SYNTHETIC STUDIES TOWARDS 4-DEMETHOXYDAUNOMYCINONE, PROSTAGLANDINS, (±) LAEVIGATIN AND DEVELOPMENT OF OTHER USEFUL SYNTHETIC METHODOLOGIES

THESIS
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TH 1143

BY

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Form-A

CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Synthetic studies towards 4-Demethoxydaunomycinone, Prostaglandins, (±) Laevigatin and development of other useful synthetic methodologies"** *by Ms Y. TRIPURA SUBBARAO* was carried out by her under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

June 1998
PUNE

S. P. Chavan
Research Guide

With Love

To my dear Mother and Father

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How often we discover words of others that reflect
the same unspoken thoughts of our minds and suddenly one-day
We discover the importance of these words.

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Tripura

Tripura

General Remarks

1. All melting points and boiling points are uncorrected and the temperatures are in the centigrade scale.
2. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.
3. Organic layers were dried over anhydrous sodium sulfate.
4. TLC analysis was carried out on glass plates using silica gel GF-254 and the plates were analyzed by keeping in iodine or under UV light.
5. In cases where chromatographic purification was done, silica gel (60-120 mesh) was used as the stationary phase.
6. IR spectra were recorded on Perkin-Elmer Infrared Spectrophotometer Model 68B or on Perkin-Elmer 1615 FT Infrared spectrophotometer.
7. ^{1}H NMR and ^{13}C NMR were recorded on **Varian FT-80A** (20 MHz), **Bruker WH-90** (22.63 MHz), **Bruker AC-200** (50 MHz) or **Bruker MSL-300** (75 MHz). Figures in parentheses refer to ^{13}C frequencies. Trimethyl silane was used as the internal standard.

Abbreviations

Ac	Acetyl
acac	acetoacetate
AIBN	2,2-Azobis(isobutyronitrile)
Ar	Aryl
BMS	Boron Dimethyl Sulfide
Bu	Butyl
^{t}Bu	*tert*-Butyl
CAN	Ceric Ammonium Nitrate
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DDQ	2,3-Dichloro-5,6-Dicyano-1,4-Benzoquinone
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DIBAL-H	Diisobutyl aluminium hydride
(+)-DIPT	Diisopropyl tartarate
DMAP	N,N-Dimethyl amino pyridine
DMF	N,N-Dimethyl formamide
DMS	Dimethyl Sulphate
DMSO	Dimethyl sulfoxide
EDC	Ethylene Dichloride
Et	Ethyl
HMDS	Hexamethyldisilane
LDA	Lithium diisopropyl amide
mCPBA	m-Chloroperbenzoic acid
Me	Methyl
Ms	Methane sulfonyl
NCS	N-Chlorosuccinamide
NMO	N-Methyl morpholine N-oxide
PDC	Pyridinium dichromate
PCC	Pyridinium chlorochromate
Pd/C	Palladized Carbon
PPTS	Pyridinium p-toluene sulfonate
Ph	Phenyl
PPh_3	TriPhenyl Phosphine
p TSA	p-Toluene sulfonic acid
^{i}Pr	Isopropyl
Py	Pyridine
TBAF	Tetrabutyl ammonium fluoride
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
TBDMSCl	*tert*-Butyldimethylsilyl chloride
Ts	Tosyl
TBHP	*tert*-Butyl Hydrogen Peroxide

ABSTRACT

The thesis entitled "SYNTHETIC STUDIES TOWARDS 4-DEMETHOXY-DUANOMYCINONE, PROSTAGLANDINS, (±)LAEVIGATIN AND DEVELOPMENT OF OTHER USEFUL SYNTHETIC METHODOLOGIES" is divided in two chapters.

The first chapter comprises of a synthetic study towards 4-Demethoxyduanomycinone, Prostaglandins, and (±) Laevigatin.

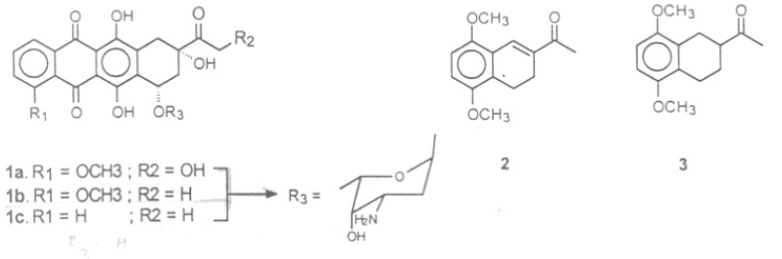
The second chapter is development of useful methodologies for organic transformations.

Chapter I: SYNTHETIC STUDIES TOWARDS 4-DEMETHOXYDUANOMYCINONE, PROSTAGLANDINS AND (±)LAEVIGATIN

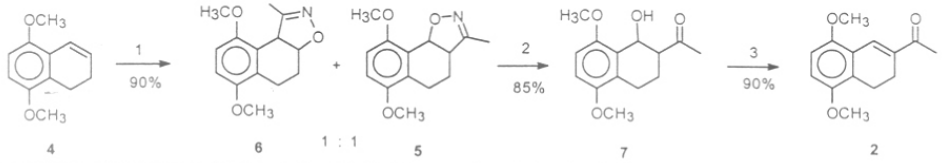
Section 1: SYNTHESIS OF AB RING SEGMENTS OF 4-DEMETHOXY DUANOMYCINONE USING A 1,3-DIPOLAR CYCLO ADDITION STRATEGY

The Anthracycline antibiotics Adriamycin **1a** and Duanomycin **1b** have significant clinical utility in the treatment of various human solid tumors and leukemias with a drawback of dose dependent cardiotoxicity[1]. Analogues like 4-demethoxy duanomycin have been reported to be less toxic and 8 to 10 times more active than adriamycin. Consequently the aglycon 4-demethoxy duanomycinone **1c** which is an important intermediate in the synthesis of 4-demethoxy duanomycin has been synthesized through various routes.

This section essentially deals with the synthesis of 2-acetyl-5,8-dimethoxy-3,4-dihydronapthalene[2] (**2**) which is a key intermediate for the synthesis of 4-demethoxy duanomycinone **1c**.

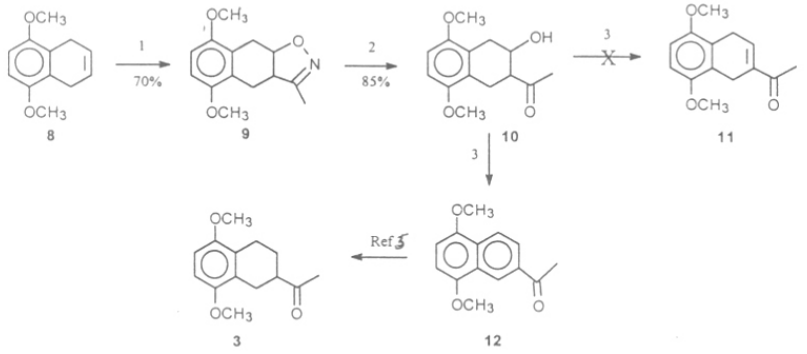


A 1,3-dipolar cycloaddition reaction of nitrile oxide[3] has been employed for the synthesis of the compound **2** starting from a simple tetralene (5,8 dimethoxy, 1,2 dihydro naphthalene (**4**) wherein two regio isomeric isoxazolines **5** & **6** where formed. The desired isomer **5** was separated and converted to the hydroxyketone **7** and was finally converted to the α, β-unsaturated ketone **2** in good yields.



1. $PhCNO$, $CH_3CH_2NO_2$, Et_3N.; **2**. Ra-Ni, H_3BO_3, $MeOH\text{-}H_2O$.; **3**. MsCl, Et_3N, DMAP.

In addition, the nirtile oxide cycloaddition has also been carried out on 5, 8-dimethoxy 1,4-dihydronaphthalene (**8**) to get a single regioisomer and the product 12 can be elaborated into 4-demethoxy duanomycinone by reported[4] procedures.

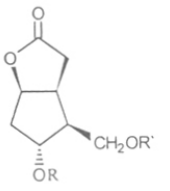


Section 2 : ATTEMPTED SYNTHESIS OF COREY'S LACTONE STARTING FROM A SIMPLE ACYCLIC PRECURSOR

Prostaglandins (PGs) are a family of C_{20} unsaturated polyoxygenated fatty acids which exhibit diverse activities in body tissues and cells such as smooth muscle contraction and relaxation, blood platelet aggregation and also as local hormones for maintaining homeostatis of the circulatory, respiratory and digestive organs. Its role in family planning is of great significance.

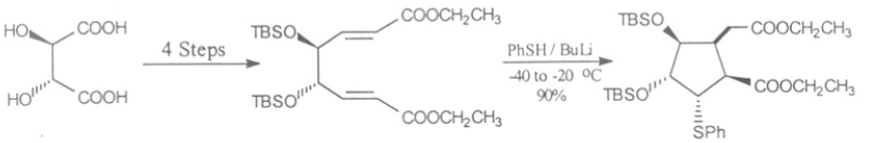
One of the major strategies utilized for the synthesis of prostaglandins has been the Corey's synthesis which utilizes the bicyclic intermediate popularly known as Corey's

lactone **13**. This bicyclic intermediate **13** of Corey which forms a key step towards the synthesis of various prostaglandins[6] has been synthesized in a variety of ways. Its popularity stems from fact that it possesses suitable functionality in correct stereochemical configuration for facile elaboration into prostaglandins $F_{2\alpha}$, E_2 and D_2 .



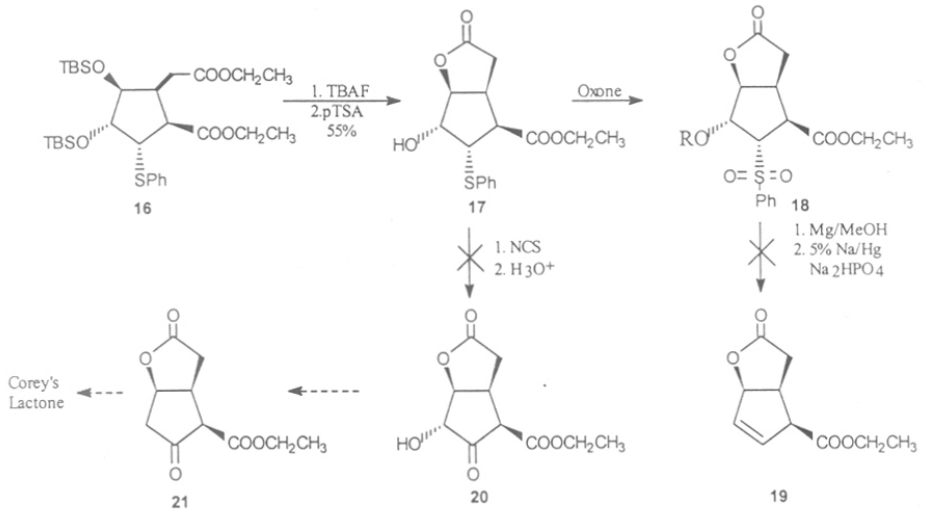
13

Keeping the configuration in mind a synthesis of Corey's lactone was attempted starting from L-tartaric acid as a model study. A Michael induced ring closure by thiophenoxide as per reported procedure[7] yielded the compound **16** which was further converted to the lactone **17**.



14 **15** **16**

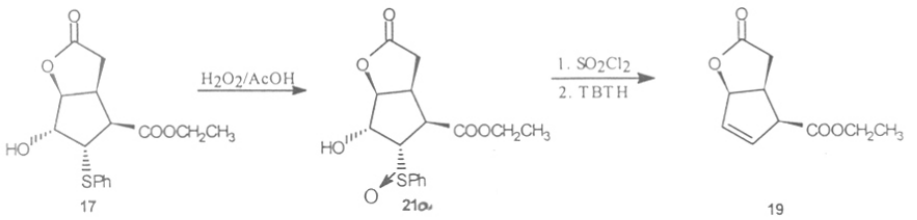
The lactone **17** was subjected to a variety of reactions in order to get the desired product **20**. Unfortunately all attempts to hydrolyze the thiophenol group or to introduce a double bond failed to furnish the desired result.



16 **17** **18**

21 **20** **19**

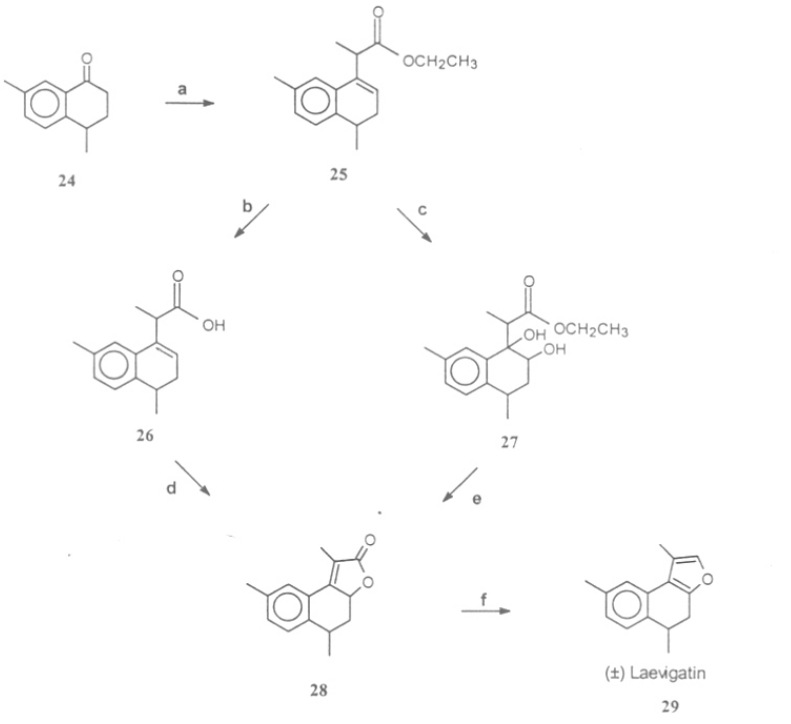
Finally the elimination was achieved with sulfuryl chloride and tributyltin hydride The olefin **19** can serve as synthon to Corey's lactone as well as other prostanoids.



Section 3 : TOTAL SYNTHESIS OF (±) LAEVIGATIN

Laevigatin, a sesquiterpene furan, with an unusual framework has been first isolated from *Eupatorium laevigatum* by de Oliviera *et. al*[8]. A total synthesis of (±) Laevigatin, has been achieved in this section using two efficient methodologies developed earlier[9] to generate butenolides *via* osmylation of β,γ-unsaturated esters and direct oxidative conversion of β,γ-unsaturated esters to butenolides by cerric ammonium nitrate (CAN) at room temperature involving two electron oxidation.

The synthesis has been achieved by carrying out a Reformatsky reaction on 4,7-dimethoxy tetralone (**24**) to furnish the corresponding β,γ-unsaturated ester **25** which was then hydrolyzed to **26** and further converted to butenolide **28** by using CAN. The butenolide **28** was also made by subjecting **25** to a osmylation reaction to yield the diol **27** which on heating with p-toluene sulfonic acid (pTSA) yielded the butenolide. This butenolide **28** on treatment with DIBAL at - 78°C yielded the furan (±) laevigatin (**29**) in good yield. This constitutes a short, efficient and practical synthesis of (±) laevigatin.



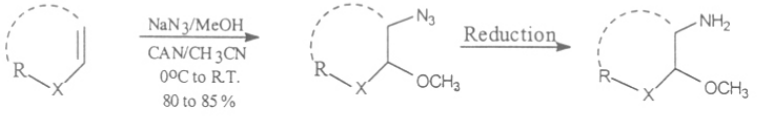
, Zn/I_2, dry ether (80%) (b) KOH/MeOH, △, (83%) (c) OsO_4, NMO, $Na_2S_2O_5$, CH_3CN/H_2O (78%)

(d) CAN, $NaHCO_3/CH_3CN$, R.T (74%) (e) PTSA/Benzene, △, (78%) (f) DIBAL-H, dry toluene, -78°C, (70%)

CHAPTER II : DEVELOPMENT OF USEFUL SYNTHETIC METHODOLOGIES FOR ORGANIC TRANSFORMATIONS

Section 1 : AZIDOALKOXYLATION OF OLEFINS.

A simple single step addition of azide and alkoxy groups to the double bond/enol ethers was achieved by ceric ammonium nitrate at room temperature. Enol ethers and electron rich olefins have been demonstrated to furnish the azidoalkoxy compounds in good yields. The present method is efficient and easy to perform as compared to the electrochemical method reported[10] in literature.



X = O, CH_2

30 31 32

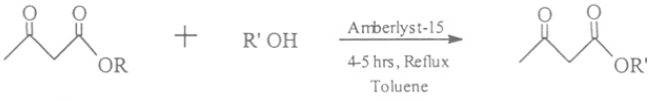
The salient feature of this methodology is that it provides one of the easiest routes for the synthesis of amino acetals which are important reagents for the synthesis of Isoquinolines and other heterocyclic compounds .

Section 2 : TRANSESTERIFICATION OF β-KETO ESTERS

β-keto esters serve as important synthons by virtue of the ease with which they can be transformed to chiral building blocks by chemical and enzymatic transformations as well as a tool for chain extension reactions. As a consequence of their importance their interconversion to different ester has received considerable attention.

Normal methods of transesterification are equilibrium driven reactions wherein excess of reactants are required. In this section Amberlyst-15 (10 mole %) was effectively utilized for interconversion of readily available β-keto esters to the corresponding transesterified products.

A one to one exchange of β keto esters was achieved in good to excellent yields utilizing Amberlyst-15 as catalyst.



33 34 35

The catalyst *viz.* Amberlyst-15 being heterogeneous in nature offers advantages over other conventional methods not only in terms of yields but ease of work up and retrieval of the products in addition to the reusability of the catalyst.

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CHAPTER I

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Synthetic studies towards 4-Demethoxydaunomycinone, Prostaglandins & Laevigatin

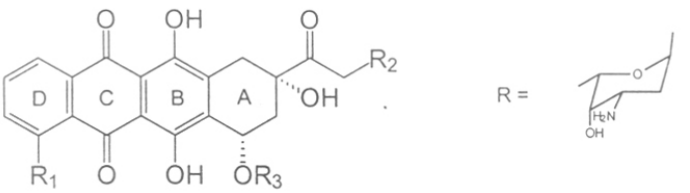
SECTION 1

Synthesis of AB ring segments of 4-demethoxydũanomycinone using a 1,3-dipolar cycloaddition strategy

1.1.0 Introduction:

Anthracycline antibiotics Adriamycin **1** and Duanomycin **2** are clinically useful drugs for the treatment of a broad spectrum of human cancers.[1] Initially due to extreme toxicity little hope was predicted for this class of compounds. However the dividing line between toxicity and desired pharmocological effects has broadened to a large extent partly through microbiological methods (new strains, mutants) and partly through semisynthetic modifications. Their remarkable antitumor properties motivated synthetic chemists to find analogs with improved antineoplastic activity and decreased toxicity.

Scheme-1:



1 $R_1 = OCH_3$, $R_2 = OH$, $R_3 = R$
3 $R_1 = OCH_3$, $R_2 = OH$, $R_3 = H$
5 $R_1 = H$, $R_2 = OH$, $R_3 = H$

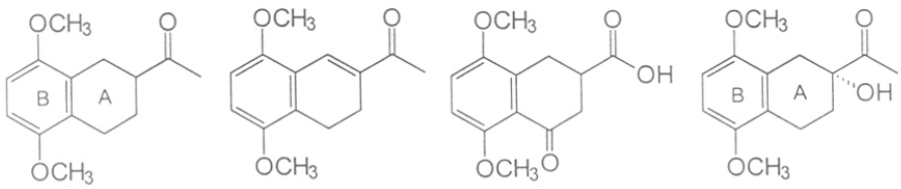
2 $R_1 = OCH_3$, $R_2 = H$, $R_3 = R$
4 $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$
6 $R_1 = H$, $R_2 = H$, $R_3 = H$

The total synthesis of the corresponding aglycone parts of Adriamycinone **3** and Duanomycinone **4** have been a subject of intense study in the last fifteen years due to lack of an efficient biosynthetic process[2] as well as the search for more active analogs with reduced cardiotoxicity.[3] The different synthetic routes to these anthracyclinones have been summarized into excellent reviews.[4] Of the several analogues studied, 4-demethoxyduanomycinone **6** has assumed considerable clinical importance as it was found to be 8-10 times more effective than its counterparts Adriamycin **1** or Duanomycin **2**. Further it was found to be orally active and coupled with its non-availability through the natural process of fermentation has provided the stimulus for many synthesis of this aglycone moiety which includes Friedel-Crafts and Fries type reactions[5], Marschalk reaction[6], Diels-Alder reactions[7], 1,4-dipole metalated anion strategy[8] and the reaction of chromium carbene complexes with acetylenes.[9]

Of these developed in general[10] the most often used approach is the convergent, regioselective coupling of chiral AB ring fragments with phthalide or phthalide anions to produce the tetracyclic skeleton. This synthetic route has been first explored by Wong *et al.*[5c]

and successively developed by Arcamone *et al.*[11] According to this synthetic strategy various structural types of unnatural anthracyclinones including 4-demethoxyadriamycinone **5** and 4-demethoxydaunomycinone **6** have been synthesized in racemic as well as optically active forms from common synthetic intermediates like **7**,[12] **8**,[13] **9**,[14] and **10**.[15].

Scheme-2:



(±) 7 **8** (±)9 (±)10

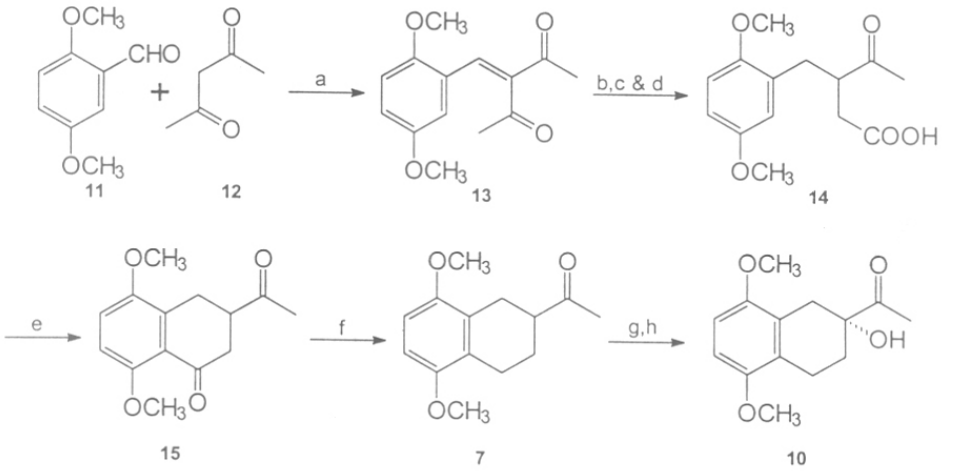
These frequently used AB building blocks which can be obtained by cyclization of the corresponding open chain precursors can be transformed into enantiomerically pure compounds by appropriate reported methods[4c] which include resolution,[17] asymmetric bromolactonisation,[18] asymmetric reduction-epoxidation,[19] Sharpless asymmetric epoxidation, asymmetric dihydroxylation[12b,20] and others[21] like asymmetric enolate oxidation protocol.[22]

1.1.1 Literature survey:

As mentioned earlier the AB ring synthons have been prepared by a variety of reactions and in this survey all the salient reports have been covered to emphasize the importance of the intermediate 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**8**) as an useful building block towards the synthesis of 4-demethoxydaunomycinone (**6**).

Wong *et al*[14a] in the year 1971 were the first to report the versatile method of AB + CD ring coupling by utilizing a key intermediate **10** in which the tetracyclic system was built by successive inter and intramolecular Friedel-Crafts acylations. Various structural types of the unnatural anthracyclinones including 4-demethoxyadriamycinone **5** and 4-demethoxydaunomycinone **6** have been elaborated in racemic or optically active forms from this common synthetic intermediate **10** which has been rather tediously prepared and condensed with phthalic acid monomethyl ether to give the main skeleton of daunomycinone (**Scheme-3**). However various improved synthesis of this intermediate (±) **10** have been subsequently reported.

Scheme-3:



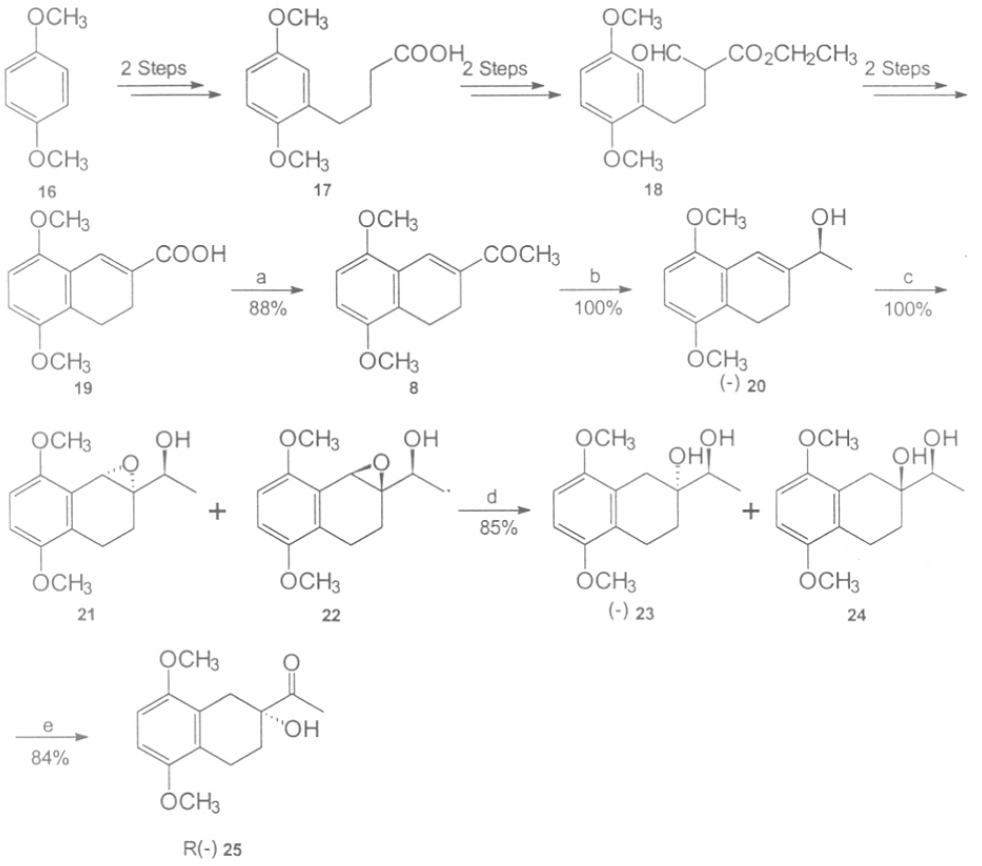
a. Piperidine, AcOH; **b**. H_2/Pd-C; **c**. $BrCH_2COOEt$, NaH; **d**. NaOH; **e**. anhydrous HF; **f**. H_2/Pd-C; **g**. $^tBuOH/O_2/^tBuOK$; **h**. Zn/AcOH.

According to their procedure 2,5-dimethoxybenzaldehyde was condensed with 2,4-pentanedione to give the diketone **13** which was transformed to keto-acid **14** in three steps. Cyclization of **14** was achieved with anhydrous hydrofluoric acid to produce the tetralone **15** in 72% yield. Hydrogenolysis of **15** with 5% Pd-C in acidic ethanolic solution gave the tetralin **7** which upon oxidation in *tert*-butyl alcohol with potassium *tert*-butoxide and oxygen followed by reduction with zinc/acetic acid afforded the desired hydroxy ketone **10** in good yields.

The same group[5c] later on in 1973 improved the synthesis in which the 2,4-pentanedione was replaced with diethylmalonate and was condensed with 2,5-dimethoxybenzaldehyde to give a diester which was further carried to the same intermediate **7** in four steps.

Tereshima *et al*[23] in the year 1980 reported an elegant asymmetric synthesis of (−)-**25** using chiral auxiliaries. They had utilized 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**8**) as a key intermediate for their synthesis (**Scheme-4**).

Scheme-4:

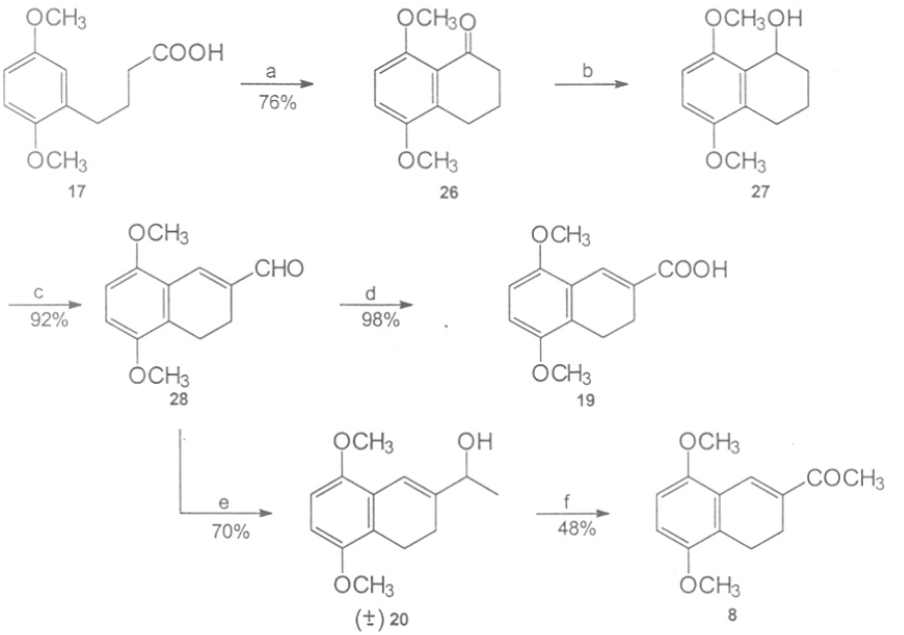


a. MeLi (excess) in ether, RT, 3 hrs; **b**. $LiAlH_4$-(-)N-methyl ephedrine, PhNHEt in ether, -78°C, 6 hrs; **c**. ^tBuOOH-$VO(acac)_2$ in benzene, RT, 1.5 hrs; **d**. LAH in THF, RT, 2 hrs; **e**. Ag_2CO_3-Celite (Fetizon's reagent), benzene, reflux, 0.5 hrs.

As shown in **Scheme-4**, 5,8-dimethoxy-3,4-dihydro-2-naphthoic acid **19** readily prepared from 1,4-dimethoxybenzene through several steps[23] was converted to the methyl ketone **8** with excess of CH_3Li which on reduction afforded the optically active allylic alcohol (–)-**20**. The epoxidation of (–)-**20** gave a diastereomeric mixture of epoxy alcohols **21** and **22** as an unstable oil which without separation was subjected to reduction giving the crystalline vicinal diols as a mixture of two diastereomers (–)-**23** and **24**. The predominant (–)-**23** was isolated by recrystallization with ether and was further converted to optically active (–)-**25** by Fetizon's reagent.

Krishna Rao *et al*[13b] in 1981 reported a shorter sequence for obtaining (±) 5,8-dimethoxy-2α-hydroxy ethyl-3,4-dihydronaphthalene (**20**) in a higher yield starting from the known 5,8-dimethoxy-*l*-tetralol (**27**) (**Scheme-5**).

Scheme-5:



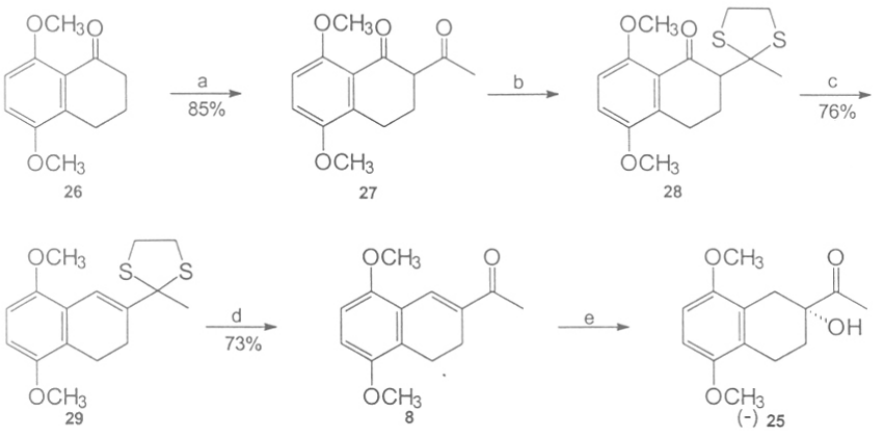
a. PPA; **b**. $NaBH_4$; **c**. $POCl_3$/DMF, 80°C; **d**. Ag_2O; **e**. CH_3MgI; **f**. PCC.

The tetralol was obtained from arylbutanoic acid by reported methods in two steps by cyclodehydration with PPA and $NaBH_4$ reduction of the 5,8-dimethoxy-l-tetralone (**26**) which was then subjected to Vilsmeier reaction to yield 5,8-dimethoxy-3,4-dihydro-2-naphthaldehyde (**28**) in 92% yield. Reaction of CH_3MgI on the aldehyde furnished the (±) alcohol **20** with an overall yield of 70% from the arylbutanoic acid. Finally the α,β-unsaturated ketone **8** was obtained in 48% yield by a PCC oxidation on the alcohol (±) **20**.

After Tereshima's approach, Rama Rao *et al.*[24] came up with an improved synthesis of **8** which was a shorter and higher yielding approach. The key intermediate 2-acetyl-5,8-dimethoxy tetralone (**8**) was synthesized starting from the same 5,8-dimethoxy tetralone (**26**) which was acetylated by condensing with $Na/CH_3COOCH_2CH_3$ or BF_3-etherate/Ac_2O[12a] in 85% yield. The acetyl ketone group was selectively protected to give the ketone **28** which

was then subjected to reduction followed by acidic work up to give **29** in 76% yield. Deketalization of **29** gave the desired intermediate **8** in 73% yield (**Scheme-6**).

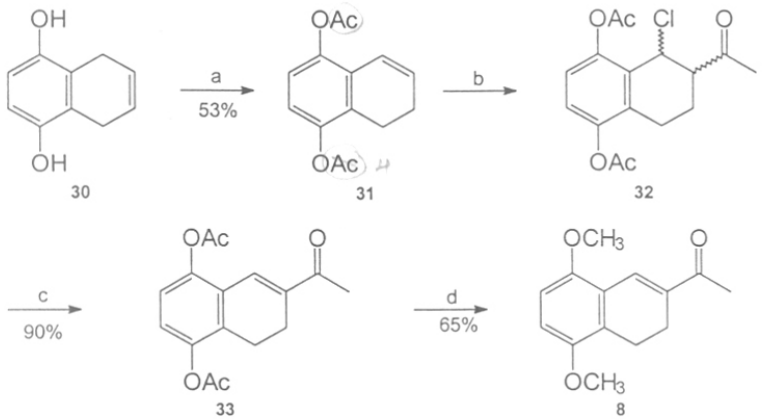
Scheme-6:



a. BF_3-etherate/Ac_2O; **b**. HS-CH_2-CH_2-SH/HCl, $CHCl_3$, 10 hrs; **c**. $NaBH_4$, MeOH, R.T., 24 hrs; **d**. NCS, $AgNO_3$, 80% aq CH_3CN, R.T., 20 min. **e**. ref 23a.

Richard Russell *et al.*[13c,25] reported a more practical approach for the synthesis of the α,β-unsaturated ketone **8** starting from 5,8-dihydroxy-1,4-dihydronaphthalene **30** which is obtained by a condensation of benzoquinone and buta-1,3-diene[26](**Scheme7**). 1,4-dihydronaphthalene **30** was conjugated under forcing conditions to yield the bis acetate **31**. Addition of acetyl chloride catalyzed by $AlCl_3$ furnished a stereoisomeric mixture of chloroketone **32** which without purification was dehydrochlorinated by LiCl to afford **33** which was later hydrolyzed and methylated to yield the α,β-unsaturated ketone **8** in moderate yields. The basic skeleton was thus assembled in two operations which was considerably shorter than those reported so far as depicted in the **Scheme-7**.

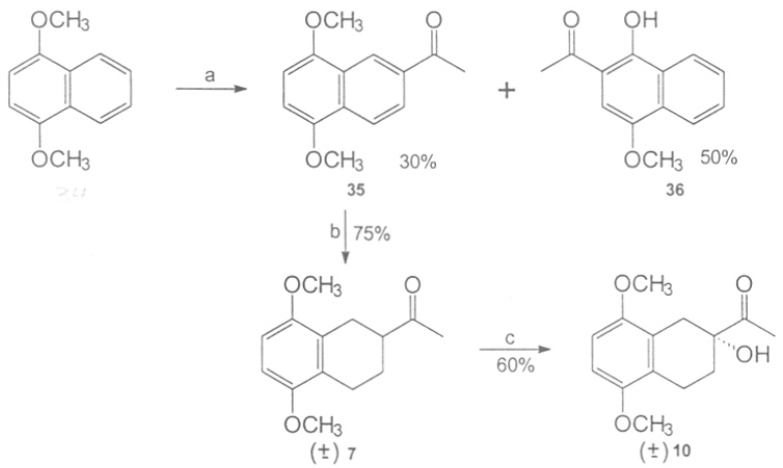
Scheme-7:



a. $NaOH/H_2O$, reflux, 4 hrs; **b**. $AcCl/AlCl_3$; **c**. LiCl; **d**. Hydrolysis, methylation.

In the year 1982 Rama Rao *et al.*[15e] reported a short synthesis for another intermediate (±) 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**10**) by using 2-acetyl-5,8-dimethoxy-naphthalene (**35**) (**Scheme-8**).

Scheme-8:



a. $(CH_3CO)_2O$, $AlCl_3$, EDC, 60°C, 3 hrs; **b**. K/NH_3, -33°C; **c.i**). KO^tBu/O_2, **ii**). Zn/AcOH.

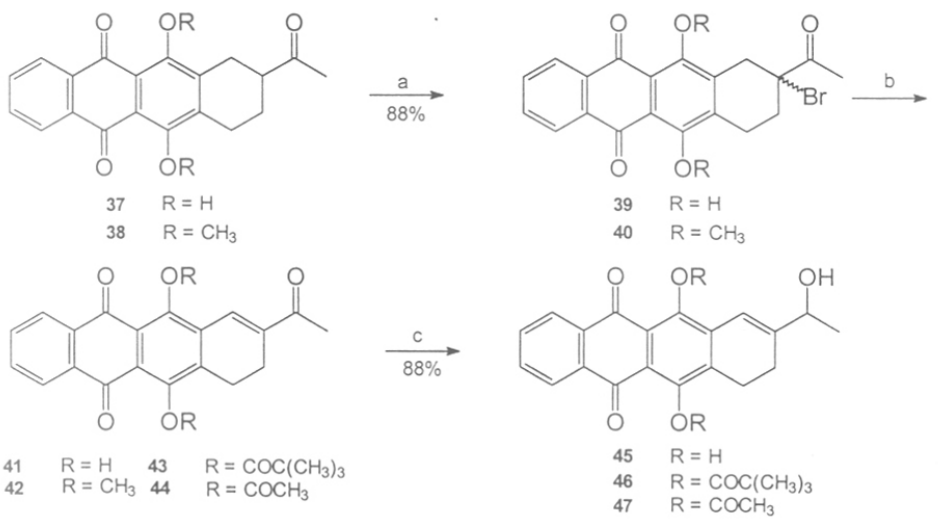
As shown in the **Scheme-8** they employed an aromatic precursor **34** and obtained **35** in a three step sequence. However the yields were less in the initial acylation step wherein a mixture of two products are obtained. The desired 2-acetyl-5,8-dimethoxynaphthalene (**35**) which was obtained as the minor product, was separated and subjected to metal ammonia

reduction to yield (±) **7** in 75% yield which was oxidized to the desired intermediate **10** by treating with potassium *tert* butoxide and oxygen followed by reduction with Zn/AcOH in 60% yield.

The reported procedures make use of a optically active AB ring synthon, which is either obtained by resolution of racemic material or by asymmetric synthesis and then transformed it into a tetracyclic intermediate according to Wong's procedure. This reaction suffers from lack of regio chemical control leading to difficult separation of regioisomers after the formation of ring D substituted anthracyclinones.

In 1983 Cava *et al.*[30] reported a synthesis of the optically active dũanomycinone starting from a racemic tetracyclic intermediate **37** (**Scheme-9**).

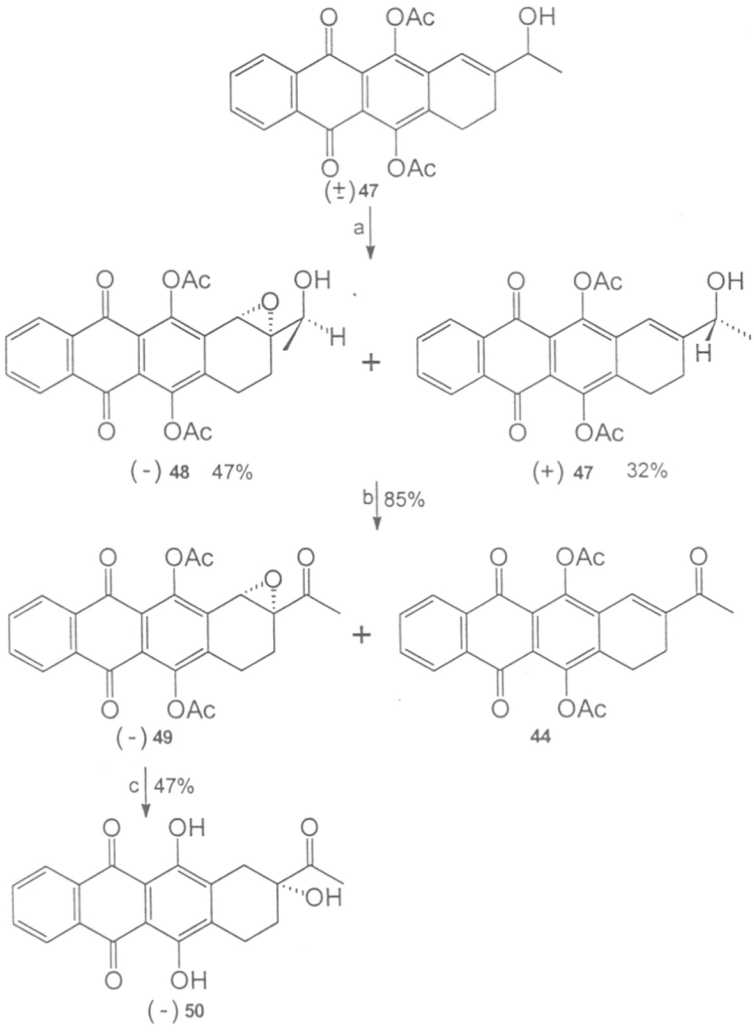
Scheme-9:



a. **i**). Br_2, R.T., 5 hrs; **ii**). 100°C, 20 hrs; **b**. Li_2CO_3; **c**. $NaBH_4$, $CeCl_3$.

Hence a method of asymmetric functionalization of the A ring after the build up of tetracyclic intermediate was first reported in this scheme. Accordingly selective bromination of ketone **37** with bromine at room temperature for 5 hrs followed by heating at 100°C for 20 hrs gave the compound **39** in 88% yield. Li_2CO_3 promoted elimination of HBr gave the enone **41**. $NaBH_4$ reduction in the presence of equimolar quantities of $CeCl_3$ gave the product (±) **45** in 88% yield. However a Sharpless epoxidation on this intermediate failed to proceed due to insoluble chelate formation between the hydroxyanthraquinone and titanium isopropoxide. So protection of the phenolic groups became imperative. But methylation of

41 proved to be difficult resulting in a completely aromatized product as the major one. An alternative of starting from the dimethoxy ketone **38** *via* bromination was abandoned due to low yields. Finally the diacetate compound **47** on epoxidation gave a mixture of alcohol and epoxide which when treated with CrO_3 gave a separable mixture of (–)-**49** and **44**. The compound (–)-**49** was finally converted to (–)-**50** using sodium dithionate.



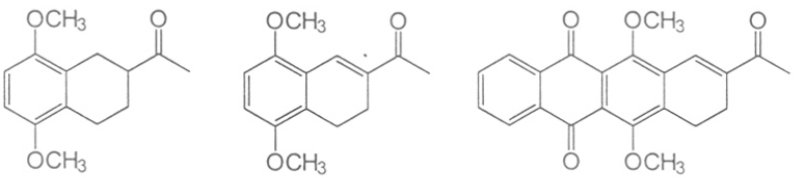
a. $Ti(^{i}PrO)_4$, (+)-DIPT, TBHP, DCM, -20°C, 2.5 hrs; **b**. Chromic acid, DCM, 6 hrs, R.T.; **c**. **i**). $Na_2S_2O_4$, NaOH **ii**). Air

This literature survey reveals that the 2-acetyl-5,8-dimethoxy-3,4-dihydro-naphthalene (**8**) was a popular intermediate during the late eighties and new reactions which provide a shorter and simpler route towards its synthesis being welcome at any time.

1.1.2 Present work:

From the above mentioned literature survey it becomes apparent that the synthons (±) **7**, **8** and **42** are crucial intermediates for the synthesis of 4-demethoxydaunomycinone and have been prepared by a variety of ways. Literature survey also reveals that the synthon **8** has been less frequently used than its counterparts (**Scheme-10**).

Scheme-10:

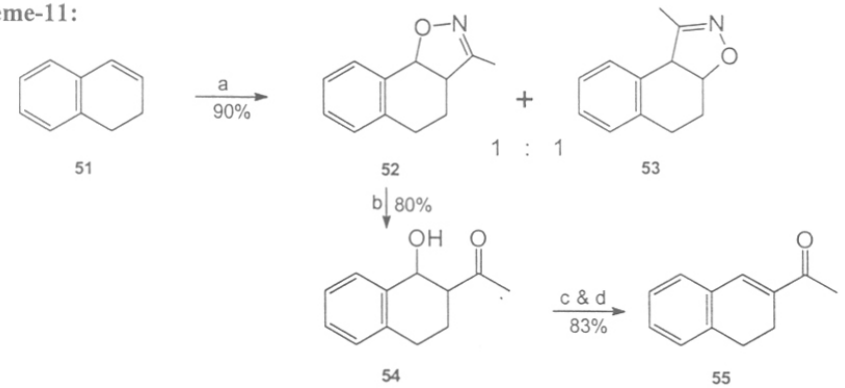


(±) **7** **8** **42**

The present work deals with the synthesis of the AB ring synthons (±) **7** and **8** and the extension of the synthon **8** towards the main framework of 4-demethoxydaunomycinone.

For this a novel approach of 1,3-dipolar cycloaddition of nitrile oxides on the corresponding dihydronaphthlenes has been studied. As shown in **Scheme-11**, a cycloaddition on a model molecule was carried out to yield a mixture of regioisomeric isoxazolines **52** and **53** in 1:1 ratio. The desired isoxazoline **52** was separated and subjected to reduction followed by elimination to yield the required α,β-unsaturated ketone **55**.

Scheme-11:



51 **52** **53** **54** **55**

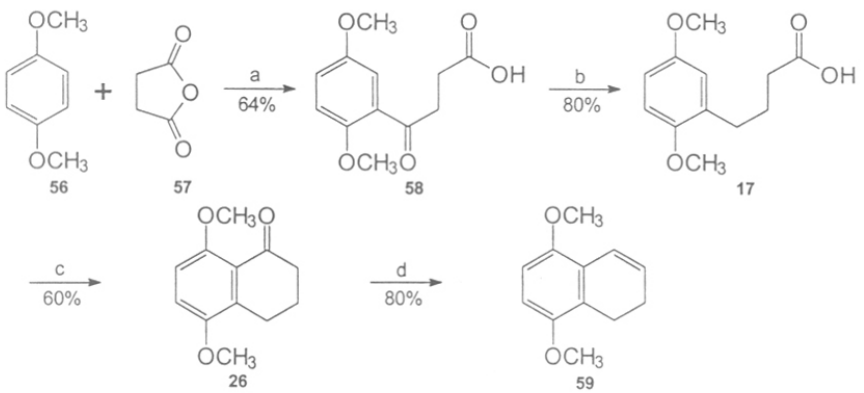
a. PhCNO, $NO_2C_2H_5$, Et_3N, Benzene; **b**. Ra-Ni, Boric acid, H_2, MeOH:H_2O(5:1); **c**. MsCl, Et_3N,CH_2Cl_2; **d**. DBU, Benzene, Reflux.

The same sequence of reactions were applied for the substituted 5,8-dimethoxy dihydronaphthalenes to yield the desired AB ring synthons which have been extended towards the synthesis of 4-demethoxyduanomycinone.

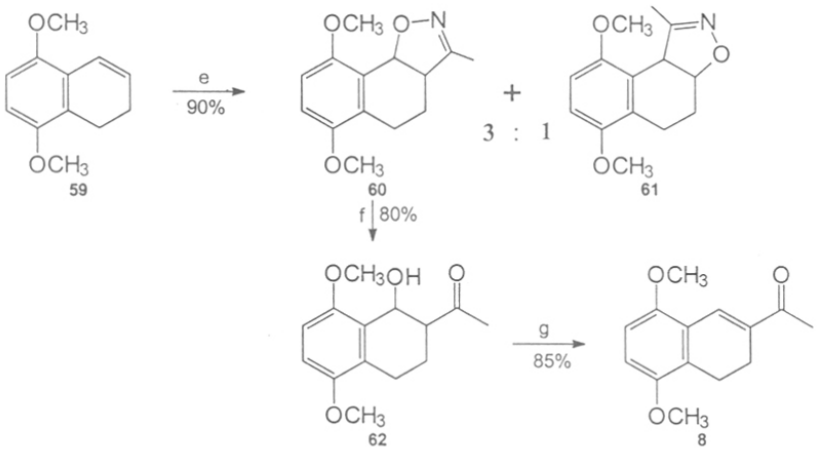
1.1.3 Results and Discussion :

As shown in **Scheme-11**, after successfully carrying out a model study on the simple 3,4-dihydronaphthalene and having obtained the α,β-unsaturated ketone **55** in good yields, the same cycloaddition reaction was extended to the 5,8-dimethoxy-3,4-dihydronaphthalene (**59**). This compound **59** was prepared according to reported procedures[29] (**Scheme-12**) starting from 1,4-dimethoxy benzene (**56**). A Friedel-Craft acylation with succinic anhydride on **56** yielded the keto-acid **58** which on Clemmensen's reduction gave the simple acid **17**. This acid **17** was then subjected to cyclization with trifluoro acetic anhydride to furnish the 5,8-dimethoxy tetralone (**26**). Further reduction of the tetralone **26** with $NaBH_4$ followed by an elimination in refluxing benzene with catalytic amount of pTSA yielded the 5,8-dimethoxy-3,4-dihydronaphthalene (**59**) whose spectral analysis was matched with that of reported[12b] values.

Scheme-12:



a. $AlCl_3$, Nitrobenzene; **b**. Zn/HCl; **c**. TFAA, TFA **d**. **i**). $NaBH_4$, **ii**). pTSA, benzene, reflux.



e. PhCNO, $NO_2C_2H_5$, Et_3N, dry EDC **f**. Ra-Ni, H_2, boric acid, MeOH:H_2O (5:1); **g**. MsCl, Et_3N, DMAP(cat) CH_2Cl_2.

The 5,8-dimethoxy-3,4-dihydronaphthalene (**59**) thus obtained was subjected to a 1,3-dipolar cycloaddition reaction with nitrile oxide. The nitrile oxide was generated from nitroethane and phenyl isocyanate by the reported procedure of Mukaiyama *et al*[27]. Accordingly two equivalents of phenyl isocyanate and one equivalent of nitroethane in presence of few drops of triethyl amine generated the nitrile oxide to which the 5,8-dimethoxy-3,4-dihydronaphthalene was added which gave a mixture of two regioisomeric isoxazolines **60** and **61** which were separated by column chromatography. These two isoxazolines were characterized by ^{1}H NMR, ^{13}C NMR, IR, Mass spectroscopy and Elemental analysis. The isoxazoline **60** was a white solid with a m.p. of 98-100°C and shows the C=N stretching in IR at 1640 cm^{-1}. The ^{1}H NMR revealed the benzylic proton next to the oxygen heteroatom at δ5.80 as a doublet with a coupling constant of 10Hz. The proton adjacent to it appeared upfield at δ3.34 as a multiplet of which one of the J value is 10Hz. A singlet at δ2.05 indicated the $-CH_3$ group of the isoxazole and the two methoxy groups of the aromatic ring appear at δ3.78 and 3.84 respectively. ^{13}C NMR also confirms the presence of two methylene groups at 20.0 and 22.5 with the methyl group at 12.5. The isomeric isoxazoline **61** was obtained as a colorless crystalline solid with a m.p. of 104-105°C. The IR spectrum of this compound was almost identical to its other regioisomer. However ^{1}H NMR revealed the presence of two protons at the region of δ5.0 contrast to the earlier isoxazoline. The proton at δ5.0 being the proton next to the heteroatom oxygen appeared as a broad

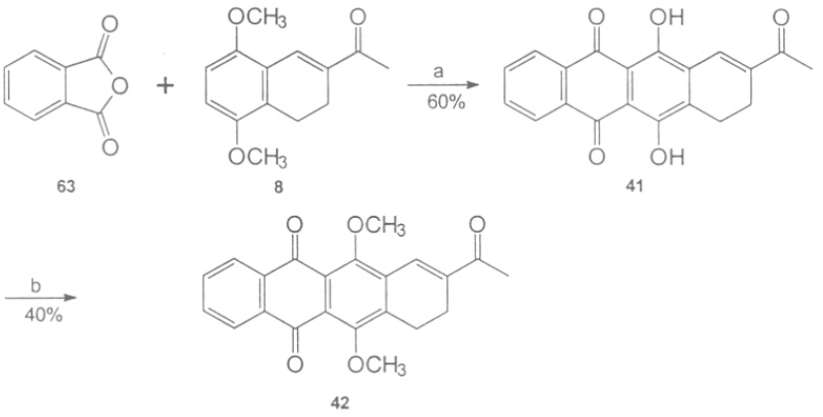
doublet with a J value of 11Hz. The benzylic proton adjacent to it also appears at δ4.86 as a clean doublet with a J value of 11Hz. Presence of $-CH_3$ group at δ1.76 confirmed the isoxazoline with the aromatic methoxy groups appearing at δ3.81 and 3.78 .

Having confirmed by spectral data that the compounds **60** and **61** are two regioisomers, the desired compound **60** was then subjected to a reduction with freshly prepared Raney-Nickel and boric acid under hydrogen atmosphere.[28] It yielded the hydroxy ketone **62** in excellent yields. IR spectrum confirmed the presence of a hydroxyl group at 3500 cm^{-1} with the keto group of the acetyl moiety appearing at 1715 cm^{-1}. In the ^1H NMR the benzylic proton next to the hydroxyl group appeared at δ5.46 as a doublet with a coupling constant of 3.4Hz. It had slightly shifted upfield as compared to the proton at δ5.8 in the isoxazoline **60**. The proton adjacent to the acetyl group *i.e.* $\underline{H}C\text{-}COCH_3$ appeared at δ2.50 as a ddt with coupling constants of 3.4 and 12.0 Hz. The methyl peak appeared slightly downfield at δ2.36 as a singlet.

The hydroxy ketone **62** was then converted to the mesylate by treating with mesyl chloride and triethyl amine was added as a base along with a catalytic amount of DMAP. Instead of the mesylate an elimination had taken place in a single pot reaction to yield the α,β-unsaturated ketone **8** in 85% yield. The m.p. of the compound **8** thus obtained as well as the spectral data was matching with that of the reported[24] for **8**. The ^1H NMR showed the required multiplets (ddt's) at δ2.50 and 2.82 with the vinylic proton appearing as a broad singlet at δ7.85. The IR spectrum showed the presence of α,β-unsaturated keto group at 1650 cm^{-1}.

This 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (**8**) was then condensed with two equivalents of phthalic anhydride[12c] along with $AlCl_3$-NaCl melt at 180°-190°C for 10min. to yield the desired tetracyclic compound 8-acetyl-6,11-dihydroxy-9,10-dihydro-5,12-naphthacene dione (**41**) (**Scheme-13**).

Scheme-13:



a. $AlCl_3$-NaCl, 180-190°C, 7 min; **b**. K_2CO_3/DMS/acetone, reflux.

The red colored compound **41** had some impurities which were difficult to separate on column chromatography, hence the product obtained was without purification subjected to methylation by the conventional method of DMS and K_2CO_3 to yield the compound **42** in 40% yield. The structure of naphthacenedione was confirmed by IR, NMR and Mass spectroscopy which matched that of reported[31] data. The ^1H NMR confirmed the presence of four aromatic protons at δ7.74 (2H, m) and 8.2 (2H, m). The aromatic methoxy groups shifted downfield to δ3.92 and 3.98 as compared with the compound **8**. IR spectra confirmed the presence of C=O (quinone) at 1676 cm^{-1} and α,β-unsaturated ketone at 1650 cm^{-1}. Mass spectroscopy revealed a M^+ ion peak at 362 with 100% intensity.

This naphthacenedione **42** can be converted into 4-demethoxydunomycinone by asymmetric functionalization of the A ring by the approach of Cava *et al.*[30] as explained in the **Scheme-9**.

Thus the synthon **8** prepared as mentioned above can be converted to optically active 2-acetyl-2-hydroxy-5,8-dimethoxytetralin (**25**) or it can be condensed with phthalic anhydride to yield the intermediate **42** which was also obtained following a different approach by Cava *et al.*

Since the cycloaddition reaction on **59** was not regioselective enough to yield a single isomer (**Scheme-12**), another isomeric substrate *viz.* 5,8-dimethoxy-1,4-dihydronaphthalene (**66**) was selected to carryout the same sequence of reactions as reported earlier. The 5,8-dimethoxy-1,4-dihydronaphthalene (**28**) was prepared by Diels-Alder reaction of quinone

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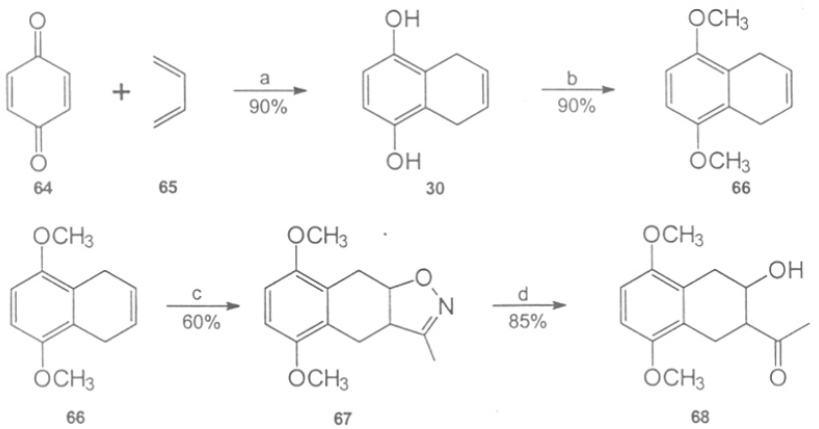
with 1,3-butadiene in acetic acid at room temperature followed by methylation with DMS and K_2CO_3, in good yields.

The 1,3-dipolar cycloaddition on this substrate **66** gave a single isoxazoline **67** in moderate yields (60%). The structure of this isoxazoline **67** was confirmed by IR, NMR and Mass spectroscopy.

Scheme-14:

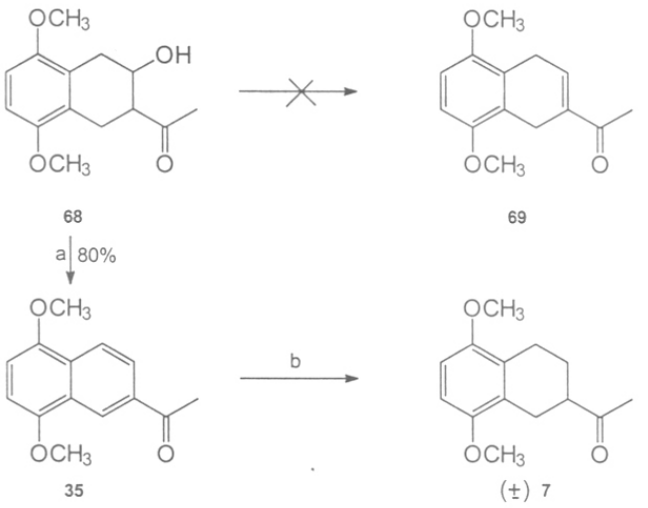


a. AcOH, R.T., 36 hrs; **b**. K_2CO_3/DMS/acetone, 36 hrs; **c**. PhCNO, $NO_2C_2H_5$, Et_3N, benzene, 12 hrs; **d**. Ra-Ni, H_2, boric acid, MeOH:H_2O(5:1).

The ^1H NMR of **67** revealed the presence of ddt at δ5.06 with coupling constants of 4.0 and 11 Hz corresponding to the proton next to the heteroatom of H-C-O-N. The allylic proton HC-C(CH_3)=N adjacent to it appeared as a multiplet at δ3.66. Of the two pairs of benzylic protons one of each pair appeared as a dd at δ3.27 and 3.12 respectively, the coupling constants of the proton at δ3.12 being 4Hz, the same as that of the proton which was adjacent to the hetero atom. The other pair of the benzylic protons (one from each set) appeared as another set of dd at δ2.6 and 2.58 respectively.

Reduction of the compound **67** with Raney Nickel yielded the hydroxy ketone **68** in 85% yield. IR spectrum confirmed the presence of the hydroxy and keto groups at 3500 and 1710 cm^{-1} respectively. The hydroxy ketone was then subjected to elimination with mesyl chloride and triethyl amine. However the product isolated in 80% yield was not the eliminated **69** but a completely aromatized 2-acetyl-5,8-dimethoxy naphthalene (**35**) (**Scheme-15**).

Scheme-15:



a. MsCl, Et_3N, CH_2Cl_2 or pTSA, benzene, reflux; **b**. K/NH_3.

PMR spectrum of **35** showed the disappearance of aliphatic protons at δ2-3 and presence of five aromatic protons which appeared in three sets. The peri proton adjacent to acetyl group appeared at δ8.85 as a doublet with coupling constant of 2Hz and the other aromatic protons in the ring containing the acetyl group appeared as dd's at δ8.05 (J=2&9Hz) and δ8.25 (J=9Hz) respectively. The other two aromatic protons of the ring containing the methoxy groups appeared at δ6.7 and 6.87 as doublets with a coupling constant of 8Hz.

The elimination was also tried under acidic conditions using pTSA to yield the same aromatized product **35**. Rama Rao *et al.*[15e] have earlier reported the synthesis of compound **35** and the data of this compound was in agreement with that of the above. This product when treated with potassium in liquid ammonia yields the 2-acetyl-5,8-dimethoxy-1,2,3,4-dihydronaphthalene (**7**) which is another useful synthon for the synthesis of 4-demethoxy duanomycinone.

1.1.4 Conclusions :

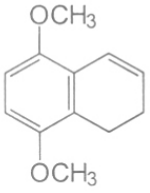
- The 1,3-dipolar cyclo addition approach for the synthesis of AB ring synthons of 4-demethoxy daunomycinone is the first report and probably one of the simplest towards the daunomycinone synthesis.

- The condensation of α,β-unsaturated ketones to phthalide ring and later on introducing the asymmetric functional group which is more advantageous is an attractive feature of this synthetic strategy.

- The products obtained are all solids and the reaction sequences are simple with good yields.

1.1.5 Experimental:

1. **5,8-Dimethoxy-3,4-dihydronaphthalene[12b] (59)**



Procedure:

This compound was prepared in moderate yields according to the reported procedure of Moore and Rahm [29].

Mol. Formula :$C_{12}H_{14}O_2$ Colorless crystals

M.P. : 70°C

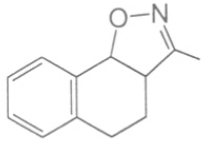
IR (neat) cm^{-1} :1200, 1251, 1437, 1481, 1607, 2880, 2944, 3018.

^{1}H NMR (CCl_4) : 2.1-2.7 (m, 4H, $-CH_2$), 3.80(s, 6H, $-OCH_3$), 5.85(m, 1H), 6.63(s, 2H), 6.83(m, 1H).

Typical procedure for preparation of Isoxazoles[27a]:

Phenyl isocyanate (0.1 mole) and unsaturated compound (0.55 mole) (5,8-dimethoxy dihydronaphthalenes) were taken in 25 ml of dry benzene to which was added nitroethane (0.55 mole) (1-nitropropane) and 10 drops of triethyl amine. An evolution of CO_2 with the formation of precipitate of diphenyl urea was observed. After stirring the reaction for 12 hrs the product was filtered and concentrated under reduced pressure. The residue was extracted with chloroform and subsequently washed with brine solution and dried with sodium sulphate. The mixture was finally chromatographed over silica gel with 10% ethyl acetate and pet. ether to give 90% yield of the combined regioisomeric isoxazoles.

2. **3-Methyl-3a,4,5,9b-tetrahydro naphtho[2,1-d] Isoxazol(52) [27b].**



Yield : 45%

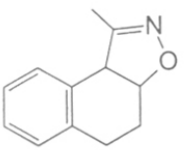
Mol. Formula : $C_{12}H_{13}NO$

IR (neat) : 1630, 1600, 1540, 1475, 1450, 1320,1200 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.87 (m, 2H); 2.07 (s, 3H); 2.65 (m, 2H); 3.41 (m, 1H); 5.45 (d, 1H), 7.1-7.4(m, 4H).

^{13}C NMR(50MHz) $CDCl_3$: 12.1(q), 23.6(t), 27(t), 49(d), 79.3(d), 126.7(d), 128.2(d), 128.3(d), 130.2(d), 132.5(s), 138.6(s), 158.2(s).

3. **1-Methyl-3a,4,5,9b-tetrahydro naphtho[1,2-d] Isoxazol (53)**[27b].



Yield : 45%

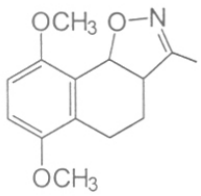
Mol. Formula : $C_{12}H_{13}NO$

IR (neat) : 1630, 1600, 1540, 1475, 1450, 1320,1200 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.8 (s, 3H); 2.15 (m, 2H); 2.68 (m, 2H), 4.36 (d, 1H); 5.1 (dt, 1H); 7.2 (m, 4H).

^{13}C NMR(50MHz) $CDCl_3$: 12.1(q), 24.6(t), 28.2(t), 54.1(d), 78.6(d), 126.6(d), 127.2(d), 128.6(d), 130.9(s), 139.4(s), 154.8(s).

4. **3-Methyl-6,9-dimethoxy-3a,4,5,9b-tetrahydro naphtho[2,1-d] Isoxazol(60).**



Procedure: Following the typical procedure mentioned above the 5,8-dimethoxy-3,4-dihydro naphthalene (1g, 5.2 mmol) was taken in 10 ml of dry EDC in two necked round bottomed flask under nitrogen. To it was added phenyl isocyanate (1.25g, 10.4 mmol) and nitroethane (0.39g, 5.2 mmol) and few drops of triethyl amine. The mixture was stirred overnight and worked up according to the reported procedure to yield mixture of isoxazoles **60** (900mg) and **61** (390mg) respectively.

Yield : 70%

Mol. Formula : $C_{14}H_{17}NO_3$

M.P. : 98-100°C

IR (neat) : 1640, 1600, 1540, 1475, 1450, 1320,1200 cm^{-1}.

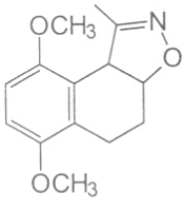
^{1}H NMR (200 MHz) $CDCl_3$: δ 1.84 (m, 2H); 2.05 (s, 3H); 2.46 (m, 1H); 2.76 (m, 1H); 3.34 (m, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 5.8 (d, J=10 Hz, 1H), 6.72 (d, J=9Hz, 1H), 6.79 (d, J=9Hz, 1H).

^{13}C NMR(50MHz) CF_3COOD : 12.5(q), 20(t), 22.5(t), 56.5(q), 75.5(q), 109(d), 112(d), 121(s), 123(d), 126(d), 129(s), 136(s), 151(s), 153(s).

Mass(m/e) :247(M^+, 9), 230(1), 212(1), 190(36), 175(15), 149(6), 147(5), 137(3), 129(7), 115(16), 97(20), 93(26), 85(30), 83(27), 81(25), 77(15), 71(55), 69(53), 57(100), 55(73).

Analysis :	Carbon	Hydrogen	Nitrogen
Calculated :	67.99%	6.92%	5.66%
Found :	67.81%	6.76%	5.60%

5. **1-Methyl-6,9-dimethoxy-3a,4,5,9b-tetrahydro naphtho[1,2-d] Isoxazol (61).**



Yield : 30%

Mol. Formula : $C_{14}H_{17}NO_3$

M.P. : 104-106°C

IR (neat) : 1640, 1600, 1540, 1475, 1450, 1320,1200 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.43 (m, 1H); 1.76 (s, 3H); 2.3-2.5 (m, 2H); 3.0 (m, 1H); 3.78 (s, 3H), 3.81 (s, 3H), 4.86 (d, J=11Hz, 1H), 5.0 (d, J=11Hz, 1H), 6.69 (d, J=9Hz, 1H), 6.74 (d, J=9Hz, 1H).

^{13}C NMR(50MHz) $CDCl_3$: 12.0(q), 16.6(t), 27.4(t), 47.2(d), 55.3(q), 55.9(q), 78.0(d) 107.6(d), 109.3(d), 120.8(s), 129.7(s), 150.5(d), 150.8(s), 156.6(s).

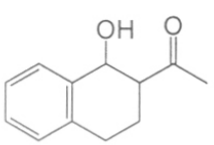
Mass(m/e) :247(M^+, 72), 235(3), 206(39), 190(94), 189(40), 175(100), 174(54), 164(21), 159(27), 147(17), 131(15), 115(28), 103(15), 91(20), 77(21).

Analysis :	Carbon	Hydrogen	Nitrogen
Calculated :	67.99%	6.92%	5.66%
Found :	68.40%	6.96%	5.67%

General procedure for conversion of isoxazolines to hydroxy ketones[28]:

To a solution of isoxazolines (1.8 mmol) in MeOH:H_2O (5:1) (10ml) was added boric acid (3.7mmol) and spatula tip of estimated 10-20mg of freshly prepared Raney Nickel. The reaction was placed under hydrogen by repeated evacuation and flushing with hydrogen gas by means of a balloon attached and then the reaction after 4-6 hrs was filtered through celite in to a separating funnel containing water and dichloromethane. After separation, the aqueous layer was extracted twice with dichloromethane and the combined layers were washed with brine dried over anhydrous sodium sulphate and concentrated under vacuum to furnish the crude hydroxy ketone (~90%) which was chromatographed to yield the pure compound as white solid.

6. **2-acetyl-1-hydroxy-1,2,3,4-tetrahydro naphthalene (54).**



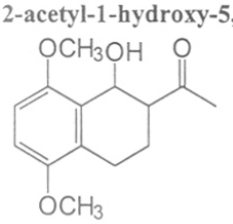
Yield : 80%

Mol. Formula : $C_{12}H_{14}O_2$

IR (neat) : 3400, 1710, 1600, 1360,1250 cm^{-1}.

^{1}**H NMR** (80 MHz) $CDCl_3$: δ 2.1 (m, 2H); 2.2 (s, 3H); 2.73 (m, 3H); 5.0 (d, 1H), 7.0-7.3 (m, 4H).

7. **2-acetyl-1-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro naphthalene (62).**



Yield : 80%

Mol. Formula : $C_{14}H_{18}O_4$

M.P. : 88-90°C

IR (neat) : 3500, 1715, 1605, 1550, 1480 cm^{-1}.

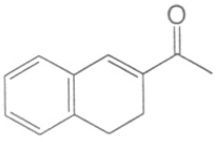
^{1}H NMR (200 MHz) $CDCl_3$: δ 2.01 (m, 2H); 2.35 (s, 3H); 2.55 (m, 2H), 3.05 (dddd, 1H), 3.78 (s, 3H), 3.87 (s, 3H), 5.46 (d, J=3.4Hz, 1H), 6.70 (d, J=9Hz, 1H), 6.75 (d, J=9Hz, 1H).

^{13}C NMR(50MHz) $CDCl_3$: 17.5(t), 23.2(t), 28.1(q), 52.4(d), 55.5(q), 55.5(q), 62.4(d), 107.4(d), 109.2(d), 126.9(s), 127.1(s), 151.2(s), 151.5(s), 209.7(s).

Mass(m/e) :250(M^+, 12), 232(42), 217(16), 201(17), 188(36), 189(100), 175(21), 174(33), 165(12), 159(25), 158(14), 147(9), 144(9), 131(14), 115(34), 103(14), 91(15), 77(20).

Analysis :	Carbon	Hydrogen
Calculated :	67.19%	7.25%
Found :	66.63%	7.08%

8. **2-acetyl-3,4-dihydro naphthalene (55)**.



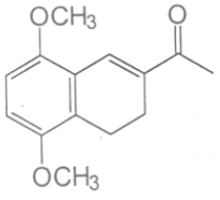
Yield : 83%

Mol. Formula : $C_{12}H_{12}O$

IR (neat) : 1645, 1590, 1500, 1480, 1261, 1105, 791cm^{-1}.

^{1}H NMR (80 MHz) $CDCl_3$: δ 2.28 (s, 3H); 2.58 (m, 4H); 7.0 (m, 4H), 7.2 (s, 1H).

9. **2-acetyl-5,8-dimethoxy-3,4-dihydro naphthalene (8)**.[24]



Procedure: The compound **62** (0.5g, 2 mmol) was dissolved in 10 ml of dry dichloromethane in two necked round bottomed flask under nitrogen and mesyl chloride (0.229g, 2 mmol) followed by triethyl amine (0.252g, 2.5 mmol) was added at 0°C. The mixture was stirred with a catalytic amount of DMAP to it. After completion of reaction (as monitored by TLC) the reaction mixture was diluted with 10 ml of dichloromethane and organic layer washed thoroughly with water. The organic layer was separated and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to yield a residue which was chromatographed over silica gel with 5% ethyl acetate : pet. ether as eluent to yield the compound **8** (0.395g) in 85% yield.

Yield : 85%

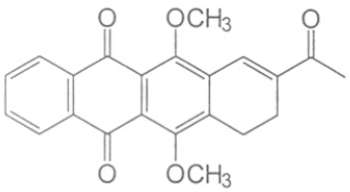
Mol. Formula : $C_{14}H_{16}O_3$

M.P. : 102-103°C (Lit[24]. m.p. 104-105°C).

IR (neat) : 1650, 1500, 1480, 1261, 1105, 791cm^{-1}.

^{1}**H NMR** (200 MHz) $CDCl_3$: δ 2.45 (s, 3H); 2.50 (m, 2H); 2.82 (m, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 6.71 (d, J=9.7Hz, 1H), 6.85 (d, J=9.7Hz, 1H), 7.85 (bs, vinylic C-H, 1H).

10. **8-acetyl--6,11-dimethoxy-9,10-dihydro-5,12-naphthacenedione (42).**[30]



A mixture of anhydrous $AlCl_3$ (0.444 mg , 45mmol) and NaCl (0.237 mg, 40mmol) was heated at 180-190°C for 5 min. To this melt was added a mixture of phthalic anhydride (0.261 mg, 17.5mmol) and the α,β-unsaturated ketone **8** (0.100 mg, 4.28mmol) and the resulting mixture was stirred at 180-190°C for 7min. After cooling, the reaction mixture was digested with saturated oxalic acid solution on water bath for 1h. The solution was then cooled and then extracted with chloroform (4x50ml). The chloroform layer was successively washed with 5% sodium bicarbonate, brine, dried and finally evaporated under reduced pressure to yield (94mg, 60%) of the 8-acetyl-6,11-dimethoxy-9,10-dihydro-5,12-naphthacene dione:

This product without purification was further subjected to methylation. To the product (94mg, 10mmol) was added anhydrous potassium carbonate (155mg, 40mmol) in dry acetone (50ml). Dimethylsulphate (88.6mg, 25mmol) was then added to the reaction mixture and it was refluxed for 24h. After cooling the reaction mixture was filtered and concentrated under reduced pressure to yield a reddish mass which was chromatographed on silica gel (25% ethyl acetate : pet. ether) to yield reddish needles (40mg, 40%).

Yield : 40%

Mol. Formula : $C_{22}H_{18}O_5$

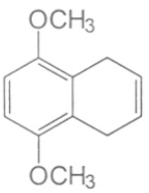
M.P. : 188-190°C (Lit[30] m.p. 189-191°C).

IR (neat) : 1676(C=O, quinone), 1650, 1589 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 2.52 (s, $CO\underline{CH_3}$); 2.62 (t, J=8Hz, 2H); 3.01 (t, J=8Hz, 2H), 3.92 (s, 3H), 3.98 (s, 3H), 7.74 (m, aromatic, 2H), 7.81 (s, 1H), 8.20 (m, 2H).

Mass(m/e) :362(M^+, 100), 348(19), 347(20), 345(16), 333(16), 331(20), 319(56).

11. **5,8-dimethoxy-1,4-dihydronaphthalene (66)**[12b].



To a solution of p-benzoquinone (5.4g, 0.5mol) in glacial acetic acid (50ml), liquid butadiene (10.8g, 2mol) was added while stirring and the clear solution was allowed to stand at room temperature for 36h. The contents were poured on crushed ice with stirring. The colorless precipitate was filtered and washed with ice cold water and dried (7.2g, 90% yield). A mixture of the above adduct (6.48g, 0.4mol), Dimethyl sulphate (DMS) (12.6g, 1mol) and K_2CO_3 (20g) in dry acetone (100ml) was refluxed for 36hrs. After completion of reaction (as monitored by TLC) the acetone was distilled off and the contents were cooled. Crushed ice was added to the mixture, the solid was filtered, washed with water (till free from carbonate) and dried to give the product in 90% yield as colorless solid.

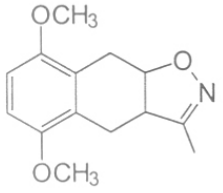
Mol. Formula : $C_{12}H_{14}O_2$

M.P. : 50-51°C (Lit[12b] M.P. 51°C)

IR (neat) : 2938, 2834, 1595, 1482, 1258, 1084. cm^{-1}.

^{1}H-NMR (200 MHz) $CDCl_3$: δ 3.26 (bs, 4H); 3.76 (s, 6H); 5.90 (bs, 2H), 6.53 (s, aromatic, 2H).

12. 3-Methyl-5,8-dimethoxy-3a,4,9,9a-tetrahydro naphtho[2,3-d] Isoxazol (67).



Procedure: Following the typical procedure mentioned earlier the compound **66** (1g, 5.2 mmol) was taken in 10 ml of dry EDC in two necked round bottomed flask under nitrogen. To it was added phenyl isocyanate (1.25g, 10.4 mmol) and nitroethane (0.39g, 5.2 mmol) and few drops of triethyl amine. The mixture was stirred overnight and worked up according to the reported procedure to yield isoxazole **67** (780mg) in 60% yield.

Yield : 60%

Mol. Formula : $C_{14}H_{17}NO_3$

M.P. : 166-168°C

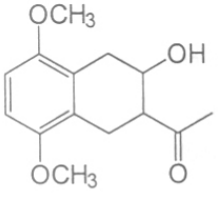
IR (neat) : 2850, 1648, 1594, 1480, 1256 cm^{-1}.

^{1}H-NMR (200 MHz) $CDCl_3$: δ 1.87 (s, 3H); 2.62 (m, 2H); 3.12 (dd,J=4.3, 15Hz, 1H), 3.27 (dd, J=4, 15Hz, 1H), 3.66 (m, 3H), 3.8 (s, 6H), 5.06 (ddt, J=4.3, 11Hz, 1H), 6.70 (s 2H).

Mass(m/e) :247(M^+, 63), 216(1), 206(2), 189(4), 175(5), 164(100), 163(14), 150(5), 149(50), 134(10), 121(12), 121(12), 115(12), 103(10), 91(21), 77(19), 65(12), 55(7).

Analysis :	Carbon	Hydrogen	Nitrogen
Calculated :	67.99%	6.92%	5.66%
Found :	67.78%	6.7%	5.5%

13. 3-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro naphthalene (68).



Procedure: The isoxazoline **67** (0.5g, 2 mmol) was taken in a two necked round bottomed flask and dissolved in 10 ml of MeOH:H_2O (5:1) and to it was added boric acid (0.25g, 4 mmol) and spatula tip of 10-20 mg of freshly prepared Ra-Ni. The reaction was placed under hydrogen by repeated evacuation and flushing with hydrogen gas by means of a balloon attached to it. After completion of reaction (as monitored by TLC) the reaction was worked up as usual to yield the compound **68** (0.43g) in 85% yield.

Yield : 85%

Mol. Formula : $C_{14}H_{18}O_4$

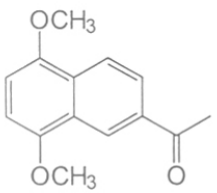
IR (neat) : 3500, 3100, 1710, 1610, 1490, 1450, 1300, 1230 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 2.28 (s, 3H); 2.84 (m, 5H); 3.73 (s, 3H), 3.79 (s, 3H), 4.66 (bs, 1H), 6.69 (s, aromatic, 2H).

Mass(m/e) :250(M^+, 5), 232(10), 215(2), 201(4), 190(9), 189(100), 188(9), 174(23), 158(11), 149(5), 132(4), 121(4), 115(9), 91(6), 83(1), 72(4), 65(2), 55(1).

Analysis :	Carbon	Hydrogen
Calculated :	67.18%	7.25%
Found :	66.89%	7.10%

14. 2-acetyl-5,8-dimethoxy naphthalene (35).[15e]



Procedure: In 25 ml round bottomed flask was taken the hydroxy compound **68** (0.25g, 1 mmole) in 10 ml of dry dichloromethane under argon atmosphere. To this was added mesyl chloride (0.114g, 1 mmole) and triethyl amine (0.101g, 1 mmole) with catalytic amount of DMAP added to it. The mixture was stirred for 2-3 hrs and the reaction monitored by TLC. After completion of reaction, the reaction mixture was filtered and washed with water. The aq. layer was extracted with dichloromethane once and the combined organic extracts are dried over Na_2SO_4 and evaporated under pressure. The crude compound then was chromatographed with (pet. ether : ethyl acetate 9:1) yielded the product **35** (0.185g) in 80% yield as pale yellow solid.

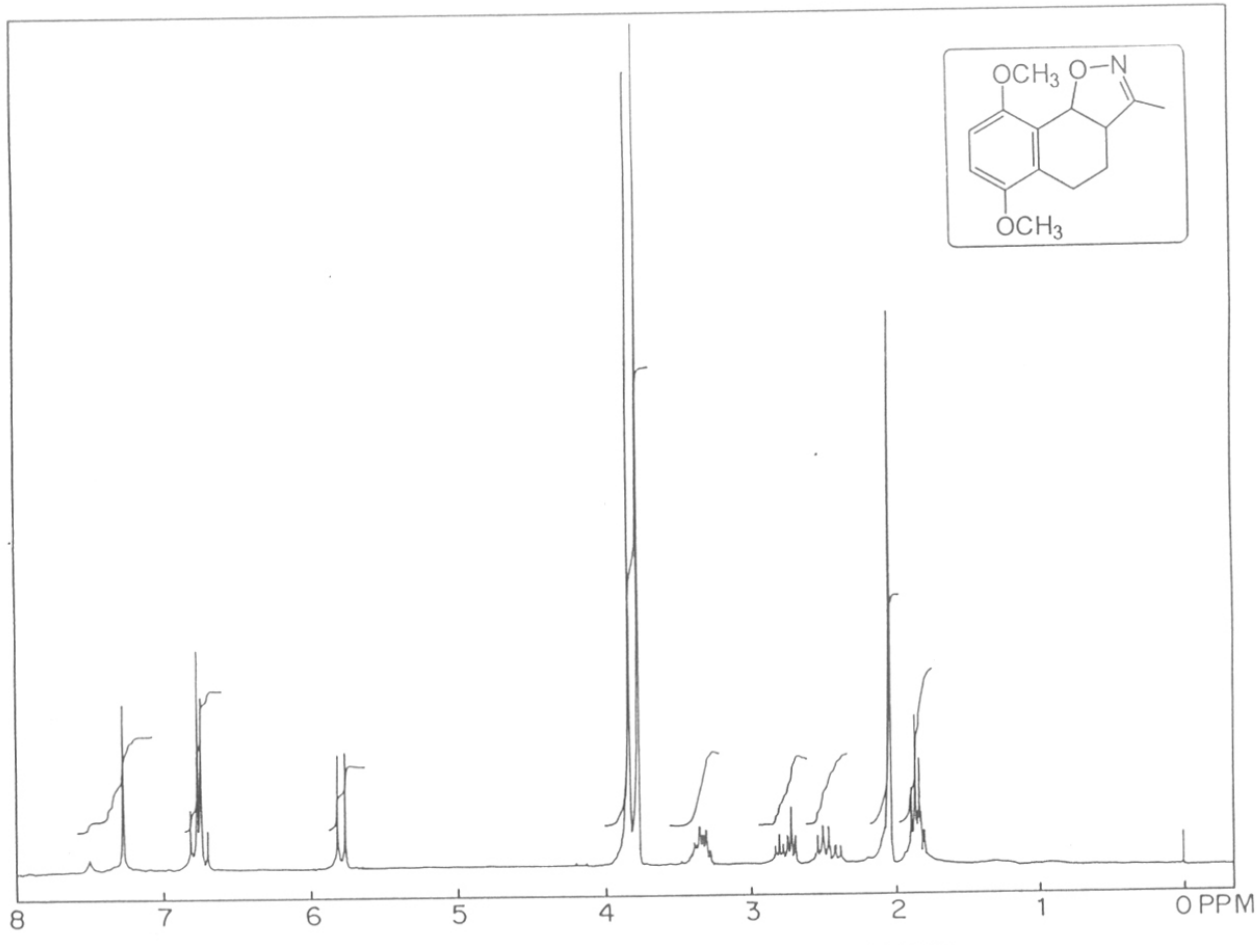
Yield : 80% pale yellow solid

Mol. Formula : $C_{14}H_{14}O_3$

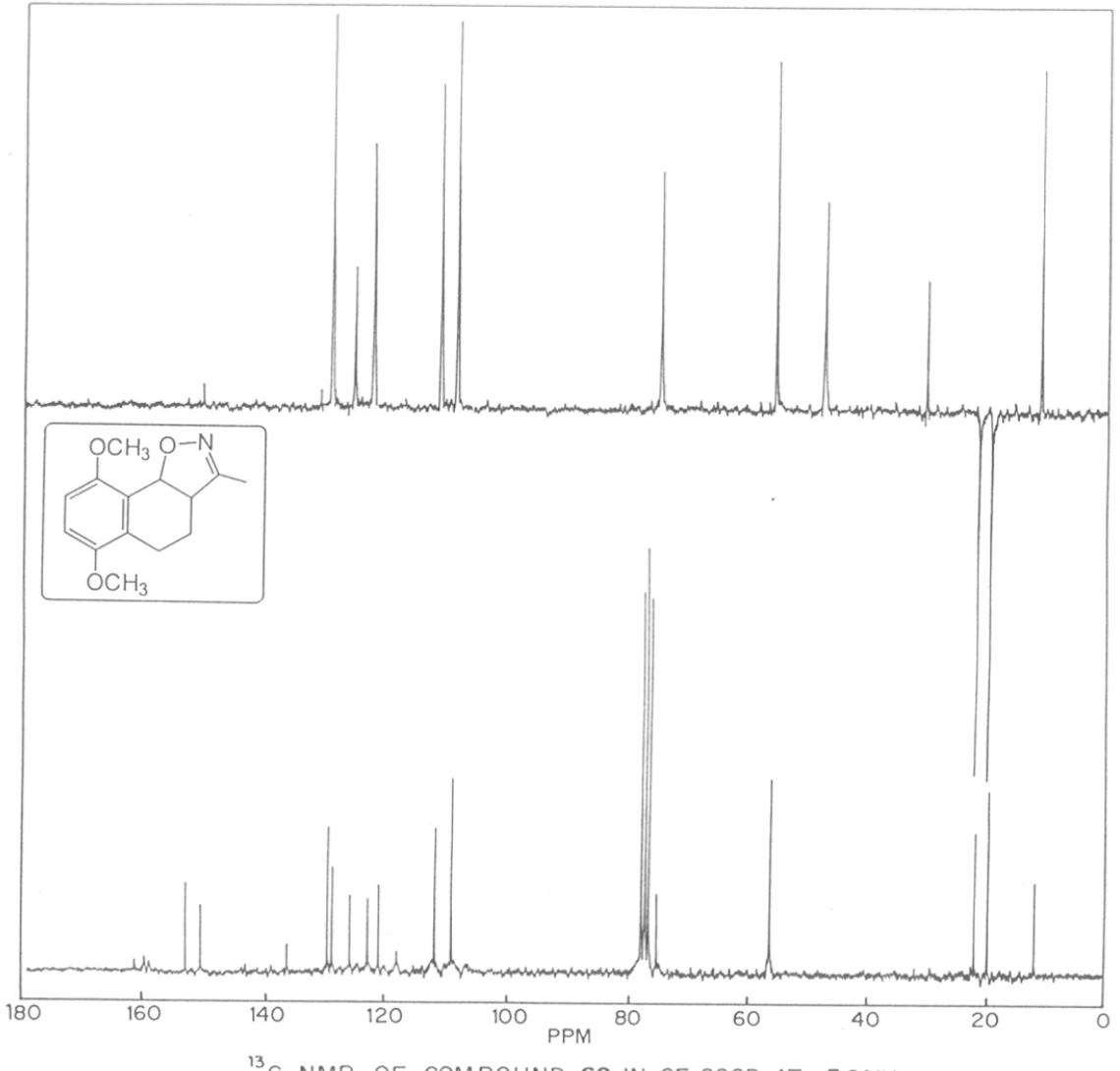
M.P : 111-112°C

IR (neat) : 1600, 1500, 1480, 1400, 1280 cm^{-1}.

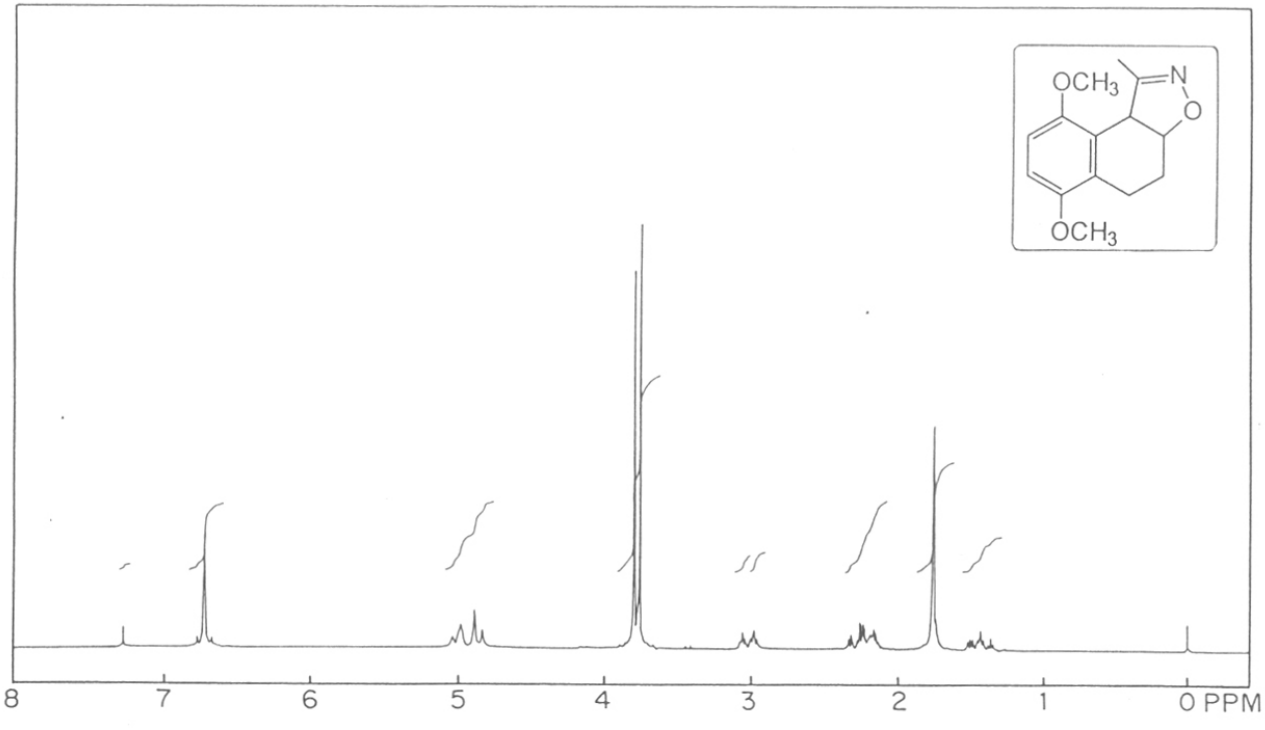
^{1}**H NMR** (200 MHz) $CDCl_3$: δ 2.75 (s, 3H); 3.95 (s, 3H); 4.00 (s, 3H), 6.78 (dd, 2H), 8.05 (dd, J=2, 9Hz, 1H), 8.25 (dd, J=9Hz, 1H), 8.85 (dd, J=2Hz, 1H).



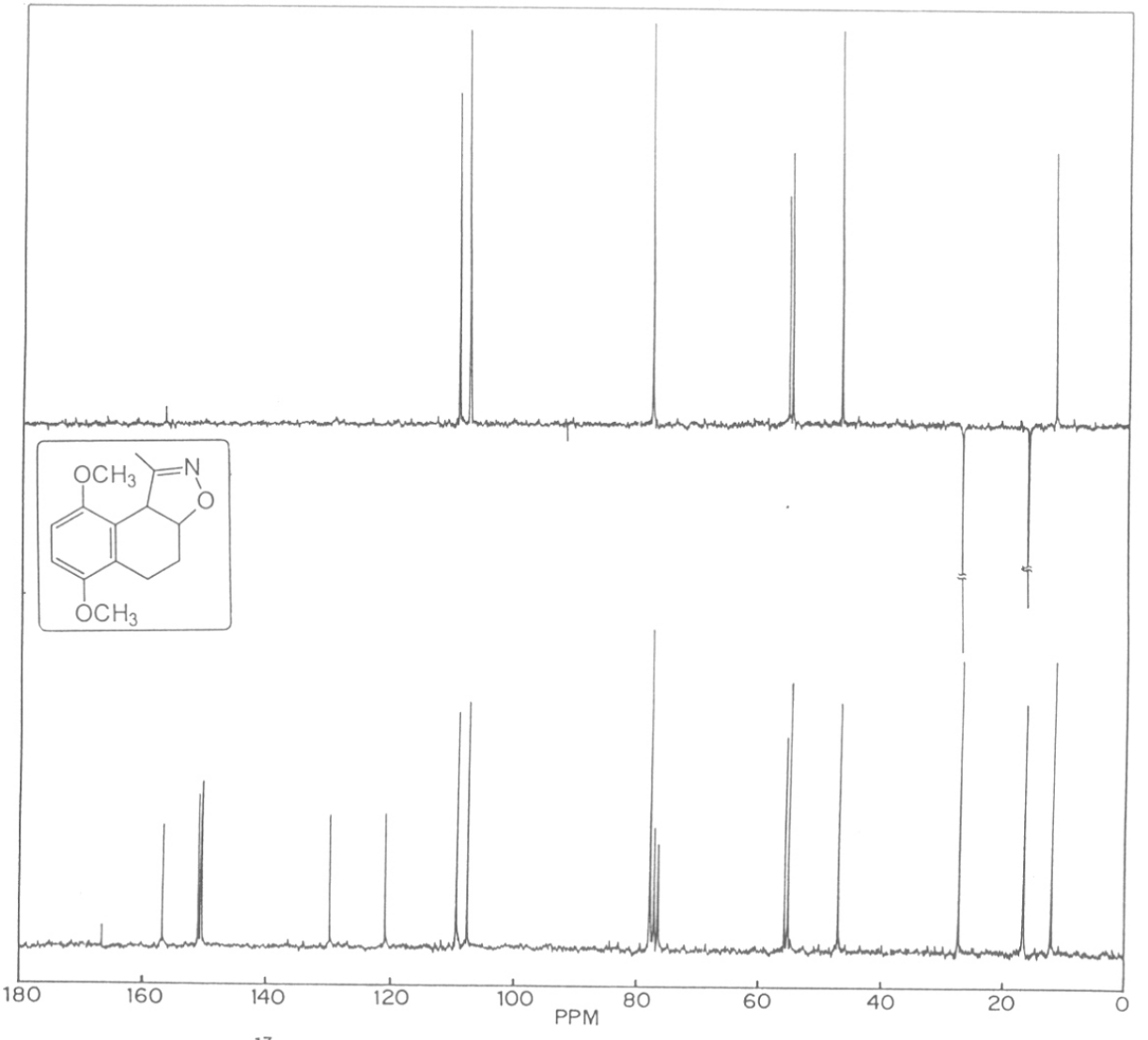
PMR OF COMPOUND **60** IN $CDCl_3$ AT 200MHz



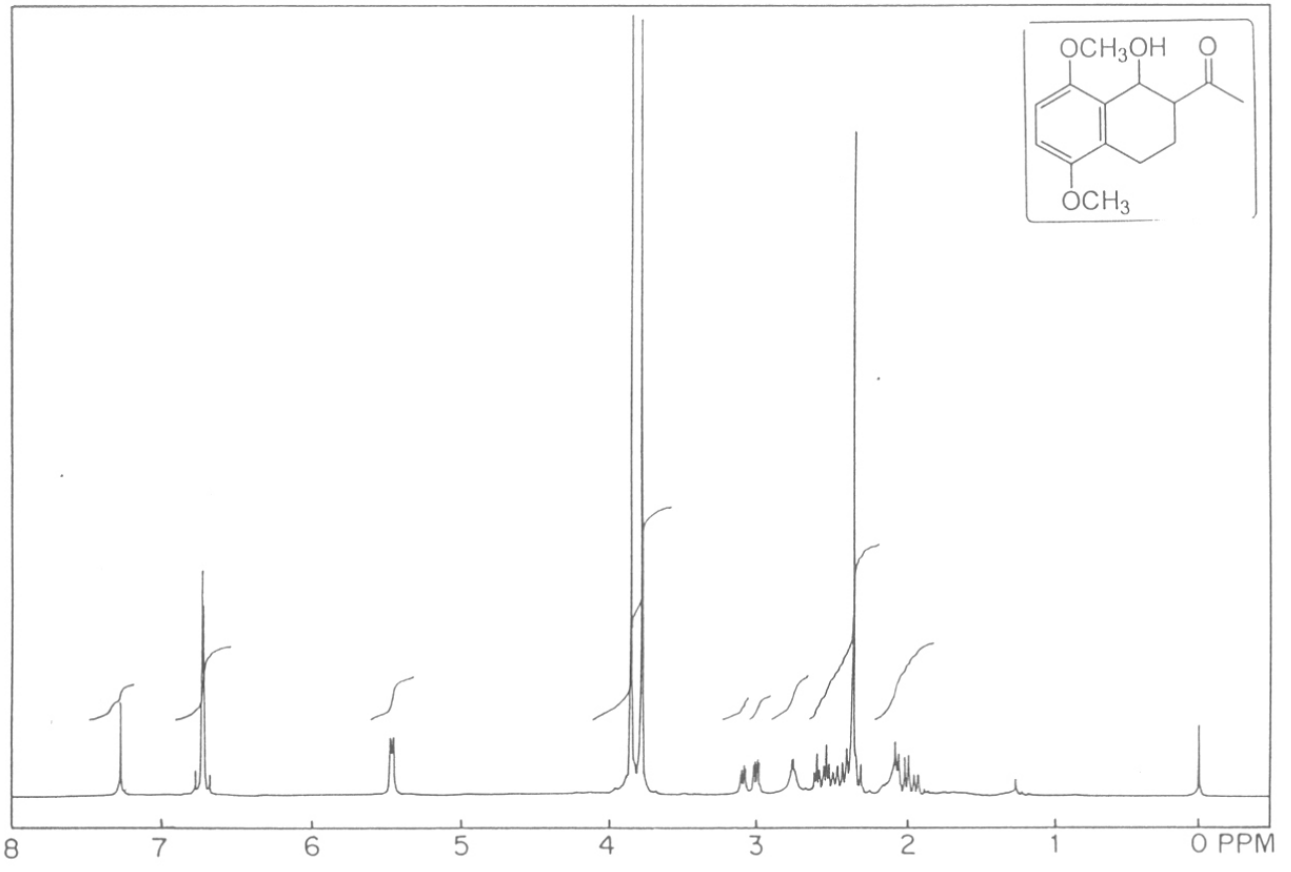
^{13}C-NMR OF COMPOUND **60** IN CF_3COOD AT 50MHz



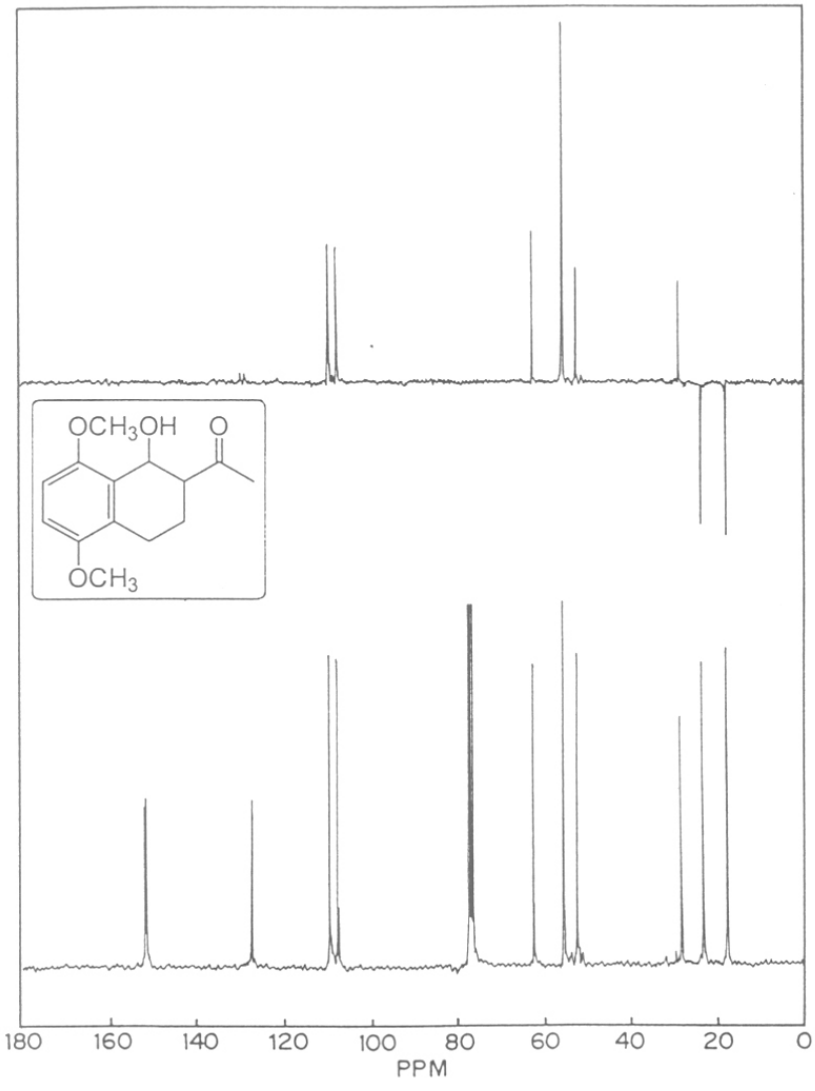
PMR OF COMPOUND **61** IN $CDCl_3$ AT 200 MHz



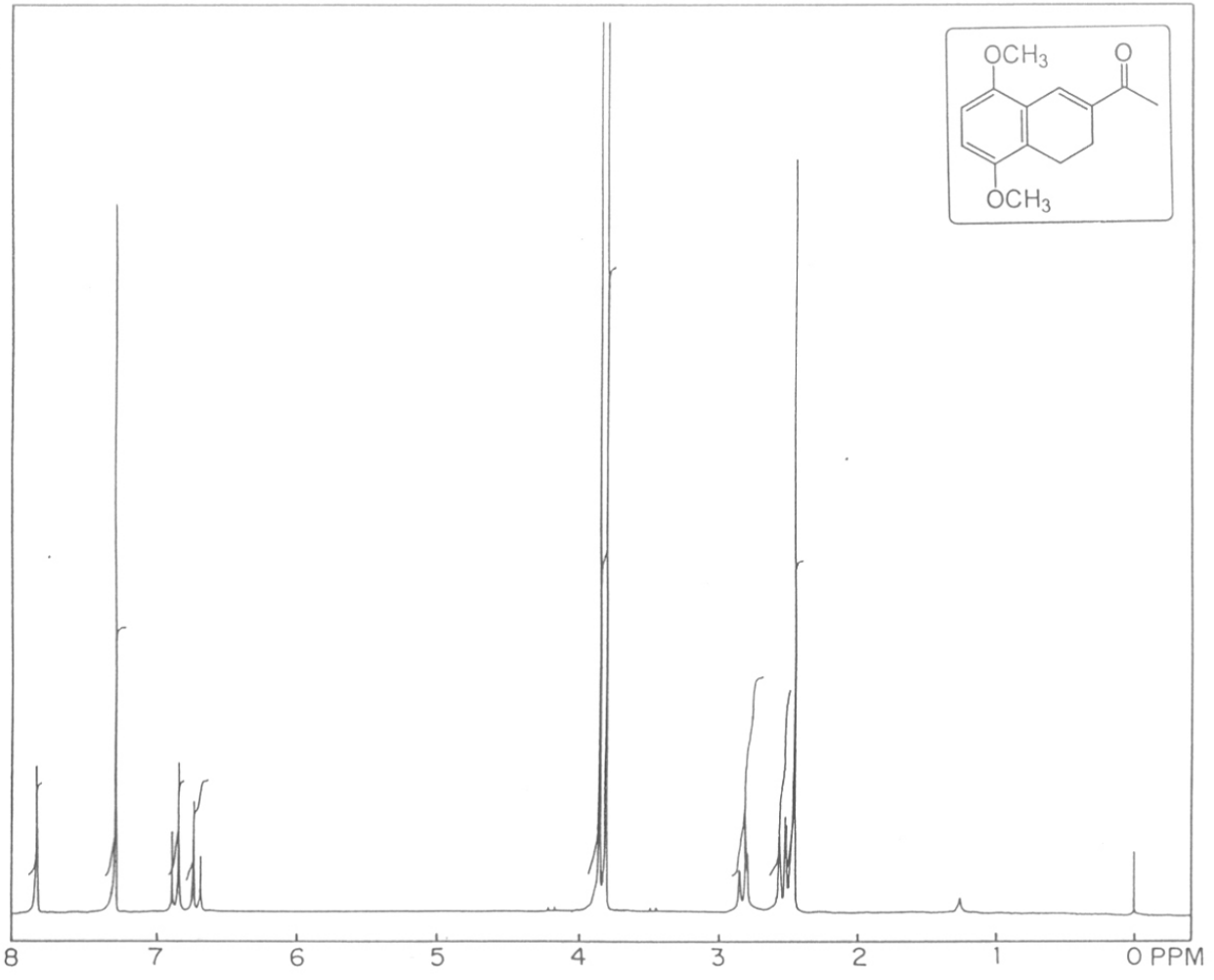
^{13}C NMR OF COMPOUND 61 IN $CDCl_3$ AT 50MHz



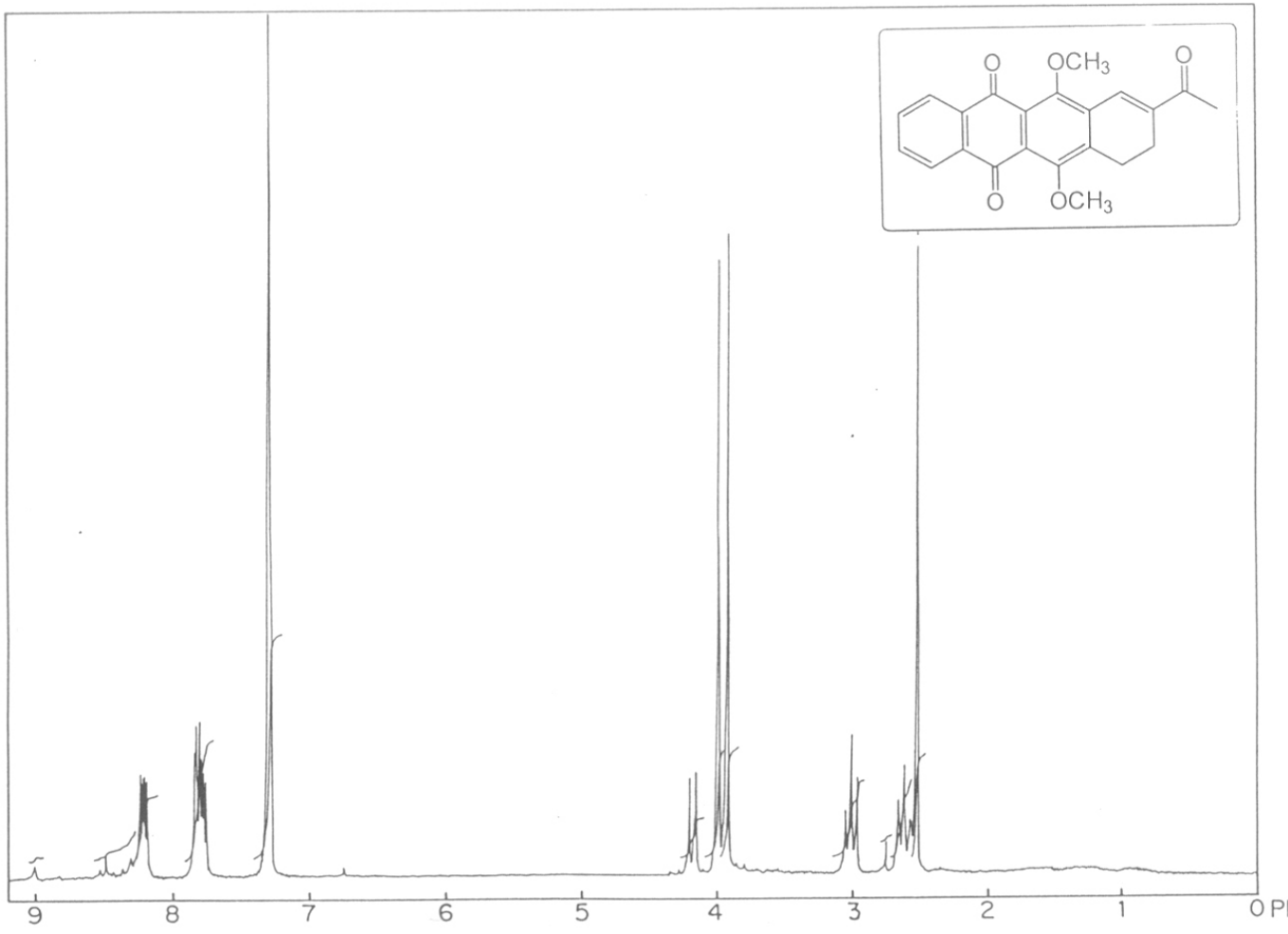
PMR OF COMPOUND **62** IN $CDCl_3$ AT 200MHz



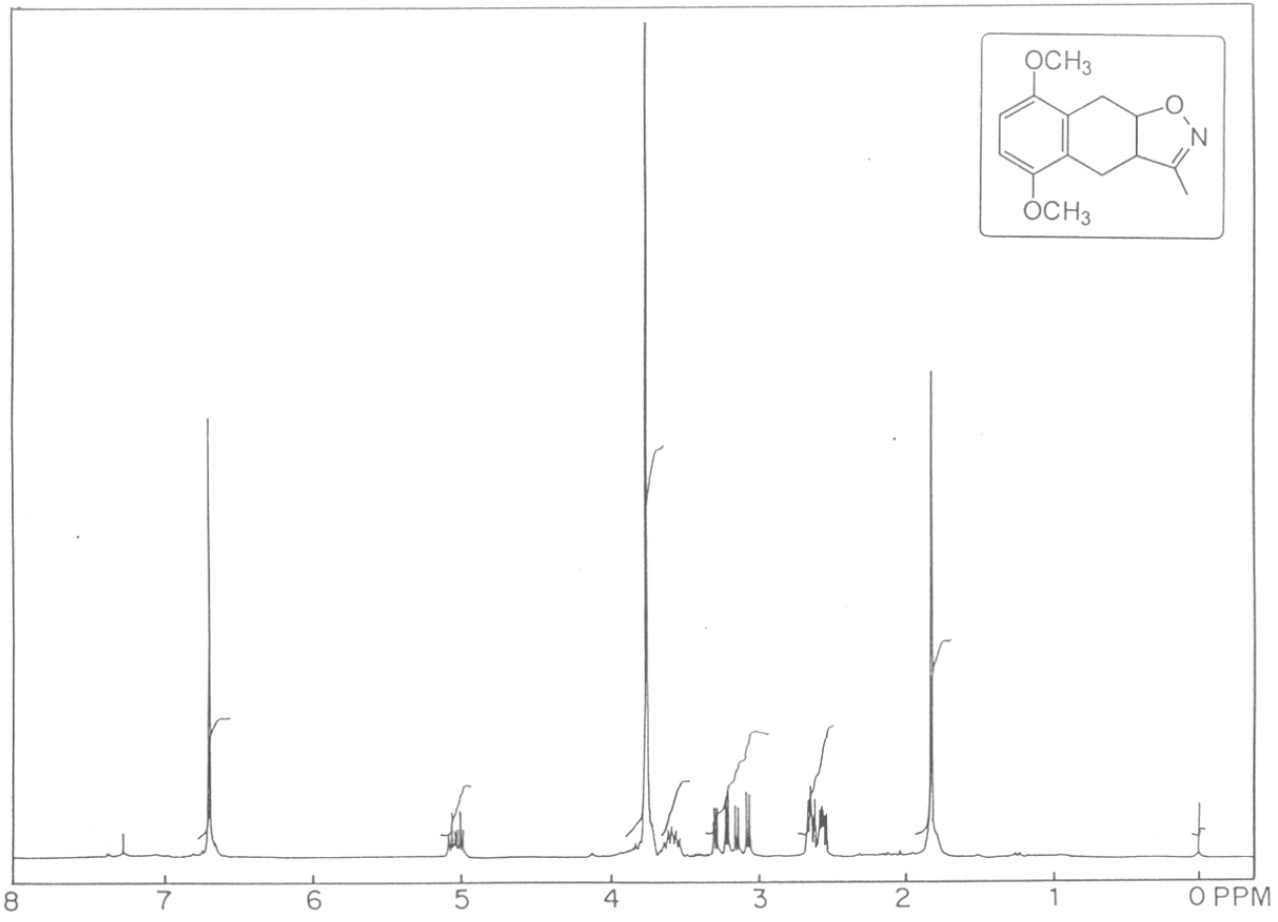
^{13}C-NMR OF COMPOUND 62 IN $CDCl_3$ AT 75 MHz



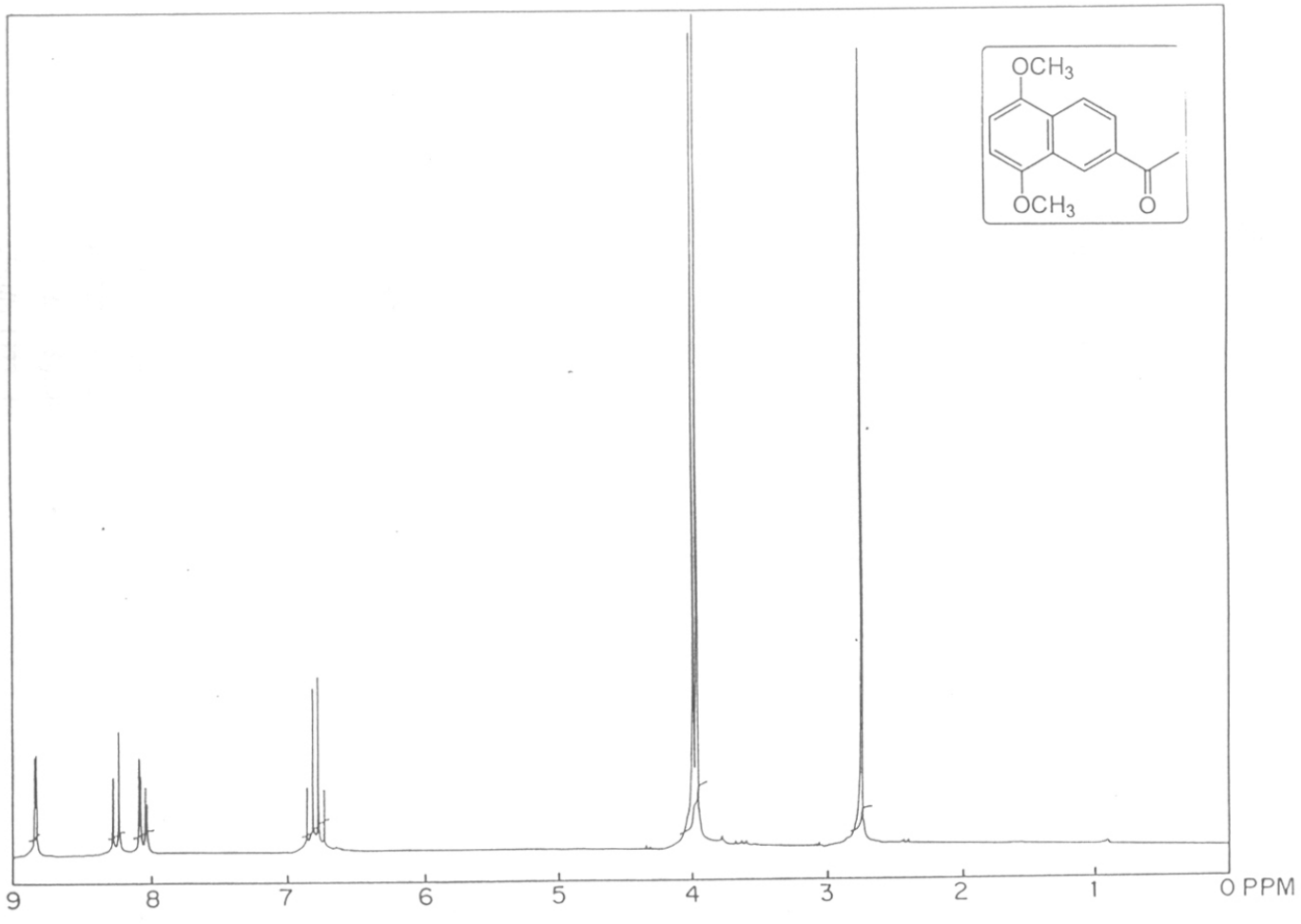
PMR OF COMPOUND **8** IN $CDCl_3$ AT 200MHz



PMR OF COMPOUND 42 IN $CDCl_3$ AT 200MHz



PMR OF COMPOUND 67 IN $CDCl_3$ AT 200 MHz



PMR OF COMPOUND **35** IN $CDCl_3$ AT 200MHz

1.1.6 References :

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SECTION 2

Attempted synthesis of Corey's lactone starting from a simple acyclic precursor

1.2.0 Introduction:

Prostaglandins, Prostacyclins and thromboxanes comprise a group of polyunsaturated, hydroxylated long chain fatty acids that can evoke a wide spectrum of biological actions at extremely low concentrations in a wide variety of tissues. Since its discovery in early 1930s by a Swedish biochemist von Euler, Prostaglandins have been subjected to much research and numerous literature reviews.

Prostaglandins per se have been implicated as playing a functional role in such physiological processes as vasodilation and vasoconstriction, regulation of body temperature, platelet aggregation, reproduction, inflammation, infection, autonomic neurotransmission, and cardiovascular and renal function.[1] The clinical and pharmacological applications of prostaglandins are dealt with extensively in a review by Elattar.[2]

Nomenclature:

Prostaglandins (PGs) are a family of C_{20} unsaturated polyoxygenated fatty acids that consist of a cyclopentane ring with a seven and a eight carbon side chains named as α and ω respectively with trans stereochemistry.

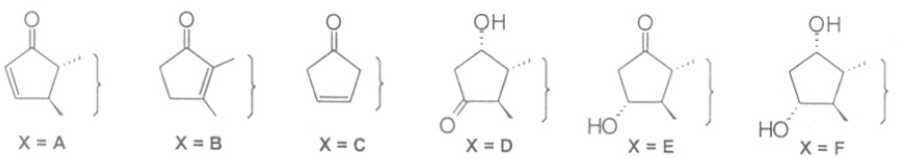
Alphabetical designation (A, B, C, ...) in prostaglandins refer to the different oxygen functions in the cyclopentane moiety. Numerical subscripts represent the number of olefinic bonds in the side chains. The subscript α in $PGF_{2\alpha}$ refers to the orientation of C_9 hydroxyl group. Prostacyclin (PGI_2) also belongs to this classification but has ether linkage between C_9 oxygen and C_6 vinylic carbon.

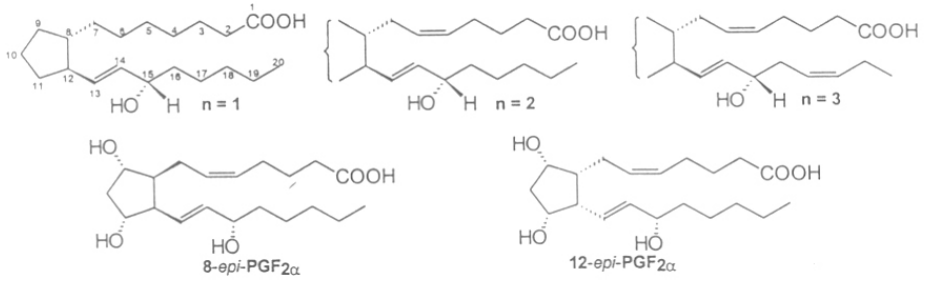
$PGX_{n\alpha}$

'X' denotes the functionality in the cyclopentanone ring.

'n' denotes the number of double bonds in the side chains.

'α' denotes the stereo chemistry of C_9 hydroxyl group.





A new class of prostaglandin-like compounds called isoprostanes were discovered recently *in vivo* in humans.[3] These natural products were found as a result of a new biochemical pathway of Arachidonic acid. In addition the isoprostanes differ from the more familiar prostanoids by the *cis* stereochemistry at the five membered ring junction. 8-*epi*-$PGF_{2\alpha}$, the main isoprostane identified so far was found to be the most potent renal vasoconstrictor, almost 10 times more potent than LTC_4.[4]

Ever since the structure elucidation of the Prostaglandins, the synthesis of this class of hormones has been a considerable challenge to synthetic chemists. With a maximum number of five asymmetric centers, four of them contiguous in the prostanoid nucleus and one in the allylic alcohol side chain, the primary problem is the stereospecific construction of these asymmetric centres.

1.2.1 Literature survey:

Prostaglandins have been synthesized by a variety of elegant ways, which have been well documented as excellent reviews by Bindra,[5] Mitra,[6] Roberts and Scheinmann[7] and Noyori.[8]

Of the various literature reports, three major strategies are utilized for the synthesis of prostaglandins.

☞ The widely used Corey's synthesis[9] which consists of a two-fold Wittig type chain extension of a chiral aldehyde possessing four different stereogenic centres. The highly functionalized key intermediate is derived from cyclopentadiene *via* a series of stereo defined bicyclic intermediates.

☞ The conjugate addition approach pioneered by Sih,[10] involved nucleophilic addition of α-side chain unit to a cyclopentenone in which the α–side chain was already installed. This directly led to prostaglandin-E type compounds.

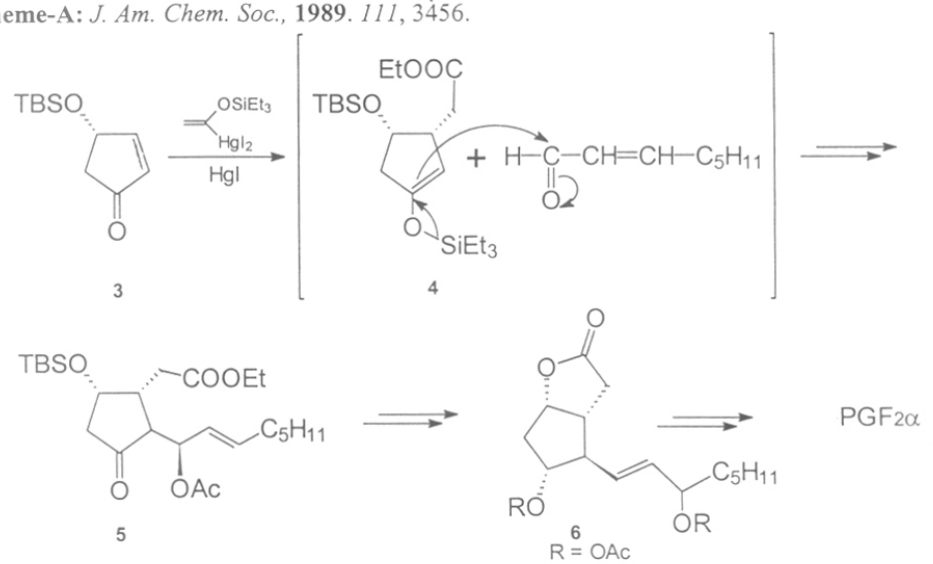
☞ The three component coupling synthesis[11] *via* consecutive linking of the ω-and α-side chains to unsubstituted 4-hydroxy-2-cyclopentenone derivatives.

Most of the syntheses of prostaglandins developed in the later years are mainly based on modification of these three major strategies.

Noyori *et al.*[12] made the three component coupling strategy much simpler by introduction of a *Zincate* reagent which overcame the difficulties usually associated with organometallic reagents for the conjugate addition of ω-side chain.

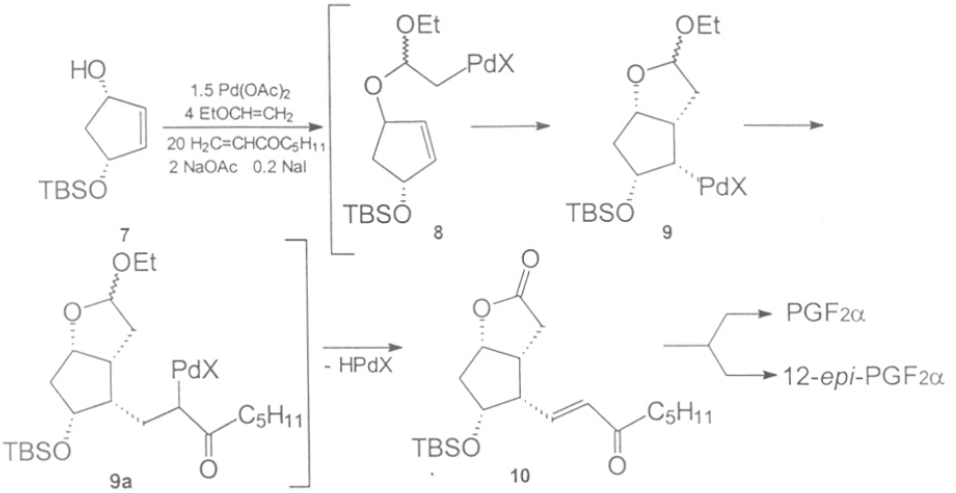
The Danishefsky[13] synthesis of prostaglandin through a novel stereospecific silyl group transfer reaction demonstrates the reversal of the order of the side chain assembly of the three component coupling (**Scheme-A**).

Scheme-A: *J. Am. Chem. Soc.*, **1989**. *111*, 3456.

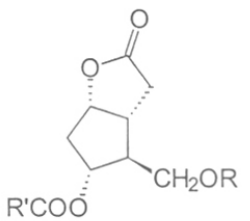


Synthesis of $PGF_{2\alpha}$ by Larock and Lee[14] in 1991 through the controlled one step palladium promoted intermolecular coupling of three different alkenes to form the bicyclic lactone having ω-side chain simplifies the multi step Corey's synthesis (**Scheme-B**).

Scheme-B: *J. Am. Chem. Soc.*, **1991**, *113*, 7815.

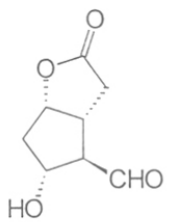


To date the bicyclic lactone commonly referred to as the Corey lactone **1** is the most widely used intermediate in the synthesis of naturally occurring prostaglandins and also in the synthesis of some of the analogs. The synthesis of lactone **1** or the Corey aldehyde **2** by diverse synthetic methods has been accepted as constituting a formal synthesis of the prostaglandins.



Corey lactone

1



Corey aldehyde

2

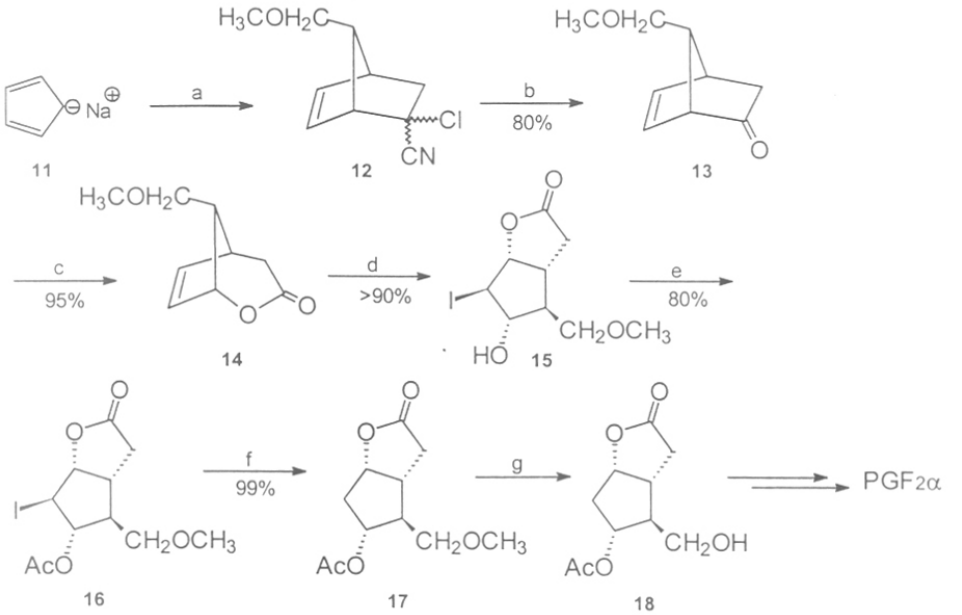
However in this survey a variety of unique syntheses are covered with an emphasis on the bicyclo Corey lactone and its similar analogs.

Corey's Synthesis:

In 1969 E.J. Corey *et al.*[15] described a stereo controlled synthesis of $PGF_{2\alpha}$ and E_2 starting from a cyclopentane derivative with sequential introduction of appropriate substituents around the ring which led to the synthesis of Corey's lactone. Thus the Diels-Alder reaction of a 5-substituted cyclopentadiene with a ketene equivalent provided the C_6 and C_7 carbons and the formation of the anti adduct gives the required *trans* orientation of

the α and β chain precursors at C_8 and C_{12} respectively. Selective Baeyer-Villiger oxidation gave the δ-lactone which was transformed to the γ-lactone *via* iodolactonisation. Subsequent elaboration led to $PGF_{2\alpha}$ (see **Scheme 1**).

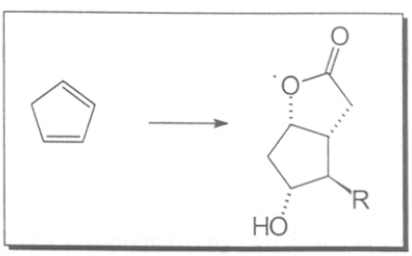
Scheme 1: *J. Am. Chem. Soc.*, **1969**, *91*, 5675.

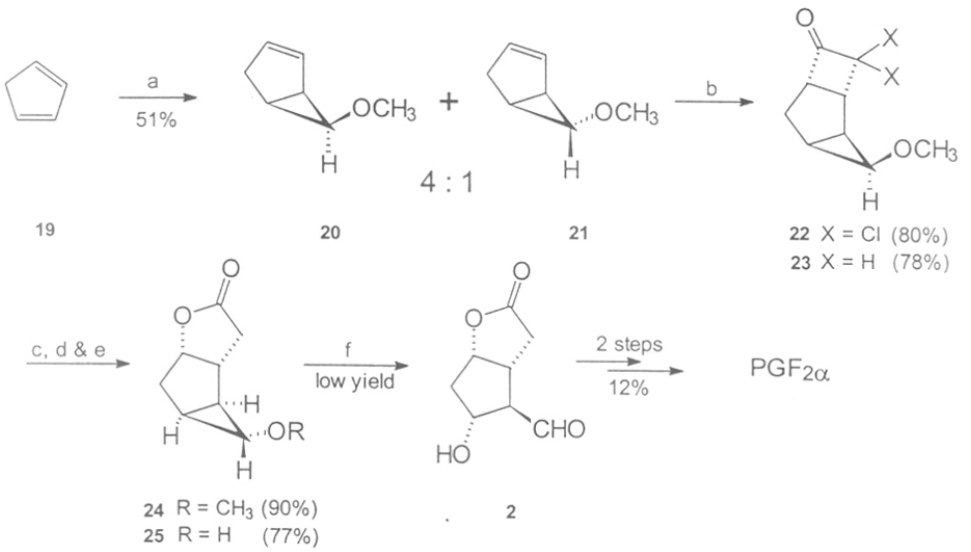


a. i). $ClCH_2OCH_3$, **ii**). 2-Chloroacetonitrile (5 eq), 0°C; **b**. KOH (2.5 eq), DMSO, 14 hrs; **c**. mCPBA, DCM, $NaHCO_3$; **d. i**). NaOH (2.5 eq), 0°C, **ii**). CO_2, **iii**). KI_3 (2.5 eq), 0-5°C, 12 hrs; **e**. Ac_2O, Pyr, 25°C, 15 min.; **f**. $^nBu_3SnH$, Benzene; **g**. BBr_3 (5.5 eq), DCM, 0°C.

In 1970 Corey *et al.*[16] reported another total synthesis of $PGF_{2\alpha}$ and PGE_2 via a tricarbocyclic intermediate. According to their synthetic strategy the functionalization of the cyclopentene double bond was done by prior formation of a cyclopropyl ether **20** *via* carbene insertion. Subsequent oxidative cleavage of the cyclopropanol **25** furnished the hydroxy aldehyde **2,** which was required for elaboration into prostaglandins.

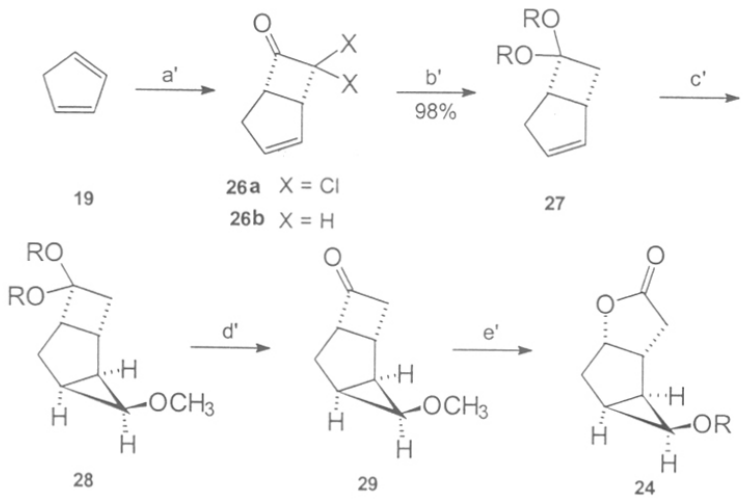
Scheme 2a: *Tet. Lett.*, **1970**, 307.





a. MeLi, Cl_2CHOMe, Et_2O, -14 °C, N_2.; **b**. $Cl_2CHCOCl$, Et_3N, reflux, pentane.; **c**. Zn/AcOH, 40 °C, 1 hr.; **d**. 30% H_2O_2, AcOH, 5-10 °C, 16 hrs.; **e**. BBr_3 (3 eq), DCM, -65 °C.; **f**. H_2O:AcOH (1:7), H_2CrO_4 (1 eq), CAN (0.05 eq), 20 °C, 1 hr.

Scheme 2b:



a'. $Cl_2C{=}C{=}O$.; **b'**. $HC(OBu)_3$, n-BuOH, TsOH.; **c'**. MeLi-LiI, Cl_2CHOMe, Et_2O.; **d'**. H_3^+O.; **e'**. H_2O_2/AcOH.

As described in the schemes above, the intermediate **2,** which is a vital synthon for conversion to various synthons was prepared by two different routes.

The starting point was 6-methoxy-bicyclo[3,1,0] hexene-2 (**20&21**) (**Scheme 2a**) which was obtained as 4:1 mixture of endo and exo forms from α,α-dichloromethyl methyl ether and cyclopentadiene (**19**) involving a carbene. Treatment of a solution of **20** and **21** with dichloroacetyl chloride (2 eq) and triethyl amine resulted in the formation of the tricyclic ketone **22** which was effectively dechlorinated using Zn and glacial acetic acid to give **23**. Further treatment of tricyclic ketone **23** with H_2O_2 in glacial acetic acid produced the methoxy γ-lactone **24** which when treated with BBr_3 in dichloro methane gave the cyclopropanol **25**.

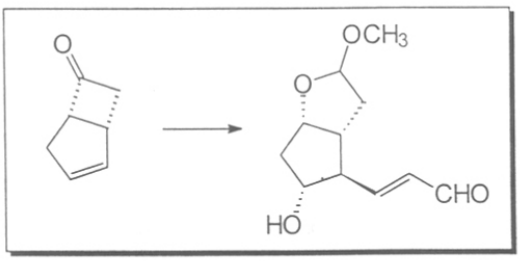
The same cyclopropanol **25** was also obtained by another route (**Scheme 2b**) starting from bicyclo [3,2,0] heptenone (**26a**) which was prepared from the adduct of cyclopentadiene (**19**) with dichloro ketene by dechlorination using Zn/AcOH. The di-n-butyl ketal **27** was prepared from **26b** using methyl orthoformate and converted to the tricyclic methoxy ketal **28** in fair yields by reaction with dichloromethyl methyl ether and methyl lithium-LiI. Acid catalyzed hydrolysis of **28** yielded the corresponding ketone **29** which was oxidized with 30% H_2O_2 to yield methoxy lactone **24**.

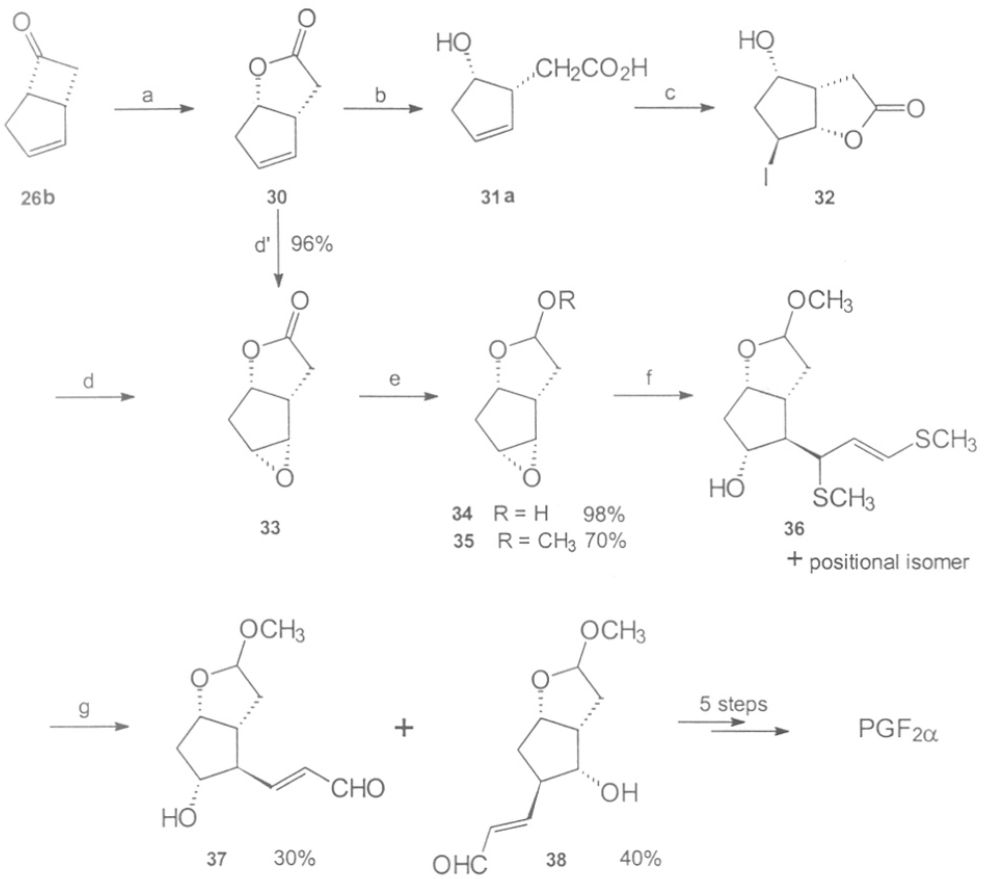
The cyclopropanol **25** was then converted to hydroxy aldehyde **2**, a key intermediate in the synthesis, with 2 molar H_2O:AcOH (1:7) and one equivalent of chromic acid along with 0.05 eq of CAN.

Corey-Noyori's Synthesis:

As reported in the Corey's synthesis,[16] since the oxidative cleavage of cyclopropanol (**25**) was a low yielding step, a better functionalisation sequence was devised in order to circumvent this step by Corey-Noyori *et al.*[17] in the same year (**Scheme 3**).

Scheme 3: *Tet. Lett.*, **1970**, 311.





a. H_2O_2/aq.AcOH.; **b**. 2 eq aq ^-OH, CO_2.; **c**. 3 eq KIO_3, 0°C, 16 hrs.; **d**. ^-OH, dil. HCl.; **d'**. AcOOH, AcOH.; **e**. **i**). DIBAL-H, **ii**). BF_3-etherate, MeOH.; **f**. LiCH(SMe)CH=CH-SMe, -78°C, THF.; **g**. $HgCl_2$, $CaCO_3$, aq. CH_3CN (4:1), 50°C, 1 hr.

As per the **Scheme 3,** the saponification of the unsaturated lactone **30** with 2 eq of alkali followed by neutralization (CO_2) and iodination at 0°C using Potassium iodate (3 eq) afforded the Iodolactone **32**. This intermediate was treated directly with aqueous alkali (to effect the hydrolysis of lactone and cyclisation of resulting iodohydrin) followed by dil. HCl (for relactonisation) to produce the pure oxidolactone **33** in fair yields. This intermediate **33** was also obtained directly from **30** by treating with peroxy acetic acid.

The sequence of reactions used so far ensures that the stereochemistry of the oxidolactone **33** is *cis-syn-cis*. Reduction of the oxidolactone **33** with 1 eq. of DIBAL-H at -78°C gave the oily oxidolactol **34** which was treated with methanol containing a catalytic

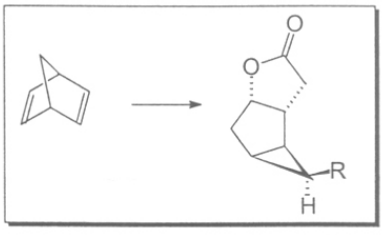
amount of BF_3-etherate to produce the cyclic acetal **35**. This was subjected to a reaction with 1 eq. of 1,3-bis(methyl thio)allyl lithium in THF to give a mixture of isomeric products containing the required product **36**. This mixture was hydrolyzed without separation using $HgCl_2/CaCO_3$ to give a mixture of two unsaturated aldehydes **37** and **38**, which were separated by preparative TLC. The desired aldehyde **37** was then converted to $PGF_{2\alpha}$ in three steps.

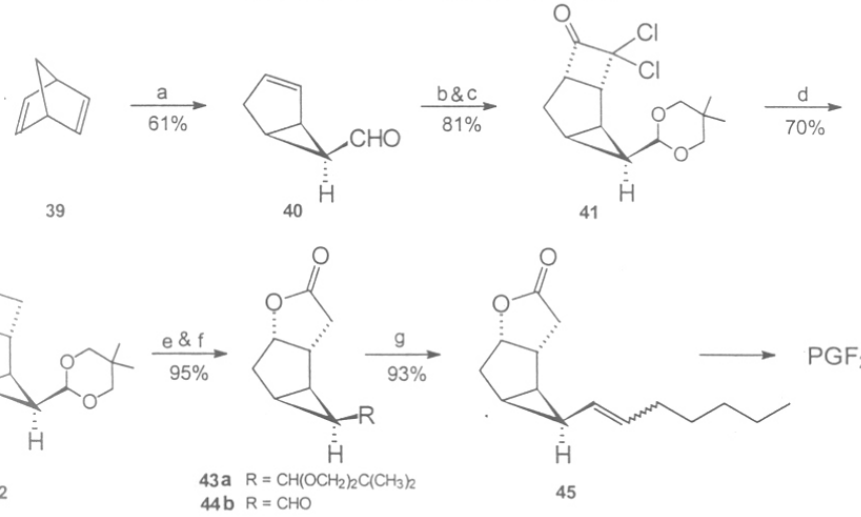
The interesting feature of this synthetic sequence is the regioselective opening of *cis-syn-cis* bicyclic epoxide by the lithio derivative of the vinyl sulfide, which already contains a latent C_{13}-C_{14} trans double bond.

Upjohn synthesis:

In the year 1973 Kelly *et al.*[18] utilized the Corey's method of constructing the α-side chain[16] but adopted the Just-Upjohn[19] method for the generation of β-chain by solvolysis of cyclopropyl carbinol derivative[20] (**Scheme 4**).

Scheme 4: *J. Am. Chem. Soc.*, **1973**, *95*, 2746.





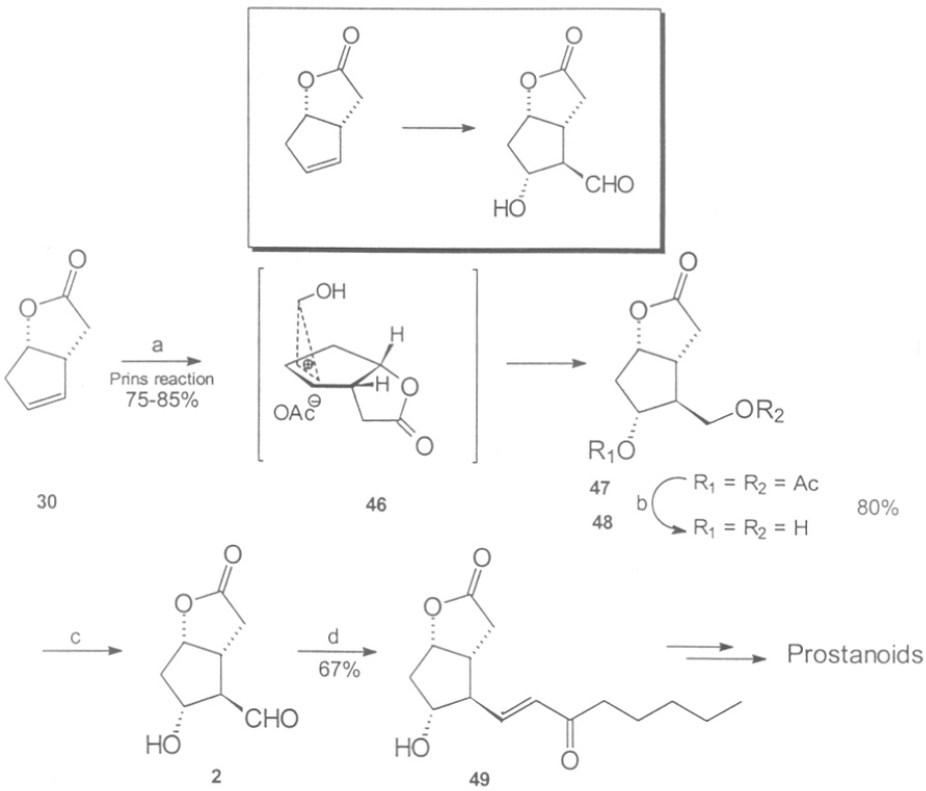
a. AcOOH, Na_2CO_3, DCM, 3 hrs, RT.; **b**. Neopentyl glycol, H^+, DCM.; **c**. $Cl_2C{=}C{=}O$.; **d**. Zn/NH_4Cl, MeOH.; **e**. mCPBA.; **f**. 88% HCOOH.; **g**. $Ph_3P{=}CH\text{-}C_5H_{11}$.

As shown in the **Scheme 4**, Norbornadiene (**39**) was oxidized as described by Meinwald *et al.*[21] to the bicyclic aldehyde **40**. Treatment of crude **40** with neopentyl glycol afforded the acetal which was further treated with dichloroketene to give the dichloro cyclobutanone **41.** This on reduction with Zn/NH_4Cl gave a quantitative yield of cyclobutanone **42** which was resolved and further oxidized with mCPBA to produce the lactone acetal **43**. The acetal was hydrolyzed with 88% formic acid to give the lactone aldehyde **44**. Wittig condensation of aldehyde **44** with n-hexyl triphenyl phosphonium bromide afforded the olefin **45** which was further carried to $PGF_{2\alpha}$ by reported procedures.

Kovac's Synthesis:

Another interesting synthetic sequence towards the prostanoid synthesis is that of Kovacs[22] which utilizes a regio as well as stereo specific Prins reaction to functionalize the C_{11}-C_{12} double bond (**Scheme 5**).

Scheme 5: *Tet. Lett.*, **1976**, 4639.



a. HCHO, H^+, AcOH, 60-80°C.; **b.** 1 eq NaOMe, MeOH.; **c.** Thioanisole-Cl_2, or Pfitzner-Moffatt oxidn. (DMSO/DCC/anhyd. Phosphoric acid); **d.** $Ph_3P{=}CHCOC_5H_{11}$.

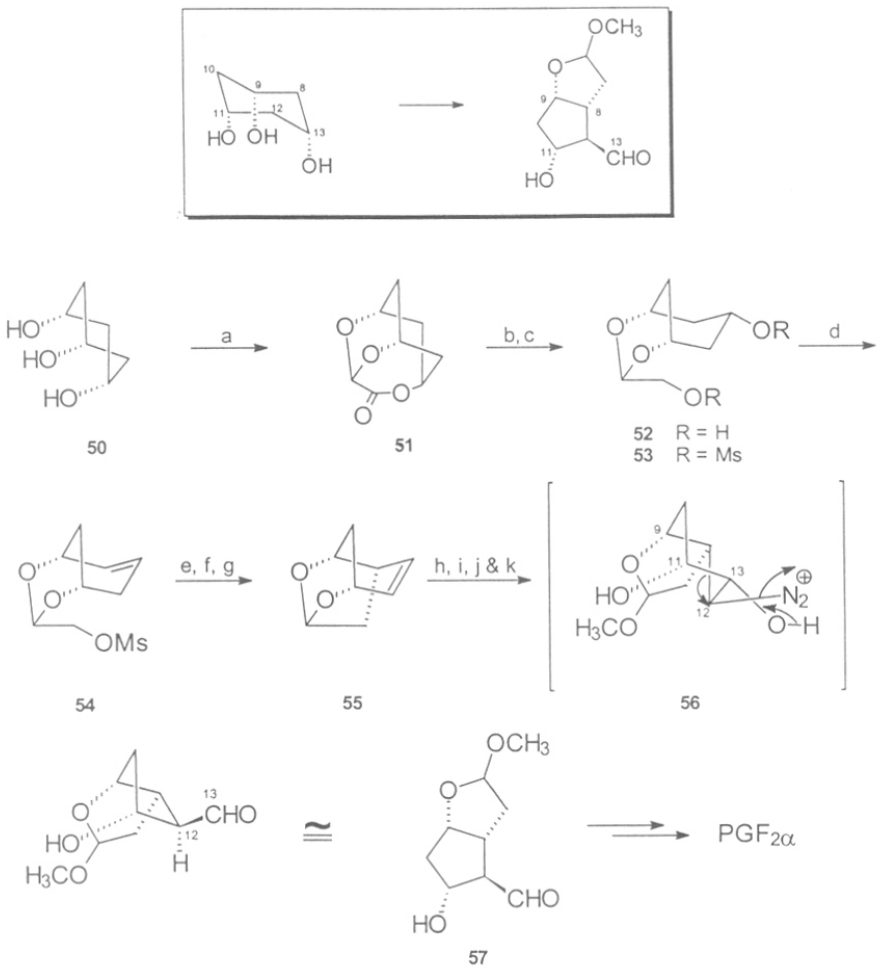
The readily available cis(-)-oxabicyclo [3,3,0] oct-2-en-7-one (**30**) was converted to **47** by addition of paraformaldehyde (which was monomerised *in situ* with H_2SO_4 in glacial acetic acid) on the olefinic bond under the conditions of Prins reaction[23]. Methanolysis (1 eq. of NaOMe) led to the known lactone diol **48**. No other regio or stereo isomeric products could be detected in the reaction mixture probably because of the preferential opening of the alleged 3-centered carbonium ion **46** at the sterically less hindered position. A selective oxidation of **48** was done by thio anisole/chlorine or more conveniently with Pfitzer-Moffatt reagent.[24] The extremely labile aldehyde **2** without isolation was carried towards **49** by treating with 2-oxo-heptylidene triphenyl phosphorane in 67% overall yield.

Woodward's Synthesis:

In this ingenious approach of Woodward[25] towards the synthesis of prostaglandin the chemistry of cyclohexanes was exploited to create the four contiguous asymmetric centres of the prostaglandin nucleus. The extra ring carbon then becomes the aldehyde attached to the cyclo pentane ring in a fascinating ring contraction. A noteworthy feature of this synthesis is that it largely succeeds in avoiding the use of extrinsic protecting groups.

As per the **Scheme 6** below cis cyclohexane-1,3,5-triol (**50**) was converted to the crystalline tricyclic lactone **51** by refluxing it in DME with glyoxylic acid mono hydrate and excess of Amberlyst-15. Sodium borohydride reduction transformed **51** to the bicyclic diol **52** which in turn when treated with methanesulfonyl chloride yielded the dimesylate **53**. When a hot suspension of dimesylate in isopropanol was mixed with a boiling solution of KOH, the olefin mesylate **54** was formed. The compound **54** was then converted to **55** by treating with K_2CO_3 in DME followed by mesylation and elimination. This tricyclic olefin **55** was then converted to the diazotized product **56** in three steps which involves epoxidation, ammonolysis and diazotization. After neutralization with aqueous sodium bicarbonate suspension, exhaustive extraction with dichloromethane yielded the hydroxy aldehyde acetal **57** as an oily product. It was further converted to $PGF_{2\alpha}$ through several steps.

Scheme 6: *J. Am. Chem. Soc.*, **1973**, *95*, 6853.

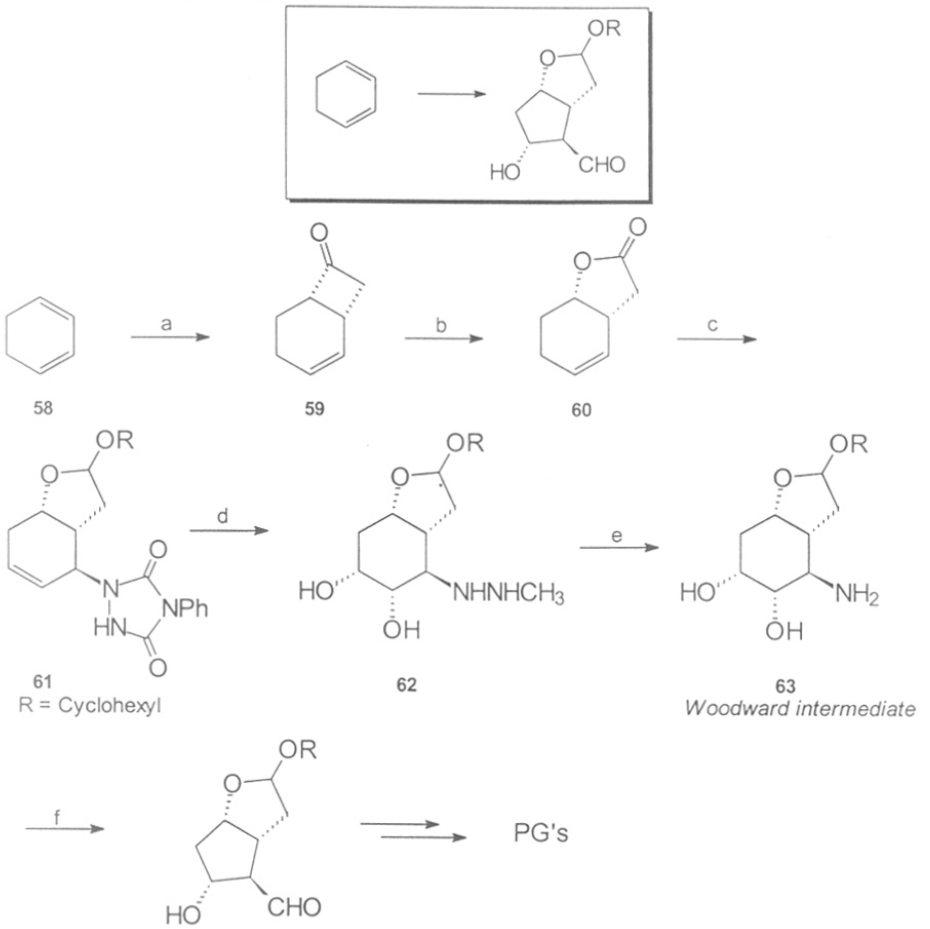


a. Amberlyst-15, OHC-COOH, DME, reflux.; (85%) **b**. $NaBH_4$, EtOH.; (97%) **c**. MsCl, Pyridine, -20°C.; (97%) **d**. KOH, EtOH, reflux.; (89%) **e**. 1 eq K_2CO_3, aq DME.; (70%) **f**. MsCl, Et_3N, DCM, 0°C.; (95%) **g**. KOH, ^iPrOH, 2 hrs.; (93%) **h**. H_2O_2, $KHCO_3$, PhCN, MeOH.; (62%) **i**. 24% aq NH_3, 100°C, 2 hrs.; (90%) **j**. 0.33N HCl, MeOH.; (99%) **k**. $NaNO_2$, NaOAc, aq AcOH (80%).

Corey-Snider's Synthesis:

In this modification of Corey[26] ring contraction, the Woodward intermediate was made from cyclohexa-1,3-diene (**58**) by allylic functionalization *via* the ene reaction followed by the cleavage of the N-phenyl triazolindione (enophile) (**Scheme 7**).

Scheme 7: *Tet. Lett.*, **1973**, 3091.

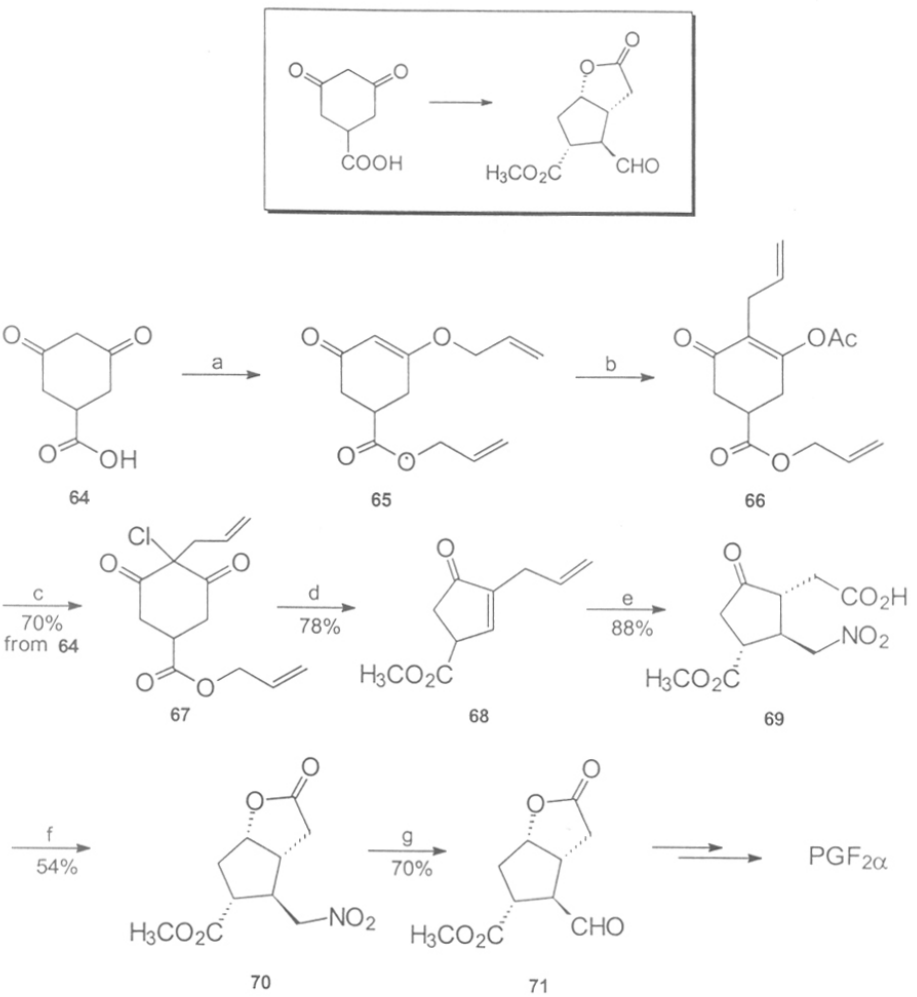


a. i).$Cl_2CHCOCl$, Et_3N, **ii**). Zn/AcOH, **iii**). H_2O_2, aq AcOH. **b**. **i**). DIBAL-H, Toluene, -78°C, 4 hrs (94%), **ii**). Cyclohexanol, BF_3-etherate, 48 hrs.; **c**. **i**). NaH, THF, 25°C, 4 hrs, **ii**). 1.5 eq of DMS (95%).; **d**. **i**). OsO_4, THF, Pyridine, 25°C, 6 hrs, **ii**). 3N KOH, aq MeOH (3:1), 110°C, 48 hrs (93%).; **e**. Adam's catalyst, 1% AcOH in MeOH, 1 atm, 24 hrs.; **f**. excess $NaNO_2$, 25% aq AcOH, 0°C, 7 hrs (59%).

Rosen's Synthesis:

In this approach by Rosen[27] the prostanoid nucleus was constructed from cyclohexadione carboxylate (**64**) by sequence involving a Favorskii-type contraction and carboxy inversion step. This procedure allows the preparation of the C_{11} ring analogs by using appropriate substituents at that position (**Scheme 8**).

Scheme 8: *J. Org. Chem.*, **1973**, *38*, 3400.



a. pTSA, Allyl alcohol.; **b.** Ac_2O, reflux, 8 hrs.; **c. i**). LiOMe, MeOH,, **ii**). ^tBuOCl, MeOH, 0°C.; **d.** Na_2CO_3, reflux, mesitylene, 1.5 hrs.; **e. i**). Excess CH_3NO_2, cat. Triton-B, 65°C, 3.5 hrs, **ii**). $NaMnO_4$, aq H_2SO_4, Acetone.; **f. i**). 2 eq LiR_3BH, THF, -78°C, **ii**). THF, reflux, 1 hr, **iii**). $NaHCO_3$.; **g. i**). LiOMe, MeOH, 0°C, **ii**). Na-tetraborate, 0.95 eq $NaMnO_4$.

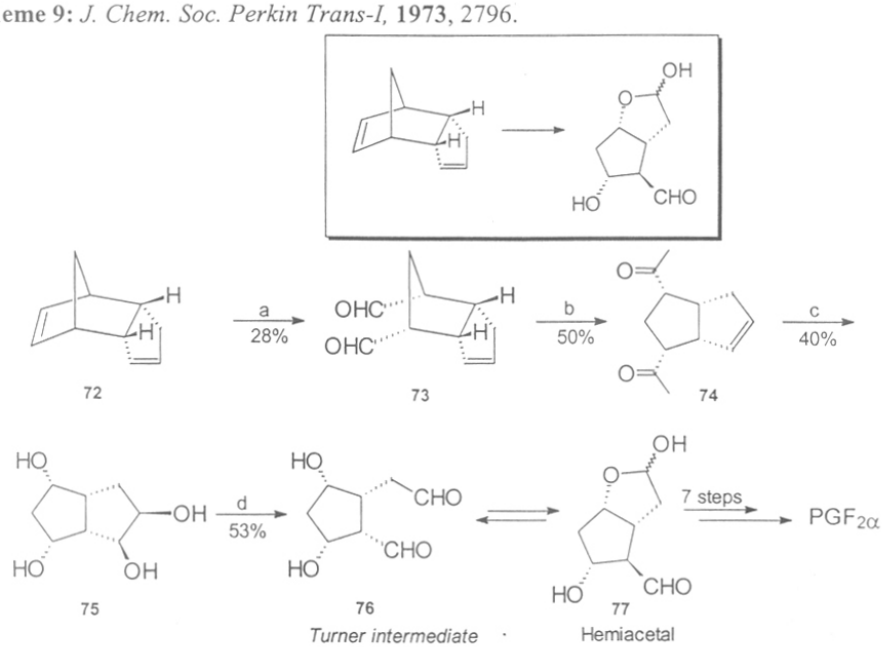
The 5-carboxy-1,3-cyclohexadione (**64**) when treated with allylic alcohol and catalytic amount of pTSA gave the intermediate **65** which when refluxed with acetic anhydride yielded **66**. This was converted to chlorodione **67** by treating with LiOMe followed by t-butyl hypochlorite at 0°C. A Buchi ring contraction was achieved to give

cyclopentenone **68** by treating with Na_2CO_3 in refluxing mesitylene. Reduction of ketone **68** with excess nitromethane and catalytic amount of Triton B yielded a 1,4-adduct which was treated further with sodium permanganate to reduce the allylic side chain which furnished the product **69** in good yields. Treatment of **69** with LiOMe and $NaBH_4$ afforded the lactone **70** which was further converted to the aldehyde **71** by treating first with LiOMe to give a lithium nitronate and further dissolving it in a saturated aqueous solution of sodium tetraborate and oxidizing with $NaMnO_4$. This aldehyde **71** was further converted to PGs by a series of steps.

Turner's Synthesis:

The Turner bicyclo[2,2,1]heptene approach[28] starts with the readily available endo-dicyclopentadiene **55**. This avoids the Diels-Alder reaction with a symmetrically substituted dienophile. The cyclopentene ring of dicyclopentadiene serves as the latent one and two carbon aldehyde units necessary for the further elaboration of the β and α-chains respectively (**Scheme9**).

Scheme 9: *J. Chem. Soc. Perkin Trans-I,* **1973**, 2796.



a. i). $KMnO_4$, **ii**). $NaIO_4$.; **b. i**). MeMgI, **ii**). Collins oxidn.; **c**. OsO_4, cat $KClO_3$, 85°C, 5 hrs.; **d**. i). Ac_2O, **ii**). mCPBA, reflux, 13 days or peroxy maleic acid, **iii**). K_2CO_3, MeOH, **iv**). Ion exchange resin, **v**). $NaIO_4$, K_2CO_3, RT, 1.5 hrs.

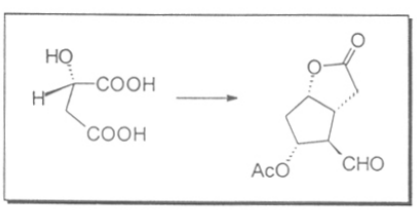
Previously reported syntheses are based essentially on racemic starting materials and depend on the resolution of some intermediates with the usual loss associated with such a process.

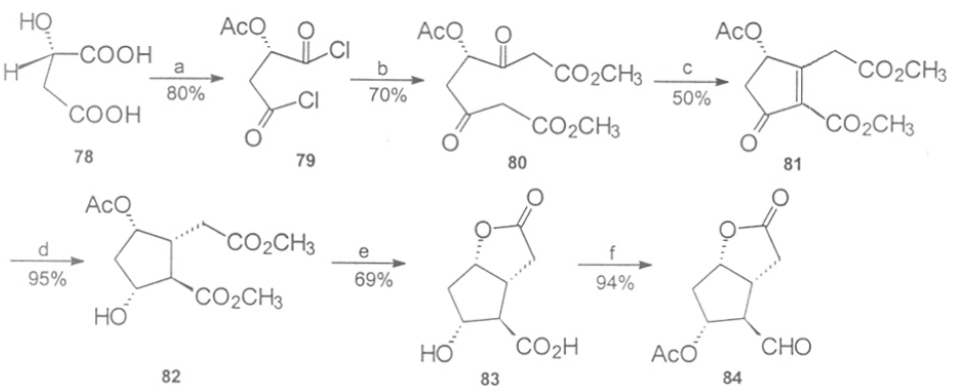
A synthesis starting with chiral precursors and which circumvents resolution has been first reported by Johnson *et al.*[29]

Johnson's Synthesis:

This approach starts from optically active malic acid **78**. The carbon atom bearing the secondary alcohol function in S-malic acid becomes the C_9 atom of the prostaglandins. The C_9 symmetry is then used to induce asymmetry at C_{12} in a catalytic hydrogenation step. This is followed by a stereospecific reduction of the C_{11} ketone to give the desired configuration of the hydroxy group at C_{11} (**Scheme 10**).

Scheme 10: *J. Am. Chem. Soc.*, **1976**, *98*, 1285.





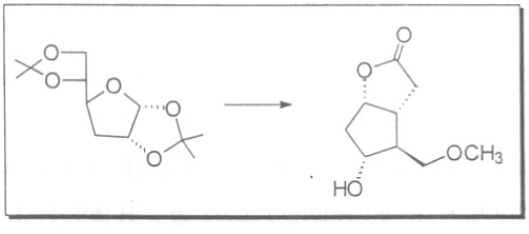
a. **i**). AcCl, **ii**). Cl_2CHOMe, $ZnCl_2$, reflux.; **b**. Methyl hydrogen malonate, $^{i}PrMgBr$, 0°C, THF.; **c**. pH 8.5, 30 min (aq buffer of triethanol amine hydrochloride).; **d**. **i**). 5% Pd-$BaSO_4$, Benzene, 1 atm, **ii**). $NaBH_4$, pH 5-7.; **e**. **i**). KOH, MeOH, **ii**). H_3^+O.; **f**. **i**). Ac_2O, Pyridine, **ii**). Cl_2CHOMe, $ZnCl_2$, **iii**). $NaBH_4$, EtOH, 0°C.

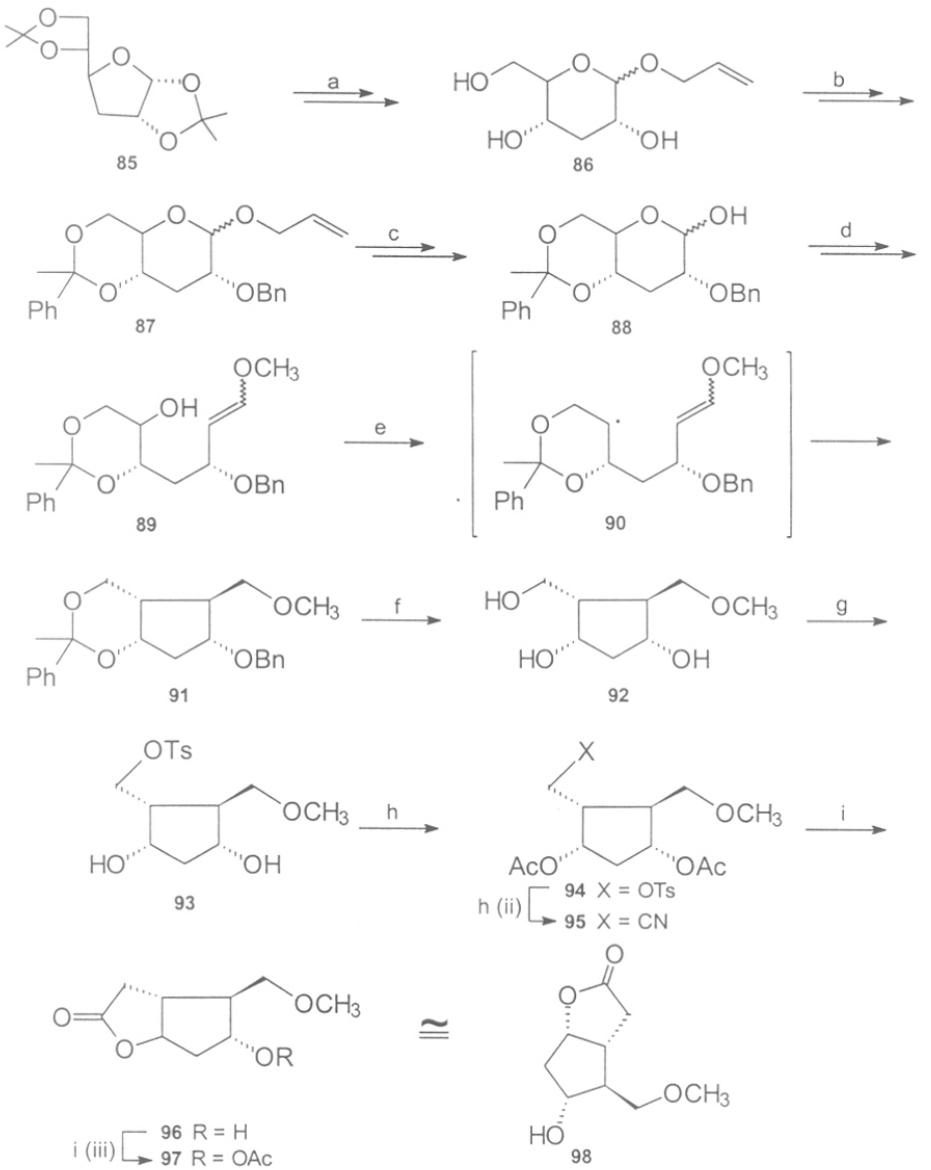
S-Malic acid **78** was treated with acetyl chloride to afford the 2-acetoxy succinic anhydride which when heated under reflux with dicholoro methyl ether in the presence of $ZnCl_2$ catalyst led to the corresponding succinyl chloride **79**. When 5 eq. of the dianion of methyl hydrogen malonate (derived from methyl hydrogen malonate and isopropyl magnesium bromide) was treated with this acid chloride **79** at 0°C in THF solution the product isolated was an unstable oil, dimethyl (S)-(-)-4-acetoxy-3,6-dioxosuberate (**80**). This oil was added to an aqueous buffer of triethanol-amine/triethanol-amine hydrochloride at pH 8.5 to effect the cyclisation within 30 min. to a mixture of cyclopentenones of which the compound **81** was predominant which was directly crystallized from the reaction mixture. Conversion of **81** to **82** was achieved by a catalytic reduction followed by epimerisation with $NaBH_4$ and aq. methanolic phosphate buffer at pH 5-7. The compound **82** was then converted to the carboxy lactone **83** by treating first with KOH in methanol and then subsequently with acid. Finally reduction of the lactone **83** was achieved after conversion of the hydroxyl group to the acetate and later on the carboxylic acid was converted to the acid chloride followed by reduction with $NaBH_4$. This gave the desired Corey's aldehyde **84**.

Rajan Babu's Synthesis:

In the year 1988 Rajan Babu[30] demonstrated that readily available pyranose sugars can be converted *via* face radical methodology into highly functionalized carbocycles such as prostaglandin intermediates. With proper choice of protecting groups the conformations of the radicals and hence the stereoselectivity of the cyclization can be controlled. He had demonstrated the versatility of converting the pyranose to cyclopentane by a novel 1,5-trans stereoselectivity arising from a cyclohexane chair like transition state which depends crucially on the stereochemical disposition of the oxy substituent at C_4 (**Scheme 11**).

Scheme 11: *J. Org. Chem.*, **1988**, *53*, 4522.



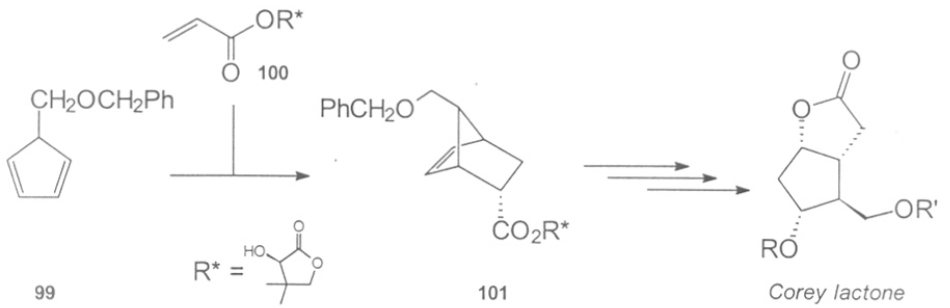


a. **i**). H^+, H_2O, EtOH, **ii**). H^+, allyl alcohol, benzene.; **b**. **i**). $PhCHBr_2$, pyridine, reflux, **ii**). BnBr, NaH, DMF.; **c**. **i**). $[Ir(COD)(PPh_2Me)]^+PF_6^-/H_2$, **ii**). $HgCl_2$, HgO, H_2O, acetone.; **d**. $Ph_3P^+CH_2OCH_3Cl^-$, n-BuLi.; **e**. **i**). Thiocarbonylbis(imidazole), EDC, reflux, **ii**). n-Bu_3SnH, AIBN, Toluene, reflux.; **f**. H_2/Pd, H^+.; **g**. TsCl, Pyridine.; **h**. **i**). Ac_2O, Pyridine, **ii**). NaCN, DMF.; **i**. **i**). OH^-, H^+, **ii**). Conc HCl, **iii**). Ac_2O, Pyridine.

According to **Scheme 11** it was found that open chain radicals cyclise predominantly to 1,5-*cis*-products. In sharp contrast the cyclic radicals derived from 4,6-O-benzylidene glucose derivatives exhibited unprecedented and exclusive 1,5-*trans* selectivity. Using this particular reaction the Corey's lactone was synthesized *via* the free radical cyclisation.

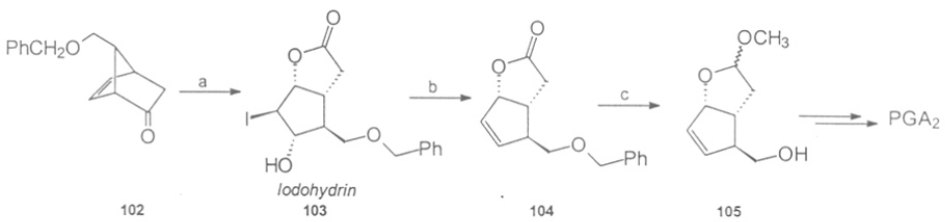
More recently Arai *et al.*[31] in 1991 reported the synthesis of Corey lactone *via* a highly stereoselective asymmetric Diels-Alder reaction. They had effectively modified the original Corey lactone synthesis by using a readily accessible recyclable and efficient chiral controlling group. They had overcome the two drawbacks reported in the earlier Corey's synthesis[32] wherein S-(-)pulegone was used which was not commercial available in high optical purity. Also the intermediate containing the chiral source was prepared rather tediously. Arai *et al.* replaced S-(-)pulegone with D-pantolactone and successfully synthesized the Corey's lactone in high optical purity (see **Scheme 12**).

Scheme 12: *Tet. Lett.*, **1991**, *32*, 4557.



Another approach of Corey,[33] which was of interest for the synthesis of PGA_2 is depicted in the **Scheme 13** given below wherein the introduction of C_{10}-C_{11} double bond was postponed to a later stage of the synthetic sequence.

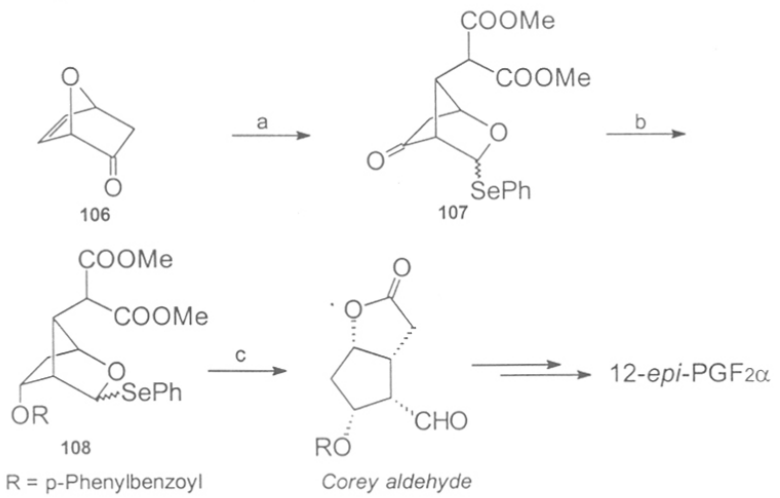
Scheme 13: *Tet. Lett.*, **1972**, 107.



a. Ref 34; **b**. MsCl, Pyr (99%); **c**. **i**). BF_3-Et_2O, Ac_2O (95%), **ii**). DIBAL-H, **iii**). BF_3-MeOH, -20°C, 1.5 hrs.

In the year 1993 Renaud *et al.*[35] reported a regioselective addition of a malonyl radical to 7-oxabicyclo[2,2,1]-hept-5-en-2-one **106** followed by rearrangement of the radical adduct which was used as a key step for the synthesis of all-*cis* Corey lactone, a potent intermediate for the preparation of prostaglandins and 12-*epi*-prostaglandins (**Scheme 14**).

Scheme 14: *J. Org. Chem.*, **1993**, *58*, 5895.



a. $PhSeCH(COOMe)_2$, Sunlamp (300 W) (73%); **b. i**). $NaBH_4$ (92%), **ii**). NaOH/MeOH, DMSO, 140°C (85%), **iii**). LiHMDS, p-PBzCl (85%); **c.** H_2O_2, acetone-water, PPTS (90%).

The literature survey revealed that the Corey lactone has been extensively used as an intermediate in various approaches. However in the later years the synthesis of all *cis* Corey lactone seems to have gained more attention due to its potential to prepare isoprostanes like 8-*epi*-$PGF_{2\alpha}$ and 12-*epi*-$PGF_{2\alpha}$ which are found to be extremely useful as vasoconstrictors.

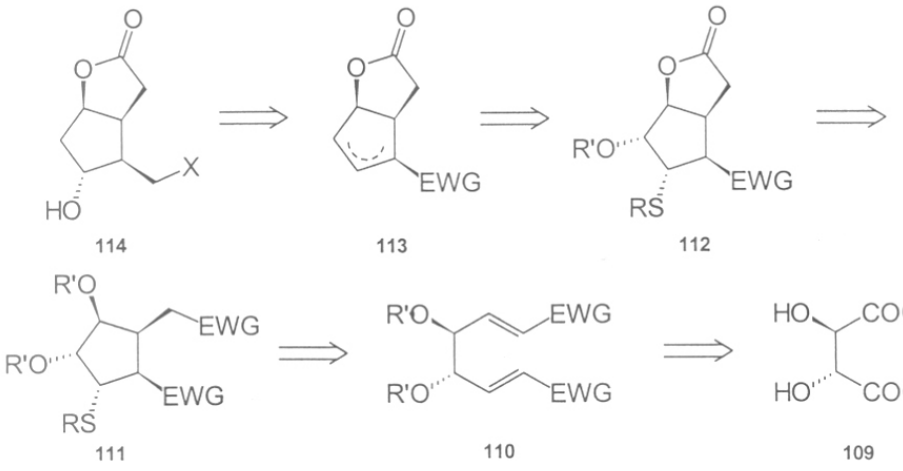
1.2.2 Present Work:

Corey's lactone **1** is one of the key intermediate in prostaglandin synthesis because of its wide applicability and availability. Its popularity stems from the fact that it possesses suitable functionality in correct stereochemical configuration for facile elaboration into prostaglandins $F_{2\alpha}$, E_2 and D_2.

Several reports about the chiral synthesis of Corey's lactone have been known and almost all are *via* optical resolution. However syntheses which circumvent resolution and start with chiral precursors are very few of which Johnson[29] was the first to report one such synthesis starting from optically active malic acid.

In this present scheme the synthesis of Corey's lactone or similar intermediates was attempted starting from a optically active acyclic precursor. L-Tartaric acid was chosen as a model molecule to form an intermediate which had the correct stereocentres to form an all *cis* Corey's lactone. The retrosynthetic analysis is given in the **Scheme 15**.

Scheme 15:

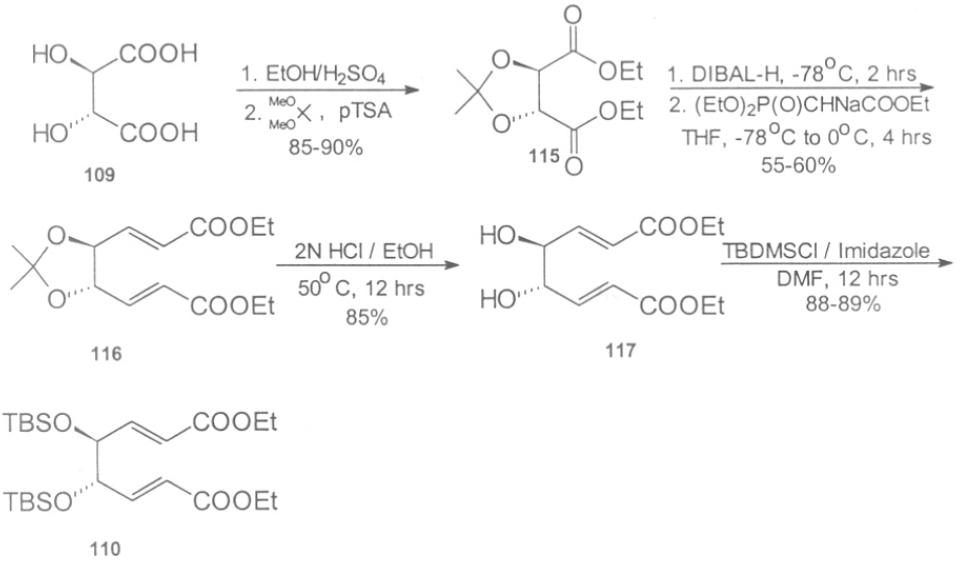


The amazing high diastereomeric excess exhibited in the tandem double Michael reaction of lithium benzenethiolate on the octadienediate (**110**) constituted the key step to form the intermediate **111** with the cyclopentane framework. This intermediate could then be converted to the bicyclo lactone **112** which can be carried forward to the Corey's lactone.

1.2.3 Results and Discussion:

As depicted in the **Scheme 15** above, the key intermediate **110** used for the double Michael addition reaction was prepared according to reported procedures[36] (see **Scheme 16**). Accordingly L-tartaric acid (**109**) was first esterified followed by an acetonide protection. Then the diethyl L-2,3-O-isopropylidene tartarate (**115**) was reduced with DIBAL-H in dry toluene at –78°C and at the same temperature, a solution of ethyl sodiodiethyl- phosphonoacetate in THF was introduced into the cold reaction. The condensation reaction finally yielded the diethyl (4S,5S)-4,5-O-isopropylidene-2(E), 6(E)-octadiendiate(Z,Z diester) (**116**) in 60% yield. The acetonide group was then removed by treating the compound with 2N HCl for 12 hrs to yield the dihydroxy compound **117** in 85% yield. This compound **117** was further converted to the silyloxy intermediate **110** by treating with t-Butyldimethyl silyl chloride(TBDMSCl) in imidazole.[37]

Scheme 16:



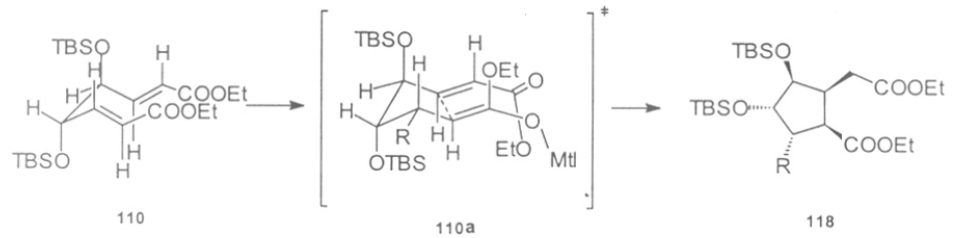
The diethyl (4S,5S)-4,5-bis(*tert* butyldimethyl silyloxy)-2E,6E-octadiendiate (**110**) was further subjected to a cyclopentane annulation reaction by the reported procedure of Moriwake *et.al.*[38]

Generally Michael addition of organocopper reagents to the α,β-unsaturated esters and subsequent intramolecular trapping of the intermediary ester enolate with an

appropriately located electrophillic center constitutes the efficient and reliable route to substituted cyclopentane framework.[39]

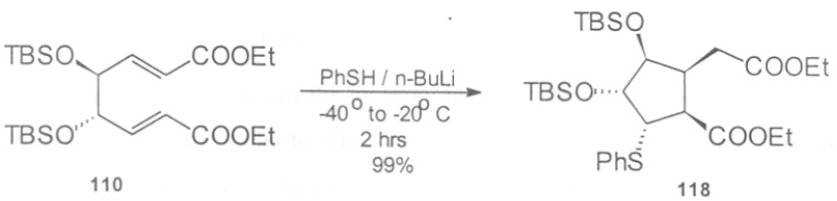
However an extremely efficient synthesis of cyclopentane derivative from the axially dissymmetric acyclic precursor **110** *via* a tandem double Michael addition reaction with superb selectivity (>>99% de) was first reported by Moriwake *et al.*[38] They had suggested a transition state wherein the diastereo-π-faces of the carbon carbon double bond of the enoate 110 can be differentiated. This enoate can exist as the conformer **110a** even at room temperature in which the α,β-unsaturated ester moieties try to arrange themselves in space to minimize nonbonded steric interactions. Hence the nucleophilic attack at the β carbon of the enoate moiety of **110a** could occur only from the two π-faces which are exposed to the outside of the molecule as depicted in the **Scheme 17** below.

Scheme 17:



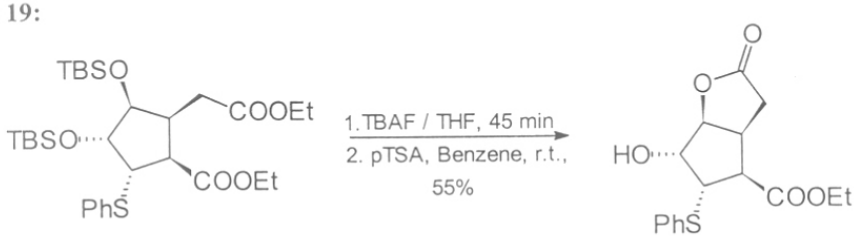
Following the same procedure lithium benzenethiolate[40] was found to react with **110** to give exclusively the corresponding adduct **118** in 99% yield (Scheme **18**). The structure of **118** was confirmed by ^{1}H NMR, IR, Mass spectroscopy and analysis. The optical rotation matched with that of the reported. ^{1}H NMR showed the presence of TBDMS group at δ0.0, 0.05, 0.1, 0.15, 0.9 and 0.95. The presence of two triplets at δ1.14 and 1.26 confirmed the two methyl groups of the ester linkage. The incorporation of thiophenyl group was indicated at the aromatic region with a multiplet at δ7.23 to 7.44. Mass confirmed the M^+ at 596. The optical rotation was $[\alpha]_D^{25}$ = - 35.15° (c=1.09, $CHCl_3$) [Reported $[\alpha]_D^{25}$ = - 38.8° (c=0.99, $CHCl_3$)].[38]

Scheme 18:



The compound **118** was then converted to the hydroxy lactone **119** by first treating it with 4 eq of TBAF in THF for 45 min. which effectively deproteced the TBDMS group[37](**Scheme 19**). Without isolation of the dihydroxy compound it was directly subjected to cyclization by treating with pTSA in benzene at room temperature.

Scheme 19:



118 119

The ^{1}H NMR of the hydroxy lactone **119** showed the absence of TBDMS group and the presence of one ethyl group with the methyl at δ1.27 as a clean triplet and the $-CH_2$ of the ester at δ4.24 as a quartet. The most deshielded proton was the ring junction hydrogen adjacent to the oxygen of the lactone which appeared as a doublet at δ4.91 with a J value of 6.7Hz. The proton adjacent to the hydroxy group appeared as doublet at δ4.13 with a coupling constant of 3.6Hz followed by the proton next to the thiophenol group which appeared as a doublet of doublet (dd) at δ3.87 with coupling constants of 3.6 and 12.2Hz. The other ring junction proton appeared at δ3.42 as a dddd with coupling constants of 3.5, 6.7, 9.6, and 10 Hz. The hydrogen adjacent to the ester group appeared at δ3.21 as dd with coupling constants of 9.6 and 12.3Hz. The two geminal protons adjacent to the lactone group appeared in a typical pattern with one of the proton at δ2.66 as a dd with coupling constant of 10 and 18.8Hz and the other proton at δ2.43 as a dd with coupling constants of 3.5 and 18.9Hz. The thiophenyl group remained intact at δ7.3 as a multiplet.

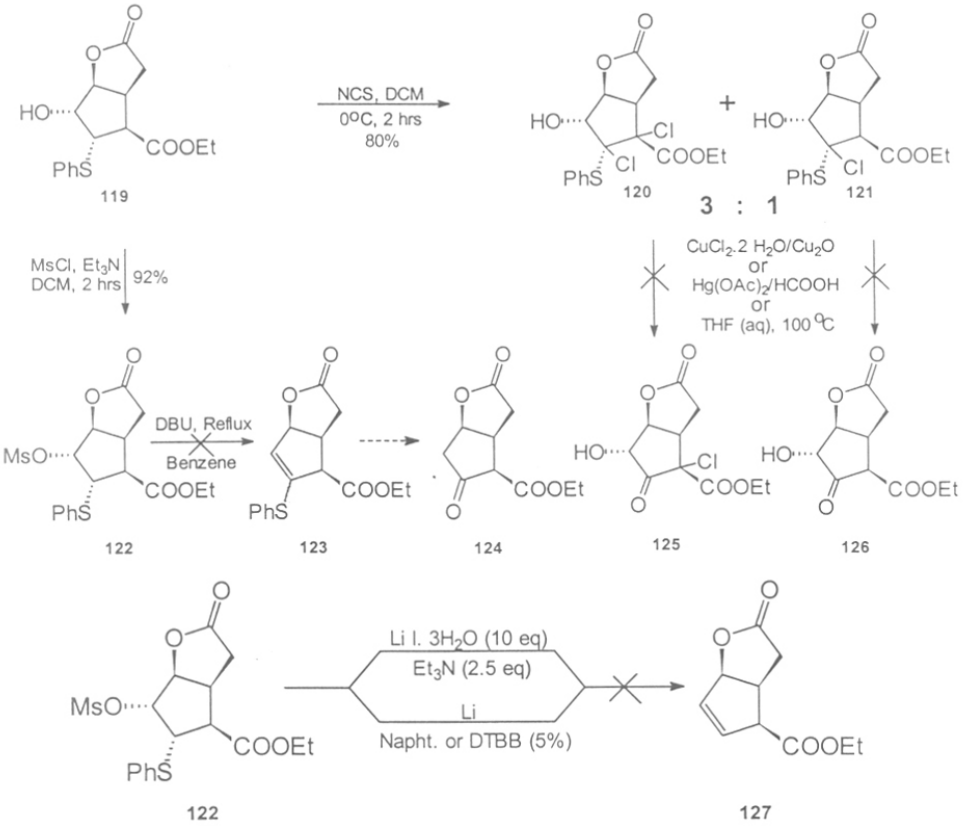
IR spectrum confirms the presence of hydroxyl group at 3400 cm^{-1} and the lactone ester at 1780 cm^{-1} along with the normal ester at 1750 cm^{-1}. Mass spectrum also confirmed the M^+ peak at 322. ^{13}C NMR indicated the methyl group at 13.9 and the two methylene groups at 30.5 and 60.4. Aromatic carbons appeared at 127.7, 129 and 132. The only quartenary carbon was at 133.1 of the carbon attached to the thiophenyl group. The carbonyls (of the ester and lactone) appeared at 170.9 and 175.7.

Having confirmed structure of the hydroxy lactone **119,** a variety of reactions were attempted on the compound in order to effect a hydrolysis to convert the carbon attached to the thiophenyl group to the ketone. As a first step the lactone **119** was treated with NCS (N-

Chloro succinimide) with a catalytic amount of benzoyl peroxide added to it in order to effect a chlorination α to the sulfide group. However the reaction failed to give the desired product with the lactone being recovered. When the reaction was carried out without benzoyl peroxide in dichloromethane, two compounds were isolated, with a major compound found to be a dichloro compound as confirmed by Mass spectroscopy with a peak appearing at 392. The ^{1}H NMR of major compound showed the presence of only five protons apart from those of the ester and aromatic regions, indicating that the chlorination has taken place at two sites. IR however showed the presence of a hydroxy group apart from the lactone and ester peaks. Hence the structure was assigned to be **120**. The other minor compound **121** also showed the presence of hydroxy group in IR spectrum and the presence of six protons in ^{1}H NMR apart from those of ester and aromatic region. It was assumed to be a mono chloro compound and both the compounds were subjected to hydrolysis which however failed to proceed with either the recovery or decomposition of the starting material during the course of the reaction. The hydrolysis was attempted using the known procedures which included aq THF[41] $Hg(OAc)_2$[42] and copper salts.[43]

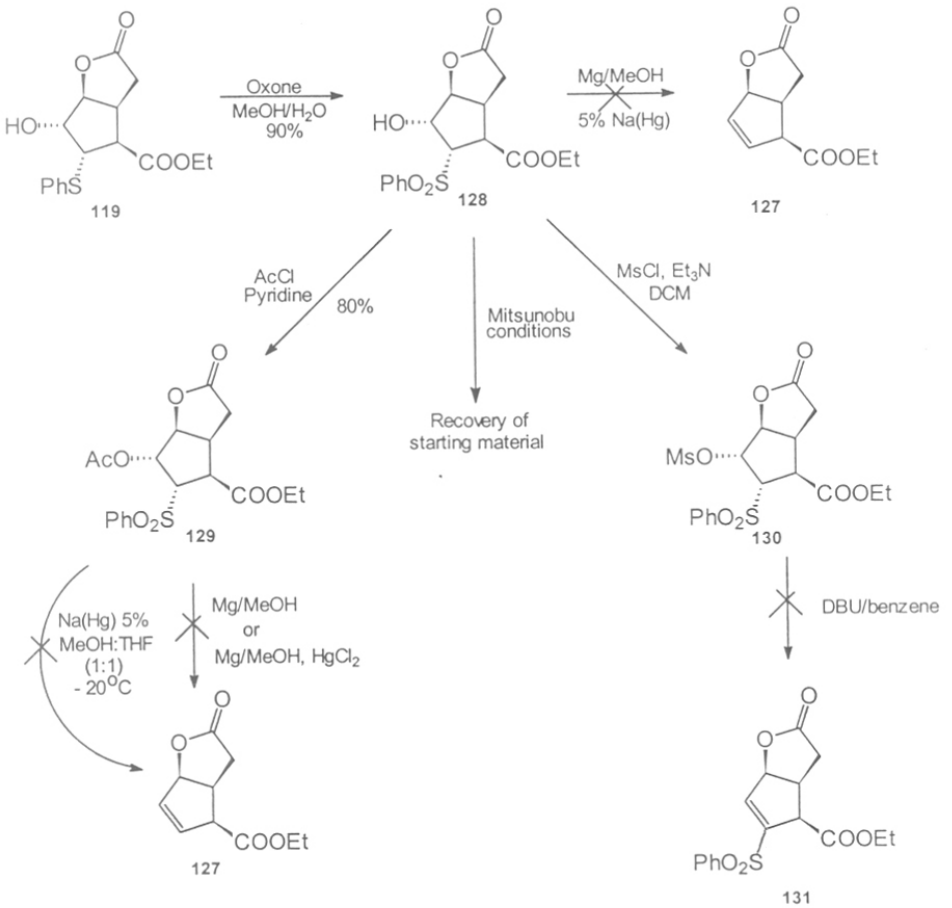
The hydroxy lactone **119** was further converted to the mesylate **122** in order to eliminate it with DBU to give a thioenol ether **123** which could be converted to the keto intermediate **124**. Mesylation proceeded smoothly to give the corresponding mesylate **122** in 92% yield. IR spectrum indicated the absence of hydroxyl group and ^{1}H NMR confirmed the mesyl group incorporation with a peak at δ3.2. However refluxing the mesylate **122** in DBU/benzene failed to furnish the required product **123**. Also the mesylate was then subjected to a LiI promoted elimination in order to obtained the olefin **127**. Reported procedures[44] for this salt mediated β-phenylthioalcohol elimination failed to furnish the product with recovery of the starting material. Li/Naphthalene mediated elimination[45] on the lactone **119** as well as the mesylate **122** also did not give the desired product (**Scheme 20**).

Scheme 20:



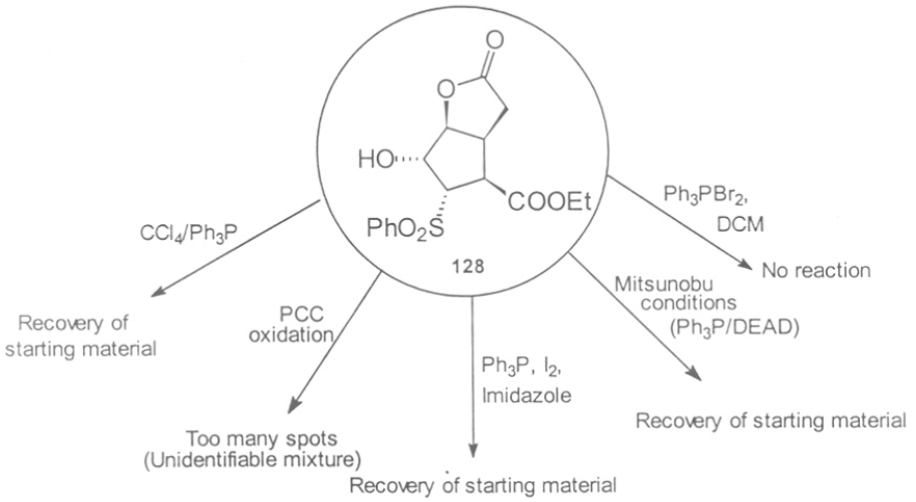
Since the hydrolysis was proving to be difficult, a Julia[46] elimination for the removal of thiophenol and hydroxy group simultaneously was pursued. Hence the hydroxy lactone 119 was converted to its corresponding sulphone **128** using oxone[47] in 95% yield. The IR spectrum confirmed the presence of sulphone group with peaks at 1315, 1220, 1150 apart from the hydroxy at 3500 and the lactone carbonyl and ester carbonyl at 1780, 1730 cm^{-1} respectively. ^1H NMR indicated a shift in the aromatic region of sulphide from δ7.32-7.46 to the sulphone at δ7.5-8.0. Mass spectrum confirmed the structure with the M^+ ion peak appearing at 354. This sulphone was then converted to the acetate **129** on which reported procedures of elimination were tried out which included the Julia elimination (see **Scheme 21**).

Scheme 21:



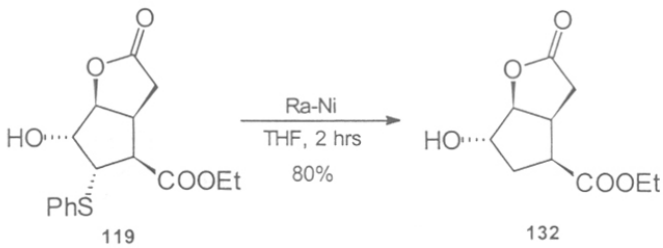
A series of attempted reactions on the sulphone **128** to convert the hydroxy to the halide in order to introduce the double bond also failed to proceed. Bromination, iodination and chlorination were unsuccessful with either very little conversion or recovery of the starting material. Since the direct conversion of alcohol to halide posed unforeseen problems, it was decided to change the stereochemistry of the alcohol and then attempt the elimination. However Mitsunobu[48] conditions too failed to provide the desired result (see **Scheme 22**).

Scheme 22:



Having had discouraging results in converting the alcohol to halide, it was thought that the sterically hindered alcohol can be converted to halide by removal of the steric bulk of thiophenol group. Hence a Raney Nickel reduction[49] was tried on the hydroxy lactone **119** which proceeded smoothly to furnish the desulphurised product **132** in 80% yield (see **Scheme 23**).

Scheme 23:

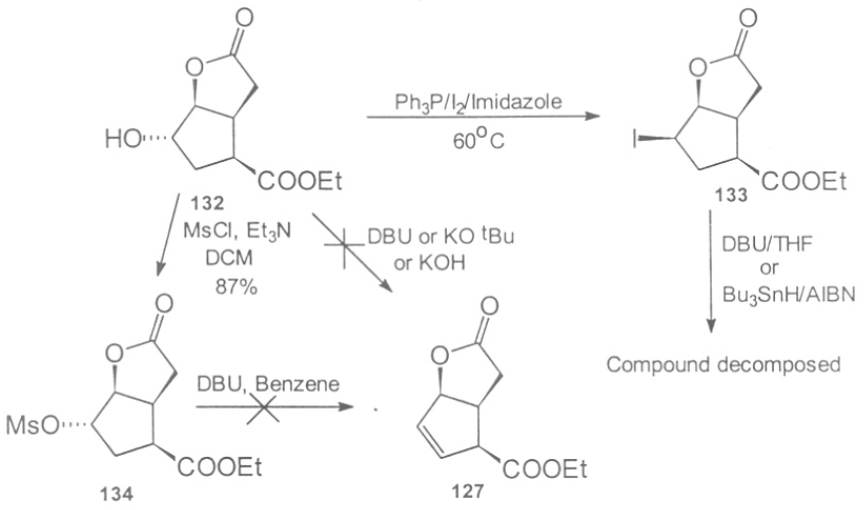


^{1}H NMR showed the absence of aromatic region and the presence of an extra methylene group in ^{13}C NMR that confirmed the success of the reaction. Mass spectrum also indicated M+1 peak at 215.

Having removed the thiophenyl group, the lactone **132** was once again subjected to a series of reactions which were tried earlier on the sulphone **128**. Bromination gave too many spots and iodination proceeded in low yields (30%). The iodinated product without isolation

when subjected to tributyl tin hydride reduction or treatment with DBU failed to furnish the eliminated product decomposing in the process (see **Scheme 24**).

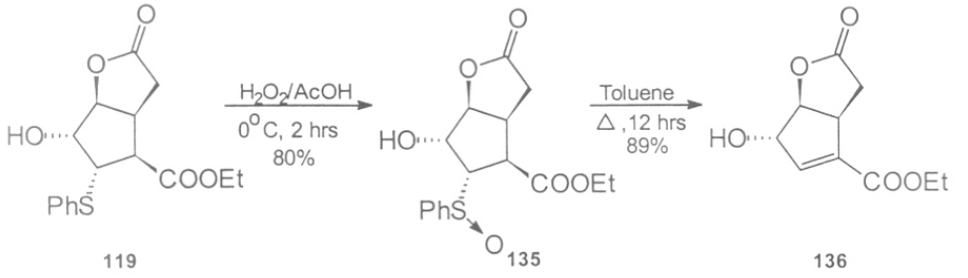
Scheme 24:



Conversion of the alcohol **132** to the mesylate **134** proceeded smoothly but once again failed to eliminate under DBU conditions.

Following a different route, the hydroxy lactone **119** was converted to the sulphoxide[40] **135** with one equivalent of H_2O_2/AcOH and refluxed to effect an elimination (see **Scheme 25**) with the hope of reducing the allylic alcohol to the desired product.

Scheme 25:

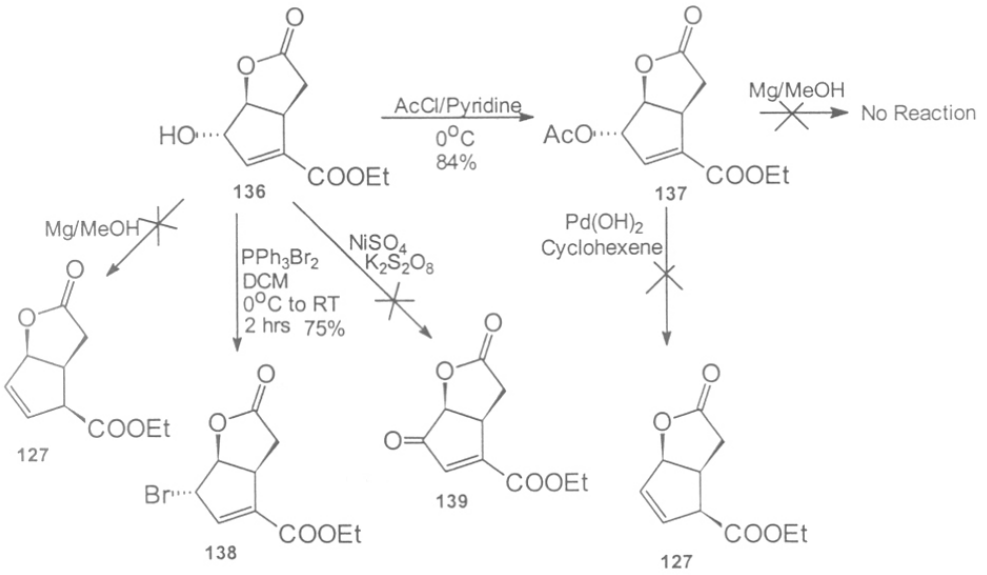


Thus the sulphoxide **135** was obtained in good yields (80%). ^{1}H NMR indicated a shift in the aromatic region from δ7.36-7.46 to δ7.63-7.75. IR spectrum confirmed the presence of S→O group at 1035 and 1430 cm^{-1}. Mass peak at 338 indicated the formation of sulphoxide. The sulphoxide **135** was then refluxed in toluene for 12 hrs to effect an elimination and as foreseen the product **136** was obtained in 89% yield. ^{1}H NMR of the compound confirmed the structure with an absence of aromatic region. The olefinic proton

(CH=CR-COOEt) appeared as a broad singlet as the most deshielded proton at δ6.75. The two protons (one adjacent to –OH group and the other ring junction proton adjacent to the oxygen) appeared almost at the same region *i.e.,* δ4.98 (d, 1H) and 4.92 (d, 1H). The proton adjacent to the ester group disappeared completely. The IR spectrum showed a shift in the ester grouping from 1700 to 1660 cm^{-1}. Mass confirmed the M^+ ion peak at 212. The compound **136** was subsequently subjected once again to a series of elimination reactions with slightly encouraging results.

An elimination as per the reported procedures of Pak, *et al.*[50]., wherein a reductive cleavage of γ-functionalized α,β-unsaturated esters mediated with Mg and MeOH was reported, failed to proceed without recovery of starting material. The hydroxy group was also derivatised to the acetate **137** and subjected to the same reaction which also did not furnish the desired product. Oxidation of the allylic moiety was tried with mild reagents like $NiSO_4$, $K_2S_2O_8$[51] which also failed to proceed (see **Scheme 26**).

Scheme 26:



Palladium catalyzed reduction[52] also failed to furnish the required olefinic compound **127**.

However the bromination proceeded smoothly to furnish the bromo compound **138** in 75% yield. The product was confirmed by IR spectrum which showed the absence of hydroxyl group. And a M^+ ion peak in Mass spectroscopy at 275 confirmed the structure. ^1H NMR indicated that the proton adjacent to the bromide had shifted downfield as compared

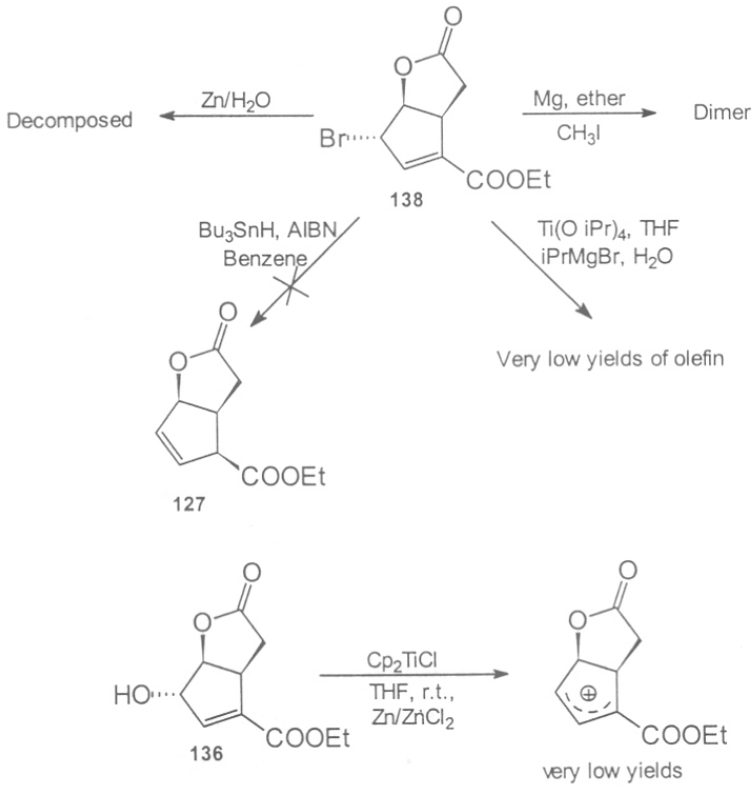
to that in **136** and appeared at δ5.14 along with the junction proton adjacent to the lactone oxygen.

The bromo compound was then subjected a tri n-butyltin hydride reduction which did not give the desired olefinic product but some other product which could not be characterized.

A Grignard reaction furnished a dimer of the product. Reformatsky conditions with Zn were also tried wherein the compound decomposed. Also an elimination with Titanium isopropoxide/isopropyl magnesium bromide[53] was tried on the compound which too failed to furnish the product.

A Titanocene dichloride reaction[54] on the alcohol **136** was tried wherein it was prepared *in situ* along with Zn and $ZnCl_2$. A product was isolated in low yields which seemed to have been the eliminated product but the yields were extremely low (10-15%) (see **Scheme 27**).

Scheme 27:

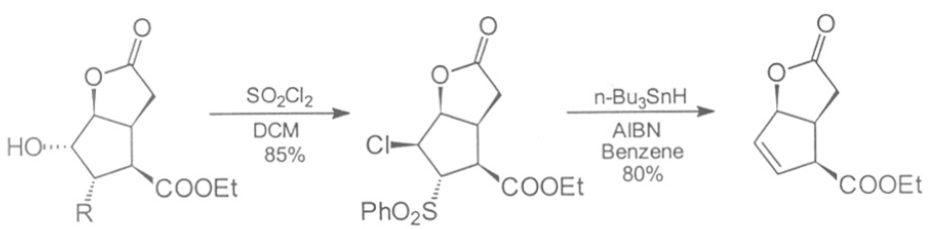


Despite trying all the reactions on various substrates the simple elimination proved to be a daunting task.

An elimination of the β-hydroxy sulphoxides to β-sultines was reported[55] with NCS/NBS/SO_2Cl_2. Since these β-sultines were generally found to have limited thermal stability, they readily lose SO_2 at room temperature to give olefins.

Applying the same to affect an elimination to the β-hydroxy sulphoxide (**135**), the compound was treated with SO_2Cl_2 in dichloromethane at room temperature. Surprisingly the reaction proceeded rather smoothly in half an hour to furnish an intermediate which was found to be the chlorosulphone **140**. The ^{1}H NMR of the compound indicated the presence of seven protons apart from the aromatic and ester protons indicating that one of the groups had been displaced by chlorine. Microanalysis confirmed the presence of chlorine however Mass spectrum failed to show a M^+ ion peak. The configuration of the chloro and sulphone group was found to be trans as per the X-ray crystallographic picture indicating the possibility of formation of a cyclic intermediate as reported by Durst *et al.*[55] The structure of the compound **140** was as confirmed by X-ray Crystallography is included. The X-ray data indicated that there were two different conformational isomers for the molecule **140** in a unit cell of the crystal. (see **Scheme 28**).

Scheme 28:



R = SOPh **135**
R = SPh **119**

140

127

The chlorosulphone **140** was then subjected a n-tributyltin hydride reduction to furnish the desired olefin **127** in 80% yield. The ^{1}H NMR of the olefin indicated the presence of two olefinic protons at δ6.16 and 6.02. Absence of aromatic protons indicated the reduction of thio group. The ring junction proton appeared as usual as a doublet at δ5.53 with a coupling constant of 6.6 Hz. In the Mass spectrum a peak at 197(M+1) confirmed the elimination.

Thus the elimination had been achieved in good yields. This olefin can serve as a important intermediate towards the synthesis of prostaglandins and isoprostanes starting from a simple and cheaply available L-tartaric acid.

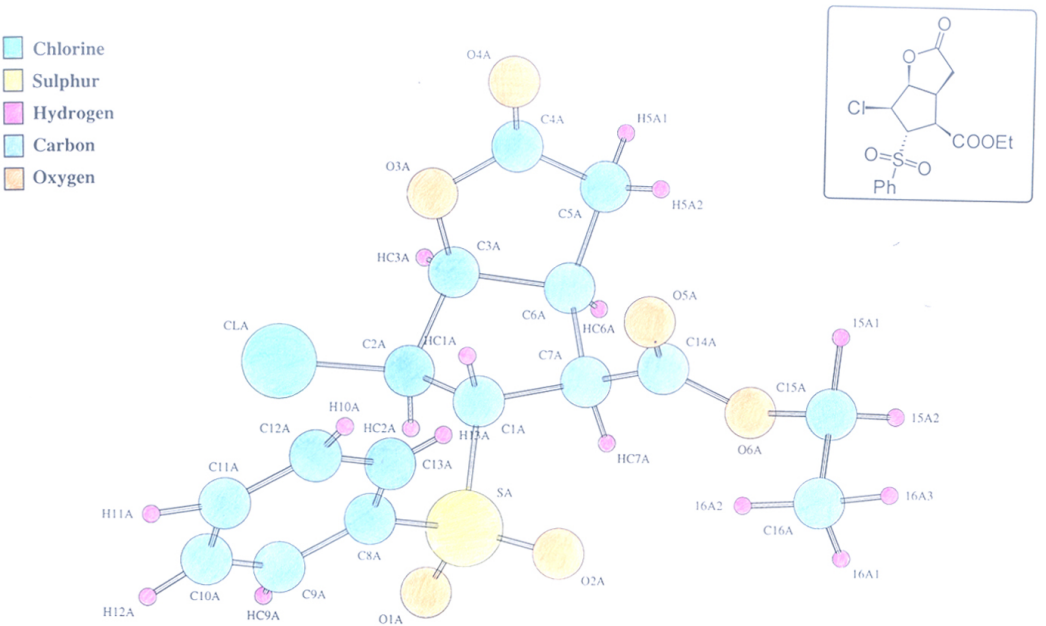
1.2.4 Conclusions:

Although the initial attempt was to obtain the Corey lactone by hydrolysis of the thio group and reduction of the adjacent alcohol, having been unsuccessful to do so, an elimination was tried out with various intermediates derived from the hydroxy lactone **119**.

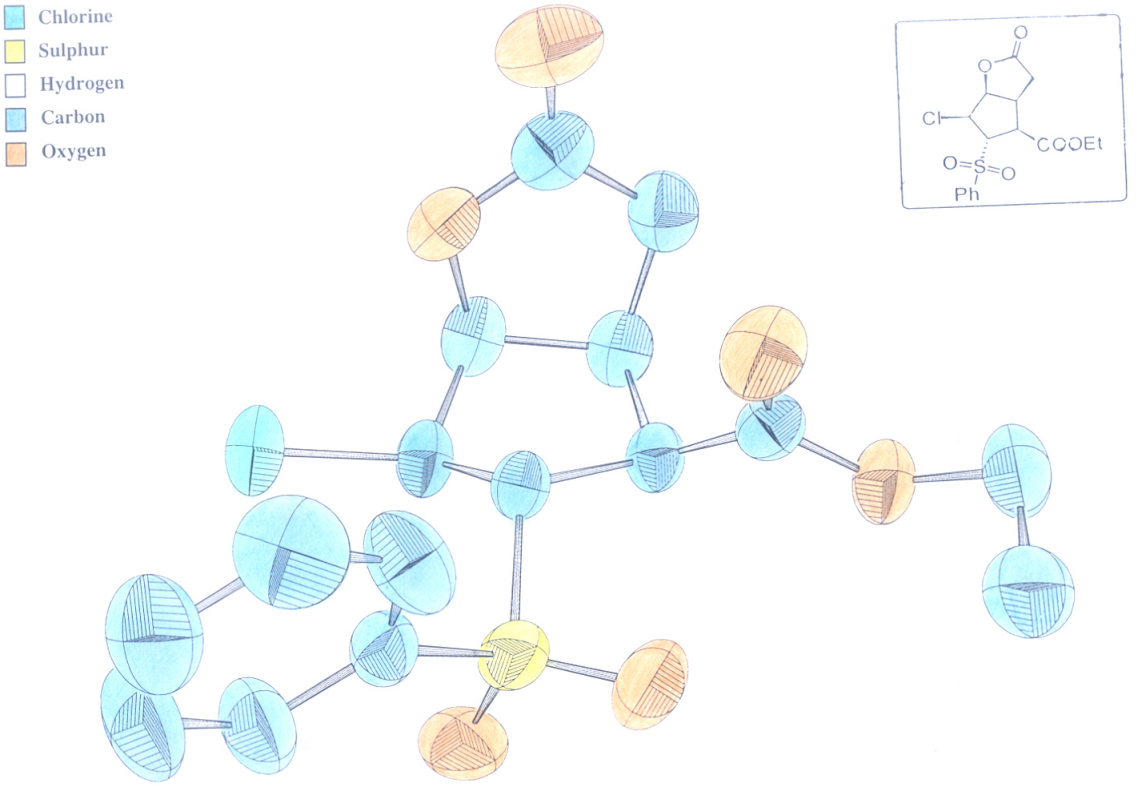
- A facile synthesis of the bicyclo lactone **127** has been achieved starting from chiral acyclic tartaric acid involving a thiol mediated highly efficient diastereo selective cyclopentane formation.

- One of the key features is that the α and ω-side chains can either be in *cis* stereochemical disposition or the *trans* as the need be. This intermediate **127** is a potential synthon for the synthesis of 8-*epi*-$PGF_{2\alpha}$ which has been shown to be a biotransformed product and known to be the most potent renal vasoconstrictor known and 10 times more potent than LTC_4. In order to study its biological activity profile, the synthesis of its enantiomer is also of utmost importance. Since tartaric acid is readily available in both forms commercially, by changing the tartaric acid one can easily access the desired enantiomers.

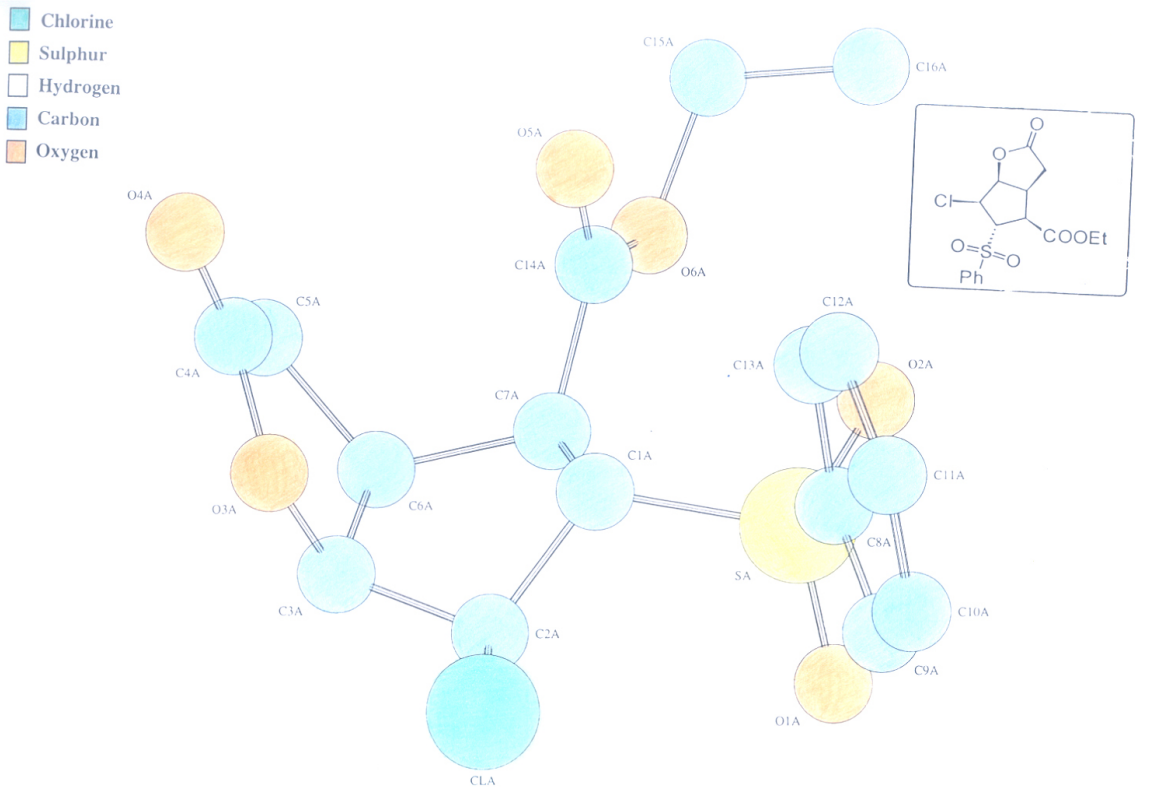
- By proper chemical manipulation, **127** can be converted to Corey's lactone and also it can serve as an important synthon for a variety of prostaglandins and isoprostanes.



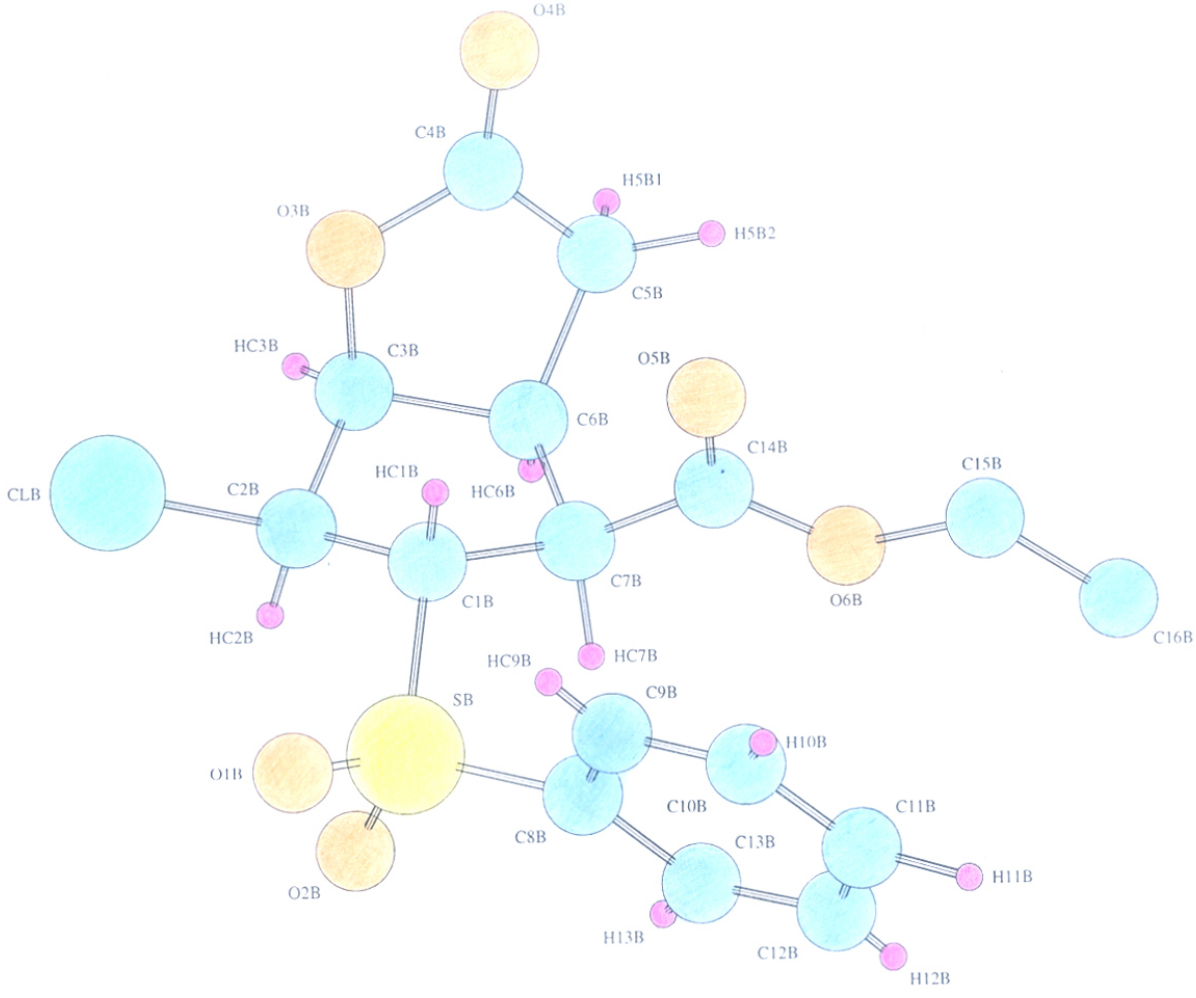
PLUTO View of Molecular Structure Of Compound **140**

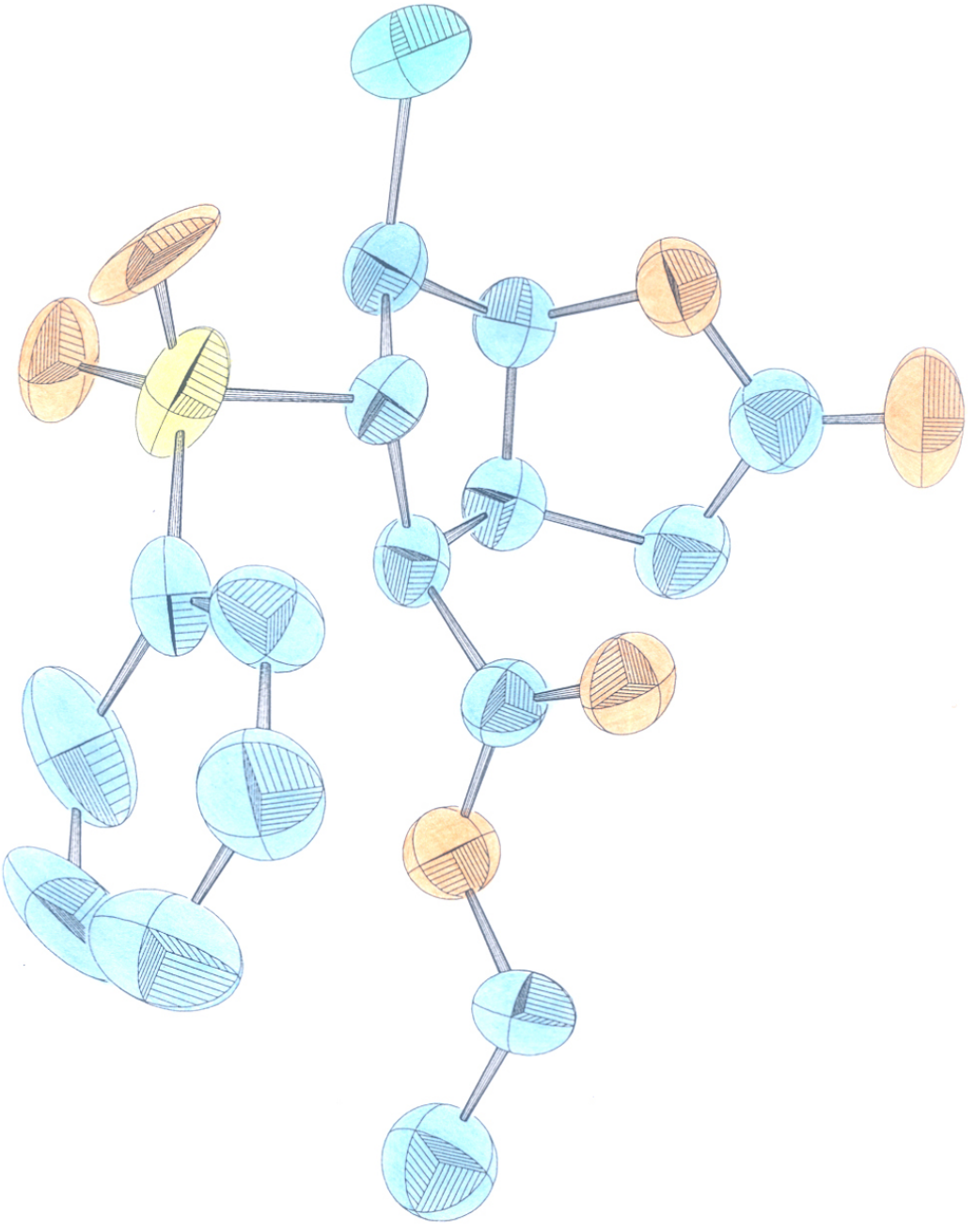


ORTEP View Of Molecular Structure Of Compound **140**



PLUTO View of Molecular Structure Of Compound **140**


O4B
C4B
H5B1
O3B
H5B2
C5B
HC3B
C3B
O5B
C6B
C14B
C15B
CLB
C2B
HC1B
HC6B
C7B
O6B
C16B
C1B
HC2B
HC9B
HC7B
C9B
SB
H10B
O1B
C10B
C11B
C8B
C13B
H11B
O2B
H13B
C12B
H12B



TABLE

Crystallographic and structure refinement parameters of chlorosulphone (140) compound

Formula		: $C_{16}\ H_{17}\ Cl_1\ O_6\ S_1$
Formula weight		: 372.82
Crystal system		: Monoclinic
Space group		: $P2_1$
Unit cell	a	: 10.943(4) Å
	b	: 15.335(7) Å
	c	: 11.445(4) Å
	α = ~~γ~~	: 90.0 °
	β	: 115.37(3) °
Unit cell volume		: 1735(1) $Å^3$
	Z	: 4
Density(cal.)		: 1.427 $Mg\ m^{-3}$
	μ	: 0.369 mm^{-1}
	F(000)	: 776
Crystal size		: 0.4 X 0.5 X 0.8 mm
Radiation		: Mo K_α (0.71069 Å)
Temperature		: 295(2) K
Scan type		: $\omega/2\theta$
Scan width		: (0.90 + 35tanθ) °
Theta range		: $0 \leq \theta \leq 25$ °
Unique reflections		: 3174
Observed reflections ($I > 2\sigma(I)$)		: 2719
No. Parameters refined		: 581
Goodness of fit S		: 0.385
Weighted R (wR)		: 0.1408
R (all reflections)		: 0.0599
R ($I > 2\sigma(I)$)		: 0.0524

TABLE

Coordinates of chlorosulphone compound (140)
Molecule A, The coordinates and temperature parameters were multiplied by 10000.

ATOM	X	Y	Z	Ueq
SA	7218(2)	5068(1)	8064(2)	559(3)
ClA	5092(2)	6297(1)	9032(2)	663(4)
O1A	5993(6)	5002(4)	6887(4)	784(14)
O2A	8475(6)	4831(3)	8058(6)	793(15)
O3A	7221(5)	7682(3)	10039(4)	578(10)
O4A	9167(7)	8055(4)	11637(5)	835(16)
O5A	10289(4)	6424(4)	9886(4)	693(13)
O6A	10224(4)	6569(3)	7915(4)	592(11)
C1A	7413(5)	6161(4)	8652(5)	417(11)
C2A	6112(6)	6681(4)	8274(6)	501(13)
C3A	6614(6)	7592(4)	8650(6)	537(14)
C4A	8472(8)	7992(4)	10482(7)	594(15)
C5A	8798(8)	8205(5)	9380(7)	606(15)
C6A	7793(6)	7682(4)	8268(6)	520(14)
C7A	8207(5)	6737(4)	8098(5)	435(11)
C8A	7033(6)	4446(4)	9286(6)	509(13)
C9A	5836(9)	4033(6)	8988(8)	747(21)
C10A	7922(11)	3914(6)	11431(9)	846(24)
C11A	6749(10)	3495(6)	11162(10)	859(25)
C12A	5733(11)	3531(7)	9967(11)	933(28)
C13A	8088(8)	4391(5)	10488(8)	690(19)
C14A	9678(6)	6548(4)	8751(5)	458(12)
C15A	11651(7)	6318(7)	8393(8)	720(19)
C16A	11762(9)	5370(7)	8314(12)	893(27)

TABLE

Bond lengths in Angstroms corresponding to Molecule A for chlorosulphone (140) compound from X-ray crystal structure analysis. Standard deviations are in brackets.

SA	-	O1A	1.441(5)
SA	-	O2A	1.425(5)
SA	-	C1A	1.785(6)
SA	-	C8A	1.774(6)
C1A	-	C2A	1.524(8)
C1A	-	C7A	1.551(7)
C2A	-	CLA	1.782(6)
C2A	-	C3A	1.496(10)
C3A	-	O3A	1.443(8)
C3A	-	C6A	1.536(8)
O3A	-	C4A	1.329(9)
C4A	-	O4A	1.215(9)
C4A	-	C5A	1.485(10)
C5A	-	C6A	1.507(10)
C6A	-	C7A	1.556(9)
C7A	-	C14A	1.483(8)
C8A	-	C9A	1.359(10)
C8A	-	C13A	1.370(10)
C9A	-	C10A	1.404(12)
C10A	-	C11A	1.343(14)
C11A	-	C12A	1.343(14)
C12A	-	C13A	1.379(12)
C14A	-	O5A	1.194(7)
C14A	-	O6A	1.329(7)
O6A	-	C15A	1.468(8)
C15A	-	C16A	1.463(14)

Bond angles in degrees for molecule A of chlorosulphone (140) compound.

O1A	-	SA	-	O2A	119.4(4)
O1A	-	SA	-	C1A	109.3(3)
O1A	-	SA	-	C8A	109.0(3)
O2A	-	SA	-	C1A	106.3(3)
O2A	-	SA	-	C8A	107.7(3)
SA	-	C1A	-	C2A	116.0(4)
SA	-	C1A	-	C7A	112.2(4)
C2A	-	C1A	-	C7A	101.8(4)
C1A	-	C2A	-	CLA	113.2(4)
C1A	-	C2A	-	C3A	102.9(5)
CLA	-	C2A	-	C3A	113.5(5)
C2A	-	C3A	-	O3A	110.1(5)
C2A	-	C3A	-	C6A	104.6(5)
O3A	-	C3A	-	C6A	105.0(5)
C3A	-	O3A	-	C4A	111.5(5)
O3A	-	C4A	-	O4A	120.4(7)
O3A	-	C4A	-	C5A	109.8(6)
O4A	-	C4A	-	C5A	129.9(8)
C4A	-	C5A	-	C6A	104.3(6)
C3A	-	C6A	-	C5A	101.8(6)
C3A	-	C6A	-	C7A	106.0(5)
C5A	-	C6A	-	C7A	117.1(5)
C1A	-	C7A	-	C6A	103.6(4)
C1A	-	C7A	-	C14A	111.1(4)
C6A	-	C7A	-	C14A	115.4(5)
SA	-	C8A	-	C9A	118.4(6)
SA	-	C8A	-	C13A	119.5(5)
C9A	-	C8A	-	C13A	122.1(7)
C8A	-	C9A	-	C10A	117.0(8)
C9A	-	C10A	-	C11A	121.4(8)
C10A	-	C11A	-	C12A	120.4(8)
C11A	-	C12A	-	C13A	120.5(9)
C8A	-	C13A	-	C12A	118.7(8)
C7A	-	C14A	-	O5A	124.1(5)
C7A	-	C14A	-	O6A	111.0(5)
O5A	-	C14A	-	O6A	124.9(5)
C14A	-	O6A	-	C15A	117.1(5)
O6A	-	C15A	-	C16A	110.0(7)

Molecule B
All coordinates and Ueq except last three were multiplied by 10000. For last three atoms X1000

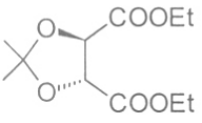
SB	4527(2)	5103(1)	2739(2)	740(6)
ClB	1540(2)	4927(1)	3143(2)	761(5)
O1B	4409(26)	4337(11)	3016(25)	901(80)
O1B'	4500(26)	4258(15)	3539(21)	709(58)
O2B	3764(18)	5045(12)	1461(15)	701(39)
O2B'	4047(20)	5417(15)	1226(17)	861(56)
O3B	1955(5)	6700(3)	4325(4)	654(12)
O4B	2846(9)	7568(6)	6050(6)	1195(26)
O5B	5703(5)	7061(3)	5251(4)	600(11)
O6B	5904(5)	7776(4)	3650(4)	733(14)
C1B	3771(6)	5912(4)	3358(5)	462(12)
C2B	2251(6)	5843(4)	2699(6)	518(13)
C3B	1755(6)	6696(4)	2983(5)	502(13)
C4B	2584(9)	7445(5)	4917(8)	713(19)
C5B	2871(8)	8001(4)	4020(8)	648(17)
C6B	2737(7)	7379(4)	2921(6)	523(14)
C7B	4025(6)	6859(4)	3075(5)	475(12)
C8B	6209(7)	5405(4)	3292(6)	555(14)
C9B	7107(7)	5196(5)	4533(6)	586(16)
C10B	8417(8)	5408(7)	4984(9)	822(25)
C11B	8913(10)	5868(9)	4295(12)	1066(34)
C12B	8047(13)	6089(9)	3059(14)	1163(46)
C13B	6690(12)	5890(9)	2538(9)	997(35)
C14B	5301(6)	7224(4)	4112(5)	496(13)
C15B	7323(37)	8039(24)	4632(42)	675(77)
C15D	6937(36)	8337(27)	4538(43)	804(98)
C16B	782(3)	863(2)	388(2)	84(6)
C16D	819(6)	833(5)	406(7)	113(19)
C16E	744(4)	895(3)	382(3)	72(9)

Coordinates and temperature parameters for Hydrogen atoms
X,Y,Z, Ueq X1000. No esd.s are shown for parameters held
during refinement.

Molecule A				
HC1A	786(5)	615(4)	956(5)	34(13)
HC2A	551(6)	660(4)	728(6)	45(15)
HC3A	583(6)	800(4)	821(6)	39(14)
H5A1	872(9)	890(7)	922(9)	99(29)
H5A2	965(5)	811(3)	955(4)	20(11)
HC6A	756(6)	791(4)	747(6)	45(16)
HC7A	791(5)	660(4)	715(5)	34(13)
HC9A	503(9)	419(6)	813(8)	83(25)
H10A	874(10)	387(7)	1212(10)	94(30)
H11A	618(10)	312(7)	1155(10)	115(34)
H12A	489(9)	325(6)	968(7)	73(22)
H13A	879(8)	463(5)	1067(7)	64(22)
15A1	1216(12)	673(9)	919(11)	135
15A2	1194	683	756	134
16A1	1146(7)	528(5)	740(7)	53(18)
16A2	1105(13)	515(9)	860(11)	135
16A3	1283(11)	534(7)	856(9)	113(34)
Molecule B				
HC1B	420(5)	582(4)	429(5)	30(12)
HC2B	189(7)	576(5)	179(7)	58(19)
HC3B	80(5)	683(4)	248(5)	31(12)
H5B1	223(8)	849(6)	372(7)	73(22)
H5B2	377(7)	836(5)	454(6)	54(17)
HC6B	223(7)	762(5)	203(7)	56(18)
HC7B	410(6)	679(5)	219(6)	53(17)
HC9B	684(8)	495(6)	495(8)	74(25)
H10B	902(10)	523(7)	567(10)	101(33)
H11B	990(9)	606(6)	456(7)	78(23)
H12B	833(12)	632(9)	266(11)	122(41)
H13B	605(10)	594(8)	183(10)	100(34)
15B1	807(14)	746(10)	512(13)	53(35)
15B2	815(13)	812(8)	469(11)	28(26)

1.2.5 Experimental:

1. **2,2-dimethyl-[1,3]-dioxolane-4,5-dicarboxylic acid diethyl ester (115) :**

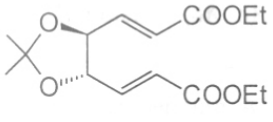


A mixture of L-Tartaric acid (100 g, 0.66mol), ethanol (230 ml), benzene (260 ml) and conc. H_2SO_4 (3ml) was refluxed azeotropically for 20 hrs. The reaction mixture was cooled to room temperature and the pH of the mixture was brought to 7.0 with Na_2CO_3 and potassium dihydrogen orthophosphate buffer. The solid was then filtered and washed with dry benzene. The filtrate was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure and the crude distilled to yield diethyl tartarate (117g) in 85% yield. (B.P. 130°C/3 m.m.)

Diethyl tartarate (R,R) (164.8 g, 0.8 mol), 2,2-dimethoxy propane (94 g, 0.9 mol), benzene (350 ml) and pTSA (0.3 g) was refluxed azeotropically for 15 hrs. The reaction mixture was cooled to room temperature and K_2CO_3 (0.38 g) was added. The reaction mixture was then filtered and the filtrate was concentrated to remove the benzene and 2,2-dimethoxy propane. Residue was distilled to afford the pure compound (**115**) (177.12 g) in 90% yield. (B.P. 105°C/1m.m.).

Yield	: 85-90 % viscous colorless liquid
Mol. Formula	: $C_{11}H_{18}O_6$
Optical Rotation	: $[\alpha]_D^{25}$=-13.46° (c=1.19, $CHCl_3$).
IR (neat)	: 2850, 1745 cm^{-1}.
^{1}**H NMR** (60 MHz) CCl_4	: δ 1.3 (t, 6H); 1.40 (s, 6H); 4.20 (q, 4H); 4.55 (d, 2H).

2. **Diethyl (4R, 5R)-4,5-O-isopropylidiene-2(E), 6(E)-octadiendiate (116)[36] :**



The diethyl L-2,3-O-isopropylidine tartarate (**115**) (12 g, 48.7 mmol) was taken in a one liter two necked flask along with 200 ml of dry toluene under argon. The flask was

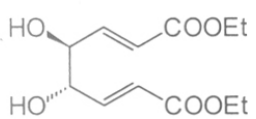
cooled under liquid nitrogen to –78°C and DIBAL-H (13.84 g, 97.4 mmol) was added slowly at –78°C. The solution was stirred for 3 hrs maintaining the same temperature. After completion of 3 hrs a solution of ethyl sodiodiethyl phosphonoacetate (30 g, 0.12 mol) was added at –78°C through a canula. The solution was then slowly brought to room temperature and stirred for 4 hrs at room temperature. After completion of reaction (by TLC) it was quenched with 30 ml of MeOH and 35 ml of H_2O. The solution was then stirred for half an hour and the solid filtered. The filtrate was evaporated under reduced pressure and the residue taken in a organic solvent like ethyl acetate and washed with water. The organic layer was then dried (anhyd. Na_2SO_4) and the product obtained was chromatographed on silica gel with 5% ethyl acetate : pet. ether to yield the product **116** in 65-70% yield.

Preparation of sodiodiethylphosphonoacetate:

NaH (50% suspension in mineral oil) (5.83 g, 0.11 mol) was then taken in 250 ml two necked flask under argon and thoroughly washed with pet. ether 2-3 times to get rid of the mineral oil . Then the NaH was dissolved in 200 ml of dry THF and to it at 0°C was added triethylphosphonoacetate (27.3 g, 0.12 mol) slowly. Liberation of hydrogen gas was observed and the solution was stirred for one hour at room temperature. This solution was then transferred to the DIBAL-H solution at –78°C through a canula.

Yield	: 55-60 % viscous colorless liquid
Mol. Formula	: $C_{15}H_{22}O_6$
IR (neat)	: 2850, 1725, 1610 cm^{-1}.
^{1}**H NMR** (200 MHz) $CDCl_3$	: δ 1.27 (t, 6H); 1.42 (s, 3H); 1.44 (s, 3H), 4.21 (m, 6H); 6.12 (d, 2H), 6.78 (dd, 1H), 6.88 (dd, 1H).

3. **4,5-dihydroxy-octa-2,6-diene dioic acid diethyl ester (117)**[38] :

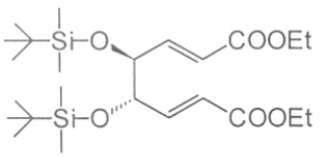


The diethyl (4R, 5R)-4,5-O-isopropylidene-2(E), 6(E)-Octadiendioate (**116**) (6 g, 20 mmol) was taken in ethanol (60 ml) and to it was added 2N HCl at 40°C and stirred for 12 hrs at room temperature. After completion of reaction (as indicated by TLC) the mixture was evaporated (under reduced pressure) to give a residue which was washed once with saturated brine solution. This residue was chromatographed with 50% pet. ether : ethyl acetate as

eluent to furnish alcohol **117** (4.5 g) as a viscous liquid in 85% yield which solidifies on keeping.

Yield	: 85% viscous liquid.
Mol. Formula	: $C_{12}H_{18}O_6$
IR (neat)	: 3400, 1720, 1620, 1590 cm^{-1}.
^{1}**H NMR** (200 MHz) $CDCl_3$	: δ 1.28 (t, 6H); 3.45 (bs, OH); 4.18 (q, 4H), 4.30 (d, 2H); 6.15 (d, 2H), 6.96 (d, 2H).

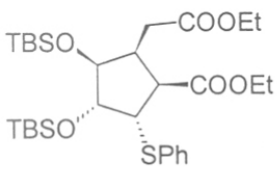
4. **Diethyl(4S,5S)-4,5-bis(tert-butyldimethyl silyloxy)-2E,6E-octadiendiate (110)[38] :**



The alcohol (**117**) (5 g, 19.4 mmol) was dissolved in 8 ml of dry DMF under argon and TBDMSCl (7.66 g, 50.8 mmol) was added to it followed by imidazole (6.9 g, 0.1 mol). The mixture was stirred at room temperature for 12 hrs. After completion of the reaction (as monitored by TLC) dichloromethane was added to the solution (50 ml) which precipitates a white solid which was filtered off. The filtrate was concentrated and washed with water (25X2 ml) and dried (anhyd. Na_2SO_4). The residue was chromatographed over silica gel (10% ethyl acetate : pet. ether) to yield the TBDMS protected alcohol **110** in 88% yield.

Yield	: 88 % viscous colorless liquid
Mol. Formula	: $C_{24}H_{46}O_6Si_2$
IR (neat)	: 2800, 1720, 1620 cm^{-1}.
^{1}**H NMR** (200 MHz) $CDCl_3$	: δ 0.095 (s, 6H), 0.097 (s, 6H), 0.95 (s, 18H), 1.28 (t, 6H); 4.19 (q, 4H), 4.36 (d, 2H), 5.97 (d, J=16Hz, 2H), 6.94 (dd, J=2.7, 16 Hz 2H).

5. **2,3-bis[[(1,1-dimethyl ethyl)dimethyl silyl]oxy]-5-(ethoxy carbonyl)-4-(phenyl thio)-cyclopentane acetic acid ethyl ester (118)[38]:**



Thiophenol (4.77 g, 43.4 mmol) was taken in 20 ml of THF and cooled to –78°C using a dry ice-acetone bath. To it was added BuLi (2.77 g, 43.4 mmol) at –78°C. The reaction mixture was stirred at –78°C for one hour and then a solution of the silyloxy compound (**110**) in THF (10 ml) (5 g, 10.2 mmol) was added at the same temperature and after 5 min the temperature was brought to –35°C and maintained for 2 hrs with stirring at the same temperature. Saturated NH_4Cl solution (20 ml) was then added to quench the reaction. The reaction mixture was diluted with 20 ml of ethyl acetate and the two layers were separated. The ethyl acetate layer was further washed with saturated brine solution and dried over anhydrous Na_2SO_4 and finally the organic layer was evaporated under reduced pressure to give a residue which was chromatographed with 5% ethyl acetate : pet. ether to yield the compound **118** (6 g) in 99% yield as colorless liquid.

Yield : 99% colorless viscous liquid.

Mol. Formula : $C_{30}H_{52}O_6SSi_2$

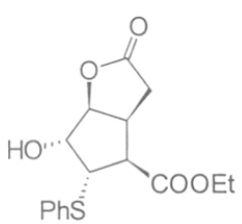
Optical Rotation : $[\alpha]_D^{25}$=-35.15° (c=1.09, $CHCl_3$).

IR (neat) : 2950, 1740, 1600, 1470,1380 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 0.0 (s, 3H); 0.05 (s, 3H); 0.10 (s, 3H); 0.15 (s, 3H); 0.9575 (9H) 0.90 (s, 9H), 1.14 (t, 3H), 1.26 (t, 3H), 2.41 (m, 2H), 3.18 (m, 2H), 4.08 (m, 6H), 4.3 (m, 1H), 7.23 (m, 3H), 7.44 (m, 2H).

Mass(m/e) :596(M^+, 1), 551(4), 541(32), 539(100), 538(21), 525(1), 403(14), 395(3), 377(7), 361(9), 355(3), 331(7), 303(4), 271(5), 243(33), 215(3), 147(5), 133(4), 115(2), 73(3).

6. **6-Hydroxy-2-oxo-5-phenylthio hexahydro cyclopenta[b]furan-4-carboxylic acid ethyl ester (119):**



The Michael adduct **118** (2.0 g, 3.35 mmol) was taken in 10 ml of dry THF under nitrogen in a two necked 50 ml round bottomed flask. The solution was cooled to 0°C and 1M solution of TBAF (13.3 ml) was added. After five min the ice bath was removed and

the solution was stirred at room temperature for an hour. The solution was then concentrated under reduced pressure to remove the THF and the residue was extracted with Et_2O (2X25 ml). The ether layer was washed with brine solution and dried over anhyd.Na_2SO_4 and further concentrated to yield a oily residue which was taken in 20 ml of dry benzene. This was stirred at room temperature with catalytic amount of pTSA added to it. After 2 hrs the benzene layer was washed once with saturated brine solution , dried over anhyd. Na_2SO_4 and concentrated to yield a residue which was chromatographed with 50% pet. ether : ethyl acetate to furnish the hydroxy lactone **119** (550 mg) in 55% yield.

Yield : 55%

Mol. Formula : $C_{16}H_{18}O_5S$ yellow viscous liquid

Optical Rotation : $[\alpha]_D^{26}$= +69.93 ° (c=1.04, $CHCl_3$).

IR (neat) : 3400, 1780, 1750, 1590. cm^{-1}.

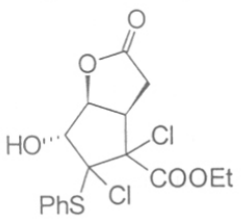
^{1}H NMR (200 MHz) $CDCl_3$: δ 1.27 (t, 3H); 2.43 (dd, J=3.5, 18.9Hz, 1H); 2.66 (dd, J=10, 18.9Hz, 1H); 2.89 (bs, OH); 3.21 (dd, J=9.6, 12.3Hz, 1H), 3.42 (dddd, J=3.5, 6.7, 9.6, 10Hz, 1H), 3.87 (dd, J=3.6, 12.2Hz, 1H), 4.13 (d, J=3.6 Hz, 1H), 4.24 (q, 2H), 4.91 (d, J=6.7Hz, 1H), 7.32 (m,3H), 7.46 (m,2H).

^{13}C NMR(50MHz) $CDCl_3$: 13.9(q), 30.5(t), 38.5(d), 50.2(d), 54.2(d), 60.4(t), 74.1(d), 86.7(d), 127.7(d), 129(d), 132(d), 133.1(s), 170.9(s), 175.7(s).

Mass(m/e) :322(M^+, 100), 276(10), 259(4), 231(8), 217(2), 213(6), 202(9), 195(30), 189(14), 167(31), 149(7), 139(24), 129(5), 123(13), 110(52), 109(44), 104(51), 95(13), 91(6), 83(31), 77(12), 69(8), 65(14),55(12).

Analysis :	Carbon	Hydrogen	Sulfur
Calculated :	59.60%	5.60%	9.90%
Found :	59.41%	5.44%	8.72%

7. **4,5-Dichloro-6-hydroxy-2-oxo-5-phenylthio-hexahydrocyclopenta[b]furan-4-carboxylic acid ethyl ester (120):**



The hydroxy lactone **119** (0.200 g, 0.62 mmol) was taken in 25 ml of dry dichloromethane under nitrogen to which was added N-Chloro succinimide (0.091g, 0.68 mmol) and stirred for 2 hrs at room temperature. After completion of the reaction (as monitored by TLC) the reaction mixture was washed with water, dried over anhyd. Na_2SO_4, concentrated under reduced pressure and chromatographed over silica gel with 10% ethyl acetate : pet. ether to furnish two products, the major one being the dichloro compound **120** in 60% yield.

Yield : 60%

Mol. Formula : $C_{16}H_{16}Cl_2O_5S$ yellow solid

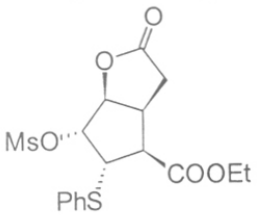
IR (neat) : 3400, 2980. 1770, 1750, 1460, 1380. cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.44 (t, 3H); 2.36 (dd, 1H); 2.80 (dd, 1H); 3.65 (dt, 1H); 4.41 (q, 2H), 4.85 (dd, 1H), 4.95 (d, 1H), 7.45 (m, 3H), 7.73 (m, 2H).

^{13}C NMR(50MHz) $CDCl_3$: 13.8(q), 31.3(t), 48.5(d), 64.5(t), 82.3(d), 83.8(s), 86.6(d), 89.7(s), 126.8(s), 128.8(d), 130.7(d), 138.05(d), 166.4(s), 170.6(s).

Mass(m/e) :392(M^+, 16), 390(21), 354(12), 319(52), 320(52), 318(53), 309(9), 273(16), 245(12), 229(16), 217(17), 201(12), 181(9), 175(13), 171(20), 163(13), 153(13), 147(23), 139(19), 121(23), 115(26), 110(100), 105(19), 97(14), 77(31), 65(76), 55(18).

8. **6-Methanesulphonyloxy-2-oxo-5-phenylthio hexahydro cyclopenta[b]furan-4-carboxylic acid ethyl ester (122)**



The hydroxy lactone **119** (0.2 g, 0.62 mmol) was taken in a 25 ml two necked flask under nitrogen and 10 ml of dry dichloromethane was added to it. The flask was cooled to 0°C and to it mesyl chloride (0.084g, 0.73 mmol) and triethyl amine (0.133 g, 1.3 mmol) were added. A catalytic amount of DMAP was also added and the solution stirred for 2-3 hrs at room temperature. After completion of reaction (as monitored by TLC), the reaction mixture was further diluted with 10 ml of dichloromethane and the organic layer washed once with water (10 ml). Dichloromethane layer was separated and dried over anhyd.

Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel with 20% ethyl acetate : pet. ether to yield the mesylate **122** (0.228 g) in 92% yield.

Yield : 92%

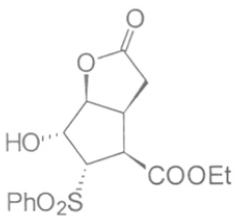
Mol. Formula : $C_{17}H_{20}O_7S_2$ colorless viscous liquid

IR (neat) : 1800, 1740, 1600, 1400, 1240, 1200, 1035, 1000.cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.25 (t, 3H); 2.45 (dd, 1H); 2.7 (dd, 1H); 3.18 (s, 3H), 3.34(dd, 1H), 3.5 (dddd, 1H), 3.95 (dd, 1H), 4.18 (q, 2H), 5.1 (d, 1H), 5.16 (d, 1H), 7.34 (m, 3H), 7.48 (m, 2H).

Mass(m/e) :400(M+1, 54), 305(29), 259(27), 241(16), 231(21), 213(14), 187(36), 167(8), 149(8), 139(10), 129(5), 123(15), 109(100), 83(28), 79(62), 69(12), 65(32), 55(16).

9. **6-Hydroxy-2-oxo-5-phenyl sulphonyl hexahydro cyclopenta[b]furan-4-carboxylic acid ethyl ester (128)**



The hydroxy lactone **119** (0.2 g, 0.62 mmol) was dissolved in methanol (10 ml) and cooled to 0°C. To this was added a solution of 49.5% $KHSO_5$ (Oxone) (1.14g, 1.85 mmol) in water (10 ml). The resulting cloudy slurry was stirred for 4 hrs at room temperature, diluted with water and extracted with chloroform. The combined layers were washed with water and brine, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed with 50% ethyl acetate : pet. ether to furnish the product **128** (197 mg)in 90% yield.

Yield : 90%

Mol. Formula : $C_{16}H_{18}O_7S$

Optical Rotation : $[\alpha]_D^{25}$= +36.9° (c=0.694, $CHCl_3$)

IR (neat) : 3480, 1785, 1730, 1450, 1380, 1310, 1230 1150 cm^{-1}.

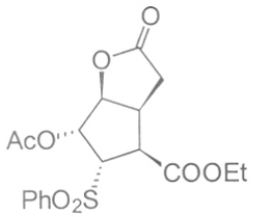
^{1}H NMR (200 MHz) $CDCl_3$: δ 1.25 (t, 3H); 2.19 (dd, J=1.2, 18.7Hz, 1H); 2.68 (dd, J=9.6, 18.6Hz, 1H), 3.58 (m, 1H); 3.95 (m, 4H), 4.63 (s, 1H), 4.78 (d, J=5.9Hz, 1H), 7.67 (m, 3H), 7.89 (m, 2H).

^{13}C NMR(50MHz) $CDCl_3$: 14.2(q), 31.5(t), 39.7(d), 45.9(d), 62.1(t), 67.9(d), 74.0(d), 86.6(d), 128.4(d), 129.7(d), 134.7(d), 139.2(s), 170.3(s), 174.8(s).

Mass(m/e) :355(M+1, 2), 213(38), 195(25), 185(8), 167(61), 139(100), 129(22), 125(47), 111(42), 97(16), 83(52), 77(59), 69(7), 55(13).

Analysis :	Carbon	Hydrogen	Sulfur
Calculated :	54.20%	5.10%	9.04%
Found :	54.16%	5.23%	8.78%

10. 6-Acetoxy-2-oxo-5-phenyl sulphonyl hexahydro cyclopenta[b]furan-4-carboxylic acid ethyl ester (129)



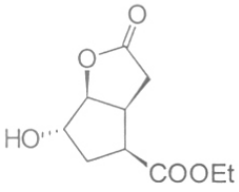
The sulphone **128** (0.2 g, 0.564 mmol) was dissolved in 20 ml of dry dichloromethane in a two necked flask under argon. To this was added pyridine (0.053g, 0.67 mmol) at 0°C and the reaction mixture was stirred for 0.5 hrs. Then acetyl chloride (0.053, 0.67 mmol) was added at the same temperature and the reaction mixture was further stirred for 2 hrs. After completion of the reaction(as monitored by TLC) the mixture was poured in to water and extracted with chloroform. The organic layer was subsequently washed with dil HCl, 10% $NaHCO_3$, water and brine. The organic layer was dried over anhyd. Na_2SO_4, concentrated and chromatographed with 20% ethyl acetate : pet. ether to furnish protected alcohol **129** (182 mg) in 81% yield.

Yield	:81%
Mol. Formula	: $C_{18}H_{20}O_8S$ colorless viscous liquid
IR (neat)	: 3025, 1798, 1732, 1700, 1590. cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.19 (t, 3H); 2.1 (s, 3H), 2.23 (dd, 1H), 2.71 (dd, 1H); 3.59 (m, 1H), 3.99 (m, 3H), 4.34 (dd, 1H), 4.83 (dd, 1H), 5.76 (d, 1H), 7.62 (m, 3H), 7.86 (m, 2H).

Mass(m/e) :397(M+1, 1), 355(1), 307(1), 279(1), 264(2), 255(25), 213(70), 195(69), 185(8), 167(60), 139(61), 125(61), 121(16), 111(19), 101(10), 95(13), 83(32), 77(100), 71(12), 65(17), 55(19).

11. 6-Hydroxy-2-oxo-hexahydro cyclopenta[b]furan-4-carboxylic acid ethyl ester (132):



To a freshly prepared suspension of neutral Ra-Ni (4g in THF) at 25°C was added under nitrogen the hydoxy lactone (**119**) (500mg, 1.55mmol) in THF solution (20 ml). The mixture was stirred at room temperature for one hour at which time TLC indicated the completion of the reaction. The Ra-Ni was removed by filtration through celite and washed thoroughly with THF. Removal of the solvent followed by column chromatography furnished the product **132** (265 mg) in 80% yield.

Yield : 80%

Mol. Formula : $C_{10}H_{14}O_5$ white solid

M.P. : 65-67°C

Optical Rotation : $[\alpha]_D^{25}$= -11.2° (c=1.01, $CHCl_3$)

IR (neat) : 3480, 2982, 1780, 1740, 1632, 1380. cm^{-1}.

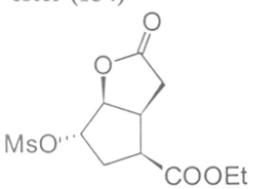
^{1}H NMR (200 MHz) $CDCl_3$: δ 1.89 (t, 3H); 2.02 (m, 2H); 2.38 (dd, 1H); 2.75 (dd, 2H); 3.39 (m, 2H), 3.39 (m, 2H), 4.17 (q, 2H), 4.36 (d, J=3.1Hz, 1H), 4.77 (d, J=5.8Hz, 1H).

^{13}C NMR(50MHz) $CDCl_3$: 14.2(q), 30.7(t), 33.8(t), 38.4(d), 45.4(d), 61.0(t), 74.5(d), 89.5(d), 172.9(s), 177(s).

Mass(m/e) :215(M+1, 2), 196(3), 170(61), 141(100), 130(27), 123(11), 113(48), 101(54), 97(20), 85(36), 73(25), 67(15), 55(28).

Analysis :	Carbon	Hydrogen
Calculated :	56.06%	6.58%
Found :	55.89%	6.49%

12. **Methanesulphonyl-2-oxo-hexahydro cyclopenta[b]furan-4-carboxylic acid ethyl ester (134)**



The compound **132** (0.2 g, 0.93 mmol) was taken in a 25 ml two necked flask under nitrogen and 10 ml of dry dichloromethane was added to it. The flask was cooled to 0°C and to it mesyl chloride (0.107 g, 0.93 mmol) and triethyl amine (0.1 g, 1 mmol) were added. A catalytic amount of DMAP was also added and the solution stirred for 2-3 hrs at room temperature. After completion of reaction (as monitored by TLC), the reaction mixture was further diluted with 10 ml of dichloromethane and the organic layer washed once with water (10 ml). Dichloromethane layer was separated and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed over silica gel with 20% ethyl acetate : pet. ether to yield the mesylate **134** (0.237 g) in 87% yield.

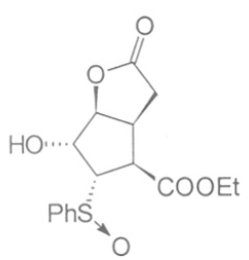
Yield : 87%

Mol. Formula : $C_{11}H_{16}O_7S$ colorless viscous liquid

IR (neat) : 3040, 1800, 1740, 1360, 1230, 1190. cm^{-1}.

^{1}**H NMR** (200 MHz) $CDCl_3$: δ 1.2 (t, 3H); 2.25 (m, 1H); 2.3 (dd, 1H); 2.68 (dd, 1H); 3.02 (s, 3H), 3.1(d, 1H), 3.38 (m, 2H), 4.16 (q, 2H), 5.0 (d, 1H), 5.1 (m, 1H).

13. **6-Hydroxy-2-oxo-5-phenyl sulphoxy hexahydro cyclopenta[b]furan-4-carboxylic acid ethyl ester (135)**



The hydroxy lactone **119** (0.600 g, 1.86 mmol) was dissolved in 2 ml of acetic acid and the mixture was cooled to 0°C. To this was added H_2O_2 solution (0.063 g, 1.86 mmol) and the mixture stirred for 2 hrs at 0°C. After completion of the reaction (as monitored by

TLC) the mixture was poured into saturated $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was separated and washed with water and dried over Na_2SO_4. After concentration the residue was recrystalised with chloroform and pet ether to give the sulphoxide **135** (0.497 g) in 80% yield.

Yield : 80%

Mol. Formula : $C_{16}H_{18}O_6S$ white solid

M.P. : 160-162°C

Optical Rotation : $[\alpha]_D^{25}$= -64° (c=1, CH_3OH)

IR (neat) :3450, 3026, 2924, 1785, 1720, 1604, 1495, 1030. cm^{-1}.

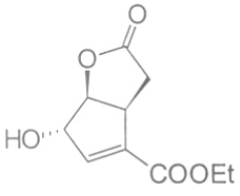
^{1}H NMR (200 MHz) $CDCl_3$: δ 1.3 (t, 3H); 1.65 (bs, 1H), 2.26 (dd, J=2.5, 18.9 Hz, 1H); 2.75 (dd, J=10, 18.9 Hz, 1H); 3.0 (dd, J=3, 12.5Hz, 1H); 3.66 (m, 1H), 4.18 (dd, J=10, 12 Hz, 1H), 4.29 (q, 2H), 4.54 (d, J=3Hz, 1H), 4.62 (d, J=6.5Hz, 1H), 7.65 (m, 3H), 7.75 (m, 2H).

^{13}C NMR(50MHz) $CDCl_3$: 14.1(q), 32.5(t), 41.3(d), 45.4(d), 62.0(t), 71.9(d), 73.2(d), 88.0(d), 126.3(d), 130.1(d), 133.1(d), 141.3(s), 170.7(s), 176.5(s).

Mass(m/e) :338(M^+, 3), 322(8), 318(14), 213(4), 195(22), 183(15), 168(33), 167(32), 155(11), 139(28), 138(38), 137(20), 126(35), 125(49), 121(10), 111(23), 110(45), 109(100), 97(43), 96(27), 83(24), 77(37), 65(26), 55(15).

Analysis :	Carbon	Hydrogen	Sulfur
Calculated :	53.80%	4.80%	8.90%
Found :	52.90%	4.90%	8.00%

14. 6-Hydroxy-2-oxo-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylic acid ethyl ester (136):



The sulphoxide **135** (0.2 g, 0.59 mmol) was dissolved in 15 ml of dry toluene in a two necked round bottomed flask equipped with a reflux condenser and the mixture was refluxed for 6 hrs. After completion of the reaction (as monitored by TLC) the toluene

was removed by distillation and the residue was chromatographed over silica gel with 40% ethyl acetate : pet. ether to furnish the alcohol **136** (0.11 g) in 89% yield.

Yield : 89%

Mol. Formula : $C_{10}H_{12}O_5$ colorless viscous liquid

IR (neat) : 3400, 1750, 1734, 1600, 1400, 1200 cm^{-1}.

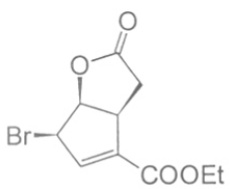
^{1}**H NMR** (200 MHz) $CDCl_3$: δ 1.31 (t, 3H); 2.63 (dd, 1H); 2.90 (dd, 1H); 3.92 (m, 1H); 4.25 (q, 2H), 4.92 (d, 1H), 4.98 (d, 1H), 6.75 (bs, 1H).

^{13}**C NMR**(50MHz) $CDCl_3$: 14(q), 32.2(t), 43.1(d), 61.2(t), 79.4(d), 88.5(d), 139.1(d), 141.3(s), 163.7(s), 176.5(s).

Mass(m/e) :212(M^+, 8), 194(2), 183(29), 167(25), 166(100), 155(28), 141(20), 138(86), 137(30), 127(15), 125(26), 110(40), 109(61), 97(20), 96(35), 95(29), 82(20), 81(40), 69(23), 68(21), 53(42).

Analysis :	Carbon	Hydrogen
Calculated :	56.60%	5.69%
Found :	56.39%	5.89%

15. 6-Bromo-2-oxo-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylicacid ethyl ester (138):



Triphenyl phosphine (0.371 g, 1.4 mmol) was dissolved in 10 ml of dry dichloromethane and solution cooled to 0°C. To this was added bromine (0.188 g, 1.17 mmol) and stirred at the same temperature for half an hour. Then the alcohol **136** (0.25 g, 1.17 mmol) was added and the solution was brought to room temperature and stirred for two hours to ensure completion of the reaction. The reaction mixture was concentrated and residue chromatographed over silica gel with 40% ethyl acetate : pet. ether to furnish the bromide **138** (0.243 g) in 75% yield.

Yield : 75%

Mol. Formula : $C_{10}H_{11}BrO_4$ pale yellow liquid

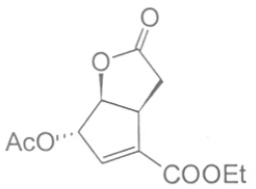
IR (neat) :2982, 1786, 1713, 1627, 1374, 1297, 1220, 1156. cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.32 (t, 3H); 2.68 (dd, 1H); 2.91 (dd, 1H); 3.84 (m, 1H); 4.25 (q, 2H), 5.14 (m, 2H), 6.82 (bs, 1H).

^{13}C NMR(50MHz) $CDCl_3$: 13.6(q), 32.6(t), 42.3(d), 61.1(d), 62.9(t), 67.3(s), 77.4(d), 88(d), 166.5(s), 176(s).

Mass(m/e) :275(M^+, 2), 230(4), 229(12), 211(4), 195(100), 189(5), 183(2), 167(32), 166(34), 149(79), 138(13), 121(58), 111(30), 105(65), 95(28), 93(33), 78(42), 77(61), 65(66), 55(34).

16. 6-Acetoxy-2-oxo-3,3a,6,6a-tetrahydro-2H-cyclopenta[b]furan-4-carboxylicacid ethyl ester (137)



The alcohol **136** (0.100 g, 0.47 mmol) was dissolved in 10 ml of dry dichloromethane in a two necked flask fitted with a guard tube. The solution was cooled to 0°C and acetic anhydride (0.096 g, 0.94 mmol) was added to it followed by Et_3N (0.071 g, 0.70 mmol). The mixture was stirred for two hours at room temperature. After completion of the reaction (monitored by TLC) the dichloromethane layer was washed twice with 10% $NaHCO_3$ (2X20 ml) and then with water. The organic layer was separated and dried over anhyd. Na_2SO_4. It was further concentrated and the residue chromatographed over silica gel with 25% ethyl acetate : pet. ether to furnish the acetate **137** (0.1 g) in 85% yield..

Yield : 85%

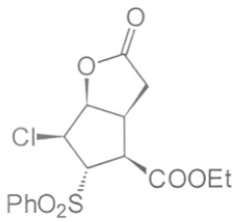
Mol. Formula : $C_{12}H_{14}O_6$ colorless viscous liquid

IR (neat) : 2934, 2363, 1789, 1721, 1718, 1376 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.33 (t, 3H); 2.1 (s, 3H), 2.67 (dd, J=2.9, 18.8Hz, 1H); 2.92 (dd, J=10, 18.8Hz, 1H); 3.93 (m, 1H); 4.26 (q, 2H), 4.99 (d, J=6.3 Hz, 1H), 5.73 (bs, 1H), 6.76 (bs, 1H).

Mass(m/e) : 254(M^+, 10), 212(86), 194(19), 182(23), 167(36), 166(100), 155(14), 149(12), 138(70), 109(29), 96(12), 81(15), 77(10), 65(11).

17. **6-Chloro-2-oxo-5-phenyl sulphonyl hexahydro cyclopenta[b]furan-4-carboxylic acid ethyl ester (140):**



The sulphoxide **135** (0.200 g, 0.6 mmol) was dissolved in 10 ml of dichloromethane in a two necked round bottomed flask under nitrogen and cooled to 0°C. To this was added sulfuryl chloride(0.080 g, 0.6mmol) at 0°C and stirred for one hour. After completion of the reaction (as monitored by TLC) the mixture was washed once with water and dried over anhyd. Na_2SO_4 and concentrated to give a residue which was chromatographed over silica gel with 40% ethyl acetate : pet. ether as a eluent to yield the chlorosulphone **140** as white crystalline solid.

Yield : 85%

Mol. Formula : $C_{16}H_{17}ClO_6S$ white solid.

M.P. : 152-154°C

Optical Rotation : $[\alpha]_D^{25}$= +105.3° (c=1.05, $CHCl_3$)

IR (neat) : 3460, 3019, 1794, 1711, 1447, 1364, 1221, 1151, 1037, 754. cm^{-1}.

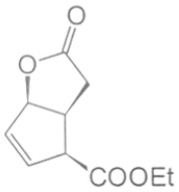
^{1}H NMR (200 MHz) $CDCl_3$: δ 1.29 (t, 3H); 1.65 (bs, 1H), 2.38 (dd, J=3, 18.5Hz, 1H); 2.75 (dd, J=9.2, 18.5 Hz, 1H); 3.4 (dddd, J=3, 9, 5.5, 10Hz, 1H); 3.69 (dd, J=10, 10Hz, 1H), 4.2 (q, 2H), 4.41 (dd, J=10, 10Hz, 1H), 4.57 (dd, J=4.8 10Hz, 1H), 5.02 (dd, J=4.8, 5.5Hz, 1H), 7.67 (m, 3H), 7.95 (m, 2H).

^{13}C NMR(50MHz) $CDCl_3$: 13.6(q), 31.7(t), 37.8(d), 45.6(d), 56.1(d), 61.8(t), 69.8(d), 83.8(d), 128.4(d), 128.9(d), 134.1(d), 137.6(s), 168.7(s), 173.6(s).

Mass(m/e) :233(23), 232(12), 231(99), 205(7), 203(23), 195(8), 185(14), 175(6), 167(28), 157(23), 147(11), 139(17), 129(10), 125(23), 124(20), 105(12), 101(21), 95(15), 83(21), 77(100), 65(19), 55(4).

Analysis :	Carbon	Hydrogen
Calculated :	51.55%	4.59%
Found :	51.46%	4.43%

18. 2-Oxo-3,3a,4,6a-tetrahydro 2H-cyclopenta[b]furan-4-carboxylic acid ethyl ester (127):



The Chlorosulphone **140** (0.200g, 0.53 mmol) was taken in 20 ml of dry benzene in a two necked flask fitted with reflux condenser. To this was added n-tributyl tin hydride (0.156g, 0.53 mmol) dissolved in 5 ml of benzene slowly and the solution was then refluxed for 2 hrs. After completion of the reaction (as monitored by TLC) the benzene layer was concentrated and residue immediately chromatographed over silica gel with 40% ethyl acetate : pet. ether as eluent to furnish (0.084g) the olefin **127** in 80%.

Yield : 80%

Mol. Formula : $C_{10}H_{12}O_4$ white low melting solid

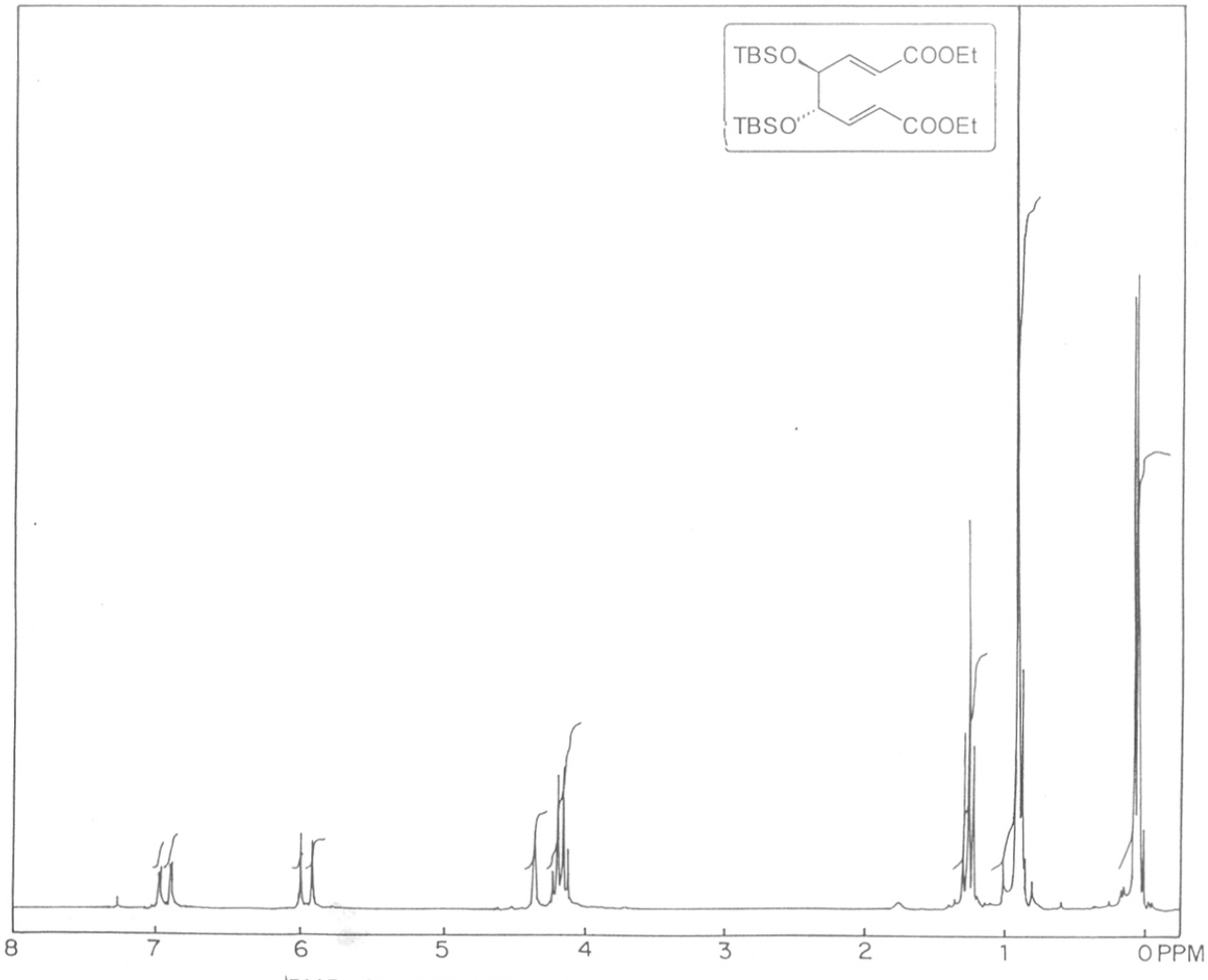
Optical Rotation : $[\alpha]_D^{25} = -18.6^{\circ}$ (c=0.66, $CHCl_3$)

IR (neat) : 2982, 1775, 1740, 1610, cm^{-1}.

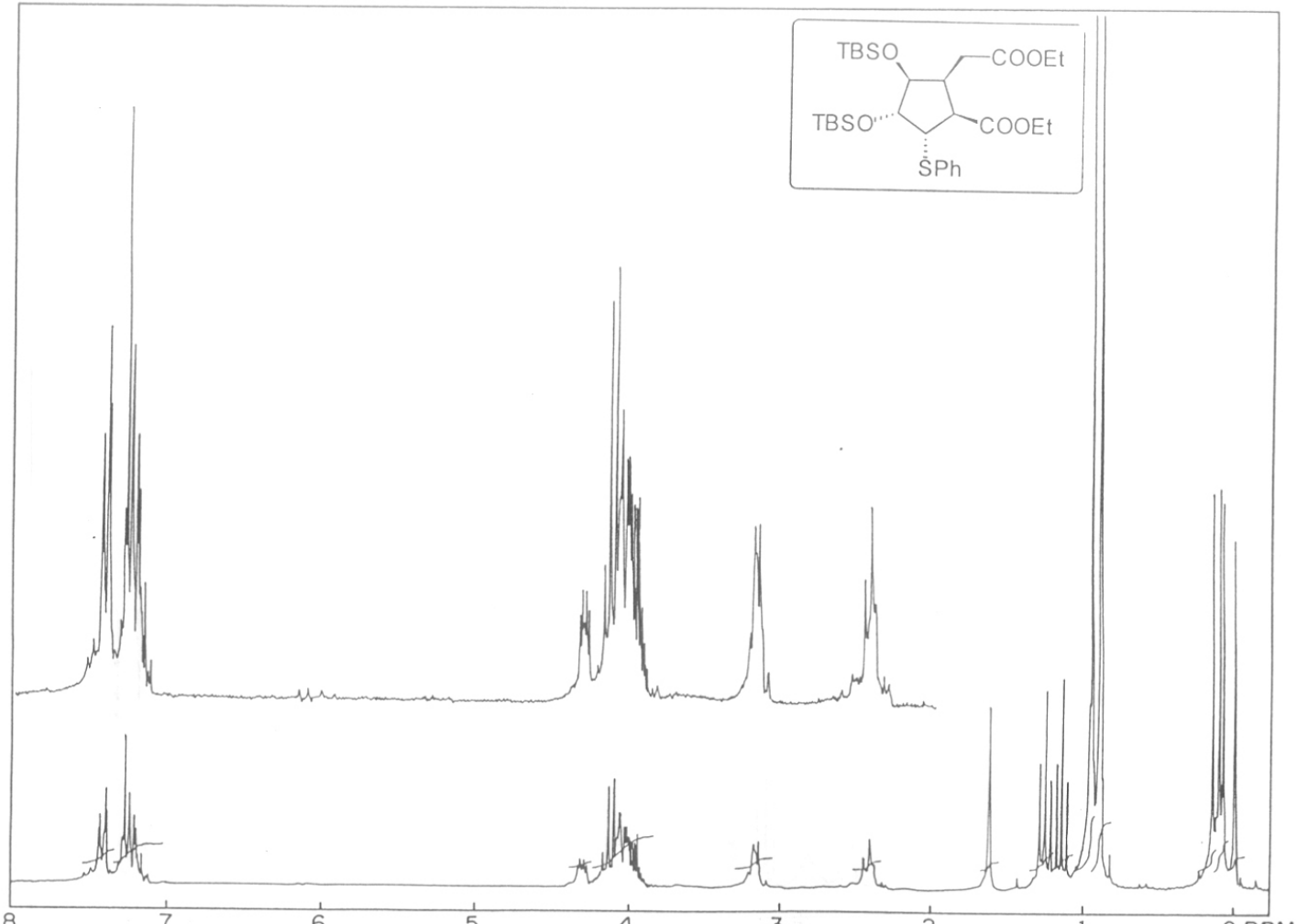
^{1}H NMR (200 MHz) $CDCl_3$: δ 1.29 (t, 3H); 2.32 (dd, 1H); 2.68 (dd, 1H); 3.53 (m, 1H); 3.79 (m, 1H), 4.23 (q, 2H), 5.53 (d, 1H), 6.02 (m, 1H), 6.16 (d, J=5.3Hz, 1H).

^{13}C NMR(50MHz) $CDCl_3$: 14.3(q), 31.5(t), 38.7(d), 52.5(d), 61.2(t), 87.7(d), 131.2(d), 133.8(d), 171.1(s), 176(s).

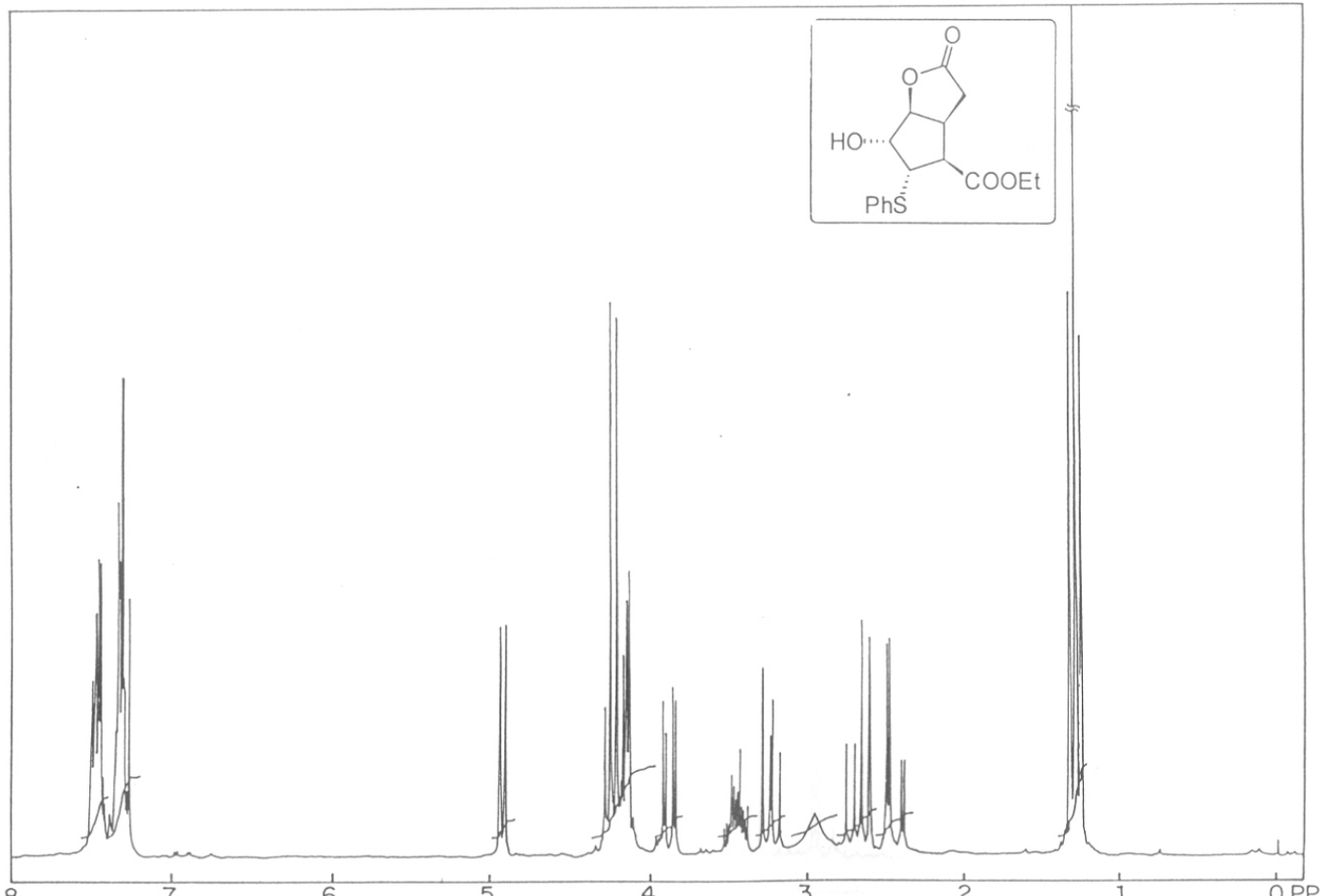
Mass(m/e) :197(M+1, 1), 179(3), 151(7), 124(32), 106(5), 95(23), 80(52), 79(100), 78(69), 67(29).



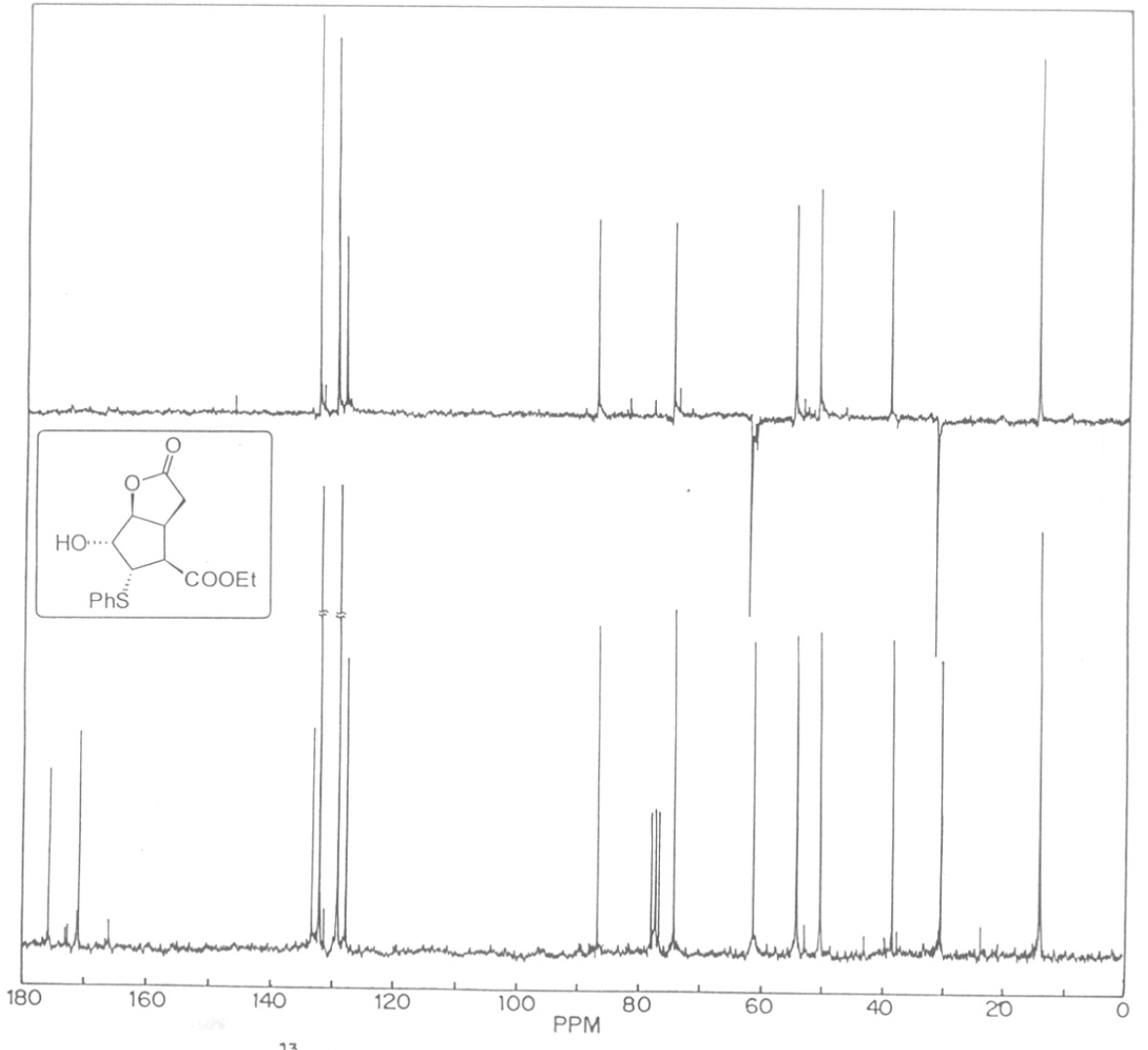
^{1}PMR OF COMPOUND **110** IN $CDCl_3$ AT 200 MHz



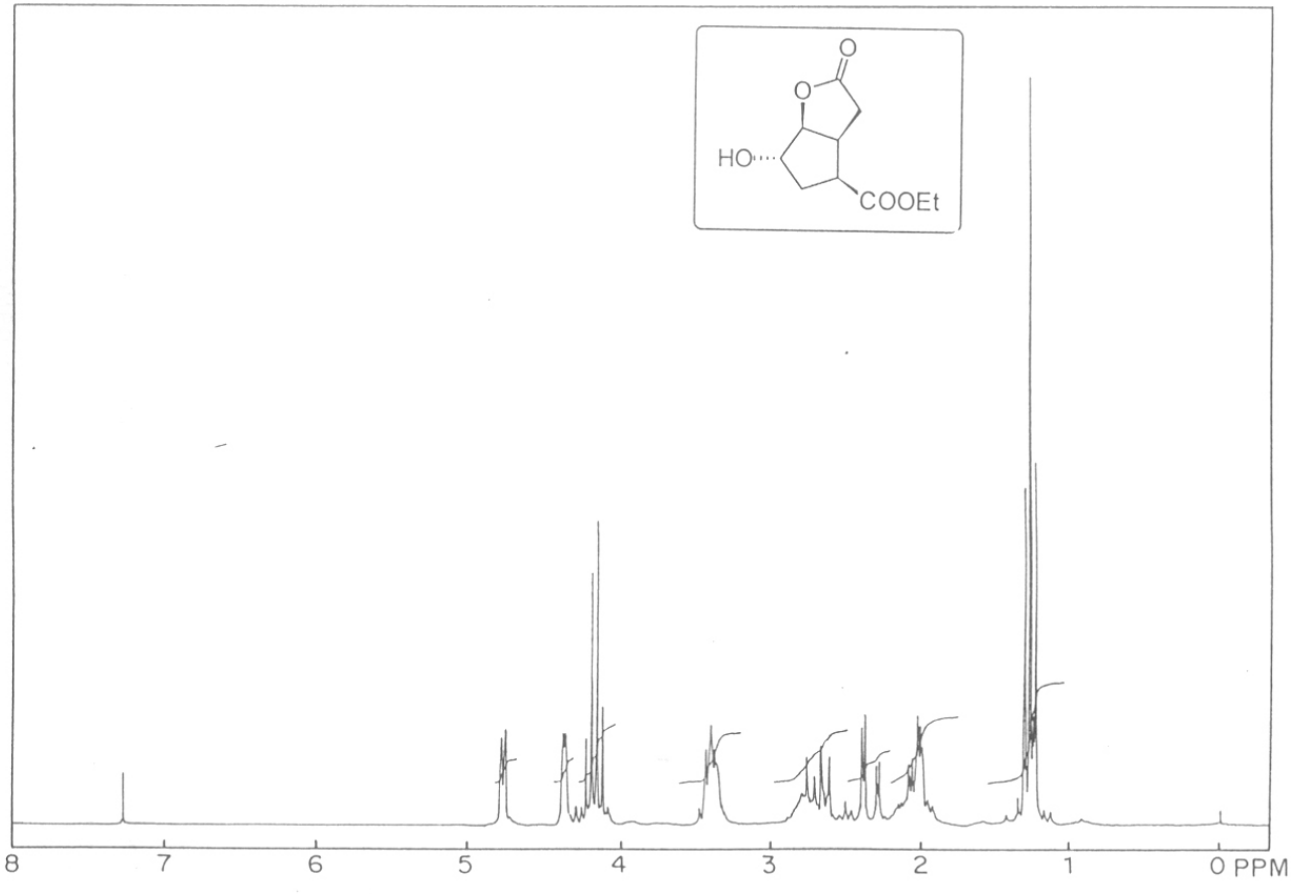
PMR OF COMPOUND 118 IN $CDCl_3$ AT 200 MHz



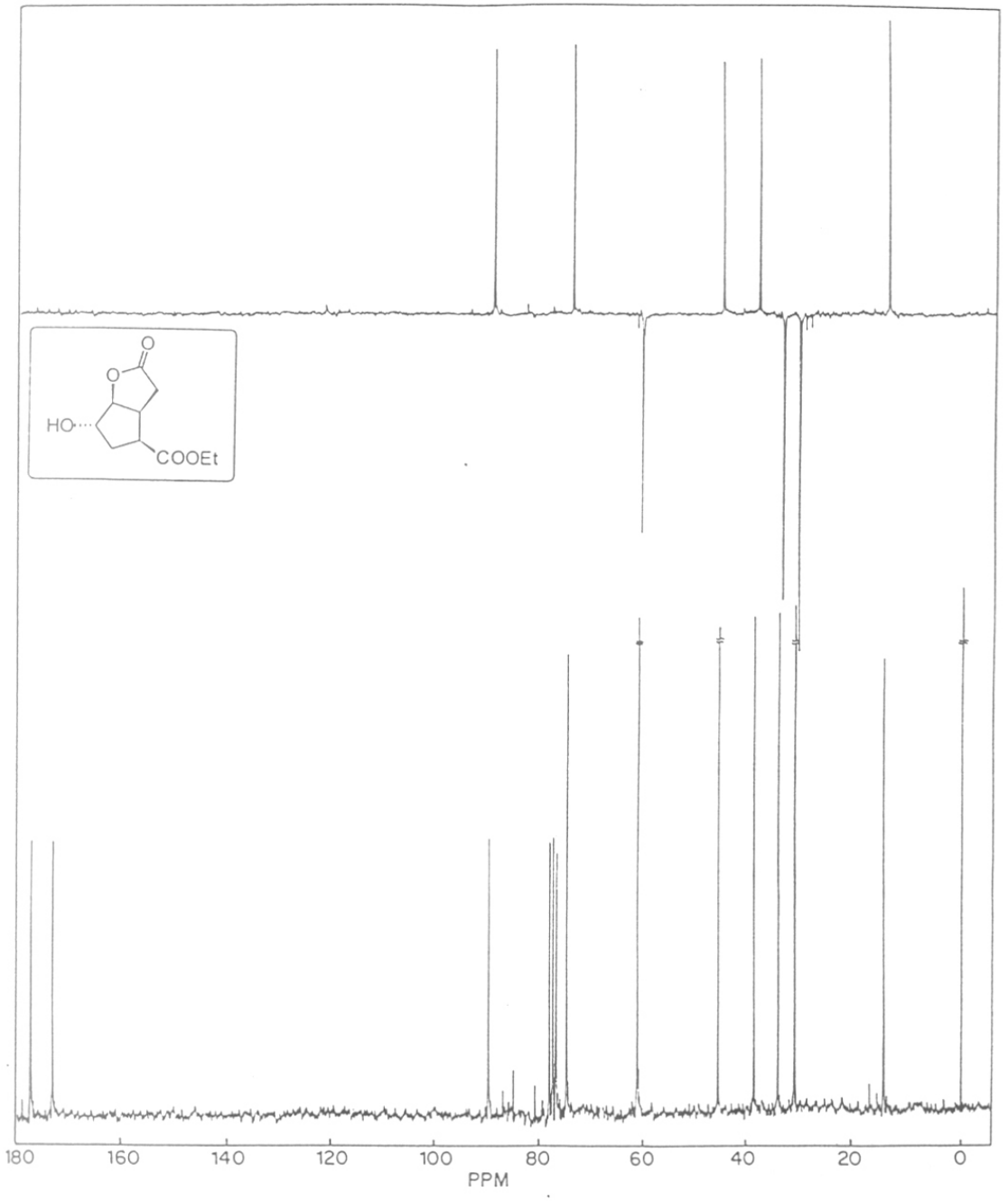
PMR OF COMPOUND **119** IN $CDCl_3$ AT 200MHz



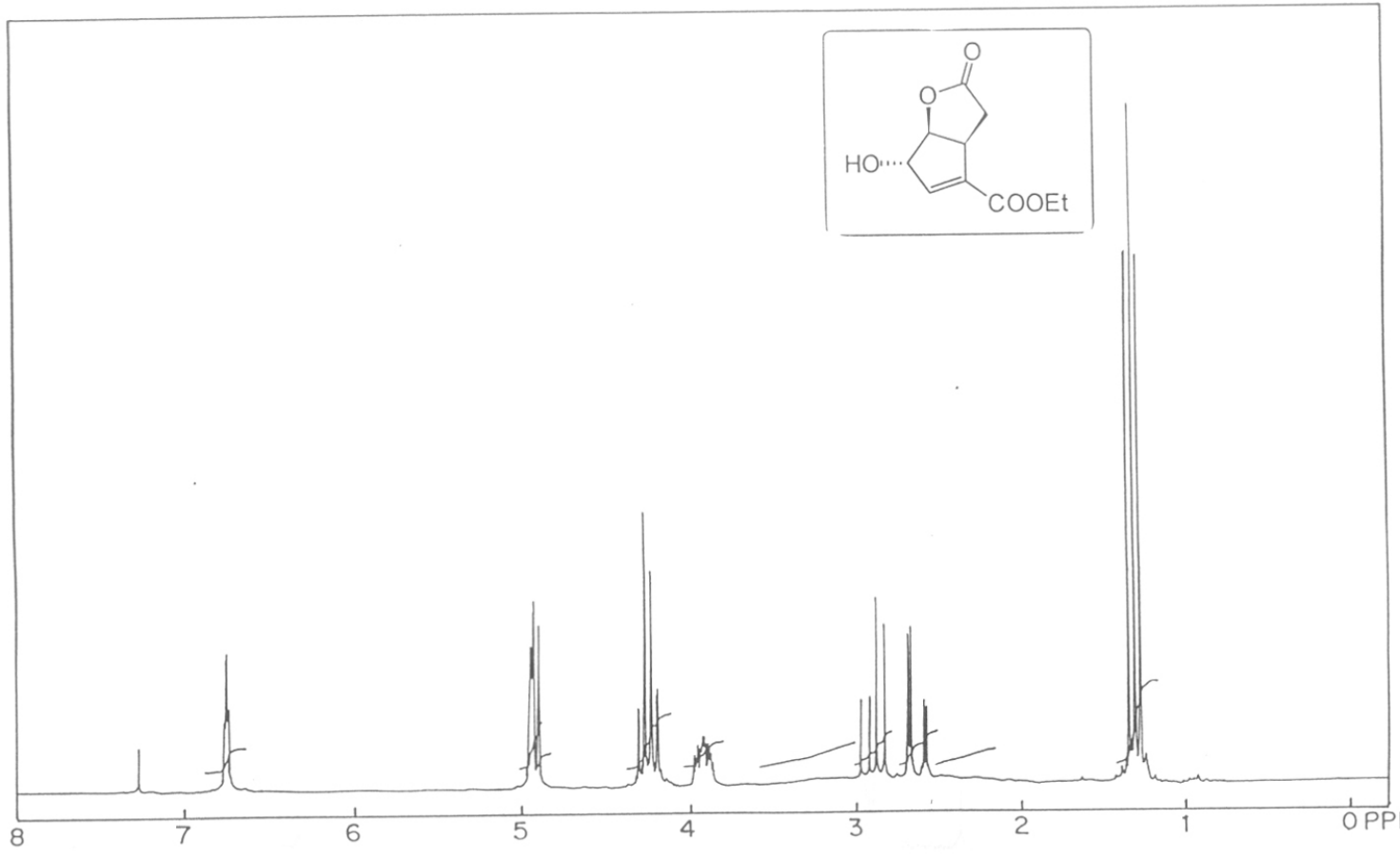
^{13}C-NMR OF COMPOUND **119** IN $CDCl_3$ AT 50 MHz



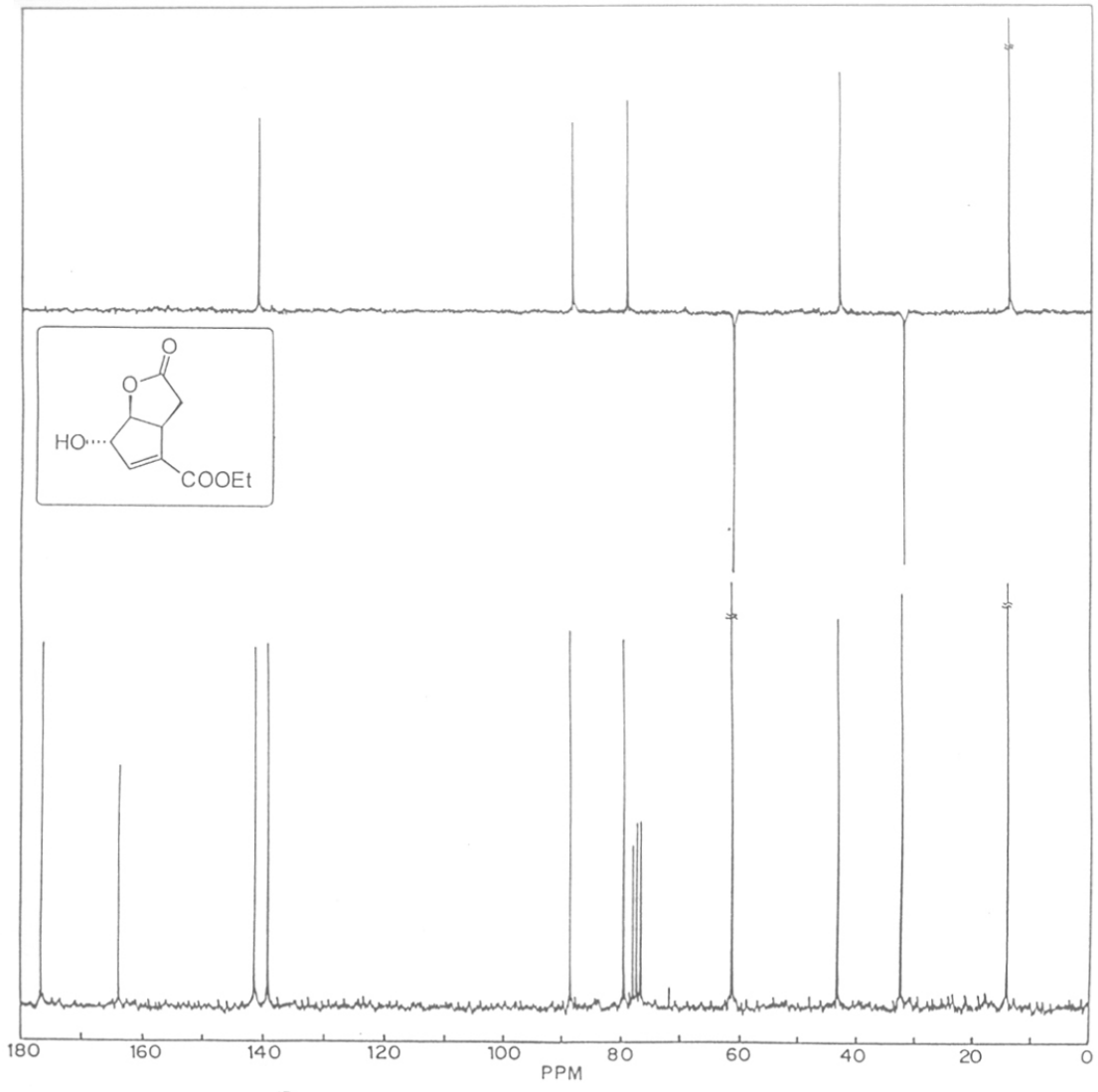
PMR OF COMPOUND 132 IN $CDCl_3$ AT 200MHz



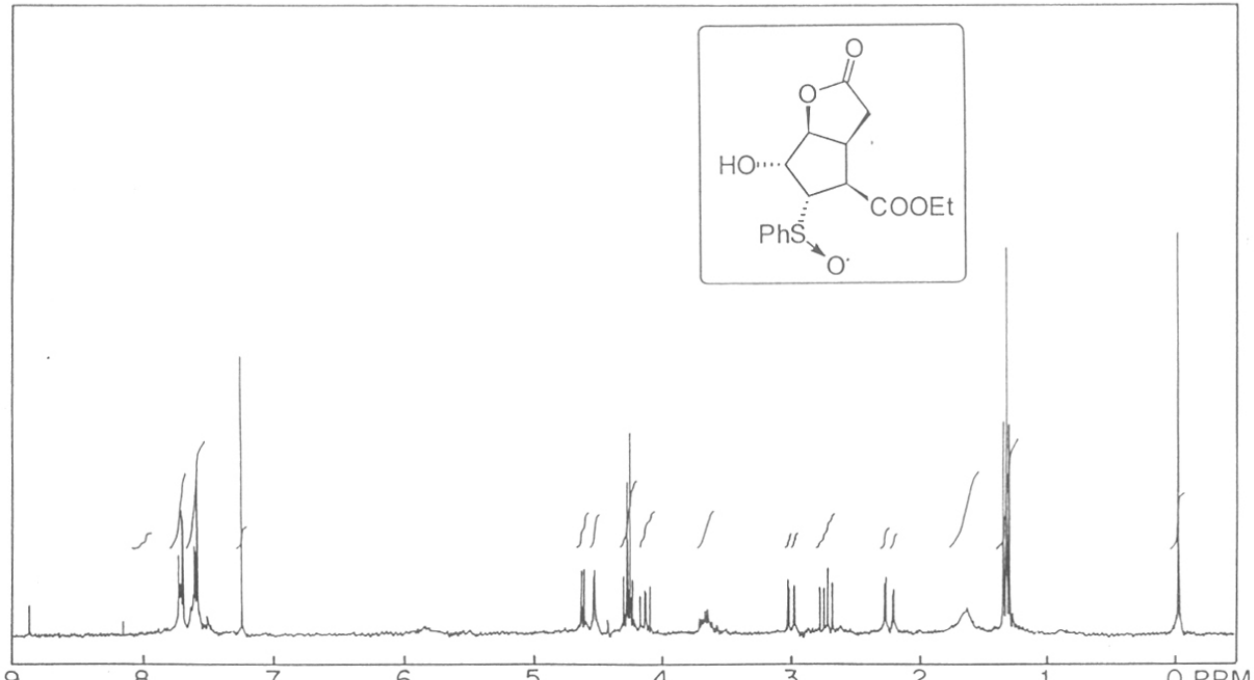
^{13}C-NMR OF COMPOUND 132 IN $CDCl_3$ AT 50MHz



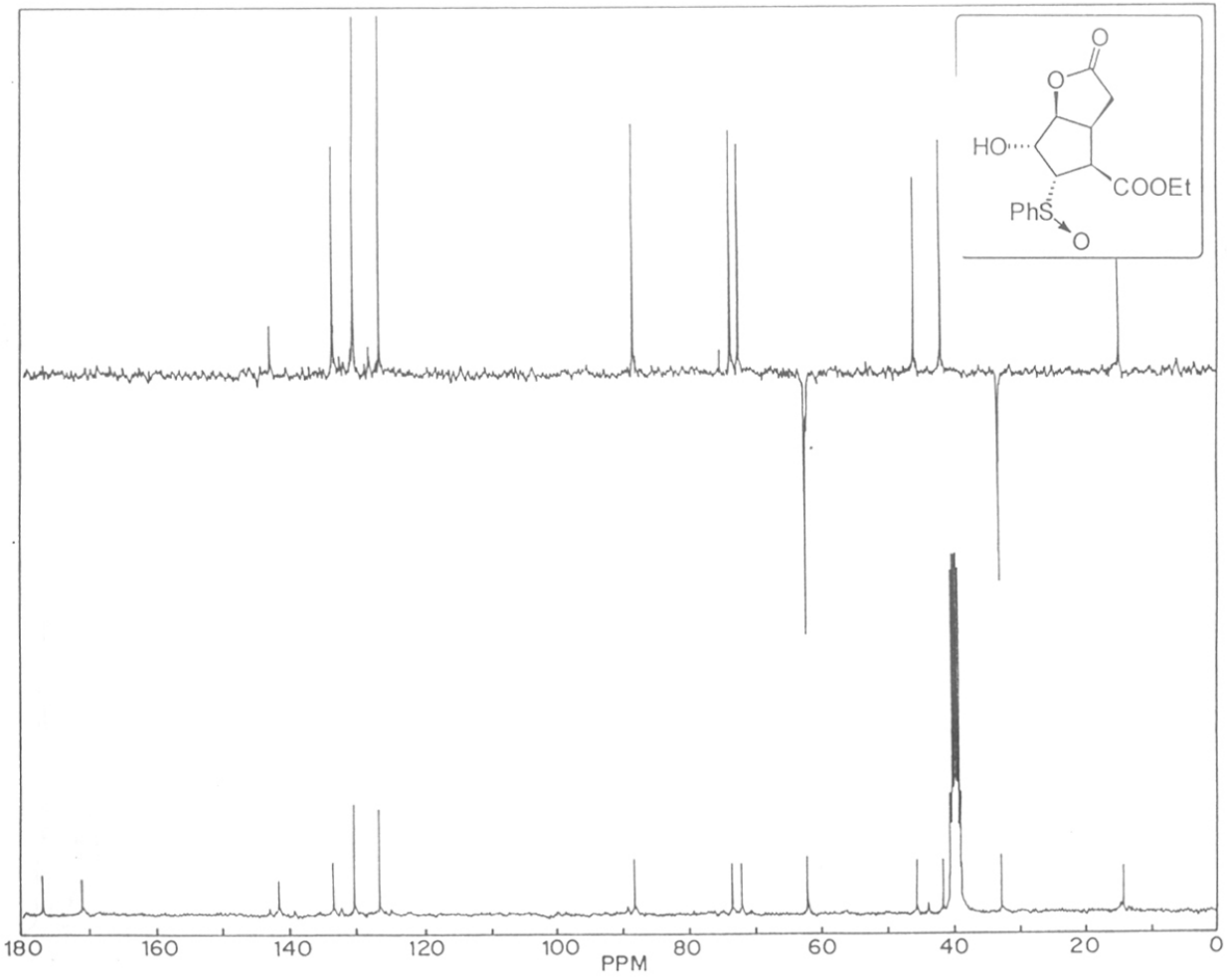
PMR OF COMPOUND **136** IN $CDCl_3$ AT 200 MHz



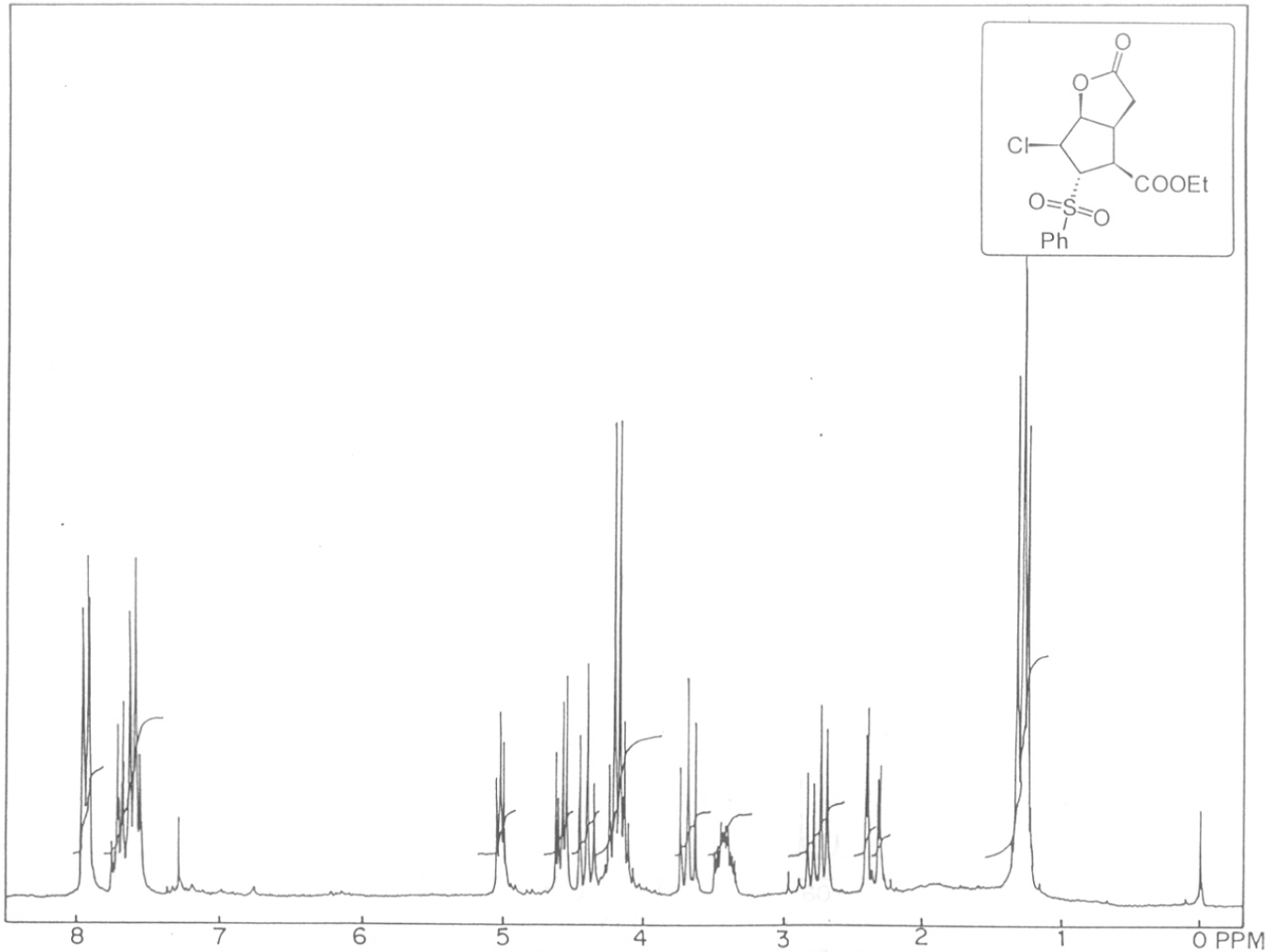
^{13}C-NMR OF COMPOUND **136** IN $CDCl_3$ AT 50MHz



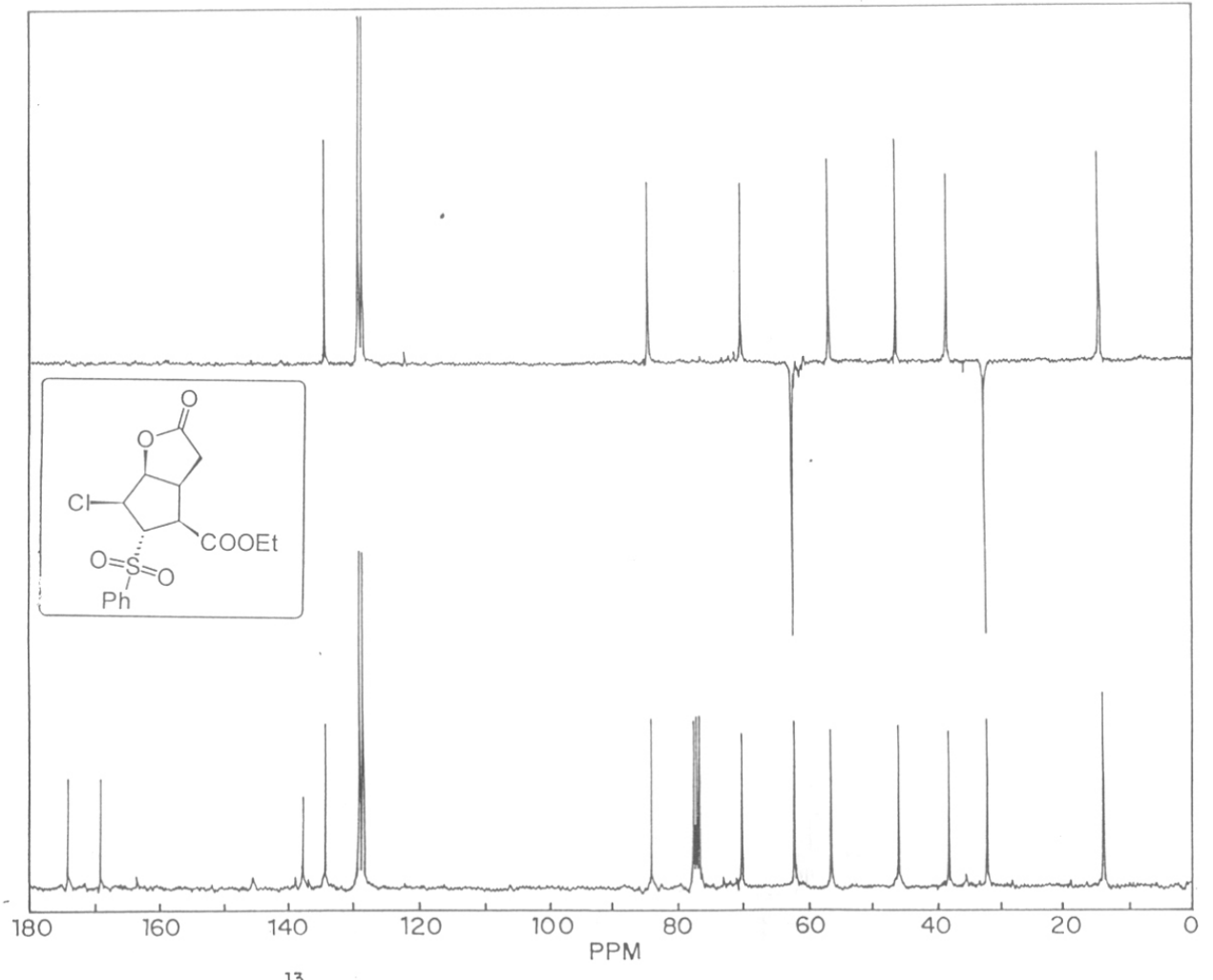
PMR OF COMPOUND **135** IN $CDCl_3$ AT 300MHz



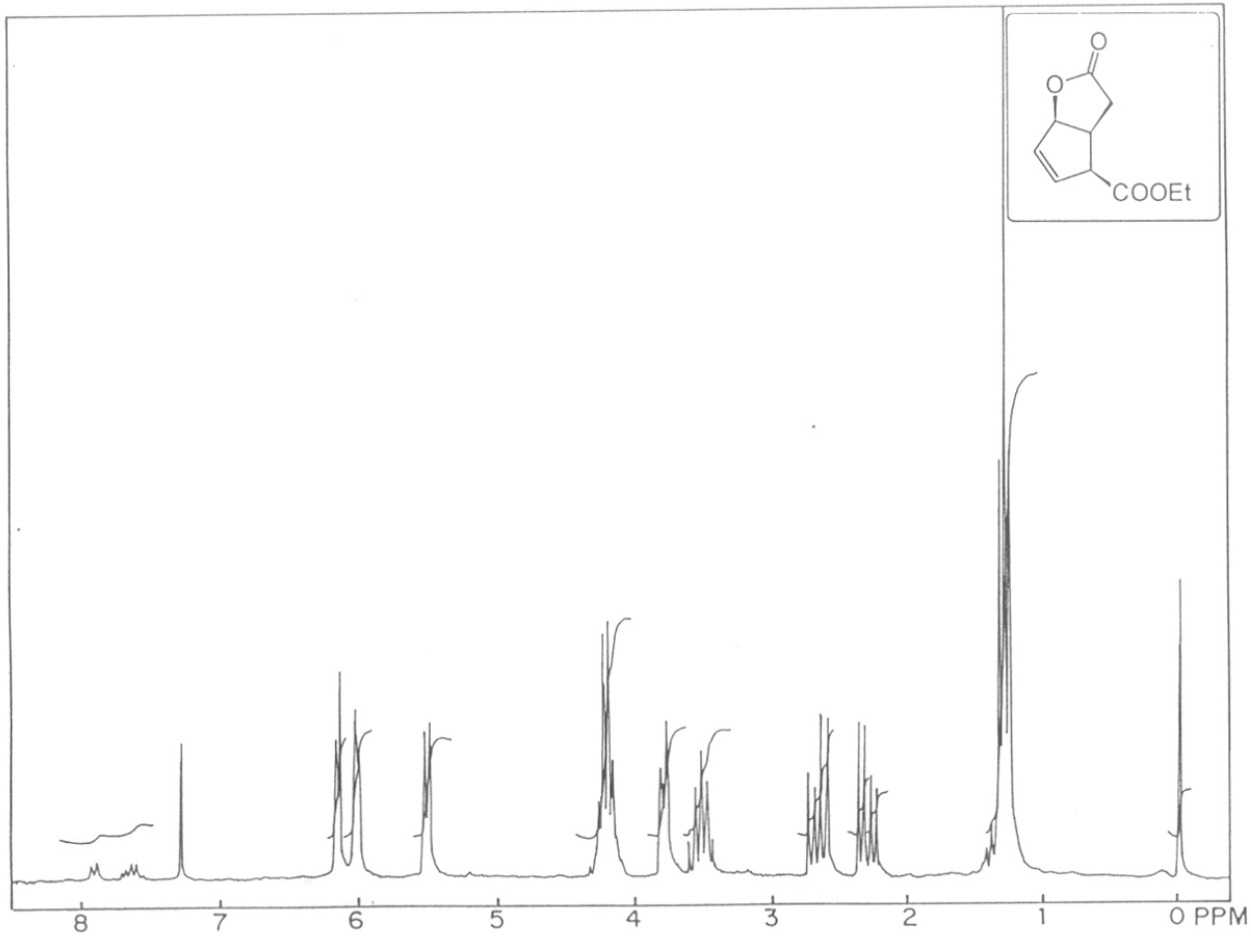
^{13}C-NMR OF COMPOUND **135** IN DMSO-d_6 AT 75 MHz



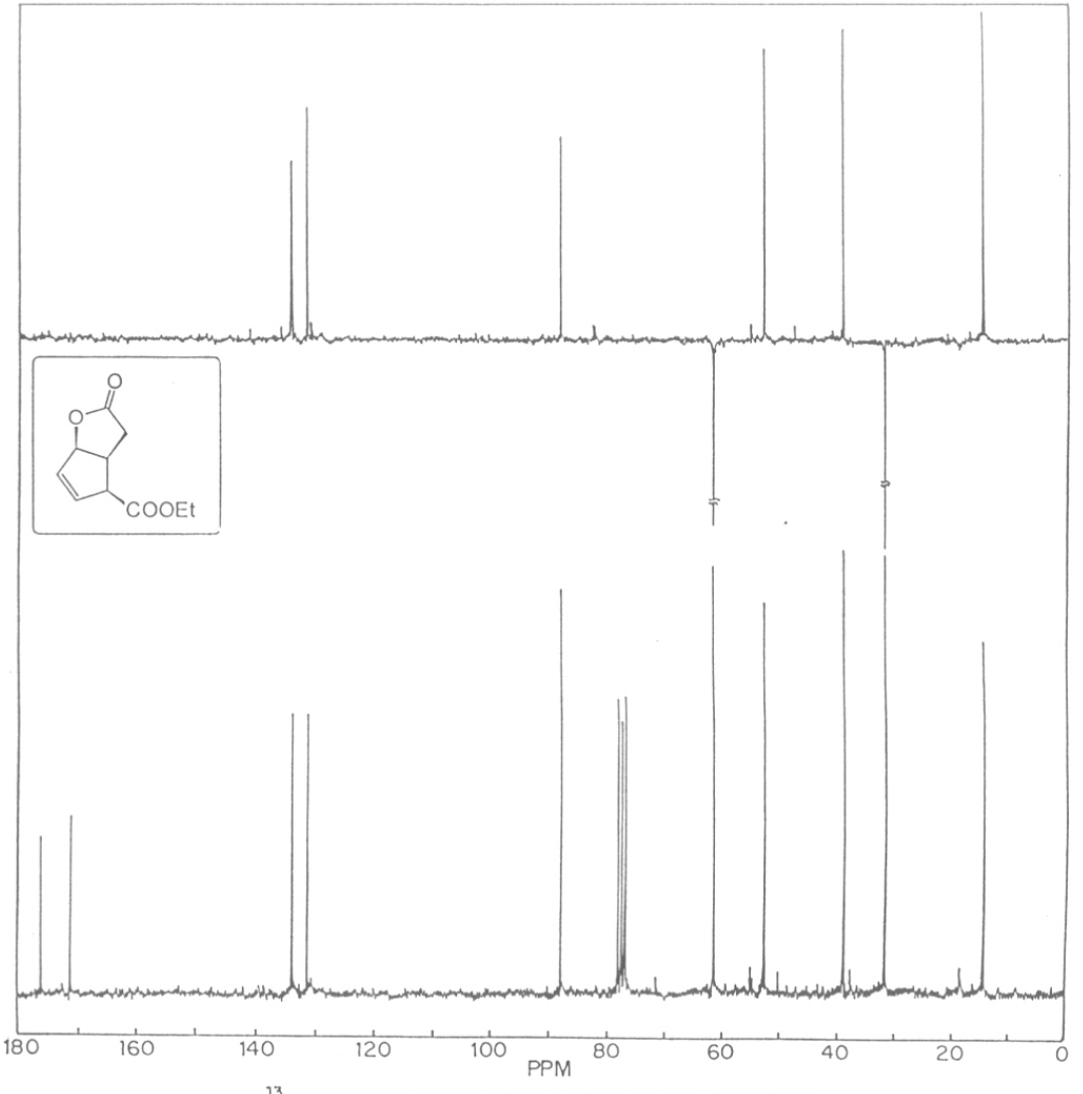
PMR OF COMPOUND **140** IN $CDCl_3$ AT 200 MHz



^{13}C-NMR OF COMPOUND **140** IN $CDCl_3$ AT 50MHz



PMR OF COMPOUND **127** IN $CDCl_3$ AT 200 MHz



^{13}C-NMR OF COMPOUND 127 IN $CDCl_3$ AT 50MHz

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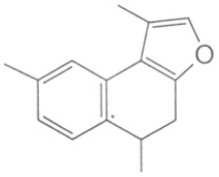
SECTION 3

Total synthesis of (±)Laevigatin

1.3.0 Introduction:

Laevigatin **1**, a sesquiterpene furan was isolated from a flowering specimen of compositae family by two different groups and has been named differently by each. Bohlmann *et al.*[1] isolated it first in the year 1977 from a species called *Chromolaena leavigata* and coined it as **Chromolaenin**. Later on in the year 1978 de Oleviera,[2] Filho *et al.* isolated it from *Eupatorium laevigatum* and reported it as **Laevigatin**.

This novel sesquiterpene **1** contains a furan ring which is not generally encountered in cadinane family and has been mostly referred to as laevigatin as revealed by literature survey. Compound **1** also has been referred to as laevigatin throughout this chapter.



(±) 1

Laevigatin

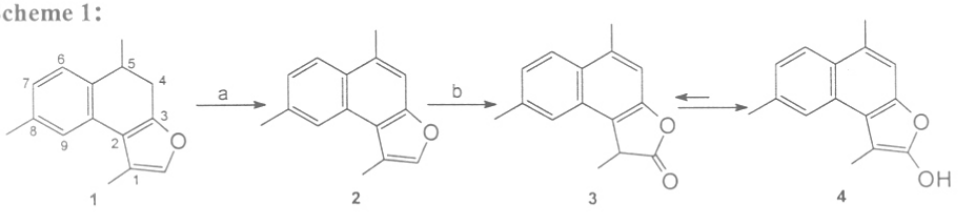
Filho *et al.*[2] determined the structure and stereochemistry of **1** from spectroscopic data and chemical transformations. The optically active (+) Laevigatin crystallized out as a white solid with a m.p. of 65°-66°C, $[\alpha]^{D}_{25} = +88°$.

Molecular formula $C_{15}H_{16}O$ was indicated by high resolution mass spectrometry (M 212.1253 found, M 212.1201 calculated) with IR values at γ^{KBr}_{Max}1623, 1604, 1553, 1500, 1100, 809 cm^{-1} confirming its aromatic nature and absence of hydroxyl and carbonyl groups. The aromatic character was also established by UV absorption at 276, 290, 302 nm, (Σ 6300, 5900, 2300). The ^{1}H NMR spectrum showed two aromatic methyl groups (δ 2.3 and 2.33), a methyl inserted in a secondary carbon atom at δ1.25 (d, J=7.0Hz, 3H), four aromatic protons at δ 6.9-7.4(m) and three benzylic protons δ 2.5–3.3. The ^{13}C NMR revealed three methyl (δ 10.74, 21.56 and 21.56), one methylene (δ 29.97), one non-aromatic (δ 34.57) and four aromatic (δ 123.41, 126.43, 127.13, 138.75) methine resonance's and six quaternary aromatic signals (δ 118.03, 125.00, 128.00, 135.50, 136.00, 153.00).

Dehydrogenation of laevigatin **1** (**Scheme 1**) with DDQ-C_6H_6 at reflux temperature gave furano cadalene **2** which was characterized by its m.p., UV, IR, Mass spectroscopy and by direct comparison with an authentic sample. Oxidation of the furanocadalene with mCPBA yielded the lactone **3**. Structure of **3** was confirmed by IR spectrum with a lactone peak at 1795 cm^{-1}. The signal at δ 7.98 in the ^{1}H NMR of furanocadalene **2** was initially

assigned to the isolated peri-proton at C_9, but it has to be assigned to the α-hydrogen on the furan ring since this signal was clearly absent in the spectrum of the lactone **3**. This lactone in $CDCl_3$ solution is mostly in the enol form **4** as evidenced by the singlet at δ 2.13 due to the methyl on the heterocyclic ring.

Scheme 1:



1 2 3 4

a: DDQ, C_6H_6, Reflux ; **b**: mCPBA, $CHCl_3$

The above chemical transformations and structural data confirmed the structure of laevigatin.

1.3.1 Literature survey:

Very few synthesis of the sesquiterpene laevigatin has been reported so far. In fact only two approaches of Kano's and Herz's have been published so far.

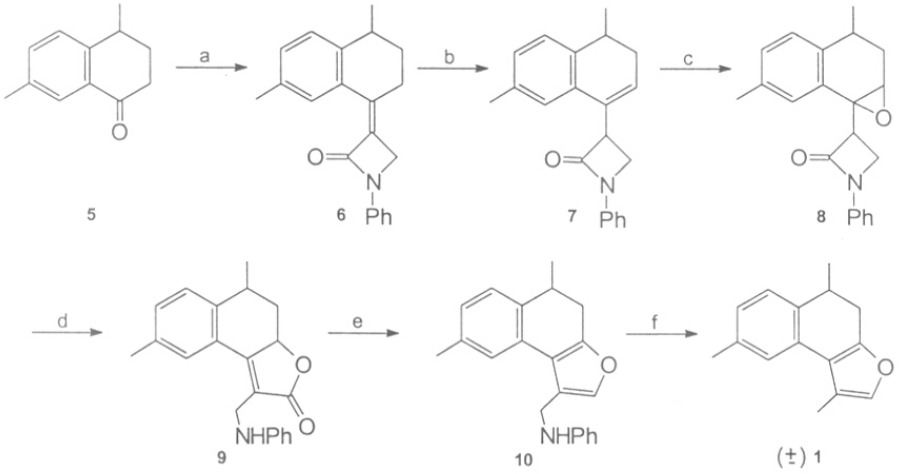
Kano's Approach:

In the year 1980 Kano *et al.*[3] reported the first racemic synthesis of (±) laevigatin employing a new methodology for synthesis of butenolides and their subsequent reduction to furans.

They had effectively utilized the epoxides of 1-benzyl-2-vinyl-azetidin-2-ones to convert to α-anilinomethyl-1,2-butenolides which were further reduced to furans by DIBAL-H (see **Scheme 2**).

Accordingly 1-phenyl, 2-azetidin-2-one was condensed with 4,7-dimethyl tetralone **5** to give the 3-akylidene azetidin-2-one **6,** treatment of which with LDA in THF at 0°C for 40 min. yielded the isomerized product **7** in quantitative yield as a mixture of stereoisomers. Epoxidation of **7** followed by treatment with methanesulfonic acid gave the butenolide **9**. The butenolide **9** was then reduced to the furan **10** with DIBAL-H at -78°C. Finally (±) laevigatin was obtained by hydrogenolysis of **10** with 10% Pd/C in 75% yield. This six step synthesis of (±) laevigatin from **5** proceeds in good yields but requires the use of strong bases and expensive reagents in stochiometric amounts.

Scheme 2 (Kano *et al., Heterocycles*, **1980**, *14*, 43) :

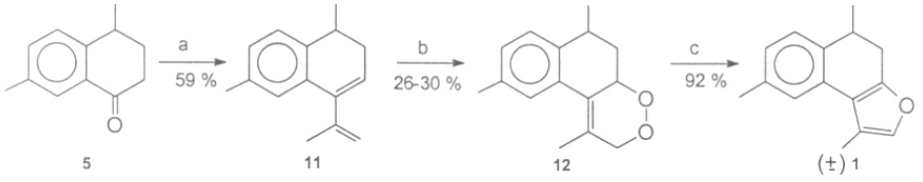


a: LDA, 1-Phenyl-β-lactam; **b**: LDA, THF, 0°C; **c**: mCPBA, CH_2Cl_2, R.T.; **d**: $MeSO_3H$, C_6H_6, Reflux; **e**: DIBAL-H, Toluene, -78°C; **f**: 10% Pd/C, H_2, EtOH, R.T.

Herz's Approach :

Herz *et al.*[4] reported the second racemic synthesis of (±) laevigatin in 1985 employing a new and general approach for synthesis of furans by photo oxygenation of dienes to endoperoxides and to finally furans by treatment with $FeSO_4$.

Scheme 3 (Herz *et al. J. Org. Chem.*, **1985**, *50*, 700) :



a: (**i**). $CH_2=C(CH_3)MgBr$; (**ii**). $POCl_3$, Pyridine; **b**: O_2, Acetone, Rose bengal, -78°C; **c**: $FeSO_4$, THF, R.T.

Thus diene **11** was prepared by addition of isopropenyl magnesium bromide to 4,7 dimethyl tetralone followed by dehydration with $POCl_3$-pyridine in 59% yield. Photoxygenation of diene **11** to the endoperoxide **12** was carried out using rose bengal and oxygen with yields ranging between 26-31%. $FeSO_4$ treatment of endoperoxide **12** yielded (±) laevigatin in 92%yield.

This synthesis though short has the shortcomings of less yields especially in their key photoxygenation step wherein only 26% of the endoperoxide has been isolated.

*After completion of our synthesis of (±) laevigatin (described later in present work), utilizing the same protocol an effective synthesis of enantiospecific (+) laevigatin was successfully carried out by our group[5] as described below.(**scheme 4**).*

Chavan's Approach :

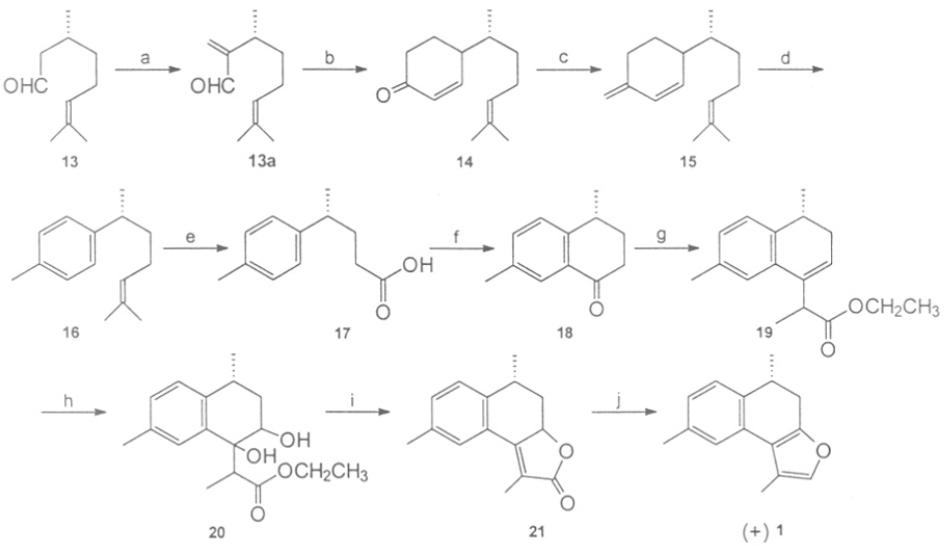
Chavan *et al.*[5] reported the first enatiospecific synthesis of (±) laevigatin starting from optically active tetralone **18** which was obtained from commercially readily available (+) citronellal **13**.

Citronellal **13** was converted to enone **14** followed by a Wittig methylenation to yield triene **15**. The aromatization of triene **15** was achieved by refluxing it in DMF in presence of sulfur to furnish the aromatic compound **16**. One pot oxidative cleavage of the double bond *via* the corresponding diol to acid **17** was achieved followed by cyclisation with triflouro acetic anhydride to yield the enantiomerically pure tetralone **18**.

This chiral tetralone **18** was converted to butenolide **21** by the protocol developed in our laboratory and was further converted to (+) laevigatin **1** in excellent yields.

Thus the first chiral synthesis of (+) laevigatin was achieved from readily available citronellal.

Scheme 4: (Chavan *et al. Tet. Asymm.*, **1997**, *8*, 2517)



a: HCHO, Piperdine acetate, Reflux. **b**: Methyl acetoacetate, MeOH, MeONa, Reflux. **c**: Ph_3PCH_3I, BuLi, THF, 0°C. **d**: Sulfur, DMF, Reflux. **e**: OsO_4(cat), Jones reagent, R.T. **f**: TFA, TFAA, 0°C. **g**: Ethyl bromo propionate, Zn, H^+. **h**: OsO_4, NMO, CH_3CN . **i**: TsOH, C_6H_6, Reflux. **j**: DIBAL-H, THF, -40°C.

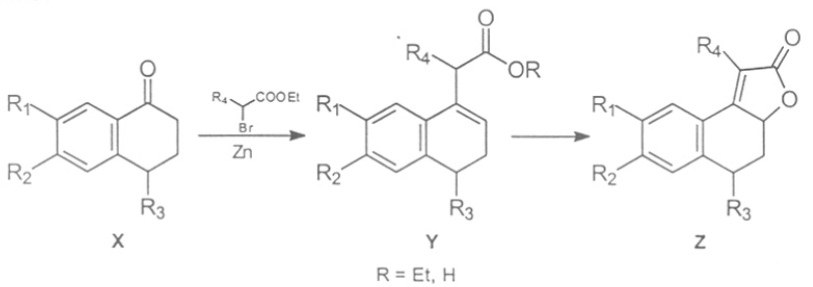
1.3.2 Present Work :

The present section deals with a short and efficient synthesis of (±) laevigatin .

Because of its unusual skeleton and as continuation of our interest in the synthesis of compounds like Heritol,[6] Heritonin and other related compounds which have the same skeletal framework, the synthesis of (±) laevigatin was undertaken.

Two efficient methodologies to generate butenolides *viz.* by osmylation of β,γ-unsaturated esters[7] and direct oxidative conversion of β,γ-unsaturated acids to butenolides by CAN (ceric ammonium nitrate) at room temperature[8] have been developed in our group. The second methodology establishes the role of cheaply available transition metals *viz.* Ce(IV) in effecting one electron oxidation (**Scheme 5**).

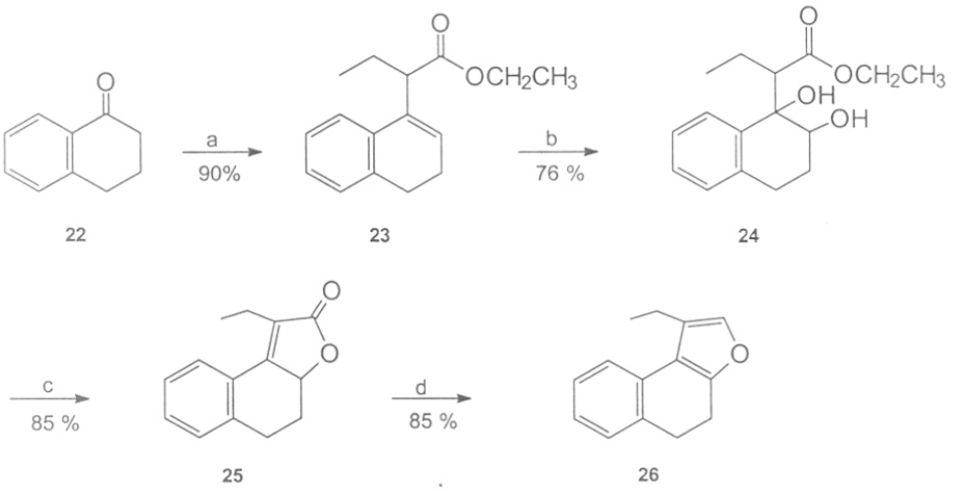
Scheme 5:



An application of the above protocols for the synthesis of butenolides finally led to the synthesis of (±) laevigatin.

Initially a model study was carried out on the easily available α-tetralone. Reformatsky reaction on this tetralone **22** yielded the β,γ-unsaturated ester **23,** which on dihydroxylation followed by pTSA condensation yielded the butenolide **25**. This was further reduced by DIBAL-H in toluene at –78°C to yield the furan **26** in good yields (**Scheme** 6).

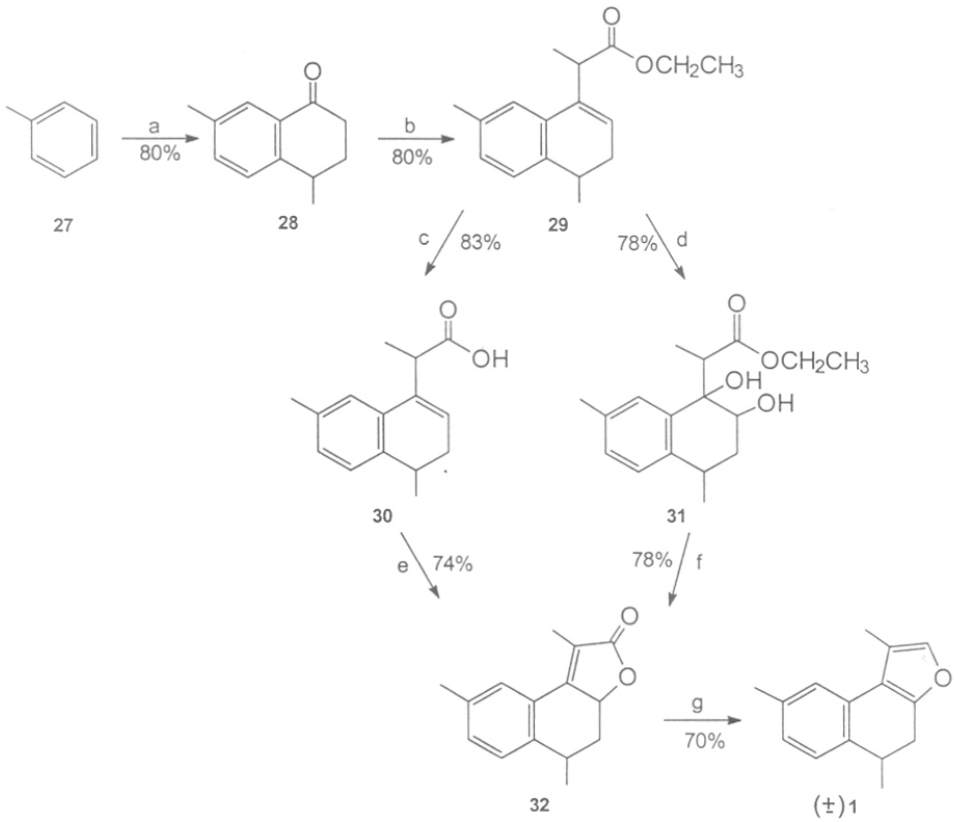
Scheme 6:



a: Ethyl bromobutyrate, Zn, ether. **b**: OsO_4, NMO, $Na_2S_2O_5$, CH_3CN/H_2O. **c**: pTSA, Benzene, Reflux. **d**: DIBAL-H(1eq), Dry Toluene, -78°C.

Having successfully obtained the furan in good yields the same sequence has been carried out on 4,7-dimethyl tetralone **27** which in turn was prepared according to the reported procedure[9] from toluene and γ-valerolactone in four steps and was converted to the butenolide **32** through the two different protocols mentioned earlier to finally yield (±) laevigatin **1** in 70% yield as given below in the **Scheme 7**.

Scheme 7 :



a: γ-Valero lactone, $AlCl_3$, $NO_2C_6H_5$, Reflux. **b**: Ethyl α-Bromo propionate, Zn, Dry ether. **c**: KOH/MeOH, Reflux. **d**: OsO_4, NMO, $Na_2S_2O_5$, CH_3CN/H_2O. **e**: CAN, $NaHCO_3$, CH_3CN, R.T. **f**: pTSA, Benzene, Reflux. g: DIBAL-H(1eq), Dry Toluene, -78°C.

1.3.3 Results and Discussion :

The 4,7-dimethyl tetralone **28** was prepared by a one pot alkylation-acylation reaction with γ-valerolactone in 80% yield.

A Reformatsky reaction[10] with ethyl α-bromo propionate on the 4,7-dimethyl tetralone **28** furnished the corresponding β,γ–unsaturated ester **29** in 80% yield. No trace of β,γ-unsaturated ester could be detected and the structure of this compound was confirmed by IR, ^{1}H NMR and mass spectroscopy. The IR spectrum of **29** showed absorption at 1740 cm^{-1} for the ester carbonyl indicating it to be an isolated ester as against a α,β-unsaturated ester which would absorb at a lower frequency. The ^{1}H NMR revealed a triplet at δ 5.3 (t, 1H) for Ar-CH=C<u>H</u> proton and doublet at δ 1.4 for C<u>H</u>$_3$-CH-COOEt. Mass spectrum confirmed the structure with a M^+ peak at 258.

The ester **29** was then hydrolyzed to the acid[5] **30** with KOH/MeOH the structure of which was confirmed by IR peaks at 2920, 1700, 1610 cm^{-1}. Also ^{1}H NMR revealed the absence of ester grouping. The acid **30** was then converted to the butenolide **32** by using CAN (ceric ammonium nitrate) and $NaHCO_3$ at room temperature in 74% yield. The structure was fully confirmed by IR, ^{1}H NMR and Mass spectroscopy. The IR spectrum displayed a characteristic carbonyl frequency at 1760 cm^{-1} for the presence of butenolide moiety with disappearance of absorption at 1700 cm^{-1}.

Additionally butenolide **32** was also obtained by osmylating the ester **29** to yield the diol[11] **31** in 78% yield. The IR spectrum of diol **31** showed the presence of hydroxyl groups at 3450 cm^{-1} with an absence of olefin proton at δ 5.9 in ^{1}H NMR spectrum. Further confirmation by mass revealed at molecular ion peak at 214 (-H_2O). This diol **31** was treated with catalytic amount of pTSA in refluxing benzene to yield the butenolide **32** in 78% yield. The butenolides obtained were as a mixture of diastereomers. Since the chirality α to oxygen would be destroyed in the subsequent step for the formation of butenolide, no attempt was made to separate the two isomers.

The butenolide **32** was then treated with DIBAL–H (1.2 eq) in toluene[12,13,14] at –78°C to yield the (±) laevigatin **1** in 70% yield. IR spectrum at 1620, 1604, 1553, 1550, 830 cm^{-1} revealed its aromatic character. ^{1}H NMR showed signals at δ2.3, 2.33 of two aromatic methyl groups with disappearance of signal at δ4.9 (ddq, 1H) of methine proton on the carbon bearing lactone oxygen atom. The Mass spectrum exhibited M^+ peak at 212. The spectral data obtained for synthetic (±) laevigatin was found to be identical to those reported for (±) laevigatin obtained from natural sources.[2]

1.3.4 Conclusions:

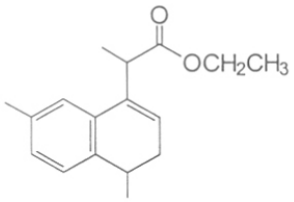
- A short and efficient synthesis of the sesquiterpene furan (±) laevigatin has been achieved in good yield.

- A much better synthesis, than those reported which had serious drawbacks of yields as well as number of steps involved, was obtained.

- An effective utilization of the two protocols for the formation of butenolides was used to achieve this synthesis and the same protocol was instrumental for the first enatiospecific synthesis of (+) laevigatin.

1.3.5 Experimental:

1. Ethyl-2 (4,7-dimethyl-3,4-dihydronaphthalene) propionate (29)[15]:



Ethyl bromopropionate (2.5g, 13.8 mmol) was added slowly to a stirred solution of the 4,7-dimethyl tetralone (2.0g, 11.5 mmol) and zinc (2.25g, 34.5 mmol) in dry ether and a gentle reflux of ether was maintained by addition of a catalytic amount of iodine. The reaction was monitored by TLC and after completion of the reaction (3-6 hrs), the reaction mixture was treated with concentrated HCl (10 ml) and extracted with $CHCl_3$ (3x10 ml). The $CHCl_3$ extracts were successively washed with freshly prepared sodium thiosulphate solution (10ml), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was chromatographed (SiO_2) with pet. ether : ethyl acetate (5%) as an eluent to furnish the β,γ-unsaturated ester as a colorless oil.

Yield : 80%

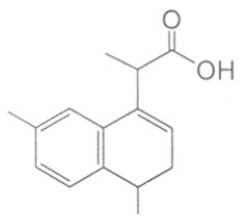
Mol. Formula : $C_{17}H_{22}O_2$ Colorless liquid

IR (neat) cm^{-1} :1740, 1640, 1600, 1510, 1500, 1470, 1460, 1380.

^{1}H NMR (80 MHz) $CDCl_3$ (δ) : 1.17 (d, 3H), 1.19 (t, 3H), 1.40 (d, 3H), 2.15 (m, 2H), 2.30 (s, 3H), 2.70 (m, 1H), 3.60 (m, 1H), 4.00 (q, 2H), 5.80 (t, 1H), 6.80-7.20 (m, 3H).

Mass (m/e) : 258 (M^+), 243 (2), 228 (3), 197 (4), 184 (26), 169 (84), 157 (100), 142 (46), 128 (40), 115 (30), 102 (58), 91 (10), 83 (4), 74 (13), 55 (8).

2. 2-(4,7, dimethyl-3,4-dihydronaphthalene) propionic acid (30)[15]:



To a solution of the ester **29** (2.58g, 10 mmol) in methanol water mixture (3:1) was added solid KOH (1.68g, 30mmol) and the mixture refluxed on a water bath for 3 hrs. When

the reaction was complete (monitored by TLC) the solvent was evaporated under reduced pressure and the residue treated with $NaHCO_3$ solution (10 ml). The aqueous layer was washed with ethyl acetate (5 ml) and then acidified with sulfuric acid and finally extracted with $CHCl_3$ (2x 10ml). The organic extracts were dried over Na_2SO_4 (anhydrous) and evaporated under reduced pressure to yield crude acid **30** which was chromatographed over silica gel with pet. ether : ethyl acetate (20%) as eluent or it can be recrystallized from hot pet. ether : ethyl acetate as white needles.

Yield : 83%

Mol. Formula : $C_{15}H_{17}O_2$ Colorless white solid.

M.P. : 139°-140°C.

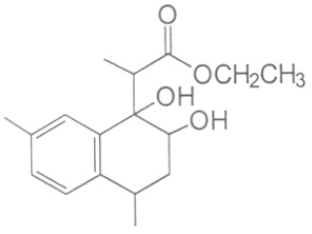
IR ($CHCl_3$) cm^{-1} :2920, 1700, 1610, 1450, 1410.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 1.25 (d, 3H), 1.50 (d, 3H), 2.15 (m, 1H), 2.35 (s, 3H), 2.50 (m, 1H), 2.85 (q, 1H), 3.80 (q, 1H), 5.95 (t, 1H), 7.00-7.05 (m, 2H), 7.20-7.30 (d, 1H).

Mass (m/e) : 230 (M^+, 24), 185(10), 169 (48), 159 (38), 158 (20), 157 (100), 156 (36), 145 (15), 143 (32), 129 (23), 128 (35), 127 (11), 115 (30), 105 (8), 91 (16), 84 (9), 77 (19), 65 (10), 56 (18), 55 (13).

Analysis :	Carbon	Hydrogen
Calculated :	78.23%	7.88%
Found :	78.00%	7.21%

3. **Ethyl 2-(1,2-dihydroxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene) propionate (31)[15]:**



A 20 ml test tube was charged with β,γ-unsaturated ester **29** (1.0g, 4 mmol) and N-methyl morpholine N-oxide (NMO) (0.68g, 6 mmol) in acetonitrile water mixture (9:1, 1ml) and a catalytic amount of osmium tetraoxide (0.005M, 0.1 ml) was injected into it. The reaction was monitored by TLC. After being stirred for 12 hrs at room temperature, the resulting solution was treated with sodium metabisulphite ($Na_2S_2O_8$) and the mixture was

stirred for another half an hour. Then the reaction mixture was filtered, the solid was repeatedly washed with CH_2Cl_2. The combined washings were further treated with 10% HCl (10ml) and dried over anhydrous Na_2SO_4 to afford the diol as a viscous liquid.

Yield : 78%

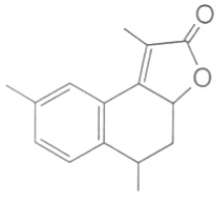
Mol. Formula : $C_{17}H_{24}O_4$ viscous liquid

IR (neat) cm^{-1} :3450, 2950, 1740, 1620, 1510, 1480, 1380, 1340.

^{1}H NMR (90 MHz) $CDCl_3$ (δ) : 1.20 (d, 3H), 1.22 (t, 3H), 1.50 (d, 3H), 2.20 (s, 3H), 1.60-3.30 (m, 4H), 4.10 (m, 3H), 6.80-7.40 (m, 3H).

Mass (m/e) : 292 (M^+), 274 (2), 213 (2), 200 (6), 191 (27), 173 (96), 157 (16), 145 (100), 129 (26), 115 (31), 105 (25), 91 (36), 77 (20), 69 (6), 65 (14), 55 (26).

4. 3,7,10-tri methyl-6,7-dihydro-naphtho-(1,2-b) furan-2 (5H one) (32)[15]:



Procedure A : From the corresponding acid **30**.

To a mixture of CAN (1.09g, 2 mmol) and $NaHCO_3$ (0.17g, 2 mmol) in 20 ml of dry CH_3CN was added the acid **30** (0.230g, 1mmol) during a period of 5min. After completion of the reaction as monitored by TLC, the reaction mixture was filtered through celite and concentrated under reduced pressure to furnish a residue which was chromatographed on silica gel column with pet. ether : ethyl acetate as eluent (9:1) to yield the butenolide **32** in 74% yield.

Procedure B : From the corresponding diol **31**.

A mixture of diol (1g, 3.4 mmol) and p-toluene sulphonic acid (catalytic) in 20ml of dry benzene was refluxed with azeotropic removal of water (using Dean-Stark apparatus). The reaction was monitored by TLC. After 0.5 hrs the reaction mixture was cooled, washed with aqueous $NaHCO_3$, dried (over anhydrous Na_2SO_4) and concentrated under vacuum to yield the butenolide **32** in 78% yield.

Yield : 78%

Mol. Formula : $C_{15}H_{16}O_2$.

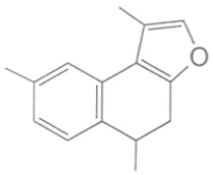
IR (Nujol) cm^{-1} :1760, 1660, 1620, 1500, 1460, 1400, 1360, 1340.

^{1}H NMR (90 MHz) $CDCl_3$ (mixture of diastereomers) (δ) : 1.40 (d, J=4Hz, 3H), 1.80 (m, 1H), 2.10 (d, J=2Hz, 3H), 2.60 (m, 1H), 3.20 (m, 1H), 4.90-5.60 (ddq, J=2, 6, 12Hz, 1H), 7.10 (d, J=8Hz, 1H), 7.20 (d, J=2Hz, 1H), 7.50 (dd, J=2, 8Hz, 1H).

Mass (m/e) : 228 (M^+,100), 213(52), 200 (70), 185 (72), 171 (46), 157 (69), 141 (99), 128 (71), 115 (75), 102 (13), 91 (30), 77 (71), 63 (50).

Analysis :	Carbon	Hydrogen
Calculated :	78.23%	7.88%
Found :	78.00%	7.21%

5. Laevigatin (naphtho-(2,1-b) furan, (4,5-dihydro-1,5,8-trimethyl) (1):



To a solution of butenolide **32** (0.5g, 2.19 mmol) in dry toluene (5ml) was added a DIBAL-H solution (0.3g, 2.19 mmol) with stirring at –78°C. The reaction mixture was stirred for 1hr and quenched at –78°C with MeOH : H_2O mixture (1ml of 1:1). The solvent was then filtered over celite and then evaporated under reduced pressure. The residue was taken up in 10ml of $CHCl_3$ and washed with water and dried over anhydrous Na_2SO_4. The compound was purified by eluting it with pet. ether over silica gel to furnish (±) laevigatin as a liquid.

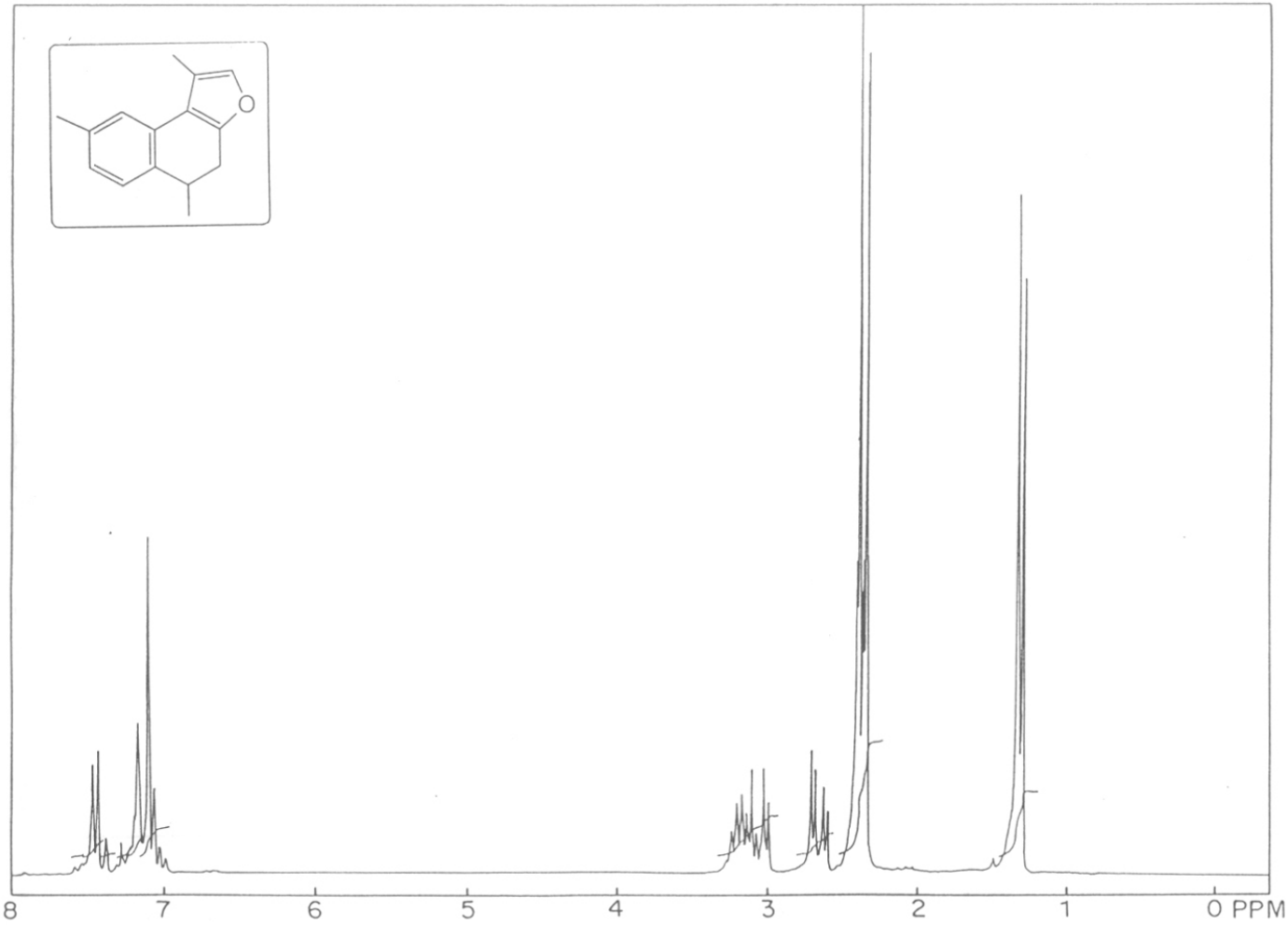
Yield : 70%

Mol. Formula : $C_{15}H_{16}O$ Colorless liquid

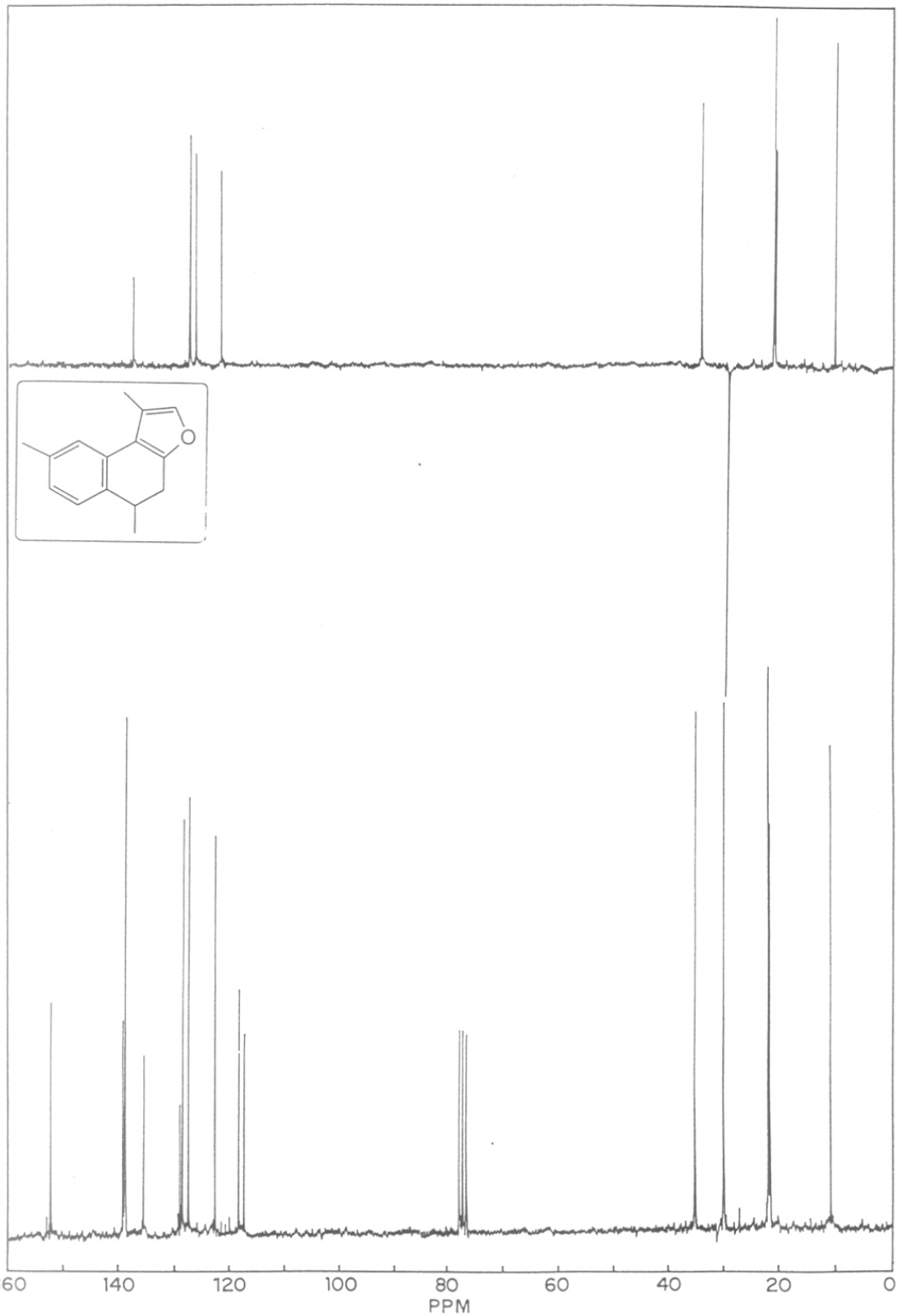
IR (neat) cm^{-1} :1620, 1604, 1553, 1550.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 1.30 (d, J=7.5Hz, 3H), 2.30 (s, 3H), 2.33 (s, 3H), 2.70 (dd, 1H), 3.10 (m, 2H), 7.00-7.50 (m, 3H).

Mass (m/e) : 212 (M^+,100), 197 (80), 182 (26), 169 (33), 154 (15), 153 (14), 152 (13), 140 (10), 130 (9), 120 (9).



PMR OF (±) LAEVIGATIN (1) IN $CDCl_3$ AT 200MHz



^{13}C NMR OF LAEVIGATIN IN $CDCl_3$ AT 50MHz

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CHAPTER II

Development Of Useful Synthetic Methodologies For Organic Transformations

SECTION 1

Azidoalkoxylation of olefins and enol ethers

2.1.0 Introduction:

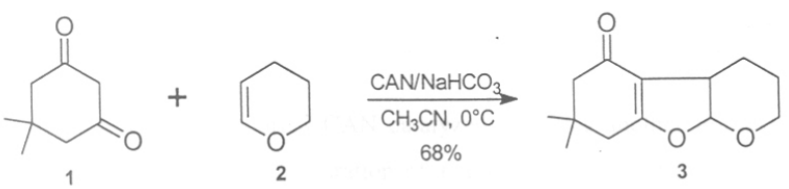
Oxidative generation of Carbon-Carbon centered radicals mediated by metal salts (Mn^{III}, Co^{II}, Cu^{II}, Ag^{I}, Ce^{IV}) is a well established topical area of research[1] since it provides a simple and attractive alternative to ionic reactions in complex carbocyclic ring construction. Among the metal oxidants, Ceric Ammonium Nitrate (CAN)[2] has been extensively utilized for a wide variety of oxidative transformations. As might be expected for very powerful one electron oxidants, the chemistry of Cerium (IV) oxidation is dominated by radical and radical cation chemistry. The fate of these reactive intermediates determined the nature of the oxidation products obtained. These intermediates are capable of undergoing fragmentation, rearrangement, C-H bond cleavage, hydrogen atom transfer or C-C bond cleavage depending on the structure of the starting material chosen.

CAN has been successfully applied for the oxidation of hydroquinones,[3] oxidative demethylation of hydroquinone ethers to quinones,[4] oxidation of alcohols,[5] oxidative cleavage of alkyl/silyl ethers[6] and vicinal diols,[7] oxidative decarboxylation,[8] nitration,[9] chemoselecitve oxidation of sulphides to sulphoxides[10] and oxidation of aromatic side chains[11a,b] to the corresponding aldehydes or ketones. It has also been effectively utilized for protection[11c] and regeneration[11d] of carbonyl compounds as well as deprotection of certain benzyl ethers,[12] benzoate esters[13] and N-protected functionalities.[14] Apart from these it is also used for radical mediated opening of epoxides[15] to give β-nitrato alcohol's and β-halohydrins.

Some of the recent transformations mediated by CAN are briefly described to highlight the potential of this readily available metal as one electron oxidant. More recently CAN is being effectively utilized for the cross coupling of silyl enol ethers to give dicarbonyl compounds,[16] addition of carbonyl compounds to enol ethers,[17] enolacetates[18] and dienes[19] to give 1,4-dicarbonyl compounds.

Roy *et al.*[20] reported formation of fused acetals by cyclo addition of 1,3-dicarbonyl compounds to cyclic enol ethers (**Scheme 1**).

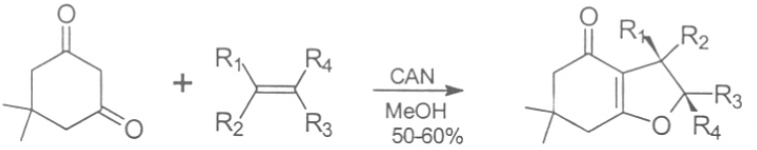
Scheme 1:



1 2 3

Nair *et al.*[21] in 1995 reported the synthesis of dihydrofurans by addition of 1,3-diketones to acyclic and cyclic alkenes (**Scheme 2**).

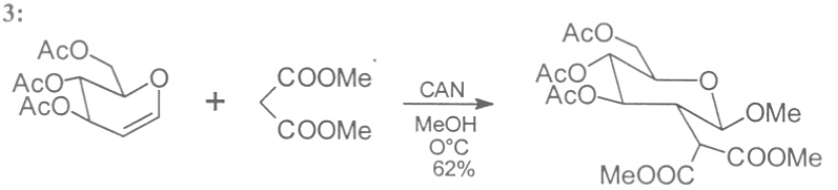
Scheme 2:



1 4 5

Linker *et al.*[22] reported the radical reaction of dimethyl malonate catalyzed by CAN as an efficient entry to 2-carbon analogues of D-glucose (**Scheme 3**).

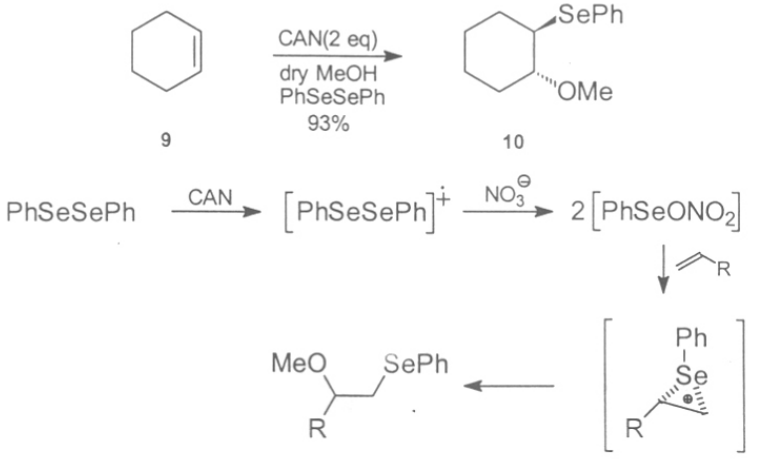
Scheme 3:



6 7 8

Another interesting report by Annibale *et al.*[23] demonstrated the versatility of CAN wherein alkenes were reacted with diphenyl diselenide in methanol to furnish β-methoxy alkyl phenyl selenides in good yields (**Scheme 4**).

Scheme 4:



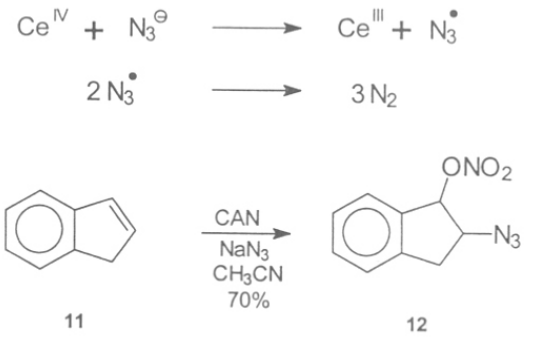
9 10

Apart from these reported CAN catalyzed reactions another important application which is of interest is that of preparation of azidonitrates wherein an addition of NaN_3 to

activated or unactivated olefins has been studied in detail. The direct introduction of azido group to organic compounds is generally accomplished by nucleophilic substitution of activated halides with sodium azide[24] or addition of sodium azide to epoxides,[25] which involved poisonous mercury salts or harsh conditions. Since these organic azides or useful as versatile substrates for the preparation of amines and nitrogen containing heterocycles, a direct introduction of azide group adjacent to a carbonyl moiety under mild conditions could prove to be a great asset in organic transformations. Some of the efforts to introduce azide moiety on to the double bond (activated and unactivated) are described below

The formation of azidonitrates by reaction of olefins with sodium azide in the presence of CAN was first reported by Trahnovsky *et al.*[26] Although it had been known for some time that ceric salts oxidize metallic azides to nitrogen, the azido radicals has been suggested as an intermediate and it was subsequently proved by them by trapping the azido radicals with the presence of olefin. (**Scheme 5**).

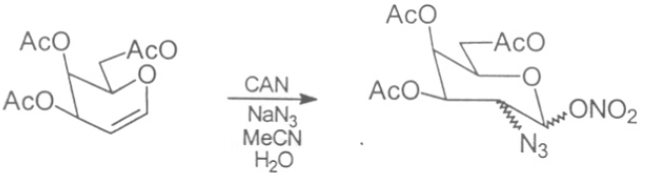
Scheme 5:



11 12

After Trahnovsky, in 1979 Lemieux and Radcliffe[27] described an extension of this azido nitration procedure to enol ethers of carbohydrate substrates (**Scheme 6**).

Scheme 6:

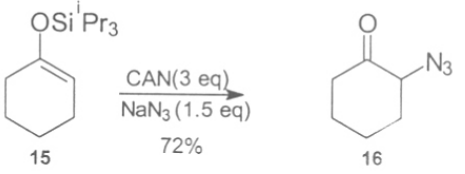


13 14

In 1990 Vogel[28] described the formation of an α-azido ketone from oxidative azidation of a *tert*-butyl dimethyl silyl enol ether. However the yields were less than 50%. In

1992 Magnus *et al.*[29] employed triisopropyl silyl enol ethers for the oxidative azidation which provided a direct method for the synthesis of α-azido ketones (**Scheme 7**).

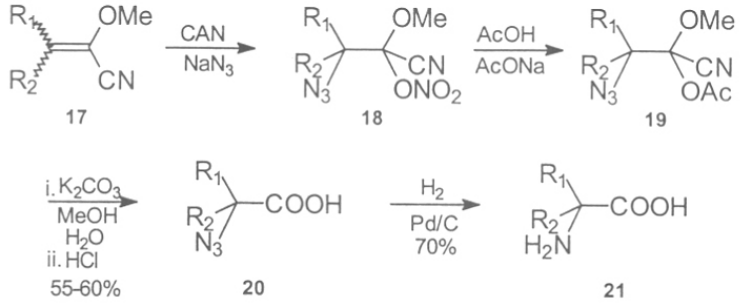
Scheme 7:



15 16

Clive and Etkin[30] reported the synthesis of 2-amino acids by addition of azido radicals to 2-methoxy acrylonitriles. The formation of azidonitrates by reaction of olefins with sodium azide has been elegantly utilized in this scheme for the construction of amino acids (**Scheme 8**).

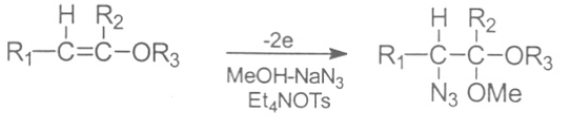
Scheme 8:



17 18 19 20 21

Nishiguchi *et al.*[31] reported a regioselective azidomethoxylation of enol ethers through anodic oxidation in methanol containing sodium azide and Et_4NOTs to give the corresponding acetals of α-azido carbonyl compounds in good yields (**Scheme 9**).

Scheme 9:



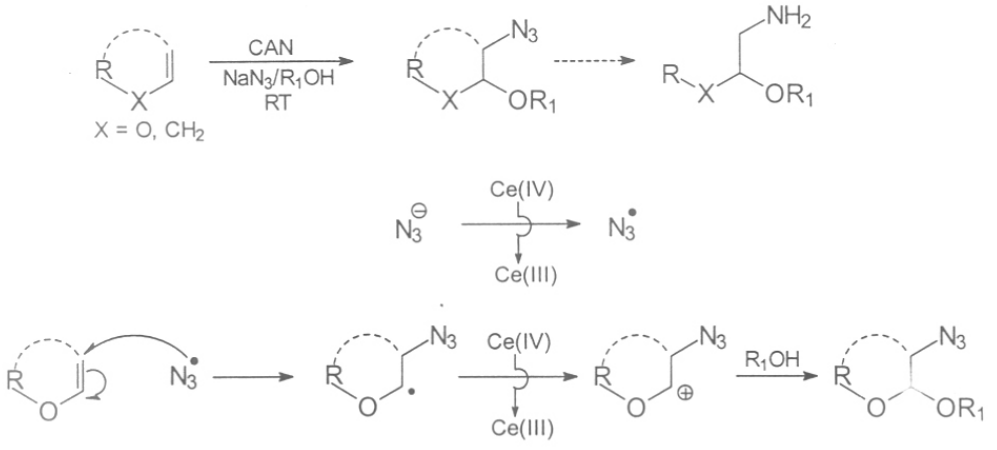
22 23

Although a variety of transformations were tried with sodium azide with CAN and alcohol with CAN, a combination of these two to yield azidoalkoxylated products has not been reported so far. In fact the only other report is that of azidomethoxylation by Nishiguchi *et al.* through anodic oxidation.

2.1.1 Present Work:

Literature survey revealed that azidoalkoxylation is a novel reaction with the only report being that of a anodic oxidation in methanol containing sodium azide and Et_4NOTs to give the corresponding acetals of a α-azidocarbonyl compounds.

Scheme:



In this present scheme, a simple route to azidoalkoxylation of olefin with Ceric Ammonium Nitrate (CAN) and sodium azide along with an alcohol as the nucleophile at room temperature was proposed to furnish the azidoalkoxy compounds in good yields.

It was also decided to screen various olefins as well as enol ethers in the present study in order to establish the synthetic utility to this methodology. This electrochemical reaction allows the azido carbonyls to be obtained in the protected form. These serve as important synthons in synthetic organic chemistry. Additionally these acetals can be readily unmasked to the corresponding carbonyl compounds.

If successful this would be advantageous over the earlier reported methods which involve the use of trialkyl silyl enol ether which are expensive and not readily available.

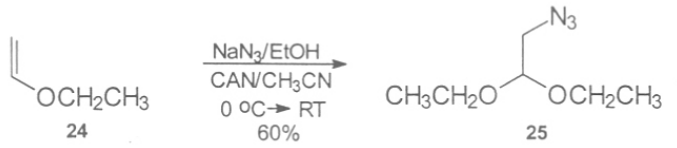
2.1.2 Results and Discussion:

A variety of olefins and enol ethers were treated with alcohols in the presence of CAN and sodium azide to yield the azidoalkoxylated products in good to moderate yields.

In a typical azidoalkoxylation, a mixture of 1 eq. of ethyl vinyl ether and 1 eq. of NaN_3 was taken in dry acetonitrile to which was added 5eq of ethanol and then ceric ammonium nitrate (2eq) in acetonitrile was added at 0°C and the reaction mixture was

brought to room temperature and left overnight to furnish the acetal **25** in 60% yield.(see **Scheme 11**). After few experimentation it soon became evident that this particular sequence of addition is critical for the success of the reaction.

Scheme 11:



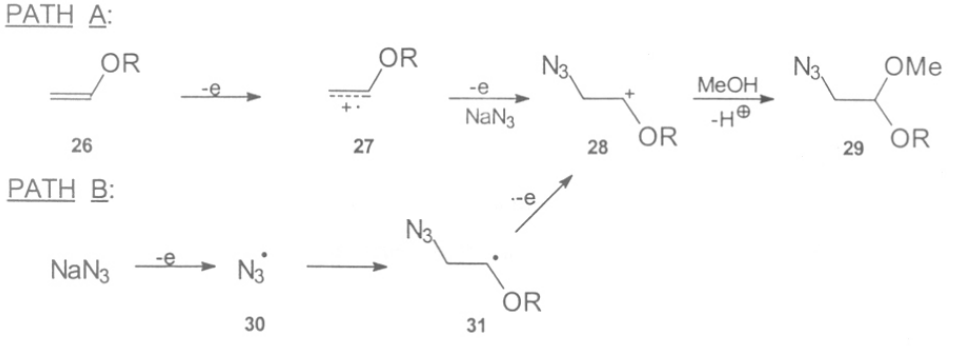
A reversal of addition in the sequence of addition of reagents failed to furnish the desired product.

The product isolated by chromatography was characterized by ^{1}H NMR, IR, Mass and Microanalysis. IR spectrum confirmed the incorporation of azide group by revealing peak at 2100 cm^{-1}. ^{1}H NMR indicated the disappearance of olefinic protons and presence of a triplet at δ4.63 corresponding to the proton adjacent to the acetal group. The other two protons adjacent to the azide group appeared at δ3.24 as a doublet. Presence of two quartets at δ3.78 and δ3.57 corresponding to the two ethoxy groups confirmed the incorporation of ethanolic moiety. Mass spectroscopy indicated a (M-45) peak at 114. ^{13}C also confirmed the presence of three methylene carbons, two of which appeared at 63 and other at 52.

Encouraged by the success of the reaction other activated and unactivated olefins were subjected to these reaction conditions. All these azidoalkoxylation reactions proceeded smoothly to afford the corresponding acetals and it was noteworthy that the addition of an azido group took place regioselectively according to Markonikov rule.

Scheme 12 depicts the two plausible paths A and B as for the formation of products.

Scheme 12:



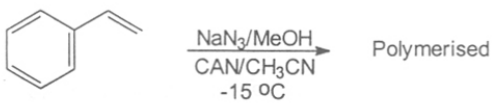
In the reaction path A enol ethers are initially subjected to one electron transfer to generate a radical cation **27**. Nucleophilic addition of azide anion to **27** followed by the second single electron oxidation gave the corresponding cation **28** which was subjected to nucleophilic attack of alcohol to afford the final product **29**. Pathway B shows the first one electron oxidation of an azide anion to an azido radical **30**. Addition of **30** to enol ether **26** followed by the second one electron oxidation of **31** provides the same cation **28** as that shown in Path B.

It was shown by Nishiguchi *et al.*[31] through measurement of oxidation potential that sodium azide was electrochemically much easier to oxidize than the olefin and their results distinctly indicated the formation and subsequent addition of an azide radical **30** to the enol ether **26** (Path B). They also explained the regioselectivity of the reaction. It is believed that a similar mechanism is operative during the electron transfer with CAN.

These azidoalkoxy reactions were also carried out on different olefins and enol ethers and the results have been summarized in the table 1.

α-Methyl styrene gave excellent yields, however when the reaction was carried out on styrene (**32**), a polymerized product was obtained even at low temperatures (**Scheme 13**).

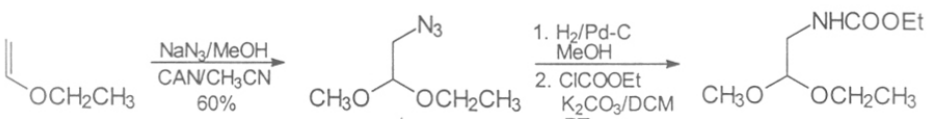
Scheme 13:



32

This reaction could prove to be a very useful synthetic procedure for the preparation of amino acetals as indicated in **Scheme 14**.

Scheme 14:



24 **33** **34**

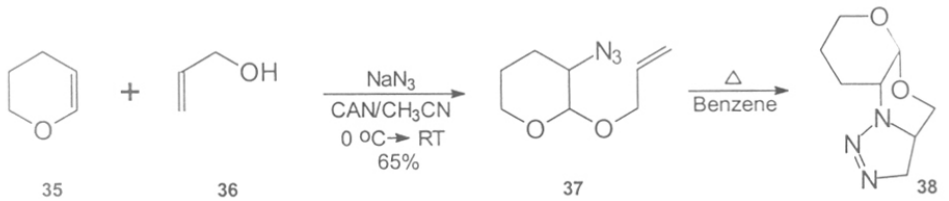
The product obtained on azidomethoxylation of ethyl vinyl ether (**33**) was volatile hence it was immediately reduced to the corresponding amine with H_2/Pd-C in 70% yield which without purification was converted to the amide **34** with ethyl chloroformate and potassium carbonate in good yields.

The amide obtained showed the characteristic IR peaks at 3300 cm^{-1} and 1700 cm^{-1} corresponding to the NH stretching and amide carbonyl respectively. ^1H NMR indicated the presence of another quartet at δ4.03 apart from the methoxy at δ3.3 and the quartet at δ3.59 corresponding to the $OC\underline{H}_2CH_3$ of the enol ether. Mass spectrum of compound **34** indicated the presence of a peak at 160 corresponding to M-31. ^{13}C NMR confirmed the presence of three methylenic carbons at 43, 60 and 62.9 and three methyl groups at 14.6, 15.3 and 54.1.

The noteworthy feature of this transformation is mixed acetals a can be readily obtained in synthetically useful yields. Thus this method to provide one of the easiest routes for the synthesis of amino acetals which are important reagents for isoquinoline preparation. These amino acetals have been effectively utilized in Pomeranz-Fritsch[32] synthesis.

It was also found that the substitution of methanol with any other alcohol especially allyl alcohol has also been tolerated as was tried out on DHP (**Scheme 15**).

Scheme 15:

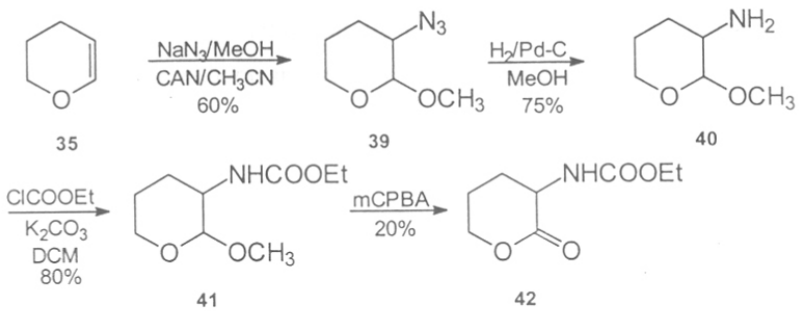


35 36 37 38

This product **37** on refluxing in benzene for 12 hr gave an unstable 1,3-dipolar cyclo adduct and was tentatively assigned the structure **38** which showed in NMR that disappearance of allylic moiety. IR showed the absence of azide peak at 2100 cm^{-1}. Literature survey revealed the instability of similar compounds.[33]

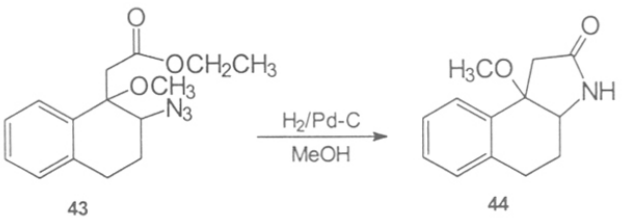
The 3-azido-2-methoxy tetrahydropyran **39** was also subjected to a similar sequence of reactions as depicted in **Scheme 14** in order to obtain the amide **41** which could be further oxidized to the corresponding valero lactone. However an mCPBA oxidation gave the product **42** in very low yields (~20%) (**Scheme 16**).

Scheme 16:



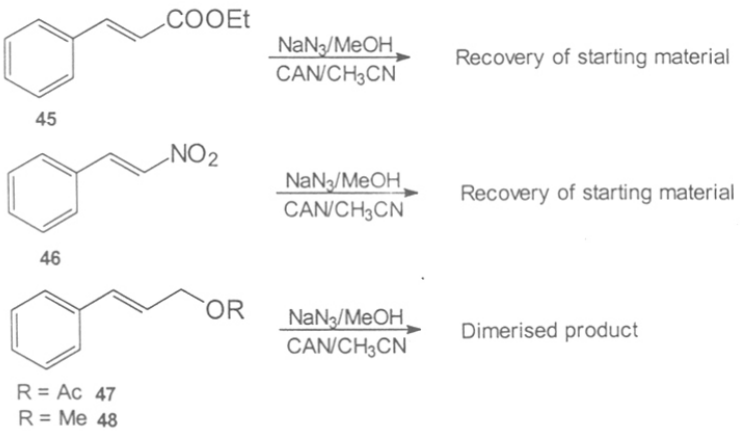
Another important observation was in the case of β,γ-unsaturated esters wherein when the ester was subjected to a H_2/Pd-C reduction, a cyclised product **44** was obtained which showed the absence of ethyl moiety in ^{1}H NMR and IR spectrum showed the presence of NH stretching at 3300 along with a peak at 1700 cm^{-1} corresponding to the amide carbonyl. Also an absence of azide peak 2100 cm^{-1} confirmed the cyclisation. This sequence could be applied to form nitrogen containing rings (**Scheme 18**).

Scheme 18:

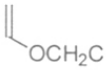
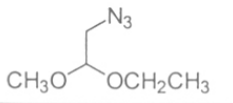
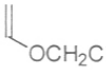
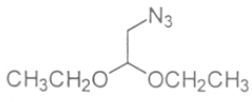
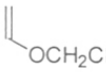
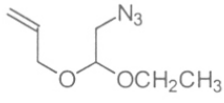
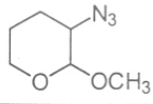
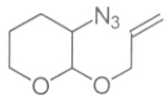
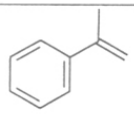
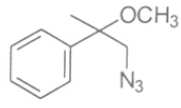
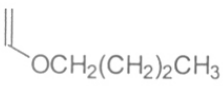
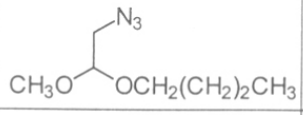
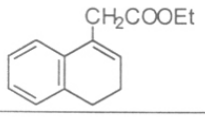
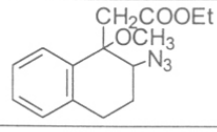
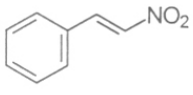
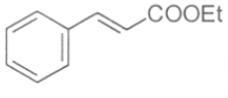


However these alkoxylation reactions did not proceed on electron deficient olefins *viz* α,β-unsaturated esters and also on nitrostyrenes (**Scheme 19**).

Scheme 19:



Therefore it was concluded that these azidoalkoxylation reactions proceed well with activated enol ethers and certain olefins but are very selective. However certain aromatic olefins possessing electron withdrawing groups *viz* COOEt, NO_2 failed to react whereas cinnamyl alcohol and its acetate furnished a product which was not expected but tentatively assigned a dimeric structure.

S.No.	Substrate	Alcohol	Product	Yield (%)
1.		Methyl		60
2.		Ethyl		60
3.		Allyl		55
4.		Methyl		65
5.		Allyl		65
6.		Methyl		90
7.		Methyl		77
8.		Methyl		80
9.		Methyl	--	--
10.		Methyl	--	--

2.1.3 Conclusions:

- Azidoalkoxylation utilizing CAN, NaN_3 and appropriate alcohol in single pot reaction is the first report of its kind to yield the azido alkoxylated products in moderate to good yields.

- It provides one of the easiest routes for the synthesis of amino acetals, which are important reagents for the synthesis of isoquinolines as well as other heterocycles.

- This methodology could also used for building rings containing the nitrogen moiety.

- Mixed azido acetals can also be readily obtained.

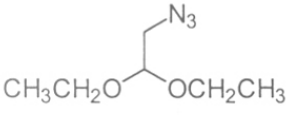
This methodology worked well for (*i.e.*, electron rich) olefins but failed for electron deficient olefins.

2.1.4 Experimental:

General Procedure:

Sodium azide (1 mmol) was taken in 10 ml of acetonitrile in a two necked round bottomed flask under argon and to it was added the olefin/enol ether (1 mmol). The reaction mixture was cooled to 0°C and alcohol (5 mmol) was added to it followed by CAN (2 mmol) which was dissolved in 10 ml acetonitrile. After addition of CAN the color slowly disappeared and the colorless reaction mixture was stirred over night. The reaction mixture was then concentrated under reduced pressure and the residue was washed with water and extracted with dichloromethane. The organic extracts were concentrated and chromatographed over silica gel with 5% ethyl acetate : pet. ether as eluent to yield the corresponding azido ethers.

1. **2-Azido-1,1-diethoxy ethane:**



Yield : 60%

Mol. Formula : $C_6H_{13}N_3O_2$ volatile liquid

IR (neat) : 2090, 1400, 1380, 1235 cm^{-1}.

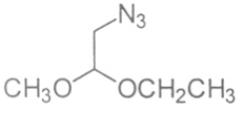
^{1}**H NMR** (200 MHz) $CDCl_3$: δ 1.23 (t, 6H); 3.24 (d, 2H); 3.57 (q, 2H); 3.78 (q, 2H) 4.63 (t, 1H).

^{13}**C NMR** (50MHz) $CDCl_3$: 15.3(q), 52.6(t), 63.1(t), 101.6(d).

Mass (m/e) :114(M-45, 20), 104(7), 103(100), 100(5), 89(4).

Analysis :	Carbon	Hydrogen	Nitrogen
Calculated :	45.27%	8.23%	26.4%
Found :	44.89%	8.10%	26.0%

2. **2-Azido-1-ethoxy-1-methoxy ethane:**



Yield : 60%

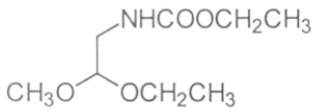
Mol. Formula : $C_5H_{11}N_3O_2$ volatile liquid

IR (neat) : 2900, 2100, 1440, 1280 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.30 (t, 3H); 3.22 (d, 2H); 3.4 (s, 3H), 3.69 (m, 2H); 4.60 (t, 1H).

^{13}C NMR (50MHz) $CDCl_3$: 15.0(q), 51.9(t), 53.8(q), 63.0(t), 102.1(d).

3. **Ethyl N-(2-ethoxy-2-methoxyethyl)carbamate:**



Yield : 80%

Mol. Formula : $C_8H_{17}NO_4$

IR (neat) : 3350, 2900, 1690, 1520, 1250 cm^{-1}.

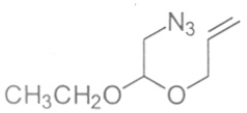
^{1}H NMR (200 MHz) $CDCl_3$: δ 1.15 (t, 6H); 3.22 (dd, 2H); 3.3 (s, 3H), 3.59 (m, 2H); 4.03 (q, 2H) 4.37 (t, 1H), 5.13 (bs, NH).

^{13}C NMR (50MHz) $CDCl_3$: 14.6(q), 15.3(q), 43.0(t), 54.1(q), 60.9(t), 62.9(t), 102.0(d), 156.8(s).

Mass (m/e) :160(M-31, 5), 146(13), 118(5), 117(9), 99(17), 89(100), 86(12), 75(24), 61(75), 58(9).

Analysis :	Carbon	Hydrogen	Nitrogen
Calculated :	50.24%	8.96%	7.32%
Found :	50.10%	8.60%	7.21%

4. **Allyl 2-Azido-1-ethoxy ethyl ether:**



Yield : 55%

Mol. Formula : $C_7H_{13}N_3O_2$ colorless liquid

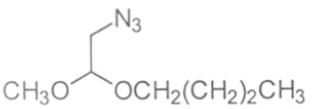
IR (neat) : 2900, 2080, 1430, 1250, 1120 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 1.25 (t, 3H); 3.29 (d, 2H); 3.6 (m, 2H), 4.13 (m, 2H); 4.65 (t, 1H) 5.29 (m, 2H), 5.93 (m, 1H).

^{13}C NMR (50MHz) $CDCl_3$: 15.2(q), 52.5(t), 62.9(t), 67.9(t), 100.9(d), 117.1(t), 134.5(d).

Mass (m/e) :126(M-45, 3), 115(2), 102(6), 101(6), 98(2), 84(5), 83(9), 72(4), 71(56), 69(77), 68(100), 61(64), 56(10), 55(10), 54(11).

5. **2-Azido-1-butoxy-1-methoxy ethane:**



Yield : 77%.

Mol. Formula : $C_7H_{15}N_3O_2$ colorless liquid

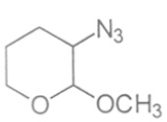
IR (neat) : 2800, 2080, 1430, 1250.cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 0.86 (t, 3H); 1.34 (m, 2H), 1.6 (m, 2H), 3.12 (d, 2H); 3.4 (s, 3H), 3.57 (m, 2H), 4.52 (t, 1H).

^{13}C NMR (50MHz) $CDCl_3$: 13.5(q), 19.2(t), 31.7(t), 51.9(t), 53.3(q), 67.2(t), 102.3(d).

Mass (m/e) :142(M-31, 6), 128(8), 117(6), 87(6), 72(13), 61(100), 57(66).

6. **3-Azido tetrahydro-2H-pyran-2-yl methyl ether:**



Yield : 65%

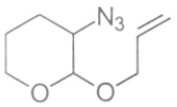
Mol. Formula : $C_6H_{11}N_3O_2$ colorless liquid

IR (neat) : 2900, 2100, 1430, 1250 1150 cm^{-1}.

^{1}H NMR (200 MHz) $CDCl_3$: δ 2.1-1.65 (m; 4H); 3.25-3.1 (m, 1H), 3.6-3.4 (m, 4H), 3.8-3.65 (m, 1H), 4.65 (d, 1H).

Mass (m/e) :126(M-31, 4), 115(3), 101(5), 83(5), 71(42), 69(80), 68(99), 61(100), 55(16).

7. **2-(Allyloxy)-3-azidotetrahydro-2H-pyran:**



Yield : 65%

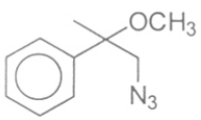
Mol. Formula : $C_8H_{13}N_3O_2$ colorless liquid

IR (neat) : 2900, 2100, 1727, 1632, 1259, 1133, 1076 cm^{-1}.

^{1}**H NMR** (200 MHz) $CDCl_3$: δ 2.15-1.45 (m, 4H); 3.6-3.38 (m, 1H), 4.15-3.85 (m, 3H), 4.25 (m, 1H), 4.63 (m, 1H), 5.42-5.1 (m, 2H), 5.97 (m, 1H).

Mass (m/e) :126(M-57, 1), 110(6), 101(10), 85(93), 82(39), 71(35), 68(100), 67(41), 55(68).

8. **1-(2-Azido-1-methoxy-1-methyl ethyl)benzene:**



Yield : 90%

Mol. Formula : $C_{10}H_{16}N_3O$ colorless liquid

IR (neat) : 2980, 2080, 1450, 1380, 1300 cm^{-1}.

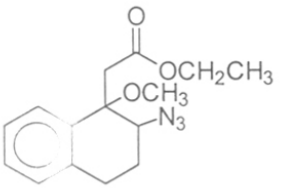
^{1}**H NMR** (200 MHz) $CDCl_3$: δ 1.7 (s, 3H); 3.15 (s, 3H); 3.19 (d, J=12Hz, 1H), 3.46 (d, J=12Hz, 1H); 7.39 (m, 5H).

^{13}**C NMR** (50MHz) $CDCl_3$: 19.9(q), 50.3(q), 61.4(t), 79.3(s), 126.1(d), 127.5(d), 128.2(d), 141.7(s).

Mass (m/e) :135(M-56, 100), 118(39), 117(15), 104(14), 91(4), 77(37).

Analysis :	Carbon	Hydrogen	Nitrogen
Calculated :	62.80%	6.85%	21.97%
Found :	62.54%	6.59%	21.05%

9. Ethyl 2-(2-azido-1-methoxy-1,2,3,4-tetrahydro-1-naphthalenyl)acetate:



Yield : 80%

Mol. Formula : $C_{15}H_{19}N_3O_3$ pale yellow liquid

IR (neat) : 2936, 2102, 1731, 1453, 1264, 1072, 762 cm^{-1}.

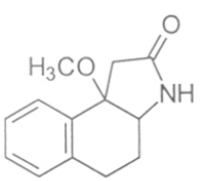
^1H **NMR** (200 MHz) $CDCl_3$: δ 1.15 (t, 3H); 2.04 (m, 1H), 2.25 (m, 1H) 2.92 (dd, 2H), 2.95 (m, 2H); 3.1 (s, 3H), 4.06 (q, 2H), 4.25 (dd, 1H), 7.4-7.1 (m, 4H).

^{13}C **NMR** (50MHz) $CDCl_3$: 14.0(q), 24.3(t), 26.8(t), 41.5(t), 50.6(q), 60.(d), 60.4(t), 79.5(s), 125.8(d), 127.1(d), 128.2(d), 129.1(d), 134.7(s), 136.7(s), 170.1(s).

Mass (m/e) : 261(M-28, 2), 246(4), 230(16), 214(8), 200(6), 184(10), 173(18), 157(16), 147(100), 130(44), 115(22), 103(15), 90(14), 83(6), 77(10), 64(3).

Analysis :	Carbon	Hydrogen	Nitrogen
Calculated :	62.26%	6.62%	14.52%
Found :	62.43%	6.48%	14.01%

10. 9b-Methoxy-1,3,3a,4,5,9b-hexahydro-2-H-benzo[e]indol-2-one:

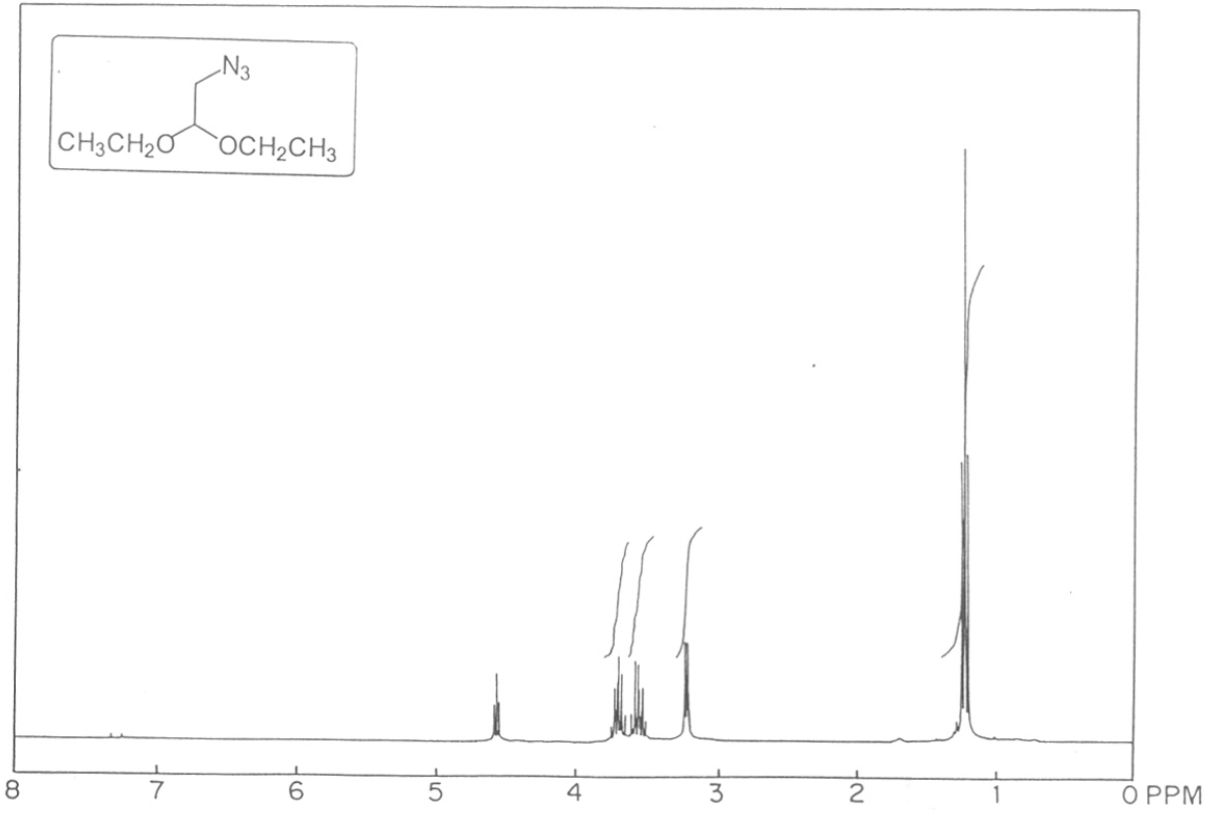


Yield : 70%

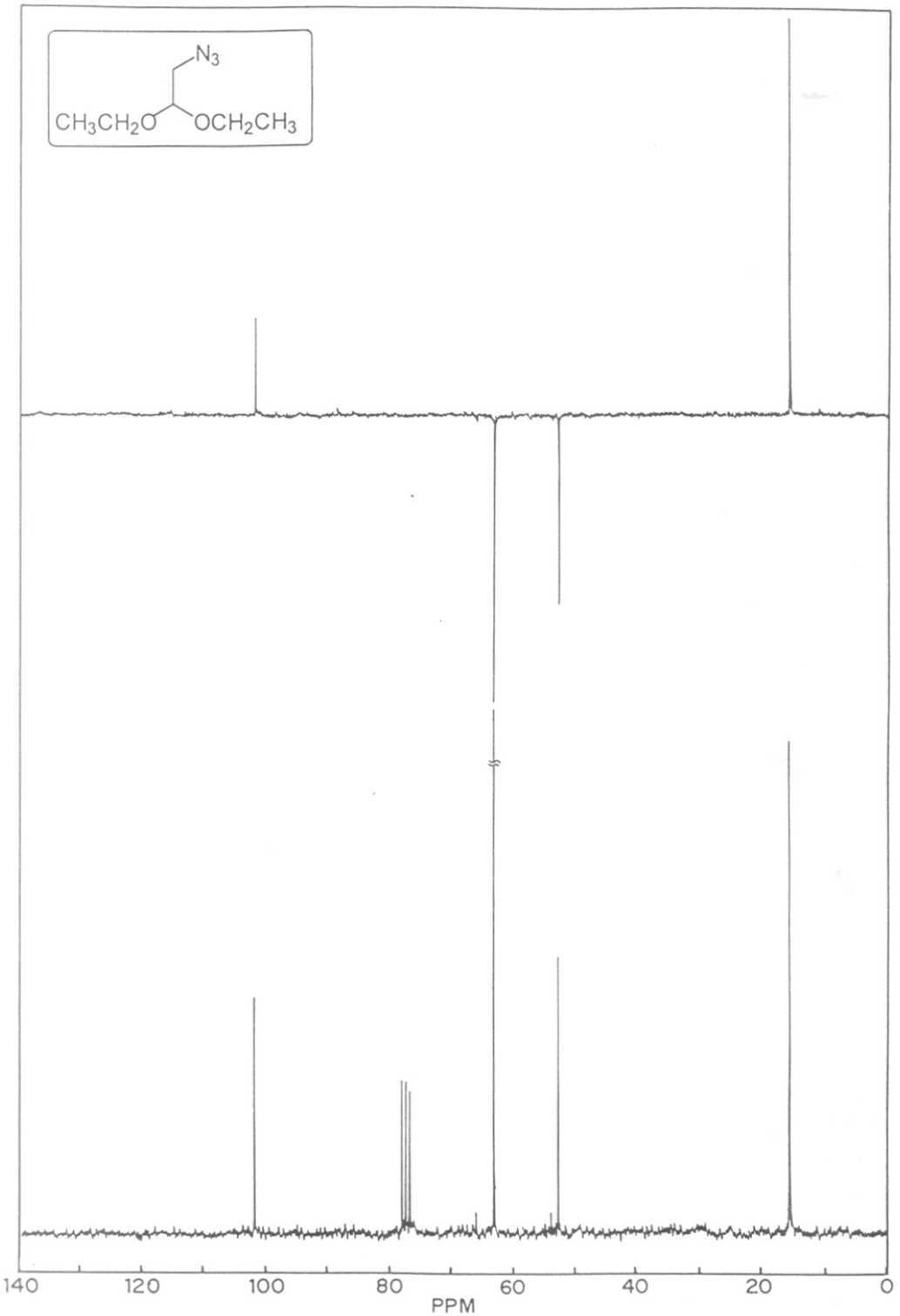
Mol. Formula : $C_{13}H_{15}NO_2$ colorless solid

IR (neat) : 3320, 2900, 1700, 1520, 1264 cm^{-1}.

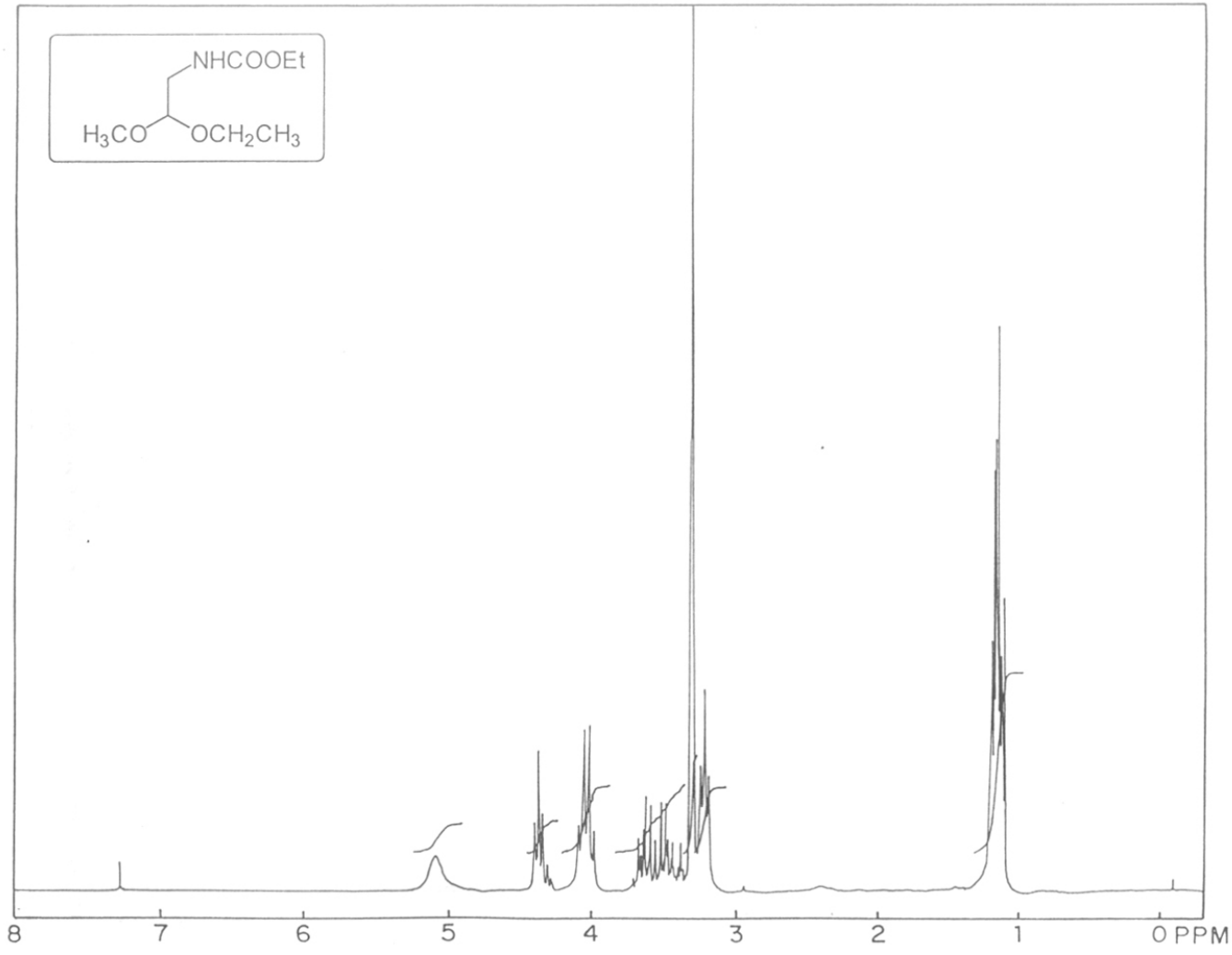
^1H **NMR** (200 MHz) $CDCl_3$: δ 1.76 (m, 1H), 2.17 (m, 1H) 2.76 (m, 2H), 2.78 (dd, 2H); 2.98 (s, 3H), 4.05 (dd, 1H), 5.85 (bs, NH), 7:05-7.45 (m, 4H).



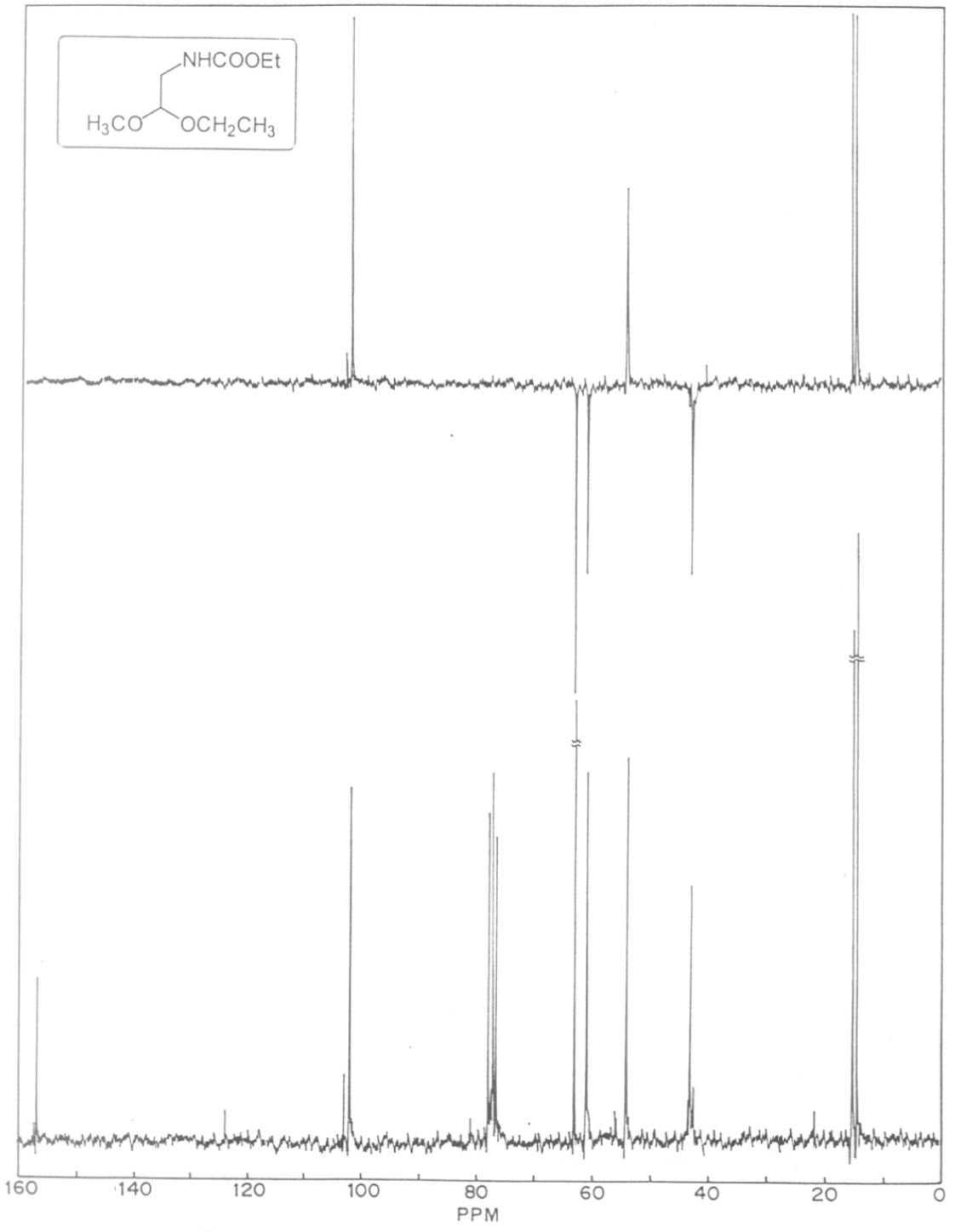
PMR OF COMPOUND 25 IN $CDCl_3$ AT 200 MHz



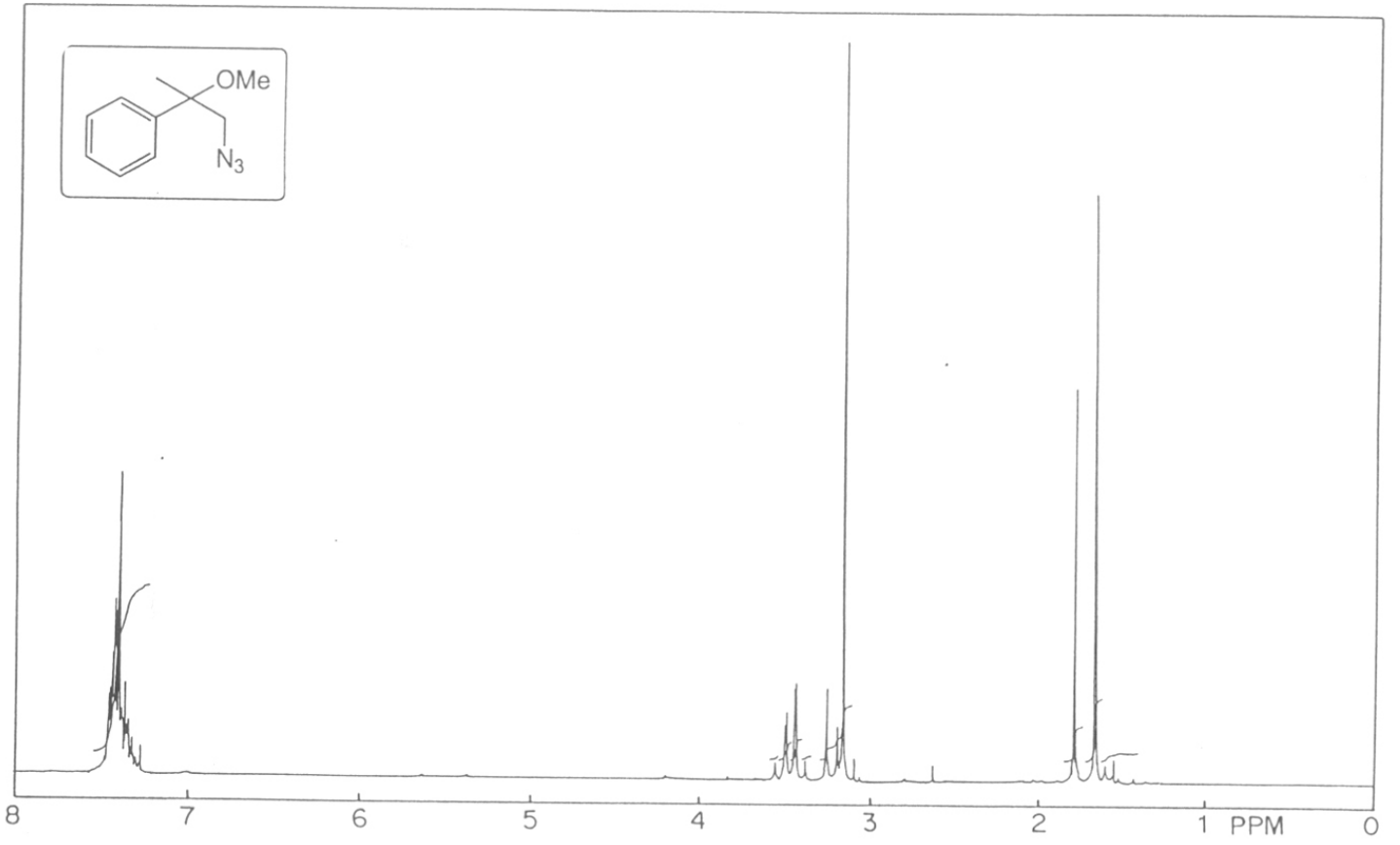
^{13}C-NMR OF COMPOUND 25 IN $CDCl_3$ AT 50MHz



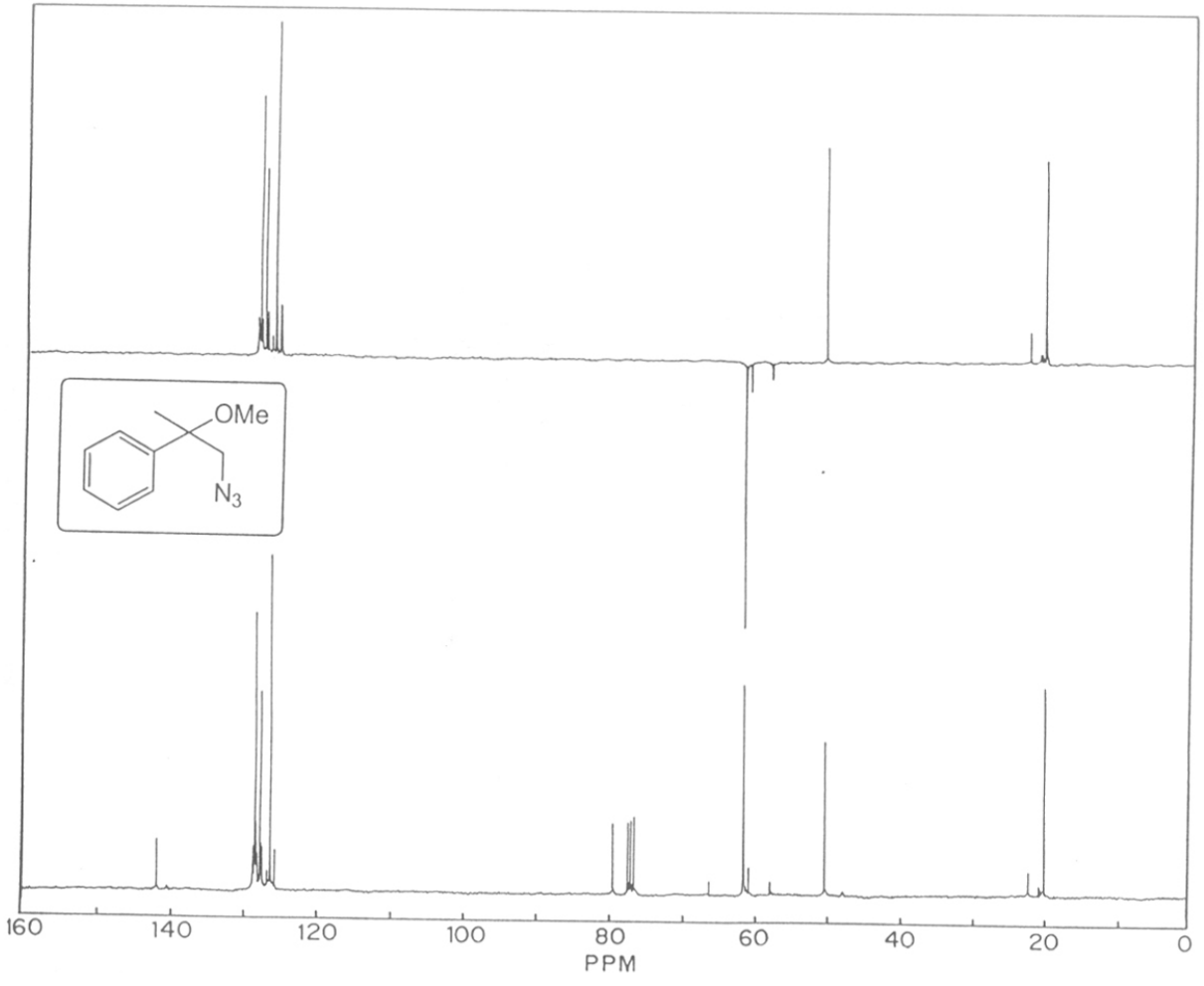
PMR OF COMPOUND 34 IN $CDCl_3$ AT 200MHz



^{13}C-NMR OF COMPOUND 34 IN $CDCl_3$ AT 50MHz



PMR OF COMPOUND 49 IN $CDCl_3$ AT 200MHz



^{13}C-NMR OF COMPOUND 49 IN $CDCl_3$ AT 75MHz

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1. For excellent reviews see.

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SECTION 2

Transesterification of β-keto esters

2.2.0 Introduction:

Transesterification,[1] a process in which an ester is transformed into another through interchange of the alkoxy moiety, is one of the classic organic reactions by virtue of its wide application in laboratory as well as industrial transformations. It is especially advantageous when the parent carboxylic acids are labile and difficult to isolate or when the parent carboxylic acids are sparingly soluble in organic solvents.

Commercially available methyl or ethyl esters can serve as starting materials for these transesterification reactions making allowances for moisture-sensitive materials essentially by their feasibility for conducting under anhydrous conditions. Apart from pure organic synthesis these transesterification reactions are widely used in polymerization especially for ring opening of lactones and also in various industries for the production of esters of oils and fats and for curing of alkylated resins in paint industry and even for polyester production.

Essentially done earlier by acidic or basic catalysts, a burgeoning need for new catalysts has increased in order to meet the requirement of making these transesterifications highly efficient, chemo, stereo and regioselective of which enzymatic reactions have experienced explosive growth.[2]

Also heterogeneous catalysts have replaced the conventional reagents due to their practical utility. These insoluble catalysts allow an easy work-up and are commercially viable due to their reusability. These can be used for continuous operation using fixed bed catalysts and functional groups remain undisturbed with purification simplified to just filtration.

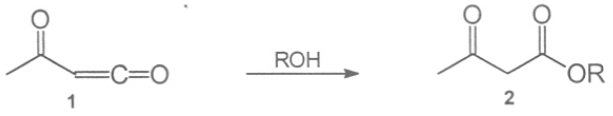
2.2.0.1 Transesterification of β-keto esters:

β-Keto esters are multi-coupling reagents with electrophilic and nucleophilic sites and are proven to be valuable tools in a wide variety of molecular systems. Their importance stems from the facile bond formation at all four carbon atoms that feature their structural unit composed of two different electrophilic carbonyls and two nucleophilic carbons which can react selectively under suitable conditions.

These important synthons which can be easily.transformed to chiral building blocks by chemical and enzymatic transformations[3] have been prepared by a variety of ways of which transesterification too received a great deal of attention. This apparently simple method requires a careful choice of experimental conditions in order to minimize the propensity of these substrates to decarboxylate.

This C_1-O_1 bond formation for the preparation of β-keto esters had been conventionally done by alcoholysis of acetyl ketenes. Although diketene is most commonly used for the preparation of acetoacetate esters and acetoacetamides, due to its high reactivity and less cost, the use of diketene is to be avoided due to its lachrymatory as well as toxic properties. Also it is harmful to the skin and respiratory tract and can cause severe burns. The other disadvantages of using diketene are that in liquid state it undergoes gradual discoloration and decomposition by liberating carbon dioxide. Hence it cannot be stored in glass bottles. Reactions of diketene are often extremely exothermic and diketene rapidly self condenses in presence of both acidic and basic catalysts thus making it unattractive as starting material for the preparation of β-keto esters on a laboratory scale (**Scheme 1**).

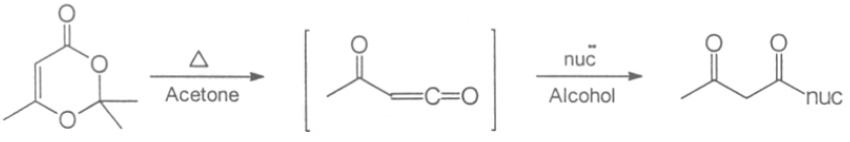
Scheme 1: *Chem. Rev* **1986**, *86*, 241.



1 2

This acetoacetylation of alcohol which has been effected by reaction with diketene in presence of suitable catalysts has been reviewed by Clemens[4] in 1986 which includes his approach of an alternative to diketene by the use of 2,2,6-trimethyl-4H-1,3-dioxin-4-one as acylating agent of alcohol[5] (**Scheme 2**).

Scheme 2: *J. Org. Chem.*, **1985**, *50*, 2431.

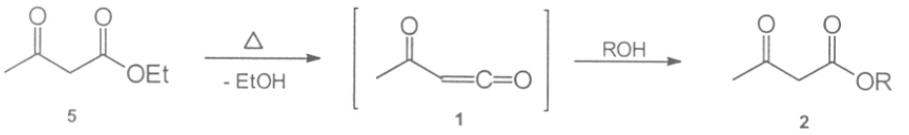


3 1 4

In order to avoid this diketene approach altogether the other alternative which involves transesterification from readily available starting materials like methyl or ethyl acetoacetate appeared to be readily amenable to industrial application.

Carroll[6] and Bader[7] independently found that β-keto ester were transesterified by heating the ester and alcohol on steam bath in the absence of catalysts. However the β-keto esters were used in large excess and the reaction times were prolonged (**Scheme 3**).

Scheme 3: *J. Am. Chem. Soc.*, **1951**, *73*, 4195.



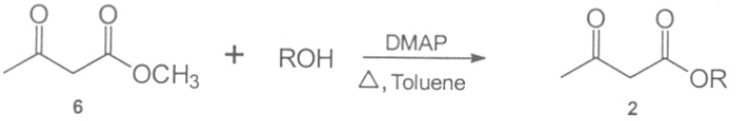
5 1 2

An acyl ketene intermediate was proposed for its mechanism making the presence of an active hydrogen as a prerequisite for these reactions.

Taber *et al.*[8] introduced a procedure of more general applicability based on the use of DMAP (4-dimethyl amino pyridine) as a catalyst (**Scheme 4**).

This protocol though gives valuable results has some limitations for instance the reactions of non-enolizable β-keto esters and tertiary alcohols fail to proceed. Additionally DMAP though a catalyst is used in fairly large amounts (25%).

Scheme 4: *J. Org. Chem.*, **1985**, *50*, 3612.



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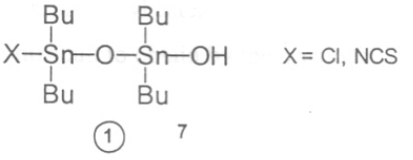
Otera *et al.*[9] were able to achieve the transesterification of non-enolizable β-keto ester under practically neutral conditions with 1,3 disubstituted tetrabutyl stannoxannes (**Scheme 5**). In fact this is one of the best methods reported to bring about transesterification. This method suffers from the draw back of the catalyst being not readily available.

Scheme 5: *Tet. Lett*, **1986**, *27*, 2383.



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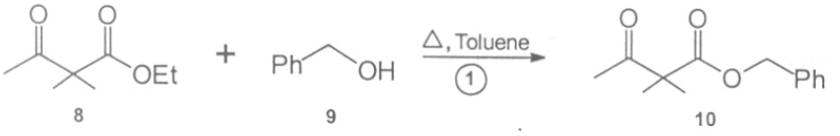
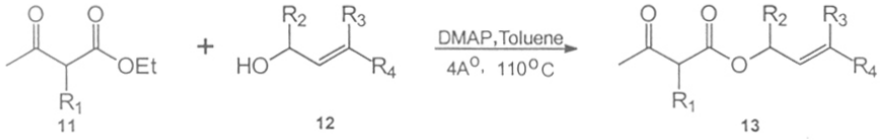


8 9 10

Gilbert and Kelly[10] modified the experimental conditions of Tabers[8] adding 4A° molecular sieves for the removal of ethanol and biased the equilibrium in order to achieve

the preparation of allyl acetoacetates (**Scheme 6**). However the same serious short comings previously encountered still remained.

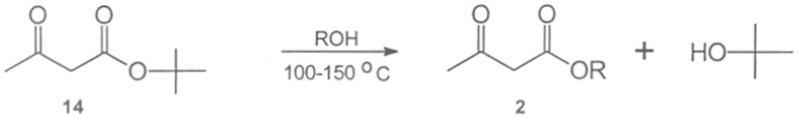
Scheme 6: *J. Org. Chem.*, **1988**, *53*, 449.



11 12 13

More recently Witzeman[11] *et al* have reported a convenient and efficient method for transesterification. The *tert*-butyl and *tert*-amyl acetoacetates reacted 10-20 fold faster than other less sterically hindered esters. These findings allowed to utilize commercially available *tert*-butyl acetoacetate as versatile acetoacetylating reagent[12] (**Scheme 7**).

Scheme 7: *J. Org. Chem.*, **1991**, *56*, 1713.

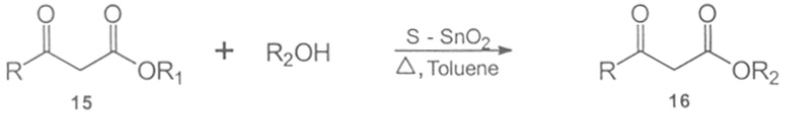


14 2

This methodology being mild also allowed the usage of allyl alcohol. However this excellent reaction was limited to the use of *tert*-butyl ketoesters as starting material which in turn are difficult to obtain and hence lacks generality.

Most recently our group reported[13] the use of solid super acids (sulfated SnO_2) as an efficient catalyst for the transesterification of ketoesters (**Scheme 8**). The salient features of the methodology developed was that the reaction proceeded with stoichiometric amounts of the keto ester and alcohol. The tertiary butyl esters could also be obtained by employing the above protocol which are rather difficult to obtain by the previously reported methods.

Scheme 8: *Tet. Lett*, **1996**, 37, 233.



15 16

The current literature survey revealed several interesting methods with wide applicability but some of them suffer from certain drawbacks like low yields, use of harsh conditions, excess of reagents and use of expensive and toxic catalysts.

2.2.1 Present Work:

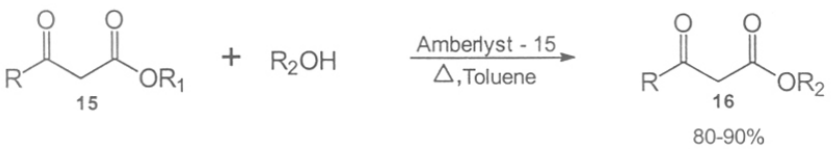
As mentioned previously, the β-keto esters which serve as important synthons for various natural product synthesis and also due to their easy transformation to chiral building blocks, can be transesterified by a variety of reagents. Although most of them are equilibrium driven reactions which utilize excess of reagents.

Use of anion or cation exchange resins in organic synthesis has received a great deal of attention during the last few years because they are handy, easily recovered from the reaction mixture and commercially available with a great number of shapes and chemical features.

Amberlyst-15 is a macro reticular ion-exchange resin which contains strongly acidic sulfonic groups. It has been widely used for a variety of reactions which include preparation of acetals from carbonyls and alcohols,[14] esters from alcohols and acids,[15] tetrahydropyranylation of alcohols and phenols,[16] hydrolysis of acetals to carbonyls,[17] and dethioacetalization.[18]

In order to explore its effectiveness as a transesterifying catalyst and also as a cheaper and commercial alternative to the reported catalysts, a transesterification of β-keto esters was attempted using Amberlyst-15 as the catalyst as depicted in **Scheme 9**.

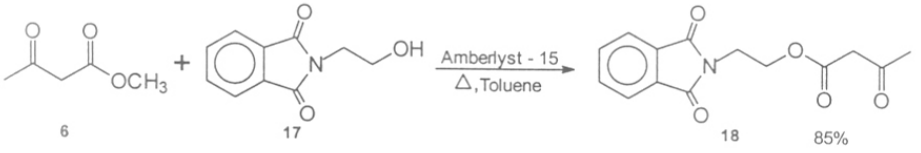
Scheme 9:



2.2.2 Results and Discussion:

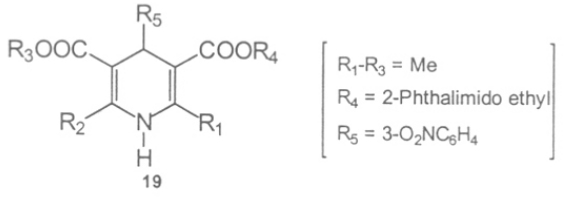
A variety of β-keto esters were treated with alcohols in the presence of Amberlyst-15 (10% by wt. of substrate) as the catalyst in refluxing toluene to give the corresponding transesterified ester in good to excellent yields. The low boiling alcohol (methanol) formed in the reaction was removed by distillation.

Scheme 10:



In a typical reaction as shown in **Scheme 10** an equivalent amount of methyl aceto acetate and N-(2-hydroxy ethyl) phthalimide and Amberlyst-15 (10% by wt of substrate (MAA) were refluxed in toluene with stirring. The low boiling methanol was removed with the help of a distillation condenser during the reaction to furnish the 2-phthalimido ethyl aceto acetate ester in 85% yield as a white solid (M.P. 88-89°C).

This transesterified product is an important reagent for the synthesis of 1,4-dihydro-pyridine derivatives **(19)**[19] which are effective Ca-channel blockers and have antihypertensive activities.

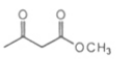
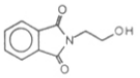
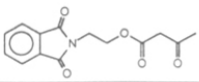
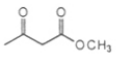
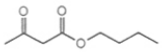
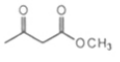
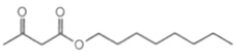
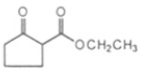
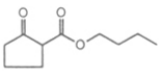
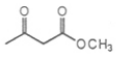
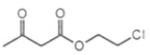
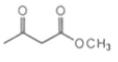
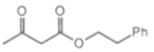
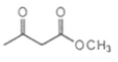
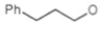
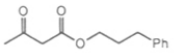
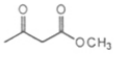
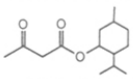
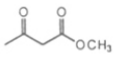
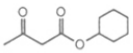
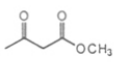
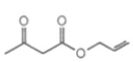
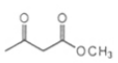
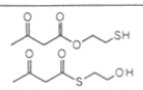
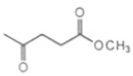
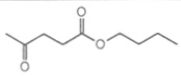


The product thus formed was characterized by IR, ^{1}H NMR and Mass spectroscopy. The IR of the compound reveals the presence of a ketone, ester and an amide carbonyls at 1712, 1744 and 1775 cm^{-1} respectively. The ^{1}H NMR shows the absence of OCH_3 group at δ3.8 and the presence of two triplets at δ4.0 and 4.4 for the $-CH_2-CH_2-$ of the phthalimidoethanol and a singlet at δ2.25 for the methyl of acetoacetate. The aromatic protons appear as multiplet at δ7.7-7.9 integrating for five protons.

This transesterified product when cyclocondensed with $NH_2(CH_3)C{=}CHCOOCH_3$ and $3\text{-}O_2NC_6H_5CHO$ in $(CH_3)_2CHOH$ gives the 1,4-dihydropyridine (**19**) which was demonstrated to exhibit Ca-channel blocking and anti hypertensive activity.[19]

In order to test the generality of the above protocol, a variety of alcohols were subjected to transesterification with methyl acetoacetate. The results have been summarized in Table1.

Table 1:

S.No.	Substrate	Alcohol	Product	Time (hrs)	Yield (%)
1.				10.0	85
2.				5.5	85
3.				2.0	89
4.				3.0	90
5.				3.0	75
6.				4.0	88
7.				2.0	64
8.		 **		6.0	94
9.				6.0	65
10.				8.0	42
11.			 #	2.0	86*
12.				10.0	54

* combined yield. ** 2 eq of alcohol. # 1:1 ratio of products.

This methodology of transesterification was found to be effective with primary, secondary as well as allyl alcohols. Noteworthy feature of the present methodology is that a one to one equivalent of β-keto esters to alcohol is sufficient for the success of the reaction to furnish the corresponding esters in good to excellent yields. Except in the case of menthol and allyl alcohol where 2eq. of alcohol were required for the reaction to proceed in good yields.

Even γ-keto esters *viz.* methyl levulinate gave the desired transesterified product albeit in moderate yields. All the products formed were purified either by distillation or column chromatography and the esters were characterized by spectral analysis like IR, ^{1}H NMR and Mass.

2.2.3 Conclusions:

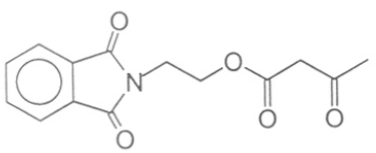
- Amberlyst-15 has been effectively utilized for the first time to achieve a one to one exchange of β-keto esters. It is in sharp contrast to conventional equilibrium driven transesterification reactions which require excess of one of the reactants to shift the equilibrium in the desired direction.
- A variety of primary, secondary and allylic alcohols as well as γ-keto esters have been effectively shown to undergo the transesterification reaction.
- The catalyst Amberlyst-15 being heterogeneous in nature offers advantages over conventional methods not only in terms of yields and reaction times but ease of work up and retrieval of products in addition to reusability of the catalyst which is of tremendous commercial importance. The short reaction times and high yields emphasize the attractive feature of this protocol.
- Amberlyst-15 is a commercial resin which is readily available.

2.2.4 Experimental:

General procedure for transesterification:

A mixture of the keto ester (1mmol), alcohol (1mmol) and the catalyst (100 mg, 10% by wt of keto ester) in toluene (20 ml) was heated at 110°C in a two necked round bottomed flask provided with a distillation condenser to remove the low boiling alcohol formed in the reaction. The reaction was monitored by TLC. After completion of reaction (*ca.* 6hrs), the catalyst was filtered and the filtrate was concentrated and the residue chromatographed (SiO_2) using pet. ether : ethyl acetate as the eluent (95 : 5) to afford the ester as a viscous colorless liquid in excellent yields.

1. **N-(2-Phthalimidoethyl)acetoacetate**[19]:



Yield : 85%

Mol. Formula : $C_{14}H_{13}NO_5$ White solid

M.P. : 88°-89°C

IR (neat) cm^{-1} :3022, 1755, 1744, 1712, 1428, 1395, 1365, 1319, 1216, 754, 720.

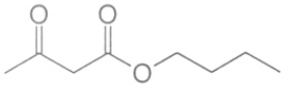
^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 2.25 (s, 3H); 3.45 (s, 2H); 4.0 (t, J=5.4Hz, 2H); 4.4 (t, J=5.4 Hz, 2H); 7.7-7.9 (m, 5H, aromatic).

^{13}C NMR (50 MHz) $CDCl_3$ (δ) : 199.6 (s); 167.6 (s); 166.5 (s); 133.7 (d); 131.6 (s); 122.9 (d); 61.9 (t); 49.2 (t); 36.5 (t); 20.7 (q).

Mass (m/e) : 275 (M^+, 0.5); 192 (3); 174 (17); 173 (42); 161 (45); 160 (100); 148 (32); 133 (23); 130 (16); 117 (6); 104 (25).

Analysis :	Carbon	Hydrogen	Nitrogen
Calculated :	61.09%	4.83%	5.05%
Found :	60.82%	4.76%	4.65%

2. n-Butyl aceto acetate[20]:



Yield : 85%

Mol. Formula : $C_8H_{14}O_3$ Colorless liquid

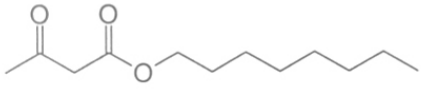
B.P. : 55°C (0.1 mm) (Lit.[20] 55/0.1mm)

IR (neat) cm^{-1} :2980, 2950, 1750, 1730, 1650, 1420, 1350, 1320, 1250, 1180, 1150, 1050, 1020, 950, 820, 750.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 0.9 (t, 3H, $-CH_3$); 1.35 (m, 2H, $-CH_2-$); 1.6 (m, 2H, CH_2-); 2.25 (s, 3H, $-CH_2-$); 3.4 (s, 2H, $-CH_2-$), 4.1 (t, 2H, $-OCH_2-$).

Mass (m/e) : 158(M^+)

3. n-Octyl aceto acetate[7]:



Yield : 89%

Mol. Formula : $C_{12}H_{22}O_2$ Colorless liquid

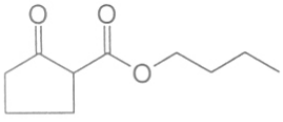
B.P. : 102°C/(0.9 mm) (Lit. [7]100/0.9mm)

IR (neat) cm^{-1} :2950, 2850, 1750, 1720, 1650, 1450, 1400, 1350, 1300, 1220, 1150, 1020.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 0.9 (t, 3H); 1.3 (m, 10H, $-CH_2-$); 1.6 (t, 2H); 2.6 (s, 2H); 4.1 (t, 2H).

Mass (m/e) : 214 (M^+)

4. Cyclopentanone-2-oxobutyl ester[25]:



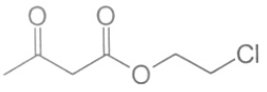
Yield : 90%

Mol. Formula : $C_{10}H_{16}O_3$ viscous liquid

IR (neat) cm^{-1} :2950, 2850, 1750, 1720, 1640, 1610, 1450, 1350, 1250, 1180, 1050, 920.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 0.9 (t, 3H); 1.3 (m, 2H); 1.6 (m, 2H); 2.1 (m, 2H); 2.3 (m, 4H); 3.15 (t, 1H); 4.2 (t, 2H).

5. 2-Chloro ethyl aceto acetate[21]:



Yield : 75%

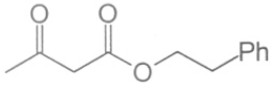
Mol. Formula : $C_6H_9O_3Cl$ Colorless liquid

IR (neat) cm^{-1} :2950, 1750, 1720, 1650,1450, 1420, 1350, 1320, 1250, 1150, 1020, 780, 650.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 2.1 (s, 3H); 3.4 (s, 2H); 3.6 (t, 2H); 4.3 (t, 2H).

Mass (m/e) : 164(M^+)

6. 2-Phenyl ethyl aceto acetate[25]:



Yield : 88%

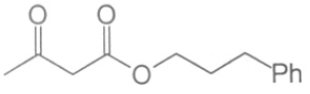
Mol. Formula : $C_{12}H_{14}O_3$ pale yellow liquid

IR (neat) cm^{-1} :3020, 2900, 1750, 1720, 1620, 1400, 1300, 1250, 1200, 1050, 1020, 920, 810, 720, 580, 550.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 2.15 (s, 3H); 3.0 (t, 2H); 3.4 (s, 2H); 4.4 (t, 2H), 7.5 (m, 5H).

Mass (m/e) : 206(M^+)

7. 3-Phenyl propyl aceto acetate[22]:



Yield : 63%

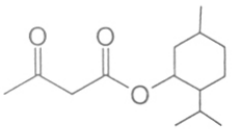
Mol. Formula : $C_{13}H_{16}O_3$ pale yellow viscous liquid

IR (neat) cm^{-1} :3030, 2860, 1740, 1720, 1650, 1600, 1500, 1455, 1360, 1260, 1170, 1150, 1030, 750, 700.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 2.0 (m, 2H); 2.2 (s, 3H); 2.7 (t, 2H); 3.5 (s, 2H); 4.2 (t, 2H); 7.25 (m, 5H).

Mass (m/e) : 220(M^+)

8. Menthyl aceto acetate[9]:



Yield : 94%

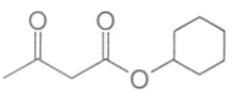
Mol. Formula : $C_{14}H_{24}O_3$ viscous liquid

IR (neat) cm^{-1} : 2980, 2820, 1740,1700, 1650, 1450, 1400, 1350, 1300, 1240, 1120, 1080, 1020, 980, 950, 900, 850.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 0.80 (d, 3H); 1.1 (d, 6H); 1.2 (m, 4H); 1.35 (m, 2H); 1.55-1.85 (m, 3H), 2.3 (s, 3H), 3.5 (s, 2H), 4.7 (dt, J=4.4 & 10.9, 1H).

Mass (m/e) : 240(M^+)

9. Cyclohexyl aceto acetate[7]:



Yield : 65%

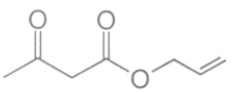
Mol. Formula : $C_{10}H_{16}O_3$ Colorless liquid

IR (neat) cm^{-1} :3010, 2980, 1750, 1720, 1650, 1560, 1420, 1350, 1250, 1180, 1020, 920, 850, 780, 700, 650.

^{1}H NMR (200 MHz) $CDCl_3$ (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^+)

10. Allyl aceto acetate[7]:



Yield : 42%

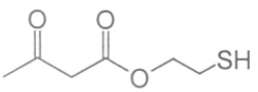
Mol. Formula : $C_7H_{10}O_3$ pale yellow liquid

IR (neat) cm^{-1} :2950, 1750, 1720, 1640, 1420, 1380, 1280, 1020, 1000, 950, 780, 550.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 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^+)

11(a). 2-Mercapto ethyl aceto acetate[23]:



Yield : 43%

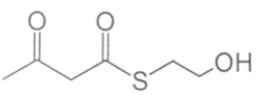
Mol. Formula : $C_6H_{10}O_3S$ Colorless liquid

IR (neat) cm^{-1} :1740, 1710, 1600, 1400, 1350, 1300, 1250, 1150, 1020.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 1.5 (t, -SH); 2.25 (s, 3H); 2.7 (dt, 2H); 3.5 (s, 2H); 4.3 (t, 2H).

Mass (m/e) : 162(M^+)

11(b). 2-Hydroxy thio aceto acetate:



Yield : 43%

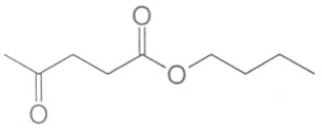
Mol. Formula : $C_6H_{10}O_3S$ Colorless liquid

IR (neat) cm^{-1} : 3400, 1740, 1710, 1600, 1400, 1350, 1300, 1250, 1150, 1020.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 1.7 (s, 2H); 2.8 (s, -OH); 3.1 (t, 2H); 3.7 (s, 2H); 4.2 (t, 2H).

Mass (m/e) : 162(M^+)

12. Butyl levulinate[24]:



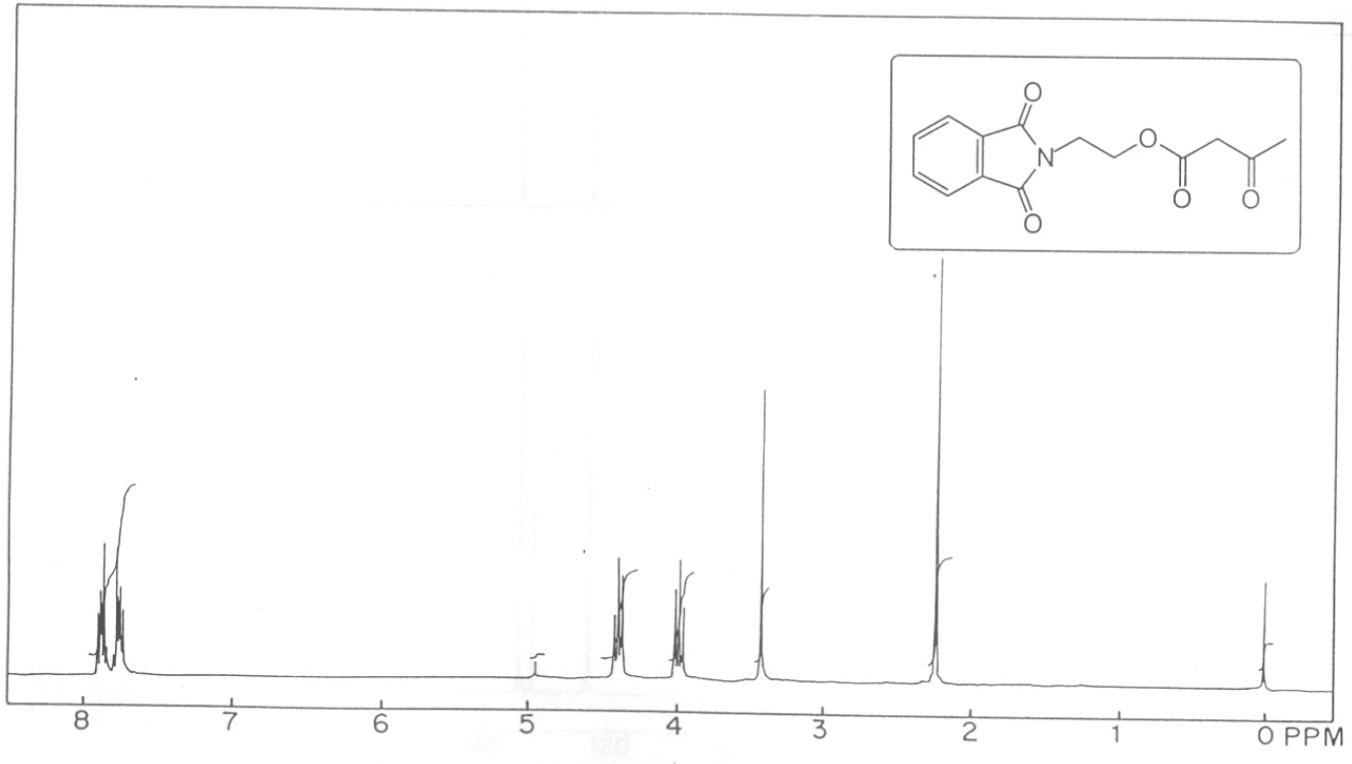
Yield : 54%

Mol. Formula : $C_9H_{16}O_3$ viscous liquid

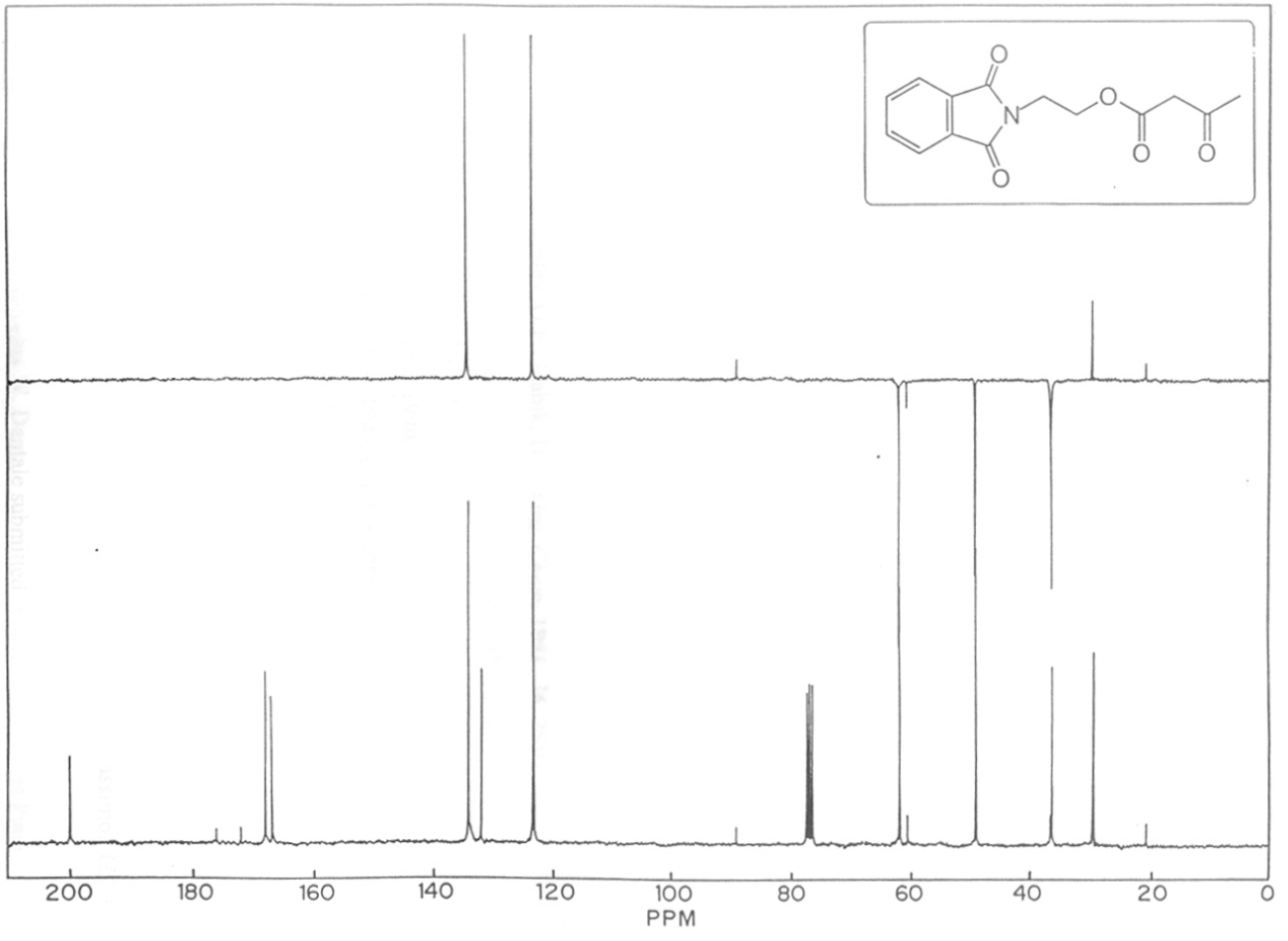
IR (neat) cm^{-1} : 2950, 2800, 1740, 1720, 1620, 1450, 1350, 1180, 1150, 1050, 1020, 950, 780, 650.

^{1}H NMR (200 MHz) $CDCl_3$ (δ) : 0.90 (t, 3H); 1.5 (m, 4H); 2.1 (s, 3H); 2.5 (t, 2H); 2.7 (t,2H), 4.1 (t, 2H).

Mass (m/e) : 172(M^+)



PMR OF COMPOUND 18 IN $CDCl_3$ AT 200 MHz.



^{13}C NMR OF COMPOUND **18** IN $CDCl_3$ AT 50MHz

2.2.5 References:

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