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CERTIFICATE

Certified that the work incorporated in the thesis entitled *"Synthetic Strategies Towards Saintopin and its Derivatives, Pyranonaphthoquinone Antibiotics and Catalytic Organic Transformations"* 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.

(V. H. Deshpande)

Research Supervisor


Dedicated to
My
Parents
&Teachers

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Vivek Bulbule

ABBREVIATIONS

Ac_2O	Acetic anhydride
AgO	Silver oxide
AIBN	2,2'-Azobisisobutyronitrile
$Al(NO_3)_2$	Aluminium nitrate
$AlCl_3$	Aluminium chloride
$AlMe_3$	Trimethylaluminium
BCl_3	Borontrichloride
$BF_3.Et_2O$	Borontrifluoride diethyl etherate
BnBr	Benzylbromide
BPO	Benzoyl peroxide
Bu_3N	Tributyl amine
Bu_3SnH	Tributyltinhydride
CAN	Cerium(IV) ammonium nitrate
$CDCl_3$	Deuterated chloroform
$Cu(NO_3)_2$	Copper nitrate
$CuSO_4.5H_2O$	Copper(II) sulfate pentahydrate
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminium hydride
DMF	Dimethylformamide
DMPU	N'N'-Dimethyl-N'N'-propylene urea
DMS	Dimethyl sulfate
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
$FeCl_3$	Iron (III) chloride
H_2O_2	Hydrogen peroxide
HMPA	Hexamethylphosphoramide
HRV	Human rhinovirus
HT	Hydrotalcites
IPA	Isopropyl alcohol
IR	Infra-red
$^{\cdot}ON(SO_3K)_2$	Potassium nitrosodisulfonate
$KOBu^t$	Potassium tert-butoxide
LAH	Lithium aluminium hydride

LDA	Lithium diisopropylamide
LDHs	Layered double hydroxides
LiTMP	Lithium tetramethylpiperidide
$Mg(NO_3)_2$	Magnesium nitrate
MnO_2	Manganese(IV) oxide
MS	Mass spectra
MsCl	Mesyl chloride
$Na_2S_2O_4$	Sodium dithionite
Na_2SO_4	Sodium sulfate
NBS	N-Bromosuccinimide
n-BuLi	n-Butyllithium
NIH	National Institute of Health
NOE	Nuclear overhauser effect
PBr_3	Phosphorus tribromide
PCC	Pyridinium chlorochromate
$Pd(OAc)_2$	Palladium(II) acetate
$Pd(OH)_2$	Palladium hydroxide
Pd-C	Palladium on carbon
PDC	Pyridinium dichromate
$POCl_3$	Phosphorus oxychloride
PPA	Polyphosphoric acid
PtO_2	Platinum(IV) oxide
PTC	Phase transfer catalyst
RT	Room temperature
S	Sulfur
$SnCl_4$	Tin(IV) chloride
TBAF	Tetrabutylammonium fluoride
TDC	Topoisomerase dependent cleavage
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
$TiCl_4$	Titanium(IV) chloride
TLC	Thin layer chromatography
TMSCN	Trimethylsilyl cyanide
Triton B	Benzyltrimethylammonium hydroxide
TsOH	*p*-Toluenesulphonic acid
$Zn(NO_3)_2$	Zinc nitrate
$ZnCl_2$	Zinc chloride

b **GENERAL REMARKS** b

+ All reactions requiring anhydrous conditions were performed under a positive pressure of argon or nitrogen using oven-dried glassware (110 ^{o}C).

+ All commercial reagents were obtained from Aldrich Chemical Co and others. Progress of the reaction was monitored by TLC and was visualized by UV absorption by fluorescence quenching or I_2 staining or by both.

+ Solvents for anhydrous reactions were dried by standard procedures. All organic layers obtained after extractions were dried over anhydrous Na_2SO_4. All evaporations were carried out under reduced pressure on Buchi rotary evaporator. Solvents used for chromatography were distilled at respective boiling points. Silica gel for column chromatography was 60-120 mesh.

+ All the temperatures are in ^{o}C. All the melting points and boiling points are in ^{o}C and are uncorrected and were recorded on a Buchi B-540 melting point apparatus.

+ IR spectra were recorded on a Perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR (ν max in cm^{-1}).

+ ^{1}H NMR spectra were recorded using TMS as internal reference on Bruker AC-200 and Bruker MSL-300 instrument using $CDCl_3$ or $CDCl_3$ + CCl_4, DMSO-d_6, Acetone-d_6 as solvent. Chemical shifts are recorded in δ. ^{13}C NMR spectra were recorded on Bruker AC-200 and Bruker MSL-300 instrument operating at 50 MHz and 75 MHz respectively.

+ Mass spectra were recorded on Finnigan-Mat 1020C Mass Spectrometer and are obtained at an ionization potential of 70 eV.

+ GLC was carried out on Hewlett Packard 5890.

+ Microanalysis was carried out in the microanalytical section of NCL.

+ Scheme numbers and reference numbers given in each section refer to the particular section only.

Thesis Abstract

Thesis Title

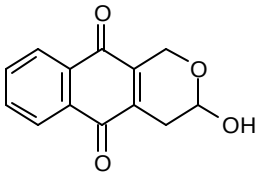
"Synthetic Strategies Towards Saintopin and its Derivatives, Pyranonaphthoquinone Antibiotics and Catalytic Organic Transformations"

Thesis is divided into three chapters.
Chapter-I: Synthetic Studies Towards Naphtho [2,3-c] pyran -5,10-diones.
Chapter-II: The Synthetic Strategies Towards the Synthesis of Saintopin and its Derivatives.
Chapter-III: Catalytic Organic Transformations.

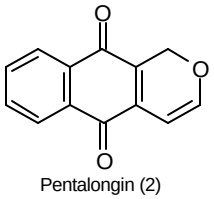
Chapter I: Synthetic Studies Towards Naphtho [2,3-c] pyran -5,10-diones

This chapter is further divided into three sections.

Section 1: Total Synthesis of Psychorubrin and Pentalongin



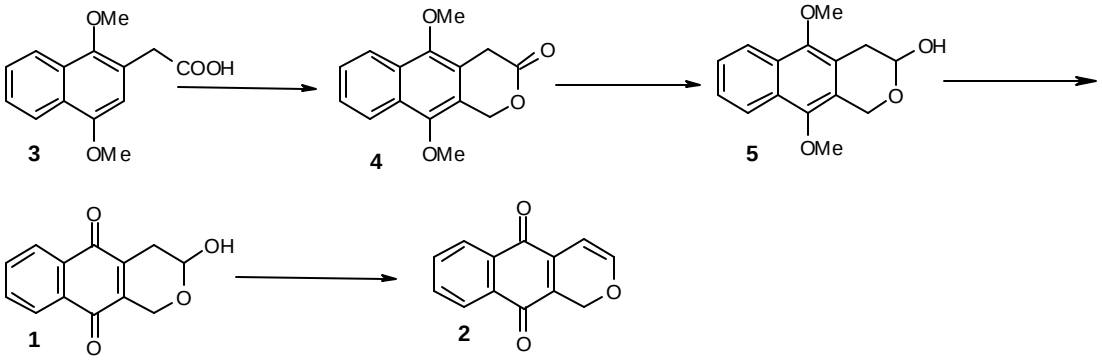
Psychorubrin (1)



Pentalongin (2)

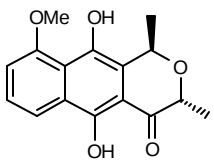
Psychorubrin (**1**)[1], a naturally occurring pyranonaphthoquinone with significant antitumor activity, was isolated from *Psychotria rubra*, while pentalongin (**2**)[2] was isolated from *Pentas longiflora* Oliv (Rubiaceae). Pentalongin and psychorubrin are both so called pyranonaphthoquinone antibiotics, a particular group of microbial and plant metabolites with a characteristic 1*H*-naphtho [2,3-c] pyran -5,10-dione nucleus and are known to possess a variety of physiological activities against Gram positive bacteria, pathogenic fungi and yeasts as well as antiviral activity. This section describes the total synthesis of psychorubrin and pentalongin. The key intermediate

Scheme-1

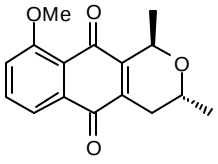


naphthopyranone **4** was prepared from 1,4-dimethoxy-2-naphtylacetic acid **(3)** by chloromethylation[3] (Scheme-1). Partial reduction of the naphthopyranone **4** gave the required hemiacetal **5**. The hemiacetal when treated with cerium (IV) ammonium nitrate gave the target molecule psychorubrin (**1**). Dehydration of the psychorubrin with catalytic amount of *p*-toluenesulfonic acid in benzene under reflux gave pentalongin (**2**).

Section 2: Attempts Towards the Synthesis of Hongconin and Related Compounds



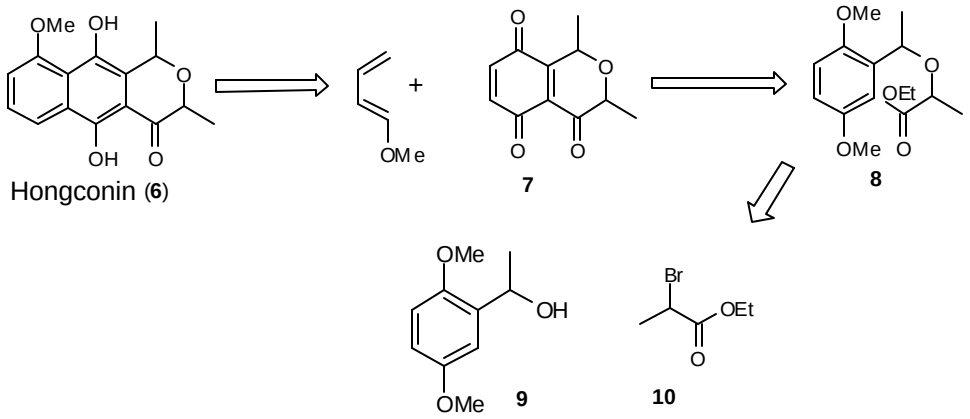
Hongconin (**6**)



Eleutherin (**7**)

Hongconin (**6**)[4] is a novel naphthohydroquinone isolated from the rhizome of *Eleutherine americana*. Merr at Heyne (Iridaceae), a herbal plant from southern China that has been used as a medicine[5]. Hongconin and related compounds eleutherol, eleutherin (**7**) and isoeleutherin have been isolated and formulation of these four purified compounds was demonstrated to increase coronary blood flow in isolated guinea pig heart[6,7]. This section describes various attempted routes towards the synthesis of hongconin and related compounds.

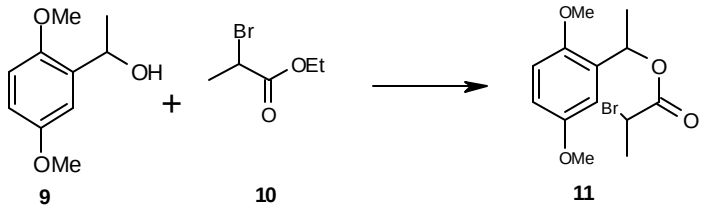
Retrosynthetic analysis suggested that the required ether **8** which could be prepared from the alcohol **9** and ethyl 2-bromo propionate (**10)** would serve as important intermediates for the synthesis of hongconin.



Route A: Diels-Alder approach.

The required alcohol **9** was prepared by Friedel-Crafts acylation of 1,4-dimethoxynaphthalene, when alcohol **9** was treated with n-BuLi and ester **10** the desired ether **8** could not be obtained, instead it gave the transesterified product **11** (Scheme-2).

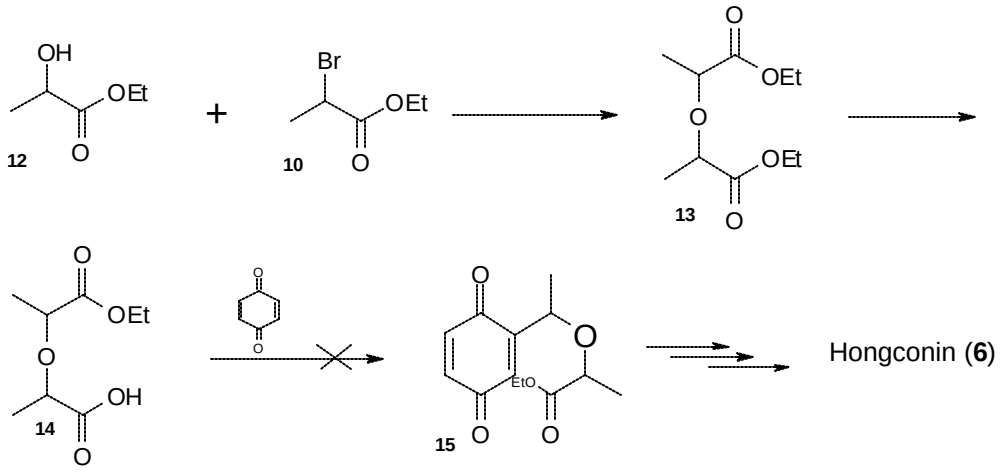
Scheme-2



Route B: **Alkoxy Carbonylation of Quinones.**

Quinones efficiently trap the radical upon decarboxylation[8]. According to this strategy **14** was treated with benzoquinone but the desired ether **15** could not be obtained (Scheme-3).

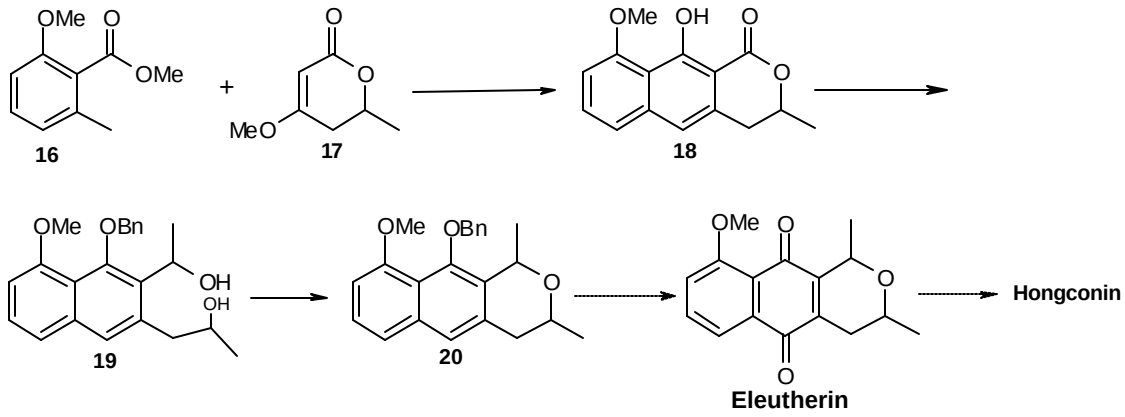
Scheme-3



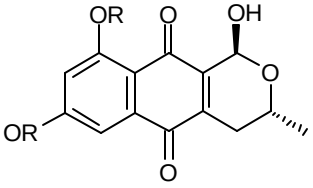
Route C: **Michael addition approach**:

The formation of two C-C bonds in a single step between methyl 2-methoxy-6-methyl benzoate (**16**) and dihydropyrone **17** was effected by Michael addition reaction to give the required tricyclic lactone **18** as shown in scheme-4. Accordingly ester **16** was reacted with dihydropyrone **17** in presence of LDA[9] to afford the desired lactone **18**. This lactone was protected and partially reduced with DIBAL-H. The resulting lactol was subjected to Grignard reaction using methyl magnesium iodide and the diol **19** thus obtained was cyclised in refluxing benzene in presence of catalytic amount of *p*-toluene sulfonic acid to give the required dimethyl pyran skeleton **20** of hongconin.

Scheme-4



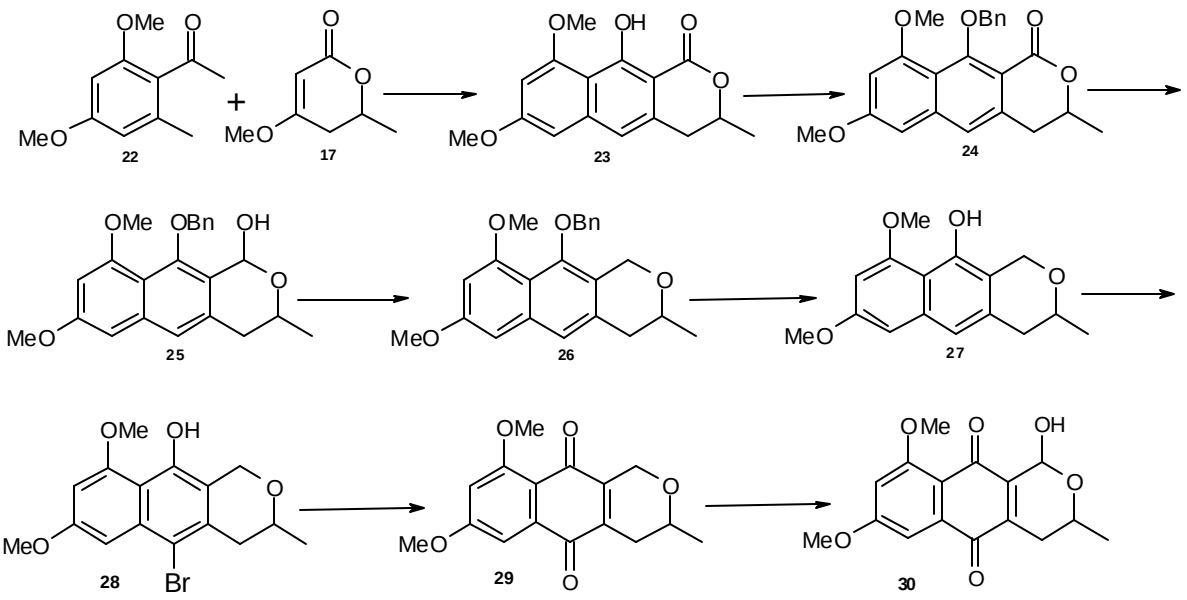
Section-3: Studies Directed Towards the Synthesis of Thysanone



R= H Thysanone(21)
R=OMe

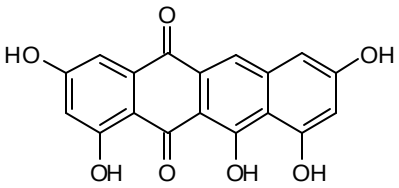
Thysanone (**21**)[10], a novel naphthoquinone with a lactol ring is an effective inhibitor of HRV 3C- protease and was isolated in 1991 by Singh *et al*. from *Thysanophora penicilloides*. Retrosynthetic studies suggested that tricyclic intermediate could be prepared by lithiation of orsellinate derivative followed by treatment with dihydropyrone. The synthesis of thysanone was based on the condensation approach applied for the synthesis of hongconin (Section -2 C, Scheme-4).

Scheme-5



Thus the tricyclic intermediate **23** was prepared by lithiation of orsellinate derivative **22** followed by treatment with dihydropyrone **17** by a Michael reaction. Phenolic functionality of the above intermediate **23** was protected as a benzyl ether. The benzyl ether **24** was first reduced to corresponding lactol **25** with DIBAL-H and then to the benzopyran **26** with sodium borohydride in presence of trifluoroacetic acid. Debenzylation of the benzopyran gave the corresponding naphthol **27**. Selective nuclear bromination at *para* position of naphthol **27** afforded monobrominated product **28** which was further treated with CAN to give quinone **29**. Benzylic bromination of quinone **29** followed by *in situ* treatment of the intermediate bromide with aqueous THF gave methoxy thysanone **30**.

Chapter-II: The Synthetic Strategies Towards the Synthesis of Saintopin and its Derivatives



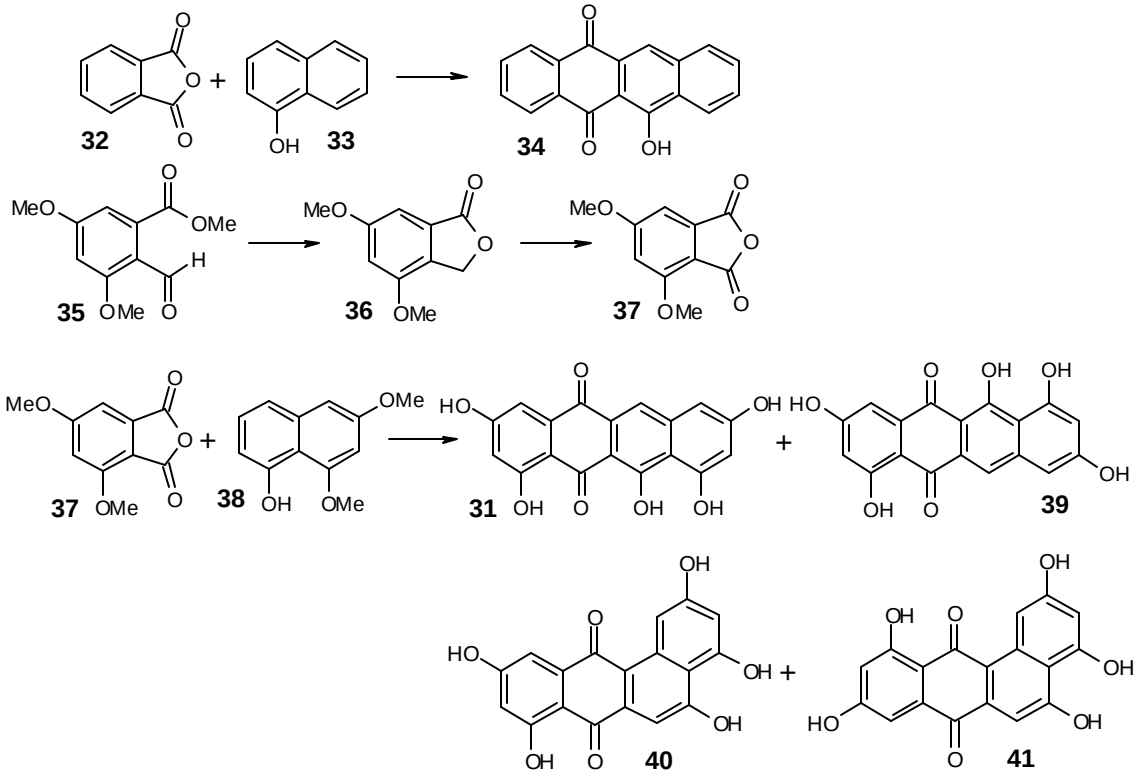
Saintopin (**31**)

In 1990, Yamashita *et al*[11] isolated a new antitumor antibiotic saintopin (**31**) which induces both topoisomerase I and II mediated DNA cleavage from the culture broth of *Paecilomyces sp*. The interesting biological activity of saintopin coupled with the low yield from natural sources necessitated the need for a synthetic route to saintopin. So far no synthesis of saintopin has been reported, various strategies attempted in the present work for the synthesis of saintopin are described in this chapter.

Part-1 : Friedel-Crafts Approach:

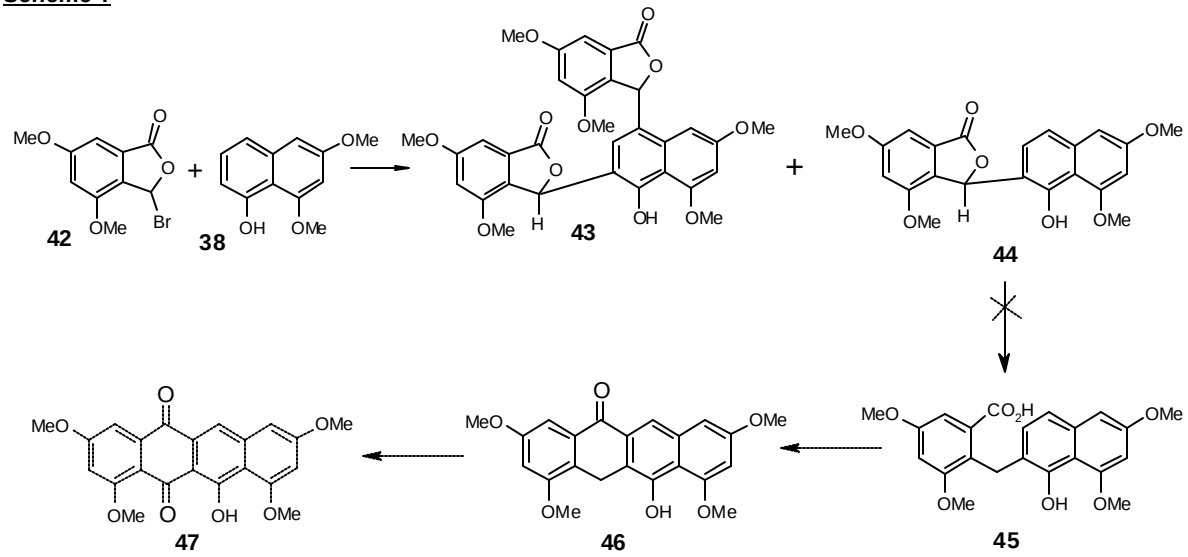
Condensation of phthalic anhydride with phenol/hydroquinone in aluminium trichloride-sodium chloride melt at 190^{o} C to afford anthraquinones is well reported in the literature[12] (Scheme-6).

Scheme-6



Using this straightforward approach, we envisaged that the condensation of 4,6-dimethoxyphthalic anhydride (**37)** and required 6,8-dimethoxy-1-naphthol (**38**) would give saintopin (**31**) along with three other regioisomers **39**, **40**, **41**. Accordingly a model study was carried out on phthalic anhydride and α-naphthol which gave the required naphthacenedione **34** in low yields. When fusion reaction was carried out on required anhydride **34** and naphthol **35** it gave a complex mixture of products which was difficult to purify. Hence this approach was discontinued. To overcome this problem we planned a different route which was based on the regiospecific alkylation[13] of naphthol **38** with bromophthalide **42**. When naphthol **38** was treated with bromophthalide **42** in presence of $SnCl_4$ at 0^OC it gave a mixture of two products, dialkylated lactone

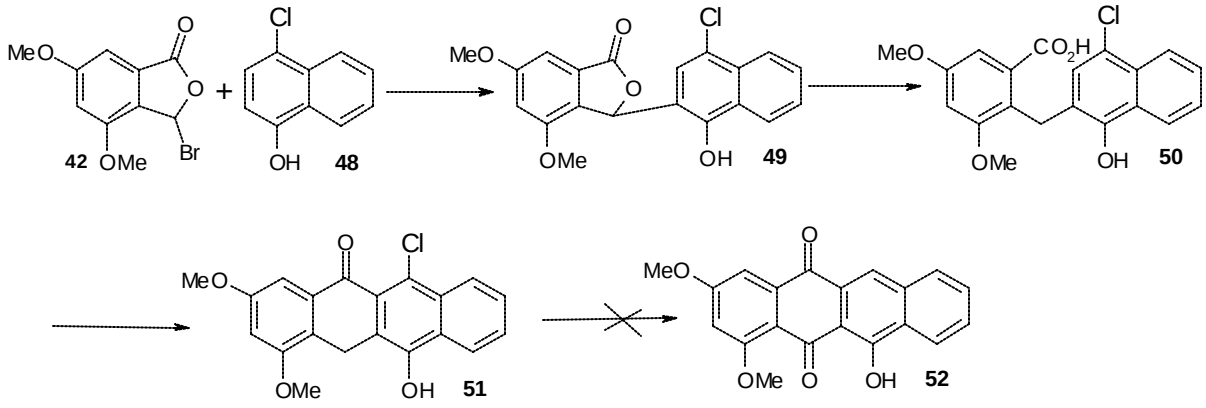
Scheme-7



43 as well as required lactone **44** (Scheme-7). Reductive opening of the lactone **44** failed to give the desired acid. **45**.

It was felt that formation of the dialkylated lactone **43** could be avoided either by blocking para position of naphthol or using less amount of bromophthalide **42**. To check the feasibility of the reaction, model study was carried out using 4-chloro-1-naphthol (**48**) to get the corresponding lactone **49** as shown in the scheme-8.

Scheme-8

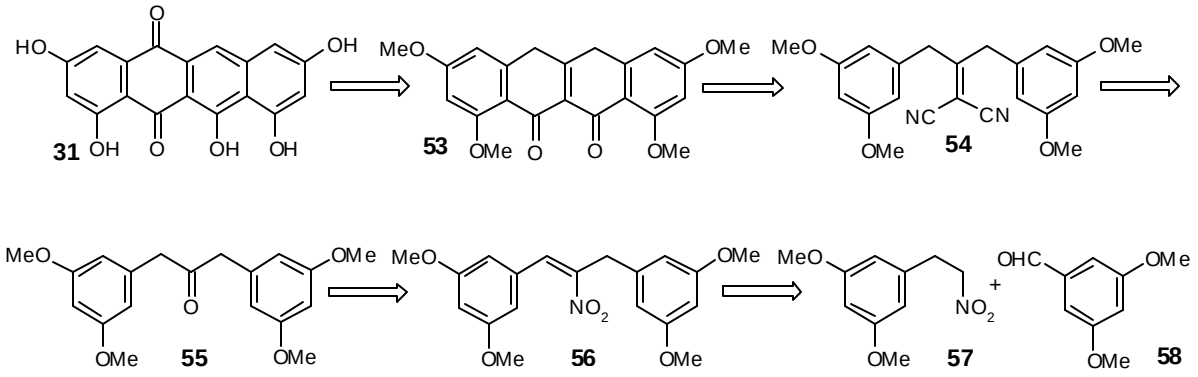


Reductive opening of the lactone **49** by Zn-$CuSO_4$- pyridine in aqueous alkali gave the corresponding acids **50** which on cyclisation gave the anthrone **51**. Oxidation of **51** could not give the quinone **52**.

Part-**2: Intermolecular Nitroaldol Condensation Approach**

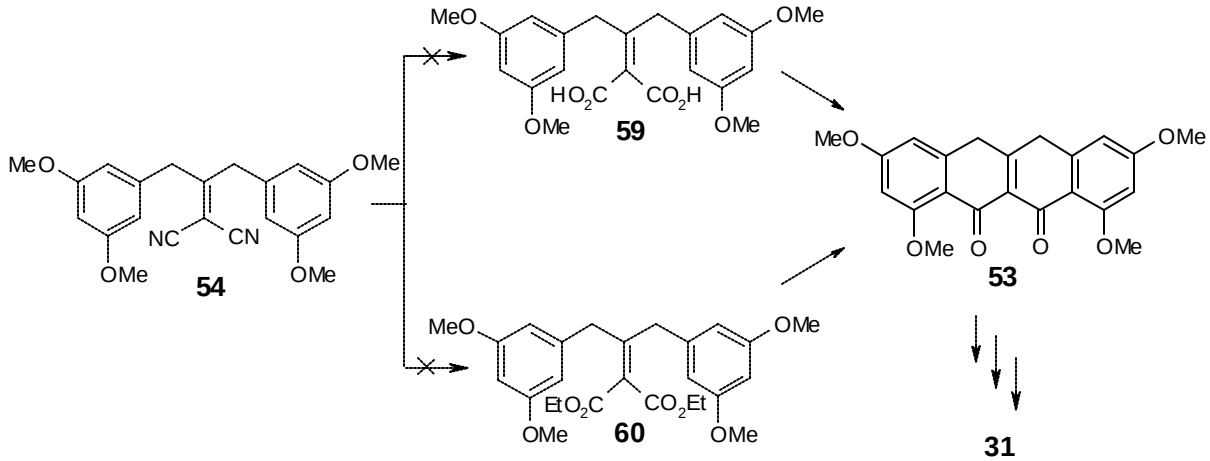
Problem of regiospecificity in earlier Friedel-Crafts route could be avoided by directly obtaining the diketo carbon framework **53** which could be elaborated to saintopin. Attempts in this direction are described in this part. Retrosynthetic analysis revealed that the key intermediate **58** which could be useful for the construction of tetracyclic carbon frame work could be prepared by successive intermolecular nitroaldol condensation (Henry reaction) followed by Nef and Knoevenagel condensation as shown in the Scheme-10.

Scheme-9



Accordingly nitroaldol condensation[14] of substituted nitroalkane **57** with the aldehyde **58** afforded the condensation product 5**6** which on Nef reaction[15] gave the desired ketone **55**. Knoevenagel type condensation[16] of **55** with malononitrile resulted in the formation of the key intermediate **54**. Further hydrolysis of **58** gave a mixture of products. Cyclisation of the impure hydrolysed product did not give the required diketo tetracyclic carbon frame **53** (Scheme-11). Hence this approach could not be continued further.

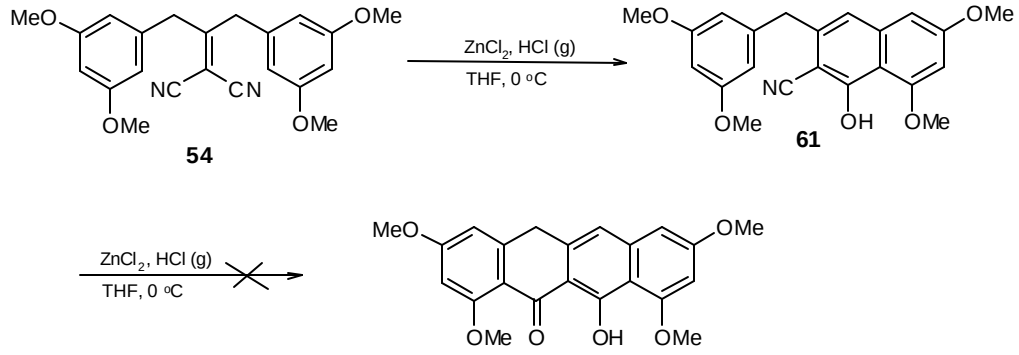
Scheme-10



Section-3: Intramolecular Houben-Hoesh Reaction Approach:

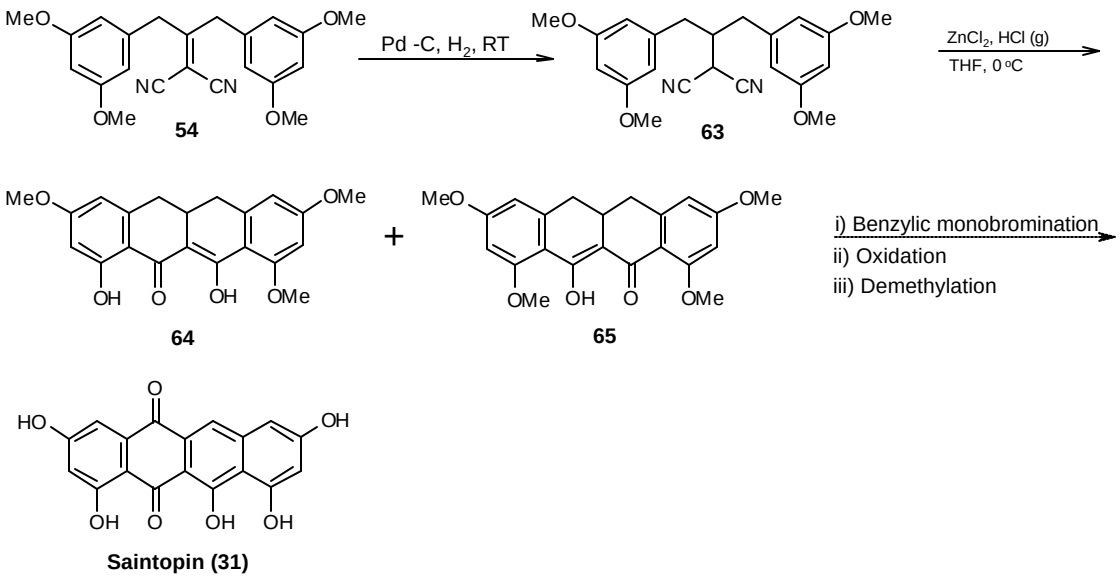
Although earlier intermolecular nitroaldol condensation approach was unsuccessful, it provided the key intermediate **54** for the Houben-Hoesh reaction approach. This approach is based on the acylative ring closure[16] of the aromatic ring via ketimine intermediate. Accordingly, dicyano compound **54** was treated with $ZnCl_2$ in anhydrous THF while dry HCl gas was bubbled in the reaction medium which gave the cyanonaphthol **61**. Cyanonaphthol was again subjected to Hoesh reaction conditions for a longer time but the expected product **62** could not be obtained.

Scheme-11



It was felt that selective reduction of double bond in dicyano compound **54** might help in the acylation reaction and thereby formation of diketo compound **53**. Accordingly reduction of double bond was effected using palladium on charcoal (10%) under hydrogen atmosphere at room temperature to give reduced dicyano compound **63.** Intramolecular Houben-Hoesh reaction of the reduced cyano compound **63** employing the reaction conditions as above gave a mixture of two products **64** in 26% and **65** in 44% yield. Compound **64** could be easily separated from compound **65** due to the considerable difference in R_f values of **64** and **65**.

Scheme-12



Benzylic monobromination of **64** or **65** and subsequent oxidation followed by demethylation would lead to the saintopin (**31**). Further work in this direction is in progress in our group.

The synthesis of saintopin was attempted by three different approaches namely Friedel-Crafts approach, nitroaldol condensation and Houben-Hoesh reaction. The Friedel-Crafts acylation suffered a problem of regioselectivity while Friedel-Crafts alkylation met with difficulties in opening of lactone ring of the required intermediate. Intermolecular nitroaldol condensation approach though unsuccessful, provided a key intermediate for the Houben-Hoesh reaction approach, which afforded the tetracyclic carbon frame-work of saintopin.

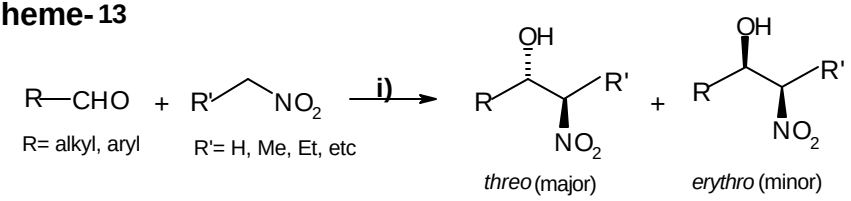
Chapter-III: Catalytic Organic Transformation.

This chapter is further divided into two sections

Section-1: Diastereoselective Synthesis of Nitroalcohol Derivatives over Mg-Al-Hydrotalcites

The Henry or nitroaldol reaction is one of the classical C-C bond forming processes by which diastereomeric mixtures of 2-nitroalcohols are formed on treatment of primary and secondary nitroalkanes and carbonyl compounds with a base. Mg-Al-Hydrotalcites (HT) have been found to catalyze the reaction between aldehydes and nitroalkanes very efficiently affording *threo* nitroalkanols in a highly diastereoselective manner (Scheme-13)[17].

Scheme-13

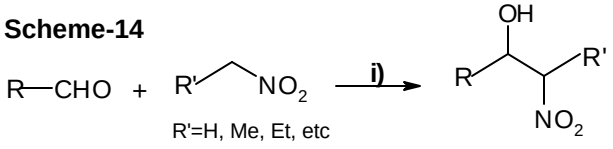


i) Mg-Al -HT (20% w/w), THF, reflux, 6-8 h.

Section -2: Benzyltrimethylammonium Hydroxide Catalyzed Nitroaldol Condensation

The classical nitroaldol reaction performed by using strong bases always results in the formation of side products like Canizzaro reaction of aldehydes or olefin formation. This section describes the study of the Henry reaction to develop a convenient and quick method for the effective synthesis of nitroaldols using Triton-B as a catalyst[18] (Scheme-14).

Scheme-14



i) Triton-B, 4-15 min, r.t.

References:

1. Hayashi, T.; Smith, F. T.; Lee, K. H. *J. Med. Chem*. **1987**, 30, 2005.
2. Hari, L.; De Buyck, L. F.; De Pooter, H. L. *Phytochemistry* **1991,** 30, 1726.
3. Finkelstein, J.; Brossi, A. *Org. Syn.* **1976,** 55, 45.
4. Zheng Xieng, C; Huizhu, H; Chengrui, W; Yuhui, L; Jianmi, D, Sankwa, U; Noguchi, H; Itaka, Y; *Chem. Pharm. Bull*. **1986**, 14, 2743.
5. Cheu, Z; Huang, H; Wang, Y.; Li, Y; Ding, J. Zhongcaoyao. 1981, 12 [*Chem. Abstr.* **1982**, 97, 20699]
6. Ding, J.; Huang, H; Zhongcaoyao. **1982**, 13, 499 [*Chem. Abstr*.**1983**, 98, 113584].
7. Hainan-Renmin Hospital Guanxinbin-keyan-Xiaozu Hainan Weisheng **1977**, 2, 43.
8. Sharma S. C. and Torssel, K. *Acta. Chimica Scandvica*, **1978**, B-32, 347.
9. Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Staunton J. and Wilkinson, M. R. ***J. Chem. Soc. Perkin I*** **1984**, 1043.
10. Singh, S. B.; Cordingley M. G.; Ball R. G.; Smith J. L.; Dombbrowski A. W. and Goetz M. A. *Tetrahedron Lett*. **1991**, 32, 5279.
11. Yamashita, Y.; Saitoh, K.; Ando, K.; Takahashi, K.; Ohno, H.; and Nakano, H. *J. Antibiotics* **1990**, 43, 1344.
12. Suzuki, F.; Trenbeath S.; Gleim, R. D. and Sih, C. J. *J. Org. Chem*.**1978**, 43, 4159.
13. Kim. K. S.; Vanotti. E.; Suato. E. and Johnson. F. *J. Am. Chem. Soc*. **1979**, 101, 2483.
14. Kodukulla, K. R. P.; Trivedi, G. K.; Vora, J. D.; Mathur, H. H. *Syn. Commun*. **1994**, 24, 819.
15. Bhide, B. H and Shah, K. K. *Ind. J. Chem*. B **1980**, (19) 9.
16. Barton, D. H. R.; Cottier, L.; Freund, K.; Luini. F.; Magnus, P. D. *J. Chem. Soc. Perkin Trans I*, **1976**, 499.
17. Bulbule, V. J.; Deshpande, V. H.; Velu, S.; Sudalai, A.; Sivasanker, S. and Sathe, V. T. *Tetrahedron* **1999**, 55, 9325.
18. Bulbule, V. J.; Jnaneshwara, G. K.; Deshmukh, R. R.; Borate, H. B and Deshpande, V. H. *Syn. Commun*. (in press).
19. Bulbule, V. J.; Deshpande, V. H and Bedekar, A.V. *J. Chem. Research* (S), **2000**, 220.

LIST OF PUBLICATIONS

- Selective Catalytic Transesterification, Transthiol Esterification and Protection of Carbonyl Compounds over Natural Kaolinitic Clay;
  D. E. Ponde, V. H. Deshpande, *V. J. Bulbule*, A. Sudalai and A. S. Gajare,
  J. Org. Chem., **1998**, 63, 1058-1063.

- Heterogeneous Henry Reaction of Aldehydes: Diastereoselective Synthesis of Nitroalcohol Derivatives over Mg-Al-Hydrotalcites;
  V. J. Bulbule, V. H. Deshpande, S. Velu, A. Sudalai, S. Sivasanker and V. T. Sathe,
  Tetrahedron, **1999,** 55, 9325-9332.

- $Cu(OTf)_2$, Catalysed Reactions of Furan and Thiophene with α,β-Unsaturated Ketones;
  V. J. Bulbule, V. H. Deshpande, A. V. Bedekar,
  J. Chem. Research(s), 2000, 220-221.

- Benzyltrimethylammonium Hydroxide Catalysed Nitroaldol Condensation;
  V.J. Bulbule, G. K. Jnaneshwara, R. R. Deshmukh, H. B. Borate and V. H. Deshpande,
  Synth. Commun., **2001,** 31, 3623-3626.

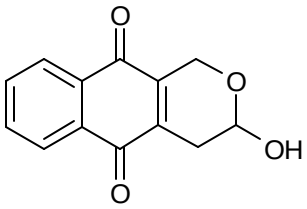
- Simple Synthesis of Two Naphthoquinones Antibiotics Psychorubrin and Pentalongin;
  V. J. Bulbule, P. S. Koranne, Y. S. Munot, H. B. Borate and V. H. Deshpande,
  Synth. Commun. (In press).

- Synthesis of Methoxy Thysanone and its Bromoderivative
  V. J. Bulbule, P. S. Koranne, H. B. Borate and V. H. Deshpande,
  (to be communicated)

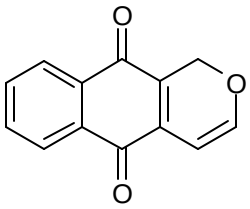
- Transterification of β-Ketoesters by Hydrotalcites (HT) like anionic clays
  V. J. Bulbule, P. S. Koranne, Y. S. Munot, H. B. Borate and V. H. Deshpande,
  (to be communicated).

1.0.1 INTRODUCTION

In the preliminary screening of crude extracts of Formosan plants, the alcoholic extracts of *Psychotria rubra,* which is known as "Chiu Chieh Mu" in Chinese folk medicine, showed significant reproducible inhibitory activity against KB cells. As a result of separation of the alcoholic extracts guided by an *in vitro* assay in KB cells, a new naphthoquinone named psychorubrin[1] and known helanin were isolated as the active principles. Psychorubrin, a naturally occurring pyranonaphthoquinone, is having significant antitumor activity. Pentalongin[2], another natural product, has been isolated from *Pentas longiflora* Oliv (Rubiaceae). The dry powder from the roots of *Pentas longiflora* is used as a folk remedy (Rwanda) to treat pityriasis versicolor, a fungal infection disease of the skin. In a bioassay guided phytochemical study of the roots, pentalongin was identified as the physiologically active compound, responsible for the antimycotic activity of the dry plant material.

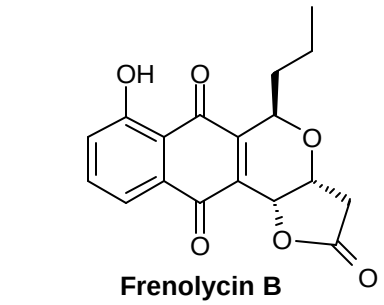


Psychorubrin (1)

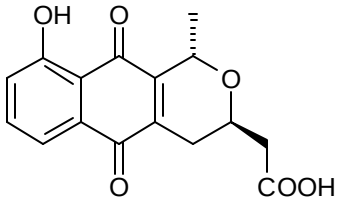


Pentalongin (2)

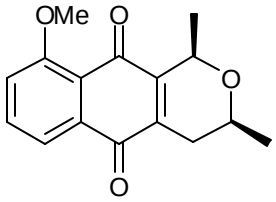
Psychorubrin and pentalongin are both so-called pyranonaphthoquinone antibiotics[3]. This particular group of microbial and plant metabolites with characteristic 1*H*-naphtho[2,3-c] pyran - 5,10-dione nucleus which includes examples such as nanaomycin A[4], frenolycin B[5] and eleutherin[6] is known to possess a variety of physiological activities. Although the synthesis of various pyranonaphthoquinones has been extensively investigated in the literature[7], a particular group of pyranonaphthoquinone antibiotics bearing a C (3)-C (4) double bond has received much less attention[8]. Examples of this group of 3, 4-dehydro-pyranonaphthoquinones include dehydroherbarin[9], anhydrofusarubin[10] and pentalongin and these pyranonaphthoquinones show significant antimicrobial, antifungal and antiparasital activities.



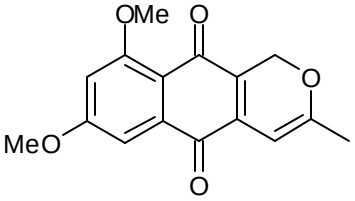
Frenolycin B



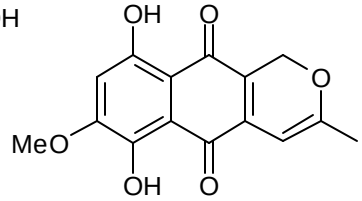
Nanaomycin A



Eleutherin



Dehydroherbarin



Anhydrofusarubin

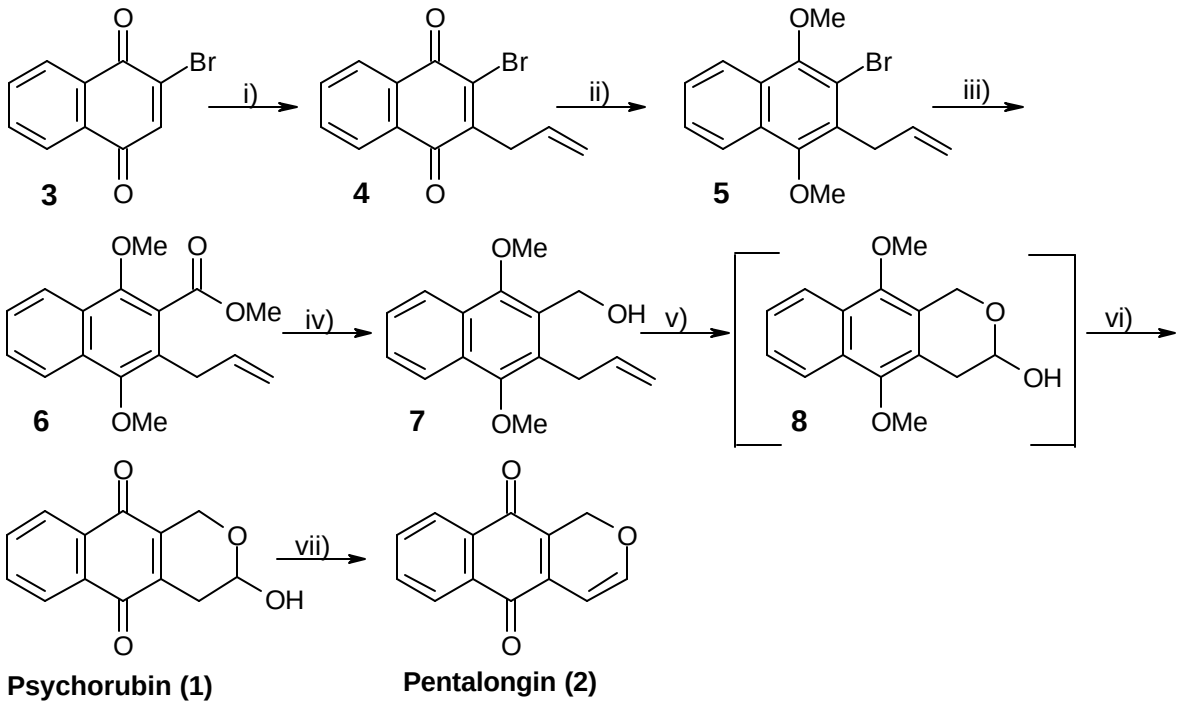
Synthesis of Psychorubrin and Pentalongin

Under this subheading, the total synthesis of psychorubrin and pentalongin is covered. This includes different approaches reported in the literature and synthesis of sulfone analogue of penatalongin is described. The present work also describes total synthesis of psychorubrin and pentalongin.

The first total synthesis of psychorubrin and pentalongin was reported by Kimpe *et al*[11]. wherein synthesis of these two naphthoquinone antibiotics was performed by two alternative cyclisation strategies of 2,3-disubstituted 1,4-naphthoquinones. In first approach the utility of 2-bromo-1, 4-naphthoquinone (**3**) which is readily available from 1-naphthol through oxidative bromination with NBS[12], was demonstrated. Radical allylation of the naphthoquinone **3** with vinyl acetic acid, using ammonium persulfate and silver nitrate in aqueous acetonitrile allowed the introduction of an allyl side chain at C2. The resulting 2-allyl-3-bromo-1, 4-naphthoquinone (**4**) was subjected to a conventional reductive methylation by means of tin (II) chloride and dimethyl sulfate to yield 2-allyl-3-bromo-1, 4-dimethoxynaphthalene (**5**). Direct conversion of this bromonaphthalene to substituted alcohol was effected *via* the introduction of a methoxycarbonyl group and subsequent reduction of this functional group with LAH. Methoxycarbonylation of bromonaphthalene was

carried out by bromine-lithium exchange and subsequent condensation of this transient anion formed with methyl chloroformate or methyl cyanoformate (Scheme-1).

Scheme-1



Reagents and conditions

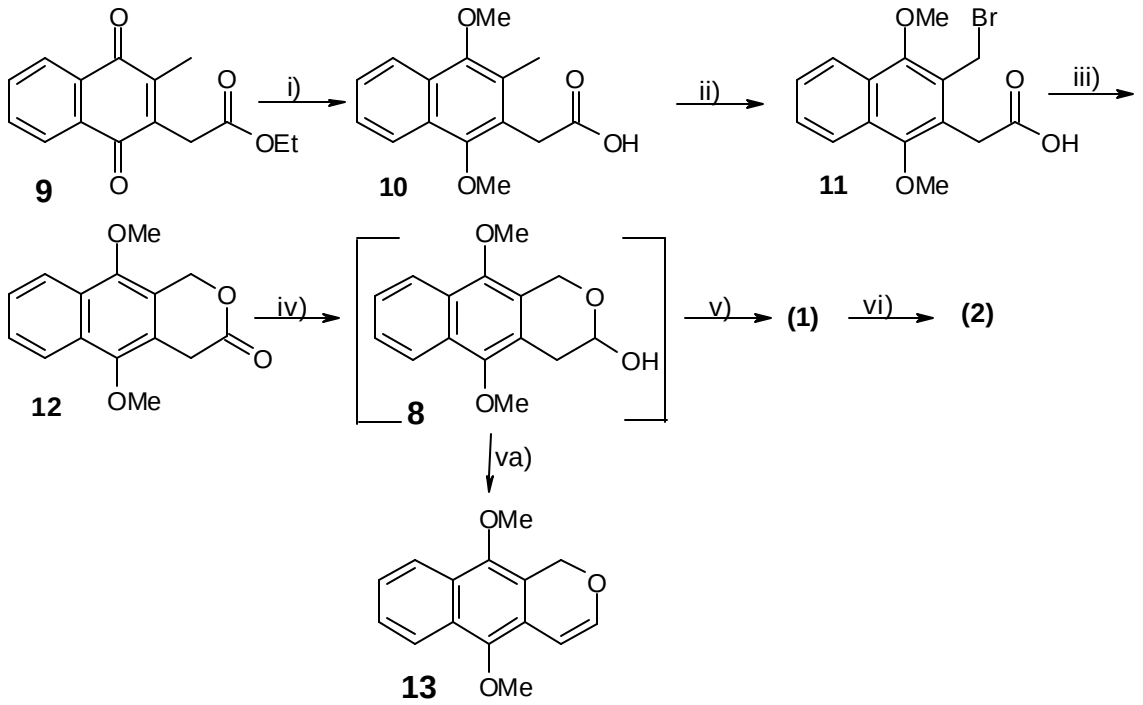
i) 1.5 eq.CH_2=CH-CH_2-CO_2H , 1.8 eq. $(NH_4)_2S_2O_8$, 0.5 eq. $AgNO_3$. ii) a) 3.5 eq $SnCl_2$, EtOH, 12 N HCl, 50 ^oC, 30 min. b) 15 eq. Me_2SO_4, KOH, 65 ^oC, 3h iii) a) 1 eq. n-BuLi , THF, -78 ^oC, 10 min. b) 1.2 eq. MeOCOCN, THF, -78 ^oC, 30 min, r.t. 2h. c) H_3O^+ iv) 1.2 eq. $LiAlH_4$, Et_2O, r.t. 16h. v) OsO_4 (cat.) 2 eq. $NaIO_4$, dioxane, H_2O 3:1, r.t. 3h. vi) 3 eq. CAN, CH_3CN, H_2O, r. t., 30 min. vii) TsOH (cat), benzene , heat, 30 min.

Lemieux-Johnson oxidation of alcohol with catalytic osmium (VIII) oxide and excess of sodium periodate resulted in lactol **8** as the sole product. These authors found that the lactol was undergoing spontaneous elimination of water in anhydrous solvents. Lactol was further treated immediately with cerium (IV) ammonium nitrate to afford psychorubrin (**1**). Finally pentalongin (**2**) was obtained by treatment of psychorubrin with *p*-toluenesulfonic acid in benzene under reflux for 30 minutes[1].

In another approach Kimpe *et al*[3]. reported the synthesis of psychorubrin and pentalongin using ethyl 3-methyl-1, 4-dioxo-2-naphthyl acetate (**9**) as starting material. Reduction of the

naphthoquinone ester with tin (II) chloride in conc. HCl and subsequent methylation of the intermediate hydroquinone ester with DMS in presence of excess potassium hydroxide gave the naphthylacetic acid **10** in 78% yield (scheme-2). Bromination of the above acid with NBS selectively occurred at methyl group. The bromomethyl naphthylacetic acid **11** thus obtained was then cyclised to lactone **12** using potassium carbonate in acetone under reflux.

Scheme-2



Reagents and conditions

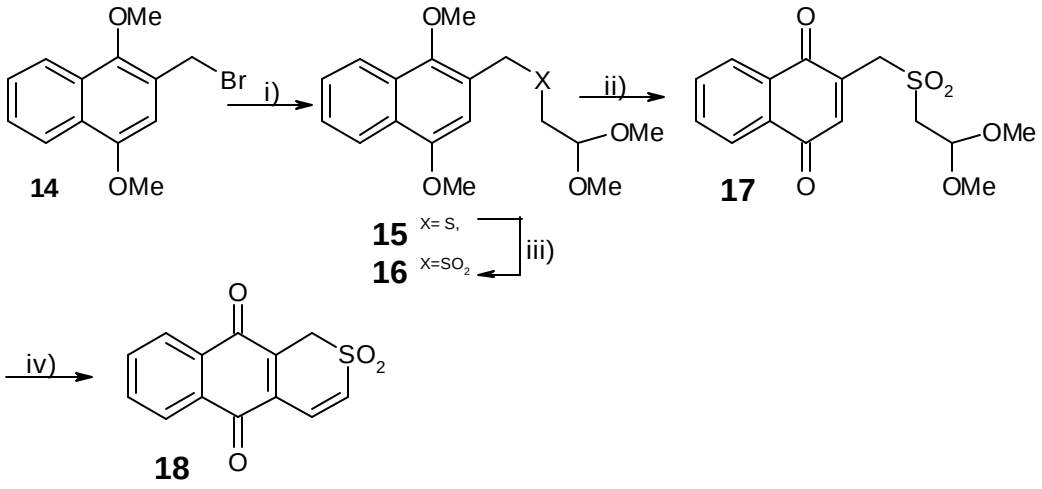
i) a) $SnCl_2$, 12 N, HCl, EtOH, 60-70 ^oC, 30 min. b) Me_2SO_4, 50% KOH, 80 ^oC, 2h. ii) NBS, BPO, CCl_4, reflux, 4h 100% iii) K_2CO_3, acetone, reflux, 2h, 99% iv) DIBAL-H, benzene, r. t., 1h, 69% v) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, H_2O, r. t., 30 min. va) Flash chromatography on silica gel, 32% vi) TsOH, benzene, reflux, 30 min., 64%.

Partial reduction of lactone **12** with 1 equivalent of DIBAL-H in benzene gave the hemiacetal **8**. Treatment of the crude lactol with cerium (IV) ammonium nitrate in aqueous acetonitrile gave psychorubrin (**1**). Dehydration of psychorubrin with *p*-toluenesulfonic acid in benzene under reflux gave pentalongin (**2**).

Recently Kimpe and co-workers reported the synthesis of a 2-thiapyranonaphthoquinone, a sulfone analogue of pentalongin[13]. The synthesis of the 1*H-2*-naphtho[2,3-c] thiapyran-5, 10-dione-

2, 2-dioxide (**18**) an unnatural 2-sulfone derivative of pentalongin was developed using the acid catalyzed cyclisation of the naphthoquinone sulfone acetal as a key step. The synthesis of 1*H-2*-naphtho[2,3-c] thiapyranoquinone has thus far been largely unexplored. A series of 3-alkoxycarbonyl and 3-carbonyl substituted 2-thiapyranonaphthoquinones have recently been claimed to possess antitumor activity. The starting point of the synthesis was the bromomethylation of 1,4 dimethoxynaphthalene with paraformaldehyde and hydrobromic acid giving the readily available 2-bromomethyl-1, 4-dimethoxynaphthalene (**14**)[14a]. A one-pot double alkylation of the above bromonaphthalene with thiourea and bromoacetaldehydedimethyl acetal afforded the sulfide acetal **15**.

Scheme-3

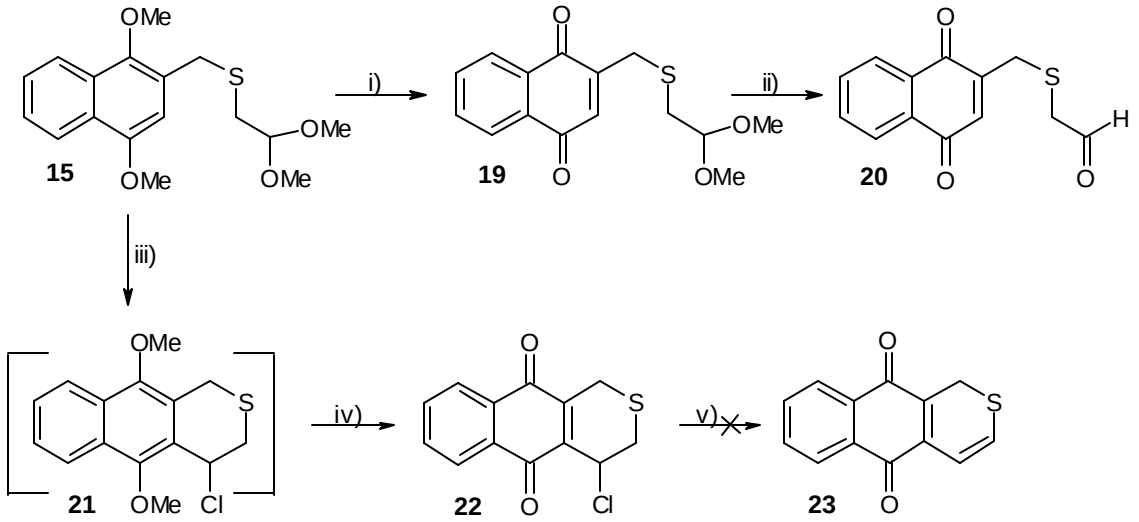


Reagents and conditions

i) a) 1.1 eq. $(NH_2)_2$-C=S, EtOH, heat, 6h. b) 2M NaOH, heat, 16h. c) 1.05 eq. $BrCH_2CH(OMe)_2$, CH_3CN heat, 4h. ii) 3 eq. CAN, H_2O, 0 ^oC, 30 min. iii) 3 eq. Oxone, MeOH, H_2O, 1:1, r. t. 16 h. iv) 12 M HCl, CH_2Cl_2, Et_2O, r. t. 16 h.

The chemoselective oxidation of the sulfide using oxone [15] in aqueous methanol gave the sulfone acetal **16** while subsequent oxidative demethylation using cerium (IV) ammonium nitrate resulted in the naphthoquinone sulfone acetal **17**. Upon treatment with conc. HCl in a biphasic system with ether compound **17** afforded, *via* hydrolysis of the acetal, intramolecular cyclisation of the intermediate aldehyde and elimination of hydrogen chloride, 1*H-2*-naphtho[2,3-c] thiapyran-5, 10-dione-2, 2-dioxide (**18**) in 49% yield.

Scheme-4



Reagents and conditions

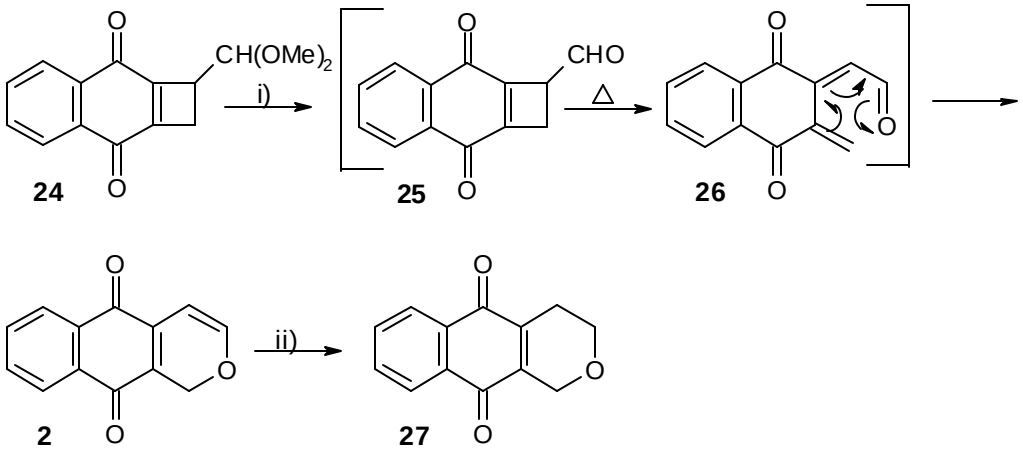
i) 3 eq. CAN, CH_3CN, H_2O, O ^oC, 30 min. ii) 12 M HCl, Et_2O, r.t. 16 h. iii) 12 M HCl, Et_2O, r.t. 6 h. iv) 2 eq. CAN CH_3CN, H_2O, r.t. 20 min. v) Et_3N, NaH, or DABCO.

In order to obtain 2-thia analogue of pentalongin, the naphthoquinone sulfide acetal **19** was treated with 12 M HCl, using the same conditions as those used for the synthesis of the 2-sulfone analogue **18**. However, in this case they got the hydrolysis of the acetal functionality **19** to the corresponding aldehyde **20** but the cyclisation did not occur (Scheme-4). The cyclisation could be accomplished in the reduced state by the reaction of the dimethoxynaphthalene sulfide acetal **15** with conc. HCl in a biphasic system with diethyl ether, giving chlorothiapyranonaphthalene **21** which was immediately oxidized to chloro-thiapyranonaphthoquinone **22**. However, these authors were unsuccessful to eliminate HCl from **22** to afford the thia derivative **23**.

Thermal Ring Opening Approach[16a]:

In 1986 a group of Japanese scientists led by Naito[16] carried out thermal ring opening reactions of 1,2-dihydrocyclobuta [b] naphthalene-3, 8-dione in order to synthesize 1*H*-2-naphtho[2,3-c] pyran-5, 10-dione, a basic skeleton of pentalongin. After several attempts they found that it was converted to desired skeleton in 55% yield by treatment with *p*-toluenesulfonic acid in refluxing acetone (Scheme-5).

Scheme-5

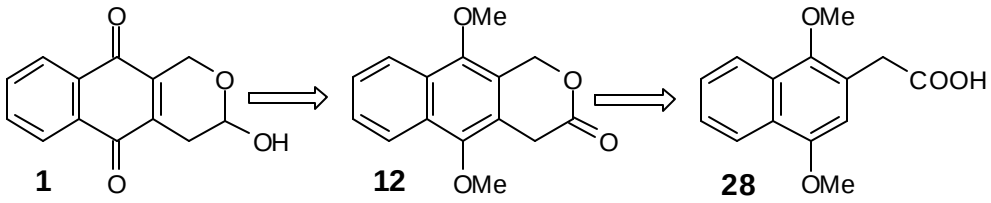


Reagents and conditions

i) TsOH, acetone, ii) H_2 / Pd-C

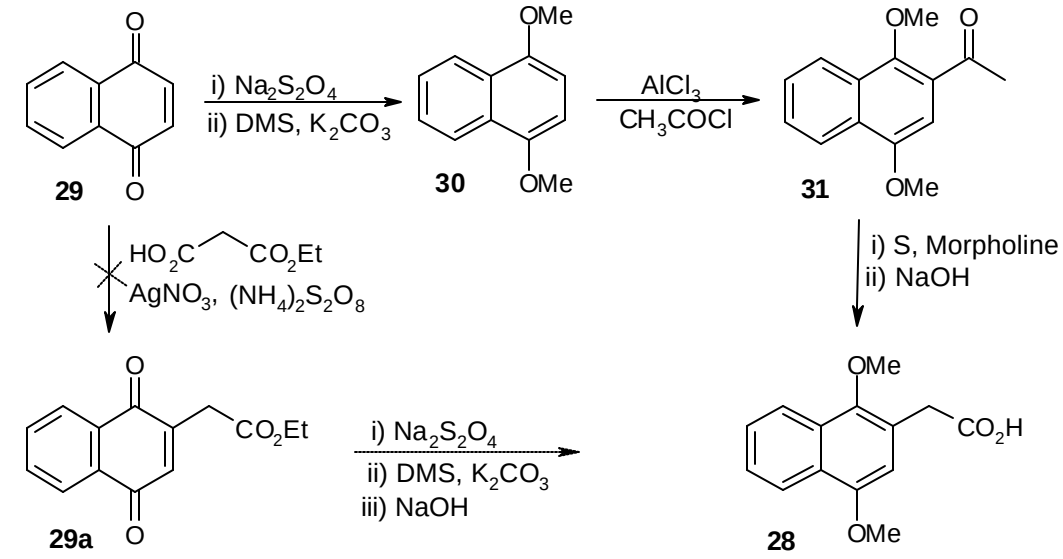
1.0.2 PRESENT WORK:

The combination of structural features and diverse biological activities have made the pyranonaphthoquinone class of antibiotics interesting and worthwhile synthetic targets as represented by the first total synthesis of psychorubrin and pentalongin by Kimpe *et al*[11]. in 1999 followed by another synthetic report from the same group in the same year. Although Kimpe *et al*. developed two alternative methodologies to construct benzopyran ring, it was necessary to explore more efficient and convenient method to construct benzopyran ring using inexpensive reagents. Therefore we focussed our attention towards the total synthesis of these two antibiotics *viz*, psychorubrin and pentalongin, and our efforts and achievements are described below.



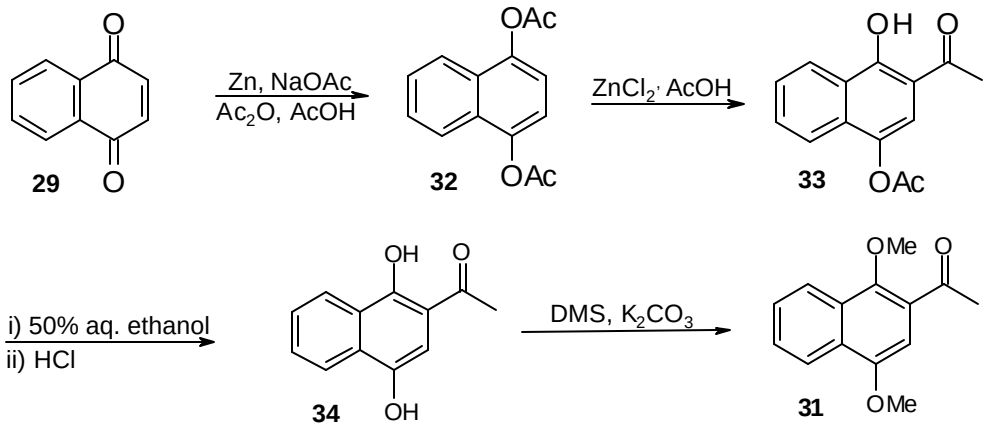
A retrosynthetic protocol indicated that the key intermediate naphthopyran **12** could be prepared from 1,4-dimethoxy-2-napthylacetic acid (**28**) as a logical intermediate. Hence, the efforts were directed towards the synthesis of requisite intermediate.

Scheme-6



For the synthesis of 1, 4-dimethoxy-2-naphthylacetic acid (**28**) the intermediate **31** was prepared by two methods as shown in scheme-6 and scheme-7. Accordingly dithionite reduction of 1,4-naphthoquinone to 1, 4-dihydroxynaphthalene and further methylation with dimethyl sulfate and potassium carbonate in refluxing acetone gave the 1,4-dimethoxynaphthalene (**30**). Friedel-Crafts acylation of the **30** afforded a mixture of three products. As the reaction mixture was showing green colouration with alcoholic $FeCl_3$ solution, it was remethylated in the usual method to give again mixture of three products. Usual workup and chromatographic separation afforded desired 2-acetyl-1, 4-dimethoxynaphthalene (**31**)[16b] in 50% yield. In addition it afforded 6-acetyl-1, 4-dimethoxynaphthalene (30%) and 5-acetyl-1, 4-dimethoxynaphthalene (10%) as byproducts. Therefore, naphthoquinone **29** was reductively acetylated in presence of zinc dust, sodium acetate in acetic anhydride and glacial acetic acid[17] which gave 1,4-diacetoxy naphthalene (**32**) in 88% yield. Fries rearrangement and hydrolysis of the resulting naphthol **33** afforded 2-acetylnaphthalene (**34**) in

Scheme-7



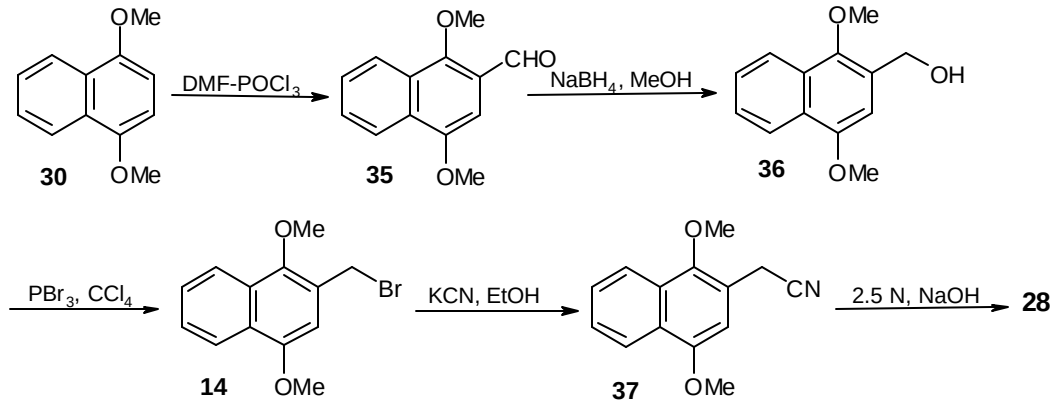
81% yield. Methylation of **34** with DMS and K_2CO_3 gave **31** in 86% yield. The treatment of **31** with sulphur and morpholine (Willgerodt reaction)[17c] at reflux temperature followed by the hydrolysis of the morpholide formed with alcoholic sodium hydroxide at reflux temperature and subsequent acidification afforded 1, 4 dimethoxy-2-naphthylacetic acid (**28**) in poor yield of 28%.

Another attempt of alkoxycarbonylation of naphthoquinone **29** with malonic acid monoethyl ester in presence of silver nitrate and ammonium persulfate failed to give the desired (1,4-dioxo-1,4-dihydronaphthalen-2-yl)-acetic acid ethyl ester (**29a**).

Therefore an alternate route was adapted to synthesize **28** (Scheme- 8) starting from 1,4-dimethoxynaphthalene (**30**). Vilsmeier-Haack formylation of 1,4-dimethoxynaphthalene (**30**) gave 2-

formyl 1,4-dimethoxynaphthalene (**35**), which was reduced with sodium borohydride in methanol to give almost quantitative yield of the alcohol **36**. The structure of the alcohol was confirmed on the basis of spectral data. The ^{1}H-NMR spectrum showed disappearance of aldehyde peak and appearance of a singlet at δ 4.89 for -CH_2OH. IR spectrum showed a band at 3440 cm^{-1} which further confirmed its structure. The alcohol on further treatment with phosphorous tribromide in dry carbon tetrachloride at 0 ^oC gave 2-bromomethyl-1, 4-dimethoxynaphthalene (**14**) in 96% yield. Its ^{1}H-NMR spectrum showed a shift of benzylic singlet from δ 4.89 to δ 4.77. The bromonaphthalene **14** was converted into the corresponding nitrile **37** by refluxing with ethanolic potassium cyanide. IR spectrum showed absorption band at 2250 cm^{-1} in support of nitrile functionality, while the molecular ion peak at m/z 227 further confirmed the structure. After having the nitrile compound prepared by one carbon homologation in hand, the next task was to hydrolyze the nitrile functionality in order to get the desired intermediate 1,4-dimethoxy-2-naphthylacetic acid (**28**). Alkaline hydrolysis of the nitrile **37** in ethanol with excess of potassium hydroxide gave the acid **28** in 89% yield.

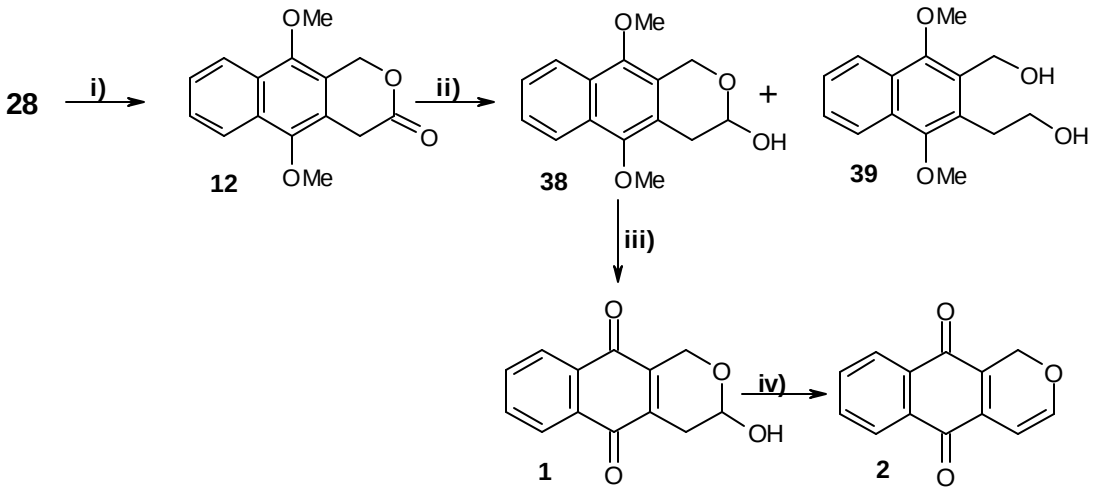
Scheme-8



Subsequently, construction of naphthopyran ring was undertaken employing chloromethylation[18] reaction of 1,4-dimethoxy-2-naphthylacetic acid (**28**) as a key step. Chloromethylation was carried out with acetic acid, 37% formalin solution and conc. HCl at 90 ^oC to give 3,4-dihydro-5, 10-dimethoxy-1*H*-naphtho [2,3-c] pyran-3-one (**12**) in 82% yield (scheme-9). The IR spectrum showed carbonyl absorption band at 1745 cm^{-1} While ^{1}H NMR spectrum revealed two singlets at δ 3.90 and 5.53 for two -CH_2 groups. Molecular ion peak m/z 258 in the mass spectrum further confirmed its structure. After successful preparation of the key intermediate naphthopyran **12,** it was partially reduced using 1.0

equivalent of diisobutyl aluminum hydride in toluene at room temperature. The lactol **38** was obtained in 88.87% yield along with over reduced product **39** in 11% yield as shown in scheme-9. Oxidation of lactol using cerium (IV) ammonium nitrate in aqueous acetonitrile gave psychorubrin (**1**) in 81% yield. Comparison of spectral data with the reported values confirmed the structure. Further dehydration of psychorubrin with *p*-toluenesulfonic acid[1] in benzene under reflux gave pentalongin (**2**) in 88% yield as red needles. Physical and spectral data were found to be consistent with the values reported in literature.

Scheme-9



Reagents and conditions:

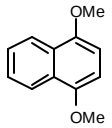
i) 37% formalin solution, AcOH, HCl, 90^o C, 1h, 82%. ii) DIBAL-H, toluene, 0 ^{o}C-r.t., 30 min. 88 % iii) 2 equivalents of CAN, CH_3CN, H_2O, 0 ^{o}C-r.t. 30 min., 81% iv) TsOH, benzene, reflux, 30 min., 88%.

1.0.3 CONCLUSION

In conclusion we have achieved total synthesis of psychorubrin and pentalongin having 1*H*-*2*-naphtho[2,3-c] pyran-5, 10-dione employing chloromethylation of 1,4-dimethoxy-2-naphthylacetic acid as a key step. Present method is the practical alternative for the preparation of the crucial intermediate, naphthopyran **12** in one step. All the steps involved in the present method give products in high yields, making it possible to have sufficient material available for further biological studies.

1.0.4 EXPERIMENTAL:

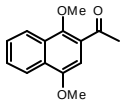
1,4-Dimethoxynaphthalene (30):



A mixture of 1,4-naphthoquinone (51.0 g, 0.32 mol), ethyl acetate (600 ml) and saturated solution of sodium dithionite was stirred well for 15 min. Ethyl acetate was removed under reduced pressure to afford 1,4-naphthohydroquinone (51.0 g, 98.75%). A mixture of 1,4 -naphthohydroquinone (51.0 g, 0.31 mol), potassium carbonate (98.97 g, 0.71 mol), dimethyl sulfate (90.36 g, 70.0 ml, 0.71 mol) and dry acetone (800 ml) was stirred under reflux for 15 h. The acetone was removed by distillation, to the residue was added water (500 ml) and the product extracted with ethyl acetate (3×200 ml), ethyl acetate layer was washed with water several times, with brine (100 ml), dried over sodium sulfate and concentrated on rotary evaporator to give a white solid (55.82g, 93.15%); mp. 85 ^{o}C [Lit.[14] mp. 84-85 ^{o}C].

^{1}H NMR ($CDCl_3$): δ 4.0 (s 6H), 6.74 (s, 2H), 7.52-7.60 (m, 2H), 8.20-8.30 (m, 2H).

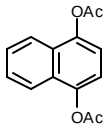
2-Acetyl - 1, 4-dimethoxynaphthalene (31):



To a stirred mixture of 1,4-dimethoxynaphthalene (5.0 g, 0.0265 mole) and aluminum trichloride (4.43 g, 0.0332 mole) in dry methylene chloride (60 ml) was added acetyl chloride (2.60 g, 4.0 ml, 0.0332 mole) dropwise at 0 ^{o}C. The reaction mixture was stirred for 4 hr at the same temperature, then quenched with ice and HCl, extracted with methylene chloride, washed with water (50 ml), brine (20 ml), dried over sodium sulfate and concentrated on rotary evaporator to give oily residue (5.6 g) which was a mixture of three products as per TLC . The residue obtained showed a green colouration with alcoholic ferric chloride indicating the presence of phenolic hydroxyl which formed due to the demethylation of product during the reaction. Hence the residue was methylated using dimethyl sulfate (10 ml) and potassium carbonate (15 g) in boiling acetone (150 ml). Usual work up of the reaction mixture yielded the mixture of products which were separated by column

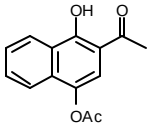
chromatography. The first fraction afforded 2-acetyl-1,4-dimethoxynaphthalene (**31**) (3.0 g, 50%) as colorless solid; m.p. 59 ^{o}C [Lit m.p.[16b] 59-60 ^{o}C]. Second fraction afforded 6-acetyl-1,4-dimethoxynaphthalene (1.8 g, 30%) as yellow solid; m.p. 111 ^{o}C. The final fraction afforded 5-acetyl-1,4-dimethoxynaphthalene (0.611 g, 10%) as yellow solid; m.p. 56 ^{o}C.

1,4-Diacetoxynaphthalene (32):



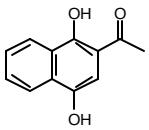
A vigorously stirred mixture of 1,4-naphthoquinone (4.5 g, 0.028 mole), zinc dust (1.0 g, 0.0153 mole) and sodium acetate (1.0 g, 0.012 mole) in 35 ml acetic anhydride was heated at 90 ^{o}C for 1 hr. During this time the color of the solution changed from yellow to almost colorless. This hot solution was treated with 20 ml of glacial acetic acid and boiled for 15 minutes and filtered. The filtrate was poured in 500 ml of water and stirred until the oil solidified into white crystals (7.8 g, 92%); m.p. 127 ^{o}C [Lit[17a] m.p. 127-128 ^{o}C].

4-Acetoxy-2-acetyl-1-naphthol (33):



1,4-Diacetoxynaphthalene (27. 0 g, 0.110 mole) was added to a solution of anhydrous zinc chloride (27.0 g, 0.197 mole) in glacial acetic acid (60 ml). The solution was refluxed for 30 min., cooled, poured into cold water (4 lit.) and stirred for 15 min. The oily residue crystallized and gave 4-acetoxy-2-acetyl-1-napthol (21 g, 78%) as pale green palates; m.p. 102 ^{o}C. (from ethanol) [Lit[17b] m.p. 103-104 ^{o}C].

2-Acetylnaphthalene-1,4-diol (34):



4-Acetoxy-2-acetyl-1-naphthol (15 g, 0.061 mole) in 50% aqueous ethanol was hydrolysed in the presence of hydrochloric acid (80 ml). The solution was refluxed for 15 min and poured into ice-cold water (4 lit). The diol (12.2 g, 98%), which separated as a yellow solid had m.p. 210 ^{o}C (from 5% ethanol-benzene) [Lit[17b] m.p. 206 ^{o}C].

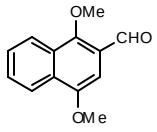
Methylation of 2-acetylnaphthalene-1,4-diol (34) to 2-acetyl-1,4-dimethoxynaphthalene (31):

A mixture of 2-acetylnaphthalene-1,4-diol (6.0 g, 0.0297 mol), potassium carbonate (10.24 g, 0.0742 mol) and dimethyl sulfate (8.2 g, 6.3 ml, 0.0653 mol) in dry acetone (120 ml) was stirred under reflux for 15 hr. The acetone was distilled off, to the residue was added water (200 ml) and the product extracted with ethyl acetate (2 × 100 ml). The ethyl acetate layer was washed with water several times, with brine (20 ml), dried over sodium sulfate and concentrated on rotary evaporator to give **31** as colourless solid (6.147, g 90 %); m.p. 59 ^{o}C [Lit[16b] m.p. 59-60 ^{o}C].

Preparation of 1, 4-dimethoxynaphthalene-2-acetic acid (28) by Willgerodt reaction:

A mixture of **31** (675 mg, 2.93 mmol), sulphur powder (139 mg, 4.34 mmol) and morpholine (1.0 ml) was refluxed for 18 hr. The reaction mixture was cooled and poured into cold water (10 ml). The brown coloured thick semisolid mass thus obtained was refluxed with 10% ethanolic sodium hydroxide solution (20 ml) for 12 hr. The ethanol was distilled off under reduced pressure, the residue was diluted with water and acidified with conc. HCl. The colourless solid so obtained was filtered, washed with cold water and air dried to afford **28** as white powder (200 mg, 28%); m.p. 122 ^{o}C [Lit[14] m.p. 124-125 ^{o}C].

2-Formyl- 1,4-dimethoxynaphthalene (35):

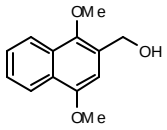


To a complex prepared from DMF (3.88 g, 4.10 ml, 0.05 mol) and $POCl_3$ (7.32 g, 4.44 ml, 0.04 mol) at 0^{O} C, was added 1,4-dimethoxynaphthalene (**30**) (10.0 g, 0.05 mol) at once, allowed to attain room temperature and then heated at 80^{O} C for 4 hours. The resulting dark red mixture was cooled and decomposed with saturated solution of sodium acetate with stirring. The aldehyde separated out as a

solid which was filtered, washed with water several times, dried and crystallized from hexane-ethyl acetate (10.78 g, 93.89%); mp. 118 ^{o}C [Lit [14b] m.p. 117-118 ^{o}C].

IR ($CHCl_3$): 1676 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$): δ 4.04 (s, 3H), 4.11(s, 3H), 7.12 (s, 1H), 7.52-7.75 (m, 2H), 8.12-8.36 (m, 2H), 10.57 (s, 1H, -CHO); **MS** (m/z): 216 (M^+, 100), 201 (64), 173 (58), 145 (62), 130 (33), 115 (60), 102 (70), 91 (42) and 75 (65).

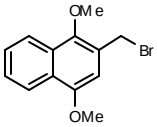
2-(Hydroxymethyl)-1,4- dimethoxynaphthalene (36):



2-Formyl-1,4-dimethoxynaphthalene (**35**) (10.5 g, 0.04 mol) was dissolved in distilled methanol (200 ml) and stirred at room temperature. To this stirred solution, sodium borohydride (1.83 g, 0.04 mol) was added in portions within half an hour. After completion of the reaction, excess methanol was distilled off, water (100 ml) was added to the residue, neutralized with acetic acid and extracted with chloroform (2 ×100 ml). The combined chloroform layer was washed with water followed by brine and dried over sodium sulfate. Removal of the solvent gave alcohol **36** as a white solid (9.98 g, 94.23%); mp. 70.3 ^{o}C.

IR ($CHCl_3$): 3440 cm^{-1} (CH_2-OH); **^{1}H NMR** ($CDCl_3$): δ 2.28 (bs, 1H, -OH), 3.94 (s, 3H), 4.01 (s, 3H), 4.89 (s, 2H), 6.82 (s, 1H), 7.42-7.60 (m, 2H), 8.04 (d, J= 8Hz, 1H), 8.25 (d, J= 8 Hz, 1H); **MS** (m/z): 218 (M^+, 73), 203 (10), 187 (8), 175 (100), 160 (45), 144 (18), 115 (53), 91 (8) and 76 (12).

2-(Bromomethyl)-1,4-dimethoxynaphthalene (14):

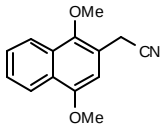


2-(Hydroxymethyl)-1,4- dimethoxynaphthalene (**36**) (9.95 g, 0.04 mol) was dissolved in dry CCl_4 (200 ml) under calcium chloride guard tube, cooled to 0^{o} C and stirred at the same temperature for half an hour. To this stirred solution was added PBr_3 (6.16 g, 2.16 ml, 0.02 mol) dropwise within 10 minutes. It was further stirred at the same temperature for half an hour and quenched with water at the same temperature. CCl_4 layer was washed with water, 10% aqueous bicarbonate, brine and dried

over sodium sulfate. Removal of the CCl_4 under reduced pressure gave white solid after column chromatographic purification (12.32 g, 96.47%); mp. 97 ^oC [Lit[14] m.p. 99.5 ^oC].

^{1}H NMR ($CDCl_3$): δ 4.01 (s, 3H), 4.02 (s, 3H), 4.77 (s, 2H), 6.71 (s, 1H), 7.45-7.60 (m, 2H), 8.05 (d, J= 8Hz, 1H), 8.24 (d, J= 8Hz, 1H); **MS** (m/z): 280 (M^+, 17), 282 (M^+, 17), 201 (100), 186 (42), 170 (22), 143 (11), 128 (29), 115 (36) and 76 (11).

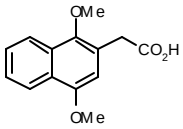
2-(Cyanomethyl)-1,4 -dimethoxynaphthalene (37):



A solution of the 2-bromomethyl-1,4-dimethoxynaphthalene (**14**) (12.10 g, 0.05 mol) and KCN (18.07 g, 0.27 mol) in ethanol (240 ml) and water (40 ml) was refluxed for 3 hours. The dark red solution was cooled and poured on ice (300 g) and the separated oil was extracted with ether. The ethereal extract was dried over sodium sulfate and the solvent was removed by distillation to give the required cyanide **37** as pale yellow solid compound (7.66 g, 75.31%); mp. 111 ^oC [Lit m.p.[14] 112-113 ^oC].

IR ($CHCl_3$): 2250 (-CN), 1595 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.91 (s, 3H), 3.92 (s, 3H), 4.01 (s, 2H), 6.72 (s, 1H), 7.46-7.60 (m, 2H), 7.99 (d, J= 8 Hz, 1H), 8.23 (d, J= 8 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ 18.26 (-$\underline{C}H_2CN$), 55.57, 61.97, 103.36, 117.98, 121.66, 122.58, 125.81, 126.04, 127.03, 128.13, 147.10, 152.39; **MS** (m/z): 227 (M^+, 62), 212 (100), 197 (10), 184 (16), 169 (15), 153 (11), 115 (15) and 76 (12).

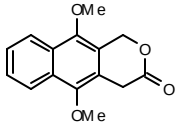
1,4-Dimethoxynaphthalene-2- acetic acid (28):



A solution of **37** (7.0 g, 0.03 mol) in ethanol (15 ml) and 2.5 N NaOH (7.0 ml) was heated under reflux for 18 hours at which point the evolution of ammonia was no longer detected. The reaction mixture was cooled and poured into ice water, pH was adjusted to 7 with conc. HCl and the white solid which separated out was filtered and dried (6.5g, 89.70%); mp. 122 ^oC [Lit[14] m.p. 124-125 ^oC].

IR ($CHCl_3$): 3449, 1709 cm^{-1} (-CO_2H); **^{1}H NMR** ($CDCl_3$): δ 3.88 (s, 2H), 3.93 (s, 3H), 3.98 (s, 3H), 6.66 (s, 1H), 7.43-7.59 (m, 2H), 8.02 (dd, J= 8 Hz, 2 Hz, 1H), 8.22 (dd, J= 8 Hz, 2 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ35.33 (-$\underline{CH_2}CO_2H$), 55.32, 61.98, 105.09, 121.19, 121.63, 122.30, 125.20, 126.04, 126.45, 128.18, 147.48, 151.70, 177.65; **MS** (m/z): 246 (M^+ 56), 231 (6), 213 (12), 187 (100), 159 (22), 143 (16), 128 (22), 115 (43), 102 (9), 89 (10) and 76 (12).

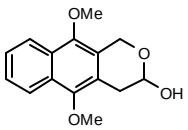
3,4-Dihydro-5, 10-dimethoxy-1*H*-naphtho [2,3-c] pyran-3-one (12):



A 50 ml round bottom flask was charged with 1,4-dimethoxynaphthylacetic acid (**28**) (0.5 g, 2.0 mmol) and 2.5 ml of acetic acid. The solution was stirred and heated at 80^O C in an oil bath, while 8.6 ml of conc. HCl was added rapidly and followed immediately by 6.17 ml of 37% formalin. The yellow solution was stirred and heated for 1 hour, during which time reaction temperature reached to 90^O C and solution assumed a dark colour. After cooling to room temperature the solution was poured into a mixture of 100 g chipped ice and 100 ml of cold water. The mixture was extracted with chloroform (100 ml), the chloroform layer was washed with 5% sodium bicarbonate until neutral, then with water and dried over sodium sulfate. Evaporation of the solvent gave crude lactone which was purified by means of column chromatography using 5% acetone in pet ether as eluent to afford pure **12** (0.433 g, 82.63%) as white solid; mp. 126 ^{o}C [Lit[3]. mp. 126 ^{o}C].

IR (KBr): 1745 cm^{-1} (C=O); **^{1}H NMR** ($CDCl_3$): δ 3.89 (s, 2H, CH_2C=O), 3.93 (s, 3H, OMe), 3.94 (s, 3H, OMe), 5.53 (s, 2H, CH_2O), 7.50-7.60 (m, 2H), 8.03-8.15 (m, 2H); **^{13}C NMR** ($CDCl_3$): δ 30.51 ($\underline{CH_2}$C=O), 62.01 (OMe), 62.60 (OMe), 64.88 (CH_2O), 119.32, 120.38 (=C quat), 122.15, 122.57, 126.30, 126.60, 127.55 (=C quat), 128.69 (=C quat), 147.99 (=$\underline{C}$-OMe), 148.69 (=$\underline{C}$-OMe), 169.79 (-C=O); **MS** (m/z): 258 (M^+, 100), 243 (15), 215 (15), 199 (36), 171 (12), 141 (18), 128 (32), 115 (28), 91 (10) and 76 (18).

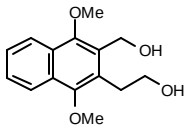
3,4-Dihydro-5, 10-dimethoxy-1*H*-naphtho [2,3-c] pyran-3-ol (38):



Under nitrogen atmosphere a solution of 3,4-dihydro-5, 10-dimethoxy-1*H*-naphtho [2,3-c] pyran-3-one (**12**) (0.126 g, 0.4 mmol) in toluene (6 ml) was treated with a solution of 2.5 M DIBAL-H in toluene (0.069 g, 0.200 ml, 0.4 mol) at 0^{O} C and after stirring for 1 hour at room temperature the mixture was poured in 2 M HCl. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and evaporated under reduced pressure to give 3,4-dihydro-5, 10-dimethoxy-1-*H*-naphtho [2,3-c] pyran-3-ol (0.079 g, 88.87%) (**38**) as a colorless oil along with an over reduced diol **39** (0.014g, 11%), which was separated by column chromatography.

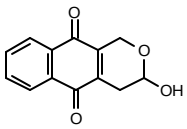
IR (Neat): 3390 cm^{-1} (OH); **^{1}H NMR** ($CDCl_3$): δ 2.95 (dd, J= 16 Hz, 4 Hz, 1H), 3.28 (dd, J= 16 Hz, 4 Hz, 1H), 3.89 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.97 (d, J=16 Hz, 1H), 5.19 (d, J= 16 Hz, 1H), 5.41 (t, J= 4 Hz, 1H), 7.40-7.60 (m, 2H), 7.95-8.15 (m, 2H); **MS** (m/z): 260 (M^{+}, 88), 242 (24), 228 (30), 214 (71), 199 (100), 171 (20), 141 (22), 128 (35), 115 (30) and 77 (14).

2-(3-Hydroxymethyl-1, 4-dimethoxynaphthalen-2-yl)-ethanol (**39**):



White needles; m.p. 152 ^{o}C ; **IR** (Nujol): 3187 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.12 (t, J= 4 Hz, 2H), 3.90 (s, 3H), 3.98 (t, J= 4 Hz, 2H), 3.99 (s, 3H), 4.88 (s, 2H), 7.45-7.55 (m, 2H), 7.99-8.12 (m, 2H); **^{13}C NMR** ($CDCl_3$): δ 29.80 (-$\underline{C}H_2$-CH_2-OH), 56.38 (-CH_2-$\underline{C}H_2$-OH), 61.71 (-CH_2-OH), 62.96 (-OCH_3), 63.62 (-OCH_3), 122.29, 122.95, 125.89, 126.44, 128.02 (=C quat), 128.09 (=C quat), 128.53 (=C quat), 129.64 (=C quat), 150.92 (-C-OMe), 151.47 (-C-OMe); **MS** (m/z): 262 (M^{+}, 100), 244 (3), 229 (7), 214 (28), 199 (42), 186 (22), 171 (17), 157 (9), 140 (17), 128 (38), 115 (40), 105 (12), 91 (9) and 77 (15); Analysis calculated for $C_{15}H_{18}O_4$: C = 68.70, H = 6.87%; Found : C = 68.29, H = 6.96%.

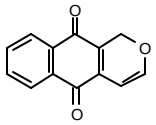
Psychorubrin (1):



3,4-Dihydro-5, 10-dimethoxy-1-*H*-naphtho [2,3-c] pyran-3-ol (**38**) (55 mg, 0.21 mmol) was dissolved in acetonitrile (3 ml). Then a solution of cerium (IV) ammonium nitrate (0.600 g, 1.07 mmol) in water (3 ml) was added at 0^{o} C and the reaction was allowed to warm to room temperature for 30 minutes. The mixture was poured into water, extracted with ethyl acetate, washed with brine, dried and evaporated *in vacuo*. Column purification using 30% acetone in petroleum ether afforded psychorubrin (0.039 g, 81.25%) as a pale yellow solid; mp. 153 ^{o}C [Lit[1]. mp. 150-152 ^{o}C].

IR ($CHCl_3$): 3410 (OH), 1660 (quinone), 1640 (quinone), 1590 (C=C) cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 2.65-2.94 (m, 2H), 4.60-4.90 (m, 2H), 5.50 (t, J=4 Hz, 1H), 7.68-7.80 (m, 2H, Ar H), 8.02-8.16 (m, 2H, Ar H); **^{13}C NMR** ($CDCl_3$): δ 22.97 (CH_2O), 57.67 ($\underline{CH_2}CHOH$), 90.64 (-CHOH), 126.15, 126.44, 132.0 (=C quat), 132.03 (=C quat), 133.75, 133.78, 139.23 (=C quat), 141.29 (=C quat), 183.01 (quinone), 183.49 (quinone); **MS** (m/z): 230 (M^{+}, 13), 212 (42), 184 (100), 156 (20), 128 (40), 115 (12) and 76 (40).

Pentalongin (2):

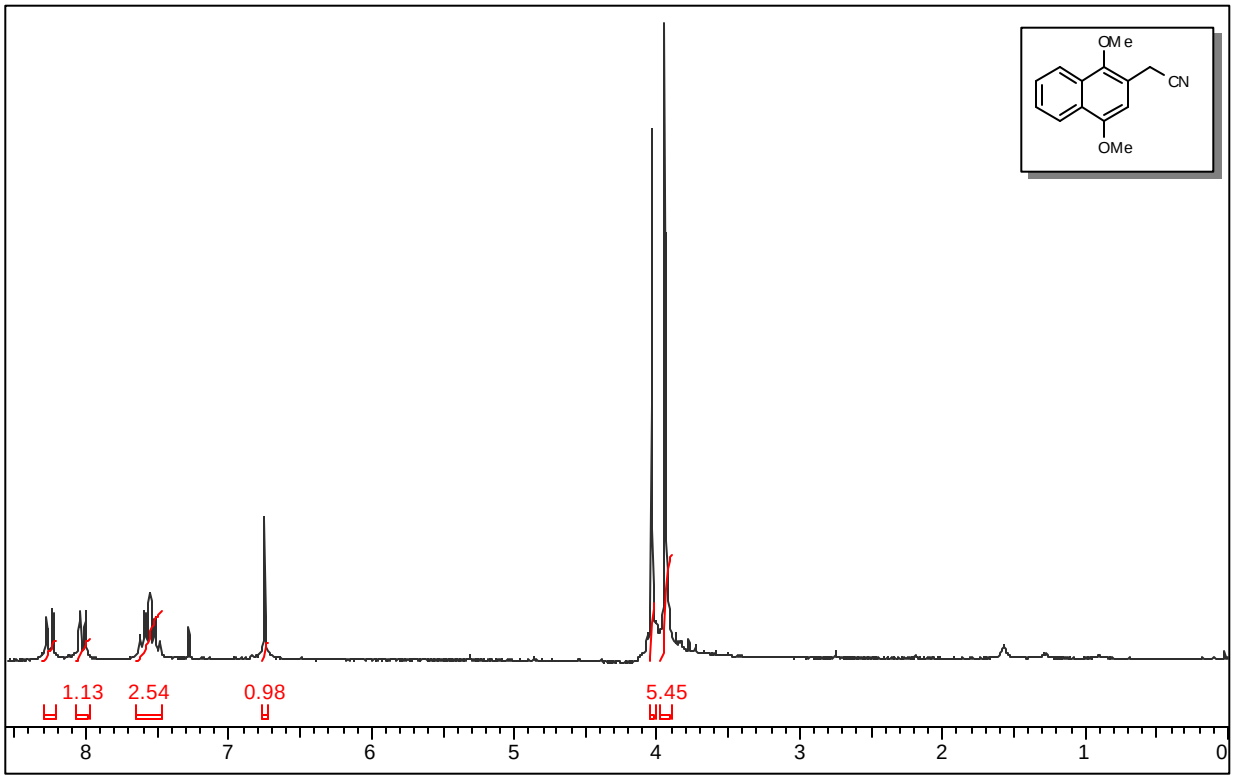


A solution of psychorubrin (**1**) (30 mg, 0.1 mmol) in benzene (5 ml) was heated under reflux for 30 minutes with a catalytic amount of *p*-toluenesulfonic acid. The mixture was cooled to room temperature, diluted with ethyl acetate, washed with water, dried over sodium sulfate and evaporated *in vacuo*. Chromatographic separation using 15% acetone in petroleum ether afforded pentalongin (**2**) (0.024 g, 88.88%) as red needles; m.p. 162 ^{o}C [Lit[1] m.p. 160-161 ^{o}C].

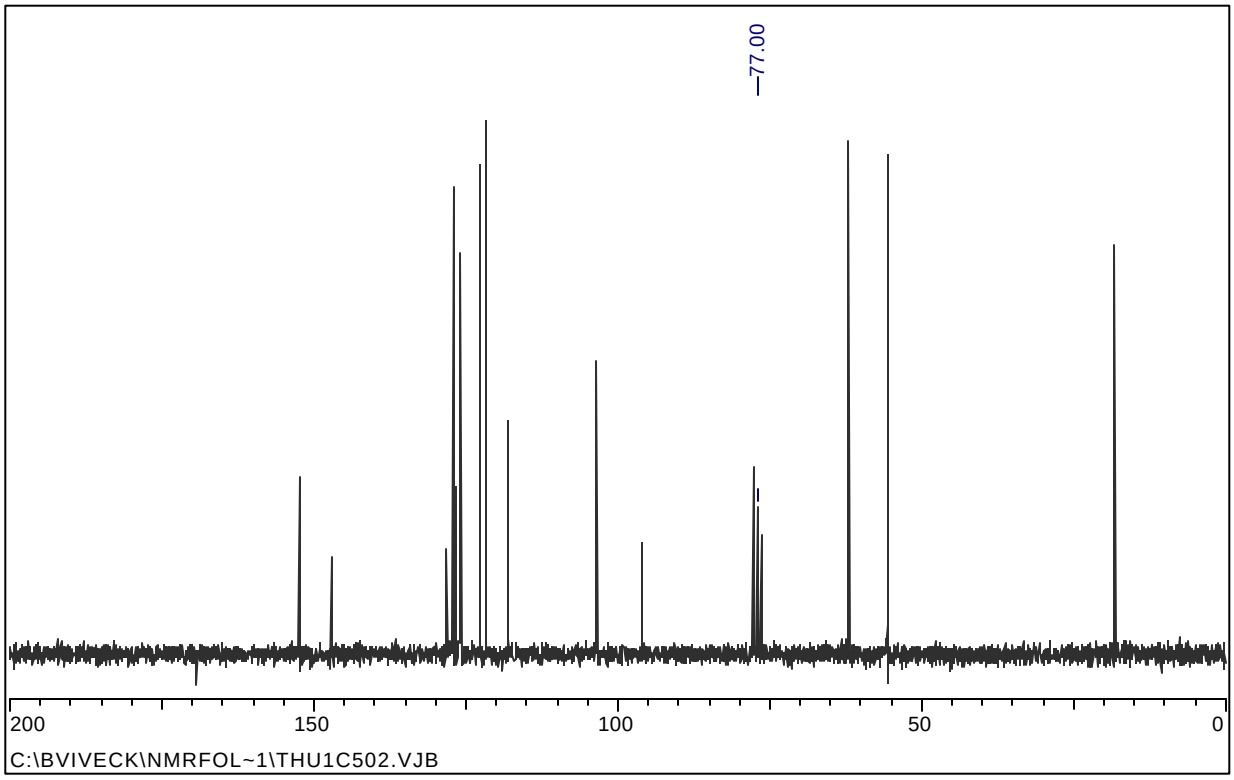
IR ($CHCl_3$): 1670 (quinone C=O), 1651 (quinone C=O), 1596 (C=C), 1553 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 5.18 (s, 2H, CH_2O), 6.13 (d, J= 6 Hz, 1H), 6.99 (d, J= 6 Hz, 1H), 7.65-7.80 (m, 2H, ArH), 8.05-8.17 (m, 2H, ArH); **^{13}C NMR** ($CDCl_3$): δ 62.20 (CH_2O), 98.06, 124.49, 126.04, 126.56, 131.75, 132.61, 133.31, 133.89, 136.64, 154.18, 181.59 (quinone -C=O), 182.06 (quinone -C=O); **MS** (m/z): 212 (M^{+}, 100), 183 (28), 155 (12), 128 (32), 104 (8), 76 (10).

1.0.5 REFERENCES:

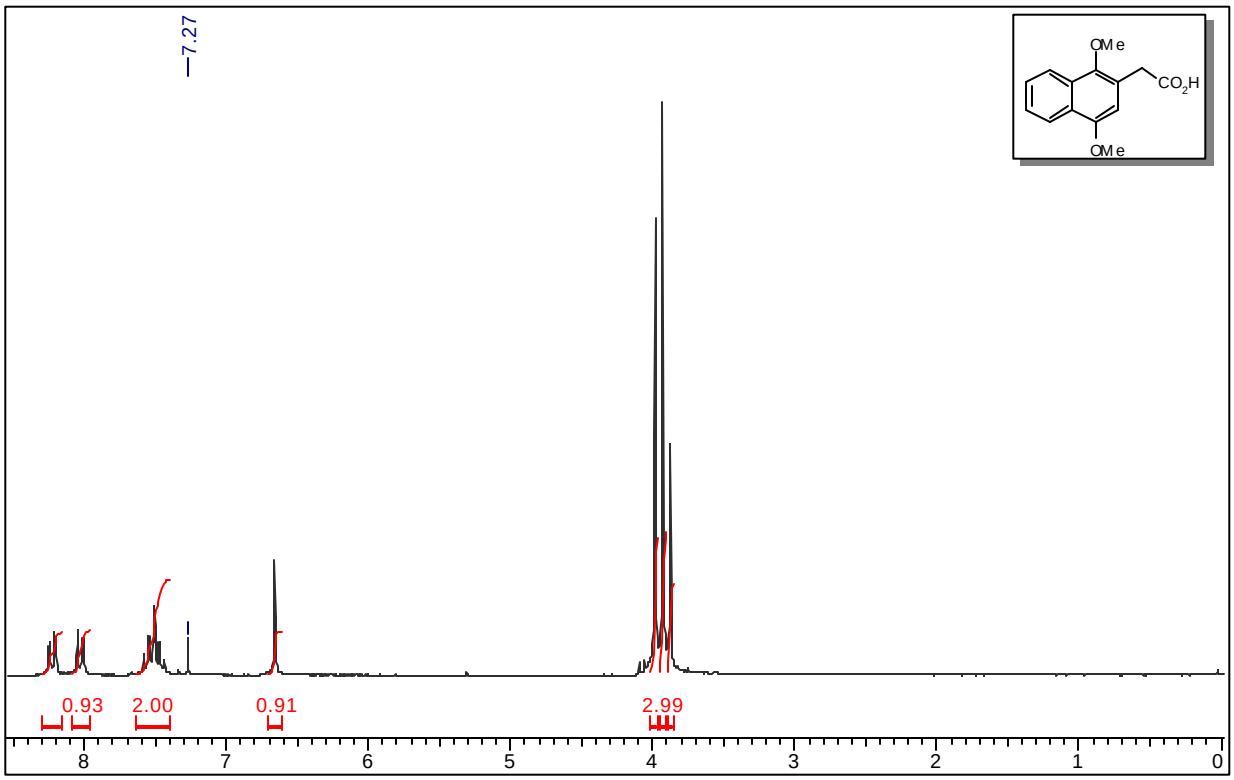
1. Hayashi, T.; Smith, F. T.; Lee, K. H., *J. Med. Chem.*, **1987**, 30, 2005.
2. Hari, L.; De Buyck, L. F.; De Pooter, H. L., *Phytochemistry*, **1991**, 30, 1726.
3. Kesteleyn, B.; Kimpe, N. D.; Puyvelde, L.V., *Synthesis*, **1999**, 1881.
4. a) Omura, S.; Tanaka, H.; Koyama, Y.; Katagiri, M., *J. Antibiot*., **1974**, 27, 363. b) Tanaka, H.; Koyama, Y.; Marumo, H.; Oiwa, R.; Katagiri, M.; Nagai, T.; Omura, S., *J. Antibiot*., **1975**, 28, 860. c) Tanaka, H.; Koyama, Y.; Nagai, T.; Omura, S., *J. Antibiot*., **1975**, 28, 868.
5. Iwai, Y.; Kora, A.; Takahashi, Y., *J. Antibiot*., **1978**, 31, 959.
6. Schmidt, H.; Ebnother, A., *Helv. Chem. Acta*, **1951**. 64, 1041.
7. Naruta, Y.; Maruyama, K., Recent Advances in the Synthesis of Quinonoid Compounds. In The Chemistry of Quinonoid Compounds; Patai, S., Rappoport, Z., Eds.; John Wiley: New York, **1988**; vol. II, p 241.
8. a) Aldersley, M. F.; Dean, F. M.; Hamzah, A. S., *Tetrahedron Lett*., **1986**, 27, 255. b) Aldersley, M. F.; Chishti, S. H.; Dean, F. M.; Douglas, M. E.; Ennis, D. S., *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2163.
9. a) Kadkol, M. V.; Gopalkrishnan, K. S.; Narasimhachari, N., *J. Antibiot*., **1971**, 24, 245. b) Nagarajan, R.; Narasimhachari, N.; Kadkol, M. V.; Gopalkrishnan, K. S., *J. Antibiot.*, **1971**, 24, 249.
10. a) Tatum, J. H.; Baker, R. A., *Phytochemistry*, **1983**, 22, 543. b) Parisot, D.; Devys, M.; Ferezou, J. P.; Barbier, M., *Phytochemistry*, **1983**, 22, 1301.
11. Kesteleyn, B.; Kimpe, N. D.; Puyvelde, L.V., *J. Org. Chem*., **1999**, 64, 1173.
12. Heinzman, S. W.; Grunwell, J. R., *Tetrahedron Lett*., **1980**, 21, 4305.
13. Kesteleyn, B.; Kimpe, N. D., *Tetrahedron Lett*., **2000**, 42, 755.
14. a) Gates, M., *J. Org. Chem*., **1982**, 47, 578. b) Morgan, G.T., *J. Chem. Soc*., **1921**, 119, 117.
15. Trost, B. M.; Curran, D. P., *Tetrahedron Lett*., **1981**, 22, 1287.
16. a) Naito, T.; Makita, Y.; Yazaki, S; Kaneko, C., *Chem. Pharm. Bull*., **1986**, 34, 1505. b) Sah, P. P. T., *Rec. Trav. Chim*., **1940**, 59, 1029.
17. a) Green, I. R., *J. Chem. Edu*., **1982**, 59, 698. b) Read, G. and Ruiz, V. M., *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2163. c) Brown, E. V., *Synthesis*, **1975**, 358.
18. Finkelstein, J.; Brossi, A., Org. Syn. 1976, vol. 55, 45. ; Coll., 1988, 6, 471.



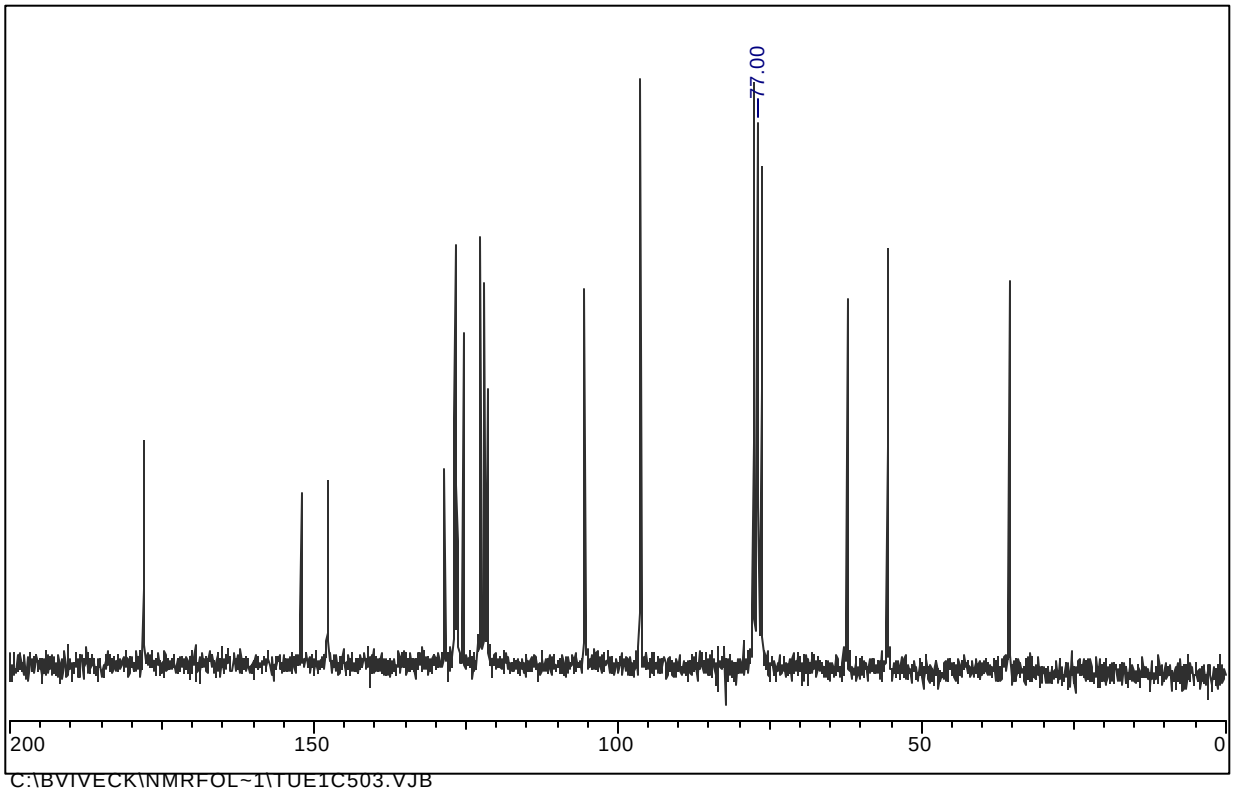
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 37 IN $CDCl_3$



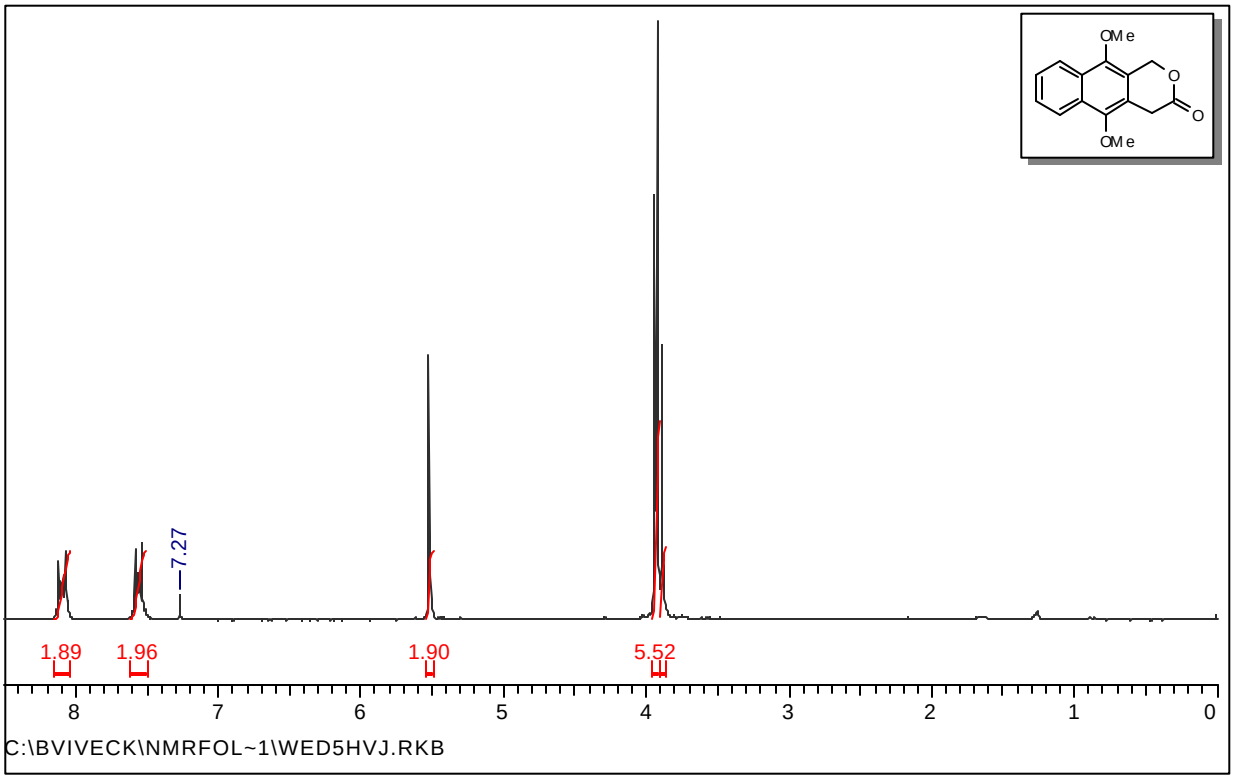
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 37 IN $CDCl_3$



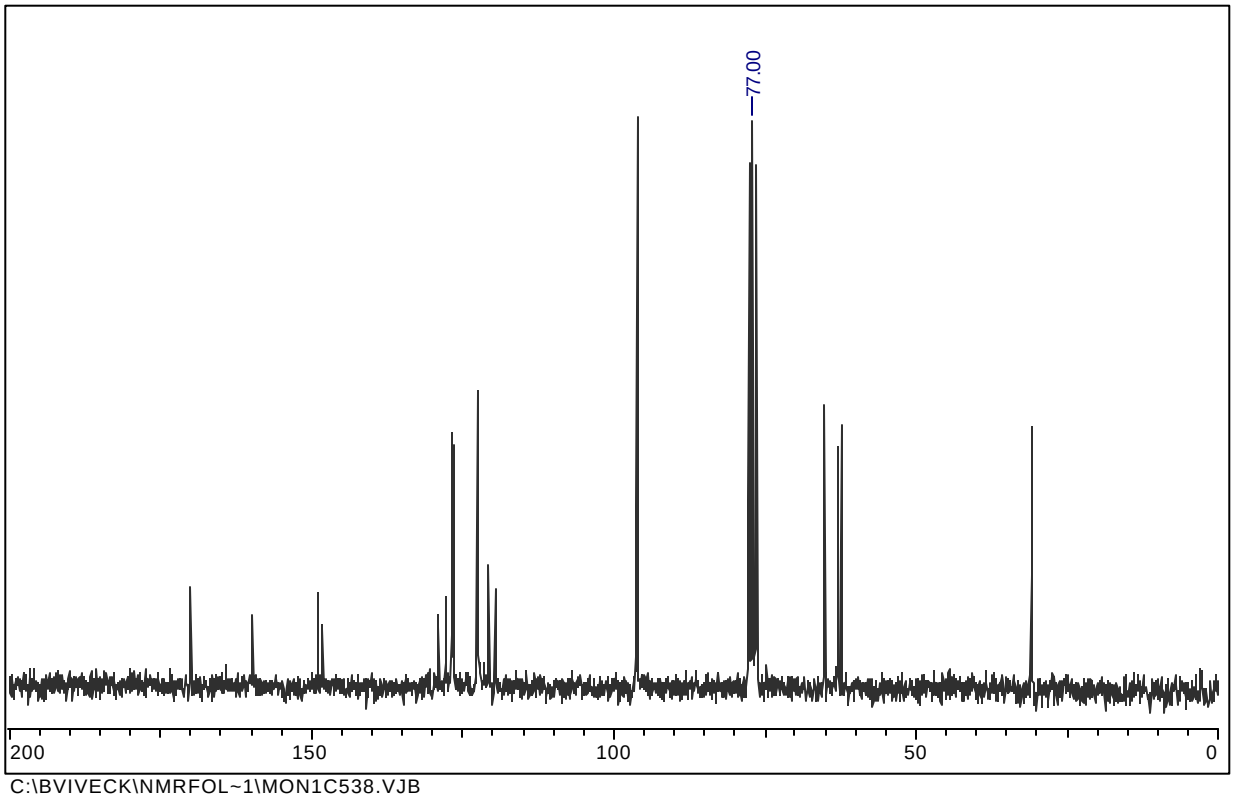
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 28 IN $CDCl_3$



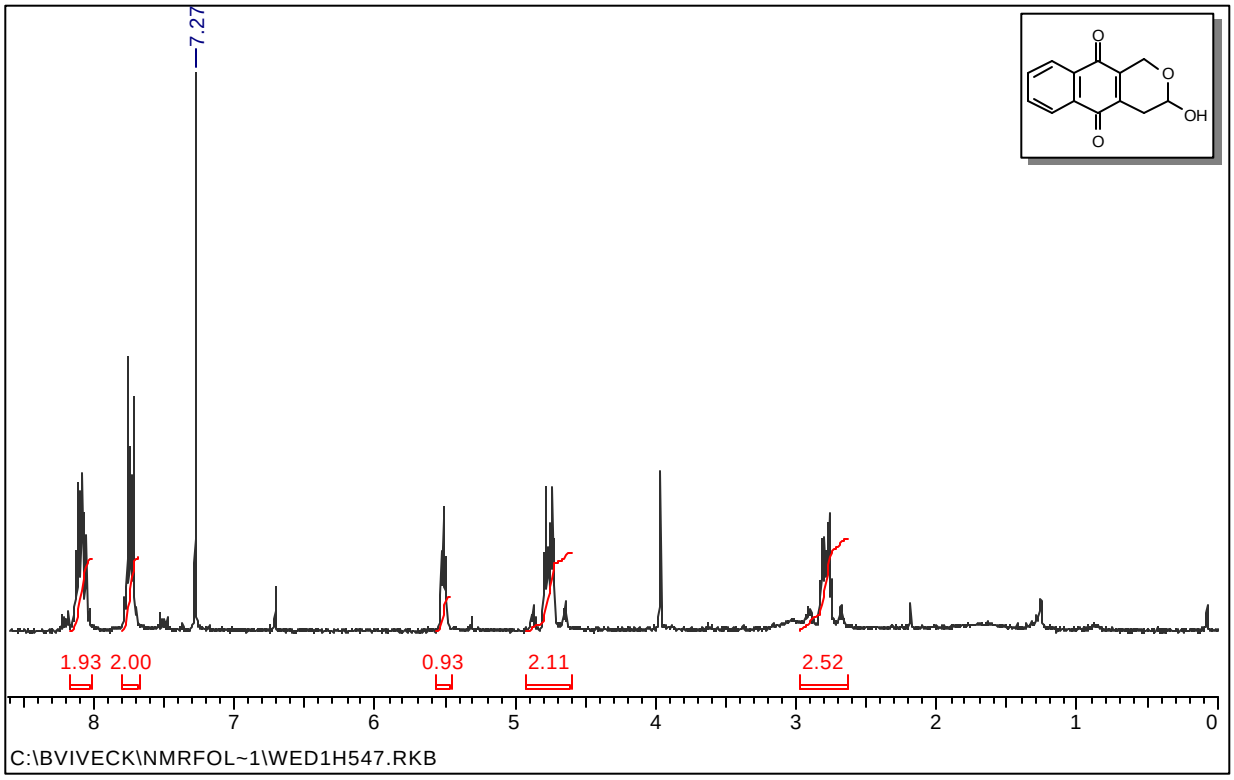
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 28 IN $CDCl_3$



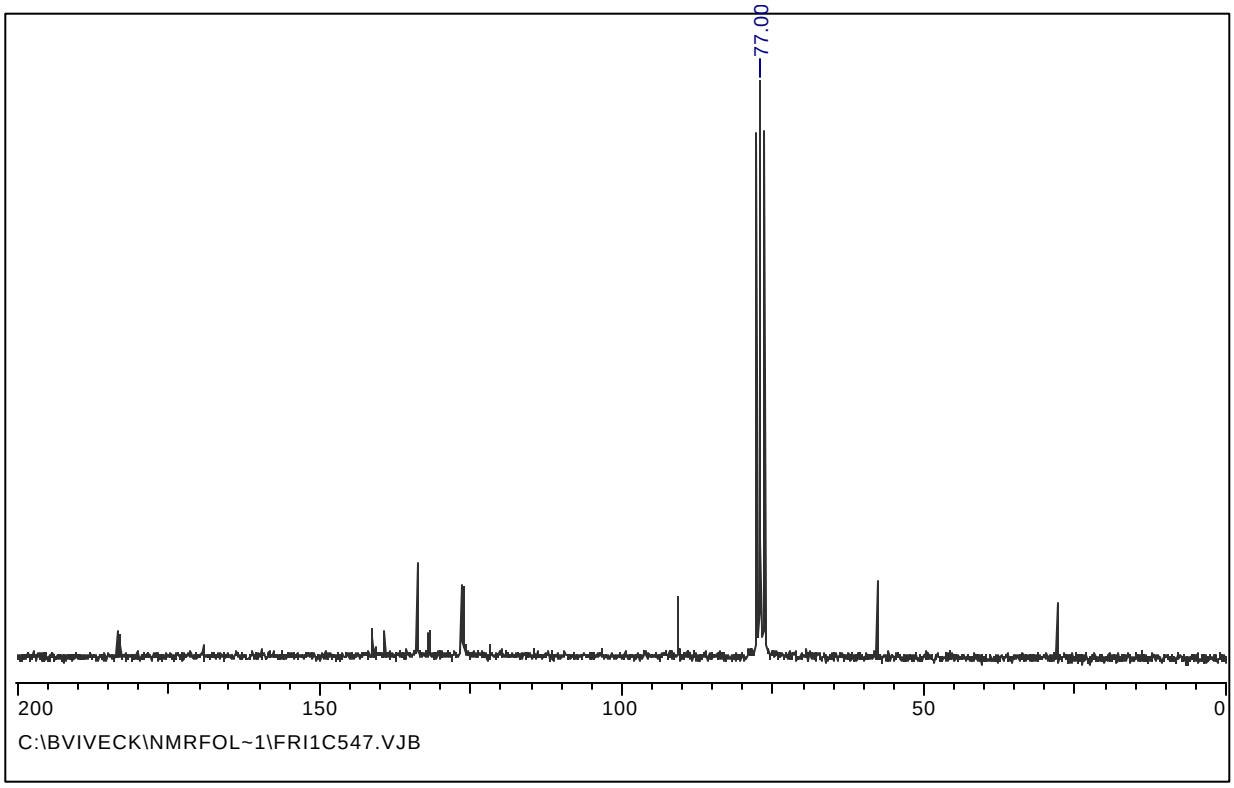
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 12 IN $CDCl_3$



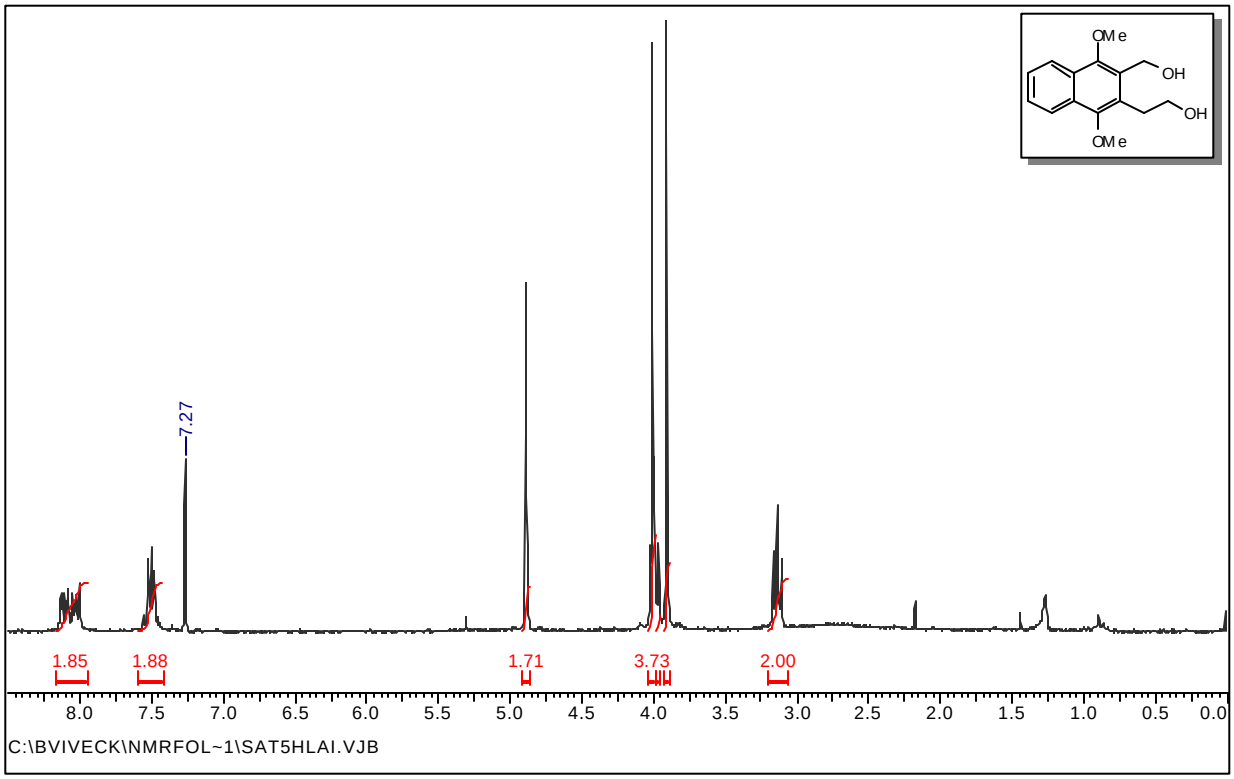
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 12 IN $CDCl_3$



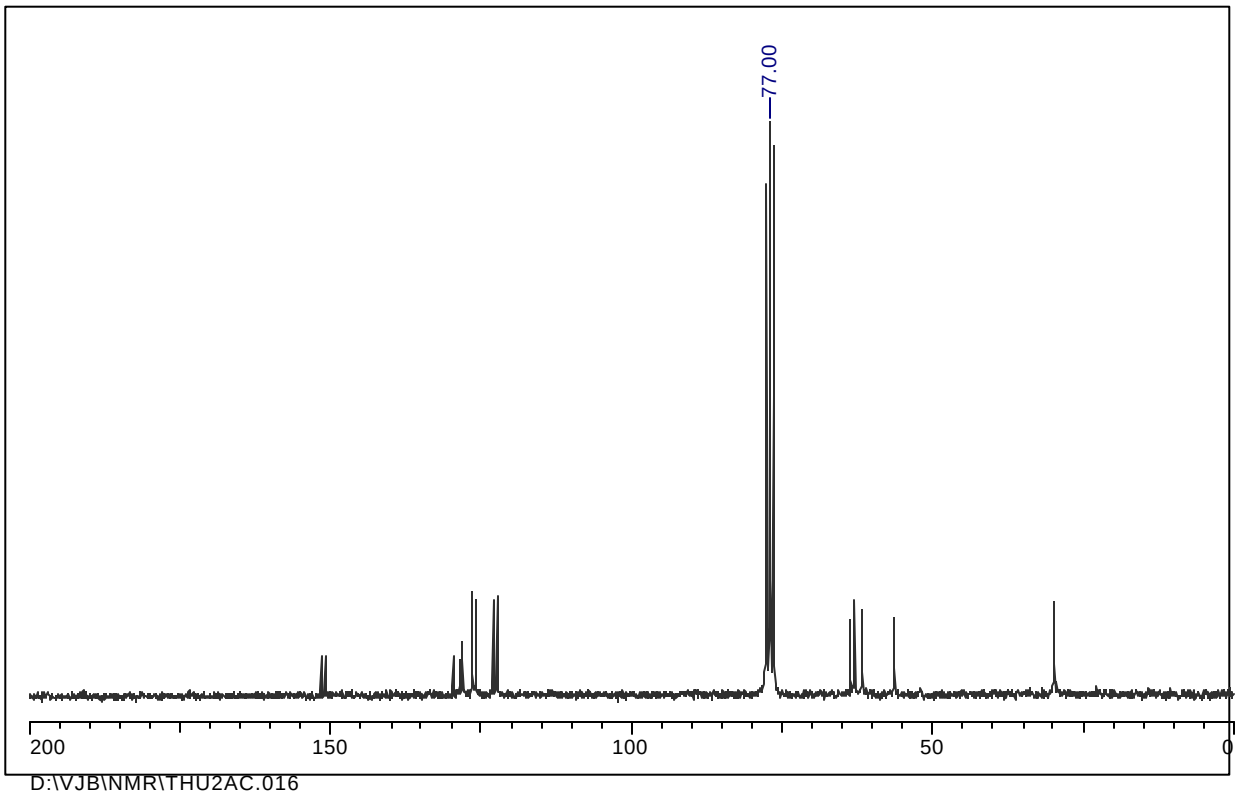
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 1 IN $CDCl_3$



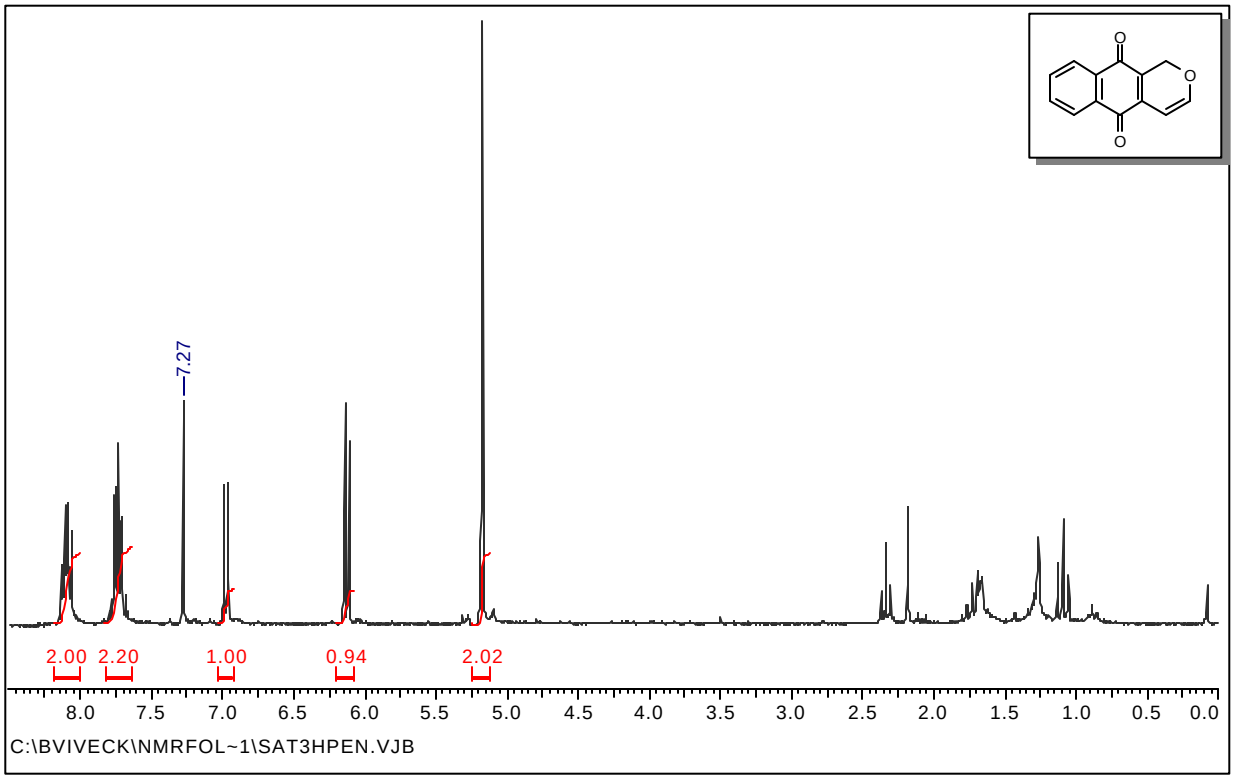
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 1 IN $CDCl_3$



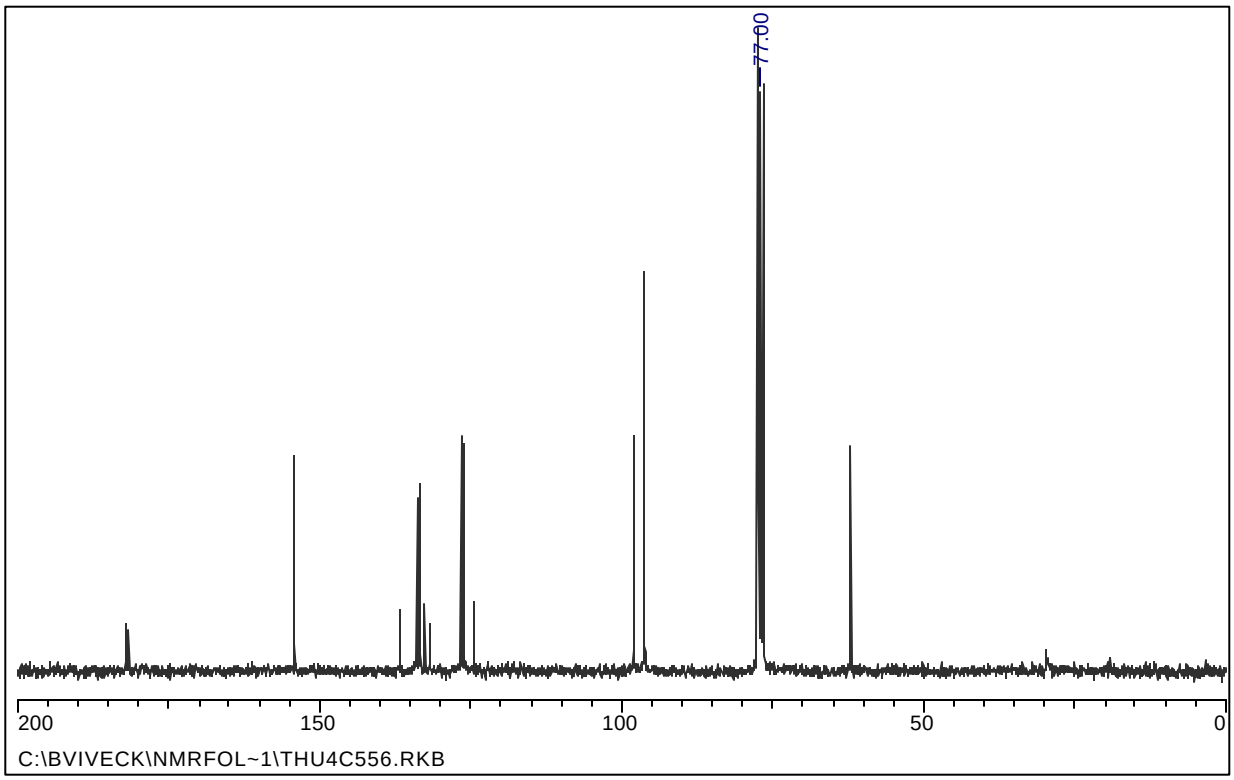
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 39 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 39 IN $CDCl_3$



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 2 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 2 IN $CDCl_3$

1.0.5 REFERENCES:

19. Hayashi, T.; Smith, F. T.; Lee, K. H., *J. Med. Chem.*, **1987**, 30, 2005.
20. Hari, L.; De Buyck, L. F.; De Pooter, H. L., *Phytochemistry*, **1991**, 30, 1726.
21. Kesteleyn, B.; Kimpe, N. D.; Puyvelde, L.V., *Synthesis*, **1999**, 1881.
22. a) Omura, S.; Tanaka, H.; Koyama, Y.; Katagiri, M., *J. Antibiot*., **1974**, 27, 363. b) Tanaka, H.; Koyama, Y.; Marumo, H.; Oiwa, R.; Katagiri, M.; Nagai, T.; Omura, S., *J. Antibiot*., **1975**, 28, 860. c) Tanaka, H.; Koyama, Y.; Nagai, T.; Omura, S., *J. Antibiot*., **1975**, 28, 868.
23. Iwai, Y.; Kora, A.; Takahashi, Y., *J. Antibiot*., **1978**, 31, 959.
24. Schmidt, H.; Ebnother, A., *Helv. Chem. Acta*, **1951**. 64, 1041.
25. Naruta, Y.; Maruyama, K., Recent Advances in the Synthesis of Quinonoid Compounds. In The Chemistry of Quinonoid Compounds; Patai, S., Rappoport, Z., Eds.; John Wiley: New York, **1988**; vol. II, p 241.
26. a) Aldersley, M. F.; Dean, F. M.; Hamzah, A. S., *Tetrahedron Lett*., **1986**, 27, 255. b) Aldersley, M. F.; Chishti, S. H.; Dean, F. M.; Douglas, M. E.; Ennis, D. S., *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2163.
27. a) Kadkol, M. V.; Gopalkrishnan, K. S.; Narasimhachari, N., *J. Antibiot*., **1971**, 24, 245. b) Nagarajan, R.; Narasimhachari, N.; Kadkol, M. V.; Gopalkrishnan, K. S., *J. Antibiot.*, **1971**, 24, 249.
28. a) Tatum, J. H.; Baker, R. A., *Phytochemistry*, **1983**, 22, 543. b) Parisot, D.; Devys, M.; Ferezou, J. P.; Barbier, M., *Phytochemistry*, **1983**, 22, 1301.
29. Kesteleyn, B.; Kimpe, N. D.; Puyvelde, L.V., *J. Org. Chem*., **1999**, 64, 1173.
30. Heinzman, S. W.; Grunwell, J. R., *Tetrahedron Lett*., **1980**, 21, 4305.
31. Kesteleyn, B.; Kimpe, N. D., *Tetrahedron Lett*., **2000**, 42, 755.
32. a) Gates, M., *J. Org. Chem*., **1982**, 47, 578. b) Morgan, G.T., *J. Chem. Soc*., **1921**, 119, 117.
33. Trost, B. M.; Curran, D. P., *Tetrahedron Lett*., **1981**, 22, 1287.
34. a) Naito, T.; Makita, Y.; Yazaki, S; Kaneko, C., *Chem. Pharm. Bull*., **1986**, 34, 1505. b) Sah, P. P. T., *Rec. Trav. Chim*., **1940**, 59, 1029.
35. a) Green, I. R., *J. Chem. Edu*., **1982**, 59, 698. b) Read, G. and Ruiz, V. M., *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2163. c) Brown, E. V., *Synthesis*, **1975**, 358.
36. Finkelstein, J.; Brossi, A., Org. Syn. 1976, vol. 55, 45. ; Coll., 1988, 6, 471.

1.1.1 INTRODUCTION

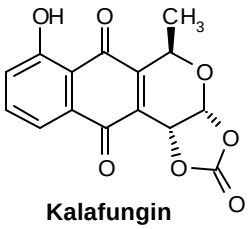
Eleutherine americana Merr. *et* Heyne (Iridaceae), is a herbal plant cultivated in Hainan Island, South China. The rhizome of this plant (Hong-Cong in Chinese) is used as a folk medicine for the treatment of coronary disorders[1]. Hongconin was isolated from *Eleutherine americanna* in 1986 by Chen and coworkers[2a] with three other known naphthalene derivatives eleutherol, eleutherin and isoeleutherin[2b-e]. A formulation of these four purified compounds was demonstrated to increase coronary blood flow in guinea pig heart and to exhibit human anti-anginal efficacy. The individual abilities of the four agents to confer cardioprotective activity have yet to be discerned. The biological activity of hongconin was confirmed by pharmacological tests using isolated guinea pig heart. However, hongconin has been shown to exhibit cardioprotective activity against angina pectoris in limited clinical trials.

Furthermore, the obvious structural similarities of the hongconin to well-known isochromanquinones such as kalafungin[3], nanaomycin[4], granatacin[5] and medermycin[6] have suggested other potential medicinal applications[7].

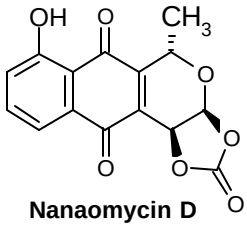
Isolation and structural elucidation:

When the alcoholic extract of *Eleutherine americana* was concentrated to a small volume under reduced pressure eleutherol precipitated. The filtrate was subjected to silica gel column chromatography using dichloromethane as an eluent to give three main fractions (A, B and C) containing naphthalene derivatives. Fraction A was recrystallised from ethanol to give eleutherol. The mother liquor upon rechromatography using petroleum ether-dichloromethane (5:2) as an eluent afforded hongconin (**38**). Fraction B was recrystallised from acetone to give eleutherin and fraction C yielded isoeleutherin upon recrystallisation from acetone. These crystalline products were identified as eleutherol, eleutherin and isoeleutherin, respectively on the basis of spectral analysis as well as comparison of spectral data with those reported in the literature. Hongconin (**38**) was obtained as yellow needles upon recrystallisation from hexane-ether. The infrared (IR) spectrum of hongconin revealed the presence of hydroxyl groups, aromatic rings and an ether linkage. The proton nuclear magnetic resonance (^{1}H NMR) spectrum was more informative and revealed the presence of two hydroxyl groups, three aromatic protons, one methoxy group and two O-CH-CH_3 groups. Irradiation of a triplet signal at δ 7.28 collapsed the doublets at δ 8.00 and 6.95 into two singlets and

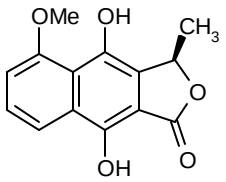
when the doublet signal at δ 8.00 was irradiated, the triplet at δ 7.28 and doublet at δ 6.95 changed to an AB-type quartet.



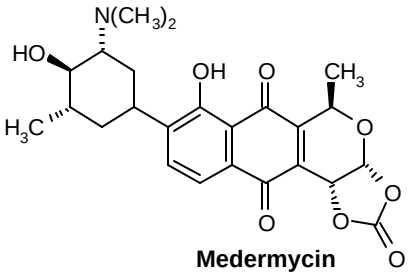
Kalafungin



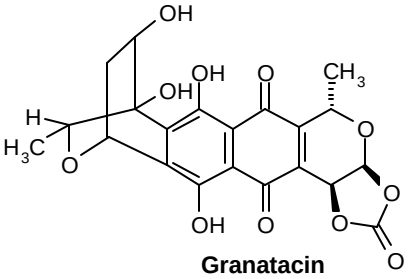
Nanaomycin D



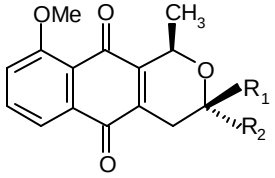
(+)-Eleutherol



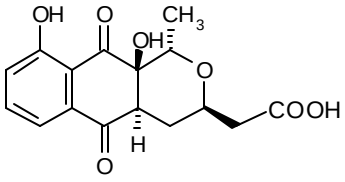
Medermycin



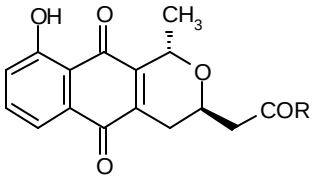
Granatacin



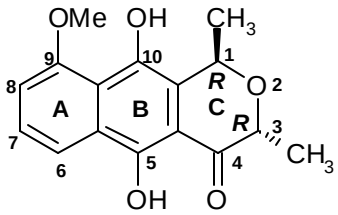
R_1 =CH_3, R_2 = H (+) Eleutherine
R_1 =H, R_2 = CH_3 (-) Isoeleutherine



Nanaomycin B



R = NH_2 Nanaomycin C



(-) Hongconin (38)

Thus the three aromatic signals were assignable to aromatic protons (C-6, C-7 and C-8) with the same substitution pattern as those of eleutherol, eleutherin and isoeleutherin. When a quartet signal at δ 5.41 was irradiated, the doublet signal of the methyl group at δ 1.58 collapsed to a singlet. The doublet signal of a methyl group at δ 1.48 also collapsed to a singlet upon irradiation of a

quartet methine signal at δ 4.63. Acetylation of hongconin with acetic anhydride and concentrated sulfuric acid yielded a diacetate, which showed absorption of a carbonyl group adjacent to aromatic ring at an unusually high wave number of 1702 cm^{-1}, besides two acetate absorptions at 1775 and 1770 cm^{-1}. This indicated the presence of acetoxyl group at the peri position to the carbonyl group. The Stereochemistry of the two chiral centers at C1 and C3 was confirmed to be (1*R* 3*R*) by preparation of both enantiomers in optically pure form[16e]. The assigned structure of hongconin (**38**) was thus confirmed on the basis of the chemical and spectral data. Important structural features of hongconin include a 1*H*-naphtho [2,3-c] pyran-4 (3*H*) one, bearing 5, 10-dihydroxy-9-methoxy-1, 3 dimethyl groups.

Earlier Methods for the Synthesis of Hongconin

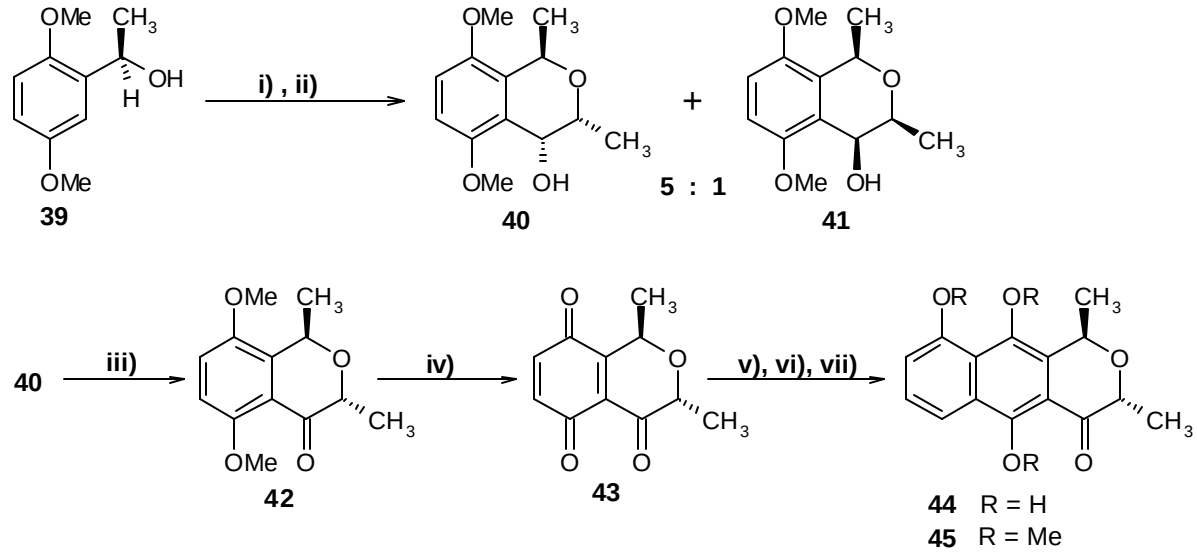
Under this subheading, the various approaches reported in the literature[16] for the total synthesis of hongconin are described. After the structure of hongconin was determined in 1986 by Chen and coworkers, hongconin has attracted the interest of synthetic chemists, since an investigation of its medicinal potential will require amounts of material in excess of its low natural occurrence. The following paragraphs describe the chemical transformations involved in the various approaches.

Kraus's approach[16b]:

Kraus and Li reported the first total synthesis of hongconin. The total synthesis of racemic hongconin has been achieved in nine steps from 2,5-dimethoxybenzaldehyde. The synthetic route features a highly regioselective Diels-Alder reaction as shown in scheme-9. Thus the reaction of 2, 5-dimethoxybenzaldehyde with methyl magnesium bromide at 0 ^{o}C resulted in the alcohol **39**. The alcohol **39** was converted into its dianion with 2 equivalents of n-BuLi at ambient temperature for 24 hr in 1:3 ether-pentane and its reaction with acrolein at -78 ^{o}C followed by acidification. An inseparable mixture of diols was isolated in 41 % yield which as such was treated with mercuric acetate in aqueous THF[8]. The resulting mercurials were reduced with $NaBH_4$ to provide a 5:1 ratio of benzopyranols **40** and **41** in 59% yield. The benzopyranol **40** was readily separated from **41** and was oxidized to ketone **42** using PCC and celite in quantitative yield. The ketone **42** was oxidized using the method of Rapports (AgO/HNO_3)[9] to afford a 94 % yield of benzoquinone **43** which was reacted with 1-[(trimethylsilyl) oxy]- butadiene in methylene chloride at -78 ^{o}C for 24 hr to afford

the Diels-Alder adduct, which was treated with Jones reagent in acetone at 0 ^{o}C. The remarkable regioselectivity[10] in the cycloaddition reaction is not clear. However, these authors believe that the carbonyl groups exert some influence on the regioselectivity. Reductive methylation of hydroxy quinone clearly generated a trimethylether **45**. Oxidation of the hydroquinone dimethyl ether **45** with AgO followed immediately by reduction with $Na_2S_2O_4$ under neutral conditions provided hongconin in 38% overall yield.

Scheme-9



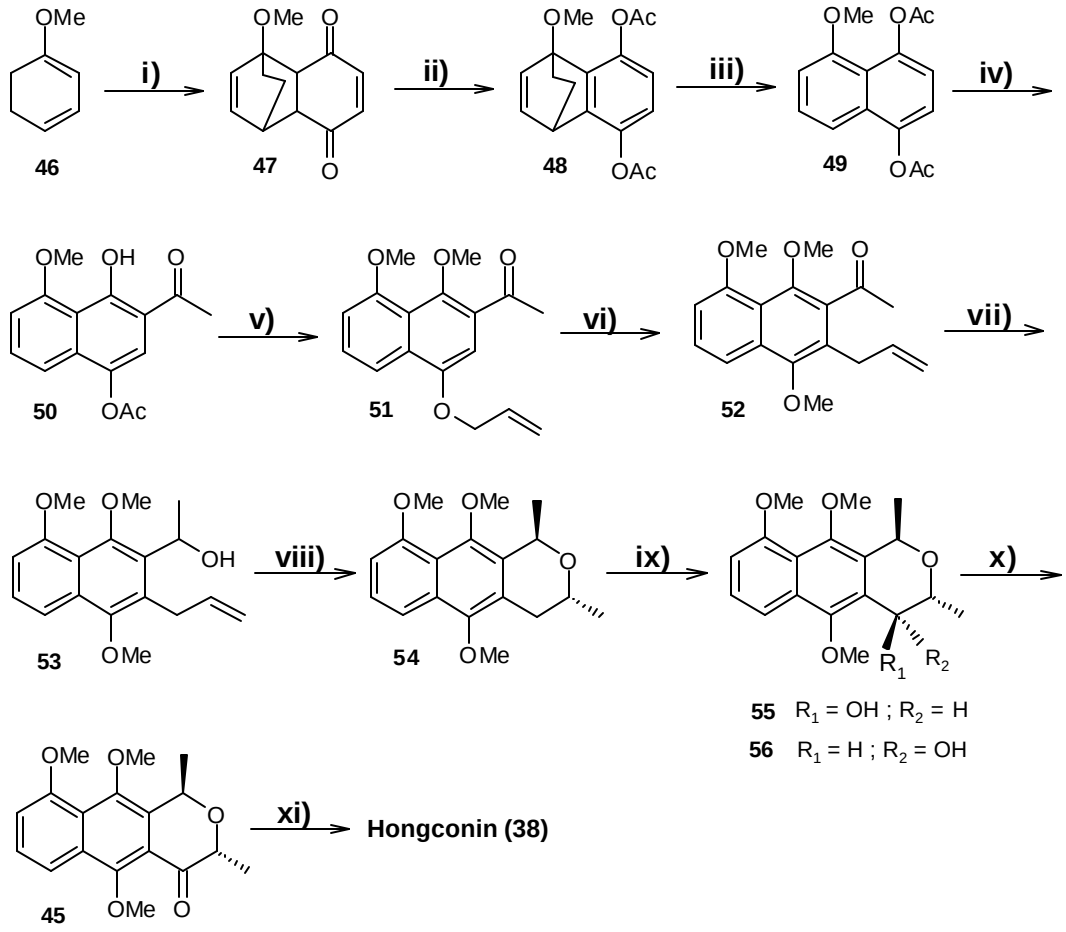
Reagents and conditions:

i) n- BuLi (2 equivalents), acrolein, 1:3 ether: pentane, 24 h. 41%. ii) Hg $(OAc)_2$, $NaBH_4$, THF-H_2O (2:1), 5h, 49% and 10% iii) PCC, Celite, CH_2Cl_2, 0 ^{o}C, 100% iv) AgO, HNO_3, THF, 1h, 94%. v) 1-[(Trimethylsilyl)oxy] butadiene, CH_2Cl_2 -78 ^{o}C, 51%. vi) Jones oxidation. vii) Me_2SO_4, $Na_2S_2O_4$, Bu_4NBr. viii) AgO, 6N HNO_3, THF ix) $Na_2S_2O_4$, THF:H_2O, 0 ^{o}C, 88%

Green's Approach[16c]:

Green reported the second total synthesis of racemic hongconin as outlined in scheme-10, wherein the starting adduct **47** was prepared by reaction between benzoquinone and 1-methoxycyclohexa-1, 3-diene **46**[11]. The Diels-Alder adduct **47** was enolised with potassium carbonate in dry acetone and then converted to diacetate **48.**

Scheme-10



Reagents and conditions:

i) Benzoquinone ii) a) K_2CO_3 , acetone b) Ac_2O, pyridine, 70 % iii) Pyrolysis, 210 ^oC, 40 min. iv) a) BF_3, 60 ^oC, 45 min. b) Ac_2O, pyridine, Zn dust, 1 hr, △, 69% v) a) CH_3I, K_2CO_3, acetone, △, 5 hr 97% b) CH_3OH/KOH, 25 ^oC, 10 min. c) Allyl bromide, K_2CO_3, acetone, △, 3 hr, 91% vi) a) Claisen rearrangement 220 ^oC, △ b) CH_3I, K_2CO_3, △, 15 hr. vii) $LiAlH_4$, ether, 30 min. 95% viii) $KOBu^t$, DMF, 60 ^oC, 10 min. ix) 7 mol. $KOBu^t$, DMF, dry oxygen, 80% x) PDC, alumina, 25 ^oC, 4 hr., 90% xi) a) AgO/HNO_3, 30 min, 70%. b) $Na_2S_2O_4$.

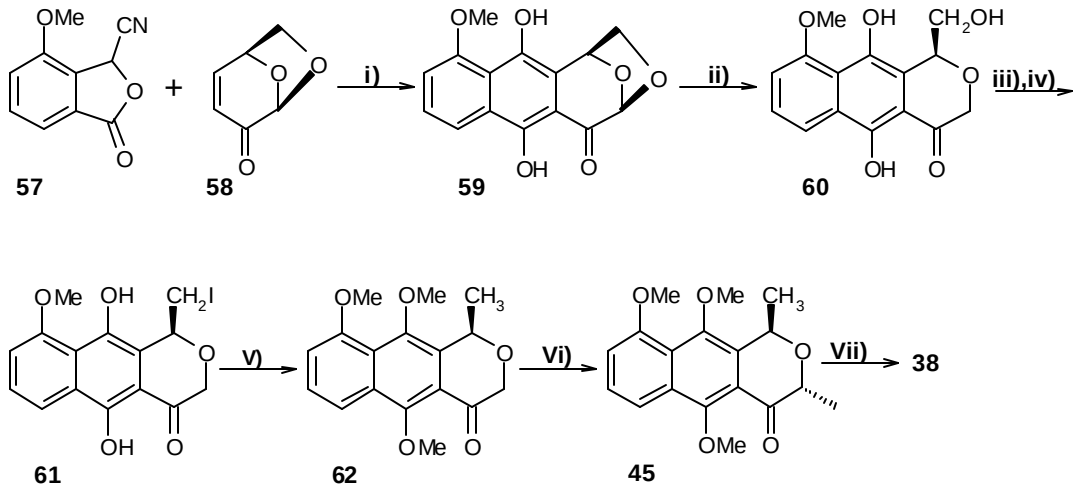
Pyrolysis[12] of the **48** resulted in elimination of the 1,4 ethano bridge to give diacetoxy naphthalene **49**, which underwent a regiospecific Fries rearrangement to afford naphthol **50**. Treatment of the naphthol **50** with potassium carbonate and iodomethane in acetone under reflux produced expected methyl ether. Alkaline hydrolysis of the acetate gave naphthol, which was converted into the allyl ether **51**. Claisen rearrangement of the allyl ether at 220 ^oC produced allyl naphthol, which was methylated again to produce the trimethoxynaphthalene **52**. Reduction of the ketone function of this system using LAH afforded the desired alcohol **53**, which was subjected to

base induced cyclisation using potassium tertiary butoxide in DMF[13] for a short period to produce exclusively the (+) *trans* 1, 3 dimethylnaphthopyran **54**. Quantitative C-4 hydroxylation was achieved by treatment of the naphthopyran **54** with 7 mol equivalents of potassium tertiary butoxide in DMF while bubbling dry oxygen through the medium. Thus epimeric mixture of 4-hydroxypyrans **55** and **56** was produced in the ratio of 4:1. The next step involved the oxidation of the C-4 alcohol. Thus treatment of the epimeric mixture of alcohols with PDC produced the pyran ketone **45**. Finally oxidation of **45** with silver (II) oxide in nitric acid[9] followed by reduction with $Na_2S_2O_4$ produced racemic hongconin (**38**), as shown in the scheme-10.

Swenton's Approach[16f]:

The various groups of organic chemists were trying to synthesise hongconin by a short and efficient route. Swenton *et al*[16f] described a total synthesis of hongconin in six steps by annelation reaction of levoglucosenone, with 3-cyano-1 (3*H*)-isobenzofuranone as well as 3-cyano-5-methoxy-1-(3*H*)-isobenzofuranone[14] (**57**). Reductive ring opening of the annelation products with zinc/copper couple with subsequent chemical transformations provided a facile entry into the naphthopyran quinone ring system. The present approach (Scheme-11) is the application of this chemistry to the preparation of hongconin having natural configuration. Thus the annelation reaction of levoglucosenone **58** with the methoxy-substituted cyanophthalide **57** furnished a crystalline, stable naphthohydroquinone **59** and the reductive ring opening gave compound **60**. Conversion of the primary alcohol to the mesylate followed by reaction with sodium iodide in acetone gave the iodide **61** in good yields. Reductive elimination of iodide by tri-n-butyltin hydride gave the required product **62**. Formation of lithium enolate of compound **62** with lithium tetramethylpiperidide followed by addition of methyl iodide (10 eq) in the presence of DMPU (10 eq) gave a 4:1 mixture of required methylated product **45** and its *cis*-isomer. Careful chromatography on silica gel gave pure methylated product **45** which was oxidatively demethylated with silver oxide[9], and then reduced with dithionite to give hongconin (**38**) as shown in scheme-11.

Scheme-11



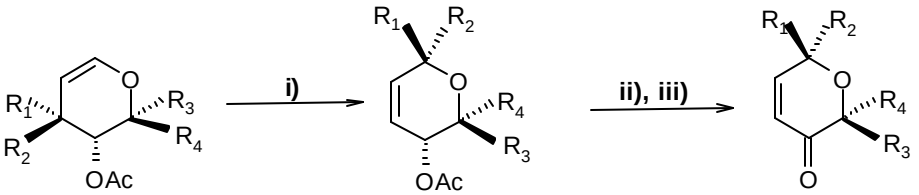
Reagents and conditions:

i) 1.5 M CH_3Li, THF:DMSO, 0 ^oC, 74% ii) Zn/Cu, THF/AcOH, △, 93% iii) MsCl, pyridine, CH_2Cl_2 iv) NaI, $Na_2S_2O_4$, acetone, △. v) a) Bu_3SnH, AIBN, benzene, △. b) DMS, K_2CO_3, acetone, △. vi) LiTMP, DMPU, CH_3I, -78 ^oC-0 ^oC, 4h., 55% vii) AgO, 6N HNO_3 then $Na_2S_2O_4$ at 0 ^oC in THF:H_2O, 57%.

Baker's Approach[16d]:

Baker *et al.* reported concise, enantioselective synthesis of (+) hongconin from 3,4-di-O-acetyl -6-deoxy-L-glucal, usually called as L-quinoval 3, 4-diacetate (**63**), allowing the absolute configuration of the natural product to be assigned for the first time. Both enantiomers of hongconin have been prepared in optically pure form in four steps from L-quinoval and D-fucal diacetates using cyanophthalide annulation chemistry. Optically pure enone **70** available in three steps from known 6-deoxy-D-galactal derivative **64** (D -fucal diacetate) was reacted with cyanophthalide **57** to directly afford the natural product (-) hongconin. The enatiomer of hongconin (**38**) and its (+)-*cis* diastereoisomer were also synthesized in a parallel fashion from the L-sugar counterpart. The advances in C-glycoside synthesis could allow conversion of the appropriate glycal into a more fully constructed Michael acceptor already possessing hongconin's dimethylpyran skeleton in its proper stereochemistry such that its reaction with cyanophthalide could provide hongconin directly with the required stereochemistry. This synthesis demonstrated the utility of commercially available 3,4-di-O-acetyl-L-quinoval [3,4-di-O-acetyl-6- deoxy-L-glucal (**63**)] as a starting material.

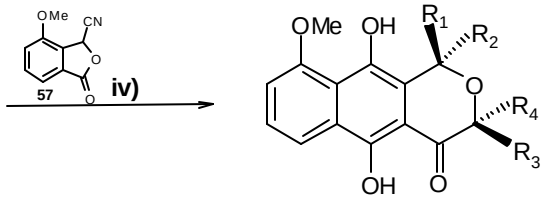
Scheme-12



63 R_1 =H, R_2 = OAc
R_3 =CH_3, R_4 =H
64 R_1 =OAc, R_2 = H
R_3 =H, R_4 = CH_3

65 R_1 =H, R_2 =CH_3
R_3 =CH_3, R_4 =H
66 R_1 =CH_3, R_2 =H
R_3 =CH_3, R_4 =H
67 R_1 =CH_3, R_2 =H
R_3 =H, R_4 =CH_3

68 R_1 =H, R_2 =CH_3
R_3 =CH_3, R_4 =H
69 R_1 =CH_3 R_2 =H
R_3 =CH_3, R_4 =H
70 R_1 =CH_3, R_2 =H
R_3 =H, R_4 =CH_3



71 R_1 =H, R_2 =CH_3 R_3 =CH_3 , R_4 =H
72 R_1 =CH_3 , R_2 =H, R_3 = CH_3, R_4 =H
38 R_1 =CH_3, R_2 =H, R_3 =H , R_4 =CH_3

Reagents and conditions:

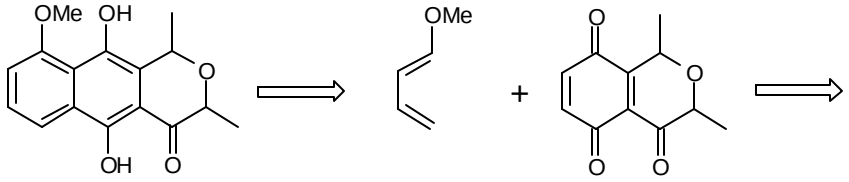
i) $TiCl_4$, $AlMe_3$, CH_2Cl_2, -78 ^oC ii) NH_3, MeOH iii) PDC-Ac_2O, CH_2Cl_2 iv) THF, -78 ^oC

Lewis acid catalysed C-1 alkylation of **63** led to 4:5 mixture of epimers **65** and **66** that were easily separated by chromatography. The stereochemistry at C-1 of these two species was tentatively assigned and later confirmed through NOE studies on their respective end products. The intermediate **65** and **66** were elaborated in parallel *via* routine O-deacetylation (ammonia-methanol) and oxidation (pyridinium dichromate-acetic anhydride[15]) into enones **68** and **69** respectively. The reaction between cyanophthalide **57** and enones **68** and **69** occurred most smoothly affording the desired naphthopyranones **71** and **72** respectively. All physical data of synthetic **71** were identical to those of naturally occurring hongconin, except the sign of optical rotation $[\alpha]_D^{20}$ + 25.8 ^{o} (c 1.94, $CHCl_3$) { lit, natural product[2e]: $[\alpha]_D^{20}$ + 26.0 ^{o} (c 1.94, $CHCl_3$). Thus absolute configuration of (-) hongconin is established by synthesis of its enantiomer. D-isomer of **63** was employed to obtain **38**. C-1 alkylation of di-O-acetyl-D-fucal (3, 4-di-O-acetyl-6-deoxy-D-galactal) (**64**) by the action of the same reagents as above led exclusively to trans-dimethyl adduct **67** in moderate yield. Processing of **67** as above led to enone **70** and finally to synthetic (-)-hongconin (**38**); $[\alpha]^{20}_D$ -25.0 ^{o} (c 1.94, $CHCl_3$). This approach confirmed the absolute stereochemistry of hongconin.

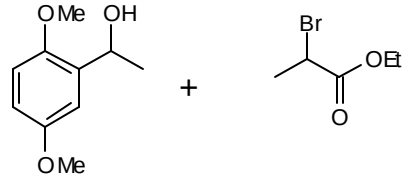
1.1.2 PRESENT WORK:

Cardioprotective activity exhibited by hongconin and its structural similarity to isochromanquinones such as kalafungin and nanaomycins, which exhibit antibiotic activity, make hongconin an attractive target for organic chemists. An examination of the structure showed it to be 5,10-dihydroxy-9-methoxy-1,3-dimethyl-4-oxo (1*H*, 3*H*) naphtho [2,3-c] pyran. Though there are a few methods reported in the literature[16] for the synthesis of hongconin, it was considered appropriate to develop a short and efficient route to hongconin as the investigation of its medicinal potential will require more quantities of hongconin. Our attempts to synthesize this novel molecule are elaborated in this section.

Route A: Diels-Alder Approach:



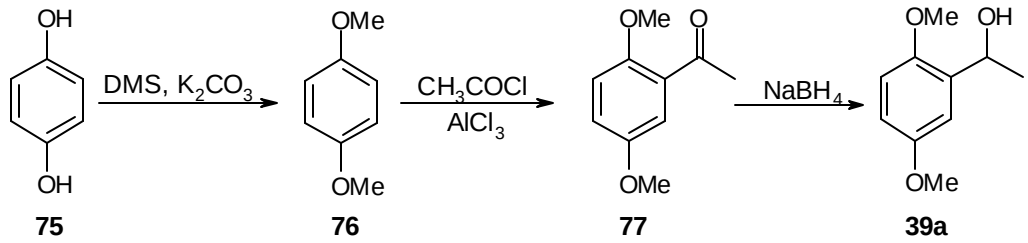
Hongconin (38) **73**



39a **74**

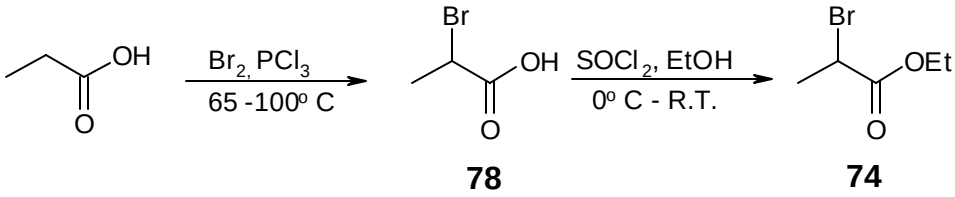
Retrosynthetic analysis suggested that the required dimethyl benzopyranone skeleton **73**, which could be prepared from ethane-1-(2, 5-dimethoxyphenyl)-1-ol (**39a**) and ethyl 2-bromopropionate (**74**), would serve as the important intermediates for the synthesis of hongconin. Ethane-1- (2, 5-dimethoxyphenyl)-1-ol (**39a**) could be prepared from hydroquinone (**75**) as shown in the scheme-13.

Scheme-13



Thus hydroquinone (**75**) was methylated with dimethyl sulfate and potassium carbonate in refluxing acetone to give 90% yield of 1, 4-dimethoxybenzene (**76**). Friedel-Crafts acylation of 1,4-dimethoxy benzene (**76**) was carried out with acetyl chloride in presence of aluminum chloride in dichloromethane at 0 ^{o}C to afford the ketone **77** in 80% yield. The ketone **77** showed physical and spectral properties consistent to those reported in the literature[17]. The ketone **77** was reduced to the corresponding alcohol with sodium borohydride in methanol to give ethane-1-(2, 5-dimethoxyphenyl)-1-ol (**39a**) in 95% yield. The spectral analysis of alcohol **39a** confirmed the structure. The ^{1}H NMR spectrum of alcohol **39a** showed a doublet (J= 7.0 Hz) at δ 1.5 for methyl group, broad singlet at δ 2.79 for alcoholic -OH, and two singlets at δ 3.78 and 3.83 for methoxyl groups and a quartet at δ 5.06 for (CH_3-C<u>H</u>-OH-) group. The aromatic protons appeared as a multiplet at δ 6.71–6.84 for two protons and another multiplet at δ 6.91-6.96 for single proton. The other starting material ethyl 2-bromopropionate (**74**) was prepared from propionic acid by α-bromination, followed by esterification as shown in scheme-14.

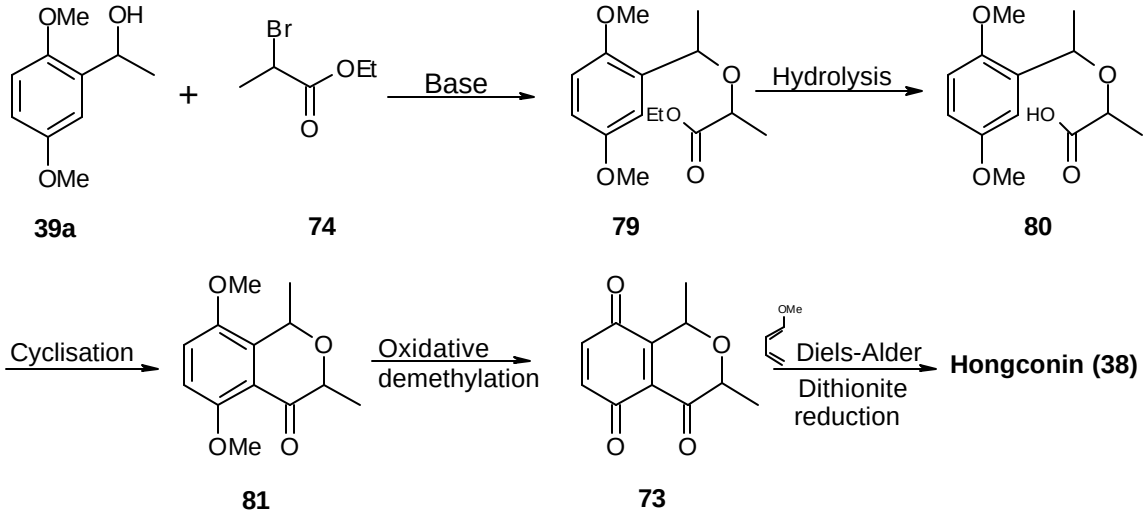
Scheme-14



The ^{1}H-NMR values for ethyl 2-bromopropionate (**74)** were in good agreement with those reported in the literature[18]. Having thus obtained both the starting materials in hand *viz* alcohol **39a** and bromo ester **74** as per the retrosynthetic plan, we assumed that preparation of BC ring synthon and then construction of ring A *via* Diels-Alder reaction would give the required tricyclic carbon

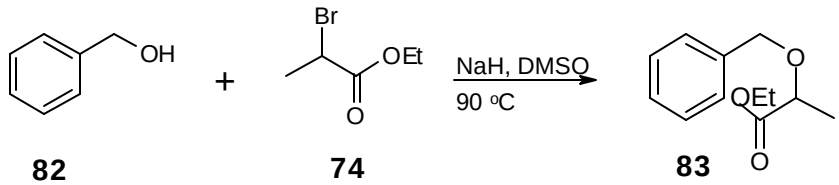
framework of hongconin. O-alkylation of the alcohol **39a** with the bromoester **74** using a base should give the O-alkylated ester **79**, which on hydrolysis followed by cyclisation should give the desired 1,3-dimethyl substituted benzopyranone **81**. Oxidative demethylation of **81** could result in quinone **73**, which will serve as dienophile for further Diels-Alder reaction with 1-methoxy 1,3-butadiene to give the target molecule hongconin as shown in scheme-15.

Scheme-15



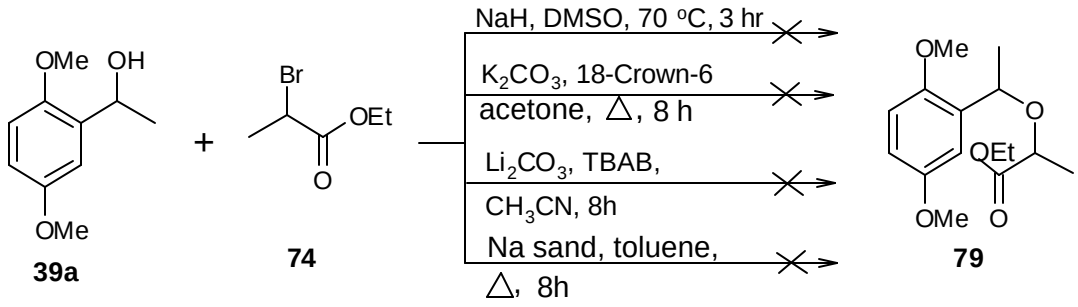
To examine the feasibility of the reaction, a model study on benzyl alcohol (**82**) and ethyl 2-bromopropionate (**74**) was carried out using sodium hydride as a base, which resulted in O-alkylated product **83**[19, 20] in good yield as shown in the scheme-16.

Scheme-16



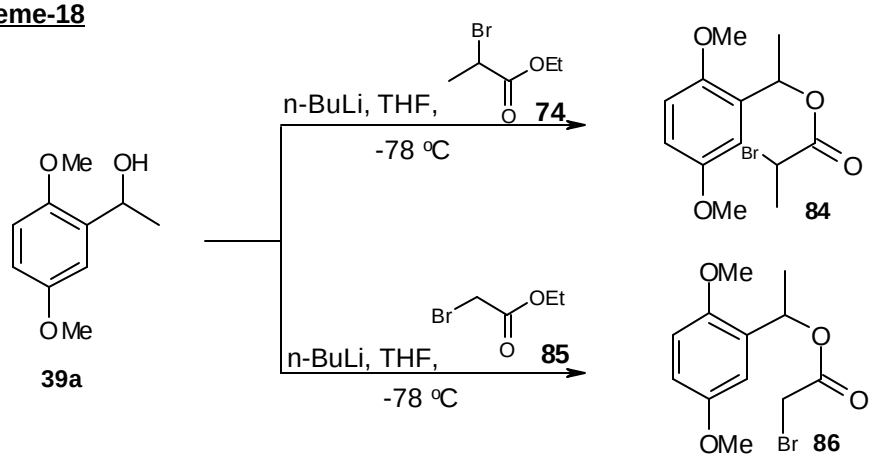
Employing the above reaction conditions, when required alcohol **39a** was treated with bromoester **74** the expected O-alkylated ester **79** could not be obtained. The various reaction conditions such as different base, temperature, time, solvent etc were tried as shown in scheme-17 but the expected O-alkylated ester could not be obtained. In all the cases starting material was recovered back.

Scheme-17



To obtain the O-alkylated ester it was thought of using strong base like n-butyllithium. Accordingly alcohol **39a** was lithiated followed by treatment with ethyl 2-bromo propionate in an attempt to obtain the required ester **79** but it gave transesterified product **84** as shown in scheme-18.

Scheme-18



The structure of transester **84** was confirmed by spectral analysis. The ^{1}H NMR spectrum showed two methyl doublets at δ 1.52 (J = 6 Hz) and at δ 1.85 (J = 6 Hz), two singlets at δ 3.79 and 3.81 for two methoxyl groups, a multiplet at δ 4.35-4.52 for the benzylic -CH and another multiplet at δ 6.15-6.32 due to the -CH-Br proton. Molecular ion peaks at m/z 316 and 318 in the mass spectrum further confirmed its structure. It was felt that methyl group in ethyl 2-bromopropionate may be posing some steric problem. To confirm the steric problem, reaction of alcohol **39a** and ethyl bromoacetate **85** was carried out using n-BuLi but that also ended up with transesterified product **86** as shown in the scheme-18. The ^{1}H NMR spectrum exhibited a singlet at δ 3.87 for -C$\underline{H_2}$Br, two singlets at δ 3.82 and 3.80 for methoxyl groups, a methyl doublet at δ 1.52 (J =7 Hz) and a quartet at δ 6.27 (J =7 Hz) for benzylic methine proton. Remaining aromatic protons resonated at their

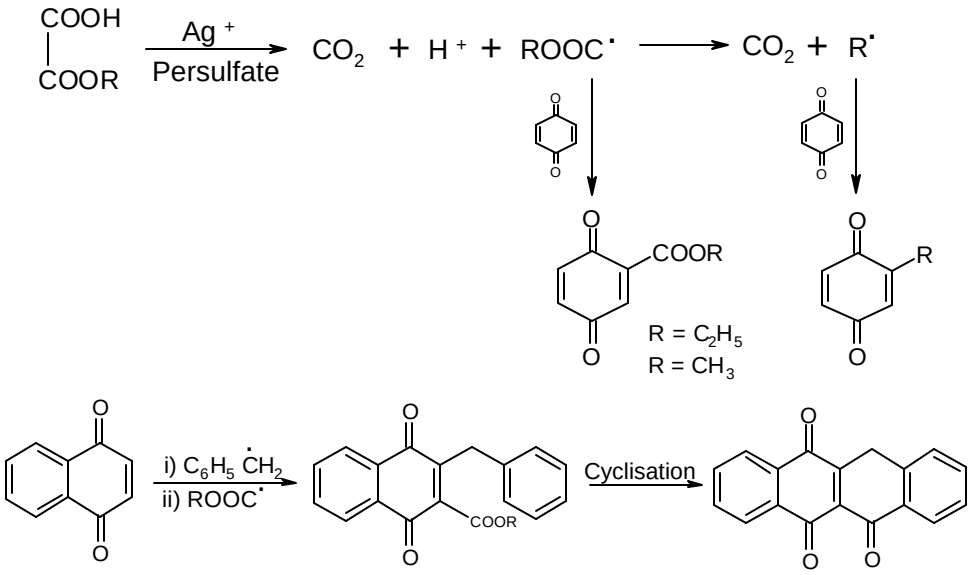
characteristic chemical shift positions. The presence of molecular ion peaks at m/z 302 and 304 in the mass spectrum confirmed its structure.

Thus the required O-alkylated ester **79** could not be obtained. Failure to effect desired alkylation led to the exploration of an alternative pathway to achieve the target. The reason why ethyl 2-bromopropionate failed to alkylate the alcohol **39a** to give the desired product **79** is unclear. It is felt that lithium anion favorably attacked on the more electrophilic ester carbonyl rather than attack on the carbon bearing halogen.

Route B: Alkoxycarbonylation of Quinones

Quinones can be alkoxycarbonylated in satisfactory yields by monoesters of oxalic acid and the $Ag+/S_2O_8^{2-}$ couple. Quinones efficiently trap the radicals with the formation of esters. Torssell and Sharma[21] reported a simple route to naphthacenequinones involving alkoxycarbonylation of naphthoquinones as shown in scheme-19.

Scheme-19

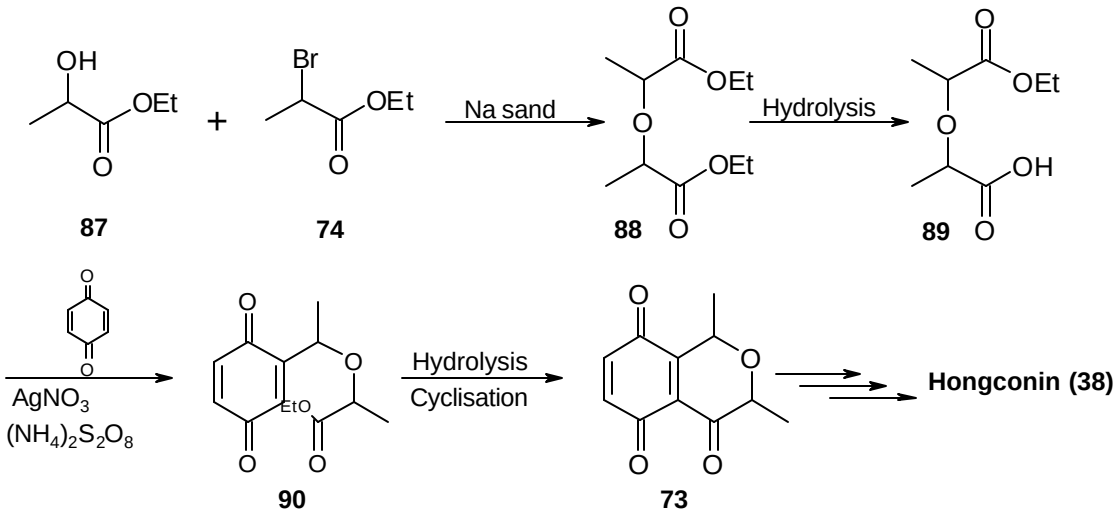


The synthesis was effected by the benzylation followed by ethoxycarbonylation. Based on the above results it was felt that synthesis of hongconin could be achieved utilizing this approach, as outlined in the scheme-20.

It was considered that 4-carbethoxy-3-oxapentane-2-carboxylic acid (**89**) could be the logical synthon for the synthesis of crucial intermediate **73**. 2,4-Dicarbethoxy-3-oxapentane (**88**) upon partial alkaline hydrolysis would give the mono carboxylic acid ester **89** that upon decarboxylation

would result in the radical. Alkoxycarbonylation of benzoquinone with the above radical followed by hydrolysis and cyclisation should give the crucial intermediate **73**. Further transformations would be same as depicted earlier in the scheme-15. Accordingly 2,4-dicarbethoxy-3-oxapentane **88** was prepared by the condensation reaction of ethyl lactate **87** and ethyl 2-bromopropionate **74**, using sodium sand[22].

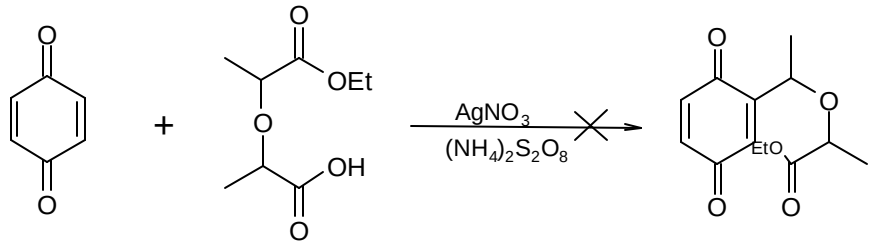
Scheme-20



The diester **88** exhibited spectral properties consistent with the assigned structure. The IR spectrum revealed the absorption band corresponding to ester carbonyl at 1742 cm^{-1}. ^1H NMR spectrum revealed a multiplet at δ 4.02-4.28 due to two methylene (-O-$\underline{CH_2}$-CH_3) groups from carboxyethyl and two -CH- groups (CH-O-CH-) from ether linkage, a doublet at δ 1.45 for two methyl groups attached to -CH-O-CH- linkage integrating for six protons and a triplet at δ 1.28 integrating for six protons for two methyl groups from carboxyethyl groups. Its mass spectrum showed (M-$CO_2C_2H_5$) fragment at m/z 145. Having the required synthon 2, 4 -dicarbethoxy-3-oxapentane in hand, partial alkaline hydrolysis was carried out with potassium hydroxide which resulted in 4-carbethoxy-3-oxapentane 2-carboxylic acid **89** structure of which was confirmed by ^1H NMR spectrum. The comparison of ^1H NMR spectra of diester and monoester showed that the ratio of integration of ester methyl group compared to ester methylene and methine protons adjacent to ether linkage together, was changed from 6:6 to 3:4. Appearance of a broad singlet at δ 7.80 for carboxylic acid proton confirmed that one ester group was hydrolyzed. When the monoester **89** was treated with benzoquinone in presence of silver nitrate and ammonium persulfate in aqueous

acetonitrile in order to generate the decarboxylated free radical as shown in scheme-21, a mixture of unidentifiable products was obtained. As all the efforts to obtain crucial intermediate **73** failed, this approach was discontinued.

Scheme-21

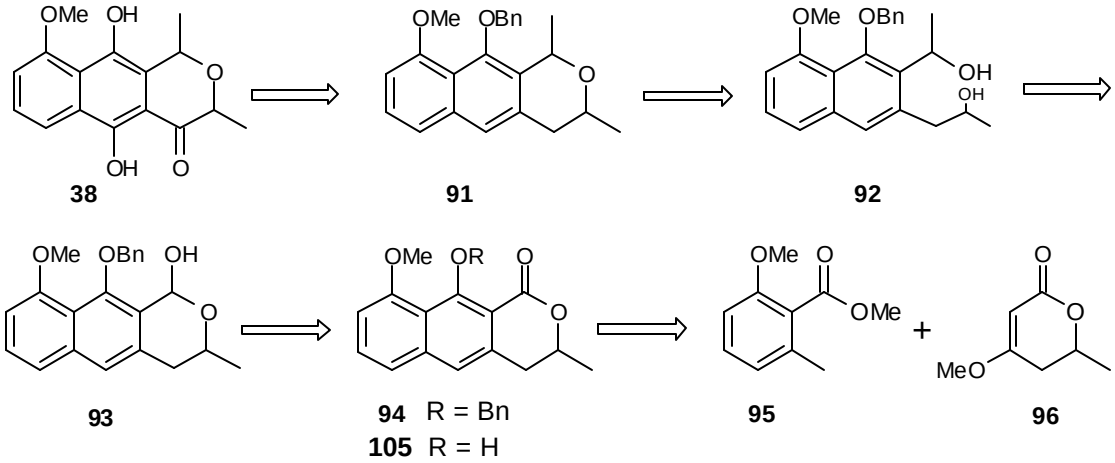


89 **73**

Having failed again at this juncture a deeper look into the retrosynthetic analysis suggested that synthesis of hongconin could best be achieved by directly obtaining tricyclic intermediate **105** and then functional group manipulations in C ring as shown in scheme-22.

Route C: Michael Addition Approach

Scheme-22



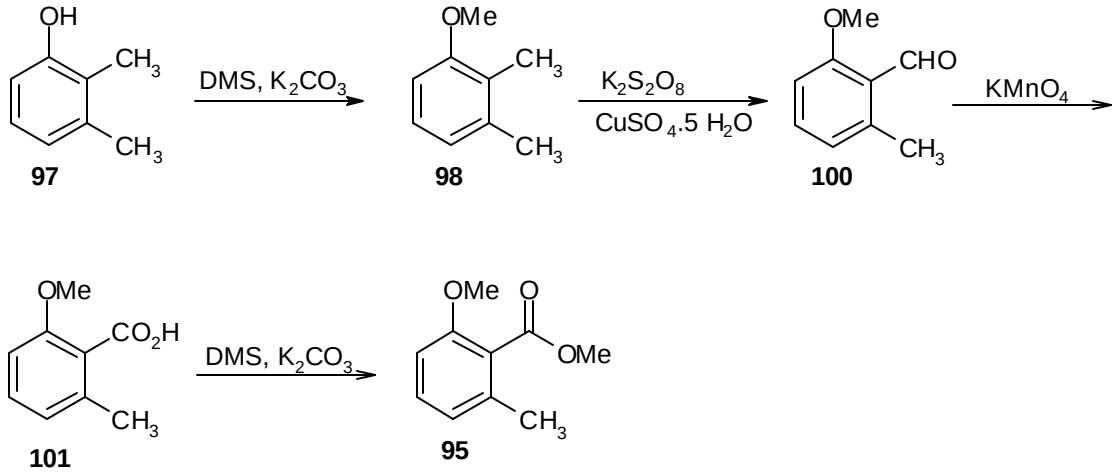
38 **91** **92**

93 **94** R = Bn **95** **96**
105 R = H

The tricyclic intermediate **105** could be effected by Michael addition reaction of the anion of methyl 2-methoxy-6-methyl benzoate (**95**) with a dihydropyrone **96**. Introduction of methyl group on the lactone carbonyl of tricyclic intermediate would lead to the dimethylpyran skeleton of hongconin. Intramolecular cyclisation of the resulting diol **92** followed by reaction sequence as shown in the retrosynthetic plan would afford hongconin. The formation of two C-C bonds in a

single step between ester **95** and dihydropyrone **96** was envisaged to give the required tricyclic intermediate **105**. The aromatic ester synthon **95,** required for the coupling reaction with pyrone **96,** could be obtained from 2, 3-dimethyl phenol by the known procedure[23] as shown in the scheme-23.

Scheme-23



Thus 2,3-dimethyl phenol (**97**) was methylated using dimethyl sulfate and potassium carbonate in refluxing acetone to afford 2,3- dimethylanisole (**98**) as a brown oil. This was used without any purification for further oxidation with aqueous potassium peroxydisulfate[24] in acetonitrile, water and pyridine to give the aldehyde **100** (70%) which was used as such for further reaction.

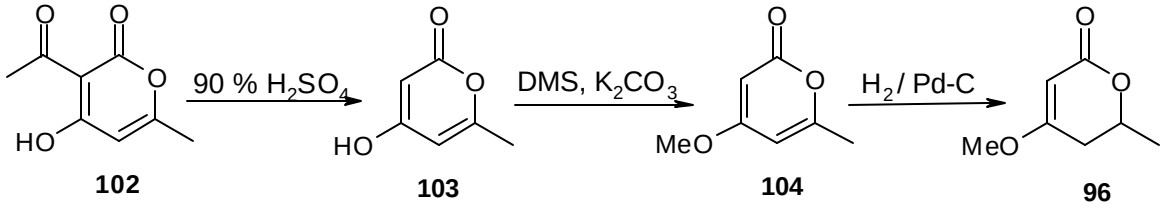
The structure of aldehyde **100** was confirmed by purification and spectral analysis. Its IR spectrum showed a carbonyl absorption band at 1686 cm^{-1}. The ^1H NMR spectrum of the aldehyde showed a methyl singlet at δ 2.58, methoxyl singlet at δ 3.90, multiplet at δ 6.80-6.85 for two aromatic protons, a triplet at δ 7.39 (J=4 Hz) for one aromatic proton and a singlet at δ 10.65 for aldehyde proton. Oxidation of the aldehyde **100** as such with powdered potassium permanganate in benzene-water and tetra-n-butyl ammonium iodide as a phase transfer catalyst yielded 2-methoxy-6-methylbenzoic acid (**101**). Methyl 2-methoxy-6-methylbenzoate (**95**) was then prepared by esterification of the acid **101** with dimethyl sulfate and potassium carbonate in refluxing acetone in 95 % yield.

The structure of ester **95** was also confirmed by spectral analysis. Its IR spectrum showed a carbonyl band at 1731 cm^{-1}. The ^1H NMR spectrum showed a singlet at δ 2.37 for methyl protons, two singlets at δ 3.90 and δ 4.00 for methyl ester and methoxyl ether respectively, a pair of *ortho*

coupled doublets at δ 6.84 (J= 6 Hz) and 6.88 (J= 6 Hz) integrating for two aromatic protons and a triplet at δ 7.33 (J=6 Hz) for the remaining aromatic proton. The appearance of the molecular ion peak at m/z 180 in the mass spectrum further confirmed the assigned structure.

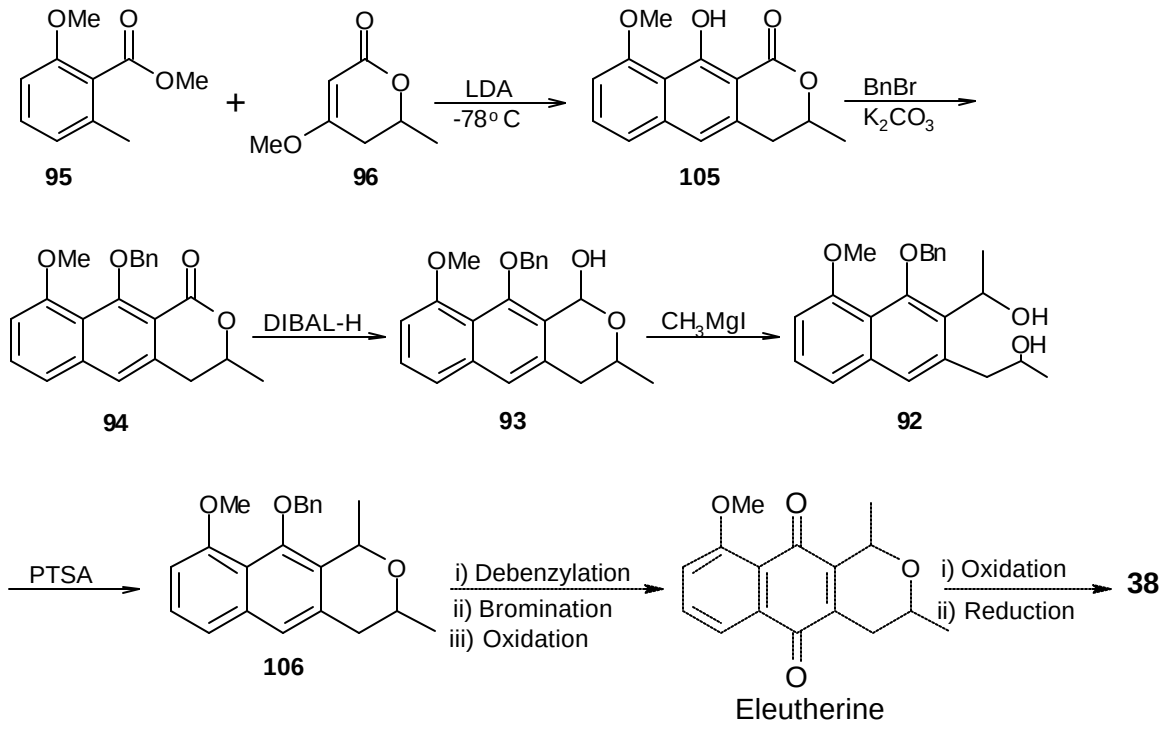
The pyrone counterpart **96** was prepared by known literature procedure[26] from commercially available dehydroacetic acid (**102**) as shown in scheme-24.

Scheme-24



Thus the dehydroacetic acid (**102**) was deacetylated[25] by heating it with concentrated sulphuric acid to give triacetic lactone (**103**) methylation[26] of which with dimethyl sulfate in presence of potassium carbonate in acetone furnished methyl ether **104**. The physical and spectral properties of the triacetic lactone methyl ether were in good agreement with those reported in the literature[25]. The triacetic lactone methyl ether **104** was hydrogenated[27] over palladium on carbon employing a hydrogen balloon at room temperature to give dihydropyrone **96**. Its physical and spectral properties were in good agreement with those reported in the literature. With key synthons dihydropyrone **96** and aromatic ester **95** in hand, the condensation reaction was carried out. Thus lithiation[28] of ester **95** at -78 ^{o}C with 2 equivalents of LDA followed by treatment with dihydropyrone **96** gave the tricyclic intermediate **105** as shown in scheme-25. The structure of tricyclic intermediate **105** was assigned on the basis of spectral data. The IR spectrum revealed absorption band at 1654 cm^{-1} for lactone carbonyl function. The ^{1}H NMR spectrum showed a methyl doublet at δ 1.57, benzylic CH_2 appeared as a multiplet at δ 3.02 and a multiplet at δ 4.66-4.86 [-CH_2-(O)-CH-CH_3]. The chelated hydroxyl proton was observed at δ 13.21. Rest of the aromatic protons resonated at the appropriate positions. The mass spectrum exhibited molecular ion peak at m/z 258 confirming the assigned structure. Tricyclic intermediate **105** was treated with benzyl bromide in presence of potassium carbonate to yield the benzyl ether **94** structure of which was assigned on the basis of ^{1}H NMR spectrum. The disappearance of singlet for chelated hydroxyl proton and appearance of benzylic ether protons as two doublets at δ 5.08 and 5.31 as well as additional aromatic protons indicated formation of the desired benzylic ether. Assigned structure for the benzyl ether **94** was further supported by presence of a molecular ion peak at m/z 348.

Scheme-25



In accordance with the plan, alkylation[29] reaction of the benzyl ether **94** was carried out using methyl magnesium iodide in ether-THF, but unfortunately this alkylation reaction did not proceed and we had to adapt a two-step sequence to accomplish this reaction. Accordingly the lactone functionality in the benzyl ether **94** was reduced to lactol **93** with DIBAL-H in toluene at -60 ^{o}C. The IR spectrum of lactol **93** revealed the presence of absorption band at 3380 cm^{-1} and absence of peak in the carbonyl functionality region. The ^{1}H NMR spectrum of lactol showed a mixture of diastereomers. A methyl doublet was observed at δ 1.39 (J= 7.0 Hz), while a multiplet at δ 4.46-4.62 was assigned to the methine proton adjacent to the methyl group [-CH_2-(O)-<u>CH</u>-CH_3]. Two benzylic protons appeared as a set of two doublets at δ 5.00 (J= 8 Hz) and at δ 5.22 (J= 8 Hz) each integrating for a single proton. The remaining aromatic protons resonated between δ 6.46-7.65 as a multiplet integrating for nine protons. The molecular ion peak at m/z 350 further confirmed its structure.

Grignard reaction on this lactol **93** was then carried out at 0 ^{o}C in order to introduce a methyl group at C1 carbon, which resulted in the diol **92**. The ^{1}H NMR of the diol **92** showed methyl doublets in two sets at δ 1.25 (J= 6.0 Hz) and 1.32 (J= 6.0 Hz) due to methyl group at C3. Another set of two-methyl doublets appeared at δ 1.55 (J= 6 Hz) and at 1.60 (J= 6 Hz) due to C1 methyl groups. Multiplet

integrating for two benzylic protons [-C<u>H</u>$_2$-CH-CH$_3$] appeared at δ 2.82-3.32. while the singlet at δ 3.85 integrating for three protons was assigned to the methoxy group. A multiplet at δ 3.99-4.16 was assigned to [-CH$_2$-C<u>H</u> (OH)-CH$_3$] and a set of two quartets at δ 5.45 (J=6 Hz) and at δ 5.61 (J= 6 Hz) was assigned to CH$_3$-C<u>H</u>-(OH)-naphthyl. Benzylic CH$_2$ of benzyl ether appeared as a multiplet at δ 4.85-5.20 and the aromatic proton adjacent to methoxy group appeared as a multiplet at δ 6.75-6.88. Remaining eight aromatic protons appeared as a multiplet at δ 7.29-7.67. The mass spectrum showed molecular ion peak at m/z 366 that further confirmed the structure. Thus after introducing a methyl group at C1 carbon, intramolecular cyclisation of diol was carried out in refluxing benzene with catalytic amount of *p*-toluenesulphonic acid which furnished the required dimethyl pyran skeleton of hongconin. The ^{1}H NMR of the dimethylpyran **91** showed a complex splitting pattern arising due to diasteromeric mixture although it showed a single spot on TLC. The ^{1}H NMR showed a multiplet at δ 1.28-1.46 integrating for three protons for C3 methyl group while another multiplet at δ 1.55-1.69 was assigned to C1 methyl group. A multiplet at δ 2.50-3.00 integrating for two protons was assigned to the benzylic methylene protons while the benzylic methine proton appeared as a multiplet at δ 5.20-5.65. Benzylic protons from the benzylic ether group showed a multiplet at δ 4.15-4.43 integrating for two protons. Methoxyl functionality exhibited a singlet at δ 4.06. Aromatic protons appeared as two multiplets at δ 6.64-6.85 and δ 7.00-7.50 integrating for two and seven protons respectively supporting the assigned structure. The presence of molecular ion peak at m/z 348 further confirmed the structure of the naphthopyran **91**. Debenzylation of **91** was attempted with H$_2$-Pd/C, EtOH, and H$_2$, Pd(OH)$_2$, EtOH, which failed to afford the corresponding naphthol as there was no reaction. Further attempts of debenzylation with H$_2$, Pd/C, cycloheaxadiene, ethanol dioxan gave a product which showed molecular ion peak at m/z 258 but the ^{1}H NMR was not clear. Repeated reactions and purification of the product yielded similar results so the further steps (bromination and oxidation) leading to hongconin could not be accomplished.

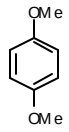
1.1.3 CONCLUSION:

The present attempts towards the synthesis of hongconin can be summarized as follows:

The initial Diels-Alder approach met with failure as the required ester **79** could not be prepared due to problems of transesterification. Alkoxycarbonylation route, which was attempted after the Diels-Alder approach, was also unsuccessful as the key intermediate **89** failed to react with benzoquinone. The final Michael addition approach, though failed at advanced stage, provided the desired naphthopyran skeleton.

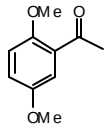
1.1.4 EXPERIMENTAL:

1,4-Dimethoxybenzene (76):



To a solution of hydroquinone (20.0 g, 0.18 mole) in dry acetone (400 ml) was added anhydrous potassium carbonate (50.20 g, 0.36 mole) and the mixture was refluxed for 10 min. Dimethyl sulfate (45.8 g, 34.0 ml, 0.36 mole) was added and the reaction mixture was refluxed for 18 h. The acetone was removed by distillation, reaction mixture was cooled and ice water was added. The solid that separated was filtered, washed with water, dried and recrystallised from ethanol-water to give 1,4-dimethoxybenzene (22.5 g 90%); m.p. 56 ^{o}C.

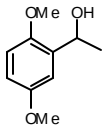
2-Acetyl-1, 4-dimethoxybenzene (77):



1,4-Dimethoxybenzene (5.0 g, 36.2 mmole) was dissolved in dry methylene chloride (50 ml), anhydrous aluminium trichloride (6.0 g, 45.2 mmole) was added at once and the contents of the flask were cooled to 0 ^{o}C with stirring. Acetyl chloride (2.84 g, 36.2 mmole) was added dropwise within 15 min. The reaction mixture was stirred for 4 hr at the same temperature, then quenched with ice and HCl, extracted with methylene dichloride, washed with water (50 ml), brine (20 ml), dried over Na_2SO_4 and concentrated on rotary evaporator to give **77** as a colorless oil (6.25 g, 80 %).

IR (Neat): 1672 cm^{-1} (-C=O). **^{1}H NMR** ($CDCl_3$): δ 2.62 (s, 3H, -$COCH_3$), 3.79, (s, 3H, OMe), 3.87 (s, 3H, OMe), 6.87-7.06 (m, 2H, aromatic), 7.29 (d, J= 7 Hz, 1H, aromatic). **^{13}C NMR** ($CDCl_3$): δ 31.42 (-CO<u>C</u>H$_3$), 55.35 (-O-CH_3), 55.61 (-O-CH_3), 112.88 (aromatic), 113.61 (aromatic) 119.82 (aromatic), 127.98 (aromatic), 153.05 (aromatic), 153.50 (aromatic), 198.82 (-C=O). **MS** (m/z): 180 (M^+, 40), 165 (100), 150 (20), 137 (18), 122 (23) and 107 (25).

Ethane-1-(2, 5-dimethoxyphenyl)-1-ol (39a):



To a solution of 2-acetyl-1,4-dimethoxybenzene (6.0 g, 27.9 mmole) in methanol (60 ml) at room temperature was added sodium borohydride (0.525 g, 13.8 mmole) in small lots over a period of five minutes. After the addition was complete the reaction mixture was stirred at room temperature for 1 hr. After completion of the reaction methanol was distilled off, water (100 ml) added to the residue, neutralized with acetic acid, extracted with chloroform, washed with water followed by brine and dried over sodium sulphate. Removal of the choroform by distillation under reduced pressure gave colorless oil. This was filtered through a short band of silica gel using petroleum ether-acetone (9:1) as an eluent to afford the pure product **39a** (5.8 g, 95%).

IR (neat): 3415 cm^{-1} (-OH). **^{1}H NMR** ($CDCl_3$): δ 1.50 (d, J= 7 Hz, 3H), 2.79 (bs, 1H, -OH), 3.78 (s, 3H, -OMe), 3.83 (s, 3H, -OMe), 5.06 (q, J= 7 Hz, 1H), 6.71-6.84 (m, 2H, aromatic), 6.91-6.96 (m, 1H, aromatic). **^{13}C NMR** ($CDCl_3$): δ 23.08 (-CH (OH)-$\underline{C}H_3$), 55.57 (-OCH_3), 55.83 (-OCH_3), 69.54 (-$\underline{C}$H-OH), 111.48 (aromatic), 111.85 (aromatic), 112.58 (aromatic), 134.53 (aromatic), 150.33 (aromatic), 151.14 (aromatic), 153.88 (aromatic), 154.19 (aromatic). **MS** (m/z): 182 (M^+, 100), 167 (91), 152 (23), 139 (73), 124 (25), 107 (10) and 91 (7).

2-Bromopropionic acid (78):

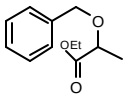
Bromine (12.16 g, 0.076 mole) was added dropwise to a stirred solution of propionic acid at 65 ^{o}C, catalytic amount of PCl_3 was also added as an initiator. When the addition was complete (30 min), stirring was continued at 65 ^{o}C for another 12 hr by which time evolution of HBr almost ceased out. Temperature of the reaction was further raised to 100 ^{o}C and stirred for another 1 hr and the product was isolated by distillation under reduced pressure to give 2-bromopropionic acid as a colorless oil, (7.0 g, 67%); b.p. 202 ^{o}C [Lit[30] b.p. 202-203 ^{o}C].

Ethyl 2-bromopropionate (74):

To a solution of 2-bromopropionic acid (7.0 g, 0.045 mole) in ethanol (100 ml) at 0 ^{o}C was added thionyl chloride (6.8 g, 4.14 ml, 0.057 mole) dropwise over a period of 25 min. It was stirred overnight at room temperature, then poured onto crushed ice, extracted with methylene chloride (2 × 50 ml), washed with saturated sodium bicarbonate solution (30 ml) and then brine, dried over sodium sulfate and concentrated under reduced pressure to give ethyl 2-bromopropionate as a colorless liquid. It was purified by distillation at atmospheric pressure at 156-160 ^{o}C [Lit[31] b.p. 158-160 ^{o}C].

^{1}H NMR ($CDCl_3$): δ 1.27 (t, J= 8 Hz, 3H), 1.78 (d, J= 8 Hz, 3H), 4.19 (q, J= 8 Hz, 2H), 4.32 (q, J= 8 Hz, 1H). **MS** (m/z): 182 (M^+, 11), 180 (M+, 11), 154 (20), 152 (18), 137 (15), 135 (17), 110 (61), 109 (95), 108 (75), 107 (100) and 73 (48).

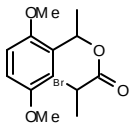
Ethyl 2-benzyloxypropionate (83):



Benzyl alcohol (0.833 g, 4.6 mmol) in dry DMSO (3.0 ml) was added dropwise to a suspension of sodium hydride (0.22 g, 9.2 mmol) in dry DMSO (4.0 ml) under nitrogen atmosphere and the mixture was allowed to stir at room temperature for 15 min. Temperature was raised to 70 ^{o}C and it was further stirred for 30 min. Ethyl 2-bromopropionate (0.76 g, 4.6 mmol) in DMSO (3.0 ml) was then added slowly. It was then heated at 90 ^{o}C for further 3 hr. The reaction mixture was cooled and diluted with ether (2 × 20 ml), washed with water, brine (10 ml), dried over sodium sulfate and concentrated to give a syrup which was purified by column chromatography over silica gel using 10 % acetone in pet ether as eluent to afford ethyl 2-benzyloxypropionate (**83**) as a colorless oil (0.71 g, 73.80 %).

^{1}H NMR ($CDCl_3$): δ 1.32 (t, J= 8 Hz, 3H), 1.48 (d, J= 8 Hz, 3H), 4.08 (q, J= 8 Hz, 1H), 4.23 (q, J= 8 Hz, 2H), 4.47 (d, J= 10 Hz, 1H), 4.73 (d, J= 10 Hz, 1H), 7.16-7.53 (m, 5H). **MS** (m/z): 207 ($M-CH_3$, 7), 178 (52), 164 (14), 155 (21), 149 (26), 135 (30), 126 (40) and 121 (100).

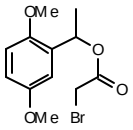
2-Bromopropionic acid 1-(2,5-dimethoxyphenyl)ethyl ester (84):



To a solution of alcohol **39a** (0.5 g, 2.7 mmol) in dry THF (10 ml) at 0 ^{o}C, was added n-BuLi (1 ml of 15 % solution in hexane, 0.147 g, 2.7 mmol) dropwise over a period of 10 min. It was further stirred for 1 hr, a solution of ethyl 2-bromopropionate (0.476 g, 2.7 mmole) in dry THF (5 ml) was then added over a period of 20 min and reaction continued for another 3 hr. After completion of the reaction, it was poured in saturated ammonium chloride solution (30 ml) and extracted with ethyl acetate, washed with water, brine, dried over sodium sulfate and concentrated to give dense oil. It was purified by column chromatography to afford the pure transester **84** as a colorless oil (0.559 g, 64.00 %).

^{1}H NMR ($CDCl_3$): δ 1.52 (d, J= 6 Hz, 3H), 1.85 (d, J= 6 Hz, 3H), 3.79 (s, 3H, -OMe), 3.81 (s, 3H, -OMe), 4.35-4.52 (m, 1H), 6.15-6.32 (m, 1H), 6.75-6.80 (m, 2H), 6.92-7.04 (m, 1H). **MS** (m/z): 318 (M^+, 12), 316 (M^+, 14), 181 (68), 165 (78), 150 (100), 135 (30), 121 (15), 107 (25), 91 (12), 77 (18).

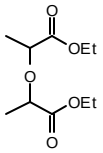
Bromoacetic acid 1-(2,5-dimethoxyphenyl)ethyl ester (86):



To a solution of alcohol **39a** (0.5 g, 2.7 mmol) in dry THF (10 ml) at 0 ^{o}C, was added n-BuLi, (1 ml of 15 % solution in hexane, 0.147 g, 2.7 mmol) dropwise over a period of 10 min. It was further stirred for 1 hr, a solution of ethyl bromoacetate (0.456 g, 2.7 mmol) in dry THF (5 ml) was then added over a period of 20 min and reaction continued for another 3 hr. Work up and purification as described for **84** afforded the pure transester **86** (0.497 g, 60.00 %) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 1.52 (d, J= 7 Hz, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 3.87 (s, 2H), 6.27 (q, J= 7 Hz, 1H), 6.75-6.82 (m, 2H), 6.92-7.02 (m, 1H). **MS** (m/z): 304 (M^+, 30), 302 (M^+, 25), 181 (25), 165 (100), 150 (52), 135 (22), 121 (19) and 77 (10).

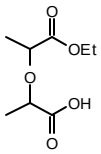
2,4-Dicarbethoxy-3-oxapentane (88):



Toluene (10 ml) was added under nitrogen atmosphere to sodium metal (1.0 g, 0.043 mmol) prewashed with dry pet ether and heated at reflux. When the sodium metal melted, it was stirred vigorously and the sodium sand thus obtained was cooled to RT. Ethyl lactate (5.0 g, 0.0427 mole) in dry ether (50 ml) was added at room temperature. Contents of the flask were stirred for 18 hr at room temperature. Ethyl 2-bromopropionate in ether (20 ml) was then added over a period of 2 hr and stirring continued for another 3 hr. The reaction mixture was washed with water (3 × 20 ml) followed by brine, dried over sodium sulphate and concentrated on rotary evaporator to provide 2,4-dicarbethoxy-3-oxapentane as a colorless oil (5.0 g, 58.74%).

IR (Neat): 1742 cm^{-1} ($-CO_2C_2H_5$). **^{1}H NMR** ($CDCl_3$): δ 1.28 (t, J= 6 Hz, 6H), 1.45 (d, J= 6 Hz, 6H), 4.02-4.28 (m, 6H). **^{13}C NMR** ($CDCl_3$): δ 13.79, 18.31, 60.61, 73.83, 172.80. **MS** (m/z): 145 (M-$CO_2C_2H_5$, 62), 117 (10), 102 (71), 89 (25), 73 (97) and 56 (100).

4-Carbethoxy-3-oxapentane-2-carboxylic acid (89):



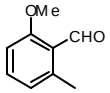
To the solution of 2,4-dicarbethoxy-3-oxapentane (1.0 g, 4.9 mmol) in ethanol (10 ml) was added aqueous potassium hydroxide (0.139 g, 2.4 mmole) in water (2.0 ml) at once. Contents of the flask were stirred at room temperature overnight, TLC showed a slower moving compound. The ethanol was removed on rotary evaporator, residual solid was dissolved in water and extracted with chloroform to remove the traces of starting material. The aqueous part was acidified with 10 N HCl, extracted with chloroform, washed with brine, dried over sodium sulfate and concentrated to afford the partially hydrolysed product **89** (0.6 g, 63.50 %).

IR (Neat): 1730 (-$CO_2C_2H_5$), 3442 cm^{-1} (-CO_2H). **^{1}H NMR** ($CDCl_3$): δ 1.30 (t, J= 6 Hz, 3H), 1.48 (d, J= 6 Hz, 3H), 1.52 (d, J= 6 Hz, 3H), 4.04-4.34 (m, 4H), 7.80 (bs, 1H, -CO_2H). **MS** (m/z): 145 (M-CO_2, 38), 117 (M^+- CO_2Et, 52), 102 (31), 89 (59), 73 (100) and 55 (82).

2,3-Dimethylanisole (98):

A mixture of 2,3-dimethylphenol (50.0 g, 0.41 mole), potassium carbonate (62.0 g, 0.45 mole) and dimethyl sulfate (64.54 g, 48.0 ml, 0.51 mole) in dry acetone (700 ml) was heated at reflux for 15 hr. After the completion of reaction, the acetone was distilled off and to the residue water (400 ml) was added. The aqueous part was extracted with ethyl acetate, washed with water, dried over sodium sulfate and concentrated under reduced pressure to give 2,3-dimethylanisole as a brownish oil (52.94 g, 95%), b.p. 199 ^oC [Lit[32] b.p.199 ^oC].

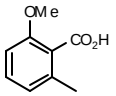
2-Methoxy-6-methylbenzaldehyde (100):



To a stirred suspension of potassium peroxydisulfate (76.23 g, 0.28 mole) in water (400 ml) were added copper (II) sulfate pentahydrate (70.63 g, 0.28 mole) and 2, 3 -dimethylanisole (19.2 g, 0.14 mole), pyridine (20.23 ml, 0.28 mole) in acetonitrile (400 ml). The mixture was heated at 70 ^oC for 6 hr, cooled and filtered. The filtrate was extracted with ethyl acetate and the extract was washed with 4 M hydrochloric acid (50 ml) and brine. The solution was dried over sodium sulfate and evaporated to give brown oil containing mainly aldehyde **100** which was used as such for further reaction. A part of the crude aldehyde **100** was purified by column chromatography to furnish pure **100** as a pale yellow solid, m.p. 40-41 ^oC [Lit[23] m.p. 41.4- 42 ^oC] for spectral analysis.

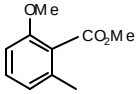
IR (Neat): 1686 cm^{-1} (-CHO). **^{1}H NMR** ($CDCl_3$): δ 2.58 (s, 3H), 3.90 (s, 3H), 6.80-6.85 (m, 2H), 7.39 (t, J= 4 Hz, 1H), 10.65 (s, 1H, -CHO). **^{13}C NMR** ($CDCl_3$): δ 21.10, 55.43, 108.81, 122.99, 123.77, 134.21, 141.59, 162.88, 168.76 and 191.95.

2- Methoxy-6-methylbenzoic acid (101):



The crude aldehyde **100** obtained above (13.70 g, 0.086 mole) was dissolved in benzene (130 ml) and it was added to a solution of potassium permanganate (13.58 g, 0.086 mole) in water (150 ml). Tetrabutylammonium iodide (0.91 g, 0.028 mole) was added and the mixture was stirred vigorously at reflux. Further quantities of potassium permanganate were added after 30 min (13.58 g) and 90 min (6.79 g). After further 30 min the reaction mixture was filtered through celite and filtrate was acidified with conc. HCl. The aqueous part was extracted with ethyl acetate (3 × 50 ml). The extract was washed with brine, dried over sodium sulfate and evaporated in vacuo to afford 2-methoxy-6-methyl benzoic acid (**101**) as a colorless solid (11.56 g, 80%), m.p. 137-139 ^{o}C [Lit[23] m.p. 139 ^{o}C].

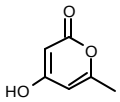
Methyl 2-methoxy-6-methylbenzoate (95):



To a mixture of above acid **101** (11.09 g, 0.066 mole) and potassium carbonate (10.0 g, 0.072 mole) in dry acetone (150 ml) was added dimethyl sulfate (9.0 g, 6.9 ml, 0.071 mole). The reaction mixture was stirred under reflux for 12 hr. After completion of reaction, the acetone was distilled off and residue was diluted with water (100 ml). The aqueous part was extracted with ethyl acetate (2 × 50 ml), washed with water, brine, dried over sodium sulfate and concentrated to give **95** as a colorless oil (11.32 g, 95%).

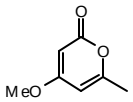
IR (Neat): 1731 cm^{-1} (-CO_2CH_3). **^{1}H NMR** ($CDCl_3$): δ 2.37 (s, 3H), 3.90 (s, 3H), 4.00 (s, 3H), 6.84 (d, J= 6 Hz, 1H), 6.88 (d, J= 6 Hz, 1H), 7.33 (t, J= 6 Hz, 1H). **^{13}C NMR** ($CDCl_3$): δ 18.78 (-CH_3), 51.67 (-$CO_2\underline{C}H_3$), 55.50 (-$O\underline{C}H_3$), 108.21, 122.03, 123.54, 129.97, 136.07, 158.18, 168.42 (-$\underline{C}O_2CH_3$). **MS** (m/z): 180 (M^+, 38), 149 (72), 148 (100), 119 (11), 105 (18), 91 (45), 77 (22) and 65 (17).

4-Hydroxy-6-methyl-2H-pyran-2-one (103):



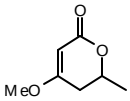
Dehydroacetic acid (**102**, 25.00 g, 0.149 mol) was added with stirring to 90% sulphuric acid (75.00 g) and the mixture was heated slowly. When the temperature of the reaction mixture reached to 130 ^{o}C it was cooled rapidly and poured into the mixture of crushed ice and cold water (100 ml). A colourless solid separated was filtered, washed with cold water and dried to obtain compound **103** (15.00 g, 80 %); m.p. 188-190 ^{o}C [Lit[25] m.p. 188-189 ^{o}C].

4-Methoxy-6-methyl-2-pyrone (104):



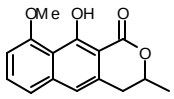
A mixture of triacetic lactone **103** (12.6 g, 0.10 mol), dimethyl sulfate (18.9 g, 0.15 mol) and anhydrous potassium carbonate (20.7 g, 0.15 mmol) in dry acetone (200 ml) was heated at reflux for 11 hr. The reaction mixture was filtered, washed with acetone and the acetone was distilled off to leave an oil. It was then chromatographed on silica gel using 10% acetone in pet ether as an eluent to obtain 4-methoxy-6-methyl-2-pyrone (**104**) (11 g, 78%); m.p. 88 ^{o}C [Lit[26] m.p. 87-88 ^{o}C].

4-Methoxy-6-methyl-5, 6-dihydro-2-pyrone (96):



In a 250 ml R.B. flask the triacetic lactone methyl ether **104** (10.0 g, 0.071 mol) was hydrogenated in ethanol (100 ml) using 10 % Pd on charcoal (0.10 g) employing hydrogen balloon for 24 hr at room temperature. The catalyst was removed by filtration to give crude viscous oil. Chromatographic purification of the crude product on silica gel using 5% acetone in pet ether as an eluent afforded **96** (8.6 g, 85%); m.p. 56 ^{o}C [Lit[26c] m.p. 56 ^{o}C].

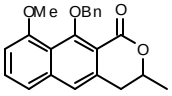
3,4-Dihydro-10-hydroxy-9-methoxy-3-methyl-1-oxo-1*H*-naphtho [2,3-c] pyran
OR 10-Hydroxy-9-methoxy-3-methyl-2-naphthopyran-1-one (105):



To the stirred solution of LDA [prepared from 1.6 M solution of n-BuLi in hexane (13. 85 ml) and diisopropyl amine (3.12 ml) at 0 ^{o}C under argon atmosphere] in THF (25 ml) at -78 ^{o}C was injected a solution of methyl 2-methoxy-6-methyl benzoate (**95**, 2.0 g, 0.011 mole) in THF (15 ml) and stirred for 15 min. To the resultant orange-red solution was added a solution of 4-methoxy-6-methyl-5, 6-dihydro-2-pyrone (**96,** 1.55 g, 0.011 mole) in THF (12 ml) and stirred further for 30 min at -78 ^{o}C. It was then warmed to room temperature by removing dry ice-acetone bath and stirred for 20 min. The reaction mixture was poured slowly into the ice-cold dilute hydrochloric acid (100 ml) and extracted with dichloromethane. The organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was chromatographed (silica gel) using 20 % acetone in pet ether as an eluent to afford naphthopyrone **105** as a crystalline yellow solid (1.90 g, 68%); m.p. 135.6 ^{o}C.

IR ($CHCl_3$): 1654 cm^{-1} (lactone carbonyl). **^{1}H NMR** ($CDCl_3$): δ 1.57 (d, J= 6 Hz, 3H), 3.02 (m, 2H), 4.05 (s, 3H), 4.66-4.86 (m, 1H), 6.88 (d, J= 8 Hz, 1H), 7.02 (s, 1H), 7.26 (d, J= 8 Hz, 1H), 7.53 (t, J= 8 Hz, 1H), 13.21 (s, 1H). **^{13}C NMR** ($CDCl_3$): δ 20.44 (-CH_3), 34.58 (-$\underline{C}H_2$-CH-CH_3), 55.87 (-O$\underline{C}H_3$), 75.58, 101.82, 105.68, 114.87, 115.75, 119.61, 130.46, 133.18,139.57, 158.87, 163.72, 170.82. **MS** (m/z): 258 (M^+, 100), 225 (19), 196 (40), 175 (40), 152 (18) and 115 (56).

3,4-Dihydro-10-benzyloxy-9-methoxy-3-methyl-1-oxo-1*H*-naphtho [2,3-c] pyran (94):

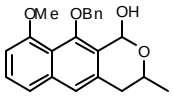


A mixture of **105** (1.0 g, 3.8 mmol), potassium carbonate (0.641 g, 4.6 mmol) and benzyl bromide (0.729 g, 0.506 ml, 4.2 mmol) was stirred under reflux for 20 hr. The acetone was removed by distillation, to the residue was added water (50 ml), the product was extracted with ethyl acetate (3 × 20 ml), washed with water several times, with brine (50 ml), dried over sodium sulfate and concentrated on rotary evaporator to provide a crude product which was chromatographed on silica gel using 10% acetone in pet ether as an eluent to afford **94** as a crystalline yellow solid (1.213 g, 90 %), m.p. 106.9 ^{o}C.

IR: 1715 cm^{-1} (lactone carbonyl). **^{1}H NMR** ($CDCl_3$): δ 1.50 (d, J= 6 Hz, 3H), 3.00 (d, J= 6 Hz, 2H), 3.87 (s, 3H), 4.41-4.64 (m, 1H), 5.08 (d, J= 10 Hz, 1H), 5.31 (d, J= 10 Hz, 1H), 6.86 (d, J= 7 Hz,

1H), 7.14-7.69 (m, 8H). **^{13}C NMR** ($CDCl_3$): δ 20.33, 35.92, 33.61, 73.64, 77.00, 106.12, 115.64, 119.85, 120.35, 121.22, 127.24, 127.72, 128.24, 129.04, 135.41, 137.61, 138.74, 157.42, 159.49 and 161.97. **MS** (m/z): 348 (M^+,6), 257 (6), 243 (4), 175 (8), 127 (10) and 91 (100).

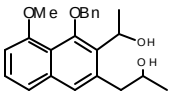
3,4-Dihydro-10-benzyloxy-9-methoxy-3-methyl-1*H*-naphtho [2,3-c] pyran1-ol (93):



Benzyl ether **94** (1.32 g, 3.7 mmol) was dissolved in dry toluene (15 ml) under argon atmosphere and cooled to -78 ^oC in a dry ice-acetone bath. DIBAL-H, (2.52 M solution in toluene, (0.592 g, 1.65ml, 4.17 mmol) was injected through syringe within 10 min. Stirring was continued at the same temperature for further 3 hr. The reaction mixture was then quenched at the same temperature by adding 1.6 ml of MeOH and 1.6 ml water and warmed to room temperature. The gelatinous precipitate was filtered through celite and the celite was washed thoroughly with ethyl acetate. Concentration of the solution on rotary evaporator furnished crude lactol, which was purified by column chromatography using 20 % acetone in pet ether as an eluent to furnish pure lactol **93** (1.03 g, 78 %) m.p. 150.5 ^oC.

IR (Neat): 3380 cm^{-1} (lactol). **^{1}H NMR** ($CDCl_3$): δ 1.39 (d, J= 7 Hz, 3H), 2.72-2.95 (m, 2H), 3.90 (s, 3H), 4.46-4.62 (m, 1H), 5.00 (d, J= 8 Hz, 1H), 5.22 (d, J= 8 Hz, 1H), 6.46-6.51 (m, 1H), 6.75-6.90 (m, 1H), 7.00-7.65 (m, 8H). **MS** (m/z): 350 (M^+, 4), 242 (28), 209 (4), 181 (6), 127 (4), 115 (8) and 91 (100).

1-Benzyloxy-2 (1'-hydroxyethyl)-3 (2'-hydroxypropyl)-8-methoxynaphthalene (92):

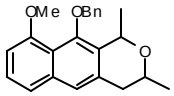


To a stirred suspension of activated magnesium metal (0.057 g, 2.4 mmol) in dry ether (10 ml) was added iodomethane (0.338 g, 0.0148 ml, 2.4 mmol) dropwise over 10 min at room temperature. To the resultant solution of methyl magnesium iodide, benzyl lactol **93** (0.700 g, 2.0 mmol) in dry THF (10 ml) was added slowly over a period of 30 min at 0-5 ^oC. Reaction mixture was allowed to warm to room temperature over 2 hr, quenched with saturated NH_4Cl solution and the resulting suspension

was stirred for another 30 min. It was then extracted with ethyl acetate, washed with brine and dried over sodium sulfate. Evaporation of the solvent gave the crude diol, which was purified on silica gel using 30 % acetone in pet ether as an eluent to afford pure diol **92** as an oil (0.477 g, 66.00 %).

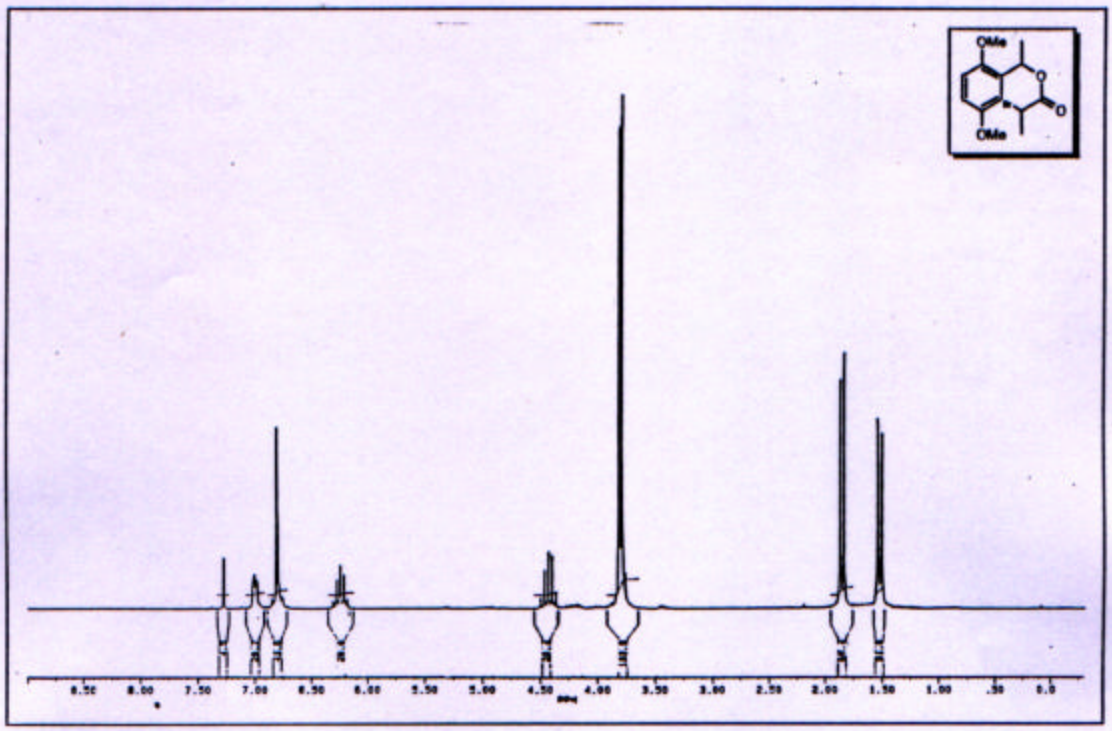
IR (Neat): 3393 cm^{-1} (-OH). **^{1}H NMR** ($CDCl_3$): δ 1.25 and 1.32 (d, J= 6 Hz, total 3H), 1.55 and 1.60 (d, J= 6 Hz, total 3H), 2.82-3.32 (m, 3H), 3.85 (s, 3H), 3.99-4.16 (m, 1H), 4.85-5.20 (m, 2H), 5.45 and 5.61 (q, J= 6 Hz total 1H), 6.75-6.88 (m, 1H), 7.29-7.67 (m, 8H). **^{13}C NMR** ($CDCl_3$): δ 20.91, 21.82, 23.10, 24.00, 24.69, 25.09, 29.24, 36.01, 42.15, 42.42, 53.93, 55.94, 62.78, 65.59, 66.26, 68.36, 69.00, 69.80, 105.14, 105.96, 118.96, 120.67, 123.39, 125.65, 126.26, 126.80, 127.63, 128.43, 134.19, 135.50, 136.24, 137.00, 137.73, 152.96, 155.65, 155.77. **MS** (m/z): 366 (M^+, 8), 348 (2), 258 (24), 215 (22) and 91 (100).

10-Benzyloxy-9-methoxy-1,3-dimethyl-(1*H*,3*H*) naphtho [2,3-c] pyran (91) :

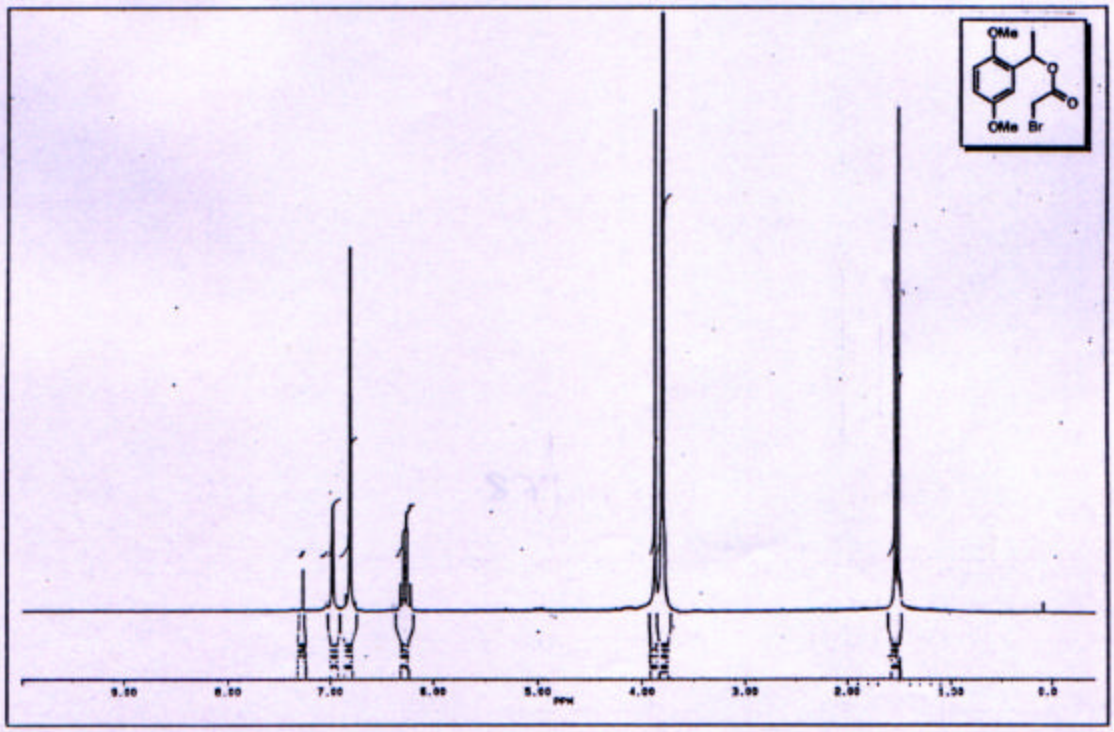


Diol **92** (0.400 g, 1.0 mmol) was dissolved in dry benzene (10 ml), catalytic amount of *p*-toluenesulphonic acid was added and the solution was stirred under reflux employing Dean-Stark water separator under argon atmosphere for 30 min. The reaction mixture was cooled and portioned between water and benzene, benzene layer was washed with water, brine and dried over sodium sulfate. Concentration under vacuo furnished syrup, which was chromatographed using 10 % acetone in pet ether to provide cyclised product **91** (0.240 g, 63.00 %) as oil.

^{1}H NMR ($CDCl_3$): δ 1.28-1.46 (m, 3H), 1.55-1.69 (m, 3H), 2.50-3.00 (m, 2H), 3.77-3.95 (m, 1H), 4.06 (s, 3H), 4.15-4.43 (m, 2H), 5.20-5.65 (m, 1H), 6.64-6.85 (m, 2H) and 7.00-7.50 (m, 7H). **MS** (m/z): 348 (M^+, 6), 333 (22), 258 (23), 243 (100), 228 (30), 181 (20) and 115 (32).



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 84 IN $CDCl_3$



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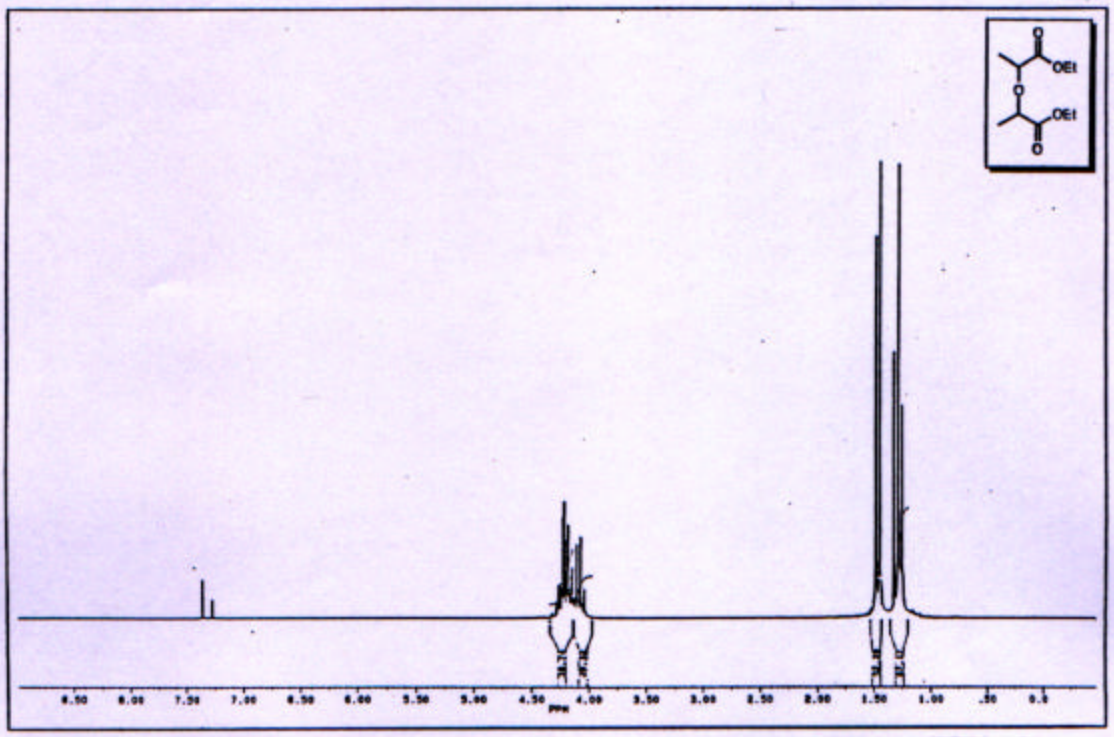
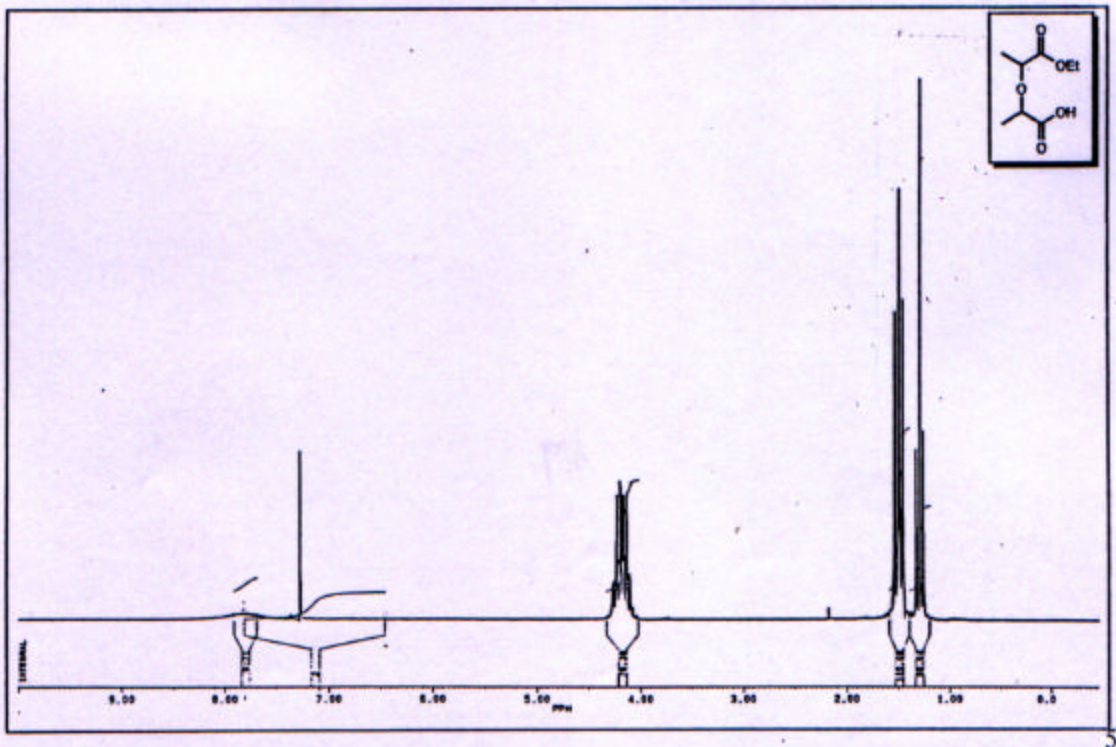
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 86 IN $CDCl_3$



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 88 IN $CDCl_3$



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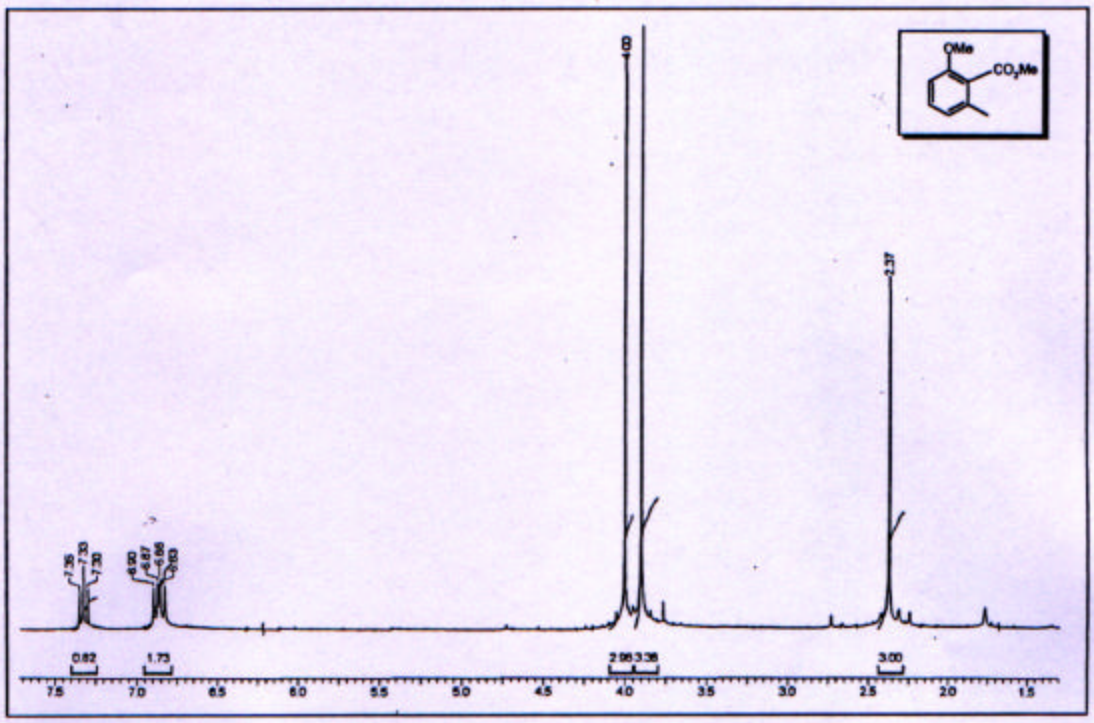
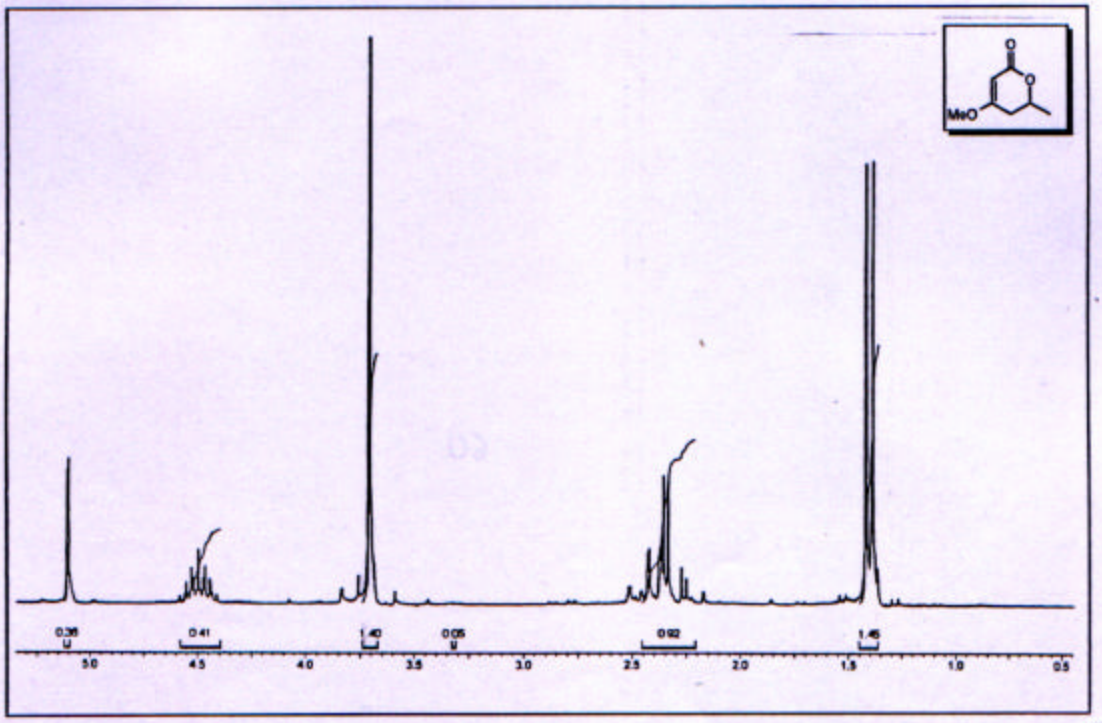
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 89 IN $CDCl_3$

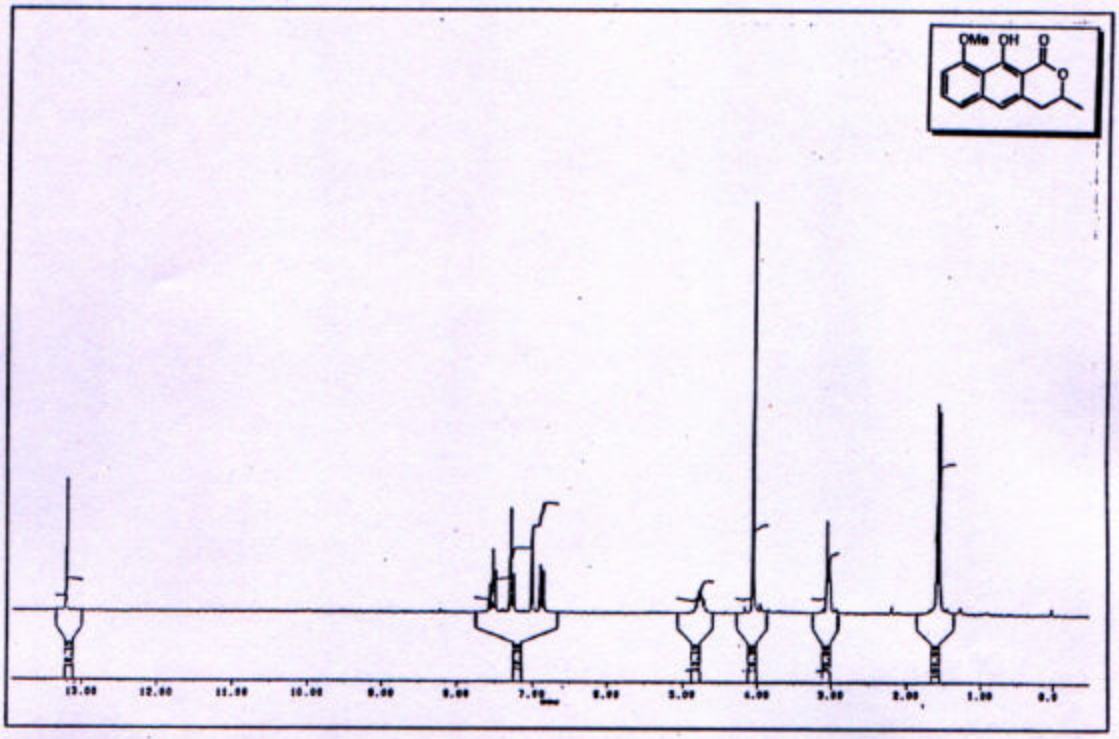


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 95 IN $CDCl_3$

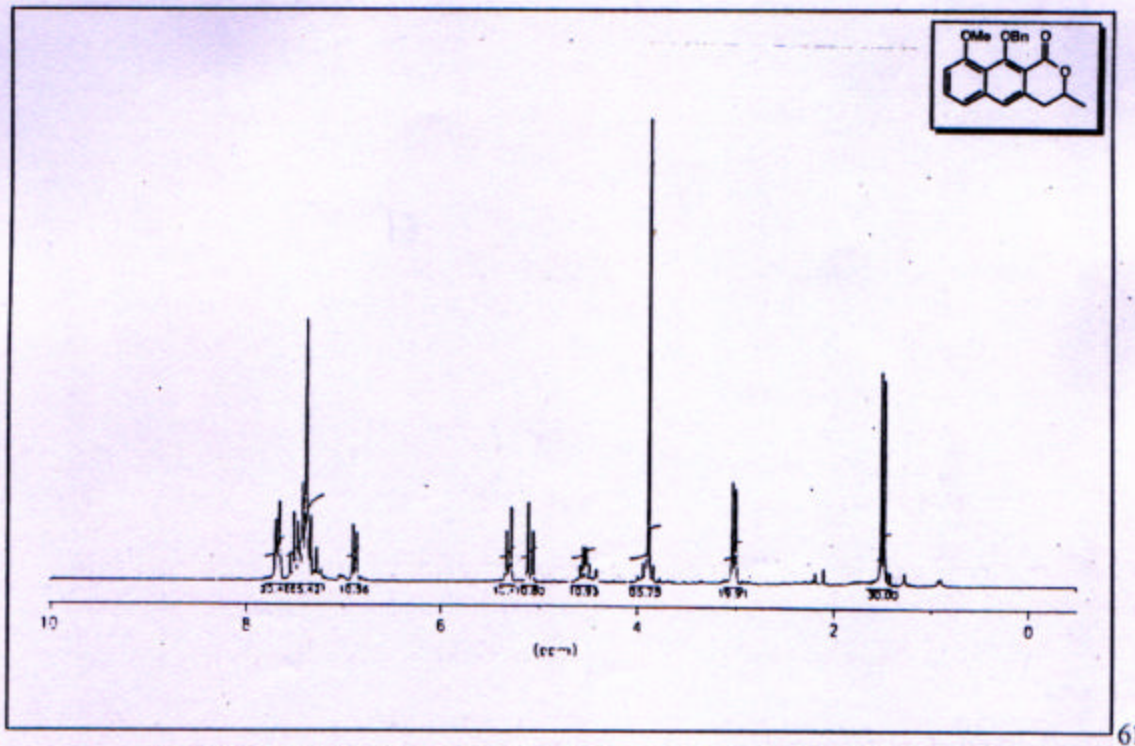


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 96 IN $CDCl_3$

60



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 105 IN $CDCl_3$



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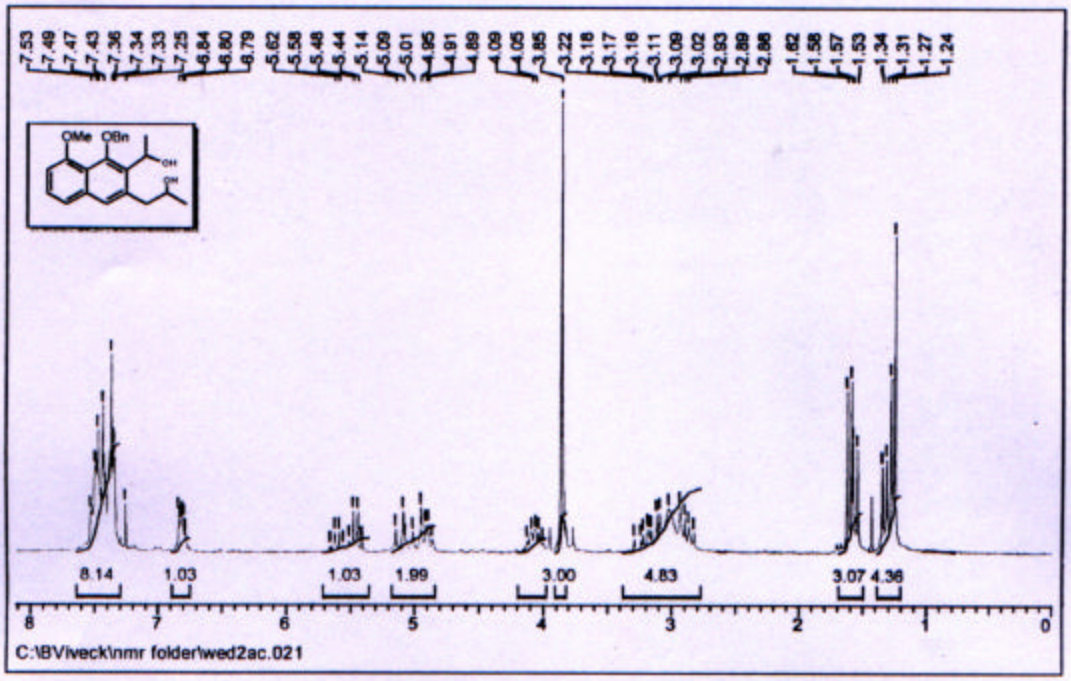
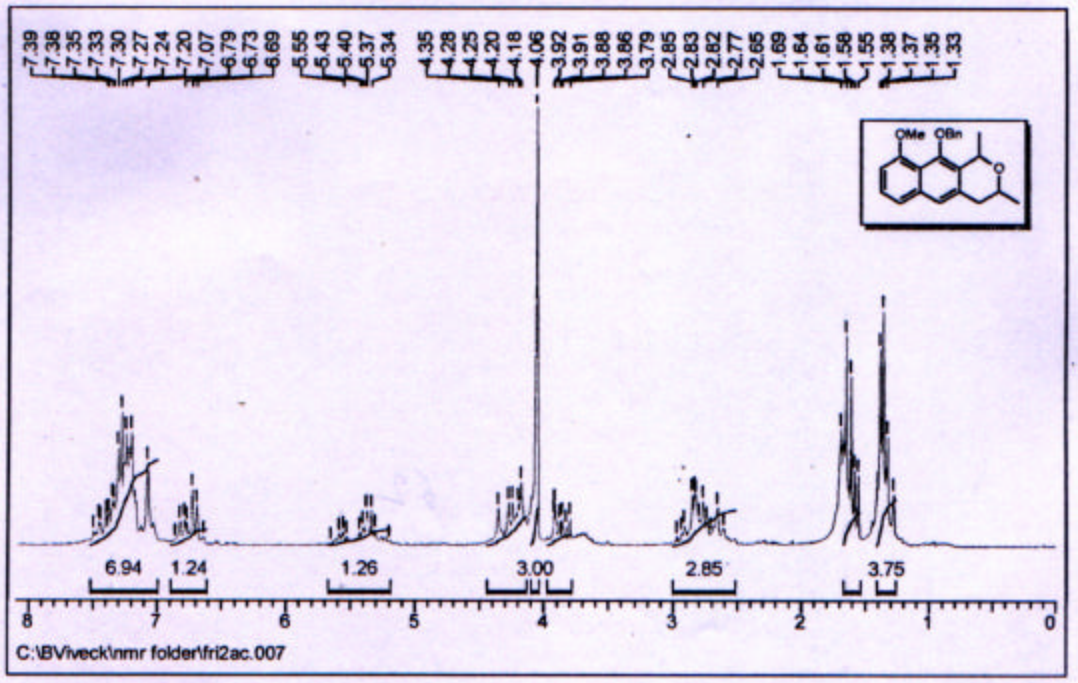
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 94 IN $CDCl_3$



^{1}H NMR SPECTRUM (200 MHz) OF THE COMPOUND 92 IN $CDCl_3$



^{1}H NMR SPECTRUM (200 MHz) OF THE COMPOUND 91 IN $CDCl_3$

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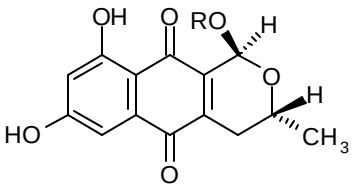
1.1.5 REFERENCES:

1. *Hainan-Renmin Hospital Guanxinloin-Keyan-Xiaozu, Hainan-Weisheng*, No.2, 43 (1977).
2. a) Chen, Z.; Huang, H.; Wang, C.; Li, Y. and Ding, J., *Zhongcaoyao*, **1981**, 12, 484. b) Schmidt, H.; Meijer, Th. M. and Ebnother, A., *Helv. Chim. Acta*, **1950**, 33, 595. c) Schmidt, H.; Ebnother, A. and Meijer, Th. M., *Helv. Chim. Acta*, **1950**, 33, 1751. d) Schmidt, H. and Ebnother, A., *Helv. Chim. Acta*, **1951**, 33, 561. e) Chen, Z.; Huang, H.; Wang C.; Li Y.; Ding J.; Ushio S.; Hiroshi N. and Yoichi I., *Chem. Pharm. Bull*., **1986**, 34, 2743.
3. Bergy, M. E., *J. Antibiot*., **1968**, 21, 454. b) Hoeksema, H. and Krueger, W. C., *J. Antibiot*., **1976,** 29, 704.
4. a) Omura, S.; Tanaka, H.; Okada, Y. and Marumo, H., *J. Chem. Soc. Chem. Commun*., **1976**, 320. b) Omura, S.; Tanaka, H.; Koyama, Y.; Oiwa, R.; Katagini, M.; Awaya, J.; Nagal, T. and Hata, T., *J. Antibiot*., **1974**, 27, 363. c) Tanaka, H.; Koyama, Y.; Nagai, T.; Marumo, H. and Omura, S., *J. Antibiot*., **1975**, 28, 868.
5. Keller-Schlierlein, W.; Brufani, M. and Barcza, S., *Helv. Chim. Acta.*, **1968**, 51, 1257.
6. a) Ogura, H. and Furuhata, K., 9th International Congress of Heterocyclic chemistry, Tokyo, August, **1983**, Abst. No. S-IV-6, P-114. b) Hopwood, D. A.; Malpartida, F.; Kieser, H. M.; Ikeda, H.; Duncan, J.; Fujii, I.; Rudd, B. A. M.; Floss, H. G.; Omura, A., *Nature*, **1985**, 314, 642.
7. a) Winters, M. P.; Strauburg, M.; Moore, H. W., *J. Org. Chem*., **1994**, 59, 7572. b) Moore, H. W., *Science*, **1977**, 197, 527.
8. Naruta, Y.; Uno, H. and Maruyama, K., *J. Chem. Soc., Chem. Commun*., **1981**, 1277.
9. Snyder, C. D. and Rapoport, H., *J. Am. Chem. Soc*., **1972**, 94, 227.
10. a) Bauman, J. G.; Hawley, R. C. and Rapoport, H., *J. Org. Chem*., **1985**, 50, 1569. b) Mc Namara, J. M.; Kishi, Y., *Tetrahedron*, **1984**, 40, 4685. c) Gesson, J. P. and Jacquesy, J. C.; Renoux, B., *Tetrahedron*, **1984**, 40, 4743. d) Kraus, G. A. and Woo, S. H., *J. Org. Chem*., **1986**, 51, 114.
11. Brich, A. J., Brutter, D. N. and Siddall, J. B., *J. Chem. Soc*., **1964**, 2932.
12. Hugo, V. I., Nicholson, J. L.; Snijman, P. W. and Green, I. R., *Synth. Commun*., **1994**, 24, 23.
13. Chorn, T. A., Giles, R. G. F, Green, I. R. and Mitchell, P. R. K., *J. Chem. Soc., Perkin Trans. I*, **1983**, 1249.

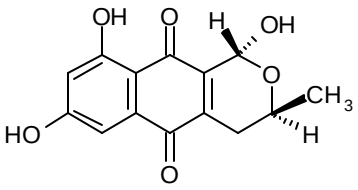
14. Freskos, J. N.; Morrow, G. W., Swenton, J. S., *J. Org. Chem*., **1985**, 50, 805.
15. Garegg, P. J., Samuelsson, B., *Carbohydr. Res*., **1978**, 67, 267.
16. a) Kraus, G. A., Li, J., *Synlett*., **1993**, 252. b) Kraus, G. A., Li, J.; Gorden, M.; Jensen, J. H., *J. Org. Chem*., **1994**, 59, 2219. c) Green, I. R., *Synth. Commun*., **1996**, 26(5), 867. d) Deshpande, P. P.; Price, K. N.; Baker, D. C., *Bioorg. Med. Chem. Lett*., **1995**, 5, 1059. e) Deshpande, P. P.; Price, K. N.; Baker, D. C., *J. Org. Chem.*, **1996**, 61, 455. f) Swenton, J. S.; Freskos, J. N.; Dalidowicz, P. and Kerns, M. L., *J. Org. Chem.*, **1996**, 61, 459.
17. Alexander, T. Shulgin C, Donald, C., *J. Med. Chem.*, **1975**, 18, 1201.
18. Paul, R. and Samuel, C., *J. Org. Chem.*, **1973**, 38, 3189.
19. Mitchell, D. and Keinig, T. M., *Synth. Commun.*, **1995**, 25, 1231.
20. MisLow, K.; Brien, R. E. O. and Schaefer, H., *J. Am. Chem. Soc*., **1962**, 84, 1940.
21. Torssell, K. and Sharma, S. C., *Acta Chemica Scandinavica*, **1978**, B, 32, 347.
22. Parsons, D. G., *J. Chem. Soc. Perkin I*, **1975**, 245.
23. Wallace, T. W., Carter, S. D., *Synthesis*, **1983**, 1001.
24. Bhatt, M. V. and Perumal, P. T., *Tetrahedron Lett*., **1981**, 22, 2605.
25. Collie, J. N., *J. Chem. Soc*., **1891**, 607.
26. a) BuLock, J. D. and Smith, H. G., *J. Chem. Soc*., **1960**, 502. b) Sib, S., *Tetrahedron*, **1975**, 31, 2229. c) Meyers, A. I.; Durandedatta, J. L. and Munovu, R., *J Org. Chem*., **1975**, 40, 2025.
27. a) Nedjav, B., Hamdi, M., Perie, J. and Heramt, V., *J. Heterocyclic Chem*., **1978**, 15, 1153. b) Scott, A. I., Guilfold, H. and Skingle, D., *Tetrahedron*, **1971**, 27, 3039.
28. Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Staunton, J. and Wilkinson, M. R.; *J. Chem. Soc. Perkin Trans. I*, **1984**, 1043.
29. Lackuer, H., Carsten, T., *Liebigs. Ann*., **1996**, 1385.
30. Brittelli, D. R., *J. Org. Chem.*, **1981**, 46, 2514.
31. Kenneth, L. R. and Perkins, E. G., *Org. Synth.* Coll. Vol. 4, **1963**, 444.
32. Box, V. and Yiannikouros, G., *Heterocycles*, **1990**, 31, 1261.

1.2.1 INTRODUCTION:

Screening of microbial extracts against human rhinovirus 3C-protease, using a small peptide containing glutamine and glycine Q-G scissile bond as a substrate, was initiated to identify a lead structure for development of a chemotherapeutic agent for eventual control/cure of the common cold. During the screening of fungal extracts Singh *et al*[1] isolated thysanone, an effective inhibitor (IC_{50} 13 µg/ ml) of HRV 3C- protease from *Thysanophora penicilloides* and reported the isolation, structure determination and HRV 3C-protease activity of thysanone, one of the first inhibitors of this type.

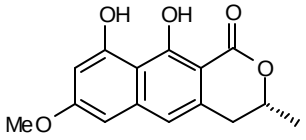


Thysanone (107) R = H
109 R = CH_3

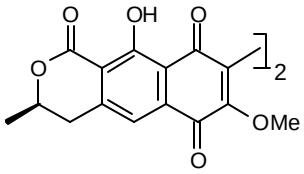


108

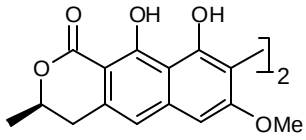
Human rhinovirus (HRV) is a picornavirus and is responsible for causing common cold in humans[2]. Many members of the picornavirus family of viruses are human pathogens, eg. Enteroviruses (polioviruses, coxsackieviruses, echoviruses and hepatitis A viruses), aphthoviruses (foot and mouth disease virus), and cardioviruses (mengo virus and encephalomyocarditis virus). In common with all picornaviruses, the positive strand RNA genome of HRVs is translated directly into a large viral polyprotein (200 KD) precursor, which undergoes a series of controlled proteolytic cleavages to generate functional viral gene products[3]. The replication of many animal and plant viruses is entirely dependent on proteolytic processing. Since processing of the polyprotein is dependent upon two virally encoded proteases ("3C- protease" and "2A-protease") these enzymes represent an attractive target for development of antiviral chemotherapeutic agents. Proteolytic processing of the polyprotein is extremely efficient and does not involve any cellular components. In fact, under normal circumstances; the intact polyprotein does not accumulate in infected cells. The polyprotein is mostly cleaved between glutamine and glycine (Q-G) and tyrosine and glycine (Y-G). The former cleavage is carried out by enzyme 3C-protease and the latter cleavage by 2A- protease. Both of these proteases are thought to be cysteine proteases[4] but with significant differences to other cysteine protease which is required for the virus maturation.



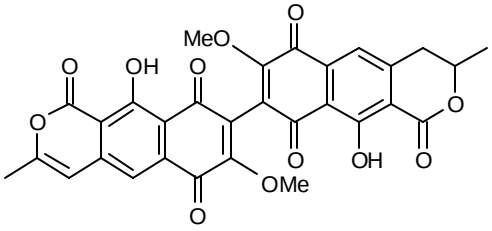
Semivioxanthin



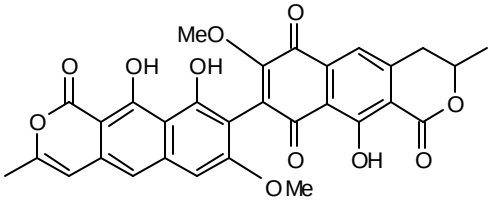
Xanthomegnin



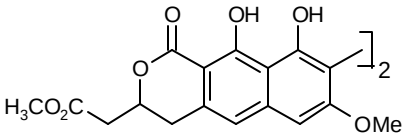
Vioxanthin



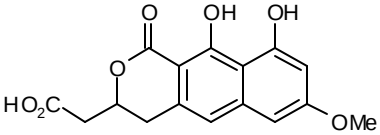
3,4-Dehydroxanthomegnin



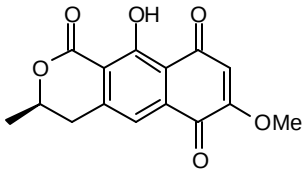
Viomellein



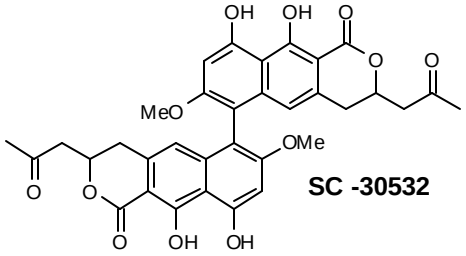
SC-28762



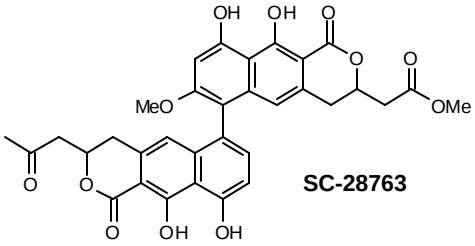
Semiviriditoxic acid



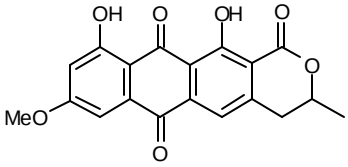
Semixanthomegnin



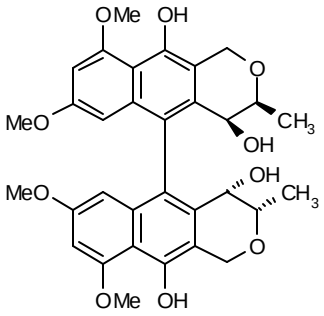
SC -30532



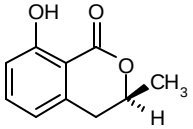
SC-28763



Dermolactone



Bloxanthracene (-)-ES-242-4

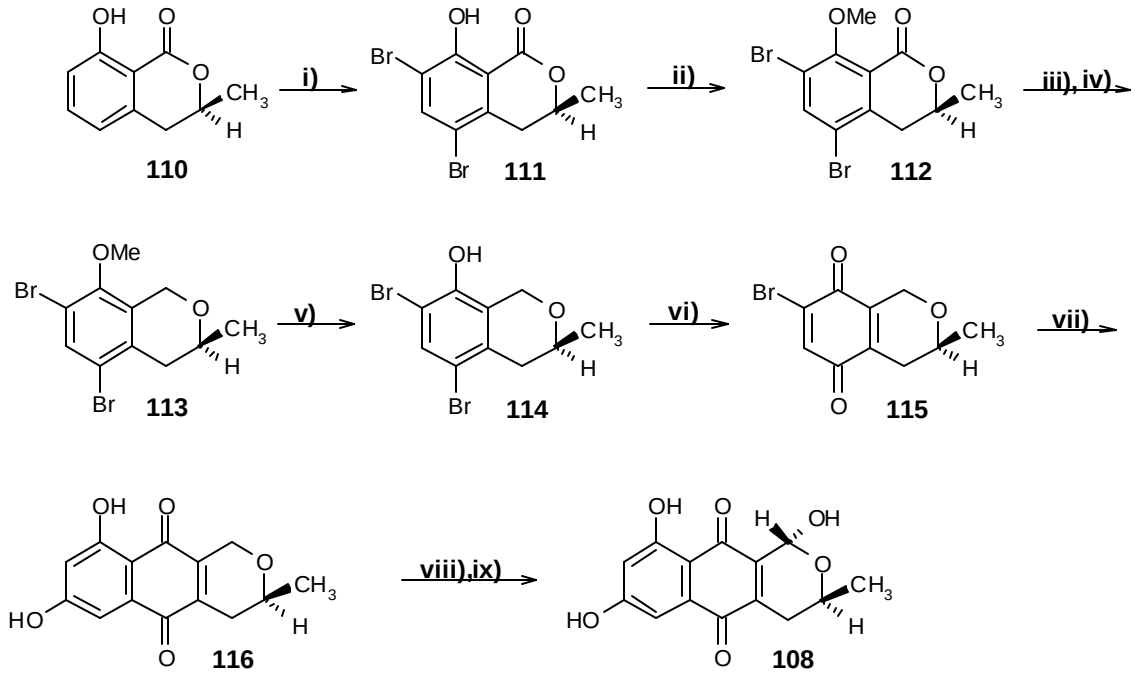


(S)-Mellein

Some other natural products having similar basic skeleton as in thysanone (**107**) are semivioxanthin[5], semixanthomegnin[6], vioxanthin[6], SC-28762[7], SC-28763[7], SC-30532[8] and semiviriditoxic acid[9]. These natural products inhibit the growth of gram-positive and gram-negative bacteria. Dermolactone[10] is another natural product having tetracyclic structure similar to thysanone skeleton. Thysanone (**107**) is a yellow crystalline benzoisochromanquinone which was isolated from solid-state fermentations of the fungus *Thysanophora penicilloides* by Singh *et al*[1] during the screening of microbial extracts for lead compounds aimed at the eventual control or cure of the common cold. The structure **107** for thysanone was proposed by Singh *et al*. from spectroscopic data and the relative stereochemistry between C-1 and C-3 stereogenic centers (but not their absolute configuration) was determined from a single crystal X-ray analysis of the methyl acetal **109**. The acetal **109** was prepared from natural thysanone by treatment with methanol in the presence of conc. Sulphuric acid. The structure and absolute stereochemistry of thysanone, was established by the total synthesis of its antipode **108** by Gill and Donner[11]. The synthesis of (1*R*, 3*S*)-thysanone **108** from (*S*)-propylene oxide[12], established the stereochemistry of the natural product **107** as (1*S*, 3*R*) as shown in the formula. For the synthesis of (1*R*, 3*S*)-thysanone **108**[11], (*S*)-mellein served as the starting material as shown in the scheme-1.

Thus, (*S*)-mellein (**110**) was first brominated with two equivalents of N-bromosuccinimide in dark and the resulting dibromophenol **111** was methylated by using dimethyl sulfate and potassium carbonate in acetone at reflux to afford the methylated benzoisocoumarin **112** which was reduced to the benzopyran **113**. Demethylation and subsequent oxidation of the resulting bromophenol **114** with ceric ammonium nitrate afforded the unique chiral bromopyranobenzoquinone **115**. Diels-Alder cycloaddition of the quinone **115** and 1-methoxy-1, 3-bis (trimethylsilyloxy)-1,3-butadiene in toluene at reflux gave the novel naphthoquinone **116**. Benzylic bromination of the naphthoquinone **116** by using molecular bromine followed by *in situ* treatment of the intermediate bromide with aqueous THF gave (1*R*, 3*S*) thysanone **108** $[\alpha]_D$ -29.7^o (c, 0.002, MeOH) in 35% yield over 7 steps from (*S*)-mellein (**110**). Comparison of the chiroptical data obtained for the synthetic material with the data published for the natural product, which shows $[\alpha]_D$ $+29^o$ (c, 1.65 in MeOH), establishes that the two substances are enantiomers. Thus the absolute configuration of natural thysanone (**107**) must be (1*S*, 3*R*).

Scheme-1

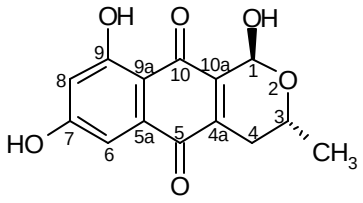


Reagents and conditions:

i) NBS (2 equiv), DMF, r.t., dark, 16 h, 91%. Ii) Me_2SO_4, K_2CO_3, acetone, reflux, 1 h, 98%. Iii) DIBAL-H, toluene, -78 ^oC. iv) $NaBH_4$, TFA, THF, 30 ^oC, 1h, 90% v) $(PhCH_2Se)_2$, $NaBH_4$,,DMF, reflux, 1h, 86% vi) CAN, MeCN, H_2O, r.t., 0.5 h, 82%. Vii) 1-Methoxy-1,3-bis (trimethylsilyloxy)-1,3-butadiene, toluene, reflux, 3h, 73%. Viii) Br_2, CCl_4, hn, 0.5 h. ix) THF, H_2O, r.t., 1h, 85%.

1.2.2 PRESENT WORK

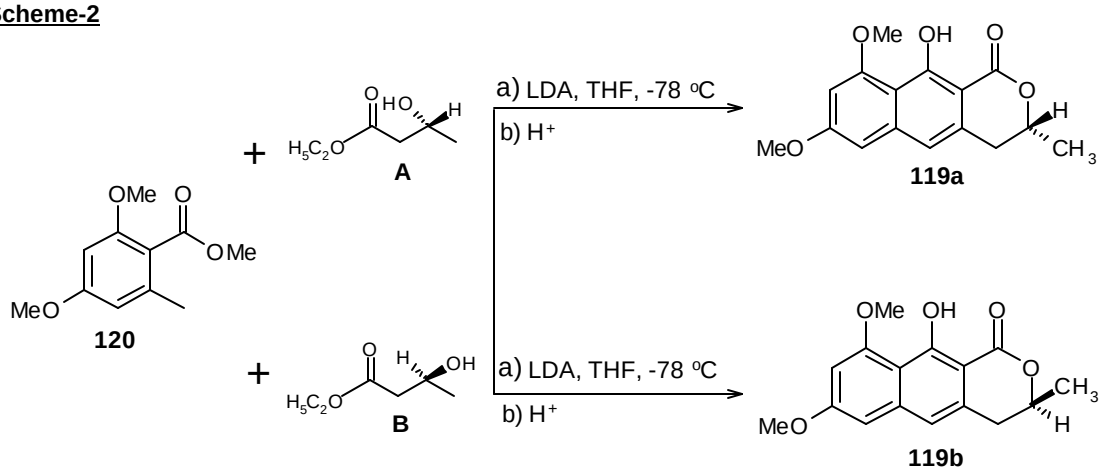
It is evident from the above discussion that the only known synthesis of thysanone involved more than a dozen individual steps with 35% overall yield. There was no synthesis of thysanone reported when the present work was undertaken in early 1999. It was felt that simple and efficient synthesis of thysanone could be achieved utilizing the expertise developed in our group in the field of various quinones and with this objective, synthesis of thysanone was undertaken and the results are described below.



Thysanone (**107**)

The methodology[5c] developed by our group for the stereospecific synthesis of semivioxanthin methyl ether using the required optically active isomer of ethyl 3-hydroxybutyrate could be extended for the stereospecific total synthesis of thysanone (**107**) and its antipode (**108**). The condensation of anion of methyl orsellinate, generated by LDA at -78 ^{o}C, with the optically active (*R* or *S*) ethyl 3-hydroxybutyrate followed by acidic work up would afford stereospecifically the (*R*) or (*S*) semivioxanthin methyl ether.

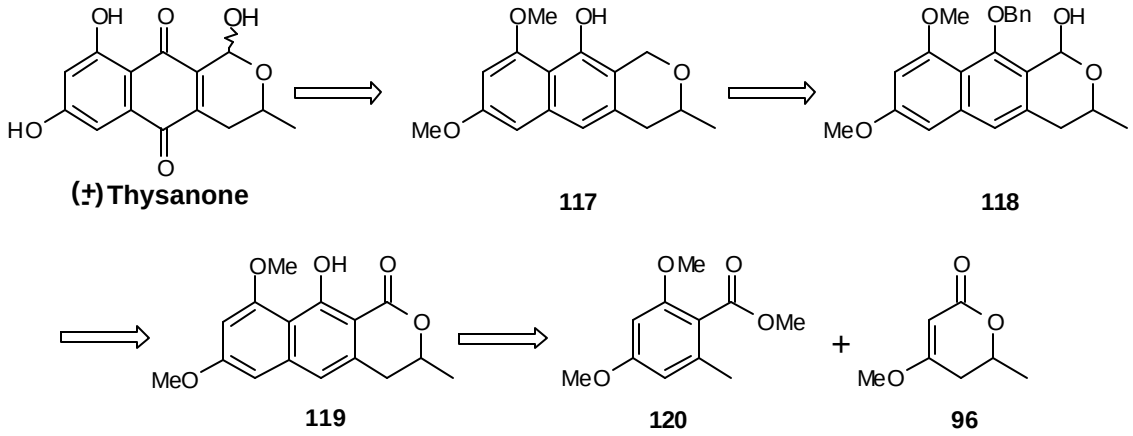
Scheme-2



(*R*)-Ethyl 3-hydroxybutyrate (**A**) is an important chiral building block used in the preparation of **119a** and many natural products including macrolides, β-lactam antibiotics and pheromones. Mori et al[5d]. reported its preparation from polyhydroxybutyrate. Alternatively, it was also prepared by

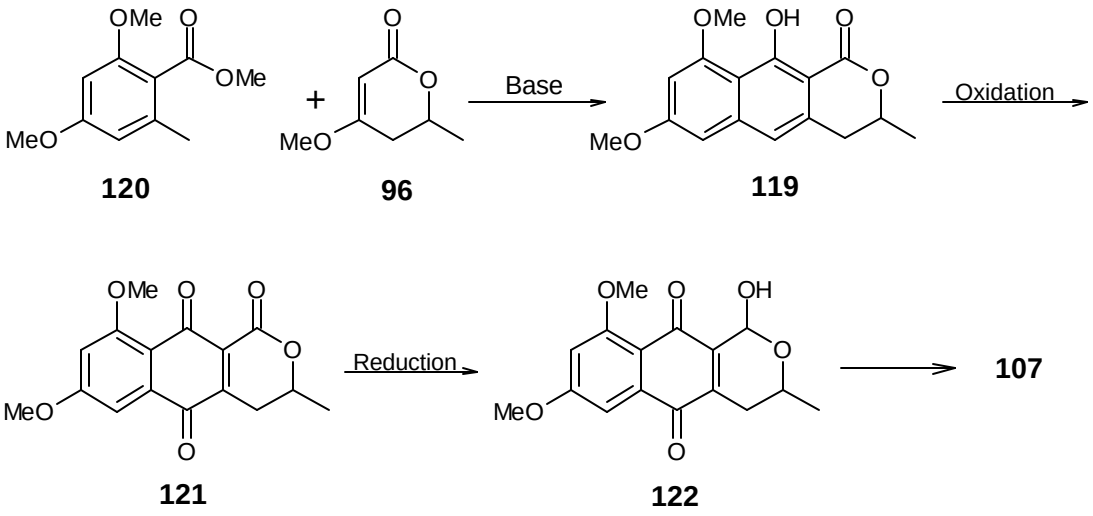
microbial reduction of ethyl acetoacetate with *Geotrichum candidum*[5e]. The condensation of *R*-(-) ethyl 3-hydroxybutyrate (**A**) with methyl orsellinate would lead to *R* (-) semivioxanthin methyl ether **119a**, which would serve as a starting material for the natural thysanone (**107**). Subsequently, (*S*)-(-) ethyl-3-hydroxybutyrate[5f] (**B**) could be used for the synthesis of (*S*)-(-) semivioxanthin methyl ether (**119b**), which would lead to the formation of antipode **108**. Hence as per the above plan employing desired optically active starting material stereoinduction is possible. Initially, it was decided to attempt total synthesis of racemic thysanone using the methodology developed by us[5b] as shown in the scheme-2. Retrosynthetic studies suggested that the basic tricyclic carbon frame could be prepared by lithiation of orsellinate derivative followed by treatment with dihydropyrone. The synthesis of thysanone (**107**) was based on the condensation approach applied for the synthesis of hongconin (section-2, scheme-25).

Scheme-2



As per the retrosynthetic plan (scheme-2) orsellinate derivative **120** and the known dihydropyrone **96** could be the logical starting points. The latter has been synthesized and utilized in the total synthesis of hongconin (section-2, scheme-24). Thus one can envisage formation of two C-C bonds in a single step between methyl orsellinate derivative **120** and dihydropyrone **96** resulting in semivioxanthin methyl ether **119**. After having the required tricyclic carbon framework, there would be two important functional group manipulations namely (a) oxidation of phenol to quinone (b) reduction of lactone to lactol for the synthesis of thysanone as shown in scheme-3.

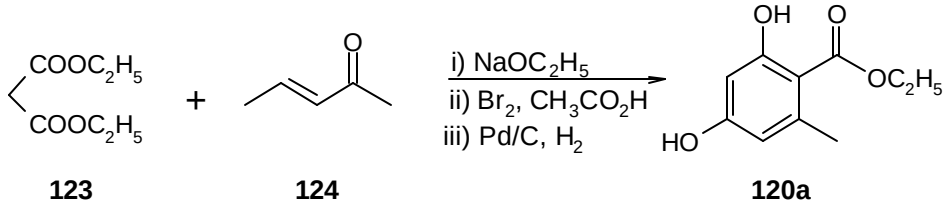
Scheme-3



There are number of methods reported in the literature for synthesis of methyl orsellinate derivative **120** or the corresponding ethyl ester **120a** required for the coupling reaction.

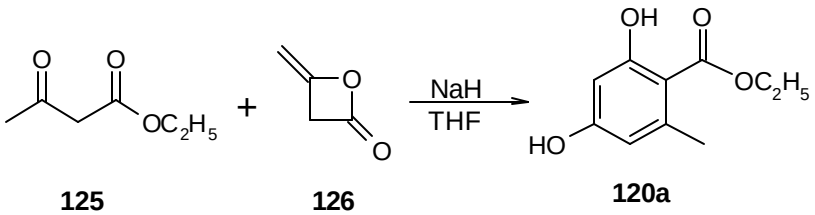
Barlett *et al.*[13] found that condensation of diethyl malonate **123** with 3-penten-2-one **124** under base catalyzed reaction condition afforded an intermediate dihydroresorcylic ester which was then brominated with bromine to furnish dibromo compound followed by hydrogenolysis in the presence of 10% palladium-carbon to give ethyl orsellinate **120a**.

Scheme-4



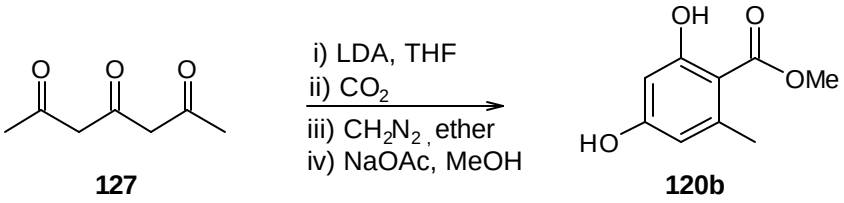
Kato and Hozumi[14] synthesized ethyl orsellinate **120a** by reaction of ethyl acetoacetate (**125**) with the diketene **126**.

Scheme-5



Howarth *et al*.[15] found that treatment of diacetyl acetone **127** with 4 equivalents of lithium diisopropylamide in THF under nitrogen and carbonylation of the soluble, yellow trilithium salt with carbon dioxide gave tetraacetic acid as an oil in 47% yield. This acid was esterified using diazomethane in ether, which on treatment with 1M methanolic sodium acetate gave methyl orsellinate in 50% yield.

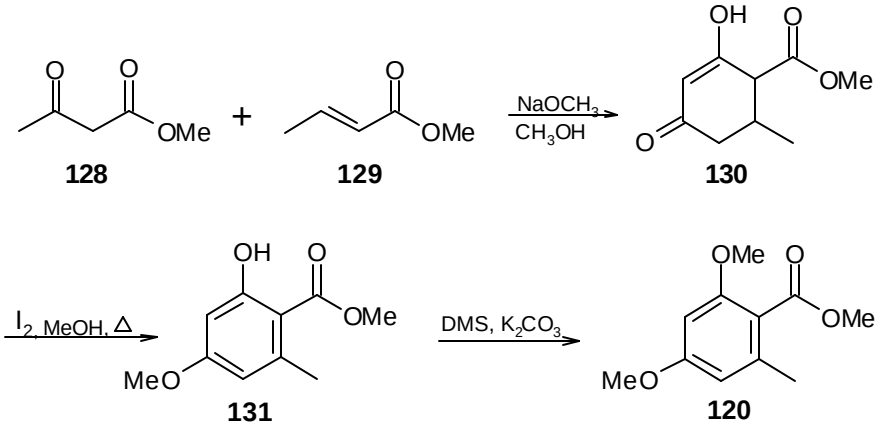
Scheme-6



127 **120b**

Methyl orsellinate was also prepared by Sargent *et al*.[16] using methyl acetoacetate **128** and methyl crotonate **129**.

Scheme-7

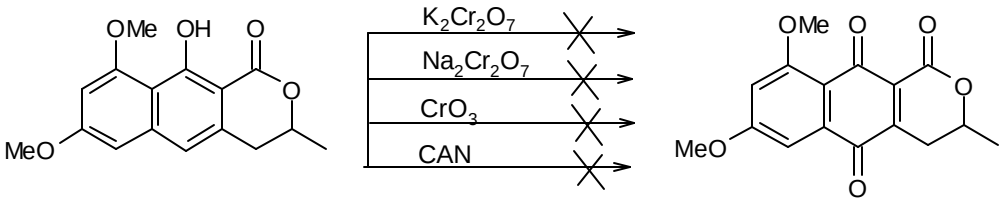


128 **129** **130** **131** **120**

In the present work modified sequence of the method reported by Sargent *et al*. was used to prepare methyl orsellinate as shown in scheme-7. Thus the methyl dihydrorsellinate **130** was obtained by reaction of methyl acetoacetate **128** and methyl crotonate **129** in presence of sodium methoxide in methanol. It was expected that dihydroorsellinate **130** on treatment with excess of iodine in refluxing methanol, would afford methyl 2,4-dimethoxy-6-methyl benzoate (**120**). But even after continuing the reaction for more than 24 hr, reaction stopped at ortho-hydroxy ester **131**[17]. The spectral and physical properties of **131** were in full agreement with those reported in the literature. It was then converted into the required ester **120**[18] by methylation with dimethyl sulfate.

The condensation of orsellinate derivative **120** with dihydropyrone **96** proved to be straightforward. Lithiation[19] of **120** at -78°C with LDA followed by treatment with dihydropyrone led to semivioxanthin methyl ether **119**. The spectral properties of compound **119** were consistent with the assigned structure. The IR spectrum revealed absorption band at 1665 cm^{-1} for lactone carbonyl function. The ^{1}H-NMR spectrum showed a methyl doublet at δ 1.53, benzylic $-CH_2$ doublet at δ 2.97 and a multiplet at δ 4.61-4.82 (-COO-C<u>H</u>-CH_3).

Scheme-8

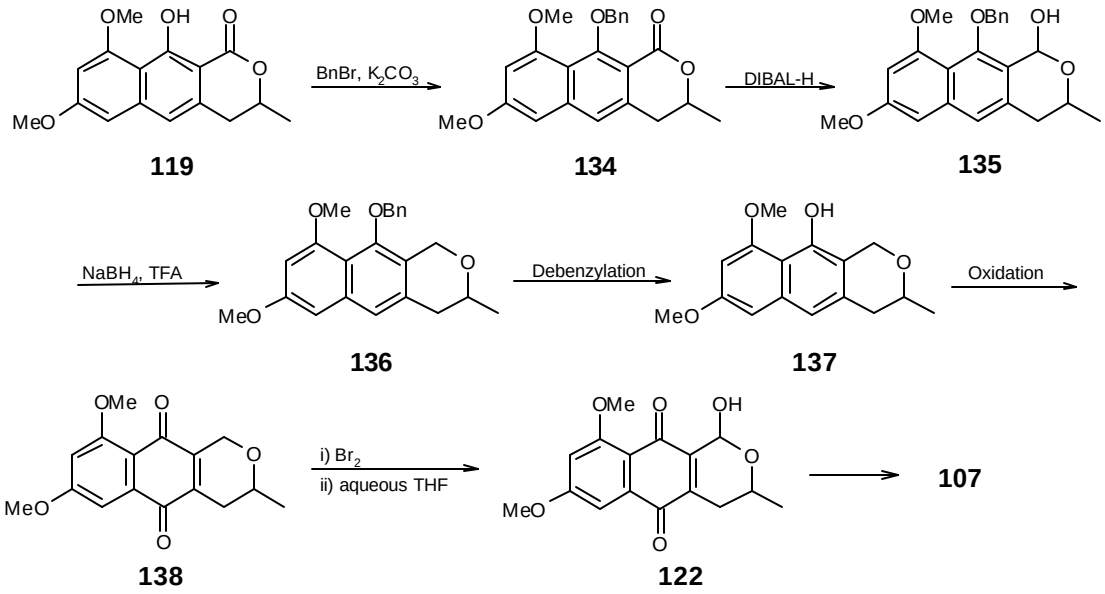


119 **133**

The two aromatic protons appeared as a pair of *meta*-coupled doublets at δ 6.47 and 6.58 (J= 2.0 Hz) and third C-5 aromatic proton appeared as a singlet at δ 6.86. The chelated hydroxyl proton was observed at δ 13.18. The mass spectrum of **119** showed a molecular ion peak at m/z. 288. Having thus obtained the required skeleton of thysanone, the next reaction i.e. formation of quinone was attempted with several well-known reagents employed in the literature. Among the known methods employed were $K_2Cr_2O_7$[20] and $Na_2Cr_2O_7$ in aqueous acetic acid, CrO_3[21] in acetic acid and cerium ammonium nitrate[22] in acetonitrile, which did not give the desired quinone, instead a mixture of polar compounds was obtained which could not be purified and characterized (scheme-8). Probably the lactone moiety could not survive the above reaction conditions.

Having failed to obtain the required quinone **133**, we thought of change in reaction sequence, as shown in the scheme-9. It was decided to protect the hydroxy functionality in **119** as benzyl ether **134** and complete reduction of lactone to benzopyran **136** to form a stable cyclic ether. The cyclic ether **136** would give hydroxynaphthopyran **137** after debenzylation. Hydroxynaphthopyran **137** could then be converted to the desired quinone **138**. Benzylic bromination of quinone **138**, followed by treatment of intermediate bromide with aqueous THF would give the target molecule thysanone.

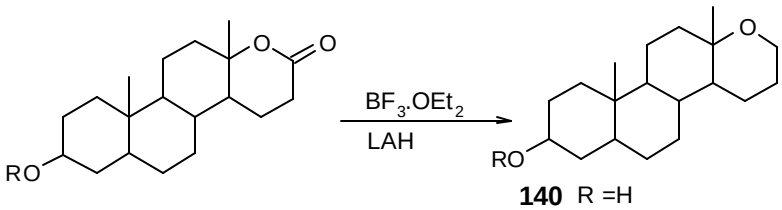
Scheme-9



Accordingly, semivioxanthin methyl ether **119** was treated with benzyl bromide and anhydrous potassium carbonate in refluxing acetone, which gave almost quantitative yields of the benzyl ether **134**. The ^{1}H NMR spectrum indicated presence of two benzylic doublets at δ 5.04 and 5.26 and absence of chelated hydroxyl proton. Its molecular ion peak at m/z 378 further supported the formation of benzyl ether.

Pettit[23] has developed a novel one step procedure for converting lactone to its corresponding ether derivative as shown in scheme-10. Attempted reduction of **134** under Pettit's conditions

Scheme-10



139

140 R =H

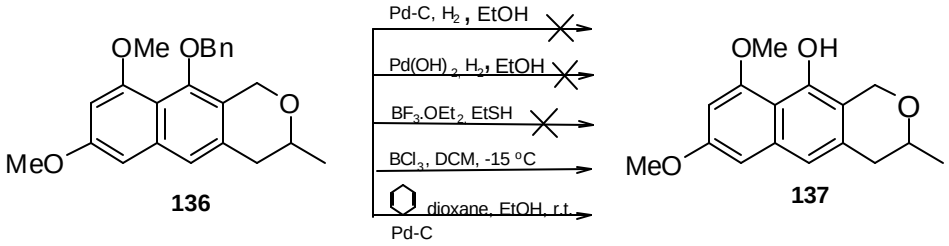
141 R = $OCOCH_3$

employing boron trifluoride etherate and LAH as the reducing agent failed to provide the desired naphthopyran **136**. The failure to reduce the lactone made us to employ a two-step reaction sequence a) reduction of benzyl ether **134** to lactol **135** and b) reduction of lactol **135** to naphthopyran **136**. The DIBAL-H reduction of the above benzyl ether **134** at -78°C gave the required lactol **135**, which

showed the presence of absorption band at 3580 cm^{-1} and absence of peaks in the carbonyl functionality region in IR spectrum. The ^1H NMR spectrum of lactol **135** showed it to be a diastereomeric mixture. Methyl doublet appeared at δ 1.39 (J= 7.0 Hz) and a multiplet was observed at δ 2.69-2.95 for [-C<u>H</u>$_2$-CH-CH_3]. Two benzylic protons appeared as a set of two doublets at δ 4.98 (J= 8.0 Hz) and at δ 5.20 (J= 8.0 Hz) each integrating for a single proton. Two aromatic protons appeared as *meta* coupled doublets at δ 6.48 (J= 2.0 Hz) and 6.67 (J= 2.0 Hz) while remaining six aromatic protons appeared as a multiplet between δ 7.15-7.68 supporting the structure assigned to lactol **135**.

The above lactol **135** was then reduced to form stable naphthopyran **136**, by stirring with sodium borohydride in anhydrous THF with catalytic amount of trifluoroacetic acid. The ^1H-NMR spectrum of naphthopyran **136** revealed, apart from benzylic peaks and methyl doublet, a singlet at δ 4.91 integrating for two protons assigned to the newly formed pyran -CH_2 [-C<u>H</u>$_2$-O-CH-CH_3] group. Rest of the peaks were present at appropriate positions. The presence of molecular ion peak at m/z 364 further confirmed the structure. With the desired naphthopyran **136** in hand the next reaction i.e. C-10 debenzylation was attempted with the well known reagents employed in the literature. Among the known methods, hydrogenolysis[24] using Pd-C, Pd $(OH)_2$, $BF_3.OEt_2$[25] were unsuccessful to give the required debenzylated product. Deprotection of benzyl ether with 1.0 M solution of BCl_3[26] in dichloromethane at -15 ^oC furnished the required hydroxynaphthopyran **137**; unfortunately the yield of the product was very low. Surprisingly mild hydrogenolysis at room temperature using Pd-C and 1,4 cyclohexadiene[27] proved to be the best method for the preparation of hydroxynaphthopyran **137**.

Scheme-11

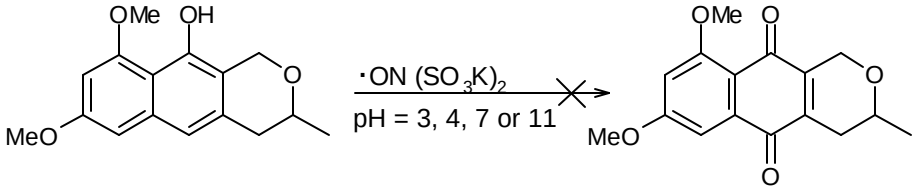


The formation of hydroxynaphthopyran **137** was confirmed by spectral analysis. The IR spectrum showed the presence of phenolic hydroxyl functionality at 3412 $cm.^{-1}$ The ^1H-NMR spectrum was in full agreement with the structure of **137**. The ^1H-NMR showed disappearance of

benzylic singlet at δ 4.91 and aromatic region showed only three protons, two *meta* coupled doublets at δ 6.37 (J= 2.0 Hz) and δ 6.61 (J= 2.0 Hz) and third C-5 aromatic proton appeared at δ 6.94. as a singlet. Remainder of the spectrum consisted of a methyl doublet at δ 1.38, benzylic -CH_2 at δ 2.78 and a multiplet at δ 3.67 -3.85 [-CH_2-C<u>H</u>-CH_3] while the other benzylic protons appeared as a set of two doublets at δ 4.77 (J= 16 Hz) and at δ 5.13 (J= 16 Hz). The molecular ion peak at m/z 274 further confirmed its structure.

The next reaction was conversion of hydroxynaphthopyran **137** to quinone **138**. For this operation the choice of very selective oxidizing agent was necessary. Potassium nitrosodisulfonate or Fremy's radical[28] selectively oxidizes phenols to the corresponding quinones. It was decided to employ Fremy's radical for the conversion of **137** to the desired quinone **138**. Fremy's radical was prepared as per the literature procedure[28]. To verify the utility of Fremy's radical a model study on phenol was carried out which resulted in benzoquinone. When hydroxynaphthopyran **137** in ethyl acetate[29] was treated with aqueous solution of Fremy's salt, desired quinone **138** could not be obtained. The same reaction was tried at different pH[30] values (scheme-12) but failed to convert **137** to **138**.

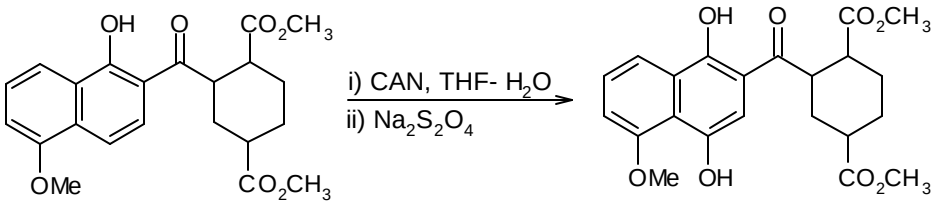
Scheme-12



137 **138**

The failure to obtain the quinone led to explore other literature methods to achieve the desired reaction. Some of the literature methods are as follows. Sih *et al*[22]. showed that oxidation of naphthol **142** with an excess of cerium ammonium nitratre in THF-H_2O (75:25) at room temperature furnished the corresponding quinone which was reduced to the dihydroxynaphthalene derivative **143** as shown in scheme-13.

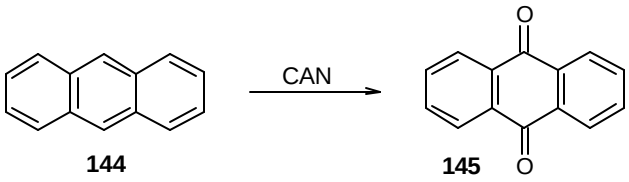
Scheme-13



142 **143**

Cerium ammonium nitrate oxidations of polynuclear aromatic hydrocarbons can be effected to quinones[31] as shown in scheme-14.

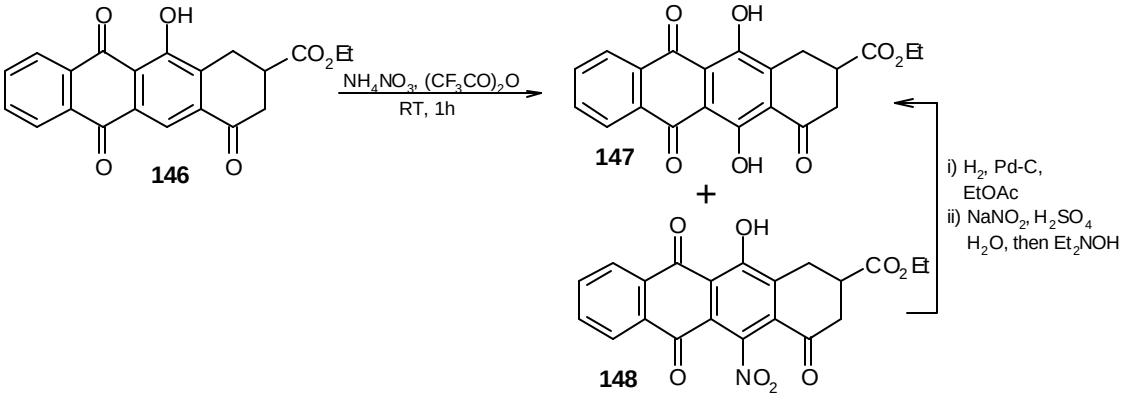
Scheme-14



144 **145**

Boeckman *et al*[32]. have shown that the metal nitrates in trifluoroacetic anhydride oxidize many aromatic compounds in high yields at room temperature. This system oxidizes phenols to quinonoid products (scheme-15).

Scheme-15

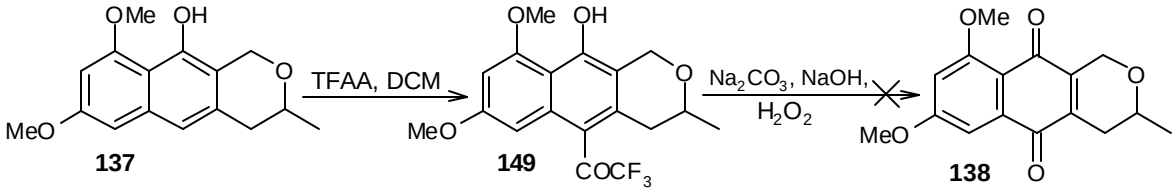


146 **147** **148**

Pavlidis[33] converted phenol to its *para* trifluoroacetyl derivative and treated it with hydrogen peroxide in aqueous base to afford the desired quinone in quantitative yield, probably *via* Bayer-Villiger type oxidation with subsequent hydrolysis to the corresponding diphenol and finally to

quinone. Accordingly hydroxynaphthopyran **137** was treated with trifluoroacetic anhydride in dichloromethane to get the *para* trifluoroacetyl derivative **149**. The formation of trifluoroacetyl derivative was confirmed by ^{1}H NMR spectrum aromatic region of which showed only two *meta*-coupled doublets while the third C-5 aromatic proton was absent. The remaining protons resonated at their characteristic chemical shifts.

Scheme-16



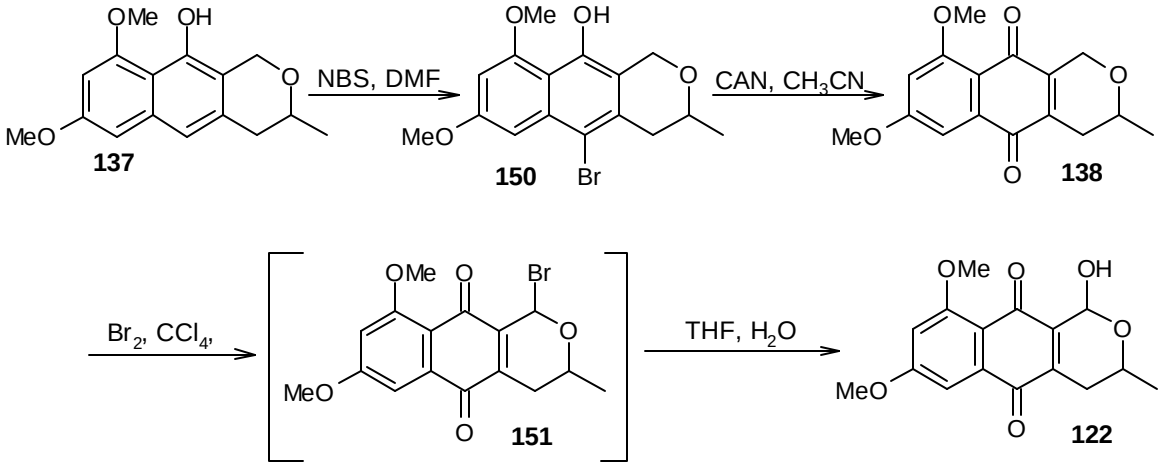
The mass spectrum exhibited the molecular ion peak at m/z 371 (M+1), which further supported the formation of trifluoroacetyl derivative **149**. The trifluoroacetyl derivative **149** was further treated with H_2O_2 and aqueous sodium hydroxide and sodium carbonate, but the desired quinone could not be obtained.

Bhatt *et al*. reported[34] that the oxidation of halophenols and halonaphthols by ceric ammonium sulphate yielded the corresponding quinones. Accordingly the hydroxynaphthopyran **137** was treated with NBS in DMF[35] at room temperature to effect selective nuclear bromination at *para* position, which afforded monobrominated product **150** (scheme-17). The formation of *para* bromo product was confirmed by ^{1}H-NMR and Mass spectral analysis. The ^{1}H-NMR showed a pair of *meta* coupled doublets at δ 6.47 (J= 2.0 Hz) and at δ 7.19 (J= 2.0 Hz) and absence of C-5 aromatic proton which confirmed that the bromination had occurred at *para* (C-5) position with respect to -OH group. Molecular ion peaks at m/z 352 and 354 and absence of peaks corresponding to dibromo compound in the mass spectrum confirmed the structure of monobromo compound **150**. When the bromonaphthol **150** was treated with ceric ammonium nitrate, the corresponding quinone **138** was obtained as a yellow solid. The spectral data of the quinone **138** was in full agreement with the assigned structure. IR spectrum showed strong absorption bands at 1640 and 1660 cm^{-1} for the quinonoid carbonyls. ^{1}H NMR spectrum exhibited a methyl doublet at δ 1.37 (J = 6.0 Hz), a multiplet between δ 2.15-2.37 and two triplets at δ 2.64 and δ 2.73 (J = 2.0 Hz) for total two protons, which were assigned to C4 methylene group. Another multiplet at δ 3.55-3.77 was assigned to

methine proton at C3 carbon. Methoxyl singlets appeared at δ 3.95 and 3.96. Methylene protons at C1 were observed at δ 4.43 and 4.53 as two triplets (J = 2.0 Hz) and integrated for total one proton, the other proton showed a set of two doublets at δ 4.79 and 4.89 (J= 2.0 Hz). Aromatic *meta* coupled doublets appeared at δ 6.71 and 7.26 (J = 2. 0 Hz) integrating for one proton each. The mass spectrum revealed a molecular ion peak at m/z 288 as a base peak supporting the structure.

Benzylic bromination of quinone **138** was carried out using 1 equivalent bromine followed by *in situ* treatment of the intermediate bromide **151** with aqueous terahydrofuran to give methoxy thysanone **122**.

Scheme-17



The methoxy thysanone **122** was fully characterized by spectroscopic analysis. IR spectrum showed strong absorption bands at 1595 and 1656 cm^{-1} for the quinonoid carbonyls. The ^1H NMR spectrum showed it to be a mixture of diastereomers. A set of two doublets appeared at δ 1.39 and 1.47 (J = 6.0 Hz) for C3 methyl group. C4 methylene protons appeared as a multiplet between δ 2.14-2.34 integrating for one proton while another proton appeared as a set of two doublets at δ 2.65 and 2.75 (J = 2.0 Hz). Methoxyl singlets appeared at δ 3.96 and 3.97. Methine proton at C3 carbon appeared as a multiplet between δ 4.20-4.40 while the characteristic methine proton at C1 carbon bearing hydroxyl group appeared as singlets at δ 6.03 and 6.07 because of diastereomers. Aromatic *meta* coupled doublets were observed at δ 6.73 and 6.75 (J = 2.0 Hz each, total 1H) and at δ 7.25 and 7.30 (J = 2.0 Hz, total 1H). The mass spectrum of **122** did not show molecular ion peak. First intense

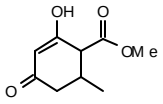
peak was found at 286 [M^+ - 18 (H_2O)] with 58 % intensity, which further supported the structure of dimethoxy thysanone **122**.

1.2.3 CONCLUSION:

In summary, the important features of the synthesis of methoxy thysanone **122** discussed in the present work are as follows: 1. The synthesis starts from easily accessible starting materials, it represents simple and efficient racemic synthesis of methoxy thysanone. 2. All the reactions are high yielding. 3. This is the first report of the total synthesis of methoxy thysanone **122**. 4. The method described here is applicable in principle to the synthesis of analogues of the natural products with the potential for modified biological profiles. 5. The present method describes short (seven steps) and efficient synthesis of methoxy thysanone **122** 6. The present methodology can be extended for the stereospecific total synthesis of thysanone **107** and its antipode **108** employing optically active (*R* or *S*) ethyl 3-hydroxybutyrate **A** or **B**.

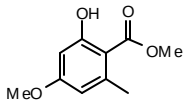
1.2.4 EXPERIMENTAL:

Methyl dihydroorsellinate (**130**):



To a well-stirred solution of sodium methoxide, prepared from sodium metal (2.0 g, 86 mmol) in dry methanol (25 ml), were added methyl acetoacetate (10.00 g, 86 mmol) followed by methyl crotonate (8.60g, 86 mmol). The mixture was stirred at reflux temperature overnight. The methanol was distilled off, the residual syrup was cooled to 5°C and acidified carefully with 5% H_2SO_4. The sodium sulfate separated was filtered and the filtrate was diluted with water and extracted with chloroform (3 × 50 ml), washed with brine (30 ml) and dried over sodium sulfate. Removal of the solvent under reduced pressure gave solid which was crystallized from ethyl acetate to give methyl dihydroorsellinate as a white solid (12.55 g, 79.68%); m.p. 122 °C (Lit[16] m.p. 122-124°C).

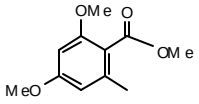
Methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**131**):



Methyl dihydroorsellinate (20.0 g, 109 mmol) was dissolved in dry methanol (250 ml), to this iodine (41.31 g, 327 mmol) was added at once and heated at reflux with stirring for 24 hr. The methanol was removed by distillation, and the residue was dissolved in ethyl acetate. The ethyl acetate layer was washed with aqueous sodium thiosulfate solution (2 × 50 ml) followed by brine, dried over sodium sulfate and concentrated to give a gummy solid which was purified by column chromatography using 5% acetone in pet ether as an eluent to furnish pure **131** as a white solid (19.27 g, 90%); m.p. 67 °C (lit.[17] m. p. 67 °C).

^{1}H-NMR ($CDCl_3$): δ 2.50 (s, 3H, -CH_3), 3.75 (s, 3H, -CO_2CH_3), 3.90 (s, 3H, -OCH_3), 6.23 (d, J = 2.0 Hz, 1H), 6.30 (d, J = 2.0 Hz, 1H), 11.78 (s, 1H, chelated -OH). **^{13}C-NMR** ($CDCl_3$): δ 24.39, 51.84, 55.34, 98.82, 105.33, 111.21, 143.22, 164.07, 165.72 and 172.34.

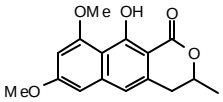
Methyl 2,4-dimethoxy-6-methylbenzoate (120):



A mixture of **131** (20.0 g, 102 mmol), dimethyl sulfate (14.14 g, 10.92 ml, 112 mmol), and anhydrous potassium carbonate (17.08 g, 123 mmol) in dry acetone (300 ml) was refluxed for 8 hr. The acetone was distilled off and cold water (150 ml) was added whereby solid separated. It was filtered, washed with cold water, and dried to give ester **120** (21.0 g, 98%); m.p. 43°C (lit.[18] m.p. 43°C).

^{1}H-NMR ($CDCl_3$): δ 2.29 (s, 3H, -CH_3), 3.81 (s, 6H, 2×OCH_3), 3.89 (s, 3H, -CO_2CH_3), 6.32 (s, 2H). **^{13}C-NMR** ($CDCl_3$): δ 19.86 (-CH_3), 51.92 (-CO_2CH_3), 55.26 (-OCH_3), 55.81 (-OCH_3), 96.14, 107.72, 116.43, 138.23, 158.26, 161.42, 168.66 (-C=O). **MS** (m/z): 210 (M^+, 46), 179 (100), 164 (5), 149 (7) and 121 (5).

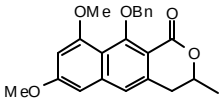
3,4-Dihydro-7,9-dimethoxy-10-hydroxy-3-methyl-1*H*-naphtho-[2,3-c]-pyran-1-one (119):



To the stirred solution of LDA [prepared from 1.6 M solution of n-BuLi in hexane (6.0 ml) and diisopropylamine (1.35 ml) at 0°C under argon atmosphere] in THF (15 ml) at -78°C was injected a solution of methyl 2,4-dimethoxy-6-methyl benzoate (**120**, 1.0 g, 4.7 mmol) in THF (10 ml) and stirred for 15 min. To the resultant orange red solution, was added a solution of 4-methoxy-6-methyl-5, 6-dihydro-2-pyrone (**96**, 0.676 g, 4.7 mmol) in THF (8 ml) and stirred further for 30 min at -78°C. It was then warmed to room temperature by removing dry ice-acetone bath and stirred for 20 min. The reaction mixture was poured slowly into the ice-cold dilute hydrochloric acid (50 ml) and extracted with dichloromethane. The organic extracts were washed with brine, dried over sodium sulfate and concentrated. The residue was chromatographed using 20% acetone in pet ether as an eluent to afford **119** as a crystalline yellow solid (0.945 g, 69%); m.p. 131°C (lit.[5b,c] m.p. 130-132 °C).

I.R. (Nujol): 1665 cm^{-1}. **^{1}H-NMR** ($CDCl_3$): δ 1.53 (d, J= 6.0 Hz, 3H, $-CH_3$), 2.97 (d, J= 6.0 Hz, 2H, $-CH_2$), 3.92 (s, 3H, $-OCH_3$), 3.99 (s, 3H, $-OCH_3$), 4.61-4.82 (m, 1H, $-CH_2-CH-CH_3$), 6.47 (d, J= 2 Hz, 1H), 6.58 (d, J= 2.0 Hz, 1H), 6.86 (s, 1H), 13.18 (s, 1H, chelated -OH). **^{13}C-NMR** ($CDCl_3$): δ 20.50 ($-CH_3$), 34.99 ($-CH_2$), 55.20 ($-OCH_3$), 55.97 ($-OCH_3$), 75.42, 98.21, 98.83, 101.16, 110.98, 115.04, 134.16, 141.40, 160.00, 161.88, 164.00 and 170.95 (-C=O). **MS** (m/z): 288 (M^+, base peak), 244 (18), 226 (18), 181 (3), 145 (3) and 121(4).

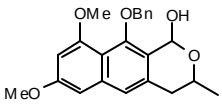
10-Benzyloxy-3,4-dihydro-7,9-dimethoxy-3-methyl-1*H*-naphtho-[2,3-c]-pyran-1-one (134):



A mixture of **119** (0.4 g, 1.3 mmol), potassium carbonate (0.22 g, 1.6 mmol) and benzyl bromide (0.35 g, 1.5 mmol) in acetone (10 ml) was stirred under reflux for 24 hr. The acetone was distilled off and to the residue water (20 ml) was added. The product was extracted with ethyl acetate (2 x 20 ml), washed with water several times followed by brine (10 ml), dried over sodium sulfate and concentrated on rotary evaporator to provide a crude product which was chromatographed on silica gel using 10% acetone in pet ether as an eluent to afford **134** as a white solid (0.472 g, 90%); m.p. 134.4 ^oC.

I.R. ($CHCl_3$): 1713, 1625 cm^{-1}. **^{1}H-NMR** ($CDCl_3$): δ 1.47 (d, J= 7.0 Hz, 3H, $-CH_3$), 2.96 (d, J= 8.0 Hz, 2H, $-CH_2$), 3.83 (s, 3H, $-OCH_3$), 3.92 (s, 3H, $-OCH_3$), 4.40-4.62 (m, 1H, $-COOCHCH_3$), 5.04 (d, J= 10.0 Hz, 1H), 5.26 (d, J= 10.0 Hz, 1H), 6.50 (d, J= 2.0 Hz, 1H), 6.60 (d, J= 2.0 Hz, 1H), 7.23-7.46 (m, 4H), 7.66 (d, J= 8.0 Hz, 2H). **^{13}C-NMR** ($CDCl_3$): δ 20.65, 36.35, 55.35, 55.94, 73.88, 77.39, 98.47, 99.28, 113.87, 116.22, 120.48, 127.62, 128.13, 128.68, 136.62, 137.87, 140.48, 159.19, 159.48, 160.00, 160.66, 162.68. **MS** (m/z): 378 (M^+, 78), 360 (12), 345 (10), 287 (98), 269 (90), 242 (53), 185 (35), 141 (38), 115 (70) and 91 (100).

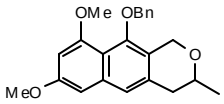
10-Benzyloxy -3,4-dihydro-7,9-dimethoxy-3-methyl-1*H*-naphtho [2,3-c]-pyran-1-ol (135):



Benzyl ether **134** (0.611g, 1.61 mmol) was dissolved in dry toluene (8 ml) under argon atmosphere and cooled to -78°C in a dry ice-acetone bath. DIBAL-H (2.529 M solution in toluene, 0.286 g, 0.8 ml, 2.0 mmol) was injected through syringe within 5 min and stirring was continued at the same temperature for further 3 hr. The reaction mixture was then quenched at the same temperature by adding 0.8 ml methanol and 0.8 ml water and warmed to room temperature. The gelatinous precipitate was filtered through celite. Concentration of the solution under reduced pressure afforded crude lactol which was purified by column chromatography using 20% acetone in pet ether as an eluent to furnish pure lactol **135** (0.446 g, 74%); m.p. 114°C.

I.R. (Nujol): 3580 cm^{-1}. **^{1}H-NMR** ($CDCl_3$): δ 1.39 (d, J= 7.0 Hz, 3H, -CH_3), 2.69-2.95 (m, 2H, -$C\underline{H}_2$-CH-CH_3), 3.87 (s, 3H, -OCH_3), 3.91 (s, 3H, -OCH_3), 4.45-4.65 (m, 1H, -CH_2-$C\underline{H}$-CH_3), 4.98 (d, J= 8.0 Hz, 1H), 5.20 (d, J= 8.0 Hz, 1H), 6.48 (d, J= 2.0 Hz, 1H), 6.67 (d, J= 2.0 Hz, 1H), 7.15-7.68 (m, 6H, aromatic). **MS** (m/z): 380 (M^+, 5), 363 (20), 289 (2), 272 (16), 243 (4), 211 (6), 91 (100).

10-Benzyloxy-3,4-dihydro-7,9-dimethoxy-3-methyl-1*H*-naphtho [2,3-c] pyran OR
10-Benzyloxy-7, 9-dimethoxy-3-methyl-3, 4-dihydro-1*H* benzo[g] isochromene (136):

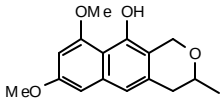


To a mixture of the above lactol **135** (0.150 g, 0.39 mmol) and sodium borohydride (0.014 g, 0.39 mmol) in dry THF under argon atmosphere was added trifluoroacetic acid (0.045 g, 0.030 ml, 0.39 mmol) at 0°C. The mixture was stirred at the same temperature for 30 min and at r.t for 30 min. THF was removed by distillation under reduced pressure, to the residue water (20 ml) was added and product was extracted with EtOAc (3 x 20 ml), washed with brine and concentrated to give crude cyclic ether which was purified by column chromatography using 5% acetone in pet ether to afford **136** (0.125, 88%) as a semisolid.

^{1}H-NMR ($CDCl_3$): δ 1.41 (d, J= 6.0 Hz, 3H, -CH_3), 2.85 (d, J= 6.0 Hz, 2H, -$C\underline{H}_2$-CH-CH_3), 3.73-3.87 (m, 1H, -CH_2-$C\underline{H}$-CH_3), 3.91 (s, 3H, -OCH_3), 3.92 (s, 3H, -OCH_3), 4.83 (d, J= 16.0 Hz, 1H), 4.91 (s, 2H), 5.28 (d, J= 16.0 Hz, 1H), 6.52 (d, J= 2.0 Hz, 1H), 6.70 (d, J= 2.0 Hz, 1H), 7.25-7.57 (m, 6H). **^{13}C-NMR** ($CDCl_3$): δ 21.48 (-CH_3), 35.89 (-CH_2), 55.12 (-OCH_3), 55.73 (-OCH_3), 65.19 (-

CH_2), 70.56 (-<u>C</u>H-CH_3), 76.02 (-CH_2), 98.33, 98.49, 114.63, 122.23, 123.60, 127.75, 128.33, 134.19, 136.70, 137.98, 150.43, 155.90, 157.69. **MS** (m/z): 364 (M^+, 28), 273 (40), 258 (10), 229 (22), 187 (11), 141 (8), 115 (18) and 91 (100).

3,4-Dihydro-7,9-dimethoxy-10-hydroxy-3-methyl-1*H*-naphtho [2,3-c]pyran OR
7,9-Dimethoxy-3-methyl-3,4-dihydro-1*H*-benzo[g] isochromene-10-ol (137):
Debenzylation by BCl_3:



To a solution of naphthopyran **136** (0.050 g, 0.137 mmol) in dry dichloromethane was added BCl_3 (0.040 g, 0.343 mmol) (1.0 M solution in DCM) at -15°C under argon atmosphere. It was further stirred at -15°C for 1 hr and quenched with methanol (1.0 ml). DCM was distilled off and water (10 ml) was added to it, extracted with chloroform, washed with brine, dried over sodium sulfate and concentrated on rotary evaporator to give crude product which was purified by column chromatography using 10% acetone in pet ether as an eluent to afford pure hydroxynaphthopyran **137** as a white solid (0.010 g, 27.02%); m.p. 133.5 ^oC.

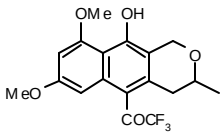
Debenzylation by hydrogenation in presence of cyclohexadiene and palladium on carbon:

To a solution of naphthopyran **136** (0.106 g, 0.291 mmol) in dry ethanol (5.0 ml) and dry dioxane (5.0 ml) was added 1, 4-cyclohexadiene (0.5 ml) and 10% palladium on charcoal (20 mg) and the reaction mixture was stirred for 15 min. The reaction mixture was filtered through celite and the residue was washed with EtOAc. The filtrate along with washings was concentrated to obtain a solid which was purified by column chromatography using 10% acetone in pet-ether as an eluent to afford pure hydroxynaphthopyran **137** as a white solid (0.063 g, 80%); m.p. 133.5 ^oC.

I.R. ($CHCl_3$): 3412 cm^{-1}. **^{1}H-NMR** ($CDCl_3$): δ 1.38 (d, J= 6.0 Hz, 3H, -CH_3), 2.78 (d, J= 6.0 Hz, 2H, -C<u>H</u>$_2$-CH-CH_3), 3.67-3.85 (m, 1H), 3.87 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 4.77 (d, J= 16.0 Hz, 1H), 5.13 (d, J=16.0 Hz, 1H), 6.37 (d, J= 2.0 Hz, 1H), 6.61 (d, J= 2.0 Hz, 1H), 6.94 (s, 1H), 9.20 (s, 1H, -OH). **^{13}C-NMR** ($CDCl_3$): δ 21.58 (-CH_3), 36.13, 55.24, 56.03, 64.76, 70.41, 97.08, 98.79,

109.05, 115.06, 116.46, 134.99, 135.66, 149.24, 157.14. **MS** (m/z): 274 (M^+, 98), 257 (10), 243 (5), 230 (100), 215 (18), 187 (18), 144 (8) and 115 (18).

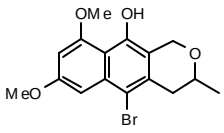
3,4-Dihydro-7,9-dimethoxy-10-hydroxy-3-methyl-5-trifluoroacetyl-1*H*-naphtho [2,3-c] pyran OR 2,2,2-Trifluoro-1-(10-hydroxy-7,9-dimethoxy-3-methyl-3,4-dihydro-1*H* benzo[g]-isochromen-5-yl)-ethanone (149):



To a solution of hydroxynaphthopyran **137** (0.33 g, 0.12 mmol) in dichloromethane (10 ml) was added trifluoroacetic anhydride (0.025 g, 0.016 ml, 0.12 mmol) at 25°C with stirring and the reaction mixture was stirred for further 5 min. It was then diluted with water (10 ml) and the organic phase was separated, washed with brine (15 ml) and dried. Evaporation of the solvent afforded the crude product, which was purified by column chromatography on silica gel with dichloromethane as an eluent. The appropriate fractions upon evaporation afforded the pure **149** as a yellow solid, (0.033g, 75%); m.p. 166.6 ^oC.

I.R. ($CHCl_3$): 3404,1631 $cm.^{-1}$ **^{1}H-NMR** ($CDCl_3$): δ 1.36 (d, J= 6.0 Hz, 3H, -CH_3), 2.73-2.82 (m, 2H, -C<u>H</u>$_2$-CH-CH_3), 3.70-3.90 (m, 1H, -CH_2-C<u>H</u>-CH_3), 3.95 (s, 3H, -OCH_3), 4.10 (s, 3H, -OCH_3), 4.72 (d, J= 16.0 Hz, 1H), 5.09 (d, J=16.0 Hz, 1H), 6.43 (s, 1H), 7.04 (s, 1H), 9.14 (s, 1H). **^{13}C-NMR** ($CDCl_3$): δ 21.50, 36.31, 56.44, 56.45, 64.50, 70.35, 91.00, 108.94, 109.68, 112.84, 116.66, 118.76, 132.28, 138.05, 149.74, 158.71 and 161.43. **MS** (m/z): 371 (M+1, 100), 353 (5), 326 (60), 302 (70), 257 (85), 241 (20), 213 (10), 170 (12) and 128 (22).

5-Bromo-3, 4-dihydro-7, 9-dimethoxy-10-hydroxy-3-methyl-1*H*-naphtho [2,3-c] pyran OR 5-Bromo-7, 9-dimethoxy-3-methyl-3,4-dihydro-1*H*-benzo[g]isochromen-10-ol (150):

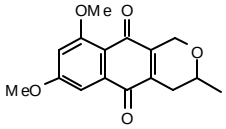


A solution of NBS (54 mg, 0.30 mmol) in dry DMF (2.5 ml) was added to a solution of **137** (84 mg, 0.30 mmol) in dry DMF (2.5 ml) and stirred at room temperature for 16 hr. The mixture

was poured into water (10 ml) and extracted with dichloromethane (2 x 20 ml). The extract was washed well with water, dried (Na_2SO_4) and evaporated under reduced pressure to yield crude monobromide, which was purified by chromatography using 5% acetone in pet ether to give pure bromocompound **150** (87 mg, 82%) as a white solid; m.p. 138.5 ^oC.

^{1}H-NMR ($CDCl_3$): δ 1.43 (d, J= 6.0 Hz, 3H, -CH_3), 2.50-2.75 (m, 1H), 2.88-3.10 (m, 1H), 3.60-3.90 (m, 1H), 3.94 (s, 3H, -OCH_3), 4.03 (s, 3H, -OCH_3), 4.69 (d, J=10.0 Hz, 1H), 5.10 (d, J=10.0 Hz, 1H), 6.47 (d, J= 2.0 Hz, 1H), 7.19 (d, J=2.0 Hz, 1H), 9.38 (s, 1H, -OH). **^{13}C-NMR** ($CDCl_3$): δ 21.61, 29.69, 38.21, 55.39, 56.40, 64.70, 70.68, 97.91, 99.22, 109.99, 112.34, 116.74, 133.83, 135.05, 149.06, 157.30, 158.24. **MS** (m/z): 354 (M^+, 100), 352 (M^+, 98), 310 (74), 308 (78), 293 (29), 273 (32), 229 (54), 214 (38), 201 (18), 155 (30) and 115 (28).

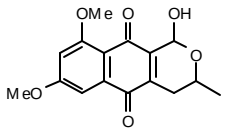
3,4-Dihydro-7,9-dimethoxy-3-methyl-1*H* naphtho [2,3-c] pyran-5,10-dione OR
7,9-Dimethoxy-3-methyl-3,4-dihydro-1*H*-benzo [g] isochromene-5,10-dione (138):



To a solution of **150** (0.046 g, 0.130 mmol) in acetonitrile (5.0 ml) was added ceric ammonium nitrate (0.106 g, 0.194 mmol) in water (2.0 ml) at 0 ^oC and stirred for 15 min at the same temperature. The stirring was further continued for 30 min at room temperature. It was then diluted with water (10 ml) and extracted with chloroform (2 × 20 ml), washed with brine, dried over sodium sulfate and concentrated under reduced pressure to afford crude **138** as a yellow solid which was purified by column chromatography using 15% acetone in pet ether as an eluent to give pure **138** (0.030 g, 81.08%) as yellow solid; m.p. 211.9 ^oC.

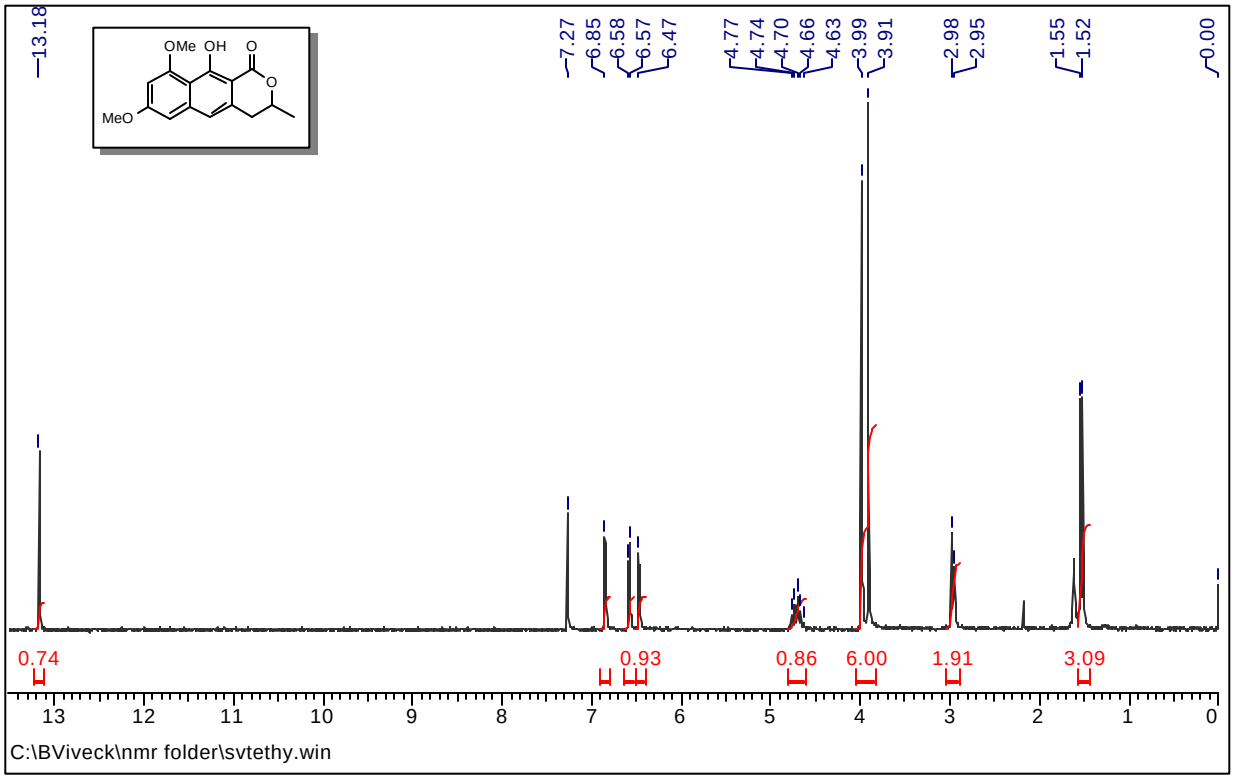
I.R. ($CHCl_3$): 1640, 1660 $cm.^{-1}$ **^{1}H-NMR** ($CDCl_3$): δ 1.37 (d, J = 6.0 Hz, 3H), 2.15-2.37 (m, 1H), 2.64 and 2.73 (t, J = 2.0 Hz, total 1H), 3.55-3.77 (m, 1H), 3.95 (s, 3H), 3.96 (s, 3H), 4.43 and 4.53 (t, J = 2.0 Hz, total 1H), 4.79 and 4.89 (d, J = 2.0 Hz, total 1H), 6.71 (d, J = 2.0 Hz, 1H), 7.26 (d, J = 2.0 Hz, 1H). **^{13}C-NMR** ($CDCl_3$): δ 21.18, 29.21, 55.94, 56.40, 63.75, 69.58, 103.61, 104.13, 114.29, 139.02, 144.45, 162.03, 164.74, 181.80 (quinone C=O), 183.88 (quinone C=O). **MS** (m/z): 288 (M^+, 100), 273 (48), 259 (42), 245 (37), 227 (29), 187 (18) and 115 (35).

3, 4-Dihydro-7, 9-dimethoxy-3-methyl-1*H*-naphtho [2, 3-c] pyran-1-ol -5, 10-dione (122):

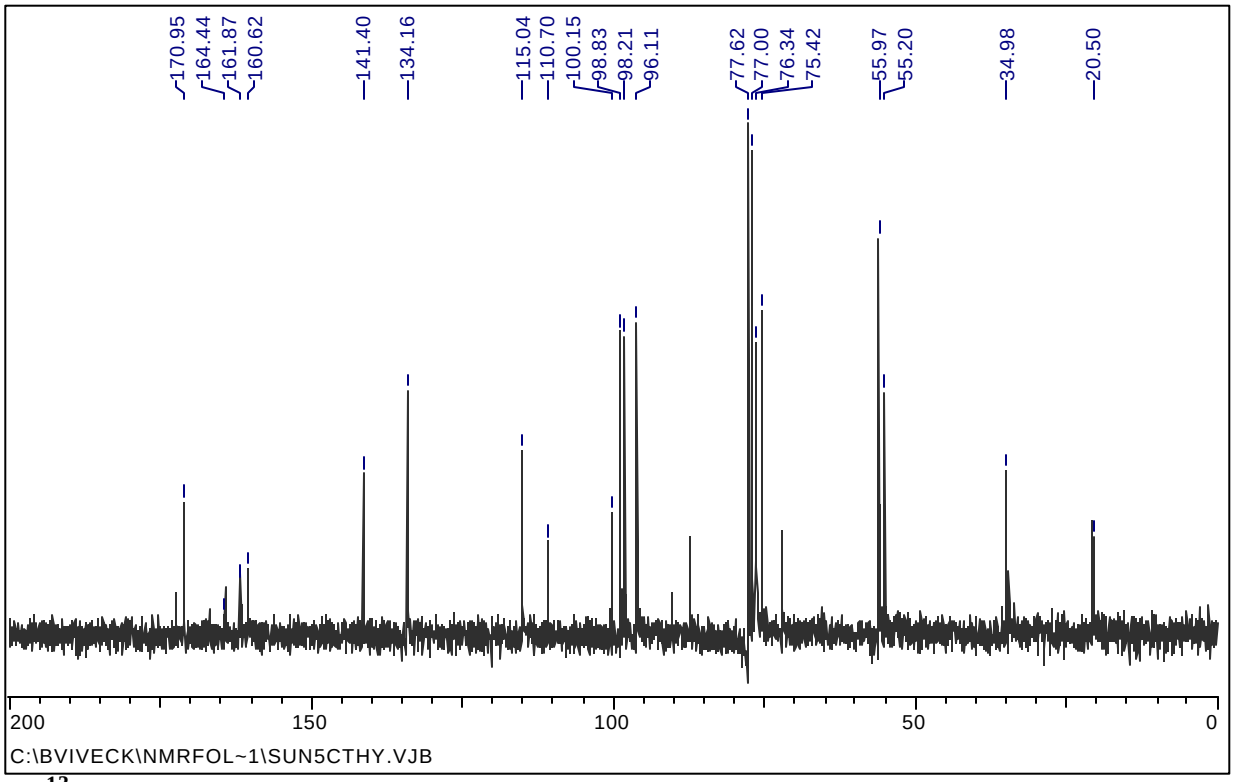


To a solution of quinone **138** (0.022 g, 0.076 mmol) in dry CCl_4 (20.0 ml) was added bromine in CCl_4 (0.012 g, 0.076 mmol) at room temperature. It was then exposed to 500 W bulb for 30 minutes with efficient stirring. The reaction mixture was then cooled, THF (10.0 ml) plus water (1.0 ml) were added successively, and stirring was continued for further 1 hr. The mixture of CCl_4 and THF was removed by distillation under reduced pressure, aqueous residue was diluted with water (20.0 ml) and was extracted with ethyl acetate (2 × 20.0 ml). The ethyl acetate layer was washed with brine, dried over sodium sulfate and concentrated to give a crude yellow solid, which was purified by column chromatography using 30% acetone in pet ether to give pure **122** (0.019 g, 82.60%) as a yellow solid; m.p. 155.5 ^{o}C.

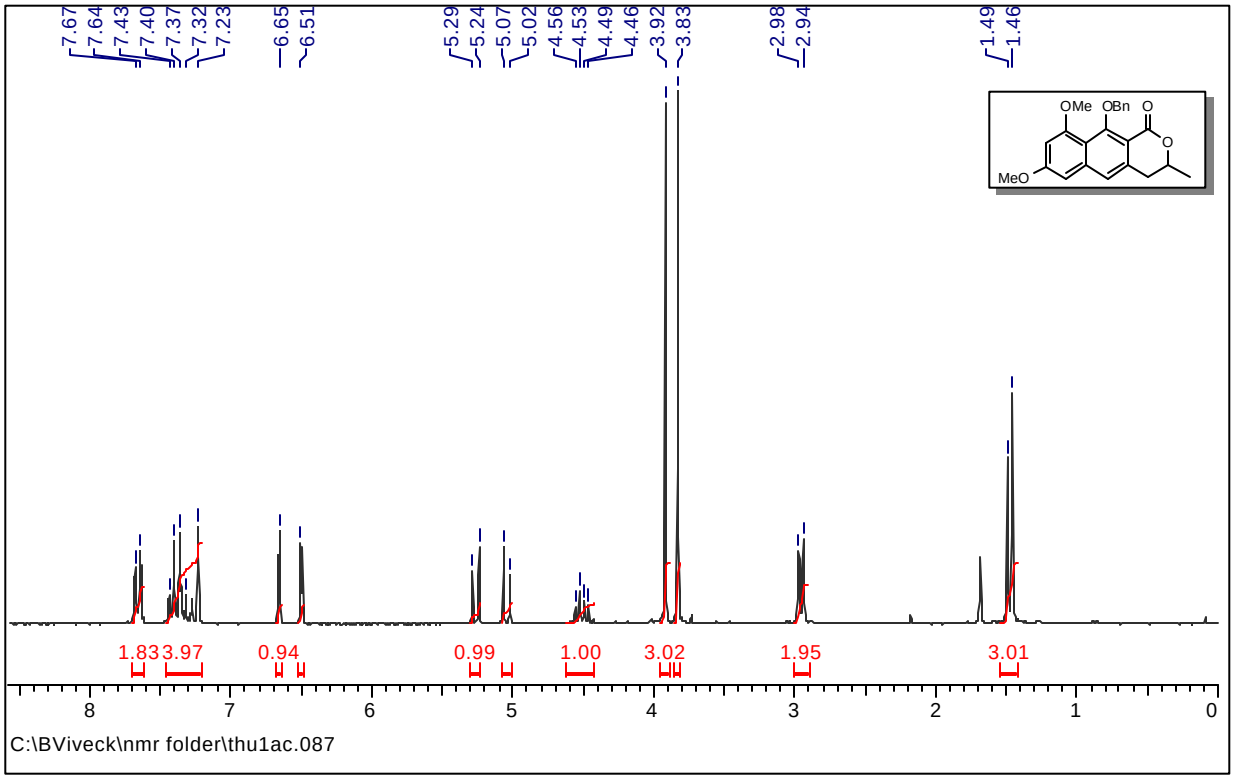
I.R. ($CHCl_3$): 1595, 1656 cm.$^{-1}$ **^{1}H-NMR** ($CDCl_3$): δ 1.39 and 1.47 (d, J = 6.0 Hz, total 3H), 2.14-2.34 (m, 1H), 2.65 and 2.75 (d, J = 2.0 Hz, total 1H), 3.95 (s, 3H), 3.97 (s, 3H), 4.20-4.40 (m, 1H), 6.03 and 6.07 (s, total 1H), 6.73 and 6.75 (d, J = 2.0 Hz, total 1H), 7.25 and 7.30 (d, J = 2.0 Hz, total 1H). **^{13}C-NMR** ($CDCl_3$): δ 21.18, 29.21, 55.94, 56.40, 63.75, 69.58, 103.61, 104.13, 114.29, 139.02, 144.45, 162.03, 164.74, 181.80 (quinone C=O), 183.88 (quinone C=O). **MS** (m/z): 286 (58, M-18), 272 (29), 243 (6), 200 (22), 171 (23), 141 (21), 105 (25), 69 (65) and 55 (100).



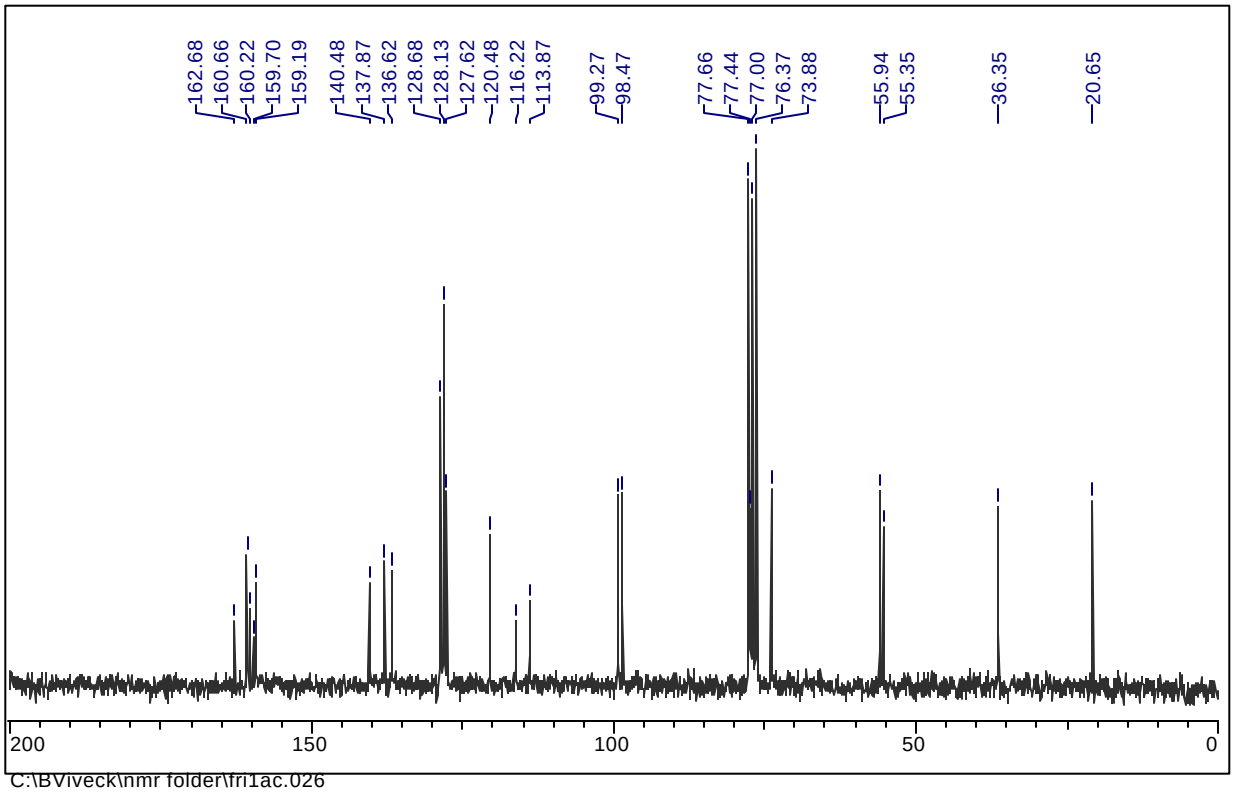
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 119 IN $CDCl_3$



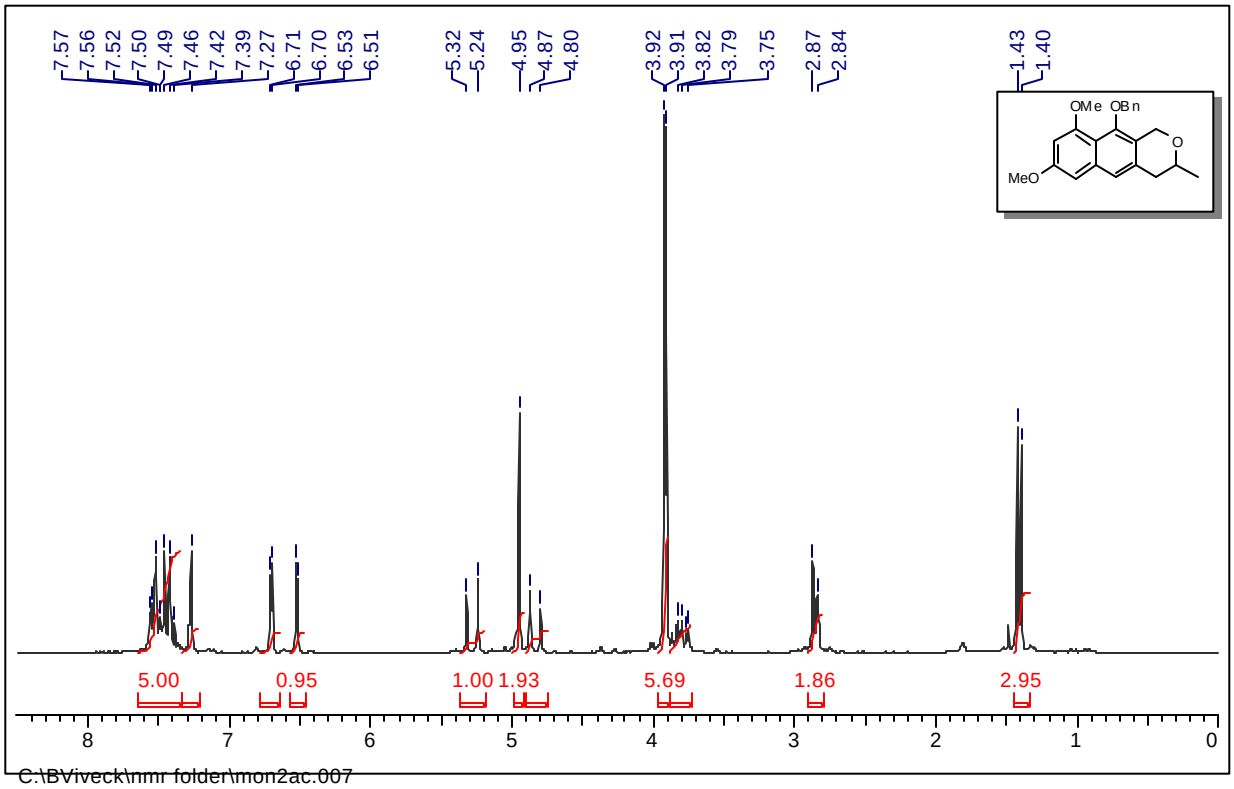
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 119 IN $CDCl_3$



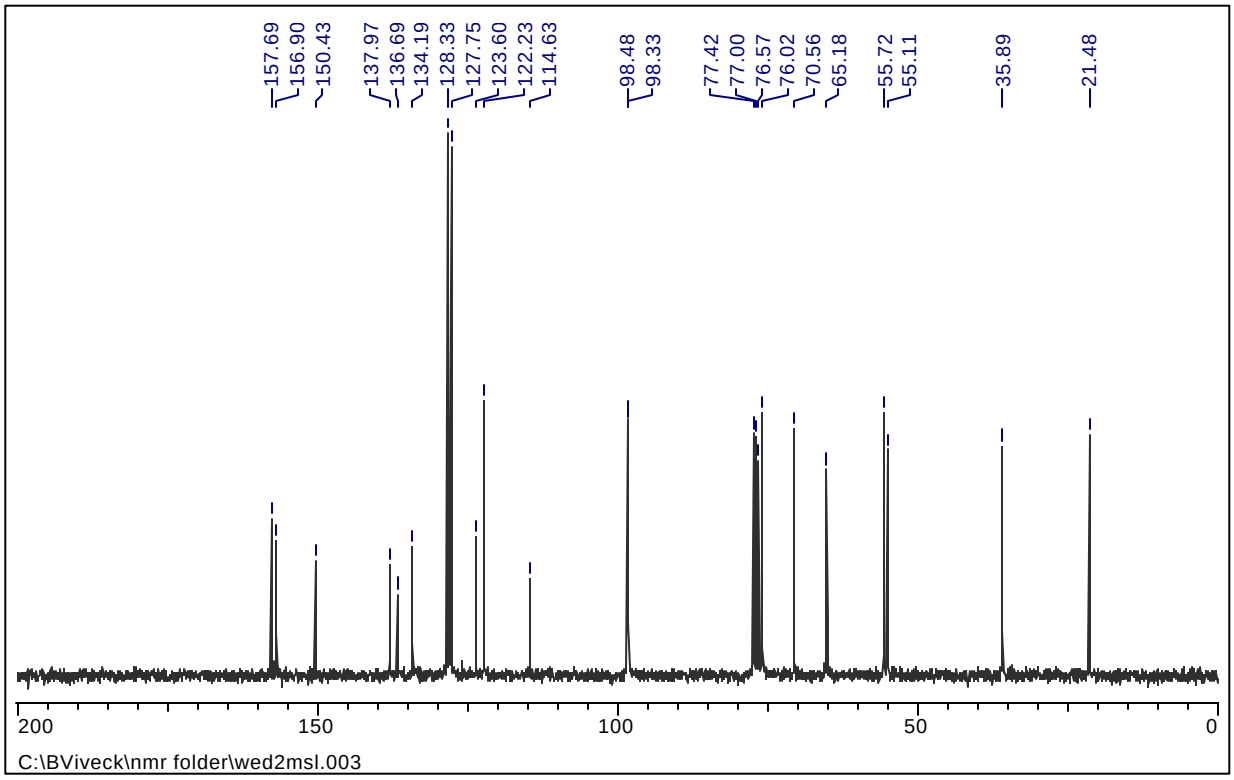
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 134 IN $CDCl_3$



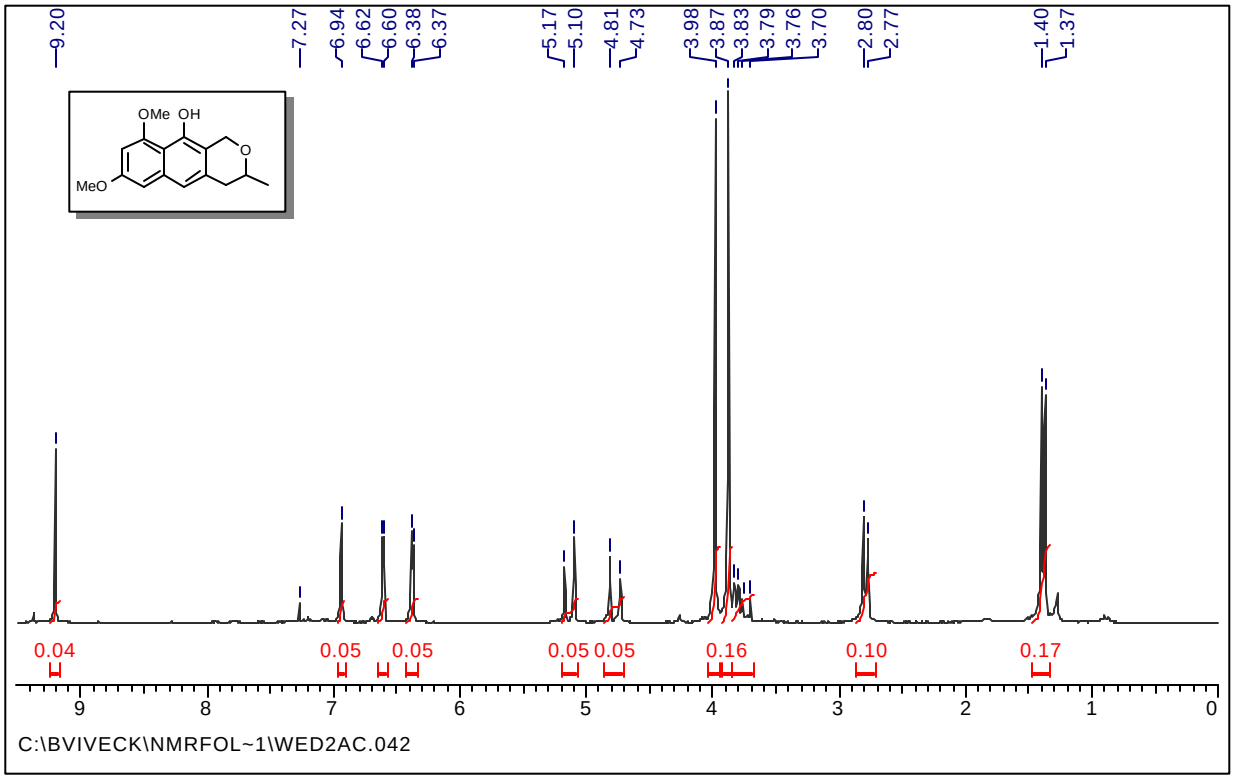
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 134 IN $CDCl_3$



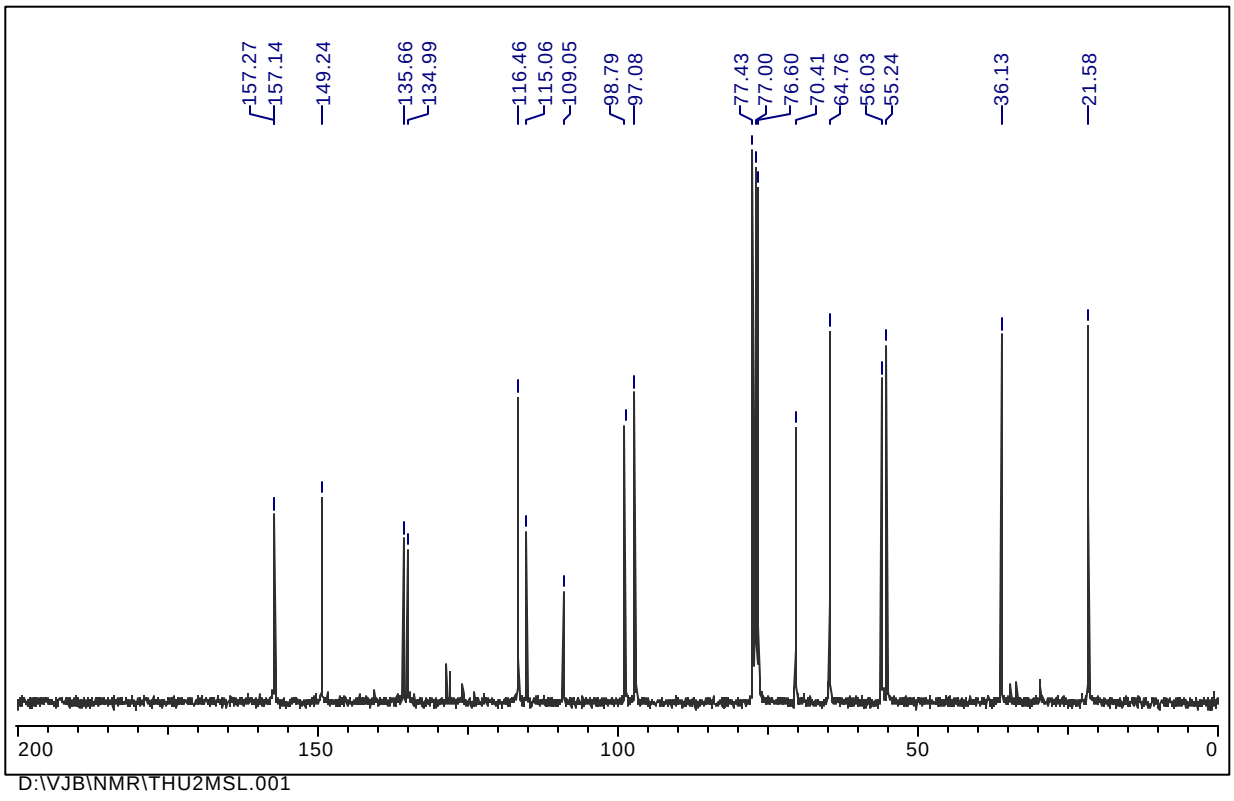
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 136 IN $CDCl_3$



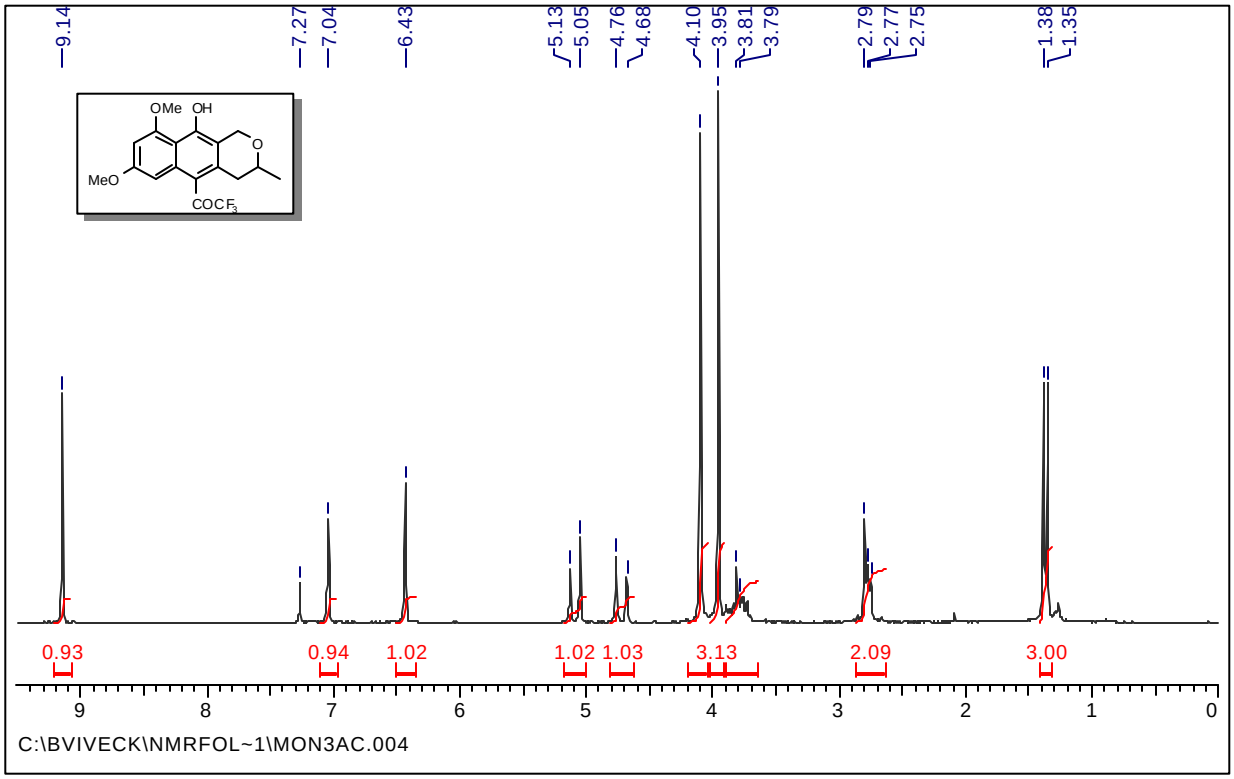
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 136 IN $CDCl_3$



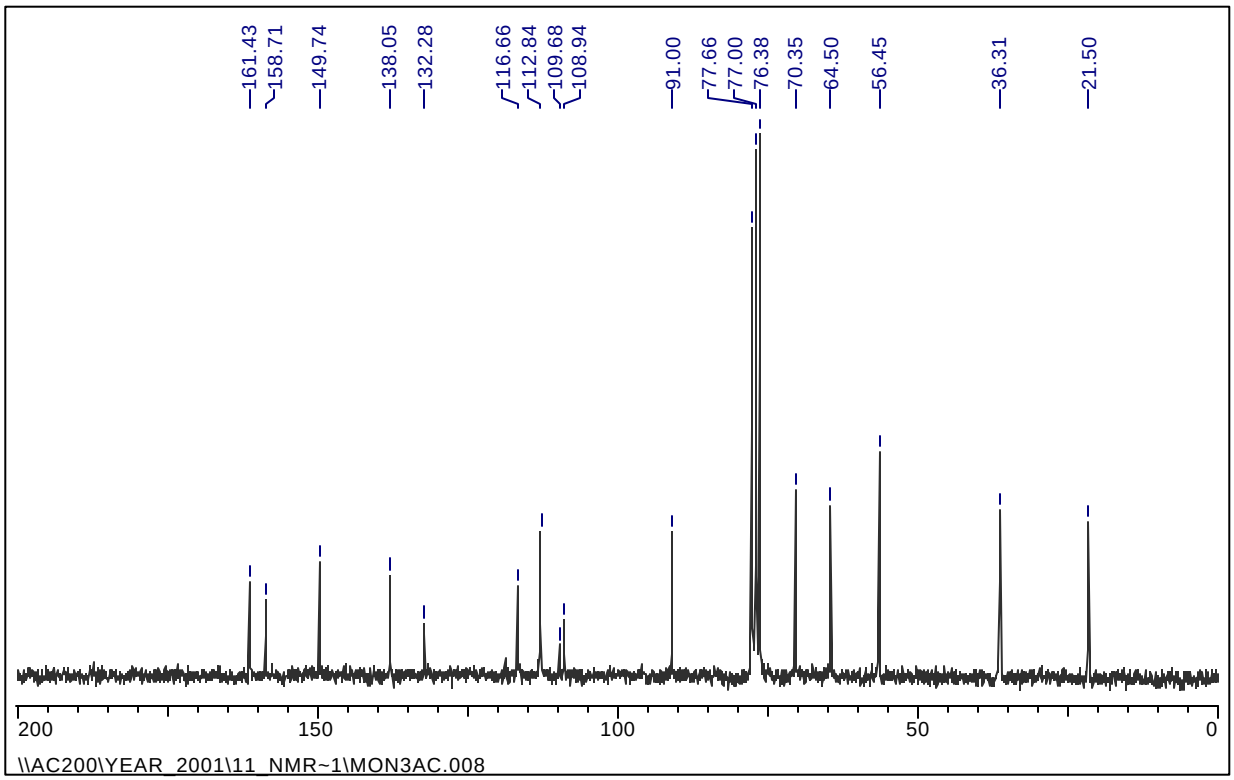
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 137 IN $CDCl_3$



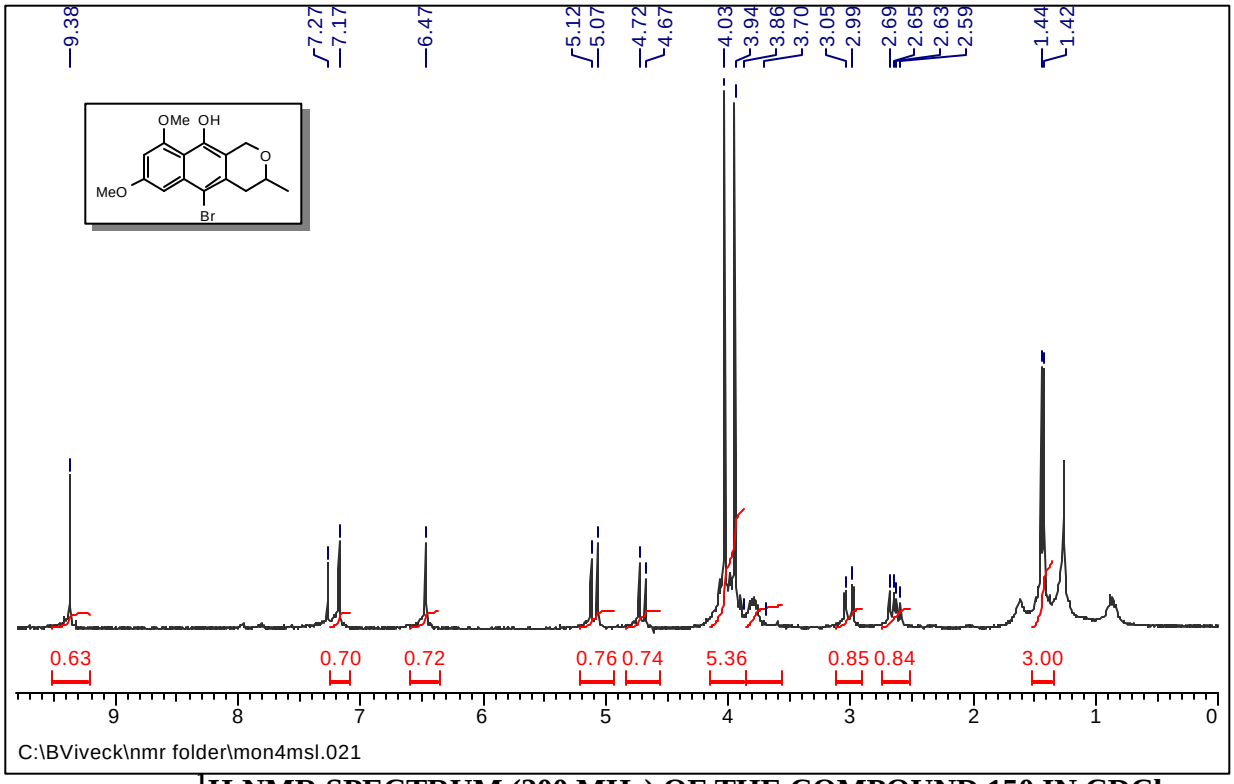
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 137 IN $CDCl_3$



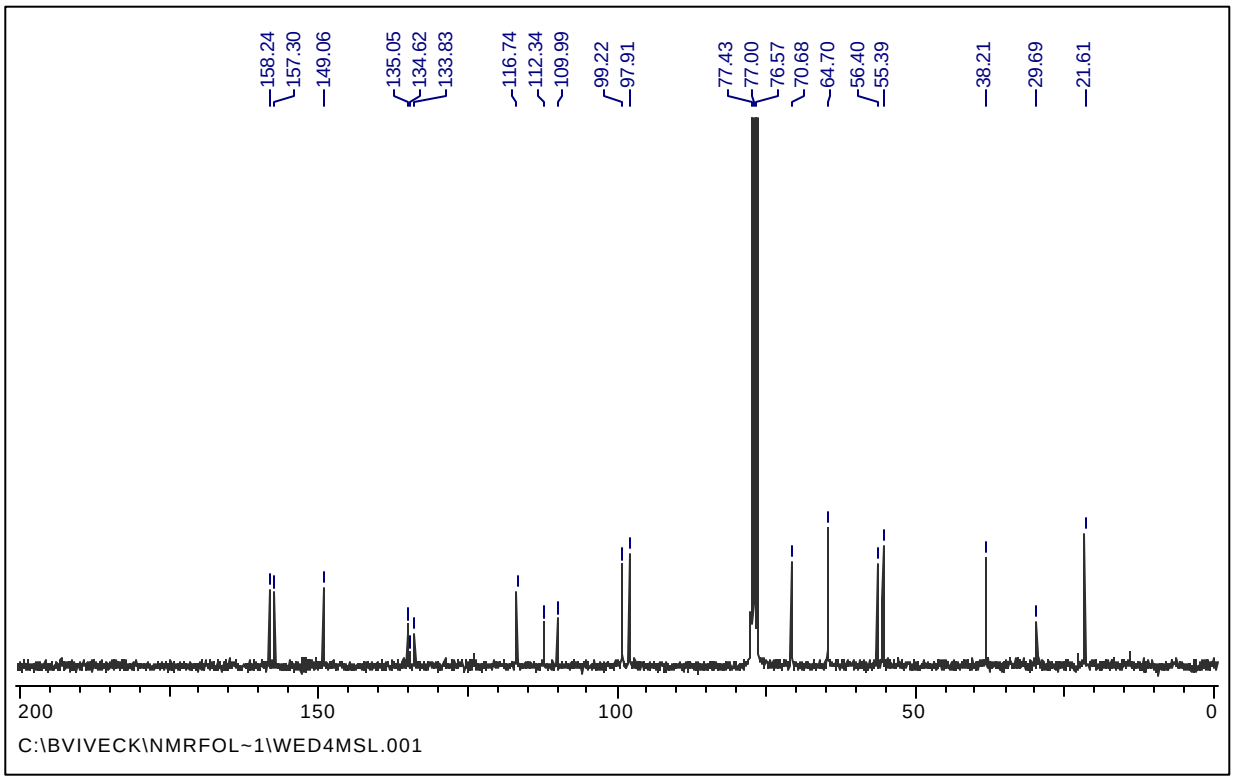
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 149 IN $CDCl_3$



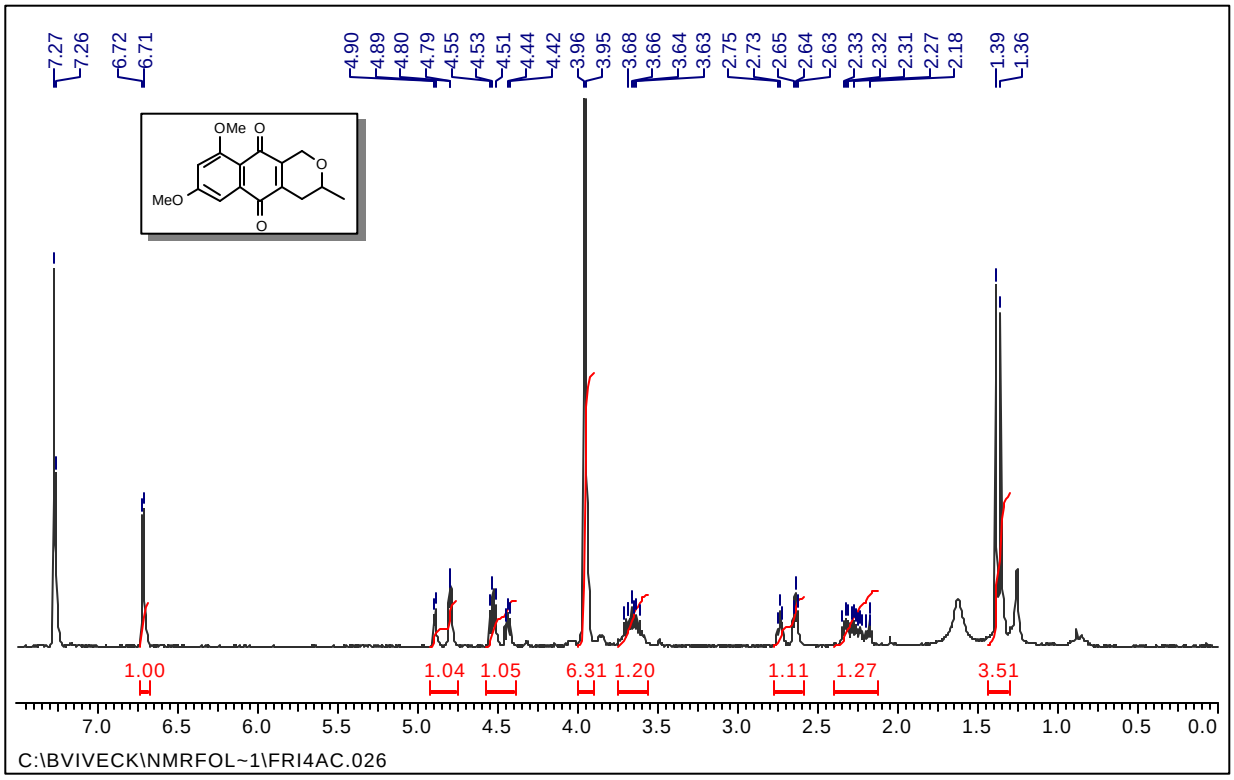
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 149 IN $CDCl_3$



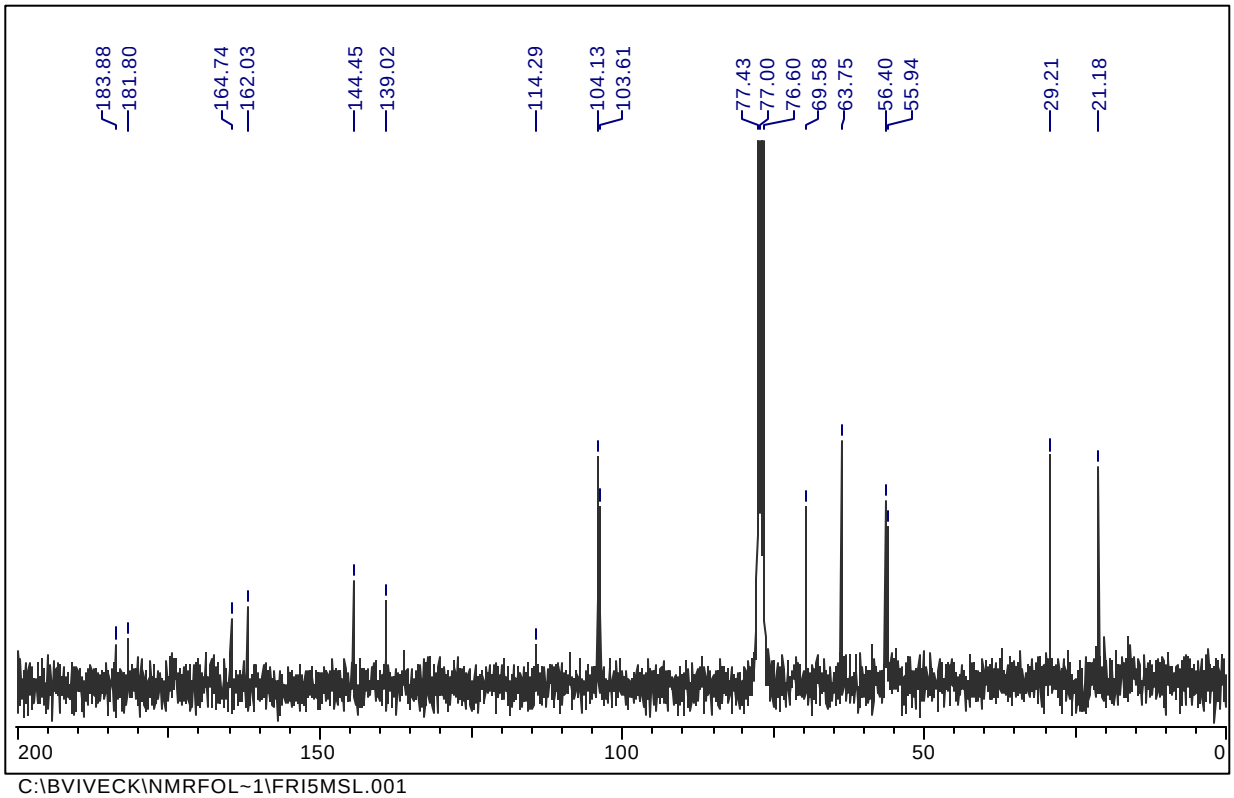
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 150 IN $CDCl_3$



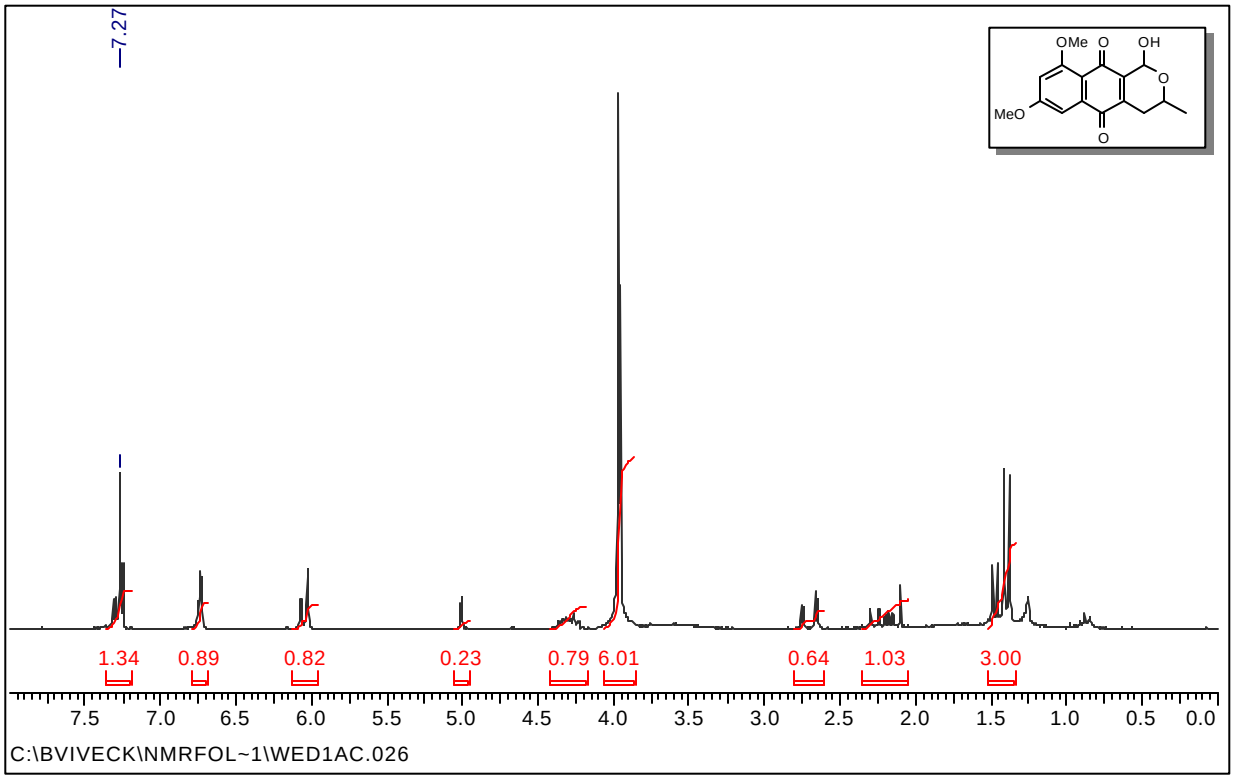
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 150 IN $CDCl_3$



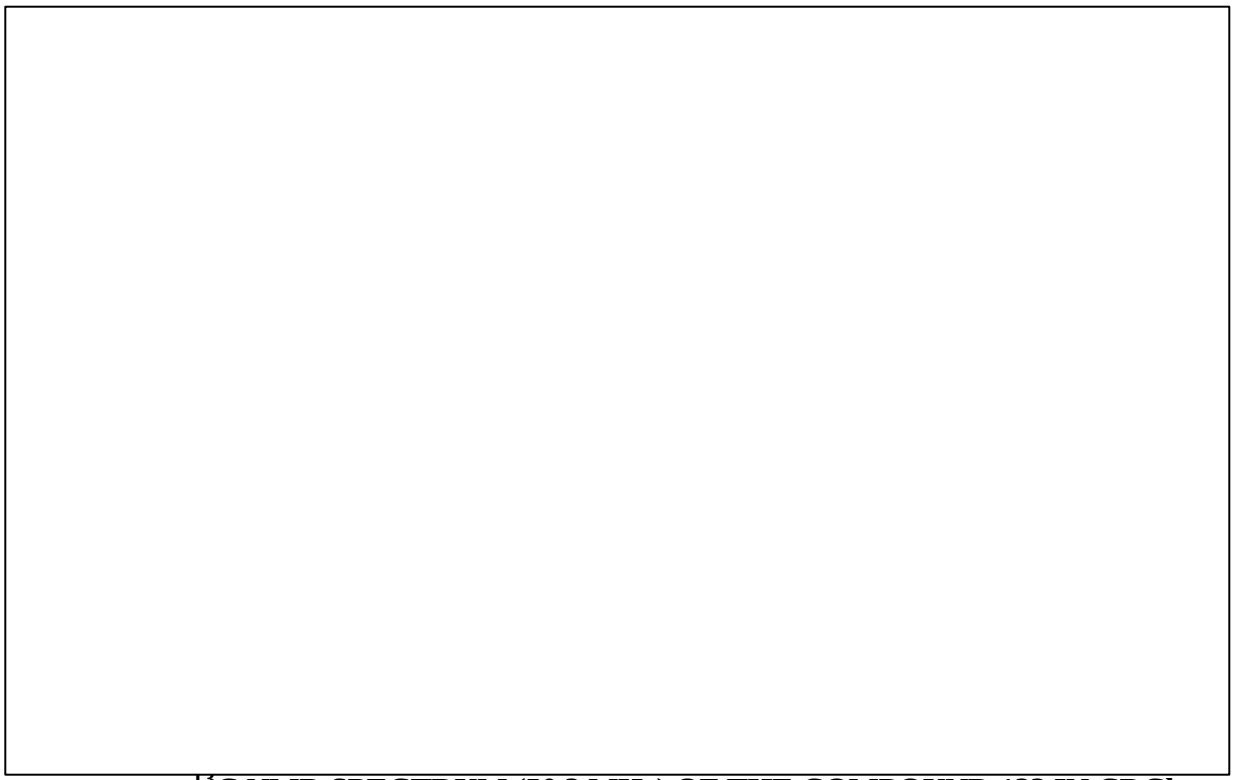
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 138 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 138 IN $CDCl_3$



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 122 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 122 IN $CDCl_3$

1.2.5 REFERENCES:

1. Singh, S. B.; Cordingley, M. G.; Ball, R. G.; Smith, J. L.; Dombrowski, A. W. and Goetz, M. A., *Tetrahedron Lett*., **1991**, 39, 5759.
2. Gwaltney, J. M. Jr. in " Viral infection of Man: Epidemiology and Control" (*Evans, E. A., ed*) 2nd Ed., pp-491. Plenum Publishing Corp., New York (1982).
3. a) Palmenberg, A. C., *J. Cell. Biochem.,* **1987**, 33, 191. b) Krausslich, H. G.; Wimmer, E., *Annu. Rev. Biochem.*, **1988**, 57, 701. c) Cordingley, M. G.; Register, R. B.; Callahan, P. L.; Garsky, V. M.; Colonno, R. J., *J. Virol.*, **1989**, 63, 5037. d) Cordingley, M. G.; Callahan, P. L.; Sardana, V. V.; Garsky, V. M.; Colonno, R. J., *J. Biol. Chem.*, **1990**, 265, 9062.
4. Skiles, J. W.; Mcneil, D., *Tetrahedron Lett*., **1990**, 31, 7277.
5. a) Yamaguchi, M.; Okuma, T.; Nakamura, S.; Minami, T., *J. Chem. Soc. Perkin Trans. 1*, **1990**, 183. b) Deshpande, V. H.; Khan, R. A.; Rai, B.; Ayyangar, N. R., *Synth. Commun.*, **1993**, 23, 2337. c) Deshpande, V. H.; Rai, B. and Khan, R. A., *Tetrahedron Lett*., **1996**, 52, 7159. d) Mori, K. and Watanabe, H. *Tetrahedron*, **1984**, 40, 299. e) Wipf, B.; Kupfer, E.; Bertazzi, R. and Leuenberger, H. G. W., *Helv. Chim. Acta.*, **1983**, 66, 485. f) Seebach, D.; Sutter, M. A.; Weber, R. H; *Org. Syn.* **1985**, 63, 1.
6. Zeeck, A.; Rub, P.; Laatsch, H.; Loeffer, W.; Wehrle, H. and Hoist, H., *Chem. Ber*. **1979**, 112, 957.
7. Jiu, J. and Mizuba, S., *J. Antibiot*., **1974**, 27, 760.
8. Suzuki, K.; Nozawa, K. and Kawai, K., *Chem. Pharm. Bull*., **1990**, 38, 3180.
9. Ayer, A. W.; Craw, P. A. and Nozawa, K., *Can. J. Chem*., **1991**, 69, 189.
10. Gill, M. and Gimenez, A., *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2585.
11. Donner, C. D.; Gill, M., *Tetrahedron Lett*., **1999**, 40, 3921.
12. Dimitriadis, C.; Gill, M. and Harte, M. F., *Tetrahedron Assym.*, **1997**, 8, 2153.
13. Barlett, A. J.; Holker, J. S. E.; Brien and Simpson, T. J., *J. Chem. Soc. Perkin Trans. 1*, **1983**, 667.
14. Kato, T. and Hozumi, T., *Chem. Pharm. Bull*., **1972**, 20, 1574.
15. Howarth, T. T.; Murphy, G. P. and Harris, T. M., *J. Am. Chem. Soc*., **1969**, 91, 517.
16. Sargent, M. V.; Vogel, P. and Elix, J. A., *J. Chem. Soc. Perkin Trans. 1*, **1975**, 1986.

17. Nicollier, G.; Rebetez, M. and Tabacchi, R. G., *Helv. Chim. Acta*, **1978**, 61, 2899.
18. Griffin, D. A.; Leeper, F. J. and Stauntomn, J., *J. Chem. Soc. Perkin Trans. 1*, **1984**, 1035.
19. Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Staunton, J.; Wilkinson, M. R., *J. Chem. Soc. Perkin Trans. 1*, **1984**, 1043.
20. Godfrey, I. M.; Sargent, M. V. and Elix, J. A., *J. Chem. Soc. Perkin Trans. 1*, **1974**, 1353.
21. Brokke, M. E. and Christenesen, B.E., *J. Org. Chem.*, **1959**, 24, 523.
22. Sih, C. J.; Massuda, D.; Corey, P.; Gleim, R. D. and Suzuki, F., *Tetrahedron Lett*., **1979**, 1285.
23. a) Pettit, G. R. and Kasturi, T. R., *J. Org. Chem.*, **1960**, 25, 875. b) Pettit G. R.; Ghatak, U. R.; Green, B.; Kasturi, T. R. and Piatak, D. M., *J. Org. Chem.*, **1961**, 26, 1685.
24. a) Shiozaki, M., *J. Org. Chem*., **1991**, 56, 528. b) Matteson, D. S.; Kandil, A. A.; Soundararajan, R., *J. Am. Chem. Soc*., **1990**, 112, 3964. c) Pearlman, W. M., *Tetrahedron, Lett*., **1967**, 17, 1663.
25. Fuji, K.; Ichikawa, K.; Node, M. and Fujita, E., *J. Org. Chem.*, **1979**, 44, 1661.
26. Dean, F. M.; Goodchild, J.; Hanghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W. and Sovichien, N., *Tetrahedron Lett*., **1966**, 4153.
27. Tatsuta, K.; Yamazaki, T.; Mase, T. and Yoshimoto, T. *Tetrahedron Lett*., **1998**, 39, 1771.
28. Zimmer, H.; Lankin, C. D. and Horgan, S. W., *Chem. Rev.*, **1971**, 71, 229.
29. Matsumoto, N.; Iinuma, H.; Sawa, T. and Takenchi, T., *Bioorg. Med. Chem. Lett.*, **1998**, 8, 2945.
30. Skibo, E. B. and Imadul, I., *J. Med. Chem.*, **1991**, 34, 2954.
31. Ho, T. L., Hall, Tse-Wai and Wong C. M., *Synthesis*, **1973**, 206.
32. Boeckman, R. K. and Cheon, S. H., *J. Am. Chem. Soc.*, **1983**, 105, 4112.
33. Perry, J. P.; Pavlidis, V. H.; Hadfield, J. A. and Coutts, G. C., *J. Chem. Soc. Perkin Trans. 1*, **1995**, 1085.
34. Gopinathan, M. B. and Bhatt, V. M., *Indian J. Chem.*, **1981**, 20B, 71.
35. Mitchell, R. H.; Lai, Y. H. and Williams, R. V., *J. Org. Chem*., **1979**, 44, 4733.

C H A P T E R - 2

THE SYNTHETIC STRATEGIES TOWARDS SAINTOPIN AND ITS DERIVATIVES

2.0.1 INTRODUCTION

Cancer as a disease in the human population is becoming a larger health problem and the medicines used for treatment have clear limitations. In the past 20 years, there has been a tremendous increase in our knowledge of the molecular mechanisms and pathophysiology of human cancer. Many of these mechanisms have been exploited as new targets for drug development in the hope that they will have greater antitumor activity with less toxicity to the patient than is seen with currently used medicines. The fruition of these efforts in the clinic is just now being realized with a few encouraging results[1].

In some areas of the world, cancer has become or shortly will become the leading disease-related cause of death of the human population. For example, in the United States and India, cancer is the second leading cause of death behind cardiovascular disease, and it is projected that cancer will become the leading cause of death within a few years. There are two main reasons for this change. First, cancer is a disease of multiple accumulating mutations that are becoming manifest in human populations, which have enjoyed an increasingly prolonged life span[2]. Second, cardiovascular-related deaths are decreasing as a result of an increased understanding of the mechanisms underlying the disease, the identification of risk factors which indicate life-style changes that can reduce the onset of disease and the development of targeted molecular therapies. In contrast, the medical treatment of cancer still has many unmet needs. The main curative therapies for cancer, surgery and radiation, are generally successful only if the cancer is found at an early, localized stage. Once the disease has progressed to locally advanced cancer or metastatic cancer, these therapies are less successful. Existing chemotherapeutic treatments are largely pallative in these advanced tumors, particularly in the case of common epithelial tumors such as lung, colorectal, breast, prostate and pancreatic cancers[3]. Cancer chemotherapy involves the use of chemicals ordinarily foreign to the body, which when administered to the host bearing tumor, will adversely affect the tumor without destroying the host. This treatment is mostly resorted to after all other methods of therapy have failed. The main disadvantage of cancer chemotherapy is the toxicity of the drug used. So far nearly 3, 00, 000 different compounds have been documented, either obtained from natural sources or synthesis, as potential anticancer agents. Out of these only about 40 are today considered useful in varying degrees, in the treatment of more than 100 types of human cancer[4a]. A large number of anticancer drugs, now being used in medical practice, have been approved by NCI,

USA. The usefulness of certain anthracycline antibiotics as antineoplastic agents is now widely accepted. The anthracyclines are a group of structurally related antitumor antibiotics[4b]. The two prototype anthracyclines are adriamycin and daunomycin produced from *Streptomyces* species[5]. Their potent activity was discovered in 1963, when adriamycin and daunomycin[6] were found to be effective as antileukemic agents[7]. The tumor cell growth inhibitory property of the anthracyclines has generally been attributed to the interaction of these drugs with DNA. Adriamycin has also shown promising results in solid tumors also.

The therapeutic use of drugs, which affect the structures and functions of DNA, has led to the virtual eradication of much infectious disease and represents one of the great triumphs of medicinal science. A great deal of interest is at present being focussed on elucidating the action of chemotherapeutic drugs.

Topoisomerase-targetting Anticancer Drugs

DNA topoisomerases are nuclear enzymes essential for controlling DNA topology in mammalian cells such as replication, transcription and recombination processes[8]. DNA topoisomerases I and II are enzymes that alter DNA conformation through a concerted breaking and rejoining of DNA strands[9]. Replication of a cell's genetic material requires separation of DNA double helix. After separation these two strands separately form new DNA double helix. The separation of double helix generally requires special aid from special topoisomerase enzyme. An anticancer drug has the ability to inhibit these enzymes and causes the cell to die.

Biology

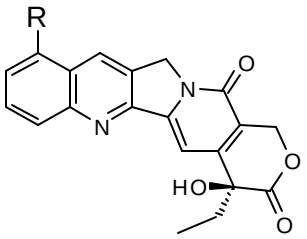
A number of clinically important anticancer drugs have recently been shown to kill tumor cells by affecting topoisomerases. The topoisomerase poisons appear to be a good tool for studying cell-killing mechanisms as they produce highly specific and reversible lesions. Topoisomerase-targetting drugs appear to interfere with breakage-reunion reaction of DNA topoisomerase. In the presence of these drugs, an aborted reaction intermediate, termed 'Cleavable complex' accumaulates. Exposure of the 'cleavable complex' to a strong protein denaturant such as SDS or alkali results in DNA breakage and the covalent linking of a topoisomerase polypeptide to a terminus of each broken DNA strand[10].

The identification of the 'Cleavable complexes' as the cytotoxic lesions of topoisomerase-targetting drugs readily explains many of the cellular effects of these anticancer drugs. The reversibility of this novel DNA damage suggests that its interaction with certain DNA metabolic machinery may trigger cell death. These antitumor drugs, termed "topoisomerase II poisons" have the common property of stabilizing the DNA-topoisomerase II complex, which upon exposure to denaturing agents results in the induction of DNA cleavage. Several lines of evidence indicate that the ability to induce topoisomerase II dependent DNA cleavage (TDC) is responsible for the antitumor activity of these drugs.

The topoisomerase dependent antitumor drugs are mainly of two types, topoisomerase I poisons such as camptothecin[11] and topoisomerase II poisons which have been identified as the site of action for some of the most widely used clinical cancer chemotherapeutic drugs, including doxorubicin (adriamycin)[12], actinomycin D[13], epipodophyllotoxins, VP-16 (etoposide)[14] and VM-26 (teniposide)[12]. The topoisomerase II poisons can be broadly categorized into the intercalators, which include the acridines[15], ellipticines[12,16], actinomycins[13], anthracenediones[13] and anthracyclines[12], and the nonintercalating epipodophyllotoxins[12,14] (Table:1). Chemical structures for representatives of each class of topoisomerase targetting antitumor drugs are shown in Fig 1.

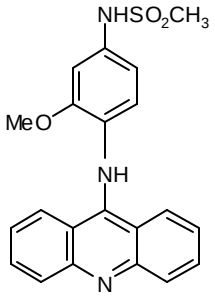
Table:1

Target	**Drug class**	**Examples**
Topoisomerase I	Camptothecins	9-Aminocamptothecin
Topoisomerase II	Acridines	Amsacrine (*m*-AMSA)
	Actinomycins	Actinomycin D
	Antracenediones	Mitoxantrone, Bisantrene
	Anthracyclines	Adriamycin (Doxorubicin), AD 41, Daunomycin (Daunorubicin)
	Benzisoquinolinediones	Amonafide, Mitonafide
	Epipodophyllotoxins	VM 26 (teniposide), VP 16 (etoposide)
	Isoflavonoids	Genistein

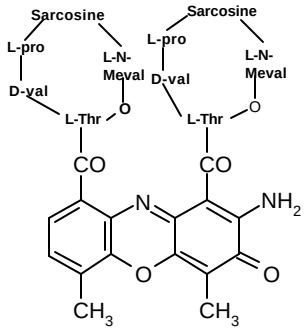


R = H, Camptothecin

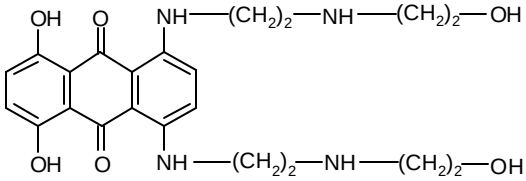
R = NH_2, 9-Aminocamptothecin



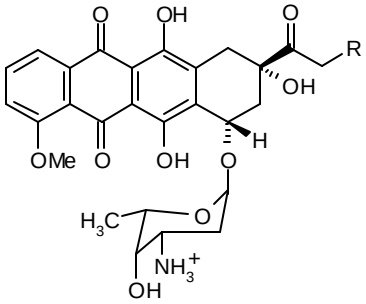
Amsacrine (*m*-AMSA)



Actinomycin D

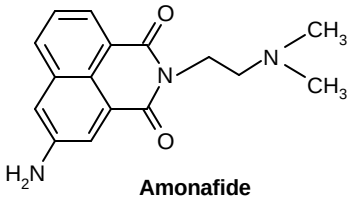


Mitoxantrone

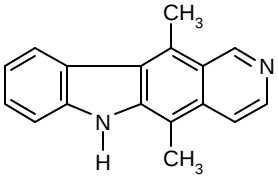


Adriamycin, R = OH

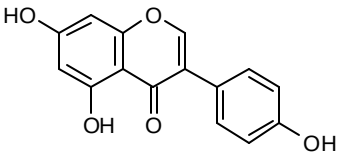
Daunomycin, R = H



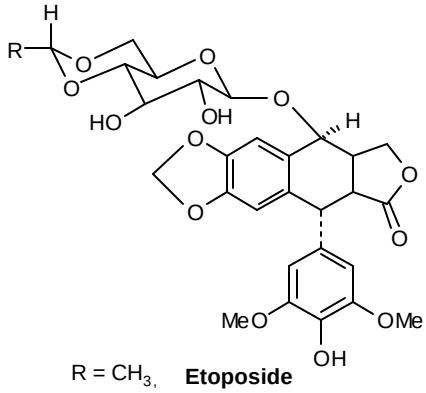
Amonafide



Ellipticin



Genistein



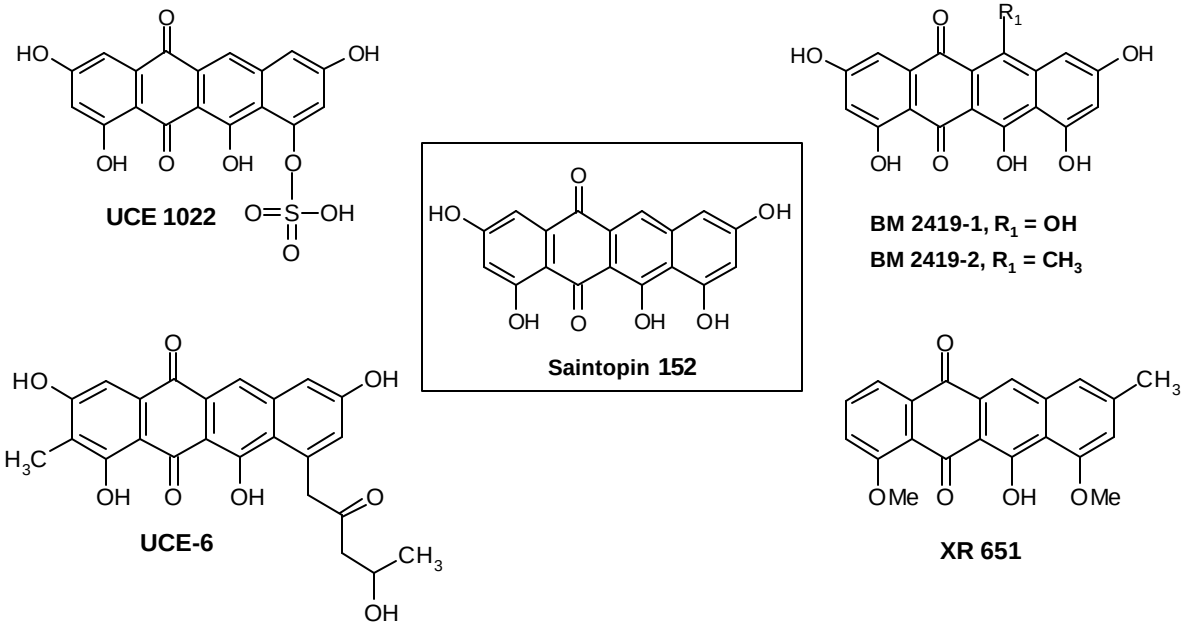
R = CH_3, **Etoposide**

R =  **Teniposide**

MODE OF ACTION

The mode of action of many chemotherapeutic agents, including certain antineoplastic drugs, has been claimed to be due to their ability to intercalate between the base pairs of the DNA double helix. The identification of both topoisomerase I and II in all eukaryotic cells as the specific targets of cancer chemotherapeutic drugs provides a rational basis for the development of improved multi-agent regimens and for the development of topoisomerase I poisons for possible clinical use. Knowledge of the molecular mechanisms of cell killing may lead to the identification of new therapies for treating cancer. These enzymes function by forming enzyme-bridged strand-breaks those act as transient gates for the passage of other DNA strands. Topoisomerase I breaks one strand of duplex DNA and allows the unbroken, complementary strand to pass through the enzyme-linked strand break, thereby effecting DNA relaxation. Topoisomerase II, which breaks both strands of duplex DNA, acts as a gate for the passage of a second duplex molecule prior to resealing. By this strand-passing mechanism it can relax supercoiled DNA and catenate/decatenate DNA circles[8].

New Antitumor Agent Saintopin: A Dual Inhibitor of Topoisomerase I and II.



In 1990, Yamashita *et al*[17]. isolated a new antitumor antibiotic saintopin, which induces both topoisomerase I and II mediated DNA cleavage from the culture broth of *Paecilomyces sp*. Saintopin is the first example of a new topoisomerase II targeting drug which has been found from microbial

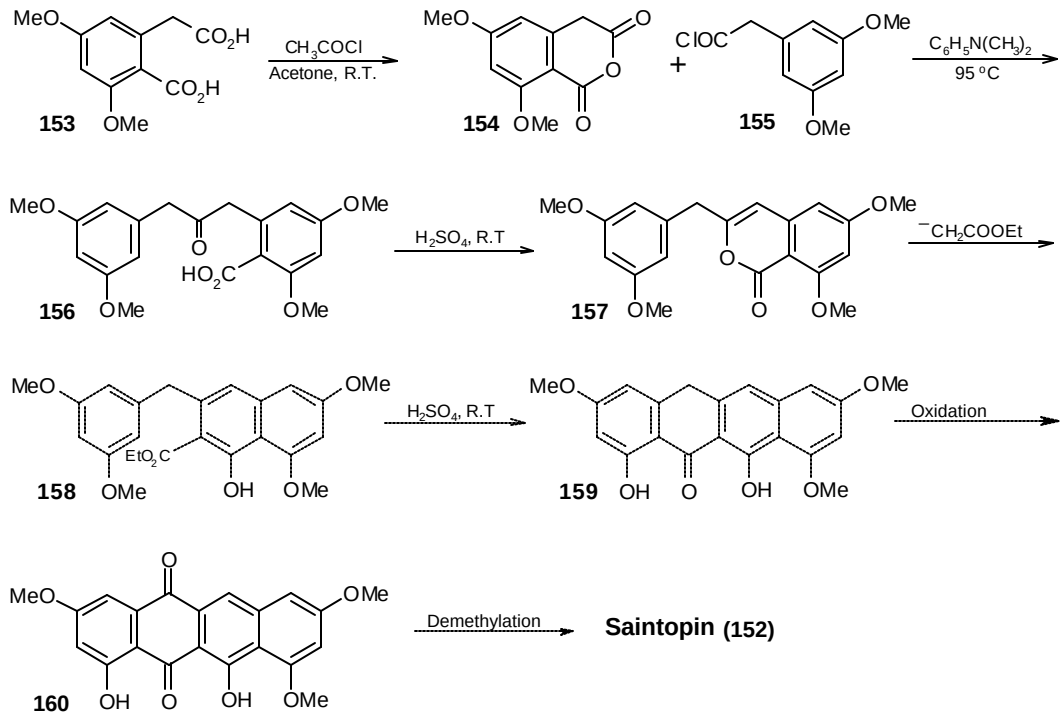
cultures using mammalian topoisomerase II in mechanistically oriented screening. BM2419-1 and 2 were also isolated from the culture broth of a fungus *Paecilomyces sp.* BM 2419[18]. It was found that BM2419-1 and 2 are new active compounds in human topoisomerase inhibition assay using recombinant yeasts. These novel compounds were artifacts derived from saintopin. UCE 1022[19], UCE 6[20] and XR651[21] are potent inducer of topoisomerase I mediated DNA cleavage having structural similarity with saintopin.

The cleavage activities of saintopin were dose-dependent and nearly potent as those of camptothecin and *m*-AMSA or VP-16 respectively. Saintopin represents a new class of topoisomerase poison that induces potent DNA cleavage with both topoisomerase I, and II at multiple sites. It shows cytotoxicity *in vitro* as well as antitumor activity *in vivo*. Both topoisomerase I and topoisomerase II mediated DNA cleavage can be induced by saintopin, so it is interesting to see which topoisomerase is the principal target of saintopin in tumor cells comparing the results of topoisomerase I and II mediated DNA cleavage assays *in vitro*. To clarify the principal target of saintopin at the cellular level, the cytotoxic effects on mammalian cells, which are resistant to saintopin were studied[22]. A drug like saintopin which acts on topoisomerase I as well as topoisomerase II is likely to exhibit cytotoxic effect on a variety of tumor cells altered in either topoisomerase I or topoisomerase II activities. The TDC activity of saintopin was studied *in vitro* using purified calf thymus topoisomerase II and plasmid DNA. Comparison of the TDC activity of saintopin with other well-known topoisomerase II poisons, m-AMSA and VP-16, was studied. In the absence of topoisomerase-II saintopin did not induce any changes on the supercoiled structure of PBR 322 DNA, indicating that saintopin is a new compound with TDC activity. Saintopin exhibits a weak antimicrobial activity against Gram-positive bacteria but not against both gram-negative bacteria and fungi. Saintopin shows cytotoxic activity against human tumor cell line, $HeLaS_3$ (IC_{50} 0.35 µg/ml) *in vitro*, and furthermore shows antitumor activity against murine leukemia P388 (ip) *in vivo*, exhibiting a statically significant increase in life span (ILS 30 %) at a dose of 25 mg/kg (ip).

2.0.2 Earlier Approaches Towards Saintopin and Related Compounds

In our group[23], in an earlier approach towards saintopin, isocoumarin **157** was condensed[24] with an anion of ethyl acetate (CH_2COOEt) to furnish naphthalene ester **158**, which was cyclised to provide the saintopin carbon frame **159**. The crucial isocoumarin intrermediate **157** was prepared from homophthalic anhydride **154** upon condensation[25] with phenylacetyl chloride **155** as shown in scheme-1. The starting material homophthalic acid **153,** for the preparation of homophthalic anhydride **154,** was prepared by method of Hauser and Rhee[26].

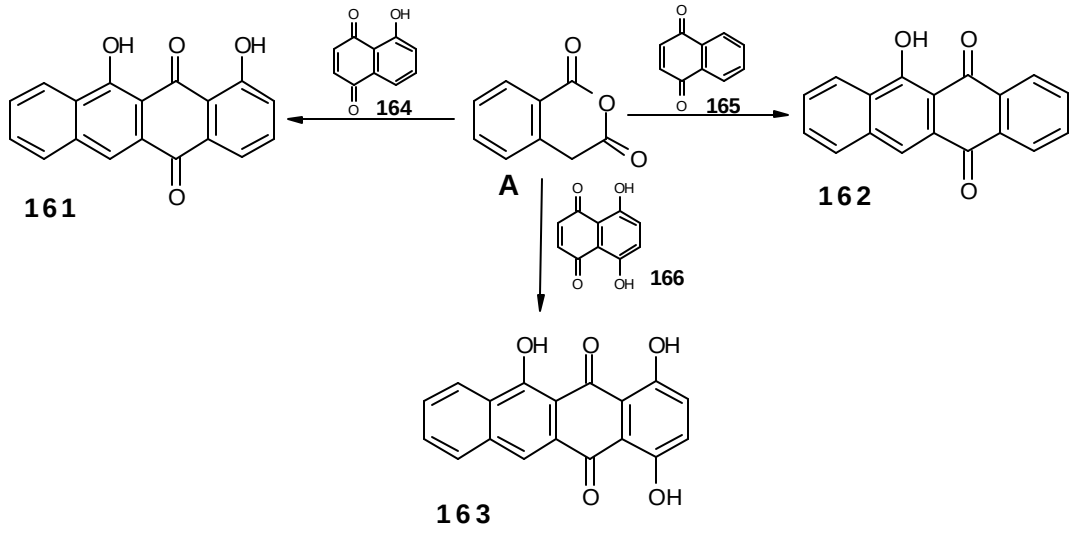
Scheme-1



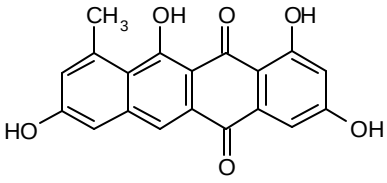
The above method represents a short and regiospecific synthesis towards saintopin. However, oxidation of tetralone **159** to the desired quinone **160** was not attempted due to lack of enough material in hand. There are a few methods reported in the literature for the construction of saintopin like structure frame.

Tamura *et al.*[27] developed a simple route for the preparation of linearly condensed phenolic compounds **161**, **162** and **163** by Diels -Alder reaction of homophthalic anhydride **A** with dienophiles **164**, **165** and **166** respectively.

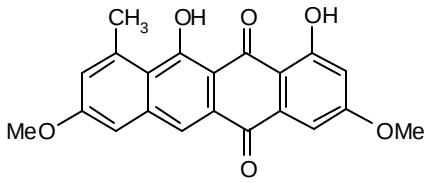
Scheme-2



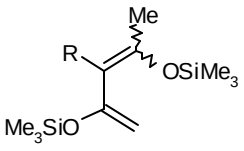
Cameron *et al.*[28] reported the synthesis of tetracenomycin D (**167**) and tetracenomycin A_2 (**168**) for the first time, by an efficient regioselective sequence based on cycloaddition methodology.



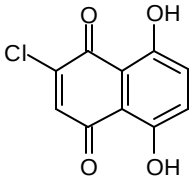
167 Tetracenomycin D



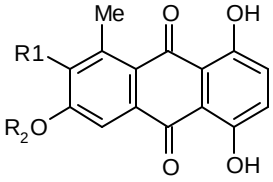
168 Tetracenomycin A_2



170 R = H
171 R = CO_2Me



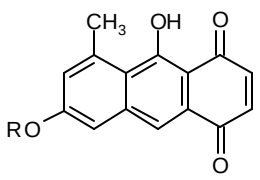
169



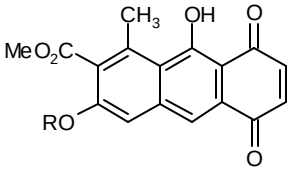
172 $R^1 = R^2 = H$
173 $R^1 = H$, $R^2 = Me$
174 $R^1 = CO_2Me$, $R^2 = H$
175 $R^1 = CO_2Me$, $R^2 = Me$

Thus addition of chloronaphthazarin **169** to diene **170** in CH_2Cl_2 at room temperature followed by aromatization with acetic acid and sodium acetate gave the 5, 10-anthraquinone **172**. Selective methylation of **172** with methyl iodide/silver (I) oxide was achieved to give **173**. In a similar manner the anthraquinonoid esters **174** and **175** were prepared. The addition of the dienyl ester **171** to **169**, in boiling benzene gave **174** and selective methylation of **174** afforded **175**. The

four new 5,10 anthraquinones **172-175** as such, were unsuitable for further cycloaddition necessary for generation of the fourth ring. However, reductive removal of the appropriate carbonyl oxygen from the central ring and reoxidation of the corresponding 1,4 anthraquinone allowed the correct oxygenation pattern for the further cycloaddition reaction. Accordingly treatment of both **172** and **173** with $NaBH_4$ at 0 ^oC followed by oxidation was found to proceed with complete regioselectivity to give respective 1,4 anthraquinones **176** and **177**. Consequent reduction and oxidation of **174** and **175** gave **178** and **179** respectively.

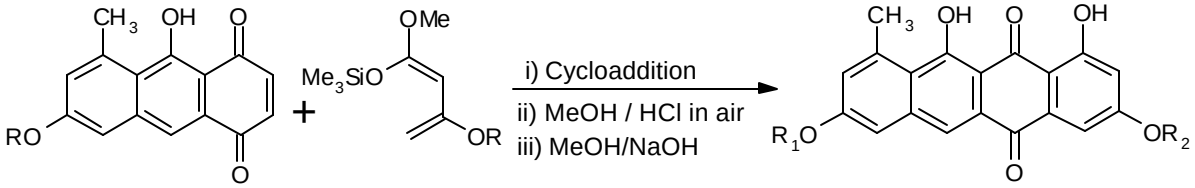


176 R = H
177 R = Me



178 R = H
179 R = Me

Cycloaddition of **176** and the diene **180**, followed by oxidative aromatization (MeOH / HCl in air) and deprotection (MeOH/NaOH), yielded tetracenomycin D (**167**) in 82% yield. Similarly, treatment of **177** with diene **181** afforded tetracenomycin A2 (**168**) in 81 % yield.



176 R = H
177 R = Me

180 R = $SiMe_3$
181 R = Me

167 $R_1 = R_2 = H$
168 $R_1 = R_2 = Me$

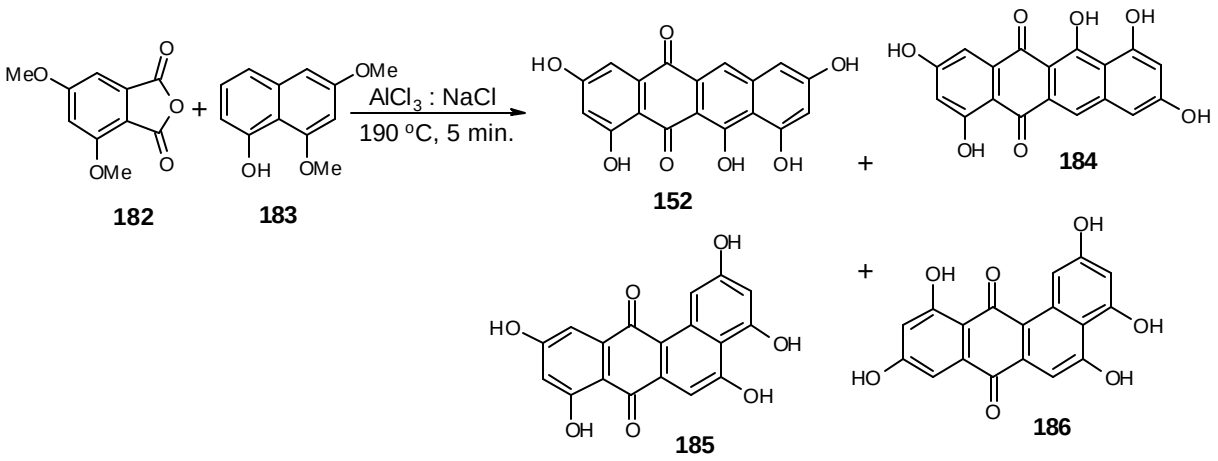
2.0.3 PRESENT WORK:

The interesting TDC activity of saintopin made it as a new class of antitumor drug, which induces both topoisomerase I and II mediated DNA cleavage, and the low yield from natural sources necessitated the need for a synthetic route to saintopin and its derivatives, which may show better activity than saintopin. To the best of our knowledge so far no synthesis of saintopin and its derivatives has been reported. The structure of saintopin was assigned on the basis of spectroscopic studies as the pentahydroxy-tetracyclic quinone. The synthesis of saintopin (**152**) was undertaken in an effort to provide a method to make it available in larger quantities as well as to prepare its derivatives and the same is described in this chapter.

2.0.4 PART-I FRIEDEL-CRAFTS APPROACH

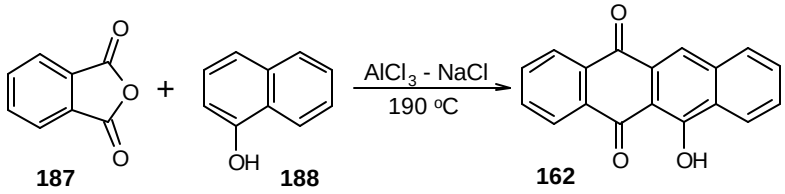
Condensation of phthalic anhydride with α-naphthol derivatives to give naphthacenedione is well documented in the literature[29]. We thought of using this straightforward approach for the direct synthesis of saintopin. Friedel-Crafts condensation between 4,6-dimethoxyphthalic anhydride (**182**) and 6, 8-dimethoxy-1-naphthol (**183**) would give saintopin (**152**) directly along with three other possible regioisomers **184**, **185** and **186** as shown in scheme-3.

Scheme-3



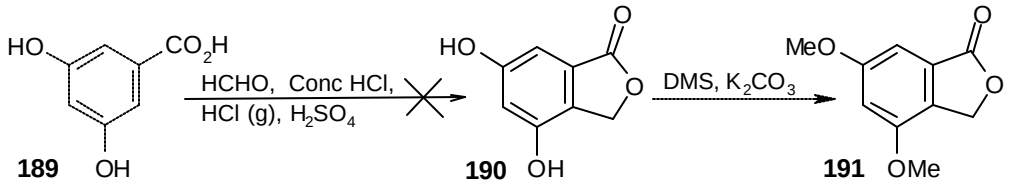
To examine the utility of this approach, a model reaction was carried out on phthalic anhydride (**187**) and α-naphthol (**188**), which gave the required linear naphthacenedione **162** in fair yields.

Scheme-4



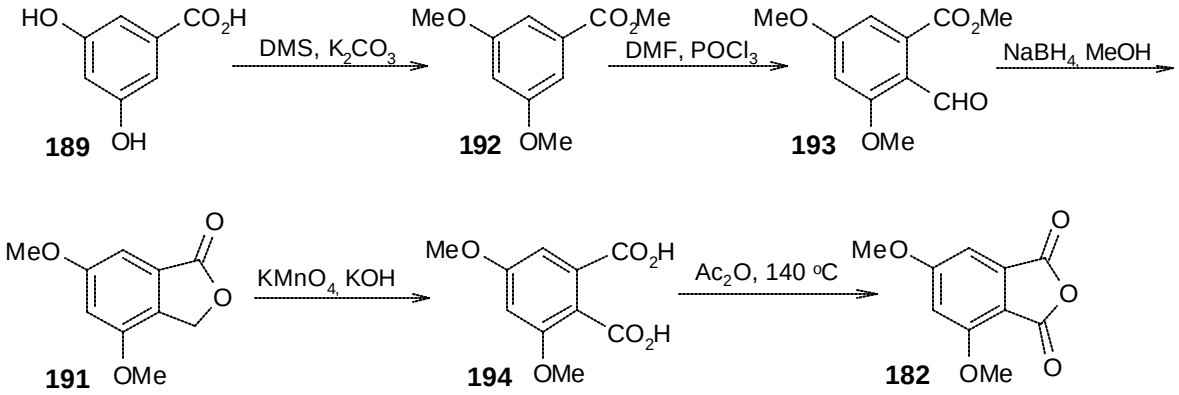
The synthesis of 4, 6-dimethoxyphthalic anhydride (**182**) required for the Friedel-Crafts condensation reaction was attempted *via* the known intermediate 4,6-dimethoxy phthalide (**191**) as follows. Procedure for the preparation of intermediate 4, 6-dimethoxy phthalide (**191**) was attempted[30] as shown in scheme-5.

Scheme-5



The treatment of 3,5-dihydroxybenzoic acid (**189**) with 37-40% formaldehyde in conc. hydrochloric acid and concentrated sulphuric acid failed to give 4, 6-dihydroxy phthalide (**190**). Therefore an alternate procedure was employed for the synthesis of phthalide **191** as shown in scheme-6.

Scheme-6

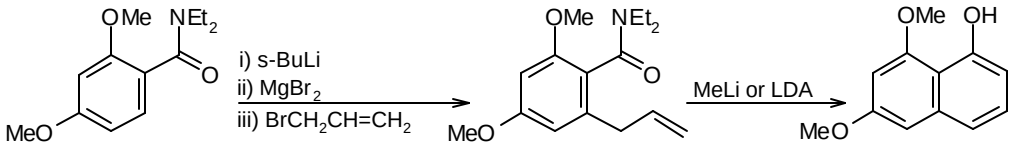


The methyl 3, 5-dimethoxy benzoate (**192**) was prepared from 3,5-dihydroxybenzoic acid (**189**) by methylation with DMS and K_2CO_3 in refluxing acetone which gave quantitative yield. Methyl 3, 5-dimethoxybenzoate (**192**) was subjected to a Vilsmeier-Haack formylation using DMF-$POCl_3$ to give methyl 3,5-dimethoxy-2-formylbenzoate (**193**) in 80% yield. The physical and

spectral properties of the aldehyde **193** were in good agreement with the reported values[31]. Methyl 3,5-dimethoxy-2-formylbenzoate (**193**) was reduced by using sodium borohydride in methanol. Hydrolysis of the resultant reduced product provided the 4,6-dimethoxy phthalide (**191**) in 90% yield. The ^{1}H NMR spectrum of phthalide **191** showed two singlets at δ 3.85 and 3.86 for two methoxyl groups and appearance of a singlet at δ 5.16 for newly formed methylene protons. IR spectrum showed a band at 1761 cm^{-1} suggesting a presence of carbonyl group. The mass spectrum exhibited the presence of molecular ion peak at m/z 194, which was in good agreement with assigned structure. After the synthesis of intermediate phthalide **191**, its oxidation[32a] with alkaline potassium permanganate yielded 4, 6-dimethoxyphthalic acid (**194**)[32b]. The formation of acid **194** was confirmed by ^{1}H NMR spectrum in DMSO-d_6, which showed two singlets at δ 3.79 and 3.82 for methoxyl groups and absence of the peak at δ 5.16, which clearly indicated that oxidation had occurred at C3 carbon. 4, 6-Dimethoxyphthalic anhydride (**182**)[32b] was then prepared by heating with acetic anhydride at 140 ^{o}C. ^{1}H NMR and MS spectra confirmed the formation of 4,6-dimethoxyphthalic anhydride. The anhydride **182** was readily soluble in $CDCl_3$ and its ^{1}H NMR spectrum showed two methoxyl singlets at δ 3.97 and 4.02 while the aromatic *meta* coupled doublets appeared at δ 6.74 and 7.02 integrating for single proton each. The presence of molecular ion peak at m/z 208 further supported the structure of anhydride **182**.

There are a number of methods[33] in the literature, which describe the multi-step synthesis of the other required synthon 6,8-dimethoxy-1-naphthol (**183**). There is only one method which provides the direct access for the preparation of **183** reported by Snieckus *et al*[34]. as shown in scheme-7.

Scheme-7

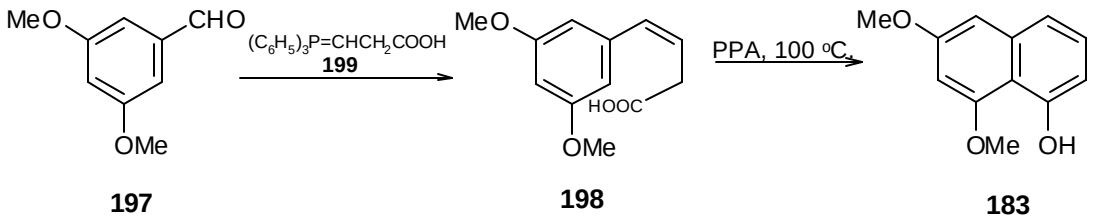


195 **196** **183**

o-Allylbenzamide **196** available from **195** by direct *ortho* metalation or transition metal catalysed cross-coupling reaction undergoes MeLi- induced cyclisation to give 1-naphthols.

Findlay *et al*[33b]. prepared 6,8-dimethoxy-1-naphthol (**183**) by condensation of 3, 5 dimethoxybenzaldehyde (**197**) with ylide **199** to furnish 4-(3',5'-dimethoxyphenyl)-3-butenoic acid (**198**) in 60 % yield. Butenoic acid **198** was then cyclised with polyphosphoric acid at 100 ^{o}C, which gave poor yield of naphthol **183** as shown in scheme-8.

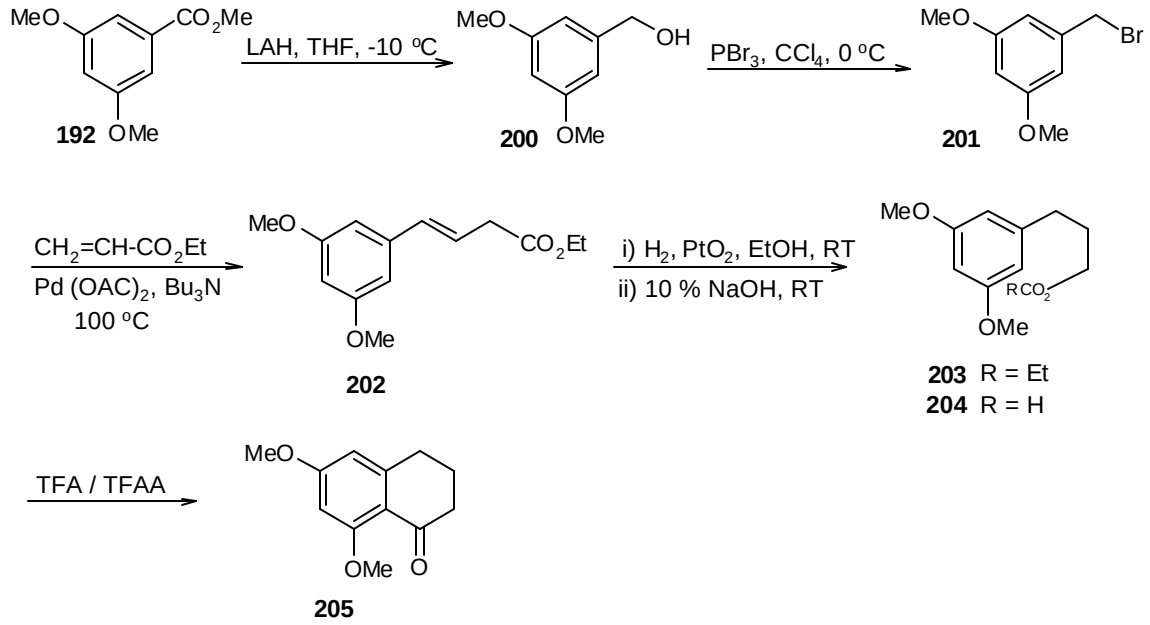
Scheme-8



197 **198** **183**

In the present work, 6,8-dimethoxy-1-naphthol (**183**) was prepared by aromatization of 6, 8-dimethoxy-1-tetralone (**205**) which was synthesized as described in scheme-9.

Scheme-9



192 **200** **201** **202**

203 R = Et
204 R = H

205

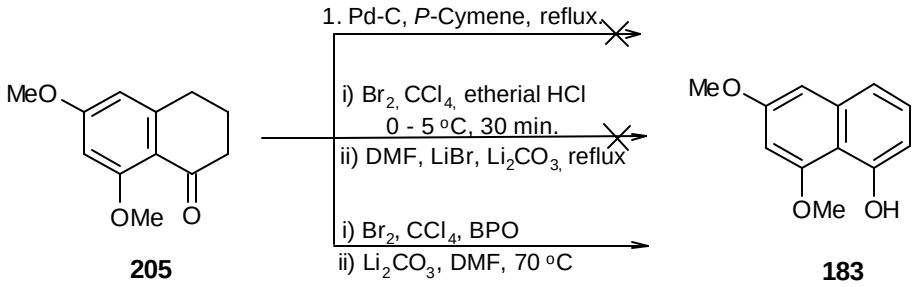
Starting material, methyl 3, 5-dimethoxybenzoate (**192**) was reduced to the corresponding 3, 5-dimethoxybenzyl alcohol (**200**)[33d] by LAH in THF at 0 ^{o}C. The alcohol **200** was then converted to 3, 5-dimethoxybenzyl bromide (**201**)[33e] by PBr_3 in CCl_4 at 0 ^{o}C. Conjugate addition[35] of the benzyl bromide **201** to ethyl acrylate, promoted by $Pd(OAc)_2$ (Heck reaction) afforded ethyl 4-(3, 5-dimethoxyphenyl)-2-butenoate (**202**) in 85% yield as a pale brown viscous oil. The formation of butenoate ester was confirmed by spectral means. ^{1}H NMR spectrum exhibited a triplet at δ 1.31 (J =

6.0 Hz) for methyl group in ethyl ester and a doublet at 3.23 (J = 6.0 Hz) for methylene protons. Two singlets at δ 3.79 and 3.81 were observed for methoxyl groups, a quartet appeared at δ 4.19 (J = 6.0 Hz) for methylene group in ethyl ester while aromatic and olefinic protons appeared as a multiplet between 6.20-6.60 for five protons. The mass spectrum revealed the molecular ion peak at m/z 250. Subsequent reduction of the above butenoate ester over Adam's catalyst in ethanol at room temperature under hydrogen atmosphere gave ethyl 4-(3,5-dimethoxyphenyl) butanoate (**203**). The formation of the reduced ester was confirmed by spectroscopic data. ^{1}H NMR spectrum showed two triplets at δ 2.29 and 2.57 (J = 6.0 Hz) and were assigned to C2 and C4 methylene protons, a quintet appeared at δ 1.92 (J = 6.0 Hz) which was due to C3 methylene protons. Ethyl triplet and quartet appeared at δ 1.24 and 4.11 (J = 6.0 Hz) respectively, aromatic multiplet was observed between δ 6.15-6.55 integrating for three protons. Further hydrolysis of the reduced ester **203** gave 3, 5-dimethoxy butanoic acid (**204**) in 95 % yield. ^{1}H NMR spectrum of acid **204** clearly showed the absence of triplet and quartet of ethyl ester at δ 1.24 and 4.11 respectively. The acid was then cyclised in equal volumes of trifluoroacetic acid and trifluoroacetic anhydride at 0 ^{o}C-RT to give the required intermediate 6,8-dimethoxy-1-tetralone (**205**). The ^{1}H NMR revealed two methoxyl singlets at δ 3.80 and 3.84, a quintet at δ 1.99 integrating for two protons, which could be assigned to methylene group at C3, two triplets at δ 2.54 and 2.84 (J = 7.0 Hz each) integrating for two protons due to methylene at C2 and benzylic protons at C4 respectively. Aromatic protons appeared as multiplet between δ 6.23-6.34 integrating for two protons. The ^{13}C NMR experiment suggested that methylene carbon signals at δ 22.56, 31.27 and 40.43 were due to C3, C4 and C2 carbons respectively; methoxyl carbons appeared at δ 54.98 and 55.50. Signals at δ 96.89 and 104.38 could be assigned to aromatic C5 and C7 respectively, while quaternary carbon signals 4a and 8a appeared at δ 116.07 and 148.79. C8 and C6 carbons bearing the mehoxyl groups gave the signals at δ 162.31 and 163.53 respectively and carbonyl carbon at C1 appeared at δ 195.29. The mass spectrum analysis showed the M^{+} peak at m/z 206 with 87% intensity along with base peak at 178 due to loss of ethylene.

The aromatization of above tetralone **205** in order to get 6,8-dimethoxy-1- naphthol (**183**) was tried using the reaction conditions as shown in the scheme-10. First two methods employing Pd-C in refluxing p-cymene and bromination-dehydrobromination[36] in DMF at reflux could not give the required naphthol (**183**). However, bromination of tetralone in CCl_4 using molecular bromine

and exposure of the solution to 500 W electric bulb gave intermediate 6,8-dimethoxy-2-bromo-1-tetralone which was used as such for further dehydrobromination reaction without purification.

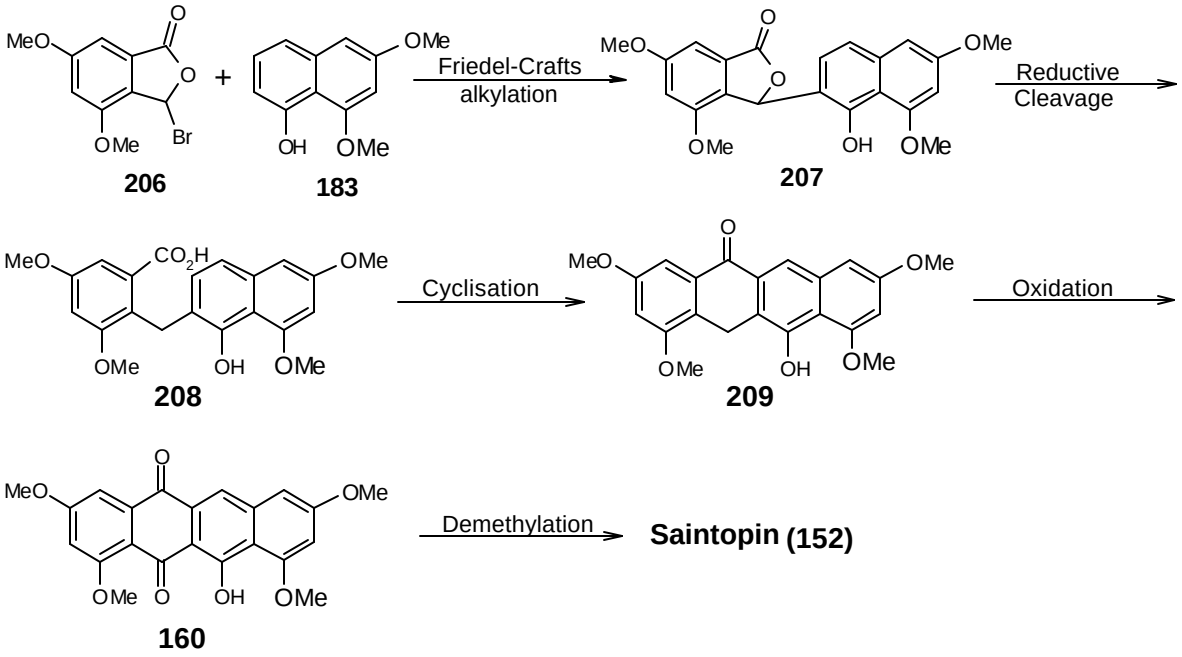
Scheme-10



Dehydrobromination reaction was carried out in dry DMF at 70 ^{o}C using lithium carbonate as a base, which gave poor yield (15.53%) of the required 6,8-dimethoxy-1-naphthol (**183**), as a white solid. ^{1}H NMR spectrum indicated two singlets at δ 3.90 and 4.05 and were assigned to two methoxyl groups. Aromatic region showed multiplet between δ 6.45-7.45 along with two *meta* coupled doublets merged with it and integrated for total five protons. The absence of peaks in the aliphatic region and presence of molecular ion peak at m/z 204 further confirmed the structure. With the desired starting materials *viz*. 4,6-dimethoxyphthalic anhydride (**182**) and 6,8-dimethoxy-1-naphthol (**183**) in hand fusion reaction was carried out at 190 ^{o}C in sodium chloride-aluminium chloride melt to get the required molecule saintopin directly, but it gave a complex mixture of products which was difficult to purify (scheme-1). Hence this approach was discontinued.

To overcome this problem we planned a modified route, which was based on the regiospecific alkylation[37] of the naphthol **183** with bromophthalide **206**. Friedel-Crafts alkylation which directly introduces a phthalide residue into the aromatic nucleus destined to be ring B of the anthracyclinones was reported by Johnson *et al*[37]. 6,8-Dimethoxy-1-naphthol (**183**) can be regiospecifically alkylated by bromophthalide **206** to construct tetracyclic carbon framework which could be elaborated to saintopin by appropriate chemical conversions as shown in the scheme-11.

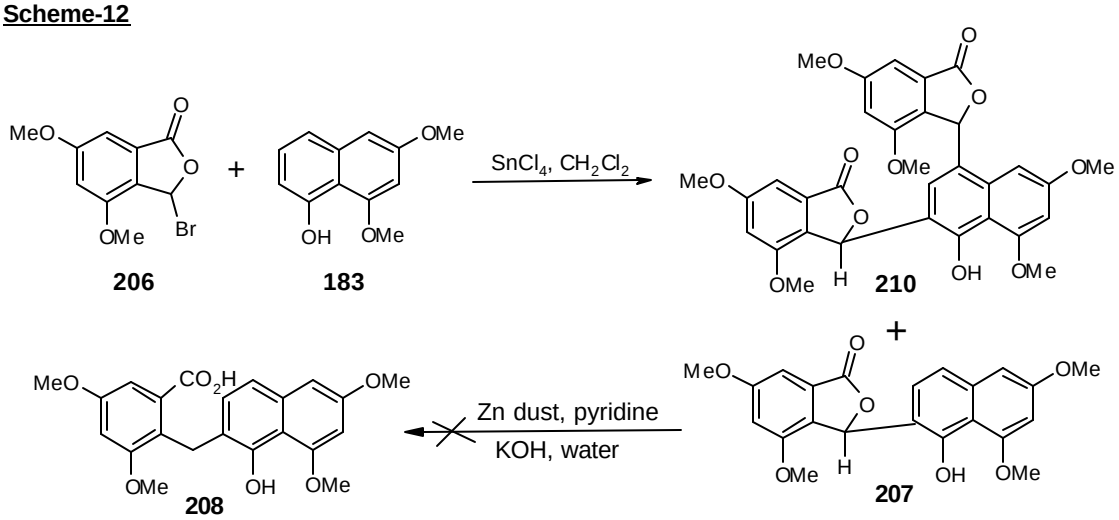
Scheme-11



When the Friedel-Crafts alkylation of 6,8-dimethoxy -1-naphthol (**183**) by bromophthalide **206** in presence of stannic chloride in methylene chloride was carried out it showed two spots on TLC. A careful chromatography of the crude mixture gave two products, which were characterized as the dialkylated naphthol **210** (9%) and the required lactone **207** (73%) as shown in scheme-12.

The ^{1}H NMR and Mass spectra confirmed the formation of **210** and lactone **207**. ^{1}H NMR

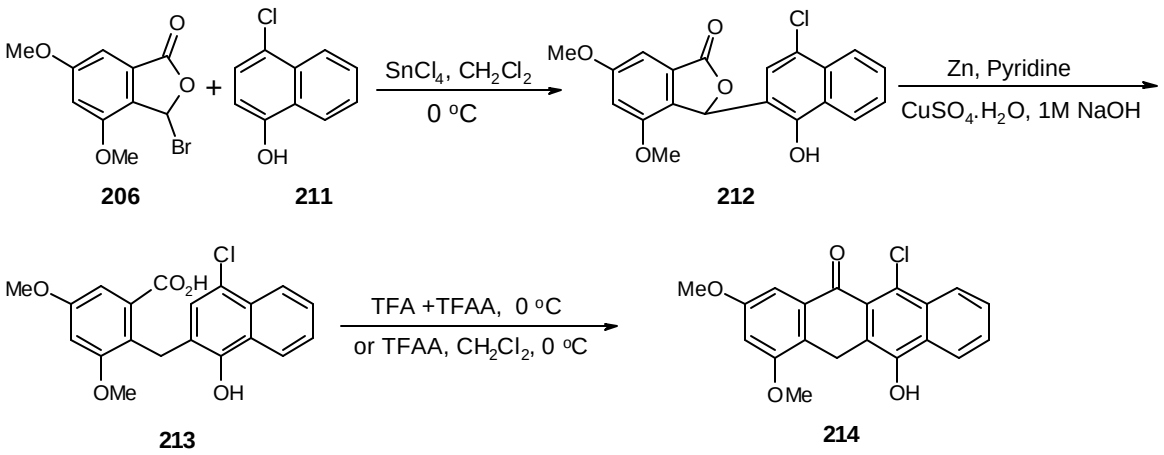
Scheme-12



spectrum of **210** indicated presence of six methoxy groups between δ 3.45-4.15 and 8 protons in aromatic region, which included 6 aromatic protons, and 2 methine protons of phthalide moiety. Its

structure was further supported by mass spectrum, which showed the molecular ion peak at m/z 588 with 80% intensity. This compound decomposed on keeping at RT so further analysis could not be done. The ^{1}H NMR spectrum of the required lactone **207** showed four methoxyl singlets at δ 3.72, 3.90, 3.95 and 4.17 each integrating for three protons. Aromatic region showed a singlet at δ 6.65 integrating for one proton which was assigned to lactone methine proton (Ar-CH-Ar), two *ortho* coupled doublets were observed, one at δ 6.77 (J = 8.0 Hz), other at δ 7.14 (J = 8.0 Hz), a multiplet appeared between δ 6.82- 7.00 integrating for total four protons and the naphthoic -OH was observed at δ 9.74. Further, the presence of molecular ion peak at m/z 396 (base peak) and other major peaks observed at 365 (M-OCH_3) and 321 (M-CO_2) were in good agreement with the assigned structure of lactone **207**. Although the required lactone **207** was prepared by alkylation of bromophthalide **206** and 6,8-dimethoxynaphthol (**183**) in satisfactory yield, the reductive cleavage of the lactone **207** failed to give the corresponding acid **208** with zinc, potassium hydroxide, pyridine, water[39]. The other alternative methods known in the literature for reductive opening of lactones involved zinc, potassium hydroxide, pyridine, cupric sulphate, water[40], acidic conditions such as zinc, formic acid, water[38], hydrgenation under acidic[42] (H_2, Pd/C, acetic acid) or basic[41] (H_2, Pd/C, methanolic potassium hydroxide) conditions. These conditions could not be tried for a want of more quantity of lactone **207**. As the 6, 8-dimethoxynaphthol (**183**) was prepared in six steps in low yield, the required lactone **207** could not be prepared in substantial quantity for further work. Also it was necessary to establish a condition to avoid the formation of unwanted dialkylated product **210**. To circumvent these problems, it was decided to employ 4-chloro-1-naphthol (**211**) to carry out a model study as shown in scheme-13.

Scheme-13



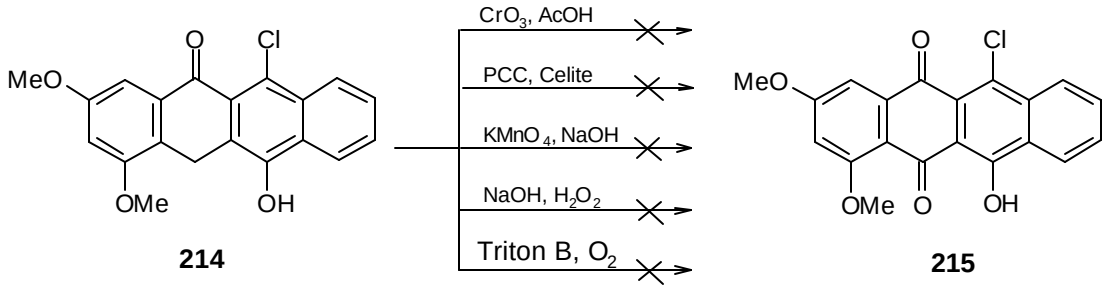
206 **211** **212** **213** **214**

Thus 4-cholro-1-naphthol (**211**) was alkylated with bromophthalide (**206**) using stannic chloride as a Lewis acid at 0 ^{o}C in dry methylene chloride for 8 hr which afforded the chloro lactone **212** in 82% yield. IR spectrum of the lactone **212** revealed the presence of hydroxyl at 3330 cm^{-1} and lactone at 1732 cm^{-1} while ^{1}H NMR spectrum showed signals as follows: 3.67 (s, 3H, -OMe), 3.87 (s, 3H, -OMe), 6.69 (s, 1H, Ar-C<u>H</u>-Ar), 6.87 (s, 1H), 6.95 (s, 1H), 6.99 (s, 1H), 7.48-7.61 (m, 3H), 8.10 (d, J = 6.0 Hz, 1H), 8.35 (d, J = 6.0 Hz, 1H). The mass spectrum of chloro lactone **212** exhibited molecular ion peak at m/z 370 and its isotopic peak at 372 with 10% and 5% intensity respectivey. It showed a base peak at 326 along with other prominent fragments at m/z 341 (15) and 339 (46), which confirmed the assigned structure **212**.

In the present work reductive cleavage of the chloro lactone **212** was smoothly effected by alkaline conditions used by Newman *et al*[40]. in 88% yield. IR spectrum of the resultant acid **213** showed a band at 3440 cm^{-1} for carboxylic acid functionality. ^{1}H NMR spectrum of the acid **213** revealed a new singlet at δ 4.37 integrating for two protons and was assigned to benzylic -CH_2, remaining protons were found at the appropriate positions. The mass spectrum of the acid **213** showed the molecular ion peak at m/z 372 (10) and its isotopic peak at 374 (3) (M + 2) indicating the presence of chlorine in the molecule. The other prominent peaks were found at 182 as a base peak, 354 (5, M-H_2O) and 319 (29, M-HCl, M-OH). Cyclisation of the above acid **213** in equal amounts of trifluoroacetic acid and trifluoroacetic anhydride resulted in the formation of chloronaphthacenone **214**. This anthrone was also obtained by reaction with excess of trifluoroacetic anhydride in methylene chloride at 0 ^{o}C followed by stirring at room temperature for 5 hr. Column chromatographic purification of the crude solid gave white crystalline solid (90.9%). Its IR spectrum showed absorption band at 1730 cm^{-1} for anthrone carbonyl group. Its ^{1}H NMR showed only six protons in aromatic region, characteristic singlet of *ortho* proton with respect to chlorine was absent. The anthrone methylene singlet was seen at δ 4.14. The mass spectrum of chloronaphthacenone **214** exhibited the molecular ion peak at m/z 354 with 42% intensity and its isotopic peak at 356 indicating the presence of chorine in the molecule. It showed a base peak at m/z 319 (M-Cl) while other prominent fragments were observed at 337 (M-OH), 295 (11), 267 (7), 233 (9) and 159 (11). Oxidation of anthrone to quinone was attempted using chromium trioxide in acetic acid[43], which could not afford the required tetracyclic quinone **215**. This oxidation was also tried under alkaline potassium permanganate conditions[32] but that also failed to give the required quinone **215**. The other

reagents tried were PCC/celite[44], $NaOH/H_2O_2$[45] and Triton B[46], which also could not give the required quinone as shown in scheme-14.

Scheme-14

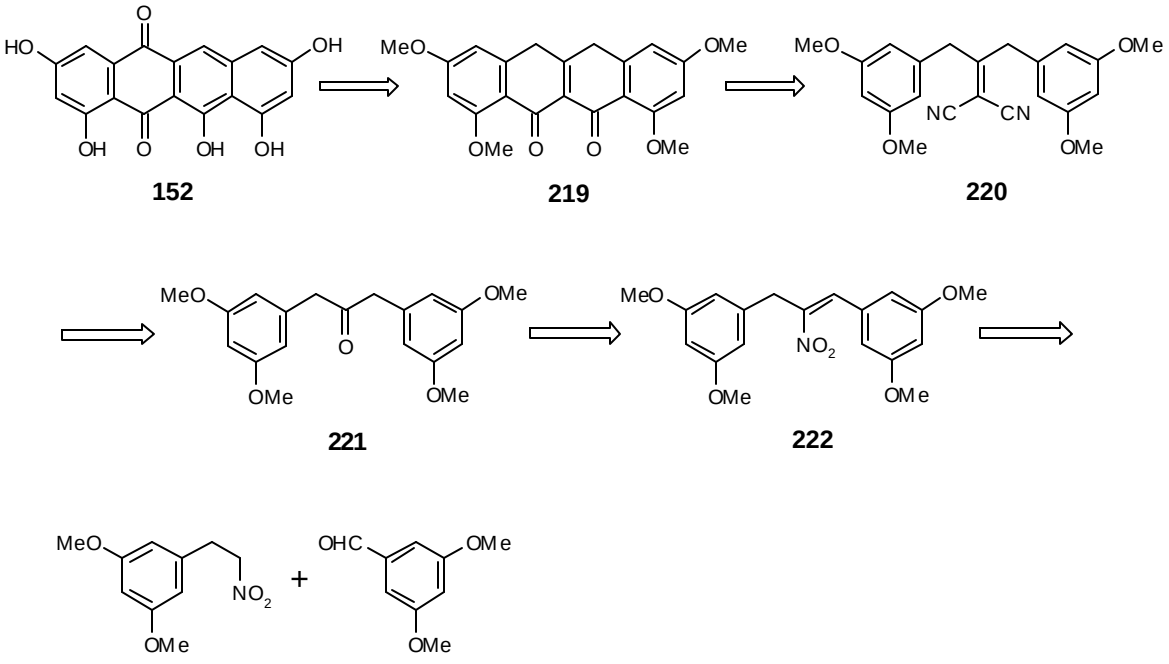


Though this model study was not successful, as the oxidation step could not be achieved, it was useful to demonstrate the utility of this approach as the lactone opening and cyclization was effected to afford the tetracyclic skeleton **214**. As the oxidation of **214** was not successful, this route was abandoned.

2.0.5 Part-II Intermolecular Nitroaldol Condensation Approach:

In the previous part we have described our attempts towards the construction of saintopin framework by Friedel-Crafts acylation and alkylation approach. It was soon realised that the problem of regiospecificity in earlier Friedel-Crafts route could be avoided by directly obtaining the diketo carbon framework **219** which could be elaborated to saintopin. The diketo carbon framework of saintopin could be obtained from 3,5-dimethoxybenzaldehyde (**197**) as shown in scheme-16. Intermolecular nitroaldol[47] reaction or Henry reaction between 3,5-dimethoxybenzaldehyde (**197**) and nitroalkane **223**, would afford substituted 1,3-diaryl-2-nitropropene **222.**

Scheme-16



152 **219** **220**

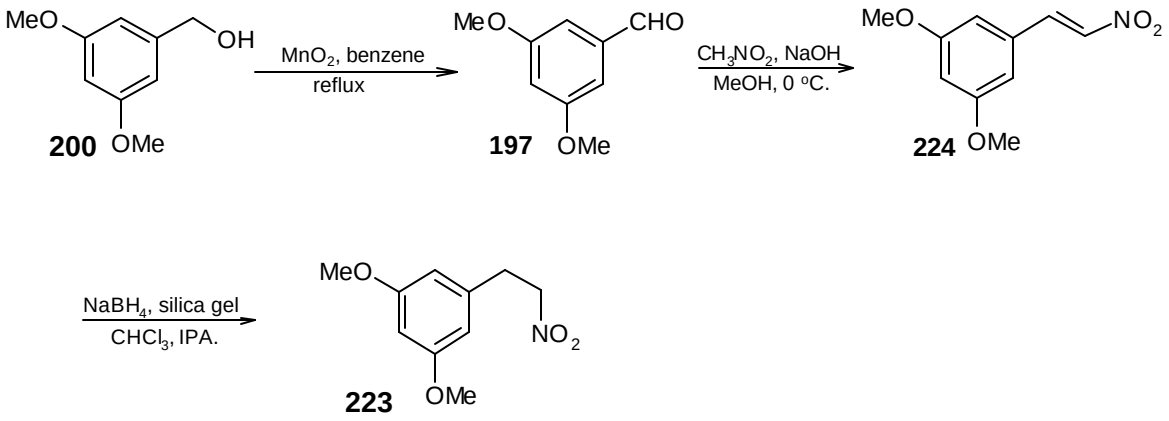
221 **222**

223 **197**

The Nef[48] reaction of **222** would give 1,3-diarylacetone **221** which could be further condensed with diethyl malonate or malononitrile under Knoevenagel conditions to obtain diketo carbon frame work **219** upon hydrolysis and cyclisation as shown in the retrosynthetic plan (scheme-16). The starting materials required for the nitroaldol condensation *viz* 3,5-dimethoxybenzaldehyde (**197**) and 1,3-dimethoxy-5-(2-nitroethyl) benzene (**223**) were prepared as shown in the scheme-17. 3,5-Dimethoxybenzaldehyde (**197**)[49a] was prepared from 3,5- dimethoxybenzyl alcohol (**200**) using

PCC[50] in methylene chloride at 0 ^{o}C or excess of manganese dioxide[51] in dry benzene at reflux, the latter method gave good yield.

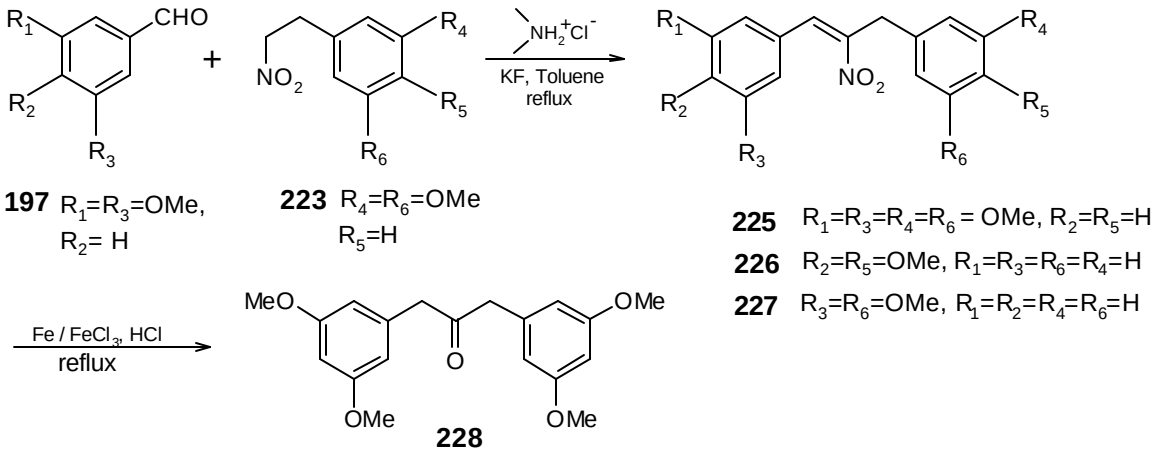
Scheme-17



The other synthon nitroethyl benzene **223** was prepared by intermolecular nitroaldol condensation between the aldehyde **197** and nitromethane in the presence of sodium hydroxide followed by reduction of the resultant nitrostyrene **224** with sodium borohydride in a biphasic system consisting of silica gel, chloroform and isopropanol[47].

The Henry or nitroaldol condensation of the above nitroalkane **223** with 3,5-dimethoxybenzaldehyde (**197**) in presence of dimethylamine hydrochloride and potassium fluoride in refluxing toluene afforded the novel nitropropene **225**, the structure of which was confirmed by spectral data. Kodukulla *et al*.[47] tested various substituted 1,3 -diaryl-2-nitropropenes against three gram positive bacteria, two gram negative bacteria and two fungi. These compounds exhibited broad-spectrum antimicrobial activity. Further study by these authors showed that methoxy, ethoxy and nitro substituents increased the activity. Results obtained above were exploited to synthesize two more novel nitropropenes **226** and **227**. Thus nitroaldol reaction on *m*-methoxybenzaldehyde and *p*-methoxybenxzaldehyde afforded the corresponding nitropropenes **226** and **227** following the same sequence of reactions as in case of **225**. The 1,3-diaryl-2-nitropropenes **225**, **226** and **227** prepared in the present work may show better antimicrobial activity.

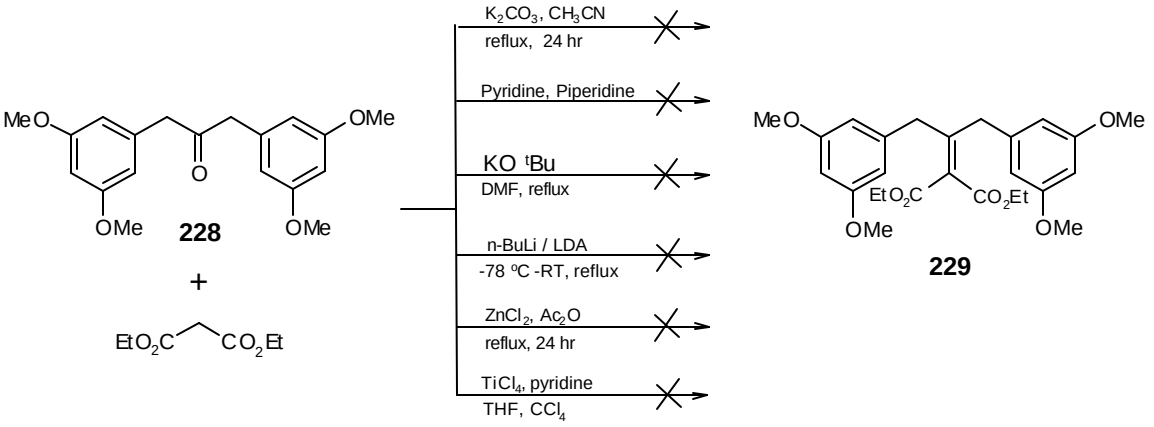
Scheme-18



Further, the 1,3-diaryl-2-nitropropene **225** was hydrolyzed to ketone **228** employing the method used by Bhide *et al*[48] by treating it with iron powder, $FeCl_3$ and 10 N HCl in ethanol at reflux for 10 hr (Nef reaction). The precipitated black iron oxide was filtered and the filtrate upon extraction with ethyl acetate gave white crystalline solid after removal of the solvent in 90 % yield. The IR spectrum of ketone **228** showed a weak absorption band at 1717 cm^{-1} indicating that the ketone group may be in enolic form. A band at 3417 cm^{-1} further supported this assumption. The ^1H NMR spectrum displayed two singlets at δ 3.63 and δ 3.76 integrating for four and twelve protons respectively, which were assigned to two benzylic methylene and four methoxyl groups. Aromatic region showed two multiplets between δ 6.24-6.31 and δ 6.33-6.38 integrating for four and two protons respectively. The ^{13}C NMR spectrum signals at δ 49.10 and δ 56.09 were assigned to methylene and methoxyl groups. The other carbon signals at δ 99.16 and δ 107.47 were assigned to aromatic methine carbons. Two quaternary carbon signals at δ 136.03 and 160.95 were assigned to C-OMe and carbonyl carbon respectively. The mass spectrum of the ketone **228** exhibited a molecular ion peak at m/z 330 with 25 % intensity. It showed a base peak at m/z 151 along with other prominent peaks at 179 (35, $COCH_2C_6H_3(OCH_3)_2$ and 121 (5, CH_2-C_6H_4- OCH_3).

In order to transform ketone **228** into the required diketo tetracyclic carbon frame **219**, Knoevenagel condensation between the ketone **228** and active methylene compound such as diethyl malonate was carried out under different conditions as shown in scheme-19.

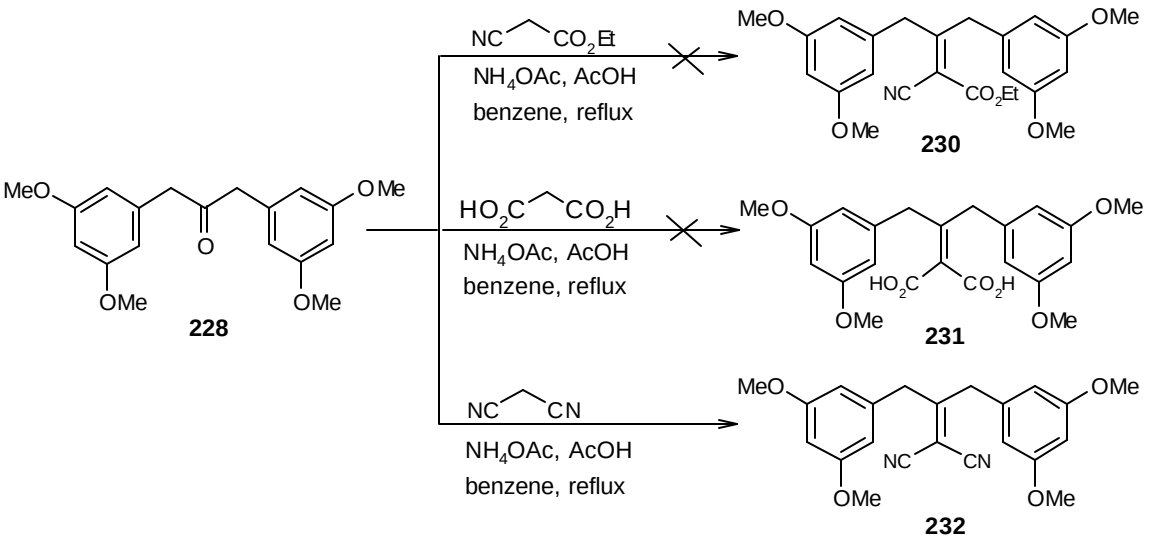
Scheme-19



Unfortunately the desired condensed product **229** could not be obtained. In most of the conditions[52] tried, either starting material was recovered or a complex mixture was obtained. The ketone **228** also failed to give the condensed products **230** and **231** with ethyl cyanoacetate[53] and malonic acid respectively using ammonium acetate and acetic acid in refluxing benzene employing Dean-Stark water separator for several hours. However, the condensation of malononitrile[54] with the ketone **228** worked well with good yield of the key intermediate dicyano compound **232**.

The failure of Knoevenagel condensation reaction to get the condensed products **229** and **230**

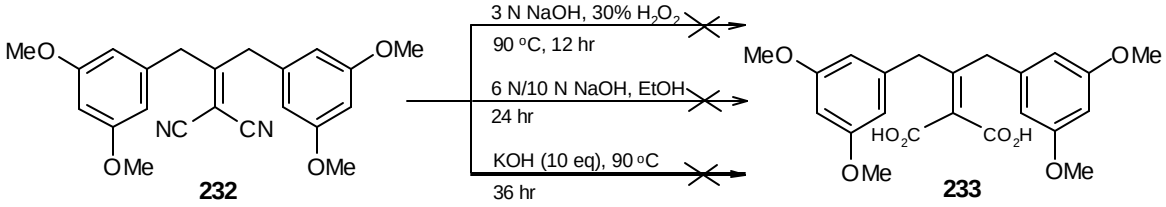
Scheme-20



was attributed to the steric hindrance of the methoxyl groups at 3 and 3' positions and the sufficient branching of the ketone **228** carbon chain, which retards or inhibits the condensation reaction[53].

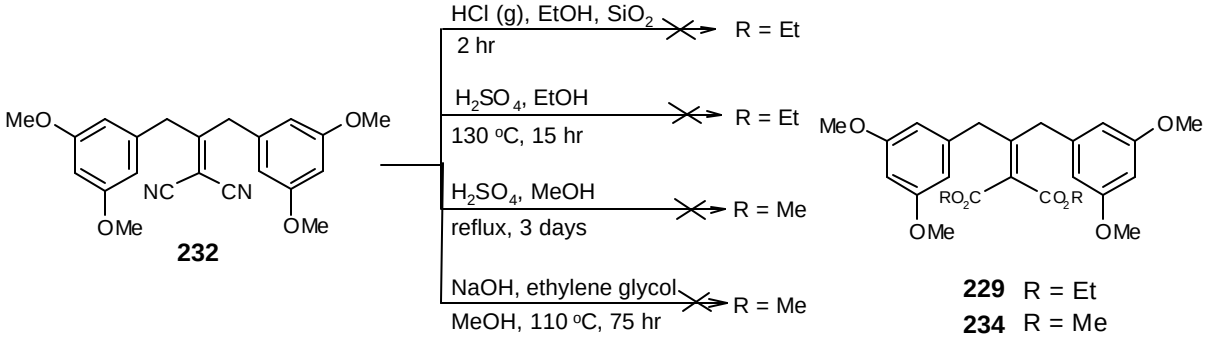
The hydrolysis of key intermediate **232** to diacid **233** or conversion into diesters **229** or **234** were attempted under the reaction conditions reported in the literature[55] as shown in scheme-21 and scheme-22.

Scheme-21



The complex reaction mixture obtained by hydrolysis could not be purified and analysed. Also, cyclisation of the impure product could not give the required tetracyclic carbon frame **219** of saintopin. It was thought to characterize the hydrolyzed product by preparing its diethyl ester **229** or dimethyl ester **234**. Accordingly the reaction conditions[56] shown in scheme-22 were tried to convert dicyano compound **232** to dimethyl or diethyl ester but none of them gave the required diester **229** or **234**. Hence this route was discontinued.

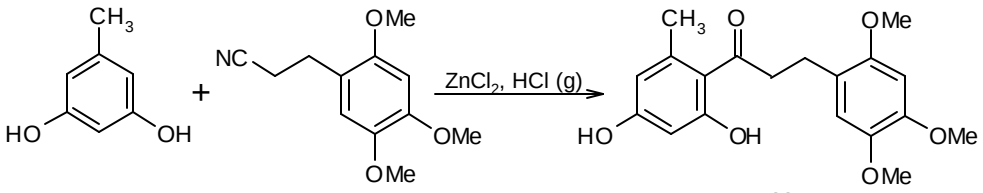
Scheme-22



2.0.6 Part-III Intramolecular Houben-Hoesh Reaction Approach:

In early years of the last century Hoesh[57] and later Houben[58] demonstrated that the acylation of phenol and phenol ethers could be achieved in good yields by reaction with an aromatic or aliphatic nitrile and dry HCl usually in the presence of Lewis acid such as $ZnCl_2$[59] or $AlCl_3$.[60] Barton *et al.*[49] applied Houben-Hoesh reaction of nitrile **236** with orcinol **235** to give dihydrochalcone **237** in the synthesis of bikaverin.

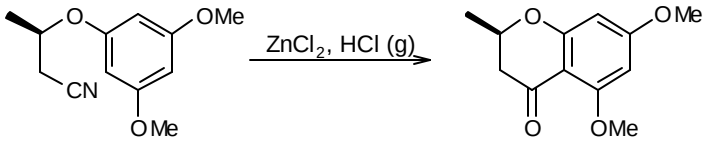
Scheme-23



235 **236** **237**

Rama Rao *et al.*[61] demonstrated the utility of inter and intramolecular Houben-Hoesh reactions for the first time in the enantioselective synthesis of both the antipodes of 5,7-dimethoxy-2-methyl chroman-4-one which is the important intermediate for the synthesis of calanolide A (scheme-24).

Scheme-24

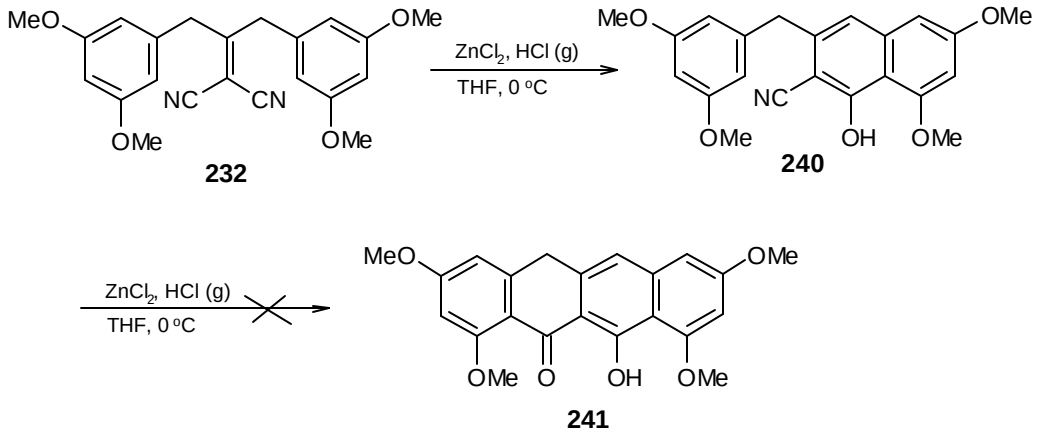


238 **239**

Based on these observations it was decided to use an intramolecular Houben-Hoesh reaction for the acylative ring closure of the key intermediate **232** for the synthesis of required diketo tetracyclic carbon frame of saintopin as shown in the scheme-25. Accordingly, dicyano compound **232** was treated with $ZnCl_2$ in anhydrous THF while dry HCl gas was bubbled in the reaction medium, which gave the cyanonaphthol **240**, which was fully characterized by spectral means. The IR spectrum showed strong bands at 2185 and 3471 cm^{-1} for the cyanide and phenolic hydroxyl functionality respectively. The ^1H NMR spectrum exhibited a singlet at δ 3.78 integrating for six

protons and was assigned to two methoxyl groups, the other two methoxyl groups appeared at δ 3.86 and 3.95. The benzylic methylene was observed at δ 4.03. The aromatic region showed a multiplet between δ 6.35-6.40 integrating for two protons, another multiplet at δ 6.45-6.54 integrating for three protons and a singlet at δ 6.63 for a single aromatic proton.

Scheme-25

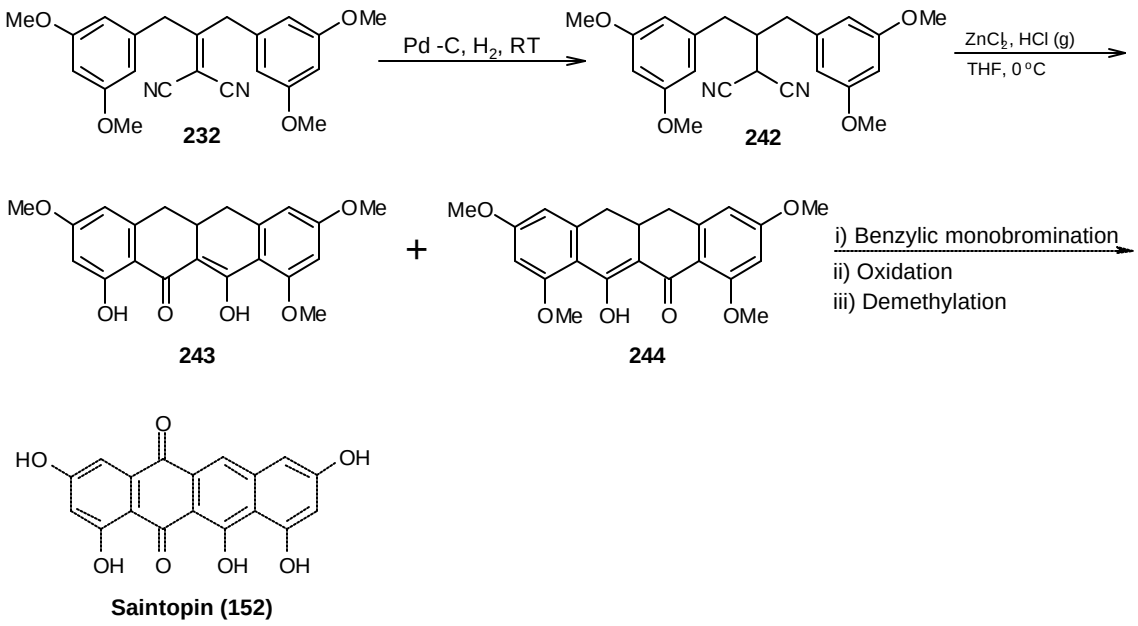


The mass spectrum showed a molecular ion peak at m/z 379 which further confirmed the assigned structure of the cyanonaphthol **240**. The cyanonaphthol **240** was again subjected to Hoesh reaction conditions for a longer time but the expected product **241** could not be obtained.

It was felt that selective reduction of double bond in dicyano compound **232** might help in the acylation reaction and thereby formation of diketo compound **220**. Accordingly reduction of double bond was effected using palladium charcoal (10%) under hydrogen atmosphere at room temperature to give reduced dicyano compound **242** (scheme-26). The IR spectrum showed a band at 2190 cm^{-1}. The ^{1}H NMR spectrum of **242** showed a multiplet between δ 2.55-2.91 integrating for five protons and was assigned to two benzylic methylene protons and a methine proton. A singlet observed at δ 3.78 integrating for twelve protons was assigned to four methoxyl groups. The methine proton of malononitrile was observed as a doublet at δ 4.24. The aromatic region showed a singlet at δ 6.30 integrating for four protons and a doublet at δ 6.38 (J= 2.0 Hz) integrating for two protons. Molecular ion peak at m/z 382 (M+ 2) further confirmed its structure. Intramolecular Houben-Hoesh reaction of the reduced cyano compound **242** employing the reaction conditions as above gave a

mixture of two products **243** in 26% and **244** in 44% yield. Compound **243** could be easily separated from compound **244** due to the considerable difference in R_f values of **243** and **244** (scheme-26).

Scheme-26



Compounds **243** and **244** were characterized by spectral means. The IR spectrum of the **243** showed absorption band at 1624 cm^{-1} for the carbonyl functionality. The ^1H NMR spectrum revealed multiplets between δ 2.58-2.80 and 2.83-3.10 for two benzylic methylenes and adjacent methine proton. Methoxyl singlets at δ 3.83, 3.84 and 3.85 were observed integrating for three protons each. A multiplet between δ 6.27-6.41 was observed as a result of merging of two *meta* coupled doublets for four aromatic protons. Two singlets at δ 8.25 and 13.63 were due to enolic hydroxyl group and a phenolic hydroxyl hydrogen bonded with the carbonyl group respectively. In addition, ^{13}C NMR analysis showed two signals at δ 35.52 and 36.81 for two benzylic methylenes and a signal at δ 188.49 for the carbonyl carbon.

The structure of **244** was also confirmed on the basis of its spectral data. The IR spectrum of this compound showed absorption band at 1646 cm^{-1} for the carbonyl functionality. ^1H NMR spectrum showed a multiplet between δ 2.52-3.12 for two benzylic methylene and a methine protons. The four methoxyl singlets were observed at δ 3.82, 3.83, 3.85 and 3.89 each integrating for three protons. The aromatic *meta* coupled doublets were observed at δ 6.29, 6.32, 6.37 (J = 2.0 Hz each) while the enolic singlet was observed at δ 8.08. ^{13}C NMR clearely showed two carbon signals

at δ 36.29 and 36.56 for benzylic methylene carbons. A carbonyl carbon was observed at δ 184.49 and the rest of the peaks were found at appropriate δ values. The mass spectrum did not show molecular ion peak. The first intense peak was found at m/z 365 (M-OH). The other intense peaks were found at m/z 352 (-OCH_3) and 334 (-OCH_3) which further supported the assigned structure of **244**.

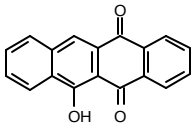
Benzylic monobromination of **243** or **244** and subsequent oxidation followed by demethylation would lead to the saintopin (**152**). Further work in this direction is in progress in our group.

2.0.7 CONCLUSION

The synthesis of saintopin was attempted by three different approaches namely Friedel-Crafts approach, nitroaldol condensation and Houben-Hoesh reaction. The Friedel-Crafts acylation suffered a problem of regioselectivity while Friedel-Crafts alkylation met with difficulties in opening of lactone ring of the required intermediate. Intermolecular nitroaldol condensation approach though unsuccessful, provided a key intermediate for Houben-Hoesh approach. The Houben-Hoesh reaction approach afforded the tetracyclic carbon frame-work of saintopin. However, total synthesis of saintopin could not be achieved.

2.0.8 EXPERIMENTAL:

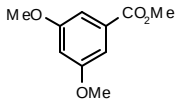
6-Hydroxynaphthacene-5, 12-dione (162):



A mixture of anhydrous aluminium chloride (17.35 g, 130 mmol) and sodium chloride (3.46 g, 59.3 mmol) was heated at 180-190 ^{o}C for 5 min. To this melt was added a mixture of phthalic anhydride (1.72 g, 11.66 mmol) and 1-naphthol (1.0 g, 6.94 mmol) and resulting mixture was stirred at 180-190 ^{o}C for 7 min. After cooling, the reaction mixture was digested with saturated oxalic acid solution on water bath for 1 hr, cooled and extracted with choloroform (4 × 50 ml). The chloroform layer was successively washed with 5% sodium bicarbonate, brine, dried and evaporated to yield **162** (0.891 g, 28.0 %) as a yellow solid; m.p.262 ^{o}C [Lit[27] m.p. 264-268 ^{o}C].

^{1}H NMR ($CDCl_3$): δ 7.60-7.90 (m, 4H), 8.00 (d, J = 8.0 Hz, 1H), 8.31 (s, 1H), 8.32-8.50 (m, 2H), 8.54 (d, J = 8.0 Hz, 1H), 14.56 (s, 1H, chelated -OH); **MS** (m/z): 274 (M^+, base peak), 246 (10), 218 (8), 189 (55), 163 (7), 113 (7) and 94 (7).

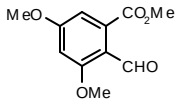
Methyl 3, 5-dimethoxybenzoate (192):



A mixture of 3,5-dihydroxybenzoic acid (20 g, 0.13 mole), potassium carbonate (62.72 g, 0.45 mole) and dimethyl sulfate (57.27 g, 44.32 ml, 0.45 mole) in dry acetone (500 ml) was stirred under reflux for 12 hours. The acetone was distilled off, to the cooled residual mixture was added water (400 ml) and extracted with ethyl acetate (3 × 100 ml). Ethyl acetate layer was washed with water several times followed by brine (50 ml), dried over Na_2SO_4, and concentrated under reduced pressure to give a crude solid, which was recrystallized in ethyl acetate-pet ether to give white needles of **192** (25.0 g, 98%); m.p. 43.8 ^{o}C (Lit m.p. 42-43 ^{o}C).

IR ($CHCl_3$): 1721, 1600, 1460, 1250, 1050 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.82 (s, 6H, 2 × OMe), 3.90 (s, 3H, CO_2Me), 6.61 (t, J = 2.0 Hz, 1H), 7.15 (d, J = 2.0 Hz, 2H); Analysis calculated for $C_{10}H_{12}O_4$: C = 61.22, H = 6.15%; Found C = 61.22, H = 6.14%.

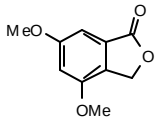
Methyl 3,5-dimethoxy-2-formylbenzoate (193):



To a complex prepared from DMF (0.447 g, 0.472 ml, 6.12 mmol) and $POCl_3$ (0.702 g, 0.426 ml, 4.59 mmol) at 0^oC was added powdered methyl 3, 5-dimethoxybenzoate (1.0 g, 5.1 mmol) at once and allowed to attain room temperature and then it was heated at 80 ^oC for 4 hr. The resulting dark red mixture was cooled and decomposed with saturated solution of sodium acetate. The aldehyde which separated out as a yellow solid was filtered, washed with water, dried and then crystallized from hexane-ethyl acetate to give aldehyde **193** (0.904 g, 80%) as a white solid; m.p. 132 ^oC [Lit[31] m.p. 134-136 ^oC].

^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H, $-CO_2Me$), 3.90 (s, 6H, 2 × OMe), 6.50-6.54 (m, 2H), 10.27 (s, 1H, -CHO); MS (m/z): 224 (M^+, 11), 209 (100), 193 (18), 165 (7), 150 (7), 135 (6) and 106 (12).

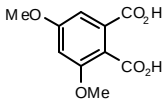
4,6-Dimethoxy-1, 3-dihydro-1-isobenzofuranone OR 4,6- Dimethoxy-3*H*-isobenzofuran-1-one (191):



To the stirred solution of aldehyde **193** (3.6 g, 16 mmol) in methanol (270 ml) under stirring was added sodium borohydride (3.76 g, 99 mmol) in lots. The mixture was stirred further for 30 minutes, methanol was distilled off and residue was acidified using 1 N HCl (50 ml), resultant solid obtained was filtered, washed with water, dried and crystallized from hexane -ethyl acetate to give the desired phthalide **191** (2.799 g, 90%) as a white solid; m.p. 167 ^oC [Lit[31] m. p. 167 ^oC].

IR ($CHCl_3$): 1761 $cm.^{-1}$; **^{1}H NMR** ($CDCl_3$): δ 3.85 (s, 3H), 3.86 (s, 3H), 5.16 (s, 2H), 6.63 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H); **MS** (m/z): 194 (M^+, 88), 165 (100), 137 (48), 122 (41) and 107 (22); Analysis calculated for $C_{10}H_{10}O_4$: C = 61.85, H = 5.18%; Found C = 61.26, H = 6.12%.

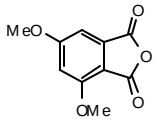
3, 5-Dimethoxyphthalic acid (194):



A solution of phthalide **191** (0.5 g, 2.57 mmol), potassium hydroxide (1.342 g, 23.9 mmol) and potassium permanganate (0.651 g, 4.12 mmol) in water (15 ml) was stirred at room temperature for 12 hr. At the end faint green colour was observed. Ethanol (5.0 ml) was added to the reaction mixture and stirred for further 30 min to destroy excess of potassium permanganate. It was then filtered, washed with water, colorless filtrate was concentrated and made distinctly acidic with 50% HCl when white turbidity appeared. NaCl was added till the solution was saturated and then it was extracted with ether to give compound **194** (0.453 g, 77.83 %) as a white solid; m.p. 152 ^{o}C [Lit[32b] m.p. 152-154 ^{o}C].

^{1}H NMR [DMSO-d_6]: δ 3.79 (s, 3H), 3.82 (s, 3H), 6.82 (s, 1H), 6.93 (s, 1H).

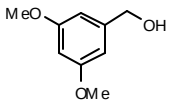
4, 6-Dimethoxy-isobenzofuran-1, 3-dione OR 4, 6-Dimethoxyphthalic anhydride (182):



3, 5-Dimethoxyphthalic acid (0.400 g, 1.76 mmol) was dissolved in acetic anhydride (5.0 ml) and heated at 140 ^{o}C for 4 hr. The excess acetic anhydride was removed by vacuum distillation, residual solid was washed with dry ether several times and dried to give anhydride **182** (0.310 g, 84.23%) as a white solid; m.p. 146.5 ^{o}C [Lit [32b] m.p. 146-147 ^{o}C].

IR ($CHCl_3$): 1841, 1769, 1626, 1590 cm.$^{-1}$; **^{1}H NMR** ($CDCl_3$): δ 3.97 (s, 3H), 4.02 (s, 3H), 6.74 (s, 1H), 7.02 (s, 1H); **^{13}C NMR** ($CDCl_3$): δ 55.54 (-OCH_3), 107.17 (aromatic), 104.16 (aromatic), 108.13 (=C quat), 133.92 (=C quat), 158.37 (-C-OMe), 158.98 (-C-OMe), 161.87 (=C=O), 167.25 (=C=O); **MS** (m/z): 208 (M^+, 60), 180 (5), 164 (100), 150 (13), 134 (40), 122 (8), 106 (94) and 91 (16); Analysis calculated for $C_{10}H_{18}O_5$: C = 57.70, H = 3.87%; Found C = 57.01, H = 3.92%.

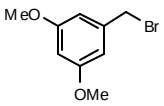
3,5 -Dimethoxybenzyl alcohol (200):



In a 100 ml round bottom flask, LAH (1.93 g, 0.05 mole) was taken under argon atmosphere and cooled to -5° C. To this was added dry THF (20 ml). To the above stirred suspension of lithium aluminium hydride, methyl 3,5-dimethoxybenzoate (**192**) (5.0 g, 0.02 mole) in THF (50 ml) was added dropwise and temperature of the reaction was not allowed to rise above 0° C. It was further stirred for 2 h at 0° C and for another one hour at room temperature. Ice water (2 ml) was then added carefully drop by drop followed by 15% KOH (2 ml) and stirred to decompose excess of lithium aluminium hydride. White solid suspension thus obtained was filtered through sintered glass funnel, washed with $CHCl_3$ (30 ml), combined filtrate was washed with brine (20 ml), dried over Na_2SO_4 and concentrated on rotary evaporator to give **200** as a white solid (4.1 g, 95.68%); m. p. 43 °C [Lit[33d] m.p. 43-45 °C].

IR ($CHCl_3$): 3416, 1599 $cm.^{-1}$; **^{1}H NMR** ($CDCl_3$): δ 2.52 (bs, 1H), 3.76 (s, 6H), 4.56 (s, 2H), 6.34 (t, J = 2.0 Hz, 1H), 6.46 (d, J = 2.0 Hz, 2H); Analysis calculated for $C_9H_{12}O_3$: C = 64.27, H = 7.18%; Found C = 64.61, H = 7.21%.

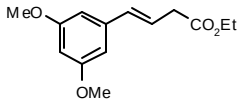
3,5-Dimethoxybenzylbromide OR 1-Bromomethyl-3, 5-dimethoxybenzene (201):



To the stirred solution of 3, 5-dimethoxybenzyl alcohol (**200**) (12.67 g, 75.4 mmol) in dry CCl_4 (130 ml) under argon atmosphere was added PBr_3 (10.213 g, 3.58 ml, 37.7 mmol) dropwise while reaction mixture was cooled externally at 0 °C. The stirring was continued for 2 hr and then it was quenched with water at 0 °C and extracted with CCl_4, washed with 10% $NaHCO_3$ solution (50 ml), brine (50 ml) and dried over sodium sulfate to give the crude solid. It was chromatographed using pet ether and acetone as eluent (95:05) to give **201** as white crystals (18.66 g, 91.30%); m.p. 69 °C [Lit[33e] m.p. 69-70 °C].

^{1}H NMR ($CDCl_3$): δ 3.81 (s, 6H), 4.43 (s, 2H), 6.34-6.43 (m, 1H), 6.53 (d, J = 2.0 Hz, 2H); **MS** (m/z): 230 (M^+, 28), 232 (M^+, 23), 151 (100), 136 (3), 121 (3) and 91 (6); Analysis calculated for $C_9H_{11}O_2Br$: C= 46.78, H = 4.80, Br = 34.57%; Found C = 47.00, H = 5.20, Br = 34.02%.

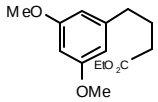
Ethyl 4-(3, 5- dimethoxyphenyl)-2-butenoate (202):



A mixture of 1-bromomethyl-3,5-dimethoxybenzene (**201**) (3.0 g, 0.13 mmol), $Pd(OAc)_2$ (0.029 g, 0.13 mmol), tri-n-butylamine (6.0 g, 7.71 ml, 32 mmol) and ethyl acrylate (2.6 g, 2.81 ml, 26 mmol) was heated at 100 ^oC for 10 hr. The reaction mixture was cooled and poured in water and extracted with ethyl acetate. The ethyl acetate layer was washed with 1 N HCl followed by water, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel using pet ether-acetone (95:05) to give **202** as a pale brown viscous oil (2.77 g, 85%).

IR ($CHCl_3$): 1728, 1595 $cm.^{-1}$; **^{1}H NMR** ($CDCl_3$): δ 1.31 (t, J = 6.0 Hz, 3H), 3.23 (d, J= 6.0 Hz, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 4.19 (q, J = 6.0 Hz, 2H), 6.20-6.60 (m, 5H); **^{13}C NMR** ($CDCl_3$): δ13.93, 37.97, 54.85, 60.32, 99.62, 104.10, 106.82, 122.00, 134.14, 138.54, 160.60, 169.16 and 170.93; **MS** (m/z): 250 (M^+, 75), 221 (7), 205 (10), 177 (100), 161 (37), 121 (35) and 91 (40).

Ethyl 4-(3,5-dimethoxyphenyl) butanoate (203):

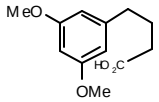


Ethyl 4-(3, 5-dimethoxyphenyl)-2-butenoate (**202**) (0.80 g, 3.2 mmol) was dissolved in distilled ethanol (15 ml), and platinum (IV) oxide (0.007g, 0.03 mmol) was added to it. The reaction flask was flushed well several times with hydrogen and the turbid brown solution was stirred under hydrogen atmosphere at room temperature for 1 hr. The catalyst was filtered off through celite bed and the filtrate was concentrated on rotary evaporator to give **203** as colorless oil (0.789 g, 97.76%).

IR ($CHCl_3$): 1722 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 1.24 (t, J = 6.0 Hz, 3H), 1.92 (quintet, J= 6.0 Hz, 2H), 2.29 (t, J = 6.0 Hz, 2H), 2.57 (t, J = 6.0 Hz, 2H), 3.75 (s, 6H), 4.11 (q, J = 6.0 Hz, 2H), 6.15-6.55 (m,

3H); **^{13}C NMR** ($CDCl_3$): δ14.25, 26.31, 33.66, 35.46, 56.24, 60.21, 98.09, 106.67, 143.87, 160.90 and 173.44.

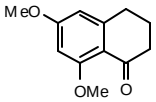
4-(3,5-Dimethoxyphenyl)butanoic acid (204):



Ethyl 4-(3,5-dimethoxyphenyl) butanoate **203** (0.789 g, 3.12 mmol) was dissolved in distilled ethanol (10 ml) and 10% NaOH (5 ml) was added to it. It was stirred for 6 hr at room temperature, ethanol was distilled off from the reaction mixture and diluted with water (20 ml). It was extracted with CH_2Cl_2 (10 ml) to get rid off the organic impurities. The aqueous part was acidified with 10 N HCl, extracted with ethyl acetate, washed with brine (20 ml) and dried over Na_2SO_4 to give the desired acid **204** (0.66 g, 95.14%) as white solid; m.p. 60.5 ^{o}C [lit[33b] m.p. 61-62 ^{o}C].

IR ($CHCl_3$)**:** 3438, 1711, 1597 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 1.97 (quintet, J = 6.0 Hz, 2H), 2.40 (t, J= 6.0 Hz, 2H), 2.63 (t, J = 6.0 Hz, 2H), 3.79 (s, 6H), 6.25-6.45 (m, 3H); **^{13}C NMR** ($CDCl_3$): δ25.85, 33.14, 35.13, 54.93, 55.24, 97.97, 106.42, 143.35, 160.50, 160.72 and 179.39.

6, 8-Dimethoxy-1-tetralone (205):

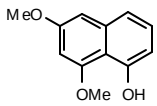


To the 4-(3,5-dimethoxyphenyl) butanoic acid **204** (0.66g, 2.9 mmol) was added trifluoroacetic acid (8 ml) at 0 ^{o}C under nitrogen atmosphere and stirred for 15 minutes. Trifluoroacetic anhydride (8 ml) was then added dropwise and stirring continued at 0 ^{o}C for 2 hr. It was then stirred at room temperature for 10 hr. The reaction mixture was poured on crushed ice and extracted with chloroform (2 × 20 ml). The chloroform layer was washed with water, brine and dried over sodium sulfate. Evaporation of the solvent gave tetralone **205** (0.52g, 84.96%) as a pale brown solid; m. p. 182.9 ^{o}C.

IR ($CHCl_3$)**:** 1689, 1598 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 1.99 (quintet, J = 7.0 Hz, 2H), 2.54 (t, J= 7.0 Hz, 2H), 2.84 (t, J = 7.0 Hz, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 6.23-6.34 (m, 2H); **^{13}C NMR** ($CDCl_3$): δ22.56, 31.27, 40.43, 54.98, 55.50, 96.89, 104.38, 116.07, 148.79, 162.31 163.53, 195.29; **MS** (m/z):

206 (M^+, 87), 189 (15), 178 (100), 160 (20), 149 (41) and 120 (35); Analysis calculated for $C_{12}H_{14}O_3$: C = 69.88, H = 6.83 %; Found C = 69.22, H = 6.53%.

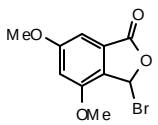
6, 8-Dimethoxy-1-naphthol (183):



6, 8-Dimethoxy-1-tetralone (**205**) (1.05 g, 5.12 mmol) in dry CCl_4 (20 ml) was stirred under argon atmosphere and bromine (0.809 g, 5.12 mmol) in CCl_4 (3.2 ml) was added dropwise (each drop was added after the previous drop was completely decolorized) at room temperature. The reaction mixture was exposed to 500 W electric bulb for 30 minutes, cooled and water (20 ml) was added to it. It was then extracted with CCl_4, washed with water, 10 % $NaHCO_3$ solution followed by brine, dried over sodium sulfate and concentrated to give 2-bromo-6, 8-dimethoxy-1, 2, 3, 4-tetrahydronaphthalene-1-one (1.386 g) as a brown oil which was used as such for further reaction. The above brown colored oil was dissolved in anhydrous DMF (10.0 ml) under nitrogen, lithium carbonate (1.798 g, 26.8 mmol) was added at once and the resulting mixture was stirred at 70 ^oC for 12 hr. Water (10 ml) was then added and the mixture was acidified with HCl, extracted with ether, washed with water, dried over sodium sulfate and concentrated to give crude 6,8-dimethoxy-1-naphthol, which was purified by column chromatography using 5% acetone in pet ether as an eluent to give **183** (0.16 g, 15.53%) as a white solid; m.p.82 ^oC [Lit[34] m.p. 84 ^oC].

IR (Nujol)**:** 3360 cm^{-1}**;** ^{1}**H NMR** ($CDCl_3$): δ 3.90 (s, 3H), 4.05 (s, 3H), 6.45 (s, 1H), 6.66-6.86 (m, 2H), 7.06-7.45 (m, 2H), 9.06 (s, 1H); **MS** (m/z): 204 (M^+, 87), 196 (100), 138 (31), 122 (28), 107 (26) and 92 (22).

3-Bromo-4, 6-dimethoxy-1,3-dihydro-1-isobenzofuranone (206):

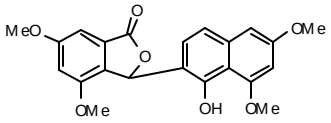


A mixture of 4, 6-dimethoxy-1, 3-dihydro-1-isobenzofuranone (**191**) (0.100 g, 0.5 mmol), N-bromosuccinimide (0.092 g, 0.5 mmol) and a pinch of benzoyl peroxide in dry CCl_4 (10 ml) was exposed to 500 W electric bulb and stirred magnetically. The reaction was continued for 1.5 hr after

the solution started refluxing. It was then cooled, succinimide was filtered and filtrate concentrated at reduced pressure to give a yellow solid, which was recrystallised from benzene-hexane (0.120 g, 86.42%); m.p. 255 ^{o}C.

IR ($CHCl_3$)**:** 1761 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.90 (s, 3H), 3.96 (s, 3H), 6.71 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 7.25 (s, 1H); **MS** (m/z): 272 (M^+, 4), 274 (2), 243 (4), 224 (10), 210 (85), 193 (56), 165 (100), 135 (50), 106 (46) and 91 (23).

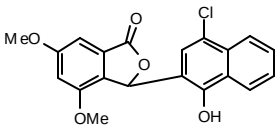
3-(1-Hydroxy-6,8-dimethoxynaphthalen-2-yl)-4,6-dimethoxy-3*H*-isobenzofuran-1-one (207):



A solution of bromophthalide **206** (0.186 g, 1.3 mmol) and 6,8-dimethoxy-1-naphthol (**183**) (0.140 g, 1.3 mmol) in dry dichloromethane (10 ml) was cooled to -5 ^{o}C. Stannic chloride (1.36 g, 0.650 ml, 10.07 mmol) was then injected dropwise through a syringe and the resulting mixture was stirred for 3 hr. It was then poured onto the mixture of crushed ice and conc HCl, stirred for 30 min and extracted with dichloromethane. The combined dichloromethane layer was washed with water, brine and dried over sodium sulfate. Evaporation of the solvent and purification by column chromatography afforded compound **207** (0.197 g, 73 %) as a white solid; m.p. 228.5 ^{o}C and 2, 4-bis [3'-(4', 6'-dimethoxy-3'H-isobenzofuran-1-onyl)-6,8-dimethoxynaphthalen-1-ol **(210)** as a white solid (0.036 g, 9.0 %); m.p. 241 ^{o}C.

Compound **207: IR** ($CHCl_3$): 1726 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.72 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 4.17 (s, 3H), 6.65 (s, 1H), 6.77 (d, J = 8 Hz, 1H), 6.82-7.00 (m, 4H), 7.14 (d, J = 8.0 Hz, 1H); **MS** (m/z): 396 (M^+, 100), 365 (20), 351 (25), 335 (40), 321 (40), 306 (17), 263 (10), 231 (12), 164 (35), 139 (20) and 106 (22).

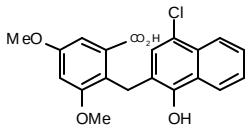
3-(4-Chloro-1-hydroxy-2-naphthalenyl)-4,6-dimethoxy-3*H*-isobenzofuran-1-one (212):



The procedure for the synthesis of **212** was similar to the synthesis of **207**. The quantities of reactants and reagents were as follows: bromophthalide **206** (0.950 g, 3.49 mmol), 4-chloro-1-naphthol **211** (0.621 g, 3.49 mmol)) and stannic chloride (6.63 g, 3.0 ml, 7.7 mmol). Crude solid was purified by column chromatography, which afforded **212** as a white solid (1.05 g, 70%); m.p. 189 ^{o}C.

IR ($CHCl_3$): 1732 (-C=O), 3330 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.67 (s, 3H), 3.87 (s, 3H), 6.69 (s, 1H), 6.87 (s, 1H), 6.95 (s, 1H), 6.99 (s, 1H), 7.48-7.61 (m, 3H), 8.10 (d, J = 6.0 Hz, 1H), 8.35 (d, J = 6.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$ + Acetone d_6): δ 54.81, 74.71, 98.18, 104.25, 116.89, 121.92, 123.30, 125.43, 126.00, 126.99, 127.54, 128.94, 130.65, 149.61, 154.43, 162.36 and 182.08; **MS** (m/z): 372 (M^+, 5), 370 (M^+, 10), 341 (15), 339 (46), 328 (34), 326 (100), 310 (7), 281 (5) and 252 (2).

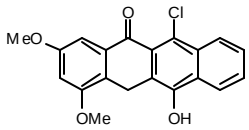
2-(4-Chloro-1-hydroxynaphthalen-2-ylmethyl)-3,5-dimethoxybenzoic acid (213):



The lactone **212** (1.6 g, 4.32 mmol) was reductively opened by heating with 1M solution of KOH (60 ml), activated zinc (8.432 g, 129.72 mmol), $CuSO_4.5H_2O$ (0.345 g, 1.38 mmol) and pyridine (6.832 g, 7.4 ml, 86.48 mmol) at 125 ^{o}C for 10 hrs under nitrogen atmosphere. After completion of the reaction (TLC) the reaction mixture was allowed to cool and filtered through a pad of celite. Acidification of the filtrate with concentrated HCl afforded the corresponding acid **213** (1.4 g, 80%) as a white solid; m. p. 209 ^{o}C.

IR ($CHCl_3$): 1679 (-C=O), 3440 (-CO_2H) cm^{-1}. **^{1}H NMR** ($CDCl_3$): δ 3.85 (s, 3H), 3.87 (s, 3H), 4.37 (s, 2H), 6.81 (d, J = 2.0 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 7.45-7.67 (m, 3H), 8.07 (d, J = 6.0 Hz, 1H), 8.29 (d, J = 6.0 Hz, 1H); **^{13}C NMR** (Acetone d_6): δ 55.59, 55.96, 103.29, 106.86, 120.23, 120.98, 122.24, 123.25, 123.86, 125.00, 126.76, 130.55, 130.76, 131.40, 150.11, 159.54, 159.90 and 171.87; **MS** (m/z): 374 (M^+, 3), 372 (M^+, 10), 354 (5), 319 (29), 291 (2), 182 (100), 109 (20) and 83 (42); Analysis calculated for $C_{20}H_{17}Cl\ O_5$: C= 64.43, H = 4.59, Cl = 9.52%; Found C = 64.11, H = 4.76, Cl = 9.85%.

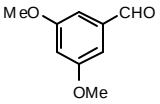
6-Chloro-11-hydroxy-1, 3-dimethoxy-12*H*-naphthacen-5-one (214):



The acid **213** (1.4 g, 3.76 mmol) was stirred with trifluoroacetic acid (6.0 ml) and trifluoroacetic anhydride (6.0 ml) at 0 ^{o}C under nitrogen atmosphere for 5 min and then at room temperature for 5 hr. It was then poured into ice-water and extracted with chloroform. Chloroform layer was washed with 5% $NaHCO_3$ solution, brine and dried over sodium sulfate. Evaporation of the solvent under reduced pressure and purification of the crude product by column chromatography gave chloronaphthacenone **214** (1.21 g, 90. 97%) as a white crystalline solid; m.p. 169.9 ^{o}C.

IR ($CHCl_3$): 1730 cm^{-1} (-C=O); **^{1}H NMR** ($CDCl_3$): δ 3.79 (s, 3H), 3.89 (s, 3H), 4.14 (s, 2H), 6.61 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 2.0 Hz, 1H), 7.51(s, 1H), 7.55-7.65 (m, 2H), 8.15-8.20 (m, 1H), 8.32-8.40 (m, 1H); **^{13}C NMR** ($CDCl_3$): δ 26.61, 55.51, 56.16, 103.86, 106.88, 122.20, 124.00, 124.82, 125.89, 127.20, 127.39, 128.00, 129.34, 129.52, 130.35, 145.33, 155.74, 159.40 and 165.20; **MS** (m/z): 354 (M^+, 42), 356 (M^+, 16), 339 (10), 337 (20), 323 (13), 319 (100), 295 (11), 267 (7), 233 (9), 199 (18) and 159 (11); **Analysis calculated for** $C_{20}H_{15}ClO_4$: C = 70.90, H = 4.45, Cl = 10.46 %; Found, C = 70.42, H = 4.10, Cl = 10.81%.

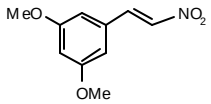
3, 5-Dimethoxybenzaldehyde (197):



3, 5- Dimethoxybenzyl alcohol (4.216 g, 0.025 mole) was dissolved in dry benzene (20 ml) under argon and MnO_2 (17.5 g, 0.2012 mole) was added at once. It was then refluxed for 15 hr after which the reaction mixture was cooled, filtered through a celite bed and filtrate concentrated under reduced pressure to give the desired aldehyde **197** (4.080 g, 97.95%); m.p. 45.9 ^{o}C [Lit[49a] m.p. 43 ^{o}C].

^{1}H NMR ($CDCl_3$): δ 3.85 (s, 6H), 6.64-6.71 (m, 1H), 6.99 (d, J = 2.0 Hz, 2H), 9.90 (s, 1H).

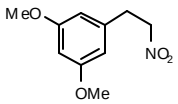
1,3-Dimethoxy-5- [2-nitro-1-ethenyl] benzene OR 1,3-Dimethoxy-5-(2-nitrovinyl)-benzene (224):



A mixture of nitromethane (3.67 g, 0.06 mole) and 3, 5-dimethoxybenzaldehyde (**197**) (10.0 g, 0.06 mole) in methanol (150 ml) was stirred at 0 ^{o}C and an aqueous solution of sodium hydroxide (2.88 g, 0.07 mole) was added over a period of 30 minutes. The stirring was continued for another half an hour in the temperature range of 0-5^{o} C. The mixture was then diluted with water (100 ml) and poured over crushed ice containing 25 ml conc HCl. The yellow solid which precipitated out was filtered, dried in a vacuum desiccator and recrystallised from ethanol to afford **224** (11.67 g, 92%); m. p. 129.8 ^{o}C.

^{1}H NMR ($CDCl_3$): δ 3.83 (s, 6H), 6.48-6.58 (m, 1H), 6.65 (d, J = 2.0 Hz, 2H), 7.53 (d, J = 14.0 Hz, 1H), 7.91 (d, J = 14.0 Hz, 1H); **^{13}C NMR** ($CDCl_3$): δ 55.46 (-O<u>C</u>H$_3$), 104.16 (aromatic), 106.99 (aromatic), 131.77 (aromatic), 137.50 (-<u>C</u>H=CH-NO$_2$), 139.05 (-CH=<u>C</u>H-NO$_2$), 161.32 (2-<u>C</u>-OMe); **MS** (m/z): 209 (M^+, 100), 178 (8), 162 (38), 148 (25), 133 (25), 119 (21), 105 (23) and 91 (33); **Analysis calculated for** $C_{10}H_{11}NO_4$: C = 57.41, H = 5.29, N = 6.69 %; Found, C = 57.68, H = 5.37, N = 6.65%.

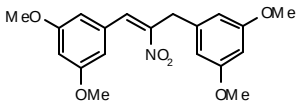
1, 3 Dimethoxy-5-(2-nitroethyl) benzene (223):



To an efficiently stirred mixture of nitrostyrene **224** (5.775 g, 0.0276 mole), silica gel (52.72 g), 2-propanol (50 ml) and chloroform (400 ml), was added sodium borohydride (4.36 g, 0.1153 mole) over a period of 15 min at 25 ^{o}C (disappearance of yellow colour). The excess borohydride was decomposed with dilute HCl followed by the washing of the silica gel cake with methylene chloride. The resultant solution was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the 2-aryl-1-nitroethane **223** (5.2 g, 89.19%) as a colorless oil.

^{1}H NMR ($CDCl_3$): δ 3.25 (t, J = 8.0 Hz, 2H), 3.78 (s, 6H), 4.58 (t, J = 8.0 Hz, 2H), 6.34 (s, 3H); **^{13}C NMR** ($CDCl_3$): δ 33.44, 55.02, 75.82, 99.05, 106.52, 137.83, 159.63, 161.10; **Analysis calculated for** $C_{10}H_{13}NO_4$: C=56.86, H = 6.19, N = 6.63%; Found, C =57.48, H = 6.76, N = 7.66%.

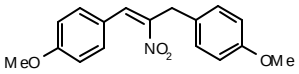
1-[3-(3, 5 Dimethoxyphenyl)-2-nitro-1-propenyl]-3, 5-dimethoxybenzene (**225**):



2-(3,5-Dimethoxyphenyl)-1-nitroethane (3.8 g, 0.018 mole), dimethylamine hydrochloride (3.66 g, 0.045 mole), 3,5-dimethoxybenzaldehyde (**197**) (2.98 g, 0.018mole), toluene (50 ml) and potassium fluoride (0.835 g, 0.0144 mole) were taken in a 100 ml RB flask fitted with a Dean-Stark water separator and the mixture was refluxed for 10 hr. The solvent was removed to give crude product. Chloroform (35 ml) and 0.2 N HCl (20 ml) were added to the crude material and the solution was heated on a water bath at 60 ^oC for 2 min. The chloroform layer was separated and the aqueous layer was extracted with chloroform. The combined chloroform layer was washed with water, followed by brine, dried over Na_2SO_4 and concentrated on rotary evaporator to give **225** as a yellow solid (4.912 g, 76.27%); m.p. 97.4 ^oC.

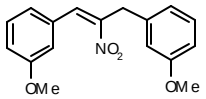
IR ($CHCl_3$): 1596, 1325, 864 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.72 (s, 6H), 3.76 (s, 6H), 4.21 (s, 2H), 6.36 (s, 3H), 6.51 (d, J = 2.0 Hz, 1H), 6.57 (d, J = 2.0 Hz, 2H), 8.23 (s, 1H); **^{13}C NMR** ($CDCl_3$): δ 33.11, 55.06, 55.17, 98.61, 102.51, 105.71, 107.40, 133.64, 135.44, 138.64, 149.71, 160.99 and 161.14; **MS** (m/z): 359 (M^+ 31), 342 (21), 325 (6), 313 (40), 297 (7), 282 (5), 267 (4), 237 (3), 175 (100) and 145 (30); Analysis calculated for $C_{19}H_{21}NO_6$: C = 63.50, H = 5.88, N = 3.89%; Found C = 63.66, H = 6.07, N = 3.88%.

1-[3-(4-Methoxyphenyl)-2-nitro-1-propenyl]-4-methoxybenzene (226):



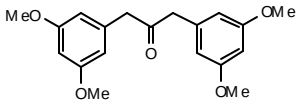
Yellow solid, m.p. 75 ^{o}C ; **^{1}H NMR** ($CDCl_3$): δ 3.79 (s, 3H), 3.84 (s, 3H), 4.23 (s, 2H), 6.86 (d, J = 6.0 Hz, 2H), 6.92 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 6.0 Hz, 2H), 7.43 (d, J = 6.0 Hz, 2H), 8.23 (s, 1H); **MS** (m/z): 299 (M^+, 68), 282 (45), 252 (100), 237 (75), 209 (25), 194 (18), 165 (30), 145 (60), 121 (42) and 91 (25).

1-[3-(3-Methoxyphenyl)-2-nitro-1-propenyl]-3-methoxybenzene (227):



Yellow solid, m.p. 72 ^{o}C ; **^{1}H NMR** ($CDCl_3$): δ 3.72 (s, 3H), 3.79 (s, 3H), 4.25 (s, 2H), 6.67-6.86 (m, 3H), 6.91-7.10 (m, 3H), 7.17-7.45 (m, 2H), 8.27 (s, 1H); **MS** (m/z): 299 (M^+, 72), 282 (45), 252 (100), 237 (75), 221 (20), 194 (10), 178 (22), 145 (60), 121 (45).

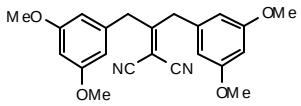
1,3-Bis (3,5-dimethoxyphenyl) acetone OR 1,3-Bis-(3,5-dimethoxyphenyl)-propan-2-one (228):



The compound **225** (4.912 g, 0.0136 mole) was dissolved in ethanol (60 ml) and hot water (60 ml). Iron powder (5.859 g, 0.104 mole) and ferric chloride (0.217 g, 0.00134 mole) were added at once followed by a dropwise addition of 10 N HCl (7.0 ml). The mixture was heated at reflux with stirring for 8 hr. It was then concentrated to half volume; the precipitated black iron oxide was filtered and washed with hot water and ethyl acetate. The combined washings were extracted with ethyl acetate, washed with brine, dried over sodium sulfate and concentrated on rotary evaporator to give **228** as a white solid (4.08 g, 90.36%); m.p. 102 ^{o}C.

IR ($CHCl_3$): 1717 (-C=O), 3417 cm^{-1} (enolic -OH); **^{1}H NMR** ($CDCl_3$): δ 3.63 (s, 4H), 3.76 (s, 12H), 6.24-6.31 (m, 4H), 6.33-6.38 (m, 2H); **^{13}C NMR** ($CDCl_3$): δ 49.10, 55.09, 99.16, 107.47, 136.03, 160.95; **MS** (m/z): 330 (M^+, 25), 179 (35), 151 (100), 121 (5); Analysis calculated for $C_{19}H_{22}O_5$:C = 69.07, H = 6.70%; Found C = 69.47, H = 6.27%.

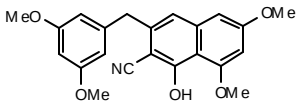
2-[1-(3,5-Dimethoxybenzyl)-2-(3',5'-dimethoxyphenyl) ethylidene] malononitrile (232):



A mixture of 1,3-bis-(3,5-dimethoxyphenyl)-acetone (**228**), (3.07 g, 0.0093 mole), malononitrile (0.927 g, 0.01395 mole), ammonium acetate (1.80 g, 0.02325 mole) and glacial acetic acid (11.16 g, 0.1860 mole) in dry benzene (50 ml) was refluxed with constant stirring for 2 days. The water formed during reaction was removed azeotropically. It was then cooled, washed with water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over sodium sulfate and concentrated to give a white solid (3.107 g, 88.36%); m. p. 120 ^{o}C.

IR ($CHCl_3$): 2232 cm^{-1} (-CN); **^{1}H NMR** ($CDCl_3$): δ 3.71 (s, 4H), 3.80 (s, 12H), 6.28 (d, J = 2.0 Hz, 4H), 6.34-6.44 (m, 2H); **^{13}C NMR** ($CDCl_3$): δ 40.22, 54.96, 99.32, 106.89, 117.75, 136.15, 161.15, 179.79; **MS** (m/z): 378 (M^+, base peak), 363 (15), 347 (12), 332 (10), 239 (10), 225 (10), 175 (30), 151 (75), 121 (35); Analysis calculated for $C_{22}H_{22}N_2O_4$: C = 69.83, H = 5.85, N = 7.40%; Found C = 70.48, H = 6.25, N = 7.25%.

3-(3,5-Dimethoxybenzyl)-1-hydroxy-6, 8-dimethoxynaphthalene-2-carbonitrile (240):

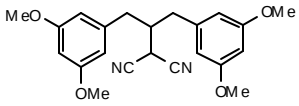


The malononitrile **232** (0.300 g, 0.793 mmol) in anhydrous THF (10 ml) at 0 ^{o}C containing anhydrous zinc chloride (0.540 g, 3.96 mmol) was treated with hydrogen chloride gas for 10 hr. The precipitare formed was filtered and dissolved in boiling water (20 ml). The mixture was heated at reflux for 2 hr, then cooled and extracted with chloroform (2 × 20 ml), washed with brine and dried over sodium sulfate. Evaporation of the solvent and purification by column chromatography gave **240** (0.258 g, 86%) as a buff colored solid; m. p. 186.3 ^{o}C.

IR ($CHCl_3$): 2185 (-CN), 3471 cm^{-1} (-OH); **^{1}H NMR** ($CDCl_3$): δ 3.78 (s, 6H), 3.86 (s, 3H), 3.95 (s, 3H), 4.03 (s, 2H), 6.35-6.40 (m, 2H), 6.45-6.54 (m, 3H), 6.63 (s, 1H); **^{13}C NMR** ($CDCl_3$): δ 40.71, 55.30, 56.00, 88.44, 97.78, 98.58, 98.82, 100.01, 107.52, 107.70, 115.97, 118.57, 139.75, 141.46,

151.35, 159.07, 160.35 and 160.90; **MS** (m/z): 379 (M^+, 75), 360 (15), 348 (13), 333 (10), 319 (10), 176 (13), 151 (15), 91 (7).

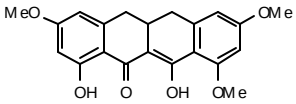
2-[1-(3,5-Dimethoxybenzyl)-2-(3,5-dimethoxyphenyl)-ethyl]-malononitrile (242):



To a solution of **232** (0.5 g, 1.32 mmol) in ethanol (10.0 ml) was added 10% palladium on charcoal (0.05 g) and stirred under hydrogen atmosphere employing a hydrogen balloon at room temperature for 8 hr. It was filtered on a celite bed and the filtrate was concentrated under reduced pressure to give **242** (0.495 g, 98.60 %) as a white solid; m. p. 127 ^oC.

IR ($CHCl_3$): 2190 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 2.55-2.91 (m, 5H), 3.76 (s, 12H), 4.24 (d, J = 10.0 Hz, 1H), 6.30 (s, 4H), 6.38 (d, J = 2.0 Hz, 2H); **MS** (m/z): 382 (M+2, 25), 365 (10), 334 (2), 299 (2), 231 (22), 214 (100), 152 (50), 122 (5) and 91 (12); Analysis calculated for $C_{12}H_{24}N_2O_4$: C = 69.46, H = 6.35, N = 7.36; Found C = 69.41, H = 5.89, N = 7.07.

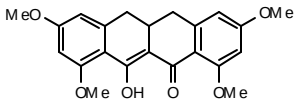
4,6-Dihydroxy-2,7,9-trimethoxy-11a,12-dihydro-11*H*-naphthacen-5-one (243) and 6-hydroxy-2,4,7,9-tetramethoxy-11a, 12-dihydro-11H-naphthacen-5-one (244):



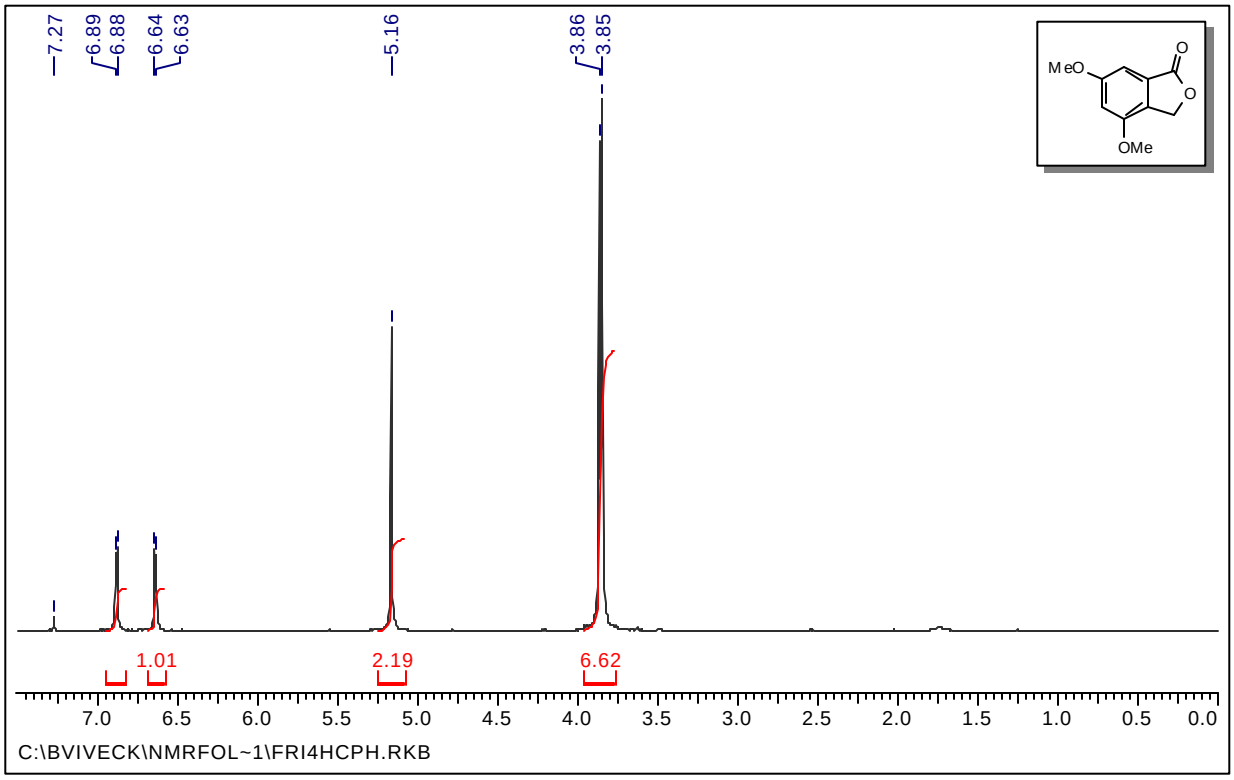
The reduced nitrile **242** (0.260 g, 0.684 mmol) in anhydrous THF (10 ml) at 0 ^oC containing anhydrous zinc chloride (0.335 g, 2.4 mmol) was treated with hydrogen chloride gas for 10 hr at which time solid separated out. The reaction mixture was diluted with hot water (20 ml) and refluxed for another 2 hr. The cooled mixture was extracted with chloroform (3 × 20 ml), washed with brine and dried over sodium sulfate. Evaporation of the solvent and purification of the crude mixture by column chromatography gave compounds **243** and **244** as yellow solids.

243: Yield- 0.065 g, (26 %); m.p. 171 ^oC; **IR** ($CHCl_3$): 1624 cm^{-1} (-C = O); **^{1}H NMR** ($CDCl_3$): δ 2.58-2.80 (m, 2H), 2.83-3.10 (m, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 6.27-6.41 (m, 4H), 8.25 (s, 1H, enolic -OH), 13.63 (s, 1H, chelated -OH, D_2O exchangeable); **^{13}C NMR** ($CDCl_3$): δ

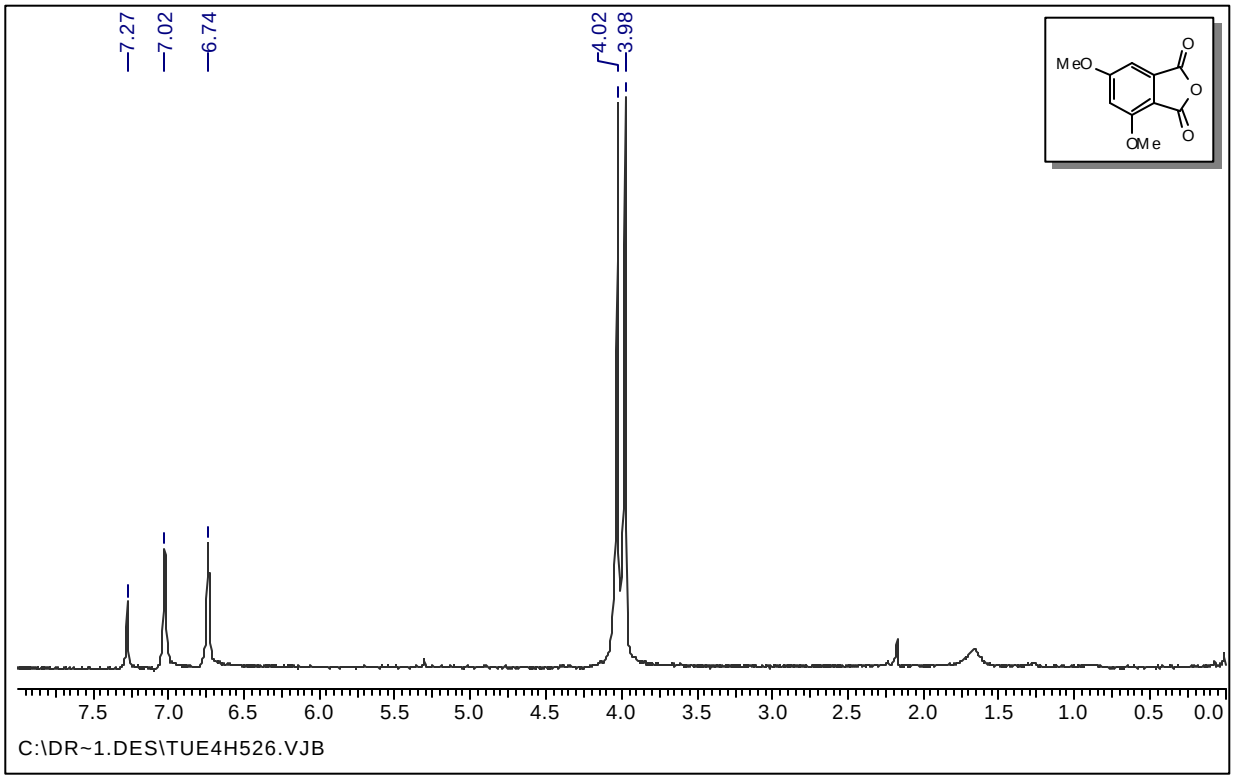
35.52, 36.81, 55.42, 55.58, 96.47, 99.07, 105.05, 106.36, 112.37, 115.64, 130.04, 130.47, 139.63, 144.33, 159.07, 162.67, 165.78, 166.36, 188.49; **MS** (m/z): 367 (M-1, base peak), 350 (60), 336 (30), 323 (15), 278 (8), 189 (16), 169 (32), 115 (8).



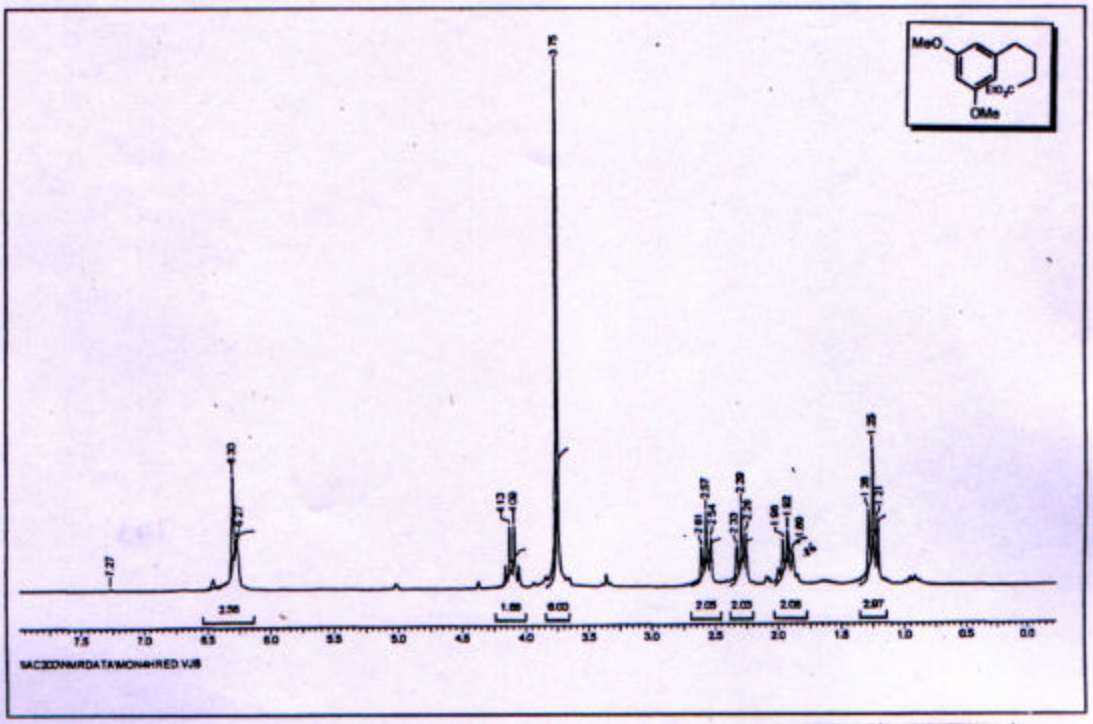
244: Yield-0.114 g, (44%); m.p. 148 ^{o}C; **IR** ($CHCl_3$): 1646 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 2.52-3.12 (m, 5H), 3.82 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 3.89 (s, 3H), 6.29-6.38 (m, 4H), 8.08 (s, 1H); **^{13}C NMR** ($CDCl_3$): δ 31.89, 36.29, 36.56, 55.36, 55.61, 56.03, 97.69, 104.59, 104.93, 116.25, 117.80, 127.78, 134.10, 139.32, 146.13, 158.73, 161.84, 162.15, 163.65, 184.49; **MS** (m/z): 365 (M- 17, 45), 352 (100), 334 (48), 321 (10), 299 (8), 267 (4), 235 (10), 214 (40), 189 (5) and 152 (15); Analysis calculated for $C_{22}H_{22}O_6$: C = 69.83, H = 5.85%; Found C = 70.48, H = 6.25%.



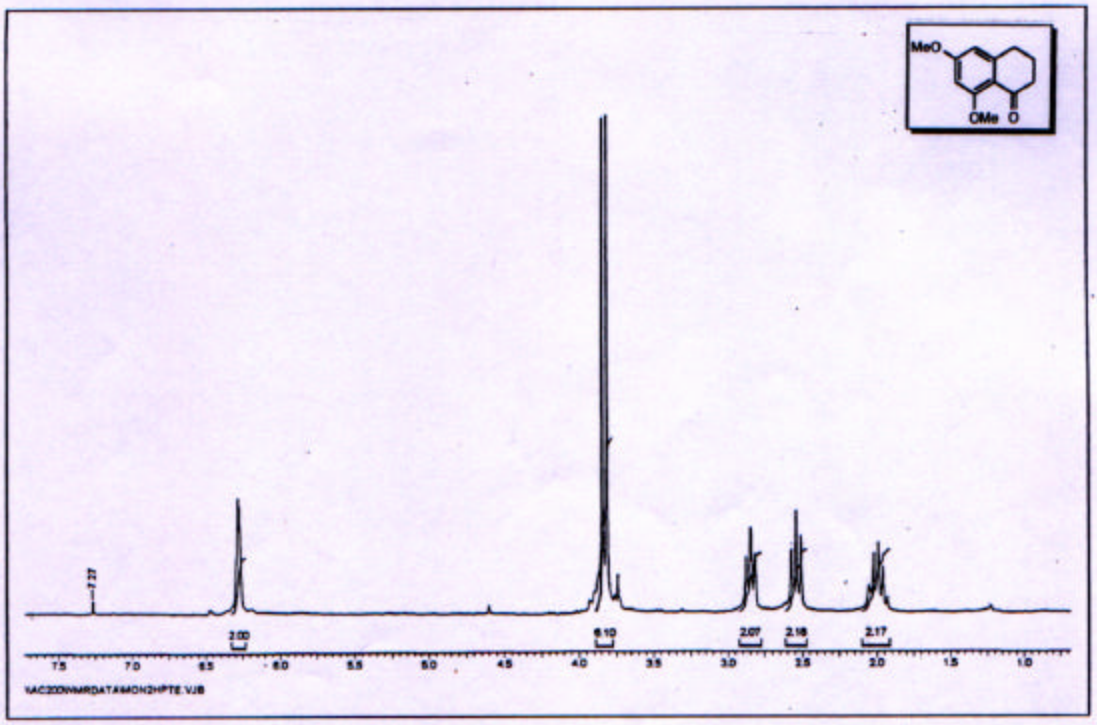
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 191 IN $CDCl_3$



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 182 IN $CDCl_3$



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 203 IN $CDCl_3$



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 205 IN $CDCl_3$

144

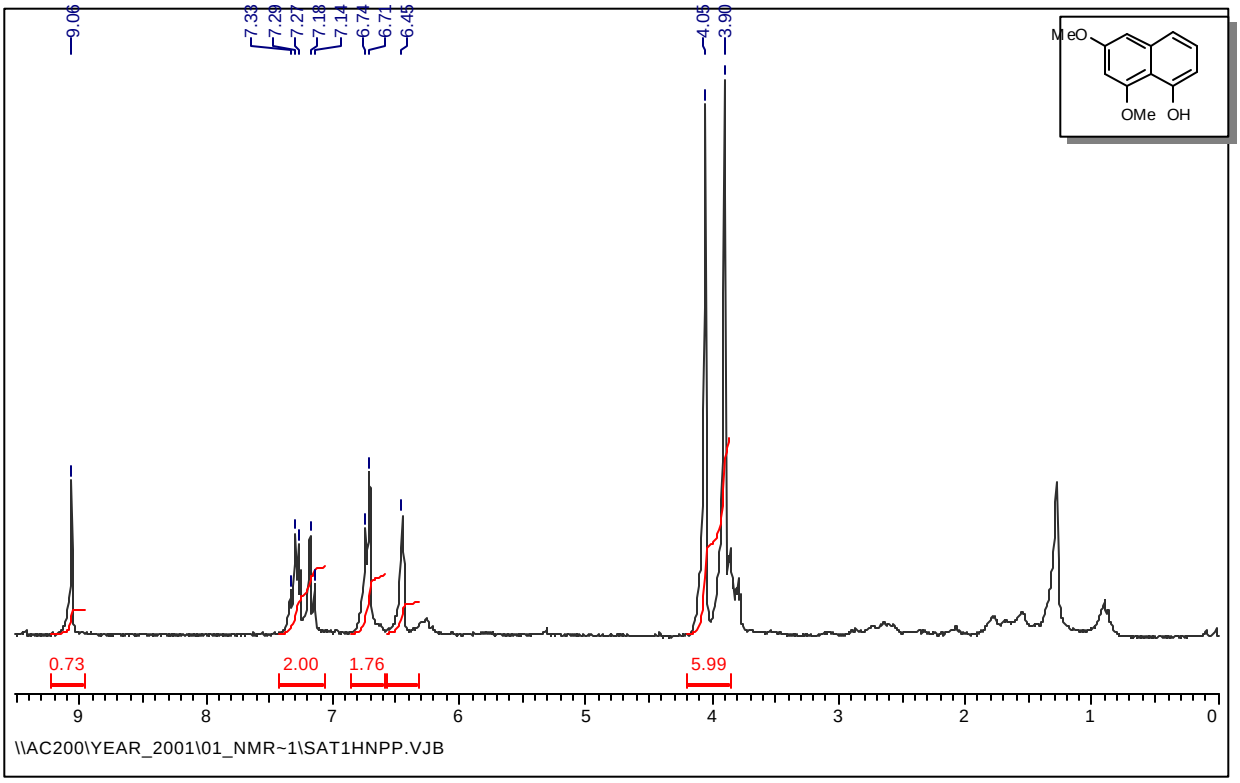
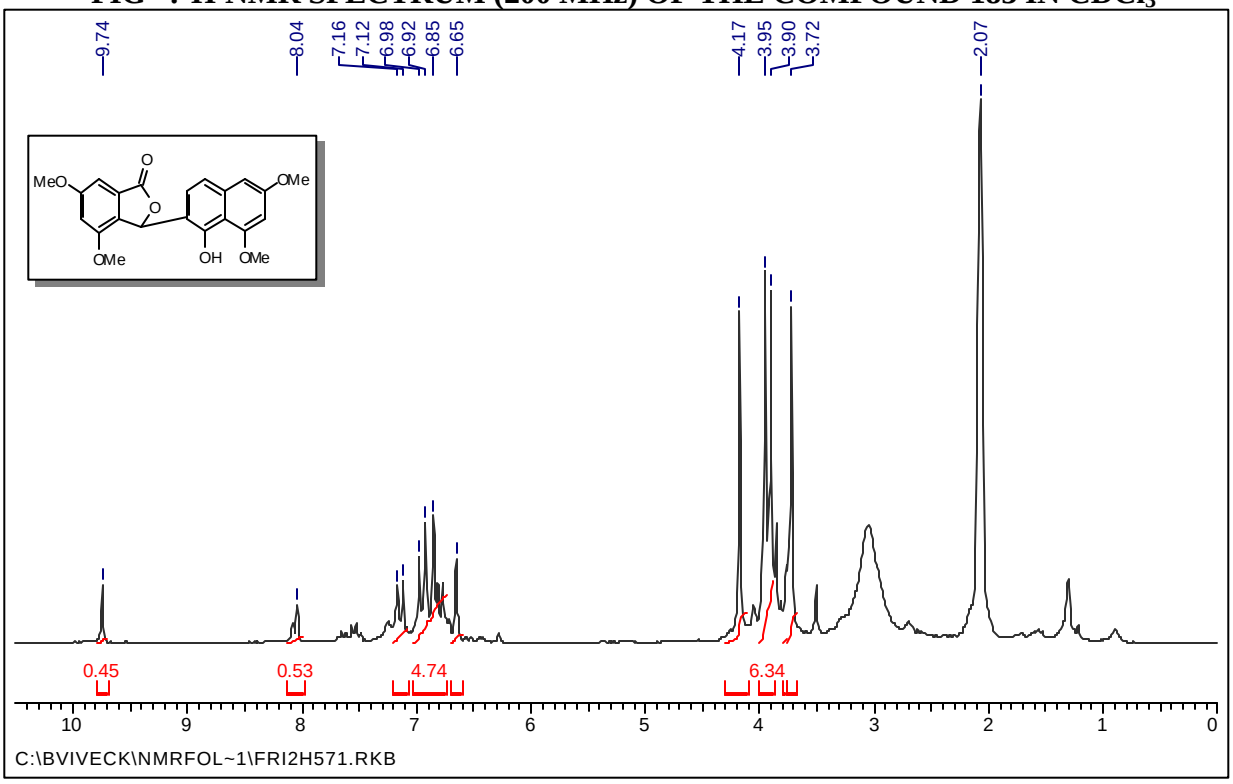
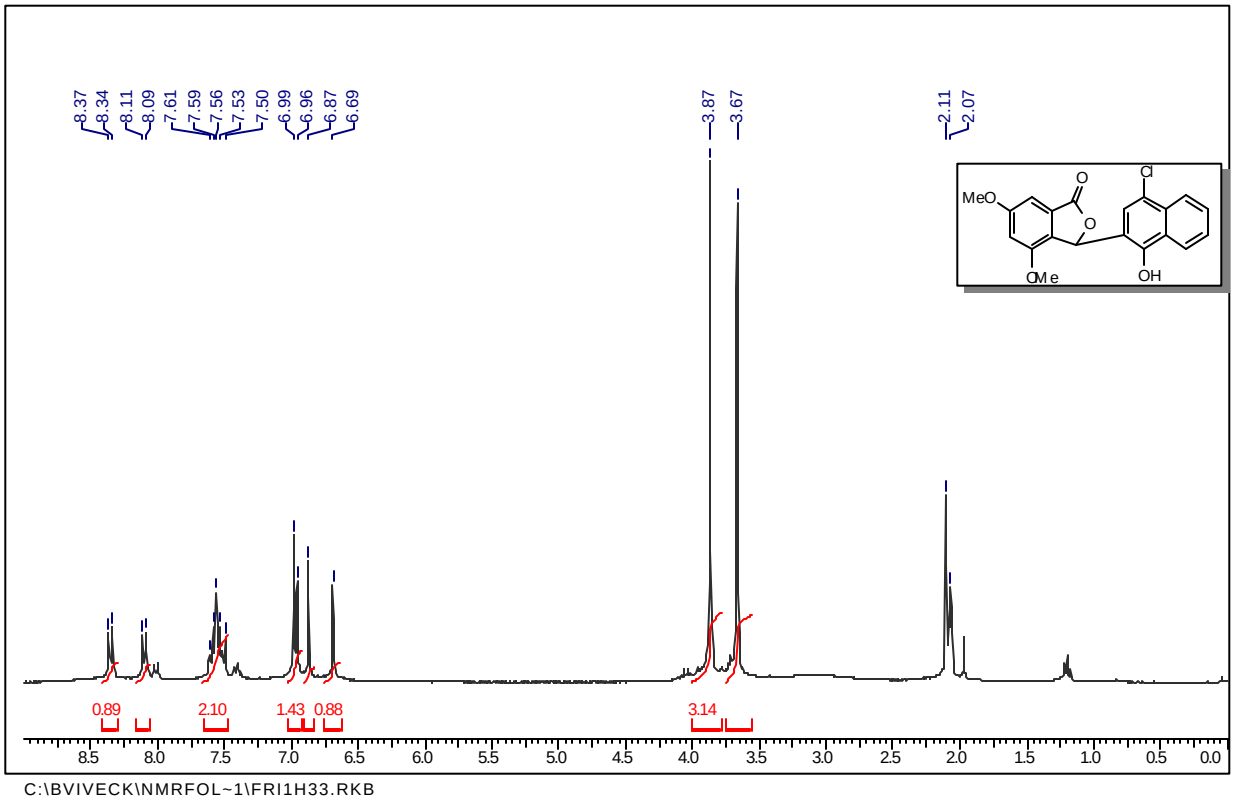


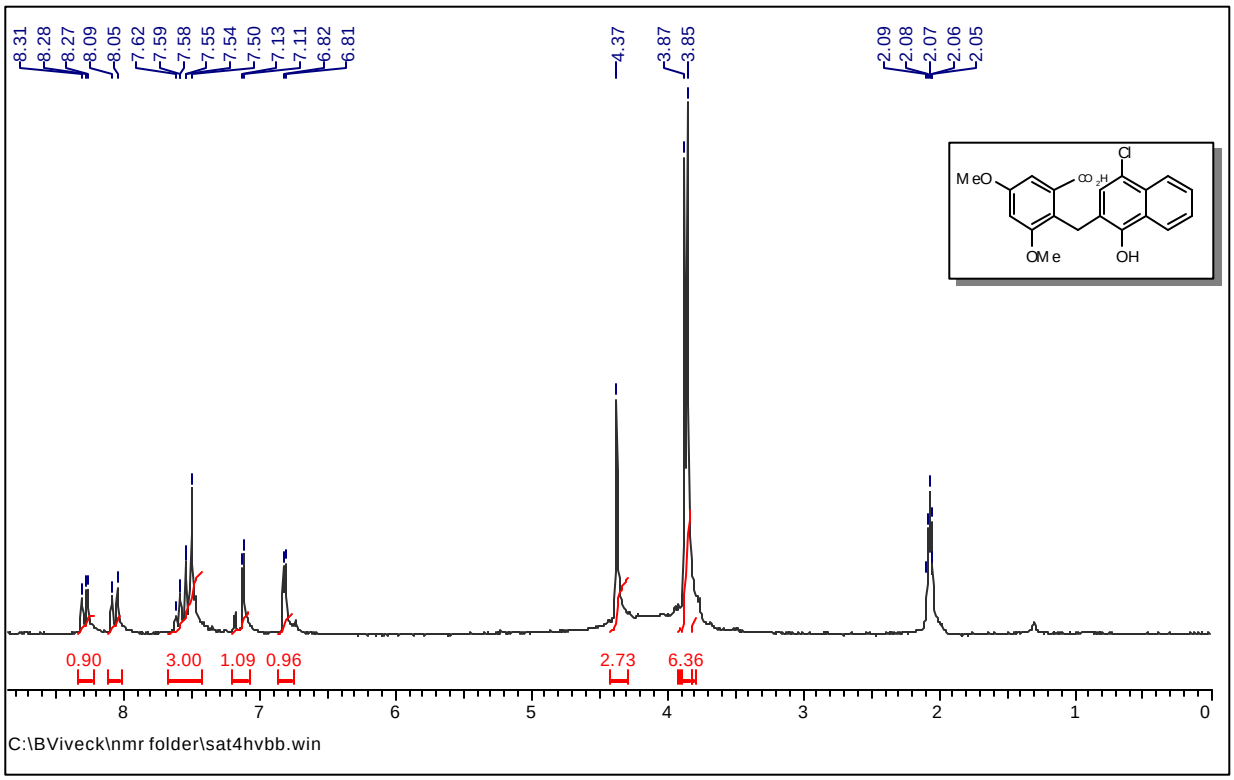
FIG :^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 183 IN $CDCl_3$



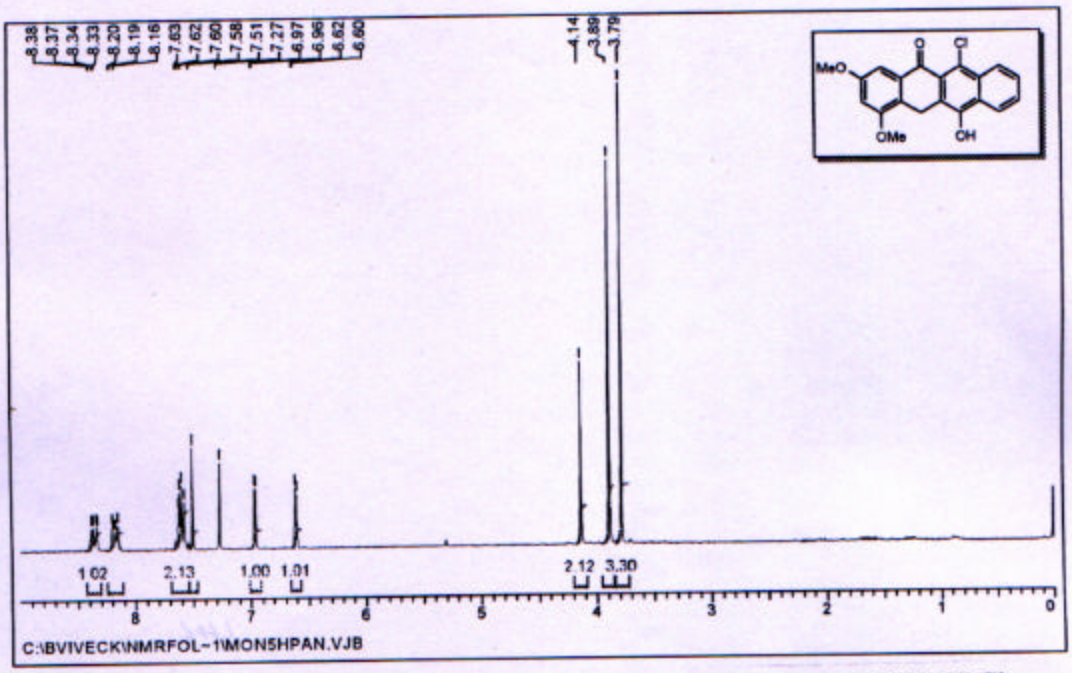
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 207 IN $CDCl_3$



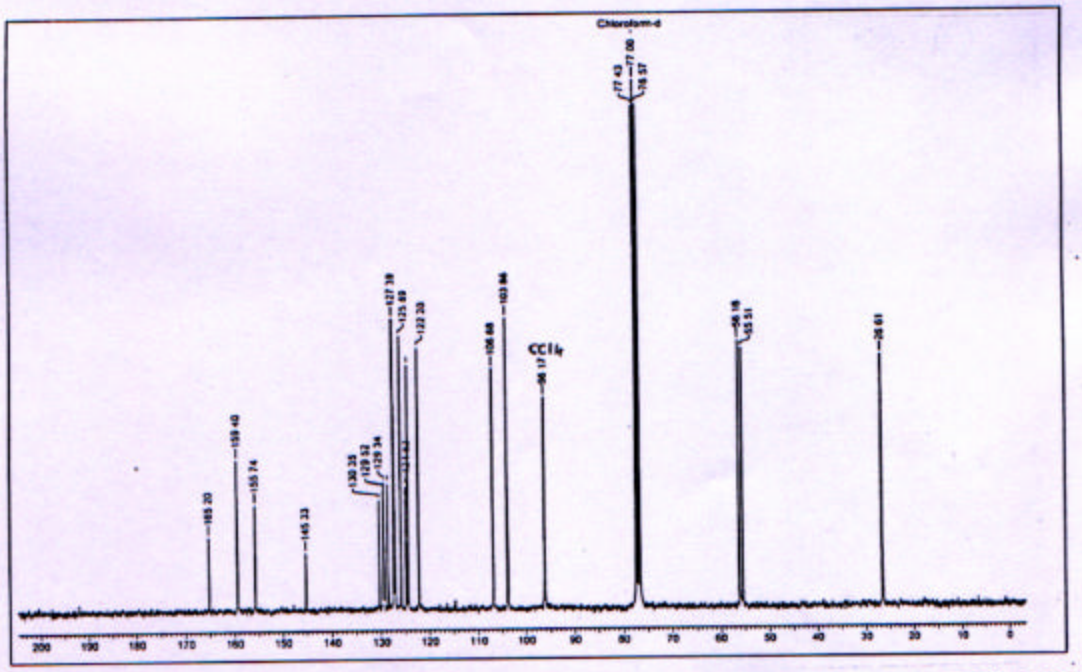
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 212 IN $CDCl_3$+ ACETONE-d_6



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 213 IN $CDCl_3$+ ACETONE-d

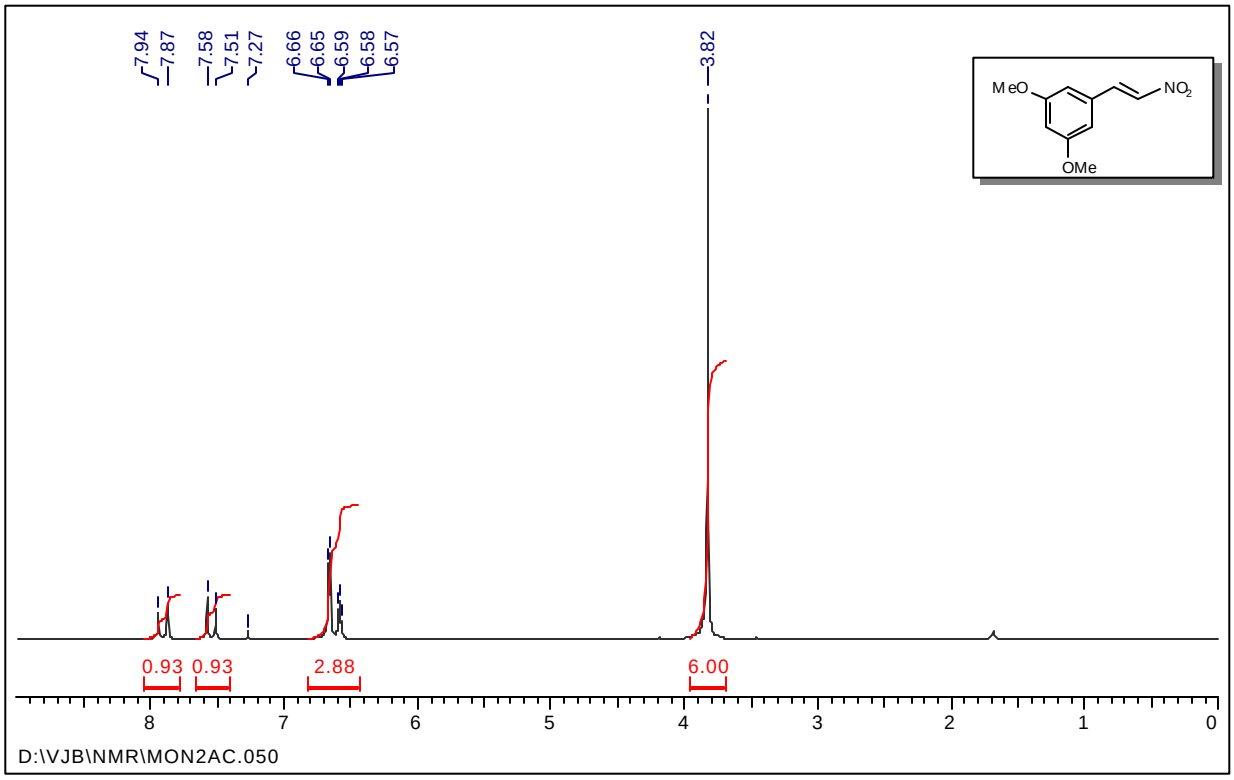


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 214 IN $CDCl_3$

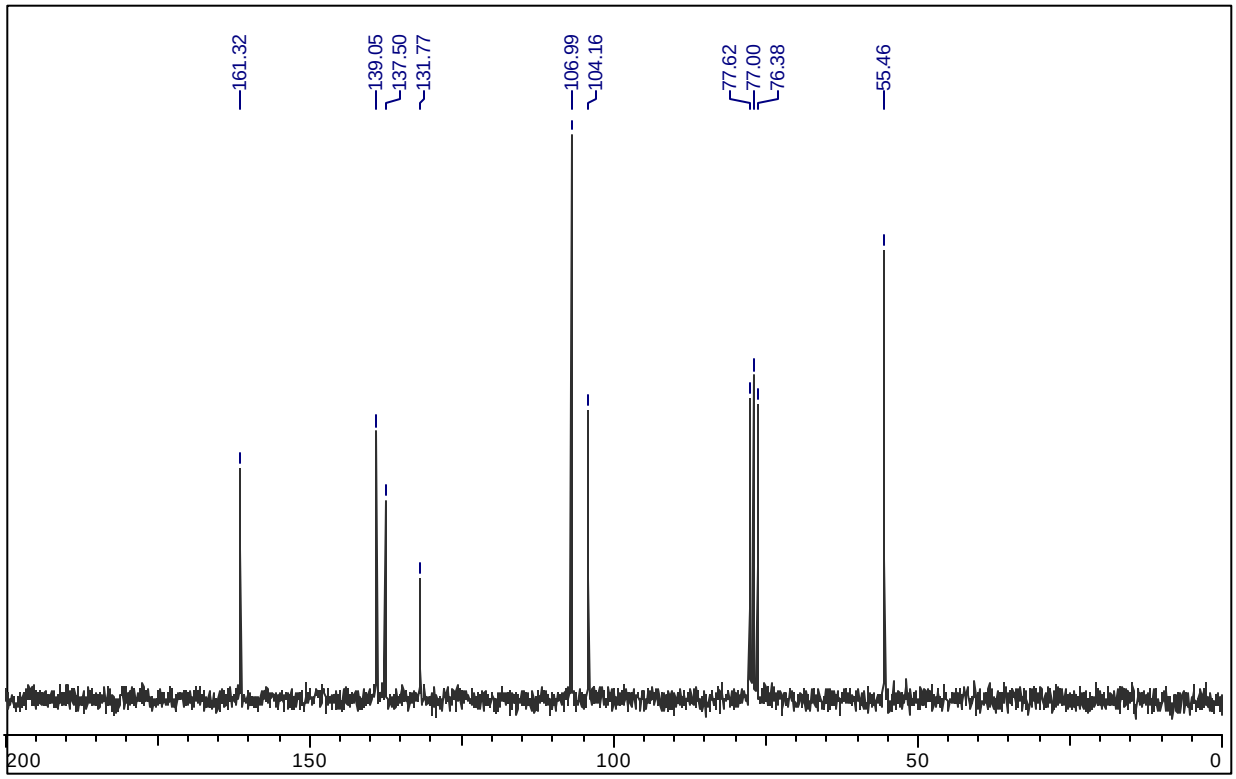


^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 214 IN $CDCl_3$+ CCl_4

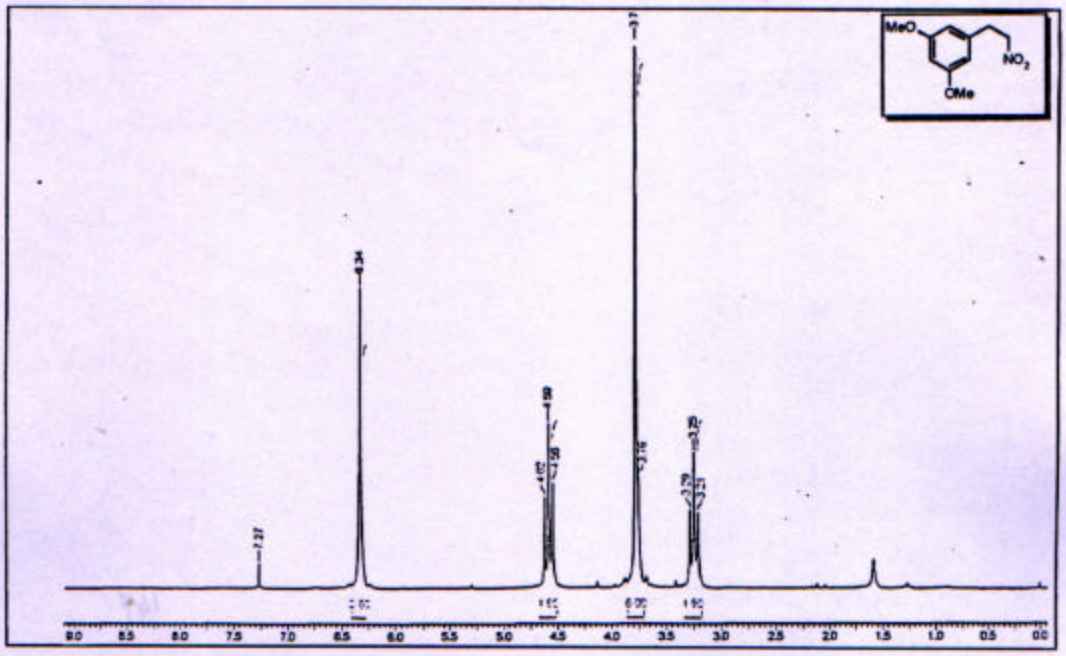
147



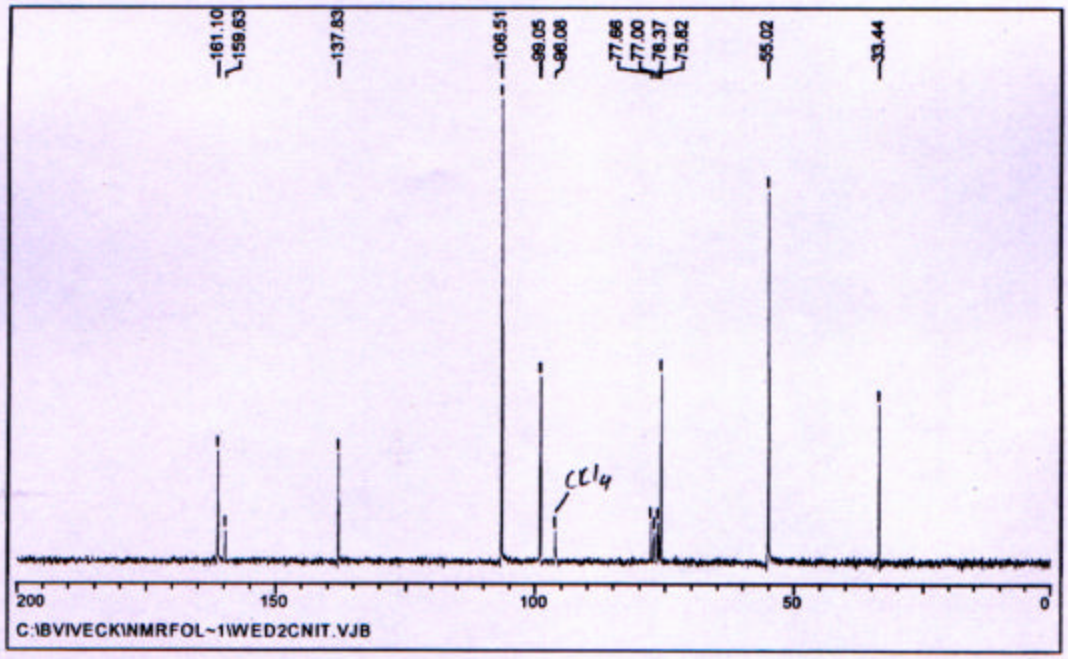
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 224 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 224 IN $CDCl_3$

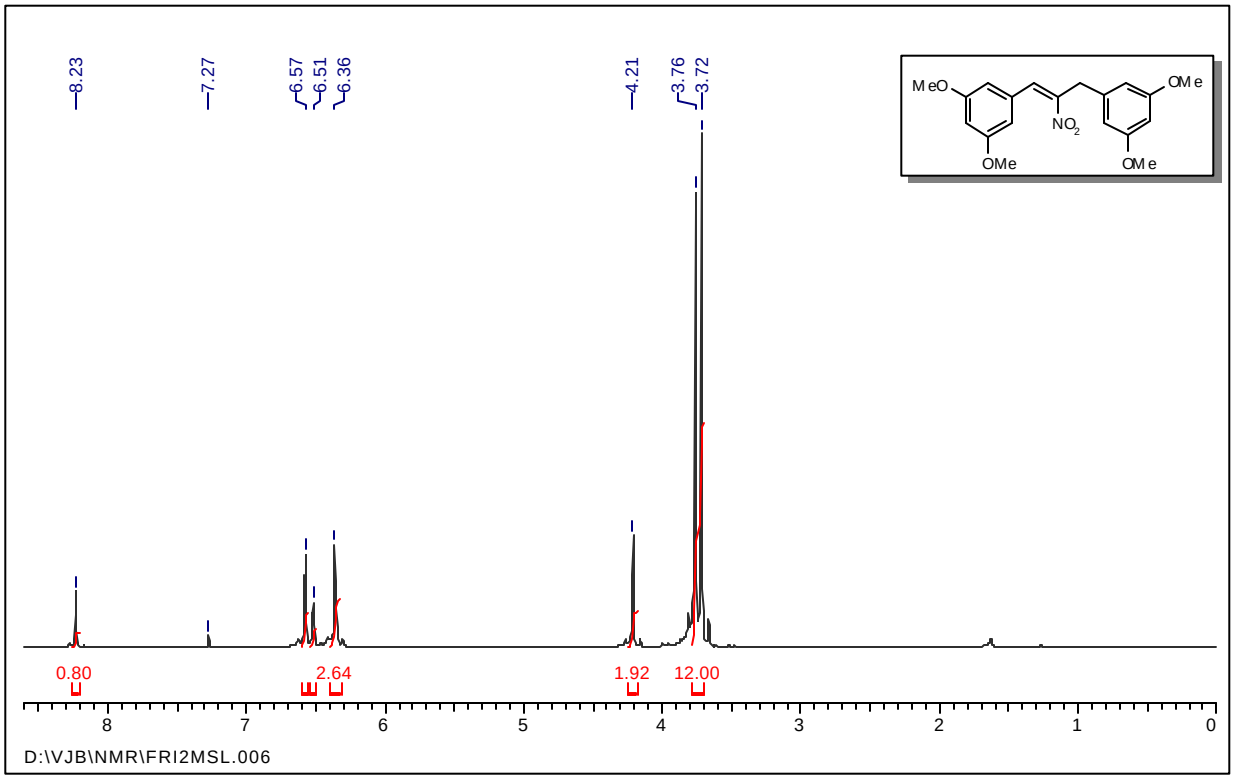


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 223 IN $CDCl_3$

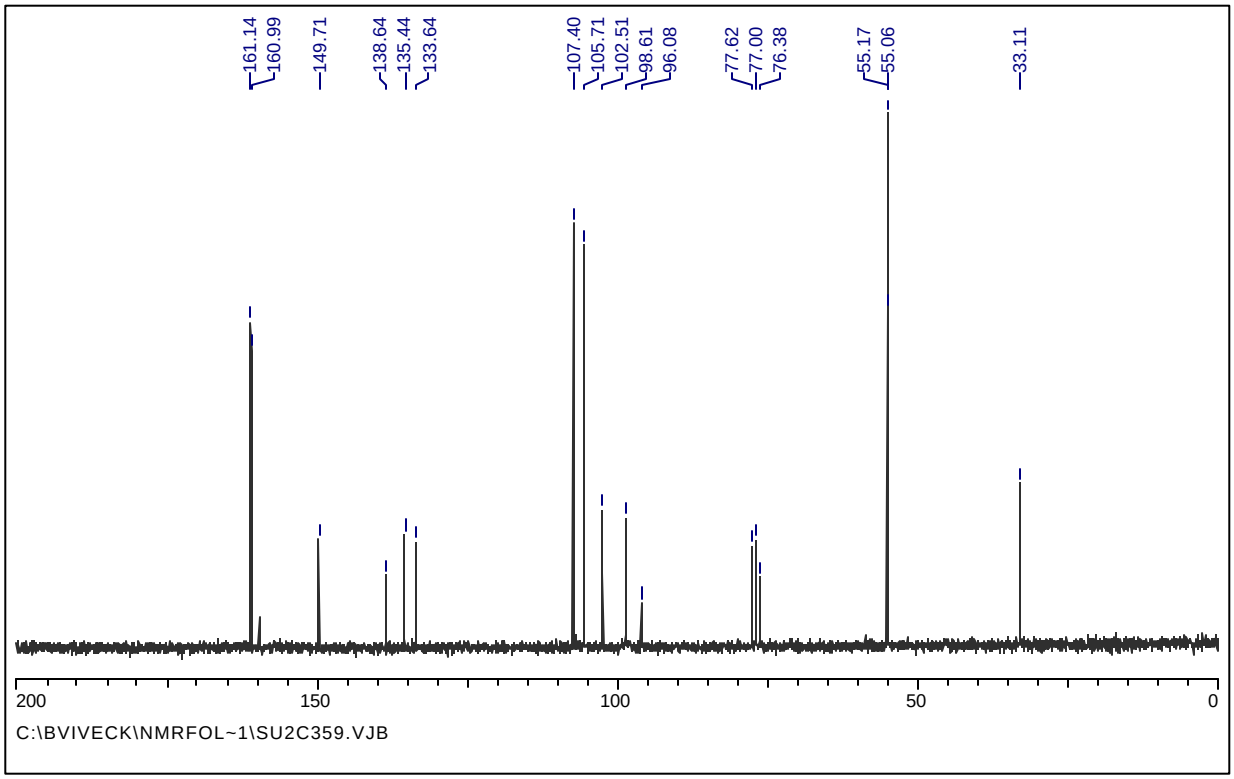


^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 223 IN $CDCl_3$ + CCl_4

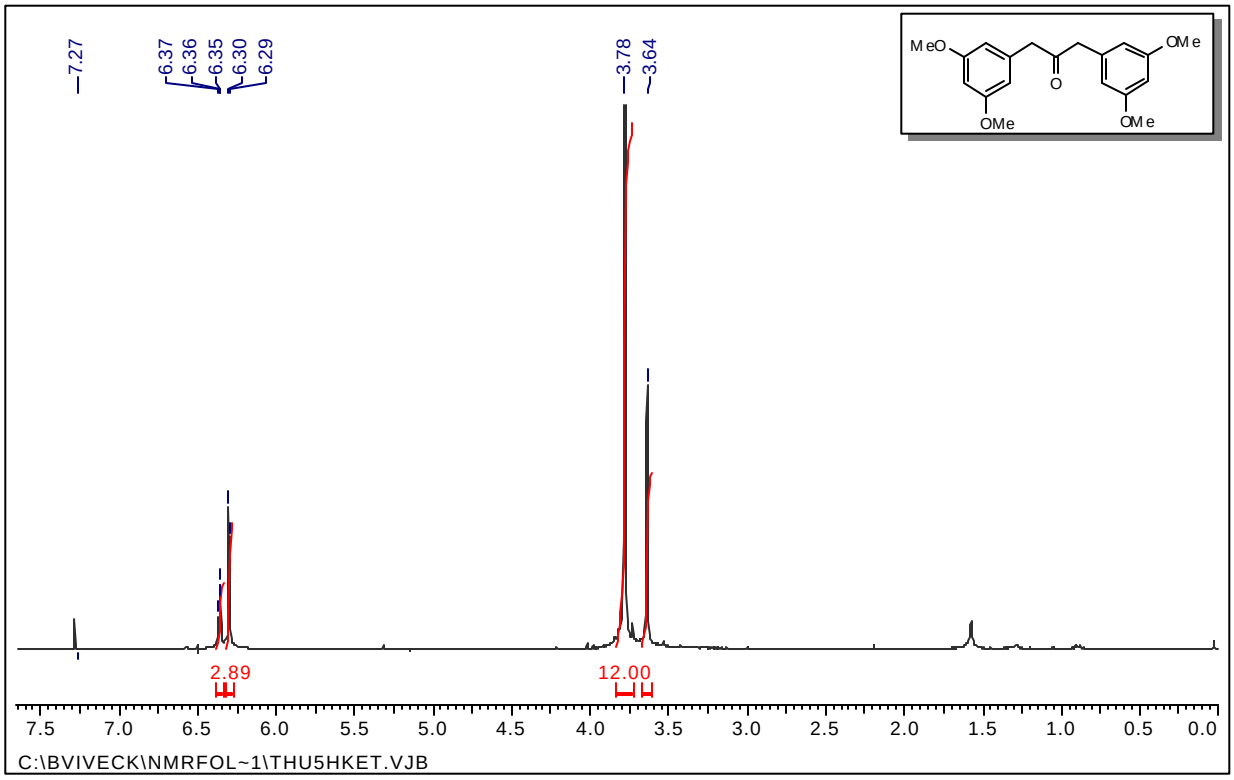
149



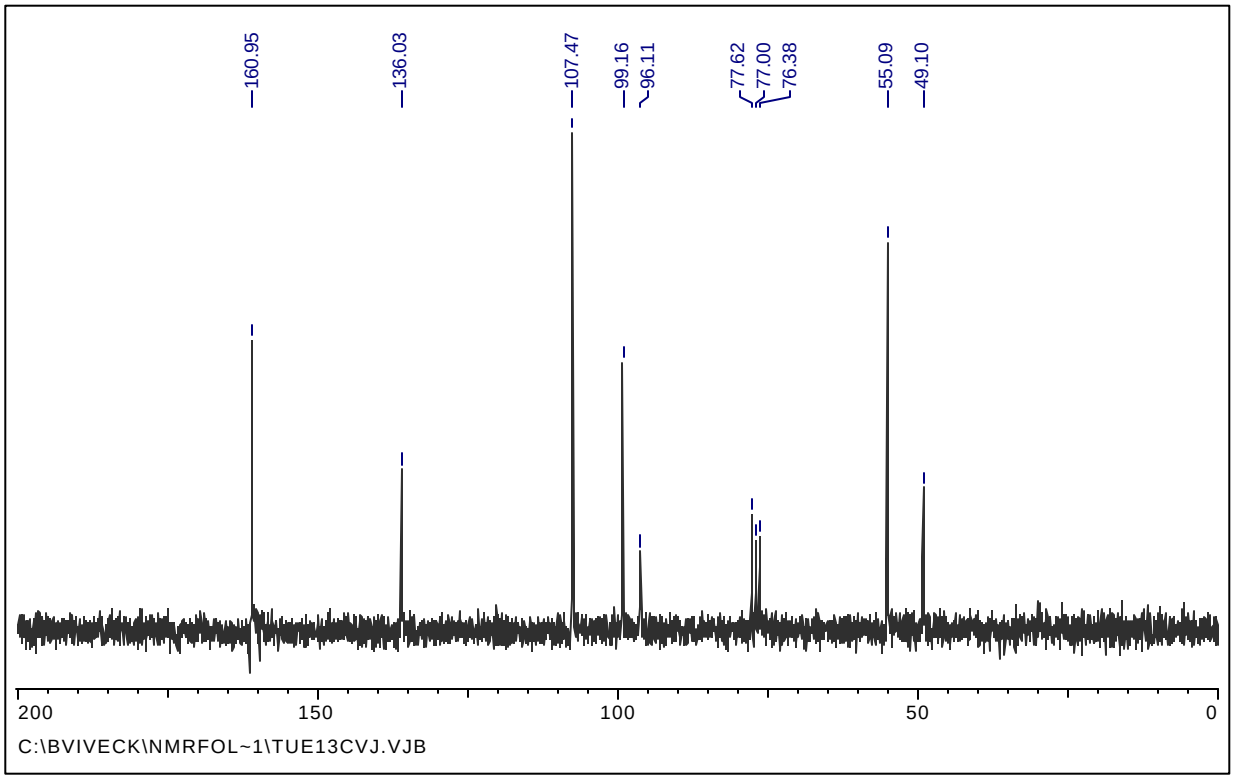
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 225 IN $CDCl_3$



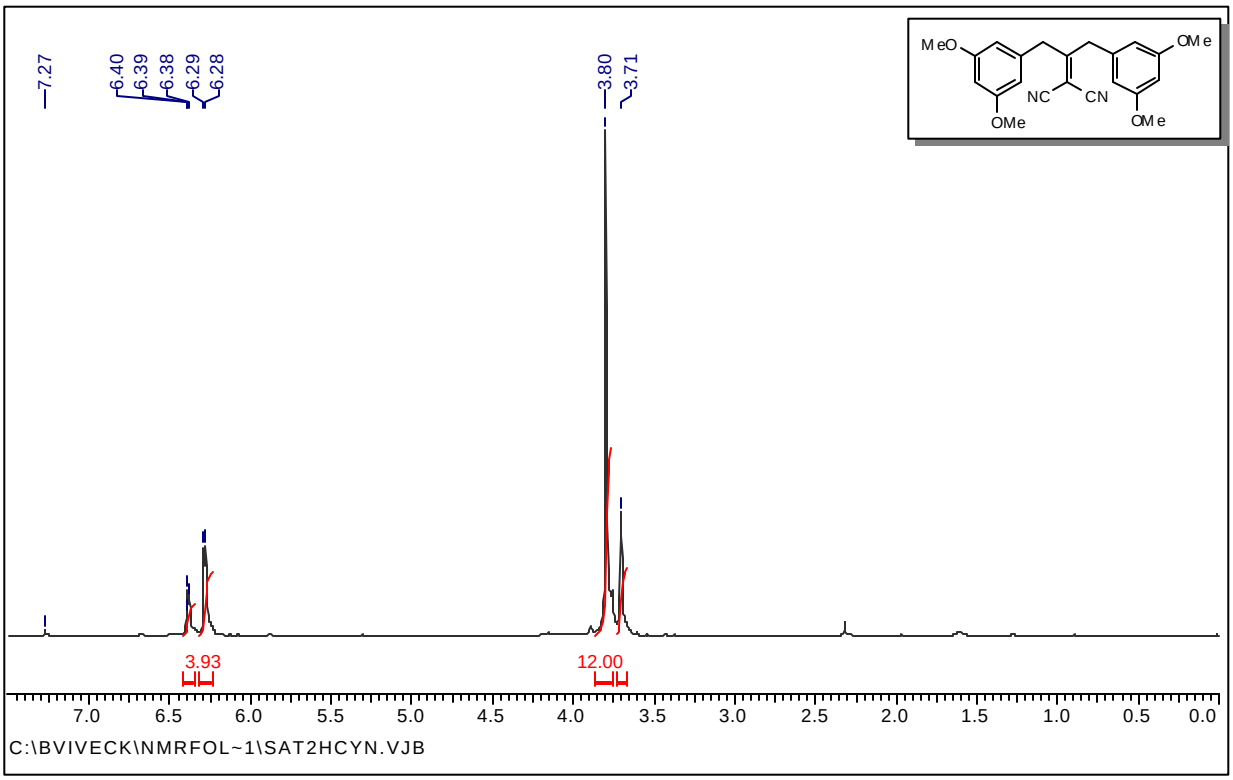
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 225 IN $CDCl_3$+CCl_4



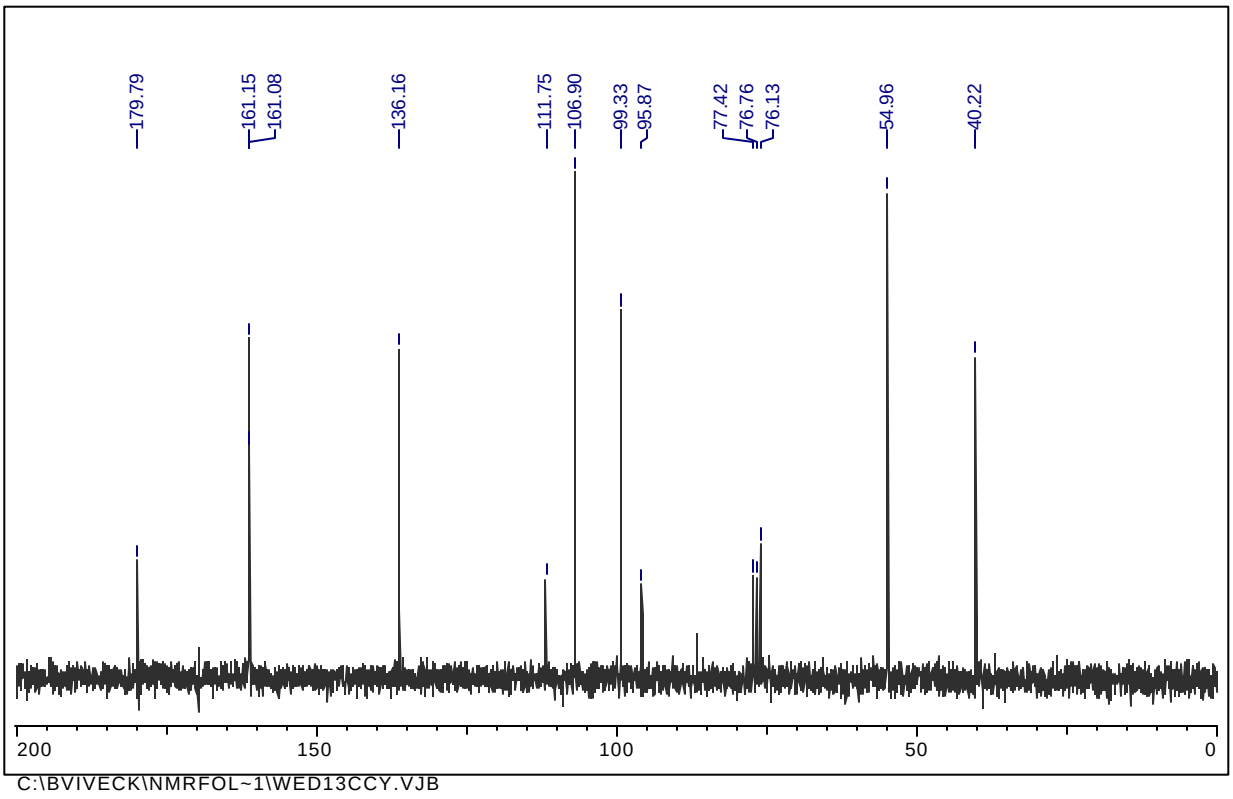
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 228 IN $CDCl_3$+CCl_4

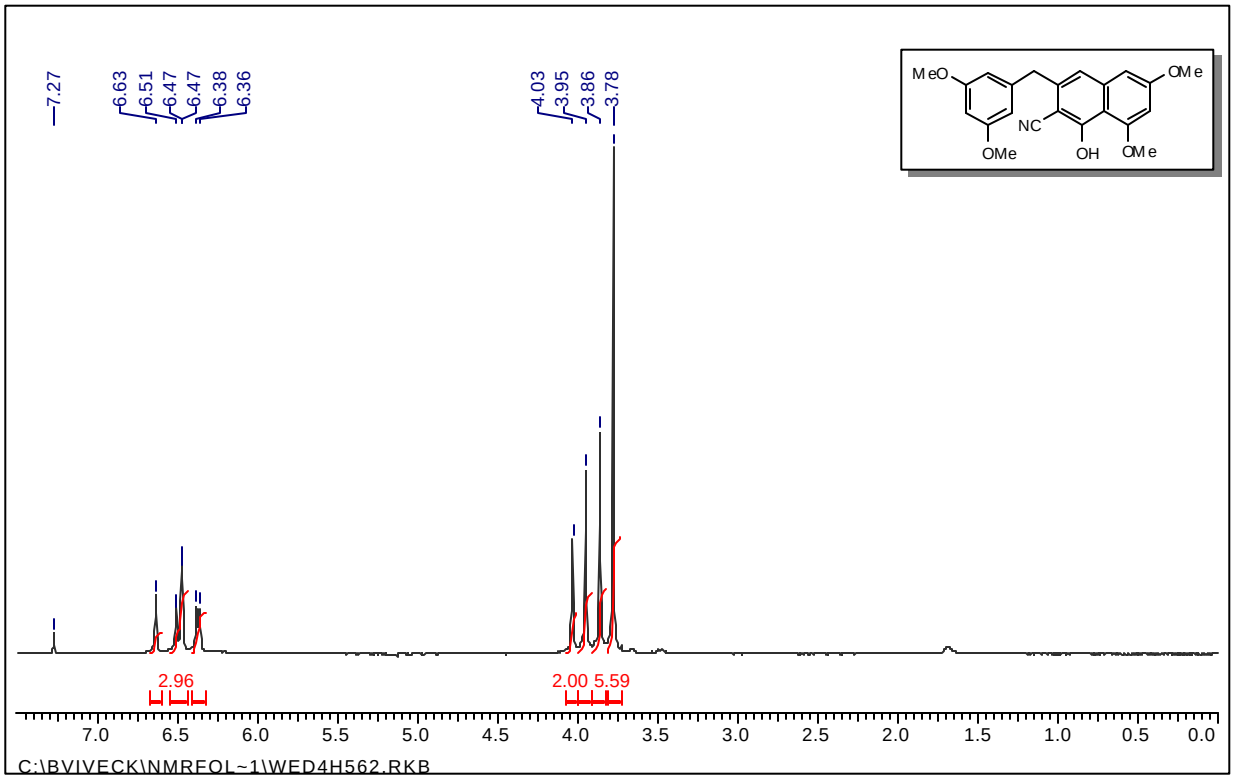


^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 228 IN $CDCl_3$+CCl_4

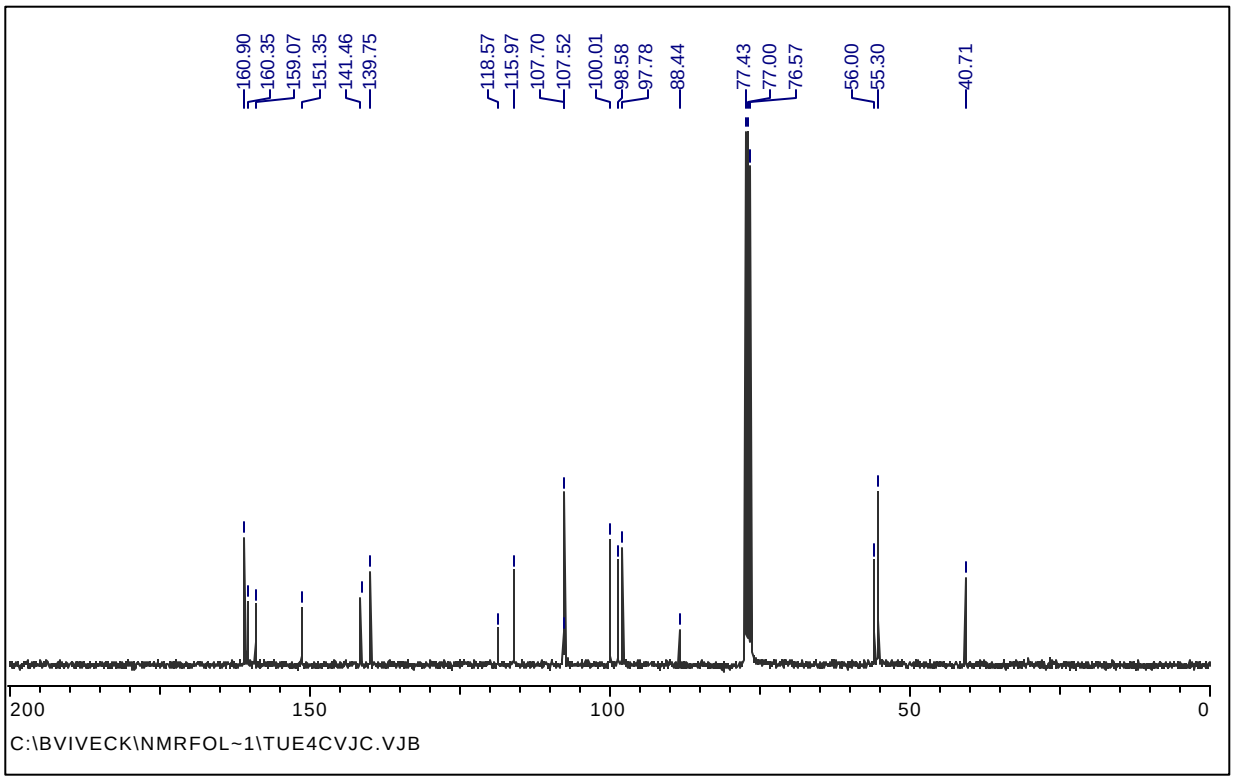


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 232 IN $CDCl_3$+CCl_4

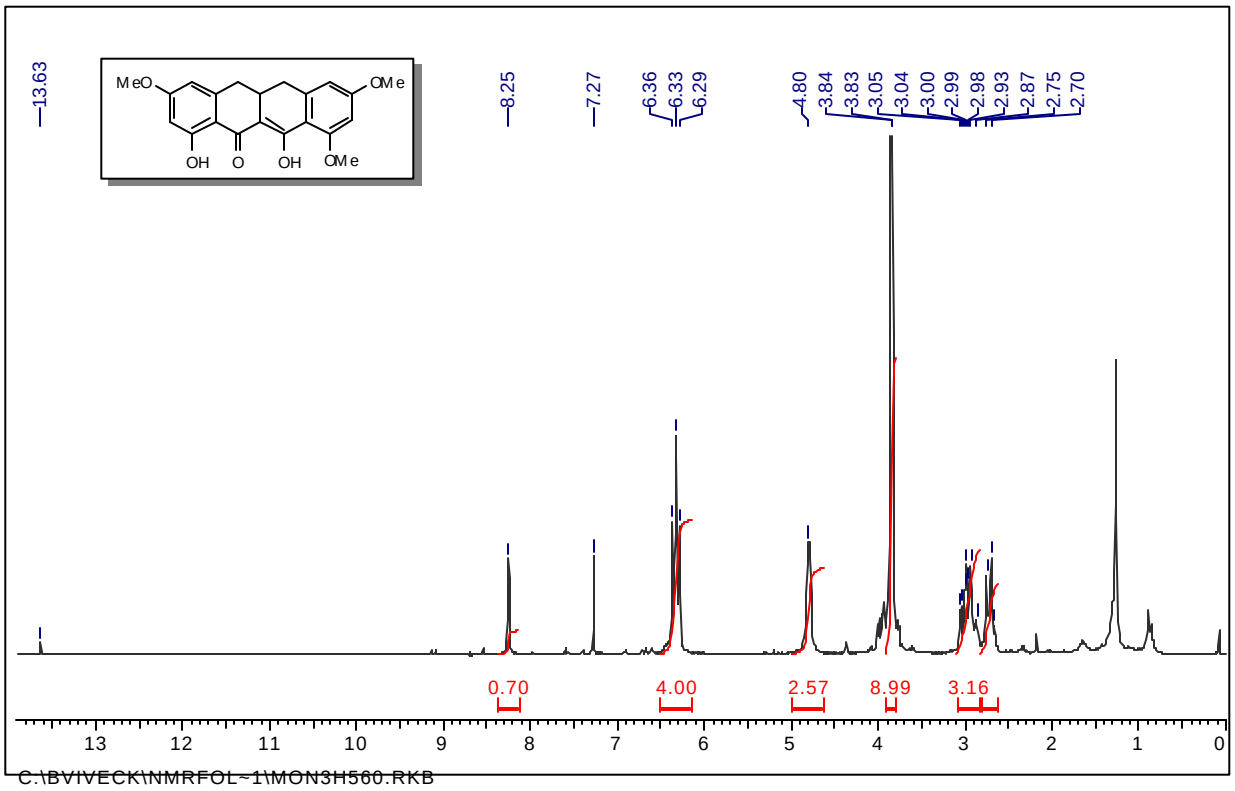




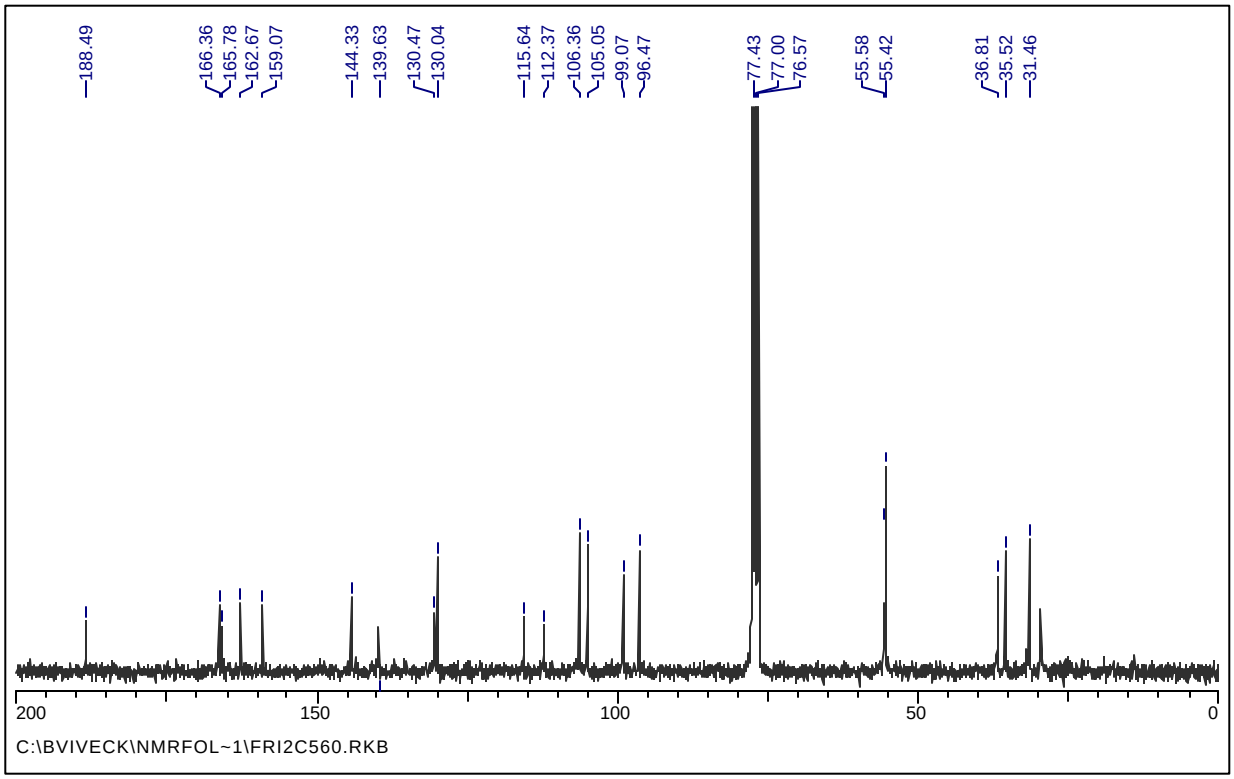
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 240 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 240 IN $CDCl_3$



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 243 IN $CDCl_3$ (after D_2O exchange)



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 243 IN $CDCl_3$+ CCl_4

2.0.9 REFERENCES:

1. Gibbs, J.B., *Science*, **2000**, 287, 1969.
2. Kelin, W.G., *J. Clin. Invest*, **1999**, 104, 1503.
3. Bishop, J. M., *Cell,* **1991**, 64, 235.
4. a) Rennie, J. and Rusting, R., *Scientific American,* **1996**, 275, 28. b) Krohn, K. and Priyano, W., *Tetrahedron*, **1984**, 40, 4609.
5 a) Brazhnikova, M. G.; Zbarsky, V. B.; Ponomarenko, V. I. and Potapova, N. P.; *J. Antibiot.*, **1974**, 27, 254. b) Jause, G. F.; Brazhnikova M. G. and Shorin V. A., *Cancer Chemother. Rep.* Part I, **1974**, 58, 25
6. a) Arcamone, F; Francheschi, G. and Penco, S., *Tetrahedron Lett.*, **1969**, 1007. b) Blum, R. H. and Carter, S. K. *Ann. Intern. Med.*, **1974**, 86, 249.
7. a) Arcamone, F.; Franceshi, G.; Orezzi, P.; Cassinelli, G.; Barbiene, W. and Mondelli, R., *J. Am. Chem. Soc.*, **1964**, 86, 5334. b) Bernard, J.; Paul, R.; Boiron, M.; Jacquillat, C. and Miral, R., Ed. "Rubidomycin" Springer Verlag, New York, **1969**. c) Livingston, R. B. and Carter, S. K., "Daunomycin" Chemotherapy Fact Sheet, National Cancer Institute, Bethesda, M. D. **1979.**
8. Wang, J. C., DNA Topoisomerases. *Annu Rev. Biochem.,* **1989**, 54, 665.
9. Yamashita, Y.; Kawada, S.; Fujii, N. and Nakano, H., *Biochemistry,* **1991**, 30, 5838.
10. Peter, D' Arpa and Leroy, F. Lin., *Biochim. Biophys. Acta,* **1989**, 989, 163.
11. a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmar, K. H. N.; McPhail, A. T. and Sim, G. A., *J. Am. Chem. Soc.*, **1966**, 88, 3888. b) Hsiang, Y-H.; Liu, L. F.; Wall, M. E; Wani, M. C.; Nicholas, A.W.; Manikumar, G.; Kirschenbaum, S.; Silber, R. and Potemesil, M., *Cancer Res.*, **1989**, 49, 4385.
12. Chaw, K. C.; Macdonald, T. L. and Ross, W. E., *Mol. Pharmacol.*, **1988**, 34, 467.
13. Tewey, K. M.; Rave, T. C.; Yang, L.; Hallingan, B. C. and Liu, L. F., *Science*, **1984**, 226, 466.
14. Loide, J. D. and Harwitz, J. D., *Lloydia,* **1977**, 40, 82.
15. Pommier, Y.; Covey, J. M.; Kerrigan, D.; Markovitis, J. and Pharm, R., *Nucleic Acids Res.*, **1987**, 15, 6713.
16. Pierson, V.; Pierr, A.; Pommier, Y. and Gros, P., *Cancer Res.*, **1988**. 48, 1404.

17. a) Yamashita, Y.; Saitoh, Y.; Ando, K.; Takahashi, K.; Onno, H. and Nakano, H., *J. Antibiotics*, **1990**, 43, 1344. b) Leteurtre, F.; Fujimori, A.; Tanizawa, A.; Chatra, A.; Mazumdar, A.; Kolhagen, G.; Nakano, H. and Pommier, Y., *J. Biol. Chem.*, **1994**, 269, 28702.
18. Ishiyama, D.; Futamata, K.; Futamata, M.; Kasuya, O.; Kamo, S.; Yamashita, F. and Kanazawa, S., *J. Antibiotics*, **1998**, 51, 1069.
19. Fuji, N.; Yamashita, Y.; Katsuhiko, A. J.; Agatsuma, T.; Saitoh, Y.; Gomi, K.; Nishie, Y. and Nakano, H., *J., Antibiot.* **1994**, 47, 949.
20. Fuji, N.; Yamashita, Y.; Chiba, S.; Vosaki, Y.; Saitoh, Y.; Tuji, Y. and Nakano, H., *J. Antibiotics*, **1993**, 46, 1173.
21. Bahl, S.; Martin, S.; Rawlins, P.; Sadeghi,; R. Smith, P.; Steel, J.; Shanu - Wilson, P.; Wood, K. and Wrigley, S., *J. Antibiotics*, **1977**, 30, 169.
22. Yamashita, Y.; Kawada, S. Z.; Fuji, N. and Nakauo, H., *Biochemistry*, **1991**, 30, 5838.
23. Rai, B., Ph. D. Thesis, University of Pune, **1993**, Chapter I, Part IV.
24. Hauser, F. M. and Pogany, S. A., *J. Heter. Chem.*, **1978**, 15, 1535.
25. Schnekenburger, *J.*, *Arch. Pharm*., **1964**, 297, 734; **1965**, 298, 4.
26. Hauser, F. M. and Rhee, R. P., *Synthesis*, **1977**, 245.
27. a) Tamura, Y.; Wada, A.; Sasho, M. and Kita, Y., *Tetrahedron Lett*., **1981**, 22, 4283. b) Tamura, Y.; Wada, A.; Sasho, M.; Fukunaga, K.; Maeda, H. and Kita, Y., *J. Org. Chem.*, **1982**, 47, 4376.
28. Cameron, D. W. and Bruyn, P. J., *Tetrahedron lett*., **1992**, 55, 5593.
29. Horii, Z. I.; Hakusui, H.; Momose, T. and Yoshino, E., *Chem. Pharm. Bull.*, **1968**, 16 (7), 1251.
30. Kim, K.; Surato, A. and Tohnion, F., *J. Am. Chem. Soc*., **1979**, 101, 2483.
31. Paradkar, M. V.; Kulkarni, S. A.; Joseph, A. R. and Ranade, A. A., *J. Chem. Res. (s)* **2000**, 364. ; *J. Chem. Res. (m),* **2000**, 944.
32. a) Bentley and Weizman, *J. Am. Chem. Soc.*, **1979**, 101, 2483. b) Tanaka, H. and Tamura, T., *Tetrahedron Lett*., **1961**,151.
33. a) Hardegger, E.; Rigassi, N.; Seres, J.; Egil, Muller, P. and Fitzi, K. O., *Helv. Chim. Acta*, **1963**, 284 - 285, 2543. b) Findlay, J. A. and Kwan, D., *Can. J. Chem.*, **1973**, 51, 3299. c) Bycroft, B. W.; Cashyap, M. M. and Leuug, T. K., *J. C. S. Chem. Comm.*, **1974**, 443. d)

Ridley, D. D.; Richie, E. and Taylor, W. C., *Aust. J. Chem*., **1968**, 21, 2979. e) Petrzilla, T.; Haefliger, W. and Sikemeier, C., *Helv. Chim. Acta,* **1969,** 52, 1102.

34. Sibi, M. P.; Dankwardt, J. W. and Snieckus, V., *J. Org. Chem*., **1986**, 51, 273.
35. Punit Kumar, *Org. Prep. Proc. Int*., **1997**, 29, 477.
36. Hulme, A. N.; Henry, S. S. and Meyers, A. I., *J. Org. Chem.,* **1995**, 60, 1265.
37. Kim, K. S.; Vanotti, E.; Suato, E. and Johnson, F., *J. Am. Chem. Soc.*, **1979**, 101, 2483.
38. Letsinger, R. L.; Jamison, J. D. and Hussey, A. L., *J. Org. Chem.*, **1961**, 26, 97.
39. Baldwin, J. E. and Bair, K. W., *Tetrahedron Lett*., **1978**, 2559.
40. Newman, M. S.; Sankaran, V. and Olson, D. R., *J. Am. Chem. Soc.*, **1976**, 98, 3237.
41. Yadav, J.; Corey, P.; Hsu, C. T.; Perlman, K. and Sih, C. J., *Tetrahedron Lett.,* **1981**, 22, 811.
42. Arnold, B. J.; Mellows, S. M. and Samnmer, P. G., *J. Chem. Soc. Perkin Trans*. I, **1973**, 1266.
43. Rangrajan, R.; Eisenbraun, E. J., *J. Org. Chem.,* **1985**, 50, 2435.
44. Khisal, A.V.; Rodriguez, J.; Diaz, M.; Moretti, R.; Wilhelm, R.; Lee, R.; Slate, D.; Crews, P., *J. Org. Chem.*, **1993**, 58, 4871.
45. Broadhurst, M. J.; Hassall, C. J., *J. Chem. Soc. Perkin. Trans. I,* **1982**, 2227.
46. a) Kende, A. S.; Rizzi, J. P., *J. Am. Chem. Soc.*, **1981**, 103, 4247. b) Wuff, W. D.; Tang, P. C., *J. Am. Chem. Soc.*, **1984**, 106, 434.
47. Kodukulla, K. R. P.; Trivedi, G. K.; Vora, J. D.; Mathur, H. H., *Synth. Commun*. ,**1994**, 24, 819.
48. a) Bhide, B. H. and Shah, K. K., *Ind. J. Chem. B,* **1980**, 19, 9. b) Pepper, J. M. and Saha, M., *Can. J. Chem.*, **1964**, 42, 113.
49. a) Ben, I.; Castedo, L.; Saa, M. J.; Seijas, J. A.; Suan, R. and Gabriel, T., *J. Org. Chem.*, **1985**, 50, 2236. b) Barton, D. H. R.; Cottier, L.; Freund, K.; Luini, F.; Magnus, P. P., *J. Chem. Soc. Perkin Trans. I*, **1976**, 499.
50. Corey, E. J. and Suggs, W., *Tetrahedron Lett*., **1975**, 2647.
51. Carter, S.; Wallace, T., *Synthesis*, **1983**, 1000.; *Synthesis* **1976**, 65, 133.
52. a) Eliel, E. L.; Hutchins, R. O. and Knoeber, M., *Org. Synth. Coll. Vol.* 6, **1988**, 442. b) Courtheyn, D.; Verhe, R.; Kimpe, N. D.; Buyck, L. D. and Schamp, N., *J. Org. Chem.*, **1981**, 46, 3226. c) Popp, F. D. and Catala, A., *J. Org. Chem.,* **1961**, 26, 2738. d) Fieser, L.

F. and Jackobsen, R. P., *J. Am. Chem. Soc.*, **1937**, 59, 2337. e) Texier-Boullet, F.; Villemin, D.; Ricard, M.; Moison, H. and Foucaud, A., *Tetrahedron*, **1985**, 41, 1259.

53. Cope, C. A.; Hofmann, C. M.; Wyckoff, C. and Hardenbergh, E., *J. Am. Chem. Soc.*, **1941**, 63, 3452.
54. a) Katritzky, A. R.; Fan, W.; Liang, D. and Li, Q., *J. Heterocyclic. Chem.*, **1989**, 26, 1541. b) Mizono, K.; Ikeda, M. and Otsuji, Y., *Chem. Lett.*, **1988**, 9, 1507.
55. a) Davis, F. A.; Reddy, G. V.; Chen, B. C.; Kumar, A. and Haque, S. M., *J. Org. Chem.*, **1995**, 60, 6148. b) Magatti, C. V.; Kaminiski, J. J.; Rothberg, I., *J. Org. Chem.*, **1991**, 56, 3102. c) Texier-Boulet, F.; Villemin, D.; Ricard, M.; Moison, H. and Foucannd, A., *J. Org. Chem.*, **1992**. 57, 441.
56. a) Schwartz, A. and Madan, P., *J. Org. Chem.*, **1986**, 51, 5463. b) Berrrian, J. F.; Royer, J. and Husson, H. P., *J. Org. Chem.*, **1994**, 59, 3769. c) Pawlak, J. H. and Berchtold, A. G., *J. Org. Chem.*, **1988**, 53, 4063. d) Stevens, R. V.; Beandien, N.; Chan, W. H.; Daniewski, A. R.; Takeda, T.; Waldner, A.; Williard, P. G. and Zulter, V., *J. Am. Chem. Soc.*, **1986**, 108, 1039.
57. Hoesh, K., *Ber.*, **1915**, 48, 1122.
58. Houben, J., *Ber.*. **1926**, 59, 2878.
59. Booth, B. L. and Noori, G. F. M., *J. Chem. Soc. Perkin. Trans. I*, **1980**, 2894.
60. Yato, M.; Ohwada, T. and Shudo, K., *J. Am. Chem. Soc.*, **1991**, 113, 691.
61. Rama Rao, A. V.; Gaitonde, A. S.; Prakash, K. R. C. and Prahlada Rao, S., *Tetrahedron Lett.*, **1994**, 35, 6347.

C H A P T E R - 3

CATALYTIC ORGANIC TRANSFORMATIONS

3.0.1 INTRODUCTION:

The definition of catalyst is a substance whose presence makes physiological and chemical reactions proceed and itself does not get altered during the course of the reaction. In other words catalyst is a substance that accelerates rate of chemical reaction but is not consumed in the reaction, its mere presence evokes chemical actions, which could not take place in its absence.

A catalyst may control a chemical reaction by increasing the reactivity between molecules brought into play in the reaction and by facilitating the interaction between the reacting molecules, by loosening certain linkages or bonds within them. For example in oxidation reaction catalyst activates oxygen and helps the reactant to absorb oxygen. In catalytic hydration or dehydration, catalyst helps either addition of water or removal of water during reaction process. In catalytic hydrogenation, catalyst helps the addition of hydrogen to substance by ionizing hydrogen gas.

The basic concept of a catalyst is that, a substance in a small amount causes a large change; it determines the path of a reaction e.g. the decomposition of ethanol over alumina catalysts yields ethylene and water; while over copper or silver catalysts, acetaldehyde and hydrogen are the products. In catalytic halogenation or dehalogenation catalyst helps addition or removal of halogens by radical or ionic mechanism. In alkylation or acylation reactions, catalysts assist in formation of cation as well as stabilizing it in the process. In polymerization, catalyst polarizes the double bonds or initiates the formation of free radicals. Catalyst even helps in rearrangement of groups within interacting molecules to form isomeric compounds during isomerisation.

Thus the catalysts may be of different types, acids, bases, organometallics, enzymes, polymer supported, molecular sieves, zeolites, clays, phase transfer catalysts, metal and metal oxides, transition metal complexes etc. They have the ability to catalyze a variety of chemical reactions such as (a) Condensation (b) Alkylation (c) Oxidation (d) Reduction (e) Hydrogenation (f) Dehydrogenation g) Halogenation and (h) Isomerisation etc.

Catalytic reactions can either take place in solutions or on surfaces. Most of metal ions or hydrogen ions function as acid base catalysts or in electron transfer reactions. Several organometallic complexes were used as single electron transfer catalyst. Enzymes are a separate class of catalysts, without them the processes of life will not take place. Enzymes, which possess complex polymeric structure catalyze biological reactions efficiently and function only at relatively mild temperatures. For example: (1) Breakdown of proteins and carbohydrates (2) Biosynthetic process that leads to

growth and replacement of living organisms (3) Photosynthesis (4) Catalytic oxidation processes that convert food into CO_2, H_2O and energy etc.

Several alumino-silicates like zeolites, clays and molecular sieves are used as catalysts. Zeolites bear catalytic sites having microscopic cavities and are comparable to enzymes. Zeolites catalyze several types of reactions like oxidation, halogenation, alkylation or acylation and isomerisation reactions. Molecular sieves, which are similar in structure to the zeolites, are also used in acid catalyzed reactions. Clays and other layered materials are also used in acid or base catalyzed reactions. Metals, metal oxides and metal sulfides some times used in combination with each other are important as industrial catalysts. Palladium, nickel and platinum as powders or on supports are used in olefin hydrogenation in food industries. Copper, nickel, platinum etc. are used in carbonyl reductions. The catalysts are classified into two main types: 1) Homogeneous catalysts 2) Heterogeneous catalysts.

1) **Homogeneous catalysts**: In recent years the term homogeneous catalysis is applied more specifically to the use of a solution of certain organometallic compounds in which a central metal atom is surrounded by a regular pattern of atoms or molecules, known as ligands with which it is coordinated. Homogeneous catalytic transition metal complex reactions enhance selectivity compared with heterogeneous catalytic reactions. In homogeneous catalytic reactions the catalysts and reactants are present in one phase and a major disadvantage of this arises from the difficulty in separating the product from the catalysts; this is a peculiar problem in large-scale conversions with open reaction systems. The reactions of industrial importance are primarily hydro-formylation (oxo synthesis), carbonylation, addition of HCN and olefin polymerization.

2) **Heterogeneous catalysts**: In heterogeneous catalysis the reaction takes place at the interface between the catalysts and the less dense phase. In other words heterogeneous catalysis describes the enhancement in the rate of a chemical reaction brought about by the presence of an interface between two phases. In general much higher temperature is used in heterogeneous catalytic reactions than in homogeneous catalytic ones. Heterogeneous catalysts can be divided naturally into two distinct groups (a) Metals and (b) Non-metals.

The former group comprised largely of the metals of groups VIII and IB. The first mentioned are the most important. The heterogeneous catalysts can be easily recovered and reused after activation.

3.0.2 HYDROTALCITES (HT) – LIKE ANIONIC CLAYS AS A HETEROGENEOUS CATALYST:

Hydrotalcite (HT)[1-4] like synthetic anionic clays (also called layered double hydroxides, LDHs) are more rare in nature than cationic clays (or clay minerals), but relatively simple and inexpensive to synthesize in laboratory and on industrial scale. Hydrotalcite (HT), a mixed hydroxycarbonate of magnesium and aluminium was first discovered in Sweden around 1842 and its name derives from the fact that it can be easily crushed into a white powder similar to talc. Hydrotalcite like anionic clays appeared in the patent and in open literature in connection with various industrial applications.

Hydrotalcites (HT) are composed of positively charged brucite like layers of divalent and trivalent metal hydroxides whose excess positive charge is compensated by anions and water molecules present in the interstitial positions. The structure[5-8] of these compounds consists of brucite [Mg $(OH)_2$] type octahedral layers in which a part of the M (II) cations are isomorphously substituted by M(III) cations. The excess positive charge of the octahedral layers resulting from this substitution is compensated for interstitial layers built of anions such as CO_3^{2-} and water molecules. Many names are used as a function of the composition and nature of the polytype forms[9] (Hydrotalcite, Mansseite, Sjorgenite, Stitchite etc). They can be represented by the general formula $[M(II)_{1-x}\ M(III)_x\ (OH)_2]^{x+}\ [(A^{n-})_{x/n}\ Y\ H_2O]^{x-}$ where M (II) and M (III) are the divalent and trivalent cations such as Mg^{+2}, Cu^{+2}, Ni^{+2}, Co^{+2}, Mn^{+2}, Zn^{+2} and Al^{+3}, Fe^{+3}, Cr^{+3}, Ga^{+3}, V^{+3}, Ru^{+3}, Rh^{+3} respectively, A^{n-} is an inter layer anion such as CO_3^{2-}, NO_3^-, SO_4^{2-} and x is the ratio of trivalent metal which is in the range from 0.1 to 0.33. for example hydrotalcite has the formula $Mg_6Al_2(OH)_{16}\ CO_3.4H_2O$ (Mg:Al = 3.1). The structure of HT-like compounds can be best visualized by starting with the structure of brucite [$Mg(OH)_2$], wherein each Mg^{2+} ion is octahedrally surrounded by hydroxyl groups (6 fold coordinated to OH^-). Each octahedron shares edges to form an infinite sheet like structure[10]. Some of the Mg^{2+} are replaced by Al^{3+} in the brucite sheet resulting in a net positive charge on the clay sheets. The positively charged Mg-Al double hydroxide sheets (or layers) are charge balanced by the carbonate anions residing in the inter layer section of the clay structure (Fig.1)[4]. Thermal calcination of these materials leads to interactive, high surface area, non-stoichiometric and well dispersed mixed metal oxides which are efficiently used in many catalytic transformations such as aldol condensation[11], epoxidation[12], cyanoethylation[13] and Meerwein Ponndorf-Verley reduction.[14]

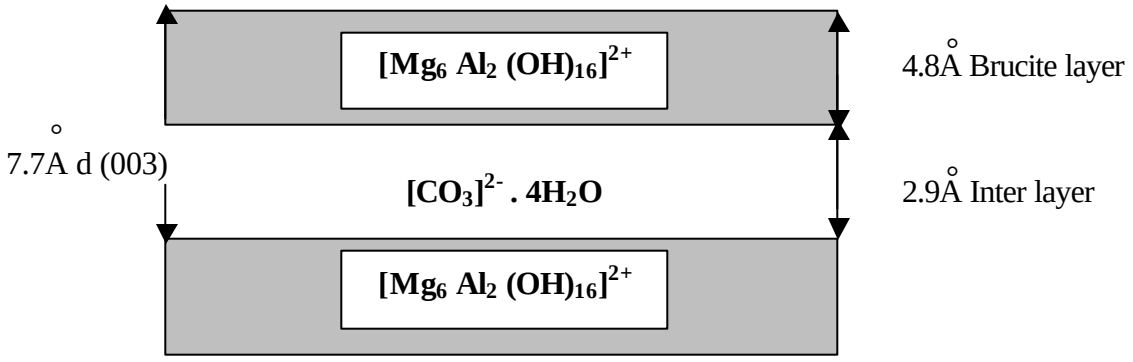


Fig 1: Schematic presentation of Mg-Al hydrotalcite

3.0.3 BASIC PROPERTIES:

Mg-Al hydrotalcite materials upon thermal calcinations at 450°C give a highly active mixed oxide. The most interesting properties of the oxides obtained by calcinations are: 1) High surface area 2) Basic properties.

Thermal treatments induce dehydration, dehydroxylation and loss of charge compensating anions resulting in mixed oxides with MgO- type structures[15]. The resulting materials possess pronounced basic properties and are used potentially as base catalysts. The high activity of these materials is attributed to the presence of a large number of OH groups generated during rehydration of thermally activated hydrotalcites, which act as Bronsted basic sites with pK values in the range of 10.7-13.3 and a few sites with pK values 16.5[16]. It is suggested by Trifiro[2] *et al*. that the basic properties of calcined hydrotalcite depend upon the Al (Al + Mg) ratio. When the amount of Al increases, the total number of basic sites decreases [17]. Thus for any base-catalyzed reaction a maximum in activity should occur for an optimum Al (Al + Mg) ratio. The optimum will depend on the base strength needed to activate the particular reactant. It was observed[18] that in case of condensation between acetophenone and benzaldehyde, a maximum activity occurs for Al (Al + Mg) ratio between 0.25 to 0.30. It was also viewed that smaller crystallites are more active than large crystals, indicating that the stronger basic sites, probably these occupied oxygens at corners, play an important role in basic catalysts. Corma *et al.*[18] compared the catalytic activity of CHT (calcined hydrotalcite) with other base catalysts such as alkali exchanged zeolites and sepiolites. It has been found that catalysts derived from hydrotalcites are most active for condensation reactions. Thus, it is clear that hydrotalcite like anionic clays are superior than alkali exchanged Y-zeolites and sepiolites.

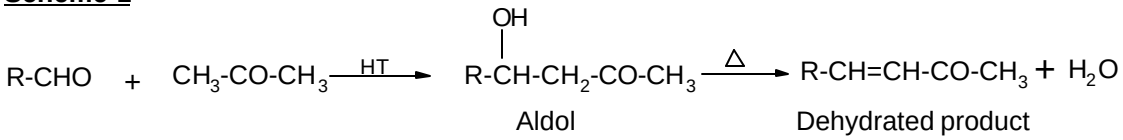
3.0.4 APPLICATIONS OF HYDROTALCITE-LIKE MATERIALS IN ORGANIC SYNTHESIS:

Hydrotalcites consist of Brucite-like layers having positive charge with anionic species in the inter layer, forming neutral materials. Combination of different elements, changing the element ratios in the Brucite like layer and selection of different anionic species can tune up the basicity of the hydrotalcites and the inter layer distance. The high surface area and the basic properties of hydrotalcite-like anionic clays coupled with thermal stability helps to utilize such materials as catalysts. The surface hydroxy groups of the hydrotalcites act as basic sites to promote many significant organic transformations.

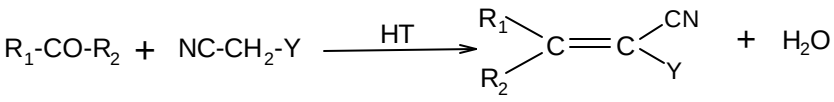
Layered double hydroxides (LDHs) or hydrotalcite-like compounds (HTLCs) upon thermal decomposition at about 450 °C give a highly active homogeneous mixed oxide which is potential basic catalyst used for a variety of organic transformations such as aldol condensation, nucleophilic halide exchange, alkylation of diketones, epoxidation of activated olefins with hydrogen peroxide or Claisen-Schmidt condensation. Some of the important catalytic transformations are discussed below:

B. M. Choudhary *et al.*[11]. performed aldol and Knoevenagel condensations with suitably activated Mg-Al hydrotalcites as catalyst in quantitative yields, in the liquid phase under mild reaction conditions at a faster rate for the first time. A general schematic diagram of reaction between acetone and substituted benzaldehyde and condensation of different carbonyl compounds with malononitrile or ethyl cyanoacetate is shown in Scheme-1 and 2 for aldol and Knoevenagel condensation respectively.

Scheme-1



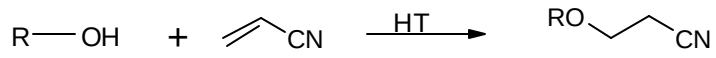
Scheme-2



Figueras *et al.*[13] found Mg-Al hydrotalcite to be highly active, reusable and air stable catalyst for cyanoethylation of alcohols (Scheme-3). These authors also studied Mg-Al hydrotalcite (Mg:Al

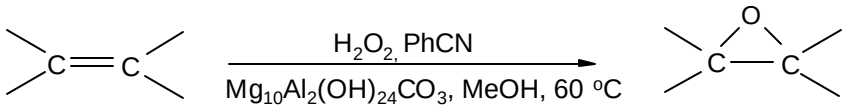
= 3:1) catalyst for Meerwein-Ponndorf-Verley[14] reduction of carbonyl compounds in the liquid phase.

Scheme-3



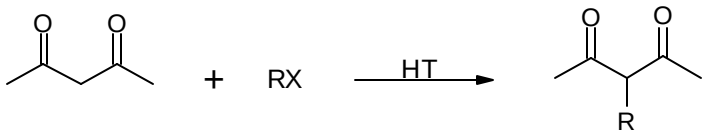
Kaneda *et al*[12]. used the layered hydrotalcite, $Mg_{10}Al_2(OH)_{24}CO_3$ as an efficient base catalyst for the epoxidation of various olefins using hydrogen peroxide in the presence of benzonitrile and with MeOH as a solvent (Scheme-4).

Scheme-4



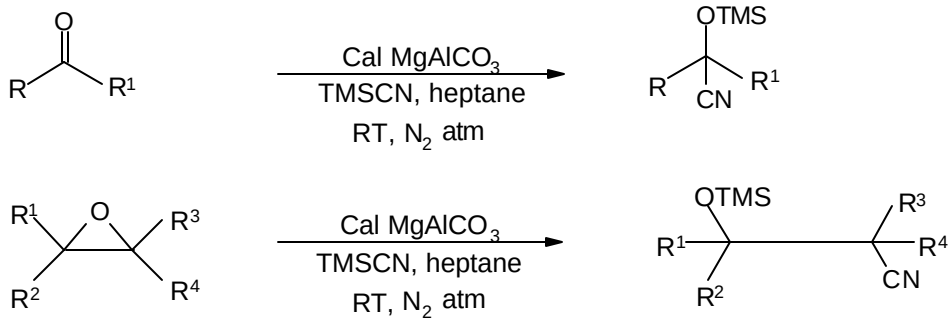
The selective C-monoalkylation of 2,4 pentanedione with reactive alkylating agents to give diketones was carried out by Figueras *et al*[19]. (Scheme-5).

Scheme-5



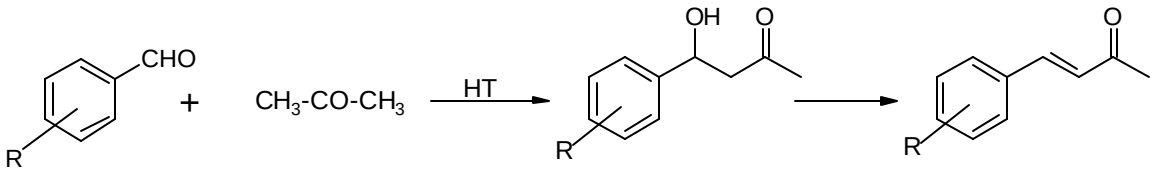
The use of basic oxides obtained from hydrotalcite precursors for the cyanosilylations of carbonyl compounds and nucleophilic ring opening of oxiranes using TMSCN was demonstrated by Choudhary's group[20] (Scheme-6).

Scheme-6



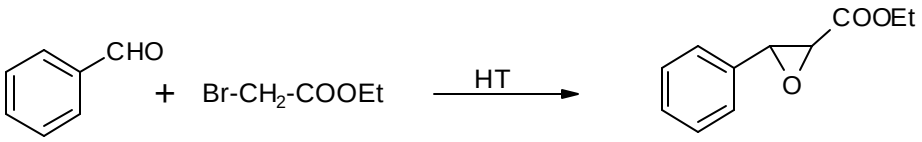
Figueras *et al*[21]. studied aldol condensation between acetone and different substituted benzaldehydes using hydrotalcite as solid catalyst. The nucleophilic strengths of the substituents were also studied and the order was found to be as follows: *p*-NO_2>*m*-Cl>*p*-Cl>Me>*p*-OMe (Scheme-7).

Scheme-7



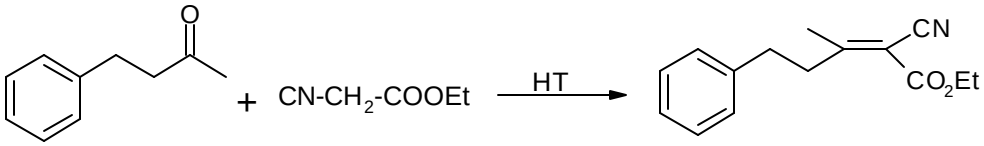
Corma's group[22] studied Darzen's glycidic ester condensation reaction between benzaldehyde and ethylbromoacetate (Scheme-8).

Scheme-8



Figueras's group efficiently carried out the first step for the production of citronitril[19] i.e. the

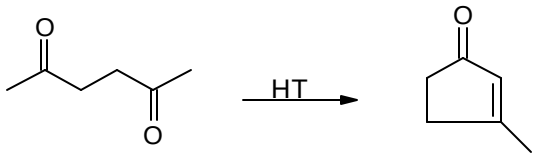
Scheme-9



condensation of benzylacetone with ethyl cyanoacetate (Scheme-9).

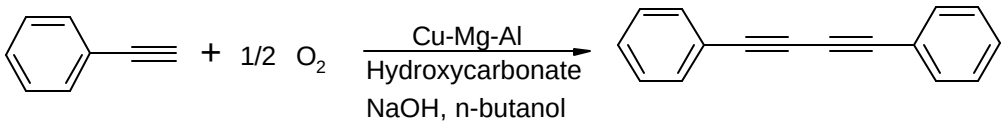
An intramolecular condensation of acetonylacetone using calcined hydrotalcite in MeOH was found to give 3-methyl cyclopent-2-ene-1-one[24] (Scheme-10).

Scheme-10



Cu-Mg-Al hydroxycarbonate, derived from Cu-Mg-Al hydrotalcite afforded the coupling of phenylethyne to 1,4 –diphenylbuta-1,3-diyne in the presence of sodium hydroxide and oxygen[25]. This method is a practical heterogeneous alternative to the conventional homogeneous reaction such as Glaser and Eglington reaction and Cadiot – Chodkiemicz reaction[26] (Scheme-11).

Scheme-11



Thus hydrotalcites are useful to effect various reactions of general utility in organic conversions.

CHAPTER-3

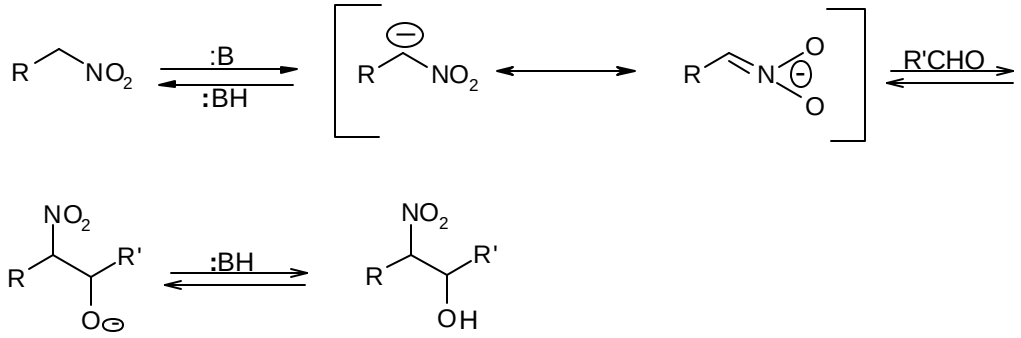
SECTION-I

DIASTEREOSELECTIVE SYNTHESIS OF NITROALCOHOL DERIVATIVES OVER Mg-Al HYDROTALCITES

3.0.5 INTRODUCTION:

Carbon-carbon bond forming reaction is of fundamental importance in organic chemistry. In 1895 Louis Henry[27] discovered the reaction which is currently known as the Henry or nitroaldol reaction. The Henry reaction is one of the classical C-C bond forming processes, in which diastereomeric mixtures of 2-nitroalcohols which are versatile intermediates are formed on treatment of primary or secondary nitroalkanes and carbonyl derivatives with a base[28]. It is clear that the Henry reaction is an aldol-type reaction and the deprotonation of primary and secondary nitroalkanes with a whole range of different bases for generating the corresponding nitronate monoanions constitutes the first step of the sequence (Scheme-12).

Scheme-12

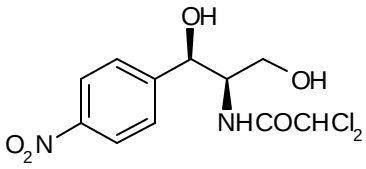


The Henry reaction and some of its recent improvements have found numerous applications in assembling carbon atoms and functional groups to build natural products structures with high chemo- and regio- selectivity. Several base catalysts including alkali metal hydroxides, carbonates, alkoxides, anion exchanged resins, organic amines, SiO_2 / microwave,[29] alumina surface,[28c] Amberlyst A-21,[30] potassium exchanged layered zirconium phosphate,[31] rhodium complex,[32] tetramethyl guanidine,[33] NaOH-catalysed process in the presence of cetyltrimethylammonium chloride (CTACl),[34] dendritic catalyst,[35] proazaphosphatranes,[36] LAH,[36] etc have been employed to bring about the Henry reaction.

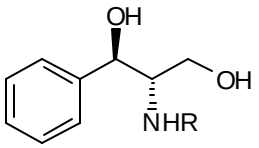
3.0.6 UTILITY OF HENRY REACTION:

The potential utility of the reaction as a chain-lengthening tool can be illustrated by the great importance of 2-nitroalcohols as pivotal synthetic intermediates in synthesis. They can be converted

into ß-amino alcohol derivatives including chloramphenicol[28b], ephedrine, norephedrine and anthracycline antibiotics[37].



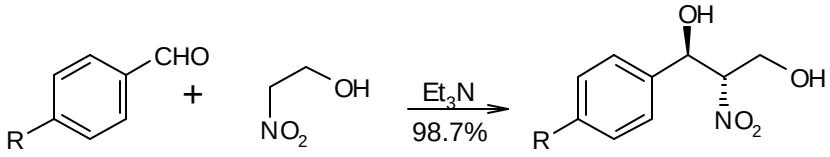
Chloramphenicol



Ephedrine R = CH_3
Norephedrine R = H

Reduction of the nitro group with lithium aluminum hydride,[38] aluminum amalgum,[39] hydrogen and palladium on carbon,[40] hydrogen and platinum[41] or using Raney nickel[42] affords the corresponding amino compounds. Vicinal amino alcohols have a broad significance in organic chemistry and their biological relevance can be seen in the structure of epinephrine (adrenalin) and related mediators of the symapathetic nervous system[43] as well as in the chemistry and biochemistry

Scheme-13



R = H
R = NO_2

R = H
R = NO_2

of sphingolipids[37a] and in the structure of some carbohydrate components of a group of biologically important anthracycline antibiotics[37]. When benzaldehyde was treated with 2-nitroethanol in the presence of triethylamine as catalyst DL-*threo*-1-phenyl-2-nitropropane-1,3-diol which is important as an intermediate in an industrial synthesis of the antibiotic chloramphenicol[28b] was obtained in 98.7% yield, with >95% ds.

2-Nitroalcohols can be oxidized to give the corresponding 2-nitro-ketones. The utility of linear a-nitro ketones has been increased recently by the discovery of some direct[44] and indirect[28c] procedures to effect the replacement of the nitro group by hydrogen. Several functionalised nitroalkanes have been reported to be useful functionalized alkyl anion synthons in the synthesis of natural products *via* 2-nitro alcohol and a-nitro ketone intermediate[44,28c]. However, the conversion of 2-nitroalcohols into conjugate nitroalkanes can be considered by far the most important. This reaction can be accomplished by dehydration with several reagents. Conjugated nitroalkenes are intermediates of a certain importance and there is a wide range of efficient methods for their

transformations into other functionalities. Among them the selective reduction to nitroalkanes[45] and the conversion of the latter into their corresponding ketones by the Nef reaction[28c] play a very important role. This key reaction which effectively reverses the polarity of the neighboring carbon from a potentially nucleophilic to an electrophilic one, is of great strategic importance[45].

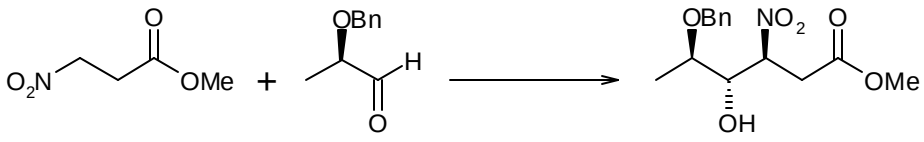
3.0.7 Problems Experienced in Henry Reaction:

Since basic reagents are also catalysts for the aldol condensation and for the Cannizzaro reaction when aldehydes are used as carbonyl sources, it is necessary to adopt experimental conditions to suppress these competitive reactions[31,46]. To obtain better yields of 2-nitro alcohols it is necessary to carefully control the basicity of the reaction medium. The concentration of carbonyl components also has to be kept to a minimum for a sufficient rate of reaction avoiding aldol condensation and the Cannizzaro reaction. Furthermore, 2-nitro alcohols formed in the Henry reaction may undergo base catalysed elimination of water to give a-nitroalkenes[46b] which readily polymerize. This elimination is difficult to avoid when aryl aldehydes and ketones are used.

Recently, several improved methods have been devised to overcome the many drawbacks of the Henry reaction by increasing their chemo-, regio-, and in specific cases, stereoselectivity. The Henry reaction performed using commercial chromatographic alumina in the absense of solvent gave mixtures of diastereomeric 2-nitroalcohols after 24 hours[47]. However, the lack of stereoselectivity is due to the reversibility of the reaction and easy epimerisation at the nitro-substituted C-atom. Barette and coworkers[48] recently have discovered an experimentally simple procedure for stereoselective preparation of *erythro*-2-nitroalkanols in which alkyl nitronates were reacted with aldehydes in the presence of isopropoxytitanium trichloride to give erythro ß-nitroalcohols. The method works well in the case of electron-deficient aromatic aldehydes but less efficient with aliphatic aldehydes.

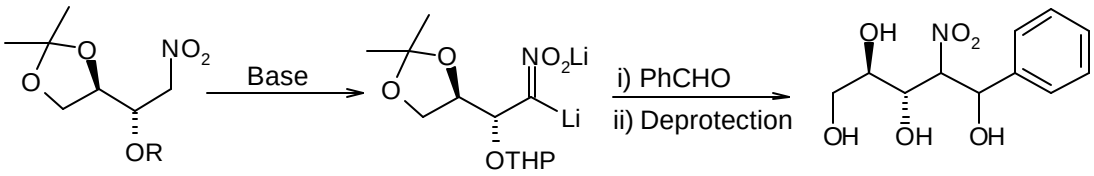
Hanessian[42] has observed some variation in selectivity in the reaction of (*S*)-(benzyloxy) propionaldehyde with methyl 3-nitropropionate using zinc or magnesium salts and potassium tert-butoxide in THF (Scheme-15).

Scheme-14



High *erythro* selectivity (4:1-> 19:1) was also observed in the fluoride-catalyzed reaction of silylnitronates with aldehydes. Limitation of this method is that the experimental conditions were critically precise for success. Known acetonide (no) of (2*S*, 3*R*)-1-nitro-2, 3, 4-butanetriol was further protected with a THP group (no) to afford the dilithio derivative which gave (no) on treatment with alkyl lithium and combined with benzaldehyde to furnish single diastereomer.

Scheme-15



R = H
R = THP

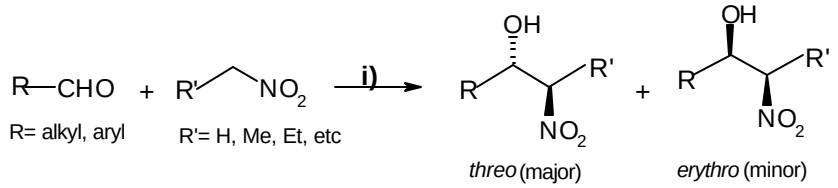
Significant improvements to the Henry reaction have been achieved by silyl nitronates in the presence of fluoride ion or alternatively a, a-doubly deprotonated primary nitroalkanes are reacted with aldehydes to give the intermediate nitronate alkoxides. Kinetic reprotonation at -100 ^{o}C in polar solvents (THF with HMPA or DMPU) gave the nitro alcohols enriched in *threo* diastereomer. Both of these procedures discovered by the Seebach group[49a,b], have proved to be useful for the stereoselective preparation of vicinal amino alcohols. However, the conditions reported are drastic and reduced diastereoselectivity is observed with aromatic aldehydes. A stereoselective synthesis of either of the *erythro* or *threo* isomers would be highly desirable.

Hence to obtain better yields and diastereoselectivity of 2-nitroalcohols, it is necessary to develop new procedures employing heterogeneous catalysts with basic character. The development of new catalysts, which can effectively overcome the problems experienced in the Henry reaction, should heighten the synthetic scope of the reaction. In this connection, the use of a heterogeneous catalysts in the liquid phase offer several advantages with their homogeneous counterparts such as ease of recovery, recycling and enhanced stability and their potential should be explored for Henry reaction.

3.0.8 Present work:

Stereochemical control in nitroaldol reactions continues to be a challenge for organic chemists.[48] In the present work, the results on the diastereoselective synthesis of nitroalkanols from aldehydes and nitroalkanes catalyzed by Mg-Al hydrotalcite (HT) are described. In the course of our work on the modifications of the nitroaldol reaction, when aldehydes were treated with an equimolar amount of nitroethane in the presence of catalytic amount of Mg-Al-hydrotalcite under reflux in THF, the corresponding nitroalcohols were obtained in good to excellent yields.

Scheme-16



i) Mg-Al -HT (20% w/w), THF, reflux, 6-8 h

We noticed in several cases that the derivatives isolated were diastereomerically enriched. The results of the Henry reaction between 3-nitrobenzaldehyde and nitroethane over various hydrotalcites are presented in the Table 1. A comparison of the results in Table 1 shows that among the catalysts screened, Mg-Al (3:1) gives best results for the Henry reaction. The higher activity of this catalyst is due to high surface area (176 m^2 g^{-1}) associated with this catalyst.

Table 1: Results of the Henry reaction betwteen 3-nitrobenzaldehyde and nitroethane over various hydrotalcites[a]

Entry	Catalyst	Surface area[b] (m^2 g^{-1})	Yield[c] (%)
1	MgAl 3.0 HT	176	95.5
2	MgAl 4.0 HT	125	72.2
3	MgAl 5.0 HT	150	81.5
4	ZnAl 3.0 HT	135	77.6
5	CuAl 3.0 HT	154	81.7

a: Reaction conditions: 3-Nitrobenzaldehyde (5mmol), nitroethane (5mmol), catalyst (20%w/w), THF (10ml), reflux 6-8h. b: Surface area determined by N_2 adsorpation-desorption method. c: Isolated yield after column chromatographic puricatioon

Table 2 lists the results of different types of aldehydes that have been condensed with nitroalkanes to the corresponding nitroalkanols in high yields using Mg-Al (3:1) as a catalyst. Both aromatic and aliphatic aldehydes could be employed successfully for Henry reaction affording the corresponding nitroalkanols in high yields. High chemoselectivity is observed since several functionalities such as hydroxyl groups, tetrahydropyranyl, C-C double bond and furyl are preserved under these conditions. It is to be noted that both primary and secondary nitroalkanes can be employed. Contrary to other methods, the success of this approach is independent from the ratio of catalyst/substrates and does not need longer reaction time or dehydrations of the 2-nitroalcohols into nitroalkenes did not take place even if aromatic aldehydes are used. The catalyst from the reaction mixture was recovered by simple filtration and was successfully reused, after activation at 450 ^{o}C, for two times without loosing its activity and stereoselectivity.

After this work was published[51], we received a request from NIH, USA for sending the 1-(2-chlorophenyl)-2-nitrobutan-1-ol (262) (Entry-6, Table-2) for screening it for anticancer activity. We had supplied the above sample and in preliminary tests it was found to be active in case of lung cancer (NCI-H4 60), Breast cancer (MCF7) and central nervous system cancer (SF-268).

3.0.9 MECHANISM AND DIASTEREOSELECTIVITY:

Mg-Al hydrotalcite materials upon thermal calcination at 450 ^{o}C give highly active mixed oxides. The high activity of these materials is attributed to the presence of a large number of OH^- groups generated during rehydration of thermally activated hydrotalcite, which acts as Bronsted basic sites with pKa in the range of 10.7-13.3 and few sites with pKa =16.5.[16] It is presumed that this basicity is responsible for the catalytic activity and selectivity by attracting acidic proton from the nitroalkanes followed by its addition onto aldehydes. It is observed that in all 9 cases studied *threo* isomer is formed predominantly (Table 2). Particularly in the case of nitroaldols derived from 4-nitrobenzaldehyde, 2-chlorobenzaldehyde and 2-chloroquinoline-3-carboxaldehyde (entries 7, 8 and 10), exclusive formation of *threo* isomer has been obtained based on their ^{1}H and ^{13}C-NMR and G.L.C. analysis. In their ^{1}H-NMR spectra the vicinal coupling constants (7.3 - 8 Hz) between the α-N-C-H and the α-O-C-H have clearly confirmed the formation of *threo* isomer. These outcomes may be rationalized in terms of transition state models based on closed chair-like structures involving coordination between the two oxygen atoms and the metal center (Scheme-17).

Table 2: Mg-Al hydrotalcite-catalyzed nitroaldol reaction between aldehydes and nitroalkanols.

Entry	Substrates	Nitroalkanes	t(h)	Products[a]	Yield[b]	*threo:erythr*
1	Benzaldehyde	Nitroethane	6	1-Phenyl-2-nitropropan-1-ol (**257**)	87	3.25:1
2	3-Nitrobenzaldehyde	Nitroethane	6	1-(m-Nitrophenyl)-2-nitropropan-1-ol (**258**)	95	12.5:1
3	4-Nitrobenzaldehyde	1-Tetrahydro pyranyloxy-2-nitroethane	8	1-(p-Nitrophenyl)-2-nitro-3-tetrahydro pyranyloxypropan -1-ol (**259**)	72	-
4	Salicylaldehyde	Nitroethane	8	1-(o-Hydroxyphenyl)-2-nitropropan-1-ol (**260**)	45	-
5	4-Methoxy-benzaldehyde	Nitroethane	8	1-(p-Methoxyphenyl)-2-nitropropan-1-ol (**261**)	62	1.23:1
6	2-Chloro-benzaldehyde	1-Nitropropane	6	1-(o-Chlorophenyl)-2-nitrobutan-1-ol (**262**)	89	1.53 :1
7	4-Nitro-benzaldehyde	Nitroethane	6	1-(p-Nitrophenyl)-2-nitropropan-1-ol. (**263**)	84	100:0
8	2-Chloro-benzaldehyde	Nitroethane	6	1-(o-Chlorophenyl)-2-nitropropan-1-ol (**264**)	82	100:0
9	Furan-2-Carboxaldehyde	Nitroethane	6	1-(2-Furyl)-2-nitropropan-1-ol (**265**)	74	1.5:1
10	2-Chloroquinoline- 3-carboxaldehyde	Nitroethane	8	1-(2-Chloro-3-quinolinyl) - 2-nitropropan-1-ol (**266**)	88	100:0
11	3-Nitrobenzaldehyde	2-Nitropropane	8	1-(m-Nitrophenyl)-2-nitro-2-methylpropan-1-ol (**267**)	80	-
12	Cinnamaldehyde	Nitroethane	6	1-Styryl-2-nitropropan-1-ol (**268**)	41	1.25:1
13	n-Hexanal	Nitromethane	6	1-Nitromethyl-1-hexanol (**269**)	82	-
14	Propionaldehyde	Nitromethane	6	1-Nitromethylpropan-1-ol (**270**)	77	-

a: Products were characterized by IR, ^{1}H, $^{13}CNMR$ and M.S.

b: Isolated yield after column chromatography.

c: Average ratios were calculated from ^{13} C NMR signals (50.3 MHz) and/or ^{1}H NMR signal intensities.

Table 2: Mg-Al hydrotalcite-catalyzed nitroaldol reaction between aldehydes and nitroalkanols.

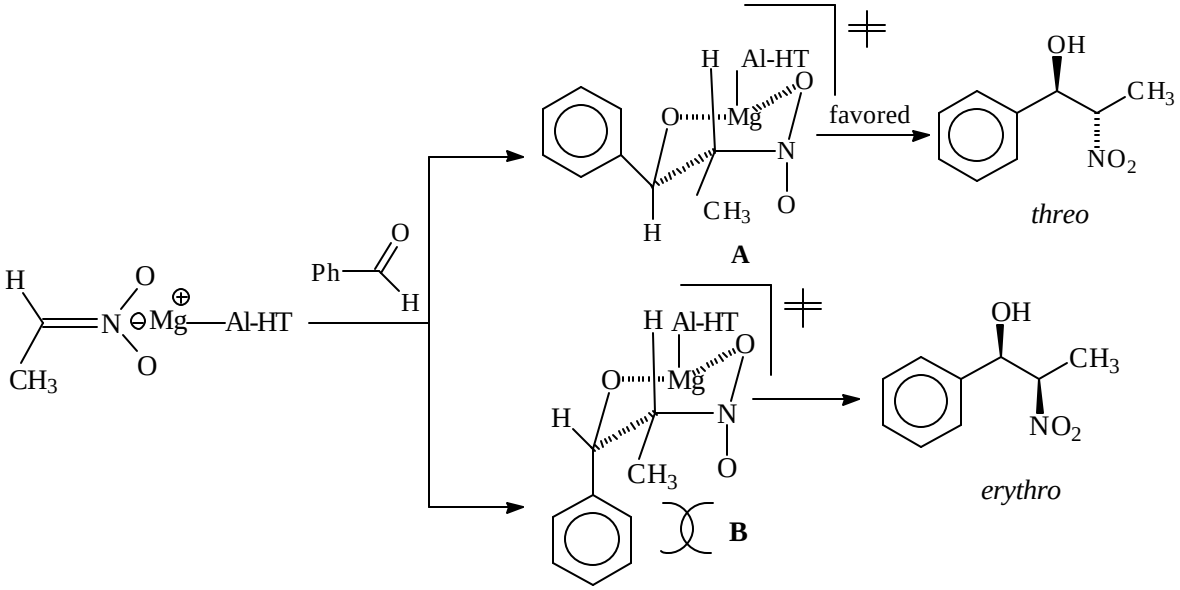
Entry	Substrates	Nitroalkanes	t(h)	Products[a]	Yield[b]	*threo:erythro*[c]
1	Benzaldehyde	Nitroethane	6	1-Phenyl-2-nitropropan-1-ol (**257**)	87	3.25:1
2	3-Nitro-benzaldehyde	Nitroethane	6	1-(m-Nitrophenyl)-2-nitropropan-1-ol (**258**)	95	12.5:1
3	4-Nitro-benzaldehyde	1-Tetrahydro pyranyloxy-2-nitroethane	8	1-(p-Nitrophenyl)-2-nitro-3-tetrahydro pyranyloxypropan -1-ol (**259**)	72	-
4	Salicylaldehyde	Nitroethane	8	1-(o-Hydroxyphenyl)-2-nitropropan-1-ol (**260**)	45	-
5	4-Methoxy-benzaldehyde	Nitroethane	8	1-(p-Methoxyphenyl)-2-nitropropan-1-ol (**261**)	62	1.23:1
6	2-Chloro-benzaldehyde	1-Nitro-propane	6	1-(o-Chlorophenyl)-2-nitrobutan-1-ol (**262**)	89	1.53 :1
7	4-Nitro-benzaldehyde	Nitroethane	6	1-(p-Nitrophenyl)-2-nitropropan-1-ol (**263**)	84	100:0
8	2-Chloro-benzaldehyde	Nitroethane	6	1-(o-Chlorophenyl)-2-nitropropan-1-ol (**264**)	82	100:0
9	Furan-2-carboxaldehyde	Nitroethane	6	1-(2-Furyl)-2-nitropropan-1-ol (**265**)	74	1.5:1
10	2-Chloroquinoline-3-carboxaldehyde	Nitroethane	8	1-(2-Chloro-3-quinolinyl) - 2-nitropropan-1-ol (**266**)	88	100:0
11	3-Nitro-benzaldehyde	2-Nitro-propane	8	1-(m-Nitrophenyl)-2-nitro-2-methylpropan-1-ol (**267**)	80	-
12	Cinnamaldehyde	Nitroethane	6	1-Styryl-2-nitropropan-1-ol (**268**)	41	1.25:1
13	n-Hexanal	Nitromethane	6	1-Nitromethyl-1-hexanol (**269**)	82	-
14	Propionaldehyde	Nitromethane	6	1-Nitromethylpropan-1-ol (**270**)	77	-

a: Products were characterized by IR, ^{1}H, ^{13}CNMR and M.S.

b: Isolated yield after column chromatography.

c: Average ratios were calculated from ^{13}C NMR signals (50.3 MHz) and/or ^{1}H NMR signal intensities.

From scheme-17, it can be readily visualized that the transition state **A** leading to anti product is favored, whereas the transition state **B** has steric interactions between Ph and O groups leading to energetically less favoured species. Also if it is assumed that chelated products are more likely to be thermodynamically more stable than nonchelated ones, this outcome may be rationalized by considering the Newman projections C and D for two aldolates.



Scheme 17 : Transition state structures for the nitroaldol reaction

For the *threo* aldolates, it can be seen that gauche interactions in C are minimized relative to confirmation D of the *erythro* aldolate (Fig. 2).

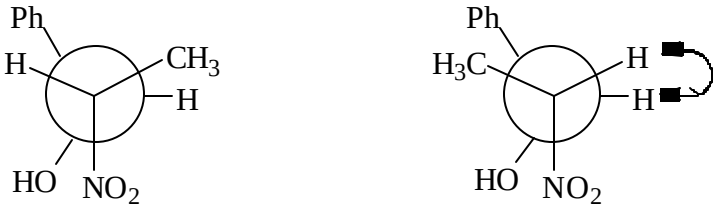


Fig. 1: Newman projections of *threo* and *erythro* aldolates

3.0.10 CONCLUSION:

In summary we have shown that the Mg-Al hydrotalcite is an effective and convenient catalyst for the condensation of nitroalkanes with aldehydes producing *threo*-nitroaldols in high yields and high diastereoselectivity. We have also shown that this new solid base catalyst is practical alternative to soluble bases in Henry reactions in view of the following advantages: high catalytic activity under mild liquid phase conditions, easy separation of the catalyst by simple filtration, waste minimization and possibility of reuse.

3.0.11 EXPERIMENTAL:

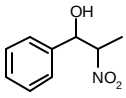
Preparation of the Mg-Al hydrotalcite (3:1) catalyst:

Two separate solutions namely solution A containing $Mg(NO_3)_2.6H_2O$ (115.38 g, 0.45 mole) and $Al(NO_3)_3.9H_2O$ (56.27 g, 0.15 mole) in 300 ml of distilled water and solution B cotaining NaOH (30 g) and Na_2CO_3 (15 g) in 200 ml of distilled water were prepared at room temperature. Both solutions A and B were added simultaneously through a burette to a 1 L beaker containing 300 ml of distilled water at room temperature. The rate of addition of metal nitrates was maintained at about 60 ml/h., while the pH of the reaction mixture was maintained alkaline by adjusting the flow rate of solution B. After completion of addition of solution A, the resulting slurry was digested at 65 ^oC for 30 min. with constant stirring. The resulting precipitate was washed with distilled water several times until the pH of the filtrate was 7.0. The catalyst was then dried at 100 ^oC and calcined at 450 ^oC respectively for 8 h in air. The other ratios of the above catalyst, Mg-Al 4.0, 5.0 were prepared by following the above procedures similarly, other catalysts, Zn-Al 3.0 and Cu-Al 3.0, were prepared using $Zn(NO_3)_2$ and $Cu(NO_3)_2$ respectively.

General procedure for the preparation of 2-nitroalcohols:

A solution of substituted benzaldehyde (2 mmol), nitroalkane (2 mmol) and Mg-Al-HT (3:1) (100 mg, 20%w/w) in THF (10 ml) was refluxed under nitrogen atmosphere for 6 h. The progress of the reaction was monitored by TLC (10% EtOAc in pet ether), the catalyst was filtered off and the product purified by flash chromatography (6% EtOAc in pet-ether as eluent) to afford nitropropan-1-ol (41-95%). Spectral data for entries 1, 2, 5, 6, 9 and 12 studied for the predominant *threo* selectivity given are for the mixtures of diastereomers.

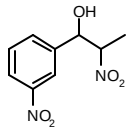
1-Phenyl 2-nitropropan-1-ol (257):[32]



Viscous liquid; **IR** (Neat): 3500, 1552 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.3 and 1.5 (d, J= 7.3 Hz, total 3H), 2.75 and 2.85 (d, J= 4.0 Hz, total 1H), 4.6-4.9 (m, 1H), 5.05 (dd, J= 8 Hz and 4Hz) and 5.40 (t, J = 4 Hz), total 1H, 7.4 (s, 5H); **^{13}C-NMR** ($CDCl_3$): δ 12.3, 16.6, 74.1, 76.4, 87.6, 88.6, 126.1, 127.1,

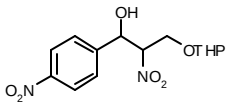
128.4, 128.6, 128.9, 129.1, 129.3, 138.6, 138.8; **MS** (m/z): 181 (M^+, 5), 107 (100), 91 (25), 77(77) and 57 (65)**.**

1-(3-Nitrophenyl)-2-nitropropan-1-ol (258):



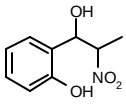
Greenish solid, m.p. 74 ^oC; **IR** (Nujol): 3510, 1520 cm^{-1}**;** ^{1}**H-NMR** ($CDCl_3$): δ 1.40 and 1.50 (d, J= 7.3 Hz, total 3H), 3.46 (d, J= 4 Hz, 1H), 4.70-4.85 (m, 1H), 5.22 (dd, J= 7.5 and 4.0 Hz and 5.55 (t, J= 4Hz), total 1H, 7.60 (t, J = 8.1 Hz, 1H), 7.70-7.80 (m, 1H), 8.15-8.30 (m, 2H); ^{13}**C-NMR** ($CDCl_3$): δ 12.0, 16.2, 73.0, 75.1, 87.0, 88.0, 122.0, 124.0, 130.2, 133.2, 140.7, 148.5; **MS** (m/z): 226 (M^+, 3), 179 (44), 149 (100), 105 (40), 90 (10) and 77 (51); Anal. Calcd. For $C_9H_{10}N_2O_5$ C = 47.79, H = 4.45, N = 12.38%; Found C = 47.51, H = 4.58, N = 12.52%.

1-(4-Nitrophenyl)-2-nitro-3-tetrahydropyranyloxypropan-1-ol (259)[48a]**:**



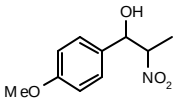
Viscous liquid; **IR** (Neat): 3440, 1558 cm^{-1}; ^{1}**H-NMR** ($CDCl_3$): δ 1.4-1.9 (m, 6H), 3.3-3.8 (m, 2H), 3.9-4.1 (m, 1H) 4.1-4.2 (m, 1H), 4.5-4.6 (m, 1H), 4.8-4.9 (m, 1H), 5.35-5.6 (m, 1H), 7.65 (d, J= 8 Hz, 2H), 8.25 (d, J= 8 Hz, 2H); Anal. Calcd. For $C_{14}H_{18}N_2O_7$ C = 51.53, H = 5.55, N = 8.58%; Found C = 51.01, H = 5.78, N = 8.03%.

1-(2-Hydroxyphenyl)-2-nitropropan-1-ol (260):



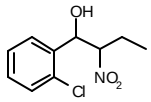
Viscous liquid; **IR** (Neat): 3510, 1551 cm^{-1}; ^{1}**H-NMR** ($CDCl_3$): δ 1.35 (d, J= 7 Hz, 3H), 3.9 (bs, 1H), 4.45 (q, J= 4.5 Hz, 1H), 4.9-5.1 (m, 1H), 6.8-7.5 (m, 4H); **MS** (m/z): 197 (M^+, 5), 179 (2), 132 (15), 123 (73), 121(100), 105 (16), 93 (10), 77 (15) and 66 (10). Anal. Calcd. For $C_9H_{11}NO_4$ C = 54.82, H = 5.61, N = 7.1 %; Found C = 54.20, H = 5.8, N = 7.3 %.

1-(4-Methoxyphenyl) –2-nitropropan-1-ol (261):

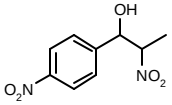


Viscous liquid; **IR** (Neat): 3500, 1630 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.30 and 1.50 (d, J= 8.1 and 6.5 Hz, total 3H), 2.80 and 2.85 (bs, total 1H), 3.84 and 3.85 (s, total 3H), 4.60-4.85 (m, 1H), 4.90 and 5.35 (d, J= 10 and 5.4 Hz, total 1H), 6.90 (d, J= 8 Hz, 2H), 7.35 (d, J= 8 Hz, 2H); **^{13}C-NMR** ($CDCl_3$): δ 12.4, 16.4, 55.2, 73.8, 75.8, 87.5, 88.5, 114.3, 127.2, 128.1, 130.4, 130.6, 159.6, 160.1; **MS** (m/z): 211 (M^+, 5), 137 (100), 135 (35), 109 (28), 94 (18), 77 (40) and 65 (15). Anal. Calcd. For $C_{10}H_{13}NO_4$ C = 56.89, H = 6.20, N = 6.63 %; Found C = 56.32, H = 6.82, N = 6.28 %.

1-(2-Chlorophenyl)-2-nitrobutan-1-ol (262):



Viscous liquid; **IR** (Neat): 3514, 1549 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 0.9-0.98, (two triplets merged together, total 3H), 1.5-1.8 (m, 2H), 2.0-2.25 (m, 1H), 2.9 and 3.1 (bs, total 1H, –OH), 4.65-4.80 (m, 1H), 5.60 (d, J = 8 Hz) and 5.65 (d, J = 4 Hz), total 1H, 7.2-7.6 (m, 4H); **^{13}C-NMR** ($CDCl_3$): δ 10.4, 10.6, 19.9, 23.6, 71.1, 71.2, 91.7, 94.9, 127.4, 127.8, 128.3, 129.8, 130.0, 130.1, 132.8, 135.9, 136.6; **MS** (m/z): 229 (M^+, 5), 182 (8), 143 (28), 141 (100), 125 (25), 111 (32), 91 (15), 77 (95) and 57 (41). Anal. Calcd. For $C_{10}H_{12}NO_3Cl$ C = 52.29, H = 5.26, N = 6.09, Cl = 15.45 %; Found C = 52.56, H = 5.42, N = 6.7, Cl = 15.32 %.



1-(4-Nitrophenyl)-2-nitropropan-1-ol (263):[34]

Solid, m. p. 91 ^{o}C; **IR** (Nujol): 3460, 1550 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.27 (d, J= 7.3 Hz, 3H), 3.50 (s, 1H, -OH), 4.65-4.81 (m, 1H), 5.21 (d, J= 8.2 Hz, 1H), 7.48 (d, J=8.0 Hz, 2H), 8.22 (d, J= 8 Hz,

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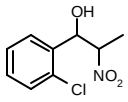
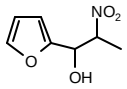
2H); **^{13}C-NMR** ($CDCl_3$): δ 16.4, 75.2, 88.0, 124.2, 128.1, 145.5, 148.5; **MS** (m/z): 226 (M^+, 5), 179 (32), 151 (100), 134 (15), 115 (12), 105 (48) and 77 (42).

1-(2-Chlorophenyl)-2-nitropropan-1-ol (264):



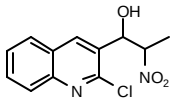
Viscous liquid; **IR** (Neat): 3512, 1548, 1462, 1282, 1196, 1098, 1050, 992, 884, 700 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.4 (d, J= 7.0 Hz, 3H), 2.85 (d, J= 4.0 Hz, 1H, -OH), 4.80-4.90 (m, 1H), 5.55-5.62 (m, 1H), 7.2-7.4 (m, 3H), 7.5 (d, J = 7.0 Hz, 1H); **^{13}C-NMR** ($CDCl_3$): δ 16.1, 72.0, 88.3, 127.8, 128.4, 130.0, 130.2, 132.9, 136.4; **MS** (m/z): 215 (M^+, 5), 168 (10), 141 (100), 138 (52), 110 (18) and 76 (8); Anal. Calcd. For $C_9H_{10}NO_3Cl$ C = 50.12, H = 4.66, N = 6.49, Cl = 16.46 %; Found C = 50.51, H = 4.85, N = 6.83, Cl = 16.43 %.

1-(2-Furyl)-2-nitropropan-1-ol (265)[34] :



Viscous liquid; **IR** (Neat): 3500, 1530 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.4 and 1.7 (d, J= 7.2 total 3H), 2.8 and 2.9 (d, J= 4.8 Hz, total 1H), 4.8-5.15 and 5.3-5.45 (m, total 2H), 6.35-6.55 (m, 2H), 7.40-7.50 (d, J= 7 Hz, 1H); **^{13}C-NMR** ($CDCl_3$): δ 13.2, 16.2, 69.0, 69.5, 85.1, 86.5, 92.3, 108.2, 109.5, 110.7, 142.9, 143.4, 150.9, 151.5; **MS** (m/z): 171 (M^+, 5), 124 (121), 108 (5), 97 (100) and 83 (42).

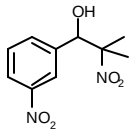
1-(2-Chloro-3-quinolinyl)-2-nitropropan-1-ol (266):



Solid, m.p. 88 ^oC; **IR** (Nujol): 3540, 1540, cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.5 (d, J= 7.2 Hz, 3H), 3.65 (bs, 1H), 5.05 (q, J= 7.2, Hz, 1H), 5.95 (s, 1H), 7.61 (t, J = 8 Hz, 1H), 7.78 (t, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 8.02 (d, J = 8 Hz, 1H), 8.5 (s, 1H); **^{13}C-NMR** ($CDCl_3$): δ 11.1, 70.3, 83.9, 127.3, 127.9, 128.3, 130.4, 131.4, 138.0, 147.5; **MS** (m/z): 266 (M^+, 5), 219 (42), 192 (95), 127 (100), 100

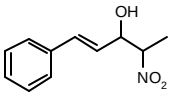
(45), 74 (60) and 57 (42); Anal. Calcd. For $C_{12}H_{11}N_2O_3Cl$ C = 54.03, H = 4.15, N = 10.50, Cl = 13.30%. Found C = 54.53, H = 4.32, N = 10.83, Cl = 13.63 %.

1-(3-Nitrophenyl)-2-nitro-2-methylpropan-1-ol (267)[50]:



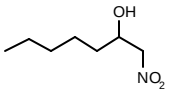
Solid, m.p. 151 ^oC [Lit[50] m.p. 154-156 ^oC]; **IR** (Nujol): 3480, 1552 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.49 (s, 3H), 1.58 (s, 3H), 3.1 (bs, 1H, –OH), 5.4 (s, 1H), 7.6 (t, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.30 (s, 1H); **MS** (m/z): 240 (M^+, 5), 194 (25), 151(42), 105 (45), 89 (78), 77 (100), 74 (33), 65 (12) and 57 (12).

1-Styryl-2-nitropropan-1-ol (268)[32]:



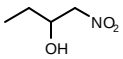
Viscous liquid; **IR** (Neat): 3438, 1550, 1496, 1390, 1300, 1026, 972, 872, 696 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.6 and 1.7 (d, J= 8.1 Hz, total 3H), 2.55 (bs, 1H, -OH), 4.55-4.75 and 4.80-4.95 (m, total 1H), 6.2 (dd, J= 12 Hz, 4 Hz, 1H), 6.8 (d, J= 12 Hz, 1H), 7.20-7.50 (m, 5H); **^{13}C-NMR** ($CDCl_3$): δ 13.0, 16.1, 73.4, 74.8, 86.3, 87.4, 125.4, 126.8, 128.1, 128.4, 128.6, 128.8, 129.0, 133.7, 134.8, 135.8; **MS** (m/z): 207 (M^+, 5), 160 (25), 133 (52), 115 (45), 103 (38), 91 (100), 77 (55), 65 (5) and 55 (81).

1-Nitromethyl-1-hexanol (269):

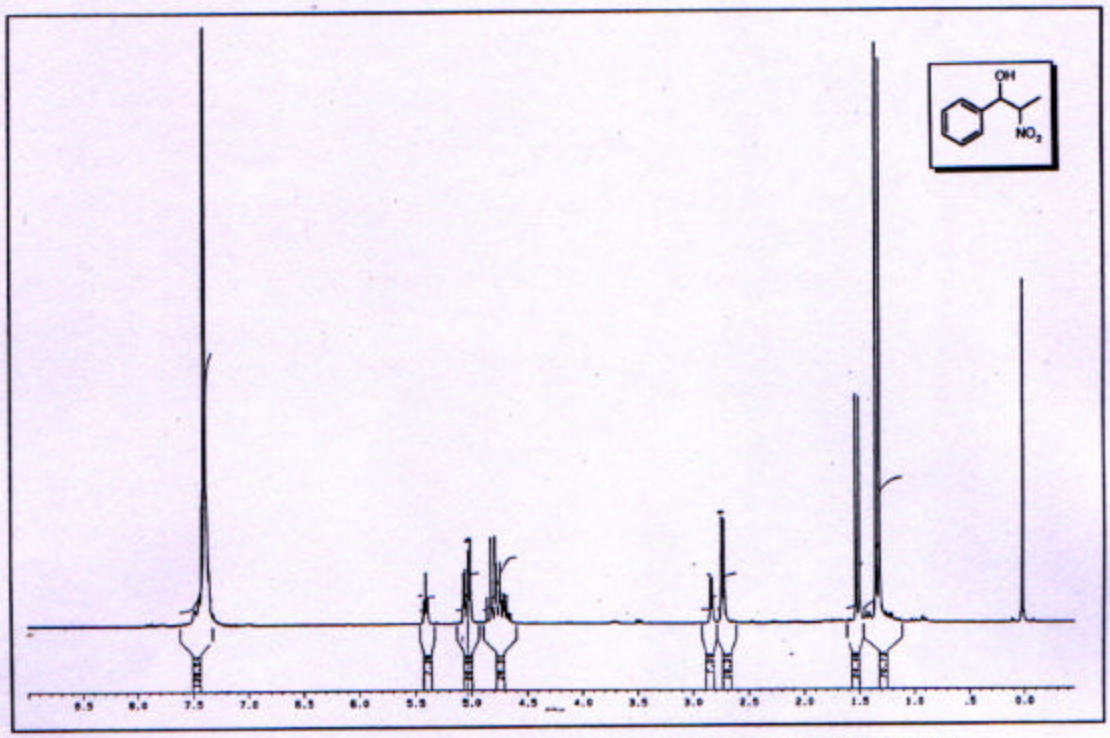


Viscous liquid; **IR** (Neat): 3492, 1570, 1496, 1296, 1210, 1132, 1090, 944, 884, 726 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 0.88 (bt, 3 H), 1.1-1.2 (bs, 4 H), 1.5-1.6 (bs, 4 H), 2.6 (bs, 1H), 4.1-4.3 (m, 1H), 4.5-4.6 (m, 2H); **MS** (m/z): 161 (M^+, 5), 97 (15), 90 (22), 81 (40), 69 (45), 55 (100) and 54 (75); Anal. Calcd. For $C_7H_{15}NO_3$ C = 52.16, H = 9.37, N = 8.68%; Found C = 52.08, H = 9.70, N = 8.12 %.

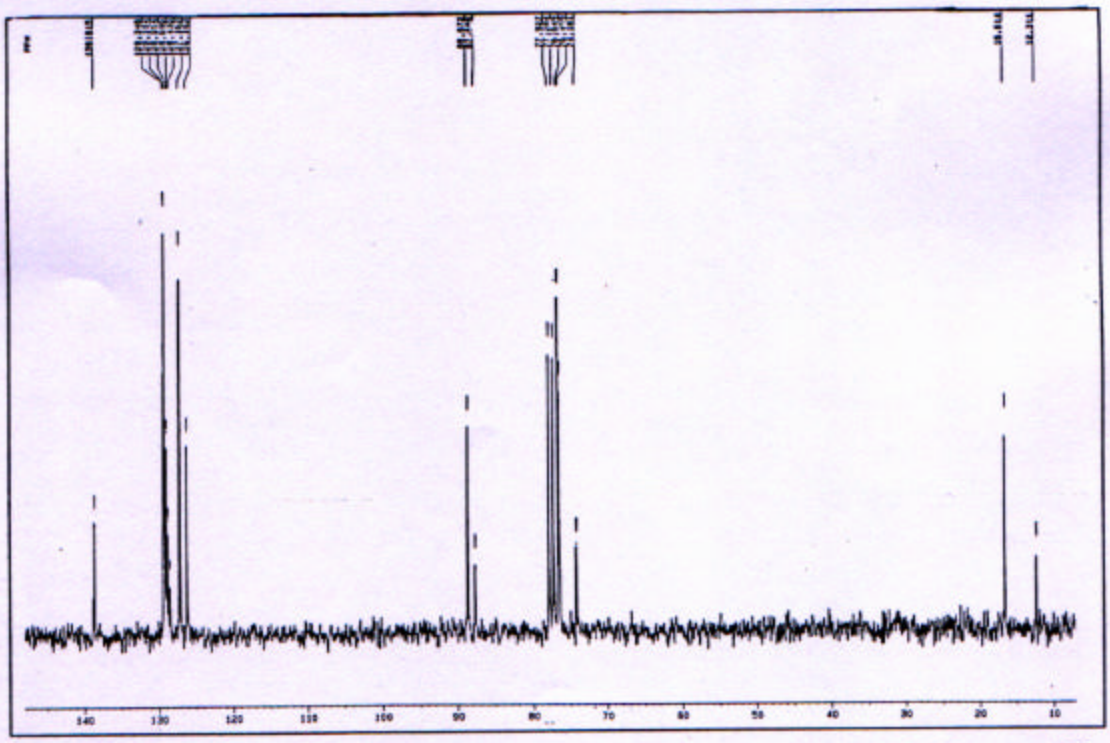
1-Nitromethyl propan-1-ol (270):



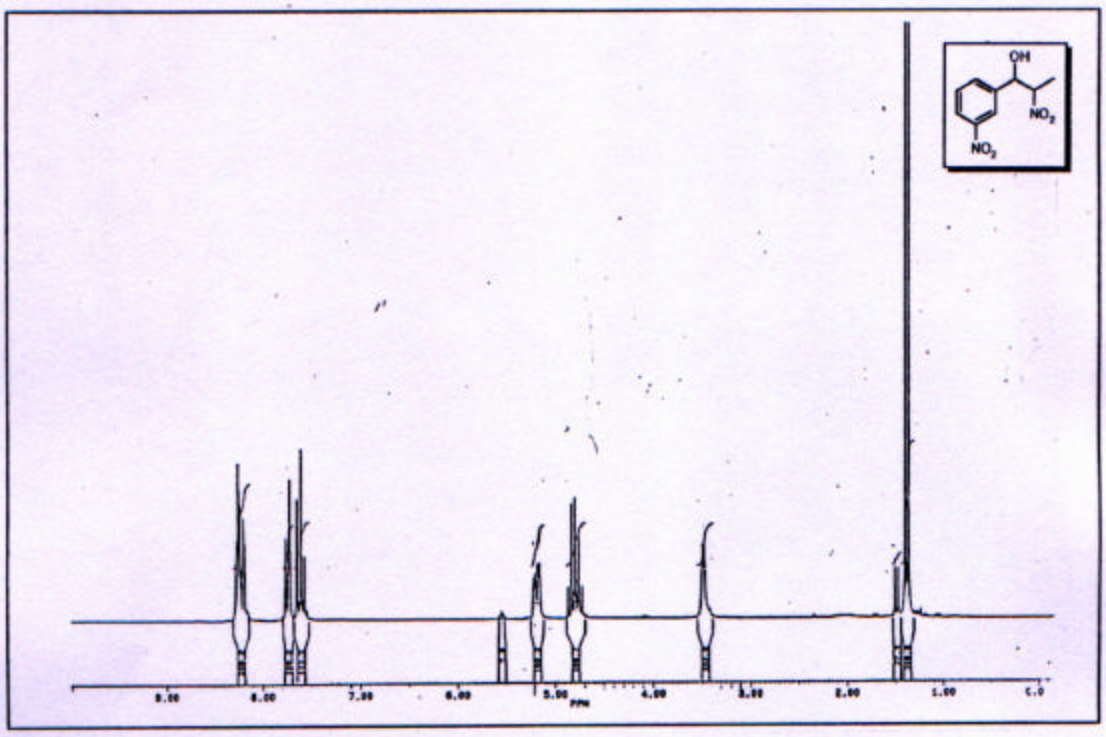
Viscous liquid; **IR** (Neat): 3490, 1558 cm^{-1}; **^{1}H-NMR** ($CDCl_3$): δ 1.05 (t, J = 8.1 Hz, 3H), 1.45-1.65 (m, 2H), 2.7 (b s, 1H), 4.22-4.3 (m, 1H), 4.4-4.55 (m, 2H); **MS** (m/z): 119 (M^+, 5), 99 (10), 90 (40), 75 (55), 62 (70) and 55 (100); Anal. Calcd. For $C_4H_9NO_3$ C = 40.33, H = 7.60, N = 11.75%; Found C = 39.83, H = 7.23, N = 12.26 %.



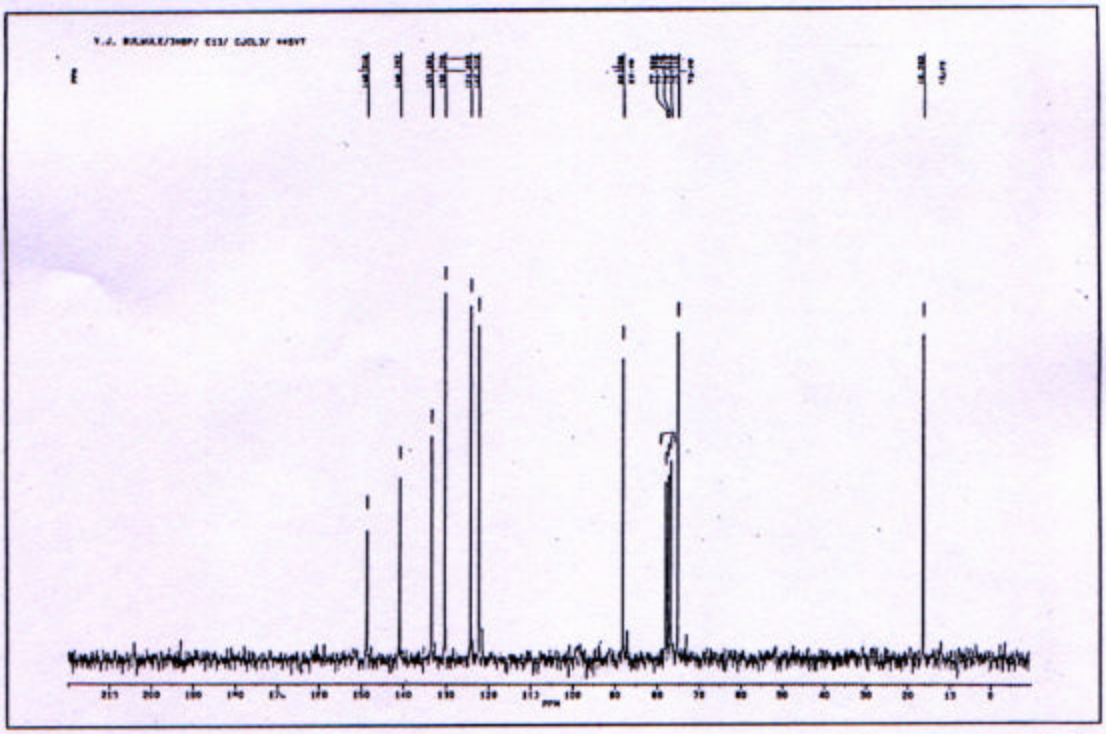
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 257 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 257 IN $CDCl_3$ 183

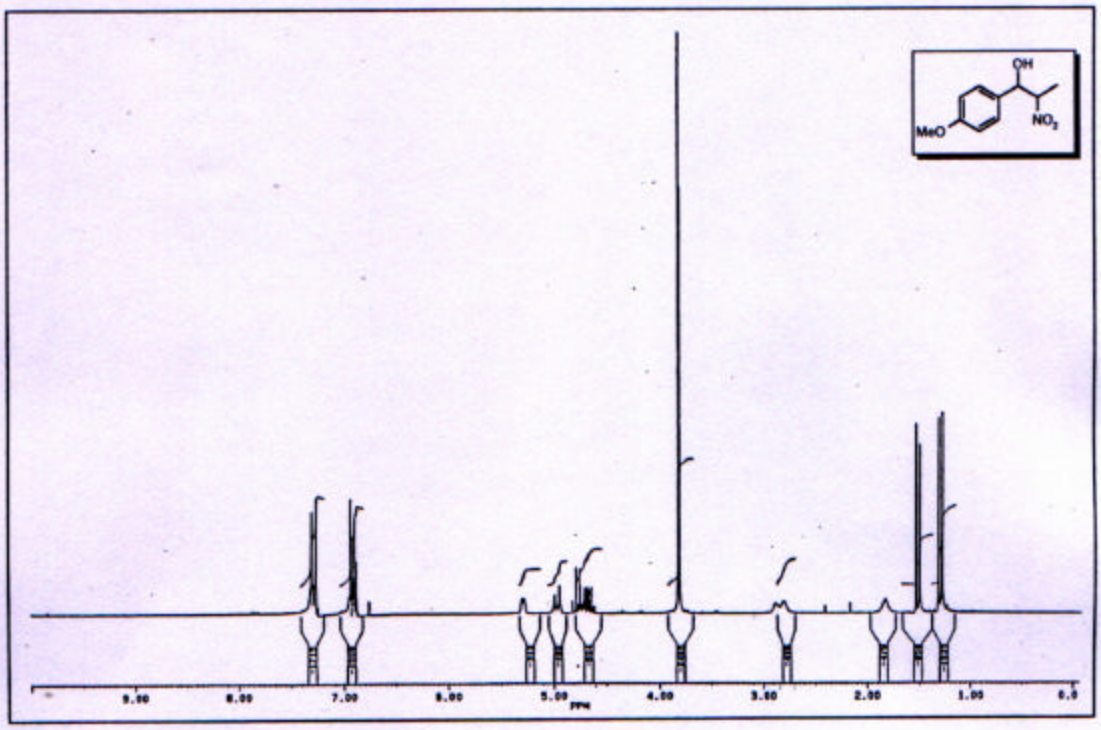


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 258 IN $CDCl_3$

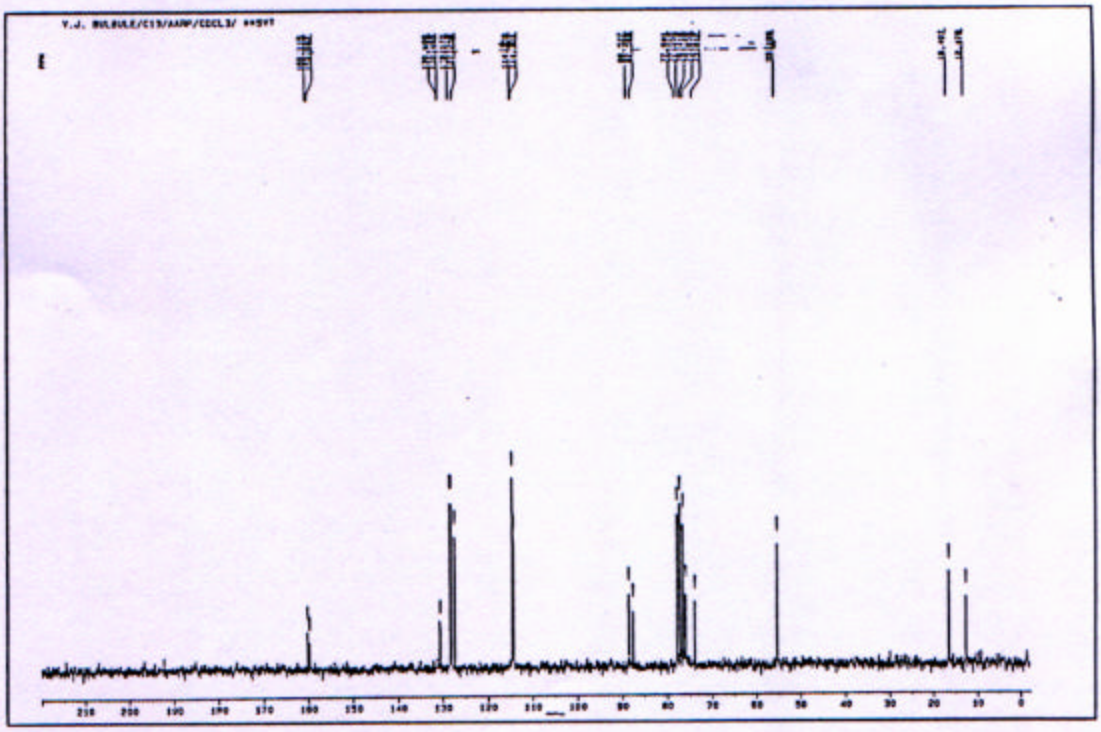


^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 258 IN $CDCl_3$

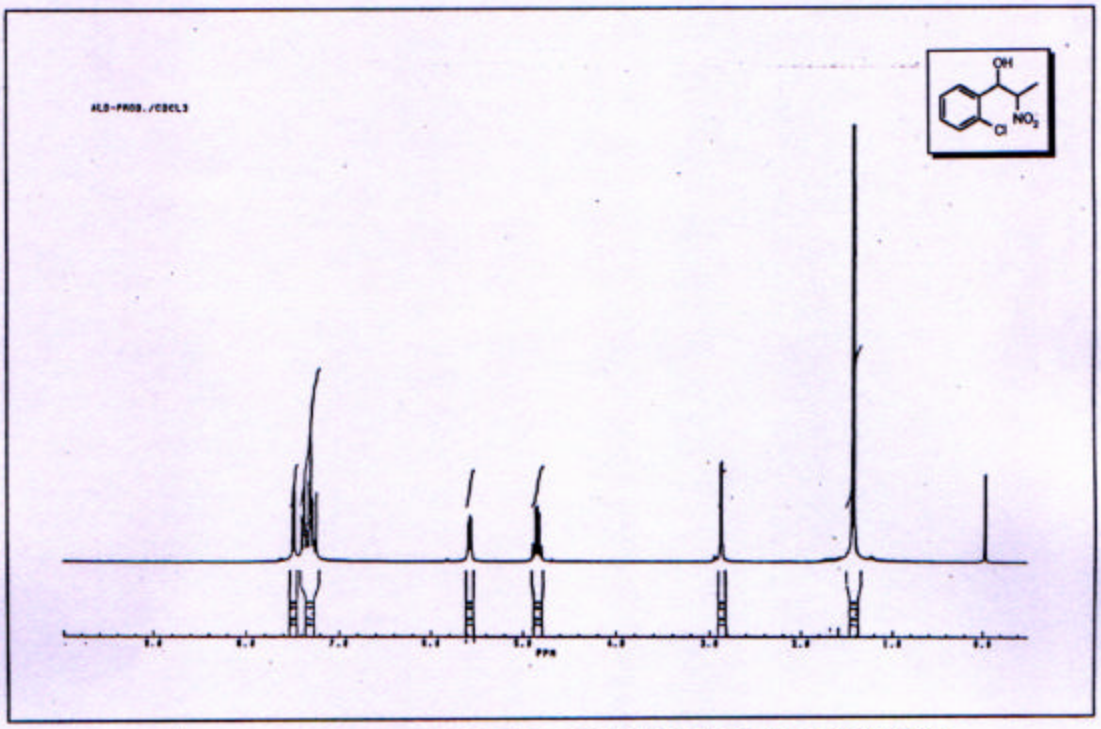
184



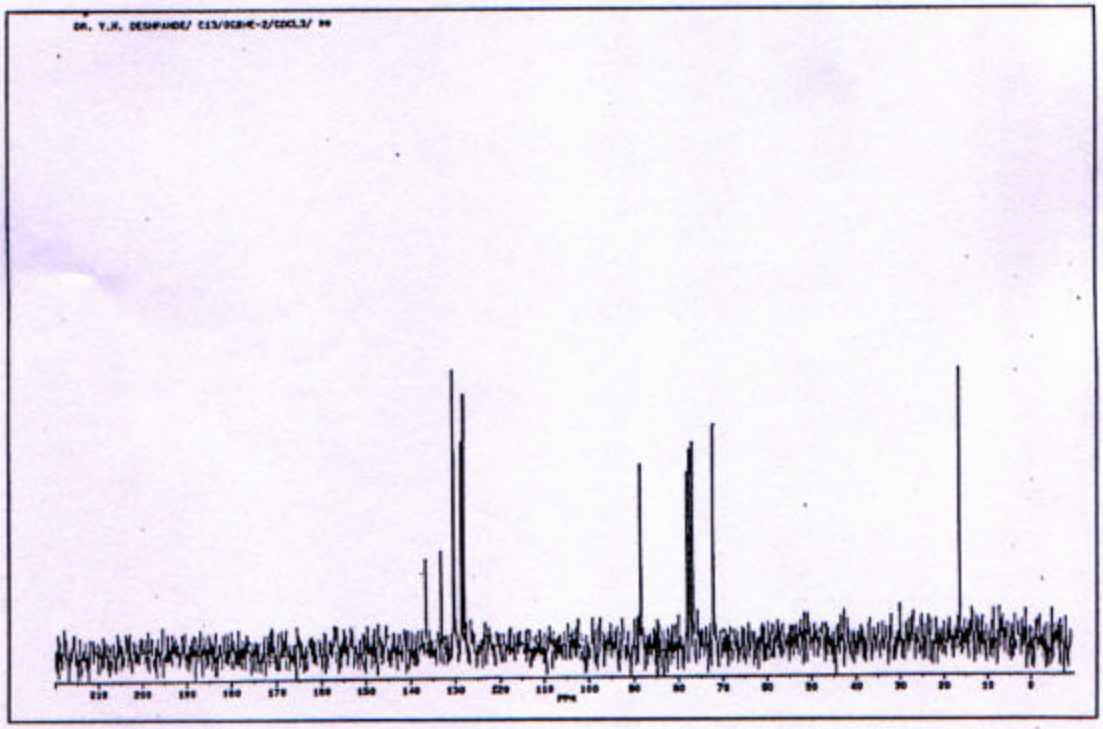
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 261 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 261 IN $CDCl_3$ 185

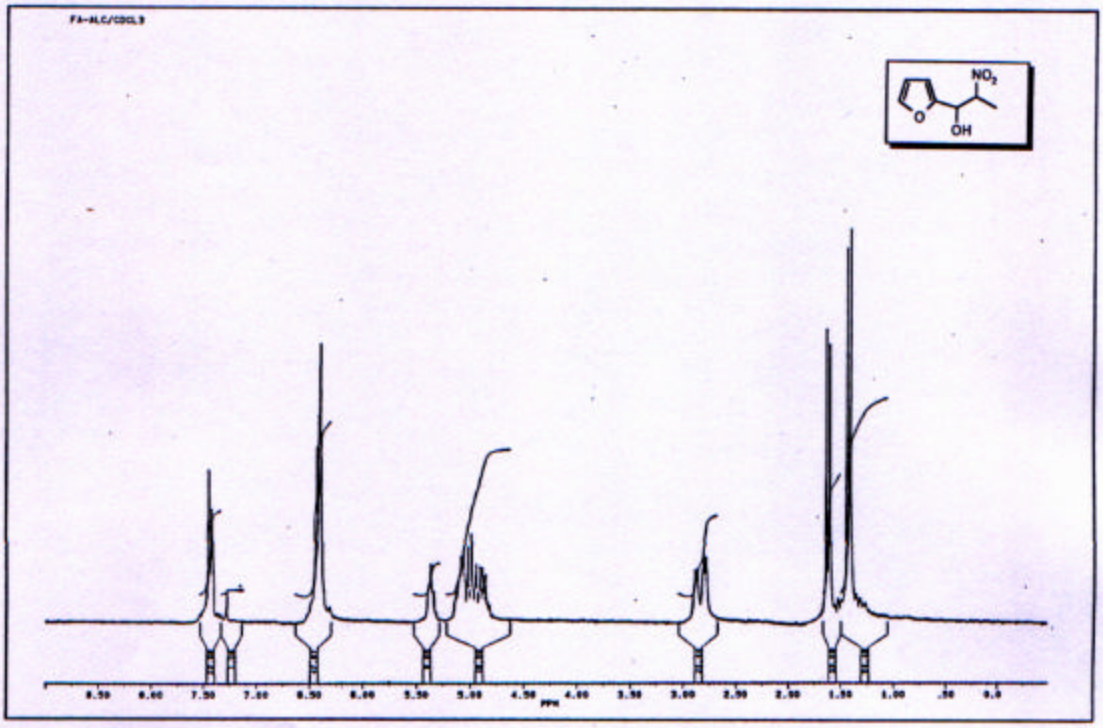


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 264 IN $CDCl_3$

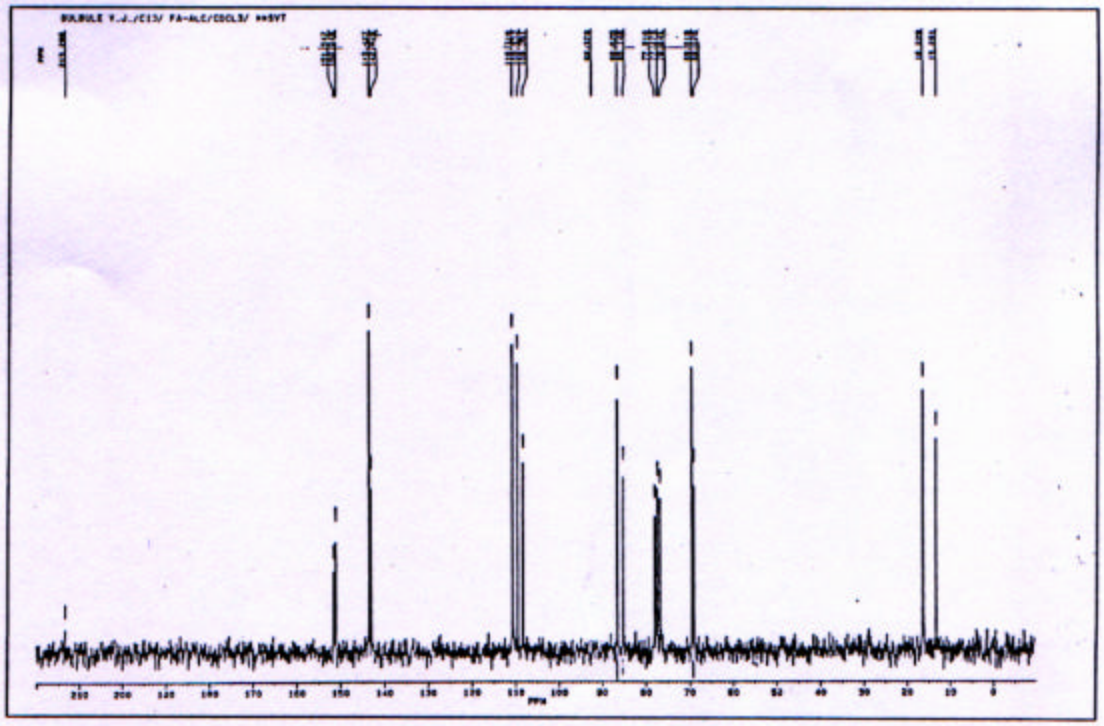


^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 264 IN $CDCl_3$

186

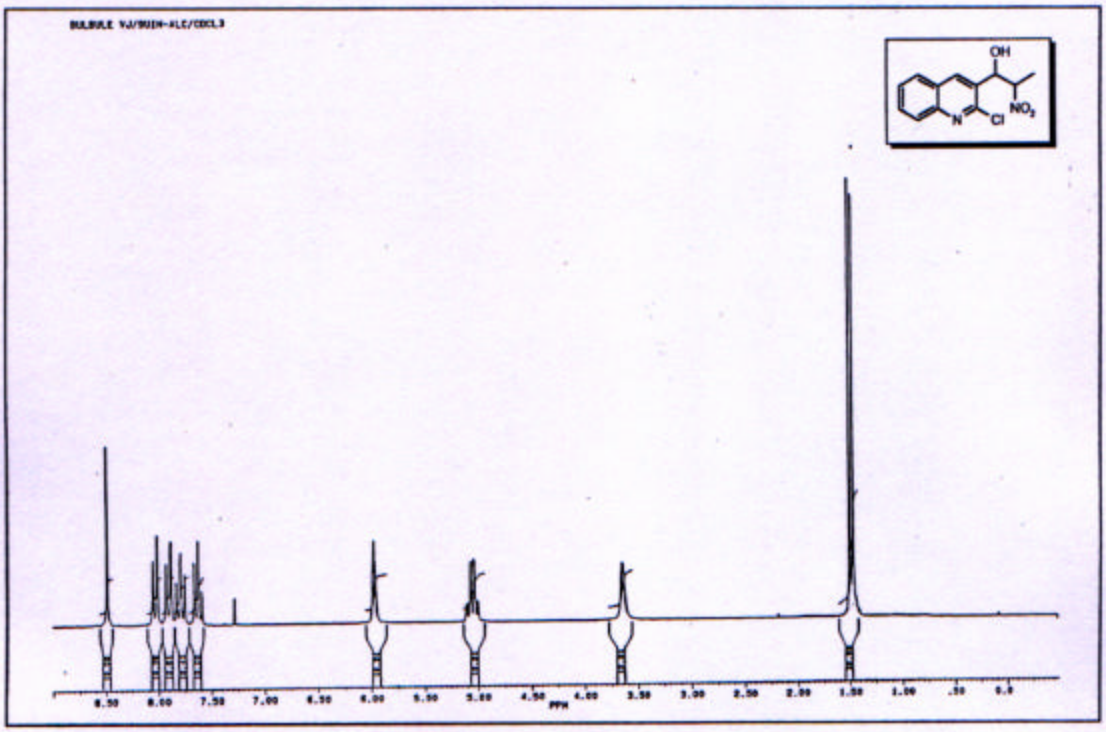


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 265 IN $CDCl_3$

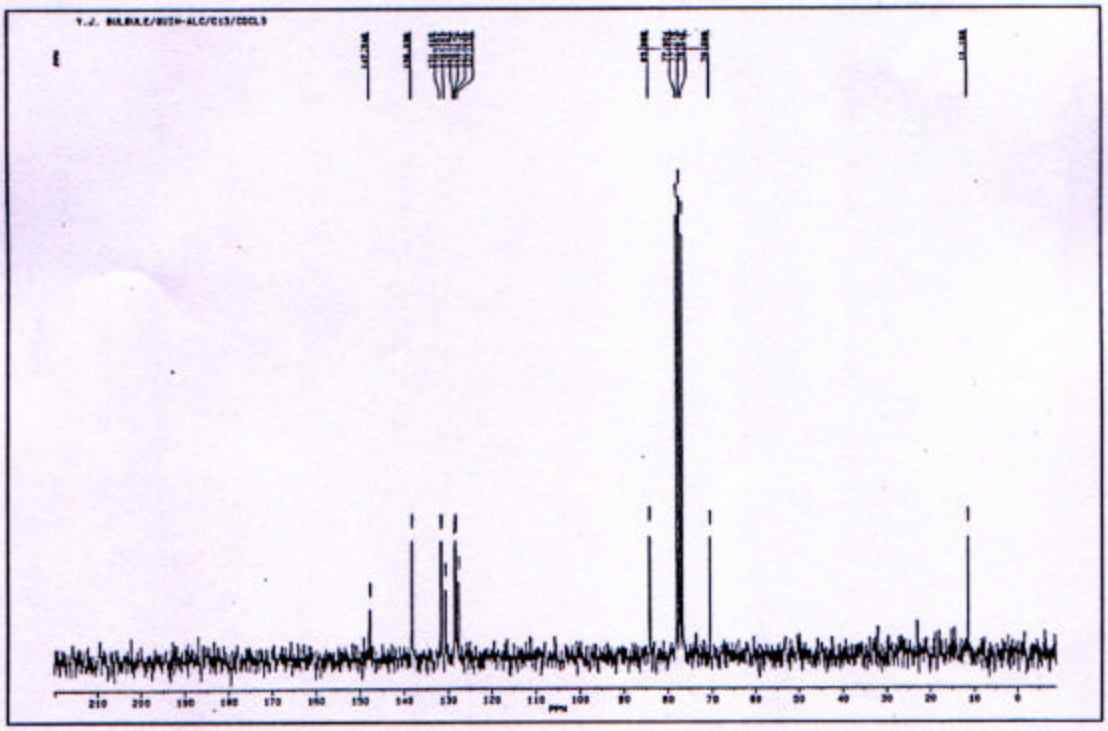


^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 265 IN $CDCl_3$

187

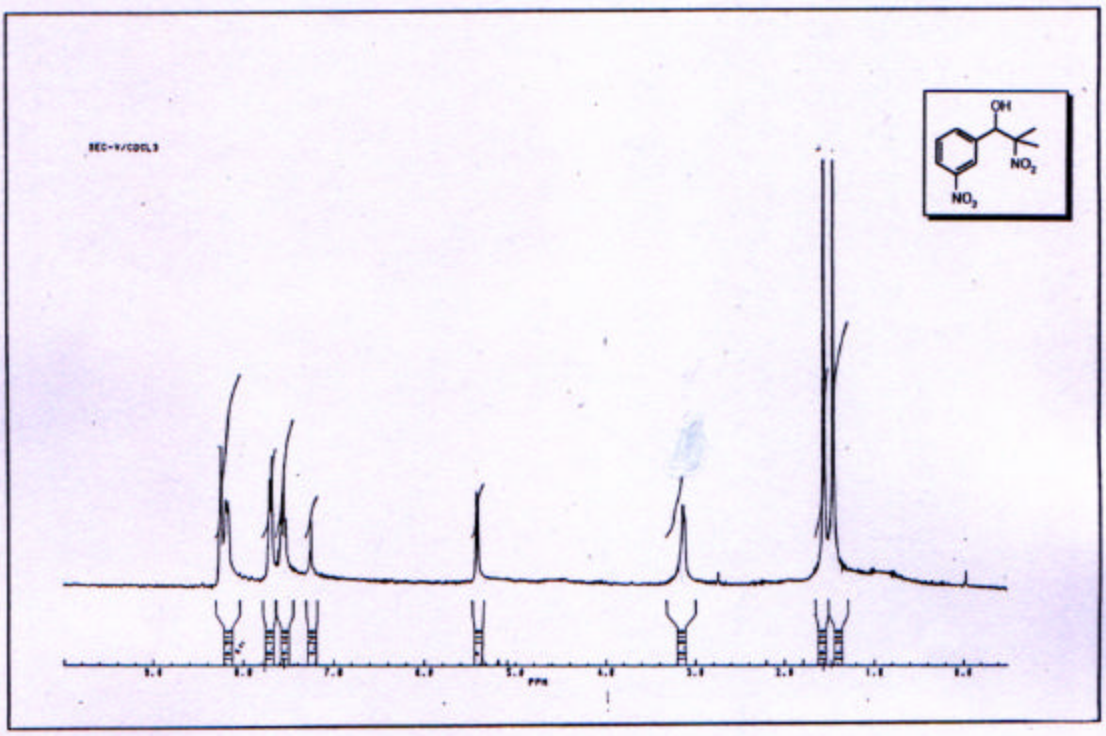


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 266 IN $CDCl_3$

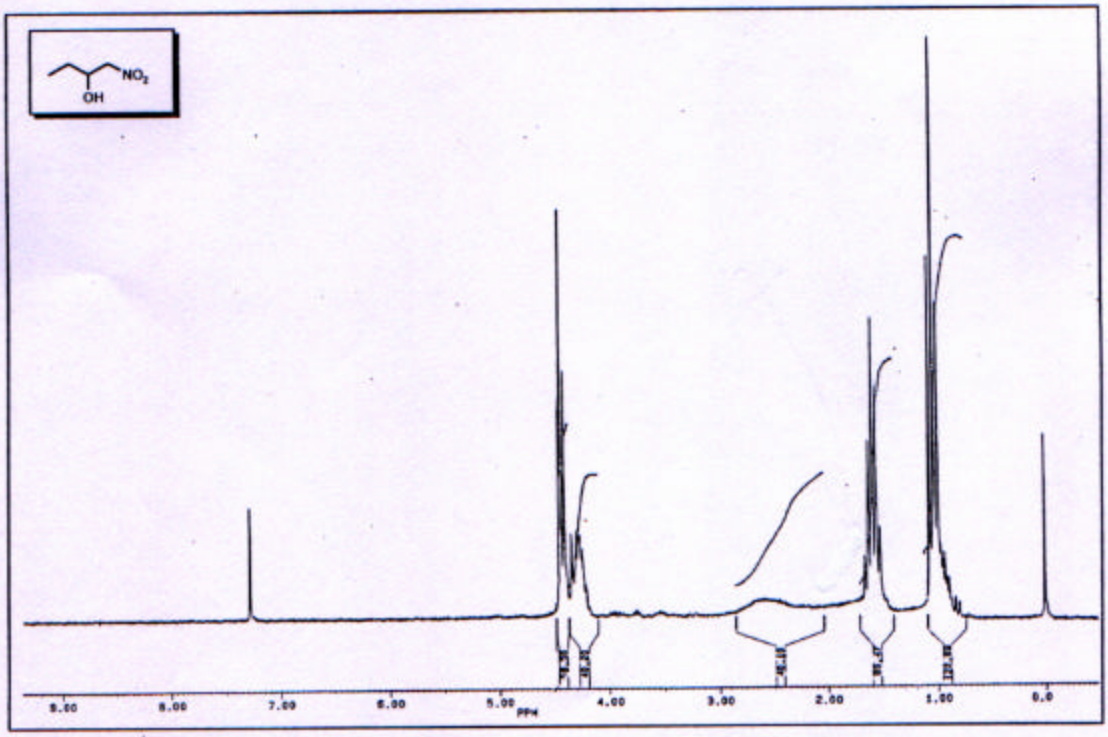


^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 266 IN $CDCl_3$

188



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 267 IN $CDCl_3$



^{1}H NMR SPETRUM (200 MHz) OF THE COMPOUND 270 IN $CDCl_3$

189

3.0.12 REFERENCES:

1. Velu, S. and Swamy, C. S., *Appl. Catal*., **1994**, 119, 241.
2. Cavani, F.; Trifiro, F. and Vaccari, *A. Catal. Today*, **1994**, **11**, 173.
3. Trifiro, F. and Vaccari, A in Atwood J. L.; Macwicol, D. D.; Davies, J. E. D. and Vogfie, F. (Editors), *Comprehensive Supramolecular Chemistry*, **7**, *Pergamon Press*, *Oxford*, **1995**, Chap-10.
4. Recent catalytic applications of hydrotalcite type anionic clays. Edited by Ticket D. and Vaccari, A in *Applied Clay Science*, **1998,** Vol.13, 311.
5. Reichle, W. T., *Chemtech*, **1986**, 16, 58.
6. A deRoy, A.; Forano, C.; Elmarki, K.; Besse, J. P. in 'Expanded Clays and other microporous solids". Eds. Occelli, M. L., Robsun, H. E.; Reinhord, New York, Vol.2 p.108 (**1992**).
7. Shannon, R. D., *Acta Crystallogr. Sect*. A, **1976**, 32, 751.
8. Allmann, R. *Chimia*, **1970**, 24, 99.
9. Drits, V. A.; Sokolova T. N.; Sokolova, G. V.; Cherkashin, V. I., *Clays and Clay Miner*, **1987**, 35, 401.
10. Velu, S.; Sabde, D. P.; Shah, N. and Sivansankar, S., *Chem. Mater*; **1998**, **10**, 3451.
11. Lakshmikantam, M.; Choudhary, B. M.; Venkat Reddy, Ch.; Koteswara Rao, K. and Figueras, F.; *Chem. Commun.*, **1988**, 1033.
12. Ueno, S.; Yamaguchi, K.; Yoshida, K.; Ebitani, K. and Kaneda, K., *Chem. Commun.*, **1998**, 295.
13. Kumbhar, P. S.; Sanchez-Valente, J. and Figueras, F., *Chem. Commun.*, **1998**, 1091.
14. Kumbhar, P. S.; Sanchez-Valente, J.; Lopez, J. and Figueras, F., *Chem. Commun.*, **1998**, 535.
15. (a) Rey F.; Formes, V., *J. Chem.* Soc. *Faraday Trans*. **1992**, 88, 2233. (b) Reichle, W. T.; Kang, S. Y.; Everhaldt, D. S. *J. Catal.*, **1986**, 101, 352. (c) Rourhet, P. G.; Taylor H. F. *Chimia*, **1969**, 23, 480.
    (d) Brindley, G. W.; Kikkawa, S., *Clays and Clay Miner*; **1980**, 28, 87.
16. (a) Mckenzie, A. L.; Finel, C. T. and Davis, R. J. *J. Catal*; **1992**, 138, 547. (b) Corma, A.; Fornes V. and Rey, F., *J. Catal*, **1994**, 148, 205.
17. Manasse, F.; *Alt. Soc. Toscana Sc. Proc. Verb.*, **1915**, 24, 92.
18. Climent, M. J.; Corma, A., Iborra, S.; Primo, J. *J. Catal*, **1995**, 151, 60.
19. Catimeila, C.; Figueras, F.; Garcia, J. I.; Mayoral, J. A.; Zurbano, M. M. *Synth. Commun*., **1995**, 25, 1745.

20. Choudhary, B. M.; Narendar, N.; Bhuma, V. *Ibid*, **1995**, 25, 2829.
21. Tichit, D.; Lhouty, M. H.; Guida, A.; Chinche, B. H.; Figueras, F.; Auroux, A.; Bartaline, D.; Garrone, E. *J. Catal.*, **1995**, 151, 50.
22. Corma, A.; Fornes, V.; Avanda, R. M. M., Rey, F.; *J. Catal.*, **1992**, 134, 58.
23. Corma, A.; Iborra, S.; Primo, J.; Rey, F., *Appl. Catal.*, **1994**, 114, 215.
24. Guida, A.; Lhouty, M. H.; Tichit, D.; Figueras, F.; Geneste, P., *Appl. Catal. A. General*, **1997**, 164.
25. Auer, S. M.; Schnider, M.; Baiker, A.; *J. Chem. Soc. Chem. Commun.*, **1995**, 2057.
26. Sonogashira, K., in "Comprehensive Organic Synthesis", Ed. B. M. Trost, I. Fleming, Pergamon Press, Oxford, 42, **1993**.
27. Henry, L, C. R. Behd. Seances Acad. Sci., **1895**, 120, 1265.
28. (a) Rosini G, in Comprehensive Organic Synthesis, ed. Trost, B M. and Fleming I, Pergamon Press, Oxford, **1991**, Vol. 2, P. 321. (b) Seebach, D. D.; Calvin, E. W.; Leher F. and Weller, T., *Chimia*, **1979**, 33, 1. (c) Rosini, G. and Ballini, R., *Synthesis*, **1988**, 833.
29. Kumar, H. M. S.; Reddy, B. V. S. and Yadav, J. S., *Chem. Lett.*, **1998**, 637.
30. (a) Rosini, G.; Ballini, R.; Petrini, M.; Sorrenti, P., *Tetrahedron*, **1984**, 40, 3809. (b) Ballini, R.; Bosica, G.; Forconi, P., *Tetrahedron*, **1996**, 52, 1677.
31. Costantino, U.; Curini, M.; Marmottini, F.; Rosati, O.; Disani, E., *Chem. Lett.*, **1994**, 2215.
32. Kiyaoka, S. I.; Tsutsui, T.; Maeda, H.; Kaneko, Y.; Isobe, K.; *Tetrahedron Lett.*, **1995**, 36, 6531.
33. Simoni, D.; Invidiata, F. P.; Manfredini, S.; Ferroni, R.; Lampronti, I.; Roberti, M.; Pollini, G. P., *Tetrahedron Lett.*, **1997**, 38, 2749.
34. Ballini, R. and Bosica, G. *J. Org. Chem.*, **1997**, 62, 425.
35. Morao, I.; Cossio, I. P., *Tetrahedron Lett.*, **1997**, 38, 6461.
36. a) Kisanga, P. B.; Verkade, J. G., *J. Org. Chem.*, **1999**, 64, 4298. b) Youn, S. W.; Kim, H. Y. *Synlett*, **2000**, 880.
37. (a) Hakomori, S. in Handbook of Lipid Research Sphingolipid Biochemistry ed. Kauger, J. N. and Hakomori, S. Plenum Press, New York, **1983**, 1.
    (b) Suami, T.; Tadono, K, -I., Suga, A. and Ueno, Y. J., *Carbohydr. Chem.*, **1984**, 3, 429.
38. Colvin, E. W.; Beck, A. K. and Seebach, D., *Helv. Chim. Acta.*, **1981**, 64, 2264.
39. Hino, T.; Nakakyama, K.; Taniguchi, M. and Nakagawa M. *J. Chem. Soc. Perkin. Trans. I*, **1986**, 1687.
40. (a) Scehter, H. and Conrad, F., *J. Am. Chem. Soc.*, **1953**, 75, 5610.

(b) Williams, T. M.; Crumbie R. and Mosher, H. S., *J. Org. Chem.*, **1985**, 50, 91.

41. Lichtenthaler, F. W., *Angew. Chem.*, **1964**, 76, 84; *Angew Chem., Int. Ed. Engl.*, **1964**, 3, 211.
42. Hanessian, S. and Kloss, J., *Tetrahedron Lett.*, **1985**, **26**, 1261.
43. Brittain, R. T.; Jack, D. and Ritchie, A. C., *Adv. Drug, Res.*, **1970**, 5.
44. Ono, N. and Kaji, A., *Synthesis*, **1986**, 693.
45. Kabalka, G. W. and Varma, R. S., *Org. Prep. Proced. Int.*, **1987**, 29, 283.
46. a) Melot, M. J.; Texier – Boullet, F. and Foucaud. F, *Tetrahedron Lett.*, **1986**, 27, 493. b) Bandgar, B. P.; Zirange, M. B.; and Wadgaonkar, P. P., *Synlett*, **1996**, 149.
47. Rosini, G.; Ballini, R. and Sorrent, P., *Synthesis*, **1983**, 1014.
48. a) Barrett, A. G. M.; Robyr, C. and Spilling, C. D., *J. Org. Chem.*, **1989,** *54*, 1234. b) Barrett, A. G. M.; Graboski, G. G., *Chem. Rev.*, **1986**, *86*, 751.
49. a) Seebach, D.; Beek, A. K.; Mukhopadyay, T. and Thomas, E., *Helv. Chim. Acta.*, 1982, **65**, 1101. b) Eyer, M.; Seebach, D., *J. Am. Chem. Soc.*, **1985**, 107, 3601.
50. Freeman, D. J.; Newcombe, P. J. and Norris, R. K., *Aust. J. Chem.*, **1976**, 29, 327.
51. Bulbule, V. J.; Deshpande, V. H.; Velu, S.; Sudalai, A.; Sivasanker, S.; Sathe, V. T., *Tetrahedron*, **1999**, 55, 9325.

CHAPTER - 3

SECTION - II

TRITON B CATALYZED NITROALDOL CONDENSATION IN AQUEOUS MEDIA

3.1.1 INTRODUCTION:

In organic synthesis it is frequently necessary to bring about the reactions of inorganic, ionic reagents (bases, nucleophilic or oxidizing agents etc) with a covalent organic compound. For reaction to occur under conventional, homogeneous conditions both these dissimilar species must have some solubility in the reaction medium, which accordingly may be a mixture of water and water-miscible solvent such as a lower alcohol, acetone, THF etc.

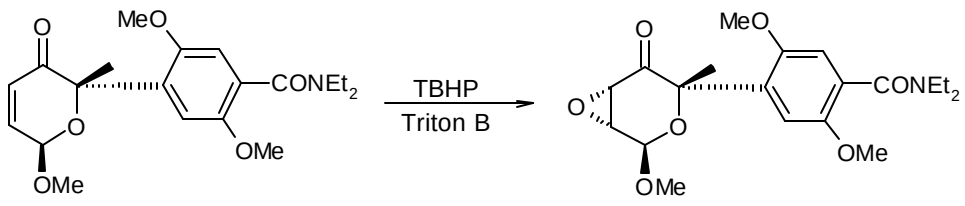
Phase transfer catalysis (PTC) methods employ a system consisting of two mutually insoluble phases, either liquid-liquid or solid-liquid in which inorganic ions are transported into the organic phase by formation of a complex which is soluble in organic solvents. Such techniques are particularly useful for base-catalyzed reactions, nucleophilic displacement and oxidation of water insoluble compounds by inorganic reagents. The classical procedures that require severe anhydrous conditions, expensive solvents and dangerous bases such as metal hydride and organometallic reagents are now replaced by aqueous solutions. The use of quaternary ammonium compounds[1] as reagents and as catalysts in homogeneous and two-phase systems has grown into a versatile preparative method[2]. The most notable developments include the use of crown ethers as PTC and introduction of solid-liquid PTC. The use of such phase-transfer catalysts, which catalyze reaction between substances located partly in an aqueous and partly in an organic phase, simplifies and accelerates numerous reactions traditionally conducted in non-aqueous media[3,4].

TRITON B IN ORGANIC REACTIONS:

Benzyltrimethylammonium hydroxide, commonly called as Triton B, functions as a quaternary ammonium salt, strong base and phase transfer catalyst. The application of this catalyst is well explored in the literature and some of the methods are described under this subheading.

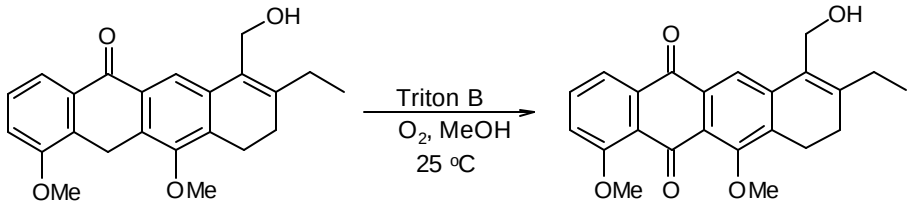
a) **Epoxidation:** Benzyltrimethylammonium hydroxide finds use as catalyst in the epoxidation of a, ß-unsaturated ketones (Scheme-1) with t-butyl hydroperoxide as demonstrated in a step toward the total synthesis of a complex anthracyclinone[5] as shown in scheme-1.

Scheme-1



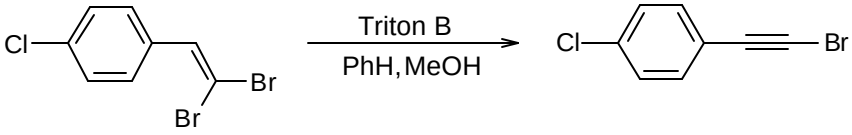
b) Oxidations: Benzyltrimethylammonium hydroxide has been used as a catalyst for the oxidation of methylene and / or methine groups. The oxidation of a tricyclic ketone to an anthraquinone was accomplished in good yields using this approach[6] (scheme-2).

Scheme-2



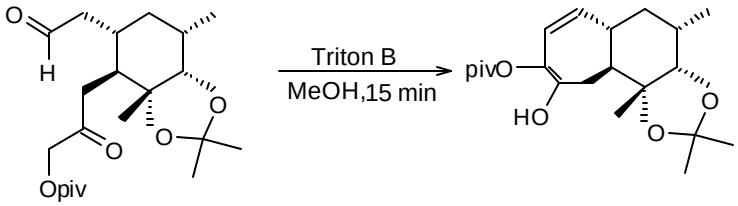
c) Dehydrohalogenation: A variety of 1-bromoalkynes have been prepared through the action of Triton B on 1,1-dibromoalkenes[7] (scheme-3).

Scheme-3



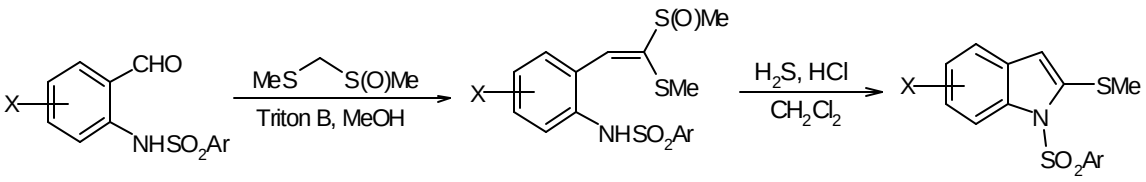
d) Aldol condensation: The aldol reaction has often been carried out with Triton B functioning as base. In the synthesis of a cytochalasin intermediate, a seven-membered ring was formed under the action of Triton B in excellent yield[8] (Scheme-4).

Scheme-4



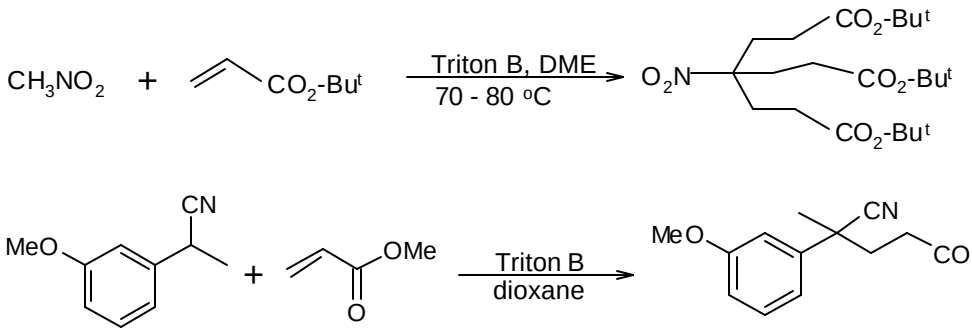
e) Conjugate addition: Triton B is an effective catalyst for the conjugate addition of carbon acids to Michael acceptors. Such is the case with the reaction of nitromethane and t-butyl acrylate mediated by a methanolic solution of Triton B[9-12].

Scheme-5



Nitroalkanes have also been added intermolecularly to a variety of unsaturated systems. The addition of a benzonitrile to methyl acrylate in a Michael fashion was reported to occur in excellent yield.

Scheme-6



From the above discussion, it is seen that Triton B is an useful reagent to effect various organic conversions.

3.1.2 PRESENT WORK:

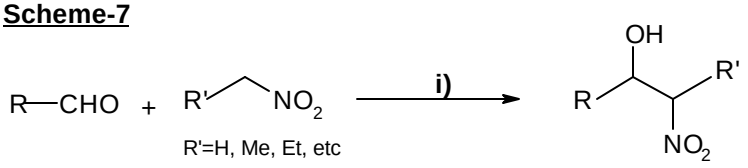
The Henry reaction, an aldol-type reaction, represents one of the classical C-C bond-forming processes, and its variants have been used extensively in many important syntheses of several biologically active compounds[13]. The classical nitroaldol reaction is performed as routine procedure, in presence of a base in an organic solvent.

The nitro group of nitroaldol products can be easily functionalised to amine[14], can be converted into carbonyl compounds[15] and easily denitrated by further functional group manipulations. Several catalysts have been reported in literature to effect the Henry reaction. Recently TBAF hydrate[17] has been used, but the use of 1 to 2 equivalents suppresses its use in synthetic organic chemistry. The strong bases, used in Henry reaction, often result in the formation of side products by the aldol and cannizzaro reaction of aldehydes or olefin formation[18-21]. In addition, these standard procedures furnish a diastereomeric mixture of nitroalkanols; nevertheless, this does not seem to be a problem since the main use of nitroalkanols is the conversion into α-nitro ketones[22] or conjugated nitroalkenes in which at least one stereogenic center is lost. If a diastereomeric synthesis of nitroalkanols, for specific purpose (eg. chloramphenicol), is required other procedures are available[23]. Recently we have developed a novel method for the diastereoselective synthesis of nitroaldols over Mg-Al-Hydrotalcites[24].

The need to reduce the amount of toxic waste and byproducts arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods[25]. The time has now come for ecological factors to be considered in the development of synthetic procedures and for them to play an important role in the assessment of the quality of any new synthesis. In this context, the reduced use of ecologically suspected solvents is of considerable significance. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions[26]. The aqueous medium with respect to organic solvent is less expensive, less dangerous and environment friendly, while it allows the control of the pH and the use of microaggregates such as surfactants. Generally, the low solubility[27] of most reagents in water is not an obstacle to the reactivity, which on the contrary is reduced with the use of cosolvents.

In our continuing interest[24] devoted to explore the utility of various catalysts to effect the Henry reaction we decided to investigate the possibility to achieve the nitroaldol reaction in water. After some trials we found that the Henry reaction can be performed under very mild reaction conditions in aqueous media using benzyltrimethylammonium hydroxide as a catalyst to give excellent yields of nitroaldols (Schme-7).

Scheme-7



i) Benzyltrimethylammonium hydroxide, 4-15 min., r.t.

When aldehydes were stirred with 1.1 equivalent of nitroalkanes in water containing a few drops of THF as a cosolvent in the presence of catalytic amount of benzyltrimethylammonium hydroxide at room temperature the desired nitroaldol products were formed in excellent yields (Table-1). The substrates containing electron-withdrawing groups were found to undergo faster reaction (Entries 2, 6, 12 and 13) compared to electron rich substituted aromatic compounds and give almost quantitative yield. An aliphatic aldehyde also underwent nitroaldol condensation (Entry 11). Efforts were made to achieve quantitative yields by modifying reaction parameters. It was observed that instead of using a mixture of water and THF as solvent, when reactions were run using an excess of nitroalkane, various aldehydes underwent nitroaldol reaction in quantitative yields and in a short period of 4-15 min.

Tedious preparation of catalyst[28], large excess of nitroalkane[19.28] or drastic reaction conditions that are too cumbersome, especially for large-scale preparation[18], are not involved in this novel method. Additionally, the very mild reaction conditions prevent the typical side reactions such as retro-aldol reaction or dehydration of the 2-nitroalcohols into nitroalkenes[29] even if aromatic aldehydes are used. High chemo-selectivity is observed since several functionalities such as hydroxyl group, furyl etc are preserved under these conditions. Compared with the conventional methods, our procedure produces excellent yields in shorter reaction times and allows performing this important reaction on a multigram scale under inexpensive and ecological conditions.

Table 1: Benzyltrimethylammonium hydroxide catalyzed preparation of nitroalkanols[a]

Entry	R	Nitroalkane	Time (min)	Yield[b] %	*threo : erythro*[e]
1	*p*-Chlorophenyl	Nitroethane[c]	10	91	1.22:1
		Nitroethane[d]	6	95	
2	*p*-Nitrophenyl	Nitroethane[d]	4	98	-
3	*p*-Methoxyphenyl	Nitroethane[c]	12	90	-
		Nitroethane[d]	8	94	
4	2-Furyl	Nitroethane[c]	8	81	-
		Nitroethane[d]	6	85	
5	*o*-Chlorophenyl	Nitroethane[d]	10	94	-
6	*m*-Nitrophenyl	Nitroethane[c]	4	98	-
7	Phenyl	Nitroethane[c]	10	83	-
		Nitroethane[d]	6	88	
8	*o*-Hydroxyphenyl	Nitroethane[c]	15	91	-
		Nitroethane[d]	12	96	
9	3,4,5-Trimethoxyphenyl	Nitroethane[c]	10	82	2.52:1
		Nitroethane	8	93	
10	2-Chloro-3-quinolinyl	Nitroethane[c]	6	80	-
11	Isobutyl	Nitroethane[c]	8	78	1.64:1
		Nitroethane[d]	5	80	
12	*m*-Nitrophenyl	Nitromethane[c]	8	92	-
		Nitromethane[d]	5	98	
13	*m*-Nitrophenyl	Nitropropane[d]	6	98	5.34:1
14	3,5-Dimethoxyphenyl	Nitromethane[d]	4	94	-

[a]All the nitroalkanols showed satisfactory spectroscopic data. [b]Isolated yield after column chromatographic purification. [c]1.1 equivalent of nitroalkane. [d] Nitroalkane used in excess. [e]Average ratio were calculated from ^{13}C NMR (50.3 MHz) and / or ^{1}H NMR signals

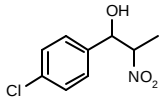
In conclusion we have demonstrated that the present method is quick and convenient way for the effective synthesis of nitroalcohols using Triton B as a catalyst to give excellent yields.

3.1.3 EXPERIMENTAL:

Typical Experimental Procedure: To a mixture of aldehyde (3.31 mmol) and nitroalkane (3.63 mmol) in water (5 ml) and THF (0.4 ml) was added 1 drop of benzyltrimethylammonium hydroxide (40% aq solution) at room temperature. The mixture was stirred at room temperature for 4-15 minutes. After the reaction was complete (TLC), excess water was added and the aqueous layer was extracted with chloroform (2 × 20 ml). The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography to afford the corresponding nitropropanols (81-98%).

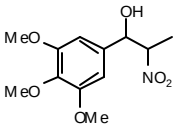
The spectral data of products in entries 2, 3, 4, 5, 6, 7, 8 and 10 were identical to those given in Section -I of this chapter. Spectral data of new compounds obtained in entries 1, 9, 11, 12, 13 and 14 are given below. The values for spectral data given are for the mixtures of diastereomers.

1-(4-Chlorophenyl)-2-nitropropan-1-ol (271):



Viscous liquid; **IR** (Neat): 3524, 1550 cm^{-1}; **^{1}HNMR** ($CDCl_3$): δ 1.30 and 1.47 (d, J= 6.0 Hz, total 3H), 3.02 (bs, 1H), 4.59-4.79 (m, 1H), 5.00 (d, J= 8.0 Hz) and 5.36 (d, J= 4.0 Hz) total 1H, 7.27-7.40 (m, 4H); **^{13}C NMR** ($CDCl_3$): δ 11.18, 16.24, 73.21, 75.42, 87.18, 88.14, 127.32, 128.20, 128.87, 129.12, 134.31, 135.00, 136.80, 136.95; Analysis calculated for $C_9H_{10}NO_3Cl$: C = 50.12, H = 4.66, N = 6.49, Cl = 16.46%; Found C = 50.48, H = 4.22, N = 6.46, Cl = 16.02%.

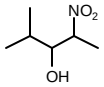
1-(3, 4, 5-Trimethoxyphenyl)-2-nitropropan-1-ol (272):



Solid, m.p.116.5 ^oC; **IR** (Nujol): 3495, 1588 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 2.05 and 2.24 (d, J= 4.0 Hz, total 3H), 4.15 (bs, 1H), 4.50 (s, 3H), 4.56 (s, 6H), 5.38-5.55 (m, 1H), 5.66 (d, J= 6 Hz) and 6.01 (d, J= 2 Hz) total 1H, 7.28 (s, 2H); **^{13}C NMR** ($CDCl_3$): δ 12.02, 16.27, 55.97, 60.61, 73.92, 76.20,

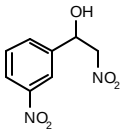
87.35, 88.26, 102.94, 103.77, 134.19, 134.59, 137.00, 137.92, 153.09, 153.21; Analysis calculated for $C_{12}H_{17}NO_6$: C = 51.36, H = 5.87, N = 5.44%; Found C = 52.00, H = 6.21, N = 5.88%.

1-Nitroethyl-2-methylpropan-1-ol (273):



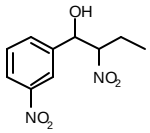
Viscous liquid; **IR** (Neat)**:** 3492, 1570 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 0.82 and 0.91 (d, J= 8.0 Hz, total 6H), 1.39 (d, J = 8.0 Hz, 3H), 1.51-1.79 (m, 1H), 3.20 (bs, 1H), 3.58-3.78 (m, 1H), 4.47-4.61 (m, 1H); **^{13}C NMR** ($CDCl_3$): δ 11.57, 14.73, 15.91, 18.08, 18.52, 19.44, 29.21, 30.65, 76.85, 77.26, 84.46, 86.37.

1-(3-Nitrophenyl)-2-nitroethanol (274):



Solid, m.p. 61.5 ^oC; **IR** (Neat)**:** 3514, 1555 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 3.44 (bs, 1H), 4.62- 4.75 (m, 2H), 5.62 (t, J = 6.0 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.31 (s, 1H); **^{13}C NMR** ($CDCl_3$): δ 69.86, 80.66, 121.10, 123.73, 130.07, 132.00, 140.36, 148.57; Analysis calculated for $C_{12}H_{17}NO_6$ C = 51.36, H = 5.87, N = 5.44%; Found C = 52.00, H = 6.21, N = 5.88%.

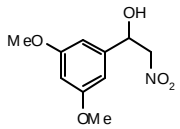
1-(3-Nitrophenyl)-2-nitrobutan-1-ol (275):



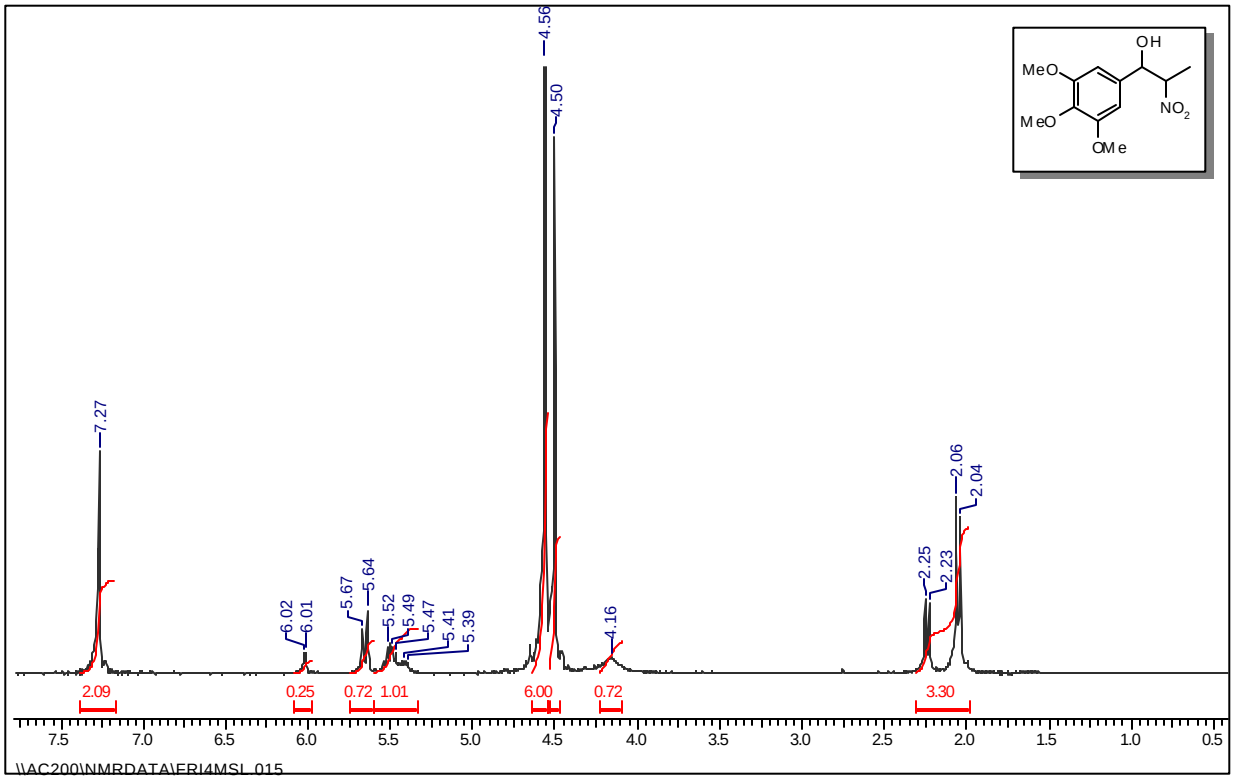
Solid, m.p. 106.5 ^oC; **IR** (Neat)**:** 3492, 1570 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 0.90-0.98 (two triplets merged together, 3H), 1.42-2.30 (m, 2H), 3.12 and 3.20 (bs, total 1H), 4.57-4.68 (m, 1H), 5.19 (d, J= 4.0 Hz) and 5.32 (d, J= 2.0 Hz), total 1H, 7.58-7.65 (m, 1H), 7.70-7.76 (m, 1H), 8.19-8.29 (m, 2H); **^{13}C NMR** ($CDCl_3$)**:** δ 9.98, 21.33, 23.80, 73.12, 74.22, 94.50, 94.55, 121.20, 121.83, 123.00, 123.91,

129.88, 130.04, 132.02, 132.76, 140.85, 148.54; Analysis calculated for $C_{10}H_{12}N_2O_5$: C = 50.00, H = 5.05, N = 11.66%; Found C = 50.20, H = 5.17, N = 11.28%.

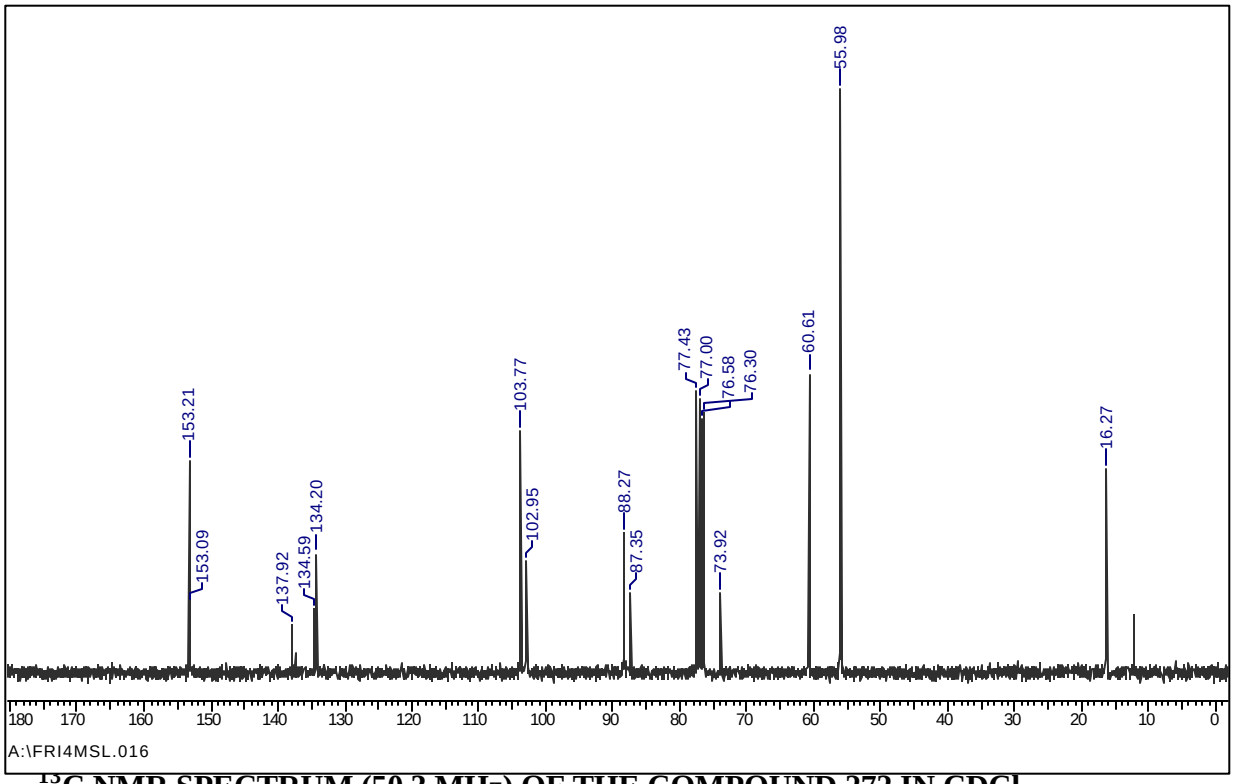
1-(3, 5-Methoxyphenyl)-2-nitroethanol (276):



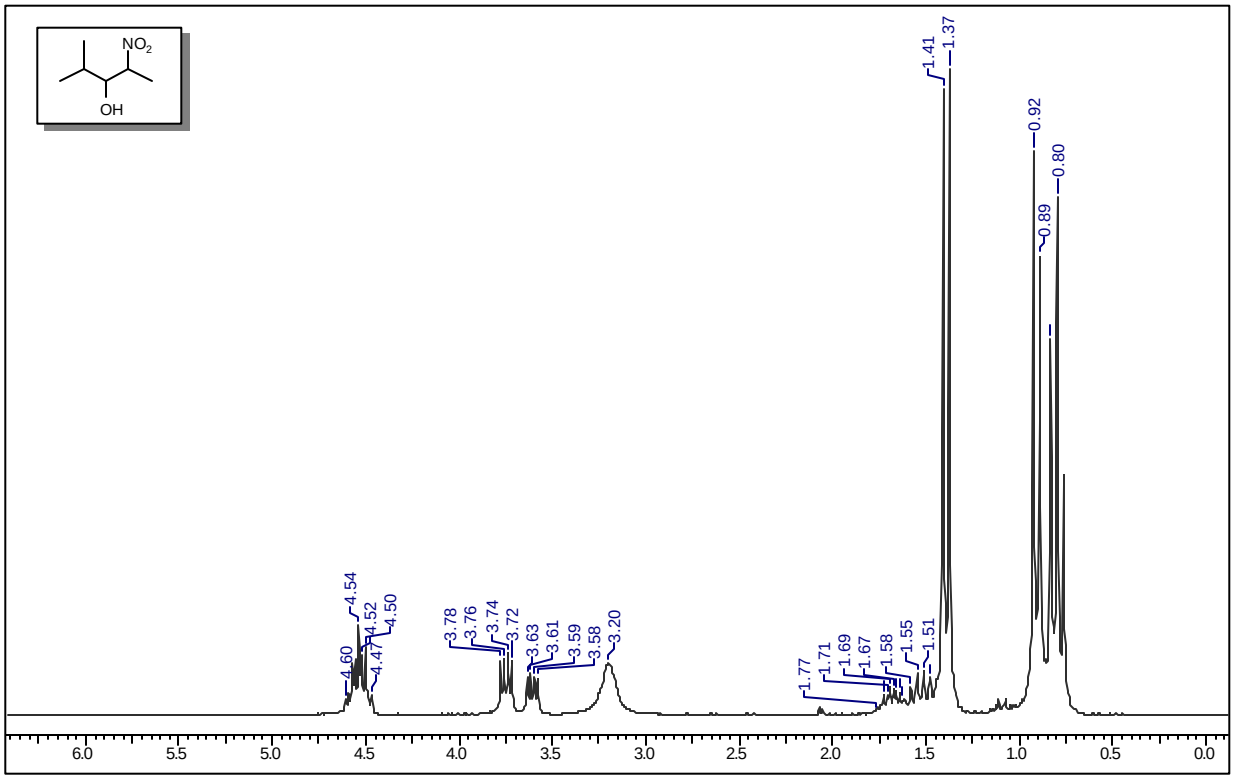
Viscous liquid; **IR** (Neat)**:** 3466, 1570 cm^{-1}; **^{1}H NMR** ($CDCl_3$): δ 4.52 (s, 6H), 5.18-5.35 (m, 2H), 6.08 (d, J= 2.0 Hz, 1H), 6.11 (d, J = 2.0 Hz, 1H), 7.15 (s, 1H), 7.27 (s, 2H); **^{13}C NMR** ($CDCl_3$): δ 55.36, 70.96, 81.21, 100.62, 103.89, 140.76, 161.26; Analysis calculated for $C_{10}H_{13}NO_5$: C = 52.86, H = 5.76, N = 6.16%; Found C = 53.01, H = 6.18, N = 5.88%.



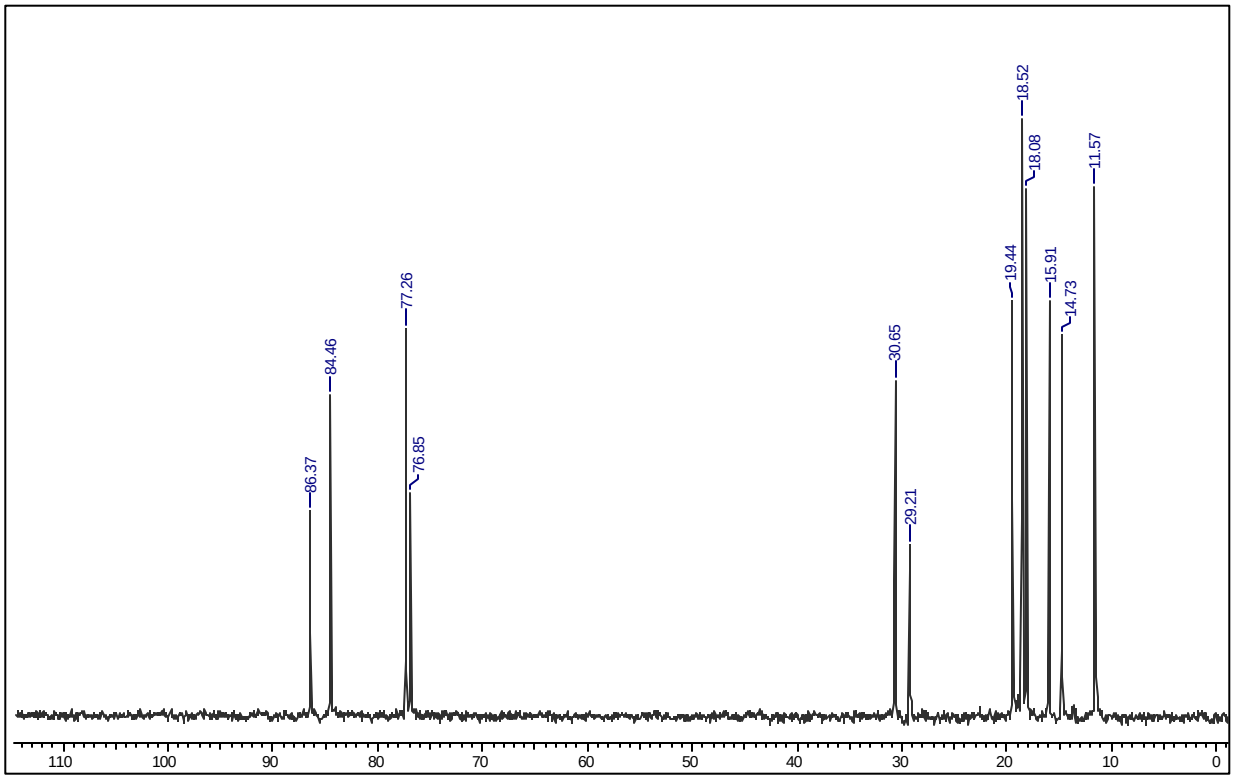
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 272 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 272 IN $CDCl_3$

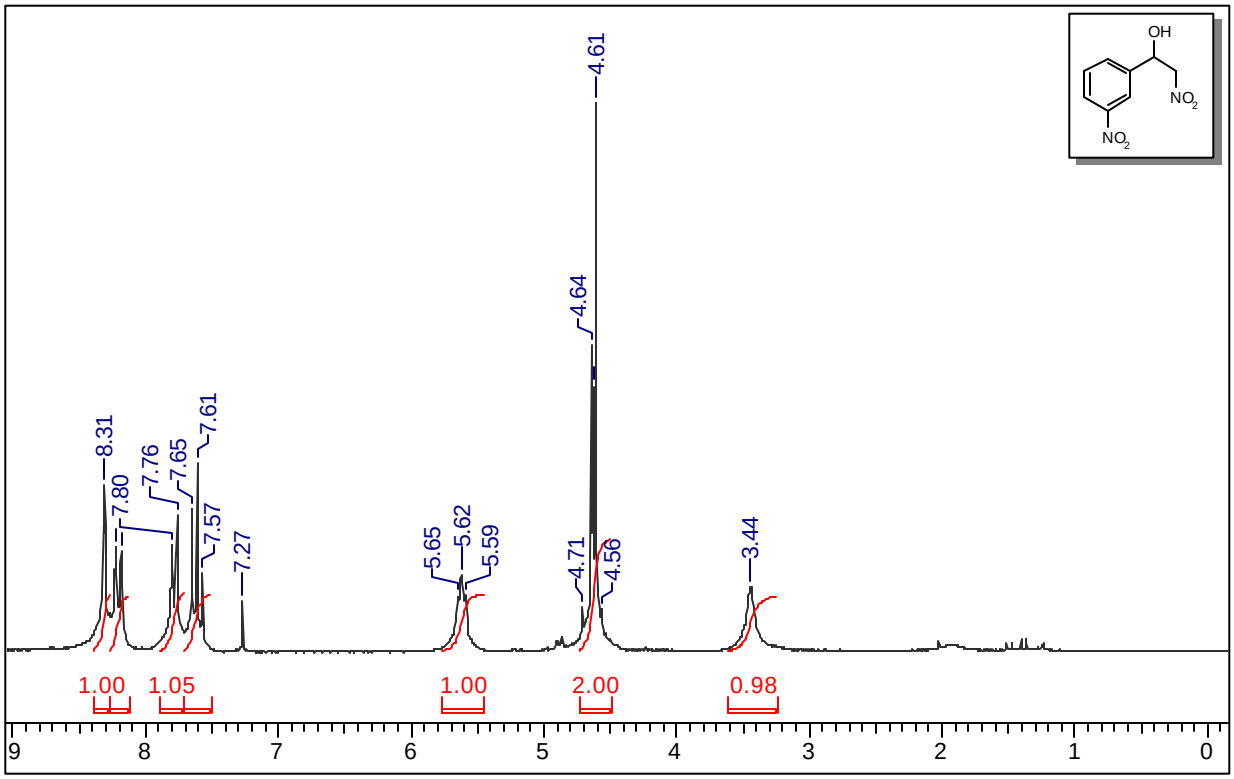


^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 273 IN $CDCl_3$

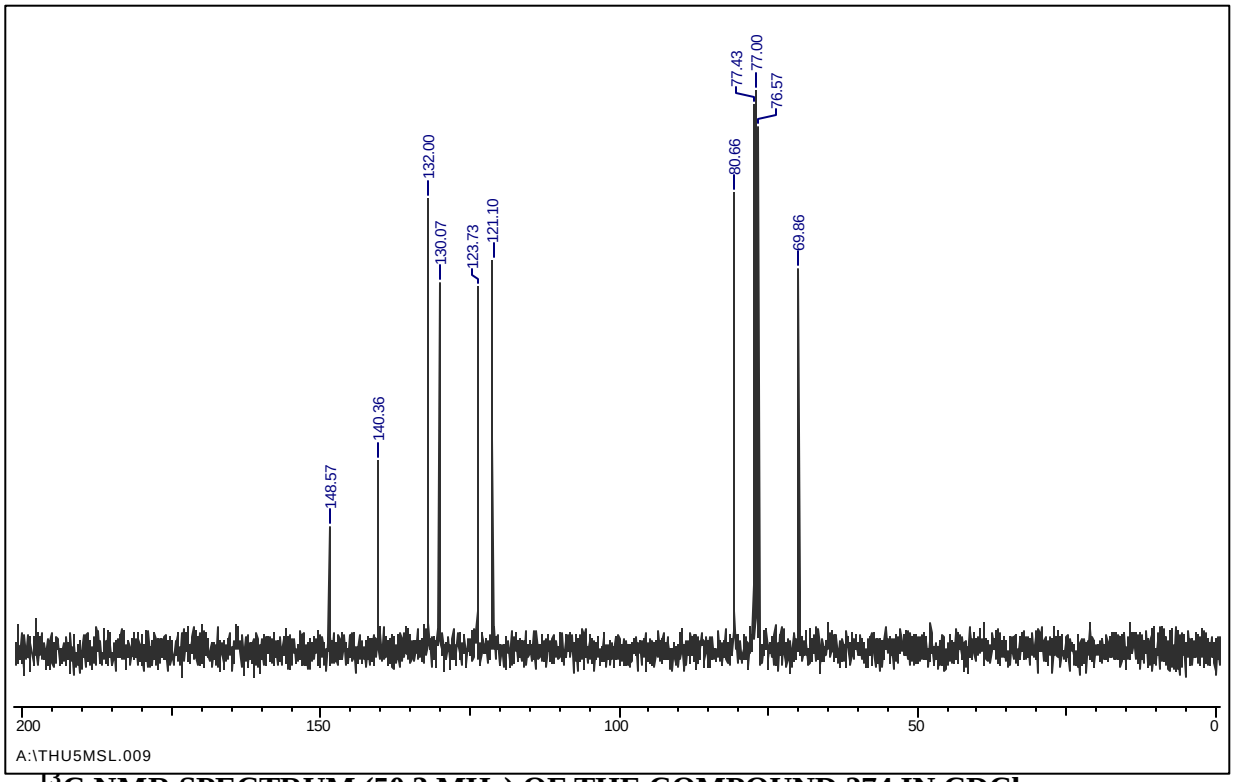


A:\THU5AC.027

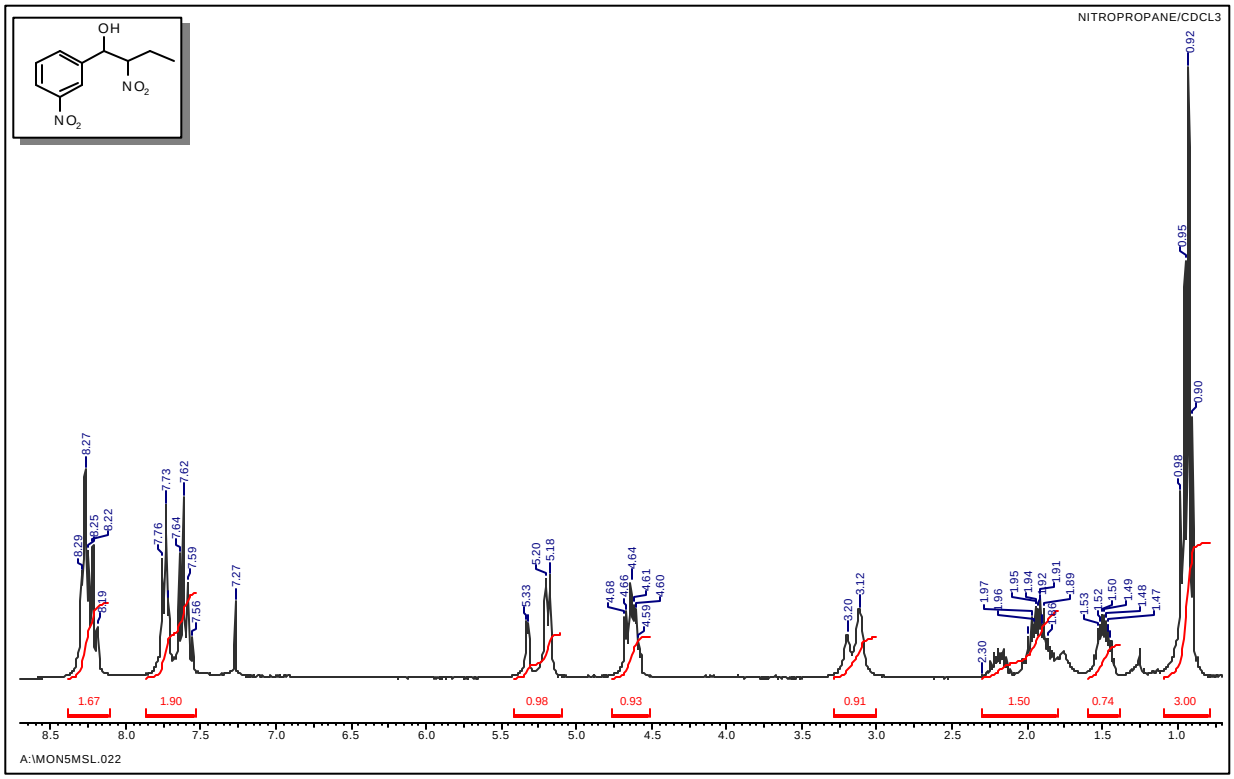
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 273 IN $CDCl_3$



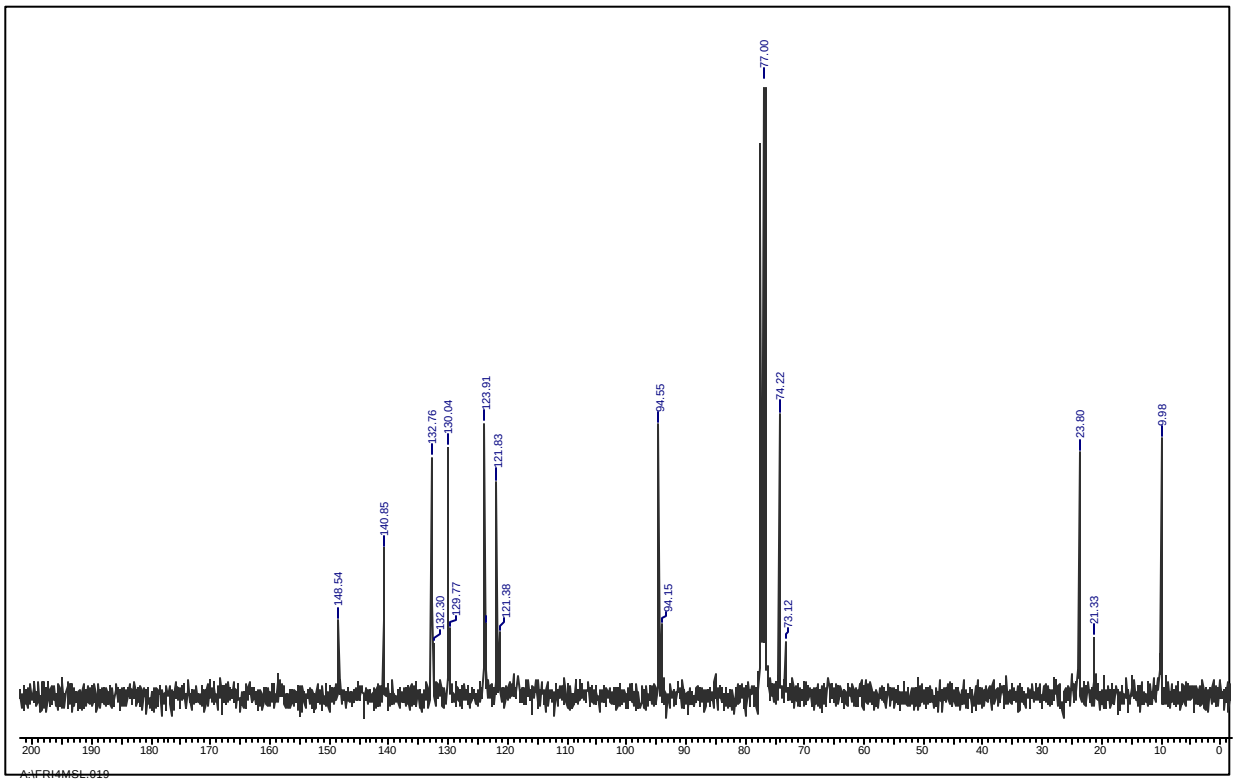
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 274 IN $CDCl_3$



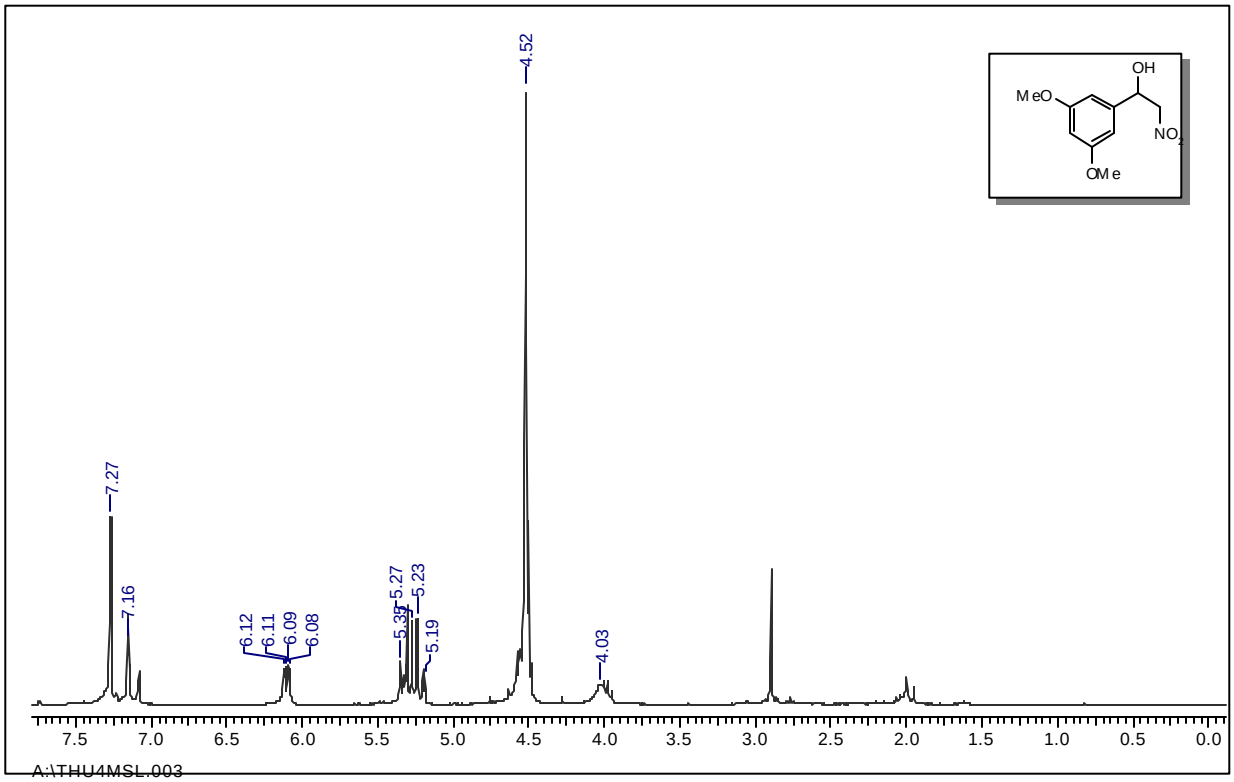
^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 274 IN $CDCl_3$



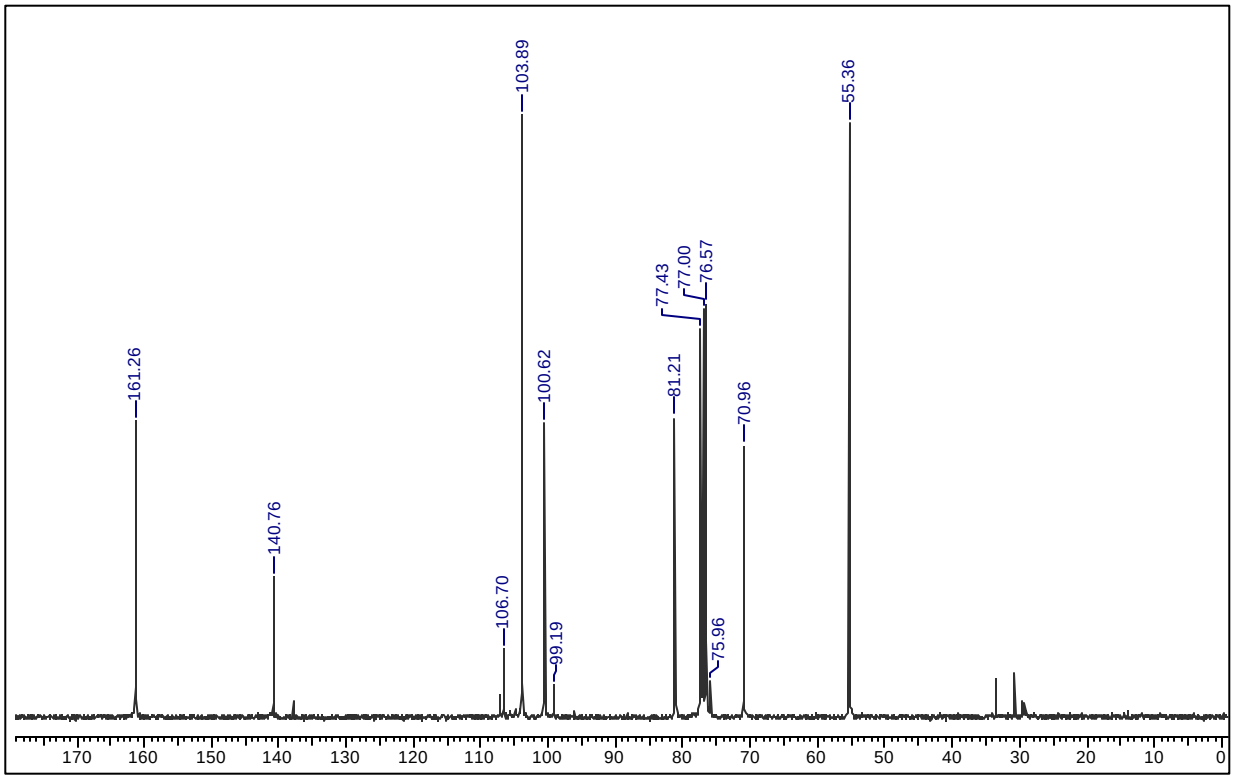
^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 275 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 275 IN $CDCl_3$



^{1}H-NMR SPECTRUM (200 MHz) OF THE COMPOUND 276 IN $CDCl_3$



^{13}C NMR SPECTRUM (50.3 MHz) OF THE COMPOUND 276 IN $CDCl_3$

3.1.4 REFERENCES:

1. Docks, J. *Synthesis,* **1973**, 441.
2. Dehmlow, E. V., *Angew. Chem. Int. Ed*., **1977**, 16, 493.
3. Dehmlow, E. V., *Angew. Chem. Int. Ed,*. **1974**, 13, 170.
4. Rabinovitz, M.; Cohen, Y.; Halpern, M., *Angew. Chem. Int. Ed*., **1986**, 25, 960.
5. Yang, N. C. and Finnegan, R. A., *J. Am. Chem. Soc.,* **1958**, 80, 5845.
6. a) Kende, A. S. and Rizzi, J. P., *J. Am. Chem . Soc.,* **1981**, 103, 4247. b) Wuff, W. D. and Tang, P. C., *J. Am. Chem. Soc.*, **1984**, 106, 434.
7. a) Bestmann, H. J. and Frey, H., *Justus Liebig Ann. Chem,*. **1980**, 2061. b) Frey, H. and Kaupp, G., *Synthesis,* **1990**, 931.
8. a) Fieser, L. S., *Org. Syn. Coll. Vol,*. 5, **1973**, 604. b) Pyne, S. G.; Spellmeyer, D. C.; Chen, S.; Fuchs, P. L., *J. Am. Chem. Soc.,* **1982**, 104, 5728. c) Hewson, A. T.; Hughes, K.; Richardson, S. K.; Sharpe, D. A.; Wadsworth, A. H., *J. Chem. Soc. Perkin Trans,. I* **1991**, 1565.
9. Newkome, G. R.; Behra, R. J.; Moorefied, C. N.; Baker, G. R., *J. Org. Chem*., **1991**, 56, 7162.
10. Weis, C. D. and Newkome, G. R., *J. Org. Chem*... **1990**, 55, 5801.
11. Patra, R.; Maiti, S. B.; Chatterjee, A.; Chakravarti, A. K., *Tetrahedron Lett*., **1991**, 32, 1363.
12. Cheng, A.; Uyeno, E.; Polagar, W.; Toll, L.; Lawson, J. A.; Degraw, J. I.; Loew, G.; Cammeraman, A.; Cammeraman, N., *J. Med. Chem..,* **1986**, 29, 531.
13. a) Koshinen, P. M. and Koshinen, A. M. P., *Synthesis,* **1998**, 1975. b) Rosini, G. and Ballini, R. *Synthesis,* **1988**, 833. c) Tsay, S. C.; Patel, V. and Hwu, J. R., *Synlett*., **1998**, 939. d) Ballini, R. and Bosica, G., *Eur. J. Chem*., **1998,** 2, 355. e) Scarpi, D.; Occhiato, E. G. and Guorna, A., *J. Org. Chem*., **1999,** 64, 1727.
14. Barett, A. G. M. and Spilling, D. C., *Tetrahedron Lett,,* **1988,** 29, 5733.
15. a) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Epifano, F.; Rosati, O., *Synth. Commun,*. **1998**, 28, 3057. b) Adam, W.; Makosza, M. C.; Moller, C. R.; Zhao, C. G., *Synlett*., **1998**, 1335. c) Ballini, R.; Papa, F.; Abate, C., *Eur. J. Org. Chem*., **1999**, 1, 87.
16. a) Ballini, R. and Bosica, G., *Tetrahedron,* **1997,** 53, 1613. b) Ono N. and Kaji, A., *Synthesis,* **1986**, 693. c) Ballini, R.; Curini, M.; Epifano, F.; Marcotulli M. C. and Rosati, O., *Synlett*., **1998,** 1049 and references cited therein. d) Rosini, G. and Ballini, R., *Synthesis,* **1988,** 833.

17. Hanessian, S.; Devasthale, P., *Tetrahedron Lett*., **1996**, 37, 987.
18. Vaderbilt, B. M.; Hass, H. B., *Ind. Eng. Chem*., **1940**, 32, 34.
19. Costantino, V.; Curini, M.; Marmottini, F.; Rosati, O.; Pisani, E., *Chem. Lett*., **1994**, 2255.
20. Perekalin, V. V. Unsaturated Nitro Compounds; Israel Progress for Scientific Translation, Jerusalem, **1964**.
21. Baer, H. H.; Urbas, L. In The Chemistry of the Nitro and Nitroso groups; Feuer, H. Ed.; Wiley Interscience: New York, **1970**; vol. 2.
22. Hurd, C. D.; Nilsun, M. E. J. Org. Chem. **1955**, 20, 927.
23. a) Seebach, D.; Beek, A. K.; Mukhopadyay, T.; and Thomas, E., *Helv. Chim. Acta,*. **1982**, 65, 1101. b) Eyer, M.; Seebach, D., *J. Am. Chem. Soc.*, **1985**, 107, 3601. c) Barrett, A. G. M.; Robyr, C. and Spilling, C. D., *J. Org. Chem,*. **1989** 54, 1234. d) Sasai, H.; Suzuki. T.; Arai, S.; Arai T.; Shibasaki, M., *J. Am. Chem. Soc.*, **1992**, 124, 4418. e) Sasai, H.; Kim, W. S.; Suzuki, T. Shibasaki, M., *Tetrahedron Lett.,* **1994**, 35, 6123. f) Chin R.; Najera, C.; Sanchez-Agullo, P. *Tetrahedron: Asymmetry,* **1994**, 5, 1393.
24. Bulbule, V. J.; Deshpande, V. H.; Velu, S.; Sudalai, A.; Sivasanker, S.; Sathe, V. T., *Tetrahedron*, **1999**, 55, 9325.
25. a) Amato, *J., Science,* **1993**, 259, 1538. b) Illman, D. L., *Chem. Eng. News,* **1993**, 71, 5. c) Illman, D. L., *Chem. Eng. News,* **1994**, 72, 22.
26. Li, C., *J. Chem. Rev*., **1993**, 93, 2023.
27. Fringuelli, F.; Pani, G.; Piermatti, O.; Pizzo, F., *Tetrahedron*, **1994**, 50, 11499.
28. Kiyooka, S. I.; Tsutsui, T.; Maeda, H.; Kaneko, Y.; Isobe, K., *Tetrahedron Lett.,* **1995**, 36, 6531.
29. a) Rosini, G.; Ballini, R.; Petrini, M.; Sorrenti, P., *Synthesis*, **1985**, 515. b) Bandgar, B. P.; Zirange, M. B. and Wadgaonkar, P. P., *Synlett*, **1996**, 149.