Development of Synthetic Methodologies towards Terpenes : Heritol, Heritianin and Pseudopterosins

THESIS
SUBMITTED TO THE
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BY

CHITRA GOVANDE

DIVISION OF ORGANIC CHEMISTRY (TECHNOLOGY)
NATIONAL CHEMICAL LABORATORY
PUNE-411 008 (INDIA)

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Form-A

CERTIFICATE

Certified that the work incorporated in the thesis titled "*Development of Synthetic Methodologies Towards Terpenes : Heritol, Heritonin and Pseudopterosins*" submitted by **Chitra Govande** was carried out by her under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

September 1997
Pune

S.P. Chavan
Research Guide

DEDICATED TO MY PARENTS

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Finally, I thank CSIR, New Delhi, for financial support and Dr. Paul Ratnasamy, Director, NCL, for allowing me to work here and submit it in form of a thesis.

C Govande

Chitra Govande

General Remarks

1. All melting points and boiling points are uncorrected and the temperatures are in the centigrade scale.
2. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.
3. Organic layers were dried over anhydrous sodium sulfate.
4. TLC analysis was carried out on glass plates using silica gel GF-254 and the plates were analyzed by keeping in iodine or under UV light.
5. In cases where chromatographic purification was done, silica gel (60-120 mesh) was used as the stationary phase.
6. IR spectras were recorded on Perkin-Elmer Infrared Spectrophotometer Model 68B or on Perkin-elmer 1615 FT Infrared spectrophotometer.
7. ^{1}H-NMR and ^{13}C-NMR were recorded on Varian FT-80A (20 MHz), Bruker WH-90 (22.63 MHz), Bruker AC-200 (50 MHz) or Bruker MSL-300 (75 MHz). Figures in parentheses refer to ^{13}C frequencies. Trimethyl silane was used as the internal standard.
8. Mass spectra were recorded at an ionization energy of 70 eV on Finnigan MAT-1020, automated GC/MS instrument.
9. The compound numbers and scheme numbers given in each chapter refer to that particular Chapter only.The same applies for the abstract.

Abbreviations

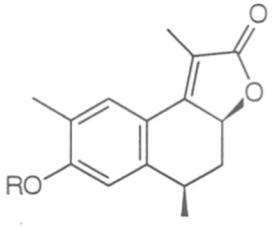
Ac	Acetyl
acac	acetoacetate
AIBN	2,2-Azoiso(bisbutyronitrile)
Ar	Aryl
BMS	Boron Dimethyl sulfide
Bu	Butyl
CAN	Ceric Ammonium Nitrate
DBU	1,8-Diazabicyclo-[5,4,0]-undec-7-ene
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DIBAL-H	Diisobutyl aluminium hydride
DMAP	N,N-Dimethyl amino pyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
Et	Ethyl
HMDS	Hexamethyldisilane
HMPA	Hexamethyl phosphoric triamide
Im	Imidazole
LDA	Lithium diisopropyl amide
*m*CPBA	*m*-chloroperbenzoic acid
Me	Methyl
MsCl	Methane sulfonyl chloride (mesyl chloride)
NBS	N-Bromosuccinimide
NMO	N-methyl morpholine N-oxide
NMR	Nuclear Magnetic Resonance
PDC	Pyridinium dichromate
PCC	Pyridinium chlorochromate
Pd/C	Palladized carbon
PPTS	Pyridinium *p*-toluene sulfonate
Ph	Phenyl
*p*TSA	*p*-toluene sulfonic acid
^{i}Pr	isopropyl
py.	pyridine
TBABr	Tetrabutyl ammonium bromide
TBA.HSO_4	Tetrabutyl ammonium hydrogen sulfate
TBAF	Tetrabutyl ammonium fluoride
TEBA	Triethylbenzyl ammonium chloride
Tf	Triflate/triflic
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TBDMSCl	*tert*-butyldimethylsilyl chloride
TMSCl	Trimethylsilyl chloride

Abstract

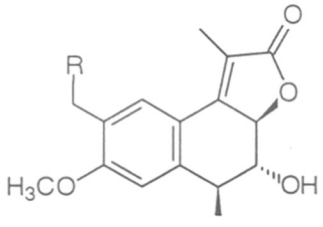
The thesis entitled "**Development of synthetic methodologies towards terpenes : Heritol, Heritianin and Pseudopterosins**" is divided into three chapters.

Chapter 1 Approaches towards butenolides

Synthesis of butenolides has been of current interest owing to their natural abundance in a variety of natural products including biologically active molecules like Heritol 1,[1] Heritonin **2**,[2] Vallapianin **3**,[2] Heritianin **4**[2] and other related compounds.



R = H **1**
R = CH_3 **2**



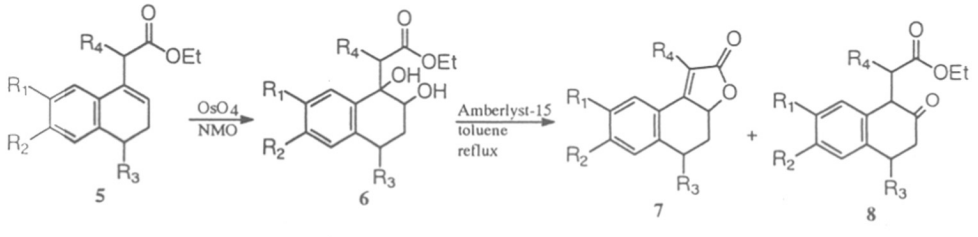
R = OH **3**
R = H **4**

This chapter is divided into three sections and deals with the development of novel conversions of β,γ-unsaturated esters to butenolides.

Section 1 Intramolecular cyclization of dihydroxy esters to butenolides

Cyclization of dihydroxy ester **6** into butenolides using acidic catalysts has been developed from these laboratories[3].

This conversion has been carried out using commercially available Amberlyst-15 resin as acid catalyst. A novel feature of this conversion is that it permits the isolation of either keto-ester **8** or butenolide **7** by choice. Keto-ester **8** has been isolated and subsequently converted into butenolide.

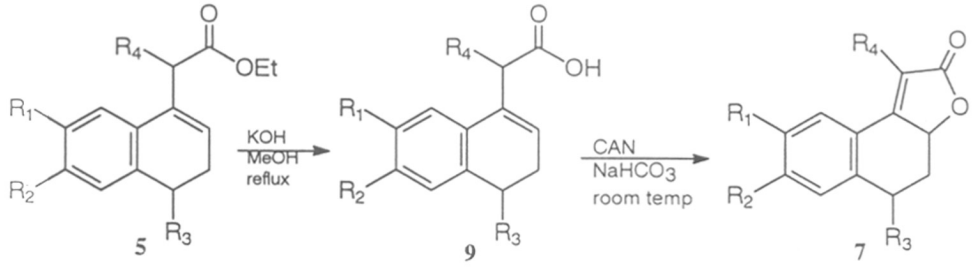


5 6 7 8

Section 2 Oxidative conversion of β,γ-unsaturated acids to butenolides

A novel, mild and efficient methodology for the oxidative conversion of β,γ-unsaturated acids **9** to the corresponding butenolides **7** using the single electron oxidant,

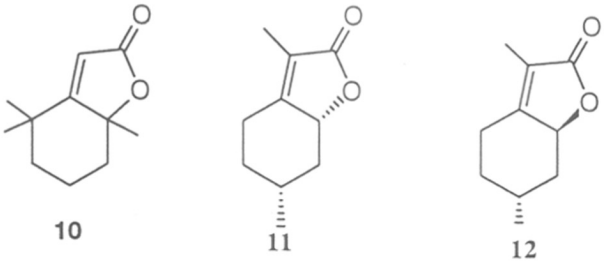
Ceric ammonium nitrate (CAN) is described. Various butenolides have been synthesized in good to excellent yields.



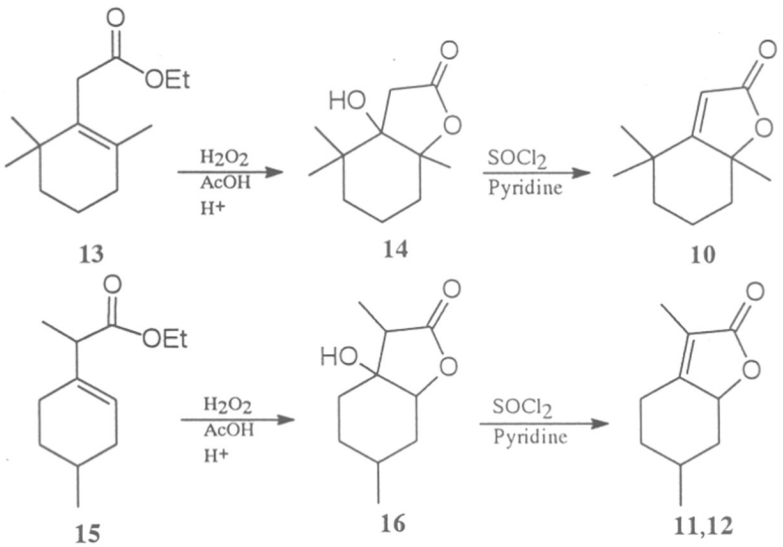
Synthesis of Heritol and Heritonin using the above protocol has been achieved.

Section 3 Synthesis of monoterpenic butenolides : (±)Dihydroactinidiolide and Mintlactones

(±)Dihydroactinidiolide **10** is a biologically active monoterpene exhibiting physiological activity against *Felidae* animals and has been isolated from the leaves of *Actinidia polygama*.[4] Mintlactone **11** and iso-mintlactone **12** are minor components of commercially important flavoring essential oils, found in peppermint oil and spearmint oil[5]. Interest in the area of butenolides led to the development of a short sequence for their synthesis.



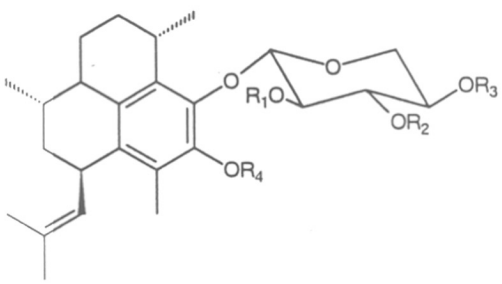
A one-pot, concomitant hydroxylation of the β,γ-unsaturated esters **13**, **15** followed by intramolecular cyclization using hydrogen peroxide under acidic conditions yielded thehydroxy lactone **14, 16** respectively. Conventional dehydration procedures furnished the target compounds.



Aeginetolide **14** is also a natural product which coexists with **10**.

Chapter 2 Synthesis of Pseudopterosins

Pseudopterosins A-D **17a-d** represent a new class of bioactive diterpenic glycosides which have been isolated from *Pseudogorgia elizabethae*[6] . They have been shown to exhibit pronounced antiinflammatory and analgesic properties.



$R_1=R_2=R_3=R_4=H$	**Ps A**	**17a**
$R_1=Ac, R_2=R_3=R_4=H$	**PsB**	**17b**
$R_2=Ac, R_1=R_3=R_4=H$	**Ps C**	**17c**
$R_3=Ac, R_1=R_2=R_4=H$	**Ps D**	**17d**

This chapter is divided into three sections.

Section 1 Synthesis of Pseudopterosins :A review

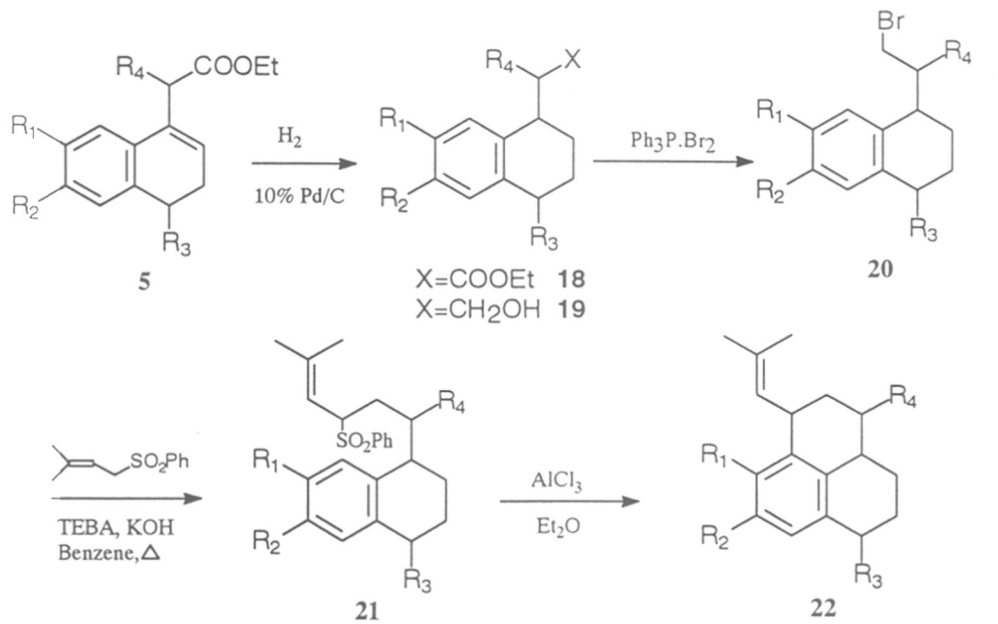
The reported syntheses of the aglycone of Pseudopterosins are reviewed in this section.

Section 2 Methodology towards the tricyclic skeleton of Pseudopterosins

The aglycones of Pseudopterosins bear a common framework with the stereochemistry of the alkyl and vinyl substituents in different dispositions.

A general protocol has been developed for the construction of these tricyclic compounds using the dual nature of allyl sulfones to act as both nucleophiles as well as electrophiles depending on the reaction conditions.

The key steps of the methodology are the alkylation of prenyl sulfone with bromo compound **20** under phase transfer conditions and the Lewis acid catalyzed cyclization of the resulting sulfones **21** to yield the tricyclic analogues of Pseudopterosins in good to excellent yields.



Section 2 Synthetic studies towards dimethyl ether of Pseudopterosin aglycone

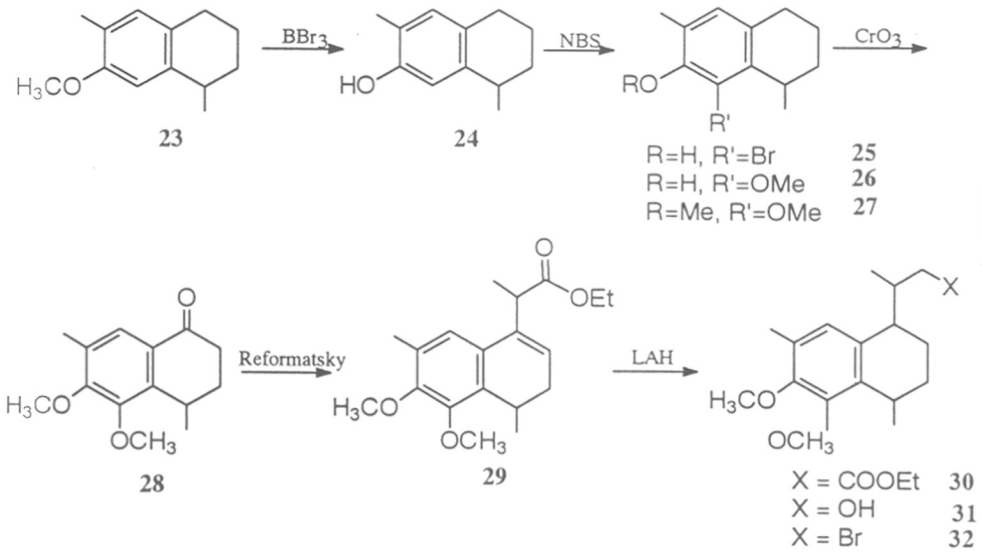
The synthesis of the dimethyl ether of Pseudopterosin aglycone was attempted using the protocol described in the previous section.

The tetralone **28** was synthesized in five high yielding steps from 6-methoxy-4,7-dimethyl tetrahydronaphthalene **23** using conventional bromination-methoxylation procedures. Reformatsky reaction on the tetralone with ethyl α-bromopropionate yielded the

β,γ-unsaturated ester which was reduced to the alcohol **30**. Transfer hydrogenation followed by bromination yielded the desired bromo compound **32**.

However, following the previously standardized protocol did not furnish the sulfone 33.

At this stage of the synthesis Kocienski *et al* reported an essentially similar strategy to the target molecule, hence the route was abandoned.



Chapter 3 Synthetic conversion using peroxide

There are wide variety of reagents available for the oxidation of aldehyde to carboxylic acids / esters. Most of these methods use strong forcing conditions and / or expensive reagents.

In this chapter a simple one pot conversion of aromatic aldehydes to the corresponding carboxylic acids or esters using readily available and cheap hydrogen peroxide in presence of TS-1 zeolite as catalyst is presented.

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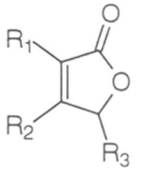
CHAPTER 1

Approaches Towards Butenolides

1.0 Introduction

The term butenolide for describing five membered unsaturated lactones was first employed by Klobb[1] in 1898. The term encompasses both α,β- and β,γ–unsaturated butyrolactones of which only the former are encountered in nature, probably on account of their greater stability.

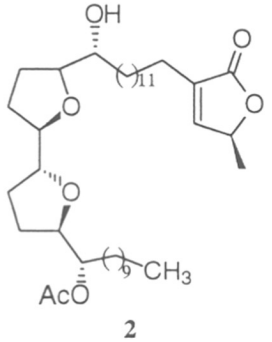
For the sake of convenience, the term butenolide in the thesis specifically refers to α,β-unsaturated butyrolactones **1** or the Δ^2-butenolides which are also termed as 2(5H)-furanones by IUPAC nomenclature.



1

Fig. 1

The butenolide moiety is present in a number of structurally diverse and biologically active natural products. The structural diversity includes long chain acetogenins represented by Uvaricin **2**[2] and the tetronic acids represented by Vertinolide **3**[3].



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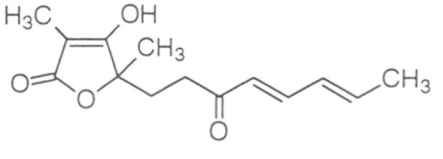
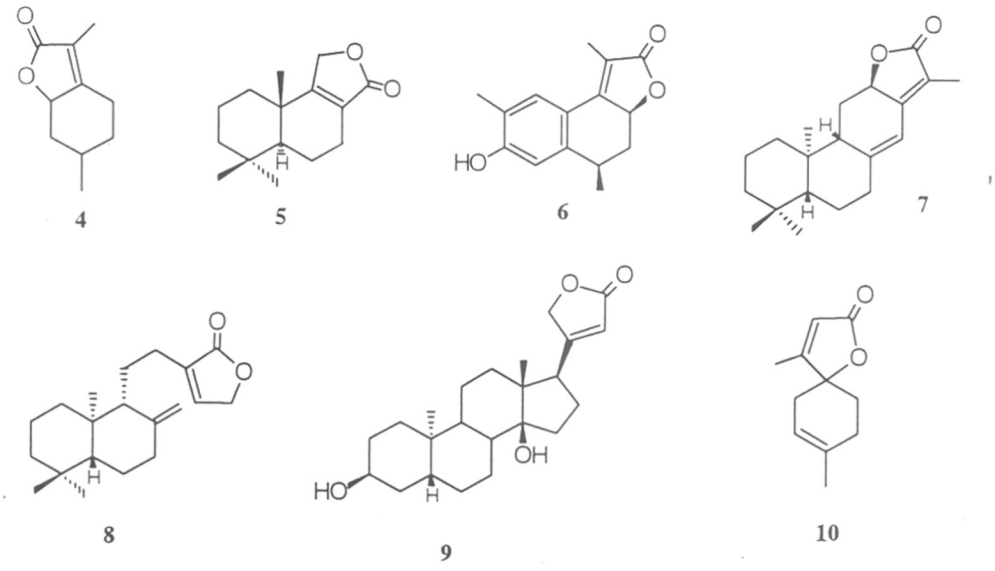


3

Fig. 2

However, most natural butenolides are terpenoid in origin. They range from simple monoterpenoid mintlactones **4**[4] to sesquiterpenes like Confertifolin **5**,[5] Heritol **6**[6] and diterpenes like Jolkinolide **7**[7] and the labdane derivative, Nivenolide **8**.[8] Digitoxigenin **9**[9] and related cardenolides are other important members of this class. Spirobutenolides like Andriolactone **10**[10] constitute yet another family of butenolides.



4 **5** **6** **7**

8 **9** **10**

Fig.3

These compounds thus form an important class of natural products exhibiting a wide range of biological and pharmacological properties.

Butenolides also serve as excellent substrates for carrying out conjugate additions and Diels-Alder reactions for conversions to other five-membered lactones.

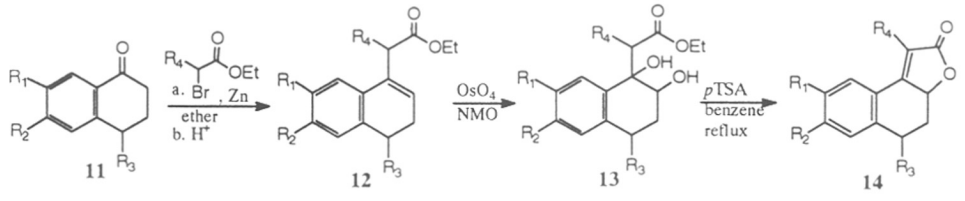
1.0.1 Review:

As a consequence of their importance and widespread occurrence, many approaches to the butenolides have been reported. The chemistry of butenolides has been reviewed extensively by Y.S.Rao[11] in 1976 and more recently by D.W. Knight[12] in 1994.

A few of the more recent approaches, not covered by the previous reviews, are presented here.

Chavan's approach:[13] (1992, *Scheme 1*)

Ketones **11** were smoothly transformed into the β,γ-unsaturated ester **12** *via* Reformatsky reaction followed by acidic workup with concomitant dehydration. Catalytic osmylation of the olefins **12** furnished diols **13** in excellent yields. Treatment of the diols with catalytic *p*TSA in refluxing benzene afforded the butenolides in good to excellent yields.



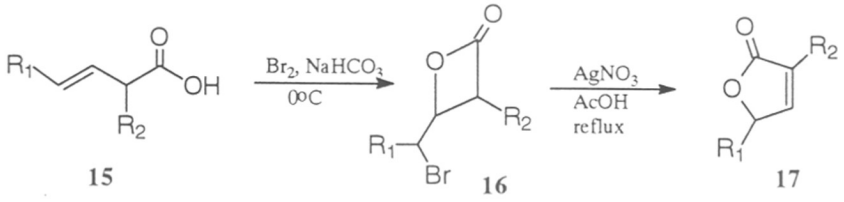
Scheme 1

The occurrence of two steps in one pot *viz.* lactonization and dehydration are the noteworthy features of this efficient transformation. An additional feature is its successful application to the synthesis of Heritol **6** and mintlactones **4** in good yields.

The sole demerit of this sequence lies in the use of toxic and highly expensive OsO_4 for dihydroxylation.

Black's approach:[14] (1993, *Scheme 2*)

Bromolactonization of β,γ-unsaturated carboxylic acids **15** using $Br_2/NaHCO_3$ gave the β-lactones **16**. Treatment of these lactones with silver nitrate in refluxing acetic acid effected the ring expansion-elimination to butenolides **17** in 30-65% yields.



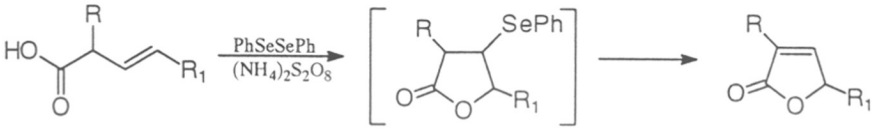
15 **16** **17**

Scheme 2

This novel two step sequence from simple β,γ-unsaturated acids, however, gives relatively poor yields of butenolides and also requires the use of expensive silver salts in stoichiometric amounts under extremely drastic conditions.

Tiecco's approach:[15] (1993, *Scheme 3*)

β,γ-unsaturated acids **18** were smoothly converted to butenolides using catalytic diphenyl diselenide and excess ammonium persulfate in acetonitrile in 21-97% yield. The reaction proceeds *via* the selenolactone intermediate **19**.



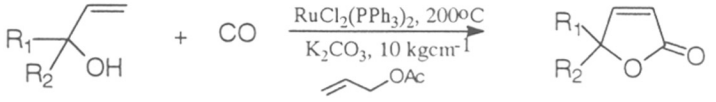
18 **19** **20**

Scheme 3

The use of simple organoselenium compound for this two-step one-pot conversion is an attractive feature. However, the exceptionally poor yields of butenolide for mono-substituted olefinic esters (R_1=H) creates doubt about the generality of this method.

Watanabe's approach:[16] (1994, *Scheme 4*)

Cyclocarbonylations have been successfully used previously for the synthesis of butenolides starting from propynyl alcohols, acetylenes and vinyl halides.[11,12] Watanabe *et al* reported the oxidative carbonylation of the allylic alcohol **21** to butenolide **22** using catalytic amount of $RuCl_2(PPh_3)_2$ in the presence of allyl acetate as hydrogen acceptor.



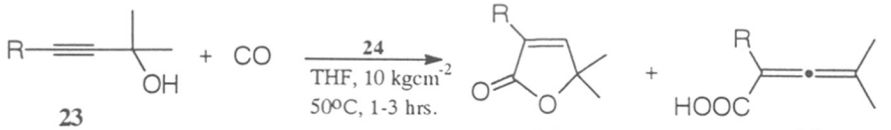
21 **22**

Scheme 4

This reaction is applicable only to 1,1-disubstituted allyl alcohols and in the case of 1-monosubstituted allyl alcohols no carbonylation occurred.

Inoue's approach:[17] (1994, *Scheme 5*)

Inoue *et al* reported the carbonylation of propargylic alcohols using the cationic palladium (II) complex, $[Pd(CH_3CN)_2(PPh_3)_2]$ $(BF_4)_2$ (**24**) to afford the γ,γ-disubstituted 2(5H)-furanones **25** and/or 2,3-dienoic acids **26** (*Scheme 5*). Addition of trace amount of *p*TSA to **26** gave the butenolide.



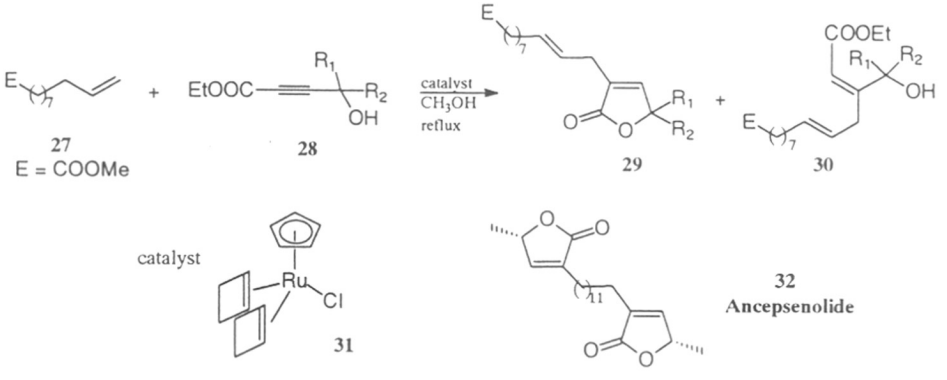
23 **25** **26**

Scheme 5

This method is similar to that reported by Alper *et al*[18] involving use of bis(dibenzilideneacetone) palladium (0) [$Pd(dba)_2$] and 1,4-bis(diphenylphosphino) butane (dppb) which required a long time for completion. The use of toxic CO and expensive catalyst diminishes the utility of this method.

Trost's approach :[19] (1994, *Scheme 6*)

Ruthenium-catalyzed Alder-Ene reaction of simple olefins with 3-hydroxyalkynoates **28** yielded the butenolide **29** by attack at α-carbon as the major product. The hydroxy dienoic ester **30** was formed by β-attack.



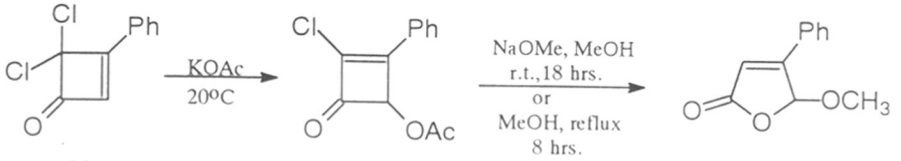
Scheme 6

This approach has also been applied for the synthesis of Ancepsenolide **32** which is a bioactive acetogenin.

The novelty of the Alder-Ene reaction as a route to butenolides is lessened by the use of expensive ruthenium complex for catalyzing the reaction.

Dillon's approach:[20] (1994, *Scheme 7*)

The reaction of 4,4-dichloro-3-phenyl-2-cyclobutenone **33** with KOAc afforded the cyclobutenone **34**. When refluxed in MeOH or treated with NaOMe in MeOH at room temperature, ring expansion occurred to give butenolide **35** in 75% yield.



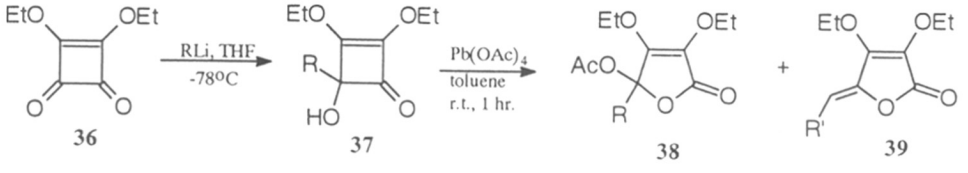
33 **34** **35**

Scheme 7

The route though proceeding in high yield and using simple reagents does not have much scope because of the difficulty in obtaining dichlorocyclobutenones which are prepared by cycloaddition of dichloroketene to alkynes.

Eguchi's approach:[21] (1994, *Scheme 8*)

4-hydroxycyclobutenones **37** when treated with stoichiometric amount of Lead tetraacetate undergo a novel oxidative ring expansion to form the highly oxygenated 5-acetoxy-2(5H)-furanone **38** in 30-77% yield alongwith the 5-alkylidene 2(5H)-furanone **39**. Other oxidants like CAN and $Mn(OAc)_3$ also give similar results.



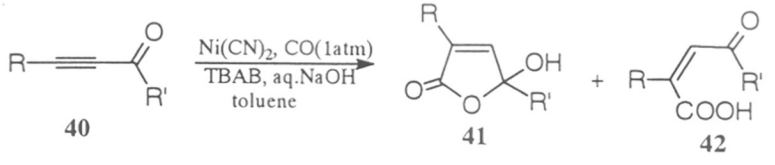
36 **37** **38** **39**

Scheme 8

The use of strong base for preparation of the hydroxy cyclobutenones coupled with the low yield of the product are the negative features of this methodology.

Arzoumanian's approach:[22] (1995, *Scheme 9*)

Recently, Arzoumanian *et al* reported the carbonylation of α-keto alkynes **40** in presence of catalytic amount of $Ni(CN)_2$ to yield γ-hydroxy α,β-unsaturated butyrolactones **41** under phase transfer conditions.



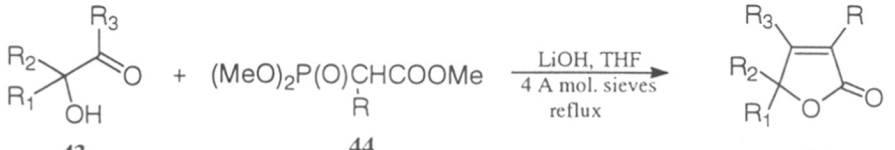
40 **41** **42**

Scheme 9

HCN is a by-product of this reaction, which coupled with the use of CO on account of its high toxicity renders this method of limited use to the synthetic chemists.

Bonadies' approach:[23] (1995, *Scheme 10*)

Linear and cyclic α-hydroxy ketones **43** under Horner-Wadsworth-Emmons (HWE) reaction with stabilized lithium phosphonates in the presence of activated 4A molecular sieves give the corresponding butenolides **45** in good yields.



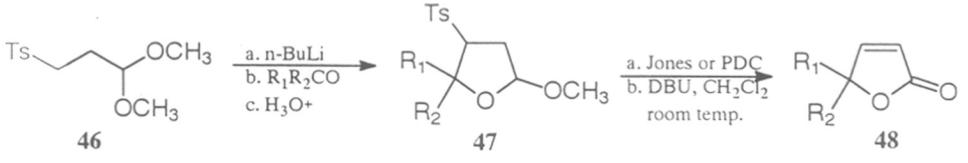
43 **44** **45**

Scheme 10

HWE reaction alongwith cyclization in one-pot occurs in good yields to give butenolides albeit with somewhat long reaction times.

Najera's approach:[24] (1995, *Scheme 11*)

Reaction of the acrolein derivative **46** with n-BuLi, followed by addition of carbonyl compounds as electrophiles gave the cyclic acetals **47** after acidic hydrolysis. Oxidation followed by elimination using DBU yielded the α,β-unsaturated butenolides in 85-99% yields.



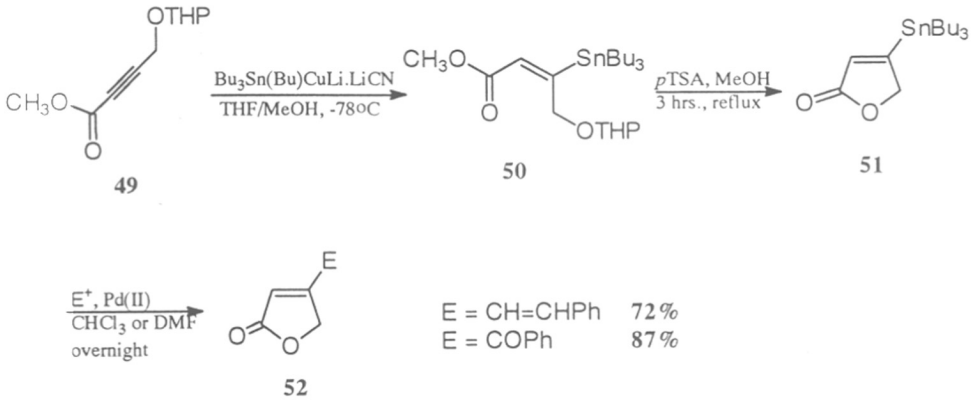
46 **47** **48**

Scheme 11

Conversion of the acetal **47** to butenolide requires strong oxidizing conditions like Jones or PDC oxidation and the use of strong base (DBU) to effect elimination of tosyl group.

Reginato's approach:[25] (1995, *Scheme 12*)

Stannylcupration of γ-hydroxyacetylenic ester **49** at -78°C followed by treatment with catalytic amount of *p*TSA yielded the stannyl γ-lactone **51**. Reaction of **51** with electrophiles gave 4-substituted 2(5H)-furanones in good yields.

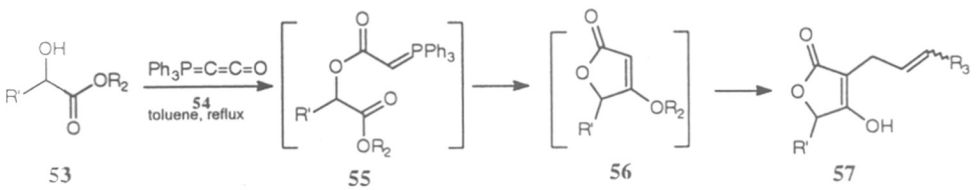


Scheme 12

As is evident, only 4-substituted butenolides can be obtained through this sequence.

Schobert's approach:[26] (1995, *Scheme 13*)

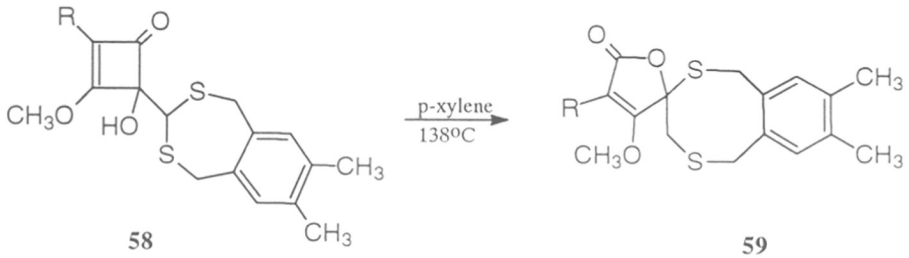
Allylic esters of α-hydroxy acids **53** were reacted with ketenylidene triphenylphosphorane **54** under toluene reflux conditions. The reaction proceeds *via* initial formation of an ester ylide **55** which undergoes 'tandem Wittig-Claisen' reaction to yield α,γ-disubstituted tetranoate in good yields.



Scheme 13

Moore's approach:[27] (1995, *Scheme 14*)

4-alkyl-4-hydroxycyclobutenones **58** in which the alkyl group bears a heteroatom substituent in its 2-position undergo an unusual ring expansion during thermolysis to give spirobutenolides **59**.

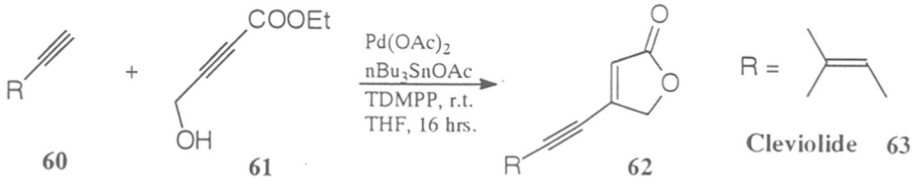


Scheme 14

This is a novel and unprecedented rearrangement. However, the applicability of the reaction is highly limited due to the restrictions of the substrate.

Trost's 2nd approach:[28] (1995, *Scheme 15*)

Addition of terminal alkynes to γ-hydroxyalkynoates **61** catalyzed by tris (2,6-dimethoxyphenyl)phosphine (TDMPP) in presence of tri-nbutyltinacetate yielded the corresponding butenolides in moderate yield. This methodology has been applied for the synthesis of Cleviolide (**63**).



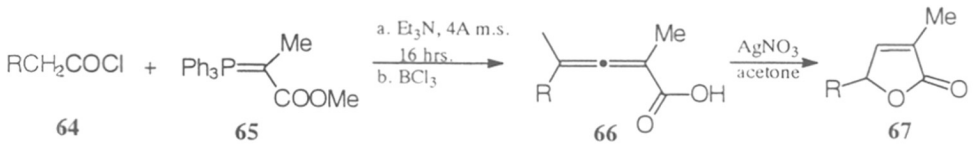
Scheme 15

This reaction has been applied for the synthesis of only 4-alkyne substituted butenolides.

Marshall's approach:[29] (1997, *Scheme 16*)

In this approach, allenic esters were prepared by the Wittig reaction of acid chlorides **64** with methyl 2-(triphenylphosphoranylidene)propionate **65** and subjected to hydrolysis with

BCl_3. The resulting allenic acids **66** were smoothly converted to butenolide **67** by treatment with 10% $AgNO_3$ in acetone.



64 65 66 67

Scheme 16

The methodology has been applied for the synthesis of only α,γ-disubstituted butenolides. Though high yielding, the use of expensive and sensitive Ag(II) salt and the long reaction time for formation of the allenic esters lowers the applicability of the reaction considerably.

1.0.2 **Conclusions**:

As observed in the literature survey, most of the methods for the synthesis of butenolides are inapplicable for a general substrate. Many use toxic and/or expensive reagents for catalyzing the reaction and are also hampered by the constraints of the availability of the substrate.

There are very few methods which are efficient and high yielding and also can be applied to any substrate at ambient temperatures and low reaction times to yield butenolides.

1.0.3 **References**:

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SECTION 1

Intramolecular Cyclization of Dihydroxy Esters to Butenolides

1.1.0 Introduction:

Heterogeneous catalysis is a fast progressing field in synthetic chemistry. This is amply demonstrated by the numerous reports which are appearing on various synthetic transformations which, till recently, used to be carried out with conventional reagents.

The use of insoluble catalysts allows easy work-up of the reaction mixture from which the products can be isolated by mere filtration and the catalyst recovered and reused after activation. Most of the catalysts can also be adopted for continuous operations using fixed bed catalysts which is of particular importance in large scale preparations. Also, because no strong acids or bases are used, sensitive groups are not affected. No neutralization is required for isolation of the product.

Solid acids like zeolites,[1,2] clays,[3-6] resins etc. have been used for effecting various transformations. Recently, the use of superacids[7-10] has been reported for catalyzing certain reactions.

1.1.1 Present Work:

As mentioned previously, butenolides are valuable synthetic intermediates and are also key structural subunits of a variety of natural products. Because of their unusual range of biological activity, there is a continuing need for the development of simple and versatile synthetic methods for this class of compounds.

Heritol **1**,[11] Heritonin **2**,[12] Heritianin **3**, Vallapin **4**,[12] Vallapianin **5**[12] and related compounds are members of the cadinane family of butenolides possessing an unusual oxygenation pattern. They were isolated by Miles and co-workers from the mangrove plant *Heritiera littoralis*. Heritol has been shown to possess itchthyotoxicity and also has been suggested to be a potential biocompatible pesticide.

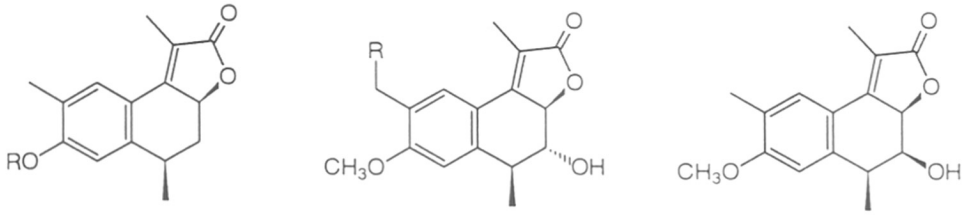
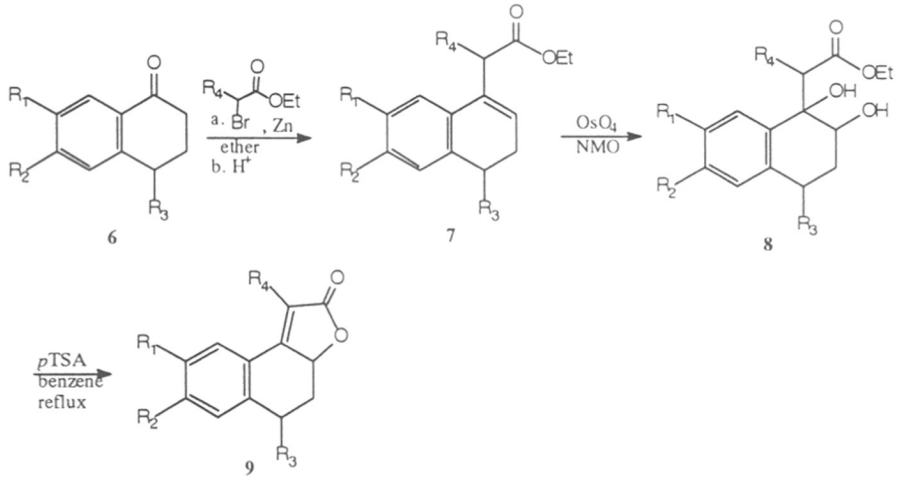


Fig. 1

In continuation of the previous work in the development of synthetic methodologies towards these unusual skeletons, an efficient entry to the same has been reported[13] from this laboratory (*Scheme 1*). Thus, Reformatsky reaction of the tetralones **6** with ethyl α-bromo esters yielded the β,γ-unsaturated esters **7** which were dihydroxylated using OsO_4 and NMO as secondary oxidant to give diols **8**. Further *p*TSA catalyzed reaction yielded the butenolides **9** in good yields.



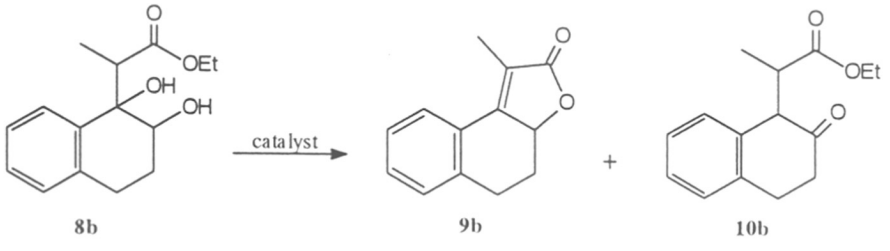
Scheme 1

Bearing in mind the potential and advantages of using solid acid catalysts, it was thought to attempt the acid catalyzed transformation of diol **8** to butenolide **9** as a new route for the synthesis of this functionality.

1.1.2 Results and Discussion:

The test substrate was the diol **8** which was prepared by the previously reported strategy of Reformatsky reaction on α-tetralone with ethyl α-bromopropionate followed by dihydroxylation using OsO_4/NMO.

Various solid catalysts were then tried for the conversion of diol **8b** to butenolide **9b**. After screening a few of the solid catalysts, it was found that most of the catalysts yielded the butenolide as a minor product alongwith an unknown compound which was subsequently characterized as the keto ester **10b** (*Scheme 2*).



8b **9b** **10b**

Scheme 2

Thus, refluxing the diol **8b** in toluene with 1:1 by weight of the acidic pentasil zeolite HZSM[14] (MFI) yielded the keto ester **10b** in 31%. Similarly, reaction with ZSM-11[15] (MEL), TS-2[16] (MFI) yielded 31% and 47% of **10b** respectively. Interestingly, when the reaction was carried out using silica gel in the absence of solvent, only **10b** was obtained in 50% yield (*Table 1*).

It was then thought to attempt the reaction in presence of ion exchange resins. However, the reaction in presence of the gel-type resin, Amberlite IR-120 did not result in any product and the starting material was obtained unchanged.

The macroreticular resin Amberlyst-15 has been greatly used for various organic transformations such as dethioacetalization,[17] deprotection of tosyl hydrazones,[18] preparation of tetrahydropyranyl[19] and enol ethers,[20] cleavage of acetals,[20,21] esterification,[22] etc. Being a weakly acidic resin with strongly bonded sulfonic groups, it was reasoned that this resin could catalyze the reaction. Upon refluxing the diol in toluene with Amberlyst-15, it was found that the butenolide **9b** was formed as the major product (82%) alongwith the keto ester in 12% yield.

Entry no.	Catalyst	Reaction time (hours)	Yield(%) **9b**	Yield(%) **10b**
1	ZSM-5	1	none	31
2	ZSM-11	3	20	31
3	TS-2	1	none	47
4	Silica gel(60-120)	3	none	50
5	Amberlite IR-120	12	none	none
6	Amberlyst-15	0.5	82	12

Table 1

The butenolide **9b** was characterized by comparison with the authentic sample (TLC, ^{1}H-NMR, IR and Mass Spectroscopy).

The keto ester **10b** showed a strong peak at 1730 cm^{-1} for the two carbonyls; the keto and ester carbonyl peaks could not be resolved even on FT-IR spectrophotometer. The ^{1}H-NMR spectrum showed presence of ethyl ester as a triplet at δ 1.50 and quartet at δ 4.15. The structure assigned was conclusively confirmed by ^{13}C-NMR, which showed the presence of carbonyl at 210 ppm in addition to the required number of CH_3, CH_2 and CH and the Mass spectrum which showed M^+ peak at 246.

Owing to the good yield of butenolide obtained in presence of Amberlyst-15, this was taken to be the catalyst of choice.

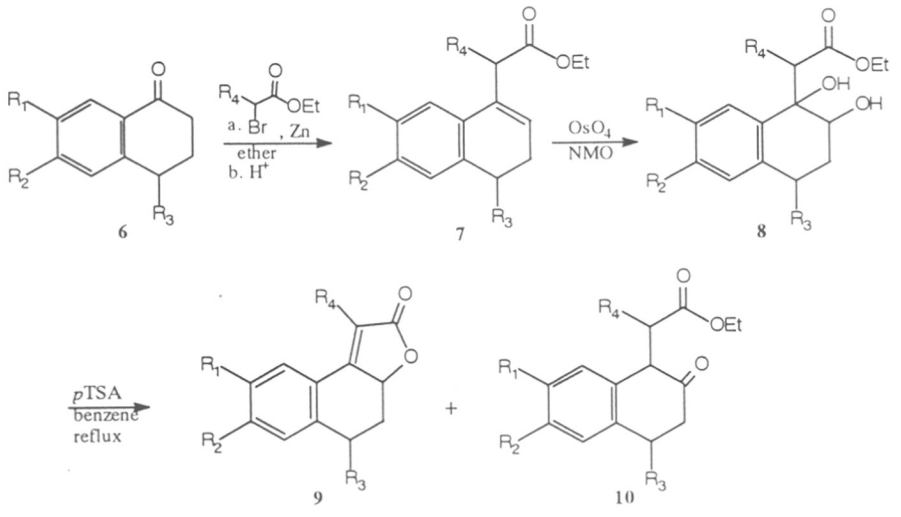
A variety of reaction conditions were attempted in order to standardize the reaction. Change of solvent from the non-polar toluene to the polar THF or the lower boiling hexane or benzene resulted in a decrease in the yield of butenolide with corresponding increase in formation of keto ester.

Interestingly, a marked difference in the ratio of the two products was also observed when the percentage of catalyst was changed. Thus, use of excess catalyst/substrate ratio (2:1 by weight) resulted in good yield of butenolide. However, when the reagent was used in catalytic amount, butenolide formation was suppressed and the keto ester was obtained as the major product.

These results led to the conclusion that the keto ester could be an intermediate step for the formation of butenolide. This was confirmed by subjecting the keto ester to the same cyclization conditions *viz.* 1:2 by weight of Amberlyst-15 in refluxing toluene, whereupon the butenolide was obtained in 50% yield with a minor amount of keto ester remaining unchanged.

In order to demonstrate the generality of this methodology for the conversion of diols to butenolides, the reaction was attempted on various substrates.

It was of interest to see the product distribution by incorporating bulky substituents α to the ester. Thus, following the same sequence of reactions on the tetralones namely α–tetralone (**6a**), 4,7-dimethyl-1-tetralone (**63**), 6-methoxy-4,7-dimethyl-1-tetralone (**6f**) and 1-suberone (**6g**) and incorporating bulkier substituents on the substrate by changing R^4=H, Me, Et, ^{i}Pr, the butenolides were prepared in good yield (*Table 2*).



Scheme 3

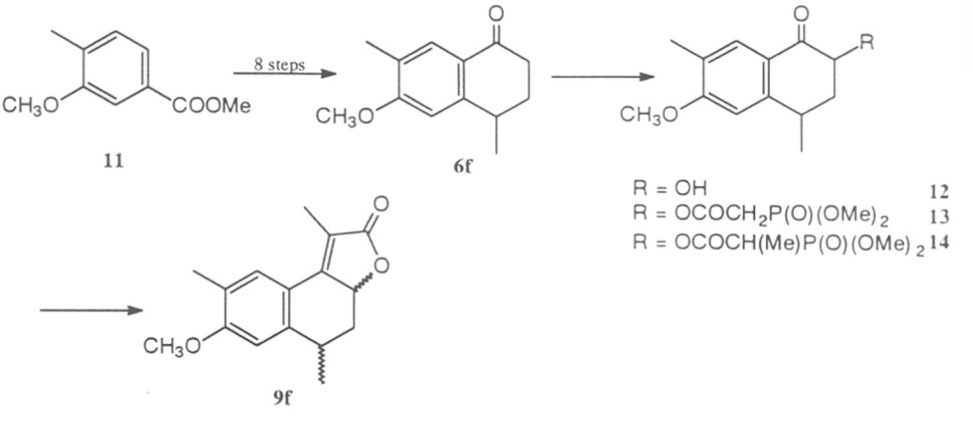
Entry	n	R^1	R^2	R^3	R^4	Yield(%) 7	Yield(%) 8	Yield(%) 9	Yield(%) 10
a	1	H	H	H	H	87	82	67	30
b	1	H	H	H	Me	90	83	82	12
c	1	H	H	H	Et	92	76	69	21
d	1	H	H	H	^{i}Pr	89	84	31	55
e	1	Me	H	Me	Me	80	78	90	7
f	1	Me	OMe	Me	Me	89	75	79	0
g	2	H	H	H	H	77	81	96	0

Table 2

Change in the bulk of the substituents on the butenolide ring resulted in a variation in the product ratio. This can be ascribed to the Thorpe-Ingold effect and the peri-interactions playing an important role in the cyclization reaction.

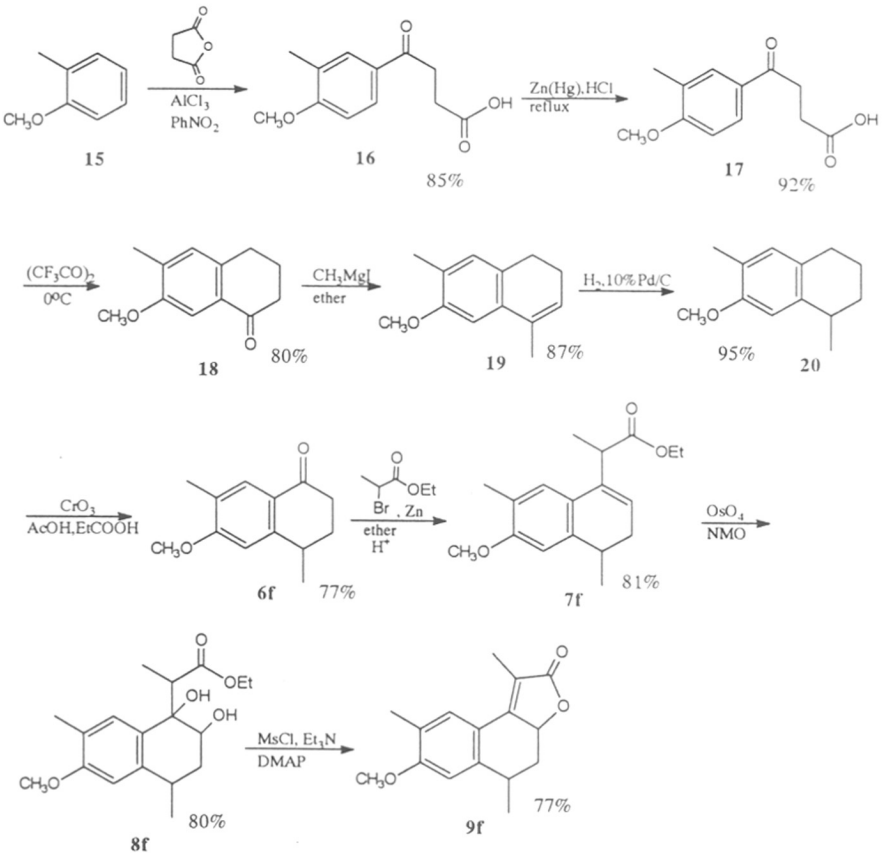
It was of interest to apply this methodology for the synthesis of heritonin (entry g) from the tetralone **6f**.

Irie *et al*[23] have reported a somewhat long route to the butenolide starting from 3-methoxy-4-methyl benzoate (**11**) which by a sequence of 8 steps was converted to the tetralone. α-hydroxylation followed by phosphonylation, alkylation and intramolecular Wittig-Horner reaction yielded heritonin**9f**. Aromatic demethylation using BCl_3 furnished heritol.(Scheme 4)



Scheme 4

A shorter and more efficient synthesis of heritol has been reported[21] from this laboratory. The tetralone was prepared in 6 high yielding steps from 2-methyl anisole (**15**). (Scheme 5) Reformatsky reaction with ethyl 2-bromopropionate, followed by dihydroxylation and *p*TSA catalyzed cyclization furnished the butenolide in just three steps in 50 % yield from the tetralone.



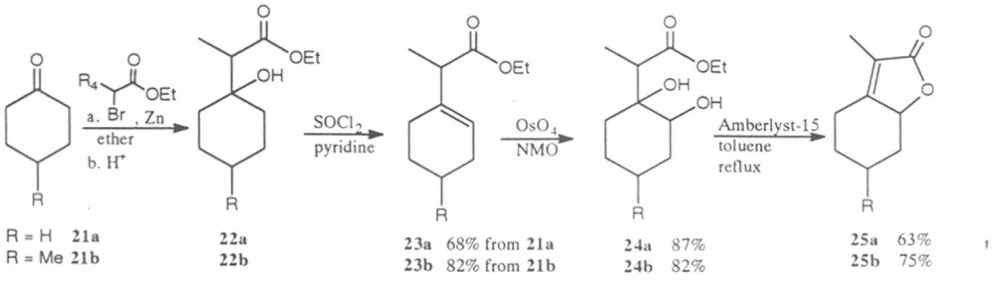
Scheme 5

The present methodology of Amberlyst-15 catalyzed reaction was similarly utilized for the cyclization of the diol **8f** under similar conditions as those developed in the present methodology. It was gratifying to note that the butenolide **9f** was formed in 79% yield under these conditions.

The conversion of (±)heritonin **9f** to heritol **1** being already reported, this constitutes a formal synthesis of **1**.

The methodology was also attempted on other cyclic ketones. The Reformatsky reaction of cyclohexanone **21a** with ethyl α-bromopropionate yielded the alcohol **22a** which

was dehydrated using $SOCl_2$/pyridine to yield the β,γ-unsaturated ester **23a** in 75% overall yield. Dihydroxylation using OsO_4/NMO, followed by work-up with sodium metabisulphite yielded the diol **24a**. **24a** was cyclized to butenolide in 63% yield using Amberlyst-15 in refluxing toluene (*Scheme 6*).

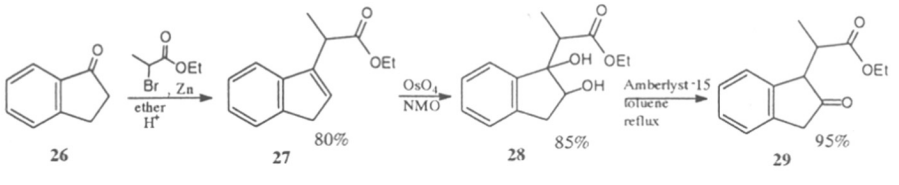


Scheme 6

Following a similar set of reactions on 4-methyl cyclohexanone (**21b**) yielded the diol **24b** which upon cyclization using the resin yielded the butenolide **25b** in 75% yield as an inseparable mixture of mint- and isomintlactones.

No keto ester was obtained during conversion of **24a** to **25a** or **24b** to **25b** and the corresponding butenolides were the sole products.

The conversion was also attempted on 5-membered cyclic ketones. 1-Indanone (**26**)was converted to the corresponding diol **28** *via* the β,γ-unsaturated ester **27**. Attempted cyclization using Amberlyst-15, however, yielded only the keto ester **29** in 95% yield. No butenolide was obtained even when the catalyst ratio to substrate was changed (*Scheme 7*).



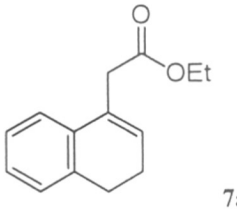
Scheme 7

1.1.4 Experimental:

General procedure for the synthesis of β,γ-unsaturated ester 7:

Ethyl bromo ester (12 mmol) was added slowly to a stirred solution of the tetralone (10 mmol) and activated zinc (30 mmol) in dry ether and a gentle reflux of ether was maintained by addition of a catalytic amount of iodine. The reaction was monitored by TLC and after completion (0.5 to 3 hrs), the reaction mixture was worked up with concentrated HCl (10 ml) and extracted with chloroform (3×10 ml). The organic extracts were washed successively with freshly prepared sodium thiosulfate solution (10 ml), water (10 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue chromatographed over silica gel using 5% ethyl acetate-pet.ether to furnish the β,γ-unsaturated ester **7** as a colourless oil.

Ethyl 2-(3,4-dihydronaphthalene)acetate (7a)



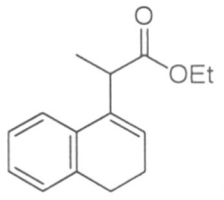
7a

Yield: 88%

IR (neat): 1740, 1630, 1610, 1500, 1460, 1440, 1400, 1360, 1340 cm^{-1}

^{1}H-NMR (80 MHz): δ 1.2 (t, J=7Hz, 3H); 2.3 (m, 2H); 2.8 (t, J=7Hz, 2H); 3.4 (d, J=2Hz, 2H); 4.1 (q, J=7Hz, 2H); 5.9 (t, J=4Hz, 1H); 7.1 (m, 4H).

Ethyl 2-(3,4-dihydronaphthalene)propionate (7b)



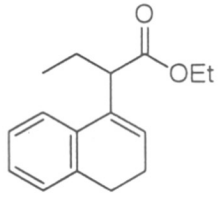
7b

Yield: 80%

IR (neat): 1730, 1610, 1470, 1430, 1350, 1300 cm^{-1}

^{1}**H-NMR** (200 MHz): 1.17 (t, J=7Hz, 3H); 1.42 (d, J=8Hz, 3H); 2.31 (m, 2H); 2.75 (t, J=7Hz, 2H); 3.75 (q, J=8Hz, 2H); 4.13 (q, J=7Hz, 2H); 6.06 (t, J=4Hz, 1H); 7.20 (m, 4H).

Ethyl 2-(3,4-dihydronaphthalene)butyrate (7c)



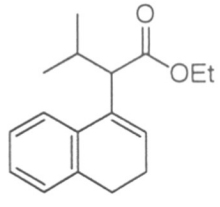
7c

Yield: 92%

IR (neat): 1740, 1640, 1620, 1500, 1480, 1460, 1440, 1400, 1380 cm^{-1}

^{1}**H-NMR** (80 MHz): δ 0.9 (t, J=8Hz, 3H); 1.2 (t, J=8Hz, 3H); 1.5-2.4 (m, 4H); 2.7 (t, J=8Hz, 2H); 3.5 (t, J=8Hz, 1H); 4.1 (q, J=8Hz, 2H); 6.06 (t, J=4Hz, 1H); 7.2 (m, 4H).

Ethyl 2-(3,4-dihydronaphthalene)-3-methylbutyrate (7d)



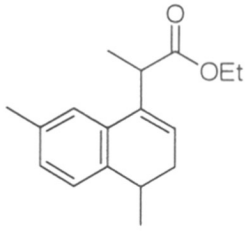
7d

Yield: 82%

IR (neat): 1736, 1653, 1600, 1568, 1540, 1376, 1330, 1310 cm^{-1}

^{1}H-NMR (80 MHz): δ 0.8 (d, J=7Hz, 3H); 1.0 (d, J=7Hz, 3H); 1.2 (t, J=7Hz, 3H); 2.3 (m, 3H); 2.7 (t, J=7Hz, 2H); 3.2 (d, J=10Hz, 1H); 4.1 (q, J=7Hz, 2H); 6.2 (t, J=5Hz, 1H); 7.0-7.5 (m, 4H).

Ethyl 2-(4,7-dimethyl-3,4-dihydronaphthalene)propionate (7e)



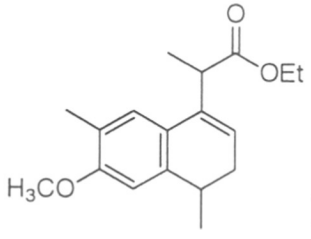
7e

Yield: 76%

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

^{1}H-NMR (80 MHz): δ 1.17 (d, J=7Hz, 3H); 1.17 (t, J=7Hz, 3H); 1.40 (d, J=7Hz, 3H); 2.15 (m, 2H); 2.30 (s, 3H); 2.70 (m, 1H); 3.60 (q, J=7Hz, 1H); 4.00 (q, J=7Hz, 2H); 5.80 (t, J=5Hz, 1H); 6.80-7.20 (m, 3H).

Ethyl 2-(6-methoxy-4,7-dimethyl-3,4-dihydronaphthalene)propionate (7f)



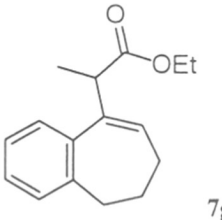
7f

Yield: 81%

IR (neat): 1740, 1330, 1310, 1280, 1250, 1200 cm^{-1}

^{1}H-NMR (90 MHz): δ 1.17 (d, J=7Hz, 3H); 1.20 (t, J=7Hz, 3H); 1.40 (d, J=7Hz, 3H); 2.20 (s, 3H); 2.40 (m, 2H); 2.60 (q, J=7Hz, 1H); 2.80 (m, 1H); 3.80 (s, 3H); 4.15 (q, J=7Hz, 2H); 5.80 (t, J=5Hz, 1H); 6.78 (s, 1H); 7.20 (s, 1H).

Ethyl 2(1-benzocyclohept-1-ene)propionate (7g)



7g

Yield: 78%

IR (neat): 1740, 1500, 1460, 1380, 1250, 1200 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.04 (t, J=6.5Hz, 3H); 1.28 (d, J=6.4Hz, 3H); 1.88 (m, 4H); 2.44 (t, J=6.5Hz, 2H); 3.56 (q, J=9.6Hz, 1H); 4.04 (q, J=6.5Hz, 2H); 6.12 (t, J=4.8Hz, 1H); 7.28 (m, 4H).

General procedure for synthesis of β,γ-unsaturated esters 13a, 13b and 22

Step-1: Synthesis of alcohol

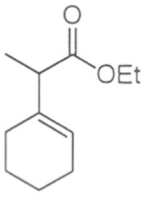
Reformatsky reaction of the ketone **11a**, **11b** or **20** (10 mmol) with ethyl 2-bromopropionate (12 mmol) and activated zinc (30 mmol) was performed in a way similar to that for the preparation of esters **7**. Similar work-up and purification furnished the crude alcohols which were subjected to further elimination (Step-2) without purification.

Step-2: Dehydration of alcohol:

To a stirred solution of the crude alcohol (1 mmol) and pyridine (2 mmol) in dry CH_2Cl_2 at 0°C, distilled thionyl chloride (1 mmol) was added dropwise and stirred for 3 hrs at room temperature. After the reaction was complete (TLC), it was quenched with aqueous $NaHCO_3$, extracted with ether (2×10 ml), dried over anhydrous Na_2SO_4 and concentrated

under reduced pressure. The residue was chromatographed over silica gel using 10% ethyl acetate-pet.ether as eluent to furnish the β,γ-unsaturated ester.

Ethyl 2-(1-cyclohexene)propionate (23a)



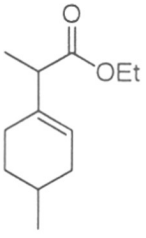
23a

Yield: 68%

IR (neat): 1740, 1460, 1390, 1340, 1250 cm^{-1}

^{1}H-NMR (80 Mhz): δ 1.2 (d, J=7Hz, 3H); 1.2 (J=7Hz, 3H); 1.4-1.9 (m, 8H); 3.0 (q, J=7Hz, 1H); 4.1 (q, J=7Hz, 2H); 5.5 (t, J=2Hz, 1H).

Ethyl 2(4-methyl-1-cyclohexene)propionate (23b)



23b

Yield: 82%

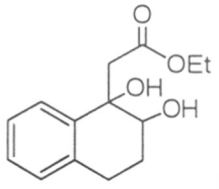
IR (neat): 1740, 1460, 1390, 1340, 1250 cm^{-1}

^{1}H-NMR (90 MHz): δ 0.93 (d, J=5Hz, 3H); 1.20 (d, J=7Hz, 3H); 1.29 (t, J=7Hz, 3H); 1.40-2.10 (m, 7H); 3.04 (q, J=7Hz, 1H); 4.15 (q, J=7Hz, 2H); 5.57 (m, 1H).

General procedure for the synthesis of β,γ-dihydroxy esters 8

A 20 ml test tube was charged with the β,γ-unsaturated ester **7** (4 mmol) and N-methylmorpholine N-oxide (NMO) (6 mmol) in acetonitrile-water mixture (9:1, 1ml) and a catalytic amount of osmium tetroxide in toluene was injected into it. The reaction was monitored by TLC. After stirring for 12 hrs at room temperature, solid sodium metabisulfite ($Na_2S_2O_5$) was added and the mixture stirred for further 0.5 hr. The reaction mixture was filtered and the solid washed with chloroform (30 ml). The combined organic layer was washed with 10% HCl (10 ml), dried over anhydrous Na_2SO_4 and the solvent evaporated in vacuum. The residue thus obtained was chromatographed over silica gel using 20% ethyl acetate-pet.ether to furnish the diol **8** as a viscous liquid.

Ethyl 2-(1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene)acetate (8a)



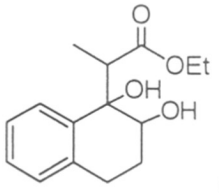
8a

Yield: 82%

IR (neat): 3450, 2950, 1745, 1620, 1500, 1470, 1460, 1380 cm^{-1}

^{1}H-NMR (90 MHz): δ 1.2 (t, J=7Hz, 3H); 2.0 (m, 2H); 2.8 (s, 3H); 2.9 (m, 2H); 4.1 (m, 3H); 7.1-7.6 (m, 4H).

Ethyl 2-(1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene)propionate (8b)



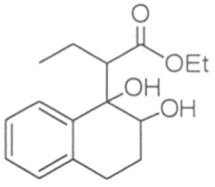
8b

Yield: 83%

IR (neat): 3450, 2950, 1750, 1610, 1500, 1460, 1440, 1380 cm^{-1}

^{1}H-NMR (90 MHz): δ 1.13 (d, J=7Hz, 3H); 1.20 (t, J=7Hz, 3H); 2.08 (m, 2H); 2.70 (m, 3H); 3.90 (dd, J=2,6Hz, 1H); 4.17 (q, J=7Hz, 2H); 7.13-7.48 (m, 4H).

Ethyl 2-(1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene)butyrate (8c)



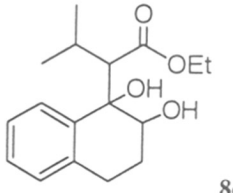
8c

Yield: 76%

IR (neat): 3500, 2900, 1740, 1725, 1500, 1470, 1460 cm^{-1}

^{1}H-NMR (90 MHz): δ 0.7 (t, J=8Hz, 3H); 1.2 (t, J=7Hz, 3H); 1.3-3.0 (m, 6H); 3.8 (t, J=4Hz, 1H); 4.1 (m, 3H); 6.9-7.6 (m, 4H).

Ethyl 2-(1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene)-3-methylpropionate (8d)



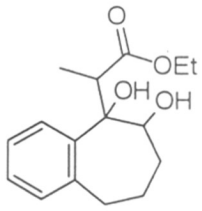
8d

Yield: 84%

IR (nujol): 3450, 2900, 1740, 1480, 1460, 1400, 1380 cm^{-1}

^{1}H-NMR (90 MHz): δ 0.60 (d, J=8Hz, 3H); 1.0 (d, J=8Hz, 3H); 1.2 (t, J=6Hz, 3H); 1.9 (m, 2H); 2.8 (m, 2H); 3.0 (d, J=5Hz, 1H); 4.2 (m, 3H); 7.0-7.6 (m, 4H).

Ethyl 2-(1,2-dihydroxybenzocycloheptane)propionate (8g)



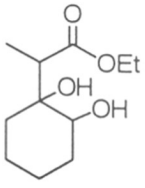
8g

Yield: 81%

IR (neat): 3450, 2900, 1750, 1500, 1460, 1400, 1360, 1340 cm^{-1}

^{1}H-NMR (90 MHz): δ 1.17 (t, J=7Hz, 3H); 1.40 (d, J=7Hz, 3H); 1.86-3.60 (m, 8H); 4.20 (q, J=7Hz, 2H); 7.20 (m, 4H).

Ethyl 2-(1,2-dihydroxy-1-cyclohexyl)propionate (24a)



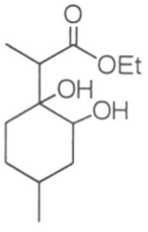
24a

Yield: 87%

IR (neat): 3450, 2950, 1745, 1470, 1460, 1420, 1390 cm^{-1}

^{1}H-NMR (90 MHz): δ 1.2 (d, J=4Hz, 3H); 1.2 (t, J=8Hz, 3H); 1.2-3.0 (m, 9H); 4.1 (m, 3H).

Ethyl 2-(1,2-dihydroxy-4-methyl-1-cyclohexyl)propionate (24b)



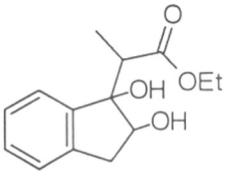
24b

Yield: 82%

IR (neat): 3450, 1745, 1653, 1560, 1540 cm^{-1}

^{1}H-NMR (90 MHz): δ 0.8 (d, J=4Hz, 3H); 1.2 (t, J=7Hz, 3H); 1.2 (d, J=7Hz, 3H); 1.0-1.6 (m, 7H), 2.8 (q, J=7Hz, 1H); 3.9 (m, 1H); 4.1 (q, J=7Hz, 2H).

Ethyl 2-(1,2-dihydroxy-1-indanyl)propionate (28)



28

Yield: 85%

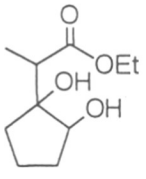
IR (neat): 3450, 1720, 1610, 1450, 1380, 1350, 1260 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.05, 1.25 (d, J=6Hz, 3H); 1.25 (q, J=6Hz, 3H); 2.70, 3.30 (q, J=6Hz, 1H); 2.85-3.25 (m, 2H); 4.10-4.75 (m, 3H); 7.15-7.45 (m, 4H).

^{13}C-NMR (50 MHz): 12.3(q); 13.3(q); 13.8(q); 13.9(q); 38.1(t); 38.4(t); 44.9(d); 46.3(d); 60.6(t) 72.1(d); 75.2(d); 81.8(s); 83.1(s); 123.6(d); 125.0(d); 125.1(d); 125.4(d); 126.4(d); 127.0(d); 128.8(d); 140.2(s); 140.4(s); 142.3(s); 142.8(s); 175.6(s); 176.4(s).

Mass (m/e): 232(34); 187(8); 158(4); 147(17); 131(100); 130(21); 119(25); 115(19); 103(44); 102(21); 91(44); 77(30).

Ethyl 2-(1,2-dihydroxy-1-cyclopentyl)propionate (33)



33

Yield: 85%

IR(neat): 3400, 1710, 1450, 1370, 1340, 1250 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.25 (d, J=7Hz, 3H); 1.30 (t, J=7Hz, 3H); 1.55-2.05 (m, 6H); 2.50, 2.75 (q, J=7Hz, 1H); 3.35 (bs, 1H); 3.45-4.10 (m, 1H); 4.20 (q, J=7Hz, 2H).

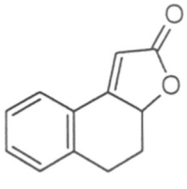
^{13}C-NMR (50 MHz): 12.6(q); 14.0(q); 18.8(t); 19.2(t); 24.0(t); 24.4(t); 31.8(t); 32.1(t); 33.9(t); 35.2(t); 35.4(t); 46.1(d); 47.0(d); 60.7(d); 61.9(t); 74.6(d); 76.3(d); 76.5(s); 77.1(s); 77.7(s); 79.3(s); 80.4(s); 176.2(s); 176.5(s).

Mass (m/e): 184(17); 157(6); 138(24); 118(23); 111(30); 110(24); 102(34); 100(28); 90(22); 83(40); 82(26); 74(35); 57(50); 57(100).

General procedure for the lactionization of diol 8:

A mixture of the diol **8** (100 mg) and Amberlyst-15 (wet)-ion exchange resin (200mg, 1:2 by weight) was refluxed in distilled toluene (10 ml) and the reaction monitored by TLC. After completion of the reaction (0.5-1 hr), the mixture was cooled and the used catalyst was filtered off and washed with ethyl acetate (10 ml). The organic washings were combined and the solvent evaporated under reduced pressure. The resulting residue was chromatographed over silica gel. The keto ester **10** was eluted out first with 5% ethyl acetate-pet.ether followed by the butenolide **9** with 20% ethyl acetate-pet.ether.

6,7-Dihydro-naptho(1,2b)furan-2(5H)one (9a)



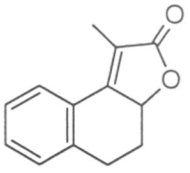
9a

Yield:67%

IR (nujol): 1760, 1640, 1620, 1480, 1440, 1360 cm^{-1}

^{1}H-NMR (90 MHz): δ 1.8 (m, 1H); 2.6 (m, 1H); 3.0 (dd, J=4,10Hz, 2H); 5.1 (ddd, J=2,6,12Hz, 1H); 6.1 (d, J=2Hz, 1H); 7.2-7.6 (m, 4H).

3-Methyl-6,7-dihydro-naptho-(1,2b)furan-2(5H)one (9b)



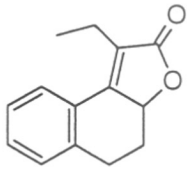
9b

Yield:82%

IR (nujol): 1760, 1670, 1620, 1500, 1400, 1360 cm^{-1}

^{1}H-NMR (90 MHz): δ 2.1 (d, J=2H, 3H); 2.6 (m, 2H); 3.1 (m, 2H); 5.0 (ddq, J=2,6,12Hz, 1H); 7.3-7.6 (m, 4H).

3-Ethyl-6,7-dihydro-naptho-(1,2b)furan-2(5H)one (9c)



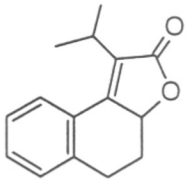
9c

Yield:69%

IR (nujol): 1750, 1660, 1620, 1470, 1460, 1440, 1380, 1360 cm^{-1}

^{1}H-NMR (80 MHz): δ 1.2 (t, J=5Hz, 3H); 1.7 (m, 2H); 2.6 (m, 2H); 3.1 (dd, J=2,6Hz, 2H); 5.0 (dd, J=2,8Hz, 1H); 7.5-7.8 (m, 4H).

3-Isopropyl-6,7-dihydro-naptho-(1,2b)furan-2(5H)one (9d)



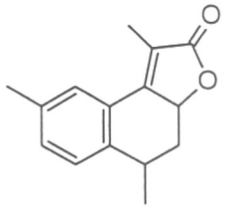
9d

Yield:31%

IR ($CHCl_3$): 1760, 1660, 1620, 1500, 1470, 1400, 1380, 1370, 1360 cm^{-1}

^{1}H-NMR (80 MHz): 1.32 (d, J=7Hz, 3H); 1.43 (d, J=7Hz, 3H); 1.75 (m, 1H); 2.65 (m, 1H); 3.20 (m, 2H); 3.27 (m, 1H); 4.88 (dd, J=5Hz, 13Hz, 1H); 7.34-7.64 (m, 4H).

3,7,10-Trimethyl-6,7-dihydro-naptho-(1,2b)furan-2(5H)one (9e)



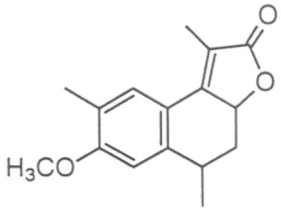
9e

Yield:90%

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

^{1}H-NMR (90 MHz)(mixture of diastereomers): δ 1.4 (d,J=4Hz,3H); 1.8 (m,1H); 2.1 (d,J=2Hz,3H); 2.6 (m,1H); 3.2 (m,1H); 4.9,5.6 (ddq,J=2,6,12Hz,1H); 7.1 (d,J=8Hz,1H); 7.2 (d,J=2Hz,1H); 7.5 (dd,J=2,8Hz,1H)

9-Methoxy-3,7,10-trimethyl-6,7-dihydronaptho-(1,2b)furan-2(5H)one (9f)



9f

Yield:79%

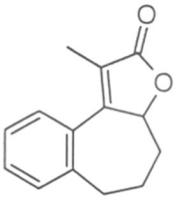
IR ($CHCl_3$): 1750, 1660, 1620, 1560, 1510, 1460, 1450, 1400 cm^{-1}

^{1}H-NMR (300 MHz)

Cis isomer: δ 1.45 (d, J=7.5Hz, 3H); 2.13 (d, J=1.7Hz, 3H); 2.24 (s, 3H); 2.63 (m, 1H); 3.13 (m,1H); 3.89 (s, 3H); 4.9 (ddq, J=1.7,5,12Hz, 1H); 6.85 (s, 1H); 7.41 (s,1H)

trans isomer: δ 1.43 (d, J=7.5Hz, 3H); 1.89 (m, 1H); 2.12 (d, J=1.7Hz, 3H); 2.24 (s, 3H); 2.40 (m, 1H); 3.30 (q, J=7.5Hz, 1H); 3.87 (s, 3H); 5.11 (ddq, J=1.6,4.2,12Hz, 1H); 6.69 (s, 1H); 7.40 (s, 1H).

3-Methylbenzosuberone-(1,2b)furan-2(5H)one (9g)



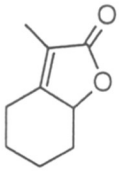
9g

Yield:96%

IR ($CHCl_3$): 1760, 1670, 1620, 1500, 1450, 1400, 1380 cm^{-1}

^{1}H-NMR (80 MHz): δ 1.76 (m, 2H); 1.96 (d, J=2.4Hz, 3H); 2.25-2.76 (m, 4H); 4.80 (m, 1H); 7.38 (m, 4H).

3-Methyl-5,6,7,7a-tetrahydro2(4H)benzofuranone (25a)



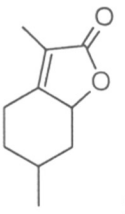
25a

Yield:63%

IR (neat): 1760, 1680, 1658, 1632, 1570, 1556, 1540, 1520 cm^{-1}

^{1}H-NMR (90 MHz): δ 1.8 (d, J=2Hz, 3H); 1.0-3.0 (m, 8H); 4.7 (m, 1H).

3,6-Dimethyl-5,6,7,7a-tetrahydro2(4H)benzofuranone (25b)



25b

Yield:75%

IR (neat): 1755, 1684, 1654, 1636, 1576, 1540, 1522, 1507, 1489 cm^{-1}

^{1}**H-NMR** (90 MHz): δ 0.95 (d, J=6Hz, 3H); 1.80 (d, J=2Hz, 3H); 2.30 (m, 7H); 4.60 (qdd, J=2,6,11Hz, 1H).

^{13}**C-NMR** (50 MHz) (mixture of diastereomers): 8.0(q); 17.2(q); 21.1(t); 21.8(t); 25.4(t); 27.3(t); 29.7(t); 31.6(t); 34.6(t); 39.6(d); 42.2(d); 79.8(d); 119.5(s); 162.3(s); 174.5(s).

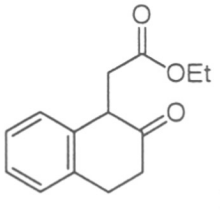
Mass (m/e): 166 (M^+, 100); 157(15); 137(62); 123(28); 109(58); 95(60); 81(80); 67(82); 55(85).

Analysis:

Calculated for $C_{10}H_{14}O_2$: C=72.20%; H=8.40%

Found : C=71.98%; H=8.12%

Ethyl 2-(3,4-dihydro-2(1H)-naphthalenone)acetate (10a)



10a

Yield: 30%

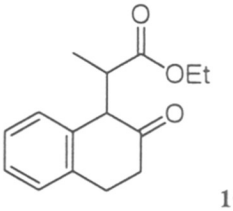
IR (neat): 1730, 1460, 1370, 1220 cm^{-1}

^{1}H-NMR (80 MHz): δ 1.30 (t, J=7Hz, 3H); 2.40-2.80 (m, 2H); 3.05 (d, J=6Hz, 2H); 3.10-3.20 (m, 2H); 3.80 (t, J=6Hz, 1H); 4.10 (q, J=7Hz, 2H); 7.10 (s, 4H).

^{13}C-NMR (50 MHz): δ 14.4(q); 28.4(t); 33.4(t); 37.5(t); 49.0(d); 61.0(t); 125.8(d); 127.2(d); 127.3(d); 128.0(d); 135.7(s); 137.6(s), 172.2(s), 210.1(s).

Mass (m/e): 233(M^+1,13); 232(M^+,25); 187(43); 186(100); 185(24); 184(19); 169(9); 158(66); 157(56); 155(17); 144(33); 130(44); 129(47); 128(39); 127(30); 117(26); 116(28); 115(56); 91(9).

Ethyl 2-(3,4-dihydro-2(1H)-naphthalenone)propionate (10b)



10b

Yield: 14%

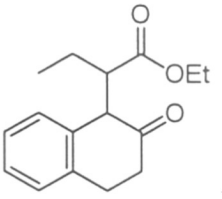
IR (neat): 1730, 1460, 1380, 1350, 1200 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of diastereo isomers): δ 1.10, 1.15 (d, J=7Hz, 3H); 1.15, 1.30 (t, J=7Hz, 2H); 2.55-2.65 (m, 2H); 2.95-3.30 (m, 4H); 3.75, 3.95 (d, J=7Hz, 1H); 4.15 (q, J=7Hz, 2H); 7.05-7.25 (m, 4H).

^{13}C-NMR (50 MHz) (mixture of diastereomers): 13.5(q), 14.2(q), 14.3(q); 28.0(t), 28.1(t), 38.2(t), 38.4(t), 41.5(d), 41.8(d), 55.8(d), 56.2(d), 60.8(t), 60.9(t), 127.0(d), 127.1(d), 127.3(d), 127.4(d), 128.2(d), 128.3(d), 128.4(d), 134.9(s), 135.8(s), 137.1(s), 137.4(s), 174.0(s), 174.8(s), 209.9(s), 210.6(s).

Mass (m/e): 246 (M^+, 1), 234(13), 218(37), 205(46), 189(36), 188(22), 177(18), 174(19), 161(26), 160(46), 159(100), 149(60), 146(40), 145(62), 144(45), 143(61), 131(97), 130(57), 117(38), 115(45), 103(58), 91(50), 77(61), 57(54).

Ethyl 2-(3,4-dihydro-2(1H-naphthalenone)butyrate (10c)



10c

Yield: 21%

IR (neat): 1720, 1460, 1220 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of diastereomers): δ 0.90, 0.95 (t, J=7Hz, 3H); 1.10, 130 (t, J=7Hz, 3H); 1.35-1.90 (m, 2H); 2.40-3.35 (m, 5H); 3.65, 3.75 (d, J=5.4Hz, 1H); 3.95 , 4.20 (q, J=7Hz, 2H); 7.05-7.35 (m, 4H).

^{13}C-NMR (50 MHz) (mixture of isomers): 12.3(q), 12.5(q), 14.2(q), 14.4(q), 23.2(t), 23.5(t), 27.9(t), 37.5(t), 37.7(t), 49.2(d), 56.6(d), 56.7(d), 60.6(t), 60.9(t), 127.0(d), 127.6(d), 128.2(d), 129.0(d), 129.4(d), 135.2(s), 135.5(s), 137.0(s), 137.3(s), 173.2(s), 174.2(s), 210.4(s).

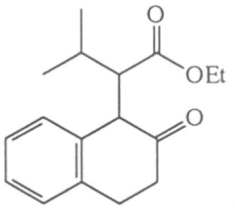
Mass (m/e): 260 (M^+, 3), 214(64), 212(85), 186(100), 185(32), 184(65), 183(93), 182(28), 171(26), 169(74), 167(43), 165(32), 157(29), 145(32), 143(34), 141(43), 129(60), 128(66), 127(49), 115(54).

Analysis:

Calculated for **$C_{16}H_{20}O_3$**: C=73.82%; H=7.74%

Found : C=73.33%; H=7.88%

Ethyl 2(3,4-dihydro-2(2H)naphthalenone)3-methylbutyrate (10d)



10d

Yield: 55%

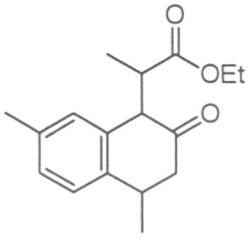
IR(neat): 1730, 1470, 1400, 1380 cm^{-1}

^{1}**HNMR**(200MHz)(mixture of isomers): δ 0.95(d, J=6Hz, 3H), 1.1(d, J=6Hz, 3H), 1.1(t,J=7Hz, 3H), 2.2-2.7(m,3H), 2.8-3.1(m,2H), 3.4(m,2H), 4.0(q,J=7Hz, 2H), 6.7-7.2(m,4H).

^{13}**CNMR**(50MHz)(mixture of isomers): 14.1(q); 18.1(q);19.3(q); 21.6(q); 27.5(t); 27.8(t); 28.0(d); 28.9(d); 36.8(t); 38.0(t); 52.8(d); 53.0(d); 55.1(d); 55.2(d); 60.1(t); 60.3(t); 126.7(d); 126.9(d); 127.2(d); 127.4(d); 128.0(d); 128.2(d); 128.6(d); 129.4(d); 135.4(s); 135.6(s); 136.9(s); 137.1(s); 171.5(s); 173.3(s); 210.0(s); 210.5(s).

Mass(m/e): 228(69); 200(95); 185(100); 184(54); 167(47); 157(40); 141(36); 129(78); 128(85); 127(65); 115(91); 91(31); 77(36).

Ethyl 2-(4,7-dimethyl-3,4-dihydro-2(1H)-naphthalenone)propionate (10e)



10e

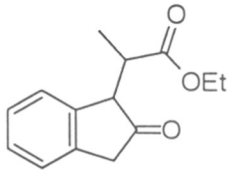
Yield: 7%

IR (neat): 1720, 1450, 1380, 1200 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of isomers): 1.00-1.45 (m, 9H); 2.35 (s, 3H); 2.25-3.60 (m, 4H); 3.80(d); 3.95 (d, J=6Hz, 1H); 4.05-4.30 (m, 3H); 6.95-7.15 (m, 3H).

Mass(m/e): 274(M^+, 1); 226(74); 211(18); 198(41); 183(100); 165(18); 153(24); 152(26); 141(21); 128(27); 115(30); 91(16).

Ethyl 2-(1,3-dihydro-2(2H)-indenone)propionate (29)



29

Yield: 95%

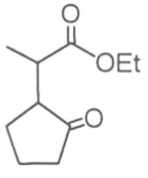
IR (neat): 1730, 1600(w), 1480, 1460, 1380, 1350, 1200 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of isomers): δ 1.00-1.35 (m, 6H); 3.25 (q, 1H); 3.55 (s, 2H); 3.75, 3.90 (d, 1H); 4.00(q); 4.15 (q, 2H); 7.15-7.35 (m, 4H).

^{13}C-NMR (50 MHz) (mixture of isomers): 13.0(q); 13.7(q); 13.9(q); 14.0(q), 41.3(q); 41.32(d); 43.1(t); 43.4(t); 54.4(d); 55.3(d); 60.4(t); 60.7(t); 124.3(d); 124.8(d), 127.3(d); 127.6(d), 137.5(s); 137.7(s); 139.2(s); 139.8(s); 172.9(s), 174.2(s), 214.9(s), 215.6(s).

Mass (m/e): 233 (M^+ + 1, 11); 232 (M^+, 81); 187(29), 186(68); 184(17); 159(32); 158(100); 156(16); 131(40); 130(44); 129(26); 128(20); 115(17); 103(5); 97(6).

Ethyl 2-(2-cyclopentanone)propionate (34)



34

Yield: 53%

IR (neat): 1730, 1460, 1380, 1340, 1200, 1160 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of isomers): δ 1.10, 1.25 (d, J=7Hz, 3H); 1.25, 1.30 (t, J=7Hz, 3H); 1.55-2.45 (m, 6H); 2.50-2.65 (m, 1H); 2.75-3.10 (m, 1H); 4.05-4.25 (q, J=7Hz, 2H).

^{13}C-NMR (50 MHz) (mixture of isomers): 13.5(q); 13.9(q), 14.9(q); 20.2(t); 20.4(t); 25.6(t); 25.7(t); 37.7(t); 37.8(t); 38.6(d); 38.7(d); 51.2(d); 51.3(d); 60.1(t); 173.7(s); 175.0(s); 218(s); 218(s).

Mass (m/e): 184 (M^+, 20); 156(8); 141(8); 139(35); 138(16); 128(9); 113(14); 111(57); 110(36); 105(29); 102(20); 95(8); 87(14); 84(36); 83(59); 82(20); 81(15); 77(15); 74(19); 69(23); 67(20); 55(100).

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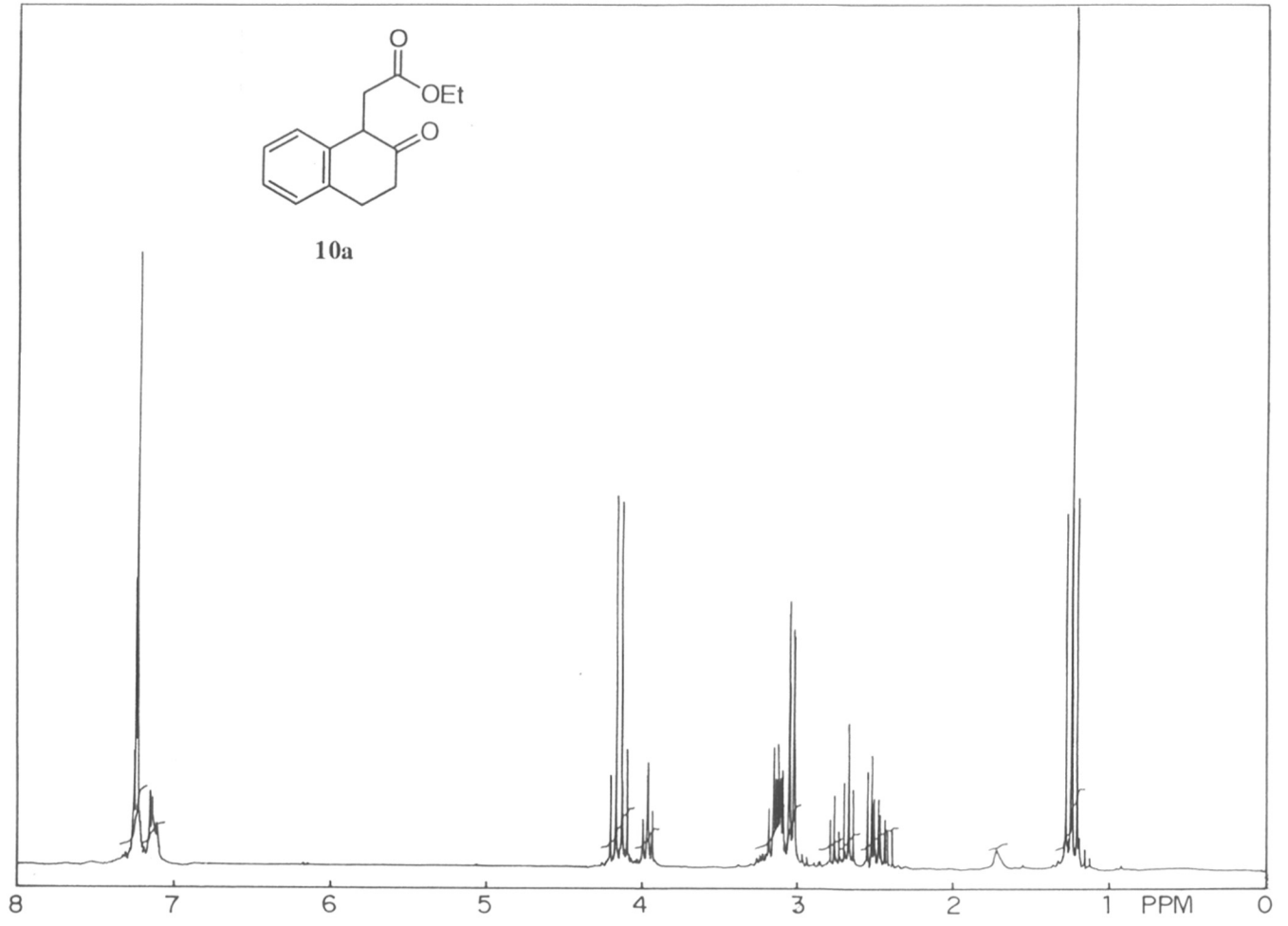
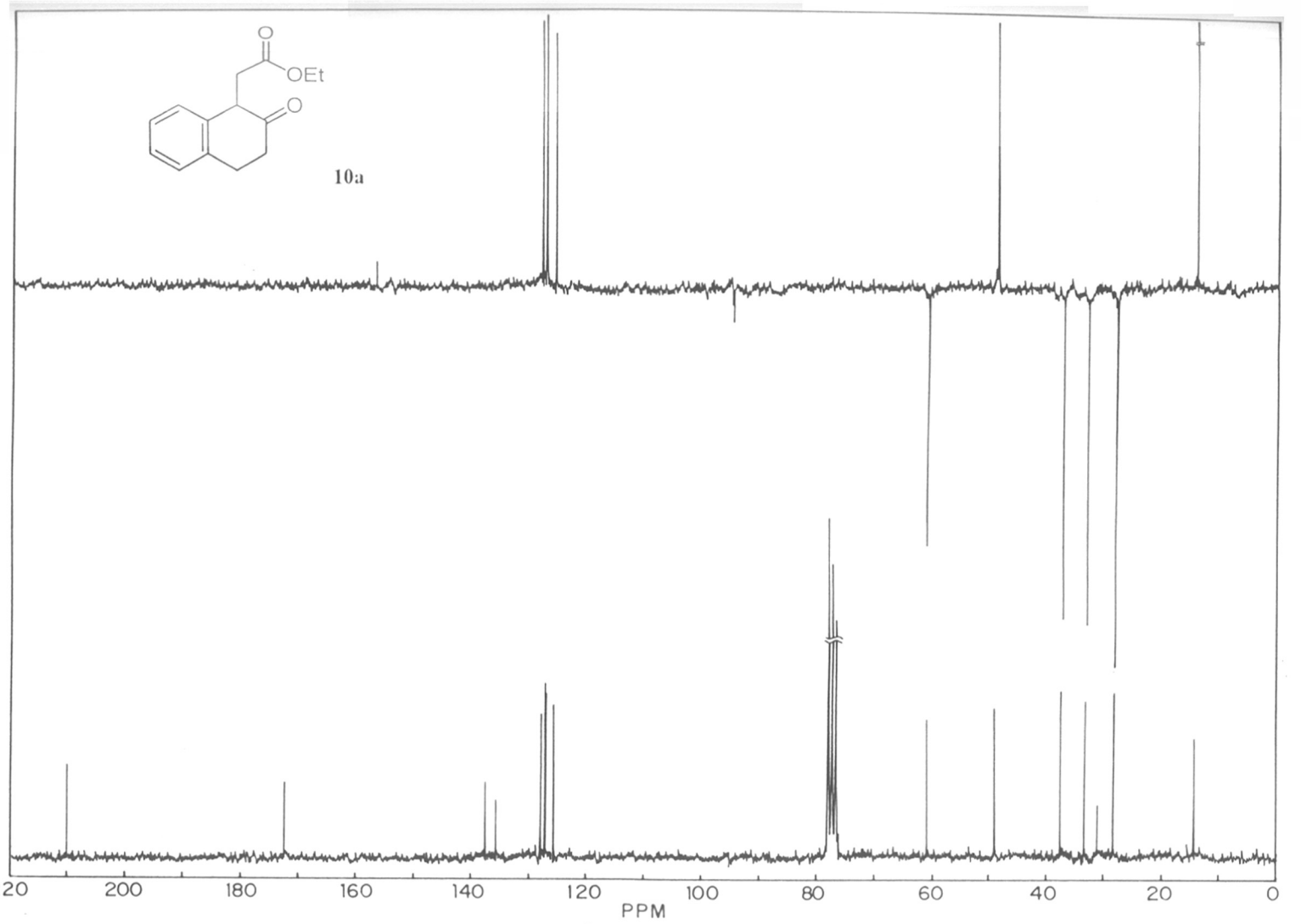


10a

Spectrum no. 1



Spectrum no. 2

SECTION 2

Oxidative Conversion of β,γ–Unsaturated Acids to Butenolides

1.2.0 Introduction

The use of radical cations as well as radical anions as reactive intermediates in the formation of carbon-carbon bonds forms an important domain of organic chemistry. Initial progress in this field was slow, mostly because the reactions could not be controlled and gave a number of products. However, recent findings have proved that these reactions can be 'disciplined' by proper use of conditions *viz.* proper choice of substrate, solvent, temperature, etc.

There are three general ways of generating radical cations.[1,2] The classical methods of radical cation generation include electrochemical, photochemical and chemical oxidation. Radiolytic method for generation of radical cations has also been reported;[3] however this method is not of general use synthetically. The intramolecular anodic coupling of silyl enol ethers has been reported [5]by Moeller *et al* by electrochemical generation of radical cations.

Photo-induced electron transfer (PET) is a mild and versatile method for radical cation generation. Gassman and co-workers have investigated[5] the photo-induced cyclization of γ,δ-unsaturated carboxylic acids to γ-lactones. Radical cation-type cyclization of isoprenoid polyene acetates has been described recently by Demuth.[6] Arene radical cations generated by PET from electron rich aromatic rings were used for the synthesis of O- and N-heterocycles by Pandey.[7] A recent publication[8] illustrates the use of PET generated arene radical cations for the intramolecular addition of enol silyl ethers. Pandey has also developed[9] a sequential electron-proton-electron transfer route for the *in situ* generation of iminium cations by excited ^{1}DCN*. Radical cation Diels-Alder reaction and sigmatropic reactions have also been reported.[10]

The principal chemical oxidants for radical cation generation include Lewis acids like $SbCl_5$,[11] bromine, peroxide anions *e.g.* peroxydisulfate anion,[12], metal ions or oxides, aminium radical cations *e.g.* triarylaminium cation[13] and certain zeolites.

The metal ions used for radical cation generation are most often transition metals (Group IB-VIIIB) and the rare earth metals-lanthanides and actinides. On account of the extremely complex chemical effects of electrochemically and photochemically induced radical cation generation, metal redox reactions are emerging as an useful alternative to classical radical cation chemistry. The redox reactions mediated by Mn^{3+}, Co^{3+}, Cu^{2+}, Fe^{3+}, Ag^{2+}, Pb^{4+}, Ce^{4+}, Mn^{4+}, V^{5+}, Ag^{+}, Cu^{+}, Fe^{2+} and Cr^{2+} have been the most widely explored.

Transition metal promoted radical cations are generated by an oxidative process in which the metal acts as an oxidant and the reaction involves generation of the radical cation by an electron transfer from the precursor to the metal complex.

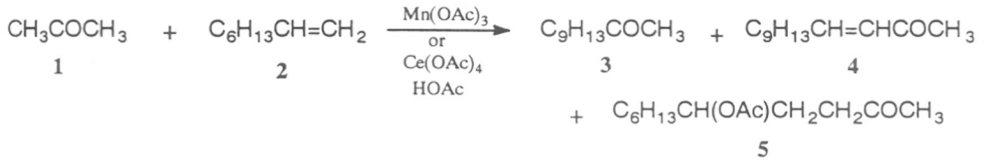
The use of organometallic reagents for the generation of carbon-centered radicals was pioneered by Kharasch,[14,15] Kochi,[16] and Minisci[17] after which there has been an explosion of literature reports on this subject. The numerous literature has been very well reviewed by Giese[18,19], Curran[20], Iqbal[21], Snider[22] and others.[23-25]

Among the oxidants used to generate cation radical, $Mn(OAc)_3$ has received the most attention, as is evinced by the large number of reports[26-29] on its use in various synthetic methodologies. However, this reagent is not always reliable and has been reported[29] to give highly erratic results. Also, it is not a very stable reagent and has to be freshly prepared prior to use from $KMnO_4$ and the commercially available $Mn(OAc)_2$. Recently, there have been also a few reports on the *in situ* generation and use of $Mn(OAc)_3$ in radical catalyzed cyclization reactions.

Hence, it is of interest to explore and develop other one-electron oxidants as better and more useful catalysts for radical cation reactions.

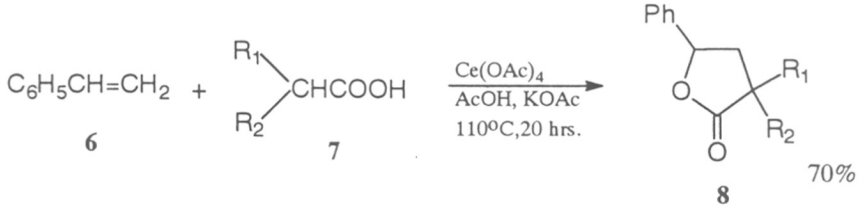
In this respect, Ce(IV), a member of the lanthanide[30] series, has been in the forefront. Ce(IV) salts with OAc^-, SO_4^{2-}, NO_3^-, *etc.* have proved to be more useful and reliable as compared to $Mn(OAc)_3$.

Pioneering work on Ce(IV) salts as radical generators was carried out by Heiba and Dessau[31] in the 1970s, who reported the addition of acetonyl radical to olefin using Cerium acetate or Manganese acetate in refluxing acetic acid (*Scheme 1*).



Scheme 1

They also reported[32,33] the synthesis of γ-butyrolactone by radical addition of carboxylate to styrene using $Ce(OAc)_4$ (*Scheme 2*).



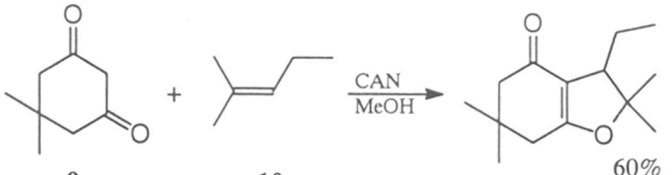
Scheme 2

Later on, Kurz *et al.* reported[34,35] the aromatic acetonylation promoted by Mn(III) or Ce(IV) salts.

CAN has been successfully applied as an oxidant[36] for a variety of synthetic transformations. It is regularly used for the oxidation of hydroquinone[37] and oxidative demethylation of hydroquinone mono/dimethyl ethers to quinone.[38] Aromatic side chains can

be oxidized cleanly to the corresponding aldehyde or ketone using CAN.[39,40] Oxidation of alcohols,[41] oxidative cleavage of alkyl/silyl ethers,[42] and vicinal diols,[43] oxidative decarboxylation,[44] nitration,[45,46] and chemoselective oxidation of sulfide to sulfoxide[47] are some other general uses of CAN. CAN has also been used for protection[48] and regeneration[49] of carbonyl compounds. Deprotection of certain benzyl ethers,[50] benzoate esters[51] and N-protected functionalities[52] has also been reported. The oxidative functionalization of olefins using CAN has been studied.[53]The CAN catalysed radical mediated opening of epoxides to give β-nitrato alcohols and β-halohydrins has been recently reported.[54-57]

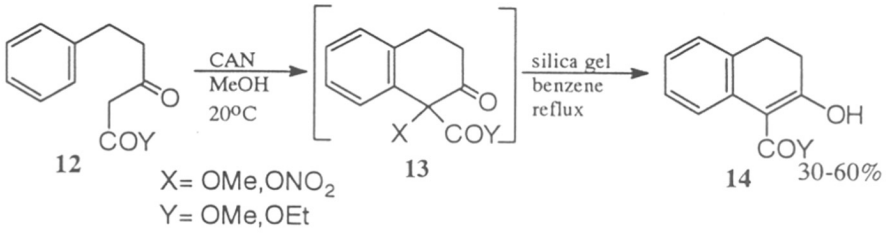
One of the more recent and synthetically important reactions of CAN is the generation of radicals from carbonyl compounds. CAN promoted cross-coupling of silyl enol ethers to give dicarbonyl compounds,[58,59] addition of carbonyl compounds to enol ethers,[60] enol acetate[61,62] and dienes[63] to give 1,4-dicarbonyl compounds has been widely used. The oxidative addition of 1,3-dicarbonyl compounds to unactivated[64] and activated olefins[65,66] has been the focus of recent interest. Nair *et al*[67,68] have very recently reported the synthesis of dihydrofuran by addition of 1,3-diketones to cyclic and acyclic alkenes. (*Scheme 3*).



9 **10** **11**

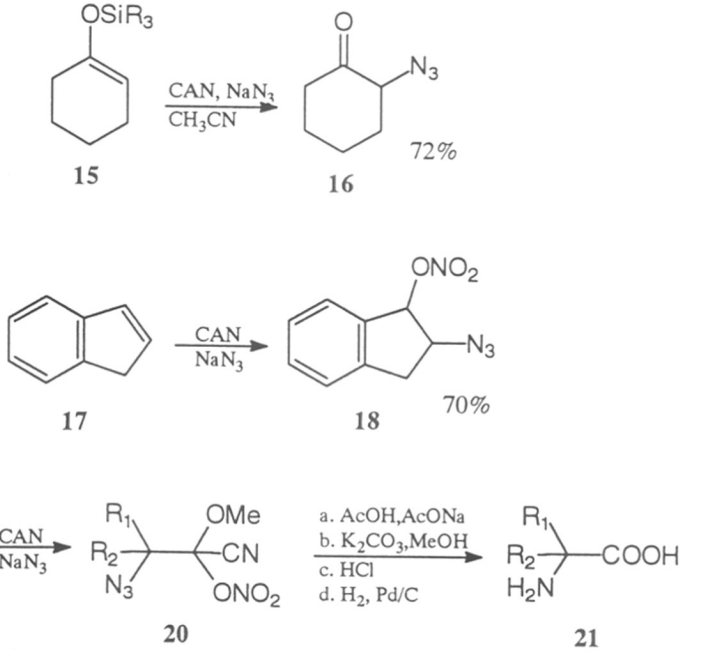
Scheme 3

An intramolecular version of oxidative radical cyclization of 1,3-dicarbonyls on aromatic ring was efficiently used by Citterio *et al.*[69] to yield dihydronaphthalenes (*Scheme 4*).



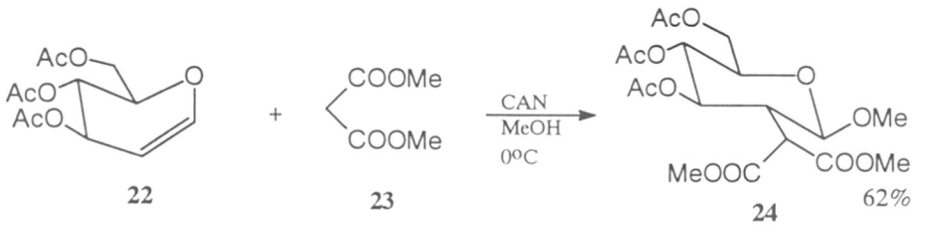
Scheme 4

The CAN-catalyzed addition of sodium azide to silyl enol ethers,[70] activated and unactivated olefins[71-73] has also been studied in great detail. The introduction of the nitrogen functionality is of great use, especially in the further conversion to α-amino acids (*Scheme 5*)



Scheme 5

Linker *et al*[74] recently reported the radical reaction of dimethylmalonate catalyzed by CAN as an efficient entry to 2-C-analogues of D-glucose (*Scheme 6*).



22 23 24

Scheme 6

Thus, it has been demonstrated unambiguously that ceric ammonium nitrate is a superior single electron oxidant for various synthetic transformations using radical and radical cation chemistry. It has been well documented in literature and continues to be of increasing interest to the organic chemists by virtue of its stability, reactivity and commercial availability.

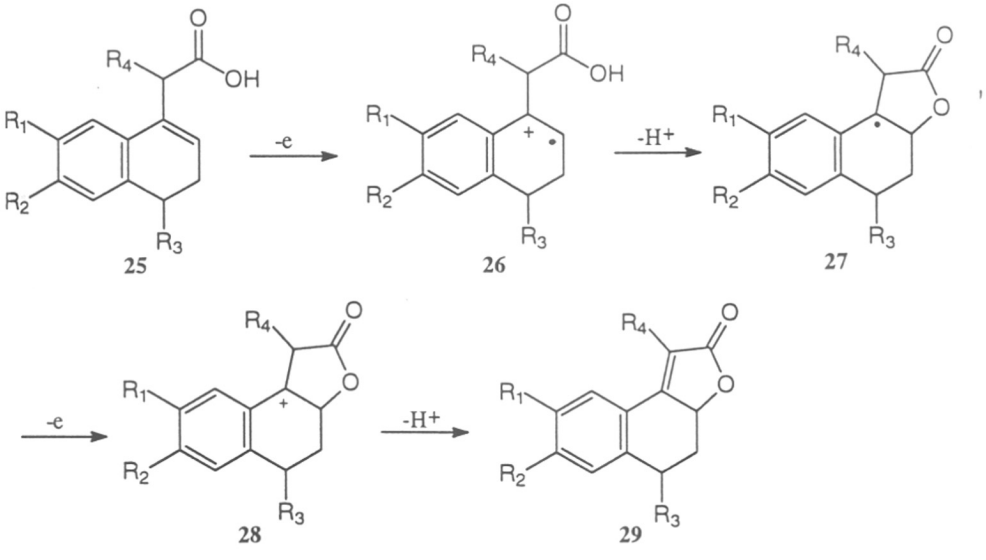
1.2.1 Present Work

The methodology described in the previous section for the conversion of diols to butenolides, though efficient for the cadinane butenolides and other monoterpene butenolides requires the use of highly expensive and toxic osmium tetroxide. Although required in catalytic amounts, its prohibitive price, toxicity and lack of ready availability may limit its applicability as the method of choice.

Accordingly, it was decided to develop a new and general methodology for the synthesis of butenolides which would avoid the use of this expensive and highly toxic reagent.

Advances in the field of transition metal catalyzed radical cation synthesis have generated a lot of interest in this area and a large number of reports have been published. A few reports on radical cation cyclizations to yield cyclic and polycyclic compounds have also appeared.

It was hence thought worthwhile to apply radical cation chemistry for the synthesis of butenolides. It was reasoned that it should be possible to directly convert the β,γ-unsaturated acid/ester to butenolide if the cation radical can be selectively and effectively generated. Intramolecular trapping of the cation radical with the carboxylic functionality would generate the butyrolactone which on further oxidation and loss of proton would generate the butenolide (*Scheme 7*).



Scheme 7

In view of the propensity of ceric ammonium nitrate (CAN) to act as a single electron oxidant, this reagent was chosen for the oxidative cyclization of β,γ-unsaturated acids/esters to butenolides.

1.2.2 Results and Discussion

The starting β,γ-unsaturated esters **30** were readily prepared by previously reported[75] Reformatsky reaction of different tetralones with ethyl bromo esters in ether at room temperature.

When β,γ-unsaturated esters were treated with CAN under a variety of conditions, no trace of butenolides could be detected. The failure of ester to act as internal nucleophile led to the exploration of carboxylic acid/carboxylate anion as the nucleophile.

The β,γ-unsaturated acids were prepared in high yields by saponification of the corresponding esters. Thus, refluxing the ester **30a** with 3 equivalent of potassium hydroxide in MeOH-H_2O system for 3 hrs led to complete disappearance of the esters (tlc). Neutralization with dilute sulfuric acid, followed by usual work-up procedure gave crude acid which was recrystallized from pet.ether-ethyl acetate solvent system yielding the crystalline acid **25a**. IR spectrum of **25a** showed broad absorption peak at 2900 cm^{-1} indicating the presence of acidic hydroxyl group. Absence of ester peaks i.e. triplet at δ 1.28 for 2H and a quartet at δ 4.10 for 3H in the ^{1}HNMR spectrum confirmed the formation of product.

With the starting material in hand, attention was diverted towards the oxidative cyclization to butenolide.

Oxidative conversion of β,γ-unsaturated acids to butenolides:

Mixture of β,γ-unsaturated acid **25a** with 2 equivalents of $NaHCO_3$ was treated with the, ceric ammonium nitrate (CAN) as single electron oxidant in acetonitrile at 0°C under N_2 atmosphere. A fast decolourization of the reaction mixture indicated the reactivity of CAN.

After completion of reaction, as confirmed by tlc, the reaction mixture was filtered and subjected to usual work-up. Chromatography over silica gel using pet.ether-ethyl acetate as eluent yielded the butenolide **29a** in 67% yield.

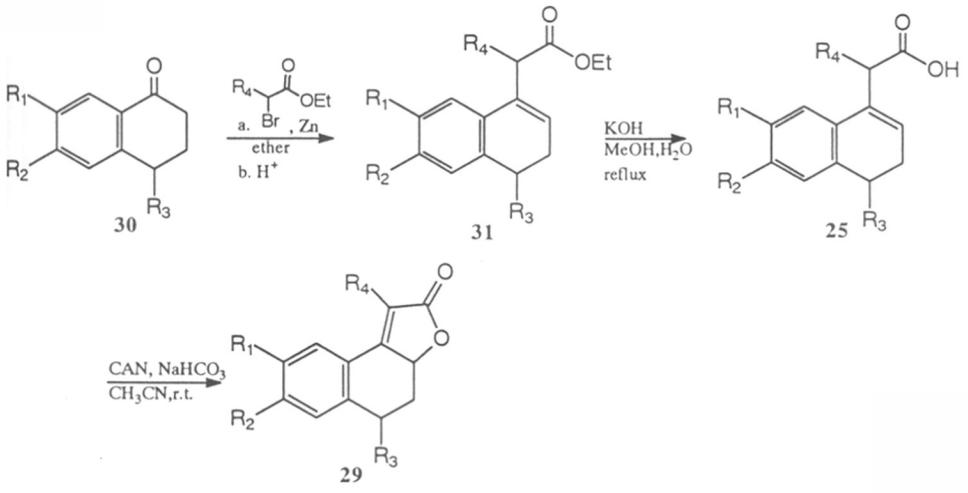
The product (butenolide) was characterized by usual techniques. IR spectrum displayed the characteristic carbonyl function at 1760 cm^{-1} for the butenolide moiety with the disappearance of the peaks at 2900 and 1700 cm^{-1}. In PMR, the aromatic protons showed small downfield shift as compared to the diol due to the deshielding imposed by the butenolide moiety. The PMR spectrum also showed the presence of multiplet at δ 5.1 integrating for 1H and a doublet at δ 6.1 integrating for 1H indicating that the product to be α,β-unsaturated butyrolactone.

The ^{13}C-NMR also showed disappearance of signal at 39 ppm for $C\underline{H}_2COOH$ and the presence of a new signal at 108 ppm corresponding to the unsubstituted olefinic carbon atom.

Thus, the structure of the product formed was unambiguously confirmed as the α,β-unsaturated butyrolactone **29a**.

The use of less than 2 equivalents of CAN or $NaHCO_3$ led to incomplete conversion of β,γ-unsaturated acid to butenolide and unreacted starting material was obtained even after allowing the reaction to continue for 12 hrs. This suggests the mechanism to involve an overall two single electron transfer followed by proton loss.

In order to delineate the generality and efficacy of this methodology, bulky groups were incorporated α to the carboxylic acid. Accordingly, various substrates of general formula **25** were treated with CAN/$NaHCO_3$ to yield the corresponding butenolides **29** (*Table 1*).



Scheme 8

Entry	R^1	R^2	R^3	R^4	Yield(%) 31	Yield(%) 25	Yield(%) 29
a	H	H	H	H	87	82	67
b	H	H	H	Me	90	86	72
c	H	H	H	Et	92	84	87
d	H	H	H	^{i}Pr	89	89	92
e	Me	H	Me	Me	80	78	74
f	OMe	Me	H	Me	90	81	70
g	Me	OMe	Me	Me	85	89	36

Table 1

A noteworthy feature of this transformation is that on progressing from R_4=H to ^{i}Pr (entries **a-d**), there is a steady increase in bulk of R_4 accompanied by a corresponding steady increase in the yield of butenolides.

This trend though surprising from the point of view of peri interactions having a detrimental effect on the efficiency of butenolide formation may be attributed to the 'Thorpe Ingold effect'. The presence of bulky groups α to the acid leads to a decrease in the distance between reacting functionalities *viz.* the double bond and carboxylic acid which enables the cyclization to proceed with high efficiency.

This observation is in stark contrast to the poor yields obtained in the intramolecular Wittig-Horner reaction ascribed to the peri interactions in Irie's[76] synthesis of Heritol.

The efficient conversion of β,γ-unsaturated acids to the butenolides is in accordance with the concept of 'atom economy' which has been of recent interest and is practised and described by Trost.[77,78]

The synthesis of heritol and heritonin has been previously reported from the β,γ-unsaturated ester **30g**.(Section 1). It was hence proposed to apply this methodology for the synthesis of these naturally occuring compounds.

Accordingly the ester **30g** was hydrolysed to the acid **25g** using KOH/MeOH-H_2O in 80% yield. Treatment of the acid **25g** with CAN (2.2equiv.) and $NaHCO_3$ (2.2equiv.) in CH_3CN as solvent furnished the corresponding butenolide i.e. heritonin **29g** in 36% yield. As the conversion of heritonin to heritol has been previously reported, this contitutes a formal synthesis of heritol in an overall yield of 27% starting from the tetralone

1.2.3 Conclusions

Thus an efficient and high yielding methodology for the synthesis of butenolides has been achieved. The starting materials *viz* β,γ-unsaturated acids are easily accessible and the reaction proceeds at ambient temperature.

The sole drawback is the utilization of more than stoichiometric amounts of CAN which is a fairly expensive reagent. However, regeneration of Ce(IV) in the reaction mixture using secondary oxidants like oxygen or sodium/potassium bromate has been reported[78] in literature. So the amount of CAN required can be greatly decreased by applying secondary oxidants.

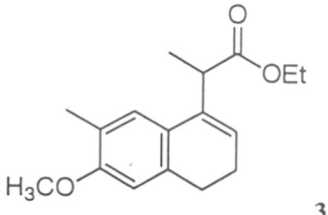
This essentially simple methodology should hence find wide application in the synthesis of a variety of butenolides.

1.2.4 Experimental

Synthesis of β,γ-unsaturated ester 30

The same procedure for the synthesis of **30** was followed as that in *Section I.*

Ethyl 2-(7-methoxy-6-methyl-3,4-dihydronaphthalene)propionate (30f)



30f

Yield: 90%

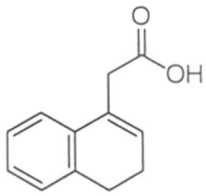
IR (neat): 1742, 1620, 1580, 1510, 1480, 1410, 1380 cm^{-1}

^{1}H-NMR (90 Mhz): δ 1.2 (t, J=7Hz, 3H); 1.4 (d, J=8Hz, 3H); 2.1 (s, 3H); 2.3 (m, 2H); 2.5 (m, 3H); 3.8 (s, 3H); 4.1 (q, J=7Hz, 2H); 5.9 (t, J=4Hz, 1H); 6.8 (s, 1H); 6.9 (s, 1H).

General Procedure for the hydrolysis of esters:

To a solution of the ester **30** (10mmol) in methanol-water mixture (3:1, 20ml) was added solid KOH (30mmol) and the mixture refluxed on a water bath for 3 hrs. When the reaction was complete, the solvent was evaporated under reduced pressure and the residue treated with sodium bicarbonate (10 ml). The aqueous layer was washed with ethyl acetate (5 ml), then acidified with sulfuric acid and extracted with chloroform (2×10 ml). The organic extracts were dried over anhydrous sodium sulfate, and evaporated under reduced pressure to yield crude acid **25** which was chromatographed over silica gel with 20% ethyl acetate-pet.ether or recrystallized from hot pet.ether-ethyl acetate as white needles.

2-(3,4-dihydronaphthalene)acetic acid (25a)



25a

Yield: 82%

Melting piont: 104-105°C

IR (nujol): 2900, 1690, 1590, 1450, 1410, 1330, 1250, 1210.

^{1}H-NMR (200 MHz): δ 2.35 (m, 2H); 2.80 (t, J=8Hz, 2H); 3.50 (s, 2H); 6.05 (t, 1H); 7.10-7.20 (m, 4H).

^{13}C-NMR (50 MHz): 23.4(t), 28.0(t), 39.0(t), 122.8(d), 126.7(d), 127.3(d), 127.9(d), 129.8(s), 129.9(d), 134.1(s), 136.4(s), 178.7(s).

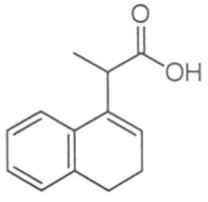
Mass (m/e): 188 (M^+, 15), 143(15), 142(19), 141(29), 138(5), 129(52), 128(100), 127(14), 116(5), 115(36), 102(5), 91(7), 88(7), 77(7), 66(11).

Analysis:

Calculated for **$C_{12}H_{12}O_2$** : C=76.57%; H=6.92%

Found : C=76.81%; H=6.61%

2-(3,4-dihydronaphthalene)propionic acid (25b)



25b

Yield: 86%

Melting point: 110-112°C

IR (nujol): 2900, 1700, 1450, 1420, 1380, 1340, 1250, 1100, 1090 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.50 (d, J=7Hz, 3H); 2.35 (m, 2H); 2.80 (t, J=8Hz, 2H); 3.80 (q, J=7Hz, 1H); 6.10 (t, 1H); 7.10-7.35 (m, 4H).

^{13}C-NMR (50 MHz): 17.0(q); 23.3(t); 28.2(t); 41.5(d); 122.7(d); 126.6(d); 126.7(d); 127.2(d); 128.0(d); 134.1(s); 135.7(s); 136.8(s); 181.8(s).

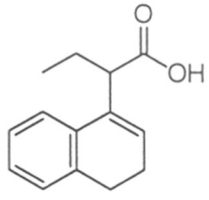
Mass (m/e): 202 (M^+, 27); 157(14); 156(10); 155(8); 142(18); 141(28); 130(16); 129(100); 127(17); 115(27); 91(6); 77(7); 74(11).

Analysis :

Calculated for $C_{13}H_{14}O_2$: C=77.20%; H=6.98%

Found : C=77.11%; H=7.00%

2-(3,4-dihydronaphthalene)butyric acid (25c)



25c

Yield: 84%

Melting point: 101-102°C

IR (nujol): 2900, 1690, 1450, 1420, 1380, 1340, 1330, 1280, 1230, 1100 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.00 (t, J=7Hz, 3H); 1.70 (m, 1H); 2.00 (m, 1H); 2.35 (dt, J=7,5Hz, 2H); 2.55 (t, J=7Hz, 2H); 3.55 (t, J=7Hz, 1H); 6.15 (t, J=5Hz, 1H); 7.1-7.6 (m, 4H).

^{13}C-NMR (50 MHz): 12.5(q); 23.3(t); 25.1(t); 28.3(t); 40.0(d); 122.7(d); 126.7(d); 127.2(d); 127.3(d); 127.9(d); 134.4(s); 134.5(s); 136.9(s); 181.3(s).

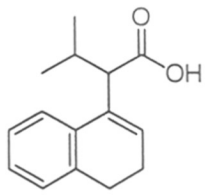
Mass (m/e): 216 (M^+, 21); 187(8); 171(6); 170(13); 169(15); 155(8); 142(12); 142(10); 141(41); 130(23); 129(100); 128(66); 127(20); 115(37); 91(14); 89(7); 88(25); 77(15); 73(13); 70(12); 63(11); 55(10).

Analysis:

Calculated for $C_{14}H_{16}O_2$: C=77.70%; H=7.40%

Found : C=77.44%; H=7.21%

2-(3,4-dihydronaphthalene)-3-methyl butyric acid (25d)



25d

Yield: 89%

IR (nujol): 2900, 1690, 1450, 1420, 1380, 1310, 1300, 1230 cm^{-1}

^{1}H-NMR (200 MHz): δ 0.90 (d, J=6.5Hz, 3H); 1.10 (d, J=6.5Hz, 3H); 1.00-1.20 (m, 1H); 2.30 (m, 2H); 2.75 (t, J=6.5Hz, 2H); 3.30 (d, J=11Hz, 1H); 6.25 (t, J=4Hz, 1H); 7.10-7.55 (m, 4H).

^{13}C-NMR (50 MHz): 20.2(q); 21.6(q); 23.4(t); 28.4(t); 31.3(d); 54.3(d); 122.9(d); 125.7(d); 126.7(d); 127.1(d); 127.8(d); 134.2(s); 135.1(s); 136.7(s); 180.5(s).

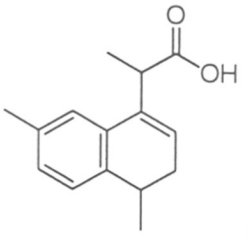
Mass (m/e): 230(M^+, 8); 202(4); 187(30); 186(10); 170(9); 169(30); 155(9); 145(14); 144(50); 143(33); 142(18); 141(59); 131(13); 130(17); 129(82); 128(54); 127(20); 121(29); 119(84); 117(100); 115(48); 102(7); 91(17); 84(14); 82(55); 77(10); 59(16).

Analysis:

Calculated for $C_{15}H_{18}O_2$: C=78.23%; H=7.88%

Found : C=78.39%; H=8.01%

2-(4,7-dimethyl-3,4-dihydronaphthalene)propionic acid (25e)



25e

Yield: 89%

Melting point : 139-140°C

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

^{1}H-NMR (200 MHz): δ 1.25 (d, J=7Hz, 3H); 1.50 (d, J=7Hz, 3H); 2.15 (m, 1H); 2.35 (s, 3H); 2.50 (m, 1H); 2.85 (q, J=7Hz, 1H); 3.80 (q, J=7Hz, 1H); 5.95 (t, J=4Hz, 1H); 7.00-7.05 (m, 2H); 7.20-7.30 (d, 1H).

^{13}C-NMR (50 MHz, DMSO-d_6): 17.0(q); 20.6(q); 21.3(q); 30.9(t); 32.3(d); 41.5(d); 122.6(d); 123.1(d); 127.1(d); 127.7(d); 131.0(s); 136.0(s); 136.7(s); 141.9(s); 176.4(s).

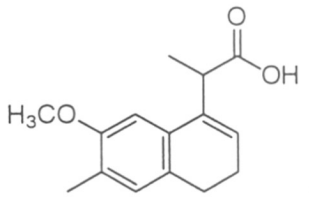
Mass (m/e): 230(M^+, 24); 185(10); 169(48); 159(38); 158(20); 157(100); 156(36); 155(24); 154(14); 153(17); 152(13); 145(15); 143(32); 142(45); 141(37); 129(23); 128(34); 127(11); 115(30); 105(8); 91(16); 84(9); 77(19); 65(10); 63(10); 57(14); 56(18); 55(13).

Analysis:

Calculated for $C_{15}H_{18}O_2$: C=78.23%; H=7.88%

Found : C=78.00%; H=7.21%

2-(6-methyl-7-methoxy-3,4-dihydronaphthalene)propionic acid (25f)



25f

Yield: 81%

Melting point: 104-105°C°°

IR (nujol): 2900, 1680, 1590, 1560, 1500, 1450, 1370, 1300, 1250, 1220. cm^{-1}

^{1}H-NMR (200 MHz): δ 1.50 (d, J=7.5Hz, 3H); 2.20 (s, 3H); 2.30 (m, 2H); 2.50 (t, J=7.5Hz, 2H); 3.65 (q, J=7.5Hz, 1H); 3.70 (s, 3H); 6.05 (t, J=7Hz, 1H); 6.85 (s, 1H); 6.95 (s, 1H).

^{13}C-NMR (50 MHz): 15.9(q); 16.7(q); 23.7(t); 27.2(t); 42.0(d); 55.6(q); 105.6(d); 125.2(s); 126.0(d); 128.5(s); 130.3(d); 132.5(s); 135.6(s); 156.5(s); 182.1(s).

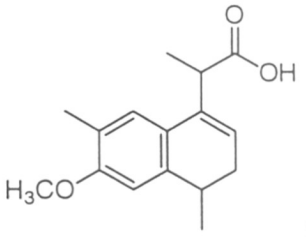
Mass (m/e): 247(M^{+}+1, 12); 246(M^{+}, 75); 201(23); 200(10); 199(16); 186(14); 185(20); 175(21); 174(15); 173(100); 172(34); 171(14); 159(10); 158(47); 157(11); 153(10); 152(10); 143(14); 142(15); 141(32); 129(28); 128(37); 127(14); 115(40); 91(13); 69(9); 65(9); 63(9); 60(7); 57(10); 55(15).

Analysis:

Calculated for $C_{15}H_{18}O_3$: C=73.15%; H=7.37%

Found : C=73.27%; H=7.49%

2-(4,7-dimethyl-6-methoxy-3,4-dihydronaphthalene)propionic acid (25g)



25g

Yield: 89%

Melting point: 113-114°C

IR ($CHCl_3$): 2900, 1690, 1600, 1550, 1500, 1450, 1250, 1210 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of isomers): δ 1.20 (d, J=7Hz, 3H); 1.5 (d, J=7Hz, 3H); 2.10-2.20(m); 2.40-2.50 (m, 2H); 2.20 (s, 3H); 2.75-2.90 (m, 1H); 3.75 (q, J=7Hz, 1H); 3.85 (s, 3H); 5.80-5.90 (m, 1H); 6.70 (s, 1H); 7.10 (s, 1H).

^{13}C-NMR (75MHz) (mixture of isomers): 16.1(q); 16.6(q); 17.0(q); 20.0(q); 20.2(q); 30.9(t); 31.0(t); 32.4(d); 32.6(d); 41.1(d); 41.3(d); 55.2(q); 55.4(q); 108.8(d); 109.0(d); 121.7(d); 121.8(d); 123.8(s); 125.3(d); 140.9(s); 156.9(s); 181.6(s).

Mass (m/e): 261(M^++1, 14); 260(M^+, 79); 258(12); 216(24); 215(20); 214(10); 213(19); 201(20); 200(19); 199(82); 188(19); 187(100); 186(47); 185(23); 184(15); 173(17); 172(59); 171(21); 170(10); 169(9); 157(14); 156(10); 155(14); 153(12); 152(10); 143(14); 142(14); 141(24); 129(25); 128(27); 127(15); 115(19); 91(10); 77(8).

Analysis:

Calculated for $\mathbf{C_{16}H_{20}O_3}$: C=73.82%; H=7.74%

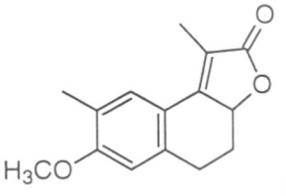
Found : C=73.32%; H=7.57%

General Procedure for the lactonization of acids:

To a mixture of ceric ammonium nitrate (CAN) (0.2mmol) and activated sodium bicarbonate (0.2mmol) in 20 ml of dry acetonitrile was added the acid (0.1mmol) dropwise at room temperature under N_2 atmosphere over a period of 5 minutes. After completion of the reaction, as monitored by TLC, the reaction mixture was filtered through celite and the residue was washed with ethyl acetate (20 ml). The solvent was evaporated under reduced pressure and the residue chromatographed over silica gel using 20% ethyl acetate-pet.ether as eluent to furnish the corresponding butenolide **29**.

The spectral (IR, ^{1}H-NMR) properties of the butenolides were consistent with the assigned structures and matched perfectly with those in the literature reports and those obtained by resin catalyzed cyclization of diols (Section I).

10-methoxy-3,9-dimethyl-6,7-dihydronaphtho(1,2b)furan-2(5)-one (29f)



29f

IR ($CHCl_3$): 1755, 1660, 1620, 1520, 1480, 1420, 1340 cm^{-1}

^{1}H-NMR (90 MHz): δ 1.2 (d, J=2Hz, 3H); 2.2 (s, 3H); 2.5 (m, 2H); 2.9 (dd, J=4,8Hz, 2H); 3.8 (s, 3H); 4.9 (ddq, J=2,4,12Hz, 1H); 7.0 (s, 2H).

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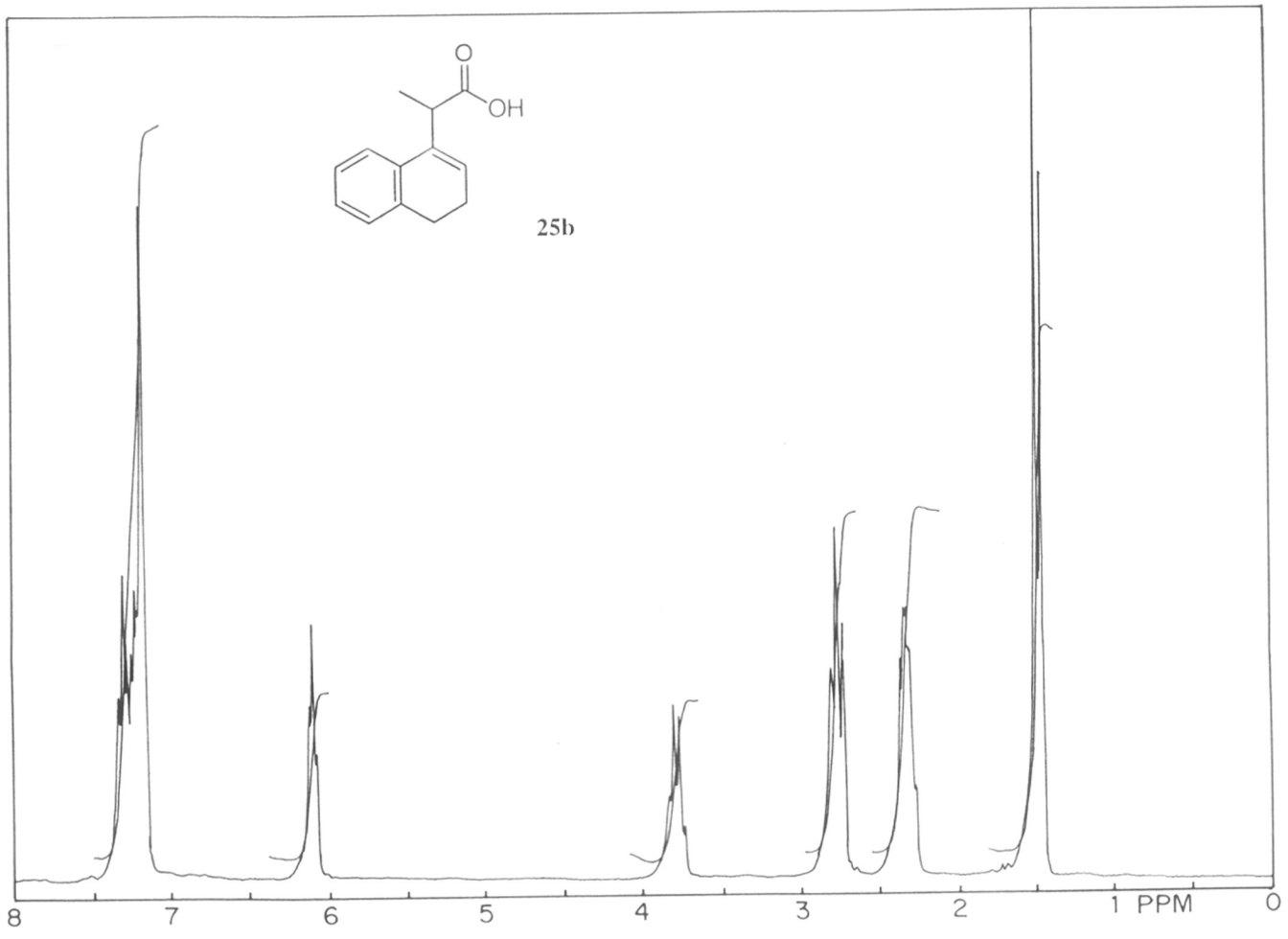
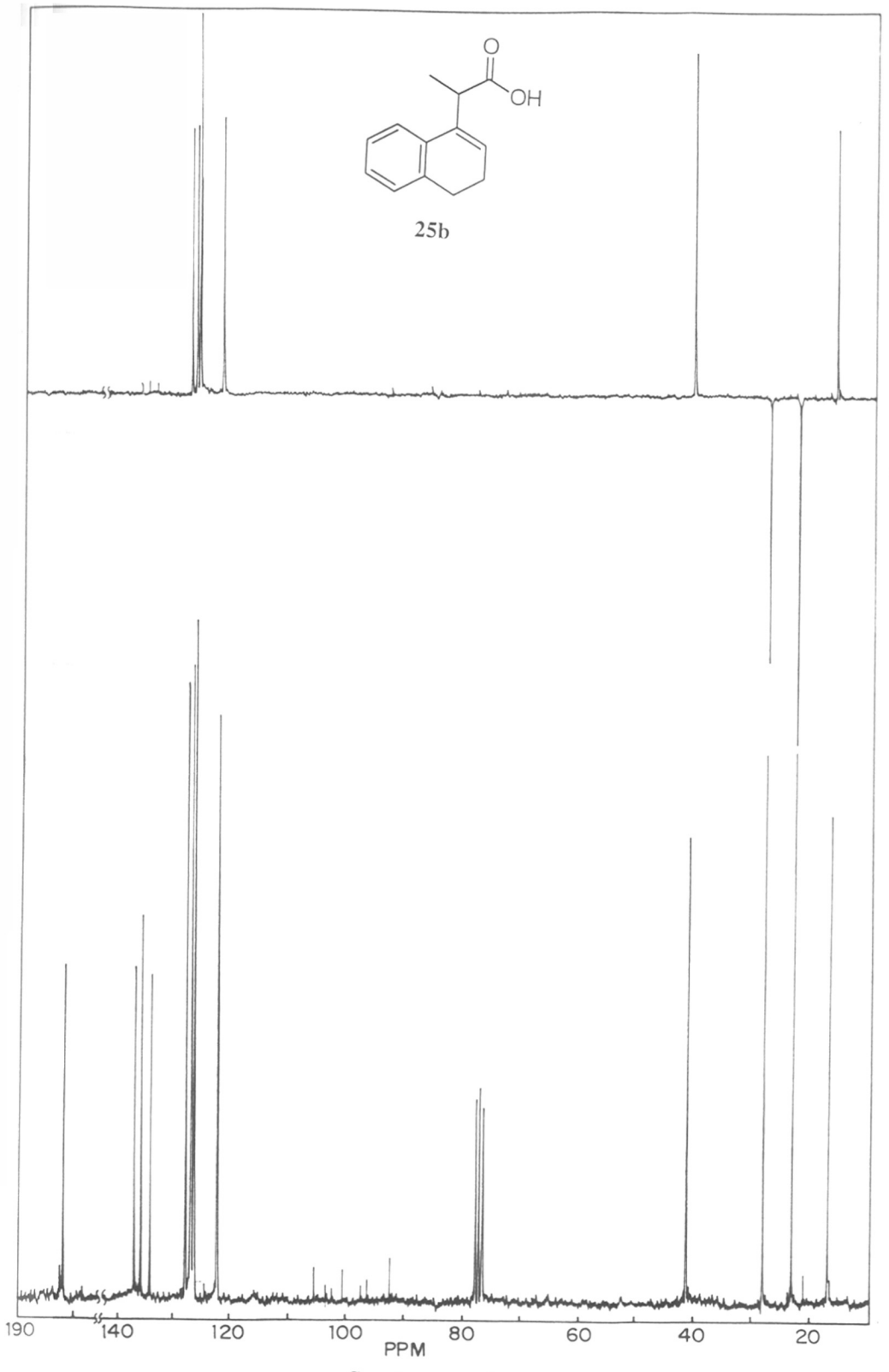


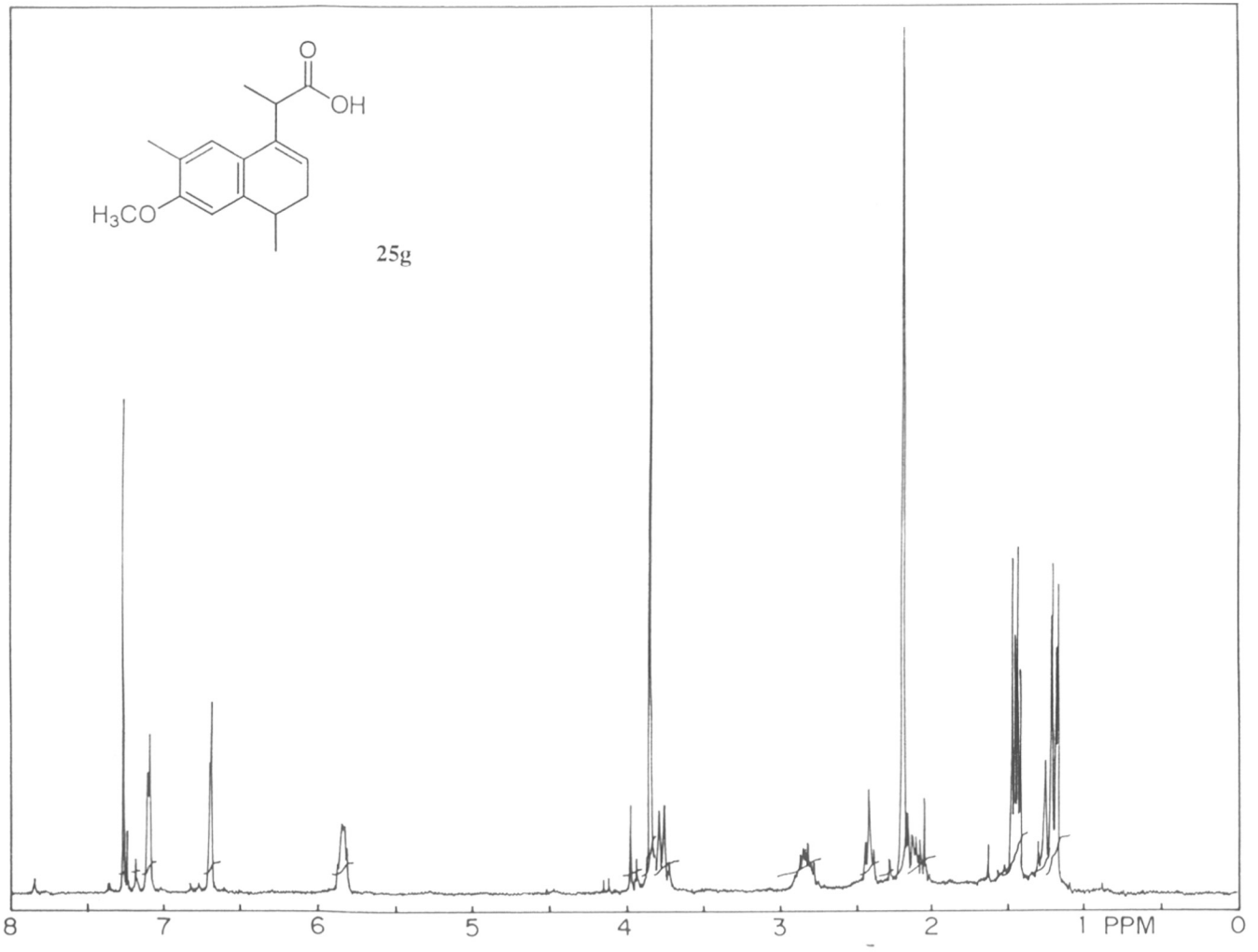
25b

Spectrum no. 1



25b

Spectrum no. 2



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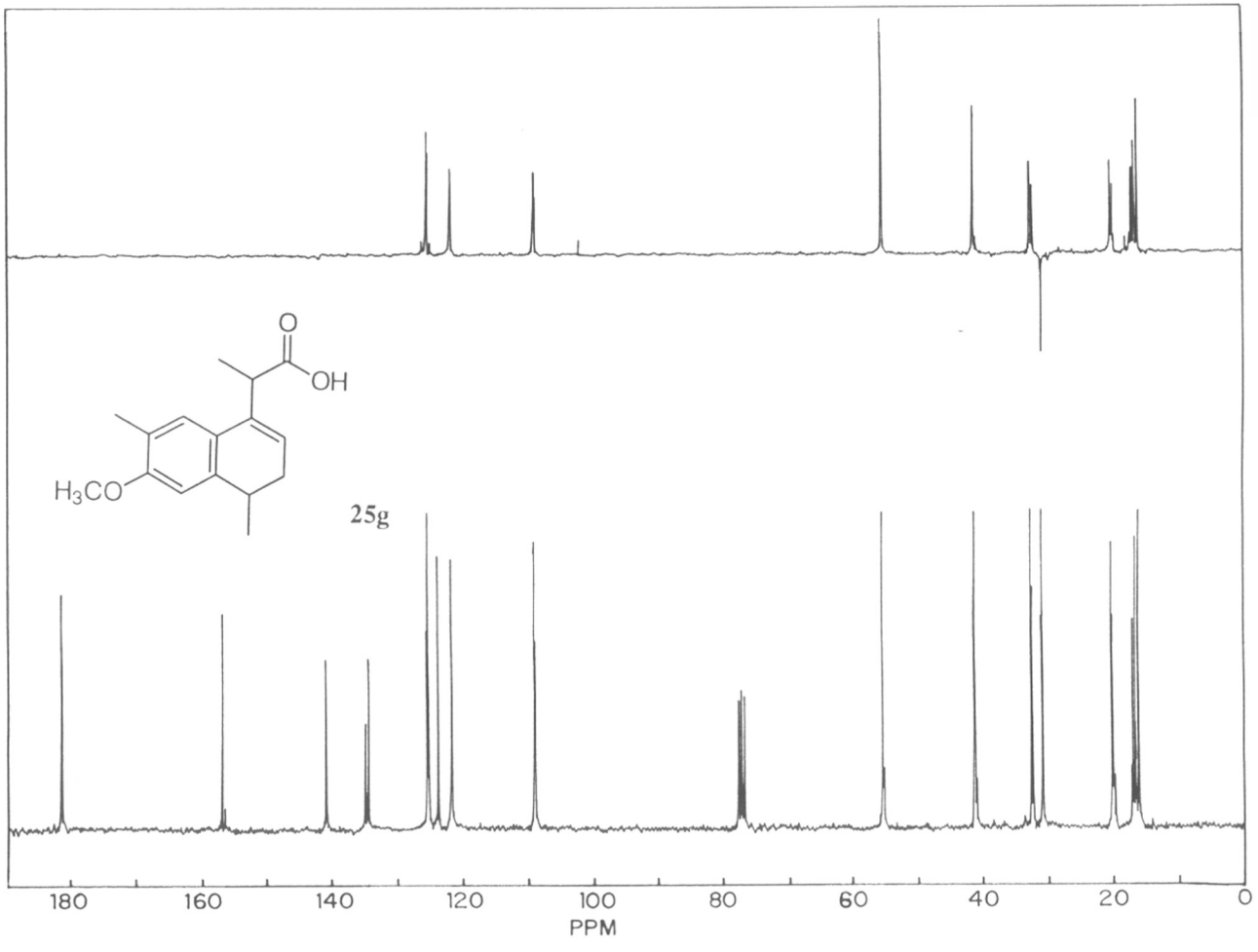
Spectrum no. 3



Spectrum no. 4

SECTION 3

Synthesis of Monoterpenic Butenolides: Dihydroactinidiolide and Mintlactones

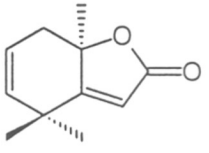
1.3.0 Introduction:

Simple monoterpenic lactones which are common components of the essential oils of plant extracts have gained importance of late and are used primarily for flavouring and in the perfume industry. Some of these compounds also exhibit bioactivity and find application on account of the same. Monoterpenoids are hence industrially one of the most important among terpenes.

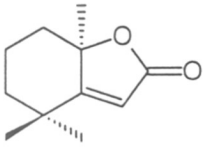
Part-A Synthesis of Dihydroactinidiolide:

1.3.1.0 Introduction:

Actinidiolide (**1**) and Dihydroactinidiolide (**2**) were isolated by Sakan *et al* as constituents of the essential oil from the leaves of *Actinidia polygama*.[1] Much interest was generated in these unusual C_{11} terpenes after Dihydroactinidiolide was isolated from the steam volatile extracts of tobacco[2-4] and black tea[5,6] and was found to be one of the principles of tea aroma.



1
Actinidiolide



2
Dihydroactinidiolide

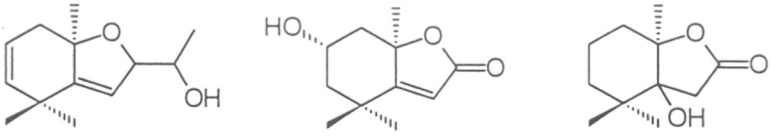
Fig. 1

Subsequently, **2** was also isolated from various other animal sources. It was found in the scent gland secretion of the red fox[7] and in marine sediments.[8] It is also a pheromone component of the red fire ant.[9]

Dihydroactinidiolide has been reported to be physiologically active for *Felidae* animals of the lower order. It is also a growth inhibitor of seed germination and root cell elongation and has been isolated as a phytotoxic compound from spikerush (*Eleocharis* sp.).[10]

Dihydroactinidiolide is also used in the perfume industry[11] and as an analeptic agent for the treatment of respiratory depression.[12]

Actinidol **3** has also been isolated from *Actinidia* sp.[1] and is presumed to be the biogenetic precursor of Actinidiolide.



3
Actinidol

4
Lolioiolide

5
Aeginetolide

Fig. 2

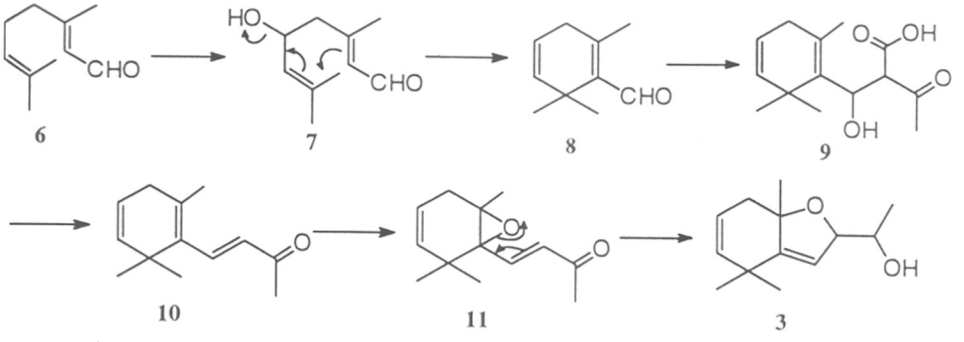
The structurally similar Loliolide **4** and Aeginetolide **5** have been isolated from rye grass (*Lolium perenne*),[13] *Digitalis purpurea*[14] and *Aeginetia indica*,[15] an Asian root parasite, respectively and also show similar biological activity though on a somewhat lower grade.

1.3.1.1 Biogenesis:

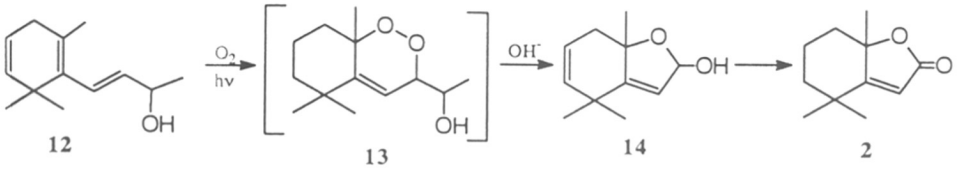
The biogenetic precursor of these unusual C_{11} terpenes seems to be Actinidol. A possible biogenetic route has been proposed by Sakan *et al.*[1]

It has been proposed that the enzymatic oxidative cyclization of citral (**6**) followed by condensation with acetoacetic acid and decarboxylation would afford the α,β-unsaturated ketone **10**. Enzymatic reduction of the carbonyl group, followed by epoxidation and cleavage of epoxide would give actinidol **3**.

Air oxidation of **3** would lead to Actinidiolide **1** which can be transformed into **2** by hydrogenation (*Scheme 1*).



The proposed biogenetic route was supported later[16] by the photosynthetic oxygenation of β-ionol (**12**) in the presence of catalytic alkali which yielded **2** (*Scheme 2*).

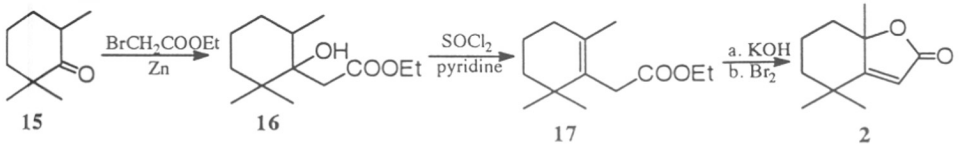


1.3.1.2 Literature Survey:

In order to provide an adequate background to the synthesis of Dihydroactinidiolide, a brief literature survey is presented.

Sakan's Synthesis:[1] (1967, *Scheme 3*)

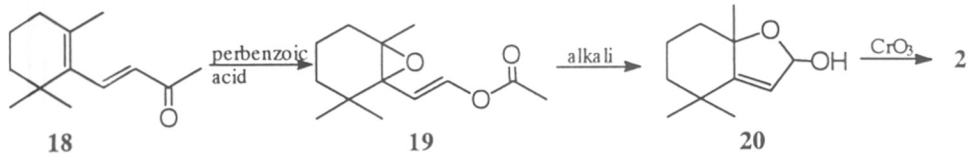
Sakan *et al* prepared Dihydroactinidiolide in 4 steps starting from 2,2,6-trimethylcyclohexanone (**15**). Reformatsky reaction of **15** with ethyl bromoacetate yielded the hydroxy ester **16** which was dehydrated with $SOCl_2$/pyridine to give the olefinic ester **17**. Alkaline hydrolysis followed by treatment with bromine furnished **2** (*Scheme 3*).



Scheme 3

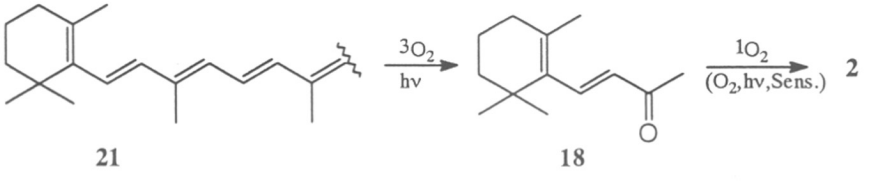
Sakan's 2nd Synthesis:[16] (1968, *Scheme 4*)

The biogenetic-type synthesis was reported starting from β-ionone (**18**). Oxidation of **18** with perbenzoic acid gave the epoxy enol acetate **19** in almost quantitative yield, which upon alkaline hydrolysis yielded the hemiacetal **20**. CrO_3 oxidation of **20** furnished **2** in good yield (*Scheme 4*).



Scheme 4

Sakan *et al* also reported[17,18] the synthesis of **2** by exhaustive oxygenation of β-carotene (**21**) under irradiation in the presence of catalytic amounts of alkali and rose bengal as the sensitizer. β-ionone was formed as the intermediate in this reaction which yielded **2** as major product after 48 hrs. (*Scheme 5*).



Scheme 5

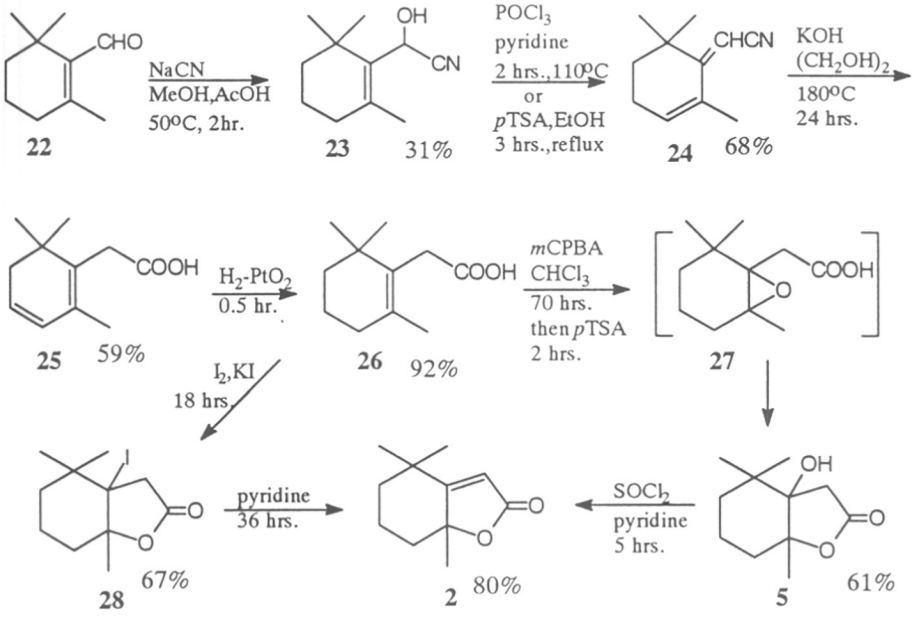
Eschenmoser *et al*[19] also reported the photooxygenation of the epoxide of carotenoids to yield Dihydroactinidiolide.

Similar oxygenation strategy was reported by Mousseron-Canet *et al*[20] who used β-ionone (**18**) as the substrate to furnish **2** in 44% yield.

Demole's Synthesis:[21] (1968, *Scheme 6*)

Homosafranic acid (**25**) was prepared in three steps from β-cyclocitral (**22**) *via* cyanide addition and dehydration using $POCl_3$, followed by alkaline hydrolysis of nitrile **23**. Hydrogenation over platinum catalyst yielded β-cyclohomogeranic acid (**26**) which upon epoxidation, hydrolysis and dehydration similar to Sakan's synthesis, yielded Dihydroactinidiolide **2**.

Alternatively, **26** was converted into the iodolactone **28** using I_2/KI which was dehydrohalogenated with pyridine to yield **2**.

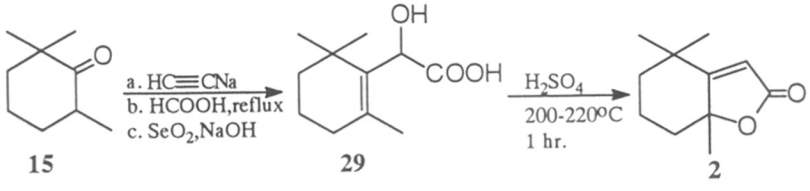


Scheme 6

Highly toxic and expensive chemicals like NaCN, PtO_2, *m*CPBA are used. The long reaction times and extremely drastic conditions for some conversions are the obvious demerits of this scheme.

Bailey's Synthesis:[3] (1968, *Scheme 7*)

2,2,6-trimethyl cyclohexanone was converted into 2,6,6-trimethylcyclohexene-1-glycolic acid (**29**) which upon treatment with aqueous H_2SO_4 at 219°C afforded **2** in high yield.

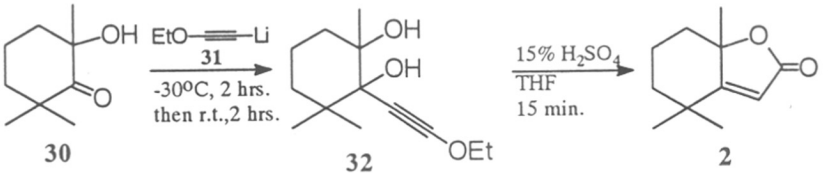


Scheme 7

This strategy though short, requires use of high temperature and acidic conditions for the lactonization-dehydration step.

Horii's Synthesis:[22] (1970, *Scheme 8*)

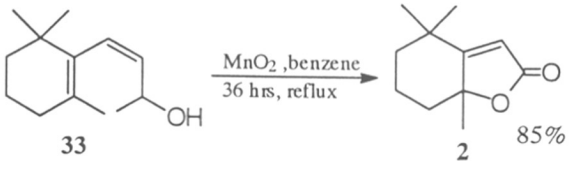
2-hydroxy-2,6,6-trimethyl cyclohexanone (**30**) when treated with lithium ethoxyacetylide (**31**) resulted in formation of the ethynyl carbinol **32**. Refluxing the compound **32** with 15% sulfuric acid in THF provided (±) Dihydroactinidiolide (**2**) in 47% yield



The synthesis though short, requires the preparation of **30** as well as the ethoxy acetylide.

Wartburg's Synthesis:[23] (1974, *Scheme 9*)

MnO_2 or Jones oxidation of β-ionol **33** in refluxing benzene furnished (±) **2** after 36 hrs in 85% yield.

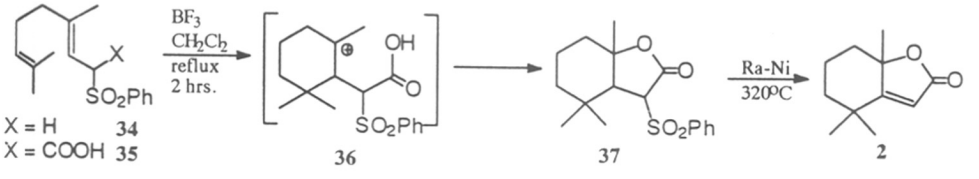


Scheme 9

The reaction requires fairly long time under reflux temperatures for completion.

Torii's Synthesis:[24,25] (1976, *Scheme 10*)

Carboxylic acid **35** was prepared quantitatively by treatment of the sulfone **34** with n-BuLi, followed by dry CO_2. Cyclization of **35** with BF_3 gave the lactone **37** in 75% yield. Thermal desulfurization with Raney Nickel at 320-350°C furnished **2** in 63% yield.

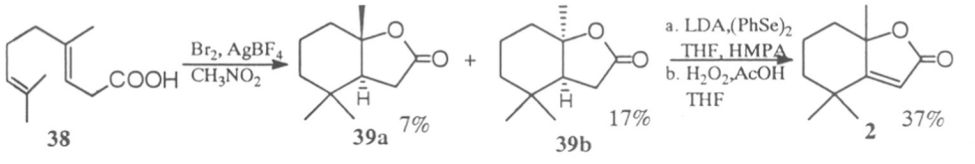


Scheme 10

This reaction sequence was developed as a general route to alicyclic butenolides. However, thermal desulfurization at extremely elevated temperatures makes it unattractive from a synthetic viewpoint.

Hoye's Synthesis:[26] (1978, *Scheme 11*)

Homogeranic acid (**38**) upon reaction with a nitromethane solution of bromine and silver tetrafluoroborate ($AgBF_4$) yielded the isomeric lactones **39a** and **39b** in very poor yields. α-Phenylselenylation of the lactones with diphenyl diselenide gave the selenides which upon oxidative elimination with H_2O_2 gave (±) **2** in 37% yield.



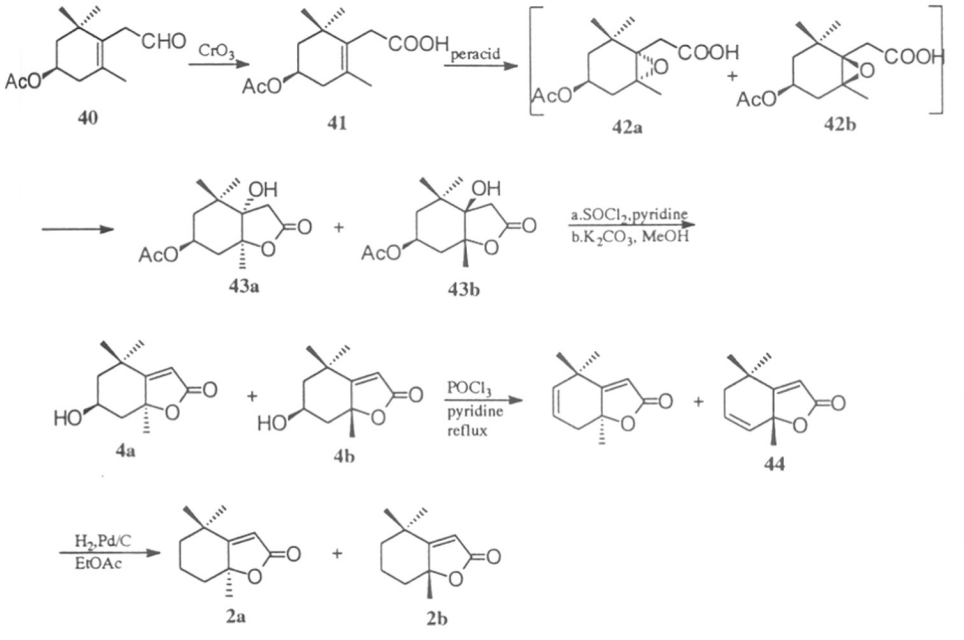
38 **39a** 7% **39b** 17% **2** 37%

Scheme 11

The brominative cyclization of homogerenic acid proceeds in extremely poor yields lowering the overall yield of **2** to less than 6%. $AgBF_4$, which is a very expensive reagent, is used in stoichiometric amounts.

Kienzle's Synthesis:[27] (1978, *Scheme 12*)

Kienzle *et al* reported the synthesis of Dihydroactinidiolide (**2**) and that of Loliolide (**4**) starting from the optically active aldehyde **40**. Jones oxidation of the aldehyde **40** followed by peracid epoxidation yielded the hydroxy lactones **43a** and **43b** which were dehydrated using pyridine/$SOCl_2$ to yield loliolide (**4a** and **4b**). Upon refluxing in pyridine/$POCl_3$ for 1 hr. the reaction furnished the olefins **1** and **44** which were hydrogenated using palladized carbon to Dihydroactinidiolide (±) **2**.

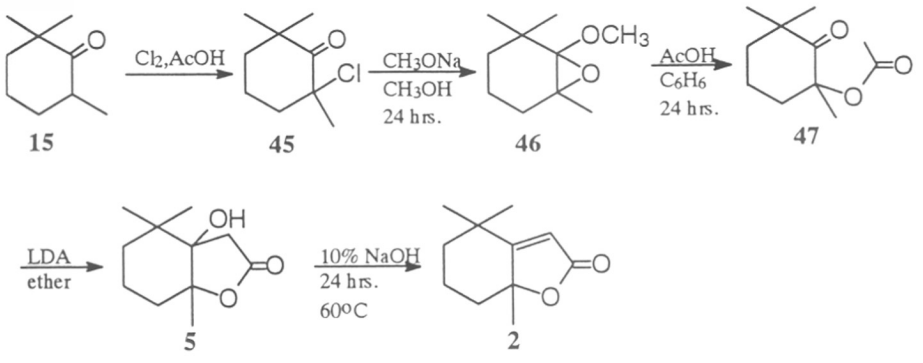


Scheme 12

This method though starting from optically pure material results in the formation of enantiomers of Dihydroactinidiolide (**2**).

Goyau's Synthesis:[28] (1979, *Scheme 13*)

The chloroketone **45** was prepared in 90% yield from 2,2,6-trimethyl cyclohexanone (**15**) and then converted into the acetate **47** *via* the epoxide **46**. LDA induced cyclization yielded Aeginetolide **5** which was dehydrated using 10% NaOH to give quantitative yield of Dihydroactinidiolide (±) **2**.

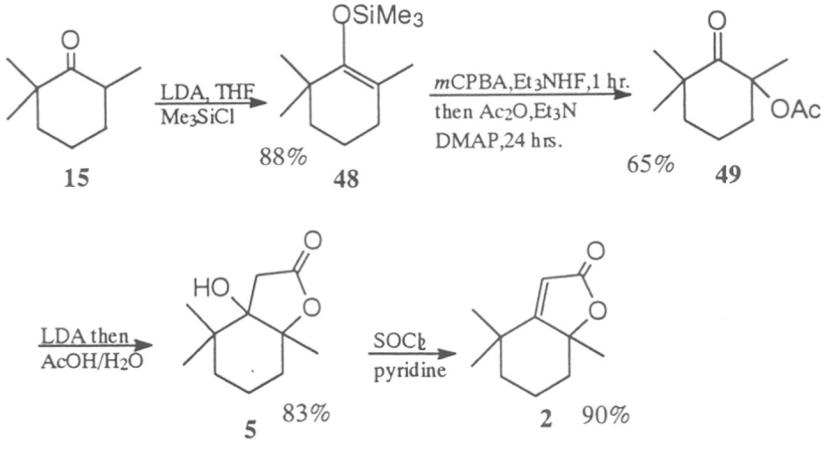


Scheme 13

Conversion of chloroketone to the epoxide and further to the acetate require long time for completion. Use of strong base *viz.* LDA is also a drawback from a practical utility standpoint.

Rubottom's Synthesis:[29] (1983, *Scheme 14*)

The silyl enol ether **48**, prepared from 2,2,6-trimethyl cyclohexanone, was converted into the keto acetate **49** by treatment with $Pb(OAc)_4$ or sequential treatment with *m*CPBA followed by Ac_2O, NEt_3 and DMAP. LDA mediated cyclization yielded the hydroxy lactone **5** which upon dehydration using thionyl chloride and pyridine gave (±) **2** in 90% yield.

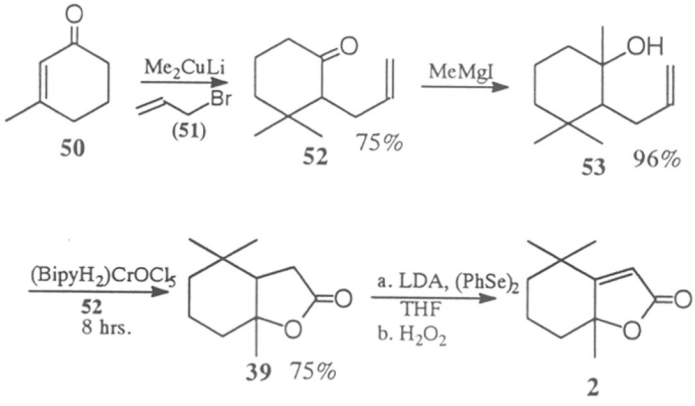


Scheme 14

The simple transformation of silyl enol ether to the acetate (**48→49**) requires fairly long time. Also, strong base (LDA) is used in two of the steps.

Chandrasekharan's Synthesis:[30] (1984, *Scheme 15*)

Conjugate addition of lithium dimethyl cuprate to 3-methylcyclohex-2-en-1-one (**50**) followed by alkylation with allyl bromide afforded **52** which upon addition of MeMgI gave the hydroxy olefin **53** in 96% yield. The key step of the synthesis was the oxidation of **53** with $(BipyH_2).CrOCl_5$ which yielded the lactone **39**. α-Phenylselenation of **39** followed by treatment with H_2O_2 gave dihydroactinidiolide **2**.



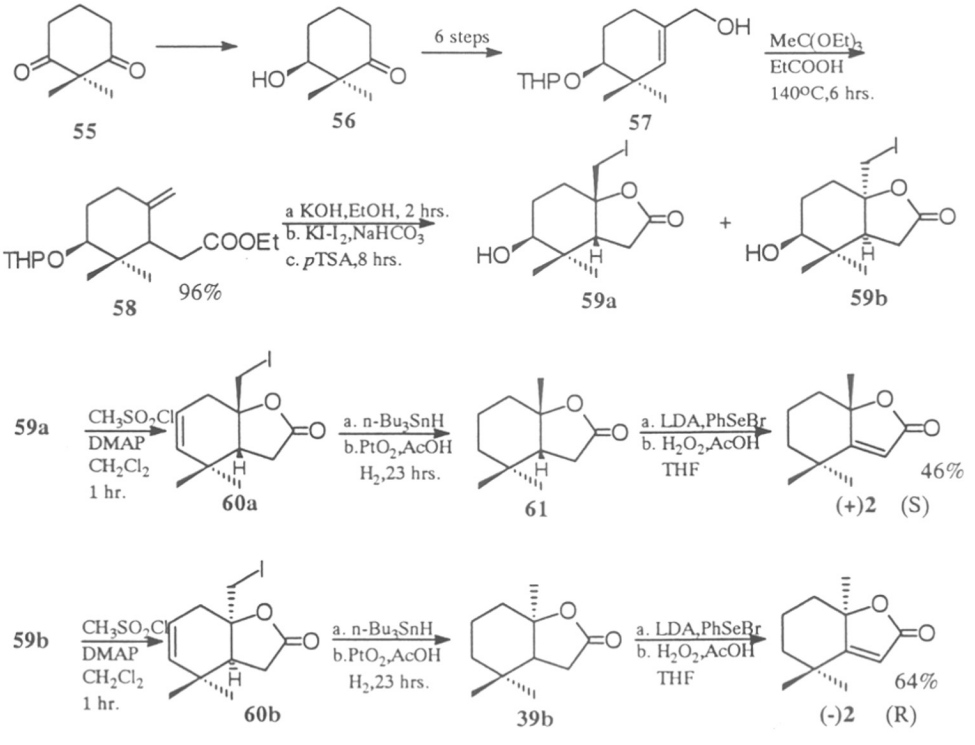
Scheme 15

This synthesis requires the use of specific oxidizing agent $(BipyH_2)\ CrOCl_5$ as the use of conventional oxidants results in poor yields of the lactone.

Mori's Synthesis:[31] (1986, *Scheme 16*)

(S)-3-hydroxy-2,2-dimethyl cyclohexanone (**56**), readily obtained by the yeast reduction of prochiral ketone **55** was chosen as the starting material. It was converted into the

alcohol **57** in 6 steps in 49% overall yield. Orthoester Claisen rearrangement of **57** with $MeC(OEt)_3$ furnished an isomeric mixture of **58** which was then hydrolyzed with KOH and the resulting unsaturated acid was subjected to iodolactonization with $KI\text{-}I_2$ and $NaHCO_3$ to give a mixture of isomers. The THP ether was cleaved to give a mixture of iodo alcohols **59a** and **59b**. These were separated and dehydrated with CH_3SO_2Cl/DMAP to yield olefinic lactones **60a** and **60b**. Treatment of **60a** and **60b** with $n\text{-}Bu_3SnH$, followed by hydrogenation using Adam's catalyst yielded the lactones **61** and **39b**. Conversion to target molecules was executed by employing Hoye's method of α-phenylselenylation followed by oxidation which yielded (+)-**2**and (-)-**2** in 5.7% and 5.8% overall yield over 15 steps.

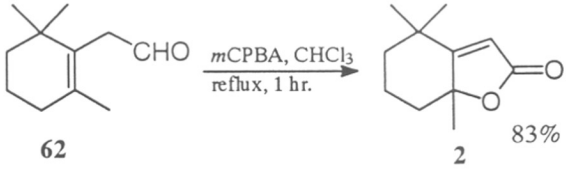


Scheme 16

The synthesis provides both the enantiomers of dihydroactinidiolide but is a very lengthy one using a variety of expensive and sensitive reagents. The overall yield is also very low.

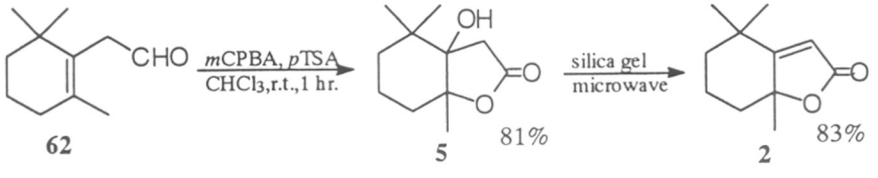
Nickson's Synthesis:[32] (1986, *Scheme 17*)

Addition of two equivalents of *m*CPBA to the commercially available aldehyde **62** in refluxing $CHCl_3$ furnished (±)2 in 83% yield after 17 hrs.



Scheme 17

Bose *et al* reported[33] an improved synthesis of **2** starting from the aldehyde **62** used by Nickson. The aldehyde **62** when treated with *m*CPBA in presence of a catalytic amount of *p*TSA at room temperature yielded Aeginetolide (**5**). Microwave irradiation of silica gel supported **5** resulted in a fast dehydration to give **2** in good yield (*Scheme 18*).

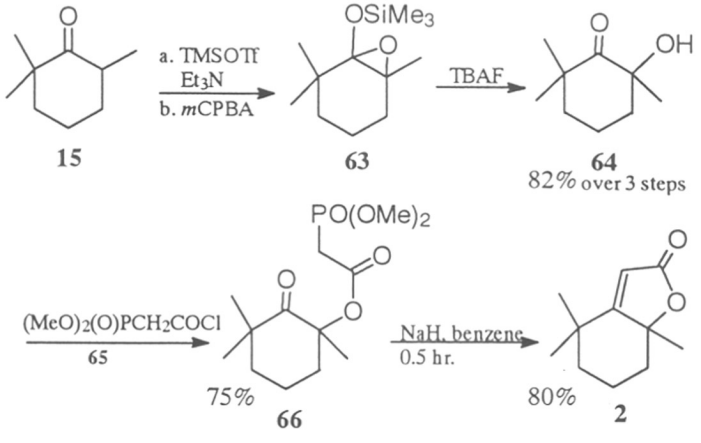


Scheme 18

Although Bose's conditions are superior to Nickson's in terms of reaction time, the synthesis still requires stoichiometric amount of the fairly expensive *m*CPBA.

Irie's Synthesis:[34] (1989, *Scheme 19*)

Irie *et al* utilized the intramolecular Wittig-Horner reaction for the synthesis of **2**. Treatment of 2,2,6-trimethyl cyclohexanone (**15**) with trimethyl silyl triflate and triethyl amine, followed by *m*-chloroperbenzoic acid gave the unstable epoxide **63** desilylation of which with tetrabutylammonium fluoride furnished the α-hydroxyketone **64** in 82% yield. Acylation of **64** with dimethyl phosphonoacetyl chloride gave the phosphonate **65**. Compound **65** was subjected to intramolecular Wittig-Horner reaction using NaH as the base furnishing dihydroactinidiolide **2** in 80% yield.



Scheme 19

The Wittig-Horner reaction has been efficiently applied for the synthesis of the α,β-unsaturated butyrolactone. However, use of expensive silylating and desilylating agents are the limiting factors of this route.

1.3.1.3 Present Work

Reviewing the literature published in connection with (±) Dihydroactinidiolide, it was observed that this molecule has been synthesized from various starting materials. Most of the syntheses utilized naturally occurring terpenes like cyclocitral (Demole) and homogeranic acid

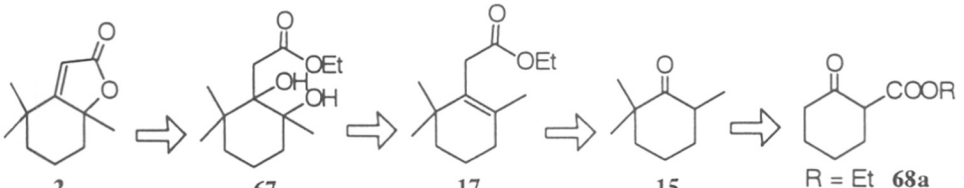
(Hoye) which, however, are not readily available. Also the syntheses are very long winded. Kienzle's synthesis as well as Mori's synthesis required very expensive starting materials.

The few syntheses reported from 2,2,6-trimethyl cyclohexanone (**15**) though short are not very high yielding. Goyau's synthesis from **15**is also very lengthy.

Interest in the synthesis of butenolides prompted an attempt towards the synthesis of (±) Dihydroactinidiolide. Approaches towards the butenolide moiety have been previously reported[35] from this laboratory. Also, an efficient methodology for butenolide synthesis from the corresponding β,γ-unsaturated acid using CAN has been developed (Section 2).

It was hence proposed to synthesize (±)**2** starting from the corresponding ketone namely, 2,2,6-trimethylcyclohexanone which has been previously used by other workers for the same, albeit with poor results.

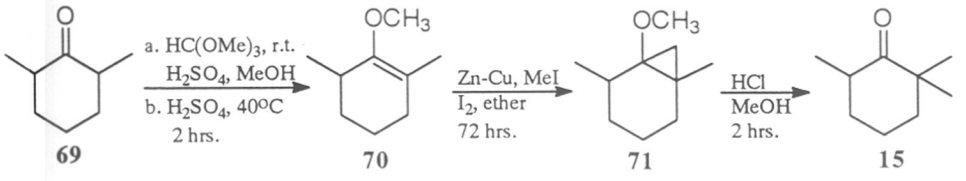
The retrosynthetic plan is as depicted in *Scheme 20*. Butenolide **2** can be accessed from the diol **67** which can be prepared from the β,γ-unsaturated ester **17**. Ester **17** in turn can be obtained *via* a Reformatsky reaction on 2,2,6-trimethylcyclohexane (**15**). **15** could be accessed from the readily prepared 2-carbalkoxy cyclohexan-1-one (**68**).



Scheme 20

1.3.1.4 Results and Discussion

There are many syntheses of compound **15** reported in literature.[36,37,38] Wenkert *et al*[36] have synthesized the molecule from 2,6-dimethylcyclohexanone *via* the enol ether, followed by cyclopropanation and hydrolysis (*Scheme 21*).



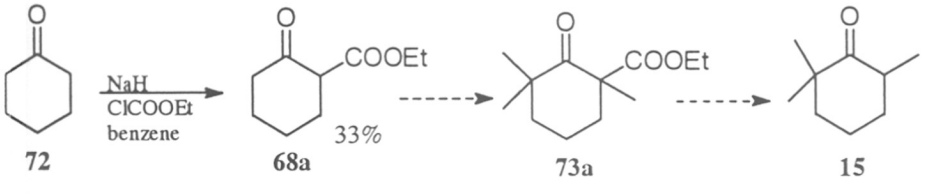
69 **70** **71** **15**

Scheme 21

However, this strategy requires a very long time and when attempted, the yields also were not very good.

It was then thought to access **15** *via* the β-ketoester **68** by exhaustive methylation and hydrolysis.

However, the shortest route to the β-keto ester **68a** by the direct alkylation of cyclohexanone using ethyl chloroformate and NaH as base resulted in very poor yield of the product (*Scheme 22*).

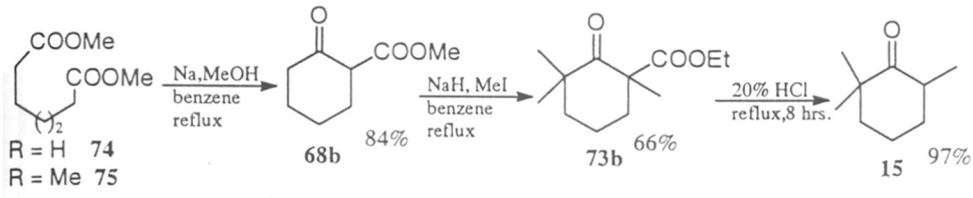


72 **68a** **73a** **15**

Scheme 22

Dieckman condensation of the dimethyl ester of pimelic acid[37] (**75**), however, furnished **68b** in very good yields. Further exhaustive methylation yielded the trimethylated keto ester **73b** in 66%yield. Compounds **68b** and **73b** were fully confirmed by spectral analysis.

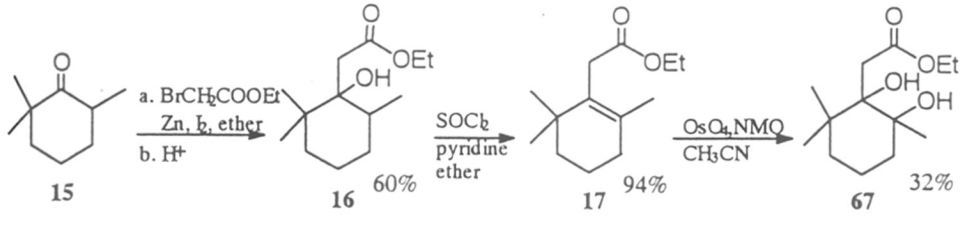
Hydrolysis-decarboxylation was carried out in one pot using 20% HCl under reflux for 8 hrs. ^{1}HNMR and IR values confirmed the formation of product **15** (*Scheme 23*).



Scheme 23

Having the starting ketone in hand, it was converted to the corresponding β,γ-unsaturated ester **17** by known reactions. Reformatsky reaction with ethyl bromoacetate furnished the hydroxy-ester **16** in 60% yield. The product **16** was confirmed by NMR spectrum which showed the required ester signals at δ 1.1 and 4.1. IR spectrum showed peak at 3400 cm^{-1}. (*Scheme 24*)

The hydroxy-ester was dehydrated using $SOCl_2$/pyridine at 0°C to yield the β,γ-unsaturated ester **17** in 94% yield.



Scheme 24

The next task was the dihydroxylation of the ester **17** to give the diol **67** which would be the required substrate for cyclization. However, dihydroxylation of **17** using catalytic OsO_4 and NMO furnished the diol **67** in extremely poor yield (32%) after more than 72 hrs. Most of the starting olefin was recovered unchanged. Modifying the conventional conditions of

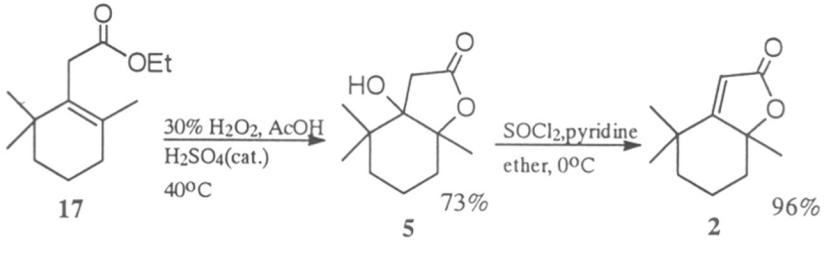
dihydroxylation did not result in any appreciable change in yield of the product. Recently reported "flash dihydroxylation"[39] using $RuCl_3$ also failed to furnish the diol.

The failure of dihydroxylation could be attributed to the extreme steric hindrance of the tetrasubstituted olefin which prohibits the formation of the osmate complex necessary for the transformation.

Since the diol **67** could not be obtained efficiently, it was necessary to modify the strategy.

Cyclization of **17** *via* the corresponding epoxide was then attempted presuming that the epoxide could be cyclized to the hydroxy butenolide under acidic conditions.

Accordingly, the olefinic ester **17** was treated with 30% H_2O_2 in acetic acid as solvent in the presence of a catalytic amount of sulfuric acid. The reaction was monitored by TLC and after a period of 5 hrs., usual work-up yielded the hydroxy lactone, Aeginetolide 5 in 73% yield as a white solid (*Scheme 25*).



Scheme 25

The product of the acid catalyzed hydrolysis and cyclization step was fully characterized by NMR, IR, Mass Spectroscopy and melting point which matched those from literature reports.

Aeginetolide (**5**) showed no peaks corresponding to the ester in NMR spectrum. Instead, there was a slight downfield shift of α-methylene protons from δ 2.60 to δ 2.70. Strong peak at 3420 cm^{-1} in IR spectrum confirmed presence of hydroxy group. M^+ peak at 198 was observed in the Mass Spectrum.

Further transformation similar to Demole's synthesis was carried out. Dehydration to (±) Dihydroactinidiolide was executed using thionyl chloride and pyridine at 0°C in CH_2Cl_2 which furnished (±) **2** in 96% yield. The product **2** corresponded totally with reported Dihydroactinidiolide in terms of spectral data.

1.3.1.5 Conclusions:

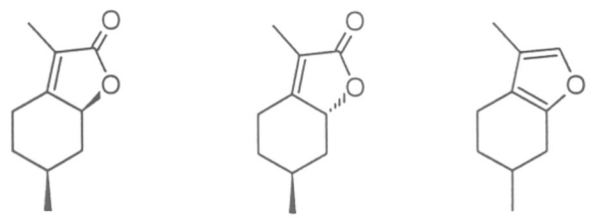
Thus, a mild, efficient and practical method of preparing dihydroactinidiolide has been achieved in just four steps starting from the readily accessible 2,2,6-trimethyl cyclohexanone at ambient and near ambient temperatures. Additional advantage of the reaction sequence is that it also gives access to the naturally occurring Aeginetolide **5**.

Part-B Synthesis of Mintlactone and isoMintlactone

1.3.2.0 Introduction

The essential oil of *Mentha piperita* (peppermint oil) is one of the most important commercial flavouring materials and is produced in many countries. Its chemical composition has been thoroughly investigated and more than 300 components have been reported.

Among the minor constituents, the menthane derivatives, (-) mintlactone (**76**) and (+) isomintlactone (**77**) were isolated from Japanese[40] and American[41] peppermint oil. Prior to their isolation as natural products, the formation of these compounds in the course of synthetic processes have been reported.[42,43] Racemic mintlactone was also an intermediate in the total synthesis of menthofuran (**78**).[44]



76 **Mintlactone** **77** **Isomintlactone** **78** **Menthofuran**

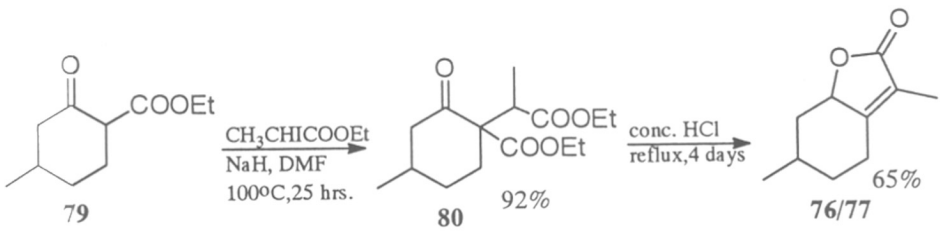
Fig. 3

1.3.2.1 Literature Survey:

A brief survey of the reported synthesis of racemic and optically pure mintlactone is presented.

Takeda's Synthesis:[44] (1980, *Scheme 26)*

Alkylation of 4-methyl-2-oxo-1-cyclohexane carboxylate (**79**) with ethyl 2-iodo propionate in DMF provided the diester **80** as the exclusive product which upon hydrolysis with conc. HCl afforded (±) mintlactone in 65% yield.

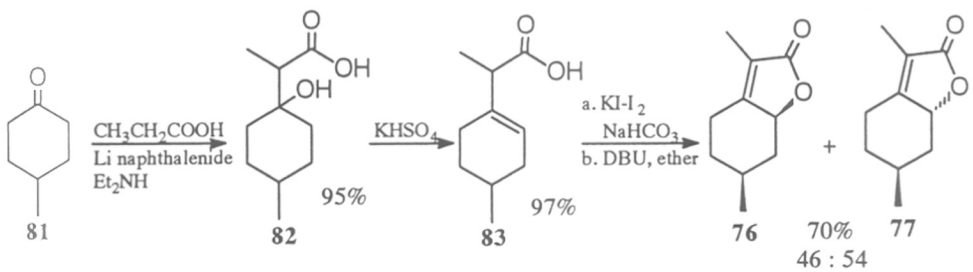


Scheme 26

The drastic conditions required for the hydrolysis and cyclization *i.e.* refluxing in acid for prolonged time and also the long time required for the C-alkylation greatly diminish the positive features of this short and straightforward synthesis.

Fujita's **Synthesis**:[45] (1985, *Scheme 27*)

Treatment of 4-methyl cyclohexanone **81** with propionic acid in the presence of lithium naphthalenide and diethylamine yielded the hydroxy acib **82** in 95% yield which upon dehydration with potassium bisulfate furnished the β,γ-unsaturated acid **83** in 97% yield. Iodolactonization followed by DBU mediated elimination furnished a mixture of mintlactone and isomintlactone (46:54) in 70% yield.

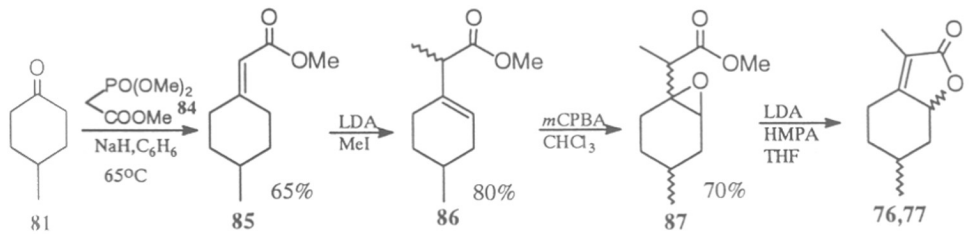


Scheme 27

Cory's **Synthesis**:[46] (1990, *Scheme 28*)

Emmons-Wadsworth olefination of 4-methylcyclohexanone with methyl phosphonoacetate (**84**) afforded the α,β-unsaturated ester **85** in 65% yield. Alkylative

deconjugation to **86** and epoxidation with *mCPBA* yielded the epoxy ester **87** which on treatment with LDA furnished a 9:1 mixture of (±)mintlactone and (±) isomintlactone from which (±) mintlactone was isolated in 68% yield.

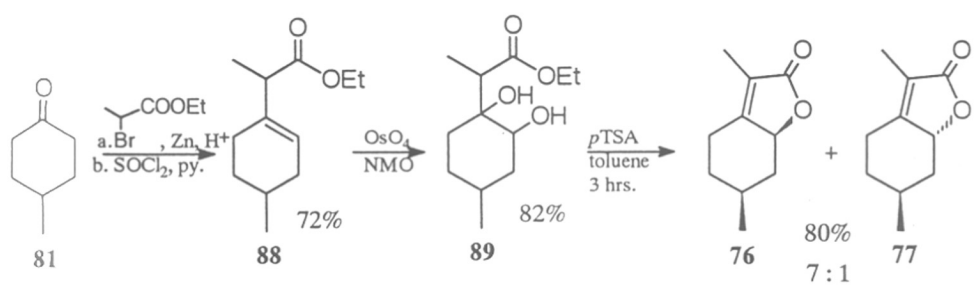


Scheme 28

Though this route is short, it requires use of strong base like LDA and stoichiometric amounts of *m*CPBA. Conversion of **87** to **76/77** also requires use of LDA in HMPA at elevated temperatures for long duration.

Chavan's Synthesis:[35] (1992, *Scheme 29*)

4-methylcyclohexanone **81** when subjected to Reformatsky reaction with ethyl 2-bromopropionate furnished the corresponding alcohol which on dehydration using thionyl chloride/pyridine furnished the β,γ-unsaturated ester **88** in 72% overall yield. Catalytic dihyroxylation using OsO_4/NMO, followed by acid catalyzed cyclization furnished (±) mintlactone (**76**) and (±) isomintlactone (**77**) in 80% yield as a mixture of diastereomers.



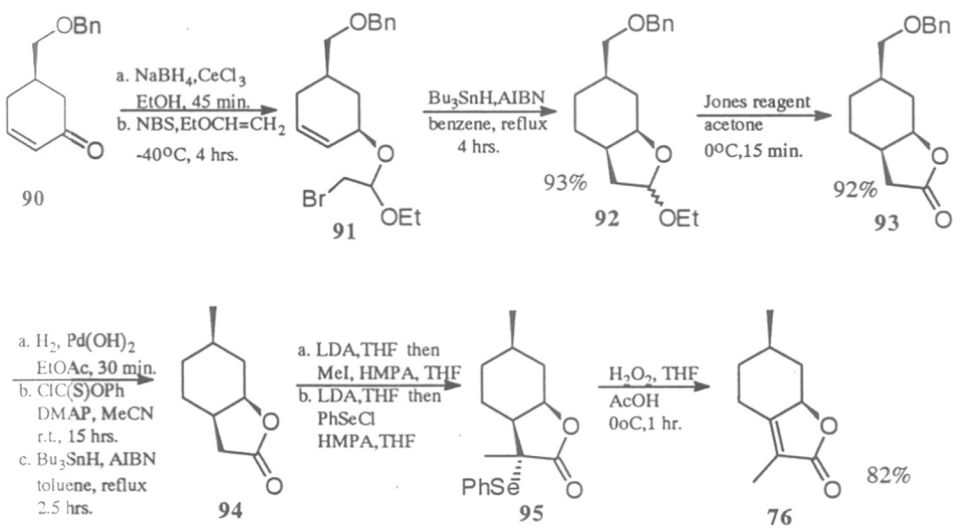
Scheme 29

Although similar to Cory's strategy, this method is much more superior in terms of efficiency and simplicity.

Carda's **Synthesis**:[47,48] (1991, *Scheme 30*)

The first stereodirected synthesis of optically active mintlactone was reported by Carda *et al.* Hydride reduction of the chiral enone **90** gave the allylic alcohol which was then transformed into the bromoacetal **91** by reaction with NBS in ethyl vinyl ether. Radical cyclisation of **91** furnished the acetal **92** which was then oxidised with Jones reagent to the lactone **93**. Debenzylation with $Pd(OH)_2$, followed by acylation with O-phenyl chlorothionoformate and treatment with n-Bu_3SnH/AIBN yielded the lactone **94**.

Methylation of **94** *via* the LDA generated enolate, followed by dehydrogenation *via* the phenylselenyl derivative **95** yielded (-) mintlactone (**76**).

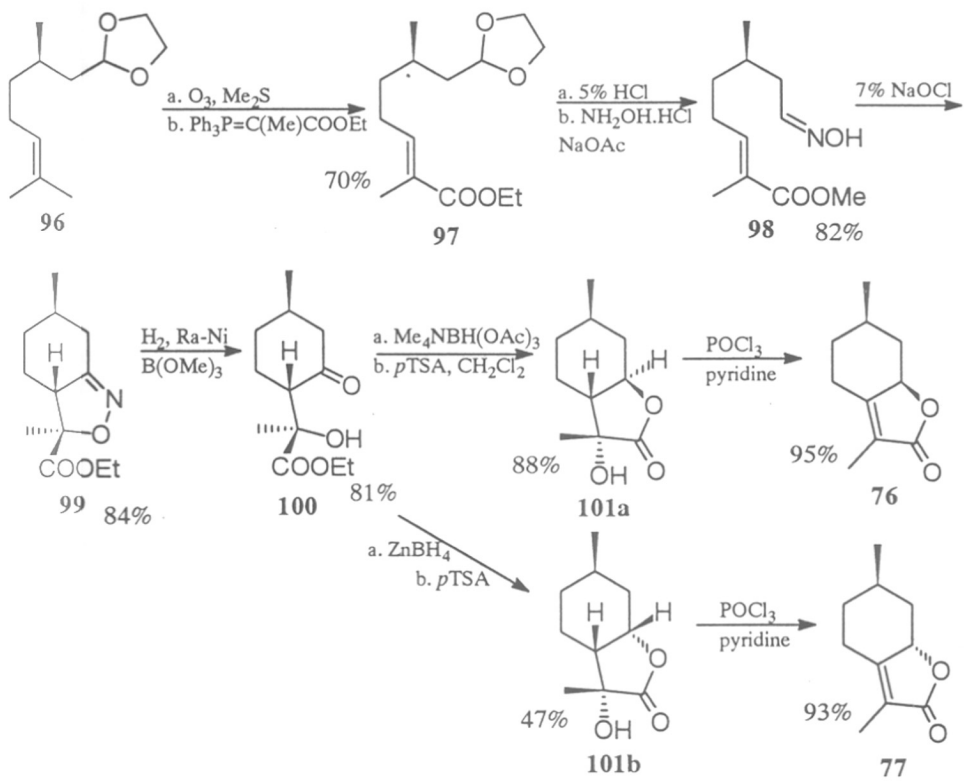


Scheme 30

This is the first chiral synthesis of (-) mintlactone. However, the procedure is extremely lengthy and requires use of strong base like LDA and sensitive reagents like n-Bu_3SnH.

Shishido's Synthesis:[49] (1992, *Scheme 31*)

The olefinic acetal **96** derived from (+) citronellal was ozonized and the resulting aldehyde condensed with ethyl 2-(triphenylphosphorenylidene)propionate to provide the unsaturated ester **97**. Acidic hydrolysis of the acetal and subsequent oxime formation provided **98**. Treatment of **98** with 7% aqueous sodium hypochlorite afforded the isoxazoline **99** as the major product reductive hydrolysis of which with trimethyl borate/Raney Nickel provided **100** in 81% yield. Treatment of **100** with tetramethylammonium triacetoxyborohydride afforded the corresponding 1,3-diol which was treated with catalytic *p*TSA to afford the lactones **101a** and **101b** in 88% yield in a ratio of 30:1. Dehydration of the lactone **101a** with $POCl_3$ in pyridine produced (-) mintlactone in 92% yield.



Scheme 31

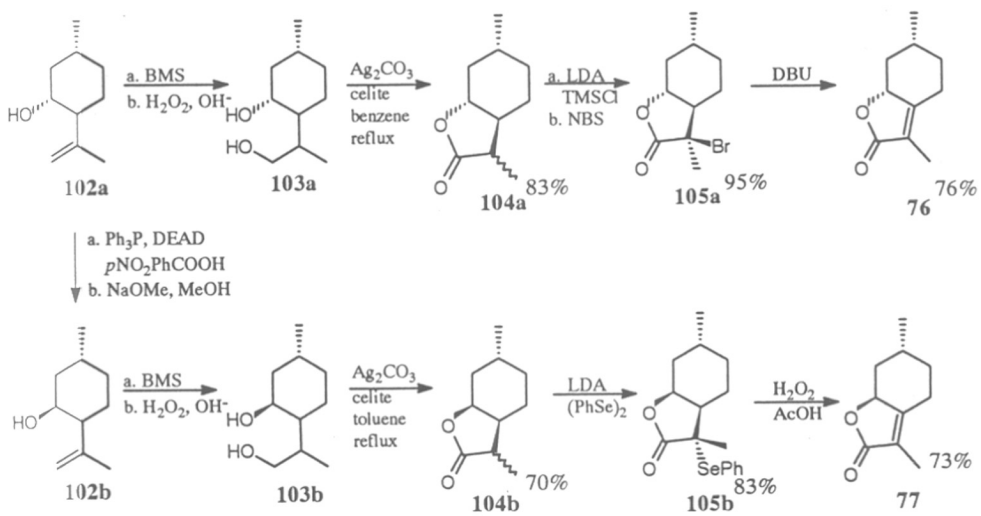
Treatment of **100** with $ZnBH_4$ in ether, followed by acidic treatment (*p*TSA) gave the lactones **101a** and **101b** in 47% yield in 1:6 ratio. Dehydration of major isomer with $POCl_3$/pyridine furnished (+) isomintlactone in 93% yield.

This synthesis is also very lengthy. However, both isomers can be accessed from the same intermediate in good yields.

Chavan's 2nd Synthesis:[50] (1993, *Scheme 32*)

Chavan *et al* reported the stereoselective syntheses of (-) mintlactone and (+) isomintlactone starting from common precursor (-) isopulegol **102a**.

Hydroboration of isopulegol **102a** furnished the 1,4-diol **103a** which was smoothly transformed to the butyrolactone **104a** using Fetizon's reagent (Ag_2CO_3/celite). Treatment of the lactone **104a** with LDA and subsequently with TMSCl and NBS in one pot furnished the bromolactone **105a** which was dehydrohalogenated using DBU to furnish (-) mintlactone.



102a 103a 104a 105a 76

102b 103b 104b 105b 77

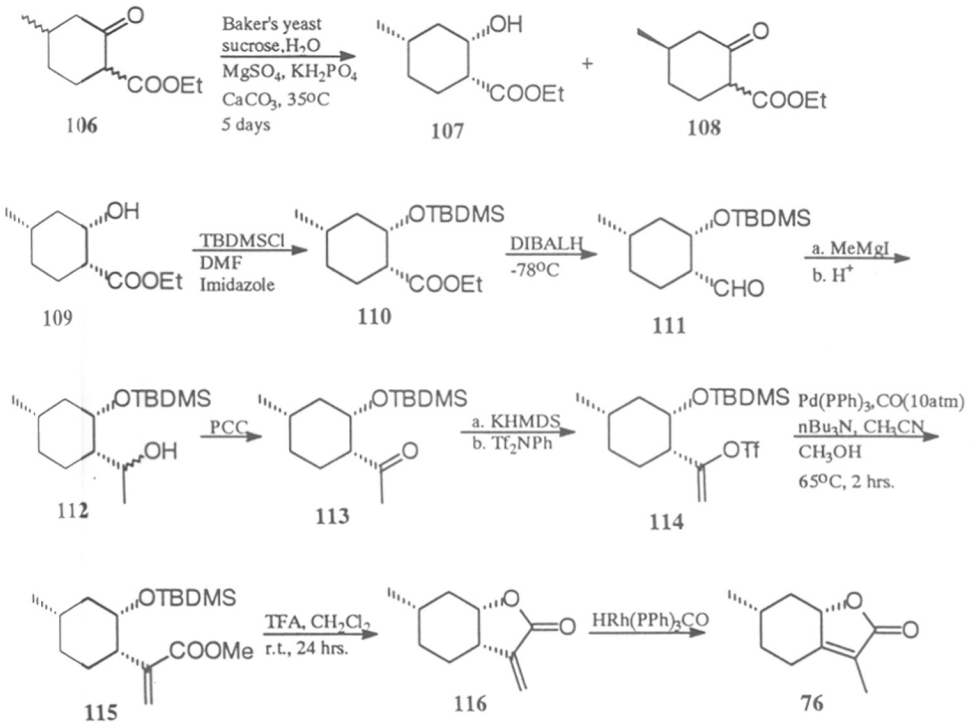
Scheme 32

For the synthesis of (+) isomintlactone, the stereochemistry was inverted by employing modified Mitsunobu conditions to give *neo*-isopulegol **102b**. Hydroboration followed by oxidation using Fetizon's reagent furnished the butyrolactone **104b**. Treatment of 104b with LDA, followed by diphenyl diselenide gave the seleno lactone **105b** which upon oxidation with H_2O_2 furnished (+) isomintlactone.

This stereoselective synthesis of **76** and **77** results in good yields of the target molecules in fewer steps. Although strong bases (LDA, DBU) are used, the excellent yields counter the negative features of the synthesis.

Crisp's **Synthesis**:[51](1995, *Scheme 33*)

Fermenting baker's yeast reduction of the β-keto ester, (±)-4-methyl-2-cyclohexanone-1-carboxylate (**106**) afforded the β-hydroxy ester **107** in 44% yield. The hydroxy group was protected as the tert-butyldimethylsilyl ether. DIBAL reduction followed by Grignard reaction with MeMgI yielded the alcohol, subsequent oxidation of which with PCC yielded the methyl ketone. Regioselective triflation gave the vinyl triflate **114** and a palladium mediated carbomethoxylation afforded the acrylate **115**. Lactonization using trifluoroacetic acid followed by rhodium-catalyzed double bond isomerization furnished (+) mintlactone in 28% overall yield from **107**.



Scheme 33

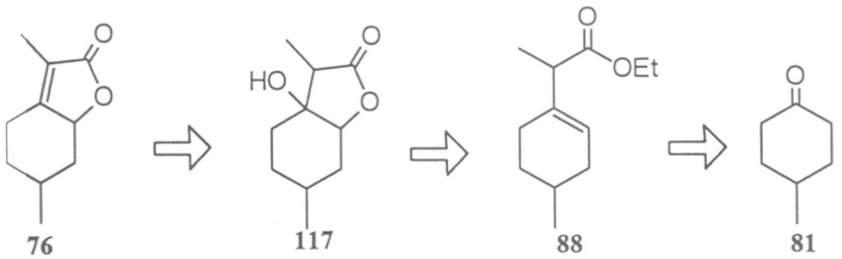
The synthesis is very long winded with some transformations requiring a lot of time and also expensive reagents.

1.3.2.2 **Present Work**

An efficient one-pot, two-step transformation of β,γ-unsaturated esters to the corresponding hydroxy-butyrolactone had been executed for the synthesis of dihydroactinidiolide (Part A).

It was proposed to apply the same strategy for the synthesis of (±) mint and isomintlactones.

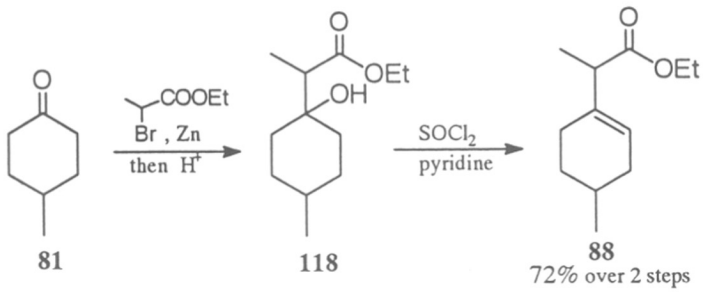
The hitherto unreported hydroxy mintlactone **117** would be an intermediate in this proposed synthesis (*Scheme 34*).



Scheme 34

1.3.2.3 Results and Discussion

The starting material for the synthesis was 4-methylcyclohexanone (**81**). It was converted into the corresponding β,γ-unsaturated ester **88** *via* previously reported[30] reactions (also see *Section I*). Thus, Reformatsky reaction of **81** with ethyl 2-bromopropionate followed by dehydration using $SOCl_2$/pyridine yielded the olefinic ester **88** in 72% yield.

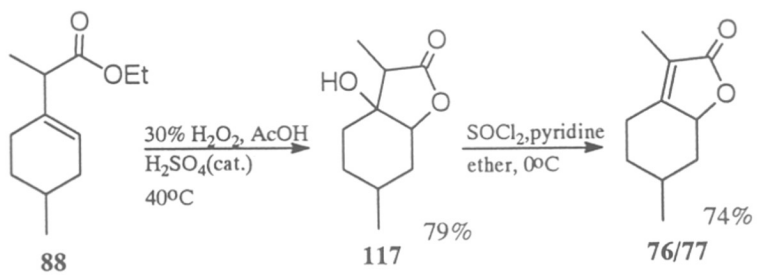


Scheme 35

The conversion of olefinic ester **88** to the hydroxylactone was attempted using the same conditions as those employed for dihydroactinidiolide. Accordingly, treatment of the ester **88** with 30% H_2O_2 in acetic acid with a few drops of sulfuric acid at 40°C furnished the

lactone **117** as an inseparable diastereomeric mixture in 79% yield. Formation of **117** was confirmed by NMR, IR and Mass Spectral analysis.

NMR of **117** showed absence of ester peaks at δ 1.2 and 4.0. The olefinic proton at δ 5.6 also disappeared. Instead, two signals at δ 4.20 and 4.48 were observed for the isomeric protons. IR spectrum showed strong peak for hydroxyl group at 3400 cm^{-1}. The mass spectrum categorically confirmed formation of **117** by presence of molecular ion peak M^+ at 184.



88 **117** **76/77**

Scheme 36

The further conversion of **117** to **76/77** was carried out by treatment with $SOCl_2$ and pyridine in dry CH_2Cl_2 at 0°C which yielded the target molecule **76/77** in 74% yield. The NMR spectrum as well as GC analysis showed formation of mintlactone and isomintlactone in a ratio of 4:1.

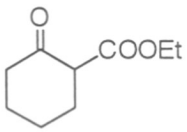
1.3.2.4 Conclusion:

Thus, a short and simple strategy for the synthesis of mint and isomintlactone in racemic form has been developed. The easy availability of 4-methyl cyclohexanone coupled with the mild conditions make this process an attractive method.

1.3.3 Experimental

1.3.3.1 Synthesis of Dihydroactinidiolide

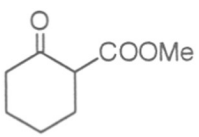
Ethyl 2-oxocyclohexanecarboxylate (68a)



68a

To a suspension of NaH (50% emulsion, 2.316g, 48 mmol, prewashed with 10×2 ml of dry hexane) in 20 ml dry benzene was added cyclohexanone **72** (4.735g, 5 ml, 48 mmol) dropwise with stirring under N_2 atmosphere. After a period of 15 minutes, ethyl chloroformate (5.24g, 4.61 ml, 48 mmol) was added slowly. The reaction was monitored by TLC and was complete in 0.5 hr. It was quenched using 20 ml of 10% HCl, and the organic layer was separated. Aqueous layer was extracted with ethyl acetate (2×10 ml). Combined organic fractions were dried (Na_2SO_4) and the solvent evaporated under vacuum. The residual liquid was distilled to yield 2.75g. (34%) of keto ester **68a**.

Methyl 2-oxocyclohexanecarboxylate (68b)

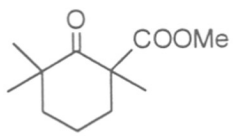


68b

Dimethyl pimelate **75** (19.38g, 100 mmol) was added in one lot to sodium(3.56g, 155 mmol) in dry benzene (100 ml), followed by dry methanol (5 ml). The reaction was heated under reflux for 12 hrs. with stirring. Completion of reaction was confirmed by TLC. The

reaction mixture was cooled in ice and carefully decomposed with ice and 6N HCl. The benzene layer was separated and the aqueous layer was extracted with ethyl acetate (2×20 ml). The organic layer was washed successively with aqueous sodium bicarbonate solution (20 ml) and H_2O (20 ml). The organic extract was dried over anhydrous Na_2SO_4 and the solvent evaporated under vacuum. The residual liquid was distilled at 220°C to furnish 13.4g (84%) of pure keto ester **68b**.

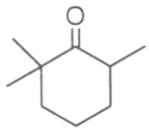
Methyl 1,3,3-trimethyl-2-oxo-cyclohexanecarboxylate (73b)



73b

Distilled 2-carbmethoxy cyclohexanone **68b** (13.18g, 85 mmol) was added dropwise over a period of 15 minutes to a stirred ice cold suspension of NaH (50% emulsion,20.28g, 425 mmol, prewashed with 2×10 ml hexane) in dry benzene (30ml). MeI (19.382g, 100 mmol) was added and the mixture heated to reflux for 4 hrs. The heating was stopped briefly for the further addition of MeI (23.99g, 10.52 ml, 170 mmol) and resumed for additional 36 hrs. The mixture was cooled in ice and decomposed with 50 ml of 10% HCl. The benzene layer was separated and the aqueous layer was extracted with ethyl acetate (2×30 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue thus obtained was distilled at 120°C/15mm to yield 12.88g (77%) yield of the alkylated keto ester **73**.

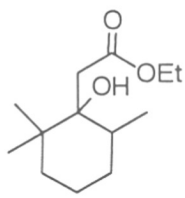
2,2,6-trimethyl cyclohexanone (15)



15

Keto ester **73b** (11.057g, 56 mmol) was refluxed in 10% HCl (50ml) for 12 hrs with stirring. After completion of reaction (monitored by TLC), the mixture was extracted with ethyl acetate (3×10 ml), washed with H_2O (10 ml), dried over Na_2SO_4 and the solvent evaporated under vacuum to yield crude product which was distilled at 177-178°C to give 7.58g (97%) of 2,2,6-trimethylcyclohexanone **15**.

Ethyl 2-(1-hydroxy-2,6,6-trimethylcyclohexane)acetate (16)



16

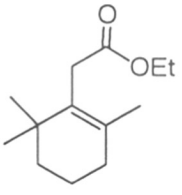
To a solution of 2,2,6-trimethylcyclohexanone (**15**) (4.295g, 31 mmol) in dry ether (20 ml) was added to ethyl bromoacetate (6.148g, 4.1 ml, 37 mmol), followed by activated zinc (6.08g, 93 mmol) and iodine crystals (0.4g, 3.1 mmol). After completion of reaction (TLC), the reaction mixture was worked up with conc. HCl (10 ml). The mixture was extracted with $CHCl_3$ (2×20 ml), washed successively with freshly prepared sodium thiosulfate solution (10 ml) and water, then dried and the solvent evaporated to yield crude product. The residue was chromatographed over silica gel using 5% ethyl acetate-pet.ether as eluent to yield 4.18g (60%) of the hydroxy ester **16**.

IR (neat): 3480, 1700, 1450, 1360, 1340, 1180 cm^{-1}

^{1}H-NMR (90 MHz): δ 0.8 (d, J=5Hz, 3H); 0.9 (s, 6H); 1.1 (t, J=7Hz, 3H); 1.0-2.0 (m, 7H); 2.30 (d, J=15Hz, 1H); 2.5 (d, J=15Hz, 1H); 4.1 (q, J=7Hz, 2H); 4.3 (bs, 1H).

Mass (m/e): 228(M^+, 14): 210(2); 195(4); 183(4); 172(4); 158(27); 157(43); 144(38); 123(19); 111(19); 107(19); 83(31); 82(100); 81(28); 70(41); 69(73); 67(29); 56(50); 55(71).

Ethyl 2-(2,6,6-trimethylcyclohex-1-ene)acetate (17)



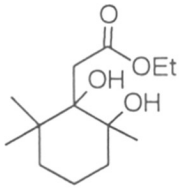
17

A solution of hydroxy ester **16** (1.83g, 8 mmol) in dry ether (10 ml) was cooled to 0°C using ice bath under N_2 atmosphere. Dry pyridine (1.27g, 1.30 ml, 16 mmol) was added and the reaction mixture was stirred for 15 min. Distilled thionyl chloride (0.96g, 0.59 ml, 8 mmol) was added dropwise to the reaction mixture and the reaction was quenched with dilute HCl after 1 hr. The mixture was extracted with ethyl acetate (2×10 ml), washed with H_2O (10 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under vacuum. The residue was chromatographed over silica gel using 5% ethyl acetate-pet.ether as eluent to yield 1.58g (94%) of β,γ-unsaturated ester **17**.

IR (neat): 1790, 1460, 1380, 1340, 1310, 1280 cm^{-1}

^{1}H-NMR (200 MHz): δ 0.95 (m, 9H); 1.05-1.65 (m, 9H); 1.90-2.40 (m, 2H); 4.00-4.15 (q,2H).

Ethyl 2-(1,2-dihydroxy-2,6,6-trimethyl cyclohexane)acetate (67)



67

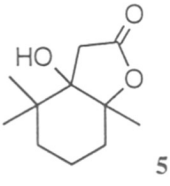
A 20 ml test tube was charged with the β,γ-ester **17** (0.525g, 2.5 mmol) and N-methylmorpholine oxide (0.035g, 3 mmol) in acetonitrile water mixture (9:1, 1 ml) and a catalytic amount of OsO_4 in toluene was injected. The reaction mixture was stirred for 36 hrs. and when no change was observed by TLC, the stirring was continued at 60°C for additional 36 hrs and the reaction quenched with solid sodium metabisulphite (~3g). Solid was filtered off and washed with ethyl acetate (10 ml). The organic extract was washed with 10% HCl (10 ml), dried over anhydrous Na_2SO_4 and the solvent was chromatographed over silica gel to yield 0.3g. of unreacted olefin and 0.435g of diol **67** which was eluted out with 20% ethyl acetate-pet.ether.

IR (neat): 3420, 1700, 1440, 1370, 1330, 1180 cm^{-1}

^{1}H-NMR (200 MHz): δ 0.95 (s, 3H); 1.00 (s, 3H); 1.35 (s, 3H); 1.35 (t, J=6.5Hz, 3H); 1.40-1.85 (m, 6H); 2.50 (d, J=15Hz, 1H); 2.75 (d, J=15Hz, 1H); 3.00 (bs, 1H); 4.15 (q, J=6.5Hz, 2H).

Mass (m/e): 244(M^+, 2); 226(55); 208(10); 181(16); 158(64); 143(26); 128(24); 123(41); 117(35); 111(77); 110(52); 109(43); 95(42); 86(51); 84(66); 71(70); 69(100); 55(42).

3a,4,5,6,7a-hexahydro-3a-hydroxy-4,4,7a-trimethyl 2(3H)benzofuranone (5)



5

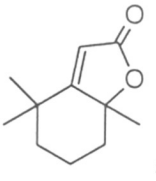
To a solution of the β,γ-unsaturated ester **17** (0.525g, 2.5 mmol) in 5 ml of acetic acid was added 30% H_2O_2 solution (0.810g, 2.7 ml, 12.5 mmol) alongwith a few drops of concentrated sulfuric acid. The reaction mixture was stirred for 12 hrs at 40°C. After disappearance of the ester (TLC), water was added and the reaction mixture was extracted with ethyl acetate (2×10 ml), washed successively with saturated $NaHCO_3$ solution and H_2O and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was chromatographed over silica gel using 40% ethyl acetate-pet.ether to furnish hydroxylactone **5**, (0.361g, 73%).

IR (nujol): 3420, 1730, 1450, 1370 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.00 (s, 3H); 1.05 (s, 3H); 1.50 (s, 3H); 1.45-2.20 (m, 6H); 1.85 (bs, 1H); 2.40 (d, J=17Hz, 1H); 2.95 (d, J=17Hz, 1H).

Mass (m/e): 198(M^+, 2); 170(6); 167(7); 139(34); 121(6); 111(15); 99(26); 86(100); 71(37); 69(53); 67(33); 55(65).

5,6,7,7a-tetrahydro-4,4,7a-trimethyl-2(4H)benzofuranone ((±)**2**)



± **2**

The same procedure for the preparation of the unsaturated ester 17 was followed.Hydroxylactone **5** (0.30g, 1.5 mmol) upon treatment with dry pyridine (0.144g, 0.15 ml, 1.8 mmol) and distilled thionyl chloride (0.216g. (0.13 ml, 1.8 mmol)and subsequent wok-up gave a residue which was chromatographed over silica gel with 20% ethyl acetate-pet.ether as eluent to yield (±) Dihydroactinidiolide **2** (0.261g, 96%).

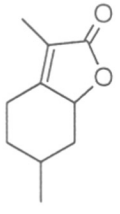
Mass (m/e): 184(M^+, 1); 154(3); 141(8); 119(10); 105(17); 97(14); 85(34); 84(19); 83(25); 71(25); 70(31); 69(37); 57(100); 54(52).

Analysis:

Calculated for $C_{10}H_{16}O_3$: C=65.19%; H=8.75%

Found : C=64.84%; H=8.79%

5,6,7,7a-tetrahydro-3,6-dimethyl 2(4H)benzofuranone (76, 77)



76,77

The same procedure as that for (±)**2** was followed.The hydroxylactone **117** (0.100g, 0.5 mmol) upon treatment with $SOCl_2$ (0.078g, 0.05ml, 0.65mmol) and dry pyridine (0.052g, 0.053ml, 0.65mmol) at 0°C furnishedof mint and isomintlactone (0.042g, 47%) in 4:1 ratio, as judged by ^{1}H-NMR.

IR ($CHCl_3$): 1760, 1690, 1460, 1410, 1260 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of diastereomers): δ 0.95, 1.10 (d, J=6.5Hz, 3H); 1.20-1.60 (m, 3H); 1.75 (s, 3H); 2.15-2.45 (m, 3H); 2.55-2.80 (m, 1H); 4.50-4.85 (m, 1H).

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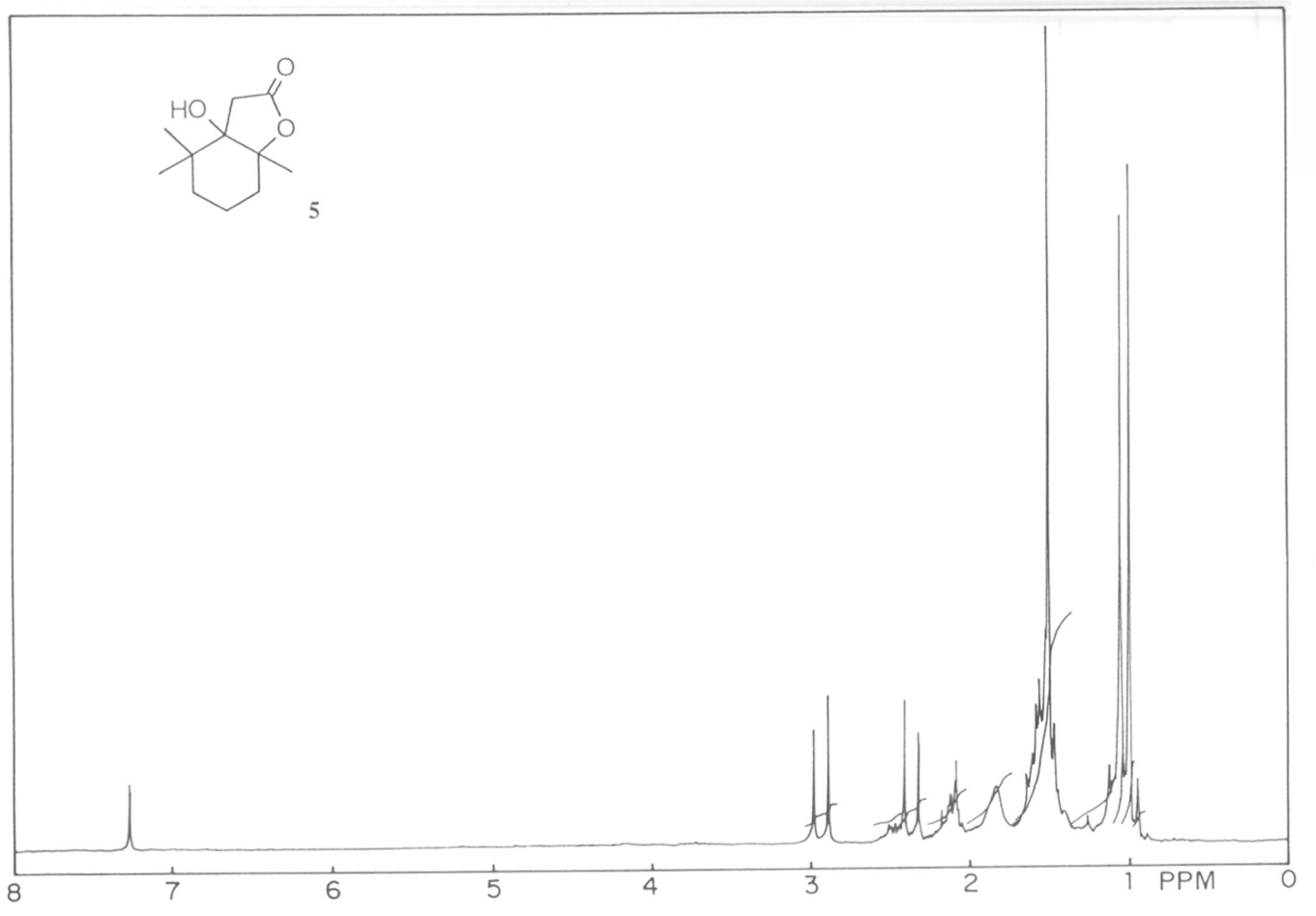

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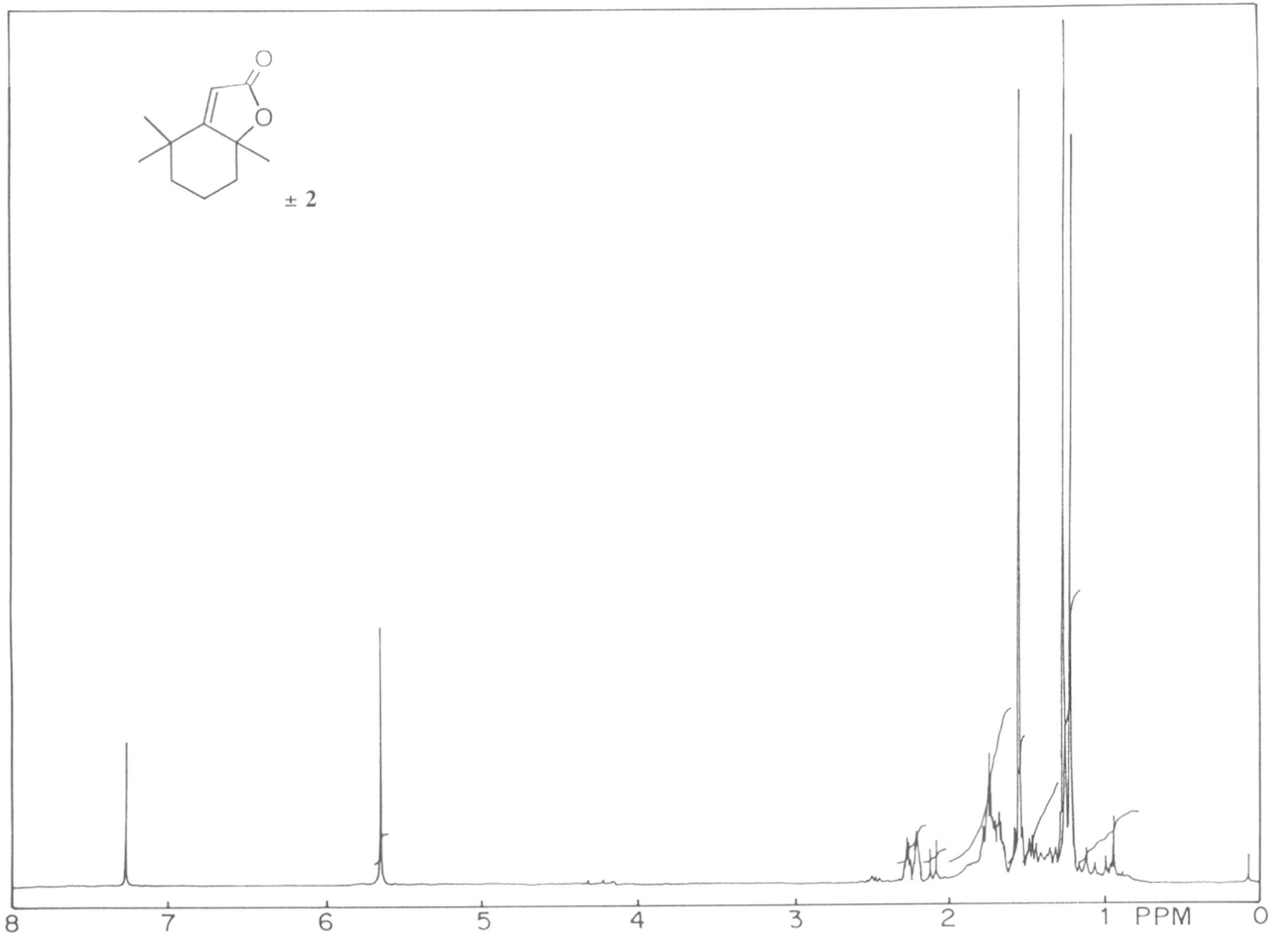

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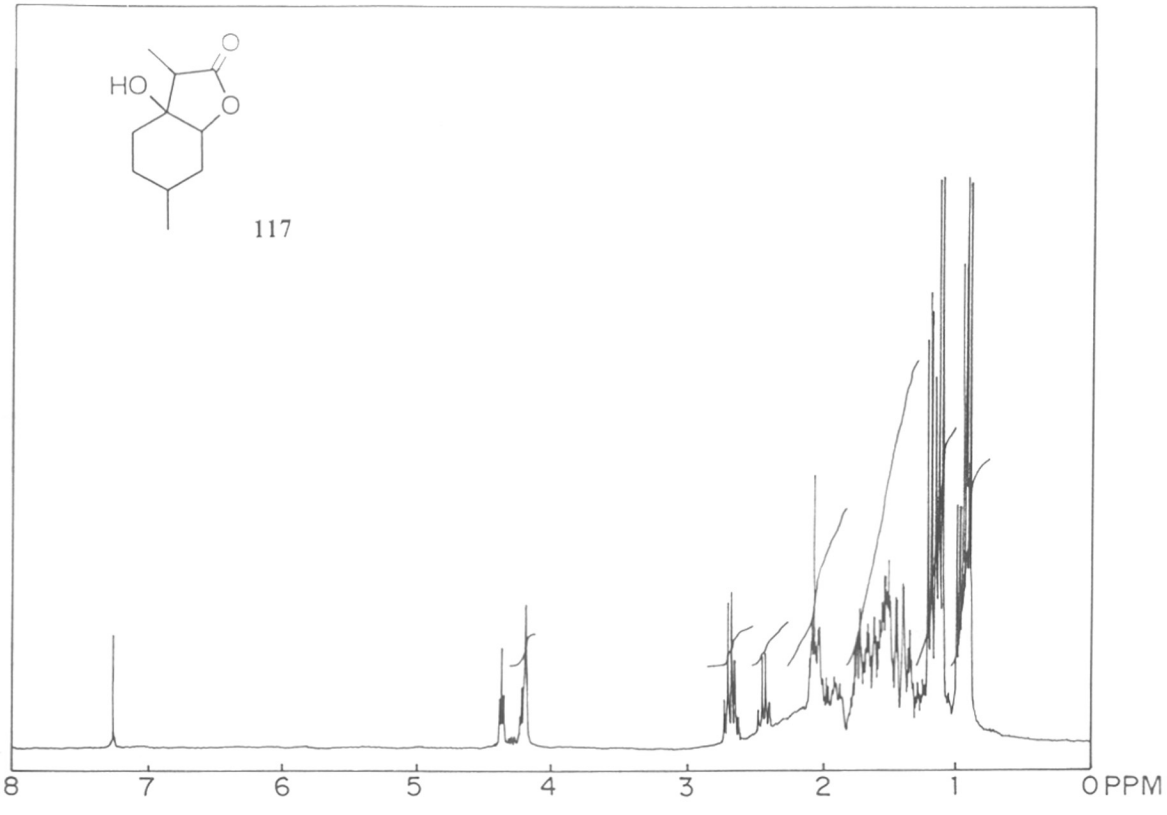

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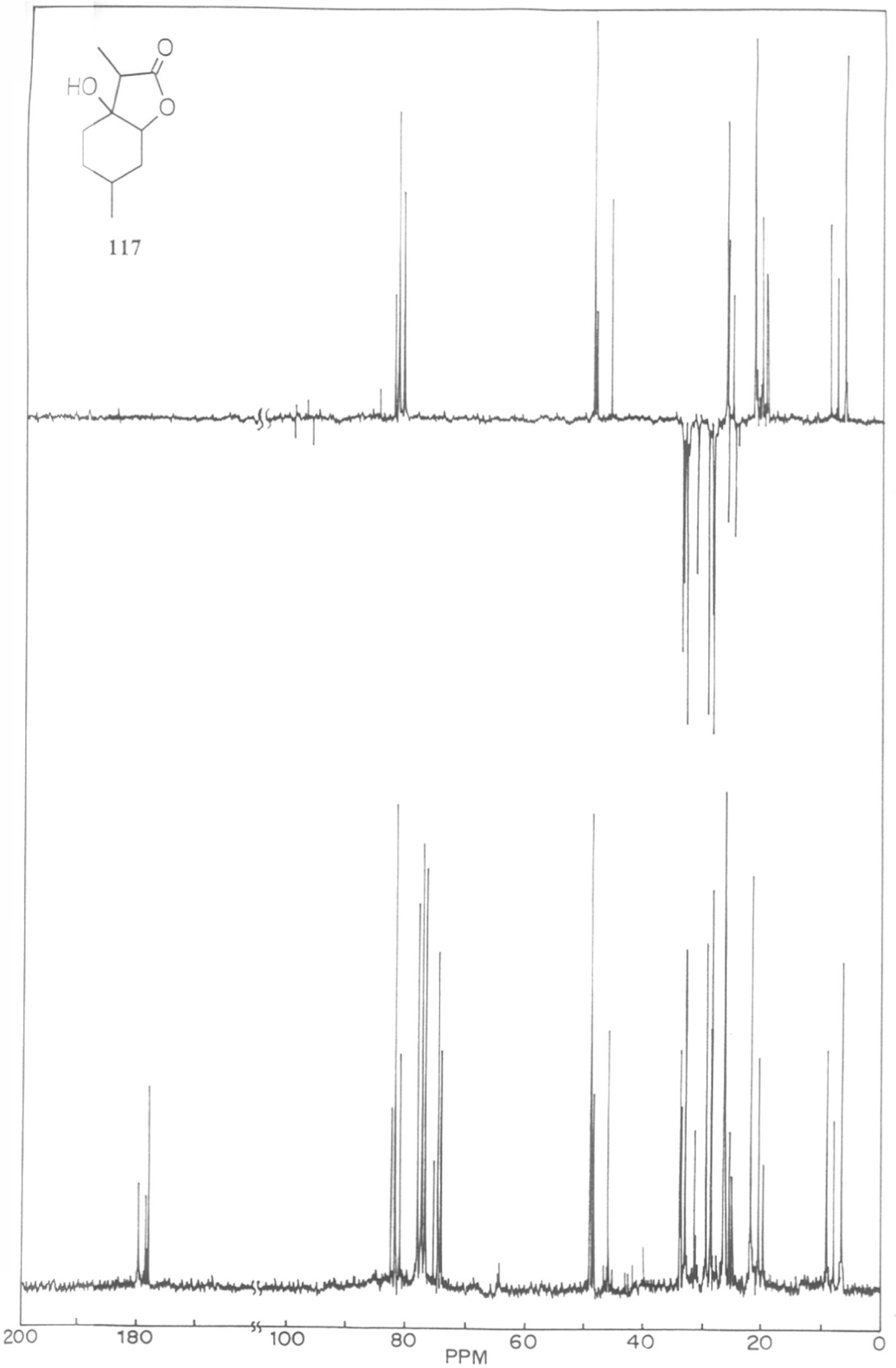

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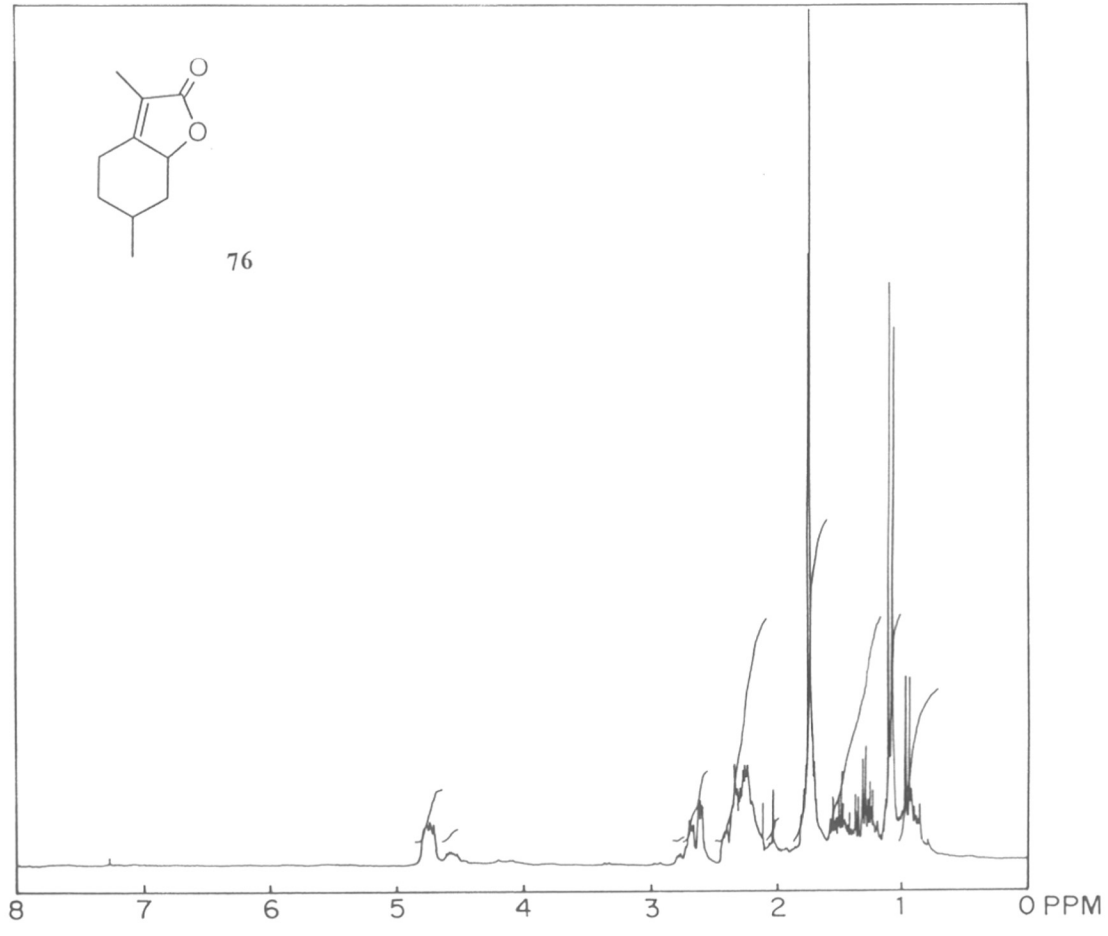


Spectrum no. 5

CHAPTER 2

Synthesis of Pseudopterosins

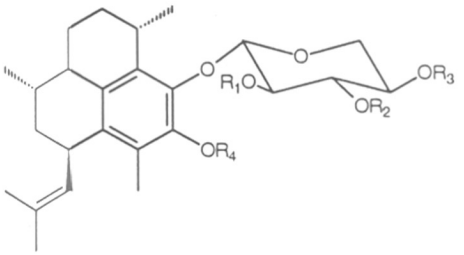
2.0 Introduction and Biological activity:

Pseudopterosins[1,2] are a new class of diterpene pentosides elaborated by the Carribean sea whips of the genus *Pseudopterogorgia* (*Gorgonidae*)

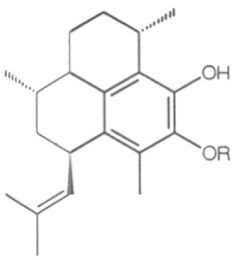
They represent a new structural class of anti-inflammatory and analgesic metabolites exhibiting potencies equivalent to and sometimes exceeding those of the standard commercial drug, Indomethacin.[1] Though active anti-inflammatory compounds, they are not prostaglandin H_2 synthase inhibitors, but appear to possess a unique, but as yet undefined pharmacological mechanism of action.

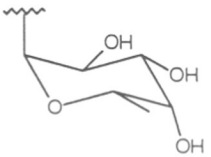
The pseudopterosins A-D (**1-4**) were isolated from *P. elizabethae* by Fenical and co-workers.[1] Though active, they also showed acute toxicities in the range of 50 mg/kg in mice. Exhaustive studies later led to the isolation of pseudopterosins E-L (**5-12**) by the same workers in 1990.[3]

The new pseudopterosins and pseudopterosin E (**5**) in particular possess superior anti-inflammatory properties and also are non-toxic in acute assays at levels in excess of 300 mg/kg. In cell studies using human neutrophils PsE inhibits the synthesis of leukotrienes, suggesting that the molecule is an antagonist of lipooxygenases or enzymes higher in the arachidonic cascade.

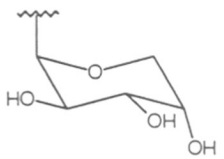


$R_1=R_2=R_3=R_4=H$	**Ps A**	**1**
$R_1=Ac, R_2=R_3=R_4=H$	**PsB**	**2**
$R_2=Ac, R_1=R_3=R_4=H$	**Ps C**	**3**
$R_3=Ac, R_1=R_2=R_4=H$	**Ps D**	**4**

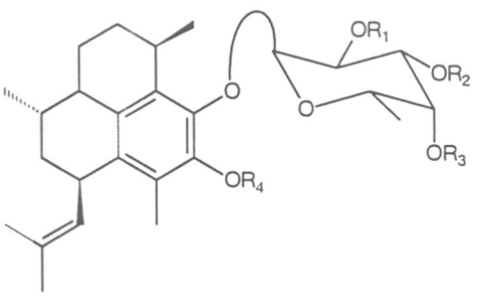


R = 

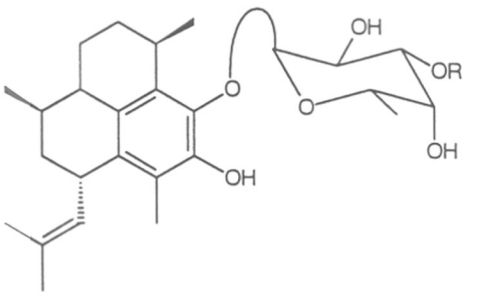
Ps E **5**

R = 

Ps F **6**



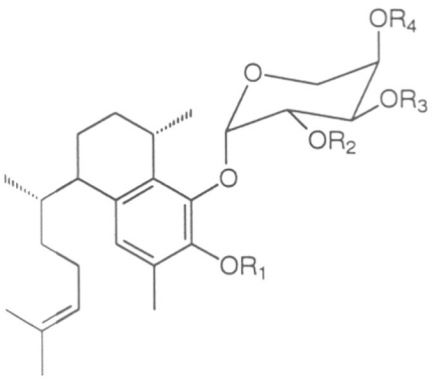
$R_1=R_2=R_3=H$	**Ps G**	**7**
$R_1=Ac, R_2=R_3=H$	**Ps H**	**8**
$R_2=Ac, R_1=R_3=H$	**Ps I**	**9**
$R_3=Ac, R_1=R_2=H$	**Ps J**	**10**



R = H	**Ps K**	**11**
R = Ac	**Ps L**	**12**

Fig.1

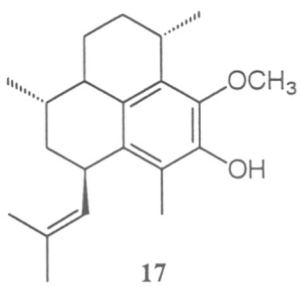
Seco-pseudopterosins A-D (**13-16**) have been isolated from *P. kallos* and show similar anti-inflammatory and analgesic properties.



$R_1=R_2=R_3=R_4=H$	**Seco A**	**13**
$R_2=Ac, R_1=R_3=R_4=H$	**Seco B**	**14**
$R_3=Ac, R_1=R_2=R_4=H$	**Seco C**	**15**
$R_4=Ac, R_1=R_2=R_3=H$	**Seco D**	**16**

Fig.2

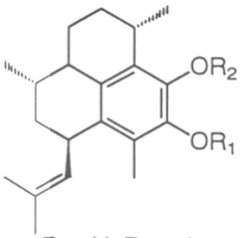
The methylated aglycone of PsE (**17**) has also been isolated from *P.elizabethae*, but was found to be an inactive metabolite.



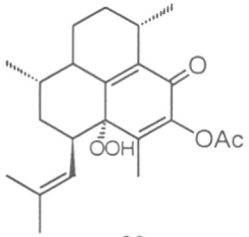
17

Fig. 3

The acetates of pseudopterosin aglycone **18** and **19**, the hydroperoxide **20** and the quinone **21** were subsequently isolated[5] from *P. elizabethae* by the same authors. No activity has been reported for these compounds.



R_1= H, R_2 = Ac **18**
R_2 =Ac, R_1= H **19**



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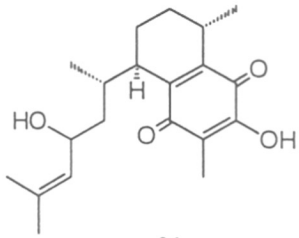
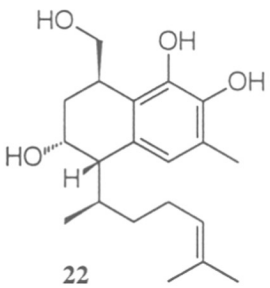


21

Fig. 4

The serrulatane diterpenes isolated[6] mostly from the genus *Eremophilia*, though differing in stereochemistry and certain substituents, are structurally similar to the seco-pseudopterosins.



22

Fig.5

Helioporins[7] are another structurally similar class of marine compounds related to the pseudopterosins. They were isolated by Higa *et al* from the blue coral *Heliopora coerulea*. Helioporins A (**23**) and B (**29**) are reported to exhibit antiviral activity while Helioporins C-G (**25-28**) show cytotoxicity.

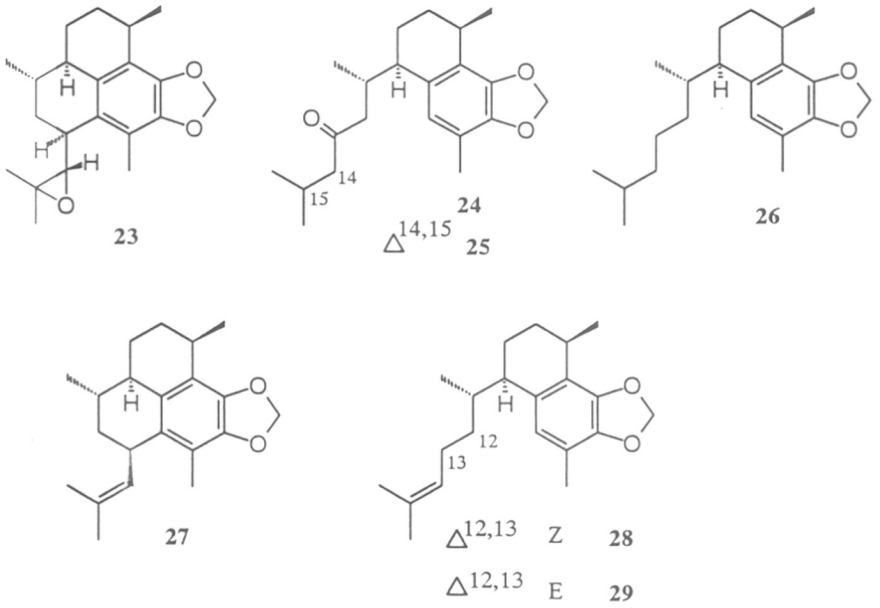


Fig. 6

The potent biological activities of these pregnane metabolites suggests that they are important new leads in the development of pharmaceuticals for the treatment of diseases involving abnormal phospholipid metabolism.

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SECTION 1

Pseudopterosins : A Review

2.1.0 Introduction

Interest in the synthesis of pseudopterosins has escalated greatly on account of their potent antiinflammatory and analgesic properties especially in view of the fact that they are more active than the standard commercial drugs.

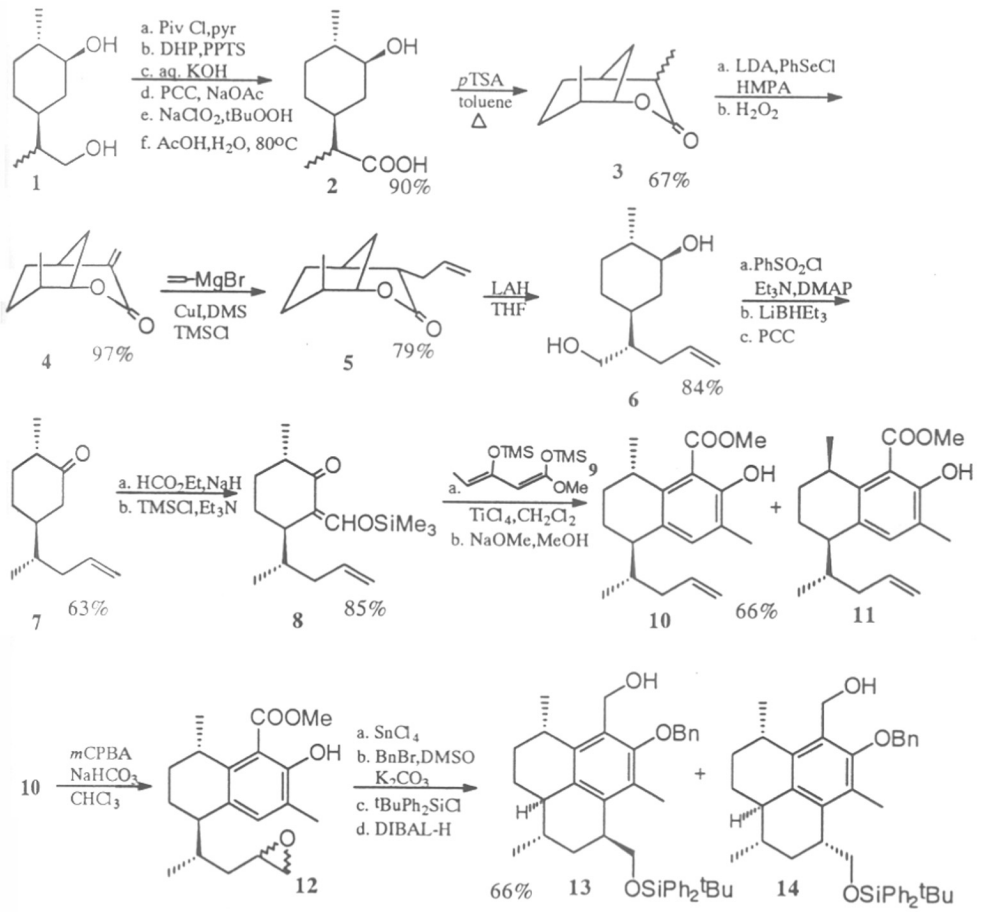
This is amply demonstrated by the number of reports of the synthesis of the aglycone, glycoside and the advanced fragments of Pseudopterosins A and E since their isolation in 1986.

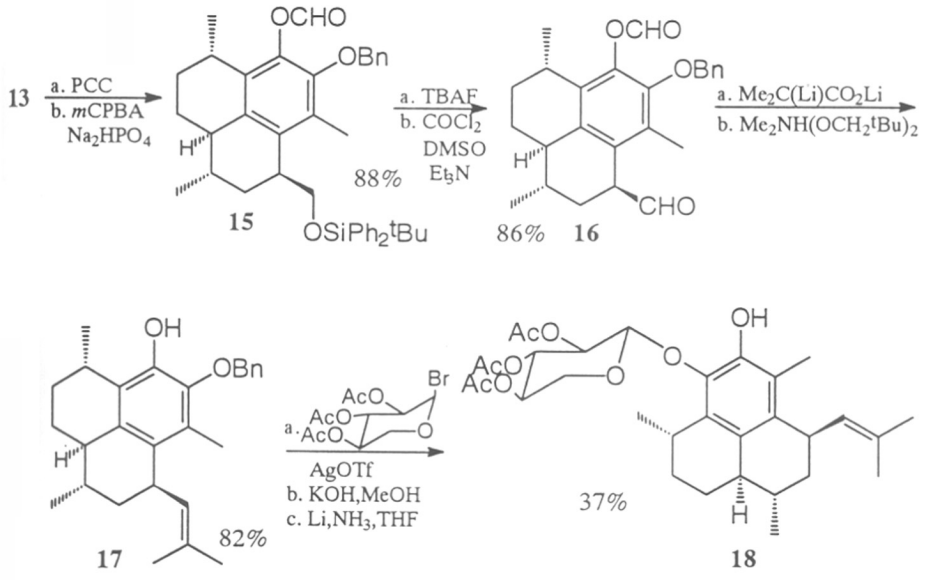
A brief review on the total synthesis and various strategies employed for the synthesis of pseudopterosins is presented in this Section.

Broka's Synthesis:[1] (1988, *Scheme 1*)

Broka *et al* reported the first total synthesis of Pseudopterosin A using S(-) Limonene as the starting material. S(-) Limonene was converted into epimeric diols **1** with thexylborane which was then converted into the hydroxy acid **2** *via* routine operations and lactonized to afford **3**. Selenation-oxidation followed by 1,4-addition of vinyl magnesium bromide provided **5** which upon reduction with LAH yielded the diol **6**. Selective sulfonylation of the primary hydroxy function, treatment with lithium triethylborohydride and PCC oxidation furnished the ketone **7**. Conversion of **7** into its hydroxymethylene derivative, followed by silylation gave **8**. $TiCl_4$ treatment of **8** in the presence of diene **9**, followed by treatment with base yielded the phenols **10** and 11. Peracid oxidation of **10** gave the epimeric epoxides **12**. Closure of the final ring was achieved by an intramolecular Friedel-Crafts alkylation using $SnCl_4$. Selective benzylation of the phenolic group, followed by silylation and DIBAL reduction gave a mixture of **13** and **14**. Oxidative removal of the benzylic methylene group was achieved by conversion of **13** to the

aldehyde using PCC, followed by Baeyer-Villiger oxidation effected by *m*CPBA. Desilylation and Swern oxidation yielded **16** which on treatment with the dianion of isobutyric acid, followed by (dimethylamino)formaldehyde dineopentyl acetal yielded the aglycone **17**. Glycosidation with acetylated xylose followed by deacetylation and debenzylation yielded PsA (**18**) in 0.84% overall yield.





Scheme 1

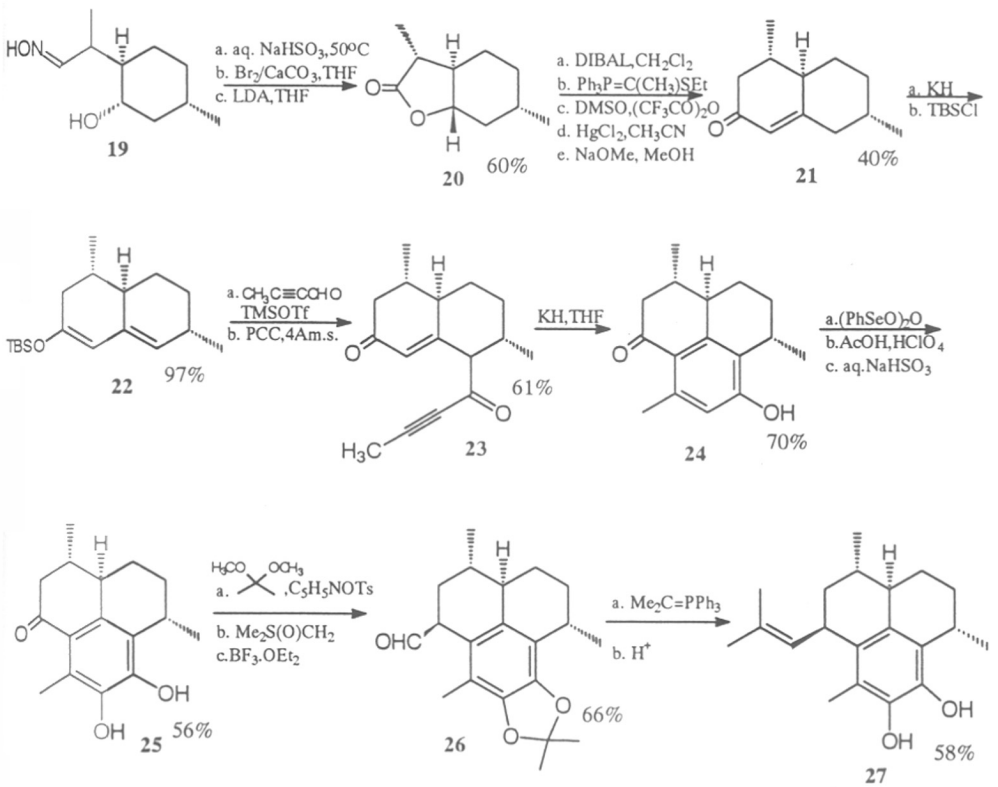
The key step involved in the synthesis is the novel and elegant construction of aromatic ring in one step by 3C+3C construction which incorporates phenol and methyl substituents in the proper disposition while the ester functionality had to be elaborated to phenol. The long synthetic strategy (32 steps) greatly reduces the yield and efficiency of the first total synthesis of Ps E.

Corey's **Synthesis**:[2] (1989, *Scheme 2*)

Oxime **19**, readily available from (+) menthol nitrite ester by photolysis, was the starting material for Corey's synthesis. Oxime hydrolysis with $NaHSO_3$, followed by oxidation of the resultant lactol to lactone and isomerization at C(8) using LDA yielded the γ-lactone **20**. Reduction of **20** using DIBAL, followed by Wittig chain extension employing $Ph_3P{=}C(CH_3)SEt$, Swern oxidation, thioester cleavage using Hg(II) and aldol cyclization of the resulting 1,5-

diketone with NaOMe yielded the enone **21**. Treatment of the enone **21** with KH, followed by treatment with TBDMSCl afforded the enol ether **22.** Aldol reaction of **22** with 2-butynal catalysed by TMSOTf, followed by PCC oxidation of resulting propargylic alcohol gave the diketone 23. Treatment of **23** with KH resulted in the cyclized compound **24** which upon orthohydroxylation yielded the catechol **25**.

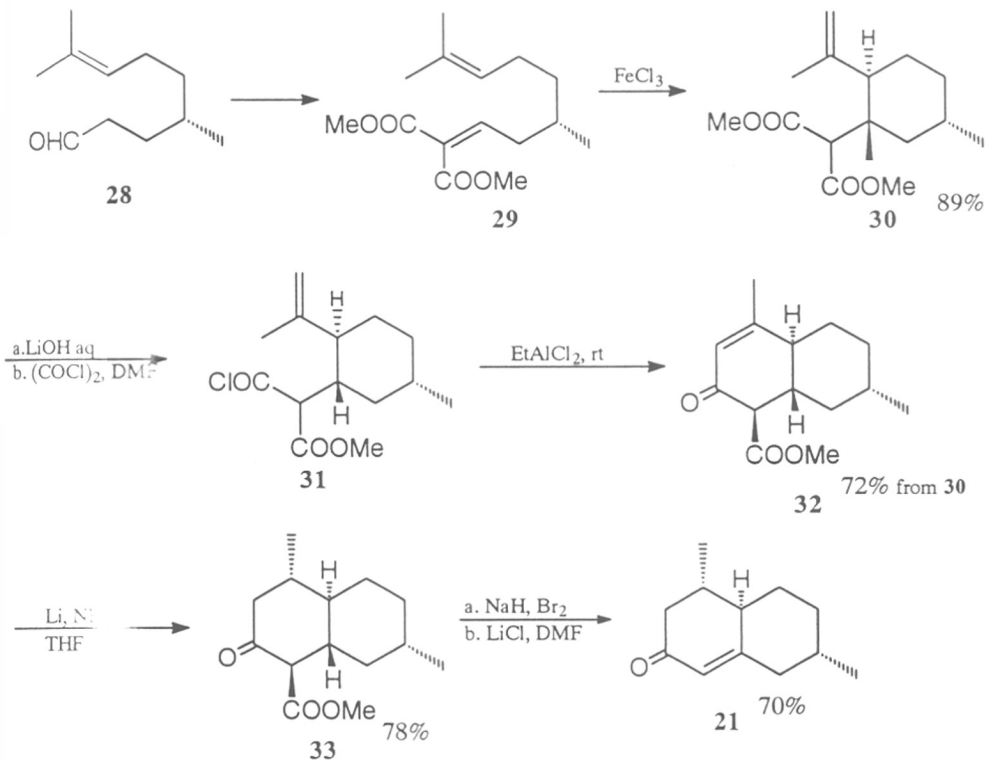
Catechol protection, followed by one-carbon homologation at the ketone yielded the aldehyde **26** which upon Wittig reaction with isopropylidenetriphenyl phosphorane and acid hydrolysis furnished the aglycone **27**.



Scheme 2

Further protection and glycosidation yielded PsA and PsE in an overall yield of 1.2 and 1.1% respectively.

Later, Corey *et al.*[3] reported a more efficient synthesis of the enone **21** from S(-) citronellal (*Scheme 3*). The unsaturated ester **29**, which was prepared by the reaction of S-citronellal with dimethyl malonate in the presence of piperidinium acetate was treated with $FeCl_3$ to yield the cyclic diester **30**. The diester **30** was converted into the monoacid chloride **31**.



Scheme 3

Treatment with ethyl aluminium dichloride, followed by reduction of the enone unit using Li in liquid ammonia afforded the saturated keto ester **33**. Compound **33** was then converted into

the pseudopterosin intermediate **21** by anion generation with NaH which was quenched with Br_2, followed by treatment with LiCl in DMF. The overall yield of **21** was 35% from **29** as compared to 24% of the previous synthesis.

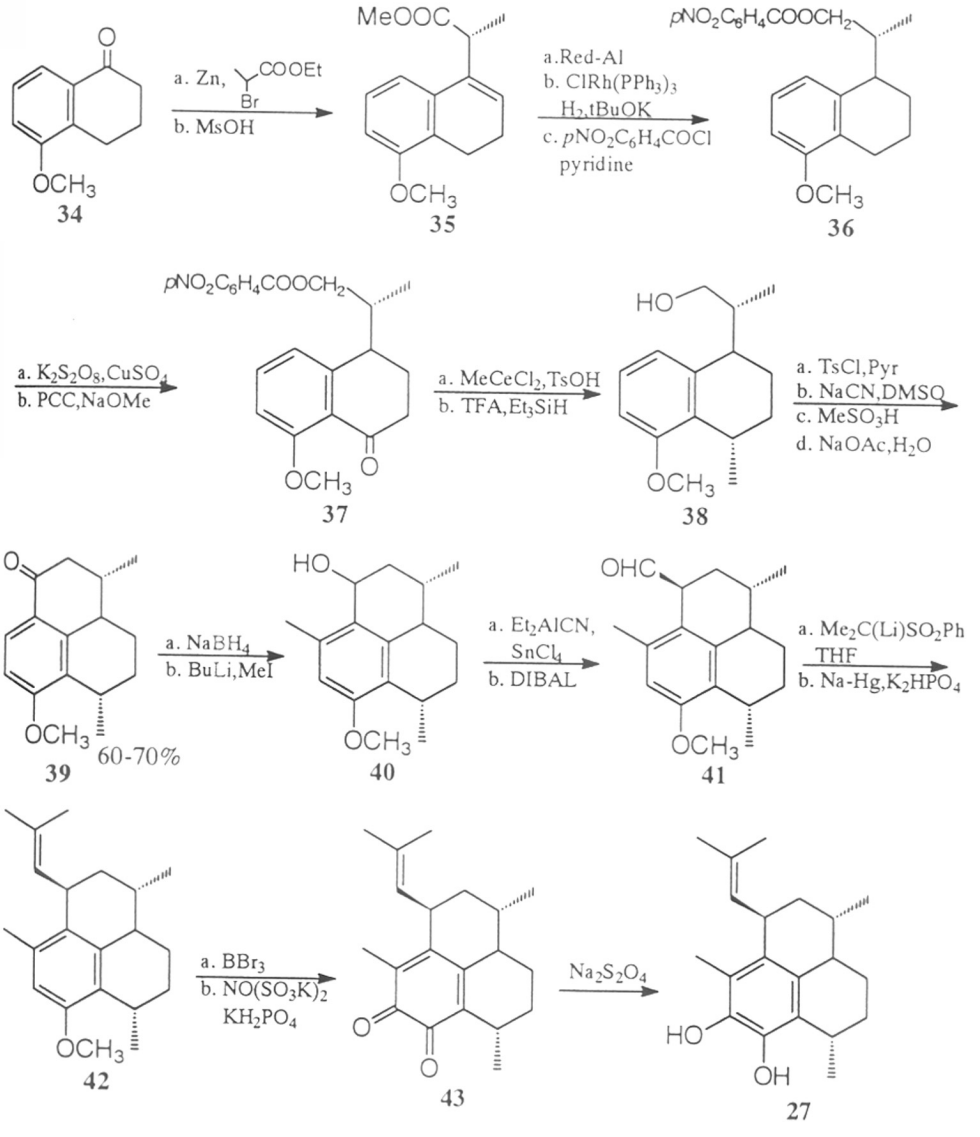
A noteworthy feature of this synthesis is that the chirality of the starting material namely menthol/citronellal is maintained throughout the sequence. However, the large number of steps decreases the overall yield of the final product. Use of toxic Hg salt is an added disadvantage of this synthesis.

McCombie's Synthesis:[4,5] (1990, *Scheme 4*)

McCombie's synthesis of PsE aglycone starts with Reformatsky reaction of 5-methoxy-1-tetralone with ethyl 2-bromopropionate, followed by dehydration to yield the olefin **35**. The ester was reduced to the alcohol which upon homogeneous hydrogenation using $ClRh(PPh_3)_3$ yielded the alcohol which was protected as its *p*-nitrobenzoate ester.

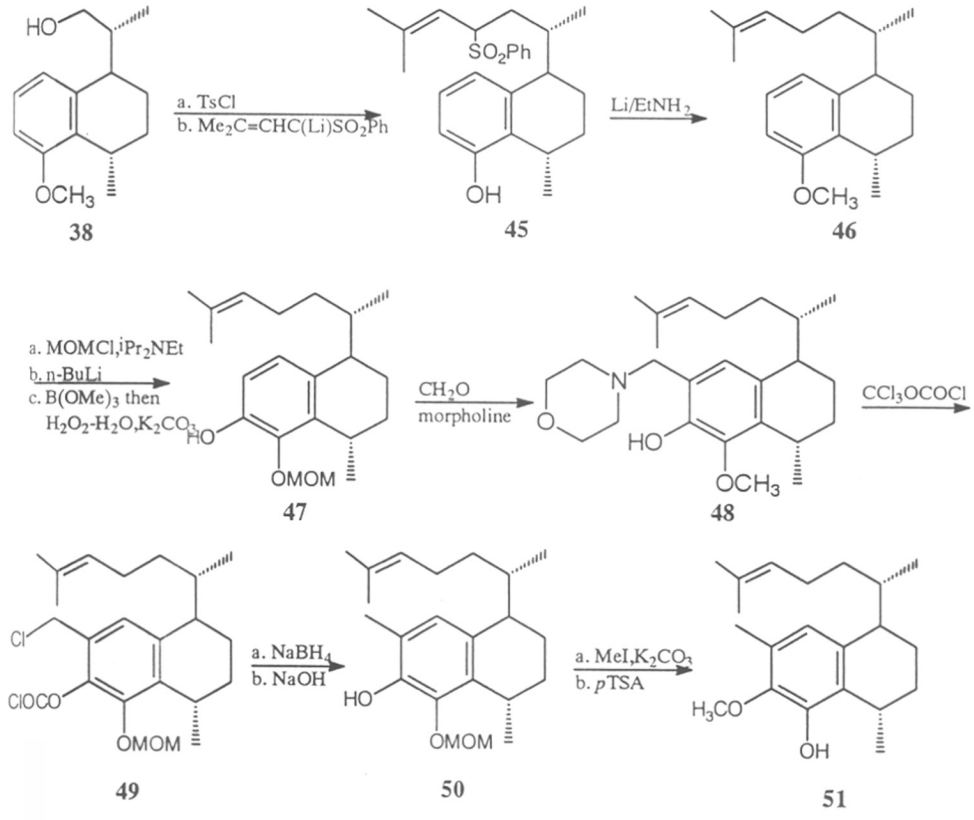
The *p*-nitrobenzoate **36** was oxidized using $K_2S_2O_8/CuSO_4$ to give a mixture of isomeric alcohols which was further oxidized to the ketone **37** using PCC. Hydrolysis followed by treatment with $MeCeCl_2$ and subsequent dehydration yielded the olefin which upon intramolecular hydride transfer of silane gave the alcohol **38**. The alcohol **38** was converted using standard reactions involving one carbon homologation into the tricyclic ketone **39**. $NaBH_4$ reduction, followed by alkoxide-directed metalation yielded the alcohol **40** which was converted into the aldehyde **41** *via* cyanation using $Et_2AlCN/SnCl_4$ and DIBAL reduction. Alkylation with $Me_2C(Li)SO_2Ph$, followed by desulfonylation yielded the deoxypseudopterosin derivative **42**.

Demethylation using BBr_3 followed by oxidation yielded o-quinone **43** which was reduced with sodium dithionite to the aglycone of PsE **27**.



Scheme 4

McCombie *et al* also reported[6] the synthesis of seco-pseudopterosin aglycone starting from the common intermediate **38** (*Scheme 5*). Tosylation followed by treatment with $Me_2C{=}CHCH(Li)SO_2Ph$ at -70°C afforded the diastereomeric mixture **45**. Desulfonylation and demethylation using $Li/EtNH_2$ yielded **46**. Protection, metallation, followed by treatment with $B(OMe)_2$ and work-up with H_2O_2-K_2CO_3 yielded the catechol ether **47**.



Scheme 5

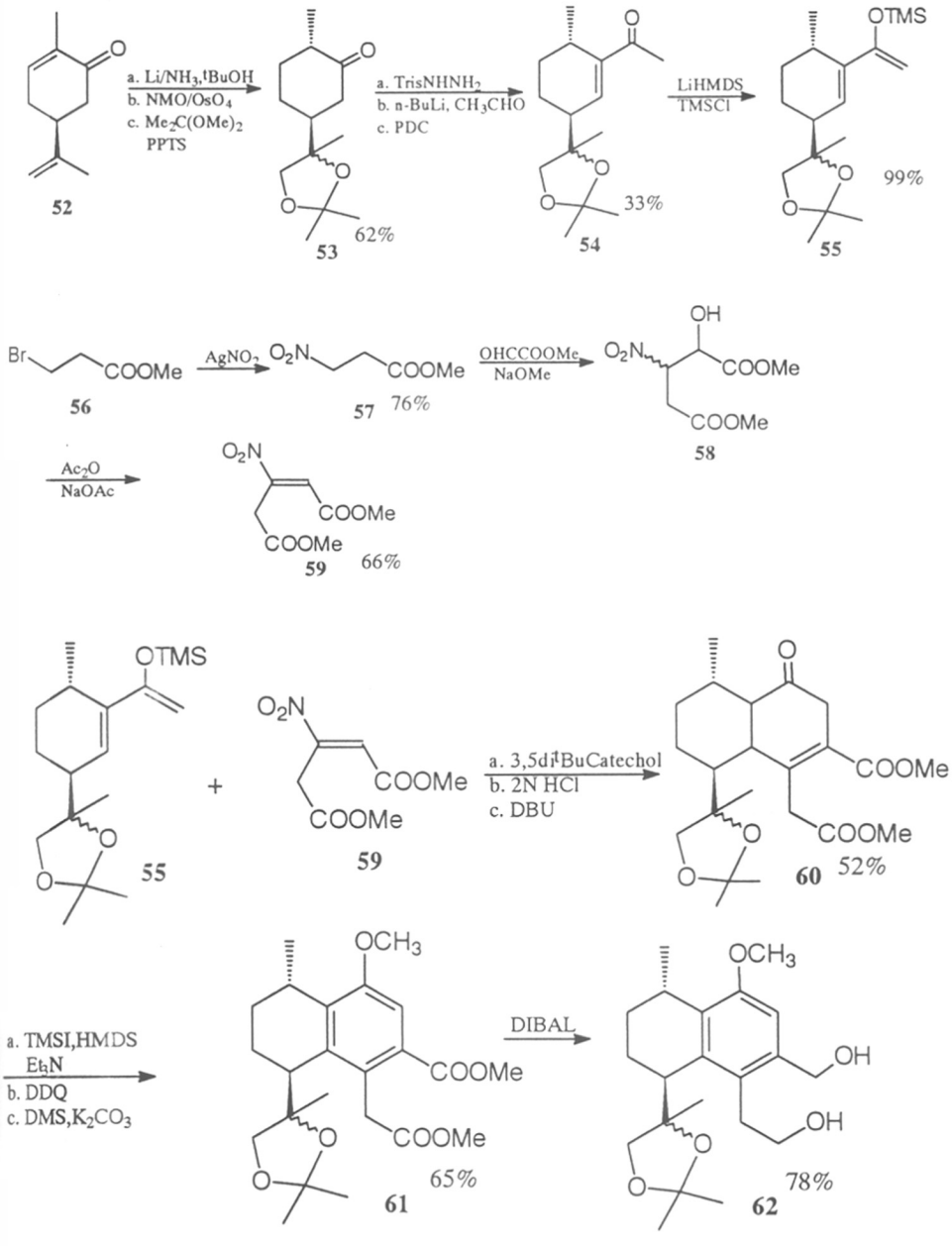
Mannich reaction with formaldehyde and morpholine yielded **48** which was converted into the chloromethyl compound **49** using CCl_3OCOCl. Reduction using $NaBH_4$, followed by

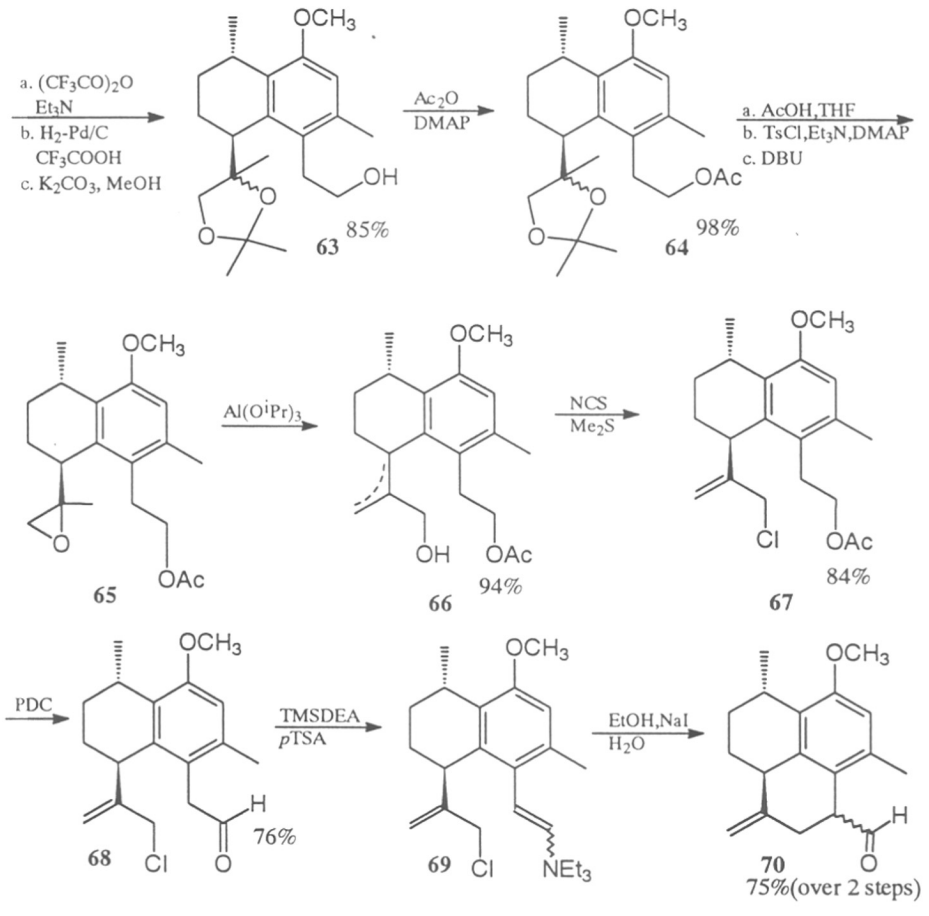
basic hydrolysis gave **50** which was converted into the methyl ether. Final hydrolysis of MOM ether with *p*TSA provided the aglycone of seco-pseudopterosin A **51**.

The use of expensive and toxic reagents are the main disadvantages in this otherwise simple and straightforward synthesis of PsE aglycone which involves elegant control of stereochemistry by intramolecular directed transfer of hydride during ionic hydrogenation.

Kozikowski's Approach:[7] (1991, *Scheme 6*)

This approach targetted the tricyclic ring structure of pseudopterosins as the key intermediate. The synthesis was initiated by the reduction of $\Delta^{2,3}$ bond of (S)-carvone using Li/NH_3. Hydroxylation of the $\Delta^{8,9}$ double bond, followed by acetonide protection of resulting diol yielded **53** which was then converted into the α,β-unsaturated ketone **54** *via* Shapiro reaction with aldehyde and PDC oxidation of resulting alcohol. The ketone was then converted into the key siloxydiene **55**. Treatment of methyl 3-bromopropionate with $AgNO_2$, followed by condensation with OHC·COOMe and elimination of resulting alcohol yielded the dienophile **59**. Diels-Alder reaction between diene **55** and dienophile **59** followed by hydrolysis and elimination of nitro group afforded a mixture of diastereomers **60** which was aromatized *via* the silyl enol ether employing DDQ as the oxidant. Methylation of resulting phenol yielded **61** which was reduced using DIBAL to yield diol **62**. Hydrogenolysis of the benzylic alcohol *via* the trifluoroacetate ester yielded the mono alcohol **63** which was protected as the acetate **64**.


a. Li/NH3,tBuOH
b. NMO/OsO4
c. Me2C(OMe)2
PPTS
52
53
62%
a. TrisNHNH2
b. n-BuLi, CH3CHO
c. PDC
54
33%
LiHMDS
TMSCl
OTMS
55
99%
Br
COOMe
56
AgNO2
O2N
57
76%
OHCCOOMe
NaOMe
OH
58
Ac2O
NaOAc
59
66%
+
a. 3,5di-tBuCatechol
b. 2N HCl
c. DBU
60
52%
a. TMSI,HMDS
Et3N
b. DDQ
c. DMS,K2CO3
OCH3
61
65%
DIBAL
62
78%



Scheme 6

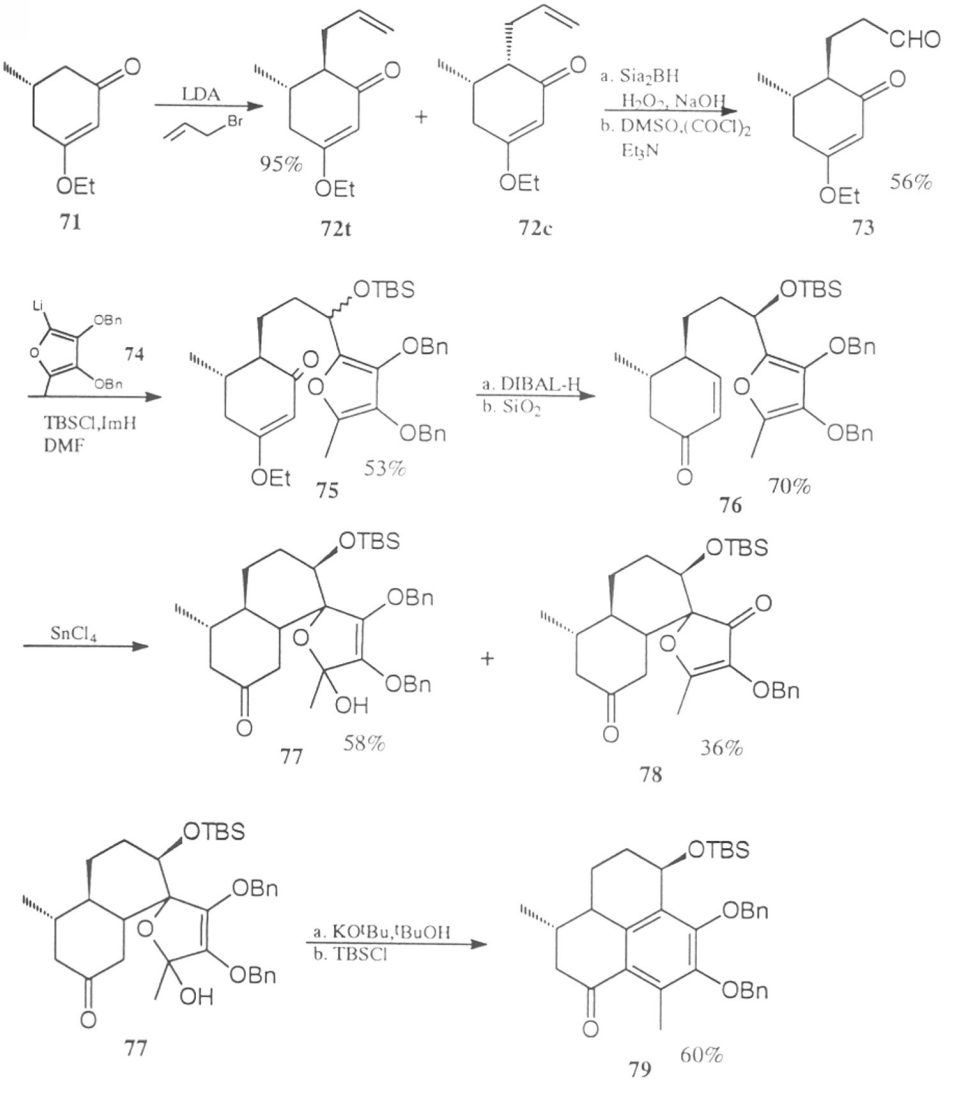
Hydrolysis of the acetonide, tosylation and treatment with DBU yielded the epoxide **65**. Ring opening of epoxide was effected by aluminium isopropoxide to furnish diol **66**. Treatment with NCS-Me_2S effected selective conversion to the allylic chloride **67** which was subsequently converted to the enamine **69** *via* the aldehyde **68**. Heating in EtOH/NaI, followed by hydrolysis

yielded the diastereomeric mixture of **70a** and **70b** which can be further elaborated to pseudopterosins.

The use of Diels-Alder reaction for B ring formation though novel for the synthesis of these skeletons has been achieved in only 52% yield. The long reaction times coupled with the low overall yield of 1.76% greatly diminishes the practical utility of this synthesis.

Jung's Approach:[8] (1993, *Scheme 7*)

Jung *et al* reported an approach to the substituted phenalene ring system of the pseudopterosin starting from 5-methyl-3-ethoxycyclohexanone **71**. Alkylation of **71** with allyl bromide yielded the alkenes **72t** and **72c**. Hydroboration-oxidation using disiamylborane/H_2O_2 followed by Swern oxidation of resulting alcohol yielded the aldehyde **73**. Reaction of **73** with the lithiated furan **74** gave the alcohol which was silylated to yield **75**. The β-ethoxy enone was converted to the enone **76** *via* DIBAL reduction followed by elimination on silica gel. Treatment of the furyl enone **76** with stannic chloride yielded the hemiacetal **77** alongwith the elimination product **78** *via* intramolecular Michael reaction. Further reaction of **77** with potassium tert-butoxide, followed by silylation yielded the phenalene **79** which can be used as an intermediate for the synthesis of pseudopterosin A.



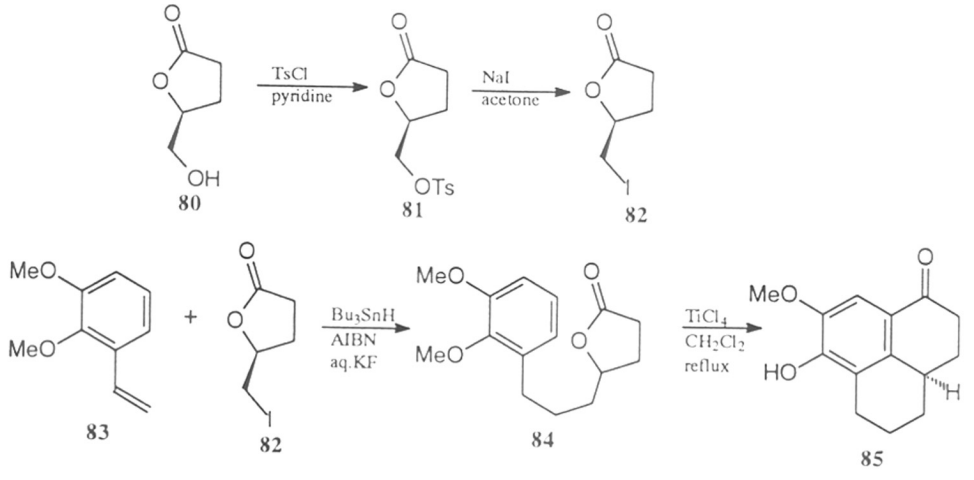
Scheme 7

The key step in this strategy is the intramolecular Michael addition of the electron rich furan onto the cyclohexenone in compound **76** which, however, proceeds in moderate yields (58%).

Harrowven's Approach:[9] (1994, *Scheme 8*)

Harrowven *et al* reported a synthetic methodology towards the tricyclic core of the pseudopterosins using intramolecular Friedel-Crafts alkylation-acylation protocol.

γ-hydroxybutyrolactone (**80**) was tosylated and converted to the iodide **82** *via* standard reaction procedures. Tin mediated radical reaction was used to couple the iodide **82** with 2,3-dimethoxystyrene (**83**) to yield the lactone **84**. Exposure of the lactone **84** to $TiCl_4$ smoothly effected intramolecular Friedel-Crafts alkylation-acylation reactions and also unmasked the para-phenolic moiety to yield the tricyclic ketone **85**.

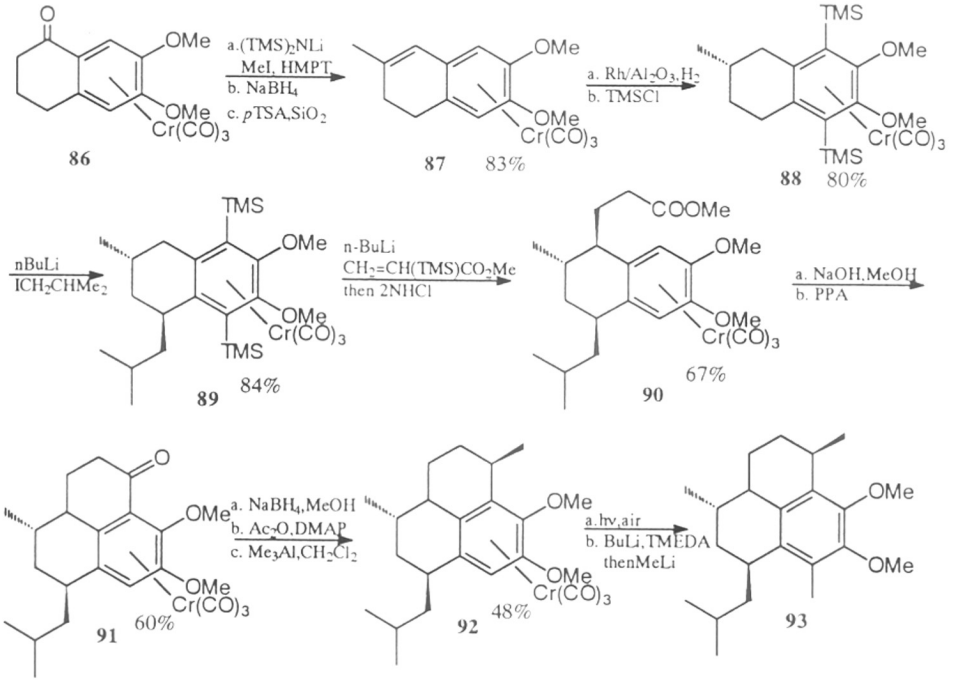


Scheme 9

The cascade reaction sequence has been elegantly used for the rapid elaboration of the tricyclic ketone intermediate which is structurally similar to Corey's intermediate. The cyclization (**84→85**) also leads to a differentiation between the two phenolic groups which is necessary for attaching the glycosidal residues.

Schmalz's Synthesis:[10] (1994, *Scheme 10*)

Schmalz's synthesis of substituted hydrophenalene of pseudopterosins starts with the conversion of 6,7-dimethoxy-1-tetralone to the non-racemic 1-tetralone $Cr(CO)_3$ derivative **86** which is then converted into the dihydronaphthalene derivative **87** *via* α-metallation, reduction and dehydration reactions. Rhodium catalyzed hydrogenation followed by bis-silylation with TMSCl yields the endo complex **88**. Benzylic deprotonation using n-BuLi, followed by treatment with isobutyl iodide furnishes the alkylated product **89**.



Scheme 10

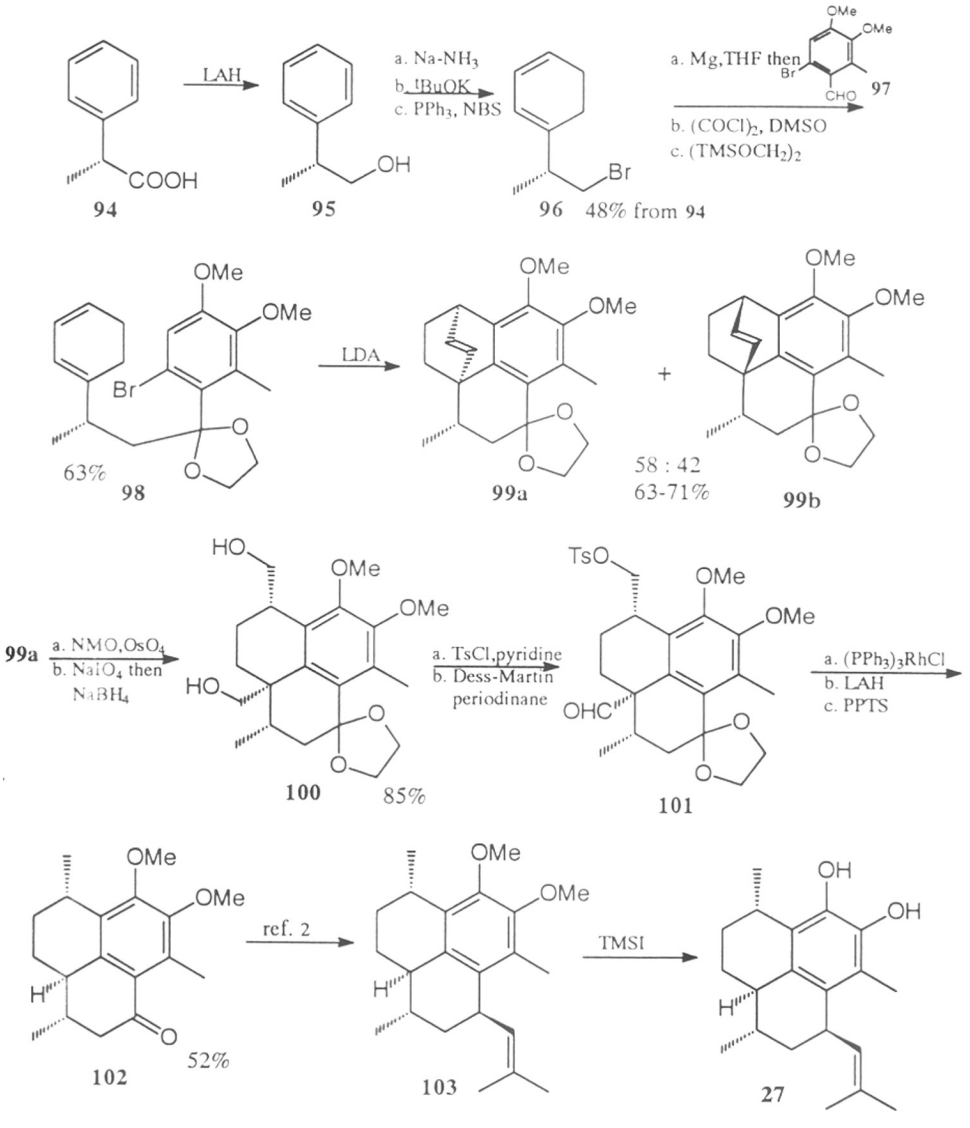
A second benzylic alkylation with methyl α-trimethylsilyl acetate, followed by desilylation using fluoride ion yielded the ester **90** as a single diastereomer. Hydrolysis followed by Friedel-Craft's cyclization using PPA furnished the tricyclic complex **91**, Boranate reduction of ketone, acetylation and treatment with Me_3Al yielded the

oxomethylated product **92**. Oxidative decomplexation followed by methylation using nBuLi/MeI yielded the hydrophenalene **93**.

A unique feature of this elegant synthesis is that almost the complete synthesis is carried out with the complexed ligand thus maintaining stereochemical information and manipulations of the alkyl substituents in a stereospecific manner. However, handling problems of the air and light sensitive chromium carbonyl complexes coupled with the low yield of the final methylation which yields significant amounts of side products greatly decrease the practical utility of this synthesis.

Buszek's Synthesis:[11] (1995, *Scheme 11*)

The synthesis commenced with (R)(-)-2-phenylpropionic acid (**94**), reduction of which with LAH yielded alcohol **95**. Birch reduction of **95**, followed by base-induced isomerization and bromination with NBS/PPh_3 yielded the 1-substituted cyclohexadiene **96**. Grignard reaction of the bromide **96** with the aldehyde **97** (derived from 2-methyl piperonal in 7 steps) yielded a mixture of benzylic alcohols which upon Swern oxidation and protection as its 1,3-dioxolane acetal under Noyori conditions furnished the benzyne precursor **98**. Intramolecular benzyne Diels-Alder reaction (IMBDA) under LDA conditions furnished a 58:42 mixture of diastereomers **99a** and **99b**. Oxidative cleavage of the olefinic bridge in **99a** using OsO_4/NMO yielded the diol **100**. Selective protection of less hindered alcohol, followed by Dess-Martin oxidation yielded the aldehyde **101**. Stereospecific decarbonylation using Wilkinson's catalyst, followed by nucleophilic displacement of the tosylate with hydride and deacetalization with PPTS yielded the hexahydrophenalen-1-one **102**. Introduction of isobutenyl side chain using Corey's method[2], followed by deprotection of the methyl ethers with TMSI provided the aglycone **27** in 19 steps.



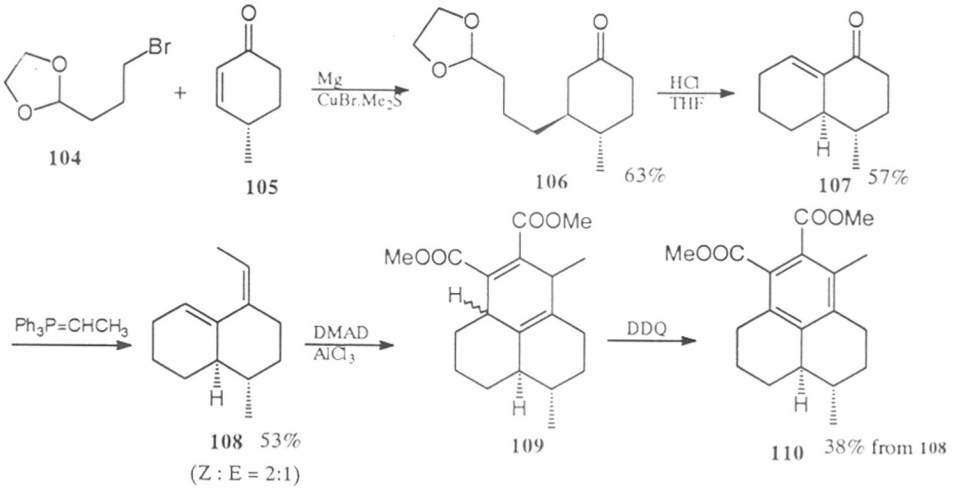
Scheme 11

The novel use of intramolecular Diels-Alder reaction involving benzyne and a tethered diene has been well demonstrated in this synthesis. Even though regiospecific, the reaction leads to a 1:1 mixture of diastereomers **99a** and **99b**.The decarbonylation with stoichiometric

amount of rhodium catalyst limits the utility of this otherwise elegant synthesis from a practical viewpoint.

Frejd's Approach:[12](1996, *Scheme 12*)

Frejd *et al* reported a synthetic route towards the tricyclic hexahydrophenalene derivative of pseudopterosins. Treatment of 4-methyl-cyclohex-2-en-1-one (**105**) with the Grignard reagent (prepared from the bromodioxolane **104**) catalyzed by $CuBr.Me_2S$ gave the protected keto aldehyde **106**. Subsequent acidic hydrolysis of **106** also induced the aldol condensation to the ketone **107** which on treatment with ethyl phosphorane furnished the diene **108** as a mixture of isomers. Diels-Alder reaction of the diene **108** with dimethyl acetylenedicarboxylate (DMAD) in presence of $AlCl_3$ yielded the diester **109**. Aromatization of **109** with DDQ furnished the tricyclic compound **110** which may serve as an intermediate in the synthesis of pseudopterosins and congeners.



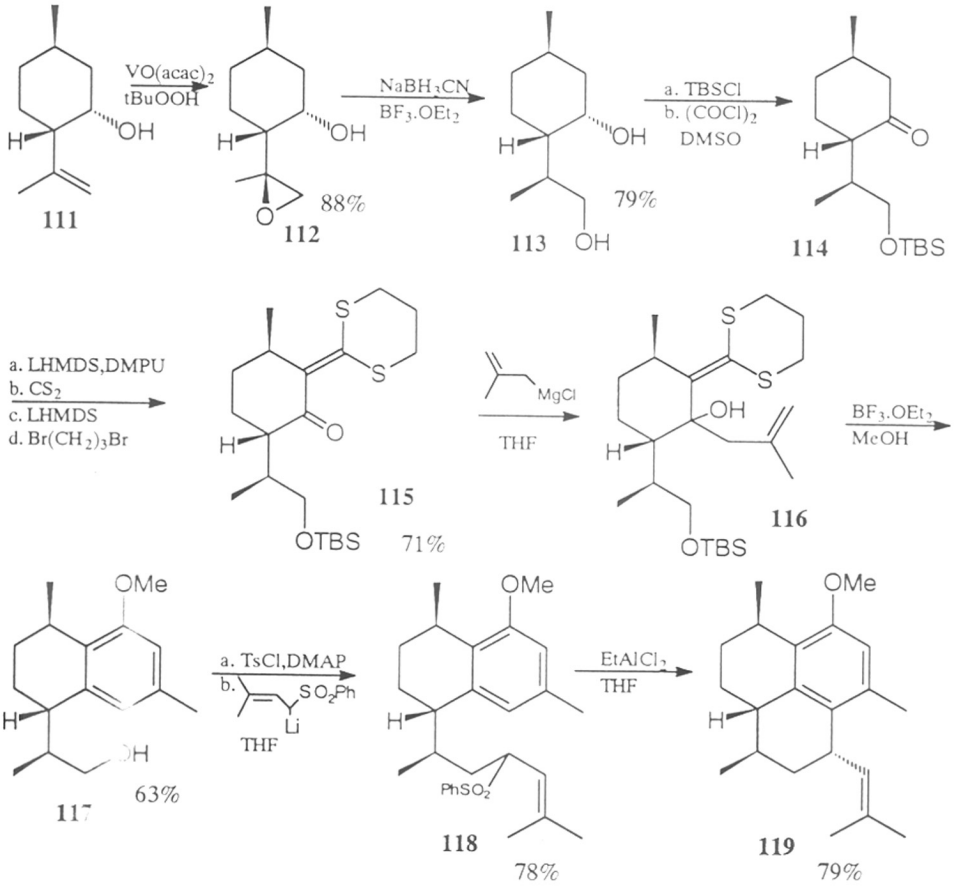
Scheme 12

This is one of the shortest synthetic route towards the tricyclic intermediate of pseudopterosins. However, the low yields especially in the Diels-Alder and aromatization reactions greatly diminish the usefulness of this methodology.

Having completed the model studies towards pseudopterosin framework and during the course of studies directed towards total synthesis of pseudoptrosin, Kocienski published a report conceptually similar to the present work.

Kocienski's Synthesis:[13] (1996, *Scheme 13*)

Kocienski's synthesis targetted the tricyclic core of pseudopterosins K and L. Hydroxy group directed epoxidation of (1S,2S,5R)-*neo*-isopulegol (**111**) readily available from commercial (1R,2S,5R)-isopulegol, yielded the oxirane **112** which was cleaved by reduction with $NaBH_3CN$ in the presence of $BF_3.OEt_2$ to give the diol **113**. Selective protection of the primary alcohol as the silyl ether, followed by Swern oxidation yielded the ketone **114**. Ketone **114** was then converted into the α-oxoketenedithioacetal **115** by a one-pot four step procedure involving reaction of lithium enolate derived from **114** with CS_2, followed by a second enolization and trapping of the intermediate ketone with 1,3-dibromopropane. Addition of methallyl magnesium chloride to the ketone **115**, followed by treatment of the crude alcohol with $BF_3.OEt_2$ in the presence of methanol gave the methoxy arene **117**. Alcohol **117** was converted into tosylate and alkylated with lithio derivative of 3-methylbut-2-enyl phenylsulfone to afford the sulfone **118** as a mixture of diastereomers (1:1). Treatment of the mixture of sulfones **118** with $EtAlCl_2$ yielded the tricyclic aglycone **119**.



Scheme 13

The 13-step stereoselective synthesis yields the aglycone of pseudopterosins K and L in an overall yield of 14%. The application of Dieter's work for the conversion of α-oxoketene dithioacetal to the aromatic ring is noteworthy. However, the use of highly expensive reagents might prove to be the main shortcomings of this otherwise elegant synthesis.

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SECTION 2

Methodology Towards the Tricyclic Skeleton of Pseudopterosins

2.2.0 Introduction

The literature survey of Pseudopterosin aglycone revealed that a wide variety of approaches had been utilized for the synthesis of these molecules.

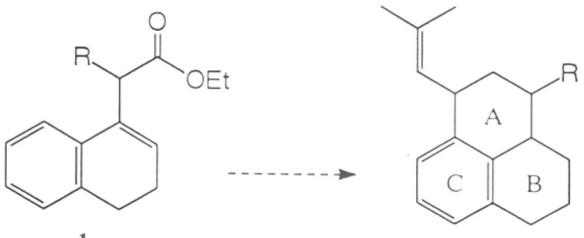
However, it was observed that none of the syntheses furnished the target molecules in good yield. They are long winded procedures and generally require the use of expensive reagents. Also most of the routes targeted a single isomer of pseudopterosins as the final product.

The aglycone of pseudopterosins bear a common tricyclic framework with the alkyl and vinyl substituents in different dispositions. In this respect, they bear a striking similarity towards Helioporin E, which is also a bioactive compound.

In view of the extremely potent bioactivities of the pseudopterosins and the related helioporins, it was proposed to develop a synthetic methodology for the carbon framework of these molecules. This methodology could be further elaborated for the synthesis of one or more isomers of the pseudopterosin aglycone.

2.2.1 Present Work

In connection with the development of methodologies towards butenolides and synthesis of a novel class of sesquiterpene lactones *viz.* Heritol, Heritonin and related compounds, a variety of β,γ-unsaturated esters had been synthesized (Chapter I). These β,γ-unsaturated esters bear a striking similarity to the pseudopterosin and helioporin skeletons. In order to convert these bicyclic molecules into the tricyclic compounds, only a one-carbon insertion between the aromatic ring and the tethered electrophile is required (*Fig. 1*).

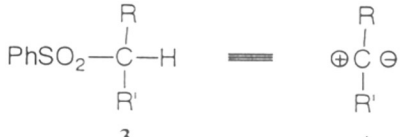


1 2

Fig. 1

Sulfones have been generally used as building blocks due to their ability to stabilize a negative charge on an adjacent carbon atom. They are utilized less frequently in Lewis acid mediated Friedel-Crafts type cyclizations, wherein the carbon-sulfur linkage is replaced by a carbon-carbon bond.

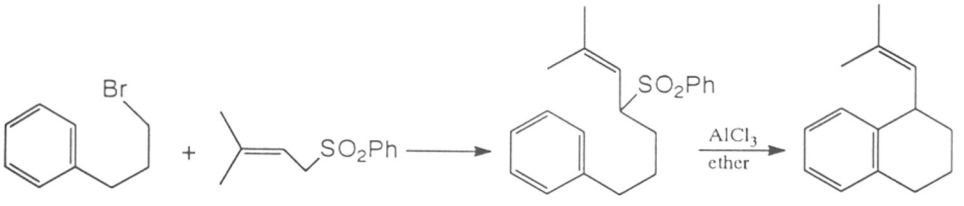
Recently, Trost *et al*[1,2] reported the 'chameleon-like' nature of sulfones demonstrating their ability to become either nucleophiles or electrophiles depending on the environment. The combination of these reactivities converts an organosulfone into a 1,1-dipole (*Fig. 2*).



3 4

Fig. 2

The authors utilized this dual reactivity for the alkylation of prenyl sulfone with the bromide **5**, followed by $AlCl_3$ mediated cyclization to yield the product **8**.(*Scheme 1*)

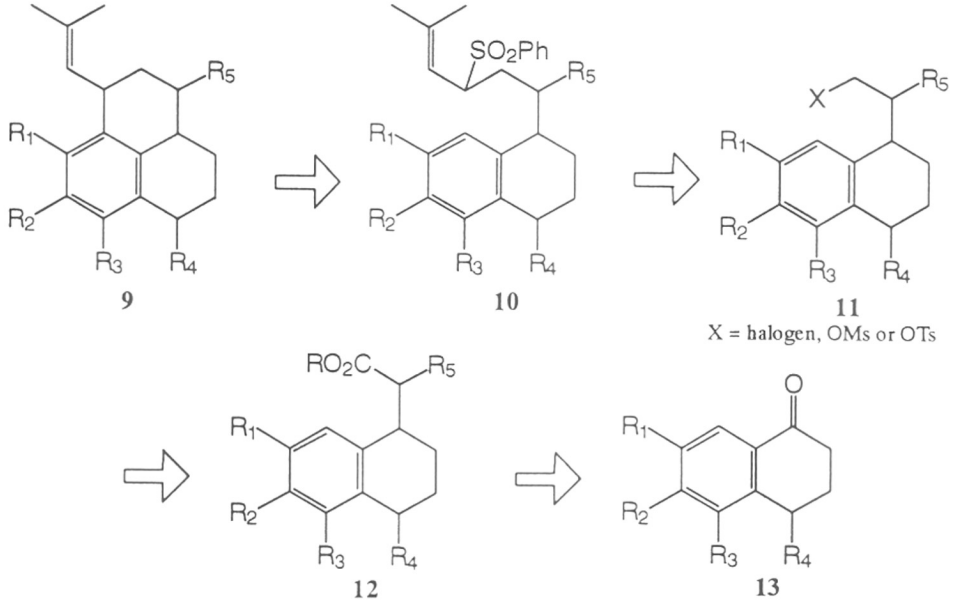


5 6 7 8

Scheme 1

It was reasoned that advantage can be taken of this remarkable dual reactivity of allyl sulfones for the development of a synthetic strategy towards the tricyclic core of pseudopterosins.

The retrosynthetic strategy of the tricyclic skeleton based on Trost's report indicates that the sulfone **10** can be a precursor to the same. The sulfone **10** could be easily prepared *via* an alkylation of the intermediate **11** which in turn can be accessed from the tetralone **13** through the ester **12** (*Scheme 2*).



9 10 11

X = halogen, OMs or OTs

12 13

Scheme 2

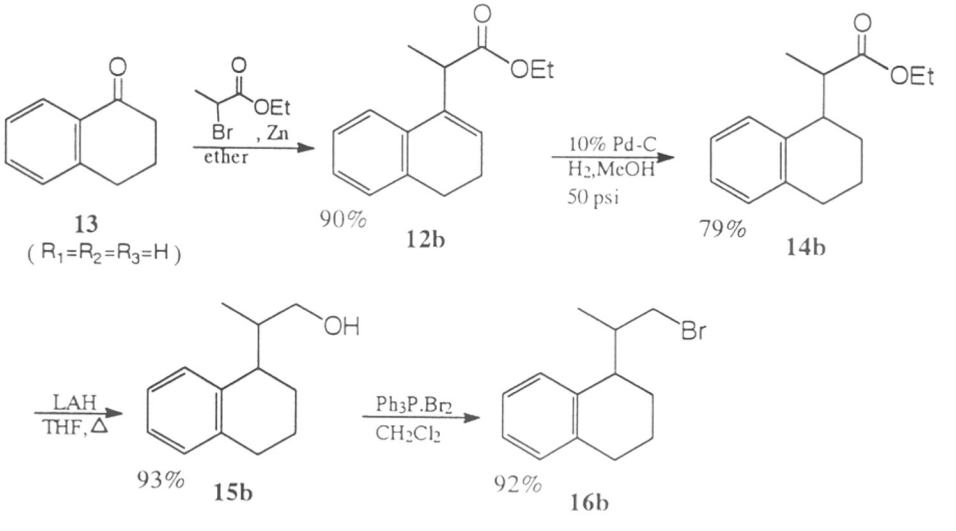
Thus, a variety of compounds with the pseudopterosin skeleton could be prepared. In the present strategy, the emphasis was laid on the construction of the tricyclic framework in a most convenient and efficient fashion without much emphasis on the stereochemical outcome.

2.2.2 Results and Discussion:

The β,γ-unsaturated esters were readily prepared by the Reformatsky reaction on the corresponding tetralones accordingly to the previous report.[3]

Thus, Reformatsky reaction on α-tetralone with ethyl 2-bromopropionate followed by acidic work-up yielded the β,γ-unsaturated ester **12b** (*Scheme 3*).

The olefin upon hydrogenation under pressure over palladized carbon as the catalyst furnished the product **14b** in good yield. The formation of product was confirmed by the disappearance of the olefinic signal at δ 6.0 in the PMR spectrum.



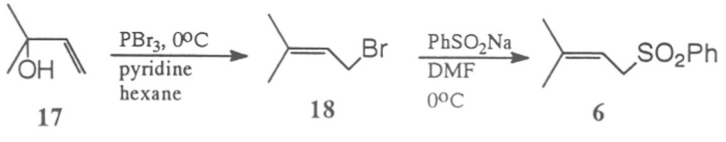
Scheme 3

The ester group was reduced with Lithium aluminium hydride in refluxing THF in 93% yield. The PMR of the product showed absence of ester signals at δ 1.2 and 4.0. The IR spectrum confirmed presence of hydroxyl group by presence of a broad peak at 3310 cm^{-1}.

A better leaving group for the alkylation was required. Hence, the alcohol **15b** was treated with phosphorous tribromide and pyridine in CH_2Cl_2. However, the reaction gave a complex mixture of unidentifiable products. The somewhat milder conditions using Triphenylphosphine-dibromide ($PPh_3.Br_2$), however, yielded the bromide **16b** in 92% yield.

The next task was the alkylation of the bromide with the side chain fragment from prenyl sulfone.

Prenyl sulfone was prepared according to the literature procedure[5,6] from 2-methyl-3-buten-2-ol (**17**). Bromination of the allylic alcohol **17** with PBr_3/pyridine furnished the bromide **18** which upon treatment with sodium benzenesulfinate ($PhSO_2Na$) yielded the sulfone (*Scheme 4*).

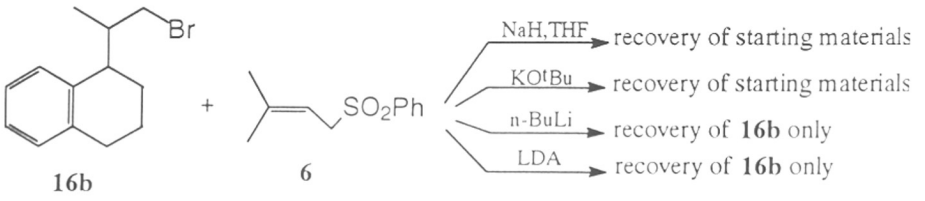


17 18 6

Scheme 4

Alkylation of prenyl sulfone with the bromide **16b** was then attempted using conventional methods.

The classical methods of anion generation, however, failed to furnish the alkylated product. Treatment of prenyl sulfone with NaH, KO^{t}Bu or LDA under various conditions resulted in the recovery of substrates.



16b 6

Scheme 5

When n-BuLi or LDA was used as the base, only the starting bromide **16b** could be isolated from the reaction mixture. This could be attributed to the formation of the terminal carbanion resulting in elimination of the sulfone at higher temperatures (*Scheme 6*).

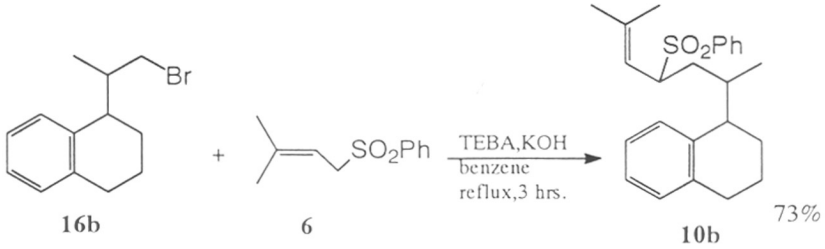
6 19 20

Scheme 6

The conventional methods not proving to be of any use for the C-C bond formation, it was thought to attempt the alkylation under phase-transfer conditions.

Generation of allyl sulfonyl carbanions has been reported[7] under PTC conditions using TBAB-HMPT. Accordingly, prenyl sulfone was treated with the bromide under aqueous PTC conditions using dichloromethane and 10% NaOH solution and also those of TBAB-HMPT which however did not result in any reaction.

But under 'anhydrous' conditions, the reaction proceeded smoothly to give the desired product. Thus, when a mixture of prenyl sulfone (**6**) and the bromide **16b** were refluxed in dry benzene with solid KOH using Triethylbenzylammonium chloride (TEBA) as the catalyst, the alkylated product **10b** was formed in 73% yield along with a minor product which could not be characterized.



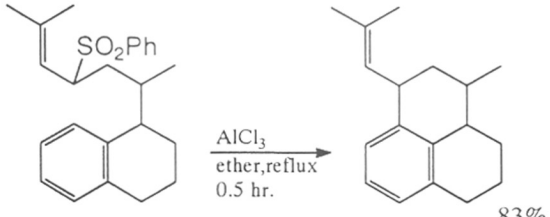
16b **6** **10b**

The product **10b** was characterized by IR, NMR and Mass spectral analysis. The IR spectrum showed the requisite sulfone peaks at 1300 and 1140 cm^{-1}. The PMR spectrum showed incorporation of the prenyl group by the presence of an olefinic peak at δ 4.9 and two singlets for 3H each at δ 1.1 and 1.7. The C<u>H</u>-SO_2Ph peak appeared at δ 3.6 as a multiplet. The aromatic protons appeared as three multiplets of 4H, 3H and 2H each. The presence of a small molecular ion peak in the mass spectrum at 382 further confirmed the formation of **10b**.

Other phase transfer catalysts like tetrabutylammonium bromide (TBAB), tetrabutylammonium hydrogen sulfate ($TBA.HSO_4$) were used without any significant increase in the yield of the alkylated product. Change in the other reaction parameters also indicated that use of TEBA/KOH in refluxing benzene were the best conditions for alkylation.

Further cyclization to form the tricyclic ring system was the next step. It was attempted using conditions similar to those of Trost.[1]

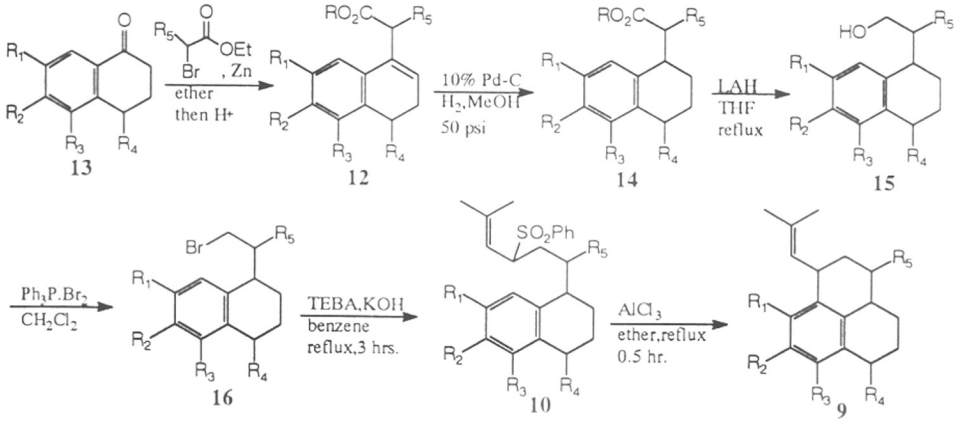
Thus, the alkylated product was treated with $AlCl_3$ at 0°C in dry ether and after refluxing for 0.5 hrs, the reaction furnished the substituted phenalene in 83% yield.



10b **9b**

The formation of product **9b** was confirmed by PMR and Mass spectral analysis. The ^{1}H-NMR showed the requisite number of peaks with the absence of 5 aromatic protons at δ 7.6. Only 3 aromatic protons were observed at δ 7.0. The Mass spectrum unambiguously confirmed the formation of cyclized product by the presence of a strong molecular ion peak at 240.

In order to test the generality and validity of this protocol, a variety of substituted tricyclic analogues of the pseudopterosin aglycone were smoothly synthesized (*Scheme 9*). The results are summarized in Table 1.



No	R^1	R^2	R^3	R^4	R^5	**12**(%)	**14**(%)	**15**(%)	**16**(%)	**10**(%)	**9**(%)
a	H	H	H	H	H	87	95	60	91	57	93
b	H	H	H	H	Me	90	79	93	92	73	83
c	H	H	H	H	Et	92	90	94	78	73	90
d	Me	H	H	Me	Me	80	85	60	77	57	64
e	H	OMe	H	H	Me	85	83	95	82	63	55

Table 1

Accordingly, substituents on the aromatic ring and on rings A and B of the phenalene ring system were variously modified by commencing with the appropriately substituted precursors.

Thus reaction of α-tetralone (**13a**) 4,7-dimethyl-1-tetralone (**13d**) and 6-methoxy-1-tetralone (**13e**) with Reformatsky reagent from ethyl 2-bromo esters yielded **12a-e** as previously reported (Chapter I, Section I and II). Hydrogenation over palladized carbon and LAH mediated reduction of ester functionality, followed by bromination with $Ph_3P.Br_2$ furnished the bromides **16a-e** in good yields.

Phase transfer catalyzed alkylation of prenyl sulfone with the bromides was carried out as that for the model substrate **16b**. Further lewis acid catalyzed cyclization of the sulfones yielded the tricyclic compounds **9a-e** in reasonable to good yields.

2.2.3 Conclusion:

The protocol developed is general and flexible in that it allows incorporation of different substituents on the tricyclic framework of pseudopterosins.

Change in the bromoester or the tetralone can variously modify the substituents on any ring. Hence, it can be applied for the synthesis of a wide variety of phenalene ring systems.

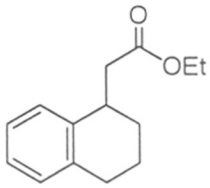
The use of sulfones for the alkylation under phase transfer conditions as against strong bases employed to effect the same transformation is a noteworthy feature in this methodology. The dual nature of sulfone functionality to act both as an electrophile as well as nucleophile has been efficiently utilized and can be further tapped for exploring other avenues of sulfone chemistry.

2.2.4 Experimental:

General procedure for the hydrogenation of β,γ-unsaturated esters 14:

A pressure bottle was charged with the β,γ-unsaturated ester **12** (2 mmol), 10% palladized carbon (10% by weight) in dry methanol (30 ml) and subjected to hydrogenation under pressure (50 psi). After the reaction was complete in 2 to 6 hrs. (as confirmed by GC analysis or PMR), the catalyst was filtered through celite and the solvent evaporated under vacuum. Column chromatography of the residue over silica gel using ethyl acetate-pet.ether mixture as eluent furnished the hydrogenated product as a viscous liquid.

Ethyl 2-(1,2,3,4-tetrahydro-1-naphthalene)acetate (14a)



14a

Yield: 95%

IR (neat): 1730, 1450, 1380, 1320, 1290, 1250, 1180 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.30 (t, J=6.5Hz, 3H); 1.70-2.00 (m, 4H); 2.65 (dd, J=16, 5.4Hz, 2H); 2.80 (m, 2H); 3.4 (m, 1H); 4.20 (q, J=6.5Hz, 2H); 7.10-7.20 (m, 4H).

^{13}C-NMR (50 MHz): 14.5(q); 19.9(t); 28.4(t); 29.8(t); 34.8(d); 42.2(t); 60.5(t); 126.0(d); 126.2(d); 128.4(d); 129.4(d); 137.2(s); 139.5(s); 172.9(s).

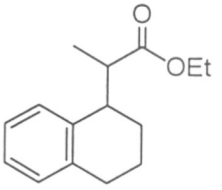
Mass (m/e): 218(M^+, 13); 172(5); 144(93); 131(100); 130(87); 129(90); 128(50); 116(20); 115(37); 103(10); 91(37); 77(9); 65(7).

Analysis:

Calculated for $\mathbf{C_{14}H_{18}O_2}$: C=77.03%; H=8.31%

Found : C=77.76%; H=8.16%

Ethyl 2-(1,2,3,4-tetrahydro-1-naphthalene)propionate (14b)



14b

Yield: 79%

IR (neat): 1720, 1480, 1440, 1370, 1350, 1250, 1160 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.20 (t, J=5Hz, 3H); 1.25 (t, J=6.8Hz, 3H); 1.70-2.10 (m, 4H); 2.75-2.90 (m, 3H); 3.05-3.20 (m, 1H); 4.10-4.25 (m, 2H); 7.10-7.25 (m, 4H).

^{13}C-NMR (50 MHz): 14.2(q); 15.8(q); 19.8(t); 26.7(t); 29.0(t); 41.2(d); 44.0(d); 60.1(t); 125.0(d); 126.2(d); 129.2(d); 129.7(d); 137.6(s); 137.9(s); 176.1(s).

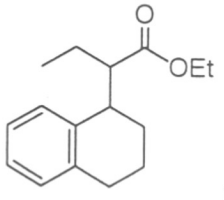
Mass (m/e): 223(M^+, 9); 186(2); 158(10); 132(13); 131(100); 129(21); 128(16); 117(6); 116(7); 115(13); 102(13); 91(23); 74(4).

Analysis:

Calculated for $\mathbf{C_{15}H_{20}O_2}$: C=77.55%; H=8.68%

Found : C=77.47%; H=8.79%

Ethyl 2-(1,2,3,4-tetrahydro-1-naphthalene)butyrate (14c)



14c

Yield: 90%

IR (neat): 1720, 1450, 1370, 1170, 1020 cm^{-1}

^{1}H-NMR (200 MHz): δ 0.90 (t, J=7Hz, 3H); 1.20 (t, J=7Hz, 3H); 1.45-2.10 (m, 6H); 2.55-2.70 (m, 1H); 2.75-2.90 (m, 2H); 3.00-3.10 (m, 1H); 4.15 (q, J=7Hz, 2H); 7.05-7.15 (m, 4H).

^{13}C-NMR (50 MHz): 12.1(q); 14.0(q); 19.4(t); 23.9(t); 25.9(t); 28.6(t); 40.5(d); 51.6(d); 59.6(t); 124.7(d); 126.0(d); 129.0(d); 129.6(d); 137.1(s); 137.9(s); 175.0(s).

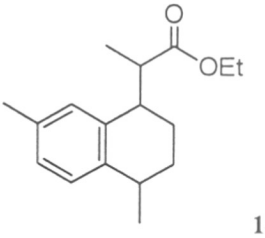
Mass (m/e):246 (M^+, 18); 173(5); 172(24); 131(100); 130(50); 129(41); 128(26); 127(13); 117(9); 116(24); 115(27); 92(9); 91(12).

Analysis:

Calculated for $\mathbf{C_{16}H_{22}O_2}$: C=78.05%; H=8.94%

Found : C=77.78%; H=8.53%

Ethyl 2-(4,7-dimethyl-1,2,3,4-tetrahydro-1-naphthalene)propionate (14d)



14d

Yield: 85%

IR (neat): 1731, 1614, 1500, 1459, 1374, 1342, 1258, 1160 cm^{-1}

^{1}H-NMR (300 MHz): δ 1.1-1.3 (m, 9H); 1.6-2.0 (m, 4H); 2.3 (s, 3H); 2.7-3.1 (m, 3H); 4.1 (q, J=7Hz, 2H); 6.9-7.1 (m, 3H).

^{13}C-NMR (50 MHz) (mixture of diastereomers): 14.2(q); 15.8(q); 21.1(q); 23.3(q); 24.1(t); 25.0(t); 28.2(t); 28.5(t); 32.0(d); 32.7(d); 41.2(d); 41.5(d); 44.0(d); 44.2(d); 60.0(t); 60.1(t); 125.8(d); 127.2(d); 128.5(d); 129.1(d); 129.6(d); 130.2(d); 134.3(s); 134.4(s); 135.5(s); 135.6(s); 142.1(s); 176.0(s).

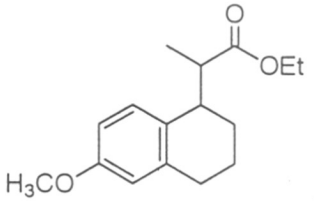
Mass (m/e): 260(M^+, 38); 214(17); 186(18); 185(11); 183(13); 159(100); 156(22); 155(17); 145(24); 144(21); 143(28); 142(24); 141(27); 131(18); 130(15); 128(70); 117(14); 115(25); 105(19); 91(7); 77(9).

Analysis:

Calculated for $C_{17}H_{24}O_2$: C=78.46%; H=9.23%

Found : C=77.96%; H=9.38%

Ethyl 2-(6-methoxy-1,2,3,4-tetrahydro-1-naphthalene)propionate (14e)



14e

Yield: 83%

IR (neat): 1710, 1600, 1500, 1450, 1370, 1240, 1220, 1170 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.15 (d, J=7Hz, 3H); 1.25 (t, J=7.7Hz, 3H); 1.65-2.05 (m, 4H); 2.65-2.80 (m, 3H); 2.95-3.10 (m, 1H); 3.80 (s, 3H); 4.05-4.20 (m, 2H); 6.60-6.70 (m, 2H); 7.00-7.05 (d, J=8.7Hz, 1H).

^{13}C-NMR (50 MHz): 13.9(q); 15.8(q); 19.6(t); 25.7(t); 29.1(t); 40.3(d); 43.8(d); 54.7(q); 59.8(t); 111.0(d); 113.4(d); 129.7(s); 130.4(d); 138.4(s); 157.7(s); 175.8(s).

Mass (m/e): 262(M^+, 3); 162(12); 161(100); 146(6); 145(4); 144(4); 131(5); 129(5); 128(5); 117(5); 115(9); 103(3); 91(11); 77(4).

Analysis:

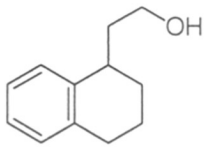
Calculated for $C_{16}H_{22}O_3$: C=73.25%; H=8.45%

Found : C=73.25%; H=8.15%

General procedure for reduction of esters 14:

The hydrogenated ester **14** (1 mmol) was dissolved in dry THF (25 ml) and LAH (0.5 mmol) was added in portions with cooling under N_2 atmosphere. After addition was complete, the mixture was refluxed for 2 hrs. The reaction mixture was quenched with saturated sodium sulfate solution and the resulting solid filtered through celite. The filtrate was concentrated under vacuum and the residue chromatographed over silica gel with ethyl acetate-pet.ether as eluent to furnish the alcohol **15** as a viscous liquid.

2-(1,2,3,4-tetrahydro-1-naphthalene)ethanol (15a)



15a

Yield: 60%

^{1}H-NMR (200 MHz): δ 1.60-2.20 (m, 6H); 2.80 (m, 2H); 3.00 (m, 1H); 3.80 (t, J=7Hz; 2H); 7.05-7.25 (m, 4H).

^{13}C-NMR (50 MHz): 19.7(t); 27.7(t); 29.6(t); 34.2(d); 39.7(t); 60.6(t); 125.6(d); 128.6(d); 129.1(d); 137.0(s); 140.8(s).

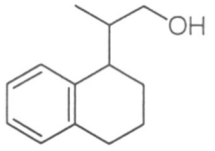
Mass (m/e): 176(M^+, 25%); 158(19); 132(17); 131(100); 130(52); 129(41); 128(20); 116(18); 115(30); 104(10); 91(47); 77(23); 65(7).

Analysis:

Calculated for $C_{12}H_{16}O$: C=81.80%; H=9.10%

Found : C=81.60%; H=8.71%

2-(1,2,3,4-tetrahydro-1-naphthalene)propanol (15b)



15b

Yield: 93%

IR (neat): 3310, 1590, 1450, 1370, 1270, 1230, 1020 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.05 (d, J=7Hz, 3H); 1.30 (bs, 1H); 1.55-1.80 (m, 2H); 1.85-2.00 (m, 2H); 2.20-2.40 (m, 1H); 2.70-2.80 (m, 2H); 2.80-2.90 (m, 1H); 3.40-3.65 (m, 2H); 7.05-7.25 (m, 4H).

^{13}C-NMR (50 MHz): 15.9(q); 21.2(t); 24.5(t); 29.9(t); 39.7(d); 40.5(d); 64.9(t); 125.2(d); 125.3(d); 128.3(d); 128.9(d); 137.7(s); 139.2(s).

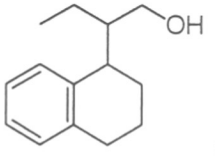
Mass (m/e): 190 (M^+, 33); 172(11); 159(8); 144(6); 131(100); 129(35); 128(29); 127(13); 117(18); 116(29); 115(34); 104(8); 103(8); 91(52); 77(17); 65(11); 63(7).

Analysis:

Calculated for **$C_{13}H_{18}O$** : C=82.06%; H=9.54%

Found : C=82.40%; H=9.44%

2-(1,2,3,4-tetrahydro-1-naphthalene)butanol (15c)



15c

Yield: 94%

IR (neat): 3300, 1600, 1450, 1380, 1040 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.05 (t, J=7.3Hz; 3H); 1.35-1.75 (m, 6H); 1.85-2.00 (m, 2H); 2.05-2.15 (m, 1H); 2.60-2.75 (m, 2H); 3.00-3.20 (m, 1H); 3.40-3.65 (m, 2H); 7.05-7.35 (m, 4H).

^{13}C-NMR (50 MHz): 12.2(q); 22.0(t); 22.4(t); 24.3(t); 30.1(t); 37.8(d); 46.9(d); 63.2(d); 125.4(d); 125.6(d); 127.8(d); 129.1(d); 138.2(s); 139.6(s).

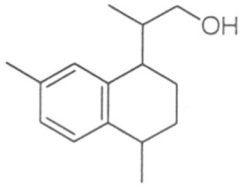
Mass (m/e): 204(M^+, 9); 186(4); 157(3); 132(13); 131(100); 129(18); 128(11); 127(5); 117(7); 116(11); 115(17); 104(5); 91(34); 77(6).

Analysis:

Calculated for **$C_{14}H_{20}O$** : C=82.35%; H=9.80%

Found : C=82.24%; H=9.91%

2-(4,7-dimethyl-1,2,3,4-tetrahydro-1-naphthalene)propanol (15d)



15d

Yield: 60%

IR (neat): 3310, 1450, 1380, 1030 cm^{-1}

^{1}H-NMR (200 MHz): δ 0.80(d); 1.10 (d, J=6.8Hz, 3H); 1.30 (d, J=7Hz, 3H); 1.55-1.90 (m, 4H); 2.20-2.35 (m, 1H); 2.30 (s, 3H); 2.75 (m, 2H); 3.40-3.80 (m, 2H); 6.95-7.20 (m, 3H).

^{13}C-NMR (50 MHz): 12.1(q); 16.2(q); 19.1(t); 21.0(d); 21.7(t); 23.1(d); 23.3(d); 28.7(t); 29.0(t); 32.7(d); 38.2(d); 38.9(d); 39.4(d); 40.7(d); 65.2(t); 66.3(t); 126.4(d); 126.5(d); 127.4(d); 128.2(d); 129.1(d); 129.4(d); 134.6(s); 134.9(s); 135.8(s); 142.5(s); 143.0(s).

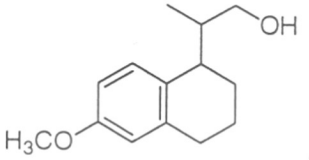
Mass (m/e): 218(M^+, 8); 160(12); 159(100); 145(13); 144(8); 143(7); 141(5); 131(10); 129(11); 128(11); 119(8); 117(6); 115(7); 105(7); 91(6); 77(2).

Analysis:

Calculated for $C_{15}H_{22}O_2$: C=82.57%; H=10.09%

Found : C=82.89%; H=10.05%

2-(6-methoxy-1,2,3,4-tetrahydro-1-naphthalene)propanol (15e)



15e

Yield: 95%

IR (neat): 3320, 1610, 1580, 1490, 1450, 1250, 1120 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.05 (d, J=6Hz, 3H); 1.50-1.70 (m, 3H); 1.80-1.95 (m, 2H); 2.15-2.35 (m, 1H); 2.70-2.85 (m, 3H); 3.40-3.65 (m, 2H); 3.80 (s, 3H); 6.60-6.75 (m, 2H); 7.15 (d, J=10Hz, 1H).

^{13}C-NMR (50 MHz): 15.9(q); 21.3(t); 25.1(t); 30.1(t); 39.8(d); 39.9(d); 55.0(q); 65.1(t); 111.5(d); 113.6(d); 129.3(d); 131.4(s); 139.0(s); 157.3(s).

Mass (m/e): 220(M^+, 9); 162(9); 161(100); 141(10); 131(9); 129(8); 128(9); 127(7); 118(9); 115(20); 103(8); 91(25); 77(11); 65(7).

Analysis:

Calculated for $C_{14}H_{20}O_2$: C=76.40%; H=9.10%

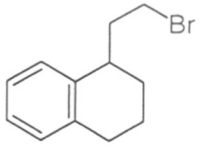
Found : C=77.02%; H=8.75%

General Procedure for bromination of 15:

Crystalline triphenylphosphine (1.2 mmol) was dissolved in dry dichloromethane (10 ml) and bromine (1.2 mmol) was added dropwise with cooling (0°C). The resulting pale

orange solution was stirred for 15 minutes at 0°C and a solution of the alcohol **15** (1 mmol) in CH_2Cl_2 was added to it. The reaction mixture was stirred for 0.5 hr. when the reaction was found to be complete (TLC). It was worked up by washing with H_2O (10 ml) and extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4, the solvent evaporated under vacuo and the residue chromatographed over silica gel using ethyl acetate-pet.ether mixture as eluent to yield the bromide **16** as an oil.

2-(1,2,3,4-tetrahydro-1-naphthalene)-1-bromoethane (16a)



16a

Yield: 91%

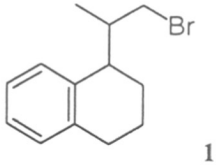
IR (neat): 1590, 1490, 1430, 1260 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.65-2.40 (m, 6H); 2.80 (t, J=5Hz, 2H); 3.05 (m, 1H); 3.55 (t, J=8Hz, 2H); 7.05-7.20 (m, 4H).

^{13}C-NMR (50 MHz): 19.7(t); 27.3(t); 29.5(t); 32.1(t); 36.1(d); 39.9(t); 125.8(d); 125.9(d); 128.5(d); 129.3(d); 137.0(s); 139.6(s).

Mass (m/e): 239(M^+, 5); 238(M^+, 5); 131(100); 129(32); 128(26); 127(15); 116(16); 115(33); 102(7); 91(35); 77(9).

2-(1,2,3,4-tetrahydro-1-naphthalene)-1-bromopropane (16b)



16b

Yield: 92%

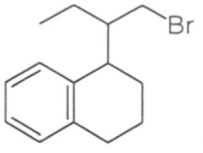
IR (neat): 1600, 1490, 1450, 1380, 1320 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.20 (d, J=6.0Hz, 3H); 1.60-2.05 (m, 4H); 2.35-2.55 (m, 1H); 2.70-2.80 (m, 2H); 2.90-3.00 (m, 1H); 3.30-3.45 (m, 2H); 7.05-7.20 (m, 4H).

^{13}C-NMR (50 MHz): 17.5(q); 21.1(t); 24.4(t); 24.5(t); 29.6(t); 38.5(t); 39.5(d); 42.1(d); 125.7(d); 125.8(d); 128.2(d); 129.2(d); 137.8(s); 138.7(s).

Mass (m/e): 254(M^+, 12); 252(M^+, 12); 212(3); 210(3); 131(100); 129(14); 127(16); 116(9); 115(13); 91(14); 77(3).

2-(1,2,3,4-tetrahydro-1-naphthalene)-1-bromobutane (16c)



16c

Yield: 78%

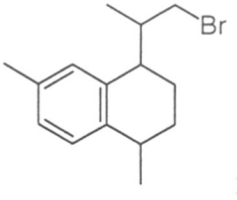
IR (neat): 1590, 1480, 1440, 1260, 1220 cm^{-1}

^{1}H-NMR (200 Mhz): 0.90(t); 1.00 (t, J=7Hz, 3H); 1.30-2.00 (m, 6H); 2.10-2.25 (m, 1H); 2.75-2.85 (m, 2H); 3.05-3.15 (m, 1H); 3.25-3.50 (m, 2H); 7.05-7.25 (m, 4H).

^{13}C-NMR (50 MHz): 120.(q); 21.4(t); 23.4(t); 24.1(t); 29.8(t); 36.6(t); 39.3(d); 46.1(d); 125.7(d); 125.9(d); 128.0(d); 129.2(d); 138.0(s); 138.6(s).

Mass (m/e): 268(M^+, 3); 266(M^+, 3); 132(15); 131(100); 129(24); 128(25); 116(12); 115(20); 91(25); 77(4); 55(8).

2-(4,7-dimethyl-1,2,3,4-tetrahydro-1-naphthalene)-1-bromopropane (16d)



16d

Yield: 77%

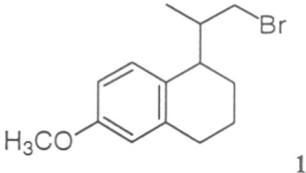
IR (neat): 1600, 1480, 1440, 1370, 1240, 1220 cm^{-1}

^{1}H-NMR (200 Mhz): δ 0.90 (d, J=6.4Hz, 3H); 1.30 (d, J=7Hz, 3H); 1.60-2.05 (m, 4H); 2.35 (s, 3H); 2.80-3.15 (m, 2H); 3.35-3.50 (m, 1H); 3.55 (d, J=6.4Hz, 2H); 6.95-7.30 (m, 3H).

^{13}C-NMR (50 MHz) (mixture of diastereomers): 14.7(q); 17.8(q); 19.5(t); 21.2(q); 21.3(q); 23.4(q); 23.5(q); 28.5(t); 28.9(t); 32.4(d); 32.7(d); 38.9(t); 39.1(d); 39.3(d); 39.8(d); 39.9(t); 42.2(d); 42.4(d); 42.5(d); 26.6(d); 126.9(d); 127.2(d); 127.6(d); 128.1(d); 128.7(d); 128.8(d); 129.4(d); 129.6(d); 134.9(s); 135.2(s); 135.3(s); 135.4(s); 142.6(s); 142.7(s).

Mass (m/e): 2829M+, 2); 280(2); 160(12); 159(100); 145(6); 144(8); 141(6); 131(7); 128(11); 127(11); 115(7); 10597); 91(5); 77(3).

2-(6-methoxy-1,2,3,4-tetrahydro-1-naphthalene)-1-bromopropane (16e)



16e

Yield: 82%

IR (neat): 1600, 1480, 1470, 1280, 1050 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.15 (d, J=6.8Hz, 3H); 1.60-1.80 (m, 2H); 1.80-2.00 (m, 2H); 2.30-2.50 (m, 1H); 2.70-2.80 (m, 2H); 2.85-2.95 (m, 1H); 3.25-3.45 (m, 2H); 3.80 (s, 3H); 6.60-6.80 (m, 2H); 7.15 (d, J=9Hz, 1H).

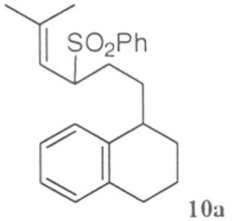
^{13}C-NMR (50 MHz): 17.6(q); 21.2(d); 24.7(d); 30.0(d); 38.8(d); 39.8(d); 41.6(d); 55.2(q); 111.9(d); 114.0(d); 129.3(s); 130.6(s); 139.1(s); 157.8(s).

Mass (m/e): 284(M^+, 4); 282(M^+, 4); 241(3); 239(3); 162(14); 161(100); 159(8); 146(7); 145(5); 144(4); 131(5); 129(6); 128(6); 117(5); 115(13); 103(4); 91(14); 77(7).

Typical procedure for alkylation of prenyl sulfone:

A mixture of the alkyl bromide **16** (1 mmol) and prenyl sulfone **6** (1 mmol) was dissolved in dry benzene (10 ml) and freshly powdered KOH (approx. 10mmol) was added with stirring. A small amount (~5mg) of triethylbenzylammonium chloride (TEBA) was added and the mixture was refluxed for 3 hrs. when the reaction was found to be complete (TLC). The reaction mixture was washed with water (10 ml) and extracted with ethyl acetate (2×10 ml). The combined organic extracts were dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The residue was chromatographed over silica gel using 20% ethyl acetate-pet.ether as eluent to furnish the alkylated product **10**.

1-[(5-methyl-3-phenylsulfonyl)-4-hexenyl]-1,2,3,4-tetrahydronaphthalene (10a)



10a

Yield: 57%

IR (nujol): 1440, 1370, 1290, 1140 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.15 (s, 3H); 1.70 (s, 3H); 1.50-1.90 (m, 8H); 2.20-2.45 (m, 1H); 2.75 (m, 2H); 3.75 (m, 1H); 5.0 (m, 1H); 7.05-7.15 (m, 4H); 7.50-7.70 (m, 3H); 7.80-7.90 (m, 2H).

^{13}C-NMR (50 MHz): 17.9(q); 19.6(t); 25.0(t); 25.5(t); 25.7(q); 26.9(t); 27.4(t); 29.5(t); 33.4(t); 33.8(t); 36.9(d); 37.5(d); 64.7(d); 65.1(d); 117.3(d); 117.5(d); 125.5(d); 128.3(d); 128.6(d); 129.0(d); 133.2(d); 136.8(s); 138.0(s); 140.3(s); 141.9(s); 142.1(s).

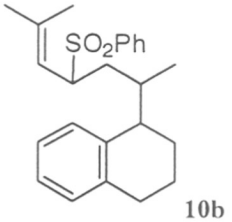
Mass (m/e): 368(M^+, 2); 307(3); 306(2); 305(5); 251(4); 249(4); 235(3); 227(29); 117(32); 157(16); 145(14); 144(26); 143(16); 131(100); 129(23); 117(31); 115(15); 95(11); 91(27); 81(12); 77(17); 69(18).

Analysis:

Calculated for $\mathbf{C_{23}H_{28}O_2S}$: C=74.96%; H=7.66%

Found : C=74.93%; H=8.17%

1-[(1,5-dimethyl-3-phenylsulfonyl)-4-hexenyl]-1,2,3,4-tetrahydronaphthalene (10b)



10b

Yield: 73%

IR ($CHCl_3$): 1580, 1430, 1300, 1220, 1140, 1080 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.00 (d, J=7Hz, 3H); 1.10 (s, 3H); 1.45-2.40 (m, 8H); 1.70 (s, 3H); 2.60-2.90 (m, 2H); 3.45-3.80 (m, 1H); 4.65-5.10 (m, 1H); 7.00-7.15 (m, 4H); 7.45-7.70 (m, 3H); 7.75-7.90 (m, 2H).

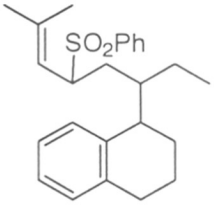
Mass (m/e): 382(M^+, 0.1); 312(0.2); 278(0.2); 256(04); 241(4); 239(1); 159(16); 137(20); 131(16); 117(24); 115(15); 109(11); 95(34); 91(23); 85(23); 84(30); 81(20); 77(89).

Analysis:

Calculated for $\mathbf{C_{24}H_{30}O_2S}$: C=75.40%; H=7.90%

Found : C=76.02%; H=8.20%

1-[(1-ethyl-5-methyl-3-phenylsulfonyl)-4-hexenyl]-1,2,3,4-tetrahydronaphthalene (10c)



10c

Yield: 73%

IR ($CHCl_3$): 1450, 1300, 1140, 1090 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.00 (t, J=8Hz, 3H); 1.15 (s, 3H); 1.70 (s, 3H); 1.20-2.05 (m, 9H); 2.50-2.80 (m, 2H); 3.05-3.30 (m, 1H); 3.50-4.25 (m, 1H); 4.50-5.10 (m, 1H); 6.95-7.15 (m, 4H); 7.40-7.65 (m, 3H); 7.70-7.95 (m, 2H).

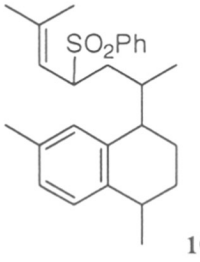
Mass (m/e): 255(11); 199(16); 185(6); 172(12); 157(6); 143(9); 131(100); 129(17); 123(9); 117(32); 95(16); 91(26); 81(12); 77(18); 69(27).

Analysis:

Calculated for **$C_{25}H_{32}O_2S$** : C=75.71%; H=8.13%

Found : C=75.32%; H=7.99%

1-[(1,5-dimethyl-3-phenylsulfonyl)-4-hexenyl]-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene (10d)



10d

Yield: 57%

IR (neat): 1440, 1370, 1300, 1140, 1080 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.20(d); 1.25 (d, J=6Hz, 3H); 1.15 (s, 3H); 1.70 (s, 3H); 1.45-2.25 (m, 7H); 2.30 (s, 3H); 2.55-2.95 (m, 2H); 3.60-3.90 (m, 1H); 4.70-5.10 (m, 1H); 6.85-7.15 (m, 3H); 7.40-7.70 (m, 3H); 7.75-7.95 (m, 2H).

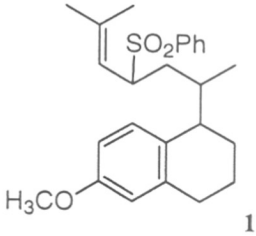
Mass (m/e): 410 (M^+, 1); 269(27); 213(26); 186(81); 171(19); 159(100); 145(52); 144(23); 143(29); 131(28); 129(29); 128(31); 119(20); 115(17); 105(15); 95(40); 91(31); 77(76); 69(74).

Analysis:

Calculated for **$C_{26}H_{34}O_2S$** : C=76.05%; H=8.35%

Found : C=75.85%; H=8.20%

1-[(1,5-dimethyl-3-phenylsulfonyl)-4-hexenyl]-6-methoxy-1,2,3,4-tetrahydronaphthalene (10e)



10e

Yield: 63%

Melting point: 146-147°C (crystallized from pet.ether)

IR (neat): 1620, 1590, 1460, 1300, 1260, 1150 cm^{-1}

^{1}H-NMR (200 MHz): δ 0.95 (d, J=6.8Hz, 3H); 1.10 (s, 3H); 1.45-2.10 (m, 7H); 1.70 (s, 3H); 2.55-2.80 (m, 3H); 3.55 (s, 3H); 3.65-3.90 (m, 1H); 4.65-4.75 (m, 1H); 6.55-6.70 (m, 2H); 6.95 (m, 1H); 7.40-4.65 (m, 3H); 7.75-7.80 (m, 2H).

^{13}C-NMR (50 MHz): 17.6(q); 17.8(q); 21.9(t); 23.8(t); 25.7(q); 28.7(t); 30.5(t); 33.5(d); 42.7(d); 55.1(q); 63.6(d); 111.9(d); 113.6(d); 117.7(d); 128.6(d); 129.0(d); 130(s); 133.3(d); 138.1(s); 139.5(s); 141.9(s); 157.3(s).

Mass (m/e): 412 (M^+, 2); 351(6); 349(6); 295(2); 293(2); 272(2); 271(14); 270(4); 241(18); 239(17); 215(13); 188(9); 161(100); 160(19); 147(11); 115(31); 91(16); 77(20); 69(35).

Analysis:

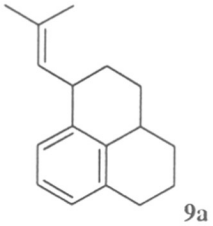
Calculated for $C_{25}H_{32}O_3S$: C=72.78%; H=7.82%

Found : C=72.66%; H=7.69%

Typical procedure for the cyclization of sulfones:

Anhydrous $AlCl_3$ (1.25 mmol) was added in portions to a stirred solution of the sulfone **10** (0.5 mmol) in dry ether (10 ml) at 0°C. The mixture was allowed to attain room temperature and then refluxed for a period of 0.5 hrs. The reaction was monitored by TLC and after it was complete, cooled to room temperature and quenched with 10% HCl (10 ml). The mixture was extracted with ethyl acetate (2×10 ml) and the combined organic extracts were dried over anhydrous Na_2SO_4, rotaryevaporated and chromatographed over silica gel using ethyl acetate-pet.ether as eluent to furnish the pure phenalene **9**.

1-(2-methyl-1-propenyl)-hexahydrophenalene (**9a**)



9a

Yield: 93%

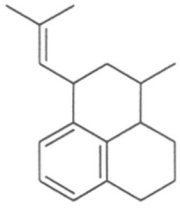
IR (neat): 1600, 1460, 1380, 1220 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.55-1.75 (m, 4H); 1.85 (s, 6H); 1.90-2.15 (m, 4H); 2.55-2.80 (m, 1H); 2.85-3.00 (m, 2H); 3.65-3.85 (m, 1H); 5.20-5.45 (m, 1H); 6.95-7.15 (m, 3H).

^{13}C-NMR (50MHz): 17.8(q); 18.0(q); 22.6(t); 22.7(t); 25.8(q); 27.5(t); 29.2(t); 29.4(t); 29.7(t); 30.8(t); 35.4(d); 36.6(d); 37.2(d); 39.4(d); 125.3(d); 125.5(d); 125.6(d); 126.0(d); 126.3(d); 129.7(d); 130.2(d); 130.9(s); 136.4(s); 137.3(s); 139.1(s).

Mass (m/e): 226(M^+, 8); 211(31); 183(22); 171(20); 170(99); 169(57); 155(38); 153(23); 142(41); 141(60); 129(31); 128(36); 115(27); 97(27); 95(23); 91(24); 83(45); 81(47); 77(24); 71(53); 69(100); 60(33); 57(96); 55(91).

3-methyl-1-(2-methyl-1-propenyl)-hexahydrophenalene (9b)



9b

Yield: 83%

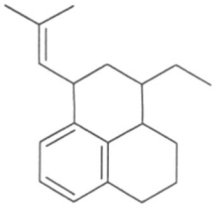
IR (neat): 1580, 1440, 1380, 1230 cm^{-1}

^{1}H-NMR (300 MHz): δ 0.9 (d, J=6.4Hz, 3H); 1.5-2.3 (m, 7H); 1.81 (s, 6H); 2.7-3.0 (m, 3H); 3.6-3.8 (m, 1H); 5.1-5.2 (m, 1H); 6.8-7.1 (m, 3H).

^{13}C-NMR (50 MHz): 13.4(q); 18.0(q); 23.7(t); 26.1(q); 28.6(t); 30.3(t); 31.9(d); 34.7(d); 38.2(t); 41.3(d); 125.5(d); 126.2(d); 127.0(d); 130.6(d); 130.9(s); 135.2(s); 137.2(s); 138.9(s).

Mass (m/e): 240(M^+, 17); 225(28); 185(22); 184(75); 183(100); 169(60); 168(43); 165(22); 155(40); 154(25); 153(23); 152(27); 141(45); 129(18); 128(20); 127(20); 115(21); 91(14).

3-ethyl-1-(2-methyl-1-propenyl)hexahydrophenalene (9c)



9c

Yield: 90%

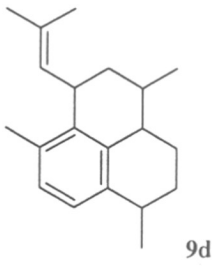
IR (neat): 1580, 1450, 1380 cm^{-1}

^{1}H-NMR (200 MHz): δ 0.90-1.10 (m, 3H); 1.10-2.15 (m, 9H); 1.80 (s, 6H); 2.70-3.05 (m, 3H); 3.55-3.80 (m, 1H); 5.25 (d, J=9Hz, 1H); 6.90-7.15 (m, 3H).

^{13}C-NMR (75 MHz) mixture of diastereomers: 12.2(q); 17.8(q); 18.0(q); 19.2(t); 22.1(t); 23.7(t); 24.1(t); 24.7(t); 25.9(q); 28.2(t); 29.4(t); 30.2(t); 33.4(t); 33.5(t); 34.3(d); 37.0(d); 37.4(d); 38.7(d); 41.9(d); 124.9(d); 125.0(d); 125.3(d); 125.4(d); 126.0(d); 126.3(d); 126.7(d); 129.7(d); 130.5(d); 131.3(d); 135.5(s); 136.7(s); 137.5(s); 138.6(s); 139.1(s); 140.1(s).

Mass (m/e): 254(M^+, 8); 239(6); 226(6); 198(38); 183(24); 170(14); 169(100); 155(21); 153(13); 141(36); 131(18); 129(14); 128(26); 115(16); 91(13); 83(11); 77(14); 69(10); 57(244); 55(20).

1-(2-methyl-1-propenyl)-3,6,9-trimethyl-hexahydrophenalene (9d)



9d

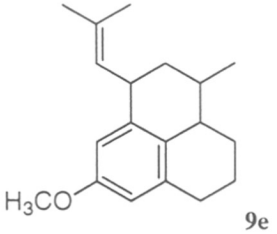
Yield: 64%

IR (neat): 1600, 1570, 1450, 1380 cm^{-1}

^{1}H-NMR (200 MHz): 1.90-1.15 (m, 3H); 1.25-1.40 (m, 3H); 1.50-2.25 (m, 13H); 2.25-2.45 (m, 3H); 2.65-3.05 (m, 3H); 3.55-3.85 (m, 1H); 5.10-5.35 (m, 1H); 6.75-7.15 (m, 3H).

Mass (m/e): 268(M^+, 73); 253(100); 225(14); 212(99); 211(85); 197(67); 183(19); 169(44); 156(36); 141(17); 129(10); 115(7).

8-methoxy-3-methyl-1-(2-methyl-1-propenyl)hexahydrophenalene (9e)



9e

Yield: 55%

IR (neat): 1600, 1450, 1380, 1350, 1300, 1280, 1250 cm^{-1}

^{1}H-NMR (200 MHz): δ 0.95 (d, J=6.8Hz, 3H); 1.50-2.25 (m, 7H); 1.80 (s, 6H); 2.70-2.95 (m, 3H); 3.65-3.95 (m, 1H); 3.80 (s, 3H); 5.15-5.30 (m, 1H); 6.45-6.65 (m, 2H).

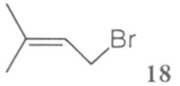
^{13}C-NMR (75MHz) (mixture of diastereomers): 12.8(q); **12.9(q)**; 17.3(q); **17.7(q)**; 22.5(t); **23.4(t)**; **25.8(q)**; 26.3(t); **28.4(t)**; 27.9(t); 30.1(t); **30.3(t)**; 30.8(t); 30.9(q); **31.6(q)**; 31.7(t); **34.5(d)**; 34.7(d); 36.4(t); 37.2(t); 37.3(d); 37.6(t); **38.0(t)**; **40.6(d)**; 41.1(d); 55.0(d); **56.0(d)**; 109.8(d); 110.5(d); 111.0(d); **111.4(d)**; **112.0(d)**; **112.5(s)**; **127.3(s)**; 129.5(d); 129.7(d); 130.0(d); **130.1(d)**; 130.7(d); 131.2(d); 138.2(d); **138.4(s)**; **140.0(s)**; 141.7(d); **157.1(s)**.

The peaks of the major isomer are in bold.

Mass (m/e): 270(M^+, 76); 215(19); 214(79); 213(100); 199(56); 198(41); 197(22); 195(14); 185(24); 184(20); 183(16); 165(22); 152(22); 141(20); 128(20); 119(20); 115(20); 105(15); 55(18).

Preparation of Prenyl sulfone 6:

1-Bromo-3-methyl but-2-ene (18)

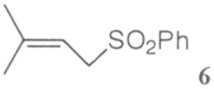


18

A mixture of 2-methyl-3-buten-2-ol (**17**) (10g, 1.8 ml, 116 mmol) and dry pyridine (1.84g, 1.88 ml, 23.3 mmol) was added slowly to a stirred solution of PBr_3 (11.9g, 4.2 ml, 44 mmol) in ether (30 ml) at 0°C. After 30 minutes, ice water was added and the ether layer separated and washed with $NaHCO_3$ solution (10 ml) and then with H_2O (10 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Distillation of the residue furnished the bromide (16g, 95%).

Boiling point 85-95°C/150mm Hg.

1-phenyl sulfonyl-3-but-2-ene (**6**)



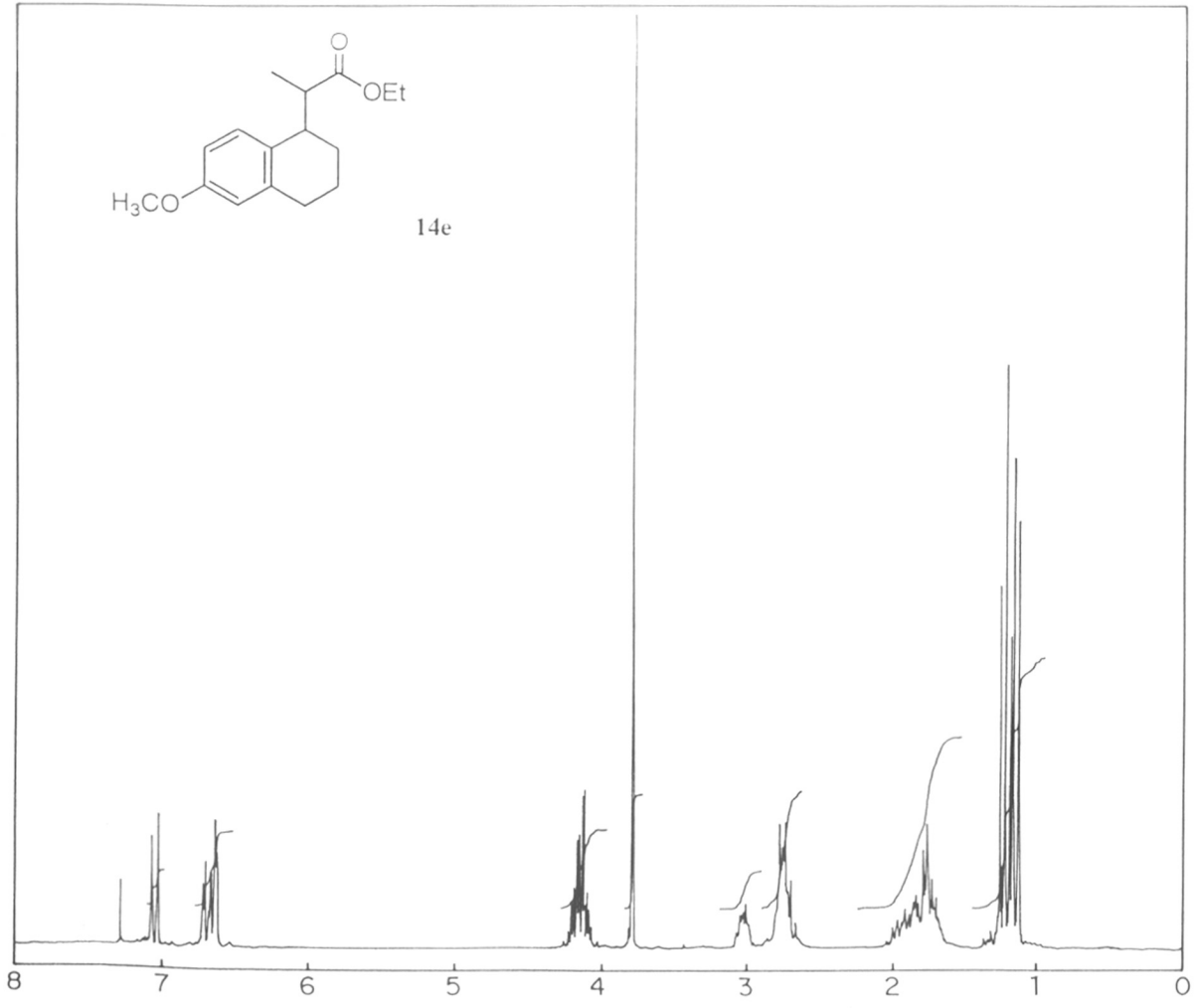
6

The bromide **18** (10g, 67 mmol) was added dropwise to a stirred solution of $PhSO_2Na$ (12.1g, 73.7 mmol) in dry DMF at 0°C and the mixture stirred at 25°C for 1 hour. Ice-cold water (50 ml) was added and the resulting solid filtered and washed with cold water (30 ml). The solid was dried under vacuum to furnish the sulfone **6** (9.44g, 67% yield) which was recrystallized from hexane.

Melting point: 50-51°C.

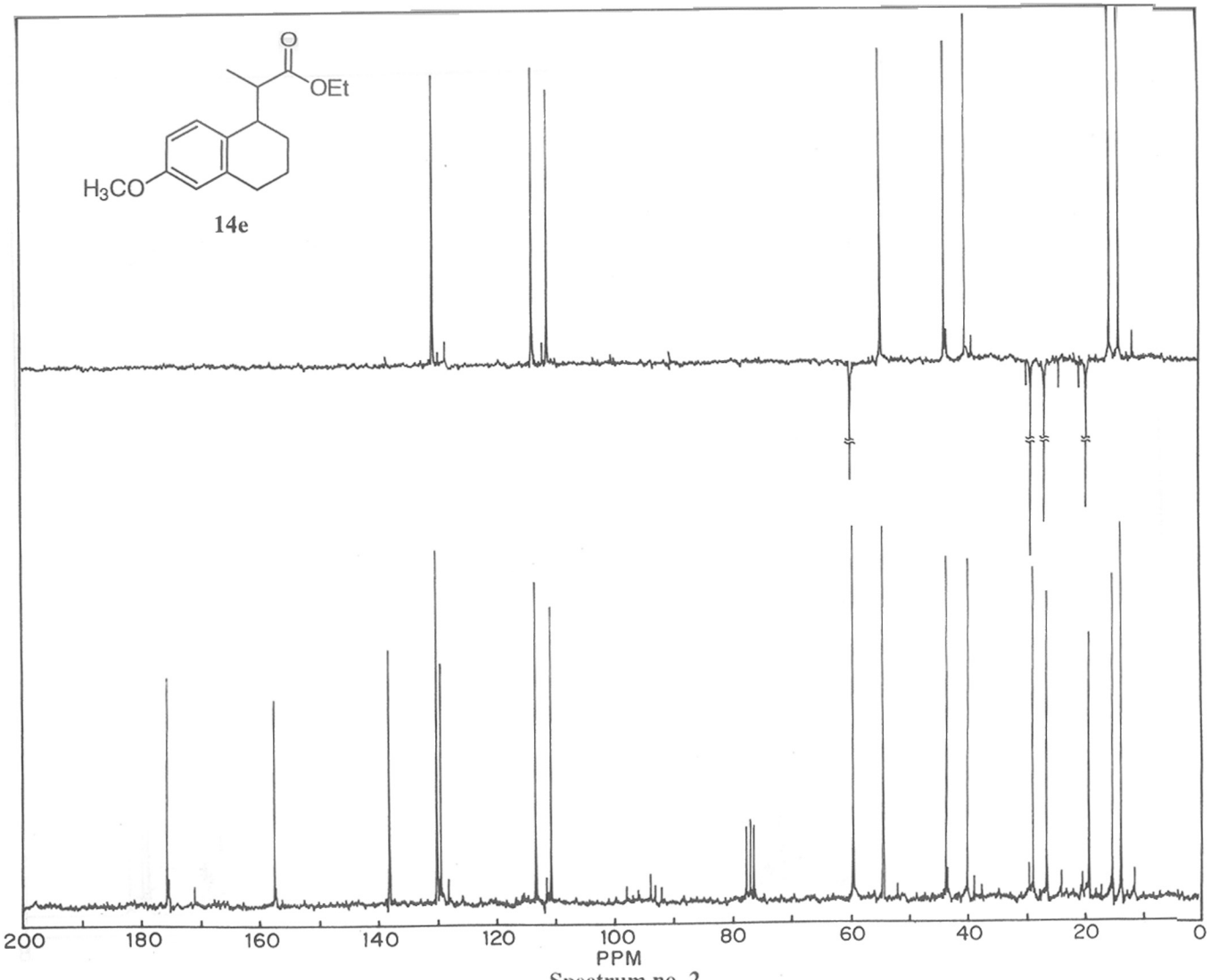
2.2.5 References :

1. Trost,B.M.; Ghadiri,M.R. *J. Am. Chem. Soc.* **1984**, *106*, 7260.
2. Trost,B.M.; Ghadiri,M.R. *J. Am. Chem. Soc.* **1986**, *109*, 1098.
3. Chavan,S.P.; Zubaidha,P.K.; Ayyangar,N.R. *Tetrahedron Lett.* **1992**, *33*, 4605.
4. Wiley,C.A.; Mershkowitz,R.L.; Rein,B.M.; Chung,B.C. *J. Am. Chem. Soc.* **1964**, *86*, 964.
5. Crombie,L.; Harper,S.H.; Sleep,K.C. *J. Chem. Soc.* **1957**, 2743.
6. Campbell,R.U.M.; Crombie,L.; Findley,D.A.R.; King,R.W.; Pattenden,G.; Whiting,D.A. *J. Chem. Soc. Perkin Trans.I*, **1975**, 897.
7. Jonczyk,A.; Radwan-Putlewski,T. *J. Org. Chem.* **1983**, *48*, 910.

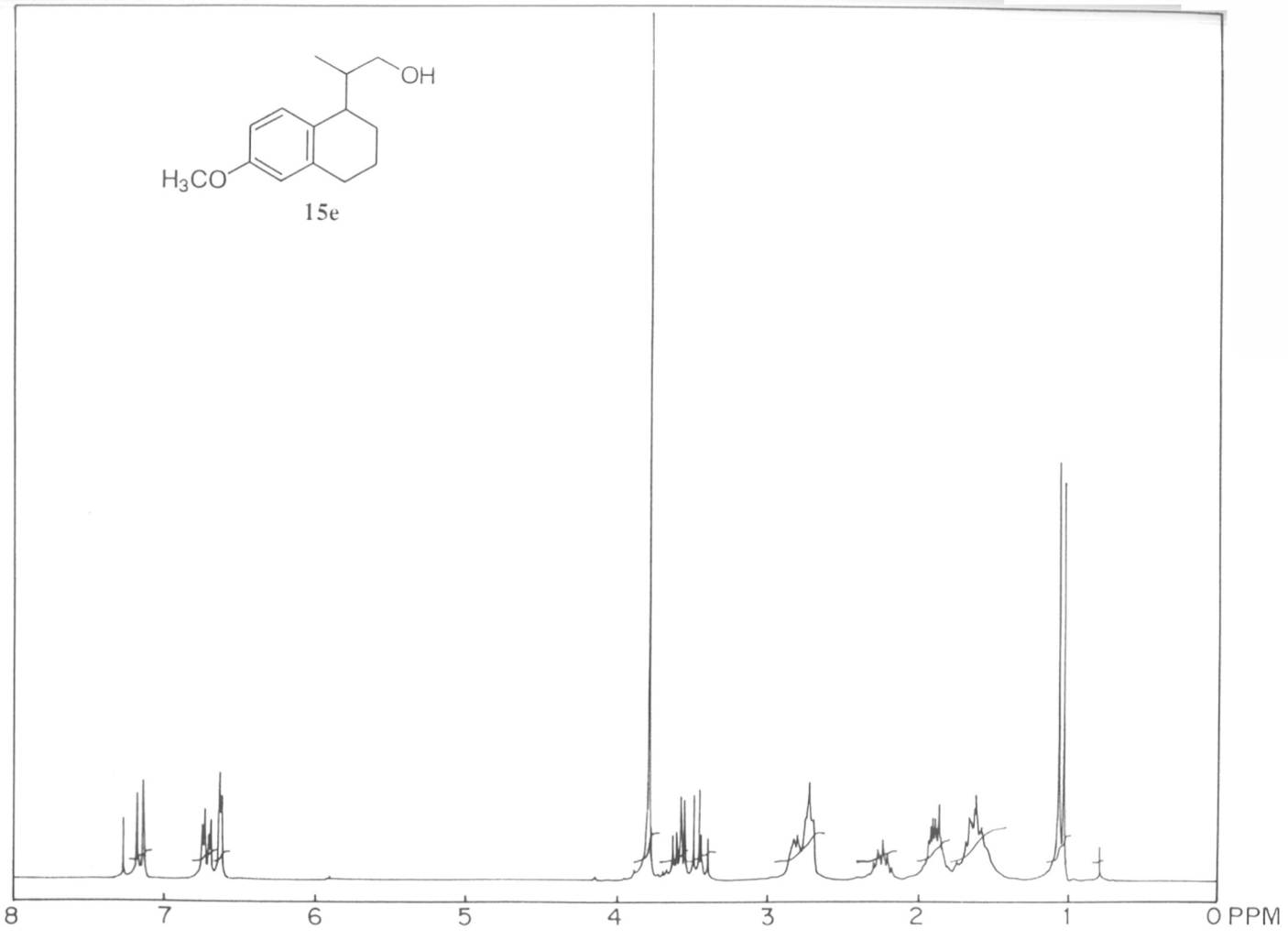


14e

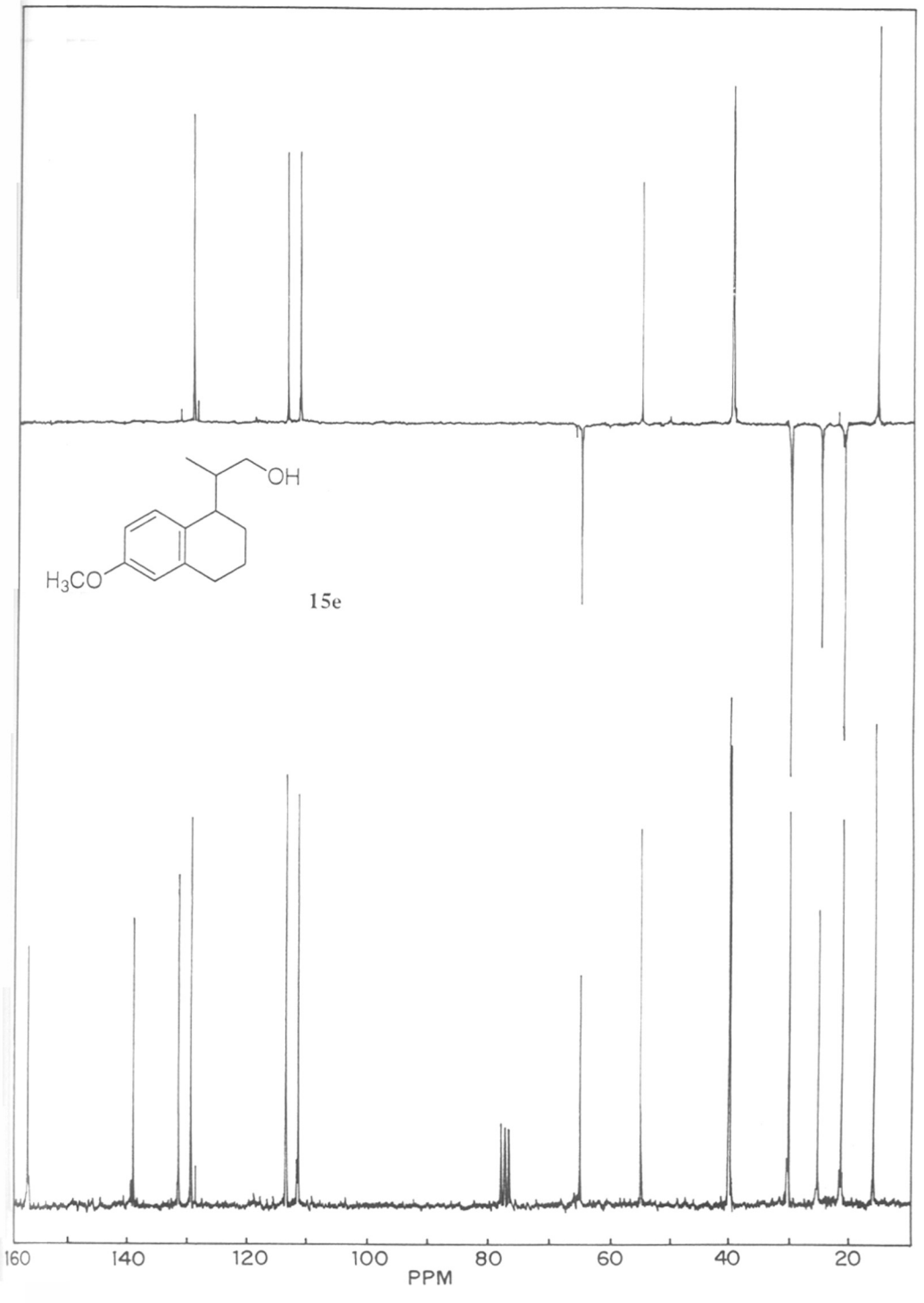
Spectrum no. 1



Spectrum no. 2

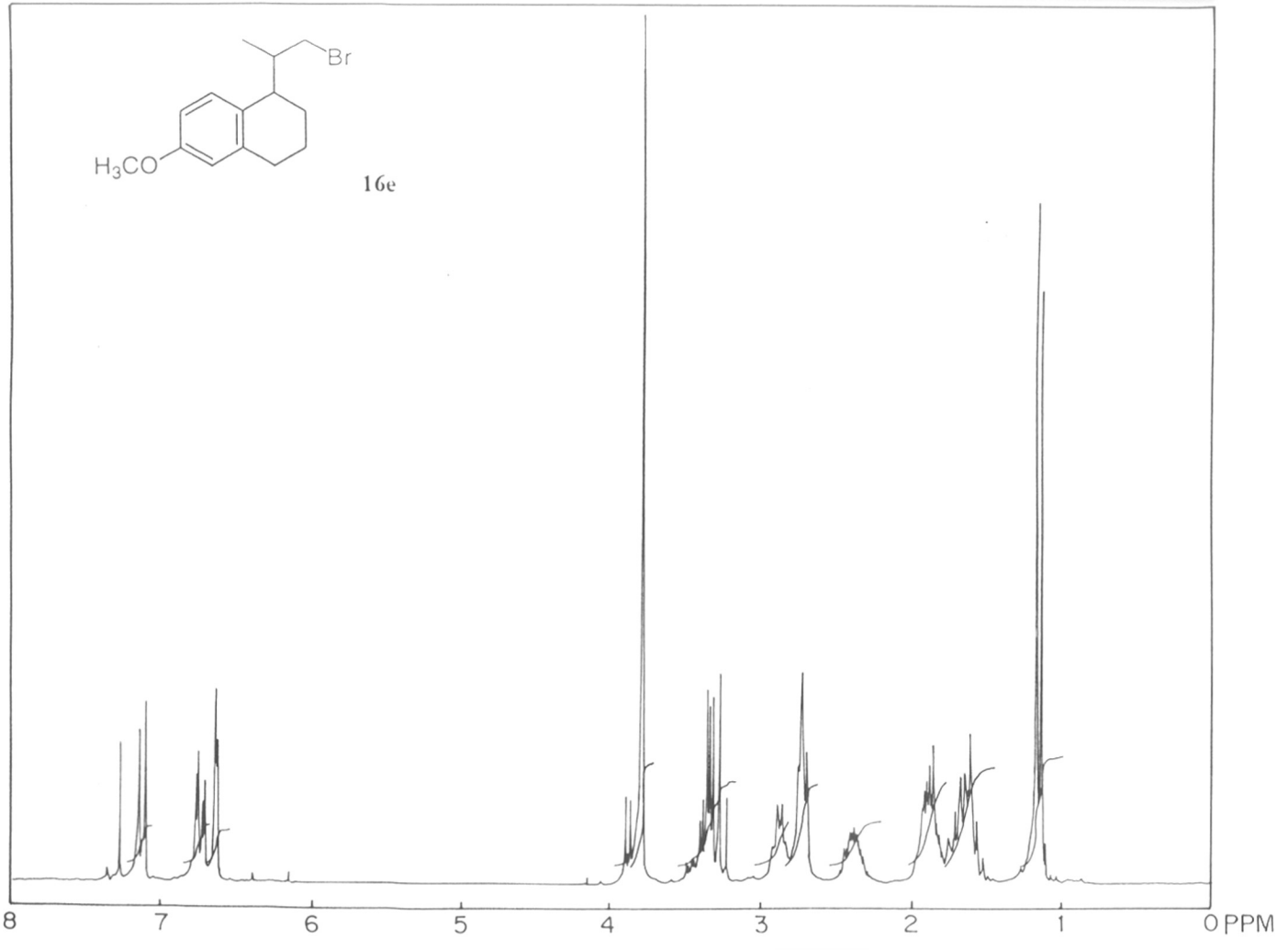


Spectrum no. 3



15e

Spectrum no. 4



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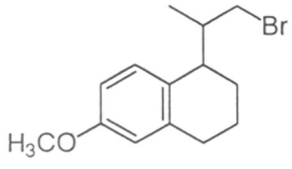
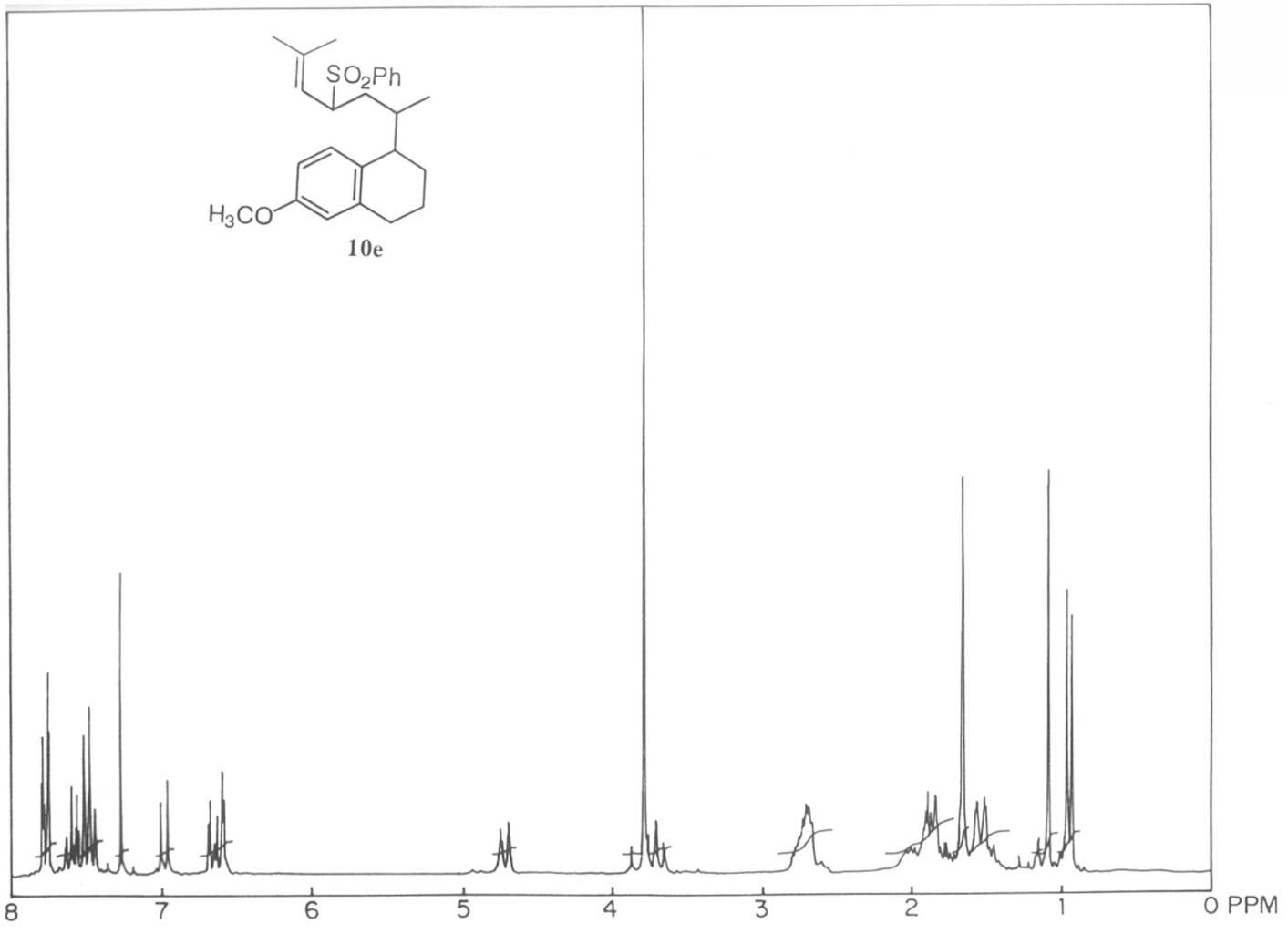


16e

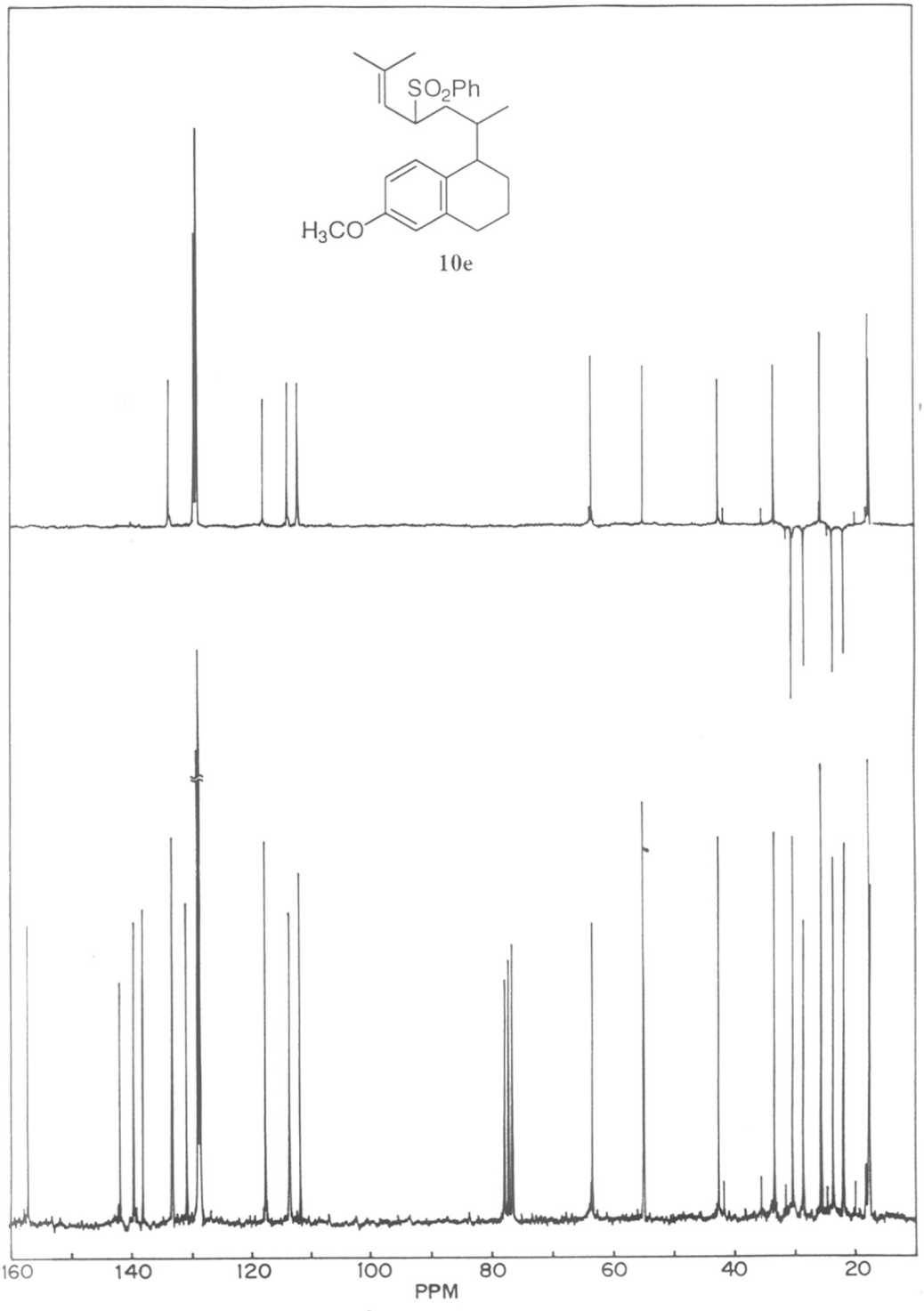
160 140 120 100 80 60 40 20

PPM

Spectrum no. 6

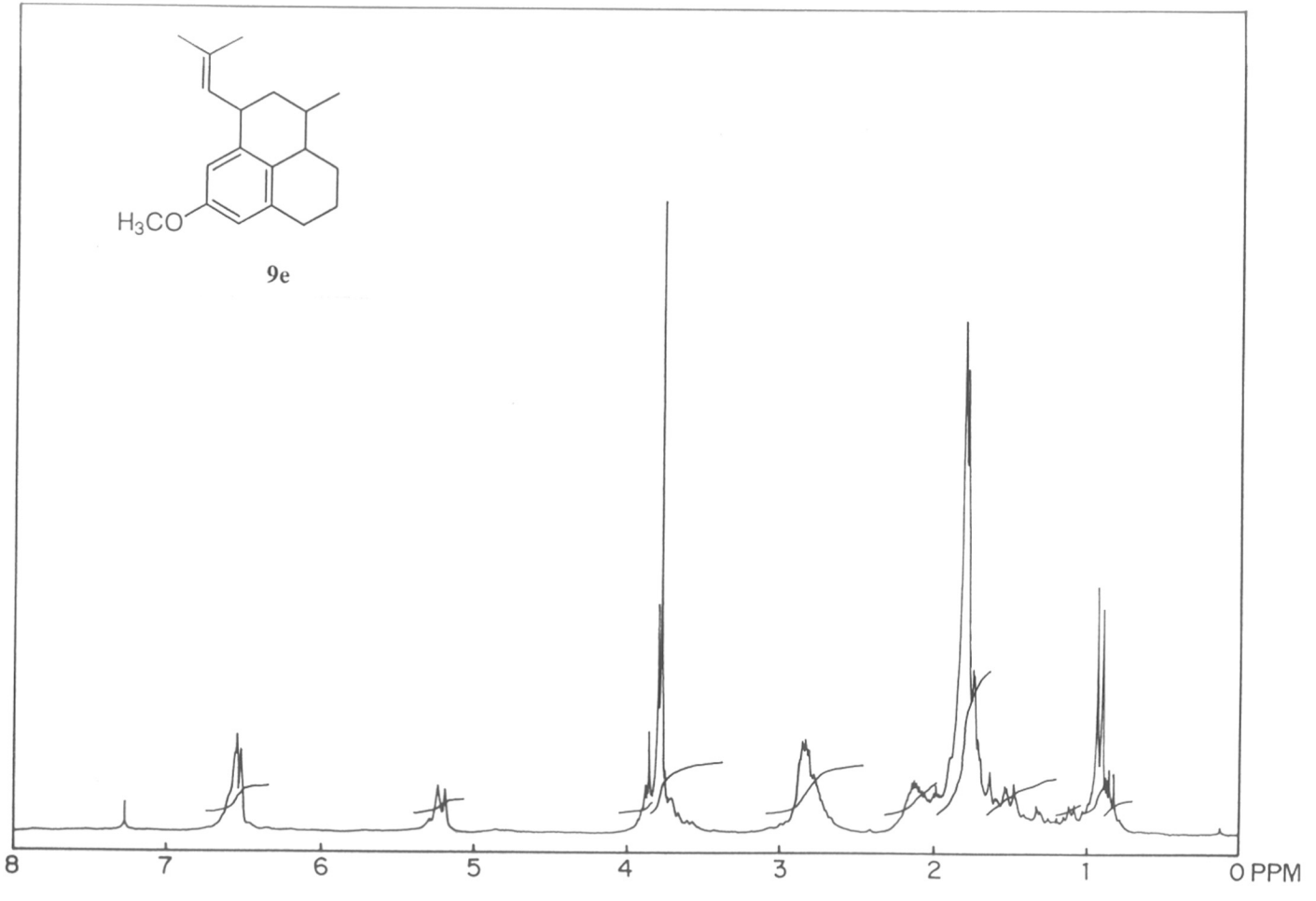


Spectrum no. 7



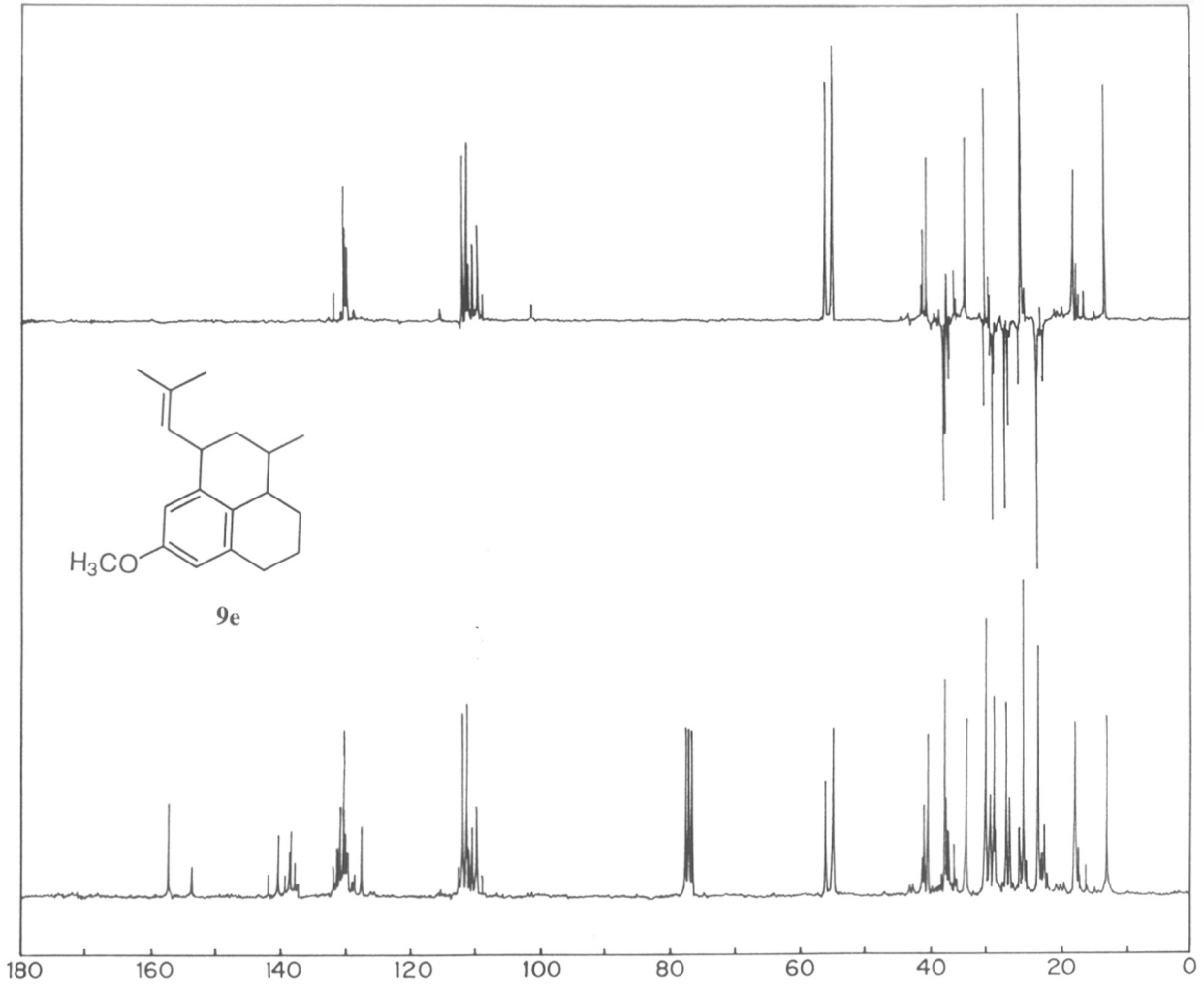
10e

Spectrum no. 8



9e

Spectrum no. 9



9e

Spectrum no. 10

SECTION 3

Synthetic studies towards the Dimethyl Ether of Pseudopterosin Aglycone

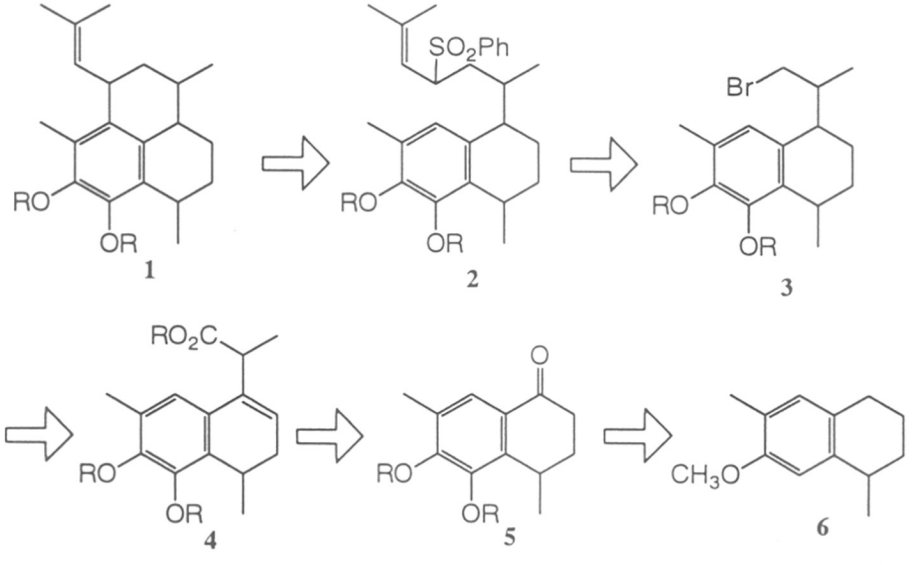
2.3.0 Introduction:

The potent antiinflammatory and analgesic activities of the pseudopterosins and helioporins have been previously highlighted in Section 1. These biological activities coupled with the extremely satisfactory results obtained in the model synthesis of the tricyclic moiety of these compounds (Section 2) acted as a spur for attempting the total synthesis of the pseudopterosin aglycone.

Hence the synthesis of the pseudopterosin aglycone was attempted based on the general protocol developed for the tricyclic core in the previous section.

2.3.1 Present Work:

Retrosynthesis of the aglycone **1** (R = Me)shows that the molecule can be obtained from the β,γ-unsaturated ester *via* the protocol developed (*Scheme 1*).



Scheme 1

The β,γ-unsaturated ester can be obtained by Reformatsky reaction on the tetralone **5**. Hydrogenation and reduction of **4**, followed by bromination would furnish the substrate bromide **3** which upon phase-transfer catalyzed alkylation with prenyl sulfone would furnish the sulfone **2**. Lewis acid catalyzed cyclization of the sulfone according to the standardized scheme would give the required alkyl ether of the Ps aglycone.

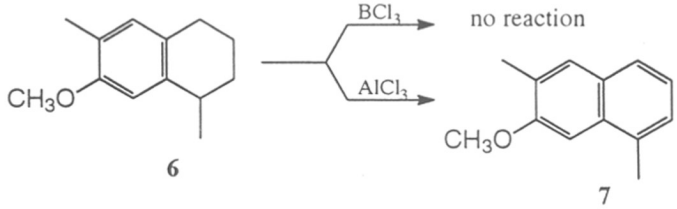
During the synthesis of Heritol and Heritonin,[1] the tetrahydronaphthalene **6** was prepared (Chapter 1, Section 1). The structure of **6** bearing a similarity to that of the required tetralone **5**, it was thought that advantage can be taken of the availability of compound **6** as a starting material for the synthesis.

It may be stressed here that no attempt was made for a stereoselective synthesis of any single isomer of the pseudopterosin aglycone.

2.3.2 Results and Discussion:

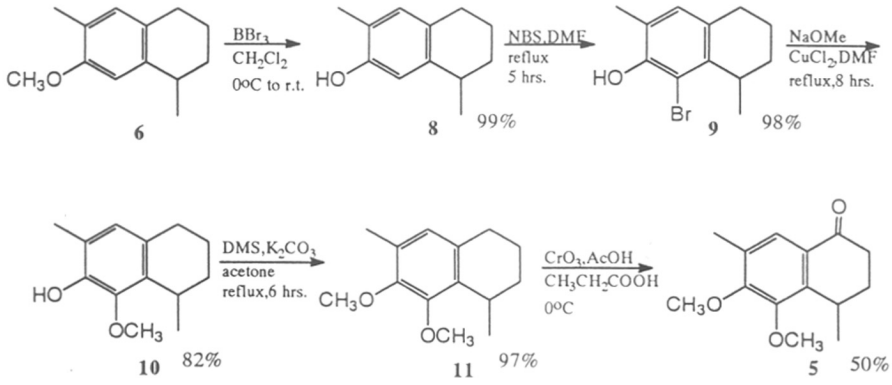
For converting the readily available tetrahydronaphthalene **6** into the required tetralone **5**, only an orthoxyfunctionalization and a benzylic oxidation were required. These were accomplished in the following way (*Scheme 2*).

Demethylation of **6** was attempted using agents like BCl_3[3,4] however which resulted in no reaction at all. Reaction with $AlCl_3$[5] in dichloromethane resulted in formation of completely aromatized product **11** rather than demethylation.Formation of compound **11** was confirmed by ^{1}H-NMR spectrum, which showed 5 aromatic protons as well as three singlets of the three Me groups.



6 **7**

Deprotection of the methyl ether **6** using BBr_3[2] gave the phenol **7** in quantitative yield.The product **7** was confirmed by ^{1}H-NMR and IR spectral analysis. Absence of any singlet at δ 3.5 for aromatic OMe and the presence of a broad peak in the IR spectrum at 3340 cm^{-1} confirmed the formation of phenol **7**.



Scheme 3

Orthobromination was effected using N-bromosuccinimide[6] in dry DMF. Under these conditions, no side-chain bromination was observed. The presence of only one aromatic H in the ^{1}H-NMR spectrum at δ 6.8 confirmed the nuclear bromination. The introduction of Br was further confirmed by the Mass spectrum, which showed molecular ion peaks at 256 and 254 of roughly equal intensity.

Ipso substitution of bromine with methoxy group was carried out using NaOMe and Copper(II) halide as reported[7] in 82% yield. The structure of product was confirmed by ^{1}H-NMR spectrum which showed a singlet at δ 3.8 corresponding to that of the aromatic OMe group.

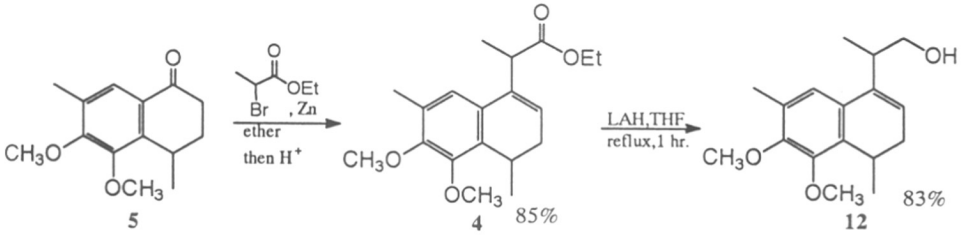
Further protection of the phenol using dimethyl sulfate-K_2CO_3 in acetone furnished the dimethoxy compound **10** in 97% yield. The product **10** was confirmed by ^{1}H-NMR, which showed two singlets at δ 3.8 and 3.9 integrating for 3H each and the IR spectrum which

showed absence of phenolic group. Mass spectrum gave M^++1 and M^+ at 221 and 220 respectively for compound **10**.

Benzylic oxidation was effected using standard chromic acid conditions to furnish the required tetralone **5** in 50% yield. IR spectrum of the product showed strong carbonyl peak at 1685 cm^{-1}. M^++1 and M^+ peaks at 235 and 234 in the mass spectrum further confirmed the structure.

Having achieved the required tetralone **5**, further transformations were performed according to the general scheme.

Reformatsky[8] reaction of tetralone **5** with ethyl α-bromopropionate furnished the β,γ-unsaturated ester **4** in 85% yield after acidic work-up. The product **4** was characterized by IR, NMR and Mass spectral analysis. The IR spectrum showed a peak at 1730 cm^{-1} for carbonyl functionality. ^{1}H-NMR spectrum showed a multiplet at δ 5.80 for one olefinic proton. M^+ at 318 in the mass spectrum further confirmed the structure.

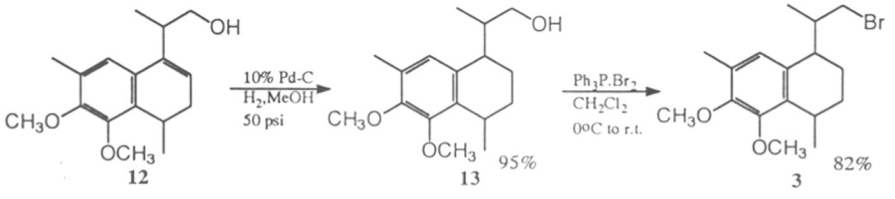


Scheme 4

LAH reduction of the ester functionality furnished the unsaturated alcohol **12** in 83% yield. The ^{1}H-NMR spectrum of **12** showed the absence of ester signals as expected and the IR spectrum confirmed the reduction by presence of a broad peak at 3360 cm^{-1} for the hydroxyl group.

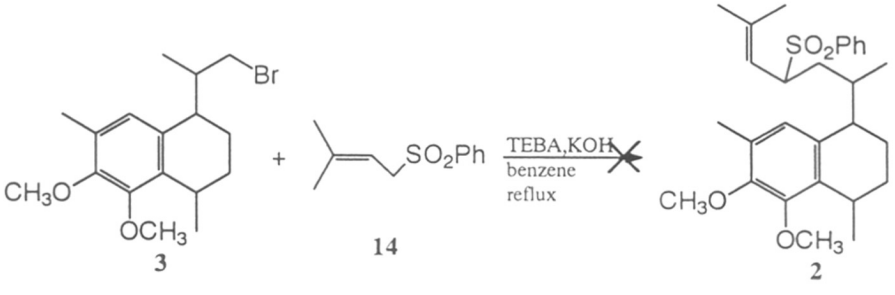
The olefinic compound **12** upon hydrogenation over palladized carbon furnished the alcohol **13** in 95% yield. The formation of **13** was confirmed by disappearance of the olefinic signal in the ^{1}H-NMR spectrum and by the presence of M^+ at 278 in the Mass spectrum.

Conversion to bromo compound **3** was effected using triphenylphospine dibromide[9] ($Ph_3P.Br_2$) which furnished compound **3** in 82% yield.



Scheme 5

Alkylation of the bromide **3** was then attempted under the standard phase transfer conditions developed for the model synthesis. However, the reaction failed to give the alkylated product **2**. Instead, the starting materials, bromide **3** and sulfone **14**, were recovered unchanged.

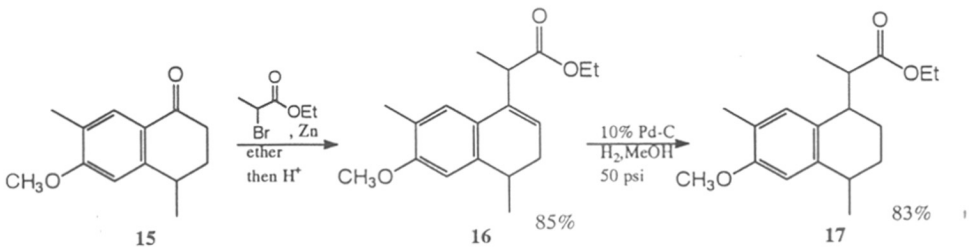


Scheme 6

At present, no explanations can be forwarded for this surprising result.

The attempted alkylation of the bromide failing to proceed to furnish sulfone **2**, it was proposed to modify the substrate in order to view the effect on the alkylation.

Hence, the β,γ-unsaturated ester **16** which had been initially prepared *via* the Reformatsky reaction on the tetralone **15** for the synthesis of Heritol (Chapter 1, Sections 1 and 2) was chosen as the starting point. Similar sequence of reactions were then attempted (*Scheme 7*).

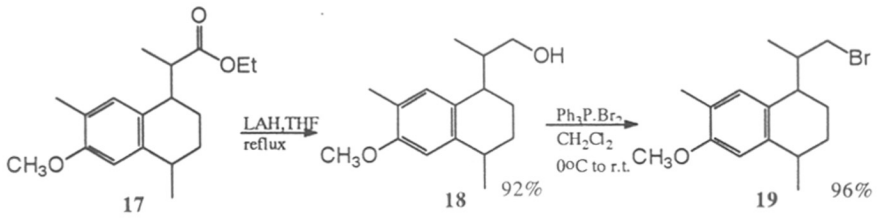


15 16 17

Scheme 7

Hydrogenation over palladized carbon furnished the ester **17** which was confirmed by the ^{1}H-NMR spectrum which showed absence of any olefinic peak.

LAH reduction of the ester functionality gave the alcohol **18** which was characterized by the presence of a peak at δ 3.5 corresponding to $\underline{CH_2}OH$ and absence of ester signals in proton spectrum and by presence of a broad peak for resulting hydroxyl group at 3390 cm^{-1} in the IR spectrum.



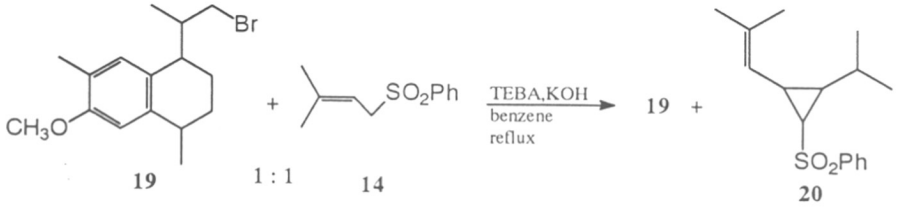
17 18 19

Scheme 8

Bromination using $Ph_3P.Br_2$ gave the bromo compound **19** which showed absence of hydroxyl peak in IR spectrum, as expected. Presence of M^+ peaks at 312 and 310 confirmed the incorporation of bromine.

Phase transfer catalyzed alkylation of the bromide **19** was then attempted which, however, gave the unreacted bromide. This was in accordance with the result obtained during alkylation with the bromide **3**.

However, the reaction also furnished a new compound which has been hitherto unreported in literature and was tentatively assigned the structure **20**.



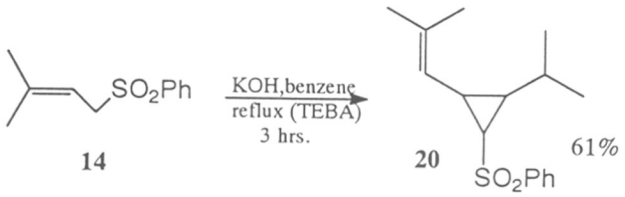
Scheme 9

The IR spectrum of **20** showed the characteristic peaks of the sulfone at 1305 and 1148 cm^{-1}.

The ^{1}H-NMR spectrum showed two multiplets at δ 7.90 and 7.60 for the 5 aromatic protons. Olefinic signal integrating for 1H appeared at δ 4.80. The proton geminal to -SO_2Ph appeared at δ 2.10 as a multiplet. Allylic proton gave a multiplet at δ 2.60. The spectrum also showed the requisite number of signals for $C\underline{H}_3$, and $C\underline{H}$ corresponding to the given structure.

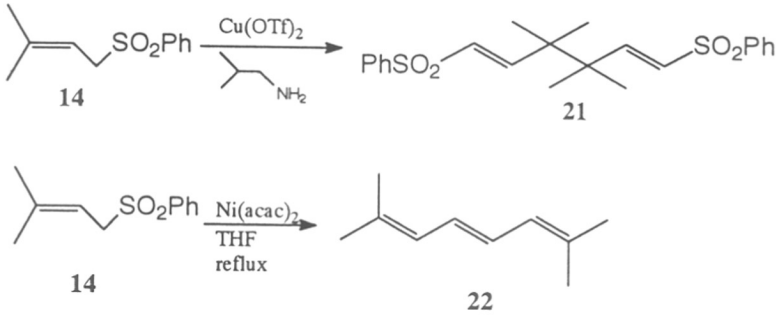
The ^{13}C-NMR spectrum further confirmed the structure by the presence of 4 methyls and 4 methines. Olefinic carbons appeared at 140.8 and 117.7 ppm.

Dimerization of prenyl sulfone was also observed when a blank reaction was carried out. Thus, prenyl sulfone in refluxing benzene in presence of KOH as base in presence or absence of catalyst (TEBA) furnished the cyclopropyl sulfone **20** in 61% yield.



Scheme 10

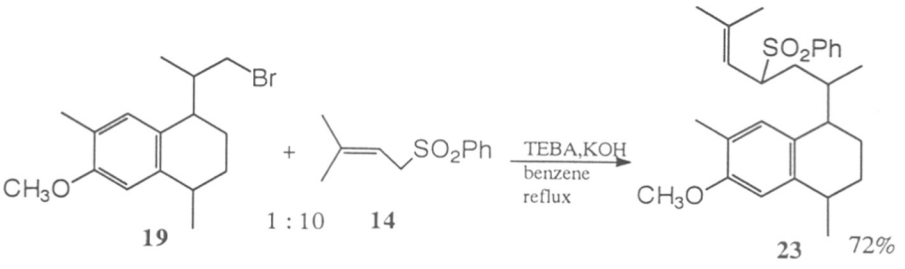
Julia *et al* have reported[10] the dimerization of prenyl sulfone in presence of $Cu(OTf)_2$ to give polyenes. The Grignard reagent of **14** on treatment with $Ni(acac)_2$[11] also gives polyenes. However, the formation of dimer **20** upon simple treatment with mild base (KOH) is unprecedented.



Scheme 11

In order to suppress the dimerization of prenyl sulfone and also to observe the effect on the alkylation with the bromide, prenyl sulfone was used in large excess to the substrate with somewhat different results.

Hence, 10 equivalent of prenyl sulfone (**14**) were treated with 1 equivalent of the bromide **19** under standard phase transfer conditions. As expected under these reaction conditions the alkylated product **23** was obtained in 72% yield.

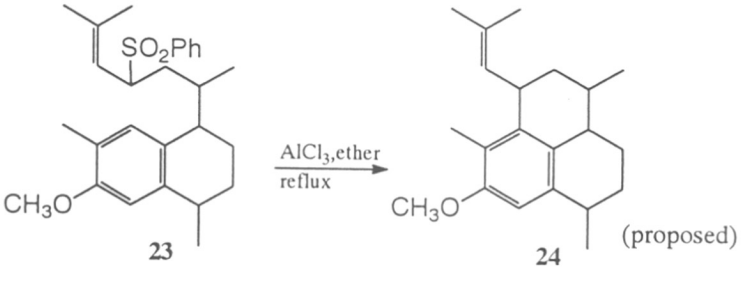


Scheme 12

The excess prenyl sulfone was converted into the cyclopropyl sulfone **20** under these conditions. The alkylated product **23** was characterized by the usual techniques.

IR spectrum of **23** showed the characteristic sulfone signals at 1300 and 1140 cm^{-1}. The ^{1}H-NMR spectrum indicated incorporation of the prenyl functionality by presence of a multiplet in the olefinic region at δ 4.8 and signals in aromatic region at δ 7.85 and 7.60 for 3 and 2H respectively. Mass spectrum showed a M^+ peak at 440 of very low intensity. This coupled with other fragmentations confirmed the product to have structure **23**.

Lewis acid catalyzed cyclization of the sulfone **23** was then attempted. Treatment with $AlCl_3$ at 0°C followed by acidic quenching of the reaction furnished a new compound which was proposed to be the cyclized product **24**.



Scheme 13

The Mass spectrum of the product showed an M^+ at 298, corresponding to that of **24**. However, complex nature of the ^{1}H-NMR spectrum of the product made an unambiguous confirmation difficult.

At this advanced stage of the synthesis of Pseudopterosin aglycone, Kocienski *et al* reported[12] their approach towards the pseudopterosins (Section 1, *Scheme 13*). This utilized an essentially similar strategy of base-catalyzed (LDA) alkylation of prenyl sulfone on the tosylate, followed by Lewis-acid catalyzed ($EtAlCl_2$) cyclization to furnish the tricyclic moiety of pseudopterosins, specifically that of Ps K.

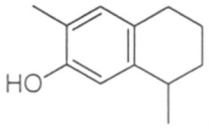
The essential strategy being similar, it was deemed superfluous to continue with the proposed route. Hence, further modifications of the conditions for cyclization and conversion to pseudopterosin aglycone were abandoned.

2.3.3 Conclusions:

Although an efficient methodology was developed for easy assembly of pseudopterosin framework, the methodology when extended to the appropriately functionalised aromatic nucleus posed some unforeseen problems. At the same time, when this work was in progress, a similar strategy was published, further establishing the efficacy and strength of the proposed strategy for the synthesis of pseudopterosin and functionalized pseudopterosin.

2.3.4 Experimental:

4,7-dimethyl-1,2,3,4-tetrahydro-6-naphthol (8)



8

The ether **6** (10g, 5.3 mmol) was dissolved in dry CH_2Cl_2 (40 ml) in a round bottom flask fitted with an addition funnel and $CaCl_2$ guard tube and the mixture was cooled to 0° to -5°C with an ice-salt mixture. A solution of BBr_3 in CH_2Cl_2 (7.58g, 30.5 ml, 5.3 mmol, 1 molar solution) was added at 0°C through the addition funnel. The solution was allowed to attain room temperature overnight with stirring when a clear brown solution was obtained. It was hydrolyzed by shaking carefully with water (50 ml) and extracted with CH_2Cl_2 (2×10 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield a residue which was chromatographed over silica gel (60-120 mesh) with 5% ethyl acetate-pet.ether as eluent to furnish the naphthol **8** (9.17g, 99%).

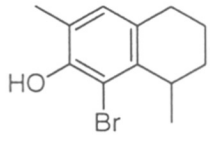
IR ($CHCl_3$): 3340, 1620, 1580, 1500, 1440, 1410, 1330 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.30 (d, J=7Hz, 3H); 1.40-2.00 (m, 4H); 2.25 (s, 3H); 2.60-2.75 (t, J=5Hz, 2H); 2.75-2.95 (m, 1H); 4.80 (bs, 1H); 6.65 (s, 1H); 6.85 (s, 1H).

^{13}C-NMR (50 MHz): 15.5(q); 21.0(t); 22.8(q); 29.2(t); 31.8(t); 32.4(d); 114.4(d); 121.6(s); 129.0(s); 131.4(d); 141.0(s); 151.7(s).

Mass (m/e): 177(M^++1,6); 176 (M^+, 48); 176(6); 161(100); 159(10); 148(15); 147(18); 146(18); 145(12); 134(36); 133(24); 131(15); 128(9); 121(13); 115(17); 105(16); 91(21); 79(11); 77(18).

5-bromo-4,7-dimethyl-1,2,3,4-tetrahydro-6-naphthol (9)



9

Naphthol **8** (9.0g, 5.1 mmol) was dissolved in 20 ml dry DMF at room temperature under N_2 atmosphere. Freshly recrystallized N-bromosuccinimide (10.9g, 6.14 mmol) was added in portions with stirring. The reaction was monitored by TLC. After 5 hours, the mixture was diluted with water (50 ml) and extracted with ethyl acetate (3×10 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The resulting residue was chromatographed over silica gel (60-120 mesh) using 5% ethyl acetate-pet.ether as eluent to give pure bromo compound **9** (12.78g, 98%) as a viscous liquid.

IR (neat): 3509, 1611, 1475, 1412, 1375, 1321, 1232, 1187, 1186 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.25 (d, J=7Hz, 3H); 1.70-1.5 (m, 4H); 2.25 (s, 3H); 2.70 (t, 2H); 3.05-3.20 (m, 1H); 5.60 (s, 1H); 6.80 (s, 1H).

^{13}C-NMR (50 MHz): 16.6(q); 17.9(t); 21.0(q); 29.0(t); 30.2(t); 32.7(d); 113.3(s); 122.9(s); 129.4(s); 130.9(d); 138.8(s); 148.6(s).

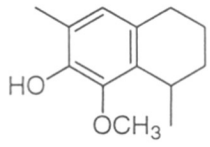
Mass (m/e): 256(M^++1,53); 254 (M^+, 45); 241(80); 239(93); 212(9); 175(9); 162(7); 160(100); 159(42); 158(15); 145(52); 132(18); 128(25); 115(39); 103(10); 91(19); 77(14).

Analysis:

Calculated for **$C_{12}H_{15}BrO$** : C=56.49%; H=5.93

Found : C=56.5%; H=5.9%

5-methoxy-4,7-dimethyl-1,2,3,4-tetrahydro-6-naphthol (10)



10

Na (4.06g, 17.64 mmol) was added in portions to dry MeOH (20 ml) in a two-necked round bottom flask fitted with a condensor and $CaCl_2$ guard tube. After the Na had completely reacted, excess methanol was distilled off and a solution of the bromo compound **9** (10g, 3.92 mmol) and anhydrous copper (II) chloride (2.11g, 1.57 mmol) in dry DMF (30 ml) was added in one portion. The green coloured mixture formed was heated at 110-115°C for 8 hrs. After the reaction was complete (TLC), the mixture was cooled and filtered through a sintered funnel to remove solid Cu salts. The filtrate was then diluted with water (100 ml) and extracted with ethyl acetate (3×10 ml). The organic layers were combined, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to furnish a brown residue which was then chromatographed over silica gel (60-120 mesh) using 5% ethyl acetate-pet.ether as eluent to furnish the pure ether **10** (6.62g, 82%).

Melting point: 82-83°C

IR (nujol): 3376, 1616, 1487, 1455, 1376, 1316, 1224 cm^{-1}

^{1}**H-NMR** (200 MHz): δ 1.25 (d, J=7Hz, 3H); 1.55-1.90 (m, 4H); 2.20 (s, 3H); 2.65 (t, 2H); 3.10 (m, 1H); 3.80 (s, 1H); 5.45 (bs, 1H); 6.65 (s, 1H).

^{13}**C-NMR** (50 MHz): 15.5(q); 18.7(t); 22.0(q); 27.8(d); 29.2(t); 30.7(t); 60.8(q); 122.7(s); 126.9(d); 128.4(s); 132.7(s); 145.0(s); 145.2(s).

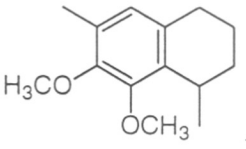
Mass (m/e): 207(M^++1,12); 206 (M^+, 77); 204(22); 192(15); 191(100); 189(27); 161(11); 159(12); 157(12); 141(11); 131(17); 129(14); 128(9); 115(13); 91(21); 77(13).

Analysis:

Calculated for $C_{13}H_{18}O_2$: C=75.69%; H=8.80%

Found : C=76.08%; H=8.60%

5,6-dimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene (11)



11

The naphthol **10** (6.5g, 3.16 mmol) was dissolved in dry acetone (20 ml) and anhydrous K_2CO_3 (10.9g, 7.9 mmol) was added to it in one portion. This was followed by dropwise addition of dimethyl sulfate (3.98g, 2.99 ml, 3.16 mmol) with stirring and after the addition was complete, the mixture was refluxed. After completion of reaction, as checked by TLC (6 hours), the mixture was cooled and the solid K_2CO_3 filtered off. The solvent was evaporated under reduced pressure and the residue dissolved in ethyl acetate (10 ml). It was washed with water (20 ml) and extracted with ethyl acetate (2×10 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. The resulting residue was chromatographed over silica gel using 5% ethyl acetate-pet.ether as eluent to furnish pure dimethyl ether **11** as a pale yellow liquid (6.73g, 97%).

IR (neat): 1609, 1483, 1408, 1337, 1320, 1232, 1118 cm^{-1}

^{1}**H-NMR** (200 MHz): δ 1.2 (d, J=7Hz, 3H); 1.6-1.8 (m, 4H); 2.2 (s, 3H); 2.6-2.7 (m, 2H); 3.1-3.2 (m, 1H); 3.8 (s, 3H); 3.9 (s, 3H); 6.6 (s, 1H).

^{13}**C-NMR** (50 MHz): 15.5(q); 18.3(t); 22.1(q); 27.4(d); 29.3(t); 30.5(t); 59.5(q); 60.0(q); 125.9(d); 129.1(s); 132.1(s); 133.8(s); 149.1(s); 160.0(s).

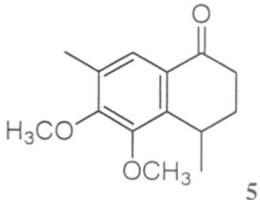
Mass (m/e): 221(M^++1, 12); 220 (M^+, 57); 205(100); 203(22); 190(24); 189(15); 175(23); 174(34); 173(17); 159(11); 145(15); 129(10); 115(13); 103(8); 91(13).

Analysis:

Calculated for $C_{14}H_{20}O_2$: C=76.33%; H=9.15%

Found : C=76.44%; H=8.9%

5,6-Dimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-one (5)



5

To a stirred ice-cooled (0°C) solution of the tetrahydronaphthalene **11** (6.5g, 2.96 mmol) in acetic acid (5ml) was added dropwise a solution of chromium trioxide (14.8g, 14.8 mmol) in propionic acid (10 ml) over 15 minutes. The temperature of the reaction mixture was maintained till the completion of reaction (4 hrs) as checked by TLC. The reaction mixture was then diluted with water (500 ml) and extracted with ethyl acetate (3×10 ml). The combined extracts were washed with saturated $NaHCO_3$ solution (10 ml) and water (10 ml), dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to give a residue. The residue was chromatographed over silica gel with 10% ethyl acetate-pet.ether to furnish the pure tetralone **5** as a yellow solid (3.46g, 50%).

IR (nujol): 1685, 1599, 1465, 1374, 1328, 1244, 1220 cm^{-1}

^{1}**H-NMR** (200 MHz): 1.35 (d, J=7Hz, 3H); 1.95-2.90 (m, 4H); 2.25 (s, 3H); 3.35 (m, 1H); 3.90 (s, 6H); 7.70 (s, 1H) cm^{-1}.

^{13}**C-NMR** (50 MHz): 15.9(q); 19.8(q); 26.9(d); 29.3(t); 33.4(t); 59.9(q); 60.6(q); 124.9(d); 127.7(s); 130.7(s); 141.9(s); 149.9(s); 156.3(s); 197.7(s).

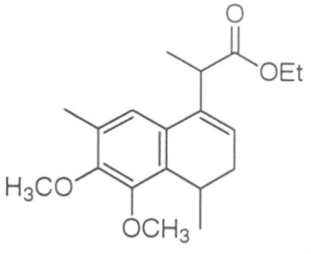
Mass (m/e): 235(M^++1, 30); 234 (M^+, 100); 220(29); 219(98); 204(23); 193(29); 192(29); 191(74); 177(17); 176(19); 175(24); 163(22); 161(14); 160(22); 159(16); 145(14); 131(15); 115(19); 105(18); 103(13); 91(32); 77(22).

Analysis:

Calculated for $C_{14}H_{18}O_3$: C=71.8%; H=7.8%

Found : C=71.29%; H=7.8%

Ethyl 2[1-(5,6-dimethoxy-4,7-dimethyl, 3,4-dihydronaphthalene)]propionate (4)



4

Reformatsky reaction was carried out according to the general procedure described in Chapter 1, Section 1 on the tetralone **5** (3.5g, 1.5 mmol) with the reagent formed from ethyl α-bromopropionate (3.25g, 1.8 mmol) and activated zinc (2.94g, 4.5 mmol). After 4 hours, the reaction upon work-up furnished the β,γ-unsaturated ester **4** (4.04g, 85%).

IR (neat): 1730, 1600, 1440, 1240, 1220, 1160 cm^{-1}

^{1}**H-NMR** (200 MHz) (mixture of diastereomers): δ 1.05, 1.10 (d, J=7Hz, 3H); 1.20, 1.25 (t, J=7Hz, 3H); 1.40, 1.45 (d, J=7Hz, 3H); 2.10-2.55 (m, 2H); 2.25 (s, 3H); 3.20-3.35 (m, 1H); 3.75 (q, J=7Hz, 1H); 3.85 (s, 3H); 3.90 (s, 3H); 4.15 (q, J=7Hz, 2H); 5.75-5.85 (m, 1H); 6.95 (s, 1H).

^{13}**C-NMR** (50 MHz) (mixture of diastereomers): 14.1(q); 15.5(q); 15.9(q); 16.4(q); 17.6(q); 19.8(q); 25.2(d); 25.5(d); 29.2(t); 30.1(t); 30.3(t); 41.5(d); 59.7(q); 60.1(q, t); 60.5(q, t);

120.4(d); 120.5(d); 122.2(d); 128.9(s); 129.0(s); 129.2(s); 132.2(s); 133.5(s); 133.8(s); 134.7(s); 135.4(s); 136.6(s); 149.6(s); 150.5(s); 150.9(s); 175.0(s).

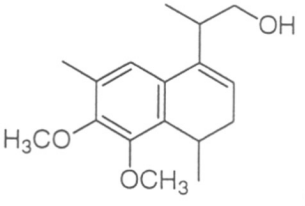
Mass (m/e): 319(M^++1, 12); 318 (M^+, 70); 245(17); 230(22); 229(100); 220(26); 217(60); 205(49); 186(14); 173(8); 159(6); 141(6); 128(9); 115(6).

Analysis:

Calculated for $C_{19}H_{26}O_4$: C=71.67%; H=8.23%

Found : C=71.71%; H=8.64%

2[1-(5,6-dimethoxy-4,7-dimethyl 3,4-dihydronaphthalene)]propanol(12)



12

The LAH reduction of ester was carried out according to general procedure described in Section 2 on the β,γ-unsaturated ester (4.0g, 0.32 mmol) with LAH powder (0.12g, 0.32 mmol) to furnish the alcohol (2.88g, 83%).

IR(Neat): 3360, 1560, 1480, 1410, 1330, 1220, 1080 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of diastereomers): δ 1.00, 1.05 (d, J=6Hz, 3H); 1.15, 1.25 (d, J=6Hz, 3H); 1.85 (bs, 1H); 2.15 (m, 1H); 2.25 (s, 3H); 2.50 (m, 1H); 3.05 (m, 1H); 3.30 (m, 1H); 3.75 (dd, J=6.8, 15Hz, 2H); 3.85 (s, 3H); 3.90 (s, 3H); 5.65 (m, 1H); 6.95 (s, 1H).

^{13}C-NMR (50 MHz): 16.0(q); 16.6(q); 17.9(q); 19.8(q); 19.9(q); 25.1(d); 25.2(d); 30.0(t); 30.3(t); 36.4(d); 36.6(d); 59.9(q); 60.7(q); 67.1(t); 119.9(d); 120.4(d); 120.5(d); 120.7(d); 129.1(s); 129.5(s); 129.8(s); 133.7(s); 136.7(s); 137.5(s); 149.7(s); 150.5(s).

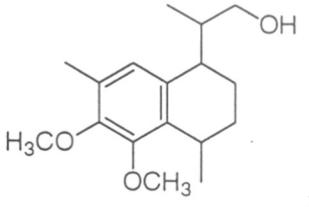
Mass (m/e): 277(M^++1, 22); 276(M^+, 100); 245(36); 243(52); 231(10); 217(77); 212(40); 202(28); 186(27); 172(18); 157(14); 141(17); 128(26); 115(22); 105(6); 91(17); 83(14); 77(14); 65(7); 55(10).

Analysis:

Calculated for $\mathbf{C_{17}H_{24}O_3}$: C=73.88%; H=8.75%

Found : C=73.78%; H=8.91%

2-[1-(5,6-dimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene)]propanol (13)



13

Hydrogenation at 50 psi for 6 hours of the olefin **12** (2.8g, 1 mmol) according to procedure described in Section 2 using 10% palladized carbon (0.28g) gave the alcohol **13** (2.68g, 95%).

IR ($CHCl_3$): 3400, 1550, 1420, 1350, 1230, 1090, 1040 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of diastereomers): δ 0.75, 1.15 (d, J=6.8Hz, 3H); 1.2 (d, J=6.8Hz, 3H); 1.65-1.75 (m, 4H); 2.25 (s, 3H); 1.90 (m, 1H); 2.80 (m, 1H); 3.15 (m, 1H); 3.65 (m, 2H); 3.80 (s, 3H); 3.9 (s, 3H); 6.80, 6.85 (s, 1H).

^{13}C-NMR (50 MHz) (mixture of diastereomers): 11.4(q); 15.95(q); 16.0(q); 17.4(t); 19.3(t); 21.8(q); 27.2(d); 27.3(d); 29.1(t); 29.3(t); 38.2(d); 39.2(d); 39.4(d); 41.1(d); 59.8(q); 60.3(q); 65.0(t); 66.6(t); 124.2(d); 124.7(d); 129.1(s); 129.2(s); 134.58(s); 134.64(s); 134.7(s); 135.2(s); 135.5(s); 148.8(s); 149.0(s); 150.5(s); 150.7(s).

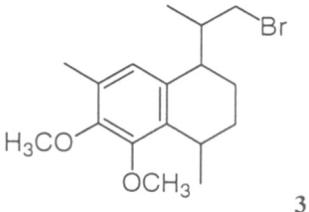
Mass (m/e): 279(M^++1, 5); 278(M^+, 30); 220(25); 219(100); 217(10); 204(12); 189(10); 188(25); 173(8); 161(4); 145(3); 131(6); 129(6); 115(4); 91(3).

Analysis:

Calculated for $C_{17}H_{27}O_3$: C=73.35%; H=9.41%

Found : C=73.65%; H=9.53%

2-[1-(5,6-dimethoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene)-1-bromopropane] (3)



3

Bromination of the alcohol **13** (2.5g, 0.9 mmol) using Ph_3P (2.83g, 1.08 mmol) and bromine (0.63 ml, 1.94g, 1.08 mmol) according to the general procedure described in Section 2 furnished the bromide **3** (2.52g, 82%).

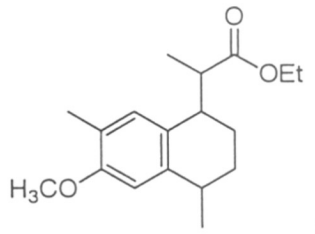
IR (CCl_4): 1480, 1400, 1320, 1230, 1070 cm^{-1}

^{1}H-NMR (200 MHz): δ 1.00, 1.10 (d, J=6Hz, 3H); 1.30 (m, 3H); 1.50-1.65 (m, 2H); 1.80-2.00 (m, 2H); 2.35 (s, 3H); 2.20-2.60 (m, 1H); 3.10-3.40 (m, 2H); 3.45 (d, J=6Hz, 2H); 3.80 (s, 3H); 3.85 (s, 3H); 7.25 (s, 1H).

^{13}C-NMR (50 MHz) (mixture of diastereomers): 13.6(q); 15.7(q); 16.9(t); 17.1(t); 18.6(t); 21.6(q); 26.9(d); 28.5(t); 28.8(t); 29.6(t); 37.77(t); 38.7(t); 39.0(t); 39.2(d); 39.4(d); 42.4(d); 59.6(q); 60.1(q); 123.9(d); 124.1(d); 129.1(s); 129.3(s); 133.4(s); 133.8(s); 135.1(s); 148.8(s); 150.4(s).

Mass (m/e): 342(M^+, 8); 340(M^+, 8); 220(16); 219(100); 204(10); 189(16); 188(18); 173(7); 159(5); 129(9); 128(7); 115(8); 105(5); 91(9); 77(6).

Ethyl-2[1-(6-methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene)]propionate (17)



17

Hydrogenation of the β,γ-unsaturated ester **16** (4.5g, 1.56 mmol) under hydrogen pressure (50 psi, 6 hrs) according to general procedure (Section 2) gave the ester **17** (4.12g, 91%).

IR (neat): 1720, 1610, 1570, 1500, 1450, 1400, 1370, 1330 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of isomers): δ 1.00-1.35 (m, 9H); 1.55-1.95 (m, 4H); 2.20 (s, 3H); 2.65-3.05 (m, 3H); 3.35 (s, 3H); 4.10-4.20 (q, 2H); 6.65 (s, 1H); 6.85 (s, 1H).

^{13}C-NMR (50 MHz) (mixture of isomers): 14.0(q); 15.7(q); 20.7(t); 23.0(q); 23.3(q); 23.9(t); 24.9(t); 28.1(t); 28.4(t); 32.0(d); 32.8(d); 39.4(d); 40.5(d); 40.6(d); 43.4(d); 44.0(d); 44.2(d); 54.8(q); 59.8(t); 59.9(t); 109.1(d); 109.3(d); 109.5(d); 122.9(s); 123.0(s); 123.8(s); 128.6(s); 128.8(s); 129.5(d); 131.6(d); 140.5(s); 140.8(s); 141.1(s); 155.9(s); 156.1(s); 156.2(s); 175.7(s); 175.8(s); 175.9(s).

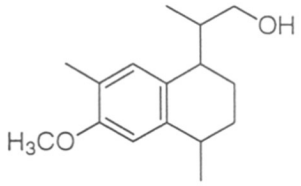
Mass (m/e): 232(2); 190(67); 188(9); 176(14); 175(100); 160(17); 148(12); 147(9); 128(13); 115(15); 91(14); 88(36); 81(14); 70(15); 55(14).

Analysis:

Calculated for $C_{18}H_{26}O_3$: C=74.48%; H=8.97%

Found : C=73.61%; H=8.98%

2-[1-(6-methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene)]propanol (18)



18

LAH (0.52g, 1.38 mmol) reduction of the ester **17** (40g, 1.38 mmol) according to procedure described in Section 1, furnished the alcohol **18** (3.15g, 92%).

IR (neat): 3390, 1610, 1560, 1500, 1460 cm^{-1}

^{1}H-NMR: (200 MHz) (mixture of diastereomers): δ 1.05, 1.10 (d, J=7Hz, 3H); 1.30 (d, J=7Hz, 3H); 1.50 (bs, 1H); 1.55-2.00 (m, 4H); 2.70-2.95 (m, 2H); 3.35-3.70 (m, 2H); 3.85 (s, 1H); 6.60, 6.65 (s, 1H); 7.00 (s, 1H).

^{13}C-NMR (50 MHz) (mixture of diastereomers): 11.9(q); 15.8(q); 15.9(q); 16.1(q); 21.7(t); 22.7(t); 23.0(q); 23.2(q); 28.7(t); 28.9(t); 30.1(t); 32.7(d); 32.8(d); 37.6(d); 38.9(d); 39.4(d); 40.1(d); 55.0(q); 65.0(t); 66.1(t); 108.7(d); 109.5(d); 109.8(d); 123.4(s); 123.5(s); 123.7(s); 129.5(d); 130.2(d); 130.4(d); 140.8(s); 141.0(s); 141.4(s); 155.4(s); 155.7(s).

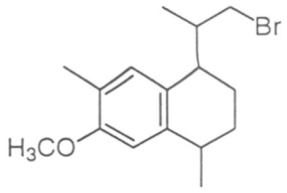
Mass (m/e): 248(M^+, 14); 190(19); 189(100); 188(19); 187(23); 174(10); 173(6); 159(8); 158(7); 129(5); 128(7); 115(7); 105(4); 91(4); 77(4); 55(7).

Analysis:

Calculated for $\mathbf{C_{16}H_{24}O_2}$: C=77.42%; H=9.68%

Found : C=77.62%; H=9.92%

2-[1-(6-methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene)]-1-bromopropane (19)



19

Bromination of the alcohol **18** (3.0g, 1.2 mmol) using PPh_3 (3.8g, 1.45 mmol) and bromine (0.75 ml, 2.32g, 1.45 mmol) according to the procedure described in *Section II*, gave the bromo compound **19** (3.61g, 96%).

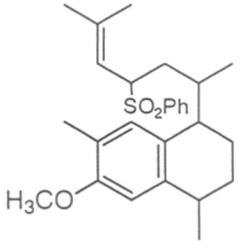
IR ($CHCl_3$): 1610, 1500, 1450, 1370, 1250, 910 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of diastereomers): δ 0.95, 1.20 (d, J=7Hz, 3H); 1.30 (d, J=7Hz, 3H); 1.55-1.95 (m, 4H); 2.20 (s, 3H); 2.30-2.50 (m, 1H); 2.75-3.05 (m, 2H); 3.25-3.55 (m, 2H); 3.85 (s, 3H); 6.65 (s, 1H); 7.00 (s, 1H).

^{13}C-NMR (50MHz) (mixture of diastereomers): 14.6(d); 16.1(d); 17.3(d); 17.7(t); 21.3(t); 23.4(d); 23.5(d); 28.5(t); 28.9(t); 32.8(q); 32.9(q); 38.8(t); 39.2(q); 39.4(q); 40.0(t); 41.8(d); 55.2(q); 109.8(d); 110.0(d); 124.0(s); 129.4(s); 129.7(s); 129.8(d); 129.9(s); 130.3(d); 141.1(s); 141.3(s); 156.0(s); 156.2(s).

Mass (m/e): 312(M^+, 4); 310(5); 269(2); 230(3); 190(14); 189(100); 187(17); 174(7); 159(7); 144(5); 128(4); 115(4); 83(5).

1-[(1,5-dimethyl-3-phenylsulfonyl)-4-hexenyl]-6-methoxy-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene (21)



21

PTC alkylation was carried out according to the general procedure given in Section 2. Bromide **19** (0.1g, 0.032 mmol) when treated with prenyl sulfone (6.675g, 0.32 mmol) in presence of powdered KOH (1.0g, 1.8 mmol) and TEBA (catalytic) gave the sulfone **21** (0.1g, 72%) and the cyclopropyl sulfone **20** (0.23g) after chromatography.

IR ($CHCl_3$): 1440, 1300, 1210, 1140, 1080 cm^{-1}

^{1}H-NMR (200 MHz) (mixture of diastereomers): δ 0.75 (d, J=6.5Hz, 3H); 0.95 (d, J=6.5Hz, 3H); 1.05-1.90 (m, 7H); 1.70 (s, 3H); 1.75 (s, 3H); 2.15 (s, 3H); 2.55-2.70 (m, 2H); 3.60-3.85 (m, 1H); 3.85 (s, 3H); 4.65-5.00 (m, 1H); 6.50-7.90 (m, 7H).

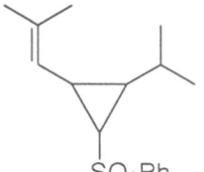
Mass (m/e): 440(M^+, 1); 299(2); 298(3); 215(1); 189(13); 188(32); 187(6); 173(3); 159(4); 137(21); 136(83); 123(6); 109(20); 108(16); 107(10); 95(100); 92(14); 91(23); 81(26); 79(23); 77(57).

Analysis:

Calculated for **$C_{27}H_{36}O_3S$** : C=73.60%; H=8.24%

Found : C=73.73%; H=8.39%

3-isopropyl-2-(2-methyl-1-propene)1-phenylsulfonyl cyclopropane (20)



20

Prenyl sulfone (1.54g, 0.7 mmol) was refluxed in dry benzene (20 ml) in presence of powdered KOH (2.0g, 3.5 mmol). After 3 hours, the reaction was worked up by adding water (10 ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate (2×10 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and the

solvent evaporated off under reduced pressure. The residue was chromatographed over silica gel (60-120 mesh) using 20% ethyl acetate-pet.ether to furnish the cyclopropyl sulfone **20** (0.622g, 61%).

IR (neat): 1447, 1305, 1148, 1087 cm^{-1}

^{1}H-NMR (200 MHz): δ 0.75 (d, J=6.6Hz, 3H); 0.95 (d, J=6.6Hz, 3H); 1.15-1.30 (m, 1H); 1.45-1.60 (m, 1H); 1.69(s, 3H); 1.71 (s, 3H); 2.05 (t, J=4.6Hz, 1H); 2.60 (m, 1H); 4.71 (dd, J=1.35,8.36Hz, 1H); 7.50-7.65 (m, 3H); 7.85-7.95 (m, 2H).

^{13}C-NMR (50 MHz): 18.3(q); 21.3(q); 22.1(q); 23.8(d); 25.6(q); 27.2(d); 33.5(d); 46.1(d); 117.6(d); 127.4(d); 128.7(d); 129.1(d); 133.2(d); 137.2(s); 140.8(s).

Mass (m/e): 279(M^++1, 1); 278(M^+, 1); 137(84); 121(8); 109(18); 95(100); 93(26); 91(26); 81(54); 77(58); 67(44); 57(57); 55(46).

Analysis:

Calculated for **$C_{16}H_{22}O_2S$** : C=69.03%; H=7.97%

Found : C=68.96%; H=8.21%

2.3.5 References:

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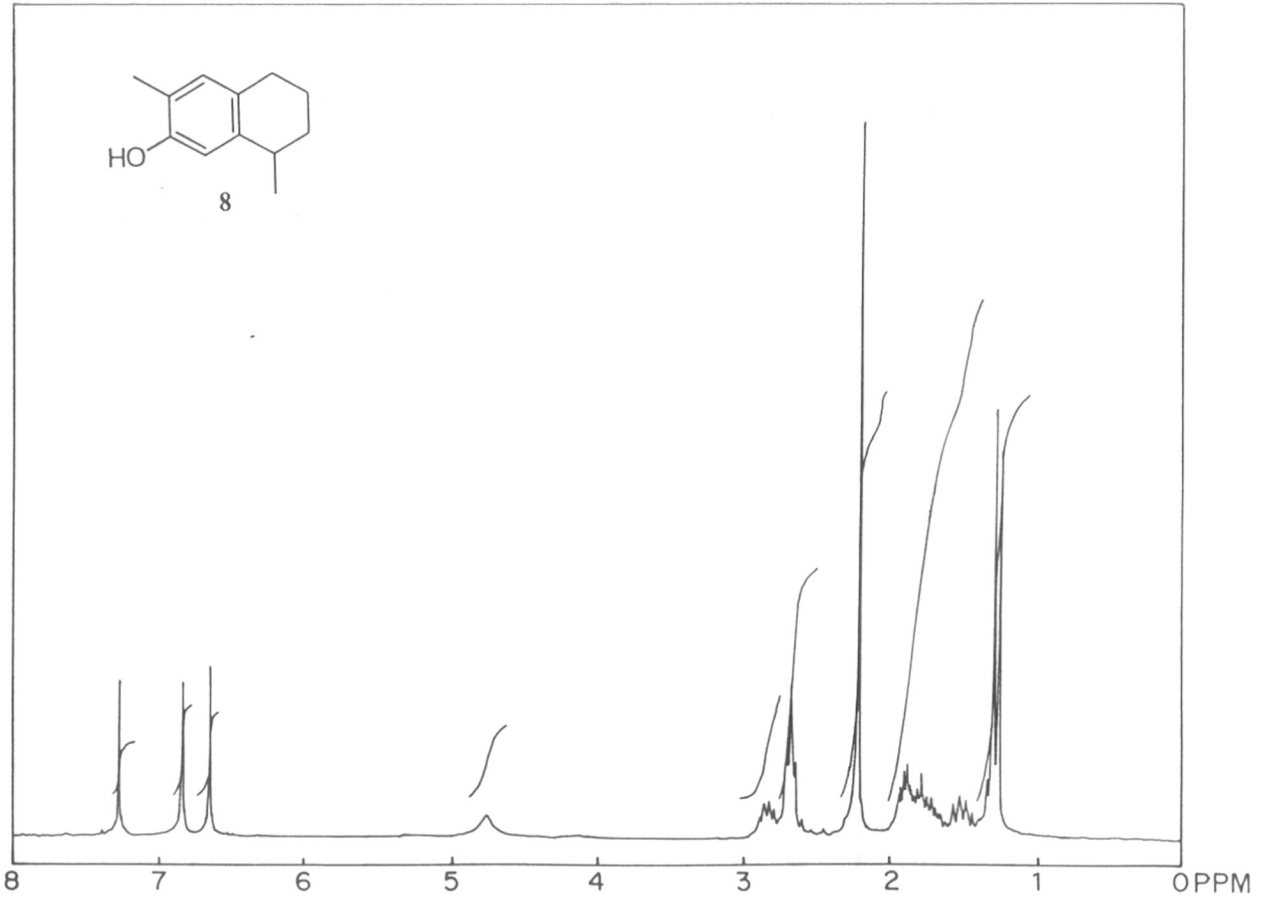

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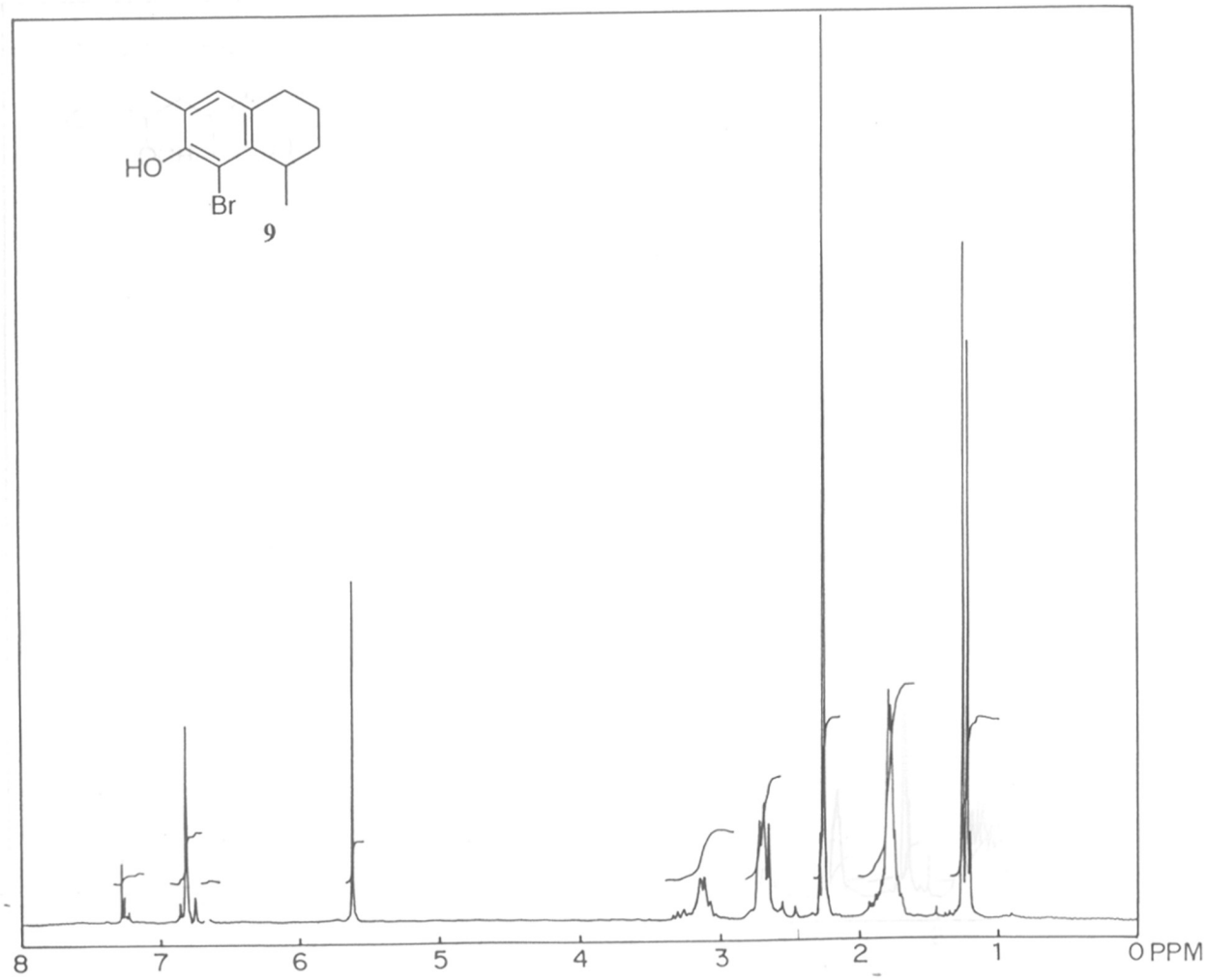

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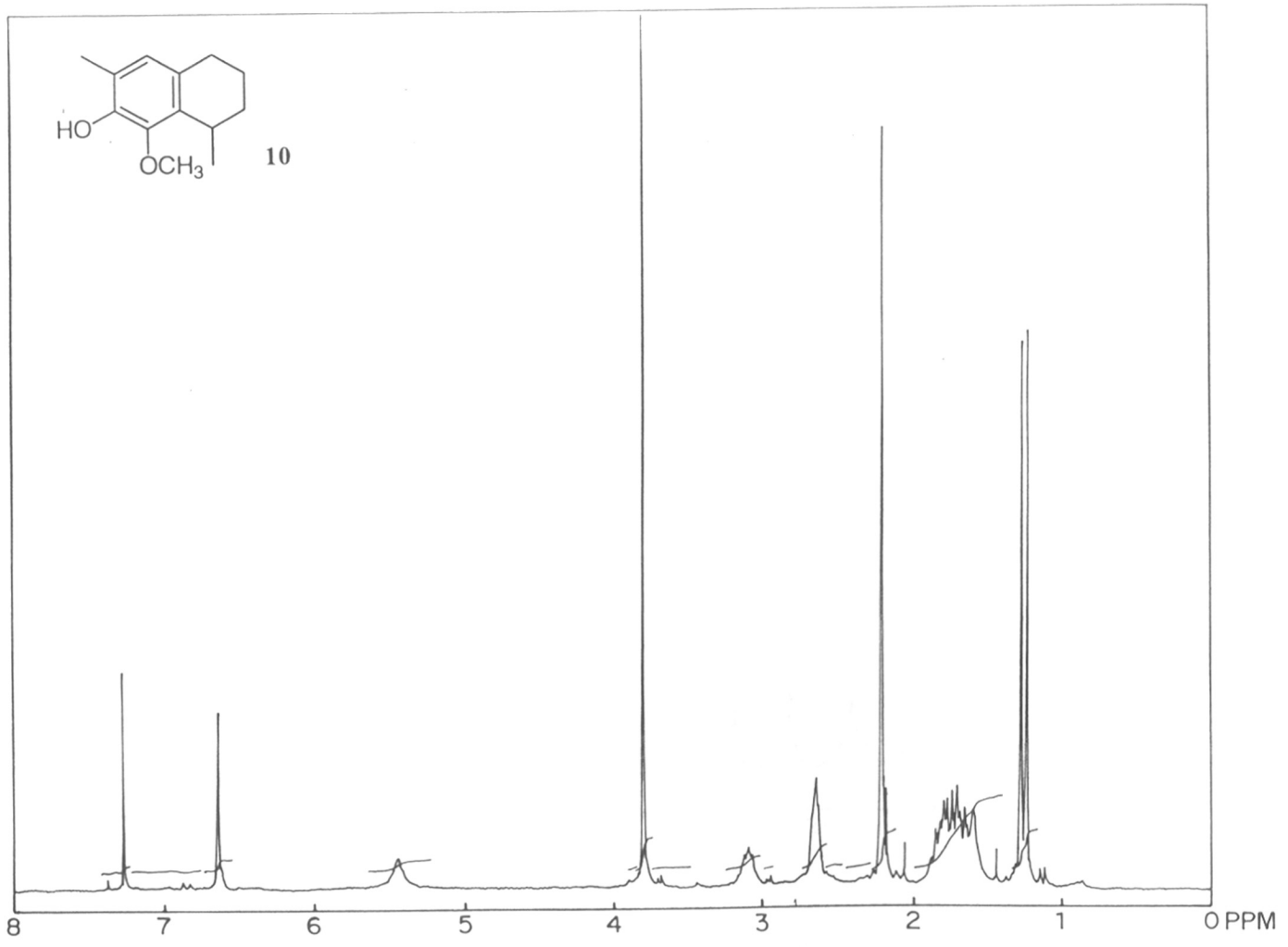

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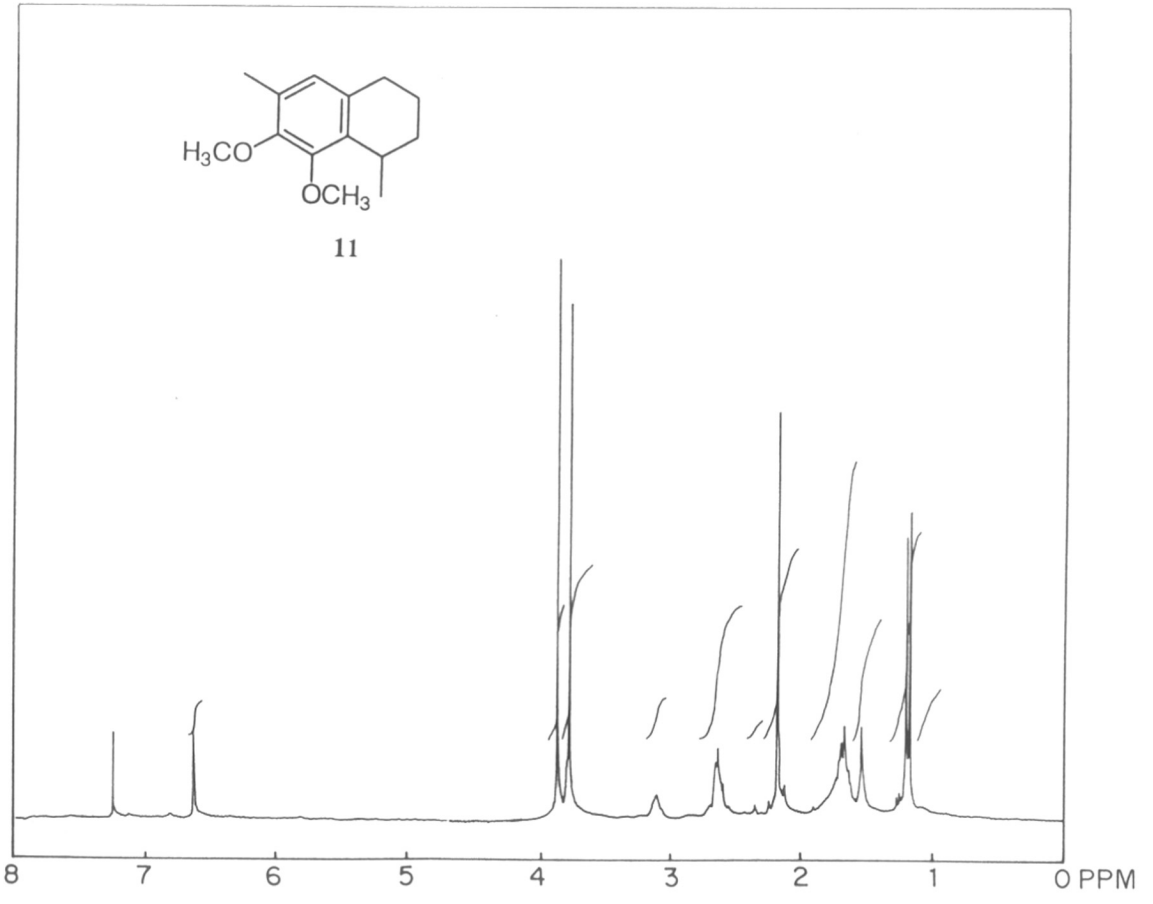

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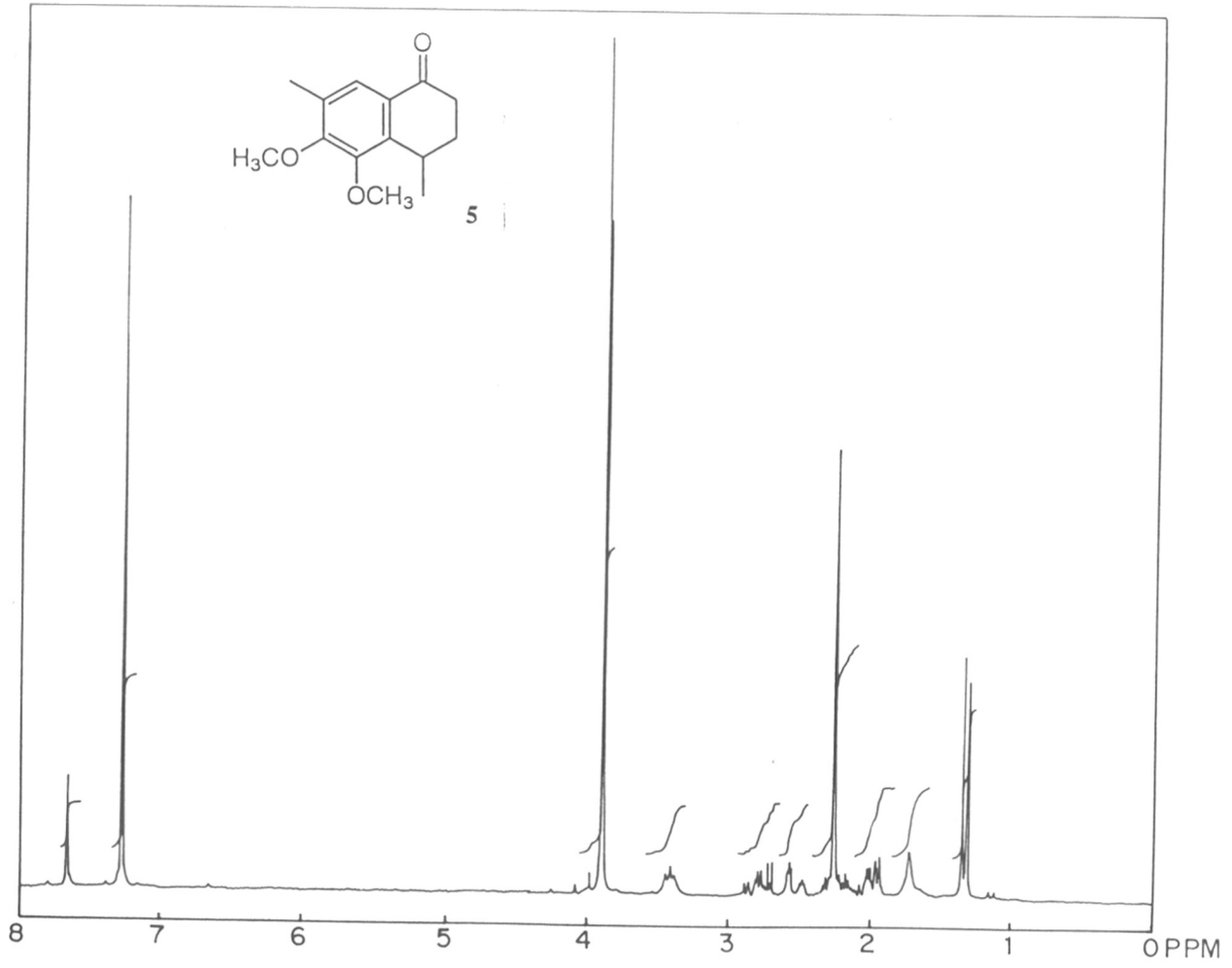

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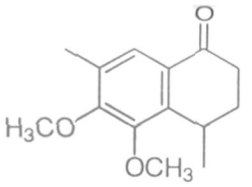

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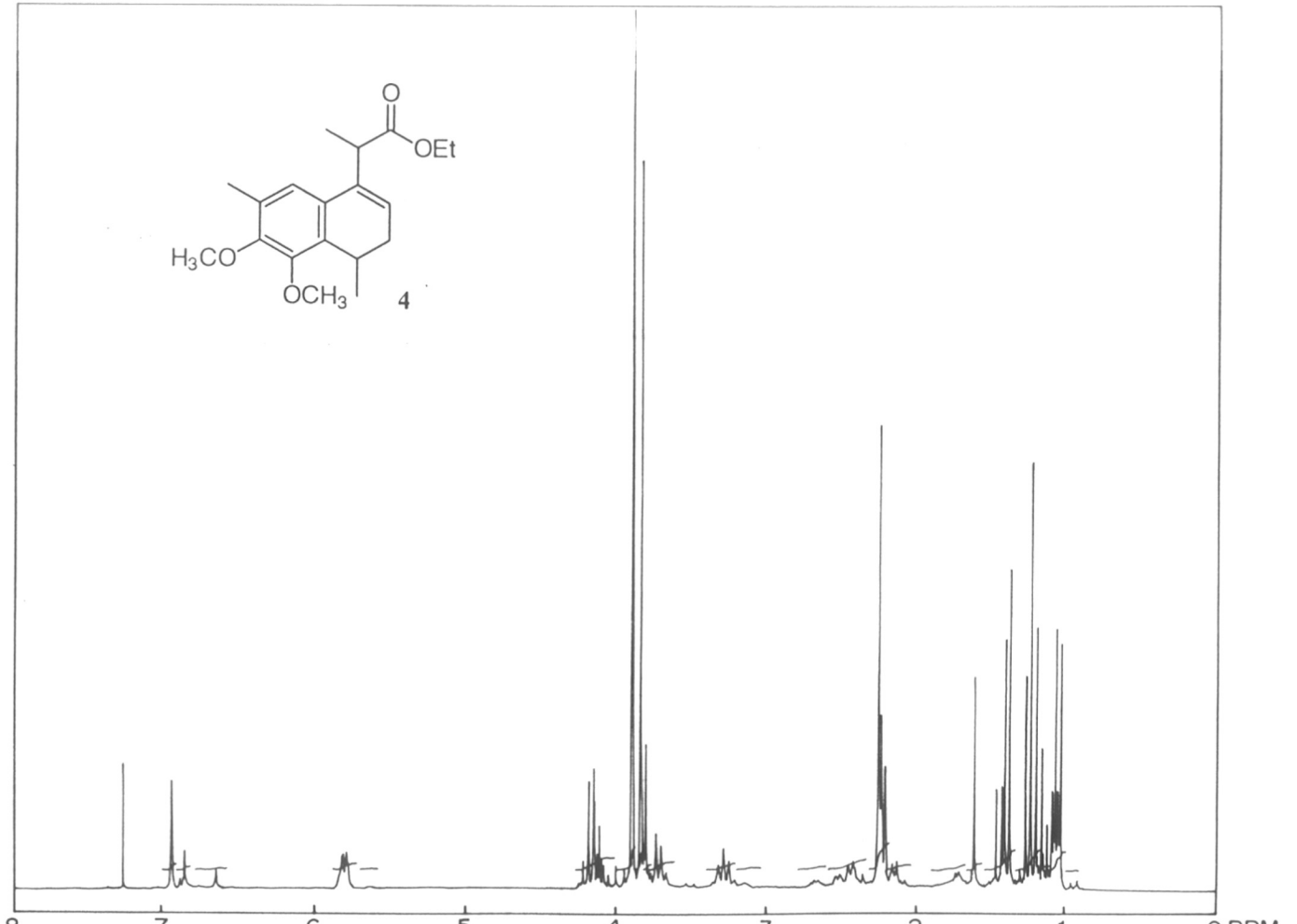

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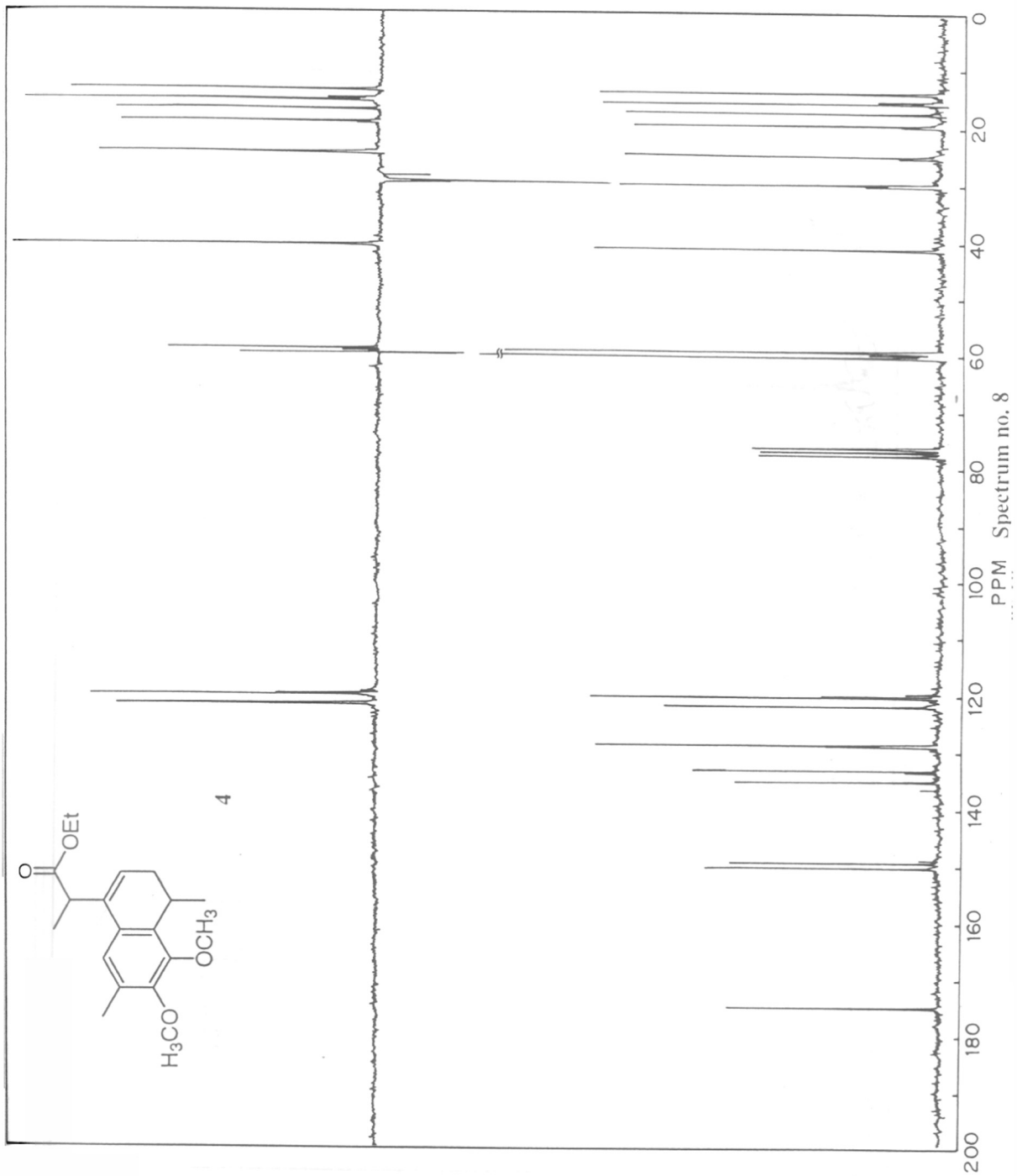
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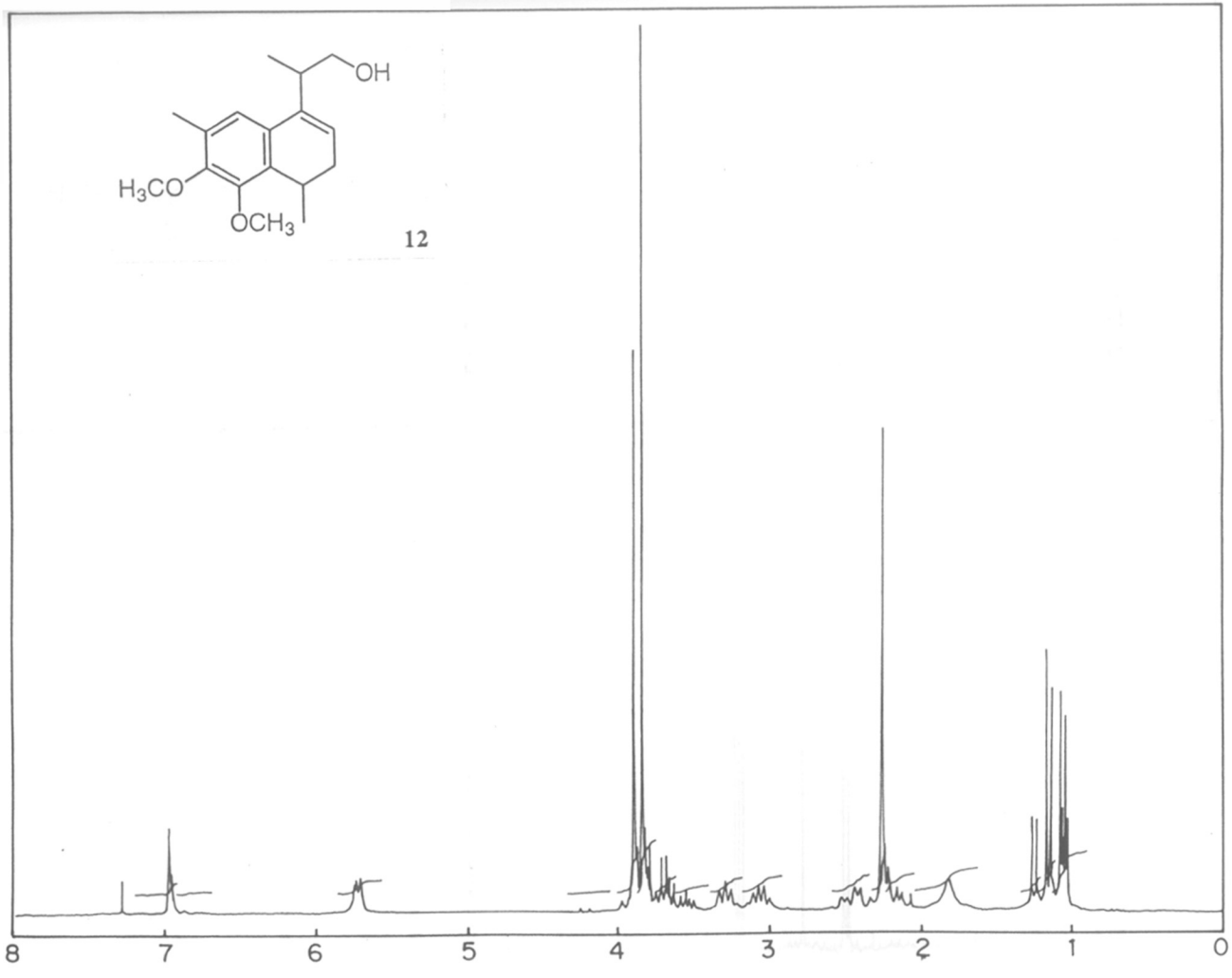

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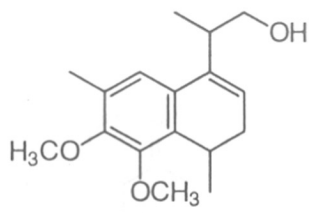

12

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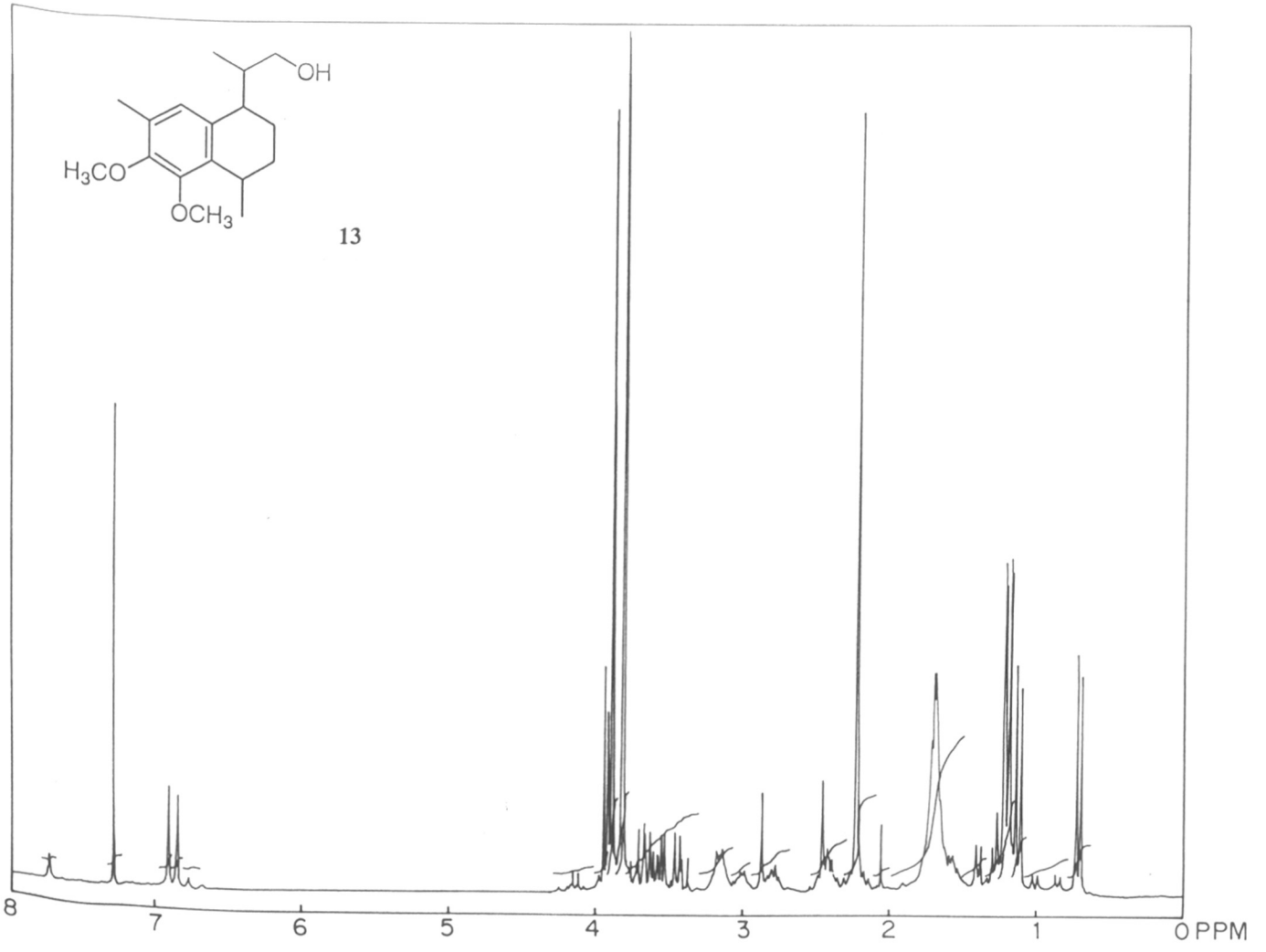

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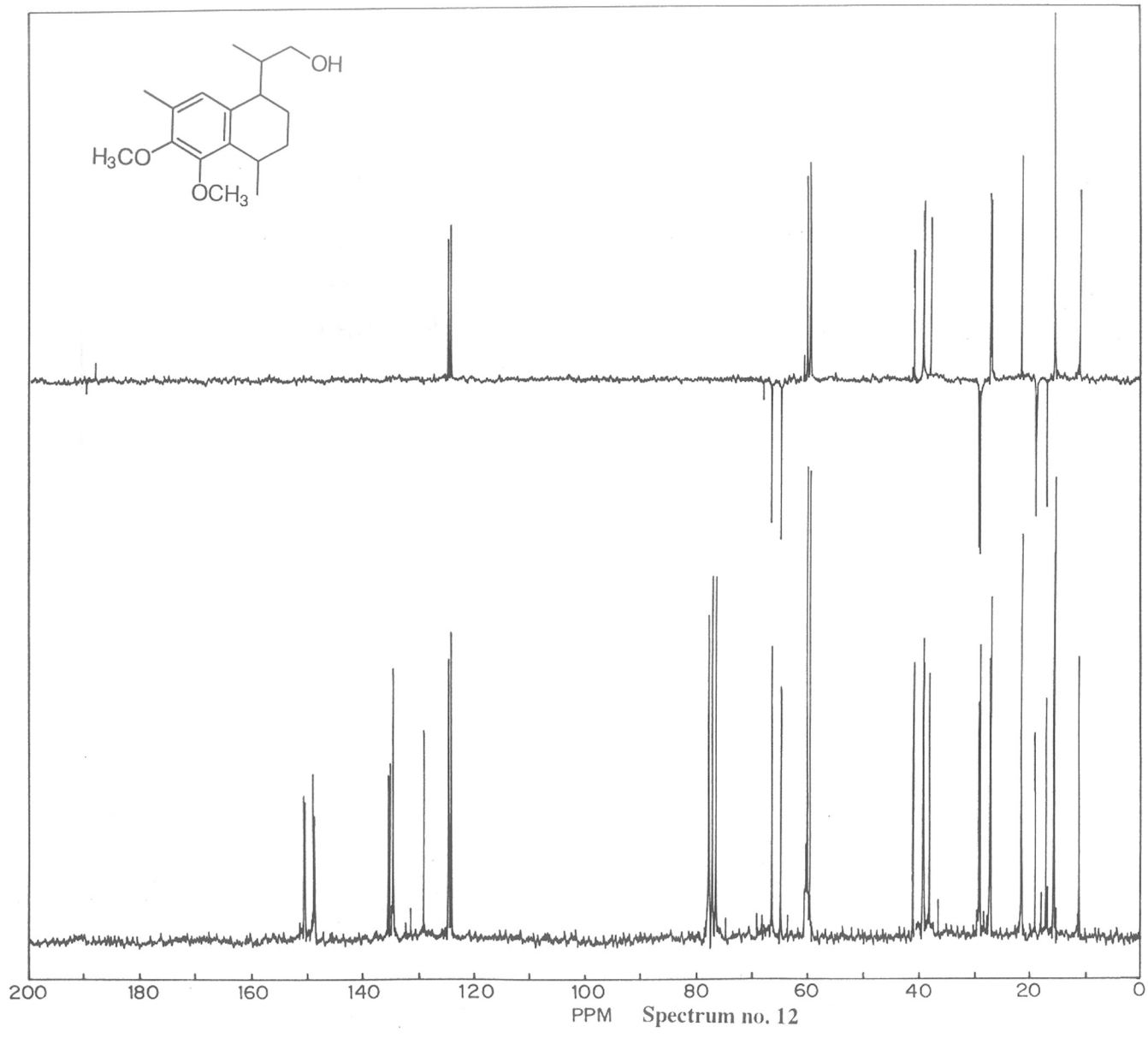

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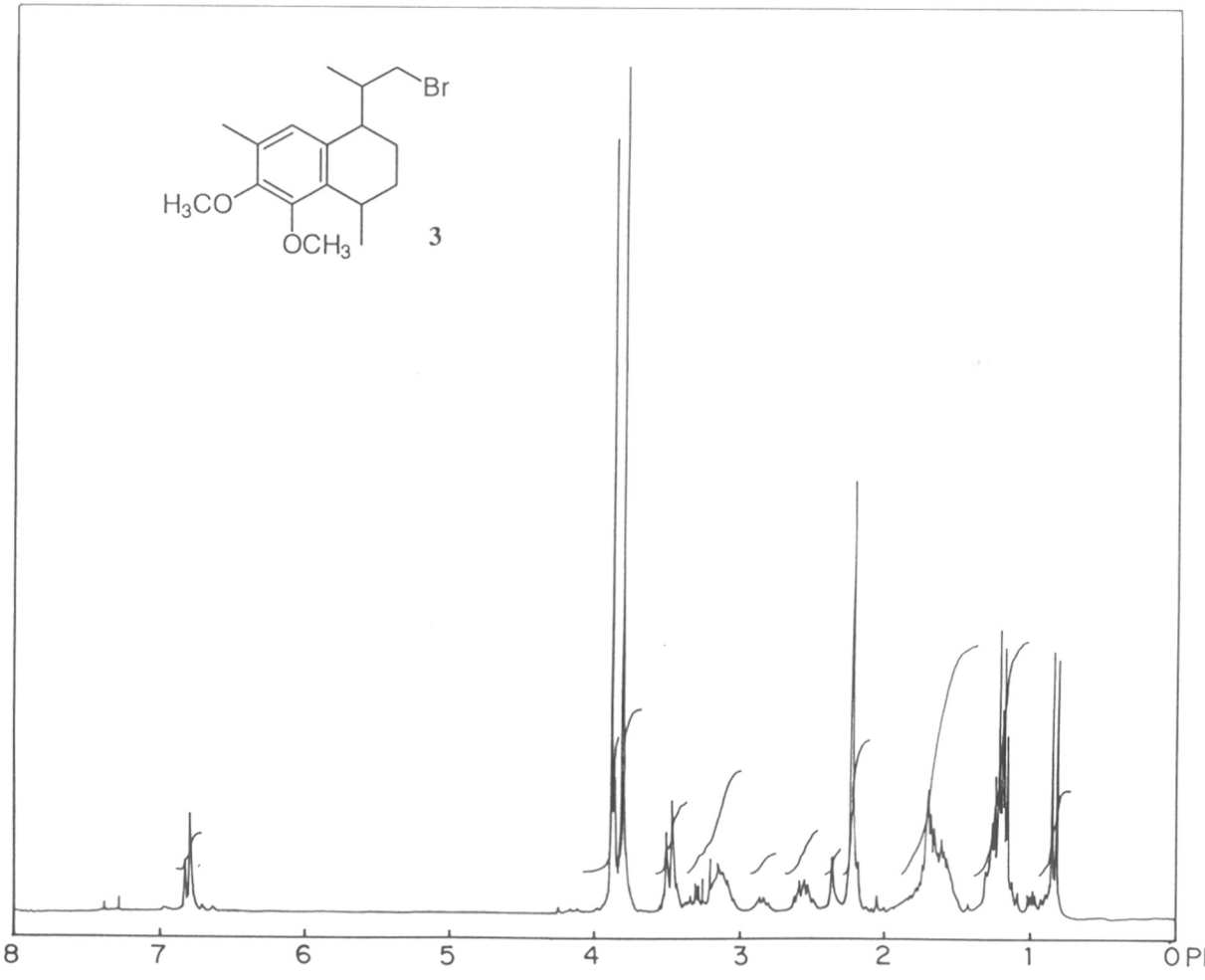

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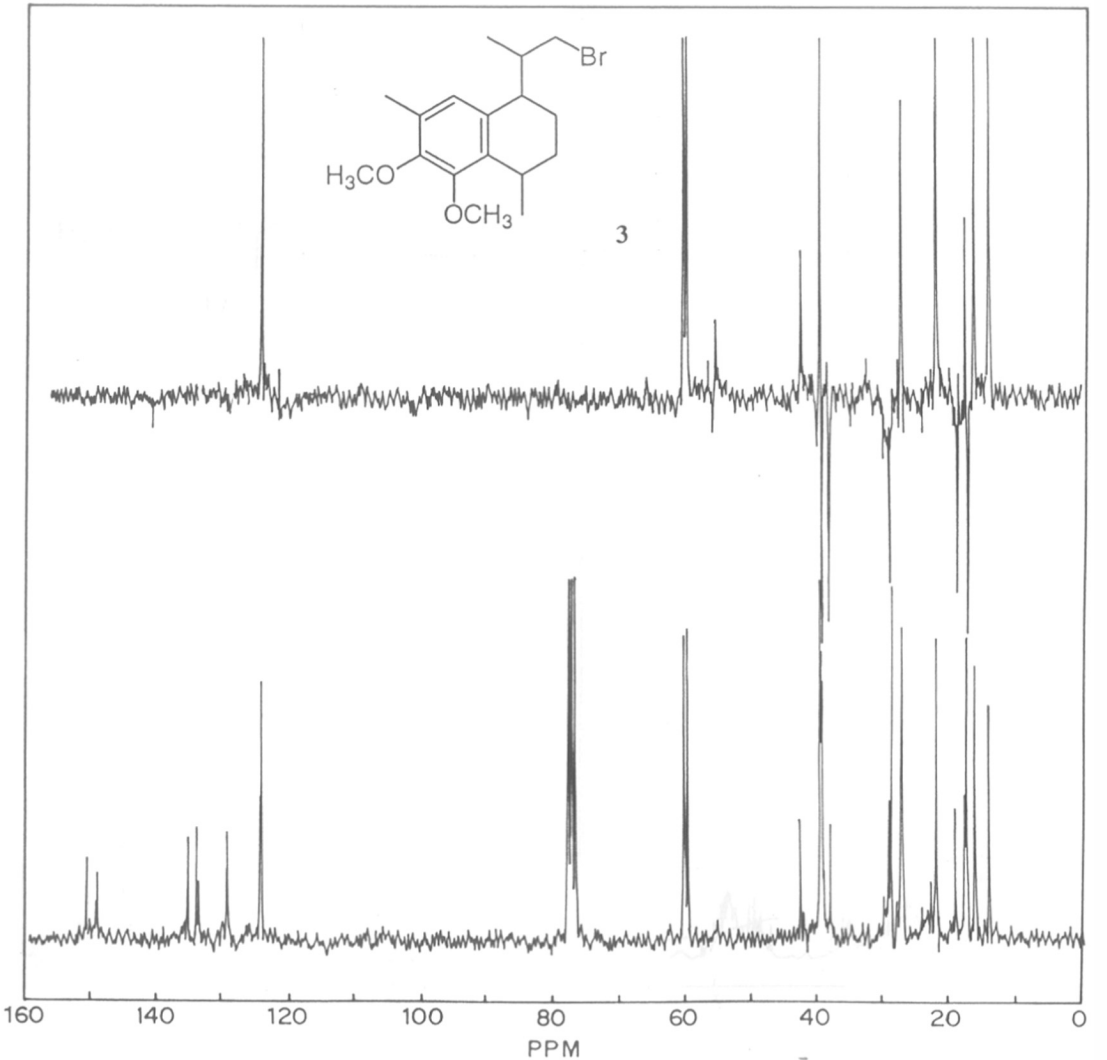

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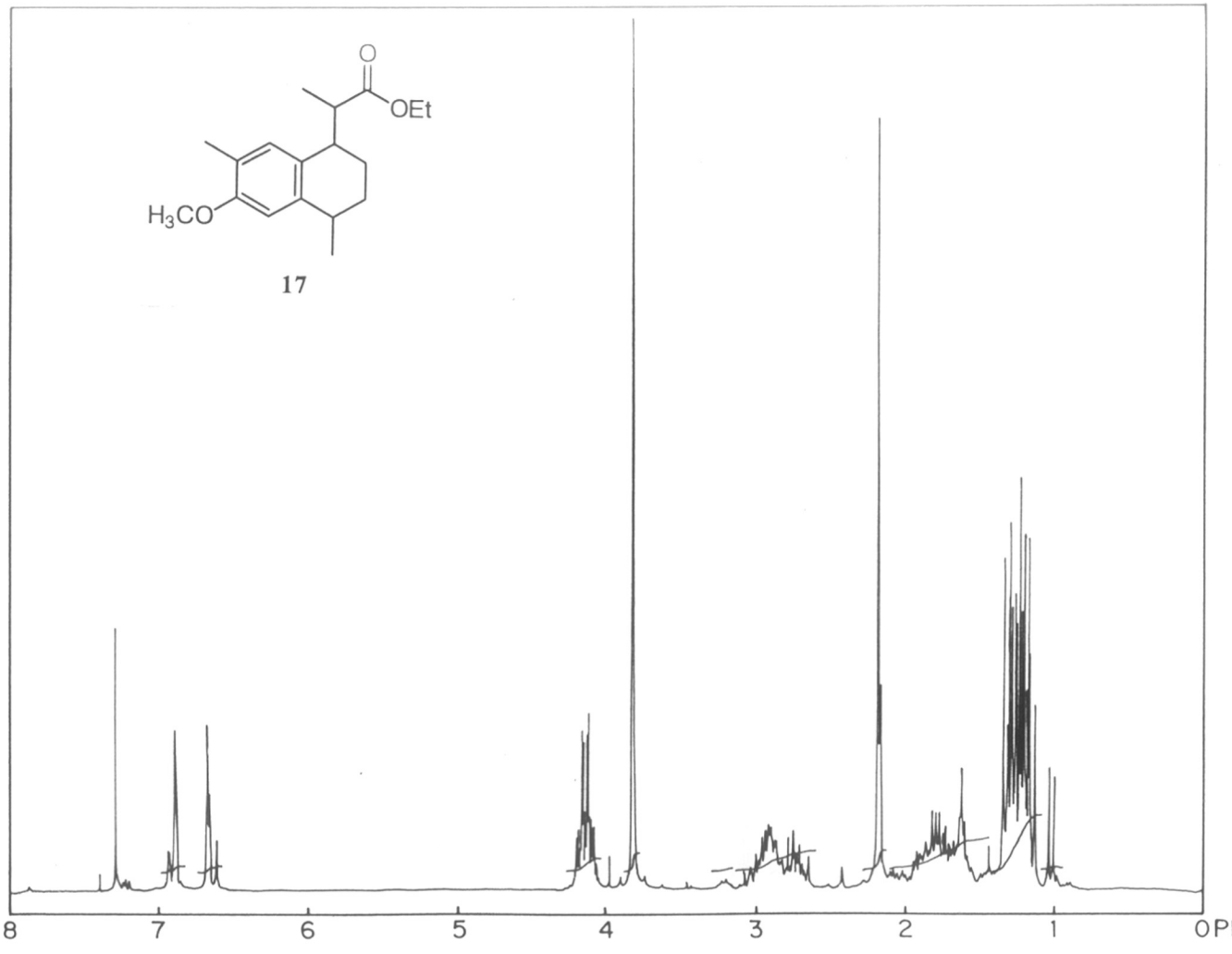

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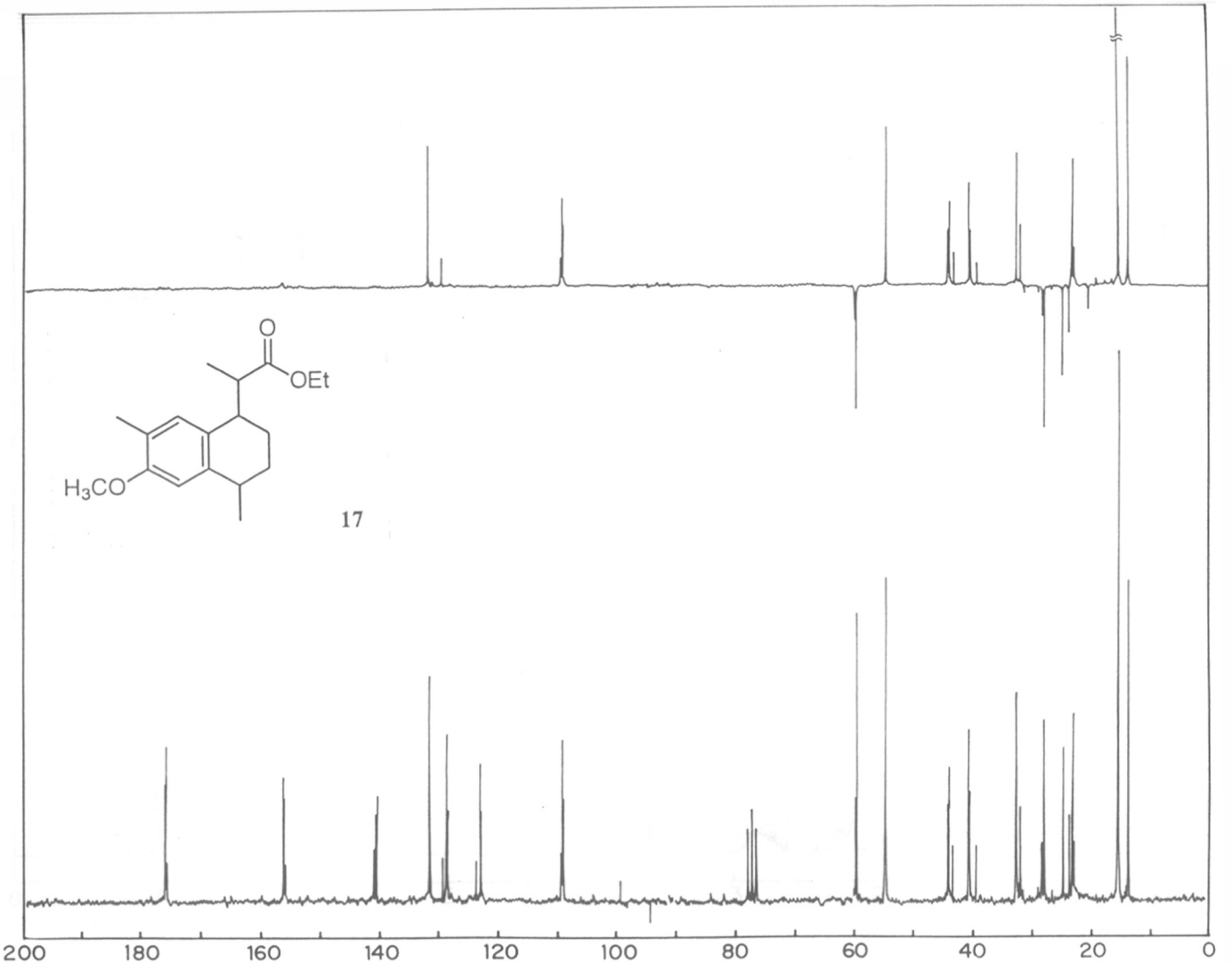

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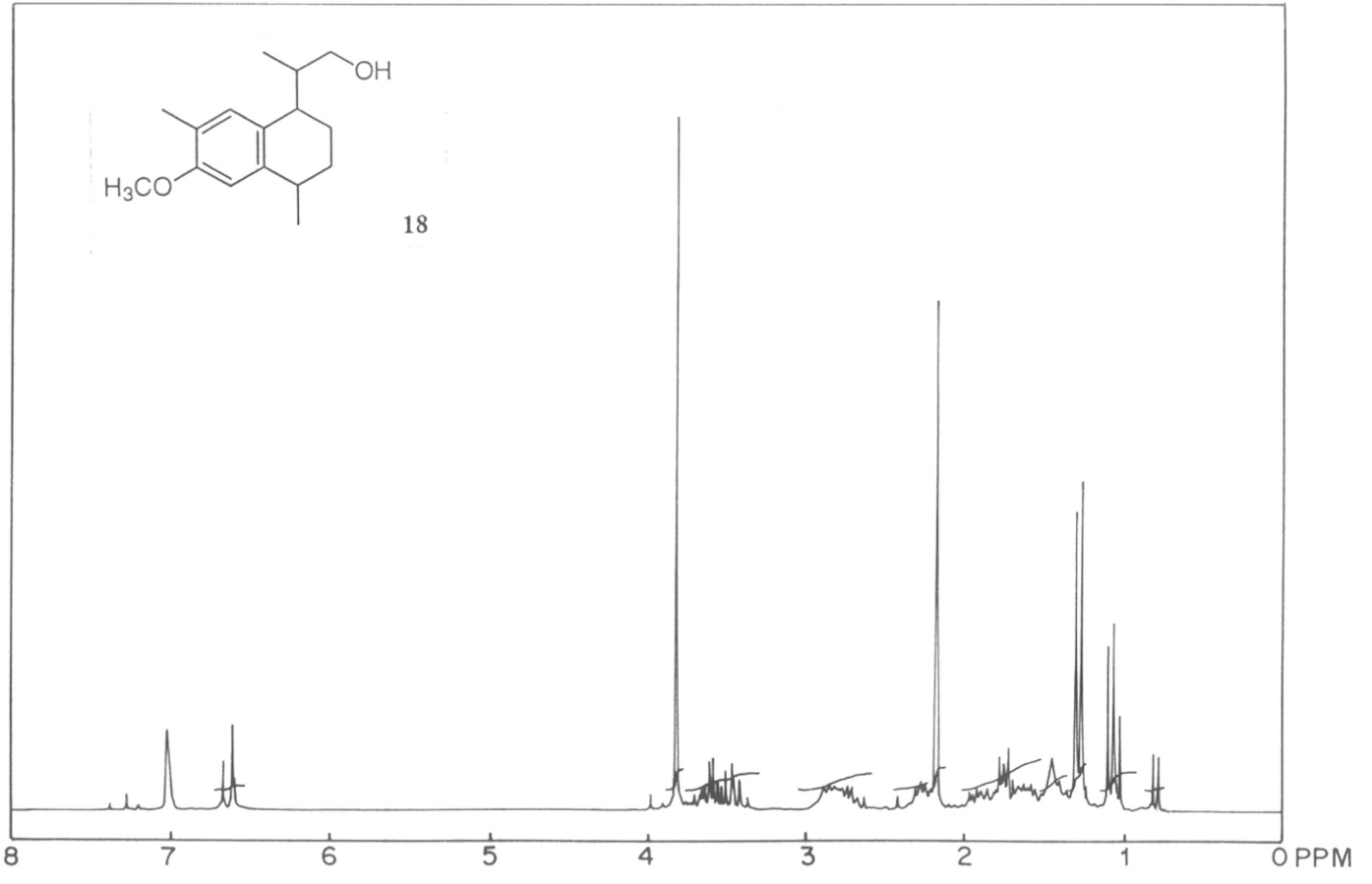

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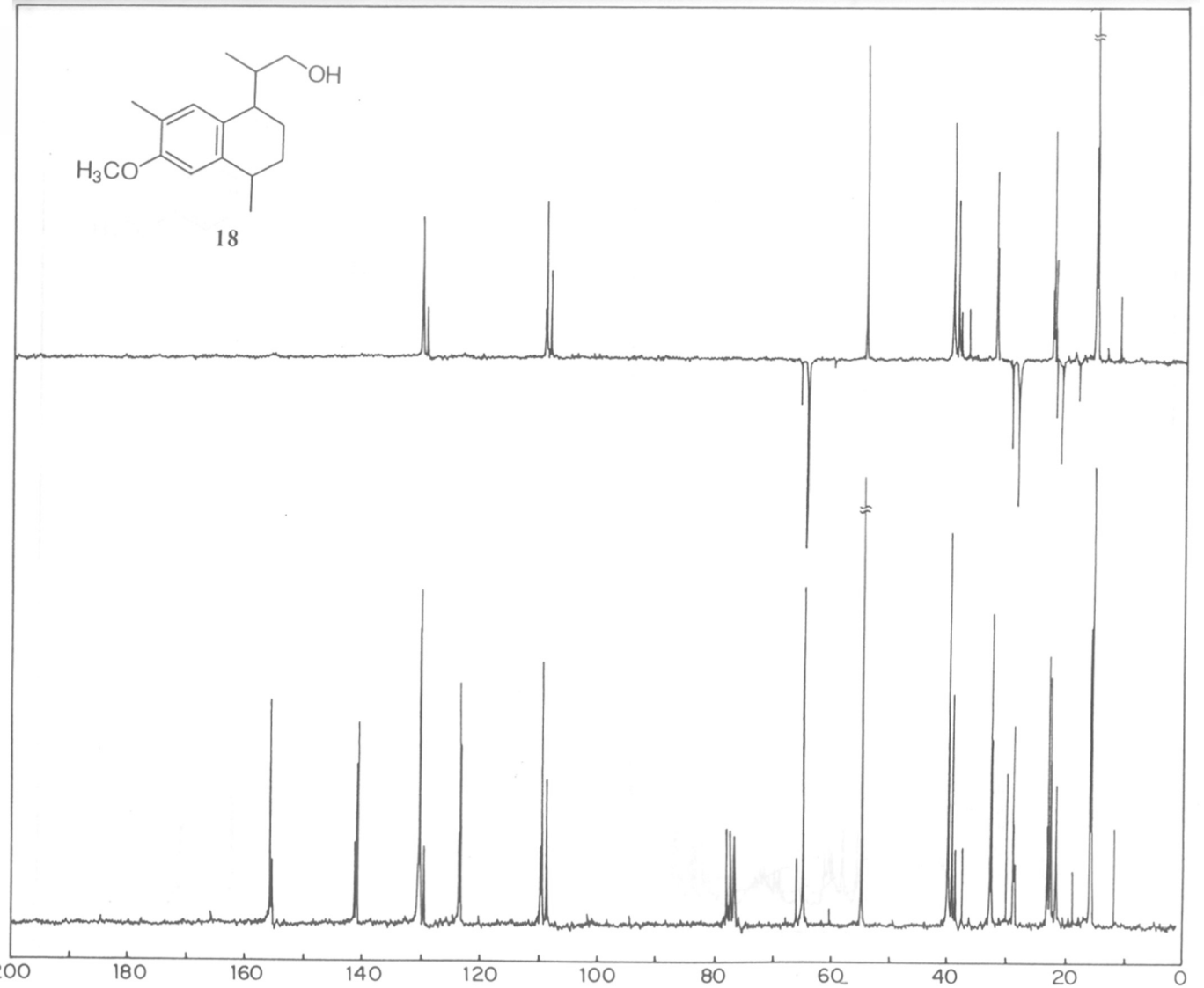

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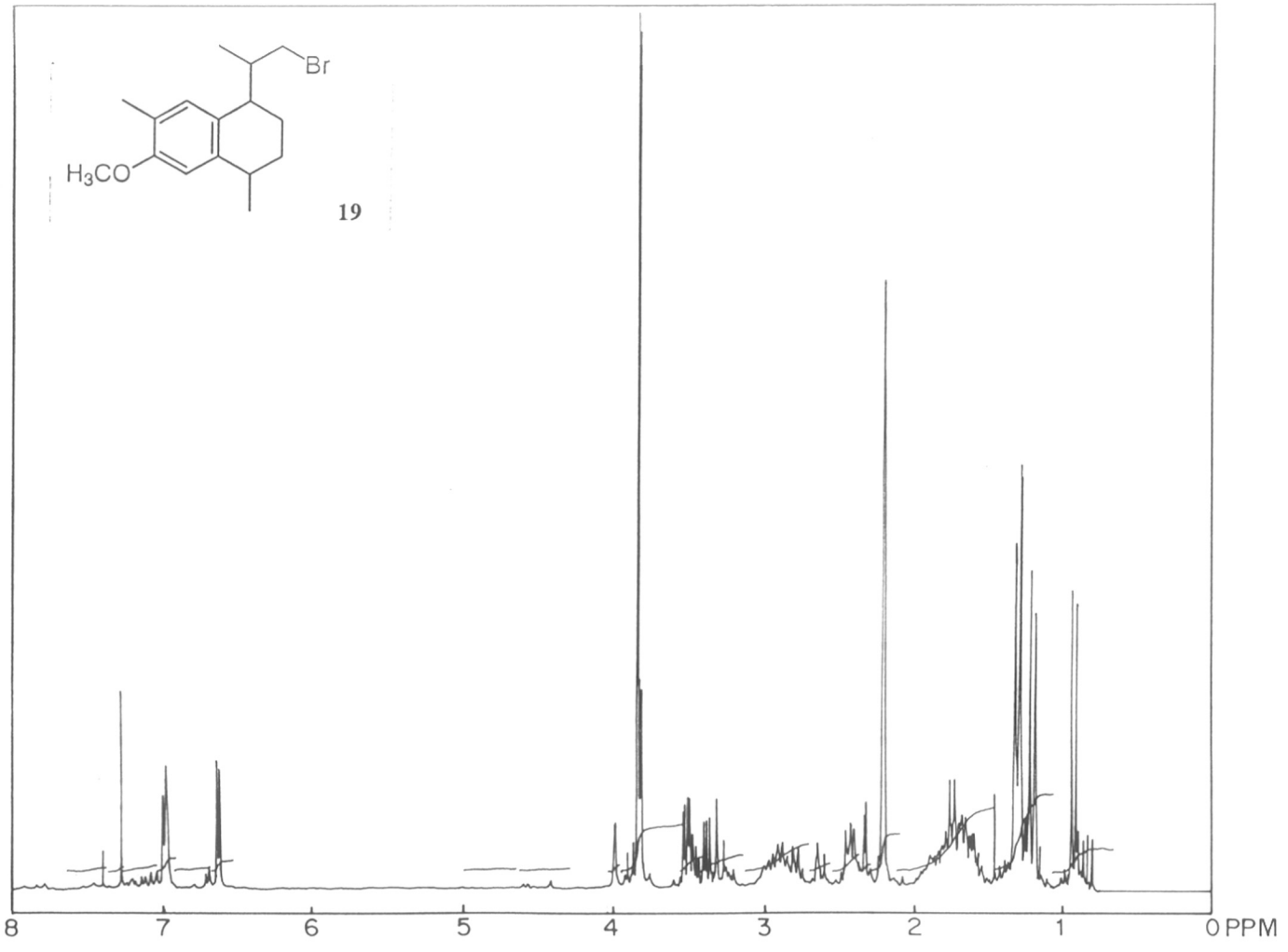

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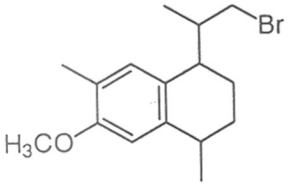

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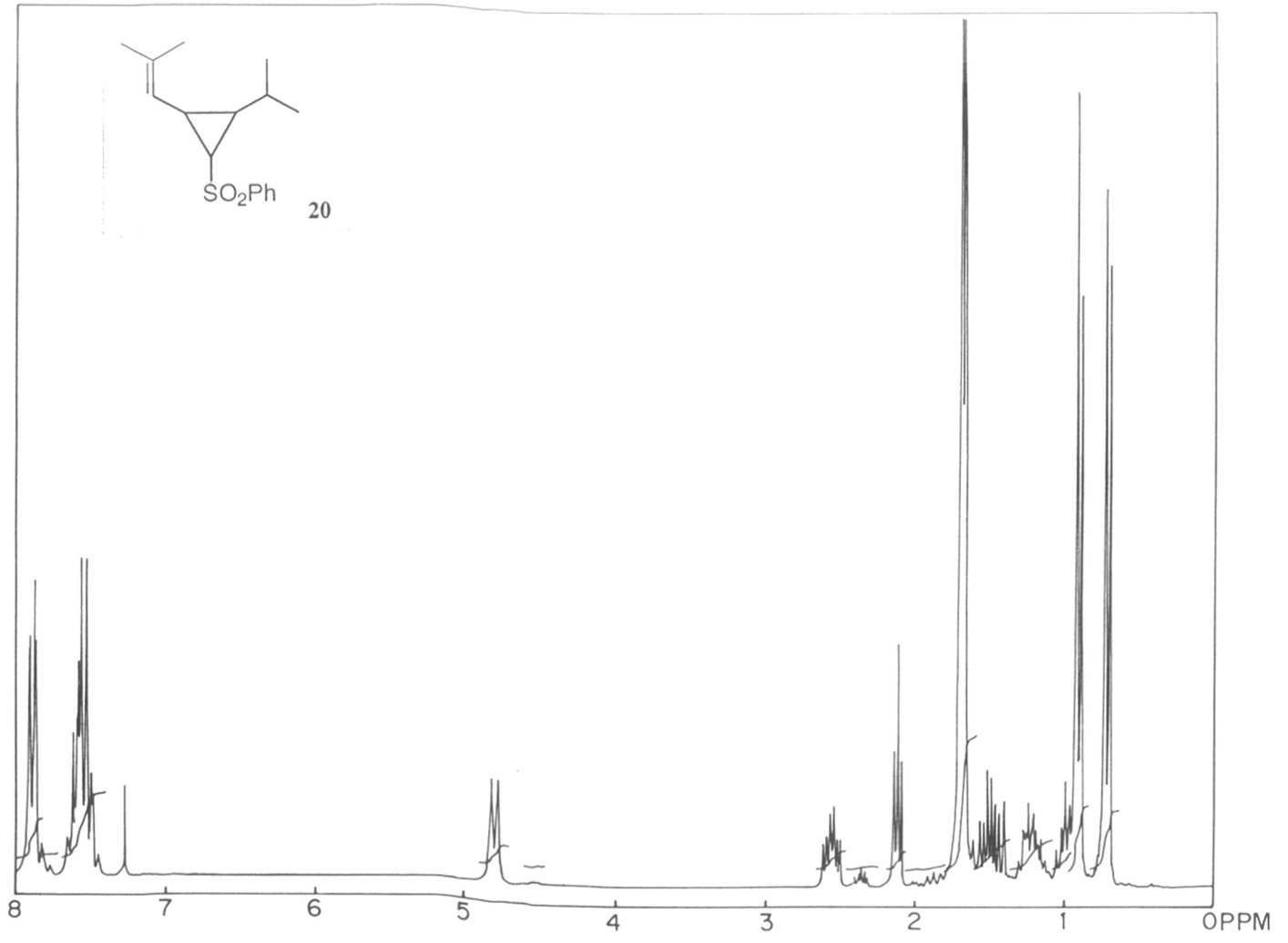

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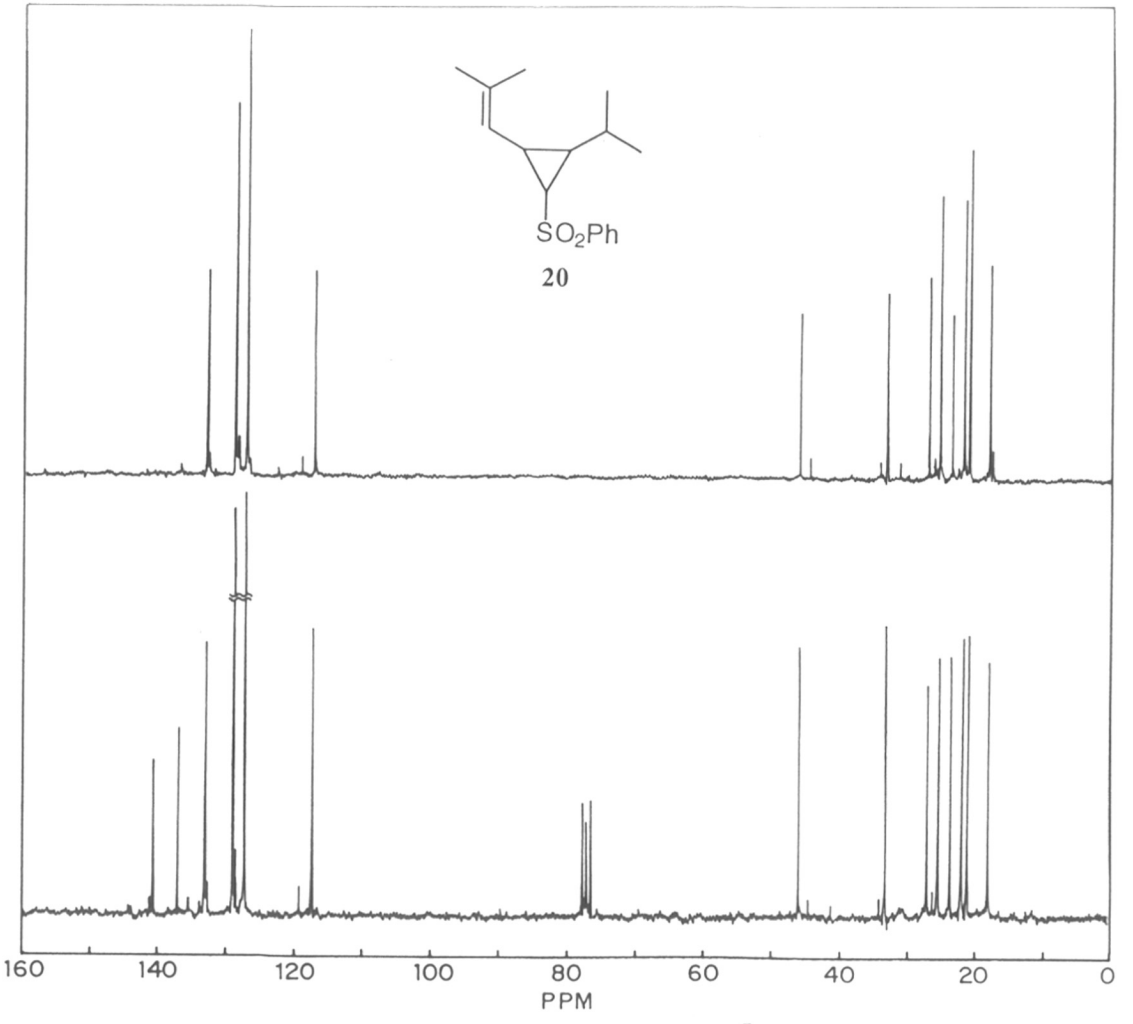


Spectrum no. 22

CHAPTER 3

Synthetic Conversions using Peroxides

3.0 Introduction:

The oxidation of aldehydes to carboxylic acids or esters is one of the most frequently encountered reactions in organic chemistry. It has been accomplished in a variety of ways which can be either two-step transformations or by direct oxidation in one pot.

Two-step transformations include the oxidation of cyanohydrins or the oxidation/ozonolysis of acetals and hemiacetals which in turn have been prepared from the starting aldehydes.

One-pot conversion of aldehydes to acids or esters is effected by oxidation of the substrate, followed by hydrolysis or alcoholysis of the intermediate without its isolation from the reaction mixture.

3.1 Literature Survey:

A wide variety of oxidation methods have been reported for the conversion of aldehydes to carboxylic acids and/or esters *via* a one-step procedure. Some are conventional reagents like permanganate or chromium reagents which are used for oxidation of other functional groups also. These regularly used methodologies along with a few more recently reported oxidants are presented here.

a. Permanganate reagents:

Potassium permanganate is one of the most popular oxidizing agent and is frequently used for oxidations of the carbonyl group in acidic, basic or neutral medium.[1] Generally, the corresponding acids are formed. The by-product of this oxidation reaction is the insoluble MnO_2 which can be removed easily from the potassium salt of the resulting carboxylic acid in aqueous solution.

However, $KMnO_4$ is unstable to heat and releases oxygen in boiling water or refluxing pyridine-H_2O solutions. Hence, the reactions have to be carried out at the lowest

temperatures possible. Also $KMnO_4$ does not dissolve easily in non-aqueous medium in which most organic substrates are soluble.

Many substrates may not be able to survive the powerful oxidizing capacity of $KMnO_4$. Hence, buffered solutions of $KMnO_4$ in ^tBuOH using 5% NaH_2PO_4 as buffer were developed[2] for the oxidation of aliphatic aldehydes. Under these conditions, MOM and TBDMS ethers were stable and the reaction proceeded in high yields.

Recently, other alkali and alkaline earth metal permanganates like $NaMnO_4$[3], $BaMnO_4$[4] have been used for oxidation of aldehydes without any particular change in efficiency of the reaction.

Manganate salts like tetrabutylammonium permanganate[5] ($^tBu_4N^+MnO_4^-$) have also been used under alkaline phase transfer conditions for oxidation of aldehydes to acids in good yields.

Solid MnO_2 was used by Corey *et al*[6] and very recently by other workers[7] for the oxidation of aldehydes directly to esters. Though the yield is quantitative, the reaction is carried out in presence of a catalytic amount of highly toxic NaCN, the use of which is not advisable for a general synthesis.

All manganate oxidants generally have to be used in a large excess. This causes handling problems during work-up and also leads to environmental problems of waste disposal.

b. **Chromium reagents**:

Cr(VI) oxidants in the form of chromic acid $HCrO_5$ i.e. Jones reagent, pyridinium dichromate (PDC)[8] have been regularly used for oxidation of carbonyl compounds. The reaction usually yields the corresponding acid, the yield of ester being extremely low.

However, in presence of MeOH-DMF as solvent, oxidation of aliphatic aldehydes with PDC yields the methyl ester. But, similar oxidation to higher esters was not effective.

Recently, a chromium complex $(Bipy)_2H_2CrOCl_5$ has been used as an oxidant for conversion of aldehyde to acids in good yields.[9]

Cr(VI) reagents suffer from similar disadvantages as Mn(VI) reagents. Usually stoichiometric or large excess of the hazardous reagent are required. The metallic by-product residues are toxic and their presence makes work-up difficult. Also the reagents are unstable and generally have to be used within a short time. Some of them have to be kept under vacuum to avoid decomposition.

c. **Silver salts:**

Silver oxide is a very specific reagent for the oxidation of aldehydes to acids. However, the high cost of the reagent makes this a very impractical method for any large scale synthesis. It is usually generated *in situ* from silver nitrate and in one report, from silver picolinate.[10] The yields of the product are also not high enough to warrant the use of these expensive oxidants for routine purposes.

Hence, use of silver oxidants is mostly restricted for laboratory purposes as a diagnostic test for the presence of aldehyde; an ammoniacal solution of silver nitrate (Tollens reagent) upon reaction with an aldehyde gets reduced to metallic silver and aldehyde gets oxidized to the corresponding acid.

Another test for aldehyde functionality is based on Cu(II), another Group B metal. Upon treatment of a mixture of $CuSO_4$ and potassium sodium dihydroxybutenodioate (Fehling's reagent) with alkali and aldehyde, Cu^{2+} is reduced to Cu^{+} and an orange-red precipitate of Cu_2O is formed. The aldehyde is oxidized to the carboxylic acid. The above two Ag^{+} and Cu^{++} based methods are diagnostic methods for detection of aldehyde functionality.

c. **Hypochlorites and chlorites:**

Ginsburg *et al*[11] first reporteded the oxidation of aldehyde to acid chloride using ^{t}BuOCl, followed by conversion of the acid chloride to ester. This was a two-step transformation. Further studies[12] on oxidation using hypochlorites by Wilson *et al* showed that a one-pot transformation can be effected using proper reaction conditions. However, activated aromatic aldehydes yielded nuclear chlorination products, while unactivated substrates did not react at all.

Alkali metal hypochlorites like NaOCl in CH_3COOH-MeOH[13] or $Ca(OCl)_2$ in CH_3COOH-CH_3CN[14] media were used for oxidative conversion of aldehyde to carboxylic esters or acid for aliphatic as well as aromatic substrates. The authors also reported similar nuclear chlorination products for oxidation of 4-methoxybenzaldehyde. The yield of aliphatic esters was poor.

Other authors reported[15] satisfactory conversion of aldehydes to acids in the case of unsaturated and aromatic substrates using NaOCl in aqueous acetonitrile as the solvent.

Oxidation of aromatic aldehydes using sodium chlorite ($NaClO_2$) and H_2O_2 as HOCl scavenger in a buffered solution of NaH_2PO_4 has also been reported[16] to furnish acids in good yields.

Though hypochlorites and chlorites are cheap and commercially available as aqueous solutions, this method of oxidation of aldehydes to carboxylic acids or esters cannot be deemed to be general for all substrates. The fact that oxidation of highly activated substrates result in nuclear chlorinated compounds and also the poor yields in the case of aliphatic substrates are the negative aspects of this otherwise efficient method of aldehyde oxidation.

d. **Peroxides and peracids:**

Peroxides have been used as secondary oxidants for the conversion of aldehydes to acids. The main oxidants reported which catalyze the conversion are OsO_4,[17] SeO_2[18] and $PhSeO_2H$.[19]

Peracids like *m*CPBA[20] oxidize aldehydes to acids in presence of $Fe^{(III)}$(pfpp)Cl, a porphyrin complex which is a model system of the active species responsible for the oxidations by cytochrome P450.

The yields are generally good for aliphatic as well as aromatic substrates. However, presence of unsaturation in the form of an olefin can also lead to epoxidation products. Steric effects in aromatic substrates are also significant for the success of the reaction.

e. **Oxygen and ozone:**

Molecular oxygen under pressure has been used for the oxidative conversion of a steroidal aldehyde to the corresponding acid under photochemical irradiation.[21]

The autooxidation of aryl propionaldehydes with oxygen using manganese stearate as the catalyst has been reported[22] to furnish the corresponding acid in high yields. Another catalyst used for autooxidation is $Fe(AAEMA)_3$ complex[23] [AAEMA = 2-(acetoacetoxy)ethyl methacrylate] which also furnished acid in good yields in a stream of oxygen at room temperature.

The one-pot ozonization[24] of aldehydes in basic media (KOH or Lithium alkoxide) gave the corresponding esters at -78°C in reasonable yields. This methodology is based on the previously reported[25] ozonization of acetals to esters.

Though this is a novel route to esters or acids, use of ozone or molecular oxygen under pressure makes it an impractical method for a general synthesis.

f. **Halo reagents**:

Treatment of simple aliphatic aldehydes with stannylated alcohols[26] in CCl_4 with N-bromosuccinimide gave esters in reasonable yields.

Trimethyl silyl ether of alcohols[27] when reacted with aliphatic and aromatic aldehydes under photochemical irradiation in presence of NBS furnished esters. However, presence of a double bond in the substrate, known to scavenge free radicals prevents ester formation.

Ester synthesis has also been reported *via* alkaline iodine oxidation in which hypoiodous acid HOI is proposed to be the oxidant. This is one of the convenient methods of synthesis of esters.

Treatment of aldehydes with NIS[28] in dark yielded the corresponding esters.

Conversion of aldehydes to esters using stannylated or silylated alcohols is essentially a two-step procedure. Esters of simple alcohols cannot be prepared by this method.

g. **Electrochemical oxidation**:

The electrochemical oxidation of aldehydes to esters was first reported by Chiba *et al*[29] using a catalytic amount of sodium cyanide in the anolyte. This method could not be applied to aliphatic or α,β-unsaturated substrates. Substituted aromatic aldehydes gave good yields of the ester. However, *p*-methoxybenzaldehyde furnished the corresponding methyl ester in only 50% yield, the side product being the nuclear cyanation product.

Recently, the same authors reported[30] an indirect electro-oxidative conversion of aromatic and aliphatic aldehyde to esters using a redox system of iodides as mediator. The reaction was carried out in NaOMe-MeOH-KI system as the anolyte. In a recent report[31] aromatic aldehydes have been electro-oxidized to esters using Flavo-thiazolo-cyclophane as a redox mediator in methanol with Et_3N as a base.

The latter methods, though superior to the previous one in terms of material yield and current efficiency, are still impractical when experimental manipulation is considered.

h. **Tischenko reaction**:

The Claisen-Tischenko reaction has long been used[32] for the synthesis of esters by self-condensation of aliphatic and aromatic aldehydes. It is generally catalyzed by homogeneous alkoxide reagents like $Al(OEt)_3$ or $Mg[Al(OEt)_4]_3$ where poor yields are reported for aromatic substrates.

More recently, use of heterogeneous catalysts like lithium tungsten (IV) oxide ($LiWO_2$) has been reported[33] for the conversion of aliphatic as well as aromatic aldehydes to the corresponding esters.

As is evident, this method of aldehyde oxidation to esters is not at all general. Self condensation of aldehydes leads to the higher esters; lower esters like methyl, ethyl etc. cannot be prepared practically by this route.

i. **Group VIII-B metals**:

RuO_4 and Rhodium complexes are the most common oxidants of this group.

Ruthenium heteropolycomplex, prepared from $K_2Ru(OH)Cl_5$ and $Na_7PW_{11}O_{39}$, has been used[34] along with $KClO_3$ as primary oxidant to convert aldehydes into acids in high yields.

$RhH(CO)(PPh_3)_3$ was used similarly for the synthesis of esters from aldehydes in boiling alcohol. However, the reaction required long time for completion and also furnished esters in poor yields.

$RuCl_2$ ($C_{12}H_{18}$) catalyzed oxidation of acrolein was reported[35] to give acrylate in very poor yields.

Direct oxidation using RuO_4 as a phase transfer catalyst in a biphasic system has been recently reported.[36] RuO_4 is electrochemically generated from $RuCl_3$ using a graphite cathode and platinized titanium as anode. RuO_4 is regenerated by the action of active chlorine species (Cl_2 or $[Cl]^+$)[16] in the aqueous phase.

Although used in catalytic amounts, Ru and Rh complexes are very expensive and their use is best avoided for a practical synthesis.

j. **Sulfuric acid**:

Treatment of aldehydes with Caro's acid, H_2SO_5, prepared from ammonium persulfate and sulfuric acid, in the presence of alcohol has been reported[37] to furnish the corresponding ester in high yields.

Use of conventional acid is not recommended as a general method for oxidation of aldehydes as sensitive substrates would not be able to sustain acidic pH of the medium.

k. **Trichloroisocyanuric acid**:

Aldehydes were reported[38] to be oxidized to the corresponding methyl esters in good yields by treatment of trichloroisocyanuric acid in pyridine-acetonitrile as solvent. Electron-withdrawing groups on the aromatic ring decreased the rate of oxidation. Activating groups on the aromatic ring gave rise to significant nuclear chlorination products.

3.2 Present Work:

As is evident from the literature survey of aldehyde oxidations, most of the methods employ stoichiometric oxidants. The disposal of the reduced by-products, usually toxic metals, becomes a problem and is environmentally unacceptable in the present context of heightened global awareness. Hence, in the manufacture of bulk chemicals and that of fine chemicals of late, catalytic oxidation has become very important.

Heterogeneous catalysis is fast developing into an important field in its own right basically on account of the inherent and obvious advantages of insoluble catalysts over soluble ones. Solid acids like ion-exchange resins, zeolites and more recently clays have been used to catalyze various transformations.

Zeolites are microporous inorganic solids having large pores and voids in their crystal structure. The effective pore size ranges from about 3 A to over 10 A, whch is sufficient to permit the diffusion of organic molecules. This feature gives rise to many of the more important applications of these materials namely ion-exchange, gas separation and heterogeneous catalysis.

Structurally, they are tridimensional, crystalline aluminosilicates represented by the general formula $[M_{x/n}[(AlO_2)_x(SiO_2)_y]\cdot zH_2O$, where M is a cation belonging to Group IA or IIA or can be an inorganic cation, while **n** is the cation valence, **z** represents the water contained in the zeolite voids. The Si and Al atoms are linked in a tetrahedral coordination by O atoms.

Isomorphous substitution of metal ions in the T sites of the zeolite results in modified catalysts which are more chemoselective and capable of catalyzing specific reactions.

Such substitution of Si^{4+} by Ti^{4+} in the pentasil zeolite ZSM-5 yielded the new catalyst TS-1 having a similar MFI structure. The synthesis of TS-1 was first claimed by Taramasso *et*

al[39] and later confirmed by other workers.[40,41] A Ti concentration of upto 4 mole % converts the material from an acid to an oxidation catalyst.

Similar titanium incorporation into ZSM-11 having MEL structure resulted in the formation of TS-2[42], another titanosilicalite.

Amorphous Ti^{IV}/SiO_2 catalyst has also been reported earlier which closely resembles the TS-1 catalyst solely from a mechanistic viewpoint. The presence of active site-isolated titanyl species (Ti=O) were postulated for explaining the unique properties of Ti zeolites.

Crystalline TS-1, however, displays a broader range of activities which may be attributed to TS-1 containing more (or more active) titanyl species. Another possible explanation is that the hydrophobic cavity of TS-1 containing the active peroxotitanium (IV) oxidant could be too small to accomodate solvent and/or water molecules such that no solvation barrier has to be overcome.

Attention was drawn to these titanium silicates on account of their being common catalysts for peroxide oxidations. Of the two crystalline zeolites, TS-1 is the more generally used material.

The cheapest and more easily available oxidant is molecular O_2. However, it is very indiscriminate and shows little chemo- or regioselectivity with the reactions also being difficult to control.

30% H_2O_2 is the most commonly used industrial oxidant. Water is formed as a by-product, which makes it an attractive oxidant for clean technologies. Bulkier alkyl peroxides are not effective because of their inability to diffuse into the zeolite channels to react with the Ti sites.

The crystal structure of TS-1 is analogous to that of ZSM-5 with two-dimensional channels of 0.55-0.60 nm in diameter. The catalytic sites are the Ti ions incorporated into the

zeolite framework which react with the oxidant to form a titanium peroxo species inside the cavities. Hence, reactions performed at these sites exhibit varying degrees of shape selectivity depending on the nature of the substrate.

TS-1 has been used for effecting various transformations. The various aspects of TS-1 catalyzed conversions have been reviewed[43-46] in great detail.

One of the most important reaction catalyzed by TS-1 is the conversion of alkenes to epoxides[47] using peroxide. Certain changes in the reaction conditions have been reported[48] to result in cleavage of the double bond.

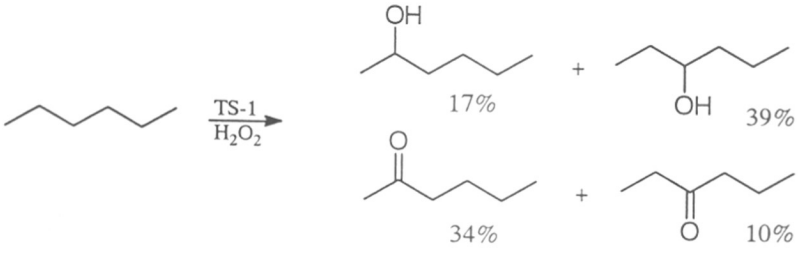
Primary and secondary alcohols[49] react with peroxide in presence of TS-1 to yield the aldehyde and ketone respectively.

TS-1 is also used for the hydroxylation of benzene to phenol and hydroquinone.[50,51] The TS-1 catalyzed conversion of phenol to a 1:1 mixture of catechol and hydroquinone has been commercialized.[52]

It has also been applied for the conversion of ketones to oximes[53] and aliphatic[53] and aryl[54] amines to corresponding oximes and compounds. The ammoximation of cyclohexanone[55] with NH_3 and H_2O_2 in presence of TS-1 to give cyclohexanone oxime is an important step in the manufacture of caprolactam.

Cleavage of tosyl hydrazones[56] and oximes[57] and sulfoxidation of thioethers[58] has also been reported by some workers. Oxidation of ethers to lactones/esters has also been recently accomplished.[59,60]

The use of TS-1 as a shape selective catalyst for the oxyfunctionalization of alkanes has been described.[61] Thus, linear alkanes are oxidized much faster than branched or cyclic alkanes.



Scheme 1

This brief survey of the synthetic conversions accomplished using TS-1 indicates that it is a very efficient catalyst for peroxide oxidations.

Aldehydes have been converted to esters by treatment of peroxides using very expensive and sometimes toxic catalysts. Accordingly, it was predicted that aldehydes could be oxidized using peroxide/TS-1 system to the corresponding acids or esters in a more economical fashion.

Oxidation of aldehyde to either acid or ester was hence attempted under the standard conditions used for TS-1/peroxide system.

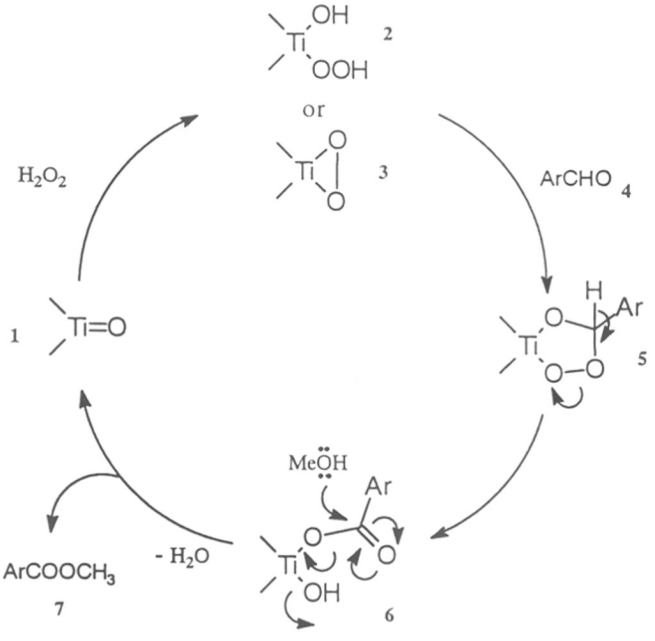
3.3 Results and Discussion:

Benzaldehyde was chosen as the model substrate for the oxidation. Upon refluxing in MeOH with TS-1 as catalyst and 30% H_2O_2 as the oxidant, the reaction yielded 65% yield of methyl benzoate in 5 hours.

The identity of the product was established by ^{1}H-NMR, IR and Mass spectral analysis. ^{1}H-NMR spectrum showed singlet at δ 3.5 for 3H for the methyl ester. The product was confirmed by presence of M^+ ion peak at 136 in the Mass spectrum.

A probable mechanism for the oxidation is depicted in *Scheme 1*. The reaction proceeds *via* the initial formation of the peroxo species **2** or **3**. This forms the intermediate

titanium adduct **5** with the aryl aldehyde. Attack of the oxygen lone pair results in formation of the ester in turn regenerating the titanyl species.



Scheme 2

The various reaction parameters were varied in order to standardize the conditions. Increase in the quantity of oxidant from 5 equivalents to 20 equivalents resulted in no appreciable difference in the rate or the yield of the reaction. However, interrupting the reaction before 5 hours resulted in appreciable formation of benzoic acid.

The conversion of aldehyde to ester was also attempted using other solid acid catalysts. In presence of Amberlyst-15 (wet) ion-exchange resin, the reaction furnished PhCOOMe in 36% yield. In presence of silica gel (60-120 mesh), PhCOOMe was formed in only trace amounts.

Interestingly, in the absence of catalyst although the ester was isolated from the reaction mixture, the reaction took longer time (10 hrs.) for completion and furnished the product in only 52% yield.

Hence, TS-1 was confirmed to be the best catalyst for this conversion. 10 mole % of catalyst coupled with 5 equivalents of oxidant per oxidizable aldehyde in refluxing methanol were taken to be standard conditions for this conversion.

Various substituted aromatic aldehydes were oxidized under these conditions to establish the efficiency and general applicability of this method (*Table 1*).

$$ArCHO \xrightarrow[\text{TS-1, MeOH}]{30\%\ H_2O_2} ArCOOMe$$
reflux

Entry	Substrate	Time (hr)	Yield (%)
1.	C_6H_5CHO	5	65
2.	2-Cl-C_6H_4CHO	8	83
3.	4-Cl-C_6H_4-CHO	8	97
4.	3-NO_2-C_6H_4-CHO	8	97
5.	4-NO_2-C_6H_4-CHO	8	89
6.	4-OMe-C_6H_4-CHO	8	82
7.	3,4,5$(OMe)_3$-C_6H_2-CHO	12	84
8.	4-OHC-C_6H_4-CHO	8	99

Table 1

As is obvious from the Table, the reaction furnished the corresponding esters in high yield. Both electron-rich as well as electron-deficient aromatic aldehydes were converted to the esters efficiently.

An interesting feature of this oxidation is that despite the presence of bulky substituents (entry **2**) ortho to the aldehyde, the corresponding ester is obtained in good yield. (This may be contrasted with some of the reported methods where low yields are obtained.) Additionally, in the case of terephthaldehyde (1,4-benzene dicarboxaldehyde) (entry **8**) as well as *p*-methoxybenzaldehyde (entry **6**), the corresponding diacid is the sole product formed in 71% and 50% respectively in the absence of the catalyst.

The efficient oxidation of terephthaldehyde (entry no.**9**) to diester in the presence of catalyst is especially important in view of the fact that the diester is used for the large scale manufacture of terylene, a synthetic polyester fibre, *via* the condensation of ethane-1,2-diol. The diester is at present commercially prepared by the esterification of the diacid which in turn is obtained by the oxidation of dialkyl benzene using a cobalt catalyst at 200°C under oxygen pressure. The present methodology could prove to be a very convenient and efficient alternative to the existing method.

The oxidation of phenolic aldehydes as expected is not a very clean reaction and results in a number of products.

Aliphatic aldehyde upon oxidation under same conditions also furnished the corresponding esters albeit in low yields. Thus, hexanal under the above oxidizing conditions gave methyl hexanoate in 39% yield while hydrocinnamaldehyde ($PhCH_2CH_2CHO$) furnished the corresponding ester in only 17% yield.

3.4 Conclusions:

Thus an efficient and high yielding methodology has been developed for the conversion of aldehydes to esters in a single step.

This present method does not require the use of stoichiometric amount of heavy metal oxidants nor any exotic catalysts for the reaction. The use of cheap and easily accessible hydrogen peroxide as the oxidant, which furnishes water as the only by-product, makes this method a part of the cleanest technologies developed to date. The obvious advantages of heterogeneous catalysis as regards easy separation by mere filtration and their recyclability and good yields are noteworthy features.

There are no nuclear oxidations observed even in the case of highly activated aromatic rings, resulting in good yields of ester as the sole product. It may be recalled that nuclear oxidations were the main side-reactions in case of other conventional oxidations.

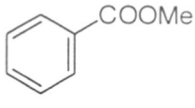
The present methodology is thus an attractive alternative to the existing conventional methods of aldehydic oxidation.

3.5 Experimental:

Typical procedure for oxidation of aldehydes:

The aromatic aldehyde (5 mmol) was dissolved in methanol (10 ml) and the activated catalyst (300°C for 8 hrs) TS-1 (10 mole %, Si/Ti = 38) was added to it with stirring. 30% H_2O_2 solution (25 mmol) was injected into the reaction and the mixture refluxed for the requisite period of time (5-12 hours). The reaction was monitored by TLC. After completion of reaction, the mixture was cooled to room temperature and the catalyst was filtered off. The filtrate was concentrated under vacuum and the residue washed with water (10 ml) and extracted with ethyl acetate (2×10 ml). Drying over anhydrous sodium sulfate and concentration under vacuum furnished the pure ester which was characterized by ^{1}H-NMR, IR and Mass spectroscopy.

Methyl benzoate



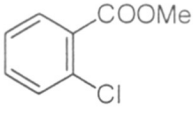
Yield: 65%

IR (neat): 1723, 1452, 1435, 1316, 1278, 1177, 1111 cm^{-1}

^{1}H-NMR (90 MHz): δ 3.78 (s, 3H); 7.13-7.42 (m, 3H); 7.67-7.96 (m, 2H).

Mass (m/e): 136 (M^+, 61); 135(44); 105(100); 104(92); 103(66); 77(51); 76(50); 75(48).

Methyl 2-chlorobenzoate



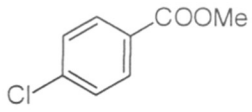
Yield: 83%

IR (neat): 1735, 1593, 1475, 1437, 1298, 1271 cm^{-1}

^{1}H-NMR (90 MHz): δ 3.8 (s, 3H); 7.0-7.7 (m, 4H).

Mass (m/e): 172 (M^+, 7); 170 (M^+, 25); 141(33); 139(100); 113(16); 111(52); 76(18); 75(61); 74(23).

Methyl 4-chlorobenzoate



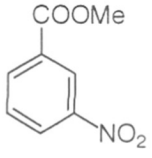
Yield: 97%

IR ($CHCl_3$): 1733, 1681, 1594, 1574, 1461, 1377, 1323 cm^{-1}

^{1}H-NMR (200 MHz): δ 3.93 (s, 3H); 7.44-7.73 (m, 1H); 8.18-8.47 (m, 2H); 8.69-8.87 (m, 1H).

Mass (m/e): 181 (M^+, 30); 180(14); 151(19); 150(100); 149(45); 135(14); 119(19); 104(54); 92(12); 77(21).

Methyl 3-nitrobenzoate



Melting point: 75-77°C

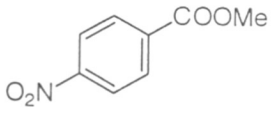
Yield: 97%

IR(nujol): 1710, 1600, 1510, 1440, 1350.

1HNMR(90MHz): 3.93(s, 3H); 7.44-7.73(m, 1H); 8.18-8.47(m, 2H); 8.69-8.87(m, 1H).

Mass(m/e): 181(M+, 31); 180(14); 151(19); 150(100); 149(45); 135(14); 119(19); 104(54); 92(12); 77(21).

Methyl 4-nitrobenzoate



Melting point: 92-95°C

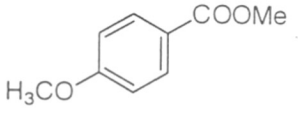
Yield: 89%

IR (nujol): 1694, 1605, 1537, 1462, 1377, 1350, 1312 cm^{-1}

^{1}**H-NMR** (200 MHz): δ 4.00 (s, 3H); 8.15-8.55 (m, 4H).

Mass (m/e): 181(0.02); 167(100); 151(21); 150(31); 145(16); 137(19); 121(21); 120(22); 109(15); 104(10).

Methyl 4-methoxybenzoate

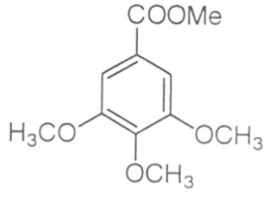


Yield: 82%

IR (nujol): 1670, 1600, 1500, 1440, 1380, 1300 cm^{-1}

^{1}**H-NMR** (90 MHz): δ 3.84 (s, 6H); 6.73-7.00 (m, 2H); 7.67-8.07 (m, 2H).

Methyl 3,4,5-trimethoxybenzoate



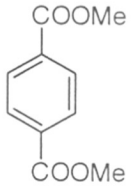
Yield: 84%

IR (Nujol): 1710, 1680, 1590, 1450, 1410, 1330 cm^{-1}

^{1}**H-NMR** (90 MHz): δ 4.06 (s, 12H); 7.44 (s, 2H).

Mass (m/e): 226 (M^+, 100); 211(52); 195(17); 194(13); 183(9); 155(23); 125(13).

Dimethyl terephthalate



Yield: 99%

IR (nujol): 1710, 1680, 1440, 1370, 1260, 1190, 1100 cm^{-1}

^{1}H-NMR (200 MHz): δ 3.95 (s, 6H); 8.10 (s, 4H).

Mass (m/e): 194 (M^+, 24); 179(5); 164(11); 163(100); 135(27); 120(9); 119(9); 104(17); 103(23); 77(19); 76(34); 75(23).

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