t), 46.56 (d), 40.38 (t), 33.87 (t), 31.02 (d), 29.36 (q), 25.74 (d), 23.01 (t), 21.59 (q), 20.30 (q), 15.78 (q)

Butanoic acid, 3-oxo-, 3-phenyl-2-propenyl ester (E)



Yield : 1.036 gm (95 %).

IR (neat) cm^{-1}

3320,1738,1695

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.4-7.2 (m, 5H), 6.65 (d, J=15Hz, 1H), 6.3-6.2 (m, 1H), 4.8 (dd, J=6.4Hz, J=1Hz, 2H), 3.45 (s, 2H), 2.2 (s, 3H)

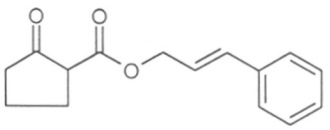
^{13}**C** NMR δ (50 MHz, $CDCl_3$)

200.30(s), 166.89 (s), 136.12 (s), 134.77, (d), 128.66 (d), 128.23 (d), 126.71 (d), 122.59 (d), 65.84 (t), 49.99 (t), 30.12 (q)

Mass (70 eV)

m/z 218 (M^+), 200, 168, 160, 133, 117 (base peak), 105, 91, 85, 77, 69, 65, 55

2-Oxo-cyclopentanecarboxylic acid 3-phenyl-2-propenyl ester (E)



Yield : 1.025 gm (84 %).

IR (neat) cm^{-1}

3320,1738,1695

^{1}H NMR δ (90 MHz, $CDCl_3$)

7.4-7.3 (m, 5H), 6.70 (d, J=15Hz, 1H), 6.3-6.2 (m, 1H), 4.8 (dd, J=6.4Hz, J=1Hz, 2H), 4.2-4.1 (m, 1H), 3.2 (t, J=9Hz, 2H), 2.5-2.0 (m, 4H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

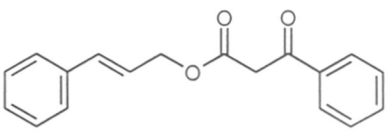
211.95 (s), 169.05 (s), 136.04 (s), 133.99 (d), 128.44 (d), 127.91 (d), 126.49 (d), 122.70 (d), 65.53 (t), 54.58 (d), 37.80 (t), 27.22 (t), 20.74 (t)

Analysis for $C_{15}H_{16}O_3$ (244.29)

Calculated C = 73.75 %, H = 6.60 %

Observed C = 73.46 %, H = 6.38 %

3-Oxo-3-phenyl-propanoic acid 3-phenyl-2-propenyl ester (E)



Yield : 924 mg (66 %).

IR (neat) cm^{-1}

3320,1738,1690,1579

^{1}H NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=7Hz, J=1.4Hz, 2H), 7.7-7.4 (m, 8H), 6.85 (d, J=14Hz, 1H), 6.4-6.3 (m, 1H), 4.9 (dd, J=4Hz, J=1.2Hz, 2H), [4.1,5.75,12.55] (s, 2H)

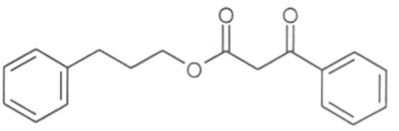
^{13}C NMR δ (50 MHz, $CDCl_3$)

192.35 (s), 167.26 (s), 136.16 (s), 136.02 (s), 134.22 (d), 128.73 (d), 128.47 (d), 128.25 (d), 126.64 (d), 122.70 (d), 87.2 (enolic), 65.73 (t), 45.75 (t)

Mass (70 eV)

m/z 280(M^+), 252, 206, 192, 146, 133, 117, 105, 91, 77 (base peak), 69, 65, 55

3-Oxo-3-phenyl-propanoic acid 3-phenyl-propyl ester



Yield : 902 mg (64 %).

IR (neat) cm^{-1}

3325,1740,1687, 1625, 1579

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

8.0 (dd, J=7Hz, J=1.6Hz, 2H), 7.5-7.4 (m, 3H), 7.3-7.15 (m, 5H), 4.25 (t, J=6Hz, 2H), [4.0,5.7,12.6] (s, 2H), 2.65 (t, J=6Hz, 2H), 2.1-2.0 (m, 2H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

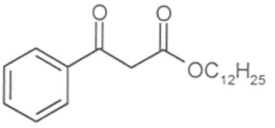
192.22 (s), 167.21 (s), 140.85 (s), 135.82 (s), 133.40 (d), 128.51 (d), 128.18 (d), 125.75 (d), 87.08 (enolic), 64.26 (t), 45.57 (t), 31.64 (t), 29.73 (t)

Analysis for $C_{18}H_{18}O_3$ (282.34)

Calculated C = 76.57 %, H = 6.43 %

Observed C = 76.34 %, H = 6.24 %

3-Oxo-3-phenyl-propanoicacid, dodecyl ester



Yield : 1.180 gm (71 %).

IR (neat) cm^{-1}

3320,1740,1695,1590

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=7Hz, J=1.4Hz, 2H), 7.4-7.2 (m, 3H), 4.05 (t, J=7Hz, 2H), 3.8 (s, 2H), 1.3-1.0 (m, 20 H), 0.9-0.7 (m, 3H)

^{13}**C** NMR (50 MHz, $CDCl_3$)

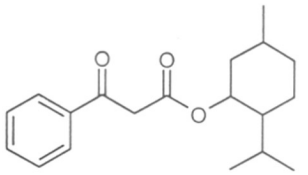
191.91 (s), 167.15 (s), 133.27 (s), 128.46 (d), 128.30 (d), 125.84 (d), 87.03 (enolic), 65.12 (t), 45.68 (t), 31.82, 29.57 (q), 29.27 (t), 29.10 (t), 28.41 (t), 25.67 (t), 22.57 (t), 13.92 (q)

Analysis for $C_{21}H_{32}O_3$ (332.49)

Calculated C = 75.86 %, H = 9.70 %

Observed C = 76.03 %, H = 9.91 %

3-Oxo-3-phenyl-propanoic 5-methyl-2-(1-methyl ethyl) cyclohexyl ester



Yield : 1.043 gm (69 %).

IR (neat) cm^{-1}

3320,1730,1698, 1595

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=7Hz, J=1.6Hz, 2H), 7.6-7.4 (m, 3H), 4.75 (dt, J=12Hz, J=6Hz, 1H), [4.0,5.65,12.6] (s, 2H), 2.1-1.9 (m, 3H), 1.75-1.65 (m, 2H), 1.5-1.4 (m, 2H), 1.2-0.9 (m, 10H), 0.85 (d, J=6Hz, 3 H)

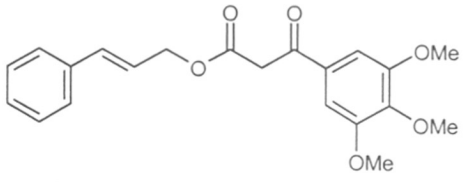
^{13}**C** NMR δ (50 MHz, $CDCl_3$)

192.02 (s), 166.70 (s), 136.00 (s), 133.28 (s), 128.46 (d), 128.25 (d), 125.80 (d), 87.35 (enolic), 75.04 (d), 46.66 (d), 46.18 (t), 40.44 (t), 33.99 (t), 31.15 (d), 25.74 (d), 23.01 (t), 21.78 (q), 20.50 (q), 15.88 (q)

Mass (70 eV)

m/z 302 (M^+), 280, 272, 259, 208, 165, 147, 138, 122, 105 (base peak), 95, 91, 81, 77

Benzenepropanoic acid, -3,4,5-trimethoxy-β-oxo,-3-phenyl-2-propenyl ester (E)



Yield : 1.148 gm (62 %).

IR (neat) cm^{-1}

3320,1738,1695

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.5-7.4 (m, 5H), 7.35 (s, 1H), 7.25 (s, 1H), 6.70 (d, J=15Hz, 1H), 6.35-6.25 (m, 1H), 4.8 (dd, J=6Hz, J=1.2Hz, 2H), 4.05,3.95 (s, 9H), [3.85,5.6,12.4] (s, 2H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

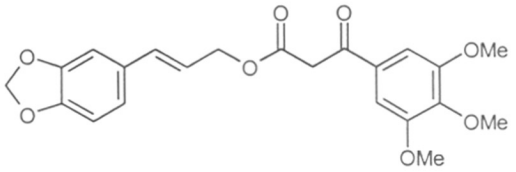
191.04 (s), 167.28 (s), 153.10 (s), 143.21 (s), 136.01 (s), 134.47 (d), 131.08 (s), 128.55 (d), 128.10 (d), 126.54 (d), 122.51 (d), 106.15 (d), 86.72 (enolic), 65.84 (t), 60.81 (q), 56.2 (q), 45.92 (t)

Analysis for $C_{21}H_{22}O_6$ (370.41)

Calculated C = 68.10 %, H = 5.99 %

Observed C = 67.84 %, H = 5.65 %

Benzenepropanoic acid, -3,4,5-trimethoxy-β-oxo,-3-benzo [1,3] dioxol-5-yl-prop-2-en-1-ol ester



Yield : 1.223 gm (59 %).

IR (neat) cm^{-1}

3320,1738,1695

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.2 (s, 2H), 6.95 (s, 1H), 6.75-6.7 (m, 2H), 6.6 (d, J=14Hz, 1H), 6.2-6.1 (m, 1H), 5.95 (s, 2H), 4.8 (dd, J=6Hz, J=1.2Hz, 2H), 4.05,3.95 (two s, 11H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

191.03 (s), 167.27 (s), 153.02 (s), 147.95 (s), 147.58 (s), 143.10 (s), 134.25 (d), 131.01 (s), 130.35 (s), 121.41 (d), 120.57 (d), 108.11 (d), 106.07 (d), 105.62 (d), 101.08 (t), 87.4 (enolic), 65.87 (t), 60.70 (q), 56.10 (q), 45.82 (t)

Analysis for $C_{22}H_{22}O_8$ (414.42)

Calculated C = 63.76 %, H = 5.35 %

Observed C = 63.52 %, H = 5.42 %

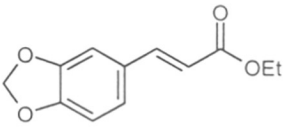
Preparation of 3-benzo [1,3] dioxol-5-yl-prop-2-en-1-ol[113]

Preparation of 3-benzo [1,3] dioxol-5-yl-acrylic acid ethyl ester

Benzo [1,3] dioxole-5-carbaldehyde (piperonal) (500 mg, 3.33 mmol) was dissolved in dry DCM (5 ml) and to this solution under N_2, a solution of stable (carbethoxymethylene)triphenylphosphorane (1.14 gm, 3.4 mmol) in dry DCM (18 ml) was added. The resultant reaction mixture was stirred over night. Removal of the solvent under reduced pressure yielded the crude product which was purified by column

chromatography to yield the 3-benzo [1,3] dioxol-5-yl-acrylic acid ethyl ester (560 mg, 81.5%).

3-Benzo [1,3] dioxol-5-yl-acrylic acid ethyl ester



M.Pt. : 65°C (Lit.[114] 66-67°C)

IR (nujol) cm^{-1}

1720,1590

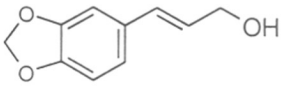
^{1}H NMR δ (200 MHz, $CDCl_3$)

7.5 (d, J=16Hz, 1H), 7.1 (s, 1H), 7.0-6.8 (m, 2H), 6.15 (d, J=16Hz, 1H), 5.9 (s, 2H), 4.15 (q, J=7Hz, 2H), 1.3 (t, J=7Hz, 3H)

Preparation of 3-benzo [1,3] dioxol-5-yl-prop-2-en-1-ol

The 3-benzo [1,3] dioxol-5-yl-acrylic acid methyl ester (412 mg, 2.0 mmol) in dry Et_2O (15 ml) was added slowly to a suspension of LAH (80 mg, 2.2 mmol) in dry Et_2O (15 ml) at 0°C under N_2. The reaction mixture was stirred at 0°C temp. for 2 hrs. and then at room temp. over night. Excess of LAH was destroyed by adding water (0.6 ml) with cooling, followed by the addition of 1.5 ml of NaOH (15%), water (0.6 ml) 8.0 gm Na_2SO_4. The solid was filtered off and washed with Et_2O. Removal of the solvent under reduced pressure yielded 3-benzo [1,3] dioxol-5-yl-prop-2-en-1-ol which was purified by column chromatography.

3-Benzo [1,3] dioxol-5-yl-prop-2-en-1-ol



Yield : 281 mg (79 %).

IR (nujol) cm^{-1}

3320, 1600

^{1}H NMR δ (200 MHz, $CDCl_3$)

7.1 (s, 1H), 6.8 (d, J=14Hz, 2H), 6.55 (s, 1H), 6.2-6.0 (m, 1H), 5.85 (s, 2H), 4.2 (d, J=5Hz, 2H), 1.5 (br, OH)

^{13}C NMR δ (50 MHz, $CDCl_3$)

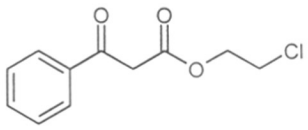
148.14 (s), 147.40 (s), 131.37 (s), 130.94 (d), 126.96 (d), 121.24 (d), 108.40 (d), 105.94 (d), 101.19 (t), 63.60 (t)

Microwave assisted transesterification

General procedure

2.5 mmol of β–keto ester and 2.5 mmol of the corresponding alcohol were mixed in a single necked 5 ml round bottomed flask. To this neat mixture 10 % (wt/wt) of β–keto ester) of the catalyst was added. The reactants were thoroughly mixed and kept for irradiation for 10-15 min. After the reaction was over [as monitored by TLC] the reaction mixture was cooled, diluted with DCM and the catalyst was filtered off. Removal of the solvent under reduced pressure yielded practically pure transesterified product.

3-Oxo-3-phenyl-propanoic acid 2-chloro-ethyl ester



Yield : 397 mg (70 %).

IR (neat) cm^{-1}

3320, 1724, 1690, 810

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.1-8.0 (m, 2H), 7.6-7.5 (m, 1H), 7.45-7.35 (m, 2H), 4.4 (t, J=7Hz, 2H), [4.05,5.75,12.35] (s, 2H), 3.75 (t, J=7Hz, 2H)

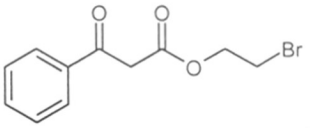
^{13}**C** NMR δ (50 MHz, $CDCl_3$)

192.00 (s), 167.06 (s), 135.70 (s), 133.68 (d), 128.65 (d), 128.31 (d), 125.97 (d), 86.68 (enolic), 64.60 (t), 45.40 (t), 41.29 (t)

Mass (70 eV)

m/z 228 (M+2), 226 (M^+), 220, 203, 190, 164, 146, 113, 105 (base peak), 91, 77, 69, 63

3-Oxo-3-phenyl-propanoic acid 2-bromo-ethyl ester



Yield : 495 (73 %).

IR (neat) cm^{-1}

3310, 1730, 1685, 690

^{1}H NMR δ (200 MHz, $CDCl_3$)

8.1-8.0 (m, 2H), 7.7-7.45 (m, 3H), 4.5 (t, J=7Hz, 2H), [4.0,5.7,12.4] (s, 2H), 3.55 (t, J=7Hz, 2H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

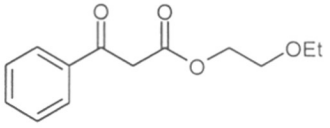
192.26 (s), 167.16 (s), 136.13 (s), 133.90 (d), 128.97 (d), 128.79 (d), 126.31 (d), 87.05 (enolic), 64.70 (t), 45.70 (t), 28.79 (t)

Analysis for $C_{11}H_{11}BrO_3$ (271.11)

Calculated C = 48.73 %, H = 4.09 %, Br = 29.47 %

Observed C = 48.51 %, H = 4.1 %, Br = 29.01 %

3-Oxo-3-phenyl-propanoic acid 2-ethoxy-ethyl ester



Yield : 425 mg (72 %).

IR (neat) cm^{-1}

3310, 1735, 1690, 1595, 1420

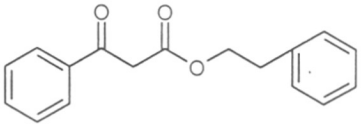
^{1}H NMR δ (200 MHz, $CDCl_3$)

8.0-7.9 (m, 2H), 7.7-7.35 (m, 3H), 4.35-4.25 (m, 2H), [3.9,5.7,12.6] (s, 2H), 3.7-3.6 (m, 2H), 3.35 (q, J=7Hz, 2H), 1.25 (t, J=7Hz, 3H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

191.61 (s), 166.81 (s), 135.63 (s), 133.07 (d), 128.21 (d), 128.09 (d), 125.57 (d), 86.75 (enolic), 67.55 (t), 65.83 (t), 63.87 (t), 45.15 (t), 14.16 (q)

3-Oxo-3-phenyl-propanoic acid, phenethyl ester



Yield : 536 mg (80 %).

M.Pt : 67°C

IR (nujol) cm^{-1}

3315, 1740, 1690, 1595, 1410

^{1}H NMR δ (200 MHz, $CDCl_3$)

8.1-8.0 (m, 2H), 7.6-7.4 (m, 4H), 7.35-7.2 (m, 4H), 4.4 (t, J=7Hz, 2H), [3.9,5.7,12.6] (s, 2H), 3.0 (t, J=7Hz, 2H)

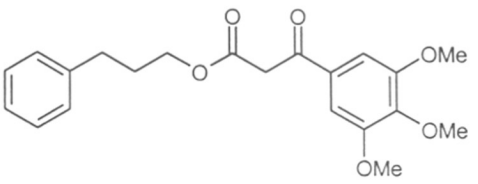
^{13}C NMR δ (50 MHz, $CDCl_3$)

192.31 (s), 167.36 (s), 137.52 (s), 133.65 (s), 128.82 (d), 128.75 (d), 128.47 (d), 126.56 (d), 87.28 (enolic), 65.76 (t), 45.76 (t), 34.86 (t)

Mass (70 eV)

m/z 268(M^+), 250, 233, 219, 209, 179, 164, 146, 122, 105 (base peak), 91, 77

Benzenepropanoic acid, -3,4,5-trimethoxy-β-oxo-, 3-phenyl-propyl ester



Yield : 642 (69 %).

IR (neat) cm^{-1}

3320,1740,1690

^{1}H NMR δ (200 MHz, $CDCl_3$)

7.25-7.15 (m, 7H), 4.25 (t, J=7Hz, 2H), [3.8,5.7,12.6] (s, 2H), 3.95,3.85 (two s, 9H), 2.65 (t, J=7Hz, 2H), 2.1-1.9 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$)

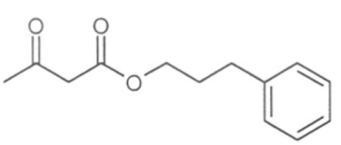
191.04 (s), 167.37 (s), 152.97 (s), 143.03 (s), 140.79 (s), 131.00 (s), 128.17 (d), 125.79 (d), 105.98 (d), 64.37 (t), 60.58 (q), 56.00 (q), 45.74 (t), 31.66 (t), 29.90 (t)

Analysis for $C_{21}H_{24}O_6$ (372.42)

Calculated C = 67.73 %, H = 6.50 %

Observed C = 67.51 %, H = 6.42 %

3-Oxo-butanoic acid 3-phenyl-propyl ester



Yield : 523 mg (95 %).

IR (neat) cm^{-1}

1740, 1695, 1590

^{1}H NMR δ (200 MHz, $CDCl_3$)

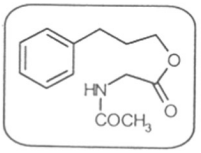
7.3-7.2 (m, 5H), 4.2 (t, J=7Hz, 2H), 3.5 (s, 2H), 2.7 (t, J=7Hz, 2H), 2.25 (s, 3H), 2.1-1.9 (m, 2H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

200.26 (s), 166.88 (s), 140.86 (s), 128.21 (d), 125.81 (d), 89.6 (enolic), 64.26 (t), 49.64 (t), 31.77 (t), 29.86 (t), 29.75 (q)

Mass (70 eV)

m/z 220(M^+), 136, 117 (base peak), 105, 91, 85, 77, 65, 57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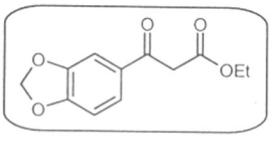
O

FT-80A Spectra No. 5
Date: 3/10/96
Proton
Carbon
Name: Belaj BS
S. No: Ethyl
Solvent: CDCl3
Remarks:
Operator


O
O
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O

SAMPLE NO. RY-3 / CDCL3
13.00
12.00
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5.00
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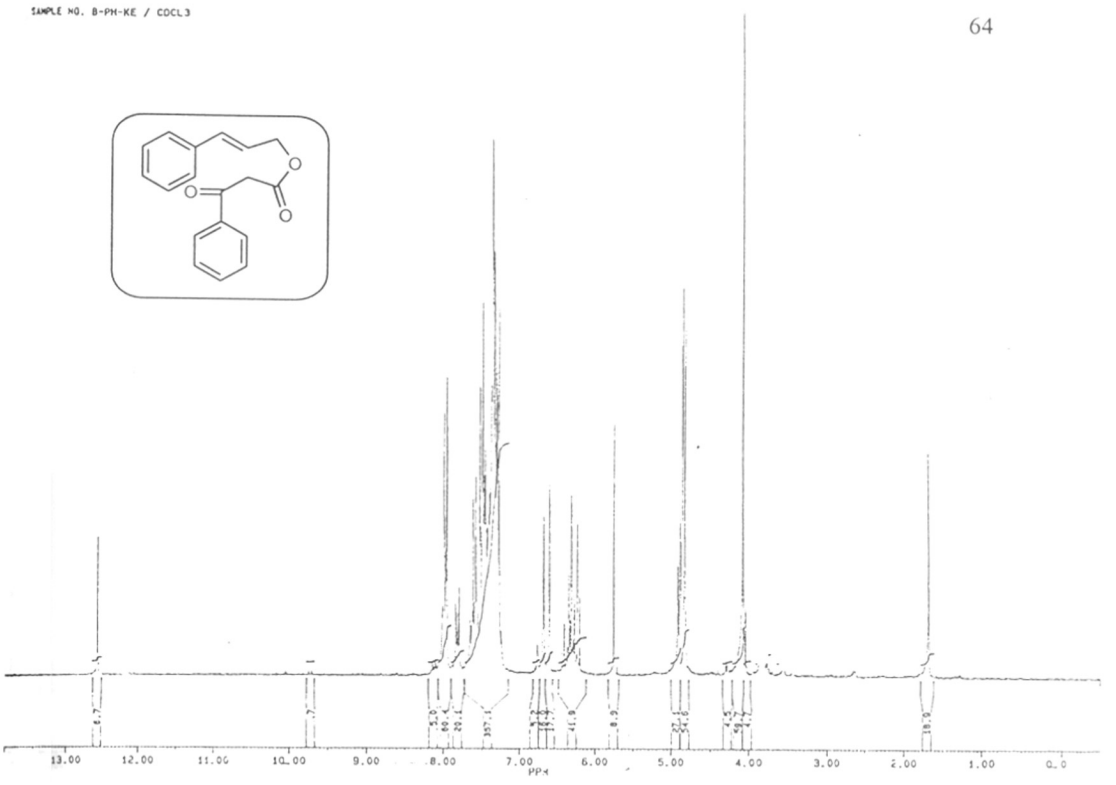
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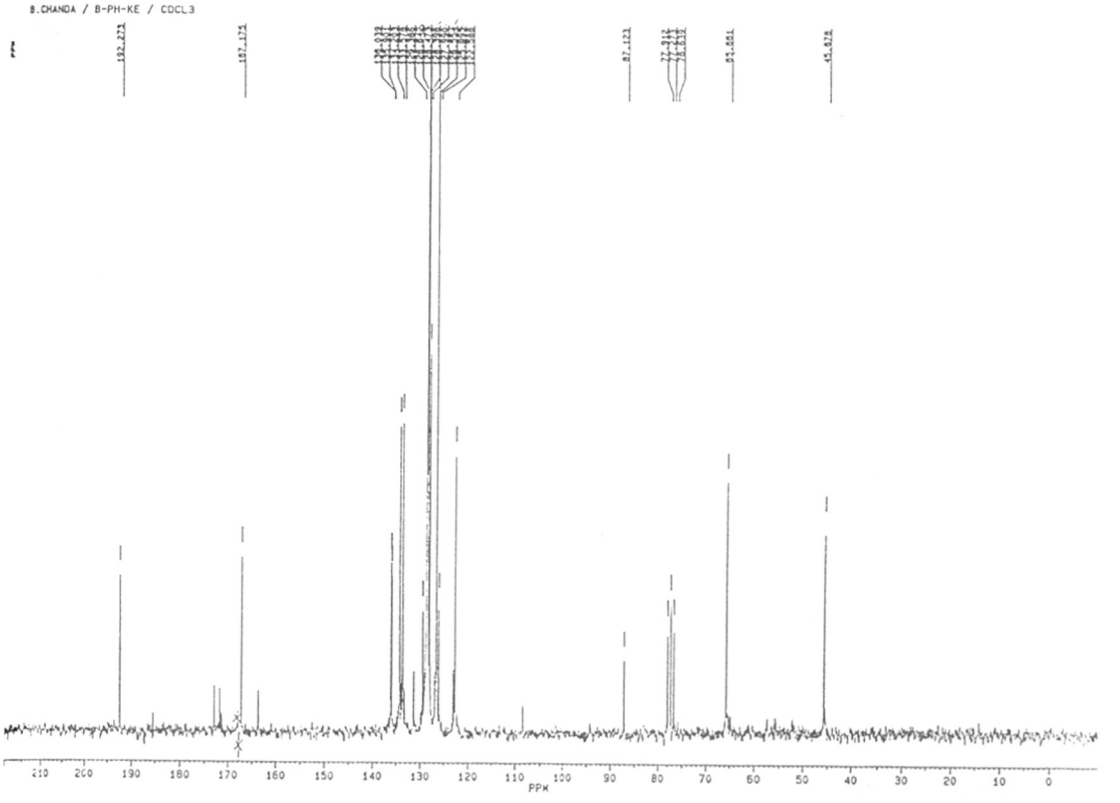
B.CHANDA / B-PH-KE / CDCL3
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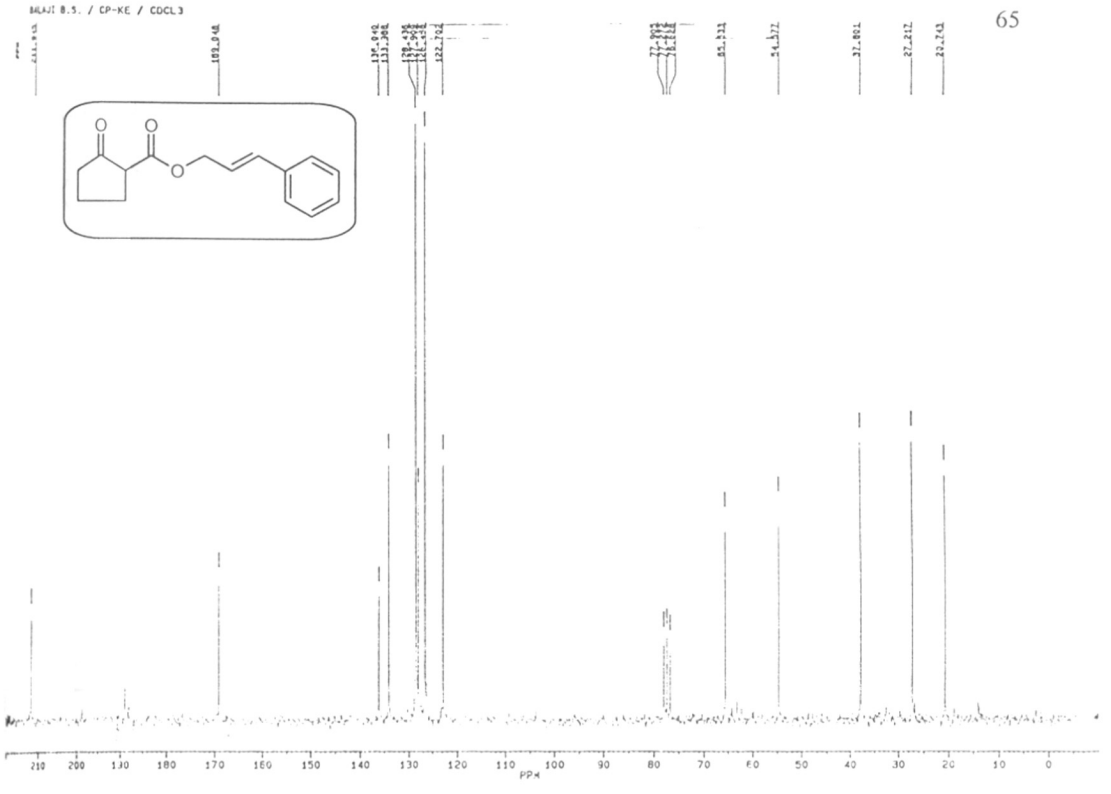
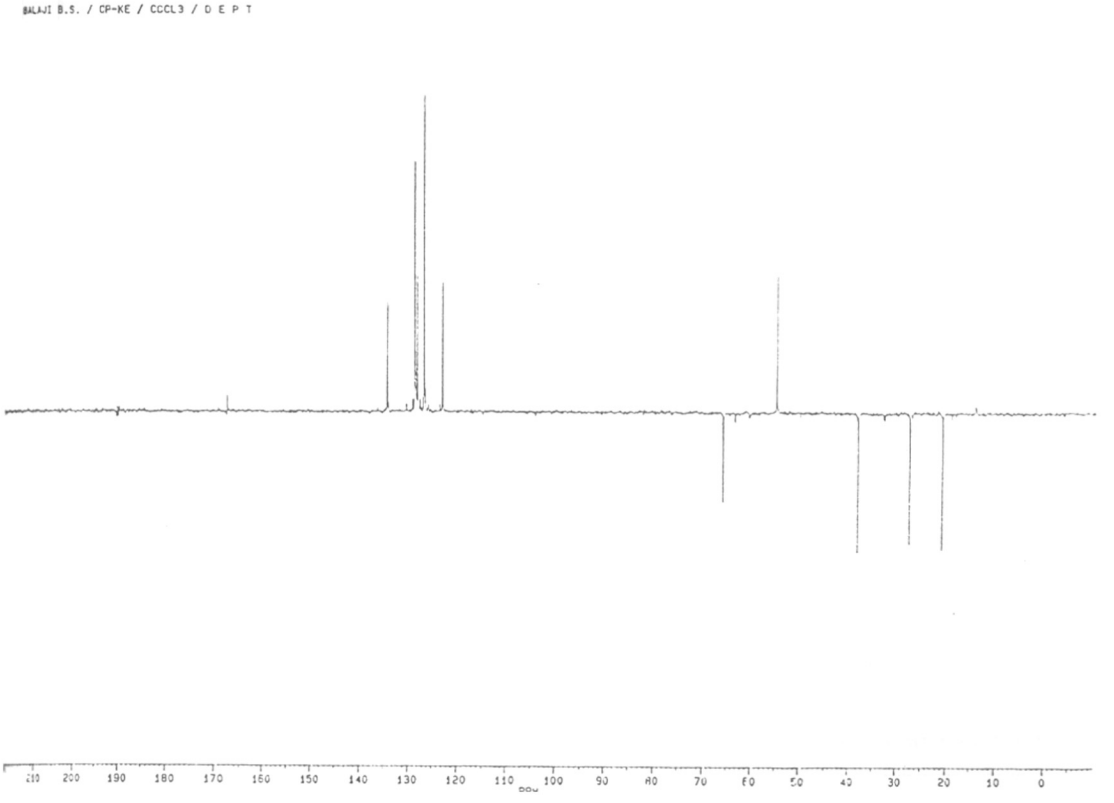
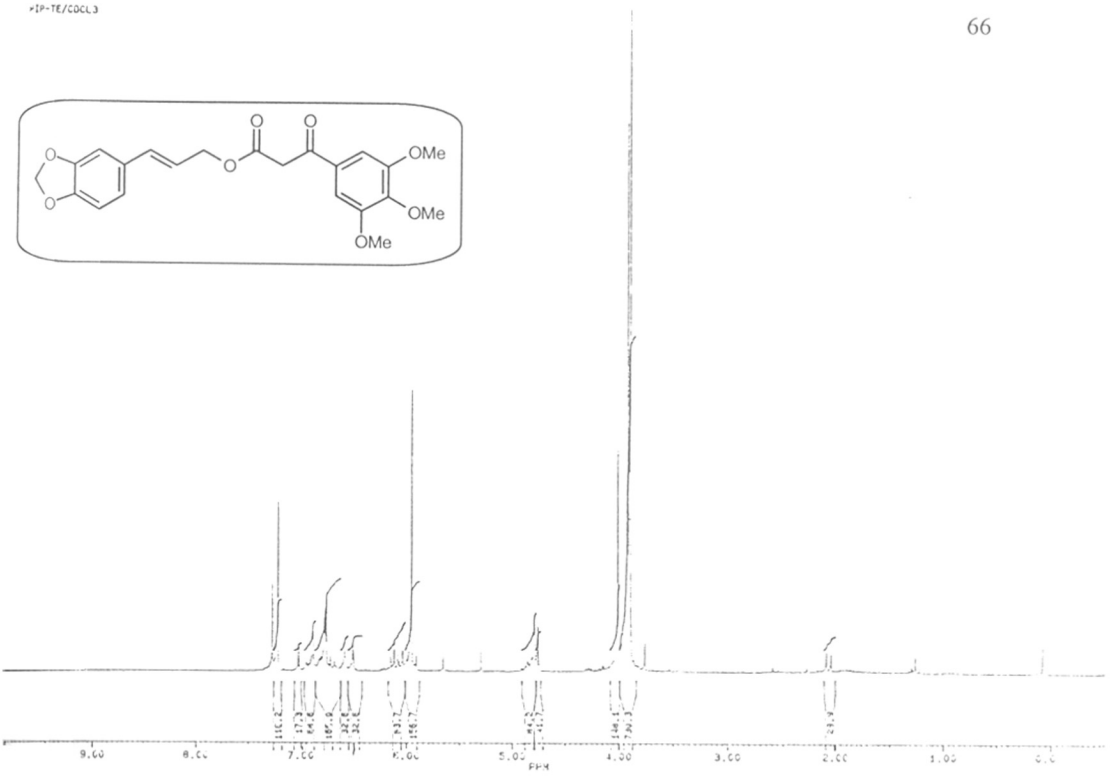
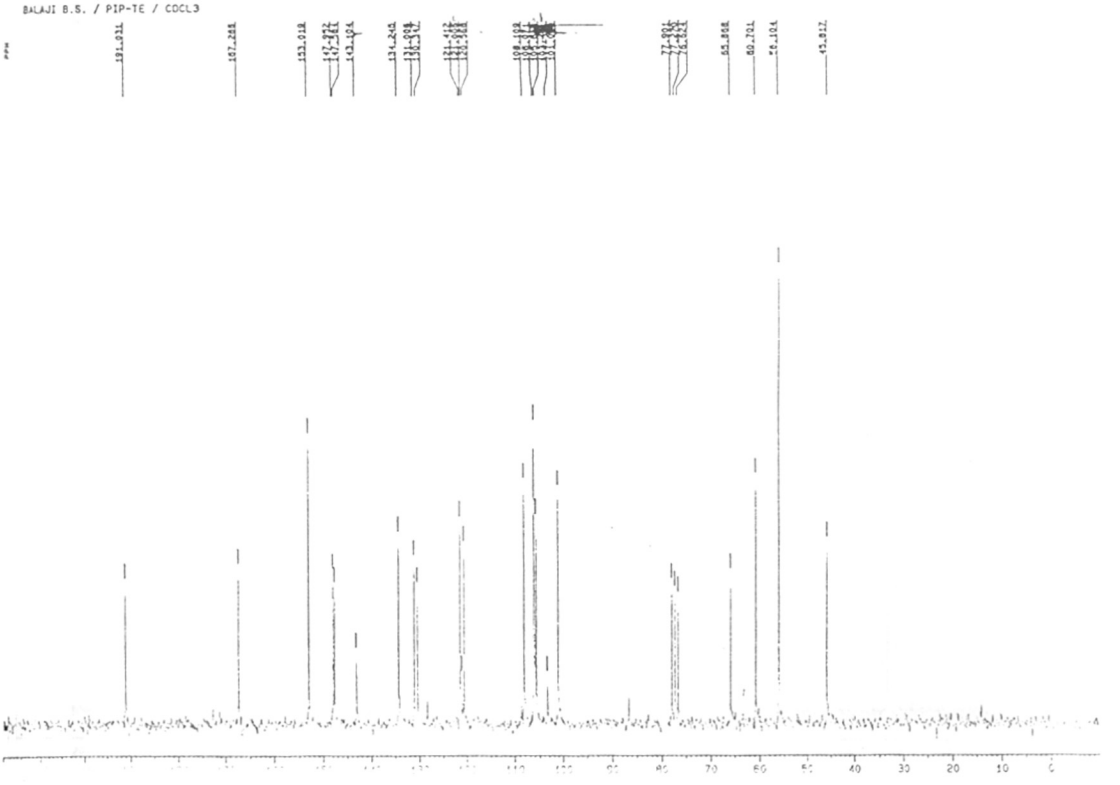
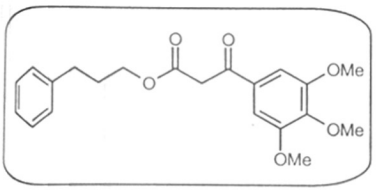

BALAJI B.S. / CP-KE / CDCL3
PPM


BALAJI B.S. / CP-KE / CDCL3 / D E P T

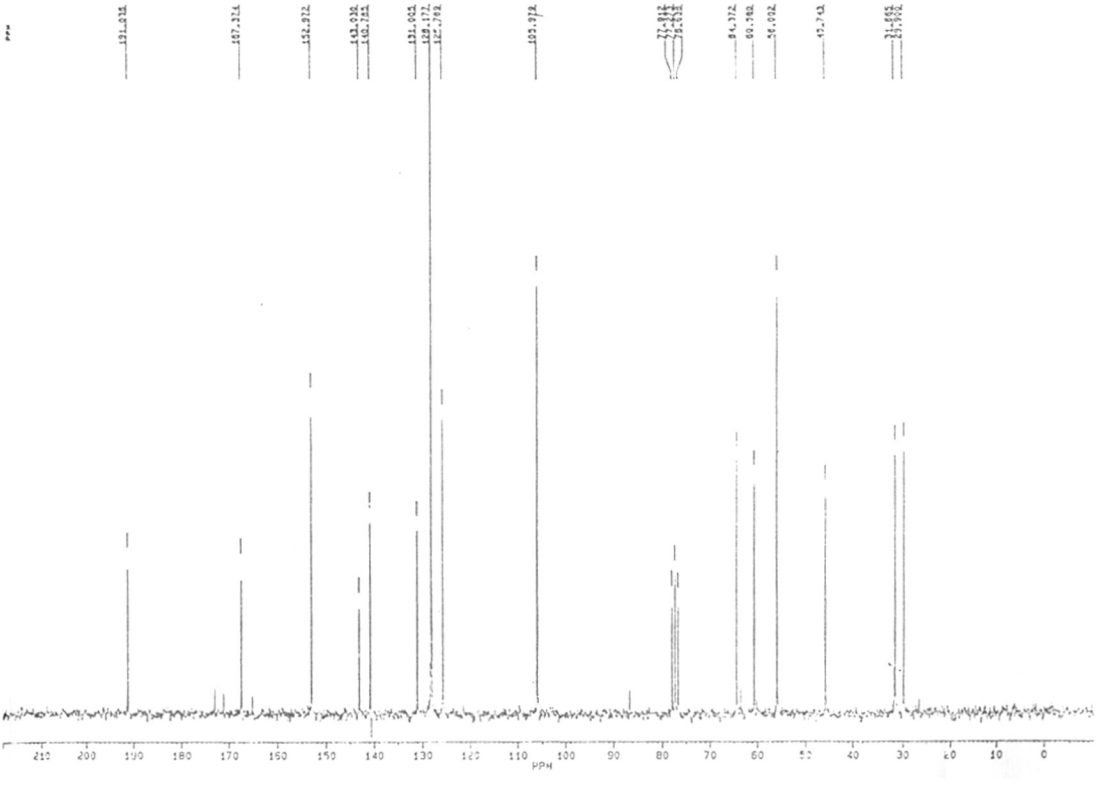

PIP-TE/CDCL3
OMe
OMe
OMe
PPM


BALAJI B.S. / PIP-TE / CDCL3
PPM

TMB-TE/CDCL3



BALAJI B.S. / B-DIHYDRO-KE / CDCL3



References:

1. Benetti, S., Romagnoli, R., De Risi, C., Spalluto, G., and Zanirato, V., *Chem.Rev.*, **1995,** (95), 1065.
2. Hoffmann, R.W., Helbig, W., Ladner, W., *Tetrahedron Lett.*, **1982,** (23), 3479.
3. Wang, C.L.J. and Salvino, J.M., *Tetrahedron Lett.*, **1984**, (25), 5243.
4. Gilbert, J.C. and Kelly, T.A., *Tetrahedron Lett.*, **1989**, (30), 4193.
5. Emmer, G., *Tetrahedron*, **1992**, (48), 7165.
6. Urban, E., Knuehl, G., Helmchen, G., *Tetrahedron*, **1995**, (51), 13031.
7. Magriotis, P.A. and Johnson, F., *J.Org.Chem.*, **1984**, (49), 1460.
8. Vig, O.P., Sharma, S.D., Soni, B.R., Sharma, M.L., *Indian J.Chem.Sect.B*, **1980**, (19), 353.
9. Benbakkar, M., Baltas, M., Gorrichon, L., Gorrishon, J.P., *Synth.Commun.*, **1989**, (19), 3241.
10. Ishida, T. and Wada, K., *J.Chem.Soc.Chem.Commun.*, **1975**, 209.
11. Decicco, C.P. and Buckle, R.N., *J.Org.Chem.*, **1992,** (57), 1005.
12. Krapcho, A.D., Diamanti, J., Caren, C., Bingham, R., *Organic Syntheses*, Wiley: New York, **1973**, *Collect. Vol V,* p 198.
13. Hauser, C.R., Swamer, F., Adams, J.T., *Org.React.*, **1954**, (8), 59.
14. Shahak, I., *Tetrahedron Lett.*, **1966**, (7), 2201.
15. Henegar, K.E.and Winkler, J.D., *Tetrahedron Lett.*, **1987**, (28), 1051.
16. Hellow, J., Kinston, J., Fallis, A.G., *Synthesis*, **1984**, 1014.
17. Pickersgill, I.F., Marchington, A.P., Rayner, C.M., *J.Chem.Soc.Chem. Commun.*, **1994**, 2597.
18. Le Noble, W.J., *Synthesis*, **1970**, 1.
19. Brandstrom, A. and Junggren, U., *Acta.Chim.Scand.*, **1969**, (23), 2204.
20. Durst, H.D.and Liebeskind, L., *J.Org.Chem.*, **1974**, (39), 3271.
21. Stork, G., Winkler, J. D., Saccomano, N., *Tetrahedron Lett.*, **1983**, (24), 465.
22. Barco, A., Benetti, S., Pollini, G.P., Baraldi, P.G., Gandolfic, C., *J.Org.Chem.*, **1980**, (45), 4776.
23. Skeean, R.W., Trammel, G.L., White, J.D., *Tetrahedron Lett.*, **1976**, (17), 525.
24. Corey, E.J., Tuis, M.A., Das, J., *J.Am.Chem.Soc.*, **1980**, (102), 1742.
25. Tsuji, J., Kobayashi, Y., Kataoka, H., Takahashi, T., *Tetrahedron Lett.*, **1980**, (21), 1475.
26. Kates, S.A., Dombroski, M.A., Snider, B.B., *J.Org.Chem.*, **1990**, (55), 2427.
27. Taber, D.F., *J.Org.Chem.*, **1977**, (42), 3513.
28. Taber, D. F.and Petty, E. H., *J.Org.Chem.*, **1982**, (47), 4808.

29. Taber, D. F., Petty, E. H., Raman, K., *J.Am.Chem.Soc.*, **1985**, (107), 196.
30. Salzmann, T.N., Ratcliffe, R.W., Christensen,B.G., Bouffard, F.A., *J.Am.Chem.Soc.*, **1980**, (102), 6161.
31. Ando, M., Büchi, G., Ohnuma, T., *J.Am.Chem.Soc.*, **1975**, (97), 6880.
32. Wassermann, H.H. and Pickett, J.E., *J.Am.Chem.Soc.*, **1982**, (104), 4695.
33. Lee, J., Oya, S., Snyder, J.K., *Tetrahedron Lett.*, **1991**, (32), 5899.
34. Hewson, A.T., MacPherson, D.T., *J.Chem.Soc.Perkin. Trans I.*, **1985**, 2625.
35. Marx, J.N., Minaskanian, G., *J.Org.Chem.*, **1982**, (47), 3306.
36. Boehme, W.R., *Organic Syntheses*; Wiley: New York, **1960**, *Collect vol. IV.* p 590.
37. Inukai. N., Iwamoto, H., Tamura, I., Yanagisawa, Y., Ishii, Y., Marakami, M., *Chem.Pharm.Bull.*, **1976**, (24), 820.
38. Lerman, O. and Rosen, S., *J.Org.Chem.*, **1983**, (48), 724.
39. Coates, R.M. and Hobbs, S.J., *J.Org.Chem.*, **1984**, (49), 140.
40. Bruggink, A., McKillop, A., *Tetrahedron*, **1975**, (31), 2607.
41. Taber, D.F., Amedio, J.C., Jr, Sherrill, R.G., *J.Org.Chem.*, **1986**, (51), 3382.
42. Singh, B. and Lesher, G.Y., *Synthesis*, **1978**, 829.
43. Jones, R.C.F. and Sumaria, S., *Tetrahedron Lett.*, **1978**, (19), 3173.
44. Bloomer, J.L. and Kappler, F.E., *Tetrahedron Lett.*, **1973**, (14), 163.
45. a) Clemo, N.G. and Pattenden, G., *Tetrahedron Lett.*, **1982**, (23), 581.
    b) Miyata, O. and Schmidt, R.R., *Tetrahedron Lett.*, **1982**, (23), 1793.
46. Rathke, M.W. and Lindert, A., *J.Am.Chem.Soc.*, **1971**,(93), 2318.
47. Damon, R.E., Luo, T., Schlessinger, R.H, *Tetrahedron Lett.*, **1976**, (17), 2749.
48. Turner, J.A. and Jacks, W.S., *J.Org.Chem.*, **1989**, (54), 4229.
49. a) Krapcho, A.P., Kashdan, D.S., Jahngen, E.G. Jr., *J.Org.Chem.*, **1977**, (42), 1189. b) Angelo. B., *C.R.Acad.Sci.*, **1973**, (276), 293.
50. Wasserman, H.H. and Wentland, S.H., *J.Chem.Soc.Chem.Commun.*, **1970**, 1.
51. Rathke, M.W. and Sullivan, D.F., *Tetrahedron Lett.*, **1973**, (14), 1279.
52. Armati, A., De Ruggeri, P., Rossi, E., Stardi, *Synthesis*, **1986**, 573.
53. Pollet, P.L., *J.Chem.Educ.*, **1983**, (60), 244.
54. Olkawa, Y., Sugano, K., Yonemitsu, O., *J.Org.Chem.*, **1978**, (43), 2087.
55. Bestmann, H.J. and Geismann, C., *Liebigs Ann.Chem.*, **1977**, 282.
56. Sanchez, I.H., Larraza, M.I., Brena, F.K., Cruz, A., Sotelo, O., Flores, H.J., *Synth.Commun.*, **1986**, (16), 299.
57. Trost, B.M. and Jungheim, L.N., *J.Am.Chem.Soc.*, **1980**, (102), 7910.
58. Ishino, Y., Nishiguchi, I., Nakao, S., Hirashima, T., *Chem.Lett.*, **1981**, 641.

59. Stamhuis, E.J., *Synthesis, Structure and Reaction,* Ed. by Cook, A.G., Marcel Dekker, New York, **1969**, p 101.

60. Tsuji, J., Nagashima, H., Hori, K., *Chem.Lett.*, **1980**, 257.

61. Kitazume, T. and Kobayashi, T., *J.Fluorine Chem.*, **1986**, (31), 357.

62. Carlson, R.M. and Ishidor, J.L., *Tetrahedron Lett.*, **1973**, (14), 4819.

63. Chan, T.H. and Brownbridge,P., *J.Chem.Soc.Chem.Commun.*, **1979**, 578.

64. a) Bestmann, H.I. and Saalfrank, R.W., *Angew.Chem.Int.Ed.Engl.*, **1970**, (9), 367.
b) Pietrusiewicz, K.M. and Monkeiewicg, J., *Tetrahedron Lett.*, **1986**, (27), 739.
c) Bodelski, X., Pietrusiewicz, K.M., Monkiewicz, J., Koszuk, J., *Tetrahedron Lett.*, **1980**. (21), 2287.

65. Boese, A.B. Jr., *Ind.Eng.Chem.*, **1940**, (32), 16.

66. Clemens, R.J. and Hyatt, J.A., *J.Org.Chem.*, **1985**, (50), 2431.

67. Otera, J., *Chem.Rev.*, **1993**, (93), 1449 and references cited therein.

68. Wagner, P.J. and El-Taliawi, G.M., *J.Am.Chem.Soc.*, **1992**, (114), 8325.

69. Pellicciari, R., Natalini, B., Cecchetti, S., Fringuelli, R., *J.Chem.Soc.Perkin Trans. I*, **1985**, 493 and references cited therein.

70. Fernadez, V.M., Herrera, L.F.J., Perez, G.C., *Carbohyd. Res.*, **1983**, (124), 333.

71. Holmquist, C.R. and Roskamp,E.J., *J.Org.Chem.*, **1989**, (54), 3258.

72. Dhavale, D.D., Patil, P.N., Mali, R.S., *J.Chem.Res. (S).*, **1994**, 152.

73. Breck, D.W., in *Zeolite Molecular Sieves*, John Wiley and Sons, New York, p 74.

74. Meier, W.M. and Olson, D.H., in *Atlas of Zeolite Structure Types*, 2nd Edn, Butterworths, London, p 87.

75. Bragg, W.L., in *The Atomic Structure of Minerals*, Cornell University Press, Ithaca New York, p 1937.

76. Barrer, R.M., *Pure App. Chem.*, **1979**, (51), 1091.

77. Venuto, P.B., *Microporous Materials*, **1994**, 297.

78. Bekkum, H.V. and Kouwenhoven, H.W., in *Studies in Surface Science and Catalysis*, Vol 41, *Heterogeneous Catalysis and Fine Chemicals*, Ed. By Guisnet, M., Barrault, J., Bouchoule, C., Duprez, D., Montassier, C., Perot, G., Elsevier Science Publishing Company Inc. New York, **1988**, p 45.

79. Hoelderich, W.F., in *Studies in Surface Science and Catalysis*, Vol 67, *Structure Activity and Selectivity Relationships in Heterogeneous Catalysis* Ed by Grasselli, R.K., Sleight, A.W., Elsevier Science Publishing Company Inc. New York, **1991**, p 257.

80. Garwood, W.E. and Chu P., in *Chemical Industries* Vol 47, *Catalysis of Organic Reactions* Ed. by, Pascor, W.E., Marcel Dekker Inc., New York, **1992**, Part II (Chap 31) p 365.

81. Basset, J.M., Candy, J.P., Choplin, A., Dufour, P., Louessard, P., Santini, C., in *Studies in Surface Science and Catalysis,* Vol 41, *Heterogeneous Catalysis and Fine Chemicals*, Ed. By Guisnet, M., Barrault, J., Bouchoule, C., Duprez, D., Montassier, C., Perot, G., Elsevier Science Publishing Company Inc. New York, **1988**, p 1.

82. Sudrik, S.G., Balaji, B.S., Singh, A.P., Mitra, R.B., Sonawane, H.R., *Synlett*, **1996**, 369.

83. Fritschi, H., Leutenegger, U., Pfaltz, A., *Hel.Chim.Acta*, **1988**, 1553.

84. Ono, N., Yamada, T., Saito, T., Tanaka, K., Kaji., *Bull. of Chem.Soc.Jpn*, **1978**, 2401.

85. Merker, R.L. and Scott, M.J., *J.Org.Chem.*, **1961**, 5180.

86. Fairhurst, J. and Horwell, D.C., *Synth.Commun.*, **1976**, (6), 89.

87. a) Kimel, W. and Cope, A.C., *J.Am.Chem.Soc.*, **1943**, (65), 1992.
b) Wilson, S.R. and Price, M.F., *J.Org.Chem.*, **1984**, (49), 3618.

88. Taber, D.F., Amedio, J.C., Jr., Patel, Y.K., *J.Org.Chem.*, **1985**, (50), 3618.

89. a) Otera, J., Yano, T., Kawabata, A., Nozaki, H., *Tetrahedron Lett.*, **1986**, (27), 2383. b) Otera, J., Pan-oh, N., Nozaki, H., *J.Org.Chem.*, **1991**, (56), 5307.

90. Gilbert, J.C. and Kelly, T.A., *J.Org.Chem.*, **1988**, (53), 449.

91. Witzman, J.S. and Nottingham, W.D., *J.Org.Chem.*, **1991**, (56), 1713.

92. Ravindranathan, T., Chavan, S.P., Dantale, S.W., Zubaidha, P.K., Keshavaraja, A., Ramaswamy, A.V., *Tetrahedron Lett.*, **1996**, (37), 233.

93. Keane, M.A., *Zeolites,* **1993**, (13), 330.

94. Corma, A., *Chem.Rev.*, **1995**, (95), 559.

95. Campbell, D.S. and Lawrie, C.W., *J.Chem.Soc.Chem.Commun.*, **1971**, 355.

96. Balaji, B.S., Sasidaran, M.S., Kumar, R., Chanda, B., *Chem.Commun.*, **1996**, 707.

97. a) Strauss, C.R. and Trainor, R.W., *Aust.J.Chem*, **1995**, (48), 1665. b) Mingos, and Baghurst, D.R., *Chem.Soc.Rev.*, **1991**, (20), 1 and references cited therein. c) Galema, S.A., *ibid*, **1997**, (26), 233. d) Caddick S., *Tetrahedron*, **1995**, (51), 10403. d) Bose A.K., Jayaraman, J., Okawa, A., Bari, S.S., Robb, E.W., Manhas, M.S., *Tetrahedron Lett.*, **1996**, (37), 6989 and references cited therein.

98. Loupy, A., Petit, A., Ramdani, .M., Yvanaeff, C., Majdoub, M., Labiad, Villemin, D., *Can.J.Chem.*, **1993**, (71), 90 and references cited therein..

CHAPTER II

SOME SYNTHETIC STUDIES DIRECTED TOWARDS THE CONSTRUCTION OF LACTONE RING PRESENT IN NATURALLY OCCURRING LIGNAN LACTONES

99. Giguere, R.J., Bray, T.L., Duncan, S.M., Majetich, G., *Tetrahedron Lett.*, **1986**, (27), 4945.

100. Abramovitch, R.A. and Bulman, A., *Synlett*, **1992**, 795.

101. Takano. S., Kijima, A., Sugihara, T., Satah, S., Ogasawara,K. *Chem.Lett.*, **1989**, 87.

102. Alajarín, R., Vaqero, J.J., García, Navío, J.L., Alvarez-Builla, J., *Synlett*, **1992**, 297.

103. Hwang, D.R., Moerlein, S.M., Lag, L., Welch, M.J *J.Chem.Soc.Chem.Commun.*, **1987**, 1799.

104. Pollington, S.D., Bond, G., Moyes, R.B., Whan, D.A., Candlin, J.P., Jennings, J.R., *J.Org.Chem.*, **1991**, (56), 1313.

105. Holker A.G. Ph.D. thesis, Pune University, p 84.

106. Serale, N.E. *Organic Syntheses, Collective Vol., IV*, John Wiley and Sons. Inc, New York. **1963**, p 424.

107. Clay, R.C., Collom, T.A., Karrick, G.L., Wemple, J., *Synthesis*, **1993**, 290.

108. *Dictionary of Organic compounds*. 5th Ed. *Vol. IV*. p 4234. Chapman and Hall. New York.

109. a) Turner, J.A. and Jacks, W.S., *J.Org.Chem.*, **1989**, (54), 4229. b) Singer S. and Zuman.P., *J.Org.Chem.*, **1974**, 836. c) Matsuo, K., Kimura, M., Kinuta, T., Takai, N., Tanaka, K., *Chem.Pharm.Bull.*, **1984**, 4197. d) Katzenellenbogen, J.A. and Utawanit, T., *J.Am.Chem.Soc.*, **1974**, (96), 6153.

110. Ghosh, S. and Datta,I., *Synth.Commun.*, **1991**, (21), 191.

111. Herbst, R.M. and Shemin, D., *Organic Syntheses, Collective Vol. II*, John Wiley and Sons. Inc, New York. **1961**, p 11.

112. Suter, C.M., *J.Am.Chem.Soc.*, **1938**, (60), 536.

113. Klemm, L.H., Gopinath, K.W., Karaboyas, G.C., Capp, G.L., Lee, D.H., *Tetrahedron,* **1964**, (20), 871

114. Bloomfield, J.J. and Fuchs, R. *J.Org.Chem.*, **1961**, (26), 2991.

"நோயற்ற வாழ்வே குறைவற்ற செல்வம்"

ஔவையார்

Chapter 2

Some synthetic studies directed towards the construction of lactone ring present in naturally occurring lignan lactones.

General Introduction

A brief introduction of anticancer and antitumour drugs would assist in the rationale behind undertaking this work.

Normal healthy body cells live in a complex interdependent condominium, regulating one another's proliferation.[1a] The controlled reproduction of a cell in collaboration with other tissues in the vicinity maintains a size and architecture needed for proper functioning of the human body.

When some cells within a normal population sustain a genetic mutation, certain variations occur in the whole process. The altered cell reproduces at a very fast pace (hyperplasia) and they proliferate in the vicinity as well. Due to this mutation, the offspring of this cell may have abnormal shape and orientation (dysplasia). These malignant cells have several properties like the ability to migrate from the site where they began, invading nearby tissues, forming masses at distant sites in the body *etc.* They become more aggressive over a period of time and become lethal when they disrupt functioning of the tissues and organs needed for the survival of the organism as a whole.

Genes which are responsible for synthesising encoded proteins play a vital role in triggering cancer. Two types of genes play this important role: (i) Proto-oncogenes (they encourage cell growth) and (ii) Tumour suppressor genes (they suppress cell growth). When mutation takes place, the function of these genes get affected leading to inappropriate growth. This is the major cause for cancer. One cannot stop or prevent mutation. However, almost 2/3 of all cancer deaths which are easily correctable, are reported to be due to tobacco and diet.[1b] Tobacco smoke (smoking) causes lung cancer. Animal fat in general, and red meat in particular, are associated with several types of cancers. Lack of roughage through insufficient consumption of vegetables and fruits can also cause cancer. Obesity in adult life is an important cause of cancer of the endorectium and early mensturation is a major risk factor for breast cancer. Higher intake of salt may lead to stomach cancer. Over eating and insufficient exercise are responsible for prostate cancer.

The cancer deaths can be avoided through (i) prevention of cancer (ii) early detection, followed by successful treatment. The prevention strategies include avoiding smoking, eating certain vegetables and foods that counteract the activity of carcinogens *etc*. The ability of medicinal science to treat many forms of cancer is limited by the disease's tendency to proliferate (metastasis). When cancer, in spite of proper precautions tends to proliferate, several methods are available[1c] for an effective control and in some cases complete remission of cancer as well.

Surgery: One of the earliest therapies and widely used methods is surgery. It is quick and effective and accounts for largest number of cures.
Short comings: (a) Microscopic extensions are not removed. (b) Healthy tissue is also being removed. (c) Cannot cure cancer that had metastasised widely throughout the body. It is painful and debilitating. It is also ineffective and prolongs survival for only a short time.

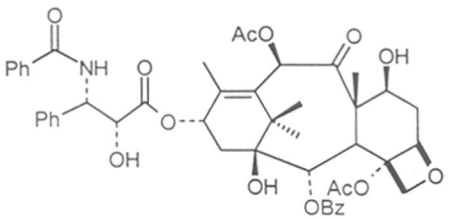
Radiation therapy: This therapy acts either by inflicting genetic damage, sufficient to kill cancerous cells directly, or by inducing cellular suicide (apoptosis). It can cure the cancer without sacrificing the patient's ability to function. Microscopic extension of cancerous cells can be destroyed. It is a safer option for older people and hospitalisation can be avoided.
Short comings: Radiation therapy fails to eradicate all the cancer cells sometime and cannot remove full-fledged tumour at numerous sites. Many a times, healthy cells are also destroyed.

Chemoprevention of cancer[1d]

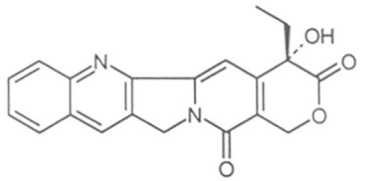
It is well known that the onset of cancer is a gradual, stepwise process that may unfold over a course of decades. Chemoprevention is the attempt to use natural and synthetic compounds to intervene in the early precancerous stages of carcinogenesis, before invasive disease begins. *i.e.* the synthetic compound should prevent or halt carcinogenesis. The basic requirements for drugs applied under chemoprevention is that they must be nontoxic, relatively free of side effects *etc*.

Chemotherapy or the systematic administration of an anti-cancer drug is the only alternative for an effective and prolonged control of cancer. It prevents cells from multiplying by interfering with their ability to replicate DNA. Several drugs are in the market as chemotherapeutic agents. Most important among them are: Paclitaxel^{TR} (1),[2a]

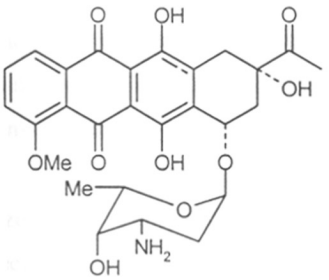
Camptothecin (**2**),[2b] Etoposide (**3a**),[2c] Teneposide (**3b**),[2c] Daunomycin (**4a**)[2d] Vinblstine (**4b**)[2e] and Vincristine (**4c**)[2e] etc. there mechanism of action are quite different. They can also induce apoptosis in cancerous cells.



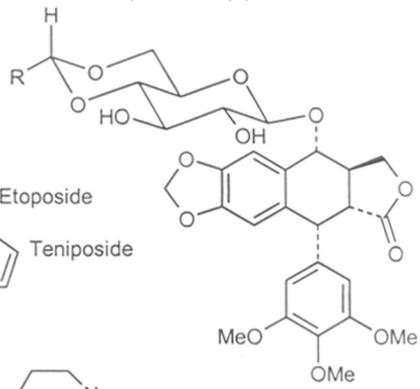
Paclitaxel^{TR} (**1**)



Camptothecin (**2**)



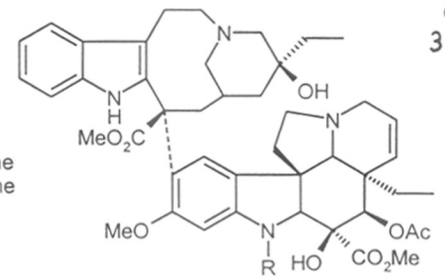
Daunomycin (**4a**)



3a R = CH_3 Etoposide

3b R =  Teniposide

3



4b R = Me, Vinblastine
4c R = CHO Vincristine

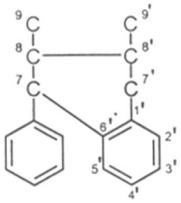
An introduction to anti cancer drugs especially lignans

Lignans[3] have long been recognised to exhibit important biological activity. Structurally, they are challenging targets in organic syntheses. In addition, lignans are representative as valuable target molecules for asymmetric synthesis[4] due to the close juxtaposition and clearly defined configuration of the chiral centres.

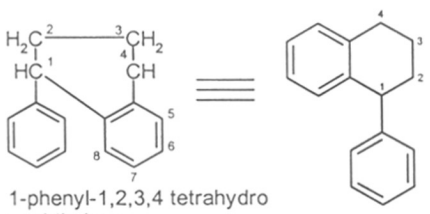
Lignans are natural products, distributed widely in the plant kingdom. At the ecological level, they play a role in plant-fungus, plant-plant, plant-insect interactions, and at molecular level, some are known to *bind tubulin of microtubes, to interrupt nucleotide transport and DNA synthesis and to be specific inhibitors of certain enzymes.*

Strcuturally, lignans[5] are dimers of phenylpropanoid units [C_6-C_3] linked by the central carbons of their side chains. Further cyclisation resulting from the introduction

of a $C_7/C_{6'}$ linkage leads to a class of compounds collectively known as cyclolignans. The latter can be tetrahydronaphthalene type or naphthalene type.



Cyclolignan



1-phenyl-1,2,3,4 tetrahydro naphthalene

Biological activity of lignans

Out of all the types of lignans, the one from podophyllotoxin group shows remarkable antitumour activity. A brief introduction to podophyllotoxin's structutre would serve as a prelude to discussion of its biological activity.

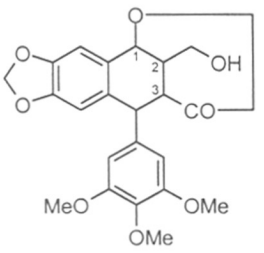
Constitution of podophyllotoxin

Podophyllotoxin has been known for long time.[6a] It was isolated from the rhizomes of *Podophyllum peltatum (Berberidaceae)* and was also found in another species, *viz. Podophyllum emodi.* In 1946 King *et.al.*[6b] demonstrated that podophyllotoxin displayed therapeutic effect. In 1932 Borsche and Niemann,[7a] and Späth *et.al.*[7b] proposed structures for podophyllotoxin based on the following evidences.

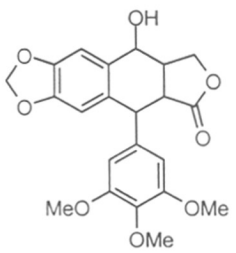
a) podophyllotoxin **(5)** was isomerised to picropodophyllin with basic reagents

b) podophyllic acid **(7)** was obtained from either compound by lactone ring opening

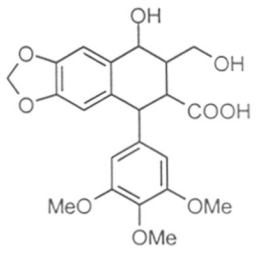
c) picropodophyllin **(6)** alone underwent dehydration, but not podophyllotoxin.



Podophyllotoxin **(5)**



Picropodophyllin **(6)**



Podophyllic acid **(7)**

Based on the following observations and facts, Hartwell *et.al.*[8a] reassigned the structure of podophyllotoxin:

a) Podophyllotoxin and picropodophyllin may be diastereoisomers because protection of the free hydroxyl group in podophyllotoxin followed by refluxing in alcoholic solution provided the protected picropodophyllin.

b) Both compounds possess the same lactone ring and that inversion or epimerisation took place at C_3, the asymmetric carbon atom α to the lactone carbonyl.

c) Failure of podophyllic acid to yield formaldehyde on periodate oxidation

d) The halides of podophyllotoxin gave an immediate precipitate of AgX with alcoholic $AgNO_3$ in cold, were rapidly hydrolysed by water and action of acetyl chloride on podophyllotoxin gave a chloride instead of an acetate.

e) Conversion of podophyllotoxin to picropodophyllin by heating with palladium black in methanol. (Please see below for the structure)

Configuration of podophyllotoxin[8b] (the numbering followed in the paper by Hartwell is now obsolete. However, for comparison, the originality of the paper is retained here)

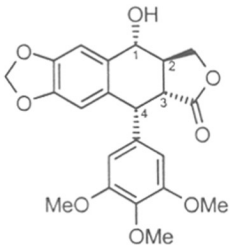
Configuration at C_1 and C_2.

Based on the pyrolysis rates of benzoates of podophyllotoxin and podophyllin, it was confirmed that preferential *cis* elimination has occured. *i.e.* the benzoyl group at C_1 is *cis* relative to the hydrogen at C_2. Therefore the non-hydrogen substituents at C_1 and C_2 are *trans*.

Podophyllin and podophyllotoxin are stereo isomers differing only in the configuration at C_3.

Configuration of C_2,C_3 and C_3,C_4

Based on the catalytic hydrogenation studies it was confirmed that podophyllotoxin and deoxy podophyllotoxin are 2,3 *trans* and 3,4 *cis*.



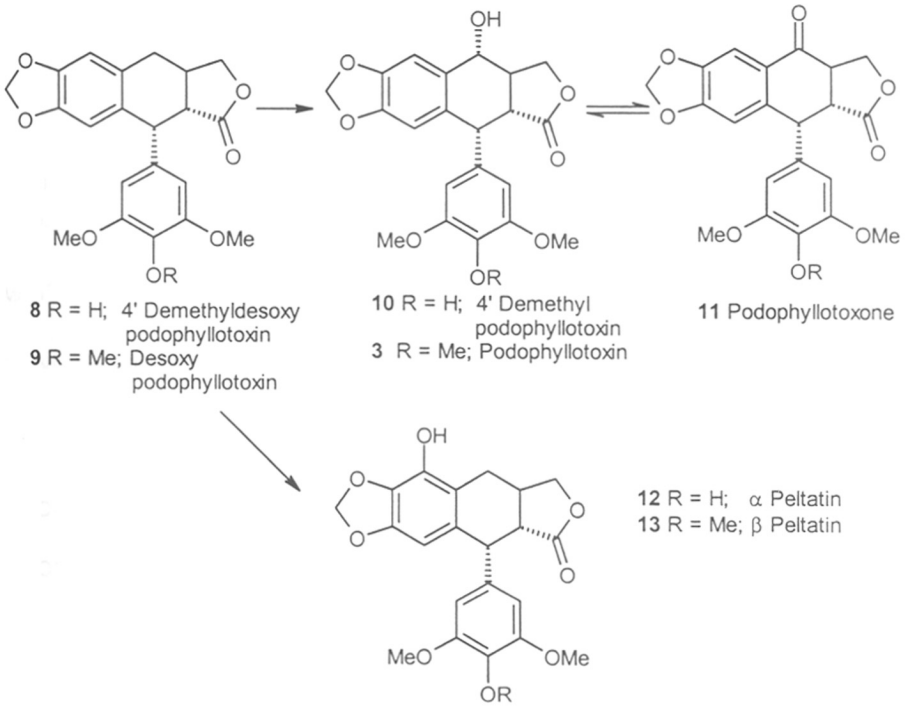
Podophyllotoxin (**3**)

When biological activities are considered, the members of podophyllotoxin group show remarkable antitumour activity. They all have a common structural feature: *a five membered lactone ring, a 3',4',5'- trimethoxy phenyl group, a 3,4 methylenedioxy group, two substituted phenyl rings separated by a four carbon chain*. It is observed that the important structural features required for antitumour activities are: *the configuration*

of hydroxy group, polarity of the substituent at C_1 rather than its size, the configuration at C_3 and the methylenedioxy unit.

Biosynthesis of podophyllotoxin

Podophyllum species contain a range of aryl tetralin lignans having valuable antitumour activity. Feeding experiment in podophyllum plants[9a] have indicated that the major lignans podophyllotoxin and 4' demethyl podophyllotoxin appear to be formed by oxidative coupling of two phenylpropane units containing ferulic acid (4-hydroxy- 3-methoxy substitution patterrn) and podophyllum lignans may be divided into two biogenitically distinct groups. One group contains 3,4,5 trimethoxy substituted pendant aromatic ring and is derived from desoxy podophyllotoxin (**9**); and the other group contains 4-hydroxy-3,5-dimethoxy substituted pendant aromatic ring and is derived from 4'demethyl desoxy podophyllotoxin (**8**) **[Scheme 1]**.



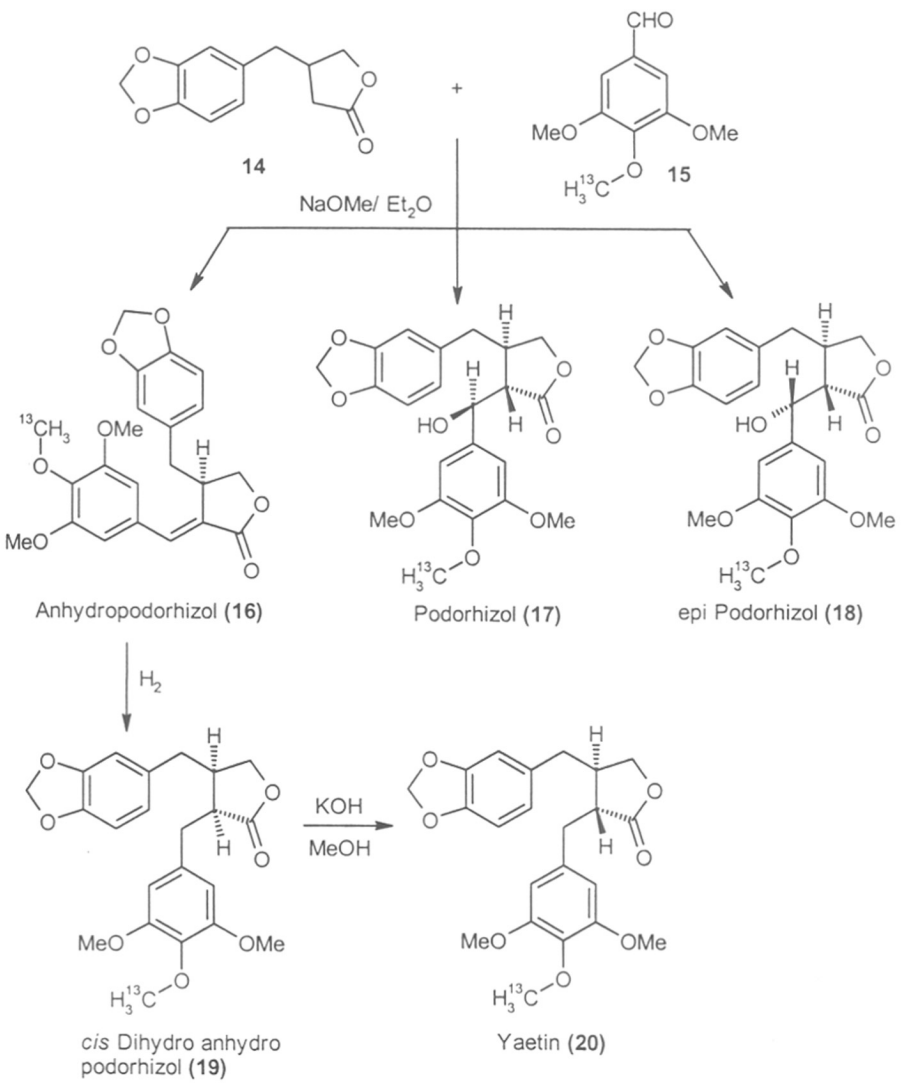
Scheme 1

It is observed that podophyllotoxin (**3**) may be derived by hydroxylation of desoxy podophyllotoxin (**9**) or by the *in vivo* reduction of podophyllotoxone (**11**). β Peltatin (**13**) is formed by an alternative 5 hydroxylation of desoxy podophyllotoxin (**9**).

The wide spread co-occurrence of aryltetralin lignan lactones with similarly substituted dibenzyl butyrolactone lignans suggests that the latter group of compounds

may function as biosynthetic precursors for desoxypodophyllotoxin (**9**) and podophyllotoxin (**3**).[9b] This hypothesis was supported by the isolation of various compounds like yaetin (**20**) anhydropodorhizol (**16**) (nemorosin) and podorhizol (**17**) [**Scheme 2**].

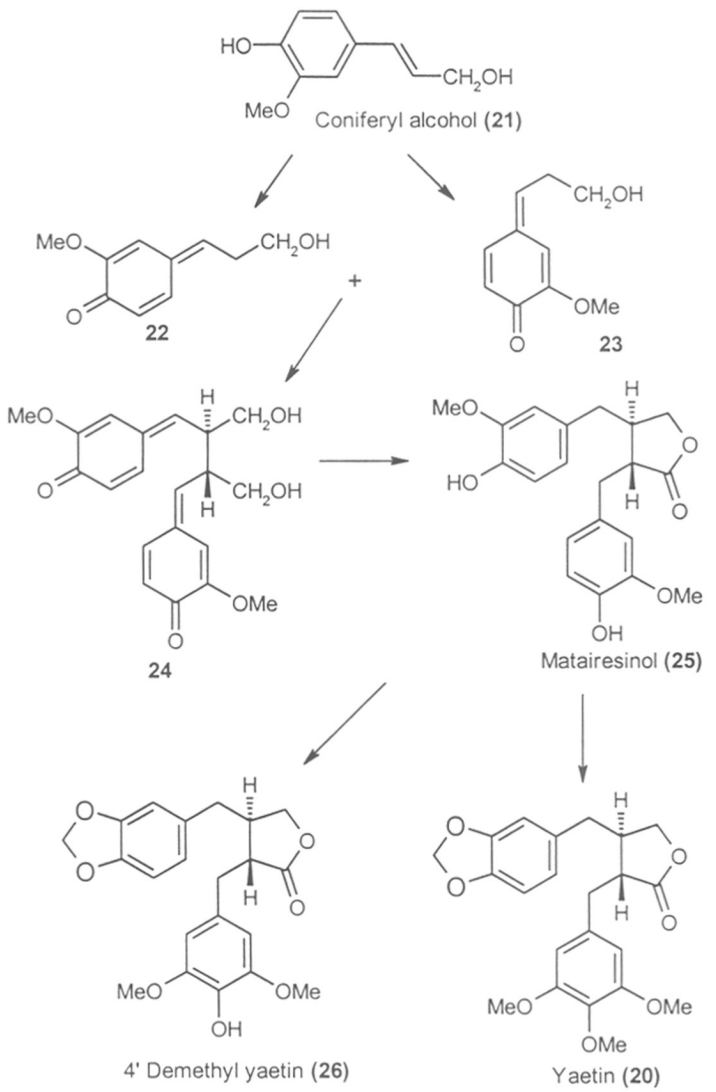
Biosynthetic pathway of podophyllotoxin group of lignans



Scheme 2

Dewick *et.al.*[10] proposed that the C18 skeleton of podophyllum lignan is derived from two C6C3 molecules followed by a phenolic oxidative coupling process. The coupling involves two phenylpropane precursors with the same 4-hydroxy-3-methoxy substitution pattern and coniferyl alcohol (**21**) may be the intermediate concerned.

Stereospecific enzyme catalysed coupling of free radical mesomers **22, 23** derived from coniferyl alcohol would lead to a diquinone methide **24 [Scheme 3]** and

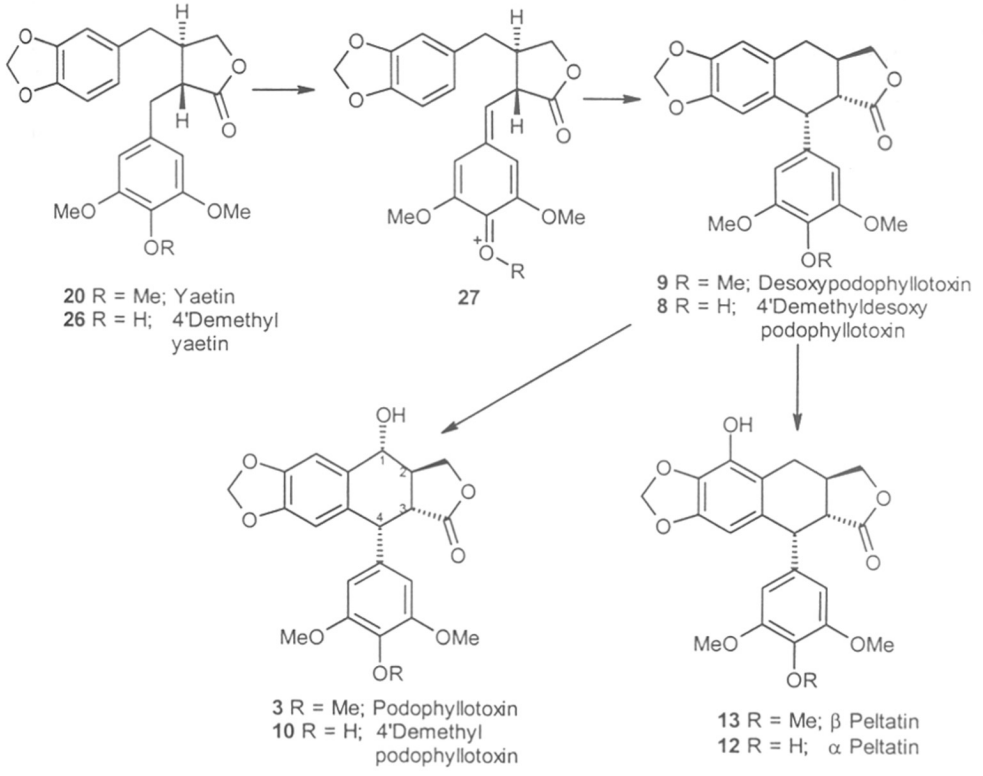


Scheme 3

the dibenzyl butyrolactone yaetin (**20**) and 4' demethyl yaetin (**26**) are persumably produced from this via reduction, lactone ring formation and appropriate modification of the aromatic substitution pattern. Matairesinol (**25**) is likely to be a common

intermediate on the pathway to yaetin (**20**) and 4'demethyl yaetin (**26**) and the probable branch point to the two series of podophyllum lignans

Similarly yaetin (**20**) is efficiently incorporated into podophyllotoxin *via* desoxypodophyllotoxin and a intermediate quinone methide **27** **[Scheme 4]**.

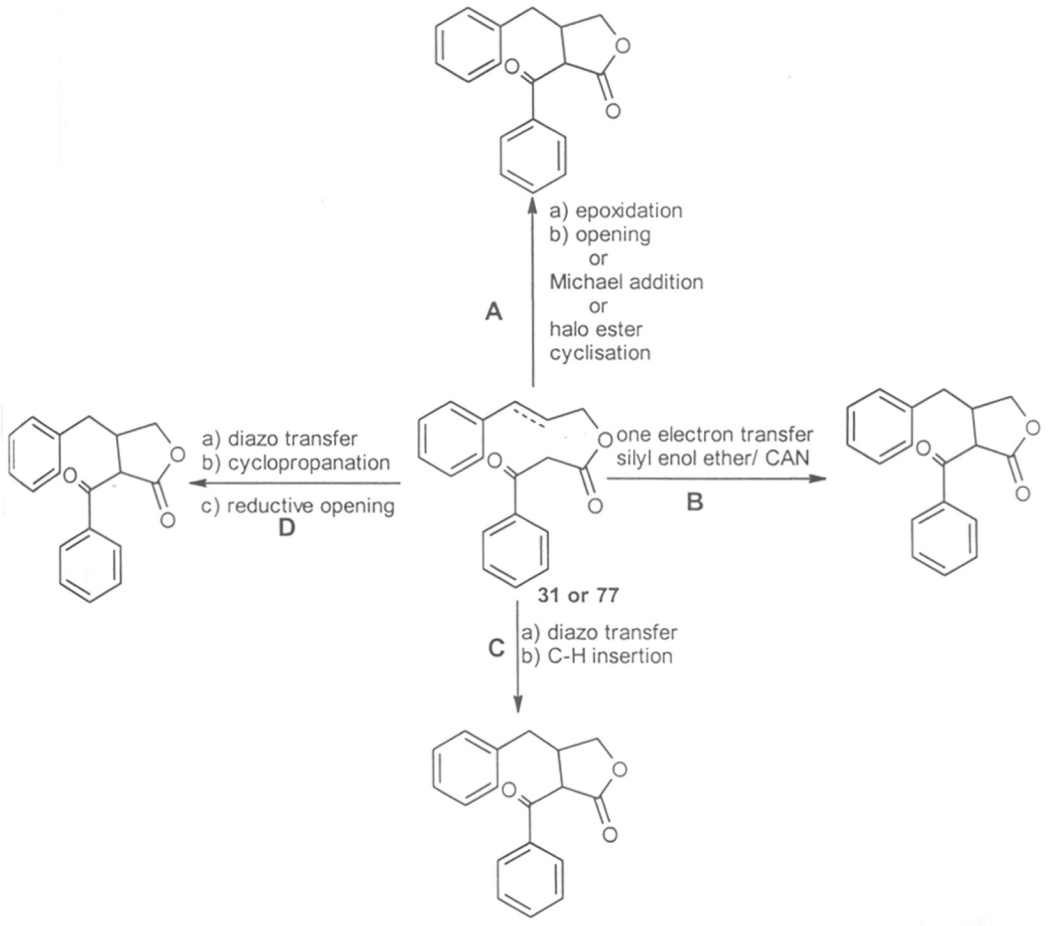


Scheme 4

Gist of present work

This chapter is divided into three main sections. The first section deals with various routes developed for the construction of the lactone ring starting from the β-keto ester **31** as the intermediate for *ionic reactions*. Studies from the application of *radicals* and *radical cations* generated from the intermediate **31** and another intermediate **47** (please see Section B for details and structure) which was prepared from ethylacetoacetate are reported in the second section. The utilisation of various β-keto ester synthons (please see Section C for details and structure) as the carbene precursors for *C-H insertion* and *cyclopropanation reactions* are described in the third section.

Proposed plan of the work



Except for Condition **C** all the three routes are based on (**31**).

Section A

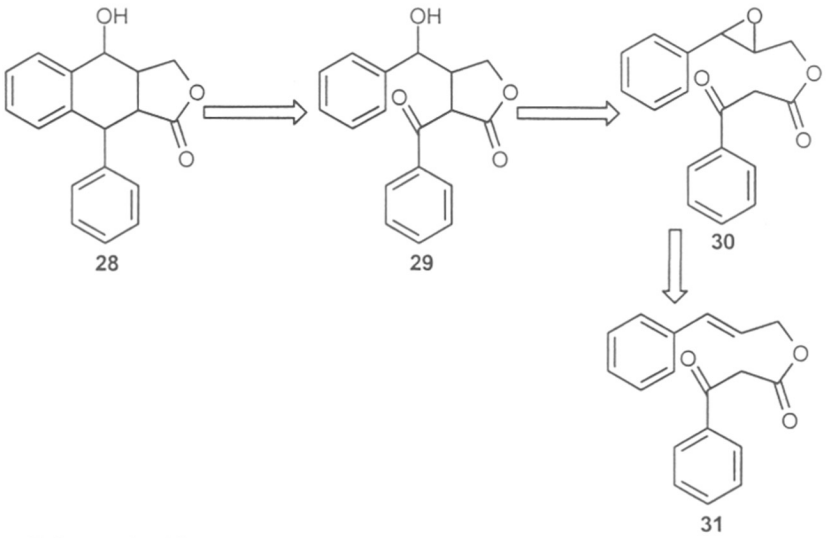
Attempted cyclisation of 3-oxo-3-phenylpropanoic acid, 3-phenyl-2-propenyl ester (E) using ionic methods

This section deals with the various routes based on ionic intermediates envisaged to produce the required lactone moiety as described under gist of proposed work (page 82).

Part I

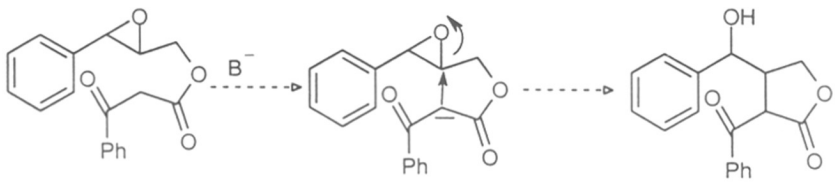
Epoxidation methods

A close look at the intermediate **31** offers several ideas for an easy entry into various aryl tetralin lignan lactones. A probable route to achieve the required lactone can be depicted as



28 **29** **30** **31**

It is worthwhile to note that a regiospecific nucleophilic opening of the epoxide **30** would result in a new synthetic route to aryl tertalin lignans. The use of external nucleophiles to open epoxides are well documented.[13] However, the proposed strategy



3 **Scheme 5** **2**

involves the use of internally generated anion at the methylene carbon which will open up the epoxide to give the required lactone as shown above **[Scheme 5]**. By this method the hydroxyl group required at the C_4 carbon of podophyllotoxin can be efficiently incorporated.

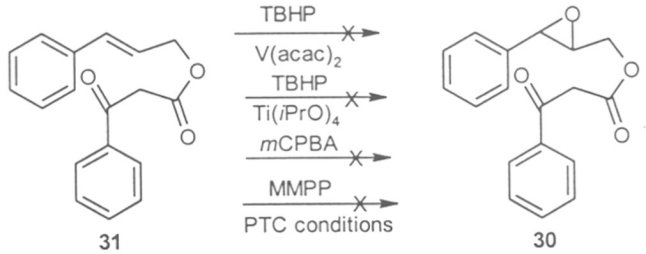
Present work

After successfully developing new synthetic methods for the preparation of various intermediates that are required for the epoxidation studies, the next logical step was to prepare the required epoxides. Here mention may be made on the various methods used for epoxidation. The simple and straight-forward method is the use of $NaOH/Br_2$. However, this method was not attempted owing to the base-sensitivity of **31**. The well-established method developed by Sharpless *et.al.*[14a] utilising *t*-butyl hydroperoxide and $VO(acac)_2$ for epoxidation was then attempted. The initial colourless solution of the β-keto ester turned green after the addition of $VO(acac)_2$; the colour disappeared when the solution reached its reflux temp. When *t*-butyl hydroperoxide was added at a slow rate, the colour of the solution turned brownish red. It was then refluxed for several hrs. However, analysis of the reaction mixture by TLC did not show any change from the original starting material. After usual work-up the compound obtained was found to be identical with the starting β-keto ester **31**.

Attention was then directed to the use of titanium mediated epoxidation procedures.[14b] In this respect, $Ti(iPrO)_4$ was added to DCM at -23°C followed by the addition of diethyl tartarate in DCM. The resultant mixture was stirred at -23°C for 10 min. then the β-keto ester **31** in DCM was added, followed by the addition of dry *t*-butyl hydroperoxide (in toluene). The mixture was kept at –20°C in a freezer for 48 hrs. Quenching the reaction mixture with aqueous tartaric acid after 48 hrs. followed by usual work-up did not yield the required epoxide. The product obtained was found to be identical in all respects with the starting β-keto ester indicating that no reaction had taken place. When *m*-CPBA was used as the epoxidising agent,[14c] the whole of the starting material was consumed but the required epoxide could not be isolated. The analysis by ^1H NMR of the crude product showed that the cinnamyl double bond was intact. It was presumed that, instead of the required epoxidation, a Baeyer-Villiger type oxidation of the carbonyl moiety to the ester could have taken place. From the crude reaction mixture, no pure product could be isolated satisfactorily. This route was therefore not pursued further.

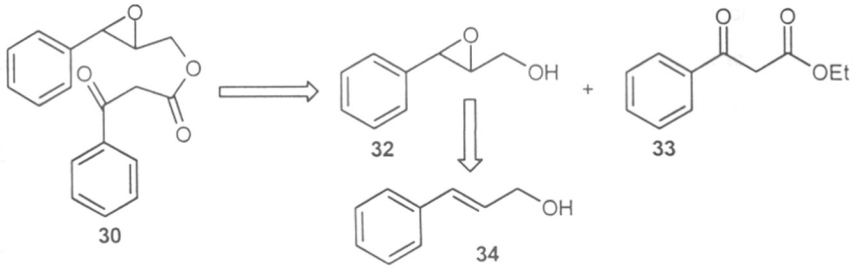
It was then decided to apply biphasic conditions to effect the epoxidation. In this regard the use of magnesium monoperoxy phthalate[14d] was sought. Thus, a solution of magnesium monoperoxy phthalate in H_2O was added over 20 min. to a stirred solution of the β-keto ester in $CHCl_3$ containing methyltrioctyl ammonium chloride (Aliquat® 336). The pH was maintained in the range of 4.5- 5.0 by the addition of aq. NaOH (5%). The mixture was stirred for 12 hrs. at 50 °C, usual work-up followed by purification

yielded only the unreacted β-keto ester **31** in quantitative yield. The various attempted epoxidation methods carried out with **31** can be schematically represented as



Finally, a few heterogeneous conditions employing TS-1[14e] and chromium silicalite[14f] in combination with H_2O_2 or *t*-butyl hydroperoxide were also tried. None of the methods gave the required epoxide. Epoxidation of **31** requires an electron rich double bond for facile reaction. But presence of *aromatic ring may be rendering the required double bond electron deficient, thus preventing epoxidation*. A parallel analogy can be drawn from literature with regard to epoxidation of cinnamyl acetate, which is rather difficult.[15] The use of Cu complex derived from sugar derivatives was used for the formation of epoxide of cinnamyl acetate. However, the yield of the epoxide was very poor. Due to this poor yield, this method was not considered. Thus, none of the direct epoxidation methods could be carried out with **31**.

A different approach comprising epoxidation of cinnamyl alcohol followed by transesterification with ethyl benzoyl acetate was considered next. This retro scheme can be depicted as follows: **[Scheme 6]**



Scheme 6

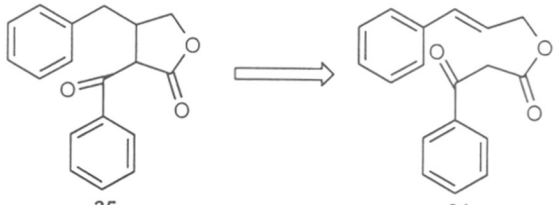
The required epoxide **32** was prepared according to the normal literature procedures employing *m*CPBA.[14c] However, attempts to prepare the required epoxide **30** by the efficient procedure developed by us (see Chapter I Section B Part I) *i.e.* transesterification of the β-keto ester with the epoxide of the allylic alcohol **32** did not meet with success and the required transesterified product could not be accessed. Only one of the starting materials *i.e.*, **33** was recovered. It may be attributed to the high acidic nature of the Hβ catalysts, probably the epoxide formed underwent decomposition and no transesterified product could be isolated.

A few commercially available and treated clays (Kaolinitic and Montmorillonite) are being considered in place of Hβ for the transesterification reaction and work on these lines is in progress.

Part II

Michael addition methods

β-Keto esters can be efficiently alkylated through Michael addition reactions (See Chapter I). Since none of the attempted epoxidation methods were successful, another route employing Michael addition for the construction of the lactone ring was considered. The following retro scheme depicts the proposed plan **[Scheme 7]**.

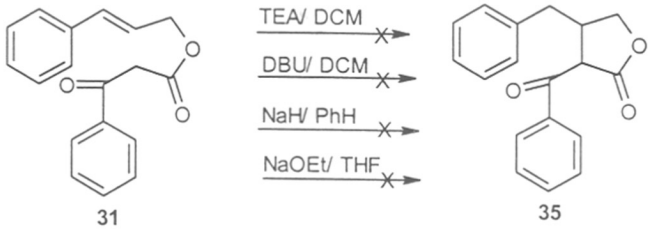


35 Scheme 7 31

As the required intermediate **31** was readily available, a single step operation through Michael addition would furnish the required lactone **35**.

Generally, both intermolecular and intramolecular Michael addition of β-keto esters proceed in good yields. It was therefore considered viable to subject the β-keto ester **31** for an intramolecular Michael addition. Thus **31** was subjected to Michael reaction in the presence of K_2CO_3 as the base. Neither stirring the reaction mixture at room temp. nor refluxing in THF yielded the required cyclic product. Various other bases and conditions that were attempted are depicted below.

Thus all the attempted methods for the construction of the lactone ring through intramolecular Michael reaction were not successful. One of the possible explanations is the high stability of the anion generated from **31**, preventing the required cyclisation reaction.

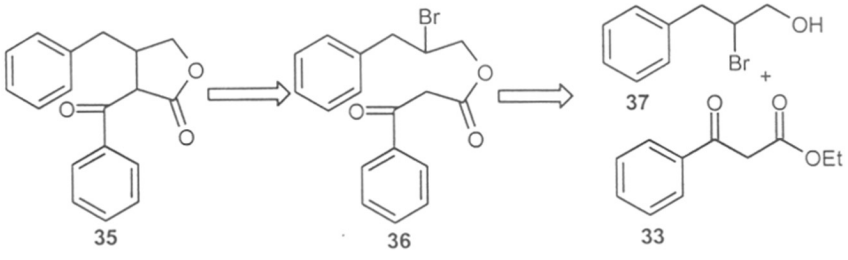


31 35

Part III

Attempted cyclisation of 3-oxo-3-phenyl-propanoic acid 2-bromo-ethyl ester

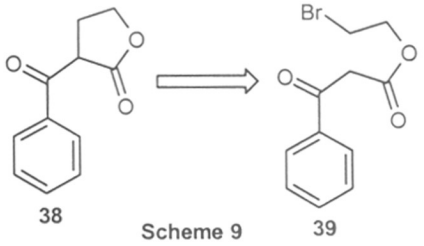
Intramolecular nucleophilic displacement of properly positioned bromine (as present in **36**) would be expected to furnish the required γ lactone **35 [Scheme 8]**.



Scheme 8

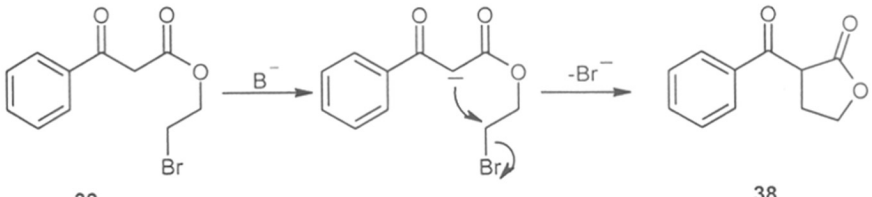
The required bromo ester **36** could be easily prepared by the transesterification of the bromo alcohol **37** with ethyl benzoyl acetate (**33**).

As a model study, cyclisation of the compound **39** was considered. The retro scheme can conveniently be represented as follows **[Scheme 9]**



Scheme 9

The required bromo ester **39** was prepared by the microwave irradiated transesterification method (Chapter I, Section B, Part II). Nucleophilic displacement of bromide *via* internally generated anion, would be expected to give the required lactone (see scheme below)



Scheme 10

The proposed scheme involves the abstraction of the acidic proton by the base as the first step followed by the concomitant removal of bromine atom to furnish the

required γ-lactone. Several bases like TEA, DBU etc. were tried for generation of the anion. However, in both the cases, the β-keto ester **33** was recovered and no cyclisation reaction was observed.

From the above experimental results, it became clear that (i) The nucleophilicity of the bromine is more or less equivalent to the acidity of the methylene proton. In other words both fall equi-distant from neutral behaviour in opposite directions. (ii) Due to delocalisation, the anion formed is highly stabilised. Due to these reasons, none of the attempted methods using the bromo ester **39** could successfully be transformed to the required γ-lactone. It has already been shown that chlorine is a poor nucleophile, (see Chapter I) hence, attempts to cyclise the chloro ester were not carried out.

Section B

Construction of lactone ring employing radical cyclisation methods: Some approaches

In the earlier part of this chapter, the various attempted cyclisations of the intermediate β-keto ester **31** through the generation of an ionic species which were unsuccessful (see Section A) have been described. In this section, reactions involving generation of a methylene radical and cyclisation reactions carried out will be presented.

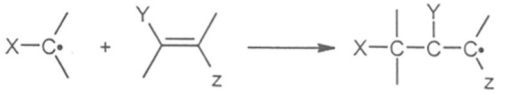
A brief outline of the radical reactions in general, and cation radical cyclisation in particular will help to understand the current study. These are the subject matter of Part I and Part II of this section.

Part I

Free radical reactions in organic chemistry

A facile and efficient method for the formation of C-C bond is the addition of free radicals to alkenes.[16] The rate of addition of alkyl radical to an alkene is controlled by substituents. They can exert polar and steric effects which will decide the product formation.

Schematically a free radical addition reaction can be represented as



X, Y, z = substituents

Y = an α substituent and z = a β substituent

(i) *β substituents present in the alkene exert only polar effects on the rate of addition of free radicals. i.e.* When z = electron withdrawing group, the rate of addition increases. A detailed study reveals that, although phenyl group can stabilise a radical better than a carbonyl group, radical stabilising effects are less important when polar effects are considered.

(ii) *α substituents exert both polar and steric effects on the rate of addition of free radicals.* When a radical approaches the olefin, the rate of addition varies to a marked extent based on the bulkiness at the α carbon (*i.e.* to the carbon where addition takes place).

(iii) Though the α substituents can exert a polar effect on the rate of addition, it is relatively less when compared to the polar effects exerted by β substituents.

During the C-C bond formation the hybridisation changes from sp2 to sp3, due to this, the influence of α substituents on the stability of the alkene is removed. For

example when the rate of addition of a radical to two olefins one of which has Y = Ph and the other with Y = *iso*Pr are considered, in the olefin which has Y = *iso*Pr, due to the bulkiness of *iso*Pr group, addition is retarded.

Effects of radical substituents

Radical substituents exert both polar and steric effects. When the number of alkyl group increases, stability of the radical also increases but the stability of the newly formed 's' bond decreases. Therefore, the alkyl and alkoxy substituents on the radical carbon increase its reactivity in the addition of electron deficient alkenes. It should be noted that reactivity and selectivity are influenced in the same way by the substituents. A phenyl group generally decreases the rate of addition. Due to the mesomeric stabilising effect of a phenyl group, benzyl radicals undergo proton abstraction readily rather than addition to a double bond.

Regioselectivity

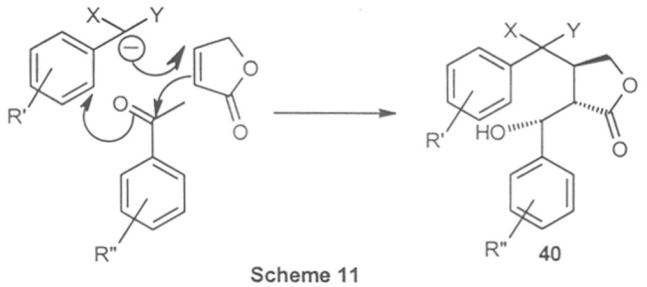
Regioselectivity in radical cyclisation reactions is mainly determined by the steric effects, though a few reports mention that the favoured addition is at the less substituted vinylic carbon in terms of difference in the stability of the newly formed radical. As it has already been explained, the stability of the radical plays a minor role only. On the grounds of steric effects, the regioselectivity changes on proceeding from H via Me, Et, *iso*-Pr, *t*-Bu.

Stereoselectivity

When the two lobes of the orbitals containing the p-electrons in radical or alkene are shielded to different levels, stereoselectivity arises. This is similar to the steric effects on the rate of addition in reactions.

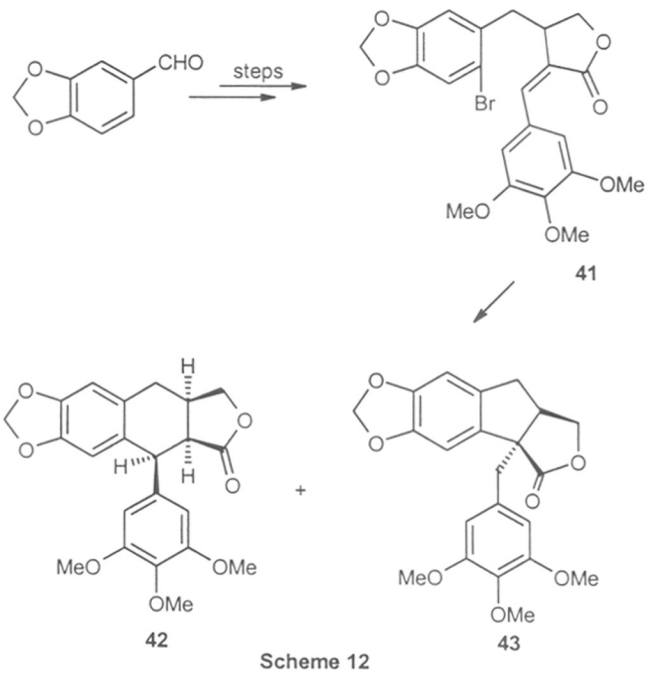
Objective of the present work

A reported synthesis, based on a tandem process that consists of successive treatment of benzylic anions with γ-crotonolactone and then with aldehydes for the formation of aryl tetralin lignan lactones,[17a] has a disadvantage. The aromatic cyclisation of the intermediate **40** leads to 1,2 *trans* configuration rather than 1,2 *cis* configuration which is a requisite for aryl lignan lactones (see **Scheme 11**)



Scheme 11

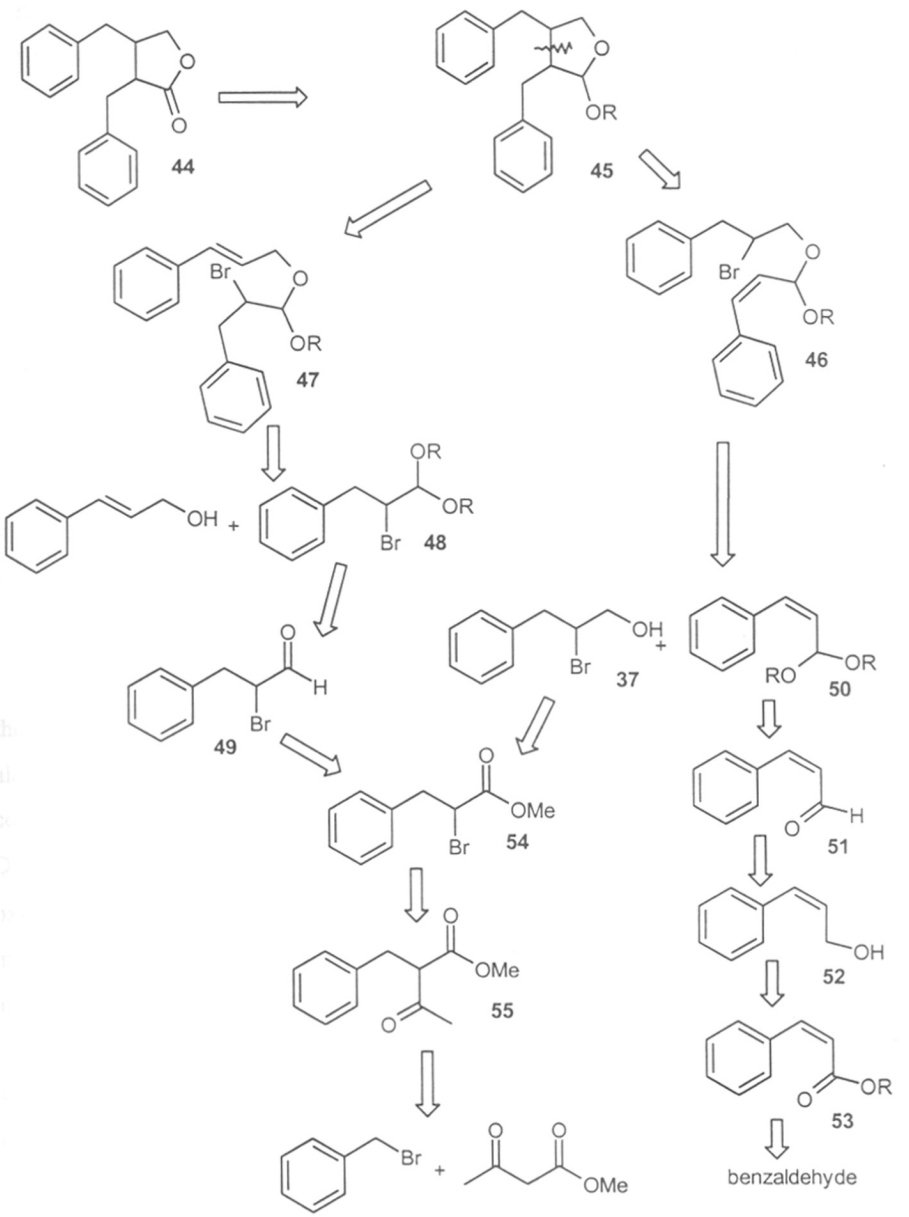
To overcome the problem described above, Ishibashi *et.al.*[17b] have developed a radical cyclisation approach. Starting from piperonal, the intermediate **41** required for free radical cyclisation was prepared in 9 steps. An important draw back of this method is the competitive 5-*exo* cyclisation [furnishing **43**] which cannot be suppressed. The schematic route is shown below. **[Scheme 12]**.



Scheme 12

It was therefore necessary to develop a convenient method, where the possibility of 5-*exo* trig cyclisation can be avoided. In order to develop an efficient method for the construction of the γ lactone moiety present in the various lignan lactones, a radical cyclisation method was considered in the present work. The following scheme outlines the proposed plan **[Scheme 13]**.

Free radical cyclisation of either **46** or **47** would yield the required lactol **45** which can be hydrolysed and oxidised to the γ-lactone **44**. A significant advantage of this method is that it leads to a single 5-*exo* trig cyclisation product and avoids any other competing cyclisation reactions.

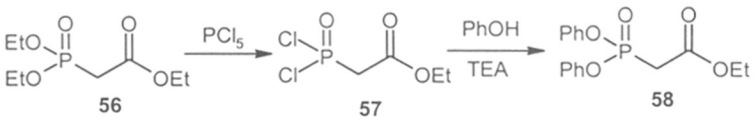


Scheme 13

A retro synthetic scheme **[Scheme 13]** reveals clearly that the intermediates **46** and **47** can be obtained via transacetalisation.

Work for both the routes was initiated simultaneously. It is well documented in literature that a *tandem cyclisation process leading to the required tricyclic frame work cannot be formulated owing to the poor reactivity of the unsubstituted benzylic radical.*

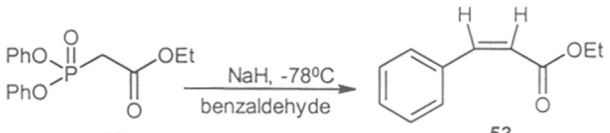
The Z selective olefination of benzaldehyde was achieved using the efficient method developed by Ando.[18] The required phosphono ester **58** was prepared in three steps starting from triethylphosphonoacetate **56** as outlined below **[Scheme 14]**.



56 57 58

Scheme 14

Compound **58** was then treated with NaH at -78°C and and then condensed with benzaldehyde (Horner- Emmons reaction) to give Z- ethyl cinnamate in 90 % yield with >95 % selectivity **[Scheme 15]**.



58 53

Scheme 15

Generally, DIBAL H (1 equivalent) at -78°C reduces esters to aldehydes. But in the case of α,β unsaturated esters, DIBAL H reduction gives the corresponding allyl alcohol only.[19] Due to this reason, the ester **53** could not be directly reduced to the corresponding aldehyde **51**. However, it was reduced to the Z-cinnamyl alcohol using DIBAL H (2 equivalent) at -78°C. The Z-cinnamyl alcohol (**52**) thus obtained was oxidised with PCC[20] to afford the required α,β unsaturated aldehyde **53**. But, various methods employed like trimethylorthoformate/pTSA[21] etc. for the protection of this aldehyde were unsuccessful. Due to this, work in this direction was not pursued further.

The required bromo alcohol **37** was prepared from the bromo ester by DIBAL H reduction[19] and not *via* LAH reduction, as with the latter, the reduction is always accompanied by dehalogenation.[22]

In the other route, the required substituted β-keto ester **55** was prepared by the benzylation of methylacetoacetate using NaH as the base.[23] Selective bromination of the latter with NaH/ Br_2 followed by deacylation with anhyd. $Ba(OH)_2$ furnished **54**. For the

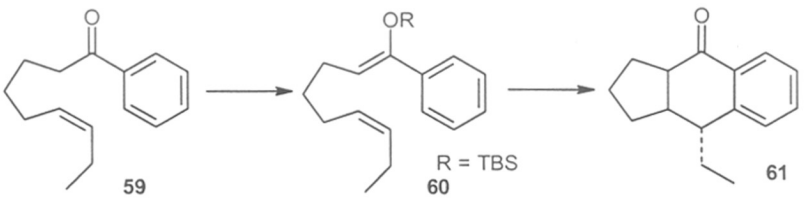
deacylation to proceed selectively, control of reaction temp. and reaction time was very crucial. The bromo ester **54** was then subjected to DIBAL H reduction at -78°C to yield the bromo aldehyde **49**. Acetalation in the presence of trimethylorthoformate gave the required protected aldehyde **48**. When the compound **48** was subjected to transacetalation[24] using cinnamyl alcohol, only 15 % of the required mono acetalated product **47** was obtained. The rest was found to be a mixture of diacetalated product and deprotected product. Efforts to optimise the conditions in order to obtain more of **47** were unsuccessful. Hence, this route was also abandoned.

Part II

Cation radical cyclisation of unsaturated silyl enol ethers

Introduction

Before going into the actual work, it is appropriate to mention the pioneering work by Snider and Kwon.[25] The oxidative cyclisation of δ,ε unsaturated ketones studied by Snider is schematically shown below **[Scheme 15]**.

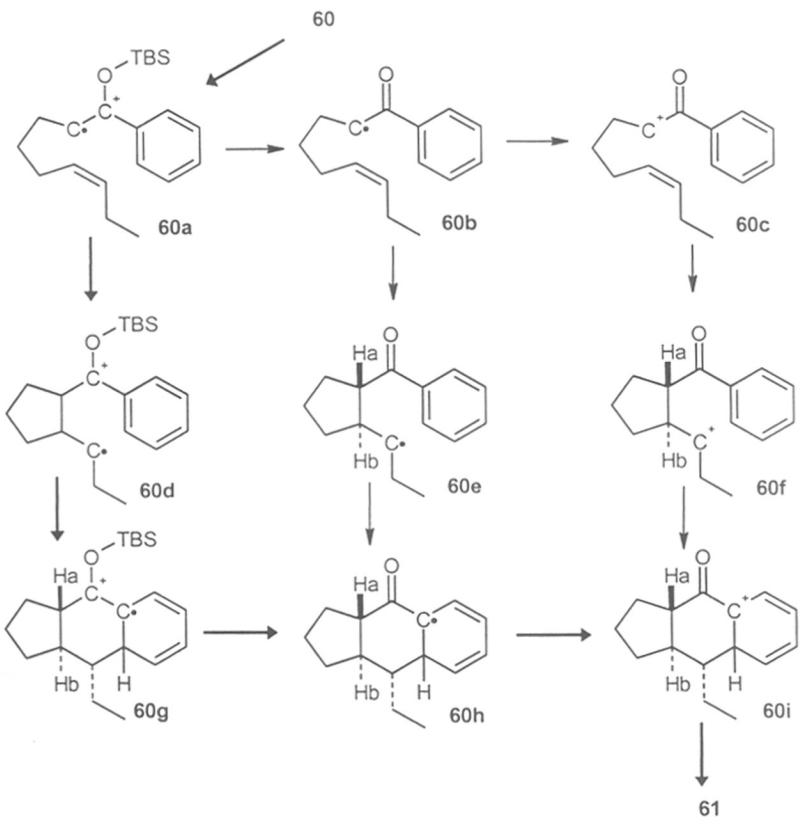


Scheme 15

The basic concepts that are considered in this cyclisation include: (i) the use of phenyl ketone has few advantages like, only one regioisomeric enol will be formed (ii) the phenyl group may act as a trap for the monocyclic intermediate (iii) the chain length was chosen to facilitate 5 *exo* trig radical cyclisation. The proposed mechanism involves 6 discrete steps. Two one electron oxidations, two cyclisations, loss of proton as well as silyl group.

First step is probably the one electron oxidation of **60** to cation radical **60a**. Loss of silyl group from the cation radical **60a** would yield the radical **60b**. The latter then undergoes one electron oxidation of radical to enol cation **60c**. Each of these *i.e.*, **60a, 60b, 60c** can cyclise to give cation radical **60d** or radical **60e** or cation **60f** respectively. The formation of **60b** and **60c** are ruled out on the basis that their presence may favour 6-*endo* trig cyclisations. Since only a five membered product was obtained, the reaction proceeds through intermediate **60a**, which only can favour a 5-*exo* trig radical cyclisation. It is therefore clear that a cation radical which is formed by one electron oxidation of silyl enol ethers can be trapped to form cyclopentane ring formation. There

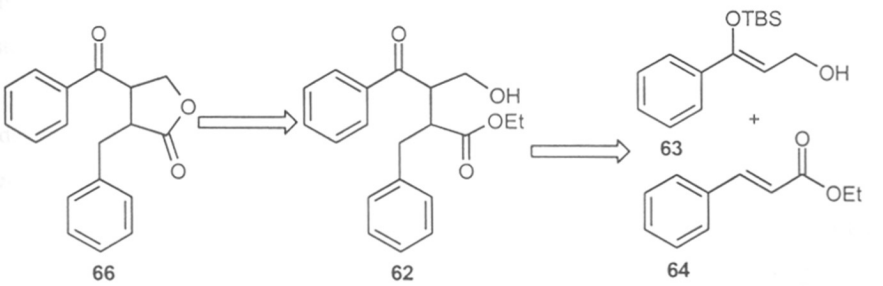
are also three distinct possibilities for the second cyclisation to form the tetralone ring. Since the possibility of radical **60e** and cation **60f** intermediates are ruled, out here also the cation radical leads to the cyclic product which loses the silyl group **60h**, undergoes oxidation **60i** and finally deprotonation leading to the observed product **61**.



Objective of the present work

A thorough literature survey revealed that application of the efficient methodology described above for the formation of γ-lactones has not been attempted. The ring strain and hybridisation of the orbitals of the reactants and products should be taken into consideration before applying this method for the formation of γ-lactones.

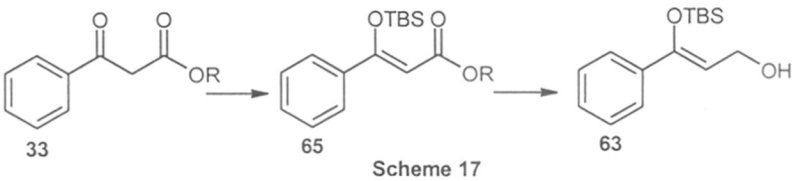
In this regard, it was decided first to apply an intermolecular cyclisation approach as depicted below **[Scheme 16]**.



Scheme 16

Present work

The retro scheme 16 may serve as alternative to fulfil the quest to construct the γ-lactone moiety. It can be rationalised from the above scheme that the required intermolecular radical cation mediated cyclisation would lead to **62** which can be further elaborated to the required γ-lactone **66**. The protected alcohol **63** was thus prepared according to the scheme given below **[Scheme 17]**.



Scheme 17

β-Keto ester **33** was protected as its TBS enol ether with TBDMSOTf.[26] Treatment of β-keto ester in the presence of TEA at 0°C afforded the silyl enol ether **65**. LAH reduction of this unsaturated ester did not yield the required allyl alcohol **63**.[27a] Later, the reduction of **65** using DIBAL H (0°C, 2 equi.) then provided the required allylic alcohol **63** in more than 90 % yield. Reduction with DIBAL H at ambient temp. led to decomposition of the OTBS protection.[27b] It was thus found necessary to carry out the reduction at 0°C. After the successful preparation of the required allylic alcohol, now the stage was set for the crucial intermolecular cyclisation.

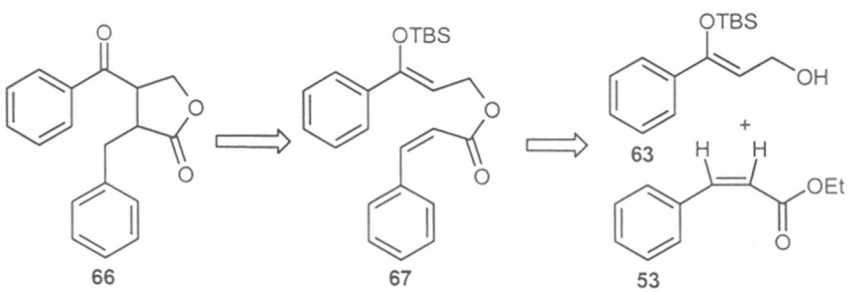
Alcohol **63** in MeCN was added slowly over a period of 3 hrs. to a well stirred solution containing CAN, ethyl cinnamate and $NaHCO_3$. After the addition was over, the reaction was stirred for 6 hrs. at room temp. Analysis of the reaction mixture revealed a slower moving spot (TLC). After the complete disappearance of the starting material, (TLC was performed by taking out aliquots and quenching the reaction with NH_4Cl and extracting it in Et_2O) the reaction was quenched with NH_4Cl and diluted with Et_2O and the usual work-up provided a clean product besides some quantity of

ethyl cinnamate. Analysis of the product revealed that it is the deprotected alcohol, *i.e.* instead of cyclisation, only deprotection had occurred.

Due to the fact that the silyl enol ether underwent cleavage and not cyclisation, understanding the rationale behind this was sought. Is it the steric crowding in the transition-state which plays a vital role in preventing intermolecular cyclisation? Because in the E-ethyl cinnamate, the bulky phenyl group that is present at the β carbon may be hindering the attack of the radical. To avoid such a steric crowding in the transition-state, Z-ethyl cinnamate was considered.

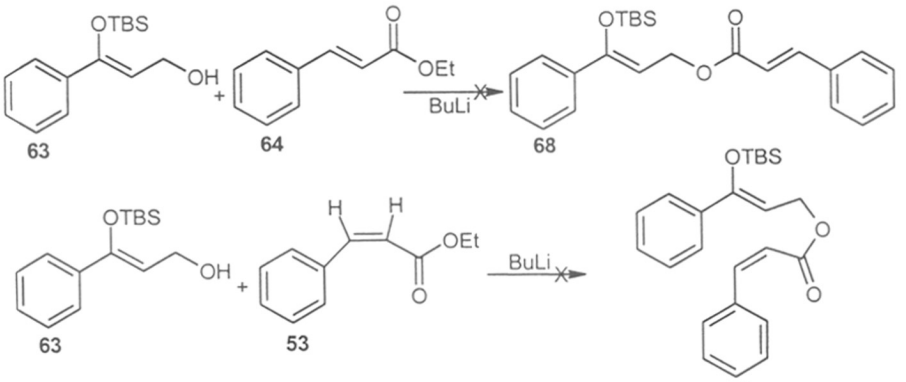
The required Z-ethyl cinnamate (**53**) can be prepared from benzaldehyde. Following known procedure, the substituted phosphono ester was prepared from triethylphosphonoacetate and the Horner-Emmons reaction was carried out using **58** as shown previously **[Scheme 14, 15]**.

Now the protected alcohol **63** was subjected to the intermolecular cyclisation with Z-ethyl cinnamate (**53**). However, this time too, no effective cyclisation took place. Even after this modification, the result obtained was not encouraging. As intramolecular cyclisations are more efficient than their counterpart, attention was focused on the preparation of an intermediate which can be used for the construction of the γ lactone moiety **[Scheme 18]**.



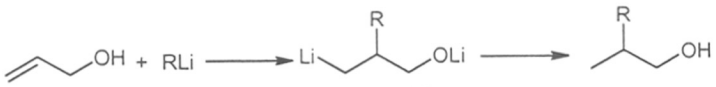
Scheme 18

Transesterification of **63** with **53** would provide the intermediate **67**, which can then be subjected to the intramolecular cyclisation. Generally, transesterification reaction requires acidic conditions. Since one of the substrate **63** contained acid sensitive functionality, (silyl enol ether) none of the acid catalysed conditions were considered. It is well known that transesterification can also be performed under basic conditions (base catalysis).[28] A thorough literature survey revealed that n-BuLi has been employed as a base in the transesterification of ethyl cinnamate. Attempted transesterification of both E and Z ethyl cinnamates with the allyl alcohol **63** did not meet with success **[Scheme 19]**.



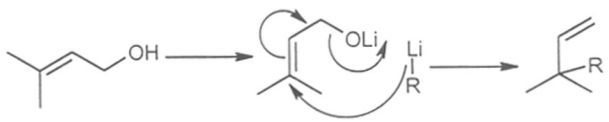
Scheme 19

Only the ethyl cinnamates were recovered and no trace of the allyl alcohol **63** was found. This result prompted a thorough literature survey in order to study the stability of silyl enol ether in the presence of n-BuLi and also to study the lithiation of allyl alcohols. It was found that lithiation of allylic alcohol led to a complex thereby preventing the transesterification. Generally allylic alcohols when treated with organo lithium reagents in hydrocarbon solvents produce the corresponding 2-substituted propanols **[Scheme 20]**.[29]



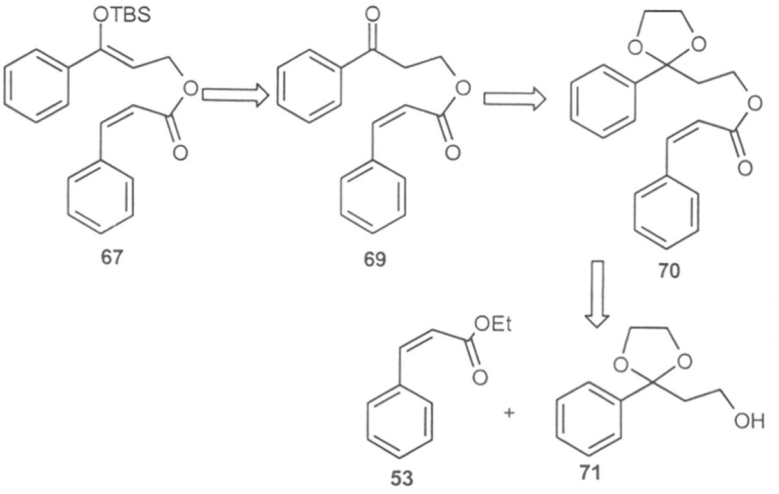
Scheme 20

However γ substituted allylic alcohols cannot generate a primary organo lithium adduct in this manner. But a cyclic intermediate may lead to γ alkylation **[Scheme 21]**.



Scheme 21

With this unsuccessful set of results, an alternate route was sought in which the allylic alcohol moiety was avoided. A retro-scheme is furnished below **[Scheme 22]**.

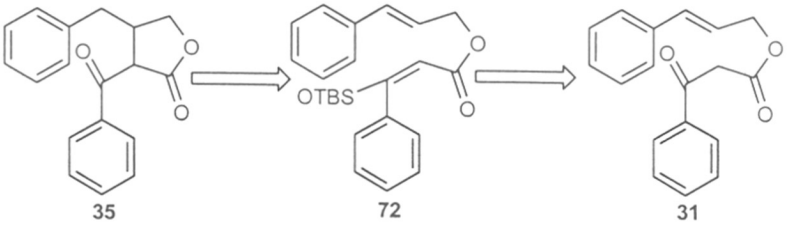


Scheme 22

Transesterification of **71** with **53** would lead to the protected ester **70**. Deprotection of the ketal **70** with oxalic acid would afford the ketoester **69**, which could be protected as the silyl enol ether using standard protocol.[30] The compound **67** is now set to undergo intramolecular cyclisation reaction.

In this regard, preparation of **71** was envisaged. The ketone moiety in the β-keto ester **37** was protected as its ketal using ethylene glycol in the presence of camphor 10 sulphonic acid as the catalyst. LAH reduction furnished the required hydroxy ketal **71**. However, transesterification of **71** with **53** did not yield the desired transesterified product. Only the starting materials were recovered quantitatively. Reluctantly, this route had to be abandoned.

However, the urge to evolve a solution to achieve the goal still remained insatiable. Intramolecular cyclisation of the intermediate β-keto ester itself was considered next and the proposed scheme is as follows.



Scheme 23

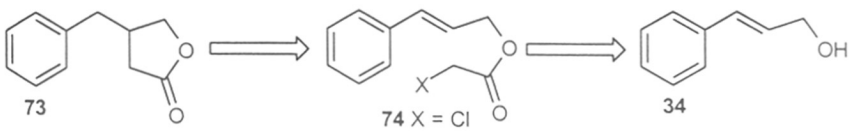
An efficient method for the preparation of β-keto ester of the type **31** has already been developed (Chapter I). The silyl enol ether **72** was obtained from **31** *via* standard

procedure. CAN assisted cyclisation of **72** was then attempted. Thus, silyl enol ether **72** in MeCN was added slowly over a period of 3 hrs. to a well stirred solution containing CAN and $NaHCO_3$. After the addition was over, the reaction was stirred for 6 hrs. at room temp. Analysis of the reaction mixture showed a slower moving spot. After the complete disappearance of the starting material (TLC was performed by taking out aliquots and quenching the reaction with NH_4Cl and extracting it in Et_2O), the reaction was quenched and diluted with Et_2O and the usual work-up was carried out. Analysis of the reaction mixture showed the presence of β-keto ester **31** only and no cyclised product **35** as expected was formed. Cyclisation of **72** using various conditions[31a,b] (*vide experimental*) were also performed. Except with $PdCl_2$ as the reagent, other conditions furnished the β-keto ester **31** only. When $PdCl_2$ was used neither deprotection nor cyclisation was observed. Thus, one could conclude that the cinnamyl double bond is probably not sufficiently electron rich to facilitate the required cation-radical cyclisation.

Part III

Attempted photo-chemical cyclisation of α halo esters

Various unsuccessful methods described in Part I and Part II of this section for the generation of C2 radical by chemical means and trapping it by cinnamyl double bond to give the required γ-lactone necessiated evolution of other routes to achieve the required cyclisation. One such route is the photochemical approach. Homolytic cleavage of C-X bond to produce radical is well documented.[32] In accordance with this well-established fact, a retro synthetic approach to construct the γ-lactone can be considered **[Scheme 24]**.



Scheme 24

After preparing the required halo compounds **74, 75** photochemical cyclisation (at 254 nm using Hanovia lamp) of the chloro ester **74** was performed. Upon homolytic scission, a chloro radical will be generated, which will abstract a proton from the solvent (methanol) to produce HCl; a good acid scavenger is therefore required to minimise the presence of the corresponding acid. For this purpose propelene oxide was used. However, the expected cyclisation did not proceed and deprotection with 15-20 %

cis-trans isomerisation of the double bond took place to give cinnamyl alcohol. Later, Zn wool was considered as the acid scavenger. The main advantage of using Zn wool is, the easy separation of the acid scavenger. When Zn wool was used a clean reaction took place. But the product was found to be cinnamyl alcohol (**34**) and not the required γ lactone. The dark reaction (performed in the absence of light) also furnished the deprotected compound. From the above experimental results, it became clear that Zn has facilitated the deprotection of chloro acetyl group.

It can be recollected from Chapter I Section B Part I that a facile deprotection of chloroacetyl group was reported. When these two results were compared, it was found that two mild and efficient methods for the deprotection of chloroacetyl group have been developed. Reported procedures employing thiourea[33] or HDTC[34] (hydrazine dithio carbonate) for the deprotection of chloroacetyl group have several limitations. They are expensive, toxic, difficult to handle etc. Moreover, HDTC is unstable. It undergoes rapid breakdown to *obnoxious* hydrogen sulphide and isothiocyanate which in turn polymerises. Work on the extension of this mild and simple procedure for the selective deprotection of chloroacetyl group is in progress. Though the exact mechanism of deprotection is still not clear at this preliminary stage, it is believed that coordination from the Zn metal to the chlorine facilitates the deprotection. If the methodology developed is explored further, it will find excellent applications in the carbohydrate field, where selective deprotection is always a challenging task.

Though the main aim of using a halo ester for free radical cyclisation was not successful, it has opened up an altogether different rewarding route to pursue further research.

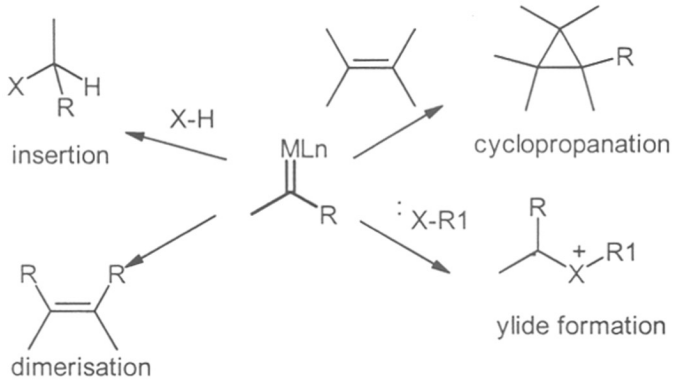
Section C

Studies on the application of carbene intermediates for the construction of lactone ring

Part I C-H insertion reactions

Introduction

As mentioned in the earlier part of this chapter, neither ionic nor radical intermediates generated from β-keto ester **31** could be transformed into γ-lactone. Attention was directed towards utilisation of carbene type intermediates for this purpose. Due to the versatile utility of catalytic methods for the generation of metallo carbenes,[35] several schemes have been reported for the synthesis of various natural products.[36] In this regard α diazo β-keto esters have attracted considerable attention during the past few years.



Typical reactions of metallocarbenes. R = alkyl, aryl, carbonyl.

Insertion reactions of carbene into unactivated C-H bond was first discovered by Werner *et.al.*[37] Due to the fact that intermolecular C-H insertions are not selective and are also synthetically less useful, intramolecular C-H insertion reactions have attracted wide attention with promising results. The regioselectivity in intramolecular C-H insertion depends on the type of the diazo function, degree of substitution at the carbon where the insertion occurs, steric and electronic factors *etc.*

Intramolecular C-H insertion reactions are widely used in the formation of cyclic systems where the carbon at which the insertion takes place, can even be an unfunctionalised carbon. C-H insertion leading to carbocyclic[38a] and heterocyclic rings[38b] are well documented. Based on their studies Taber *et.al.* demonstrated that the

formation of 5 membered ring is the preferred one and electronic, steric and conformational factors could influence the site selectivity.

Electronic effects[39]

Methine > methylene > methyl

It is observed that the methine carbon is more reactive either for insertion or for elimination than a methylene carbon which in turn is more reactive than a methyl carbon. A detailed study of α-diazo β-keto ester by Taber *et.al.* has been reported in this regard. Generally methyl carbons are not at all the preferred sites for insertion. In the case of metal bound carbenes (generated using $Rh_2(OAc)_4$), insertion into allylic or benzylic methylenes is disfavoured when compared to insertion into aliphatic methylenes. The alkyl groups are inductively electron donating, resulting in increase in the electron density at the C-H bond, making it more susceptible to be attacked by the electrophilic Rh-carbene species. Vinyl and phenyl groups are inductively electron withdrawing and decrease the reactivity of the adjacent C-H bond.

Intermolecular reactions are synthetically less useful, as they demonstrate poor selectivity along with the competing intramolecular insertion reactions. Intermolecular aryl insertions generally predominate over aliphatic insertions. Selective aryl insertion may occur owing to the fact that initial coordination of the rhodium complex with π system of arene is possible whereas in the case of aliphatic intermolecular reactions, such pre-coordination is not possible.

Steric effects

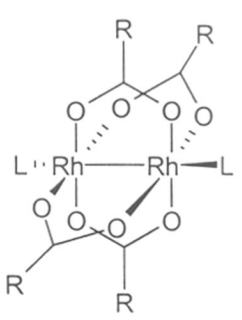
When electronic effects are nearly equal, steric effects play a vital role in insertion reactions. On the basis of vander Waals interactions between the bulky groups and the ligand on the rhodium, insertion into carbons α to bulky groups is disfavoured. Moreover, the steric effects on the C-H insertion is less addressed. A detailed study would throw some light on this important, yet under-developed area.

Effect of ligands[35a]

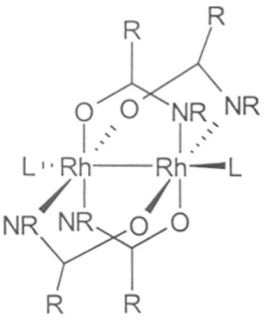
Generally, catalysts that are available can be broadly divided into two categories: (i) carboxylates (ii) carboxamides. In order to understand the structure and formation of the catalyst, knowledge of the coordination on Rh metal is vital.

Out of the entire group of Rh complexes that are available, Rh (II) was found to be the efficient catalyst for diazo decomposition. Rh (II) is a d^7 transition metal and due to its tendency to form Rh-Rh metal bond, Rh (II) complexes are present as dimers. In

the case of carboxylates and carboxamides, the ligands can be categorised as bridging ligands or axial ligands. These structures can be represented as:



Carboxylates



Carboxamides

The axial ligand forms a much weaker bond with Rh metal than the bridging ligand. The axial ligand can easily be removed by photolysis or by heating in vacuum. In the catalytic diazo decomposition, it is believed that the axial positions are the sites of binding the carbene centres and therefore the axial ligands are usually absent. Depending on the bridging ligand the Rh-Rh distance varies, which in turn may be partially responsible for the reactivity of the carbenoid species. The electron donating trimethyl acetate ligand shortens the Rh-Rh metal bond while electron withdrawing trifluoro acetate ligand has the opposite effect. The effect of this variation in metal bond distance can be clearly seen from the product distribution of Rh catalysed diazo decomposition reactions (please see **Table I**).

A knowledge of the effect of ligand, electronic and steric factors governing rhodium catalysed decomposition of diazo compounds may assist in appreciating the usefulness of these type of reactive intermediates as versatile synthons in organic synthesis and in the syntheses of various natural products. The important points to note are

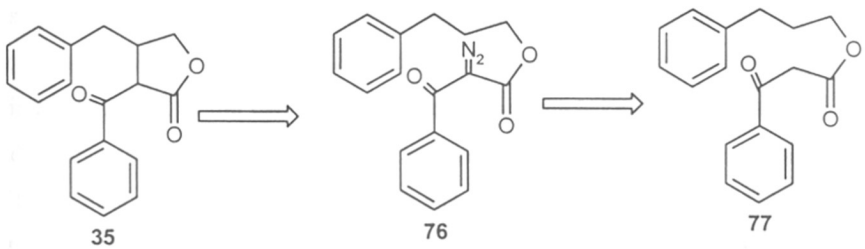
- Strong electron withdrawing groups on the ligand favour β hydride elimination
- Strong electron donating groups on the ligand favour 1,5 insertion
- β hydride elimination is entropically less demanding
- C-H insertion occurs with retention in configuration
- Carboxylate and carboxamides are electrophilic in nature
- In the case of selectivity, fluorinated ligands fall in one extreme of the scale and acetamide/caprolactam fall in the other extreme
- There is always a balance between steric and electronic effect operative on the product formation

- Electron donating groups activate adjacent C-H bonds for C-H insertion

Till date, the exploitation of steric effects for site selective C-H insertion is very limited. A detailed study would be helpful in better understanding of this area which is still at a nascent stage.

Objective of the present study

When the present work was initiated in 1995, application of diazo decomposition of α-diazo β-keto esters for the formation of γ-lactones had not attracted much attention and was a relatively new field of study. Though scattered examples were available in the literature, none of them were successfully applied to synthesise various aryl tetralin lignan lactones. In order to develop a much simpler and efficient method for the formation of various lignan lactones, the following retro scheme was proposed **[Scheme 25]**.



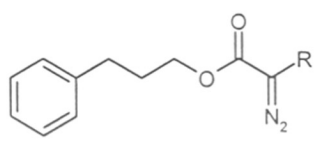
35 **76** **77**

Scheme 25

Present work

A closer look into the detailed studies of Doyle's[35b] work provides an insight into understanding the various parameters governing the C-H insertion reactions leading to γ-lactone formation. The competitive reactions studied included insertion of tertiary C-H vs primary C-H, tertiary C-H vs secondary C-H, primary C-H vs secondary C-H and primary C-H vs benzylic C-H. However, an important aspect of these studies was that, none of the reactions reported by Doyle contained a site for β-lactone formation.

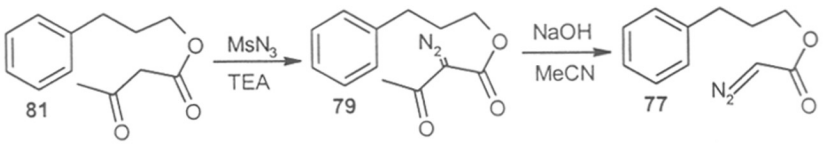
As a preliminary step towards achieving the goal of γ-lactone formation, a model study with simple systems was undertaken. The various compounds considered are given below.



78 R = H
79 R = OCH_3
80 R = CH_3CO
76 R = PhCO

When R = H, 78

In Chapter I it was stated that preparation of this kind of diazo ester **78** was not easy. However, after the successful preparation of various β-keto esters by transesterification (Section B, Chapter I), preparation of the required diazo ester was achieved by the following sequence of reactions, employing the same technique of transesterification **[Scheme 26]**.

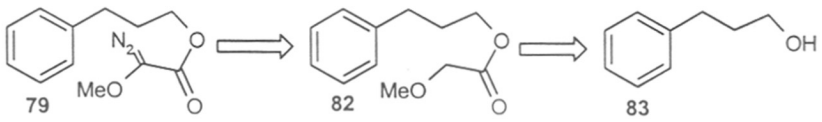


Scheme 26

Compound **81** was prepared according to the procedure developed and reported in Chapter I. The diazo transfer to the β-keto ester was successfully carried out with MsN_3.[40] The required deacylation was performed with NaOH in MeCN.[41] With the required diazo ester **78** in hand, two conditions were considered for cyclisation reaction using $Rh_2(OAc)_4$ as the catalyst (one reaction in which DCM was used as the solvent and another reaction where the solvent was benzene). It is important to note that the fate of the metallocarbene is not very much altered by varying the solvent. Thus, the diazo ester **78** was subjected to the normal cyclisation procedure described as follows. The diazo compound (200 mg in 5 ml DCM) was added at a rate of 0.5 ml/hr. to a refluxing solution of the catalyst ($Rh_2(OAc)_4$ 2 mol % in 10 ml DCM). After the completion of the reaction, the catalyst was removed by filtration through celite. When DCM was used as the solvent only fumarates and maleates were obtained and no cyclic product could be isolated. In benzene, the product isolated was solvent insertion product. *i.e. Buchner reaction* product[42] and here also formation of the required product was not observed.

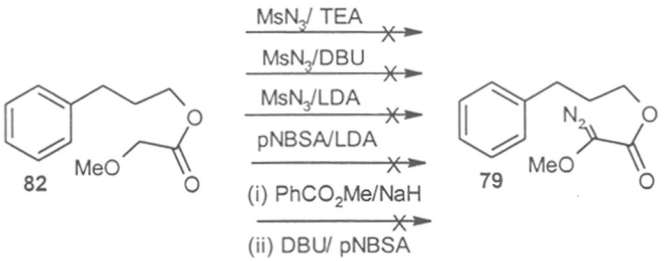
When R = OCH_3, 79

It was debated that, if the stability of the metallo carbene is increased, whether the expected cyclisation will occur?. To find out the answer, the replacement of H with an electron donating group, OMe was considered. In this regard, a simple route involving esterification of methoxy acetic acid by 3-phenylpropan-1-ol followed by diazo transfer was found to be a suitable method. The retro scheme can be represented as follows **[Scheme 27]**.



Scheme 27

The required ester **82** was obtained by the esterification of methoxy acetyl chloride which in turn was prepared from methoxy acetic acid. The stage was now set for the diazo transfer. The normal diazo transfer using MsN_3/TEA and MsN_3/DBU[43] did not proceed to give the expected diazo ester. Since the α methylene group was not sufficiently active, diazo transfer probably did not take place. In this respect, a method that is generally employed for the preparation of diazo esters from this kind of unactivated esters was undertaken. Diazo transfer using MsN_3 or pNBSA to the ester enolate generated with the help of LDA[44] was also unsuccessful. Even the strategy benzoylation, followed by diazo transfer developed by Taber *et.al.*[45] did not provide the required diazo ester.



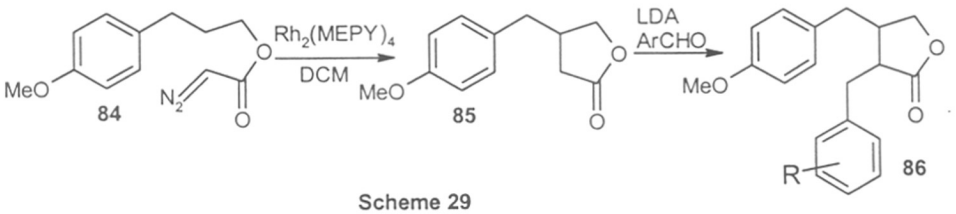
Scheme 28

Thus all attempts to prepare the required diazo ester were unsuccessful. Therefore further study using this type of compounds could not be continued.

When R = $COCH_3$, 80

This compound was prepared by the method outlined previously (Chapter I). The diazo transfer of the β-keto ester **81** was achieved as usual with MsN_3. This diazo ester was subjected to normal cyclisation procedure. Thus, the diazo compound (200 mg in 5 ml DCM) was added at a rate of 0.5 ml/hr. to a refluxing solution of the catalyst ($Rh_2(OAc)_4$ 2 mol % in 10 ml DCM). After the completion of the reaction, the catalyst was removed by filtration through a plug of celite. Purification of the crude material produced the required γ-lactone. Thus, for the first time the required lactone was obtained successfully. Cyclisation of the crucial intermediate **76** was the next obvious target to be looked for.

When the present work was in progress, a similar report as mentioned in the following scheme was published by Doyle *et.al.*[36a] In his approach, Doyle had constructed the lactone ring by C-H insertion followed by alkylation in the presence of a strong base like LDA **[Scheme 29]**.



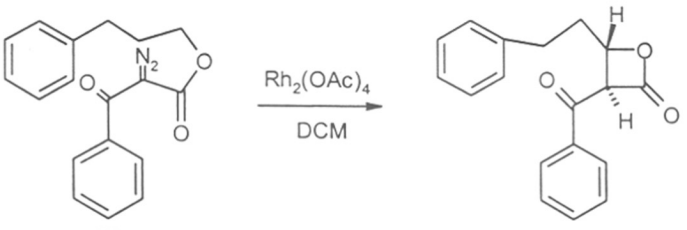
Scheme 29

Additionally, Doyle achieved this reaction with the chiral catalyst $Rh_2(MEPY)_4$. Further, Doyle has mentioned in his report that, the above cyclisation did not proceed when $Rh_2(OAc)_4$ was used as the catalyst. Several difficulties were encountered in the preparation of the chiral catalyst utilised by Doyle. For example, Doyle prepared $Rh_2(MEPY)_4$ by the ligand exchange procedure (exchange requires 6 days) followed by purification on special grade μ Bonda pack HPLC grade silica.[46] This special preparation procedure limits the general use of this type of catalysts. Although $Rh_2(MEPY)_4$ is also available commercially (Aldrich), its price is exorbitant which prevents purchase of this catalyst. According to the retro **Scheme 25**, the γ-lactone can be constructed by the use of the intermediate α-diazo β-keto ester **76** whose preparation has been reported earlier. This preparation would avoid the alkylating step and use of strong bases like LDA. The intermediate α-diazo β–keto ester **76** is easily obtained from the corresponding diazo carbonyl which in turn can be obtained from the β-keto ester.

When R = PhCO, 76

The required diazo ester was prepared by the usual diazo transfer procedure. This diazo ester was subjected to the normal cyclisation procedure. Thus, the diazo compound (200 mg, in 5 ml DCM) was added at a rate of 0.5 ml/hr. to a refluxing solution containing the catalyst ($Rh_2(OAc)_4$, 2 mol % in 10 ml DCM). After the completion of the reaction the catalyst was removed by filtration through celite.

The reaction resulted in a clean conversion however, to our pleasant surprise, the product formed was found to be a β-lactone instead of γ–lactone **[Scheme 30]**.



76 87

Scheme 30

The product (**87**) gave a band in the IR at 1822 cm^{-1} characteristic of β lactones.[47] NMR splitting further proved the structure (*vide experimental*).

The following questions need to be answered to explain the observed product formation

1. Is it the **conformational preference**, which placed the reacting C-H bond in close proximity to the carbenoid centre that led to β-lactone formation?
2. Is it because of the **electronic nature** of the reacting carbenoid centre?
3. Or is it due to the fact that electrophilic carbene can attack the α **carbon** of the ester functionality which was activated by the ester oxygen?

In order to understand the product formation, it became necessary to perform some control experiments to determine whether it is the steric factor or the electronic factor that predominates in such cyclisations.

Study of electronic effects

Under this category, the nature of the ligand on Rh and the substituents that stabilise the carbene are considered. To find out the effect of ligands on the site selectivity, various substituted Rh catalysts were prepared[48] and used for the cyclisation reaction.

Table I: Variation of ligands on Rh for the C-H insertion of 76

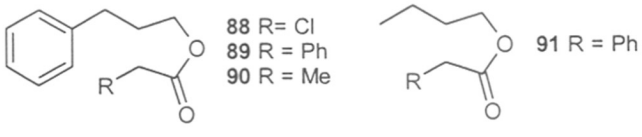
Ligand	Yield %
Acetate	55
Trimethylacetate	58
Methoxyacetate	60
Octanoate	59
Caprolactam	63
MEPY*	67

* reaction was carried out on 70 mg scale.

In the above table, the yield refers to the amount of β-lactone obtained. Except in the case where trifluoroacetate (not mentioned in the Table) was used as the ligand, all the other ligands gave β-lactone as the major product along with varying amounts of dimer. Due to the difference in the electron donating nature of the various ligands, the yields of the product varied. It was speculated that, the product obtained from trifluoroacetate mediated cyclisation could be as a result of cyclo addition reaction. However, this product could not be fully characterised.

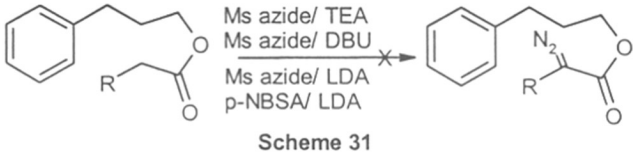
As decided earlier, modifications of the substrate that bring about stabilisation of the carbene and a study of the results was undertaken.

Various electron donating substituents which could stabilise the electrophilic carbene were selected and the results are presented below.



All the compounds were prepared from the corresponding acids and alcohols. The acid was converted into acid chloride with $SOCl_2$ and then treated with alcohol in the presence of a base.

The substituted esters were then treated with azides to form the diazo ester. But none of the methods tried were successful in realising the target **[Scheme 31]**.

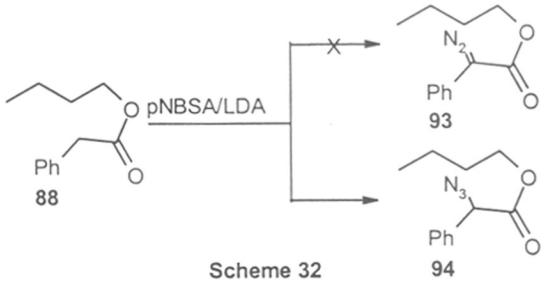


Scheme 31

The α methylene group was not sufficiently active enough to allow diazo transfer. A method that is generally used for the preparation of diazo esters from this kind of unactivated esters was undertaken. Diazo transfer using MsN_3 or pNBSA to the ester enolate generated with the help of LDA was also unsuccessful. Even the strategy of benzoylation followed by diazo transfer developed by Taber did not provide the required diazo ester.

However, a different set of results were obtained when the compound **91** was subjected to diazo transfer using pNBSA/LDA method. Instead of diazo transfer product **93**, azide transfer product **94** only was observed **[Scheme 32]**.

Azide transfer is a competitive reaction and although reports by Evans mention that a combination of pNBSA and LDA is the ideal reagent for diazo transfer,[44] it did

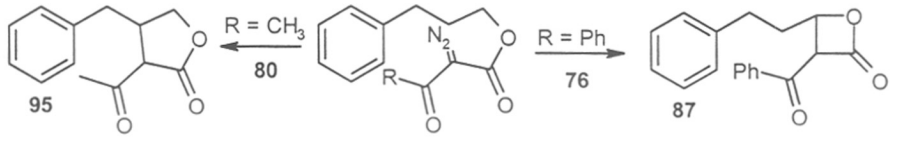


Scheme 32

not work in the present case. Therefore, the study of varying the carbene stability by different groups could not be pursued. However, these disappointing results did not reduce the enthusiasm to continue with the present study.

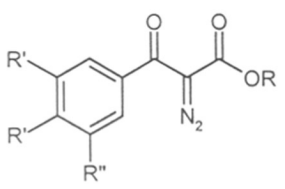
Studies on steric effects

It was decided to study the fate of **carbonyl stabilised** metallo carbenes. It was very interesting to note that, there is site selectivity in the product formation when the bulkiness of the carbonyl group is varied. These observations can be schematically represented as **[Scheme 33]**



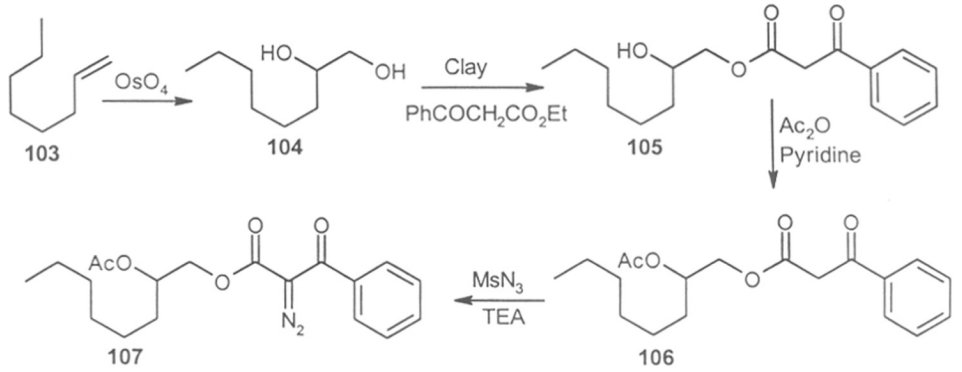
Scheme 33

Based on the above findings, it was obvious to consider an assumption that if it was the bulkiness which was responsible for site selectivity, then it should have given the same type of β-lactones when the ester moiety is modified. To probe this reasoning in detail, following compounds were prepared by the efficient transesterification method developed and reported in this thesis, followed by diazo transfer with MsN_3 and subjecting the diazo ester to C-H insertion in the normal fashion.



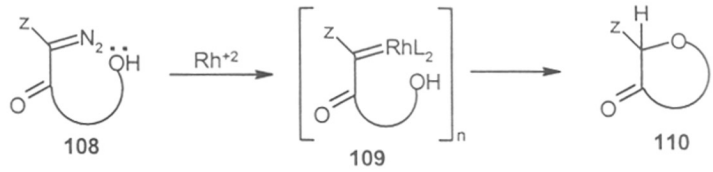
96	R = CH_2CH_3	R' = R" = H
97	R = CH_2CH_2Ph	R' = R" = H
98	R = CH_2CH_2OEt	R' = R" = H
99	R = CH_2CH_2Cl	R' = R" = H
100	R = CH_2CH_3	R' = R" = OMe
101	R = $CH_2CH_2CH_2Ph$	R' = R" = OMe
102	R = CH_2CH_3	R' = O-CH_2-O R" = H

Except entries **98** and **99** all the compounds furnished the corresponding β-lactones (as analysed by IR). The results obtained were in good agreement with the assumption (more details will be presented under results and discussion). However to confirm our findings, it was decided to prepare a substrate where the possibility of both β-lactone as well as γ-lactone formation existed. The following model compound was prepared in 4 steps starting from octene as outlined in the following scheme **[Scheme 34]**.



Scheme 34

The Rh (II) catalysed decomposition of diazo compound is believed to involve a rhodium carbenoid intermediate **109** which retains the high electrophilic properties associated with free carbenes. Therefore in an appropriate acyclic substrate **108** such an intermediate would be intercepted intramolecularly by a nucleophile to effect overall cyclisation leading to cyclic ring ethers **110**[49] as depicted below (z = electron withdrawing group). Therefore it is necessary to protect the free hydroxy group.



Scheme 35

Octene (**103**) was dihydroxylated-using OsO_4.[50] The diol **104** was selectively transesterified to give **105** using clay as the catalyst.[51] To avoid the possible O-H insertion the free hydroxyl was protected as its acetate **106**.[52] Diazo transfer using MsN_3 furnished the required compound **107**. However the compound did not undergo the required cyclisation. It resulted in a complex mixture which could not be purified.

Few reports mention that some diazo compounds decompose in the presence of transition metal catalysts.[53] From the results of the present study, one could rationalise

that in the Rh catalysed diazo decomposition reactions, site selectivity depends not only on electronic factors but also on steric factors. Further studies in this area are in progress.

Part II: Cu (II) catalysed cyclopropanation of intermediate (112)

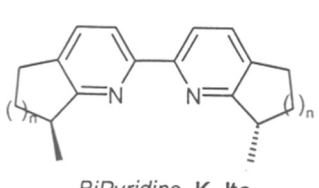
Introduction

A variety of natural products contain cyclopropyl unit[54] as their structural subunits. Some of these compounds are albene,[55a] thapas 7(15)-ene,[55b] 1-aminocyclopropane carboxylic acid,[55c] (+)- cis-chrysanthemic acid.[55d]

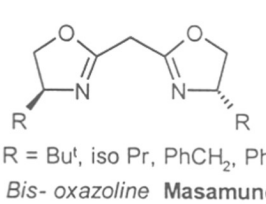
Cyclopropanes have also been reportedly used as mechanistic probes to define specific details of reaction pathways. One of the most common method for the formation of cyclopropane is the formal addition of a carbene or carbene equivalent to an alkene. Generally carbenes are electrophilic in nature. The strains associated with these classes of compounds have attracted various groups to develop new synthetic methods for their formation. Diazo compounds are most commonly used as the alkylidine source and the process can be carried out thermally, photochemically or in the presence of a metal catalyst. However, dibromides,[56a] sulphur ylides[56b] and iodonium ylides[56c] have also been used as carbene precursors.

Out of the several methods mentioned above the diazo decomposition reaction appeared to be straightforward and operationally simple. An exercise in the attempts to cyclopropanate β-keto esters of the type **112** given below was considered worthwhile. brief introduction about cyclopropanation reaction may therefore be appropriate here.

It was only during the earlier part of this decade that cyclopropanation using Cu catalyst[57] has emerged as a powerful tool in synthetic organic chemistry. Various groups like Pfaltz, Ito, Masamane, Evans, Katsuki and Aratani have contributed for the development of different catalysts using Cu as the central metal. The following pictorial representation depicts some of the ligands used by the different groups. Various Rh based catalysts are also available for cyclopropanation.[58]



BiPyridine **K. Ito**

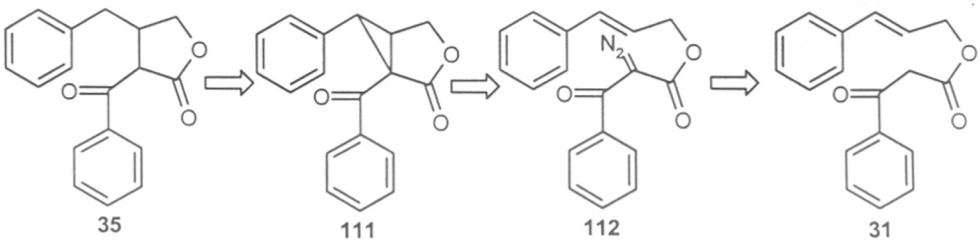


Bis- oxazoline **Masamune**

Semicorrin **Pfaltz**

Objective of the present work

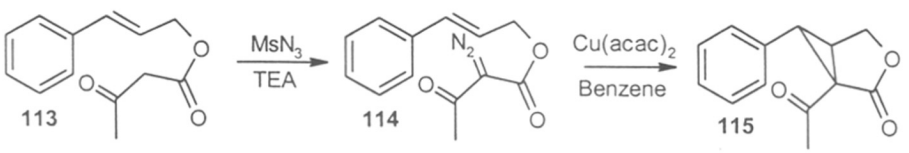
Cyclopropanation of the β-keto ester **112** would be expected to yield the required lactone. A facile and efficient diazo decomposition of the properly positioned double bond in the cinnamyl ester **112** would give the required cyclopropyl lactone, which could then be selectively cleaved to furnish the required lactone (retro scheme shown below) **[Scheme 36]**.



Scheme 36

Present work

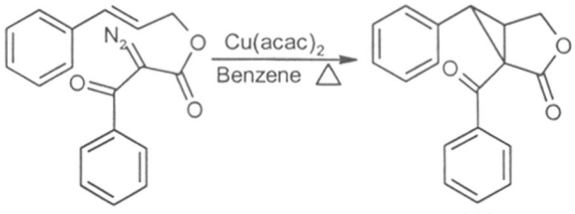
Application of diazo decomposition for the C-H insertion resulted only in the β-lactone formation and not the expected γ-lactone (see Chapter II, Section C, Part I). However, the required γ-lactone could be envisaged to be prepared by a two step sequence comprising (i) cyclopropanation of the intermediate **112** (ii) reductive cleavage of the cyclopropyl lactone **111**. A model study on compound like the one given below **[Scheme 37]** was first pursued. The most commonly used catalysts for decomposition of diazo compounds which leads to cyclopropanation are copper based. Amongst all the available copper catalysts, extensively used one is based on 1,3 diketone *i.e.* acetylacetone. The required diazo compound was prepared from the corresponding β-keto ester by the usual diazo transfer method. This diazo compound was subjected to Cu catalysed cyclopropanation. The diazo compound (200 mg in 5 ml benzene) was added to a refluxing solution containing $Cu(acac)_2$ over a period of 5 hrs. after the addition was over the reaction was refluxed further for one more hr. Removal of the catalyst by filtration through celite followed by purification afforded the expected cyclopropyl lactone **115**.



Scheme 37

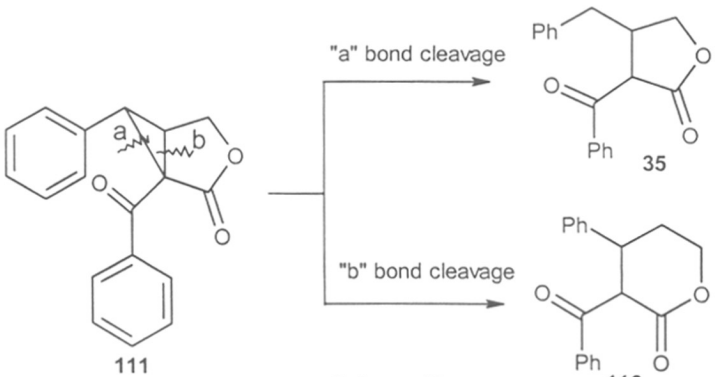
In order to increase the yield of the cyclopropanation product Rh catalyst was used. However, it was found out that Cu catalyst worked better than the Rh catalyst. After successfully constructing the required cyclopropyl lactone **115** as a model study, efforts were directed to subject the diazo β-keto ester **112** for cyclopropanation. Since the electronic properties of the cyclopropyl lactones **115** and **111** are different, the cyclopropyl lactone arising out of the former was not considered for cleavage studies.

The diazo ester **112** was subjected to the Cu catalysed cyclopropanation **[Scheme 38]**, and indeed the expected cyclopropyl lactone **111** was formed in more than 65% yield.



112 **Scheme 38** **111**

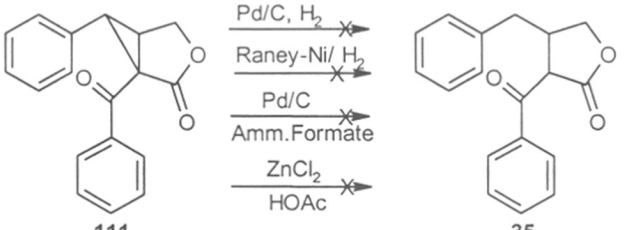
After successfully preparing the required cyclopropyl lactone, the selective cleavage of cyclopropyl bond leading to the γ lactone was sought next. Analysis of the molecular model of the cyclopropyl lactone showed that two bonds are overlapping on the π orbitals of the carbonyl group. The following schematic representation depicts the possible mode of cleavage **[Scheme 39]**.



Scheme 39

No reports are available for the selective cleavage of the cyclopropyl bonds present in cyclopropyl lactones, although many methods are reported for the cleavage of cyclopropyl bonds present in cyclopropyl ketones.[59] It was thus considered that application of some of these methods would enable cleavage in cyclopropyl lactone.

Reductive cleavage of cyclopropyl bond is well documented.[60] Simplest one among them is hydrogenation. Thus the cyclopropyl lactone **111** was subjected to hydrogenation using Pd/C as the catalyst. However, this method did not yield any of the expected γ-lactone **35** or δ lactone **116**. Only starting material **111** was recovered. Similarly, application of Raney-Ni /H_2 also did not yield the required product. Even the application of transfer hydrogenation conditions using Pd/C and ammonium formate did not yield the cleaved product. Application of $ZnCl_2$/HOAc also did not yield the reduced product. The following scheme **[Scheme 40]** depicts the various reactions performed for the required bond cleavage.



Scheme 40

Under metal ammonia reduction (Na/NH_3) conditions, it was observed that the cyclopropyl lactone was consumed completely. But, from the analysis of the reaction mixture it was found out that neither the γ-lactone **35** nor the δ-lactone **116** was formed. A highly polar compound was isolated. It was assumed that complete reduction of the lactone ring might have taken place during this reduction.

Work in this route to selectively cleave the cyclopropyl bond is in progress in our group.

Results and discussions

Section II Part A

The required Z- ethyl cinnamate was prepared by the elegant procedure developed by Ando. Triethylphosphonoacetate was converted to its dichloro derivative with PCl_5. It is important to note that, prolongation of the reaction time always led to poor yield of the desired dichloride **57**. It was also observed that, if the distillation temp. exceeded 120°C, decomposition of the dichloride occurred. For all the reactions, the dichloride was freshly distilled and used. Attempted storage of this dichloride even at 0°C for more than few days led to decomposition. This dichloride was treated with phenol at 0°C to furnish the required phosphono ester **58**. Treatment of compound **58** with NaH at –78°C followed by the condensation with benzaldehyde led to exclusive

formation of the Z-ethyl cinnamate (**53**). The product showed IR peaks at 1720 cm^{-1} for ester carbonyl. That the product was only the *cis*-isomer was further confirmed by the ^1H NMR analysis. A doublet at 6.9 δ (1H, J=12.5Hz) and a doublet at 6.0 δ (1H, J=12.5Hz) and absence of doublets at 7.7 δ and 6.4 δ (characteristic of *trans* isomer) proved that >95 % of the cis isomer was formed. This α,β unsaturated ester, was then subjected to DIBAL H reduction to get the allyl alcohol **52**. The latter, was then oxidised to the aldehyde with PCC. Formation of the aldehyde was confirmed by the IR analysis. *i.e.* a peak at 1690 cm^{-1}. Several attempted methods of converting this aldehyde to its protected acetal **50** proved unsuccessful. Since the required acetal **50** for transacetalisation with the bromo alcohol **37** could not be prepared this route could not be pursued further.

A different route as depicted in **Scheme 13** was attempted next. Following the literature procedure methylacetoacetate was selectively mono benzylated using benzyl bromide. The formation of the benzylated product **55** was confirmed by the presence of a multiplet between 4.0-3.8 δ (1H, $COCHCO_2$) and a doublet at 3.0 δ (benzylic) in ^1H NMR. Compound **55** was brominated and then deacylated to obtain the required bromo ester **54**. Though the bromination went smoothly, the deacylation initially gave poor yield of the product **54**. It was later found out that, the reaction time and temp. played a crucial role in the product formation. Reducing the temp. from 0°C to –10°C did not yield the deacylated product even after few hrs. Similarly, if the reaction was prolonged at 0°C, it led to hydrolysis of the ester group as well. A careful control of both the temp. (0°C) and the reaction time (30-45 min.) finally furnished the required ester **54** in more than 75 % isolated yield. The product formed was confirmed by the presence of peaks at 1740 cm^{-1} corresponding to ester in the IR. A triplet at 4.2 (1H, BrC*H*), a multiplet between 3.3 and 3.1 δ (2H, $C_6H_5CH_2$) in ^1H NMR further lent support to the structure. DIBAL H reduction of **54** at –78°C furnished the aldehyde **49** which was confirmed by the presence of a peak at 1695 cm^{-1} and the disappearance the ester peak at 1740 cm^{-1} in IR. This compound was directly subjected to acetalaisation using trimethyl orthoformate and the product formed **48** was confirmed by its spectral analysis. Disappearance of the aldehyde carbonyl at 1695 cm^{-1} in IR and appearance of singlet at 3.5 δ (6H, OCH_3,) in ^1H NMR proved that the required protection had occurred. Compound **48** was ready for the next step of transacetalaisation.

Transacetalaisation gave the required product **47** in only 15 % yield. The incorporation of cinnamyl moiety (appearance of multiplets between 6.8-6.7 δ (1H) and 6.35-6.2 δ (1H) in ^1H NMR) in the product and the presence of methoxy group

(appearance of a singlet at 3.5 δ (3H) in ^{1}H NMR) indicated the formation of mono transacetalated product. Owing to the poor yield of the required transacetalated product, further work with this compound could not be carried out.

Section B Part II

Intermolecular silyl enol ether condensation

Preparation of the silyl enol ether for the CAN mediated intermolecular condensation (see **Scheme 16**) was initiated. The ketone functionality of β-keto ester **33** was converted into its silyl enol ether **65** by standard procedure. Formation of the product **65** was confirmed by the disappearance of the ketone carbonyl in IR at 1690 cm^{-1}and the disappearance of a singlet at 3.9 δ ($COCH_2CO_2$) and appearance of a singlets at 5.0 δ (1H, $COCH$=C), 0.9 δ (9H, $C(CH_3)_3$) and at 0.0 δ (6H, $Si(CH_3)_2$) in ^{1}H NMR. In the mass spectrum a peak at 307 (M^+) was observed. DIBAL H reduction of **65** at 0°C furnished the required allyl alcohol **63** whose IR showed a peak at 3320 cm^{-1} and whose ^{1}H NMR recorded a triplet at 4.9 δ (1H, C=$CHCH_2$). However, the attempted CAN mediated intermolecular silyl enol ether condensation of **63** with ethyl cinnamate (**64**) did not proceed and deprotection of silyl enol ether only was observed. The keto alcohol thus obtained was characterised by its spectral analysis. IR showed absorption at 3320, 1685, 1590 cm^{-1} corresponding to hydroxyl, ketone and aromatic ring, triplets at 4.0 δ (2H, OCH_2) and at 2.4 δ (2H, $COCH_2$) in ^{1}H NMR confirmed that only deprotection of the silyl enol ether had occurred. Even the attempted intermolecular condensation of **63** with Z ethyl cinnamate (**53**) did not yield the required product **66**.

Intramolecular cyclisation of silyl enol ether

The attempted transesterification of **63** with either **53** or **64** did not proceed. It was later found out that lithiation of allyl alcohol is problematic, since concomitant rearrangement takes palce (see **Scheme 21**). It was then decided to employ a different route to prepare the required intermediate **67** (see **Scheme 22**)

The ketone carbonyl of the β-keto ester **33** was protected as its cyclic acetal according to standard literature procedure. The protected compound (as analysed by IR) was subjected to LAH reduction to furnish the hydroxy ketal **71**. In its IR, the compound **71** had no ester carbonyl band at 1735 cm^{-1} and showed a broad peak at 3320 cm^{-1}, the ^{1}H NMR had a broad peak at 2.8 δ (OH) and a triplet at 2.1 δ (CCH_2CH_2). These data confirmed formation of the required product **71**. However, the attempted transesterification with Z-ethyl cinnamate (**53**) did not yield the required product **70**.

In a different approach (see **Scheme 23**) the keto group in the β-keto ester **31** was protected as its silyl enol ether **72** using the standard procedure. The disappearance of the ketone carbonyl at 1690 cm^{-1} in IR and a singlet at 4.1 δ (2H, $COCH_2CO_2$) in ^1H NMR and appearance of singlets at 5.75 δ (1H, $COCH$=C), 1.0 δ (9H, $C(CH_3)_3$) and a singlet at 0.1 δ (6H, $Si(CH_3)_2$) in ^1H NMR further confirmed the silyl enol ether formation. When this silyl enol ether was subjected to the CAN mediated intramolecular cyclisation, it was observed that only deprotection of the silyl group had occurred (*vide experimental*). Similarly, attempted cyclisation with $Pd(OAc)_2$ also led to deprotection only. When $PdCl_2$ was used, not even the deprotection of the compound **72** was observed. The starting material was quantitatively recovered quantitatively. As there was no scope of work with **72**, this scheme was also not taken up further.

Section B part III

The required chloro ester **74** was prepared by the usual procedure and its structure was confirmed by spectral analysis. IR peaks at 1740, 970 cm^{-1} corresponding to ester and chloro group respectively, a singlet at 4.0 δ (2H, $ClCH_2CO_2$) in ^1H NMR and the mass peak at m/z 210 and the base peak at 115 collectively confirmed the structure. This chloro ester **74** was converted to its iodide by exchange reaction. The product had IR peaks at 1730, 620 cm^{-1} for ester and iodo groups respectively. A singlet at 3.8 δ (2H, ICH_2CO_2) in ^1H NMR and a peak at m/z 302 in the mass spectrum confirmed the structure. First the chloro ester **74** was subjected to photo-chemical cyclisation. Use of zinc wool as acid scavenger resulted in deprotection of the chloro acetyl group. It was however gratifying to note that a mild and efficient deprotection had taken place, opening up avenues for general deprotection studies. A detailed work on this particular aspect is underway. Since with chloro ester **74** deprotection had occurred the corresponding iodo ester **75** was not subjected to photo-chemical cyclisation.

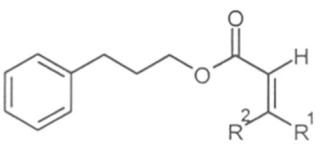
Section C Part I

The diazo compound **78** required for the model study was prepared from the acetyl diazo ester **80**, which in turn was prepared by the diazo transfer reaction using MsN_3 as the reagent. The structure of the diazo compound **80** was confirmed by the appearance of IR peaks at cm^{-1} 2146 ($C=N_2$), 1730 (ester) and 1690 (C=O). The appearance of a quaternary carbon at 76.10 ppm in ^{13}C NMR further confirmed the product formation.

This diazo ester **80** was subjected to deacylation in the presence of NaOH in MeCN. The deacylated product **78** was identified by its spectral analysis. The

disappearance of 1690 cm^{-1} (ketone) and a shift of ester from 1730 cm^{-1} to 1740 cm^{-1} in IR spectra, the disappearance of singlet at 2.10 δ (3H, CH_3CO) and appearance of a broad peak at 5.9 δ ($CH{=}N_2$) in ^1H NMR, a tertiary carbon at 41.3 ppm in ^{13}C NMR ($CH{=}N_2$); the disappearance of a quaternary carbon at 189.66 ppm (CH_3CO) and a methyl carbon at 31.0 ppm (CH_3CO) in ^{13}C NMR confirmed the structure.

C-H insertion reaction of **78** with $Rh_2(OAc)_4$ in DCM was carried out as follows. The diazo ester (**78,** 200 mg), dissolved in rigourously dried DCM was added slowly over 10 hr. (using syringe pump 0.5 ml /hr) to a refluxing solution containing $Rh_2(OAc)_4$ (8 mg, 2.0 mol %) and DCM (10 ml). After the addition was over, the reaction mixture was refluxed for 3 hrs. more. The reaction mixture was then cooled and was passed through a small plug of celite to remove the catalyst. The products were isolated by chromatographic purification using flash silica gel (230-400 mesh). Purification yielded two compounds **78a** and **78b**. The compounds were found to be dimers from their spectral analyses. The compound **78a** showed a singlet at 6.85 δ in ^1H NMR for an olefinic proton and a tertiary carbon at 107.4 ppm in ^{13}C NMR. Similarly, the other product **78b** showed a singlet at 6.25 δ in ^1H NMR and a tertiary carbon at 94.1 ppm in ^{13}C NMR. Based on spectral analyses it was rationalised that these compounds were formed by the dimerisation of the carbene formed yielding fumarate ester **78a** and the maleate ester **78b**.



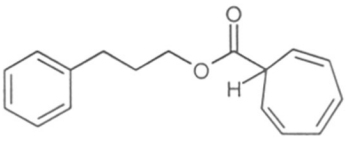
78a Fumarate $R^1 = C_6H_5(CH_2)_3OCO$, $R^2 = H$

78b Maleate $R^1 = H$, $R^2 = C_6H_5(CH_2)_3OCO$

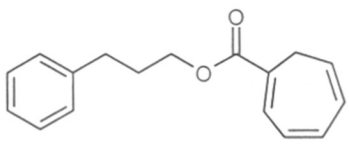
In another experiment, 200 mg of the diazo ester **78** dissolved in rigourously dried benzene was added slowly over 10 hr. (using syringe pump 0.5 ml /hr) to a refluxing solution containing $Rh_2(OAc)_4$ (8 mg, 2.0 mol %) and benzene (10 ml). After the addition was over the reaction mixture was refluxed further for 3 hrs. It was then cooled and passed through a small plug of celite to remove the catalyst. The products were isolated by chromatographic purification using flash silica gel (230-400 mesh). A single product was isolated and it was found to be different from either of the products mentioned above **78a** and **78b**. A peak at 1735 cm^{-1} in IR spectrum showed that the ester group was intact. Analysis of the ^1H NMR showed 5 aromatic protons (7.34-7.19 δ), a triplet centered at 6.68 δ (J=2.86Hz, 2H), a multiplet between 6.32 and 6.26 δ (2H), a doublet of doublet at 5.46 δ (J=8.82, 5.60Hz, 2H), a triplet at 4.24 δ (J=6.54Hz,

2H), a triplet at 2.74 δ (J=7.29Hz, 2H), a multiplet between 2.61and 2.58 δ (m, 1H) and a multiplet between 2.08-1.98 δ (m, 2H). A total number of 18 protons were present as analysed by ^{1}H NMR values. ^{13}C NMR showed the presence of 11 carbons. The mass spectra showed the molecular weight to be 254 with base peak at 91. After obtaining all the spectral values the compound's structure was deduced as follows.

The M^{+} ion peak corresponded to a molecular formula $C_{17}H_{18}O_2$. The base peak at 91 (m/e) showed the presence of a cycloheptatriene moiety. ^{1}H NMR exhibited peaks at 6.68 δ (t, 1H), 6.32-6.2 δ (m, 2H), 5.46 δ (dd, 2H), 2.61-2.58 δ (m, 1H) further confirming the presence of cycloheptatriene moiety. In the IR a peak at 1735 cm^{-1} and a quaternary carbon at 172.86 ppm in ^{13}C NMR indicated the presence of ester functionality. Finally, the presence of aromatic protons at 7.34-7.19 δ (m, 5H) and triplets at 4.24 δ (2H) and 2.74 δ (2H) and a multiplet between 2.08-1.98 δ (2H) showed the presence of $PhCH_2CH_2CH_2$ moiety. Based on the above data, the following alternate structures **78c, 78d** could be given to the isolated reaction product.



78c



78d

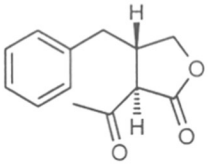
The connectivity between ^{1}H and ^{1}H relations by 2D NMR was determined and this data coupled with the presence of a tertiary carbon at 43.98 ppm in ^{13}C NMR established the structure to be **78c** and not **78d**.

When R = OCH_3

Methoxy acetic acid was converted to its acid chloride by treatment with thionyl chloride. 3-Phenylpropanol was mixed with TEA and the mixture was added to the freshly distilled acid chloride at 0°C. After usual work-up the ester was identified from its spectral analysis. The presence of peaks at 1730 cm^{-1} and 1590 cm^{-1} in the IR for ester and olefinic bond, a singlet at 3.5 δ (OCH_3, 3H) in ^{1}H NMR confirmed the product formation. Additional proof for the structure was furnished by the ^{13}C NMR resonances. *i.e.* a singlet at 169.89 ppm (ester) and a quartet at 58.86 ppm (OCH_3). However, the attempted conversion of this ester **82** to the corresponding diazo ester **79** did not meet with success.

When R = $COCH_3$ (80)

The diazo ester **80** (125 mg), dissolved in rigourously dried DCM was added slowly over 10 hr. (using syringe pump 0.5 ml /hr) to a refluxing solution containing $Rh_2(OAc)_4$ (8 mg, 2.0 mol %) and DCM (10 ml). After the addition was over the reaction mixture was refluxed for 3 hrs. more. It was cooled and was passed through a small plug of celite to remove the catalyst. Isolation by chromatographic purification using flash silica gel (230-400 mesh) yielded a single product. The compound **80a** which showed in its IR, peaks at, 1764, 1695, 1590 cm^{-1} attributed to lactone, keto carbonyl and olefinic bond respectively. ^1H NMR splitting confirmed the formation of γ

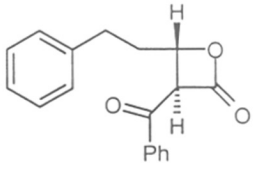


80a

lactone *viz.* doublet of doublet at 4.4 δ (1H), doublet of doublet at 4.0 δ (1H), doublet 3.4 δ (1H) and a doublet at 2.9 δ (2H).

When R = COPh (73)

The diazo ester **73** (200 mg), dissolved in rigourously dried DCM was added slowly over 10 hr. (using syringe pump 0.5 ml /hr) to a refluxing solution containing $Rh_2(OAc)_4$ (8 mg, 2.0 mol %) and DCM (10 ml). After the addition was over the reaction mixture was refluxed for a further period of 3 hrs. The reaction mixture was then cooled and passed through a small plug of celite to remove the catalyst. Isolation by chromatographic purification using flash silica gel (230-400 mesh) afforded a single product **73a** which was characterised as follows. The compound in its IR exhibited peaks at 1822, 1710, 1600 cm^{-1} for β lactone, ketone and double bond respectively. A multiplet between 5.3-5.2 δ (1H) and a doublet at 4.75 δ (J = 4.4 Hz, 1H) in ^1H NMR confirmed the stereo chemistry to be *trans*. The appearance of doublet resonances at 72.81 ppm and at 65.01 ppm corresponding to O*C*H and CO*C*HCO$_2$ in the ^{13}C NMR further confirmed the structure.



73a

Attempted diazo transfer of 91

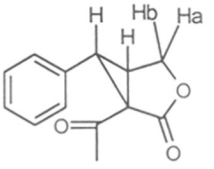
The ester **91** was prepared in the usual manner. It had peaks at 1740 cm^{-1} corresponding to the ester carbonyl and 1590 cm^{-1} for the aromatic ring in the IR, singlet at 3.6 δ (2H, benzylic) in the ^1H NMR confirmed the product formation. The diazo transfer of **91** using pNBSA/LDA combination furnished a compound **94** which was identified as the azide from its IR, ^1H NMR and ^{13}C NMR. Thus in the IR, peaks were observed at 2088, 1740 cm^{-1} corresponding to C-N_3 and ester stretching. A singlet at 4.9 δ in ^1H NMR was observed together with the disappearance of a singlet at 3.6 δ (2H). Similarly, in the ^{13}C NMR, appearance of a doublet at 65.28 ppm ($C_6H_5CHN_3$) and the disappearance a triplet at 30.38 ppm ($C_6H_5CH_2$) lent further support to the structure of the product.

Using standard procedure 1-octene was dihydroxylated. The product formation was confirmed by the disappearance of olefinic protons in ^1H NMR and a broad IR band at 3350 cm^{-1}. Selective mono transesterification was achieved using K10 clay. The product **105** showed IR absorptions at 3315, 1738, 1684 cm^{-1} for hydroxyl, ester and ketone functionalities respectively. The mass peak corresponding to a m/z 292 and the base peak at 105 confirmed that only mono transesterification had taken place. This compound **105** was then converted to its acetate derivative in the presence of Ac_2O/pyridine and the formation of acetate **106** was confirmed by spectral analysis. The presence of a singlet at 2.1 δ (3H, CH_3CO) in ^1H NMR and a singlet carbon at 170.49 ppm (acetate) in ^{13}C NMR and the mass peak at m/z 334 were observed. The required diazo transfer reaction was carried out. In the product disappearance of a broad IR peak at 3310 cm^{-1} corresponding to enolic hydroxyl and appearance of a sharp peak at 2140 cm^{-1} corresponding to $C{=}N_2$ were seen. Disappearance of a CH_2 proton at 4.1 δ in ^1H NMR and a triplet at 45.64 ppm in ^{13}C NMR and the appearance of a singlet at 75.74 ppm in ^{13}C NMR confirmed the product formation. The mass spectral analysis showed the corresponding m/z peak at 360. When this diazo compound was subjected to C-H insertion reaction, no insertion took place and the expected product could not be isolated.

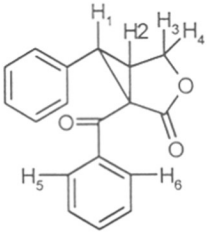
Section C Part II

β-Keto ester **113** was subjected to diazo transfer reaction using MsN_3 as the diazo transfer reagent. After the usual work-up, the product formed was identified and characterised by spectral data. IR peaks at 2160, 1730 and 1670 cm^{-1} corresponding to diazo, ester and ketone were observed. The disappearance of a singlet at 3.45 δ (2H) in ^1H NMR together with, the appearance of a singlet at 77.93 ($C{=}N_2$) ppm and the

disappearance of a triplet at 49.99 ($COCH_2CO_2$) ppm in ^{13}C NMR were the added proof for the structure. This diazo compound **114** was subjected to standard cyclopropanation reaction conditions. *i.e.* Addition of the diazo compound (200 mg in 5 ml benzene) to a refluxing solution containing the catalyst (10 mol % $Cu(acac)_2$ in 10 ml benzene). After the reaction was over, the mixture was passed through a short plug of celite to remove the catalyst. Removal of the solvent followed by column chromatography (using Flash silica gel) furnished the required cyclopropyl lactone in more than 70% yield. It was charecterised by its IR peaks at 1760 and 1700 cm^{-1} corresponding to lactone and ketone carbonyl respectively and in the ^1H NMR appearance of a doublet of doublet at 4.45 δ (1H, J=9Hz, 4.3Hz) and a doublet (1H, J=8.6Hz, 4.4Hz), triplet at 3.4 δ (1H, J=4.3Hz), doublet at 3.0 δ (1H, J=4.4Hz) were characteristic of OCH_2, $COCHCO_2$ and benzylic protons respectively.



Similarly, the β-keto ester **31** was converted to diazo ester by the usual procedure. The product showed IR bands at 2145, 1735, 1660 cm^{-1} corresponding to diazo, ester and ketone groups. The disappearance of the methylene protons at 4.1 δ also confirmed the assigned structure. Finally, the disappearance of a triplet at 45.75 ($COCH_2CO_2$) ppm and appearance of a singlet at 75.48 ppm ($C=N_2$) in ^{13}C NMR were additional supports for the product formation. This diazo ester **112** was then subjected to the cyclopropanation reaction as mentioned above. Analysis of the isolated product showed IR peaks at 1755 and 1700 cm^{-1} indicating the formation of cyclopropyl lactone



111

111. The ^1H NMR showed peaks at δ 7.8 (H5, H6, d, J=7.3Hz), 4.65 (H4, dd, J=4Hz, 6Hz), 4.45 (H3, d, J=8.6Hz), 3.45 (H1, t, J=4.4Hz) and 3.05 (H2, t, J=4.4Hz) corresponding to ortho protons in the aromatic ring which is bearing the carbonyl group, CHaHbO, CHaHbO, $COCHCO_2$ and the benzylic protons respectively. The required

carbons in ^{13}C NMR appeared at the following resonances (ppm): 170.44 (ester), 43.83 ($COCCO_2$), 37.13 (benzylic), 25.71 ($CHCHCH2$). Mass spectrum showed the required m/z value corresponding to the molecular weight 278 and a base peak at 105.

Conclusion

The efficient method developed during this thesis work for transesterification (see Chapter I section B part A) was extended to construct the lactone moiety present in the various aryl tetralin lignan lactones through cyclopropanation reaction. The advantage of this method was: even the bulky group (*viz* COPh) present in the diazo ester did not hinder the cyclopropyl lactone formation. It should be noted that in Section C Part I, it was demonstrated that the presence of a bulky COPh group on the diazo ester did not favour the required γ lactone formation. However, the conformational demand posed by the steric reasons due to phenyl ring was completely avoided in this present strategy. Work on the selective cleavage of the cyclopropyl bond has been initiated but till now success is elusive. Further work is in progress.

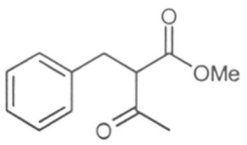
Experimental

Preparation of 2-bromo-3-phenyl-propanoic acid methyl ester

Preparation of 2-benzyl-3-oxo-butanoic acid methyl ester

NaH (950 mg, 20.6 mmol, 50 % dispersion in mineral oil) was taken in a 2 necked round bottomed flask under N_2 and it was washed with dry hexane (3 X 10 ml). Dry THF (40 ml) was added to the flask through the septum. The mixture was cooled to 0°C and to this stirred mixture methylacetoacetate (2.32 gm, 20 mmol) in dry THF (15 ml) was added slowly and stirring was continued at 0°C for 20 min. more after which benzyl bromide (3.75 gm, 22 mmol) in dry THF (20 ml) was added. The ice bath was removed and the reaction mixture was stirred at 40°C for 24 hrs. At the end of 24 hrs. the solvent was removed under reduced pressure and the yellow solid obtained was taken in Et_2O (50 ml) and the organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded crude benzylated product which was purified by column chromatography to yield (3.40 gm, 82.5%) 2-benzyl-3-oxo-butanoic acid methyl ester as a pale yellow oil.

2-benzyl-3-oxo-butanoic acid methyl ester



IR (neat) cm^{-1}

1738, 1697, 1595

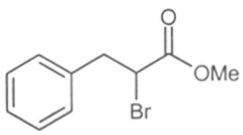
^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.3-7.1 (m, 5H), 4.0-3.8 (m, 1H), 3.7 (s, 3H), 3.0 (d, J=8Hz), 2.05 (s, 3H)

NaH (425 mg, 10.3 mmol, 50 % dispersion in oil) was taken in a 2 necked round bottomed flask under N_2 and it was washed with dry hexane (3 X 6 ml). Dry THF (20 ml) was added to the flask through the septum. The mixture was cooled to 0°C and to this stirred mixture 2-benzyl-3-oxo-butanoic acid methyl ester (2.06 gm, 10.0 mmol) in dry THF (15 ml) was added slowly and stirring was continued at 0°C for 20 min. more after which bromine (1.83 gm, 11.0 mmol) in dry DCM (20 ml) was added rapidly in a single lot to this reaction mixture. The reaction mixture was stirred at 0°C for one hr. The solvent was removed under reduced pressure and the yellow solid obtained was taken in Et_2O (40 ml) and the organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded crude bromo product which was used as such without further purification for the next step.

The bromo compound obtained as above was taken in abs. EtOH (25 ml) and was added at 0°C to anhyd. $Ba(OH)_2$ (5.0 mmol) (obtained by fusing $Ba(OH)_2.8H_2O$ at or above 160°C and cooling it under a stream of N_2). The resultant suspension was stirred at 0°C for ½ hr. The deacylated bromo ester was separated from the reaction mixture by partitioning it between petroleum ether and brine. The organic layer was dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded the 2-bromo-3-phenyl-propanoic acid methyl ester (2.04 gm, 84%).

2-bromo-3-phenyl-propanoic acid methyl ester



IR (neat), cm^{-1}

1740, 1590, 1000

^{1}H NMR δ (90 MHz, $CDCl_3$)

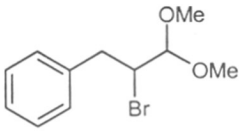
7.2-7.0 (m, 5H), 4.2 (t, J=8Hz, 1H), 3.7 (s, 3H), 3.3-3.1 (m, 2H)

Preparation of (2-bromo-3,3-dimethoxy-propyl)-benzene

The 2-bromo-3-phenyl-propanoic acid methyl ester (486 mg, 2.0 mmol) in dry toluene (10 ml) was cooled to -78°C in a dry ice-acetone bath under N_2. To this cooled solution DIBAL-H (284 mg, 0.7 ml, 2.0 mmol, 2.8 M solution in toluene) was added drop-wise. The reaction mixture was stirred at -78°C for 1½ hrs; it was then quenched by the addition of methanol (0.5 ml) followed by water (0.5 ml) after which the reaction mixture was allowed to warm to room temp. The solid obtained was extracted with hot methanol (4 X 15 ml). The organic solvent was distilled off under reduced pressure to afford the pure aldehyde which was used as such for the next step.

The bromo aldehyde obtained as above was diluted with dry benzene (15 ml) and trimethylorthoformate (636 mg, 6.0 mmol) was added to it followed by the addition of pTSA (25 mg). The mixture was refluxed for 6 hrs. under N_2. Solvent was removed under reduced pressure and the crude material obtained was taken in Et_2O and the organic layer was washed with $NaHCO_3$, water finally with brine and the organic layer was dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by flash chromatography on silica gel yielded 2-bromo-3,3-dimethoxypropylbenzene as a pale yellow liquid (472 mg, 91%).

2-Bromo-3,3-dimethoxypropylbenzene



IR (neat) cm^{-1}

1595

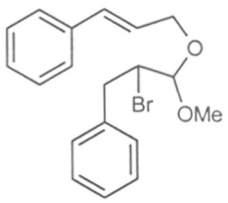
^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.3-7.2 (m, 5H), 4.4 (d, J=6Hz, 1H), 4.3-4.2 (m, 1H), 3.5 (s, 6H), 3.4 (dd, J=7Hz, 4Hz, 1H), 3.05 (dd, J= 13z, 9Hz, 1H)

Transacetalisation of 2-bromo-3,3-dimethoxypropylbenzene with cinnamyl alcohol

To the 2-bromo-3,3-dimethoxypropylbenzene (259 mg, 1.0 mmol) dissolved in dry toluene (15 ml), cinnamyl alcohol (134 mg, 1.0 mmol) and pTSA (10 mg) were added and the mixture was refluxed with azeotropic removal of methanol (Dean-Stark). After refluxing for 6 hrs. the reaction mixture was cooled to room temp. and solid $NaHCO_3$ was added, stirring was continued at room temp. for 20 min. after which the inorganic materials were removed by passing the mixture through a short plug of celite. Removal of the solvent under reduced pressure yielded the crude material which was purified by flash chromatography to afford the mono transacetalated product (55 mg, ~15 %).

(2-Bromo-3-methoxy-3-phenyl-prop-2-en-1-oxy -propyl)-benzene



IR (neat) cm^{-1}

1595

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.3-7.2 (m, 10H), 6.8-6.7 (m, 1H), 6.35-6.2 (m, 1H), 4.45 (d, J=6Hz), 4.3-4.2 (m, 1H), 3.5 (s, 3H), 3.4 (dd, J=11Hz, 4Hz, 1H), 3.05 (dd, J= 13Hz, 9Hz, 1H)

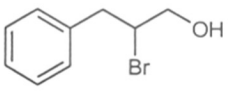
^{13}**C** NMR δ (50 MHz, $CDCl_3$)

138.17 (s), 136 (s), 132.43 (d), 128.79 (d), 128.43 (d), 127.74 (d), 127.40 (d), 126.57 (d), 126.11 (d), 122.45 (d), 105.75 (d), 73.1 (t), 55.81 (q), 54.96 (d), 37.96 (t)

Preparation of 2-bromo-3-phenylpropan-1-ol

The 2-bromo-3-phenyl-propanoic acid methyl ester (243 mg, 1.0 mmol) in dry toluene (10 ml) was taken under N_2. To this solution DIBAL-H (284 mg, 0.7 ml, 2.8 M solution in toluene, 2.0 mmol) was added drop-wise. The reaction mixture was stirred at room temp. for 1½; hrs it was then quenched by slow addition of methanol (0.5 ml) followed by water (0.5 ml) after which the solid obtained was extracted with hot methanol (4 X 15 ml). The organic solvent was distilled off under reduced pressure to afford the crude bromo alcohol. Filtration through a short plug of silica gel furnished the bromo alcohol (206 mg, 96%).

2-Bromo-3-phenylpropan-1-ol



IR (neat) cm^{-1}

3320, 1595

^{1}H NMR δ (90 MHz, $CDCl_3$)

7.2-7.1 (m, 5H), 4.3-4.1 (m, 2H), 3.9-3.8 (m, 1H), 3.1 (dd, J=8Hz, 2Hz, 2H), 2.1 (br, OH)

Preparation of Z-ethyl cinnamate

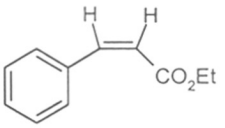
PCl_5 (15.6 gm, 75 mmol) was added in portions to triethylphosphono acetate (5.95 gm, 30 mmol) at 0°C. When the exothermic reaction was complete, the mixture was heated at 75 °C for 10 hrs. $POCl_3$ and excess of PCl_5 were removed by distillation. High vacuum distillation afforded the dichloride (5.85 gm) (b.p. 85°C /1 mm) [Lit.b.p. 105-110°C /3 mm]

The dichloride in benzene (30 ml) was reacted with a solution of phenol (5.49 gm 58 mmol) and TEA (9.8 ml, 71.0 mmol) in benzene (10 ml) at 0°C and the resultant mixture was stirred at 25°C for one hr. The HCl salt was filtered off and the clear filtrate was diluted with EtOAc (25 ml). The organic layer was washed successively with 1N NaOH (20 ml), saturated NH_4Cl, brine and was dried over Na_2SO_4. Distillation of the solvent and purification of the crude product afforded (5.5 gm, 57 %) of the phosphono ester.

To a suspension of NaH (60 mg, 50 % dispersion in oil, 1.25 mmol) in THF (2 ml) was added the phosphonoester (320 mg, 1.0 mmol) in THF (4 ml) at -78°C under Ar. Aftr stirring for 15 min. benzaldehyde (115 mg, 1.1 mmol) was added and the reaction was gradually warmed to room temp. over 2 hrs. The reaction was then

quenched with NH_4Cl and was exhaustively extracted with EtOAc. The combined organic layer was washed with water, brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded crude cinnamate ester which was purified by column chromatography to yield Z-ethyl cinnamate (170 mg, >95 %).

Z- Ethyl cinnamate



IR (neat) cm^{-1}

1720, 1605

^{1}H NMR δ (200 MHz, $CDCl_3$)

7.65-7.55 (m, 2H), 7.45-7.35 (m, 3H), 6.9 (d, J=12.5Hz, 1H), 6.0 (d, J=12.5Hz, 1H), 4.25 (q, J=7.0Hz, 2H), 1.25 (t, J= 7.0Hz, 3H)

Preparation of TBDMSOTf

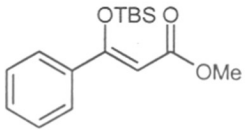
*t-B*utyl dimethyl silyl chloride (7.54 gm, 50 mmol) was gradually added over a period of ½ an hour to trifluoromethane sulphonic acid (7.5 gm, 50 mmol) with stirring under protection from moisture. The mixture was heated until the hydrogen chloride evolution ceased [checked by moist pH paper] and the product was isolated by vacuum distillation to afford 10.9 gm (82 %, 41.3 mmol) of TBDMSOTf (bath temp. 85 °C) [Lit. b.p 63°/ 10 mm].

Attempted intermolecular cyclisation of 3--(*t*-butyl-dimethyl-silanyloxy)-3-phenylprop-2-en-1-ol with Z-ethyl cinnamate

Preparation of 3--(*t*-butyl-dimethyl-silanyloxy)-3-phenylprop-2-en-1-ol

In a 2 necked round bottomed flask (192 mg 1.0 mmol) of **33** was taken in dry DCM (8 ml) and the mixture was cooled in ice. TBDMSOTf (304 mg, 1.15 mmol) in DCM (4 ml) was added under Ar via syringe. After stirring for 3 min. TEA (125 mg, 1.25 mmol) in DCM (1 ml) was added and the solution was stirred at 0°C for one hr. Saturated $NaHCO_3$ solution (2 ml) was added and the reaction mixture was transferred to a separating funnel. The separated organic layer was washed successively with water, brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded the crude silyl enol ether that was purified by flash chromatography to afford 3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid methyl ester as pale yellow oil (283 mg, 97 %).

3-(*t-buty*l-dimethyl-silanyloxy)-3-phenyl-acrylic acid methyl ester



IR (neat) cm^{-1}

1720,1595

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.4-7.2 (m, 5H), 5.0 (s, 1H), 3.4 (s, 3H), 0.9 (s, 9H), 0.0 (s, 6H)

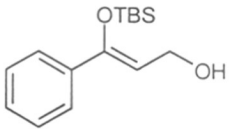
Mass (70 eV)

m/z 307 (M^+), 295, 274, 249, 235, 224, 207, 191, 178, 146, 133, 122, 105 (base peak), 91, 77, 69, 59

DIBAL H reduction of 3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid methyl ester

To 3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid methyl ester (200 mg, 0.68 mmol) in 4 ml dry toluene was added under Ar. DIBAL H (193 mg, 1.36 mmol, 0.5 ml, 2.8 M solution in toluene) at 0°C. The reaction mixture was stirred at 0°C for 4 hrs. After the reaction was over (as monitored by TLC) the reaction mixture was cooled to -20°C and then quenched by the addition of methanol (0.5 ml) followed by water (0.25 ml) The gelatinous precipitate was extracted with hot methanol (4 X 10 ml). Removal of the solvent under reduced pressure followed by filtration through flash silica gel yielded (204 mg, 78 %) allyl alcohol **63** as a pale yellow oil.

3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-prop-2-en-1-ol



IR (neat) cm^{-1}

3320,1595

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.4-7.2 (m, 5H), 4.9 (t, J=8 Hz, 1H), 4.0 (d, J=8Hz, 2H), 2.1 (br, OH), 1.0 (s, 9H), 0.0 (s, 6H)

Preparation of 2-(2-phenyl-[1,3]dioxolan-2-yl)-ethanol

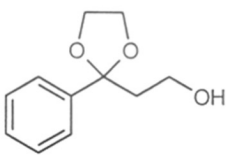
Preparation of phenyl-[1,3]dioxolan-2-yl-acetic acid ethyl ester

A mixture of 3-oxo-3-phenylpropanoic acid ethyl ester (1.94 gm, 10 mmol) ethylene glycol (1.86 gm, 30 mmol) and camphor 10 sulphonic acid (25 mg) in benzene

(40 ml) was refluxed for 24 hrs. with azeotropic removal of water (Dean- Stark). The solution was then cooled and diluted with Et_2O (35 ml). The organic layer was successively washed with $NaHCO_3$ solution water and finally with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded phenyl-[1,3]dioxolan-2-yl-acetic acid ethyl ester (2.08 gm, 86.8 %) as an oil. It was used as such without further purification for the next step.

In a flame dried 100 ml 2 necked round-bottomed flask LAH (76 mg, 2.0 mmol) was placed and dry Et_2O (15 ml) was added to it. The suspension was cooled to 0°C with stirring. A solution of phenyl-[1,3]dioxolan-2-yl-acetic acid ethyl ester (450 mg, 1.9 mmol) in dry Et_2O (5 ml) was added drop-wise. After the addition the cooling bath was removed and the reaction was stirred at room temp. for 20 hrs. water (0.3 ml), NaOH (0.4 ml, 15 %) followed by water (0.4 ml) were added while the reaction mixture was cooled. The reaction mixture was then dried with Na_2SO_4 (7 gm) and the mixture was filtered and the solid was washed with Et_2O. The combined Et_2O solution was distilled off to afford (343 mg, 88.4%) of **71** as a colourless oil.

2-(2-Phenyl-[1,3]dioxolan-2-yl)-ethanol



IR (neat) cm^{-1}

3340

^{1}H NMR δ (90 MHz, $CDCl_3$)

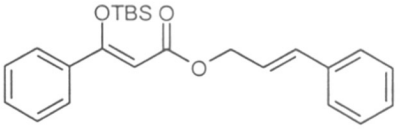
7.4-7.1(m, 5H), 4.0-3.5 (m, 6H), 2.8 (br, OH), 2.1 (t, J=5Hz, 2H)

Preparation of 3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid 3-phenylprop-2-en-1-yl ester

In a 2 necked round bottomed flask (280 mg 1.0 mmol) of β-keto ester **31** was taken in dry DCM (8 ml) and the mixture was cooled in ice. TBDMSOTf (304 mg, 1.15 mmol) in DCM (4 ml) was added under Ar via syringe. After stirring for 3 min. TEA (125 mg, 1.25 mmol) in DCM (1 ml) was added and the solution was stirred at 0°C for one hr. Saturated $NaHCO_3$ solution (2 ml) was added and the reaction mixture was transferred to a separating funnel. The separated organic layer was washed successively with water, brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded the crude silyl enol ether which was purified by flash chromatography

to afford 3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid 3-phenylprop-2-en-1-yl ester **72** (359 mg, 91 %) as a pale yellow oil.

3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid 3-phenylprop-2-en-1-yl ester



IR (neat) cm^{-1}

1728, 1595

^{1}H NMR δ (200 MHz, $CDCl_3$)

8.1-8.0 (m, 2H), 7.55-7.35 (m, 8H), 6.5 (d, J=15Hz, 1H), 6.3 (dt, J=15Hz, 4Hz, 1H), 5.75 (s, 1H), 4.8 (dd, J=4Hz, 2Hz, 2H), 1.0 (s, 9H), 0.1 (s, 6H)

Ceric ammonium nitrate mediated cyclisation of 3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid 3-phenylprop-2-en-1-yl ester

A solution of 3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid 3-phenylprop-2-en-1-yl ester (180 mg 0.5 mmol) in dry MeCN (8 ml) was added slowly over 3 hrs to a solution of ceric ammonium nitrate (548 mg 1.0 mmol) and $NaHCO_3$ (212 mg, 2.0 mmol) in dry MeCN (4 ml) at 25°C. The mixture was stirred at 25°C for a further period of 4 hrs. the reaction mixture was diluted with Et_2O (25 ml) and neutalised with 5 % HCl. The organic layer was washed with water, brine and dried. The crude product was purified by flash chromatography to afford a product (134 mg, 96%) that was identified as 3-oxo-3-phenyl-propanoic acid 3-phenyl-2-propenyl ester (E)

Palladium (II) acetate mediated cyclisation of 3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid 3-phenylprop-2-en-1-yl ester

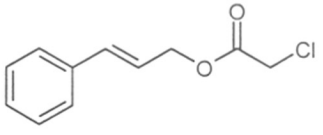
A solution of 3-(*t*-butyl-dimethyl-silanyloxy)-3-phenyl-acrylic acid 3-phenylprop-2-en-1-yl ester (180 mg 0.5 mmol) in dry MeCN: DCM (1:1, 6 ml) was added slowly over 3 hrs to a solution containing Palladium acetate (112 mg 0.5 mmol) in dry MeCN (10 ml) at 25°C. The mixture was stirred at 25°C for a further period of 4 hr. under Ar for 14 hrs. The solvent was removed in vacuum and the residue was taken in 15 ml hexane. Palladium was removed by filtration through celite. The combined filtrate was washed with $NaHCO_3$, water and finally with brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded a product (130 mg, 92.8%) that was identified by comparison with authentic sample **72**.

Preparation of α halo esters

Condensation of chloroacetyl chloride with cinnamyl alcohol

Cinnamyl alcohol (1.34 gm, 10 mmol) was mixed with TEA (1.11 gm, 1.53 ml, 11.0 mmol) in 30 ml of dry DCM at 0°C. To this solution chloroacetyl chloride (1.13 gm, 0.8 ml, 10mmol) in 6 ml of DCM was added drop-wise. The reaction mixture was stirred at 0°C for ½ an hr. and then at room temp. for 2 hrs. The precipitated TEA.HCl was filtered off and the organic layer was washed with dil. HCl (5 ml), brine and dried. Removal of the solvent under reduced pressure yielded chloro-acetic acid 3-phenyl-allyl ester which was purified by column chromatography (1.92 gm, 92%).

Chloro-acetic acid 3-phenyl-allyl ester



IR (neat) cm^{-1}

1740, 1600, 970

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.4-7.2 (m, 5H), 6.6 (d, J=15Hz, 1H), 6.3-6.1(m, 1H), 4.8 (d, J=6Hz, 2H), 4.0 (s, 2H)

Mass (70 eV)

m/z 212 (M+2), 210 (M^+), 175, 161, 133, 115 (base peak), 105, 91, 77, 63, 58

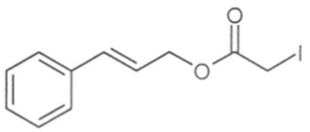
UV (MeOH) λ_{max}

210, 252, 292 nm.

Preparation of iodo-acetic acid 3-phenyl-allyl ester

α Chloro acetic acid 3-phenyl-allyl ester (630 mg, 3.0 mmol), NaI (750 mg, 5.0 mmol), K_2CO_3 (690 mg, 5.0 mmol) were mixed in dry acetone (15 ml). The mixture was refluxed for 2 hrs. Solid NaCl formed was filtered off and solvent was removed under reduced pressure. Residue was taken up in EtOAc, washed with water brine and dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded iodo-acetic acid 3-phenyl-allyl ester followed by purification gave the product **75** (900 mg, >95 %) as a colourless oil.

Iodo-acetic acid 3-phenyl-allyl ester



IR (neat) cm^{-1}

1730, 1600, 1100

^1H NMR δ (90 MHz, $CDCl_3$)

7.4-7.2 (m, 5H), 6.7 (d, J=15Hz, 1H), 6.3-6.1 (m, 1H), 4.8 (d, J=6Hz, 2H), 3.8 (s, 2H)

Mass (70 eV)

m/z 302 (M^+), 270, 254, 234, 210, 186, 175, 169, 141, 133, 115 (base peak), 105, 97, 91, 77

UV (MeOH) λ_{max}

210, 252, 292 nm.

Photochemical Cyclisation

Chloro-acetic acid 3-phenyl-allyl ester (420 mg 2.0 mmol) and zinc wool (165 mg 2.5 mmol) were taken in a quartz tube and dry Methanol [0.2 M Solution] was added while N_2 was bubbled for 20 min. and then the reaction mixture was kept in the photochemical reactor for irradiation at 300 nm using Hanovia lamp for 3 hrs (TLC analysis showed complete disapperance of starting material). The reaction mixture was cooled to room temp. and the zinc wool was filtered, washed off with Methanol (2 X 4 ml) and the solvent was removed under reduced pressure. Purification of the crude material provided cinnamyl alcohol which was confirmed by NMR analysis.

Cinnamyl alcohol

IR (neat) cm^{-1}

3340, 1600

^1H NMR δ (60 MHz, CCl_4)

7.4-7.4 (m, 2H), 6.7 (d, J=14Hz, 1H), 6.3-6.2 (m. 1H), 4.2 (d, J=8Hz, 2H), 1.9 (br, OH)

Dark reaction

Chloroacetic acid 3-phenyl-allyl ester (420 mg 2.0 mmol) and zinc wool (165 mg 2.5 mmol) were mixed in dry Methanol [0.2 M Solution] and covered with carbon paper and stirred under N_2 for 6 hrs (TLC analysis showed complete disapperance of starting material). The zinc wool was filtered, washed off with Methanol (2 X 4 ml) and

the solvent was removed under reduced pressure. Purification of the crude material provided cinnamyl alcohol which was confirmed by its NMR analysis.

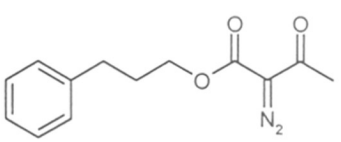
General procedure for the diazo transfer reaction

Preparation of mesyl azide

To a well-stirred solution containing 5.7 gm (50 mmol) of mesyl chloride dissolved in 30 ml of absolute methanol was added over ½ hr. 4.25 gm (65 mmol) of sodium azide in portions of 500 mg each. The solution was stirred for 30 min. at room temp. and filtered under N_2. Methanol was removed under reduced pressure and the product obtained as a liquid was stored at 0°C in the fridge. This was used as such for all the diazo transfer reactions. Yield 3.9 gm (64%).

A solution of mesyl azide (1.2 mmol) in dry DCM (5ml) was added drop wise over 10 min. to a stirred solution containing β-keto ester (1.0 mmol) and TEA (1.15 mmol) in 5 ml of dry DCM. The resulting yellow solution was stirred over night at room temp. After the completion of the reaction (as monitored by TLC) the reaction mixture was transferred to a separating funnel. The reaction flask was rinsed with more DCM (8-10 ml). The combined organic layer was washed successively with water, aq. NaOH (5%), water and finally with brine. It was dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded the crude diazo ester which was purified further by column chromatography using DCM as the eluent.

2-Diazo-3-oxo-butyric acid 3-phenyl-propyl ester



Yield : 212 mg (86 %)

IR (neat) cm^{-1}

2146, 1730, 1690, 1600

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

7.3-7.1 (m, 5H), 4.3 (t, J=6Hz, 2H), 2.7 (t, J=6Hz, 2), 2.5 (s, 3H), 2.1-2.0 (m, 2H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

189.66 (s), 161.16 (s), 140.69 (s), 128.40 (d), 128.22 (d), 126.05 (d), 76.10 (s), 64.61 (t), 32.06 (t), 30.04 (q), 28.03 (t)

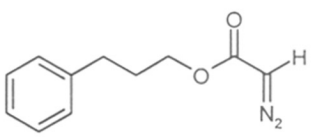
Mass (70 eV)

m/z 247 (M+1), 238, 228, 218, 200, 185, 175, 163, 157, 134, 129, 118 (base peak), 91, 83, 77, 65

Preparation of diazoacetic acid 3-phenylpropyl ester

The α-diazo β-keto ester obtained as above (246 mg, 1.0 mmol) was dissolved in MeCN (10 ml) and to this stirred solution, 0.1N NaOH (2 ml) was added and the mixture was stirred over night at room temp. The reaction mixture was diluted with Et_2O (25 ml). The organic layer was separated and washed successively with water, 0.01N HCl, water and finally with brine. After drying with Na_2SO_4 the removal of the solvent under reduced pressure yielded the deacylated product as an yellow oil. Further purification using silica gel column chromatography yielded the pure product.

Diazo-acetic acid 3-phenyl-propyl ester



Yield : 149 mg (73 %)

IR (neat) cm^{-1}

2150, 1735, 1590

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.3-7.2 (m, 5H), 4.7 (s, 1H), 4.25 (t, J=7Hz, 2H), 2.75 (t, J=7Hz, 2H), 2.1-2.0 (m, 2H)

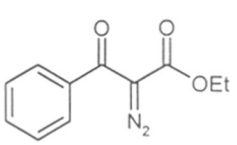
^{13}**C** NMR δ (50 MHz, $CDCl_3$)

166.42 (s), 141.17 (s), 128.63 (d), 128.56 (d), 126.23 (d), 64.21 (t), 46.04 (d), 32.31 (t), 30.68 (t)

Mass (70 eV)

m/z 205 (M+1), 194, 176, 158, 130, 117, 104, 91 (base peak), 77, 69, 65

2-Diazo-3-oxo-3-phenylpropanoic acid ethyl ester



Yield : 174 mg (86 %)

IR (neat) cm^{-1}

2140, 1730, 1690, 1595

^{1}H NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=7Hz, 1.5Hz, 2H), 7.75-7.65 (m, 1H), 7.45-7.3 (m, 2H), 4.3 (q, J=7Hz, 2H), 1.35 (t, J=7Hz, 3H)

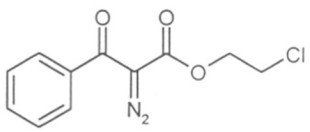
^{13}C NMR δ (50 MHz, $CDCl_3$)

186.36 (s), 160.67 (s), 136.96 (s), 131.94 (d), 128.15 (d), 127.59 (d), 75.84 (s), 61.29 (t), 13.91 (q)

Mass (70 eV)

m/z 219 (M+1),218 (M^+), 217, 208, 182, 173, 162, 156, 146, 134, 117, 105 (base peak), 89, 77, 63

2-Diazo-3-oxo-3-phenylpropanoic acid 2-chloroethyl ester



Yield : 200 mg, 79 %

IR (neat) cm^{-1}

2138, 1734, 1695, 1595

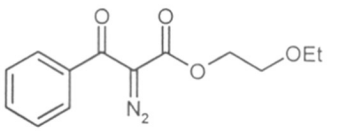
^{1}H NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=7Hz, 1.2Hz, 2H), 7.6-7.5 (m, 1H), 7.45-7.35 (m, 2H), 4.4 (t, J=5Hz, 2H), 3.75 (t, J=5Hz, 2H)

Mass (70 eV)

m/z 254 (M+2), 253 (M+1), 252 (M^+), 224, 161, 145, 117, 105 (base peak), 89, 77, 63

2-Diazo-3-oxo-3-phenylpropanoic acid 2-ethoxyethyl ester



Yield : 225 mg, 86 %

IR (neat) cm^{-1}

2140, 1730, 1690, 1595

^{1}H NMR δ (200 MHz, $CDCl_3$)

7.7-7.6 (m, 5H), 4.3-4.2 (m, 2H), 3.7-3.6 (m, 2H), 3.45 (q, J=7Hz, 2H), 1.25 (t, J=7Hz, 3H)

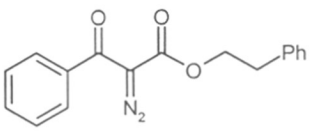
^{13}C NMR δ (50 MHz, $CDCl_3$)

185.95 (s), 160.44 (s), 136.73 (s), 131.78 (d), 128.07 (d), 127.40 (d), 75.74 (s), 67.50 (t), 65.99 (t), 64.16 (t), 14.65 (q)

Mass (70 eV)

m/z 264 (M+2), 263 (M+1), 262 (M^+), 252, 234, 219, 205, 190, 173, 162, 145, 133, 117, 105 (base peak), 89, 77, 72, 59

2-Diazo-3-oxo-3-phenylpropanoic acid phenethyl ester



Yield : 215 mg, 73 %

IR (neat) cm^{-1}

2135, 1720, 1690, 1590

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=7Hz, 1.8Hz, 2H), 7.6-7.5 (m, 4H), 7.35-7.2 (m, 4H), 4.4 (t, J=5Hz, 2H), 3.0 (t, J=5Hz, 2H)

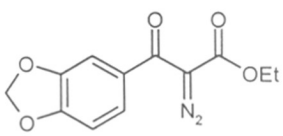
^{13}**C** δ (50 MHz, $CDCl_3$)

186.00 (s), 160.41 (s), 137.11 (s), 136.77 (s), 131.93 (d), 128.56 (d), 128.19 (d), 127.52 (d), 126.35 (d), 75.8 (s), 65.51 (t), 34.66 (t)

Mass (70 eV)

m/z 264 (M+2), 263 (M+1), 262 (M^+), 252, 234, 219, 205, 190, 173, 162, 145, 133, 117, 105 (base peak), 89, 77, 72, 59

Benzenepropanoic acid, -3,4-methylenedioxy-α-diazo--β-oxo-, ethyl ester



Yield : 220 mg, 84 %

IR (neat) cm^{-1}

2148, 1725, 1620, 1590

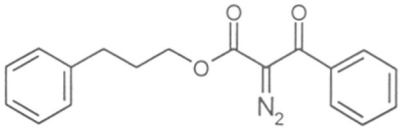
^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.6 (dd, J=6Hz, 1.5Hz, 1H), 7.4 (d, J=1.2Hz, 1H), 6.95 (d, J=6Hz, 1H), 6.1 (s, 2H), 4.2 (q, J=7Hz, 2H), 1.3 (t, J=7Hz, 3H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

184.35 (s), 160.88 (s), 151.15 (s), 147.22 (s), 130.78 (s), 124.56 (d), 108.80 (d), 107.26 (d), 101.68 (t), 75.84 (s), 61.29 (t), 14.07 (t)

2-Diazo-3-oxo-3-phenylpropanoic acid 3-phenylpropyl ester



Yield : 247 mg, 80 %

IR (neat) cm^{-1}

2145, 1727, 1631, 1495

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=7Hz, 1.6Hz, 1H), 7.5-7.35 (m, 3H), 7.3-7.15 (m, 5H), 4.3 (t, J=7Hz, 2H), 2.65 (t, J=7Hz, 3H), 2.1-1.9 (m, 2H)

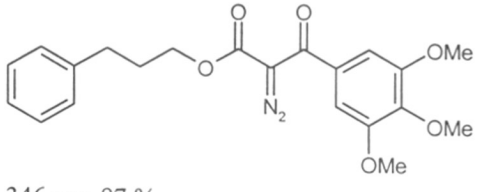
^{13}C NMR δ (50 MHz, $CDCl_3$)

186.80 (s), 161.29 (s), 141.25 (s), 137.65 (s), 132.55 (s), 128.78 (d), 128.22 (d), 126.45 (d), 78.56 (s), 65.24 (t), 32.36 (t), 30.38 (t)

Mass (70 eV)

m/z 308 (M^+), 280, 262, 252, 238, 210, 191, 178, 162, 145, 129, 118, 105 (base peak), 91, 77, 65

Benzenepropanoic acid, -3,4,5-Trimethoxy-α-diazo-β-oxo-, 3-phenylpropyl ester



Yield : 346 mg, 87 %

IR (neat) cm^{-1}

2148, 1725, 1620, 1590

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.3-7.1 (m, 7H), 4.25 (t, J=6Hz, 2H), 3.95 (s, 6H), 3.85 (s, 3H), 2.7-2.6 (m, 2H), 2.1-2.0 (m, 2H)

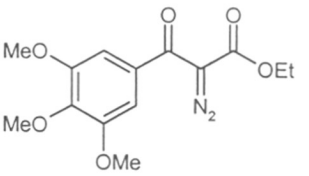
^{13}C NMR δ (50 MHz, $CDCl_3$)

185.05 (s), 160.98 (s), 152.86 (s), 142.71 (s), 142.57 (s), 131.97 (s), 128.64 (d), 127.26 (d), 126.94 (d), 107.25 (d), 107.06 (d), 76.02 (s), 60.83 (t), 56.45 (q), 39.14 (t), 30.67 (t)

Mass (70 eV)

m/z 398 (M^+), 370, 355, 308, 294, 280, 265, 252, 237, 226, 221, 210, 195 (base peak), 181, 165, 149, 136, 125, 117, 110, 105, 99, 91, 81, 77, 65

Benzenepropanoic acid, -3,4,5-Trimethoxy-α-diazo-β-oxo-, ethyl ester



Yield : 209 mg, 68 %

IR (neat) cm^{-1}

2148, 1725, 1620, 1590

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.0 (s, 2H), 4.1 (q, J=7Hz, 2H), 3.8 (s, 9H), 1.3 (t, J=7Hz, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

184.35 (s), 160.88 (s), 151.15 (s), 147.22 (s), 130.78 (s), 124.56 (d), 108.80 (d), 107.26 (d), 101.68 (t), 75.84 (s), 61.29 (t), 14.07 (t)

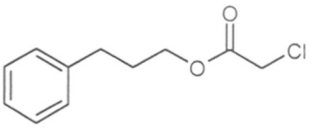
Mass (70 eV)

m/z 309 (M+1), 308 (M^+), 280, 265, 252, 237, 221, 209, 195 (base peak), 179, 165, 149, 137, 121, 109, 93, 81, 77, 66

General procedure for the preparation of 88, 89, 90, 91

The corresponding acid (10.0 mmol) was converted to its acid chloride by treatment with thionyl chloride (12.0 mmol) in benzene. Removal of the solvent under reduced pressure followed by vacuum distillation afforded the corresponding acid chloride. Treatment of this acid chloride with the corresponding alcohol (8.0 mmol) in the presence of TEA (10.0 mmol) at 0°C followed by usual work-up furnished the crude esters. The esters were purified by silica gel column chromatography.

Chloroacetic acid, 3-phenylpropyl ester



Yield : 1.98 gm, 93 %

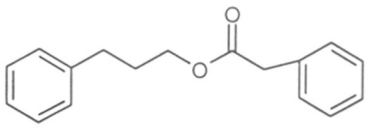
IR (neat) cm^{-1}

1732, 1590, 960

^{1}H NMR δ (200 MHz, $CDCl_3$)

7.5-7.4 (m, 5H), 4.1 (t, J=7Hz, 2H), 3.9 (s, 2H), 2.8 (t, J=7Hz, 2H), 2.1-2.0 (m, 2H)

Phenylacetic acid, 3-phenylpropyl ester



Yield : 2.29 gm, 90 %

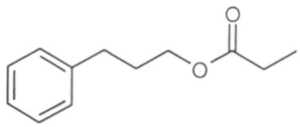
IR (neat) cm^{-1}

1736, 1595

^{1}H NMR δ (200 MHz, $CDCl_3$)

7.6-7.4 (m, 10H), 4.1 (t, J=7Hz, 2H), 3.6 (s, 2H), 2.8 (t, J=7Hz, 2H), 2.1-2.0 (m, 2H)

Propanoic acid, 3-phenylpropyl ester



Yield : 1.86 gm, 97 %

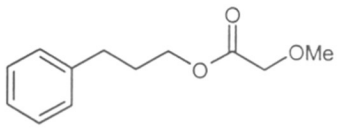
IR (neat) cm^{-1}

1741, 1596

^{1}H NMR δ (200 MHz, $CDCl_3$)

7.5-7.4 (m, 5H), 4.15 (t, J=7Hz, 2H), 2.8 (t, J=7Hz, 2H), 2.3 (t, J=6.5Hz, 2H), 2.1-2.0 (m, 2H), 1.15 (t, J=6.5Hz, 3H)

Methoxy-acetic acid, 3-phenylpropyl ester



Yield : 1.87 gm, 90 %

IR (neat) cm^{-1}

1730, 1590

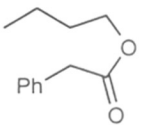
^{1}H NMR δ (200 MHz, $CDCl_3$)

7.5-7.4 (m, 5H), 4.25 (t, J=7Hz, 2H), 4.05 (s, 2H), 3.5 (s, 3H), 2.75 (t, J=7Hz, 2H), 2.05-1.95 (m, 2H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

169.89 (s), 140.75 (s), 128.14 (d), 128.08 (d), 125.75 (d), 69.37 (t), 63.71 (t), 58.86 (q), 31.80 (t), 29.84 (t)

Phenylacetic acid, butyl ester



Yield : 1.57 gm, 82 %

IR (neat) cm^{-1}

1742, 1590

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.5-7.3 (m, 5H), 4.2 (t, J=7Hz, 2H), 3.6 (s, 2H), 1.7-1.6 (m, 2H), 1.4-1.3 (m, 2H), 0.9 (t, 3H)

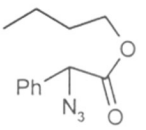
^{13}C NMR δ (50 MHz, $CDCl_3$)

169.06 (s), 134.25 (s), 128.91 (d), 128.41 (d), 127.55 (d), 64.52 (t), 30.38 (t), 23.21 (t), 18.85 (t), 13.51 (q)

Attempted diazo transfer of compound phenylacetic acid, butyl ester

In to a 2 necked round bottomed flask dry diisopropyl amine (202 mg, 0.28 ml, 2.0 mm0l) was taken in dry THF (8 ml). The solution was cooled to 0°C. n-BuLi (128 mg, 1.0 ml, 2.0 M solution in hexane, 2.0 mmol) was added to this cold solution and it was stirred at 0°C for ½ hr. It was then cooled to –78°C and a solution of the ester **91** (384 mg, 2.0 mmol) in dry THF (5 ml) was added slowly. After 45 min. at –78°C pNBSA (456 mg, 2.0 mmol) in dry THF (20 ml) was added slowly. The reaction mixture was stirred at –78°C for 2 more hrs. The reaction was quenched by the addition of saturated solution of NH_4Cl. the solid materials obtained were filtered off and the organic layer was separated and washed with brine. Drying over Na_2SO_4 followed by removal of the solvent under reduced pressure gave the crude product which was purified by silica gel column chromatography.

2-Azido-phenyl-acetic acid butyl ester



Yield : 312 mg, 67 %

IR (neat) cm^{-1}

2088,1740, 1590

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.5-7.4 (m, 3H), 7.35-7.25 (m, 2H), 4.9 (s, 1H), 4.25 (t, J=7Hz, 2H), 1.7-1.6 (m, 2H), 1.4-1.3 (m, 2H), 0.9 (t, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

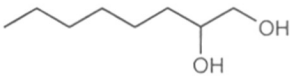
171.39 (s), 134.18 (s), 129.17 (d), 129.07 (d), 128.25 (d), 65..73 (t), 65.28 (d), 23.28 (t), 19.01 (t), 13.25 (q)

Preparation of compound 107

Preparation of diol 104

Potassium ferricyanide (3.30 gm, 10.0 mmol) and potassium carbonate (1.38 gm, 10.0 mmol) were added to a solution (containing *t*-BuOH:water, 1:1, 20 ml). A solution of OsO_4 (50 µl, 6.0 mg, 0.5 M in toluene, 0.01 mmol) was added at 0°C and stirred for 10 more min. Octene (1.32 gm, 10.0 mmol) was added and the reaction mixture was stirred at room temp. for 24 hrs. The reaction was quenched with sodium metabisulfite (2.08 gm, 12.0 mmol) and extracted with EtOAc (3 X 20 ml), washed with brine and dried over Na_2SO_4. Removal of the solvent furnished the crude diol which was purified further by silica gel column chromatography (1.4 gm, 96 %).

Diol 104



IR (neat) cm^{-1}

3315

^{1}**H** NMR δ (90 MHz, $CDCl_3$)

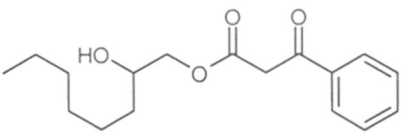
3.75-3.6 (m, 2H), 3.5-3.4 (m, 1H), 2.95 (br, OH), 1.4-1.2 (br, 10 H), 0.95-0.85 (m, 3H)

Selective transesterification of the diol 104

β Keto ester **33** (1.92 gm, 10. mmol) and the diol (1.46 gm, 10.0 mmol) were mixed in dry toluene (30 ml) to which 10 % (195 mg,) of the kaolinitic clay catalyst was added. The resultant mixture was heated to 110°C (bath temp.) with azeotropic removal of ethanol. After 8 hrs. The reaction mixture was cooled, the catalyst was filtered off and washed with more solvent (10 ml). The combined solvent was removed under

reduced pressure. Purification by column chromatography yielded the mono transesterified product (1.43 gm, 49%).

Compound 105



IR (neat) cm^{-1}

3315, 1738, 1690

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=7Hz, 1.9Hz, 2H), 7.65-7.45 (m, 3H), 5.1-5.0 (m, 1H), 4.3-4.05 (m, 4H), 2.75 (br, OH), 1.55-1.45 (m, 2H), 1.4-1.25 (m, 8H), 0.95-0.85 (m, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

192.18 (s), 167.02 (s), 135.84 (s), 133.55 (d), 128.61 (d), 128.37 (d), 125.94 (d), 86.83 (enolic), 72.34 (d), 65.37 (t), 45.77 (t), 32.99 (t), 31.38 (t). 28.76 (t), 24.68 (t), 22.35 (t), 14.36 (q)

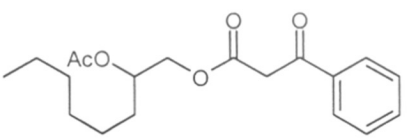
Mass (70 eV)

m/z 292 (M^+), 275, 257, 246, 233, 212, 200, 178, 165, 147, 120, 105 (base peak), 97, 77, 69, 55

Preparation of 106

Compound **105** (584 mg, 2.0 mmol) and acetic anhydride (255 mg, 2.5 mmol) were taken in DCM (10 ml). The resultant mixture was cooled to 0°C. To this mixture pyridine (316 mg, 4.0 mmol) in DCM (2 ml) was added at a slow rate. The reaction mixture was stirred at room temp. over night. After the reaction was over the reaction mixture was washed with water followed by brine. After drying over Na_2SO_4 and removal of the solvent under reduced pressure furnished the crude product which was purified by column chromatography to yield the pure acetate (574 mg, 86%).

Compond 106



IR (neat), cm^{-1}

3310, 1740, 1690, 1590

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=6.8Hz, 1.7Hz, 2H), 7.55-7.45 (m, 3H), 5.1-5.0 (m, 1H), 4.3-4.2 (m, 2H), [4.0, 5.75, 12.45] (s, 2H), 2.1 (s, 3H), 1.65-1.55 (m, 2H), 1.3-1.2 (m, 8H), 0.95-0.85 (m, 3H)

^{13}**C** NMR (50 MHz, $CDCl_3$)

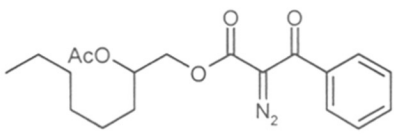
192.02 (s), 170.46 (s), 167.19 (s), 136.04 (s), 133.69 (d), 128.77 (d), 128.54 (d), 86.95 (enolic), 71.34 (d), 65.80 (t), 45.64 (t), 31.60 (t), 30.56 (t)28.98 (t), 25.01 (t), 22.51 (t), 20.90 (q), 14.02 (q)

Mass (70 eV)

m/z 334 (M^+), 319, 292, 221, 207, 190, 178, 171, 165, 147, 120, 110, 105 (base peak), 97, 77, 69, 55

Diazo compound 107

Prepared according to the general procedure 295 mg, 82 %.



IR (neat), cm^{-1}

2140, 1735, 1680, 1560

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.7-7.4 (m, 5H), 5.1-5.0 (m, 1H), 4.45 (dd, J=6Hz, 1.4Hz, 1H), 4.3 (dd, J=7Hz, 1.5Hz, 1H), 4.1-4.0 (m, 1H), 2.1 (s, 3H), 1.65-1.55 (m, 2H), 1.3-1.2 (m, 8H), 0.95-0.85 (m, 3H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

185.97 (s), 169.98 (s), 160.30 (s), 136.69 (s), 131.89 (d), 128.41 (d), 128.01 (d), 127.50 (d), 75.74 (s), 70.86 (d), 65.61 (t), 31.18 (t), 30.09 (t), 28.55 (t), 24.62 (t), 22.10 (t), 20.13 (q), 13.61 (q)

Mass (70 eV)

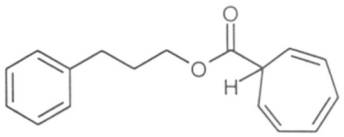
m/z 360 (M^+), 342, 332, 317, 299, 290, 282, 274, 256, 247, 229, 220, 204, 191, 176, 171, 162, 146, 128, 118, 110, 105 (base peak), 97, 81, 77, 69

General procedure for diazo decomposition

In a typical experiment 200 mg of the diazo ester dissolved in rigourously dried DCM/benzene (5 ml) was added slowly over 10 hr. (using syringe pump 0.5 ml /hr) to a refluxing solution containing $Rh_2(OAc)_4$ (8 mg, 2.0 mol %) and the solvent DCM/benzene (10 ml). After the addition was over the reaction mixture was refluxed

further for 3 hrs. The reaction mixture was cooled and was passed through a small plug of celite to remove the catalyst. The products were isolated by chromatographic purification using flash silica gel (230-400 mesh).

When reaction was performed with 77 using benzene as the solvent



Yield : 172 mg, 68 %

IR (neat) cm^{-1}

1742, 1590

^1H NMR δ (200 MHz, $CDCl_3$)

7.34-7.28 (m, 2H), 7.23-7.19 (m 3H), 6.68 (t, J=2.86Hz), 6.32-6.26 (m, 2H), 5.46 (dd, J=8.82, 5.60Hz, 2H), 4.24 (t, J=6.54Hz, 2H), 2.74 (t, J=7.29Hz, 2H), 2.61-2.58 (m, 1H), 2.08-1.98 (m,2H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

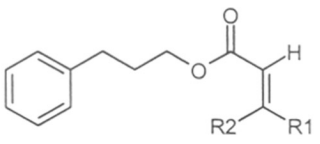
172.86 (s), 140.92 (s), 130.77 (d), 128.28 (d), 125.93 (d), 125.52 (d), 117.01 (d), 64.24 (t), 43.98 (d), 32.03 (t), 30.09 (t)

Mass (70 eV)

m/z 254 (M^+), 245, 236, 222, 206, 191, 182, 165, 149, 136, 118, 105, 91 (base peak), 84, 77, 65

When reaction was performed with 77 using benzene as the solvent

Fumarate and maleate



Fumarate R1= $C_6H_5(CH_2)_3OCO$, R2 = H

Maleate R1= H, R2 = $C_6H_5(CH_2)_3OCO$

Isomer I (53 mg)

IR ($CHCl_3$) cm^{-1}

1738, 1595

^1H NMR δ (200 MHz, $CDCl_3$)

7.3-7.2 (m, 5H), 6.85 (s, 1H), 4.25 (t, J=5.6 Hz, 2H), 2.75 (t, J=7.3Hz, 2H), 2.1-1.95 (m, 2H)

Isomer II (62 mg)

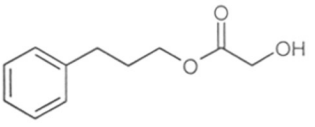
IR ($CHCl_3$) cm^{-1}

1742,1600

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.3-7.2 (m, 5H), 6.25 (s, 1H), 4.25 (t, J=5.6 Hz, 2H), 2.75 (t, J=7.3Hz, 2H), 2.1-1.95 (m, 2H)

Water insertion product



Yield : 43 mg

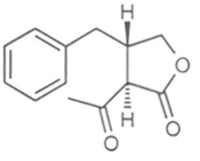
IR (neat) cm^{-1}

3320, 1738, 1590

^{1}**H** NMR (200 MHz, $CDCl_3$)

7.3-7.2 (m, 5H), 4.25 (s, 2H), 4.25 (t, J=7Hz, 2H), 2.75 (t, J=7Hz, 2H), 2.1-1.9 (m, 2H)

When R = $COCH_3$



Yield : 152 mg, 63 %

IR (neat) cm^{-1}

1764,1708, 1602

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

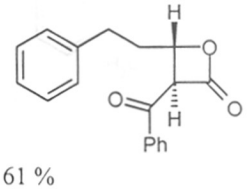
7.3-7.2 (m, 5H), 4.45 (dd, J=8Hz, 4Hz, 1H), 4.0 (dd, J=8Hz, 4Hz, 1H), 3.4 (d, J=8Hz, 1H), 2.85 (d, J=8HZ, 2H), 2.7-2.6 (m,1H), 2.35 (s, 3H)

Analysis for $C_{13}H_{14}O_3$ (Mol. Wt 218.25)

Calculated C = 76.25 %, H = 6.83 %

Observed C = 76.01 %, H = 6.70%

When R = COPh



Yield : 119 gm, 61 %

IR (neat) cm^{-1}

1822, 1710, 1600

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.1-8.0 (m, 2H), 7.72-7.6 (m, 1H), 7.6-7.48 (m, 2H), 7.35-7.1 (m, 5H), 5.3-5.2 (m, 1H), 4.75 (d, J=4.4Hz, 1H), 3.0-2.85 (m, 1H), 2.85-2.7 (m, 1H), 2.5-2.15 (m, 2H).

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

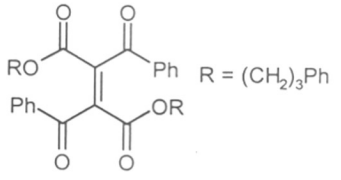
188.11 (s), 167.65 (s), 142.05 (s), 139.77 (s), 134.33 (d), 129.19 (d), 128.84 (d), 128.68 (d), 128.36 (d), 126.47 (d), 72.81 (d), 65.01 (d), 35.38 (t), 31.17 (t)

Analysis for $C_{18}H_{16}O_3$ (Mol. Wt 280.33)

Calculated C = 76.57 %, H = 6.43 %

Observed C = 76.34 %, H = 6.20 %

Dimer



Yield : 35 mg

IR ($CHCl_3$) cm^{-1}

1740, 1690, 1580

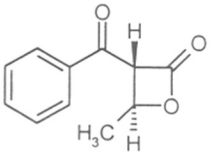
^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.0 (dd, J=6Hz, 1.3Hz, 4H), 7.5-7.35 (m, 6H), 7.3-7.15 (m, 10H), 4.3 (t, J=7Hz, 4H), 2.65 (t, J=7Hz, 4H), 2.0-1.9 (m, 4H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$)

191.83 (s), 170.08 (s), 140.61 (s), 134.83 (d), 131.71 (s), 129.00 (d), 128.52 (d), 128.47 (d), 126.20 (d), 92.09 (s), 66.18 (t), 31.55 (t), 29.79 (t)

3-Benzoyl-4-methyl-oxetan-2-one



Yield : 93 mg, 53 %

IR (neat) cm^{-1}

1820, 1720, 1595

^{1}H NMR δ (200 MHz, $CDCl_3$)

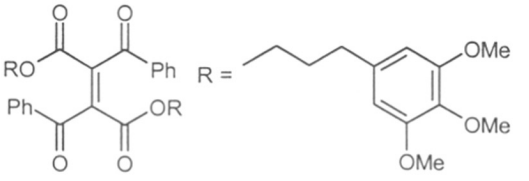
8.1-8.0 (m, 2H), 7.7-7.6 (m, 1H), 7.6-7.45 (m, 2H), 5.4-5.3 (m, 1H), 4.85 (d, J=4.4Hz, 1H), 1.85 (d, J=7.3Hz, 3H)

Analysis for $C_{11}H_{10}O_3$ (Mol. Wt 190.20)

Calculated C = 75.14 %, H = 6.20 %

Observed C = 74.95 %, H = 6.09 %

Dimer compound



Yield : 78 mg

IR ($CHCl_3$) cm^{-1}

1734, 1590

^{1}H NMR δ (200 MHz, $CDCl_3$)

7.3-7.1 (m, 14H), 4.25 (t, J=6Hz, 4H), 3.95 (s, 12H), 3.85 (s, 6H), 2.7-2.6 (m, 4H), 2.1-2.0 (m, 4H)

^{13}C NMR δ (50 MHz, $CDCl_3$)

190.52 (s), 170.34 (s), 170.23 (s), 153.07 (s), 152.95 (s), 144.06 (s), 140.38 (s), 128.40 (s), 128.22 (d), 126.32 (d), 126.09 (d), 107.92 (d), 107.54 (d), 92.24 (s), 65.86 (t), 60.92 (q), 56.24 (q), 31.35 (t), 29.72 (t)

Preparation of various Rh (II) catalysts

With trifluoro acetic acid

$Rh_2(OAc)_4$ (75 mg) was dissolved in trifluoro acetic acid (1.5 mg) and evaporated to dryness on a steam bath and this process was repeatedagain. The residue was dried briefly at 110°C. It was then dissolved in acetone and filtered through G4 crucible, allowed to crystalise slowly. After the evaporation of the solvent, the product was filtered and dried at 110°C.

With trimethyl acetic acid

$Rh_2(OAc)_4$ (100 mg) was mixed with trimethyl acetric acid (2.0 ml). The mixture was heated to 130°C under Ar for 9 hrs. The excess of the acid was removed by placing the mixture in vacuum decicator over phosphorous pentoxide for several days (10-15). The residue was recrystalised from $CHCl_3$:benzene (1:1) (3 ml).

With methoy acetic acid

$Rh_2(OAc)_4$ (100 mg) was mixed with methoy acetric acid (2.0 ml). The mixture was heated to 130°C under Ar for 9 hrs. The excess of the acid was removed by placing the mixture in vacuum decicator over phosphorous pentoxide for several days (10-15). The residue was recrystalised from $CHCl_3$:benzene (1:1) (3 ml).

Preparation of pNBSA

To a well-stirred solution containing 5.7 gm (50 mmol) of p-nitro benzenesulphonyl chloride dissolved in 30 ml of absolute methanol was added over ½ hr. 4.25 gm (65 mmol) of sodium azide in portions of 500 mg each. The solution was stirred for 30 min. at room temp. and filtered under N_2.

Yield : 4.14 gm (68 %)

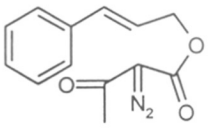
M.Pt 102°C (Lit.ref. 101-102°C).

IR (nujol) cm^{-1}

2137, 1391, 1346, 1175, 853.

Preparation of compound 114

Following the general procedure the diazo compound was prepared.



Yield : 200 mg, 82 %

IR ($CHCl_3$) cm^{-1}

2160, 1735, 1684, 1598

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.4-7.3 (m, 5H), 6.7 (d, J=16Hz, 1H), 6.4-6.3 (m, 1H), 4.9 (d, J=5.4Hz, 2H), 2.55 (s, 3H)

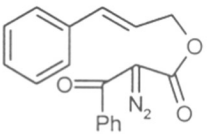
^{13}**C** NMR δ (50 MHz, $CDCl_3$)

190.01 (s), 161.33 (s), 136.05 (s), 135.50 (d), 128.84 (d), 128.55 (d), 126.89 (d), 122.47 (d), 77.93 (s), 66.02 (t), 28.35 (t)

Mass (70 eV)

m/z 244 (M^+), 232, 216, 208, 198, 187, 171, 155, 145, 133, 117 (base peak), 110, 103, 91, 83, 77

Preparation of compound 112



Yield : 230 mg, 73 %

IR ($CHCl_3$) cm^{-1}

2145, 1735, 1660, 1585

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

8.1-8.0 (m, 2H), 7.7-7.4 (m, 8H), 6.85 (d, J=16Hz, 1H), 6.4-6.3 (m, 1H), 4.9 (d, J=5.4Hz, 2H)

^{13}C NMR δ (75 MHz, $CDCl_3$)

185.78 (s), 160.11 (s), 136.48 (s), 135.37 (s), 134.22(d), 131.67 (d), 128.02 (d), 127.85 (d), 127.65 (d), 127.28 (d), 126.07 (d), 121.70 (d), 75.48 (s), 65.29 (t)

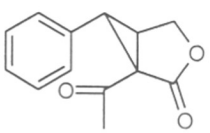
Mass (70 eV)

m/z 306 (M^+), 291, 278, 260, 247, 233, 215, 203, 191, 178, 172, 167, 157, 147, 133, 117 (base peak), 105, 91, 77, 63

General procedure for cyclopropanation

The diazo compound (200 mg, 5 ml benzene) was added to a refluxing solution containing the catalyst (10 mol % $Cu(acac)_2$ in 10 ml benzene) over a period of 8 hrs.. After the reaction was over the reaction mixture was passed through a short plug of celite to remove the catalyst. Removal of the solvent followed by column chromatography (using flash silica gel) furnished the required cyclopropyl lactone.

Cyclopropyl lactone 115



Yield : 131 mg, 73 %

IR ($CHCl_3$) cm^{-1}

1768, 1684, 1595

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.4-7.3 (m, 3H), 7.2-7.1 (m, 2H), 4.45 (dd, J=9Hz, 4.3Hz, 1H), 4.4 (d, J=8.6Hz, 1H), 3.4 (t, J=4.3Hz, 1H), 3.0 (d, J=4.4Hz, 1H), 2.35 (s, 3H)

Mass (70 eV)

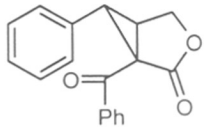
m/z 216 (M^+), 198, 186, 174, 155, 144, 129 (base peak), 115, 110, 105, 91, 85, 82, 77, 68, 63

Analysis for $C_{13}H_{12}O_3$ (216.24)

Calculated C = 72.21 %, H = 5.59 %

Observed C = 71.97 %, H = 5. 45 %

Cyclopropyl lactone 111



Yield : 127 mg, 70 %

IR ($CHCl_3$) cm^{-1}

1771, 1664, 1595

^{1}**H** NMR δ (200 MHz, $CDCl_3$)

7.85-7.7 (d, J=7.3Hz, 2H), 7.45-7.35 (m, 3H), 7.1-7.0 (m, 5H), 4.7 (dd, J=9Hz, 4Hz, 1H), 4.45 (d, J=8.7Hz, 1H), 3.45 (t, J=4.4Hz, 1H), 3.0 (d, J=4.4Hz, 1H)

^{13}**C** NMR δ (50 MHz, $CDCl_3$:CD_3COCD_3)

189.04 (s), 170.44 (s), 135.24 (s), 132.77 (s), 129.39 (d), 128.22 (d), 127.93 (d), 127.62 (d), 127.33 (d), 127.20 (d), 126.96 (d), 67.38 (t), 43.83 (s), 37.13 (d), 25.71 (d)

Mass (70 eV)

m/z 278 (M^+), 272, 254, 247, 226, 215, 200, 189, 172, 165, 151, 144, 128, 122, 115, 105 (base peak), 91, 77

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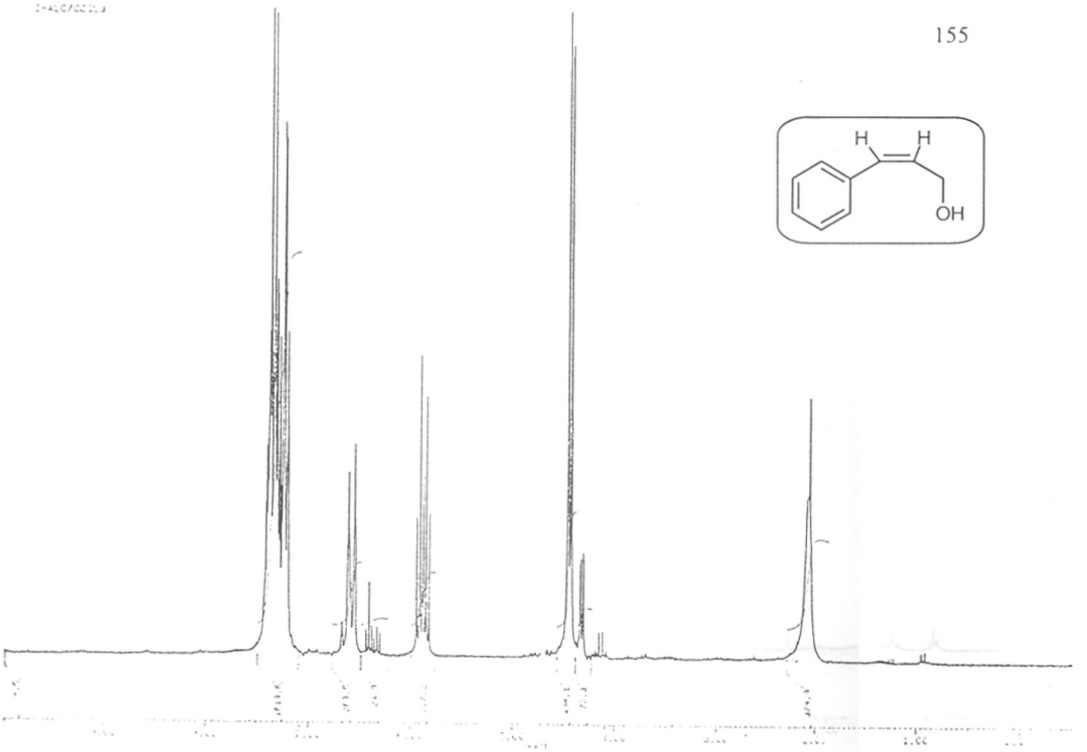
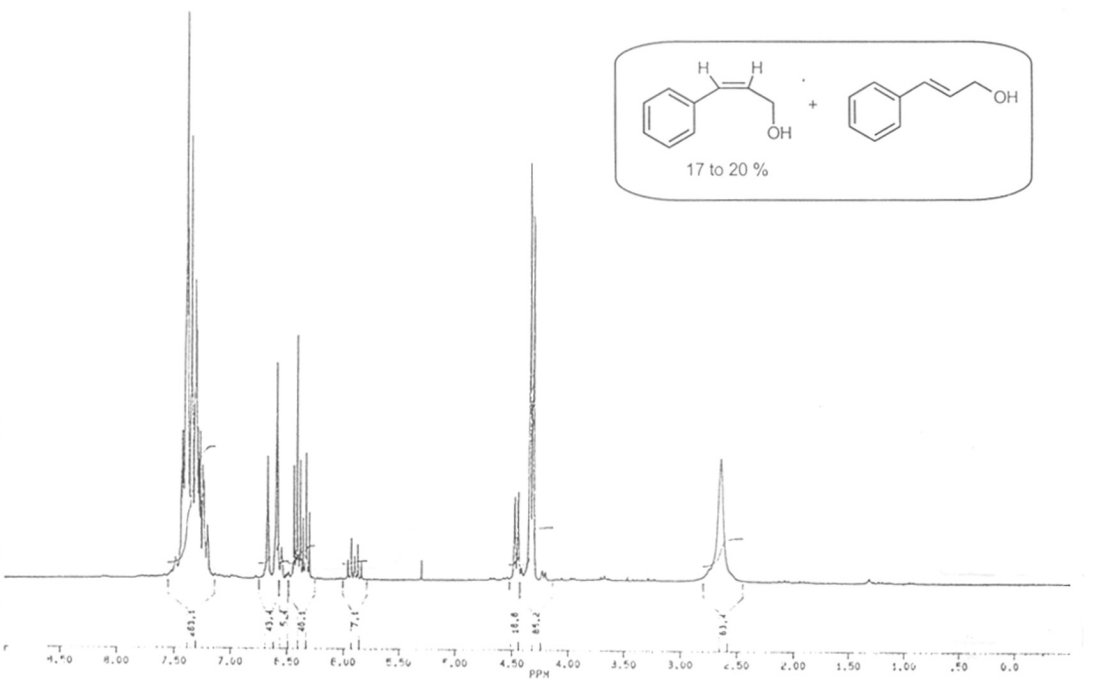
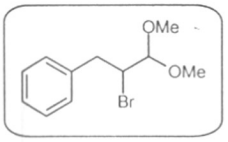
H
CO2Et
ppm



SAMPLE NO. PHOTO-CL-1 / CDCL3

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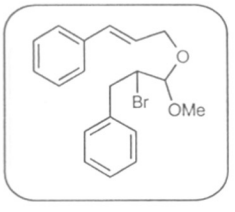
OMe
Br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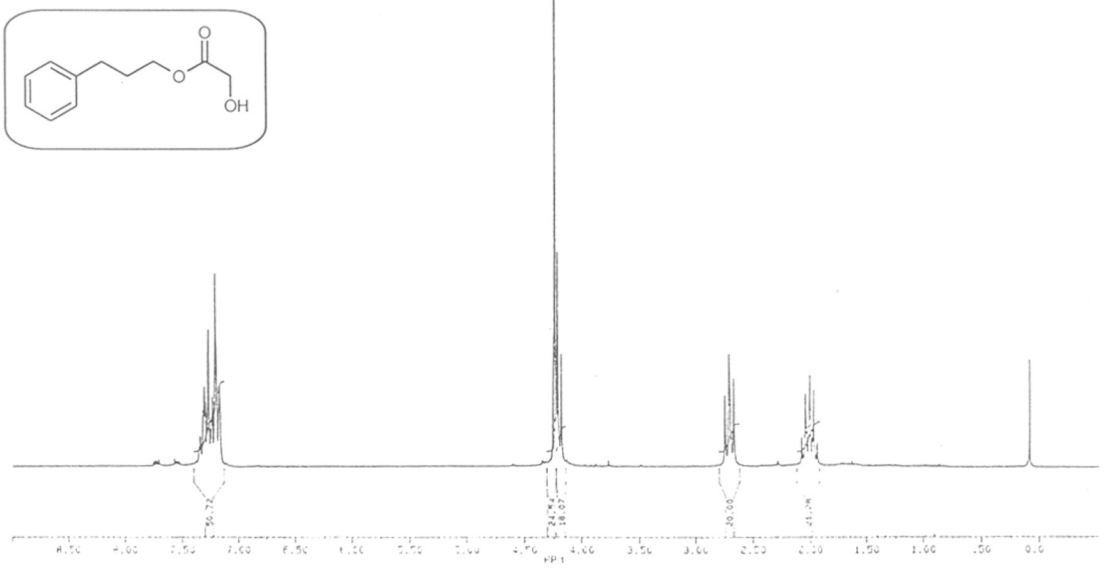
Br
OMe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OH
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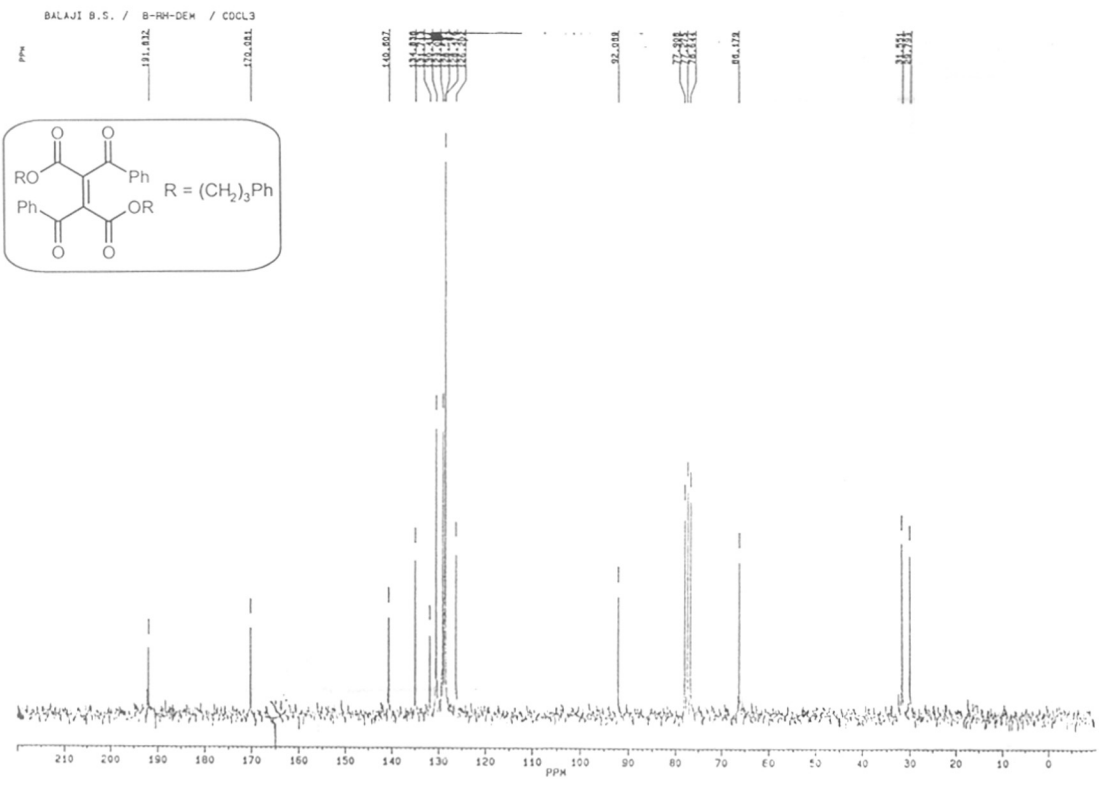
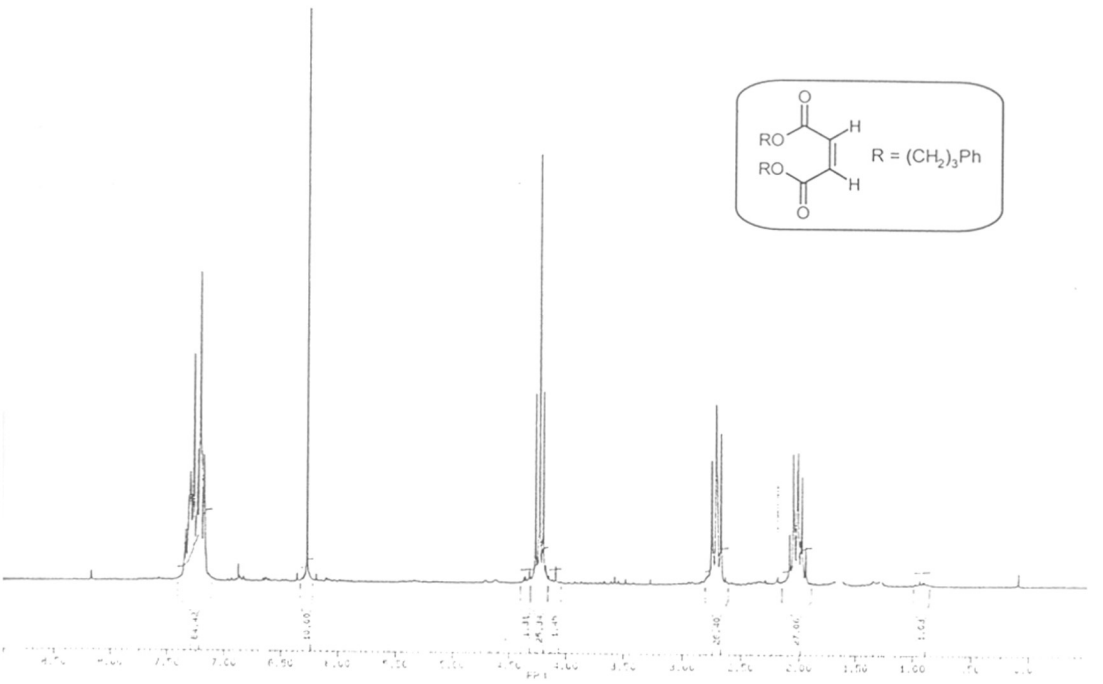
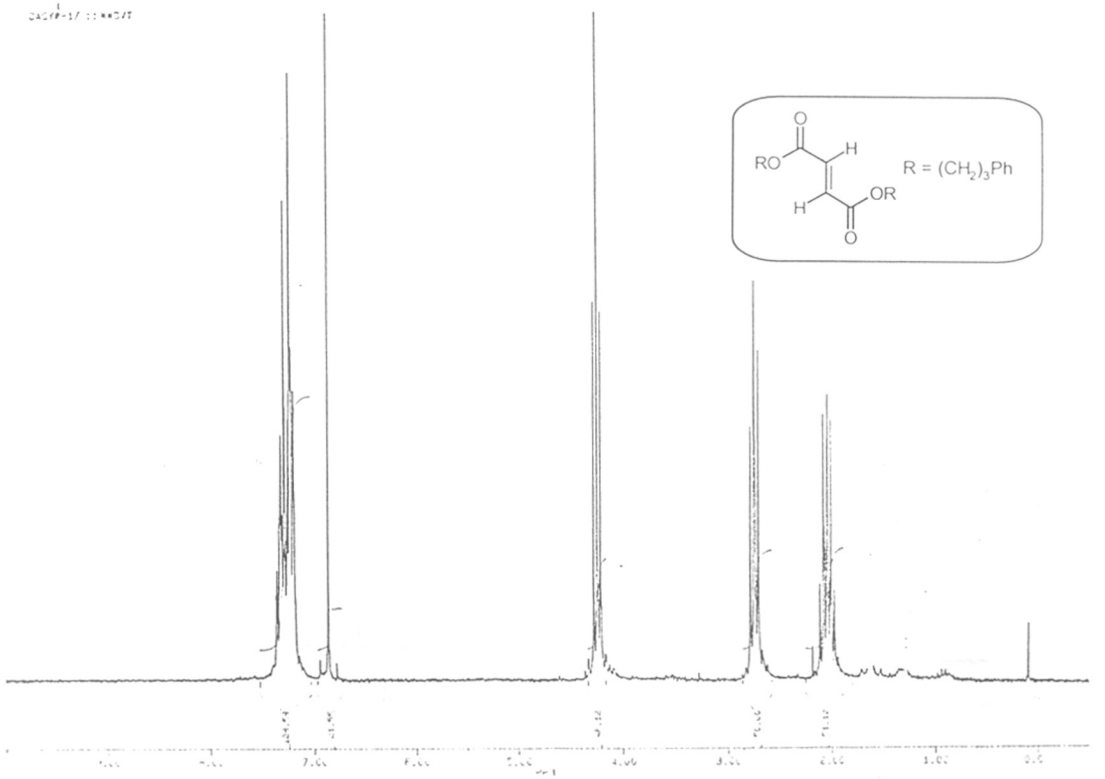
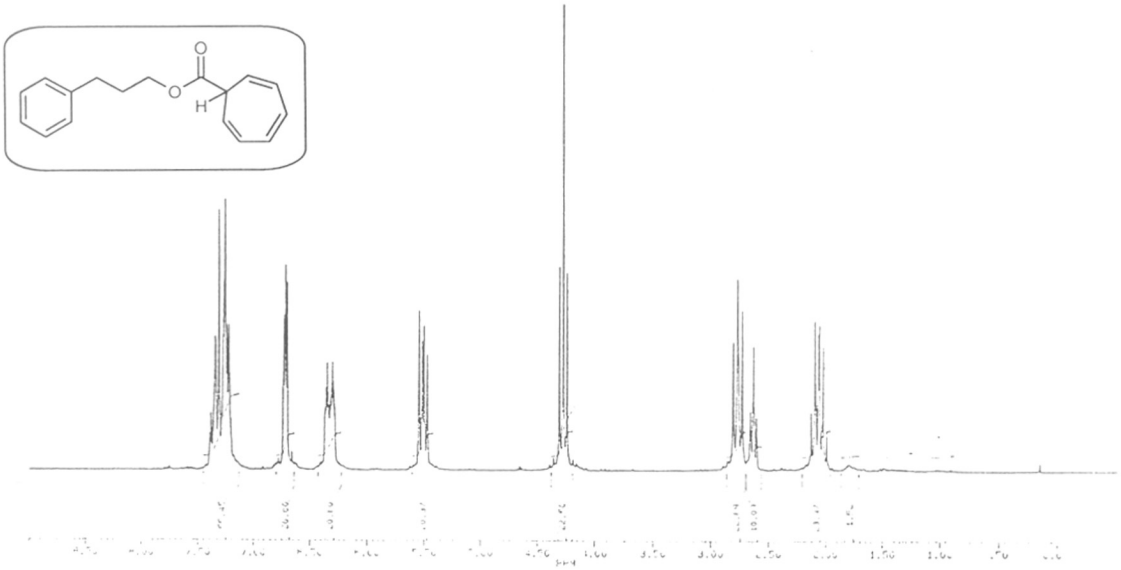

BALAJI B.S. / B-RH-DEM / CDCL3
PPM
RO
Ph
Ph
OR
R = (CH2)3Ph
PPM


RO
RO
H
H
O
O
R = (CH2)3Ph


RO
H
H
OR
O
O
R = (CH2)3Ph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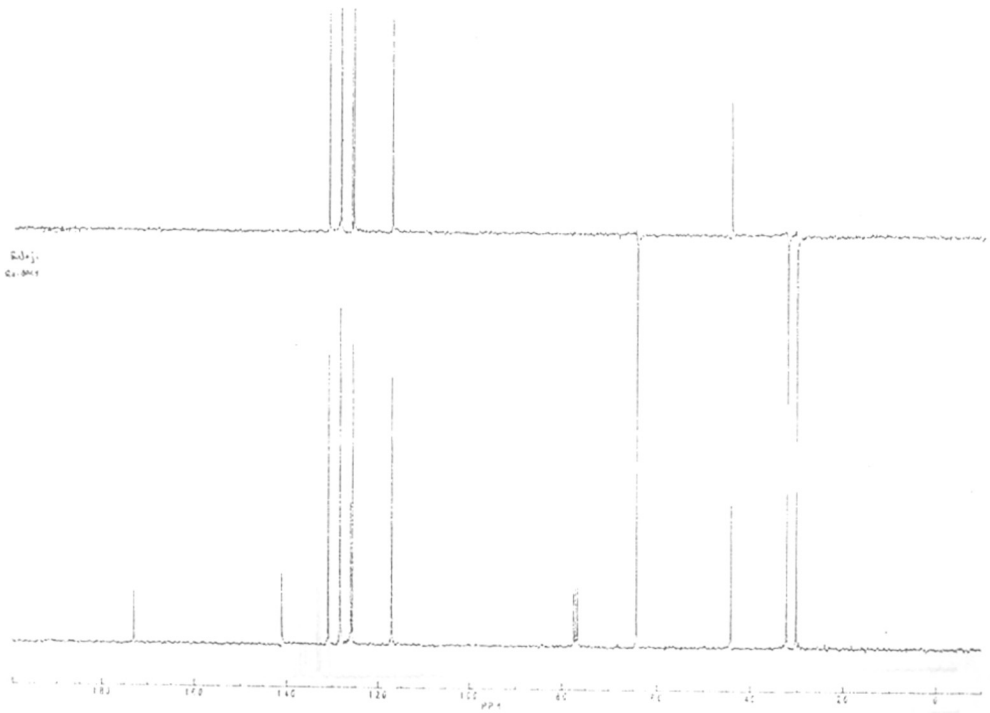
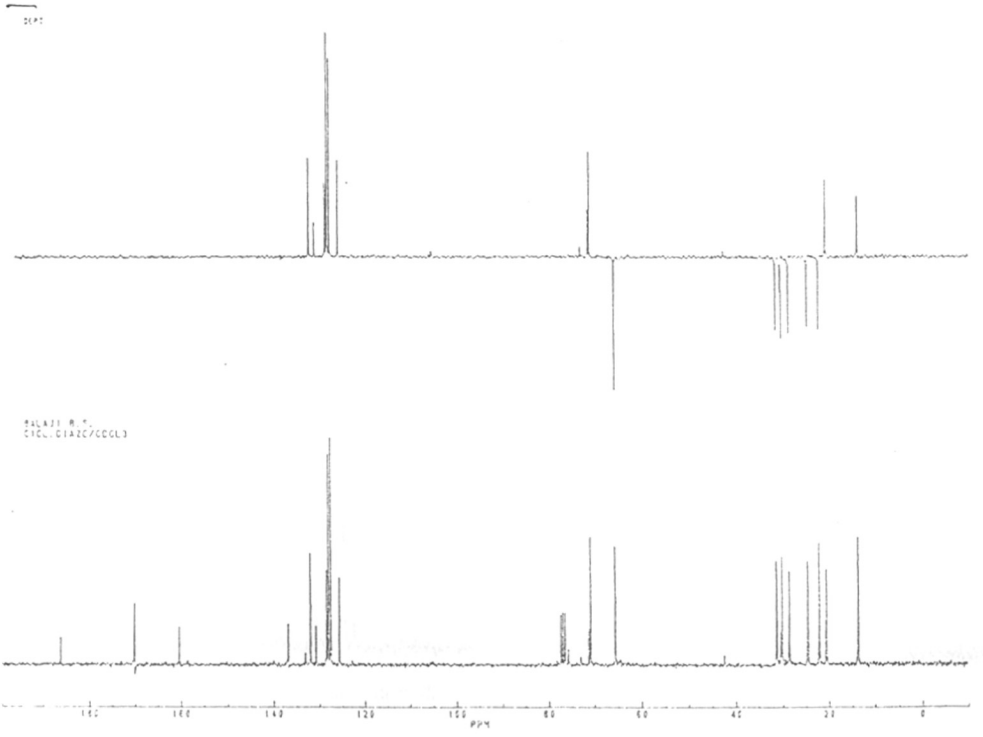
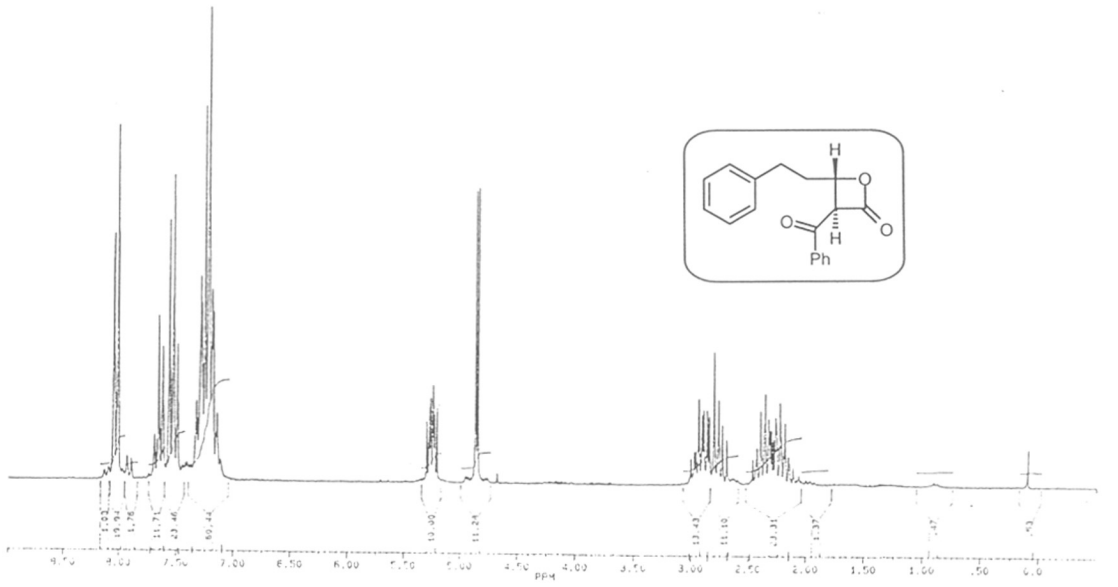
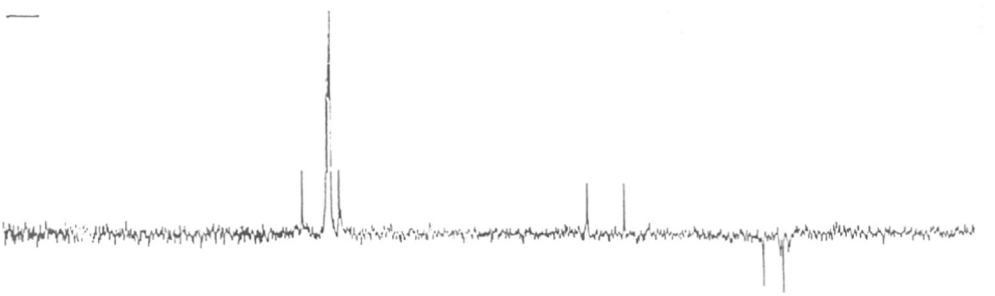
O
H

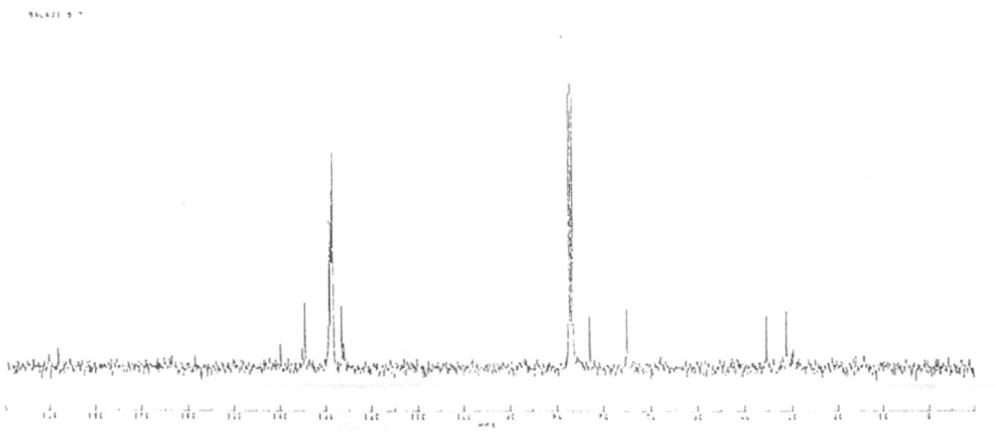


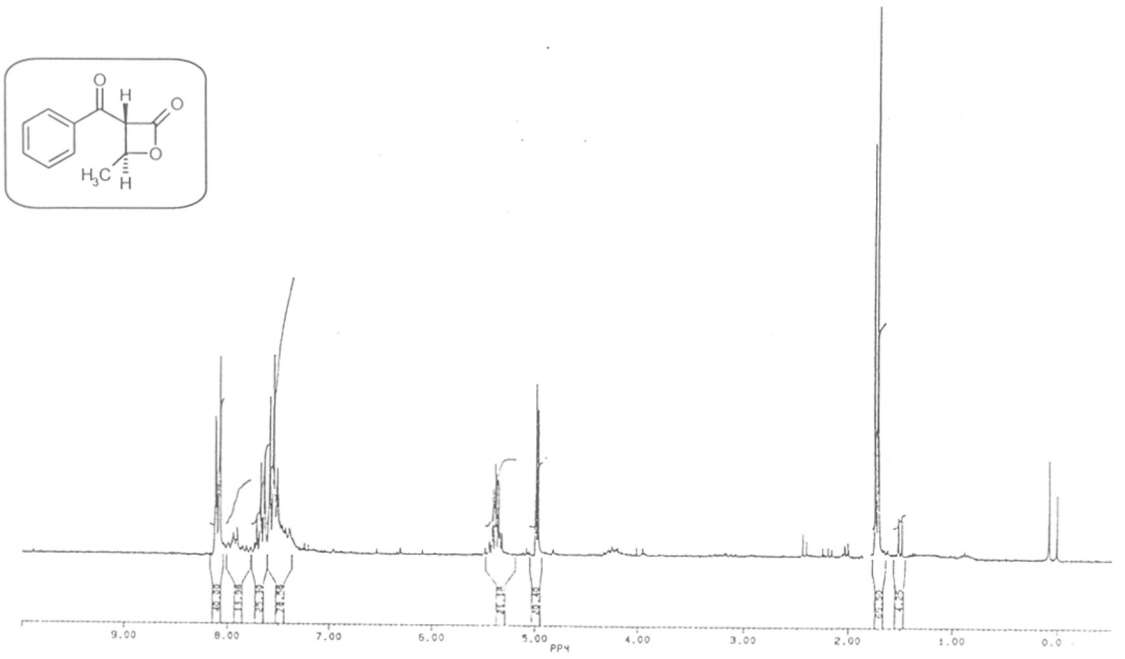

AcO
O
O
O
N_2
PPM

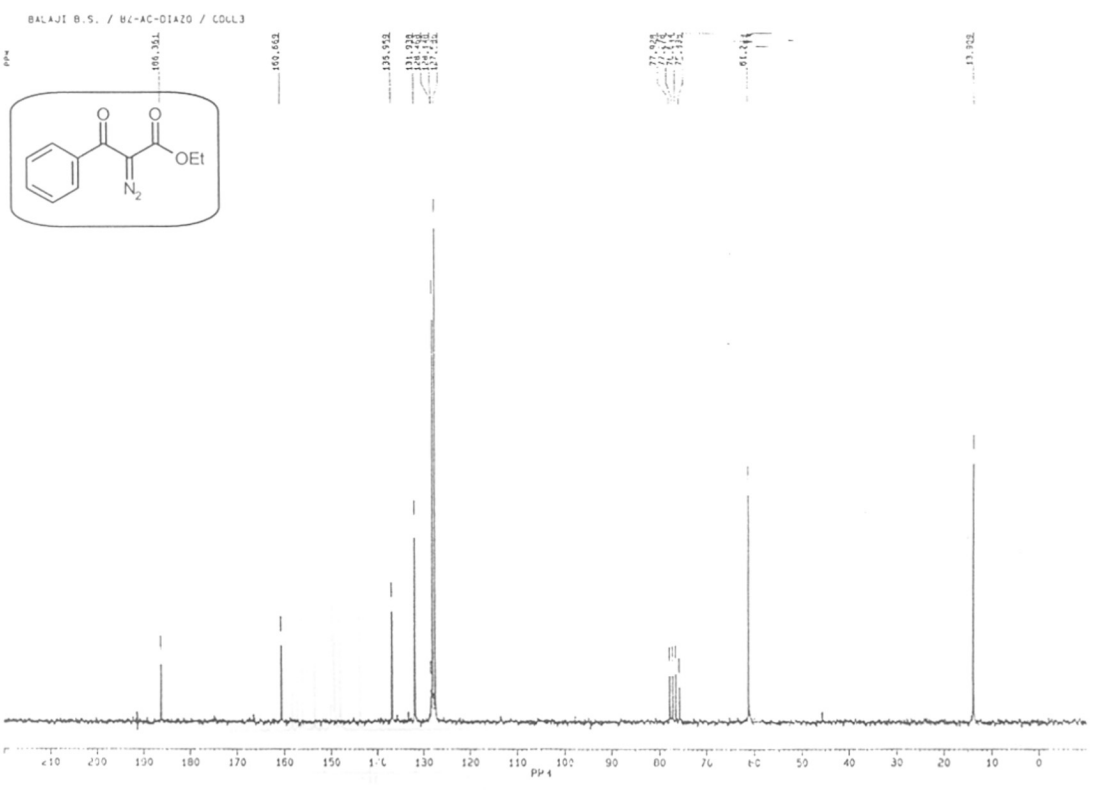

DEPT
PPM


H
O
O
O
H
Ph
PPM






BZ-AC/CDCL3
O
H
O
O
H3C
H
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.0
PPM


BALAJI B.S. / BZ-AC-DIAZO / CDCL3
PPM
O
O
OEt
N2
200
190
180
170
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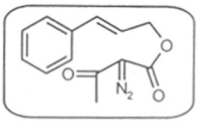
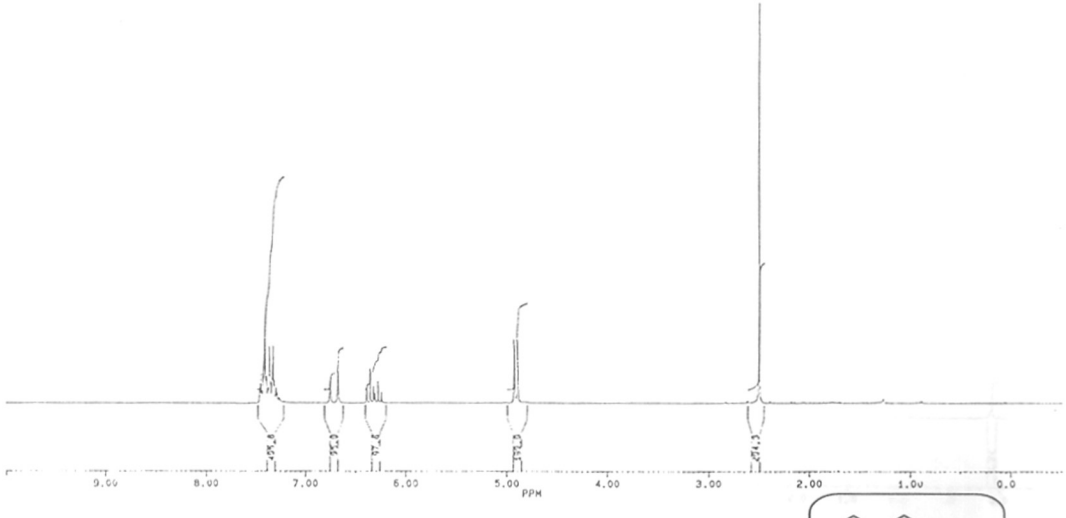
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
PPM




9.00
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3.00
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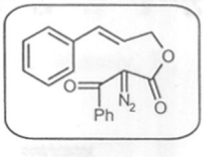
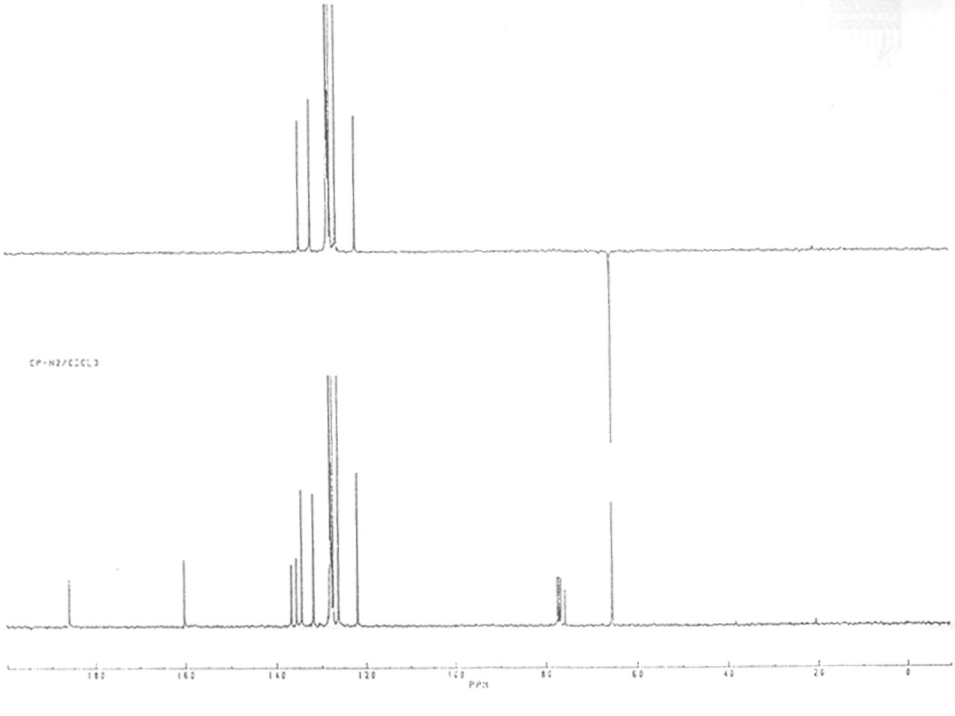
1.00
0.0
PPM




160
140
120
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80
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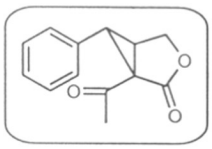
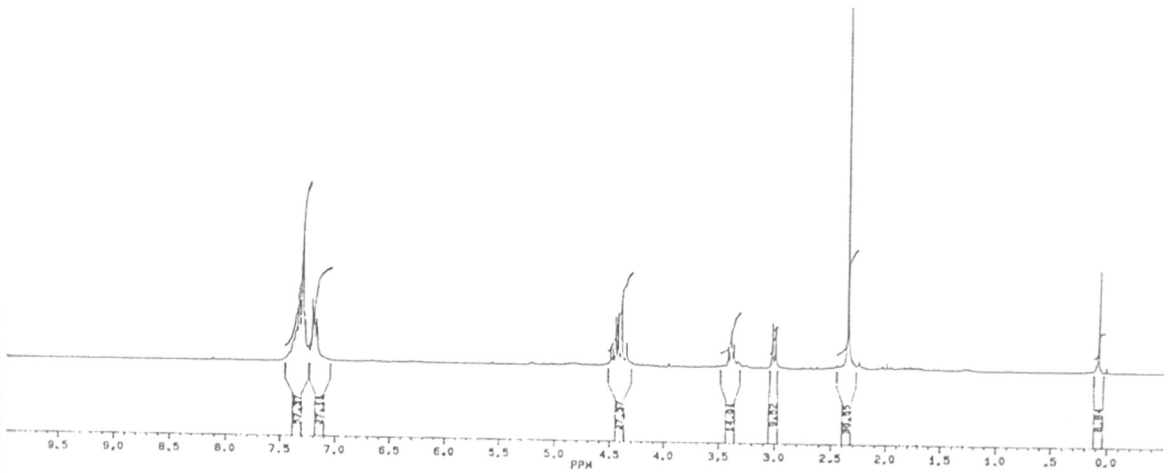
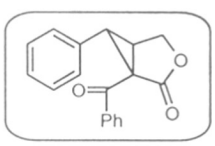
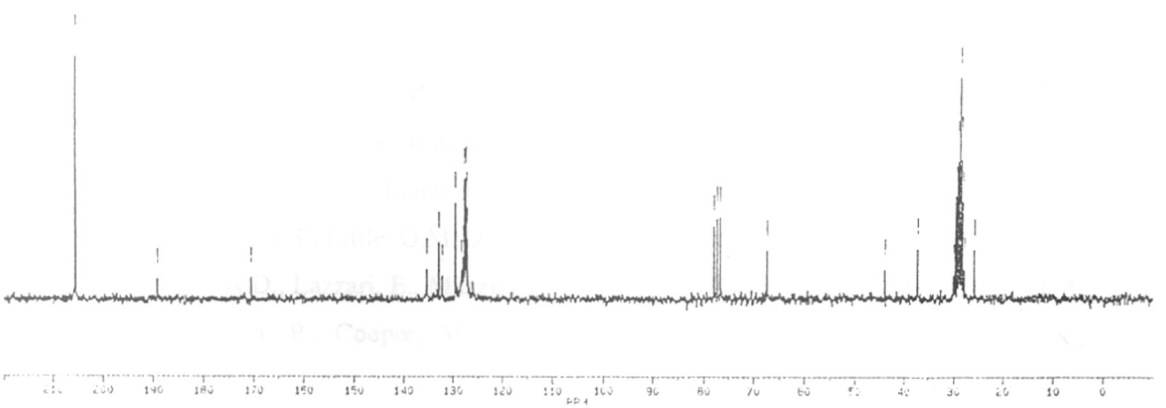
40
20
0
PPM





B-CHANDA--/ACETONE-D6/CDCL3





References

1. Weinberg, R.A., *Scientific American*, **1996**, (275), issue 3, p 32. b) Trichopoulos, D., Li, F.A., Hunter, D.J., *ibid.*, p 50. c) Greenwald, P., *ibid.*, p 64. d) Hellman, G. and Vokes, E.E., *ibid.*, p 84.
2. For **Taxol:** Nicolaou, K.C., Dai, Wei-Min, Guy, R.K., *Angew.Chem.Int.Ed. Engl.*, **1994**, (33), 15. For **Camptothecin:** Potmesil, M. and Pinedo, H., in *Camptothecins: New Anticancer Drugs*, CRC Press Inc. Florida, USA, **1995**. For **Etoposide** and **Teniposide:** *The Merck Index*, 12th Edn. Merck Research Laboratories, Division of Merck and Co. Inc., Whitehouse Station, NJ, **1996**, p 659, p 1562. For **Daunomycin:** Wagner, D., *J.Basic Microbiology*, **1991**, (31), p 223. For **Vinblastine** and **Vincristine:** Martindale in *The Extra Pharmacopoeia*, 30th Edn., Pharmaceutical Press, London, **1993**, p 504.
3. MacRae, W.D. and Towers, G.H.N., *Phytochemistry*, **1984**, (23), 1207.
4. Ward, R.S., *Tetrahedron*, **1990**, (46), 5029. Ward, R.S., *Synthesis,* **1992**, 719.
5. Freudenberg, K. and Weinges, K., *Tetrahedron*, **1961**, (15), 115.
6. Podwyssotzki, V., *Arch.Exp.Path*, **1881**, (13), 29. b) King, L.S. and Sullivan, M.S., *Science*, **1946**, (104), 244.
7. a) Borsche, J. and Niemann, J., *Ann*, **1932**, (499), 59. b) Späth,E., Wessely, F., Nadler, E., *Ber.*, **1932**, (65), 1773.
8. a) Hartwell, J.L. and Schrecker, A.W. *J.Am.Chem.Soc.*, **1951**, (73), 2909. b) Schrecker, A.W. and Hartwell, J.L. *ibid.*, **1953**, (75), 5916.
9. a) Kamil, W.M. and Dewick, P.M., *Phytochemistry*, **1986**, (25), 2089. b) Kamil, W.M. and Dewick, P.M. *ibid*, 2093.
10. Broomhead, A.J., Rahman, M.A.A., Dewick, P.M., Jackson, D.E., Lucas, J.A., *Phytochemistry*, **1991**, (30), 1489.
11. Long, B.Y., Musial, S.T., Brattain, M.G., *Biochemistry*, **1984**, (23), 1183.
12. Terada, T., Fujimoto, K., Nomura, M., Yamashita,J-i., Kobunai,T., Takeda,T., Wierzba, K., Yamada, Y., Yamaguchi, H., *Chem.Pharm.Bull.* **1992**, (40), 2730.
13. a) Muehlbacher, M. and Poulter, C.D., *J.Org.Chem.*, **1988**, (53), 1026.
    b) Alvarez, E., Nunez, M.T., Martin, V.S., *J.Org.Chem.*, **1990**, (55), 3429.
    c) Caron, M. and Sharpless, K.B., *J.Org.Chem.*, **1985**, (50), 1560.
14. a) Sharpless, K.B., Michaelson, R.C., *J.Am.Chem.Soc.*, **1973**, (95), 6136. b) Pelter, A., Ward, R.S., Little, G.M., *J.Chem.Soc.Perkin Trans.1,* **1990**, 2775. c) Melloni, P., Torre, A.D., Lazzari, E., Mazzini, G., Meroni, M. *Tetrahedron*, **1985**, (41), 1393. d) Brougham, P., Cooper, M.S., Cummerson, D.A., Heaney, H., Thompson, N.,

Synthesis, **1987**, 1015. e) Kumar, S.B., Mirajkar, S.P., Pais, G. C.G., Kumar, P., Kumar, R., *J.Catal.*, **1995**, (156), 163. f) Joseph, R., Sasidharan, M., Kumar, R., Sudalai, A., Ravindranathan, T., *J.Chem.Soc.Chem.Commun.*, **1995**, 1341.

15. Tanase, T., Mano, K., Yamamoto, Y. *Inorg. Chem.*, **1993**, (32), 3995.
16. Giese, B., *Angew.Chem.Int.Ed. Engl*, **1985**, (22), 753.
17. a) Zeigler, F.E. and Schwartz, J.A., *J.Org.Chem.*, **1978**, (43), 985. b) Ishibashi, H., Ito, K., Hirano, T., Tabuchi, M., Ikeda, M., *Tetrahedron*, **1993**, (49), 4173.
18. Ando, K., *Tetrahedron Lett.*, **1995**, (36), 4105.
19. Winterfield, E., *Synthesis*, **1975**, 617 and references cited therein.
20. Corey, E.J. and Schmidt, G., *Tetrahedron Lett.*, **1979**, 399.
21. Meskens, F.A.J., *Synthesis* **1981**, 501 and references cited therein.
22. Krishnamurthy, S. And Brown, H.C., *J.Org.Chem.*, **1982**, (47), 276.
23. Stotter, P.L. and Hill, K.A., *Tetrahedron Lett.*, **1972**, 4067.
24. Lorette, N.B. and Howard, W.L., *J.Org.Chem.*, **1960**, (25), 521
25. Snider, B.B. and Kwon, T., *J.Org.Chem.*, **1992**, (57), 2399.
26. Emde, H., Domsch, D., Feger, H., Frick, U., Gotz, A., Hergott, H.H., Hofmann, K., Kober, W., Krageloh, K., Ocesterle, T., Steppan, W., West, W., Simchen, G. *Synthesis*, **1982**, 1.
27. Corey, E.J. and Jones, G.B., *J.Org.Chem.*, **1992**, (57), 1028.
28. Otto, M-C., *Organic Syntheses*, John Wiley and Sons, New York, **1990**, *Vol. 68*, 155.
29. Crandall, J.K. and Clark, A.C. *Tetrahedron Lett.*, **1969**, 325.
30. Hitchcock, S.R., Perron, F., Martin, V.A., Albizati, K.F., *Synthesis* **1990**, 1059.
31. a) Kende, A.S., Roth, B., Sanfilippo, P.J., *J.Am.Chem.Soc.*, **1982**, (104), 1784. b) Kende, A.S.and Wustrow, D.J., *Tetrahedron Lett.*, **1985**, (26), 5411.
32. Kropp, P.J., Poindexter, G.S., Pienta, N.J., Hamilton, D.C. *J.Am.Chem.Soc.*, **1976**, (98), 8135.
33. Claudemans, C.P.J. and Bertolini, M.J. in *Methods in Carbohydrate Chemistry*, Ed. by, Whistler, R.J. and BeMiller, J.N, Academic Press, New York, **1980**, *Vol, XIII*, p 272.
34. van Boeckel, C.A.A. and Beetz, T. *Tetrahedron Lett.*, **1983**, (24), 3775.
35. For general understanding on C-H insertion reactions please see a) Padwa, A and Austin D.J., *Angew.Chem.Int.Ed.Engl.*, **1994**, (33), 1797. b) Doyle, M.P., Westrum, L.J., Wolthuis, W.N.E., See, M.M., Boore, W.P., Bagheri, V., Pearson, M.M., *J.Am.Chem.Soc.* **1993**, (115), 958. c) Taber, D.F., Hennessy, M.J., Louey, J.P.,

J.Org.Chem., **1992**, (57), 436. d) Ye, T. and McKervey, M.A. *Chem.Rev.*, **1994**, (94), 1029 and references cited therein.

36. a) Bode, J.W., Doyle, M.P., Protopopova, M.N., Zhou, Q., *J. Org. Chem.* **1996**, (61), 9146. b) Taber, D.F. and You, K.K. *J.Am.Chem.Soc.*, **1995**, (117), 5757.
37. Meerwin, H., Rathjen, H., Werner, H. *Ber.Dtsch.Chem.Ges.*, **1942**, (75), 1619.
38. a) Sonawane, H.R., Bellur, N.S., Ahuja, J.R., Kulkarni, D.G., *J.Org.Chem.*, **1991**, (56), 1434. b) Jefford, C.W., Tang, Q., Zalsona, A., *J.Am.Chem.Soc.*, **1991**, (113), 3513.
39. Taber, D.F. and Ruckle, R.E. Jr., *J.Am.Chem.Soc.*, **1986**, (108), 7686.
40. Hendrickson, J.M. and Wolf, W.A. *J.Org.Chem.*, **1968**, (33), 3610.
41. Doyle, M.P., Shanklin, M.S., Pho, H.Q., Mahapatro, S.N. *J.Org.Chem.*, **1988**, (53), 1017.
42. von E. Doreing, W., Laber, G., Vonderwahl, R., Chamberlain, N.F., Williams, R.B., *J.Am.Chem.Soc.*, **1956**, (78), 5448.
43. Davies, H.M.L., Huby, N.J.S., Cantrell, Jr., W.R., Olive, J.L., *J.Am.Chem.Soc.*, **1993**, (115), 9468.
44. Evans, D.A., Britton, T.C., Ellman, J.A., Dorow, R.L., *J.Am.Chem.Soc.*, **1990**, (112), 4011.
45. Taber, D.F., You, K., Song, Y. *J.Org.Chem.*, **1995**, (60), 1093.
46. Doyle, M.P., Bagheri, V., Wandless, T.J., Harn, N.K., Brinker, D.A., Eagle, C.T., Loh, K.L. *J.Am.Chem.Soc.*, **1990**, (112), 1906.
47. For previous reports on β lactone formation from diazo compounds please see a) Lee, E., Jung, K.W., Kim, Y.S. *Tetrahedron Lett.*, **1990**, (31), 1023. b) Box, V.G.S., Marinovic, N., Yiannikouros, G.P. *Heterocycles*, **1991**, (32), 245.
48. For general method to prepare Rh (II) carboxylates please see Kitchens, J. and Bear, J.L. *Thermochim.Acta.*, **1970**, (1), 537. Ross, G.H.P. and McKervy, M.A., *Synthetic Commun.*, **1992**, (22), 1751.For exact procedures please see (a) **Pivalic acid**: Cotton, F.A. and Felthouse, T.R. *Inorg.Chem.*, **1980**, (19), 323. (b) **Methoxy acetic acid**: Howard, R.A., Sherwood, E., Erck, A., Kimball, A.P., Bear, J.L. *J.Med.Chem.*, **1977**, (20), 943. (c) **Trifluoro acetic acid**: Johnson, S.A., Hunt, H.R., Newmann, h.M. *Inorg.Chem.*, **1963**, (2), 960.
49. Heslin, J.C. and Moody, C.J., *J.Chem.Soc.Perkin Trans. 1.*, **1988**, 1417.
50. Nandanan, E., Ph.D. thesis, Pune University, **1997**, p 70.
51. Ponde. D.E., Deshpande, V.H., Bulbule, V.J., Sudalai, A., Gajare, A.S., *J.Org.Chem.*, **1998**, (63), 1058.
52. Höfle, G., Steglich, W., Vorbrüggen, H., *Angew.Chem.Int.Ed.Engl.*, **1978**, (17), 569.

53. a) Cox, G.G., Moody, C.J., Austin, D.J., Padwa, A., *Tetrahedron*, **1993**, (49), 5109. b) Padwa, A., Dean, D.C., Fairfax, D,J., Xu, S.L., *J.Org.Chem.*, **1993**, (58), 4646.

54. For general introduction about cyclopropanation please see: Armstrong, A., in *Comprehensive Organic Functional Group Transformations*, Ed. by, Roberts, S.M., Editors-in-Chief, Katritzky, A.R., Meth-Cohn, O., Rees, C.W., Vol. I, *Synthesis: Carbon with no attached Heteroatom*. Elsevier Science Ltd. Cambridge University Press, **1995**, p 293.

55. a) Srikrishna, A. and Nagaraju, S. *Phytochemistry*, **1995**, (40), 1699. b) Srikrishna, A. and Krishnan, K. *J.Chem.Soc.Perkin Trans.1*, **1993**, 667. c) Koskinen, A.M.P. and Munoz, L. *J.Org.Chem.*, **1993**, (58), 879. d) Yadav, J.S., Mysorekar, S.V., Rao, A.V.R. *Tetrahedron*, **1989**, (45), 7353.

56. Cyclopropanation using a) α,α Dibromo compounds: Yoshida, J., Yano, S., Ozawa, T., Kawabata, N., *J.Org.Chem.*, **1985**, (50), 3467. b) Sulphur ylide: Gillespie, R.J. and Porter, A.E.A., *J.Chem.Soc.Chem.Commun.*, **1979**, 50. c) Iodonium ylide: Hatjiarapoglou, L., Varvoglis, A., Alcock, N.W., Pike, G.A., *J.Chem.Soc.Perkin Trans., 1*, **1988**, 2839.

57. Catalysts derived from Copper and a) **Salicylaldehyde derived imine**: Aratani, T., *Pure Appl. Chem.*, **1985**, (57), 1839. b) **Semicorrin**: Muller, D., Umbricht, G., Weber, B., Pfaltz, A., *Helv.Chim.Acta.*, **1991**, (74), 232. **5-Aza Semicorrin**: Leutenegger, U., Umbricht, G., Fahrni, C., Matt, P.von, Pfaltz, A., *Tetrahedron*, **1992**, (48), 2143. c) **Bisoxazoline**: Lowenthal, R.E. and Masamune, S., *Tetrahedron Lett.*, **1991**, (32), 7373. d) **Bipyridine**: Ito, K. and Katsuki, T., *Tetrahedron Lett.*, **1993**, (34), 2661.

58. Catalysts derived from Rhodium a) **Carboxamide**: Doyle, M.P., Austin, R.E., Bailey, A.S., Dwyer, M.P., Dyatkin, A.B., Kalinin, A.V., Kwan, M.M.Y., Liras, S., Oalmann, C.J., Pieters, R.J., Protopopova, M.N., Rabb, c.E., Ross, G.H.P., Zhou, Qi-Lin, Martin, S.F., *J.Am.Chem.Soc.*, **1995**, (117), 5763. b) **Carboxylates**: Callot, H.J. and Metz, F., *Tetrahedron*, **1985**, (41), 4495.

59. For various methods of cyclopropanation Clark, R.D. and Heathcock, C.H. *Tetrahedron Lett.*, **1975**, 529. Kondo, K., Umemoto, T., Takahatake, Tunemoto, D. *Tetrahedron Lett.*, **1977**, 113.

60. Wong, H.N.C., Hon, M-Y, Tse, C-W., Yip, Y-C., Tanko, J., Hudlicky, T., *Chem.Rev.*, **1989**, (89), 165.

CHAPTER III

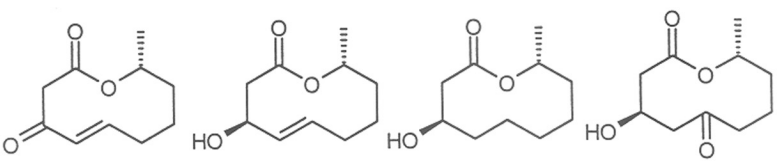
TOTAL SYNTHESIS OF DIPLODIALIDE A

Chapter III

Total Synthesis of Diplodialide A

Introduction

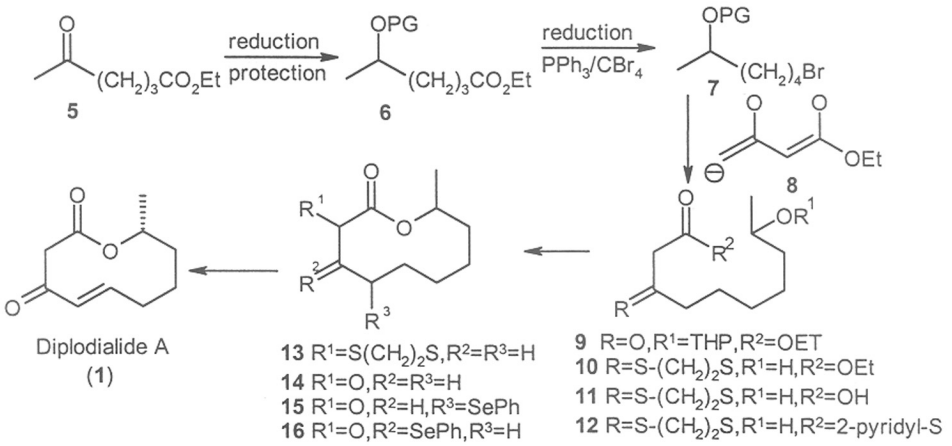
In 1975, Wada and Ishida isolated a steroid hydroxylase inhibitor called, *diplodialide A,* a ten membered lactone from the culture filtrate of *Diplodia pinea*.[1] The structure was confirmed by spectral analysis.[2] The mass spectrum showed the molecular weight to be 182 corresponding to the molecular formula $C_{10}H_{14}O_3$. The compound showed IR absorption at 1740, 1700, 1645 for ester, keto carbonyl and olefinic bond. The $\lambda_{(max)}$ was found to be 232. Based on these observations, it was deduced that an α,β unsaturated moiety was present. From ^{1}H NMR analysis the presence of olefinic protons *i.e.* a singlet at 5.68 δ and multiplet between 6.3 δ and 6.8 δ further proved the presence of unsaturation. The compound showed a doublet at 1.28 δ (3H), multiplet between 1.3 and 2.5 δ (6H), a doublet at 3.35 δ (2H) and a multiplet between 4.9 and 5.2 δ (1H). From the above facts coupled with the ^{13}C NMR values {195.16 (*C*=O), 168.17 (O-*C*=O)} the compound was assigned the structure **1**. The unique biological activity and structure have attracted many groups to synthesise diplodialide A and related compounds (**1-4**).



Diplodialide A (**1**) | Diplodialide B (**2**) | Diplodialide C (**3**) | Diplodialide D (**4**)

Wada's approach[3]

Wada reported the first total synthesis of diplodialide A in 1977 and the route is outlined in the following scheme **[Scheme 1]**.



Scheme 1

The key reactions involved are condensation of bromo compound **7** with dianion of ethylacetoacetate **8** to obtain the required C10 unit **9** and selenylation, deselenylation process to give the required double bond. The detailed reaction sequence starts from the keto ester **5**. The keto ester was reduced with $NaBH_4$ to give the hydroxy ester which was protected as its THP ether **6**. This compound was reduced with LAH to furnish the hydroxy compound which was further converted into the corresponding bromo compound **7** using PPh_3/CBr_4.

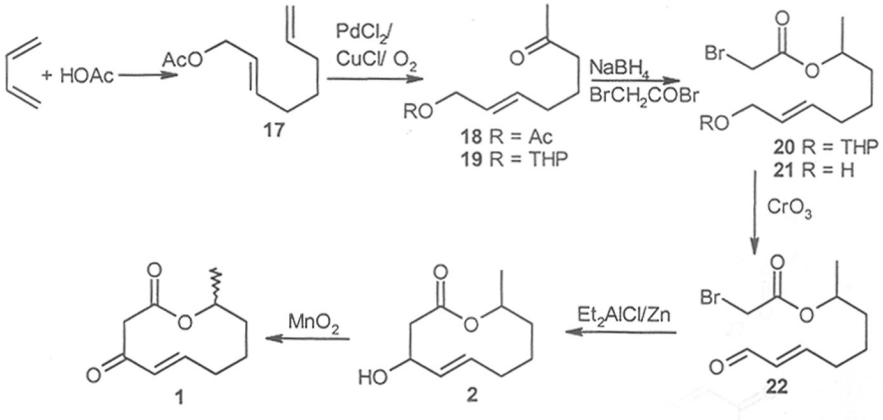
This bromo compound was then condensed with dianion of ethylacetoacetate **8** to afford the required C10 fragment **9**. The keto group in **9** was protected as its dithioacetal and the THP protection was removed to give **10**. This hydroxy ester **10** was hydrolysed and then was converted to its thiol ester **12**. This thiol ester **12** was then subjected to macrolactonisation to furnish the required lactone **13**. Now the ketone masking was removed to give the keto lactone **14**. The latter was then subjected to selenenylation using benzeneselenenyl bromide to get the required compound **15** in 34 % isolated yield along with the undesired product **16**. Deselenenylation using sodium metaperiodate yielded diplodialide A (**1**). The overall yield starting from the keto ester **5** was less than 5%.

Some of the limitations of this route are: (i) total number of steps involved are 12. (ii) to achieve the required macrolactonisation, three steps are required from the corresponding hydroxy ester. (iii) the yield in the selenenylation step is low. (iv) it involves the separation of the required selenenylated product from its positional isomer.

(v) even the oxidation of the selenylated product which furnishes diplodialide A proceeded in only 28 % yield.

Tsuji's approach[4]

Shortly following Wada's approach a linear route by Tsuji was reported for the total synthesis of diplodialide A. Details of the route are shown below **[Scheme 2]**.



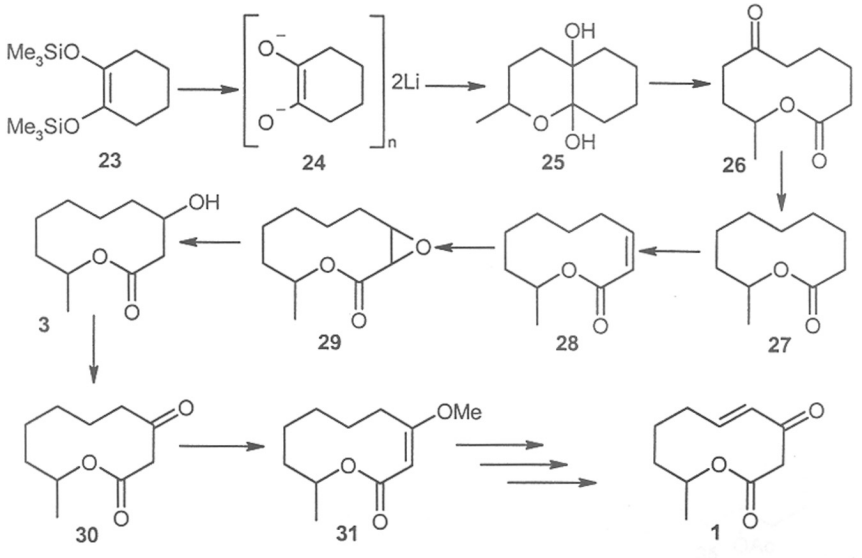
Scheme 2

Butadiene was treated with HOAc in the presence of $Pd(OAc)_2$/TPP to provide the butadiene telomer **17**. The terminal double bond in **17** was selectively oxidised with aq. DMF, $PdCl_2$/CuCl under oxygen atm. to give **18**. The acetate protection was hydrolysed and the free hydroxyl was converted to its THP ether **19**. The carbonyl group present in **19** was reduced using $NaBH_4$ to the secondary alcohol which was condensed with bromo acetyl bromide to furnish the bromo ester **20**. THP protection was removed and the free hydroxyl group in 21 was oxidised using CrO_3 to afford the aldehyde **22**. A modified Reformatsky reaction on **22** using Et_2AlCl_2 and Zn furnished the hydroxy compound i.e. diplodialide B (**2**). This was then subjected to MnO_2 oxidation to give diplodialide A (**1**).

The limitations encountered in this strategy are: (i) highly lachrymatic and corrosive bromo acetyl bromide is used. (ii) expensive and moisture sensitive Et_2AlCl_2 is used for condensation.

Wakamastu approach[5]

An elegant synthesis of diplodialide A utilising oxidative cleavage of bicyclic glycols for the construction of ten membered lactone was reported by Wakamastu *etal.* The following scheme **[Scheme 3]** explicitly depicts the various operations involved in their strategy.



Scheme 3

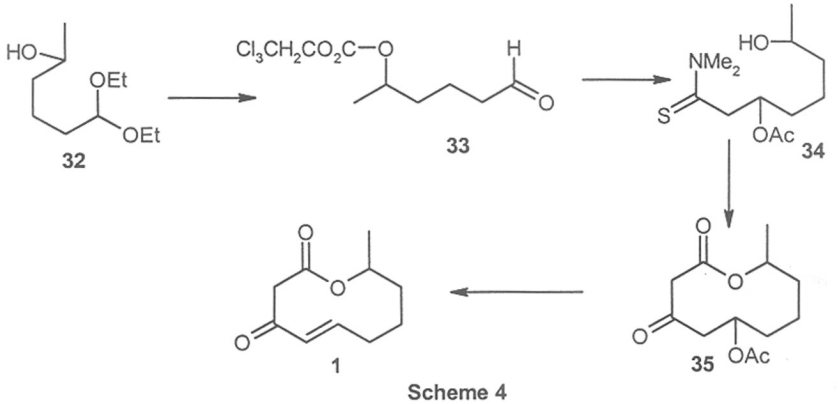
The modified acyloin condensation of diethyladipate in the presence of TMS furnished the enediol bis (TMS) enol ether **23**. Addition of MeLi (2 equi) gave **24**, which was alkylated using 3-hydroxy-1-iodobutane to produce the bicyclic glycol **25**. LTA mediated ring opening yielded the keto lactone **26**. The ketone functionality was reduced *via* thioketalisation followed by desulphurisation using Raney-Ni to yield the C_{10} lactone **27**.

This lactone was treated with phenylselenenyl bromide in the presence of LDA followed by oxidation with H_2O_2 to provide the α,β unsaturated lactone **28**. The latter was converted to the corresponding epoxy lactone **29** with mCPBA. Reduction of **29** with Li/NH_3 furnished diplodialide C **3**. This was oxidised to lactone **30** with chromic anhydride in pyridine. Treatment of the lactone **30** with DMS in refluxing methyl ethyl ketone gave the enol lactone **31**. Treatment of **31** with sodium selenophenolate followed by H_2O_2 mediated oxidation and hydrolysis of the diene lactone by TFA in HOAc furnished diplodialide A (**1**).

Some of the limitations of this method are: (i) here also the number of steps involved are more than 12. (ii) the introduction of the required trans double bond was not selective. (iii) toxic selenium metal was used for the introduction of the double bond. (iv) overall yield of diplodialide A was less than 5 %.

Ireland's approach[6]

In this approach, Eschenmosher sulphide contraction has been used as the crucial step for the lactone formation. The various steps involved can schematically be represented as



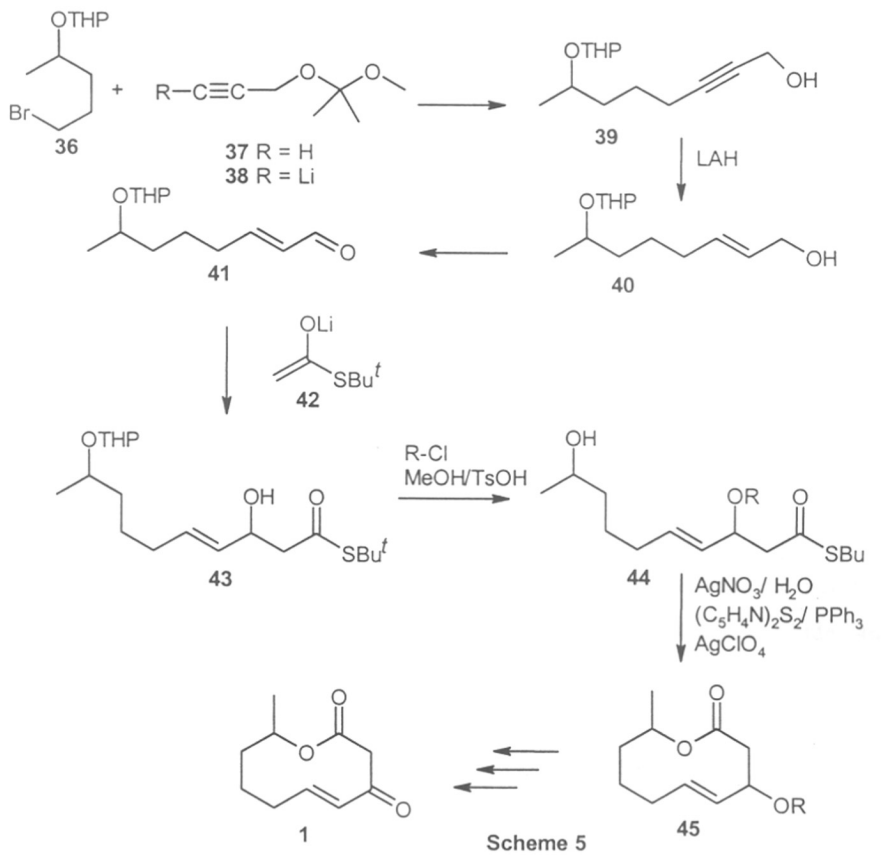
Scheme 4

The hydroxy acetal **32** was converted to the protected aldehyde **33** by the following steps. First the hydroxyl group was protected as its trichloro carbonate and the acetal masking was removed by acid treatment to furnish **33**. The aldehyde, thus obtained was reacted with Zn enolate of N,N dimethyl thioacetamide to funish the alcohol **34**. The compound **34** was then subjected to sulphide contraction method to furnish the acetoxy macrolactone **35**. Elimination using LDA led to the formation of diplodialide A (**1**).

Some of the limitations of this approach are (i) the starting hydroxy acetal is difficult to prepare. (ii) the final deacylation step has competing reactions. (iii) the yield of the sulphur contraction step is 40 % only. Though the number of steps involved are less, the over all yield is 8-10 % only.

Shenvi's approach[7]

The following scheme **[Scheme 5]** represents the various operations involved.



Scheme 5

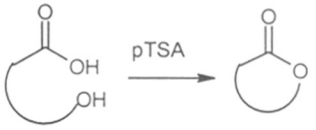
Condensation of bromo compound **36** with lithio derivative of the acetylenic compound **37** furnished the actylenic alcohol **39**. It was then reduced with LAH to furnish the trans allyl alcohol **40**. MnO_2 oxidation of the allyl alcohol afforded the α,β unsaturated aldehyde **41**. Thioester enolate **42** was condensed with this unsaturated aldehyde to furnish the hydroxy thioester **43**. The free hydroxyl was protected as its methyl ether **44**. Now the selective deprotection of the THP ether followed by application of Corey and Nicolaou conditions for macrolactonisation yielded **45**. The methyl ether **45** was deprotected and it was then oxidised with MnO_2 to give diplodialide A (**1**).

Short comings: (i) The total number of steps involved are more. (ii) LAH reduction was not selective. (iii) In two reactions, air sensitive lithio derivatives are used.

Macrolactonisation[8]

The construction of macrocyclic framework is a frequent and challenging problem in synthetic organic chemistry. Generally the lactonisation of long-chain hydroxy acids is a direct and well-establishedmethod.

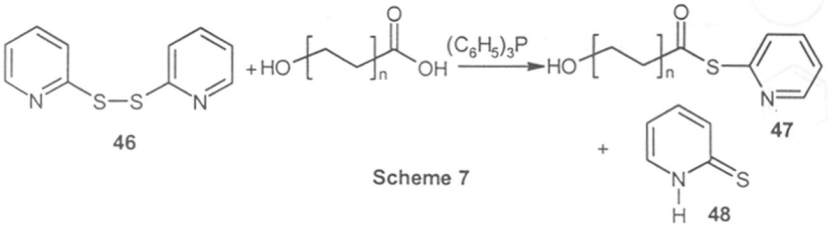
The methods used to cyclise the hydroxy acids involve either activation of carboxylic acid group or the hydroxy moiety or both of them simultaneously. Some of the commonly employed methods are given below. Intramolecular esterification of hydroxyalkanoic acids using pTSA under high dilution .[9]



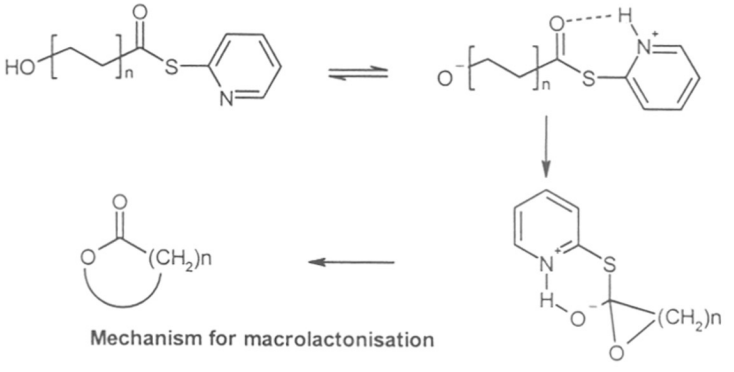
Scheme 6

Corey-Nicolaou method of double activation

Here, simultaneous activation of both hydroxyl and carboxyl groups by the use of 2-pyridinethiol esters **47** of hydroxyacids is involved.[10] The required pyridinethiol esters can easily be prepared by the combination of di(2-pyridyl)disulphide (**46**) and TPP in refluxing benzene or xylene.



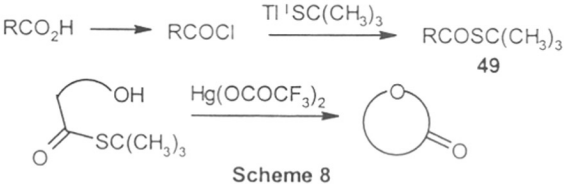
Scheme 7



Mechanism for macrolactonisation

Masumane method

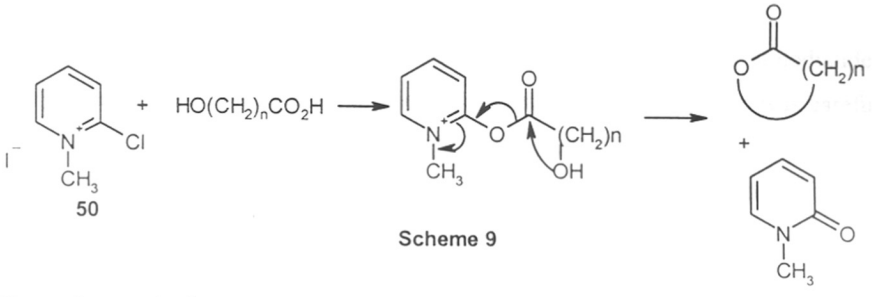
Masumane *et.al.*[11] developed a new method which utilises S-*t*-butyl thioesters of hydroxy acids and mercuric trifluoroacetate as an activating agent. Conversion of the acid to acid chloride and treatment with thallous 2-methylpropane-2-thiolate gives the required thio ester **49**.



Scheme 8

Mukaiyama method

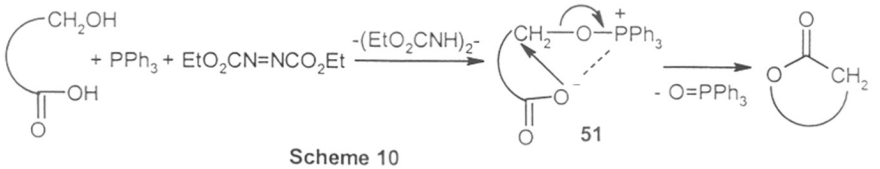
1-Methyl-2-chloropyridinium iodide (**50**) was used as the cyclisation reagent by Mukaiyama *et.al.*[12] Slow addition of the reagent **50** in the presence of TEA in refluxing solution of hydroxy alkanoic acid in DCM or MeCN resulted in the formation of the required product **[Scheme 9]**.



Scheme 9

Mitsunobu method

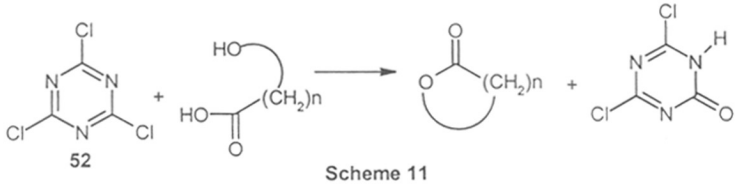
A 'reverse activation' wherein the hydroxyl group is activated and the carboxylate anion functions as the nucleophile was developed by Mitsunobu *et.al.*[13] Thus, reaction of the hydroxyalkanoic acids with TPP and DEAD at room temp. effects the ring-closure via an alkoxyphosphonium carboxylate **51**.



Scheme 10

Cyanuric chloride mediated macrolactonisation

Application of cyanuric chloride (**52**) and TEA in acetone at room temp. converts hydroxy acids to the corresponding lactones[14] **[Scheme 11]**.



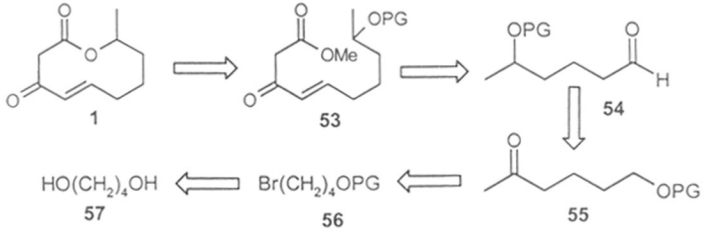
52

Scheme 11

Present work

As it can be seen from the various reported synthesis of diplodialide A, all approaches are lengthy and the over all yields are not very good. After developing an efficient method for intermolecular transesterification of β–keto esters (see Chapter I) it was decided to extend this study towards intramolecular transesterification leading to macrocyclic lactones. Generally macrolactonisation is a difficult task to achieve. They quite often involve high dilution techniques or activation methods or thiol ester formation etc. For practical purposes, the above mentioned methods cannot be synthetically viable. In this regard, a simple and efficient synthesis of diplodialide A based on intramolecular transesterification as the crucial cyclisation step was carefully planned. The following scheme depicts the proposed plan of work.

Commercially available 1,4 butane diol (**57**) may serve as the starting material



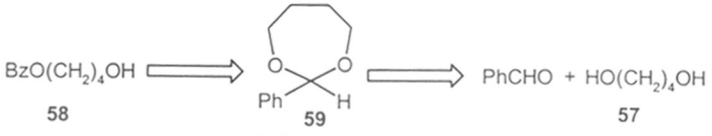
Scheme 12

for the C6 aldehyde **54** unit. Work was initiated to obtain the required compound **54**. The diol **57** was selectively monobrominated using the HBr[15] to get **56a.** The free hydroxyl group was protected as its THP ether to give **56**.

$HO(CH_2)_4OH$ $HO(CH_2)_4Br$ $THPO(CH_2)_4Br$

Having obtained the protected bromo compound **56**, the stage was set for the required Grignard reaction.[16] However, the Grignard reaction did not proceed and only the deprotected bromo compound was obtained. Though scattered reports[17] on THP

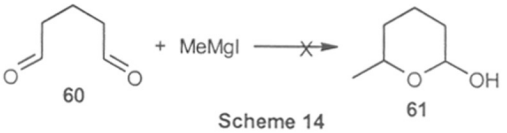
deprotection mentions that Mg (which is used for the preparation of the Grignard reagent) may facilitate cleavage of THP ether at or above room temp., in this case, only deprotection occurred at 0°C itself. It was then decided to use a different protecting group which will withstand the stringent Grignard reaction conditions. For this purpose, benzyl protection of hydroxyl group was resorted to. The retro scheme was therefore slightly modified as shown below **[Scheme 13]**.



Scheme 13

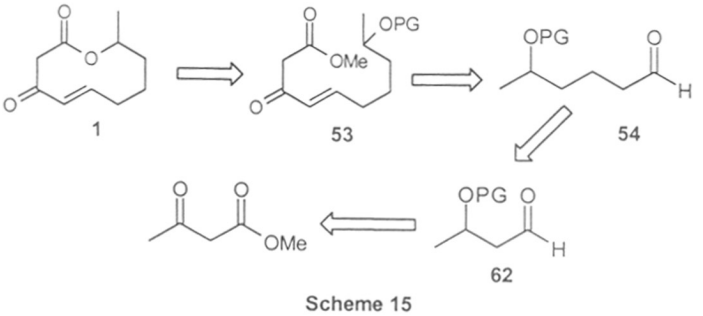
Protection of benzaldehyde by 1,4-butane diol[18] followed by LAH reduction[19] would give the monoprotected diol **58**, which could then be brominated to yield the starting material for Grignard reaction. For this purpose the butane diol was mixed with benzaldehyde in the presence of pTSA was used as the catalyst for the protection. However, no protection was observed even after refluxing for 24 hrs. It was presumed that, if the protection had taken place, that will give raise to a compound **59** which will be a substituted 7 membered oxepane. Since medium size rings are very difficult to obtain, the required protection did not take place.

Later it was decided to modify the scheme and attempt a single step conversion of glutaraldehyde (**60**)[20] to the required lactol **61** as depicted in the following scheme.



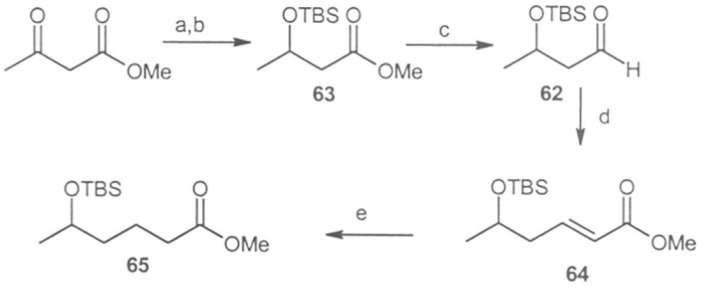
Scheme 14

However, here also the required cyclisation did not take place. Finally it was decided to employ a linear approach starting from commercially available methylacetoacetate. The following scheme represents the proposed plan.



Scheme 15

As planned, methylacetoacetate was reduced with $NaBH_4$[21] to give the required hydroxy ester. The hydroxyl group was protected as its TBS ether **63**. The latter was then subjected to DIBAL-H reduction at –78°C to furnish the required aldehyde **62** which was converted to the α,β unsaturated ester **64** *insitu* using Wittig reaction. Having obtained the required C6 unit the next step *i.e.* the Pd/C catalysed hydrogenation was carried out to get **65**. However, the overall yield was not very good necessitating a

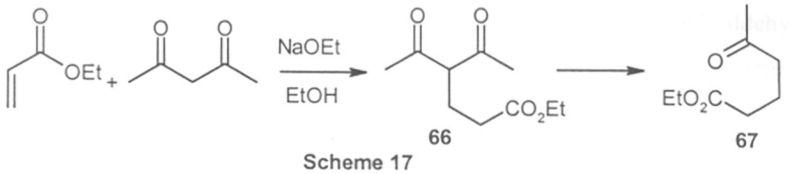


Scheme 16

change in strategy.

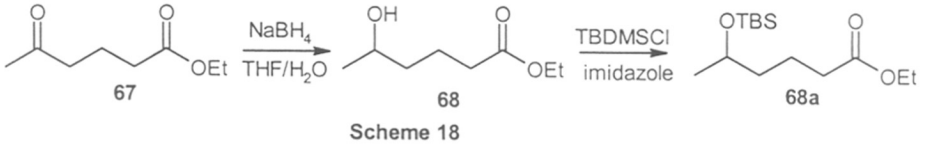
a) $NaBH_4$/ EtOH. b) TBDMSiCl/imidazole. c) DIBAL H /-78°C. d) $(MeO)_2(O)P{=}CHCO_2Me$. e) Pd/C/ H_2.

Thus, a three step sequence for the preparation of the ester **67** was attempted.



Scheme 17

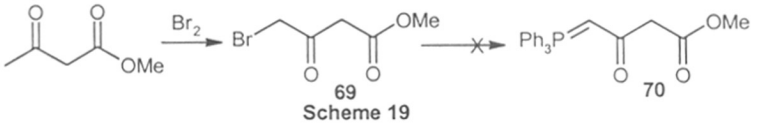
Ethylacrylate was condensed with acetylacetone to produce the Michael adduct **66**.[22] This was deacylated in the presence of NaOH to produce the keto ester **65**. Reported reduction of this keto ester **67** was not successful here and it gave only the over reduced product.



Scheme 18

Later, the reduction was standardised using $NaBH_4$/THF/water system. Thus the hydroxy ester **68** could be obtained in more than 90 % yield. Using the standard procedure was protected as its TBS ether **68a**.

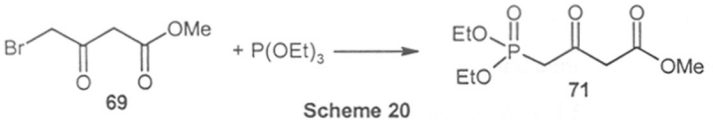
Having obtained the required C6 unit (**65**) in an attractive yield, the preparation of the other part namely the C4 building block was taken-up. Selective mono bromination of methylacetoacetate was achieved using the standard procedure. However, the attempted conversion of this bromo ester **69** to the required phosphorane **70** failed.



69 70

Scheme 19

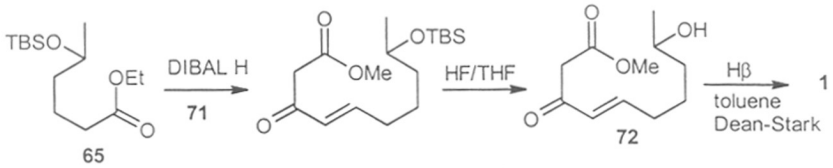
It was then planned to prepare the Horner-Emmons reagent **71** from this bromo ester. An advantage of using this reagent is that, the required trans geometry in the product can be nicely incorporated. Based on the reported[23] procedure the bromo ester was converted to the required phosphono ester **71**.



69 71

Scheme 20

After obtaining the reagent **71** for olefination, the required aldehyde was prepared by the DIBAL H reduction of the C6 ester unit. It was converted to the required C10 unit **72** by Horner-Emmons reaction (*insitu*). The C10 unit thus obtained was subjected to deprotection of the TBS ether. Only the HF/THF combination was found to be effective among the various methods for deprotection. The hydroxy compound thus obtained was subjected to intramolecular transesterification to furnish the macrolide **1**.



65 72

Scheme 21

The product was identified as diplodialide A by spectroscopic comparison with known compound. Though the required macrolide was obtained in moderate yield

(48%) efforts to optimise the yield was not undertaken. Work on some improvements in the scheme and yields is currently in progress.

Thus, a short and convenient route involving eight steps (over all yield ~13 %) to diplodialide A, employing the crucial intramolecular transesterification has been achieved. Though the total yield starting from acetylacetone is not high, this method avoids the various short-comings encountered in the several previously reported total syntheses.

Results and discussion

1,4 Butane diol was selectively mono brominated with HBr. It was observed that prolonging the reaction time led to the formation of dibromo compound only. However, only a maximum of 45 % of the required mono bromo compound was obtained by carefully controlling the reaction conditions. The product formed was characterised as follows. A multiplet between 3.6 and 3.5 δ (2H, OC*H*$_2$), a multiplet between 3.4 and 3.3 δ (2H, BrC*H*$_2$) in ^{1}H NMR. The hydroxy group in compound **56a** was subjected to protection with DHP in the presence of commercial kaolinitic clay. The required THP ether **56** was obtained as a colourless oil. It was characterised by its spectral analysis. The compound did not show any hydroxyl absorption in IR at 3320 cm^{-1}. ^{1}H NMR showed peaks at 4.5-4.4 δ (broad singlet, 1H, O-C*H*-O) and a multiplet between 2.2 and 1.5 δ (10H). However, attempted preparation of the compound **57** by Grignard reaction did not yield the required product. Only deprotection of the THP ether took place to yield **56a**.

Methylacetoacetate was reduced with $NaBH_4$ to give the hydroxy ester. The structure of the hydroxy ester was confirmed as follows. The presence of hydroxyl and keto absorptions at 3310, 1730 cm^{-1} respectively in IR and appearance of a multiplet between 4.3 and 4.2 δ (1H, OC*H*CH$_3$), singlet at 3.75 δ (3H, OMe), doublets at 3.45 δ (2H, CHC*H*$_2$CO$_2$) and 1.2 δ (3H, C*H*$_3$CH) in ^{1}H NMR confirmed the product formation. Using standard procedures the hydroxyl group was protected as its TBS ether **63**. The disappearance of hydroxyl peak at 3310 cm^{-1} and appearance of a strong peak at 1260 cm^{-1} for C-Si stretching in IR and appearance of two singlets at 0.9 δ (9H, C(C*H*$_3$)$_3$) and at 0.0 δ (6H, Si(C*H*$_3$)$_2$) in ^{1}H NMR confirmed the structure as **63**. The TBS ether was then subjected to DIBAL H reduction at –78°C followed by Wittig olefination (*insitu*) of the intermediate aldehyde to furnish the required α,β unsaturated ester **64**. The ester showed in its IR peaks at 1680, 1590, 1260 corresponding to ester, olefin and C-Si functionalities respectively. Further, ^{1}H NMR showed a multiplet

between 7.0 and 6.9 δ (1H, CH_2CH=CH), a doublet at 5.85 δ (2H, CH=$CHCO_2$) and a singlet at 3.65 δ (3H, OCH_3) which lent further proof to the structure. Pd/C catalysed hydrogenation furnished the C6 ester unit **65**. The structure of the hydrogenated product was confirmed by the disappearance of olefinic protons in ^{1}H NMR and appearance of multiplet between 1.7 and 1.4 δ (4H). Since the yield obtained in this route from methylacetoacetate was poor, a different route was pursued.

In the other route, ethyl acrylate was condensed with acetylacetone. The Michael adduct **66** was directly subjected to deacylation using NaOH and the product **67** obtained was confirmed by the following facts. The appearance of IR peaks at 1740 and at 1700 cm^{-1} corresponding to ester and ketone carbonyls respectively was observed. ^{1}H NMR showed the following peaks: quartet at 4.0 δ (2H, OCH_2), singlet at 2.05 δ (3H, $COCH_3$), and a triplet at 1.2 δ (3H, CH_2CH_3). Reported reduction with $NaBH_4$ at –23°C in methanol gave over reduced product only. However, reduction using $NaBH_4$/THF/water combination at 0°C for 25 min. selectively gave the required hydroxy ester **68**. The product showed IR peaks at 3310, 1735 cm^{-1} corresponding to hydroxyl and ester functionalities. A multiplet between 3.8 and 3.7 δ (1H, CH_3CHCH_2) and a doublet at 1.2 δ (3H, CH_3CH) confirmed the structure further. The hydroxyl group was protected as its TBS ether using standard procedure. The disappearance of hydroxyl absorption in IR at 3315 cm^{-1} and appearance of a band at 1260 cm^{-1} for C-Si together with the appearance of singlets at 0.9 δ (9H, $C(CH_3)_3$) and at 0.1 δ ($Si(CH_3)_2$) in 1H NMR confirmed the product formation.

For the other building unit *i.e.* C4 part, the phosphono ester **71** was prepared from methylacetoacetate using standard procedure. Selective bromination of methylacetoacetate with bromine at 0°C furnished the required γ bromo derivative **69**. Three singlets at 3.6 δ (3H, OCH_3), 3.5 δ (2H, $BrCH_2$) and 3.3 δ (2H, $COCH_2CO_2$) in ^{1}H NMR confirmed the structure. This was converted to the required phosphono ester **71** under microwave conditions (*vide experimental*). The phosphono ester showed in IR its peaks at 1732, 1690, 1250 cm^{-1} corresponding to ester, ketone and P=O functionalities respectively. Further, ^{1}H NMR showed a sharp triplet at 5.0 δ (1H, POC*Ha*HbCO), a broad singlet at 4.75 δ (1H, POCHa*Hb*CO), a multiplet between 4.3 and 4.1 δ (4H, OCH_2) and a multiplet between 1.45 and 1.35 δ (6H, CH_2CH_3) and there was no singlet at 3.5 δ, thereby proving the structure. One pot reaction involving DIBAL H reduction at –78°C of TBS ether **65**, followed by, condensation with the phosphonium ylide generated from phosphono ester using NAH as the base, furnished

the C10 unit **72**. The product showed IR peaks at 1730, 1680, 1590 and 1260 cm^{-1} corresponding to ester, ketone, olefinic bond and C-Si functionalities respectively. Multiplets between 6.9 and 6.8 δ (1H, CH_2CH=CH), 5.9 and 5.8 δ (1H, CH=CHCO) and singlets at 3.6 δ (3H, OCH_3), 3.3 δ (2H, $COCH_2CO_2$), 0.9 δ (9H, $C(CH_3)_3$), 0.0 (6H, $Si(CH_3)_2$) in ^{1}H NMR further confirmed the structure. Deprotection using aq. HF furnished the hydroxy ester, which was directly subjected to intramolecular transesterification to provide the required macrolide in 48 % yield. The spectral values of the product were comparable with that reported in the literature.

Conclusion

Thus, intramolecular transesterification has been efficiently applied for the total synthesis of diplodialide A. As conversion of diplodialide A to various macrolides like diplodialide B etc. have already reported, the present route offers a formal synthesis of various macrolides belonging to this group. Some of the salient features are (i) *Trans* geometry required in diplodialide A has been efficiently incorporated by Horner-Emmons reaction. (ii) The total number of steps are less, when compared to the previously reported syntheses. (iii) All the starting materials used in this syntheses are commercially available.

Experimental

Preparation of 2-(4-bromo-butoxy)-tetrahydropyran

Preparation of 4-bromobutan-1-ol

A mixture of 1,4-butanediol (1.80 gm, 20 mmol) and aq. HBr (1.60 gm, 20 mmol) in benzene (50 ml) was vigorously stirred under reflux with azeotropic removal of H_2O for 4 hrs. Then the reaction mixture was cooled to room temp. and quenched with solid $NaHCO_3$ and stirred for 15 min. The organic layer was decanted and concentrated. The crude material was purified by column chromatography to yield 4-bromo butan-1-ol (1.225 gm, 40 %).

4-Bromobutan-1-ol

$Br(CH_2)_4OH$

IR (neat) cm^{-1}

3310, 690

^{1}**H** NMR (90 MHz, $CDCl_3$)

3.6-3.5 (m, 2H), 3.35-3.25 (m, 2H), 2.3-2.1 (m, 4H)

Preparation of 2-(4-bromobutoxy)-tetrahydropyran

4-Bromobutan-1-ol (460 mg, 3.0 mmol) was dissolved in dry CCl_4 (15 ml) and to this stirred solution, DHP (672 mg, 6.0 mmol) was added followed by the addition of clay catalyst (70 mg, 15 % wt/wt). The reaction mixture was stirred for 4 hrs. After the reaction was over (as monitored by TLC), the catalyst was filtered off and washed with more CCl_4 (3 X 4ml). The combined organic layer was concentrated under reduced pressure to yield the crude protected bromo compound. Column chromatography on neutral alumina gave 700 mg (98 %) of the compound as a colourless oil.

2-(4-Bromobutoxy)-tetrahydropyran

$Br(CH_2)_4OTHP$

IR (neat) cm^{-1}

2938, 1446, 1260, 690

^{1}**H** NMR (90 MHz, $CDCl_3$)

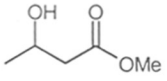
4.5-4.4 (m, 1H), 3.9-3.7 (m, 2H), 3.5-3.4 (m, 4H), 2.2-1.5 (m, 10H)

$NaBH_4$ reduction of methylacetoacetate

$NaBH_4$ (92.5 mg, 2.5 mmol) was added slowly to a solution of methylacetoacetate (1.16 gm, 10 mmol) in isopropanol (25 ml). The reaction mixture was stirred at room temp. for 15 min. and then refluxed for 10 min. after which dil. HCl was carefully added to make the solution strongly acidic. Isopropanol was removed

under reduced pressure. The residue was taken in DCM, the organic layer was washed with $NaHCO_3$, water and finally with brine and was dried over Na_2SO_4. Removal of the solvent under reduced pressure followed by vacuum distillation (bath temp. 120°C) yielded the hydroxy ester.

3-Hydroxy-butanoic acid methyl ester



IR (neat) cm^{-1}

3310, 1730

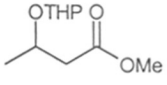
^{1}**H** NMR (90 MHz, $CDCl_3$)

4.2-4.1 (m, 1H), 3.75 (s, 3H), 3.45 (d, J=8Hz, 2H), 3.2-3.1 (br, OH), 1.2 (d, J=8Hz, 3H)

Preparation of 3-(tetrahydropyran-2-yloxy)-butanoic acid methyl ester

3-Hydroxy-butanoic acid methyl ester (590 mg, 5.0 mmol) was taken in dry CCl_4 (25 ml) and to this stirred solution, DHP (1.12 gm, 10.0 mmol) was added followed by the addition of clay catalyst (90 mg, 15 % wt/wt). The reaction was stirred for 4 hrs. After the reaction was over (as monitored by TLC), the catalyst was filtered off and washed with few CCl_4 (3 X 8ml). The combined organic layer was concentrated under reduced pressure to yield the protected bromo compound. Column chromatography on neutral alumina gave 967 mg (96 %) of 3-(tetrahydropyran-2-yloxy)-butanoic acid methyl ester as a colourless oil.

3-(Tetrahydropyran-2-yloxy)-butanoic acid methyl ester



IR (neat) cm^{-1}

2940, 2870, 1735, 1430

^{1}**H** NMR (90 MHz, $CDCl_3$)

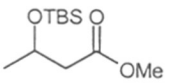
4.7-4.6 (m, 1H), 4.1-4.0 (m, 1H), 3.9-3.7 (m, 2H), 3.5 (s, 3H), 2.5-2.4 (m, 2H), 1.9-1.3 (m, 6H), 1.2 (d, J=8Hz, 3H)

Preparation of 3-(*t*-butyldimethylsilanyloxy)-butanoic acid methyl ester 63

3-Hydroxy-butanoic acid methyl ester (1.18, gm, 10.0 mmol) was dissolved in dry DMF (3 ml) and to this TBDMSCl (2.25 gm, 15.0 mmol) and imidazole (1.36 gm, 20.0 mmol) in DCM (5 ml) were added under N_2. The reaction mixture was stirred at room temp. for 24 hrs. The contents were then diluted with hexane (30 ml) and the combined organic layer was washed with water followed by brine and dried over

Na_2SO_4. Removal of the solvent under reduced pressure yielded the crude product which was purified by column chromatography to afford the silyl ester **63** (1.95 gm, 84 %) as a colourless oil.

3-(*t*-Butyldimethylsilanyloxy)-butanoic acid methyl ester



IR (neat) cm^{-1}

2930, 1735,1260

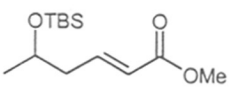
^{1}**H** NMR (90 MHz, $CDCl_3$)

3.8 (m, 1H), 3.65 (s, 3H), 2.25 (d, J=5Hz, 2H), 1.25 (d, J=4.5Hz, 3H), 0.9 (s, 9H), 0.05 (s, 6H)

Preparation of α,β unsaturated ester 64

3-(*t*-Butyl-dimethyl-silanyloxy)-butanoic acid methyl ester (464 mg, 2.0 mmol) in dry toluene (12 ml) was cooled to –78°C under Ar. using dry ice-acetone bath. To this cooled and stirred solution, DIBAL H (284 mg, 0.7 ml, 2.8 M solution in toluene) was added slowly and the reaction mixture was stirred at –78°C for 3½ hrs. The reaction was then quenched by the addition of methanol (1 ml).

In another experiment, trimethylphosphonoacetate (364 mg, 2.0 mmol) in dry THF (5 ml) was added to a previously washed NaH (95 mg, 50 % dispersion in mineral oil, 2.0 mmol) in dry THF (6 ml) at 0°C. The reaction mixture was stirred at 0°C for 15 min., the contents were then transferred to the –78°C reaction mixture with the help of a cannula, and the reaction was stirred at –78°C for 4 more hrs. The reaction mixture was allowed to warm to 0°C and stirred at that temp for 1 more hr. Then the reaction mixture was kept at room temp. for 10-15 min. when the whole reaction mixture turned to a gelatinous precipitate, the precipitate thus obtained was extracted with hot methanol and the extracts were passed through a short plug of celite to remove the inorganic hydroxide. The filtrate thus obtained was concentrated under reduced pressure and the crude material obtained was purified by filtration column using flash silica gel to yield the α,β unsaturated ester **64** (485 mg, 94 %).



IR (neat) cm^{-1}

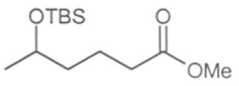
2930,1740,1595,1260

^{1}**H** NMR (200 MHz, $CDCl_3$)

7.0 (dt, J=8.9,14.4Hz, 1H), 6.85 (d, J=14.4Hz, 1H), 4.0-3.9 (m, 1H), 3.75 (s, 3H), 2.35 (t, J=5Hz, 2H), 1.2 (d, J= 7Hz, 3H), 0.9 (s, 9H), 0.05 (s, 6H)

Hydrogenation of α,β unsaturated ester 64

The above α,β unsaturated ester **64** (258 mg, 1.0 mmol) in dry ethanol (8 ml) was taken in a hydrogenation flask and to this solution Pd/C (12 mg, 5% wt/wt) was added and the reaction mixture was hydrogenated for 3 hrs. After the reaction was over (as monitored by TLC) the catalyst was removed by filtration through a short plug of celite. It was further washed with ethanol (10 ml). The combined filtrate was concentrated under reduced pressure followed by purification through a short plug of silica gel to yield the silyl ester **65** (254 mg, >95 %).



IR (neat) cm^{-1}

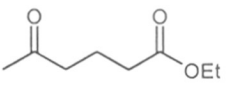
2956, 1740, 1260

^{1}**H** NMR (90 MHz, $CDCl_3$)

3.8-3.7 (m, 1H), 3.6 (s, 3H), 2.3 (t, J=7Hz, 2H), 1.8-1.7 (m, 2H), 1.4-1.3 (m, 2H), 1.2 (d, J=7Hz, 3H), 0.9 (s, 9H), 0.0 (s, 6H)

Michael addition of ethyl acrylate with acetylacetone

A mixture of ethyl acrylate (25.0 gm, 0.25 mole) and acetylacetone (25.0 gm, 0.25 mole) was added drop-wise over 1½ hr. to a boiling solution of absolute ethanol in which sodium (0.18 gm) has been dissolved. The reaction mixture was refluxed for one more hr. then, the reaction mixture was cooled to room temp. and HOAc (0.5 ml) was added and the solvent was removed under reduced pressure. The residue was subjected to vacuum distillation to afford 40 gm of a mixture which was deacylated with NaOH (1 N) in MeCN to afford the ethy-5-oxo hexanoate. A simple filtration column on silica gel furnished the pure product as a colourless liquid **67** (21.4 gm, 54%).



IR (neat) cm^{-1}

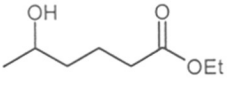
1736, 1700, 1170, 1020

^{1}**H** NMR (200 MHz, $CDCl_3$)

4.0 (q, J=7Hz, 2H), 2.4 (t, J=7Hz, 2H), 2.25 (t, J=7Hz, 2H), 2.05 (s, 3H), 1.9-1.8 (m, 2H), 1.2 (t, J=7Hz, 3H)

$NaBH_4$ reduction of keto ester 67

The keto ester **67** (1.56 gm, 10.0 mmol) was dissolved in THF (20 ml) and to this solution water (1 ml) was added and the reaction mixture was cooled to 0°C using an ice bath. To this stirred cold solution $NaBH_4$ (370 mg, 10.0 mmol) was added in 25 mg portions each, over 3 min. Then, the reaction mixture was stirred at 0°C for 25 min. more. After that the reaction mixture was carefully quenched with dil. HCl (0.5 N) to pH ~2. It was then diluted with $CHCl_3$ and the aqueous layer was separated and extracted further with $CHCl_3$ (3 X 5ml). The combined organic layer was washed with $NaHCO_3$, water and finally with brine. Drying over Na_2SO_4 followed by removal of the solvent under reduced pressure yielded the pure hydroxy ester **68** (1.5 gm, >95 %).



IR (neat) cm^{-1}

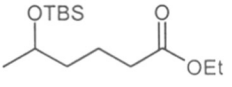
3310, 1735

^{1}**H** NMR (200 MHz, $CDCl_3$)

4.1 (q, J=7Hz, 2H), 3.8-3.7 (m, 1H), 2.3 (t, J=7Hz, 2H), 1.8-1.7 (m, 2H), 1.5-1.4 (m, 2H), (1.25 (t, J=7Hz, 3H), 1.2 (d, J=7Hz, 3H)

TBS protection of compound 68

As per the procedure reported for **63**. Quantities taken hydroxy ester **68** (800 mg, 5.0 mmol), TBSCl (1.125 gm, 7.5 mmol), imidazole (680 mg, 10.0 mmol) yield of **68a** (1.34 gm, > 95 %).



IR (neat) cm^{-1}

1740, 1260

^{1}**H** NMR (200 MHz, $CDCl_3$)

4.15 (q, J=7Hz, 2H), 3.8-3.7 (m, 1H), 2.4-2.3 (m, 2H), 1.7-1.3 (m, 4H), 1.2 (t, J=7Hz, 3H), 1.1 (d, J=7Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H)

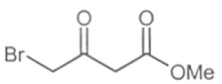
^{13}**C** NMR (50 MHz, $CDCl_3$)

173.38 (s), 68.03 (d), 59.91 (t), 38.86 (t), 34.20 (t), 25.73 (q), 23.57 (q), 21.11 (t), 14.09 (q), -4.55 (q), -4.91 (s)

Preparation of Horner-Emmons reagent 71

Preparation of 4-bromo-3-oxo-butanoic acid methyl ester 69

To a solution of methylacetoacetate (11.6 gm, 0.10 mole) in $CHCl_3$, Br_2 (5.2 ml, 0.1 mole) in $CHCl_3$ was added at 0°C. Then the reaction mixture was kept at room temp. for 16 hrs. A stream of air was bubbled through the solution for 1 hr. The organic layer was washed with saturated $NaHCO_3$ solution (7 X 20 ml) followed by brine and was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was vacuum distilled to afford 4-bromo-3-oxo-butanoic acid methyl ester **69** (b.p 89°C/5 mm).



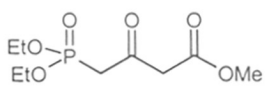
IR (neat) cm^{-1}

1742, 1690, 770

^{1}**H** NMR (60 MHz, CCl_4)

3.7 (s, 3H), 3.4 (broad s, 4H)

To 4-bromo-3-oxo-butanoic acid methyl ester **69** (585 mg, 3.0 mmol) obtained as above, triethylphosphite (498 mg, 3.0 mmol) was added while cooling the contents. After the exothermic reaction was subsided the cooling bath was removed and the reaction mixture was kept in the microwave oven (at 40 % of its power) for irradiation. When no further vigorous reaction took place, (as the bubbles coming from the reaction mixture ceased) the reaction mixture was kept further for 2 to 3 more min. The reaction mixture was removed from the microwave oven and purified by column chromatography to afford the pure phosphono ester.



IR (neat) cm^{-1}

1735, 1698,

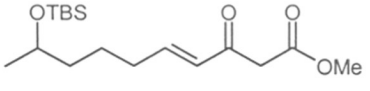
1H NMR

5.0 (t, J=1.2Hz, 1H), 4.75 (s, 1H), 4.3-4.2 (m, 4H), 3.7 (s, 3H), 3.25 (s, 2H), 1.45-1.35 (m, 6H)

Preparation of intermediate 72

3-(*t*-Butyl-dimethyl-silanyloxy)-hexanoic acid ethyl ester (200 mg, 0.77 mmol) in dry toluene (12 ml) was cooled to –78°C under Ar. using dry ice-acetone bath. To this stirred solution DIBAL H (109 mg, 0.27 ml, 2.8 M solution in toluene) was added slowly. The reaction was stirred at –78°C for 3½ hrs. after which it was quenched by the addition of methanol (1 ml).

In another experiment phosphono ester **71** (194 mg, 0.77 mmol) in dry THF (5 ml) was added to a previously washed NaH (74 mg, 50 % dispersion in mineral oil, 1.54 mmol) in dry THF (6 ml) at 0°C. The reaction mixture was stirred at 0°C for 15 min., then the contents were then transferred to the –78°C reaction using cannula, and the reaction was stirred at –78°C for 4 more hrs. It was then allowed to warm to 0°C and stirred at that temp for 1 more hr. then the reaction mixture was kept at room temp. for 10-15 min. when it turned to a gelatinous precipitate. The precipitate thus obtained was extracted with hot methanol and the extracts were passed through a short plug of celite to remove the inorganic hydroxide. The filtrate thus obtained was concentrated under reduced pressure and the crude material obtained was purified by filtration column using flash silica gel to yield the α,β unsaturated ester **72** (292 mg, 89 %).



IR (neat) cm^{-1}

2930,1740,1595,1260

^{1}**H** NMR (90 MHz, $CDCl_3$)

6.9-6.8 (m, 1H), 5.7 (m, 1H), 4.0-3.9 (m, 1H), 3.75 (s, 3H), 3.4 (s, 2H), 2.35 (t, J=5Hz, 2H), 1.8-1.5 (m 4H), 1.2 (d, J= 7Hz, 3H), 0.9 (s, 9H), 0.05 (s, 6H)

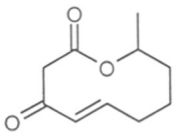
Deprotection of TBS ester 72

TBS ester **72** (254 mg, 0.77 mmol) was treated with aq. HF (0.7 ml) in THF (10 ml). The reaction mixture was stirred at room temp. for 30 min. The solvent was removed under reduced pressure and the residue was taken in DCM. The organic layer was washed several times with water, followed by brine. It was then dried over Na_2SO_4. Removal of the solvent followed by purification afforded the hydroxy compound (129 mg, 78%).

IR (neat) cm^{-1}

3320, 1740,1595

The hydroxy ester (69 mg) was dissolved in 5 ml of tolune. Catalyst Hβ (10 mg) was added and the alcohol was azeotropically removed using Dean-Stark apparatus. After the reaction was over (as analysed by TLC) the catalyst was removed by filtration. The catalyst was washed with toluene (2 X 3ml). The filtrate was combined and the solvent was removed under reduced pressure. Purification of the crude material by column chromatography afforded diplodialide A (28 mg, 48 %).



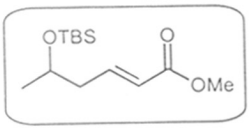
IR ($CHCl_3$) cm^{-1}

3310, 1741, 1685, 1590

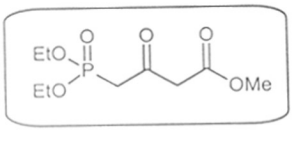
^{1}**H** NMR (90 MHz, $CDCl_3$)

6.9-6.8 (m, 1H), 5.7 (m, 1H), 4.0-3.9 (m, 1H), 3.4 (d, J=6Hz, 2H), 2.35 (t, J=5Hz, 2H), 1.8-1.5 (m 4H), 1.2 (d, J= 7Hz, 3H).

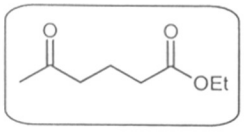
SAMPLE NO. VS/III/52 / CDCL3 / WEAK LOCK....?



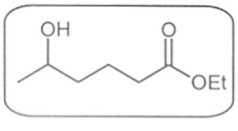
PHOS-ESTER/CDCL3

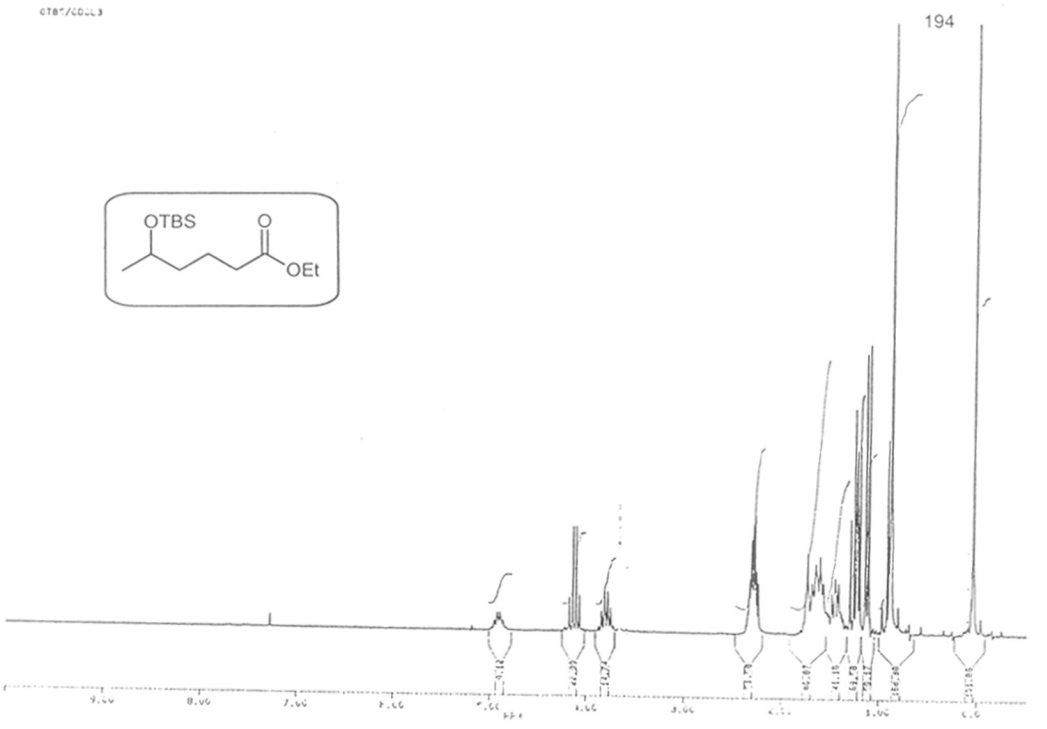


HEX-DEACYL/CDCL3



SAMPLE NO. CH-H.N / CDCL3

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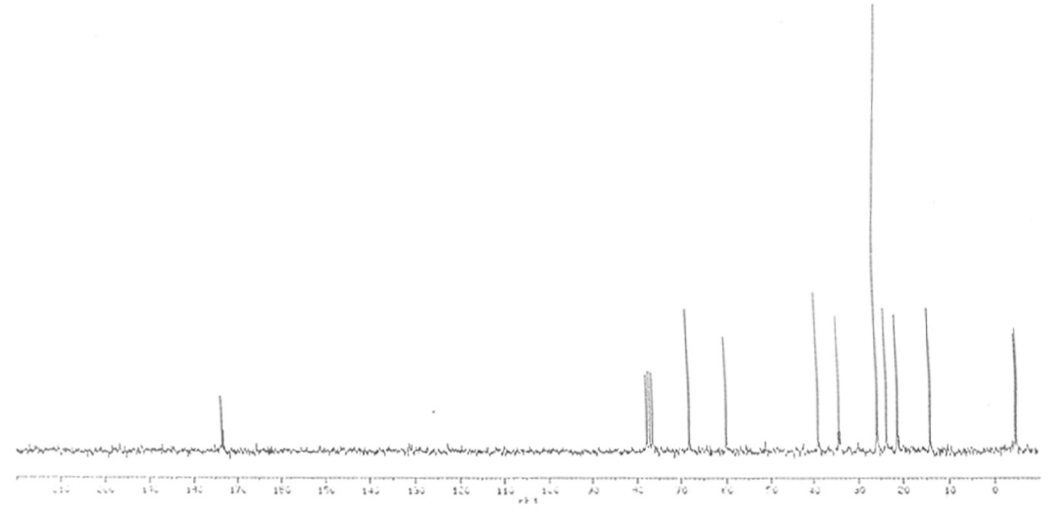

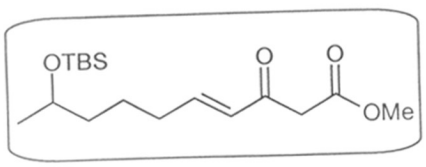
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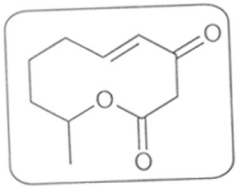
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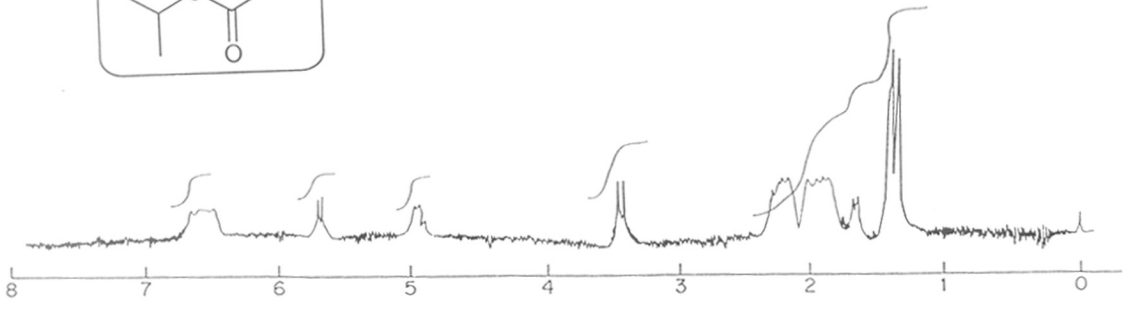
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References:

1. Ishida, T. And Wada, K., *J.Chem.Soc.Chem.Commun.*, **1975**, 209.
2. Wada, K. and Ishida, T., *J.Chem.Soc.Perkin Trans. 1*, **1979**, 1154
3. Ishida, T. And Wada, K., *J.Chem.Soc.Chem.Commun.*, **1977**, 337.
4. Tsuji, J. And Mandai, T., *Tetrahedron Lett.*, **1978**, 1817.
5. Wakamatsu, T., Akasaka, K., Ban, Y., *J.Org.Chem.*, **1979**, 44, 2008.
6. Ireland, R.E. and Brown, F.R. Jr., *J.Org.Chem.*, **1980**, 45, 1868.
7. Shenvi, A.B. and Gerlach, H., *Helv.Chim.Acta*, **1980**, 63, 2426.
8. Nicolaou, K.C., *Tetrahedron*, **1977**, (33), 683.
9. Stoll, M. And Rouve, *Helv.Chim.Acta*, **1934**, 17, 1283.
10. Corey, E.J. and Nicolaou, K.C., *J.Am.Chem.Soc.*, **1974**, (96), 5614.
11. Masumune, S., Kim, C.U., Wilson, K.E., Spessard, G.O., Georgiou, P.E., Bates, G.S., *J.Am.Chem.Soc.*, **1975**, (97) 3512
12. Mukaiyama, T., Usui, M., Saigo, K., *Chem.Lett.*, **1976**, 49.
13. Kurihara, T., Nakajima, Y., Mitsunobu, O., *Tetrahedron Lett.*, **1976**, (16), 2455.
14. Venkatraman, K. and Wagle, D., *Tetrahedron Lett.*, **1980**, (21), 1893.
15. Kasar, R.A., Ph.D., thesis, Pune university, p 86.
16. Percinal, W.C., Wagner, R.B., Cook, N.C., *J.Am.Chem.Soc.*, **1953**, (75), 3731.
17. Kim, S. and Ho Park, J., *Tetrahedron Lett.*, **1987**, (28), 439.
18. Wilson, T.M., Kocienski, P., Jarowicki, K., Isaac, K., Hitchcock, P.M., Faller, A., Campbell, S.F., *Tetrahedron*, **1990**, (46), 1767.
19. Eliel, E.L., Badding, V.G., Rerick, M.N., *J.Am.Chem.Soc.*, **1962**, (84), 2371.
20. Rosenberger, M., Andrews, D., DiMaria, F., Duggan, A.J., Saucy, G., *Helv.Chim.Acta*, **1972**, 55, 249.
21. Chartlon, J.L. and Allauddin, M.M., *J.Org.Chem.*, **1986**, (51), 3490.
22. Chong, R. And Clezy, P.S., *Aust.J.Chem.*, **1967**, (21), 123.
23. Svendsen, A. and Boll, P.M., *Tetrahedron*, **1973**, (29), 4251.

List of Publications

1. *Zeolite-mediated synthesis of β-keto esters: Condensation of ethyldiazoacetate with aldehydes.*

   Sudrik, S.G., **Balaji, B.S.**, Singh, A.P., Mitra, R.B., Sonawane, H.R., *Synlett.* 1996, 369-370.

2. *A facile and selective synthesis of β-keto esters via zeolite catalysed transesterification.*

   Balaji, B.S., Sasidharan, M., Kumar, R., Chanda, B., *Chem.Commun.*, **1996**; 707-708.

3. *Site Selective C-H Insertion of Unactivated α-diazo-β-aroyl esters Catalysed by Rh (II) Carboxylates.*

   Balaji, B.S., Chanda, B. (*communicated*)

4. *Microwave assisted preparation of novel Horner-Emmons reagents and their applications in organic synthesis.*

   Balaji, B.S., Chanda, B., (to be communicated).

5. *Some studies on Michael addition of β keto esters with benzylidene ketones catalysed by hydrotalcites*

   Balaji, B.S., Sarita, M., Ramani, A., Chanda, B., (to be communicated).

6. *Preparation and applications of a novel phosphorous free water soluble rhodium catalyst.*

   Balaji, B.S., Chanda, B., (Indian Patent to be filed).