USE OF ZINC IN REFORMATSKY REACTION OF CHLOROESTER, TRANSESTERIFICATION OF KETOESTERS, SYNTHESIS OF LIPOIC ACID AND UTILITY OF DIELS-ALDER REACTION TOWARDS THE FRAMEWORK OF CAMPTOTHECIN AND STREPTONIGRIN.

A thesis submitted to
The University of Pune
for the degree of

DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

By
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Pune-411 008, India.

APRIL 2002

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TO

MY TEACHERS

CERTIFICATE

Certified that the work incorporated in the thesis entitled "Use of zinc in Reformatsky reaction of chloroester, transesterification of ketoesters, synthesis of lipoic acid and utility of Diels-Alder reaction towards the framework of camptothecin and streptonigrin" submitted by Mr. Shivasankar. K was carried out by the candidate under my supervision. Such material as has been obtained from other sources and has been duly acknowledged in the thesis.

April, 2002 Dr. Subhash P. Chavan

Abbreviations

Ac	Acetyl
Ar	Aryl
B. P.	Boiling point
CAN	Ceric ammonium nitrate
DCM	Dicholoromethane
DIBAL	Diisobutylaluminum hydride
DMF	*N*, *N*-dimethyl formamide
Et	Ethyl
EtOAc	Ethyl acetate
g	Gram
hr.	Hour
mg	Milligram
ml	Milligram
Me	Methyl
M. P	Melting point
M^+	Molecular ion
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
Ph	Phenyl
pTSA	*p*-Toluene sulphonic acid
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
XRD	X-ray diffraction
XRF	X-ray fluorescence

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Words fall short to thank my family (my first school) members for their never ending encouragement and support. The thesis is a form to pay respect to their attributes.

Support from CSIR for financial assistance is also duly acknowledged.

Shivasankar. K

GENERAL REMARKS

1. All melting points and boiling points are uncorrected and the temperature is expressed in degree Celsius.
2. The compound numbers, scheme numbers and reference numbers given in each section refer to that particular section only.
3. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80^{o}C.
4. Organic layers were dried over anhydrous sodium sulphate (Na_2SO_4).
5. TLC analyses were carried out on glass plates using silica gel: GF-254and the plates were analysed by keeping in the iodine chamber.
6. In cases where chromatographic purification was done, SiO_2 was used as a stationary phase.
7. The IR spectra were recorded on Perkin-Elmer infrared spectrophotometer model 683B or 1605 FTIR and IR absorbance is expressed in cm^{-1}.
8. The 1H NMR and 13C NMR spectra were recorded on Bruker AC200, MSL 300 and DRX 500. 1H NMR and 13C NMR spectra are reported in parts per million from internal standard (tetramethylsilane) on d scale.
9. Mass spectra were recorded at an ionization energy 70eV on Finnigan MAT-1020 automated GC/MS instrument and mass values are expressed as m/e.

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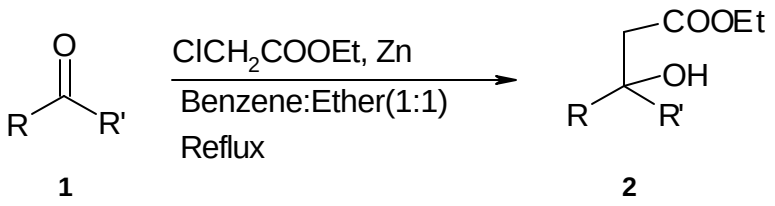
ABSTRACT

The thesis entitled "**Use of zinc in Reformatsky reaction of chloroesters, transesterification, synthesis of Lipoic acid and utility of Diels-Alder reaction towards the framework of camptothecin and streptonigrin**" is divided into two chapters. The first chapter deals with the modified Reformatsky reaction, a study towards the dehydration mechanism using thionyl chloride and pyridine, synthesis of lipoic acid and 4-aryl-2(*5H*)-furanone using the above modification of Reformatsky reaction. Second chapter deals with some synthetic methodologies using zinc and iodine namely the transesterification and the synthesis of 4-methylcoumarin and synthesis of substituted qunolines using a Diels- Alder reaction.

Chapter 1: The chapter is divided into four sections. This chapter concentrates on the synthetic methodology using activated Zinc and Iodine for two-carbon homologation as a modification to the normal Reformatsky reaction. The second section puts some light on the dehydration mechanism of tertiary alcohols, by the usage of thionyl chloride and pyridine, through a theoretical study. The third section deals with the usage of the Reformatsky reaction in the synthesis of 4-aryl-2(*5H*)-furanone and the fourth deals with the synthesis of lipoic acid using the above methodology.

Section 1A: **Modification of Reformatsky reaction**

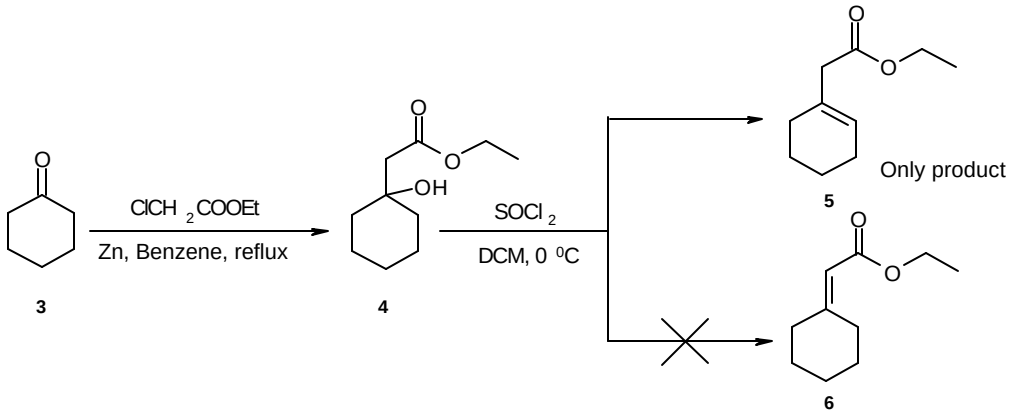
Two-carbon homologation has a tremendous importance in synthetic organic chemistry. This section has brief introduction on Reformatsky reaction and their modifications. α-haloester when treated with Zinc and carbonyl compound usually give the β-hydroxy ester.[1] In literature most of the cases known with halogen atom substituted as Bromine.[2] The reactions with chloroesters are lesser known, modification for the condensation of chloroester using zinc is also discussed. This section also discusses the condensation of α-chloroester to carbonyls using Zinc and iodine.



Scheme -1

Section 1B: **Dehydration mechanism: A theoritical insight**

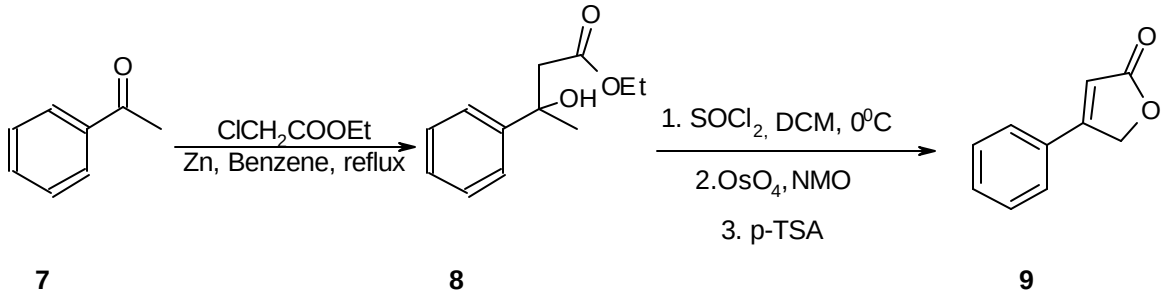
This section gives an insight to the path way for dehydration of alcohols using thionyl chloride and pyridine. The section aims at giving an explanation to the scheme **2**. The study involves the energy minimization and study on similar systems both cyclic and acyclic. The calculations done are mostly at *ab inito* and in some cases, at semi-empirical level.



Scheme 2

Section 1C: **Synthesis of 4-aryl-2(*5H*)-furanone**

The section deals with the synthesis of substituted 4-aryl-2(*5H*)-furanone. The compound, though looks very simple, has striking activity and is reported to be highly

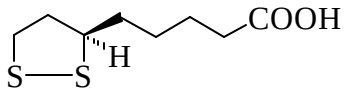


Scheme 3

effective against fungal diseases in plants of agronomic importance.[3] We have applied our methodology to synthesis this intermediate. Modified Reformatsky reaction was done on acetopheneone and substituted acetophenones. The hydroxy product obtained was then subjected to elimination using thionyl chloride and pyridine. The β,ϒ unsaturated ester was then subjected to dihydroxylation using OsO_4. The diol obtained was then immediately subjected to elimination followed by cyclisation in one pot using p-TSA.

Section 1D: **Synthesis of** a **- Lipoic acid**.

The section deals with a general introduction, reports and the synthesis known on Lipoic acid. α - Lipoic acid and its reduced form dihydrolipoic acid are physiologically occurring substances in plants and animals. It is identified as a vital cofactor in the multienzyme complexes that catalyze oxidative decarboxylation of α-Keto acids. It is also known to assume crucial roles in photosynthesis[4] as well as in the tricarboxylic acid cycle. It has recently shown beneficial effects[5] on diabetic rabbits during glucose tolerance test. Lipoic acid is used for diabetic polyneuropathy.

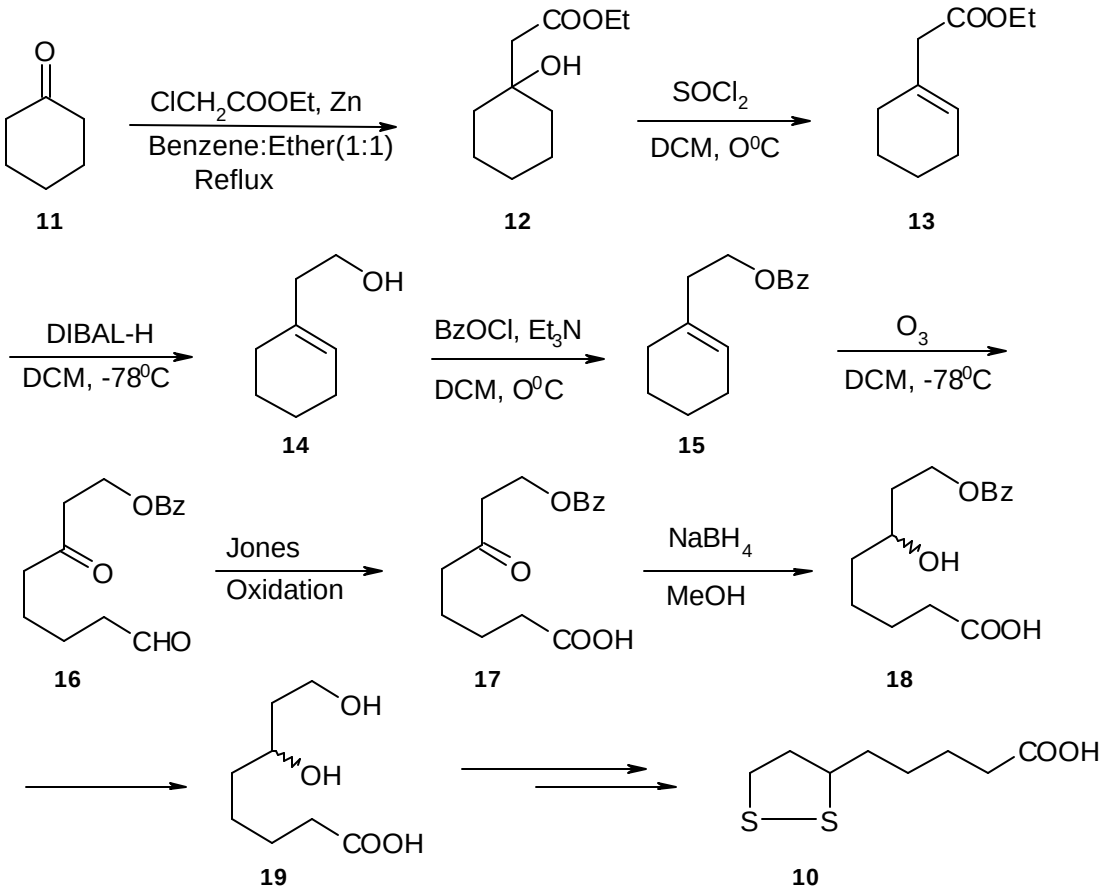


10

R (+) a **- Lipoic acid**

α - Lipoic acid was first isolated from processed liver in 1950 by Reed and co-workers[6] and characterized as the cyclic disulfide. The biological activity of α - Lipoic acid is confined to the naturally occurring ‘ R ` isomer [7](1).

In our appoarch towards the synthesis of lipoic acid, we have tried to adopt the modified Reformatsky methodology towards the synthesis. The elimination of the alcohol to furnish only the ß, ? unsaturated ester is another feature of the synthesis. Reformatsky reaction with Chloroester was done on Cyclohexanone as the first step towards the synthesis. The alcohol thus obtained was then set for elimination using thionyl chloride and pyridine. ß, ? ester thus obtained was then subjected to an ester reduction using DIBAL-H. The alcohol was then protected using benzoyl chloride. The benzoate thus obtained was subjected to ozonalysis. The aldehyde thus obtained was then subjected to



Scheme 4

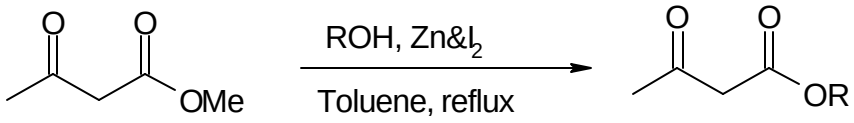
Jones oxidation. The keto-acid was then reduced followed by esterification to give the alco-ester. The intermediate was subjected to ester hydrolysis followed by the mesitylation and the treatment with Na_2S and S in DMF to give methyl lipoate.

Chapter2: This chapter is divided into four sections the first deals with the transesterification with β-ketoesters, second with the synthesis of substituted 4-methyl coumarins, both the methodologies involve the use of zinc and iodine. Third section discusses with the synthesis of substituted quniloines using Deals- alder reaction, while the last section deals with transferhydrogenation.

Section 2A: **Zinc and Iodine: Catalyst for the transesterification**

Transesterification is one of the classic organic reactions that have enjoyed numerous laboratory uses and industrial applications.[8] There has always been a never-ending quest

to find out the catalyst for this reactions.[9]This section contains an introduction of the reagents and modifications for the reaction namely transesterification.



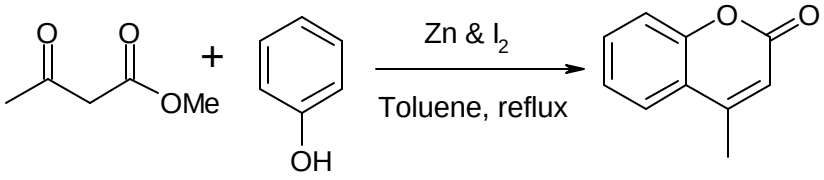
20 **21**

Scheme 5

The section gives more emphasis on the use of zinc and iodine as an effective catalyst for the transesterification. The reaction has been done on variety of alcohols. The yields of the reaction are good to very good in some of the cases.

Section 2B: **Zinc and Iodine: Reagent for the synthesis of Coumarins**

Coumarins are used as additives to food and cosmetics, optical brightening agents and dispersed fluorescent and laser dyes.[10] The derivatives of coumarins usually occur as secondary metabolitics present in seeds, roots and use of many plant species. Their function is far from clear, though suggestion includes waste product plant growth regulator, fungistats and bacteriostats.[11] Coumarins occupy a special place in the realm of



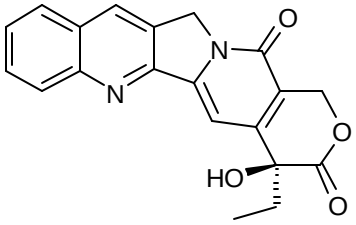
20 **22** **23**

Scheme 6

natural and synthetic organic chemistry because many products, which contain these subunit exhibit useful and diverse biological activities such as molluscacides, have anthelmintic, hypnotic and insecticidal properties or serve as a anticoagulant agents. [12] It is therefore of utmost important that the synthesis of coumarin and its derivatives should be achieved by a simple and effective method. Here we report a short and effective synthesis of substituted 4-methyl coumarin. This section also contains a brief introduction on the report of recent synthesis of coumarins.

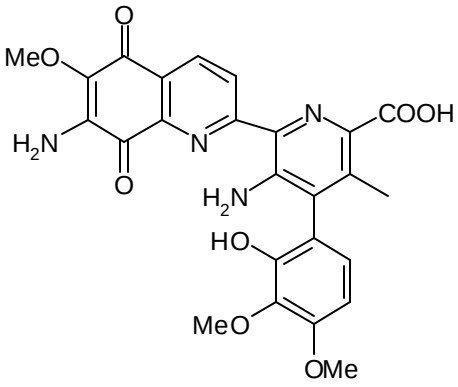
Section 2C: Synthesis of Qunolines: A Diels-Alder approach

The synthesis of qunoline alkaloide like streptonigrin, camptothecin, lavendamycin etc. have been in the air in the recent years.[13] These alkaloids show striking activity against animal tumors



24

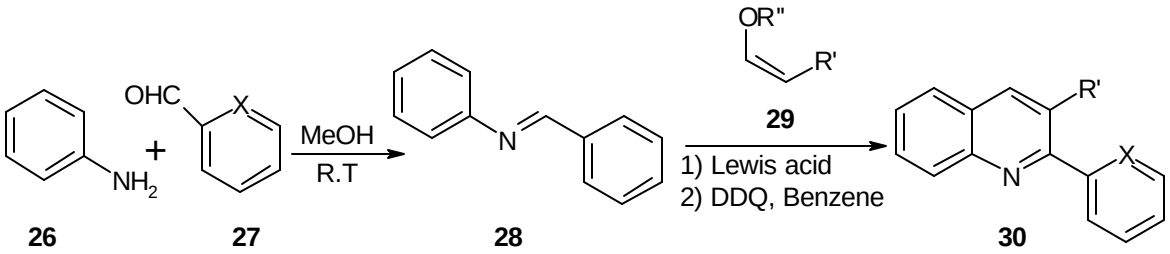
Camptothecin



25

Streptonigrin

The construction of the quinoline ring in these compounds has been the key reaction in many syntheses. In this section we take a look of the construction of these ring using DA reaction. Termed as father of cyclo-addition, DA is the most effective reaction to prepare the cyclo compounds. In recent years the hetero Diels-Alder has received greater importance.[14] The use of Diels-Alder reaction to prepare the quinoline ring using imine and an enol ether has been taken up.

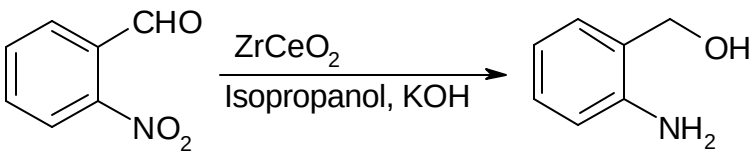


26 **27** **28** **30**

Scheme 7

Section 4D: Zirconium based Hetereogenous catalyst for transferhydrogenation

This section deals with transferhydrogenation. The Chemoselective reduction of organic compounds is synthetically important, both in the laboratory as well as in the industry. In comparison with catalytic reduction using molecular hydrogenation, transfer reaction using hydrogen donors, viz. propan-2-ol, have real and potential advantages because



31 **32**

Scheme 8

neither hydrogen containment nor a pressure vessel is required. Moreover, the transfer hydrogenation method could offer enhanced selectivity in the reduction process. A wide variety of homogenous and heterogeneous catalytic systems in combination with different hydrogen donors have been employed to selectivity reduce most major functional groups attached to aliphatic and aromatic structures. In the present work, $ZrCeO_2$, a reusable, solid catalyst has been used as a **t**ransfer Hydrogenation of, $-NO_2$, >C= 0 was attempted using $ZrCeO_2$ as the catalyst as depicted in scheme **8.**

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CHAPTER I

SECTION A
Modification of Reformatsky reaction

SECTION B
Dehydration mechanism: A theoretical insight

SECTION C
Synthesis of 4-aryl-2(5H)-furanone

SECTION D
Synthesis of a **- Lipoic acid**

SECTION A
Modification of Reformatsky reaction

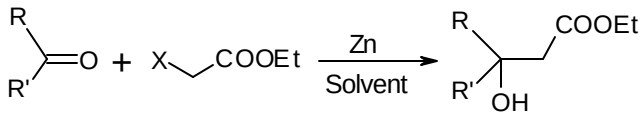
1.1.1 Introduction

Carbon-carbon bond formation has always fascinated the organic chemists. This can be achieved in a variety of ways, which utilize free radical, nucleophilic addition, electrophilic addition to coupling and so on. Out of these nucleophilic additions are perhaps the most outstanding of them all. Many named reaction go with nucleophilic addition to the carbonyl group. Grignard, Perkin, Knoevenagal, Wittig, Reformatsky to name a few. Subsequent modification in substrates, conditions, reagents have always been the in the front so as to increase the efficiency and effectiveness of the reaction in terms of yield and also the reaction time.

In this sub-section we take a brief out look on Reformatsky reaction, its utility and its modifications.

1.1.2 Reformatsky reaction an insight

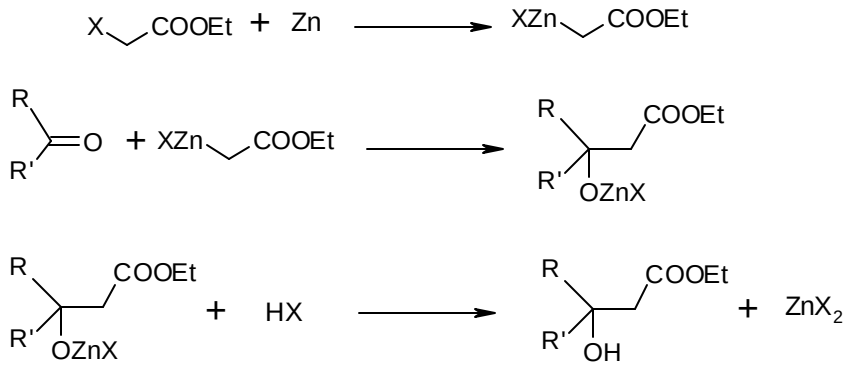
Ever since the first report by Reformatsky in 1887,[1] the reaction has been studied extensively.[2] A simple Reformatsky reaction is depicted in Scheme 1.



Scheme 1

A look into the mechanism suggests the reaction is a three-step process. (Scheme 2).

Mechanism:



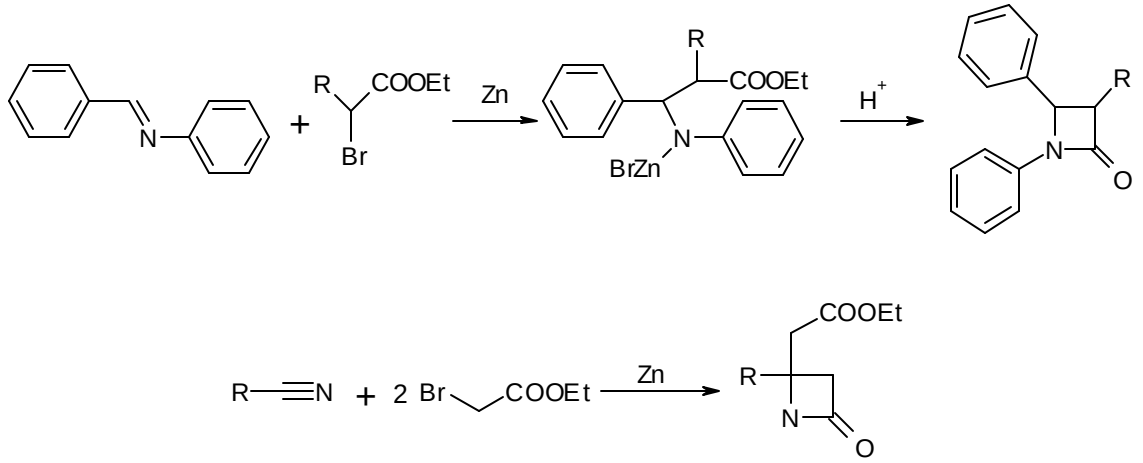
Scheme 2

The first step involves the formation of organozinc halide. The second involving the addition to the carbonyl group of the aldehyde or ketone and the third involves the

decomposition by dilute acids. Thus an aldehyde or a ketone leads to a ß-hydroxy ester as the end product.

Utility of the reaction

Reformatsky reaction is generally done on aldehydes and ketones. They are also done on imines,[3] nitriles,[4] esters,[5] acid chlorides.[6]



Scheme 3

This reaction has been used for the synthesis of wide variety of compounds like indanones,[7] tetralones,[8] isoquinolines,[9] azaphenantheren,[10] butenolides,[11] mintlactone,[12] etc. Modifications to the reactions are many and they can be broadly classfied into four catagories. A) Modifications on the halo-ester B) Solvents used for the reaction C) Modification of the type of Zinc used for the reaction and D) Substitution of the metal.

Modification on the haloester

Bromoacetates are generally used for the reaction since iodoacetates are generally not available and the reaction with that is highly exothermic. Chloroesters are usually very slow to react. Other than haloacetates reagents like benzyl halides have been used for the reaction.[13] Addition of t-bromo ß-methyl crotonate to cyclohexanones is also reported.[14]

Solvent used for the reaction

Many solvents have been tested and although ether solvents such as diethylether, tetrahydrofuran, 1-4-dioxane or dimethoxymethane are generally preferred, mixture of these with aromatic hydrocarbons or the more polar acetonitrile, dimethylformamide, dimethylsulphoxide or hexamethylphosphoric triamide were found to be approprite in some specific transformation.[2c]

Modification on the Zinc

Activation of zinc metal is the key step. The metal can be activated in two ways.

i) Effectively removing the zinc oxide which is formed by chemical means employing reagents like Iodine,[2b] 1,2dibromoethane,[2b] Copper(I)halide,[15] Mercuric halide,[16] molecular sieves.[17] Even a simple dil. acid washing of the zinc in the form of dust, foil, pellets or turnings[2a] are still used. These methods are used even on large-scale preparation.

ii) Coupling of other metals with Zinc: A Special type of zinc activation was accomplished by the use of coupling other metals like Zinc-Copper couple,[18] Zinc-Silver,[19] amalgamation of Zinc.[2c]

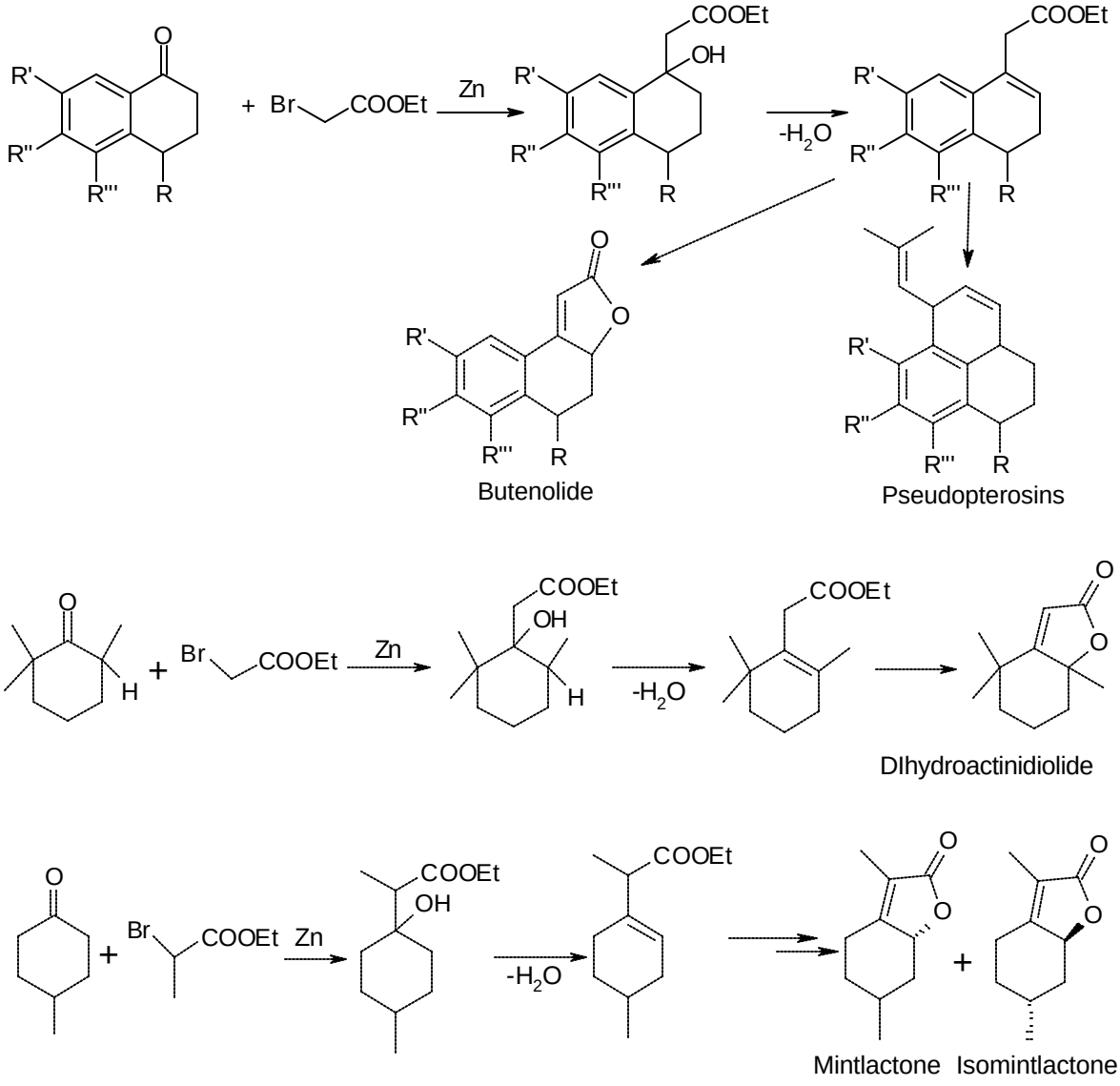
Reduction of Zinc halides ($ZnCl_2$) was a big achievement in the history of zinc activation (Rieke Zinc).[20] $ZnCl_2$ was reduced by potassium and thus allowing the reaction to go under milder conditions. However, shortcoming of Rieke metals is that the reaction of molten potassium THF is liable to go out of control and the change from THF to diethylether recommended to improve the yield complicates handling.[20]

D) Substitution of metals

Substitutions of metals instead of zinc have also been done. Metals like Cadmium,[21] Nickel,[22] Indium,[23] Cerium,[24] Lithium,[25] have found their way out with limited utility.

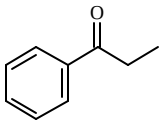
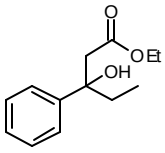
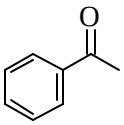
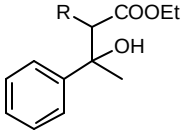
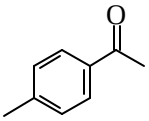
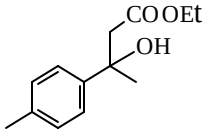
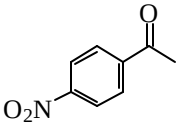
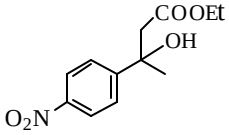
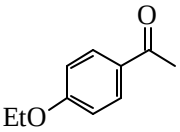
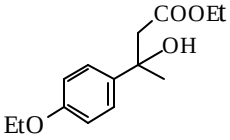
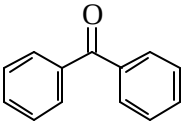
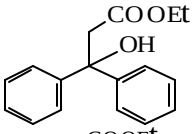
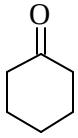
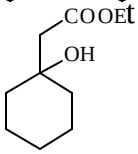
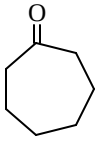
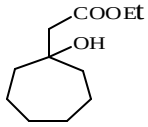
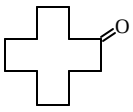
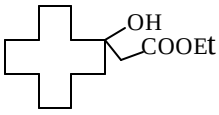
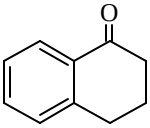
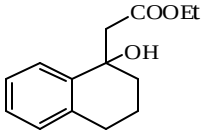
1.1.3 Present work

As mentioned earlier Reformatsky reaction is indeed a very useful reaction in preparing reactive intermediates. Syntheses of many molecules like butenolides, pseudopterosins, mintlactone, isomintlactone *etc*. have been successfully achieved using Reformatsky reaction as the key step to effect C-C bond formation. (Scheme 4)

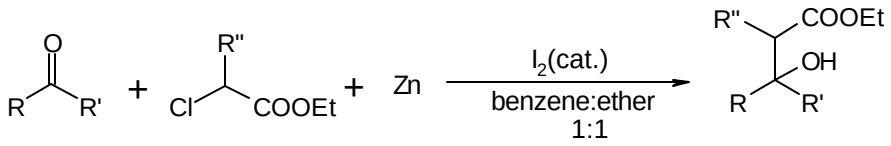


Scheme 4

Table 1 **Yield obtained in reaction using** a **-chloroesters**

SL. No:	Substrate	Product	$ClCH_2RCOOEt$
1			83%
2			R= H 71% R= Me 70%
3			72%
4			73%
5			82%
6			69%
7			66%
8			74%
9			86%
10			75%

Many modifications have been mentioned above. The use of a-chloroesters for C-C bond formation in the Reformatsky reaction of is not all well explored. In this protocol we have explored a simple way of activation of zinc and simpler conditions for the reaction as a whole.(Scheme 5)



Scheme 5

1.1.4 Results and Discussion:

a-Chloroesters are more easier to handle as compared to a-bromoesters. Bromoesters are highly lachrymatory and irritant as compared to their chloro counterpart. The latter is cheaper as compared to the former. In the protocol (Scheme 5) there are two noteworthy aspects: one is ease in the activation of zinc and the other being the reaction condition. Washing the zinc using distilled water followed by 5% dil. hydrochloric acid activates the zinc. Zinc was stirred and the dil. hydrochloric acid was decanted. It was washed with distilled water so as to remove acid traces. Then it was washed with acetone and kept in the oven at 100^{o}C for 8hrs.

Extending our work on the characterization of zinc we found that the reaction doesn't work with all types of zinc. We made a brief survey of the impurities present using XRF (x-ray fluorescence). It revealed that the metal impurities like Al and Fe in ppm level catalyzed the reaction. These impurities were present in the zinc obtained from Loba chemicals where as the reaction failed to go with zinc without the impurity.

Reformatsky reactions are generally carried out in ether solvents like diethyl ether, tetrahydrofuran, dioxane *etc*. In this protocol we have added benzene to ether so that reaction can be performed at a higher temperature. The condition involves the reflux of the reaction mixture. In a typical procedure to a suspension of zinc in benzene ether was added cyclohexanone followed by ethyl chloroacetate in benzene ether (1:1, 5ml). A crystal of iodine was added and the reaction mixture was refluxed for 6 hrs (80^{0}C, oil bath temp). In the cases of use of cyclic ketones especially cyclohexanone greater care

was taken that the reaction mixture is vigorously stirred and the conditions are made absolutely dry.

It was also observed that the Reformatsky reactions could also be performed in benzene alone as a solvent.

It is evident from the table that α-chloroesters participate well in the reaction to furnish the corresponding alcohols in synthetically useful yields. A point worth to note is that even α-substituted chloroesters participate efficiently as compared to α-chloroacetate (entry 1: i.e. α-chloropropionate).

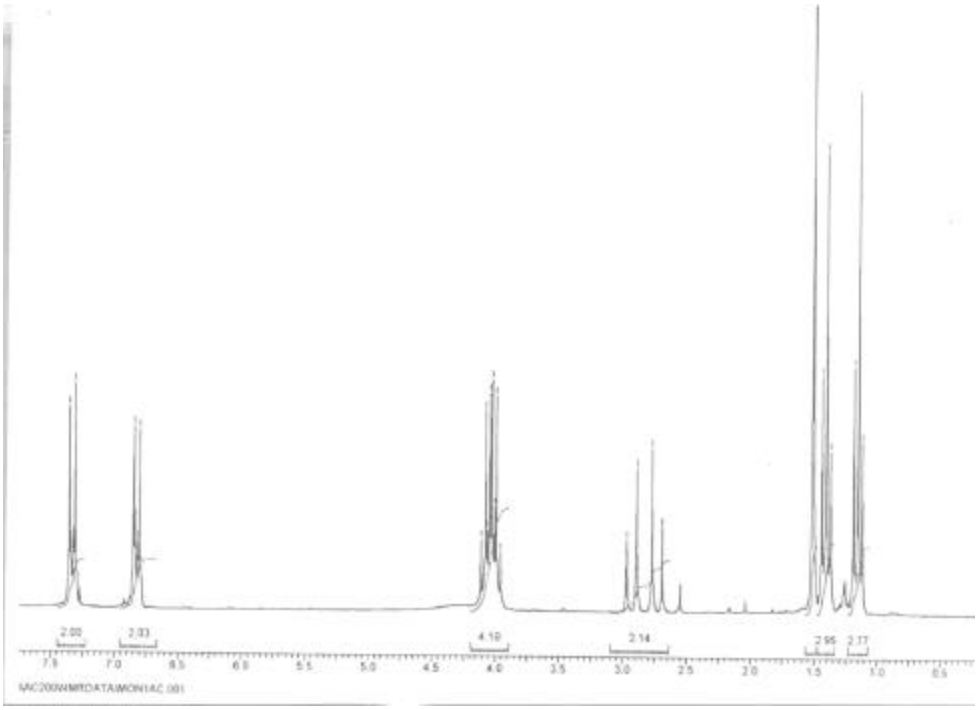
From the table 1 it is evident that Reformatsky reaction can be efficiently performed on a wide range of ketones ranging from cyclic, acyclic and aromatic.

In conclusion, we have demonstrated that relatively unreactive chloroesters can readily participate under Reformatsky conditions. Development of this protocol has established that readily available chloroesters could be readily used in place bromoesters for C-C bond formation.

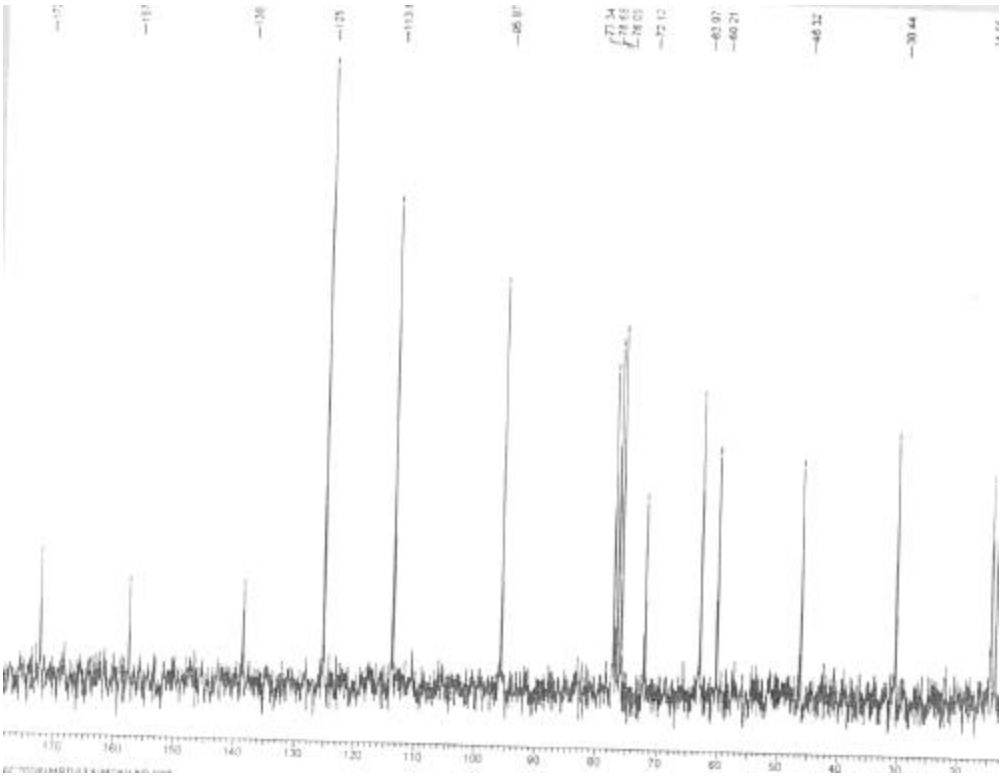
Commercially available zinc without any metal additives has been shown to undergo facile Reformatsky reaction.

1.1.5 Conclusion

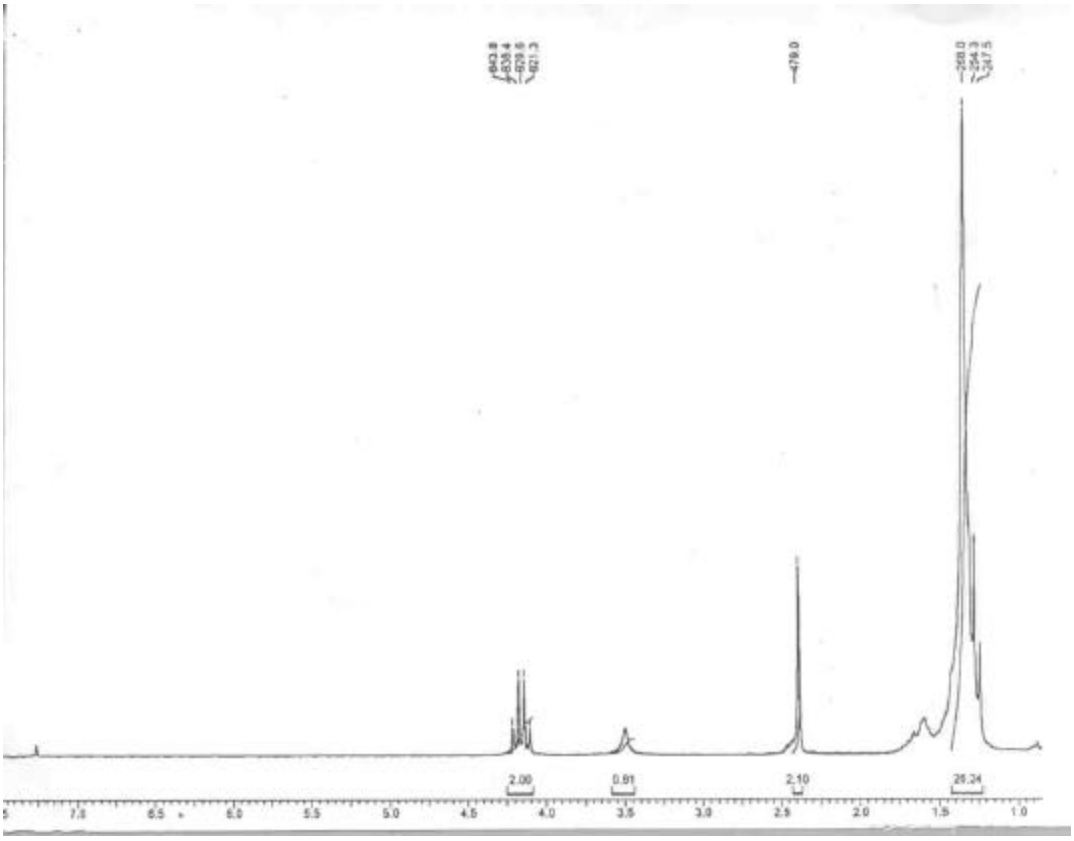
1. The present protocol is comparable with the conventional Reformatsky reaction which involve bromoester s in terms of yield.
2. The use of chloroester makes the protocol more attractive in terms of costing and handling.
3. Activation of zinc doesn't involve any complicated process as compared to the preparation of Reike zinc.
4. The duration of this reaction is almost same as compared to the reaction with bromoesters.
5. Overall this protocol is better than the existing protocol with zinc in terms of handling and costing. This reaction protocol is simple, attractive and is industrially viable as compared to the earlier protocol.



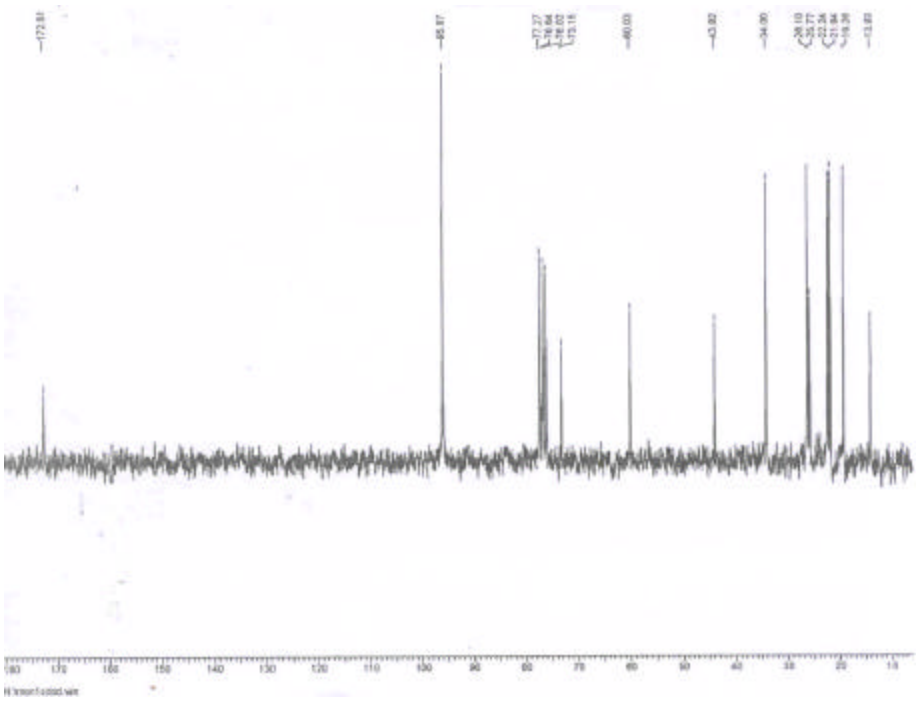
^{1}HNMRof 3-(4-Ethoxy-phenyl)-3-hydroxy-butyric acid ethyl ester(200 MHz, $CDCl_3$)



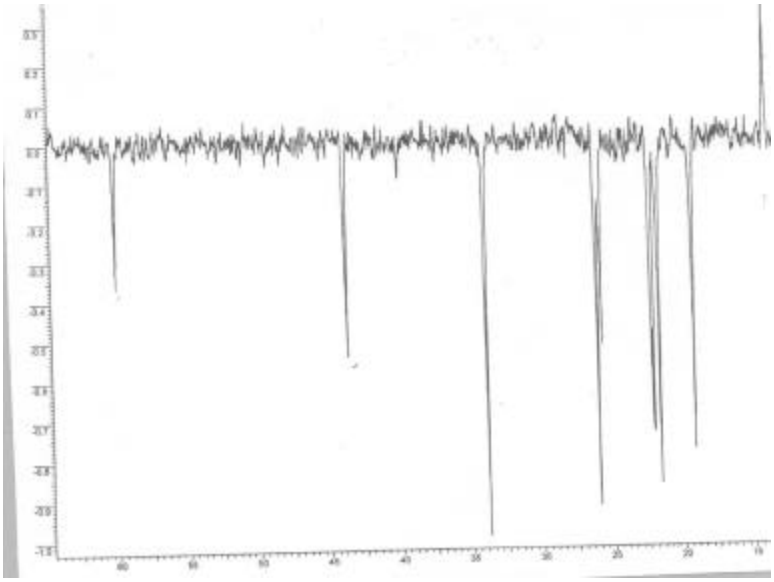
^{13}CNMRof 3-(4-Ethoxy-phenyl)-3-hydroxy-butyric acid ethyl ester(50 MHz, $CDCl_3$)



^{1}HNMR of (1-Hydroxy-cyclododecyl)-acetic acid ethyl ester (200 MHz, $CDCl_3$)



^{13}CNMR of (1-Hydroxy-cyclododecyl)-acetic acid ethyl ester (50 MHz, $CDCl_3$)



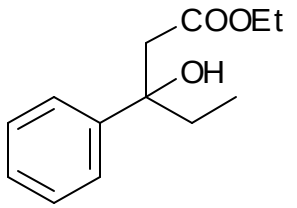
DEPT of (1-Hydroxy-cyclododecyl)-acetic acid ethyl ester (50 MHz, $CDCl_3$)

1.1.6 Experimental

Zinc activation: 50gm of zinc (supplied by Loba, India) was washed with distilled water (2×50ml). After decanting the water layer it was treated with 5% dil. HCl (2×30ml) with vigorous stirring. The acid was decanted and the zinc was treated with distilled water (3×50ml). It was then washed with acetone to remove the traces of water (2×50ml). The Zinc was then dried in an oven for 8hrs at 100^0C.

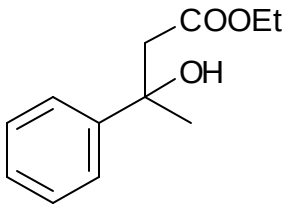
Typical procedure: To a suspension of zinc (1.63g, 25mmol supplied by Loba, India) in benzene ether (1:1, 5ml) was added acetophenone (1g, 8.33mmol) followed by ethyl chloroacetate (1.224 g, 10mmol) in benzene-ether (1:1, 5ml). A crystal of iodine was added and the reaction mixture was refluxed for 6 hrs (80^0C, oil bath temp). After completion (TLC), the reaction mixture was cooled and quenched with 10% HCl (15 ml). The product was extracted with ethyl acetate (2×25ml) and washed with water (3×10ml). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and solvent removed under vacuum. The residue thus obtained was purified by column chromatography (SiO_2) using 5% ethyl acetate-pet ether as the eluent.

1. **3-Hydroxy-3-phenyl-pentanoic acid ethyl ester**[2a]



Yield:	*83%*
Molecular Formula:	$C_{13}H_{18}O_3$
^{1}H NMR:	0.8 (t, 3H, J= 6 Hz), 1.1 (t, 3H, J= 7 Hz), 1.8 (q, 2H, J= 6 Hz), 2.8 (d, 1H, J= 12Hz), 3.0 (d, 1H, J= 12Hz), 4.0 (q, 2H, J = 7Hz), 4.35 (b, 1H), 7.2-7.6 (m, 5H).
^{13}C NMR:	7.46(q), 13.68(q), 35.62(t), 44.77(t), 60.17(t), 74.88(s), 124.87 (d), 126.38(d), 127.68(d), 144.94(s), 172.47(s).

2. **3-Hydroxy-3-phenyl-butyric acid ethyl ester**[2b]

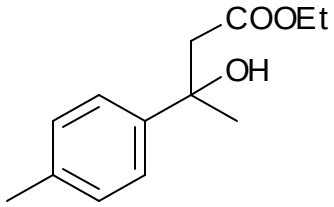


Yield: 71%

Molecular formula: $C_{12}H_{16}O_3$

^{1}H NMR: 1.2 (t, 3H, J= 6Hz), 2.29 (s, 3H), 2.38(d, 1H, J= 14Hz), 2.76(d, 1H, J= 14Hz), 4.02 (q, 2H, J= 6Hz), 4.5 (br, 1H).

3. **3-Hydroxy-3-p-tolyl-butyric acid ethyl ester**[20]

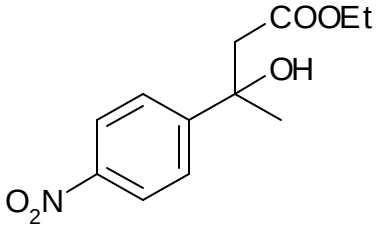


Yield: *72%*

Molecular Formula: $C_{13}H_{18}O_3$

^{1}H NMR: *1.12 (t, 3H, J= 6Hz), 1.5 (s, 3H), 2.29(s, 3H), 2.76(d, 1H, J=12Hz), 2.88(d, 1H, J=12Hz), 4.02(q, 2H, J= 6Hz), 4.1(b, 1H), 7.20(d, 2H, J=8Hz), 7.82(d, 2H, J=8Hz).*

4. **3-Hydroxy-3-(4-nitrophenyl)-butyric acid ethyl ester**[2c]



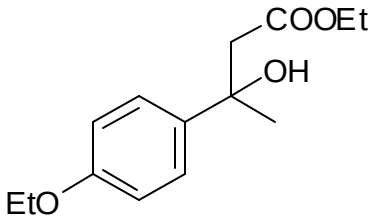
Yield: 73%

Molecular formula: *$C_{12}H_{15}NO_5$*

IR (Neat) cm^{-1}: 3108, 2924, 2344, 1718, 1458, 1430.

^{1}H NMR: 1.3 (t, 3H, J= 6Hz), 2.46 (s, 3H), 2.65 (d, 1H, J= 14Hz), 2.8 (d, 1H, J= 14Hz), 4.19 (q, 2H, J= 6Hz), 8.1 (d, 2H, J= 8Hz), 8.3 (d, 2H, J= 8Hz).

5. **3-(4-Ethoxy-phenyl)- 3-hydroxy-butyric acid ethyl ester**



Yield: 82%

Molecular formula: $C_{14}H_{20}O_4$

IR (Neat) cm^{-1}: 3390, 2978, 1712, 1604, 1514 and 1478.

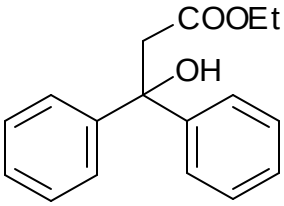
^{1}H NMR: 7.33 (d, 2H, J = 8Hz), 6.82 (d, 2H, J = 8Hz), 4.26 (b, 1H), 4.03 (m, 4H), 2.98 (d, 1H, J=16Hz), 2.75 (d, 1H, J=16Hz), 1.51 (s, 3H), 1.41(t, 3H, J=6Hz) and 1.15(t, 3H, J=7Hz).

^{13}C NMR: 172.3(s), 157.5(s), 138.7(s), 125.3(d), 113.8(d), 72.1(s), 63.0(t), 60.2(t), 46.3(t), 30.4(q), 14.6(q), and 13.8(q).

Mass (m/e): 252(m+), 234, 206, 189, 165, 149 and 134.

Elemental analysis C 66.8, H 8.3 (calculated C 66.7, H 8.0)

6. **3-Hydroxy-3, 3-diphenyl-proponic acid ethyl ester**[2a]

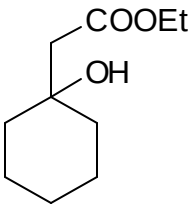


Yield: *69%*

Molecular formula: $C_{17}H_{18}O_3$

^{1}H NMR: 1.2 (t, 3H, J=6Hz), 3.32(s, 2H), 4.13(q, 2H, J=6Hz), 5.2(br, 1H), 7.2-7.8(m, 10H).

7. **(1-Hydroxy-cyclohexyl)-acetic acid ethyl ester**[2a]

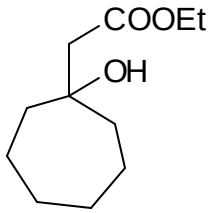


Yield: 66%

Molecular formula: $C_{10}H_{18}O_3$

^{1}H NMR: 1.2 (t, 3H, J = 7Hz), 1.3-1.8 (m, 10H), 2.4 (s, 2H), 3.8(br, 1H), 4.1 (q, 2H, J= 7Hz)

8. **(1-Hydroxy-cycloheptyl)-acetic acid ethyl ester**[2a]



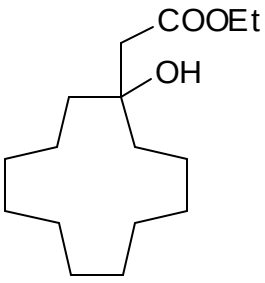
Yield: 74%

Molecular formula: $C_{11}H_{20}O_3$

IR ($CHCl_3$, cm^{-1}): 3523, 2925, 1716, 1201.

^{1}H NMR: 1.25(t, 3H, J=6Hz), 1.3-1.95(m, 12H), 2.47(s, 2H), 3.3 (br, 1H), 4.15(q, 2H, J=6Hz)

9. **(1-Hydroxy-cyclododecyl)-acetic acid ethyl ester**

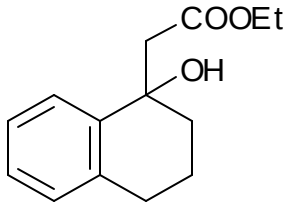


Yield: *86%*

Molecular formula: $C_{16}H_{30}O_3$

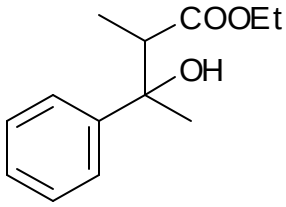
IR ($CHCl_3$) cm^{-1}:	3510, 2932, 2862, 1710, 1470, 1446, 1398, and 1370.
^1H NMR:	4.15(q, 2H, J=7Hz), 3.5(b, 1H), 2.4(s, 2H) and 1.2-1.65(m, 25H).
^{13}C NMR:	172.5(s), 73.2(s), 60.0(t), 43.8(t), 34.0 (t), 26.1(t), 25.2(t), 22.2(t), 21.8(t), 19.3(t) and 13.9 (q).
Mass (m/e):	*270(m+), 252, 241, 225, 207, 182, 143 and 130.*
Elemental analysis:	C 71.2, H 11.1 (calculated C 71.0, H 11.2)

10. **(1-Hydroxy-1, 2, 3, 4-tetrahydronapthalen-1-yl) acetic acid ethyl ester**[8]



Yield:	75%
Molecular formula:	$C_{14}H_{18}O_3$
^1H NMR:	1.29 (t, 3H, J= 7Hz), 1.75-2.2 (m, 4H), 2.69-2.91(m, 4H), 4.0(brs, 1H), 4.18 (q, 2H, J=7Hz), 7.04-7.5 (m, 4H).

11. **3-Hydroxy-2-methyl-3-phenyl-butanoic acid ethyl ester**[11]



Yield:	70%
Molecular formula:	$C_{13}H_{18}O_3$
^1H NMR:	1.1(d, 2H, J=6Hz), 1.29 (t, 3H, J= 8Hz), 1.65 (s, 3H), 3.5(m, 1H), 4.18 (q, 2H, J=7Hz), 5.6(brs, 1H), 7.04-7.5 (m, 5H).

1.1.7 References

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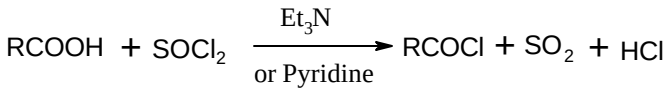
SECTION B

Dehydration mechanism: A theoretical insight

1.2.1 Introduction

Oxy-halogen compounds of sulphur like chlorosulphonic acid, sulphuryl chloride and thionyl chloride have a vast application in both laboratory as well as in industry. Out of these thionyl chloride is the one that is extensively used. Thionyl chloride is generally used for the conversion of acid to acid-chloride.[1] It is often used in presence of a base like triethylamine or pyridine.[2] Thionyl chloride also displaces hydroxyl group from tropolones and in DMF solution from highly acidic phenols.[3]

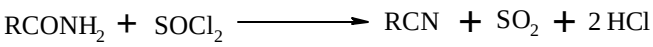


Scheme 1

Allyl or alkyl sulphonyl chlorides are prepared by heating the acid with thionyl chloride. Dimethyl formamide catalyzes the reaction. This reaction is used to generate (+)Camphorsulphonyl chloride from camphor.[4]

Thionyl chloride dehydrates primary amides to form nitriles. The best example is in generating 2-ethylhexanonitrile. Benzonitriles have been generated from benzamide.[5]

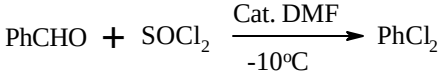
Scheme 2 (Goldstein *et. al*. *Helv. Chim. Acta* **1943**, *26*, 1125)



Scheme 2

Aromatic aldehydes are converted to gem-dichlorides by treatment with $SOCl_2$; with neat or in inert solvent such as nitromethane. This process is catalyzed either by HMPA or DMF.[6]

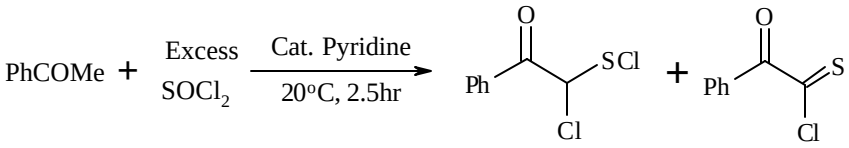
Scheme 3 (Davis *et. al. Asian. J. Chem.* **1977**, *30*, 433)



Scheme 3

$SOCl_2$ can oxidize methyl groups attached to benzonoid without addition of catalyst. The product may be monochlorinated or further oxidized to the trichloromethyl aromatic system.[7] Extensive oxidation adjacent to carbonyl groups is possible with $SOCl_2$ under relatively mild conditions.[8] The process often stops after formation of the α-chlorosulfenyl chloride. Thionyl chloride acts as the dehydrating agent in Beckmann,[9] Lossen rearrangement[10] and promotes Pummerer reaarangement.[11]

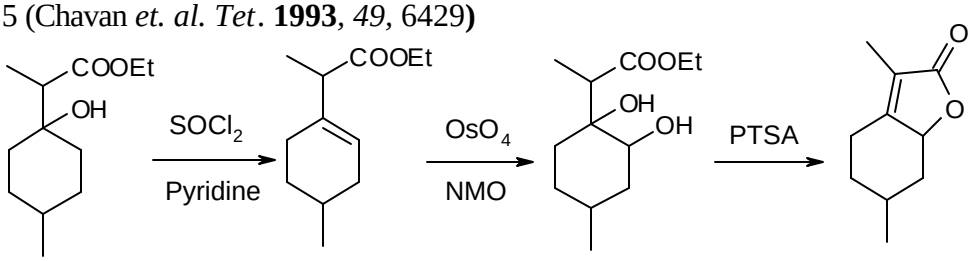
Scheme 4 (Donaruma. *et. al. Org. React*. **1960**, *11*, 1)



Scheme 4

The reagent also converts amides to chloroamines[12] and nitroalcohols to nitrochlorides.[13] The use of thionyl chloride and pyridine for elimination of alcohols is also known in the synthesis of mintlactone. This was used to eliminate alcohol to give ß,?-unsaturated ester.[14]

Scheme 5 (Chavan *et. al. Tet*. **1993**, *49*, 6429**)**

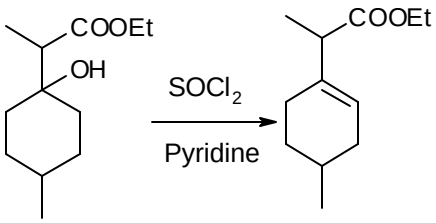


Scheme 5

1.2.2 Definition of the Problem

Curiosity to know the mechanism of elimination of tertiary alcohols, using thionyl chloride and pyridine, of cyclic compound arose from the observed experimental results. In our attempts towards the total synthesis of a natural product mintlactone, elimination of alcohol gave exclusively endocyclic double bond as compared to the exocyclic double bond, which is conjugated and was expected to be the more stable form.[14] (Scheme 6)

Scheme 6(Chavan *et. al. Tet.* **1993,** *49*, 6429*)*



Scheme 6

This was the general trend that was observed in the synthesis of butenolide. Thus, β-hydroxyester gave β, γ unsaturated ester when treated with thionyl chloride and pyridine. These β, γ unsaturated esters were subsequently converted to butenolide.[15] (Scheme 7)

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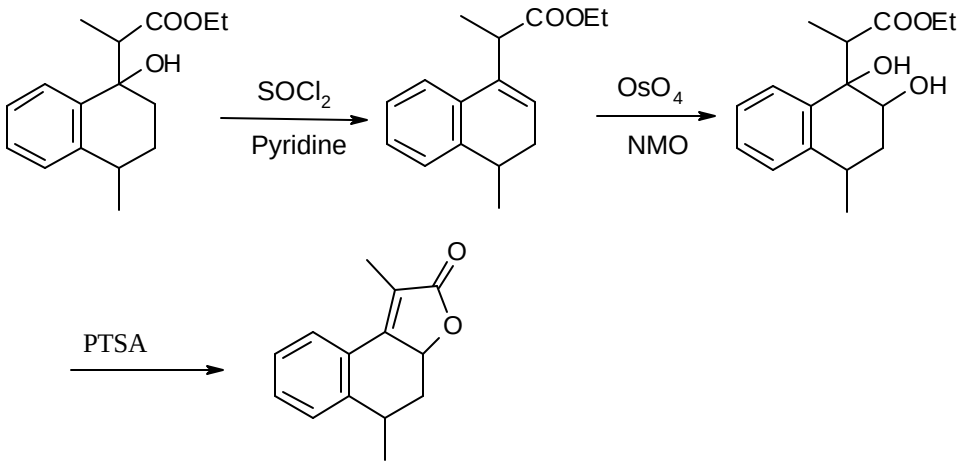
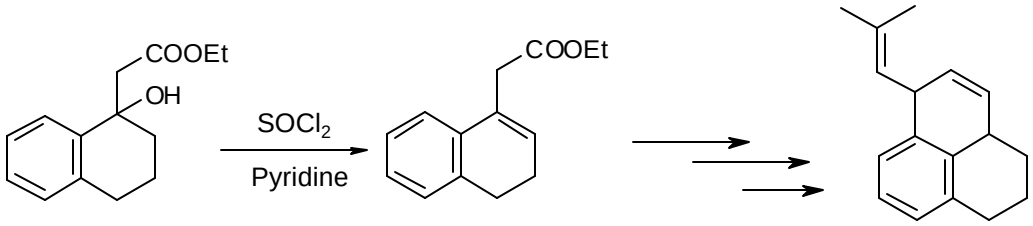
Scheme 7 (Chavan *et. al*. *Tet. Lett* **1992**, *33*, 4605)



Scheme 7

During the synthesis of Pseudepterosins also it was observed that the elimination gave only the β, γ unsaturated ester showing that there was no change in the observation with the difference in the substitution at α-position with respect to the ester, and also that the substitution at the para-position had any effect on the selectivity.[16] (Scheme 8).

Scheme 8 (Thesis of Chitra Govande, University of Pune, **1998**, pp 90-110)

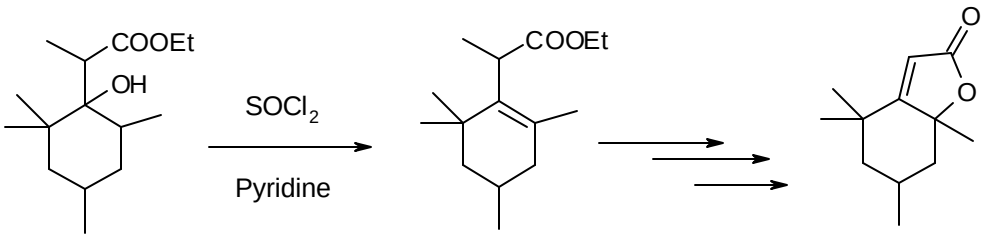


Scheme 8

With tetralones showing such an effect, it was thought to try out simpler systems like substituted cyclohexanes. In our synthesis of dihydroactininolide also it was observed

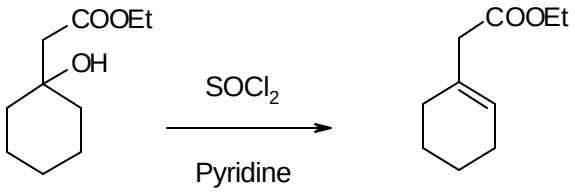
that there was exclusive formation of β, γ unsaturated ester. Exclusive formation of β, γ unsaturated ester exclusively supported this unusual effect.[16] (Scheme 9)

Scheme 9 (Thesis of Chitra Govande, University of Pune, **1998**, pp 90-110)



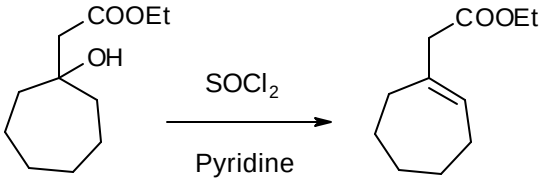
Scheme 9

It was later thought to simplify the system still and then check this effect. So we did the reaction was performed on simpler cyclohexane systems. But here also the effect was seen and it exclusive β, γ unsaturated ester formation was observed. (Scheme 10)



Scheme 10

It was then decided to go further and do some more experimental studies and to take help of theoretical calculation to understand this unusual happening. In order to ascertain that this was not confined to six membered ring, reaction was performed on a seven membered ring where the same trend of formation of β, γ unsaturated ester was observed. (Scheme 11)



Scheme 11

Having witnessed seemingly counterintuitive selectivity in the dehydration of cyclic alcohols possessing a β-ester functionality considered in the study, it was decided

to seek the assistance of computational chemistry approaches to shed light on the above observation. A cursory description of the popular computational techniques available for modeling is given below.

1.2.3 Molecular Mechanics

Molecular mechanics, which is based on the Newtonian equations of motion, is a quite useful and computationally attractive methodology in treating systems of large size. This method does not consider the electrons explicitly and the energy is given only as a function of the nuclear positions. Energies are associated with the extent of deviation in the geometric parameters such as the bond lengths, bond angles and the dihedral angles from the reference or the equilibrium values obtained in model compounds.

$$V_{tot} = V_{str} + V_{bend} + V_{tors} + V_{colombic} + V_{vdW} + V_{cross}$$

V_{str} is the stretching potential; V_{bend} is the bending potential; V_{tors} is the potential with respect to bond rotation; $V_{colombic}$ is the columbic attractive and repulsive potential; V_{vdW} is the van der Waals term and V_{cross} consists of cross terms involving the first three bonded terms. Many force fields are available depending on the functional form of the potential terms, the number of cross terms included and the type of information used for fitting the parameters. This method can provide results comparable to high-level quantum mechanical calculations provided the empirical parameters are accurate and it has proved to be a very reliable approach for hydrocarbons and devoid of three- and four-membered rings.

1.2.4 *Ab Initio* Method

The term *ab initio* implies a rigorous, nonparametrized molecular orbital treatment. This is a totally non-empirical approach and based on Hartree-Fock Self Consistent Field Theory. After taking an appropriate basis function, all the electron repulsion integrals are rigorously calculated and importantly it is possible to systematically improve the results of ab initio calculations by increasing the basis set as well as going to post-SCF techniques, such as MBPT (MP2, MP3), CI (CIS, CID, CISD), CCA (CCSD, CCSDT, CCSD(T)), CASSCF, MRCI and MCSCF. But these calculations are very expensive in terms of computational time and are not practical for larger systems. The optimal choice of method to be used in any research project will depend on

the computer time available, the extent of calculations required and the nature of the problem.

1.2.5 Semiempirical Methods

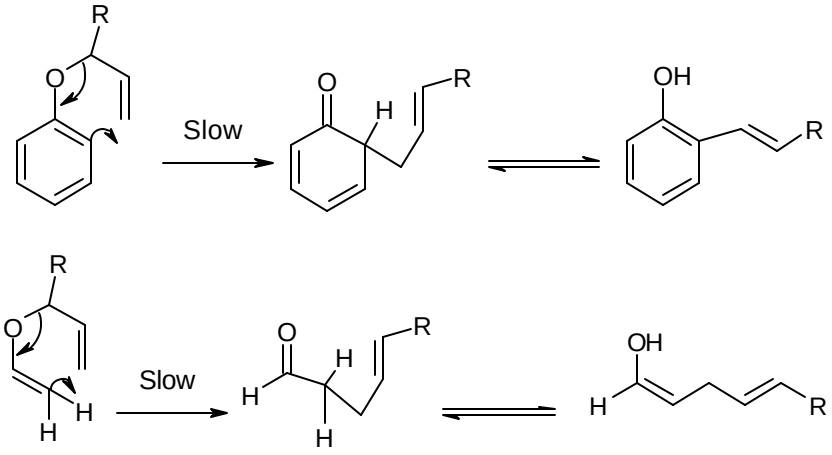
Ab initio calculations are themselves not always applicable, as they require the fourth power of the number as basis function in the molecule. A great deal of effort has been put in devising so called semi-empirical molecular orbital methods; with determinantal equations but employs a range of approximations to reduce the amount of computer requirement. Some of the major approximations done in the semiempirical methodology are, consideration of only the valence electrons, use of a minimal basis set, neglect of repulsive integrals, use of empirical or computed parameters.

Recently, the density functional theory has become an attractive alternative to model problems of chemical interest. In the Kohn-Sham implementation, DFT models the exact density via a set of non-interacting electrons described by auxiliary one-electron wave functions such as they are used in the Self Consistent Field theory. The exchange and correlation effects are expressed as functionals of that density. This makes that the DFT calculations are very similar to the *ab initio* HF-SCF calculations, but it should be kept in mind that in the DFT formalism it is the density which is optimized variationally and not the wave function. The present study uses calculations based on the density functional theory, using the gradient corrected exchange functional of Becke, combined with the correlation functional given by Lee, Yang and Parr (LYP). The exact functional used here is the famous Becke's three-parameter (B3) exchange functional which is a hybrid method and contains about one-third of Hartree-Fock exchange.

We take a brief look at some of the reactions explored through computational techniques.

One of the most widely studied rearrangement reactions is the Claisen rearrangement of allyl vinyl ether.[18] Davidson *et al* have described the use of theoretical methods for exploring the rearrangement reaction.[17] Calculations were done at various levels including the *ab initio* and density functional methodologies. The effect of aqueous media on the reaction also has been studied in this communication. *Ab initio* level calculation has been done on the reactant, the transition states and the product involved in the Claisen rearrangement.

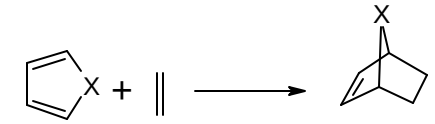
Scheme 12 (Davidson et.al. *Chem. Phy. Lett.* **1995**, *246*, 536)



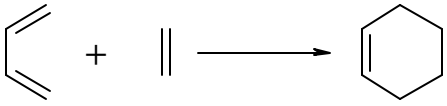
Scheme 12

Diels-Alder reaction, the father of (4+2) cycloadditions, has also been studied extensively.[19-20] Standard examples of Diels-Alder reaction with five membered dienes include furan, thiophene, maleic anhydride *etc*. have been studied by theoretical methodologies.[21] There has been a lot of publications highlighting the transitions states of various Diels-Alder reactions.[22, 21b] In a recent paper,[23] *ab initio* calculations were done on a wide variety of substrates, mainly five membered cyclic dienes and with ethylene as a dienophiles (Scheme 13). *Ab initio* and DFT calculations were done on those substrates. Comparisons of the results obtained show that results obtained from CCSD(T) level with 6-31G* basis set gave results almost matching with what was obtained from experiments.

Scheme 13 (Dinadayalane *et. al. J. Phys. Chem. A* **2002**, *106*, 1627-1633)



X= CH_2, O, NH, PH, S

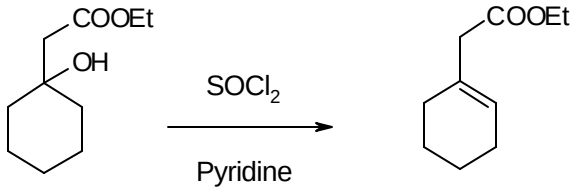


Scheme 13

1.2.6 Results and discussions

The elimination of substituted cyclohexanol using thionyl chloride and pyridine gave selectively endo-cyclic double bonded product. However, the exocyclic product is

expected to be more stable due to the conjugative stabilization. Now we plan to scrutinize the problem so as to discern the effect of various factors on the reaction under study.



Scheme 14

The problem appears to be two fold. The first is to identify various factors that control the regioselectivity of dehydration reactions. This involves selecting the model structures and reactions, which will mimic the original situation, in one or more ways, and provide insight. The second one is to choose a theoretical method, which would provide reasonable quantitative accuracy. Unfortunately, sizes of the systems are not small enough to apply state of the art *ab initio* methods. So careful selection of methods is essential to understand. The two forms of the reactants, (a) with axial –OH and (b) with equatorial –OH, were optimized at the semiempirical AM1 method and the natures of the stationary points were characterized by frequency calculations. The geometries were further refined at HF/3-21G level. Single point energies were evaluated on AM1 and HF/3-21G geometries with HF and B3LYP levels using 6-31G* basis set. The qualitative trends obtained at all the levels of theory are essentially the same and therefore further calculations are restricted to AM1 optimization followed by single point calculations at the HF/6-31G* level. This strategy seem to be economical and reliable under the facilities available.

Firstly two model set of compounds were considered to evaluate the magnitude of stability due to the conjugation of the double bond with the carbonyl group. Next, the relative stabilities of the exocyclic and the endocyclic rings are explored. For testing the conjugation effect we considered a 4-carbon straight chain in which we have a carbonyl at one end with different substitutions attached to the carbonyl like H, CH_3, OH, OMe, and OEt was considered (Figure 1). Geometry optimization was done using AM1 method and single point calculation was done at HF/6-31G*. The systems here are small enough and hence we could do the B3LYP/6-31G* calculations also. The results are tabulated in the form of a Table 1.

Figure 1

3 **4**

a H

b CH_3

c OH

d OMe

e OEt

Table 1: Energetics of compounds given in Figure 1 at AM1 and HF/6-31G* levels. Relative energies are given in kcal mol^{-1} and total energies in hartrees.

Structure	AM1	HF/6-31G*[a]	B3LYP/6-31G*[a]
3a	0.0 (-0.04306)	0.0 (-229.79413)	0.0 (-231.22966)
4a	3.12	6.75	8.73
3b	0.0 (-0.05522)	0.0 (-268.83834)	0.0 (-270.55361)
4b	3.84	6.24	8.78
3c	0.0 (-0.13926)	0.0 (-304.68454)	0.0 (-306.47754)
4c	3.24	6.51	8.01
3d	0.0 (-0.12859)	0.0 (-343.70799)	0.0 (-345.78384)
4d	3.10	6.20	7.83
3e	0.0 (0.13781)	0.0 (-382.74662)	0.0 (-385.10228)
4e	3.00	6.74	8.06

a) Single point calculations on AM1 geometries.

Table 1 shows that in acyclic system the conjugated ones are more stable than the unconjugated ones at all levels of theory. The stability of the conjugated species is expected to be more stable than the unconjugated counterpart by around 6-8 kcal/mol. This indicates that the reaction is not controlled by the stability due to the conjugation effect.

Let us consider another factor *i.e.* the position of the double bond in the cyclic systems *viz* the endocyclic and exocyclic. The choice of the substrate for the calculation should be so that we consider this effect alone. So we considered 1-methylcyclohexene and methylene cyclohexane so that we can estimate the effect due to the position of the double bond. Two possible forms that will give an estimate of the effect of the position of the double bond were considered (Figure 2). Optimization of both the structures was done at the semiempirical and HF/6-31G* levels of theory. The results of the calculations obtained are tabulated in the table below (Table 2). The computations show that, endocyclic double bonded species is more stable than the exocyclic double bonded one by about 3 kcal/mol.

Figure 2

5 **6**

Table 2: Model systems used to assess the stability of exo- versus endo- double bonds. The energetics are given at AM1 and HF/6-31G* levels.

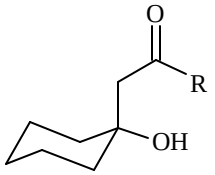
Method	**5**	**6**
AM1	0.0 (- 0.0236)	- 3.1
HF/6-31G*	0.0 (-271.94621)	- 2.6

The results from Tables 1 and 2 indicate that the stabilization due to conjugation and the preference for endocyclic double bond over the exocyclic double bond seem to be mutually opposite. One of the two probable products of the dehydration of ß-hydroxy ester reaction has conjugation and exocyclic double bond, and the other is not conjugated and has endocyclic double bond. In effect it does not seem to be straightforward to predict the relative stabilities of the twin products, as the conjugative abilities and *endo* vs. *exo* cyclic double bond preferences are in conflict, *i.e.*, the conjugative stabilization prefers **3**, while the **6** is preferred as it has endocyclic double bond.

The hydroxyl group present in the six membered ring in the reactant can either be in the axial or in the equatorial position (Figure 3). The reactant in both the forms can have many conformations. Conformational search is performed at the semiempirical AM1 level and the most stable conformer in both the cases was taken for further analysis. Comparing the stabilities of the axial and equatorial forms of the reactants at different levels of theory, it was concluded that the hydroxyl at axial position is more stable than hydroxyl at the axial (Table 3).

The results obtained are tabulated in Table 3. In all the cases, the hydroxyl at the axial position is stable than its equatorial counterpart. The reason ascertained to this is the size of the functional groups compared to the hydroxyl group. The hydroxyl group being smaller in size prefers to occupy the axial position as compared to the other groups. In case of aldehyde, which is a relatively smaller group, the difference between the axial and the equatorial forms is very less -0.34 kcal/mol, whereas in the case of ethyl ester, which is a bulkier group compared to the other groups, it is as high as -10.84 kcal/mol.

Figure 3



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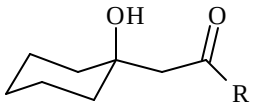

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Table 3: Energetics of compounds given in Figure 3 at AM1 and HF/6-31G* levels. Relative energies are given in kcal mol^{-1} and total energies in hartrees

Structure	AM1	HF/6-31G*[a]	B3LYP/6-31g*[a]
9a	0.00	0.00	0.00
	(-0.18251)	(-460.79972)	(-463.71046)
10a	0.92	-0.11	-0.34
9b	0.00	0.00	0.00
	(-0.19235)	(-499.84270)	(-503.03678)
10b	0.00	-1.78	-0.98
9c	0.00	0.00	0.00
	(-0.27813)	(-535.68990)	(-538.96160)
10c	0.36	-1.87	-1.21
9d	0.00	0.00	0.00
	(-0.26423)	(-574.70474)	(-578.27442)
10d	-3.98	-11.31	-9.02
9e	0.00	0.00	0.00
	(-0.27362)	(-613.74036)	(-617.59312)
10e	-3.94	-13.25	-10.84

a) Single points on AM1 optimized geometries.

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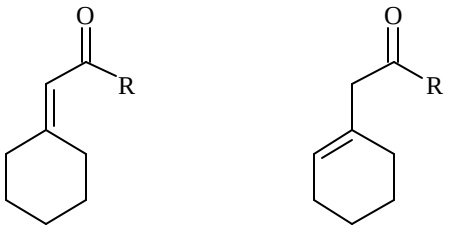
Computations were also done on the two possible products, since the model set of compounds **3**, **4**, **5** and **6** could not provide the qualitative trend of their relative stabilities. (Figure 4). The things that are to be noted is that there are now two effects operating in the products, *i.e.* the endocyclic and the exocyclic compounds. The effects are mainly the effect due to the conjugation and the position of the double bond. Calculations are done on the two possible products at AM1, HF/3-21G, HF/6-31G* and B3LYP/6-31G* levels of theory. The results obtained are tabulated in the form of a Table 4.

Figure 4



7 **8**

Table 4: Energetics of compounds given in Figure 4 at AM1 and HF/6-31G* levels. Relative energies are given in kcal mol^{-1} and total energies in hartrees

Structure	AM1	Hf/3-21G	Hf/6-31G*[a]	B3LYP/6-31g*[b]
7a	0.0	0.0	0.0	0.0
	(-0.07532)	(-382.64279)	(-384.76786)	(-387.28422)
8a	-0.5	5.7	2.5	3.7
7b	0.0	0.0	0.0	0.0
	(-0.08709)	(-421.47351)	(-423.81109)	(-426.60840)
8b	0.3	5.0	2.0	---
7c	0.0	0.0	0.0	0.0
	(-0.17201)	(-457.12159	(-459.65849)	(-462.53390)
8c	(-0.2)	4.7	3.1	---
7d	0.0	0.0	0.0	0.0
	(-0.16117)	(-465.93438)	(-498.68160)	(-501.84028)
8d	-0.4	4.5	2.7	3.1
7e	0.0	0.0	0.0	0.0
	(-0.17033)	(-534.75852)	(537.72014)	(-541.15901)
8e	-0.5	4.5	2.6	3.1

a) Single points on AM1 optimized geometries.

b) Single points on HF/3-21G optimized geometries.

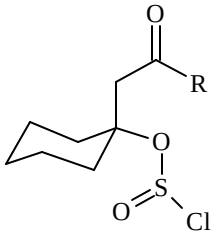
A brief look into the table tells that exocyclic compounds are stable as compared to endocyclic ones. In the case of methyl ester and the ethyl ester the exocyclic

conjugated compounds are stable than the endocyclic unconjugated ones by a difference of 3.1 kcal/mol.

Taking a brief look into results obtained it is observed that the product, which is stable, is the exocyclic compound. One thing that can be concluded is that conjugation and the position of the double bond counter each other. The position of the alcohol in the axial position is stable than the one at the equatorial position, but the difference is not much. That means that the alcohol will always coexists in both the forms having hydroxyl at equatorial and axial position. The above results clearly indicate that the reaction is not controlled by product stability. If it were a thermodynamic controlled reaction, conjugated *exo*-double bonded product is the one, which is expected. So, this reaction is a kinetically controlled reaction. Since the product stabilities don't tell any reasons for their exclusive formation it was decided to look into the reaction pathway. The reaction is a multi step reaction, so a through literature search was done to find out the possible reaction pathway.

From the literature reported on the reaction of thionyl chloride with alcohols it has been observed thionyl chloride attacks on the hydroxyl to give the sulphonyl chloride compounds.[24] However to our knowledge, computational modeling of the transition states or the intermediates of dehydration reactions using thionyl chloride have not been reported in the literature.

Figure 5



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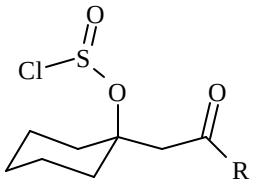


12

For modeling the intermediates, we substituted both the axial and the equatorial hydroxyl groups with sulphonyl chloride group. The intermediates obtained were optimized with

AM1 and single point calculations were done using HF/6-31G*. The results obtained are tabulated in the form of a table.

Table 5: Energetics of compounds given in Scheme 6 at AM1 and HF/6-31G* levels. Relative energies are given in kcal mol^{-1} and total energies in hartrees

Structure	AM1	HF/6-31G*[a]	B3LYP/6-31g*[a]
11a	0.0 (-0.12918)	0.0 (-1391.97052)	0.0 (1396.65593)
12a	-0.06	1.01	1.72
11b	0.0 (-0.14335)	0.0 (-1431.01589)	0.0 (-1435.97914)
12b	1.89	1.78	-0.04
11c	0.0 (-0.22546)	0.0 (-1466.86018)	0.0 (-1471.90530)
12c	-0.25	-0.10	0.19
11d	0.0 (-0.21530)	0.0 (-1505.88469)	0.0 (-1511.21215)
12d	-0.27	0.33	0.45
11e	0.0 (-0.22557)	0.0 (-1544.92310)	0.0 (-1550.53170)
12e	-0.02	0.85	1.88

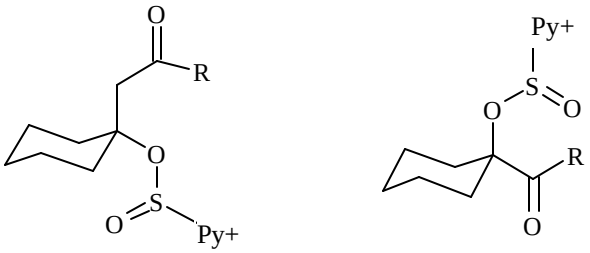
a) Single points on AM1 optimized geometries.

The differences that were there in the positioning of the hydroxyl group almost disappeared. The sulphonyl chloride substitution in the axial and equatorial position did not give any information regarding the pathway that would be taken for the reaction.

The reaction of thionyl chloride in presence of pyridine gives one more intermediate as reported in the literature. The reaction of sulphonyl chloride with pyridine gave the pyridinium complex (Figure 6). [24] So it was thought worthwhile to model this intermediate also. So the complexes were considered at both the equatorial and axial

positions. AM1 optimized geometry was used and calculation of single point were done using HF/6-31G*. The results obtained are tabulated in the form of a table. Attempts were made to model the anionic intermediates, which would lead to two different products. However these results did not provide conclusive evidence for the preference of the unconjugated product. Attempts were made to model the reaction intermediates and the transition states involved in the reaction but to no avail. However, modeling the transition state structures, which would provide the insight to the reaction barrier are very demanding computationally and outside the purview of the available infrastructural facilities. It is desirable to undertake such studies for further understanding of the problem as and when they become viable.

Figure 6



13 **14**

Table 6: Energetics of compounds given in Figure 6 at AM1 and HF/6-31G* levels. Relative energies are given in kcal mol^{-1} and total energies in hartrees.

Structure	AM1	HF/6-31G*[a]
13a	0.0 (0.2238266)	0.0 (-1178.9676072)
14a	5.9	5.8
13b	3.3	4.1
14b	0.0 (0.2020539)	0.0 (-1218.0214165)
13c	0.1	0.4
14c	0.0 (0.1262718)	0.0 (-1253.8536017)
13d	0.0 (0.331937)	0.0 (-1292.8736529)
14d	4.3	2.4
13e	0.0 (0.1102501)	0.0 (-1331.9186016)
14e	7.8	3.1

1.2.7 Conclusion

Computations at various levels of theory were performed to explore the endo/exo-selectivity of the dehydration in tertiary alcohols containing ? -ester functionality. Model calculations to discern the various factors operating in the selective preference for the unconjugated ester indicate that endocyclic is preferred over exocyclic double bonds. However, the conjugative effect seems to overweigh the *endo*- vs. *exo*-cyclic effect as indicated in the relative stabilities of the products. If the reaction were to depend on product stability, conjugated ester is the one, which would have been preferred over the unconjugated ester. Since the major product formed is the unconjugated ester, this reaction is appears to be a kinetically controlled one.

1.2.8 References

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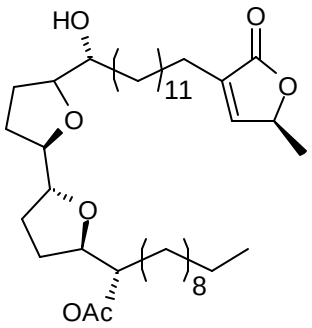
24. Patai, S. "*Chemistry of the hydroxyl group*", pp 593-639, **1969**.

SECTION C
Synthesis of 4-aryl-2(5H)-furanone

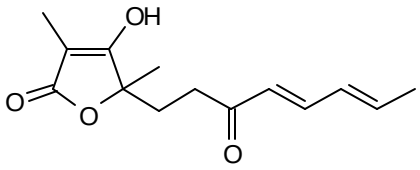
1.3.1 Introduction

The term butenolides for five membered unsaturated lactones was first employed by Klobb[1] in 1898. The term includes both a, ß- and ß, ?-unsaturated butyrolactones of which the former one is encountered more in nature, probably because of its greater stability. Butenolide moiety is present in a number of structurally diverse and biologically active natural products. Some of the products include Uvarricin 1,[2] Vertinolide 2,[3] Mintlactone 3,[5] Heritiol 4,[6] Andriolactone 3.[7]



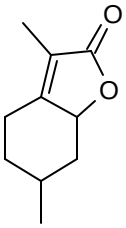
1

Uvarricin



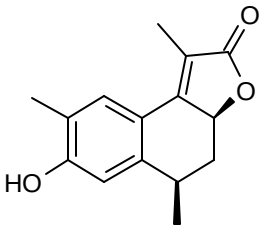
2

Vertinolide



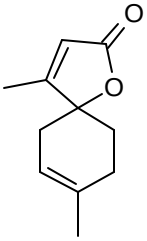
3

Mintlactone



4

Heritiol



5

Andriolactone

Figure 1

?-Butyrolactone and ? ^{2}-butenolides (furan-2-(*5H*)ones) are versatile synthetic modules in organic synthesis. They serve as best substrates to carry out conjugate additions and Diels-Alder reactions.[8]

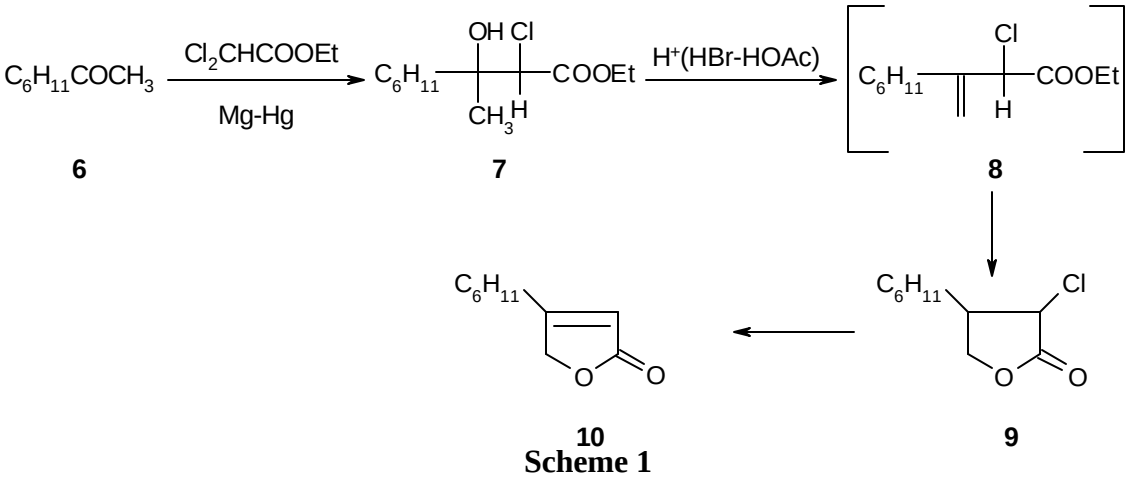
Taking into the utility of this reactive intermediate we now take a look at the different approaches available for the synthesis of butenolide.

1.3.2 Methods of preparation of ? ^{a,ß} butenolide

Variation of Darzen's method[4]

A variation of the Darzen's glycidic ester synthesis lead to the formation of a ? ^{a,ß} butenolide. ß-cyclohexyl-? ^{a,ß}-butenolide was prepared by this method.

Scheme 1 Blout, E. R. *et. al. J. Org. Chem*. **1943**, *8*, 29.

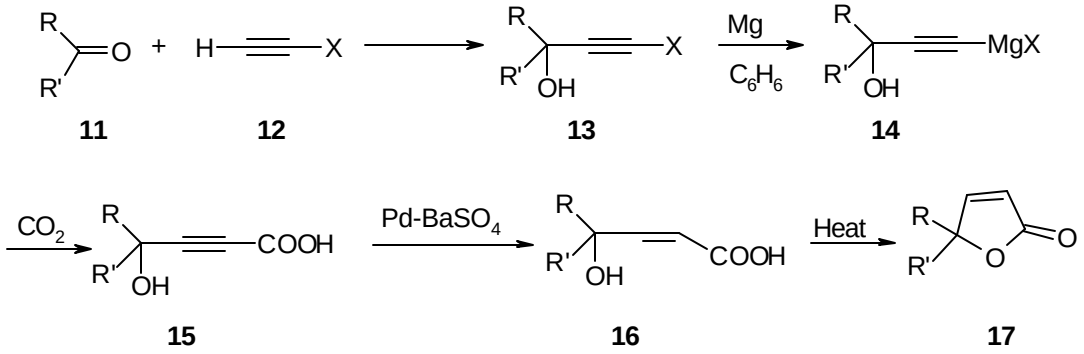


Scheme 1

From acetylenic compounds

Acetylenic carboxylic acids are obtained by treating the corresponding Grignard reagents with CO_2.[9] These acids are selectively reduced to give the ethylenic acids, which on heating cyclize to give ? ^{a,ß}-butenolide.

Scheme 2 Haynes, L. J. *et. al. J. Chem. Soc.* **1946**, 954.

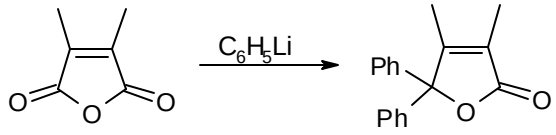


Scheme 2

From substituted Maleic anhydride

The reaction of phenyllithium with dimethyl maleic anhydride provides a,ß-dimethyl-?,?-diphenyl ?^{a,ß}-butenolide.[10] Mono and dialkyl maleic anhydride react with alkyl magnesium or aralkylmagnesium halides at low temperatures to give products which yield ?-hydroxy-?-alkyl- ?$^{a,?}$-butenolides when decomposed with water.

Scheme 3 Tarbell, D. S. *et. al. J. Amer. Chem. Soc.* **1940**, *62*, 2747.



18 **19**

Scheme 3

2-Acetoxyfuran reacts with bromine in CCl_4 at low temperature to form ?-bromo-?^{a,ß}-butenolide.[11] The chloro and acetoxy analogs are obtained by treatment of acetoxy furan with chlorine and lead tetraacetate, respectively.

Scheme 4 (Elming, N. *et. al. Acta. Chem. Scad.* **1953**, *6*, 565)

20 **21**

X= Br, Cl, $OCOCH_3$

Scheme 4

From ?$^{ß,?}$-butenolide

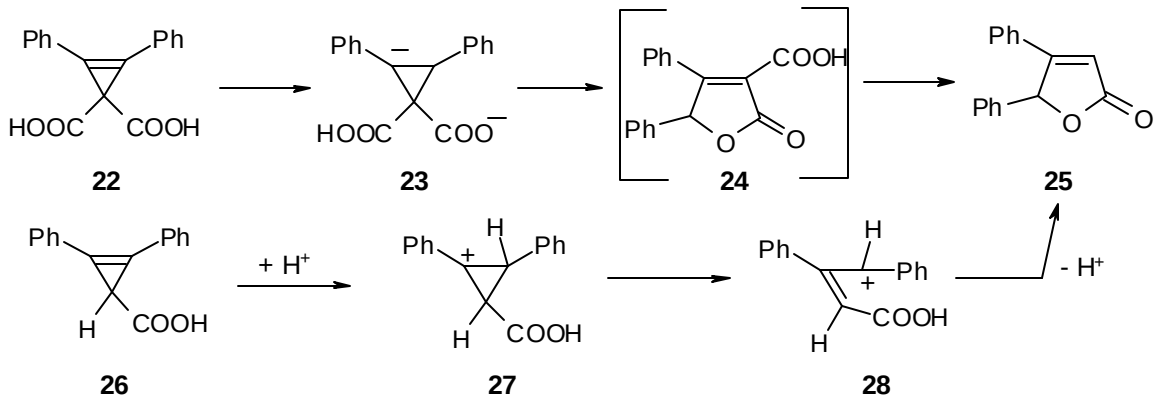
By the action of bases such as triethylamine, piperidine and even benzylamine, ?$^{ß,?}$-butenolide are converted to their ?^{a,ß} isomer.[8] Acetic anhydride has also been employed to effect this isomerisation. On a large scale, a-angelica lactone is converted to ß-angelica lactone by passing its vapor over Tuller earth.[9]

From cyclopropane derivatives

Diphenyl acetylene reacts with diazomalonic ester in the presence of copper dust to afford the ester of 22. The free acid, 1,2-diphenylcyclopropane-3,3-dicarboxylic acid,

gives on thermal decomposition, ß, ?-diphenyl- ?a,ß-butenolide.[10] Compound 25 was also obtained from 1, 2-diphenylcyclopropane-3-carboxylic acid 26.[11]

Scheme 5 Thiele, J. *et. al. Ann.* **1901**, *319*, 155.

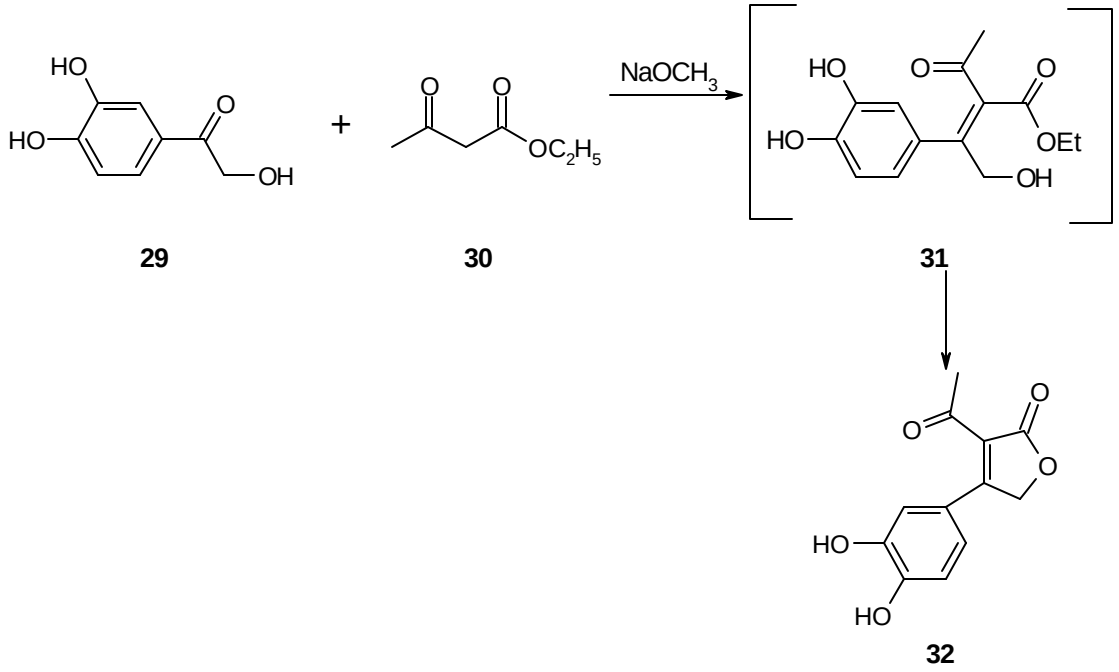


Scheme 5

From ketonic compounds

? -Hydroxy acetophenones, which bear hydroxyl substituents on the aromatic ring, react with ethyl acetoacetate (sodium salt) in methanol to form ? [a,ß]-butenolides.[17]

Scheme 6 Sintesa, S. A. *Chem Abstr*. **1962**, *57*, 13692g

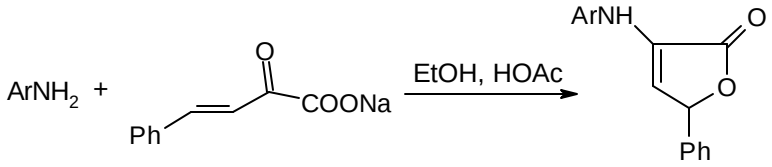


Scheme 6

From pyruvic acid derivatives

Benylidenepyruvic acid and aromatic amines react to form ?-aryl-a-arylamino-?^{a,ß}-butenolides.[18]

Scheme 7 Lutz, R. E. *et. al. J. Org. Chem.* **1960**, *25*, 346



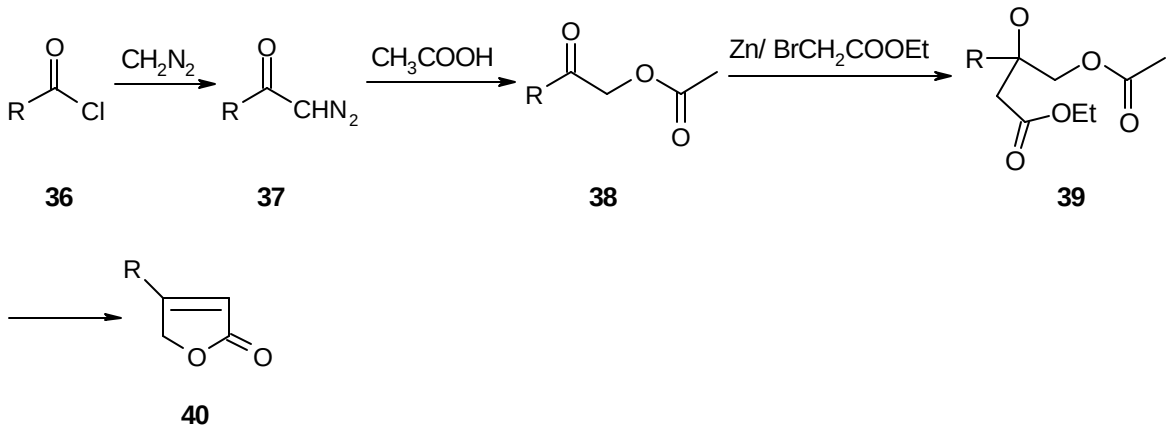
33 **34** **35**

Scheme 7

Reformatsky-Elderfield method

The reaction of acetoxy ketones with bromoacetic acid under Reformatsky conditions was a method of choice for the synthesis of ?^{a,ß}-butenolides.[19] This method has been employed for the synthesis of ß-4-allyl-3-hydroxylphenyl-?^{a,ß}-butenolide starting from 4-allyl-3-acetoxybenzoic acid.

Scheme 8 F. El Said, *Proc. Pharm. Soc. Egypt, Sci. Ed.* **1953**, *35*, 81.



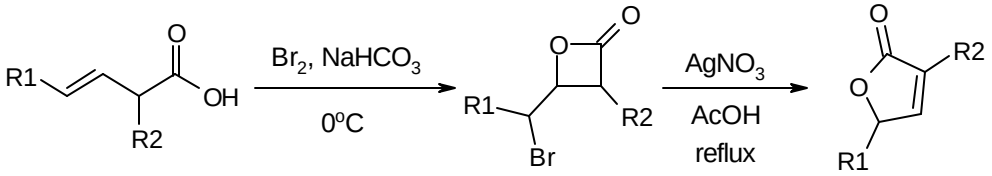
36 **37** **38** **39** **40**

Scheme 8

Black's approach

Bromolactonisation of ß, ?-unsaturated carboxylic acids using $Br_2/NaHCO_3$ gave the ß-lactone.[20] Treatment of these lactones with silver nitrate in refluxing acetic acid effected the ring expansion-elimination to the butenolide. This method, though novel, involves the use of expensive silver salts.

Scheme 9 Black, T. H. *et. al. Tet. Lett*. **1993**, *34*, 1411



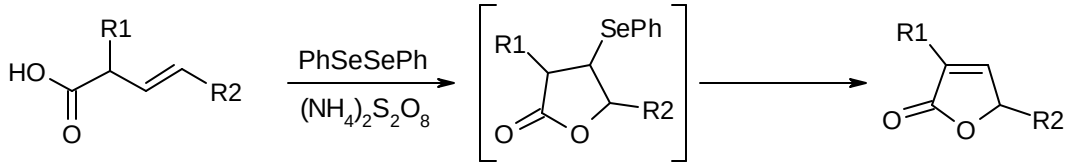
41 **42** **43**

Scheme 9

Tiecso's approach (Tiecco, M. *et. al. Synlett*. **1993**, 798)

ß, ?-Unsaturated acids were smoothly converted to butenolide using catalytic diphenyl diselenide and excess ammonium persulfate in acetonitrile.[21] This reaction proceeds *via* the selenolactone intermediate.

Scheme 10 Tiecco, M. *et. al. Synlett*. **1993**, 798



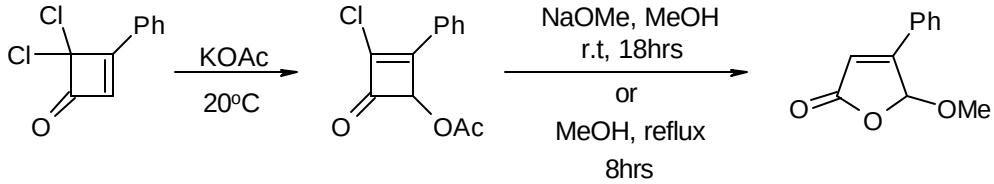
44 **45** **46**

Scheme 10

Dillon's approach (Dillon, J.; Gao, Q. *J. Org. Chem.* **1994**, *59*, 6868)

Reaction of 4,4-dichloro-3-phenyl-2-cyclobutenone with KOAc afforded cyclobutenone.[22] When refluxed in MeOH or treated with NaOMe in MeOH at room temperature, ring expansion occurred to give butenolide. The route though involves the use of simple chemicals, the scope is limited due to difficulty in the preparation of dichlorobutenones.

Scheme 11 Dillon, J.*et. al. J. Org. Chem.* **1994**, *59*, 6868



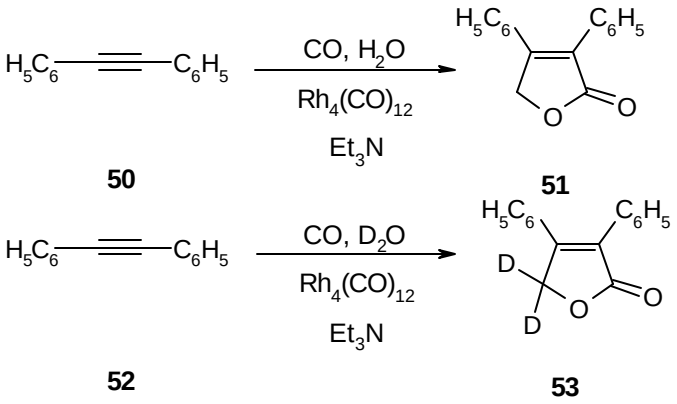
47 **48** **49**

Scheme 11

Rhodium catalyzed carbonylation of acetylenes

Diphenylacetylene when reacted with carbonmonoxide (100 atm) and water[23] in the presence of triethylamine and a catalytic amount of $Rh_4(CO)_{12}$ in THF at 100°C, the reaction proceeded smoothly to give 3,4–diphenylfuran2(*5H*)-ones. The main disadvantage of this reaction is the drastic conditions involved in it.

Scheme 12 Joh, T. *et. al. Organometallics* **1991**, *10*, 2493

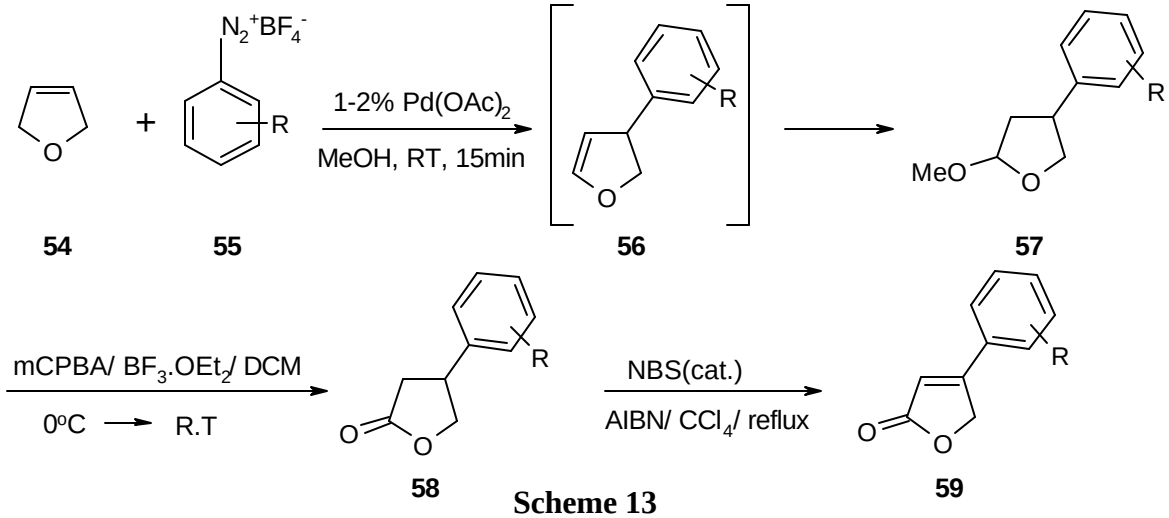


Scheme 12

Heck Reaction

Mehta *et. al* have reported[24] a facile Heck reaction of arenediazonium salts with the inexpensive 2,5-dihydrofuran leading to 4-aryl-?-butyrolactone. Oxidation of this ?-butyrolactone, with benzylic bromination-debromination sequence with NBS in CCl_4, avoids the use of selenium dioxide.

Mehta, G. *et. al. Tet. Lett.* **1996**, *37*, 8625.

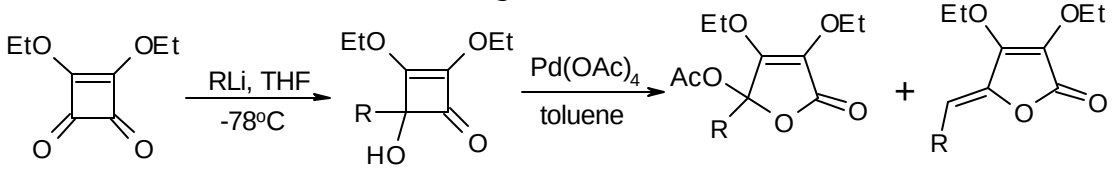


Scheme 13

Eguchi's approach

4-Hydroxycyclobutenones when treated with stoichiometric amount of lead tetraacetate[25] undergo a novel oxidative ring expansion to form the highly oxygenated 5-acetoxy-2(*5H*)-furanone along with the alkylidene 2(*5H*)-furanone. Other oxidants like CAN and $Mn(OAc)_3$ also gave similar results.

Scheme 14 Yamamoto, Y. *et. al. J. Org. Chem.* **1994**, *17*, 4707



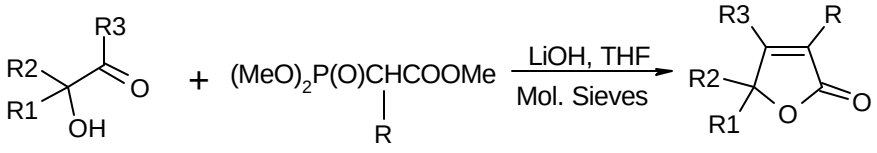
60 **61** **62** **63**

Scheme 14

Bondies approach

a-Hydroxy ketones under Horner-Wadsworth-Emmons reaction[26] with stabilized lithium phosphonates in presence of molecular sieves give the corresponding butenolide.

Scheme 15 Bonadies, F.*et. al. Tet. Lett*. **1995**, 2838.



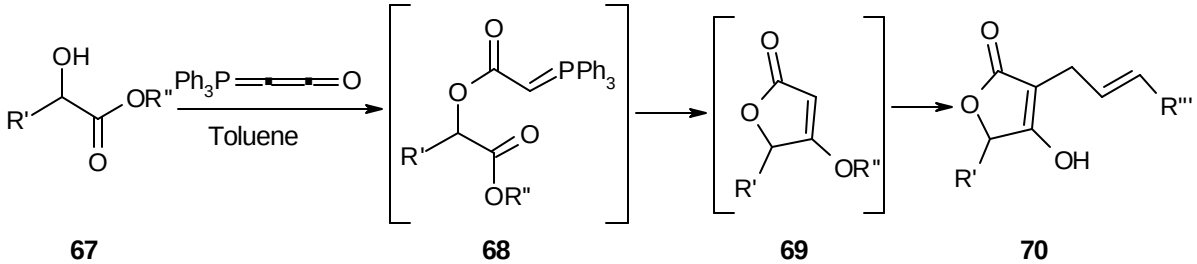
64 **65** **66**

Scheme 15

Schobert's approach

Allylic esters of a-hydroxy acids were reacted with ketenylidene triphenylphosphorane under reflux conditions.[27] The reaction proceeded *via* the formation of ester ylide which undergoes tandem Wittig-Claisen reaction to yield a, ?-disubstituted tetranoate.

Scheme 16 Schobert, R. *et. al. Synlett* **1995**, *5*, 425



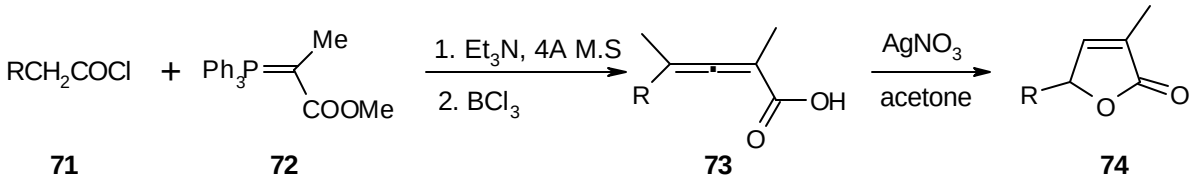
67 **68** **69** **70**

Scheme 16

Marshall's approach

In this approach,[28] allenic esters were prepared by the Wittig reaction of acid chlorides with methyl-(triphenylphosphoranylidene)propionate and was subjected to hydrolysis with BCl_3. The resulting allenic acids were smoothly converted to butenolide by treatment with 10% $AgNO_3$ in acetone.

Scheme 17 Marshall, J. A. *et. al. J. Org. Chem.* **1997**, *62*, 367



71 **72** **73** **74**

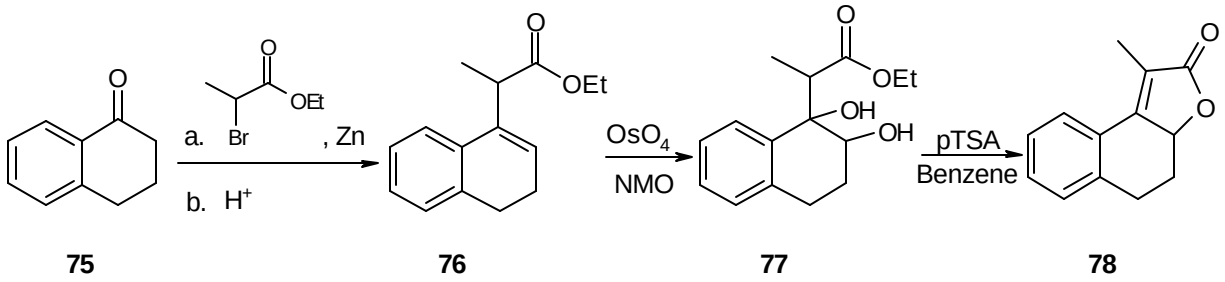
Scheme 17

1.3.3 Present work

Earlier reports[29,30] from our group on the synthesis of butenolides were done on tetralones and its derivatives. The scheme included a Reformatsky reaction on tetralone followed by elimination, which gave selectively ß, ?-unsaturated ester. The unsaturated ester was then subjected to dihydroxylation using osmium tetraoxide and *N*-methylmorpholine-*N*-oxide. One pot cyclisation and elimination of the hydroxyl group was done using *p*TSA, to give butenolide in good yields. Notable feature of the reaction is the one pot cyclisation of using *p*TSA.

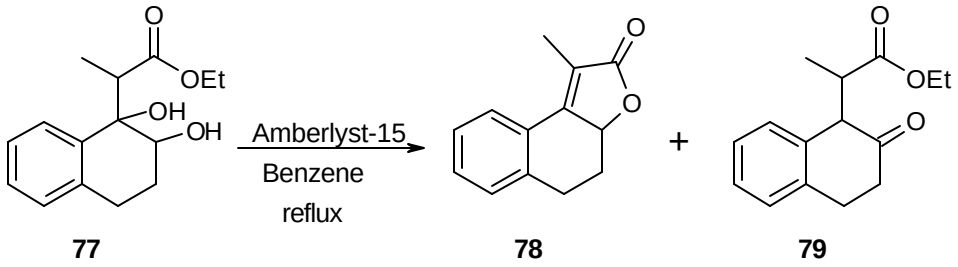
In yet another modification to the cyclisation process,[30] the reaction was carried out with Amberlyst-15 as a heterogeneous acid to give the cyclized product. Very recently it was demonstrated that by varying substrate to catalyst ratio one could change the course of the reaction in favour of either the keto-ester or the butenolide. Feature to be noted here that the reaction gave ?-ketoester also.

Chavan's approach:



75 **76** **77** **78**

Scheme 18

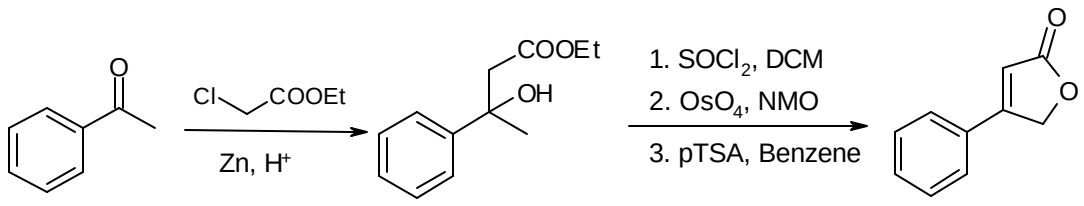


77 **78** **79**

Scheme 19

With the report of modification on the Reformatsky reaction it was then decided to perform the same set of reactions on the substrates already available (section1).

In a typical example, acetophenone was chosen as the starting material. Modified Reformatsky reaction as described in section 1 was done. The hydroxy compound obtained was then eliminated to give a mixture of a, ß unsaturated ester and ß, ? unsaturated ester. However, there was problem intervened as the elimination gave varied ratios of the unsaturated ester. The product obtained was subjected to dihydroxylation using osmium tetraoxide, which was then subjected to cyclisation using pTSA in benzene. The butenolide obtinaed was carefully chromatographed using Silica gel 60-120 with 15% pet-ether ethylacetate was eluent.

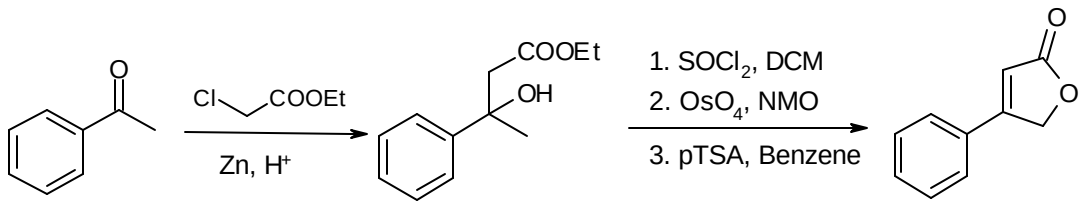


80 **81** **82**

Scheme 20

1.3.4 Results and discussions

Modification to Reformatsky reaction as done in section 1 was repeated. The hydroxy ester obtained was subjected to elimination using thionyl chloride and pyridine. The reaction however did not give consistent results. The ratio of the unstaurated ester varied considerably. The product obtained was subjected dihydroxylation using osmium tetraoxide and NMO. The product obtained was subjected to elimination and cyclisation



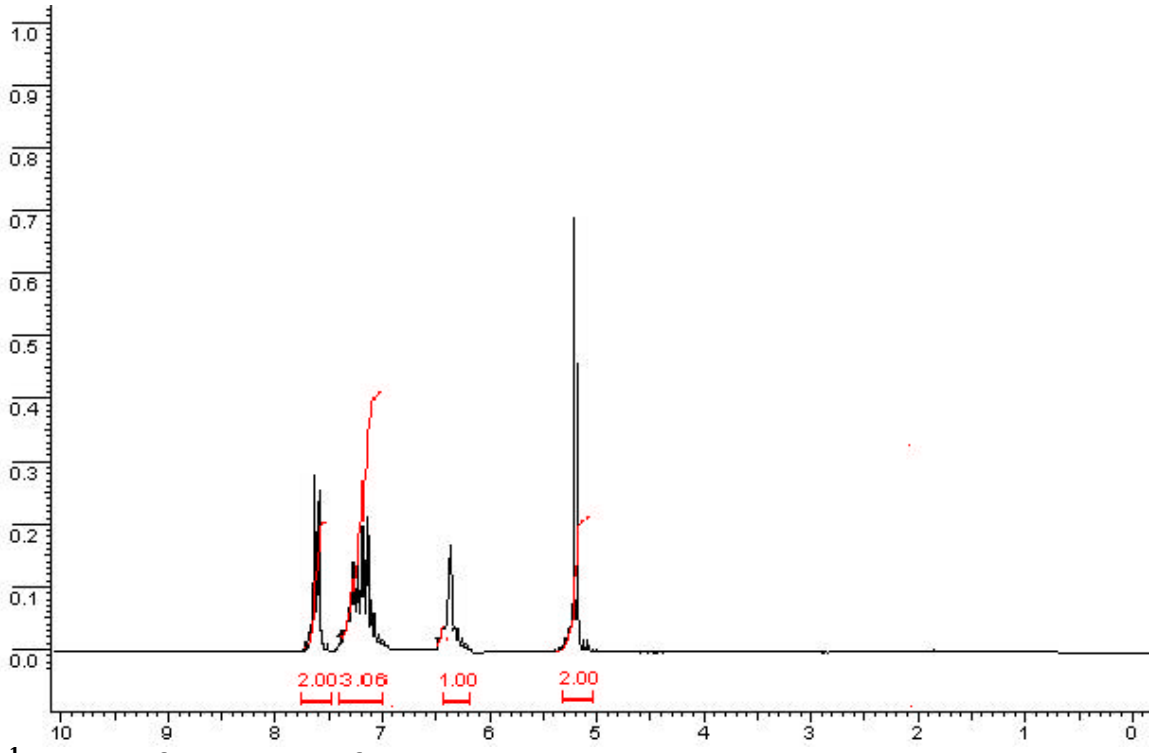
80 **81** **82**

Scheme 20

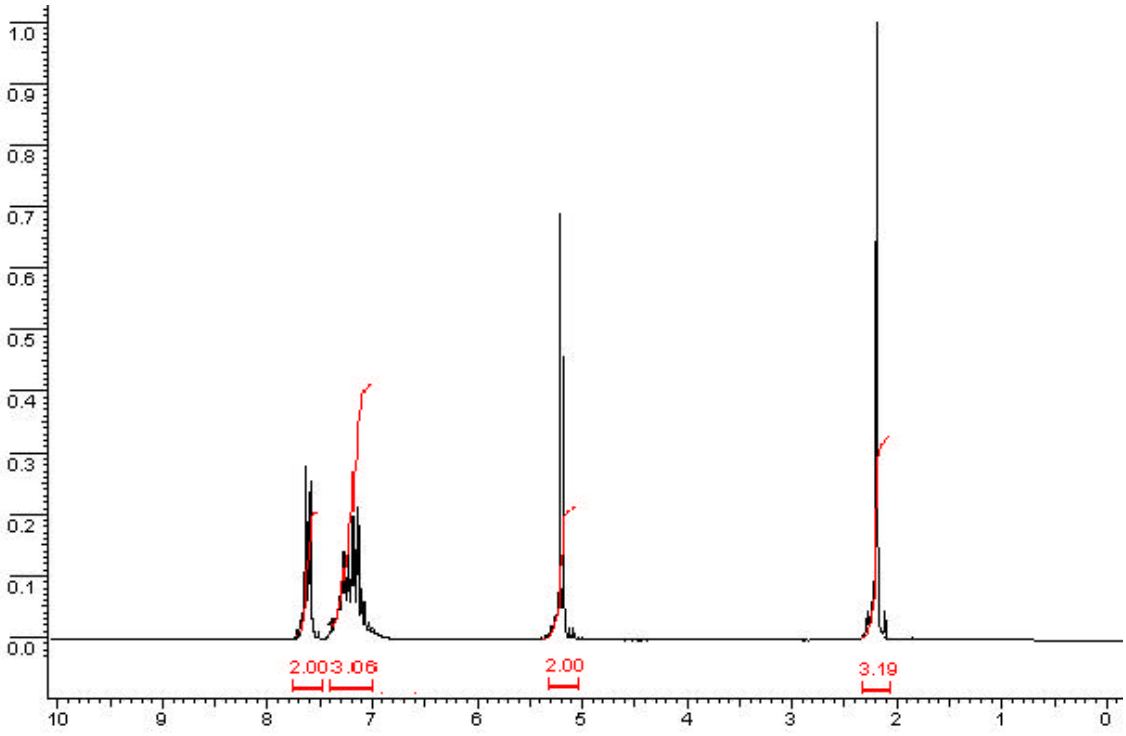
using *p*TSA to furnish the butenolide 82. The product obtained was characterized by ^{1}H NMR, which showed olefinic proton and the lactone CH_2. The spectral and physical properties of the compound obtained was compared with the available data. Results obtained matched with the literature values.

1.3.5 Conclusions

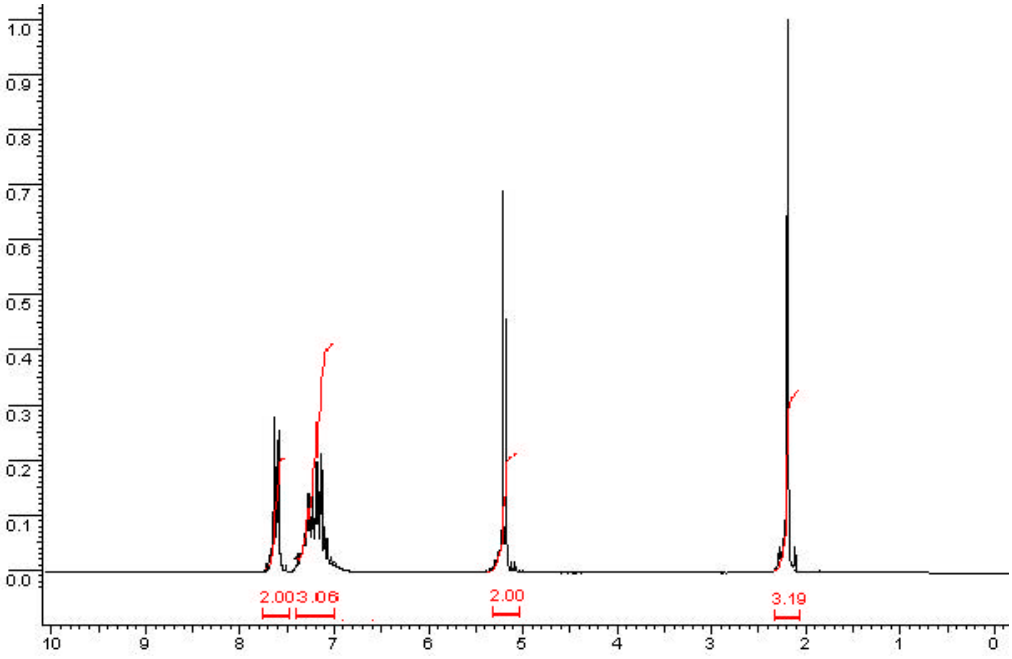
The use of chloroester for Reformatsky reaction has been successfully applied in the synthesis of butenolide. The synthesis is short and the yields of the reaction overall is good. Use of *p*TSA to do one pot reaction of cyclisation and elimination is another fact to be noted in the synthesis.



^{1}H NMR of 4-Phenyl-*5H*-furan-2-one (200MHz, $CDCl_3$)



^{1}H NMR of 4-p-Tolyl-*5H*-furan-2-one (200MHz, $CDCl_3$)



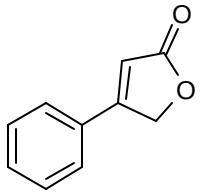
^{1}H NMR of 3-Methyl-4-phenyl-*5H*-furan-2-one (200MHz, $CDCl_3$)

1.3.6 Experimental

Typical procedure

To a two-necked round bottom flask attached with a two-way stopcock and an additional funnel hydroxy ester (200mg, 0.96mmol) was taken in 10ml of DCM. Dry pyridine (0.08ml, 0.98mmol) was added and the reaction mixture was set for cooling at 0^{o}C using an ice bath. Thionyl chloride (0.07ml, 0.96mmol) was added dropwise using the addition funnel. The reaction was monitored by TLC. After the completion of the reaction, 10ml of water was added to the reaction mixture dropwise and the organic layer was separated and washed with 10ml 5% HCl solution followed by 10ml water. Later the organic layer was washed with 5% bicarbonate solution. The organic layer was then again washed with 2×10ml water. It was then dried over anhydrous sodium sulphate and the concentrated under vacuum. 190mg of crude product was obtained. The crude product was taken in 10ml of a mixture of acetonitrile and water in the ratio 9:1. The reaction mixture was cooled to 0^{o}C using an ice bath. Catalytic amount of osmium tetraoxide was added followed by the addition of NMO(60mg, 0.52mmol). The reaction was stirred at room temperature and was monitored by TLC. After the completion of the reaction, the reaction was quenched with 10ml of 5% HCl. And the product was extracted in 2×10ml of ethyl acetate. The organic layer was then washed with 2×10ml of water. The organic layer was then dried over sodium sulphate and then concentrated in vacuum. The crude product obtained (102mg) was then taken in benzene and catalytic amount of *p*TSA was added and the reaction mixture was set for azeotropic distillation using a Dean-Stark apparatus. After the completion of the reaction, as monitored by TLC, reaction was quenched using 5% aqueous sodium bicarbonate solution. The organic layer was washed with water and was then dried over sodium sulphate. The crude product obtained was then subjected to column chromatography using 60-120 silica gel with 15% pet-ether ethylacetate as the eluent furnished 53 mg of pure butenolide.

4-Phenyl-*5H*-furan-2-one[31]



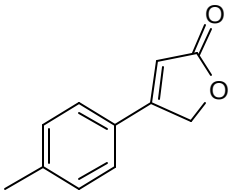
Yield: 34%

Molecular formula: $C_{10}H_8O_2$

Melting point: 90°C

^{1}H NMR: 5.2 (s, 2H), 6.4(s, 1H), 7.4-7.6(m, 5H)

4-p-Tolyl-*5H*-furan-2-one[31]



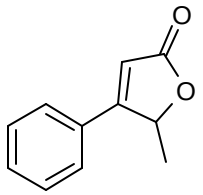
Yield: 32%

Molecular formula: $C_{11}H_{10}O_2$

Melting point: 117°C

^{1}H NMR: 2.4 (s, 3H), 5.2 (s, 2H), 6.4(s, 1H), 7.3 (d, 2H, J=8Hz), 7.6(d, 2H, J=8Hz).

5-Methyl-4-phenyl-*5H*-furan-2-one[32]



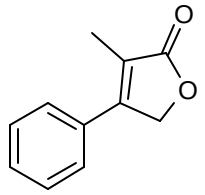
Yield: 35%

Molecular formula: $C_{11}H_{10}O_2$

Melting point: 58°C

^{1}H NMR: 1.2 (d, 3H, J=7Hz), 5.0 (m, 1H), 6.4 (s, 1H), 7.4-7.7(m, 5H)

3-Methyl-4-phenyl-*5H*-furan-2-one[33]



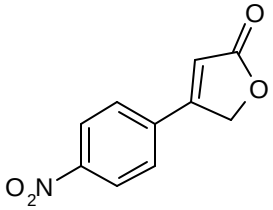
Yield: 35%

Molecular formula: $C_{11}H_{10}O_2$

Melting point: 117°C

^{1}H NMR: 2.12 (s, 3H), 5.0 (s, 2H), 7.2-7.7(m, 5H)

4-(4-Nitro-phenyl)-*5H*-furan-2-one[31]



Yield: 33%

Molecular formula: $C_{10}H_7NO_4$

Melting point: 230°C

^{1}H NMR: 5.35 (s, 2H), 6.8 (s, 1H), 7.9 (d, 2H, J=8Hz), 8.3 (d, 2H, J=8Hz)

1.3.7 References

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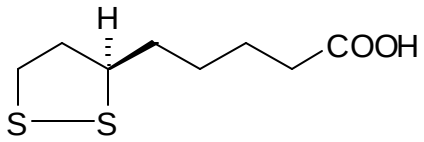
SECTION D

Synthesis of a **- Lipoic acid**

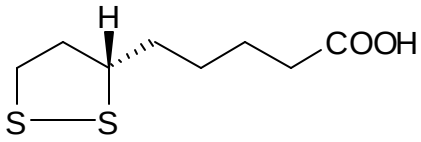
1.4.1 Introduction

a-Lipoic acid (1,2-dithiolane 3-pentanoic acid) **1a** and its reduced form dihydrolipoic acid (6,8-dimercaptooctanoic acid) are physiologically occurring substances. Lipoic acid is a naturally occurring cofactor reported in a diverse group of microorganisms[1] and a variety of plant and animal tissues. [2] It serves as acyl carrier in the oxidative decarboxylation of a-ketoacids such as pyruvate and a-ketoglutarate and as aminomethyl carrier in glycine-cleavage enzyme systems.[3] There are two enantiomeric forms of α-Lipoic acid, they do not exhibit the same biological activity. Generally the naturally occurring (R)-enantiomer **1a** is much more active than (S)-enantiomer **1b**.



1a

R-(+)-a **-Lipoic acid**



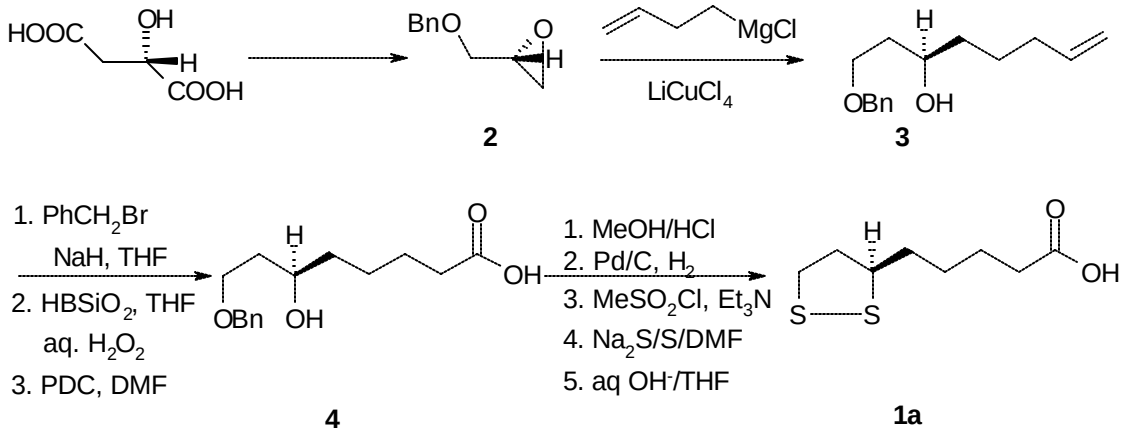
1b

S-(-)-a **-Lipoic acid**

Lipoic acid is widely distributed in mouse tissues, bacterial cells and foods. In food samples, Lipoic acid contents are high in those derived from animals, but the levels in those from plants are low or not detectable. Lipoic acid has been shown to provide potent antioxidant abilities against attack by free radical[4] and inhibitory effect against HIV replication[5] and interplay between lipoic acid and gluthione in the protection against lipid peroxidation and metal toxicity has been demonstrated.[6] A dietary supplement of lipoic acid is effective for resistance of tissues to lipid peroxidation and maintaining the life span of the mouse.[7] Moreover lipoic acid is used extremely in the treatment of various diseases such as alcoholic liver disease,[8] mushroom poisoning,[9] metal poisoning,[6] diabetes[10] and neurodegenerative disorder.[11] Apart from pharmacological importance lipoic acid is used in cosmetic preparation, skin lotions, ointments which prevent darkening of the skin.[12] a-Lipoic acid was first isolated by Reed and coworkers in 1950 and characterized as the cyclic disulphide 5-[3-(1,2-dithiolanyl)]-pentanoic acid.[13] Ever since the isolation in 1950 there has been a quite a lot of working in the efforts to synthesize this molecule. We take a brief look into the reported syntheses of this molecule.

Golding Synthesis

Golding *et al* were the first to synthesis optically active lipoic acid[14a] (Scheme 1). The crucial step in the synthesis is the opening of the epoxide obtained from malic acid with but-3-enyl magnesium chloride catalyzed by lithium chlorocuprate to give compound **3**. The free hydroxy of compound **3** was then protected as benzyl and hydroboration was done so as to get a hydroxyl group at the end of the side chain. The alcohol was then oxidized to acid using PDC to give the dibenzyl acid **4**. This was then esterified using methanol and hydrochloric acid. The ester thus obtained was then debenzylated to get the free hydroxy group. This was later mesylated. The dimesylated compound was then treated with sodium sulphide, sulphur in DMF to furnish methyl lipoate in good yields. Methyl lipoate obtained was then hydrolyzed using aqueous sodium hydroxide in THF to get lipoic acid. The overall yield of the 5 step reaction sequence was 25%.

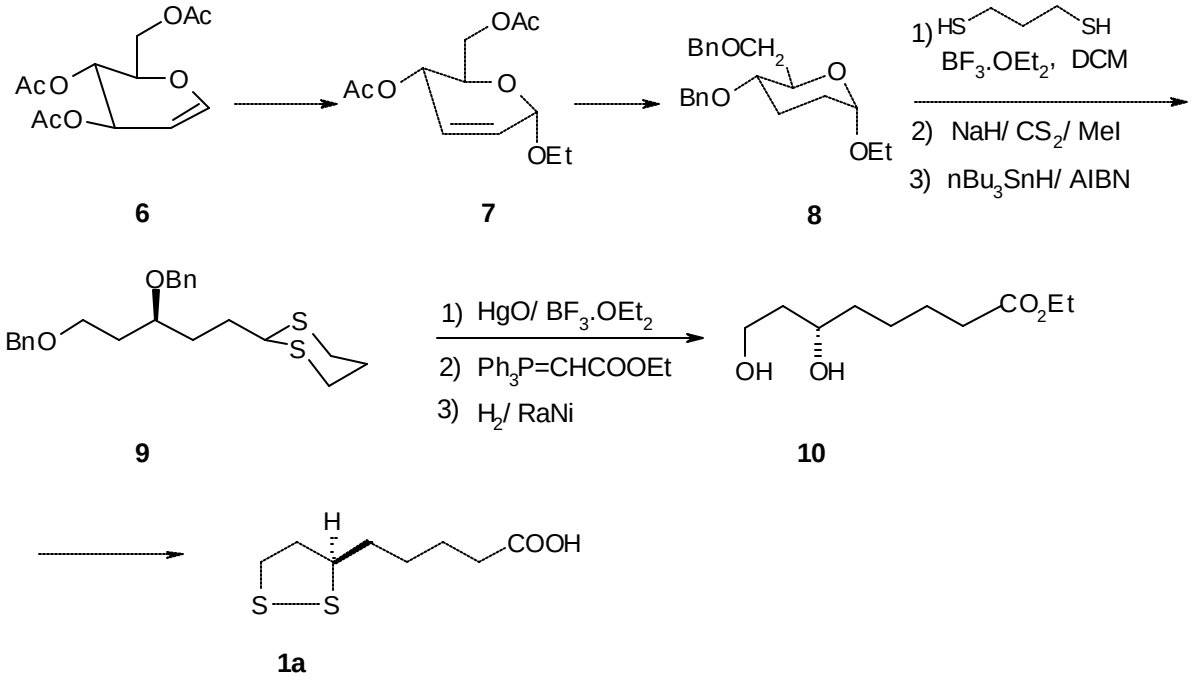


Scheme 1

Later in 1988 Golding synthesised the R-isomer starting from S-maleic acid which involved the inversion in configuration at oxirane intermediate.[14b]

RamaRao's synthesis

RamaRao *et al* have reported four different routes for the synthesis of lipoic acid. The first of which starts with 3,4,6-tri-O-acetyl-D-glucal **6** that is derived from D-glucose.[15]

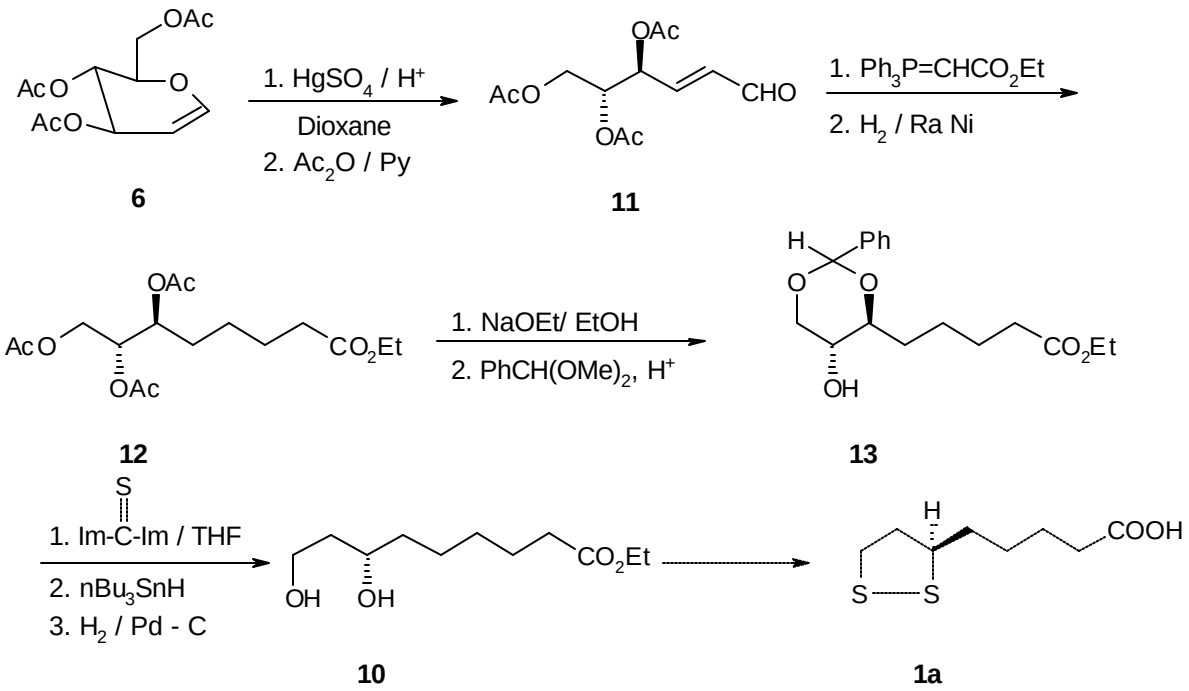


Scheme 2

The tri-O-acetyl-D-glucal **6** was then converted to 4,6-di-O-benzyl derivative by known methods. The key step in the synthesis was the treatment of compound **8** with propanediol and to furnish dithiane **9**. Two carbon Wittig olefination followed by hydrogenation using Raney nickel was done on dithiane **9** to furnish 1,3-dihydroxyester which in a sequence of 3 steps was converted to lipoic acid.

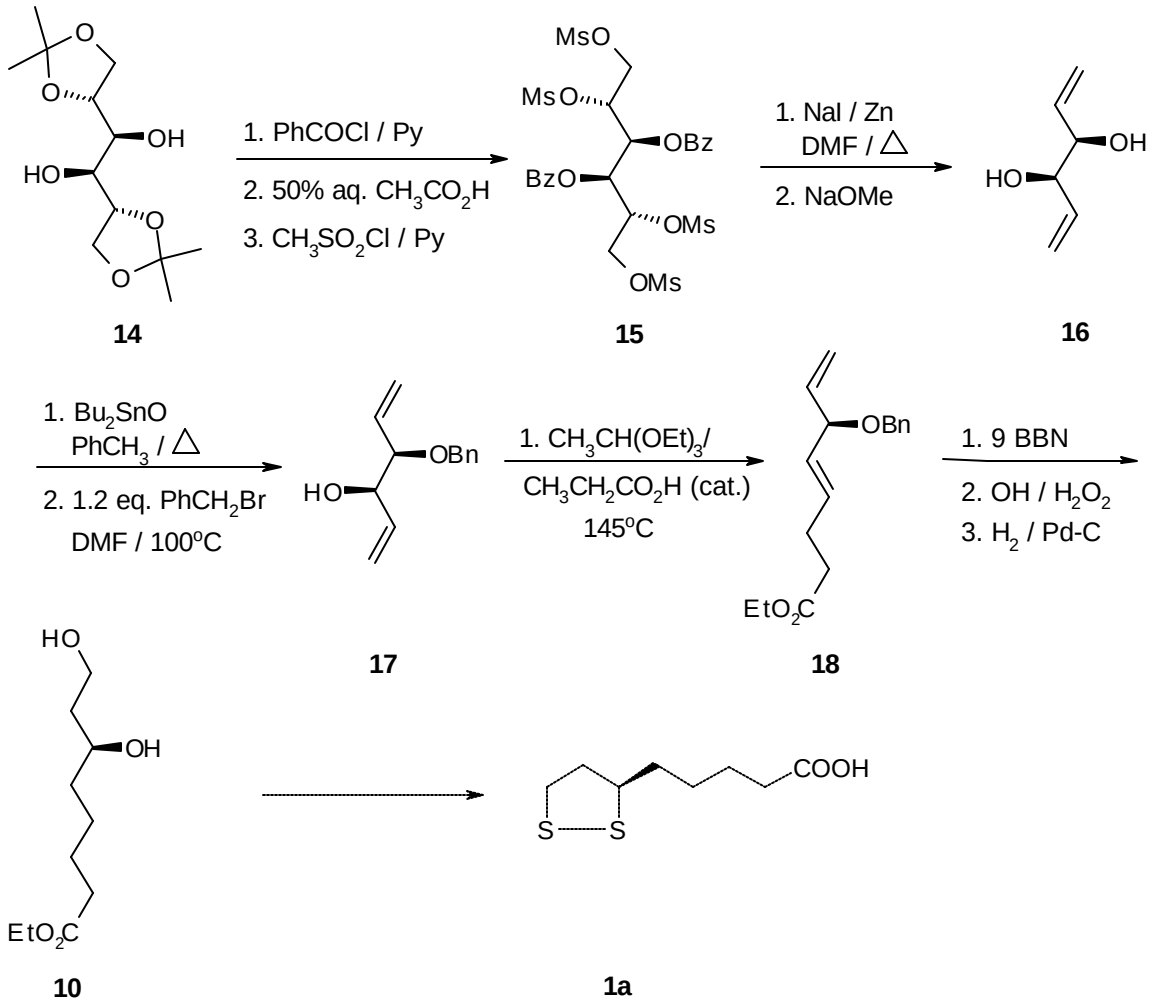
In the second synthesis[16] (Scheme 3) tri-O-acetyl-D-glucal **6** was opened with mercurous sulphate followed by protection using acetic anhydride and pyridine to furnish compound **11**. Two carbon Wittig olefination was done on **11** followed by hydrogenation using Raney nickel to furnish the triacetate ethylester **12**. Compound **12** has the same number of carbons as that of lipoic acid. Functional group transformations involved deprotection of the three acetates and selective protection of the triol with benzaldehyde

dimethylacetal to get only dioxane. Deoxygenation of free hydroxyl was accomplished *via* xanthate. The diol ester **10** thus obtained is a known intermediate for the synthesis of lipoic acid.

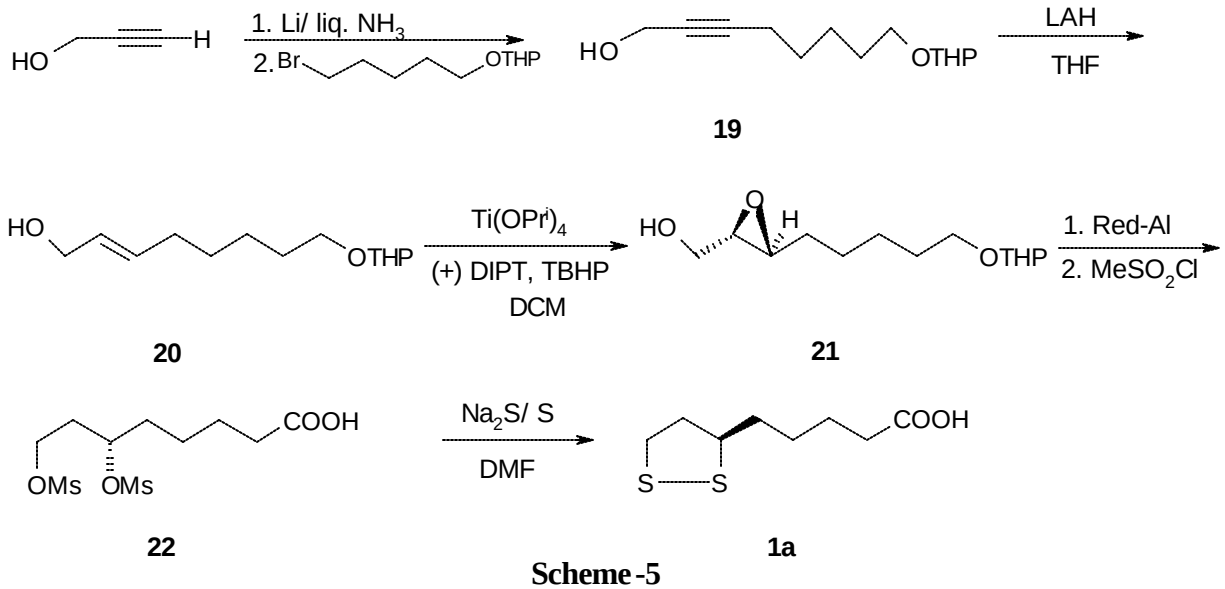


Scheme 3

The third synthesis[17] (Scheme 4) involved the use of manitol diacetonide **14**, which was treated with benzoyl chloride to protect two free hydroxyl groups. The acetonides were cleaved and the resultant hydroxyls were treated with mesylchloride to furnish compound **15**. **15** was then treated with sodium iodide and zinc followed by sodium to furnish (3R, 4R)-1,2-divinyl-glycol **16**. Divinyl glycol was then selectively benzylated to furnish compound **17**. Two carbon homologation was done on **17** *via* a Clasien ester rearrangement to give compound **18**. In a sequence of three steps involving hydroboration, oxidation and reduction of the double bond using palladium charcoal the diol-ester **10** was obtained which is a known intermediate in the synthesis of lipoic acid.



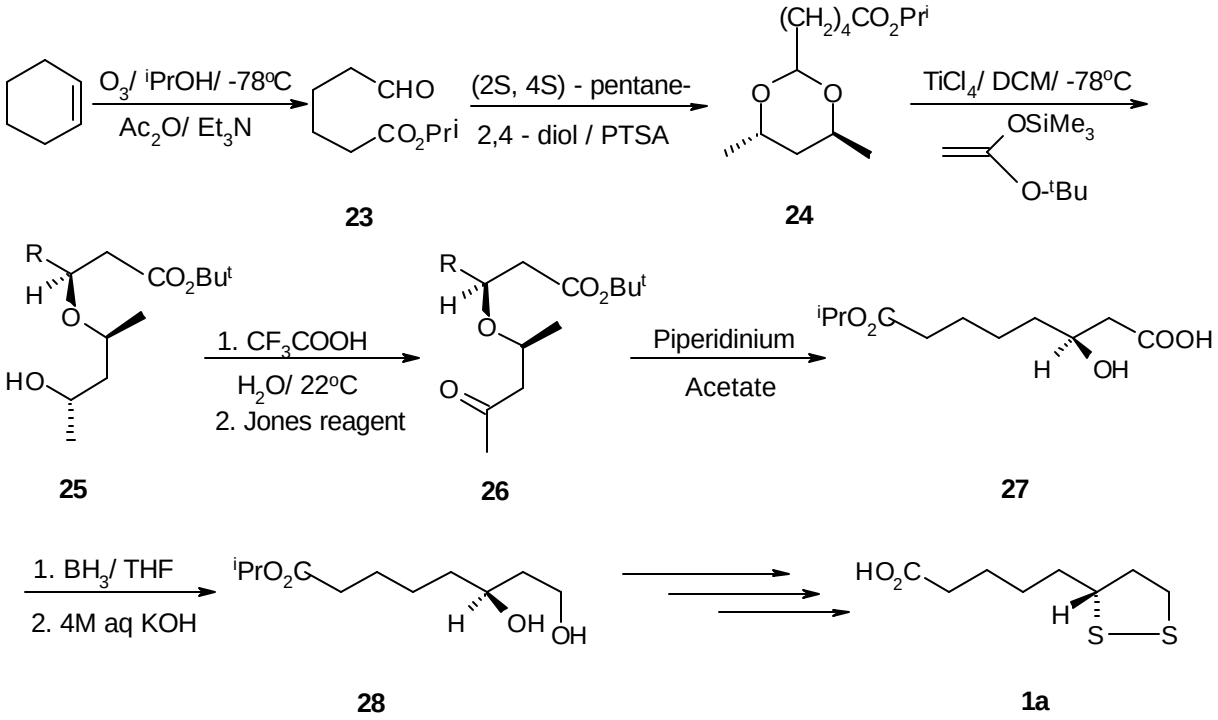
Scheme 4



Scheme -5

In the fourth synthesis,[18] (Scheme 5) RamaRao *et al* have started with propargyl alcohol, which was alkylated, to furnish the eight carbon skeleton that is required for lipoic acid. Compound **19** thus obtained was then partially reduced to give the allylic alcohol **20**. Asymmetric epoxidation was done on **20** using titanium isopropoxide. The epoxide **20** was then opened and mesylated to give the dimesyl compound **22**. Compound **22** was then treated with sodium sulphide sulfur to furnish lipoic acid,

Elliott synthesis

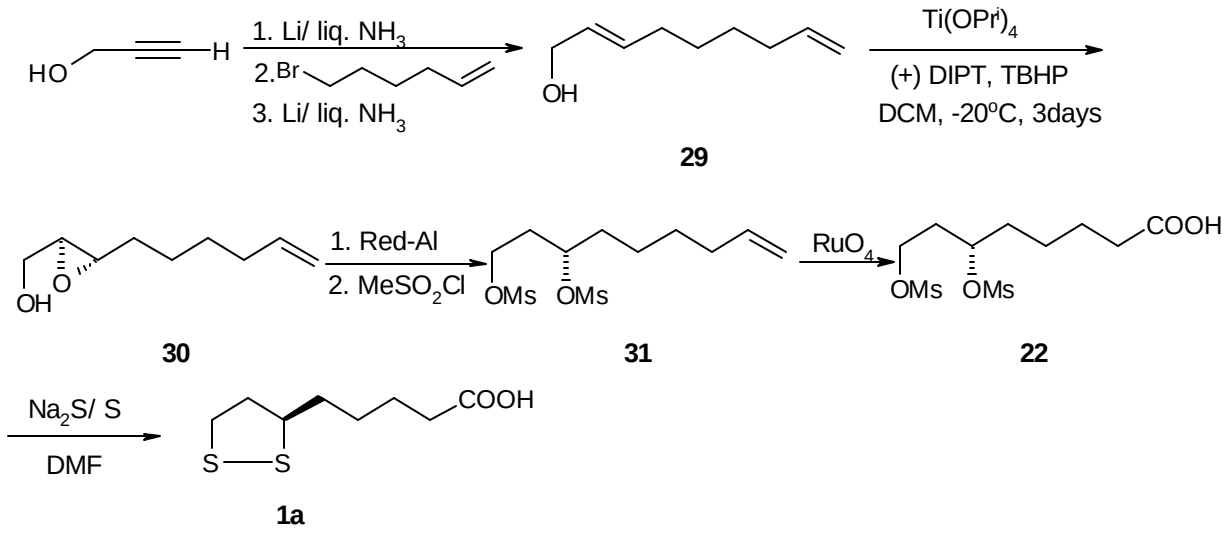


Scheme 6

In this approach[19] (Scheme 6) the chiral center is obtained by asymmetric synthesis *via* chiral acetal templates. The most significant reaction in this synthetic strategy is the $TiCl_4$ catalyzed coupling of chiral acetal **24** with the ketone acetal **25** to generate the β-alkoxy carboxylate **25** in which the new asymmetric center is formed with excellent diasteroselection. The hydrolysis of ester **25** followed by oxidation with Jones reagent gives **26**. Removal of chiral auxiliary was achieved by treating **26** with

piperidinium acetate in the boiling benzene to afford the β-hydroxy acid **27**, which is converted to the diol **28** by hydroboration.

Sutherland approach

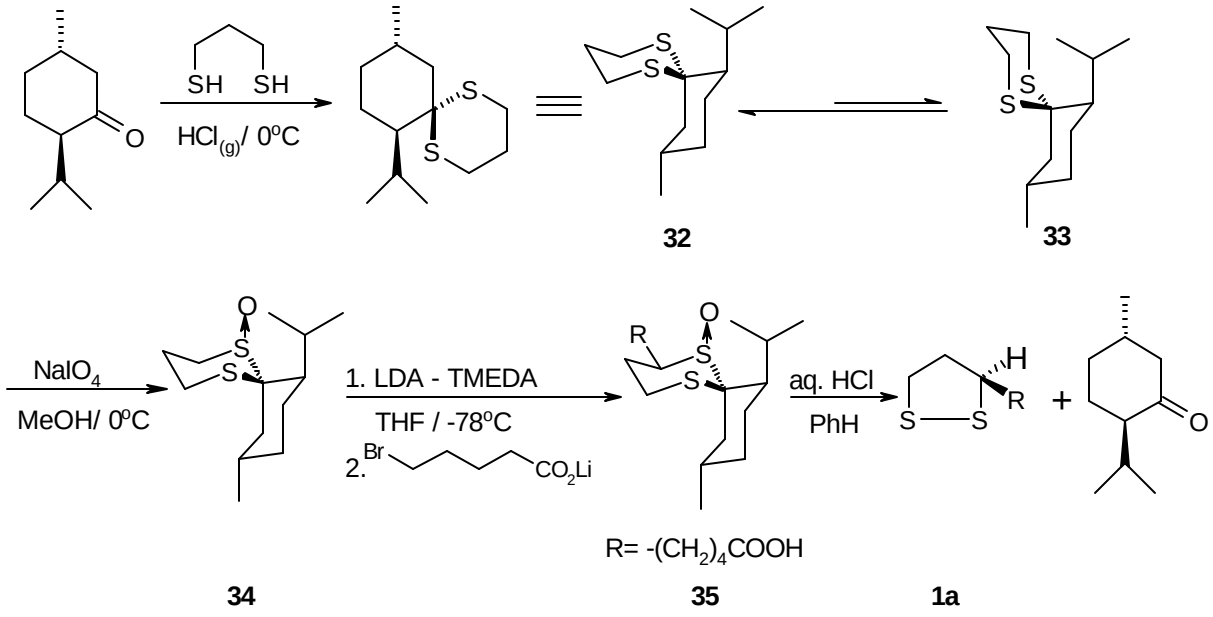


Scheme 7

Sutherland approach[20] (Scheme 7) also starts with propargyl alcohol as same as Ramaraos synthesis. Lipoic acid has been synthesized in the enantioselective manner from achiral precursor using the Sharpless asymmetric epoxidation as a key step in the reaction sequence to control the absolute configuration of the chiral center. Alkylation of the lithiodianion of propargyl alcohol in liquid ammonia solution with 6-bromohex-1-ene followed by dissolving metal reduction of the resultant disubstituted acetylene *in situ* gave the allylic alcohol **29**. Sharpless asymmetric epoxidation of **29** using L-(+)-diisopropyl tartarate as a chiral auxiliary gave the (2S, 3S)-epoxy alcohol **30**. Regioselective reduction of epoxy alcohol using Red-Al followed by mesylation gave **31**. Ruthenium tetraoxide oxidation of the terminal double bond using the catalytic procedure by Sharpless results in the formation of **22** which on treatment with sodium disulfide proceeded with the inversion of configuration to give R-(+)-Lipoic acid.

Ravindranathan synthesis

This (Scheme 8)is the shortest synthesis reported to date.[21] The characteristic feature of this synthesis is the recovery of menthone, which induces chirality in the molecule. Dithiane **32** was prepared from menthone as reported in the literature. The thioacetal **32** was selectively oxidized to monosulfoxide **33** by aqueous solution of sodium metaperiodate in methanol. Alkylation of sulfoxide **33** with two equivalents of LDA-TMEDA and δ-bromo valeric acid resulted in **35**. Hydrolysis of **35** in aqueous hydrochloric acid and benzene affords α Lipoic acid. Both forms of Lipoic acid could be accessed following this route.

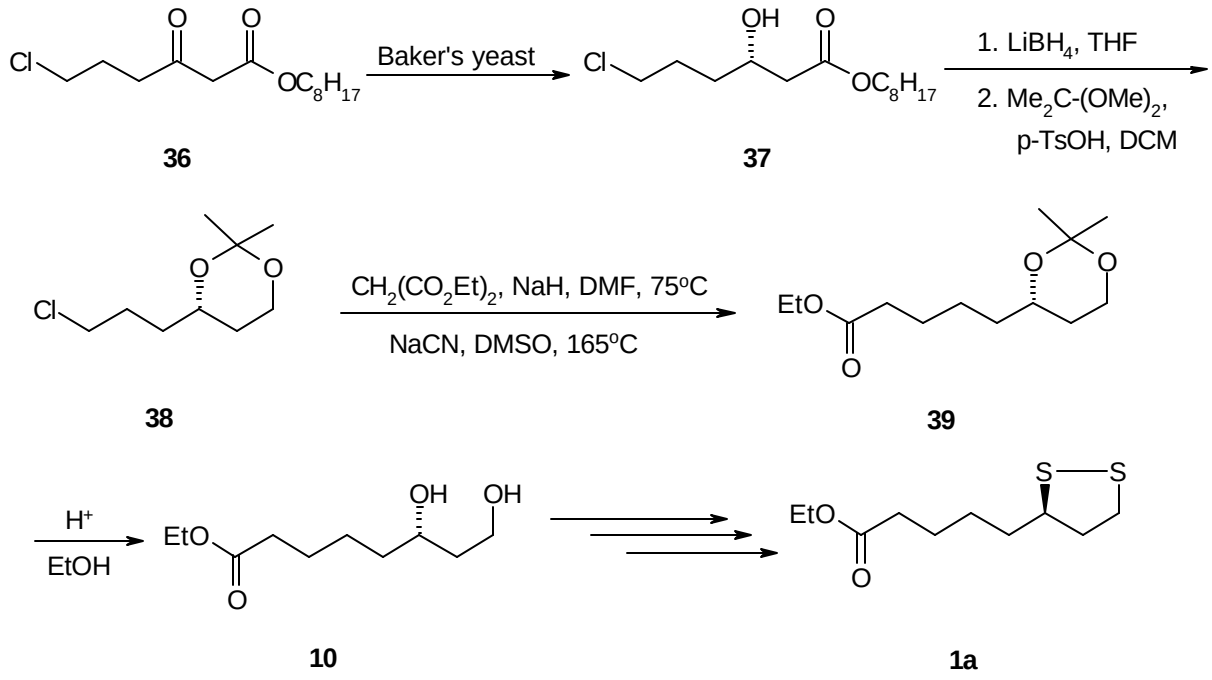


Scheme 8

Hollie synthesis

Selective reduction of carbonyl ß to the ester using Baker's yeast is the highlight of the synthesis (Scheme 9).[22] 6-chloro-3-oxohexanoate was reduced using Bakers yeast

to give alcohol **37**. Compound **37** was reduced using Lithium borohydride. The 1,3 diol thus obtained was then protected as acetonide to give compound **38**. Two-carbon homologation was



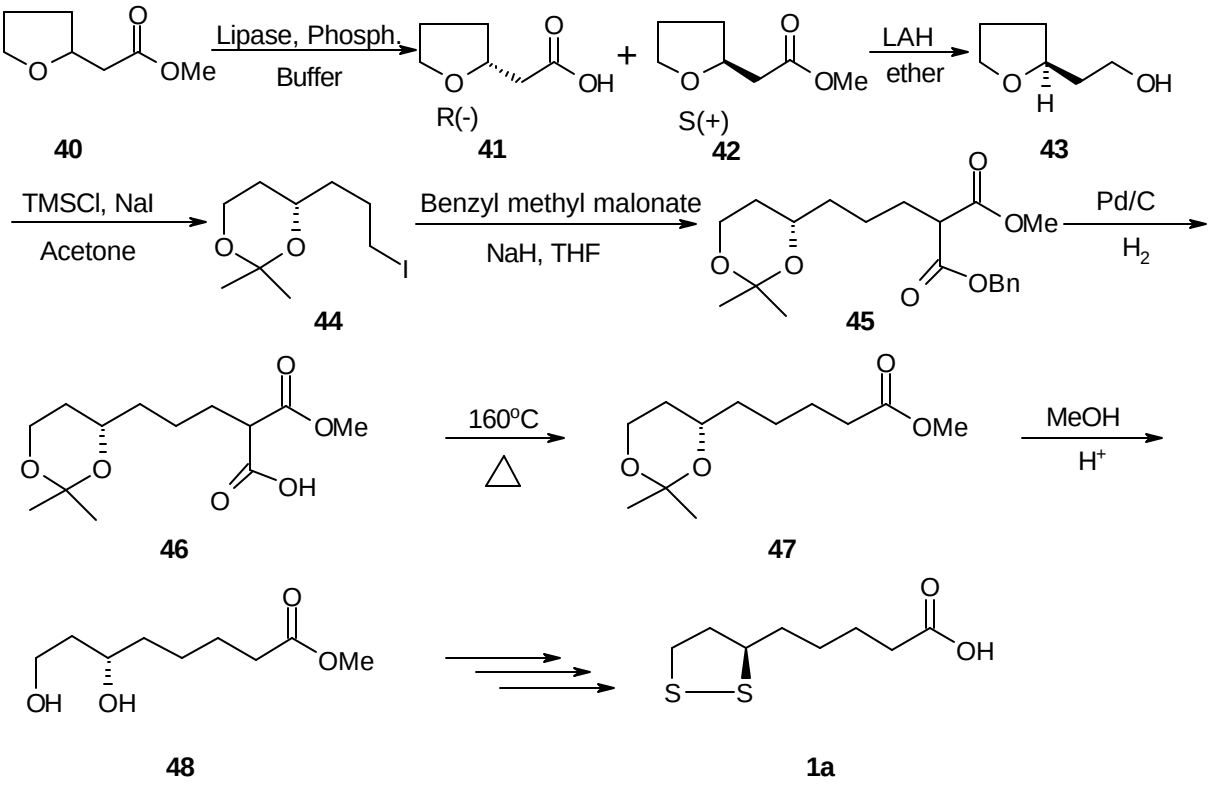
Scheme 9

done using diethylmalonate to furnish the acetonide **39**. Cleavage of the acetonide **39** in acidic conditions gave the diol-ester **10** which was then converted to lipoic acid by standard protocol.

Iyengar approach

Feature of this synthesis (Scheme 10) is selective hydrolysis of methyl tetrahydro-2-furylacetic acid **40** using enzyme.[23] Lipase was used to hydrolyse the ester **40**. The S(+) isomer did not under go hydrolysis. The S(+) isomer (**42**) was then reduced using LAH does give compound **43**. The alcohol **43** was then treated with TMSCl, sodium iodide in acetone to give iodoacetonide **44**. The iodo acetonide **44** was then alkylated to benzylmethylmalonate to give compound **45**. Debenzylation was performed using

Palladium charcoal in hydrogen atmosphere to afford acid **46**. Decarboxylation of **46** by heating furnished diacetonide-ester **47**, which was hydrolysed in acidic condition to give the diol-ester **48**, which was converted to lipoic acid in three steps.

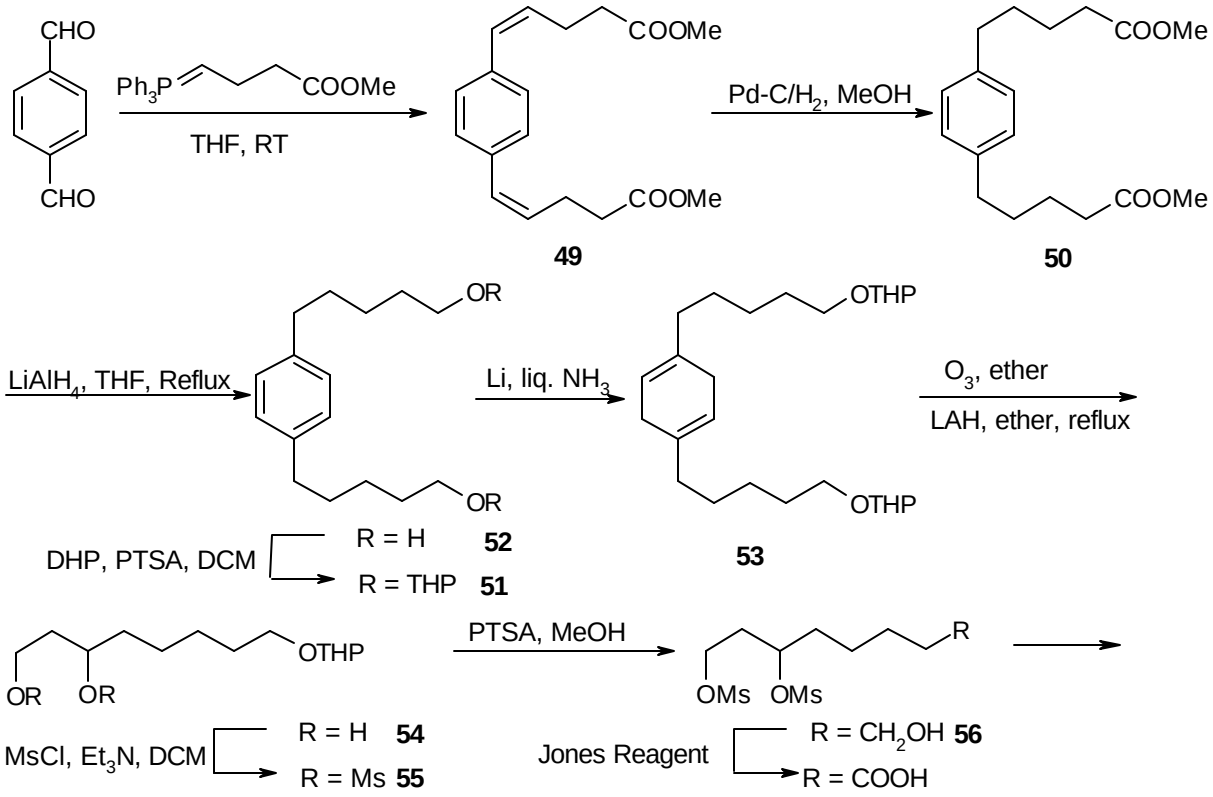


Scheme 10

Rao, B. V synthesis

Preparation of two moles of 1,3 diol precursor **53** from the Birch reduction product **52** was the key step (Scheme 11).[24] Wittig reaction of dihydrophthalaldehyde with the ylide obtained from (3-carbomethoxy) propyl triphenyl phosphonium bromide in THF gave the olefinic derivative **37** as a mixture of *cis* and *trans* isomers. Hydrogenation of **49** with Pd-C followed by reduction with LAH gave the diol **51**, which was subsequently converted to the di-THP ether **52**. Ozonolysis of 1,4 diene product **53** and quenching the ozonide with LAH gave **54**. Two molecules are generated from

benzene ring in this synthesis. Conversion of **54** to the dimesylate **55** was accomplished using triethyl amine and mesyl chloride. Hydrolysis of THP ether moiety in **55** yielded primary alcohol **56**, which upon Jones oxidation gives racemic α-Lipoic acid.

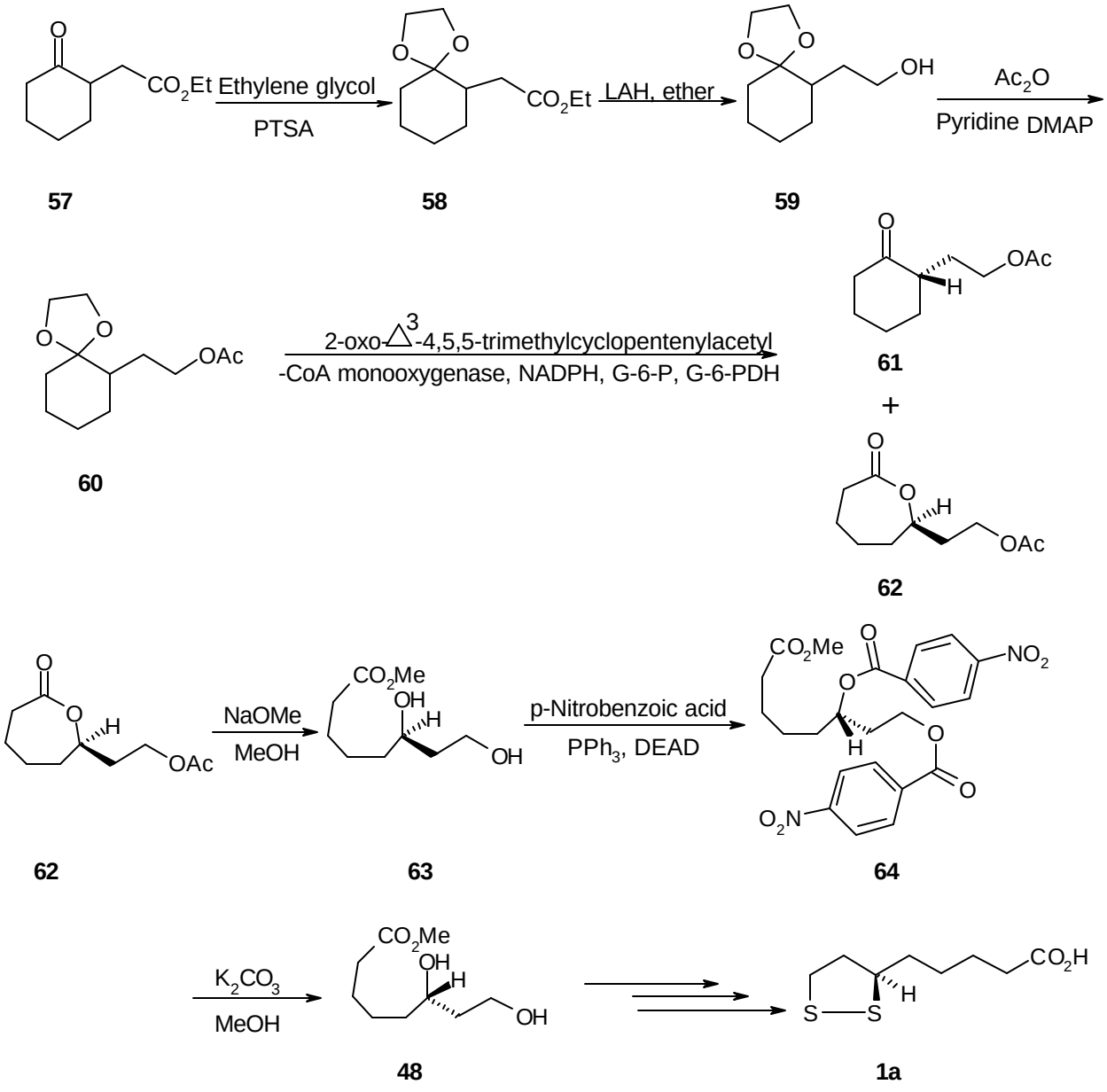


Scheme 11

Adger synthesis

Adeger *et al* have used enzyme for enantioselective Bayer-Villiger oxidation. Thus starting from cyclohexanone, alkylation was done at a position *via* an enamine. The product **57** thus obtained was then protected with ethylene glycol to get **58**. The ester of acetal **58** was then reduced using LAH to give alcohol **59**, which was then protected as acetate using acetic anhydride. Bayer- Villiger oxidation was performed on this substrate using 2-oxo-Δ^3-4,5,5,trimethylcyclopentenylacetyl-CoA monooxygenase. The lactone obtained was then subjected for hydrolysis using sodium methoxide in methanol to furnish the diol-ester **64**. The diol ester has an inverted configuration as per the

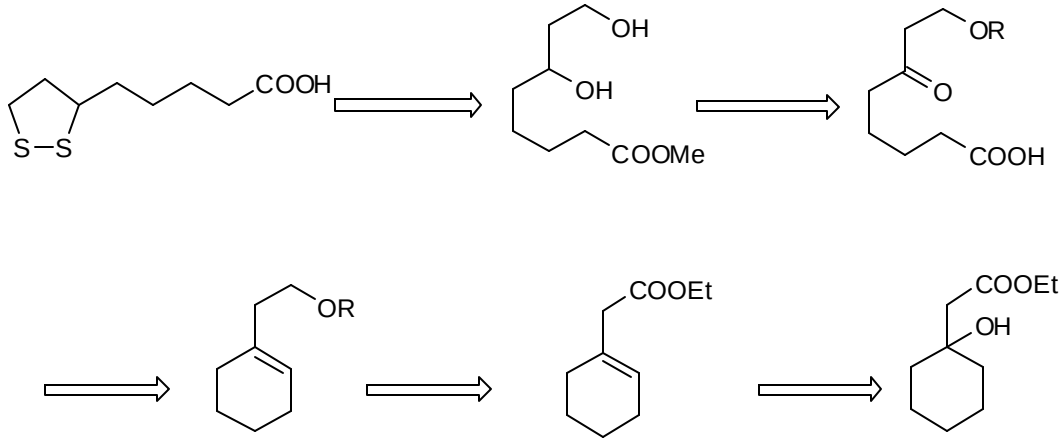
requirement of R (+) lipoic acid. Configuration was corrected by doing a Mitsonobu reaction and hydrolysis with potassium carbonate to give the correct configuration of diol-ester, which was then converted to lipoic acid in three steps.



Scheme 12

1.4.2 Present Work

The previous section (1A) dealt with the usage of zinc and chloroester as a modification to Reformatsky reaction. In order to establish the utility of this protocol our idea was to apply this protocol in the synthesis of a molecule. Lipoic acid is a molecule that has invited a great lot of interest with so many syntheses being reported. A retro synthetic analysis of lipoic acid revealed that (1-hydroxy-cyclohexyl)-acetic acid ethyl ester could serve as the starting material for the synthesis of lipoic acid.(Scheme 13).

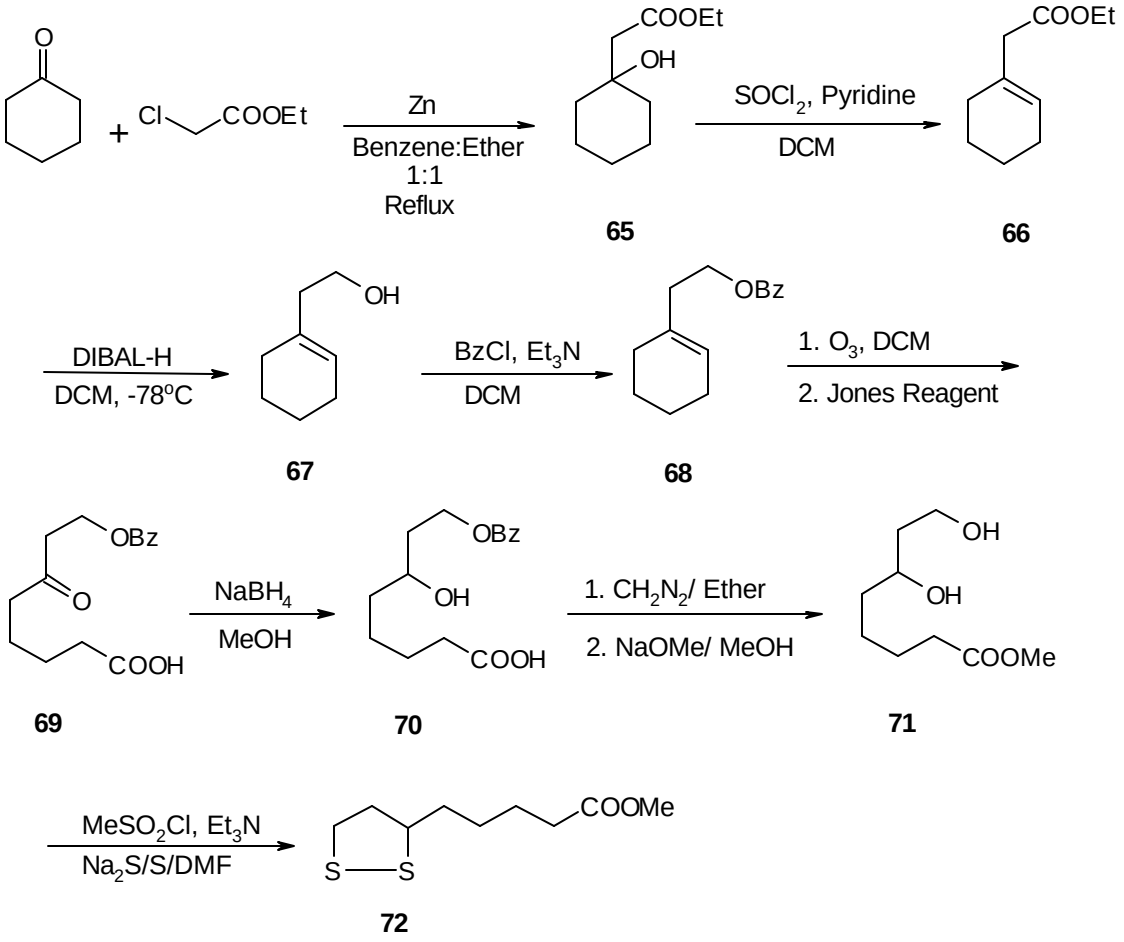


Scheme 13

Looking at the importance of lipoic acid as vital cofactor in animals, it was therefore thought to pursue the synthesis of lipoic acid.(scheme 14)

Cyclohexanone was taken and our protocol of modified Reformatsky was done and the hydroxy product **65** was obtained. The hydroxy ester **65** was subjected to elimination using thionyl chloride and pyridine. The olefin ester **66** obtained was subjected to reduction with DIBAL-H at $-78^{o}C$ to give olefin alcohol **67**. Alcohol was then protected as benzoate using benzoyl chloride and triethylamine. The benzoate **68** was then subjected to ozonolysis followed by oxidation using Jones reagent to furnish **69**. Compound **69** was then subjected to reduction with sodium borohydride, to selectively reduce the ketone. The acid thus obtained was then esterified using diazomethane and the benzoate ester was hydrolyzed with sodium methoxide. Taking care that methyl ester remains intact. The diol ester **71** is a key intermediate in the synthesis for lipoic acid.

Mesylation followed by the treatment with sodium sulphide and sulphur gave methyl lipoate.



1.4.3 Results and discussion

Ethyl chloroacetate was added to zinc to generate the Reformatsky reagent and to which cyclohexanone was added later. Care was taken to perform the reaction with vigorous stirring under anhydrous conditions. Otherwise formation of cyclohexanone dimer which is a competing reaction predominates. Appearance of ethyl ester peaks and singlet around 2d confirmed the formation of the product **65**. IR spectrum also supported the evidence by revealing the OH peak. Hydroxy ester was then subjected to elimination using thionyl chloride and pyridine. Pyridine was added and care was taken that the reaction mixture was cooled well and thionyl chloride was added dropwise. The reaction was highly exothermic. The appearance of olefinic peak around 5d indicated the presence

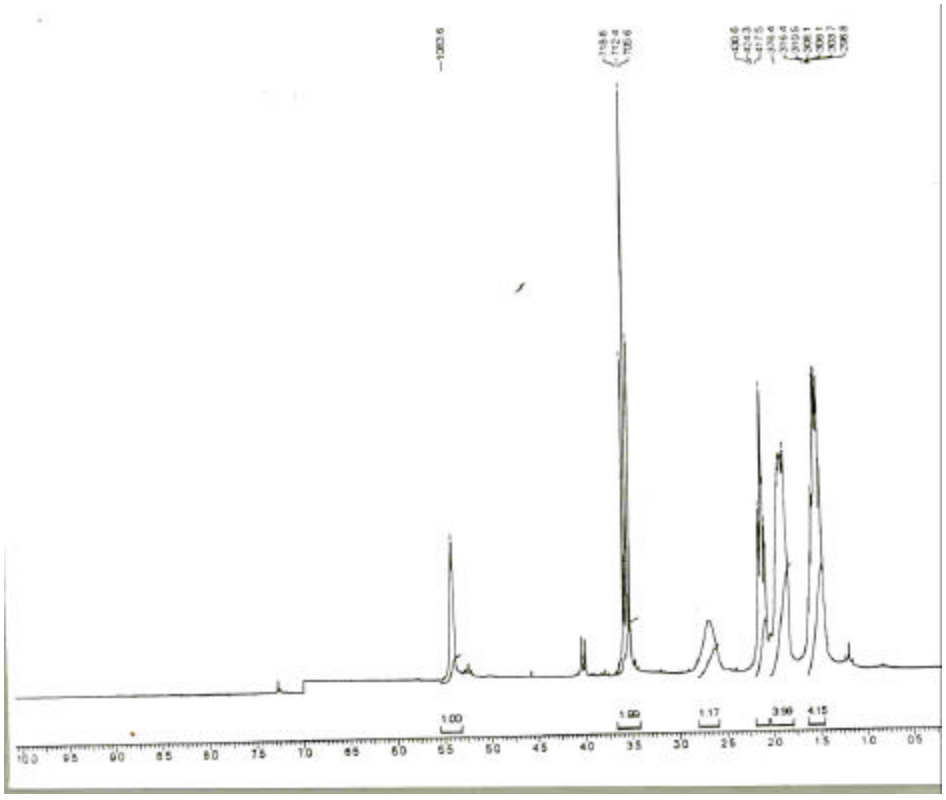
of 66. The product obtained is a sweet smelling compound. Then **66** was subjected to DIBAL-H reduction. The choice of DIBAL-H was to take care that the double bond remains intact and selective reduction of ester to alcohol takes place. Reaction was carefully carried at -78^{o}C. While removing the solvent under *vacuuo* care was taken that the water bath temperature was not very high, otherwise **67** starts distilling along with toluene. The disappearance of the singlet around 2d and the appearance of a triplet at 3.6d and the olefin proton remaining unmoved indicated the presence of the product **67**. Simple benzoate protection of the alcohol was done using benzoyl chloride and triethylamine. Cleavage of double bond was done using ozonolysis at -78^{o}C. Extreme care was taken by cooling the reaction mixture below -78^{o}C. After quenching the reaction with dimethyl sulphide reaction mixture was left so as to come to room temperature on its own. The crude product obtained was subjected to oxidation with Jones reagent. The **69** obtained after chromatography showed 3peaks in ^{13}C NMR in the carbonyl region (166.5, 179.1, and 207.3), corresponding to three carbonyls present in the molecule. The compound **70** was then subjected to reduction with $NaBH_4$. Disappearance of one of the carbonyls in ^{13}Cspectra and appearance of a new peak at 68.6 confirmed that the carbonyl was reduced. Esterification using diazomethane was done with utmost care. After addition of diazomethane the reaction was left overnight to ensure the evaporation of excess diazomethane. Debenzoylation was done with sodium methoxide in methanol. Conditions maintained for this reaction were absolutely dry. Reaction mixture was quenched with acidic resin (IR 120). The diol ester obtained after work up is a key intermediate in the synthesis of lipoic acid. The diol was converted to lipoic acid via dimesylate.

1.4.4 Conclusions

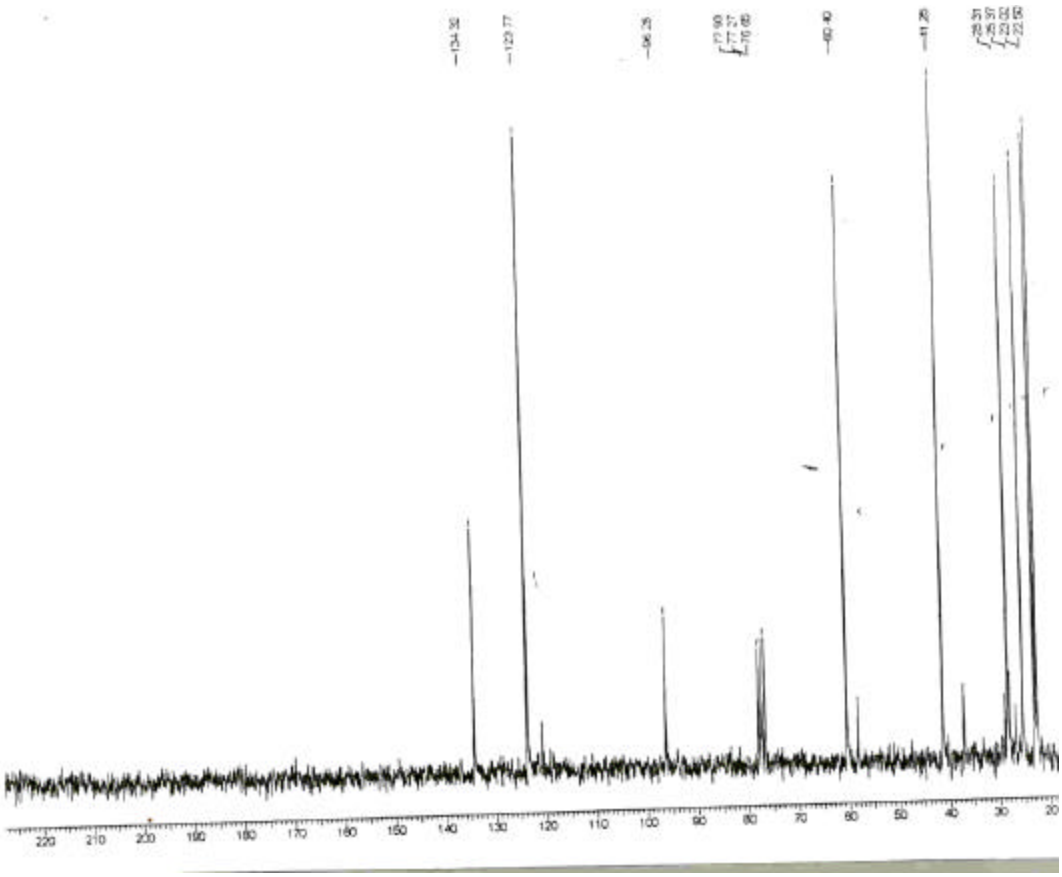
A practical synthesis of (±) lipoic acid has been achieved starting from readily available starting materials like cyclohexanone and ethyl chloroacetate.

The efficiency of chloroester to participate in Reformatsky reaction has been successfully exploited in the synthesis of lipoic acid.

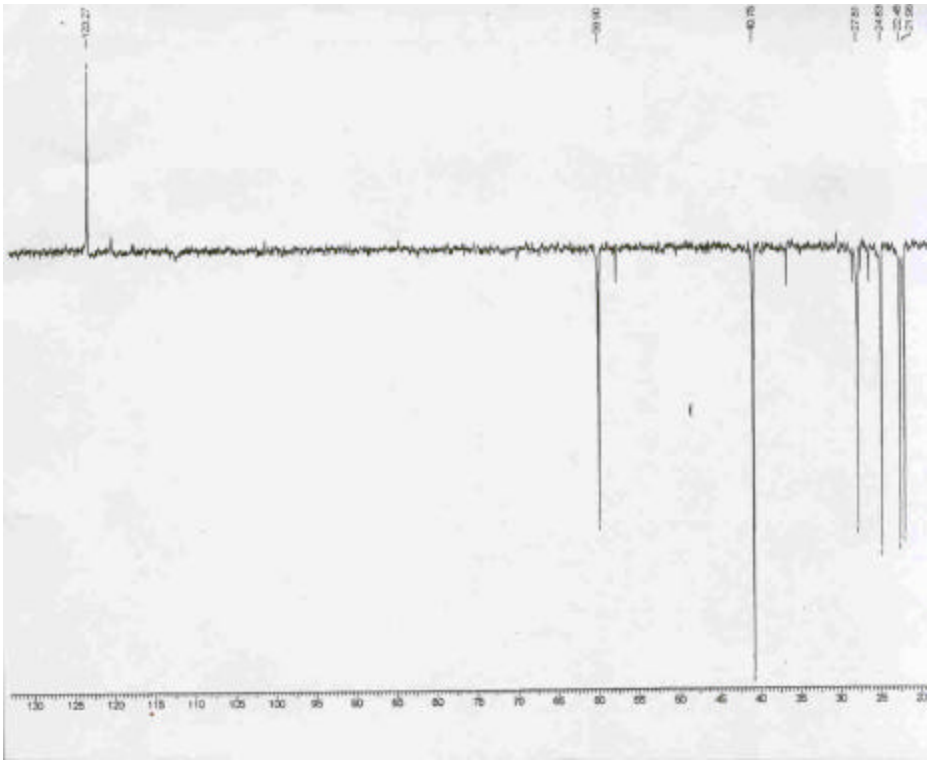
Since the synthesis involves prochiral carbonyl intermediate, it has the potential of being reduced to optically active alcohol by enzymatic or chemical means thus giving access to optically pure lipoic acid.



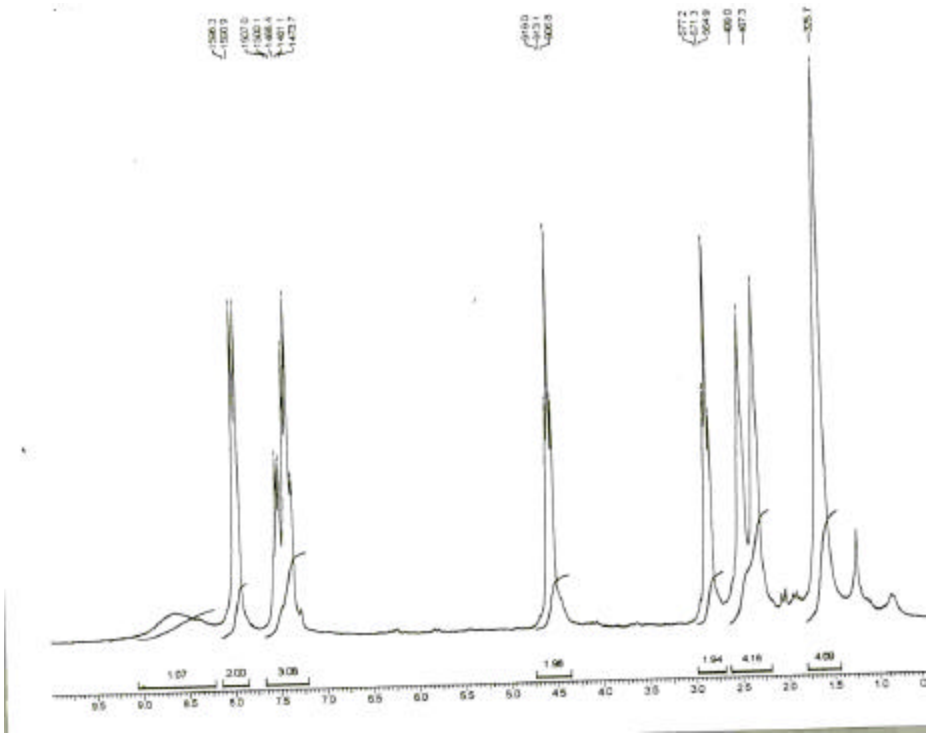
^{1}H NMR of 2-Cyclohex-1-enyl-ethanol (200 MHz, $CDCl_3$)



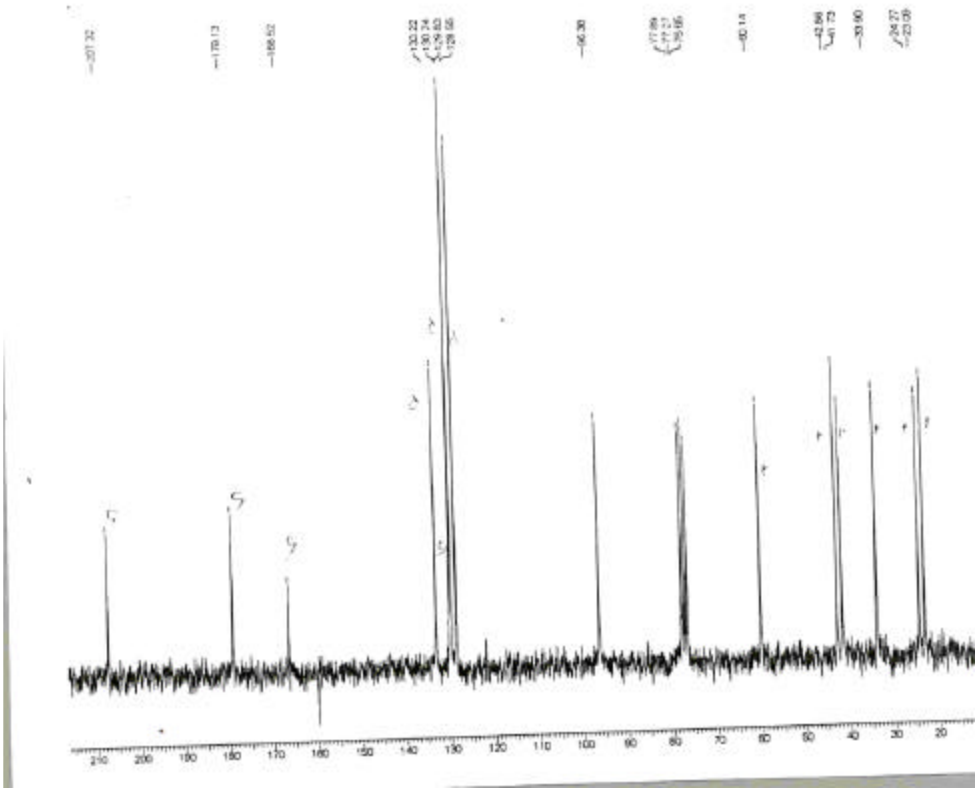
^{13}C NMR of 2-Cyclohex-1-enyl-ethanol (50 MHz, $CDCl_3$)



DEPT of 2-Cyclohex-1-enyl-ethanol (50 MHz, $CDCl_3$)



^{1}H NMR of Benzoic acid 7-carboxy-3-oxo-heptyl ester (200MHz, $CDCl_3$)



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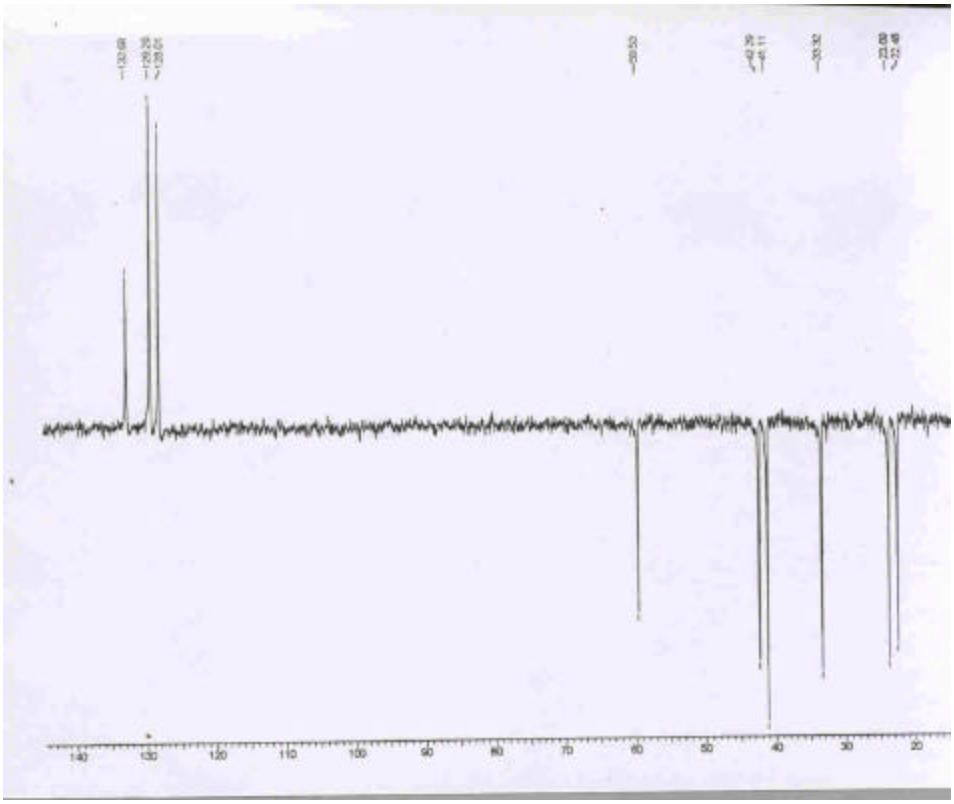
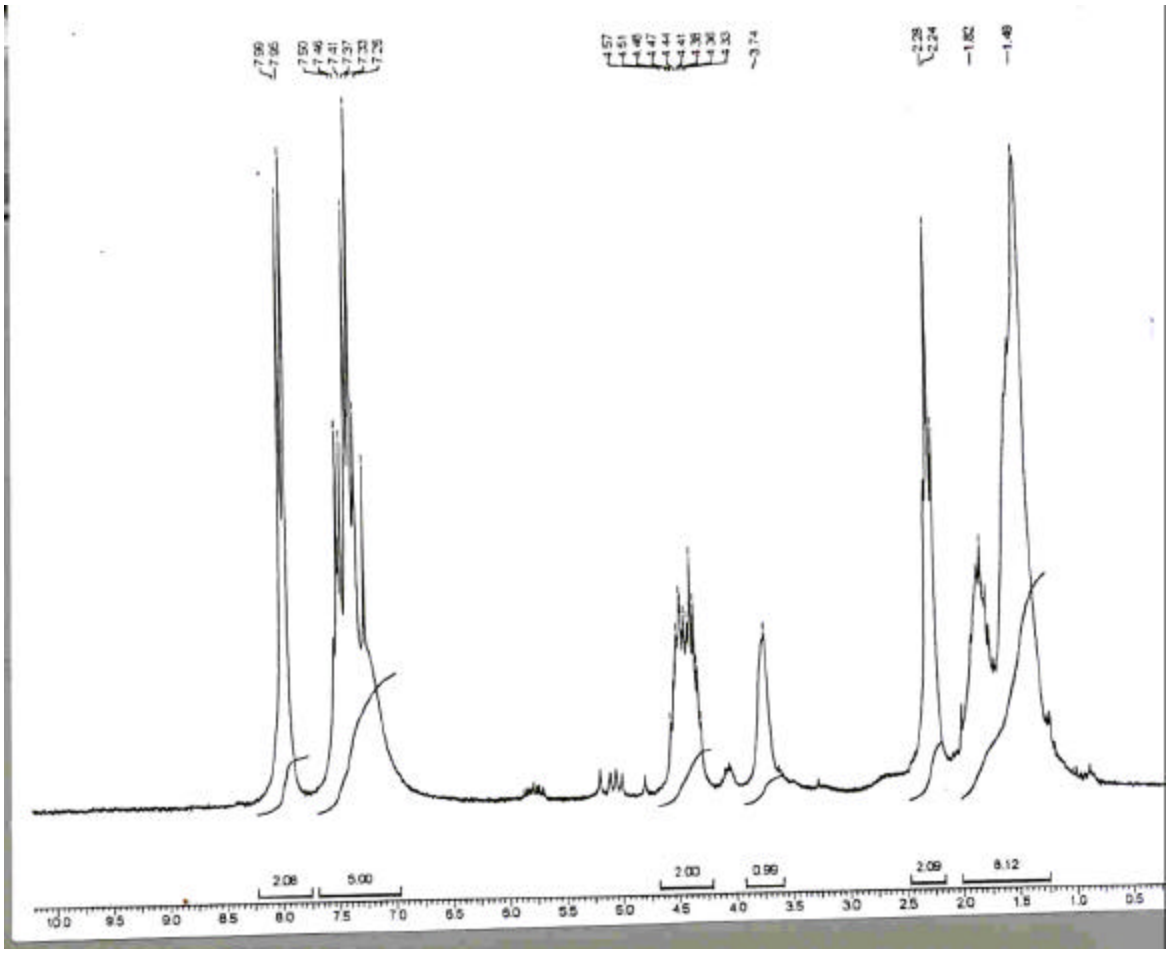
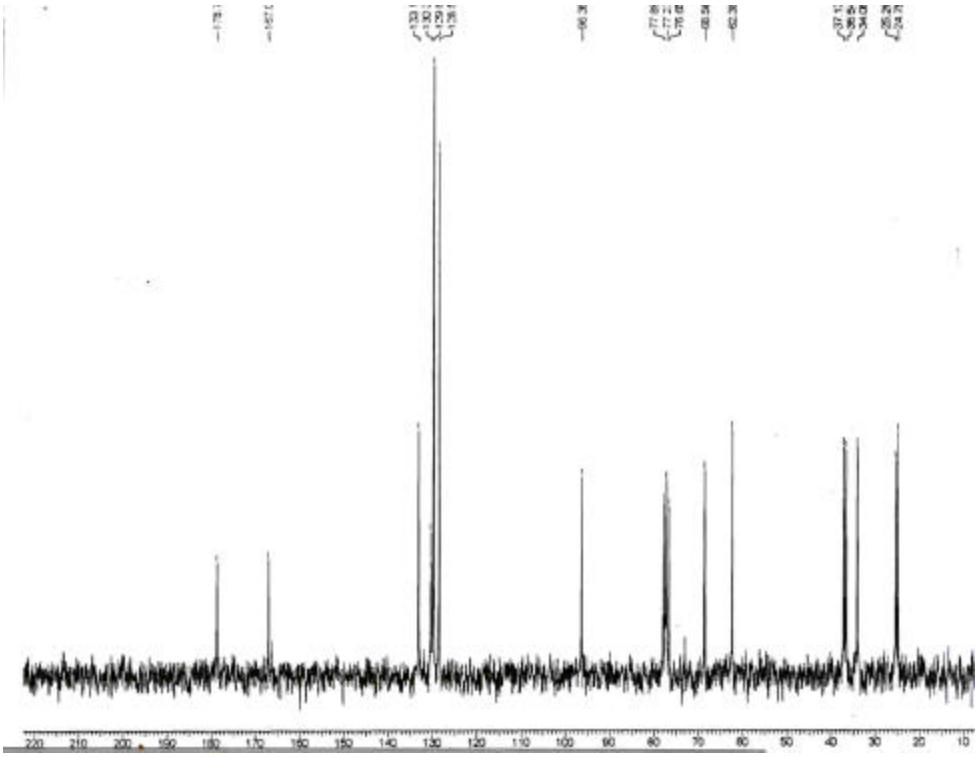


DEPT of Benzoic acid 7-carboxy-3-oxo-heptyl ester (50MHz, $CDCl_3$)



^{1}H NMR of Benzoic acid 7-carboxy-3-hydroxy-heptyl ester (200MHz, $CDCl_3$)



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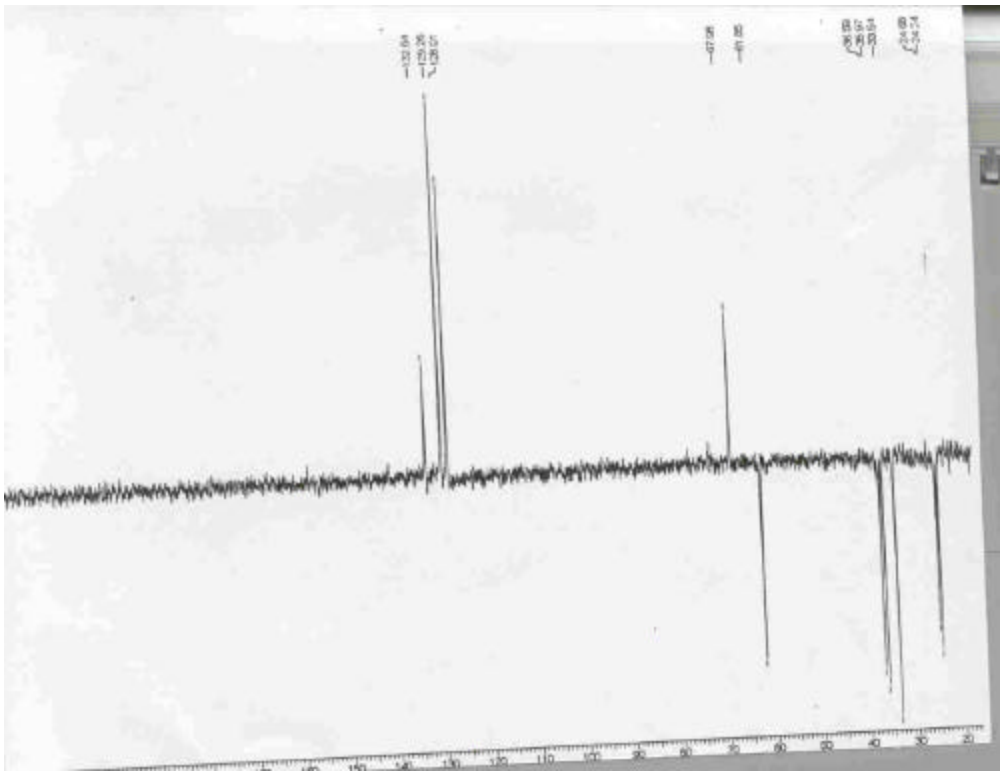
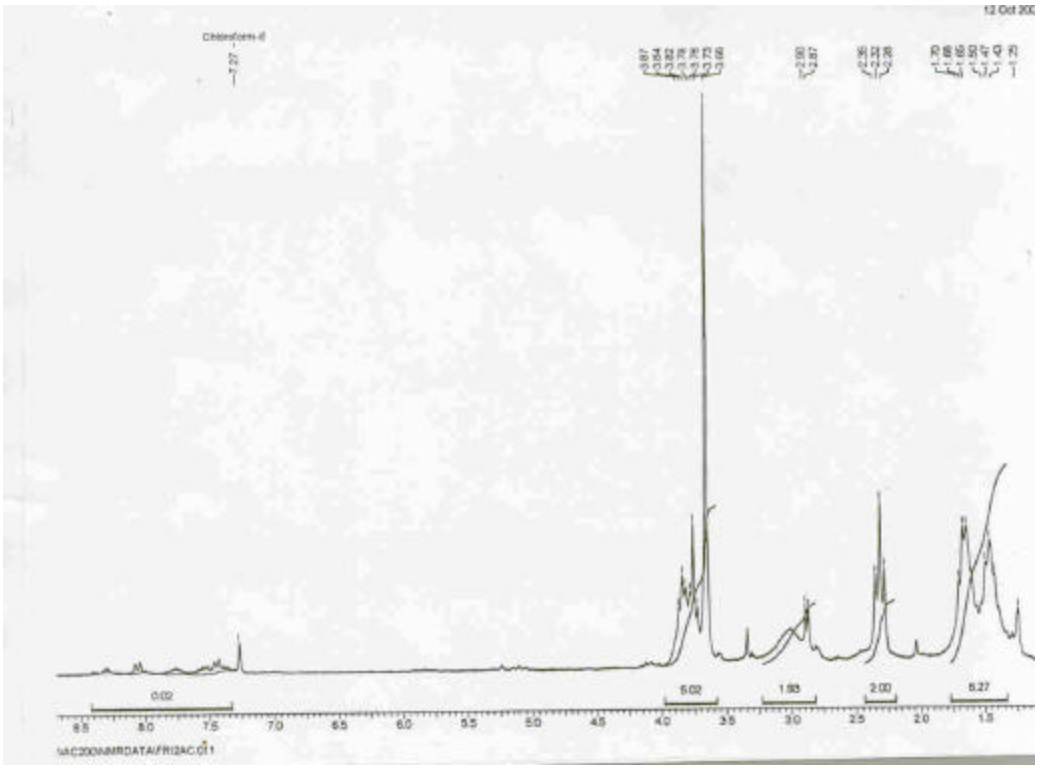
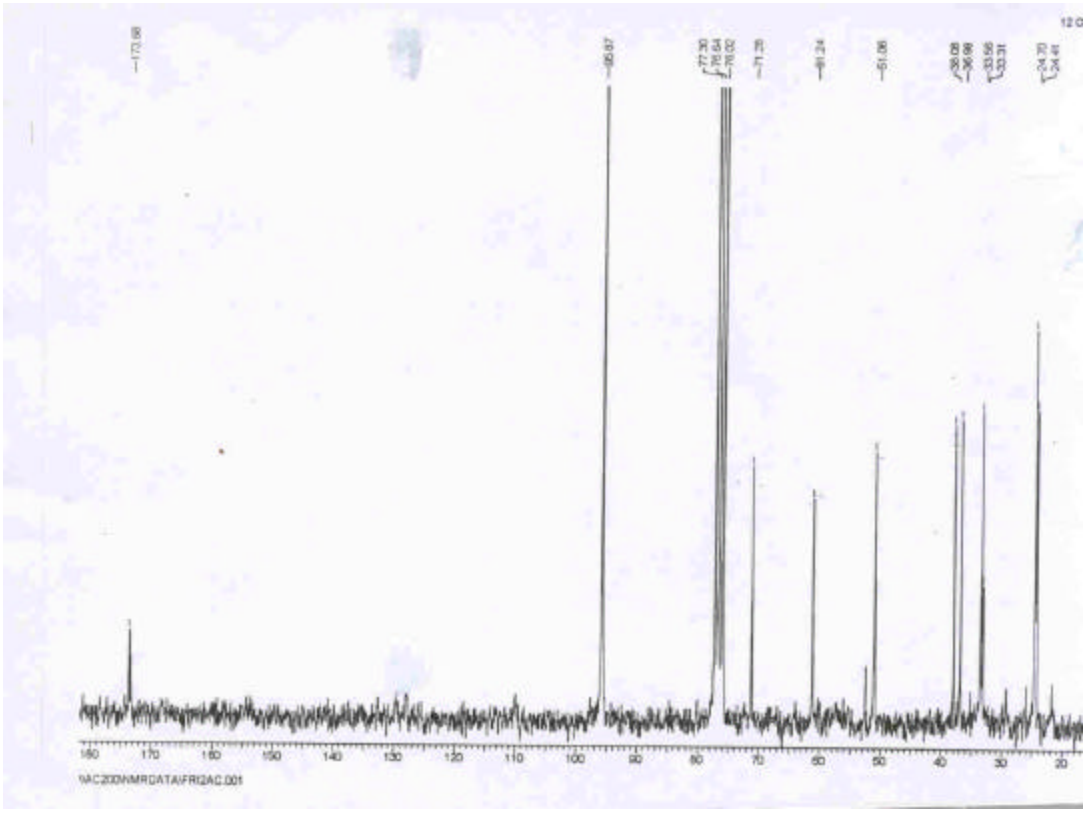


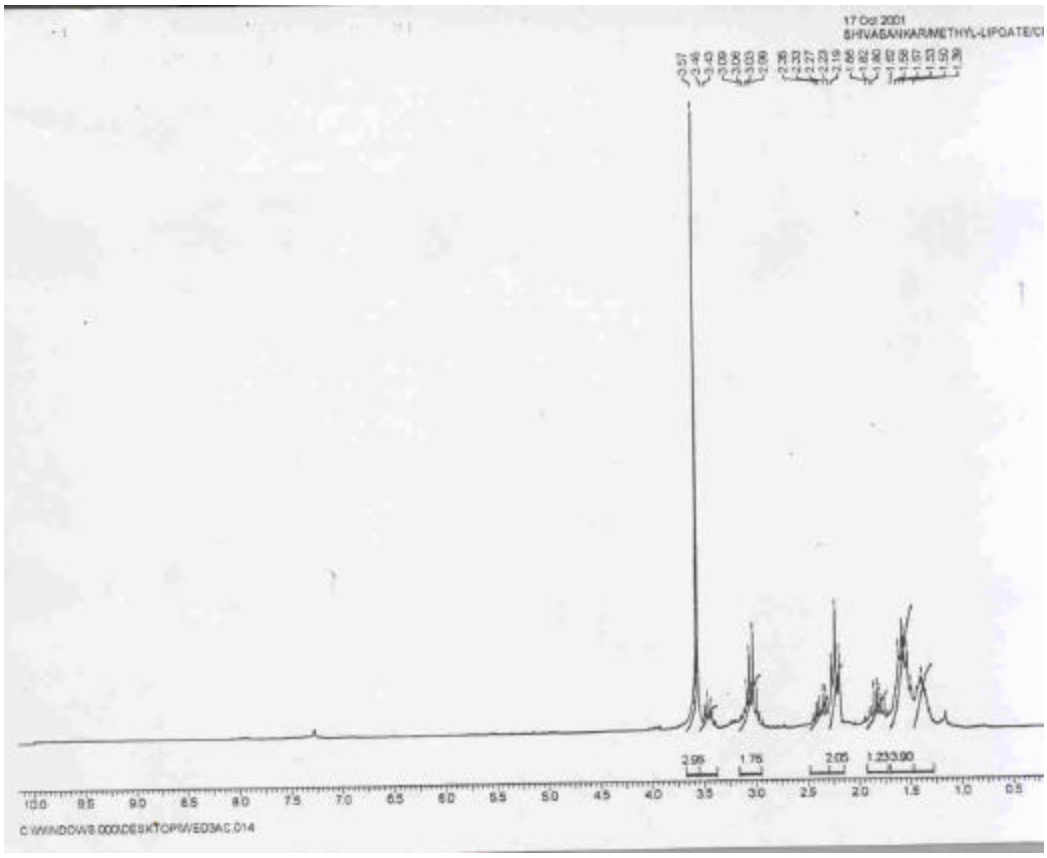
DEPT of Benzoic acid 7-carboxy-3-hydroxy-heptyl ester (50MHz, $CDCl_3$)



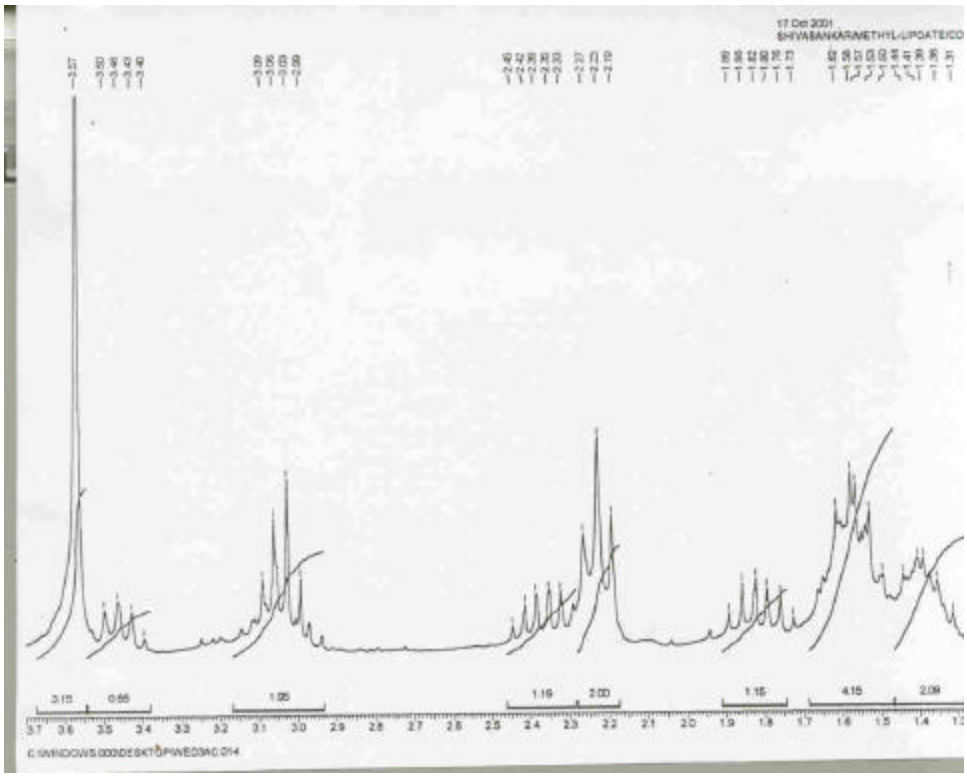
^{1}H NMR of 6-8-dihydroxy-octanoic acid methyl ester (200 MHz, $CDCl_3$)



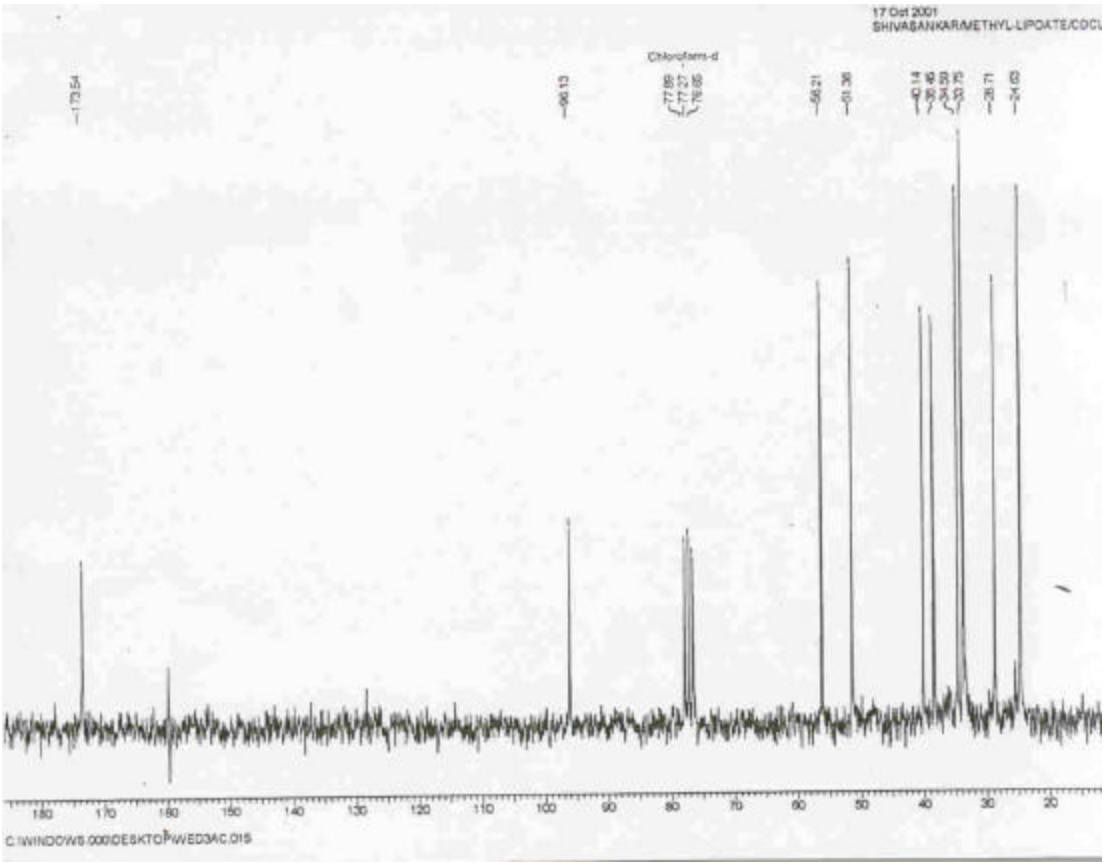
^{13}C NMR of 6-8-dihydroxy-octanoic acid methyl ester (50 MHz, $CDCl_3$)



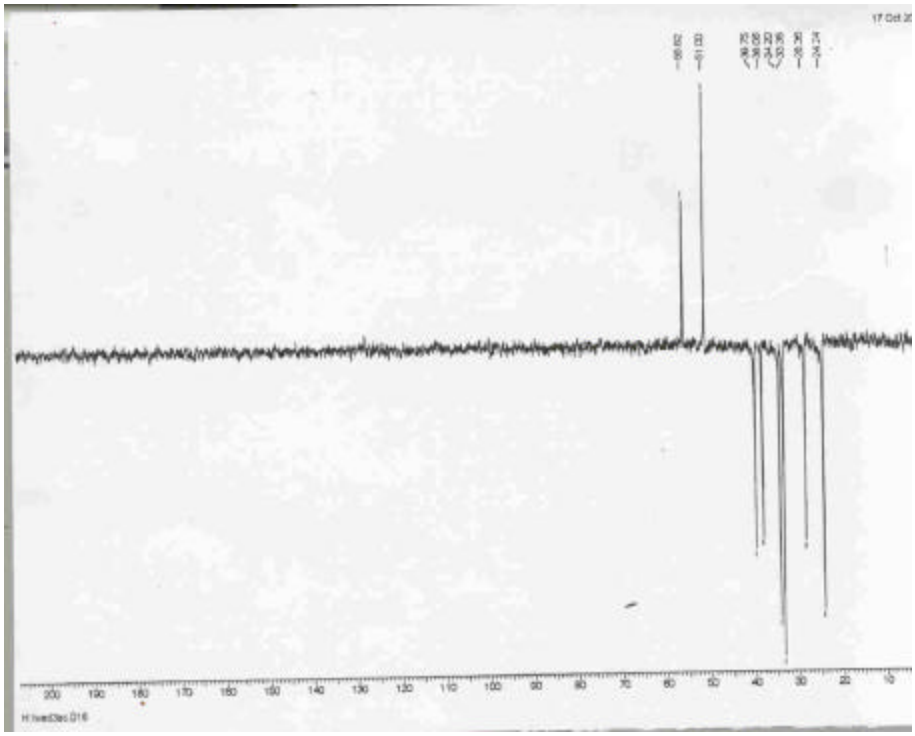
^{1}H NMR of Methyl Lipoate (200 MHz, $CDCl_3$)



^{1}H NMR of Methyl Lipoate (expanded) (200 MHz, $CDCl_3$)



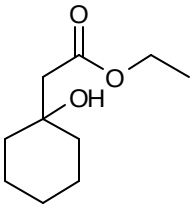
^{13}C NMR of Methyl Lipoate (50 MHz, $CDCl_3$)



DEPT of Methyl Lipoate (50 MHz, $CDCl_3$)

Experimental

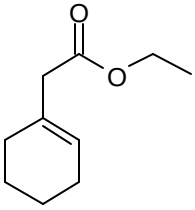
1. **1-(Hydroxy-cyclohexyl)-acetic acid ethyl ester (65)**



Procedure: Zinc (830mg, 12.8mmol) was taken in a 50ml two-necked round bottom flask attached with a reflux condenser and septa. Reaction vessel was evacuated and flushed with argon and set to argon atmosphere. 15ml of 1:1 mixture of dry benzene and ether was added. Reaction was set for vigorous stirring. Ethyl chloroacetate (750mg, 6.12 mmol) was added dropwise, followed by a crystal of Iodine for initiation of the reaction. Cyclohexanone (500 mg, 5.1 mmol) was added dropwise after 15 minutes. The reaction was set to reflux at 80^{o}C. Completion of the reaction was monitored by TLC (10% Ethyl acetate in pet ether). Reaction was quenched after 6hrs with 10% hydrochloric acid. The compound was extracted in ether and washed with dil. HCl (1×5ml), followed by water (2×10ml). The organic layer was combined and dried over sod. sulphate, and concentrated in vacuum. The product was then chromatographed to furnish 616mg (65%) of pure hydroxy ester.

Yield:	66%
Molecular formula:	$C_{10}H_{18}O_3$
^{1}H NMR:	1.2 (t, 3H, J = 7Hz), 1.3-1.8 (m, 10H), 2.4 (s, 3H), 3.8(br, 1H), 4.1 (q, 2H, J= 7Hz)

2. **Cyclohex-1-enyl acetic acid ethyl ester (66)**



Procedure: 1-(Hydroxy-cyclohexyl)-acetic acid ethyl ester (500mg, 2.7mmol) was taken in a 50ml two necked round bottom flask attached with an additional funnel and a guard

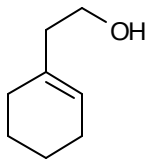
tube. Dry DCM (20ml) was added to the compound. Dry pyridine (255mg, 3.2 mmol) was added and the reaction mixture was cooled to 0^oC using ice-salt mixture. After 10min, thionyl chloride (353mg, 3.0mmol) was added dropwise for 10 minutes. Reaction was monitored by TLC using 5% ethyl acetate and pet ether. The reaction was stirred for 30 minutes and quenched by addition of ice-cold water, followed by DCM 20 ml. The organic layer was separated and washed with 5%dil. HCl (2×5ml), water (2×10ml), 5% sod. bicarbonate (1×5ml). Organic layer was dried over anhydrous sodium sulphate and concentrated in vacuum. The residue thus obtained was chromatographed (SiO_2) with 5% ethyl acetate and pet ether to furnish 388mg (86%) of pure product.

Yield: 86%

Molecular formula: $C_{10}H_{16}O_2$

^1H NMR: 1.2 (t, 3H, J = 7Hz), 1.3-2.1 (m, 8H), 2.9 (s, 2H), 4.1 (q, 2H, J= 7Hz), 5.5 (m, 1H)

3. **2-Cyclohex-1-enyl-ethanol (67)**

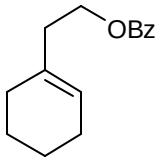


Procedure: Cyclohex-1-enyl acetic acid ethyl ester (500mg, 3.0mmol) was taken in an 50ml dry two-necked round bottom flask fitted with a two way stop cork and a septa. The round bottom flask was flushed with argon. Dry DCM (20ml) was added to the compound and was set for cooling at -78^oC in cryostat. 3M solution of DIBAL-H (3ml, 9.0mmol) was added dropwise with constant stirring. After complete addition of the DIBAL-H solution the reaction was stirred for 3hrs at -78^oC. Reaction was monitored on TLC. Reaction was then gradually quenched with 3ml of 5:1 Methanol- water mixture. Reaction mixture was allowed to come to room temperature. It was filtered through celite and then concentrated in vacuum. 244mg (65%) of 2-Cyclohex-1-enyl-ethanol was obtained.

Yield: 65%

Molecular formula:	$C_8H_{14}O$
^{1}H NMR:	1.2-2.0 (m, 8H), 2.25(t, 2H, J=6Hz), 3.6 (t, 2H, J=6Hz), 5.5 (m, 1H).
^{13}C NMR:	22.5(t), 23.0(), 25.4(t), 28.3(t), 41.3(t), 60.4(t), 123.7(d), 134.3(s).
IR (Neat):	3350, 2924, 1439.

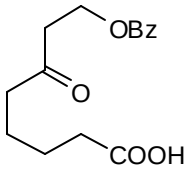
4. **Benzoic acid 2-cyclohex-1-enyl-ethyl ester (68)**



Procedure: 2-Cyclohex-1-enyl-ethanol (500mg, 4.0mmol) was taken in a 50ml round bottom flask with a guard tube and addition funnel. Dry DCM (20ml) was added to the compound followed by triethylamine (481mg, 4.8mmol). The reaction was cooled to 0°C in an ice-bath. Benzoyl chloride (613mg, 4.4mmol) was added dropwise. Reaction was monitored by TLC and after completion quenched with water and the product was extracted in DCM. Organic layer was washed with 2% aqueous sod. bicarbonate solution(3×10ml). Organic layer was dried over anhydrous sodium sulphate and concentrated in vacuum to furnish 840mg (92%) of benzoic acid 2-cyclohex-1-enyl-ethyl ester.

Yield:	92%
Molecular formula:	$C_{15}H_{18}O_2$
^{1}H NMR:	1.2-2(m, 8H), 2.25(t, 2H, J=6Hz), 4.2(t, 2H, 6Hz), 5.5 (m, 1H)
IR(neat):	3063, 2930, 2672, 1685, 1595, 1419.
Mass:	230.

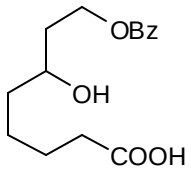
5. **Benzoic acid 7-carboxy-3-oxo-heptyl ester (69)**



Procedure: A solution of benzoic acid 2-cyclohex-1-enyl-ethyl ester (500mg, 2.2mmol) was taken in a 100ml round bottomed flask in 30ml of dry DCM. Reaction mixture was cooled to -78^{o}C and ozone was bubbled through. Persistence of blue coloration was seen at the end of the reaction. Oxygen was passed for and additional 10minutes and later N_2 was passed for 10minutes. 2ml of dimethyl sulphide was added. Reaction mixture was allowed to attain room temperature. 10ml of water was added to the reaction mixture and organic layer was separated and concentrated in vacuum. The crude product thus obtained was put for Jones oxidation at 0^{o}C in acetone. The reaction was quenched with isopropanol and filtered through celite and concentrated in vacuum to furnish 488mg (85%) of Benzoic acid 7-carboxy-3-oxo-heptyl ester.

Yield:	85%
Molecular formula:	$C_{15}H_{18}O_5$
^{1}H NMR:	1.65(m, 4H), 2.4(t, 2H, J=7Hz), 2.51(t, 2H, J=7Hz), 2.87(t, 2H, J=6Hz), 4.59(t, 2H, J=6Hz), 7.4-7.6(m, 3H), 8.0(d, 2H, J=8Hz).
^{13}C NMR:	23.1(t), 24.3(t), 33.9(t), 41.7(t), 42.9(t), 60.1(t), 128.5(d), 129.8(d), 130.24(s), 133.2(d), 166.5(s), 179.1(s), 207.3(s).
IR(CHCl3):	3438, 3020, 2956, 1713, 1414.

6. **Benzoic acid 7-carboxy-3-hydroxy-heptyl ester (70)**

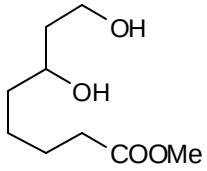


Procedure: Benzoic acid 7-carboxy-3-oxo-heptyl ester (500mg, 1.9mmol) was taken in a single necked round bottom flask. 10ml of methanol was added and reaction mixture was cooled to 0^{o}C in an ice-bath. Sodium borohydride (135mg, 3.6mol) was added slowly. The reaction was mointored by TLC in 30% ethyl acetate in pet ether. Reaction was quenched with saturated ammonium chloride solution. The product was extracted in ethyl acetate. The organic layer was dried over sodium sulphate and concentrated with vacuum.

The product obtained was chromatographed (SiO_2) using 30% pet ether and ethyl actetate as an eluent to furnish 453mg (90%) of benzoic acid 7-carboxy-3-hydroxy-heptyl ester.

Yield:	90%
Molecular formula:	$C_{15}H_{20}O_5$
^{1}H NMR:	1.25-2.0(m, 8H), 2.3(t, 2H, J=6Hz), 3.75(m,1H), 4.34-4.57(m, 2H), 7.07(br, 1H), 7.4-7.6(m, 3H), 8.0(d, 2H, J=8Hz).
^{13}C NMR:	24.8(t), 25.2(t), 34.1(t), 36.5(t), 37.1(t), 62.4(t), 68.6(t), 128.5(d), 129.8(d), 130.4(s), 133.1(d), 167.1(s), 178.7(s).
IR($CHCl_3$):	3446, 2934, 1711, 1599

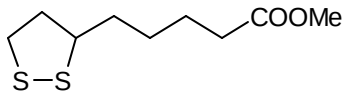
7. **6-8-dihydroxy-octanoic acid methyl ester (71)**



Procedure: Benzoic acid 7-carboxy-3-hydroxy-heptyl ester (500mg, 1.9mmol) was taken in ether and cooled to 0^{o}C. Diazomethane (~ 7eq.) was added to the compound. Reaction mixture was left over night. Reaction mixture was then concentrated and the crude product was taken in a 50ml 2-neck round bottom flask attached with a two-way stop cork and a stopper. 10ml of dry Methanol was added to the compound followed by 15mg of sodium methoxide. Reaction was stirred for 3-4hrs at 0^{o}C. Reaction was quenched with acidic resin (IR 120) till the reaction medium was neutral. The reaction mixture was then filtered and concentrated in vacuum. After chromatography 340mg (91%) of 6-8-dihydroxy-octanoic acid methyl ester was obtained.

Yield:	91%
Molecular formula:	$C_9H_{18}O_4$
^{1}H NMR:	1.2-1.75 (m, 8H), 2.32 (t, 2H, J=6Hz), 2.9 (m, 1H), 3.73(s, 3H), 3.76-3.87(m, 2H)
^{13}C NMR:	24.4(t), 24.7(t), 33.6(t), 37.0(t), 38.1(t), 51.1(t), 71.3(d), 173.7(s)

8. **Methyl Lipoate (72)**



Procedure: 6-8-dihydroxy-octanoic acid methyl ester (300mg, 1.58mmol) was taken in a two necked round bottom falsk attached with a two way stop cork and a septa. 10ml of dry dichlroromethane was added followed by triethylamine (319mg, 3.16mmol). The reaction was cooled at 0^{o}C. Methanesulphonyl chloride (463mg, 3.16mmol) was added dropwise. The reaction was monitored by TLC. The reaction was quenched with 5ml of water. the organic layer was washed with 10ml of 2% aqueous sodium bicarbonate solution. Organic layer was dried over anhydrous sodium sulphate and then concentrated in vacuum. The crude compound was then subjected for the next reaction. Finely ground sodium sulphide monohydrate (410mg, 1.7mmol) and sulphur (54mg, 1.7mmol) were dissolved in dry DMF (5ml). The mixture was heated at 80^{o}C for 24hrs. Then the mixture was stirred at room temperature for 1hr. The reaction mixture was poured into ice cold water ans was extracted in ethylacetate (3×20ml) The combined organic extracts were dried over sodium sulphate and evaporated under reduced pressure to give yellow oil (257mg).

Yield: 60%

Molecular formula: $C_9H_{16}O_2S_2$

^{1}H NMR: 1.3-1.7(m, 1H), 1.8(m, 1H), 2.23(t, 2h, J=8Hz), 2.35(m, 1H), 3.03(m, 2H), 3.43(m, 1H), 3.57(s, 3H)

^{13}C NMR: 24.63(t), 28.71(t), 33.75(t), 34.6(t), 38.45(t), 40.1(t), 51.4(q), 56.2(d), 173.5(s).

IR($CHCl_3$): 2932, 1735, 1435.

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CHAPTER II

SECTION A
Zinc and Iodine: Catalyst for the transesterification

SECTION B
Zinc and Iodine: Reagent for the synthesis of Coumarins

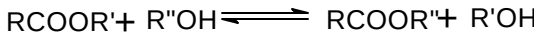
SECTION C
Synthesis of Quinolines: A Diels-Alder approach

SECTION D
Zirconium based Heterogeneous catalyst for Transfer hydrogenation

SECTION A
Zinc and Iodine: Catalyst for the transesterification

2.1.1 Introduction

One of the classic reactions in organic synthesis, transesterification has been enjoying its usage in many laboratories. Some occasions transesterifications are more simpler than the esterification itself. Applications of this reaction are many for example: used in paint industry for curing of alkylated resins, also used for polymerizations *i.e.* ring opening of lactones.[1] A classic reaction would look like (Scheme 1).



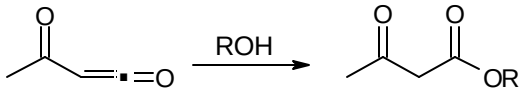
Scheme – 1

As is obvious from the above scheme–1, transesterification reaction is an equilibrium driven reaction. The intention of the reaction condition is to drive it in a forward direction. The forward drive includes mainly the use of various catalysts. Reports include the usage of both acidic as well as basic catalysts. The use of metals and metal chelated compounds for transesterification has now been in the run as a good catalyst for the reaction. Reactions involve mainly the usage of transition metals like Zn, W and Cu.[2]

2.1.2 Transesterification of b-ketoesters

Transesterification of β-ketoesters is the most interesting part of them. With two nucleophilic and electrophilic sites they have proven to be a valuable tool in the synthesis of mainly molecular systems. Synthesis of β-ketoesters via C1-O1 bond formation is generally by the alcoholysis of diketene in presence of a suitable catalyst.[3]

Scheme 2 (Clemens, R. J. *Chem. Rev*. **1986**, *86*, 241)

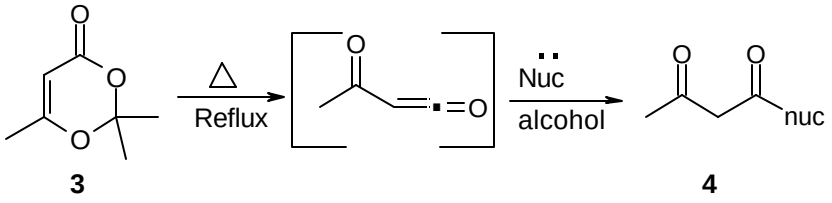


1 **Scheme 2** **2**

Though diketenes are highly toxic and lachrymatory, it still remains most popular and easy mode of preparation of β-ketoesters as it is cost effective and easily available. The other disadvantage of using diketene is that it undergoes decomposition liberating CO_2, also self-condensation in both acidic and basic medium and thereby makes it unattractive for preparation of β-ketoesters.[4]

Modifications to diketene intermediate includes the addition of acidic as well as basic catalysts. Clemens has reviewed this in 1985. He suggested the usage of 2,2,6-trimethyl-4H, 1,3-dioxin-4-one as acylating agents of alcohols.[5]

Scheme 3 (Clemens *et. al J. Org. Chem.*, **1985**, *50*, 2431)

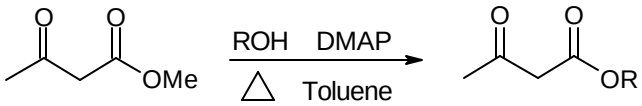


3 **4**

Scheme 3

A modification to the diketene protocol was suggested by Taber *et al*[6] by the usage of DMAP (Scheme 4). This protocol gives valuable results although with some

Scheme 4 (Taber *et. al J. Org. Chem*. **1985**, *50*, 3618)



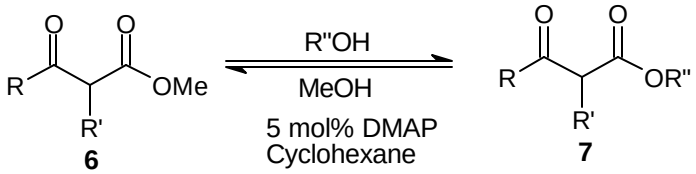
5 **2**

Scheme 4

limitations for instance, non-enolisable β-ketoesters and the formation of esters with tertiary alcohols fail to proceed. The usage of large amount of DMAP adds a disadvantage to the protocol.

A modification of the above protocol has been suggested recently.[7] The modification suggests the simultaneous removal of methanol generated during the

Scheme 5 (Jens *et. al*. *Eur. J. Org. Chem*. **2000**, *8*, 1633)



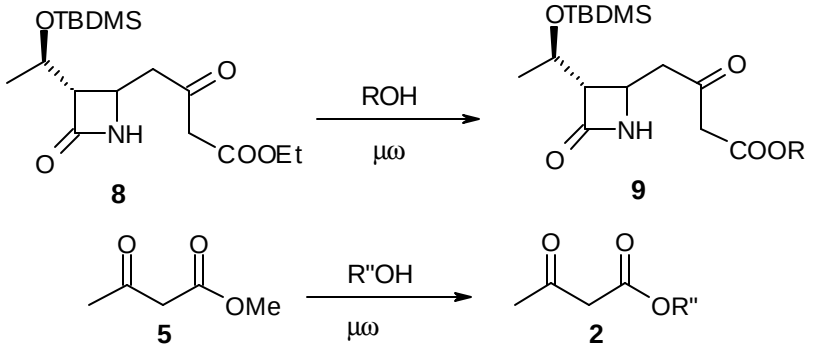
6 **7**

Scheme 5

course of the reaction. In this case only very high boiling alcohols have been used and the duration of the reaction is very high. It takes 9-10hrs for the completion of the reaction. The yields are comparable to the parent protocol.

Recent modifications to transesterification methods include the usage of microwave.[8] Massimo *et al* have reported the usage of microwave. The yields obtained

Scheme 6 (Massimo *et. al. Syn. Comm.* **2000**, *30*, 1725.)

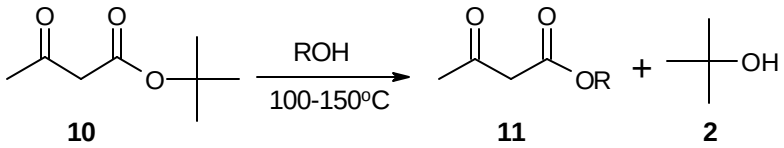


Scheme 6

are good to excellent in some cases. The disadvantage of the process being that only enolizable β-ketoesters gave rise to transesterified products.(Scheme 6)

Witzemann *et al* reported a convenient method for transesterification.[9] The usage of *tert*-butyl acetoacetates makes the reaction 10-20 fold faster than the other less

Scheme 7 (Otera *et. al. J. Org. Chem*. **1991**, *56*, 1713)

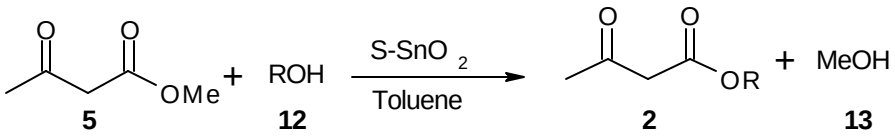


Scheme 7

sterically hindered esters. This reaction however was limited to the use of tert-butyl acetoacetates as starting material, which in turn is very difficult to obtain and hence lacks generality.

Reports from our group on transesterification of β-ketoesters for the first time demonstrated the utility of S-SnO_2 as heterogenous catalyst.[10-11] The reaction condition

Scheme 8 (Chavan et. al. *Tetrahedron Lett*. **1996**, *37*, 233)

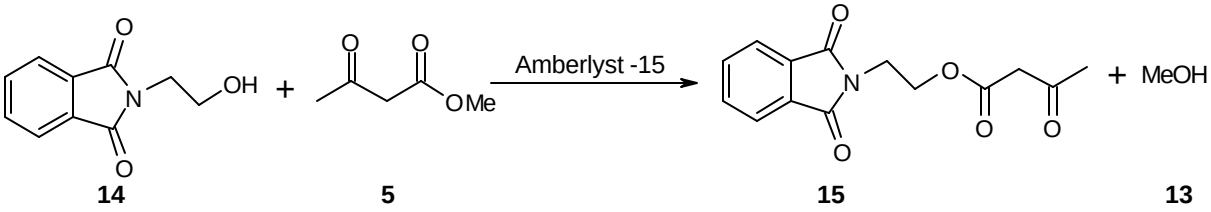


Scheme 8

involving only simple toluene reflux and simultaneous distillation of the lower boiling alcohol. The yields are good to very good in some cases. The other feature of this methodology is that *tert*-butyl esters can also be accessed using this protocol. The recovery of the catalyst is the salient feature in this reaction (Scheme 8).

Usage of Amberlyst –15 as an efficient catalyst for transesterification was also

Scheme 9(Chavan *et. al. Syn. Comm*. **2001**, *31*, 289)

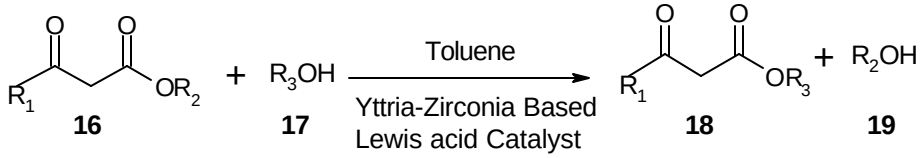


Scheme 9

reported from our group.[12] The conditions remaining same as that of the previous scheme (Scheme 8) involving the simultaneous distillation of the lower boiling alcohol. The transesterification could even be performed on allyl alcohols, which is usually very difficult.

Yttria-Zirconia based catalyst has also been used as an effective and selective catalyst to effect transesterification of β-ketoesters.[13] Wide variety of alcohols has been

Scheme 10 (Kumar *et. al. Synlett* **2000**, 251)



Scheme 10

used. The procedure has also been extended to a wide variety of nucleophiles such as thiols and amines. Note worthy feature here is that unsaturated alcohols of β-ketoesters have also been synthesized.

2.1.3 Present Work

As mentioned earlier, β-ketoesters are very important synthons for various natural syntheses and can be transformed easily into chiral building blocks.[14] The reactions are equilibrium driven and in most of the cases utilize excess of reagent.

The use of zinc has gained popularity of late in effective synthetically useful transformations like ene cyclization,[15] Diels–Alder reaction,[16] synthesis of AF4,[17] synthesis of benzhydrols[18] to add a few. Large organozinc complexes were also reported to transesterify efficiently.[2](figure 1)

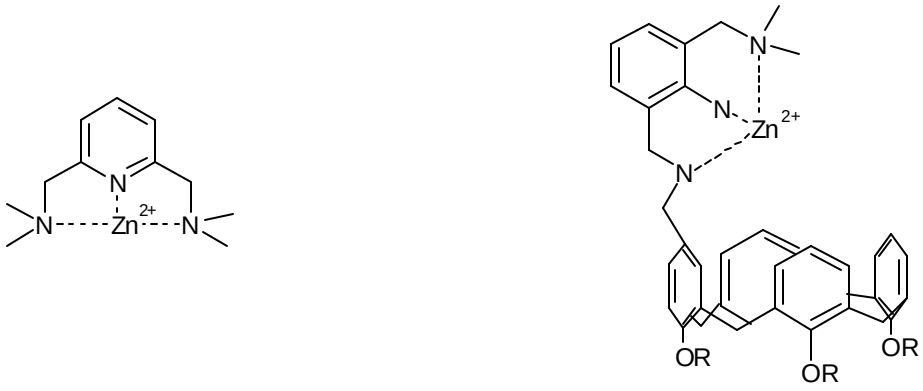
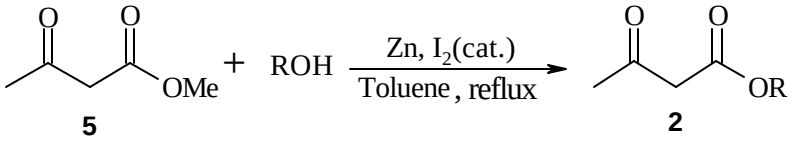


Figure 1



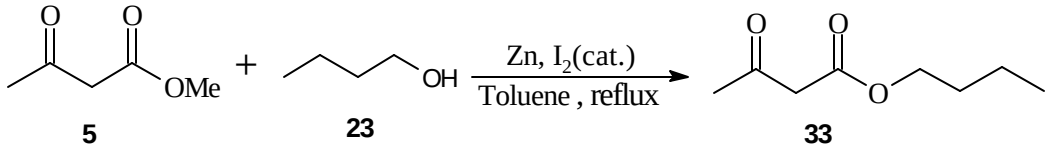
Scheme 12

So it was thought worthwhile to try out a combination of zinc and iodine for transesterification. (Scheme 12)

2.1.4 Results and Discussion

A wide variety of alcohols have been used to transesterify methyl acetoacetate using zinc and iodine to yield the corresponding transesterfied products in moderate to excellent yields. The reaction was pushed in the forward direction by simultaneous distillation of low boiling alcohol (methanol).

In a typical procedure (Scheme 13) mole to mole ratio of methyl acetoacetate, n-butanol was taken in toluene and to the mixture was added 2 equivalents of Zn followed



5 **23** **33**

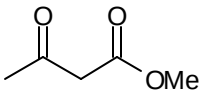
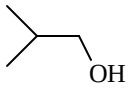
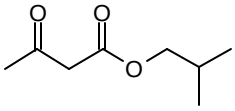
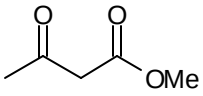
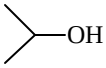
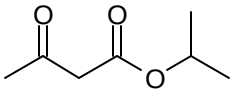
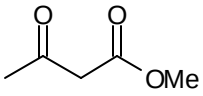
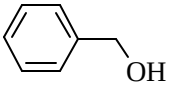
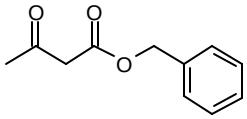
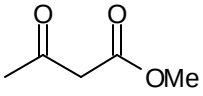
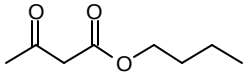
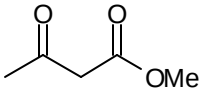
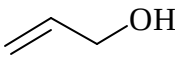
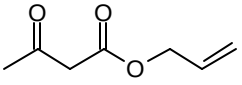
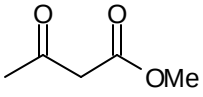
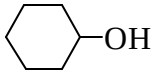
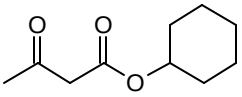
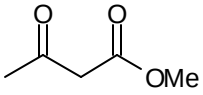
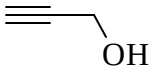
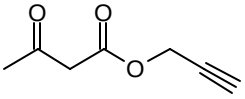
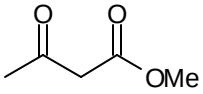
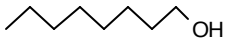
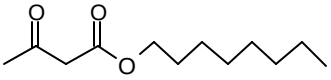
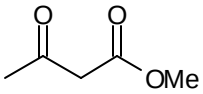
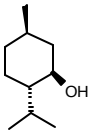
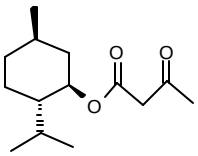
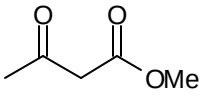
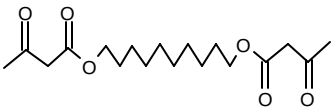
Scheme 13

by catalytic amount of iodine. The reaction was set to distillation so as to remove methanol. The transesterfied product was furnished in 78% yield. The product was characterized by IR, ^{1}H and Mass Spectroscopy. The ^{1}H NMR spectrum displayed the presence of a triplet at 4.1 δ and a singlet at 2.25 δ is corresponding to –OC-CH_2. The disappearance of the –OCH_3 group from methyl acetoacetate confirmed the formation of 33 transesterified product.

It was however noted that the increase in the equivalence of zinc does not increase product formation, but a decrease in the amount of zinc the reaction does not go to completion. The reaction also failed to proceed in the presence of zinc alone. The reaction also failed to proceed to completion if the lower boiling alcohol is not distilled off.

The reaction done with various alcohols, the results of which are tabulated in Table 1. From the table it is evident that a variety of alcohols allyl, propargyl as well as optically active alcohol *viz*. menthol can be efficiently transesterified using this protocol. In the entry 10 the use of 1, 10 decanediol two equivalent of methyl acetoacetate was used.

Table 1

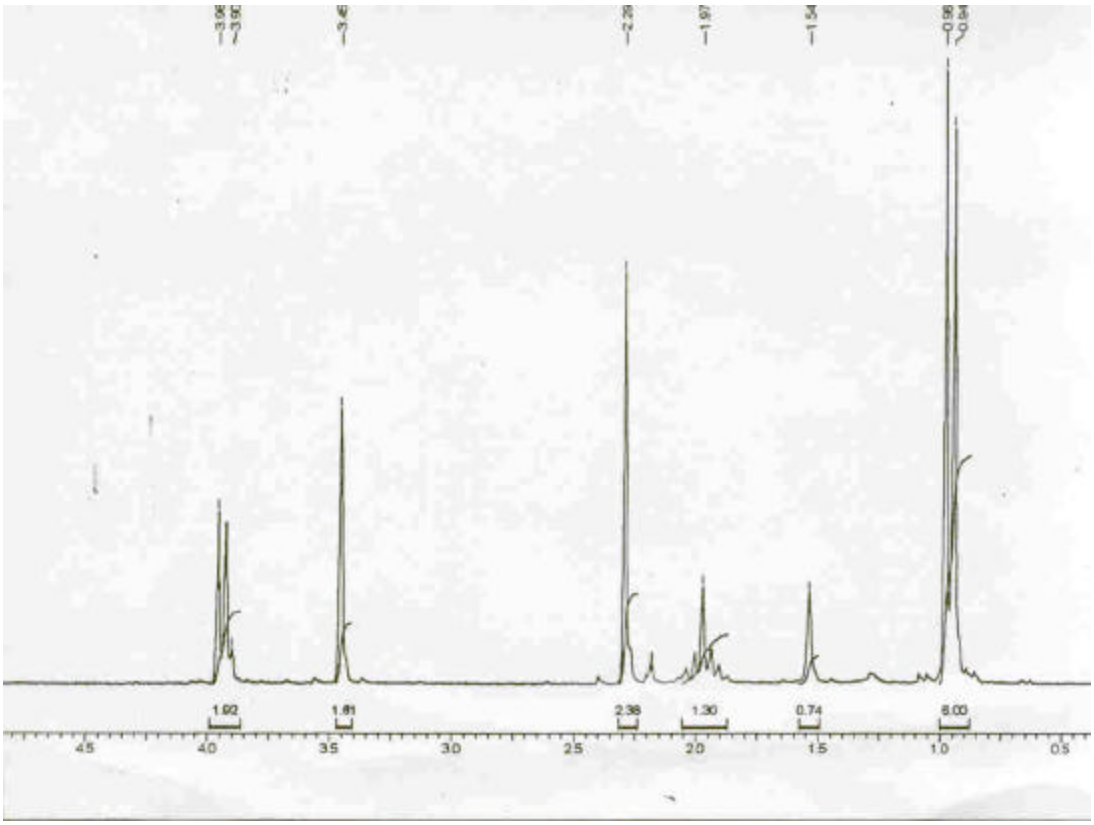
Sl.No	β-Ketoester	Alcohol	Product	Yield
1				85
2				62
3				66
4				78
5				45
6				60
7				71
8				79
9				89
10				66[#]

[#] 2eq. of methyl acetoacetate was used.

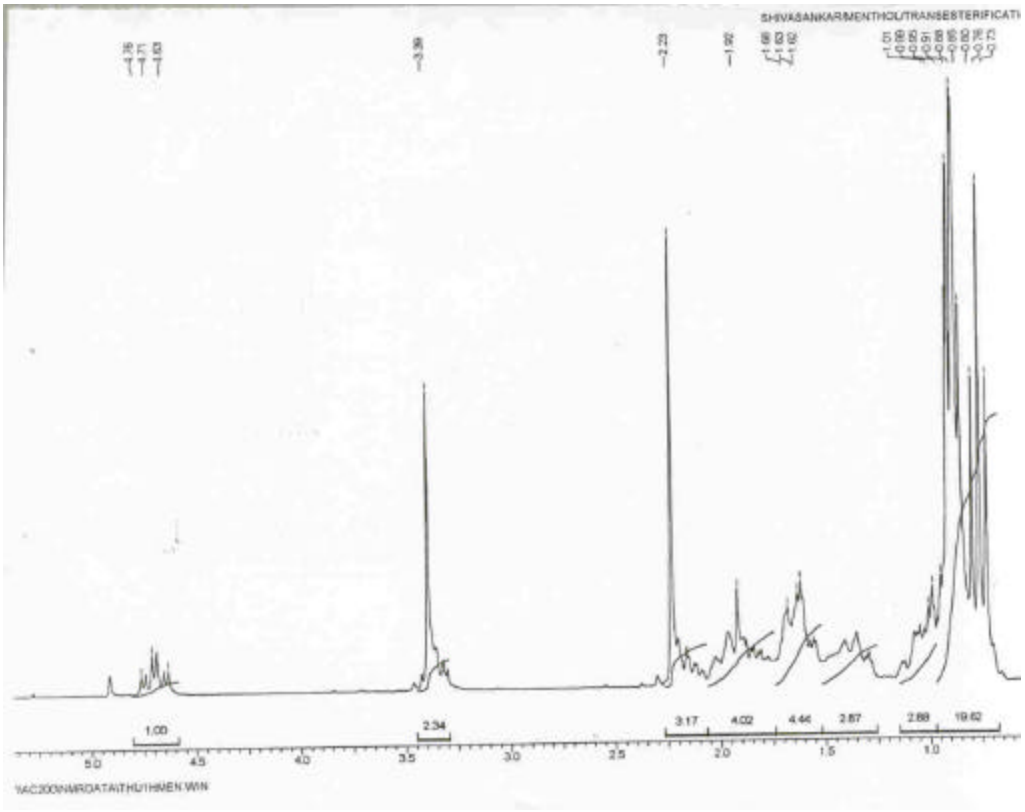
2.1.5 Conclusions

Ketoesters have been successfully transesterified using metal zinc. The yields are excellent to good in some of the cases. Transesterification has been done on primary and secondary alcohols. The alcohols include a wide variety of substrates like allylic, benzylic and propargylic. The time taken by the reaction is short compared to some of the existing methods. The conditions used for the reaction are also very simple. The reaction doesn't have the formation of any hazardous intermediates.

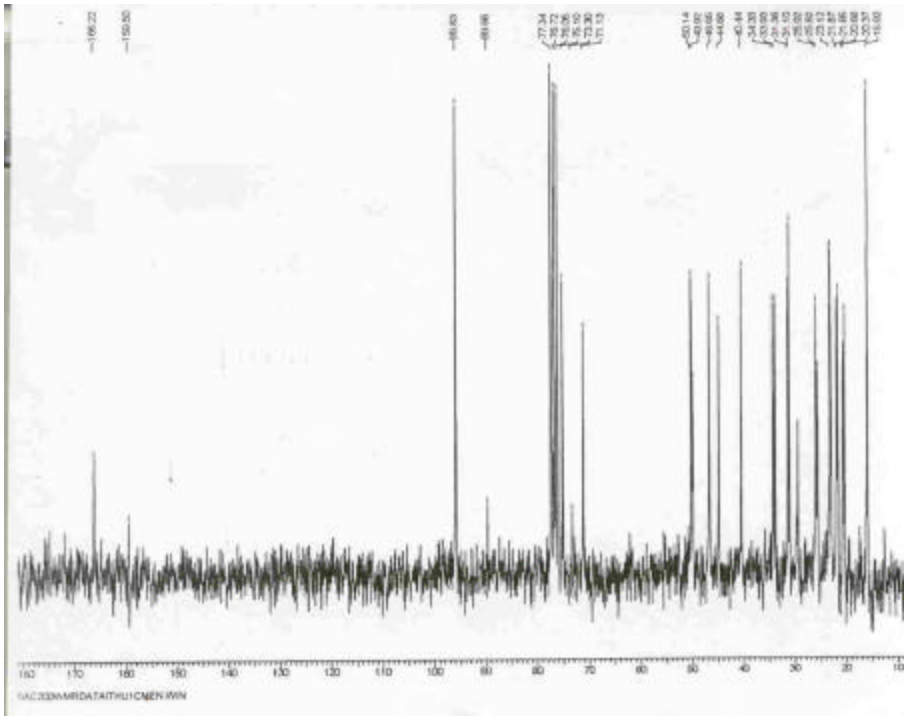
In short this is a novel method in which metal has been used for transesterification of ß-ketoesters and the yields obtained are good to excellent.



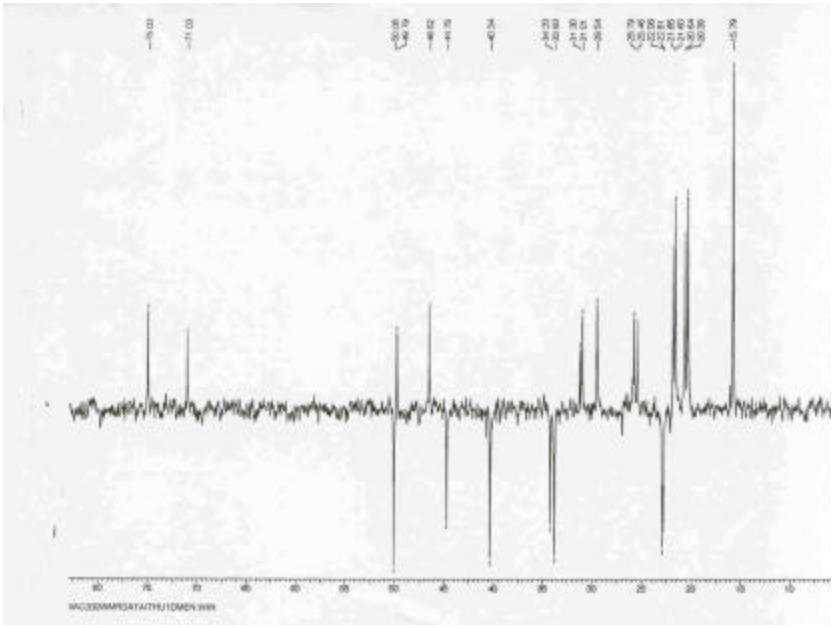
^{1}H NMR of 3-Oxo-butyric acid isobutyl ester (200 MHz, $CDCl_3$)



^{1}H NMR of 3-Oxo-butyric acid menthyl ester (200 MHz, $CDCl_3$)



^{13}C NMR of 3-Oxo-butyric acid menthyl ester (50 MHz, $CDCl_3$)

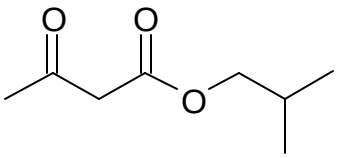


DEPT of 3-Oxo-butyric acid menthyl ester (50 MHz, $CDCl_3$)

2.1.6 Experimental

In a typical example zinc (1.10g, 16.95 mmol) was taken in a round bottom flask attached with a reflux and a distillation condenser. Methylacetoacetate (1g, 8.47 mmol) in toluene (10ml) was added followed by the addition of cyclohexanol (0.93g, 9.32 mmol) in toluene (5ml). Catalytic amount of Iodine was added and the reaction was refluxed for 5 hrs. and was monitored by TLC. The reaction was quenched with dil. HCl (20ml) or with saturated NH_4Cl. The reaction mixture was filtered and the compound was extracted in ether and was chromatographed using silica gel (60-120 mesh).

1. **3-Oxo-butyric acid isobutyl ester**[19]

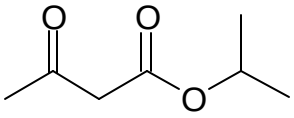


Yield: 85%

Molecular formula: $C_8H_{14}O_3$

^{1}H NMR: 0.96(d, 6H, J=8Hz), 1.97(m, 1H), 2.29(s, 2H), 3.45(s, 3H), 3.93(d, 2H, J=6Hz).

2. **3-Oxo-butyric acid isopropyl ester**[19]

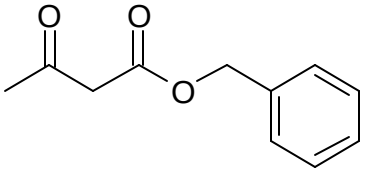


Yield: 62%

Molecular formula: $C_7H_{12}O_3$

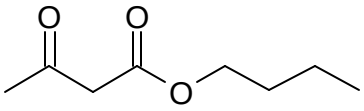
^{1}H NMR: 1.28 (d, 6H, J=6.2Hz), 2.28(s, 2H), 3.43(s, 3H), 5.08(m, 1H).

3. **3-Oxo-butyric acid benzyl ester**[12]



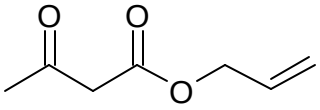
Yield:	66%
Molecular formula:	$C_{11}H_{12}O_3$
IR ($CHCl_3$, cm^{-1}):	3320, 1738, 1695.
^1H NMR:	2.2 (s, 3H), 3.45(s, 2H), 5.1(s, 2H), 7.3-7.1(m, 5H)
^{13}C NMR:	29.73(q), 49.70(t), 66.76(t), 128.14(d), 128.22(d), 128.43(d), 135.37(s), 166.81(s), 200.19(s)

4. **3-Oxo-butyric acid butyl ester**[12]



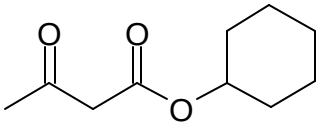
Yield:	78%
Molecular Formula:	$C_8H_{14}O_3$
IR (neat) cm^{-1}:	2980, 2950, 1750, 1720, 1650, 1560, 1420, 1350.
^1H NMR($CDCl_3$):	0.9 (t, 3H); 1.35 (m, 2H); 1.60 (m, 2H); 2.24 (s, 3H), 3.4 (s, 2H); 4.1 (t, 2H)
Mass (m/e):	158 (M^+)

5. **3-Oxo-butyric acid allyl ester**[19]



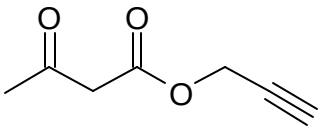
Yield:	45%
Molecular Formula:	$C_7H_{10}O_3$
IR (neat) cm^{-1}:	3010, 2980, 1750, 1720, 1650, 1560, 1420, 1350.
^1H NMR$CDCl_3$:	2.2 (s, 3H); 3.4 (s, 2H); 4.6 (d, 2H); 5.25 (d, 2H), 5.8 (m, 1H).
Mass (m/e):	142 (M^+)

6. **3-Oxo-butyric acid cyclohexyl ester**[12]



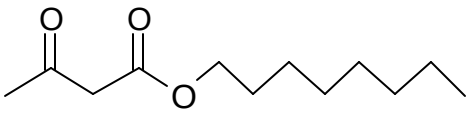
Yield:	60%
Molecular Formula:	$C_{10}H_{16}O_3$
IR (neat) cm^{-1}:	3010, 2980, 1750, 1720, 1650, 1560, 1420, 1350.
^1H NMR $CDCl_3$ (δ):	1.35 (m, 6H); 1.70 (m, 2H); 1.80 (m, 2H); 2.4 (s, 3H), 3.4 (s, 2H); 4.8 (m, 1H)
Mass (m/e):	184 (M^+)

7. **3-Oxo-butyric acid propargyl ester**[19]



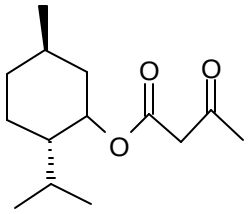
Yield:	71%
Mol. Formula:	$C_7H_8O_3$
^1H NMR $CDCl_3$ (δ)	2.2(s, 3H), 2.5(t, 1H, J=2Hz), 3.45(s, 2H), 4.65(d, 2H, J=2Hz)

8. **3-Oxo-butyric acid octyl ester**[12]



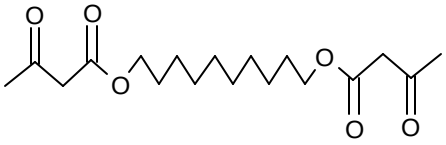
Yield:	79%
Mol. Formula:	$C_{12}H_{22}O_3$
IR(neat):	2950, 2850, 1750, 1720, 1650, 1450, 1400, 1350
^1H NMR $CDCl_3$ (δ):	0.9 (t, 3H); 1.3 (m, 10H); 1.6 (t, 2H); 2.6 (s, 2H); 4.1 (t, 2H)
Mass:	214 (M^+)

9. **3-Oxo-butyric acid menthyl ester**[12]



Yield:	89%
Molecular formula:	$C_{14}H_{24}O_3$
^{1}H NMR:	0.85 (d, 3H, J= 6Hz), 1.2-0.9(m, 10H), 1.5 – 1.4(m, 2H), 1.75-1.65(m, 2H), 2.1-1.9(m, 3H), 2.25(s, 3H), 3.45(s, 2H), 4.75(dt, 1H, J=2hz, J=6Hz)
^{13}C NMR:	15.78(q), 20.30(q), 21.59(q), 23.01(t), 25.74(d), 29.36(q), 31.02(d), 33.87(t), 40.38(t), 46.56(d), 49.86(t), 74.60(d), 162.22(s), 199.70(s).

10. **3-Oxo-butyric acid 10-(3-oxo-butyryloxy)-decyl ester**[13]



Yield:	66%
Molecular formula:	$C_{18}H_{36}O_6$
^{1}H NMR:	1.3-1.6(m, 16H), 2.38(s, 6H), 3.4(s, 4H), 4.25(t, 4H, J=7Hz)

2.1.7 References

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SECTION B
Zinc and Iodine: Reagent for the synthesis of Coumarins

2.2.1 Introduction

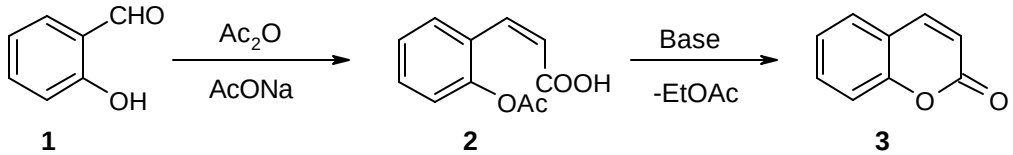
Coumarin is one of the most widely distributed chemical constituents in the plant kingdom. Formerly, coumarin was an important food flavoring material often used in the conjunction with vanillin for flavoring chocolates candies confections and baked goods.[1] Since 1954, the use of coumarins in foods has been suspended, because of its toxicity.[2] Its odor strength, tenacity, stability to alkali and cheapness in availability has made its market in the perfumery.[3] It is extensively used to enhance the character of fragrance based on natural essential oils such as lavender, citrus.[4] Addition of coumarin to the electroplating bath causes deposits of metals with reduced porosity and increased brightness, especially with nickel, zinc and cadmium.[5] Several derivatives of coumarin have anticoagulant properties, for example, dicoumarol, warfarin, coumadin *etc*.[6] Some coumarins are used as optical brighteners, for example, 7-hydroxy and its derivatives.[7] 4-Methyl-7-aminocoumarin derivatives are used for brightening wool and nylon, either in soap powders or detergents as salts under dyeing conditions.[7]

Vogel first isolated coumarin in 1820 by extraction from tonka beans (*Dipteryx odorata*), which contains 1.5% coumarin.[8] This method remained the source of coumarin until the synthetic methods pioneered by Perkin in 1868 largely displaced coumarins from natural sources. There are many synthetic routes for the synthesis of coumarin including Perkin reaction,[9] Pechmann,[10] Knovenagel[11] and Wittig reaction.[12] We take a brief look at the known synthetic methods.

Perkin reaction (Perkin, W. H. *J. Chem. Soc.* **1868**, *21*, 53)

Perkin synthesized coumarin[9] in 1868 by heating the sodium salt of salicylaldehyde with acetic anhydride. Perkin later found that sodium acetate could serve as the base catalyst instead of sodium salicyladehyde.[9]

Scheme 1(Perkin, W. H. *J. Chem. Soc.* **1868**, *21*, 53)



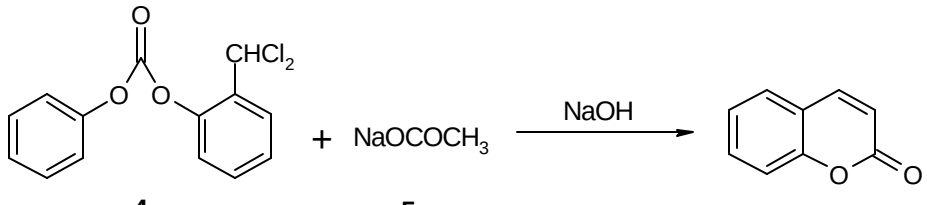
1 **2** **3**

Scheme 1

Raschig method (U.S. Pat. 1,920,494 (Aug. 1, 1933), Britton, E.C. and Reed)

Raschig method is considered as a practical way for the preparation of coumarin.[13] Benzal chloride, obtained from *o*-cresol, on heating with anhydrous sodium acetate gives coumarin.

Scheme 2 (U.S. Pat. 1,920,494 (Aug. 1, 1933), Britton, E.C. et. al.)



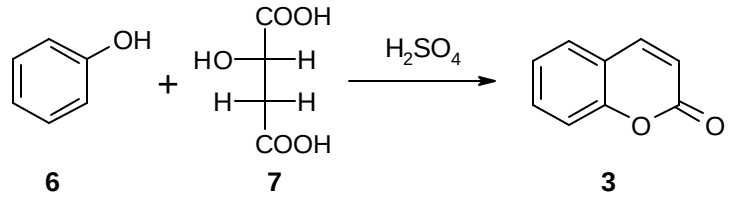
4 **5** **3**

Scheme 2

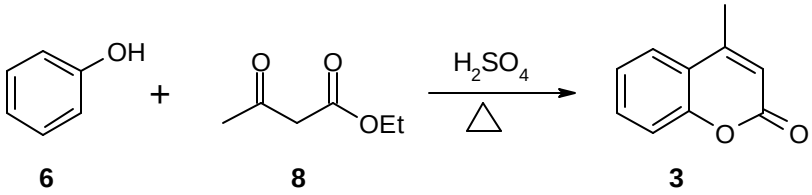
Pechmann condensation (Pechmann, H. V. *Ber.* **1883**, *16*, 2119)

Coumarins have been synthesized by Pechmann condensation *i.e.* by condensation of substituted phenols with ketoesters, malic acid, maleic or fumaric acids in presence of conc. H_2SO_4. [14]

Scheme 3 (Pechmann, H. V. *Ber.* **1883**, *16*, 2119)



6 **7** **3**



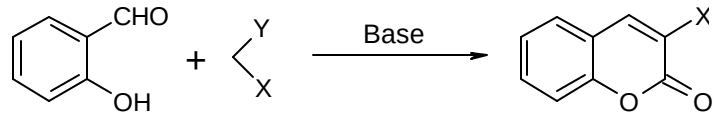
6 **8** **3**

Scheme 3

Knoevenagal method (Jones, G. *Org. React.* **1967**, *15*, 204.)

Salicylaldehyde is condensed with an active methylene compound to give 3-substituted coumarin. Various bases like pyridine, piperidine, have been used.[15]

Scheme 4 (Jones, G. *Org. React.* **1967**, *15*, 204.)



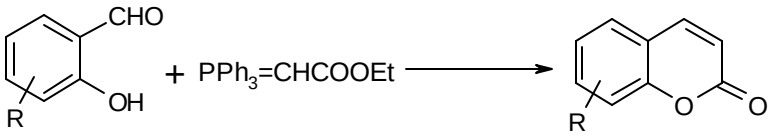
9 **10**

Scheme 4

Wittig reaction (Harayama, T.; Nakatsuka, K.; Katsuro, K.; Nishioka, H.; Murakami, K.; Fuji, M. *Chem. Express* **1993**, *8*, 245)

Phosphorous ylides have been condensed with substituted salicylaldehydes[16] in presence of base *viz.* N, N-diethylaniline to furnish coumarin in good yields.

Scheme 5 (Harayama, T. *et. al. Chem. Express* **1993**, *8*, 245)



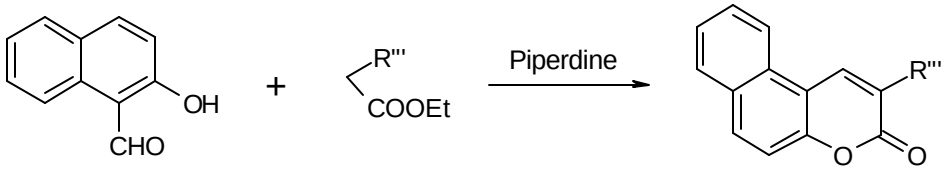
10 **12**

Scheme 5

The above mentioned were some of the general procedures for the synthesis of coumarins. We now take a look at some of the reported methods for the synthesis of coumarins.

Bodgal reported similar condensation in microwave. Knoevenagal condensation of substituted salicylaldehydes and active methylene compounds was done in microwave. The reaction was catalyzed by piperidine.[17] The reaction time taken was short.

Scheme 6 (Bogdal, D. *J. Chem. Res. (Synopsis)* **1998**, 468-69)



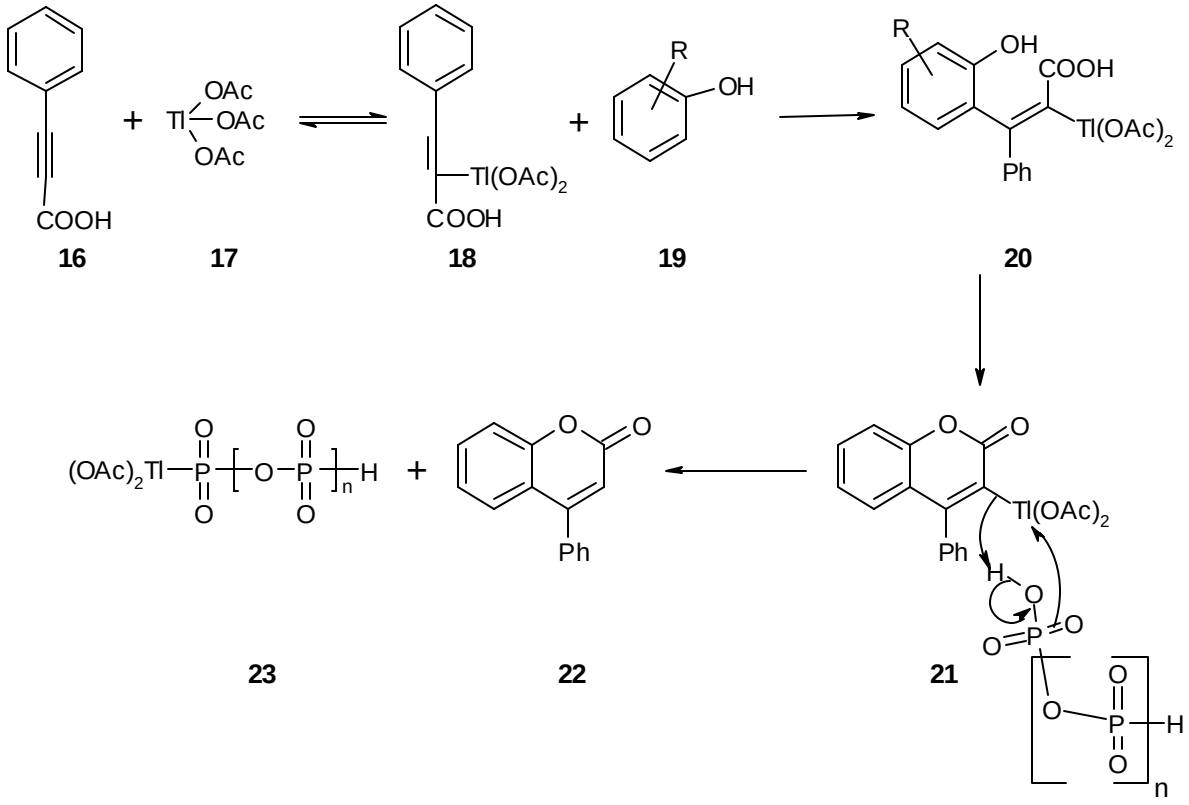
13 **14** **15**

Scheme 6

A one pot synthesis of 4-phenylcoumarins in good yields was achieved by the action of phenylpropiolic acid with phenols in polyphosphoric acid in presence of

Thallium acetate.[18] The reaction involved simple mixing of these substrates and heating over a water bath.

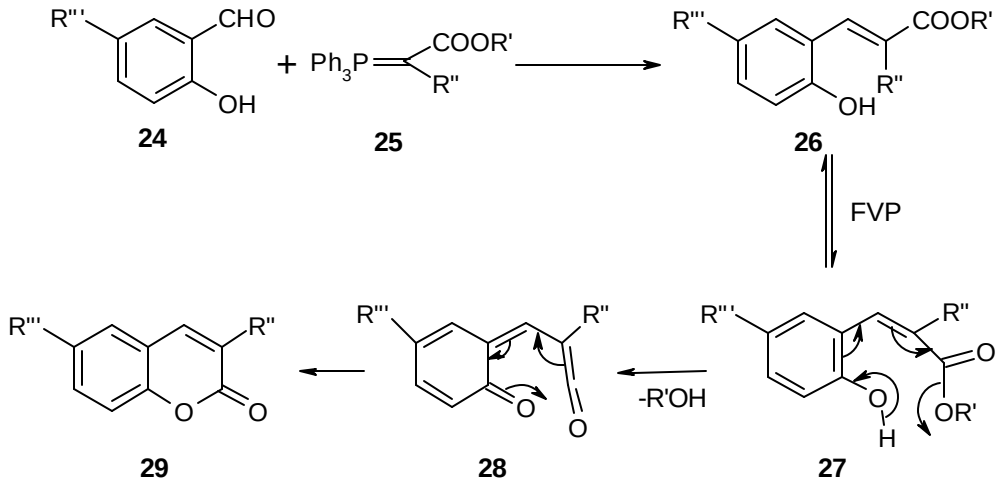
Scheme 7 (Shamsuddin, K. M. *et. al. J. Chem. Res. (Synopsis)* **1998**, 392)



Scheme 7

In a more recent paper,[19] synthesis of coumarins has been reported *via* flash vacuum pyrolysis (FVP) of 3-(2-hydroxyaryl) propenoic esters. Wittig reactions of the appropriate aldehyde with the phophoranes take place under very mild condition to give corresponding alkene. The alkene thus obtained was subjected to FVP at 750^{o}C, under these conditions *E* and *Z* alkenes are known to equilibrate and the latter are able to eliminate the appropriate alcohol.

Scheme 8 (Cartwright, G. A. *et. al. J. Chem. Res. (Synopsis)* 1997, 297)

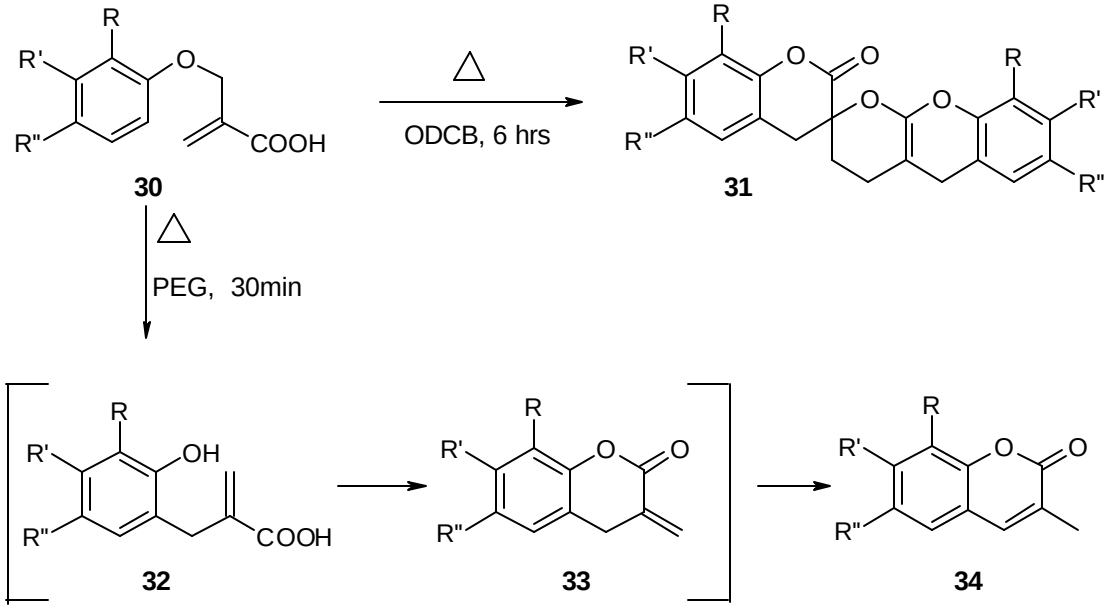


Scheme 8

Sunitha, K.; Balasubramanian, K. K.; Rajagopalan, K. *J. Org. Chem.* **1985**, *50*, 1530.

3-Methylcoumarin was synthesized by the thermal transformation of a–(aryloxy) methylacrylic acid.[20] In this report Sunitha *et al* have described the use of PEG-200 to be a superior solvent for Clasien rearrangement of a–(aryloxy)methylacrylic acid which afforded 3-methylcoumarin.

Scheme 9 (Sunitha, K. *et. al. J. Org. Chem.* **1985**, *50*, 1530.)



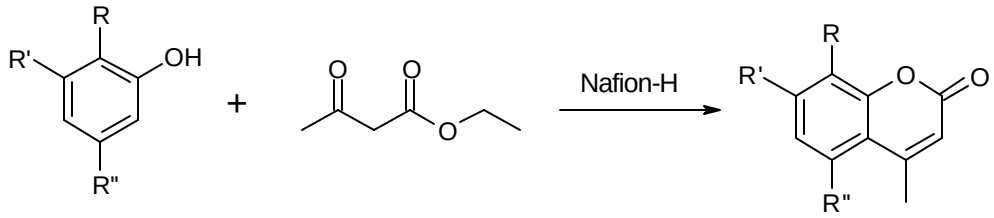
Scheme 9

Though there are reports on the synthesis of coumarins, 4-methyl coumarins have always been treated as a special class of compounds. 4-methylcoumarin-7yl-ß-D-glactofuranoside, was reported to be a fluorogenic substrate for galactofuranosidase.[21] 3-Chloro-7-[(chlorocarbonyl)methoxy]4-methylcoumarin was shown to be a fluorescent label.[22] 7-(4, 6-Dichloro-1, 3, 5-triazinylamino)-4-methylcoumarin, a chemiluminescent material, is used to determine concentration of H_2O_2.[23] New tetracyclic psoralen-like compounds have been synthesised which are charactereised by two furan rings angularly condensed on the coumarin nucleus. The structural feaure of these favor interchelation into DNA helix. During the determination of the constitution of ekersenin isolated from *Ekerbegia senegalensis*, eight isomeric monomethoxy monomethyl coumarins were synthesized. These studies proved that ekersenin was 4-methoxy-5-methylcoumarin, a constitution with novel biosynthetic implication.[24]

In an early report Nadkarni *et al* have reported the synthesis of 8-methoxy-4-methylcoumarins. This compound was synthesized by the condensation of ß-uraminocrotonic ester with guaiacol in the presence of polyphosphoric acid. Authors have reported the synthesis of 4-methyl, 4-methyl-7-hydroxy, 4, 8-dimethyl, 4, 7-dimethyl and 4, 6-dimethyl coumarins starting from ß-uraminocrotonic ester with the corresponding ester.

Nafion-H catalyzed Pechmann condensation[25] of phenol and ethyl acetoacetate has been reported. Stirring of equimolar quantities of phenol and ethyl acetoacetate with

Scheme 10 (Chaudhari, D. D. *Chem. Ind.* **1983**, 568)



35 **8** **36**

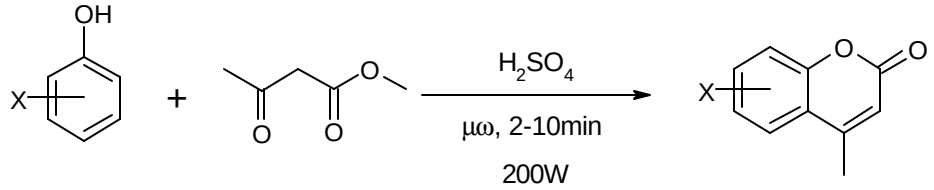
Scheme 10

10% (by weight) of Nafion-H yielded the respective coumarins.

Synthesis of coumarins[26] via a microwave accelerated Pechamnn reaction was reported by Singh *et al*. In this report authors claim good yields starting from phenol and methylacetoacetate. Sulfuric acid was used as a catalyst and the reaction mixture was

placed in the microwave. The reaction time taken for the reaction is short as compared to earlier methods.

Scheme 11 (Singh, V. *et. al. J. Chem. Res.* **1997**, 58.)

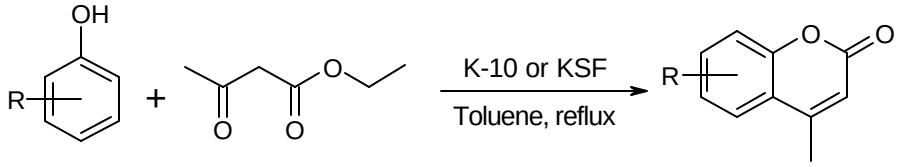


37 **38** **39**

Scheme 11

Pechmann condensation of phenols with ethylacetoacetate was reported using[27] montmorillonite clay by Li *et al*. Reaction of various phenols like resorcinol, cresols and napthols with ethylacetoacetate with and without solvent has been reported. The reaction condition involves the use of catalytic amount of montmorillonite clay.

Scheme 12 (Li, T. S. *et. al. J. Chem. Res.* **1998**, 38)

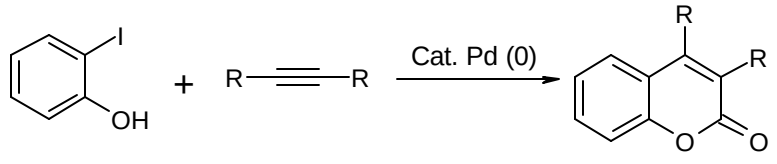


40 **8** **41**

Scheme 12

Propensity of unsaturated compounds such as alkenes, alkynes and carbon monoxide to undergo insertion into a carbon-metal bond makes them some of the most versatile substrates for transition metal catalyzed organic transformation.[28] In a recent paper Ksdnikov *et al* describe synthesis of a variety of substituted coumarins in good yield by the palladium catalysed coupling of *o*-iodophenols with internal alkynes and 1 atm. of carbonmonoxide. The highlight of this synthesis is that it employs simple

Scheme 13 (Kadnikov, D. V. *et. al. Org. Lett.* **2000**, *2*, 3643)



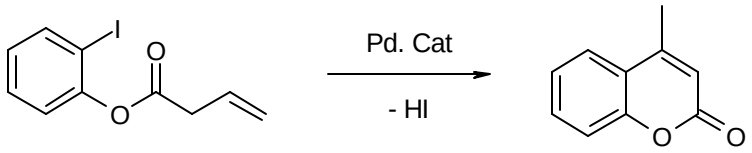
42 **43** **44**

Scheme 13

conditions that are very mild and a variety of functional groups on both alkynes and phenol have been used. The main disadvantage is the use of carbon monoxide and the costly palladium catalyst.

In a much earlier reference, Catellani *et al* have described the synthesis of 4-methylcoumarin *via* an intramolecular Heck cyclization.[29] The achievement of the six membered ring closure is attribute to the prevention of ester cleavage and isomerization of *o*-iodophenylester of 3-butenoic acid.

Scheme 14 (Coleman, R. S. *et. al. J. Org. Chem*. **1998**, *63*, 5700)



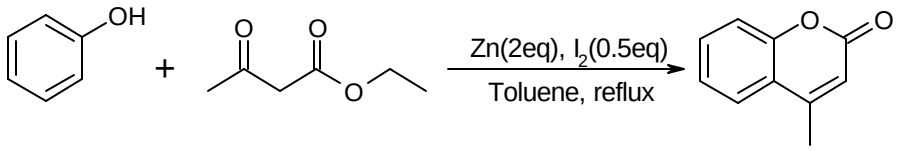
45 **46**

Scheme 14

2.2.2 Present work

As seen in the literature the synthesis of 4-methylcoumarins and coumarins as a whole have a great importance, as they are a part of the daily life starting from cosmetic industry to the food industry. In the present work we planned to undertake the utilization of Zinc and Iodine as catalyst for the synthesis of coumarins. As seen in the previous section use of Zinc and Iodine as an efficient catalyst for transesterification, we wanted to replace alcohols with phenols.

Scheme 15



Scheme 15

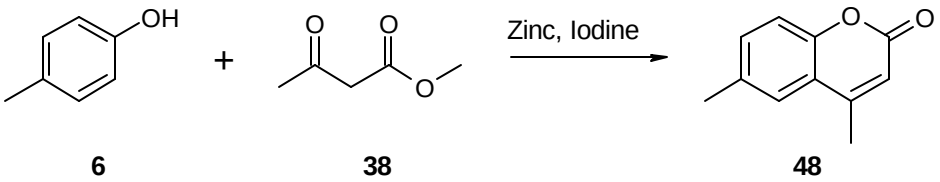
In a typical procedure zinc (2eq.) was taken and methyl acetoacetate was added in toluene. Phenol was added followed by the addition of iodine (0.5eq). The reaction was

set for reflux and was monitored by TLC. The reaction was the worked up using either dil HCl (10%) or using saturated NH_4Cl. The compound was extracted with ethyl acetate. The solvent was the concentrated under reduced pressure and later precipitated using pet ether. The solid thus obtained was then filtered and then dried.

2.2.3 Results and discussions

In a typical procedure zinc (2eq.) was taken and methyl acetoacetate (1eq) was added in toluene and *p*-cresol (1.1eq) was added followed by the addition of iodine (0.5eq). The reaction was set for reflux and was monitored by TLC. The reaction was worked up using either dil. HCl (10%) or using saturated NH_4Cl. The compound was extracted with ethyl acetate. The solvent was then concentrated under reduced pressure and the residue thus obtained was precipitated using pet ether. The compound was then filtered and dried to furnish coumarin.

Scheme 15



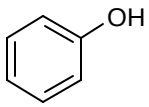
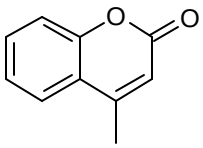
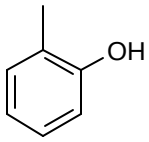
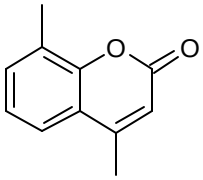
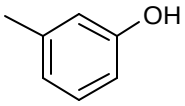
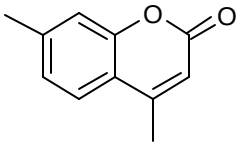
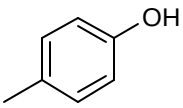
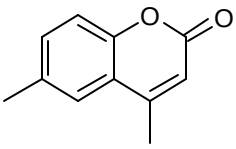
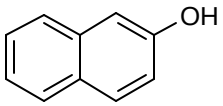
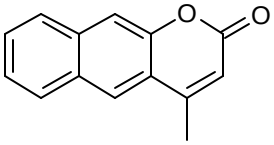
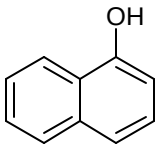
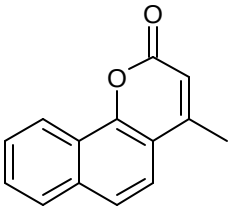
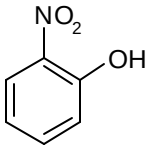
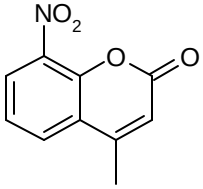
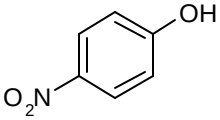
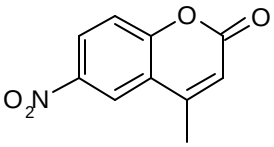
Scheme 15

Product obtained was characterized by ^1H NMR spectral analysis. Presence of singlet at d 2.37 corresponding to 6 protons indicated two methyl groups in the coumarin. Disappearance of the methylenic and the ester singlet of methyl acetoacetate confirmed that the reaction had gone. Conformation of the reaction was also obtained by the presence of a singlet present at d 6.18, indicating the presence of olefinic proton. ^{13}C NMR indicated the presence of carbonyl at d 160.2 and the two-methyl groups resonated at d 18.2 and d 20.6. Mass spectra of the compound showed a peak at m/z 174 that corresponds to the molecular ion peak.

The mechanism for the reaction is believed to be a Pechamann condensation though there are no concrete evidences to show that. As seen in the earlier section that transesterification of ß-ketoester has been achieved by the use of Zinc and catalytic amount of Iodine, this reaction is also believed to go *via* the transesterification and

followed by an intramolecular condensation. The details of this study was not undertaken due to time constraint. However, the study towards the mechanism is still in progress.

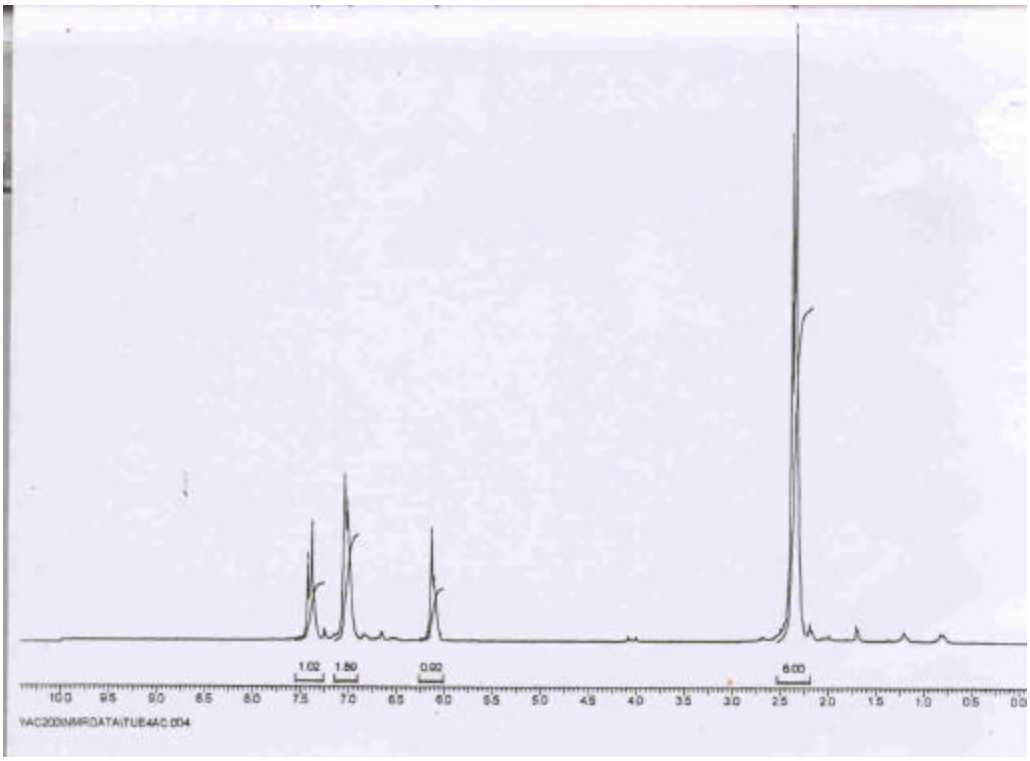
Table I

Sl. No.	Phenol	Coumarin	Time(hrs)	Yield
1.			5	78%
2.			5	71%
3.			5	64%
4.			5	72%
5.			6	56%
6.			6	63%
7.			8	25%
8.			8	40%

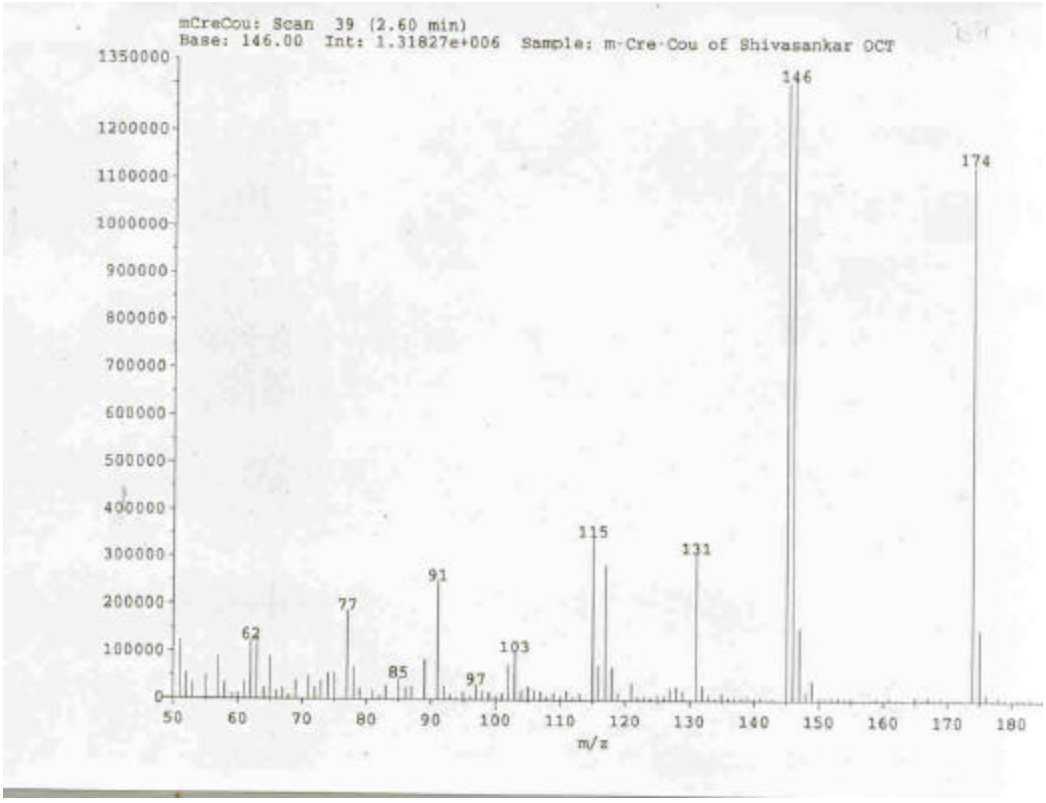
2.2.4 Conclusions

Ketoesters have been successfully condensed with phenols to give substituted coumarins. The yields are good to moderate in some cases. Various phenols have been condensed with methylacetoacetate, which include cresols, napthols and nitrophenols. The conditions used in this case are not drastic as compared to earlier procedures.

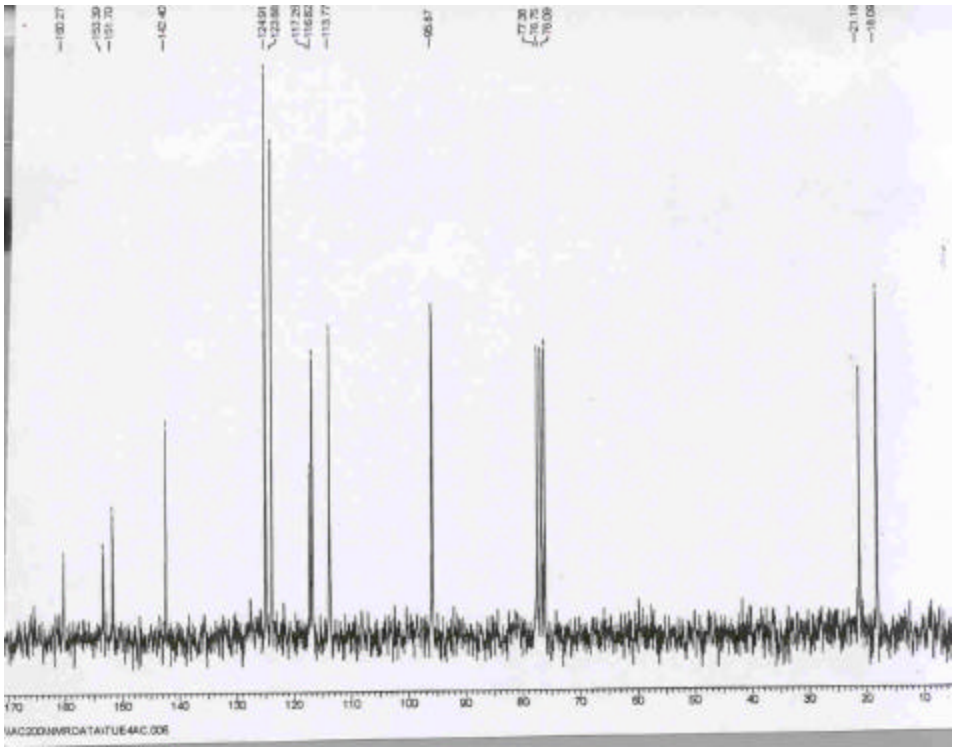
In short this is a novel method in which coumarins have been synthesized.



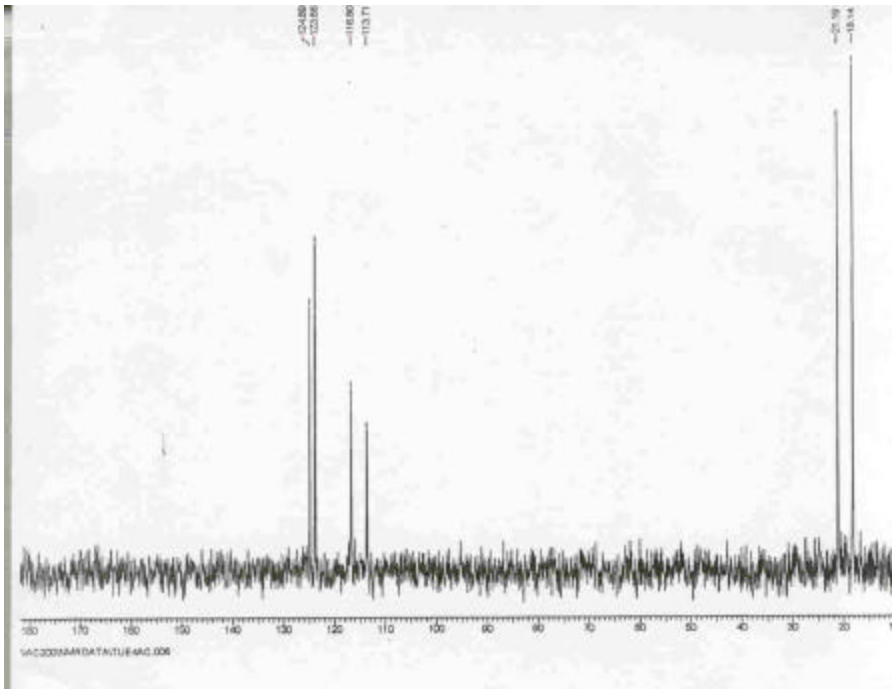
^{1}H NMR of 4,7-Dimethyl-chromen-2-one (200 MHz, $CDCl_3$)



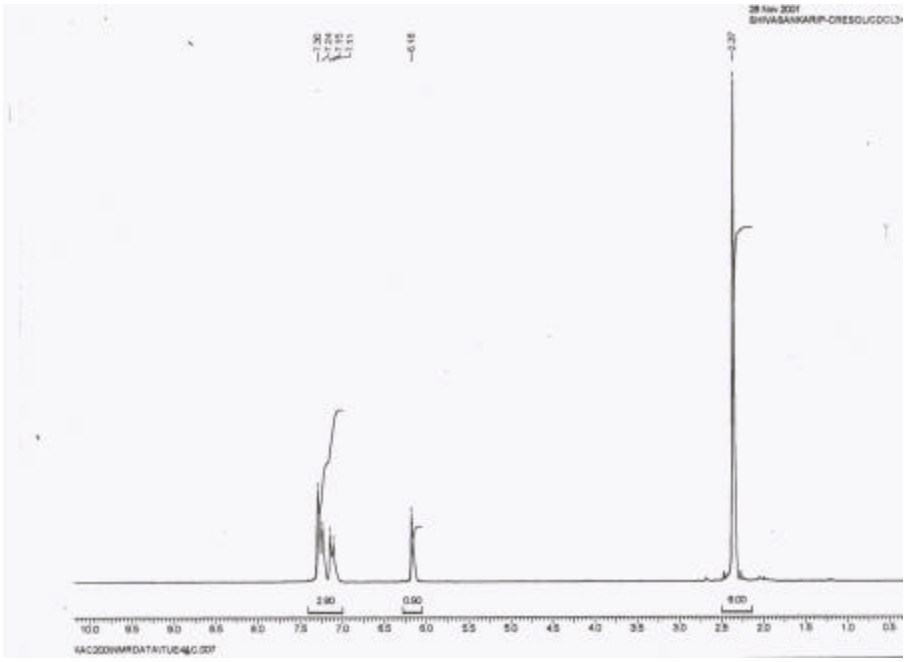
Mass spectra of 4,7-Dimethyl-chromen-2-one



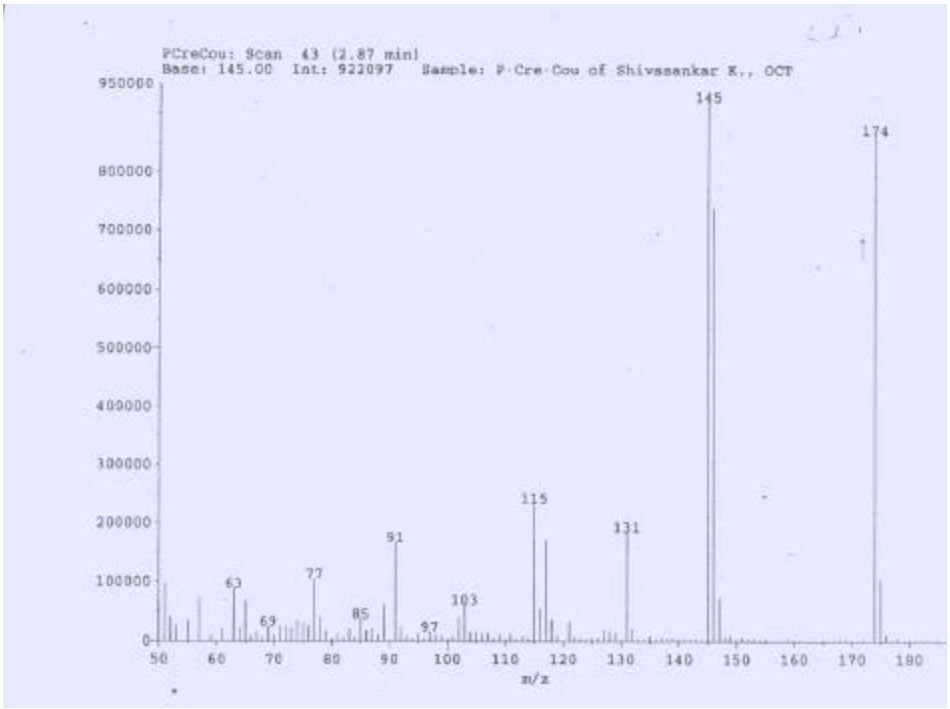
^{13}C NMR of 4,7-Dimethyl-chromen-2-one (50 MHz, $CDCl_3$)



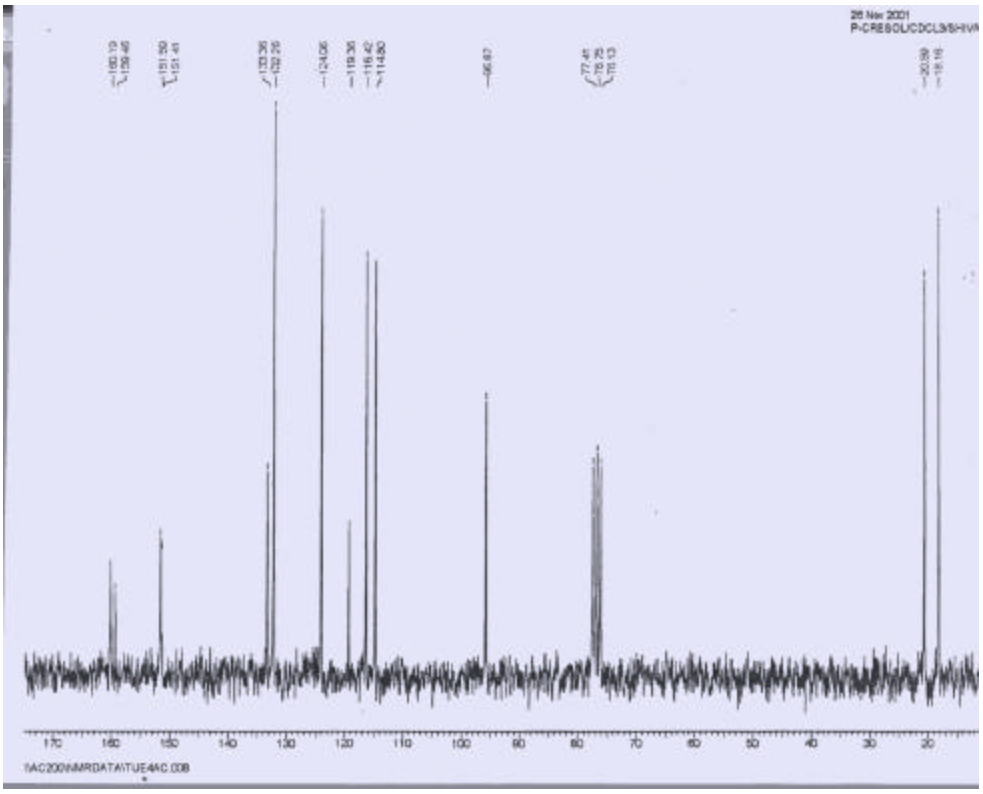
DEPT of 4,7-Dimethyl-chromen-2-one (50 MHz, $CDCl_3$)



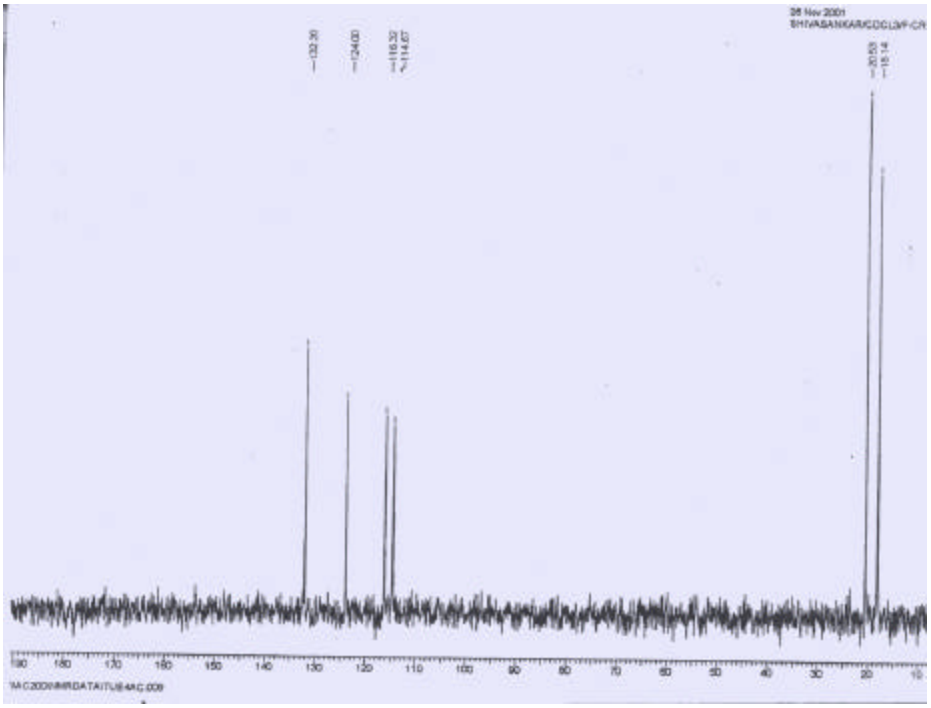
^{1}H NMR of 4,6-Dimethyl-chromen-2-one (200 MHz, $CDCl_3$)



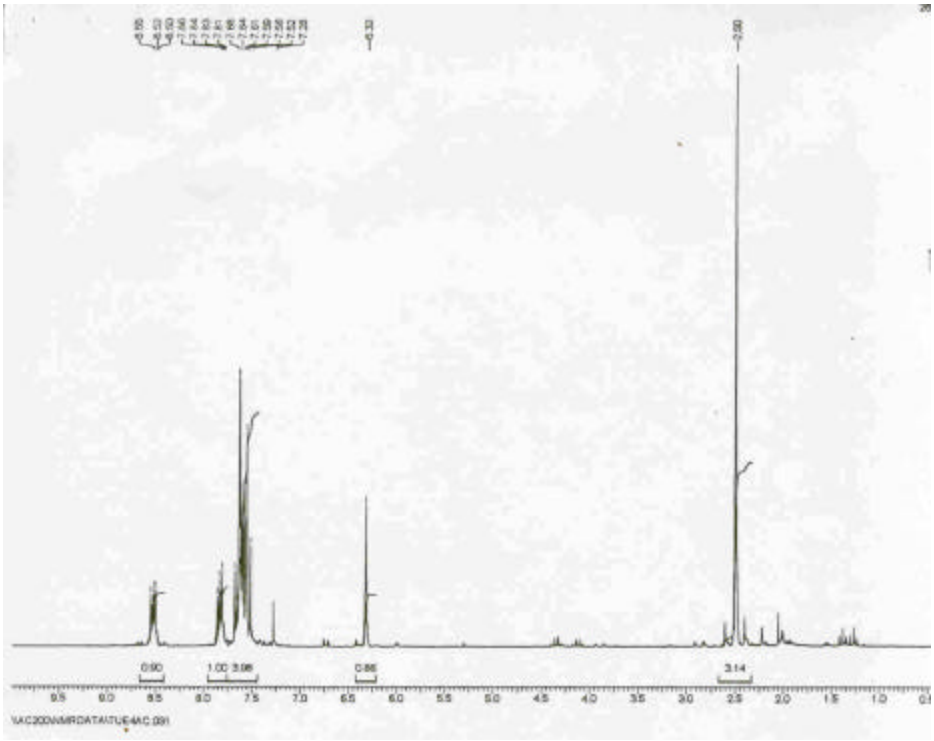
Mass spectra of 4,6-Dimethyl-chromen-2-one



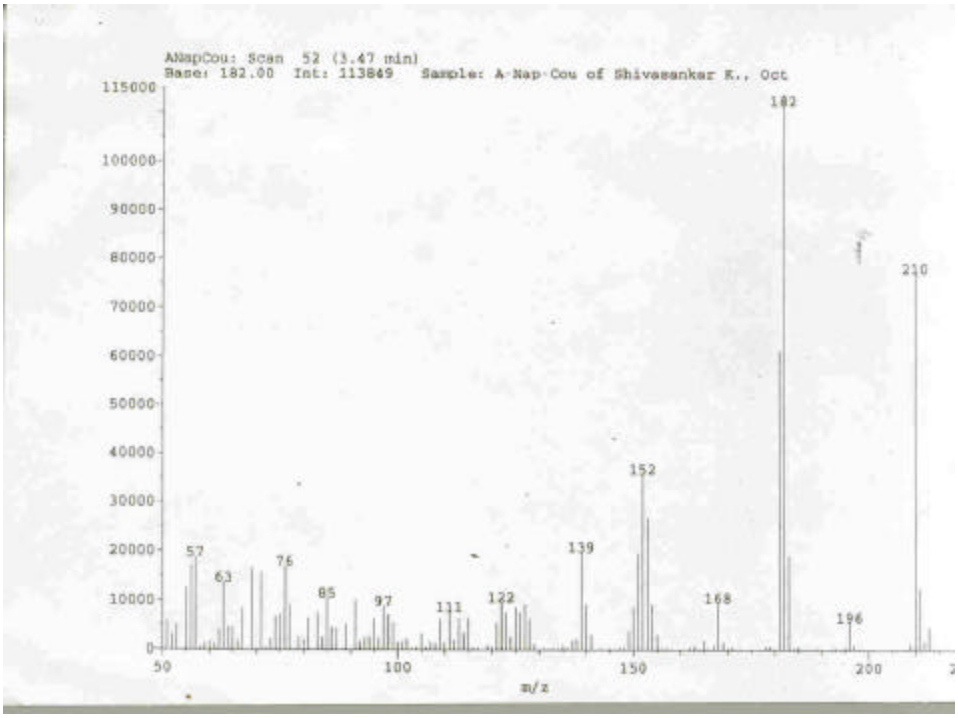
^{13}C NMR of 4,6-Dimethyl-chromen-2-one (50 MHz, $CDCl_3$)



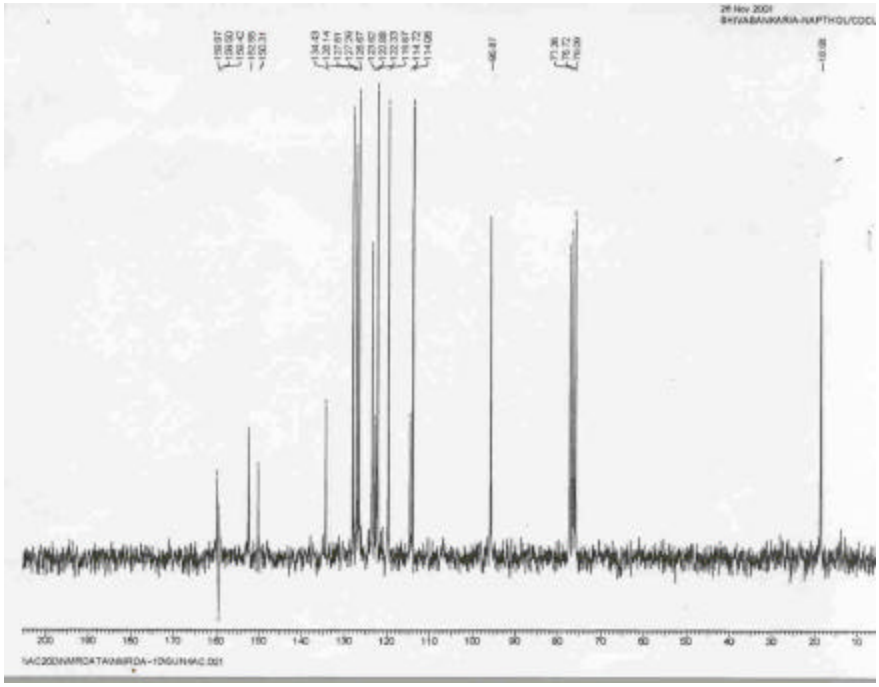
DEPT of 4,6-Dimethyl-chromen-2-one (50 MHz, $CDCl_3$)



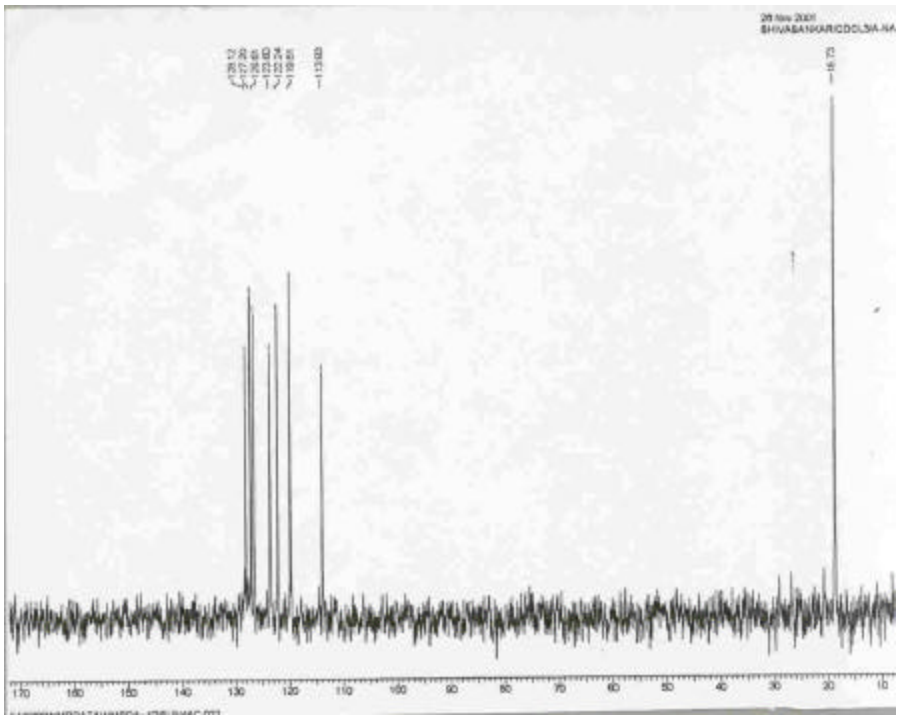
^{1}H NMR of 4-Methyl-benzo[h]chromen-2-one (200 MHz, $CDCl_3$)



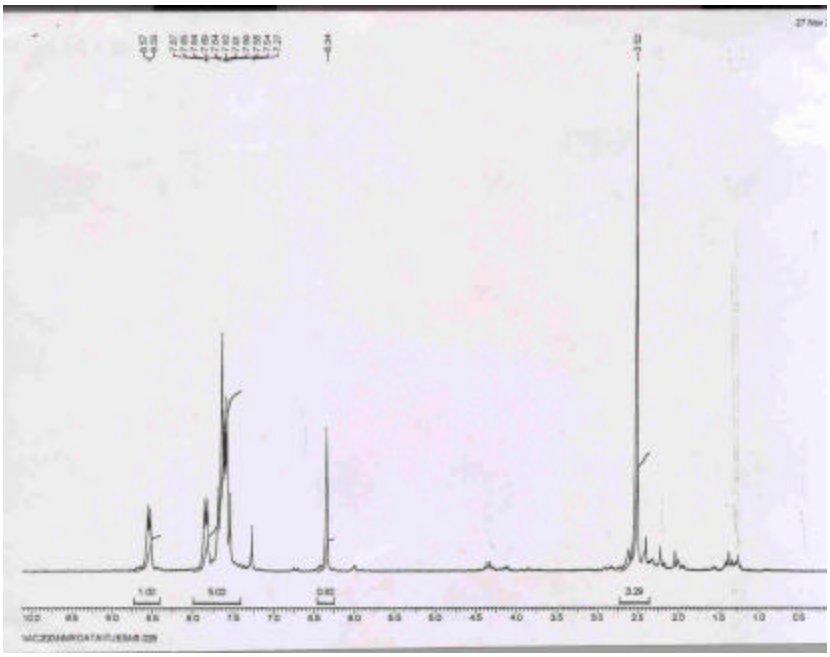
Mass spectra of 4-Methyl-benzo[h]chromen-2-one



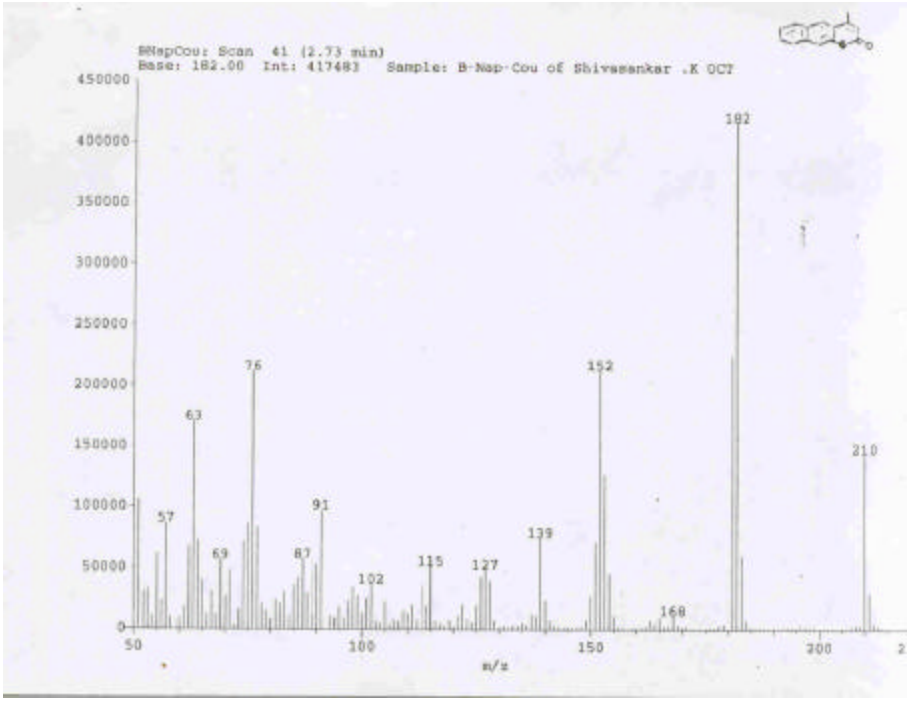
^{13}C NMR of 4-Methyl-benzo[h]chromen-2-one (50 MHz, $CDCl_3$)



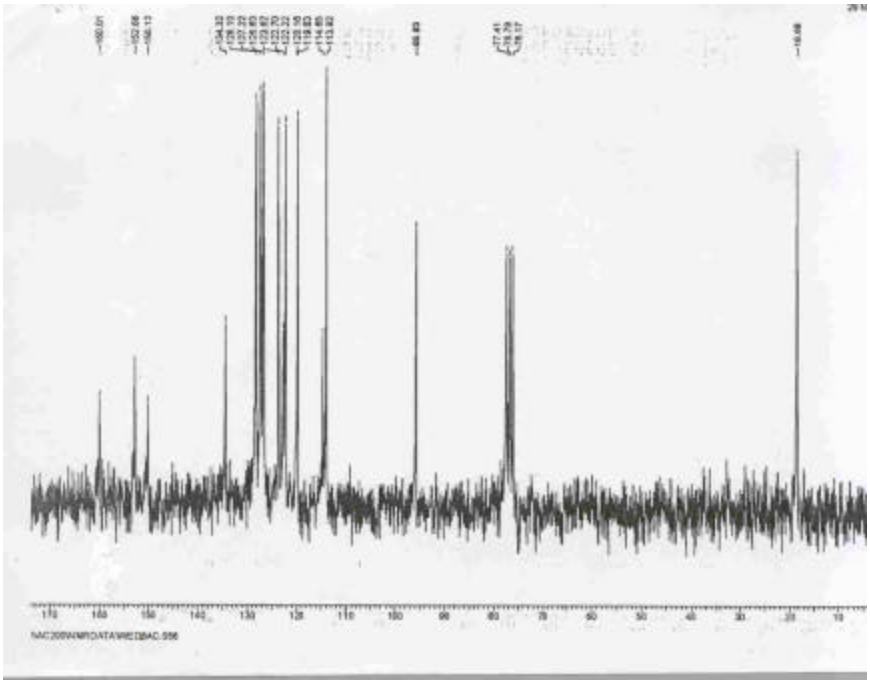
DEPT of 4-Methyl-benzo[h]chromen-2-one (50 MHz, $CDCl_3$)



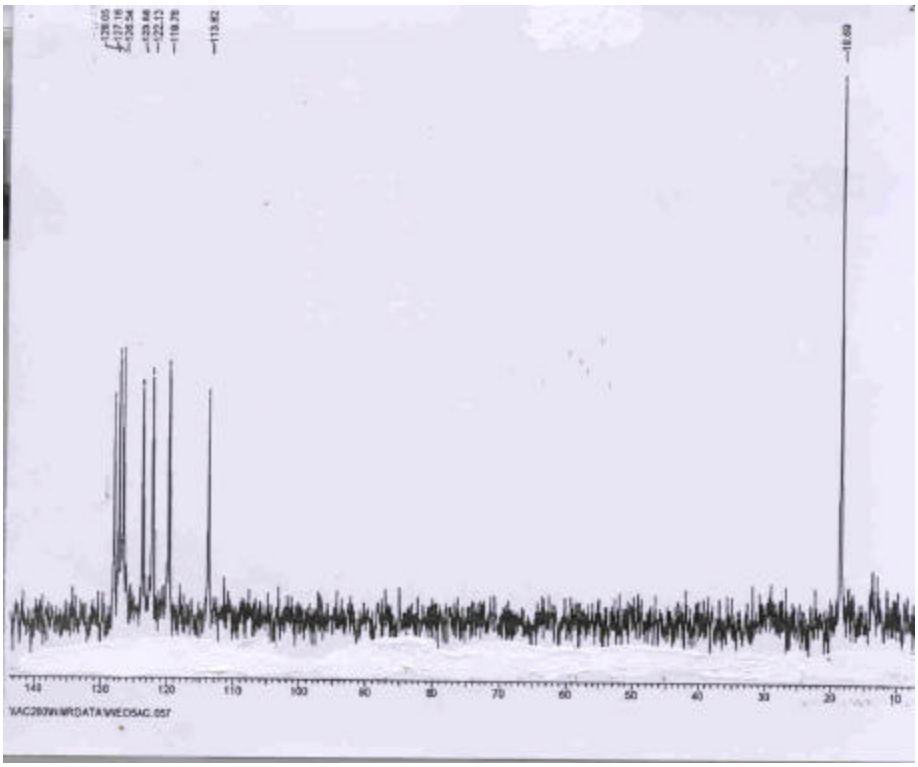
^{1}H NMR of 4-Methyl-benzo[g]chromen-2-one (200 MHz, $CDCl_3$)



Mass spectra of 4-Methyl-benzo[g]chromen-2-one



^{13}C NMR of 4-Methyl-benzo[g]chromen-2-one (50 MHz, $CDCl_3$)

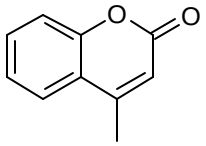


DEPT of 4-Methyl-benzo[g]chromen-2-one (50 MHz, $CDCl_3$)

2.2.5 Experimental

Typical procedure: In a typical example zinc (1.10g, 16.95 mmol) was taken in a round bottom flask attached with a reflux and a distillation condenser. Methylacetoacetate (1g, 8.47 mmol) in toluene (10ml) was added followed by the addition of phenol (0.876g, 9.32 mmol) in toluene (5ml). Iodine (0.537g, 4.23 mmol) was added and the reaction was refluxed for 5 hrs. and was monitored by TLC. The reaction was quenched with dil. HCl (20ml) or with saturated NH_4Cl. The organic layer was washed with sodium thiosulphate solution. The organic layer was dried over sodium sulphate and concentrated under vacuum. The product obtained was chromatographed using silica gel (60-120 mesh) to furnish 961mg of the desired product.

1. **4-Methyl-chromen-2-one**[29]



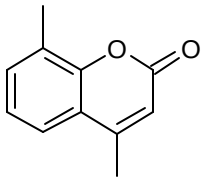
Molecular formula: $C_{10}H_8O_2$

Yield: 71%

Melting point: 118°C

^{1}H NMR: 2.2 (s, 3H), 6.0 (s, 1H), 6.89-7.18 (m, 4H).

2. **4,8-Dimethyl-chromen-2-one**[27]



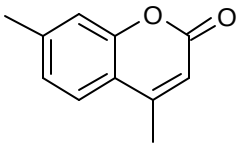
Molecular formula: $C_{11}H_{10}O_2$

Yield: 71%

Melting point: 118°C

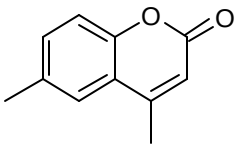
^{1}H NMR: 2.35 (s, 3H), 2.2 (s, 3H), 6.2 (s, 1H), 6.5-7.0 (m, 3H), 7.3 (m, 1H).

3. **4,7-Dimethyl-chromen-2-one**[25]



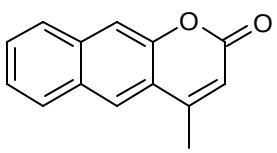
Molecular formula:	$C_{11}H_{10}O_2$
Yield:	64%
Melting point:	132^{o}C
^{1}H NMR:	2.38 (s, 6H), 6.13(s, 1H), 7.0-7.4(m, 3H)
^{13}C NMR:	18.1(q), 21.2(q), 113.8(d), 116.8(d), 117.3(s), 123.9(d), 124.9(d), 142.4(s), 151.7(s), 153.4(s), 160.3(s).
Mass(m/e):	174(M^{+}).

4. **4,6-Dimethyl-chromen-2-one**[27]



Molecular formula:	$C_{11}H_{10}O_2$
Yield:	72%
Melting point:	152^{o}C
^{1}H NMR:	2.37 (s, 6H), 6.18 (s, 1H), 7.1-7.3 (m, 3H)
^{13}C NMR:	18.2(q), 20.6(q), 114.8(d), 116.4(d), 119.4(s), 124.1(d), 132.3(d), 133.4(s), 151.5(s), 159.5(s), 160.2(s).
Mass(m/e):	174(M^{+}).

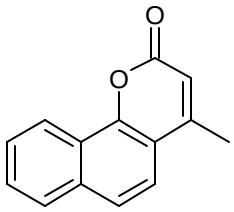
5. **4-Methyl-benzo[g]chromen-2-one**[27]



Molecular formula:	$C_{14}H_{10}O_2$

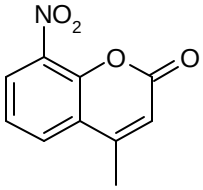
Yield:	56%
Melting point:	183^{o}C
^{1}H NMR:	2.52 (s, 6H), 6.34 (s, 1H), 7.5-7.87 (m, 5H), 8.56 (m, 1H)
^{13}C NMR:	18.7(q), 113.9(d), 114.7(s), 119.8(d), 122.2(d), 122.7(s), 123.6(d), 126.6(d), 127.2(d), 128.1(d), 134.3(s), 150.1(s), 152.7(s), 160.0(s).
Mass(m/e):	210(M^{+}).

6. **4-Methyl-benzo[h]chromen-2-one**[27]



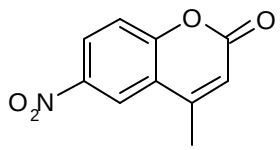
Molecular formula:	$C_{14}H_{10}O_2$
Yield:	63%
Melting point:	152^{o}C
^{1}H NMR:	2.52 (s, 6H), 6.34 (s, 1H), 7.5-7.87 (m, 5H), 8.56 (m, 1H)
^{13}C NMR:	18.7(q), 113.9(d), 114.7(s), 119.8(d), 122.2(d), 122.7(s), 123.6(d), 126.6(d), 127.2(d), 128.1(d), 134.3(s), 150.1(s), 152.7(s), 160.0(s).
Mass(m/e):	210(M^{+}).

7. **4-Methyl-8-nitro-chromen-2-one**[14f]



Molecular formula:	$C_{10}H_7NO_4$
Yield:	25%
Melting point:	148^{o}C
^{1}H NMR:	2.20 (s, 3H), 6.1 (s, 1H), 7.3 (m, 1H), 7.9-8.1 (m, 3H)

8. **4-Methyl-6-nitro-chromen-2-one**[14d]



Molecular formula:	$C_{10}H_7NO_4$
Yield:	40%
Melting point:	164^{o}C
^{1}H NMR:	2.40 (s, 3H), 6.2 (s, 1H), 7.5-8.0 (m, 3H)

2.2.6 References

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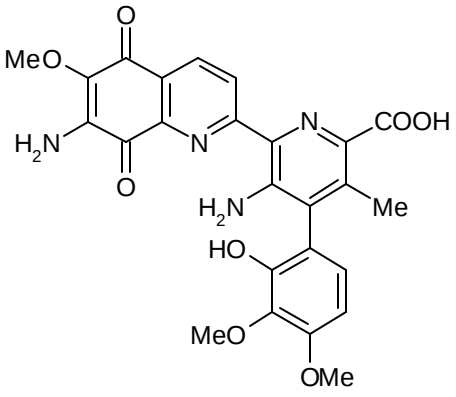
SECTION C
Synthesis of Quinolines: A Diels-Alder approach

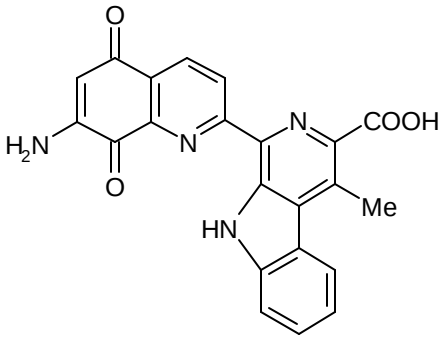
2.3.1 Introduction

The alkaloids are also some of the most interesting molecules we know of. Some of the effects of the alkaloids on the psyche are profound, such as have been reported with the use of peyote, which contains the alkaloid mescaline. Some of the alkaloids are responsible for profoundly relieving the suffering of terminal illnesses, such as morphine, which is derived from a constituent in the poppy plant. The poppy plant is Gods gift to suffering humanity. It is unfortunate that alkaloids can be and are so easily misused. Indeed, our whole law enforcement system is often occupied with the consequences of the misuse of the alkaloids.[1] The alkaloids are often classified according to the kind of chemical structures or forms from which they are formed: pyridine, piperidine, quinoline, isoquinoline are some of the general classes of alkaloids that we come across in day-to-day life. In this section we restrict ourselves to quinoline alkaloids. Quinoline alkaloids are named from quinoline in the cinchona plant, and refers to the quinoline alkaloids developed in the nucleus from tryptophan. Included in this group are quince, the anti-malaria medication, and quinidine, which calms the heart in tachycardiasis and arrhythmia, and others.[2] Some of the quinoline alkaloids which exhibit anticancer properties are shown in figure 1.



1

Streptonigrin

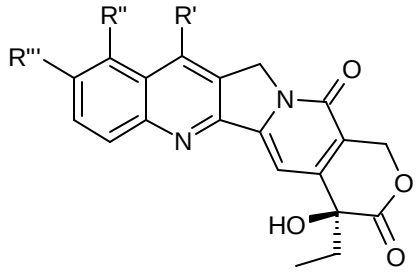


2

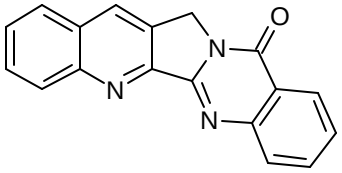
Lavendamycin

Figure 1

Figure 1 contd..



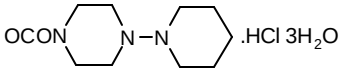
3

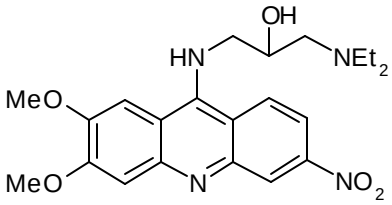


4

R’= R’’= R”’= H **Camptothecin** **Luotonin**

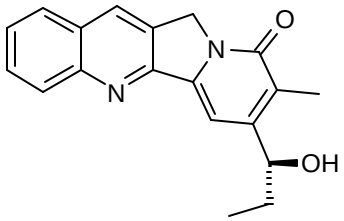
R’= H R”= CH_2NMe_2.HCl R”’= OH **Topotecan**

R’= Et R”=H R”’=  **Irinotecan**



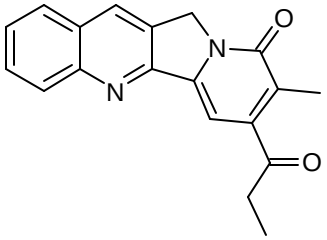
5

Nitroakridin



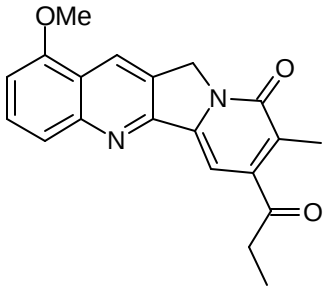
6

Mappicine



7

Nothapodytine B



8

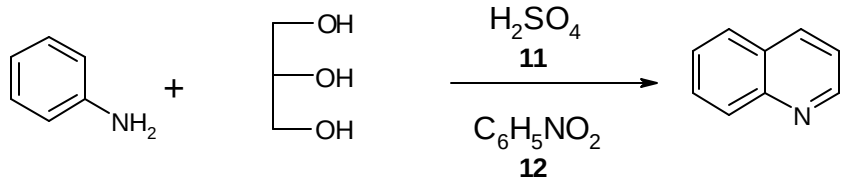
Nothapodytine A

Figure 1

Some of typical classical synthesis of quinolines are Skraup synthesis,[3] Friedländer’s synthesis,[4] Conrad-Limpach synthesis,[5] Knorr-quinoline synthesis,[6] Pfitzinger reaction[7] to name a few. (**Scheme 1-5**)

Skraup synthesis[3](Skraup, Z. H. *Ber*. **1880**, *13*, 2086)

Scheme 1 (Skraup, Z. H. *Ber*. **1880**, *13*, 2086)

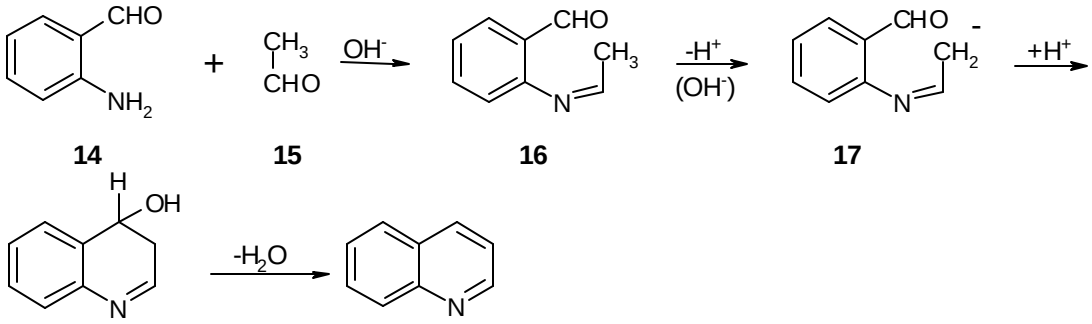


9 **10** **13**

Scheme 1

Friedländer's synthesis[4](Friendländer, *Ber*. **1882**, *15*, 2572)

Scheme 2 (Friendländer**,** *Ber***. 1882,** ***15*****,** 2572)

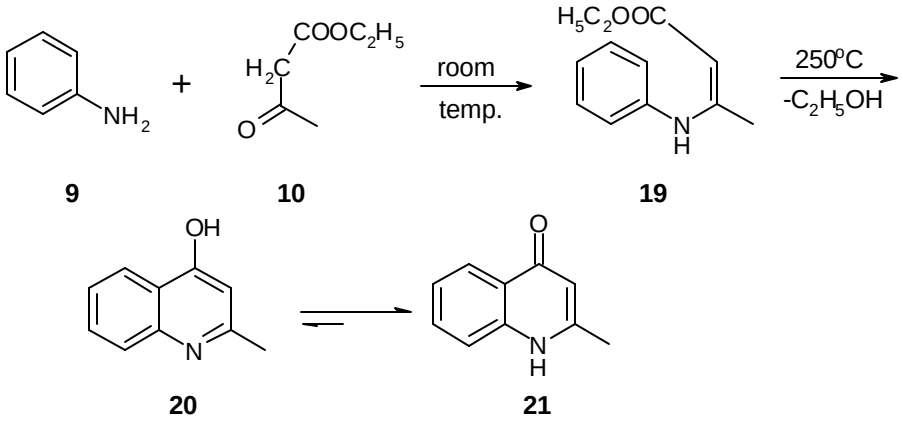


14 **15** **16** **17** **18** **13**

Scheme 2

Conrad-Limpach synthesis[5](Conrad, M.; Limpach, L. *Ber*. **1887**, *20*, 944)

Scheme 3 (Conrad, M. *et. al*. *Ber*. **1887**, *20*, 944)

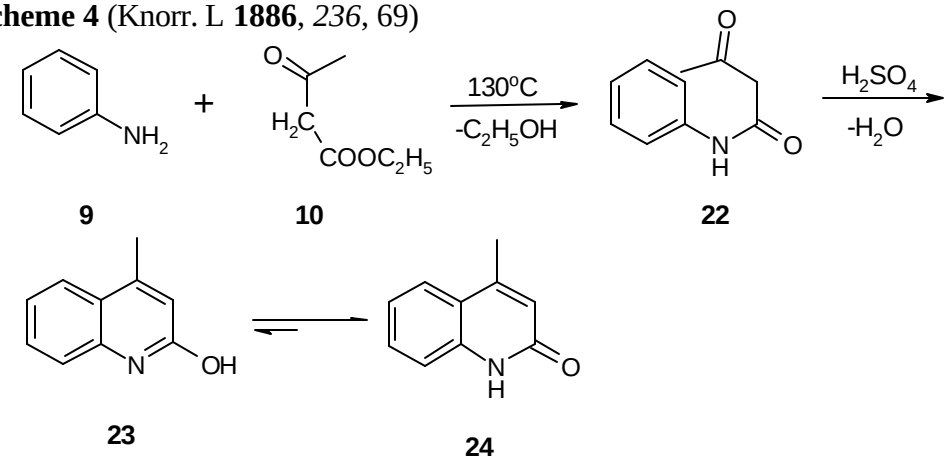


9 **10** **19** **20** **21**

Scheme 3

Knorr-quinoline synthesis[6](Knorr. L **1886**, *236*, 69)

Scheme 4 (Knorr. L **1886**, *236*, 69)

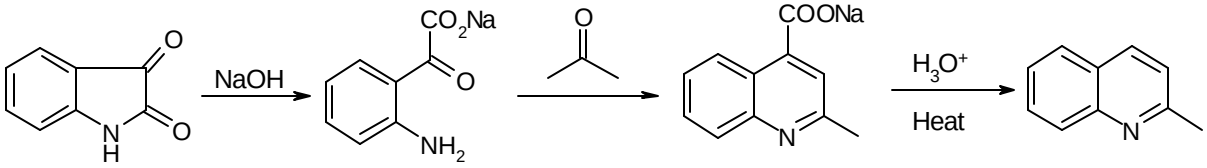


9 **10** **22** **23** **24**

Scheme 4

Pfitzinger reaction[7](Pfitzinger, W. *J. Prakt. Chem.* **1888**, *38*, 582)

Scheme 5 (Pfitzinger, W. *J. Prakt. Chem.* **1888**, *38*, 582)



25 **26** **27** **28**

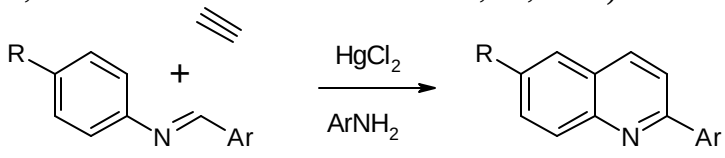
Scheme 5

The above mentioned were some of the old typical methods for the synthesis of quinolines. Now we take a look at other approaches towards quinoline synthesis.

Kozlov, N. S and Pinegina, L. Y *Zh. Obshch. Kim.* **1963**, *33*, 1079, (Chem. Abst. 59, 9976, 1963.[8]

The Schiff base from $PhNH_2$ and *o*-HOC_6H_4CHO was treated as above with (Scheme 6) C_2H_2 in the presence of $HgCl_2$ and p-$MeOC_6H_4NH_2$ for 30hrs to yield a precipitate of the Schiff

Scheme 6 (Kozlov, N. S *et. al. Zh. Obshch. Kim.* **1963**, *33*, 1079)



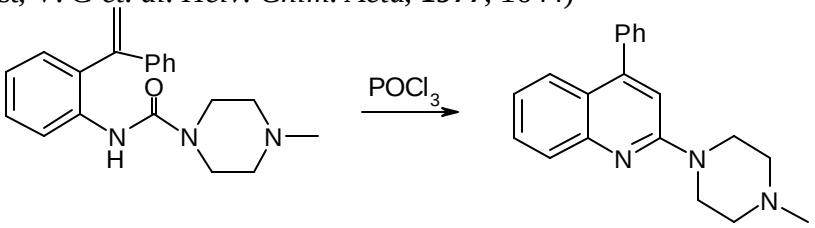
29 **30**

Scheme 6

base of *p*-anisidine with the aldehyde, while the residue gave **30** on distillation. The Schiff base of *p*-anisidine and salicylaldehyde treated as above with C_2H_2 in the presence of $PhNH_2$ and $HgCl_2$ gave a range of distillable fractions from which the corresponding quinoline was isolated.

Gast, V. G.; Schmutz, J. Sorg. D. *Helv. Chim. Acta*, **1977**, 1644. [10]

Scheme 7 (Gast, V. G *et. al. Helv. Chim. Acta*, **1977**, 1644)



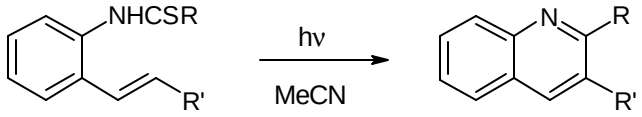
31 **32**

Scheme 7

Gast *et. al.* have attempted the cyclization of urea derivative with $POCl_3$ to give 2-(4-methyl-1-piperazinyl)-4-phenylquinoline.(Scheme 7)

Mayo. P. D.; Sydnes, L. K.; Wenska, G. *J. C. S. Chem. Comm.* **1979**, 499. [11]

Scheme 8 (Mayo. P. D. *et. al. J. C. S. Chem. Comm.* **1979**, 499)



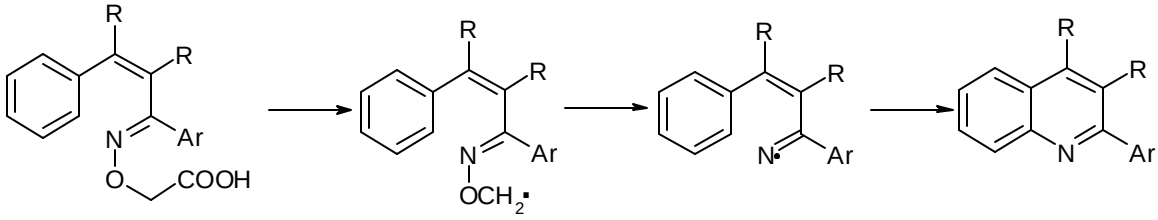
33 **34**

Scheme 8

Styryl amine precursor was prepared by the versatile Heck reaction.[11] The amine was converted to the thioamides which was irradiated at ambient temperature in acetonitrile to

Forrester, A. R.; Gill, M.; Thomson, R. H. *J. C. S. Chem. Comm.* **1976**, 677. [12]

Scheme 9 (Forrester, A. R. *et. al. J. C. S. Chem. Comm.* **1976**, 677)



35 **36** **37** **38**

Scheme 9

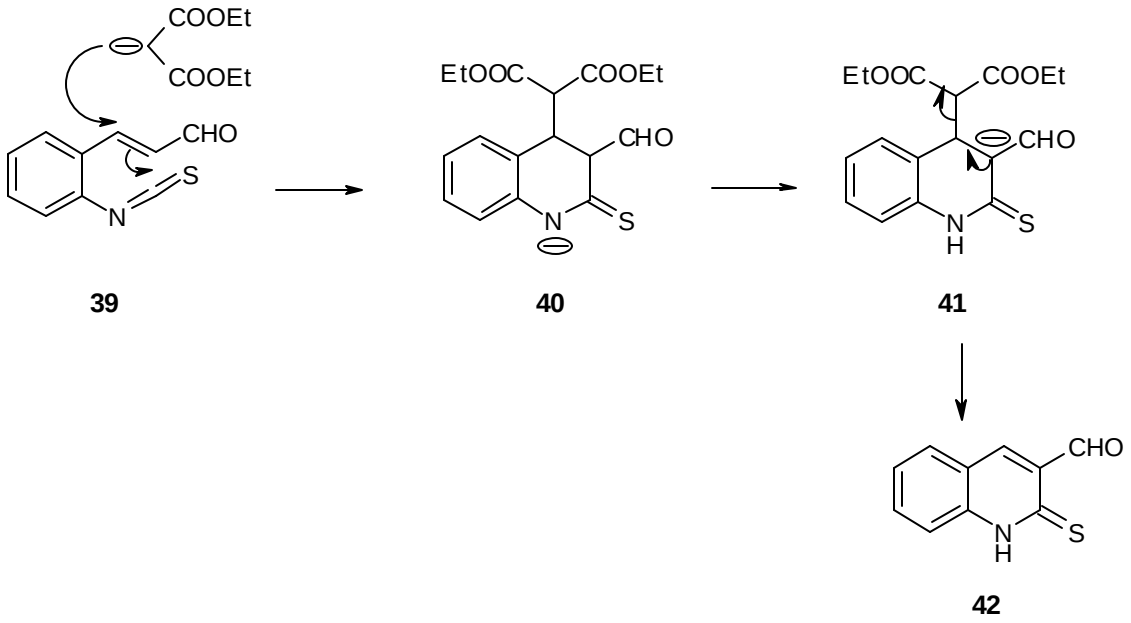
give quinolines (scheme 8). The irridiation times are low and the yields are moderate.

The advantage of this method is that quinolines obtained dissolve in acetonitrile where as thioanilides don't.

Iminyl radicals which can be conveniently generated from oximinoacetic acids by oxidation with persulphate, readily cyclise onto an adjacent aromatic ring or intramolecularly abstract benzylic ?–hydrogen atoms.[12] The potentially of this reaction has been illustrated by oxidative decarbonylation of oximinoacetic acids (R=Ar=Ph) in boiling aq. solution giving the corresponding quinoline in 91% yield.

Hull, R. *J. C. S. Perk. Trans I*, **1973**, 2911. [13]

Scheme 10 (Hull, R. *J. C. S. Perk. Trans I*, **1973**, 2911.)



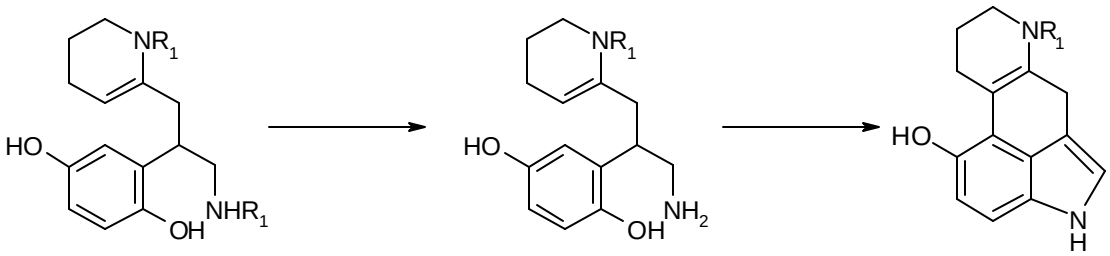
39 **40** **41** **42**

Scheme 10

Reaction of *o*-isothiocyanato trans-cinnamaldehyde, a scisson product from quinoline and thiophosgene, with diethylsodiomalonate give 3-formylquinolines-2(1H)-thione (Scheme 10). These compounds have been used as intermediates in the synthesis of thieno(2,3-b)quinolines.

Moore, J. A ; Capaldi, E. C. *J. Org. Chem* **1964**, 2860.[14]

Scheme 11(Moore, J. A. *et. al*. *J. Org. Chem* **1964**, 2860)



43 **44** **45**

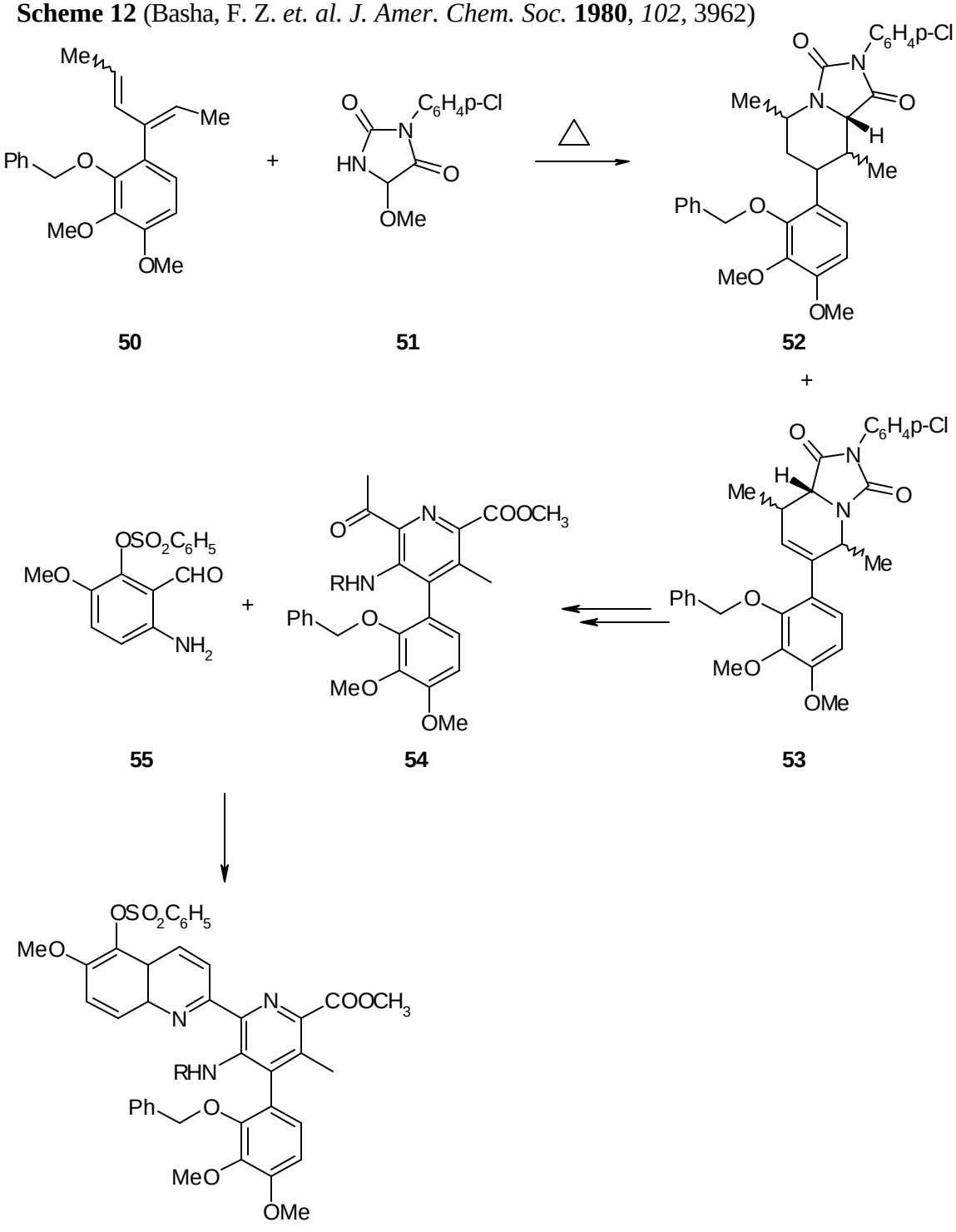
Scheme 11

To determine the direction of ring closure of **44**, whether a 1,2 addition to the qunione carbonyl or 1,4-addition to the double bond, a model study was done on 2–(2, 5-dihydroxyphenyl) propyl amine (Scheme 11). The amine was prepared by a standard sequence from 2,5-dimethoxycinnamic acid and cleaved to dihydroxyamine salt which was successfully oxidized using AgCl to give 6-hydroxyquinoline.

Now having taken a look at the different strategies that can be used in the synthesis of quinoline alkaloids. We take a look at how actually these techniques are being employed in synthesis of these alkaloids (figure 1). Due to do the presence of so many alkaloids in this class, we now define ourselves to streptonigrin and camptothecin classes of alkaloids. First we take a look at streptonigrin and later camptothecin.

In a very early synthesis towards streptonigrin Weinreb *et al*[15] have employed imino Diels-Alder reaction as a key step, in their synthesis.(Scheme 12)

Scheme 12 (Basha, F. Z. *et. al. J. Amer. Chem. Soc.* **1980**, *102*, 3962)

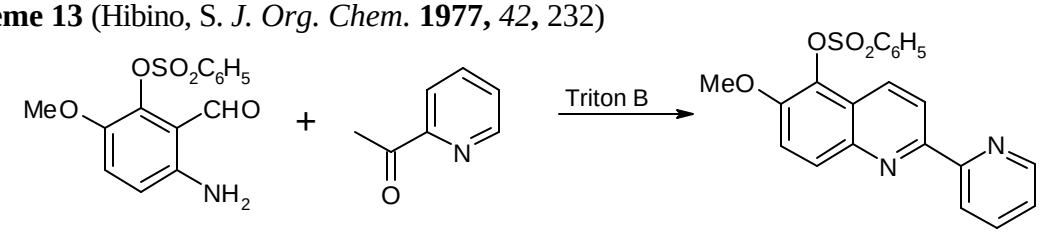


Scheme 12

After a sequence of organic transformation the intermediate **53** was obtained. The intermediate was then coupled with nitro-aldehyde in presence of potassium hydride in benzene. The aminochalcone 54 thus obtained was then reductively cyclised which gave the tetracyclic framework required for the molecule. Sulphonate protecting group was removed with sodium methoxide and gave the phenol on ring A. This was subsequently converted to streptonigrin.

In yet another synthetic effort towards streptonigrin framework, Weinreb *et al*[16] have tried the construction of the quinoline ring through a Friedländer condensation.(Scheme 13)

Scheme 13 (Hibino, S. *J. Org. Chem.* **1977,** *42***,** 232)

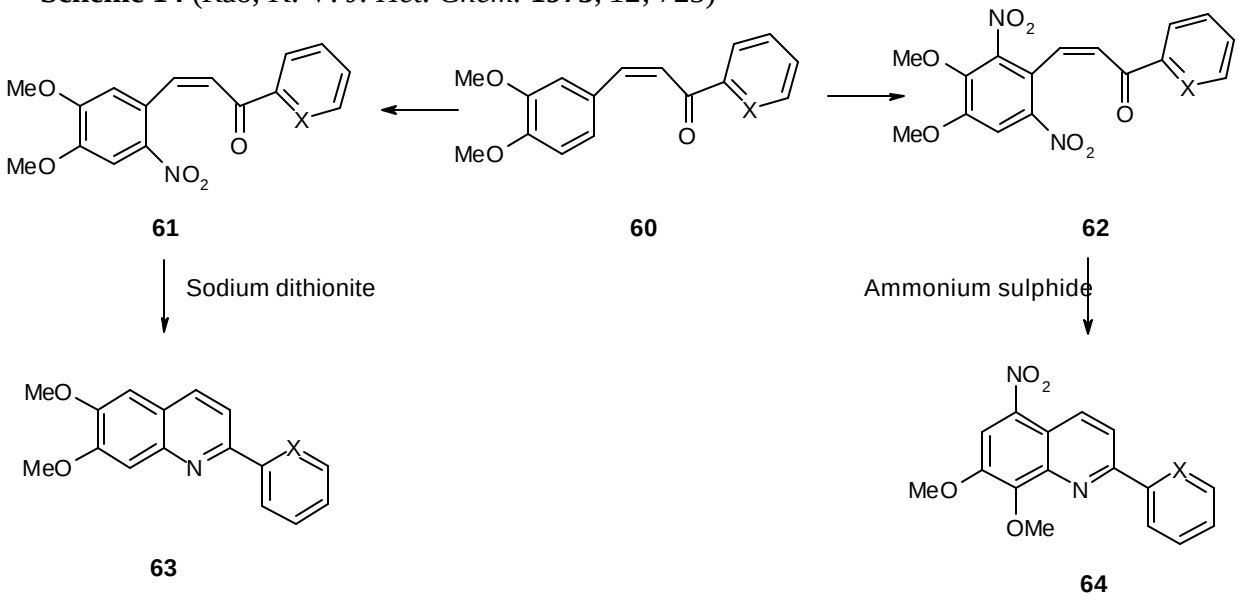


57 **58** **59**

Scheme 13

The preparation of the aminoaldehyde was done in a sequence of reaction starting from o-vanillin. The condensation with 2-acetylpyridine was done using triton B as a catalyst. The overall yield of the reaction is less than 40%.

Scheme 14 (Rao, K. V. *J. Het. Chem.* **1975**, *12*, 725)

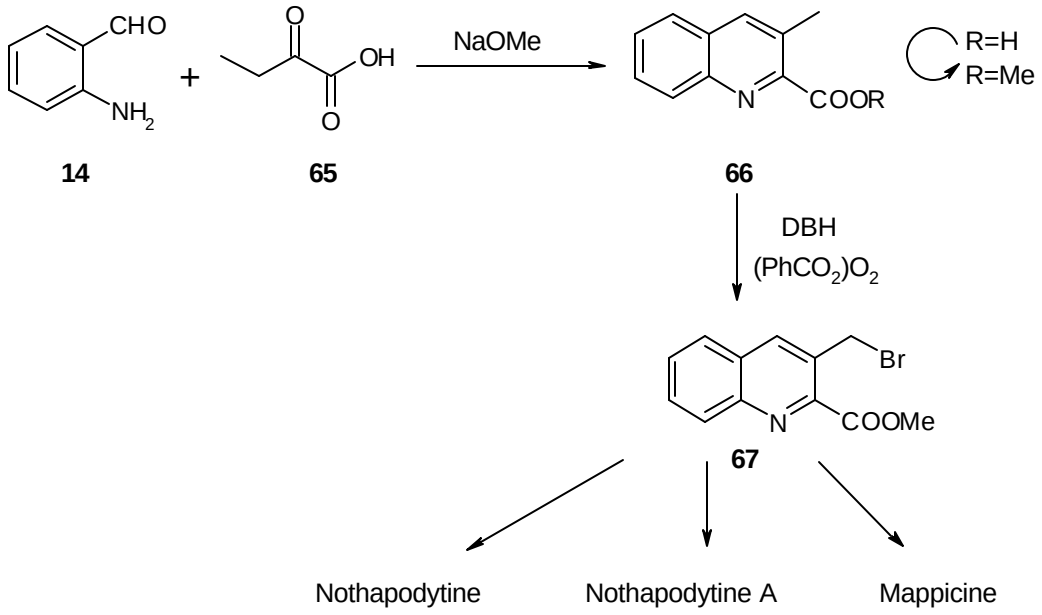


Scheme 14

Rao, K. V, [17, 9] has done pioneering efforts towards the synthesis of streptonigrin. The strategy involved in quinoline construction involves a Friendländer condensation (Scheme14). Chalcone **60** on nitration gave 3:1 mixture of 2,6-dinitro and 6-nitro derivatives. In the case of dinitro the compounds were cyclised using ammounium sulphate but in the case of 6-nitro the cyclisation was done with sodium dithionite.

Synthetic strategy towards synthesis of nothapodytine and mappicine involved the simple Friedländer condensation of 2-aminobenzaldehyde with 2-oxobutyric acid[18] and the subsequent acid thus obtained was esterfied to provide methyl 3-methylquniloine-2-carboxylate (Scheme 15).

Scheme 15 (Boger, D. L. *et. al. J. Amer. Chem. Soc.* **1998,** 1219)



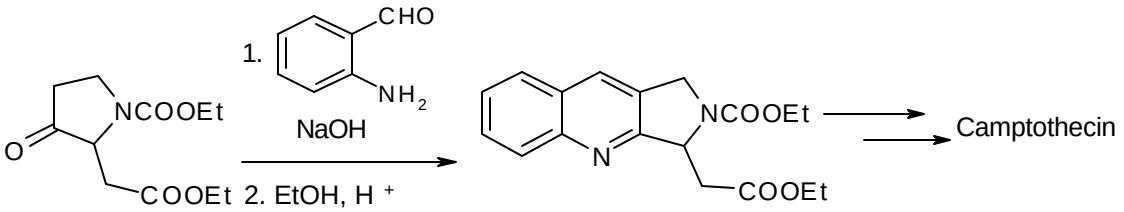
Scheme 15

The ester was then brominated using dibromohydantoin to give the bromo intermediate, which is supposed to be a key intermediate for the synthesis of nothapodytine, nothapodytine A and mappicine.

After having a look at the synthesis of the streptonigrin nucleus we now take a look at the effort taken to synthesis the quinoline nucleus of camptothecin and its analogues.

Early synthesis of camptothecin by Stork *et al*[19] followed a Friedländer condensation using *o*-aminobenzaldehyde and urethane 68 (Scheme 16).

Scheme 16 **(Stork, G.*et. al. J. Amer. Chem. Soc.*** 1971**, 4074)**

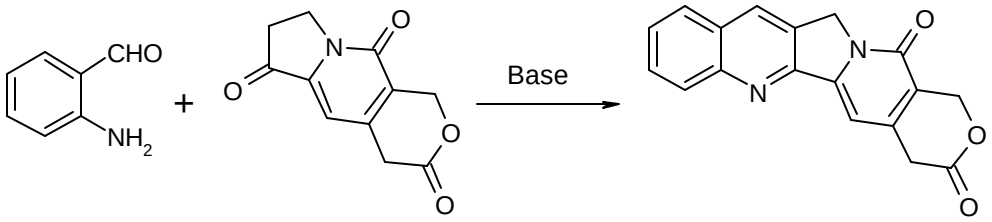


68 **69**

Scheme 16

Shamma *et al*[20] reported synthesis of camptothecin in 1973, which also involves a Friedländer condensation using *o*-aminobenzaldehyde. (Scheme 17)

Scheme 17 (Shamma, M. *et. al. Tet*. **1973**, 1949)

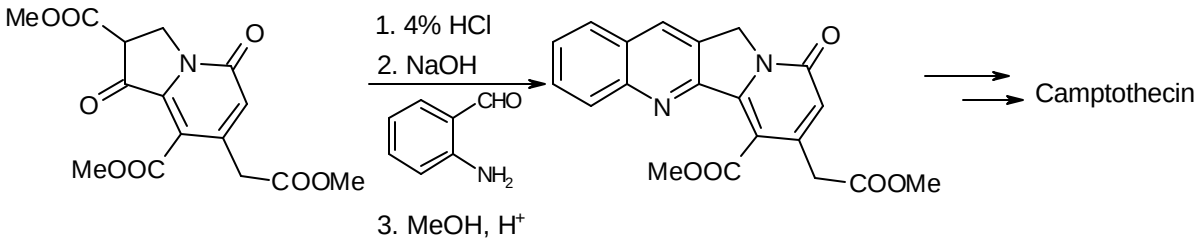


14 **70** **71**

Scheme 17

Danishefsky's report[21] on the synthesis of camptothecin also involves a Friedländer condensation using the same *o*-aminobezaldehyde. (Scheme 18)

Scheme 18 (Volkmann, R. *et. al. J. Amer. Chem. Soc.* **1971**, 5571)

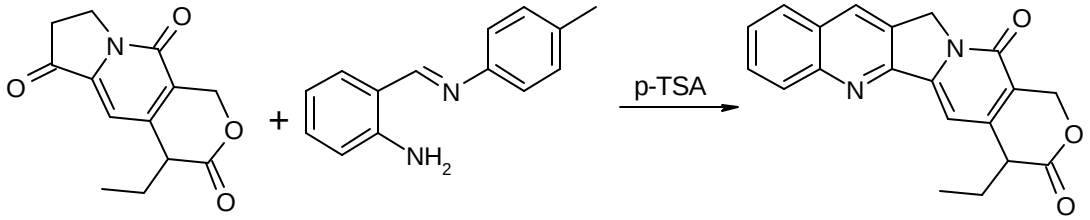


72 **73**

Scheme 18

In 1995 Danishefsky *et al* reported[22] a modification to the above synthesis. In this they used N-(*o*-aminobenzilidene)-p-toludine for Friedländer condensation. (Scheme 19)

Scheme 19 (Shen, W. *et. al. J. Org. Soc.* **1995**, 611)

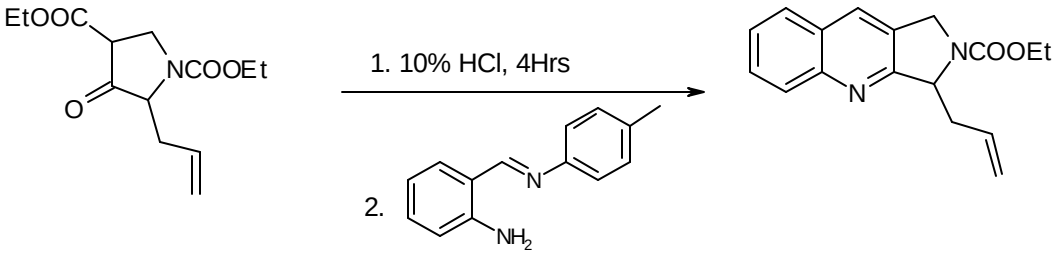


71 **72** **73**

Scheme 19

Chavan *et al* have also used the above procedure[23] of Friedländer condensation. Condensation of N-(o-aminobenzylidene)-*p*-toludine with the amino compound has been performed for the quinoline construction. (Scheme 20)

Scheme 20 (Chavan, S. P. *et. al. Tet. Lett*. **1998,** *39***,** 6745)

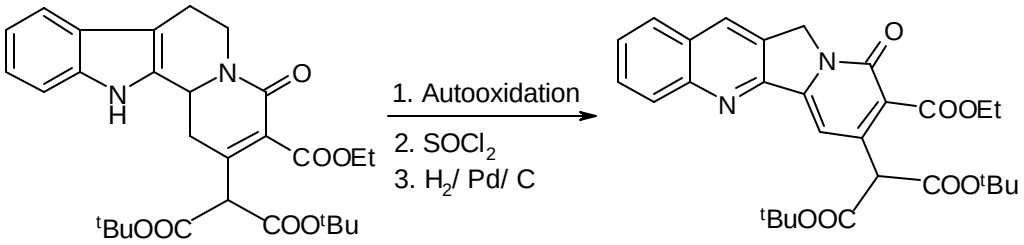


77 **75** **78**

Scheme 20

In a totally different approach Winterfeldt *et al* used autooxidation[24] of indole skeleton to obtain the quinoline skeleton (Scheme 21). The same strategy was used by Kamatani *et al*[25] towards the synthesis of camptothecin.

Scheme 21 (Winterfeldt, E. *et. al*. *Angew. Chem. Int. Ed.* **1972**, 289)

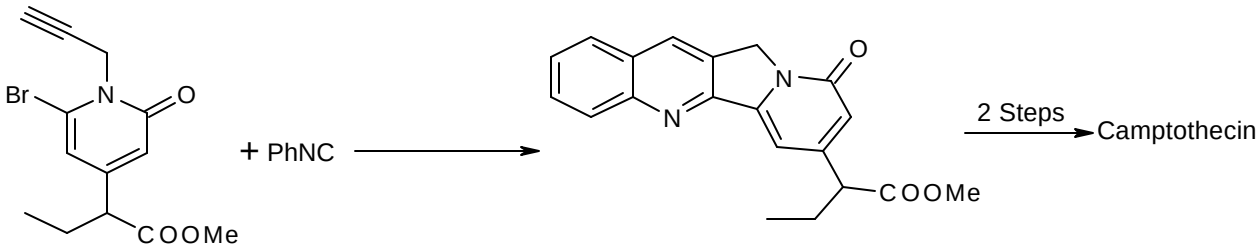


79 **80**

Scheme 21

However, Curran's approach[26] towards the construction of the quinoline ring is totally different (Scheme 22). He has employed radical annulation using phenylisocyanide and bistrimethyltin to generate the tetracyclic intermediate, which was converted to camptothecin in 2 steps.

Scheme 22 (Curran, D.P. *et. al. J. Amer. Chem. Soc.* **1992,** 5863)



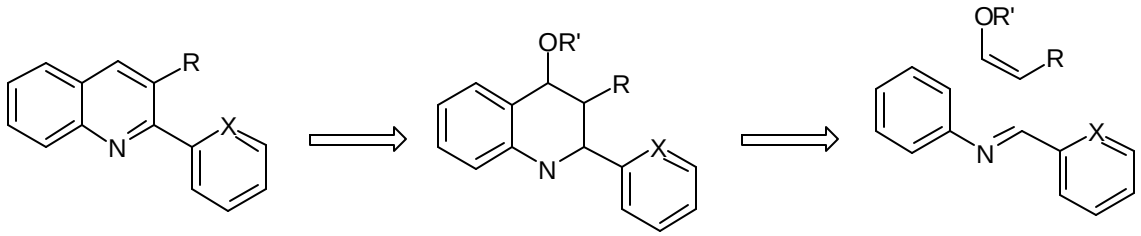
81 **82**

Scheme 22

2.3.2 Present Work

Looking into the previous synthesis of quinoline alkaloids, Friendlander condensation has been mostly employed for the construction of the quinolines and substituted quinolines. The condensation to form the 2-pyridylquinolines involves more complication. Preparation of the starting material and the yields of the reactions are just moderate. It was therefore thought to have an approach, which is short and has the potentiality to get substituted quinolines. In keeping with the interest in synthesis of camptothecin and lavendamycin, it was decided to have a common strategy towards the construction of the quinoline skeleton of both the alkaloids.

Retro-synthetic analysis revealed a possibility of a Diels-Alder reaction, with vinyl ether as a possible intermediate.



83 **84** **85**

Scheme 23

Lewis acid catalyzed Diels-Alder reaction has been known for long. Immense work has been done on both Diels-Alder reaction as well as on quinolines from our group. So it was thought to club both of them. In a typical scheme, benzylidene-phenyl-amine was

86 **87** **88**

X = CH, N

R = H R' =Et

R = H R' =Bu

R = CH_3 R' =Et

taken in dry

Scheme 24

dichloromethane and was cooled to -78^oC. One equivalent $BF_3.OEt_2$ was added, which was followed by the slow addition of one equivalent of ethyl vinylether. After completion, of the reaction, the reaction mixture was quenched with solid sodium bicarbonate and the mixture was allowed to come to room temperature. The reaction mixture was then quenched with water and the product was extracted with dichloromethane. The crude product obtained was given a dil. HCl treatment and the product was got extracted in DCM after quenching the solution with sodium bicarbonate. This product was then subjected to aromtisation using 2 equivalents of DDQ in benzene.

In this section we have demonstrated the use of different lewis acids for the hetero Diels-Alder reaction. The results obtained are tabulated in the form of a table 1.

Table 1

X	R	R'	Lewis acid	Yield %
CH	H	Et	$BF_3.OEt_2$	64
			$AlCl_3$	62
	H	n-Bu	$BF_3.OEt_2$	54
			$AlCl_3$	68
			$SnCl_4$	49
	CH_3	Me	$BF_3.OEt_2$	40
			$AlCl_3$	55
			$SnCl_4$	57
N	H	n-Bu	$BF_3.OEt_2$	48
			$SnCl_4$	49
	CH_3	Et	$BF_3.OEt_2$	46
			$SnCl_4$	42

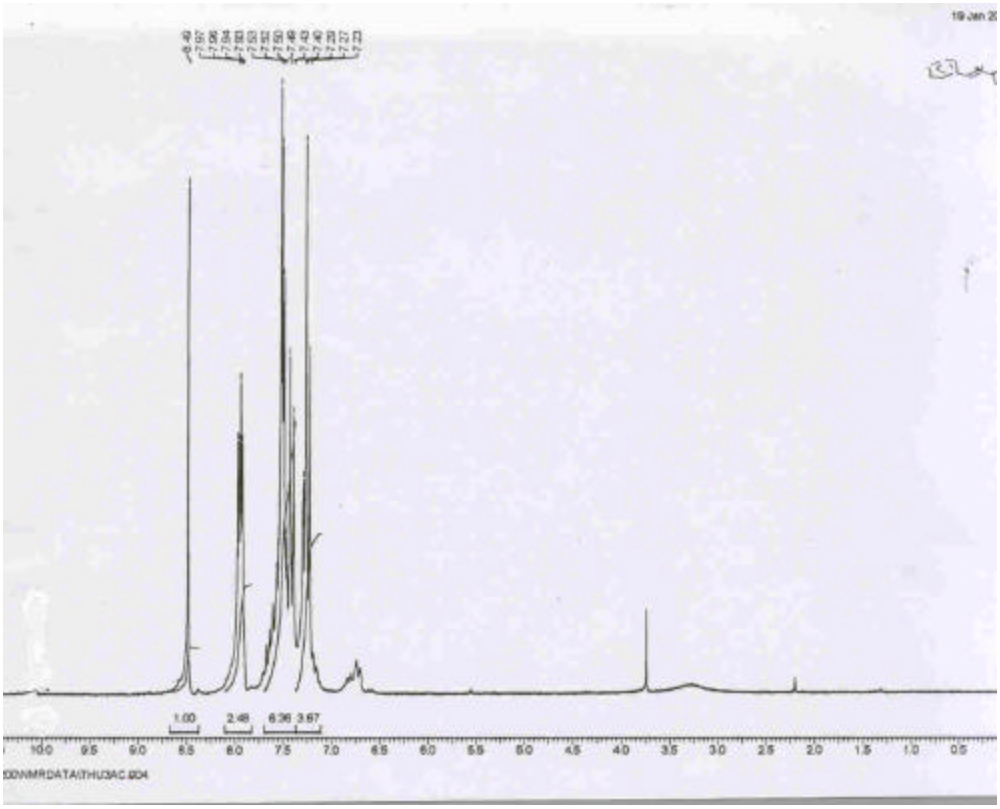
2.3.3 Results and Discussion

In a typical reaction condition for the Diels-Alder reaction, reaction was performed at –78°C. The reaction was however tried at various temperatures starting from room temperature, 0°C, -20°C. In all these cases the extensive decomposition of the strating materials was observed and there was no desired product obtained in reaction. The reaction was then standardised at –78°C. Aromatisation reaction was performed following literature precedence.[23] Substituted quinolines are very important intermediates towards synthesis of camptothecin and streptonigrin classes of compounds.

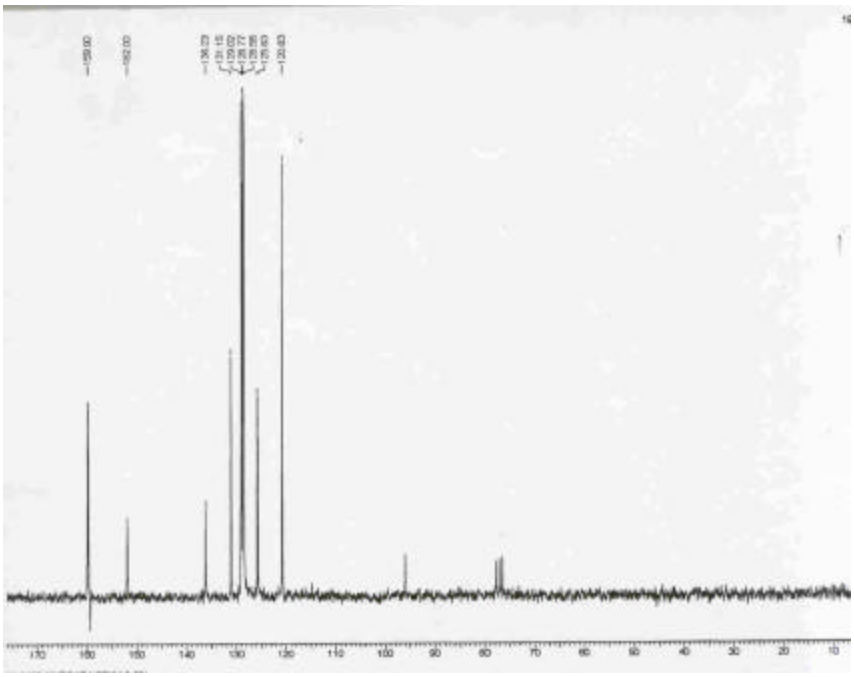
Synthesis of 2-phenylquinoline was done from benzylindine-phenyl-amine and ethyl vinyl ether, followed by aromatisation using DDQ. The formation of the desired product was confirmed using ^{1}H NMR, ^{13}C NMR and Mass spectral analysis. The ^{1}H NMR showed a typical pattern for the quinoline ring and the ^{13}C NMR showed the presence of 4 quaternary carbons. The Mass spectra revealed the peak corresponding to the molecular ion peak. The final confirmation of the structure was done with literature value on the melting point. The melting point of the compound matched with the reported melting point.

2.3.4 Conclusions

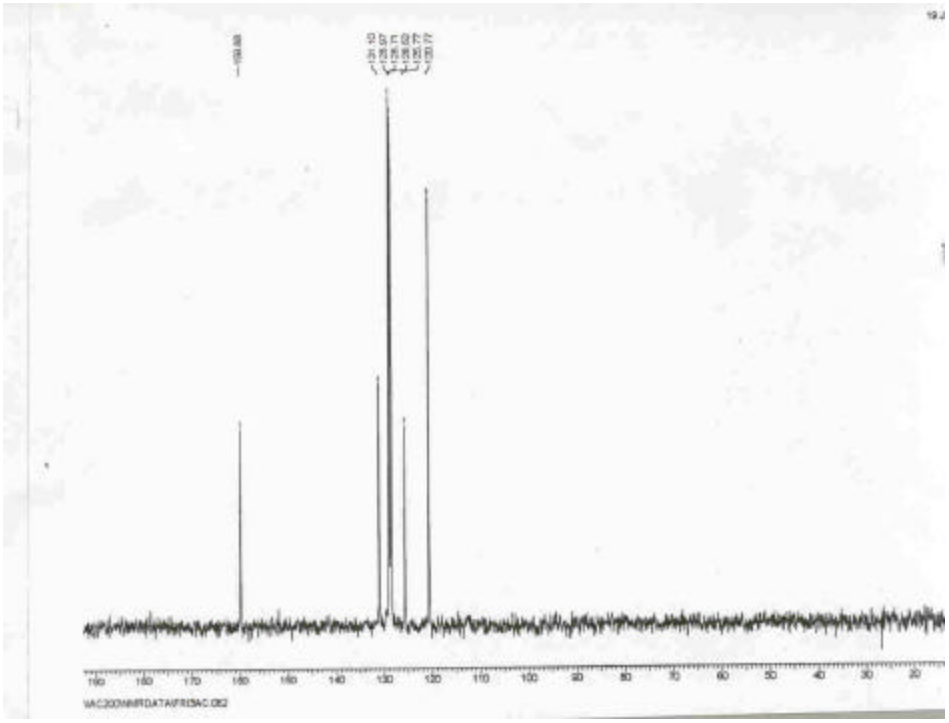
The use of Lewis acid mediated Diels-Alder reaction has been shown here. It proves to be an easy path for the synthesis of quinolines. The use of different Lewis acids has also been demonstrated. The highlight of the protocol is the intermediates obtained can be used for the synthesis of camptothecin and streptonigrin intermediates.



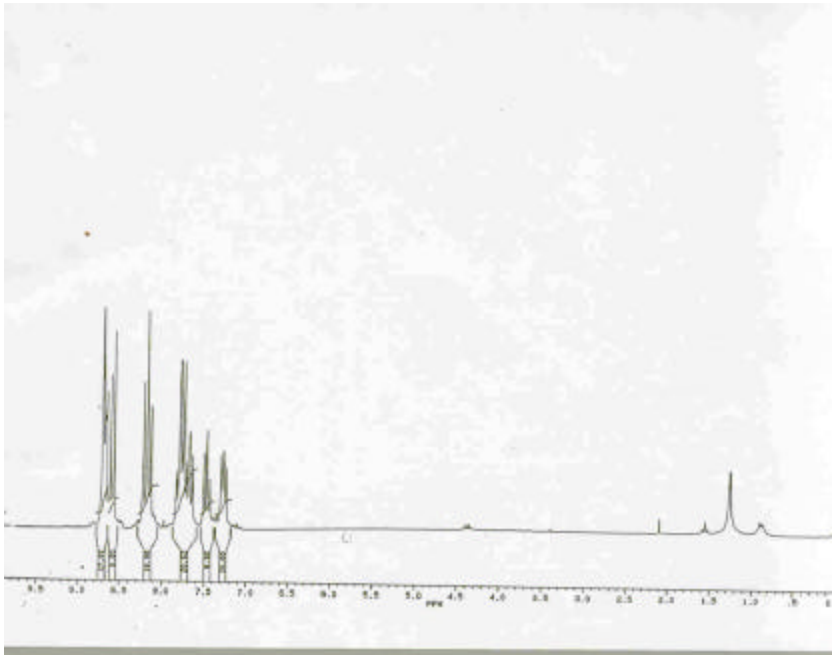
^{1}H NMR of Benzylinedene -phenyl-amine (200 MHz, $CDCl_3$)



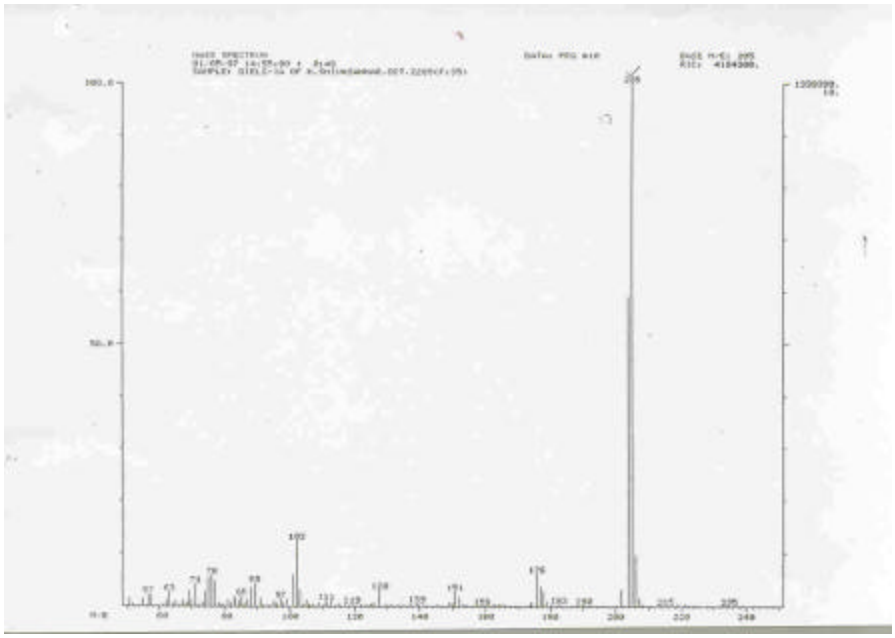
^{13}C NMR of Benzylinedene-phenyl-amine (50 MHz, $CDCl_3$)



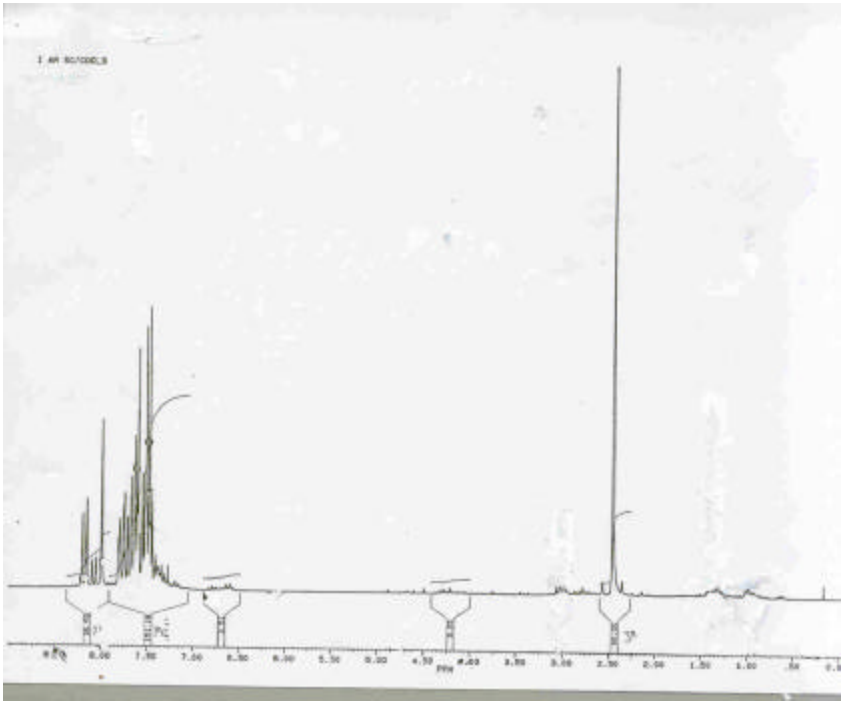
DEPT of Benzylinedene-phenyl-amine (50 MHz, CDCl3)



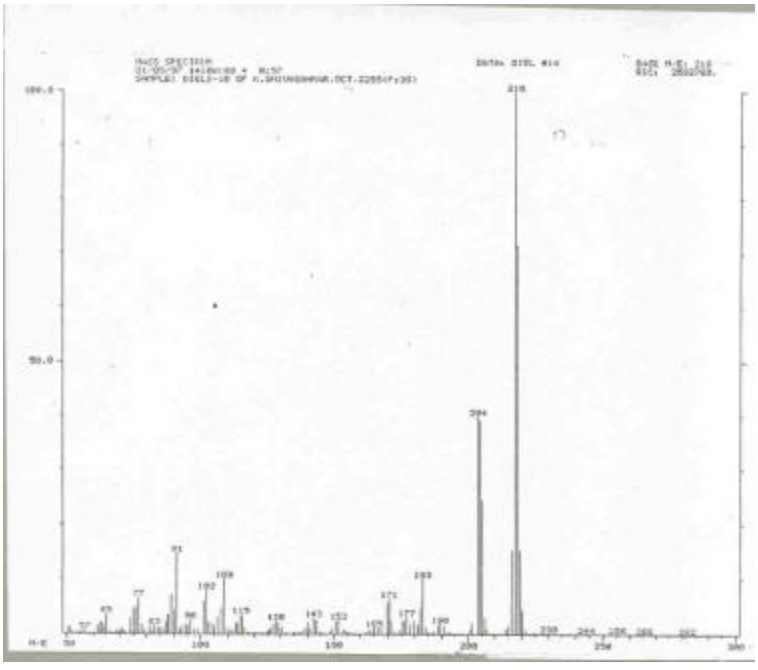
^{1}H NMR of 2-Phenylquinoline (200 MHz, $CDCl_3$)



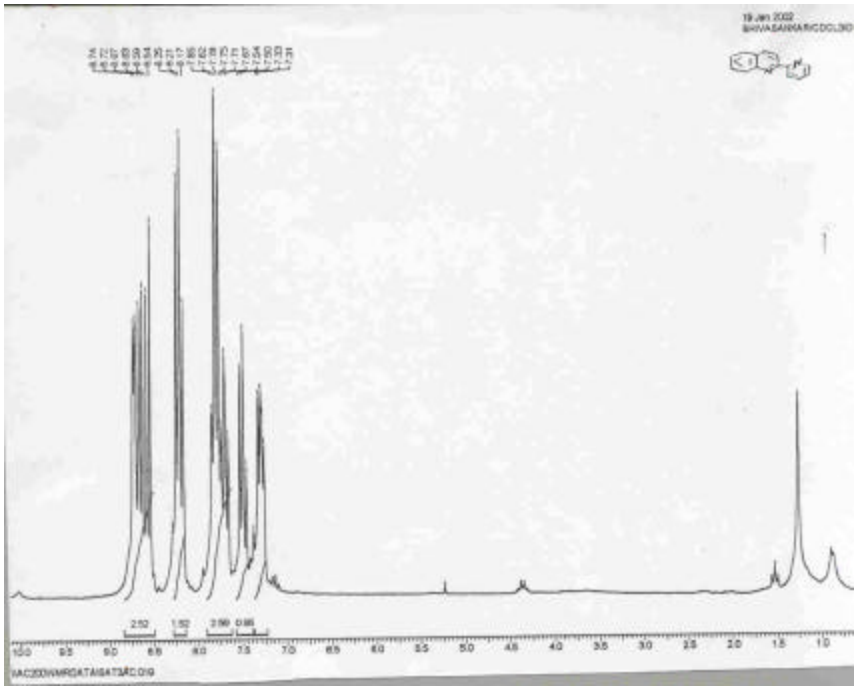
Mass spectra of 2-Phenyl quinoline



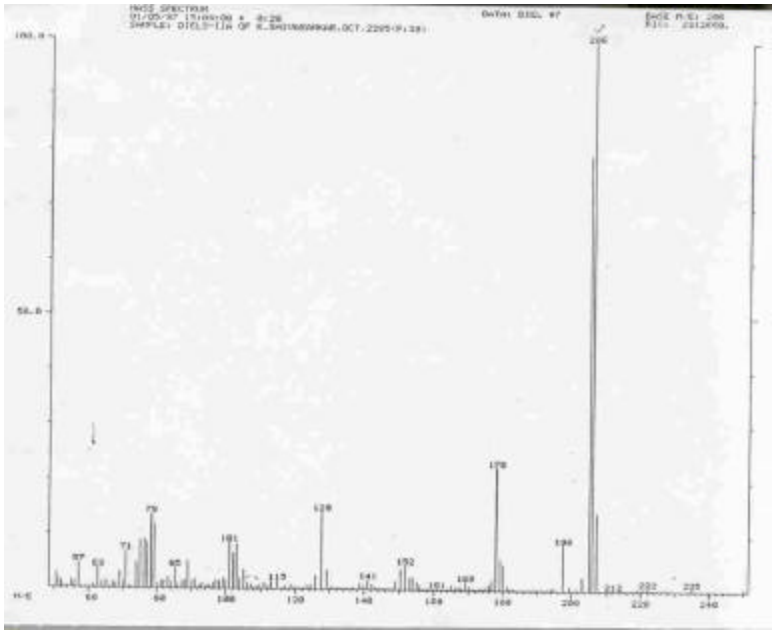
^{1}H NMR of 3-Methyl-2-phenyl quinoline (200 MHz, $CDCl_3$)



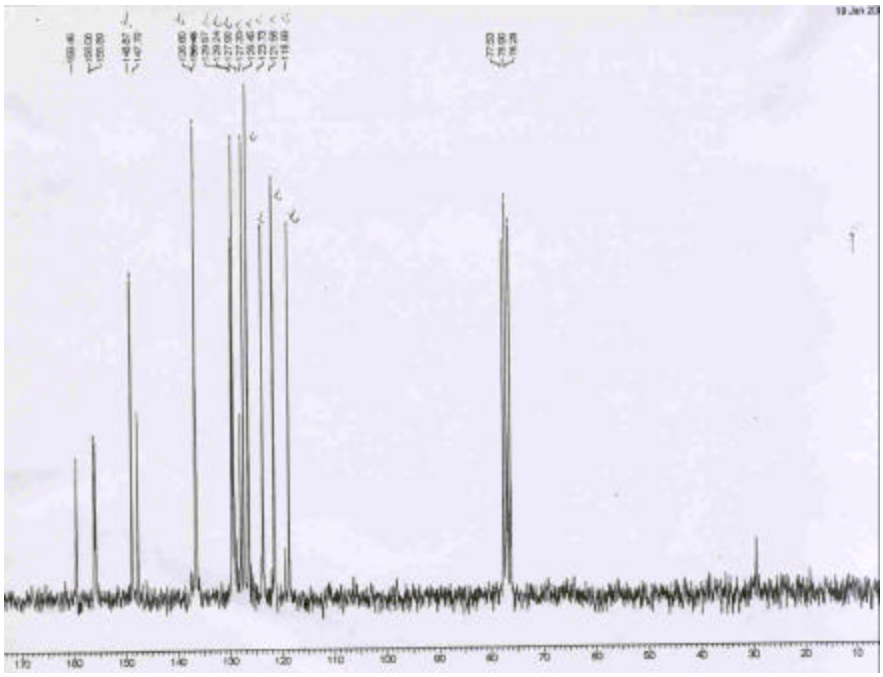
Mass spectra of 3-Methyl-2-phenyl quinoline



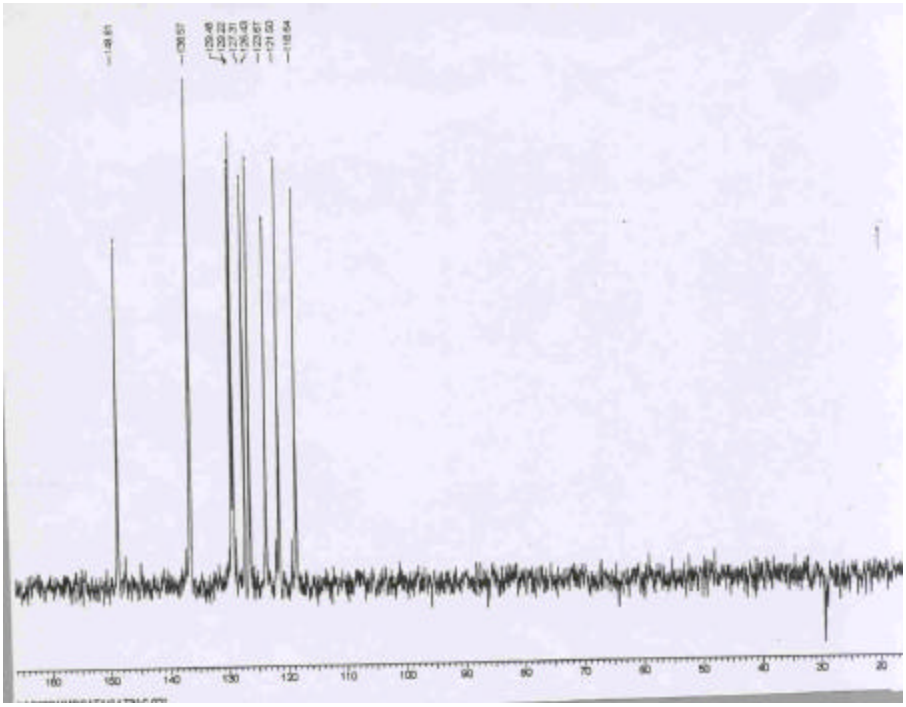
^{1}H NMR of 2-Pyridin-2-yl quinoline (200 MHz, $CDCl_3$)



Mass Spectra of 2-Pyridin-2-yl quinoline



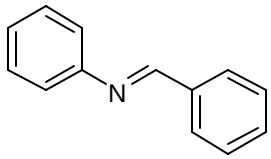
^{13}C NMR of 2-Pyridin-2-yl quinoline (50 MHz, $CDCl_3$)



DEPT of 2-Pyridin-2-yl quinoline (50 MHz, $CDCl_3$)

2.3.5 Experimental

Benzylinedene-phenyl-amine

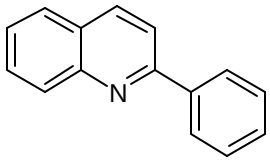


89

In a typical procedure towards the synthesis of benzylidene-phenyl-amine, a solution of aniline (1gm,10.5mmol) in methanol (10ml) to which benzaldehyde (1.12gm,10.5mmol) was added. The mixture was stirred at room temperature for 3hrs. The reaction was monitored by TLC. The reaction mixture was concentrated under vacuum. The mixture was then dissolved in DCM and was washed with sodium bisulphite. The organic layer was then separated and dried over sodium sulphate and concentrated in vacuum.

The same procedure was adopted for the synthesis of phenyl-pyridin-2-ylme thylene amine. The imine was prepared from aniline and pyridine-2-carboxaldehyde.

2-Phenylquinoline

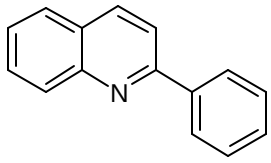


91

In a typical procedure towards the synthesis of substitued quinolines, a two necked round bottom flask attached with a two way stop cock and a septa, imine **89** (500mg, 2.76mmol) was taken and 10ml of dry THF was added. The reaction mixture was cooled to $-78^{o}C$ in a cryostat. $BF_3.OEt_2$ (0.35ml, 2.76mmol) was added dropwise through a syringe. The reaction mixture was stirred for two minutes and ethylvinyl ether (0.32ml, 3.31mmol) was added dropwise through a syringe. The reaction mixture was stirred for 5hrs and reaction was monitored through TLC. The reaction was quenched with sodium bicarbonate and the reaction was allowed to come to room temperature. Water 5ml was added and the product was extracted in DCM. The compound was treated with dil. HCl (10%) treatment (2×10ml) and the organic layer was discarded. The acidic solution was then neutralized using sodium

bicarbonate. The organic compound was extracted in DCM. DCM layer was then dried over sodium sulphate and concentrated in vacuum. The crude compound (580mg) was then taken in a two neck round bottom flask attached with a reflux condenser and a guard tube. 15ml of dry benzene was added to the crude product. DDQ (1.04gm, 4.6mmol) was added and the reaction mixture was allowed to reflux for 4hrs. The reaction was monitored by TLC. After completion of the reaction mixture was passed over a celite bed and was washed with benzene. The organic layer was washed with sodium bicarbonate solution (2×10ml). Organic layer was dried over sodium sulphate and then concentrated in vacuum. The product obtained was then subjected to a column chromatography and was eluted in 30% pet-ether and ethylacetate.

2-Phenyl quinoline[9]

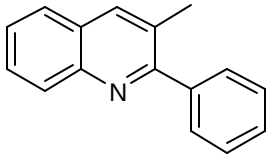


Molecular formula: $C_{15}H_{11}N$

Melting point: 83-85^{o}C

^{1}H NMR: 7.3-7.6 (m, 4H), 7.7-8.3(m, 7H)

3-Methyl-2-phenyl quinoline[27]

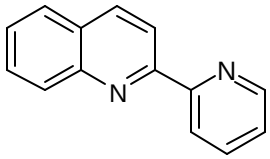


Molecular formula: $C_{16}H_{13}N$

Melting point: 48-50^{o}C

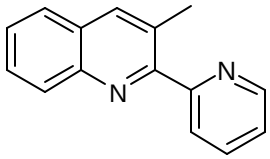
^{1}H NMR: 2.45(s, 3H), 7.3-8.2(m, 10H)

2-Pyridin-2-yl quinoline[27]



Melting point:	98-100^{o}C
^{1}H NMR:	7.1-7.9 (m, 5H), 8.83(m, 2H), 8.4-8.8(m, 3H)
^{13}C NMR:	118.7(t), 121.6(t), 123.7(t), 126.5(t), 127.3(t), 128.0(t), 129.2(t), 129.6(t), 136.6(t), 147.7(s), 148.9(t), 155.9(s), 156.1(s), 159.5(s).

3-Methyl-2-pyridin-2-yl quinoline[28]



Molecular formula:	$C_{15}H_{12}N_2$
Melting point:	45-47^{o}C
^{1}H NMR:	2.5(s, 3H), 7.3-8.2(m, 9H)

2.3.6 References

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SECTION D
Zirconium based Heterogeneous catalyst for Transfer hydrogenation

2.4.1 Introduction

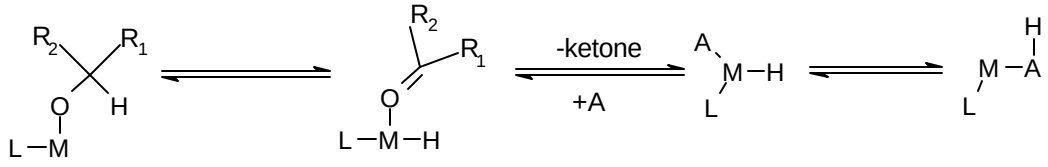
Catalytic hydrogenation is one of the most powerful weapons in the arsenal of the synthetic organic chemist. Most functional groups can be readily reduced often under mild conditions and frequently result in high chemo-, regio- and stereoselectivity. In laboratory experiments where economics is not a factor, noble metal blacks (finely divided metal) or metal oxides are sometimes used, but these catalysts are seldom seen in industrial practice. More commonly, noble metals are supported, usually as a high surface material such as carbon or alumina to facilitate metal dispersion and to aid metal recovery. The shortcomings of the normal hydrogenation are over come by hydrogen-transfer hydrogenation more commonly called as transfer hydrogenation. In comparison with catalytic reduction using molecular hydrogen, transfer reduction using hydrogen donors has real and potential advantages. Molecular hydrogen, a gas of low molecular weight and therefore high diffusablity is easily ignited and presents considerable hazards, particularly on the large scale. The use of hydrogen donors obviates these difficulties in that no gas containment is necessary, no pressure vessels are needed, and simple stirring of solutions is usually all that is required. Many catalytic hydrogenations with molecular hydrogen actually involve atomic hydrogen dispersed in and over the catalyst. For suitable hydrogen-donor properties, it seems clear that compounds containing hydrogen bonded to elements or groups with similar electronegativity to that of hydrogen itself provide the best hydrogen donors. In this respect formic acid and formates, phosphinic acid and phosphites, phosphorous acid and phosphites, hydrides of boron, aluminium and silicon alcohols, amines and hydrocarbons are all hydrogen donors in catalytic reduction. An added advantage is gained when the product decomposing donor have large negative enthalpies of formation. Hydrogen donors for heterogeneous catalytic transfer hydrogenation comprise of cyclohexene, 1,4- cyclohexadiene, *etc*. Generally these donors are used with noble metal catalysts (either finely divided or supported on carriers), but sometimes with other metals such as copper and nickel,[1] often for use at high temperature with the noble metals particularly Pd, Pt and Rh. These hydrogen donors give up hydrogen to the substrate under mild conditions with reaction temperatures rarely exceeding 100^{o}C. After giving up their hydrogen, the other reaction products from the

hydrogen donors are frequently easily removable from the reaction system like CO_2 and CO coming from formic acid.

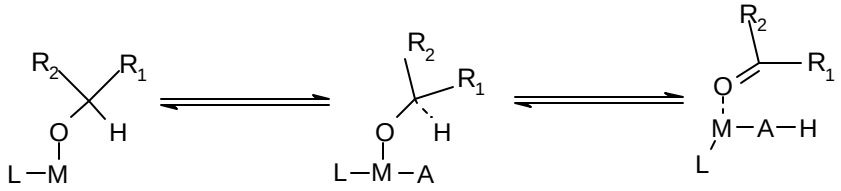
Secondary alcohols in the presence of a homogenous catalyst get converted to a ketone and the hydrogen is transferred to the acceptor but not as molecular hydrogen. The use of primary alcohols is less likely than that of a secondary alcohol to react as a hydride species because of the smaller electron- releasing effect of one alkyl group as against two. Ethanol and n-propanol have been exceptions. They have been used successfully for the transfer reduction of carboboranes,[2] aldehydes,[3] alkynes.[4] Benzyl alcohols have also been used for the reduction of unsaturated ketones.[5] Inspite of a wide variety of alcohols 2-propanol remains the most popular donor because of its simplicity, cheapness, availability and the ease of removal of both it and its dehydrogenated product (acetone). The mechanism of hydrogen transfer in 2-propanol has been extensively studied.[6] A synergist for the reaction is KOH, which is believed to be effective by removing a proton from the reacting complex during part of the catalytic cycle. Certainly, many other homogeneous catalyst systems using an alcohol as the hydrogen donor appear to need base (KOH) for their activity.

2.4.2 Mechanism of transfer hydrogenation

There are two general reaction paths,[7] which can be taken into consideration for hydrogen transfer. A) Hydridic route involves the formation of a metal hydride derivative by interaction of the catalyst with the hydrogen by interaction of the catalyst with the hydrogen donor, followed by hydride transfer from the metal to the substrate. B) Direct hydrogen transfer implying a concerted process where both the hydrogen donor and the acceptor are held together in close proximity by the catalyst.



Hydridic route



Direct hydrogen transfer

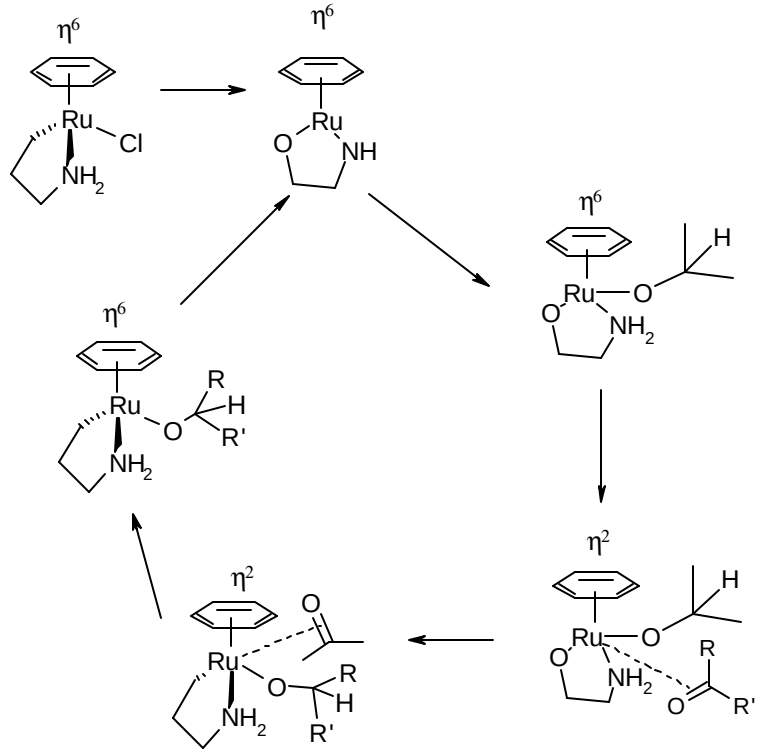
L= Ligand; A= hydrogen acceptor

Transfer hydrogenation has been an area where in lot of papers are being published, at a brisk pace. A brief look at some of the recent publication in this area, are being presented.

Alonso, D. A.; Brandt, P.; Nordin, Sofia. J. M.; Andersson, P. G. *J. Amer. Chem. Soc.* **1999**, *121*, 9580. [8]

Alonso. *et. al.*[8] have reported (Scheme 1) transfer hydrogenaton of ketones using isopropanol as hydrogen source and Ru(arene)(aminoalcohol) as the catalyst.

Scheme 1 (Alonso *et. al. J. Amer. Chem. Soc.* **1999**, *121*, 9580)



Scheme 1

Kinetics and thermodynamic factors that control the enantioselectivity of carbonyls have also been described in their publication. The authors have also described various ligands and the selectivity of these ligands towards transfer hydrogenation. Description of mechanism is highlight of the protocol. Yields in this protocol are good to excellent in some of the cases. Use of Ruthenium complexes are costly, that is the only set back in the procedure.

Mao, J.; Baker,D. C. *Org. Lett*. **1999**, *1*, 841. [9]

Enantioselective reduction of imines

Mao *et. al.*[9] have described (scheme 2) the use of chiral Rhodium catalyst (figure 1) for transfer hydrogenation. Hydrogen source for this reaction is formic acid and triethylamine azeotrope. Reduction of several compounds has been reported mainly heterocyclic imines. The yields obtained in the reaction are good.

Scheme 2 (Mao, J. *et. al. Org. Lett*. **1999**, *1*, 841)

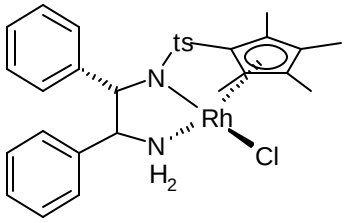
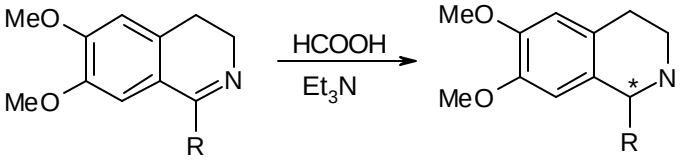


Figure 1



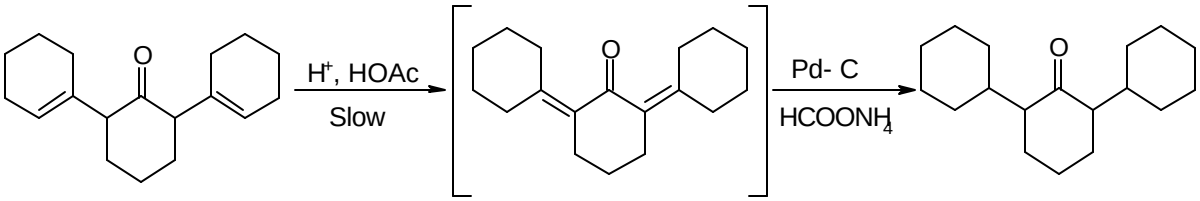
R= methyl, ethyl, isopropyl

Scheme 2

Pande, P. P.; Joshi, G. C.; Mathela, C. S. *Synth. Comm*. **1998**, *28*, 4193.[10]

Pande *et. al.*[10] have described (scheme 3) the use of palladium charcoal and ammonium formate as an efficient catalyst for the reduction of double bond. Reduction of

Scheme 3 **(Pande *et. al. Synth. Comm.*** 1998***, 28,*** **4193)**



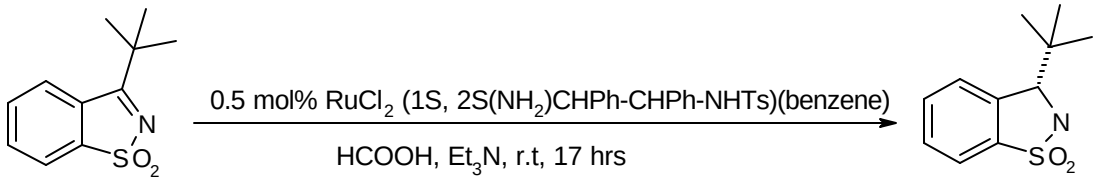
Scheme 3

a, ß-unsaturated ketones and cyclic enones to their saturated analogues. The system also converts eneimides to saturated imides. An unsaturated non-conjugated cyclic dienones was also reduced by this system.

Palmer, M. J.; Martin, W. *Tet. Assy.* **1999**, *10*, 2045 [11]

Palmer *et. al.*[11] have described (Scheme 4) in brief various ligands and complexes available for transfer hydrogenation. The paper also describes possible mechanism through which the reaction takes place. Various hydrogen sources have also been described. Out of which formic acid and triethylamine has been found to be more effective. Various substrates like 1,2 diketone, ß-ketoester, imines, ketones have been reduced enantioselectively.

Scheme 4 (Palmer *et. al. Tet. Assy.* **1999**, *10*, 2045)

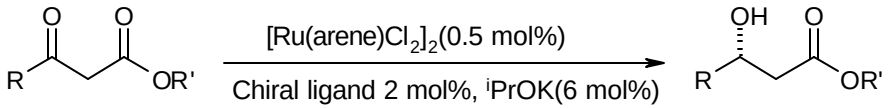


Scheme 4

Everaere, K.; Carpentier, J. F.; Mortreux, A.; Bulliard, M. *Tet. Assy*. **1998**, *9*, 2971. [12]

Everaere *et. al.* in this paper[12] have described (Scheme 5) the effect of various arenes in selectivity. Use of various chiral ligands has also been discussed. The effect of these ligands has been studied mainly on ß-ketoester where in ester is methyl, ethyl, *tert*-butyl, *iso*-propyl *etc*. Hydrogen source in these reactions is from iso-propanol and potassium hydroxide.

Scheme 5 (Everaere *et. al. Tet. Assy*. **1998**, *9*, 2971)

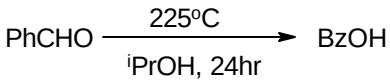


Scheme 5

Laurence, B.; Strauss, C. R. *Chem. Comm.* **1999**, *3*, 287[13]

Laurence *et. al.*[13] have reported (Scheme 6) uncatalysed transfer hydrogenation. They have reported reduction of aldehydes and ketones to their respective alcohols using alcohols like ethanol, iso-propanol, n-propanol. The reaction condition involves autoclaving of carbonyl compound with iso-propanol at 220-230^{o}C for 24-30 hrs. Aromatic as well as aliphatic ketones have been reduced successfully by this protocol. The salient feature of this methods is that double bond doesn't get reduced. Conversion are good in some of the cases. Although this is a very good protocol, the use of high temperature and autoclave for the success of the reactions will limit its practical utility.

Scheme 6 (Laurence *et. al. Chem. Comm.* **1999**, *3*, 287)

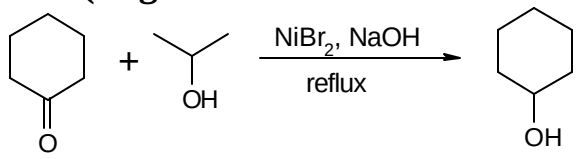


Scheme 6

Le Page, M. D.; James, B. R. *Chem. Comm.* **2000**, *17*, 1647. [14]

Page *et. al.*[14] have described the use of Nickel bromide as an additive for transfer hydrogenation. In a simple conversion of cyclohexanone to cyclohexanol, addition of Nickel bromide increased the conversion three folds. Substrates like acetophenone, nitrobenzene, bezaldehydes, octene, butanones have been reduced in excellent yields. The

Scheme 7 **(Page *et. al. Chem. Comm.* 2000*, 17,* 1647)**



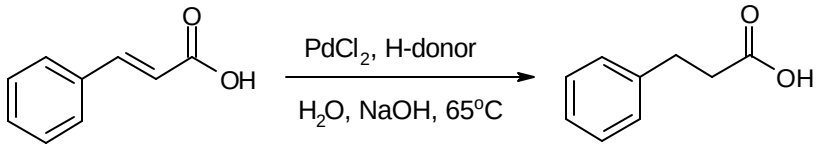
Scheme 7

time taken for the completion of the reaction is very short, thus making the protocol more attractive.

Aterburn, J. B.; Pannala, M.; Gonzalez, A. M.; Chamberlin, R. M. *Tet. Lett*. **2000**, *41*, 7847.[15]

Catalytic transfer hydrogenation using Palladium chloride, formic acid and aqueous sodium hydroxide is effective for reduction of unsaturated carboxylic acids, azalactones and a-ketocarboxylic acids. 10-mol% Palladium chloride and 4 equivalence of hydrogen donor is used for the reduction. This protocol only reduces only double bond and active carbonyls.

Scheme 8 **(Aterburn *et. al. Tet. Lett.* 2000*, 41,* 7847)**

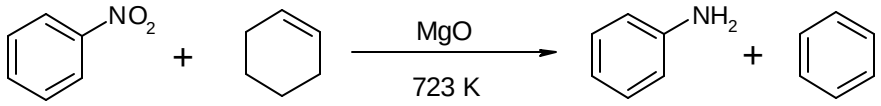


Scheme 8

Glinski, M.; Wolski, R. *Pol. J. Chem*. **2000**, *74*, 1793. [16]

Glinski *et. al.*[16] have reported MgO as an effective catalyst for transfer hydrogenation. MgO is being generated by thermal decomposition of $Mg(OH)_2$ at 873K for 1hr in air, followed by 5hrs in a stream of dry deoxygenated nitrogen. Authors also report that the use of strong bases like 10% potassium hydroxide increases the conversion. 10%H_3PO_4 on MgO is also reported. However, it has a shortcoming, as the rise in temperature activity decreases as H_3PO_4 starts decomposing.

Scheme 9 **(Glinski *et. al. Pol. J. Chem*.** 2000**, *74*, 1793)**

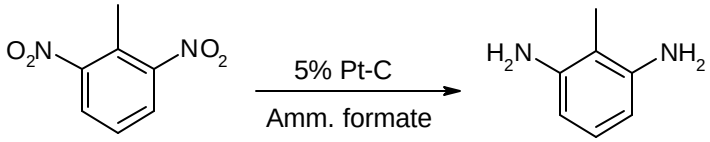


Scheme 9

Gowda, D. C.; Mahesh, B. *Syn. Comm.* **2000**, *30*, 3639.[17]

Aromatic nitro compounds were reduced to respective amines in high yields by using 5% Platinum on carbon with ammonium formate or formic acid as hydrogen donor. Ammonium formate has been found to be more effective than formic acid. Yields reported are good to excellent in some of the cases. (Scheme 10)

Scheme 10 (Gowda *et. al. Syn. Comm.* **2000**, *30*, 3639)



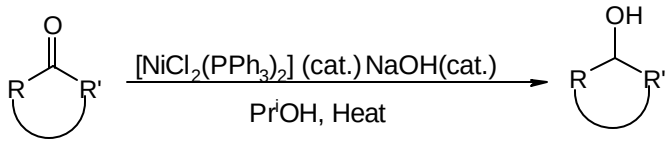
Scheme 10

Iyer, S.; Varghese, J. P. *J. Chem. Soc. Chem. Comm* **1995**, 465.

Aliphatic, allylic and aromatic ketones have been reduced using nickel catalyst[18] under specified conditions. Aromatic and aliphatic aldehydes also undergo reduction,

albeit in slightly lower yields. The reaction however takes longer time (12hrs) in case of aromatic aldehyde. The yields of the reaction are however moderate.

Scheme 11 (Iyer *et. al. J. Chem. Soc. Chem. Comm* **1995**, 465)



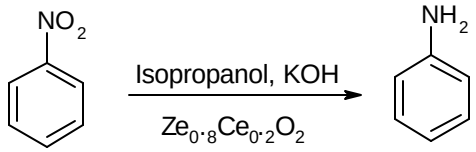
Scheme 11

Upadhya, T. T.; Katdare, S. P.; Sabde, D. P.; Ramaswamy, V.; Sudalai, A. *J. Chem. Soc. Chem. Comm.* **1997**, 1119.

Zirconia samples stabilized by Cr, Mn, Fe, Co or Ni were prepared by precipitation technique.[19] Conversion of aniline to nitrobenzene has been tested. $Zr_{0.8}Ni_{0.2}O_2$ has the greatest conversion of 96%. Various carbonyls have been converted using the above catalyst.

2.4.3 Present work

As seen from the above-mentioned reports earlier there are so many methods and different catalyst for transfer hydrogenation. The disadvantage of most of them is the cost, non-recoverable catalyst, time taken for the reaction and the yield obtained. Keeping this in mind it was envisaged to try zirconia mixed oxides as a tool for transfer hydrogenation. Since the use of isopropanol is very cheap and effective it was then thought to use it as the hydrogen donor. In a typical example with nitrobenzene, nitrobenzene was taken in isopropanol and potassium hydroxide was added and catalytic amount of $ZeCeO_2$ was added. Various mole ratios of zirconia and cerium were tried out and $Ze_{0.8}Ce_{0.2}O_2$ was found to be the best. Our primary focus of the present study is the development of the practical conversion protocol and on the catalyst structure and activity.



Scheme 12

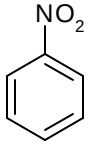
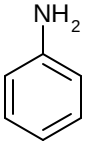
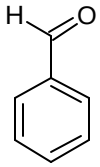
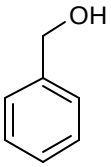
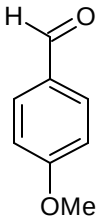
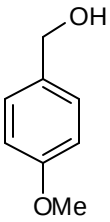
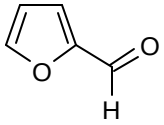
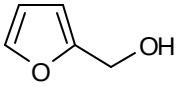
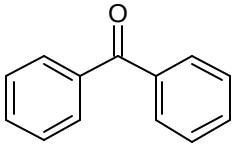
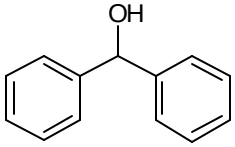
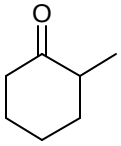
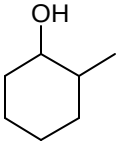
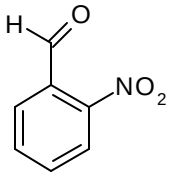
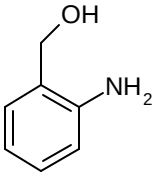
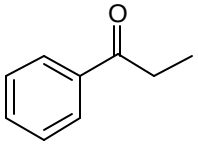
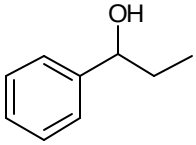
2.4.4 Results and discussions

The use of zirconia-metal oxides gives an advantage that they can be recycled number of times. The recovery is very simple. They have to washed with water and then calcined at 500^{o}C for 5hrs. The catalyst was characterized by different techniques. It was characterized by XRD, FT-IR, surface area measurements *etc*. Functional groups like nitro and carbonyl have been successfully reduced. The yields of the reaction are good to excellent. A noteworthy feature of this protocol is reduction of nitrobenzene, benzaldehyde, ketones, aldehydes to aniline, cyclic alcohol respectively were efficiently performed in very good yield. The results are all tabulated in the form of a table.

2.4.5 Conclusions

Functional groups like nitro and carbonyl have been successfully reduced using zirconia-metal oxide catalyst. The yields of the reaction are good to excellent in some cases. The recovery of the catalyst is an interesting feature of this reaction. Conditions involved in the reaction are not drastic.

Table 1

Sl. No.	Starting material	Product	Time (hrs)	Yield
1			2	96%
2			2	92%
3			2	88%
4			2	74%
5			2	91%
6			2.5	89%
7			3	78%
8			2.5	90%

2.4.6 Experimental

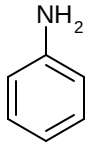
Preparation of the catalyst:

$Zr_{0.8}Ce_{0.2}O_2$ was prepared by treating an aqeous solution of Zirconyl nitrate and Cerium nitrate with tetramethyl ammonium hydroxide (25% aq. solution) as a precipitating agent under vigorous stirring. The hydroxide precipate was then washed with distilled water followed by acetone and dried in oven at 110^{o}C for 24hrs. It was later calicined at 500^{o}C. It was characterized by XRD, FT-IR, surface area measurements *etc.*[20]

Typical Procedure:

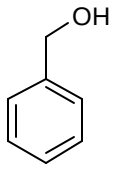
Nitrobenzene (500mg, 4.1 mmol) was taken in a two necked round bottom flask attached with a reflux condenser and a stopper. 15ml of isopropanol was taken as the solvent. 500mg of KOH was added and the reaction was set for stirring until all of KOH dissolved. 2mg of $ZrCeO_2$ was added, and the reaction was set for reflux for 2hrs. Completion of the reaction was checked by TLC. Reaction mixture was filtered through filter paper. 10ml of water was added to the filtrate and product was extracted in ethyl acetate and concentrated under reduced pressure, to furnish 363 mg (96%) of aniline. Analogously the carbonyl compounds were also reduced to the corresponding alcohols, under similar conditions.

1. **Aniline**



Molecular formula:	C_6H_7N
Yield:	96%
IR (Neat, cm^{-1}):	3420-3460, 1620, 1490, 1280.
^{1}H NMR:	3.45 (b, 2H), 6.3-6.6 (m, 3H), 6.9-7.25 (m, 2H).

2. **Benzyl alcohol**



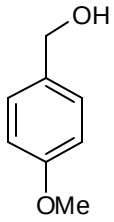
Molecular formula: C_7H_8O

Yield: 92%

IR (Neat, cm^{-1}): 3300-3350, 1600, 1480, 1420, 1210.

^1H NMR: 1.9 (b, 1H), 4.7 (s, 2H), 7.3 (s, 5H).

3. **4-Methoxy benzyl alcohol**



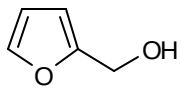
Molecular formula: $C_8H_{10}O_2$

Yield: 88%

IR (Neat, cm^{-1}): 3350-3450, 1600, 1500, 1450, 1250.

^1H NMR: 1.7 (b, 1H), 3.8(s, 3H), 4.6 (s, 2H), 6.75 (d, J=8hz, 2H), 7.25 (d, J=8hz, 2H).

4. **2-Furfuryl alcohol**



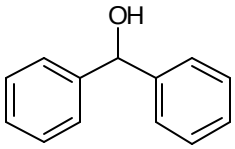
Molecular formula: $C_5H_6O_2$

Yield: 74%

IR (Neat, cm^{-1}): 3300-3400, 1600, 1500, 1380, 1250.

^1H NMR: 3.5 (b, 1H), 4.6 (s, 2H), 6.3 (m, 2H), 7.4 (m, 1H).

5. **Benzhydrol**[19]



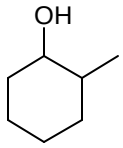
Molecular formula: $C_{13}H_{12}O$

Yield: 91%

IR (Neat, cm^{-1}): 3200-3300, 1460, 1380, 1280.

^1H NMR: 2.35 (b, 1H), 5.8 (s, 1H), 7.3 (s, 10H)

6. **2-Methylcyclohexanol**



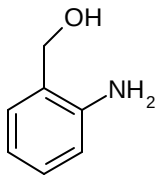
Molecular formula: $C_7H_{14}O$

Yield: 89%

IR (Neat, cm^{-1}): 3300-3400, 1450, 1380, 1220.

^1H NMR: 0.95(d, J=6Hz, 3H), 1.1 – 1.8 (m. 8H), 3.05 (m, 1H), 3.8 (m, 1H).

7. **2-Amino benzyl alcohol**[19]



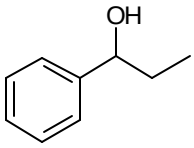
Molecular formula: C_7H_9NO

Yield: 78%

IR (Neat, cm^{-1}): 3400-3100, 1600, 1480, 1370, 1350, 1290, 1200.

^1H NMR: 3.4 (b, 1H), 4.5 (s, 2H), 6.5-7.1 (m, 4H),

8. **1-Phenyl-1-propanol**



Molecular formula: $C_9H_{12}O$

Yield: 90%

^{1}H NMR: 0.89(t, 3H, J=7Hz), 1.7(m, 2H), 2.97(brs, 1H), 4.5(q, 1H, J=6Hz), 7.3 (m, 5H).

2.4.7 References

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