SYNTHETIC STUDIES ON BALANOL, ANGUCYCLINES AND CATALYTIC ORGANIC TRANSFORMATIONS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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MAY 2001

DEDICATED TO MY BELOVED PARENTS

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CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Synthetic Studies on Balanol, Angucyclines and Catalytic Organic Transformations"** by **Mr. Mahesh L. Patil** was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

MAY 2001

(V. H. DESHPANDE)
RESEARCH GUIDE

ACKNOWLEDGEMENTS

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MAY 2001

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CONTENTS

SECTION C: SELECTIVE BENZYLIC OXIDATION OVER Mn-Zr USING 70% TBHP

GENERAL REMARKS

1. All the temperatures are in °C. All the melting points and boiling points are in °C and are uncorrected.
2. ^{1}H NMR and ^{13}C NMR spectra were recorded either on Brucker WH-90, Brucker AC-200 or DRX-500 spectrometer in $CDCl_3$ containing TMS as an internal standard with chemical shift (8) expressed in ppm downfield from TMS. The following abbreviations are used: s = singlet, d=doublet, t= triplet, q= quartet, m= multiplet and b= broad.
3. Infrared spectra (v max in cm^{-1}) were recorded as either thin film or nujol mull or in $CHCl_3$ on Perkin-Elmer Infra-red 683 B or 160S FT IR spectrometer with sodium chloride optics.
4. Mass spectra were recorded at an ionization energy of 70eV on Finnigan MAT-1020, Automated GGMS instrument.
5. All solvents and reagents were purified and dried by standard procedures. All evaporations were carried out under reduced pressure on Buchi rotary evaporator.
6. TLC was carried out on silica gel plates prepared by spreading the slurry (in CCI_4) and drying at room temperature. The plates were analysed by keeping in iodine chamber.
7. Microanalysis was carried out in the micro analytical section of NCL.
8. GLC was carried out on Hewlett Packard 5890.
9. Column chromatography was performed on silica gel (60-120 mesh). Petroleum ether refers to the fraction boiling in the range of 60-80 °C.
10. The compound numbers, scheme numbers and reference numbers given in each chapter refers to that particular chapter only.

ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
AIBN	2, 2'-Azobisisobutyronitrile
Allyl-B (^{l}Ipc)$_2$	l-Allyldiispinocampheylborane
9-BBN	9-Borabicyclo[3.3.1]nonane
BnBr	Benzyl bromide
b.p.	Boiling point
^{t}BuOH	Tertiary butanol
CSA	Camphorsulfonic acid
Cr-Zr	Chromium stabilized zirconia
Co-Zr	Cobalt stabilized zirconia
DBU	1, 8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano- 1,4-b~nzoquinone
DEAD	Diethyl azodicarboxylate
DIBAL H	Diisobutylaluminium hydride
DMF	Dimethylformamide
DMAP	4-(Dimethylamino)pyridine
DMS	Dimethyl sulphate
DMSO	Dimethyl sulphoxide
Et_3Si H	Triethyl silane
g	Gram/s
hr	Hour/s
HMPA	Hexamethylphosphoramide
$^{i}pr_2NH$	Diisopropylamine
IR	Infrared
$LiAlH_4$	Lithium aluminum hydride
LiHMDS	Lithium hexamethyldisilazane
MsCI	Mesyl chloride
m-CPBA	m-Chloroperoxybenzoic acid
MOM-Cl	Methoxymethylene chloride
Mn-Zr	Manganese stabilized zirconia

M^+	Molecular ion
Min	Minutes
Me	Methyl
NBS	N-bromosuccinimide
Ni-Zr	Nickel stabilized zirconia
NMO	4-Methylmorpholine N-oxide
NMR	Nuclear magnetic resonance
Ph	Phenyl
$PhCCl_3$	Benzotrichoride
PPA	Polyphosphoric acid
TBHP	Tertiary butylhydrogen peroxide
TBAF	Tetrabutylammonium fluoride
TBDMS	Tertiary butyldimethylsilyl
p-TSA	p-Toluenesulphonic acid
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic acid
TIPS	Triisopropylsilane
TLC	Thin layer chromatography
THF	Tetrahydrofuran
TMEDA	N,N,N',N'-Tetramethylethyle-nediamine
TMS-CN	Trimethylsilyl cyanide

Thesis Abstract

Thesis Title

"Synthetic Studies on Balanol, Angucyclines and Catalytic Organic Transformations"

The thesis has been divided into three chapters. Chapter I deals with the synthetic studies on angucyclines and contains three sections. Section A describes the synthesis of (+-)-brasiliquinone B. Section B contains attempted synthesis of brasiliquinone C and synthesis of (+-)-8-deoxybrasiliquinone B while section C deals with the synthetic approaches towards AH-1763 Ila.

Chapter II deals with the studies towards synthesis of balanol, a novel protein kinase C inhibitor, which is subdivided into two sections. Section A covers literature review on balonol while section B describes synthesis of benzophenone precursor for balanol.

Applications of heterogeneous catalysts for organic transformations are discussed in chapter III. This chapter is further divided into three sections. Section A deals with the regiospecific acylation of aromatics over hydrated zirconia whereas section B and C describe use of heterogeneous catalysts for oxidation reactions.

Chapter I: Synthetic Studies on Angucycline Antibiotics

This chapter is further divided into three sections.

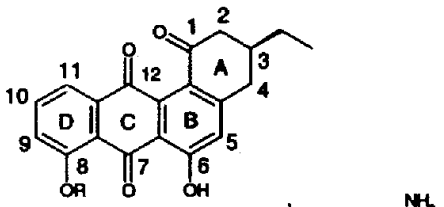
Section A: Synthesis of (t)-Brasiliquinone B

Introduction

Angucycline antibiotics are the class of benz(a)anthracene antibiotics possessing a typical tetracyclic structure having different groups at different positions. These are derived from the secondary metabolites of microorganisms. These compounds showed remarkable antimicrobial and antiviral activities. There are several reports on isolation and biological activities of these molecules but a very few attempts have been made to synthesize these bioactive molecules.

Brasiliquinones A-C, isolated from the pathogenic species of Nocardia of the strain IFM-0089, are the novel cytotxic benz(a)anthraquinones commonly known as angucyclines. Most of the reported angucycline antibiotics possess a methyl group at C-3 position whereas brasiliquinones are the first angucyclines, which possess an ethyl group at C-3 position.

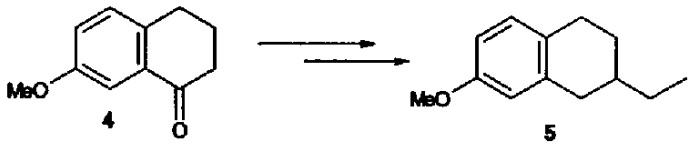
These brasiliquinone antibiotics showed a very good antitumor activity along with antimicrobial and antiviral activities. Brasiliquinones B (2) and C(3) are more effective than brasiliquinone A (1).



We envisioned the use of Friedel-Crafts acylation and alkylation approaches to buiki up the angucycline skeleton and achieved the synthesis of (+-)-brasiliquinone B starting from 7- ethoxy-1 tetralone.

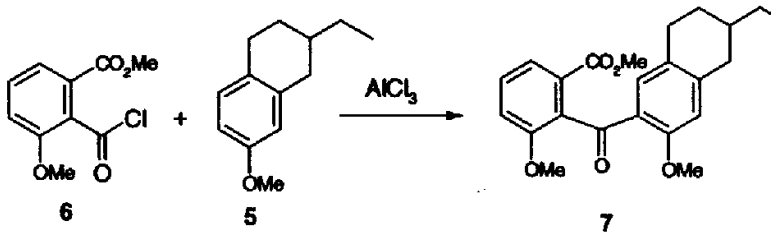
The key intermediate 5 was prepared by acylating the 7-methoxy-1-tetralone (**4**) with acetic anhydride in presence of boron trifluoride etherate to obtain 2-acetyl-7-methoxy-1-tetralone which was hydrogenated followed by Clemmenson's reduction to afford the required tetralin derivative as shown in scheme-1.

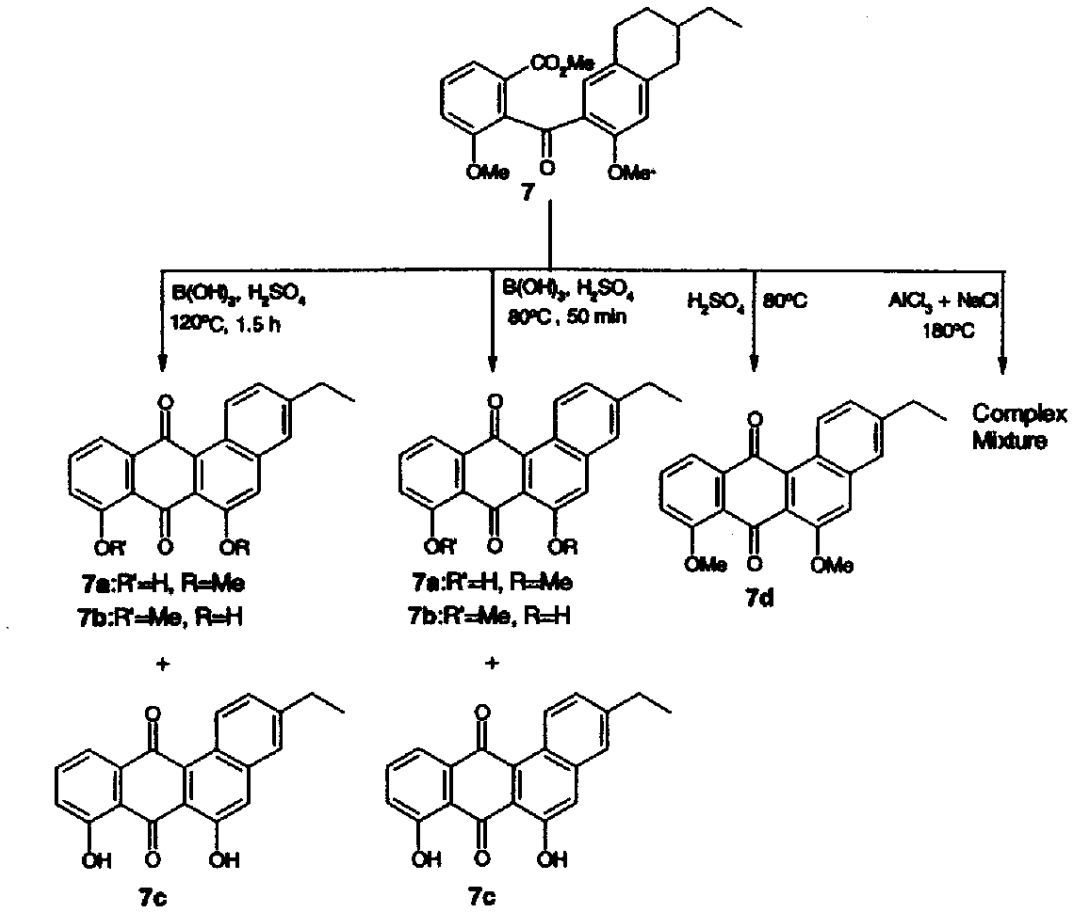
Scheme-1



Friedel-Crafts acylation approach for the synthesis of (±)-brasiliquinone B

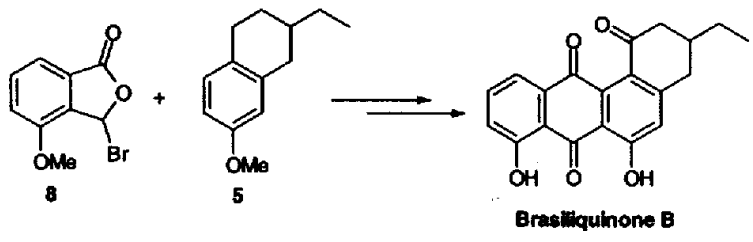
Friedel-Crafts acylation approach for the construction of ring C of brasiliquinone B was attempted. Ethyl tetralin **5** on benzoylation with the benzoyl chloride **6** followed by cyclization under various conditions yielded A ring aromatized products as shown in scheme-2.





Friedel-Crafts alkylation approach for the synthesis of (±)-brasiliquinone B

This approach started with the construction of angucydine skeleton via Friedel-Crafts alkylation of ethyl tetralin **5** with 3-methoxy-4-bromophthalide (**8**) using stannic chloride followed by reductive opening, cyclization, oxidation and demethylation to give the required brasiliquinone B as shown in scheme-3.



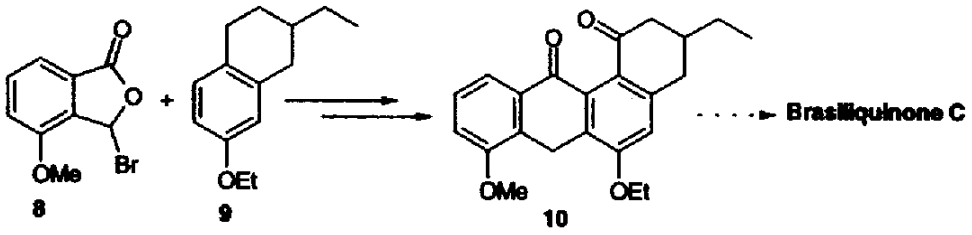
Section B: Attempted Synthesis of Brasiliquinone C and Synthesis of (+.)8-deoxybrasiliquinone B

This section is subdivided into two parts.

Part-1: Attempted synthesis of brasiliquinone C

Brasiliquinone C (3) is the benz(a)anthraquinone possessing ethyl group at C-3 position and methoxy group at C-8 position. Like brasiliquinone B it also showed a very good antitumor activity alongwith antiviral and antimicrobial activities. Its synthesis was undertaken using the Friedel-Crafts alkylation approach similar to the one applied for brasiliquinone B by protecting the hydroxy group of tetralin with an ethyl group as shown in scheme-4.

Scheme-4

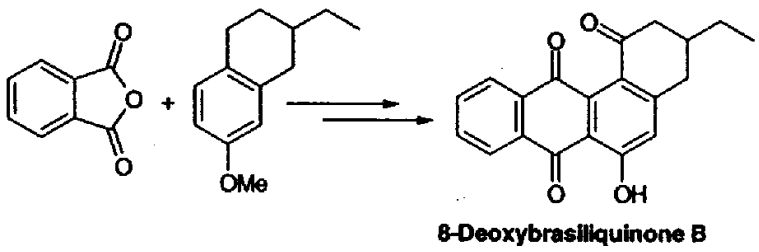


Thus tetralin derivative 9 on Friedel-Crafts alkylation with bromophthalide 8 followed by reductive opening, cyclization yielded anthrone 10, which on oxidation and selective de-thylation would give the brasiliquinone C.

Part-II: Synthesis of (+-}-8-deoxybrasiliquinone B

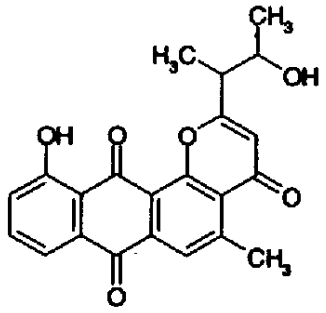
During the synthetic studies on anthracydines it has been shown that 4~lemethoxydaunomycinpossesses 8-12 times more activity than daunomycin and adriamycin. On this background we have synthesized 8-demethoxybrasiliquinone C or 8- deoxybrasiliquinone B, a new analogue of brasiliquinones as shown in scheme-5, which may show a good activity.

Scheme-5



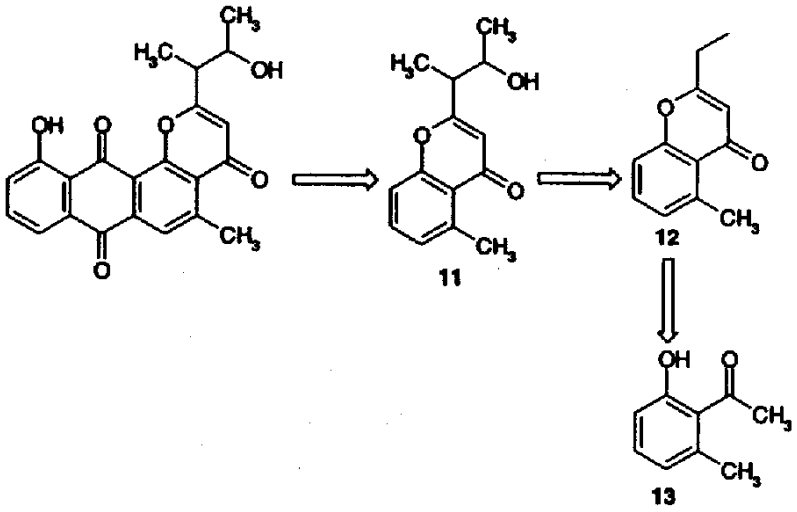
Section C: Studies Directed Towards Synthesis of AH-1763 IIa

AH-1763 IIa, a new antiherpetic agent was isolated from the culture broth of strain No. 1763 identified as stryptomyces cyaneus. AH-1763 IIa is structurally related to angucyclines but belongs to pluramycin group of antibiotics.



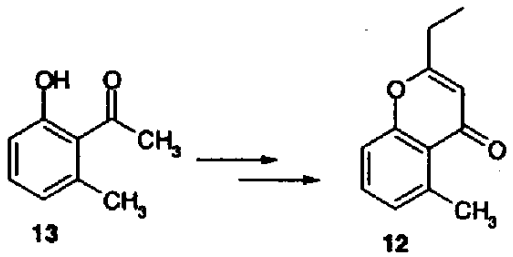
AH-1763 IIa

Retrosynthetic studies revealed chromone **12** as the key intermediate for the synthesis of AH 1763 IIa.



Thus chromone **12** was prepared by using Baker-Venkataraman rearrangement starting from substituted acetophenone as shown in scheme-6.

Scheme-6



Part-II: Synthetic methods for hexahydroazepine portion of balanol

This part deals with the various syntheses of hexahydroazepine portion of balanol.

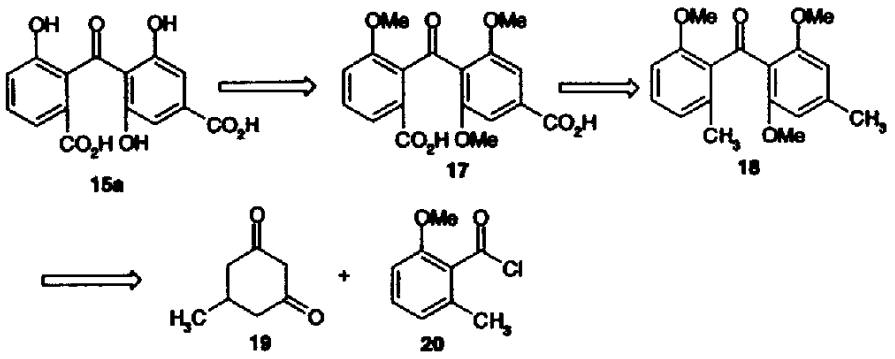
Part-III: Design and synthesis of new analogues of balanol

In this part design, synthesis and protein kinase C inhibitory activity of new analogues of balanol are presented. .

Section B: Synthesis of Benzophenone Precursor for Balanol

The structure activity relationship studies on balanol revealed the critical importance of benzophenone portion **15** for the efficacy of balanol. Synthesis of this benzophenone portion is challenging as it is sterically congested.

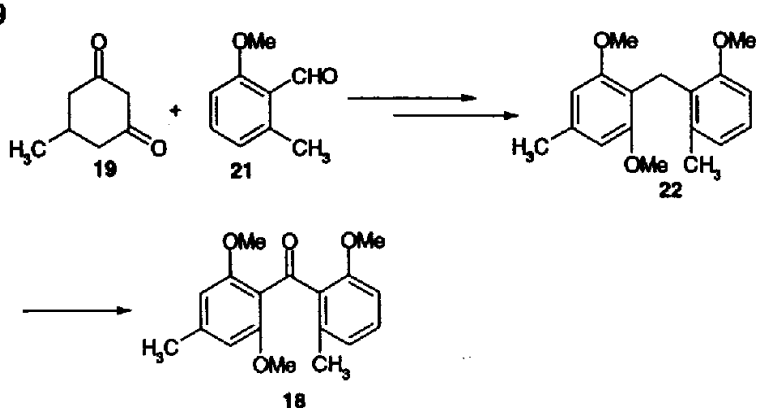
Scheme-8



As per the retrosynthetic route our plan was to start with less hindered system like 5 methykyclohexane-1,3-dbne (**19**) to form a triketone, followed by aromatization which would lead to the benzophenone portion of balanol as shown in scheme-8.

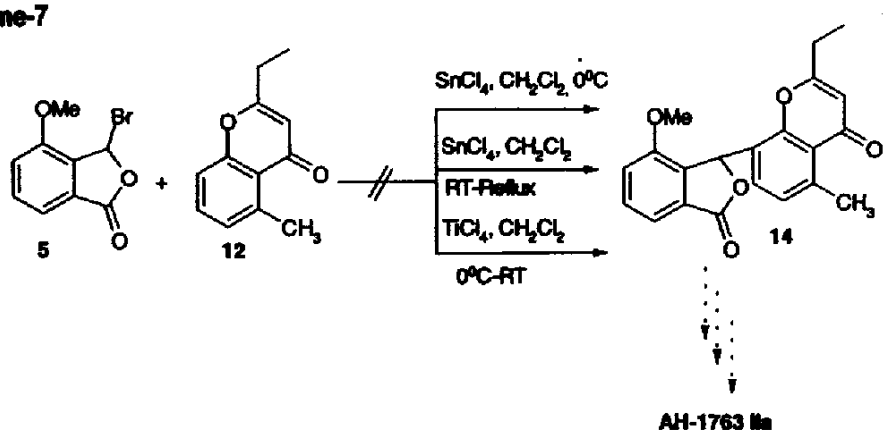
Knoevenagel condensation approach was also used for this synthesis as shown in scheme-9

Scheme-9



Attempted Friedel-Crafts alkylation of chromone **12** with 3-bromo-4-methoxyphthalide failed to give the required product **14** as shown in scheme-7. Further work on the synthesis of AH-1763 IIa is in progress.

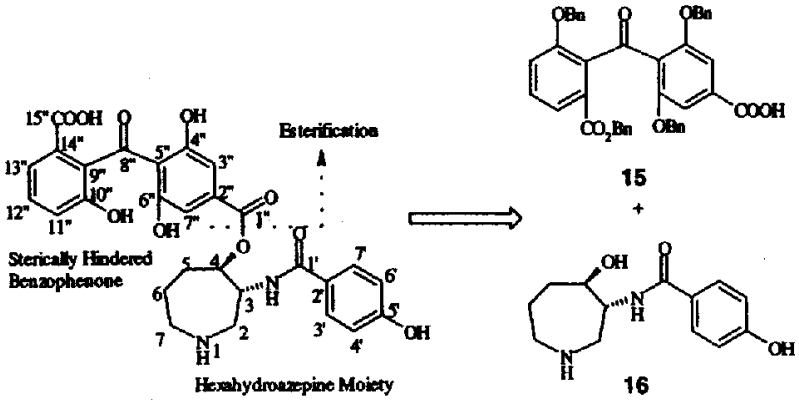
Scheme-7



AH-1763 IIa

Chapter-II: Synthetic Studies Towards Benzophenone Precursor for Balanol.

Balanol, a novel protein kinase C inhibitor isolated from verticillium balonoides, has potential application in treatment of various ailments like cancer, asthma, HIV infection, rheumatoid arthritis, diabetes, central nervous system disorders etc. There has been a continuous flow of research papers describing synthesis of balanol and its intermediates.



This chapter is divided into two sections.

Section A: Review on Syntheses of Balanol and its Intermediates

This section is further divided into three parts.

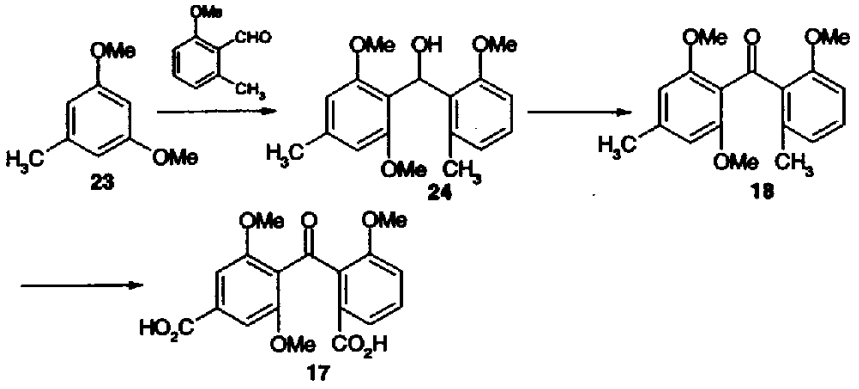
Part-I: Syntheses of benzophenone domain of balanol

This part describes various syntheses of benzophenone domain of balanol and its intermediates.

Oxidation of compound **22** resulted into either no reaction or a complex mixture under attempted conditions (TLC).

Finally synthesis of benzophenone precursor **17** was carried out using ortholithiation approach in three steps starting from 3,5-dimethoxytoluene (**23**) and 2-methoxy-6-methylbenzaldehyde as shown in scheme-10.

Scheme-10



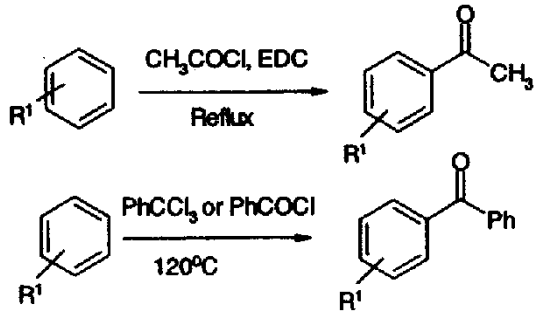
Chapter-111: Applications of Heterogeneous Catalysts in Organic Transformations

Heterogeneous catalysts are found to be very effective in many organic transformations. We explored use of some heterogeneous catalysts for Friedel-Crafts acylation and oxidation reactions.

This chapter is divided into three sections.

Section A: Regiospecific acylation of aromatics over hydrated zirconia

We have developed a very simple, regiospecific methodology for the benzoylation of the aromatics under Friedel-Crafts conditions. For the first time we have reported the benzoylation of less activated arenes like naphthalene and acetanilide using hydrated zirconia catalyst whereas zeolite failed to benzoylate these compounds even at higher temperatures.



Section B: Oxidation of primary and secondary benrylic alcohols and sulfides over LaCoO3 using 70% TBHP

Oxidation of benzylic alcohols is an important transformation in many complicated molecules. The traditional chromium complexes used for this transformation create problem like pollutions, tedious workup and loss of selectivity. LaCoO3 proved to be very effective and selective catalyst for this oxidation. We have also made sulfides to undergo oxidation to the corresponding sulfoxides under these conditions.

Section c: Selective Benrylic Oxidation over Mn-Zr using 70% TBHP

Mn-Zr catalyst has been found to be very effective for the oxidation of compounds containing benrylic methylene group to the corresponding acetophenones or benzophenones. Selective oxidation of methylene group in presence of methyl has been achieved. 4-Methylethylbenzene was oxidized to 4-methylacetophenone in 75 % yield whereas tetralin was oxidized to tetralone in 80 % yield.

CHAPTER-I

SYNTHETIC STUDIES ON ANGUCYCLINE ANTIBIOTICS

This chapter is divided into sections

INTRODUCTION

Cancer a most dreaded disease is the foremost killer disease in western countries and India. Cancer, the growth of abnormal body tissues, is actually referred to more than hundred forms of the disease. Tumor is a general term indicating any normal mass or growth of tissues that is not necessarily life threatening. A "Cancerous tumor" is a malignant neoplasm of potential danger. Cancer can arise in any organ of the body even though some sites are more prone than others. The most dangerous property of cancer cells, which normal cells lack, is their ability to enter other body organs through blood and lymph vessels. This disease has attracted worldwide attention and search for reliable methods to cure it is continuously going on.

Among the most common reasons for cancer are smoking, chewing tobacco, high intake of fatty food, consumption of large amount of alcoholic beverages, environmental pollution, exposure to different light radiations and the signals of cellular phones etc.

The cancer treatment can be divided into four types: surgery, radiation, chemotherapy and combined modality therapy based on the therapy used. Treatment of tumor by surgery is quick and safe, but removal of the tumor from affected sites is some times critical and surgeons may need to cut large amount of the healthy tissues, which may damage patient. Radiation therapy is effective than the surgery but in this method, powerful x-rays and ~y-rays may inflict genetic damages and may kill healthy cells.

In the early 1940 chemotherapeutic drugs have been developed. Physicians found that "Combination of drugs" may cure leukemia's, lymphomas and testicular cancers etc. Unfortunately the majority of the most common cancers like breast, lung colorectal and prostate cancers are not yet curable with chemotherapy alone.

Combined modality therapy requires the efforts of a wide assortment of specialists, oncologists, surgeons, pathologists and radiologists etc. Breast cancer can be cured by the combination of surgery and radiotherapy followed by chemotherapy.

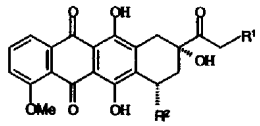
So far nearly 3,00,000 different compounds have been documented, either from natural sources or synthesis, as potential anticancer agents. Out of these only about 40 are today considered useful in the treatment of more than 100 types of human cancers.

The effective chemotherapy can be achieved by understanding the mechanism of the anticancer drugs and type of the cancer cells. These drugs should be non-toxic to the host cells during their prolonged administration and at the same time they have to be sufficiently toxic to the cancer cells, hence the quest to find a better drug goes on.

A large number of anticancer drugs are now being used in medical practice, which have been approved by the National Cancer Institute, USA. Further many are undergoing clinical trials. All these drugs can be broadly classified into 1) Alkylating agents 2) Antimetabolites 3) Antibiotics and 4) Miscellaneous compounds.

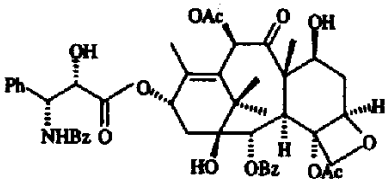
Among the various compounds, which are promising as antitumor agents, natural products, either of plant or microbial origin, are showing much more specificity in their anticancer properties. Many of them possess structures and clinical properties, which suggest that they may act by selective alkylation of the growth regulatory macromolecules. Busulfan and chlorambucil are the examples of the alkylating agents used in the treatment of the cancer.

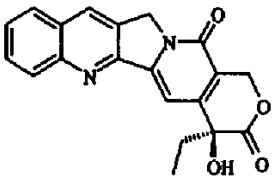
5-Fluorouracil and methotrexate are the examples of antimetabolites which are useful to cure some types of cancers. The usefulness of certain anthracycline antibiotics as antineoplastic agents is now widely accepted. The two prototype anthracyclines are adriamycin and daunomycin produced from Streptomyces species. Their potent activity was discovered in 1%3, when adriamycin and daunomycin first isolated by Di Marco et al. were found to be effective as antileukemic agents.



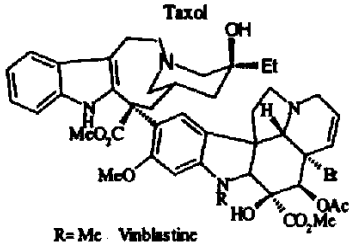
Adriamycin: R^1 = OH, R^2= Daunosaminyl
Daunomycin: R^1 = H, R^2= Daunosaminyl

The antitumor activity of the anthracyclines is generally due to their interaction with DNA. Adriamycin has shown promising results in solid tumors also.

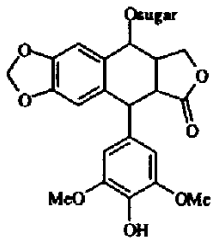




Camptothecin



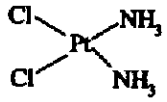
R= Me Vinblastine
R= CHO Vincristine



Podophyllotoxin

Some of the plant-derived compounds can also prevent cell division by binding to the proteintubulin (a fiber which helps in orchestrate cell division). The fiber pulls duplicate DNA chromosomes to either side of the parent cell, ensuring that each daughter cell receives a full set of genetic blueprints. Drugs, which interfere with the assembly or dissemble these tubule fibers can prevent cells from dividing successfully e.g. vinblastin, vinorelbine, vincristine, taxol, camptothecin, podophyllotoxin etc.

Among the miscellaneous agents cis-diammineplatinum (II) dichloride demonstrated significant activity in carcinomas of urinary bladder.



Cisplatin

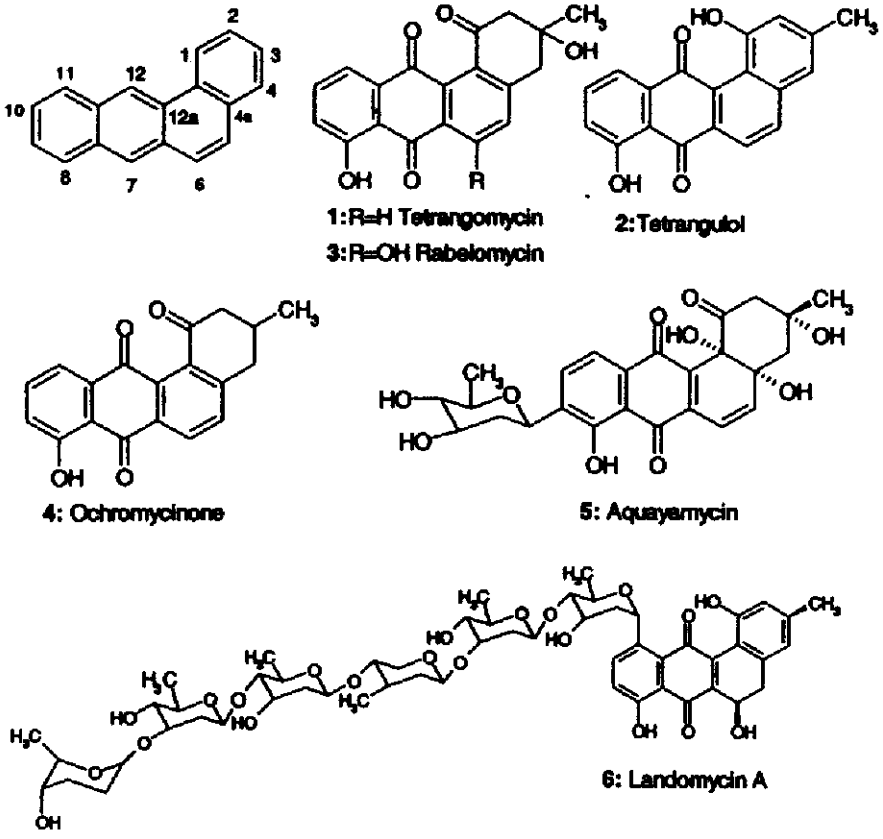
Major problem in the treatment of cancer is the development of resistance to the antibiotics. To overcome this problem research on improvement of known antibiotics and search for new class of antibiotics is necessary.

Quinonoid angucyclines[1, 2] are the new emerging group of antibiotics, which in contrast to the related linearly condensed anthracyclines, show not only anticancer activity but also a wide range of biological activities such as antibacterial and antiviral properties and enzyme inhibition.

The angucycline group of antibiotics comprises more than one hundred secondary metabolites of microbial origin. In 1966 after some of the important antibiotics of the tetracycline[3, 4] and anthracycline groups,s,[5-9] a novel type of microbial natural product bearing an unsymmetrically assembled tetracyclic ring frame was described. These antibiotics were later named as "angucycline group antibiotics" referring to the characteristic four ring frame of the aglycone moiety, which is assembled in angular manner.

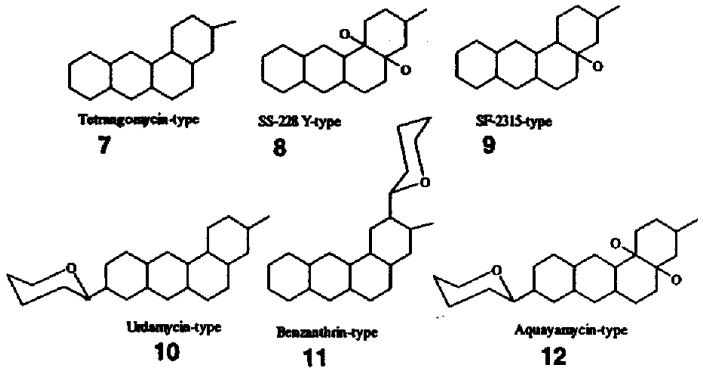
Tetrangomycin (1) and tetrangulol (2), the first members of this class of antibiotics were reported by Dann et al. as well as by Kunstmann and Mitscher in 1965 and 1966 respectively. [10,11] The structure of ochromycinone (4) was described in 1967 followed by aquayamycin (5) [13-15] and rabelomycin (3) [16] both in 1970. In the following decade only five further examples were published and these molecules seemed to remain a discrete but limited group. A renaissance of the angucycline group occurred in the eighties. Now these secondary metabolites of the microbial origin have formed the third separate group of tetracyclic decaketides (after the related group of tetracyclines and anthracyclines).

The tetracyclic benz(a)anthracene frame

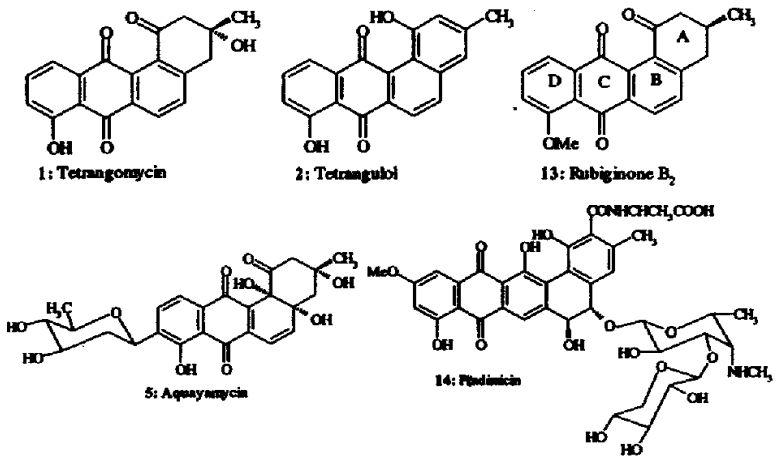


The earliest published structures are examples of simple (sugarless) angucyclinones with molecular weights of slightly more than 300 e. g. ochromycinone (4)[12] while some of the members reached molecular weight of more than 1000 e. g. landomycin A (6)[17], m.w. 1087; PI-080[18], m.w. 1071, due to their saccharide moiety.

Rohr and Thiericke[2] classified the angucyclinone based on the degree of oxygenation and C-glycoside formation.



Krohn et al.[19] summarized some angucyclines, which possess additional structural features in addition to the classification of angucyclinones by Rohr and Thiericke. ~



Tetrangomycin (1)[10]possesses a labile tertiary hydroxyl group at C-3 position but lacks a phenolic hydroxyl group at C-6. Elimination of the tertiary hydroxyl group of the tetrangomycin (1) by treatment with mild acid or base yielded 1,8-dihydroxybenz (a) anthraquinone named ' tetrangulol (2). In aquayamycin (5), a tyrosine[20] and dopamine2l hydroxylase inhibitor, a sugar is attached in ortho position to the phenolic hydroxyl group at C-8. Since it has no hydrolysable sugar it is also a member of angucyclinones. Other glycosidic angucyclines are udramycins[22], [19], p-1g94 B[23] etc. Pradimicin (14)[24] is also a member of angucycline antibiotics.. Rubiginone BZ (13)[25] is an example of simple angucyclinone with an aromatic ring B but lacking the tertiary hydroxyl group at C-3. Despite the simple structure, the rubiginone showed interesting vincristine cytotoxicity potentiating activity[26].

Biological Activities

Angucycline antibiotics showed a wide range of biological activities. Besides an interesting antitumor activity, some of the angucyclines act as hydroxylase and/or monooxygenase inhibitors, some act as potent inhibitors of platelet aggregation and some exhibit antibacterial and antiviral activities. The most toxic compounds are aggreticin[27], antibiotic SS-228Y[9], yoronomycin[28] and saquayamycin [29] Angucyclines are found to be very good inhibitors of platelet aggregation, e.g. PI-080, PI-083, PI-085, PI-087[18,30]and kerriamycin B and C.[27] Angucyclines exhibit a weak antibacterial activity especially against grampositive bacteria. The most potent are vineomycin Al3lantibiotic PI-083[30] and SS-228Y.[32]

In some cases a weak antifungal activity is also observed e. g. emycin A[33] and the antibiotic SM 196 A/B.[34] Angucyclinones SF-2315 A and B[35] have been reported to possess antiviral activities.

Structure Activity Relationship

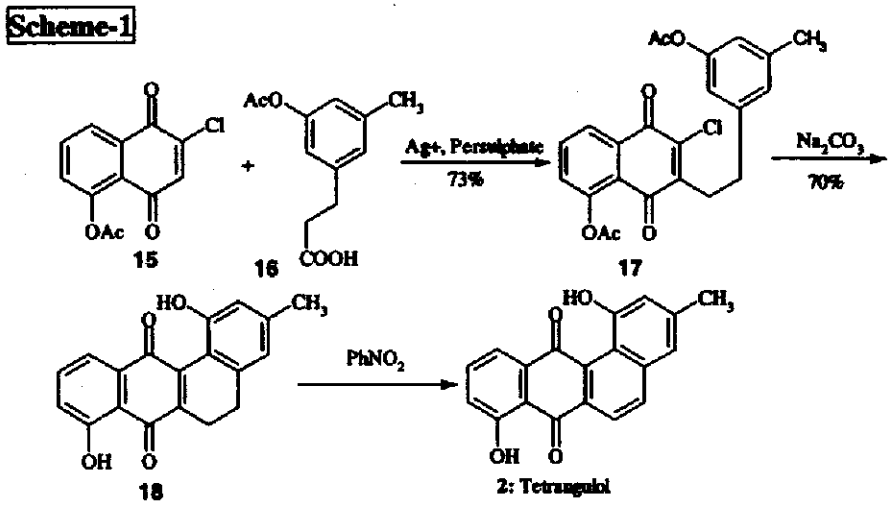
Though the mode of action of angucyclines/angucyclinones is not yet clear, it is assumed that the most important part of the angucyclines is the aglycone, due to the antitumor activities of the chromophoric system. This statement was supported by the observation that the natural angucyclinone antibiotics PD-116779[36] and SS-228Y[9] exhibit antitumor activities. Although modifications of the sugar moieties of the saquayamycins have resulted in the preservation of in vitro cytotoxic activity, a change in the aglycone structure has always led to loss of the biological activity.[37]

Brief Review on Synthetic Approaches

There are several reports on isolation and biological activities of these angucycline antibiotics but unfortunately a very few attempts have been made towards their total syntheses. The synthetic approaches to the angucyclines reported so far have centered around elaboration of a prefabricated naphthoquinone by nucleophilic reactions, Friedel Crafts reactions, Diels-Alder reactions and biomimetic type syntheses.

Brown and Thomson[38] synthesized a simple aromatic bisphenol tetrangulol (2) using Michael type reaction. (Scheme-1).

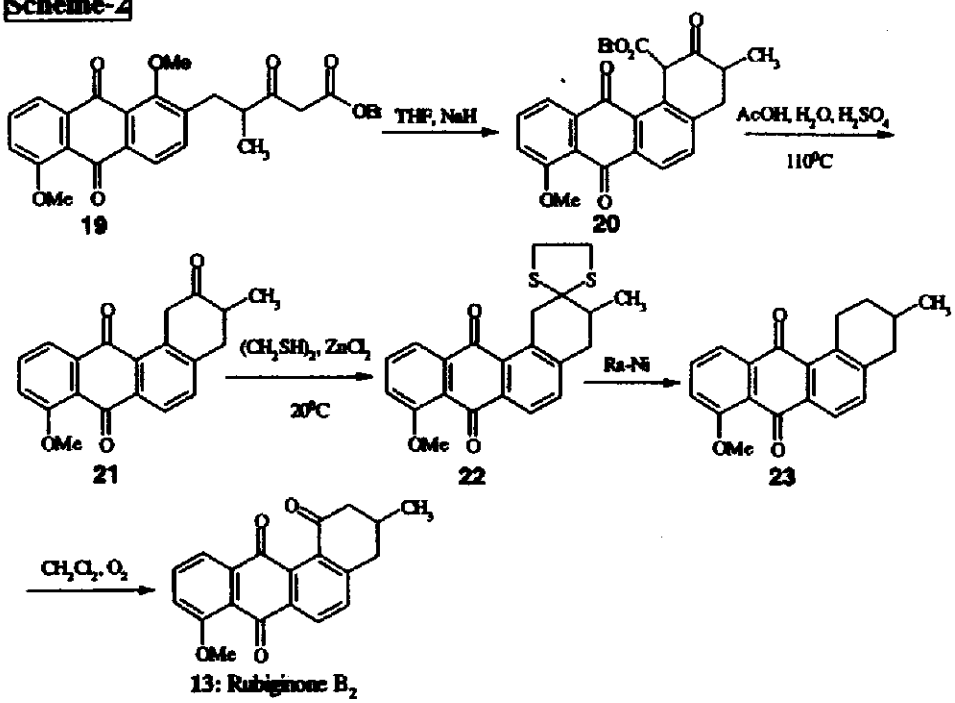
Scheme-1



Radical alkylation of the chloronaphthoquinone **15** with carboxylic acid **16** in the presence of silver ions and persulfate with concomitant decarboxylation and dehydrogenation of the compound **18** yielded tetrangulol (2).

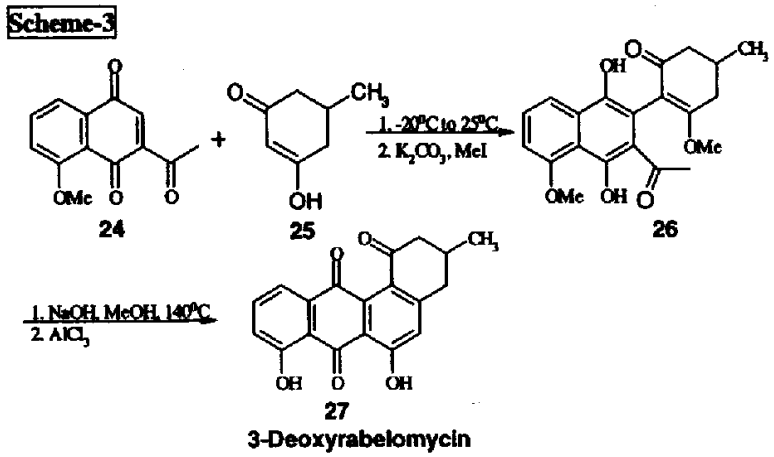
Krohn et a1.[39] synthesized rubiginone B_2 (**13**) by using intramolecular nucleophilic addition to produce dihydrobenzo(a)napthoquinone and its transformation to rubiginone B_2 as shown in Scheme-2.

Scheme-2



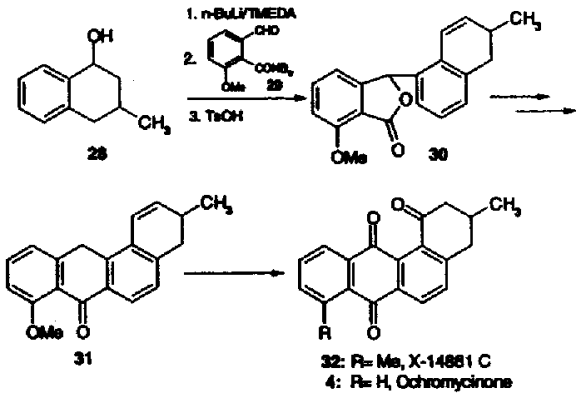
3-Deoxyrabelomycin has been synthesized by Kraus and Wu[40] using the Michael addition reaction (Scheme-3). The intramolecular Michael addition reaction of 5-methyl 1,3-cyclohexanedione (**25**) to the extremely electron deficient 3-acetyl-5-methoxy-1,4napthoquinone (**24**) followed by base induced cyclization yielded 27 % of a tetracyclic intermediate which was demethylated with aluminum chloride to give 3-deoxyrabelomycin (**27**)

Scheme-3



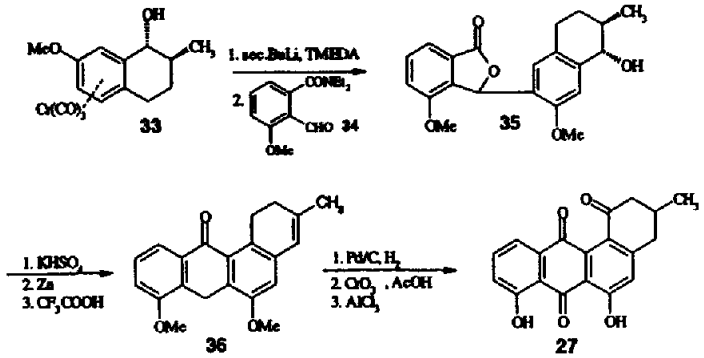
Katsuura and Snieckus[41, 42] have synthesized ochromycinone (**4**) and its methyl ether X-14881 C by using Friedel-Crafts reaction of a carboxylic acid to give an anthrone, which was further oxidized to give a dihydrobenzo(a)anthraquinone as shown in scheme-4. This synthesis involved coupling of dianion formed by directed metalation of tetralol **28** with substituted benzaldehyde **29** followed by cyclization and dehydration to give phthalide 30.

Scheme-4



Introduction of carbonyl group at C-1 position was carried out by a series of reactions including selenohydroxylation and chromium (VI) oxidation followed by radical deselenation. Demethylation of X-14881 C (**32**) to the phenolic ochromycinone (**4**) was achieved using aluminum trichloride. Umera et a1.[43,44] used similar Friedel-Crafts reaction approach for the synthesis of 3-deoxyrabelomycin (**27**) as shown in scheme-5.

Scheme-5

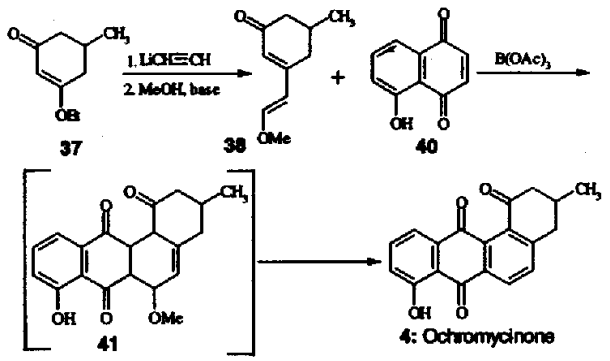


This synthesis demonstrated utility of (6-arene) chromium tricarbonyl complex **33** for the directed metalation.

Guingant and Barreto45 synthesized ochromycinone (**4**) by using a novel Diels-Alder approach as shown in scheme-6. Dienone **38**, which was prepared from 3-ethoxy-5-methyl 2-cyclohexen-1-one 37 in two steps, on Diels-Alder reaction with 5-hydroxy-1,4naphthoquinone

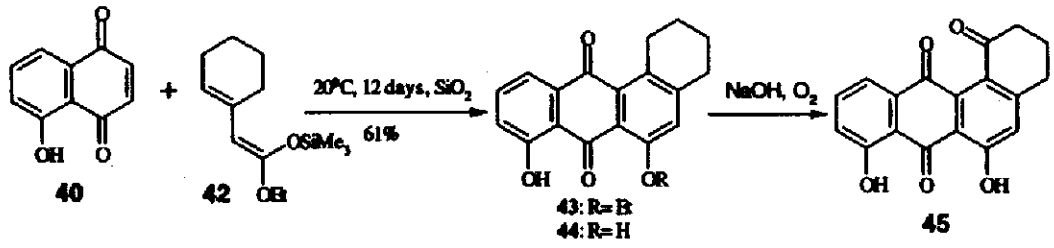
(**40**) in presence of borontriacetate yielded the intermediate adduct **41**, which was subjected directly to elimination and oxidation to afford ochromycinone (**4**).

Scheme-6

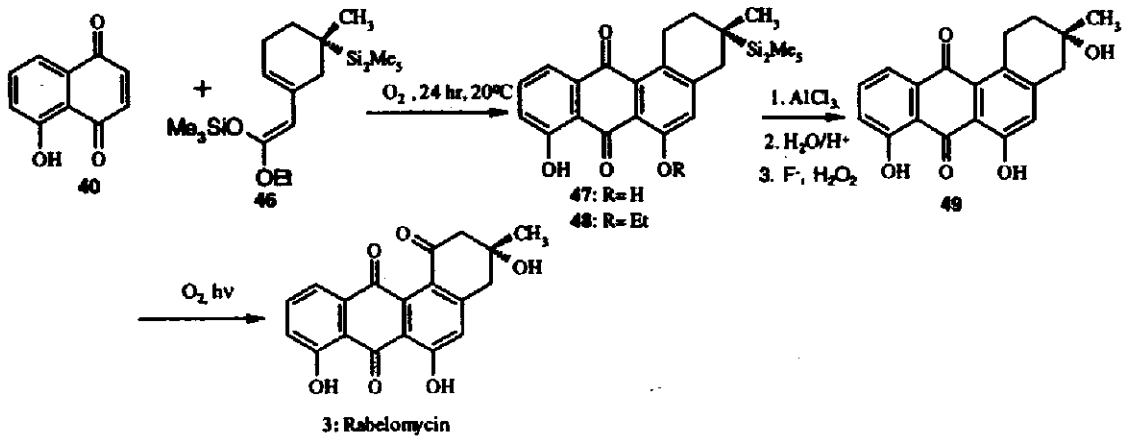


Valderram et al.[46] constructed the angular anthraquinone structural framework by Diels-Alder reaction using ketene acetal and base catalyzed air oxidation as shown in scheme-7.

Scheme-7

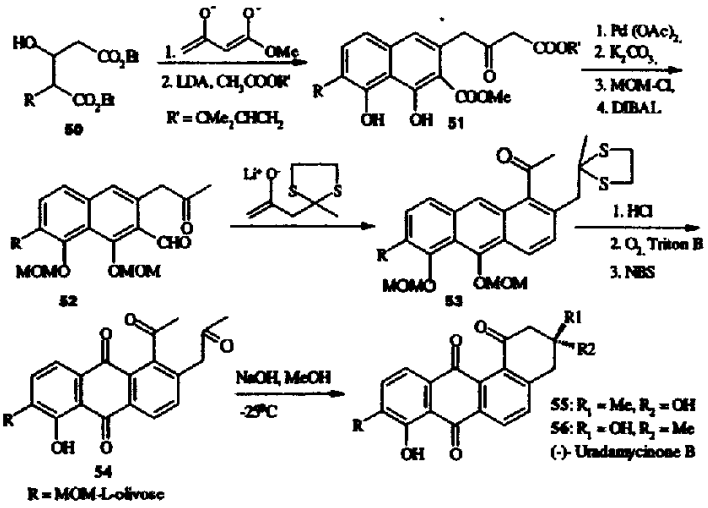


Scheme-8



Biomimetic type condensation and cyclization are proved to be very useful in the synthesis of anthracyclines. Yamaguchi et al.[48] synthesized (-) urdamycinone B using biomimetic type condensation (Scheme-9).

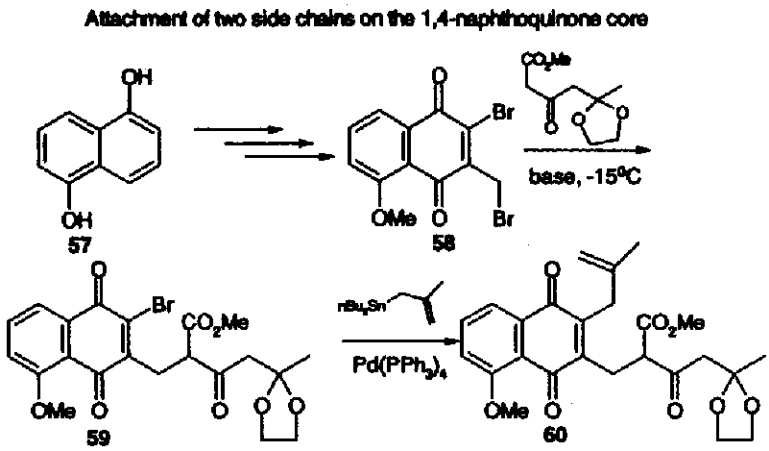
Scheme-9



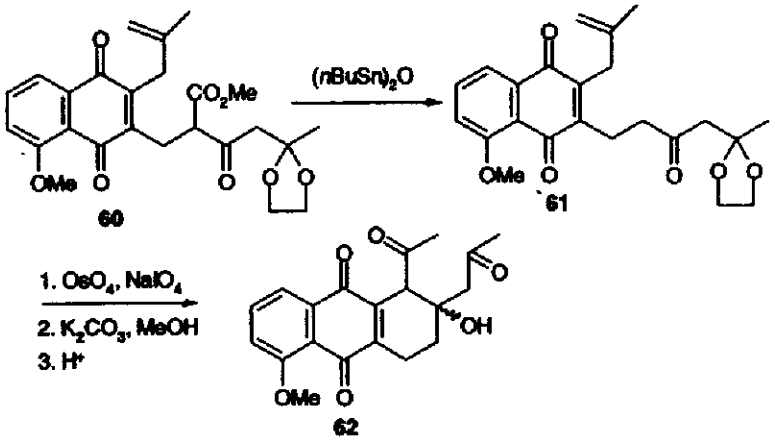
Compound **51** was prepared by successive condensation of glutaric ester **50** with vacetoacetate and acetate anion. Preparation of aldehyde **52** was achieved by using a series of reactions. Finally the base catalyzed cyclization afforded (-)uradamycine B (**56**).

Krohn et a1.[49] synthesized angucyclines in a biomimetic manner as shown in

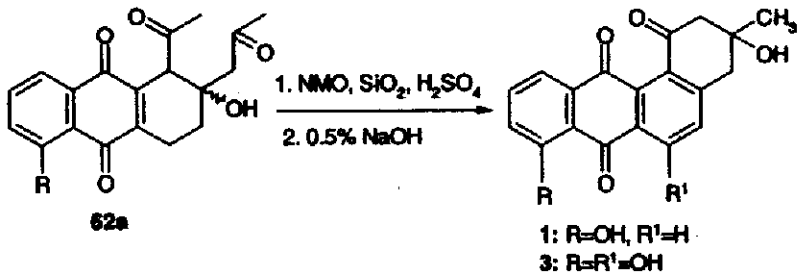
Scheme-10



Construction of ring B in the biomimetic type angucycline synthesis



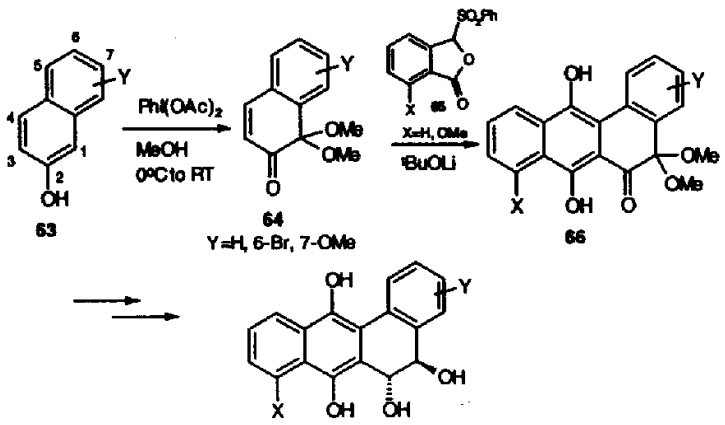
Construction of A ring and hydroxylation at C-6 in biomimetic type synthesis



This synthesis involved attachment of two side chains on the 1,4-naphthoquinone core followed by its linear cyclization and construction of rings B and A along with hydroxylation at C-6 as shown in scheme-10.

Phthalide annulation strategy was explored by Mal et al.[50] for the synthesis of benz(a)anthraquinone skeleton.

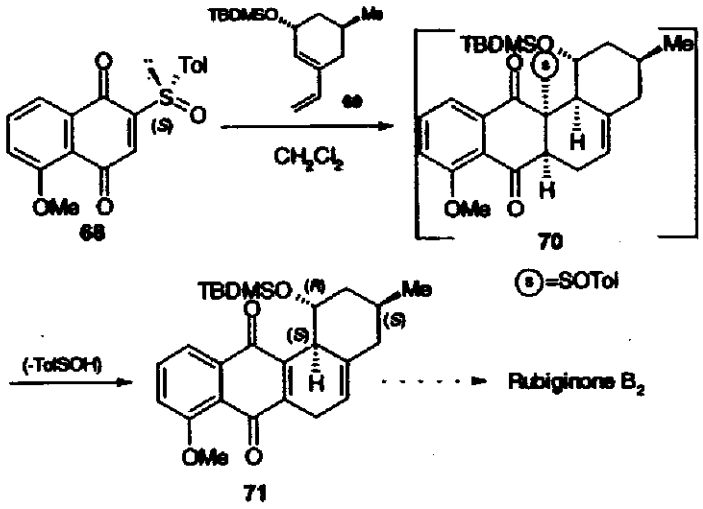
Scheme-11



This approach involves synthesis of quinone monoketal and its utilization in facile fabrication of a number of hydroxylated benz(a)anthraquinones as shown in scheme-1 l.

Recently Carreno et a1.51 reported enantioselective total synthesis of (+)-rubiginone B_2 and (+)-ochromycinone from enantiopure (S)-5-methoxy-2-(p-tolylsulfinyl)-1,4naphthoquinone (**68**) and a racemic vinylcyclohexene **69** through a reaction sequence involving Diels-Alder reaction, sulfoxide elimination with kinetic resolution of the racemic diene, followed by controlled aromatization and functional group deprotection as shown in scheme-12.

Scheme-12



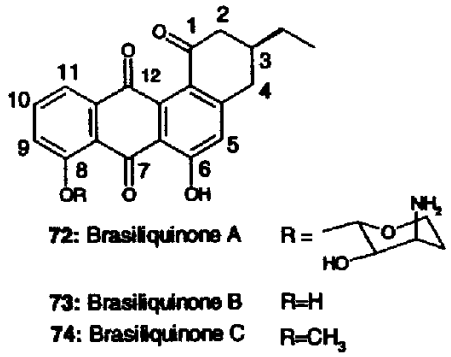
SECTION-A

SYNTHESIS OF (+-)-BRASILIQUINONE B

1.1.0 INTRODUCTION

Brasiliquinones A-C[52, 53] new cytotoxic benz(a)anthraquinone antibiotics, were isolated from the pathogenic species of Nocardia of the strain IFM 0089. Brasiliquinones belong to a large group of antibiotics commonly called as angucyclines. Brasiliquinone A (**72**) is the first benz(a)anthraquinone antibiotic possessing ristosamine as an O-glycoside linkage. Special feature of these brasiliquinones is the presence of an ethyl group at C-3 position whereas all other angucyclines reported possess a methyl unit at C-3 position.

Scheme-13



The stereochemistry of the only chiral center at C-3 of brasiliquinones was determined to be S by comparison of the optical rotations with that of rubiginone B_2[25] which has S configuration. These antibiotics are soluble in methanol, chloroform, acetone and ethyl acetate, but insoluble in water. The molecular formulae of brasiliquinones A, B and C were determined as $C_{25}H_{25}NO_7$, $C_{20}H_{16}O_5$ and $C_{21}H_{18}O_5$ respectively, by HRFABMS, which supported the assigned structures.

Brasiliquinones A-C showed a remarkable antitumor activity along with very good antiviral and antimicrobial activities but they were inactive against Gram -ve bacteria and fungi. In vitro antitumor activity of brasiliquinones against L1210 and P388 proved brasiliquinones B (**73**) and C (**74**) more effective than brasiliquinone A (**72**).

The IC_{50} value of these antibiotics against L1210 and P388 tumor cells ranged from 2.0 to 7.0 g/ml. Benz(a)anthraquinones are reported to be active against multidrug resistant tumor cells, hence brasiliquinones were tested against multidrug resistant tumor cell P388/ADR and found to be active against P388/ADR as well as P388 cells. These antibiotics thus appeared to overcome the multidrug resistance of P388 cells.

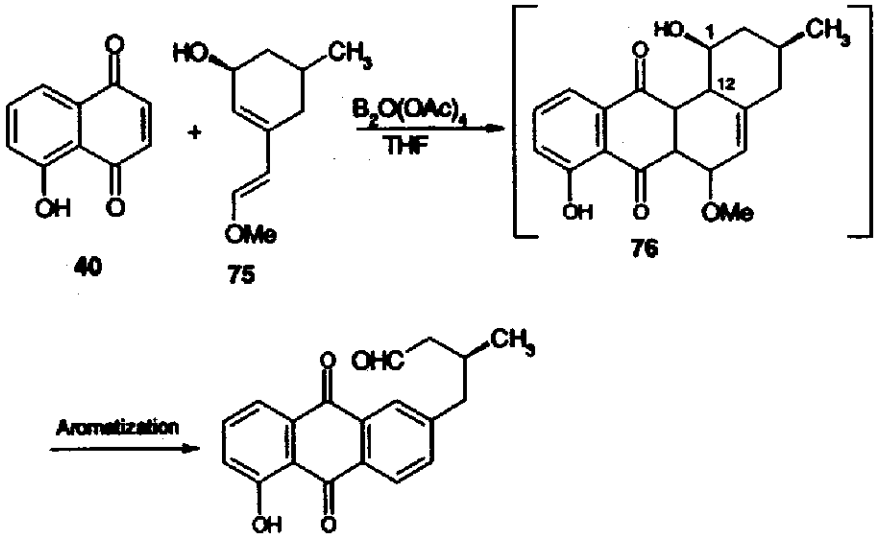
Brasiliquinones possess an ethyl group at C-3 position and hydroxyl group at C-6 position. The presence of a hydroxyl group at C-6 position poses problems in the synthesis, as

there are reports of spontaneous aromatization or carbon-carbon bond cleavage in reactions using Diels-Alder approach.

Guingant et al [45] synthesized ochromycinone (**4**) using a novel Diels-Alder approach as discussed in scheme-6. Spontaneous aromatization and aerial oxidation of the intermediary cycloadduct **41** yielded angucycline ochromycinone (**4**) lacking hydroxyl group at C-6 position.

Larsen et al.[54] used same Diels-Alder reaction approach for the construction of benz(a)anthracene structural framework (Scheme-14). Stereoselective reduction of the carbonyl group of the dienone **38** resulted into increase in the reactivity of the diene and lack of electron withdrawing carbonyl group at C-1 of the corresponding cycloadduct increased its stability. Tetra-O-acetyldiborate promoted cycloaddition of 5-hydroxy-1, 4-napthoquinone (**40**) and dienol **75** afforded the cycloadduct **76** in 84 % yield, but aromatization of the adduct **76** was problematic as it cleaved C_1-C_{12} bond to give substituted anthraquinone **77** as shown in scheme-14.

Scheme-14



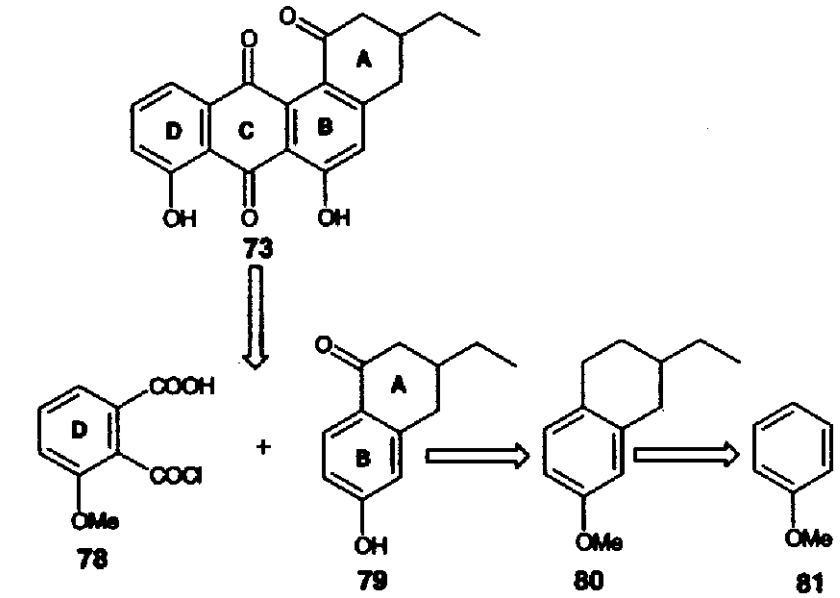
III PRESENT WORK

Problems in the synthesis of angucyclines possessing hydroxyl group at C-6 position, presence of an ethyl group at C-3 position making brasiliquinones structurally different from other angucyclines and interesting biological activities of these brasiliquinones prompted us to undertake the synthesis of these compounds. Syntheses of these compounds are not reported hence it was felt necessary to develop synthetic methodology, which could provide substantial amount of material to be used for further biological studies. In vitro antitumor activity against

multidrug resistant tumor cells P388 showed that brasiliquinones B (**73**) and C (**74**) are more potent than brasiliquinone A (**72**), hence it was decided to undertake the synthesis of brasiliquinone B (**73**).

The retrosynthetic scheme for brasiliquinone B (**73**) is shown in scheme-15.

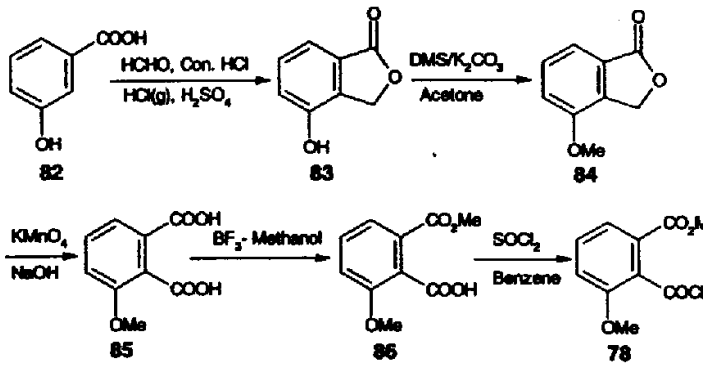
Scheme-15



As per the retrosynthetic analysis we assumed that preparation of functionalised AB ring synthon and its condensation with D ring synthon for the construction of ring C via Friedel-Crafts acylation reaction would give the desired tetracyclic angular framework.

Obviously the most appropriate D ring synthon considered was acid chloride **78**, which has been widely used in the syntheses of anthracyclines. The D ring synthon **78** was prepared from 3-hydroxy benzoic acid (**82**) by known method,[55] as shown in scheme-16. Treatment of 3-hydroxybenzoic acid (**82**) with 37-40 % formaldehyde in conc. hydrochloric acid and concentrated sulfuric acid yielded 4-hydroxyphthalide (**83**), which on treatment with dimethyl sulphate and potassium carbonate gave 4-methoxy phthalide (**84**). Oxidation of **84** with alkaline potassium permanganate yielded 3-methoxy phthalic acid (**85**)[55a]. Selective esterification[55b] of the less hindered carboxylic group of the diacid **85** was achieved using BF_3-methanol at 60°C in absolute methanol to give compound **86**. Preparation of acid chloride **78**, the desired D ring synthon, was achieved by treating acid **86** with thionyl chloride in refluxing benzene.

Scheme-16

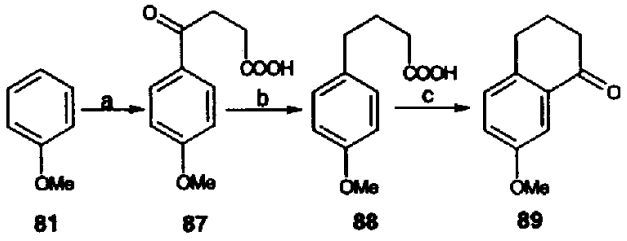


After synthesizing the D ring synthon **78**, efforts were directed towards the synthesis of AB ring synthon **79**. According to the retrosynthetic plan tetralone **79** was assumed to be the most appropriate AB ring synthon. Deactivation of tetralones towards electrophilic attack due to the presence of electron withdrawing ketone is well documented in literature,[56] so we considered tetralin derivative **80** as an ideal AB ring synthon.

Although the key intermediate tetralin **80** looked structurally simple it has not been reported in literature. We undertook the synthesis of this substituted tetralin **80** starting from readily available anisole, involving 7-methoxy-1-tetralone (**89**) as an important intermediate. 7-Methoxy-1-tetralone (**89**) was prepared from anisole[57] in three steps as shown in scheme-17.

Anisole (**81**) on Friedel-Crafts acylation with succinic anhydride in nitrobenzene afforded the ketoacid **87** in 72% yield which was reduced under Clemmensen's reduction condition (Zn-Hg/HCl) to give the acid 88 in 87% yield. Cyclization of the acid **88** with polyphosphoric acid yielded 7-methoxy-1-tetralone (**89**) as an yellow solid in 85 % yield.

Scheme-17



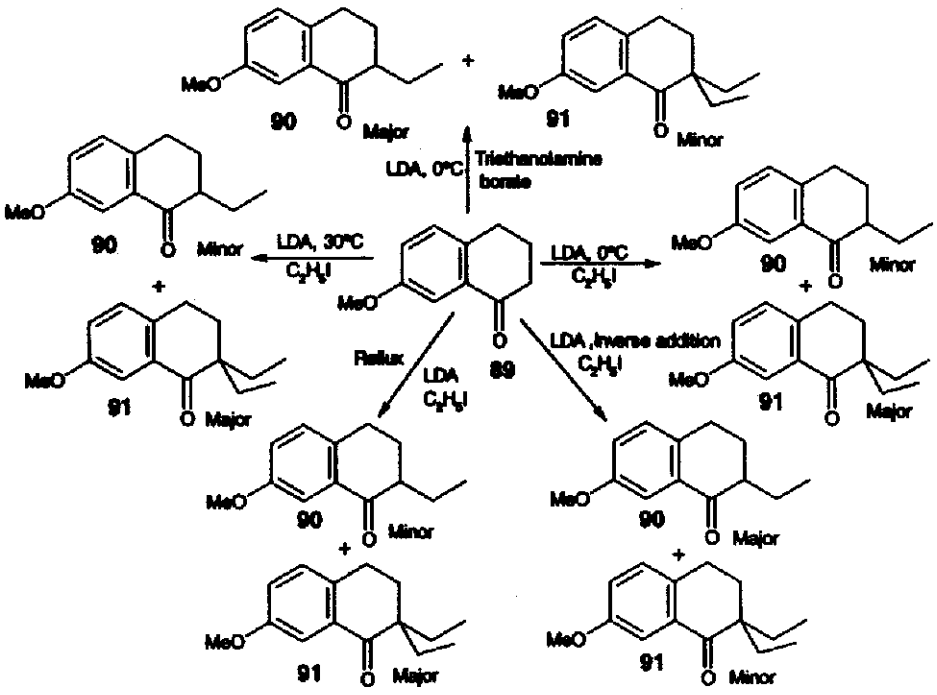
Reagents and conditions:

a. Succinnic anhydride, $AlCl_3$, nitrobenzene, 0°C, RT, 12 hrs, 72%

b. Zn-Hg, Conc. HCl. Reflux, 12 hrs., 87% c. PPA, 80°C, 2 hrs. 85%

Thus, as per the plan, alkylation of tetralone **89** with ethyl iodide followed by reduction of ketone functionality would give the desired AB ring synthon. Unfortunately, attempted monoalkylation of 7-methoxy-1-tetralone (**89**) with ethyl iodide under various conditions ended up with a mixture of monoalkylated product **90** and dialkylated product **91**. Exclusive monoalkylation of tetralone **89** was not as simple as expected and most of the conditions attempted resulted into the mixtures of mono and dialkylated products as shown in scheme-**18**. Main difficulty in this reaction was the separation of the monoalkylated product **90** from dialkylated product **91**. Percentage of monoalkylated product **90** and dialkylated product **91** was determined by gas chromatographic and GC-MS analysis. Exclusive formation of monoallcylated product by inverse addition of lithium enolate to a large excess of ethyl iodide is documented in the literature but under this condition we ended up with the formation of major monoalkylated product **90** along with traces of dialkylated product **91** which could not be separated as both the products were having same R_f values.

Scheme-18

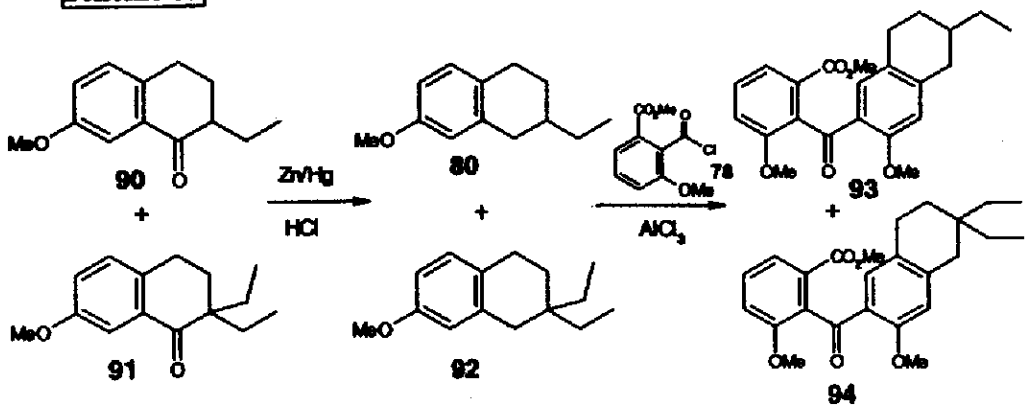


Triethanolamine borate along with LDA[58]is reported to be a very good reagent for exclusive formation of monoalkylated product. To explore the utility of this method triethanolamine borate was prepared from triethanolamine and boric acid, by the known

procedure.[59] Attempted monoalkylation of 7-methoxy-1-tetralone (**89**) by generation of boron enolate, which was accomplished by reacting the lithium enolate of **89** with triethanolamine borate in DMSO, followed by treatment with ethyl iodide resulted into major monoalkylated product **90** but still containing traces of dialkylated product **91**.

We felt that separation of these products can be achieved after reduction of ketone functionality of the tetralones ,and hence the mixture obtained by alkylation of boron enolate of **89** with ethyl iodide was reduced under Clemmensen's condition but the reduction yielded a tnixture of **80** and **92** which could not be separated. Separation of monolakylated product from dialkylated product could not be achieved even after Friedel-Crafts reaction of this mixture with benzoyl chloride **78** as shown in scheme-19.

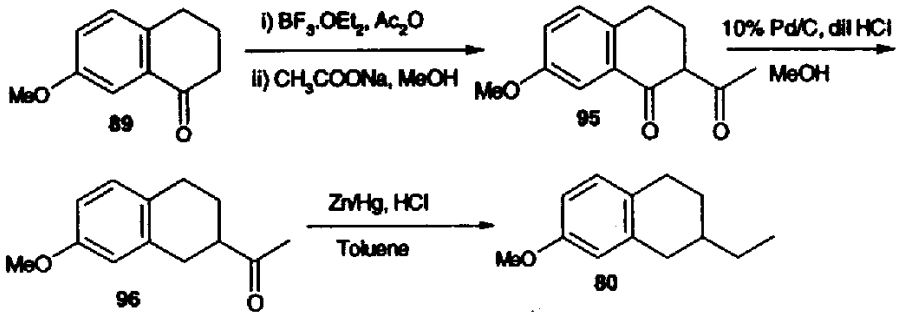
Scheme-19



The mass spectrum of the product obtained showed molecular ion peaks at m/z 410 and 382, indicating it to be a mixture of compounds **94** and **93** respectively.

Difficulties in the exclusive monoalkylation of tetralone forced us to undertake another route for the synthesis of tetralin derivative **80** as shown in scheme-20.

Scheme-20



Accordingly 7-methoxy-1-tetralone (**89**) was acylated using acetic anhydride and $BF_3.Et_2O$ at room temperature followed by decomposition of boron complex with sodium acetate in refluxing methanol to give 2-acetyl-7-methoxy-1-tetralone (**95**) in 65 % yield.

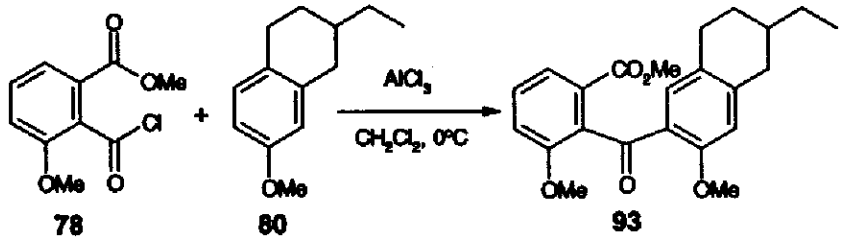
Structure of compound **95** was confirmed by spectral means. ^1H NMR spectrum of the compound **95** revealed presence of a singlet at 8 2.25 for $COCH_3$ and rest of the peaks were at appropriate positions with proper integrations. The IR spectrum showed absorption band at 1640 and 3300 cm^{-1} indicating presence of a Bdicarbonyl group. The mass spectrum also supported the assigned structure for compound **95**. Hydrogenation of the compound **95** using 10 °Xo Pd/C and HCl in methanol afforded compound **96** in 60% yield. Structure assigned to the compound % was confirmed by its spectral analysis. A singlet at 8 2.25 in ^1H NMR spectrum and a band at 1675 cm^{-1} in IR spectrum suggested presence of an acetyl group. The compound **96** was then reduced under Clemmensen conditions (Zn/Hg/HCl) to afford the desired tetralin **80** in 77 % yield. The 'H NMR spectrum of tetralin **80** showed the disappearance of a singlet at 8 2.25 for acetyl group and appearance of newly formed ethyl group. The mass spectrum exhibiting presence of molecular ion peak at m/z 190 (M^+) was in good agreement with the assigned structure **80**.

After the synthesis of required D ring synthon **78** and AB ring synthon **80**, FriedelCrafts acylation approach was attempted (Scheme-21) for the construction of the benz(a)anthracene structural framework of brasiliquinone B (**73**).

1.1.2 Friedel-Crafts acylation approach for brasiliquinone B

The tetralin **80** on Friedel-Crafts acylation with the benzoyl chloride **78** in presence of aluminum chloride yielded compound **93** in 70% yield.

Scheme-21



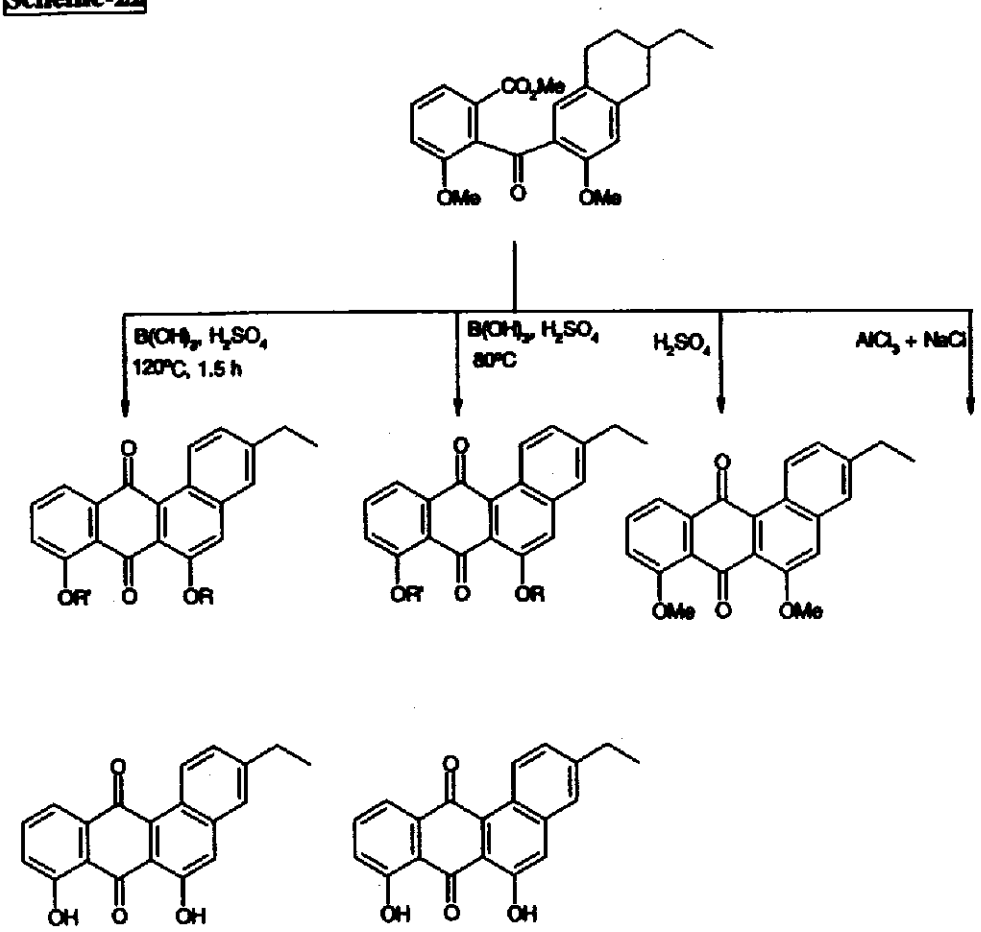
78 80 93

Structure of the compound **93** was assigned on the basis of its ^1H NMR spectrum which revealed two singlets, each integrating for one proton at 8 6.58 and at 8 7.68 indicating regioselectivity in acylation reaction. Formation of the compound **93** was further confirmed by its IR spectrum showing absorption band at 1700 cm^{-1} for ketone carbonyl

and a band at 1750 cm^{-1} for ester carbonyl and the mass spectrum which exhibited molecular ion peak at m/z 382 (M^+). Next aim was the cyclization of compound **93** and its oxidation to give the desired dimethyl ether of brasiliquinone B. Accordingly cyclization of the compound **93** was attempted under boric acid and H_2SO_4[60] condition but surprisingly it resulted into A ring aromatized product as shown in scheme-22.

Treatment of compound **93** with boric acid in presence of H_2SO_4 at 120°C resulted into the formation of mixture of compounds **97a+976** and **98**, members of tetrangulol (2)[11] group of angucycline antibiotics as shown in scheme-22.

Scheme-22



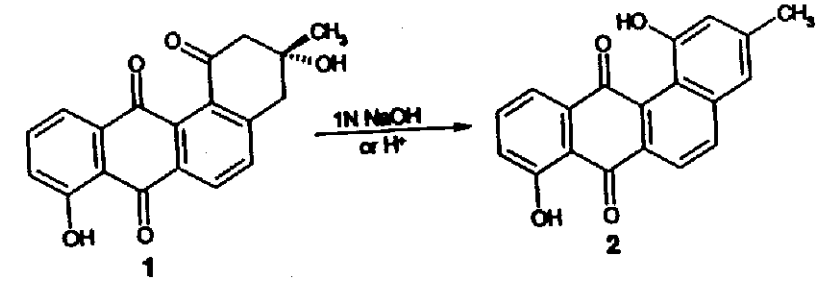
The ^1H NMR spectrum of the compound **(97a+97b)** showed mixture of two regioisomers possessing one methoxy group and one hydroxy group which could not be separated while compound **98** possesses hydroxyl groups at C-6 and C-8. Decreasing the temperature and time of the reaction also resulted into the same products. Assuming boric acid to be responsible for the aromatization of A-ring, cyclization was attempted with

H_2SO_4 at 80°C resulting into cyclized and arornatized product **99** having both methoxy groups intact.

The structure of compound **98** were established with the help of spectral data. Shifting of triplet of methyl protons from 8 0.97 to 8 1.39 and appearance of a quartet at 8 2.82 indicated the presence of an aromatic ethyl group as well as presence singlets for chelated -0H groups at 8 12.20 and 12.38 however ^{1}H NMR of compound **97** suggested presence of regioisomers **97a** and **97b**. The molecular ion peaks at m/z 332, 318 and 346 for the compounds **97a+97b**, **98** and **99** respectively in their mass spectra supported the existence of A-ring aromatized product. Cyclization of the **93** with H_2SO_4 at room temperature resulted into no reaction while the cyclization with aluminum chloride, sodium chloride melt at 180°C resulted into a complex mixture.

In the literature angucyclines possessing aromatic A ring have been reported. Tetrangomycin (**1**)[10] and tetrangulol (**2**)[11] were isolated by Kunstman and Mitscher in 1965[8, 9]. Mild base or acid treatment to tetrangomycin (**1**) yielded a natural product tetrangulol (**2**) as shown in scheme-23.

Scheme-23



1 **2**

Tetrangulol (**2**) was synthesized by Brown and Thomson using Michael reaction, as shown in scheme-1. Compounds **97a+97b**, **98** and **99** obtained in the present work are the novel analogues of brasiliquinone B (**73**) of the tetrangulol type of angucyclines.

Although the attempted Friedel-Crafts acylation approach for the synthesis of brsiliquinone B resulted in the synthesis of these new analogs of brasiliquinone B, the synthesis of targeted molecule brasiliquinone B remained as a challenge. We assumed that cyclization under mild condition was necessary to avoid the aromatization of ring A. Deactivation of the compound **93** for cyclization under mild condition was probably due to the presence of ketone functionality and hence we planned to utilize Friedel-Crafts alkylation approach for the synthesis of brasiliquinone B.

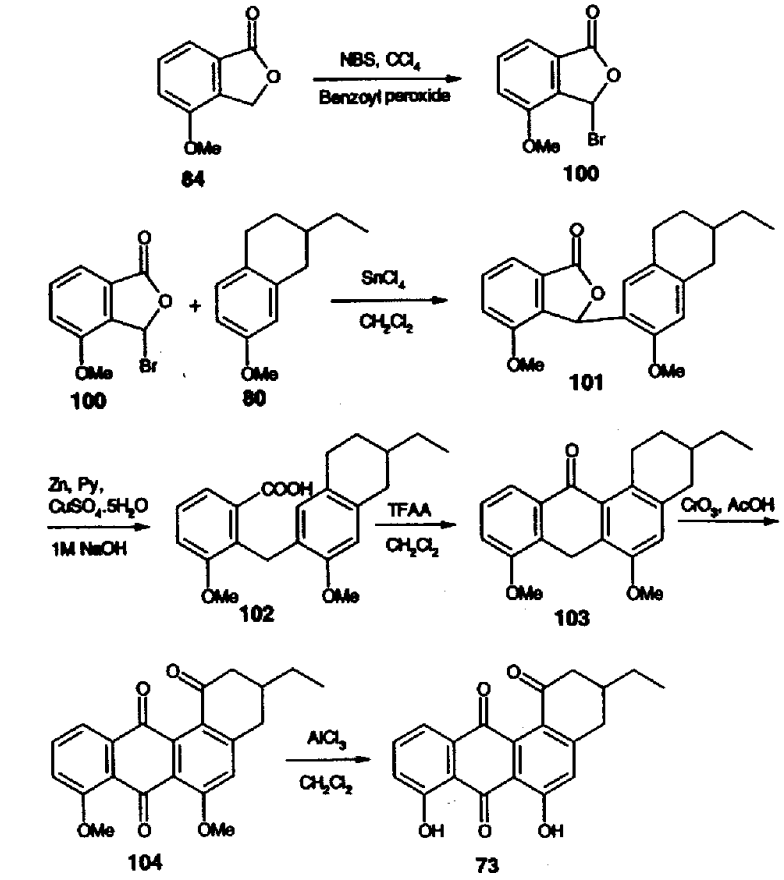
1.1.3 Friedel-Crafts alkylation approach

After being unsuccessful in obtaining brasiliquinone B by Friedel-Crafts acylation approach it was modified to Friedel-Crafts alkylation approach.

Jonhnson et a1.[55] introduced a phthalido-residue into the aromatic nucleus by Friedel-Crafts reaction of an appropriate AB ring synthon with 3-bromo-4 methoxyphthalide (**100**) in presence of stannic chloride. It was thought to utilize this approach for the construction of benz(a)anthraquinone structural framework.

Accordingly, 3-bormo-4-methoxyphthalide (**100**) was prepared by benzylic bromination of 4-methoxyphthalide (**84**) with N-bromosuccinimide in carbon tetrachloride. Friedel-Crafts alkylation of tetralin **80** with 3-bromo-4-methoxyphthalide (**100**) in presence of stannic chloride in methylene chloride at 0°C afforded regiospecifically the lactone **101** in 84 % yield as shown in scheme-24.

Scheme-24



The structure of lactone **101** was fully confirmed by spectral means. IR spectrum of lactone **101** showed an absorption band at 1745 cm^{-1} for the lactone system. The ^{1}H NMR spectrum showed a triplet at 8 0.99 for three protons, a multiplet at 8 1.22-2.92 for nine protons, singlets at S 3.75 and 3.80 for two methoxy groups and a characteristic singlet at 8 6.50 (Ar-CH-Ar) in addition to the rest of the peaks at appropriate positions. The ^{13}C NMR spectral data was in good agreement with assigned structure. The mass spectrum showed molecular ion peak at m/z 352 (M^{+}) thus confirming the structure **101**.

It has been demonstrated in the literature that the reductive cleavage of lactonic system could be effected with zinc under acidic[61] (zinc formic acid, water) or alkaline (zinc, potassium hydroxide, pyridine, water[62] zinc, potassium hydroxide pyridine, cupric sulphate, water[63]) conditions. Another method for the reductive opening of the lactones involves hydrogenation under basic (H_2, Pd/C, methanolic potassium hydroxide)[64]or acidic (H_2, Pd/C, acetic acid)[65] condition. The lactone **101** underwent smooth reductive opening with refluxing zinc in 1N sodium hydroxide, pyridine, and catalytic cupric sulphate for 10 hrs to give acid 102 in 85 % yield. ^{1}H NMR analysis of the compound **102** revealed a singlet at S 4.26 for two protons suggesting the presence of benzylic methylene group, whereas the IR spectrum showed a band at 3450 cm^{-1} for carboxylic acid. The mass spectrum of acid **102** showing presence of molecular ion peak at m/z 354 was in good agreement with the assigned structure.

Cyclization of the acid **102** to the anthrone **103** was achieved effectively using trifluoroacetic anhydride in methylene chloride. Excess of trifluoroacetic anhydride was added to the acid **102** in dry methylene chloride at 0°C and then the mixture was allowed to stir at room temperature overnight: Removal of the trifluoroacetic anhydride and methylene chloride under reduced pressure followed by stirring the residue with the saturated solution of potassium carbonate, extraction with methylene chloride and purification by column chromatography afforded anthrone **103** in 64% yield, as a pale yellow solid. Anthrone **103** was fully characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectra. The IR spectrum of the anthrone **103** showed absorption band at 1734 cm^{-1} indicating the presence of carbonyl function. The ^{1}H NMR spectrum revealed disappearance of a singlet from aromatic region of C ring. The ^{13}C NMR spectrum revealed the presence of a peak at 8 186 for carbonyl carbon of the anthrone **103**.

Next target was to oxidize the anthrone **103** to the dimethyl ether of brasiliquinone B (**104**). The desired oxidation was carried out under chromium trioxide-acetic acid

conditions to afford the compound **104** in 93 % yield. Disappearance of multiplets at 8 3.12-3.35 and 3.43-3.62 as well as a multiplet at 8 3.78-4.12 in ^{1}H NMR suggested conversion of C-1 and C-7 benzylic methtylene groups to the carbonyl groups in one step. The structure of compound **104** was further confirmed by IR, ^{13}C NMR and mass spectra. The IR spectrum showed strong absorption bands at 1705 and 1675 cm^{-1} while ^{13}C NMR spectrum revealed presence of three carbonyl carbons at S 182.35, 186.83 and 198.63. Finally the desired synthesis of (f)-brasiliquinone B (**73**) was achieved by demethylating the dimethyl ether of brasiliquinone B **104** using aluminum chloride in 80 % yield. This compound was characterized by IR, IH NMR and Mass spectra. All spectral data for compound **73** was in good agreement with the values reported in literature.

1.1.4 CONCLUSION

Thus a short, simple and regioselective methodology has been developed for the total synthesis of (f)-brasiliquinone **B** (**73**) using Friedel-Crafts alkylation approach. Although the Friedel-Crafts acylation approach failed to give brasiliquinone **B**, it can be utilized for the synthesis of tetrangulol type of angucyclines. This synthesis of (f) brasiliquinone **B (73)** is regioselective and mild, and would prove to be a convenient route towards synthesis of other angucycline antibiotics especially angucyclines possessing a hydroxy group at C-6 position.

1.1.5 EXPERIMENTAL

4-Hydroxyphthalide (83):

Dry HCl gas was passed through a solution of 3-hydroxy benzoic acid (41.4 gm, 0.3 mole), formaldehyde (800 ml, 40 %), conc. hydrochloric acid (800 ml) and sulfuric acid (80 ml) at 30-40°C for 2 hr. The separated solid was filtered, washed with water till free from acid, dried and crystallized from acetone to give **83** (12 gm, 28 %) as colourless crystalline product; m.p. 251-2 °C (lit. [55a] m.p. 253-4 °C).

4-Methoxyphthalide (84):

A mixture of 4-hydroxyphthalide (12 gm, 0.08 mole), potassium carbonate (50 gm, 0.36 mole), dimethyl sulfate (12.6 gm, 0.1 mole) and dry acetone (500 ml) was heated at reflux for 6 hr. The acetone was distilled off and crushed ice was added to give a solid which was filtered, dried and recrystallized from hexane-benzene (1:1) to give **84** (12.1 gm, 93 °Xo) as colourless needles; m.p. 126.6 °C (lit. [55a]m p. 127 °C).

3-Methoxyphthalic acid (85):

A mixture of compound **84** (8.2 gm, 0.5 mole), aqueous NaOH (10 °,~o, 250 ml) and aqueous potassium permanganate (12 gm in 360 ml of water) was stirred at room temperature for 12 hr. Ethanol (5 ml) was added to destroy excess of potassium permanganate and mixture stirred for 30 min, washed with hot water and the filtrate was concentrated to **80** ml under reduced pressure. The concentrated aqueous solution was cooled to 0°C and acidified with dil. hydrochloric acid (50%) till acidic to congo red, the solution was saturated with sodium chloride and extracted with ether (3 X 100 ml). The ethereal layer was dried (Na_2SO_4) and concentrated when **85** separated as colourless solid. It was filtered and crystallized from benzene to afford **85** (8.9gm,90 %) as colourless crystals; m.p. 173-4 °C (lit.[55b] m.p. 173-4 °C).

Methyl 2-carboxy-3-methoxybenzoate (86):

A mixture of the acid 85 (1.96 gm, 0.01 mole), BF_3-methanol (14 %, 5 ml) and dry methanol (25 ml) was heated under reflux for 6 hrs. The methanol was removed to give thick slurry. It was treated with saturated sodium chloride solution. The precipitated compound was filtered, dissolved in saturated sodium bicarbonate solution and extracted with ether. The aqueous layer was acidified with dil. HCl to precipitate acid. Filtration and

crystallization of the precipitated solid from benzene-hexane (1:1) afforded the ester **86** (1.47 gm, 70 %) as colourless crystals; m.p. 1 SO-2 °C (lit. [55c] m.p. 1 S 1-3 °C).

4-Oxo-4-(4'-methoxyphenyl)butyric acid (87):

Aluminum chloride (94 gm, 0.7 mole) was added slowly at 0°C to a stirred mixture of succinic anhydride (36 gm, 0.36 mole) and anisole (3S.7 gm, 0.33 mole) in nitrobenzene (1S0 ml). The resulting mixture was stirred overnight at room temperature. The solution was then poured into the mixture of crushed ice and conc. HCl (20 ml). The chilled mixture was stirred for 1S min. and solid obtained was filtered through sintered funnel washed with pet-ether (3X100 ml) to remove the nitrobenzene. Recrystallization from absolute ethanol afforded crystals of 87 (49.5 gm, 72 96); m.p. 147-S °C (lit [57]m.p. 146 °C).

4-(4'-Methoxyphenyl)butyric acid (88):

Zinc wool (53.5 gm, 0.8 mol), mercuric chloride (S.3 gm), concentrated HC1 (4.S ml) and water (120 ml) were mixed together with stirring for 10 min. The aqueous layer was decanted and residue was washed with water. The compound 87 (22.2 gm, 0.1 mole) was then added to the above prepared zinc amalgam followed by slow addition of concentrated hydrochloric acid (76 ml) and water (38 ml). The mixture was refluxed for 12 hr. The hot aqueous layer was decanted and allowed to cool. The solid separated was filtered and dried to give crystals of compound **88** (18 gm, 87 %); m.p. 60.5-61.5 °C (lit. [57] 61 °C)

7-Methoxy-1-tetralone (89):

Phosphorus (V) oxide (114 gm) and phosphoric acid (8S 9n, S6 ml) were mixed with mechanical stirring and heated to 80-90 °C for 4 hr. The compound **88** (7.S gm, 38.6 mmol) was added to it and the resulting mixture was heated at 70-80 °C for 2 hr. Ice-water (300 ml) was added to decompose the polyphosphoric acid, and the mixture was extracted with dichloromethane (3X150 ml). The organic layer was washed with brine, dried over sodium sulphate and evaporated to give a yellowish solid (6.4 gm, 94 %). The crude product was recrystallized from EtOAc/hexane (lS:8S) to afford colourless prismatic crystals of 89 (S.7 g, 8S °b); m.p. 61 °C (lit.[57] m.p. 62 °C).

Typical experimental procedure for the alkylation of 7-methoxy-1-tetralone

n-BuLi (7.15 ml of 1.4 M solution in hexane, 0.01 mole) was added dropwise to a stirred solution of diisopropylamine (1 g, 0.01 mole) in anhydrous THF (10 ml) at -30 °C temperature. The reaction mixture was stirred for1/2hr at the same temperature and allowed to warm-up to 0 °C. Then 7-methoxy-1-tetralone (1.7 g, 0.01 mole) in THF (S ml) was

added dropwise and the resulting mixture was stirred at room temperature. After 1 h triethanolamine borate (1.88 g, 0.012 mole) in anhydrous DMSO (5 ml) was introduced to the above reaction mixture and stirred vigorously at room temperature. After 2 hr ethyl iodide (4.1 ml, 0.05 mole) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. Evaporation of the solvent under reduced pressure followed by column chromatographic purification on silica gel afforded inseparable mixture of compounds **90** and **91** (same Rf values) (1.2 g) as a colourless liquid.

Compound **90**: (75 %, GC). Mass (m/z): 204 (M^+).

Compound **91**: (8 %n, GC). Mass (m/z): 232 (M^+).

2-Acetyl-7-methoxy-1-tetralone (95):

BF_3-etherate (7.5 ml) was added dropwise to a stirred mixture of 7-methoxy-1 tetralone (2.46 gm, 0.014 mole) in 25 ml acetic anhydride. The dark brown solution was then stirred at room temperature for 2 hr. It was then poured into ice-water (250 ml), stirred for 1 hr, filtered and the residue was dissolved in methanol (150 ml). As saturated solution of sodium acetate (100 ml) was added to it, followed by refluxing for 4 hr. The methanol was removed by distillation and the solution was extracted with chloroform. The chloroform layer was washed successively with water (3 X 50 ml), brine and dried over sodium sulphate. Evaporation of the solvent followed by purification by column chromatography afforded 95 as yellow solid (1.98 gems. 65 %); m.p. 60-62 °C.

IR ($CHCI_3$):	3300, 1640 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz):	8 2.25 (s, 3H, $CO\underline{CH_3}$, 2.55-2.65 (m, 2H), 2.75-2.90 (m, 2H), 3.85 (s, 3H, -OMe), 6.92-7.200 (m, 1H, aromatic), 7.05-7.25 (m, 1 H, aromatic), 7.45 (s, 1 H, aromatic), 16.45 (s, 1H, -OH).
Mass (m/z):	218 (M^+).
Analysis:	Calculated for $C_{13}H_{14}O_3$, C 71.55, H 6.42;
	Found C 71.00, H 6.60 %.

2-Acetyl-7-methoxytetralin (96):

2-Acetyl-7-methoxy-1-tetralone (2.18 gm, 10 mmole) was dissolved in methanol (50 ml), followed by addition of conc. HCl (1 ml) and water (1 ml). 10 % Pd/C (0.5 gm) was then added to it and the mixture was subjected to hydrogenation at 50 psi pressure for

8 hr. The mixture was filtered through Celite and methanol was removed from the filtrate under reduced pressure. The oily residue was extracted with chloroform thrice. The combined organic layer was washed with water, brine and dried over sodium sulphate. Evaporation of the solvent and purification of the residue by column chromatography yielded compound **96** as colourless liquid. (1.22 gm, 60 %).

IR ($CHCl_3$): 1675 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): S 1.60-1.78 (m, 2H), 2.15-2.22 (m, 1H), 2.25 (s, 3H,$CO\underline{CH_3}$), 2.70-2.80 (m, 2H), 2.90-2.98 (m, 2H), 3.79 (s, 3H, -OMe), 6.61 (s, 1H, aromatic), 6.70 (d, J=6.06 Hz, 1H, aromatic), 7.00 (d, J=6.06 Hz, 1H, aromatic).

Mass (m/z): 204 (M+).

Analysis: Calculated for $C_{13}H_{16}O_2$, C 76.47, H 7.84;
Found C 76.23; H 7.95 %.

2-Ethyl-7-methoxy-1, 2,3,4-tetrahydronaphthalene (80):

Zinc wool (7 gm), mercuric chloride (700 mg), conc. HCl (2 ml) and water (10 ml) were mixed together with stirring for 10 min. The aqueous layer was decanted and the residue was washed with water twice. 2-Acetyl-7-methoxytetralin (2.99 gm, 14.70 mmol) in 20 ml toluene was added to above prepared zinc amalgam, followed by concentrated HCl (5 ml). After cooling, water (5 ml) was added and the mixture was refluxed for 12 hr. Then the mixture was filtered through Celite, toluene layer was separated and washed with water, brine and dried over sodium sulphate. Removal of the toluene under reduced pressure and purification of the residue by column chromatography afforded compound **80** as colourless liquid (2.14 gm, 77 %).

IR ($CHCl_3$): 1608 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 1.00 (t, J=7.29 Hz, 3H), 1.35-1.50 (m, 3H), 1.52-1.75 (m, 1H), 1.80-2.05 (m, 1H), 2.15-2.55 (m, 2H), 2.65-2.95 (m, 2H), 3.90 (s, 3H, -OMe), 6.55-6.80 (m, 2H, aromatic), 7.00 (d, J=7.8 Hz, 1H, aromatic).

Mass (m/z): 190 (M^+).

Analysis: Calculated for $C_{13}H_{18}O$, C 82.10, H 9.47;
Found C 82.00 H 9.52%.

3-Ethyl-6-methoxy-7-(2'-Carbomethoxy-6'-methoxybenzoyl)-1,2,3,4-tetrahydro--naphthalene (93):

A mixture of **86** (432 mg, 2 mmole), thionyl chloride (550 mg, 5 mmole) dimethylformamide (catalytic amount 0.1 ml) and dry benzene (25 ml) was heated at reflux for 4 hr (paper chromatography indicated the formation of a new compound). The solvent was distilled to give 2-carbomethoxy-6-methoxybenzoyl chloride (**78**) as colourless semisolid compound . IR (neat): 1800 cm^{-1} (acid chloride).

The compound **80** (380 mg, 2 mmole) in dichloromomethane (5 ml dry) under nitrogen atmosphere, was cooled to 0°C. Anhydrous aluminum chloride (400 mg, 3 mmole) was added to it slowly and allowed to stir for 15 min. The acid chloride **78** (456 mg, 2 mmol) in 5 ml dry dichloromethane was added dropwise to the above reaction mixture at 0°C. The resulting mixture was allowed to stir at 0°C for i/z hr and at room temperature overnight. After completion of reaction (TLC), the reaction mixture was poured on the mixture of crushed ice and conc. HCl (2 ml), allowed to stir for 10 min and extracted with dichloromethane thrice (3X20 ml). The combined organic layer was washed with water, brine and dried over sodium sulphate. Evaporation of the solvent followed by . column chromatographic purification yielded compound **93** as a colourless semisolid (534.8 mg, 70 °l6).

IR ($CHCl_3$): 1700, 1750 cm^{-1}.

^1H NMR ($CDCI_3$, 200 MHz): S 0.99 (t, J--7.02 Hz, 3H), 1.30-1.50 (m, 3H), 1.51- 1.80 (m, 2H), 1.89-2.00 (m, 1H), 2.30-2.55 (m, 1H), 2.65-2.97 (m, 2H), 3.50 (s, 3H, -OMe), 3.72 (s, 3H, -OMe), 3.75 (s, 3H, CO_2Me), 6.58 (s, 1H, aromatic), 7.10 (d, J=8.1 Hz, 1 H, aromatic), 7.40 (t, J=8.1 Hz, 1H, aromatic), 7.62 (d, J=8.1 Hz, 1H, aromatic), 7.68 (s, 1H, aromatic).

Mass (m/z): 382 (M^+).

Cylization of compound 93:

A mixture of ester **93** (382 mg, 1 mmol), conc. H_2SO_4 (2 ml) and boric acid (100 mg) was heated at 120°C for 1.5 h with stirring. The reaction mixture was cooled and poured over crushed ice. 1fie dark brown aqueous part was extracted with chloroform and the chloroform layer was washed successively with saturated solution of sodium

bicarbonate, water, brine and dried over sodium sulphate followed by column chromatographic purification to afford compounds (**97a+97b**) and **98** as reddish foam.

Compound 98:

Yield: 111 mg (35 %).

^{1}H NMR ($CDCl_3$, 200 MHz): 8 1.39 (t, J=7.8 Hz, 3H, -$CH_2\underline{CH_3}$), 2.82 (q, J=6.2 Hz, 2H, -$\underline{CH_2}CH_3$), 7.30 (s, 1H, aromatic), 7.38 (t, J=7.8 Hz, 1H, aromatic), 7,47 (d, J=7.8 Hz, 1H, aromatic), 7.61 (s, 1H, aromatic), 7.68 (d, J=7.8 Hz, 1H, aromatic), 7.85 (d, J--7.8 Hz, 1H, aromatic), 9.50 (d, J=7.8 Hz, 1H, aromatic), 12.20 (s, 1H, -OH), 12.38 (s, 1H, -OH).

Mass (m/z): 318 (M^+).

Compound 97a+97b:

Yield: 97 mg (30 %).

^{1}H NMR showed inseparable mixture of regioisomers **97a** and **97b**.

Mass (m/z): 332 (M^+).

Compound 99:

A mixture of ester 93 (382 mg, lmmol) and conc. H_2SO_4 (2 ml) was heated at 80 °C for 1/2 hr with stirring. The reaction mixture was cooled and poured over crushed ice. The dark brown aqueous part was extracted with chloroform and chloroform layer was washed successively with saturated solution of sodium bicarbonate, water, brine and dried over sodium sulphate followed by column chromatographic purification to afford compounds **99** (155.7 mg, 45 %) as reddish foam.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.38 (t, *J* = 7.5 Hz, 3H, - $CH_2\underline{CH_3}$), 2.75-2.95 (m, 2H,-$\underline{CH_2}CH_3$), 4.05 (s, 3H, -OMe), 4.08 (s, 3H, -),7.25(d, J--7.6 Hz, 1H, aromatic), 7.48 (s, 1H, aromatic), 7.52 (d, J--7.6 Hz, 1H, aromatic), 7.58 (s, 1H, aromatic), 7.65 (t, J=7.6 Hz, 1H, aromatic), 7.78 (d, J=7.6 Hz, 1H, aromatic), 8.95 (d, J=7.6 Hz, 1H, aromatic).

Mass (m/z): 346 (M^+)

3-Bromo-4-methoxyphthalide (100):

A mixture of 4-methoxyphthalide (**84**) (3.32 gm, 0.02 mole), N-bromosuccinimide (3.56 gm, 0.02 mole) and catalytic amount of benzoylperoxide in carbon tetrachloride (150 ml) was exposed to 500 W electric bulb and the solution was allowed to reflux for 1 hr. Then the solution was cooled, filtered and concentrated at reduced pressure. White solid obtained was recrystallized from 50:5 pet-ether:benzene to give white crystals of compound **100** (3.5 gm, 71.32 %); m. p. 114-116 °C (lit.[55] m. p. 114-5 °C).

3-(6-Ethyl-3-methoxy-5,6,7,8-tetrahydro-2-napthalenyl)-4-methoxy-1(31~-isobenzo -furanone (101):

The tetralin derivative **80** (570 mg, 0.003 mole) was added with stirring to a solution of 3-bromo-4-methoxyphthalide (1.09 gm, 0.0045 mole) in dry methylene chloride at 0°C. Stannic chloride (6.5 gm, 0.252 mole) was then introduced and the resulting mixture was stirred at 0°C for 1 hr. It was then poured into the mixture of crushed ice and conc. HCl (3 ml), stirred for 30 min and extracted with methylene chloride. The combined methylene chloride layer was washed with water, brine and dried over sodium sulfate. Evaporation of the solvent and purification by column chromatography afforded compound **101** (887 mg, 84 %) as white solid; m.p.132-133 °C

IR (Nujol):	1745 (lactone), 1690 (ketone), 1596 cm^{-1} (aromatic).
^{1}H NMR (CDCl3, 200 MHz):	8 0.99 (t, J=7.29 Hz, 3H), 1.22-1.49 (m, 3H), 1.50- 1.65 (m, 1H), 1.80-1.99 (m, 1H), 2.30-2.51 (m, 1H), 2.55-2.65 (m, 2H), 2.75-2.92 (m, 1H), 3.75 (s, 3H, - OMe), 3.80 (s, 3H, -OMe), 6.50 (s, 1H, aromatic), 6.62 (s, 1H, phthalide), 6.75 (s, 1H, aromatic), 7.00- 7.15 (m, 1H, aromatic), 7.45- 7.58 (m, 2H, aromatic).
^{13}C NMR ($CDCl_3$, 50 MHz):	8 11.94, 28.81, 29.69, 36.31, 36.79, 56.27, 56.42, 112.32, 115.93, 117.47, 121.59, 128.94, 129.45, 131.44, 137.80, 139.86, 155.11, 156.43, 171.36.
Mass (m/z):	352 (M^+).
Analysis:	Calculated for $C_{22}H_{24}O_4$, C 75.00, H 6.81;
	Found C 74.52, H 6.36 %.

2-{(6-Ethyl-3-methoxy-5,6,7,8-tetrahydro-2-naphthalenyl)methyl}-3-methoxybenzoicacid (102):

The lactone **101** (704 mg, 0.002 mole) was reductively opened by heating with 1M solution of NaOH (40 ml), activated zinc (3.7 gm, 0.058 mole), $CuSO_4.5H_20$ (catalytic) and pyridine (10 ml) at 125 °C for 10 hrs under nitrogen atmosphere. The mixture was then allowed to cool and filtered through a pad of celite. Acidification of the filtrate with concentrated HCl afforded the corresponding acid **102** (601 mg, 85%) as white solid; m. p. 198-200 °C.

IR (Nujol):	3450, 1609 cm^{-1}.
^1H NMR (Acetone d_6, 200 MHz):	S 0.86 (t, J=7.29 Hz, 3H), l.l l-1.36 (m, 3H), 1.37-1.56 (m, 1H), 1.68-1.86 (m, 1H), 2.16-2.38 (m, 1H), 2.44-2.56 (m, 2H), 2.66-2.78 (m, 1H), 3.71 (s, 6H, 2XOMe), .26 (s, 2H, benzylic),6.38 (s, 1H,aromatic), 6.44 (s, 1H, aromatic), 6.% (d, J=8.1 Hz,1H, aromatic), 7.21 (t, J=8.1 Hz, 1H, aromatic), 7.42(d, J--8.1 Hz, 1H, aromatic).
^{13}C NMR (Acetone d6, 50 MHz):	8 11.87, 25.%, 28.53, 29.19, 36.06, 40.95, 41.36, 55.65, 56.35, 110.83, 114.32, 122, 126.78, 127.70, 128.58,134.65, 155.45, 158.57, 164.19, 170.92, 175.96.
Mass (m/z):	354 (M^+).
Analysis:	Calculated for $C_{22}H_{26}O_4$, C 74.57, H 7.34;
	Found C 74.20, H 7.17 %.

6,8-Dimethoxy-3-ethyl-l, 2, 3, 4, 7-pentahydro-benz(a)anthracene-12(1F~-one (103):

The acid 102 (495 mg, 0.0014 mole) in dry methylene chloride (15 ml) was cooled to 0°C, and freshly distilled trilluoroacetic anhydride (5 ml) was added to it under nitrogen atmosphere. The mixture was allowed to stir at 0°C for 30 min and the stirring was continued overnight at room temperature. The TFAA and methylene chloride were removed under reduced pressure and saturated solution of potassium carbonate (20 ml) was added to it. This mixture was extracted with chloroform. The combined chloroform layer was washed with water and brine, followed by drying over sodium sulphate and evaporation of the chloroform to yield yellow coloured crude anthrone **103**. Its purification

by column chromatography over silica gel yielded anthrone **103** (300 mg, 64 %) as a pale yellow solid; m. p. 220-222 °C.

IR (Nujol): 1734 (retone), 1597 cm^{-1}.

^{1}H NMR ($CDCI_3$, 200 MHz): & 1.02 (k J=7.29 Hz, 3H), 1.21-I.50 (m, 2H), 1.51-1.78 (m, IH), 1.99-2.12 (ro, 1H), 2.40-2.60 (m, H),2.95 (d, l-12.42 Hz, 2H), 3.12-3.35 (m, 1H), 3.43- 3.62 (m, IH), 3.78-4.18 (m. 2H, benzylic), 3.90 (s, 3H, OMe), 3.95 (s, 3H, -OMe), 6.80 (s, IH, aromatic), 7.05 (d, J=8.1 Hz, 1H, ammatic), 7.40 (k J=8.1 Hz, IH, aromatic), 7.85 (d, J=8.1 Hz, 1H, amnoatic).

^{13}C NMR ($CDCI_3$, 50 MHz): 8 11, 22, 28, 29, 34, 37, 55, 111, 114, 118, 126, 128, 130, 131, 134, L36, 153, 156, 186.

Mass (m/z): 336 (M^+, 100), 332 (15): 321(30), 307 (40).

Analysis: Calculated for $C_{22}H_{24}O_3$, C 78.52%, H 7.19;
Found C 78.60, H 7.17 %.

Dimethyl ether of brasiliquidone B (104):

Chromium trioxide (150 mg, l.5 mmole) in 80 % acetic acid (3 ml) was added slowly to the mixture of compound **103** (36.96 mg, 0.11 mmole) in glacial acetic acid (2 ml) at 0°C. The reaction mixture was allowed to stir at 0°C for 15 min and overnight at room temperature. After this reaction mixture was poured into the ice-cold water (20 mt). stirred for 10 min and then extracted with chloroform. The combined organic layer was wasted with water, brine and dried ova sodium sulphate. Evaporation of the solvent under reduced pressure followed by column chromatographic purification afforded compound **104** (37.23 mg, 93 %) as a yellow coloured semisolid.

IR (nujol): 1705 cm^{-1} (ketone), 1675 (quinone), 1595 (aromatic).

^{1}H NMR ($CDCI_3$, 200 MHz): 8 1.00 (t, J=7.3 Hz, 3H), 1.40-1.65 (m, 3H), 2.35-2.75 (m, 2H), 2.85-3.05 (m, 2H), 3.97 (s, 3H, -OMe), 4.00 (s, 3H, -OMe), 6.90 (s, 1H, aromatic), 7.2- .32 (m, 1H, aromatic), 7.60-7.75 (m, 2H, aromatic).

^{13}C NMR ($CDCI_3$, 50 MHz): 8 11.64, 21.28, 29.18, 37.26, 37.52, 45.98, 5b.97,57.19, 115.15, 117.69, 118.90, 124.45, 127.87, 134.86,

137.47, 139.97, 151.32, 159, 26, 161.51, 117.64, 182.35, 186.83, 98.63.

Mass (m/z): 364 (M^+, 12), 350 (20), 335 (55), 321 (22), 306 (25).

Analysis: Calculated for $C_{22}H_{20}O_5$, C 72.52, H 5.49;

Found C 72.70, H 5.20 %.

(+)-Brasiliquinone B (73):

To the solution of brasiliquinone dimethyl ether (**104**) (35.67 mg, 0.098 mmole) in methylene chloride (10 ml) was added anhydrous aluminum chloride (50 mg, 0.38 mmole) at 0°C. 'The mixture was stirred for 2 hr. and allowed to warm up to room temperature. The reaction mixture was stirred at room temperature for 12 hr. It was then poured into a mixture of crushed ice and conc. HCl (2 ml) and digested on water bath for 20 min. After cooling to room temperature, it was extracted with methylene chloride. The combined methylene chloride part was dried over sodium sulphate and concentrated to afford a residue which on column chromatographic purification yielded (t)-brasiliquinone B (26.34 mg, 80 °6) as a yellow solid; m. p. 187-191 °C (lit, [52-53] m. p. 187-190 °C).

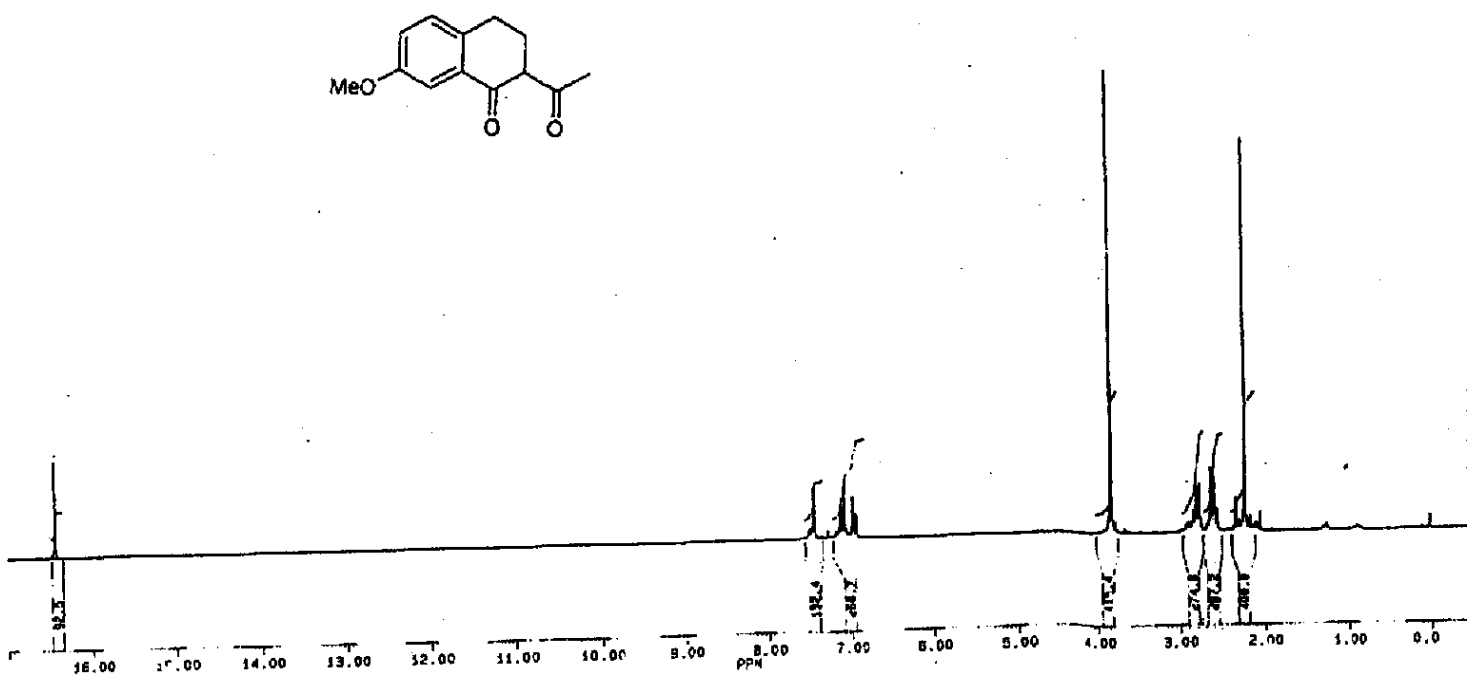
IR ($CHCl_3$): 3435, 1980, 1690, 1640 cm^{-1}'.

^1H NMR ($CDCl_3$, 200 MHz): 8 1.00 (t, 3H), 1.40-1.80 (m, 2H), 2.00-2.20 (m, 1H), 2.35-2.70 (m, 2H), 2.90-3.08 (m, 2H), 7.02 (s, 1H), 7.22-7.32 (m, 1H, aromatic), 7.60-?.75 (m, 2H, aromatic), 11.70 (s, 1H, -OH), 12.30 (s, 1H, -OH).

Mass (m/z): 337 (M+1, 26), 336 (M^+, 38), 308 (55), 280 (100).

Analysis: Calculated for $C_{20}H_{16}0_5$, C 71.42, H 4.76;

Found C 71.50, H 5.00 %


MeO
O
O
16.00
14.00
13.00
12.00
11.00
10.00
9.00
8.00
PPM
7.00
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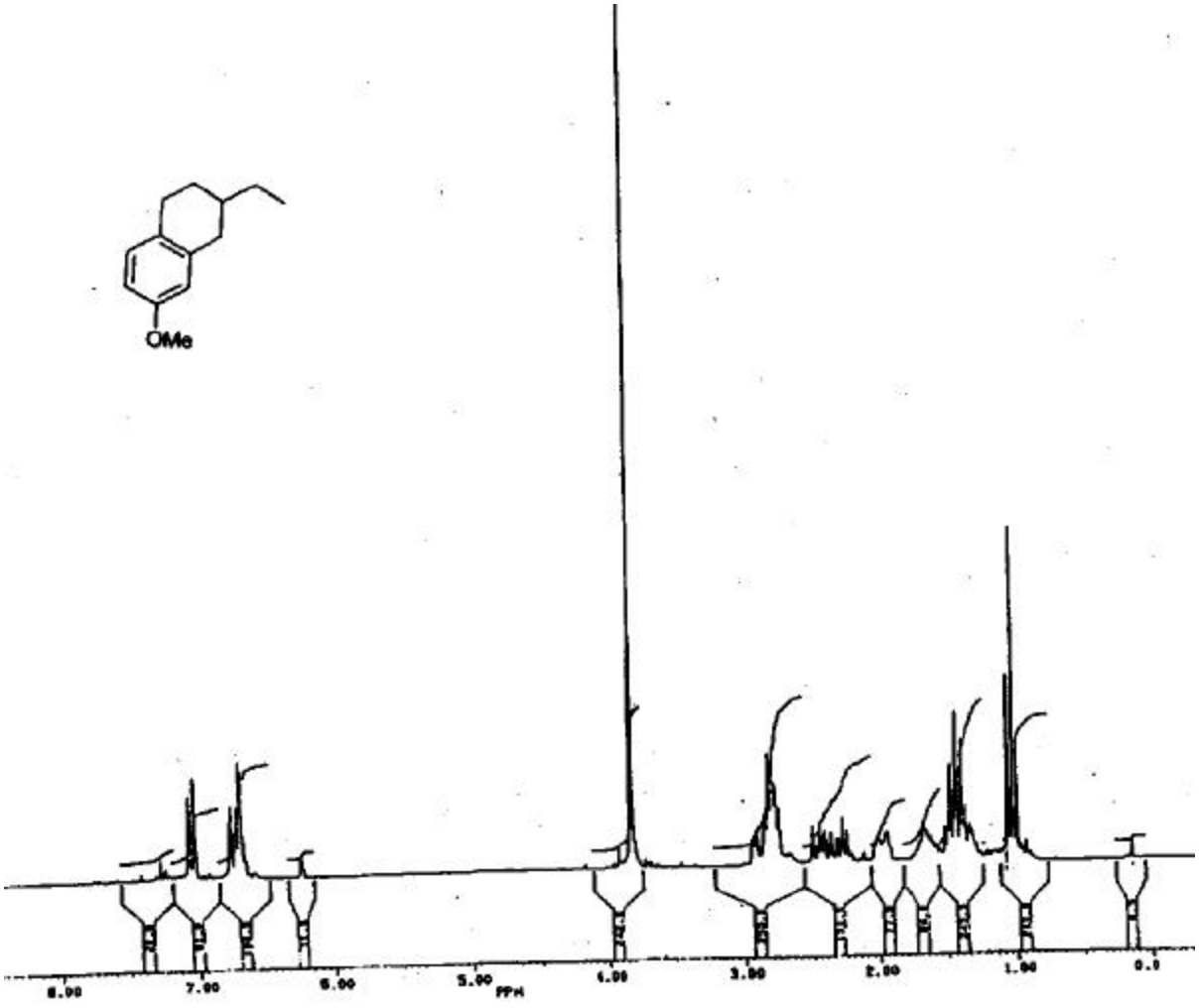
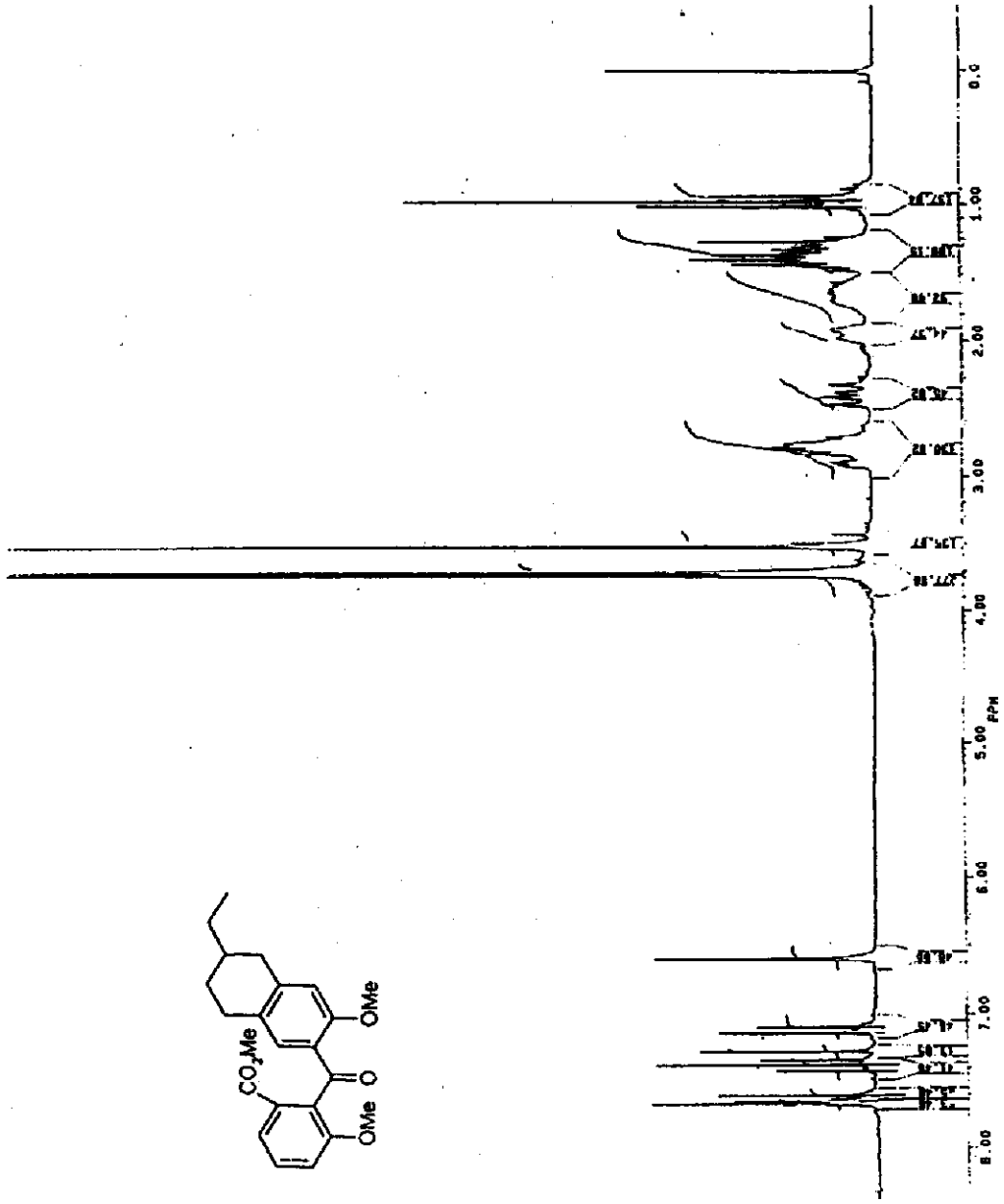
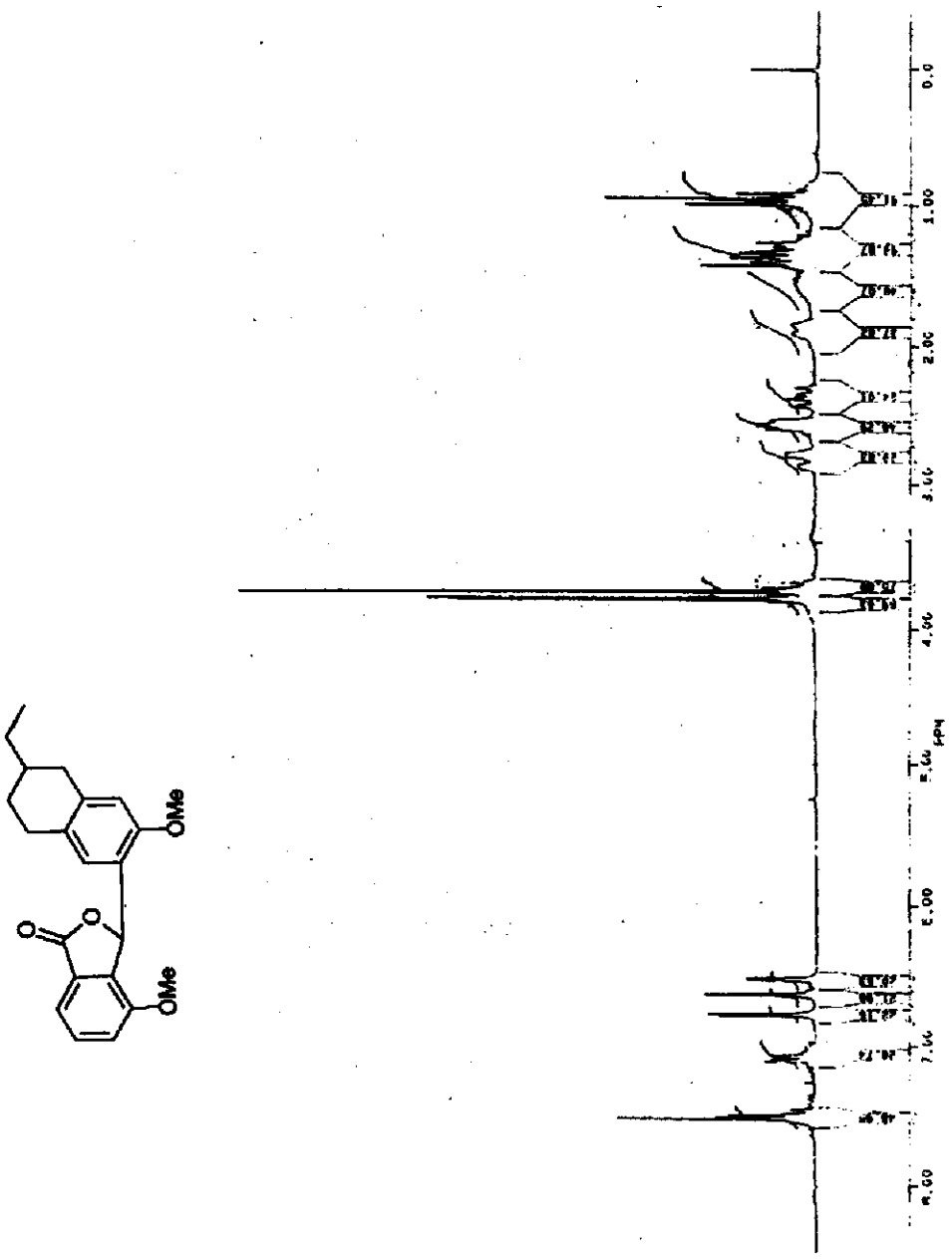
5.00
4.00
3.00
2.00
1.00
0.0



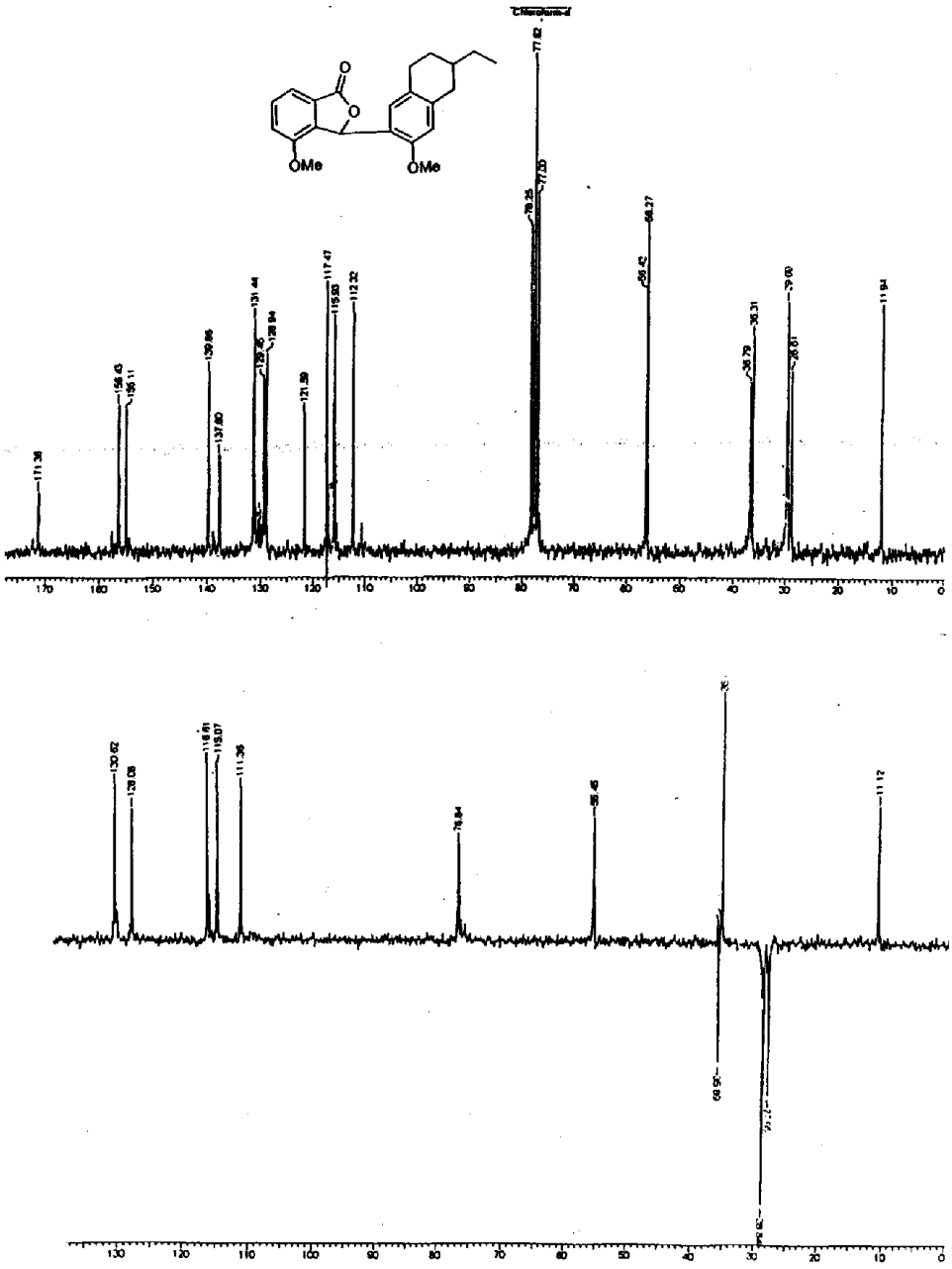
^{1}H MNR SPECTRUM (200MHz) OF THE COMPOUND 80 IN $CDCI_3$



^{1}H MNR SPECTRUM (200MHz) OF THE COMPOUND 93 IN $CDCI_3$



^{1}H MNR SPECTRUM (200MHz) OF THE COMPOUND 101 INCDCI$_3$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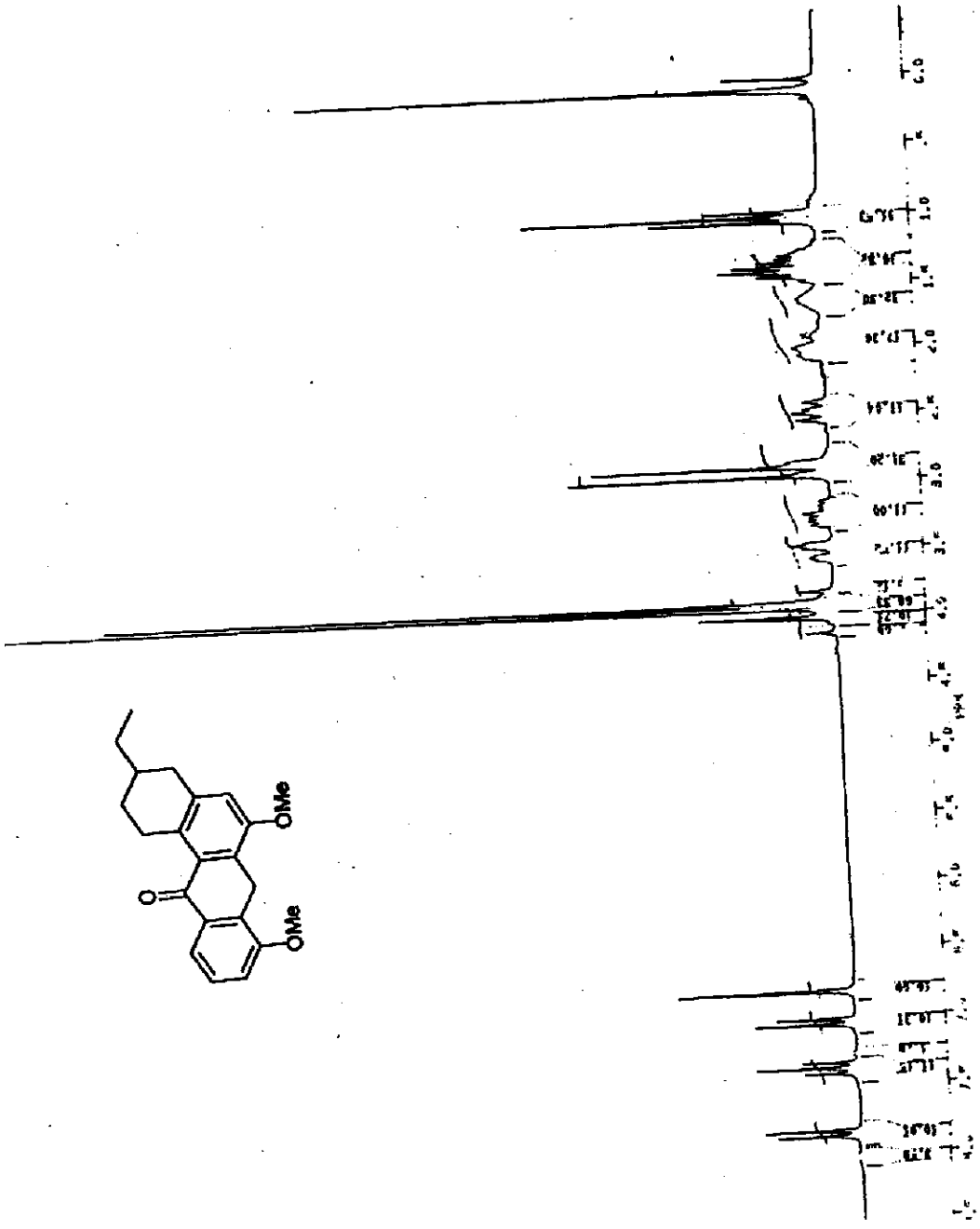
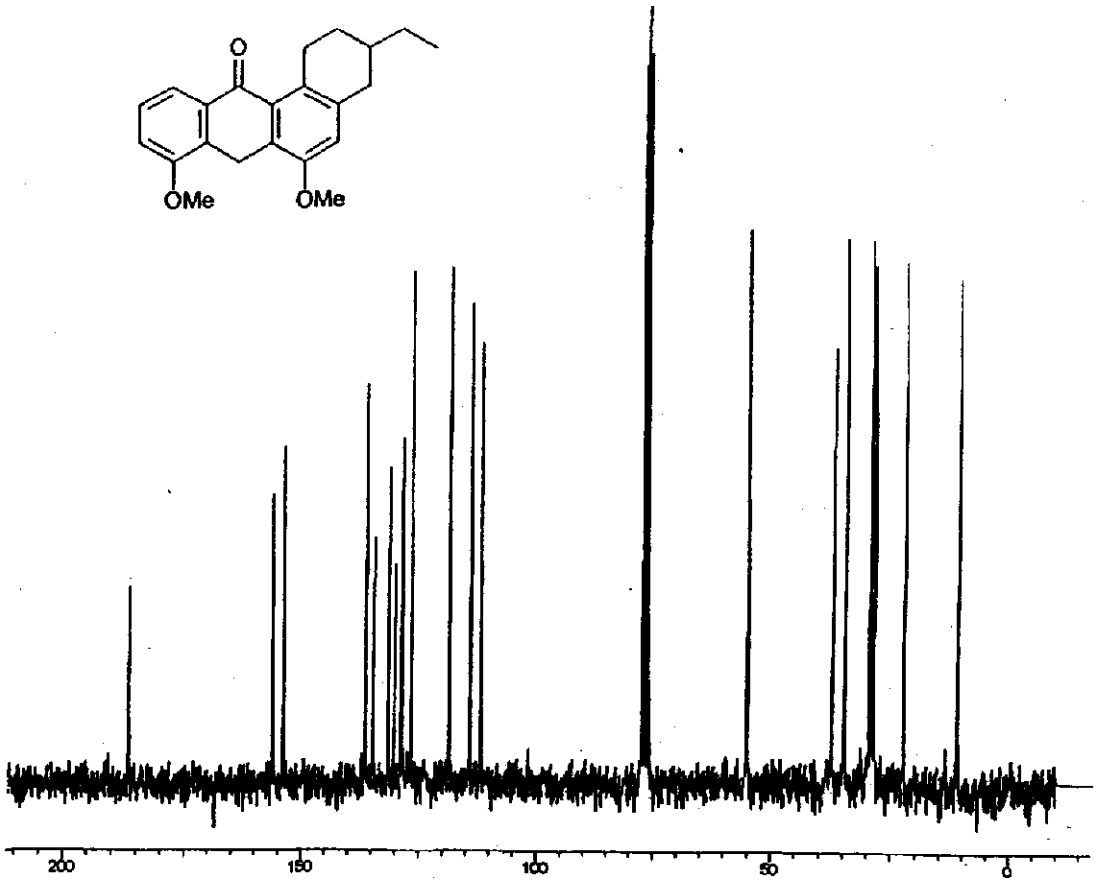
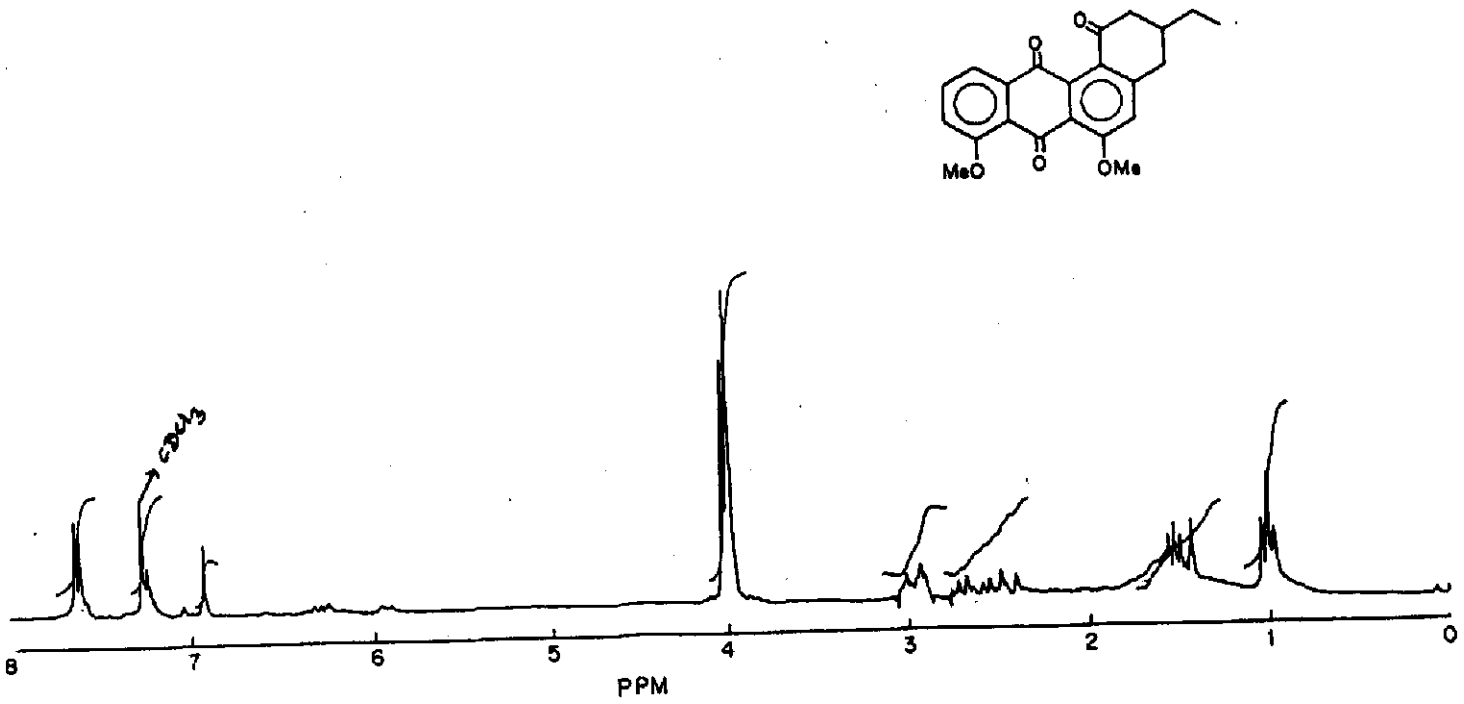
O
OMe
OMe
77.82
77.00
78.25
56.27
55.42
39.00
36.31
36.79
28.01
11.94
117.47
115.83
112.22
131.44
139.66
137.80
121.59
111.36
130.62
129.08
118.61
115.07
78.84
55.45
36
11.12



^{1}H MNR SPECTRUM (200MHz) OF THE COMPOUND103INCDCI$_3$



^{13}C NMRSPECTRUM (50MHz) THCOMPOUND 80 IN $CDCI_3$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OMe
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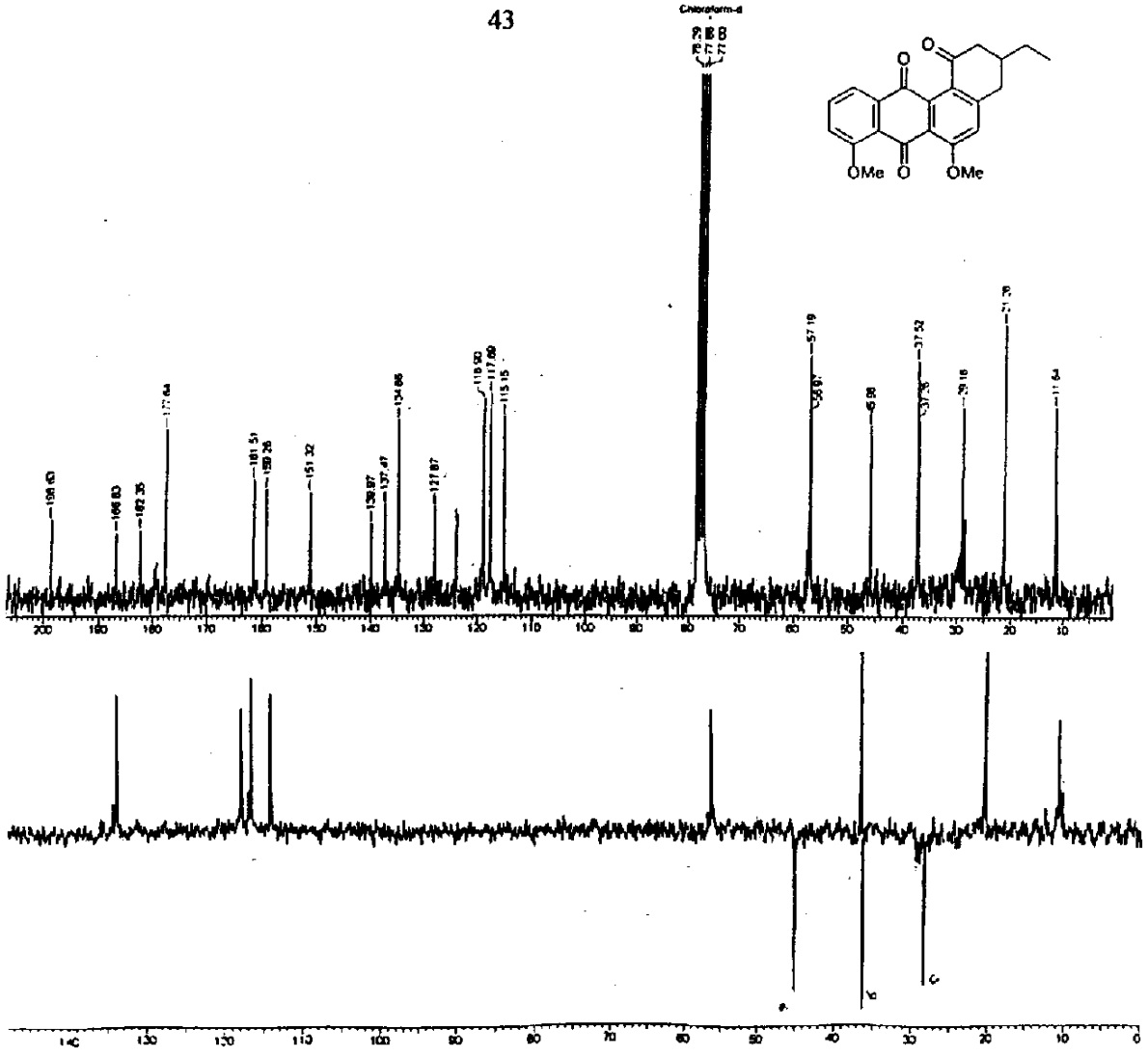
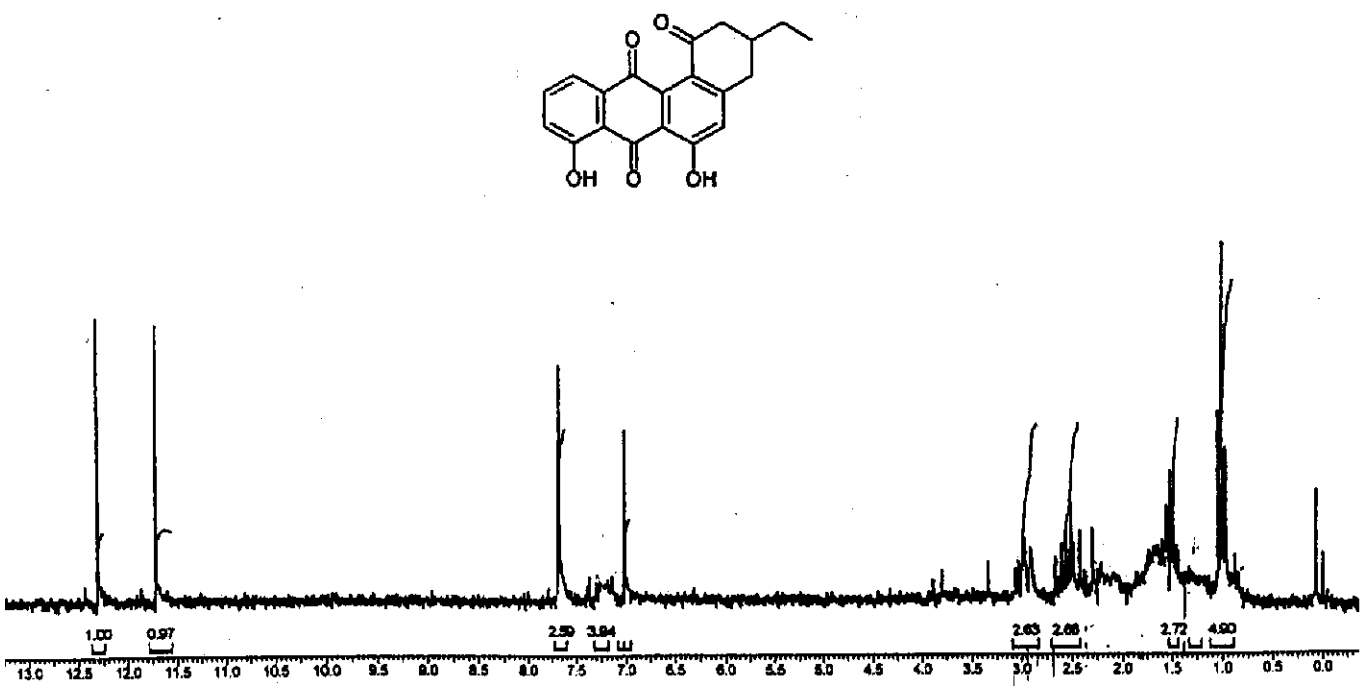
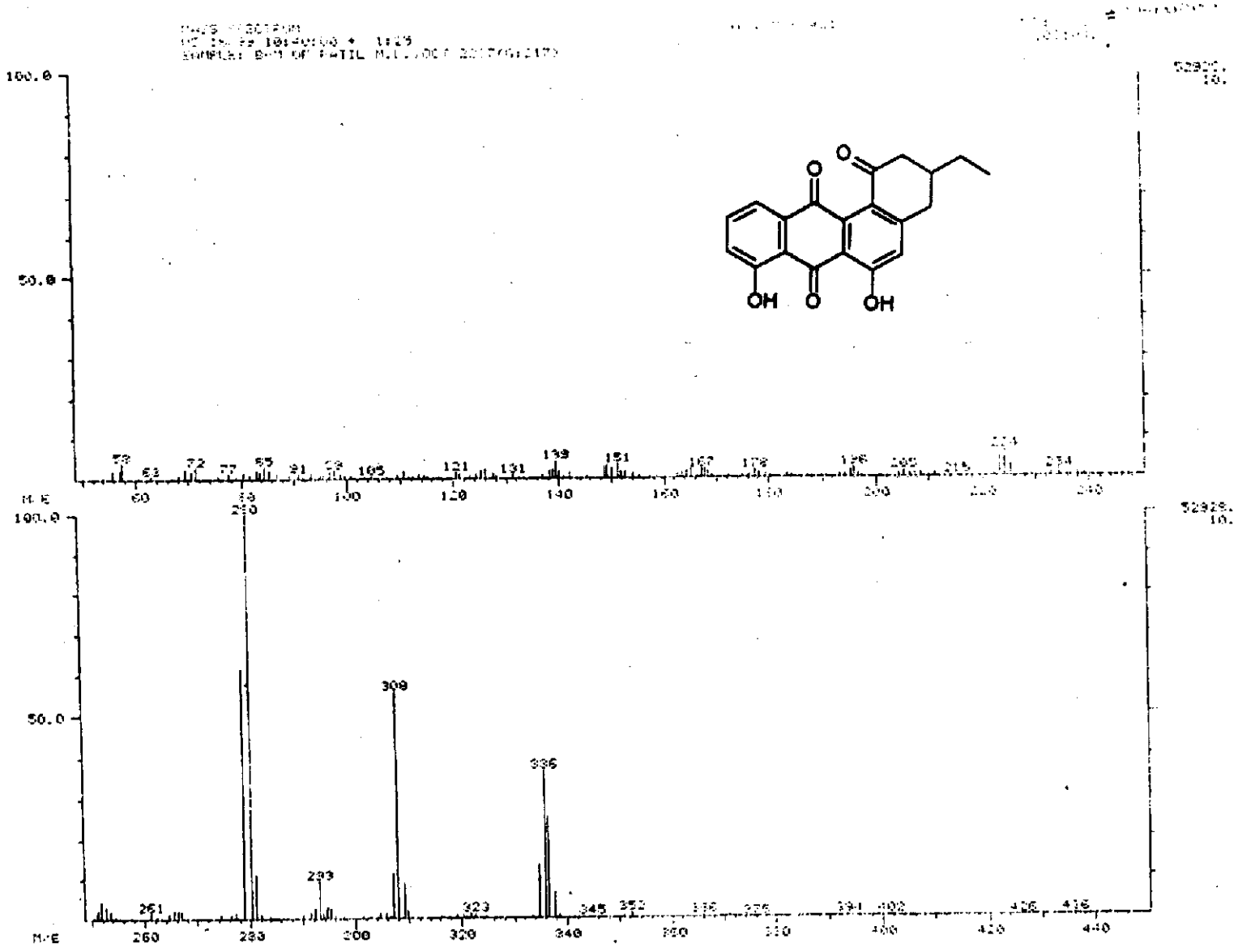
7
6
5
4
3
2
1
0
PPM


Chloroform-d
OMe
O
OMe


O
O
OH
O
OH
1.00
0.97
2.59
3.84
2.63
2.66
2.72
4.90
13.0
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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50.0
M/E
60
80
100
120
140
160
180
200
220
240
139
151
224
100.0
50.0
M/E
260
280
300
320
340
360
380
400
420
440
250
309
336
293
323
345

SECTION-B

ATTEMPTED SYNTHESIS OF (+-)-BRASILIQUINONE C AND SYNTHESIS OF (+-)-8-DEOXYBRASILIQUINONE B

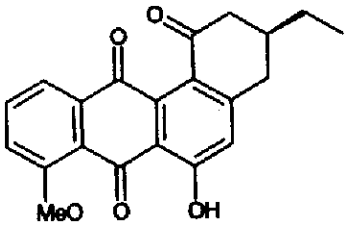
This section is subdivided into two parts

PART-I

ATTEMPTED SYNTHESIS OF (+-)-BRASILIQUINONE C

1.2.0 INTRODUCTION

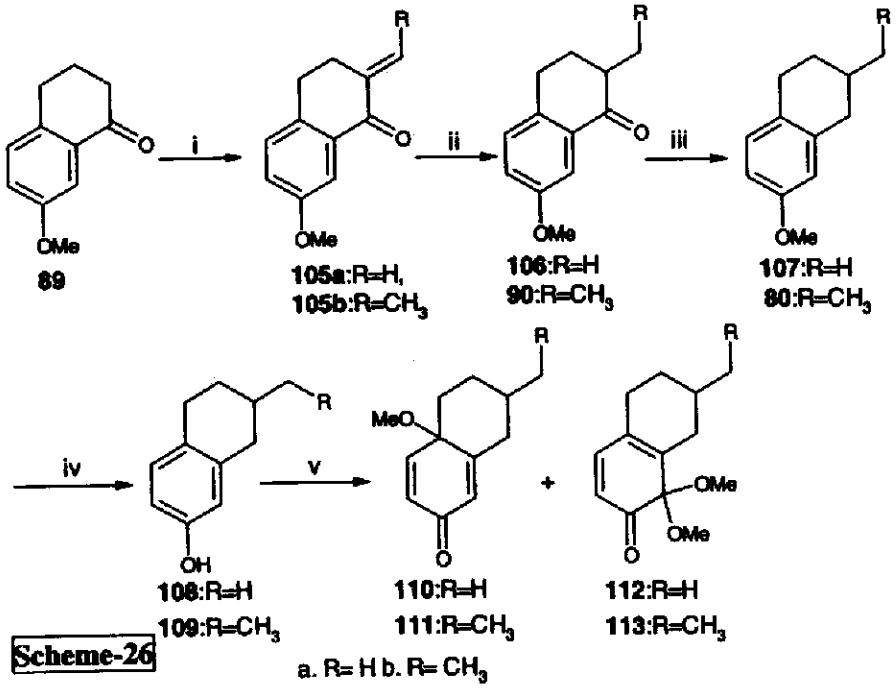
Brasiliquinone C (**74**)[52, 53] is another member of brasiliquinone family isolated from the pathogenic species of Nocardia of the strain IFM 0089. Brasiliquinone C (**74**) possesses a methoxy group at C-8 position, a hydroxy group at C-6 position and ethyl group at C-3 position. Like brasiliquinone B (**73**) stereochemistry of chiral C-3 center is 'S'. Brasiliquinone C (**74**) is found to be more potent than brasiliquinone A (**72**) against L1210 tumor cells.



74: Brasiliquinone C

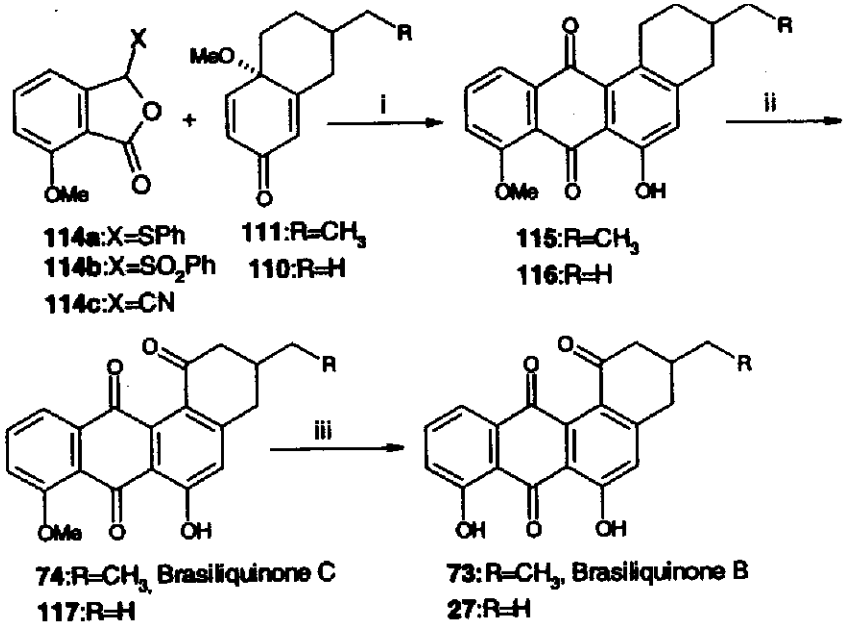
After our first successful synthesis of brasiliquinone B (**73**),[66a] Mal et al.[66b]reported second synthesis of (±)-brasiliquinone B (**73**) and C (**74**), involving phthalide annulation and photoxygenation as the key steps as shown in scheme-25.

Scheme-25



Scheme-26

Reagents and conditions: i. $(HCHO)_n$, $PhNH_2CH_3CF_3CO_2$ ii. a. Zn, AcOH b.CH_3MgI, CuI iii. NH_2NH_2, KOH, diethylene glycol iv. BBr_3, CH_2Cl_2 v. PIDA



Reagents and conditions: i. ^{t}BuOLi, THF. ii. hv, O_2. iii. $AlCl_3$.

The compound **114a** was prepared from N, N-diethyl-3-methoxy-benzamide through directed orthometallation.[17] The corresponding precursor **111** and **112** were prepared in five steps starting from tetralone **89**. Treatment of 89 with paraformaldehyde in the presence of N-methylanilinium trifluoroacetate in THF afforded compound **105a** in 72 % yield. Conjugate addition of CH_3MgI to the compound **105a** in the presence of cuprous iodide yielded the compound **90** in 66 % yield. The tetralone **90** under HuangMinlon reduction afforded tetralin **80** in 46 % yield. The tetralin 80 was demethylated with 1M solution of BBr3 in CH_2Cl_2 to give compound **109**. Further reaction of PIDA on **109** in dry methanol afforded napthalenone lll in 52 % yield along with monoketal **113** (8 %) as shown in scheme-25.

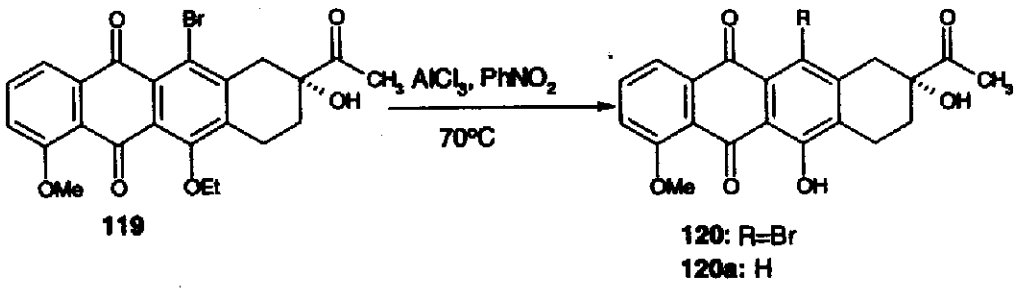
1.2.1 PRESENT WORK

After the development of a new successful methodology for the synthesis of brasiliquinone B, it was proposed to synthesize brasiliquinone C using the same strategy. Accordingly retrosynthetic plan for brasiliquinone C (**74**) was proposed as shown in scheme-27.

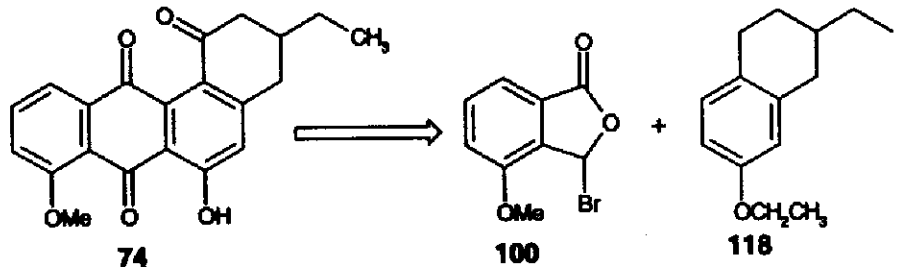
Johnson et a1.[67] reported a regiospecific total synthesis of 7,11dideoxydaunomycinone (**120a**) using a Friedel-Crafts alkylation approach. The total synthesis of 7,11-dideoxydaunomycinone was achieved by selective de-ethylation of compound **119** to compound **120** as shown in scheme-28. On the basis of above observation we planned to synthesize

brasiliquinone C (**74**) by the protecting hydroxyl group of compound **109** as ethyl ether, which could be selectively deprotected in the final step

Scheme-27

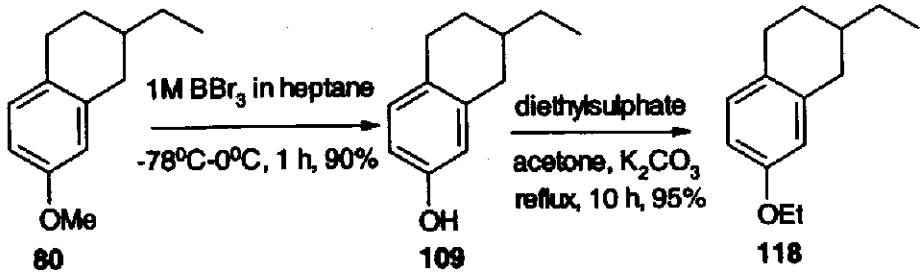


Scheme-28



Synthesis of the compound **118** was achieved from the tetralin **80** in two steps. The tetralin 80 was demethylated using 1M solution of BBr_3 in heptane at -78 °C. The ^1H NMR spectrum of compound **109** showed disappearance of a singlet at 8 3.73 for -0Me group and the IR spectrum revealed absorption band at 3353 cm^{-1} for hydroxyl group.

Scheme-29



The compound **109** was again protected as ethyl ether using diethylsulphate in presence of potassium carbonate in refluxing acetone as shown in scheme-29, to afford the desired tetralin derivative **118**.

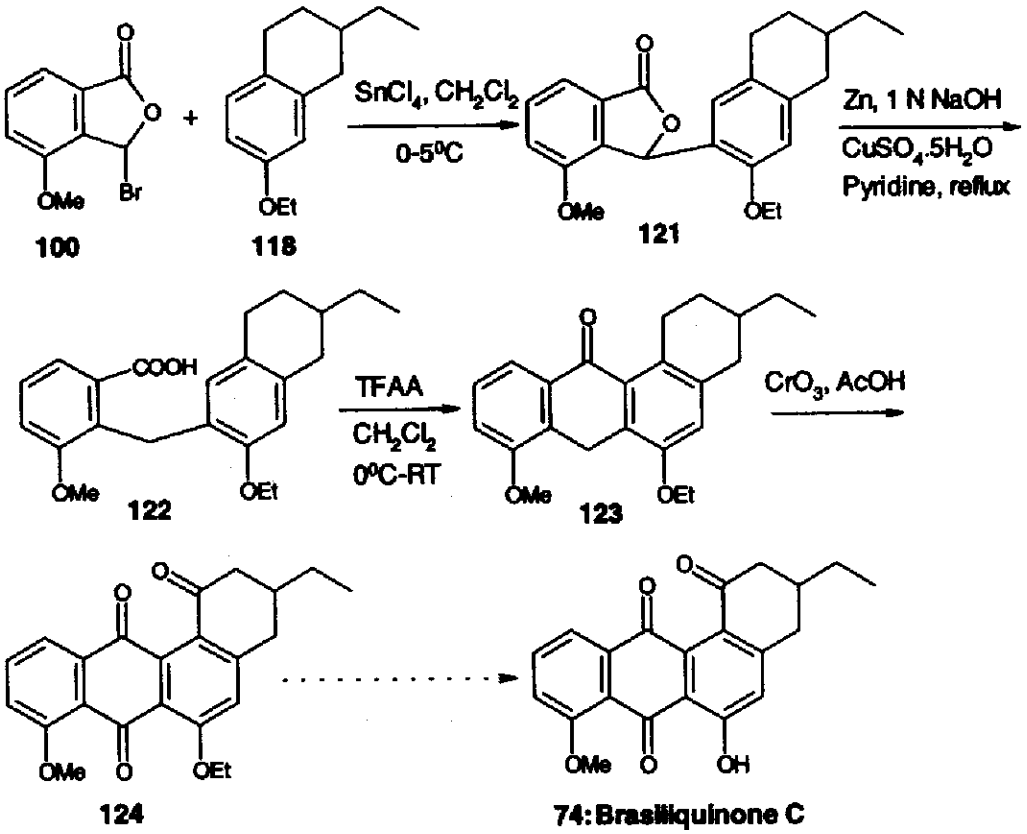
The structure of compound **118** was confirmed by its ^1H NMR, mass, and IR spectra. 'The ^1H NMR spectrum of compound **118** showed a quartet at 8 4.05 and triplet at 8 1.42

indicating the presence of -OCH_2CH_3 group. The mass spectrum exhibiting molecular ion peak at m/z 204 further supported the structure of compound **118**.

After synthesizing the AB ring synthon **118** for brasiliquinone C, efforts were directed towards the synthesis of brasiliquinone C (**74**) using the Friedel-Crafts alkylation approach used for the synthesis of brasiliquinone B as shown in scheme-30.

The compound **118** on Friedel-Crafts alkylation with bromopthalide 100 in presence , of stannic chloride at 0°C yielded expected alkylated compound **121** as white solid;

Scheme-30



This compound was fully characterized by ^{1}H NMR, ^{13}C NMR, IR and Mass spectra. The ^{1}H NMR spectrum of compound **121** showed triplet at 8 1.40 merged with multiplet of A ring protons as well as presence of multiplet at 8 3.86-4.05 integrating for two protons suggesting presence of –OCH_2CH_3 group. ^{13}C NMR showed presence of two methyl groups at 8 11.24 and 14.44 along with presence of lactone carbonyl group at 8 170.84. The IR spectrum revealed absorption band at 1745 cm^{-1} indicating presence of lactone system. The mass spectra exhibiting molecular ion peak at m/z 366 further supported the structure assigned to **121**.

Reductive opening of compound **121** was carned out using zinc in refluxing pyridine and 1N sodium hydroxide to afford acid **122** as a white solid; m.p.166-168 °C in 80 % yield. The ^{1}H NMR spectral data for acid **122** revealed presence of characteristic doublet at 8 4.30 for benzylic methylene group (Ar-CH_2-Ar) indicating reductive opening. The IR spectrum showed absorption band at 3450 cm^{-1} for carboxylic acid. The mass spectrum showing presence of molecular ion peak at m/z 368 was in good agreement with structure **122**.

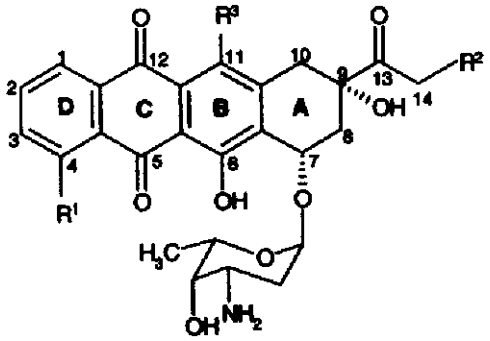
The acid **122** could be converted into brasiliquinone C (**74**) by cyclization, oxidation followed by selective de-ethylation. Accordingly cyclization of acid **122** was attempted using trifluoroacetic anhydride in methylene chloride to yield anthrone **123**. The formation of anthrone was confirmed by its mass spectrum which revealed presence of molecular ion peak tn/z at 350 and presence of carbonyl group at 1695 cni lin the IR spectrum whereas the ^{1}H NMR spectrum was not clean and it indicated the product to be a complex mixture. TLC of the NMR sample showed a complex mixture. Same experiment was repeated two times, which resulted into the formation of a complex mixture. Hence it was decided to carry out oxidation of the anthrone immediately without purification. Accordingly oxidation of anthrone **123** was carried out using chromium trioxide in acetic acid but this conversion also resulted into the formation of a complex mixture. The mass spectrum of crude reaction mixture showed presence of molecular ion peak at (m/z) 378 indicating formation of quinone **124** but isolation of pure **124** could not be achieved hence this route for the synthesis of brasiliquinone C was abandoned.

PART-II

SYNTHESIS OF (+-)-DEOXYBRASILIQUINONE B

1.2.2 INTRODUCTION

The anthracycline antibiotics, adriamycin (**125**)[68] daunomycin (**126**),[69] carminomycin (**127**)[69a] have occupied an important position in the list of anticancer drugs because of their activity against various types of solid tumors as well as leukemias. Their potent anticancer activity has made them the subject of interest of many synthetic chemists all over the world and extensive work has been carried out with regard to their isolation, structure determination and preparation on large scale. Subsequently second generation anthracycline 11-deoxydaunomycin (**129**)[69b] and 11-deoxyadriamycin (**128**)[69c] were reported.



125: R^1=OCH_3, R^2=R^3=OH **126:** R^1=OCH_3, R^2=H, R^3=OH

127: R^1=R^3=OH, R^2=H **128:** R^1=OCH_3, R^2=OH, R^3=H

129: R^1=OCH_3, R^2=R^3=H **130:** R^1=R^2=H, R^3=OH

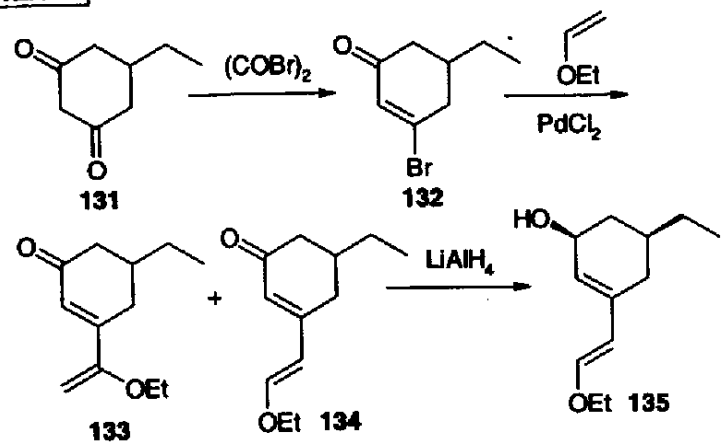
The antineoplastic activity of anthracyclines has been explained by various theories, out of which DNA interaction[70] is the first and certainly the best documented one. A detailed study of DNA-daunomycin molecular model shows that the intercalation of aglycone is partial and one might speculate the removal of the bulky methoxy group, which would result in a molecule that could intercalate more effectively. In fact 4-demethoxydaunomycin (**130**), a synthetic analogue, binds to DNA better than daunomycin (**126**) and in vivo testing of it in mouse cancer shows that it is as effective as daunomycin at dose levels 8 to 10 times less than daunomycin itself.[71,72,73]

The glycosidic bond in daunomycin joining the daunomycinone and daunosamine is very labile to chemical and enzymatic cleavages and cleavage of this bond inactivates daunomycin. Since the glycosidic bond is split in the gastrointestinal tract, daunomycin cannot be given orally. On the other had, it has been found that glycosidic bond in 4-demethoxydaunomycin is not cleaved that easily, so it can be given orally. One more additional advantage of 4-demethoxydaunomycin over daunomycin is its less toxicity. The enhanced

potency of 4-demethoxydaunomycin as compared to daunomycin prompted us to undertaken synthesis of 8-deoxybrasiliquinone B analogue of brasiliquinone.

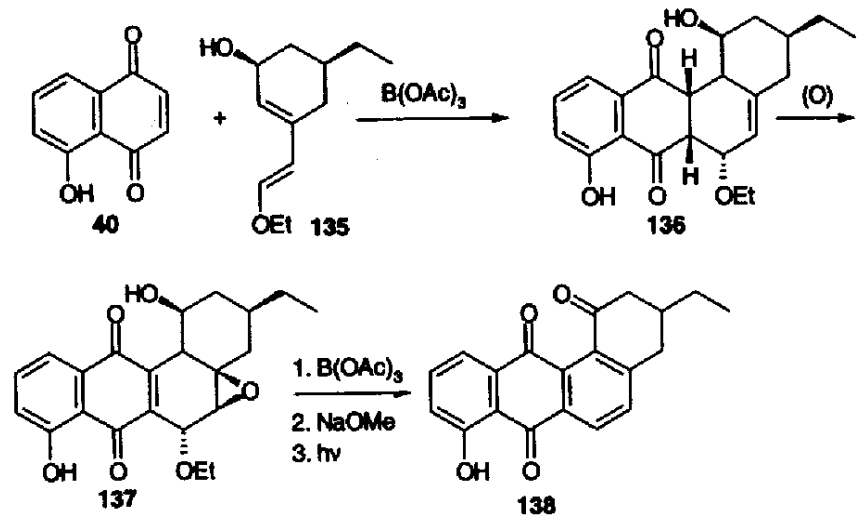
Recently Krohn et a1.[74] reported synthesis of (+-)-6-deoxybrasiliquinone B (**138**) by a boron triacetate mediated Diels-Alder reaction as shown in scheme-31 and scheme-32.

Scheme-31



Compound **134** was synthesized by making use of Heck reaction of vinyl bromide **132** and vinyl ethyl ether. In this reaction ~i addition product **134** predominated over 2ethoxy diene **133**. The allylic alcohol **135** was prepared by LAH reduction of **134** to afford stereoselectively the alcohol. The boron triacetate catalyzed Diels-Alder reaction of electron rich diene **135** with the juglone **40** as shown in scheme **32** afforded intermediate **136**.

Scheme-32

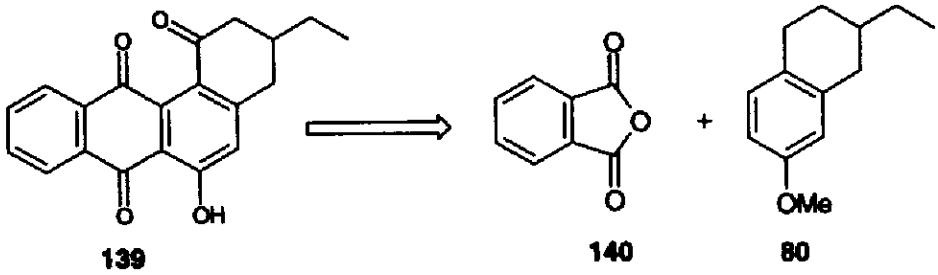


The compound **136** on oxidation with yielded the epoxide 137, which on treatment with mild Lewis acid boron triacetate followed by photooxidation in diffused sunlight resulted into the (+-)-6 deoxybrasiliquinone B (**138**).

1.2.3 PRESENT WORK

Retrosynthetic studies on 8-deoxybrasiliquinone B suggested phthalic anhydride **140** and tetralin **80** as key intermediates as shown in scheme-33.

Scheme-33

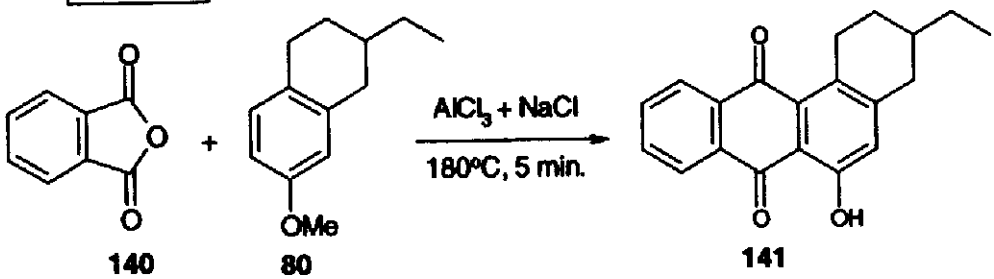


139 **140** **80**

During the studies on anthracycline antibiotics one pot Friedel-Crafts acylation and cyclization to give the tetracyclic framework is reported and hence construction of benz(a)anthraquinone was attempted using the similar strategy.

Accordingly fusion of phthalic anhydride **140** with tetralin **80** in the presence of aluminum chloride and sodium chloride melt at 180 °C, as shown in scheme 34, yielded compound **141** as raddish solid; m.p.180 °C in 40% yield. The characteristic yellow colour of the compound and absorption band at 3435 and 1680 cm^{-1} in IR spectrum suggested formation of quinonoid structure. Formation of compound **141** was further confirmed on the basis of its ^{1}H NMR spectrum, which revealed presence of A-ring protons as well as presence of five aromatic protons with a chelated -0H group at 8 13.00, and mass spectrum showed molecular ion at m/z 306.

Scheme-34



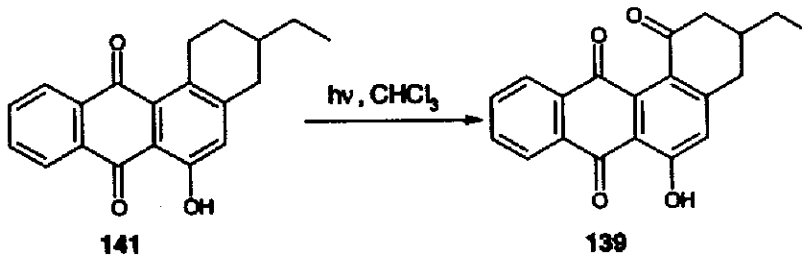
140 **80** **141**

Next target was to oxidize the compound **141** to the desired 8-deoxybrasiliquinone B, which was carried out by exposing compound **141** in chloroform, to sunlight.

The photooxidation was effected by exposure of the compound **141** to sunlight. This reaction proved to be very important for the synthesis of angucyclines possessing (i-hydroxy group at C-3 position, which is easily eliminated under basic or acidic conditions. Thus oxygen atom at C-1 can be introduced under mild neutral conditions by photooxidation, which was discovered by serendipity by leaving NMR solution of deoxygenated precursor on the bench in diffuse sunlight.[75]

Compound **141** was exposed to sunlight for 12 hrs in chloroform to give (±)-8-deoxybrasiliquinone B in 90 % yield as shown in scheme-35.

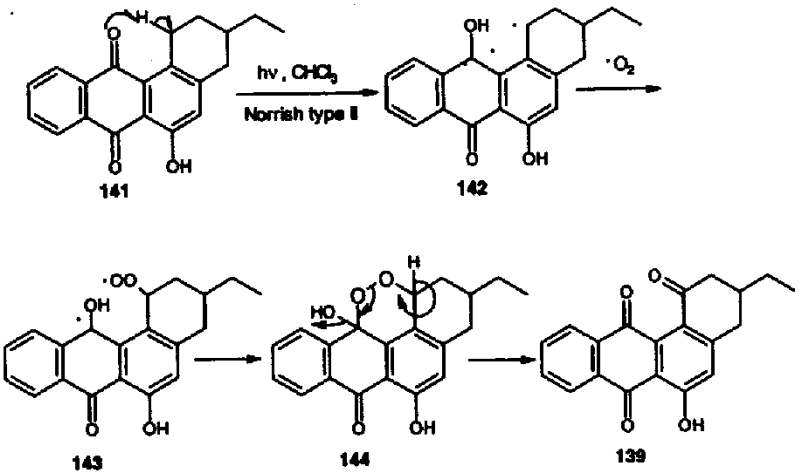
Scheme-35



141 **139**

This reaction is assumed to be initiated by Norrish type II γ-hydrogen abstraction of the excited carbonyl in **141** to yield a diradical **142** as shown in scheme 36.

Scheme-36



141 **142** **143** **144** **139**

The H-abstraction requires a very definite steric environment in which the benzylic protons have to be in proximity of the excited carbonyl group. Subsequent addition of the diradical **142** with singlet oxygen is supposed to yield a peroxyradical **143** which can cyclize to an unstable hydroxy-1,2-dioxane **144**. This intermediate is then opened up by proton abstraction

to generate the C-1 carbonyl compound **139**. The structure of this compound was further confirmed by ^{1}H NMR, IR and Mass spectra. The ^{1}H NMR spectrum of this compound showed disappearance of benzylic protons from S 3.40 and rests of the signals in the 'H NMR spectrum were at expected positions. ^{13}C NMR indicated presence of three carbonyl groups at 8 184, 188 and 198. The presence of carbonyl group at 1690 cm^{-1} in IR spectrum and molecular ion peak at m/z 320 in mass spectrum further supported the assigned structure of 8-deoxybrasiliquinone B.

1.2.4 CONCLUSION

Thus, in conclusion we have attempted a simple synthesis of (±)-brasiliquinone C and we have achieved a short and efficient synthesis of (±)-8-deoxybrasiliquinone B, a new analog of brasiliquinone, which may show better activity.

1.2.5 EXPERIMENTAL

2-Ethyl-l, 2, 3, 4-tetrahydro-7-hydroxynaphthalene (109):

To a stirred solution of tetralin derivative (**80**) (1.90 g, 0.01 mmole) in dry methylene chloride (20 ml) was introduced 1M BBr_3 solution in hexane (15 ml, 0.015 mmol) at -78 °C. The mixture was stirred for 1 hr at 0°C and then at room temperature for 1/20 hr. 1fie reaction mixture was then quenched with 1M HCI (10 ml), extracted with ethyl acetate, the extract were washed with water and dried over sodium sulphate. Evaporation of the solvent afforded compound 109 as colourless oil (1.60 g, 91 %).

IR (nujol): 3353, 1613, 1257 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 0.97 (t, J=7.2 Hz, 3H), 1.20-1.70 (m, 4H), 1.88-1.95 (m, 1H), 2.28-2.40 (m, 1H), 2.67-2.83 (m, 3H), 6.526.58 (m, 2H, aromatic), 6.91 (d, J=8 Hz, 1H, aromatic).

2-Ethyl-l, 2, 3, 4-7-ethoxynaphthalene (118):

A mixture of compound 109 (880 mg, 5 mmole), diethylsulphate (1.50 g, 7.5 mmole) and anhydrous potassium carbonate (2.07 g, 15 mmole) in anhydrous acetone (15 ml) was refluxed for 8-10 hr. After the reaction, acetone was removed under reduced pressure and residue was diluted with water (50 ml). The aqueous part was extracted with ethyl acetate, the extracts were washed with water and dried over sodium sulphate to give compound **118** as colourless liquid (969 mg, 95 °lo).

IR (nujol): 1570 Cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 1.00 (t, J=7.2 Hz, 3H), 1.42 (t, J=7.2 Hz, 3H $O\underline{CH_2}CH_3$), 1.55-1.70 (m, 2H), 1.90-2.05 (m, 1H), 2.35-2.50 (m, 1H), 2.70-2.95 (m, 3H), 4.05 (q, J=7 Hz, 2H, $-OCH_2\underline{CH_3}$), 6.68 (s, 1H, aromatic), 6.70 (d, J=8.4 Hz, 1H, aromatic), 7.00 (d, J=8.4 Hz, 1H aromatic).

Mass(m/z): 204 (M^+).

3-(6-ethyl-5, 6, 7, 8 -tetrahydro-3-ethoxy-2-naphthalenyl)-4-methoxy-1(3H) isobenzo-furanone (121):

The tetralin derivative **118** (204 mg, 1 mmol) was added with stirring to a solution of 3-bromo-4-methoxyphthalide (100) (290.4 mg, 1.2 mmole) in dry methylene chloride (10 ml) at 0°C. Stannic chloride (295 mg, 2.2 mmole) was then introduced and the resulting mixture was stirred at 0°C for 1 hr. It was then poured into the mixture of crushed ice and conc. HCl (3 ml)

stirred for 30 min and extracted with methylene chloride. The combined methylene chloride layer was washed with water, brine and dried over sodium sulfate. Evaporation of the solvent and purification by column chromatography afforded compound **121** (329.4 mg, 90 %) as white solid; m.p.l 14-116 °C.

IR (Nujol): 1745 (lactone), 1690 (ketone), 1596 (aromatic) cni 1.

^{1}H NMR ($CDCl_3$, 200 MHz): 8 0.95 (t, J=6.2 Hz, 3H), 1.20-1.76 (m, including triplet J=6.15 Hz, 3H for OCH_2CH_3 at S 1.40, 8H), 1.80-2.00 (m, 1H), 2.25-2.45 (m, 1 H), 2.50-2.70 (m, 1H), 2.75-2.90 (m, 1H), 3.74 (s, 3H, -OMe), 3.86- 4.05 (m, 2H, OCH_2CH_3), 6.56 (s, 1H, phthalide), 6.60-6.72 (m, 2H, aromatic), 6.94-7.15 (m, 1H, aromatic), 7.40-7.65 (m, 2H, aromatic).

^{13}C NMR ($CDCl_3$, 50 MHz): 8 11.24, 14.44, 28.11, 29.02, 35.65, 36.02, 55.57, 63.80, 78.14, 112.47, 115.15, 116.59, 120.93, 128.53, 128.98,130.56, 137.39, 139.01, 154.41, 155.11, 170.84.

Mass (m/z): 366 (M^+, 100), 337 (50), 321 (75 %), 307 (70).

Analysis: Calculated for $C_{23}H_{26}0_4$, C 75.40, H 7.10;

Found C 75.23, H 7.00 %.

2-{(6-Ethyl-5, 6, 7, &tetrahydro-3-ethoxy-2-naphthalenyl)methyl}-3-methoxybenzoic acid (122):

The lactone **121** (732 mg, 2 mmole) was reductively opened up by heating with 1M solution of sodium hydroxide (40 ml), activated zinc (3.7 gm, 0.058 mole), $CuSO_4.5H_2O$ (catalytic) and pyridine (10 ml) at 125 °C for 10 hrs under argon atmosphere. The mixture was then allowed to cool and filtered through a pad of Clite. Acidification of the filtrate with concentrated HCl afforded the corresponding acid **122** (588 mg, 80 %) as white solid; m.p. 166-168 °C.

IR (Nujol): 3450 (acid), 1609 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): 8 0.90-1.05 (m, 3H), 1.18-1.70 (m, including triplet J=6.15 Hz, 3H for OCH_2CH_3 at 8 1.36, 7H)), 1.72- 2.00 (m, 1H), 2.22-2.46 (m, 2H), 2.48-2.69 (m, 1H),

2.70-2.90 (m, 1H), 3.80 (s, 3H, -OMe), 3.90-4.10 (m, 2H), 4.30 (d, J=11.53 Hz, 2H, benzylic), 6.44 (s, 1H, aromatic), 6.50 (s,

1H, aromatic), 6.90 (t, J=7.00 Hz, 1H, aromatic), 7.08 (d, J=7.00 Hz, 1H, aromatic), 7.55 (d, J=7.00 Hz, 1H, aromatic).

Mass (m/z): 368 (M^+, 100), 350 (30), 321 (20), 203 (95).

Analysis: Calculated for $C_{23}H_{28}O_4$, C 75.00; H 7.60;

Found C 75.20; H 7.50 %.

3-Ethyl-6-hydroxy-1, 2, 3, 4-tetrahydro-7, 12 (21~-one benz(a)anthracene (141):

A mixture of anhydrous aluminum chloride (2.82 g, 22.5 mmol) and sodium chloride (1 g, 20 mmol) was heated at 180-190 °C for 5 min. To this melt was added a mixture of phthalic anhydride (1.26 g, 8.75 mmol) and tetralin derivative 80 (407 mg, 2.14 mmol) and resulting mixture was stirred at 180-190 °C for 7 min. After cooling the reaction mixture was digested with saturated oxalic acid solution on water bath for 1 h, cooled and extracted with chloroform (4X50 ml). The chloroform layer was successively washed with 5 % sodium bicarbonate, brine, dried and evaporated to yield **141** (262 mg, 40 %) as reddish solid; m. p. 180°C.

IR ($CHCl_3$): 3435, 1680, cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 0.75-1.10 (m, 3H), 1.25-1.40 (m, 3H), 1.90-2.00 (m, 1H) 2.30-2.50 (m, 2H), 2.90 (d, J=10 Hz, 1H), 2.98- 3.20 (m, 1H), 3.40 (d, J=10 Hz, 1H), 7.20 (s, 1H,aromatic), 7.65-7.80 (m, 2H, aromatic), 8.10-8.20 (m,2H, aromatic), 13.00 (s, 1H, -OH).

Mass (m/z): 306 (M^+, 100), 291 (15), 277 (80), 263 (85).

Analysis: Calculated for $C_{20}H_{18}O_3$, C 78.43; H 5.88;

Found C 78.10; H 6.00 %.

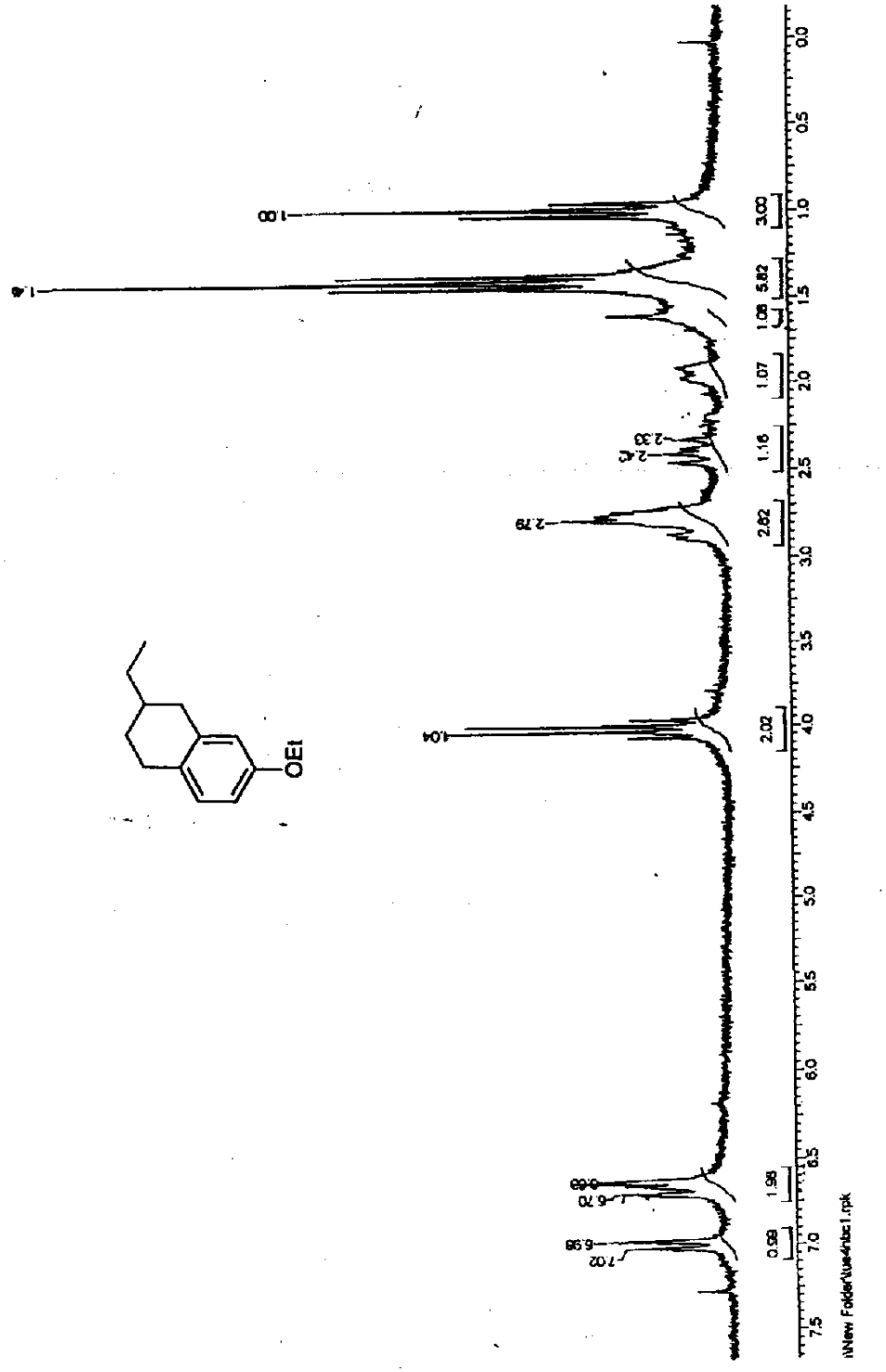
(±)-8-Deoxybrasiliquinone B (139):

Compound **141** (31 mg, 0.1 mmol) in chloroform (5 ml) was exposed to sunlight for 12 h. After the reaction, checked by TLC, chloroform layer was concentrated under reduced pressure and residue was purified by flash chromatography to afford (±)-8-deoxybrasiliquinone B (29 mg, 90 %) as reddish coloured solid; m. p. 168-170 °C.

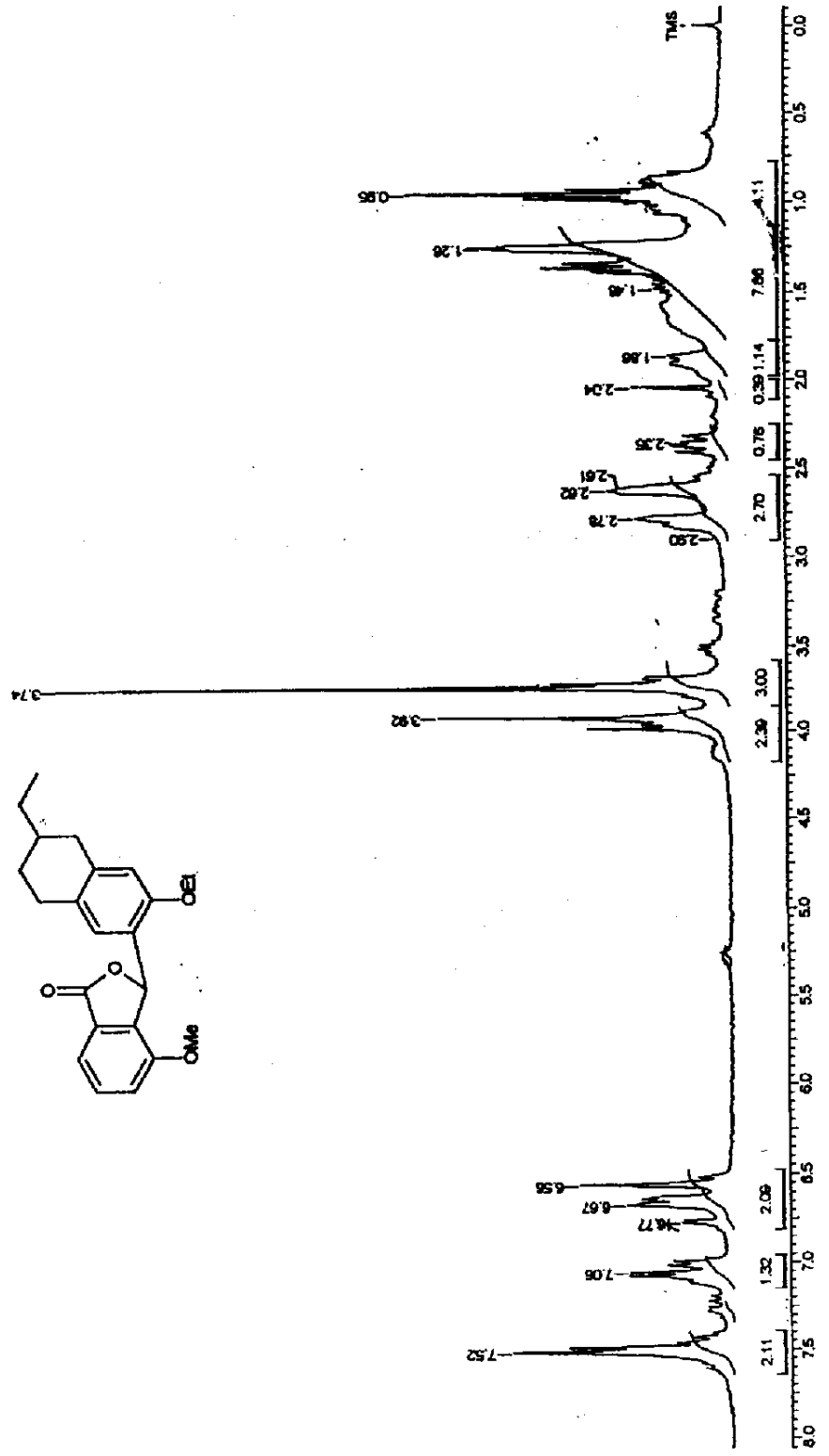
IR ($CHCl_3$): 3430, 1690, 1640 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 0.99-1.05 (m; 3H), 1.40-1.55 (m, 2H), 1.80-2.00 (m, 1H), 2.45-2.65 (m, 2H), 2.80-3.05 (m, 2H), 7.00 (s,
1H, aromatic), 7.70-7.80 (m, 2H, aromatic), 8.18 (d, J=7.00 Hz, 1H, aromatic), 8.22 (d, J=7.00 Hz, 1H, aromatic), 12.80 (s, 1H, -OH).

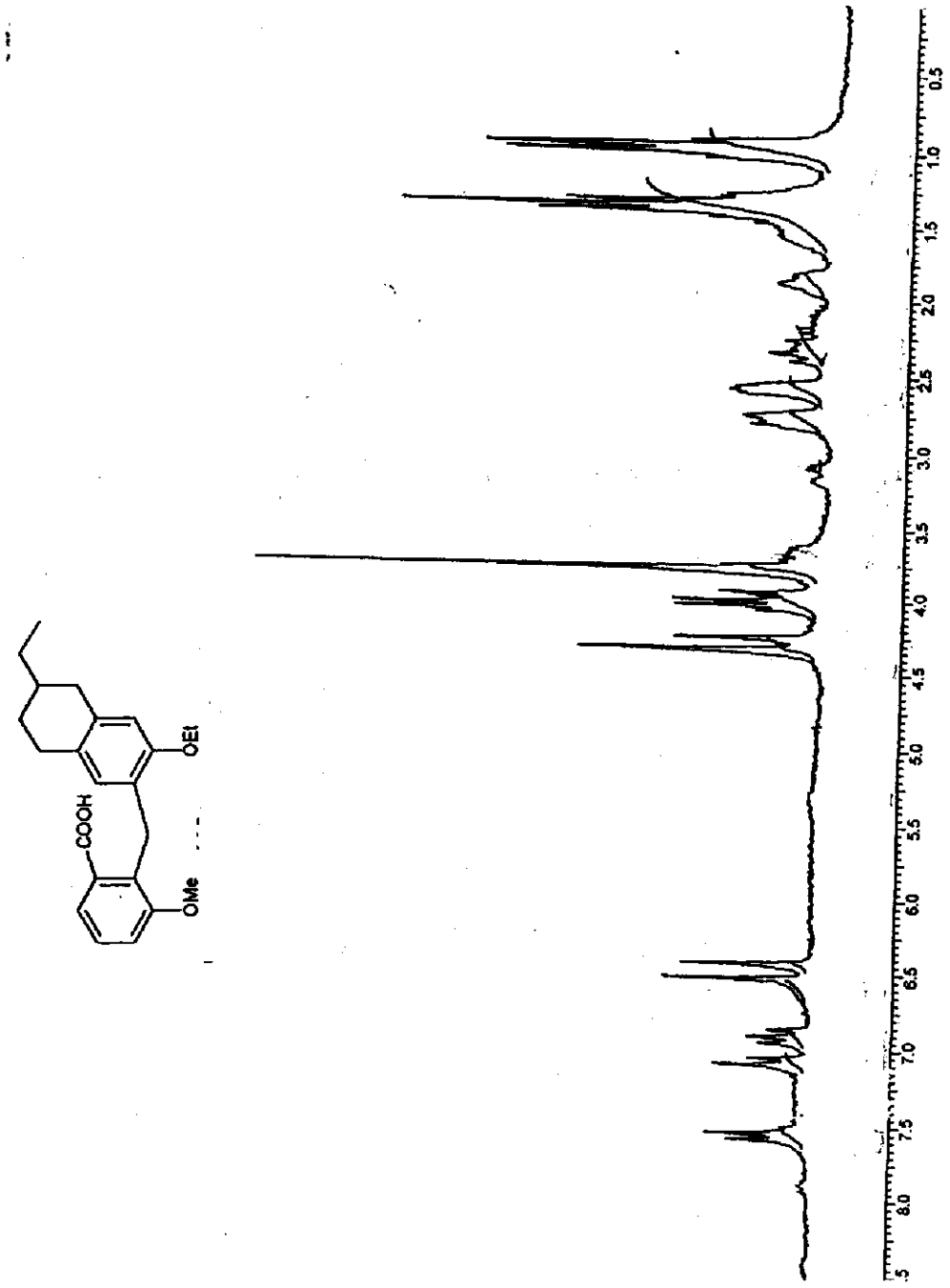
^{13}C NMR ($CDCl_3$, 125 MHz):	8 11, 28, 35.90, 36, 45, 116, 120, 126, 127, 130, 132, 134, 136, 138, 152, 163, 184, 188, 198.
Mass (m/z):	320 (M^+, 40), 292, (50), 277, (15), 264, (100), 152 (50).
Analysis:	Calculated for $C_{20}H_{16}O_4$, C 75.00; H 5.00 %.
	Found C 75.20 H 4.90%.



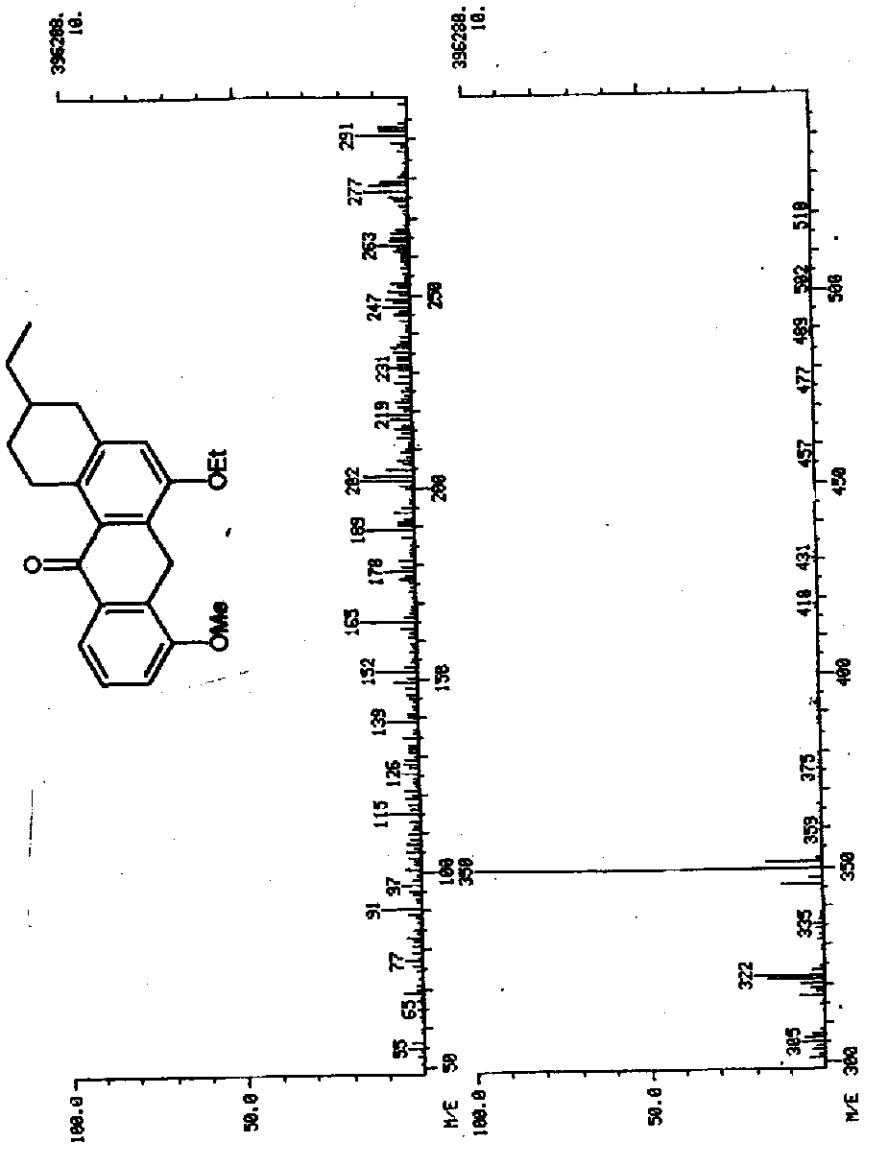
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **118** IN $CDCI_3$.



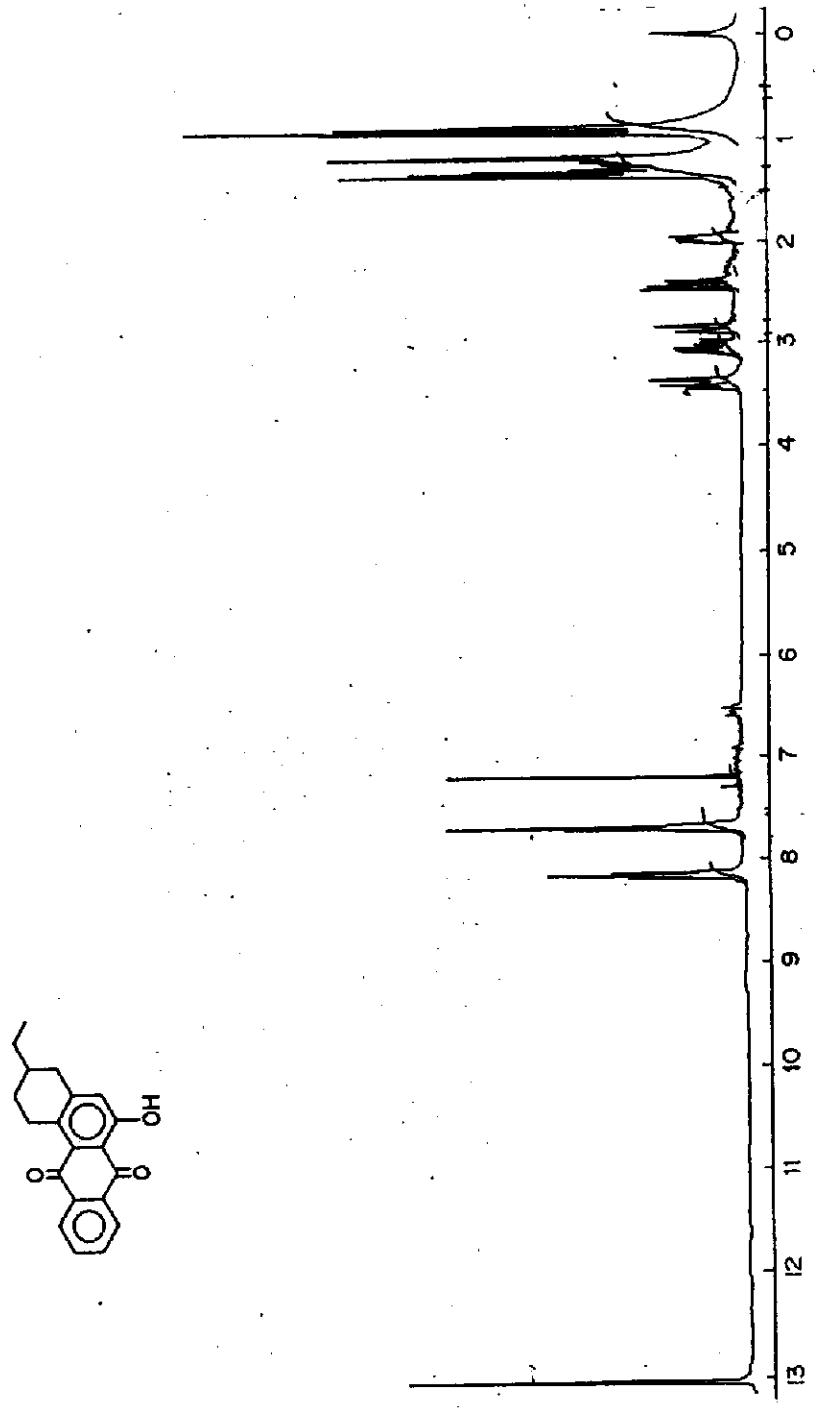
[1]HNMR SPECTRUM (200MHz) OF THE COMPOUND **121** IN $CDCl_3$.



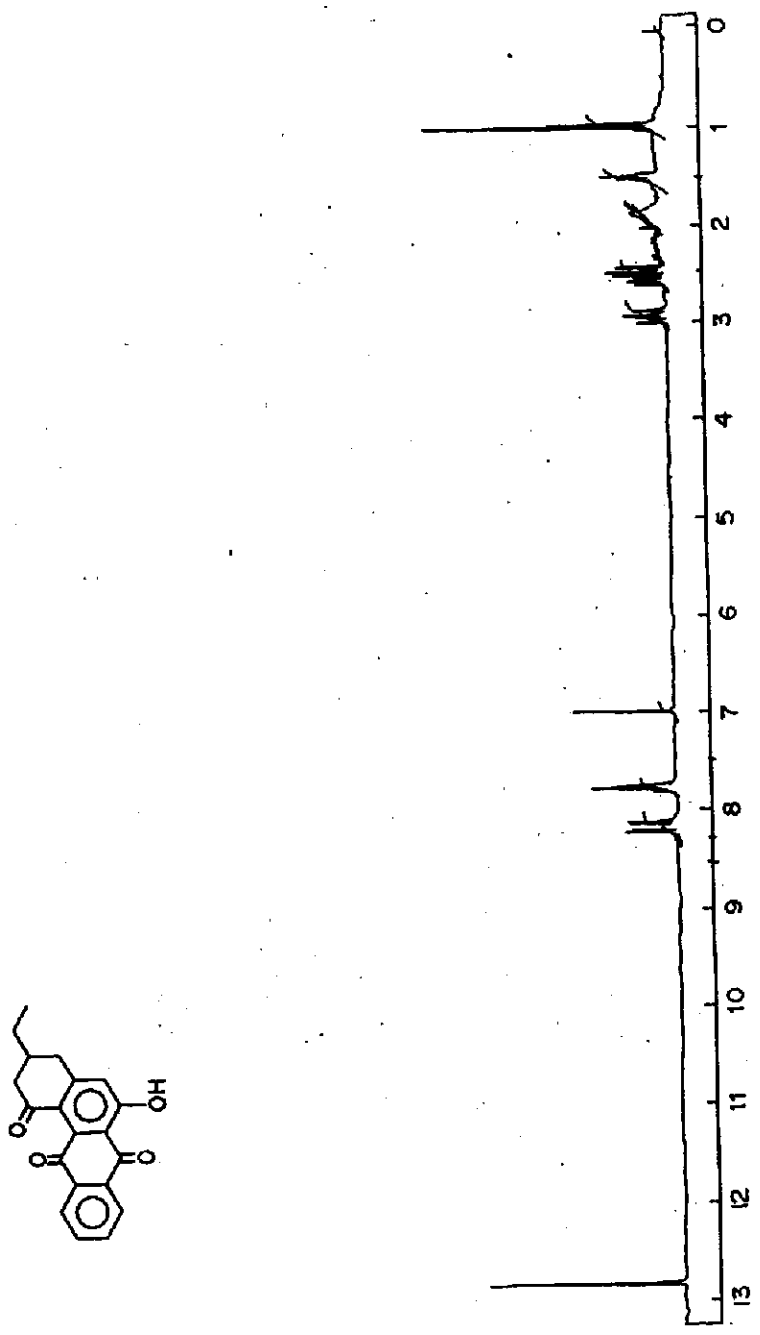
^{1}HNMR SPECTRUM (200MHz) OF THE COMPOUND **122** $CDCI_3$



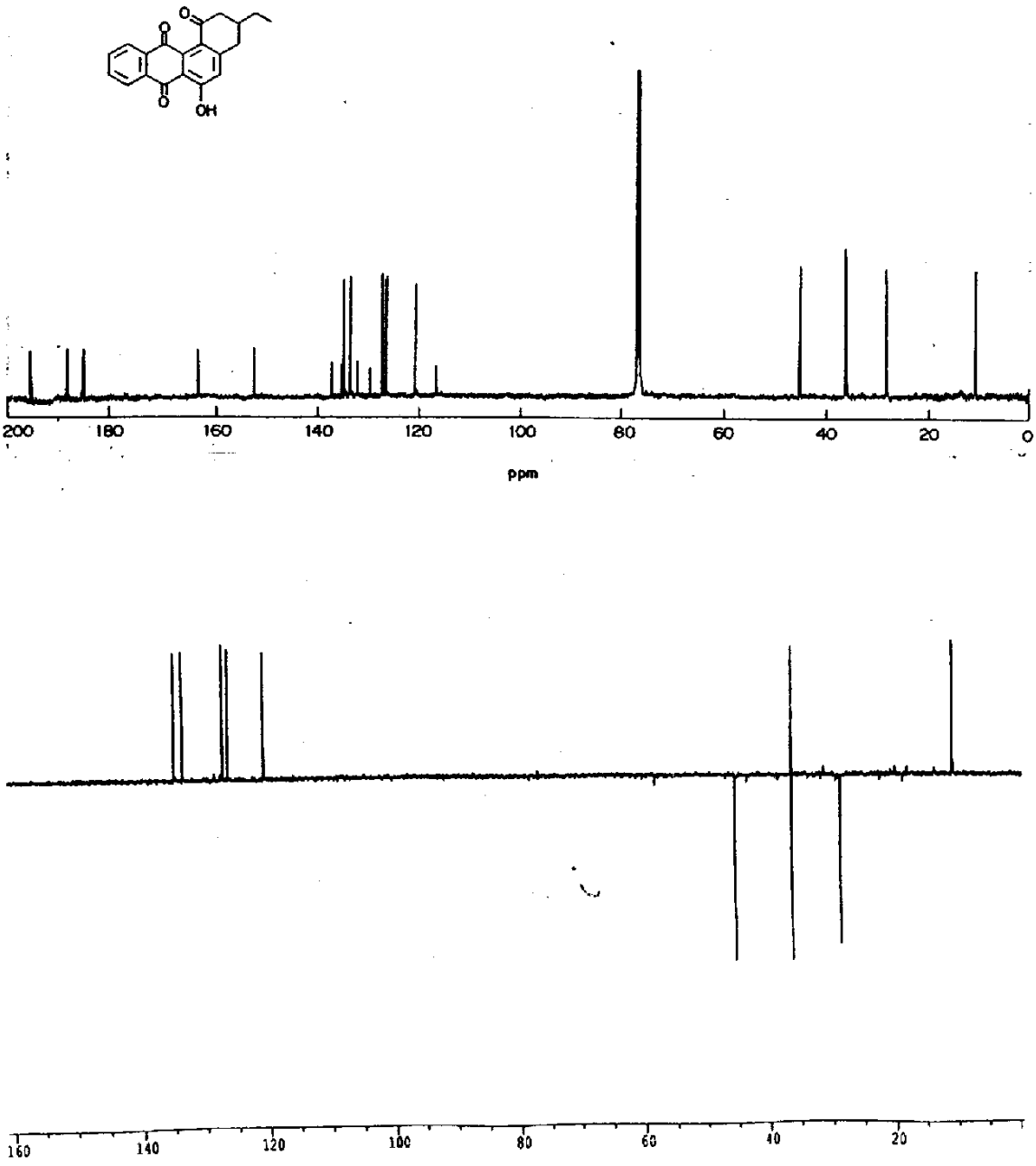
MASS SPECTRUM (200MHz) OF THE COMPOUND **123**



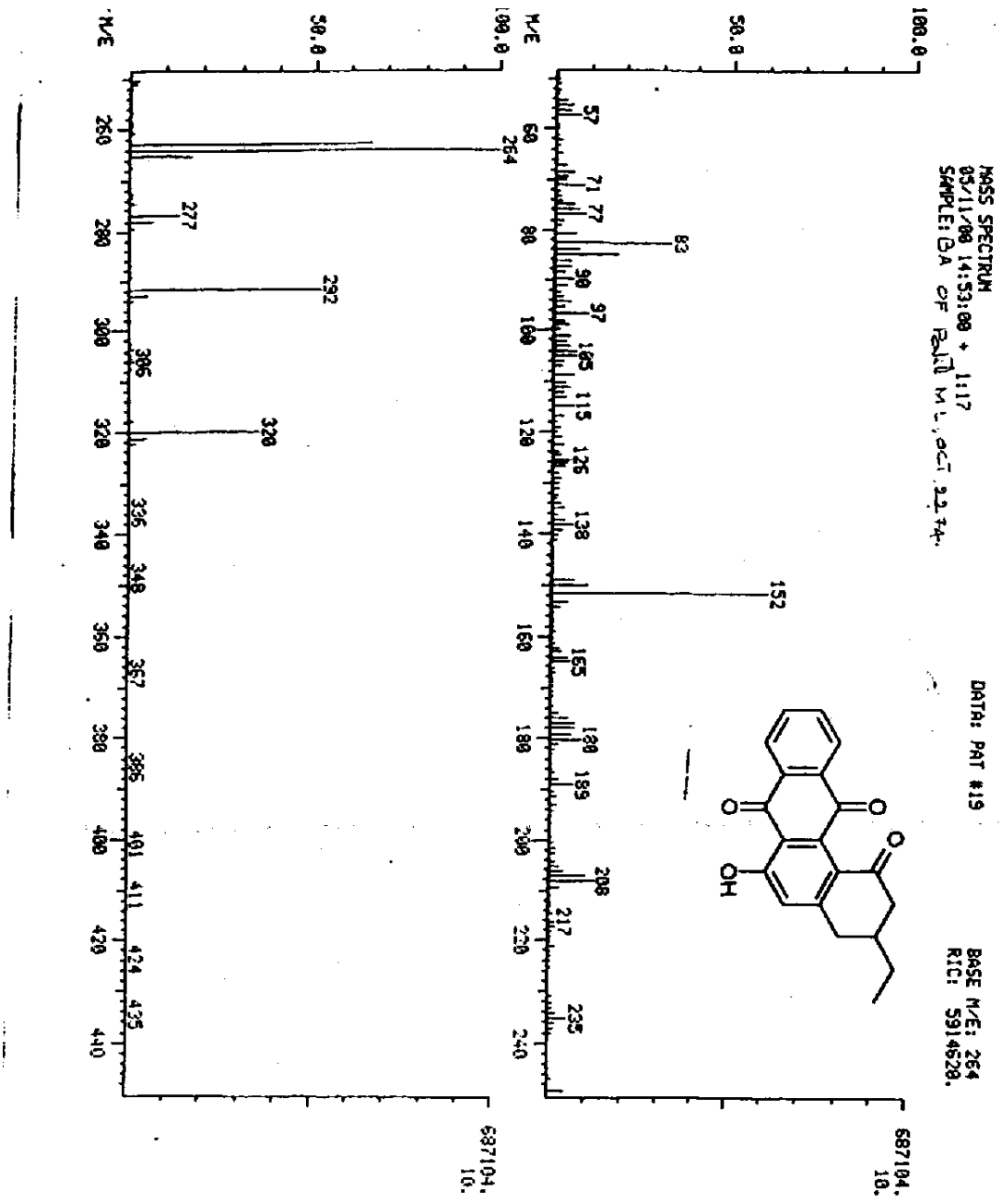
^{1}HNMR SPECTRUM (200MHz) OF THE COMPOUND **141** IN $CDCl_3$



^{1}HNMR SPECRUM (200MHz) OF(±)- **DEOXYBRASILIQUINONE B (139)** IN $CDCI_3$



^{13}C NMR SPECTRUM (125MHz) AND THE DEPT OF
(±)-DEOXYBRASILIQUINONE B (139) IN $CDCl_3$



MASS SPECTRUM OF (±)- **DEOXYBRASILIQUINONE B (139)**

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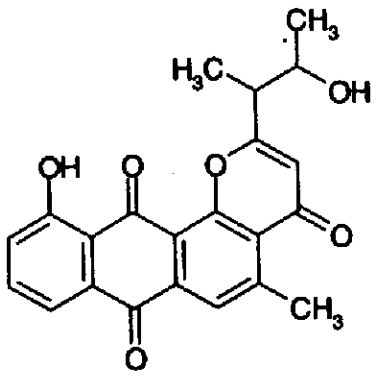
SECTION C

STUDIES DIRECTED TOWARDS SYNTHESIS OF AH-1763 IIa

1.3.0 INTRODUCTION

AH-1763 IIa[1] (**145**), a new antiherpetic agent was isolated by Uyeda et al. in 1997 from a culture broth of strain 1763 identified as Streptomyces cyaneus. Along with the antiherpetic activity, AH-1763 IIa (**145**) also showed antibacterial activity against Gram positive bacteria.



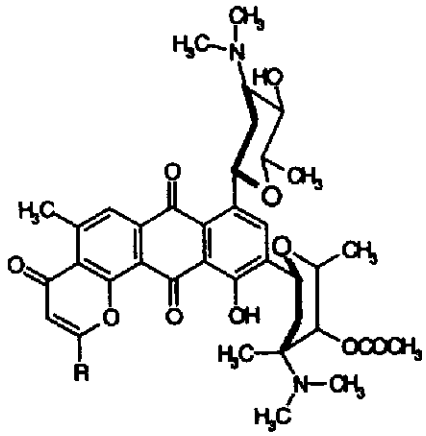
145: AH-1763 IIa

AH-1763 IIa (**145**) was isolated as yellow needles with m.p. 224-226 °C. It is readily soluble in acetone, methanol and chloroform, but insoluble in water. The UV maxima of AH1763 IIa in MeOH were observed at 239.5 (g 22,600), 267 (E 12,000), 287 (shoulder; s 7,000) and 417 nm (s 6,400). Its IR spectrum revealed absorption bands at 3500 and 1639 cm^{-1} due to the presence of hydroxyl and carbonyl groups. The EI-MS of AH-1763 IIa showed an ion peak at m/z 378. The elementary analysis of AH-1763 IIa afforded $C_{22}H_{18}O_6$ as molecular formula, which was in good agreement with m/z 378 (M^+). The ^{13}C NMR spectrum of AH-1763 IIa suggested the presence of 22 carbons as well as DEPT suggested that AH-1763 IIa consisted of the following functional groups: CH_3x3, CHxI, CH-Oxl, CH=x5, C=x6, O-C=x3, C=0x3. ^1H-NMR spectrum of AH-1763 IIa suggested three coupled aromatic protons at 8H 7.82 (dd), 8H 7.69 (t) and 8H 7.36 (dd) and two singlets were observed at 8H 8.09 and 8H 6.28, along with presence of C-methyl at 8H 3.02 singlet, two methyl 8H 1.43, 1.30 doublets, two methane protons 8H 4.32, 2.88, a phenolic hydroxyl SH 12.64 and a alcoholic hydroxyl 8H 3.88. On the basis of ^{13}C NMR, ^1H NMR, UV, IR, Mass spectrum and microanalysis the structure of AH1763 IIa was deduced to be 11-hydroxy-5-methyl-2-(2-hydroxy-1-methylpropyl)-4Hanthraceno { 1,2-b } pyran-4, 7, 12-trione. Exact stereochemistry of the chiral centers remains to be determined.

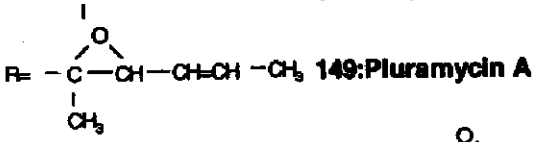
Thus the structure of AH-1763 IIa (**145**) was determined on the basis of various spectroscopic analysis and it was found that AH-1763 IIa belonged to a pluramycin group of

antibiotics. Pluramycin antibiotics are structurally related to angucyclines and possess a typical 4H-anthraceno [1,2-b } pyran-4, 7, 12-trione structural framework.

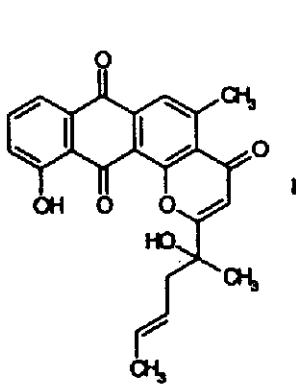
Other pluramycin antibiotics are hedamycin (**146**)[2], SF-2330[3], saptomycin4, espicufolin5, neopluramycin(**148**)[6], pluramycin A (**149**)[6], kidamycin (**147**)[7] and (3indomycinone (**150**).[8]



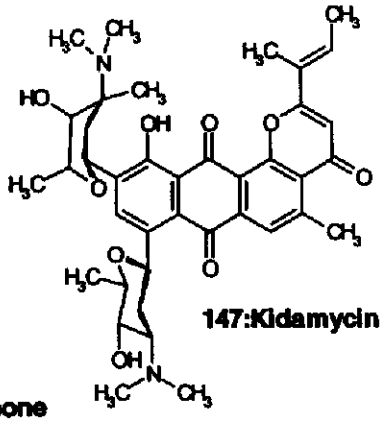
148:Neopluramycin



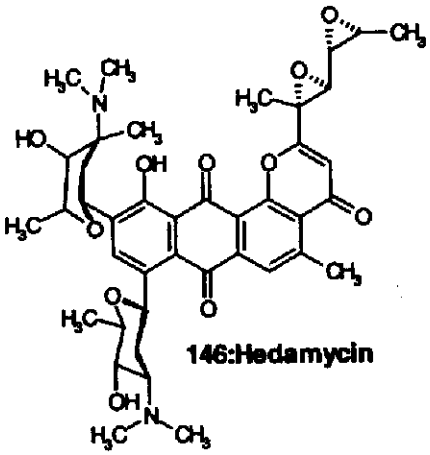
149:Pluramycin A



150:ß-Indomycinone



147:Kidamycin



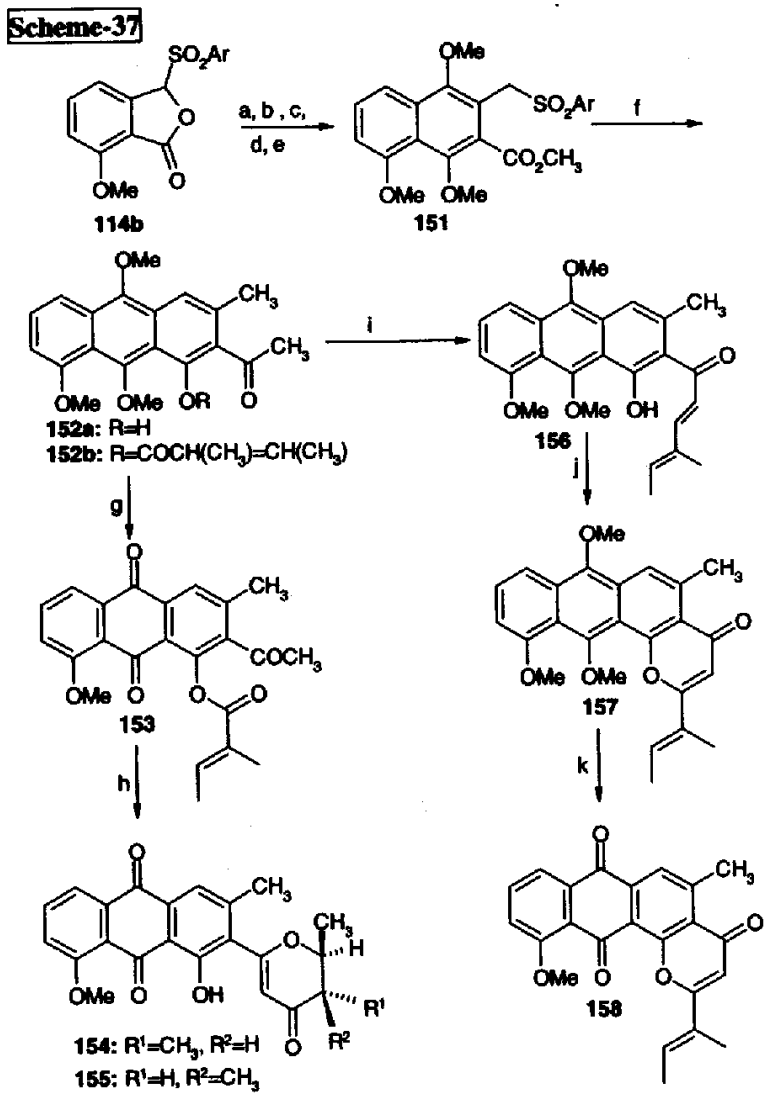
146:Hedamycin

AH-1763 IIa differs from the other pluramycin type antibiotics in the alkyl side chain attached at C-2. It is the only pluramycin type of antibiotic, which showed antiherpetic activity along with antibacterial activity. Structural novelty, less availability from natural sources and biological activity make this compound different from other pluramycin antibiotics and prompted us to undertake its synthesis.

Although there are many reports about the biological activities of these pluramycin antibiotics, synthetic part of these highly potent compounds has been less studied. AH-1763 IIa is a newly isolated compound and its synthesis is not yet reported.

Hauser et al[9] reported total synthesis of the methyl ether of kidamycinone i.e., the methyl ether of aglycone of the anticancer antibiotic kidamycin as shown in scheme-37.

Scheme-37



Reagents and conditions: a. LDA, THF, -78°C, methyl crotonate b. K_2CO_3, DMS c. NBS, CCl_4 d. Sodium thiophenoxide, EtOH e. m-CPBA, CH_2Cl_2 f. LDA, THF, -78°C, 3 penten-2~ne g. $CuBr_2$, THF h. i). NaH, dioxane ii). AcOHMCI i. 2.2 eq. LDA, tiglaldehyde j. SeO_2, tert-amyl alcohol k. AgO, HNO_3.

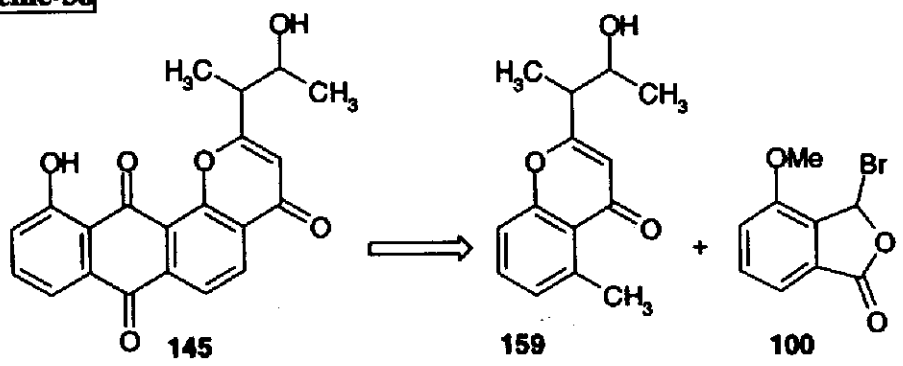
The synthetic plan for the preparation of O-methyl kidamycinone (**158**) involved, regioselective construction of the hexasubstituted anthracene, followed by annelation of the pyrone portion from the O-hydroxyl and acetyl functionalities. Thus the condensation of the methyl crotonate with the anion of 7-methoxy-3-phenylsulfonyl-1 (3H)-isobenzofuranone (**114b**) followed by a series of reactions including bromination with NBS, treatment with sodium thiophenoxide and oxidation with m-CPBA afforded the sulfoxide **151** in 95 % yield. The anion of sulfoxide **151** was then condensed with 3-penten-2-one to give anthracene **152a**. Construction of the pyrone portion from anthraquinone **153** which was obtained by oxidation of anthracene **152b**, was then attempted by transferring the acyl group of tigloyl ester **153** to the methyl ketone by base treatment followed by cyclization resulting into the cyclized products **154** and **155**. Finally the condensation of dianion of anthracene **152a** with tiglaldehyde followed by cyclization, dehydrogenation and oxidation afforded the methyl ether of kidamycinone **158**.

1.3.1 PRESENT WORK

The pluramycin type antibiotic AH-1763 IIa (**145**), a novel antiherpetic compound is structurally related to the kidamycinone but differs in the alkyl side chain attached at C-2 position. Careful examination of structures of both these compounds AH-1763 IIa (**145**) and kidamycinone suggested that dehydration of the alkyl chain of AH-1763 (**145**) may result into the kidamycinone, a potent anticancer compound. Thus the activity of these molecules in combination with the novel chemical structure prompted us to undertake synthesis of these molecules. This work also forms a part of our programme on antitumor antibiotics.

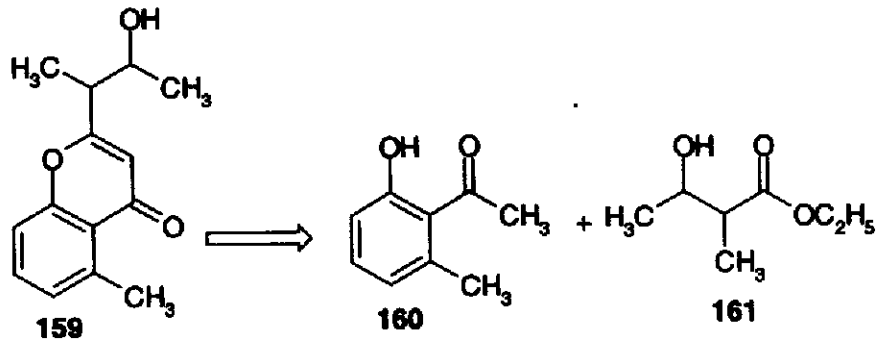
The antithetic analysis of AH-1763 IIa (**145**) suggested that its synthesis could best be achieved first by obtaining the chromone system 159 and then the construction of anthraquinone framwork, by using bromophthalide 100 as shown in scheme-38.

Scheme-38



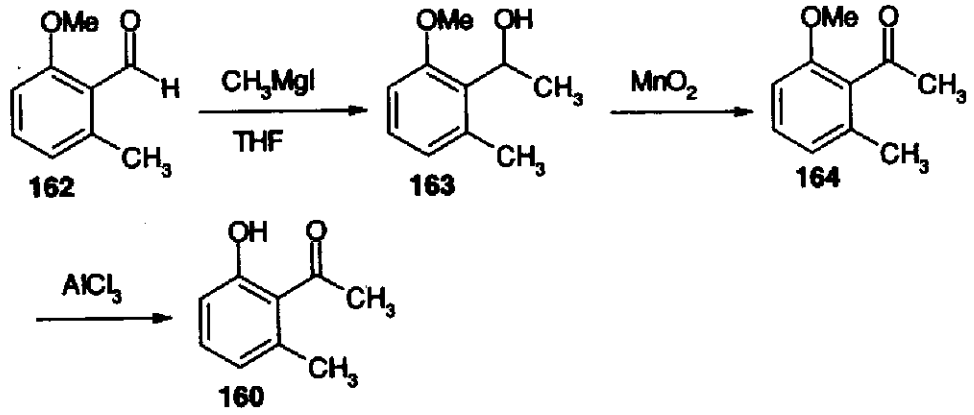
Further retrosynthetic studies on chromone **159** suggested **160** and **161** as important key intermediates as shown in scheme-39.

Scheme-39



Thus as per the retrosynthetic plan, condensation of the ester **161** with 2-hydroxy~methyl acetophenone (**160**) would give the diketone compound, which on cyclization followed by reduction would give the desired chromone synthon **159**. The required acetophenone **160** was prepared from 2-methoxy-6-methylbenzaldehyde (**162**), whose preparation is described in chapter II, by known procedure[10] as shown in scheme-40.

Scheme-40

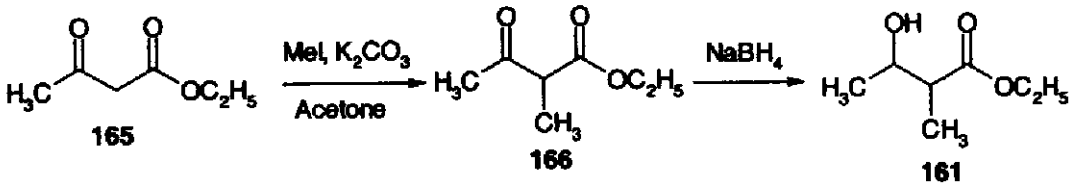


Accordingly Grignard reaction of methyl magnesium iodide with 2-methoxy-6methylbenzaldehyde (**162**) in anhydrous ether at room temperature yielded the alcohol **163**. Oxidation of the alcohol **163** to the corresponding acetophenone **164** was achieved using Mn02 in refluxing benzene. Further demethylation of acetophenone **164** was effected smoothly with aluminum chloride to give the required 2-hydroxy-6-methylacetophenone (**160**). The structure of acetophenone **160** was confirmed on the basis on its ^{1}H NMR spectrum, which showed disappearance of a singlet at 8 3.77 for methoxy group, and appearance of a singlet at

8 12.31 for chelated -0H. Rest of the signals were at appropriate positions. The IR spectrum revealed absorption band at 3320 cm^{-1} suggesting the presence of -OH group.

After the synthesis of the desired acetophenone **160** the efforts were directed towards the preparation of required ester moiety **161** as shown in scheme 41.

Scheme-41

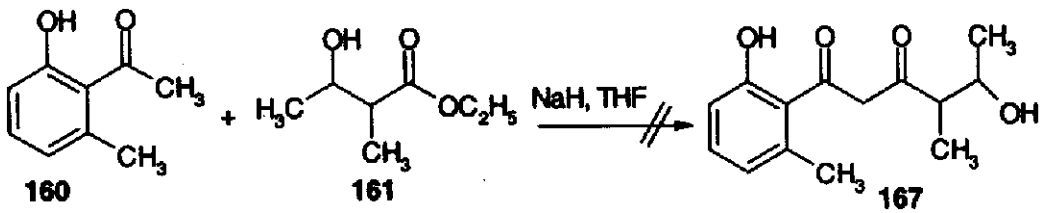


165 **166** **161**

Thus treatment of ethylacetoacetate (**165**) with methyl iodide in acetone in the presence of potassium carbonate yielded compound **166**, which was reduced to the desired ester **161** under sodium borohydride conditions without purification. Structure of the ester **161** was confirmed by its ^1H NMR spectrum, which showed multiplet at 8 1.07-1.35 integrating for 9 protons ($3XCH_3$) along with presence of a broad singlet at 8 2.75-2.95 for -0H group.

Next aim, after the synthesis of required intermediates **160** and **161**, was the condensation of ester **161** with acetophenone **160** to give the diketone compound **167**, which can be converted into the desired chromone **159**.

Scheme-42

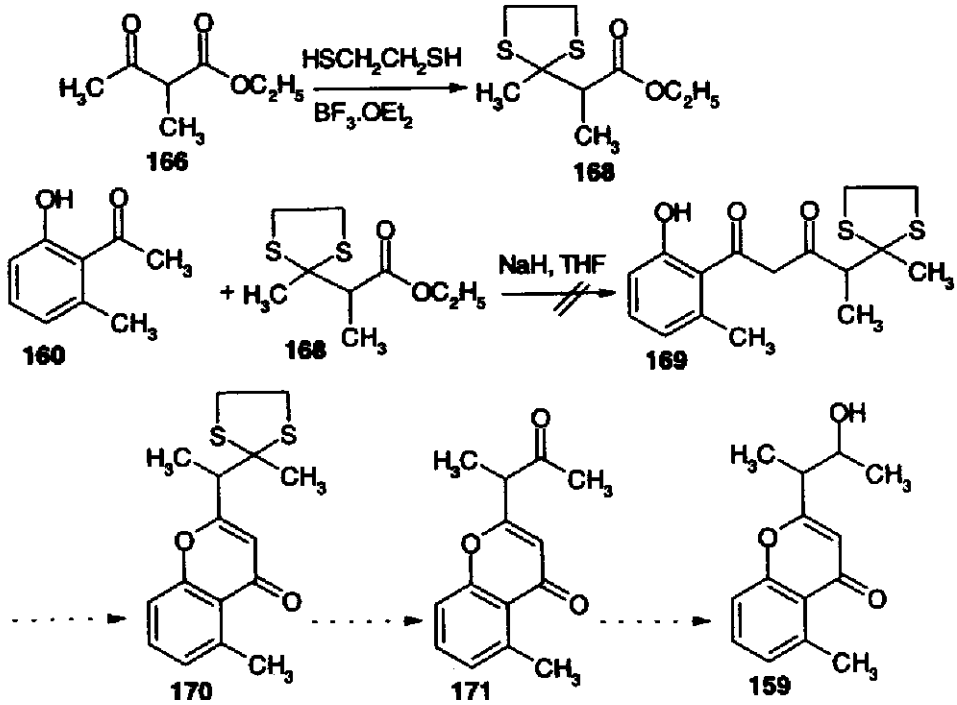


160 **161** **167**

Accordingly condensation of ester **161** with acetophenone **160** was attempted with sodium hydride in THF as shown in scheme-42, which resulted into the formation of a complex reaction mixture. Assuming the presence of free -0H group in ester **161** responsible for the formation of complex reaction mixture in this condensation reaction, we planned to protect the carbonyl group of compound **166** which can be deprotected and reduced to the corresponding alcohol after the chromone formation as shown in scheme-43. Accordingly the compound **166** was treated with ethanedithiol in chloroform in the presence of catalytic borontrifluoride diethyl etherate to give the protected ester **168**, which was characterized on the basis of ^1H NMR spectrum. The presence of a singlet at 8 1.88 and a doublet at 8 1.40 indicated presence of two

methyl groups as well as multiplet at S 3.25-3.40 (S$\underline{CH_2CH_2}$S) supported the assigned structure of compound **168**. Further its condensation with acetophenone160 was attempted using sodium hydride in THF as shown in scheme-43.

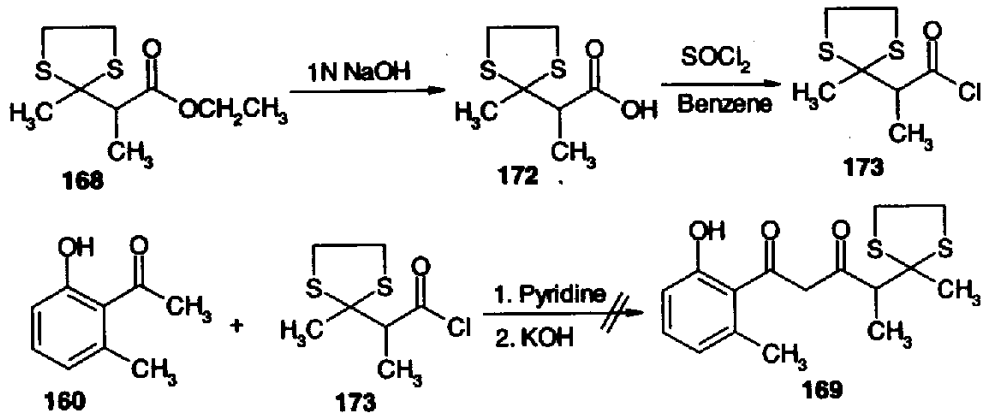
Scheme-43



Attempted condensation of ester **168** with acetophenone **160** using sodium hydride in THF did not proceed at room temperature and resulted into a complex mixture at 80 °C. The failure in the above condensation reaction prompted us to plan another route. As an alternative approach we planned to utilize the well known Baker-Venkataraman approach' 1 for the synthesis of chromone **159**. This rearrangement involves reaction of the acid chlorides with the O-hydroxy acetophenones followed by rearrangement to give the diketone compounds.

Acid chloride **173** required for this reaction was prepared from the ester **168** by the hydrolysis and treatment of the resulting acid **172** with thionyl chloride as shown in scheme44. Thus the treatment of ester **168** with 1N sodium hydroxide yielded the acid **172**, which was converted into the required acid chloride **173** by treating with thionyl chloride in refluxing benzene.

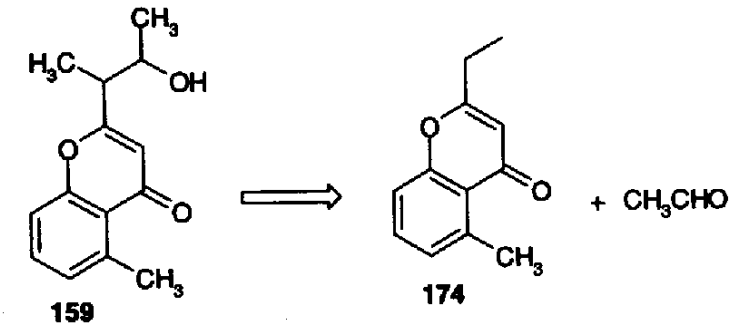
Scheme-44



Next target was the formation of diketone compound **169** utilizing the Baker Venkataraman rearrangement. First event of this rearrangement is the O-acylation followed by rearrangement by another equivalent of base to the acetyl group, resulting into the formation of the diketone compound. This rearrangement can be carned out under two conditions, one is the use of pyridine and potassium hydroxide at 120 °C and another is use of potassium tert. butoxide in THF at 0°C. Accordingly acid chloride **173** was treated with the acetophenone **160** in pyridine at 120 °C for 10 min (TLC showed faster moving spot), cooled and KOH was added to it. This mixture was further heated at 120 °C temperature. TLC analysis of the reaction mixture showed a complex mixture formation.

Failure in the condensation reaction and Baker-Venkataraman rearrangement made us to think about another strategy for the synthesis of **159**, the pyrone portion of AH-1763 IIa. An alternative retrosynthetic plan for chromone **159** is as shown in scheme 45.

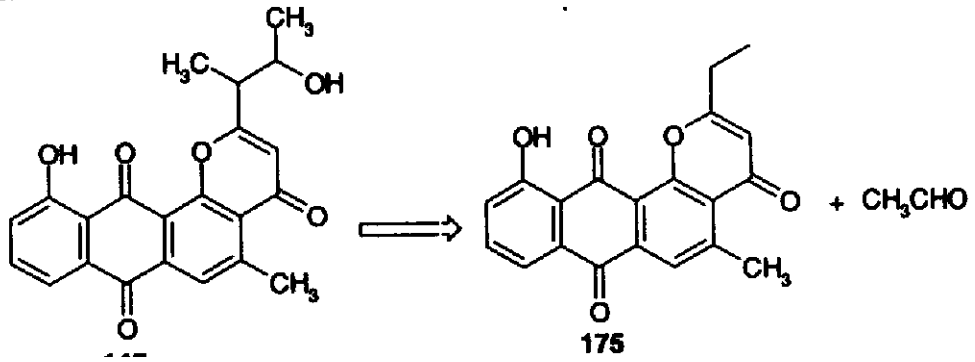
Scheme-45



Thus the synthesis of desired chromone **159** can be achieved by treating chromone **174** with acetaldehyde. We assumed that synthesis of AH-1763 IIa could best be achieved by

introducing the alcoholic functionality in the side chain after the synthesis of anthraquinone ring system as shown in the retrosynthetic scheme, which suggested chromone **174** as an important precursor for the synthesis of the desired anthraquinone by making use of Friedel-Crafts alkylation approach utilized successfully for the synthesis of brasiliquinone B. cheme-4

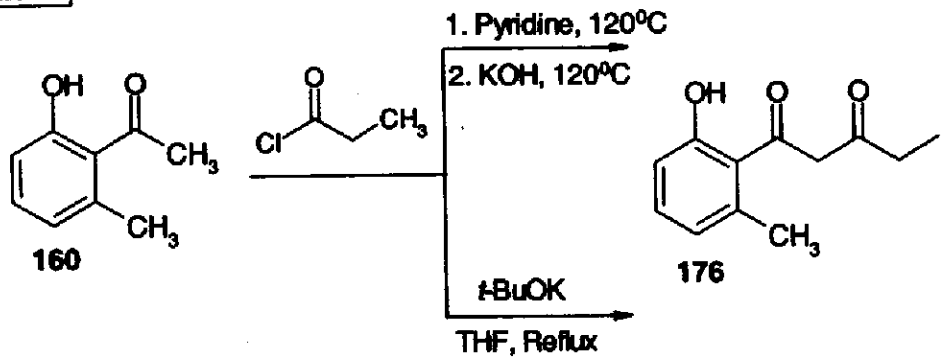
Scheme-46



175

Accordingly synthesis of chromone **174** was attempted by using Baker-Venkataraman rearrangement starting from acetophenone **160** as shown in scheme 47.

Scheme-47



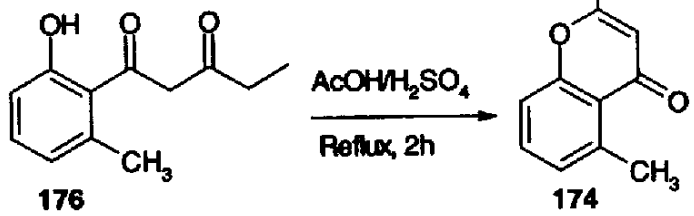
Thus acetophenone **160** was treated with proiponyl chloride in pyridine at 120 °C for 10 min. The reaction mixture was then cooled and potassium hydroxide powder was added to it and again heated at 120 °C for 1 hr resulting in the formation of diketone compound **176** in 65 % yield. The structure assigned to the diketone compound **176** was confirmed on the basis of ^{1}H NMR which revealed presence of a triplet at 8 1.04 (-$COCH_2\underline{CH_3}$), a quartet at 8 1.88 (-$CO\underline{CH_2}CH_3$) group, a singlet at 8 2.58 (Ar-$\underline{CH_3}$), two doublets at 8 2.72 and 2.85 (-$CO\underline{CH_2}CO$-) each integrating for one proton in addition to the rest of the peaks at expected positions with appropriate integrations. IR showing absorption bands at 3300 cm-1 and 1650 cm-1 further confirmed it. Mass spectrum showing presence of molecular ion peak at m/z 206,

was in good agreement with assigned structure. This rearrangement was also achieved effectively in one step by using potassium tert. butoxide in THF at 80 °C to get compound **176** in 0 % yield.

After the formation of diketone compound **176**, next aim was to cyclize it to form the chromone **174**. This cyclization was effected by acetic acid/sulfuric acid as shown in scheme48. The compound **176** was refluxed for 2 h in acetic acid in the presence of 4-5 drops of sulfuric acid to afford chromone **174** in 62 % yield.

: acid to afford chromone 174 in 62 % yield.

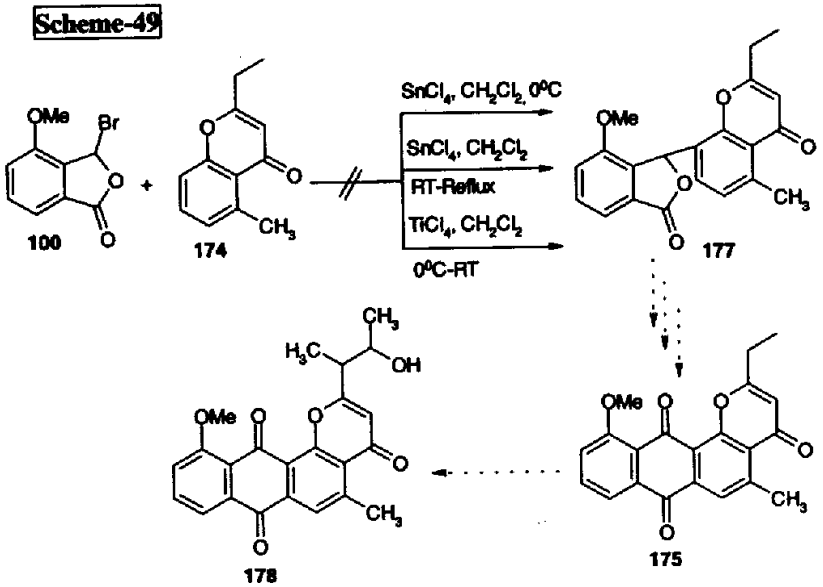
Scheme-48



The ^{1}H NMR spectrum of chromone **174** showed singlets at 8 6.05 and 8 2.83 for olefinic proton and aromatic methyl group respectively. Rest of the signals were at present expected positions. The IR spectrum revealed absorption band at 1700 cm^{-1} for carbonyl group. Finally mass spectrum indicating molecular ion peak at m/z 188 supported the assigned structure.

After the successful synthesis of chromone **174** efforts were directed towards the synthesis of anthraquinone ring system of the molecule AH-1763 IIa.

Scheme-49

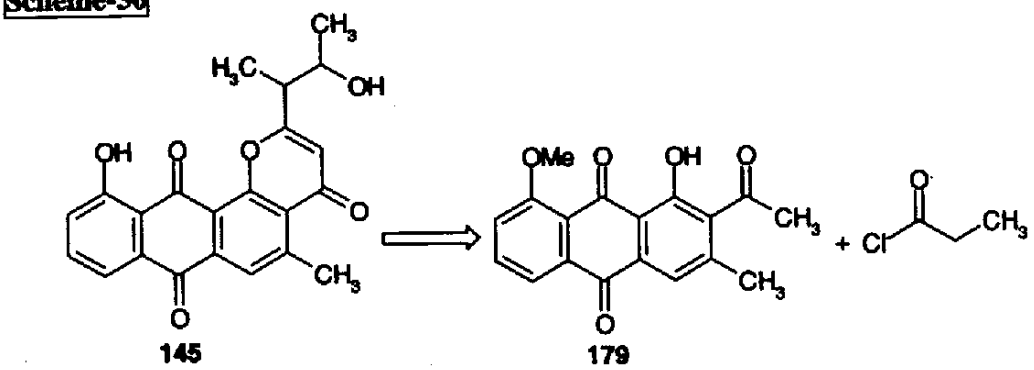


We adopted the method used for the synthesis of brasiliquinone B, of execution of Friedel- rafts alkylation reaction, for the construction of quinone framework, as shown in scheme-49.

Treatment of chromone **174** with bromophthalide **100** under various conditions was unsuccessful and we had to give up this approach.

After the failure in this key step alkylation reaction, we planned another method involving initial construction of anthraquinone framework and then utilization of Baker Venkatraman rearrangement for the construction of pyrone ring system as shown in the scheme-50.

Scheme-50



The synthesis of quinone **179** was undertaken starting from 2,3-dimethyl anisole (**180**) using Friedel-Crafts alkylation approach as shown in scheme-51.

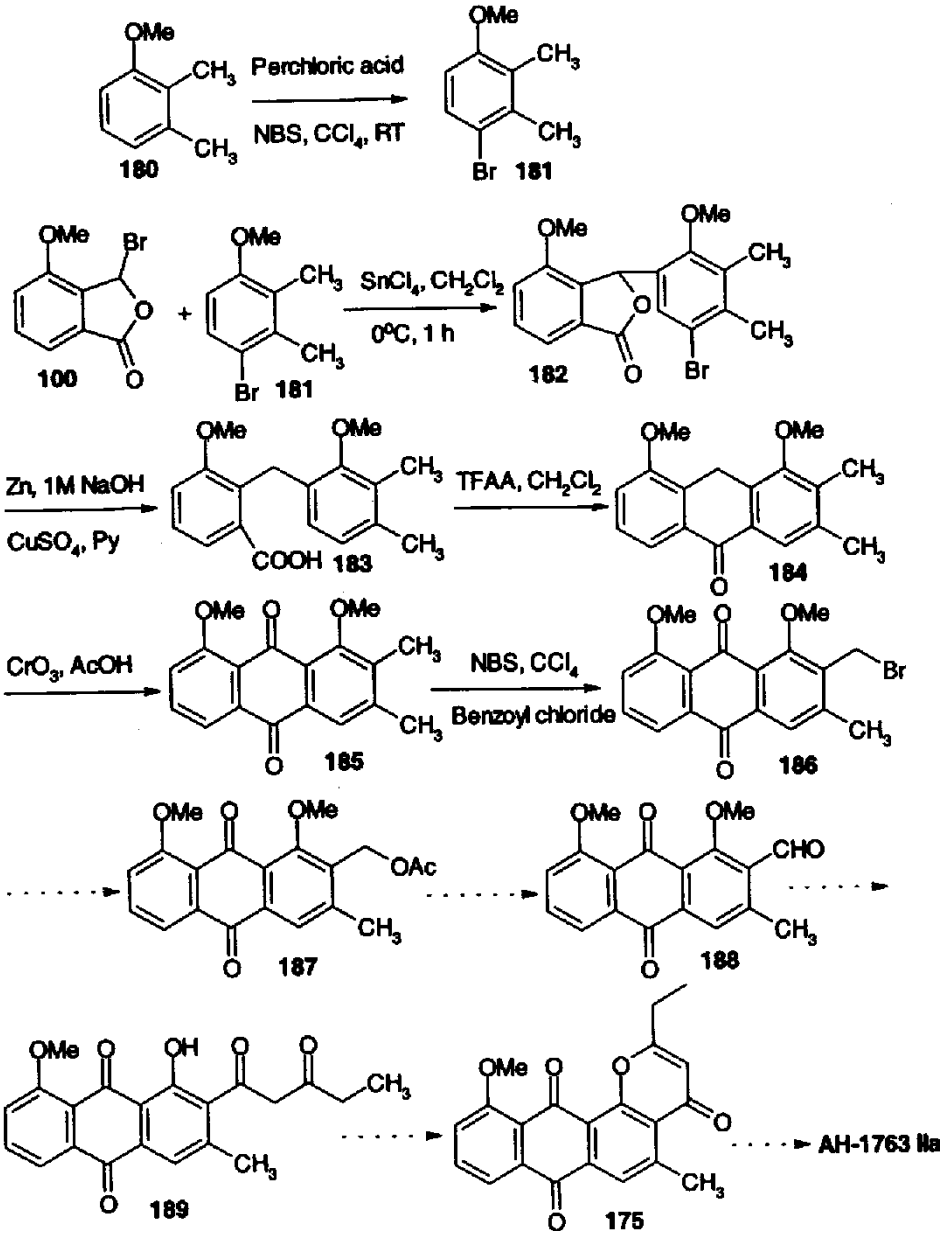
Alkylation of **180** was expected to result into formation of both ortho and para alkylated products, hence we planned to block the para position of **180** by bromination.

Alper et a1.[12] reported regioselective electrophilic bromination of **180** with NBS catalyzed by 70 % perchloric acid in quantitative yield. Thus bromination of **180** with 1 equivalent of NBS in presence of catalytic 70 % perchloric acid in CCl_4 at room temperature afforded desired brominated product **181** in 90 % yield. The ^1H NMR spectrum showed two singlets of two non equivalent $-CH_3$ groups and a $-OCH_3$ group and also a doublet of the ortho coupled aromatic protons indicating selectively para brominated product.

The compound **181** was then subjected to the Friedel-Crafts alkylation reaction with bromophthalide **100** in presence of stannic chloride in CH_2Cl_2 to give the alkylated product **182** in 75 % yield. Structure of the compound **182** was confirmed by spectroscopic analysis. The ^1H NMR spectrum indicated presence of two singlets for aromatic methyl groups at 8 2.32

and 8 2.37, two singlets for -0Me groups at 8 3.75 and 8 3.82, a singlet at 8 6.75 for phthalide proton and rest of the peaks were at expected positions. The IR spectrum showing absorption band at 1745 cm^{-1} indicated presence of lactone system. Mass spectrum showing presence of molecular ion peak at m/z 376 supported the assigned structure.

Scheme-51



Reductive opening of the lactone **182** as well as debromination to the acid **183** was achieved by refluxing the lactone **182** in 1M solution of sodium hydroxide, pyridine in the presence of zinc, and copper sulfate. The ^{1}H NMR of the acid **183** showed expected signals but it was not clean. Hence it was characterized after converting it to the anthrone **184**. Treatment of acid **183** with trifluoroacetic anhydride in methylene chloride yielded the anthrone **184**, whose structure was determined on the basis of ^{1}H NMR, IR and Mass spectrum.

The ^{1}H NMR spectrum of the anthrone **184** indicated presence of two singlets at S 2.30 and 2.37 (2XAr-$\underline{CH_3}$), two singlets at 8 3.85 and 3.98 (2X-0Me) and a singlet at 8 4.10 (Ar$\underline{CH_2}$-Ar). The IR spectrum showed absorption band at 1705 cm^{-1} for ketone functionality. The molecular ion peak at m/z 282 in mass spectrum supported the structure of anthrone **184**. Conversion of the anthrone **184** to the anthraquinone **185** was then achieved by oxidation using chromium trioxide in acetic acid in 90 % yield. Disappearance of the benzylic proton at 8 4.10 and presence of the molecular ion peak at m/z 296 in mass spectrum supported the assigned structure of quinone **185**.

Next target was to convert the quinone **185** into the aldehyde **188** which when followed by a series of reactions as shown in scheme-51 would give the desired chromone **175**. Finally the reaction of chromone **175** with acetaldehyde would give the target molecule AH-1763 IIa.
This work is in progress.

1.3.2 EXPERIMENTAL

2-Methoxy-6-methylacetophenone (164):

Iodomethane (0.7 ml, 11.2 mmol) in ether (10 ml) was added dropwise over magnesium (0.175 gm, 7.2 mmol) in ether (5 ml) at 0°C., To this solution of methylmagnesium iodide the aldehyde **162** (0.72 gm, 4.8 mmol) in dry ether (10 ml) was added dropwise over 30 min. The mixture was then heated under reflux for 30 min and treated with saturated aqueous ammonium chloride (25 ml). The aqueous layer was extracted with ether, washed with brine, water and dried over sodium sulphate. Evaporation of ether yielded the alcohol **163** as an oil, which was heated under reflux in benzene (10 ml) with activated manganese dioxide for 10 hr. Filtration through Celite and evaporation of the filtrate afforded the acetophenone **164** as a pale yellow oil.

Yield:	683 mg (87 %).
IR(nujol):	1685 cm^{-1}.
^{l}HNMR ($CDCl_3$, 200 MHz):	8 2.20 (s; 3H), 2.43 (s, 3H), 3.77 (s, 3H), 6.60-7.00 (m, 2H), 7.10-7.40 (m, 1H).

2-Hydroxy-6-methylacetophenone (160):

Aluminum chloride (1.30 gm, 10 mmol) was added portionwise at 0°C to the stirred solution of acetophenone **164** (1.14 gm, 7 mmol) in methylene chloride (20 ml) over a period of 30 min. It was stirred at same temperature for 2 hr and allowed to warm up to room temperature slowly. After completion of the reaction (TLC) reaction mixture was poured into ice cold water (20 ml) and concentrated hydrochloric acid (5 ml). The methylene chloride layer was separated and aqueous layer was extracted with chloroform. The combined organic layer was washed with water, dried over sodium sulphate and evaporated to give acetophenone **160** as a pale yellow oil.

Yield:	1.12 g, (95 %).
IR (nujol):	3320, 1630 cm^{-1}.
^{1}H NMR ($CDCI_3$, 200 MHz):	8 2.61 (s, 3H, Ar-CH_3), 2.68 (s, 3H, -$COCH_3$), 6.74 (d, J--7.2 Hz, 1H, aromatic), 6.88 (d, J=7.2 Hz, 1H, aromatic), 7.25-7.40 (m, 1H, aromatic), 12.31 (s, 1H, -OH).
Mass (m/z):	150 (M^+).

3-Methyl-2-(1', 3'-dioxopentyl)phenol (176):

Method A:

Acetophenone **160** (300 mg, 2 mmol) in dry THF (5 ml) was added to the mixture of potassium tert. butoxide (224 mg, 2 mmol) in dry THF (5 ml) at 0°C over a period of 15 min. Reaction mixture was then allowed to warm up to room temperature and stirred for additional 35 min. It was again cooled to 0°C and propionyl chloride (185 mg, 2 mmol) was added slowly followed by another equivalent of potassium tert. butoxide (224 mg, 2 mmol), and the mixture was then refluxed for 10 hr. After completion of reaction, the dark coloured solution was poured into the mixture of crushed ice and concentrated hydrochloric acid (3 ml). Reaction mixture was then extracted with ethyl acetate, washed with water, dried over sodium sulphate and concentrated to give dark coloured liquid. Column chromatographic purification afforded compound **176** as colourless liquid.

Yield: 288 mg (70 %).

Method B:

A mixture of acetophenone **160** (300 mg, 2 mmol) and propionyl chloride (185 mg, 2 mmol) in pyridine (5 ml) was heated at 120 °C for 10 min. The reaction mixture was allowed to cool and powdered potassium hydroxide (224 mg, 4 mmol) was added to it. The resulting mixture was again heated at 120 °C for 1 hr. After cooling, reaction mixture was poured on crushed ice, acidified with concentrated hydrochloric acid and extracted with chloroform. The organic layer was then washed with water, dried over sodium sulphate and evaporated followed by column chromatographic purification of residue to afford compound **176** as colourless liquid.

Yield:	267.8 mg (65 %).
IR (nujol):	3300, 1650 cm^{-1}.
^{1}H-NMR ($CDCl_3$, 200 MHz):	51.04 (t, J = 6.4 Hz, 3H,-$\underline{CH_2}CH_3$) , 1.88 (q, J = 5.12 Hz, 2H, -CH_2CH_3), 2.58 (s , 3H, Ar - $\underline{CH_3}$), 2.72 (d, J = 12.90 Hz, 1 H , -CO$\underline{CH_2}$CO-), 2.85 (d, J=12.90 Hz, 1H,-CO$\underline{CH_2}$CO-) 6.76 (d, J=6.4 Hz, 2H, aromatic), 7.28 (t, J=6.4 Hz, 1H, aromatic).
Mass (m/z):	206(M^+).

3-Ethyl-8-methylchromone (174):

A mixture of compound **176** (103 mg, 0.5 mmol) and conc. sulfuric acid (4-5 drops) in galacial acetic acid (3 ml), was refluxed for 2hr. The reaction mixture was then cooled and poured on crushed ice. The aqueous layer was extracted with chloroform, washed with water,

dried over sodium sulphate and concentrated. Purification of the residue by column chromatography yielded chromone **174** as a colourless oil.

Yield: 58.28 mg (62 %)

IR (nujol): 1700 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz): 8 1.25 (t, J=6.6 Hz, 3H, -$CH_2\underline{CH_3}$), 2.57 (q, J=6.6 Hz, 2H, -$CH_2\underline{CH_3}$), 2.83 (s, 3H, Ar-CH_3), 6.05 (s, 1H, olefinic), 7.05 (d, J=6.6 Hz, 1 H, aromatic), 7.23 (t, J=6.6 Hz, 1H, aromatic), 7.42 (d, J=6.6 Hz, 1 H, aromatic).

Mass (m/z): 188 (M^+).

4-Bromo-2,3-dimethylanisole (181):

70 % Perchloric acid (0.1 ml) was added to a stirred mixture of 2,3-dimethylanisole (1.36 gm, 0.01 mole) and NBS (1.78 gm, O.Olmole) in dry CCl4 (25 ml), and stirred for 1 hr at room temperature. After completion of reaction (GC analysis), solid potassium carbonate (100 mg) was added to it, stirred for additional 30 min and filtered. The CCl4 was removed under reduced pressure and the residue was subjected to vacuum distillation (180 °C/2 mm) to give compound 181 as colourless liquid.

Yield: 1.93 g (90 %).

^{1}H-NMR ($CDCl_3$, 200 MHz): S 2.20 (s, 3H, Ar-CH_3), 2.36 (s, 3H, Ar-CH_3), 3.79 (s, 3H, -OMe), 6.58 (d, J=7.5 Hz, 1H, aromatic), 7.34(d, J--7.5 Hz, 1H, aromatic).

4-Bromo-6-(4'-methoxy-3'-phthalido)-2,3-dimethylanisole (182):

Compound **181** (1.6 gm, 0.0075 mol) was added with stirring to a solution of 3-bromo-4-methoxyphthalide (100) (2.7 gm, 0.011 mol) in dry methylene chloride (20 ml) at 0°C under nitrogen atmosphere. Stannic chloride (3.9 gm, 0.015 mole) was then introduced and the resulting mixture was stirred at 0°C for lhr. It was then poured into a mixture of conc. hydrochloric acid (10 ml) and ice-water (50 ml) and extracted with chloroform. The chloroform layer was washed with water, brine, dried over sodium sulphate, concentrated and purified by column chromatography to yield 182 as white solid, m. p. 182 °C.

Yield: 2.1 gm (75 %).

IR(nujol): 1745 cm^{-1}(lactone), 1596 cm^{-1} (aromatic).

^{1}H-NMR (Acetone-d6, 200 MHz): 8 2.32 (s, 3H, Ar-.CH_3), 2.37 (s, 3H, Ar-CH_3), 3.75 (s, 3H, -OCH_3), 3.82 (s, 3H, -OCH_3), 6.75 (s, 1H, phthalide),6.94

(s, 1H, aromatic), 7.38 (d, J=7.7 Hz, 1H, aromatic),7.52 (d, J=7.7 Hz, 1H, aromatic), 7.68 (t, J=7.7 Hz, 1H, aromatic).

Mass (m/z): 376 (M^+).

2,3-Dimethyl-6-(2-carboxy-6-methoxybenzyl)anisole (183):

The lactone **182** (752 mg, 0.002 mole) was reductively opened up by heating with 1M sodium hydroxide solution (70 ml), activated zinc (11 gm, 0.17 mole), a pinch of copper sulphate and pyridine (15 ml) at 125 °C for 20 h. The solution was filtered through a pad of Celite, filtrate acidified and extracted with ethyl acetate. Evaporation of the ethyl acetate under reduced pressure afforded the corresponding acid **183** as white semisolid.

Yield: 300 mg (60 %).

IR (nujol): 3400 cm^{-1}.

Mass (m/z): 300 (M^+).

Anthrone 184:

To a stirred solution of ketoacid **183** (300 mg, 0.001 mole) in dry methylene chloride (10 ml) was added trifluoroacetic anhydride (1 ml) at 0°C under nitrogen atmosphere. Reaction mixture was then allowed to warm up to room temperature and stirred for 10 hrs. It was then poured into ice-water (15 ml) and stirred for 1/z hr. The methylene chloride layer was washed with saturated solution of potassium carbonate, water and dried over sodium sulphate. Evaporation of the methylene chloride and column chromatographic purification over silica gel afforded anthrone **184** as yellow solid; m. p. 187 °C

Yield: 234 mg (83 °Io).

IR (nujol): 1705 cm^{-1} (ketone), 1595 cm^{-1} (aromatic).

^{1}H-NMR (CDCl3, 200 MHz): 8 2.30 (s, 3H, Ar-CH_3), 2.37 (s, 3H, Ar-CH_3), 3.85 (s,3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 4.10 (s, 2H, benzylic),

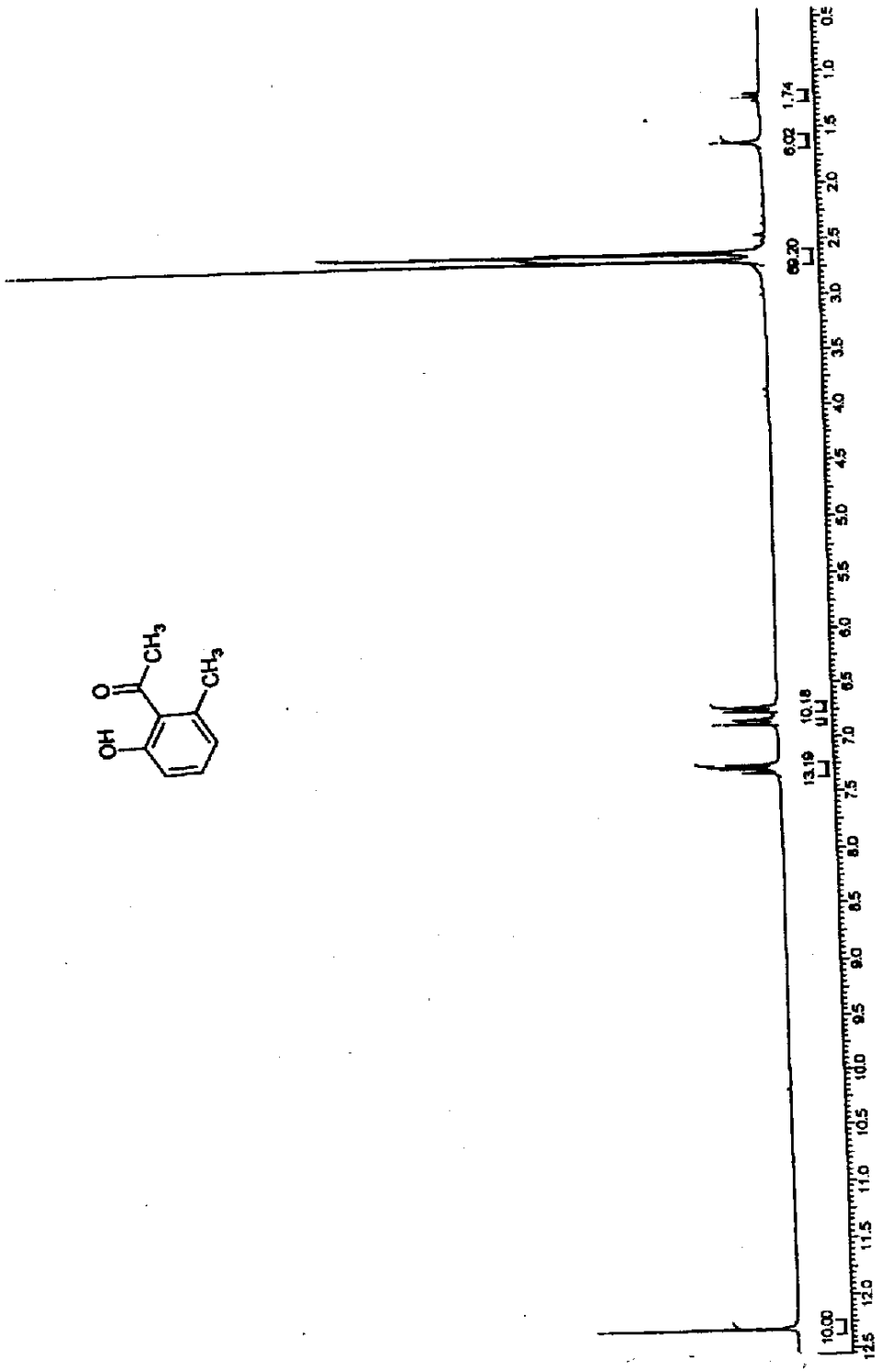
7.10 (d, J=7.5 Hz, 1H, aromatic), 7.42 (t, J--7.5 Hz, 1H, aromatic), 7.90-8.00 (m, 2H, aromatic).

Mass (m/z): 282 (M^+).

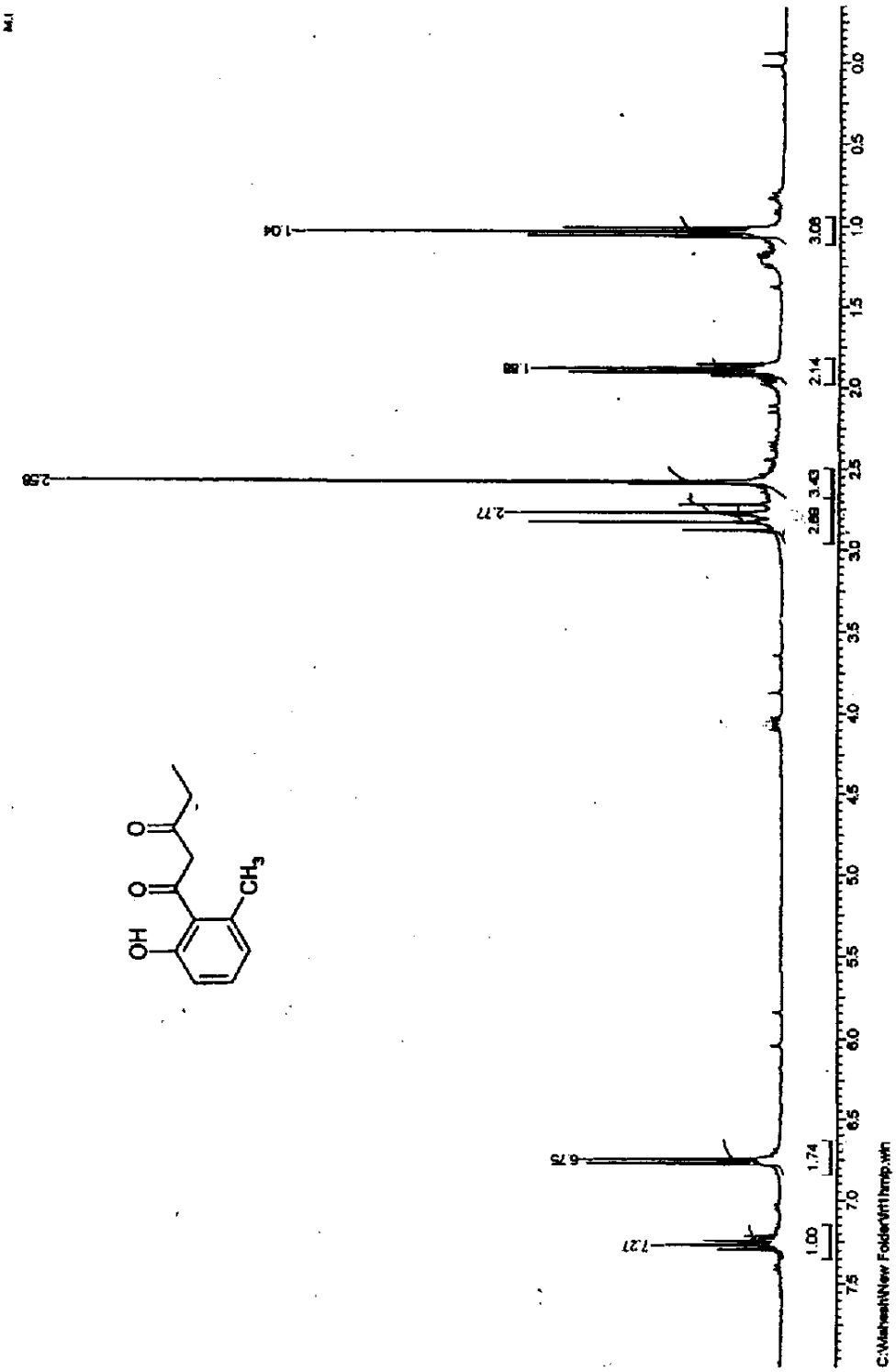
1,8-Dimethoxy-2,3-dimethylanthraquinone (185):

To a stirred ice cold solution of anthrone **184** (197.4 mg, 0.7 mmol) in glacial acetic acid (2 ml), chromium trioxide (140 mg, 1.4 mmol) in 80% acetic acid (2 ml) was added. The reaction mixture was allowed to warm up to room temperature (30 min) and stirred for 2 hr. After completion of reaction (TLC), mixture was poured into cold water (10 ml) and stirred for 10 min. Aqueous layer was extracted with chloroform, washed with water, dried over sodium sulphate and concentrated to give quinone **185** as reddish solid; m. p. 110 °C

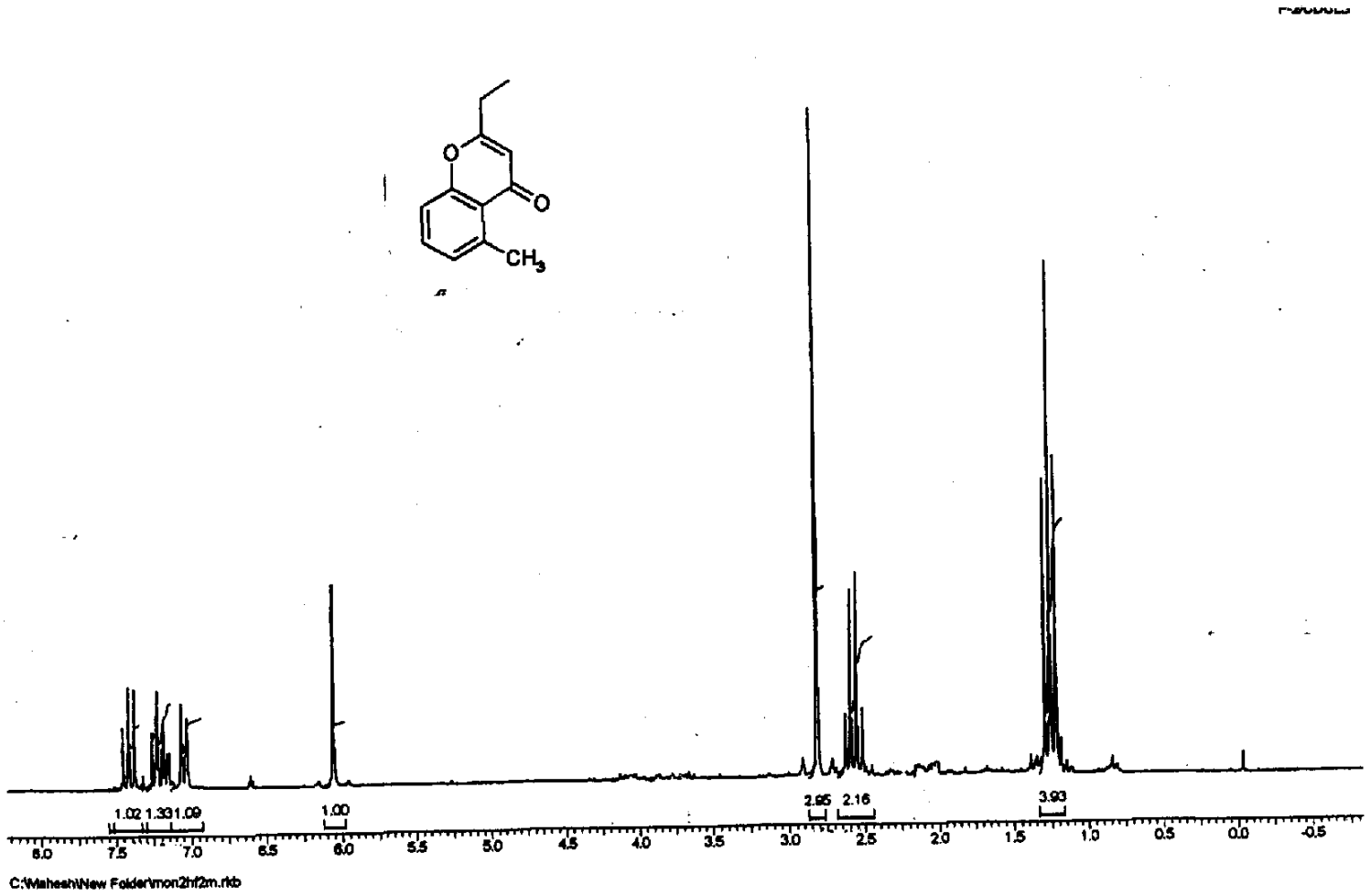
Yield:	186.4 mg (90 %).
IR (nujol):	1680 cm^{-1} (quinone carbonyl), 1595 cm^{-1}(aromatic).
^{1}H-NMR (CDCl3, 200 MHz):	8 2.32 (s, 3H, Ar-CH_3), 2.40 (s, 3H, Ar-CH_3), 3.94 (s, 3H, -OCH_3), 4.02 (s, 3H, -OCH_3), 7.30 (d, J--7.6 Hz, 1H,aromatic), 7.64 (t, J--7.6 Hz 1H, aromatic), 7.83-7.88 (m, 2H, aromatic).
Mass (m/z):	296 (M^+).



^{1}H NMAR SPECTRUM (200MHz) OF THE COMPOUND 160 IN $CDCI_3$.



^{1}H NMAR SPECTRUM (200MHz) OF THE COMPOUND 176 IN $CDCI_3$.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3.93
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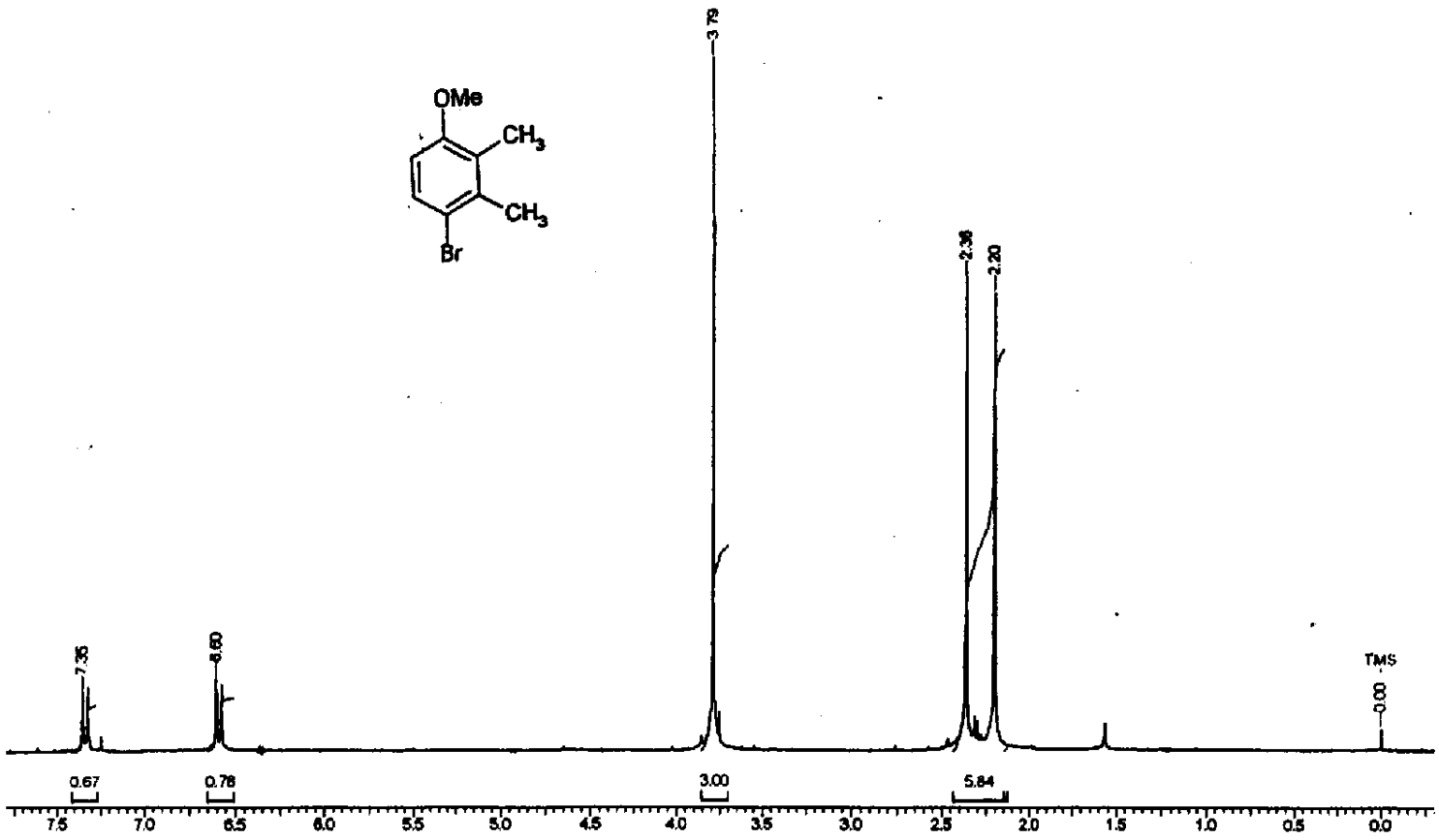
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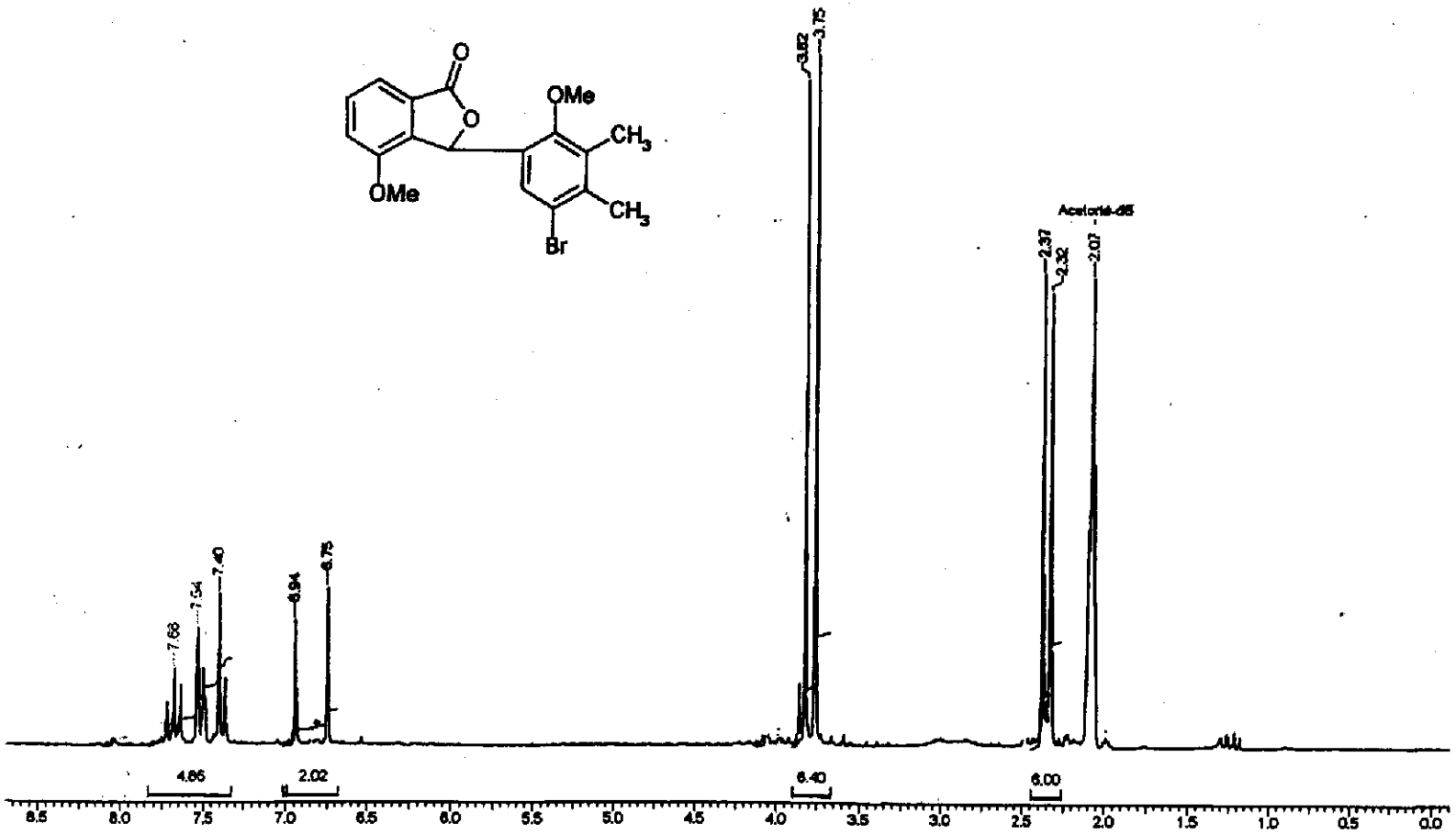
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7.54
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26 Jun 2000
PATIL M. L. ANTHRONE - F IN @CL3

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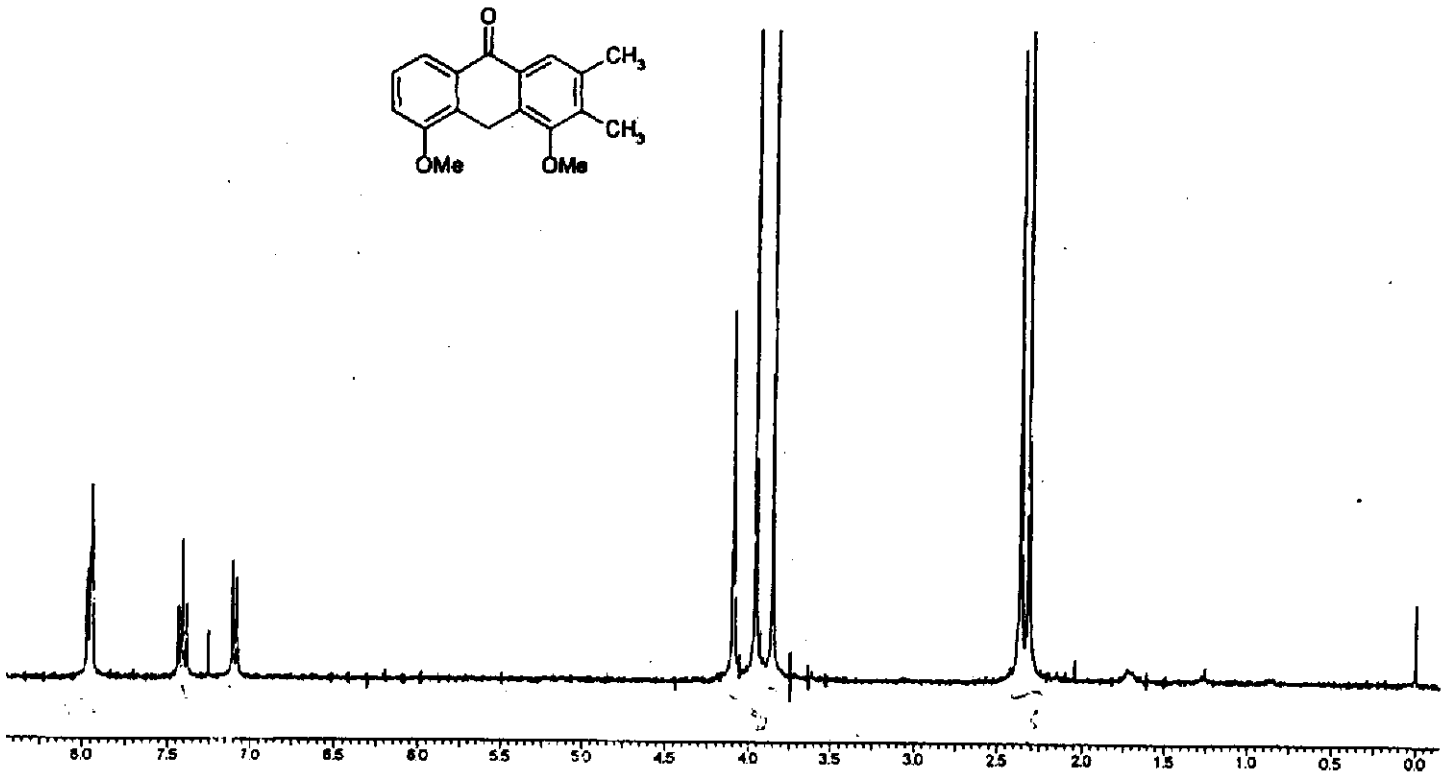

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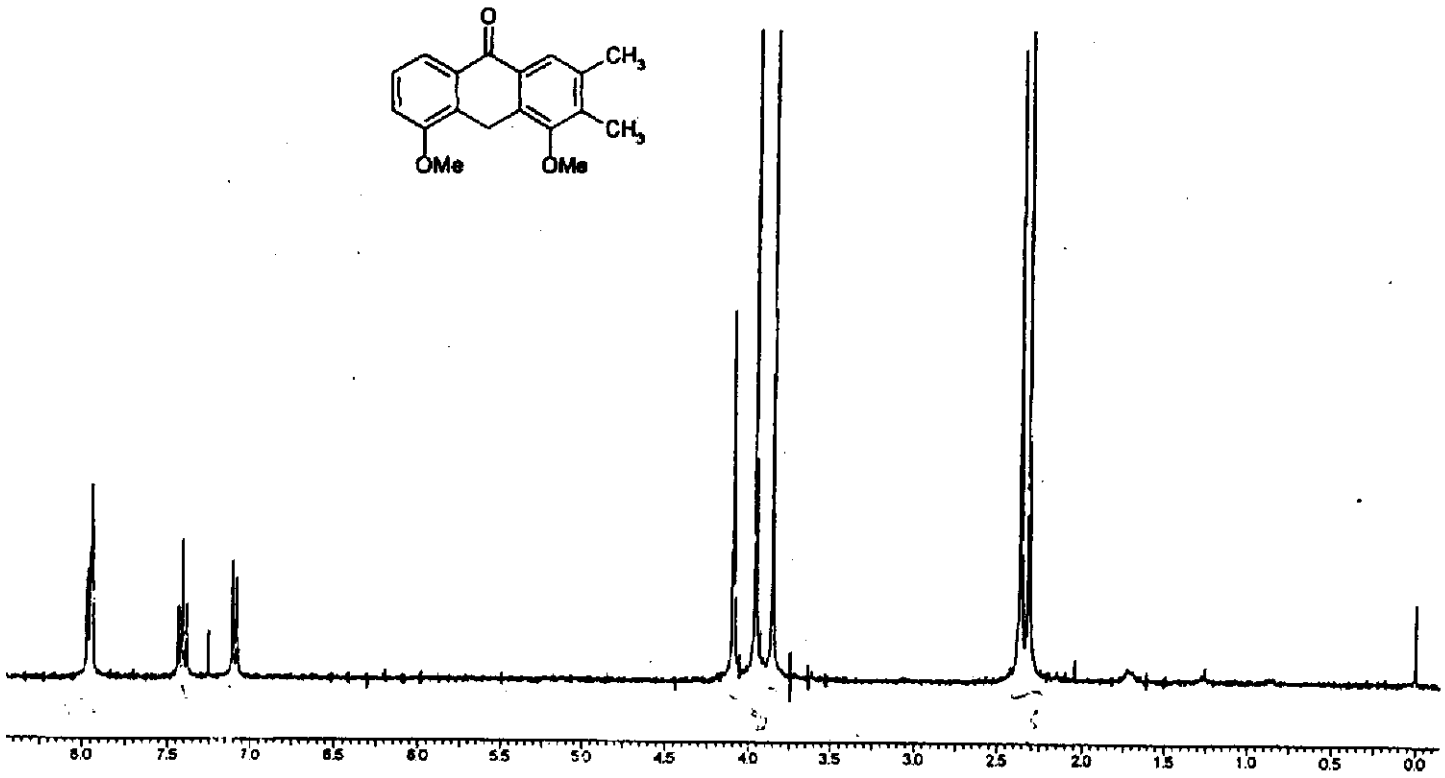
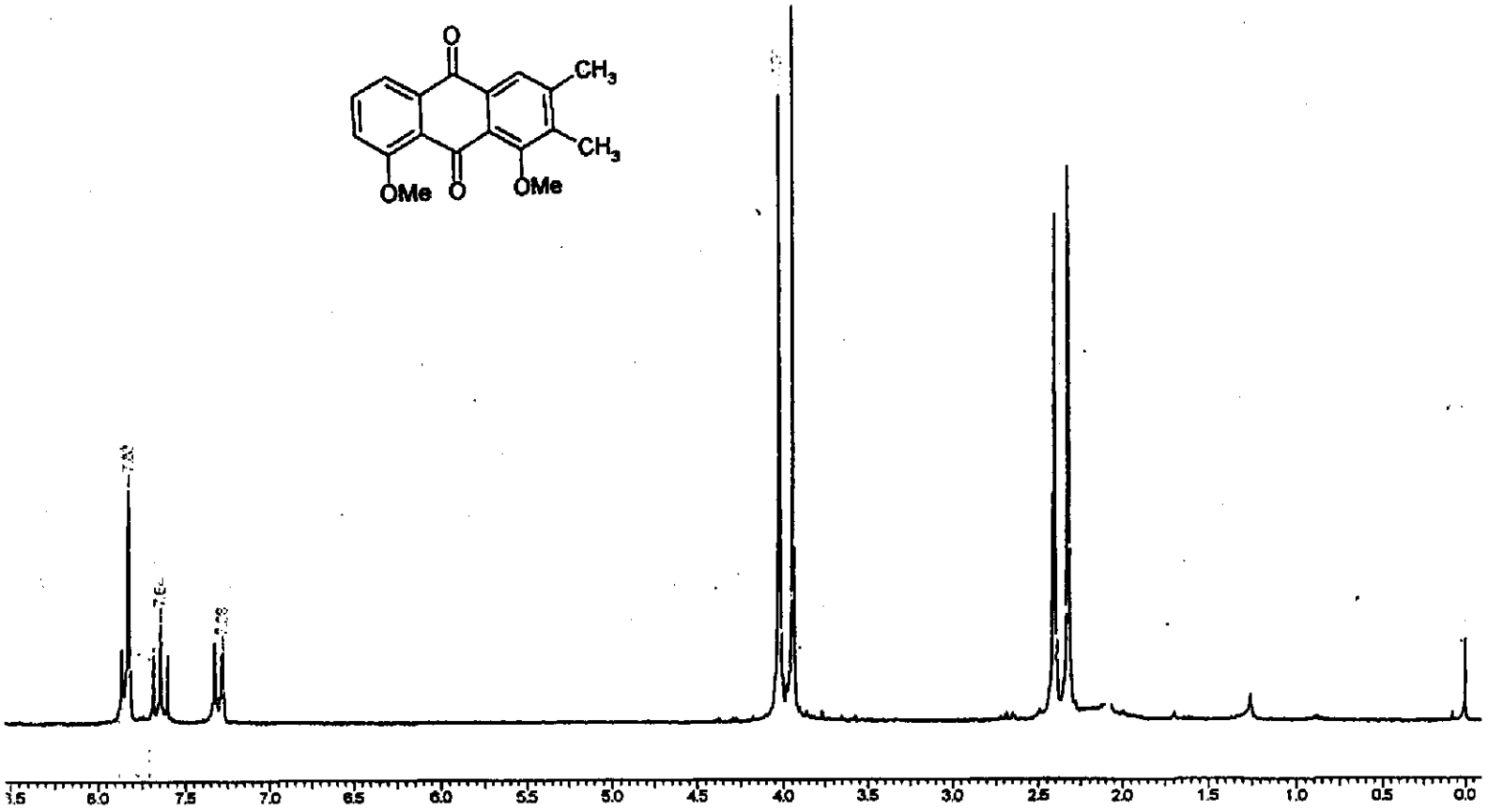
Sweep Width (Hz)	3602.31	Temperature (deg C)	24.000						

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1.3.3 REFERENCES

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CHAPTER-II

SYNTHETIC STUDIES TOWARDS BENZOPHENONE PRECURSOR FOR BALANOL

INTRODUCTION

The Role of Protein Kinase C in the Cell Surface Signal Transductions and Tumor Promotion:

Transduction of extracellular signals into intracellular events and cellular proliferation is a subject of great interest. When a ligand binds to. certain receptors on the cell surface inositolphospholipid hydrolyzes producing diacyl glycerol and inositolphosphates both thought to act as "secondary messengers". It is thought that primary effect of diacyl glycerol is to activate protein kinase C (PKC), first found in 1977 as a proteolytically activated protein kinase in many tissues, which in turn phosphorylates a range of cellular proteins.

Protein kinase C is a Ca^{2+}-activated, phospholipid-dependent enzyme that is activated by diacyl glycerol.[1,2] Diacyl glycerol is normally almost absent from membranes but is transiently produced from inositolphospholipid in response to extracellular signals. It was proved by kinetic analysis that a small amount of diacyl glycerol dramatically increases the affinity of protein kinase C for Ca^{2+}, fully activating the enzyme without any change in Ca^{2+} levels.[2' 3] 1fie active diacyl glycerol appears to contain at least one unsaturated fatty acid. Triacyl glycerol, monoacyl glycerol and free fatty acids are totally inactive.

The extracellular signals which activate cellular functions and proliferation by interaction with membrane receptors have repeatedly been shown to provoke the breakdown of inositolphospholipid in their target tissues. The products of inositolphospholipid breakdown are diacyl glycerol and inositolphasphates [4] This signal induced reaction is directly linked to the activation of protein kinase C which is confirmed by experiments with platelets. Diacyl glycerol is only transiently produced in membranes presumably due to both to its conversion back to inositolphospholipids and to its further degradation to arachidonic acid for thromboxane and prostaglandin synthesis.

On the basis of various experiments it is proved that the protein kinase C is indeed activated by extracellular signals in physiological processes and that diacyl glycerol, transiently produced from inositolphospholipids in response to the extracellular signals reaching their target cell membranes, serves as the direct activator of this protein kinase .

The primary effect of diacyl glycerol is to activate protein kinase C, which in turn phosphorylates a range of cellular proteins. Several phorbolesters such as 12-tetradecanoylphorbol-13-acetate (TPA) are well known as potent tumor promoters. Recent studies in this field provided evidences that PKC is a target for phorbolesters, as the tumor

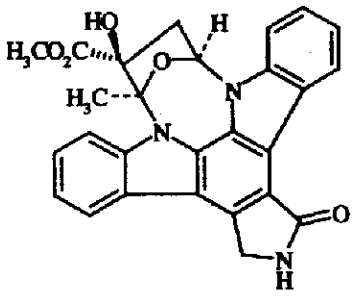
promoters directly activate this enzyme both in vitro and in vivo, and there is an approximate correlation between the ability of individual phorbolesters to promote tumors and activate the enzymes.[5,6] TPA is structurally similar to diacyl glycerol and it is able to substitute for diacyl glycerol at extremely low concentrations. Like diacyl glycerol, TPA dramatically increases the affinity of the enzyme for Ca^{2+} to the 10^{-7} M range resulting into the full activation of enzyme.

Protein kinase C also appears to be the receptor protein for tumor promoting phorbolesters. The evidence available to the date strongly suggests that some, if not all, of the pleiotropic actions of tumor promoters are mediated through this protein kinase. It is attractive to suggest that the uncontrollable production of an active protein kinase C, whether the product of a cellular or of a viral gene, may promote carcinogenesis, just like tumor promoting phorbolesters do. Protein kinase C may be located on the crossover point of various pathways in hormone action and cell proliferation, involving Ca^{2+}, inositolphospholipids, arachidonic acids, prostaglandins and cyclic nucleotides as well as tumor promoters.

The functional role of Ca^{2+} is well recognized as secondary messengers for control of a variety of cell functions such as secretion, contraction, phototransduction, cell division and differentiation and alteration of the transport ions.~ There appears to be two branches by which various extracellular informational signals flow from the cell surface to the cell interior.[8, 9] One is mediated by rise in the Ca^{2+} concentration in the cystol, leading to the modulation of the function of calmodulin-dependent reactions and other by a rise in the diacyl glycerol content of the plasma membrane, leading to the activation of protein kinase C. Both routes usually become available as the result of an interaction of a signal ligand and a receptor and act synergistically to evoke subsequent cellular responses.[8]

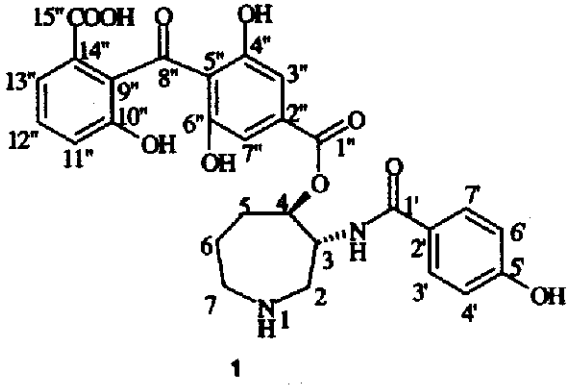
Protein proliferation mediated by PKC is known to lead range of cellular responses including gene expression and cell proliferation. Activated PKC has been implicated in conditions as diverse as cancer, cardiovascular disorders, asthma, inflammation, diabetes, CNS disorders, HIV infections etc. and effective inhibitors of PKC could prove useful in cancer chemotherapy.

Continuous efforts to develop agents to fight against various types of cancer have resulted into isolation of natural products which inhibit protein kinase C. K-252a[10] isolated from Nocardiopsis sp. K-252, inhibited protein kinase C and calmodulin.



K-252a

It was found that K-252a seriously affects the function of various cells and tissues such as platelets, mast cells and vascular smooth muscle. This newly developed compound may be useful for clarifying the in vitro and in vivo functions of protein kinase or calmodulin.



1

Balanol

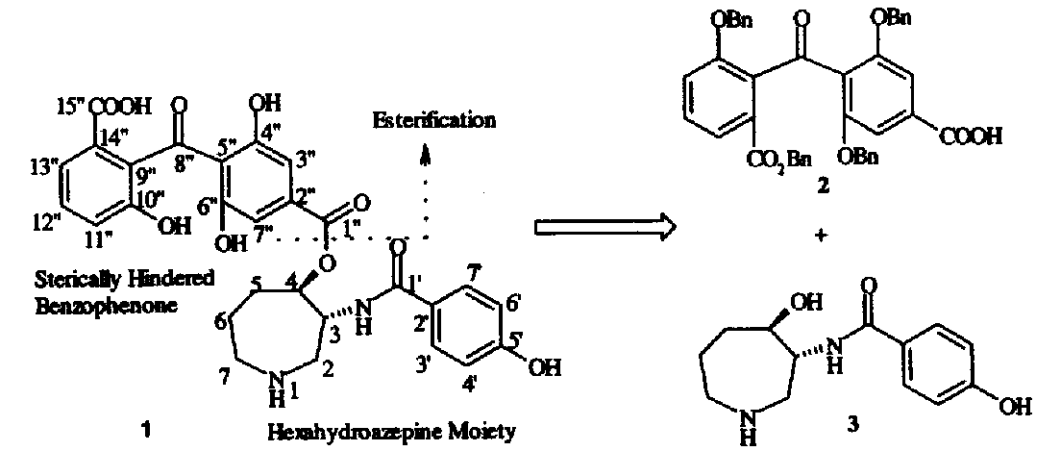
Balanol was isolated in 1993 by Kulanthaivel et al[ll] as an unusual metabolite produced by the fungus Verticillium balanoides. It represents a novel class of protein kinase C inhibitors. IC_{50} values of 4~9 nM were observed in assays against human PKC enzymes a, /3-I, B-II, y, 8, s and n with the exception of ~ (150 nM). Approximately 12 mg of balanol was obtained from 40 lit. culture.

The molecular formula of balanol was established as $C_{28}H_{26}N_2O_{10}$ by HR-FABMS {$(M+H)^+$, m/z 551.1685, ^ 2.7 mmu}. The IR spectrum revealed presence of hydroxyl, ester and amide functionalities. Detailed analysis of ^1H, ^{13}C and 2D NMR (COSY, NOESY, TOCSY, HMQC and HMBC) data suggested the exact structure for balanol. Absolute stereochemistry of balanol was assigned by X-ray diffraction and spectroscopic analysis. The relative stereochemistry at C- and C-4 was assigned as trans on the basis of the observed$^1H^1H$ coupling constant ($J_{3,4}$= 7.6 Hz) and NOE data. X-ray analysis showed the anti disposition of the substituents at C-3 and C-4 and the absolute configuration as 3R, 4R. The discovery of balanol

has provided a new structural motif to the PKC inhibitor area and the combined structural novelty and low availability from natural sources has stimulated a great interest in the development of synthetic approaches to the natural material and related compounds.

Retrosynthetic Analysis

Scheme-1



The synthetic approaches mainly began with obvious disconnection of balanol at its ester linkage to yield the hexahydroazepane and the benzophenone carboxylic acid. The retrosynthesis of balanol is as shown in scheme-1.

Total synthesis of balanol was achieved by coupling the protected benzophenone domain and hexahydroazepine moiety by esterification using modified Mukaiyama procedure.

SECTION-A

A REVIEW ON SYNTHESIS OF BALANOL AND ITS INTERMEDIATES

Part I

Syntheses of Benzophenone Domain of Balanol

2.1.0 INTRODUCTION

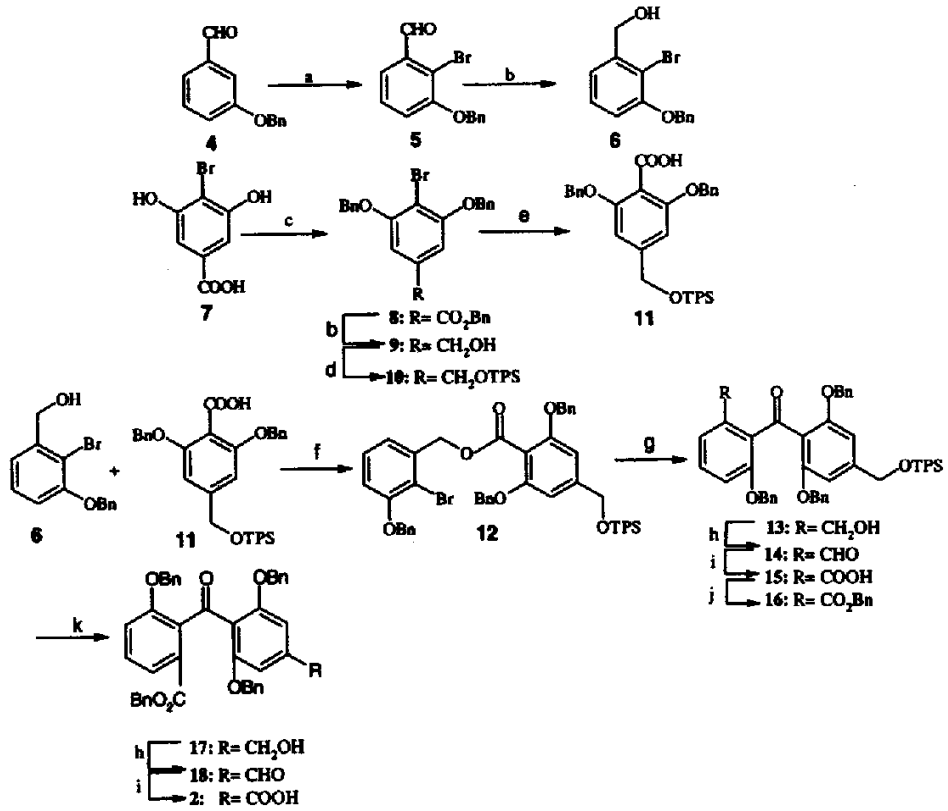
Benzophenone 2, is an important portion of highly potent molecule balanol (**1**). SAR studies proved the critical importance of benzophenone portion for the efficacy of balanol. In the literature, attempts have been made to synthesize this benzophenone portion using various approaches which are summarized below.

2.1.1 Nicolaou's Approach

Nicolaou et a1.[15] reported total synthesis of balanol (**1**), describing the synthesis of benzophenone domain **2** by making use of homo-Fries rearrangement.

Scheme-2

Nicolaou's approach (*Chem. Eur. J.* 1995, *1*, 454):



ReagentS and COItdztioriS: a. n-BuLi, $MeNHCH_2CH_2Nme_2$, 0-25°C, 4, 0-25°C, 0.5 h, PhLi 0-25°C, 1,2dibromotetrafluoroethane, THF, -78-25°C. b. DIBALH, CHzCIz, -78-0°C. c. BnBr, K_2CO_3, DMF, 25°C. d. TPSCI, imidazole, DMF, 25°C. e. n-BuLi, THF, -98-78°C, excess CO_2, -78-25°C, aq. $KHSO_4$.. f. DEAD, Ph_3P, THF, 025°C. g. n-BuLi, THF, -98-78°C. h. NMO, TPAP, CH_3CN, 25°C. i. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, t-BuOH, H_20, 25°C. j. BnBr, K_2CO_3, DMF, 25°C. k. TBAF, THF, 25°C.

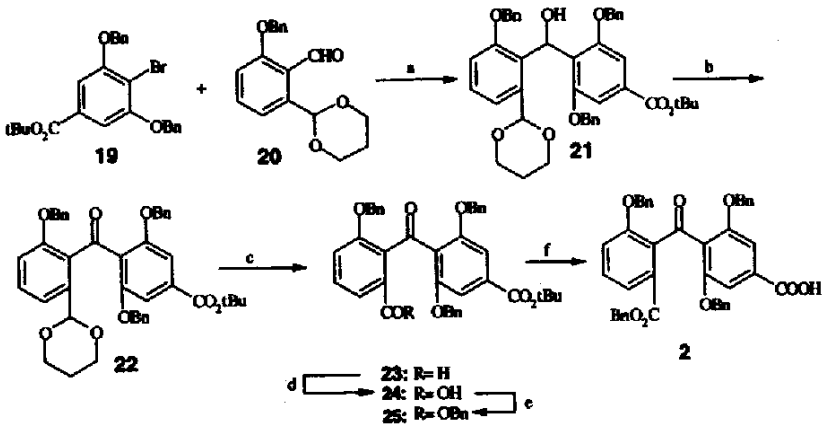
This approach involved intramolecular attack of aryl lithium species at ester moiety **12** prepared by coupling of **6** and **11** resulting into generation of the desired ketone linkage between the two aromatic components as shown in scheme-2. Benzophenone **13** was then converted into the desired benzophenone **2** via a series of reactions.

2.1.2 Hollinshead's Approach

Hollinshead et a1.[16] reported two efficient syntheses of benzophenone portion of balanol.

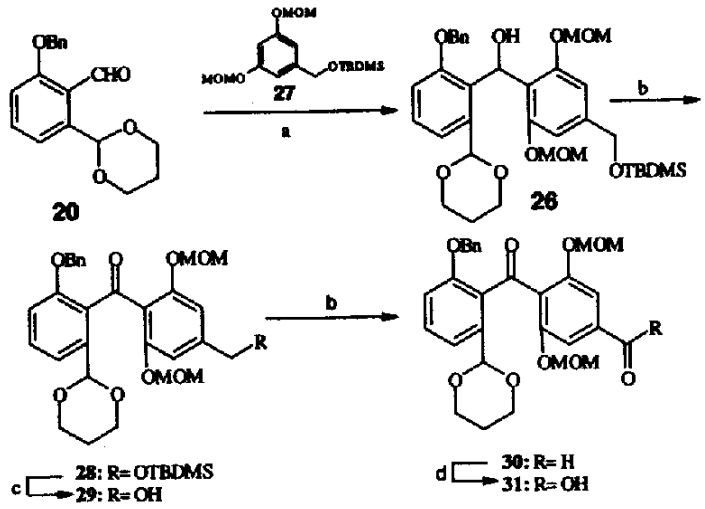
Scheme-3

Hollinshead's approach (*J. Org. Chem.* 1994, *59*, 6703-6709):



Reagents and conditions:
a. n-BuLi, THF, -78°C, 61% b. MnO_2, CH_2Cl_2, 96 % c. p-TSA, acetone, H_2O, reflux, 95%
d. $NaClO_2$, H_2NSO_3H, MeCN, H_2O e. BnBr, K_2CO_3, DMF, 97% f. Quinoline, 205°C, 68%

Scheme-4



Reagents and conditions:
a. n-BuLi, THF, 0°C, 73% b. MnO_2, CH_2Cl_2, 93% c. TBAF, THF, 88%
d. $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN-H_2O, 98%

The key step of this synthesis was the utilization of ortho lithiation reactions for the generation of carbinol **21** by coupling of aryl bromide **19** with aldehyde **20**, which was then converted to benzophenone **22** by oxidation using manganese dioxide. The resulting benzophenone **22** was then subjected to a series of reactions to afford benzophenone **2** as shown in scheme-3.

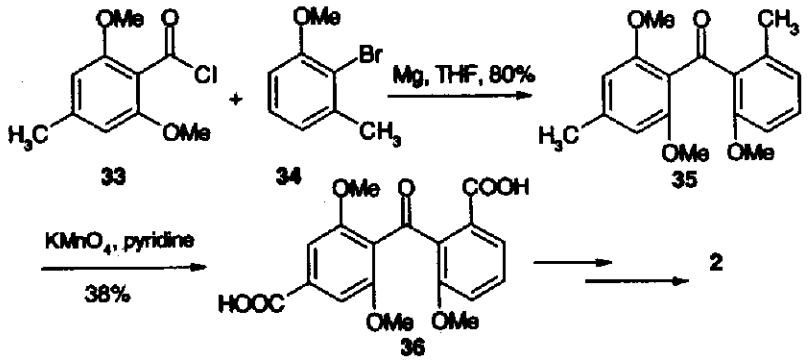
As an alternative approach Hollinshead reported another method for the synthesis of this benzophenone portion (scheme-4).

2.1.3 Vicker's Approach

Vicker et al.[17] reported the total synthesis of balanol involving the synthesis of benzophenone portion starting from 2,6-dimethoxy-4-methylbenzoyl chloride (**33**) and 2-bromo-3-methoxytoluene (**34**) as shown in Scheme-5. Formation of the Grignard reagent of 2-bromo-3-methoxytoluene (**34**) and its reaction with 2,6-dimethoxy-4-methylbenzoyl chloride (**33**) afforded the hindered benzophenone **35**. Potassium permanganate oxidation of this benzophenone yielded diacid **36** in 38 % yield. Further protection-deprotection of this diacid and finally selective hydrolysis resulted into the desired benzophenone domain for balanol.

Scheme-5

Vicker's approach (*J. Chem. Soc. Perkin Trans 1*, **1995**, 2355):

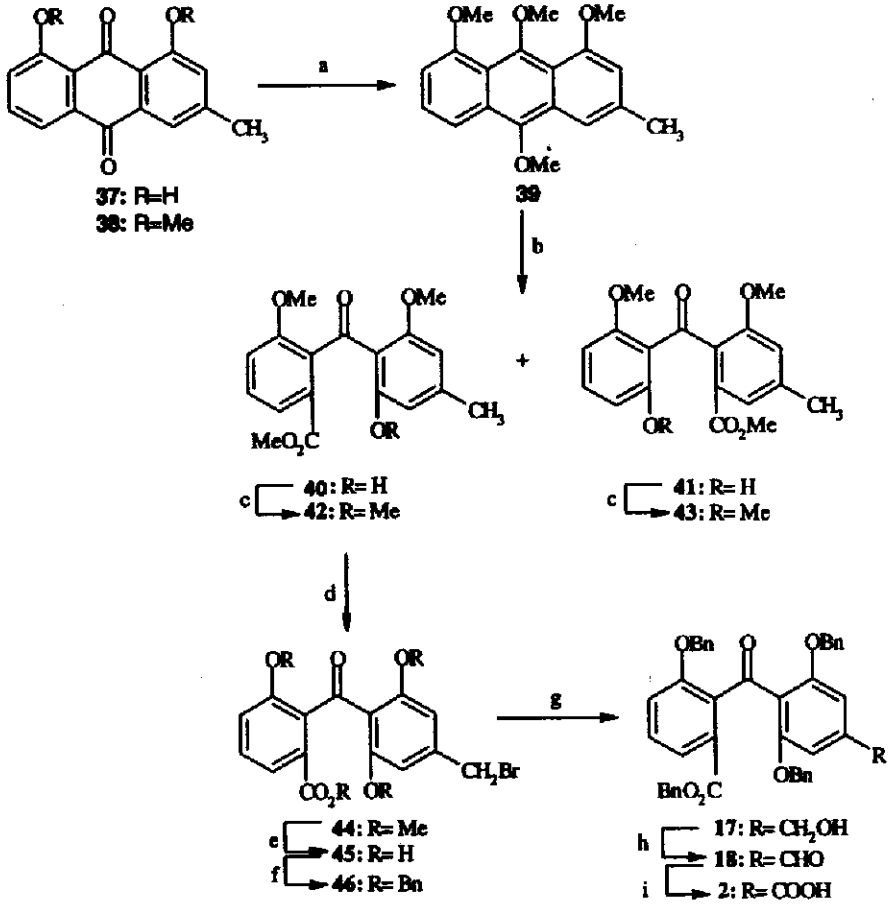


2.1.4 Naito's Approach

The total synthesis of (-)-balanol was described by Naito er al.[18] involving biomimetic route for the benzophenone fragment (Scheme-6). Irradiation of an ethereal solution of the anthracene **39**, which also serves as sensitizer, with halogen lamp under bubbling oxygen followed by treatment of the resulting oxygen adduct with a catalytic amount of sulphuric acid in acetone gave an inseparable mixture of two regioisomeric benzophenones **40** and **41**.

Scheme-6

Naito's approach (*Synlett* 1997, 580):



Reagents and conditions:

a. $Na_2S_2O_8$, $Bu_4N^+Br^-$, THF, H_2O, rt, 15 min; 6N KOH, rt, 5 min; Me_2SO_4, rt, 12 h, 85%

b. $O_2/h\nu$, Et_2O, 30°C, 7 h; cat H_2SO_4, acetone, rt, 10 h, 57% (40+41) + 30% 38

c. NaH, MeI, DMF, rt, 30 min, 39% 42 + 41% 43 d. NBS, cat. AIBN, CCl_4, reflux, 30 min, 57%

e. BBr_3, CH_2Cl_2, rt, 5 days f. BnBr, K_2CO_3, DMF, rt, 5 h g. $CaCO_3$, H_2O, dioxane, reflux, 10 h, 79% h. Pr_4NRuO_4, 4-methylmorpholine N-oxide, MeCN, rt, 30 min, 61%

i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF, t-BuOH, H_2O, rt, 1 h, 84%

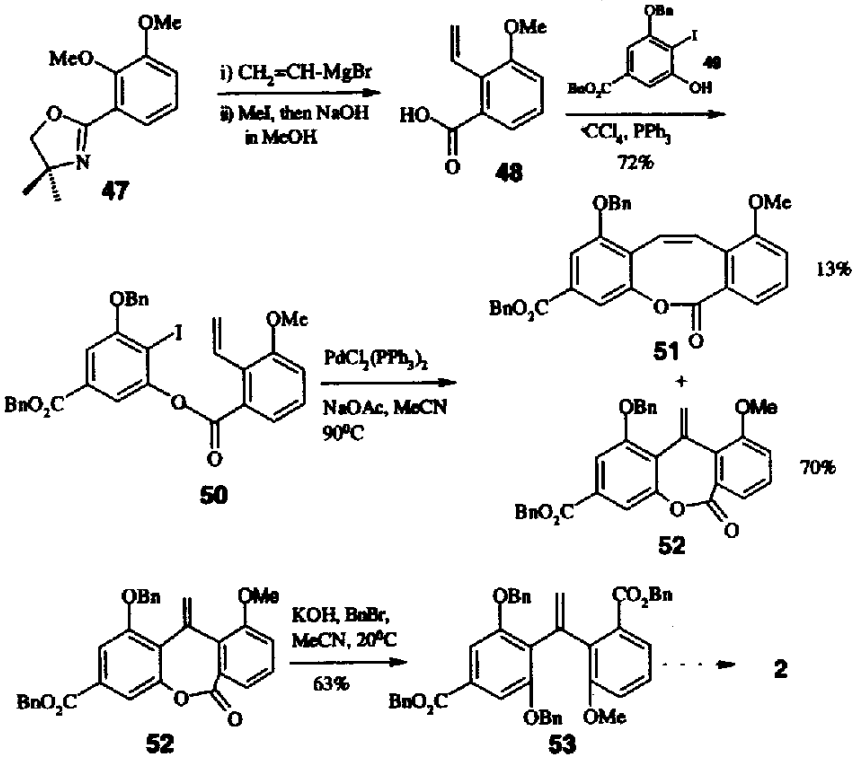
The separable benzophenones **40** and **41** were characterized as the corresponding methyl ethers **42** and **43**. The benzophenone 42 was then converted into the known intermediate **2** by a series of reactions.

2.1.5 Intramolecular Heck Reaction Approach

Skrydstrupl9 used intramolecular Heck reaction approach for the construction of benzophenone core of balanol as shown in scheme-7.

Scheme-7

Skrydstrup approach (*Tetrahedron Letters* **1999**, *40*, 4901-4904):



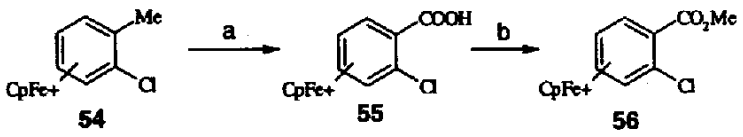
Ester **50** obtained by esterification of acid **48** with phenol **49**, on intramolecular Heck reaction afforded lactone **52** which on opening under basic condition yielded compound **53** representing the methylene analog of balanol benzophenone fragment. A three step procedure involving epoxidation, hydrolysis and periodate oxidation led to the desired benzophenone **2**.

2.1.6 Andersson's Approach

Andersson et a1.[20] used an organoiron approach for the synthesis of this highly substituted benzophenone core (schemes 8 and 9).

Scheme-8

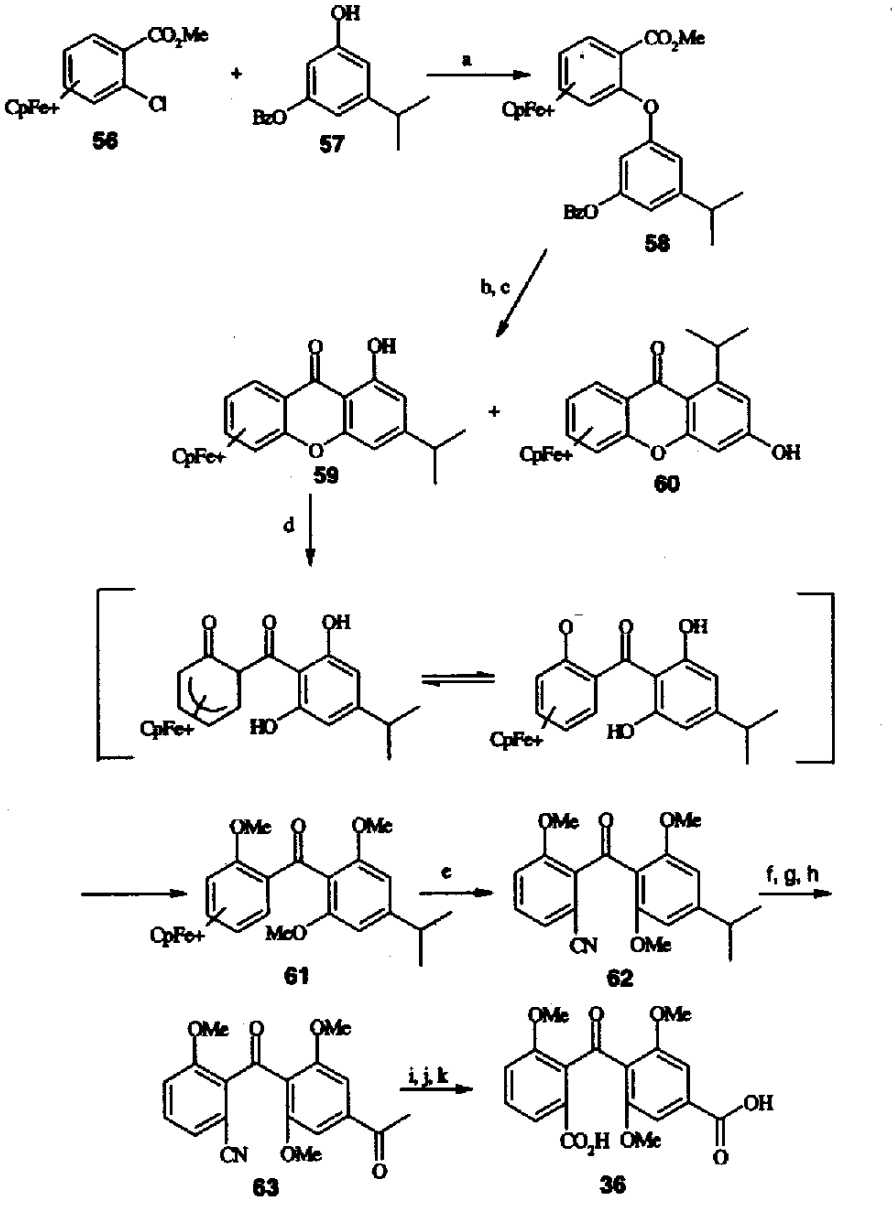
Andersson's approach: (*Organic Letters* **1999**, *1*, 1451-1453)



Reagents and conditions:
a. i) $KMnO_4$, $MgSO_4$, H_2O, reflux ii) HPF_6 (60% in water), 83%
b. i) $SOCl_2$, reflux ii) MeOH, rt, 91% over two steps.

Thus η6-o-chlorotoluene- η5-cyclopentadienyliron hexafluorophosphate (**54**) was oxidized using aqueous potassium permanganate and converted into methyl ester **56** as shown in scheme-8

Scheme-9



Reagents and conditions: a) K_2CO_3, DMF, rt, 79% b) LiOH, MeOH/H_2O, rt, 95% c) $MeSO_3H$, rt, 72% d) KOH, MeI, DMSO e) n-$Bu_4N^+CN^-$, DDQ, CH_2Cl_2, rt, 72% f) NBS, AIBN, reflux g) NaOAc, DMF, 60°C, h) OsO_4, $NaIO_4$, THF, rt, 70% i) NaOH, Br_2, H_2O, dioxane, 5-10°C, 56% j) Conc. HCl, MeOH k) LiOH, MeOH/H_2O, 50% over two steps.

The xanthone complex **59** obtained by hydrolysis and intramolecular Friedel-Crafts reaction of **58** was subjected to a series of reactions to obtain the substituted benzophenone intermediate for balanol as shown in scheme-9, involving opening of xanthone complex **59** and addition of cyanide ion as the important reactions.

Part II

Syntheses methods for hexahydroazepine portion of Balanol

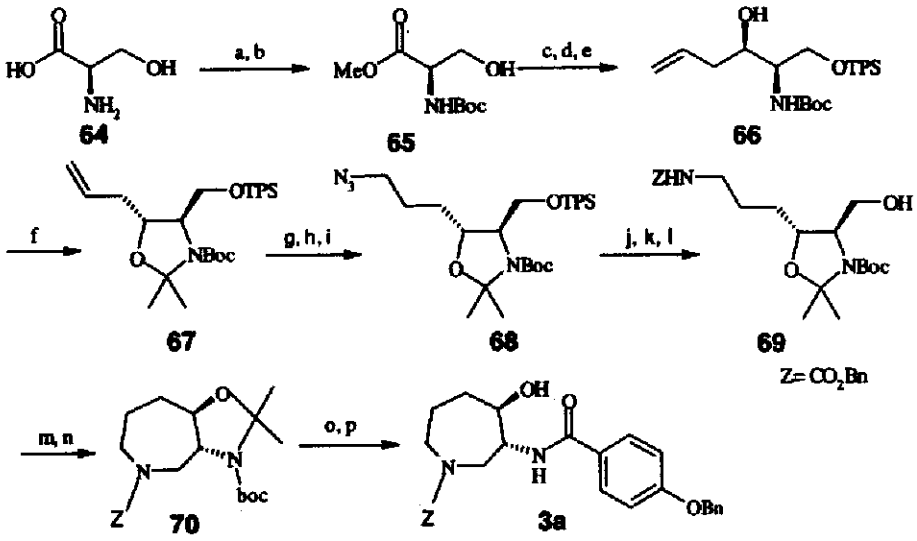
Hexahydroazepine moiety (3) is the another important part of balanol, a novel protein kinase C inhibitor. Various synthetic routes have been reported in the literature for the synthesis of this seven membered heterocyclic ring.

2.1.7 Nicolaou's Approach

Nicolaou et a1.[15] synthesized this hexahydroazepine portion starting from readily available amino acid D-serine.

Scheme-8

Nicolaou's approach: (*Chem. Eur. J.* **1995**, *1*, 454)



Reagents and conditions:
a. $(Boc)_2O$, NaOH, 1,4-dioxane, H_2O, 0-25°C, 2 h, 100% b. K_2CO_3, MeI, DMF, 0-25°C, 2 h, 100%
c. TPSCl, imidazole, DMF, 25°C, 14 h, 100% d. DIBAL-H, toluene, -78°C, 1.5 h e. Allyl-B(^{i} Ipc)$_2$, Et_2O, -78°C, 3.5 h, ethanolamine f. 2,2-Dimethoxypropane, CSA, CH_2Cl_2, 25°C, 3 h, 68% over three steps .g. 9-BBN, THF, 0-25°C, 20 h, NaOH, H_2O_2, 0-25°C, 5 h, 97% h. MsCl, Et_3N, CH_2Cl_2, 0°C, 10 min i. NaN_3, DMF, 25°C, 24 h, 98% j. H_2, Pd/C, THF, 19 h k. Benzyl chlorocarbonate, NaOH, 1,4 -dioxane, H_2O, 0°C, 15 min, 100% l. TBAF, THF, 25°C, 16 h, 96% m. MsCl, Et_3N, CH_2Cl_2, 0°C, 20 min n. KOtBu added over 1 h at 0.02M, THF, 25°C, 80% o. Excess TFA, CH_2Cl_2, 25°C, 1 h p. p-(Benzyloxy)benzoyl chloride, Et_3N, CH_2Cl_2, 0-25°C, 1.5 h, 73%

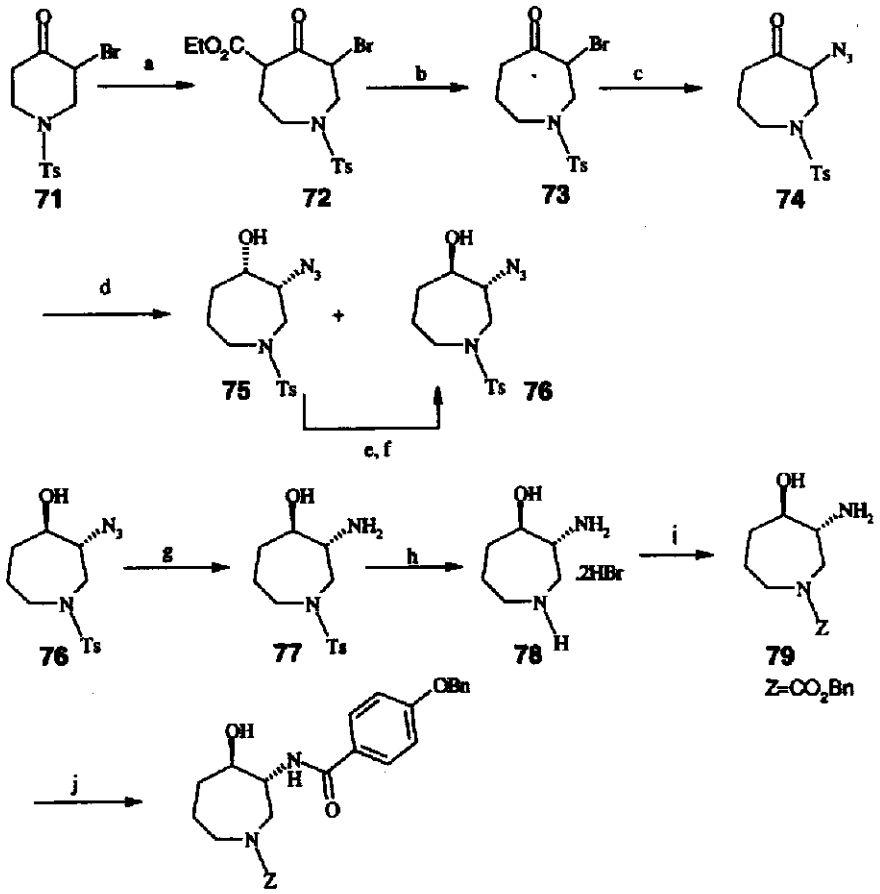
The main strategy utilized by Nicolaou et al. was the base induced 7-exo-tet ring closure of compound **69**, which was prepared from D-serine in 12 steps including the diastereoselective allylboration of a derived amino aldehyde as shown in scheme-8.

2.1.8 Vicker's Approach

Vicker et al.[17] used regiospecific ring expansion method for the synthesis of azepine portion of balanol as shown in scheme-9.

Scheme-9

Vicker's approach: (*J. Chem. Soc. Perkin Trans I* **1995**, 2355)



Reagents and conditions:
a. N_2CHCO_2Et, $BF_3.Et_2O$ CH_2Cl_2, 71% b. HCl (aq), dioxane, 90% c. NaN_3, AcOH, DMF, 73%
d. $NaBH_4$, EtOH, 88% e. PPh_3, DIAD, THF, p-nitrobenzoic acid, 84% f. NaOH, MeOH, dioxane, 99%
g. $LiAlH_4$, THF, 85% h. HBr (aq), 68% i. Et_3N, CH_2Cl_2, 18-crown-6, benzyl chloroformate, 88%
j. 4-(Benzyloxy)benzoyl chloride, Et_3N, CH_2Cl_2, 65%

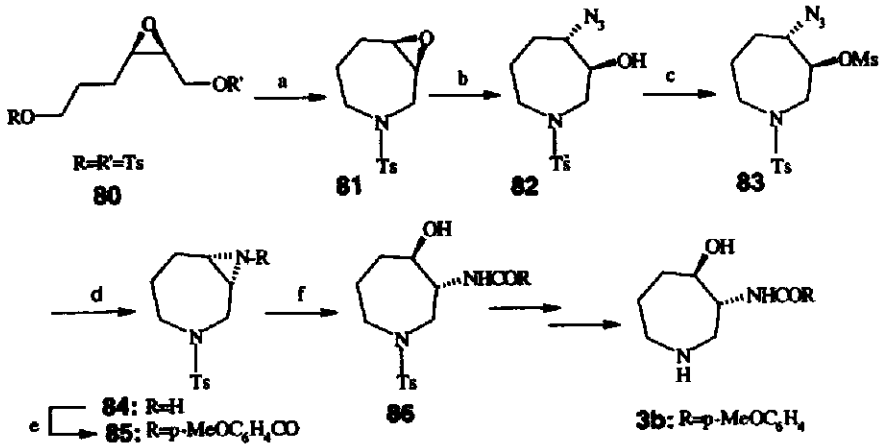
Thus conversion of **71** to the azepine portion was carned out in 10 steps involving regiospecific homologation of unhindered a-bromoketone, nucleophilic displacement of bromine to azide, inversion of cis isomer **75** to trans isomer **76** using Mitsunobu inversion and reduction of azide with lithium aluminum hydride as main reactions.

2.1.9 Tanner's Approach

Tanner et a1.[21] synthesized hexahydroazepine unit by using acid catalyzed ring opening of bicyclic aziridine as shown in scheme-10.

Scheme-10

Tanner's approach: (*Tetrahedron* 1995, *51*, 6061)

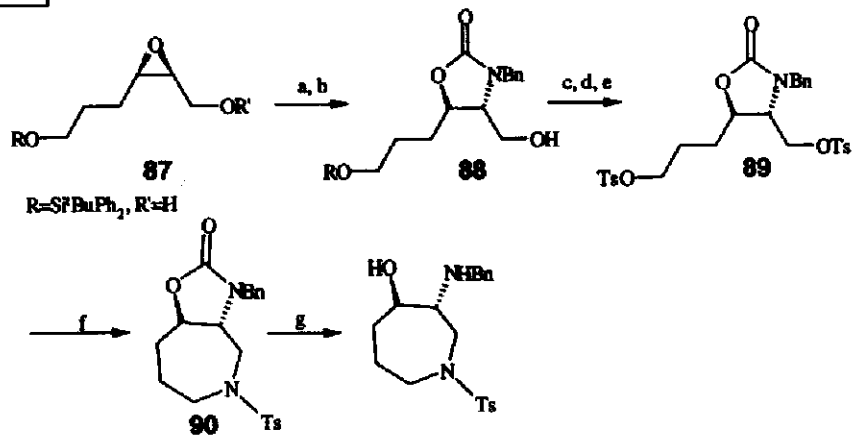


Reagents and conditions:
a. p-TolSO$_2$NH$_2$, Cs$_2$CO$_3$, DMF, rt, 88% b. LiN$_3$, DMF, 90°C, 87% c. MsCl, Et$_3$N, CH$_2$Cl$_2$, 96%
d. LiAlH$_4$, THF, 50°C e. p-MeOC$_6$H$_4$COCl, Et$_3$N, CH$_2$Cl$_2$, 86% f. pTsOH, H$_2$O, THF, rt, 71%

The regiochemistry required for desired hexahydroazepine was achieved by converting the alcohol **82** to the aziridine **84**. Ring opening exclusively at C-4 yielded the desired azepine **86**, which was then converted into hexahydroazepine portion of balanol in two steps.

In another approach the compound **87** was converted into **88** in two steps. Conversion of the compound **88** into enantiomerically pure hexahydroazepine has been carned out in five steps as shown in scheme-11.

Scheme-11



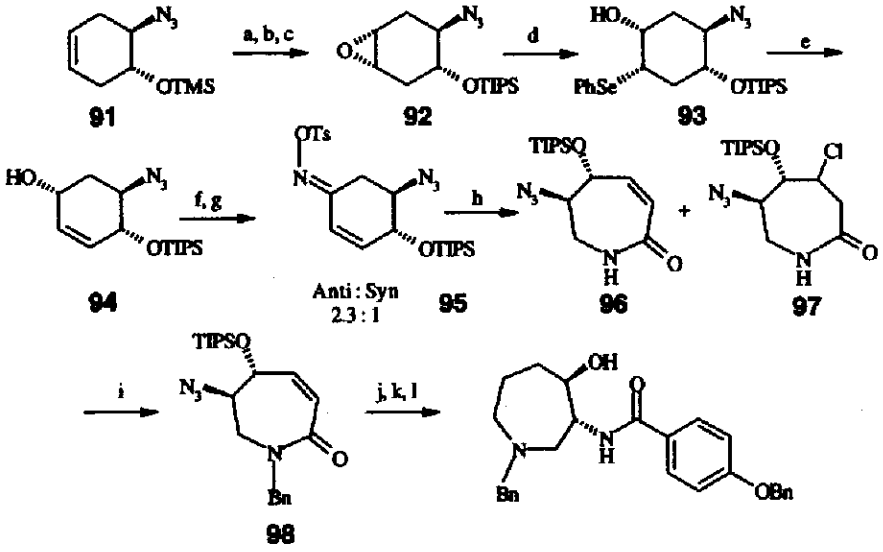
Reagents and conditions:
a. BnN=C=O, Et$_3$N, 90% b. NaH, THF, rt, 90% c. p-TsCl, Et$_3$N, CH$_2$Cl$_2$, 97% d. Bu$_4$N$^+$F$^-$, HF, 0°C, 90%
e. p-TsCl, Et$_3$N, DMAP, 88% f. p-TolSO$_2$NH$_2$, DMF, rt, 55% g. LiOH, THF, H$_2$O, Reflux, 98%

2.1.10 Jacobsen's Approach

Jacobsen et a1.[22] described an efficient synthesis of azepine portion in thirteen steps via asymmetric epoxide ring opening. Compound **91** was converted into epoxide **92** in three steps. Epoxide opening followed by oxidation and elimination sequences led to allylic alcohol **94**. Further Beckmann rearrangement of **95** afforded amide **96** and saturated amide **97**. This mixture was converted into N-benzyl derivative **98**, which on reduction and hydrogenolysis of the amide followed by acylation of amine afforded the desired hexahydroazepine moiety of balanol as shown in scheme-12.

Scheme-12

Jacobsen's approach (*Tetrahedron Letters* 1997, *38*, 1693)



Reagents and conditions:
a. Cat. TFA, MeOH, rt b. $Mo(CO)_6$, TBHP, PhH, reflux c. TIPSCl, KH, THF, 0°C
d. PhSeSePh, $NaBH_4$, EtOH e. H_2O_2, $NaHCO_3$, THF, then i.Pr_2NH, PhH, reflux
f. TEMPO, NaOCl, CH_2Cl_2 g. $H_2NOH.HCl$, Py, CH_2Cl_2 then TsCl, Et_3N, CH_2Cl_2
h. $TiCl_3$(Oi-pr), CH_2Cl_2, rt i. KH, BnBr, THF j. AlH_3, THF, 0°C k. H_2, PtO_2, EtOAc then ArCOCl, Et_3N, CH_2Cl_2, 0°C to rt l. TBAF, THF, rt

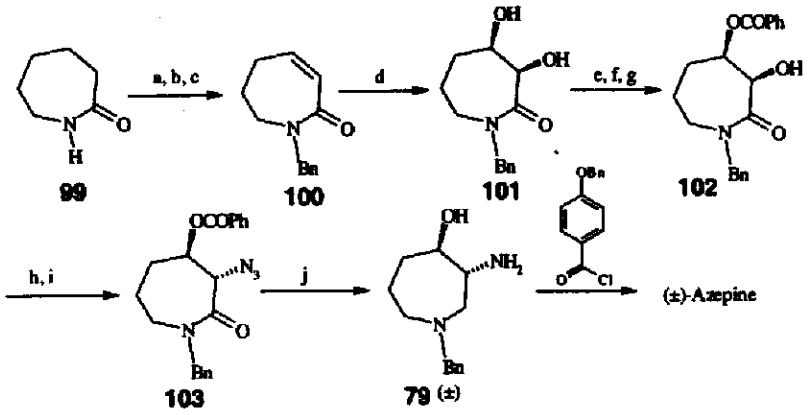
2.1.11 Lampe's Approach

Total synthesis of (-) and (+)-balanol was described by Lampe et a1. [23] The synthesis of benzophenone portion was similar to that reported by Nicolaou et a1.[15] involving homo-Fries rearrangement.

Synthesis of azepine portion was achieved starting from caprolactam **99** in 11 steps involving dihydroxylation of caprolactam, insertion of nitrogen at a-position using sodium azide and reduction of azide as key reactions as shown in scheme-13.

Scheme-13

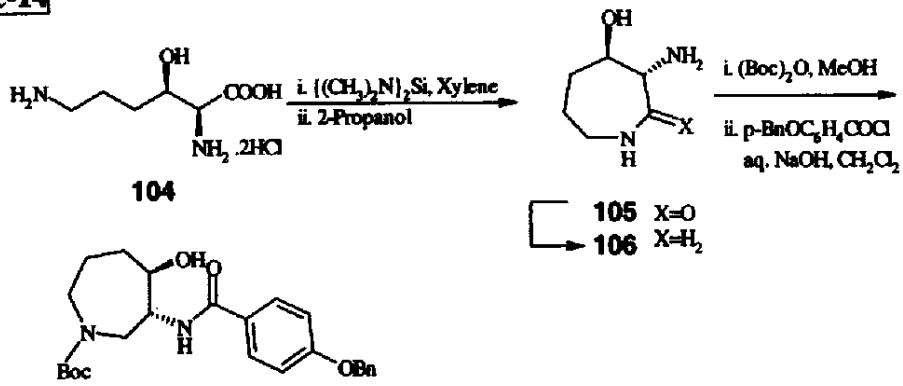
Lampe's approach: (*J. Org. Chem.* **1996**, *61*, 4575)



Reagents and conditions:
a. NaH, BnBr b. LiHMDS, PhSeCl c. $NaIO_4$ or H_2O_2 d. OsO_4, NMO e. $PhCH(OCH_3)_2$, $BF_3.OEt_2$
f. H_2O g. DBU h. Tf_2O, 2,6 lutidine i. NaN_3 j. $LiAlH_4$

After the synthesis of racemic balanol enantioselective synthesis of azepane was completed starting from the hydroxysilane.

Scheme-14



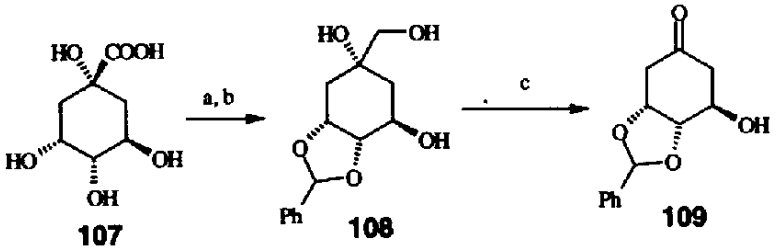
Thus caprolactam **105** was obtained from **104** by slow addition to the hexamethyldisilazene followed by slow addition of 2-propanol. Finally boron reduction of the caprolactam **105**, protection of azepane and acylation with 4-(benzyloxy)benzoyl chloride resulted into desired azepine portion of balanol (scheme-14).

2.1.12 From D-(-)-Quinic Acid

Pollini et a1.[24] used D-(-)-quinic acid (**107**) for the synthesis of epoxide **84a**, an important precursor for azepine moiety of balanol. Acid catalyzed acetalization of **107** with benzaldehyde, further reduction followed by oxidative cleavage of vicinal diol afforded cyclohexanone 109 as shown in scheme-15.

Scheme-15

Pollini's approach: (*Synlett* **1996**, 29-30)



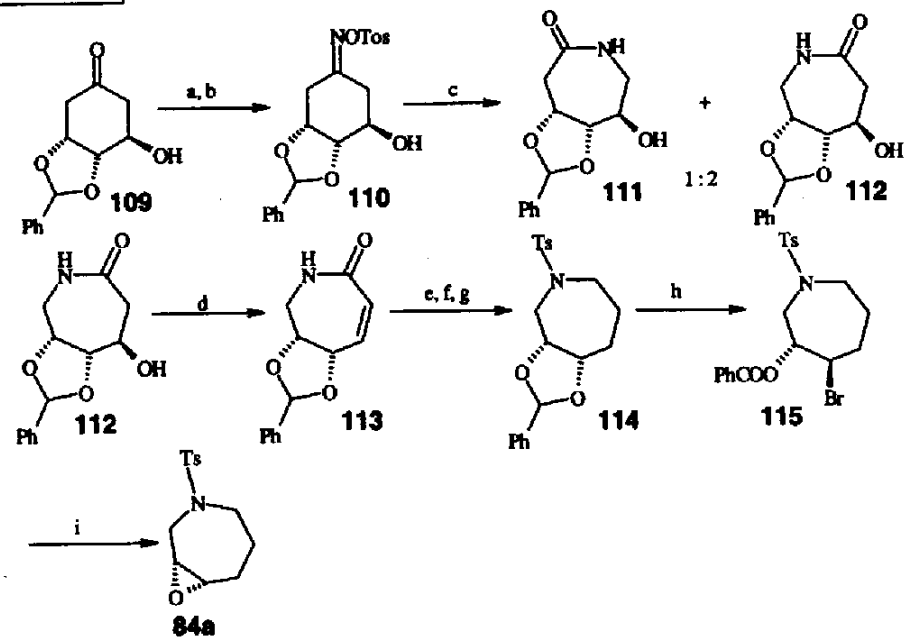
107 **108** **109**

Reagents and conditions:
a. PhCHO, pTsOH, C_6H_6, reflux b. $LiAlH_4$, THF, 25°C c. $NaIO_4$, 25°C

Basic alumina promoted Beckmann rearrangement of the oxime tosylate of the cyclohexanone **109**, dehydration of **112** to a, B unsaturated lactam followed by two reductive steps and a series of reactions afforded epoxide **84a** (scheme-16).

Transformation of the epoxide moiety **84a** into the corresponding aziridine **84** in order to obtain the desired azepine portion of balanol has been already described by Tanner et al.[21] (See scheme-10).

Scheme-16



109 **110** **111** **112** **112** **113** **114** **115** **84a**

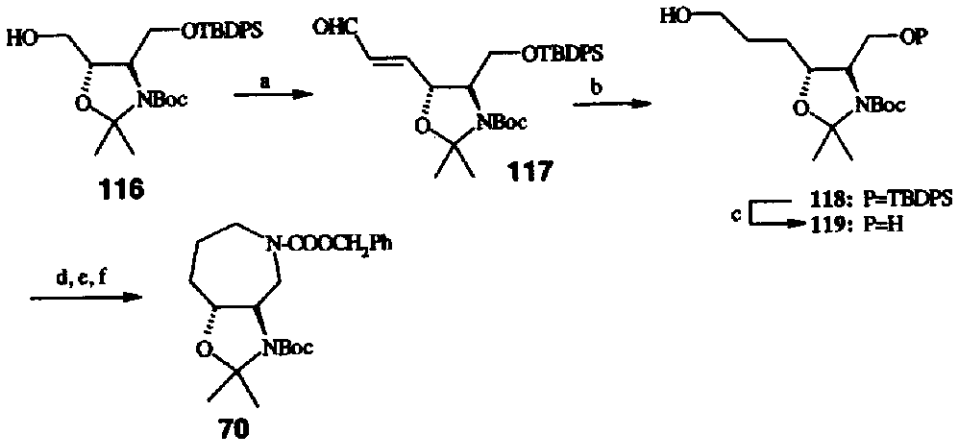
Reagents and conditions:
a. $NH_2OH.HCl$, AcONa, MeOH b. p-TsCl, pyridine c. Basic Al_2O_3, MeOH
d. $MeSO_2Cl$, Et_3N, DBU, CH_2Cl_2, rt e. H_2, 50 psi, $Pd(OH)_2$, 12h f. $LiAlH_4$ THF g. p-TsCl, pyridine, 0°C h. NBS, CCl_4, reflux i. MeONa, MeOH, rt

2.1.13 Merrer's Approach

Merrer et a1.[25] described a four step synthesis of an important precursor for balanol core as shown in scheme-17. Swern oxidation of the free primary alcohol **116** into an aldehyde followed by in situ formation of the a,B- ethylenic aldehyde provided the intermediate **117** which was then converted into the intermediate **119** in two steps . It was then converted into the known intermediate **70** reported by Nicolaou et al.[15] (See scheme-8).

Scheme-17

Merrer's approach: (*Tetrahedron Asymmetry* **1996,** *7,* 2901)



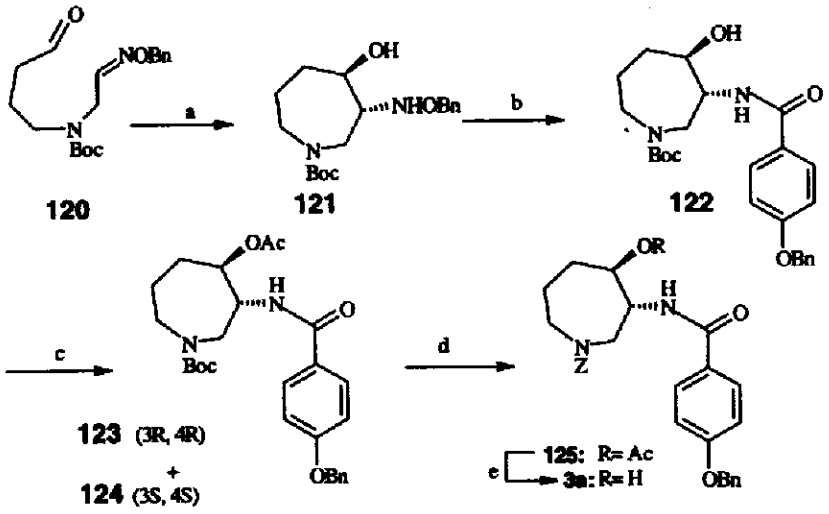
Reagents and conditions:
a. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 1 h then $Ph_3P{=}CHCHO$, 24 h b. H_2, Ni, EtOH
c. $nBu_4N^+F^-$, THF, 20 h, 20°C d. $(CF_3SO_3)_2O$, CH_2Cl_2, 2,6-lutidine then $PhCH_2NH_2$,
20°C, 20 h e. H_2, Pd/C 10%, EtOH, 24h f. $PhCH_2OCOCl$, CH_2Cl_2, Et_3N, 0°C

2.1.14 Naito's Approach

Naito et al.[18] used free radical mediated cyclization approach for the synthesis of azepine portion of balanol as shown in scheme-18. Cyclization of aldehyde **120** with SmI_2 yielded the trans cyclized product **121**. Hydrogenolysis of the benzyloxyamino group in the trans product **121** followed by N-acylation with p-(benzyloxy)benzoyl chloride afforded the racemic azepine **122**. The lipase catalyzed optical resolution by enzymatic esterification of the racemic **122** afforded the acetate **123**. Further deprotection, protection and hydrolysis yielded desired azepine moiety of balanol.

Scheme-18

Naito's approach: (*Synlett* 1997, 580)



Reagents and conditions:
a. SmI_2, HMPA, t-BuOH, -78°C, rt, 5 h, 46% b. H_2, PtO_2, MeOH, rt, 5 h and then p-(benzyloxy)benzoyl chloride, $NaHCO_3$, H_2O, CH_2Cl_2, rt, 2 h, 58%
c. Immobilized lipase, vinyl acetate, t-BuOMe, 20-45°C, 20 h, 42% ((3R, 4R) 96% ee + (3S, 4S) 82% ee] d. TFA, CH_2Cl_2, rt, 2 h, and then benzyloxycarbonyl chloride, Na_2CO_3, H_2O, Me_2CO, rt, 14 h, 87% e. KOH, MeOH, rt, 5 min

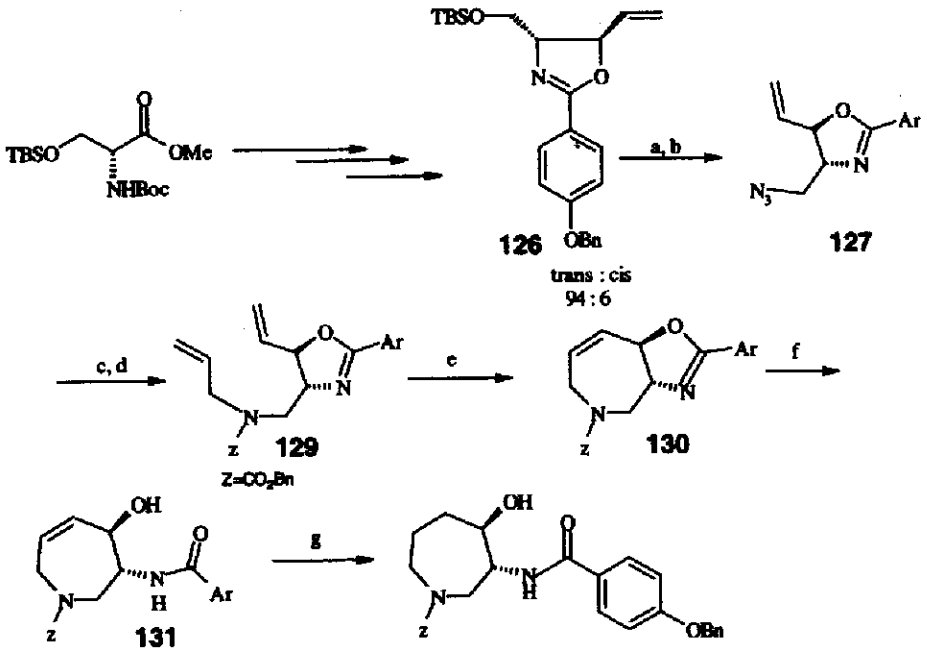
2.1.15 Cook's Approach

Cook et a1.[26] achieved the synthesis of hexahydroazepine portion of balanol starting from D-serine utilizing a palladium catalyzed epimerization and oleim metathesis (Scheme19).

Thus compound **126** was prepared from the ester of D-serine in five steps involving addition of vinyl bromide and palladium catalyzed oxazoline formation/epimerization as key steps. Intermediate **129** was prepared in four steps from **126** involving removal of tertbutyldimethylsilyl protecting group, Mitsunobu reaction with diphenylposphonyl azide, reduction with triphenyl posphine, protection with benzoyl chloroformate and allylation. The olefin metathesis reaction with 10 mole % of the Grubb's ruthenium alkylidene catalyst afforded the desired seven membered heterocycle **130**. Finally, hydrolysis of the oxazoline and base treatment yielded compound **131**, which on hydrogenation with Wilkinson's catalyst resulted into required hexahydroazepine moiety.

Scheme-19

Cook's approach: (*Organic Letters* **1999**, *1*, 615-617)

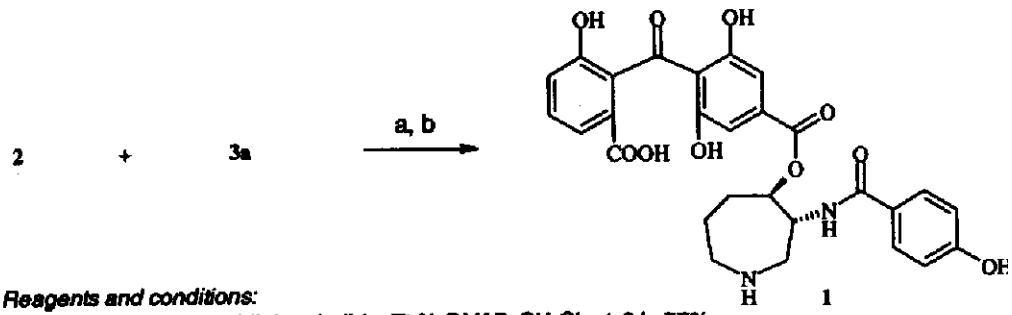


Reagents and conditions:
a. TBAF, THF, 83% b. DPPA, PPh_3, DEAD, 88% c. PPh_3, THF-H_2O, then BnOCOCl, Et_3N, 70%
d. NaH, allyl bromide, 87% e. $Cl_2(PCy_3)_2Ru$=CHPh, 45°C, 77% f. 2 N HCl, THF, rt then excess Et_3N, MeOH, rt, 72% g. $(PPh_3)_3RhCl$, H_2, 94%

2.1.15 Coupling of benzophenone 2 and hexahydroazepine 3a:

The coupling of two fragments **2** and **3a** was accomplished by Mukaiyama's procedure to afford the protected balanol[15], which was then deprotected by palladium-catalyzed hydrogenolysis into balanol (**1**) as shown in scheme-20.

Scheme-20



Reagents and conditions:
a. 2-chloro-1-methylpyridinium iodide, Et_3N, DMAP, CH_2Cl_2, rt, 3 h, 77%
b. HCOOH, Pd/C, rt, 30 h, 79%

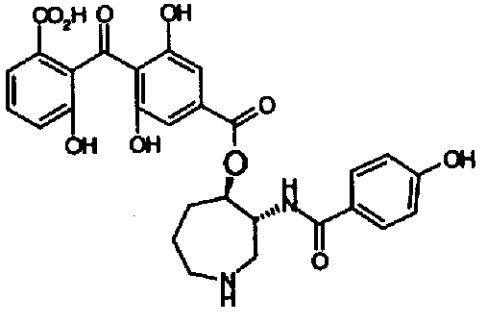
Part III

Design and synthesis of new analogs of balanol

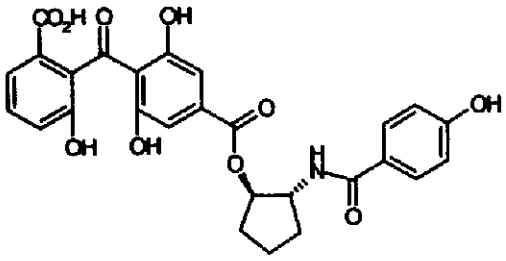
2.1.16 INTRODUCTION

A variety of new analogs have been synthesized involving replacement of hexahydroazepine moiety and benzophenone portion of balanol and evaluated for protein kinase C inhibitory activity.

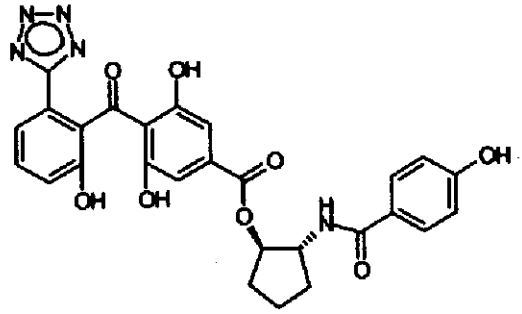
2.1.17 Protein kinase C inhibitory activities of balanol analogs bearing carboxylic acid replacements[27]: (Biorg. Med. Chem. Lett. **1995**, S, 1839)

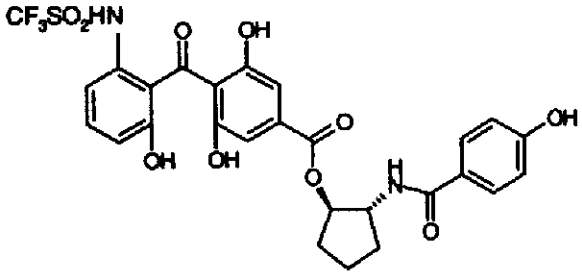


Balanol (1)



(±)-132

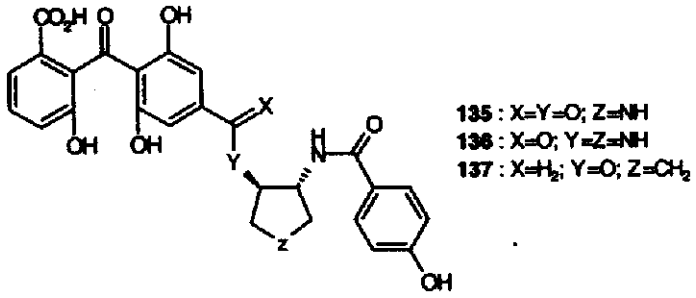




In general PKC inhibitory activity of these compounds is closely related to the approximate pKa of the acidic proton. Tetrazole **133** and trifluoromethylsulfonamide **134** showed potent PKC activity like cyclopentane analog of balanol **132** and display selectivity for PKC over PKA.

2.1.18 Protein kinase C inhibitory activity of ester functionality replaced analogs of balanol[28]: (Biorg. Chem. Lett. **1995**, 5, 2015.)

The presence of an ester functionality in this molecule has prompted concern over the metabolic stability of balanol, and has led to search for active analogs lacking this moiety. Analogs possessing amide and ether derivatives in the place of ester linkage were synthesized.

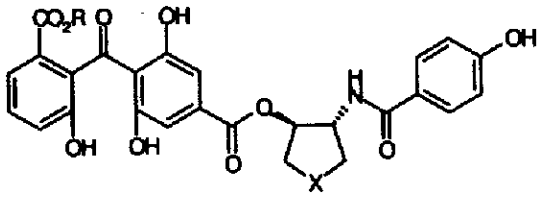


The analogs **136** and **137** showed slightly greater stability to serum esterases than **135** with which they were compared. However the magnitude of this enhancement , the trade-off in activity make it unlikely that any of the subject analogs are preferable compounds to substitute balanol.

2.1.19 Increasing the cellular PKC inhibitory activity of balanol: a study of ester analogs[29]:

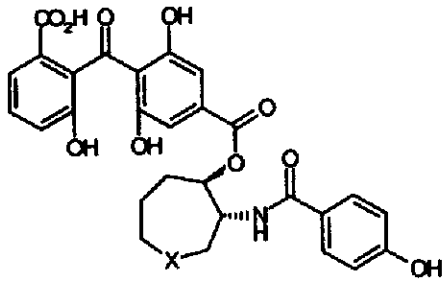
(Biorg. Med. Chem. Lett. **1995**, 5, 2133)

During investigations on balanol analogs the azepine replacement by a pyrrolidine ring and a cyclopentane ring, were prepared which displayed comparable PKC inhibitory activity to balanol.



Study of ester analogs of balanol showed that masking the carboxylic acid functionality of balanol analogs with small groups such as methyl can result in analogs with good enzyme inhibitory activity while larger groups interfere with PKC. Compounds **138** and **139** showed good cellular activities. Thus, this study has shown that PKC inhibitory activity can be maintained and cellular activity can be increased by masking the polar functionality of cyclopentyl and pyrrolidine balanol analogs.

2.1.20 Heteroatom effect in the PKC inhibitory activities of perhydroazepine analogs of balanol[30]: (Biorg. Med. Chem. Lett. 5 (18), **1995**, 2147)



140a : X=O,
140b : X=S
140c : X=SO_2
140d : X=CH_2

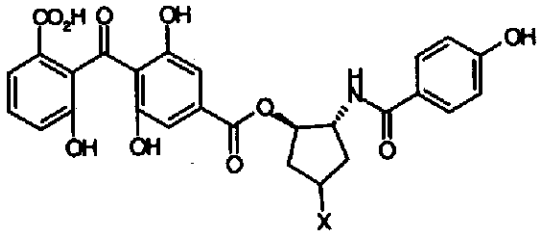
Analogs of balanol in which perhydroazepine nitrogen was replaced with O, S, or C were synthesized and evaluated for PKC inhibitory activity. Despite of enhanced isoenzyme selectivity these analogs did not get any importance as they were less potent PKC inhibitors relative to balanol.

2.1.21 Ring size effect in the PKC inhibitory activities of perhydroazepine analogs of balanol[31]**:** (Biorg. Med. Chem. Lett. **1995**, 5, 2151)

Study on ring size effect in the PKC inhibitory activities of perhydroazepine analogs of balanol showed that a five membered ring is favored over the seven membered ring for PKC inhibitory activity in the balanol series of compounds and six membered ring proved to be an unfavorable ring size.

2.1.22 Balanol analogs with a cyclopentane substructure[32]**:**

(Biorg. Med. Chem. Lett. **1995**, 5, 2155)

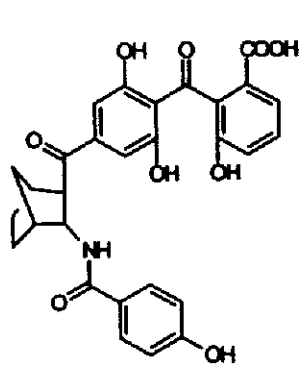


132a : X=β-NH_2, 132b : X=β-CH_2NH_2

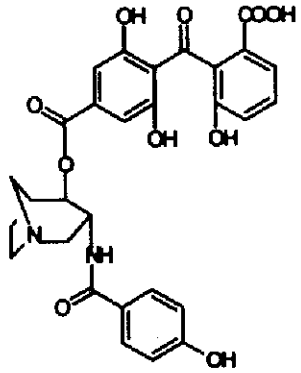
Synthesis of balanol analogs with perhydroazepine ring replaced with substituted cyclopentane ring (**132a and 132b**) and evaluation for PKC inhibitory activities showed that these analogs were more potent PKC inhibitors than racemic balanol. The biological results also indicated that attachment of an exocyclic amino or aminomethyl group to the core cyclopentane ring increased the potency against PKC.

2.1.23 Conformationally constrained bicyclic and tricyclic analogs of balanol[33]: (Biorg. Chem, Lett. **1995**, 5, 2211)

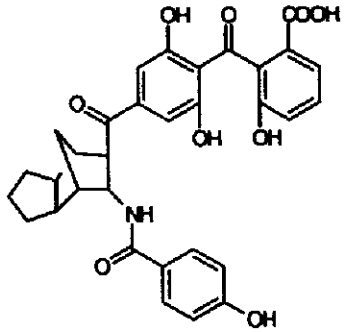
A series of conformationally constrained bicyclic and tricyclic analogs of balanol were synthesized and evaluated as inhibitors of protein kinase C. Thus substitution of the perhydroazepine ring of balanol with bicyclic or tricyclic ring resulted into the analogs which have been shown to be selective and very efficient inhibitors of PKC. Bicyclic analogs **141** and **142** and tricyclic analogs **143**, which not only retain the nanomolar activity for most PKC isoenzymes but also display good selectivity over PKA.



141



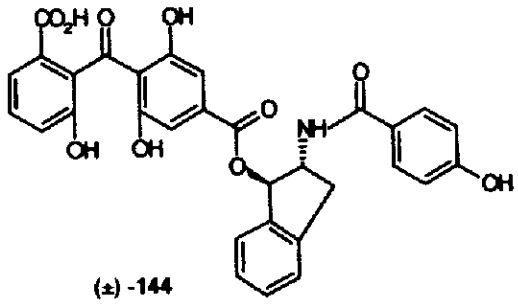
142



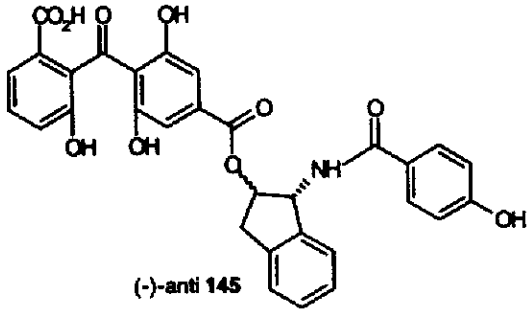
143

2.1.24 Protein kinase C inhibitory activities of indene analogs of balanol[34]: (Biorg. Med. Chem. Lett. **1996**, 6, 973)

Regio and stereoisomeric indene analogs of balanol were synthesized in which the perhydroazepine ring of balanol was replaced by indene nucleus and evaluated for PKC inhibitory activities.



(±) -144

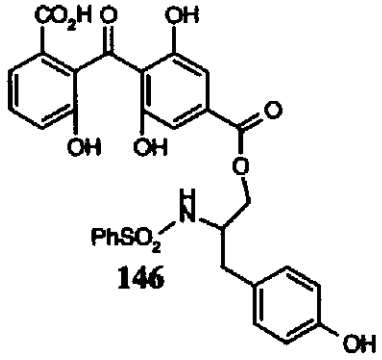


(-)-anti 145

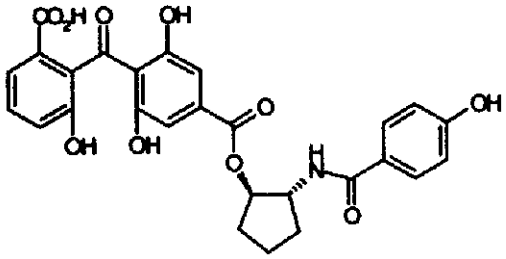
Indane derivative **144** and its regioisomer **145** were found to have highly potent PKC inhibitory activities. In addition, compound (-)-**145** displayed excellent kinase selectivity for PKC over PKA.

2.1.25 Protein kinase C inhibitory activity of acyclic and cyclopentane analogs[35]: (J. Med. Chem. **1996**, 39, 5215)

A series of balanol analogs in which hexahydroazepine moiety was replaced by acyclic and five membered ring were synthesized and evaluated for protein kinase C inhibitory activity.



146



132

The type and number of atoms linking the benzophenone ester to the p-hydroxyphenyl group necessary for optimal PKC were also investigated.

The compound **146** was tested against a panel of serine/threonine kinases and found to be highly selective for PKC. Reintroduction of a ring for the perhydroazepine portion in the form of an anti-substituted pyrrolidine and an anti substituted cyclopentane ring was also studied. The Compound **132** possessing cyclopentane ring showed equipotent PKC inhibitory activity to that of balanol.

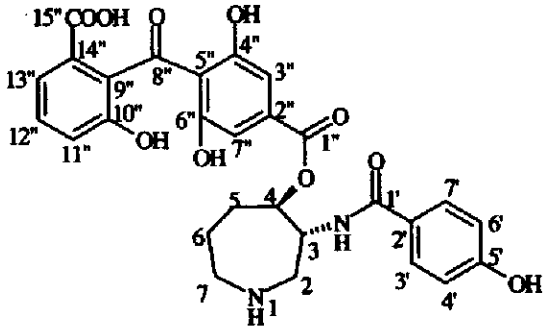
Recently[36] it has been shown that the perhydroazepine moiety of balanol possesses special properties that are important for its potency against PKC and PKA. The structure activity relationship studies in this regard suggested that the azepine nitrogen is replaceable as long as the replacement is able to raise the two aromatic side chains in a stereochemically correct manner. Any deviated conformation about the azepine replacement may result in decrease in activity.

SECTION-B

SYNTHESIS OF BENZOPHENONE PRECURSOR FOR BALANOL

2.2.0 INTRODUCTION

As discussed in earlier section, balanol (**1**)[11], a novel protein kinase 'C' inhibitor, showed remarkable activity against cancer, HIV infection, rheumatoid arthritis, diabetes, central nervous system disorder etc. A wide range of biological activities associated with this compound has attracted researchers to undertake synthesis of balanol and its intermediates.

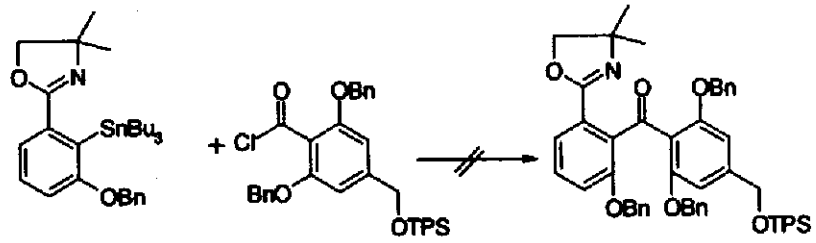


1

The structure activity relationship studies[36] on balanol (**1**) proved the critical importance of benzophenone portion (**2**) for the efficacy of balanol. Any attempted change to this tetraortho-substituted benzophenone portion resulted into decrease in its activity.

Synthesis of this tetraortho-substituted benzophenone **2** is challenging as it is highly sterically congested. Nicolaou et al.[15] attempted Stille coupling approach for the synthesis of benzophenone moiety using functionalised acid chloride **148** and arylstannane **147** as shown in scheme-21.

Scheme-21



147 **148** **149**

Failure to obtain the required benzophenone **149**, suggested that the coupling might be difficult due to an overpowering degree of steric congestion.

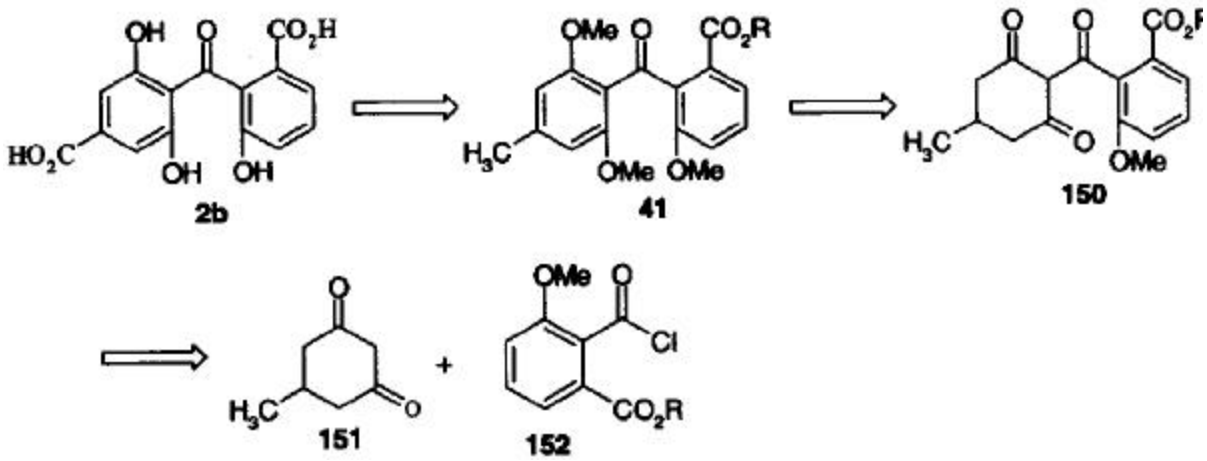
2.2.1 PRESENT WORK

The reexamination of the structure of benzophenone portion **2** was done in a slightly different fashion than what has been reported. Accordingly we planned to synthesize this benzophenone domain starting from an alicyclic compound 5-methylcyclohexane-1,3-dione

(**151**), where the steric hindrance will be less as compared to the aromatic ring. Our retrosynthetic route for benzophenone domain is shown in scheme-22.

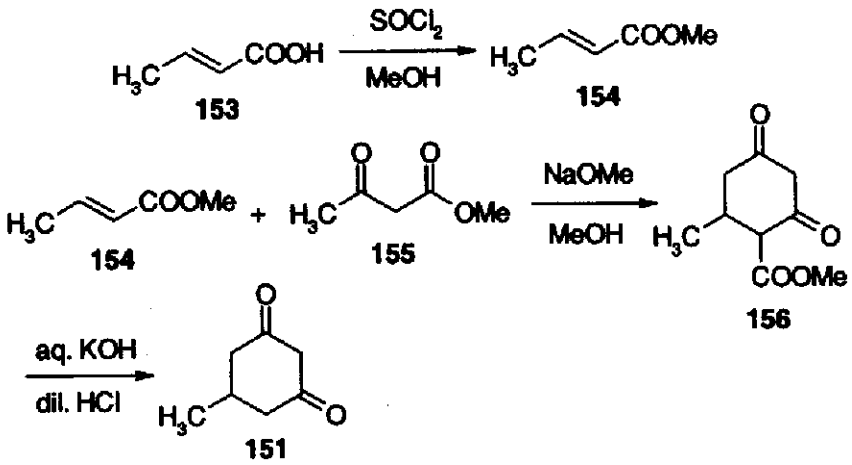
As per retrosynthetic analysis the synthesis of triketone compound **150** followed by its aromatization would give the required benzophenone domain **41**.

Scheme-22



Accordingly 5-methylcyclohexane-1,3-dione (**151**)[37] was prepared by the condensation of methyl crotonate (**154**) with methyl acetoacetate (**155**) as shown in scheme-23.

Scheme-23



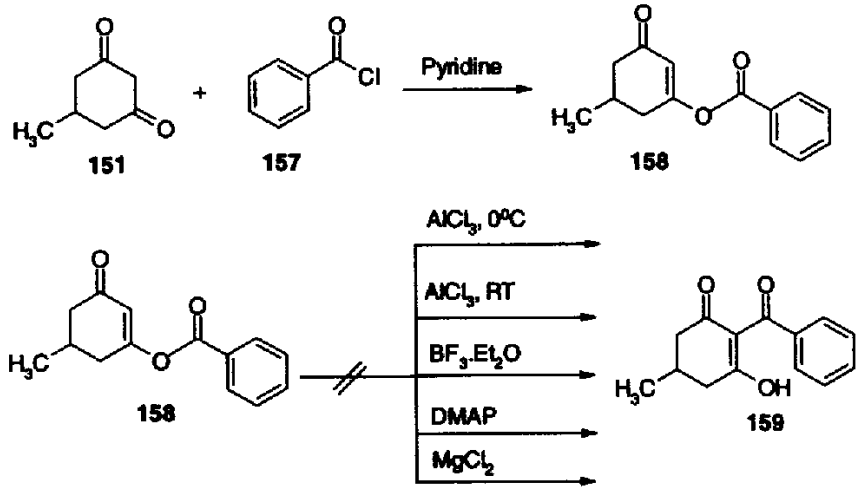
Methyl crotonate (**154**) was prepared by a known method[38] in which thionyl chloride was added dropwise to a cold solution of crotonic acid (**153**) in methanol affording methyl crotonate (**154**) in 70 % yield.

Michael-Aldol type addition of methyl acetoacetate (**155**) with methyl crotonate (**154**) in the presence of sodium methoxide in methanol afforded sodium salt of methyl

dihydroorcellinate which was further hydrolysed and decarboxylated in situ by refluxing in aq. KOH and slow addition of dil. HCl to give 5-methylcyclohexane-1,3-dione (**151**) (scheme-23).

After obtaining 5-methylcyclohexane-1,3-dione (**151**) attention was focused towards its benzoylation to give the triketone compound. To check the feasibility of this reaction we started with benzoyl chloride as a model study and carried out the reaction under various conditions as shown in scheme-24.

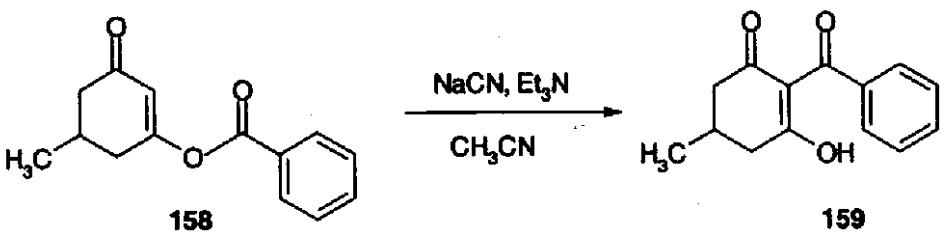
Scheme-24



Thus 5-methylcyclohexane-1,3-dione (**151**) was treated with benzoyl chloride (**157**) in presence of pyridine to give the ester **158**. The structure assigned to the ester **158** was confirmed by its ^{1}H NMR, which showed the presence of 5 aromatic protons along with olefinic proton at 8 6.05 and rest of the peaks were seen at expected positions. This was further supported by mass spectrum showing presence of molecular ion peak at m/z 230. Next target was to isomerize this ester to give the compound **159** but under most of the conditions tried isomerization of ester **158** failed to give the compound **159**.

The isomerization of compound **158** to compound **159** was achieved in 80 % yield by using triethylamine and sodium cyanide[39] in acetonitrile as shown in scheme-25.

Scheme-25

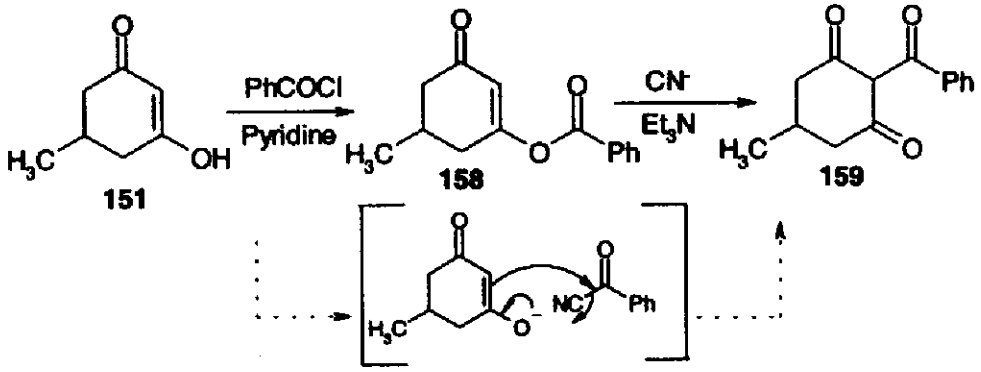


The structure assigned to the compound **159** was confirmed on the basis of its ^{1}H NMR spectrum, which showed disappearance of olefinic proton at 8 6.05 and rest of the peaks were at expected positions with appropriate integrations.

2.2.2 Mechanistic details of cyanide catalyzed rearrangement[39]:

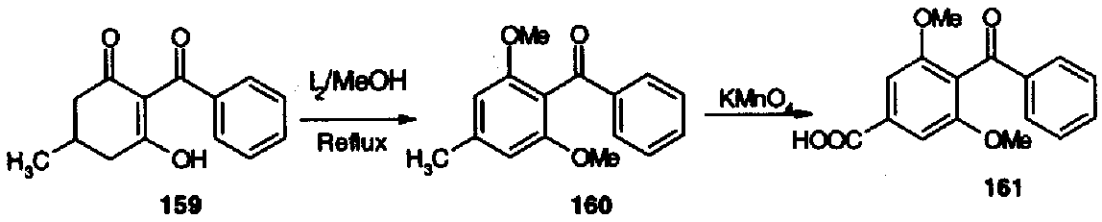
Mechanism for cyanide catalyzed isomerization of enol ester involves initially the cyanide ion attack at the carboxylic carbon atom of the ester, with the cleavage of enol ester and formation of acyl cyanide. 5-Methylcyclohexane-1,3-dione has an unreactive anion, under basic condition it reacts with acyl cyanide to give the triketone compound as shown in scheme-26.

Scheme-26



Further aromatization of the compound 159[40] and oxidation of the methyl group in compound **160** yielded smoothly the acid **161** (Scheme-27).

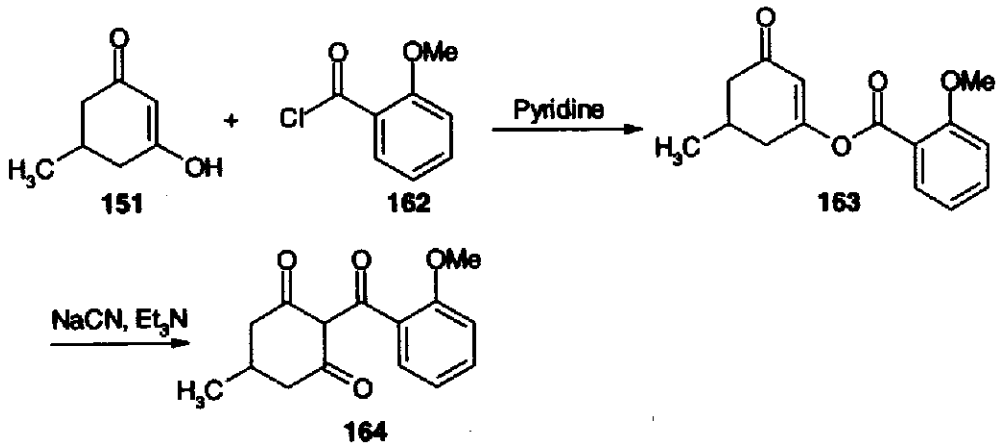
Scheme -27



Aromatization of the compound **159** was carried out by the treatment of **159** with iodine in refluxing methanol to give the required compound **160** in 61.6 % yield. ^{1}H NMR spectrum of the compound **160** revealed shifting of a doublet for methyl protons from 8 1.05 to a singlet for benzylic methyl protons at 8 2.38 as well as presence of two methoxy groups at S 3.68. The IR spectrum, which showed absorption band for carbonyl group at 1675 cm^{-1}, and mass spectrum which exhibited a molecular ion peak at m/z 256 confirmed the formation of compound **160**. Oxidation of the compound **160** to carboxylic acid **161** was achieved by using

aq. $KmnO_4$ and pyridine in 45 % yield. The structure assigned to the carboxylic acid 161 was confirmed by ^1H NMR showing disappearance of methyl group. The IR spectrum showed a band at 3450 cm^{-1} for acid and molecular ion peak at m/z 286 in the mass spectrum. After completion of this model study successfully another model study was undertaken to study steric hindrance as shown in scheme-28.

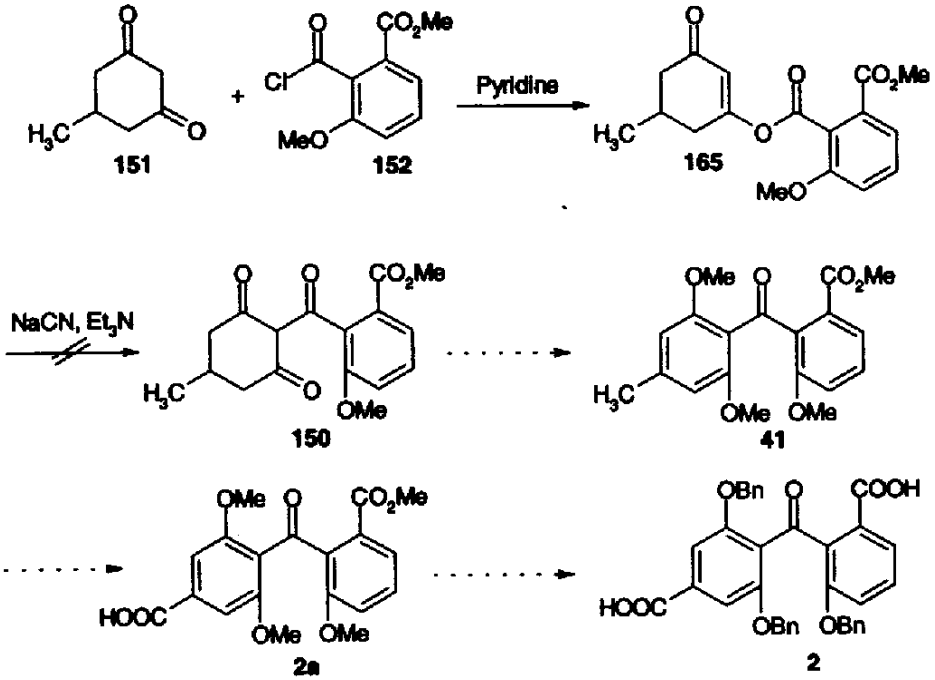
Scheme-28



Thus 5-methylcyclohexane-1,3-dione (**151**) was treated with 2-methoxy benzoyl chloride (**162**) in the presence of pyridine to give ester **163**, whose ^1H NMR was in good agreement to the assigned structure. Its isomerization was achieved using sodium cyanide and triethylamine to give the compound **164**, whose ^1H NMR spectrum showed characteristic disappearance of olefinic proton at 8 5.96 indicating O-acyl to C-acyl rearrangement. This structure was further confirmed by its mass spectrum showing presence of molecular ion peak at m/z 260.

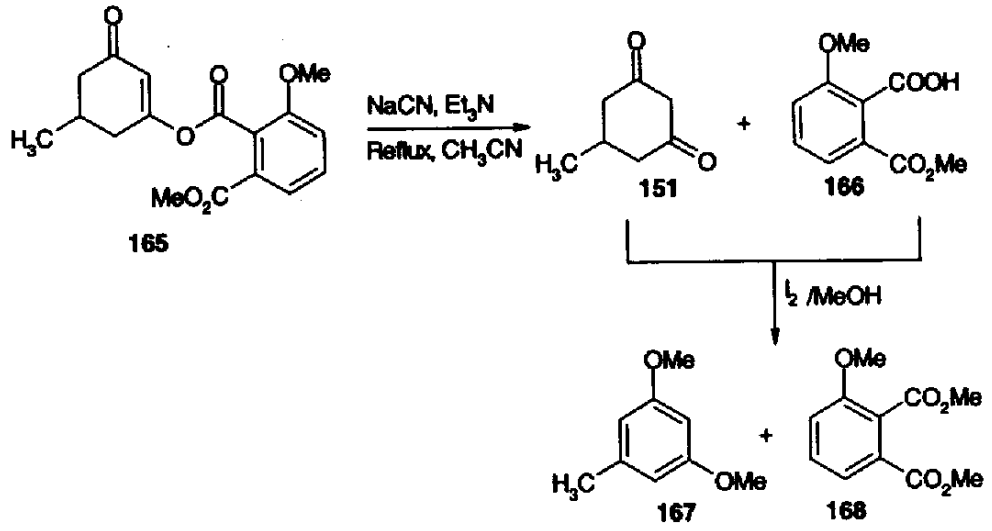
After the completion of two successful model studies this approach was extended for the synthesis of benzophenone portion of balanol as shown in scheme-29. Thus 5-methylcyclohexane-1,3-dione (**151**) was treated with acid chloride **152**, which has also been used in the synthesis of brasiliquinone B and was prepared from m-hydroxybenzoic acid as discussed in chapter-I, in presence of pyridine to give the ester **165**. Structure of the ester 165 was established on the basis of spectral analysis. The ^1H NMR of ester **165** showed presence of characteristic olefinic proton at 8 6.05 as well as presence of both methoxy and carbomethoxy protons at 8 3.89 integrating for six protons. The structure was further confirmed by mass spectrum exhibiting molecular ion peak at m/z 318.

Scheme-29



Next goal was to isomerize the ester **165** to the compound **150** as per the model study but unfortunately it failed to isomerise under sodium cyanide, triethylamine conditions even at reflux temperature. Instead of isomerization, the ester bond cleaved to give back 5-methylcyclohexane-1,3-dione (**151**) and acid **166** as shown in scheme-30.

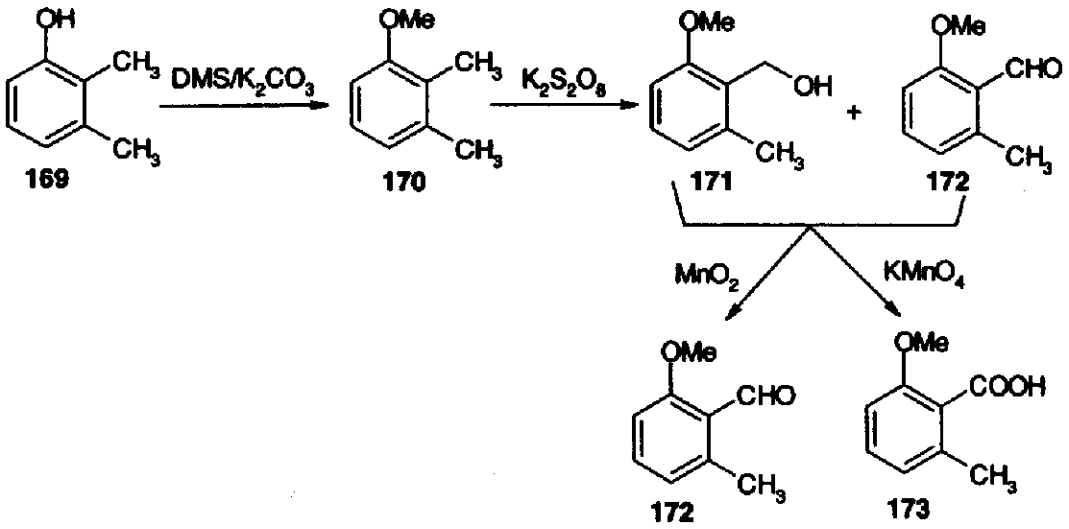
Scheme-30



5-Methylcyclohexane-1,3-dione (**151**) and acid **166** were difficult to isolate as both are highly polar and having almost same Rf values. The crude reaction mixture was refluxed in methanol in presence of iodine to afford 3,5-dimethoxytoluene (**167**) and diester **168**. Formation of the compounds **167** and **168** was confirmed by their spectral data, thus, the formation of 3,5-dimethoxy toluene (**167**) and diester **168** supported the cleavage of ester bond and regeneration of starting materials.

The failure in the isomerization may be due to either steric hindrance or as per the mechanism the acyl cyanide intermediate had not formed. To rule out these possibilities we planned to reduce the steric hindrance of aryl chloride **152** by replacing carbomethoxy group with methyl group, which could be oxidized later on to the corresponding acid. Thus acid chloride **174** was prepared from acid **173**, which was obtained from commercially available 2,3-dimethyl phenol as per known procedure[41] as shown in scheme-31.

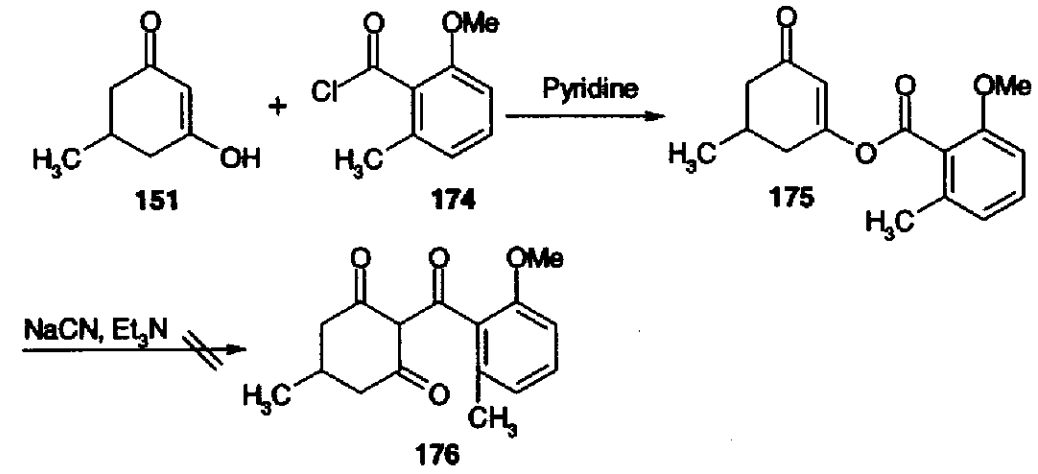
Scheme-31



Thus, 2,3-dimethylphenol (**169**) was methylated using dimethylsulfate and potassium carbonate in refluxing acetone to afford 2,3-dimethyl anisole (**170**) as thick oil. Oxidation of the 2,3-dimethyl anisole (**170**) with potassium persulphate in acetonitrile in presence of $CuSO_4$ and pyridine yielded a mixture of alcohol **171** and aldehyde **172**. Further oxidation of this mixture with MnO_2 afforded aldehyde **172** in 54% yield while oxidation with $KMnO_4$ yielded acid **173** in 23 % yield. Acid chloride **174** was then prepared by refluxing the acid **173** in presence of thionyl chloride and catalytic amount of dimethyl formamide in benzene. Formation of acid chloride **174** was confirmed by its IR spectrum which showed absorption band at 1800 cm^{-1}. It

was assumed that by replacing the carbomethoxy group of the acid chloride **152** with the methyl group the steric hindrance would be reduced considerably. Our next target was to prepare the compound **176** as per model scheme. Hence, the acid chloride **174** was treated with 5-methylcyclohexane-1,3-dione (**151**) in presence of pyridine to give ester **175** in 80 % yield, as shown in scheme-32.

Scheme-32

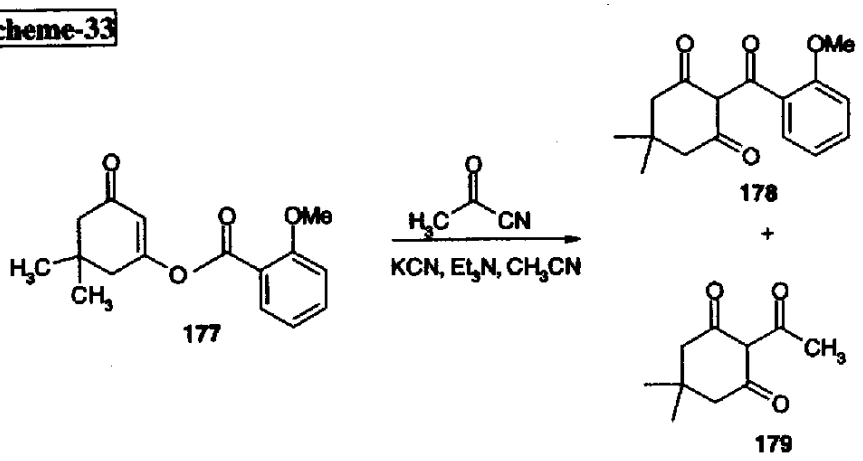


^{1}H NMR spectrum of ester **175** revealed presence of aromatic methyl group at 8 2.25, methoxy group at 8 3.75 alongwith characteristic olefinic proton at 8 5.85. Mass spectrum showed presence of molecular ion peak at m/z 274, thus supporting the assigned structure **175**.

Isomerization of the ester **175** to the corresponding compound **176** was attempted under sodium cyanide, triethylamine condition which resulted into cleavage of ester linkage producing the 5-methylcyclohexane-1,3-dione (**151**) and acid **173**.

These results suggested that resistance of enol esters to isomerize into the corresponding triketones may not be due to steric hindrance as even after replacing the bulky carbomethoxy group in ester **165** with methyl group in ester **175** could not result into ismerization. Hence, the second possibility of the formation of acyl cyanide as per mechanism was to be checked. In literature in situ acyl cyanide formation during the isomerization of enol esters is well documented. Burger et a1.[39] reported the cross over experiments to unveil that the mechanism of the cyanide catalyzed isomerization of enol esters involves cleavage of enol esters by cyanide with transient formation of acyl cyanides, as shown in scheme-33.

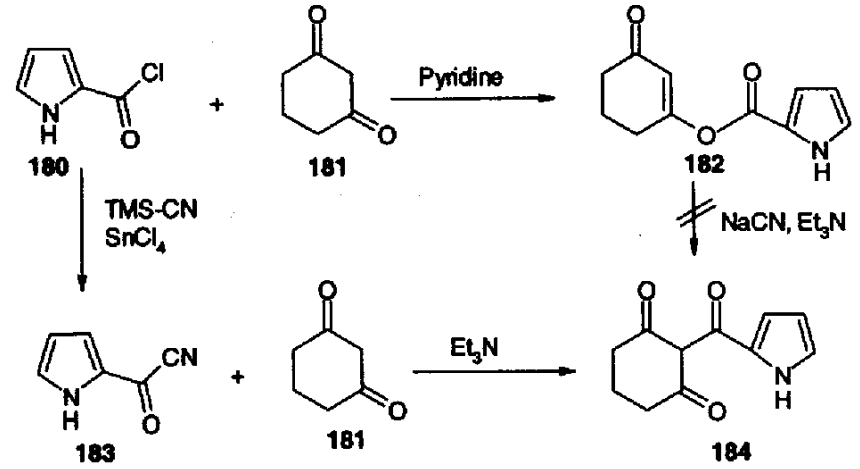
Scheme-33



Thus the enol ester **177** derived from 5,5-dimethyl cyclohexane-1,3-dione when allowed to react in 1M acetonitrile solution with KCN in presence of an equivalent of pyruvonitrile afforded the normal C-acylation product **178** along with the O-acyl counterpart **179** in a 3:1 ratio. Thus formation of acyl cyanide was confirmed by cross experiments with external acyl cyanide.

Burger showed that treatment of acyl cyanide **183** with 1,3 cyclohexanedione (**181**) in presence of triethylamine yielded the desired C-acylated product **184** directly in 78% yield as shown in scheme-34.

Scheme-34

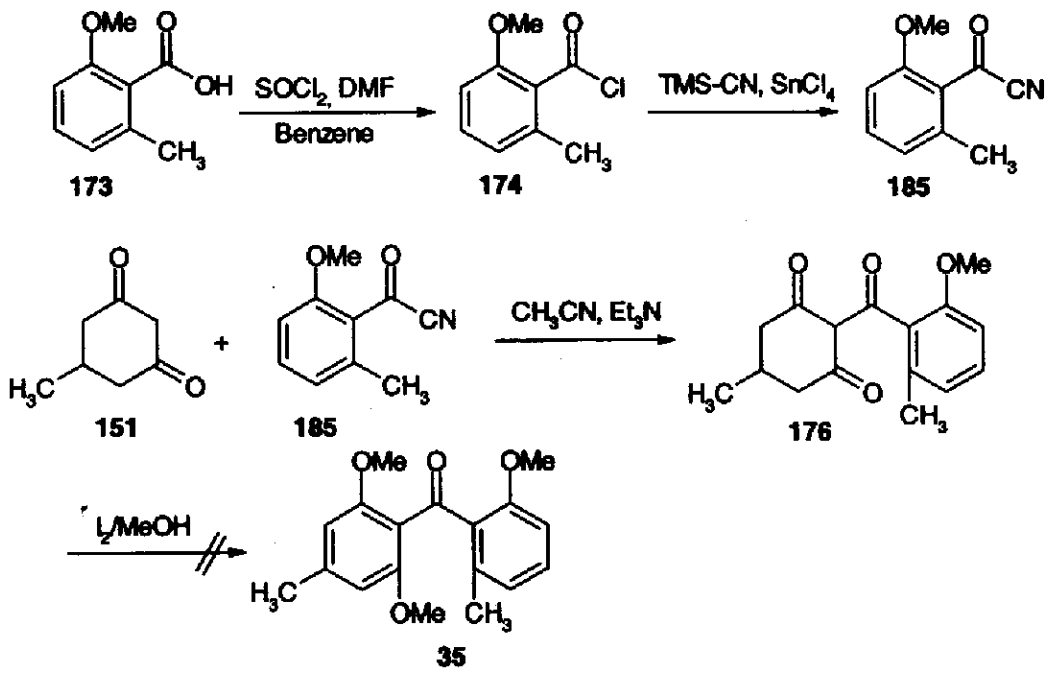


It was clear from the above experiments that isomerization of enol ester involves acyl cyanide formation. Accordingly we planned to prepare acyl cyanide **185** starting from the acid chloride **174**. Preparation of acyl cyanide from acyl chloride is well documented in literature using KCN

and phase transfer catalyst, KCN and ultrasound, NaCN and phase transfer catalyst, but under most of the conditions this conversion failed to give the desired acyl cyanide.

Finally the required acyl cyanide **185** was prepared by treating the acid chloride **174** with trimethylsilyl cyanide[42] in presence of catalytic stannic chloride at room temperature in quantitative yield. This acyl cyanide was used for further reaction without purification. Synthesis of the compound **176** was then attempted using the method reported by Burger et a1.[39] Thus aryl cyanide **185** was treated with 5-methylcyclohexane-1,3-dione (**151**) in presence of Et_3N to give the compound **176** as a pale yellow thick oil in 70 % yield as shown in scheme-35.

Scheme-35

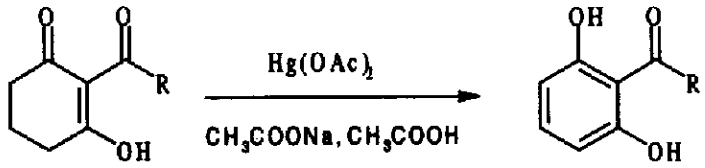


The structure assigned to the compound **176** was fully confirmed by spectral means. Its ^1H NMR spectrum showed a doublet at 8 1.12 for methyl and singlets at 8 2.17 and 8 3.72 for aromatic methyl and methoxy groups suggesting condensation of the two reactants. The ^{13}C NMR spectrum exhibited signals at 8 193.56, 197.16 and 199.04 representing the three carbonyl groups in addition to other peaks. Presence of absorption band at 1673 cm^{-1} in the IR spectrum and peaks at m/z 274 (M^+) and 259 (M-15) in the mass spectrum supported the assigned structure of compound **176**.

After successful synthesis of compound **176**, next aim was to convert compound **176** into the desired benzophenone **35**, but unfortunately the attempted aromatization of the compound **176** using I_2/MeOH, DDQ in benzene or Pd/C failed to give the desired compound **35** and resulted into either recovery of starting material or a complex reaction mixture.

Oliver et a1.[43] reported aromatization of 2-acyl-3-hydroxy-2-cyclohexen-1-ones with mercuric acetate as shown in scheme-36.

Scheme-36

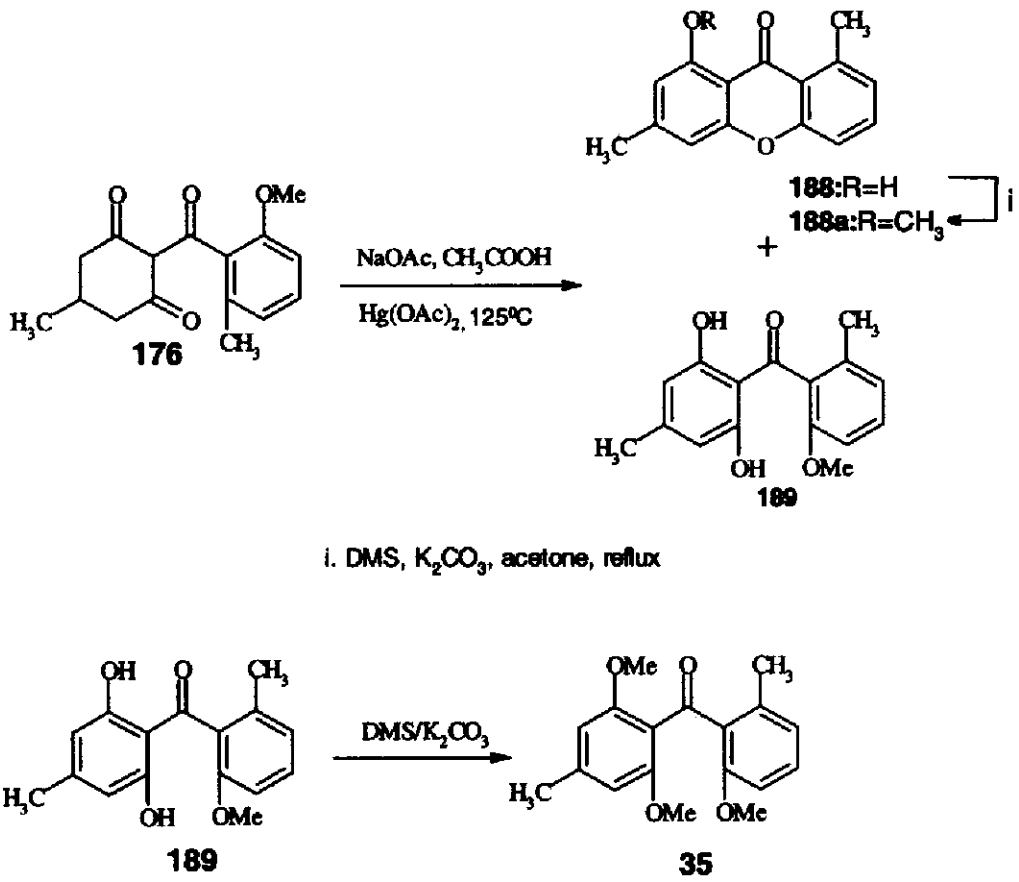


186 **187**

According to Oliver these compounds are surprisingly resistant to dehydrogenation under most of the conditions used like cupric bromide/lithium bromide in refluxing acetonitrile, DDQ in refluxing dioxane, dimethylformamide or collidine, pyridinium hydrobromide dibromide in acetic acid or dimethylformamide, palladium chloride in refluxing tert-butyl alcohol, palladium chloride in acetic anhydride, palladium on carbon in refluxing decalin containing 1-decene and lead (IV) acetate in refluxing benzene. Finally aromatization was achieved using mercuric acetate and sodium acetate in acetic acid at 125 °C in 32-70 % yields.

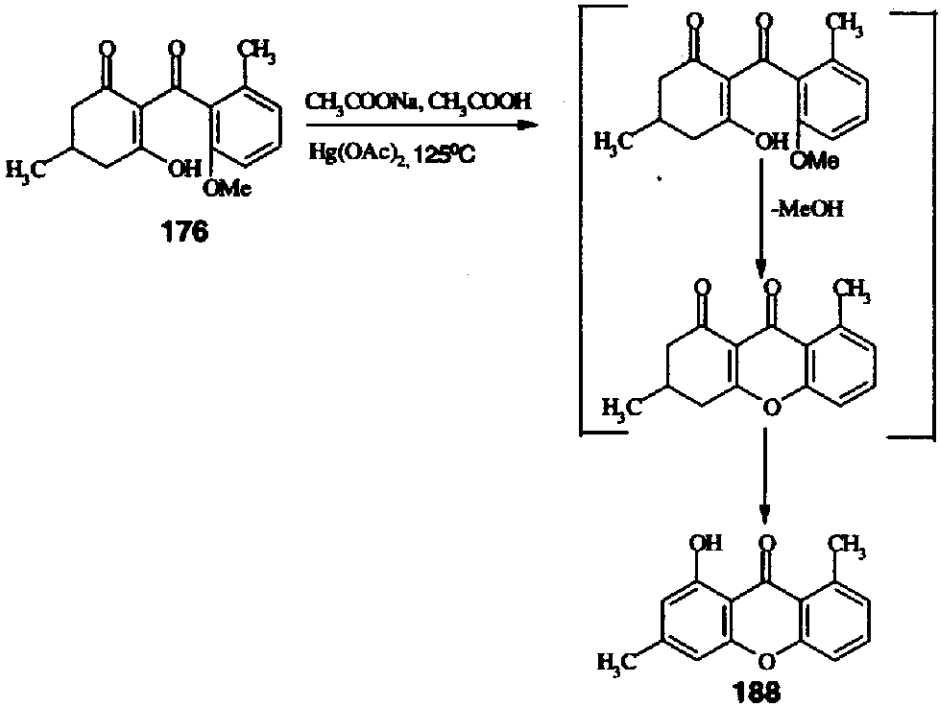
Based on these findings of Oliver, aromatization of compound **176** was carned out using mercuric acetate as shown in scheme-37. Aromatization of the compound **176** under these conditions resulted into formation of aromatized product **189** in 20% yield. Formation of compound **189** was confirmed by converting it into the known intermediate **35**. Treatment of the compound **189** with dimethyl sulphate in presence of potassium carbonate in refluxing acetone afforded compound **35**, an important benzophenone precursor for balanol. Spectral data for the compound **35** was identical to those reported by Adams et al.[17] Surprisingly aromatization of triketone **176** in the presence of mercuric acetate and sodium acetate in acetic acid afforded only 20 % of the required product **189** along with formation of xanthone **188** in 40% yield.

Scheme-37



Formation of xanthone **188** was based on its ^{1}H NMR which exhibited singlets at S 2.41 and 2.89 for aromatic methyls, singlets at 8 6.55 and 6.65 each integrating for one proton and a singlet at S 12.86 for chelated -OH group. Although it was difficult to assign the structure of compound 188 only on the basis of ^{1}H NMR, the molecular ion peak at m/z 240 in mass spectrum supported the assigned xanthone structure for the compound **188**. It was then methylated using DMS/K_2C0_3 in refluxing acetone to give the corresponding methyl ether 188a whose ^{1}H NMR showed presence of only one methoxy group at 8 4.01 confirming the assigned structure of the xanthone. Probable reason for the formation of xanthone may be the loss of methanol during aromatization due to the presence of highly acidic mercuric acetate as shown in scheme-38

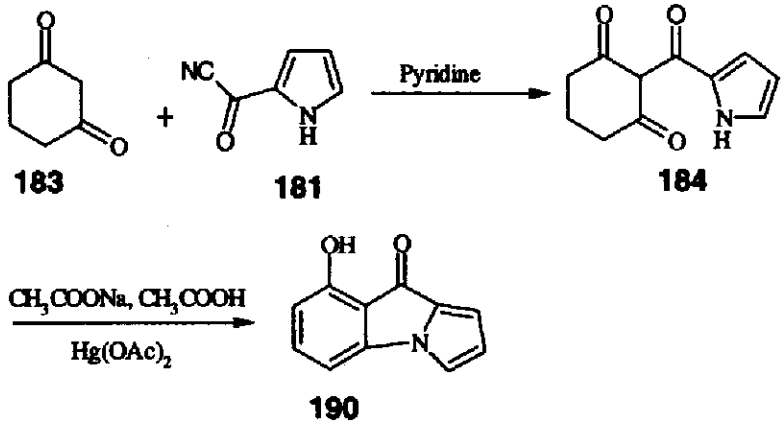
Scheme-38



176 188

Burger et a1.[39] reported similar results of dehydration during the synthesis of antibiotic pyoluteorin (**190**), a secondary metabolite of various species of pseudomonas, as shown in scheme-39.

Scheme-39



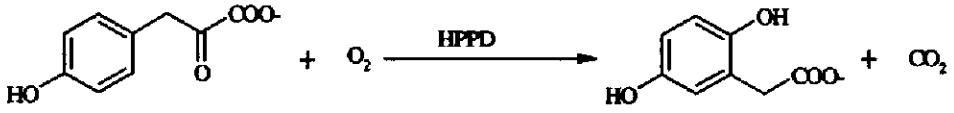
183 181 184 190

Thus, formation of product **190** during the attempted aromatization of compound **184** with mercuric acetate and sodium acetate in acetic acid supported the formation of the xanthone **188** during aromatization of the compound **176**.

In conclusion using cyanide catalyzed isomerization, we have achieved synthesis of triketone compounds such as **159**, **164** and **176**. Recently Yang et al.[44] showed that triketone compounds are good inhibitors of 4-hydroxyphenylpyruvate dioxygenase (HPPD), an important enzyme involved in the biosynthesis of plastoquinones and tocopherols in plants as well as in the catabolism of the aromatic acids phenylalanine and tyrosine in most of the organisms. 4-Hydroxyphenylpyruvate dioxygenase catalyzes oxidative decarboxylation, hydroxylation of the aromatic ring and a 1,2 shift of the carboxymethyl group from 4-hydroxyphenylpyruvate **191** to homogentisate **192** in the presence of oxygen as shown in scheme-40.

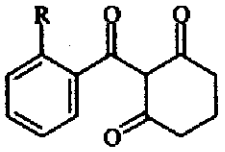
HPPD is the target site of certain bleaching herbicides that contain the 2-benzoylcyclohexane-1,3-dione moiety referred to as triketones.

Scheme-40



191 **192**

Inhibition of HPPD activity by triketone herbicides decreases tocopherol and plastoquinone levels in plants, indirectly reducing phytone desaturation and leading to development of bleaching symptoms. Yang and co-workers[44] synthesized a series of 2-O-substituted benzoylcyclohexane-1,3-diones and tested their relative competence as inhibitors of 4-hydroxyphenylpyruvate dioxygenase. Some of the triketone compounds like **193** showed a very good HPPD inhibition potency.



R= H, Cl, Br, NO_2, CH_3, OMe

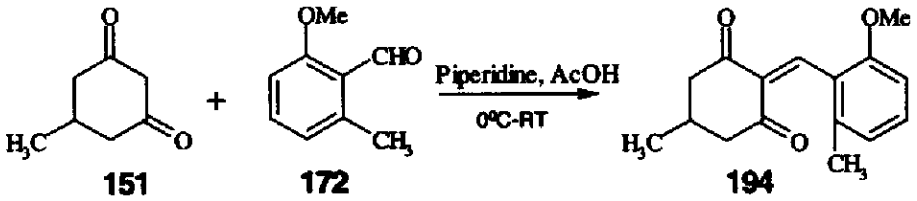
193

On this background we feel that triketone compounds **159**, **164** and **176** obtained during the synthesis of benzophenone precursor of balanol may show good HPPD inhibitory activity.

Although we have achieved synthesis of compound **35**, an intermediate for benzophenone portion of balanol, the poor yield in aromatization of the compound **176** prompted us to find a better and economical route.

In another approach we planned to utilize the Knoevenagel condensation for the synthesis of benzophenone domain of balanol. Accordingly 5-methylcyclohexane-1,3-dione (**151**) was treated with aldehyde **172** in presence of sodium methoxide but it afforded a complex mixture. Similar results were obtained using sodium hydride. Finally the condensation was achieved using catalytic piperidine in acetic acid, as shown in scheme-41.

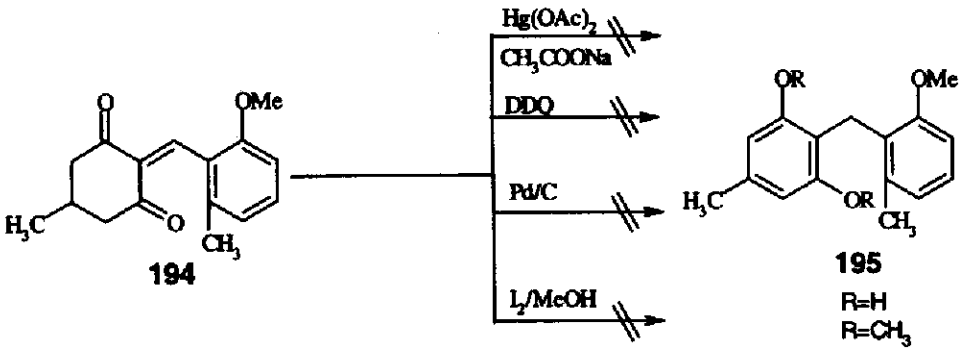
Scheme-41



5-Methylcyclohexane-1,3-dione (**151**) was treated with catalytic piperidine in glacial acetic acid at 0°C and then stirred at room temperature for 6-7 hr to afford reddish colored solid in 60 % yield, m. p. 95-97 °C. The ^{1}H NMR spectrum of compound **194** exhibited a doublet for methyl group at 8 1.15, a singlet at 8 3.75 for methoxy group and a singlet at S 7.90 for olefinic proton. The IR spectrum showed absorption band at 1721 cm^{-1} which was in good agreement with the assigned structure.

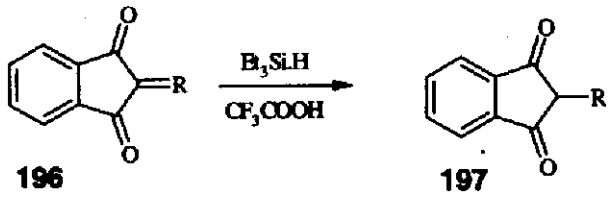
Attempts towards aromatization of this condensed product **194** to convert it directly into 195 failed under most of the conditions (Scheme-42).

Scheme-42



The results obtained above made it clear that the resistance to aromatization was due to the presence of double bond and hence selective reduction of double bond was attempted under hydrogenation condition using 10 % Pd/C but unfortunately it resulted into a complex mixture.

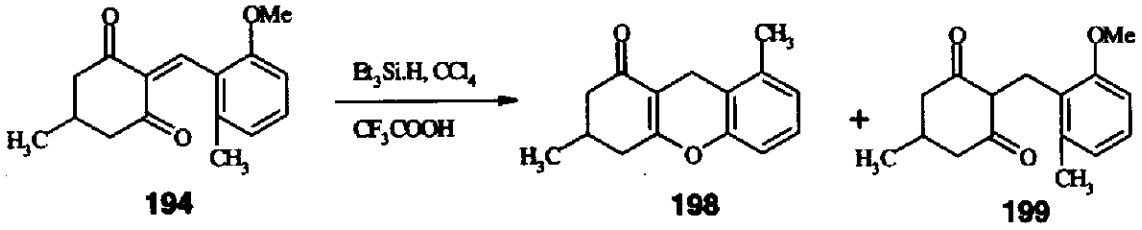
There are reports of reductions of this kind in literature using trifluoroacetic acid and triethylsilane in refluxing carbon tetrachloride.[45]



196 **197**

Reduction of compound **196** was carried out under these conditions to yield compound **197**. Similar strategy was used for the selective reduction of exocyclic double bond of compound **194** as shown in scheme-43. Thus the compound **194** in carbon tetrachloride was treated with triethylsilane and trifluoroacetic acid at 50-60 °C.

Scheme-43

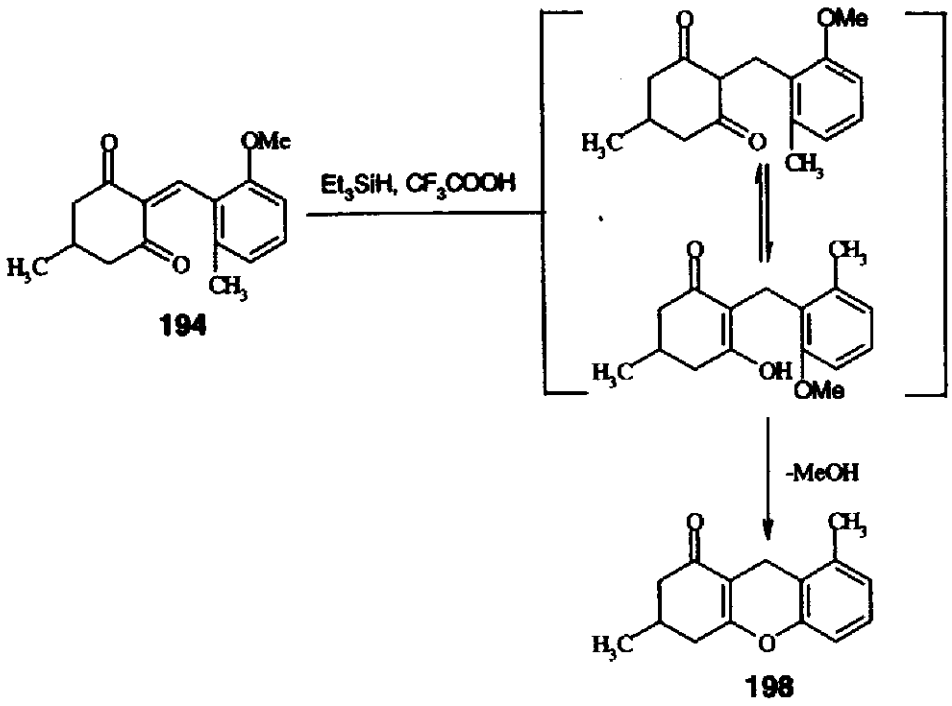


194 **198** **199**

TLC analysis of this reaction showed a mixture of two compounds. Its column chromatographic separation afforded the desired compound **199** along with the side product **198** in 40:50 ratio.

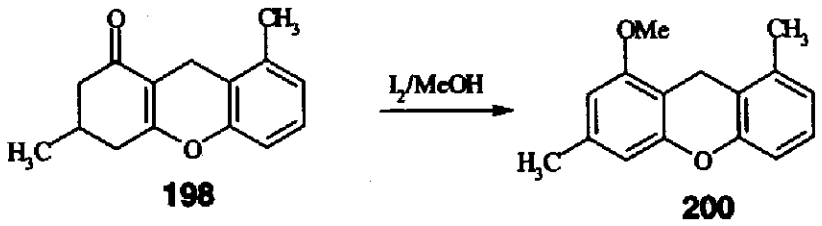
Careful structural analysis of the compound **198** using spectroscopic methods suggested cyclized product whose ^{1}H NMR showed disappearance of olefinic proton at 8 7.90 (exocyclic double bond) as well as disappearance of a singlet at 8 3.75 for OMe group. The rest of the peaks were at appropriate positions expected for the compound **198**. ^{13}C NMR spectrum of the compound **198** showed peak at 8 198 indicating presence of only one carbonyl group, which was in good agreement with assigned cyclized structure **198**. The final evidence came from mass spectrum indicating presence of molecular ion peak at m/z 228. The probable mechanism for the formation of compound **198** is shown in scheme-44. Initially reduction of double bond might have taken place followed by the loss of methanol due to the presence of highly acidic reaction medium (Scheme-44).

Scheme-44



Formation of the cyclized product **198** was confirmed by its aromatization which was carried out by treating compound **198** with iodine in refluxing methanol to afford compound **200** as white solid melting at 97-100 °C in 75 % yield as shown in scheme-45.

Scheme-45



[1]H NMR spectrum of the compound **200** revealed presence of two aromatic methyl groups as a singlet at 8 2.32 as well as presence of a methoxy group as a singlet at S 3.85 along with benzylic protons at S 3.75 and rest of the peaks at appropriate positions in good agreement with assigned structure. The mass spectrum showed molecular ion peak as expected at m/z 240.

Oxidation of the compound 200 would give the methyl ether of the xanthone **188**, obtained during the aromatization of the compound **176**.

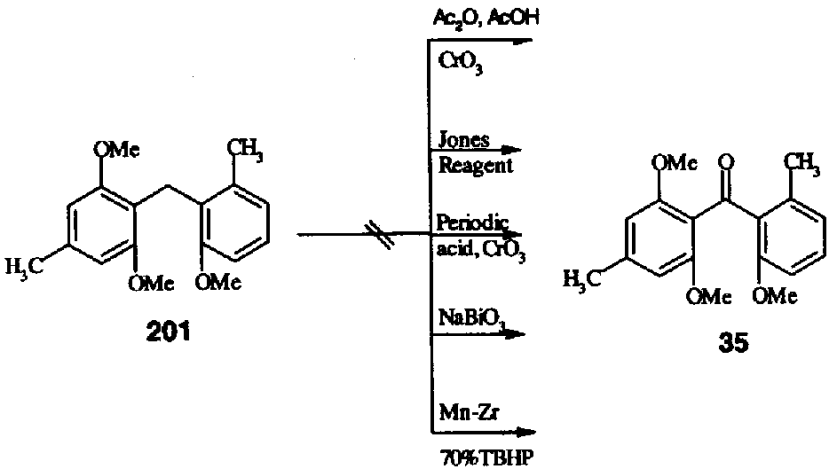
As discussed in scheme-43, reduction of compound **194** under triethylsilane, tirfluoroacetic acid condition afforded desired product **199** in 40 % yield. This compound was characterized after aromatization as ^{1}H NMR spectrum although showed required signals was not clean. The compound **199** was subjected for the aromatization under iodine/methanol conditions as shown in scheme-46. Treatment of the compound **199** with iodine in refluxing methanol resulted into white crystalline product **201** in 70 % yield as white crystals melting at 108-111 °C.

Scheme-46

199 **201**

The compound **201** was characterized by means of spectral data. ^{1}H NMR spectrum of the compound **201** exhibited presence of two aromatic methyl groups at 8 2.45 and 2.52, presence of three methoxy groups at 8 3.86 (two methoxy groups) and 3.94 (one methoxy group) along with presence of benzylic protons at 8 4.22. Remaining peaks were present at expected positions with appropriate integrations. ^{13}C NMR spectrum and mass spectrum were also in good agreement with assigned structure **201**. Further attempts to oxidize the compound **201** to desired intermediate **35** under most of the conditions tried resulted into either a complex mixture or no reaction as shown in scheme-47.

Scheme-47



201 **35**

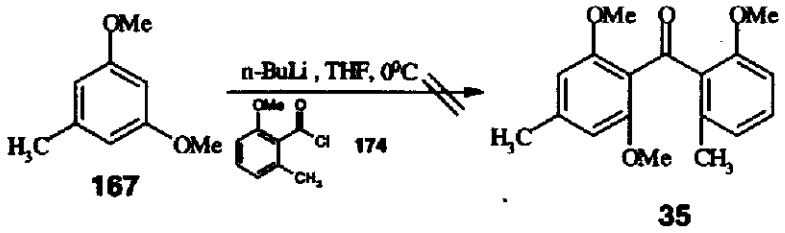
Oxidation of compound **201** under CrO_3, AcOH, acetic anhydride condition as well as Jones oxidation, yielded a complex mixture of products. Recently Yamazaki[46] reported use of CrO_3 as an efficient catalyst for benzylic oxidation with periodic acid as the terminal oxidant in acetonitrile. Unfortunately under these conditions also desired product could not be obtained. Sodium bismuthate in acetic acid is another catalyst used for such benzylic oxidations but this condition also met with failure for selective oxidation of benzylic methylene group to give the desired product **35**. We assumed that formation a of complex mixture was due to the over oxidation of compound **201**, so to obtain exclusively desired product there was a need to develop a methodology which can oxidize selectively benzylic methylene group in presence of methyl groups. A new methodology was developed using Mn-Zr catalyst and 70 % TBHP as co-oxidant, which will be discussed in Chapter-III (SectionIII). Mn-Zr catalyst along with 70 % TBHP as co-oxidant was found to be very effective and selective for the oxidation of various compounds possessing benzylic methylene group to the corresponding ketones including selective oxidation of 4-methylethylbenzene to 4-methylacetophenone in 70 % yield. Attempted oxidation of targeted compound **201** under this condition failed to give the desired intermediate **35** with recovery of starting material.

Failure in oxidation of compound **201** and poor yield of aromatization of triketone **176** to the desired intermediate **35**, in both the earlier approaches prompted us to find out another better route for the synthesis of benzophenone precursor **35** for balanol.

Stille coupling of compound **147** with **148** attempted by Nicolaou et al.[15] failed due to the high power of steric hindrance. We assumed that utilization of a less hindered acid chloride like **174** could solve this problem of coupling. Moreover in the literature all attempts have been made by using 2,6-dimethoxy-4-methylbenzoyl chloride **33** or its derivatives like 148, hence we directed our efforts towards the synthesis of benzophenone precursor **35** by utilizing acid chloride **174** and its coupling with 3,5-dimethoxytoluene (**167**). Thus 3,5-dimethoxytoluene (**167**) was prepared by refluxing 3,5-dihydroxytoluene in dry acetone in presence of dimethyl sulphate and potassium carbonate.

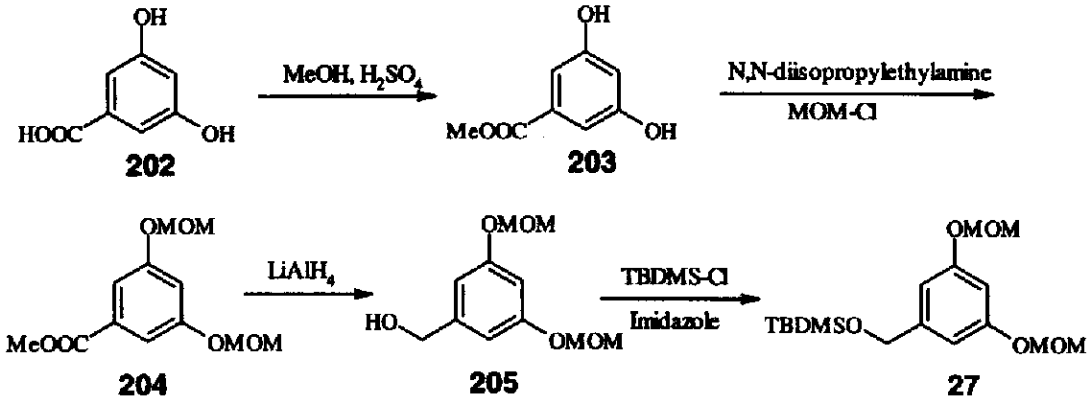
Ortho lithiation of 3,5 dimethoxytoluene (**167**) was carried out using n-BuLi at 0°C and its coupling with acid chloride **174** was expected to give the desired product **35** as shown in scheme-48, but this coupling resulted only in the recovery of starting materials **167** and acid **173** instead of the desired product **35**.

Scheme-48



The probable reasons for the failure of this reaction were either anion formed by ortho lithiation of **167** was not sufficiently stable to couple with acid chloride **174** or less reactivity of acid chloride **174** to afford the desired product **35**. To check these possibilities we planned to carry out this coupling reaction on the substrate **27** reported by Hollinshead et a1.[16] The presence of two MOM groups in compound **27** stabilizes the resulting anion through a six membered complex. Thus compound **27** was prepared starting from 3,5-dihydroxybenzoic acid (**202**) as shown in scheme-49. Esterification of acid **202** was carned out in refluxing methanol in presence of 2-3 drops of sulphuric acid to **203** in almost quantitative yield which was followed by MOM protection of the hydroxyl groups using MOM-CI in presence of N, N-diisopropylethyl amine to afford compound **204** in 76.6 % yield. ^{1}H NMR spectrum of the compound **204** displayed a singlet at 8 3.48 for 6 protons and a singlet at 8 5.18 for four protons indicating presence of two MOM groups and ester OMe at 8 3.88. Further reduction of this compound using lithium aluminum hydride afforded alcohol **205** in 79 % yield. Structure of benzyl alcohol **205** was confirmed by ^{1}H NMR showing presence of benzylic protons at 8 4.61.

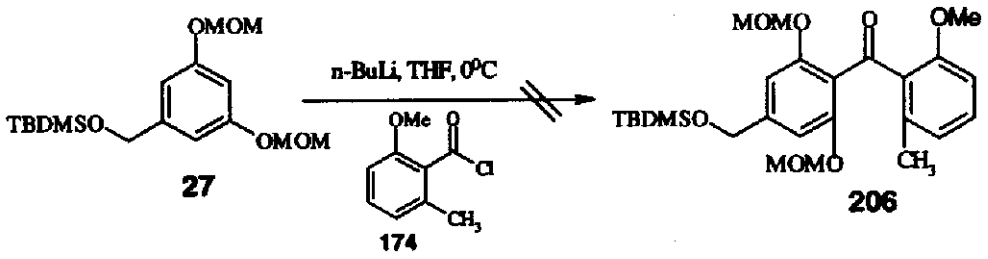
Scheme-49



Protection of the benzyl alcohol **205** as TBDMS ether **27**, was carried out by treating the compound **205** with TBDMS-Cl in presence of imidazole. The ^{1}H NMR spectrum of **27** revealed peaks at appropriate positions as reported by Hollinshead.l6

After the preparation of compound **27**, ortho lithiation was carried out under standard conditions using n-BuLi. Its coupling with acid chloride **174** was expected to give the desired intermediate **206** (scheme-50) but unfortunately this reaction failed even after stirring for 48 hrs as well as elevating temperature to 80 °C.

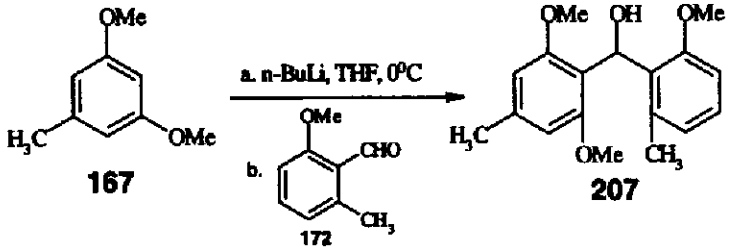
Scheme-50



Frustrations in these coupling approaches even after using compound **27**, which has been already utilized for ortho lithiation reaction by Hollinshead et a1.[16] suggested that less reactivity of acid chloride **174** was responsible for the failure in coupling reaction.

It was then decided to replace the acid chloride **174** by aldehyde **172** for coupling reaction, hence 3,5-dimethoxytoluene (**167**) was ortho lithiated using n-BuLi in refluxing THF followed by addition to aldehyde **172** at 0°C. The stirring was continued overnight. Usual workup followed by column chromatography yielded alcohol **207** in 30 % yield as shown in scheme 51.

Scheme-51



This alcohol **207** was fully characterized by means of spectroscopic analysis. The ^{1}H NMR revealed presence of two methyl groups as singlets at 8 2.30 and 2.32, presence of three methoxy groups as singlets at S 3.75 (two methoxy groups), 3.78 (one methoxy group) along with a doublet at 8 5.80 (exchanges with D_20), a doublet at 8 at 6.43 which collapses to a singlet

on D20 exchange (benzylic proton) and rest of the peaks at proper positions with appropriate integrations. The ^{13}C NMR displayed peaks at 8 19.96 and 22.16 indicating presence of two aromatic methyl groups while other peaks were in good agreement with the assigned structure. The structure for alcohol **207** was further confirmed by mass spectrum showing molecular ion peak at m/z 302.

Although this reaction resulted into the desired product, it was necessary to improve the yield to make it economical. To improve the yield in the lithiation reaction some modifications were carried out. The coupling of aldehyde **172** with 3,5-dimethoxytoluene (**167**) was attempted in refluxing THF for 24 hrs in presence of n-BuLi without improvement in the yield. Finally 3,5-dimethoxytoluene (**167**) was ortho lithiated using n-BuLi in presence of TMEDA at 0°C and coupled with the aldehyde **172** to afford the alcohol 207 in 70% yield.

Further oxidation of the benzylic alcohol **207** to desired intermediate **35** was carried out using Mn02 in methylene chloride at room temperature in 90 % yield. This compound showed spectroscopic data in good agreement with the compound **35** reported by Adams et al.[17] Oxidation of the compound **35** to the dicarboxylic acid **36**, an important precursor for benzophenone portion of balanol (**1**), has been reported by Adams et al.[17] using $KMnO_4$ and pyridine under reflux condition in 38 % yield. We directed our efforts towards the improvement of yield for this oxidation reaction.

Table-1: Oxidation of 1-methylnaphthalene to 1-naphthoic acid

Entry No.	Catalyst	Oxidant	Solvent	Yield
1	Cr-Zr	30%H_2O_2	CH_3CN	Complex mixture
2	Cr-Zr	70% TBHP	MeOH	No reaction
3	Cr-Zr	70% TBHP	CH_3CN	35%
4	Mn-Zr	70% TBHP	CH_3CN	33%
5	CO-Zr	70% TBHP	CH_3CN	30%
6	None	70% TBHP	CH_3CN	30%

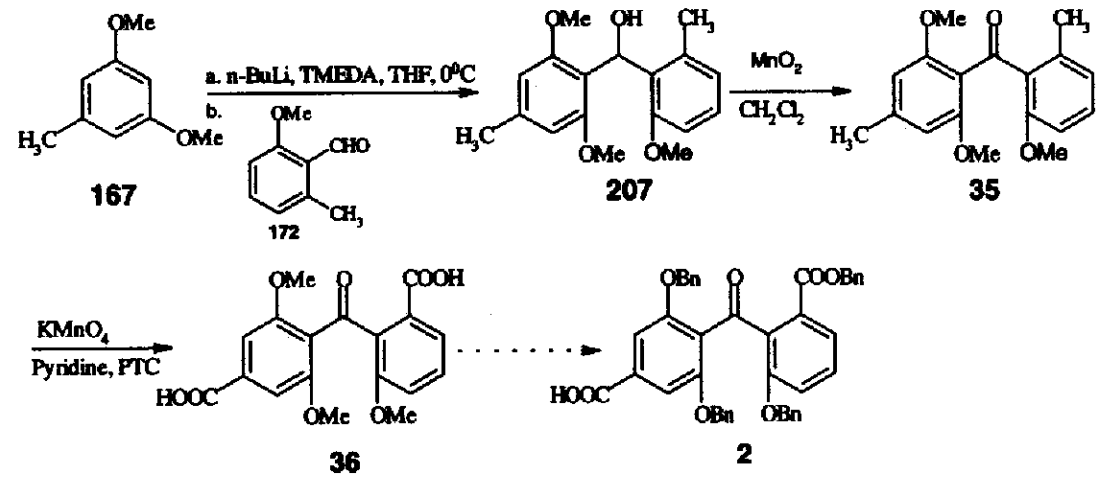
As a part of this study we explored use of different heterogeneous catalysts like Mn-Zr, Co-Zr, Cr-Zr under different conditions using 70 % TBHP and 30 % H_2O_2 as co-oxidants. Substrate selected for this study was 1-methyl naphthalene and results are shown in table-1.

Use of different catalysts could not improve the yield. Cr-Zr catalyst in refluxing acetonitrile using 70 % TBHP as co-oxidant improved yield only up to 35 %. Use of 30 % H202 resulted into complex reaction mixture whereas reaction did not proceed in refluxing methanol.

We also attempted use of $NaBiO_3$ in acetic acid, CrO_3 in acetic acid and anhydride, CrO_3 and periodic acid conditions for the oxidation of compound **35** to **36** but reaction ended up with the formation of a complex mixture.

Use of phase-transfer catalysts in oxidation reactions is well documented in the literature.[48] Considerable improvement in yields has been achieved by using phase transfer catalysts in many reactions. On this background we planned to oxidize compound **35** under similar conditions adopted by Admas et al.[17] by using $KMnO_4$, pyridine along with use of phase transfer catalyst tetrabutylammonium bromide as shown in scheme-52.

Scheme-52



Fortunately, this modification resulted into the improvement in yield up to 55 %. Thus a solution of potassium permanganate and pyridine in water was heated to 100 °C. To this mixture a solution of the compound **35** in pyridine was added followed by water and tetrabutylammonium bromide and allowed to reflux for 1 hr after which further quantities of $KMnO_4$ were added portionwise with continued stirring and heating. After 8 hr usual work yielded dicarboxylic acid.**36** in 65 % crude yield and 55 % yield after purification, which showed all spectroscopic data in good agreement with the values reported by Adams et al.[17]

2.2.3 CONCLUSION

In summary, an improved synthesis of dicarboxylic acid **36**, an important precursor for balanol benzophenone portion **2**, has been achieved via a short and efficient route starting from

commercially available chemicals in three steps using ortho-lithiation as the key step. In the earlier approach triketone compounds **159**, **164** and **176** have been synthesized which can be utilized as inhibitors of 4-hydroxyphenylpyruvate dioxygenase, an important enzyme involved in the biosynthesis of plastoquinones and tocopherols in plants as well as in the catabolism of the aromatic acids phenylalanine and tyrosine in most of the organisms. Aromatization of triketone **176** yielded xanthone **188** in 40 % yield. Triethylsilane reduction of compound **194** resulted into unexpected cyclized product **198** which can be oxidized to xanthone **188**, hence this method would be useful for the synthesis of a few substituted xanthones.

2.2.4 EXPERIMENTAL

Methyl crotonate (154):

To an ice cold solution of crotonic acid (100 gm, 1.16 mole) in dry methanol (1 lit) was added dropwise thionyl chloride (127 ml, 1.74 mole) over a period of 90 min at 0-5 °C. It was stirred overnight at room temperature. The reaction mixture was poured on crushed ice and extracted with ether. The combined ether layer was washed with sodium bicarbonate solution followed by dilute hydrochloric acid, water, dried (Na2S04) and concentrated. It was distilled under atmospheric pressure to afford methyl crotonate as colourless liquid (81.39 gm, 70 %); b.p. 121 °C (lit.[38] b.p.121 °C).

5-Methylcyclohexane-1,3-dione (151):

Sodium metal pieces (5.17 g, 0.226 mole) were added to dry methanol (1 lit) at a rate sufficient to maintain a gentle reflux. After all sodium reacted, methyl acetoacetate (29 g, 0.25 mole) was added dropwise over 1/2 hr. Methyl crotonate (22.6 g, 0.226 mol) was then added more rapidly. The yellow solution was very carefully heated to a gentle reflux for 44 hr, cooled and methanol was then removed under reduced pressure. KOH (25.31 g, 0.452 mol), dissolved in water (1 lit) was added to a stirred solution of above dione salt. The dark orange solution was heated to reflux and allowed to stand at that temperature for 4 hr. Most of the water was then removed by distillation under reduced pressure. Conc. HCl was added dropwise to adjust the pH of the reaction mixture (pH=6) at such a rate to maintain the gentle reflux. Carbon dioxide gas evolves at this stage, and then HCl was added until the colour of the solution turned to yellow and pH changed to 1 or 2. The yellow solution was kept at reflux until no more $C0_2$ was evolved. The solution was then quickly cooled to 0°C in order to precipitate the product out of acidic solution. The precipitate was filtered and mother liquor was extracted with ethyl acetate. The organic layer was then dried over sodium sulphate and evaporated in vacuo. The crude dione was recrystallized from ethyl acetate to give 5-methylcyclohexane-1,3-dione (**151**) as colourless needles, m. p. 128-130 °C(lit [37] m.p. 129.5-130 °C).

TYPICAL EXPERIMENTAL PROCEDURE FOR ENOL-ESTERS

A solution of benzoyl chloride (5 mmole) in anhydrous methylene chloride (Sml) was added dropwise to a stirred solution of 5-methyl-1, 3 cyclohexanedione (5 mmole) and pyridine (5.5 mmole) in anhydrous methylene chloride (lOml). The resulting mixture was then stirred overnight at room temperature. After completion of the reaction, the mixture was poured on crushed ice, followed by extraction with methylene chloride. The organic layer was washed

successively with dil HCI, a saturated solution of sodium bicarbonate, water, brine and dried over sodium sulphate. Evaporation of the solvent in vacuo yielded corresponding enolesters.

5-Methyl-3-oxo-1-phenylcarbonyloxy-1-cyclohexene (158)

Oil, (1.03 gm, 90%).

^{1}H-NMR ($CDCl_3$, 200 MHz): 8 1.10 (d, J=6 Hz, 3H), 2.10-2.70 (m, SH), 6.05 (s, 1H, olefinic), 7.48 (t, J=7.3 Hz, 2H, aromatic), 7.57-7.68 (m, 1H, aromatic), 8.08 (t, J=7.3 Hz, 2H, aromatic).

Mass (m/z): 230 (M^+).

1-(2-Methoxyphenylcarbonyloxy)-5-methyl-3-oxo-1-cyclohexene (163)

Oil, (1.10 gm, 84.6%).

^{1}H-NMR ($CDCl_3$, 200 MHz): 8 1.05 (d, J=6 Hz, 3H), 2.00-2.65 (m, SH), 3.87 (s, 3H, -OMe), 5.96 (s, 1H, olefinic), 6.92-7.00 (m, 2H, aromatic), 7.50 (t, J =7.2 Hz, 1H, aromatic), 7.85 (d, J=7.2 Hz, 1H, aromatic).

Mass (m/z): 260 (M^+).

1-Methyl 2-(5-methyl-3-oxo-1-cyclohexenyl) 3-methoxyphthalate (165)

A mixture of 2-carbomethoxy-6-methoxybenzoic acid (365 mg, 1.7 mmole), thionyl chloride (550 mg, 5 mmole), and dimethylformamide (catalytic amount 0.1 ml) was heated at reflux in dry benzene (25 ml) for 4 hr. Paper chromatography indicated the formation of a new compound. The solvent was distilled out to give crude 2-carbomethoxy-6-methoxybenzoyl chloride (**152**) as colourless semisolid. IR 1800 cm^{-1} (acid chloride).

A solution of 2-carbomethoxy-6-methoxybenzoyl chloride (387.6 mg, 1.7 mmole) in dry methylene chloride (5 ml) was added dropwise to a stirred solution of 5-methylcyclohexane-1,3-dione (201.6 mg, 1.6 mmole) and pyridine (0.14 ml, 1.76 mmole) in methylene chloride (10 ml). It was then stirred overnight at room temperature. After completion of the reaction, the mixture was poured on crushed ice and extracted with methylene chloride. The organic layer was washed successively with dil HCI, a saturated solution of sodium bicarbonate, water, brine and dried over sodium sulphate. Evaporation of the solvent in vacuo yielded ester **165** as a clear oil (386.6 mg, 76 %).

^{1}H-NMR ($CDCl_3$, 200 MHz): 8 1.15 (d, J=5.8 Hz, 3H), 2.07-2.85 (m, 5H), 3.89 (s, 6H, -0Me and -CO_2Me), 6.05 (s, 1H, olefinic), 7.18 (d, J=7.8 Hz, 1H, aromatic), 7.45 (t, J=7.3 Hz, 1H, aromatic), 7.65 (d, J--7.8 Hz, 1H, aromatic).

Mass (m/z): 318 (M^+).

2, 3-Dimethylanisole (170)

A mixture of 2, 3-dimethylphenol (23.18 gm, 0.19 mole), potassium carbonate (39.33 gm, 0.28 mole) and dimethyl sulphate (39.24 ml, 0.28 mole) in dry acetone (250 ml) was heated at reflux for 10 hr. After the completion of reaction, acetone was evaporated under reduced pressure and the residue was diluted with water (100 ml). The aqueous part was extracted with ethyl acetate, washed with water, dried over sodium sulphate and concentrated in vacuum to give compound **170** as brownish oil (23.25gm, 90 %); b.p. 199 °C (lit [48] b.p.199 °C).

Peroxydisulphate oxidation of 2, 3-dimethylanisole

To a stirred suspension of potassium peroxysulphate (21.6 g, 80 mmole) in water (140 ml) were added copper (II) sulphate pentahydrate (2 g, 8 mmole), 2, 3-dimethylanisole (5.44 g, 40 mmole) in acetonitrile (140 ml), and pyridine (6.5 ml, 80 mmole). The mixture was heated at 66-69 °C for 3 hr, cooled and filtered. The filtrate was extracted with ethyl acetate and the extract was washed with 2 M sodium hydroxide (2x100 ml), 4 M hydrochloric acid (50 ml) and brine. The solution was dried over sodium sulphate and evaporated to give brown oil containing alcohol **171** and aldehyde **172** in the ratio 1:2 by G. C. analysis.

2-Methoxy-6-methylbenzaldehyde (172)

The above mixture of aldehyde **172** and alcohol **171** (6 g) was heated under reflux in benzene (50 ml) with activated manganese dioxide (7.5 g) for 5 hr. The reaction mixture was filtered through Celite and evaporation of the filtrate yielded yellow oil. The column chromatographic purification over silica gel afforded pale yellow solid, (3.2 g, 54 %); m. p. 40-41 °C (lit.[41] m.p. 41.5-42 °C).

2-Methoxy-6-methylbenzoic acid (173)

The above mixture of aldehyde **172** and alcohol **171** (6 g) was dissolved in benzene (48ml) and added to powdered potassium permanganate (7.2 g, 45.6 mmole) in water (60 ml). Tetrabutylammonium iodide (0.42 g, 1.14 mmole) was added and the mixture was stirred vigorously at 34-36 °C. Further quantities of potassium permanganate were added after 30 min (7.2 g) and 90 min (3.6 g). After a further 30 min, reaction mixture was filtered through Celite and filtrate was acidified with conc. HCI. The aqueous part was extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulphate and evaporated in vacuum to give 2-methoxy-6-methylbenzoic acid (**173**) as a colourless solid (1.55 g, 23 %), m. p. 137-139 °C (lit.[41] m. p. 139 °C).

5-Methyl-3-oxo-1-cyclohexenyl 2-methoxy-6-methylbenzoate (175)

A mixture of 2-methyl-6-methoxybenzoic acid (**174**) (415 mg, 2.5 mmole), thionyl chloride (550 mg, 5 mmole), dimethylformamide (catalytic amount) and dry benzene (10 ml) was heated at reflux for 4 hr (paper chromatography indicated the formation of a new compound). The solvent was distilled out to give crude 2-methyl-6-methoxybenzoyl chloride as brownish semisolid. IR 1800 cm^{-1} (acid chloride).

A solution of 2-methyl-6-methoxybenzoyl chloride (460 mg, 2.5 mmole) in dry methylene chloride (5 ml) was added dropwise to a stirred solution of 5-methyl-1,3cyclohexanedione (**151**) (315 mg, 2.5 mmole) and pyridine (0.20 ml, 2.5 mmole) in methylene chloride (5 ml). It was then stirred overnight at room temperature. After the reaction, the mixture was poured on crushed ice and extracted with methylene chloride. The organic layer was washed successively with dil. HCI, a saturated solution of sodium bicarbonate, water, brine and dried over sodium sulphate. Evaporation of the solvent in vacuo yielded ester **175** (800 mg, 80 %) as a clear oil.

^{1}H-NMR ($CDCl_3$, 90 MHz):	S 1.13 (d, J--6 Hz, 3H), 2.00-2.65 (m including singlet for benzylic methyl at 8 2.25, 8H), 3.75 (s, 3H, -OMe), 5.85 (s, 1H, olefinic), 6.60-6.75 (m, 2H, aromatic), 7.15 (t, J=7.8 Hz, 1H, aromatic).
Mass (m/z):	274 (M^+)

TYPICAL EXPERIMENTAL PROCEDURE FOR ISOMERIZATION OF ENOL-ESTERS

Enolesters (2 mmole) in dry acetonitrile (5 ml) were treated with triethylamine (0.5 ml) and sodium cyanide (4 mmole). The reaction mixture was stirred at room temperature overnight. After completion of reaction (TLC), most of the acetonitrile was removed under reduced pressure, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulphate and concentrated to leave a residue which after the column chromatographic purification (silica gel 60-120 mesh, ethyl acetate-pet ether as fluent) afforded the corresponding triketone compounds as a turbid oils.

2-Benzoyl-3-hydroxy-5-methyl-2-cyclohexen-1-one (159)

Yield: 368 mg (80 %).

IR ($CHCl_3$): 1673 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz): 8 1.05 (d, J--5.8 Hz, 3H), 1.80-2.90 (m, SH), 7.25-7.57 (m, 3H, aromatic), 8.05 (d, J--7.8 Hz, 2H, aromatic).

Mass (m/z): 230 (M^+).

3-Hydroxy-2-(2'-methoxybenzoyl)-5-methyl-2-cyclohexen-1-one (164)

Yield: 374.4 mg (72 %).

IR ($CHCl_3$): 1680 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz): 8 1.15 (d, J=5.8 Hz, 3H), 2.09-2.88 (m, SH), 3.80 (s, 3H,-OMe), 6.90 (d, J=7.6 Hz, 1H, aromatic), 7.02 (t, J=7.6 Hz, 1H, aromatic), 7.30 (d, J--7.6 Hz, 1H, aromatic), 7.45 (t, J=7.6 Hz, 1H, aromatic).

Mass (m/z): 260 (M^+).

2,6-Dimethoxy-4-methylphenyl-phenylmethanone (160)

A solution of the compound **159** (920 mg, 4 mmole) and iodine (1 gm, 8 mmole) in dry methanol (10 ml) was heated under reflux for 6 hr. The solvent was evaporated under reduced pressure, chloroform was added and the chloroform layer was washed with saturated solution of sodium bicarbonate, saturated solution of sodium thiosulphate and water. Evaporation of the solvent in vacuo afforded a residue, which was purified over a silica gel column using pet ether-ethyl acetate as an eluent to yield **160** as a thick oil (614 mg, 61.6 %).

IR ($CHCl_3$): 1675 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 200 MHz): 8 2.38 (s, 3H, Ar-CH_3), 3.68 (s, 6H, 2X-OMe), 6.42 (s, 2H, aromatic), 7.38-7.42 (m, 2H, aromatic), 7.50-7.58 (m, 1H, aromatic), 7.82 (d, J--6.8 Hz, 2H, aromatic).

Mass (m/z): 256 (M^+, 50), 239 (20), 179 (100), 164 (25).

4-Benzoyl-3, 5-dimethoxybenzoic acid (161)

To a stirred solution of potassium permanganate (474 mg, 3 mmole) in water (3 ml) and pyridine (1 ml), 1N sodium hydroxide (2 ml) was added. To this stirred mixture, a solution of compound **160** (256 mg, 1 mmole) was added in pyridine (2 ml), followed by water (1 ml) and a pinch of tetrabutylammonium bromide. The mixture was then heated at 100 °C. After 1 hr, further quantities of potassium permanganate (474 mg, 3 mmole) were added and heating was continued until a total 15 equivalent of potassium permanganate had been added. The reaction mixture was then filtered through Celite, the residue obtained was washed with water and the filtrate was acidified by conc. HCI. Aqueous solution was saturated with sodium chloride and extracted with ethyl acetate. The combined extract was dried over sodium sulphate and evaporated to give **161** as a white foam (129 mg, 45 %).

IR (nujol): 3450, 1685 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz): 8 3.80 (s, 6H, 2X-OMe), 7.40 (s, 2H, aromatic) 7.41-7.55 (m, 2H, aromatic), 7.50 (d, J=8 Hz, 2H, aromatic), 7.85 (d, J=8 Hz, 2H, aromatic).

Mass (m/z): 286 (M^+, 100), 269 (15), 209 (90).

2-(2'-Methoxy-6'-methylbenzoyl)-5-methyl-1, 3-cyclohexanedione (176)

To a stirred solution of 2-methoxy-6-methyl benzoic acid (**173**) (498 mg, 3 mmole) in dry benzene (10 ml), thionyl chloride (0.43 ml, 6 mmole) and a drop of dimethylformamide were added. The resulting mixture was then refluxed for 6 hr. After completion of the reaction (checked by paper chromatography), benzene was removed by distillation to leave the acid chloride **174** as brownish semisolid.

IR (neat):1800 cm^{-1} (acid chloride).

Acid chloride **174** obtained above was used as such in further reaction without purification.

To a stirred solution of the acid chloride **174** and cyanotrimethylsilane (0.48 ml, 3.6 mmole) in dry methylene chloride (5 ml) under nitrogen atmosphere was added stannic chloride

(0.2 ml) at room temperature. The stirring was continued for further 2 hr, the colour of the solution changed from initial light yellow to dark brown. After the reaction, the mixture was poured into ice-cold water (10 ml) and extracted with methylene chloride. The combined methylene chloride layer was washed with brine, and dried over sodium sulphate. Evaporation of the solvent under reduced pressure afforded crude aryl cyanide **185** as brown coloured oil (334.6 mg, 85 %).

IR ($CHCl_3$): 2150, 1680 cm^{-1}.

Triethyl amine (1 ml) was added to a stirred solution of above aryl cyanide **185** (472 mg, 2.7 mmole) and 5-methylcyclohexane-1,3-dione (**151**) (378 mg, 3 mmole) in dry acetonitrile (5 ml) at room temperature and stirring was continued overnight. After completion of the reaction, acetonitrile was evaporated and the mixture was poured into ice-cold dil. HCl (10 ml). The reaction mixture was extracted with methylene chloride, the organic layer washed with water and dried over sodium sulphate. Evaporation of the solvent and purification by column chromatography over silica gel using 10 % ethyl acetate in pet ether afforded the triketone **176** (574 mg, 70 %) as pale yellow thick oil.

IR ($CHCl_3$):	1673 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz):	8 1.12 (d, J--5.8 Hz, 3H), 2.10-2.88 (m including singlet for benzylic methyl at 8 2.17, 9H), 3.72 (s, 3H, -OMe),6.65-6.90 (m, 2H, aromatic), 7.15-7.35 (m,1H, aromatic).
^{13}C NMR ($CDCl_3$, 50 MHz):	8 19.25, 21.05, 26.86, 41.09, 46.53, 55.97, 96.52, 108.50, 114.79, 122.91, 130.04, 135.08, 155.96, 193.56 (C=O), 197.16 (C=O), 199.04 (C=O).
Mass (m/z):	274 (M^+, 5), 259 (M-15, 8), 243 (90), 166 (50), 148(100).
Analysis:	Calculated for $C1_6H_{18}O_4$, C 70.06, H 6.60;
	Found. C 70.00, H 6.61 %.

Aromatization of compound 176

The compound **176** (274 mg, 1 mmole) was taken in glacial acetic acid (3 ml) in a round bottom flask attached with a small path distillation condenser under argon atmosphere.

To this was added mercuric acetate (956 mg, 3 mmole) and sodium acetate (246 mg, 3 mmole). The reaction mixture was heated at 120 °-125 °C so that the clear liquid turned to voluminous precipitate that was again redissolved to give brown coloured liquid with separation of mercury (2-3 hr). The mixture was cooled and then 1N HCl (5 ml) was added and allowed to boil for 30 min. Ethyl acetate was added after cooling and the mixture was filtered through a pad of Celite. The ethyl acetate layer was separated, washed with brine, dried over sodium sulphate and concentrated in vacuo. TLC of the reaction mixture indicated the formation of two compounds. The column chromatographic separation on silica gel afforded the xanthone **188** (96 mg, 40 %, non polar) and the required compound **189** (54.40 mg, 20 %, polar). Both the compounds were characterized by spectroscopic means.

1-Hydroxy-3,8-dimethyl-9H-9-xanthenone (188)

Pale yellow thick oil, (96 mg, 40%).

IR ($CHCl_3$): 3290, 1670 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 2.41 (s, 3H, Ar-CH_3), 2.89 (s, 3H, Ar-CH_3), 6.55 (s,1H, aromatic), 6.65 (s, 1H, aromatic), 7.07 (d, J=8 Hz,1H, aromatic), 7.25 (d, J=8 Hz, 1H, aromatic), 7.52 (t, J--8 Hz, 1H, aromatic), 12.86 (s, 1H, -OH).

Mass (m/z): 240 (M^+, 100), 222 (12), 211 (30).

1-Methoxy-3, 8-dimethyl-9H-9-xanthenone (188a)

To the stirred solution of compound **188** (90 mg, 0.37 mmole) and potassium carbonate (76 mg, 0.55 mmol) in dry acetone (2 ml) was added dimethyl sulfate (51.28 mg, 0.40 mmole). The resulting reaction mixture was refluxed for 8 hrs. The acetone was then removed under reduced pressure and the residue was diluted with ice-cold water (5 ml) followed by extraction with ethyl acetate. The combined ethyl acetate layer was washed with water, brine and dried over sodium sulphate to leave white foam, (81 mg, 85 %).

IR ($CHCl_3$): 1680 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 2.45 (s, 3H, Ar-CH_3), 2.90 (s, 3H, Ar-CH_3), 4.01 (s,3H, -Me), 6.56 (s, 1H,aromatic), 6.81 (s, 1H,aromatic), 7.06 (d, J=7.2Hz, 1 H, aromatic), 7.24(d, J=7.2 Hz, 1 H, aromatic), 7.46 (t, J=7.2 Hz, 1 H,aromatic).

Mass (m/z): 2S4 (M^+, 100), 240 (70).

2,6-Dimethoxy-4-methylphenyl-2'-methoxy-6'-methylphenylmethanone (35)

A mixture of the compound **189** (54 mg, 0.2 mmole), dimethyl sulphate (O.OS ml, O.SS mmole) and potassium carbonate (100 mg, 0.72 mmole) in dry acetone (S ml) was refluxed for 6 hrs. The acetone was then evaporated under reduced pressure and the residue was diluted with water (S ml), extracted with ethyl acetate and concentrated to give the benzophenone **35** as a white solid (S4 mg, 90 %), m.p. 133-3S °C (lit. [17] m.p.132-133 °C).

IR ($CHCl_3$): 1675 cm^{-1}.

^1H NMR ($CDCl^3$, 200 MHz): 8 2.32 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3), 3.58 (s,3H, -OMe), 3.66 (s, 6H, -OMe), 6.35 (s, 2H, aromatic), 6.68 (d, J=8 Hz, 1 H, aromatic), 6.79 (d, J=8 Hz, 1 H, aromatic), 7.17 (t, J--8 Hz, 1H, aromatic).

Mass (m/z): 300 (M^+, 15), 269 (100).

Analysis: Calculated for $C_{18}H_{20}O_4$, C 71.99; H 6.70;
Found C 72.23, H 6.90 %.

2-(2'-Methoxy-6'-methylphenylmethylene)-5-methyl-1,3-cyclohexanedione(194)

Piperidine (500 mg) was added to a stirred solution of 5-methylcyclohexane-1,3-dione (**151**) (1.26 gm, 0.01 mole) and the aldehyde **172** (1.8 gm, 0.012 mole) in glacial acetic acid (3 ml) at 0°C under nitrogen atmosphere. The stirring was continued for 30 min and slowly allowed to warm up to room temperature. After completion of the reaction, the mixture was poured into ice-cold water (10 ml) and extracted with chloroform. The combined organic layer was washed with brine and dried over sodium sulphate. Evaporation of the solvent under reduced pressure yielded compound **194** as a reddish solid (1.54 gm, 60 %), m. p. 9S-97 °C.

IR ($CHCl_3$): 1721 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 1.15 (d, J--S.6 Hz, 3H), 2.25 (s, 3H), 2.10-2.50 (m, SH), 3.75 (s, 3H -OMe), 6.72 (d, J=8 Hz, 1H, aromatic), 6.80 (d, J=8 Hz, 1H, aromatic), 7.20 (t, J=8 Hz, 1H, aromatic), 7.90 (s, 1H, olefinic).

Reduction of compound 194

To a stirred solution of the compound **194** (2.58 gm, 0.01 mole) in dry carbon tetrachloride (20 ml) was added triethyl silane (1.16 gm, 1.59 ml, 0.01 mole) and trifluroacetic acid (11.4 gm, 7.76 ml, 0.1 mole) at room temperature under argon atmosphere. The reaction mixture was then stirred at 55-60 C for 3 hr. After completion of the reaction, the mixture was poured into ice-cold water (50 ml) and extracted with ethyl acetate. The organic layer was washed with water, brine and dried over sodium sulphate. TLC examination of the reaction mixture showed formation of two compounds. The column chromatographic separation afforded compound **198** in 50 % yield and compound **199** in 40 % yield as white crystals (characterized after aromatization).

3,8-Dimethyl-2, 3, 4, 9-tetrahydro-1H-1-xanthenone (198)

Colourless solid, (1.14 gm, 50 %); m.p. 141-142 °C.

IR ($CHCl_3$): 1680 cm^{-1}.

^1H NMR($CDCl_3$, 200 MHz): 8 1.13 (d, J--5.6 Hz, 3H), 2.07-2.70 (m including singlet for benzylic methyl at 8 2.27, 8H), 3.31 (d, J=14.8 Hz, 1H, C-9), 3.43 (d, J--14.8 Hz, 1H, C-9), 6.80 (d, J=7.8 Hz, 1 H, aromatic), 6.92 (d, J=7.8 Hz, 1 H, aromatic), 7.07 (t, J--7.8 Hz, 1H, aromatic).

^{13}C NMR ($CDCl_3$, 50 MHz): 8 18, 20, 22, 28, 35, 45, 109, 114, 119, 126, 128, 138,150, 165, 198 (C-1, C=O).

Mass (m/z): 228 (M^+, 100), 213 (M-15, 25), 195 (10), 185 (15), 171 (20).

l, 3-Dimethoxy-2-(2'-methoxy-6'-methylbenzyl)-5-methylbenzene (201)

The compound **199** (260 mg, 1 mmole) was treated with iodine (254 mg, 2 mmole) in dry methanol (10 ml) under reflux for 6 hr. After completion of the reaction, methanol was evaporated under reduced pressure, chloroform was added and chloroform layer was washed with saturated solution of sodium thiosulphate and water. Evaporation of the solvent and column chromatographic purification of the residue afforded compound **201** (200 mg, 69.93%) as white crystals; m. p.108-111 °C.

IR ($CHCl_3$): 1582 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 2.45 (s 3H, Ar-CH_3), 2.52 (s, 3H, Ar-CH_3), 3.86 (s, 6H,-OMe), 3.94 (s, 3H, OMe), 4.22 (s, 2H, benzylic),

	6.54 (s, 2H, aromatic), 6.85-6.97 (m, 2H, aromatic), 7.22 (t, J--7.2 Hz, 1H, aromatic).
^{13}C NMR ($CDCl_3$, 50 MHz):	8 18.85, 19.58, 21.09, 54.95, 104.53, 107.73, 114.53,121.88, 124.82, 128.68, 135.67, 137.54, 157.50, 157.79.
Mass (m/z):	286 (M^+, 25), 165 (35), 134 (100).
Analysis:	Calculated for $C_{18}H_{22}O_3$, C 75.50, H 7.73;
	Found C 76.48, H 7.68 %.

1-Methoxy-3, 8-dimethyl-9H-xanthene (200)

The compound **198** (228 mg, 1 mmole) was treated with iodine (254 mg, 2 mmole) in refluxing methanol (10 ml) for 8 hrs. After completion of the reaction, the methanol was removed under reduced pressure and chloroform was added to it. The chloroform layer was washed with saturated solution of sodium thiosulphate followed by washing with water. Evaporation of the chloroform afforded yellowish residue which on column chromatographic purification on silica gel (60-120 mesh) yielded compound **200** (180 mg, 75 %) as white soilid; m. p. 97-100 °C.

IR ($CHCl_3$):	1577 cm^{-1}.
^{1}H NMR($CDCl_3$, 200 MHz):	8 2.32 (s, 6H, Ar-CH_3), 3.75 (s, 2H, benzylic), 3.85 (s, 3H, - Me), 6.39 (s, 1H, aromatic), 6.50 (s, 1H, aromatic), 6.80-6.95 (m, 2H, aromatic), 7.10 (t, J=7.2 Hz, 1 H, aromatic).
Mass (m/z):	240 (M^+, 50), 239 (80), 225 (70), 209 (100).

Methyl-3, 5-dihydroxybenzoate (203)

To a stirred solution of 3, 5-dihydroxy benzoic acid (1.54 gm, 0.01 mole) in dry methanol (10 ml), conc. sulphuric acid (2-3 drops) was added and the reaction mixture was refluxed for 5-6 hr, methanol was then removed under reduced pressure and the residue was diluted with water (10 ml), followed by extraction with ethyl acetate. The combined organic layer was washed with brine and dried over sodium sulphate. Evaporation of the solvent afforded methyl 3, 5-dihydroxybenzoate as a white solid (1.59 gm, 95 %); m.p. 167-169 °C (lit.[49] m.p. 168-170 °C).

Methyl 3,5-bis-(methoxymethoxy) benzoate (204)

MOM-Cl (2.98 ml, 0.039 mole) was added dropwise to an ice-cold solution of N,N diisopropylethylamine (7.59 ml, 0.044 mole) and methyl 3,5-dihydroxy benzoate (3.0 gm, 0.017 mole) in dry methylene chloride (20 ml). After addition, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was then poured into water and the organic layer was separated. The aqueous part was extracted with methylene chloride and the combined organic layer was washed with 10 % CuSO4 solution and dried over sodium sulphate. Evaporation of the solvent followed by column chromatographic purification on silica gel (60-120 mesh) afforded compound **204** as a clear oil (3.45 gm, 76.6 %).

^{1}H NMR($CDCl_3$, 200 MHz): 8 3.48 (s, 6H), 3.88 (s, 3H), 5.18 (s, 4H), 6.85-6.87 (m, 1H), 7.30-.40 (m, 2H).

3, 5-Bis(methoxymethoxy)phenyhnethanol (205)

The compound **204** (1.28 gm, 0.5 mmole) in dry THF (S ml) was added to lithium aluminum hydride (247 mg, 0.65 mmole) in THF (6.5 ml) dropwise at 0°C under argon atmosphere. After the addition, the mixture was stirred at room temperature for 2.5 hr. After the completion of the reaction, 0.1 ml H_2O, and 15 % KOH were added subsequently to decompose the excess lithium aluminum hydride. The mixture was stirred overnight, filtered and the filtrate was washed with ethyl acetate. The combined ethyl acetate layer was dried over sodium sulphate and concentrated in vacuo to give 205 as clear oil (900 mg, 79 %).

^{1}H NMR($CDCl_3$, 200 MHz): 8 3.45 (s, 6H), 4.61 (s, 2H), 5.14 (s, 4H), 6.62-6.64 (m,1H), 6.68-6.70 (m, 2H).

3,5-Bis (methoxymethoxy)-1-{(tert-butyldi-methylsilyl)oxy}methyl benzene (27)

A solution of tert-butyldimethylsilyl chloride (0.85 ml, 0.46 mmole) in anhydrous methylene chloride (10 ml) was added to a stirred mixture of imidazole (313 mg, 0.46 mmole) and alcohol 205 (889 mg, 0.39 mmole) in dry methylene chloride (5 ml). The reaction mixture was stirred overnight and poured into water. The organic layer was separated, washed with 10 % $CuSO_4$ solution, brine, dried over sodium sulphate and evaporated. The residue was filtered through a column of silica (SiO_2, 10:1 pet-ether-ethyl acetate elution) to give compound 27 (.06 mg, 80 %) as a colourless oil.

IR ($CHCl_3$): 1560 cm^{-1}

^{1}H NMR($CDCl_3$, 200 MHz): 8 0.10 (s, 6H), 0.95 (s, 9H), 3.48 (s, 6H), 4.70 (s, 2H), 5.15 (s, 4H), 6.62-6.65 (m, 1H), 6.68-6.70 (m, 2H).

1-{(2,6-Dimethoxy-4-methyl)phenyl}hydroxymethyl-2'-methoxy-6'-methylbenzene (207)

n-BuLi (1.5 ml of a 1.4 M solution in hexane, 2.1 mmole) was added dropwise to a stirred solution of the compound **167** (304 mg, 2 mmol) and TMEDA (0.31 ml, 2.1 mmole) in anhydrous THF (5 ml) at room temperature under argon atmosphere. The mixture was stirred for 5 hr whereupon it was added to a solution of the aldehyde **172** (345 mg, 2.3 mmole) in anhydrous THF (5 ml) at 0°C. The resulting light yellow solution was stirred at 0°C for 2 hr and at room temperature overnight (the colour changes from light yellow to dark brown). The reaction mixture was then quenched with saturated solution of ammonium chloride, ice cold water was added and extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine and dried over sodium sulphate. Evaporation of the solvent and purification by column chromatography afforded alcohol **207** (423 mg, 70 %) as yellow solid; m. p. 125-28°C.

^{1}H NMR ($CDCl_3$, 200 MHz): 8 2.30 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 3.75 (s, 6H, 2XOMe), 3.78 (s, 3H, -OMe), 5.80 (d, J=10 Hz, 1H,exchanges with D20), 6.37 (s, 2H, aromatic), 6.43 (d, J=8.2 Hz, 1H, aromatic), 6.75 (d, J=8.2 Hz, 1H,aromatic), 7.07 (t, J=8.2 Hz, 1 H, aromatic).

^{13}C NMR ($CDCl_3$, 50 MHz): 8 19.96, 22.16, 56.16, 67.69, 105.99, 109.96, 117.13,123.69, 127.36, 131.05, 137.61, 138.41, 158.40, 159.0.

Mass (m/z): 302 (M^+, 25), 284 (85), 269 (60), 253 (40), 179 (100).

Analysis: Calculated for $C_{18}H_{22}O_4$, C 71.50, H 7.32;
Found C 71.58, H 7.24 %.

2, 6-Dimethoxy-4-methylphenyl 2'-methoxy-6'-methylphenyl ketone (35)

Manganese dioxide (1.304 g, 15 mmole) was added in portions to a stirred solution of the alcohol **207** (302 mg, 1 mmole) in anhydrous methylene chloride at room temperature and mixture was stirred overnight. The catalyst was removed by filtration through Celite and the residue was washed with methylene chloride. The filtrate was evaporated to provide the benzophenone **35** (270 mg, 90 %) as white crystals; m.p. 133-135 °C (lit.[17] 132-133 °C).

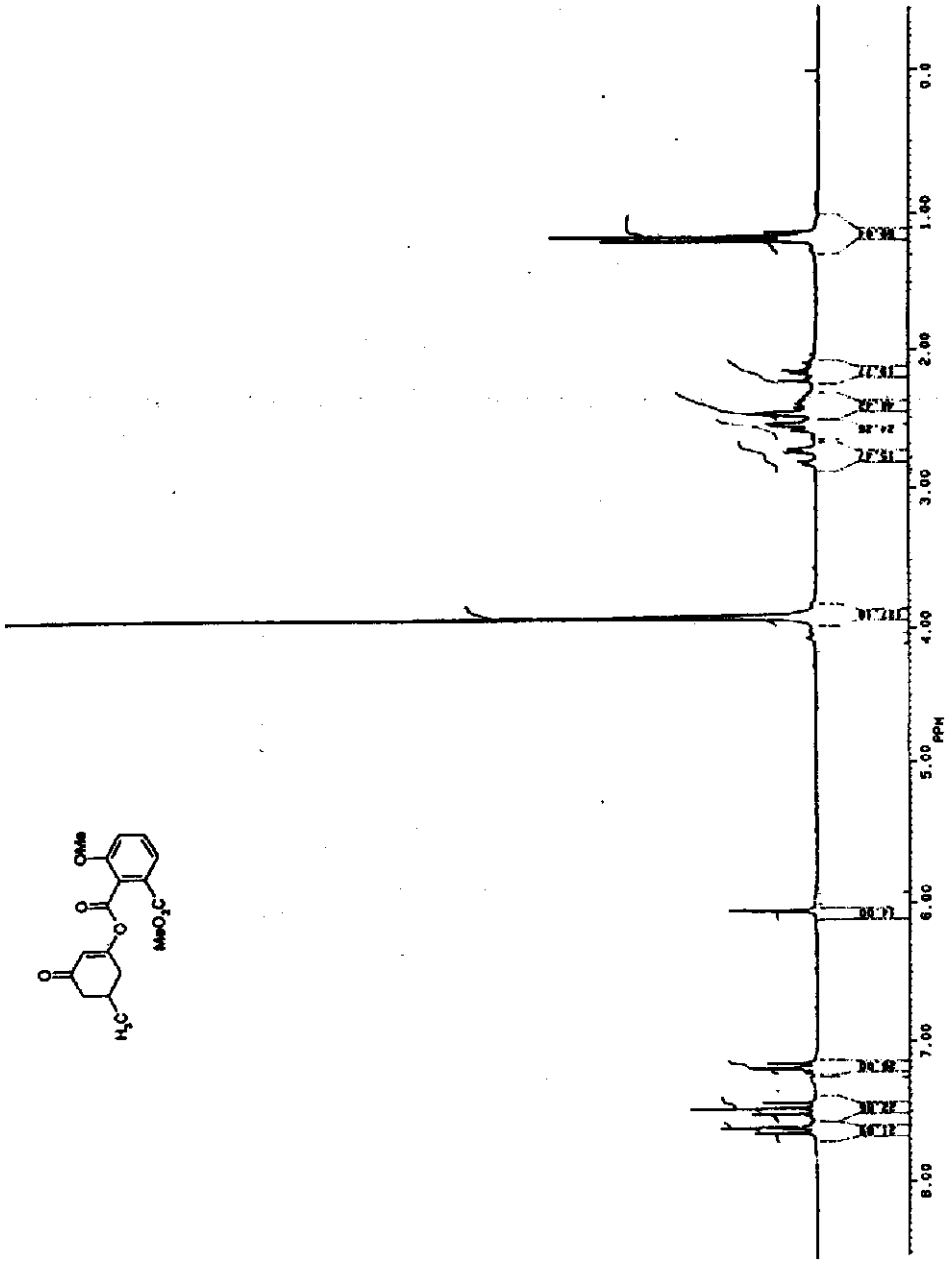
IR ($CHCl_3$): 1675 cm^{-1}.

^{1}H NMR ($CDCl_3$, 200 MHz):	8 2.32 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3), 3.58 (s, 3H, - e), 3.66 (s, 6H, 2X-OMe), 6.35 (s, 2H, aromatic), 6.68 (d, J=8 Hz, 1H, aromatic), 6.79 (d, J=8 Hz, 1H, aromatic), 7.17 (t, J=8 Hz, 1H, aromatic).
Mass (m/z):	300 (M^+,15), 269 (100).
Analysis:	Calculated for $C_{18}H_{20}O_4$, C 71.99; H 6.70;
	Found C 72.23; H 6.90 %.

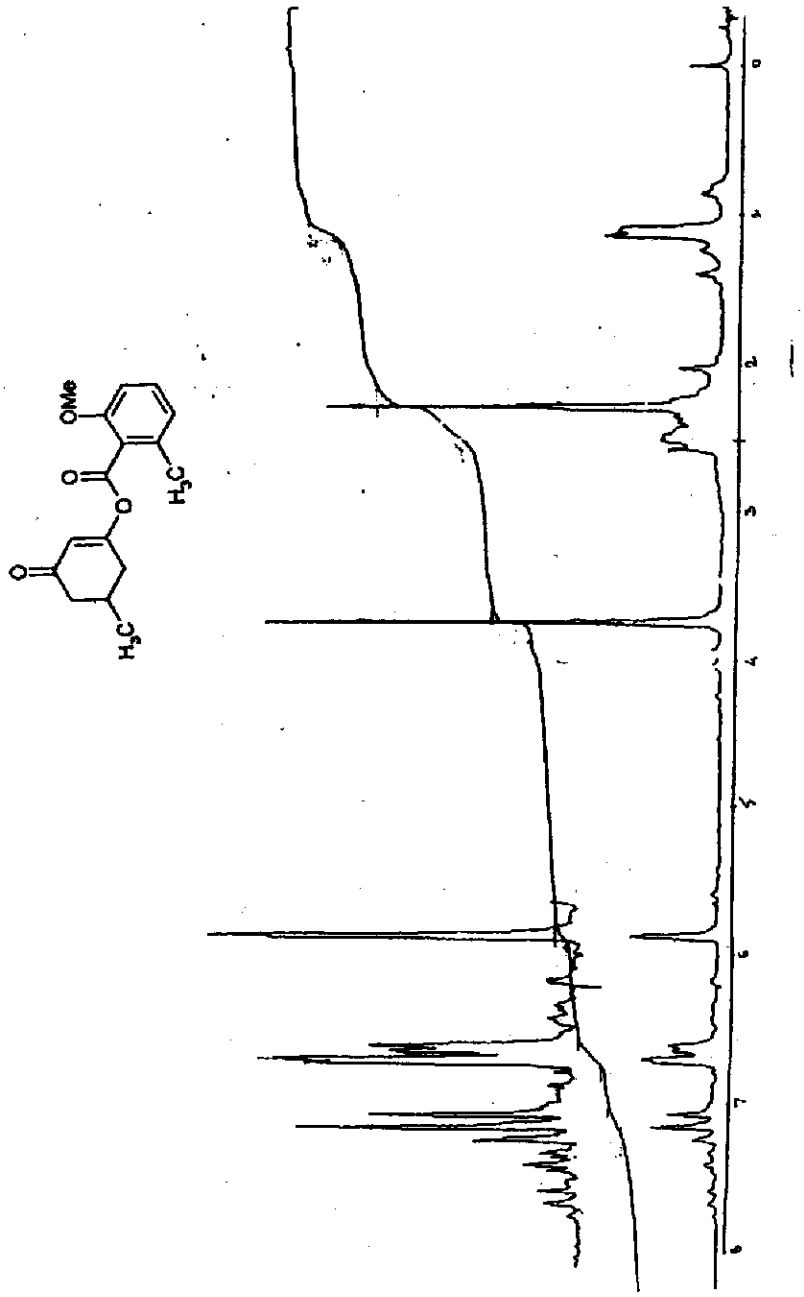
4-Carboxy-2, 6-dimethoxyphenyl 2'-car6oxy-6'-methoxyphenyl ketone (36):

To a stirred solution of potassium permanganate (284 mg, 1.8 mmole) in water (3 ml) and pyridine (1 ml), a solution of the compound **35** (180 mg, 0.6 mmole) was added in pyridine (2 ml), followed by water (1 ml) and pinch of tetrabutylammonium bromide. The mixture was then heated at 100 °C. After 1 hr further quantities of potassium permanganate (284 mg, 1.8 mmol) were added and heating was continued until a total of 24 equivalents had been added. The reaction mixture was then filtered through Celite. The residue was washed with water (5 ml) and the filtrate was acidified with conc. HCI. The aqueous solution was saturated with sodium chloride and extracted with ethyl acetate. The combined extract was dried over sodium sulphate and evaporated to give white solid which on column chromatographic purification yielded acid 36 as colourless solid (118.8 mg, 55 %); m.p. 25355 °C (lit.[17] 253-256 °C).

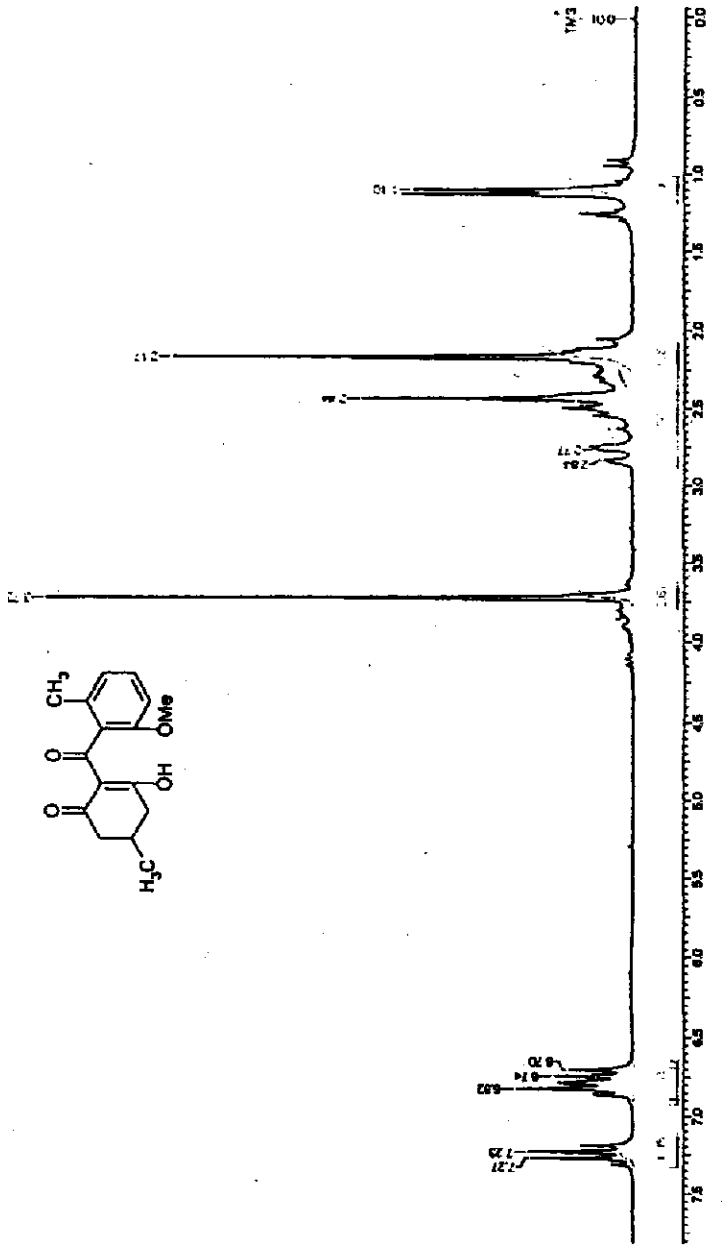
IR ($CHCl_3$):	3400, 1675 crri 1.
^{1}H NMR (Acetone d6, 200 MHz):	8 3.76 (s, 3H, -OMe), 3.82 (s, 6H, 2X-OMe), 7.33 (d, J=8 Hz, 1H, aromatic), 7.38 (s, 2H, aromatic), 7.50 (d, J—8 Hz, 1H, aromatic), 7.57 (t, J=8 Hz, 1H, aromatic).
Mass (m/z):	360 (M^+, 10), 342 (8), 315 (25), 299 (30), 285 (90), 209 (98), 195 (100).
Analysis:	Calculated for $C_{18}H_{16}O_8$, C 60.01; H 4.47;
	Found C 60.07; H 4.60 %.



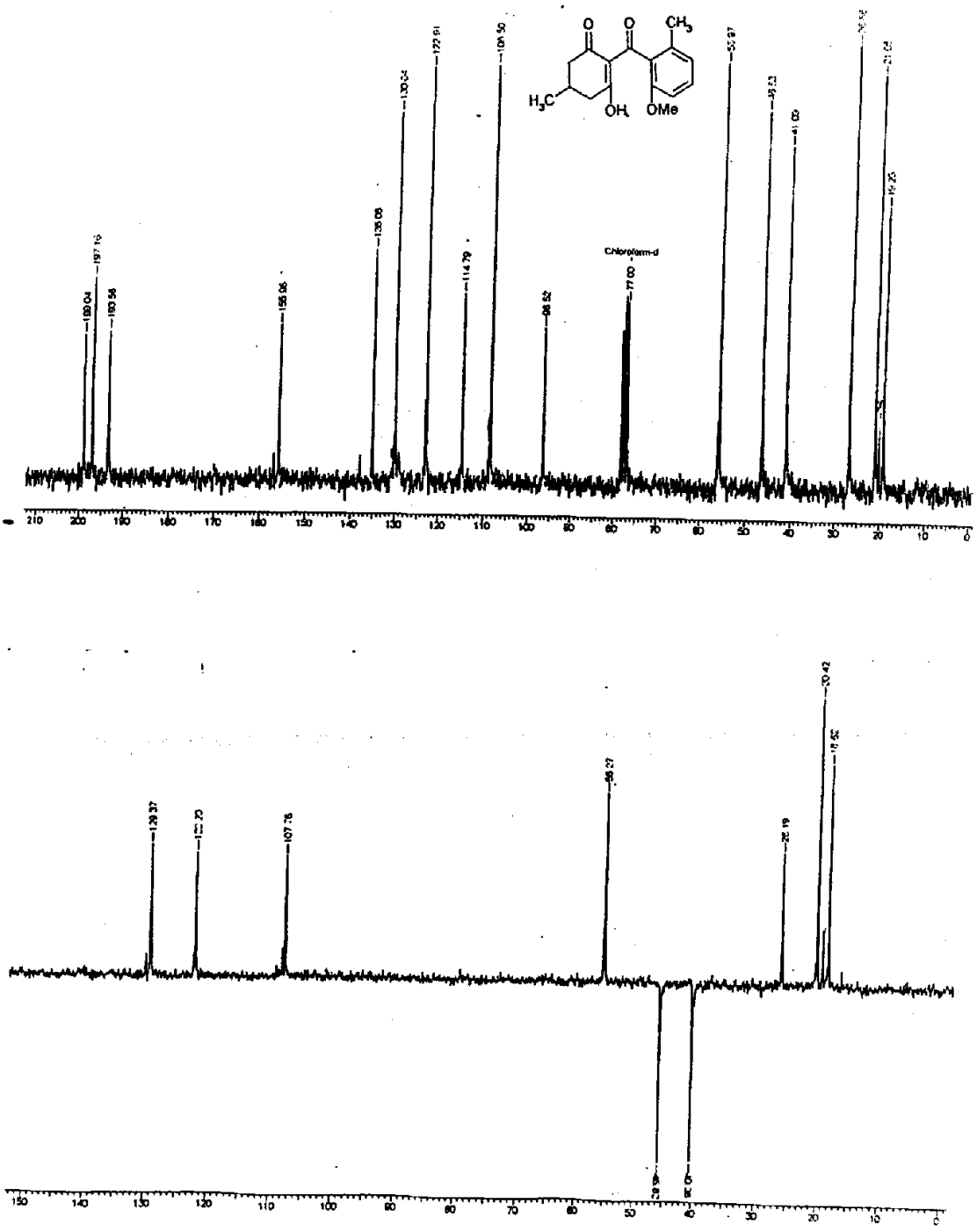
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **165** IN $CDCl_3$



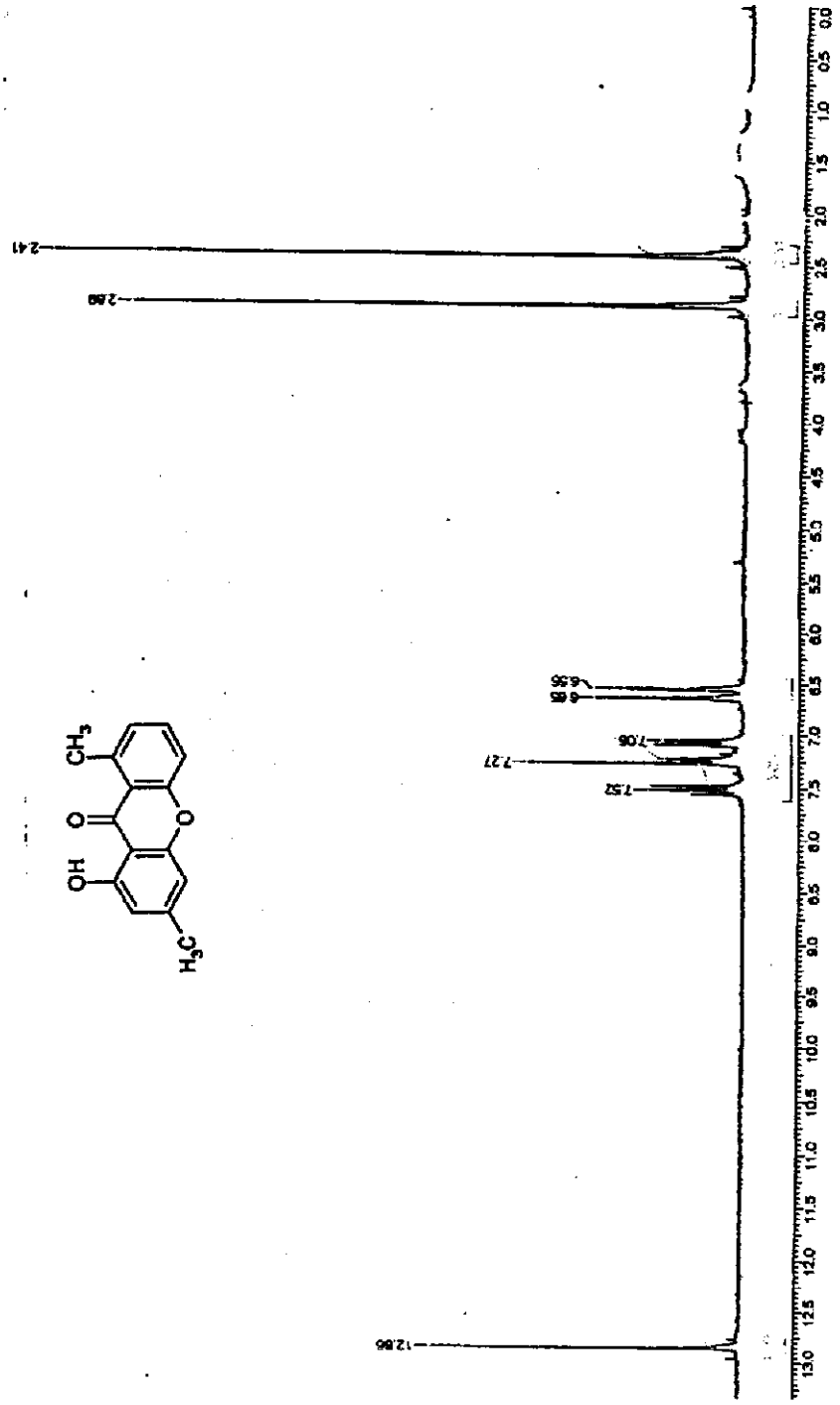
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **175** IN $CDCl_3$



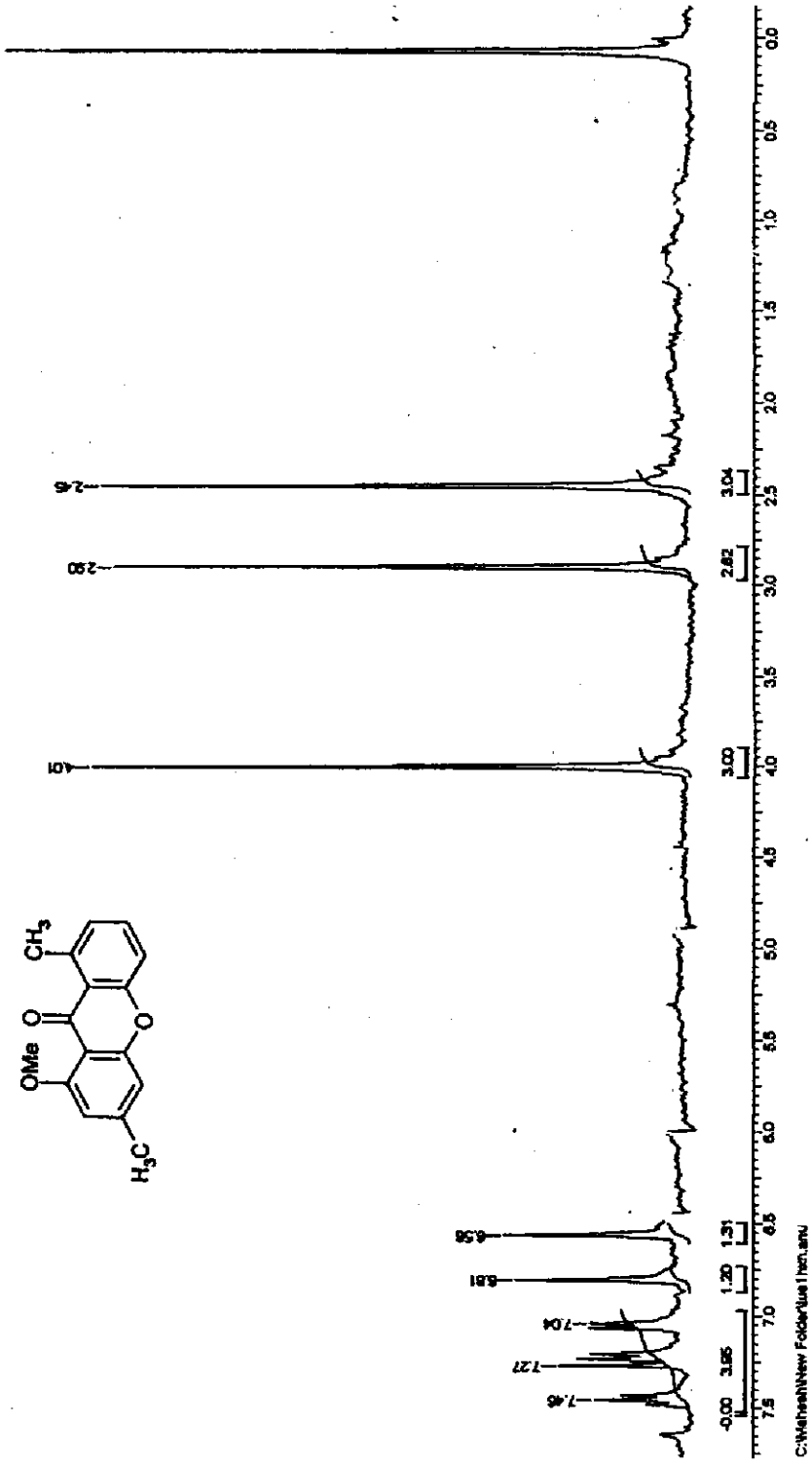
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **176** IN $CDCl_3$



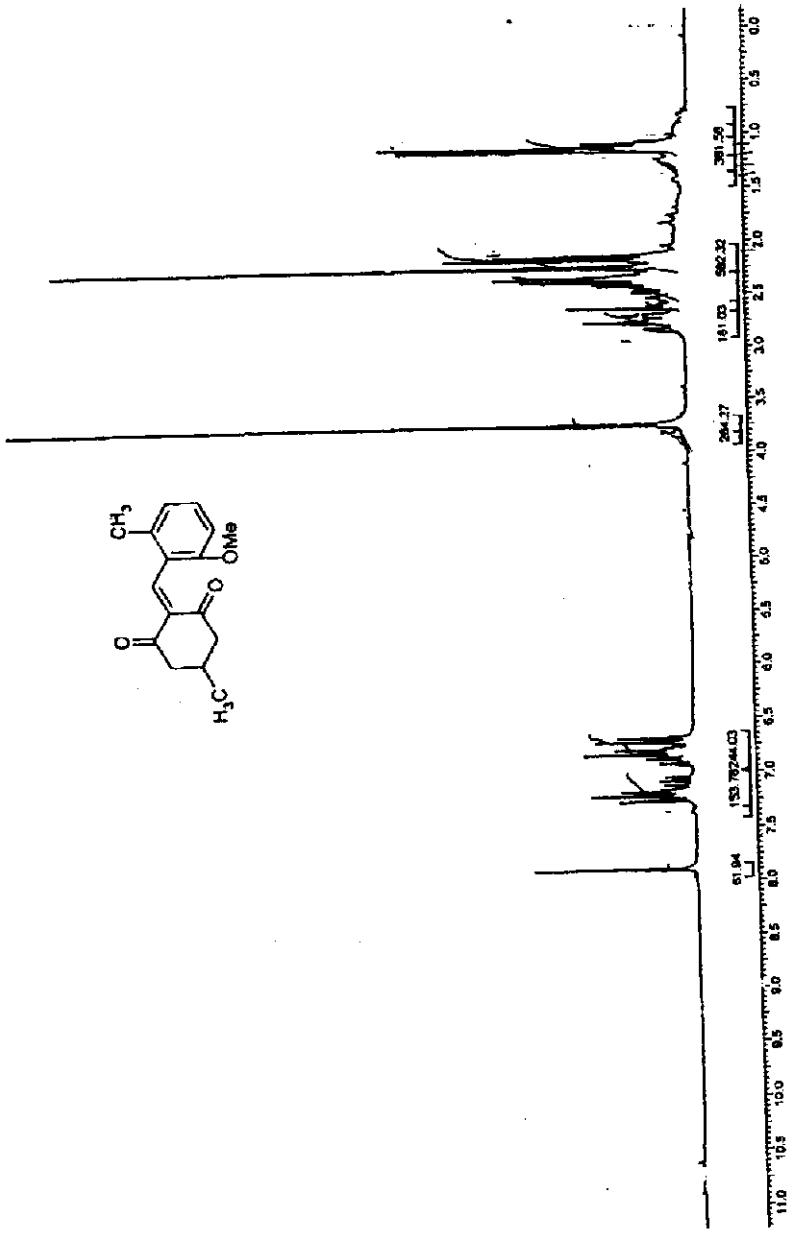
^{13}C NMR SPECTRUM (50MHz) AND DEPT OF THE COMPOUND **176** IN $CDCl_3$



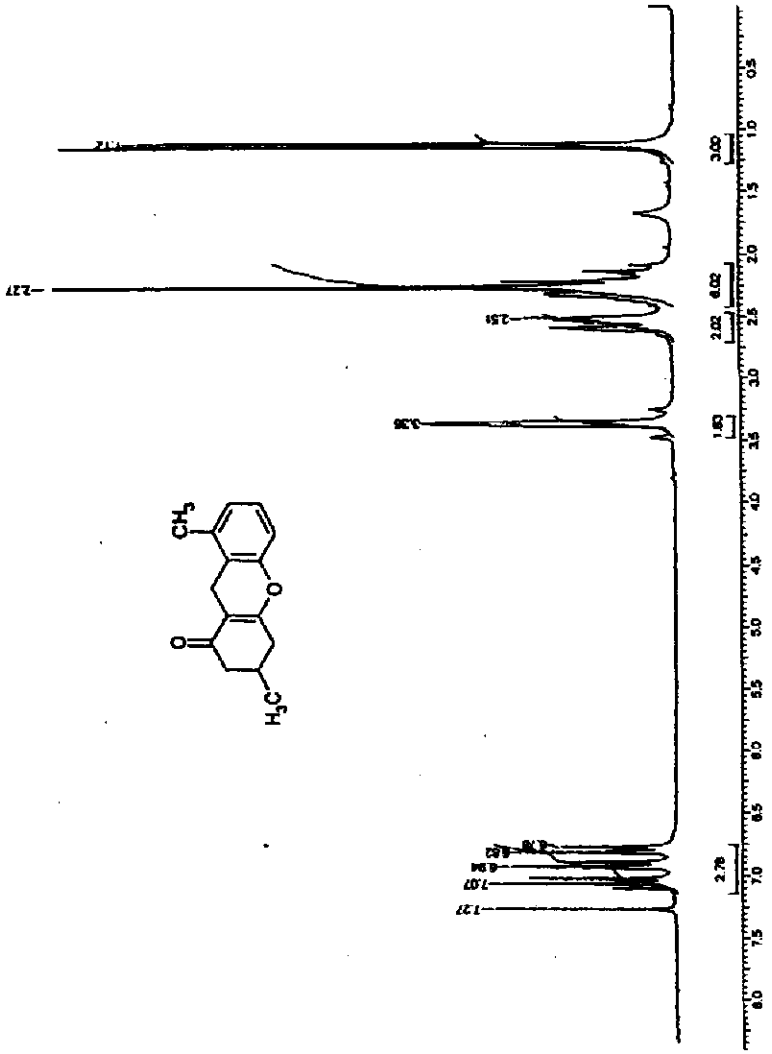
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **188** IN $CDCI_3$



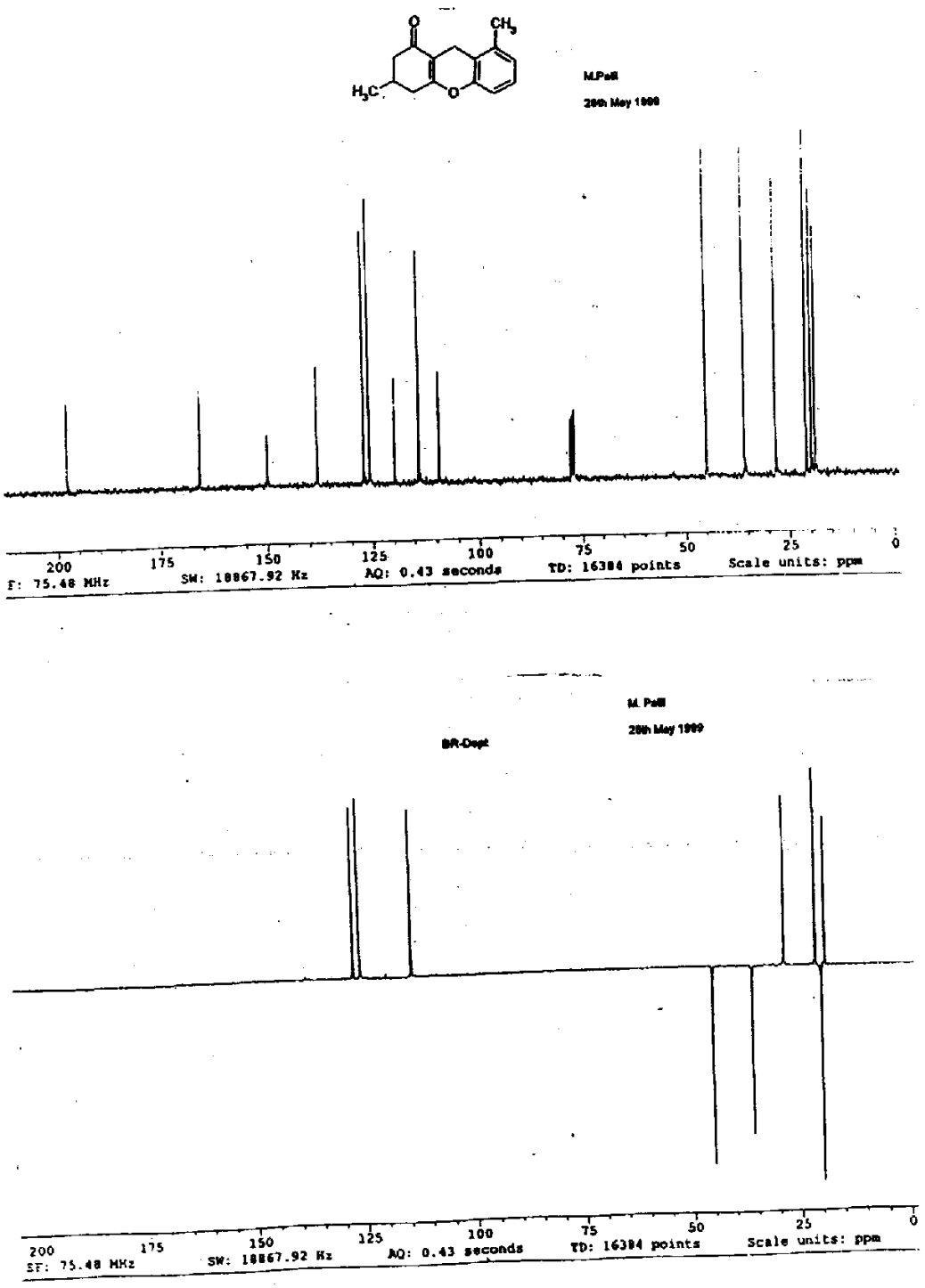
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **188a** IN $CDCI_3$



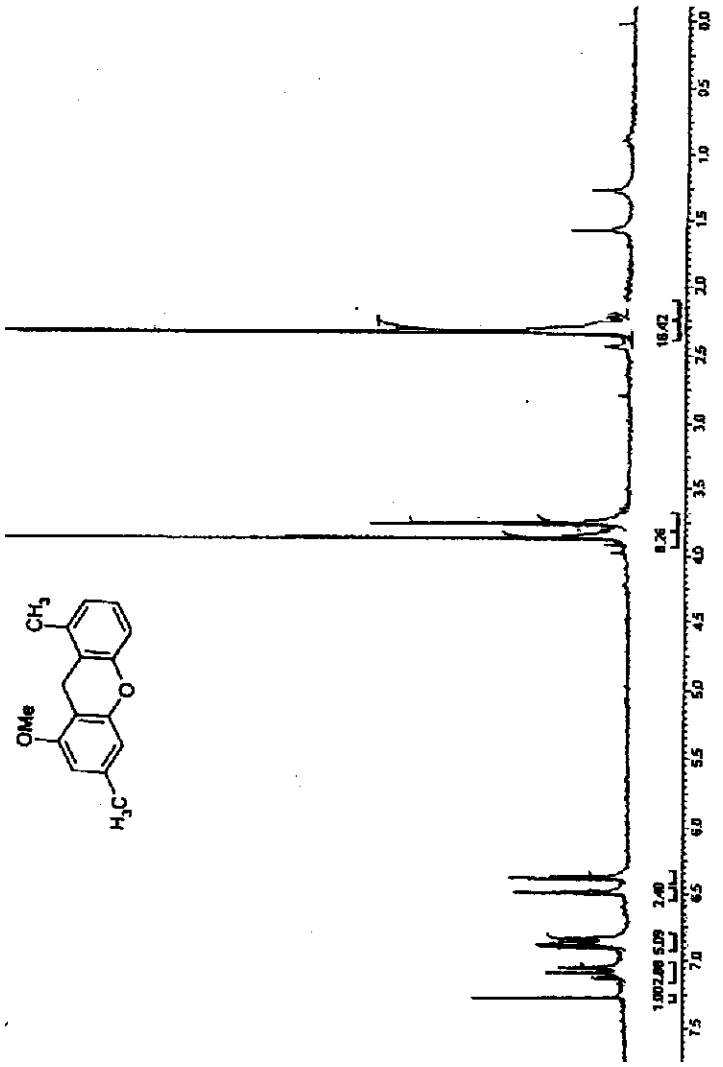
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **194** IN $CDCl_3$



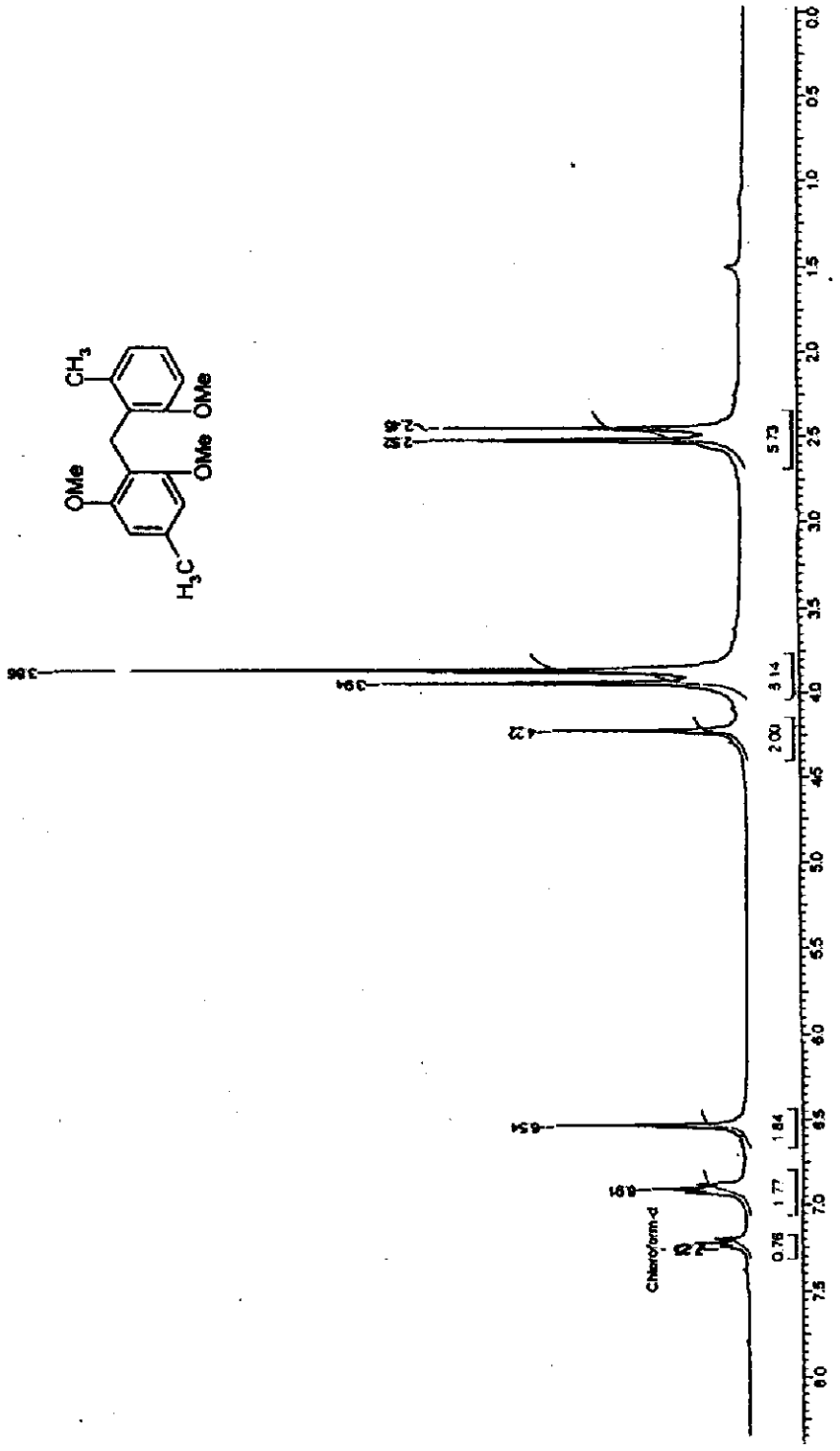
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **198** IN $CDCl_3$



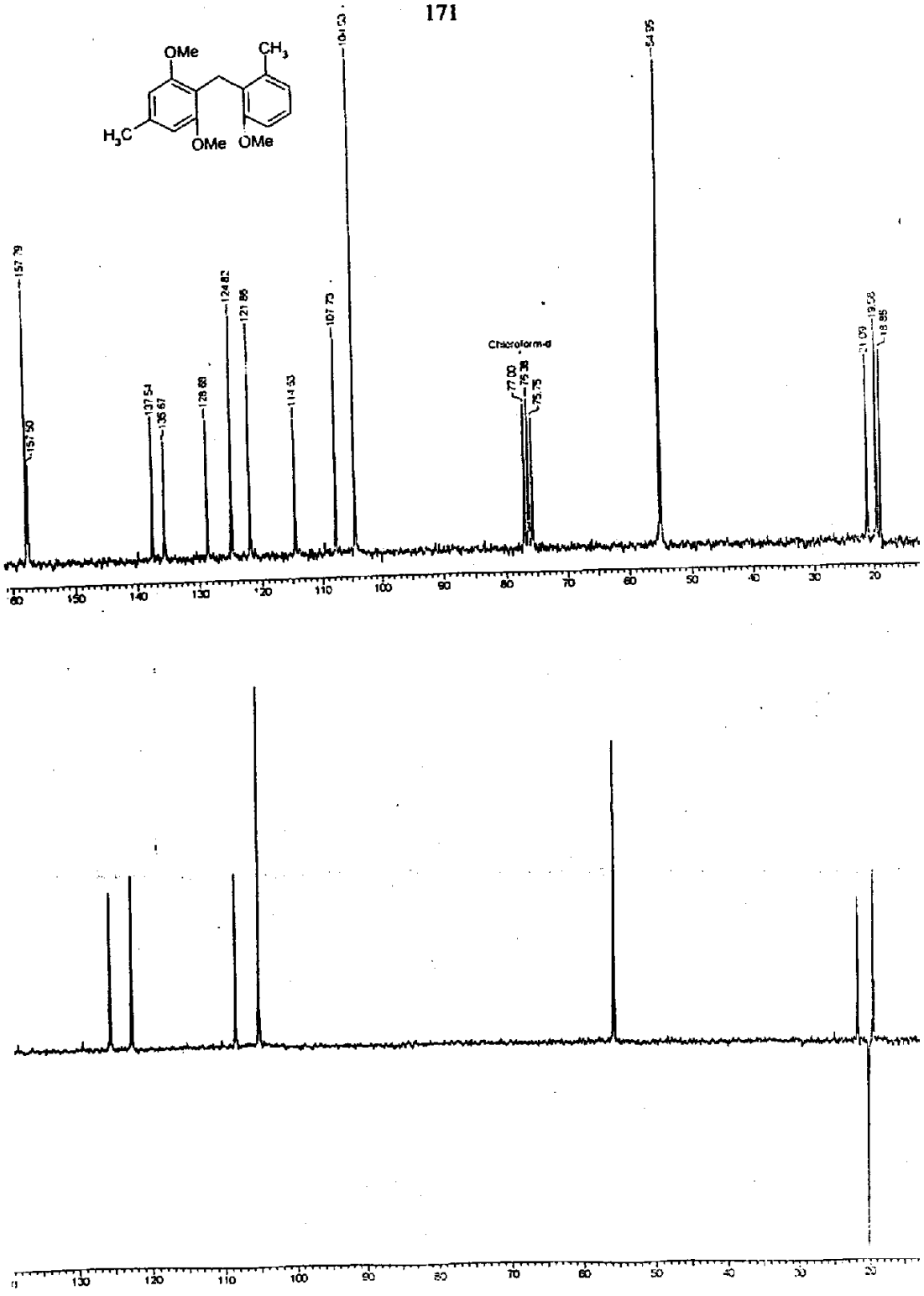
^{13}C NMR SPECTRUM (50MHz) AND DEPT OF THE COMPOUND **198** IN $CDCI_3$



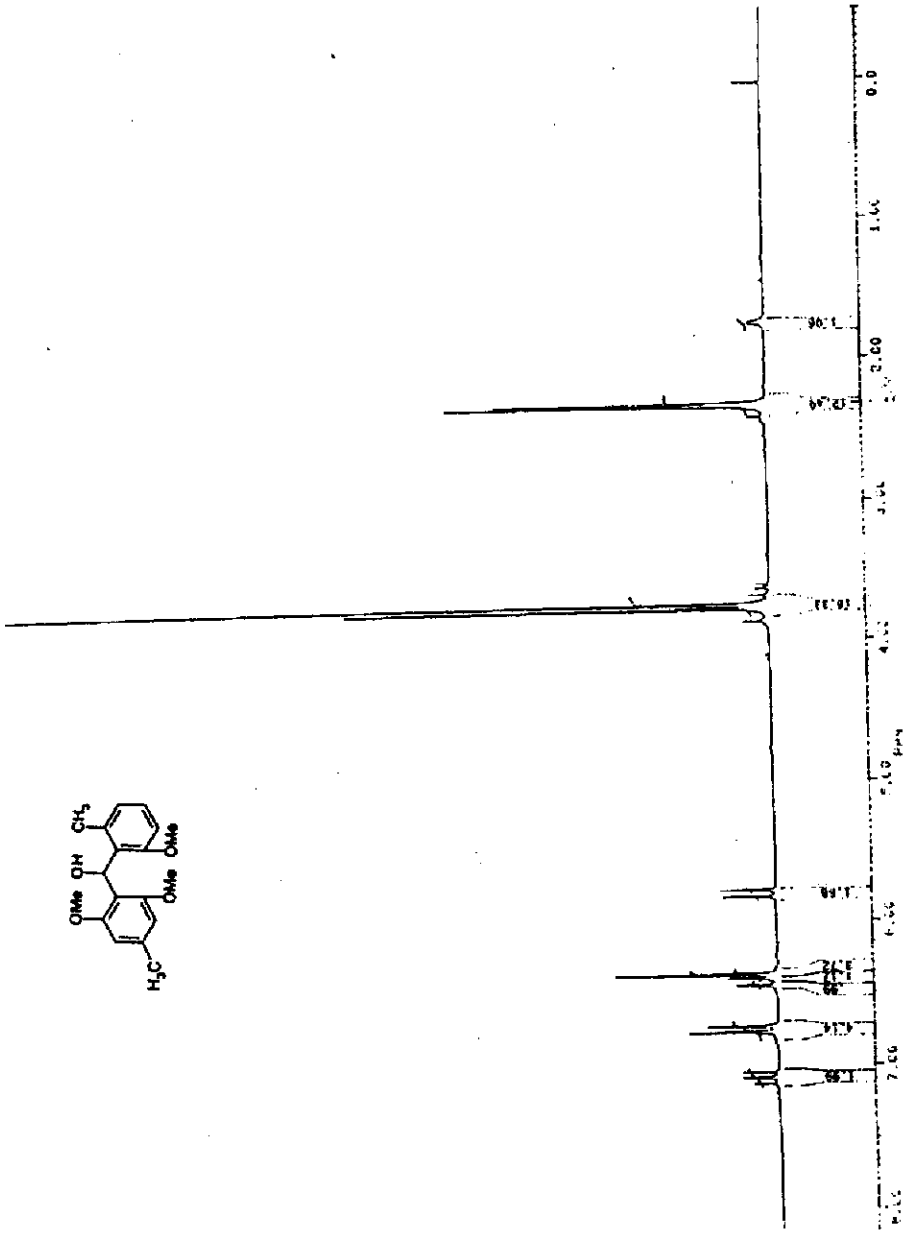
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **200** IN $CDCI_3$



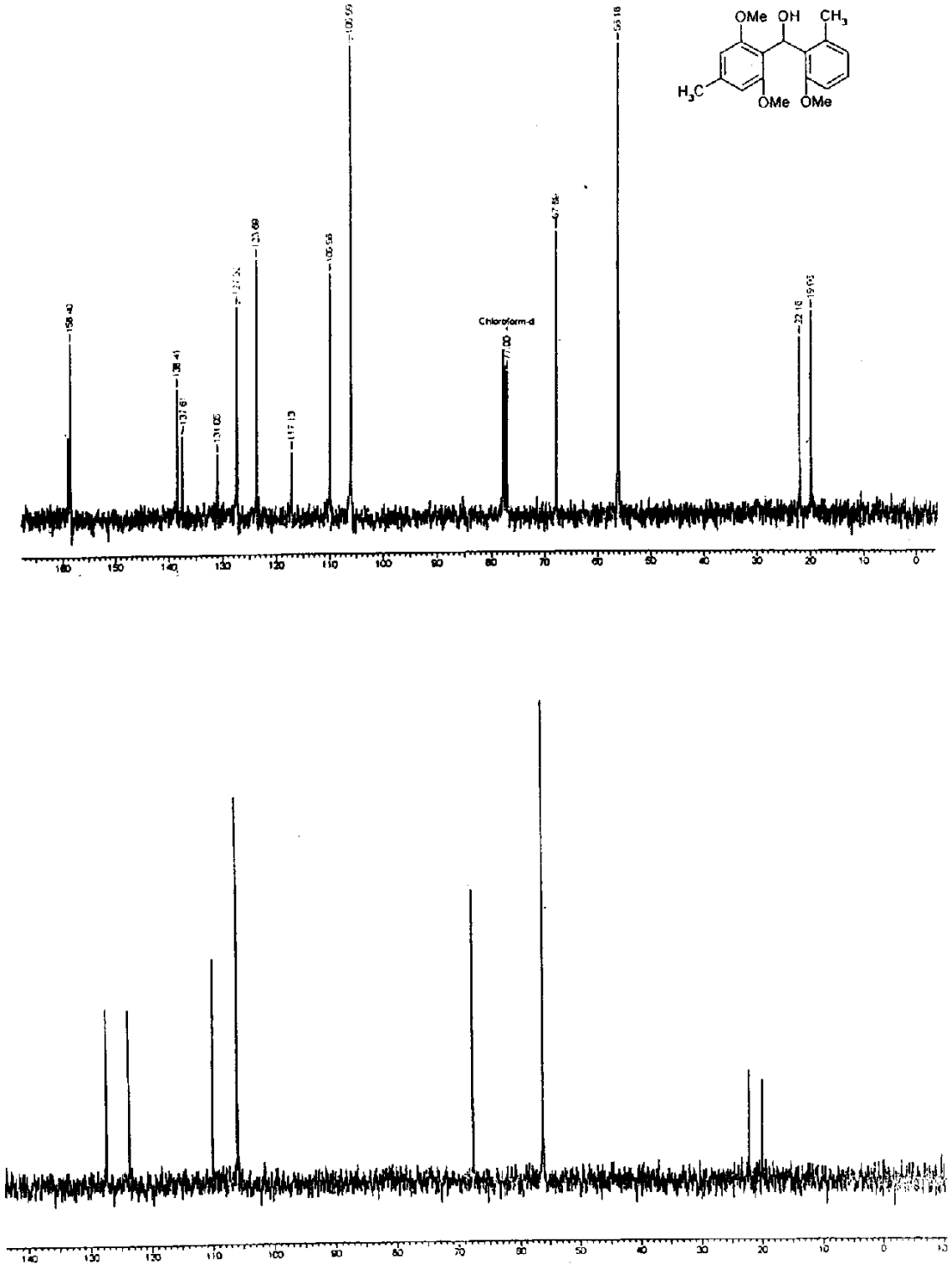
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **201** IN $CDCl_3$



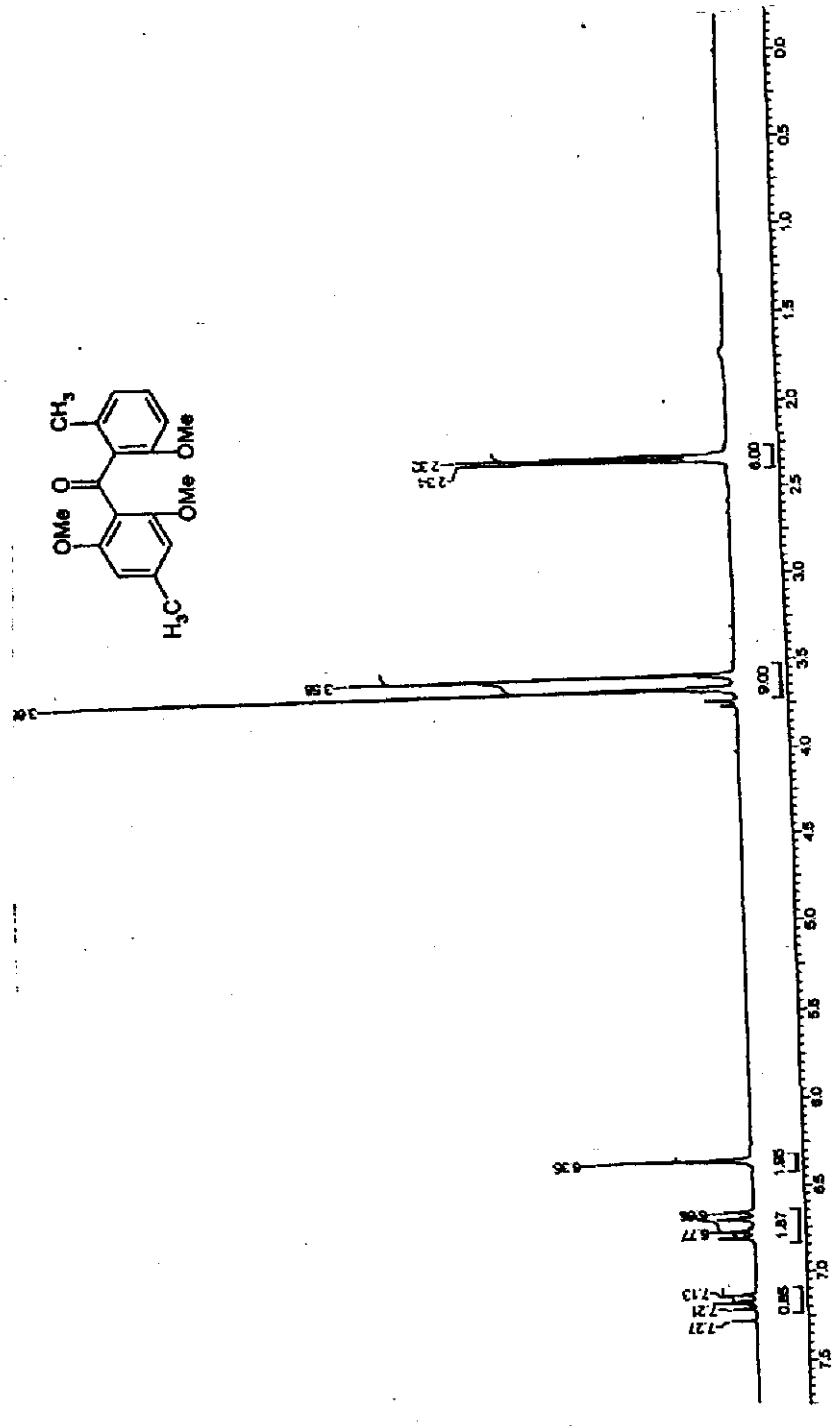
^{13}C NMR SPECTRUM (200MHz) AND DEPT OF THE COMPOUND **201** IN $CDCl_3$



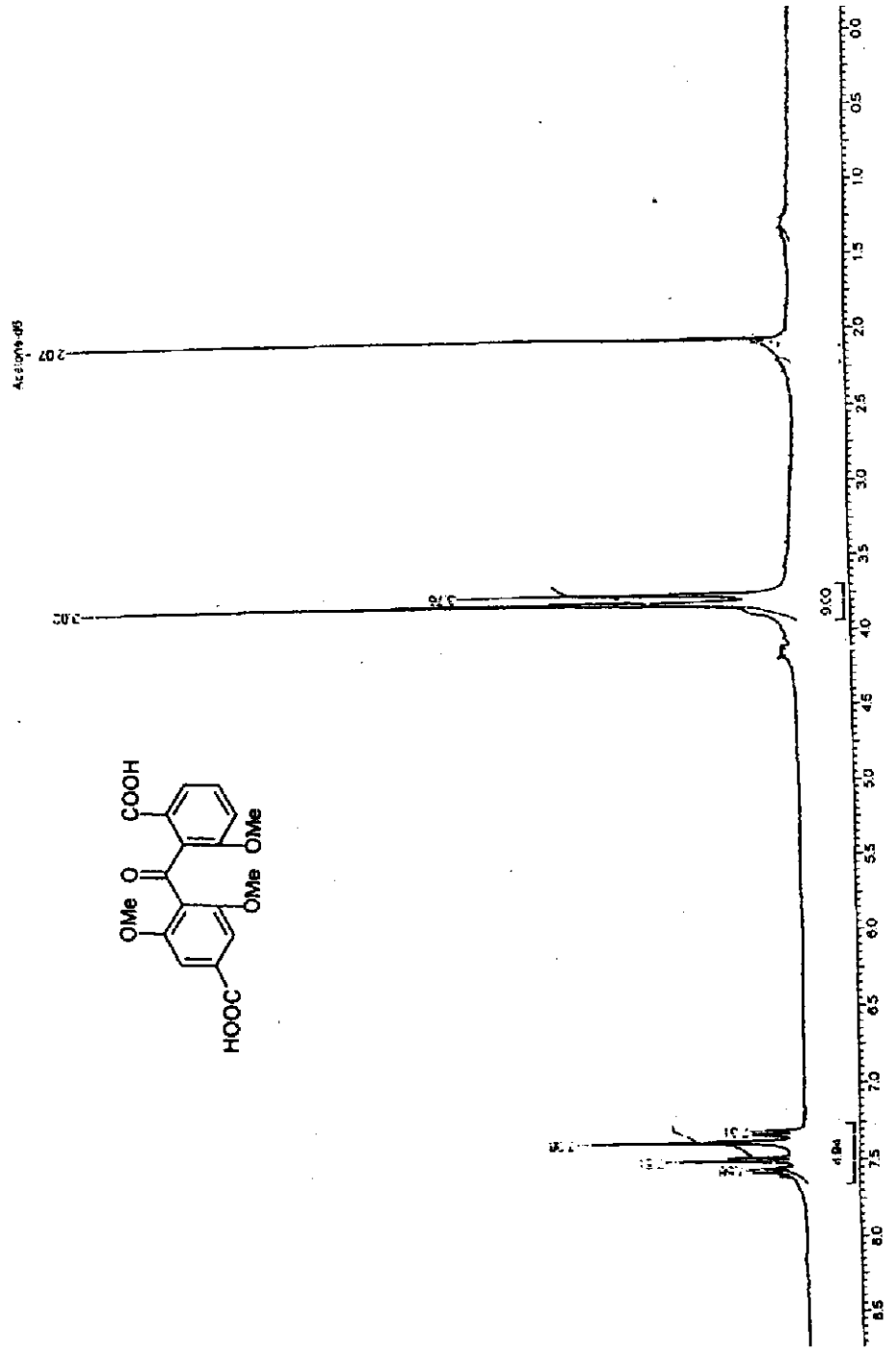
^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **207** IN $CDCI_3$



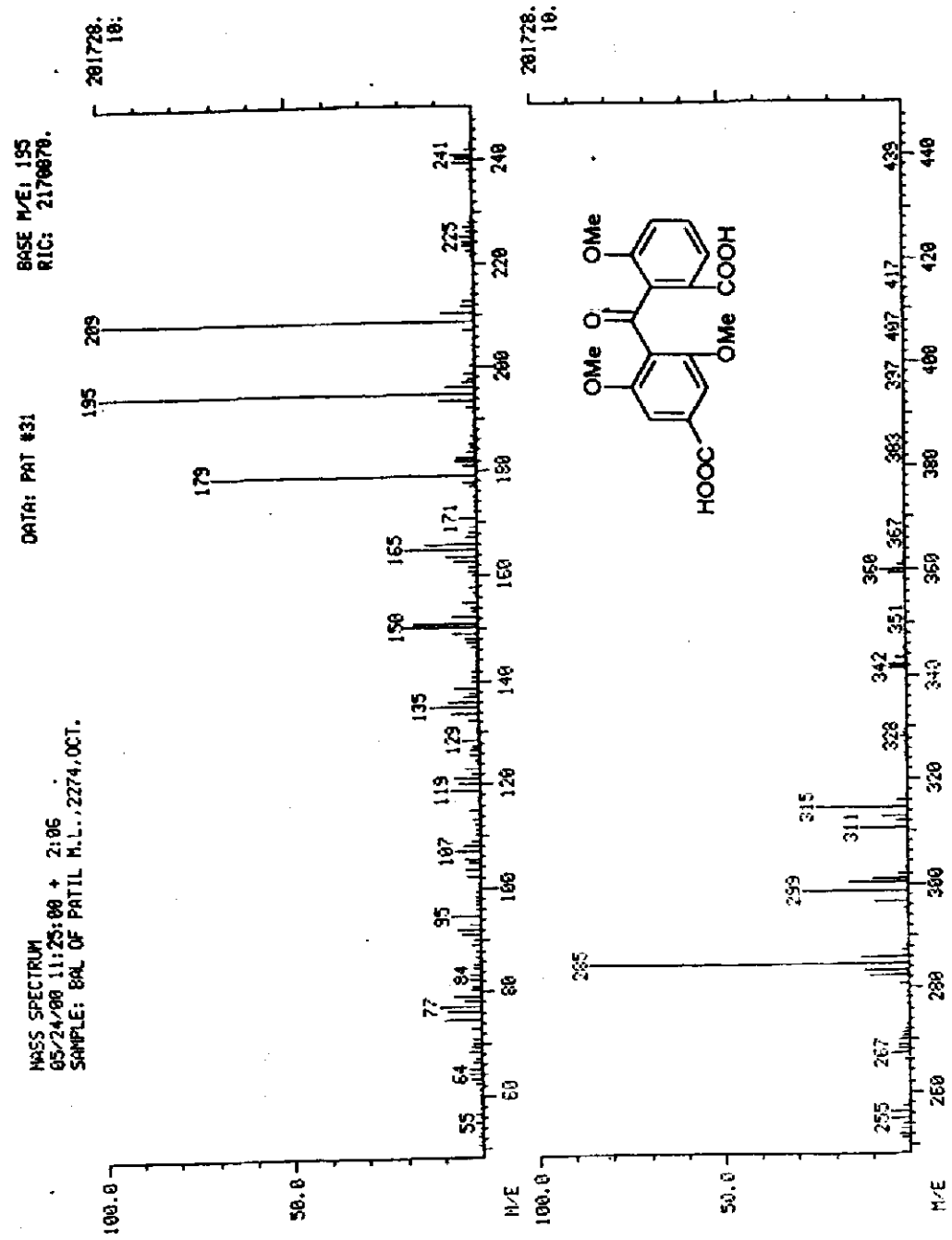
^{13}C NMR SPECTRUM (200MHz) AND DEPT OF THE COMPOUND **207** IN $CDCI_3$



^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **35** IN $CDCl_3$



^{1}H NMR SPECTRUM (200MHz) OF THE COMPOUND **36** IN ACETONE d_6.



MASS SPECTRUM OF THE COMPOUND **36**

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CHAPTER-III

APPLICATIONS OF HETEROGENEOUS CATALYSTS IN ORGANIC TRANSFORMATIONS

Introduction

Heterogeneous catalysis is widely used in petroleum refining and plays an ever increasingly important role in organic synthesis (specialty and fine chemicals). This development is quite natural, as processes employing solid catalysts are definitely more advantageous from an environmental and functional point of view than non-catalytic processes or those using soluble catalysts.

Around 90 % of all chemicals involve a catalyst at some stage of their manufacture hence catalysis is critical to the chemical industry. The development of profitable production of already established fine chemicals could only be achieved with innovative methods, which have ecological and economical benefits. In this regard catalysts in general are of key importance due to their abilities to open up new reaction pathways and to improve all kinds of selectivity (chemo-, regio- and stereo selectivity) in a given reaction. Consequently, it is possible to use cheaper feedstocks and to avoid unwanted side products.

Heterogeneous catalysts are proved to be very effective in the synthesis of fine chemicals even on industrial scales. The main advantages of these heterogeneous catalysts are:

1) High catalytic activity under mild reaction conditions.
2) Selectivity in the formation of desired product (chemo-, regio- and stereo selectivity).
3) Easy separation of the catalyst after the reaction.
4) Low cost, as catalyst can be recycled.
5) No corrosion of the reactor and free from environmental problems.

Heterogeneous catalysts are found to be very important in many reactions including selective hydrogenation, oxidation, Diels-Alder reactions, acylations of amines and aromatics, catalytic hydrogen transfer reactions etc.

Recent years have witnessed the use of heterogeneous catalysis in liquid phase organic reactions owing to their potential advantages in practical synthesis e. g. the ease of recovery and recycling the catalyst.

SECTION-A

REGIOSPECIFIC ACYLATION OF AROMATICS OVER HYDRATED ZIRCONIA

3.1.0 Introduction

Acylation under Friedel-Crafts acylation is an important unit process for the preparation of many industrially valuable chemicals. In the Friedel-Crafts acylation, the recommended procedure calls for the use of one mole of anhydrous aluminum chloride per mole of acyl halide[1]. The use of Lewis acid catalysis, e g. $AICl_3$ in the conventional homogeneous FriedelCrafts acylation of arenes entails problems of corrosivity, workup and effluent pollution. Replacement of homogeneous catalysts with heterogeneous catalyst like zeolite has been reported by Srinivasan et a1.[2] to circumvent the problems mentioned above. Srinivasan et al. used H-ZSM-5 catalyst for regiospecific benzoylation of activated aromatic compounds using benzoyl chloride and benzotrichloride. Although activated arenes underwent benzoylation efficiently, benzene, halobenzene and naphthalene failed to undergo benzoylation under the reaction condition even at 200 °C temperature.

Substituted benzophenones constitute an important class of organic intermediates, which are commercially important. Various methods are available in the literature for their synthesis. The most common method, which is also commercially practiced, is the Friedel-Crafts acylation of aromatics with benzoyl chloride as the acylating agent in the presence of stoichiometric amounts of aluminium chloride. Generally, in case of the benzoylation of aromatic ring using an acid, acid halide, anhydride or a ketene in the presence of acid catalysts, high temperatures are generally employed. The temperature ranges from 130 °C to 300 °C.

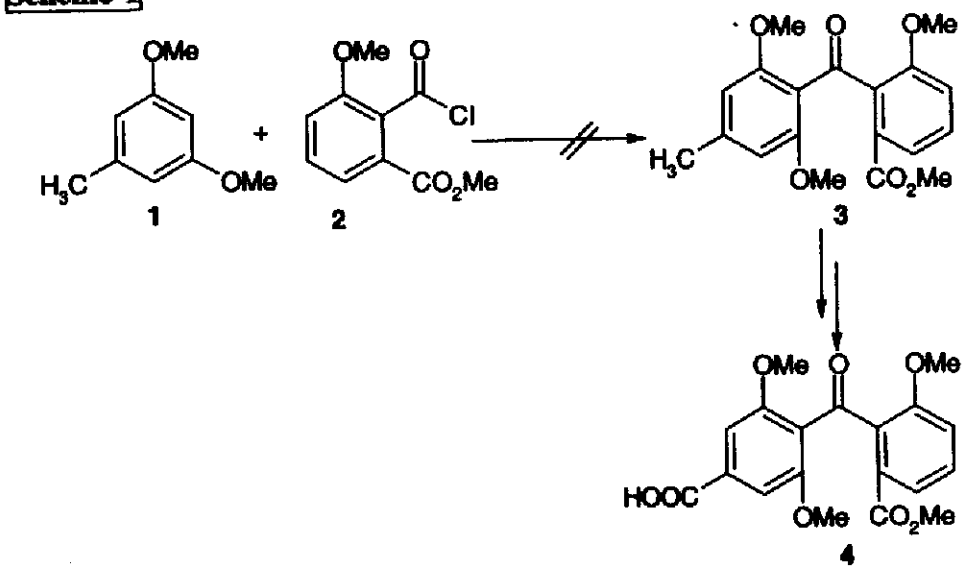
In addition to the aluminium chloride several other catalysts have been reported in the literature e. g. Nalfion-H,[3] $FeCl_3$, $ZnCl_2$ or Fe,[4] HF,[5] N-methyl-2-pyrrolidine.[6] All these catalysts are homogeneous catalysts and some of which are very expensive. They are not easily recoverable, thus giving rise to toxic effluents leading to complex effluent treatment methods prior to their disposal.

It is interesting to note that the use of benzotrichloride (a precursor to benzoyl chloride during its manufacture and used in the present work) as a benzoylating agent has been mentioned by Newmann et al.[7, 8] in early fifties. More recently, the use of benzotrichloride as a more reactive and cheaper benzoylating agent in the presence of aluminium chloride as Lewis acid catalyst has been reported. [9]

Use of zeolite for acylation of aromatics was found to be effective and environment friendly but it failed to acylate the less activated arenas like naphthalene and acetanilide even at 200°C temperature. During the initial stage of the synthesis of balanol we have attempted

regioselective benzoylation of 3,5-dimethoxytoluene to get 4-benzoyl-3,5-dimethoxytoluene. If it would have been successful, it could be extended to the synthesis of benzophenone portion of balanol using the acid chloride **2** as shown in scheme 1.

Scheme-1



Use of aluminium chloride, H-ZSM-5 resulted into the formation of 2-benzoyl-3,5 dimehoxytoluene, hence we undertook screening of different heterogeneous catalysts for the regioselective benzoylation of 3,5-dimethoxy toluene. During this study we envisioned the use of hydrated zirconia catalyst for Friedel-Crafts acylation reaction.

3.1.1 Use of Hydrated Zirconia in Organic Chemistry

The hydrated zirconia is a composition of zirconium oxide and its hydroxide that was prepared from zirconium dichloride and aqueous solution of sodium hydroxide at room temperature. According to the X-ray diffraction analysis the oxide was shown to be amorphous in nature. Hydrated zirconia is a solid supported acid catalyst, which exhibits both Bronsted and Lewis acid characteristics. It is capable of catalyzing various types of reactions. Recently, the applications of hydrated zirconia for the reduction of aldehydes and ketones, [10] vapour phase reduction of aldehydes and ketones[11], amidation of carboxylic acids[12], esteriiication of carboxylic acids[13], preparation of acetals[14], various organic reactions[15] and reduction of azobenzenes[16], have been studied. Hydrated zirconia has the following advantages:

1. The hydrated zirconia is easily prepared by neutralization of an aqueous solution of zirconium dichloride oxide.

2. The products can be easily isolated by filtering off the catalyst and subsequently evaporating the solvent, because the catalyst is insoluble in organic solvents.
3. The catalyst is stable at room temperature in air:
4. The hydrated zirconia does not have a strong acid strength on the surface, hence undesirable side reactions such as dehydration can be avoided, unlike as in the case of other acid catalysts.
5. The catalyst is reusable for at least three times without loss in activity.

This section deals with the use of hydrated zirconia for acylation of aromatics using acetyl chloride, benzoyl chloride and benzotrichloride as the acylating agents in ethylene dichloride solvent at 80 °C temperature or under solvent free conditions at 120 °C temperature with excellent yields.

3.1.2 Preamble

Most of the Friedel-Crafts acylation reactions including the benzoylation reactions require stoichiometric amount of a metal chloride as Lewis acid catalyst that cannot be reused. The required hydrolysis of the reaction mixture results in a metal and chlorine containing aqueous waste stream that is difficult and expensive to handle and dispose off in an environmentally acceptable way. The unwanted complexation of the catalyst by the product of the acylation reaction is the main reason for this negative behavior. Moreover the various catalysts already reported are homogeneous in nature, some of them are toxic in nature and others highly expensive. They are not easily recoverable for recycling. The zeolites were found to be effective for Friedel-Crafts reaction but failed to acylate the less activated arenes such as naphthalene and acetanilide even at elevated temperatures. Keeping these drawbacks in view, the present work in this section describes supportive research for the eventual development of an environmentally friendly Friedel-Crafts acylation procedure by using hydrated zirconia catalyst.

3.1.3 Results and Discussion

Hydrated zirconia is found to be very effective catalyst for the acylation of aromatics, using acetyl chloride, benzoyl chloride and benzotrichloride. Several arenes have been acylated to the corresponding acylated products using hydrated zirconia catalysts as shown in scheme-2 and in table-1. The yields and selectivities for the activated arenes that underwent acylation are summarized in Table 1.

Scheme-2

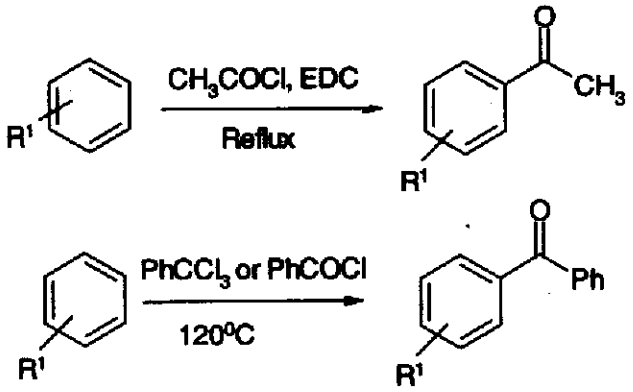


Table-1 shows the benzoylation/acylation of various arenes catalyzed by hydrated zirconia. Notably the reaction was found to be highly regiospecific and in all the cases studied either the para or ortho substituted product was the regio-isomer formed and the rest was essentially the starting material. This was confirmed by the GC analysis of the reaction mixture.

It is remarkable that naphthalene underwent benzoylation at 1-position under the present conditions in 80. and 70 % yields using benzoyl chloride and benzotrichloride as benzoylating agents respectively (entry 8 and 9 of table-1). Acetanilide was also acylated under these conditions at 60 °C in 80 % yield whereas aniline on acylation yielded both the N-acylated and 4-position acylated product in 65 % yield.

In this connection it should be noted that zeolites have failed to benzoylate naphthalene even at elevated temperatures. Our targeted reaction, benzoylation of 3,5-dimethoxytoulene with benzotrichloride and benzoyl chloride both resulted into the usual benzoylated product 2-benzoyl-3, 5-dimethoxytoluene in 60 and 80% yields respectively. Attempted acylation of 1-naphthol afforded only acetate in 96% yield but further benzoylation could not be achieved even after heating the resultant product 1-naphthylacetate with hydrated zirconia at 120-150 °C temperature. The less activated arenes such as benzene, toluene and halobenzenes have failed to undergo benzoylation under present conditions. The yields obtained with benzotrichloride ranged from 60-75 %. The yields obtained in the benzoylation of anisole and 2methoxynaphthalene using benzotrichloride were higher than yields obtained by using benzoyl chloride. Benzotrichloride forms a more electrophlilic and reactive carbocation with a Lewis acid such as aluminium chloride. On this basis we feei that benzoyl chloride forms a weaker co-ordination complex with the acid sites in the hydrated zirconia whereas benzotrichloride may

form a more electrophilic charge transfer complex with the Lewis acid sites in hydrated zirconia.

Table-l:

Entry	Substrate	Acylating agent	Temp (^{O}C)	Time (h)	Yield (%)	Product
1	Acetanilide	Acetyl chloride	60	10	80	4-Acetylacetanilide
2	Aniline	Acetyl chloride	60	10	65	4-Acetylacetanilide
3	Anisole	Benzoyl chloride	120	12	65	4-Benzoylanisole
4	Anisole	Benzotrichloride	120	10	75	4-Benzoylanisole
5	2-Methoxy-naphthalene	Acetyl chloride	60	8	60	1-Acetyl-2-methoxy-naphthalene
6	2-Methoxy-naphthalene	Benzoyl chloride	120	12	62	1-Benzoyl-2-methoxnaphthalene
7	2-Methoxy-naphthalene	Benzotrichloride	120	10	70	1-Benzoyl-2-methoxynaphthalene
8	Naphthalene	Benzoyl chloride	120	10	80	1-Benzoylnaphthalene
9	Naphthalene	Benzotrichloride	120	12	70	1-Benzoylnaphthalene
10	3, 5-Dimetho-xytoluene	Benzoyl chloride	120	10	80	2-Benzoyl-3, 5-dimethoxytoluene
11	3, 5-Dimetho-xytoluene	Benzotrichloride	120	10	60	2-Benzoyl-3, 5-dimethoxytoluene

The yields and selectivity results found to be constant after carrying out the reactions twice or thrice. The catalyst was recovered by simple filtration and reused three times with no loss of activity and selectivity.

Mechanistically it can be presumed that Lewis acid sites in hydrated zirconia can activate benzotrichloride and benzoyl chloride by the way of co-ordination resulting into phenylcarbenium ion and phenyldichlorocarbenium ion respectively which in turn react with the aromatic nucleus to produce benzophenones. Similarly in the case of acetyl chloride acylcarbenium ion may be forming which on reaction with aromatic nucleus results into acetophenones. The selectivity part of this reaction is unknown.

3.1.4 CONCLUSION

In summary the salient features of the present methodology are:

1. We have developed a simple method for the acylation of arenes.
2. The present methodology is environmentally friendly since it makes use of solid hydrated zirconia in catalytic amounts instead of aluminium chloride avoiding the problems of toxic wastes.
3. The catalyst can be recovered by simple filtration and reused three times without loss in activity and selectivity making the process economic.
4. All reactions are high yielding and with excellent selectivities.
5. For the first time we have benzoylated less activated arenes like naphthalene and acetanilides under heterogeneous conditions whereas zeolites failed to benzoylate these compounds even at elevated temperatures.

3.1.5 EXPERIMENTAL

Hydrated zirconia catalyst was prepared according to the literature procedure[10] by the treatment of aq. solution of zirconium oxychloride ($ZrOCl_2$. 8 H_2O) with aq. NaOH at room temperature and the catalyst was heated at 300 °C for 5 hr before use.

Typical Experimental Procedure for Acylation of Aromatics

In a typical experimental procedure, acetanilide (1.32 g, 0.01 mole) and hydrated zirconia (110 mg, 10 % by wt.) in dichloroethane (10 ml) was stirred at room temperature and acetyl chloride (1.1 ml, 0.0015 mole) was introduced into the above mixture. The Resulting reaction mixture was heated at 60 °C for 10 h. After completion of reaction (TLC), reaction mixture was cooled and catalyst was filtered off. The dichloroethane filtrate was washed with water, saturated solution of sodium bicarbonate, brine, dried over sodium sulphate and evaporated under reduced pressure. The residue was purified by flash chromatography to afford 4-acetylacetanilide as white solid.

4-Acetylacetanilide

Yield:	1.14g, 80%
M. P.	169 °C (lit.[17] m. p. 166-169 °C).
IR (nujol):	1690, 1570 cm^{-1}
^1H NMR ($CDCl_3$, 200 MHz):	8 2.20 (s, 6H, -$COCH_3$), 7.10 (d, J=8.1 Hz, 2H, aromatic), 7.30-7.50 (m, 3H, aromatic).

Typical Experimental Procedure for Benzoylation of Aromatics

In a typical experiment, a mixture of anisole (1.08g, O.Ol mol) benzoyl chloride (2.10 g, 0.015 mole) or benzotrichoride (2.9 g, 0.015 mole) and hydrated zirconia (110 mg, 10 % by wt.) was heated at 120 °C temperature for 10-12 hr. The reaction was monitored by TLC and after the reaction was over, the mixture was diluted with cold water (10 ml), catalyst was iiltered off and the mixture was made alkaline with aq. NaOH (10% w/v) to remove excess benzotrichloride or benzoyl chloride. The aqueous part was then extracted with ethyl acetate, the extracts were washed with water, brine, dried (Na_2SO_4) and concentrated to afford 4 enzoylanisole as yellowish white solid.

4-Benzoylanisole

Yield:	Using benzoyl chloride as benzoylating agent, 1.37 g (65 %).
Yield:	Using benzotrichloride as benzoylating agent, 1.59 g (75 %).
M. P.:	60 °C (lit.[18] m. p. 60-63 °C)
IR (nujol):	1690, 1660, 1510 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz):	S 3.90 (s, 3H, -OMe), 6.90 (d, J--8 Hz, 2H, aromatic), 7.30- .55 (m, 5H, aromatic), 7.60-7.78 (m, 2H, aromatic).
Mass (m/z):	212 (M^+).

The MPs., IR, ^1H NMR and mass spectral data of the products of benzoylation and acylation reactions are summarized below.

1-Acetyl-2-methoxynaphthalene

Yield:	64 %
M, P.:	59 °C. (lit. [19] m. p. 57.5-58 °C). Faint yellow prisms in pet-ether.
IR (nujol):	1680, 1620, 1460, 1570, 1270 cm^{-1}.
^1H NMR ($CDCl_3$, 90 MHz):	8 2.50 (s, 3H, $-COCH_3$), 3.80 (s, 3H, -OMe), 6.90-7.30 m, 3H, aromatic), 7.40-7.70 (m, 3H, aromatic).
Mass (m/z):	200 (70), 185 (95), 170 (46), 155 (8), 142 (60), 128 (100).

1-Benzoylnaphthalene

Yield:	80 % (PhCOCI)	70 % ($PhCCl_3$)
M. P.:	75.5-76 °C (lit.[20] m. p. 76 °C).	
IR (nujol):	1690, 1570 cm^{-1}.	
^1H NMR ($CDCl_3$, 200 MHz):	8 7.40-7.58 (m, 5H), 7.60-7.75 (m, 2H) 8.05-8.25 (m, 5H).	
Mass (m/z):	232 (M^+, 100), 215 (10), 202 (15), 155 (80).	

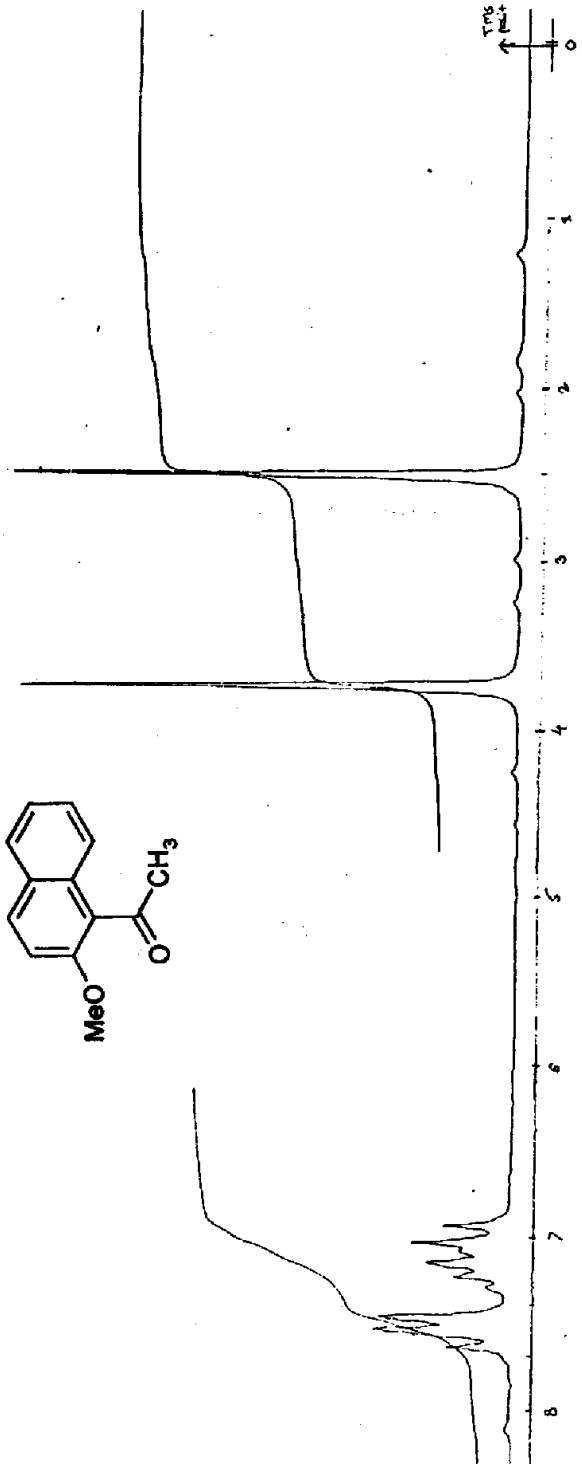
1-Benzoyl-2-methoxynaphthalene

Yield:	62 % (PhCOCI)	70 % ($PhCCl_3$)
M. P.:	85-87 °C (lit. 21 m. p. 87 °C).	
IR (neat):	1670, 1630, 1600, 1530 cm^{-1}.	
^1H NMR ($CDCl_3$, 200 MHz):	8 3.80 (s, 3H, -OMe), 7.25-7.65 (m, 7H, aromatic), 7.80-8.10 (m, 4H, aromatic).	

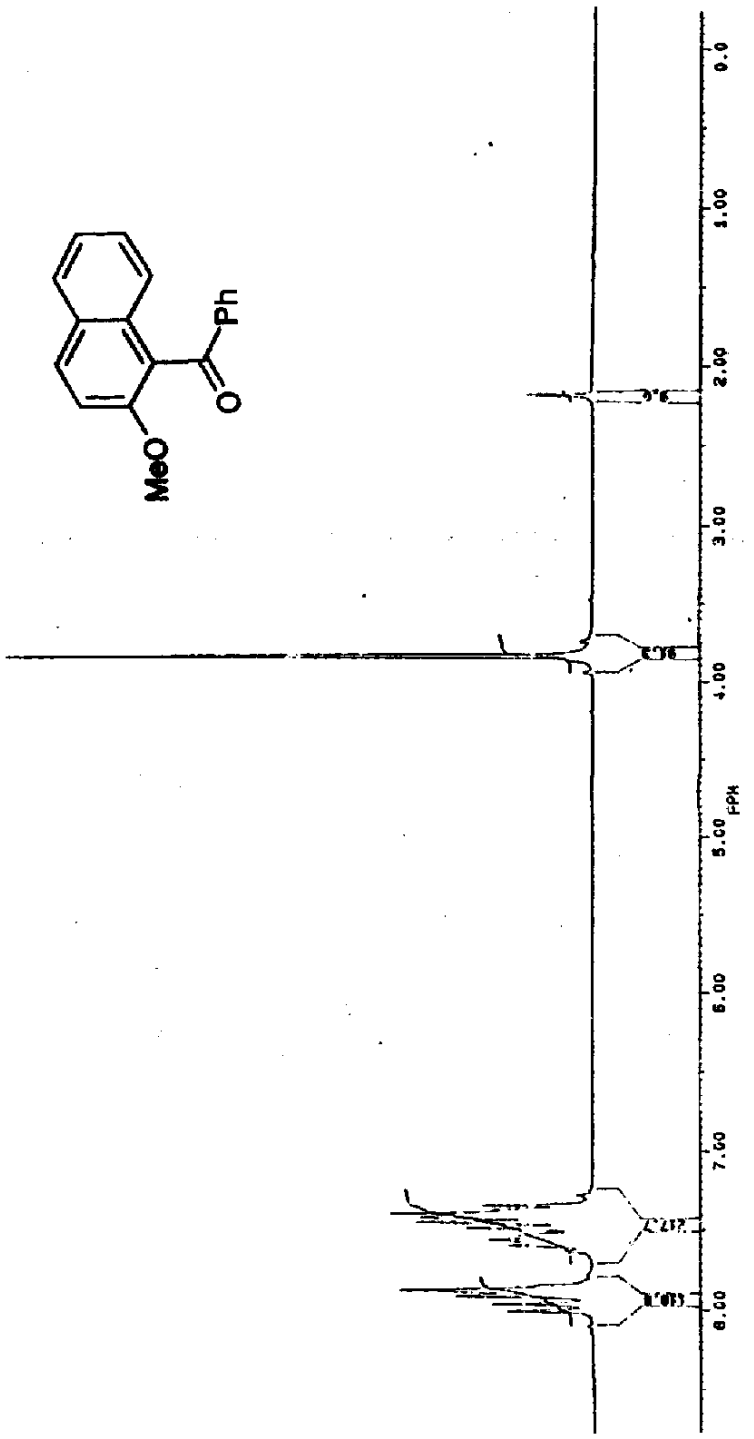
Mass (m/z):	262 (M^+, 10), 247 (5), 231 (30), 154 (20), 126 (50), 105 (100).

2-Benzoyl-3, 5-dimethoxytoluene

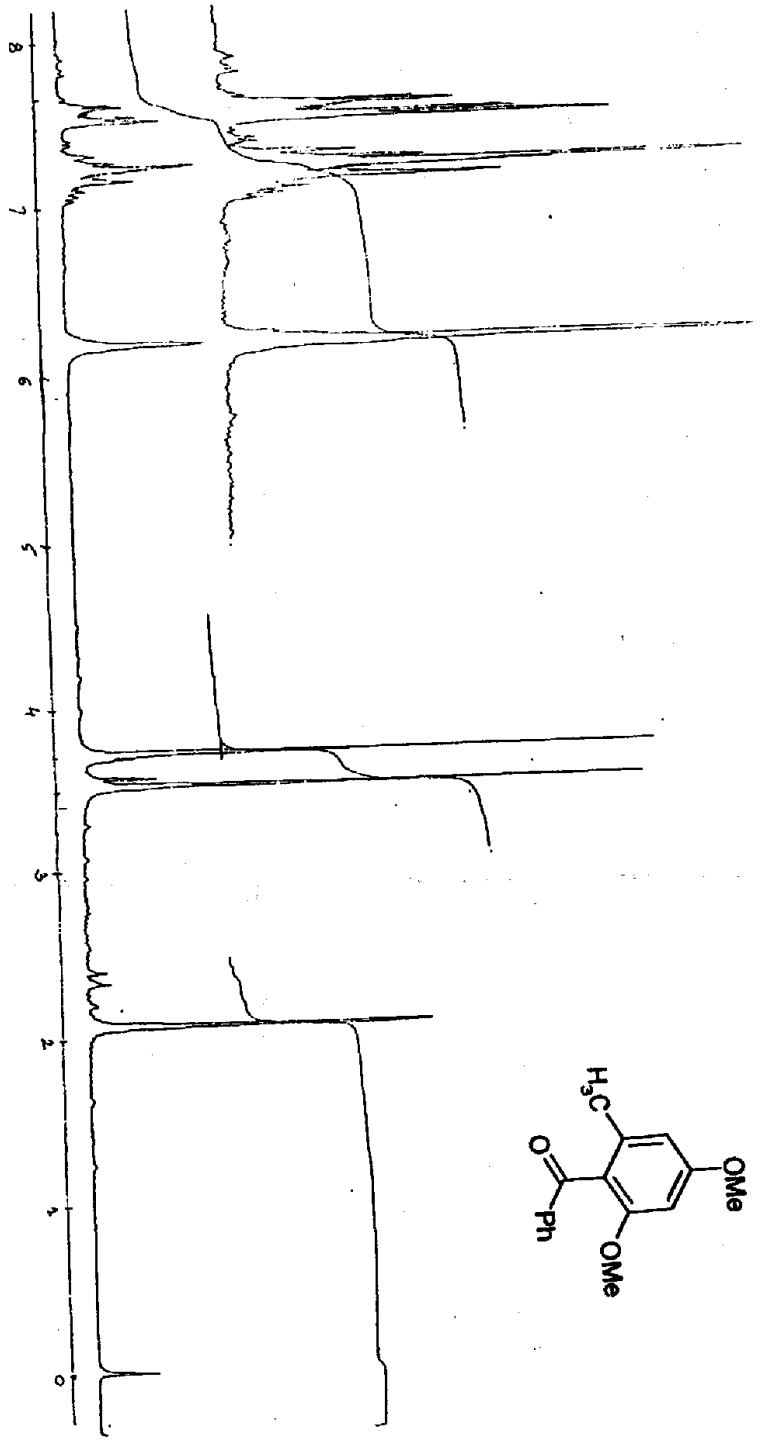
Yield:	80 % (PhCOCI) 60 % ($PhCCl_3$)
IR (nujol):	1685, 1530 cm^{-1}.
^1H NMR ($CDCl_3$, 90 MHz):	8 2.06 (s, 3H, Ar-CH_3), 3.50 (s, 3H, -OMe), 3.75 (s, 3H, -OMe), 6.20 (s, 2H, aromatic), 7.05-7.35 (m, 3H, aromatic), 7.50-7.70 (m, 2H, aromatic).
Mass (m/z):	256 (M^+, 100), 242 (40).



^{1}H NMR SPECTRUM (90MHz) OF 1-ACETYL-2-METHOXYNAPHTHALENE IN $CDCI_3$



^{1}H NMR SPECTRUM (200MHz) OF 1-BENZOYL-2-METHOXYNAPHTHALENE IN $CDCI_3$



^{1}H NMR SPECTRUM (90MHz) OF 2-BENZOYL-3, 5 DIMETHOXYTOLUENE IN $CDCI_3$

3.1.6 REFERENCES

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SECTION-B

OXIDATION OF PRIMARY AND SECONDARY BENZYLIC ALCOHOLS AND SULFIDES OVER $LaCo_3$ USING 70% TBHP

3.2.0 INTRODUCTION

Oxidation of primary and secondary alcohols to the corresponding carbonyl compounds is an important transformation in organic chemistry. The traditional chromium complexes used for this transformation entail problems like effluent pollution, loss of selectivity and tedious workup.[1] The more recent reagents are 1, 8-naphthylridinium chlorochromate,2 nicotonium dichromate,[3] quinolinium chlorochromate,[4] $RuCl_2(Ph_3)P$,[5] $PdCl_2$,[6] $CuCl_2$-PTC[7] and Cr-AlPO5.[8] Oxidation under heterogeneous condition provides solution to some of above mentioned problems but the cost of catalyst and selectivity are always the limiting factors.

3.2.1 Preamble

To circumvent all these problems many researchers have focused their attention on the use of zeolite catalysts for the above transformation. TBHP has been recently used as the cooxidant for the oxidation of benzylic alcohols along with chromium silicate-2 [9] to the corresponding ketones. The use of Cr(VI) oxide and TBHP combination is a selective oxidant for alcohols, however the oxidation of benzyl alcohols is nonselective and results in a mixture of benzaldehyde and benzoic acid even in the presence of argon atmosphere and molecular sieves.[10] We undertook the work to explore the use of various heterogeneous catalysts as oxidizing agents and this section describes our results using $LaCoO_3$-TBHP as co-oxidant for benzylic alcohols and sulphides.

Because of scarcity and high cost of noble metals, worldwide efforts are being made to replace noble metal-catalysts by non-noble metal catalysts, particularly ABO_3 type perovskite oxides where A=rare earth metal and B=transition metal such as Cr, Mn, Fe, Co, Ni etc.[11-16]

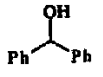
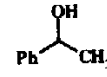
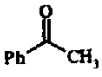
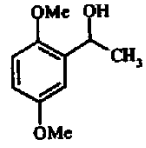
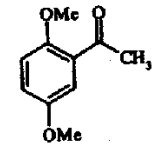
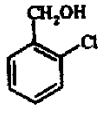
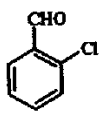
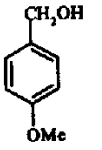
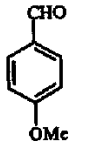
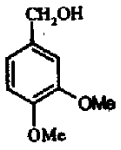
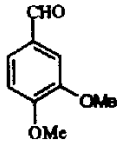
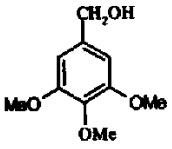
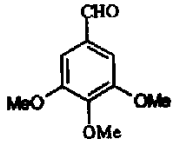
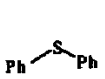
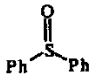
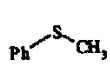
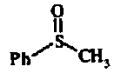
The combinations of metal oxides are known to lead the formation of perovskite structure ABO_3. The cation site in the perovskite lattice can be easily substituted for foreign cations without a large change in crystal structure. Voorhoeve et a.[17] classified the oxidation over perovskite type oxide into suprafacial and intrafacial reactions. The reaction between adsorbed species on the surface proceeds at relatively low temperatures for the suprafacial reactions, whereas the intrafacial reaction is a high temperature process in which reaction rate is correlated with the thermodynamic stability of the lattice oxygen bonded to transition metal ion. Earlier studies [18, 19] showed that $LaCoO_3$ with partial substitution of La by Sr and of Co by Fe or Ni has high methane combustion activity.

3.2.2 Results and Discussion

We envisioned the use of this perovskite type metal oxide for the oxidation of benzylic alcohols to corresponding ketones and sulfides to the corresponding sulfoxides.

Among the various catalysts studied $LaCoO_3$ was found to be very efficient catalyst for the oxidation of benzylic alcohols and sulfides in combination with 70 % TBHP. Secondary alcohols underwent oxidation to the corresponding ketones in very good yields (Table-1). Sterically hindered alcohols were also oxidized under these conditions. Primary alcohols were oxidized to the corresponding aldehydes in good to moderate yields. Long chain alcohols remained unreacted even after 48 hr.

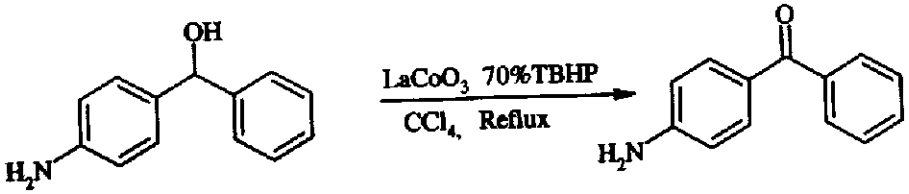
Table-l: Oxidation of benzylic alcohols and sulfides over $LaCoO_3$.

Entry	Substrate	Product	Time (hr)	% Yield
1.			6	95[a]
2.			6	92[a]
3.			10	65[a]
4.			10	75[a]
5.			10	55[a]
6.			10	65[a]
7.			10	55[a]
8.	$Ph\text{-}NH_2$	No Reaction	12	
9.			10	85[b]
10.			10	80[b]
11.	$CH_3(CH_2)_{16}OH$	NO Reaction	12	

a. Reactions carried out in CCl_4 under reflux. b. Reactions carried out in methanol under reflux.

Phase transfer catalyst tetrabutylammonium bromide was used to improve the yield. Upon addition of tetrabutylammonium bromide, to the reaction mixture of 2-chlorobenzyl alcohol and $LaCoO_3$-TBHP system in carbon tetrachloride, improvement in yield was observed hence all reactions were carried out using tetrabutylammonium bromide along with $LaCoO_3$ catalyst and 70 % TBHP.

CrS-2 zeolites along with 70 % TBHP are known to oxidize alcohols as well as amino compounds[21] to the corresponding ketones and nitro compounds respectively whereas $LaCoO_3$-BHP system oxidized selectively benzylic alcohols while amino group remained unaffected.



To check this selectivity oxidation of aniline was carned out under $LaCoO_3$-TBHP conditions but the reaction failed even after refluxing for 12 hr and only starting material was recovered from the reaction mixture. This selectivity is very important for the oxidation of benzylic alcohols in the presence of amino groups. The probable reason for this selectivity may be the less reactivity of the catalyst. $LaCoO_3$ is a mild oxidizing catalyst but it is very effective for the oxidation of benzylic alcohols.

Selective oxidation of sulfides to the corresponding sulfoxides is an important transformation as in many cases oxidation of sulfides results into the formation of sulfones due to the over oxidation. Selective oxidation of sulfides to sulfoxides is necessary in the synthesis of many natural products hence this conversion is very important. In literature different methods are available[22] for this conversion. Hydrogen peroxide, either alone or associated with various solvents or catalysts, is the most widely used agent for oxidizing organic sulfides. Different catalysts such as vanadium salts[23], molybdenum salts[24], titanium salts[25] etc are known to catalyze oxidation of sulfides to sulfoxides effectively. CrS-2 and molybdenum silicates in combination with H_2O_2 is another method for the oxidation of sulfides to sulfoxides.[26]

A mild catalyst is required to avoid the over oxidation of sulfides to the sulfones. $LaCoO_3$ was found to be a mild, efficient and selective catalyst for the oxidations of benzylic alcohols to the corresponding ketones. The less reactivity of $LaCoO_3$ prompted us to utilize this catalyst for the selective conversion of sulfides to sulfoxides. Accordingly oxidations of sulfides to the corresponding sulfoxides were carried out by using $LaCoO_3$-TBHP system in excellent yields. No traces of sulfones have been formed during this conversion.

Exact mechanism of the $LaCoO_3$-TBHP catalyzed oxidation reaction is not known but it is believed that the lattice oxygen bonded to the transition metal Co is responsible for this conversion.

3.2.3 CONCLUSION

1. We have developed a simple, mild and efficient methodology for the oxidation of primary and secondary benzylic alcohols to the corresponding aldehydes and ketones.
2. Selective oxidation of benzylic alcohols in the presence of amino group has been achieved using $LaCoO_3$-TBHP system.
3. Selective oxidation of suliides to the corresponding sulfoxides has been carried out. Hence we have avoided the over oxidation of sulfides to the sulfones.
4. This methodology is environmentally friendly as it avoids use of corrosive reagents.
5. Catalyst is reusable after filtration from the reaction mixture.

6. Yields obtained are excellent in the case of oxidations of secondary benzylic alcohols and sulfides and good to moderate in the case of primary benzylic alcohol oxidations.

3.2.4 EXPERIMENTAL

LaCoO3 catalyst was prepared by known procedure.[20]

A Typical Experimental Procedure for the Oxidation of Benzylic Alcohols to the Corresponding Ketones

Benzhydrol (552 mg, 3 mmol) in CCl_4 (10 ml) was taken in a flask flushed with argon . To this was added 70 % TBHP (540 mg, 6 mmol), a pinch of tetrabutyl ammonium bromide as a phase transfer catalyst and $LaCoO_3$ (10 % by wt). The mixture was then stirred under reflux. Reaction was monitored by TLC. After completion of the reaction (6 hr), mixture was filtered and washed with CCl_4. The CCl_4 layer was washed three times with saturated sodium sulphite solution to remove excess TBHP and concentrated. Column purification afforded benzophenone (518 mg, 95 %) as colourless solid.

Benzophenone

M.P.: 48-49 °C.

IR (nujol): 1700, 1640 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 7.40-7.52 (m, 4H), 7.53-7.60 (m, 2H,), 7.75-7.85 (m, 4H).

Acetophenone

Pale yellow liquid.

Yield: 92 %.

IR (neat): 1640,1710 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 2.60 (s, 3H, $-COCH_3$), 7.40-7.60 (m, 3H), 7.90 (d, J= 6 Hz, 2H).

2, 5-Dimethoxyacetophenone

colourless oil.

Yield: 65 %.

IR (neat): 1675, 1560 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 2.62 (s, 3H, $-COCH_3$), 3.79 (s, 3H, -OMe), 3.87 (s, 3H, Me), 6.90 (d, J=8.5 Hz, 1H), 7.00-7.06 (m, 1H), 7.28 (d, J=6.4 Hz, 1 H).

Mass (m/z): 180 (M^+, 70), 165 (100), 150 (20).

2-Chlorobenzaldehyde:

Pale yellow liquid.

Yield: 75 %.

IR (neat): 3000, 1720, 1650 cm^{-1}.

^1H NMR ($CDCl_3$, 90 MHz): 8 7.30-7.48 (m, 2H), 7.50-7.60 (m, 1H), 7.80-7.90 (m, 1H), 9.80 (s, 1H, aldehyde).

4-Methoxybenzaldehyde

Pale yellow liquid.

Yield: 55 %.

IR ($CHCl_3$): 3010, 1650, 1600, 1430, 1270 cm^{-1}.

^1H NMR ($CDCl_3$, 90 MHz): 8 3.80 (s, 3H, -OMe), 6.90 (m, 2H, aromatic), 7.70 (m, 2H, aromatic), 9.40 (s, 1H, aldehyde).

4-Aminobenzophenone

Yellow solid.

Yield: 90 %. M.P.: 121 °C.

IR (nujol): 3420, 1670, 1450, 1580, 1310, 1280 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 4.40 (br s, 2H, NH2), 6.60 (d, J=7.6 Hz, 2H, aromatic), 7.50 (d, J=7.6 Hz, 2H, aromatic), 7.6S-7.75 (m, SH, aromatic).

Mass (m/z): 198 (M+1, 13), 197 (M^+, 48).

3, 4-Dimethoxybenzaldehyde

Yield: 65 %.

IR (nujol): 1650, 1590 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 3.80 (s, 3H, -OMe), 3.82 (s, 3H, -OMe), 6.85 (d, J=7 Hz, 1H, OMe), 7.25 (s, 1H, -OMe), 7.32 (d, J=7 Hz, 1H, aromatic), 9.70 (s, 1H, aldehyde).

Mass (m/z): 166 (M^+).

3, 4, 5-Trimethoxybenzaldehyde

Yield: 55 %.

IR (nujol): 1660, 1570 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 3.90 (s, 9H, 3X-OMe), 7.10 (s, 2H, aromatic), 9.80 (s, 1H, aldehyde).

Mass (m/z): 196 (M^+).

Typical Experimental Procedure for the Oxidation of Sulfides to Sulfoxides

A mixture of thioether (0.0034 mole), $LaCoO_3$ (10% by wt) and 70% TBHP (0.0068 mole) in methanol (10 ml) was refluxed for 10 hr. The reaction was monitored by TLC. After completion of the reaction, mixture was filtered and washed with methanol. The methanol was removed under reduced pressure and residue was diluted with water (10 ml), and extracted with chloroform. The chloroform layer was washed three times with saturated sodium sulphite solution to remove excess TBHP, dried and concentrated. Column purification afforded corresponding sulfoxides.

Diphenyl sulioxide

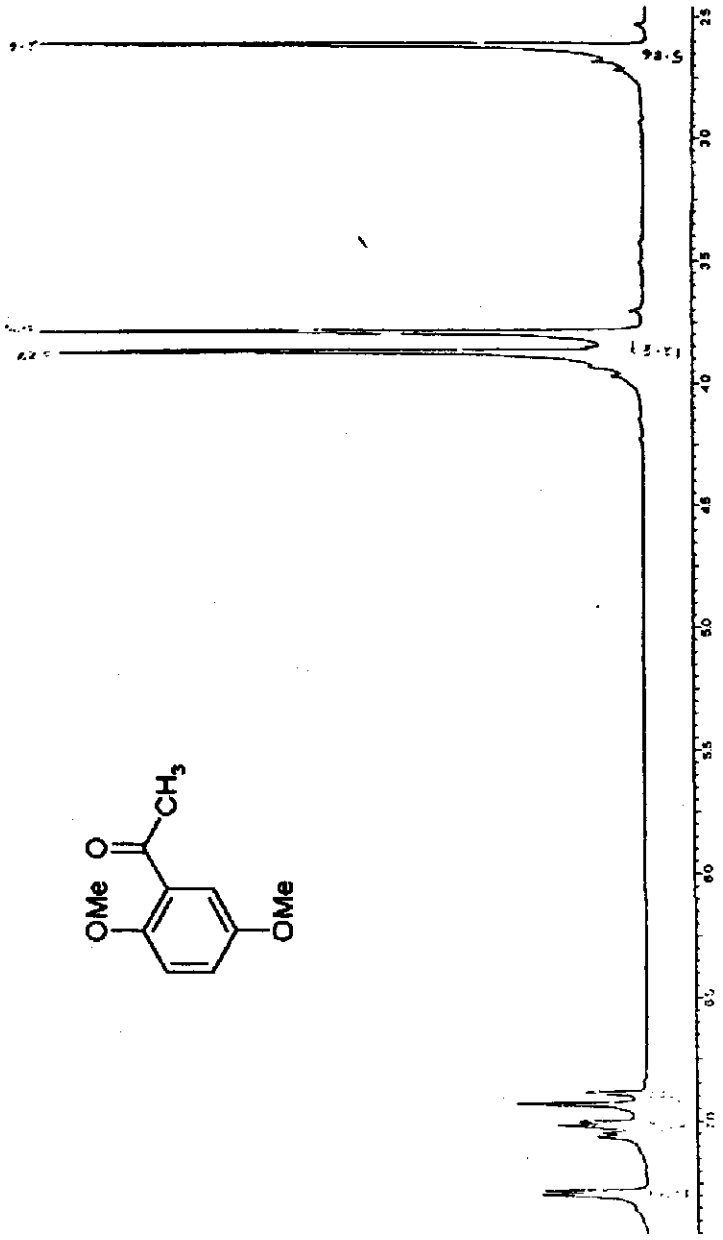
Colourless liquid.

Yield:	85 %.
IR (neat):	1590, 1450, 1390, 1170, 1090 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz):	8 7.30-7.40 (m, 6H), 7.50-7.65 (m, 4H).
Mass (m/z):	203 (M+1, 52), 202 (M^+, 60).

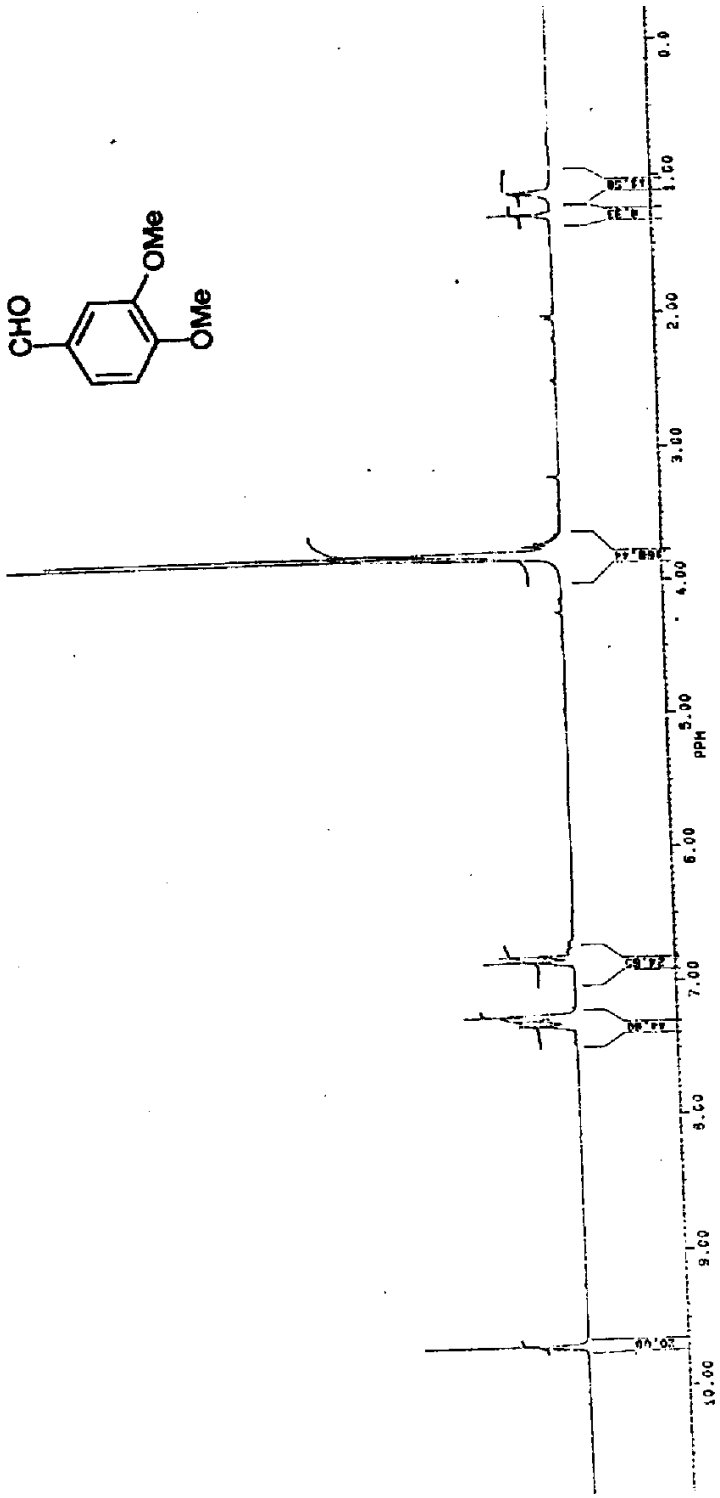
Methyl phenyl sulfoxide

Pale yellow liquid.

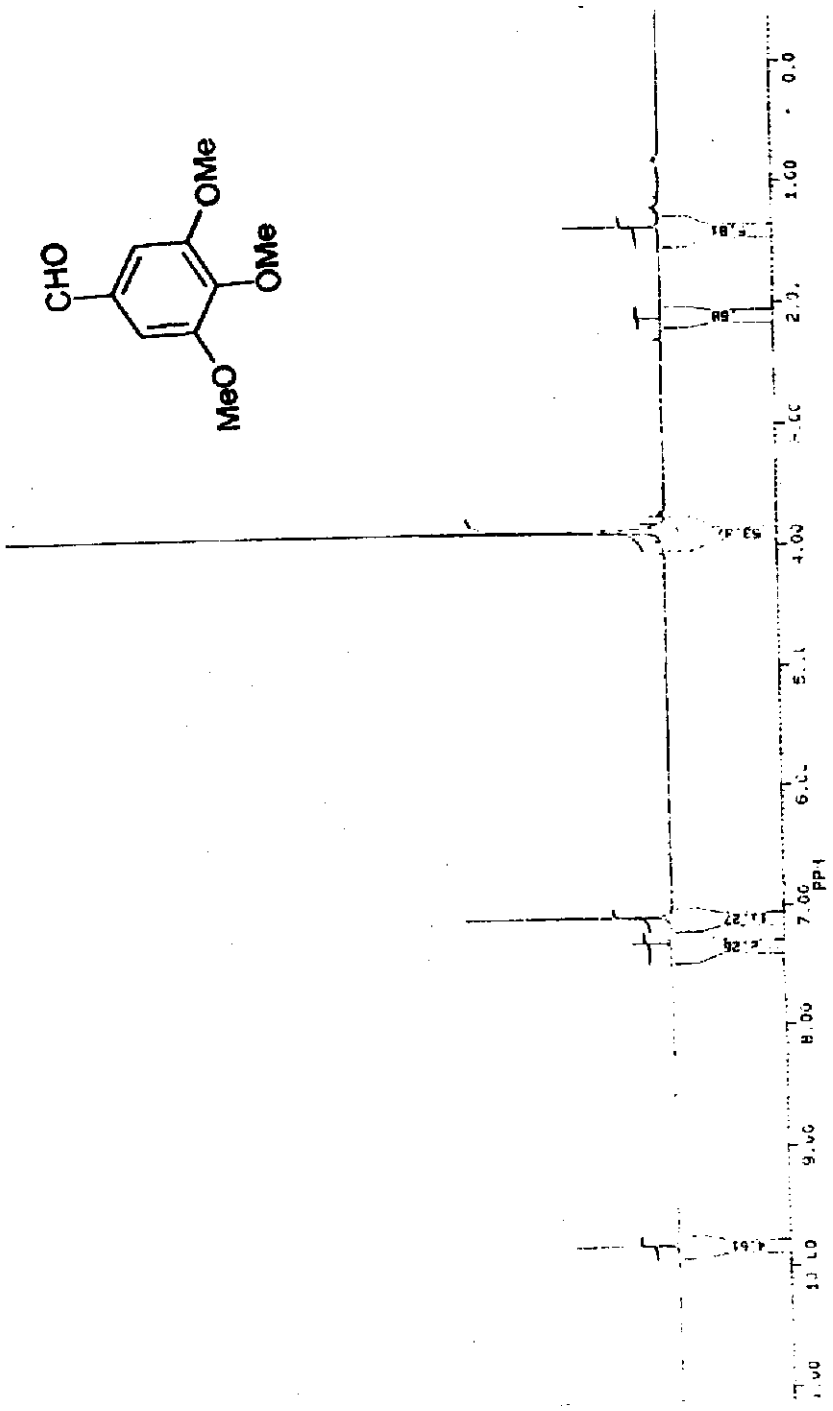
Yield: IR (neat):	80 %.
IR (neat):	1480, 1450, 1220, 1090, 1050 cm^{-1}.
^1H NMR ($CDCl_3$, 200 MHz):	8 2.75 (s, 3H, $-CH_3$), 7.50-7.60 (m, 3H), 7.65-7.70 (m, 2H).
Mass (m/z):	141 (M+ l, 10), 140 (M^+, 40).



^{1}H NMR SPECTRUM (200MHz) OF.2;5-DIMETHOXYACETOPHENONE IN $CDCI_3$



^{1}H NMR SPECTRUM (200MHz) OF 4,5 DIMETHOXYBENZALDEHYDE IN $CDCI_3$



^{1}H NMR SPECTRUM (200MHz) OF 3,5 DIMETHOXYBENZALDEHYDE IN $CDCI_3$

3.2.5 REFERENCES

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SECTION-C

SELECTIVE BENZYLIC OXIDATION OVER Mn-Zr USING 70% TBHP

3.3.0 INTRODUCTION

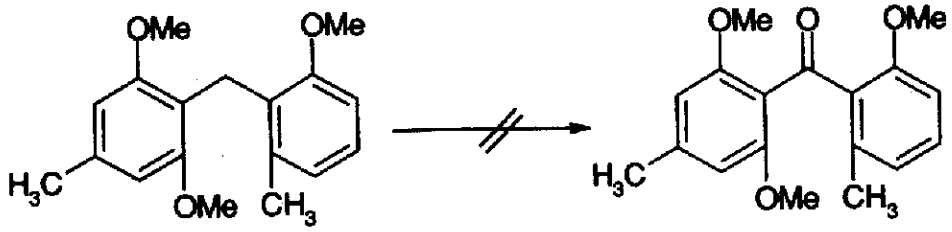
The C-H bond activation at the benzylic position of aromatics and fucntionalization of the alkanes by transition metal complexes under mild conditions is an important transformation in organic chemistry.[1] Stoichiometric amount of Co and Cr reagents are known under homogeneous conditions for these transformations.[1, 2] Soluble chromium catalysts[2, 3] as well as heterogeneous catalysts such as Cr-PILC [4] and Cr-APO [5] in combination with TBHP or O_2 are reported to effect these oxidations, however, these methods employ either anhydrous TBHP or reaction takes longer time.

Recently Sudalai et a1.[6] reported use of Cr-MCM-41 along with 70 % TBHP for the benzylic methyl and methylene group oxidations to corresponding acids and ketones.

3.3.1 Preamble

During the synthetic studies towards benzophenone portion of balanol, a novel protein kinase C inhibitor, the oxidation of compound 1 to the benzophenone 2 either failed or resulted into the formation of a complex reaction mixture (Scheme-1). We assumed that the formation of complex reaction mixture in this transformation is due to oxidation products of methyl groups to acid.

Scheme-1



Although this over oxidation is desired, the reaction was not clean as it might have resulted into products containing various combinations of methyl, carboxylic acid, benzylic methylene and/or benzylic ketone functionalities. Hence it was necessary to develop a new methodology to oxidize selectively the benzylic methylene group to the corresponding ketones without affecting the benzylic methyl group.

3.3.2 Results and Discussion

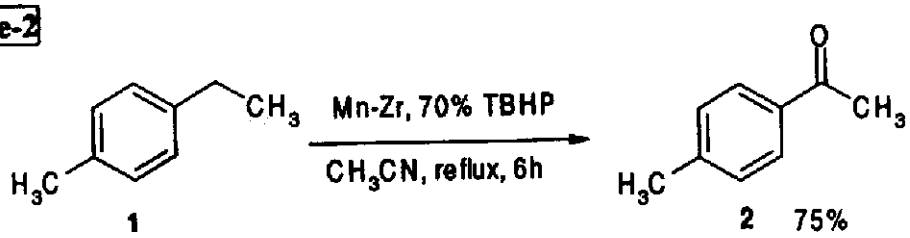
To achieve the selective oxidation of benzylic methylene group in the presence of methyl group, the catalyst used should be sufficiently mild and at the same time it should be sufficiently active for the oxidation of benzylic methylene group. As discussed in the section

II, perovskite type metal oxides[7, 8] like $LaCoO_3$ are sufficiently mild to oxidize the benzylic alcohols in the presence of amino group in good to excellent yields. The other catalysts like Cr-MCM-41 reported are known to oxidize both the benzylic methyl and methylene groups to the corresponding acids and ketones. We planned to use less reactivity of $LaCoO_3$ for this selcective oxidation of benzylic methylene group to the corresponding ketones but unfortunately this transformation failed to give the desired ketone and only starting material was recovered from the reaction mixture.

Recently Ramaswamy et a1.[9] reported synthesis and application of the novel metal oxide materials of fluorite structure based on zirconia and stabilized with 3d transition metal ions. A new series of zirconia base fluorite type oxides stabilized by Cr, Mn, Fe, Co and Ni are found to be active for the oxidation of hydrocarbons. Assuming fluorite type catalysts are more reactive than perovskite type catalysts we undertook screening of these Mn-Zr, Cr-Zr, Fe-Zr, Co-Zr and Ni-Zr catalysts for oxidation of benzylic methylene group. These stabilized zirconia catalysts were prepared by mixing aq. solution of $Zr(N0_3)_2$ and nitrates of Mn, Fe, Co and Ni in the molar ratio of 80:20, to which aq. solution of tetramethylammonium hydroxide (25 %) was added under vigorous stirnng upto pH-8. The resulting precipitate was washed with deionised water, dried at 383° K for 24 h and calcined at 773° K for 8 hr.

Substrate selected for the screening of these catalysts was 4-methylethylbenzene and reactions were carried out using 30 % H_2O_2 and 70 % TBHP as co-oxidants along with a pinch of phase transfer catalyst tetrabutylammonium bromide as shown in scheme-2

Scheme-2



1 2 75%

The results obtained are summarized in table-1. Results obtained showed that Mn-Zr along with 70 % TBHP as co-oxidant in acetonitrile was the best system for the selective oxidation of 4-metylethylbenzene to the 4-methylacetophenone. Use of other catalysts (Fe-Zr, Co-Zr and Ni-Zr), methanol solvent and replacement of 70 % TBHP with 30 % H_20_2 resulted either into the formation of complex mixture or no reaction. Cr-Zr catalyst along with 70 % TBHP in acetonitrile yielded 4-methylacetophenone in 40 % yield.

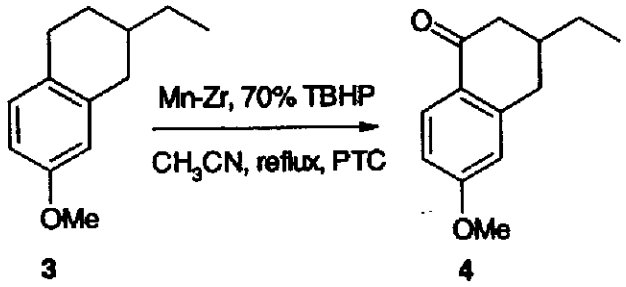
Table-1

Entry	Catalyst	Oxidant	Solvent	Yield (%)
1	Cr-Zr	30% H_2O_2	MeOH	Complex mixture
2	Cr-Zr	30% H_2O_2	CH_3CN	No reaction
3	Cr-Zr	70% TBHP	CH_3CN	40
4	Mn-Zr	70% TBHP	CH_3CN	75
5	Co-Zr	70% TBHP	CH_3CN	No reaction
6	Fe-Zr	70% TBHP	CH_3CN	No reaction
7	Ni-Zr	70% TBHP	CH_3CN	No reaction
8	No Catalyst	70% TBHP	CH_3CN	No reaction

To generalize this methodology various compounds possessing benzylic methylene groups were subjected for oxidation under this Mn-Zr-70 % TBHP-PTC conditions in acetonitrile solvent to give corresponding ketones in good to excellent yields. (Table-2).

Selective oxidation of benzylic methylene group at G-4 has been carned out in 60 % yield under this Mn-Zr-TBHP-PTC conditions (Entry-4), as shown in scheme.

Scheme-3



3 4

Table-2

Entry	Substrate	Time (hr)	Product	Yield (%)
1	Tetralin	8	1-Tetralone	80
2	4-Methylethylbenzene	10	4-Methylacetophenone	75
3	Diphenylmethane	10	Benzophenone	65
4	2-Ethyl-1,2,3,4-tetrahydro-7-methoxynaphthalene	10	3-Ethyl-6-methoxy-1-tetralone	60
5	Toluene	24	No reaction	-

Thus tetralin **3** on oxidation under this Mn-Zr catalyzed condition resulted into the formation of tetralone **4**. Although tetralin **3** possesses two benzylic positions, only the CH_2 at C-4 position underwent oxidation whereas CH_2 at C-1 position remained unaffected. Toluene remained unaffected under these reaction conditions.

This methodology was then extended for the synthesis of desired benzophenone portion of balanol **2** but unfortunately under these conditions the required oxidation of benzylic CH_2 of compound **1** failed and only starting material was recovered from the reaction mixture. Probable reason for this failure may be the steric hindrance, as compound **1** is sterically congested.

Exact mechanism of this transformation is not known.

3.3.3 CONCLUSION

1. A mild, effective and selective methodology has been developed using the stabilized zirconia based catalyst, Mn-Zr along with 70 % TBHP.
2. Selective oxidation of benzylic CH_2 in presence of benzylic CH_3 has been achieved under these reaction conditions.
3. The present methodology is environmentally friendly as it avoids use of corrosive chemicals/reagents.
4. Catalyst is reusable and recyclable at least for three times without loss in activity and selectivity, after filtration from reaction mixture and calcination.

3.3.4 EXPERIMENTAL

Mn-Zr, Fe-Zr, Cr-Zr, Ni-Zr and Co-Zr catalysts were prepared by known procedure reported by Ramaswamy et al.[9]

Typical Experimental Procedure for Benzylic,Oxidation

In a typical experimental procedure a mixture of diphenyl methane (1.68 g, 0.01 mole), 70 % TBHP (1.5 ml, 0.01 mole) and a pinch of tetrabutylammonium bromide in acetonitrile (15 ml) was heated under reflux for 10 hr. After completion of the reaction (TLC), the catalyst was filtered off, acetonitrile was removed under reduced pressure and the residue was diluted with chloroform (10 ml). The chloroform layer was washed successively with saturated solution of sodium sulfite, water and dried over sodium sulphate. Evaporation of the solvent followed by column chromatography afforded benzophenone (1.18 g, 65 %).

Benzophenone

IR (nujol): 1700, 1640 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 7.40-7.52 (m, 4H), 7.53-7.60 (m, 2H), 7.75-7.85 (m, 4H).

1-Tetralone

Pale yellow liquid.

Yield: 80 %.

IR (Neat): 1660, 1580 cm^{-1}.

^1H NMR ($CDCI_3$, 200 MI-iz): 8 2.00-2.25 (m, 2H), 2.55-2.75 (m, 2H), 2.80-3.05 (m, 2H), 7.15-7.35 (m, 2H), 7.40-7.50 (m, 1H), 7.95-8.10 (m, 1H).

3-Ethyl-6-methoxy-1-tetralone:

Colourless liquid.

Yield: 60 %

IR (neat): 1700, 1630 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): 8 0.98 (t, J=6.6 Hz, 3H), 1.19-1.30 (m, 1H), 1.40-1.55 (m, 2H), 2.28 (d, J=9.9 Hz, 1H), 2.60-2.78 (m, 2H), 2.89-3.05 (m, 1H), 3.85 (s, 3H, -OMe), 6.71 (s, 1H, aromatic), 6.81 (d, J=7.5 Hz, 1H, aromatic), 7.98 (d, J=7.5 Hz, 1H, aromatic).

Mass (m/z): 204 (M^+)

4-Methylacetophenone Colourless liquid

Yield:	75 %.
IR (Neat):	1705, 1640, 1320, 950, 850 cm^{-1}
^1H NMR ($CDCl_3$, 200 MHz):	8 2.40 (s, 3H), 2.55 (s, 3H), 7.25 (d, J=8 Hz, 2H), 7.85 (d, J=8 Hz, 2H).

3.3.5 REFERENCES

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LIST OF PUBLICATIONS

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4. A Short and Efficient Synthesis of Benzophenone Precursor for Balanol

Mahesh L. Patil, S. Ramlingam, Hanumant B. Borate and V. H. Deshpande

(To be Communicated)

5. An Efficient and Selective Oxidation of Benzylic Alcohols over LaCoO3 using 70% TBHP,

Mahesh L. Patil, Hanumant B. Borate and V H. Deshpande (To be Communicated)

6. A Short and Regiospecific Synthesis of (±)- Brasiliquinone B and (±)- 8-Deoxybrasiliquinone B **Mahesh L. Patil**, Hanumant B. Borate and V H. Deshpande

(To be Communicated)

7. Selective Benzylic Oxidation over Mn-Zr using 70% TBHP

Mahesh L. Patil, Hanumant B. Borate and V. H. Deshpande

(To be Communicated)