SYNTHESIS OF BENZOFURANS AND BENZOPYRANS

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I dedicate this thesis to the memory of my late mother.

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Last but not least, my family for providing me with the financial and moral support in making this research possible.

Abstract

Syntheses of 2,3-dihydrobenzofurans and 3,4-dihydrobenzopyrans normally involve several stages, therefore efficient syntheses of these compounds are desirable.

A number of 3,4-dihydrobenzopyrans derivatives were prepared in one pot syntheses. The reaction is thought to proceed through cation intermediates, involving allylic cations generated by the reaction of allyl alcohols, 1,3-dienes, or diols in the presence of acids such as trifluoroacetic acid (TFA), or in a solution of glacial acetic and a metal catalyst or glacial acetic acid and sulphuric acid, followed by reaction with nucleophiles such as phenols or hydroquinones. This leads to the formation of allyl aryl ethers which rearrange via a [3,3]-sigmatropic rearrangement and acid-catalysed intramolecular cyclisation, to give the corresponding 3,4-dihydrobenzopyrans. 5-Formyl-2,3-dihydrobenzofuran and 6-formylamino-3,4-dihydrobenzopyran were synthesized by several routes and the isolated products exhibited *cis-trans* isomerism.

It was found that the introduction of an alkyl substituent at carbon-4 in the model benzopyran locks the 2,3,4-alkyl substituents into axial and equatorial orientations. This may influence the peroxyl-radical scavenging activity of these compounds by altering the extent of orbital overlap between the 2p-type lone pair on the pyran oxygen and the aromatic π-electron system.

2,3-Dihydrobenzofurans such as 5-hydroxy-2,3-dihydrobenzofuran have been shown to have better antioxidant activity than alpha-tocopherol due to the influence of the smaller, more strained ring, which allows better overlap of the oxygen lone pair and the π-electrons in the aromatic system.

5-Hydroxy-2,3-dihydrobenzofuran was efficiently synthesised in an improvement on the yields previously reported in the literature.

A series of substituted 2,3-dihydrobenzofurans were synthesised by the reaction of phenols with allylic alcohols or aldehydes in the presence of trifluoroacetic acid or catalytic amounts of sulphuric acid, which also promoted the acid-catalysed intramolecular cyclisation.

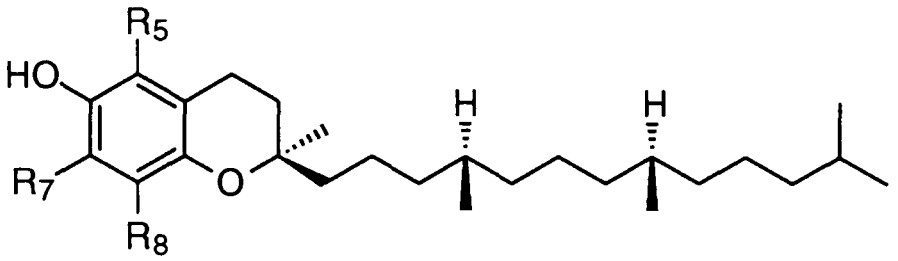
^{1}H NMR	Proton nuclear magnetic resonance	IR	Infra red
^{13}C NMR	Carbon-13 nuclear magnetic resonance	υ	Frequency (cm^{-1})
D_2O	Deuterated proton NMR	KBr	Potassium bromide
(DMSO)	Dimethylsuphoxide	def.	deformation
(DMSO-d_6)	Deutrated dimethylsulphoxide	symm	symmetric
(TMS)	Tetramethylsilane	asymm	asymmetric
($CDCl_3$)	Deuteated chloroform	MS	Mass spectrometry
(m)	multiplet	m/z	mass to charge ratio
(q)	quartet		(in amu)
(t)	triplet	$M^{+\cdot}$	radical cation
(d)	doublet	TLC	Thin layer
(*o*)	ortho		chromatography
(*m*)	multiplet	GC	Gas
(*p*)	para		chromatography
(*J*)	Coupling constant	R_t	Retention time
(δ)	Coupling shift in parts per million		(min)
(Hz)	Hertz	M.pt.	Melting point (^oC)
B.pt.	Boiling point (^oC)	hrs	hours
PPA	Polyphosphoric acid	sat	saturated
OBu^t	tertiary-butoxide	*gem*	geminal
ml	millilitres	Ar	Aromatic or Aryl
(EI)	Electron impact	(CI)	Chemical Ionization
DMAP	Dimethylaminopyridine	EtOH	Ethanol
$LiAlH_4$	Lithium Aluminium Hydride	N-BuLi	Butyllithium
NBS	N-bromosuccinamide	THF	Tetrahydrofuran
p-TSA	para-Toluene sulphonic acid	Et_2O	Diethyl ether
H_3PO_4	Phosphoric acid	Et_3N	Triethylamine
Ac_2O	Acetic anhydride	$PbCl_2$	Lead chloride
MeMgI	Methyl magnesiun chloride	CuCl	Copper chloride
$AlCl_3$	Aluminium chloride	CH_2Cl_2	Dichloromethane
PhMe	Toluene	K_2CO_3	Potassium chloride
HCl	Hydrochloric acid	MeOH	Methanol
$Sc(OTF)_3$	Scandium triflate	$NaBH_4$	Sodium BoroHydride
$Pb(OAc)_2$	Lead acetate	NaH	Sodium Hydride
BOC	*tert*-Butoxycarbonyl	CH_3CO_2H	Ethanoic acid
Tol-BINAP	2,2-*bis*(Di-*p*-tolyphosphino)-1,1'-binaphthyl	Br_2	Bromine
		NaOH	Sodium hydroxide
CF_3CO_2H	Trifluoroacetic acid	Cl_2	Chlorine
H_2SO_4	Sulphuric acid	NBS	N-bromosuccinimide

HF	Hydrofluoric acid
SbF_5	Antimony pentafluoride
$FeCl_3$	Iron chloride
Torr	Unit of pressure
Ho	Hammett acidity parameter
eV	electron Voltage
Mg	Magnesium
$MeAlCl_2$	Methyl aluminium chloride
IUPAC	International Union of Pure and Applied Chemists
DPPF	1,1-*bis*(Diphenylphosphino)-ferrocene
DPPB	1,4-*bis*(Diphenylphosphino)-butane
$Na_2S_2O_4$	Sodium dithionite
$NaNO_2$	Sodium Nitrite
HCO_2H	Formic acid
H_2O_2	Hydrogen peroxide
Pd_2dba_3	Tris (dibenzylidene acetone) dipalladium
$(PPh_3)_3$ RhCl	Triphenylphosphine Rhodium chloride
Tf_2O	Trifluoromethanesulphonic acid anhydride
L-Dopa	3-(3,4-Dihydroxyphenyl)-L-alanine
Pd/C	Palladium / charcoal
$SnCl_4$	Tin pentachloride
$AlCl_3$	Aluminium chloride
$ZnCl_2$	Zinc chloride
HCOOH	Formic acid
FT-IR	Fourier transformation
IR	Infra Red
H_2	Hydrogen
$SnCl_4$	Tin chloride

1.00 INTRODUCTION

1.01 Vitamin E

Vitamin E (**1**) which has a molecular formula $C_{29}H_{50}O_2$, is a naturally occurring antioxidant with various other biological functions[1-8]. It is a fat soluble vitamin[9,10] and is implicated in defending unsaturated lipid molecules in cell membranes from degradation by autoxidation. This can occur either from normal dioxygen metabolism or various pathological and infectious disease states.

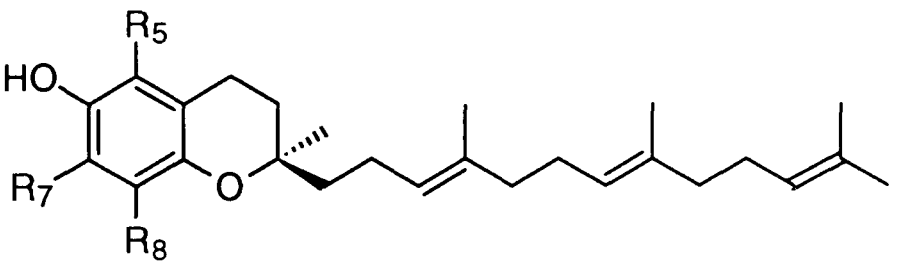


1

α-T $R_5, R_7, R_8 = CH_3$
β-T $R_5, R_8 = CH_3, R_7 = H$
γ-T $R_5 = H, R_7, R_8 = CH_3$
δ-T $R_5, R_7 = H, R_8 = CH_3$

Therefore, vitamin E is an essential molecule in maintaining life (and is also essential for fertility and reproduction in rats[11]). The word 'vitamin' comes from 'vital amine' - although not all vitamins are amines as originally thought. Vitamin E is a member of a group of four structurally related compounds called the tocopherols of which α-tocopherol (vitamin E) is considered the most potent[12].

Included in this group are tocotrienols (**2**), which are very similar in structure but have an unsaturated lipophilic tail (a polyenic tail). However, tocotrienols have very little biological activity in mammals under high oxygen tension situations[13].



2

α-T $R_5, R_7, R_8 = CH_3$
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γ-T $R_5 = H, R_7, R_8 = CH_3$
δ-T $R_5, R_7 = H, R_8 = CH_3$

The richest natural sources of α-tocopherol are wheat-germ oil, various vegetable oils and green leafed vegetables such as lettuce[8]. Rubber latex from *Hevea brasiliensis* has

recently been discovered to be a rich source of free and esterified tocotrienols which can be extracted using non-polar, lipophilic solvents such as diethylether, or petroleum ether.

1.02 A Brief History of Vitamin E

Vitamin E **(1)** was first discovered in 1922 by Evans and Bishop[14] and isolated as a crystalline allophanate in 1936. It is a viscous yellow oil, with a boiling point of 140° (at reduced pressure)[15], has a melting point of 2.5-3.5°, and can be recrystallised from methanol at -35°[16]. The first chemical synthesis[17] of tocopherol was carried out in 1938 and since then many analogues have been made and many different syntheses have been reported. As well as an antioxidant, vitamin E has also been used to promote fertility[15]. Synthetic analogues of vitamin E are used as preservatives[18] and to treat various medical conditions such as trauma and diabetes. Vitamin E has also been used in the treatment of peripheral vascular disease[19] and to improve the action of insulin in diabetes (diabetes may be associated with lipid metabolism[20]). It also acts as a diuretic, and has been used as an antipollutant[11] (where it has been claimed that α-tocopherol protects the lungs from damage caused by air pollutants such as ozone and nitrogen dioxide). It has been reported to increase the ability of white blood cells to resist infection[21], and claims have been made that it can slow down the ageing process.

It has been proposed that the membrane damage caused by autoxidation in lipids is associated with the ageing process[22]. Theoretically, it would therefore be possible to slow down this process using vitamin E. This may be partly true as vitamin E has been shown to increase the life span of mice[23].

Benzofuran analogues of α-tocopherol have been shown to protect mice from autoxidation[24]. It is known that antioxidants tend to decrease in concentration with age so that the amount of oxidation products and cell oxidation in the body increases[25].

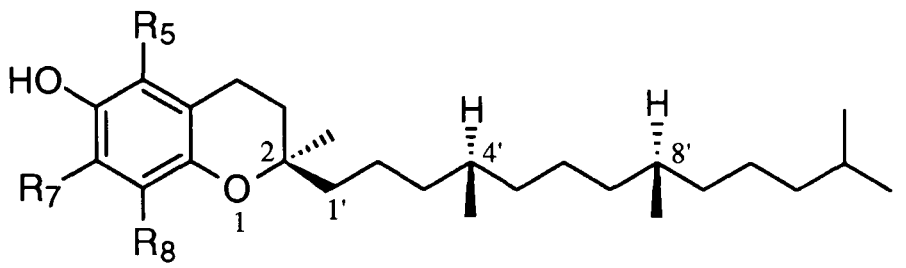
Recent studies have shown that the antioxidant vitamins (A,C & E) can lower coronary heart disease risk and mortality. It was found that low blood vitamin E levels served as strong predictors of heart disease mortality[26]. Free radical lipid peroxidation contributes to abnormal metabolism and ventricular function that is frequently seen after cardiac operations. Antioxidants, such as vitamin E, have been shown to improve the metabolic recovery in patients after cardiac by-pass treatment[27,28].

Vitamin E is present in vitamin supplements as *dl*-α-tocopheryl acetate or the *d*-α-tocopheryl succinate. The recommended daily allowance (RDA) of vitamin E is 10mg[21], but this figure is an understatement since increased consumption of unsaturated fats can increase the RDA for normal health.

Under IUPAC nomenclature vitamin E is 3,4-dihydro-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)-2H-1-benzopyran-6-ol[15] although it has been given other names such as 5,7,8-trimethyltocol[29]. Difficulties with the stereochemical nomenclature of

tocopherols and related molecules have been reported[30]. There were no problems concerning the nomenclature of natural vitamin E but there had been considerable difficulties in naming the synthetic products with vitamin E activity.

In α-tocopherols, there are three chiral centres, at position 2, 4', and 8'. In natural α-tocopherol the configuration was assigned as 2R, 4'R, 8'R and it had been called *d*-α-tocopherol.



1

Natural α-tocopherol (2R, 4'R, 8'R)

Whereas, the α-tocopherol obtained from natural phytol or phytylbromide, respectively, was not a racemic mixture but a mixture of two enantiomers of α-tocopherols with the configurations 2R, 4'R, 8'R and 2S, 4'S, 8'S (referred as *dl*-α-tocopherol). However, the α-tocopherol obtained from synthetic phytol and isophytol, respectively, had also been referred to as *dl*-α-tocopherol. This material is a mixture of of all eight possible stereoisomers of α-tocopherol. Considering the fact a) the symbols *d* and *dl* were not in accord with IUPAC rules of stereochemistry and b) the old system did not provide distinguishing names for the two, chemically different, syntheic materials having the structures of α-tocopherol. Hoffman[30] proposed a system for designation of these products. It was suggested that :

a) Natural α-tocopherol should be called RRR-α-tocopherol.

b) The diastereoisomer of RRR-α-tocopherol being its epimer at C-2, thus having the configuration 2S, 4'R, 8'R should be called 2-*epi*-α-tocopherol.

c) The mixture of RRR-α-tocopherol and 2-*epi*-α-tocopherol, obtained by synthesis using natural phytol or phytyl bromide, respectively, should be called 2-*ambo*-α-tocopherol.

d) The totally synthetic products, obtained by synthesis from synthetic phytol or isophytol should be called all-*rac*-α-tocopherol.

Selenium and vitamin E are closely related physiologically[31]. Therefore, it is difficult to induce vitamin E deficiency since selenium can partially substitute for α-tocopherol.

Antioxidants are usually highly subsituted phenols, aromatic amines, or, less commonly, sulphur compounds (thiols). They can act either as electron or hydrogen atom donors. These antioxidants can be added to food to slow down the rate of oxidation by removing peroxyl and alkyl radicals. They are also added to rubbers and plastics to slow autoxidation and photochemical degradation[32]. The chemical properties of tocopherol are due to the free phenolic hydroxy group which can be acylated, etherified or

phosphorylated[30]. This results in loss of antioxidant activity, and such derivatives become essentially prodrugs .

1.03 Vitamin E as an Antioxidant

Vitamin E is distributed around the body by the blood in which it is bound by the plasma-proteins[33]. The main site of action of Vitamin E is in the membranes of biological cells. The cellular membranes consist of two layers that surround the cell and are about 7-10nm thick[34,35]. They are composed of lipids or fats in which proteins are located. Such membrane bilayers act as selectively permeable barriers for molecules and ions that need to pass in and out of the cell. The bilayer is a prime site of oxygen radical damage since it contains polyunsaturated fats with autoxidation-prone allylic sites in the form of phospholipids and glycolipids as well as cholesterol.

The highest concentration of oxygen is found in the erythrocytes and this makes them susceptible to oxidation and damage by free radicals. In the case of mature human erythrocyte, there is no synthesis of new material so that damaged molecules and structures cannot be replaced or repaired.

Metabolism in the human erythrocyte defends the cell against oxygen toxicity. Defective enzymes lead to the breakdown of this protection and cause haemolytic anaemia. Glutathione, in its reduced state, protects the cell membrane by rapidly destroying any peroxide in a reaction which is catalysed by the enzyme glutathione peroxidase (GP)[36]. Various organelles (subcellular structures) are also thought to be susceptible to radical damage, such as the endoplasmic reticulum and lysosomes. The products of lipid peroxidation and lipid peroxides are known to inactivate enzymes and proteins in the cell. Lipid peroxides are formed by several mechanisms: namely autoxidation; chemical catalysis with haematin; and enzymic catalysis with lipoxidase[20].

In any biological cell where dioxygen is used during metabolism, free radicals are formed, both as by-products and as useful intermediates. These free radicals need to be removed by the cell otherwise they will cause damage to the cell by destructive oxidation[18,25]. The reactive oxygen species (ROS) produced[25] are:-

Superoxide anion radical	$O_2^{-}\cdot$
Hydrogen Peroxide	H_2O_2
Hydroxyl radical	$HO\cdot$

To eliminate these destructive radicals which initiate cell peroxidation, the cell's defence system uses biological preventive antioxidants which function by converting hydroperoxides to molecular products that are not potential sources of free radicals. Glutathione peroxidase reduces lipid hydroperoxides to the corresponding alcohols **(5)** and it can also reduce hydrogen peroxide to water.

$$ROOH \xrightarrow[\text{Glutathione peroxidase}]{[2H]} ROH + H_2O \qquad (5)$$

The enzyme superoxide dismutase (SOD)[37] catalyses the reaction in **(6)** and the resulting hydrogen peroxide is decomposed by catalase to water.

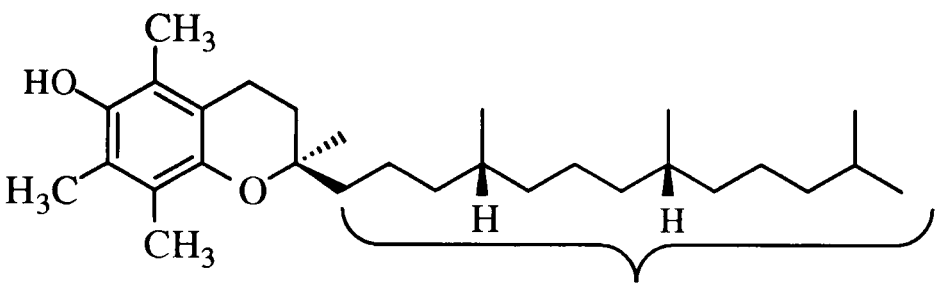
$$2O_2^{-\bullet} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2 \qquad (6)$$

$$H_2O_2 \xrightarrow{\text{Catalase}} H_2O$$

The second defensive mechanism consists of a lipid soluble chain-breaking antioxidant, namely α-tocopherol. These antioxidant properties inhibit the autoxidation of:-

1) Vitamin A
2) Unsaturated fatty acids e.g. linolenic acid
3) Phospholipids

Vitamin E can stop these free radicals at the propagation step and thus stops destructive oxidation.



1 Phytyl moiety

The major role of the phytyl moiety of the tocopherols seems to be to increase the solubility of the hydroxychroman moiety in those non-polar, lipophilic regions of biological systems (such as biomembranes) which require protection against autoxidation[38]. In fact the phytyl side chain has been shown to penetrate monolayers of phospholipid molecules. The autoxidation of micelles and model membranes has been studied and quantitative kinetic measurements made using water or lipid soluble initiators and water and lipid soluble antioxidants[39].

As well as scavenging active free radicals such as hydroxyl (HO·) and peroxyl (ROO·), tocopherols can also act as efficient scavengers of singlet oxygen ($^1O_2$) (the structure-activity

relationship in the quenching reaction of singlet oxygen with Vitamin E has been investigated by Mukai[40]) .

Autoxidation is promoted by the following[41]:-

1) Heat
2) Light
3) Metals such as Fe^{2+}

4) Radical producing species

Peroxides are known to affect proteins by initiating the formation of free radicals that result in polymerisation reactions which in turn leads to protein denaturation. Another consequence of peroxide formation is membrane damage leading to increased permeability which in the case of lysosomes (cellular bags of enzymes) would release destructive enzymes causing further cellular damage[20].

1.04 Mechanism of Action of Tocopherol

The autoxidation of most organic substrates in homogenous solution is a free radical chain process. It can generally be represented by the reaction sequence given as equations (**a-d**)[42-50].

1) Initiation:

Production of $R^{\bullet}$ or $ROO^{\bullet}$

$$\underset{\text{Initiator trace}}{R^{\bullet}} + \underset{\text{Substrate}}{R\text{-}H} \xrightarrow[\text{H-abstraction}]{} Ra\text{-}H + R^{\bullet} \qquad \textbf{(a)}$$

The first step for each chain involves the production of a radical from some molecular precursor. Such chain initiation may be non enzymic, being caused by heat, or light, or by single electron transfer (SET) from a reducing agent such as Fe^{2+} to an acceptor such as the hydroperoxide, ROOH, or it may be an enzyme - catalysed SET reaction (or $^1O_2$ in an Alder-ene reaction with a lipid double bond).

2) Propagation:

$$R^{\bullet} + O_2 \longrightarrow ROO^{\bullet} \qquad \textbf{(b)}$$

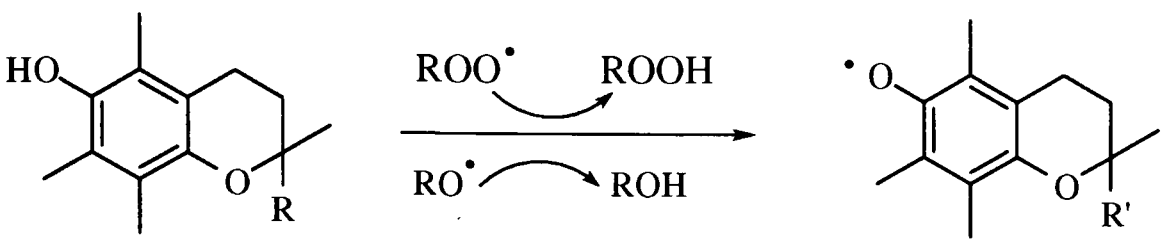
$$ROO^{\bullet} + RH \longrightarrow ROOH + R^{\bullet} \qquad \textbf{(c)}$$

The radical R· reacts extremely rapidly with oxygen to form the peroxyl radical ROO· **(b)** which, in a subsequent much slower step, abstracts a hydrogen from the substrate RH to form ROOH and a new radical R· **(c)** (or possibly adds to a double bond). The new carbon centered radical proceeds through the propagation stage to yield another peroxyl radical. Thus a chain reaction is set in motion that proceeds through the propagation reactions **(b)**, **(c)**, until the propagation sequence is eventually broken when any two of the chain-carrying radicals (peroxyl radical ROO• or R·) react together to form non radical products (R· to R-R or R-O-O-R).

3) Termination:

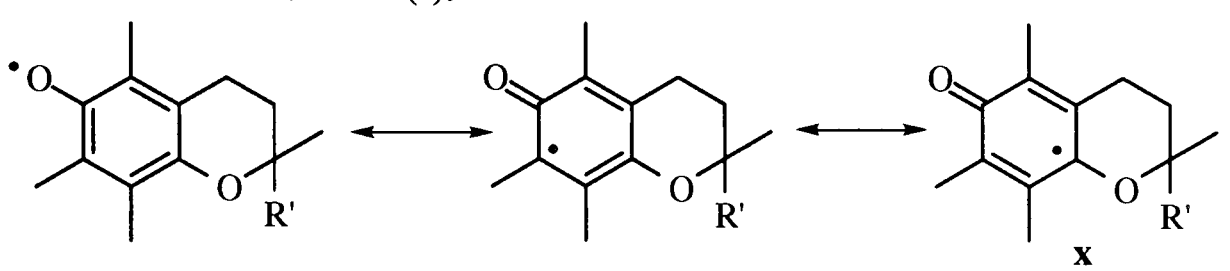
$$ROO^{\bullet} + ROO^{\bullet} \longrightarrow \text{non radical products} \qquad \textbf{(d)}$$

In the presence of chain breaking phenolic antioxidants, ArOH, the oxidation chains are shortened and chain termination by **(d)** is suppressed and termination occurs via reaction **e**.



(e)

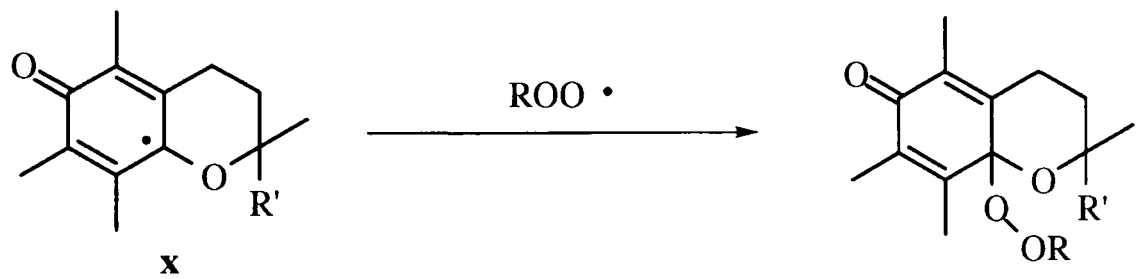
The tocopheroxyl radical then reverts to its most stable form **x** by delocalisation of the free radical as shown in **(f)**.



x **(f)**

This resonance stabilised tocopheroxyl radical is relatively unreactive towards RH and O_2 and therefore it does not continue the chain, hence the term "chain breaking". It can be trapped by a second peroxyl radical to form a nonradical product.

In model systems phenolic antioxidants, including vitamin E, have been shown to trap two peroxyl radicals. The first is terminated via reaction **(e)** which yields a molecule of lipid hydroperoxide (ROOH), and an α-tocopheroxyl radical. The second chain is terminated by the fast coupling of an ROO· radical with the α-tocpheroxyl radical **x (g)**.



x **(g)**

If the mechanism stops at step **(e)**, vitamin E can be regenerated from the α–tocopheroxyl radical by reaction with a hydrophilic reducing agent such as the ascorbate anion, AH^-, (vitamin C[51]).

$$ArO^{\bullet} + AH \longrightarrow ArOH + A^{-\bullet} \qquad \textbf{(h)}$$

Vitamin C (ascorbic acid) quenches free radicals in the aqueous environment[52] and is then transformed through this process into semi-dehydroascorbic acid. Uric acid may perform the same function *in vivo*.

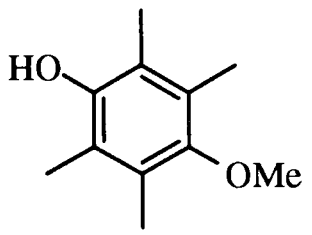
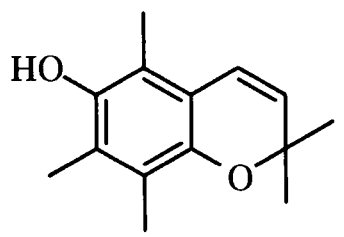
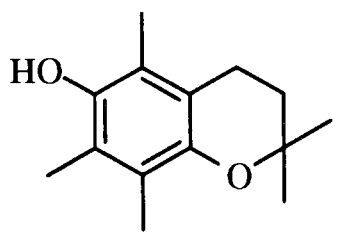
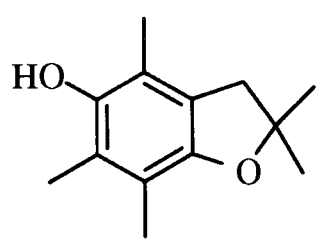
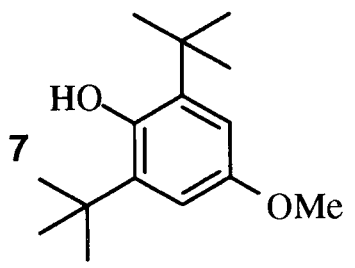
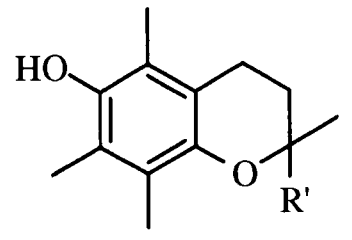
The effectiveness of a chain breaking antioxidant depends on a number of factors, including its reactivity towards peroxyl radicals. That is if a chain breaking antioxidant is to be effective, a relatively small quantity must protect a much greater quantity of the

organic substrate (RH). The rate constant for reaction **(e)** must therefore be much greater than that for reaction **(c)**[12] i.e. $k_5 >> k_3$.

$$ROO^{\bullet} + RH \xrightarrow{k_3} ROOH + R^{\bullet} \quad \textbf{(c)}$$

$$ROO^{\bullet} + ArOH \xrightarrow{k_5} ROOH + ArO^{\bullet} \quad \textbf{(e)}$$

Ingold *et al* [12] have compared the different chain-breaking antioxidants by measuring their k_5 **(e)** values under similar conditions **(Table 1)**, which shows that the benzofuran analogue of α-tocopherol **(6)** has a higher k_5 value than other antioxidants and therefore, is the superior antioxidant.

Phenol	$10^4 k_5$ ($M^{-1}s^{-1}$).	Dihedral angle (θ ')
3 	39	89 °
4 	250	38 °
5 	380	17 °
6 	570	6 °
7 	130	-
1 	320	17 °*

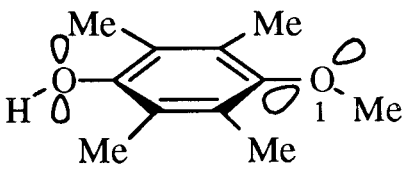
R' = $C_{16}H_{33}$ (Phytyl)

Table 1

* The dihedral angle for (**1**) cannot be determined by x-ray diffraction, studies as it is an oil at room temperature.

They showed that α-tocopherol (**1**) and the structurally related model compound, pentamethylhydroxychroman (**6**) were very much better antioxidants than the major phenolic antioxidants used in commerce, such as 2,6-di-*tert*-butyl-4-methoxyphenol

(BHA) (**7**). They attributed the increase in antioxidant activity to stereoelectronic factors because 4-methoxytetramethylpenol (**3**) had only about 10% of the reactivity of α-tocopherol (**1**). This was due to the methoxy group in (**3**) being found to be perpendicular to the plane of the aromatic ring ($\theta=90^{o}$). In this position, the p-type lone pair on the ethereal oxygen is in the plane of the aromatic ring (w.r.t the hydroxyl oxygen) and so can not stabilize the corresponding phenoxyl radical.



3

Lone pair orbital of the 1-oxygen is not held in the plane of the aromatic ring

The extent of overlap will depend on the dihedral angle θ' between the p-type orbital on the oxane ring oxygen, and the perpendicular to the aromatic plane (**see Figure 1**), and this angle should be equal to the dihedral angle θ' between the O_1-C_2 bond and the aromatic plane. Stabilisation (by delocalisation) will be maximised when $\theta'=0^{o}$ and will be at a minimium when $\theta'=90^{o}$.

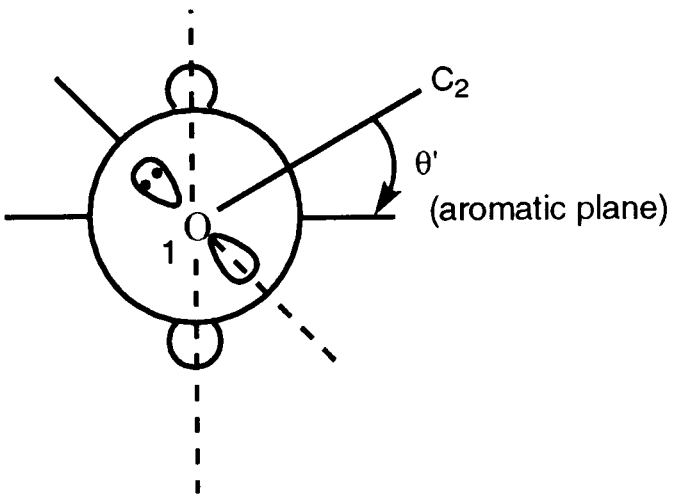
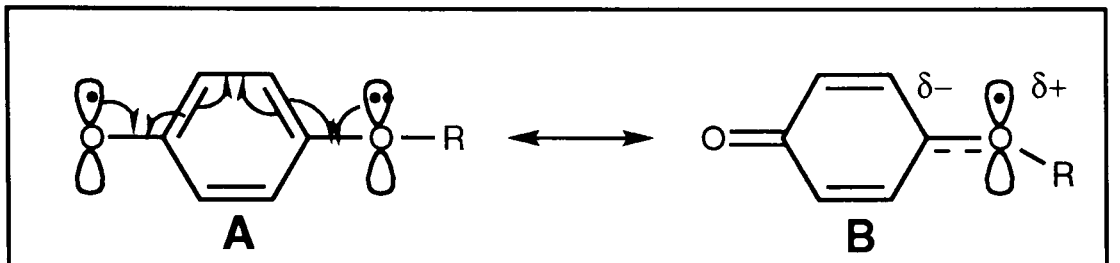


Figure 1

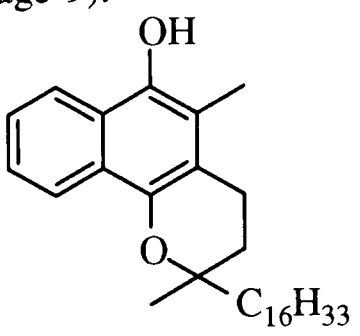
However, in α-tocopherol (**1**) the saturated oxane ring adopts a half-chair conformation and holds the ethereal oxygen (O_1) in such a position ($\theta=17^{o}$) that the lone pair orbital can therefore overlap with the singly-occupied molecular orbital (SOMO) containing the radical. Hence stabilization of the phenoxyl radical by conjugative electron delocalisation, **A** to **B** is as shown in **Scheme 1**.



Scheme 1

X-ray values of θ' for various phenols are also shown in **Table 1** (page 9), and the data supported this stereoelectronic explanation for the high reactivity of α-tocopherol. The dihedral angle (θ') decreases along the series **6**,**5**,**4**,**3**, the compound **(6)** (benzofuran analogue of α-tocopherol) being the most active simple phenolic antioxidant. Also, the O-H bond in α-tocopherol **(1)** is weak which will therefore, result in the hydrogen atom being cleaved more readily by an attacking peroxyl radical (ROO·), i.e. the more effective it will be as an antioxidant[53].

The synthesis, and kinetic studies of antioxidant activity, for new tocopherol related compounds have been reported by other researcher[54]. The chain breaking abilities of naphtholic antioxidants, such as polyalkylbenzochromanol, have been compared to those of vitamin E and were found to have higher activity than vitamin E itself[55]. Burton *et al*[56-58] have measured the second rate constants (k_5) (equation **(e)**, page 8) for the reactions of α-,β-, γ-, and δ-tocopherol and other related phenols with poly (styrylperoxyl) peroxyl radicals by the inhibition of styrene. They concluded that α-tocopherol **(1)** and α-tocopherol model compound such as **(5)** were the best phenolic antioxidants known. Furthermore, they found that a better tocopherol compound **(6)**, which had a five membered heterocyclic ring instead of the six-membered one in **5**, reported that the rate of reaction of **(6)** was 1.8 times higher than that of α-tocopherol **(1)** (see **Table 1**, page 9).



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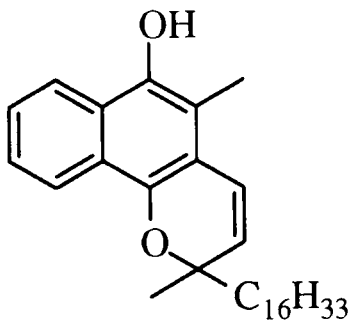

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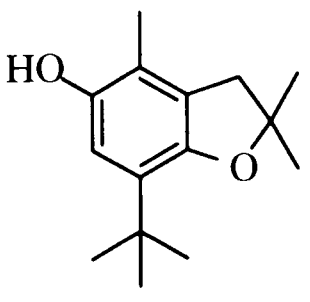

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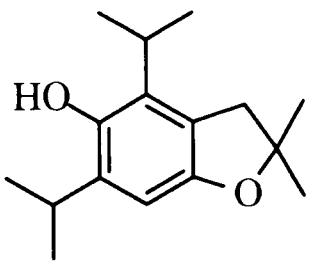
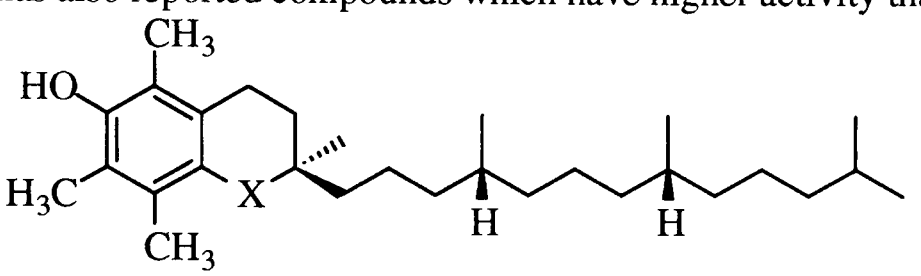


11

Also, Mukai *et al*[59] found that vitamin K_1- chromanol (**8**) and K_1- chromenol (**9**) were 6.9 amd 4.5 times more active than α-tocopherol (**1**). Also, two new tocopherol derivatives (**10**) and (**11**) were found to be 1.8 and 1.1 times more active than (**1**). Barclay *et al*[60] has also reported compounds which have higher activity than vitamin E.

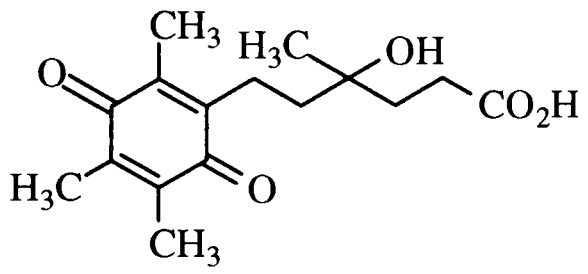


12, X = S
13, X = N

The antioxidant activities of 1-thia-α-tocopherol (**12**) and 1-aza-α-tocopherol (**13**) and their related compounds have also been reported[51] but were found to be less than that of α-tocopherol. In an *in-vitro* study of all-*rac*-1-thio-α-tocopherols they were found to be less effective antioxidants than α-tocopherol. The number of peroxyl radicals trapped per molecule of these thio compounds was between 1.0 and 1.8 for **12** and**13** whereas it it was 2.0 for α-tocopherol.

1.05 Oxidised Forms of Vitamin E

One of the mysteries surrounding vitamin E is its metabolic fate[11]. Various reports have indicated that not all of the vitamin E that was shown to be absorbed *in vivo* is actually oxidised irreversibly[11,63,64]. The major *in vivo* oxidation products which have been unequivocally identified are the Simon metabolites (**14** and its γ–lactone **15**)[65,66].



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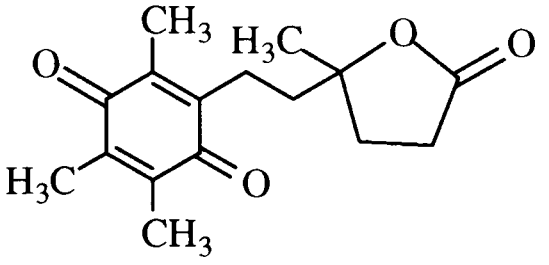
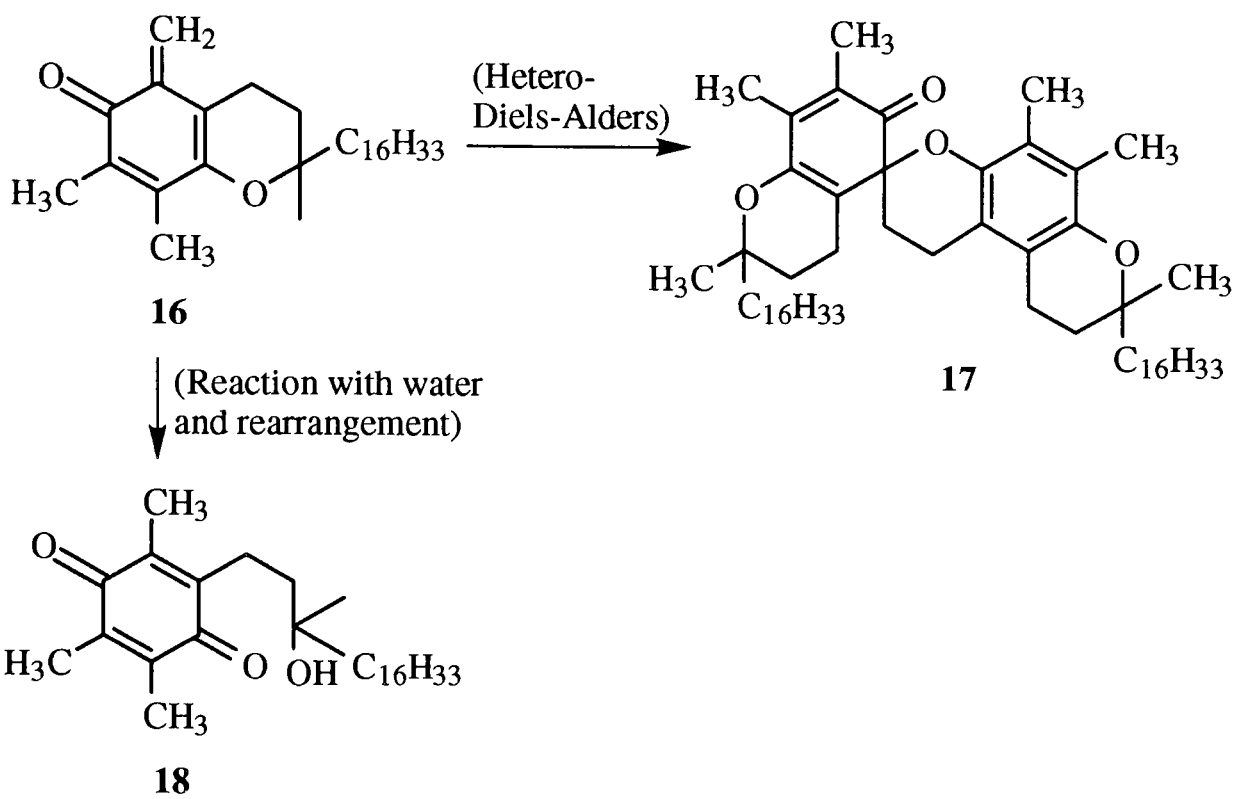


15

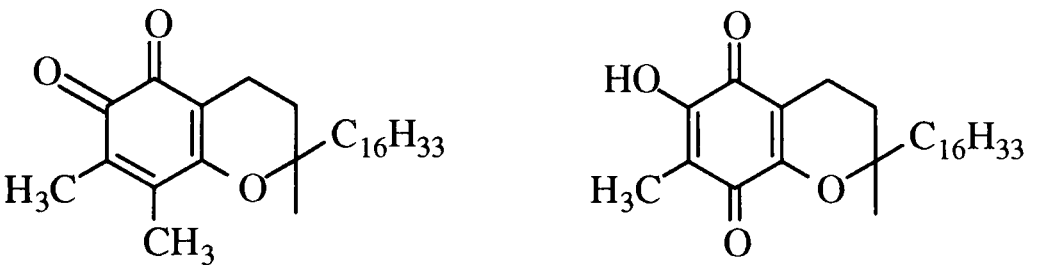
These two metabolites have been found in the urine of rabbits[65], humans[66,67,68] and rats in which they are mainly present as glucuronic acid conjugates. Also vitamin E has been shown to be regenerated from α-tocopheryl quinone (**18**)[69]. It has been shown that α-tocopheryl quinone is a potent anticoagulant that may be responsible for the beneficial effects of α-tocopherol in preventing heart attacks and strokes[70]. α-Tocopherylquinone (**18**) and trace amounts of the spiro-dimer of (**17**) (which can be formed from quinone methide (**16**) reacting with another molecule of **16** via a hetero Diels-Alders reaction) are both natural metabolites of α-tocopherol[71]. α-Tocopherylquinone (**18**) is considered to

be one of the first oxidative products of α-tocopherol in the human body. This quinone has been shown to cure nutritional muscular dystrophy in animals[11].



16 **17** **18**

The reactions of various benzoquinone methides with phenols have been investigated[73], in order to identify the by-products that are formed during the oxidation of tocopherols. Two oxidation products of α-tocopherol are α-tocopurple **(20)**[73] and tocored **(19)**[74]. The iodine oxidation of α-tocopherol in alkaline methanol was also shown to give quinones[75].



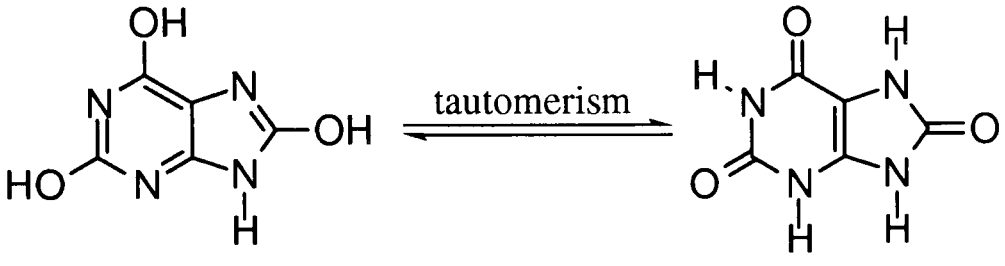
19 **20**

1.06 Other fat and water soluble Vitamins

There are three other fat soluble vitamins - A, D, and K[76] all have different functions compared to α-tocopherol. Vitamin D is required for the optimal intestinal absorption of dietary calcium[77]. It also elicits effects elsewhere in the body. Vitamin K is important in blood coagulation and electron transport. (It has been studied by E.S.R.[78]) and Vitamin A which plays an essential role in the function of the retina and is required for growth of bone, reproduction and embryonic development[79], such as β-Carotene **(22)** which quenches singlet oxygen[53] and may prevent the onset of carcinogenesis[80-81].

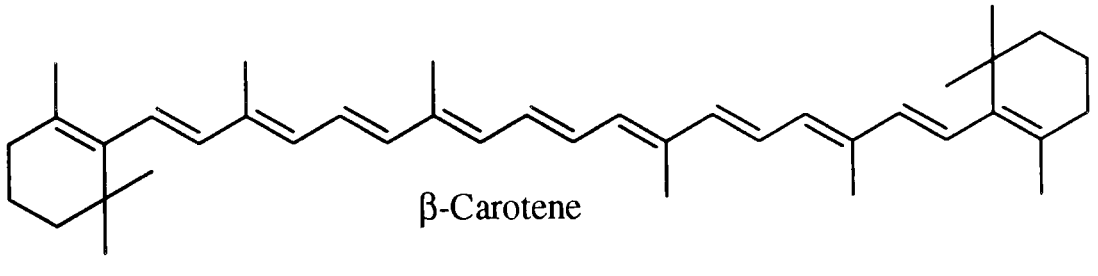
$$^1O_2 + \beta\text{-carotene} \longrightarrow {}^3O_2 + \beta\text{-carotene} + \text{heat} \qquad \textbf{(i)}$$

There are also water soluble antioxidants such as Vitamin B complex, Ascorbic acid (Vitamin C) and uric acid **(21)**.



Uric acid

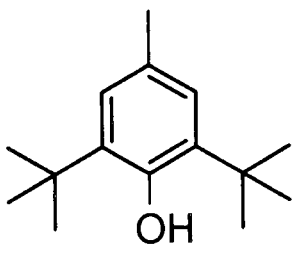
21



β-Carotene

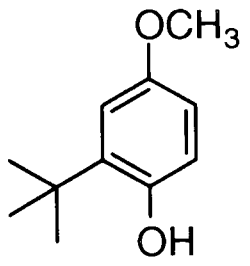
22

Other synthetic chain breaking antioxidants include BHT **(23)** (butylated hydroxy toluene), BHA **(24)** (butylated hydroxyanisole) TBHQ (*t*-butylhydroquinone) and propyl gallate which are common food additives.



BHT

23



BHA

24

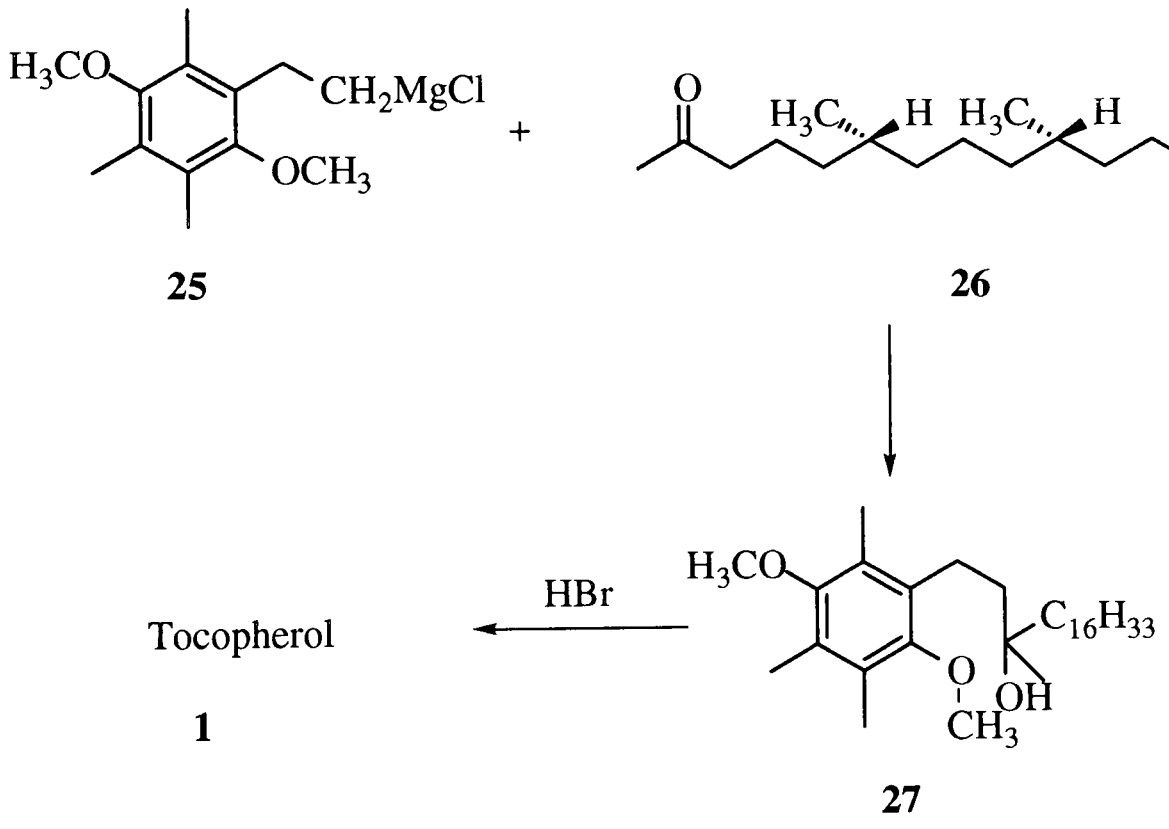
Fat soluble vitamins tend to accumulate in membranes and lipid cells and can prove toxic if high levels are reached[83]. However, the toxic effects of vitamin E are unproven although it may cause hypervitaminosis syndrome when taken in large doses[84].

1.07 Syntheses of racemic tocopherol

The first recorded synthesis of *dl*-α-tocopherol was carried out by Karrer *et al* [17] in which trimethylhydroquinone was condensed with phytyl bromide in the presence of anhydrous zinc chloride in petroleum ether to give the product in almost quantitative yield. A second synthesis of *dl*-α-tocopherol was achieved by Bergal *et al* [85] who used phytol, trimethylhydroquinone and zinc chloride and modified the synthesis by adding decalin (b.pt.189-191°) as the solvent. Smith and Ungnade[86-88] found that better results were obtained by conducting the condensation in the absence of any catalyst or solvent. Under these circumstances, excellent yields of fairly pure product were obtained which could be further purified by high vacuum distillation.

Racemic α-tocopherol can also be synthesised in excellent yield by reacting racemic isophytol with trimethylhydroquione in the presence of Lewis acids catalysts such as BF_3-diethyl etherate at 85-95°C[89].

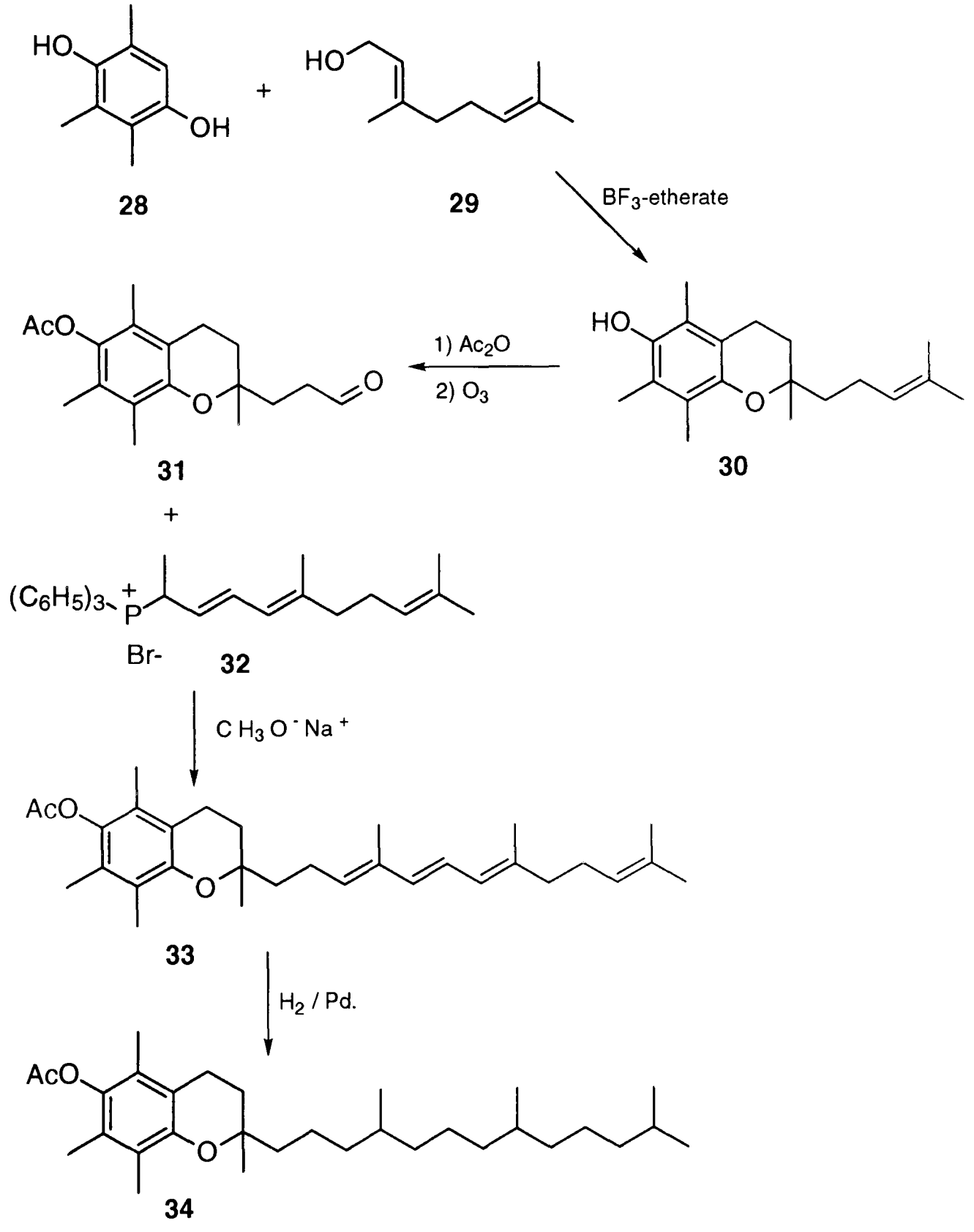
Other reported approaches have involved the coupling of chromans and side chain moietes[90-92], or involving the preformed chroman units, such as in the addition of Grignard reagent **(25)** to ketone **(26)** in ether followed by protonolysis to give the alcohol **(27)** as shown in **Scheme 2**. Addition of HBr afforded α-tocopherol itself by removing the methoxy protecting groups, and facilitating the formation of the oxane ring.



Scheme 2

Another synthetic approach included the Wittig reaction between the homologues chroman aldehyde **(32)** and the side chain synthons **(33)**[93-96] as shown in **Scheme 3**, such as the acid-catalysed reaction of trimethylhydroquinone **(28)** with the allylic alcohol **(29)** affording the chroman **(30)**. Acetylation of this chroman **(30)**, followed by ozonolysis led to the

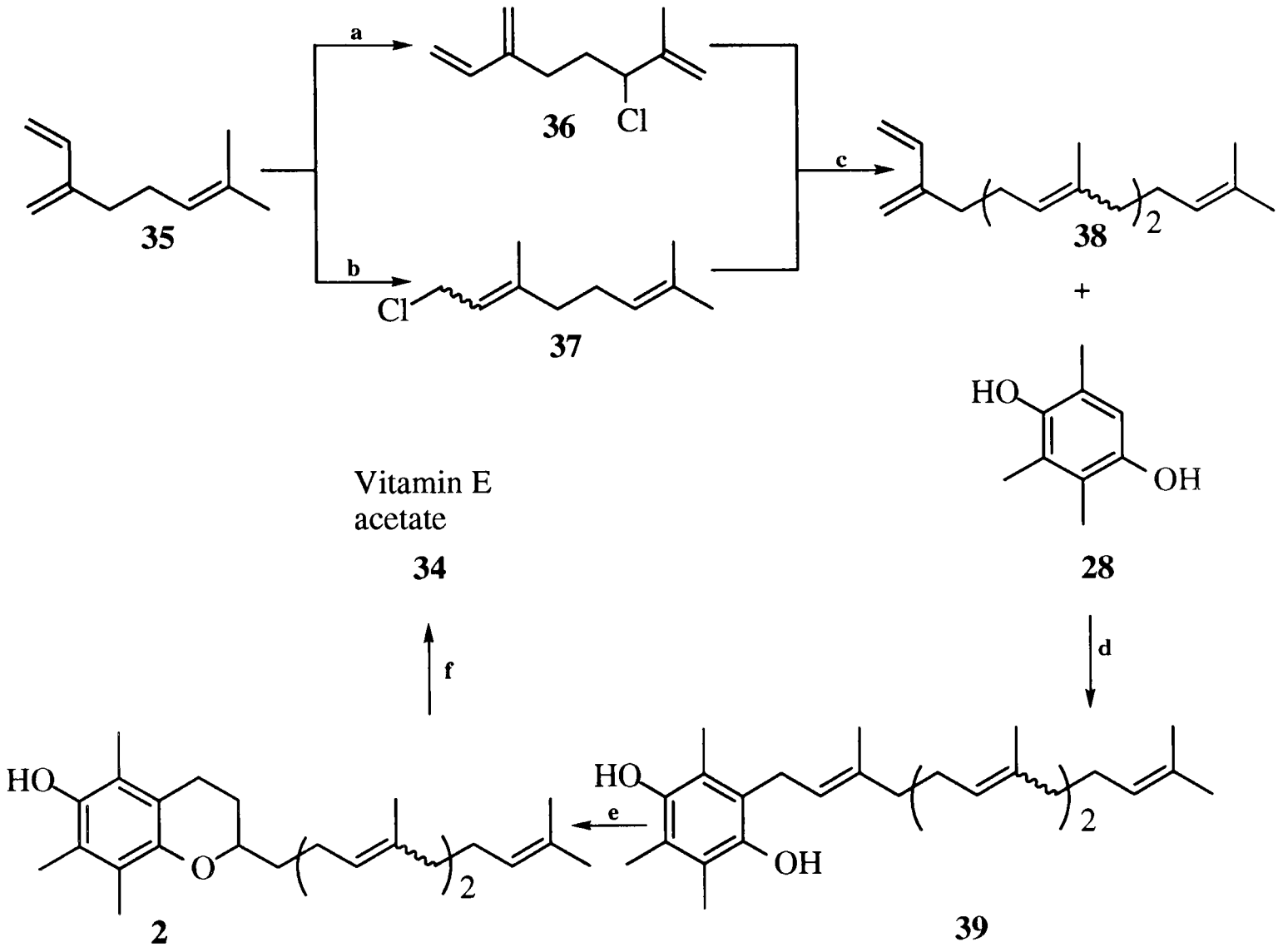
desired aldehyde **(31)**. Wittig coupling of the phosphonium salt **(32)** with the aldehyde **(31)** gives tocotrienol **(33)**. Catalytic hydrogenation then afforded the α-tocopheryl acetate **(34)**[97].



Scheme 3

Recently, Bienayme *et al*[98] have proposed a highly convergent and atom-economical synthesis of *dl*-α-tocopherol **(1)** by using Rhodium(I)-catalysed arylation of β-springene **(38)** with trimethylhydroquinone **(28)** as outlined in **Scheme 4**. The ene-type chlorination of myrcene **(35)** resulted in chloro-3-myrcene **36**, whereas, its hydrochlorination in the presence of copper (I) chloride gave geranyl chloride **(37)**. Reductive coupling of **37** with

36 was achieved by reaction with Grignard reagent followed by copper (I) chloride to afford diene **38**. β-Springene **38** was condensed with trimethylhydroquinone **(28)** under Rhodium (I) catalysis to afford **39**. This was converted into the tocotrienol **(2)** by acid catalysis which was hydrogenated and acetylated to form vitamin E acetate **(34)**.



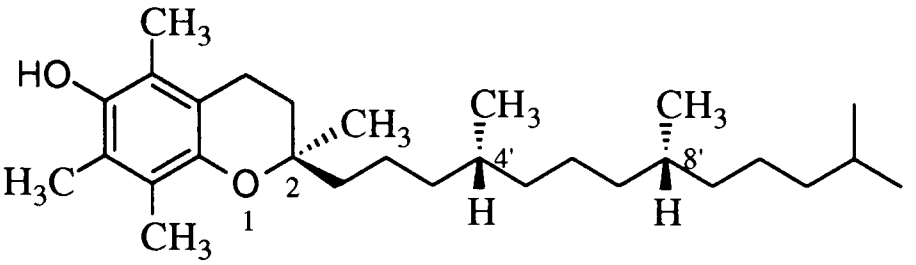
a) Cl_2 (g), pentene, reflux; **b)** CuCl, HCl (g), CH_2Cl_2, 0^oC; **c)** Mg^o, THF, -20^oC then CuCl ; **d)** $[RhCl(COD)]_2$, dppb , K_2CO_3, toluene, 110^oC; e) $MeAlCl_2$ or pTSA, hexane, 100^oC: **f)** H_2, Pd/C, EtOH then Ac_2O, Et_3N, 25^oC.

Scheme 4

Vitamin E has been the synthetic objective of numerous studies directed towards the synthesis of the natural occurring form (2R, 4'R, 8'R)-α-tocopherol. The renewed interest in this vitamin is due to the development of new syntheses of the chiral centres in the side chain and chroman portions of the molecule.

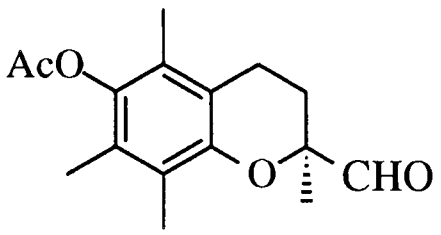
1.08 Syntheses of (2R, 4'R, 8'R) α-Tocopherol

The first formal total synthesis of natural (2R,4'R,8'R)-α-tocopherol **(1)** was reported by Mayer and Isler in 1963[99].



1

This group utilised a convergent approach in which the molecule was assembled via Wittig coupling between the chroman-2-carboxaldehyde **(40)** and the carbon-15 phosphonium salt **(41)**.



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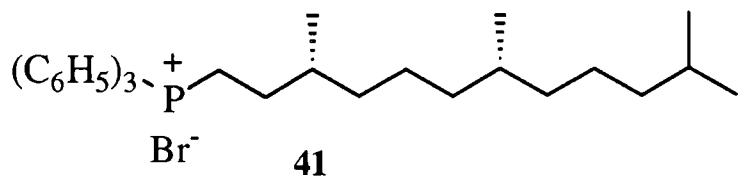
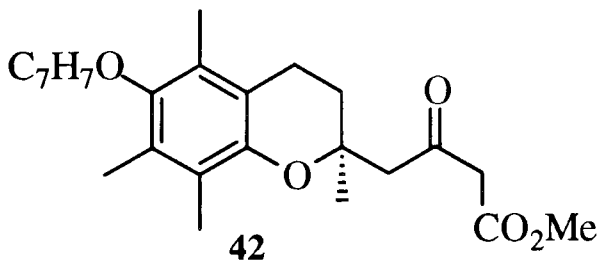


41

A related scheme described by Scott *et al* [96] involved coupling of the homologous units, chroman-2-acetaldehyde and the carbon-14 phosphonium salt. In both these approaches the chain intermediates were derived from naturally occurring (7R,11R)-phytol[100]. *d*-α-Tocopherol is the naturally occurring form of vitamin E. As wheat germ oil contains a relatively large amount of racemic α-tocopherol (0.02 to 0.20%) the latter can be obtained by saponification. Alternatively, hot ethanol extraction of the wheat germ followed by the removal of the solvent gives the required vitamin E. However, analysis shows the presence of α,β,γ, and τ-tocopherol. Therefore, the stereoslective synthesis of the (2R,4'R,8'R)-isomer of α-tocopherol is desirable.

Coffen *et al*[101] have synthesized natural vitamin E (2R,4'R,8'R)-α-tocopherol based on (S)-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl) methyl keto ester **(42)** and allylic carbonate **(43)**.



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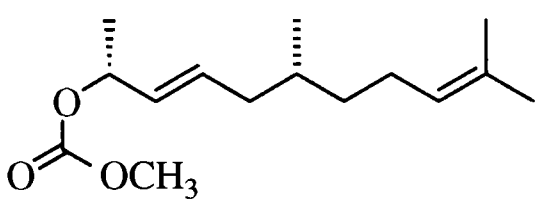
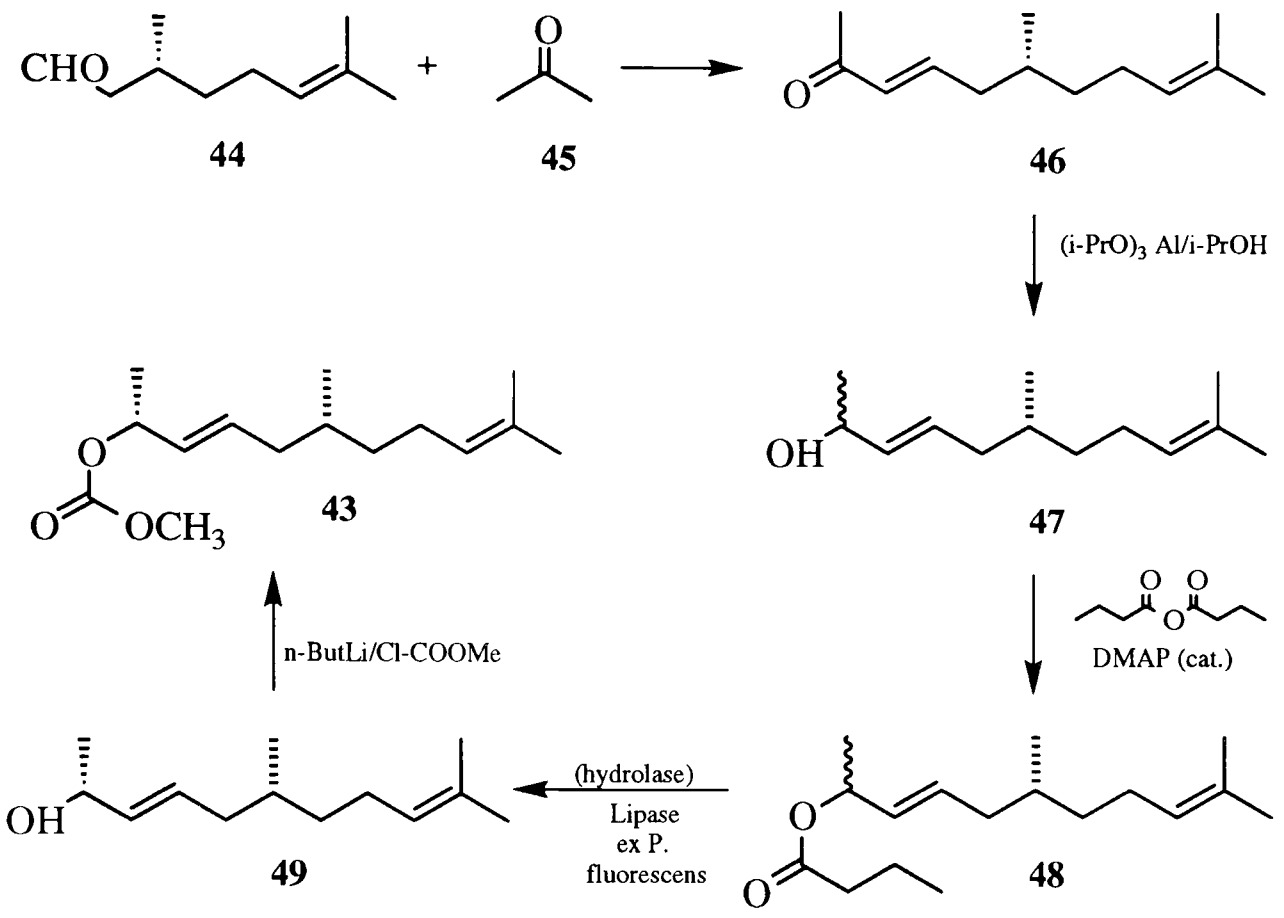


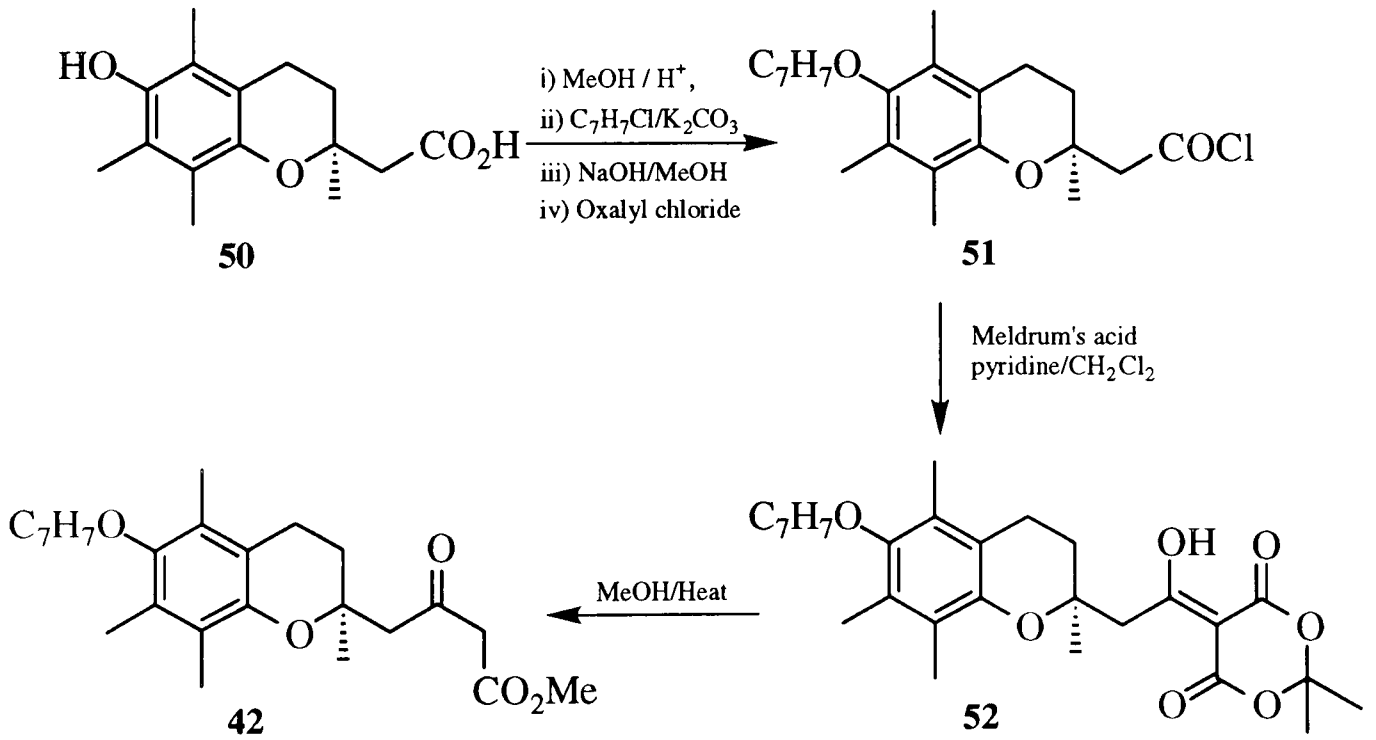
43

The carbonate **(43)** was synthesized by the reaction of (R)-citronellal **(44)** and acetone **(45)** under basic conditions to afford the allylic ketone **(46)**. Reduction of this ketone gave the corresponding allylic alcohol **(47)** which on esterification afforded the diastereomeric ester **(48)**. The important reaction in this scheme was the hydrolase-catalyzed kinetic resolution of the diasteromeric ester into the single isomer **(49)**. Finally, acetylation of the allylic alcohol **(49)** afforded the corresponding carbonate **(43)** as outlined in **Scheme 5**.



Scheme 5

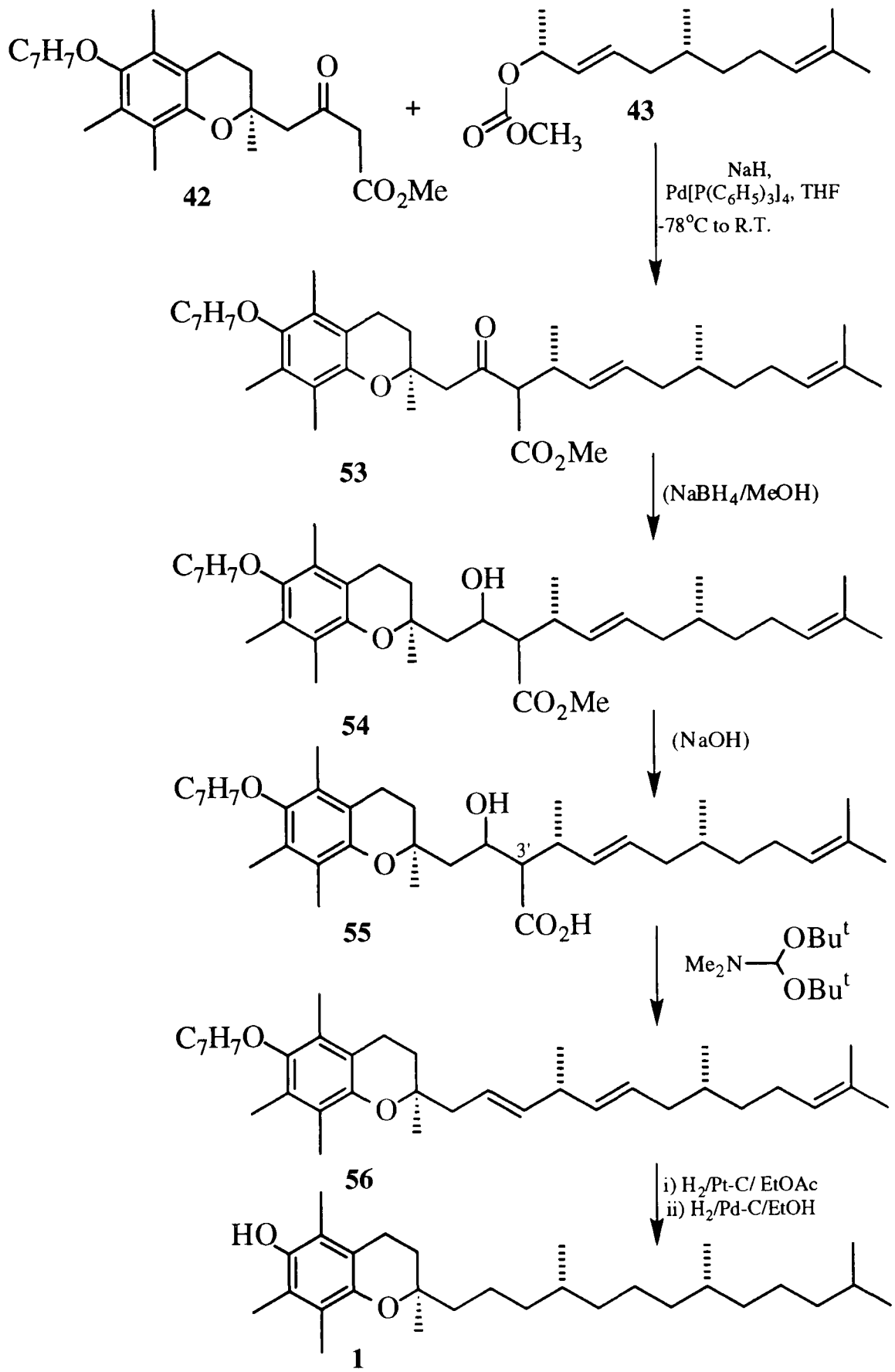
The methyl keto ester **(42)** was prepared from chromanylacetic acid **(50)** as shown in **Scheme 6**. The conversion of chromanylacetic acid **(50)** into the O-benzyl chloride **(51)** had been followed according to the method of Cohen *et al*[102]. The Meldrum's acid adduct of the acid chloride[103] **(52)** refluxed in methanol afforded the methyl keto ester **(42).**



Scheme 6

The methyl keto ester **(42)** was coupled with allylic carbonate **(43)** using palladium which led to the formation of the coupling product **(53)** as shown in **Scheme 7**. Borohydride

reduction of **53** afforded the hydroxy methyl ester **(54)**. Hydrolysis of **(54)** afforded the β-hydroxy acid **(55)**. Removal of the carboxylic acid in **55** afforded the tocotrienol **(56)**. Catalytic hydrogenation of the tocotrienol **(56)** and deprotection of the benzyl group afforded vitamin E, (*d*)-α-tocopherol **(1)** in 84% yield.



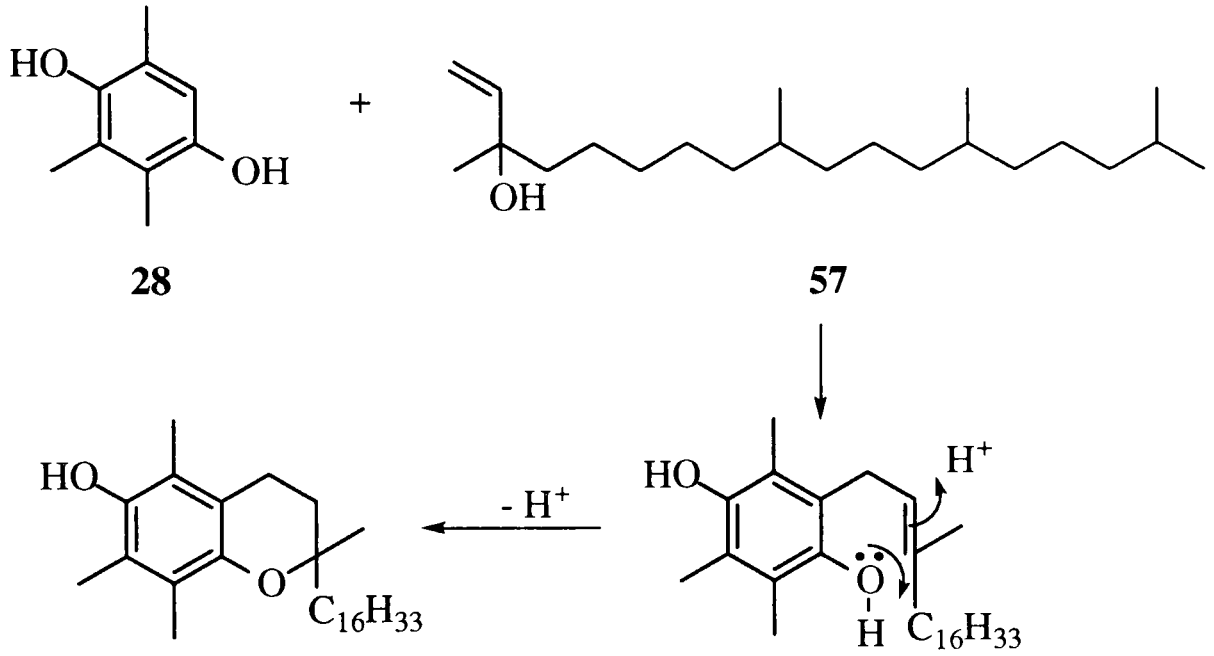
Scheme 7

1.09 Acid - Catalysed Syntheses of Vitamin E

The condensation of an hydroquinone or a phenol with an allylic alcohol is an important step in the synthesis of *dl*-α-tocopherol and its related compounds. The rate of reaction is

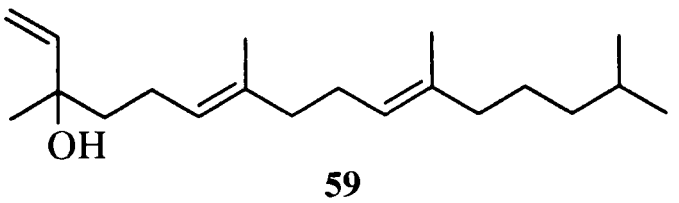
significantly accelerated in the presence of Lewis acids .such as zinc chloride[85], aluminium chloride[104], boron trifluoroetherate[89], formic acid, acetic acid, rare earth metal (III) trifluoromethanesulfonates (triflates)[105,106], sulphuric acids, or combinations of strong Bronsted acids.

Recently, a number of researchers have utilised heterogeneous catalysis such as metal ion-exchanged montmorillonites[107], Nafion NR 50[108], for the condensation reaction of hydroquinone **28** with the allylic alcohol **57** to give **(58)** which on deprotonation afforded α-racemic tocopherol **1** as shown in **Scheme 8**.



Scheme 8

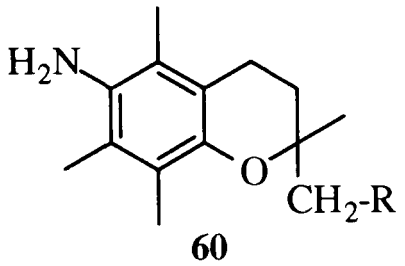
Natural phytol and isophytol **(57)** have both been used in the synthesis of tocopherols. Tocotrienols have been synthesised in a similar way but using *trans*-geranyllinalool **(59)** instead of isophytol[99].



59

Tocol and the lower homologues of α-tocopherol can also be synthesised by the route[109] outlined in **Scheme 8.**

α-Tocopherol is an oil, therefore its conversion into a solid analogue retaining its high biological activity would offer many advantages. The amino analogue of α-tocopherol **(60)** which is a solid that can be prepared by condensation of 2,3,5-trimethyl-4-aminophenol with phytol. This is known to possess high biological activity[110].



60

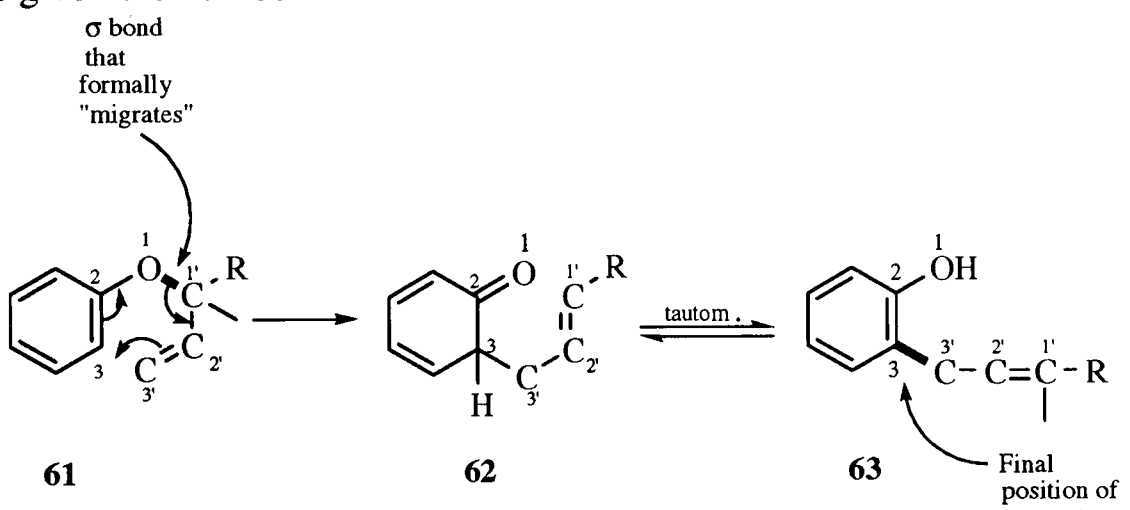
R = 3,7,11-trimethyldodecyl

If the phenolic hydroxy group in α-tocopherol is absent or is masked as an ether or as the allophanate, complete inactivity results. However, many carboxylic esters of α-tocopherol are active due to their metabolic hydrolysis to give the free phenol group. Some simple esters of α-tocopherol have been synthesised which show biological activity but are liquids[65].

1.10 The 3,3-Sigmatropic Claisen Rearrangement

The 3,3-sigmatropic rearrangment of allyl aryl ethers provides an efficient and selective method for constructing carbon-carbon bonds and has increasingly been employed in the syntheses of Vitamin E and sub-units which are present in vitamin E, namely 2,3-dihydrobenzofurans and 3,4-dihydrobenzopyrans[111-114].

A sigmatropic rearrangement is a concerted reaction in which an atom e.g. H or a group e.g. CH_3 or a sigma bond migrates from one site to another. An example is the intramolecular claisen rearrangement of allylic aryl ethers **(61)** via intermediate **(62)** to give the *o*-allylphenols **(63)**[115-123] **(Scheme 9).** The order of a sigmatropic rearrangment is expressed by two numbers set in brackets:[i.j]. These numbers can be determined by counting the atoms over which each end of the s-bond has moved. Each termini is given the number 1.



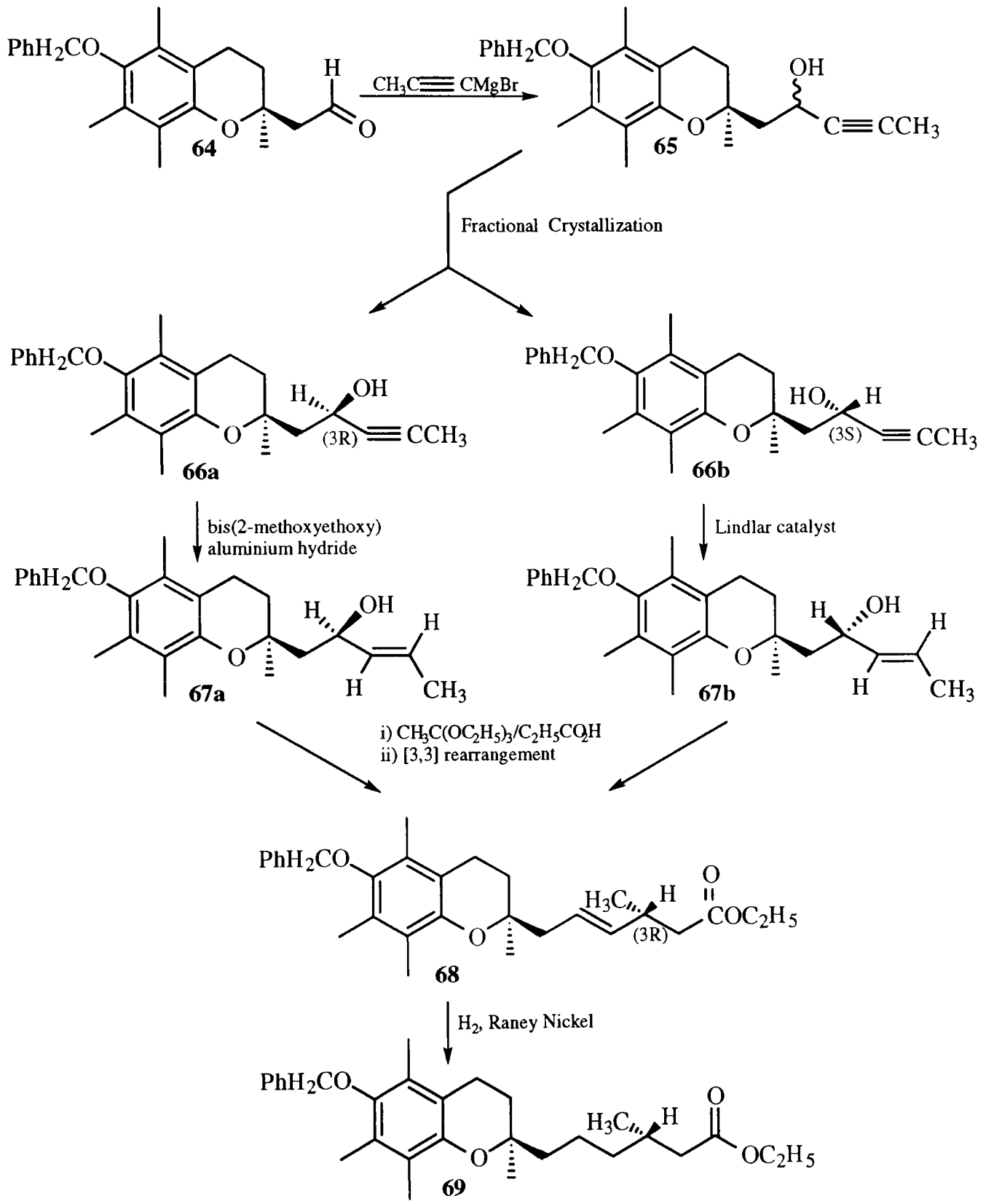
61 **62** **63**

Scheme 9

Thus in the example shown in **Scheme 9**, each terminus of the σ-bond has migrated from C-1' and O-1 to C-3 and C-3', so the order is [3,3] hence, [3,3]-sigmatropic rearrangement. If both the ortho positions are blocked, the allylic group migrates to the para position by a further Claisen rearrangement. The [3,3]-sigmatropic Claisen rearrangement process has a condsiderable potential in the synthesis of optically active substances.

The synthesis of (2R,4'R,8'R)-α-tocopheryl acetate utilises a stereoselective (3,3)-sigmatropic Claisen rearrangement of allylic alcohols[124]. Treatment of the (S-) chromanylacetaldehyde **(64)** with Grignard reagent gave the acetylenic carbinol **65**. Crystallisation of **65** gave the two diastereomeric acetylenic carbinols **66a** and **66b**, respectively, which on reduction afforded **67a** and **67b**, respectively. Orthoester Claisen rearrangement of allylic alcohols **67a** and **67b**, respectively, yielded the same unsaturated ester **(68)**. Reduction of ester **(68)** resulted in the formation of the corresponding saturated ester **(69)**. Further reduction of the saturated ester **(69)** gave the chromanyl alcohol **(70)** which was converted into tosylate **(71)**. Coupling of **(71)** with Grignard reagent **(72)**

furnished the benzyl ether (**73**) which on hydrogenation and acetylation afforded the acetate **34** as shown in **Scheme 10**.



Scheme 10

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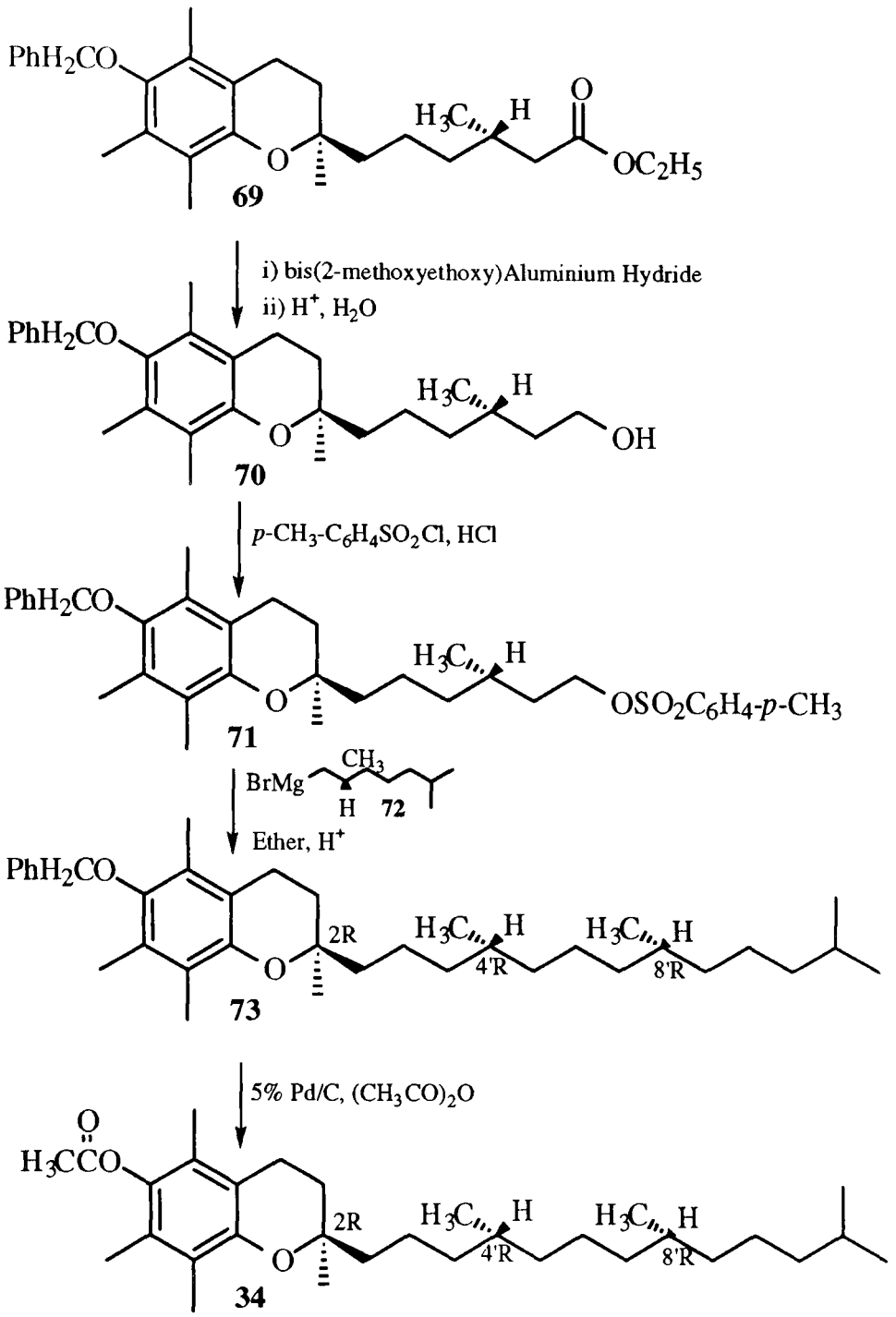
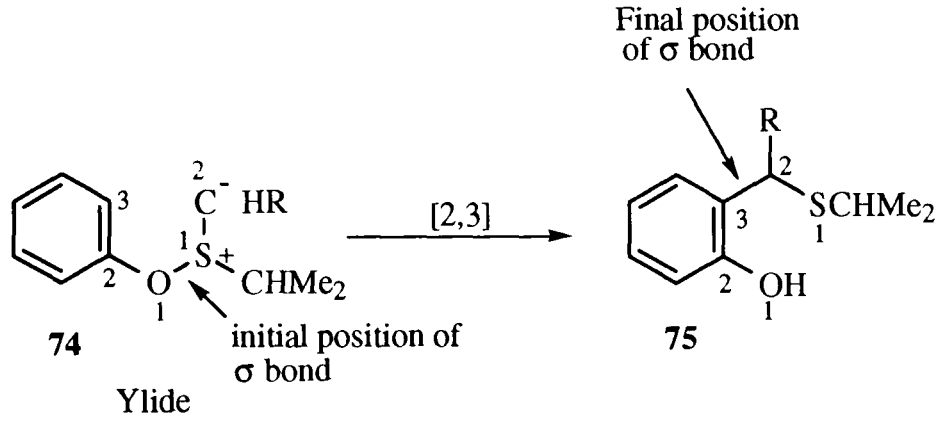


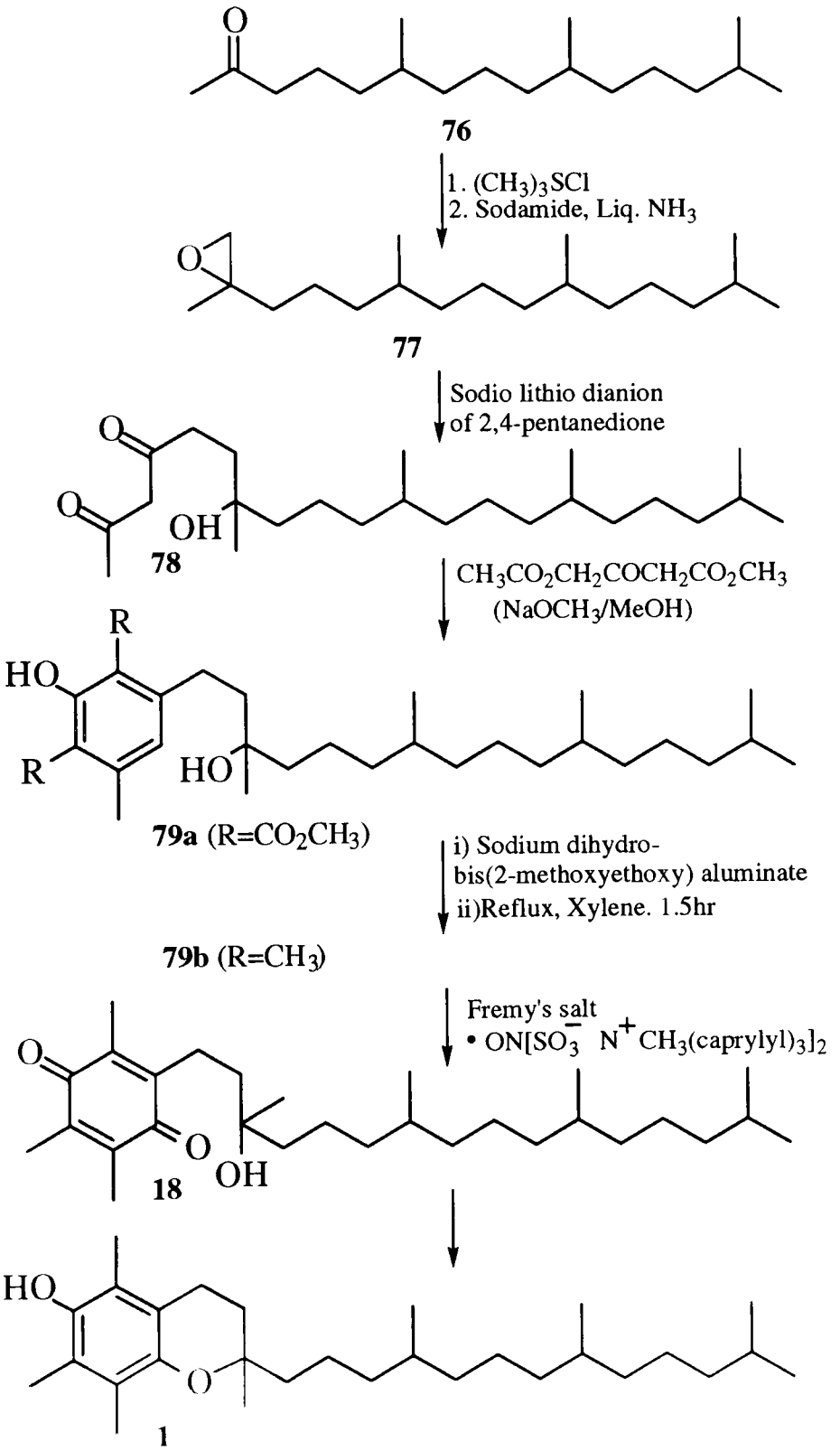
Scheme 10

Thioalkyl groups have been introduced regioslectively into the *ortho* position of phenols **(74)** via [2,3] sigmatropic rearrangement of isopropylphenoxysulphonium alkylides **(75)** as shown in **Scheme 11**, producing an efficient synthesis of precursors for chromans, chromenes, coumarins and *d*-α-tocopherol[125].



Scheme 11

A different synthesis of racemic α-tocopherol has been described by Olson[126] where hexahydrofarnesylacetone **76** was converted to the epoxide **(77)**. The aromatic ring of the chroman was constructed by the addition of the dianion of 2,4-pentanedione to 1, 2-epoxy-2,6,10,14-tetramethylpentadecane **(77)** to afford the hydroxy diketone **(78).** This diketone upon condensation with dimethyl acetonedicarboxylate affords the phenolic diester **(79a)** and upon reduction affords the trimethylphenol **(79b)**. The phenol **(79b)** on oxidation with Fremy's salt gives tocopherylquinone **(18)** , a known precursor of α-tocopherol **(1)** as shown in **Scheme 12.**



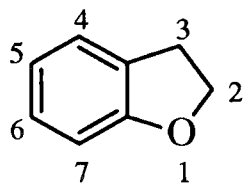
Scheme 12

1.11 The Nomenclature of Benzofurans and Benzopyrans

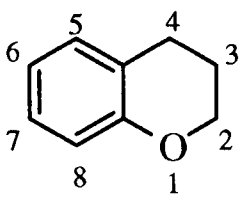
The benzopyrans mentioned in this thesis are known as 1-benzopyrans. The naming of these heterocyclic compounds will be followed by the rules adopted by the IUPAC.

1. In numbering the polycyclic compound, an oxygen hetero atom is given the lowest number consistent with rule 4, as shown in the examples below[127-129].

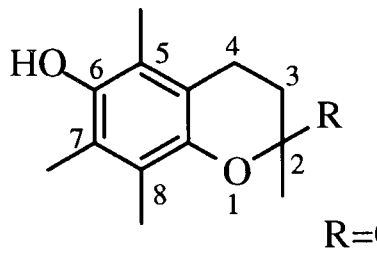
2. Partially reduced ring compounds are often referred to as the dihydro derivatives of the parent unsaturated compound. Saturation is also indicated by attaching the symbol *H* together with the number denoting the position of saturation to the name of the parent unsaturated compound. Since the pyran ring system does not have a double bond at the 3,4-position, is referred to as 3,4-dihydro-2*H*-benzopyran. The number 1 in the dihydro-**1**-benzopyrans denotes the position of attachment of the hetero atom to the benzene ring, so the full name is 3,4-dihydro-2*H*-1-benzopyran. Whereas, in the furan ring systems the double bond is not present at the 2,3 positions and therefore, will be referred to as 2,3-dihydrobenzofurans.



2H-Benzofuran



3,4-2*H*-1-Benzopyran

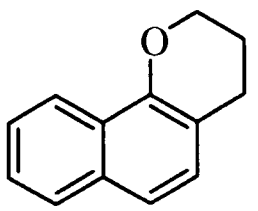


R=$C_{16}H_{33}$

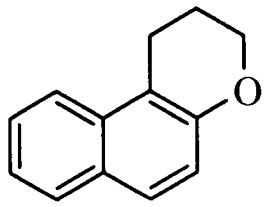
Vitamin E

The polycyclic rings (indicated below) are named by the following rules:

3. The name of the hetero ring is chosen as the parent compound and the fused ring is attached as a prefix. Therefore, the parent compound is the pyran and the fused ring is naphthalene and hence, is named as dihydronaphthopyran.



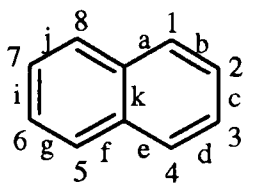
Dihydronaphtho[1,2-*b*]pyran



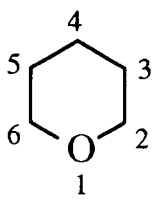
Dihydronaphtho[2,1-*b*]pyran

4. It is also neccessary to indicate in the name the position of the ring junction. This is done by numbering the parent ring, in this case naphthalene and the sides of the parent ring system. The following breakdown of the structure with the appropriate numbering and the lettering will serve to illustrate how this is done.

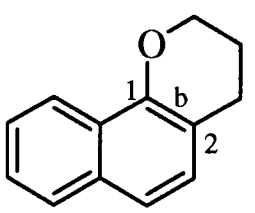
The pyran ring **y** is joined to the naphthalene **x** at the 1, 2-bond and fused to bond b. This is written as [1, 2-*b*], as indicated below.



x

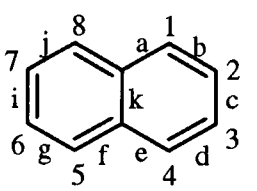


y

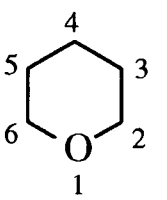


Dihydronaphtho[1,2-*b*]pyran

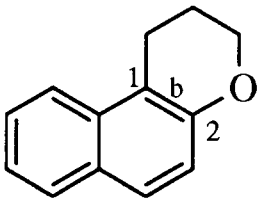
Whereas, in the other structure, the pyran **y** is joined to the naphthalene **x** at the 2, 1-bond and fused to bond b. This is written as [2,1-*b*], as indicated below.



x



y



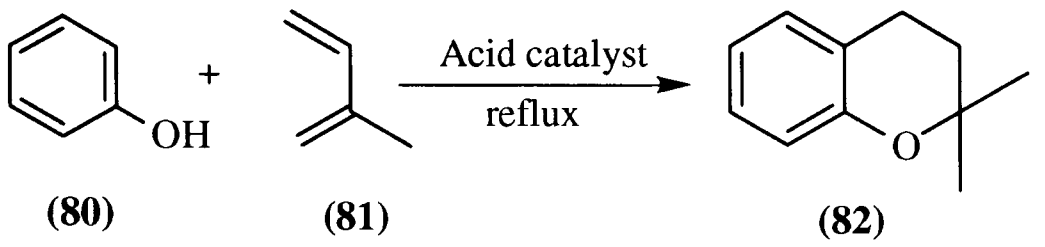
Dihydronaphtho[2,1-*b*]pyran

1.12 Synthesis of Benzofurans and Benzopyrans

2,2-Dimethylchromans are a type of benzopyrans which rarely occur in plants: they are however, obtained as degradative products during the structural elucidation of many naturally-occurring phenolic products bearing isoprenoid units. The Lewis acid mediated reactions of phenols with a variety of allylic alcohols[130-131], aldehydes[132-133], and dienes[104,134,135] have been studied within the context of developing new synthetic routes to benzopyrans (chromans) and benzofurans. Certain of the latter have utility as antioxidants and have skeletal features that are also present in many naturally occurring benzocyclic ethers, such as coumarans, coumarins, flavones, rotenones, pterocarpans, hematoxylins and so on.

1.13 Acid-catalysed syntheses of Benzofurans and Benzopyrans

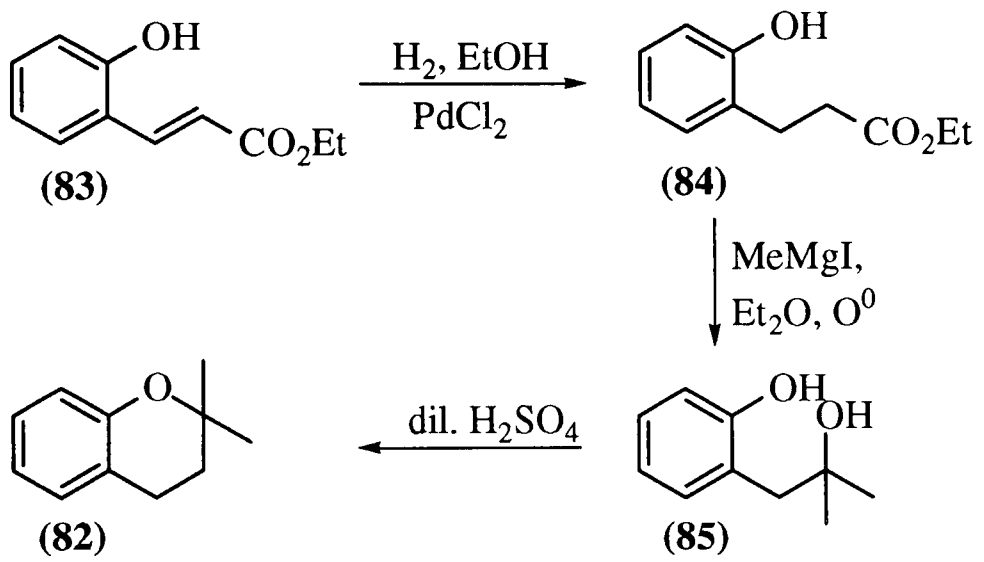
Dihydro-2*H*-benzopyran **(82)** was first synthesized by Claisen[136,137] in 1921 from phenol **(80)** and 2-methylbutadiene **(81)** in the presence of an acidic catalyst **(Scheme 13)**.



(80) **(81)** **(82)**

Scheme 13

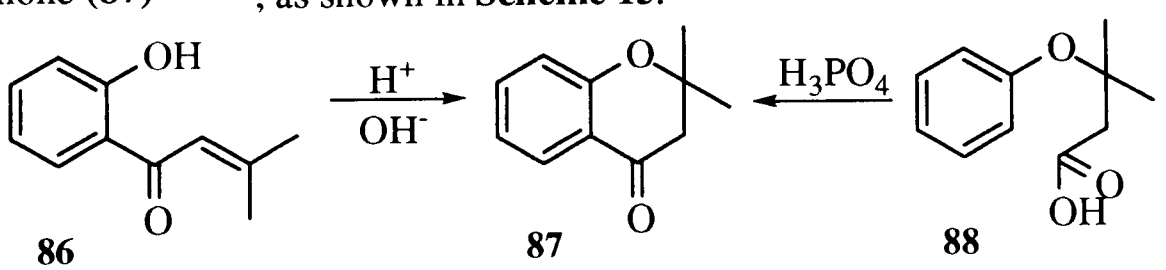
Its structure was confirmed by its synthesis from ethyl coumarate **(83)**. This was reduced to the dihydro derivative **(84)** by hydrogen using a palladium chloride catalyst, and was then converted into 1-(2-hydroxyphenyl)-2-methylpropan-2-ol **(85)** by Grignard reaction with methyl magnesium iodide. Cyclisation of the alcohol **85** in the presence of sulphuric acid afforded dihydrobenzo-2*H*-benzopyran **(82)** as shown in **Scheme 14.**



(83) **(84)** **(82)** **(85)**

Scheme 14

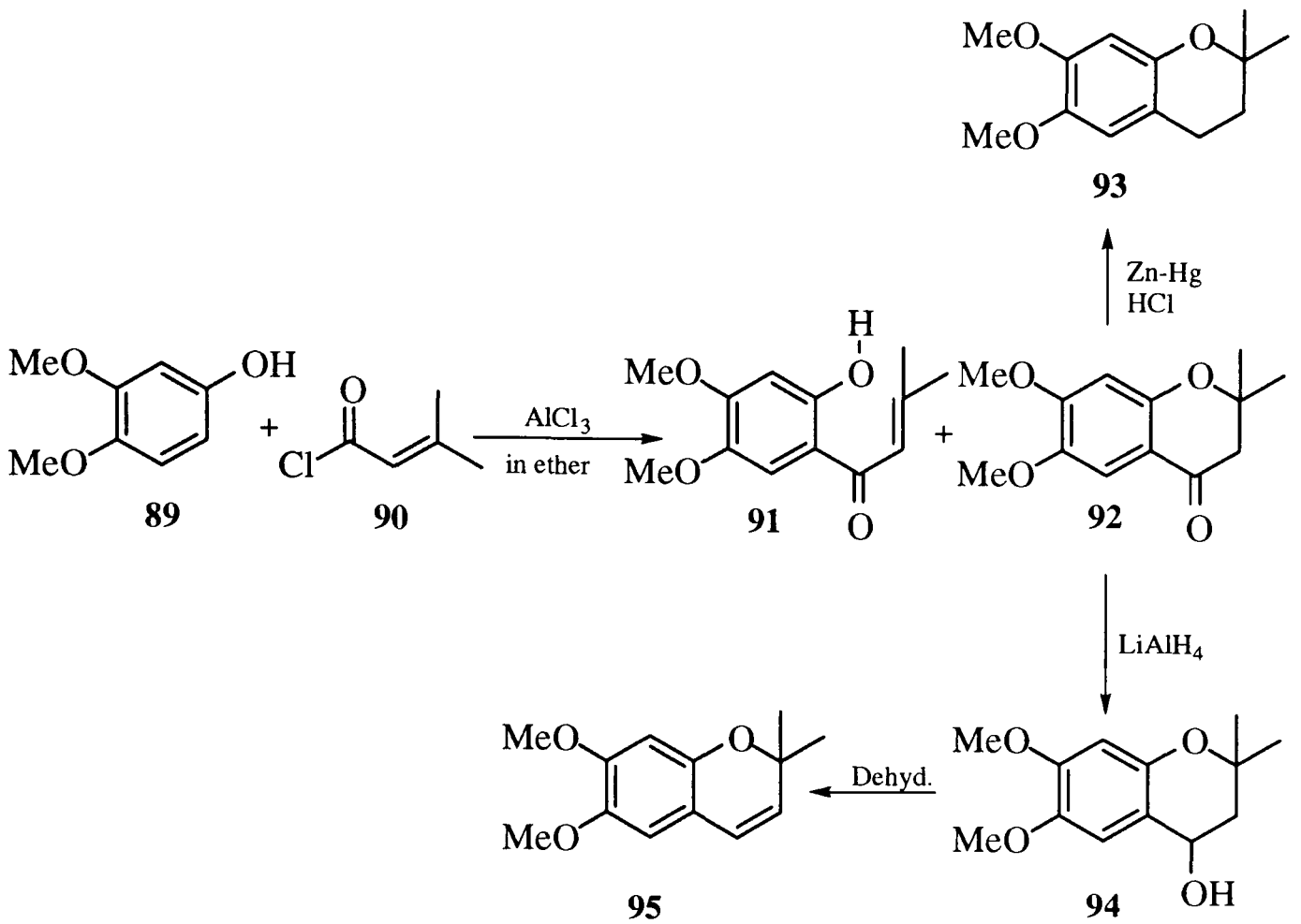
Dihydro-2*H*-benzopyran **(82)** and dihydro-2*H*-benzochromanone **(87)** can both be produced from chroman-4-ones. These latter ketones can be prepared by Friedel-Crafts reaction of phenols and the appropriate acrylic acids to afford **(86)** which cyclise to the desired Chromanone **(87)**[138-140]. Alternatively, Michael addition of phenols to acrylates leads to **(88)** which can also be cyclised by polyphosphoric acid (PPA) to chromanone **(87)**[141-142], as shown in **Scheme 15.**



86 **87** **88**

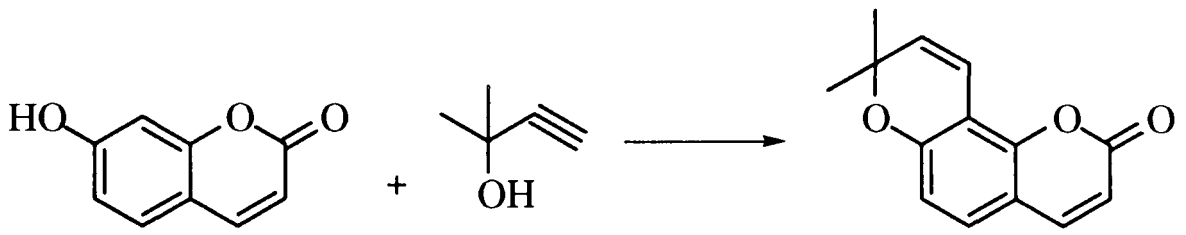
Scheme 15

Acylation of phenol **89** with acid chloride **90** affords a mixture of **(91)** and **(92)**. Isolation of chromanone **(92)** followed by Clemmensen reduction affords the chroman **(93)**[143-144], whereas lithium aluminium hydride reduction of **(67)** to the alcohol **(94)**, followed by dehydration affords the chromene[145] **(95)** as outlined in **Scheme 16**.



Scheme 16

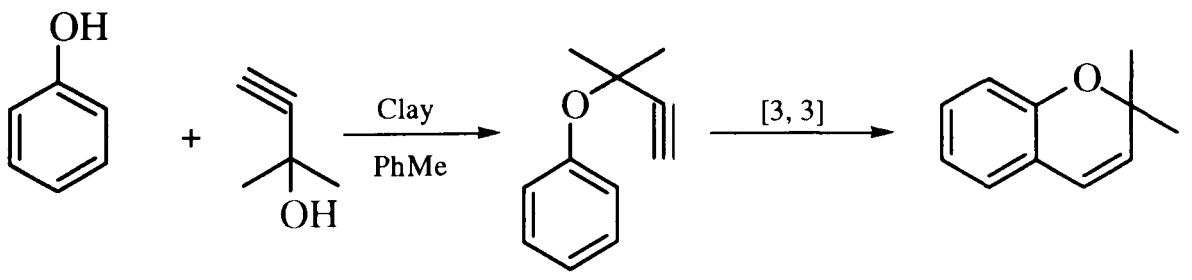
The phenol **(96)** when reacted with propargyl alcohol **(97)** yields the 2,2-dimethylchromene **98** directly, as in the Spath synthesis of seslin[146] **(73)**, **(Scheme 17)**.



96 **97** **98**

Scheme 17

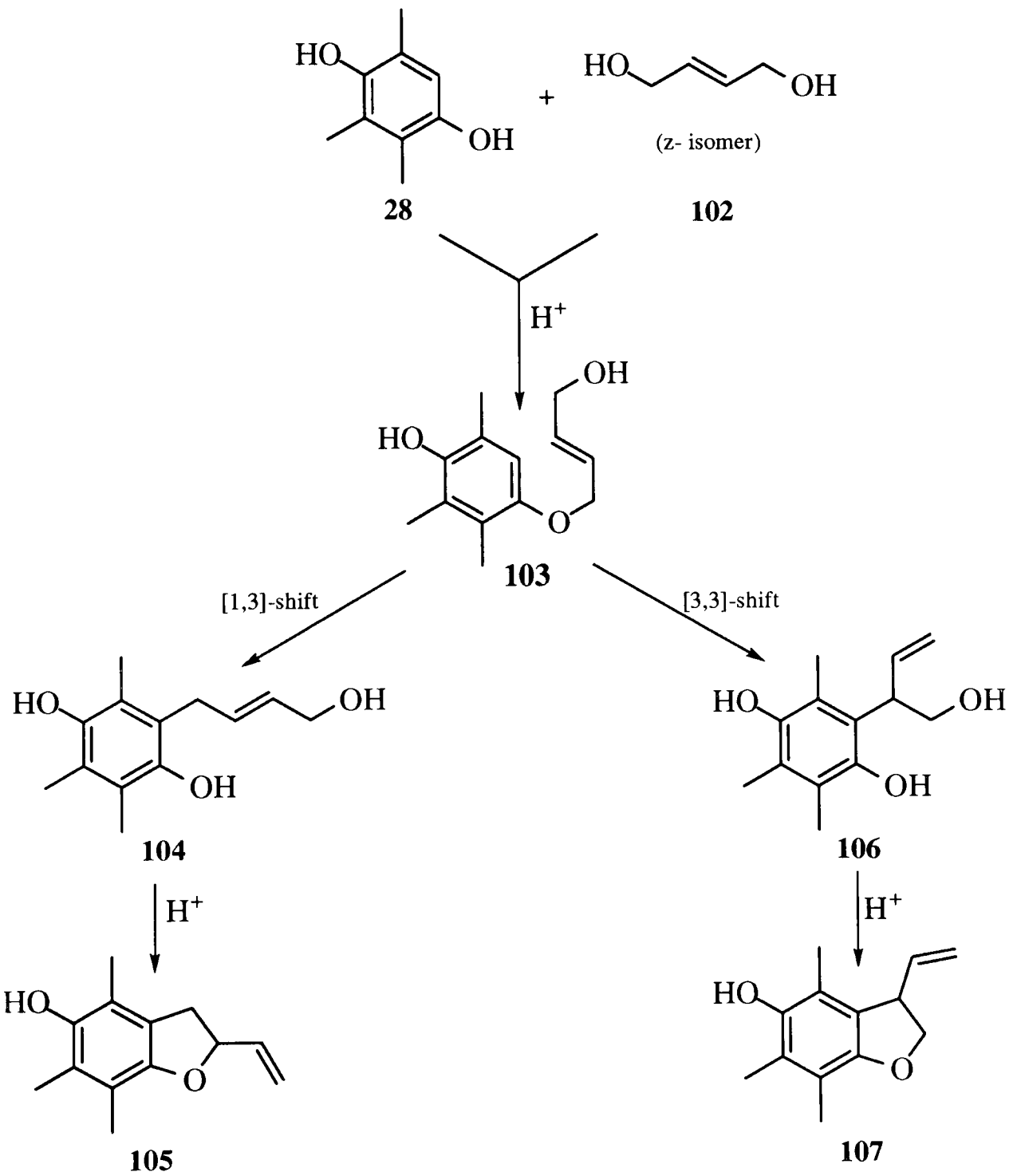
Direct condensation of phenol **(80)** with propargyl alcohol **(99)** yields the corresponding aryl propargyl ether **100**, which undergoes a 3,3-sigmatropic shift in the presence of Mexican bentonite clay in toluene to afford the dimethyl-2*H*-benzopyran **(101)** in good yield[147] **(Scheme 18)**.



80 **99** **100** **101**

Scheme 18

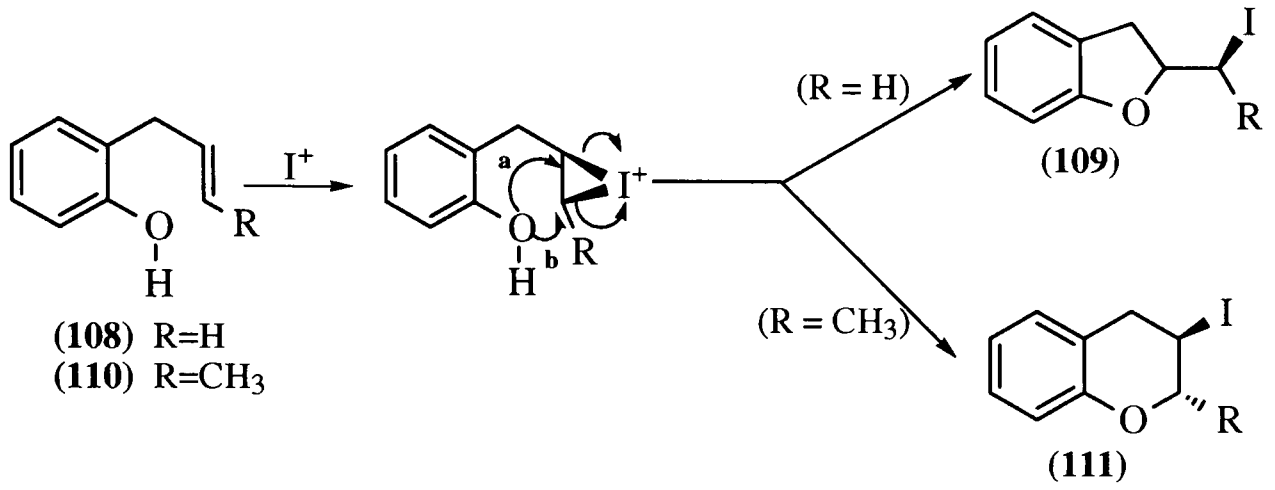
However, *in situ* generation of the related allyl aryl ethers from hydroquinone **(28)** and (Z)-2-butene-1,4-diol **(102)** heated in toluene at 70°C in the presence of *p*-toluenesulphonic acid resulted in a mixture of the dihydrobenzofurans[148] **105** and **107**, respectively. The reaction is temperature dependant. At 50°C **105** was the major product, resulting from a 1, 3-shift in ether **(103)** to the hydroquinone **(104)** which on acid-catalysis afforded **(105)**, whereas in boiling toluene (112°C) the 3,3-shift is favoured with the hydroquinone **106** being formed, which on acid-catalysis afforded **107** as shown in **Scheme 19**.



Scheme 19

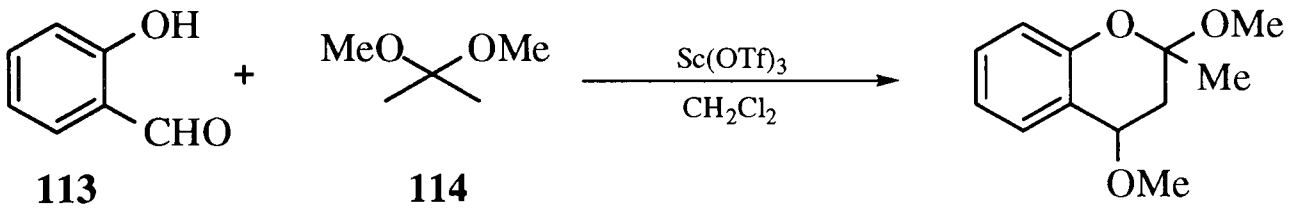
1.14 Metal and Base-catalysed Syntheses of Benzofurans and Benzopyrans

A tin (IV) chloride assisted iodo-cyclisation of 2-allylphenol **(108)** gave the 2-iodomethyl-2,3-dihydrobenzofuran **(109)**. A similar cyclisation of 2-crotylphenol **(110)** gave 3-iodo-2-methyl-3,4-dihydrobenzo-2*H*-benzopyran[149] **(111)**, **(Scheme 20)**.



Scheme 20

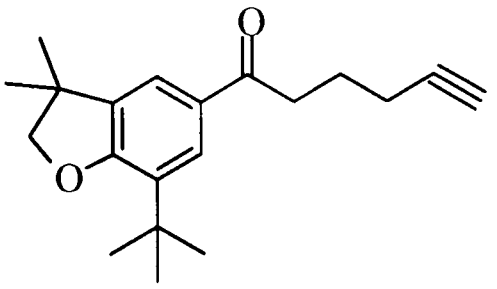
Recently, Yadav *et al*[150-151] have synthesized 2,4-dimethoxy-2-methylbenzopyran **112** by reacting *o*-hydroxybenzaldehyde **113** with 2,3-dimethoxypropane **114** using a catalytic amount of scandium triflate, as shown in **Scheme 21**.



113 **114** **112**

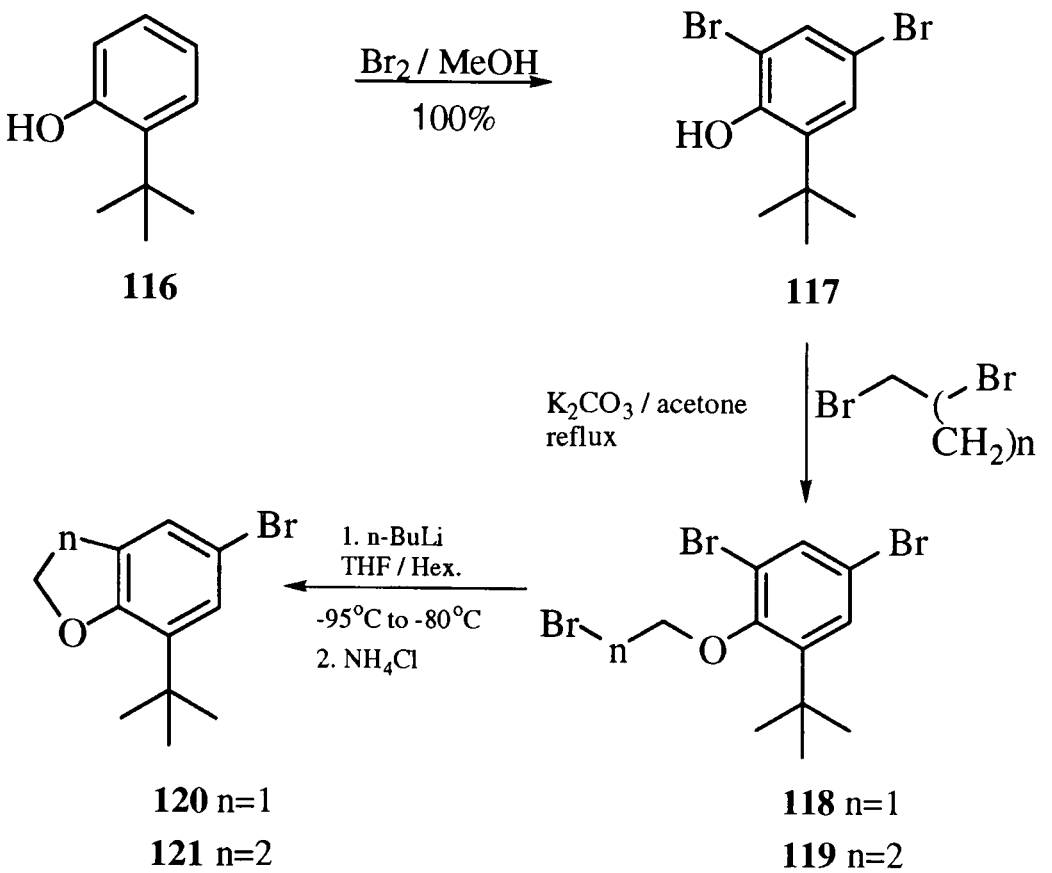
Scheme 21

A known precursor in the preparation of tebufelone **115** a nonsteriodal antiinflammatory and an analgesic agent has been prepared by Janusz *et al*[152] as shown in **Scheme 22**.



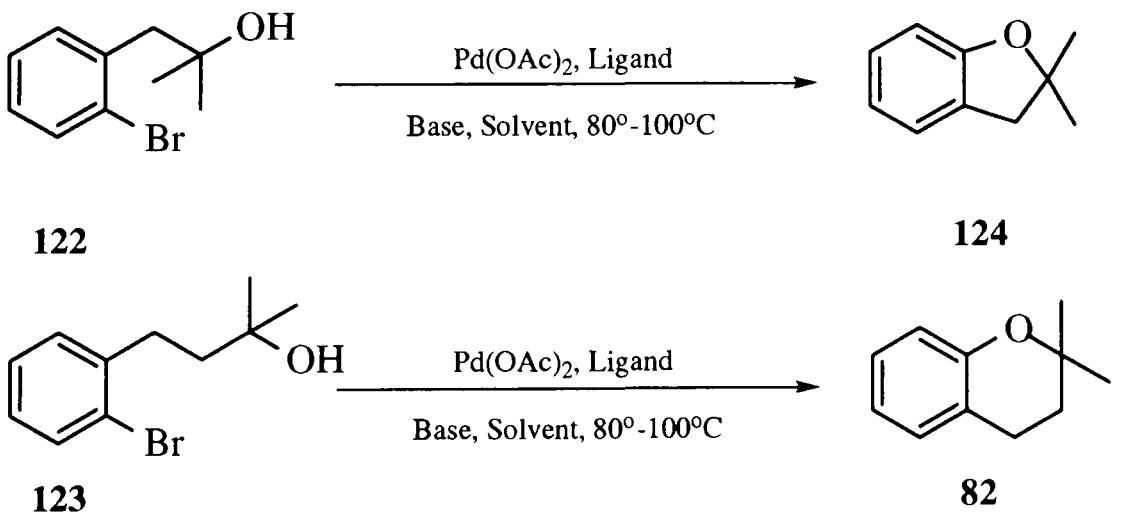
115

The di-*tert*-butylphenol **116** was initially brominated to give the corresponding dibromophenol **(117)**. Alkylation of this phenol **(117)** in the presence of a base (potassium carbonate/acetone) affords the bromo ethers **(118)** or **(119)**. The bromo ether ring was cyclised by lithium-halogen exchange to give the dihydrobenzofuran **(120)** or dihydrobenzopyran **(121)** (Parham cycloalkyation) as shown in **Scheme 22**.



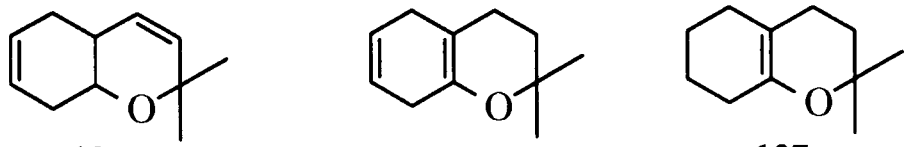
Scheme 22

Palladium-catalyzed cross coupling reactions of Ar-X (where X=I, Br, and OTf) with carbon nucleophiles (R-MgX) have found wide application in the syntheses of complex organic molecules, due in part, to the mild reaction conditions and high functional group compatibility. Buchwald *et al*[153] have utilised this methodology for effecting the intramolecular Pd-catalysed *ipso* substitution of aryl halides **(122)** and **(123)** in the presences of potassium carbonate and a ligand (Tol-BINAP) to afford 2,2-dimethylbenzofuran **(124),** or using sodium *tert* -butoxide and a ligand (DPPF) to afford 2,2-dimethylbenzopyran **(82)** in moderate to good yields **(Scheme 23)**.



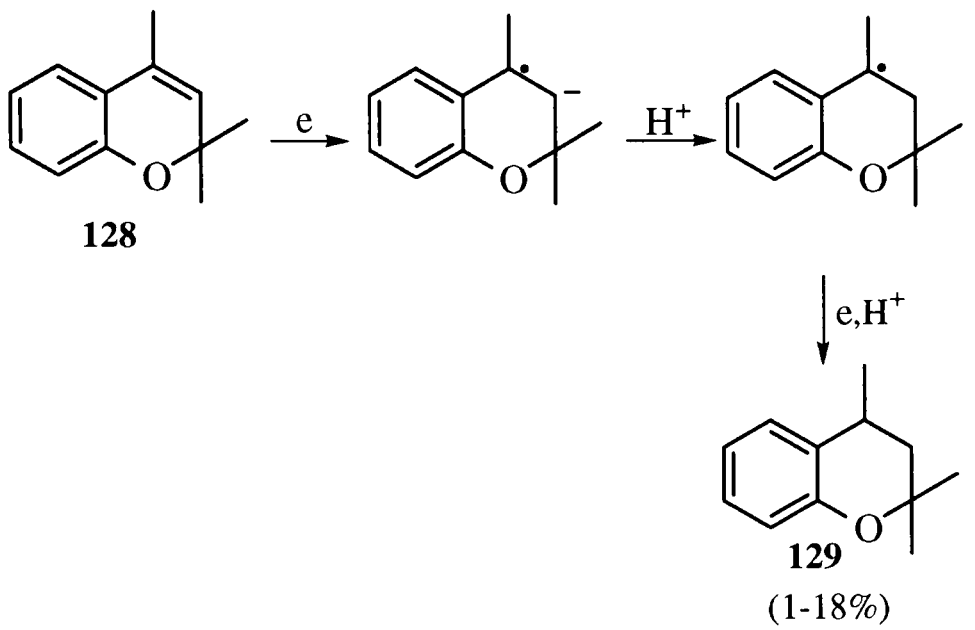
Scheme 23

The alkali-metal ammonia reduction of aromatic systems (the Birch reduction) is a well known method in synthetic chemistry for the preparation of non-conjugated cyclohexadiene derivatives such as prococenes (**125**, **126** and **127**)[154].



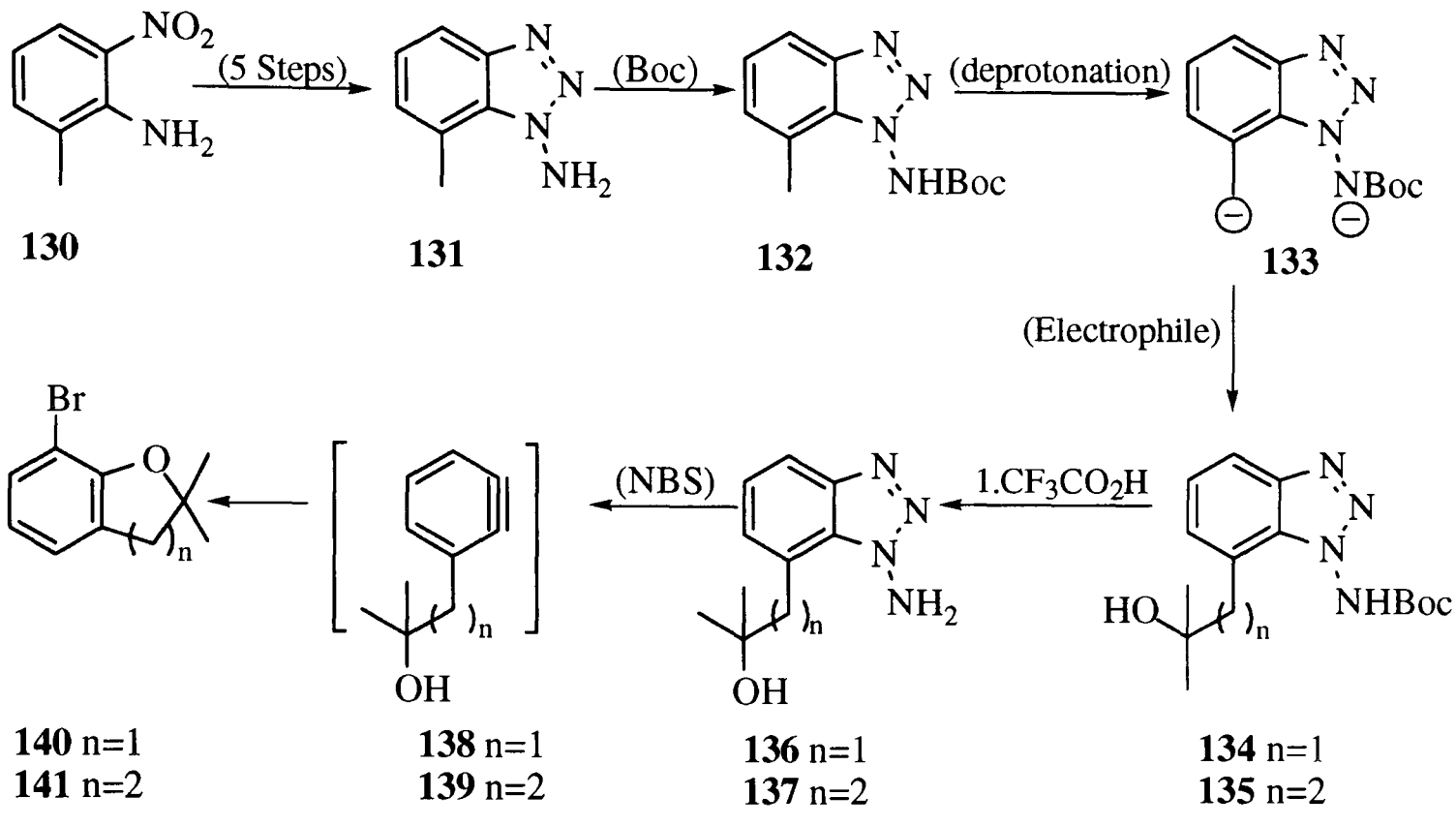
125 **126** **127**

As well as producing the above prococene analogues, the Birch reduction of 2, 2-dimethyl-2*H*-chromene **(128)** with sodium or lithium in liquid ammonia in the presence of alcohol as the proton donor, can also afford the chroman **(129)** albeit in low yields **(Scheme 24)**.



Scheme 24

Recently, a new approach to the synthesis of dihydrobenzofurans or dihydrobenzopyrans has been established by Knight *et al*[155-156]. They utilised 1-aminobenzotriazoles containing a 7-hydroxy alkyl substituents which were converted into the corresponding benzyne using N-bromosuccinimide (NBS). Intramolecular trapping by the hydroxyl group lead to the formation of dihydrobenzofuran or dihydrobenzopyrans **(Scheme 25)**.

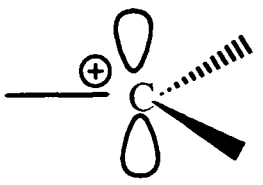


Scheme 25

The 1-aminobenzotriazole **(133)** was obtained in five steps from nitroaniline **(130)** by a modification of the Campbell and Rees method[157-159], and the amino group in **131** was then protected **(132)**. Lateral deprotonation of **(132)** gave the dianion **(133)**. This can react with an electrophile (generated from aldehydes, ketones or epoxides) to produce the substrate **(134)** or **(135)**. Deprotection of the amino group in **134** and **135** afforded **(136)** and **(137)**, respectively. Treatment of **136** and **137** with N-bromosuccinimde afforded the dihydrobenzofuran **(140)** and dihydrobenzopyran **(141)** respectively via the benzyne intermediates **(138)** and **(139)**.

1.15 Carbocations as intermediate in routes to Benzopyrans / furans

The formation of deep yellow colours in the solutions of triphenyl methyl halides in certain solvents was reported in 1902 by Gomberg and Norris[160-161], among other workers. They attributed these reversible changes to what would today be called ion dissociation, the ion being intensely coloured. The name carbocation was applied to these species by Von Baeyer[162]. The electron - deficient carbon of the carbocation is sp^2-hybridised and therefore has a trigonal planar geometry: (the π-orbital on this carbon contains no electrons).

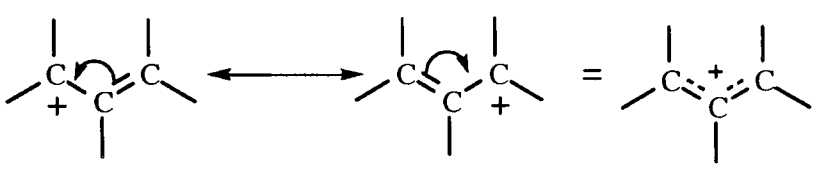


Carbocations are highly reactive intermediates and only have a short lifetime in solution, and are quickly converted into more stable molecules. The stability of the saturated alkyl carbocation varies depending on the groups attached to the electron deficient carbon. Themore alkyl groups that are attached, the more stable the cation

formed. The stability, and hence the life time, of the carbocation increases from primary to tertiary. The tertiary system is the most stable because the positive charge is spread over a several centres due to C-H σ-bond orbital - p-orbital interactions (hyperconjugation) and due to the Inductive effect - (+I for alkyl groups)[163].

1.16 Allylic Carbocations

Allyl cations **(142)** can be generated from suitable precursors such allylic halides and alcohols[130-131], and 1,3-dienes[104,134,135] and are relatively stable compared to the corresponding saturated alkyl cations. This is due to the resonance stabilisation[164] of the charge species i.e. the +M mesomeric effect, as shown in **Scheme 25**.

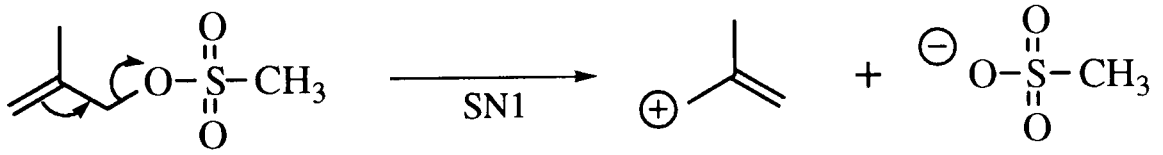


142

Scheme 25

The formation of an allyl cation depends on the nature of the leaving group Y present on the original molecule. The rate at which Y leaves depends on : the strength of the R-Y bond, the polarisability of the R-Y bond and the stability of Y^- species (delocalised anion of strong acid).

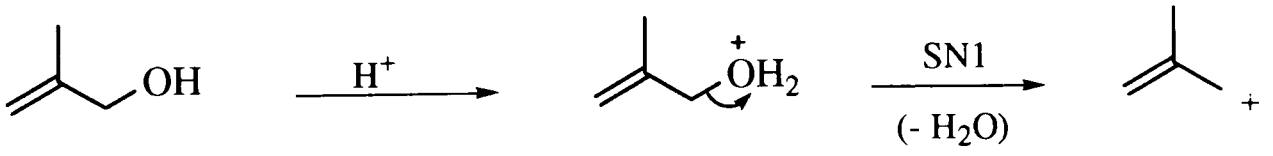
Mesylates **(143)** are example of good leaving groups as shown in **Scheme 26** . This is due to the fact that the C-O bond is much weaker than the S-O bond, and to the resonance stabilisation of the mesylate anion formed.



143

Scheme 26

An example of a poor leaving group (requiring protonation to break the C-O bond) is given in **Scheme 27.**



Scheme 27

Other good leaving leaving groups include halide anions and triflates[165].

1.17 Generation of Carbocations using Superacids in the Syntheses of Benzofurans and Benzopyrans.

Over 60 years ago, J.B. Conant[166] pioneered the use of the name 'superacid' by calling attention to acid systems more acidic than the conventional mineral acids. Subsequently, R.J. Gillespie[167] introduced an arbitrary but widespread definition according to which superacids are systems whose acidity, as characterised by Hammett acidity function (H_o) exceeds that of 100% sulphuric acid (H_o= -12). Significant progress in developing new superacid systems and studying their chemistry has been made by Olah *et al*[168].

Bronsted/Lewis acid mixtures of $HF\text{-}SbF_5$, $HF\text{-}HSO_3F$, $HSO_3F\text{-}SbF_5$, etc, with superacidties up to 10^{15}-10^{18} ($H_o \leq -30$) times stronger than 100% H_2SO_4 have been developed.

Carbocations can be generated from electrophilic reactions since Meerwein's pioneering studies have been carried out[169], especially, superacids can be used to generate carbocations from allylic alcohols or halides and dienes. The fast and efficient syntheses of carbocations from superacids could be used in the syntheses of 2,3-dihydrobenzofurans and 2*H*-1-benzopyrans.

In this study, trifluoroacetic acid which possesses 'near superacidity', sulphuric acid or a mixture of acids (sulphuric and glacial acetic acid) and metallic acid catalyst such as zinc chloride will be used in the reactions of phenols and allylic alcohols or 1,3-dienes as acid catalysts in the context of developing one-pot syntheses of 2,3-dihydrobenzofurans and 2*H*-1-benzopyrans.

1.18 Aim and Objectives

- Syntheses of 2,3-dihydrobenzofurans and 2*H*-1-benzopyrans in general involves several steps and often give low yields. Therefore an efficient syntheses of these compounds were achieved by condensing phenols and the appropriate dienes, allylic alcohols, aldehydes and diols using a number of different acid catalyst systems. These compounds were synthesised in a one-pot syntheses.
- Exploration of side reactions and mechanistic aspects of these compounds.
- An industrially viable process for the production of α-tocopherol on a multi-kilogram scale.
- Syntheses of antioxidants superior to that of α-tocopherol :

  i) Benzofuran model compound of α-tocopherol.

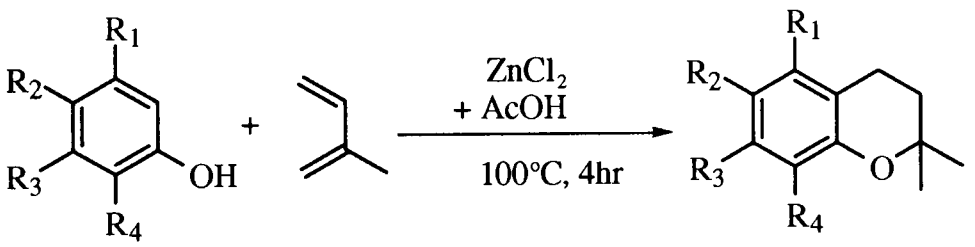
  ii) By substituting the benzopyran at the 4-position with an alkyl group to give a conformationally locked system.

2.00 Discussion

2.01 Synthesis of 2,2-Dimethyl-3,4-dihydrobenzopyrans (82)

2,2-Dimethyl-3,4-dihydrobenzopyrans are usually prepared by multistep syntheses with not very satisfactory yields[170]. Direct syntheses based on the reactions of suitability substituted phenols with isoprene, catalysed acidic species or aluminium phenoxide give poor to moderate yields[171]. Better yields are obtained by reacting the sodium or potassium phenoxide salt with isoprene in the presence of a Lewis acid ($AlCl_3$, $FeCl_3$, or $SnCl_4$)[104,172]. Since these methods still give only low to moderate yields of 3,4-dihydrobenzopyrans, attempts to improve the yields using the method of Smith[9] were investigated. Also, previously unreported spectral properties of 2,2-dimethyl-3,4-dihydrobenzopyrans and proposed mechanisms of reactions will be discussed.

The methodology of Smith[86,88], was extended to other substituted phenols. Phenols (**28a-f**), isoprene (**81**), and zinc chloride were heated under reflux in glacial acetic acid to afford the 2,2-dimethyl-3,4-dimethylbenzopyrans (**82a-f**) in greater than 30% yield as the main products. However, the 2,2-dimethyl-3,4-dimethylbenzopyrans **28b, 28c,** and **28f** reacted further with isoprene (**81**) to afford the 4-isopentenyl-2,2-dimethyl-3,4-dimethylbenzopyrans (**144b, 144c, 144f**) respectively, as by-products, while 2,2-dimethyl-3,4-dimethylbenzopyran **82e** similarly afforded the dichroman **145e** as shown in **Scheme 25**. The reaction was modified by adding the isoprene dropwise using a hypodermic needle which was positioned at the base of the flask, to the reaction mixture and performed by efficiently stirring the heterogeneous mixture at 100°C for 4 hours in an atmosphere of argon.



28 **81** **82, 144 and 145**

28a, 82a $R_1, R_3, R_4 = CH_3, R_2 = OH$
28b, 82b $R_1, R_3, R_4 = CH_3, R_2 = H$
28c, 82c $R_1, R_3, R_4 = H, R_2 = Cl$
28d, 82d $R_1, R_3, R_4 = H, R_2 = OH$
28e, 82e $R_1, R_2 = H, R_3, R_4 = OH$
28f, 82f $R_1, R_4 = H, R_2\text{-}R_3 = CH{=}CH\text{-}CH{=}CH$

144b $R_1, R_3, R_4 = CH_3, R_2 = CH_2CH{=}C(CH_3)_2$
144c $R_1{=}H, R_2 = Cl, R_4 = CH_2CH{=}C(CH_3)_2$
144f $R_1{=}H, R_2 - R_3 = CH{=}CH\text{-}CH{=}CH, R_4 = CH_2CHC(CH_3)_2$
145e $R_1 = H, R_2 - R_3 = CH_2CH_2(CH_3)_2CO, R_4 = OH$

Scheme 25

The results are summarized in **Table 2.**

Cpd.	R_1	R_2	R_3	R_4	M.pt [°C]	Yield (%)	Lit. M.pt [°C]
82a	CH_3	OH	CH_3	CH_3	92-94	37	92-94[88,173]
82b	CH_3	H	CH_3	CH_3	39-40	42	40-41[88]
144b	CH_3	$CH_2CHC(CH_3)_2$	CH_3	CH_3	Oil	<2	N/R
82c	H	Cl	H	H	Oil	34	83-85[172]
144c	H	Cl	H	$CH_2CHC(CH_3)_2$	Not isolated	<1	N/R
82d	H	OH	H	H	Oil	11	77-80[173,174]
82e	H	H	OH	OH	Oil	47	N/R
145e	OH	$CH_2CH_2OC(CH_3)_2$		H	Oil	Trace	120-121[175]
82f	H	CH=CH-CH=CH		H	Oil	52	Gum[134]
144f	H	CH=CH-CH=CH		$CH_2CHC(CH_3)_2$	Oil	5	N/R

Table 2: N/R = not reported in the literature, therefore novel compounds.

It was found that the benzopyrans **82a** and **82b** were formed in moderate yields, whereas, benzopyrans **82c**, **82d**, and **82f** were obtained in low yields. This can be attributed to the fact that the reaction appears to be favoured by the presence of electron-donating substituents (R_1, R_2, R_3, R_4 in **Table 2**) on the benzene ring which increased the rate of cyclization, and hence gave higher yields of benzopyran, while the electron-withdrawing substituents decreased the rate of cyclisation. Hydroquinone **(28d)** was found to be slightly inactive towards isoprene **(81)** and resulted in a low yield of **82d**. The inactivity may be due the partial insolubility of the hydroquinone **(28d)** in acetic acid. The benzopyrans **82b**, **82c** and **82f** reacted further with isoprene **(81)** to afford isopentenyl-2,2-dimethyl-3,4-dihydrobenzopyrans **144b**, **144c**, and **144f** respectively. In one case, **28e** led to the

formation of double chroman **145e**. In all cases, the 2,2-dimethyl-3,4-dihydromethylbenzopyrans were accompanied by the corresponding phenols **28a-f**. These were removed by treatment of the crude product with Claisens alkali[176], which was prepared by dissolving potassium hydroxide (35g) in water (25ml) and methanol (100ml). The spectral evidence in support of the structures proposed for the 3,4-dihydrobenzopyrans (**82a-82f**) is discussed below.

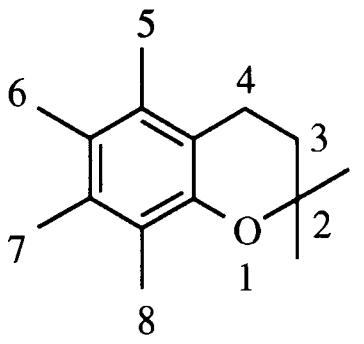
2.02 Spectral Analysis of the 2,2-dimethyl-3,4-dihydrobenzopyrans

The infra red absorptions of compounds **82a** and **82b** are shown in **Table 3** and are consistent with their literature values and with the structures proposed. The various bands in the infra red spectra of 2,2-dimethyl-3,4-dihydrobenzopyrans and tocopherols have been reported by several researchers[171,177]. Rosenkrantz[178] has assigned the band near 1587 cm^{-1} (stretching) to the absorption of the conjugated C=C system in the benzene ring, the band near 1368 cm^{-1} (stretching) to the geminal dimethyl group and a band near 1250 cm^{-1} to the phenolic C-O (stretching) absorption, which is characteristic of the chroman moiety in **82a** and **82b**. The bands at 3000, 2950 and 2860 cm^{-1} are typical C-H stretching frequencies. The absorptions at 3640 and 3420 cm^{-1} (free and bonded OH stretching, respectively) are characteristic of **82a**.

Compound	**Absorption** (cm^{-1})
82a	
(3,4-Dihydro-6-hydroxy-2,2,5,7,8-pentamethylbenzopyran)	3251 (OH), 2981-2929 (C-H), 1366 (gem-dimethyl), 1264 (C-O)[179].
82b	
(3,4-Dihydro-2,2,5,7,8-pentamethylbenzopyran)	2971-2910 (C-H), 1363 (gem-dimethyl), 1219 (C-O).

Table 3

The proton shifts (in ppm) in the ^{1}H NMR spectra of the 3,4-dihydrobenzopyrans are listed in **Table 4** (see **Appendix** for spectrum) and are consistent with their proposed structures.



82

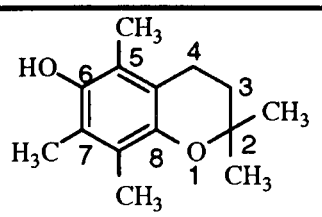
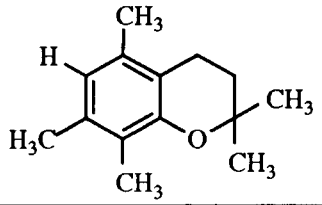
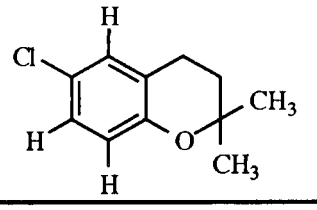
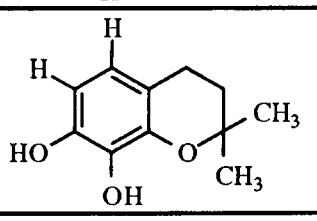
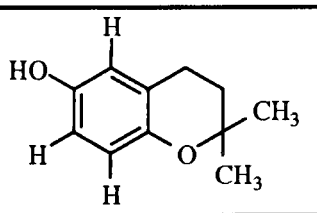
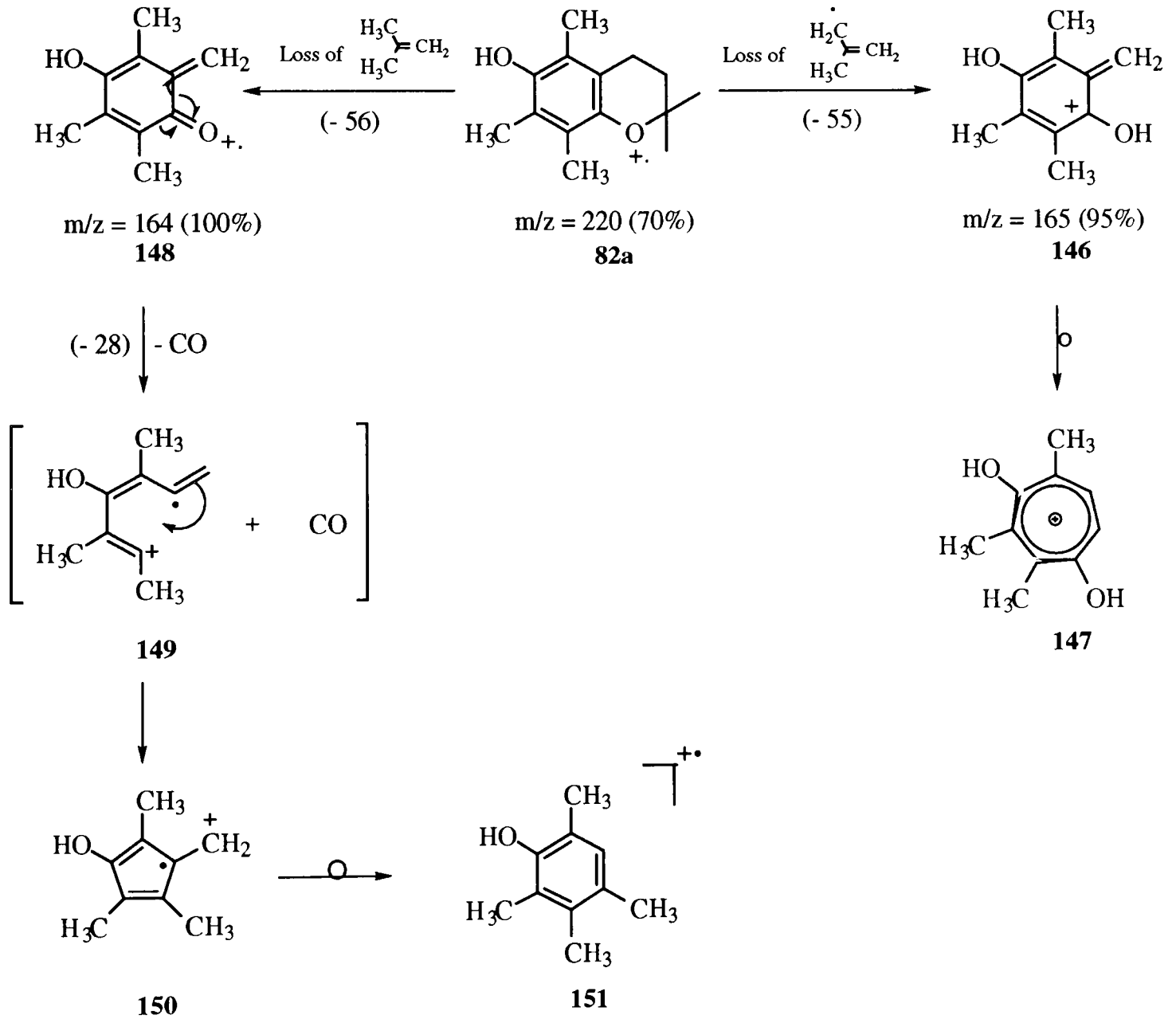
Structure	**Cpd.**	C-2-$(CH_3)_2$	C-3-CH_2	C-4-CH_2	H-5	H-6	H-7	H-8
	**82a**	1.28	1.81	2.61	(CH_3) 2.10	(OH) 4.22	(CH_3) 2.10	(CH_3) 2.15
	**82b**	1.29	1.77	2.59	(CH_3) 2.07	(H) 6.54	(CH_3) 2.10	(CH_3) 2.15
	**82c**	1.31	1.76	2.72	(H) 6.99	-	(H) 6.77 - 6.71	(H) 7.03
	**82d**	1.34	1.75	2.69	(H) 6.50	(H) 6.52	(OH) 5.64	(OH) 5.64
	**82e**	1.25	1.74	2.69	(H) 6.50	(OH) 2.99	(H) 6.50	(H) 7.68

Table 4

The geminal dimethyl protons C-2-$(CH_3)_2$ in 2,2-dimethyl-3,4-dihydrobenzopyrans **82a-82e** in **Table 4** are found to be magnetically equivalent, and therefore come into resonance at the same frequency. The geminal dimethyl protons are increasingly deshielded in going from **82a-82d**. This can be attributed to the increasing electron donating effect (+M effect) of the groups present on the aromatic ring which are more likely to reach into the saturated part of the ring. However, the geminal dimethyl protons in **82e** are deshielded in comparison to those in **82a-b**, possibly due to the CH_3 groups in **82a-b** being more electronegative than the hydrogen atoms attached to the aromatic ring in the **82e**. The benzylic methylene protons (C-4-CH_2) are most affected by the deshielding of the circluating π electrons and are found at

low field compared to the methylene protons on C-3 which resonate at higher field. The methylene protons C-3-CH_2 and C-4-CH_2 on the heterocyclic ring system in **82a-e** appear as triplets (J = 6-7 Hz)[173]. The phenolic protons in **82a**, **82d** and **82e** respectively, are exhanged in deuterium oxide (D_2O) to give the corresponding deuterated species. The phenolic proton can appear as a sharp singlet (due to rapid exchange, no coupling), or more usually as a broad singlet (slow exchange, coupled) that can resonate between 4-8 ppm, depending on the concentration, solvent and temperature.

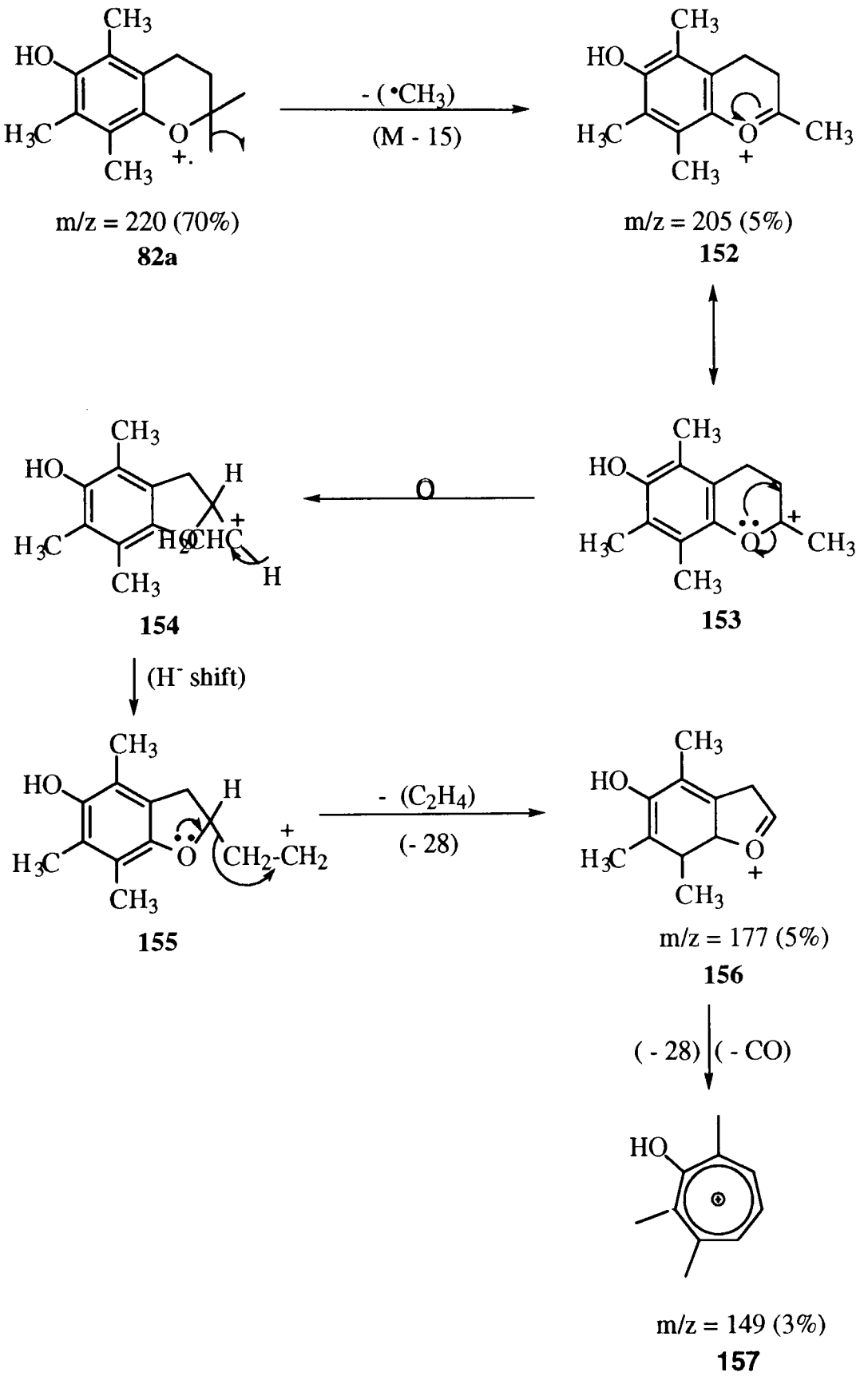
An extensive mass spectrometric study of aromatic ethers in which the oxygen forms part of a saturated 6-membered ring system was conducted by Williams, Thomas and Gautschi[180]. They reported and explained the fragmentation pathways for typical 3,4-dihydrobenzopyrans. The mass spectrometry results for compound **82a-e** were consistent with their proposed structures.



Scheme 26. Fragmentation pathway of 2, 2-dimethylbenzopyrans (Path A).

Thus the fragmentation scheme for compound **82a** (**Scheme 26**) shows that the molecular ion of, **82a** could lose a 4-carbon fragment from the heterocyclic ring (a retro Diels-Alder). This reaction may occur with or without hydrogen transfer and the peaks appear at M-55

(146) and M-56 **(148)** respectively, (although Williams[180] reported that the 3,4-dihydrobenzopyrans always fragment with hydrogen transfer to form the conjugated system **146**). Loss of CO from the quinone methide **148** via **(149)** and the rearrangement of **(150)** gave the phenol **151**. Fragmentation of **146** could rearrange to form the stable tropylium ion **(147)**, (Path A). Another possible fragmentation patttern of **82a** (Path B) is outlined in **Scheme 27**.



Scheme 27 : Fragmentation pathway of 2,2-dimethyl-3,4-dihydrobenzopyran (Path B).

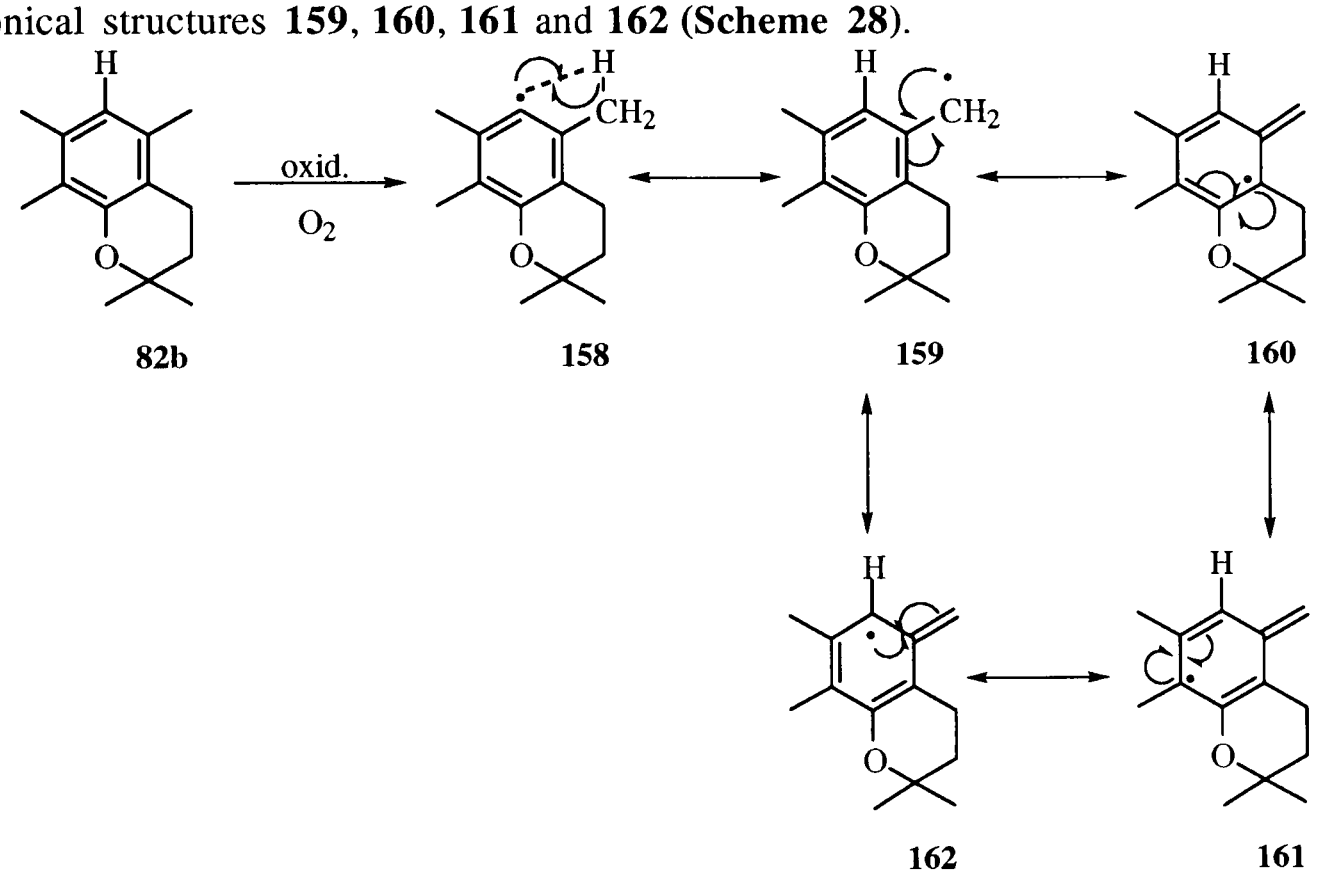
This involves the loss of one of the geminal methyl groups from the M^{+}·to give **152**, which has also been reported in related compounds by Nilsson[181] and Williams[180]. It is proposed

that the oxonium ion **152** could be in resonance between the tertiary carbocation **153.** Rearrangement of **153** affords the secondary carbocation **154**. Further degradation of **154** may occur by ring contraction involving the hydride shift to form the primary carbocation **155** followed by loss of ethene to give **156**. Nillson[181] found that this kind of fragmentation occurs in γ-tocotrienols. The oxonium ion **(156)** could further ring contract with the elimination of CO to form the stable tropylium ion **(157)**.

2.03 Oxidation of 2,2-dimethyl-3,4-dihydrobenzopyrans

The 2,2-dimethyl-3,4-dihydrobenzopyrans can undergo atmospheric oxidation. The (CI) mass spectrum of the mother liquor of **60b** showed the presence of a dimeric compound **163** (m/z =407, M+1).

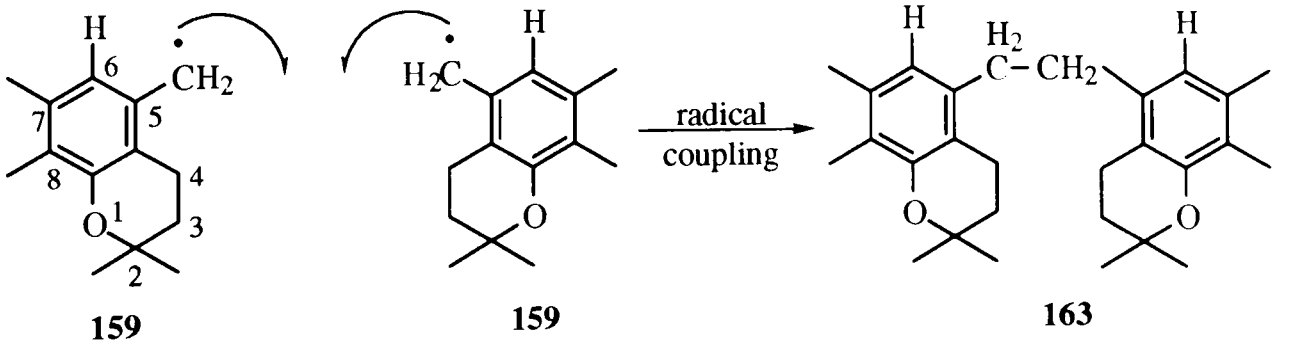
Initially, compound **82b** could be oxidised by atmospheric oxygen in the presence of light to give the benzylic radical **158**. This radical is probably stabilised by resonance involving the canonical structures **159**, **160**, **161** and **162 (Scheme 28)**.



82b **158** **159** **160** **162** **161**

Scheme 28

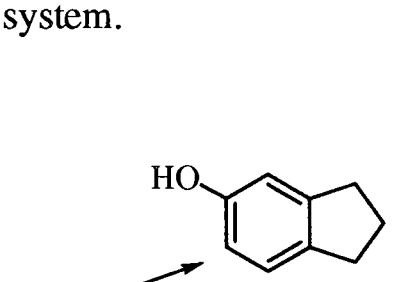
Formation of **163** is most likely to arise by the dimerisation of **159** (C-C radical coupling at the 5-position) as shown in **Scheme 29**. A similar reaction has also been observed by Nilsson *et al* in γ-tocopherols[179].



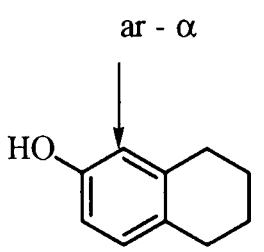
159 **159** **163**

Scheme 29

The benzylic radical **159** forms dimers only by coupling at the 5-position irrespective of whether a methyl group is present at the 8-position, and regardless of whether the ortho-position (7-position) is substituted or not, as observed in this study and also by other researchers[179]. This is also found in the electrophilic substitution of 5-hydroxyindane[182], 6-hydroxytetralin[182], and bromination of α-tocopherol[183]. The observation that electrophilic substitution only occurs at the 6-position (ar-β) of 5-hydroxyindane **(164)** and at the 5-position (ar-α) of 6-hydroxytetralin **(165)** is interpreted to be the result of the directing effect of the cyclic ring system.

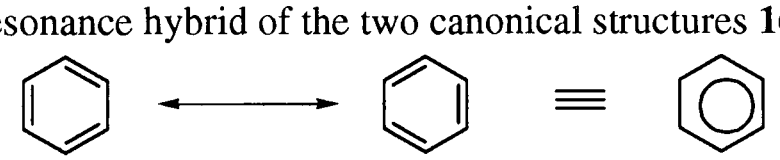


164



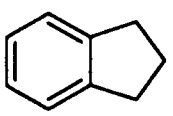
165

This phenomenon has been referred to as The Mills-Nixon effect[184]. According to Kekule, benzene exists as a resonance hybrid of the two canonical structures **166a** and **166b**.

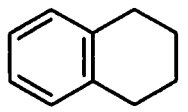


166a **166b**

Mills and Nixon[184] suggested that when 'strained' cyclic groups were attached to the benzene ring, in indane for example it lead to bond fixation in the ground state, such that, **167** would be the preferred canonical form for indane (where a single bond is common to the two rings), while for tetralin the preferred canonical form would be **168** (where a double bond is common to the two rings).



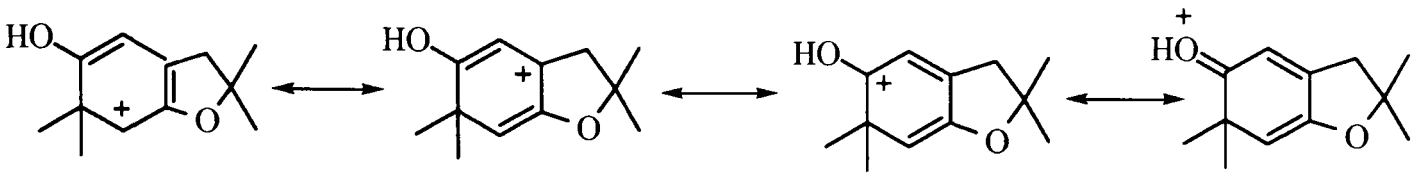
167



168

However, Vaughan *et al*[185] suggested that the ground states of **167** and **168** are the same for both positions of substitution, factors determining the product distribution are the relative distribution of the two transition states of **167** and **168** which are transition state **1** and **2** are shown in **Scheme 30** below.

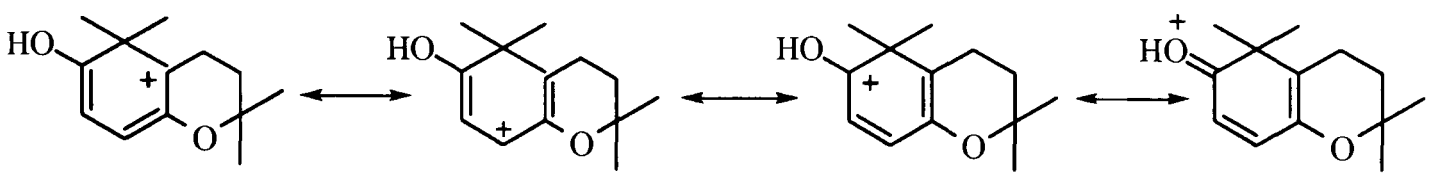
ar-β substitution



169 **170** **171** **172**

Transition state 1

ar-α substitution



173 **174** **175** **176**

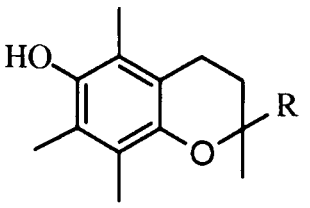
Transition state 2

Scheme 30

Thus, in the canonical structures **(169-172)** of the transition state for ar-β substitution, three of the four forms have a single bond between the carbons common to the three rings. Therefore, going from the ground state to the transition state would involve lengthening of the common bond, this would result in decrease in strain when the fused ring is a five-membered and an ar-β intermediate would therefore be favoured. In the canonical structures **(173-176)** for ar-α substitution, three of the four resonance forms have double bonds between the carbons common to the three rings. Therefore, this bond would decrease on going from the ground state to the transition state, and strain if present in the adjacent ring should be reduced, resulting in enhancement of reactivity at the ar-α position[186]. Meir[187] indicated that the condensation of small saturated rings (6-membered or smaller) to the benzene molecule always causes a distortion of the aromatic ring and thus induces a certain strain into the system. This may favour reaction at one position over another, and hence, account for this effect. Today, the Mills-Nixon effect[184,188-193] is known as the effect causing an aromatic moiety to localize its bonds (e.g. alternating arrangement of single and double bonds instead of the usual symmetric arrangement) due to the strain imposed by small annelated ring(s) and hence, to change the systems structure and reactivity. Some chemists claim that the effect is real[194-199] whereas others suggest that it is an artifact of theoretical approximations, and higher level calculations show that the effect is not real[200-202]. However, the debate on the Mills-Nixon effect is still under study today.

In summary, this study has shown that 2,2-dimethyl-3,4-dihydrobenzopyrans can be synthesised by condensing both phenols and hydroquinones with carbocations generating from butadiene in the presence of glacial acetic acid. An overview of the mechanistic pathway of these 2,2-dimethyl-3,4-dihydrobenzopyrans is proposed together with the analysis of the spectral data.

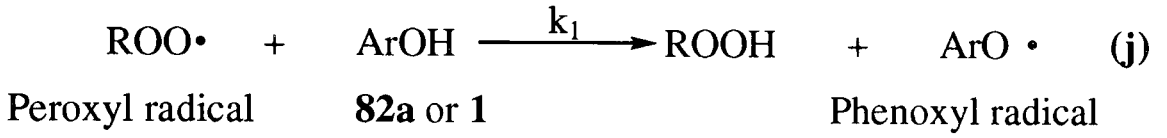
2.04 Synthesis of 2,2-dimethyl-3,4-dihydro-4-isopropyl-benzopyran (178)



82a R = CH_3

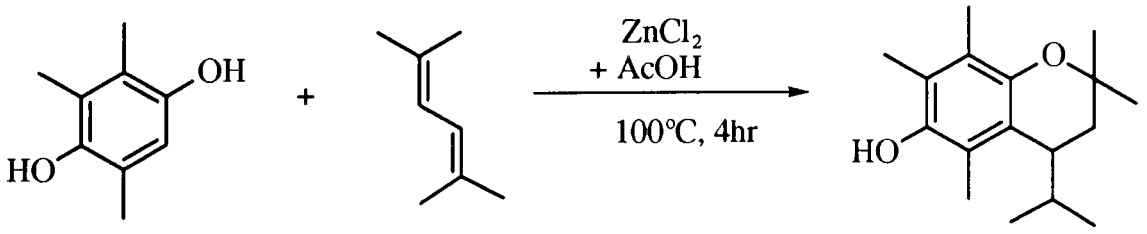
1 R = $C_{16}H_{33}$

It is well established that α-tocopherol **(1)** is one of the two best chain-breaking, phenolic antioxidants known[56] (the other being **82a**). That is α-tocopherol **(1)** and the structurally related model compound **82a** react more rapidly with peroxyl radicals **(j)** than any of the numerous other phenols investigated by Ingold *et al*[56].



Ingold[56] has compared the rate constant value (k_1) for the trapping of the peroxyl radical (ROO·) by α-tocopherol **1** (or **82a**) (as shown in **j**), with those found for structurally related phenols that lacked the fused 6-membered heterocyclic ring and has shown that this ring is largely responsible for the high reactivity of α-tocopherol. This ring exerts a stereoelectronic effect by constraining the ring oxygen in such a manner that the p-type lone pair is well orientated to stabilize the developing phenoxyl radical. With this in mind, it was decided to introduce an isopropyl grouping in the C-4 postion of **82a** to form compound **178**, since the isopropyl group in **178** may constrain the ring oxygen even further, and thus make it potentially better antioxidant than α-tocopherol.

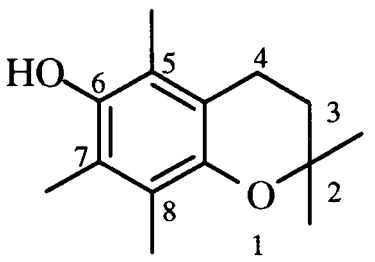
This was achieved by using the method of Smith[86-88]. Phenol **28a** was reacted this time with 2,5-dimethylhexa-2,4-diene **(177)** to form the 2,2-dimethyl-3,4-dihydrobenzopyran **178** as shown in **Scheme 31**.



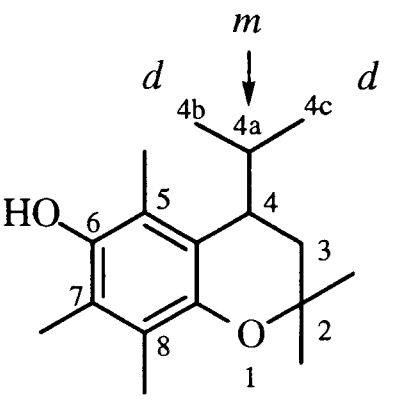
28a **177** **178**

Scheme 31

Compound **178** showed some interesting features in its ^1H NMR spectrum, and the chemical shift values are compared with those of compound **82a** in **Table 4** (see **Appendix** for spectrum).



82a



178

Cpd.	C-2-$(CH_3)_2$	C-3-CH_2	H-4	C-4a-H	C-4b-CH_3	C-4c-CH_3	C-5-CH_3	C-6-OH	C-7-CH_3	C-8-CH_3
82a	1.28	1.81	(CH_2) 2.61	-	-	-	2.10	4.22	2.10	2.15
178	(CH_3) 1.05 (CH_3) 1.48	1.63(ax) 2.02 (eq)	(CH) 2.84	0.89-0.98	0.77-0.80(ax)	0.83-0.86(eq)	2.11	4.35	2.15	2.15

Table 4

The *gem* -dimethyl groups on C-2 were chemically equivalent in **82a**. However, in **178** they were found to be non-equivalent, one methyl group adopting an axial conformation, the other an equatorial conformation, and resonating at 1.05ppm and 1.48 ppm respectively. The methylene protons on C-3 in **178** were also observed to be chemically non-equivalent compared to those in **82a,** and they too adopted either an axial or an equatorial conformation. Due to the adjacent vicinal proton on (C-4), which further couples with each of the axial- and equatorial - orientated doublets protons on C-3 into two doublets resonating at 1.63ppm and 2.02ppm (approx. 6-7 Hz), respectively. Chemical shift non-equivalence of the methyl groups of the isopropyl group on the chiral centre (C-4) formed an A_6X system (as is frequently observed[203]). The methine proton on the chiral centre (C-4) was split by the adjacent methylene protons (C-3) and equally by the vicinal methine proton (C-4a) into a quartet which resonated at 2.84 ppm. The methine proton (C-4a) itself was split by the methine proton at C-4 and equally by the two methyl groups (C-4b and C-4c) into a multiplet which resonated between 0.89-0.98 ppm. The equivalent methyl protons (C-4b) and (C-4c) were split by the methine proton at C-4a into two doublets which were shielded and resonated at 0.78 ppm and 0.84 ppm, each having coupling constant of approximately 7 Hz.

The introduction of the isopropyl grouping at C-4 has conformationally locked the protons on C-2, C-3, and C-4 which suggested that the compound **178** adopts a more rigid conformation than that formed in **82a**. This phenomenom has been seen in 4-substituted flavans[204] and will be further discussed in **Chapter 4**.

2.05 Proposed Mechanism for the Formation of substituted 2,2-dimethyl-3,4-Dihydrobenzopyran

Using the method of Smith[86,88,173] the moderate yields (30%) obtained, could be accounted for by the fact that initially, zinc chloride could hydrolyse to form zinc hydroxide as shown below **(k)**.

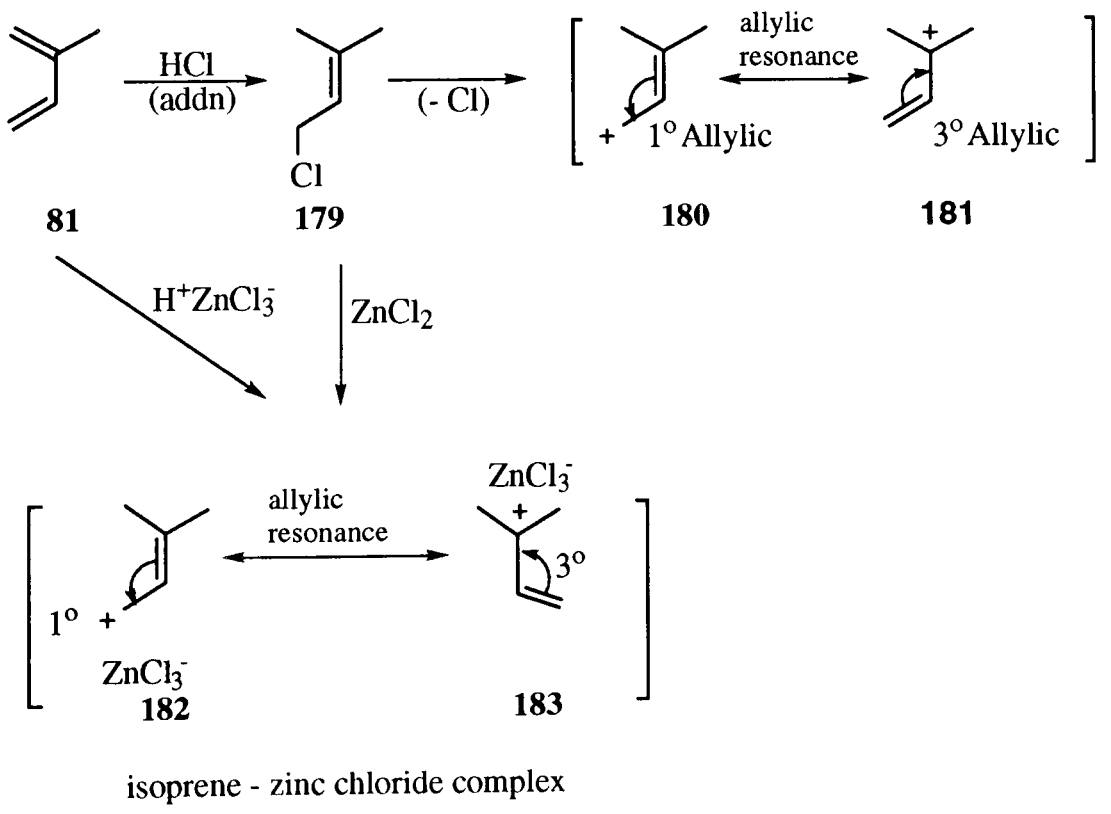
$$ZnCl_2 + 2H_2O \rightleftharpoons Zn(OH)_2 + 2HCl \qquad \textbf{(k)}$$

In situ generation of HCl could lead to the transformation of isoprene **(81)** into 1-chloro-3-methyl-2-butene **(179)**. This in fact, is the commercial process for producing such compounds[43]. It was found that addition of excess isoprene lead to polyisoprenylation of the phenol and therefore failed to increase the yield of the mono-isoprenylated 2,2-dimethyl-3,4-dihydrobenzopyrans. Therefore, the availability of HCl could be the limiting factor in benzopyran formation in converting the isoprene to 1-chloro-3-methyl-2-butene and not the quantity of isoprene.

Alternatively, Olah[206] has shown that $H^+AlCl_4^-$ and $H^+BF_4^-$ similarly act as superacid catalysts (Ho = -15 to -16) and by analogy, $H^+ZnCl_3^-$ which could be generated from zinc chloride and hydrogen chloride **(l)** may act as a catalyst in this reaction.

$$ZnCl_2 + HCl \rightleftharpoons H^+ZnCl_3^- \qquad \textbf{(l)}$$

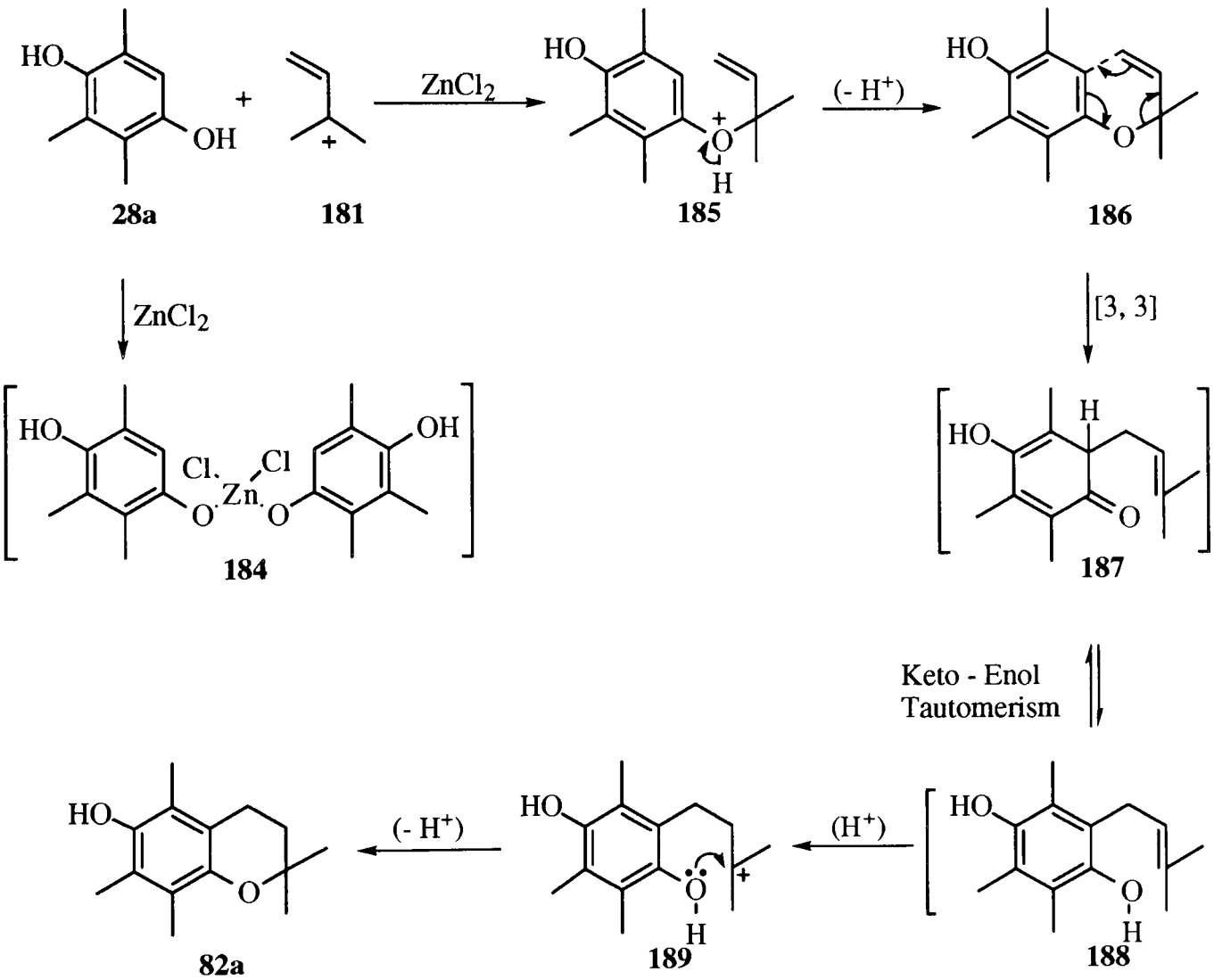
This could form a complex with the isopentenyl cation as shown in **Scheme 32.**



Scheme 32 : Mechanistic pathway for the generation of isopentenyl cation

Smith[88] observed that conc. hydrochloric acid alone can promote the coupling of isoprene with trimethylhydroquinone to form the allyl ether. However, cyclisation of the ether to the chroman was not observed, presumably as the value of Ho for HCl is below-3.0[207] .

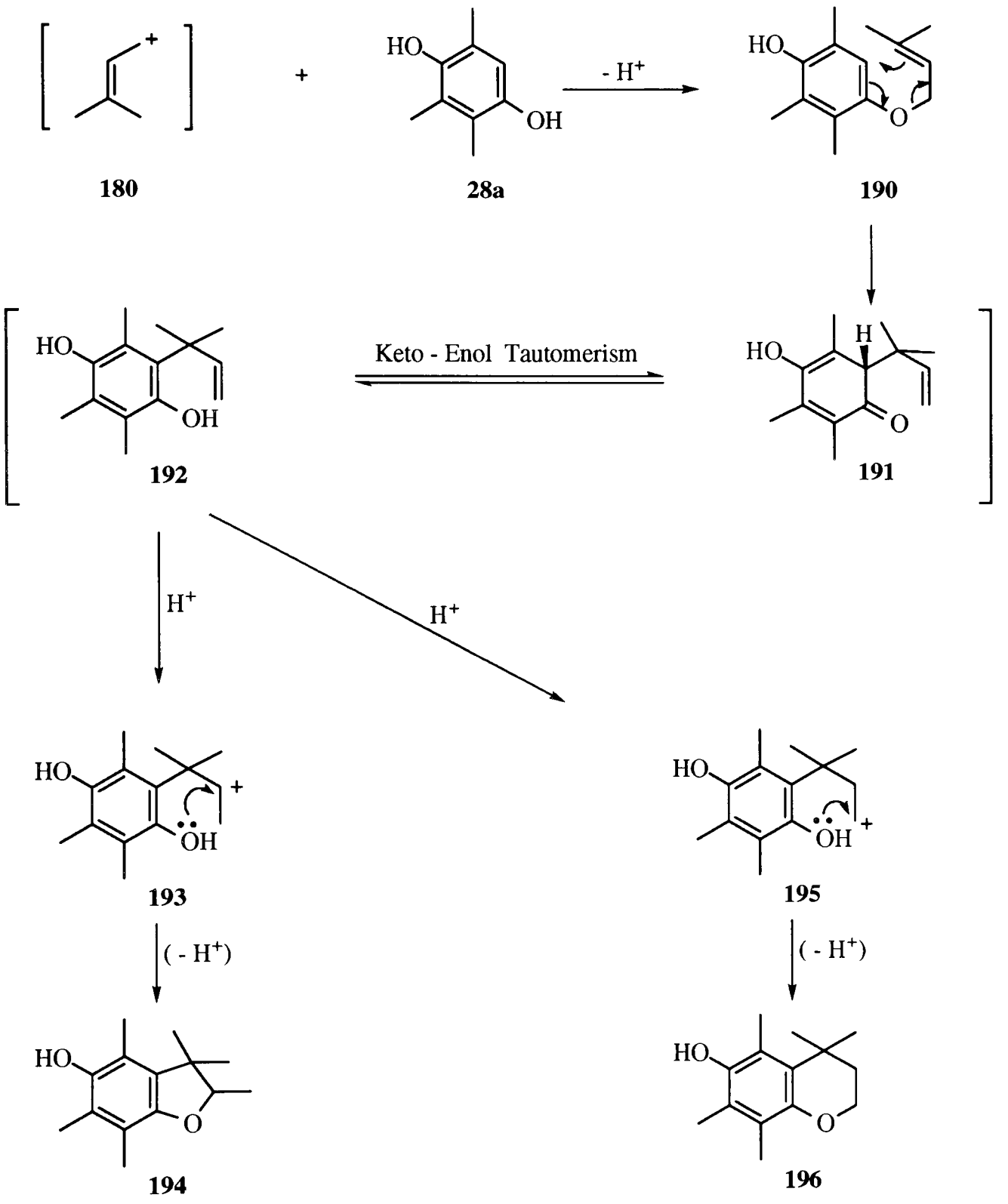
Concerning the mechanistic pathway, there is no guarantee that all phenol allylation reactions proceed in the same manner. However, in many instances it has been shown that the reaction involves previous formation of allyl aryl ethers followed by [1,3] or [3,3] sigmatropic rearrangement[208]. It is proposed that the isopentenyl cation **181** attacks the more nucleophilic part of the phenol **28a** to form the allyl aryl ether **186** via **185**, which then proceeds via [3,3] sigmatropic rearrangement to form **187** which tautomerises to **188** (driven by aromatisation). Protonation of the double bond in **188** leads to the formation of the tertiary carbocation **189**. With subsequent cyclisation and deprotonation, this leads to the formation of the 2,2-dimethyl-3,4-dihydrobenzopyran **82a**. It is possible that zinc chloride could form complex **(184)** with trimethylhydroquinone **28a** as shown in **Scheme 33**.



Scheme 33: The mechanism of formation of a 2,2-dimethyl-3,4-dihydrobenzopyran

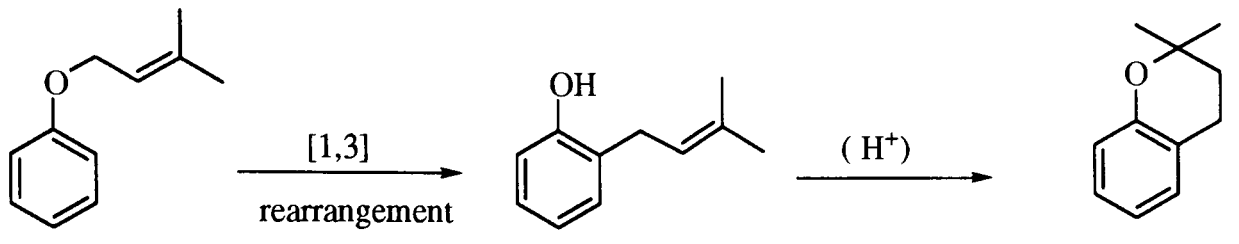
A second possible mechanistic scheme is outlined in **Scheme 34**. The phenol **28a** could react with the primary carbocation **180** to form the the allyl aryl ether **190** which then undergoes a [3,3] - sigmatropic rearrangement to form **191**, which in turn tautomerise to give **192**. Protonation of **192** leads to the formation of the secondary carbocation **193** or the primary carbocation **195.** Subsequent cyclisation and deprotonation of each leads to the formation of the benzofuran **(194)** and the benzopyran **(196)**, Since neither of these two products were obtained, the former route involving the more stable tertiary carbocation

appears to prevail (as would be expected, based on the relative stabilities of the allylic carbocations involved).



Scheme 34

Bigi[174] suggested that isopentenyl cation (**181** in **Scheme 33**) reacts with phenols in the presence of strong acid zeolite HSZ-360 catalysts to form the ether **197**. This subsequently rearranges via [1,3] sigmatropic shift to form **198** which then under acid promoted cyclisation forms **82** as outlined in **Scheme 34**.



197 **198** **82**

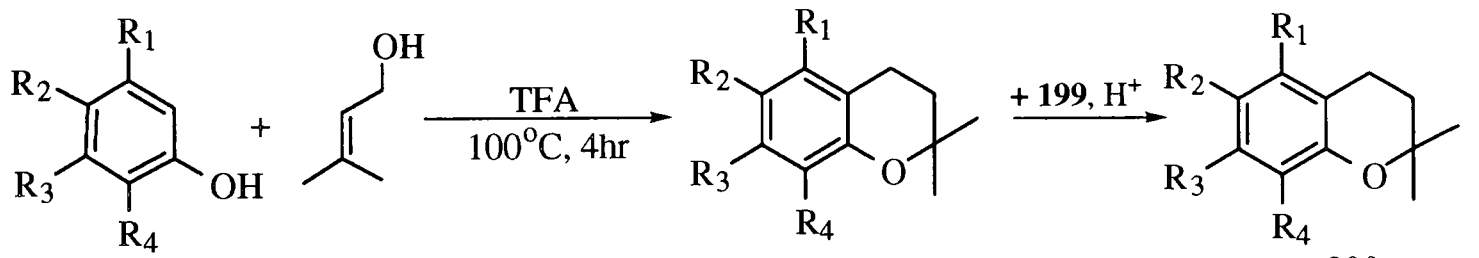
Scheme 34

Casnati *et al*[209], have condensed isoprene with a 1:1 mixture of phenol / potassium phenoxide salt in the presence of aluminium chloride in a solvent such as benzene. They did not present any mechanistic evidence. It is probable that $H^+AlCl_4^-$ is the superacid responsible for promoting the condensation and subsequent cyclisation of the allyl phenylether to form the benzopyran **(82)**.

2.06 Improved syntheses of 2,2-dimethyl-3,4-dihydrobenzopyrans

Generally, 2,2-dimethyl-3,4-dihydrobenzopyrans are prepared in two step syntheses with not very satisfactory yields[170], so the method of Ismail *et al*[210] was used in an attempt to improve these yields. 2,2-Dimethyl-3,4-dihydrobenzopyrans **(82a-82j)** can be synthesized in one-pot syntheses, in the presence of a solvent and an acid[211] or in the presence of an acid such as trifluoroacetic acid which acts as both the solvent and promotes the acid-catalysed cyclisation of the allyl aryl ether to the 2,2-dimethyl-3,4-dihydrobenzopyrans. The advantage of using trifluoroacetic acid as a solvent is that its physical properties provide benefits over alternative acids[212].

Using the method of Ismail *et al*[210], various phenols **(28a-28j)** and allyl alcohol **199** were heated under reflux in trifluoroacetic acid to afford 2,2-dimethyl-3,4-dihydrobenzopyrans **(82a-82j)** in moderate yields. However, the 2,2-dimethyl-3,4-dihydrobenzopyrans **82g** and **82h** reacted further with the alcohol to afford the corresponding 4-isobutenyl-2,2-dimethyl-3,4-dihydrobenzopyrans **144g and 144h**, respectively. Without isolation, **144g** and **144h** by acid-catalysis, further cyclised to afford **200g** and **200h,** respectively, as outlined in **Scheme 36**.



28 **199** **82/144** **200**

28a, 82a $R_1, R_3, R_4 = CH_3, R_2 = OH$
28b, 82b $R_1, R_3, R_4 = CH_3, R_2 = H$
28g, 82g $R_1, R_2 = H, R_3, R_4 = CH_3$
28h, 82h $R_1, R_4 = CH_3, R_2, R_3 = H$
28i, 82i $R_1, R_3 = CH_3, R_2, R_4 = H$
28j, 82j $R_1, R_4 = H, R_2 = Cl, R_3 = CH_3$

144b $R_1, R_3, R_4 = CH_3, R_2 = CH_2CHC(CH_3)_2$
144g $R_1, R_3, R_4 = CH_3, R_2 = CH_2CHC(CH_3)_2$
144h $R_1 = H, R_2 = CH_2CHC(CH_3)_2, R_3, R_4 = CH_3$
144i $R_1, R_4 = CH_3, R_3 = CH_3, R_2 = CH_2CHC(CH_3)_2$
200g $R_1 - R_2 = C(CH_3)_2\,CH_2\,CH_2, R_3, R_4 = CH_3$
200h $R_1, R_2 = CH_3, R_3 - R_4 = CH_2\,CH_2C(CH_3)_2$

Scheme 36

The phenols **28a, 28b** and **28j** gave good yields of the corresponding 2,2-dimethyl-3,4-dihydrobenzopyrans **82a, 82b** and **82j**, respectively as shown in **Table 36**. Compounds **144b, 144g, 144h,** and **144i** were not isolated and on further acid-catalysed cyclisation of the isopentenyl grouping in these molecules lead to the formation of **200g-200h**. These were easily identified by their respective ^1H NMR spectra, which showed the complete absence of any aromatic protons. Any unreacted phenols **(28a-28j)** were removed by treatment with Claisen's alkali[176].

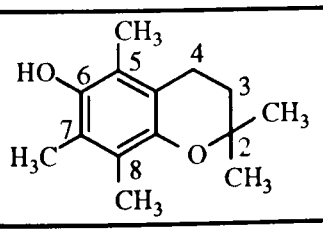
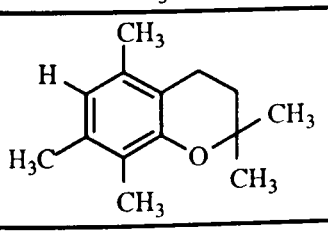
Cpd.	R_1	R_2	R_3	R_4	B.pt [°C / torr]	Yield (%)	Lit. B.pt [°C / torr]
82a	CH_3	OH	CH_3	CH_3	90-92 (M.pt)	57	92-94[88,173] (M.pt)
82b	CH_3	H	CH_3	CH_3	128-132/2	51	40-41[88] (M.pt)
82g	H	H	CH_3	CH_3	148-152/3	5	N/C
82h	CH_3	H	H	CH_3	108-112/1	4	N/C
82i	CH_3	H	CH_3	H	108-110/1	trace	N/C
82j	H	Cl	CH_3	H	54-56 (M.pt)	73	N/C

Table 6 : N/C = novel compound, therefore not reported.

The ^1H NMR spectra of compounds **82a-82j** were consistent with their proposed structures and are summarized in **Table 7.** One of the interesting features observed was that the peak heights of the C-4 methylene proton and the aromatic methyls in **82a-82j** were found to fall relative to the peak heights of the C-3 methylene protons and some broadening of the signals was observed but the multiplicities and the shift in band positions were not affected. This effect can be attributed to the presence of traces of trifluoroacetic acid present in the sample. It is thought that the effect is produced by the aromatic nucleus of the benzopyrans that is very easily oxidisable by the presence of acid or oxidising agents to the cation radical state **(m)**[213].

$$[\text{Phenol}] \xrightarrow{H^+} [\text{Phenol}]^{+\bullet} \qquad \textbf{(m)}$$

Similar affects have been observed by Dean[213], who noticed that small traces of acid present in deuterated solvents such as *d*-chloroform induced line broadening of the C-4 methylene protons of 3,4-dihydrobenzopyrans, especially tocopherol and its related compounds.

Structure	No.	C-2-$(CH_3)_2$	C-3-CH_2	C-4-CH_2	H-5	H-6	H-7	H-8
	**82a**	1.28	1.80	2.61	2.03	(OH) 4.23	2.03	2.07
	**82b**	1.30	1.78	2.59	2.04	6.54	2.09	2.15

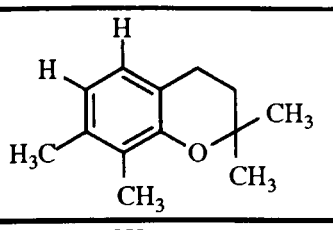
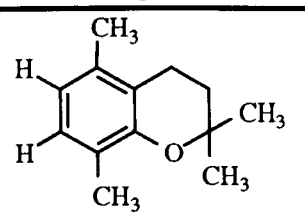
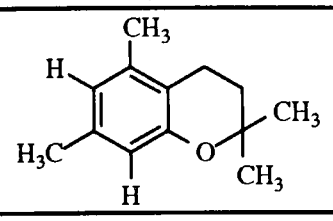
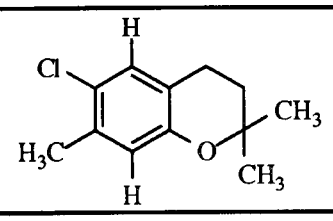
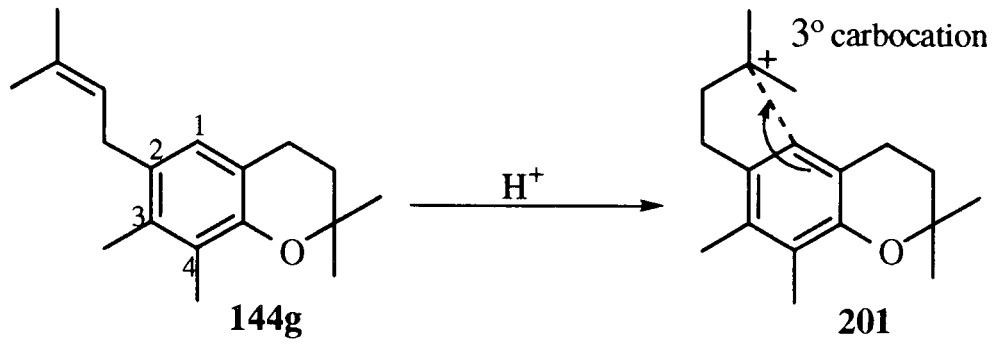
	**82g**	1.31	1.76	2.73	6.03	6.80	2.09	2.21
	**82h**	1.30	1.79	2.60	2.13	6.60	6.87	2.18
	**82i**	1.30	1.80	2.57	2.17	6.49	2.22	6.54
	**82j**	1.30	1.77	2.70	6.64	-	2.26	7.01

Table 7

The mass spectra of **82a-82j** were consistent with their structures. The fragmentation patterns are similar to the ones shown in **Scheme 26-27** (p.42-43).

The formation of the novel oxacyclopentanaphthalene **200g** as outlined in **Scheme 37** (p.56) can be accounted for the fact that the isopentenyl grouping in **144g** under these more strongly acidic condition leads to the formation of the tertiary carbocation **(201)** which on cyclisation and deprotonation leads to the formation of **200g** (provided that the *ortho*-position to the isopentenyl group is unsubstituted) in low yields as shown in **Table 8** (see **Appendix** for spectrum). This can be also account for by the formation of the novel oxacyclopentanaphthalene **(200h)** from **144h**.



Scheme 37

Cpd.	R_1	R_2	R_3	R_4	B.pt [°C / torr]	Yield (%)	Lit. B.pt [°C / torr]
200h			CH_3	CH_3	126-132/3	16	N/C
200g	CH_3	CH_3			148-152/3	25	N/C

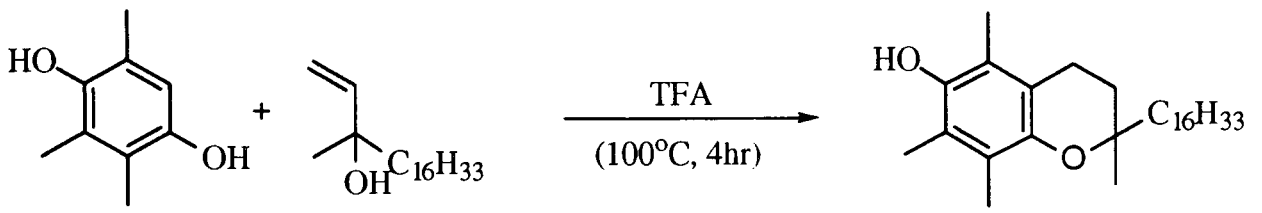
Table 8 : N/C= novel compounds

The ^1H NMR spectra of **200g-200h** showed signals for six methyl groups resonating at 1.29-1.39 ppm, and signals for four methylene groups resonating around 1.71-1.89ppm respectively, and a complete absence of any aromatic protons, hence, confirming the presence of oxacyclopentanaphthalenes (as far as we are aware) **200g-200h**.

Their mass spectra also showed the required molecular ion peaks for **200g** and **200h**.

Thus condensation reaction of an allyl alcohol with a suitable hydroquinone is an important process in the synthesis of benzopyran heterocycles. For example, although there are numerous reports in the literature concerning the synthesis of *rac*-α-tocopherol **1**[214], the development of a more effective and practical system is still being sought. On this basis, the methology of Ismail *et al*[210] was employed to seek a more effective and practical acid catalyst for the synthesis of α-tocopherol **(1)**, as outlined in **Scheme 38**.

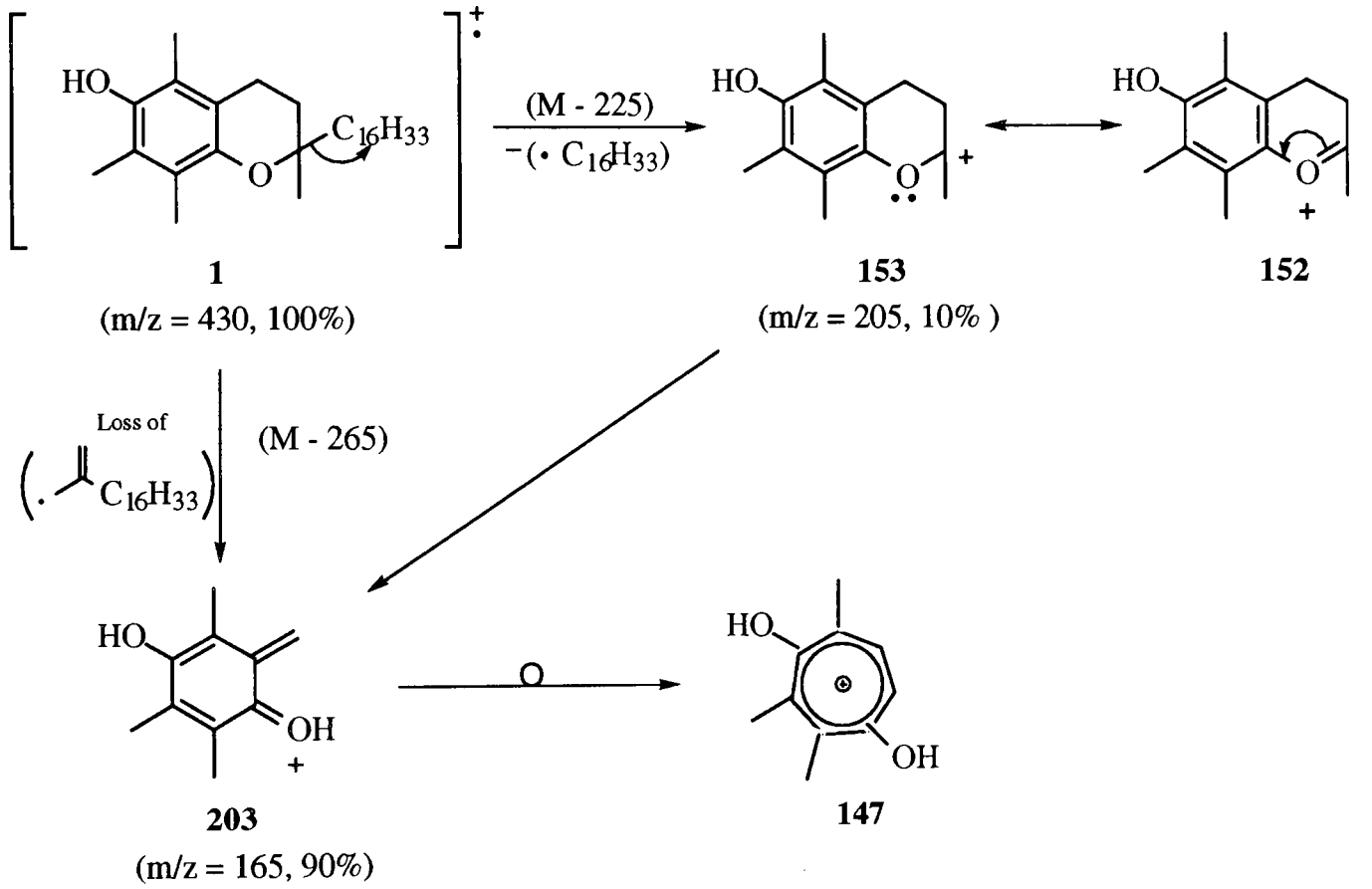
Trimethylhydroquinone **(28a)** was reacted with isophytol **(36)** in the presence of trifluoroacetic acid to afford α - tocopherol **1**, 83% yield.



28a **36** **1**

Scheme 38

The ^1H NMR spectrum of the product was consistent with the proposed structure. A possible mass spectral fragmentation of α-tocopherol **1** is shown in **Scheme 39**.



1 (m/z = 430, 100%)

153 (m/z = 205, 10%)

152

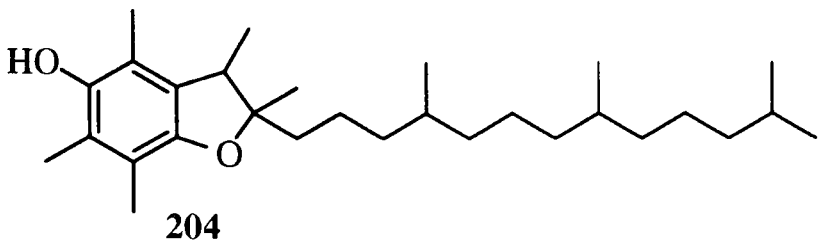
203 (m/z = 165, 90%)

147

Scheme 39

The molecular ion **1**, loses the phytyl side chain (M-225) to afford the tertiary carboaction **153**, which is resonance stabilised. Alternatively, the molecular ion **1k** (via a retro-Diels-Alder reaction) can lose the phytyl chain to afford **203** which forms the more stable tropylium ion **(147)**.

Recently, Yamamoto *et al*[215] have used rare earth metals trifluoromethanesulfonate (triflates) to catalyse the reactions. In particular, Scandium (III) trifluoromethanesulphonate ($Sc(OTf)_3$) was found to be the most effective catalyst for the condensation of trimethylhydroquinone with phytol to afford α-tocopherol in good yield (88%), together with the minor impurities of the diastereomers of the dihydrobenzofuran **204**, in contrast to the 83% yield of the pure α-tocopherol obtained in this work.



204

Hall[207,216] found that the threshold of acidity (Ho) required for pyran formation was approximately -3.0, and observed that no reaction occurred with hydrogen chloride, formic acid (Ho = 2.2)[217], formic-hydrochloric acid, or 50:50 (v/v) formic-trifluoroacetic acid mixtures. Trifluoroacetic acid (TFA; Ho = -3.0[207,216]) fulfills the aforementioned criterion and has been used to synthesise efficiently a variety of racemic benzopyrans as well as α-tocopherol, as shown in this study. Swanholm and Parker[218] have studied the *ortho*-Claisen rearrangement of allyl ethers where trifluoroacetic acid has been used to synthesize *ortho*-cresol from allyl-*p*-tolyl ether, and they have shown that trace quantities of water (up to 10%), which are not tolerated by other condensation procedures, actually enhance the rate of cyclisation and condensation by (approximately) twenty fold. This observation could be due to the fact that TFA is a strong acid in aqueous solution (pKa = +0.3)[198], and a weak acid in the pure state[199] and the presence of water might allow the possibility of catalysis by H_3O^+. Therefore, it is thought that a combination of various acids might induce this "acidity jump phenomenon" (near Superacid mediated catalysis by TFA). Superacids have been used by Olah to generate carbocations[206].

The advantage of using trifluoroacetic acid is that it avoids the use of catalysts such as $FeCl_3$, $SnCl_4$ or $AlCl_3$ because these catalysts can introduce metallic impurities into the reactions. Trifluoroacetic acid acts as both the solvent and the catalyst for the rearrangement and subsequent condensation of phenols and allylic alcohols in the formation of benzopyrans. In similar work, phenols and propargyl alcohols when heated together can directly yield 2,2-dimethylchromenes, as in the Spath synthesis of the natural product seselin[146].

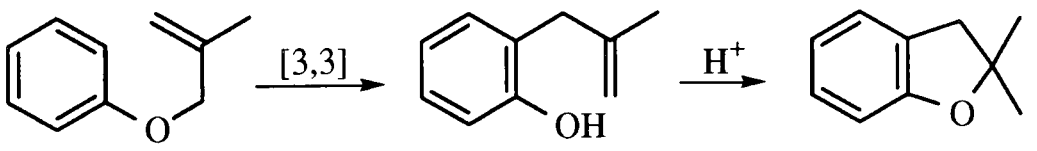
In summary, this study has shown that 2,2-dimethyl-3,4-dihydrobenzopyrans can be efficiently synthesised by reacting both phenols and substituted hydroquinones with carbocations generated from the appropriate allylic alcohol in trifluoroacetic acid under an atmosphere of argon in a one pot synthesis.

2,2-Dimethyl-3,4-dihydrobenzopyrans have been synthesised in low to average yield (5-54%) by using Smith's methods[86,173]. The method undertaken in this study using trifluoroacetic acid also gave low-average yields together with novel compounds whose spectral data have not been reported in the literature before.

2.07 Synthesis of 2,2-dimethyl-2,3-Dihydrobenzofurans (124a-r)

2,2-Dimethyl-2,3-dihydrobenzofurans are important intermediates in natural product chemistry[219-221], and they have been shown to exhibit a range of different bioactivity[222]. The 5-hydroxy-2,3-dihydrobenzofurans and 5-hydroxy-2,3-dihydronaptho[1,2-b]furans have been shown to be extremely effective antioxidants in a variety of systems[60,223,224]. In particular, they were found to be even more efficient than α-tocopherol, the major lipid-soluble chain-breaking antioxidant in human blood[225]. In addition, 5-hydroxy-2,3-dihydrobenzofurans have proved to be effective free radical scavengers in biological systems working, for example, as lipoperoxidation inhibitors[220] or as inhibitors of leukotriene biosynthesis[226]. Therefore, the synthesis of 2,3-dihydrobenzofurans are of interest.

[3,3] Sigmatropic rearrangements of allyl aryl ethers (the Claisen rearrangement) provide an efficient method for constructing carbon-carbon bonds and have been increasingly employed in synthesis[111-114]. Though there are some reports of 2,3-dihydrobenzofurans **(124)** being obtained as minor products during Claisen rearrangements[227-232], they are generally synthesized in two steps from allyl aryl ethers **(205)** utilising the [3,3] sigmatropic reaction followed by cyclisation of the resulting 2-allylphenols **(206)** in the presence of strong acid catalysts[233-237] as outlined in **Scheme 40**.

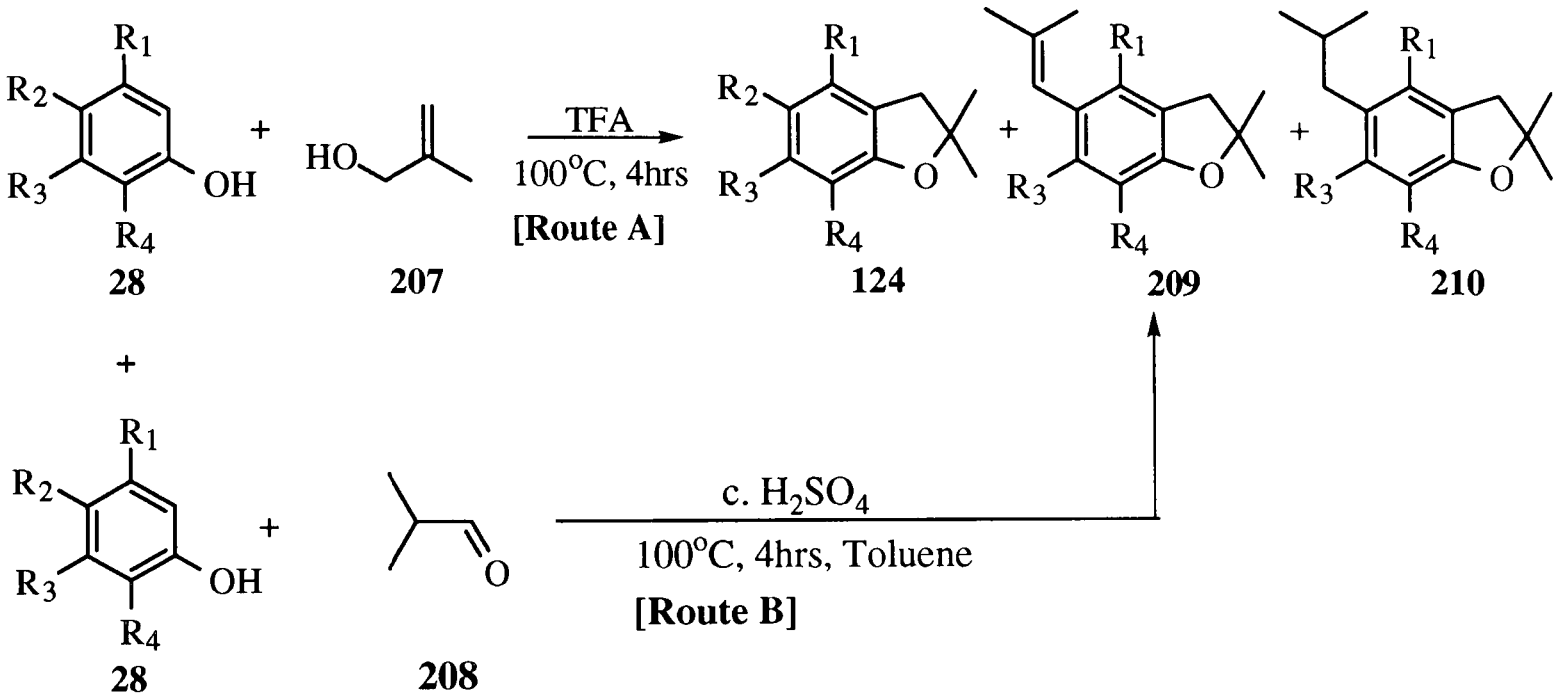


205 **206** **124**

Scheme 40

These procedures resulted in low yields and required vigorous conditions during all the steps[133,238]. A [3,3] sigmatropic reaction has been reported involving heating 2-methyl allyl *p*-tolyl ether at 140°C for 9hrs in the presence of zinc chloride[239] but with poor yields of the product **124**. The reaction conditions, however, were still unsatisfactory (longer reaction times) with comparatively low yields. Saidi[240] has reported that the rearrangement of allyl naphthyl ethers promoted by titanium tetrachloride produced 2,3-dihydronaphthofurans in average to good yields, while recently, Ryu[241], synthesised 2,2-dimethyl-2,3-dihydrobenzofurans from aryl methyl allyl ethers using aluminium chloride in the presence of potassium carbonate and mixed solvent systems (acetone / DMF, 5:1) to generate the methyl allyl ethers followed by a [3,3] sigmatropic rearrangement and cyclisation of the ethers using aluminium chloride as the catalyst, to afford the corresponding 2,2-dimethyl-2,3-dihydrobenzofurans. They stated that the best results were achieved by using aluminium chloride as the catalyst.

In this study[242], however a campaign was undertaken to improve the yields and carry out a one-pot syntheses, where various phenol derivatives **(28)** and allylic alcohol **(207)** were heated under reflux using trifluoroacetic acid, which acts as both the catalyst and the solvent **(see Scheme 41)** to afford 2,3-dihydrobenzofurans **(124)** in poor to moderate yields. The 2,3-dihydro-isopropenyl-benzofurans **(209)** were obtained in less than 2% yield, while 2,3-isopropyl-dihydrobenzofurans **(210)** in poor to moderate yields, were also obtained as side products **(Route A)**. The results are summarized in **Table 9** (where the various % figures are given).



Scheme 41

Also, mechanistic pathways will be proposed, compared to other workers and spectral data of 2,2-dimethyl-2,3-dihydrobenzofurans will be discussed.

The methodology of Martini[133] **(Scheme 41, Route B)** was also extended to other phenols and compared with that of the method outlined in **Scheme 40, Route A**. The appropriate phenol **28a-r** was dissolved in a solvent such as toluene and heated under reflux with isobutyraldehyde **(208)** in the presence of catalytic amount of concentrated sulphuric acid to afford the 2,3-dihydrobenzofurans **28a-r (in Table 9)**. The isopropenyl-2,3-dihydrobenzofurans **(209)** (trace amounts), and isopropyl-2,3-dihydrobenzofuran **210** were obtained as side-products, **(Route B)** as shown in **Scheme 41**.

In comparison of the results obtained in **Table 9**, it can be seen generally that the yields of the 2,3-dihydrobenzofurans synthesised using both **Routes A** and **B** as outlined in **Scheme 41**, increase as the aromatic ring is increasingly substituted by the electron donating weakly (+I) methyl groups. The best results were obtained in the case of the most hindered phenols **28a-28b**. The presence of electron withdrawing (-I) groups such as Cl, OCH_3 and Br in the aromatic ring gave comparatively low yields as in **124c**, **124p**, and **124q**, respectively. The presence of *ortho* substituents **(28m)**, led to low yields of the corresponding dihydrobenzofuran **(124m)** probably as a consequence of a

steric hinderance. The unsubstituted phenol **28r** gave also very poor yield of the corresponding dihydrobenzofuran **(124r).**

124	R_1	R_2	R_3	R_4	B.pt[a] [°C / mmHg]	Yield[a] (%)	B.pt[b] [°C / mmHg]	Yield[b] (%) /	B.pt.[lit] [°C/mm Hg]
a	CH_3	OH	CH_3	CH_3	118-120 (M. Pt.)	37	oil	22	122-123[130] (m.pt)
b	CH_3	H	CH_3	CH_3	43-45 (M. Pt.)	35	46-47	83	47[241] (m.pt)
c	H	Cl	H	H	82-84 / 0.18	6	60-62 / 0.13	6	117[238] (1Torr)
f	H	H	CH=CH-CH=CH		58-60 / 0.20	6	64-66 / 0.22	46	Gum[240]
g	H	H	CH_3	CH_3	82-86 / 0.11	26	N/C	N/C	45 /0.05[241]
h	CH_3	H	H	CH_3	92-96 / 0.06	11	58-64 / 0.04	15	48/0.03 [241]
i	CH_3	H	CH_3	H	84-86 / 0.10	27	50-56 / 0.08	38	88-89 / 0.01[243]
j	H	Cl	CH_3	H	72-78 / 0.12	31	62-66 / 0.09	12	N/R
l	H	CH_3	CH_3	H	52-60 / 0.1	13	64-66 / 0.12	46	50-65[244] (1 Torr)
m	H	H	H	CH_3	80-82 / 0.25	3	42-48 / 0.15	8	32 / 0.1[241]
n	H	H	CH_3	H	80-82 / 0.28	32	42-44 / 0.16	32	131[133] (m.pt)
o	H	CH_3	H	H	68-72 / 0.22	10	48-50 / 0.15	10	32 / 0.1[241]
p	H	OCH_3	H	H	62-66 / 0.13	4	N/C	N/C	NMR evidence [245]
q	H	Br	H	H	82-84 / 0.09	3	62-64 / 0.07	2	NMR evidence [246]

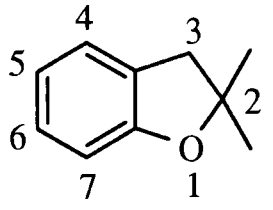
r	H	H	H	H	52-54 / 0.17	1	56-62 / 0.19	3	31 / 0.1[241]

Table 9: [a] in this study, [b] by Martini's method, N/C=not carried out, N/R = not reported.

The yields of 2,2-dimethyl-2,3-dihydrobenzofuran **124a** and **124j** obtained in this study **(Route A)** were better than those obtained by the Martini *et al*[133] **(Route B)**. The 2,2-dimethyl-2,3-dihydrobenzofurans **124c**, **124o**, **124q**, and **124r** were obtained in similar yields, by both routes. However, the rest were obtained in lower yields compared to those of Martini *et al*[133].

In this study[242], however, it has been shown that the 2,3-dihydrobenzofurans can be synthesized in a one-pot reaction by reacting phenols with an allylic alcohol in the presence of TFA which acted as both the catalyst and the solvent. The 2,2-dimethyl-2,3-dihydrobenzofurans synthesized by the Martini *et al*[133] **(Route B)** where toluene was used as the solvent and concentrated sulphuric acid as the catalyst (two different species). However, both **Routes A** and **B** gave comparatively low to moderate yields together with side products.

The ir spectra of the 2,3-dihydro-2,2-dimethylbenzofurans were consistent with the proposed structures. The absorption bands at around 2967 and 2852 cm^{-1} present in all the spectra of all the benzofurans, this was attributed to the C-H stretching vibrations of the CH_3 and CH_2 groups. The bands appearing at around 1370 cm^{-1} were attributed to the 2,2-dimethyl groupings present in the benzofurans. The other bands observed between 1500 and 1600 cm^{-1} were mainly from the aromatic moiety. The bands at around 1270-1215 cm^{-1} attributed to the C-O-C (ether C-O stretch) grouping present in the benzofuran ring system. The ir spectrum of compound **124a** showed the expected O-H stretching vibrations at 3446 cm^{-1} (broadened due to the intermolecular H-bonding).



124

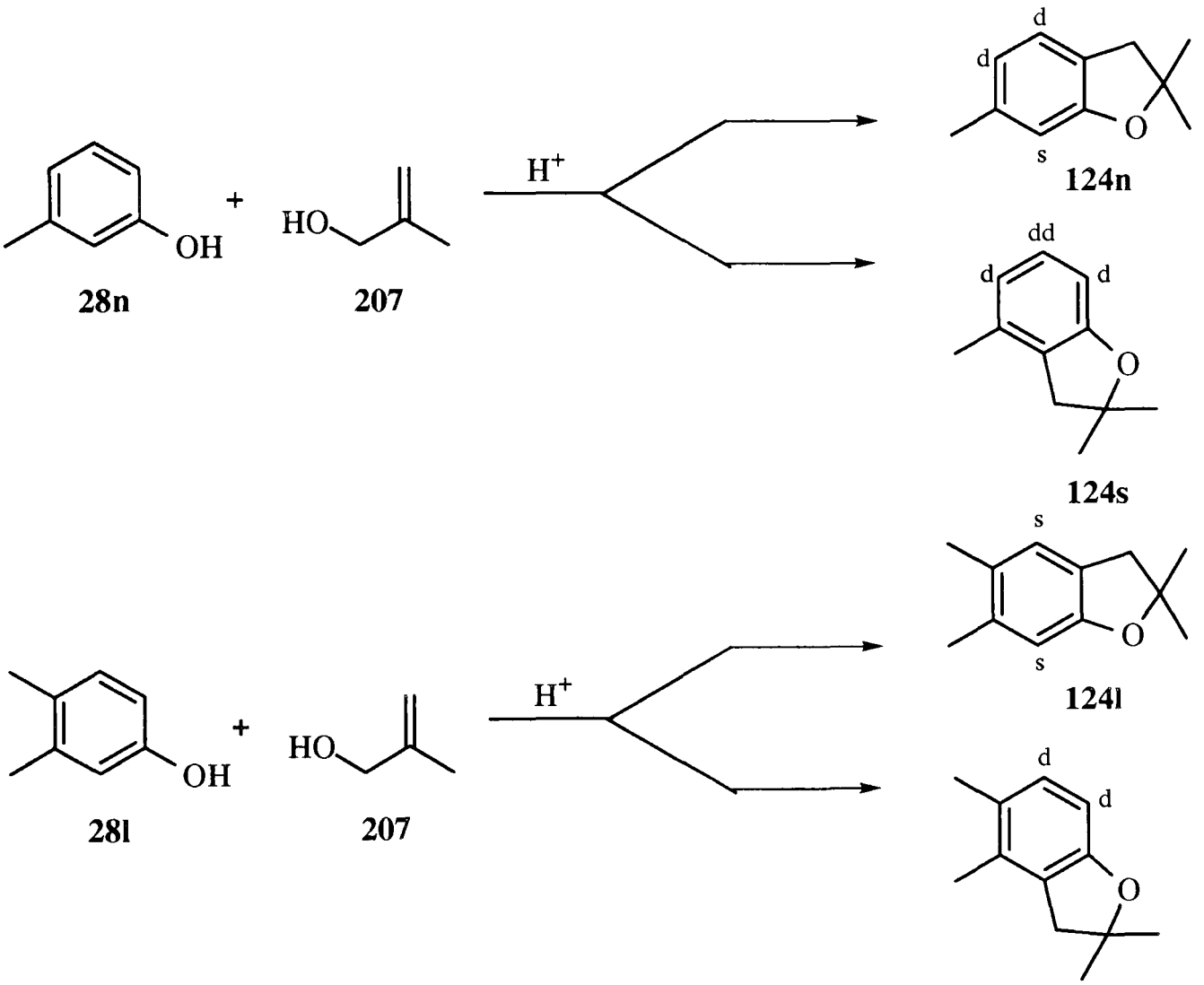
The proton nmr spectra were also consistent with the structures proposed for all the 2,2-dimethyl-2,3-dihydro-2,2-dimethylbenzofurans **(124)** and the chemical shifts of the various protons are listed in **Table 10**.

124	$(CH_3)_2$ (C_2)	CH_2 (C_3)	Ar-H (C_4)	Ar-H (C_5)	Ar-H (C_6)	Ar-H (C_7)
a	1.44	2.89	[CH_3] 2.09	[OH] 4.27	[CH_3] 2.09	[CH_3] 2.09
b	1.41	2.90	[CH_3] 2.07	[H] 6.47	[CH_3] 2.10	[CH_3] 2.14
c	1.46	2.98	[H] 7.02-7.03	[Cl] -	[H] 7.05-7.09	[H] 6.61-6.64
g	1.46	2.97	[H] 6.61-6.64	[H] 7.24	[CH_3] 2.11	[CH_3] 2.22
h	1.49	2.92	[CH_3] 2.18	2 x [H] 6.53-6.87		[CH_3] 2.19
i	1.49	2.87	[CH_3] 2.13	[H] 6.40	[CH_3] 2.21	[H] 7.19
j	1.44	2.93	[H] 7.06	[Cl] -	[CH_3] 2.28	[H] 6.58
l	1.44	2.93	[H] 6.54	2 x [CH_3] 2.15-2.17		[H] 6.89
m	1.45	2.97	3 x [H] 6.68-6.95			[CH_3] 2.18
n	1.45	2.94	[H] 6.97-7.00	[H] 6.60-6.63	[CH_3] 2.28	[H] 6.55
o	1.44	2.95	[H] 6.94	[CH_3] 2.26	[H] 6.87-6.90	[H] 6.60-6.63
p	1.45	2.96	[H] 7.06-7.04	[OCH_3] 3.71	[H] 6.60	[H] 6.59
q	1.44	2.96	[H] 7.15-7.14	[Br] -	[H] 7.24-7.17	[H] 6.59-6.56
r	1.49	3.02	4 x [H] 6.73-7.16			

Table 10

The protons of the geminal methyl present on C-2 appeared as a singlet and resonated in the region 1.41-1.49 ppm. The methylene protons present on C-3 showed a singlet, and resonated around 2.87-3.02 ppm, respectively in ^1H nmr spectra. The signal for the OH group in **124a** which is exchangeable by deuterium oxide, resonated around 4.77 ppm. Two regioisomeric products are possible from the reactions of the allylic alcohol **(207)**

with both the phenols **28l** and **28n**. Thus, the phenol **28n** could produce 2,2,6-trimethylbenzofuran **124n** or 2,2,4-trimethylbenzofuran **124s** while the phenol **28l** could produce 2,2,5,6-tetramethylbenzofuran **(124l)** or 2,2,6,7-tetramethylbenzofuran **(124t)** as outlined in **Scheme 42**.



28n **207** **124n** **124s**

28l **207** **124l** **124t**

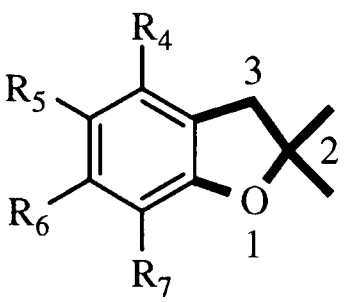
Scheme 42

The ^1H nmr spectrum of the product from **28n** showed a doublet resonating at 6.97-7.00 ppm (1H), a second doublet resonating at 6.60-6.63 ppm (1H), and finally, a singlet at 6.55 ppm (1H) which nearly superimposed on one peak of the latter doublet. Such a pattern indicated that the 2,3-dihydrobenzofuran obtained from phenol **28n** was 2,2,6-trimethylbenzofuran **(124n)** and not the 2,2,4-trimethyl isomer **(124s)** which would have been expected to show a doublet (*meta*-coupled), a doublet of doublets (*ortho*-coupled), and another doublet (*meta*-coupled) in the aromatic region of ^1H nmr spectrum.

The 2,3-dihydrobenzofuran obtained from phenol **28l** was 2,2,5,6-tetramethylbenzofuran **(124l)** and not 2,2,6,7-tetramethylbenzofuran **(124t)**. This was confirmed by the ^1H nmr spectrum of the product which showed two singlets resonating at 6.89 ppm and 6.54 ppm, respectively each integrating for one proton. Compound **124t** would have been expected to show two doublets *ortho*-coupled to each other. From a steric point of view a moderate regioselective control favours the

formation of the less hindered 2,3-dihydrobenzofurans **124n** over the alternative **124s,** and **124l** over **124t.**

The carbon-13 spectra of the 2,2-dimethyl-2,3-dihydrobenzofurans and 2,2-dimethyl-2,3-dihydrobenzonaphthofuran **(124f)** were consistent with their proposed structures and are summarised in **Table 11.**



124

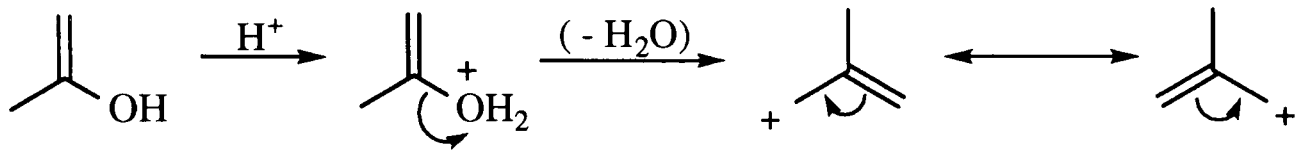
The chemical shift of the carbon at C-2 in 2,2-dimethyl-2,3-dihydrobenzofurans **124a-r** is relatively deshielded from the geminal methyl groups present at C-2 and the carbon at C-3. The carbon at C-2 in **124c**, **124j**, **124q** and **124p** is relatively deshielded in comparison to the other carbons at C-2 present in dihydrobenzofurans. This is possibly due to the electronic nature of polar groups (Cl and Br are weak π-donor, σ-acceptor whereas OCH_3 is a strong π-donor, σ-acceptor) present on the aromatic part of the system. The carbon at C-2 in the dihydrobenzonaphtofuran **(124f)** is also deshielded possibly due to the anisotropic effect of the naphthalene ring.

124	R_4	R_5	R_6	R_7	C-2	C-2-$(CH_3)_2$	C-3-CH_2
a	CH_3	OH	CH_3	CH_3	85.08	28.45	42.84
b	CH_3	H	CH_3	CH_3	85.83	28.62	42.83
c	H	Cl	H	H	87.46	28.07	42.75
f	H	H	CH=CH-CH=CH		87.53	28.63	43.86
g	H	H	CH_3	CH_3	85.97	28.36	43.29
h	CH_3	H	H	CH_3	85.76	28.60	42.27
i	CH_3	H	CH_3	H	86.38	28.45	41.69
j	H	Cl	CH_3	H	87.36	28.05	42.55
l	H	CH_3	CH_3	H	86.39	28.25	42.86
m	H	H	H	CH_3	85.80	28.31	43.29
n	H	H	CH_3	H	86.61	28.19	42.61
o	H	CH_3	H	H	86.31	28.16	42.96
p	H	OCH_3	H	H	86.49	28.12	43.34
q	H	Br	H	H	87.35	27.49	42.64
r	H	H	H	H	86.48	28.23	42.89

Table 11

2.08 Mechanism of Formation of the 2,2-dimethyl-2,3-dihydrobenzofuran (124a-r)

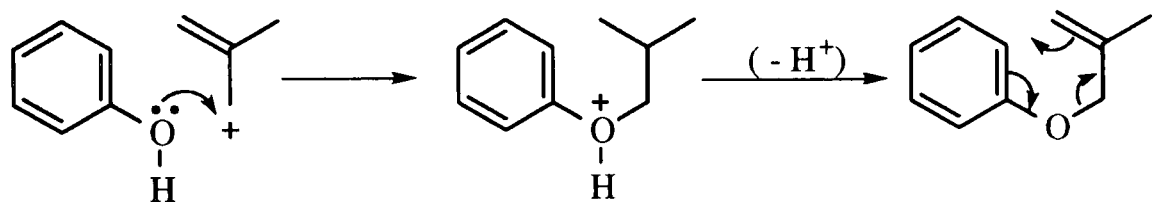
Protonation of the allyl alcohol **207** by the TFA to afford **211** followed by eliminaion of water leads to the formation of the symmetrical carbocation **212a** which undergoes allylic resonance resonates with **212b** as shown in **Scheme 43**.



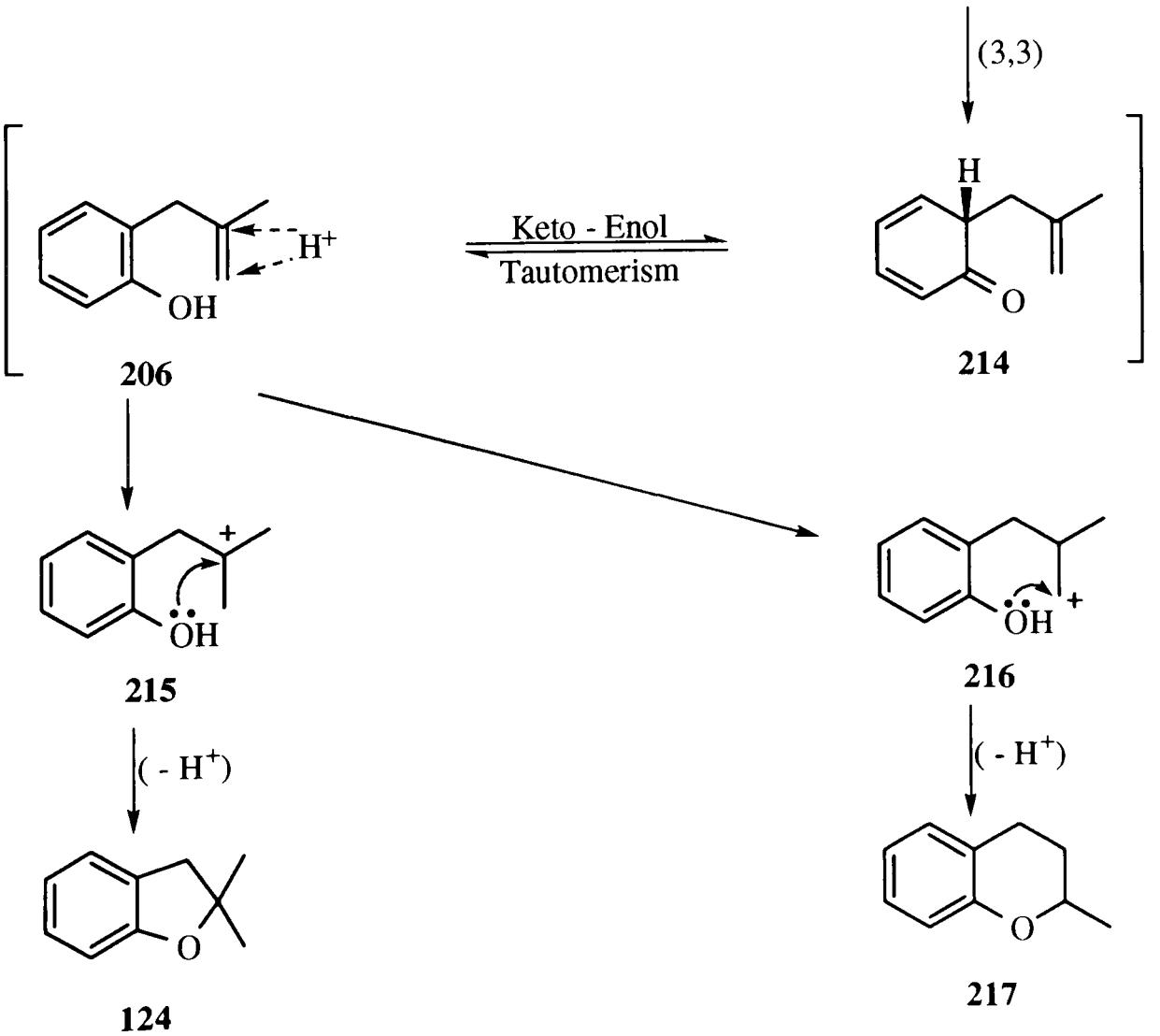
207 **211** **212a** **212b**

Scheme 43

Nucleophilic attack by the phenol **28** (OH) on the carbocation **212a-212b (Scheme 44)** leads to the formation of the aryl allyl ether **205** which could rearrange by a [3,3]-sigmatropic shift to form the ketone **214**. Ketone **214** would tautomerise to the enol **206** (to restore aromaticity).



28 **213** **205**

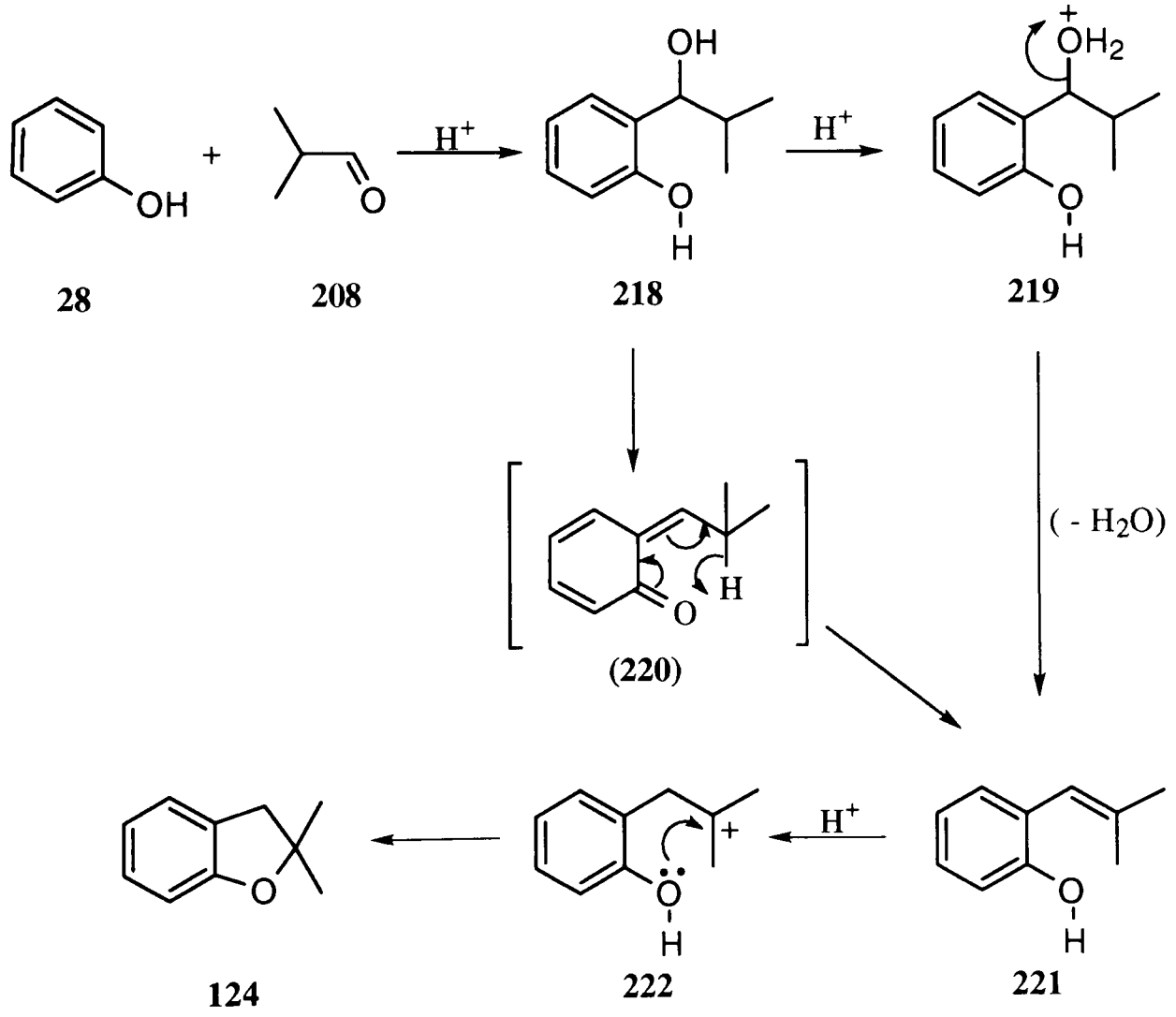


Scheme 44

Protonation of the double bond in **206** leads to the formation of either the 3° carbocation **215** or the 1° carbocation **216**. As the former would be energetically favoured, cyclisation by intramolecular nucleophilic attack on the more stable intermediate carbocation **215** and deprotonation affords the benzofuran **124**.

2.09 Mechanism of formation of the substitited 2,3-Dihydrobenzofuran.

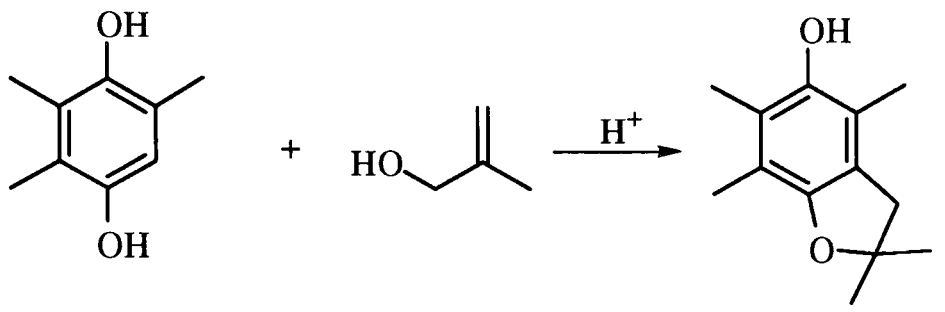
Martini *et al*[133], proposed that on acid-catalysis, the phenol **(28)** reacts with isobutraldehyde **(208)** to form the benzylic alcohol **(218)**, as outlined in **Scheme 45**. Protonation of 2-hydroxybenzyl alcohol **(218)** with subsequent loss of water leads to the formation of the substituted styrene **(221)**. Further protonation of the alkenyl phenol **(221)** leads to the intermediate 3° cation **(222)** which by intramolecular nucleophilic attack by the lone pair of the oxygen on this cation leads to the formation of the 2,3-dihydrobenzofuran **(124)**.



Scheme 45

Arduni *et al*[238], on the other hand, has stated that the 2-hydroxybenzyl alcohols such as **(218)** can be thermally dehydrated via an ortho-quinonemethide **(220)** to give a 2-alkenylphenol **(221)** by carrying out the reaction in hexane. The resulting 2-alkenylphenol **(221)** on further protonation generates the cation **(222)** and intramolecular cyclisation to 2,3-dihydrobenzofuran **(124)** at room temperature using

catalytic amounts of polymer-supported sulphonic acid (Amberlyst 15). Further confirmation was afforded by Arduni *et al*[238], when the 2-hydroxybenzyl alcohol **(218)** was cyclised to give the 2,3-dihydrobenzofuran **(124)** in toluene at 80°C, also using amberlyst 15.



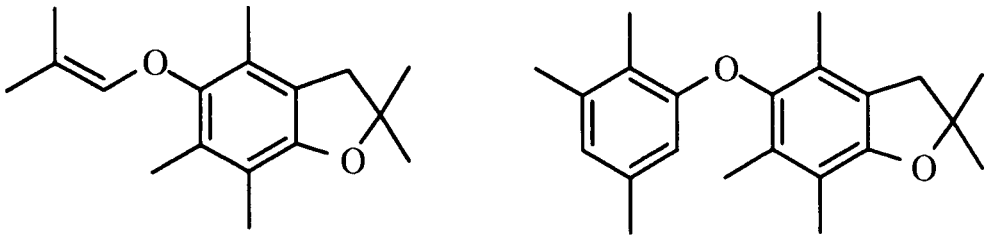
28a **207** **124a**

Scheme 46

The reaction of trimethylhydroquinone **(28a)** with methallyl alcohol **(207)** has been investigated by both Lars *et al*[247] and Ingold *et al*[57]. They performed the reactions in anhydrous formic acid in the presence of catalytic amounts of concentrated sulphuric acid and isolated the benzofuran **(124a)** in yields of 29% and 12%, respectively **(Scheme 46)**.

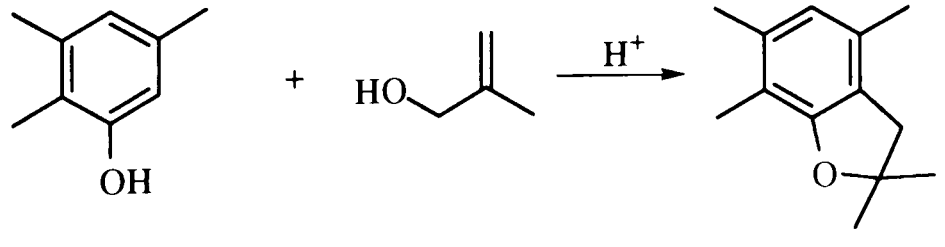
However, Novak *et al* [130] performed the reaction in the presence of toluene and *p*-toluene sulphonic acid as the catalyst and obtained benzofuran **(124a)** in yields of 11%.

In this study[242], when the reaction was repeated using trifluoroacetic acid as the catalyst, with a reaction time of 4hrs, **124a** was produced in 37% yields, together with 2-methyl propenyloxy- 2,3-dihydrobenzofuran **(223)** and the 5-phenoxyl-2,3-dihydrobenzofuran **(224)** with their respective molecular ion present in the mass spectra.



223 **224**

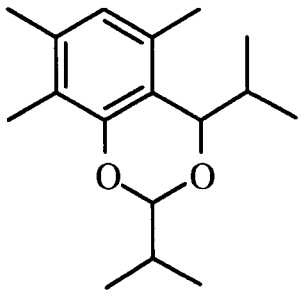
Also, the reaction of 2,3,5-trimethylphenol **(28b)** with methallyl alcohol **(207)** in the presence of trifluoroacetic acid as a catalyst led to the formation of the expected dihydrobenzofuran **(124b)** in 35% yield, as shown in **Scheme 47**.



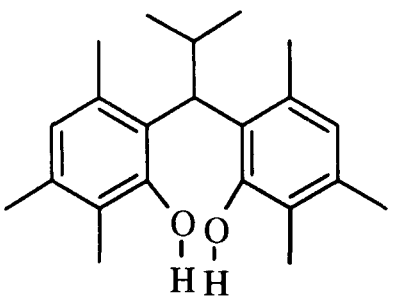
28b **207** **124b**

Scheme 47

However, traces of the 1,3-dioxine **(225)** and an intermediate **(226)** were observed in the CI mass spectral analysis (m/z=263 and m/z=337, M+1, repectively).

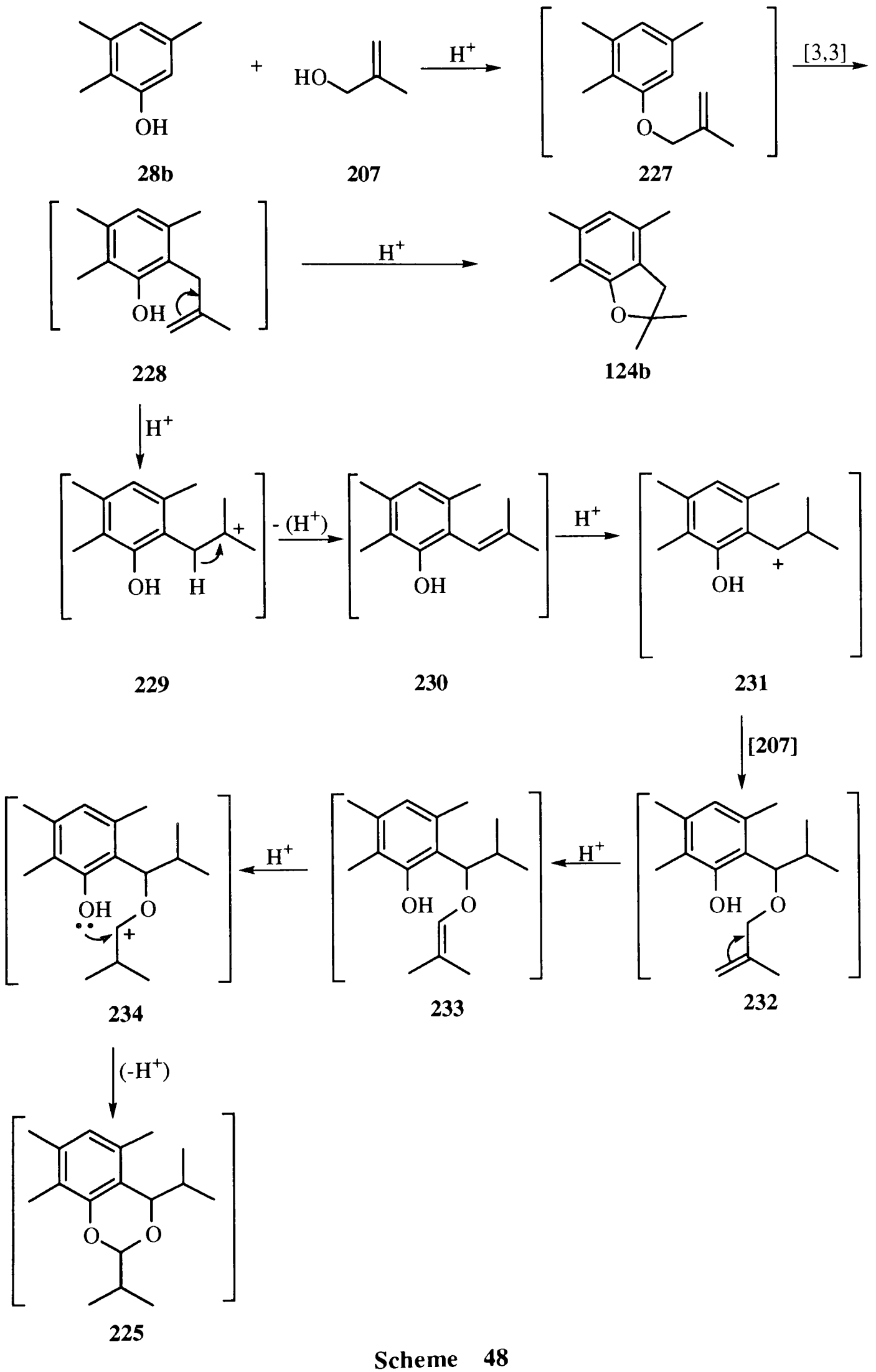


225



226

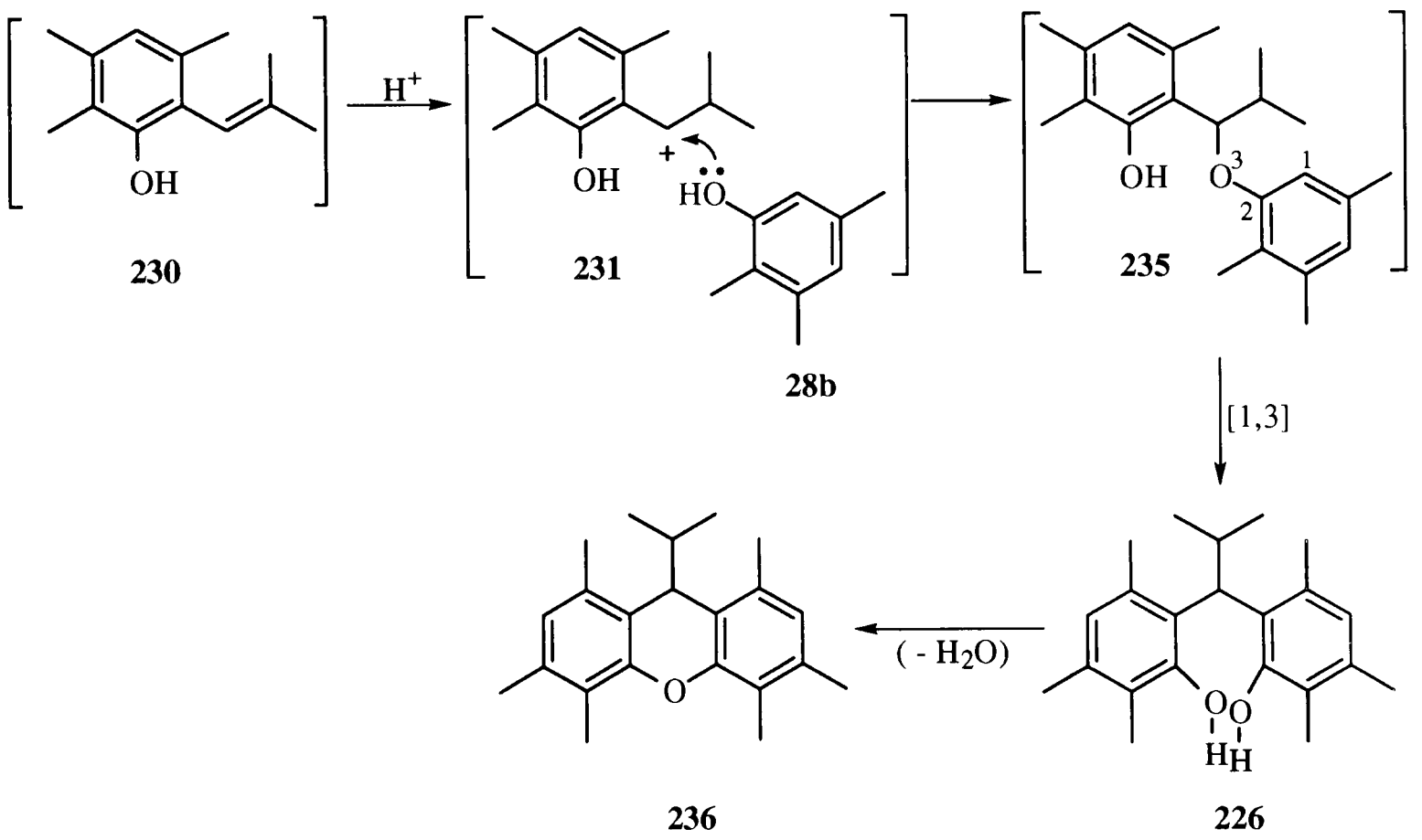
Novak *et al* [130] have proposed a mechanistic route for the formation of compound **225**, and **226 (Schemes 48 and 49)**. The acid-catalysed reaction between **28b** and **207** forms the allyl ether **227**, which then undergoes a [3,3] sigmatropic rearrangement, tautomerism, protonation of the double bond in **228**, and subsequent cyclisation to produce **124b**.


OH
HO
H+
[3,3]
O
28b
207
227
OH
H+
O
228
124b
H+
OH
H
+
- (H+)
OH
H+
OH
+
229
230
231
[207]
OH
O
H+
OH
O
H+
OH
O
+
234
233
232
(-H+)
O
O
225

Scheme 48

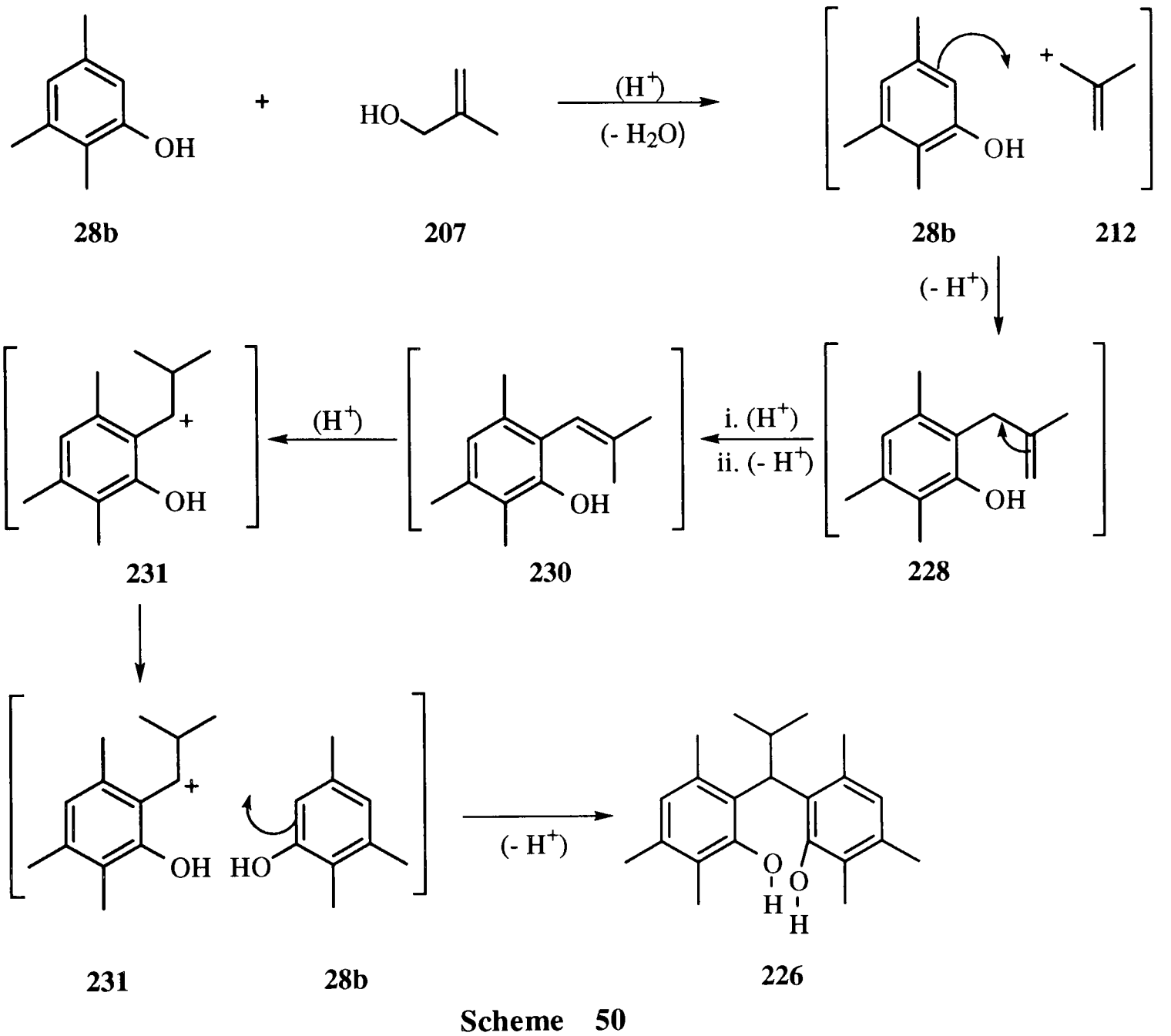
The acid-catalysed shift of the double-bond in **(228)** into conjugation with the benzene ring (via carbocation **229**) leads to the formation of 2-methylpropenyl phenol **(230).** Protonation of the double bond in **230** affords the 2° carbocation **(231)**. Nucleophilic attack by the allylic alcohol **(207)** on this cation forms **232** which on further acid-catalysed double bond migration gives **233**. Protonation of the double bond in **233** generates the 2° carbocation **(234)** and subsequently undergoes intramolecular cyclisation to give the 1,3-dioxine derivative **(225)**.

Novak *et al*[130] also proposed that the styrene **230** on acid-catalysed addition of phenol **(28b)** via cation **231** could generate the phenoxylpropyl phenol **235**. On [1,3]-sigmatropic migration of the side chain in the phenoxylpropyl phenol **(235)** gives the intermediate **226** and subsequent elimination of water affords the xanthene **199**, as outlined in **Scheme 49.** However, the xanthene **(236)** was not observed in this study.



Scheme 49

Due to the acidic conditions used, an alternative mechanism for the formation of intermediate **236** could involve direct aromatic electrophilic substitution between **28b** and **207** to afford **228**. Acid catalysed double-bond migration in **228** gives 2-methyl-isopropenyl phenol **(230)**. Further acid catalysis affords the cation **231** and electrophilic substitution reaction between the intermediate **231** and the substituted phenol **(28b)** gives **(226)**, as outlined in **Scheme 50**.



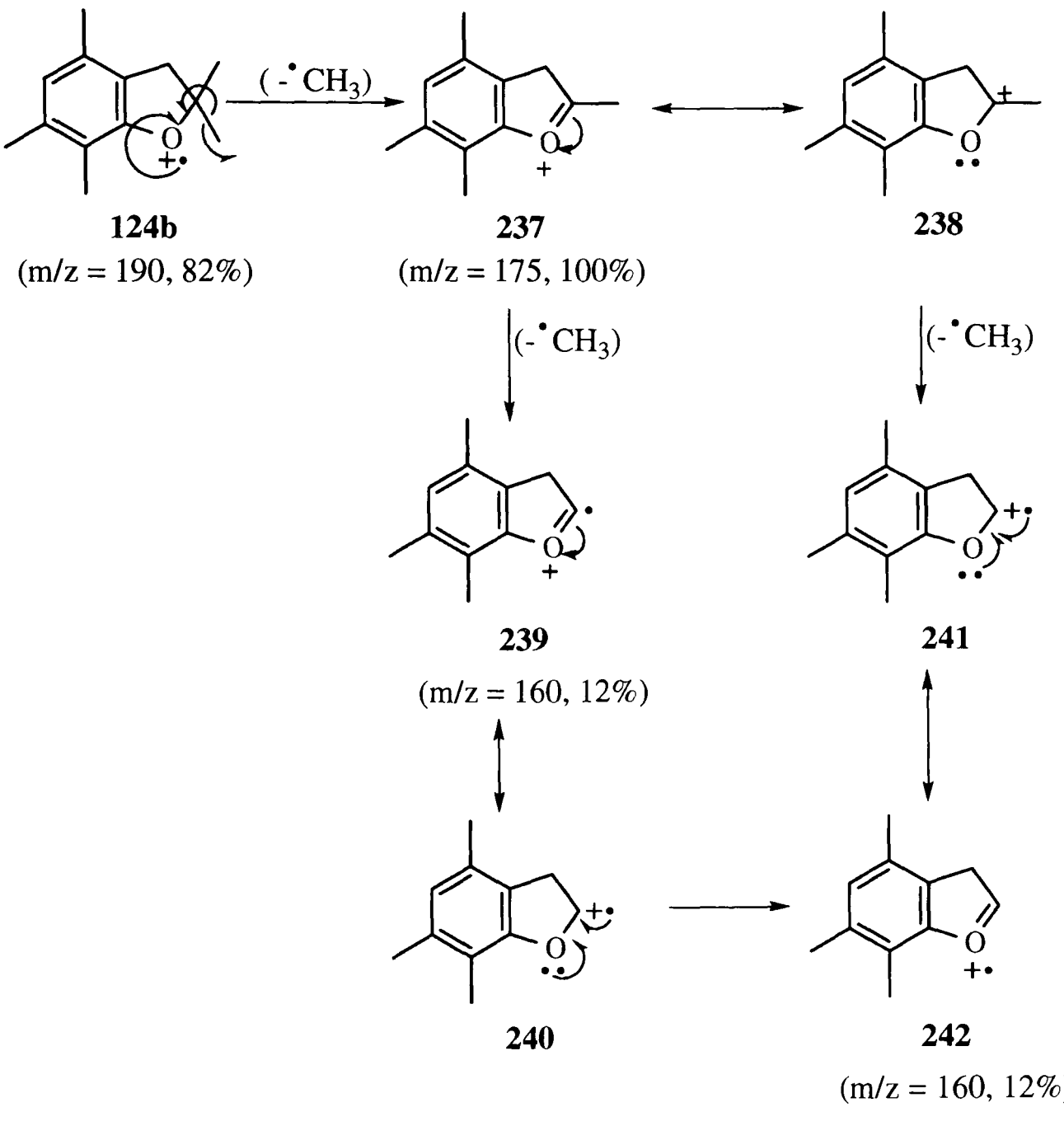
Scheme 50

In summary, it is proposed that the mechanism of formation of the dioxine **(225)** **(Scheme 48,** p.70) and the intermediate **226 (Scheme 50)** in this study, is identical with that proposed by Novak *et al*[130].

2.10 Spectral analysis of substituted 2,3-Dihydrobenzofurans (124)

The mass fragmentation patterns observed in the mass spectra of these compounds were consistent with their proposed structures. The benzofuran **124b** could lose a methyl radical to form the oxonium ion **237** (which is resonance stabilised). From either canonical form, a further loss of a methyl radical could afford **242** as shown in **Scheme 51**.

These characteristic fragmentation patterns were observed in all of the 2,3-dihydrobenzofuran derivatives **(124a-r)**.



124b
(m/z = 190, 82%)

237
(m/z = 175, 100%)

238

239
(m/z = 160, 12%)

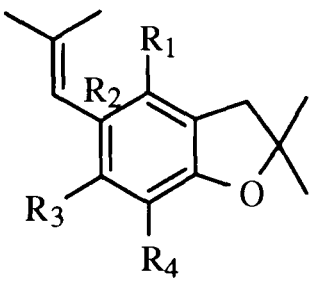
241

240

242
(m/z = 160, 12%)

Scheme 51

Besides the expected 2,3-dihydrobenzofuran **(124a-r)**, the formation of *ortho* and *para*-(2-methylpropenyl)-2,3-dihydrobenzofurans **(209)** was observed. The formation of these by-products depended on the substitution pattern in the initial phenol **(Table 12)**.

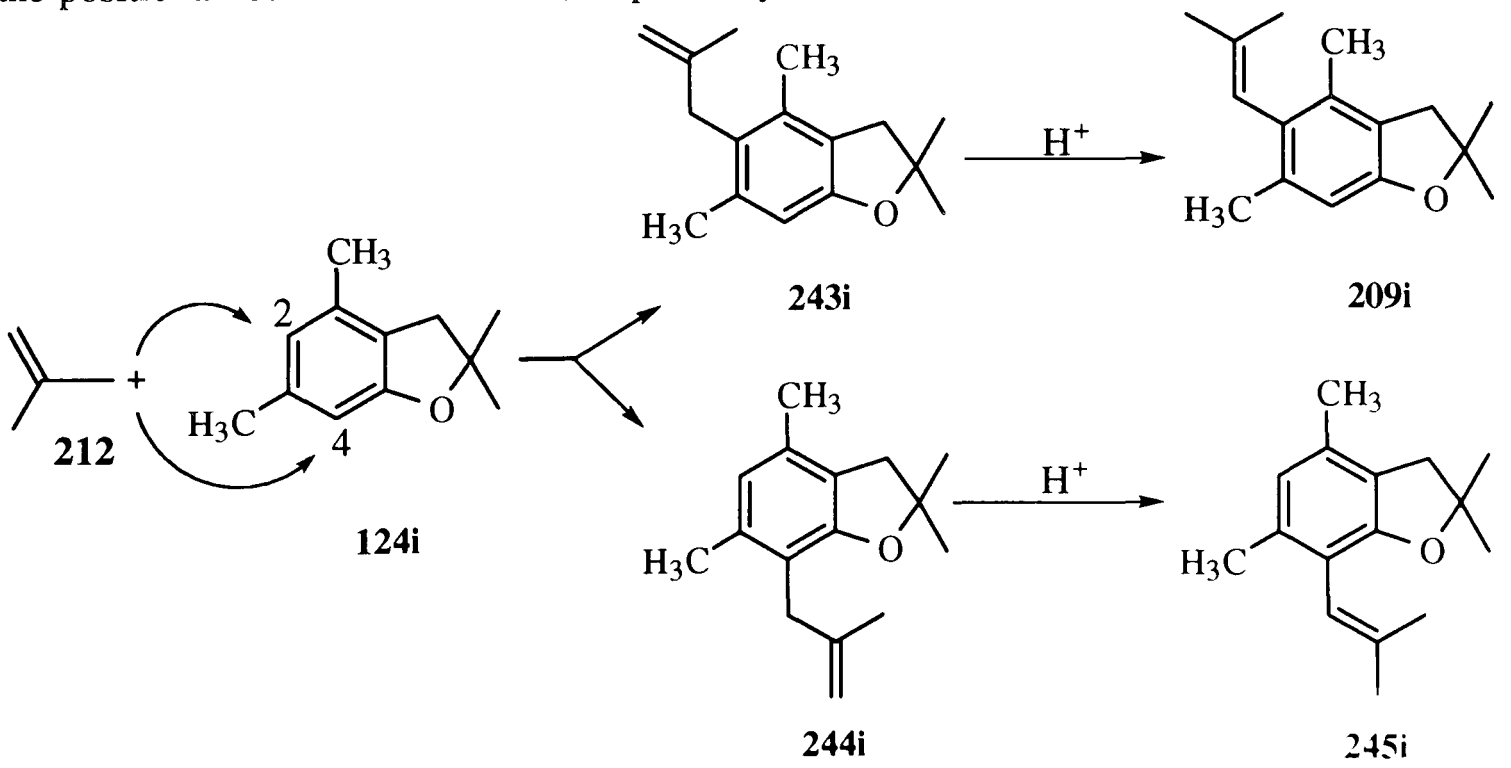


210

Compd.	R_1	R_2	R_3	R_4
209b	CH_3	*	CH_3	CH_3
209c	H	Cl	H	$CHC(CH_3)_2$
209f	H	*	CH=CH-CH=CH	
209g	H	*	CH_3	CH_3
209h	CH_3	*	H	CH_3
209i$^+$	CH_3	*	CH_3	H
209j	CH_3	Cl	CH_3	$CHC(CH_3)_2$
209l	H	CH_3	CH_3	$CHC(CH_3)_2$
209m	H	*	H	CH_3
209n^{++}	H	*	CH_3	H
209o	H	CH_3	H	$CHC(CH_3)_2$
209p	H	OCH_3	H	$CHC(CH_3)_2$
209q	H	Br	H	$CHC(CH_3)_2$
209r	H	*	H	H

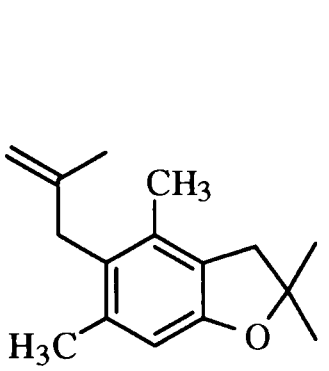
Table 12 : [*] $CHC(CH_3)_2$, [+] **243i** exists as an isomer of **209i** where R_2=H, R_4 = $CHC(CH_3)_2$, [++] **245n** exist as an isomer of **209n** where R_2= H, R_4 = $CHC(CH_3)_2$.

For example, the allylic carbocation **212** can attack the 2,2-dimethyl-2,3-dihydrobenzofuran **(124i)** at the 2-position or at the 4-position in the aromatic ring to afford the *para*-(2-methylpropenyl)-2,3-dihydrobenzofuran **(243i)** or the *ortho*-(2-methylpropenyl)-2,3-dihydrobenzofuran **(244i)**, respectively. The *ortho*- or the *para*-(2-methylpropenyl)-2,3-dihydrobenzofurans **(244i** or **243i)** on acid catalysis can afford the positional isomer **245i** or **209i**, respectively, as outlined in **Scheme 52**.

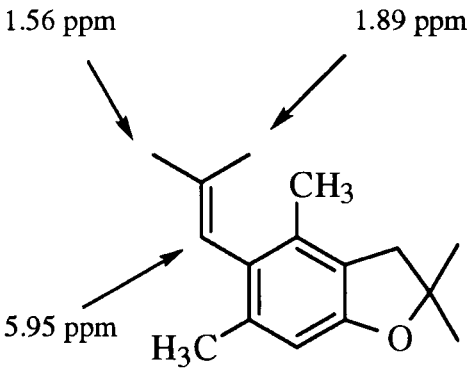


Scheme 52

The proton NMR spectra of the isopropenyl-2,3-dihydrobenzofuran derivatives **(209i)** were consistent with the proposed structures. These products were isolated by high vacuum distillation.



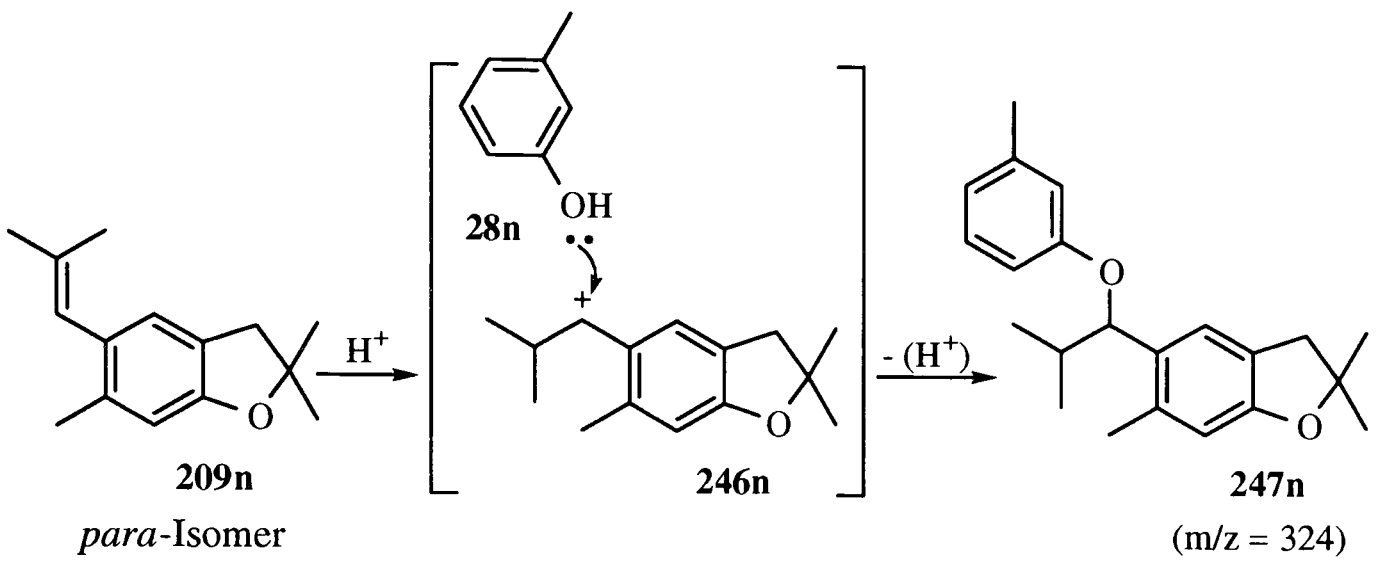
243i



209i

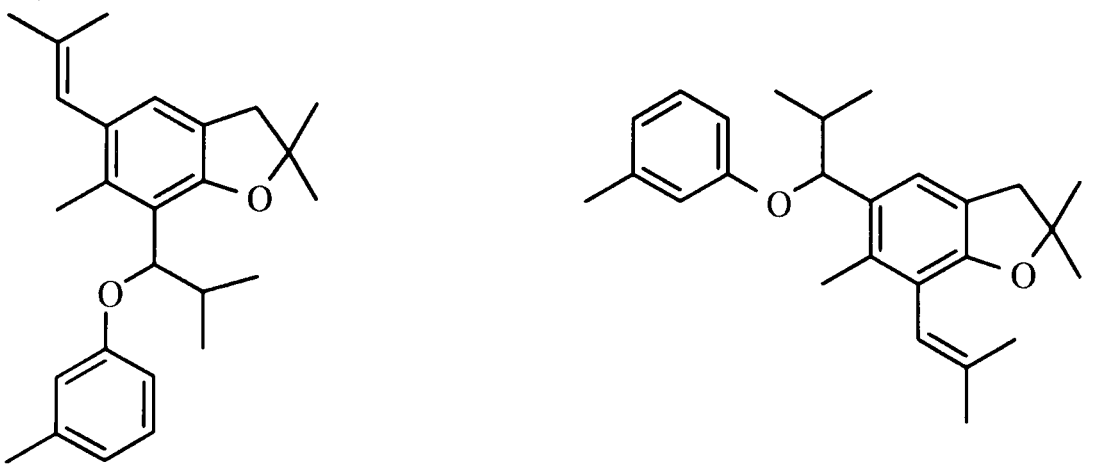
The ^{1}H NMR spectrum of isopropenyl-2,3-dihydrobenzofuran **(209i)** is typical of the isopropenyl-2,3-dihydrobenzofurans derivatives **(209)** showing the characteristic vinylic proton resonating at around 5.95 ppm, and the two methyl singlets resonating at 1.56 ppm and 1.89 ppm, respectively. However, the other possible isomer of **209i**, namely **243i**, was not detected in the ^{1}H NMR spectrum as the two vinylic proton signals required for this isomer were absent. The GC-MS analysis showed the presence of a single peak confirming the presence of just one isomer.

The *ortho* and *para*-isopropenyl-2,3-dihydrobenzofurans **(245n, 209n)** (Martini[133] **Route B,** p.60) reacted further (via carbocations **248** and **246**, respectively) with the corresponding phenol **(28n)** in an acid catalysed reaction to afford the 2-methyl-1-*p*-tolyloxypropyl-2,3-dihydrobenzofurans **(247n)** and 2-methyl-1-*o*-tolyloxy-propyl-2,3-dihydrobenzofurans **(249n)** as outlined in **Scheme 53**, respectively .



Scheme 53

This was further substantiated by the GC-MS analysis, which showed two peaks, having the retention time 27.59 min and 27.84 min, respectively, and both having the same mass (m/z=324) and could be attributed to **247n** or **249n**. A further two peaks were observed with the retention time of 20.06 min and 29.01 min, again both having the same mass (m/z=378) which could possibly be attributed to **250n** or **251n**.

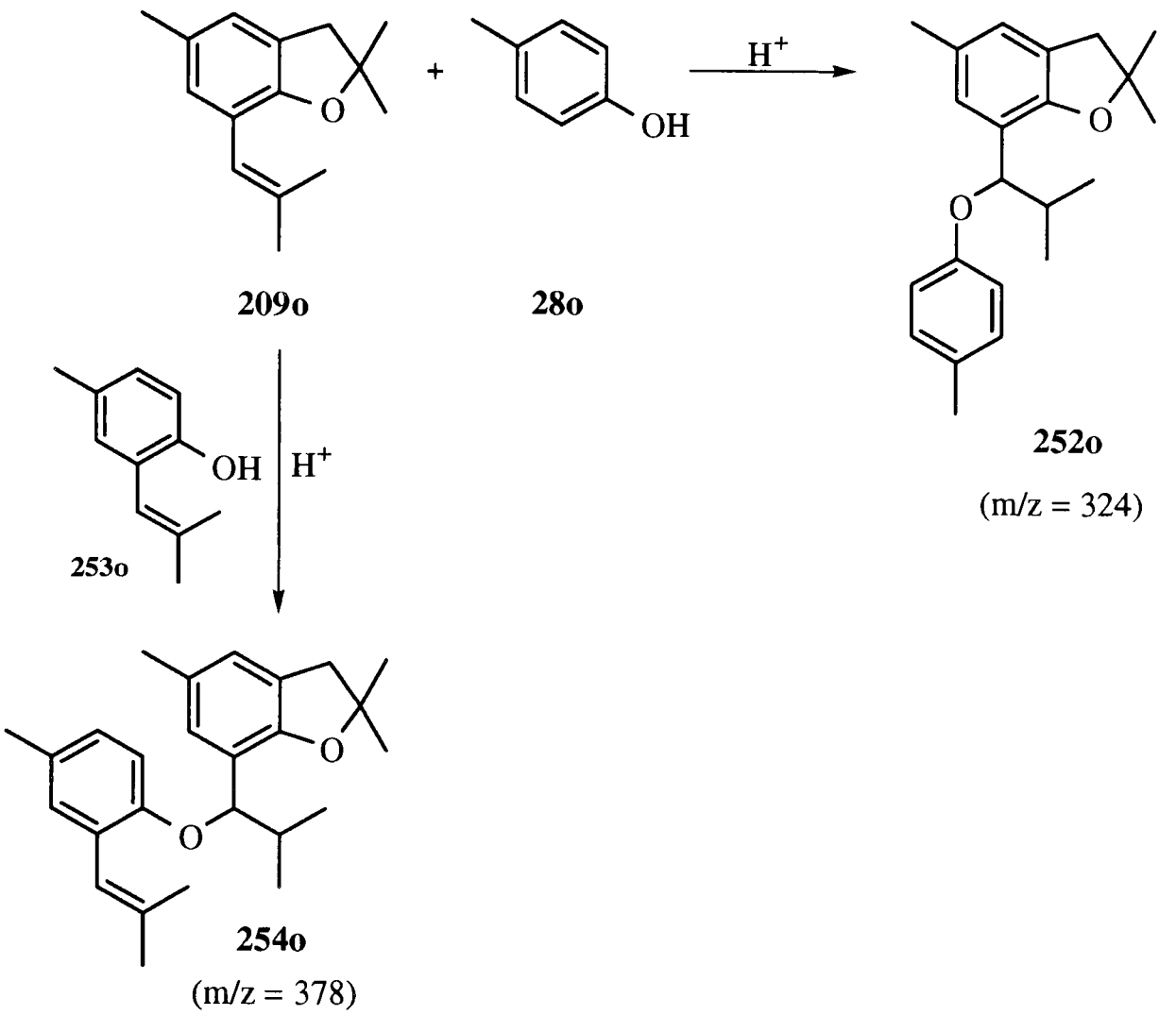


250n
(m/z = 378)

251n
(m/z = 378)

Similarly, the *ortho*-isopropenyl-2,3-dihydrobenzofuran **(209o)** reacted with the corresponding phenol **(28o)** to afford the *ortho*-tolyloxypropyl-2,3-dihydrobenzofuran **(252o).** The *ortho*-isopropenyl-2,3-dihydrobenzofuran **(209o)** also reacted in an

acid-catalysed reaction with the phenol (**253o**) to afford **254o** as outlined in **Scheme 54.**



209o **28o** **252o**

(m/z = 324)

253o

254o

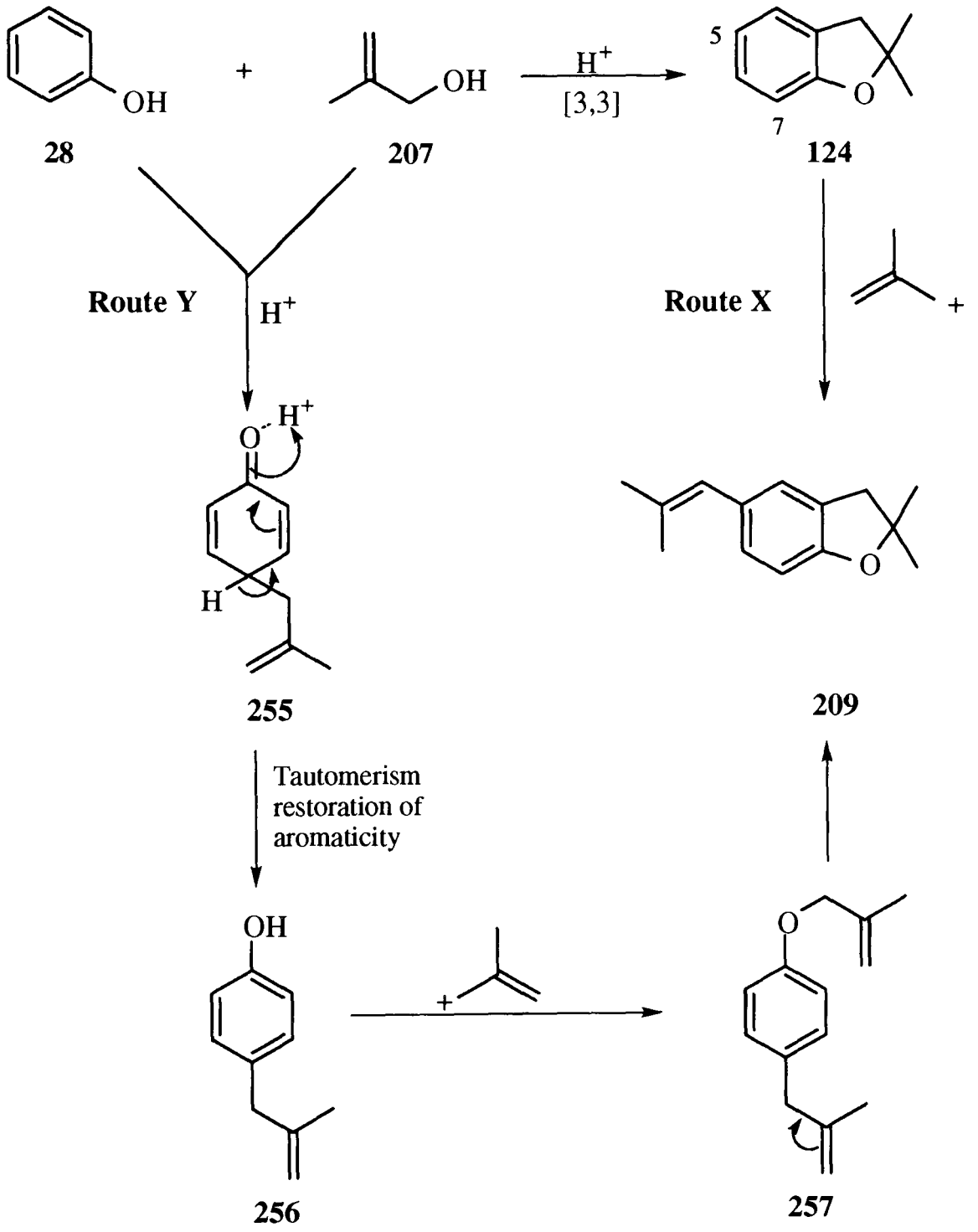
(m/z = 378)

Scheme 54

The GC-MS analysis showed the presence of two peaks, having the retention time 25.53 min and 27.39 min, respectively, and both having different mass (m/z=324 and m/z=378) and could possiblybe attributed to **252o** and **254o.**

2.11 Mechanism of formation of isopropenyl-2,3-dihydrobenzofuran (209b-r)

There are two possibilities as to how the isopropenyl-2,3-dihydrobenzofuran **209** may be formed (**Routes X** and **Y**, in **Scheme 55**). Firstly, **Route X** (see **Scheme 55** on p.78 for mechanism) shows the formation of benzofuran **124** which is further attacked by electrophilic aromatic substitution by the allylic carbocation on C-5 position to form isopropenyl-2,3-dihydrobenzofuran **(209)**. If this position is not available then the carbocation can attack by electrophilic aromatic substitution at the C-7 position.



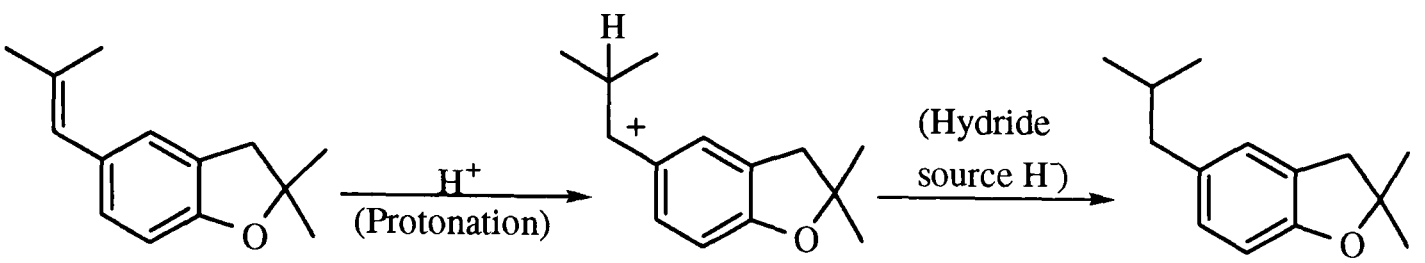
Scheme 55

Secondly, it is possible that the allylic carbocation derived from **207** electrophilically attacks the phenol **(28)** at the *para*-position to afford the *para*-alkylated ketone **(255)** which rearranges to form the *para*-alkylated phenol **(256)**, followed by cyclisation to give **209 (Route Y)**. **Route X** would be favoured over **Route Y** because it is possibly obtained by alkylation in a one step process from the 2,2-dimethyl-2,3-dihydrobenzofuran **(124)** which is stable (retains aromaticity). However, if the reaction proceeds by **Route Y** then the alkylated ketone **255** could be trapped by means of a Diels-Alder reaction[248].

Generally, in unsaturated systems double bonds can be reduced by catalytic hydrogenation where the catalyst can be a metal such as palladium (Pd), nickel (Ni), etc[249].

Besides the expected 2,3-dihydrobenzofuran **(124a-r)**, *ortho* and *para*-(2-methylpropenyl)-2,3-dihydrobenzofurans **(209)**, the isopropyl-2,3-dihydrobenzofurans

(210) were also observed. The isopropyl-2,3-dihydrobenzofurans **(210)** could be formed by ionic hydrogenation of **(209)** via the cation **(258)** as shown in **Scheme 56**.



209 **258** **210**

Scheme 56

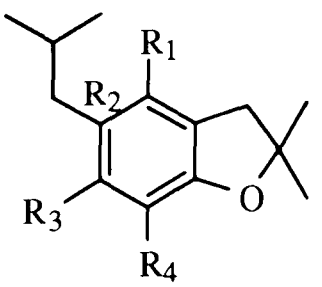
This is usually observed in reactions in which hydrosilanes function as a selective reducing agent[250] such as in the conversion of alcohols to carbocations by acid-catalysis, followed by reduction of carbocation by means of a hydride donor, such as a hydrosilanes[250] (though other reducing agents agents heve been used[251-254]). This process is known as 'Ionic Hydrogenation'. However, in this study it was difficult to state what the hydride source was. One possible source could be silicon grease which was used to seal the apparatus in the experiment led to the formation of **210**.

The presence of a number of isopropyl-2,3-dihydrobenzofurans **(210)** as listed in **Table 13**, formed by **Routes A** and **B** (see **Scheme 41**, p.60) were not isolated in some cases but detected mainly by GC-MS and in others by ^1H NMR spectroscopy.

210	R_1	R_2	R_3	R_4
b	CH_3	*	CH_3	CH_3
c	H	Cl	H	$CH_2CH(CH_3)_2$
i	CH_3	*	CH_3	H
j	H	Cl	CH_3	$CH_2CH(CH_3)_2$
o	H	CH_3	H	$CH_2CH(CH_3)_2$
r	H	*	H	$CH_2CH(CH_3)_2$

Table 13 : * $CH_2CH(CH_3)_2$

However, the % figures of the isolated isopropyl-2,3-dihydrobenzofurans **(210g-n)** are shown in **Table 14.**



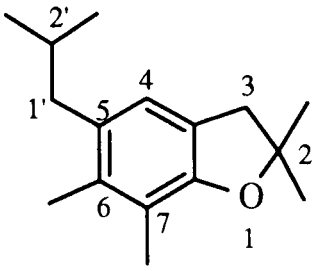
210

210	R_1	R_2	R_3	R_4	B.pt [°C/ torr][a]	Yield (%)[a]	B.pt [°C/ torr][b]	Yield (%)[b]
g	H	*	CH_3	CH_3	116-120 / 0.16	12	N/R	N/R
h	CH_3	*	H	CH_3	124-127 / 0.1	16	96-110 / 0.06	6
i[c]	CH_3	*	CH_3	H	N/R	N/I	N/R	N/I
j	H	Cl	CH_3	$CH_2CH(CH_3)_2$	N/R	N/I	N/R	N/I
l	H	CH_3	CH_3	$CH_2CH(CH_3)_2$	72-76 / 0.13	8	N/R	N/I
m	H	*	H	CH_3	60-64 / 0.20	36	60-64 / 0.22	2
n[d]	H	*	CH_3	H	64-68 / 0.20	3	116-120 / 0.43	11

Table 14 : * $CH_2CH(CH_3)_2$, [a] Obtained by **Route A**, [b] Obtained by **Route B**, [c] can exist as an isomer of **210i**, where R_2=H, R_4=$CH_2CH(CH_3)_2$, [d] **210n** can exist as an isomer where R_2=H, R_4=$CH_2CH(CH_3)_2$, N/I=not isolated, N/R=not reported.

As a typical isopropyl-2,3-dihydrobenzofuran spectrum, the ^1H nmr spectrum of **210g** is summarized in **Table 15**.

The proton on carbon-2' (C-2'-C<u>H</u>) in **210g** exhibits a typical pattern of an A_6X system (C<u>H</u>$(CH_3)_2$). The methylene protons on carbon-1' (C-1'-C<u>H</u>$_2$) showed a doublet at (9.0 Hz) due to the splitting of the proton on carbon-2' (C-2'-C<u>H</u>). The methylene protons (C-3-C<u>H</u>$_2$) in **210g** showed a singlet and resonated at around 2.94 ppm. The geminal dimethyl groups on carbon-2 (C-2-C<u>H</u>$_3)_2$) appeared as a singlet at around 1.46 ppm.



210g

Compd	H-2	H-3	H-4	H-5	H-6	H-7	H-1'	H-2'	H-2'
210g	(C<u>H</u>$_3)_2$	(C<u>H</u>$_2$)	(Ar-<u>H</u>)	Ar-C) -	(Ar-C<u>H</u>$_3$)	(Ar-C<u>H</u>$_3$)	(C-1'-C<u>H</u>$_2$)	(C<u>H</u>$_3)_2$	(C-2'-C<u>H</u>)
	1.43	2.94	6.71		2.12	2.13	2.39-2.42	0.88-0.92	1.75-1.78

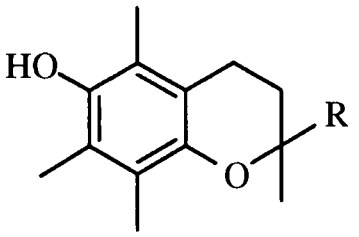
Table 15

The mass spectral analyses were consistent with the proposed structures of all the isopropyl-2,3-dihydrobenzofurans in the series.

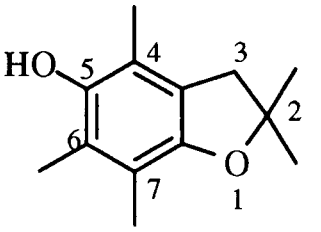
In summary, 2,2-dimethyl-2,3-dihydrobenzofurans were prepared by two synthetic routes. Firstly, by **Route A**, in a one-pot synthesis using trifluoroacetic acid (TFA), where it acts as both the solvent and as the catalyst[242]. This reaction is thought to proceed via 3,3-sigmatropic rearrangement and has the advantage of using simple reaction conditions. It is convenient and has produced low to moderate yields (4-32%). Secondly, by **Route B**, using the method of Martini[133] where phenols were condensed with isobutyraldehyde in the presence of toluene and concentrated sulphuric acid to afford 2,3-dihydrobenzofurans in low to high yields (4-84%). Here the solvent and the catalyst were different compared to the former method. Nevertheless, the reaction is thought to proceed initially via *ortho*-alkylation of the phenol (regioslectively), only in selected phenols. However, in this study, some polyalkylation of the 2,3-dihydrobenzofurans does seem to occur using the two methods (**Routes A and B**) stated in **Scheme 41** (p.60).

2.12 Synthesis of substituted 5-Amino-2,3-dihydrobenzofurans and substituted 6-Amino-3,4-dihydrobenzopyrans

Tocopherol **(1)**, and the substitued 2,3-dihydro-2,2,5,7,8-pentamethylbenzofuran **(124a)** are known to be efficent inhibitors of lipid peroxidation *in vivo*[58,255]. Recently, these compounds have become the focus of attention for investigators in the treatment of traumatic and ischemic central nervous system (CNS) injury[256-258]. It is proposed that the reactive oxygen radicals which are commonly formed in normal cell metabolism and subsequent lipid peroxidation are a factor which contribute to CNS trauma and ischemia[259]. Under normal condition their production is localised by the body's natural defenses including antioxidants (A, C, and E), glutathione, superoxide dismutase (SOD), and catalase which protect against the damaged caused by oxygen radicals[260]. However, under pathological conditions, these systems can be overwhelmed and the generation of these radicals enhanced[261]. Lipid peroxidation initiated by these oxygen radicals results in membrane degradation and cell death. Therefore, the synthesis of these compounds which are capable of reducing post-traumatic tissue damage, and which enhance neurological recovery is of interest. Recently, Ohkawa *et al*[262] have shown that the 5-amino-2,3-dihydrobenzofuran **(260)** was effective against the degradative processes mentioned above.

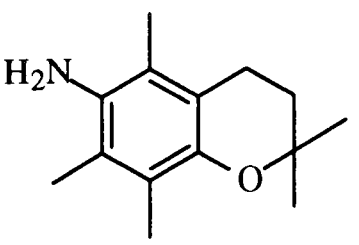


1

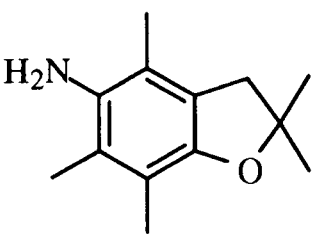


124a

1 R = $C_{16}H_{33}$
82a R = CH_3



259

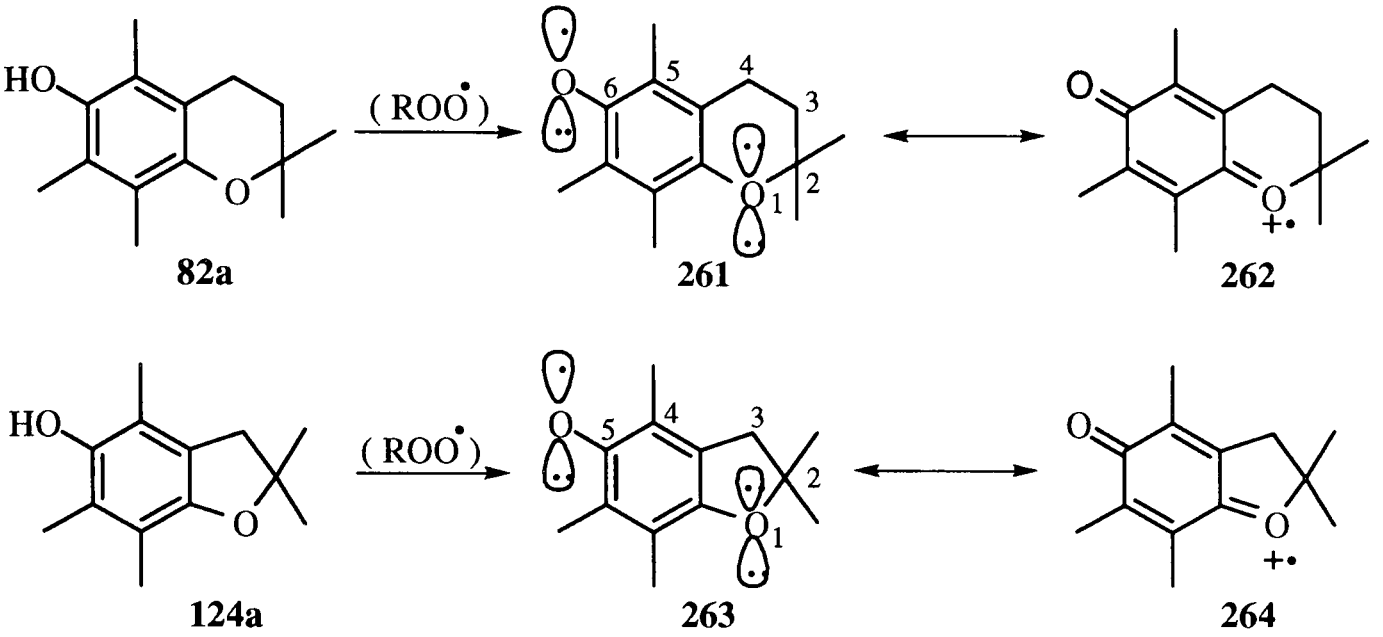


260

Introduction of the amino group (in place of the hydroxyl group) in the model α-tocopherol compound **259**, and in the 2,3-dihydrobenzofuran **(260)** would be expected to improve the hydrophilicity and the metabolic stability of the compounds.

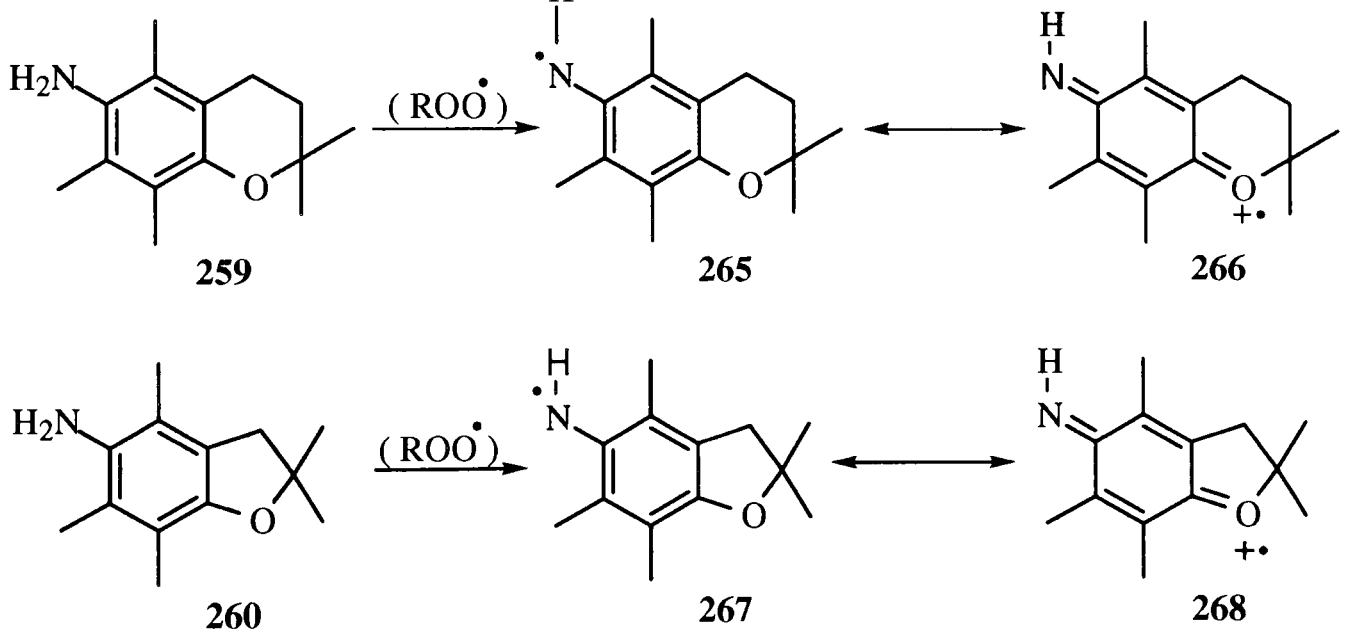
The 5-coumaranoxyl **(263)** and 6-chromanoxyl **(261)** radicals formed by reaction of **(82a)** and **(124a)** with peroxyl radicals are reported to be stabilised by the unpaired electron on the p-type lone pair of oxygen in position 1 and SOMO of the phenoxy

radical attached at position 6 by conjugative electron delocalisation[56] to afford **(264)** and **(262)**, as outlined in **Scheme 57**.



Scheme 57

The same effect is expected in the case of the 5-coumaranaminyl radical **(267)** and 6-chromanaminyl radical **(265)**, generated in the same way from **(259)** and **(260)** by peroxyl radicals, as shown in **Scheme 58**, since the amino group like the hydroxyl group can also donate an electron, and hence stabilise the oxygen radical[263].

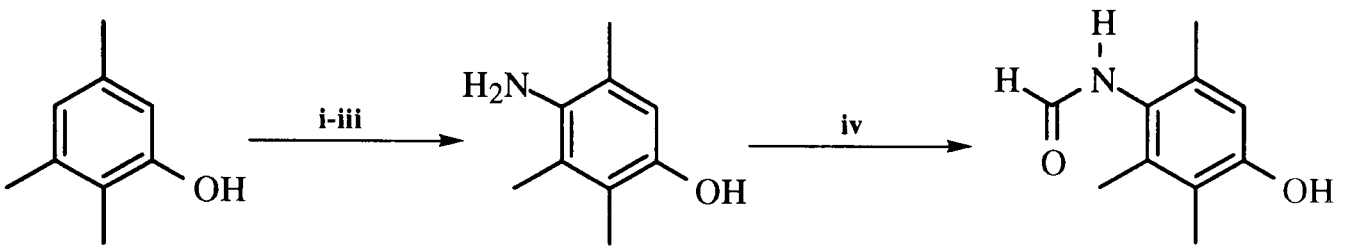


Scheme 58

Electron-donating substituents such as methyl groups[264] should also enhance the antioxidant activity due to the stabilization of the aminyl radical making methyl substituted 2,3-dihydrobenzofurans and 3,4-dihydrobenzopyrans potentially better lipid peroxidation inhibitors.

Synthetic routes to the methyl substituted 5-aminobenzofuran **(260)** and 6-aminobenzopyran **(259)** were investigated, with the intention of making them one pot syntheses. The 2,3,5-trimethylphenol **(28b)** was converted into formylamino-2,3,5-trimethylphenol **(270)** utilizing a slightly modified method of Smith *et al*[265] in which the phenol **(28b)** was dissolved in methanol, in the presence of excess NaOH prior to C-

coupling using diazotised sulphanilic acid. The resultant azo-compound was reductively cleaved by the action of sodium hydrosulphite to produce the aminophenol (**269**). Smith *et al*[265] found that this method of preparing the aminophenol (**269**) was superior to that of Claisen[266], which involved nitrosation of the phenol (**28b**) and reduction of the nitrosophenol to the aminophenol (**269**). Formylation of 4-aminophenol (**269**) resulted in the formation of the N-formylaminophenol (**270**) as outlined in **Scheme 59**.



28b **269** **270**

i) MeOH, NaOH, ii) Sulphanilic acid, $NaNO_2$, HCl, 0^oC, iii) $Na_2S_2O_4$, iv) HCO_2H, reflux.

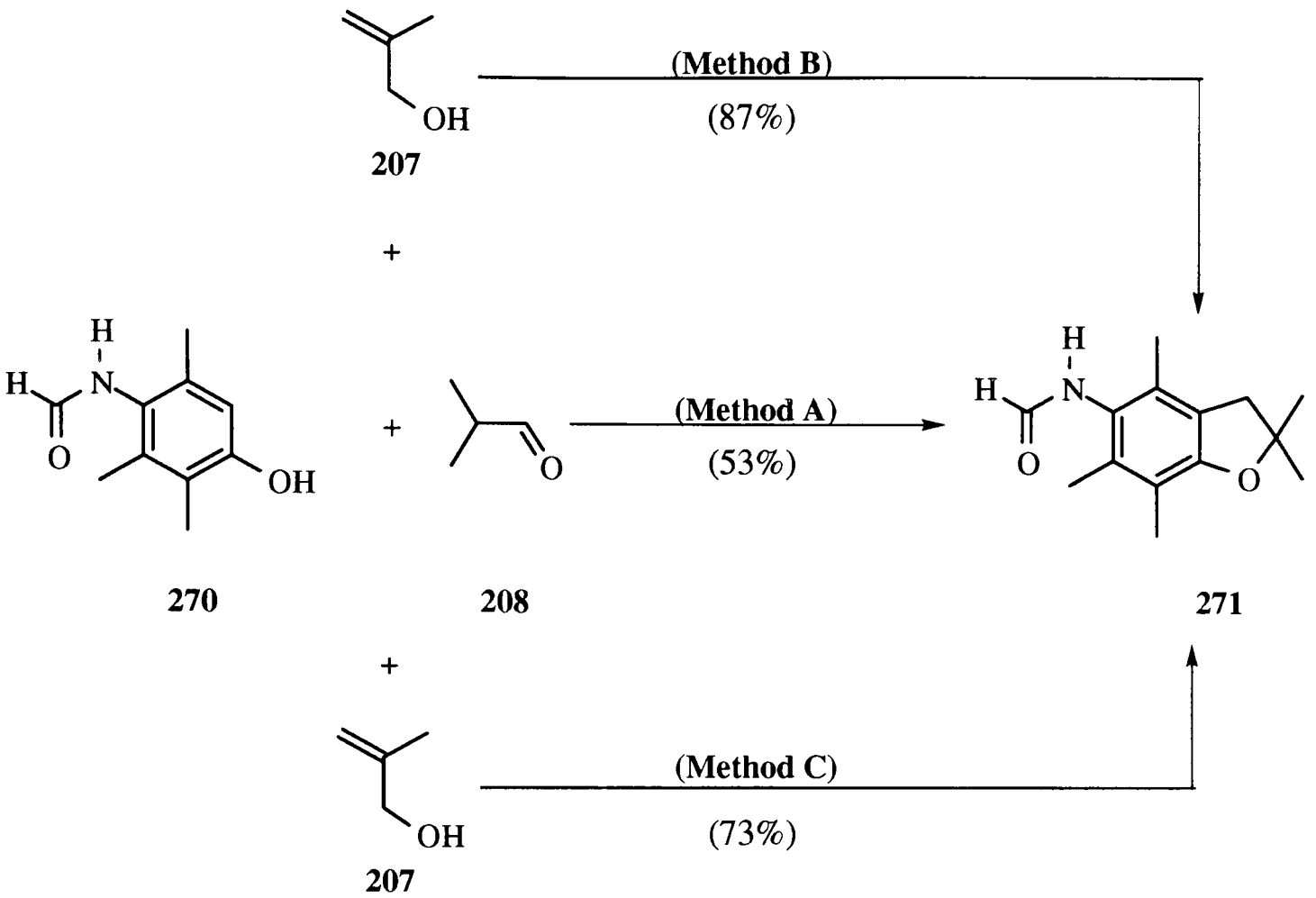
Scheme 59

Previous syntheses of 5-aminocoumaran (**260**), by Cruickshank *et al*[267], involved the methallylation of the phenol (**269**) using methallyl chloride and potassium carbonate as the base, to give the corresponding ether. Claisen rearrangement of the ether in N,N-diethylaniline or N,N-dimethylaniline afforded the C-methallylated compound. This was cyclised in methanol under acidic conditions or in the presence of magnesium chloride to afford (**260**). Deprotection of the formamide or acetamide group afforded the corresponding 5-aminocoumaran[267].

Therefore, 5-formylamino-2,3-dihydro-2,2,4,6-7-pentamethylbenzofuran (**271**) was synthesized using three different methods all involving one pot syntheses, as outlined in **Scheme 60**.

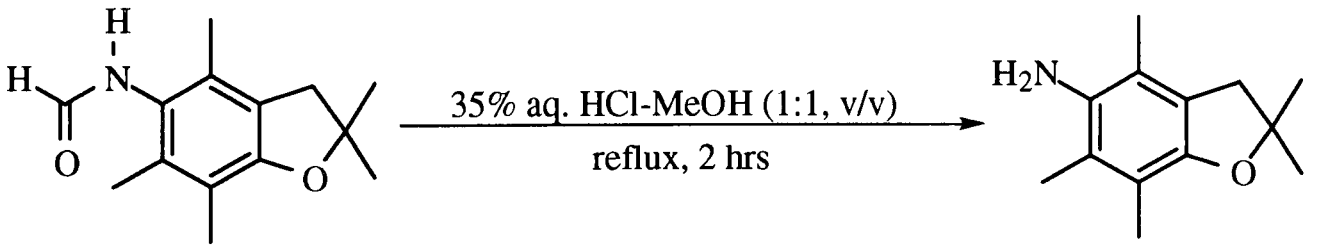
Using method A, (Martini *et al*[133]) the phenol (**270**) was reacted with isobutyraldehyde (**208**) in the presence of toluene and catalytic amounts of concentrated sulphuric acid to form the 5-formylamino-2,3-dihydro-2,2,4,6-7-pentamethylbenzofuran (**271**) in moderate yields (53%). The moderate yield can be accounted for by the limited solubility of the phenol (**28b**) in toluene: prolonged heating under reflux did not increase the yield.

Using method B (Smith *et al*[110]), the 5-formylamino-2,3-dihydro-2,2,4,6-7-pentamethylbenzofuran (**271**) was produced in high yield (87%), when anhydrous formic acid was used. However, longer reaction times 22hrs were required. Using TFA[242] (Method C) the 5-formylamino-2,3-dihydro-2,2,4,6-7-pentamethylbenzofuran (**271**) was produced in excellent yields (73%).



Scheme 60

The hydrolysis of the formyl group was accomplished by heating the formylamino compound (**271**) under reflux with methanol in acidic conditions[262], (**Scheme 61**).



271 **260**

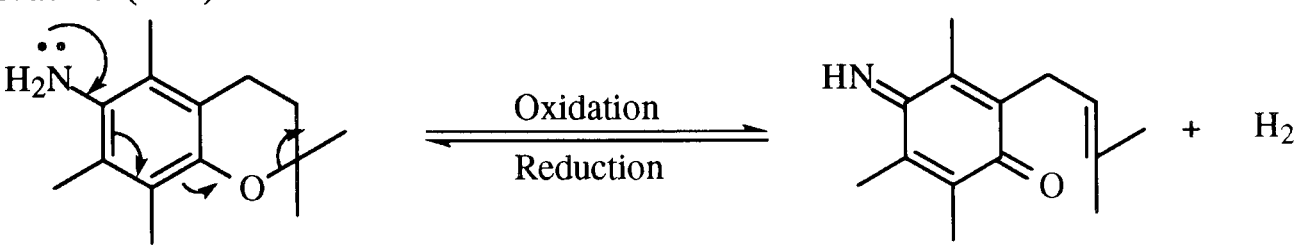
Scheme 61

Since α-tocopherol (**1**) is an oil, its conversion into a solid derivative of high biological activity would be of advantage. Solid derivatives of α-tocopherol (**1**) are limited in number, and the easiest of these to prepare are the allophanate and the 3,5-dinitrophenylurethan which unfortunately are not suitable for biological purposes[268]. The 6-amino-3,4-dihydrobenzopyran (**259**) an analogue of the model compound **82a** should form a solid salt and hence might offer a highly effective radical-trapping agent which could retard the rate of oxidative degradation of organic materials of commercial and biological importance[269] .

Thus, several one-pot syntheses of the formyl protected 6-amino-3,4-dihydrobenzopyran (**274**) were attempted (**Scheme 62**).

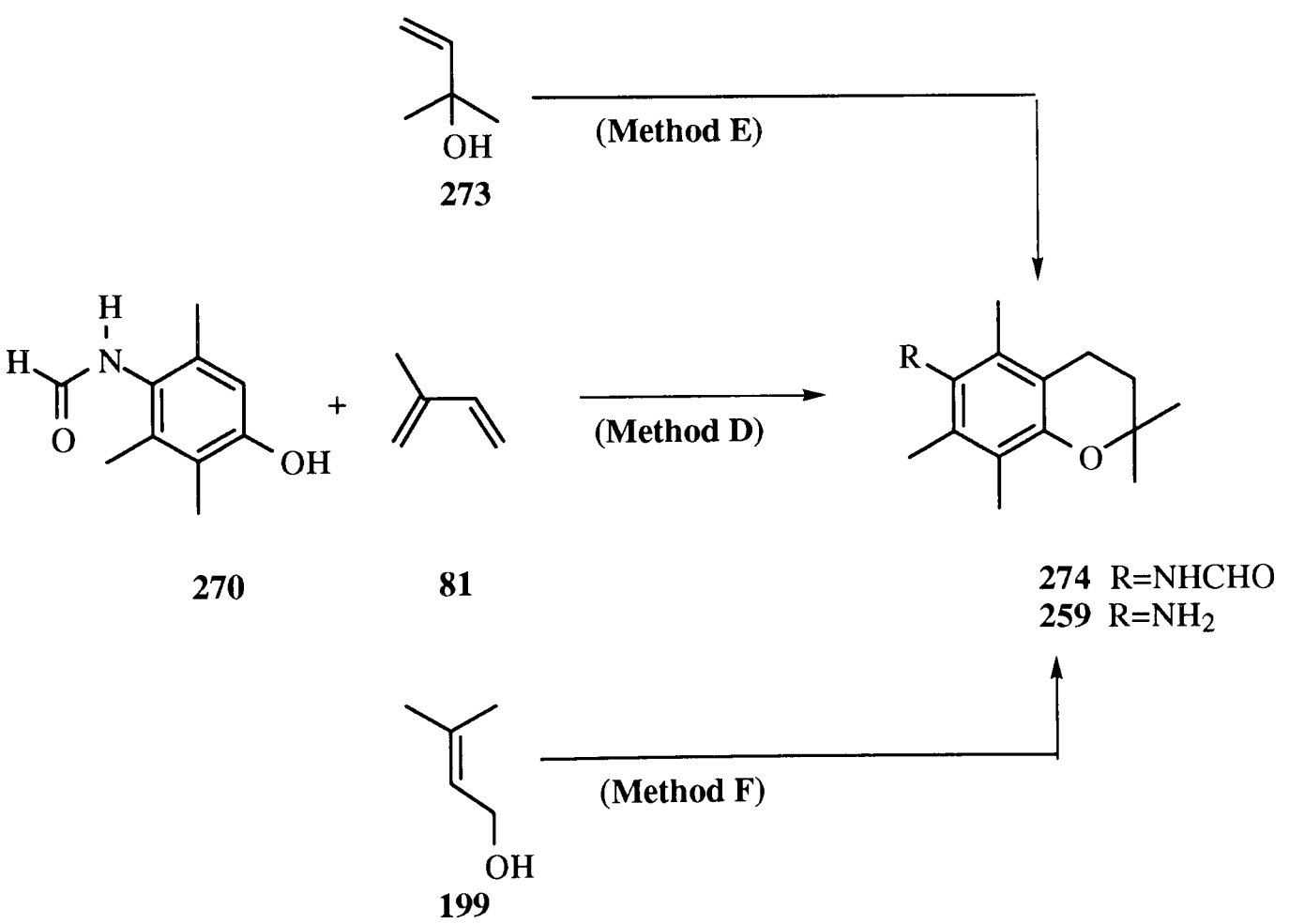
The reaction of the formyl protected aminophenol (**270**) with various allylic alcohol (**273** and **199**) and the diene (**81**) under acidic conditions gave the corresponding 6-formylamino-2,3-dihydrobenzopyran (**274**) in good yields (63, 69, and 74% respectively).

The reaction between phenol (**270**) and isoprene (**81**) under acidic conditions afforded **273** together with the deprotected amine (**259**) in low yields (17%) (**Method D**). It was thought that the amine (**259**) was susceptible to deprotection and on standing oxidised to the oxa-imine (**272**). It was therefore, converted to the more stable formyl derivative (**273**).



259 **272**

This was also observed in **Method E** where the amine (**259**) was obtained in 35% yield.



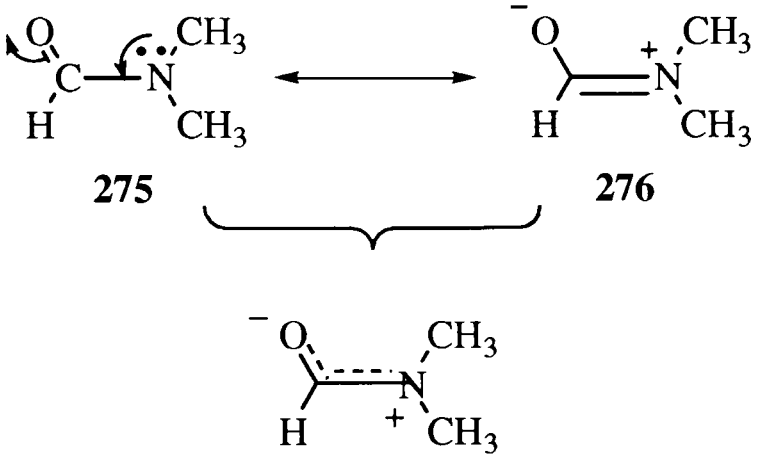
Scheme 62

However, the reaction of the formyl protected aminophenol (**270**) with the allylic alcohol (**273**) by heating under reflux in trifluoroacetic acid for 4 hours (**Method F**) afforded the desired compound (**274**).

The i.r. spectra of the substitued 5-amino-2,3-dihydrobenzofurans and the substituted 6-amino-3,4-dihydrobenzopyrans were consistent with the proposed structures. They

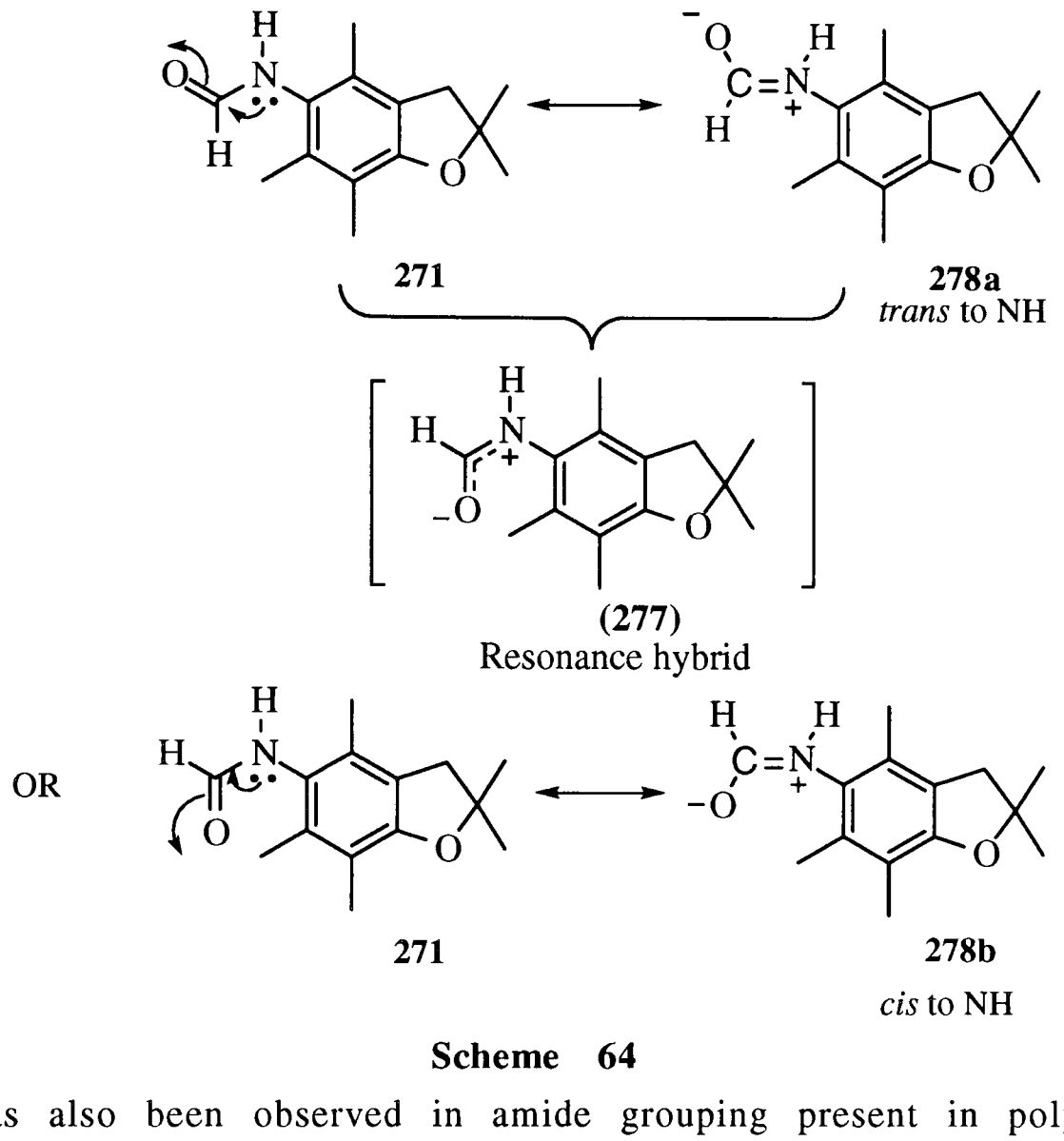
showed typical bands for N-H stretching at 3258 cm^{-1}, a sharp doublets was observed between 1696 and 1660 cm^{-1} corresponding to the amide C=O stretching and N-H bending, respectively.

The proton NMR spectra of N-formyl groups have been extensively reported[270]. The classical case is the proton NMR spectrum of dimethylformamide taken at various temperatures. At room temperature, it shows two sharp singlets at 2.84 ppm and 3.0 ppm for the N-methyl protons. Whereas, at higher temperature the two sharp singlets broaden and coalesce. This is because π-bonding between the nitrogen atom and the carbonyl carbon atom slows the rotation about this bond as shown in **Scheme 63**.



Scheme 63

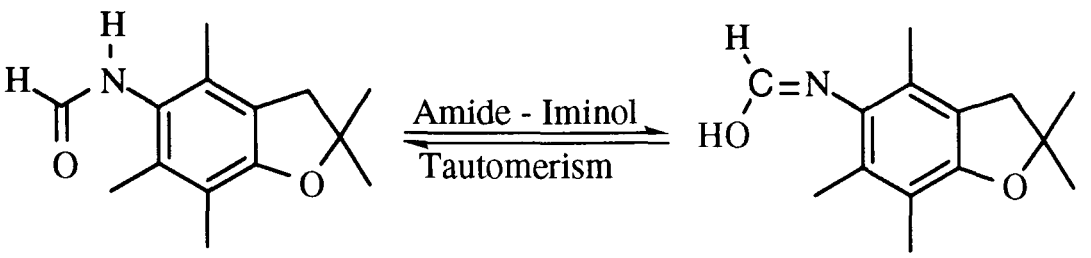
A similar effect can be observed in the proton nmr spectra of the N-monosubstituted formamide **(271)**. Due to the restricted rotation about the C-N bond caused by the partial double bond character between the nitrogen atom and the carbonyl carbon atom in the resonance hybrid **(277)**, the hydrogen on the carbon can either be cis to the NH proton **(278b)** or trans to the NH proton **(278a)**, which in turn can result in the non-equivalence of the two hydrogens on the C-N atoms, producing four deshielding hydrogens (doublets) in a different chemical environment, as shown in **Scheme 64**[270].



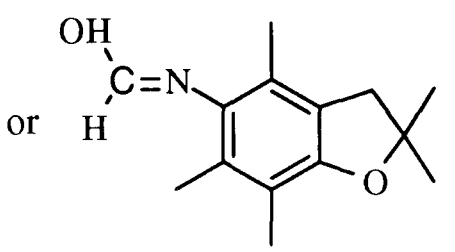
Scheme 64

This has also been observed in amide grouping present in polypeptide macromolecules[271], where almost invariably the -C=O and -N-H bonds are parallel or nearly parallel and so, there is little twisting about the C-N bond. The atoms O, C, N and H are reported to be nearly coplanar because the peptide bond has substantial fraction of double bond character.

Alternatively, Potapov *et al*[272] have shown that amides (including monosubstituted amides) can also exihibit tautomerism. For example, the N-monosubstituted amide **(271b)** can undergo tautomerism to give its iminol form **(279a)** or **(279b)** which in turn can also result in the non-equivalence of the two hydrogens on the C-N atoms, producing four deshielding hydrogens (doublets) in a different chemical environment **(Scheme 65)**.



271b **279a**

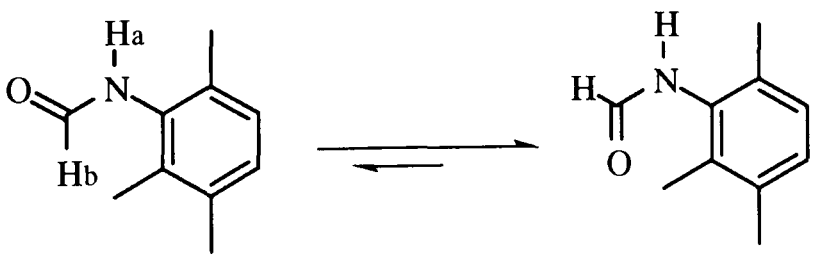


279b

Scheme 65

From the proton NMR of **(271)** two sets of geminal dimethyl groups and methylene protons were observed around 1.46-148 ppm and 2.93-2.94 ppm, respectively. The N-formyl group showed a very broad singlet resonating at around 6.83 ppm (N-H, D_2O exhangeable (no coupling observed), a broad doublet resonating at around 6.89-6.94 ppm (N-H, $^3J_{H-H}$=12.5 Hz, D_2O ecxhangeable), a sharp doublet between 7.94-7.99 ppm (CHO, $^3J_{H-H}$=12.5 Hz) and a very sharp doublet around 8.39-8.40 ppm (CHO, $^3J_{H-H}$=1.6 Hz). The latter two doublets, on the addition of deuterium oxide showed two singlets. This indicated that two compounds were present in the proton NMR spectrum, in the ratio of 1 : 1 (by evaluating the integral steps of the ^1H NMR spectrum).

In N-monosubstituted amides, the *trans* conformer **(280b)** has been shown to be strongly preferred over the *cis* conformer **(280a)**[273]. It is noteworthy, however, that even the bulky phenyl group strongly prefers to be *cis* to the carbonyl group **(280a)** rather than to the much less sterically demanding hydrogen as in **(280b)**, **(Scheme 66)**.



280b **280a**

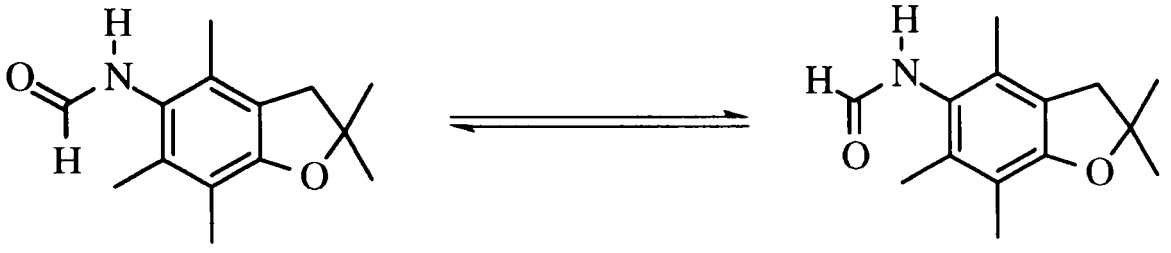
(10%) (90%)

$^3J_{H-H}$ = 11.0 Hz $^3J_{H-H}$ = 2.0 Hz

Scheme 66

The proton H_b has been quoted to resonate between 8.2 ppm and 8.7 ppm while the proton H_a can resonate between 7.5 ppm and 9.5 ppm[274].

If the amide **(271)** was to exhibit tautomerism, from the proton nmr spectrum, the conjugated iminol form (**279a** or **279b**) would be strongly favoured over the non-conjugated form **(271)** to give a 2:1 or 3:1, or whatever, ratio but not 1:1 ratio. So, it is unlikely that the amide-iminol tautomerism would be favoured in this case. The only other possibilty would be the *cis* and *trans* conformation (**Scheme 67**), even though the *trans* conformation **(271a)** as discussed earlier, would be favoured over the *cis* conformation **(271b)**. It is possible that the bulky 2,3-dihydrobenzofuran substituent on the N-formyl group may force the *cis* conformer **(271b)** to exist in equilibrium with the trans conformer **(271a)**, in 1:1 ratio (see **Appendix** for spectrum).

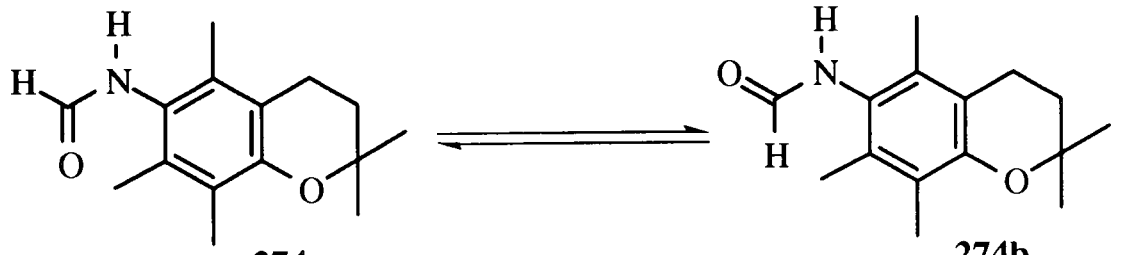


271a (50%) $^3J_{H-H}$ = 12.5 Hz

271b (50%) $^3J_{H-H}$ = 1.6 Hz

Scheme 67

The ^{1}H nmr spectrum of **274** was consistent with the proposed structure and also showed the presence of the cis conformer **(274a)** and trans conformer **(274b)** in 1:1 ratio **(Scheme 68)**.

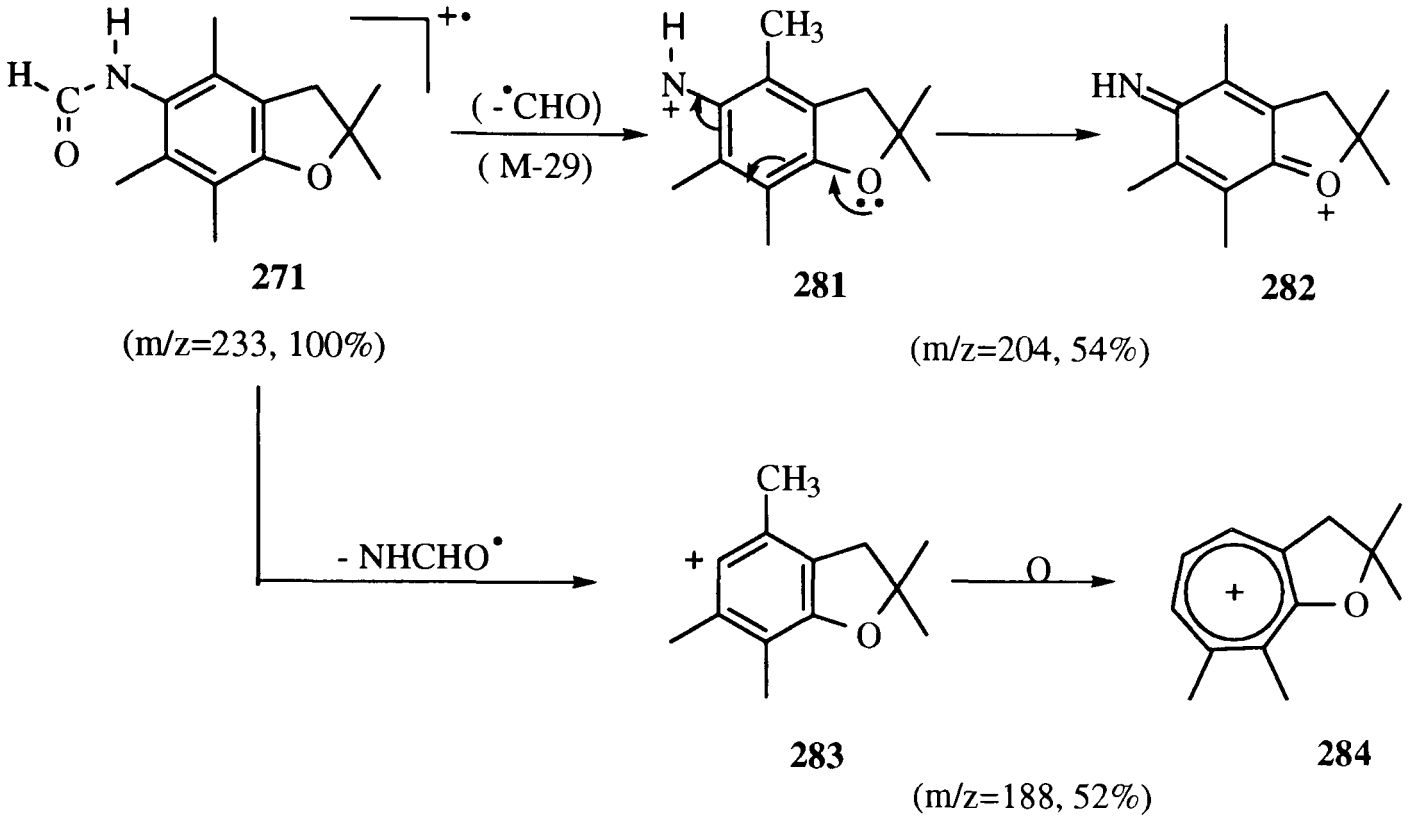


274a *cis*

274b *trans*

Scheme 68

Mass spectral analysis of 5-formylamino-2,3-dihydrobenzofuran **(271)** was consistent with its proposed structure. The mass fragmentation pattern is proposed in **Scheme 69.** Initially, CNO cleavage of the molecular ion **(271)** leads to the formation of **281** which could be resonance stabilised (the oxonium ion, **(282)**). The loss of the formylated amino group from **(271)** leads to the cation **(283)**, which on rearrangement forms the stable tropylium ion **(284)**.

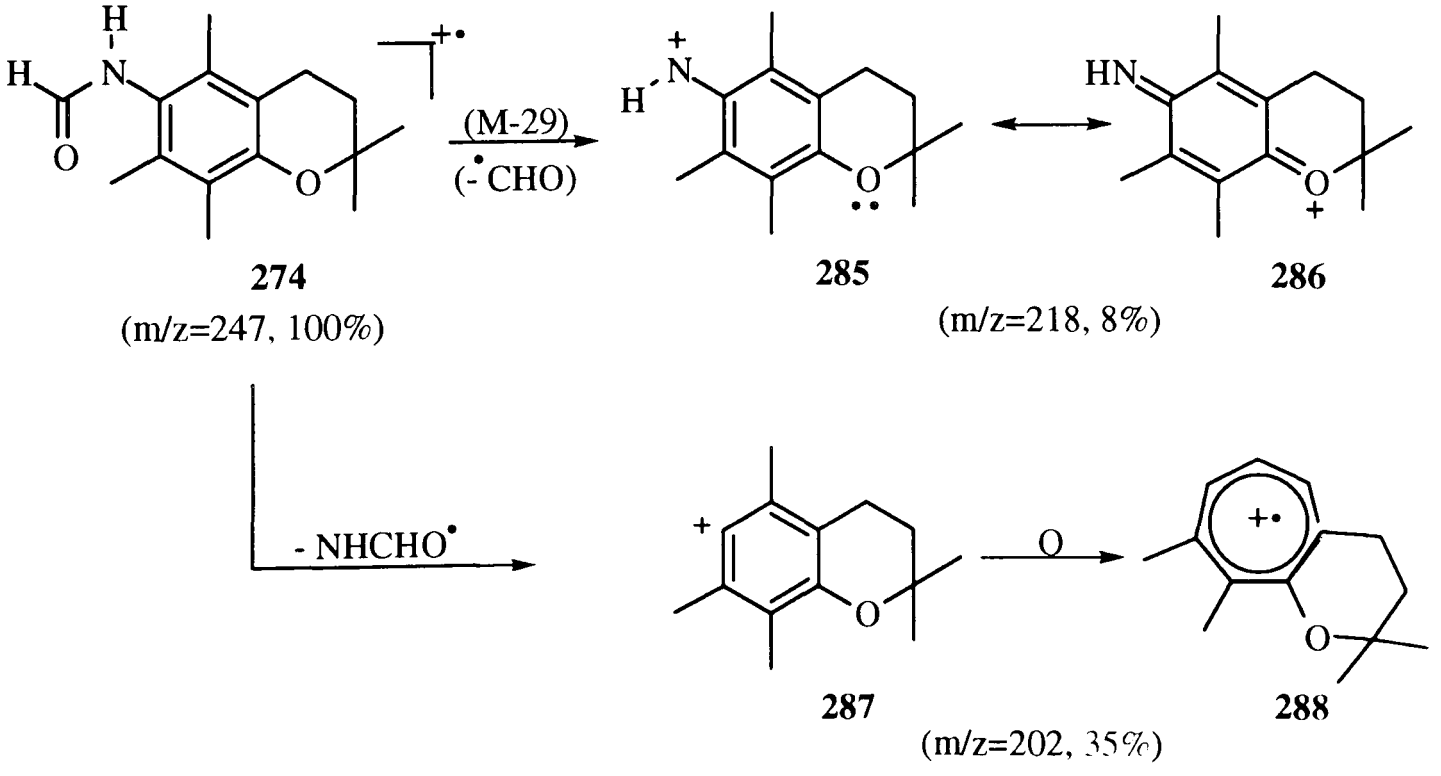


Scheme 69

The mass spectrum for compound **274** was consistent with its proposed structure. Several possible mass fragmentations are outlined in **Schemes 70** and **71**.

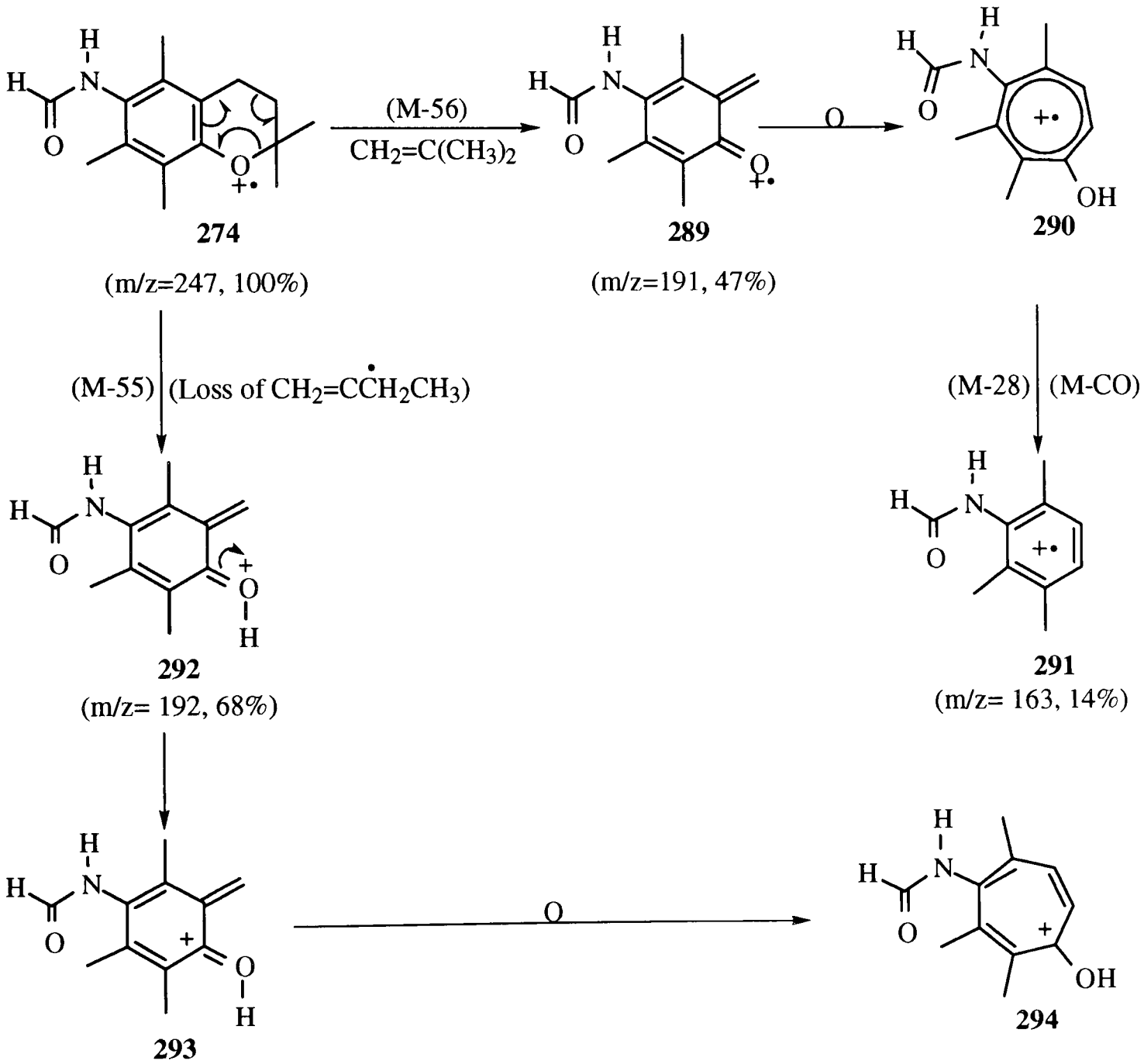
Firstly, the mass fragmentation pattern for **274** shows that a loss of a formyl radical (•CHO) could lead to the formation of cation **(285)** which could be resonance stabilised (the oxonium ion, **286**).

Secondly, direct loss of the N-formylated amino group from the molecular ion **(274)** could afford cation **(287)** which on rearrangement could give tropylium ion **(288)**, as outlined in **Scheme 70**.



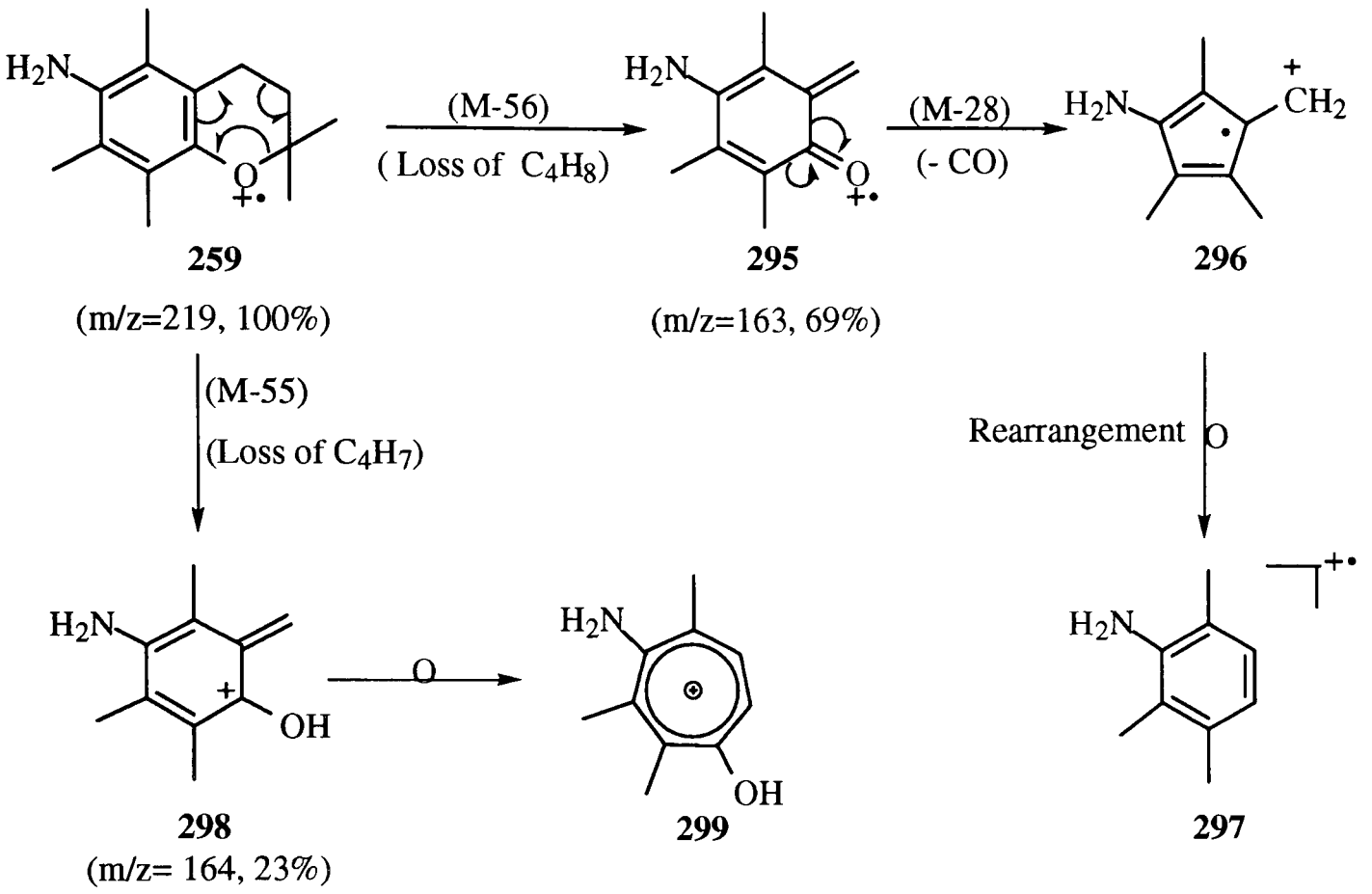
Scheme 70

A third possiblity is the fragmentation shown in **Scheme 71**, could result from the loss of an alkene from the molecular ion **(274)** via a retro-Diels-Alder fragmentation (without hydrogen abstraction) to give the oxonium **(289)** which on rearrangement gives the tropylium ion **(290)**. Expulsion of carbon monoxide results in the formation of **291**. Fourthly, a retro Diels-Alder with H-abstraction could form the oxonium ion **(292)** which could on form the cation **293**. Rearrangement of **293** leads to the formation of the tropylium ion **(294)**.



Scheme 71

The mass fragmentation pattern of amine **259** was consistent with its proposed structure and is outlined in **Scheme 72**. A retro-Diels-Alder fragmentaion of **259** (without H-abstraction) leads to the formation of **295**. Expulsion of carbon monoxide from **295** via **296** leads to the stable aromatic ring containing ion **(297)**. Alternatively, a retro-Diels-Alder (with H-abstraction) leads to the cation **(298)** which on rearrangment forms the tropylium ion **(299)**.

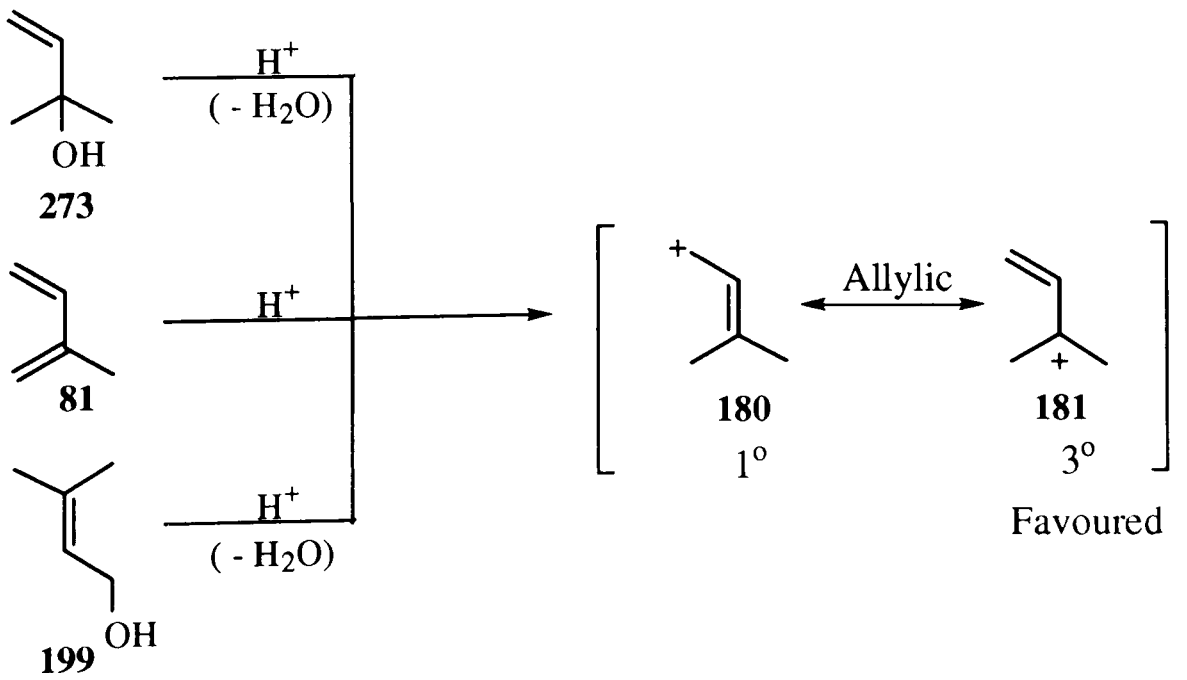


Scheme 72

In summary, the spectral data for the monosubstituted formamide **(271)**, **(274)** and **(259)** is consistent with the proposed structures.

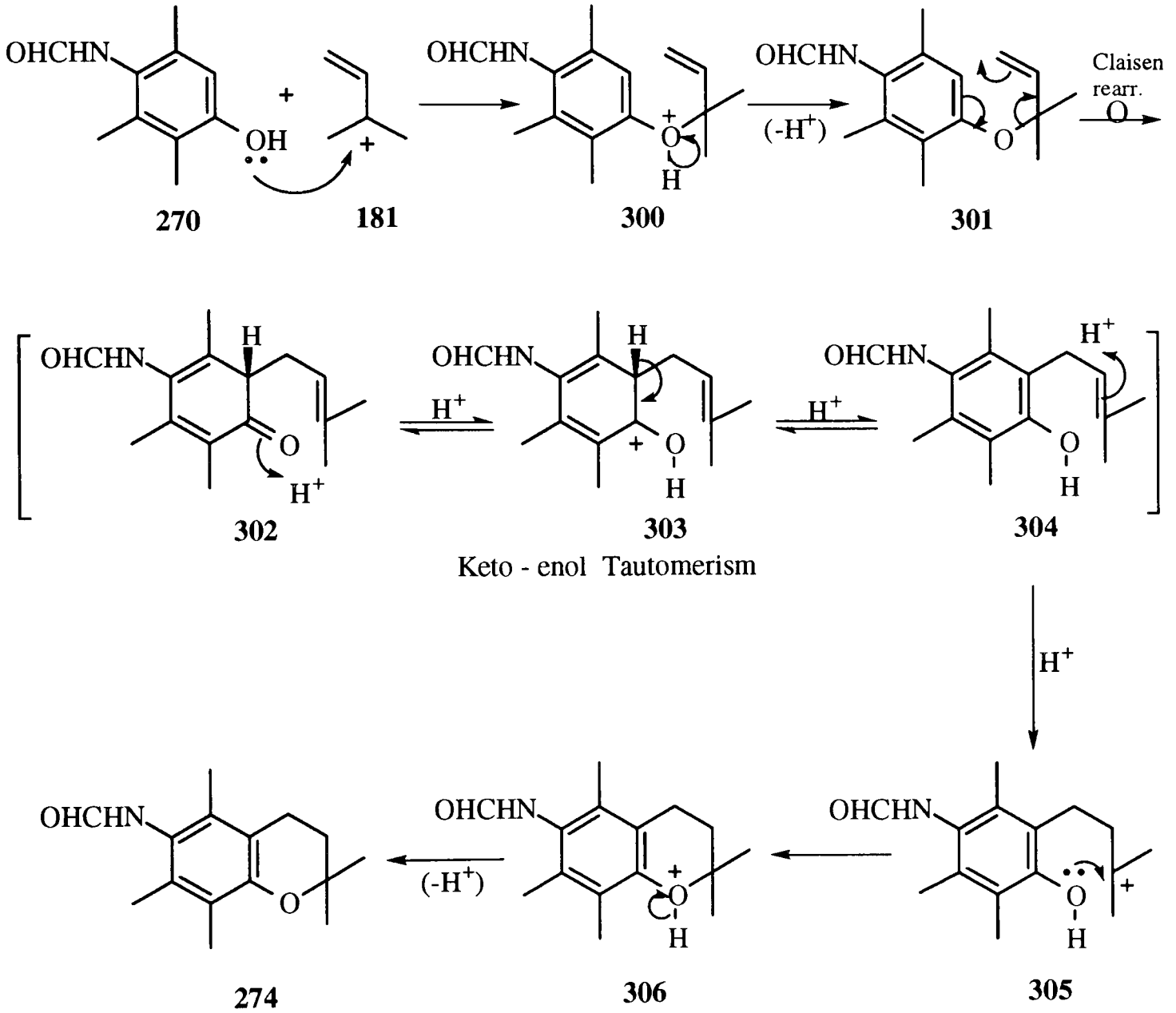
2.13 Mechanism of formation of 6-Formylamino-3,4-dihydrobenzopyran (274)

The tertiary carbocation **(181)** which could be resonance stabilised by the primary carbocation **(180)**, was generated from the allylic alcohols **(273**and **199)**, under acidic conditions with the elimination of water or via protonation of the diene **(81)**, as outlined in **Scheme 73**.



Scheme 73

The reaction steps involved the initial formation of the corresponding methallyl ether **(300)**, deprotonation of **300** affords **301.** Claisen rearrangement to the ketone **302** which tautomerises to its enol form **(304)** (a three step process **302-304**), Protonation of the the alkenic double bond in **(304)** affords the tertiary cation **(305)** and finally cyclisation to the desired compound **274** via protonation of **(306)**. Similar mechanisms **(Scheme 74)** are proposed to apply in all the related syntheses.



270 181 300 301

302 303 304

Keto - enol Tautomerism

274 306 305

Scheme 74

In conclusion, 5-formylamino-2,3-dihydrobenzofurans have been synthesized using several different methods, in one pot syntheses. The method of Martini *et al*[133] gave moderate yields (53%) where toluene was used as the solvent and concentrated sulphuric acid was the acid catalyst. The method of Smith *et al*[110] provided good yields (87%) however, longer reaction times were required (22 hrs). The method involving TFA[242] also gave good yields (73%) with shorter reaction times (4hrs). The advantage of this method was that trifluoroacetic acid (TFA) acted as both the solvent and as the catalyst in the reaction.

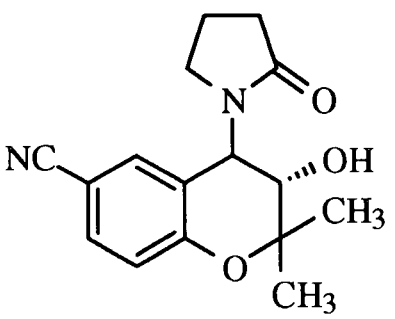
A similar methodology was employed in the syntheses of 6-formylamino-3,4-dihydrobenzopyrans using N-formylaminophenol which was condensed with the

appropriate allylic alcohols and diene using a number of acidic catalysts. All the methodologies used produced good yields of the desired compound. However, in some cases this resulted in the deprotection of the formyl grouping to yield the 6-amino-3,4-dihydrobenzopyrans (35%).

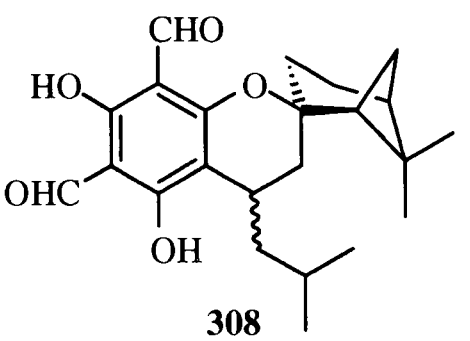
The 5-formylamino-2,3-dihydrobenzofurans and 6-formylamino-3,4-dihydrobenzopyrans exhibited *cis-trans* isomerism. This was evident from the proton NMR spectra.

2.14 Syntheses of substituted 3,4-Dihydro-2,2,4-trimethylbenzopyrans (309)

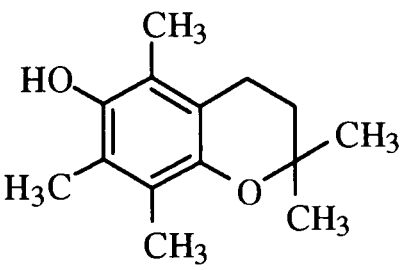
3,4-Dihydrobenzopyrans containing substituents at the C-4 position (of which chromakalin **(307)** is an example), along with many other analogues have been shown to be potassium channel activators or openers[275-277]. This class of compounds has attracted considerable attention because of the evidence for their potential in the treatment of those disorders in which smoothe muscles contraction is involved. Besides providing active antihypertensive agents, it has been established that potassium channel activators have potential for use in the treatment of bronchial asthma, and certain analogues have been shown to be potent relaxants of guinea pig trachealis *in vitro*[278]. Also, compounds like Robustadial A **(308)** which contain the 3,4-dihydrobenzopyran moiety have been shown to be effective in the treatment of malaria[279].



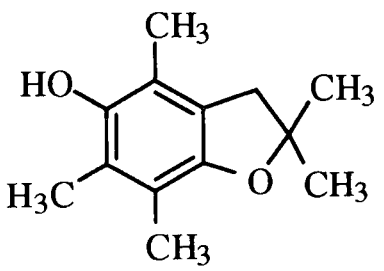
307



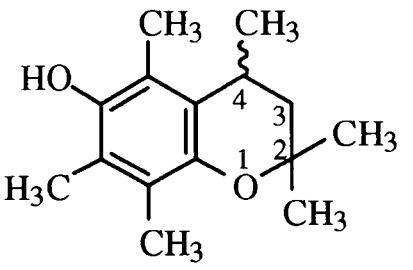
308



82a



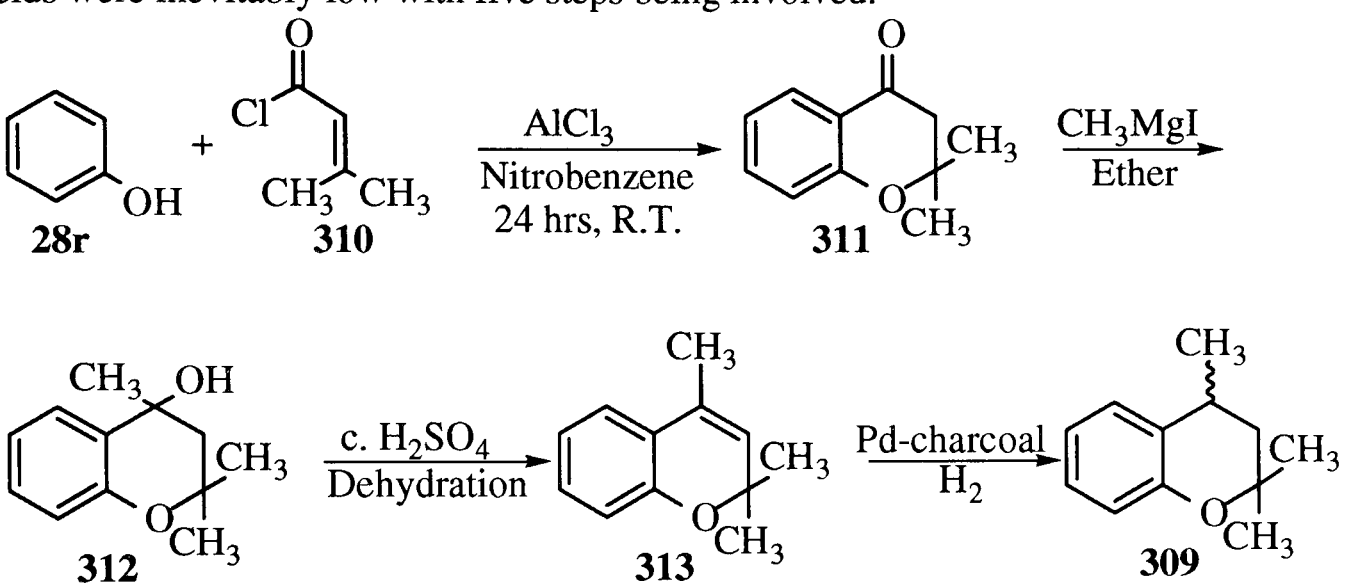
124a



309a

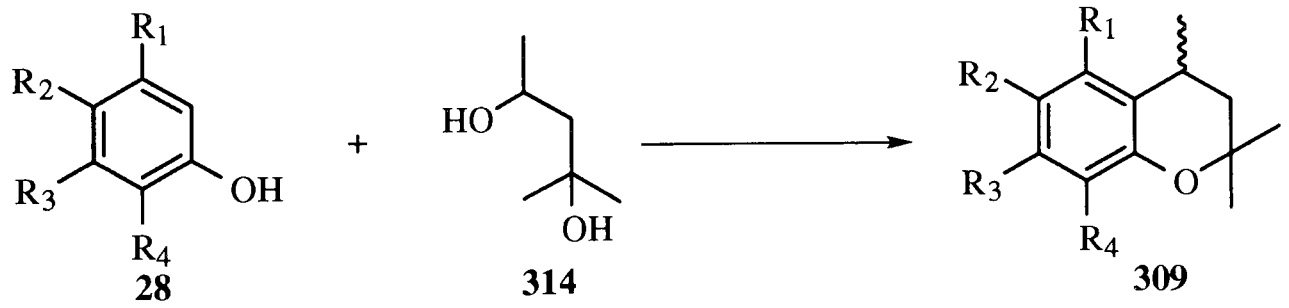
Secondly, 3,4-dihydrobenzopyran **(82a)** and 2,3-dihydrobenzofuran **(124a)** have been shown to be efficient inhibitors of lipid peroxidation *in vivo*[57]. The latter **(124a)** is known to be a superior antioxidant to **82a**[225]. With this in mind it was decided to investigate the further possibility of enhancing the antioxidant activity of **82a** by introducing a methyl group at the 4-position. This should cause the ring to exert a stereoelectronic effect by constraining the ring oxygen in such a manner that its p-orbital lone pair is better able to stabilize the developing phenoxyl radical and hence, make it a

better antioxidant. Earlier syntheses by Bridge *et al*[143] and later by Baker *et al*[280] of 3,4-dihydro-2, 2, 4-trimethylbenzopyrans involved the condensation of phenol (**28r**) with 3,3-dimethylacryloyl chloride (**310**) to afford the chromanone (**311**). On reaction with Grignard reagents these afforded the alcohol (**312**), subsequent dehydration of which gave **223**, which in turn gave the desired compound **309** (**Scheme 75**). The overall yields were inevitably low with five steps being involved.



Scheme 75

The 3,4-dihydro-2,2,4-trimethylbenzopyrans (**309**) were synthesised in a one-pot synthesis by reacting the appropriate phenol (**28**) with 2-methyl-2,4-pentanediol (**314**) in the presence of a 1:3 mixture of concentrated sulphuric and concentrated acetic acid at room temperature or at reflux temperature, using the method of Ryu *et al*[241] , (**Scheme 76**). The results are summarized in **Table 16** (on p.97 and p.98).



Scheme 76

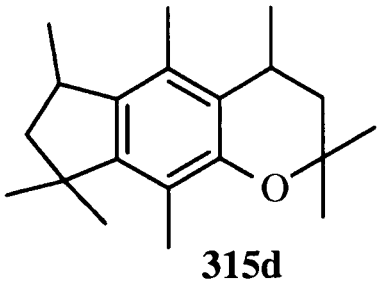
309	R_1	R_2	R_3	R_4	Yield (%)
a	CH_3	OH	CH_3	CH_3	23
b	CH_3	H	CH_3	CH_3	31
c	H	CH_3	CH_3	H	39
d	CH_3	H	H	CH_3	34

e	CH_3	H	CH_3	H	39
f	H	Cl	CH_3	H	40
g	H	H	CH_3	CH_3	42
i	H	H	CH_3	CH_3	9
j	H	CH_3	H	H	5
k	H	OCH_3	H	H	18
l	H	Br	H	H	7
m	OH	H	OH	OH	4
n	CH_3	NO_2	CH_3	CH_3	74

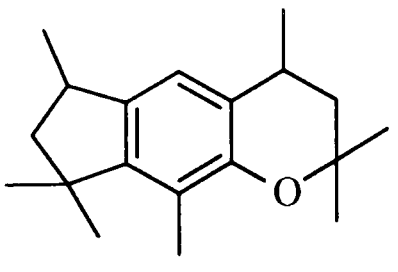
Table 16: [b] = observed in GC-MS analysis only .

Compound **309n** was obtained by nitration of **309b** using concentrated nitric acid in acetic acid at 0°C[281].

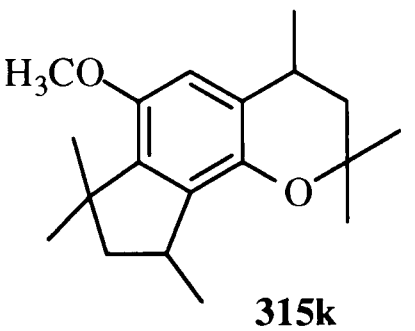
Compounds **309a**, **309b** and **309f** gave moderate yields. On several occasions **309d**, **309g**, **309h**, and **309k** were reacted further with **314** via acid promoted cyclisation to afford the novel **315d**, **315g**, **315h**, and **315k**, in moderate to good yield (see page 95). The additional hydroxyl group available at the 6-position in **309m** reacted further with **314** to afford the double chroman **316m**.



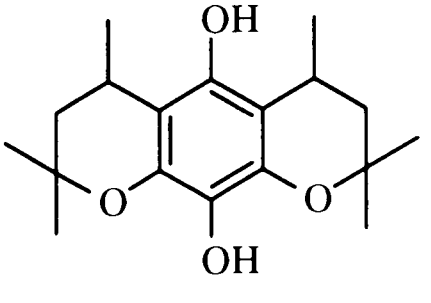
315d



315h



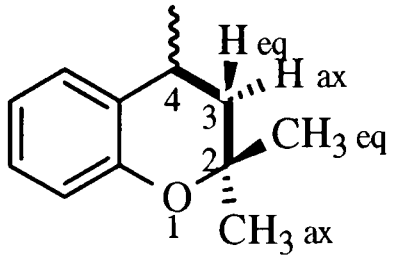
315k



316m

Their ir spectra were consistent with their proposed structures, showing several bands at 2970-2840 cm^{-1} corresponding to the aliphatic C-H stretch, bands around 1600-1578cm^{-1} corresponding to the C=C benzene ring stretching, and around 1250 cm^{-1} corresponding to the C-O stretch of the ether linkage. Their nmr spectra showed that the geminal methyls at C-2, and the geminal hydrogens at C-3 were magnetically non-equivalent. This non-equivalence has also reported by Nowakowska *et al*[282] who stated that its was due to the heterocyclic ring in **309** being non-planar. The geminal coupling constants of approximately 13 Hz, and the ^3J vicinal coupling constants of 6.6 Hz are entirely consistent with the structures for **309a-309m**. Nowakowska *et al*[282] stated that in the unsubstituted compound **309** (where R_1-R_4=H) only one proton gave a doublet; coupling of the second proton was not observed. Both of the methylene protons on carbon-3 axial appeared as doublet of doublet for compounds **309a**, **b**, **d**, **e**, **g** and **m**. The carbon at C-4 in **309a-m** shows a doublet at around 26.4 ppm. The proton chemical shifts for compounds **(309a-m)** are documented in **Table 17** below.

A study performed by Milstein and Cohen[283,284] on the rate of lactonization of o-hydroxyhydrocinnamic acid and its methyl derivatives have shown that the substitution of hydrogen by groups such as CH_3 on the ring or the side chain of the o-hydroxyhydrocinnamic acid has conformationally restricted the molecule ('trialkyl lock') such that it promoted rapid lactonization. However, it is proposed that the groups on C-2, C-3 and C-4 interlock in such a way that it conformationally restricts the molecules (trialkyl locks) such as in **309a-m** (nmr evidence). As a result the methylene protons on C-3 and the methyl groups on C-2- $(CH_3)_2$ are chemically non-equivalent.



309

309	C-2-CH_{3ax}	C-2-CH_{3eq}	C-3-H_{ax}	C-3-H_{eq}	C-4-CH_3	C-4-**H**
a	1.15 (s)	1.41 (s)	1.67-1.75 (dd)	1.95-2.03 (dd)	1.24-1.27 (d)	2.97-3.11 (m)
b	1.18 (s)	1.42 (s)	1.67-1.74 (dd)	1.94-2.02 (dd)	1.30-1.27 (d)	2.95-3.09 (m)
c	1.22 (s)	1.38 (s)	1.47-1.56 (t)	1.76-1.84 (dd)	1.28-1.31 (d)	2.80-2.95 (m)
d	1.33 (s)	1.42 (s)	1.58-1.65 (dd)	1.90-2.00 (dd)	1.22-1.25 (d)	3.16-3.20 (m)

e	1.22 (s)	1.39 (s)	1.67-1.75 (dd)	1.92-2.04 (dd)	1.29-1.31 (dd)	2.92-3.06 (m)
f	1.21 (s)	1.39 (s)	1.43-1.53 (t)	1.77-1.85 (dd)	1.28-1.30 (d)	2.80-2.96 (m)
g	1.22 (s)	1.38 (s)	1.63-1.72 (dd)	1.95-2.03 (dd)	1.28-1.31 (d)	2.92-3.06 (m)
i	1.24 (s)	1.39 (s)	1.46-1.56 (t)	1.78-1.86 (dd)	1.29-1.32 (d)	2.83-2.98 (m)
j	1.23 (s)	1.39 (s)	1.47-1.57 (t)	1.78-1.86 (dd)	1.30-1.33 (d)	2.88-2.93 (m)
k	1.22 (s)	1.38 (s)	1.45-1.52 (t)	1.77-1.84 (dd)	1.27-1.31 (d)	2.82-2.97 (m)
l	1.22 (s)	1.39 (s)	1.50-1.56 (t)	1.77-1.87 (dd)	1.29-1.32 (d)	2.83-2.99 (m)
m	1.18 (s)	1.43 (s)	1.70-1.78 (dd)	1.96-2.01 (dd)	1.26-1.29 (d)	2.99-3.12 (m)

Table 17

Equatorial and axial hydrogens on the same carbon (e.g. Carbon-3) of a conformationally locked six-membered ring constitute an AMX system, depending on the nature of the substituent on the adjacent carbon[285]. This is evident from columns 4 and 5 of **Table 17**, where, typically, the equatorial H is dehsielded relative to the axial H by about 0.1 - 0.7 ppm[285]. In **309m** and **309n** these protons are deshielded, relative to those in the other molecule, due to the presence of the strongly electron-withdrawing nitro group on the aromatic ring.

The ^{13}C spectra of **309a-309m** are consistent with the proposed structures and are listed in **Table 18.**

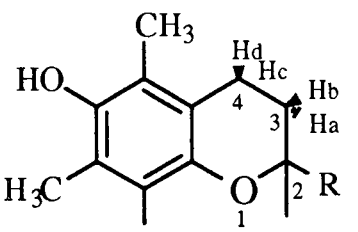
309	C-2	C-2-$CH_{3(ax)}$	C-2-CH_3 (eq)	C-3-CH_2	C-4-CH_3	C-4-H
a	73.72	26.10	29.73	43.76	22.10	26.70
b	73.95	26.73	29.57	43.43	21.71	26.33
c	73.92	24.37	30.07	42.96	20.38	25.97
d	73.68	29.34	29.81	51.82	10.94	35.41
e	73.68	26.34	29.05	43.54	20.81	25.97
f	74.55	24.37	29.94	42.38	20.21	26.08
g	73.66	28.36	29.05	43.56	21.65	25.87
i	74.32	29.74	30.11	42.89	19.17	26.06

j	74.28	24.40	30.05	42.83	20.31	26.29
k	73.92	30.05	30.05	42.76	20.41	26.70
l	74.65	24.40	29.87	42.20	18.46	26.35
m	73.37	26.53	29.34	43.19	21.69	26.58

Table 18

The quaternary sp^3 carbon (C-2) is bonded directly to oxygen, and hence is strongly deshielded, with a chemical shift of 73ppm. This has also been observed by Nowakowska *et al*[282] in other chromans. The *gem*-dimethyl groups on C-2 are axial and equatorial, therefore magnetically non-equivalent, and therefore resonate at two different positions, as shown (24.37 to 30.05 ppm) in **Table 18**. The methyl carbon on C_4 resonates at around 20 ppm, while the carbon-4 resonates at around 26 ppm, respectively.

It is possible to predict the conformations of chromans from the coupling constant of the C_3 and C_4 protons. Ekiel *et al* [286] have found that in α-tocopherol **(1)** and its model compound **(82a)** all four vicinal coupling constants for the protons on carbon 3 and 4 are similar.



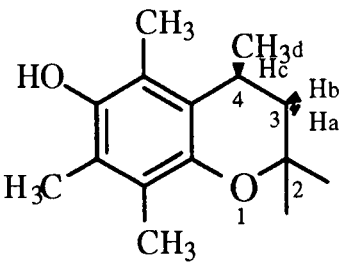
1, R=Phytyl
82a, R=CH_3

They suggested that this would exclude the possibility of a single conformation (planar, half-chair or half-boat forms), since eclipsed or antiperiplanar protons would lead to high values for some of the coupling constants, while the coupling for the gauche protons would be low. Therefore, very similar values for the coupling constants as shown in **Table 19** would indicate that approximately equal populations of two interconverting conformers are present.

Compd	Coupling Constant (*J*) Hz					
	$^3J_{ac}$	$^3J_{ad}$	$^3J_{bc}$	$^3J_{bd}$	$^3J_{cd}$	$^2J_{ab}$
1	6.9	6.9	7.1	7.1	-	-
82a	6.9	6.9	6.9	6.9	-	-
309	6.89	-	7.65	-	6.98	13.67

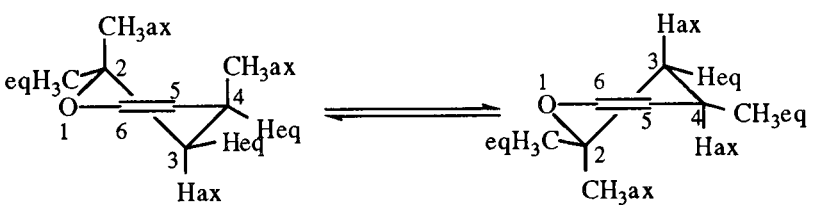
Table 19

This would imply that the two half-boat states interconvert or the two half-chairs interconvert. The latter would seem more probable since half-chair conformations have been found for **(82a)** in the solid state. Also, half-chair conformers have been found to be the most stable forms in cyclohexenes by Eliel *et al*[287], since cyclohexene has some resemblance to the structure of the chroman in **(309)**. Therefore by analogy this would be observed in the 4-substitued chromans **(309)**, since all the vicinal coupling constants have almost similar values **(see Table 19)**. This has also been seen in 4-substituted flavans[204].



309

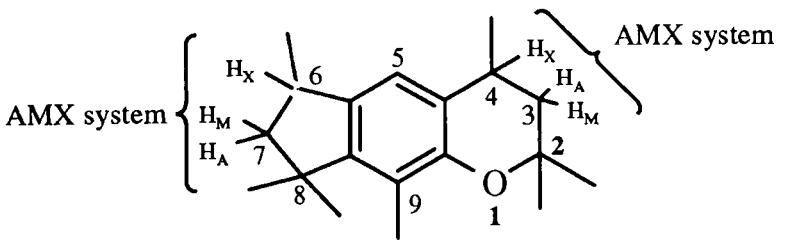
Therefore the two half-chair conformers (**A** and **B**) are possible for the 4-methyl substitued chromans **(309a-m)** as shown below.



A **B**

where 5 and 6 are fused to benzene ring

The formation of the products with the additional fused 5-membered rings (**315d, 315h** and **315k**) was confirmed by nmr spectroscopic analysis. Compound **315h** is used as a representative sample for this trio.



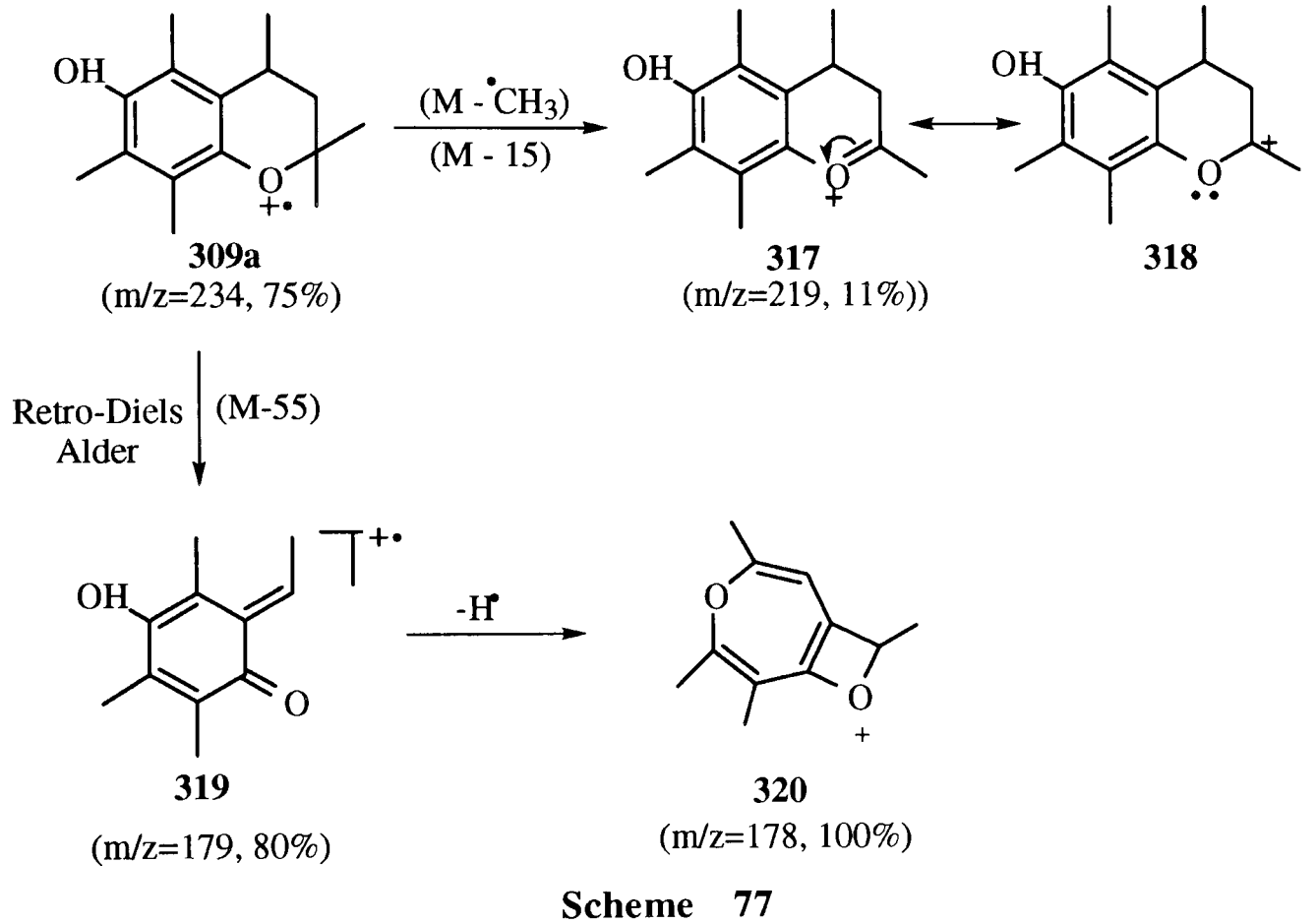
315h

The proton nmr spectrum of **315h** showed signals for the two sets of *gem*-dimethyl groups at 1.23 ppm and 1.27 ppm, and 1.31 ppm and 1.35 ppm. The protons on C-3 and C-7 are chemically non-equivalent and with the protons on C_4 and C_6 formed two AMX systems, with two sets of doublets of doublets each. The methyl protons on C4 and C6 gave rise two set of doublets for the methyl groups at 1.39 ppm and 1.41 ppm, respectively. The protons on C_4 and C_6 each appeared as sextets which resonated at 2.85-2.95 ppm and 3.01-3.11 ppm, respectively. The aromatic proton on C_5 gave rise to

a singlet and resonated at 6.85 ppm. All of the assignments were consistent with the proposed structure (see **Appendix** for spectrum).

Similar patterns were observed for **315d**, **315h** and **315k**, again they were consistent with their proposed structures.

The mass spectra of **309a-m** were consistent with the proposed structures and a fragmentation pattern for **309a** is outlined in **Scheme 77**.



309a (m/z=234, 75%) — **317** (m/z=219, 11%)) — **318**

319 (m/z=179, 80%) — **320** (m/z=178, 100%)

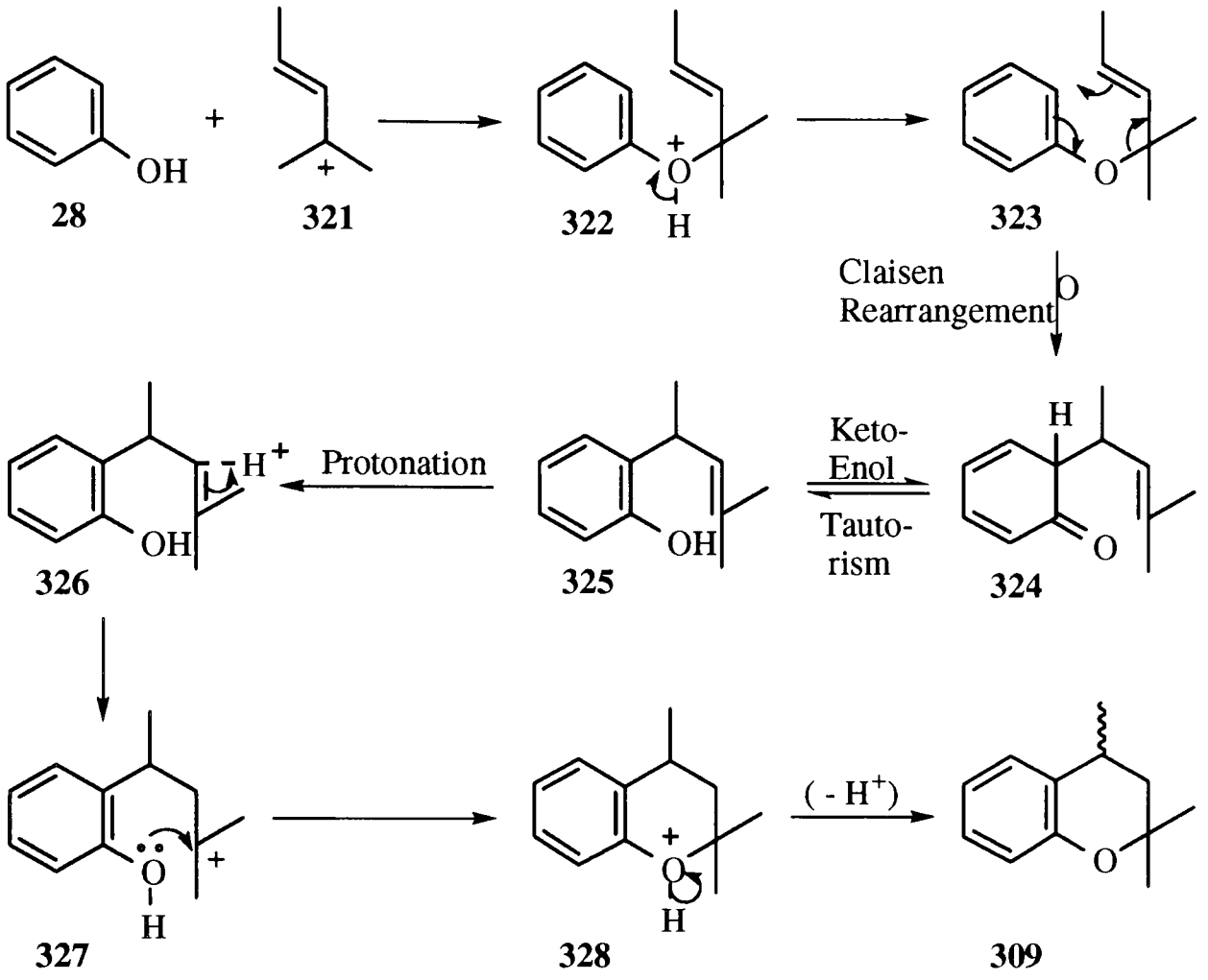
Scheme 77

Loss of a methyl radical from the molecular ion leads to the formation of the resonance stablised oxonium ion **(317)**.

Alternatively, a retro-Diels Alder fragmentation leads to the formation of the conjugated phenol **(319)** which upon loss of a hydrogen radical atom forms the oxatropylium ion **(320)**.

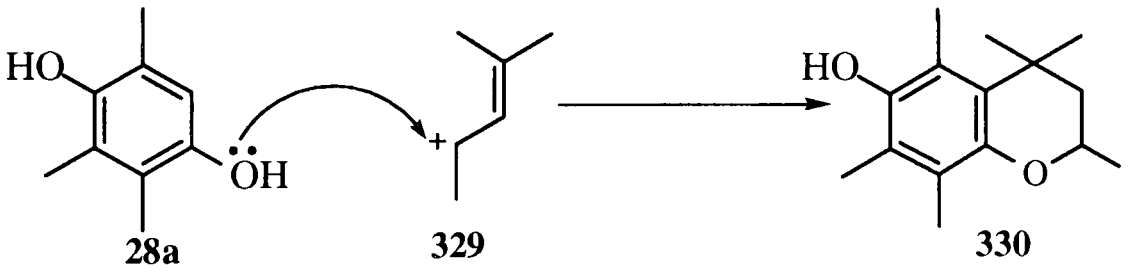
2.15 Mechanism of Formation of 3,4-Dihydro-2,2,4-trimethylbenzopyran (309)

The stable carbocation **321** would attack the phenol **(28)** to form the oxy-cation **322** which, with deprotonation, leads to the aryl ether **323**. This is followed by [3,3]-sigmatropic rearrangement to afford the ketone **324** which rapidly tautomerises to give the phenol **(325)**. On protonation of the alkenic double bond in the phenol **(326)** and subsequent intramolecular cyclisation **(327)** and deprotonation of **328** gives rise to the desired 3,4-dihydro-2,2,4-trimethylbenzopyran **(309)**.



Scheme 78

The secondary carbocation (**329**) could attack the phenol (**28a**) via the mechanistic path shown in **Scheme 78** to afford the 3,4-dihydro-2,4,4-trimethylbenzopyran (**330**), as outlined in **Scheme 79**.

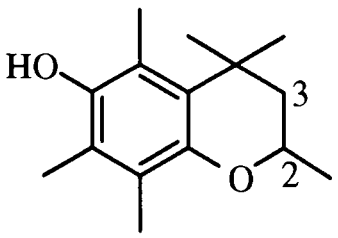


Scheme 79

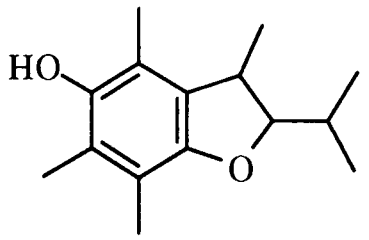
However, there was no evidence in the proton nmr spectrum for the presence of **330**. It would have been expected to show a sextet, and a doublet of doublets for the proton on C-2 and protons on C-3, respectively. The ^{13}C nmr spectrum of **330** shows that the C-2 quaternary sp^3 carbon is bonded directly to the oxygen (δ 75.8 ppm), as discussed earlier, while in **330** it would be attached to the aromatic ring and would be expected to resonate at around 30 ppm.

The ^{13}C nmr spectra of **309a-m** confirms this, in that the carbon signal for C-4 appears as a doublet at 26.4 ppm , while the carbon spectrum of **330** would show signals resonating at 70 ppm and 31.5 ppm. The mass spectrum of **330** would be expected to show the characteristic fission of the Ar-O bond while subsequent expulsion of a methyl

radical and ketene would lead to an abundant peak at m/z=192. Instead observed, elimination of the C-4 fragment of the pyran ring gives rise to the base peak at m/z=178 of **309a** (**Scheme 77**, p.103).



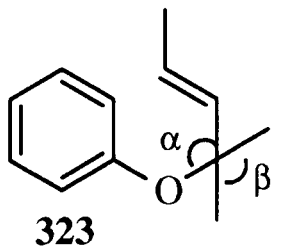
330



331

Alternatively, 2,3-dihydro-2-isopropyl-3-methylbenzofuran (**331**) could be formed, since ring closure to form five-membered rings and six-membered ring is highly favoured over competing intermolecular reactions such as polymerisation and is favoured over formation of rings of other sizes. Ruzicka and others[288-290] viewed this situation as the result of two competing factors: (i) an unfavourable strain energy that hinders formation of small rings, which strain becomes negligible for five- and six-membered rings, (ii) while the probability of ends meeting is most favourable for closing three-membered rings and progressively diminishes throughout the homologous series as the ring size becomes larger. However, in this case there was no evidence for the formation of the five membered ring system **331**.

This could be due to the structural factors which enhance the rate of cyclisation leading to the formation of the more stable six-membered ring system **330** . A well known example is the alkyl substituent effect 'the *gem*-dialkyl effect' or the well known Thorpe-Ingold effect[287,291-296]. In this the *gem*-dimethyl groups cause, by mutual repulsion, an increase in the angle β and a concomitant decrease in the angle α (**323**).

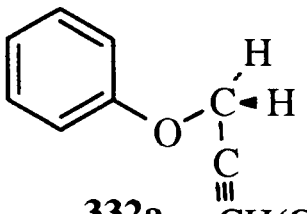


323

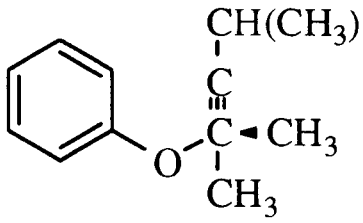
Kirby *et al*[297] confirmed this effect by X-ray studies, for instance, for malonic acid and dimethylmalonic acid. If the bonds forming the angle α are within a six-membered ring, this would result in ring stabilization. Ashwood[298], recently, stated that the geminal dimethyl groups at C-2 of the benzopyran moiety in the syntheses of chromakalins greatly enhanced the yields of the Claisen rearrangement.

Harfenist *et al*[299] stated that the *gem* dimethyl effect resulted in an increase in the rate of cyclisation in the thermal rearrangement of aryl propargyl ethers to chromenes when the hydrogens at the C-2 of **332a** were replaced by CH_3 (**332b**). If one or both groups are hydrogen, the rotamer with that H nearer the benzene ring's *ortho* H would predominate

332a, and the ethenyl group would not be situated in a position to react, without overcoming a substantial energy barrier to rotation.



332a



332b

However, in **332b** where at C-2 there are two methyl groups, the rotamer would have the ethenyl group in a better position to react, since the methyl groups would be more bulky at least that the ground state ethenyl group and therefore would be away from the benzene ring.

Engbert *et al*[300] stated that the rate enhancement (g*em*-dimethyl effect) could not be due to the restrictions in rotamer population alone. Milstein *et al* [283,284] found that very high rate enhancements were observed in some systems upon alkyl substitution. This was demonstrated, for example, by the high efficiency of the 'trialkyl lock effect' in the lactonization of some 3-(2-hydroxyphenyl)propionic acids. Overall, these effects probably operate in the initial cyclisation step of the [3,3]-rearrangement (**323** to **324**) see **Scheme 78**, p.104).

3.00 Conclusion

This study has shown that 2,2-dimethyl-3,4-dihydrobenzopyrans can be efficiently synthesised by reacting both phenols and substituted hydroquinones with carbocations generated from the appropriate 1,3-diene such as isoprene or allylic alcohol in the presence of zinc chloride and glacial acetic acid or trifluoroacetic acid under an atmosphere of argon in a one pot synthesis.

2,2-Dimethyl-3,4-dihydrobenzopyrans have been synthesised in low to average yield (5-54%) using Smith's methods[86,173]. The use of trifluoroacetic acid also gave low to average yields together with novel oxacyclopentanaphthalenes whose spectral data have not been reported in the literature.

2,2-Dimethyl-2,3-dihydrobenzofurans were prepared by two synthetic routes. Firstly, in one-pot syntheses using trifluoroacetic acid (TFA), in which the acid acts both the solvent and as the catalyst[242]. This reaction is thought to proceed via [3,3]-sigmatropic rearrangement and has the advantage of using simple reaction conditions. It is convenient and has produced low to moderate yields (4-32%).

Secondly, where phenols were condensed with isobutyraldehyde in the presence of toluene and concentrated sulphuric acid to afford 2,3-dihydrobenzofurans in low to high yields (4-84%). Here by contrast, concentrated sulphuric acid acts only as the catalyst. Nevertheless, the reaction is thought to proceed initially via an initial, regioslective *ortho*-alkylation of the phenol in selected cases. However, some polyalkylation of the 2,3-dihydrobenzofurans does seem to occur in both methods.

5-Formylamino-2,3-dihydrobenzofurans have been synthesized in one pot syntheses using several different methods.

Firstly, the method of Martini *et al*[133] gave moderate yields (53%) when toluene was used as the solvent and concentrated sulphuric acid was the acid catalyst. Secondly, the method of Smith *et al*[110] provided good yields (87%); however longer reaction times were required (22 hrs). Finally, the method involving TFA[242] also gave good yields (73%) and shorter reaction times (4hrs). The advantage of this method was that trifluoroacetic acid (TFA) acted as both the solvent and as the catalyst in the reaction.

A similar methodology was employed in the syntheses of 6-formylamino-3,4-dihydrobenzopyrans using N-formylaminophenol which was condensed with the appropriate allylic alcohols and diene using a number of acidic catalysts. All the methodologies used produced good yields of the desired compound. However, in some cases, deprotection of the formyl grouping to yield the 6-amino-3,4-dihydrobenzopyrans (35%) occurred.

The 5-formylamino-2,3-dihydrobenzofurans and 6-formylamino-3,4-dihydrobenzopyrans exhibited *cis-trans* isomerism. (As confirmed by their proton NMR spectra).

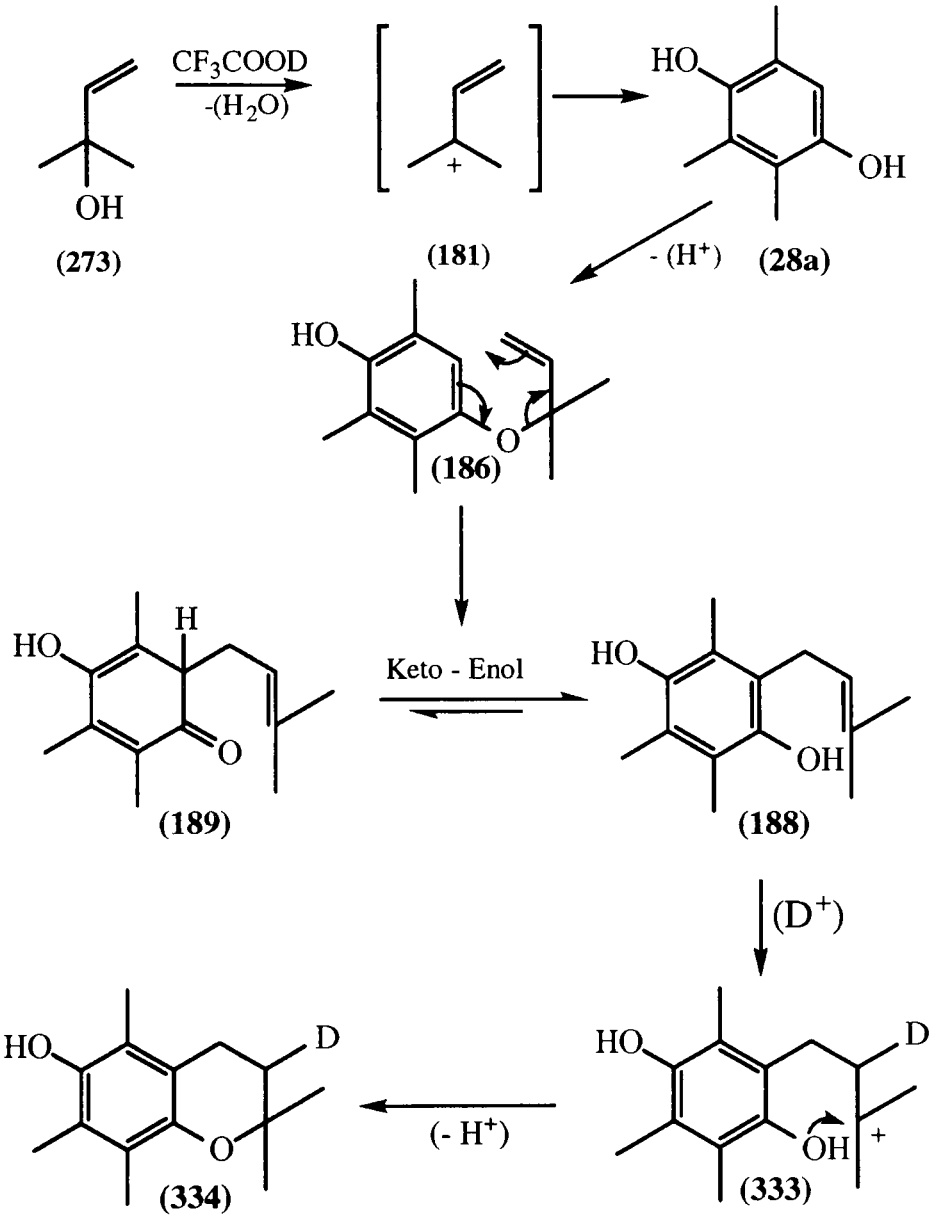
3,4-Dihydrobenzopyrans substituted with a methyl at the 4-position were synthesised in one pot syntheses by the reactions of phenols with 1,2-diols in the presence of a mixture of glacial acetic acid and concentrated sulphuric acid in low to high yields together with novel oxacyclopentanaphthalenes in low to average yields.

In summary, it has been shown that 3,4-dihydrobenzopyrans and 2,3-dihydrobenzofurans can be efficiently synthesised in one pot syntheses: an improvement on all the previous multistage syntheses.

4.00 Future Work

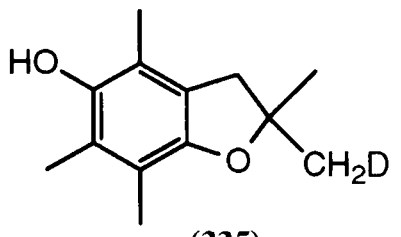
1. Confirmation of the proposed mechanisms by labelling studies - it has been shown in this study that TFA, glacial acetic and sulphuric acid mediated reaction of hindered phenols with the appropriate dienes, allyl alcohols, aldehydes and diols have afforded 2,3-dihydrobenzofurans and 3,4-dihydrobenzopyrans.

Due to the availability of time the deuteruim labelling studies were not carried out, in order to confirm the mechanisms which have been proposed in this thesis. For example, as shown in **Scheme 79**, the deuterium should be incorporated at the position C-3 in **188** If the proposed mechanism is correct, elimination of the proton from carbocation **333** should afford the deuterated model compound **334**.

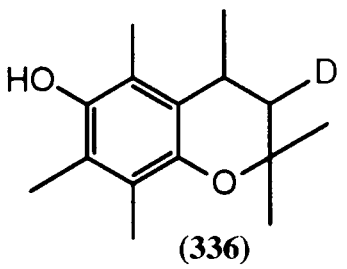


Scheme 79

Labelling studies should also be extended to the 5-membered ring analogue of the model compound **335** and the tri-alkyl locked compound **336** to verify that the deuterium is incorporated in the positions which we have proposed.



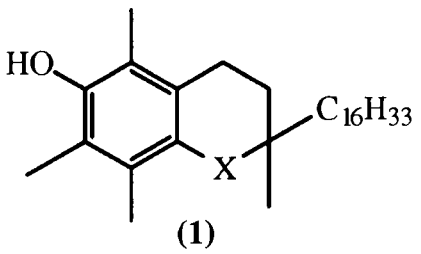
(335)



(336)

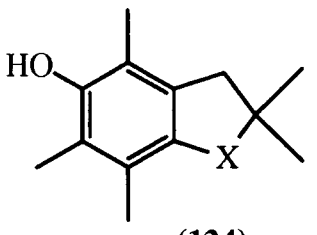
2. Improving the Antioxidant activity - α-tocopherol, the main component of vitamin E, the 6-hydroxychroman, the 6-aminochormans, as well as the corresponding ring contracted analogues-2,3-dihydrobenzofurans are some of the most active peroxyl radical trapping agents known[12,55,56,59,60,301,302]. Ingold and co-workers have attributed the improved antixoxidant activity of these compounds to the stereoelectronic effect[57], involving the p-type lone pair orbital of the nonphenolic oxygen. Sulfur analogues should be considered to be more effective than oxygen at stabilising the neighbouring radical centre[303]. However, they have been found to be slightly less reactive towards peroxyl radicals than their corresponding chroman derivatives[61,304].

1-Seleno-α-tocopherol **(1)** and 1-telluro-α-tocopherol **(124)** derivatives have not yet been prepared. Organoselenium and organotellurium compounds have shown interesting antioxidant properties. As you go down the group six of the periodic table, the elements become less electronegative.



(1)

1a X=O
b X=S
c X=Se
d X=Te



(124)

124 a X=O
t X=S
u X=Se
v X=Te

Thus the electron transfer to the reactive alkoxyl and peroxyl radicals becomes more likely to occur. Also the selenium containing glutathione peroxidases[305] have shown to catalyse the reduction of hydrogen peroxides, fatty acids hydroperoxides and organic peroxides using the tripeptide glutathione and other thiols as reducing agents. Other researchers have reported organo selenium and organotellurium compounds with chain breaking[306,307] or thiol peroxidase activity[308].

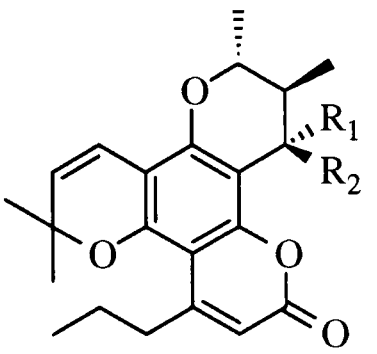
3. Design and Construction of Natural product libraries based on the Benzopyran Moiety - the 2,2-dimethylbenzopyran moiety is present in more than 4000 compounds including natural products and design structures[309]. The relatively high incidence of this benzopyran unit and its derivatives in natural products is partially attributable to the

numerous prenylation and cyclisation reactions in many polyketide biosynthesis pathways.

Moreover, the derivatives of the benzopyran unit remain sufficiently lipophilic to cross cell membranes, a key features of any biologically relevant small molecule library[310]. Furthermore, a topographical analysis of structure therapautics have identified the benzopyran moiety as a prefrential framework for drug design.[311]

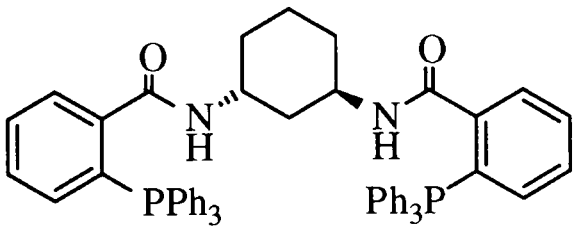
Therefore, further design and synthesis of the natural product libraries based on the benzopyran moiety would still be desirable.

4. Coumarins such as calanolides **A** and **B**, have shown to be HIV-1 specific reverse transcriptase inhibitors.[312]



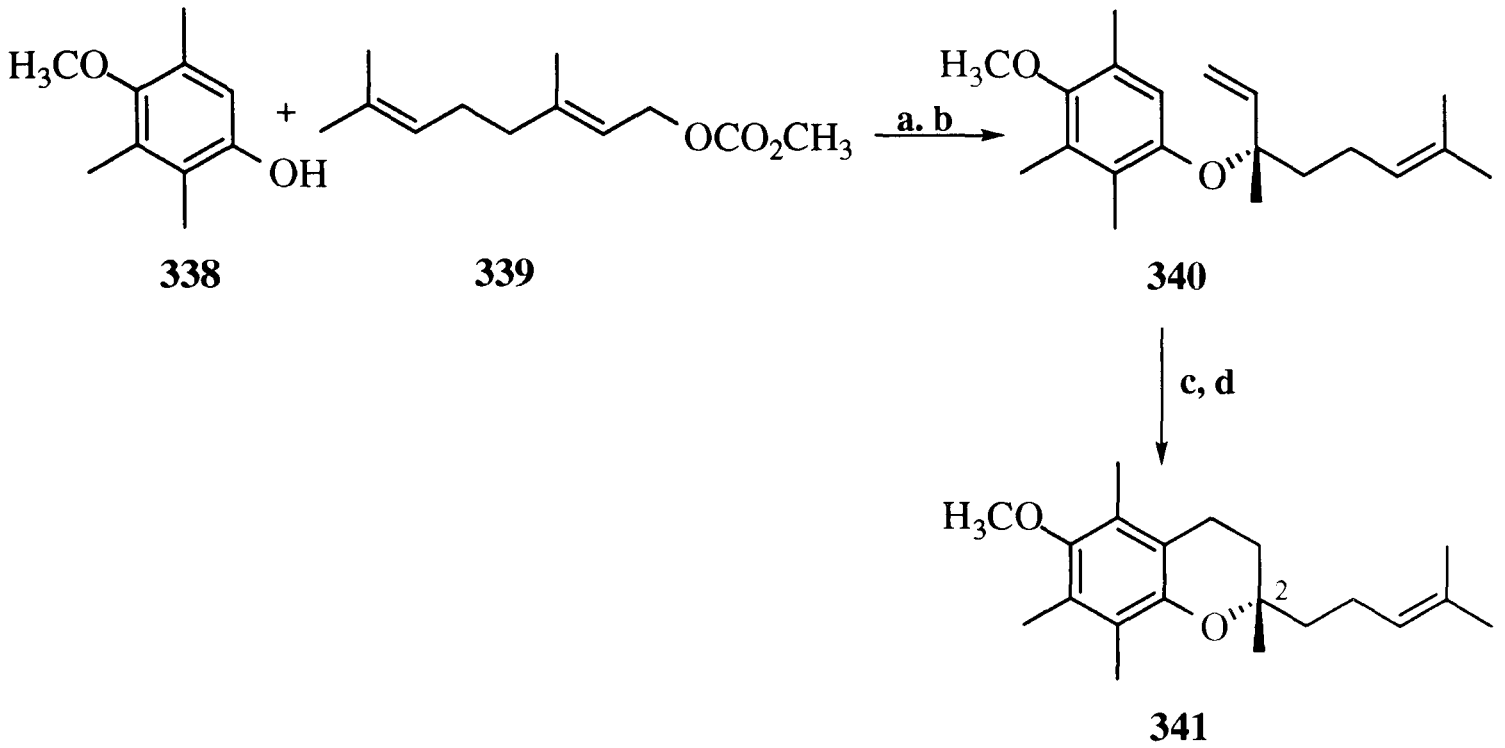
Calanolide **A** R_1=H, R_2=OH
Calanolide **B** R_1=OH, R_2=H

These compounds are of special interest because they are active against AZT-resistant strains of HIV-1. The key structural feature, both synthetically and biologically, of the calanolides is the trisubstituted chroman ring.[313]. Furthermore, chiral chromans are prevalent in other natural products, such as Vitamin E[314].



337

Trost *et al*[315] has sought a general route to the enantioselective preparations of chroman in which the chirality has been introduced at the C-2 position, by the use of ligand such as **337** and in a catalytic reaction, as outlined in **Scheme 80**.



338 **339** **340** **341**

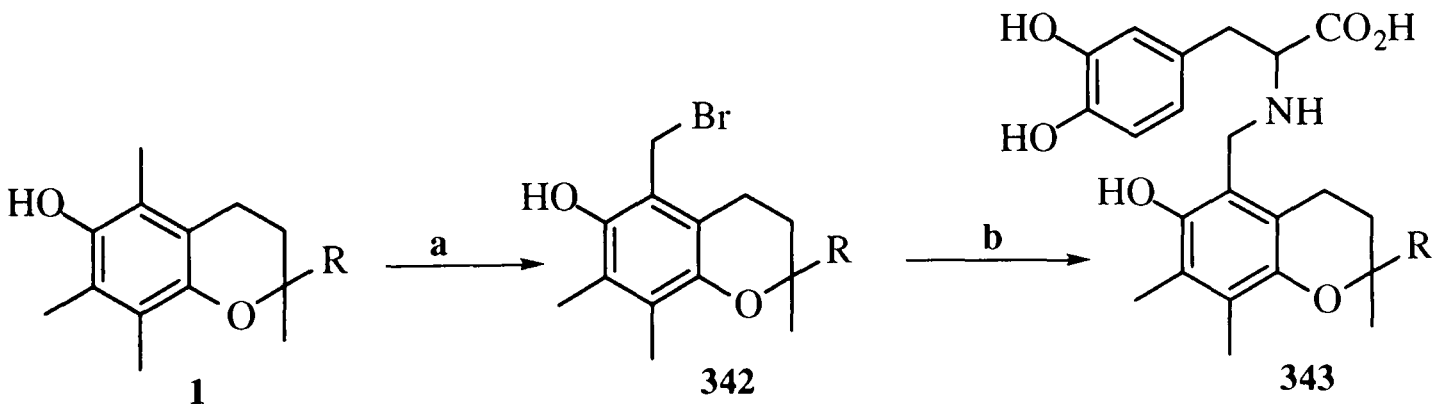
a) 1% Pd_2dba_3, **b)** 3% **4**, **c)** Catecholborane, 2% $(PPh_3)_3RhCl$, then NaOH, H_2O_2 (88%), **d)** Tf_2O, 2,6-di-*t*-butylpyridine, CH_2Cl_2 (78%).

Scheme 80

The palladium-catalysed reaction of phenol **338** with geranyl methyl carbonate **(339)** in the presence of ligand **337**, afforded the tertiary ether **340**. Cyclisation of the ether **340** afforded the chiral chroman **341**.

Introduction of chirality at C-2 by the use of the catalyst and ligand stated above, could be explored in the syntheses of 2,3-dihydrobenzofurans and 3,4-dihydrobenzopyrans, mentioned in this study.

5. Lipophilicity of α-tocopherol **1** could be increased by the introduction of amino groups such as L-Dopa. This can be achieved by the bromination of α-tocopherol to give the 5a-bromo-α-tocopherol **342**, followed by nucleophilic substitution to give the antioxidant **343**, as outlined in **Scheme 81**.



1 **342** **343**

R=$C_{16}H_{33}$

a) Br_2, in CH_2Cl_2 **b)** L-Dopa in EtOAc.

Scheme 81

Preliminary synthesis of antioxidant **343** has been carried out by Ismail *et al.*[316] Compound such as **343** could be screened against CNS disorders.[317]

6. The antioxidant activity of all the antioxidants synthesised in this study should be conducted as well as X-ray crystallography and molecular modelling of all the compounds.

5.00 Experiment

Reagents

All were purchased from the Aldrich Chemical Co. and Lancaster Synthesis, and were used without further purification.

Purification of Zinc Chloride

Anhydrous zinc chloride was obtained by sublimation over a slow stream of hydrogen chloride gas, followed by heating at 400°C under nitrogen.

Solvents

Solvents were purified according to the methods described by D.D. Perrin & W.L.F. Armarego in 'Purification of Laboratory Chemicals', 3rd Edition, Pegamon Press, New York, 1988.

Short-Path High Vacuum Distillation

All compounds (unless otherwise stated) were purified by short-path vacuum distillation.

NMR Spectra

^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AC-250 (250 MHz) instrument with tetramethylsilane as the internal standard. The spectrometer frequency was 250 MHz for proton NMR, (equivalent to a field strength of 5.87 TESLA) and 62.896 MHz for carbon-13 and DEPT (Distortionless Enhancement by Polarisation Transfer).

Mass Spectra

EI mass spectra were recorded on a VG MICROMASS 7070H (70eV) instrument at 200°C-250°C, with a scan time of 3 seconds/decade from 750 to 20 Daltons (mass units).

For chemical ionisation (CI) experiments, ammonia gas was used, and the spectrometer was operated at 50eV.

Infra-red Spectra

Infra-red spectra were recorded on a GALAXAY™, series 5000 FT-IR spectrometer GL-7020. Spectra were plotted using an HP 7440 Colourpro printer. Solid samples were run as their KBr discs; oils as neat liquids.

Melting Point

Melting points were recorded on a Gallenkamp apparatus, and are uncorrected.

Column chromatography

Thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates. Chromatographic purification was performed on silica gel columns; the silica gel Merck Kieselgel 60 of 0.063-0.200mm and using ethyl acetate : petroleum ether 30-40° (10:90) as the solvent system under argon, unless otherwise stated.

Gas Chromatography - Mass Spectrometry

Gas chromatography was performed on a Varian 3800 GC instrument linked to a Varian Saturn 2000 mass spectrometer equipped with an ion trap. Gas chromatograph conditions: column used was 30mm DB5, 0.25mm i.d. 0.25 υm film thickness, column temp = 230°C; pressure = 10.0 psi; split ratio = 200; run time = 35.00 mins unless otherwise stated.

Glassware

Removal of plasticiser contamination (e.g. dioctyl phthalate present in solvents from plastic bottles and acetone used for washing), after washing with acetone and distilled water (acid washed if necessary), all the glassware used was annealed at 650°C for 3 hours, prior to use.

All reactions were carried out on double vacuum manifold equipped with Teflon taps and under an atmosphere of argon (pre-dried using 3A molecular sieves).

Elemental Analysis

CHN analysis carried out by MEDAC LTD, BRUNEL SCIENCE CENTRE, COOPER'S HILL LANE, ENGLEFIELD GREEN, EGHAM, SURREY.

2,2-Dimethyl-3,4-dihydro-6-hydroxy-2,2,5,7,8-pentamethylbenzopyran (82a)

Trimethylhydroquinone **(28a)** (6.15g, 0.05mol) and freshly fused zinc chloride (5.24g, 0.39mol) were dissolved in acetic acid (30 ml) under argon with constant stirring. The solution was heated under reflux for 3hrs during which isoprene **(81)** (3.43g, 0.05mol) was added dropwise. The reaction was monitored by TLC (ethyl acetate : petroleum ether 30-40°, 10:90). After completion of the reaction, the solution was poured onto ice, neutralised with 5% w/v sodium bicarbonate solution (300ml) and extracted with ethyl acetate. The extract was dried with magnesium sulphate. Evaporation of the solvent gave a brown oil. To this was added methanol (40ml) and concentrated hydrochloric acid (10ml) and the solution was heated under reflux for 1hr. The methanol was removed *in vacuo*, the solution was neutralised with 5% w/v sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was washed with water and dried with magnesium sulphate. Evaporation of the solvent gave a dark brown oil which was crystallised from petroleum ether (b.pt 40-60°) to afford the title compound (4.06g, 37%) as a light brown crystalline solid, m.pt. 92-94°C.(Lit. m. pt 92-94°C)[88,173]. TLC (ethyl acetate : petroleum ether, 40-60°, 10:90), R_f 0.56.

IR (KBr) : υ 3251 (O-H), 2981-2929 (C-H), 1366 (*d*, geminal CH_3), 1264 (C-O-C), 1168 (C-O), 850 (C-H) bend cm^{-1}.

1H NMR ($CDCl_3$) : δ 1.28 (6H, s, C-2-2xCH_3), 1.81 (2H, t, *J* 6.88 Hz, C-3-CH_2), 2.10 (6H, s, C-5,7-2xCH_3), 2.15 (3H, s, C-8-CH_3), 2.61 (2H, t, *J* 6.80 Hz, C-4-CH_2), 4.22 (1H, s, C-6-OH, exchangeable with D_2O) ppm.

13C NMR ($CDCl_3$) : δ 11.30 (C-5-CH_3), 11.81 (C-8-CH_3) ,12.24 (C-7-CH_3), 21.12 (C-4-CH_2), 26.70 (C-2-2xCH_3), 33.11 (C-3-CH_2), 72.51 (C-2), 117.17 (C-5), 118.60 (C-6), 121.13 (C-8), 122.62 (C-7), 144.63 (C-9), 145.74 (C-10) ppm.

MS (EI) : m/z 220 ($M^{+\cdot}$, 70%), 205 ($M^{+\cdot}$ - CH_3, 5%), 177 (6%), 165 (95%), 164 (100%), 149 (3%), 136 (18%), 121 (12%), 105 (4%), 91 (9%).

Analysis calcd. for $C_{14}H_{20}O_2$ (220) C, 76.33; H, 9.15. Found: C, 76.17; H, 9.21%.

3,4-Dihydro-2,2,5,7,8-pentamethylbenzopyran (82b)

2,3,5-Trimethylphenol **(28b)** (8.23g, 0.06mol), and freshly fused zinc chloride (8.44g, 0.06mol) were dissolved in acetic acid (40 ml) under argon with constant stirring. The solution was heated under reflux for 3hrs during which isoprene **(81)** (3.42g, 0.05mol) was added dropwise. The reaction was monitored by TLC (ethyl acetate : petroleum ether 30-40°, 10:90). After completion of the reaction, the solution was poured onto ice, neutralised with 5% w/v sodium bicarbonate solution (300ml) and extracted with ethyl acetate. The organic layer was dried with magnesium sulphate. Evaporation of the

solvent afforded a reddish-brown oil. The oil was purified by column chromatography (ethyl acetate / petroleum ether 30-40°, 10:90) to afford the title compound (4.65g, 46%) as light yellow crystalline solid, m.pt 39-40°C (Lit. m.pt 40-41°C), R_f 0.78. Analysis of the mother liquor of **28b** by mass spectrometry showed the presence of the title compound, 3,4-dihydro-6-isopentenyl-2,2,5,7,8-pentamethylbenzopyran **(144b)**, and **163**.

IR (KBr) : υ 2971-2910 (C-H), 1363 (d, geminal CH_3), 1219 (C-O-C), 1157 (C-O) cm^{-1}.

1H NMR ($CDCl_3$) : δ 1.29 (6H, s, C-2-2xCH_3), 1.77 (2H, t, *J* 6.48 Hz, C-3-CH_2), 2.07 (3H, s, C-5-CH_3), 2.10 (3H, s, C-7-CH_3), 2.15 (3H, s, C-8-CH_3), 2.59 (2H, t, *J* 6.87 Hz, C-4-CH_2), 6.54 (1H, s, C-6-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 11.34 (Ar-CH_3), 18.82 (Ar-CH_3), 19.75 (Ar-CH_3), 21.39 (CH_2), 26.88 (2xCH_3), 32.73 (CH_2), 72.99 (C-2), 116.57 (Ar-C), 121.95 (Ar-C), 122.25 (C-6-CH), 133.33 (Ar-C), 134.60 (Ar-C), 151.65 (Ar-C) ppm.

MS (EI): m/z 204 ($M^{+\cdot}$, $C_{14}H_{20}O$, 40%), 189 ($C_{14}H_{20}O$ - CH_3, 10%), 149 (100%), 105 (12%), 91 (8%), 55 (9%).

Evidence for the formation of 3,4-dihydro-6-isopentenyl-2,2,5,7,8-pentamethylbenzopyran **(144b)**

MS (EI) : m/z 272 ($M^{+\cdot}$, $C_{19}H_{28}O$, 8%), 257 ($M^{+\cdot}$, $C_{19}H_{28}O$ - CH_3, 18%).

MS (CI) : m/z 273 (M+H, $C_{14}H_{20}O$, compound **144b**, 8%).

Evidence for the formation of **(163).**

MS (CI) : m/z 407 (M+H), $C_{28}H_{38}O_2$, 18%).

The following compounds were synthesised using the method outlined above.

3,4-Dihydro-6-chloro-2,2-dimethylbenzopyran (82c)

p-Chlorophenol **(28c)** (6.43g, 0.05ml), was reacted with isoprene **(81)** (3.41g, 0.05mol) to afford a dark brown oil . Purification by column chromatography (ethyl acetate : petroleum ether 40-60°, 15:85) afforded the title compound **(82c)** (2.74g, 28%) as a light brown oil, (Lit. m. pt 83-85°C)[172], R_f 0.68 and **144c** (<1%).

1H NMR ($CDCl_3$) : δ 1.31 (6H, s, C-2-2xCH_3), 1.76 (2H, t, *J* 7.01 Hz, CH_2), 2.72 (2H, t, *J* 6.77 Hz, CH_2), 6.67-6.71 (1H, m, *meta*-coupled, *J* 9.41 Hz, J_m 3.67 Hz, Ar-H), , 6.99-7.03 (2H, m, *meta*-coupled, *J* 6.77 Hz, J_m 3.20 Hz, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 22.36 (C-4-CH_2), 26.71 (C-2-2xCH_3), 32.39 (C-3-CH_2), 74.22 (C-2), 118.52 (Ar-CH), 122.07 (Ar-C), 124.19 (Ar-C), 127.18 (Ar-CH), 128.92 (Ar-CH) ppm.
MS (EI) m/z : 196 (M+., $C_{11}H_{13}OCl$, 60%), 181 (M+. $C_{11}H_{13}OCl$ - CH_3,45%), 167 (35%), 155 (32%), 141 (100%), 123 (43%), 77 (33%), 69 (47%), 43 (65%).

Formation of 3,4-dihydro-6-chloro-5-pentenyl-2,2-dimethylbenzopyran **(144c)**
MS : (EI) : m/z 264 ($M^{+\cdot}$,$C_{16}H_{21}OCl$, 22%), 249 ($C_{16}H_{21}OCl$ - CH_3, 10%), 223 (95%), 209 (58%), 196 (M+., $C_{11}H_{13}OCl$, compoumd **82c**, 60%), 181 (M+. $C_{11}H_{13}OCl$ - CH_3,45%), 167 (35%), 155 (32%), 141 (100%), 123 (43%), 77 (33%), 69 (47%), 43 (65%).

3,4-Dihydro-6-hydroxy-2,2-dimethylbenzopyran (82d)
Hydroquinone **(28d)** (3.43g, 0.03mol) was reacted with isoprene **(81)** (3.44g, 0.05 mol) to a dark brown oil. The oil was purified by column chromatography (methanol : dichloromethane, 5:95) to afford the title compound **(82d)** as a light brown oil (0.98g, 11%), (Lit. m.pt 77-80°C)[173,174], R_f 0.40.
^1H NMR (Acetone-d_6) : δ 1.25 (6H, s, C-2-2xCH_3), 1.74 (2H, t, *J* 6.81 Hz, C-3-CH_2), 2.69 (2H, t, *J* 6.81 Hz, C-4-CH_2), 2.99 (1H, s, C-6-OH), 6.50 (2H, s, 2xAr-H), 7.68 (1H,s, Ar-CH) ppm.
^{13}C NMR (Acetone-d_6) : δ 23.21 (CH_2), 26.96 (C-2-2xCH_3), 33.70 (CH_2), 73.87 (C-2), 115.11(Ar-CH), 115.90 (Ar-CH), 118.23 (Ar-CH), 122.19 (Ar-C), 147.92 (Ar-C), 151.15 (Ar-C) ppm.

3,4-Dihydro-7,8-Dihydroxy-2,2-dimethylbenzopyran (82e)
Pyrogallol **(28e)** (2.53g, 0.02mol) was reacted with isoprene **(59)** (2.75g, 0.02mol) to afford the title compound as a red oil **(82e)** (1.82g, 51%) and **(145e).**
^1H NMR ($CDCl_3$) : δ 1.34 (6H, s, C-2-2xCH_3), 1.75 (2H, t, *J* 8.10 Hz, CH_2), , 2.69 (2H, t, *J* 7.23 Hz, CH_2), 6.05 (Ar-H), 6.54 (Ar-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 21.58 (CH_2), 26.71 (C-2-2xCH_3), 32.87 (CH_2), 75.85 (C-2), 107.27 (Ar-CH), 113.08 (Ar-C), 119.57 (Ar-CH), 131.89 (C-8-C-OH), 141.37 (Ar-C).
MS (EI) : 194 ($M^{+\cdot}$, $C_{11}H_{14}O_3$, 58%), 179 ($M^{+\cdot}$, $C_{11}H_{14}O_3$ - CH_3, 12%), 139 (100%), 138 (95%), 126 (39%), 43 (22%).

Evidence for the formation of 2,2,8,8-tetramethyl-3,4,6,7-tetrahydro-2*H*,6*H*-pyrano[3,2-*g*]chromen-5-ol **(145e)**
MS (EI) : m/z 262 ($M^{+\cdot}$, $C_{16}H_{22}O_3$, 10%), 247 ($M^{+\cdot}$, $C_{16}H_{22}O_3$ - CH_3, 8%), 236 (8%), 207 (18%).

3,4-Dihydro-2,2-dimethyl-3*H*-naphtho-[2,1-*b*]pyran (82f)

2-Naphthol **(28f)** (11.63g, 0.08mol) was reacted with isoprene **(81)** (6.81g, 0.1mol) to afford a red oil. The oil was purified by column chromatography (ethyl acetate : petroleum ether 40-60°, 10:90) to afford the title compound **(82f)** (11.02g, 52%) as a light yellow oil, (Lit. NMR evidence only[134]), R_f 0.62 and a red oil 3,4-dihydro-2,2-dimethyl-4-pentenyl-3*H*-naphtho-[2,1-b]-pyran **(144f)**.

IR (film) : υ 3437 (O-H), 2975-2927 (C-H), 1391 (geminal CH_3), 1267 (-C-O-C-), 1157 (C-O) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.38 (6H, s, C-2-2xCH_3), 1.85 (2H, t, *J* 6.70 Hz, CH_2), 2.82 (2H, t, *J* 6.95 Hz, CH_2), 7.10-7.13 (1H, d, *J* 8.35 Hz, Ar-CH), 7.26-7.29 (1H, d, *J* 8.32 Hz, Ar-CH), 7.37-7.41 (2H, m, *meta*-coupled, *J* 8.85 Hz, J_m 3.22 Hz, 2xAr-H), 7.82-7.88 (1H, d, meta-coupled, *J* 9.42 Hz, J_m 3.60 Hz, Ar-H), 8.35 (1H, d, meta-coupled, *J* 9.75 Hz, J_m 4.30 Hz, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 22.72 (CH_2), 27.60 (C-2-2xCH_3), 32.72 (CH_2), 74.37 (C-2), 114.17 (Ar-C), 118.79 (Ar-CH), 121.58 (Ar-CH), 125.28 (Ar-CH), 125.40 (Ar-H), 125.42 (Ar-CH), 127.68 (Ar-CH), 133.26 (Ar-C), 148.61 (Ar-C) ppm.

MS (EI) : m/z 212 ($M^{+\cdot}$,$C_{15}H_{16}O$, 70%), 195 (10%), 181 (8%), 170 (10%), 157 (100%), 156 (57%), 141 (7%), 128 (28%), 115 (7%).

Evidence for the formation of 3,4-dihydro-2,2-dimethyl-4-pentenyl-3*H*-naphtho-[2,1-b]-pyran **(144f).**

MS (EI) : m/z 280 ($M^{+\cdot}$, $C_{20}H_{24}O$, 40%), 225 (25%).

3,4-Dihydro-2,2-(4-isopropyl)-5,6-hydroxy-7,8-pentamethylbenzopyran (178)

Trimethylhydroquinone **(28a)** (0.02 mol) was reacted with 2,5-dimethyl-hexa-2,4-diene **(177)** (2.21g, 0.02 mol) to afford the title compound **(178)** (1.36g, 26%) as a red oil.

^1H NMR ($CDCl_3$) : δ 0.77-0.80 (3H, d, *J* 6.67 Hz, C-4'a-CH_3), 0.83-0.86 (3H, d, *J* 6.83 Hz, C-4'b-CH_3), 0.89-0.98 (1H, m, *J* 6.87 Hz, C-4'-H), 1.05 (3H, s, C-2-CH_3ax), 1.48 (3H, s, C-2-CH_3eq), 1.59-1.67 (3H, m, *J* 7.65 Hz, C-3-Hax), 2.00-2.03 (1H, m, *J* 6.19 Hz, C-3-Heq), 2.11 (3H, s, Ar-CH_3), 2.15 (6H, s, 2xAr-CH_3), 2.76-2.84 (1H, m, *J* 7.22 Hz, C-4-CH), 4.35 (1H, broad, C-6-OH, D_2O exchangeable) ppm.

^{13}C NMR ($CDCl_3$) : δ 11.83 (Ar-CH_3), 12.20 (Ar-CH_3), 12.48 (Ar-CH_3), 18.05 (C-4'-CH_3ax), 21.28 (C-4'-CH_3eq), 26.97 (C-2-CH_3ax), 30.03 (C-4-CH), 30.84 (C-2-CH_3eq), 36.43 (C-3-CH_2), 38.61 (C-4'-CH), 75.37 (C-2), 118.16 (Ar-CH_3), 120.12 (Ar-CH_3), 123.92 (Ar-CH_3), 126.82 (Ar-CH_3), 146.10 (Ar-CH_3), 146.34 (Ar-CH_3) ppm.

3,4-Dihydro-6-hydroxy-2,2,5,7,8-pentamethylbenzopyran (82a) - Method II

Trimethylhydroquinone **(28a)** (12.61g, 0.11 mol) was dissolved in trifluoroacetic acid under reflux in an atmosphere of argon. 3-Methyl-2-buten-1-ol **(199)** (6.89g, 0.08mol) was added slowly over a period of 3hrs. After completion of the reaction, the mixture was poured onto ice. The organic layer was extracted with ethyl acetate (250ml), neutralised with 5%w/v sodium bicarbonate solution and washed with water (100ml x 2). The ethyl acetate was removed under reduced pressure. To the organic layer, methanol (100ml) and concentrated hydrochloric acid (5ml) were added and the solution was heated under reflux for 1hr. The methanol was removed under reduced pressure. The solution was neutralised with 5%w/v sodium bicarbonate solution, and extracted with ethyl acetate (150ml). The extract was washed with water (100ml), dried over anhydrous magnesium sulphate and the solvent removed *in vacuo*. On standing the brown oil solidified. Crystallisation from petroleum ether (40-60°) afforded the title compound (10.09, 57%) as a light brown solid, m.pt. 88-90°C (Lit. 92-94°C[88,173]). TLC (ethyl acetate : petroleum ether 40-60°, 10:90), R_f 0.34.

IR (KBr) : υ 3243 (O-H), 2980-2929 (C-H), 1367 (d, geminal CH_3), 1224 (C-O-C), 1167 (C-O) cm^{-1}.

1H NMR ($CDCl_3$) : δ 1.28 (6H, s, C-2-2xCH_3), 1.80 (2H, t, *J* 6.87 Hz, C-3-CH_2), 2.03 (6H, s, C-5,7-2xCH_3), 2.07 (3H, s, C-8-CH_3), 2.61 (2H, t, *J* 6.79 Hz, C-4-CH_2), 4.23 (C-6-OH, D_2O exchangeable) ppm.

^{13}C NMR ($CDCl_3$) : δ 11.69 (C-5-CH_3), 11.72 (C-8-CH_3), 12.65 (C-7-CH_3), 20.46 (C-4-CH_2), 26.38 (C-2-2xCH_3), 32.46 (C-3-CH_2), 71.88 (C-2), 116.36 (C-5), 120.20 (C-6), 120.77 (C-8), 122.47 (C-7), 144.53 (C-9), 145.01 (C-10) ppm.

MS (EI) : m/z 220 ($M^{+\cdot}$, 68%), 205 ($M^{+\cdot}$ - CH_3, 5%), 190 (3%), 165 (93%), 164 (100%), 149 (3%), 136 (13%), 121 (12%), 105 (4%), 91 (10%).

The following compounds were synthesised using the above general procedure.

3,4-Dihydro-2,2,5,7,8-pentamethylbenzopyran (82b)

2,3,5-Trimethylphenol **(28b)** (6.81g, 0.05mol) was dissolved in trifluoroacetic acid at 100°C under an atmosphere of argon. 3-Methyl-2-buten-1-ol **(199)** (4.31g, 0.05mol) was added slowly over a period of 3hrs. After completion of the reaction, the mixture was poured onto ice. The organic layer was extracted with ethyl acetate (200ml), neutralised with 5%w/v sodium bicarbonate solution, washed with water (75ml x 2), and dried over anhydrous magnesium sulphate. The ethyl acetate was removed *in vacuo* to afford a crude brown oil.

TLC (ethyl acetate : petroluem ether 40-60°, 15:85) : 2 spots; R_f 0.35, 0.65. Purification by column chromatography afforded the title compound as a pale yellow oil (3.01g, 30%), (Lit m.pt 40-41°C).
IR (film) : υ 2980-2928 (C-H), 1367 (*d*, geminal CH_3), 1223 (C-O-C), 1168 (C-O) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.30 (6H, s, C-2-2xCH_3), 1.78 (2H, t, *J* 6.83 Hz, C-3-CH_2), 2.04 (3H, s, C-5-CH_3), 2.09 (3H, s, C-8-CH_3), 2.15 (3H, s, C-7-CH_3), 2.59 (2H, t, *J* 6.86 Hz, C-4-CH_2), 6.54 (1H, s, C-6-CH) ppm.
^{13}C NMR ($CDCl_3$) : δ 11.33 (C-5a-CH_3), 18.80 (C-8-CH_3), 19.74 (C-7-CH_3), 20.44 (C-3-CH_2), 26.68 (C-2-2xCH_3), 32.77 (C-4-CH_2), 73.03 (C-2), 116.61 (C-5), 121.97 (C-8), 122.28 (C-6-CH), 133.34 (C-7), 133.34 (C-9), 151.67 (C-10) ppm.
MS (EI) : m/z 204 ($M^{+\cdot}$, 23%), 189 ($M^{+\cdot}$ - CH_3, 10%), 174 (4%), 163 (10%), 149 (100%), 133 (7%), 105 (10%), 91 (5%).

3,4-Dihydro-2,2,7,8-tetramethylbenzopyran (82g)
2,3-dimethylphenol **(28g)** (10.66g, 0.1 mol) was reacted with 3-methyl-2-buten-1-ol **(199)** (8.62g, 0.1 mol) to afford a crude yellow oil. Fractional distillation yielded two main fractions.
Fraction 1 (0.99g, 5%) the title compound **(82g)**. B.pt. 128-132°C / 2 torr, TLC (ethyl acetate / 40-60° pet ether,15:85), R_f 0.69.
^1H NMR ($CDCl_3$) : δ 1.31 (6H, s, C-2-2xCH_3), 1.75 (2H, t, *J* 6.81 Hz, C-3-CH_2), 2.09 (3H, s, Ar-CH_3), 2.21 (3H, s, Ar-CH_3), 2.70 (2H, t, *J* 6.73 Hz, C-4-CH_2), 6.61-6.64 (1H, d, *J* 7.66 Hz, Ar-H), 6.78-6.81 (1H, d, *J* 7.71 Hz, Ar-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 11.60 (Ar-CH_3), 19.96 (Ar-CH_3), 22.60 (CH_2), 26.96 (2xCH_3), 32.90 (CH_2), 73.88 (C-2), 117.88 (Ar-C), 120.80 (Ar-H), 124.51 (Ar-C), 126.05 (Ar-H), 127.48 (Ar-C), 135.33 (Ar-C), 151.85 (Ar-C) ppm.
MS (EI) : m/z 190 ($M^{+\cdot}$, $C_{13}H_{18}O$, 9%), 175 ($M^{+\cdot}$, $C_{13}H_{18}O$ - CH_3, 38%), 149 (12%), 135 (100%), 122 (25%), 91 (10%),77 (8%), 57 (9%).

Evidence for the formation of 1,1,4,5,7,7-hexamethyl-1,2,3,7,8,9-hexahydro-6-oxa-cyclopenta[a]naphthalene **(200g)** as a yellow oil. Fraction 2 (4.66g, 25%). Bpt 148-152°C / 3 torr
^1H NMR ($CDCl_3$) : δ 1.31 (6H, s, 2 x CH_3), 1.33 (6H, s, 2 x CH_3), 1.72-1.78 (2H, t, *J* 6.82 Hz, CH_2), 1.84-1.88 (2H, t, *J* 7.13 Hz, CH_2), 2.08 (3H, s, Ar-CH_3), 2.12 (Ar-CH_3), 2.70-2.76 (2H, t, *J* 7.27 Hz, CH_2), 2.80-2.85 (2H, t, *J* 6.79 Hz, CH_2) ppm.
^{13}C NMR ($CDCl_3$) : δ 11.81 (Ar-CH_3), 16.04 (Ar-CH_3), 22.08 (CH_2), 27.03 (2xCH_3), 27.20 (2xCH_3), 28.45 (CH_2), 32.32 (CH_2), 43.31 (CH_2), 45.77 (Aliphatic-C), 72.73

(Aliphatic-C), 114.17 (Ar-C), 122.89 (Ar-C), 130.05 (Ar-C), 132.64 (Ar-C), 145.43 (Ar-C), 150.69 (Ar-C) ppm.
MS (EI) : m/z 258 ($M^{+\cdot}$, 58%), 243 ($M^{+\cdot}$ - CH_3, 75%), 229 (19%), 203 (70%), 187 (58%), 175 (100%), 159 (18%), 149 (20%), 135 (27%), 91 (18%).

3,4-Dihydro-2,2,5,8-tetramethylbenzopyran (82h)
2,5-Dimethylphenol **(28h)** (12.21g, 0.1 mol) was reacted with 2-methyl-3-buten-2-ol **(199)** (8.64g, 0.1 mol) to afford a pale green oil **(82h)** and a green oil **(200h).**
Fraction 1 contained the title compound **(82h)** (0.72g, 4%) as a pale green oil. B.pt. 108-112°C / 1 torr. TLC (ethyl acetate : petroleum ether 40-60°, 15:85), R_f 0.67
^1H NMR ($CDCl_3$) : δ 1.30 (6H, s, C-2-2xCH_3), 1.78 (2H, t, *J* 8.71 Hz, C-3-CH_2), 2.13 (Ar-CH_3), 2.18 (Ar-CH_3), 2.60 (2H, t, *J* 6.88 Hz,C-4-CH_2), 6.58-6.61 (1H, d, *J* 7.48 Hz, Ar-H), 6.85-6.88 (1H, d, *J* 7.44 Hz, Ar-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 15.94 (Ar-CH_3), 18.95 (Ar-CH_3), 20.85 (CH_2), 26.77 (C-2-2xCH_3), 32.80 (CH_2), 72.99 (C-2), 119.04 (Ar-C), 120.16 (Ar-H), 123.77 (Ar-C), 127.65 (Ar-CH), 134.32 (Ar-C), 152.01 (Ar-C) ppm.

Evidence for the formation of 3,3,4,6,6,9-hexamethyl-1,2,3,6,7,8-hexahydro-5-oxa-cyclopenta[b]naphthalene **(200h)**
Fraction 2 as a green oil (3.01g, 16%). B.pt. 126-132°C / 3 torr. TLC (ethyl acetate : petroleum ether 40-60°, 15:85) R_f 0.71.
^1H NMR ($CDCl_3$) : δ 1.29 (6H, s, C-2-2xCH_3), 1.39 (6H, s, 2xCH_3), 1.73-1.79 (2H, t, *J* 6.86 Hz, CH_2), 1.81-1.89 (2H, t, *J* 8.75 Hz, CH_2), 2.05 (3H, s, Ar-CH_3), 2.18 (3H, s, Ar-CH_3), 2.58-2.63 (2H, t, *J* 6.83 Hz, CH_2), 2.69-2.75 (3H, t, *J* 7.27 Hz, CH_2) ppm.
^{13}C NMR ($CDCl_3$) : δ 11.07 (Ar-CH_3), 15.17 (Ar-CH_3), 20.84 (CH_2), 26.95 (2xCH_3), 27.74 (2xCH_3), 28.16 (CH_2), 32.85 (CH_2), 42.95 (CH_2), 45.59 (Aliphatic-C), 72.68 (Aliphatic-C), 116.97 (Ar-C), 119.33 (Ar-C), 128.77 (Ar-C), 132.53 (Ar-C), 147.21 (Ar-C), 150.89 (Ar-C) ppm.

3,4-Dihydro-2,2,5,7-tetramethylbenzopyran (82i)
3,5-Dimethylphenol **(28i)** (12.28g, 0.1 mol) was reacted with 2-methyl-3-buten-2-ol **(199)** (8.60g, 0.1 mol) to afford the title compound as a yellow oil (7.14g, 38%). Bpt 108-110°C / 1 torr, TLC (ethyl acetate : petroleum ether 40-60°, 15:85) R_f 0.66.
^1H NMR ($CDCl_3$) : δ 1.30 (6H, s, C-2-2xCH_3), 1.77-1.82 (2H,t , *J* 6.85 Hz, CH_2), 2.17 (Ar-CH_3), 2.22 (Ar-CH_3), 2.54-2.60 (2H, t, *J* 6.80 Hz, CH_2), 6.49 (1H, s, Ar-H), 6.54 (1H, s, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 19.04 (Ar-CH_3), 20.02 (CH_2), 20.95 (Ar-CH_3), 26.68 (C-2-2xCH_3), 32.95 (CH_2), 73.24 (C-2), 115.42 (Ar-H), 116.58 (Ar-C), 122.17 (Ar-H), 136.46 (Ar-C), 136.88 (Ar-C), 153.73 (Ar-C) ppm.

3,4-Dihydro-6-chloro-2,2,5-trimethylbenzopyran (82j)

4-Chloro-3-methylphenol **(28j)** (71.35g, 0.5 mol) was reacted with 2-methyl-3-buten-2-ol **(199)** (43.11g, 0.5 mol) to afford the title compound (76.58g, 73%) as a pale yellow solid, m. pt. 54-56°C.

IR (film) : υ 2976-2828 (sat. C-H str.), 1614-1563 (C=C), 1489-1453 (C-H def.) 1376 (d, geminal CH_3), 1157 (C-O), 874 (C-H bend), 776 (C-Cl) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.30 (6H, s, C-2-2xCH_3), 1.73-1.81 (2H, t, *J* 6.79 Hz, CH_2), 2.26 (Ar-CH_3), 2.67-2.72 (2H, t, *J* 6.77 Hz,CH_2), 6.64 (Ar-H), 7.01 (Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 19.71 (Ar-CH_3), 21.41 (CH_2), 26.75 (C-2-2xCH_3), 32.59 (CH_2), 74.30 (C-2), 119.30 (Ar-H), 119.87 (Ar-C), 124.60 (Ar-C), 129.20 (Ar-H), 134.69 (Ar-C), 152.43 (Ar-C) ppm.

MS (EI) : m/z 210 ($M^{+\cdot}$, $C_{12}H_{15}ClO$, 39%), 195 ($M^{+\cdot}$, $C_{12}H_{15}ClO$ - CH_3, 12%), 175 (16%), 155 (100%), 149 (6%), 135 (15%), 91 (19%), 77 (7%).

Analysis calcd. for $C_{12}H_{15}OCl$ (210) C, 69.48; H, 7.62. Found: C, 69.32; H, 7.93%.

Racemic α-Tocopherol (1)

Trimethylhydroquinone **(28a)** (15.30g, 0.1 mol) was reacted with phytol **(36)** (27.28g, 0.1 mol) to afford the title compound (35.66g, 83%)[34] as a red oil, TLC (100% chloroform) : R_f 0.80.

^1H NMR ($CDCl_3$) : δ 0.84 (3H, d, *J* 6.0 Hz, CH_3), 0.85 (3H, d, *J* 6.25 Hz, CH_3), 0.87 (6H, d, *J* 6.40 Hz, 2xCH_3), 1.08-1.60 (24H, m), 1.78 (2H, m, *J* 6.68 Hz, C-3-CH_2), 2.10 (6H, s, C-5,7-2xCH_3), 2.15 (3H, s, C-8-CH_3), 2.60 (2H, t, *J* 6.83 Hz, C-4-CH_2), 4.18 (1H, s, C-6-OH) ppm.

^{13}C NMR ($CDCl_3$) : δ 11.27 (C-5-CH_3), 11.78 (C-8-CH_3), 12.21 (C-7-CH_3), 19.70 (C-4'-CH_3), 19.76 (C-8'-CH_3), 20.78 (C-4-CH_2), 21.08 (C-2'-CH_2), 22.64 (C-13'-CH_3), 22.73 (C-12'-CH_3), 23.81 (C-2-CH_3), 24.47 (C-6'-CH_2), 24.83 (C-10'-CH_2), 27.99 (C-12'-CH), 31.59 (C-3-CH_2), 32.72 (C-4-CH), 32.81 (C-8'-CH), 37.31 (C-7'-CH_2), 37.42 (C-5'-CH_2), 38.36 (C-9'CH_2), 39.40 (C-3'-CH_2), 39.84 (C-11'-CH_2), 39.92 (C-1'-CH_2), 74.53 (C-2), 117.34 (C-5), 118.54 (C-6), 121.09 (C-8), 122.61 (C-7), 144.56 (C-9), 145.58 (C-10) ppm.

MS (EI) : m/z 431 (M+1, 33%), 430 ($M^{+\cdot}$, 100%), 205 (10%), 165 (90%), 149 (18%), 121 (5%), 91 (<5%), 71 (10%), 57 (19%), 43 (22%).

2,3-Dihydro-5-hydroxy-2,2,4,6,7-pentamethylbenzofuran (124a)

Trimethylhydroquinone **(28a)** (15.38g, 0.1 mol) was mixed with trifluoroacetic acid (30 ml) at 100°C under an atmosphere of argon. 2-Methyl-2-propen-1ol **(207)** (7.31g, 0.1 mol) was added dropwise over a period of 30 mins and the reaction mixture was heated under reflux for 3-4 hrs. The reaction mixture was poured into ice, neutralised with 10%w/v sodium bicarbonate solution (500 ml), and the organic layer was extracted with ethyl acetate (200 ml), washed with water, and dried with anhydrous magnesium sulphate. Solvent was evaporated to give a brown oil. To the oil was added methanol (100 ml), and concentrated hydrochloric acid (10 ml), and the mixture was heated under reflux for 1hr. The resulting solution was poured into ice, extracted with ethyl acetate (200 ml), neutralised with 10%w/v sodium bicarbonate solution (300 ml), was treated with Claisens alkali, acidified with concentrated hydrochloric acid, washed with water (2x100ml), and dried with anhydrous magnesium sulphate. The solvent was removed *in vacuo* to afford a brown oil which solidified on standing. Crystallisation from petroleum ether (b pt 40-60°) gave the title compound (7.67g, 37%) as a light brown solid, m.pt. 118-120°C (Lit. m.pt. 122-123°C[57,130]), TLC (ethyl acetate : petroleum ether 40-60°, 15:85), R_f 0.38. The mother liqour from recrystallisation was analysed by mass spectrometry and was shown to contain compounds **224**, **225**, **226**. These were not isolated.

IR (KBr) : υ 3446 (O-H), 2967-2852 (sat. C-H str.), 1630 (C=C), 1457-1414 (C-H def.), 1368 (d, geminal CH_3), 1273-1214 (C-O), 833 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.44 (6H, s, C-2-2xCH_3), 2.09 (6H, s, C-4,C-6-CH_3), 2.11 (3H, s, C-7-CH_3), 2.89 (2H, s, C-3-CH_2), 4.27 (1H, s, C-5-OH) ppm.

^{13}C NMR ($CDCl_3$) : δ 11.99 (C-4-CH_3), 12.18 (C-7-CH_3), 12.81 (C-6-CH_3), 28.45 (C-2-2CH_3), 42.84 (C-3-CH_2), 85.08 (C-2), 115.71 (C-4), 117.60 (C-5), 121.60 (C-7), 123.04 (C-6), 145.29 (C-8), 151.07 (C-9) ppm.

M.S. (EI) : m/z 206 ($M^{+\cdot}$, $C_{13}H_{18}O_2$, 56%), 191 ($M^{+\cdot}$, $C_{13}H_{18}O_2$ - CH_3, 100%), 176 (16%), 163 (10%), 91 (7%), 77 (6%), 43 (11%).

Analysis calcd. for $C_{13}H_{18}O_2$ (206) C, 75.69; H, 8.79. Found: C, 75.66; H, 8.89%.

Evidence for the presence of 2,2,4,6,7-pentamethyl-5-(2,3,5-trimethyl-phenoxy)-2,3-dihydro-benzofuran **(224)** in the recrystallisation mother liquor.

M.S. (CI) : m/z 325 (M+1, $C_{22}H_{28}O_2$, 3%).

Evidence for the presence of 2,4-diisopropyl-6,7,8-trimethyl-4*H*-benzo[1,3]dioxane **(225)** in the recrystallisation mother liquor.

M.S. (CI) : m/z 263 (M+1, $C_{17}H_{26}O_2$, 2%)

Evidence for the presence of **(226)** in the recrystallisation mother liquor.
M.S. (CI) : m/z 337 (M+1, $C_{22}H_{30}O_2$, 2%).

2,3-Dihydro-2,2,4,6,7-pentamethylbenzofuran (124b)

2,3,5-Trimethylphenol **(28b)** (13.62g, 0.1 mol) was dissolved in trifluoroacetic acid (30ml) under an atmosphere of argon at 100°C. 2-Methyl-2-propen-1-ol **(207)** (7.21g, 0.1 mol) was added dropwise over a period of 30mins. The solution was heated under reflux for 1hr. Formation of the benzofuran was monitored by tlc (ethyl acetate : petroleum ether 40-60°, 15:85). The solution was poured into ice, neutralised with 10%w/v sodium bicarbonate solution, washed with water (2x100ml), extracted with ethyl acetate (200 ml) and dried with magnesium sulphate. Evaporation of the solvent gave a dark brown oil. Crystallisation from methanol-water (3:1) afforded the title compound (6.72g, 35%) as a pale yellow crystalline solid, m.pt. 43-45°C (Lit. m.pt. 47°C[241]) , (ethyl acetate : petroleum ether 40-60°, 15:85), R_f 0.76. Mass spectrometric analysis of the mother liquor confirmed the presence of 2,3-dihydro-2,2,4,6,7-pentamethyl-(2-methyl-1-propenyl)-benzofuran **(209b)**.
IR (KBr) : υ 2979-2864 (sat. C-H str.), 1599 (C=C), 1366 (d,geminal CH_3) 1285 (C-O), 833 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.41 (6H, s, C-2-CH_3), 2.07 (3H, s, C-4-CH_3), 2.10 (3H, s, C-6-CH_3), 2.14 (3H, s, C-7-CH_3), 2.90 (2H, s, C-3-CH_2), 6.47 (1H, s, C-5-CH) ppm.
^{13}C NMR ($CDCl_3$) δ 11.53 (C-4-CH_3), 18.49 (C-7-CH_3), 19.30 (C-6-CH_3), 28.62 (C-2-$2CH_3$), 42.83 (C-3-CH_2), 85.83 (C-2), 115.29 (C-4), 122.12 (C-5-CH), 122.68 (C-7), 131.16 (C-6) 136.38 (C-8), 157.32 (C-9) ppm.
M.S. (EI) : m/z 190 ($M^{+\cdot}$, $C_{13}H_{18}O$, 82%), 175 ($M^{+\cdot}$, $C_{13}H_{18}O$ - CH_3, 100%), 160 (12%), 147 ($M^{+\cdot}$, $C_{13}H_{18}O$ - C_3H_7, 15%), 115 (16%), 105 (16%), 91 (19%), 77 (16%).
Analysis calcd. for $C_{13}H_{18}O$ (190) C, 82.06; H, 9.53. Found: C, 81.14; H, 9.52%.

Evidence for the presence of 2,3-Dihydro-2,2,4,6,7-pentamethyl-(2-methyl-1-propenyl)-benzofuran **(209b)** in the mother liquor.
M.S. (EI) : m/z 244 ($M^{+\cdot}$, $C_{17}H_{24}O$, 29%), 229 ($M^{+\cdot}$, $C_{17}H_{24}O$ - CH_3, 29%), 203 (52%), 190 (98%), 187 (15%), 175 (100%), 173 (19%), 147 (14%), 145 (14%), 91 (17%), 43 (19%).

The following compounds were prepared using the above method.
Those compounds which were obtained as oils were purified by short-path high vacuum distillation.

2,3-Dihydro-5-chloro-2,2-dimethylbenzofuran (124c)

4-Chlorophenol **(28c)** (25.76g, 0.20mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (15.16g, 0.21mol) to afford the title compound as a pale yellow oil (2.10g, 6%). B.pt. 82-84°C / 0.18mmHg, (Lit. b.pt. 117°C / 12 Torr[238]), TLC (ethyl acetate : petroleum ether 40-60°, 25:75), R_f 0.80, G.C. R_t 12.29 min.

^{1}H NMR ($CDCl_3$) : δ 1.46 (6H, s, C-2-2xCH_3), 2.98 (2H, s, C-3-CH_2), 6.61-6.64 (1H, d, *J* 7.50Hz, C-7-H), 7.02-7.03 (1H, s, *J* 3.0 Hz, C-4-H), 7.05-7.09 (1H, d, m, *J* 7.50 Hz, *J* 3.88 Hz, C-6-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 28.07 (C-2-2xCH_3), 42.75 (C-3-CH_2), 87.46 (C-2), 110.37 (Ar-CH), 116.73 (Ar -C), 125.20 (Ar-CH), 127.80 (Ar-CH), 129.00 (Ar-C), 157.53 (Ar-C) ppm.

GC-MS : m/z 184 ($M^{+\cdot}$, $C_{10}H_{11}OCl$, 28%), 182 ($M^{+\cdot}$, $C_{10}H_{11}OCl$, 72%), 169 ($M^{+\cdot}$, $C_{10}H_{11}OCl$ - CH_3, 36%), 167 ($M^{+\cdot}$, $C_{10}H_{11}OCl$ - CH_3, 100%), 147 (18%), 141 ($M^{+\cdot}$, $C_{13}H_{18}O$ - C_3H_7, 27%), 139 ($M^{+\cdot}$, $C_{13}H_{18}O$ - C_3H_7, 48%), 132 (18%), 119 (9%), 103 (28%), 91 (18%), 77 (27%).

2,3-Dihydro-2,2-dimethylnaphtho[2,1-b]furan (124f).

1-Napthol **(28f)** (28.84g, 0.2 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (14.44g, 0.2 mol) to afford the title compound (2.31g, 6%) as a red oil. B.pt. 58-60°C / 0.2mmHg, (Lit. Gum[240]).

^{1}H NMR ($CDCl_3$) : δ 1.50 (6H, s, C_2-2xCH_3), 3.08 (2H, s, C_3-CH_2), 7.21-7.24 (1H, d, *J* 8.0 Hz, Ar-H), 7.29-7.32 (1H, d, *J* 8.0Hz,Ar-H), 7.31-7.34 (1H, d, *J* 8.0Hz, meta-coupled, Ar-H), 7.97-8.00 (1H, d, meta-coupled, *J* 8.0 Hz, J_m Hz, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 28.63 (C-2-2xCH_3), 43.86 (C-3-CH_2), 87.53 (C-2), 119.69 (Ar-CH), 120.64 (Ar-C), 121.79 (Ar-CH), 122.87 (Ar-C), 123.39 (Ar-CH), 124.63 (Ar-CH), 125.13 (Ar-CH), 127.99 (Ar-CH), 134.18 (Ar-C), 154.37 (Ar-C) ppm.

2,3-Dihydro-2,2,6,7-tetramethylbenzofuran (124g)

2,3-Dimethylphenol **(28g)** (28.76g, 0.24 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (18.87g, 0.26 mol) to afford **(124g)** and **(210g)** which were separated by fractional distillation.

The first fraction was the title compound as a pale yellow oil (11.11g, 26%). B.pt. 82-86°C / 0.11mmHg, (Lit. b. pt 45°C / 0.05mmHg[241]) TLC (ethyl acetate : petroleum ether 40-60°, 25:75), G.C. R_t 12.03 min.

IR (film) : υ 3031 (ar. C-H str.), 2953-2867 (sat. C-H str), 1620 (C=C), 1459 (C-H def.), 1368 (d, geminal CH_3), 1081 (C-O) cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.46 (6H, s, C-2-2xCH_3), 2.11 (3H, s, C-6-CH_3), 2.22 (3H, s, C-7-CH_3), 2.97 (2H, s, C-3-CH_2), 6.61-6.64 (1H, d, *J* 7.44 Hz, C-4-H), 7.24 (1H. d, *J* 7.44 Hz, C-5-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 11.73 (C-6-CH_3), 19.43 (C-7-CH_3), 28.36 (C-2-2CH_3), 43.29 (C-3-CH_2), 85.97 (C-2), 118.26 (C-6), 121.07 (C-4-CH), 121.63 (C-5-CH), 123.73 (C-7), 136.41 (C-8), 157.66 (C-9) ppm.
GC-MS : m/z 176 ($M^{+\cdot}$, $C_{12}H_{16}O$, 58%), 161 ($M^{+\cdot}$, $C_{12}H_{16}O$ - CH_3, 100%), 143 (12%), 133 ($M^{+\cdot}$, $C_{12}H_{16}O$ - C_3H_7, 39%), 115 (7%), 105 (12%), 91 (16%), 77 (9%).

The second fraction was a yellow oil, b.pt. 116-120°C / 0.16mmHg, G.C. R_t 16.51 min, identified as 2,3-dihydro-5-isopropyl-2,2,6,7-tetramethylbenzofuran **(210g)**.
IR (film) : υ 2953-2867 (C-H str), 1620 (C=C), 1468 (C-H), 1367 (d, geminal CH_3), 1081 (C-O) cm^{-1}.
^{1}H NMR ($CDCl_3$) : δ 0.88-0.92 (6H, d, *J* 9 Hz, C-2'-2xCH_3), 1.43 (6H, s, C-2-2xCH_3), 1.75-1.78 (1H, m, *J* 7.5 Hz, C-2'-H), 2.12 (3H, s, C-6-CH_3), 2.13 (3H, s, C-7-CH_3), 2.39-2.42 (2H, d, *J* 7.1 Hz, C-1'-CH_2), 2.94 (2H, s, C-3-CH_2), 6.71 (1H, s, C-4-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 12.40 (C-6-CH_3), 15.27 (C-7-CH_3), 22.61 (C-2'-2xCH_3), 28.36 (C-2-2xCH_3), 29.53 (C-2'-CH), 43.28 (C-3-CH_2), 85.35 (C-2), 118.04 (C-6), 122.71 (C-7), 123.97 (C-4-CH), 131.17 (C-5), 134.04 (C-8), 155.90 (C-9) ppm.
GC-MS : m/z 232 ($M^{+\cdot}$, $C_{16}H_{24}O$, 25%), 189 ($M^{+\cdot}$, $C_{16}H_{24}O$ - C_3H_7, 100%), 159 (5%), 147 (7%), 119 (9%), 105 (4%), 91 (6%), 77 (3%).

Dihydro-2,2,4,7-tetramethylbenzofuran (124h)
2,5-Dimethylphenol **(28h)** (12.76g, 0.10 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (11.24g, 0.16 mol) to afford a mixture of the title compound **(124h)** and **210h** which were separated by fractional distillation.
The first fraction **(124h)** was a pale yellow oil (1.99g, 11%), b.pt 92-96°C / 0.06mmHg (Lit. b. pt 48°C / 0.03[241]), GC R_t 12.18 min.
IR (film) : υ 2954-2868 (C-H str.), 1594 (C=C), 1469-1415 (C-H def.), 1368 (d, geminal CH_3), 1268 (C-O), 879 (C-H bend) cm^{-1}.
^{1}H NMR ($CDCl_3$) : δ 1.47 (6H, s, C-2-2xCH_3), 2.16 (3H, s, C-4-CH_3), 2.17 (3H, s, C-7-CH_3), 2.91 (2H, s, C-3-CH_2), 6.53-6.56 (1H, d, *J* 7.46 Hz, Ar-H), 6.82-6.85 (1H, d *J* 7.61 Hz, Ar-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 15.10 (Ar-CH_3), 18.61 (Ar-CH_3), 28.60 (C-2-2xCH_3), 42.27 (C-3-CH_2), 85.76 (C-2), 116.64 (Ar-C), 120.54 (Ar-CH), 125.18 (Ar-C), 129.04 (Ar-CH), 131.98 (Ar-C), 157.06 (Ar-C) ppm.

GC-MS : m/z 176 ($M^{+\cdot}$, $C_{12}H_{16}O$, 52%), 161 ($M^{+\cdot}$, $C_{16}H_{24}O$ - CH_3, 100%), 133 ($M^{+\cdot}$, $C_{16}H_{24}O$ - C_3H_7, 38%), 105 (17%), 91 (22%), 77 (18%), 39 (32%).

The second fraction was also a yellow oil, B.pt. 124-127°C / 0.1mmHg, GC R_t 16.74 min and was identified as 2,3-dihydro-2,2,4,7-tetramethyl-5-isopropyl-benzofuran **(210h)**

IR (film) : υ 2953-2867 (sat. C-H str.), 1595 (C=C), 1462-1415 (C-H def.), 1367 (d, geminal CH_3), 1267 (C-O), 877 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.89-0.92 (6H, d, *J* 6.61 Hz, C-2'-2xCH_3), 1.46 (6H, s, C-2-2 x CH_3), 1.73-1.81 (1H, m, *J* 6.70 Hz, C-2'-H), 2.16 (3H, s, C-4-CH_3), 2.17 (3H, s, C-7-CH_3), 2.35-2.38 (2H, d, *J* 7.10 Hz, C-1'-CH_2), 2.92 (2H, s, C-3-CH_2), 6.67 (1H, s, C-6-CH) ppm.

^{13}C NMR ($CDCl_3$) : δ 15.09 (C-4-CH_3), 15.70 (C-7-CH_3), 22.60 (C-2'-2xCH_3), 28.23 (C-2-2xCH_3), 29.71 (C-2'-H), 41.97 (C-1'-CH_2), 42.97 (C-3-CH_2), 85.65 (C-2), 116.56 (Ar-C), 125.17 (Ar-C), 129.92 (Ar-C), 130.94 (C-6-CH), 131.16 (Ar-C), 155.05 (Ar-C) ppm.

GC-MS : m/z 232 ($M^{+\cdot}$, $C_{16}H_{24}O$, 32%), 189 ($M^{+\cdot}$, $C_{16}H_{24}O$ - C_3H_7, 100%), 147 (8%), 119 (13%), 91 (7%), 77 (6%), 39 (17%).

2,3-Dihydro-2,2,4,6-tetramethylbenzofuran (124i)

3,5-Dimethylphenol **(28i)** (24.45g, 0.20 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (15.15g, 0.21mol) to afford a mixture of the title compound which was separated by vacuum distillation and **210i** which was present in the mother liquor and was identified by GC/MS).

The title compound **(124i)** (9.51g, 27%) was a pale green oil. B.pt 84-86°C / 0.1mmHg (Lit. b. pt 88-89°C / 0.01 mmHg[243]), TLC (ethyl acetate : pet. ether 40-60°, 25:75), R_f 0.89, G.C. R_t 9.25 min.

IR (film) : υ 2972-2866 (C-H str.), 1620-1600 (C=C), 1492-1460 (C-H def.), 1369 (d, geminal CH_3), 1284 (C-O), 831 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.49 (6H, s, C-2-2xCH_3), 2.13 (3H, s, C-4-CH_3), 2.21 (3H, s, C-6-CH_3), 2.87 (2H, s, C-3-CH_2), 6.40 (1H, s, C-5-H), 7.19 (1H, s, C-7-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 18.80 (C-4-CH_3), 21.42 (C-6-CH_3), 28.45 (C-2-2xCH_3), 41.69 (C-3-CH_2), 86.38 (C-2), 107.56 (C-5-CH), 121.74 (C-7-CH), 122.95 (C-4), 134.44 (C-6), 137.98 (C-8), 158.85 (C-9) ppm.

GC-MS : m/z 176 ($M^{+\cdot}$, $C_{12}H_{16}O$, 68%), 161 ($M^{+\cdot}$, $C_{12}H_{16}O$ - CH_3, 100%), 146 (8%), 133 ($M^{+\cdot}$, $C_{12}H_{16}O$ - C_3H_7, 26%), 91 (16%), 71 (18%), 57 (44%), 43 (73%).

Analysis calcd. for $C_{12}H_{16}O$ (176) C, 81.77; H, 9.15. Found: C, 81.49; H, 9.06%.

The presence of 2,3-dihydro-5-isopropyl-2,2,4,6-tetramethylbenzofuran **(210i)** was confirmed by GC/MS.
G.C. R_t 12.51 min, G.C. R_t 12.47 min ($M^{+\cdot}$, $C_{16}H_{24}O$ - CH_3, 1%), 189 ($M^{+\cdot}$, $C_{16}H_{24}O$ - C_3H_7, 100%), 159 (4%), 147 (22%), 119 (8%), 91 (8%), 77 (3%).

2,3-Dihydro-5-chloro-2,2,6-trimethylbenzofuran (124j)
4-Chloro-3-methylphenol **(28j)** (28.52g, 0.20 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (16.35g, 0.22 mol) to afford a mixture of the title compound and **209j**. The compound **(124j)** was a yellow oil (12.0g, 31%) which was separated by fractional distillation. TLC (ethyl acetate : petroleum ether 40-60°, 25:75) R_f 0.81, b.pt. 72-78°C / 0.12mmHg, G.C. R_t 10.84 min.
IR (film) : υ 2973-2870 (sat. C-H str.), 1620-1583 (C=C), 1486-1458 (C-H def.) 1370 (d, geminal CH_3), 1262 (C-O), 867 (C-H bend), 779 (C-Cl) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.44 (6H, s, C-2-2CH_3), 2.28 (3H, s, C-6-CH_3), 2.93 (2H, s, C-3-CH_2), 6.58 (1H, s, C-4-CH), 7.06 (1H, s, C-7-CH) ppm.
^{13}C NMR ($CDCl_3$) : δ 20.35 (C-6-CH_3), 28.05 (C-2-2CH_3), 42.55 (C-3-CH_2), 87.36 (C-2), 111.58 (C-4-CH), 124.57 (C-5), 125.33 (C-7-CH), 126.27 (C-6), 135.34 (C-8), 157.70 (C-9) ppm.
GC-MS : m/z 198 ($M^{+\cdot}$, $C_{11}H_{13}ClO$, 37%), 196 ($M^{+\cdot}$, $C_{11}H_{13}ClO$, 100%), 183 ($M^{+\cdot}$, $C_{11}H_{13}ClO$ - CH_3, 32%), 181 ($M^{+\cdot}$, $C_{11}H_{13}ClO$ - CH_3, 90%), 161 (29%), 155 ($M^{+\cdot}$, $C_{11}H_{13}ClO$ - C_3H_7, 28%), 153 ($M^{+\cdot}$, $C_{11}H_{13}ClO$ - C_3H_7, 32%), 146 (25%), 119 (15%), 117 (15%), 105 (15%), 91 (22%).

The presence of 2,3-dihydro-5-chloro-2,2,6-trimethyl-7-(2-methyl-1-propenyl)-benzofuran **(209j)** was confirmed by GC/MS.
G.C. R_t 10.84 min.
GC-MS : m/z 252/250 ($M^{+\cdot}$, $C_{15}H_{19}ClO$, 100%), 237/235 ($M^{+\cdot}$, $C_{15}H_{19}ClO$ - CH_3, 90%), 219 (8%), 207 (7%), 193 (15%), 179 (6%), 141 (<5%), 115 (5%), 93 (<5%).

Dihydro-2,2,5,6-tetrabenzofuran (124l)
3,4-Dimethylphenol **(28l)** (24.25g, 0.2 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (15.26, 0.2 mol) to afford a mixture of **209l**, which was separated by fraction distillation and **210l** which was present in the mother liquor.
The first fraction was the title compound as a yellow oil (4.51g, 13%). B.pt. 52-60°C / 0.1mmHg (Lit. b. pt 50-65°C / 1 Torr[244]), TLC (ethyl acetate : pet. ether 40-60°, 25:75), R_f 0.95, GC R_t 10.11 min.
^1H NMR ($CDCl_3$) : δ 1.44 (6H, s, C-2-2xCH_3), 2.15 (3H, s, Ar-CH_3), 2.17 (3H, s, Ar-CH_3), 2.93 (2H, s, C-3-CH_2), 6.54 (1H, s, Ar-H), 6.89 (1H, s, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 19.42 (Ar-CH_3), 20.15 (Ar-CH_3), 28.25 (C-2-2xCH_3). 42.86 (C-3-CH_2), 86.39 (C-2), 110.72 (Ar-CH), 124.21 (Ar-C), 126.16 (Ar-CH), 127.66 (Ar-C), 136.10 (Ar-C), 157.22 (Ar-C) ppm.
GC-MS : m/z 176 ($M^{+\cdot}$, $C_{12}H_{16}O$, 62%), 161 ($M^{+\cdot}$, $C_{12}H_{16}O$ - CH_3, 100%), 143 (15%), 133 ($M^{+\cdot}$, $C_{12}H_{16}O$ - C_3H_7, 39%), 115 (8%), 105 (16%), 91(17%), 77 (11%).
Analysis calcd. for $C_{12}H_{16}O$ (176) C, 81.77; H, 9.15. Found: C, 80.90; H, 9.49%.

The presence of 2,3-dihydro-2,2,5,6-tetramethyl-7-(2-methyl-1-propenyl)-benzofuran **(209l)** (2.97g, 8%) was confirmed by GC/MS. GC R_t 14.30 min.
GC- MS : m/z 230 ($M^{+\cdot}$, $C_{16}H_{22}O$, 47%), 215 ($M^{+\cdot}$, $C_{16}H_{24}O$ - CH_3, 100%), 200 (13%), 187 (7%), 173 (14%), 159 (5%), 145 (5%), 129 (4%), 115 (5%), 91 (4%), 77 (4%).

The second fraction was a brown oil, B.pt. 72-76°C / 0.13mmHg, GC R_t 13.16 min and identified as 2,3-dihydro-2,2,5,6-tetramethyl-7-isopropyl-benzofuran **(210l)**
^1H NMR ($CDCl_3$) : δ 0.89-0.92 (6H, d, *J* 7.2 Hz, C-2'-2xCH_3), 1.44 (6H, s, C-2-2xCH_3), 2.08 (3H, s, C-5-CH3), 2.15 (3H, s, C-6-CH3), 2.29-2.42 (1H, m, *J* 8.9 Hz, C-2'-H), 2.12 (3H, s, C-6-CH_3), 2.91 (2H, s, C-3-CH_2), 6.69 (1H, s, C-4-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 15.99 (C-5-CH_3), 22.52 (C-6-CH_3), 28.52 (C-2'-2xCH_3), 28.34 (C-2-2xCH_3), 29.13 (C-2'-CH), 42.83 (C-3-CH_2), 85.53 (C-2), 120.31 (Ar-C), 124.76 (Ar-C), 127.11 (Ar-C), 130.27 (C-4-CH), 132.31 (Ar-C), 155.27 (Ar-C) ppm.
GC-MS : m/z 232 ($M^{+\cdot}$, $C_{16}H_{24}O$, 25%), 217 ($M^{+\cdot}$, $C_{16}H_{24}O$ - CH_3, 1%), 189 ($M^{+\cdot}$, $C_{16}H_{24}O$ - C_3H_7, 100%), 159 (4%), 147 (18%), 119 (8%), 105 (4%), 91 (8%), 77 (4%).

Dihydro-2,2,7-trimethylbenzofuran (124m)
2-Methylphenol **(28m)** (21.65g, 0.20 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (15.43g, 0.21 mol) to afford the title compound **124m** and **210m** (11.61g, 36%) which were separated by fractional distillation.
The first fraction was a pale yellow oil (0.82g, 3%), B. pt. 80 - 82°C / 0.25mmHg (Lit. b.pt 32°C / 0.1 mmHg[241]), TLC (ethyl acetate : pet. ether 40-60°, 25:75), R_f 0.77, R_t 9.81 min.
IR (film) : υ 3022 (aromat. C-H str.), 2971-2867 (sat. C-H str), 1598 (C=C), 1468 (C-H def.), 1368 (d, geminal CH_3), 1263 (C-O), 881 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.45 (6H, s, C-2-2xCH_3), 2.18 (3H, s, C-7-CH_3), 2.97 (2H, s, C-3-CH_2), 6.68-6.71 (1H, d, *J* 7.37 Hz, Ar-H), 6.89-6.95 (2H, m, *J* 8.02 Hz, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 15.58 (C-7-CH_3), 28.31 (C-2-2xCH_3), 43.29 (C-3-CH_2), 85.80 (C-2), 119.52 (Ar-C), 119.68 (Ar-CH), 122.41 (Ar-CH), 126.18 (Ar -C), 129.09 (Ar-CH), 157.43 (Ar-C) ppm.
GC-MS : m/z 162 ($M^{+\cdot}$, $C_{11}H_{14}O$, 59%), 147 ($M^{+\cdot}$, $C_{11}H_{14}O$ - CH_3, 100%), 129 (8%), 119 ($M^{+\cdot}$, $C_{11}H_{14}O$ - C_3H_7, 42%), 105 (7%), 91 (27%), 77 (11%), 39 (15%).

The second fraction was a dark yellow oil (11.61g, 36%). B.pt. 60-64°C / 0.2mmHg, G.C. R_t 14.81min and was identified as 2,3-dihydro-2,2,7-trimethyl-5-isopropyl-benzofuran **(210m)**.
IR (film) : υ 3022 (arom. C-H str.), 2971-2867 (sat. C-H str), 1598 (C=C), 1466 (C-H def.), 1368 (d, geminal CH_3), 1263-1135 (C-O), 861 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 0.86-0.89 (6H, d, *J* 7.5Hz, C-2'-2xCH_3), 1.46 (6H, s, C-2-2xCH_3), 2.16 (3H, s, C-7-CH_3), 1.70-1.82 (2H, m, *J* 7.5Hz,C-2'-H), 2.33-2.36 (2H, d, *J* 7.5Hz, C-1'-CH_2), 2.96 (2H, s, C-3-CH_2), 6.69 (1H, s, Ar-H), 6.73 (1H, s, Ar-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 15.39 (C-7-CH_3), 22.42 (C-2'-2xCH_3), 28.37 (C-2-2xCH_3), 30.53 (C-2'-H), 43.31 (C-1'-CH_2), 44.97 (C-3-CH_2), 85.87 (C-2), 118.75 (Ar-C), 122.99 (Ar -CH), 125.97 (Ar-C), 129.81 (Ar-CH), 133.09 (Ar-C), 155.55 (Ar-C) ppm.
GC-MS : m/z 218 ($M^{+\cdot}$, $C_{15}H_{22}O$, 30%), 175 ($M^{+\cdot}$, $C_{15}H_{22}O$ - C_3H_7, 100%), 147 (5%), 133 (8%), 105 (9%), 91 (5%), 77 (4%), 39 (8%).

2,3-Dihydro-2,2,6-trimethylbenzofuran (124n)
3-Methylphenol **(28n)** (21.62g, 0.20 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (15.20g, 0.21 mol) to afford the title compound **124n** and **210n** which were separated by fractional distillation.
The first fraction was a colourless oil (10.38g, 32%. B.pt. 80-82°C / 0.28mmHg (Lit. b. pt 131°C / 50 mmHg[133]), TLC (ethyl acetate: pet ether 40-60°, 25:75), R_f 0.76, G.C. R_t 10.56 min.
IR (film) : υ 3049 (ar. C-H str.), 2973-2862 (sat. C-H str.), 1621-1590 (C=C), 1498-1466 (C-H def.), 1369 (d, geminal, CH_3), 1277 (C-O), 798 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.45 (6H, s, C-2-2xCH_3), 2.28 (3H, s, C-6-CH_3), 2.94 (2H, s, C-3-CH_2), 6.55 (1H, s, C-7-H), 6.60-6.63 (1H, d, meta-coupled, *J* 7.5 Hz, J_m 0.65 Hz, C-5-H), 6.97-7.00 (1H, d, *J* 7.50 Hz, C-4-CH_3) ppm.
^{13}C NMR ($CDCl_3$) : δ 21.49 (C-6-CH_3), 28.19 (C-2-2xCH_3), 42.61 (C-3-CH_2), 86.61 (C-2), 110.24 (Ar-CH), 120.61 (Ar-CH), 123.98 (Ar-C), 124.70 (Ar-CH), 138.01 (Ar-C), 159.06 (Ar-C) ppm.
GC-MS: m/z 162 ($M^{+\cdot}$, $C_{11}H_{14}O$, 77%), 147 ($M^{+\cdot}$, $C_{11}H_{14}O$ - CH_3, 100%), 129 (6%), 119 ($M^{+\cdot}$, $C_{11}H_{14}O$ - C_3H_7, 37%), 105 (8%), 91 (20%), 77 (9%), 39 (12%).

Analysis calcd. for $C_{11}H_{14}O$ (162) C, 81.44; H, 8.70. Found: C, 81.29; H, 8.87%.

The second fraction was a yellow oil (0.84g, 3%), b.pt. 64-68°C / 0.25mmHg, G.C. R_t 15.64 min, G.C. R_t 14.46 min was identified as 2,3-dihydro-2,2,6-trimethyl-5-isopropylbenzofuran **(210n)**.
IR (film) : υ 2954-2867 (C-H str), 1622-1591 (C=C), 1493-1464 (C-H saturated def.), 1367 (d,geminal CH_3), 1271 (C-O), 877 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 0.89-0.92 (6H, d, *J* 7.50 Hz, C-2'-2xCH_3), 1.44 (6H, s, C-2-2xCH_3), 1.72-1.83 (1H, m, *J* 7.50 Hz, C-2'-H), 2.21 (3H, s, C-6-CH_3), 2.36-2.39 (2H, d, *J* 7.50 Hz, C-1'-CH_2), 2.94 (2H, s, C-3-CH_2), 6.52 (1H, s, Ar-H), 6.84 (1H, s, Ar-H) ppm.
^{13}C NMR ($CDCl_3$) : δ18.65 (C-6-CH_3), 22.57 (C-2'-2xCH_3), 28.21 (C-2-2xCH_3), 29.54 (C-2'-CH), 42.20 (C-1'-CH_2), 42.81 (C-3-CH_2), 86.35 (C-2), 110.88 (Ar-CH), 124.51 (Ar -C), 126.28 (Ar-CH), 131.05 (Ar-C), 135.72 (Ar-C), 157.02 (Ar-C) ppm.
GC-MS : m/z 218 ($M^{+\cdot}$, $C_{15}H_{22}O$, 39%), 175 ($M^{+\cdot}$, $C_{15}H_{22}O$ - C_3H_7, 100%), 157 (5%), 133 (7%), 105 (8%), 91 (4%), 77 (5%), 39 (7%).

2,3-Dihydro-2,2,5-trimethylbenzofuran (124o)
4-Methylphenol **(28o)** (21.62g, 0.20 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (15.43g, 0.21 mol) to afford the title compound **124o** containing traces **210o**.
The title compound **124o** was a yellow oil (3.24g, 10%), B.pt. 68-72°C / 0.22mmHg Lit. b.pt 32°C / 0.1 mmHg[241]), TLC (ethyl acetate : pet ether 40-60°, 25:75), R_f 0.77, G.C. R_t 10.53 min
IR (film) : υ 2973-2866 (C-H str), 1618 (C=C), 1468 (C-H def.), 1491, 1369 (d, geminal, CH_3), 1256 (C-O), 809 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.44 (6H, s, C-2-2xCH_3), 2.26 (3H, s, Ar-CH_3), 2.95 (2H, s, C-3-CH_2), 6.60-6.62 (1H, d, *J* 8.0 Hz, Ar-H), 6.87-6.90 (1H, d, *J* 8.0 Hz, Ar-H), 7.00 (1H, s, C-4-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 20.74 (Ar-CH_3), 28.16 (C-2-2xCH_3), 42.96 (C-3-CH_2), 86.31 (C-2), 109.03 (Ar-CH), 125.73 (Ar-CH), 127.05 (Ar-C), 128.28 (Ar-CH), 129.09 (Ar-C), 156.77 (Ar-C) ppm.
GC-MS : m/z 162 ($M^{+\cdot}$, $C_{11}H_{14}O$, 67%), 147 ($M^{+\cdot}$, $C_{11}H_{14}O$ - CH_3, 100%), 129 (8%), 119 ($M^{+\cdot}$, $C_{11}H_{14}O$ - C_3H_7, 45%), 105 (10%), 91 (29%), 77 (15%), 39 (13%).

The presence of 2,3-dihydro-2,2,4-trimethyl-7-isopropyl-benzofuran **(210o)** was confirmed by GC/MS.
GC R_t 14.33 min.

GC-MS : m/z 218 ($M^{+\cdot}$, $C_{15}H_{22}O$, 23%), 175 ($M^{+\cdot}$, $C_{11}H_{14}O$ - C_3H_7, 100%), 161 (6%), 147 (4%), 133 (38%), 119 (6%), 105 (8%), 91 (6%), 77 (5%).

2,3-Dihydro-5-methoxy-2,2-dimethylbenzofuran (124p)

4-Methoxyphenol **(28p)** (24.80g, 0.20mol) was reacted with 2-methylpropen-1-ol **(207)** (15.62g, 0.21mol) to afford the title compound (1.33g, 4%) as a yellow oil.

B.pt. 62-66°C / 0.13mmHg (Lit. nmr evidence[245]), TLC (ethyl acetate : pet. ether 40-60°, 25:75), R_f 0.83.

IR (film) : υ 2965 (sat. C-H str), 1512 (C=C), 1488 (C-H def.), 1368 (d,geminal CH_3), 1254 (C-O), 823 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.45 (6H, s, C-2-2xCH_3), 2.96 (2H, s, C-3-CH_2), 3.71 (3H, s, C-5-OCH_3), 6.59 (1H, s, Ar-H), 6.60 (1H, s, Ar-H), 7.06-7.09 (1H, s, meta-coupled, *J* 3.04 Hz, C-6-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 28.12 (C-2-2xCH_3), 43.34 (C-3-CH_2), 55.99 (C-5-OCH_3), 86.49 (C-2), 109.29 (Ar-CH), 111.58 (Ar-CH), 112.82 (Ar-CH), 128.05 (Ar-C), 153.07 (Ar-C), 153.80 (Ar-C) ppm.

Analysis calcd. for $C_{11}H_{14}O_2$ (178) C, 74.13; H, 7.79. Found: C, 74.36; H, 9.14%.

2,3-Dihydro-5-bromo-2,2-dimethylbenzofuran (124q)

4-Bromophenol **(28q)** (34.15g, 0.20 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (15.15g, 0.21mol) to afford the title compound as a yellow oil (1.48g, 3%) and was obtained by fractional distillation, b.pt. 56-60°C / 0.09mmHg (Lit. NMR evidence[246]), TLC (ethyl acetate : pet. ether40-60°, 25:75), R_f 0.91, GC R_t 13.76 min.

IR (film) : υ 2961-2871 (C-H saturated str.), 1475 (C-H saturated def.), 1370 (d, geminal CH_3), 1258 (C-O), 809 (C-H bend), 661 (C-Br) cm^{-1}.

^1H NMR ($CDCl_3$) : δ1.44 (6H, s, C-2-2xCH_3), 2.96 (2H, s, C-3-CH_2), 6.56-6.59 (1H, d, *J* 7.50Hz, C-7-H), 7.15-7.14 (1H, s, meta-coupled, J_m 2.95 Hz, C-4-H), 7.7.17-7.21 (1H, d, meta-coupled, *J* 6.37 Hz, J_m 2.07 Hz, C-6-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 27.49 (C-2-2xCH_3), 42.64 (C-3-CH_2), 87.35 (C-2), 111.00 (Ar-CH), 111.53 (Ar-C), 128.03 (Ar-CH), 129.53 (Ar-C), 130.67 (Ar-CH), 158.01 (Ar-C) ppm.

GC-MS : m/z 228 ($M^{+\cdot}$, $C_{10}H_{11}OBr$, 100%), 226 ($M^{+\cdot}$, $C_{16}H_{24}O$, 87%), 213 ($M^{+\cdot}$, $C_{16}H_{24}O$ - CH_3, 57%), 211 ($M^{+\cdot}$, $C_{16}H_{24}O$ - CH_3, 56%), 185 ($M^{+\cdot}$, $C_{16}H_{24}O$ - C_3H_7, 12%), 147 (21%), 132 (71%), 119 (13%), 91 (22%), 77 (23%).

2,3-Dihydro-2,2-dimethylbenzofuran (124r)

Phenol **(28r)** (32.92, 0.35 mol) was reacted with 2-methyl-2-propen-1-ol **(207)** (25.96g, 0.36 mol) to afford the title compound **124r** which was separated by fraction distillation and **210r** which was present in the mother liquor.

The title compound **(124r)** was a yellow oil (0.30g, 1%). B.pt. 52-54°C / 0.17mmHg (Lit. b.pt 31°C / 0.1 mmHg[241]). TLC (ethyl acetate : pet. ether 40-60°, 25:75), R_f 0.87, GC R_t 8.33 min.

^{1}H NMR ($CDCl_3$) : δ 1.49 (6H, s, C-2-2xCH_3), 3.02 (2H, s, C-3-CH_2), 6.73-6.76 (1H, d, J_o 7.50 Hz, J_m 0.95 Hz, Ar-H), 7.09-7.12 (1H, d, J 7.50 Hz, Ar-H), 7.12-7.16 (1H, m, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 28.23 (C-2-2xCH_3), 42.87 (C-3-CH_2), 86.48 (C-2), 109.54 (Ar-CH), 119.95 (Ar-CH), 125.17 (Ar-CH), 127.09 (Ar-C), 127.98 (Ar-CH), 158.86 (Ar-C) ppm.

GC-MS : m/z 148 ($M^{+\cdot}$, $C_{10}H_{12}O$, 67%), 133 ($M^{+\cdot}$, $C_{16}H_{24}O$ - CH_3, 100%), 119 (7%), 105 ($M^{+\cdot}$, $C_{16}H_{24}O$ - C_3H_7, 63%), 91 (16%), 77 (20%), 63 (10%), 50 (13%).

The presence of 2,3-dihydro-2,2-dimethyl-5-isopropylbenzofuran **(210r)** was confirmed by GC/MS.

GC R_t 14.18 min.

GC-MS : m/z 204 ($M^{+\cdot}$, $C_{14}H_{20}O$, 33%), 161 ($M^{+\cdot}$, $C_{14}H_{20}O$ - C_3H_7, 100%), 143 (6%), 133, (5%), 119 (12%), 104 (7%), 91 (13%), 77 (10%), 55 (20%).

2,3-Dihydro-2,2,4,6,7-pentamethylbenzofuran (124a)

Trimethylhydroquinone **(28a)** (45.82g, 0.30 mol) was stirred in toluene (30 ml) at room temperature under an atmosphere of argon. Isobutyraldehyde **(208)** (22.58g, 0.30 mol) and concentrated sulphuric acid (1ml) were added over 30mins and the reaction mixture was heated under reflux for 4 hrs. The mixture was poured onto ice (200g), neutralised with 10%w/v sodium bicarbonate solution (500 ml), extracted with ethyl acetate (200 ml) washed with water and dried over anhydrous magnesium sulphate. The solvent was removed *in vacuo* to give a brown oil which was treated with Claisens alkali, acidified with concentrated hydrochloric acid washed water (2 x 100ml), and dried over anhydrous magnesium sulphate. Filtration of the drying agent and removal of the solvent *in vacuo* afforded a red oil. To this oil was added methanol (100 ml), and concentrated hydrochloric acid (10 ml); the mixture was heated under reflux for 1hr. The resulting solution was poured into ice (100g), extracted with ethyl acetate (200 ml), neutralised with 10%w/v sodium bicarbonate solution, washed with water (2x100 ml) and dried with anhydrous magnesium sulphate. Filtration of the drying agent and removal of the solvent *in vacuo* afforded the title compoumd as a brown oil (13.86g, 22%), (Lit. m.pt 122-

123°C[130]). Analysis of the mother liquor of **124a**, by GC/MS showed the presence of **223.**

GC R_t 18.66 min.

GC-MS : m/z 206 ($M^{+\cdot}$, $C_{13}H_{18}O_2$, 100%), 191 ($M^{+\cdot}$, $C_{13}H_{18}O_2$ - CH_3, 73%), 173 (18%), 163 ($M^{+\cdot}$, $C_{13}H_{18}O_2$ - C_3H_7, 19%), 145 (10%) 135 (13%), 121 (8%), 105 (8%), 91 (9%), 77 (8%).

The presence of 2,2,4,6,7-pentamethyl-5-(2-methyl-propenyloxy)-2,3-dihydrobenzofuran **(223)** was identified by GC/MS.

GC R_t 27.96 min.

GC-MS : m/z 262 ($M^{+\cdot}$, C_{17}, $H_{26}O_2$, 28%), 203 (100%), 189 (37%), 173 (43%), 163 (12%), 149 (12%), 133 (17%), 119 (10%), 91 (14%).

2,3-Dihydro-2,2,4,6,7-pentamethylbenzofuran (124b)

2,3,5-Trimethylphenol **(28b)** (40.83g, 0.30 mol) was dissolved in toluene (75 ml) under an atmosphere of argon. To the solution was added isobutyraldehyde **(208)** (21.63g, 0.30 mol) and concentrated sulphuric acid (2.0g) and the reaction mixture was heated under reflux for 4 hrs in a Dean and Stark apparatus. The solvent was removed *in vacuo* to afford a brown oil. The oil was dissolved in ethyl acetate (200 ml), washed with Claisens alkali solution and acidified with concentrated hydrochloric acid . The organic layer was washed with brine (2x200ml) and water (2x200ml) and dried over anhydrous magnesium sulphate. After the filtration of the drying agent and removal of the solvent *in vacuo* a dark brown oil was obtained which solidified on standing. Crystallisation from aqueous methanol afforded the title compound as a pale yellow solid (50.99g, 83%). M.pt 46-47°C (Lit. M.pt 47°C[241]), G.C. R_t 13.54 min.

^{1}H NMR ($CDCl_3$) : δ 1.45 (6H, s, 2xC-2-CH_3), 2.07 (3H, s, C-4-CH_3), 2.13 (3H, s, C-6-CH_3), 2.19 (3H, s, C-7-CH_3), 2.89 (2H, s, C-3-CH_2), 6.47 (1H, s, C-5-CH) ppm.

^{13}C NMR ($CDCl_3$) δ 11.64 (C-4-CH_3), 18.59 (C-7-CH_3), 19.41 (C-6-CH_3), 28.71 (C-2-2CH_3), 42.37 (C-3-CH_2), 85.90 (C-2), 115.37 (C-4), 122.23 (C-5-CH), 122.75 (C-7), 131.22 (C-6) 136.45 (C-8), 157.40 (C-9) ppm.

GC-MS : m/z 190 ($M^{+\cdot}$, $C_{13}H_{18}O$, 95%), 175 ($M^{+\cdot}$, $C_{13}H_{18}O$ - CH_3, 100%), 157 (15%), 147 ($M^{+\cdot}$, $C_{13}H_{18}O$ - C_3H_7, 18%), 133 (5%), 119 (9%), 105 (9%), 91 (8%).

Analysis calcd. for $C_{13}H_{18}O$ (190) C, 82.06; H, 9.53. Found: C, 81.73; H, 9.40%.

The following compounds were synthesised using the method outlined as above.

The compounds which were obtained as oils were purified by high vacuum distillation.

2,3-Dihydro-5-chloro-2,2-dimethylbenzofuran (124c)

4-Chlorophenol **(28c)** (2.20g, 0.20mol) was reacted with isobutyraldehyde **(208)** (14.55g, 0.21mol) to afford the title compound (2.22g, 6%) as a yellow oil. B.pt 60-62°C / 0.13mmHg (Lit. b. pt 117°C / 12 Torr), GC R_t 12.68 min.

IR (film) υ 2967-2874 (sat. C-H str), 1756-1717 (C=C), 1475 (C-H def.), 1370 (d,geminal CH_3), 1256 (C-O), 823 (C-H bend) 781 (C-Cl) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.46 (6H, s, C-2-2xCH_3), 2.98 (2H, s, C-3-CH_2), 6.61-6.64 (1H, d, *J* 8.43 Hz, C-7-H), 7.02-7.03 (1H, s, meta-coupled, J_m 2.30 Hz, C-4-H), 7.05-7.08 (1H, d, meta-coupled, *J* 7.89 Hz, J_m 3.79 Hz, C-6-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 28.03 (C-2-2xCH_3), 42.74 (C-3-CH_2), 87.42 (C-2), 110.35 (Ar-CH), 124.48 (Ar-C), 125.19 (Ar-CH), 127.77 (Ar-CH), 128.99 (Ar-C), 157.37 (Ar-C) ppm.

GC-MS : m/z 184 ($M^{+\cdot}$, $C_{10}H_{13}OCl$, 23%), 182 ($M^{+\cdot}$, $C_{10}H_{13}OCl$, 70%), 169 ($M^{+\cdot}$, $C_{10}H_{13}OCl$ - CH_3, 33%), 167 ($M^{+\cdot}$, $C_{10}H_{13}OCl$ - CH_3, 100%), 141 ($M^{+\cdot}$, $C_{10}H_{13}OCl$ - C_3H_7, 28%), 139 ($M^{+\cdot}$, $C_{10}H_{13}OCl$ - C_3H_7, 47%), 119 (12%), 103 (48%), 91 (22%), 77 (34%), 63 (17%), 51 (28%).

2,3-Dihydro-2,2-dimethylnaphtho[2,1-b]benzofuran (124f)

1-Naphthol **(28f)** (28.25g, 0.20 mol) was reacted with isobutyraldehyde **(208)** (14.62g, 0.20 mol) to afford the title compound (9.02g, 23%) as a yellow semi-crystalline solid. B.pt 64-66°C / 0.22mmHg (Lit. Gum[240]), GC R_t 17.43 min.

IR (film) υ 3058 (arom. C-H str.), 2972-2854 (C-H saturated str), 1632-1600 (C=C), 1466 (C-H saturated def.), 1371 (d, geminal CH_3), 1261 (C-O), 809 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.53 (6H, s, C-2-2xCH_3), 3.23 (2H, s, C-3-CH_2), 7.04-7.08 (1H, d, *J* 8.0 Hz, Ar-H), 7.23-7.29 (1H, dd, meta-coupled, *J* 8.18, *J* 8.12, J_m 1.37 Hz, Ar-H), 7.39-7.43 (1H, dd meta-coupled, *J* 8.28 Hz, *J* 7.95 Hz, *J* 1.27 Hz, Ar-H), 7.49-7.53 (1H, d, meta-coupled, *J* 8.23 Hz, J_m 0.54 Hz, Ar-H), 7.62-7.66 (1H, d, *J* 8.74 Hz, Ar-H), 7.75-7.78 (1H, d, *J* 8.21 Hz, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 28.52 (C-2-2xCH_3), 41.68 (C-3-CH_2), 87.41 (C-2), 112.38 (Ar-CH), 118.13 (Ar -C), 122.56 (Ar-CH), 126.49 (Ar-CH), 128.68 (Ar-CH), 128.90 (Ar-CH), 129.00 (Ar-C), 131.13 (Ar-C), 131.13 (Ar-C), 156.21 (Ar-C) ppm.

GC-MS : m/z 198 ($M^{+\cdot}$, $C_{14}H_{14}O$, 100%), 183 ($M^{+\cdot}$, $C_{14}H_{14}O$ - CH_3, 84%), 165 ($M^{+\cdot}$, $C_{14}H_{14}O$ - C_3H_7, 38%), 153 (19%), 139 (11%), 128 (13%), 91 (<5%), 77 (11%).

Analysis calcd. for $C_{14}H_{14}O$ (198) C, 84.81; H, 7.12. Found: C, 84.51; H, 7.82%.

2,3-Dihydro-2,2,4,7-tetramethylbenzofuran (124h)

2,5-Dimethylphenol **(28h)** (36.70g, 0.30 mol) was reacted with isobutyraldehyde **(208)** (21.95g, 0.30 mol) to afford a mixture of **124h**, **209h** and **210h** which were separated by fractional distillation.

The first fraction was the title compound **(124h)** as a pale yellow oil (7.72g, 15%), b.pt 58-64°C / 0.04mmHg (Lit. b. pt 48°C / 0.03 mmHg[241]), G.C. R_t 11.64 min.

IR (film) υ 3051 (arom. C-H), 2972-2923 (sat. C-H str.), 1594 (C=C), 1460 (C-H def.), 1368 (d, geminal CH_3), 1267 (C-O), 867 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.49 (6H, s, C-2-2xCH_3), 2.18 (3H, s, C-4-CH_3), 2.19 (3H, s, C-7-CH_3), 2.92 (2H, s, C-3-CH_2), 6.53-6.50 (1H, d, *J* 7.61 Hz, Ar-H), 6.84-6.87 (1H, d *J* 7.75 Hz, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 15.22 (Ar-CH_3), 18.72 (Ar-CH_3), 28.70 (C-2-2xCH_3), 42.36 (C-3-CH_2), 85.89 (C-2), 116.73 (Ar-C), 120.68 (Ar-CH), 125.26 (Ar-C), 129.17 (Ar-CH), 132.07 (Ar-C), 157.15 (Ar-C) ppm.

GC-MS : m/z 176 ($M^{+\cdot}$, $C_{12}H_{16}O$, 68%), 161 ($M^{+\cdot}$, $C_{12}H_{16}O$ - CH_3, 100%), 143 (14%), 133 ($M^{+\cdot}$, $C_{12}H_{16}O$ - C_3H_7, 35%), 115 (9%), 105 (12%), 91 (15%), 77 (9%).

Analysis calcd. for $C_{12}H_{16}O$ (176) C, 81.77; H, 9.15. Found: C, 81.18; H, 9.89%.

The second fraction was a yellow oil (4.16g, 6.0%) and was identified as 2,3-dihydro-2,2,4,7-tetramethyl-5-(2-methyl-1-propenyl)benzofuran **(209h)**.

Compound **124h** has 80% of **209h** (^1H NMR). B.pt 112-116°C / 0.06mm Hg, G.C. R_t 16.51 min.

IR (film) : υ 2970-2868 (sat. C-H str.), 1592 (C=C), 1460 (C-H def.), 1366 (d, geminal CH_3), 1258 (C-O), 878 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.47 (6H, s, C-2-2xCH_3), 1.67 (3H, s, C-2'-CH_3), 1.86 (3H, s, C-2'-CH_3), 2.04 (3H, s, Ar-CH_3), 2.23 (3H, s, Ar-CH_3), 2.92 (2H, s, C-3-CH_2), 6.14 (1H, s, C-1'-H), 6.73 (1H, s, Ar-CH) ppm.

^{13}C NMR ($CDCl_3$) : δ 15.13 (Ar-CH_3), 16.58 (Ar-CH_3), 19.02 (C-2'-CH_3), 26.03 (C-2'-CH_3), 28.90 (C-2-2CH_3), 85.94 (C-2), 115.81 (Ar-C), 123.94 (C-1'-CH), 129.58 (C-2'), 130.25 (Ar-CH), 133.71 (Ar-C), 136.91 (Ar-C), 152.67 (Ar-C), 155.39 (Ar-C) ppm.

GC-MS : m/z 230 ($M^{+\cdot}$, $C_{16}H_{22}O$, 100%), 215 ($M^{+\cdot}$, $C_{16}H_{22}O$ - CH_3, 54%), 187 ($M^{+\cdot}$, $C_{16}H_{22}O$ - C_3H_7, 16%), 173 (41%), 159 (24%), 145 (11%), 131 (8%), 91 (9%).

Analysis calcd. for $C_{16}H_{22}O$ (230) C, 83.436; H, 9.63. Found: C, 80.22; H, 10.48%.

The third fraction was a yellow oil (3.12g, 6%), b.pt. 96-110°C / 0.06mm Hg, G.C. R_t 16.19 min and identified as 2,3-dihydro-2,2,4,7-tetramethyl-5-isopropylbenzofuran **(210h)**.

IR (film) : υ 2953-2867 (sat. C-H str.), 1595 (C=C), 1462-1415 (C-H def.), 1367 (d, geminal CH_3), 1267 (C-O), 877 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 0.89-0.92 (3H, d, *J* 9.15 Hz, C-2'-2xCH_3), 1.46 (6H, s, C-2-2x CH_3), 1.73-1.80 (1H, m, *J* 6.75 Hz, C-2'-H), 2.16 (3H, s, C-4-CH_3), 2.17 (3H, s, C-7-CH_3), 2.35-2.38 (2H, d, *J* 7.09 Hz, C-1'-CH_2), 2.91 (2H, s, C-3-CH_2), 6.67 (1H, s, C-6-CH) ppm.
^{13}C NMR ($CDCl_3$) : δ 14.49 (C-4-CH_3), 22.63 (C-7-CH_3), 28.30 (C-2'-2xCH_3), 28.67 (C-2-2xCH_3), 29.54 (C-2'-H), 41.80 (C-1'-CH_2), 43.03 (C-3-CH_2), 85.81 (C-2), 114.54 (Ar-C), 116.74 (C-6-CH), 125.64 (Ar-C), 132.05 (Ar-C), 134.79 (Ar-C), 151.72 (Ar-C) ppm.
GC-MS : m/z 232 ($M^{+\cdot}$, $C_{16}H_{24}O$, 22%), 189 ($M^{+\cdot}$, $C_{16}H_{24}O$ - C_3H_7, 100%), 159 (5%), 147 (7%), 119 (12%), 105 (3%), 91 (6%), 77 (3%).
Analysis calcd. for $C_{15}H_{24}O$ (232) C, 82.70; H, 10.41. Found: C, 81.41; H, 10.19%.

2,3-Dihydro-2,2,4,6-tetramethylbenzofuran (124i)
3,5-Dimethylphenol **(28i)** (36.85g, 0.30 mol) was reacted with isobutyraldehyde **(208)** (19.08g, 0.26 mol) to afford a mixture of the title compound **(124i)** which was separated by fractional distillation. Compound **209i** which was confirmed by NMR.
The title compound was a pale yellow oil (19.79g, 38%), b.pt 50-56°C / 0.08mmHg (Lit. b. pt 88-89°C / 0.01 mmHg[243]). TLC (ethyl acetate : pet ether 40-60°, 25:75) R_f 0.80, G.C. R_t 12.10 min.
IR (film) : υ 2972 (sat. C-H str.), 1620-1600 (C=C), 1492-1460 (C-H def.), 1368 (d, geminal CH_3), 1284 (C-O), 872-831 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.43 (6H, s, C-2-2xCH_3), 2.15 (3H, s, C-4-CH_3), 2.24 (3H, s, C-6-CH_3), 2.84 (2H, s, C-3-CH_2), 6.38 (1H, s, C-5-H), 6.45 (1H, s, C-7-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 18.77 (C-4-CH_3), 21.15 (C-6-CH_3), 28.40 (C-2-2xCH_3), 41.69 (C-3-CH_2), 86.25 (C-2), 107.56 (C-5-CH), 121.21 (C-7-CH), 122.90 (C-4), 134.33 (C-6), 137.86 (C-8), 158.86 (C-9) ppm.
GC-MS : m/z 176 ($M^{+\cdot}$, $C_{12}H_{16}O$, 100%), 161 ($M^{+\cdot}$, $C_{12}H_{16}O$ - CH_3, 60%), 143 (8%), 133 ($M^{+\cdot}$, $C_{12}H_{16}O$ - C_3H_7, 20%), 117 (5%), 105 (8%), 91 (2%).
Analysis calcd. for $C_{16}H_{22}O$ (230) C, 81.27; H, 9.15. Found: C, 81.30; H, 9.28%.

Evidence for the presence of 2,3-dihydro-2,2,4,6-tetramethyl-5-(2-methyl-1-propenyl)-benzofuran **(209i)** was confirmed by NMR.
Compound **124i** contains 18% pure of **(209i)** (^1H NMR), G.C. R_t 17.31 min.
^1H NMR ($CDCl_3$) : δ 1.45 (6H, s, C-2-2xCH_3), 1.56 (3H, s, C-2'-CH_3), 1.89 (3H, s, C-2'-CH_3), 2.10 (3H, s, Ar-CH_3) 2.24 (3H, s, Ar-CH_3), 2.92 (2H, s, C-3-CH_2), 5.95 (1H, s, broad, C-1'-H), 6.72 (1H, s, Ar-H) ppm.

GC-MS : m/z 230 ($M^{+\cdot}$, $C_{16}H_{22}O$, 48%), 215 ($M^{+\cdot}$, $C_{16}H_{22}O$ - CH_3, 100%), 200 (8%), 185 (9%), 173 (12%), 159 (9%), 142 (8%), 128 (5%), 115 (<5%), 91 (10%), 77 (5%).

2,3-Dihydro-5-chloro-2,2,6-trimethylbenzofuran (124j)

4-Chloro-3-methylphenol **(28j)** (42.90g, 0.30 mol) was reacted with isobutyraldehyde **(208)** (121.96g, 0.30 mol) to afford a mixture of the title compound **124j** which was separated by fractional distillation, **209j** and **210j** which were present in the mother liquor of **124j** and were identified by GC/MS.

The title compound was a yellow oil (7.01g, 12%), TLC (ethyl acetate : pet. ether 40-60°, 25:75) R_f 0.79, b.pt 62-66°C / 0.09mmHg, G.C. R_t 13.88 min.

IR (film) : υ 2976-2855 (sat. C-H str.), 1619-1583 (C=C), 1485-1460 (C-H def.) 1370 (d, geminal CH_3), 1285 (C-O), 867 (C-H bend), 778 (C-Cl) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.44 (6H, s, C-2-2xCH_3), 2.28 (3H, s, C-6-CH_3), 2.94 (2H, s, C-3-CH_2), 6.58 (1H, s, C-4-H), 7.06 (1H, s, C-7-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 20.33 (C-6-CH_3), 28.03 (C-2-2CH_3), 42.54 (C-3-CH_2), 87.36 (C-2), 111.60 (C-4-CH), 124.63 (C-5), 125.35 (C-7-CH), 126.26 (C-6), 135.34 (C-8), 157.63 (C-9) ppm.

GC-MS : m/z 198 ($M^{+\cdot}$, $C_{11}H_{13}OCl$, 32%), 196 ($M^{+\cdot}$, $C_{11}H_{13}OCl$, 91%), 183 ($M^{+\cdot}$, $C_{13}H_{18}O$ - CH_3, 33%),181 ($M^{+\cdot}$, $C_{13}H_{18}O$ - CH_3, 100%), 161 (31%), 155 ($M^{+\cdot}$, $C_{13}H_{18}O$ - C_3H_7, 33%), 153 ($M^{+\cdot}$, $C_{13}H_{18}O$ - C_3H_7, 38%), 146 (28%), 117 (16%), 115 (18%), 105 (12%), 91 (30%).

Analysis calcd. for $C_{13}H_{18}O$ (198) C, 67.18; H, 6.66. Found: C, 69.58; H, 7.78%.

Evidence for the presence of 2,3-dihydro-5-chloro-2,2-6-trimethyl-7-isopropenyl-benzofuran **(209j)** in the mother liquor.

G.C. R_t 18.12 min

GC-MS : m/z 252 ($M^{+\cdot}$, $C_{15}H_{19}OCl$, 32%), 250 ($M^{+\cdot}$, $C_{15}H_{19}OCl$, 27%), 237 ($M^{+\cdot}$, $C_{15}H_{19}OCl$ - CH_3, 33%), 235 ($M^{+\cdot}$, $C_{15}H_{21}OCl$ - CH_3, 100%), 220 (9%), 193 (22%) 179 (11%), 141 (5%), 128 (4%), 115 (5%), 91 (17%), 77 (6%).

Evidence for the presence of 2,3-dihydro-5-chloro-2,2-6-trimethyl-7-isopropyl-benzofuran **(210j)** in the mother liquor.

G.C. R_t 17.86 min.

GC-MS : m/z 254 ($M^{+\cdot}$, $C_{15}H_{21}OCl$, 9%), 252 ($M^{+\cdot}$, $C_{15}H_{21}OCl$, 29%), 211 ($M^{+\cdot}$, $C_{15}H_{21}OCl$, 29%), 209 ($M^{+\cdot}$, $C_{15}H_{21}OCl$, 100%), 174 (27%), 169 (%) 167 (24%), 145 (17%), 115 (11%), 91 (17%), 77 (13%).

2,3-Dihydro-2,2,5,6-tetramethylbenzofuran (124l)

3,4-Dimethylphenol **(28l)** (40.93g, 0.34 mol)was reacted with isobutyraldehyde **(208)** (40.93g, 0.30 mol) to afford a mixture of the title compound **124l** which was separated by fractional distillation, **209l** which was confirmed by NMR and **210l** which was present in the mother liquor of **124l** and was identified by GC/MS.

The title compound was a pale yellow oil (46%), b.pt 64-66°C / 0.12mmHg (Lit. b. pt 50-65°C / 1 Torr[244]), G.C. R_t 12.65 min.

IR (film) : υ 3017 (arom. C-H str.), 2972-2861 (sat. C-H str.), 1623-1592 (C=C), 1495 (C-H def.), 1368 (g, geminal CH_3), 1267 (C-O), 880 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.43 (6H, s, C-2-2xCH_3), 2.16 (3H, s, Ar-CH_3), 2.18 (3H, s, Ar-CH_3), 2.92 (2H, s, C-3-CH_2), 6.53 (1H, s, Ar-H), 6.88 (1H, s, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 19.15 (C-6-CH_3), 20.04 (C-5-CH_3), 28.16 (C-2-2xCH_3), 42.82 (C-3-CH_2), 86.21 (C-2), 110.67 (C-7-CH), 124.13 (Ar-C), 126.22 (C-4-CH), 127.50 (Ar-C), 135.96 (Ar-C), 157.24 (Ar-C) ppm.

GC-MS : m/z 176 ($M^{+\cdot}$, $C_{12}H_{16}O$, 88%), 161 ($M^{+\cdot}$, $C_{12}H_{16}O$ - CH_3, 100%), 143 (11%), 133 ($M^{+\cdot}$, $C_{12}H_{16}O$ - C_3H_7, 21%), 115 (7%), 105 (15%), 91 (15%), 39 (14%).

Analysis calcd. for $C_{12}H_{16}O$ (176) C, 81.77; H, 9.15. Found: C, 81.30; H, 9.282%.

Evidence for the presence of 2,3-Dihydro-2,2,5,6-tetramethyl-7-(2-methyl-1-propenyl)-benzofuran **(209l)** by NMR.

Compound **(124l)** contains 18% purity of **(209l)** by (^1H NMR), G.C. R_t 17.24 min.

^1H NMR ($CDCl_3$) : δ 1.46 (6H, s, C-2-2xCH_3), 1.69 (3H, s, C-2'-CH_3), 1.90 (3H, s, C-2'-CH_3), 2.04 (3H, s, Ar-CH_3), 2.31 (3H, s, Ar-CH_3), 2.92 (2H, s, C-3-CH_2), 5.98 (1H, s, C-1'-H), 6.80 (1H, s, Ar-H) ppm.

GC-MS : m/z 230 ($M^{+\cdot}$, $C_{16}H_{22}O$, 23%), 215 ($M^{+\cdot}$, $C_{16}H_{22}O$ - CH_3, 100%), 200 (9%), 173 (15%), 159 (9%), 145 (8%), 91 (<5%).

Evidence for the presence of 2,3-dihydro-2,2,5,6-tetramethyl-7-isopropylbenzofuran **(210l)** was identified by GC/MS.

G.C. R_t 15.90 min.

GC-MS : m/z 232 ($M^{+\cdot}$, $C_{16}H_{24}O$, 32%), 189 ($M^{+\cdot}$, $C_{16}H_{24}O$ - C_3H_7, 100%), 147 (22%), 119, (6%), 105 (3%), 91 (7%), 39 (8%).

2,3-Dihydro-2,2,7-trimethylbenzofuran (124m)

2-Methylphenol **(28m)** (32.48g, 0.30 mol) was reacted with isobutyraldehyde **(208)** (21.83g, 0.31 mol) to afford a mixture of the title compound (3.99g, 8%), **210m** which were separated by fractional distillation, and 56m was present in the mother liquor of **124m**.

The first fraction was the title compound as a colourless oil (3.99g, 8%), b.pt 42-48°C / 0.15mmHg (Lit b. pt. 32°C / 0.1 mmHg[241]), TLC (ethyl acetate : pet. ether 40-60°, 25:75), R_f 0.77, G.C. R_t 9.86 min.
IR (film) : υ 3025 (arom. C-H str.), 2973-2926 (sat. C-H str), 1598 (C=C), 1466 (C-H def.), 1369 (d, geminal CH_3), 1263 (C-O), 881 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.44 (6H, s, C-2-2xCH_3), 2.18 (3H, s, C-7-CH_3), 2.95 (2H, s. C-3-CH_2), 6.66-6.72 (1H, t, *J* 7.40 Hz, Ar-H), 6.91-6.94 (2H,t , *J* 7.68 Hz, Ar-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 15.30 (C-7-CH_3), 28.30 (C-2-2xCH_3), 43.19 (C-3-CH_2), 85.76 (C-2), 119.52 (Ar-C), 119.50 (Ar-CH), 122.41 (Ar-CH), 126.16 (Ar -C), 129.08 (Ar-CH), 157.44 (Ar-C).
GC-MS : m/z 162 ($M^{+\cdot}$, $C_{11}H_{14}O$, 92%), 147 ($M^{+\cdot}$, $C_{11}H_{14}O$ - CH_3, 100%) 129 (7%), 119 ($M^{+\cdot}$, $C_{11}H_{14}O$ - C_3H_7, 42%), 105 (10%), 91 (17%), 77 (4%), 39 (11%).
Analysis calcd. for $C_{11}H_{14}O$ (162) C, 81.44; H, 8.70. Found: C, 81.15; H, 8.58%.

Evidence for the presence of 2,3-dihydro-2,2,7-trimethyl-5-(2-methyl-1-propenyl)-benzofuran **(209m)** confirmed by GC/MS.
G.C. R_t 15.25 min.
GC-MS : m/z 216 ($M^{+\cdot}$, $C_{15}H_{20}O$, 57%), 201 ($M^{+\cdot}$, $C_{15}H_{22}O$ - CH_3, 100%), 186 (8%), 173 (10%), 159 (14%), 145 (9%), 131 (8%), 115 (8%), 91 (<5%), 77(<5%).

The second fraction was a dark yellow oil (0.75g, 2%), b.pt 60-64°C / 0.22mmHg, G.C. R_t 14.86min and was identified as 2,3-dihydro-2,2,7-trimethyl-5-isopropyl-benzofuran **(210m)**.
IR (film) : υ 2971-2867 (sat. C-H str), 1598 (C=C), 1466 (C-H def.), 1366 (d, geminal CH_3), 1262-1130 (C-O), 861 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 0.86-0.90 (6H, d, J=7.5 Hz, C-2'-2xCH_3), 1.46 (6H, d, *J*=2.21 Hz, C-2-2xCH_3), 2.16 (3H, s, C-7-CH_3), 1.70-1.82 (2H, m, *J* 7.15 Hz, C-2'-H), 2.33-2.37 (2H, d, *J* 7.5Hz, C-1'-CH_2), 2.96-2.99 (2H, d, *J* 7.04, C-3-CH_2), 6.68-6.69 (1H, s meta-coupled, *J* 1.73 Hz, Ar-H), 6.73-6.74 (1H, s, meta-coupled, *J* 2.37 Hz, Ar-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 15.38 (C-7-CH_3), 22.43 (C-2'-2xCH_3), 28.32 (C-2-2xCH_3), 30.52 (C-2'-CH), 43.32 (C-1'-CH_2), 44.97 (C-3-CH_2), 85.78 (C-2), 118.74 (Ar-C), 122.99 (Ar-CH), 125.94 (Ar-C), 129.82 (Ar-CH), 133.08 (Ar-C), 155.54 (Ar-C) ppm.
GC-MS : m/z 218 ($M^{+\cdot}$, $C_{15}H_{22}O$, 55%), 175 ($M^{+\cdot}$, $C_{15}H_{22}O$ - C_3H_7, 100%), 147 (5%), 133 (8%), 115 (<5%), 105 (9%), 91 (5%), 77 (4%), 39 (8%).
Analysis calcd. for $C_{15}H_{22}O$ (218) C, 82.52; H, 10.16. Found: C, 81.47; H, 10.24%.

2,3-Dihydro-2,2,6-trimethylbenzofuran (124n)

3-Methylphenol **(28n)** (43.25g, 0.4 mol) was reacted with isobutyraldehyde **(208)** (29.02g, 0.4 mol) to afford a mixture of the title compound **209n**, **210n** were separated by fractional distillation. The presence of compounds **247n**, **249n**, **250n** and **251n** were identified by GC/MS.

The first fraction was the title compound as a colourless oil (20.88g, 32%), b.pt 42-44°C / 0.16mmHg (Lit. m. pt. 131°C[133]), (ethyl acetate : pet ether 40-60°, 25:75), R_f 0.76, G.C. R_t 10.58 min.

IR (film) : υ 3049 (arom. C-H str.), 2973-2862 (sat. C-H str.), 1621-1590 (C=C), 1498-1466 (C-H def.), 1369 (d,geminal CH_3), 1277 (C-O), 798 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.45 (6H,s,C-2-2xCH_3), 2.28 (3H,s,C-6-CH_3), 2.94 (2H,s,C-3-CH_2), 6.55 (1H,s,C-7-H), 6.61-6.64 (1H,d, *J* 7.45 Hz, C-5-H), 6.98-7.01 (1H,d, *J* 7.45 Hz, C-4-CH_3) ppm.

^{13}C NMR ($CDCl_3$) : δ 21.49 (C-6-CH_3), 28.20 (C-2-2xCH_3), 42.64 (C-3-CH_2), 86.61 (C-2), 110.25 (Ar-H), 120.62 (Ar-CH), 123.99 (Ar-C), 124.70 (Ar-CH), 138.02 (Ar-C), 159.09 (Ar-C) ppm.

GC-MS : m/z 162 ($M^{+\cdot}$, $C_{11}H_{14}O$, 58%), 147 ($M^{+\cdot}$, $C_{11}H_{14}O$ - CH_3, 100%), 129 (6%), 119 ($M^{+\cdot}$, $C_{11}H_{14}O$ - C_3H_7, 37%), 105 (9%), 91 (21%), 77 (12%), 40 (13%).

Analysis calcd. for $C_{11}H_{14}O$ (162) C, 81.44; H, 8.70. Found: C, 81.10; H, 9.39%.

Presence of 2,3-dihydro-2,2-6-trimethyl-5-(2-methyl-1-propenyl)benzofuran **(169n)** detected by GC/MS.

G.C. R_t 15.94 min.

GC-MS : m/z 216 ($M^{+\cdot}$, $C_{15}H_{20}O$, 100%), 201 ($M^{+\cdot}$, $C_{15}H_{20}O$ - CH_3, 40%), 173 (22%), 159 (31%), 145 (20%), 131 (9%), 115 (11%), 91 (12%).

The second fraction was a yellow oil (7.11g, 11%), b.pt 116-120°C / 0.43mmHg, G.C. R_t 15.44 min and identified as 2,3-dihydro-2,2,6-trimethyl-5-isopropylbenzofuran **(210n)**.

IR (film) : υ 2954-2867 (C-H str), 1622-1591 (C=C), 1493-1464 (C-H saturated def.), 1367 (d,geminal CH_3), 1271 (C-O), 877 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 0.89-0.92 (6H,d *J* 6.46 Hz, C-2'-2xCH_3), 1.44 (6H,s,C-2-2xCH_3), 1.72-1.83 (1H,m,*J* 7.50 Hz,C-2'-H), 2.21 (3H,s,C-6-CH_3), 2.36-2.39 (2H,d,*J* 7.50 Hz,C-1'-CH_2), 2.94 (2H,s,C-3-CH_2), 6.52 (1H,s,Ar-H), 6.84 (1H,s,Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 18.59 (C-6-CH_3), 22.43 (C-2'-2CH_3), 28.19 (C-2-2CH_3), 29.26 (C-2'-CH), 42.27 (C-1'-CH_2), 42.83 (C-3-CH_2), 86.70 (C-2), 110.97 (Ar-CH), 124.50 (Ar-C), 125.80 (Ar-CH), 132.18 (Ar-C), 136.27 (Ar-C), 154.83 (Ar-C).

GC-MS : m/z 218 ($M^{+\cdot}$, $C_{15}H_{22}O$, 29%), 175 ($M^{+\cdot}$, $C_{15}H_{22}O$ - C_3H_7, 100%), 160 (8%), 147 (16%), 133 (20%), 121 (9%), 105 (13%), 91 (8%), 77 (5%), 39 (10%).

The presence of 2,2,6-trimethyl-5-{2-methyl-1-[3-methylphenoxyl]propyl}-2,3-dihydrobenzofuran **(247n)** or 2,2,6-trimethyl-7-{2-methyl-1-[3-methylphenoxyl]propyl}-2,3-dihydrobenzofuran **(249n)** detected by GC/MS
GC R_t 27.59 min.
GC-MS : m/z 324 ($M^{+\cdot}$, $C_{22}H_{25}O_2$, 3%), 281 ($M^{+\cdot}$, $C_{22}H_{25}O_2$ - CH_3, 100%), 263 (5%), 210 (<5%), 178 (<5%), 144 (<5%), 121 (<5%), 91 (<5%).
GC R_t 27.84 min.
GC-MS : m/z 324 ($M^{+\cdot}$, $C_{22}H_{25}O_2$, 38%), 281 ($M^{+\cdot}$, $C_{22}H_{25}O_2$ - CH_3, 100%), 263 (5%), 238 (<5%), 223 (<5%), 207 (<5%), 180 (<5%), 159 (<5%), 144 (<5%), 120 (<5%), 91 (<5%).

The presence of 2,2,6-trimethyl-5-(2-methylpropenyl)-7-{2-methyl-1-[3-methylmethyl-phenoxyl]-propyl}2,3-dihydrobenzofuran **(250n)** or 2,2,6-trimethyl-5-{2-methyl-1-[3-methyl-phenoxylpropyl]-(2-methylpropenyl)}-2,3-dihydrobenzofuran **(251n)** detected by GC/MS
GC R_t 20.06 min.
GC-MS : m/z 378 ($M^{+\cdot}$, $C_{26}H_{34}O_2$, 38%), 335 ($M^{+\cdot}$, $C_{22}H_{25}O_2$ - C_3H_7, 100%), 320 (5%), 274 (<5%), 239 (<5%), 223 (<5%), 201 (<5%), 175 (<5%), 145 (<5%), 115 (<5%), 91 (<5%).
GC R_t 29.01 min.
GC-MS : m/z 378 ($M^{+\cdot}$, $C_{26}H_{34}O_2$, 4%), 335 ($M^{+\cdot}$, $C_{22}H_{25}O_2$ - C_3H_7, 100%), 317 (5%), 281 (<5%), 223 (<5%), 223 (<5%), 174 (<5%), 133 (<5%), 105 (<5%), 91 (<5%).

2,3-Dihydro-2,2,5-trimethylbenzofuran (124o)

4-Methylphenol **(28o)** (32.43g,0.30 mol) was reacted with isobutyraldehyde **(208)** (21.71g, 0.30 mol) to afford a mixture of the title compound **124o** which was separated by fractional distillation, **209o** (<5%), **210o**, **250o** and **254o** were present in the mother liquor and were detected by GC/MS.
The title compound was a yellow oil (4.86g, 10%). B.pt 48-50°C / 0.15mmHg (Lit. b. pt 32°C / 0.1 mmHg[241]), G.C. R_t 10.58 min.
IR (film) : υ 2973-2867 (C-H str), 1617 (C=C), 1491 (C-H def.), 1369 (d,geminal CH_3), 1257 (C-O), 809 (C-H bend) cm^{-1}.

^{1}H NMR ($CDCl_3$) : δ 1.44 (6H, s, C-2-2CH_3), 2.25 (3H, s, Ar-CH_3), 2.94 (2H, s, C-3-CH_2), 6.59-6.63 (1H, d, *J* 8.0 Hz, Ar-H), 6.87-6.90 (1H, d, meta-coupled, *J* 8.0 Hz, J_m 0.82 Hz, Ar-H), 6.93 (1H,s, meta-coupled J_m 0.63 Hz,C-4-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 20.71 (Ar-CH_3), 28.13 (C-2-2xCH_3), 42.96 (C-3-CH_2), 86.21 (C-2), 109.02 (Ar-CH), 125.72 (Ar-CH), 127.00 (Ar-C), 128.27 (Ar-CH), 128.99 (Ar-C), 156.81 (Ar-C) ppm.
GC-MS : m/z 162 ($M^{+\cdot}$, $C_{11}H_{14}O$, 78%), 147 ($M^{+\cdot}$, $C_{11}H_{14}O$ - CH_3, 100%), 129 (5%), 119 ($M^{+\cdot}$, $C_{15}H_{22}O$ - C_3H_7, 39%), 105 (8%), 91 (20%), 77 (10%), 39 (13%).
Analysis calcd. for $C_{11}H_{14}O$ (162) C, 81.44; H, 8.70. Found: C, 81.04; H, 8.97%.

The presence of 2,3-dihydro-2,2-5-trimethyl-7-(2-methyl-1-propenyl)benzofuran **(209o)** was detected by GC/MS.
G.C R_t 25.53 min.
GC-MS : m/z 216 ($M^{+\cdot}$, $C_{15}H_{20}O$, 32%), 201($M^{+\cdot}$, $C_{15}H_{20}O$ - CH_3, 100%), 186 (4%), 159 (19%), 145 (5%), 131 (5%), 115 (4%), 91 (3%).

The presence of 2,3-dihydro-2,2,5-trimethyl-7-isopropylbenzofuran **(210o)** was detected by GC/MS.
G.C. R_t 15.24 min.
GC-MS : m/z 218 ($M^{+\cdot}$, $C_{15}H_{22}O$, 40%), 175 ($M^{+\cdot}$, $C_{15}H_{22}O$ - C_3H_7, 100%), 147 (19%), 133 (30%), 121 (15%), 105 (18%), 91 (10%), 44 (19%).
Analysis calcd. for $C_{15}H_{22}O$ (218) C, 82.52; H, 10.16. Found: C, 81.16; H, 9.32%.

The presence of 2,2,5-trimethyl-7-(2-methyl-1-*p*-tolyloxypropyl)-2,3-dihydrobenzofuran **(252o)** was detected by GC/MS.
GC R_t 25.53 min
GC-MS : m/z 324 ($M^{+\cdot}$, $C_{22}H_{28}O_2$, 18%), 281 ($M^{+\cdot}$, $C_{22}H_{28}O_2$ - C_3H_7, 100%), 263 (<5%), 239 (<5%), 225 (<5%), 195 (<5%), 172 (<5%), 145 (<5%), 121 (7%), 91 (5%).

The presence of 2,2,5-trimethyl-7-{2-methyl-1-[4-methyl-2-(2-methylpropenyl)-phenoxyl]propyl}-2,3-dihydrobenzofuran **(254o)** was detected by GC/MS.
GC R_t 27.39 min
GC-MS : m/z 378 ($M^{+\cdot}$, $C_{26}H_{34}O_2$, 8%), 335 ($M^{+\cdot}$, $C_{26}H_{34}O_2$ - C_3H_7, 100%), 317 (<5%), 281 (<5%), 248 (<5%), 217 (<5%), 175 (<5%), 133 (<5%), 91 (5%),

2,3-dihydro-5-bromo-2,2-dimethylbenzofuran (124q)

4-Bromophenol **(28q)** (26.31g, 0.15 mol) was reacted with isobutyraldehyde **(208)** (15.15g, 0.21mol) to afford the title compound which was separated by fractional distillation.

The title compound was a yellow oil (0.73g, 2%), b.pt 62-64°C / 0.07mmHg (Lit. NMR evidence[246]), GC R_t 14.11 min.

IR (film) : υ 2970-2873 (C-H saturated str.), 1475 (C-H saturated def.), 1370 (d, geminal CH_3), 1258 (C-O), 809 (C-H bend), 662 (C-Br) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.46 (6H, s, C-2-2xCH_3), 2.97 (2H, s, C-3-CH_2), 6.58-6.61 (1H, d, *J* 8.33Hz, C-7-H), 7.16-7.17 (1H, s, meta-coupled, J_m 2.15 Hz, C-4-CH), 7.20-7.23 (1H, d, meta-coupled, *J* 6.87 Hz, J_m 3.73 Hz, C-6-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 28.06 (C-2-2xCH_3), 42.71 (C-3-CH_2), 87.44 (C-2), 111.04 (Ar-CH), 111.58 (Ar-C), 128.07 (Ar-CH), 129.59 (Ar-C), 130.73 (Ar-CH), 158.05 (Ar-C) ppm.

GC-MS : m/z 228 ($M^{+\cdot}$, $C_{10}H_{13}OBr$, 81%), 226 ($M^{+\cdot}$, $C_{10}H_{13}OBr$, 73%), 213 ($M^{+\cdot}$, $C_{10}H_{13}OBr$ - CH_3, 74%), 211 ($M^{+\cdot}$, $C_{10}H_{13}OBr$ - CH_3, 68%), 185 (10%), 147 (20%), 132 (100%), 107 (13%), 91 (28%), 77 (29%), 63 (22%), 51 (31%).

2,3-Dihydro-2,2-dimethylbenzofuran (124r)

Phenol **(28r)** (28.88g, 0.30 mol) was reacted with isobutyraldehyde **(208)** (21.74g, 0.30 mol) to afford a mixture of the title compound, which was separated by fractional distillation **209r** and **210r** were detected by GC/MS.

The title compound was a yellow oil (1.33g, 3%), b.pt 56-62°C / 0.19mmHg (Lit. 31°C / 0.1 mmHg[241]), GC R_t 8.29 min.

IR (film) : υ 2974-2855 (C-H saturated str.), 1481 (C-H saturated def.), 1369 (d, geminal CH_3), 1260 (C-O), 882 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.45 (6H, s, C-2-2xCH_3), 2.97 (2H, s, C-3-CH_2), 6.70-6.82 (2H, m, Ar-H), 7.04-7.12 (2H, m, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 28.78 (C-2-2xCH_3), 42.93 (C-3-CH_2), 86.48 (C-2), 109.58 (Ar-CH), 120.05 (Ar-CH), 125.71 (Ar-CH), 127.13 (Ar-C), 128.04 (Ar-CH), 158.93 (Ar-C) ppm.

GC-MS : m/z 148 ($M^{+\cdot}$, $C_{10}H_{12}O$, 63%), 133 ($M^{+\cdot}$, $C_{10}H_{12}O$ - CH_3, 100%), 119 (6%), 105 ($M^{+\cdot}$, $C_{10}H_{12}O$ - C_3H_7, 48%), 91 (12%), 77 (18%), 63 (9%), 50 (12%).

Analysis calcd. for $C_{10}H_{12}O$ (148) C, 81.04; H, 8.16. Found: C, 80.35; H, 8.19%.

The presence of 2,3-dihydro-2,2-dimethyl-5-(2-methyl-1-propenyl)benzofuran **(209r)** was detected by GC/MS.

GC R_t 15.25 min

GC-MS : m/z 202 ($M^{+\cdot}$, $C_{14}H_{18}O$, 15%), 187 ($M^{+\cdot}$, $C_{10}H_{12}O$ - CH_3, 100%), 159 (8%), 145 (43%), 128 (7%), 115 (6%), 105 (55), 91 (6%), 77 (5%).

The presence of 2,3-dihydro-2,2-dimethyl-5-isopropylbenzofuran **(210r)** was detected by GC/MS
GC R_t 14.09 min
GC-MS : m/z 204 ($M^{+\cdot}$, $C_{14}H_{20}O$, 37%), 161 ($M^{+\cdot}$, $C_{14}H_{20}O$ - C_3H_7, 100%), 159 (8%), 145 (43%), 128 (7%), 115 (6%), 105 (5%), 91 (6%), 77 (5%).

4-Amino-2,3,5-trimethylphenol (269)

4-Amino-2,3,5-trimethylphenol **(269)** was prepared by the method of Smith[268] from 2,3,5-trimethylphenol **(28b)**. M. pt. 150-152°C (Lit.[268])
IR (KBr) : υ 3391-3327 (N-H str., d, sharp), 3095 (O-H str., broad), 2973 (C-H str.), 1596 (N-H bend or C=C), 1469-1422 (C-H def.), 1244 (O-H bend), 1089 (C-O str.), 867 (C-H bend) cm^{-1}.
^1H NMR (DMSO-*d*) : δ 1.96 (3H, s, Ar-CH_3), 1.99 (6H, s, 2xAr-CH_3), 3.44 (H_2O), 3.83 (2H, broad, D_2O exchangeable, NH_2), 6.34 (1H, s, Ar-H), 8.11 (1H, s, D_2O exchangeable, Ar-OH) ppm.
^{13}C NMR (DMSO-*d*) : δ 12.04 (Ar-CH_3), 13.46 (Ar-CH_3), 17.76 (Ar-CH_3), 114.15 (Ar-CH), 118.81 (Ar-C), 119.66 (Ar-C), 120.92 (Ar-C), 136.06 (Ar-C), 145.97 (Ar-C) ppm.
MS (EI) : m/z 151 ($M^{+\cdot}$, $C_9H_{13}NO$, 100%), 149 ($M^{+\cdot}$ - 1, $C_9H_{12}NO$, 10%), 136 ($M^{+\cdot}$, $C_8H_{10}NO$ - CH_3, 37%), 121 ($M^{+\cdot}$, $C_{18}H_{10}NO$ - C_2H_6, 19%), 106 (17%), 91 (7%), 77 (8%), 53 (8%), 39 (11%).

4-(Formylamino)-2,3,5-trimethylphenol (270)

4-Amino-2,3,5-trimethylphenol **(28b)** (8.96g) was dissolved in anhydrous formic acid (60 ml) and heated under reflux for 1 hour. The solution was poured onto ice (100g) and allowed to stand for 15 min. A pale grey solid precipitated (7.47g). The solid was dried under an atmosphere of argon. Crystallisation from petroleum ether 40-60° afforded the title compound as a white solid (7.32g, 92%), m.pt 206-208°C.
^1H NMR (DMSO-*d*) : δ 2.00 (3H, s, Ar-CH_3), 2.02 (6H, s, 2xAr-CH_3), 3.83 (1H, broad, D_2O exchangeable, NH), 6.57 (1H, s, Ar-H), 8.19 (1H, s, D_2O exchangeable, Ar-OH), 9.14-9.18 (1H, d, *J* 8.91 Hz, -CHO) ppm.
^{13}C NMR (DMSO-*d*) : δ 11.87 (Ar-CH_3), 14.76 (Ar-CH_3), 18.15 (Ar-CH_3), 113.39 (Ar-CH), 119.89 (Ar-C), 125.09 (Ar-C), 132.05 (Ar-C), 134.35 (Ar-C), 153.33 (Ar-C), 159.68 (-CHO) ppm.

MS (EI) : m/z 179 ($M^{+\cdot}$, $C_{10}H_{13}NO_2$, 73%), 162 ($M^{+\cdot}$, $C_{10}H_{13}NO_2$ - OH, 27%), 150 ($C_{10}H_{13}NO_2$ - CHO, 68%), 136 (17%), 121 (12%), 107 (13%), 91 (11%), 77 (11%), 65 (10%), 53 (12%), 44 (27%), 40 (100%).

5-(Formylamino)-3,4-dihydro-2,2,4,6,7-pentamethylbenzofuran (271) - (Method A)

4-(Formylamino)-2,3,5-trimethylphenol **(270)** (2.31g, 0.013 mol) was stirred in toluene (30 ml) at room temperature under an atmosphere of argon. Isobutyraldehyde **(208)** (0.93g, 0.13 mol) and concentrated sulphuric acid (ml) were added over a period 30 mins and the reaction mixture was heated under reflux for 4 hrs. The reaction the mixture was poured onto ice (100g), neutralised with 10%w/v sodium bicarbonate (400 ml) solution, extracted with ethyl acetate (150 ml), washed with water, and dried over anhydrous magnesium sulphate. Filtration of the drying agent and removal of the solvent *in vacuo* afford a lime green oil (2.93g). Crystallisation (MeOH) afforded the title compound as a light brown solid (1.60g, 53%). TLC (ethyl acetate : pet ether 40-60°, 25:75), R_f 0.20, GC R_t 22.43 min.

*GC/MS conditions: Oven temp. 60°C, rate (0°C / min, held for 5 min, then oven temperature increased to 220°C, rate 16.67°C / mins, held for 10.50 min.

^{1}H NMR (DMSO-*d*) : δ 1.46-1.48 (6H, d, *J* 5.28 Hz, 2 x CH_3), 2.09 (3H, s, Ar-CH_3), 2.11 (3H, s, Ar-CH_3), 2.16 (1.5H, s, Ar-CH_3), 2.17 (1.5H, s, Ar-CH_3), 2.93-2.94 (2H, d, *J* 3.44 Hz, CH_2), 6.89 (0.5H, b, D_2O exchangeable, NH), 7.07-7.12 (0.5H, d, D_2O exchangeable, *J* 11.62 Hz, N-H), 7.94-7.98 (0.5H, d, *J* 12.05 Hz, CHO), 8.38 (0.5H, s, CHO) ppm.

^{13}C NMR (DMSO-*d*) : δ 12.31 (2xAr-CH_3), 14.76 (Ar-CH_3), 15.03 (Ar-CH_3), 15.30 (Ar-CH_3), 15.48 (Ar-CH_3), 28.52 (2xCH_3), 28.62 (2xCH_3), 85.99 (Aliphatic-C), 86.30 (Aliphatic-C), 116.10 (Ar-C), 116.36 (Ar-C), 123.33 (Ar-C), 123.58 (Ar-C), 124.11 (Ar-C), 124.93 (Ar-C), 129.10 (Ar-C), 129.77 (Ar-C), 133.86 (Ar-C), 134.75 (Ar-C), 156.69 (Ar-C), 160.29 (Ar-NH-CHO), 165.98 (Ar-NH-CHO) ppm.

GC-MS : m/z 233 ($M^{+\cdot}$, $C_{14}H_{19}NO_2$, 100%), 204 ($M^{+\cdot}$, $C_{14}H_{19}O_2$ - CHO), 30%), 188 (31%), 173 (24%), 159 (8%), 146 (5%), 131 (5%), 105 (4%), 91 (5%), 39 (8%).

*The GC/MS conditions outlined above were used for all the compounds in this section, unless otherwise stated.

5-(Formylamino)-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran (271) - (Method B)

4-(Formylamino)-2,3,5-trimethylphenol **(270)** (3.60g, 0.02 mol) was dissolved in formic acid (30 ml) and conc. sulphuric acid (5 drops) at 100°C under an atmosphere of argon. 2-Methyl-2-propen-1-ol **(207)** (1.45g, 0.02 mol) was added over a period of 30 mins and the reaction mixture was heated under reflux for 4 hrs. The mixture was poured into ice, neutralised with 10%w/v sodium bicarbonate (2x200 ml), extracted with ethyl acetate (150 ml) washed with water, and dried over anhydrous magnesium sulphate. Filtration of the drying agent and removal of the solvent *in vacuo* afforded the title compound as a white solid (4.07g, 87%), m.pt 175-177°C. TLC (ethyl acetate : pet ether 40-60°, 25:75); R_f 0.20.

5-(Formylamino)-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran (271) - (Method C)

4-(Formylamino)-2,3,5-trimethylphenol **(270)** (4.59g, 0.026 mol) was dissolved in trifluoroacetic acid (30 ml). To this was added 2-methyl-2-propen-1-ol **(207)** (5.01g, 0.07 mol) over a period of 20 min. The reaction mixture was heated under reflux for 4 hours. After cooling the residue was worked up as usual to afford the title compound as a brown solid (4.43g, 73%), m.pt 176-178°C, GC R_t 22.91 min

^{1}H NMR ($CDCl_3$-*d*) : δ 1.46 (6H, s, 2 x CH_3), 1.48 (6H, s, 2 x CH_3), 2.08-2.16 (18H, m, 6 x Ar-CH_3), 2.93 (2H, s, CH_2), 2.94 (2H, s, CH_2), 6.82 (0.5H, s, D_2O exchangeable, NH), 6.99-7.03 (0.5H, d, D_2O exchangeable, NH), 7.94 (0.5H. d, CHO), 8.40 (0.5H, s, CHO) ppm.

GC-MS : m/z 233 ($M^{+\cdot}$, $C_{14}H_{19}NO_2$, 100%), 218 ($M^{+\cdot}$, $C_{14}H_{19}O_2$ - CH_3, 15%), 204 ($M^{+\cdot}$, $C_{14}H_{19}NO_2$ - CHO, 52%), 188 (57%), 173 (59%), 159 (17%), 105 (8%), 91 (10%), 77 (12%), 39 (17%).

Analysis calcd. for $C_{14}H_{19}NO_2$ (233) C, 72.07; H, 8.21; N, 6.00. Found: C, 72.35; H, 8.44; N, 5.23%.

5-Amino-2,3-dihydro-2,2,4,6,7-pentamethylbenzo-5-furanamine hydrochloride (260)[265]

5-(Formylamino)-2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran **(271)** (4.12g) was dissolved in methanol (100 ml). To it was added 35% hydrochloric acid (60 ml) with ice-water bath cooling. The mixture was heated under reflux in an atmosphere of argon for 2 hours. After cooling, the reaction mixture was neutralised with aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with brine, and dried with anhydrous magnesium sulphate. Filtration of the drying agent and removal of the solvent *in vacuo*. a residue which was treated with hydrochloric acid

4M and ethanol (6 ml) to afford the title compound as a brown oil (3.98g, 97%). GC : R_t 19.28 min

GC-MS : m/z 205 ($M^{+\cdot}$, $C_{13}H_{19}NO$, 95%), 190 ($M^{+\cdot}$, $C_{13}H_{19}NO$ - CH_3, 9%), 162 (69%), 147 (60%), 111 (42%), 97 (61%), 91 (22%), 83 (62%), 69 (85%), 63 (44%), 57 (100%), 41 (96%).

6-(Formylamino)-3,4-dihydro-2,2,5,7,8-pentamethylbenzopyran (274) - (Method D)

4-(Formylamino)-2,3,5-trimethylphenol **(270)** (3.19g, 0.018 mol) was dissolved in glacial acetic acid (30 ml) and zinc chloride (2.84g, 0.021 mol). To the mixture was added isoprene **(81)** (1.25g, 0.018 mol) over a period of 30 min and the reaction mixture was heated under reflux for 4 hours. The standard work-up produced an orange oil. Recrystallisation from pet. ether (40-60°) afforded a mixture of the title compound as a white solid (3.34g, 74%), m.pt 206-208°, GC R_t 26.04 min and **3** as an oil (0.76g, 17%).

^{1}H NMR ($CDCl_3$-*d*) : δ 1.29 (6H, s, 2 x CH_3), 1.31 (6H, s, 2 x CH_3), 1.75 -1.81 (2H, t, *J* 6.90 Hz, CH_2), 2.10-2.18 (18H, m, 6 x Ar-CH_3), 2.59-2.66 (4H, m, *J* 6.71 Hz, 2 x CH_2), 6.86 (0.5H, broad, D_2O exchangeable, NH), 6.96 (0.5H, d, broad, D_2O exchangeable, NH), 7.92-7.97 (0.5H, d, J 12.06 Hz, CHO), 8.36 (0.5H, d, *J* 1.61 Hz, CHO ppm.

GC-MS : m/z 247 ($M^{+\cdot}$, $C_{15}H_{21}NO_2$, 100%), 232 ($M^{+\cdot}$, $C_{15}H_{21}NO_2$ - CH_3, <5%), 218 ($M^{+\cdot}$, $C_{15}H_{21}NO_2$ - CHO, 5%), 202 (23%), 192 (35%), 174 (7%), 162 (15%), 147 (19%), 135 (14%), 91 (7%).

6-Amino-3,4-dihydro-2,2,5,7,8-pentamethylbenzopyran (259)

^{1}H NMR ($CDCl_3$-*d*) 1.28 (6H, s, 2 x CH_3), 1.75-1.81 (2H, t, *J* 6.92 Hz, CH_2), 2.05-2.16 (9H,m, 3 x Ar-CH_3), 2.58-2.67 (2H, t, *J* 7.15 Hz, CH_2), 3.28 (2H, broad, D_2O exchangeable, NH_2) ppm. GC-MS : m/z 219 ($M^{+\cdot}$, $C_{14}H_{21}NO$, 100%), 203 ($M^{+\cdot}$, $C_{14}H_{21}NO$, <5%), 189 (<5%), 163 (42%), 135 (21%), 120 (15%), 106 (<5%), 91 (<5%).

6-(Formylamino)-3,4-dihydro-2,2,5,7,8-pentamethylbenzopyran (274) - (Method E)

4-(Formylamino)-2,3,5-trimethylphenol **(270)** (3.20g, 0.018 mol) was dissolved in formic acid (30 ml) and concentrated sulphuric acid (5 drops). To this was added 2-methyl-3-buten-2-ol **(273)** (4.43g, 0.05 mol) over a period of 30 min at room temperature. The reaction mixture was heated under reflux for 44 hours. After cooling, the residue was extracted with ethyl acetate (100 ml), washed with brine, dried with

magnesium sulphate, and concentrated to afford the title compound as a brown residue. This residue, was purified on an alumina gel column, eluting the column with i) methanol / diethyl ether (1:9), and ii) methanol (100%) to afford a mixture of the title compound as an oil (2.63g, 63%)) and 6-amino-3,4-2,2,5,7,8-dihydrobenzopyran as an oil **(259)** (1.48g, 35%).

^{1}H NMR ($CDCl_3$-*d*) : δ 1.30 (6H, s, 2 x CH_3), 1.32 (6H, s, 2 x CH_3), 1.75 -1.79 (2H, t, *J* 6.90 Hz, CH_2), 1.81-1.85 (2H, t, *J* 6.84 Hz, CH_2), 2.10-2.18 (18H, m, 6 x Ar-CH_3), 2.59-2.66 (4H, m, J 6.71 Hz, 2 x CH_2), 6.84 (0.5H, broad, D_2O exchangeable, NH), 6.91-6.96 (0.5H, d, broad, D_2O exchangeable, NH), 7.93-7.98 (0.5H, d, *J* 12.11 Hz, CHO), 8.40 (0.5H, d, *J* 1.47 Hz, CHO) ppm.

GC-MS : m/z 247 ($M^{+\cdot}$, $C_{15}H_{21}NO_2$, 100%), 218 ($M^{+\cdot}$, $C_{15}H_{21}NO_2$ - CHO, 8%), 202 (23%), 192 (35%), 174 (8%), 162 (17%), 147 (19%), 135 (16%), 119 (12%), 91(8%).

Analysis calcd. for $C_{15}H_{21}NO_2$ (247) C, 72.84; H, 8.56; N, 5.66. Found: C, 66.25; H, 7.20; N, 7.33%.

Evidence for the presence of 6-amino-3,4-2,2,5,7,8-dihydrobenzopyran **(259)**

Brown oil , GC R_t 21.16 min.

^{1}H NMR ($CDCl_3$-*d*) : δ 1.27 (6H, s, 2 x CH_3), 1.74-1.79 (2H, t, *J* 6.75 Hz, CH_2), 2.04 (3H, s, Ar-CH_3), 2.09 (3H, s, Ar-CH_3), 2.12 (3H, s, Ar-CH_3), 2.57-2.66 (2H, t, *J* 6.84 Hz, CH_2), 3.23 (2H, broad, D_2O exchangeable, NH_2) ppm.

^{13}C NMR ($CDCl_3$-*d*) : δ 12.52 (Ar-CH_3), 13.52 (Ar-CH_3), 14.16 (Ar-CH_3), 21.44 (CH_2), 26.76 (2xCH_3), 33.40 (CH_2) 72.20 (C-2), 116.86 (Ar-C), 117.63 (Ar-C), 120.43 (Ar-C), 122.29 (Ar-C), 134.97 (Ar-C), 144.98 (Ar-C) ppm.

GC-MS : m/z 219 ($M^{+\cdot}$, $C_{14}H_{21}NO$, 100%), 164 ($M^{+\cdot}$, $C_{14}H_{21}NO$ - C_4H_7, 23%), 163 ($C_{14}H_{21}NO$ - C_4H_8, 69%), 135 (28%), 120 (20%), 91 (6%), 77 (5%), 65 (<5%), 51 (5%), 39 (9%).

6-(Formylamino)-3,4-dihydro-2,2,5,7,8-pentamethylbenzopyran (274) - (Method F)

4-(Formylamino)-2,3,5-trimethylphenol **(270)** (1.69g, 0.01 mol) was dissolved in trifluoroacetic acid (40 ml). To the reaction mixture was added 2-methyl-3-buten-2-ol **(199)** (2.98g, 0.03 mol) over a period of 30 min and the reaction mixture was heated under reflux for 4 hours. The cooled solution was worked up to afford the title compound (1.68g, 69%)as a brown oil (purity 87% by NMR), GC R_t 21.08 min.

^{1}H NMR ($CDCl_3$-*d*) : δ 1.29 (6H, s, 2 x CH_3), 1.32 (6H, s, 2 x CH_3), 1.75-1.82 (4H, m, *J* 6,82 Hz, 2 x CH_2), 2.04-2.17 (18H, m, 6 x Ar-CH_3), 2.59-2.66 (4H, m, *J* 6.71 Hz, 2 x CH_2), 6.89 (0.5H, s, broad, D_2O exchangeable, NH), 6.98-7.02 (0.51H, d,

broad, D_2O exchangeable, NH), 7.92-1.97 (0.5H, d, *J* 12.06 Hz, D_2O exchangeable CHO), 8.38-8.39 (0.5H, d, *J* 1.54 Hz, CHO) ppm.
GC-MS : 247 ($M^{+\cdot}$, $C_{15}H_{21}NO_2$, 62%), 218 ($M^{+\cdot}$, $C_{15}H_{21}NO_2$ - CHO, 7%), 202 (34%), 192 (43%), 174 (9%), 162 (18%), 147 (32%), 135 (27%), 119 (14%), 104 (12%), 91 (16%), 44 (100%).
Analysis calcd. for $C_{15}H_{21}NO_2$ (247) C, 72.84; H, 8.56; N, 5.66. Found: C, 74.16; H, 9.49; N, 4.72%.

3,4-Dihydro-6-hydroxy-2,2,4,5,7,8-hexamethylbenzopyran (309a)
Trimethylhydroquinone **(28a)** (7.67g, 0.05 mol) was dissolved in glacial acetic acid. To this was added 2-methyl-2,4-pentanediol **(314)** (8.97g, 0.076 mol) followed by a mixed solution of glacial acetic acid (76.16g, 1.26 mol) and concentrated sulphuric acid (25.62g, 0.26 mol) added dropwise over a period of 1hr. After completion of the addition, the temperature was gradually raised to 30°C over a period of 30 min and stirring was continued for 5 hrs at 30°C. The mixture was poured onto ice, neutralised with 10%w/v sodium bicarbonate solution, and extracted with ethyl acetate (200 ml). Removal of the solvent afforded a red oil. To the oil was added methanol (100 ml) and concentrated hydrochloric acid (10 ml) when the mixture was heated under reflux for 1hr. The resulting solution was poured onto ice, extracted with ethyl acetate (200 ml), neutralised with 10%w/v sodium bicarbonate, was treated with Claisens alkali, acidified with concentrated hydrochloric acid, washed with water (2x100 ml), and dried (anhydrous magnesium sulphate). Filtration of the drying agent and removal of the solvent *in vacuo* afford a red oil. Crystallisation from petroleum ether (b.pt.40-60°) afforded the title compound as a white solid (2.78g, 23%), m.pt 72-74°C. TLC (ethyl acetate : petroleum ether 40-60°, 15:85) R_f 0.41.
IR (KBr) : υ 3457-3289 (O-H str.), 2975-2867 (sat. C-H str.), 1613 (C=C), 1449 (C-H def.), 1366 (d, geminal CH_3), 1246 (O-H bend), 1228 (C-O), 1144-1082 (C-OH str.), 912 (C-H bend) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.15 (3H, s, C-2a-CH_3), 1.24-1.27 (3H, d, *J* 6.89 Hz, C-4-CH_3), 1.41 (3H, s, C-2b-CH_3), 1.67-1.73 (1H, q, *J* 6.89 Hz, C-3-H_{ax}), 1.92-2.03 (1H, q, *J* 7.65 Hz, C-3-H_{eq}), 2.11 (3H, s, Ar-CH_3), 2.14 (3H, s, Ar-CH_3) 2.18 (3H, s, Ar-CH_3), 2.97-3.11 (1H, m, *J* 6.98 Hz,C-4-H), 4.28 (1H, s, C-6-OH) ppm.
^{13}C NMR ($CDCl_3$) : δ 11.90 (Ar-CH_3), 12.20 (Ar-CH_3), 12.62 (Ar-CH_3), 22.10 (C-4-CH_3), 26.10 (C-2-CH_{3ax}), 26.70 (C-4-CH), 29.73 (C-2-CH_{3eq}), 43.76 (C-3-CH_2), 73.72 (C_2), 118.40 (Ar-C), 120.80 (Ar-C), 123.45 (C-6-CH), 124.74 (Ar-C), 145.39 (Ar-C), 145.69 (Ar-C-OH) ppm.
M.S. (EI) : m/z 234 ($M^{+\cdot}$, $C_{15}H_{22}O_2$, 75%), 219 ($M^{+\cdot}$, $C_{15}H_{22}O_2$ - CH_3, 11%), 191 (9%), 179 (80%), 178 (100%), 161 (5%), 135 (8%), 91 (5%).

Analysis calcd. for $C_{15}H_{22}O_2$ (234) C, 76.88; H, 9.46. Found: C, 76.21; H, 9.46%.

3,4-Dihydro-2,2,4,5,7,8-hexamethylbenzopyran (309b)

Trimethylphenol **(28b)** (13.60g, 0.1 mol) was dissolved in glacial acetic acid (51g). To this was added 2-methyl-2,4-pentanediol **(314)** (17.82g, 0.1 mol) followed by a mixed solution of glacial acetic acid (100g) and concentrated sulphuric acid (49g) which was added dropwise over a period of 1hr. After completion of the addition, the temperature was gradually raised to 30°C over a period of 30 min and stirring continued for 5 hrs at 30°C. The mixture was poured onto ice, neutralised with 10%w/v sodium bicarbonate solution, and extracted with ethyl acetate (200 ml). Removal of the solvent afforded a yellowish-brown oil. The resulting oil was poured into ice, extracted with ethyl acetate (200 ml), neutralised with 10%w/v sodium bicarbonate solution, treated with Claisens alkali, acidified with concentrated hydrochloric acid, washed with water (2x100 ml), and dried over anhydrous magnesium sulphate. Filtration of the drying agent and removal of the solvent *in vacuo* afforded the title compound as a pale yellow oil which was distilled under high vacuum.

Pale yellow oil **309b** (6.82g, 31%). B.pt 100-102°C / 1Torr, TLC (ethyl acetate : pet. ether 40-60°, 20:80), R_f 0.70.

IR (KBr) : υ 2973-2870 (sat. C-H str.), 1611-1570 (C=C), 1459 (C-H def.), 1381 (d, geminal CH_3), 1219 (C-O), 846 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.19 (3H, s, C-2a-CH_3), 1.27-1.30 (3H, d, *J* 6.91 Hz, C-4-CH_3), 1.42 (3H, s, C-2b-CH_3), 1.63-1.71 (1H, q, *J* 6.69 Hz, C-3-H_{ax}), 1.94-2.02 (1H, q, *J* 7.47 Hz, C-3-H_{eq}), 2.07 (3H, s, Ar-CH_3), 2.19 (3H, s, Ar-CH_3) 2.32 (3H, s, Ar-CH_3), 2.95-3.09 (1H, m, *J* 6.96 Hz, C-4-H), 6.55 (1H, s, C-6-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 11.50 (Ar-CH_3), 19.67 (Ar-CH_3), 19.71 (Ar-CH_3), 21.71 (C-4-CH_3), 26.33 (C-4-CH), 26.73 (C-2-CH_{3ax}), 29.57 (C-2-CH_{3eq}), 43.43 (C-3-CH_2), 73.95 (C_2), 122.64 (Ar-C), 123.71 (Ar-C), 123.87 (C-6-CH), 133.04 (Ar-C), 134.60 (Ar-C), 151.55 (Ar-C) ppm.

M.S. (EI) : m/z 218 ($M^{+\cdot}$, $C_{15}H_{22}O$, 48%), 203 ($M^{+\cdot}$, $C_{15}H_{22}O$ - CH_3, 40%), 175 (M+ - CO-CH_3, 18%), 163 (100%), 147 (18%), 119 (16%), 105 (10%), 91 (17%).

Analysis calcd. for $C_{15}H_{22}O$ (218) C, 82.52; H, 10.16. Found: C, 82.39; H, 10.36%.

The following compounds were synthesised using the method outlined as above.

3,4-Dihydro-2,2,4,6,7-pentamethylbenzopyran (309c)

3,4-Dimethylphenol **(28c)** (24.43g, 0.2 mol) was reacted with 2-methyl-2,4-pentandiol **(314)** (23.76g, 0.2 mol) to afford the title compound (15.72g, 39%) as a red oil. B.pt 86-88°C / 1torr, TLC (ethyl acetate : petroleum ether (40-60°), 15:85) R_f 0.76

IR (film) : υ 2975-2879 (sat. C-H str.), 1624-1570 (C=C), 1455 (C-H def.), 1382 (d,geminal CH_3), 1212 (C-O), 886 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.22 (3H, s, C-2a-CH_{3ax}), 1.28-1.31 (3H, d, *J* 6.03 Hz, C-4-CH_3), 1.38 (3H, s, C-2b-CH_{3eq}), 1.47-1.56 (1H, t, *J* 7.91 Hz, C-3-H_{ax}), 1.76-1.84 (1H, q, *J* 5.95 Hz, C-3-H_{eq}), 2.16 (Ar-CH_3), 2.17 (Ar-CH_3), 2.80-2.95 (1H, m, *J* 6.28 Hz, C-4-H), 6.58 (1H, s, Ar-H), 6.97 (1H, s, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ = 18.92 (Ar-CH_3), 19.40 (Ar-CH_3), 20.38 (C-4-CH_3), 24.37 (C-2-CH_{3ax}), 25.97 (C-4-CH), 30.07 (C-2-CH_{3eq}), 42.96 (C-3-CH_2), 73.93 (C-2), 118.09 (Ar-CH), 123.35 (Ar-C), 127.60 (Ar-C), 127.93 (Ar-CH), 135.58 (Ar-C), 151.29 (Ar-C) ppm.

Analysis calcd. for $C_{14}H_{20}O$ (204) C, 82.30; H, 9.87. Found: C, 82.31; H, 10.03%.

3,4-Dihydro-2,2,4,5,8-pentamethylbenzopyran (309d)

2,5-Dimethylphenol **(28d)** (12.22g, 0.1 mol) was reacted with 2-methyl-2,4-pentanediol **(314)** (17.95g, 0.15 mol) to afford a mixture the title compound which was separated by fractional distillation.

The first fraction was a green oil, b.pt 158-160°C / 2 torr, TLC (ethyl acetate : pet. ether 40-60°, 15:85) R_f 0.75.

^1H NMR ($CDCl_3$) : δ 1.22-1.25, (3H, d, *J* 7.02 Hz, C-4-CH_3), 1.33 (3H, s, C-2a-CH_{3ax}), 1.42 (3H, s, C-2b-CH_{3eq}), 1.58-1.65 (1H, m, *J* 9.32, C-3-H_{ax}), 1.90-2.00 (1H, m, C-3-H_{eq}), 2.17 (3H, s, Ar-CH_3), 2.24 (3H, s, Ar-CH_3), 3.16-3.20 (1H, m, *J* 7.06 Hz, C-4-H), 6.41 (1H, s, Ar-H), 6.64 (1H, s, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 10.94 (C-4-CH_3), 18.77 (Ar-CH_3), 201.93 (Ar-CH_3), 29.34 (C-2-CH_{3ax}), 29.81 (C-2-CH_{3eq}), 35.41 (C-4-CH), 51.82 (C-3-CH_2), 73.68 (C_2), 115.29 (Ar-CH), 121.58 (Ar-CH), 131.73 (Ar-C), 138.71 (Ar-C), 150.10 (Ar-C), 152.93 (Ar-C) ppm.

MS (EI) : m/z 204 ($M^{+\cdot}$, $C_{14}H_{20}O$, 25%), 189 ($M^{+\cdot}$, $C_{14}H_{20}O$ - CH_3, 100%), 174 (12%), 159 (10%), 145 (5%), 128 (11%), 115 (9%), 91 (10%).

The second fraction was a pale green oil, b.pt 160-162°C / 2 torr and identified as 1,1,3,4,6,6,8,9-octamethyl-1,2,3,6,7,8-hexahydro-5-oxa-cyclopenta[*b*]naphthalene **(225d)**

MS (EI) : m/z 286 ($M^{+\cdot}$, $C_{20}H_{30}O$, 60%), 271 ($M^{+\cdot}$, $C_{20}H_{30}O$ - CH_3, 100%), 231 (30%), 215 (41%), 204 (18%), 189 (53%), 173 (11%), 159 (7%), 141 (5%), 128 (9%), 115 (10%), 91 (10%).

3,4-Dihydro-2,2,4,5,7-pentamethylbenzopyran (309e)

3,5-Dimethylphenol **(28e)** (24.45g, 0.2 mol) was reacted with 2-methyl-2,4-pentandiol **(314)** (28.92g, 0.2 mol) to afford the title compound as a pale blue oil (13.61g, 39%). B.pt 82-88°C / 1 torr, TLC (ethyl acetate : petroleum ether 40-60°,15:85) R_f =, GC R_t 14.81 min.

IR (film) : υ 2974 (sat. C-H str.), 1618 (C=C), 1458 (C-H def.), 1375 (d, geminal CH_3), 1250 (C-O), 898 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.22 (3H, s, C-2a-CH_{3ax}), 1.29-1.31 (3H, d, *J* 6.84 Hz, C-4-CH_3), 1.39 (3H, s, C-2b-CH_{3eq}), 1.67-1.75 (1H, q, *J* 6.75 Hz, C-3-H_{ax}), 1.92-2.04 (1H, q, *J* 8.68 Hz, C-3-H_{eq}), 2.21 (Ar-CH_3), 2.28 (Ar-CH_3), 2.92-3.06 (1H, m, *J* 6.98 Hz, C-4-H), 6.45 (1H, s, Ar-H), 6.49 (1H, s, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 18.39 (Ar-CH_3), 20.15 (Ar-CH_3), 20.81 (C-4-CH_3), 25.97 (C-4-CH), 26.34 (C-2-CH_{3ax}), 29.05 (C-2-CH_{3eq}), 43.54 (C-3-CH_2), 73.68 (C_2), 116.05 (Ar-CH), 122.92 (Ar-C), 123.74 (Ar-CH), 136.33 (Ar-C), 136.91 (Ar-C), 153.58 (Ar-C) ppm.

GC-MS : m/z 204 ($M^{+\cdot}$, $C_{14}H_{20}O$, 65%), 189 ($M^{+\cdot}$, $C_{20}H_{30}O$ - CH_3, 58%), 174 (7%), 161 (22%), 149 (100%), 133 (25%), 119 (18%), 91 (27%), 77 (27%).

Synthesis of 3,4-dihydro-6-chloro-2,2,4,6,7-pentamethylbenzopyran (309f)

4-chloro-3-methylphenol **(28f)** (28.50g, 0.2 mol) was reacted with 2-methyl-2,4-pentanediol **(314)** (23.76g, 0.2 mol) to afford the title compound as a yellow solid, which was reaction mixture from aqueous methanol (17.97g, 40%). M.pt 31-33°C. TLC (ethyl acetate / 40-60° petroleum ether, R_f 0.75.

IR (KBr) : υ 2978-2871 (sat. C-H str.), 1614-1556 (C=C), 1491 (C-H def.), 1381 (d, geminal CH_3), 1209 (C-O), 880 (C-H bend), 679 (C-Cl) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.21 (3H, s, C-2a-CH_{3ax}), 1.28-1.30 (3H, d, *J* 6.73 Hz, C-4-CH_3), 1.39 (3H, s, C-2b-CH_{3eq}), 1.43-1.53 (1H, t, *J* 13.27 Hz, C-3-H_{ax}), 1.77-1.85 (1H, q, *J* 5.96 Hz, C-3-H_{eq}), 2.26 (C-7-CH_3), 2.80-2.93 (C-4-H), 6.64 (1H, s, Ar-H), 7.17 (1H, s, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 19.65 (C_7-CH_3), 20.21 (C-4-CH_3), 24.37 (C-2-CH_{3ax}), 26.08 (C-4-CH), 29.94 (C-2-CH_{3eq}), 42.38 (C-3-CH_2), 74.55 (C_2), 119.29 (Ar-CH), 124.93 (Ar-C), 125.43 (Ar-C), 127.22 (Ar-CH), 134.79 (Ar-C), 151.95 (Ar-C) ppm.

3,4-Dihydro-2,2,4,6,8-pentamethylbenzopyran (309g)

2,3-Dimethylphenol **(28g)** (24.51g, 0.2 mol) was reacted with 2-methyl-2,4-pentandiol **(314)** (23.47g, 0.2 mol) to afford the title compound (16.95g, 42%) as a brown oil. B.pt 82-86°C / 1 torr, TLC (ethyl acetate : petroleum ether 40-60°, 15:85) R_f 0.75.

^{1}H NMR ($CDCl_3$) : δ 1.22 (3H, s, C-2-CH_{3ax}), 1.28-1.31 (3H, d, *J* 6.89 Hz, C-4-CH_3), 1.38 (3H, s, C-2-CH_{3eq}), 1.47-1.56 (1H, dd, *J* 15.01, *J* 7.96 Hz, C-3-H$_{ax}$), 1.95-2.04 (1H, dd, *J* 13.4, J 7.42 Hz, C-3-H$_{eq}$), 2.20 (Ar-CH_3), 2.27 (Ar-CH_3), 2.92-3.06 (1H, m, *J* 6.97 Hz, C-4-H) 2.80, 6.49 (1H, s, Ar-H), 6.54 (1H, s, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 20.13 (Ar-CH_3), 20.81 (Ar-CH_3), 21.65 (C-4-CH_3), 25.87 (C-4-CH), 26.36(C-2-CH_{3ax}), 29.05 (C-2-CH_{3eq}), 43.56 (C-3-CH_2), 73.66 (C-2), 116.07 (Ar-CH), 122.92 (Ar-C), 123.74 (Ar-CH), 136.32 (Ar-C), 136.87 (Ar-C), 153.60 (Ar-C) ppm.

3,4-Dihydro-2,2,4,8-tetramethylbenzopyran (309h)

2-Methylphenol **(28h)** (5.2g, 0.05 mol) was reacted with 2-methyl-2,4-pentanediol **(314)** (7.10g, 0.06 mol) to afford a mixture of the title compound (detected by GC/MS) and **315h** (4.72g, 50%).

GC-MS : m/z 190 ($M^{+\cdot}$, $C_{13}H_{18}O$, 30%), 175 ($M^{+\cdot}$, $C_{13}H_{18}O$ - $CH_{3\%}$), 160 (12%), 147 (14%), 115 (8%), 91 (7%), 77 (5%), 39 (6%).

The presence of 1,1,3,4,6,6,8-Heptamethyl-1,2,3,6,7,8-hexahydro-5-oxa-cyclopenta[b]naphthlene **(315h)** was confirmed by GC/MS.

GC R_t 18.89 min.

^{1}H NMR ($CDCl_3$) : δ 1.23 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.31-1.35 (3H, d, *J* 9.36 Hz, CH_3), 1.39 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.46-1.49 1H, d, *J* 7.96 Hz, C-H), 1.75-1.78 (1H, dd', *J* 1.98 Hz, J_m 1.89 Hz, C-H), 2.00-2.07 (1H, m, *J* 7.16 Hz, C-H), 2.19 (3H, s, Ar-CH_3), 2.21-2.28 (1H, m, *J* 5.29 Hz, C-H), 2.85-2.95 (1H, m, *J* 6.41 Hz, C-H), 3.01-3.11 (1H, m, *J* 6.97 Hz, C-H), 6.85 (Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 11.47 (CH_3), 19.83 (CH_3), 19.96 (CH_3), 25.07 (CH_3), 26.65 (C-H), 29.14 (CH_3), 30.28 (CH_3), 35.06 (C-H), 42.83 (CH_2), 43.90 (CH_3), 53.23 (CH_2), 73.76 (Aliphatic-C), 73.83 (Aliphatic-C), 118.06 (Ar-H), 121.56 (Ar-C), 123.91 (Ar-C), 138.41 (Ar-C), 147.64 (Ar-C), 150.38 (Ar-C) ppm.

GC-MS : m/z 272 ($M^{+\cdot}$, $C_{19}H_{28}O$, 70%), 257 ($M^{+\cdot}$, $C_{19}H_{28}O$ - CH_3, 100%), 217 (95%), 201 (63%), 187 (9%), 173 (15%), 159 (8%), 115 (5%), 91 (4%), 77 (4%).

Analysis calcd. for $C_{19}H_{28}O$ (272) C, 83.77; H, 10.36. Found: C, 82.92; H, 10.33%.

3,4-Dihydro-2,2,4,7-tetramethylbenzopyran (309i)

3-Methylphenol **(28i)** (10.89, 0.1mol) was reacted with 2-methyl-2,4-pentandiol (**314**) (12.10g, 0.1mol) to afford the title compound (1.66g, 9%) as a pale yellow oil and **315i** as a contaminant (detected by GC/MS).

Pale yellow oil. B.pt 84-90°C / 1 torr, GC R_t 15.23 min.

^{1}H NMR ($CDCl_3$) : δ 1.24 (3H, s, C-2-CH_{3ax}), 1.29-1.32 (3H, d, *J* 6.72 Hz, C-4-CH_3), 1.39 (3H, s, C-2-CH_{3eq}), 1.46-1.56 (1H, t, *J* 6.96 Hz, C-H$_{ax}$), 1.78-1.86 (1H, m, *J* 5.91 Hz, C-H$_{eq}$), 2.25 (3H, s, C-7-CH_3), 2.83-2.98 (1H, m, *J* 6.53 Hz, C-4-CH), 6.61 (1H, s, C-8-CH), 6.66-6.70 (1H, d, meta-coupled, *J* 7.79 Hz, J_m 1.17 Hz, C-6-CH), 7.10-7.13 (1H, d, *J* 7.80 Hz, C-5-CH) ppm.

^{13}C NMR ($CDCl_3$) : δ 19.17 (C-4-CH_3), 24.55 (C-7-CH_3), 26.06 (C-4-CH), 29.74 (C-2-CH_{3ax}), 30.11 (C-2-CH_{3eq}), 42.89 (C-3-CH_2), 74.32 (C-2), 117.65 (Ar-CH), 120.86 (Ar-CH), 123.37 (Ar-C), 126.94 (Ar-H), 137.22 (Ar-C), 153.30 (Ar-C) ppm.

GC-MS : m/z 190 ($M^{+\cdot}$, $C_{13}H_{18}O$, 74%), 175 ($M^{+\cdot}$, $C_{13}H_{18}O$ - CH_3, 55%), 160 (7%), 147 (15%), 135 (100%), 105 (14%), 91 (26%), 77 (12%).

The presence of 1,3,3,4,7,7,9-heptamethyl-1,2,3,7,8,9-hexahydro-6-oxa-cyclopenta[a]naphthalene **(315i)** was detected by GC/MS.

GC R_t 18.83 min

GC-MS : m/z 272 ($M^{+\cdot}$, $C_{19}H_{28}O$, 30%), 257 ($M^{+\cdot}$, $C_{13}H_{18}O$ - CH_3, 100%), 217 (27%), 201 (32%), 187 (6%), 173 (11%), 159 (5%), 128 (<5%), 91 (<5%).

Analysis calcd. for $C_{19}H_{28}O$ (272) C, 82.06; H, 9.53. Found: C, 82.60; H, 10.21%.

3,4-Dihydro-2,2,4,6-tetramethylbenzopyran (309j)

4-Methylphenol **(28j)** (10.31g, 0.1mol)) was reacted with 2-methyl-2,4-pentanediol **(314)** (11.59g, 0.1mol) to afford the title compound (0.97g, 5%) as a pale yellow oil, B.pt 88-95 °C / 2 torr.

^{1}H NMR ($CDCl_3$) : δ 1.23 (3H, s, C-2-CH_{3ax}), 1.30-1.33 (3H, d, *J* 6.73 Hz, C-4-CH_3), 1.39 (3H, s, C-2-CH_{3eq}), 1.47-1.57 (1H, t, *J* 12.4 Hz, C-3-H$_{ax}$), 1.78-1.86 (1H, q, *J* 5.95 Hz, C-3-H$_{eq}$), 2.26 (C-6-CH_3), 2.88-2.93 (1H, m, *J* 6.15 Hz, C-4-H), 6.65-6.69 (1H, d, *J* 8.22 Hz, Ar-H), 6.87-6.90 (1H, d, meta-coupled, *J* 6.08 Hz, J_m 2.15 Hz, Ar-H), 7.03 (1H, s, meta-coupled, *J* 0.61 Hz, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 20.31 (C-4-CH_3), 20.67 (C-6-CH_3), 24.40 (C-2-CH_{3ax}), 26.29 (C-4-CH), 30.05 (C-2-CH_{3eq}), 42.83 (C-2), 116.97 (Ar-CH), 125.96 (Ar-C), 127.45 (Ar-CH), 127.95 (Ar-CH), 128.81 (Ar-C), 151.20 (Ar-C) ppm.

3,4-Dihydro-4-methoxy-2,2,4,-trimethylbenzopyran (309k)

4-Methoxyphenol **(28k)** (12.48g, 0.1 mol) was reacted with 2-methyl-2,4-pentanediol **(314)** (17.82g, 0.15 mol) to afford a mixture of the title compound (3.65g, 18%) and **315k** (4.35g, 21%) which were separated by fractional distillation.

The first fraction was the title compound as a yellow oil, B pt 128-130°C / 3 torr, TLC (ethyl acetate : pet. ether 40-60°, 15:85) R_f 0.74.

IR (film) : υ 2955-2866 (sat. C-H str.), 1609 (C=C), 1482-1454 (C-H def.), 1380-1366 (d, geminal CH_3), 1208 (C-O), 838 (C-H bend) cm^{-1}.

^1H NMR ($CDCl_3$) : δ 1.22 (3H, s, C-2-CH_{3ax}), 1.27-1.31 (3H, d, *J* 6.72 Hz, C-4-CH_3), 1.38 (3H, s, C-2-CH_{3eq}), 1.45-1.52 (1H, t, *J* 13.03 Hz, C-3-H_{ax}), 1.77-1.84 (1H, q, *J* 6.04 Hz, C-3-H_{eq}), 2.82-2.97 (1H, m, *J* 6.64 Hz, C-4-H), 3.78 (3H, s, C-6-CH_3), 6.78 (1H, s, meta-coupled *J* 2.62 Hz, Ar-H), 6.81-6.84 (1H, d, *J* 8.13 Hz, Ar-H), 6.96-6.70 (1H, d, *J* 9.13 Hz, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 20.41 (C-4-CH_3), 24.32 (C-6-CH_3), 26.70 (C-4-CH), 30.05 (C-2-CH_{3ax}), 30.05 (C-2-CH_{3eq}), 42.76 (C-3-CH_2), 55.68 (C-6-OCH_3), 73.92 (C-2), 112.45 (Ar-CH), 112.95 (Ar-CH), 117.67 (Ar-CH), 127.09 (Ar-C), 147.56 (Ar-C), 153.19 (Ar-C).

The second fraction was a yellow oil, B.pt 152-156°C / 2 torr. and identified as 2,3,3,5,5,7-hexamethyl-9-methoxy-1,2,3,3,5,5,7-heptahydro-4-oxa-cyclopenta[c]naphthalene **(315k)**.

^1H NMR ($CDCl_3$) : δ 1.22 (3H, s, C-CH_{3ax}), 1.27-1.30 (3H, d, *J* 6.30 Hz, CH_3), 1.29-1.31 (3H, d, *J* 5.88 Hz, CH_3), 1.33-1.34 (3H, d, *J* 2.32 Hz, CH_3), 1.36-1.39 (3H, d, *J* 6.04 Hz, CH_3), 1.41 (3H, s, C-CH_{3eq}), 1.50 (2H, m, *J* 5.03 Hz, C-Hax, C-Hax), 1.76-1.84 (1H, m, *J* 5.95 Hz, C-Heq), 2.08-2.17 (1H, m, *J* 6.54 Hz, C-Heq), 2.83-2.96 (1H, m, *J* 6.63 Hz, C-H), 3.20-3.31 (1H, m, *J* 6.52 Hz, C-H), 3.75 (3H, s, C-6-OCH_3), 6.57 (1H, s, Ar-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 20.41 (CH_3), 21.20 (CH_3), 24.15 (CH_3), 25.22 (CH_3), 26.70 (CH), 28.15 (CH_3), 30.05 (CH_3), 36.20 (CH), 42.76 (CH_2), 44.24 (CH_3), 51.15 (CH_2), 55.23 (O-CH_3), 73.18 (Ar-C), 73.92 (Ar-C), 108.06 (Ar-H), 124.43 (Ar-C), 135.90 (Ar-C), 138.18 (Ar-C), 144.37 (Ar-C), 149.65 (Ar-C) ppm.

MS (EI) : m/z 288 ($M^{+\cdot}$, $C_{12}H_{16}O$, 90%), 273 ($M^{+\cdot}$, $C_{13}H_{18}O$ - CH_3, 43%), 233 (100%), 217 (70%), 203 (10%), 189 (9%), 129 (6%), 91 (6%), 55 (5%).

3,4-Dihydro-6-Bromo-2,2,4,-tetramethylbenzopyran (309l)

4-Bromophenol **(28l)** (17.35g, 0.1 mol) was reacted with 2-methyl-2,4-pentanediol **(314)** (17.73g, 0.15 mol) to afford the title compound (1.84g, 7%) as an orange oil.

IR (film) : υ 2956 (sat. C-H str.), 1764 (C=C), 1479 (C-H def.), 1383 (d, geminal CH_3), 1212 (C-O), 898 (C-H bend), 662 (C-Br) cm^{-1}.
^1H NMR ($CDCl_3$) : δ 1.22 (3H, s, C-2-CH_{3ax}), 1.29-1.32 (3H, d, *J* 6.75 Hz, C-4-CH_3), 1.39 (3H, s, C-2-CH_{3eq}), 1.50-1.56 (1H, t, *J* 12.4 Hz, C-3-H_{ax}), 1.77-1.87 (1H, q, *J* 5.94 Hz, C-3-H_{eq}), 2.26 (C-6-CH_3), 2.83-2.99 (1H, m, *J* 6.73 Hz, C-4-H), 6.63-6.65 (1H, d, *J* 5.96 Hz, Ar-H), 7.13-7.18 (1H, d, meta-coupled, *J* 8.75 Hz, J_m 1.60 Hz, Ar-H), 7.45 (1H, s, meta-coupled, *J* 2.19 Hz, Ar-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 18.46 (C-4-CH_3), 24.40 (C-2-CH_{3ax}), 26.35 (C-4-CH), 29.87 (C-2-CH_{3eq}), 42.20 (C-3-CH_2), 74.65 (C-2), 111.93 (Ar-C), 119.05 (Ar-CH), 128.05 (Ar-C), 129.85 (Ar-CH), 130.15 (Ar-CH), 152.65 (Ar-C) ppm.

2,2,4,6,8,8-Hexamethyl-3,4,6,7-tetrahydro-2H,6H-pyrano[3,2-g]chromen-5-ol (309m)

Pyrogallol **(28m)** (12.68g, 0.1 mol) was reacted with 2-methyl-2,4-pentanediol **(314)** (18.20g, 0.2 mol) to afford the title compound as light brown solid (1.19g, 4%), b.pt 102-106°C / 2 torr, TLC (ethyl acetate : pet ether 40-60°, 15:85) R_f 0.29.
^1H NMR ($CDCl_3$) : δ 1.26-1.32 (12H, m, 4 x CH_3), 1.45 (6H, s, 2 x CH_3), 1.48 1.59 (2H, t, *J* 13.04 Hz, 2 x C-H_{ax}), 1.78-1.86 (2H, m, *J* 5.73 Hz, 2 x C-H_{eq}), 2.81-2.98 (2H, m, *J* 6.50 Hz, 2 x C-H), 5.35 (1H, s, broad, C-5-OH), 6.36 (1H, s, C-8-H) ppm.
^{13}C NMR ($CDCl_3$) : δ 20.36 (CH_3), 20.42 (CH_3), 24.57 (CH_3), 24.69 (CH_3), 25.91 (C-H), 25.97 (C-H), 30.04 (CH_3), 30.07 (CH_3), 43.07 (CH_2), 43.11 (CH_2), 75.01 (Aliphatic-C), 75.09 (Aliphatic-C), 113.81 (Ar-H), 118.39 (Ar-C), 118.41 (Ar-C), 132.84 (Ar-C), 139.25 (Ar-C), 139.34 (Ar-C) ppm.
MS (EI) : m/z 290 ($M^{+\cdot}$, $C_{18}H_{26}O_3$, 55%), 275 ($M^{+\cdot}$, $C_{18}H_{26}O_3$ - CH_3, 30%), 235 (100%), 219 (29%), 201 (10%), 191 (25%), 165 (5%), 179 (60%), 91 (9%), 83 (8%), 77 (9%).

3,4-Dihydro-2,2,5-7,8-pentamethyl-6-nitro-benzopyran (309n)

3,4-Dihydro-2,2,5,7,8-pentamethylbenzopyran **(28n)** (10.93g, 0.05mol) was dissolved in a cooled solution of conc. sulphuric acid (10ml) at 0°C. A mixture of conc. sulphuric acid and conc. nitric acid (5ml) at 0°C was added dropwise over a period 10 mins with constant stirring. The reaction mixture was allowed to stand with constant stirring at room temperature for a further 15 mins. The resultant solution was poured onto ice (50g) with stirring. On standing an orange oil formed which was taken up in ethyl acetate (50 ml). The organic layer was washed with water (2x100ml) and dried over anhydrous magnesium sulphate. Filtration of the drying agent and removal of the solvent *in vacuo* afforded the title compound as a light orange oil.

^{1}H NMR ($CDCl_3$) : δ 1.18 (3H, s, C-2a-CH_3), 1.26-1.29 (3H, d, *J* 8.70 Hz, C-4-CH_3), 1.43 (3H, s, C-2b-CH_3), 1.70-1.78 (1H, q, *J* 6.96 Hz, C-3-H_{ax}), 1.96-2.01 (1H, q, *J* 6.32 Hz, C-3-H_{eq}), 2.10 (6H, s, 2xAr-CH_3), 2.18 (3H, s, Ar-CH_3), 2.99-3.12 (1H, m, *J* 6.94 Hz, C-4-H) ppm.

^{13}C NMR ($CDCl_3$) : δ 11.42 (Ar-CH_3), 14.49 (Ar-CH_3), 14.54 (Ar-CH_3), 21.69 (C-4-CH_3), 26.53 (C-2-CH_{3ax}), 26.58 (C-4-CH), 29.34 (C-2-CH_{3eq}), 43.19 (C-3-CH_2), 73.37 (C_2), 124.35 (Ar-C), 124.50 (2xAr-C), 126.84 (Ar-C), 147.46 (Ar-C), 152.46 (Ar-C) ppm.

M.S. (EI) : m/z 263 ($M^{+\cdot}$, $C_{15}H_{21}NO_3$, 67%), 243 ($M^{+\cdot}$, $C_{15}H_{21}NO_3$ - CH_3, 25%), 233 (8%), 217 ($M^{+\cdot}$ - NO_2, 18%), 208 (100%), 190 (34%), 174 (22%), 161 (14%), 149 (14%), 128 (10%), 115 (15%), 105 (17%), 91 (30%), 77 (23%).

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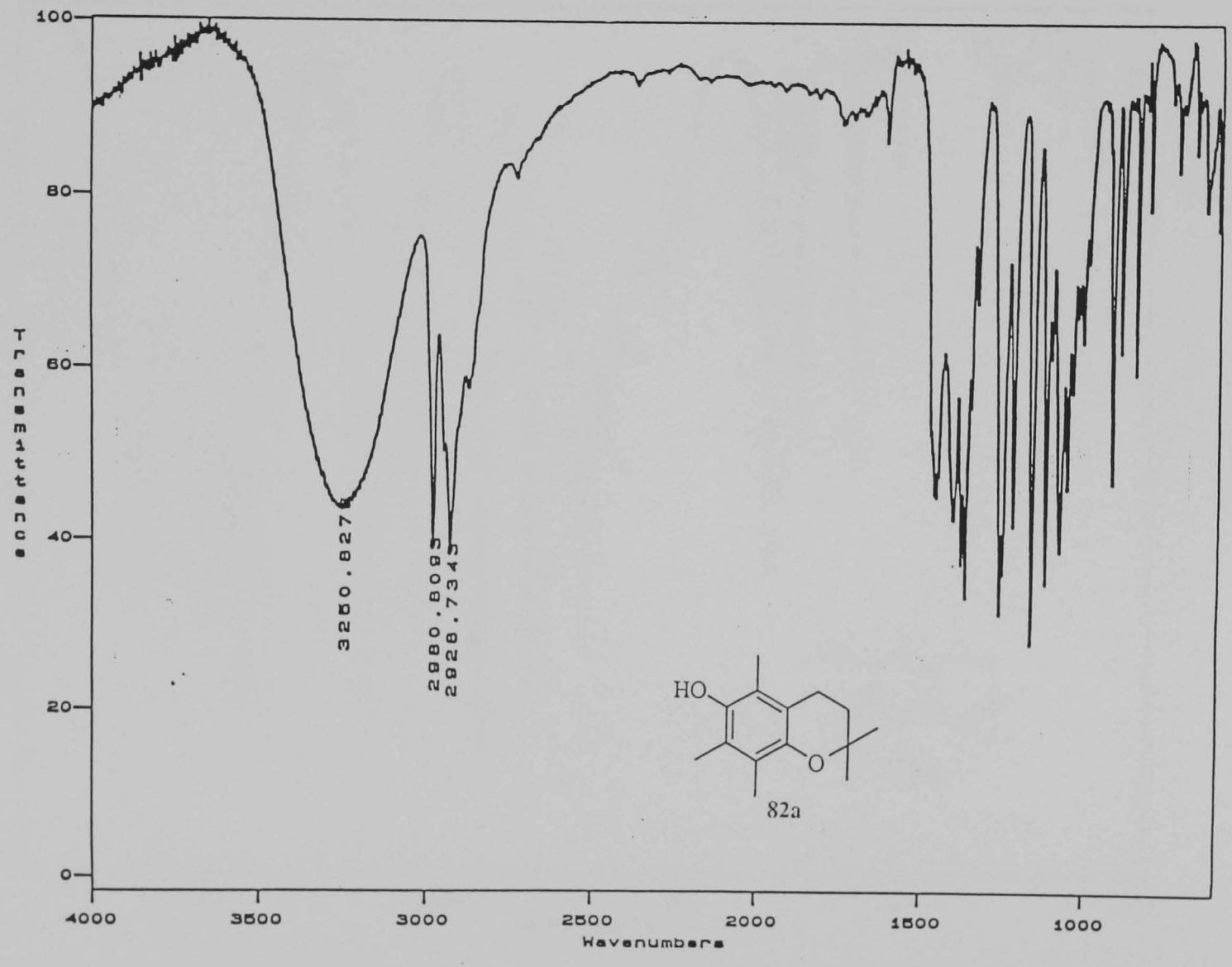
APPENDIX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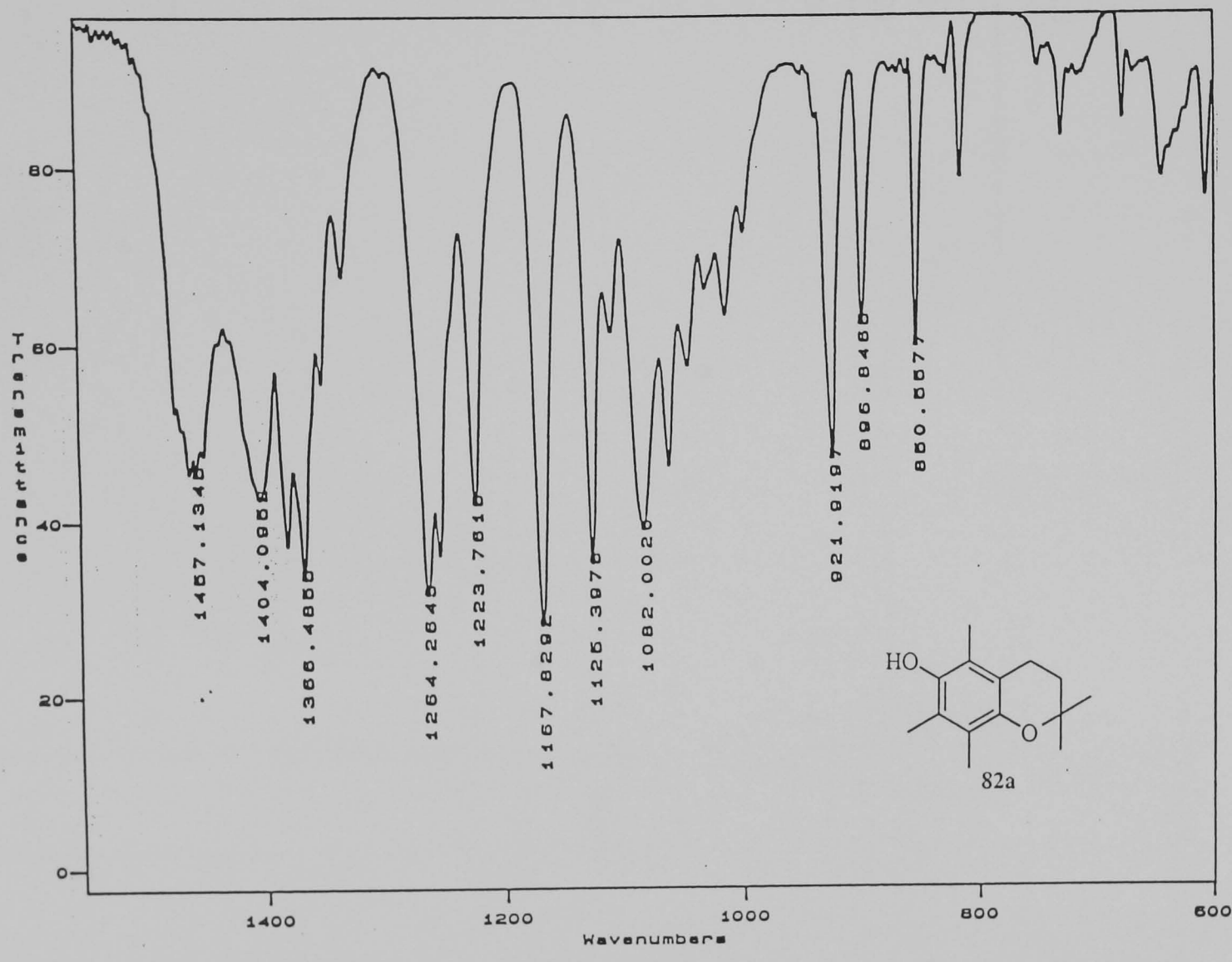
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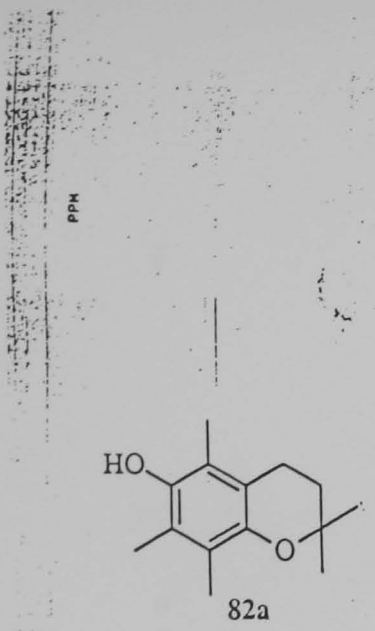

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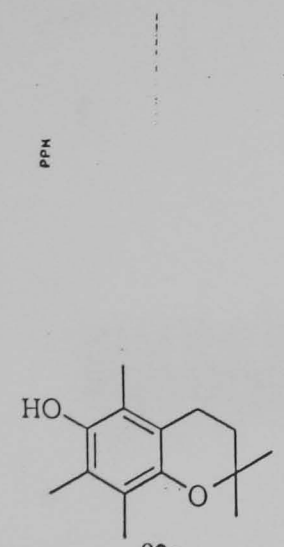

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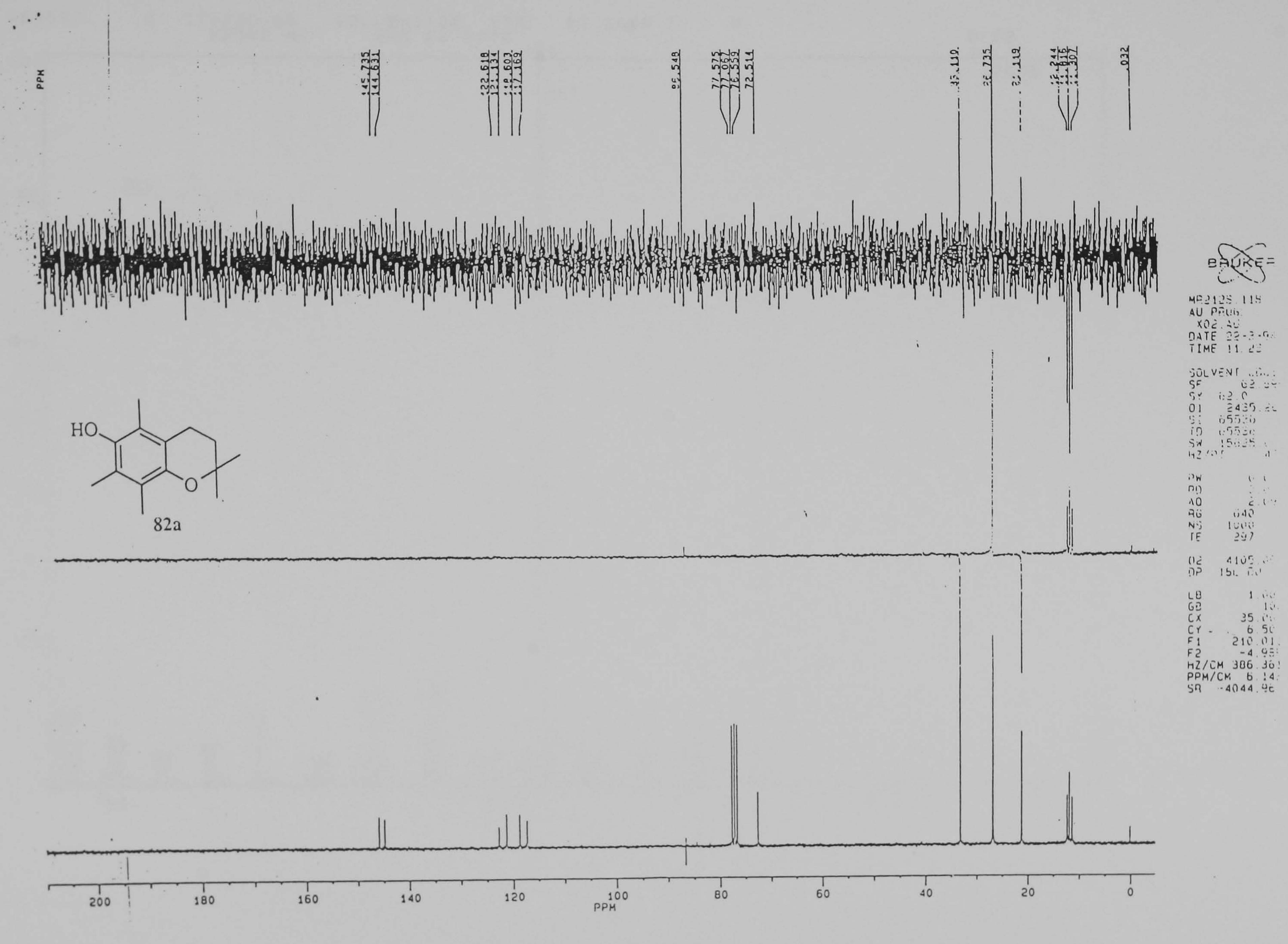

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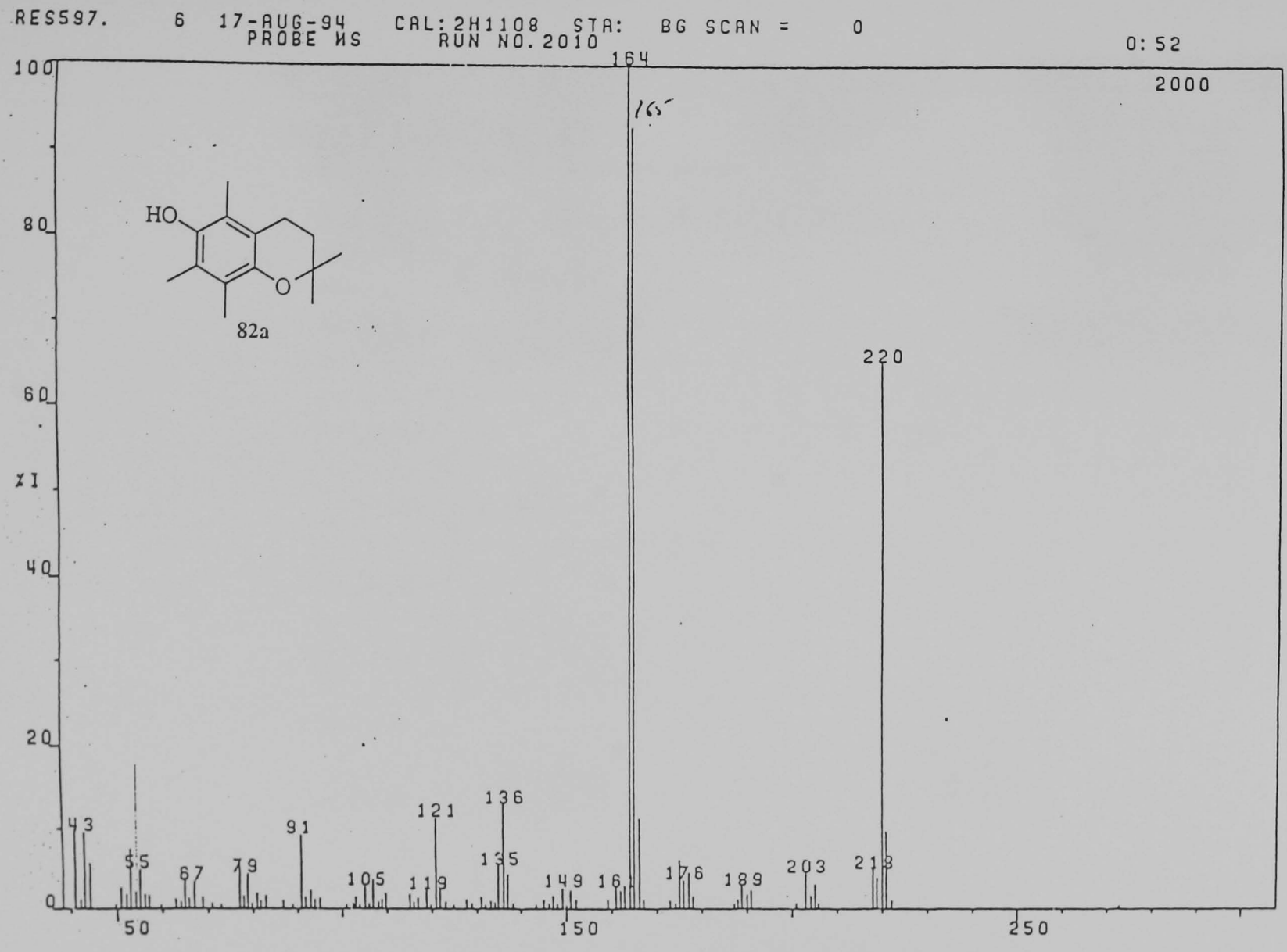
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Date 31 [illegible]

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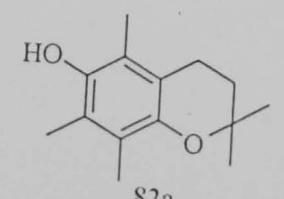

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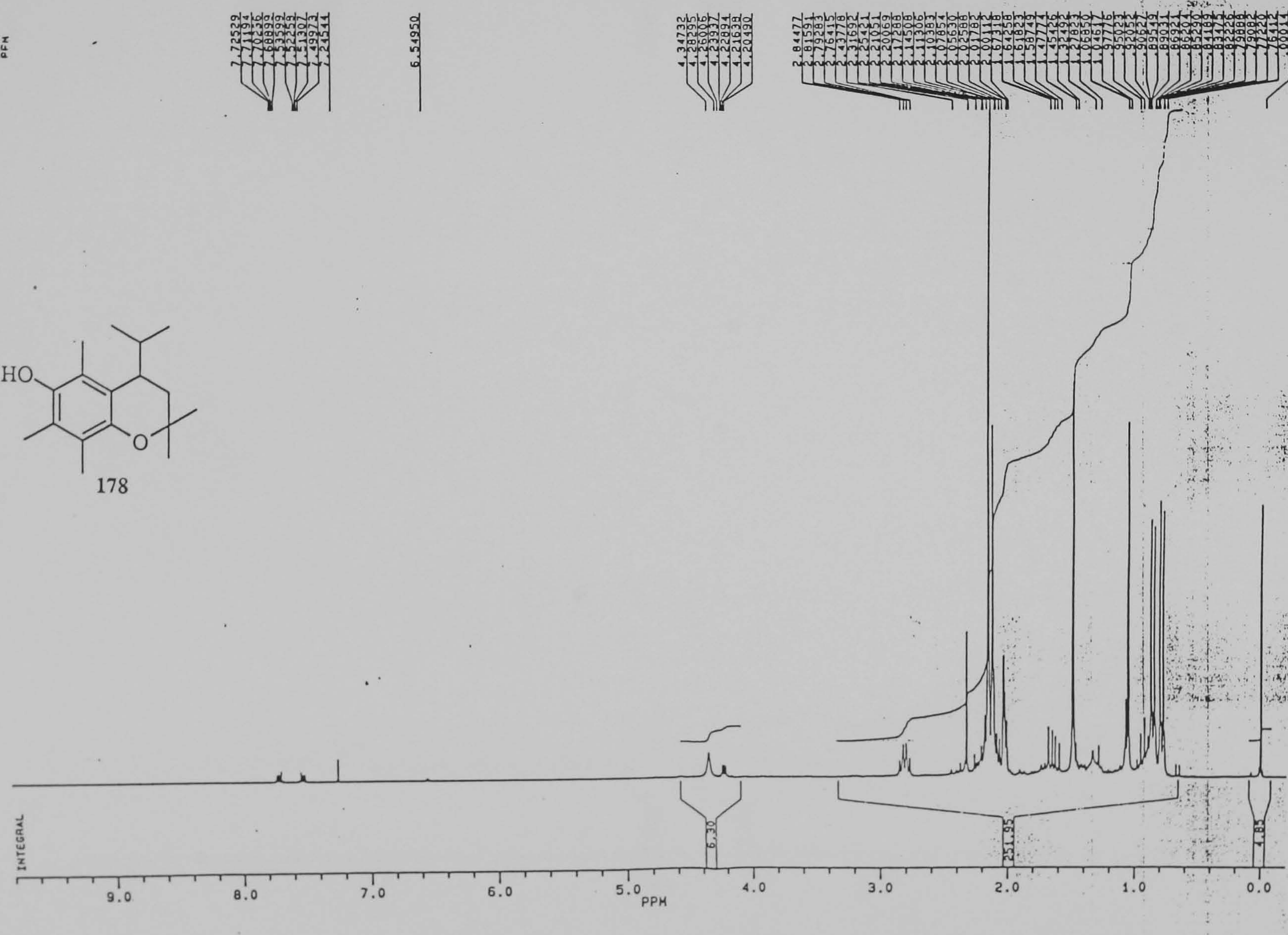

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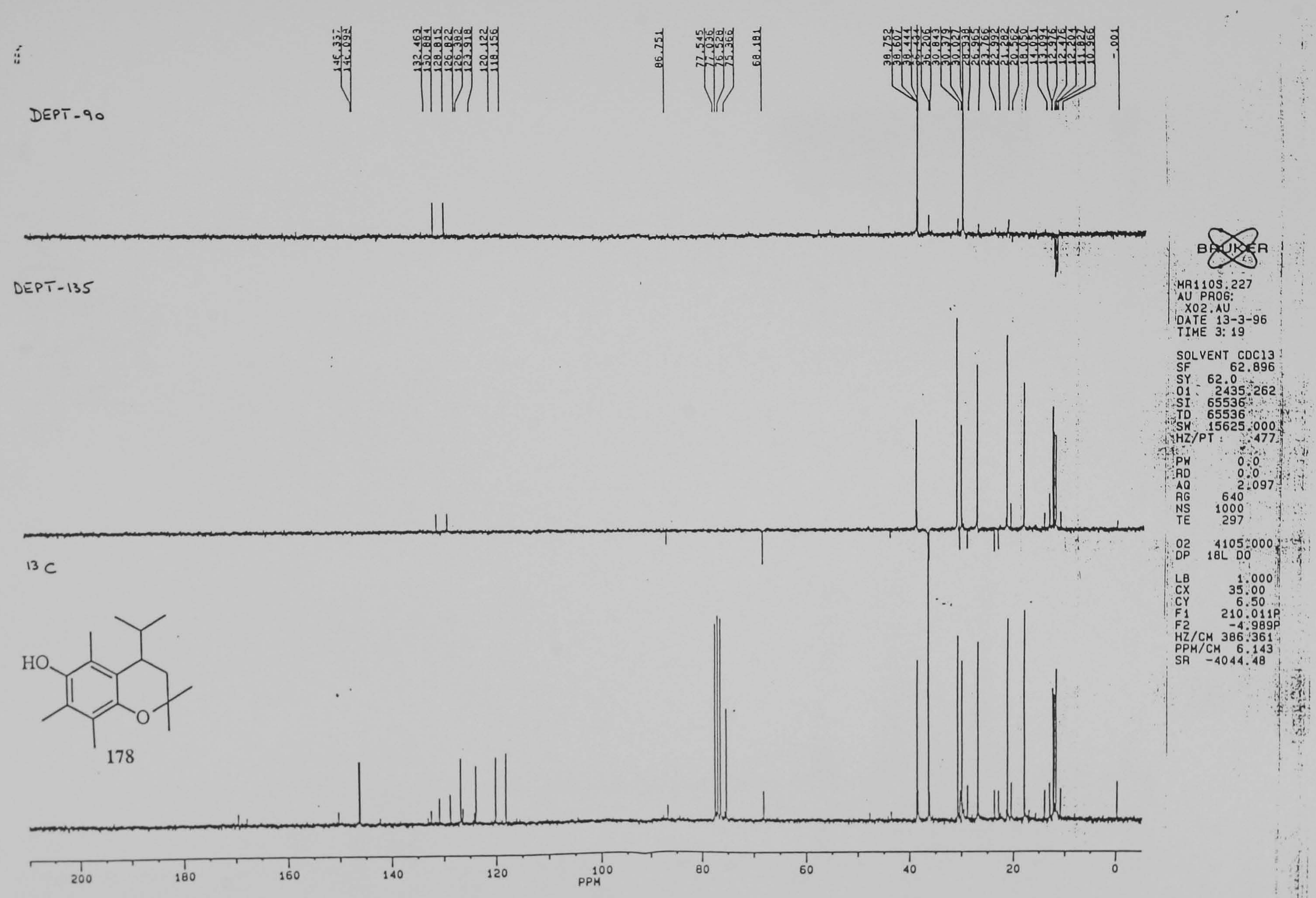
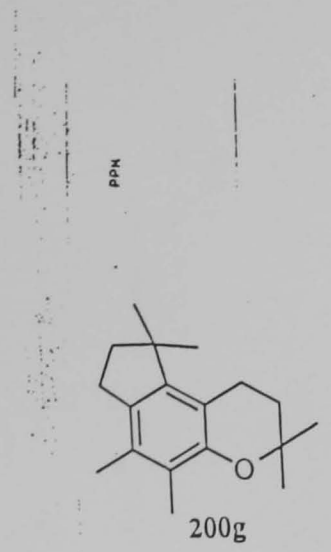

DEPT-90
DEPT-135
13C
HO
O
178
PPM
MR110S.227
AU PROG:
X02.AU
DATE 13-3-96
TIME 3:19
SOLVENT CDCl3
SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477
PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297
O2 4105.000
DP 18L DO
LB 1.000
CX 35.00
CY 6.50
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4044.48



200g

BRUKER

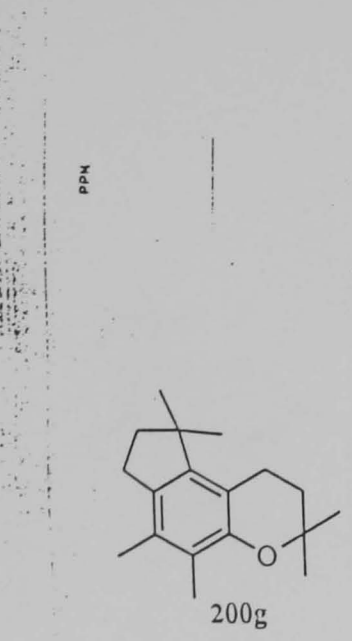
AP100S.123
AU PROG:
X00.AU
DATE 10-4-97
TIME 13:15

SOLVENT CDCl3
SF 250.133
SY 100.0
O1 4358.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 4
NS 96
TE 297

O2 0.0
DP 63L PO

LB .200
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 2871.49



200g

[WITH D2O]

BRUKER

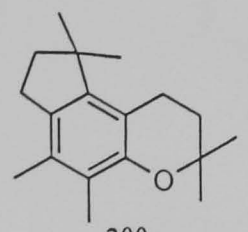
AP100S.126
AU PROG:
X00.AU
DATE 10-4-97
TIME 13:47

SOLVENT CDCl3
SF 250.133
SY 100.0
O1 4358.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 4
NS 64
TE 297

O2 0.0
DP 63L PO

LB .200
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 2870.88



200g

CDCL3

BRUKER

AP100S.123
AU PROG:
X00.AU
DATE 10-4-97
TIME 13:15

SOLVENT CDC13
SF 250.133
SY 100.0
O1 4358.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

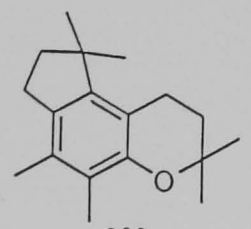
PW 0.0
RD 0.0
AQ 3.277
RG 4
NS 96
TE 297

O2 0.0
DP 63L P0

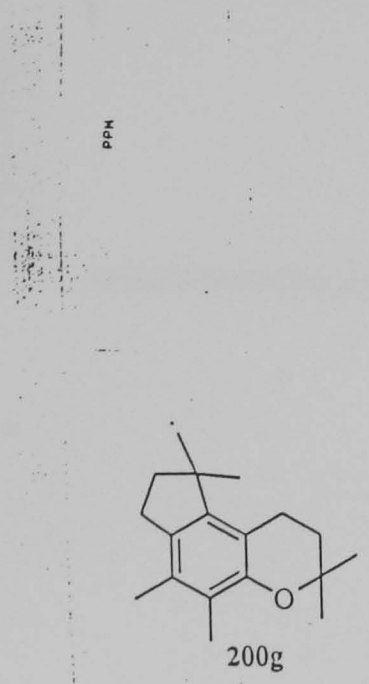
LB .200
CX 35.00
CY 0.0
F1 13.601P
F2 -.399P
HZ/CM 100.054
PPM/CM .400
SR 2871.49

20Hz/cm Expansions

CDCL3



200g



200g

BRUKER

APR91S.113
AU PROG:
X02.AU
DATE 9-4-97
TIME 18:43

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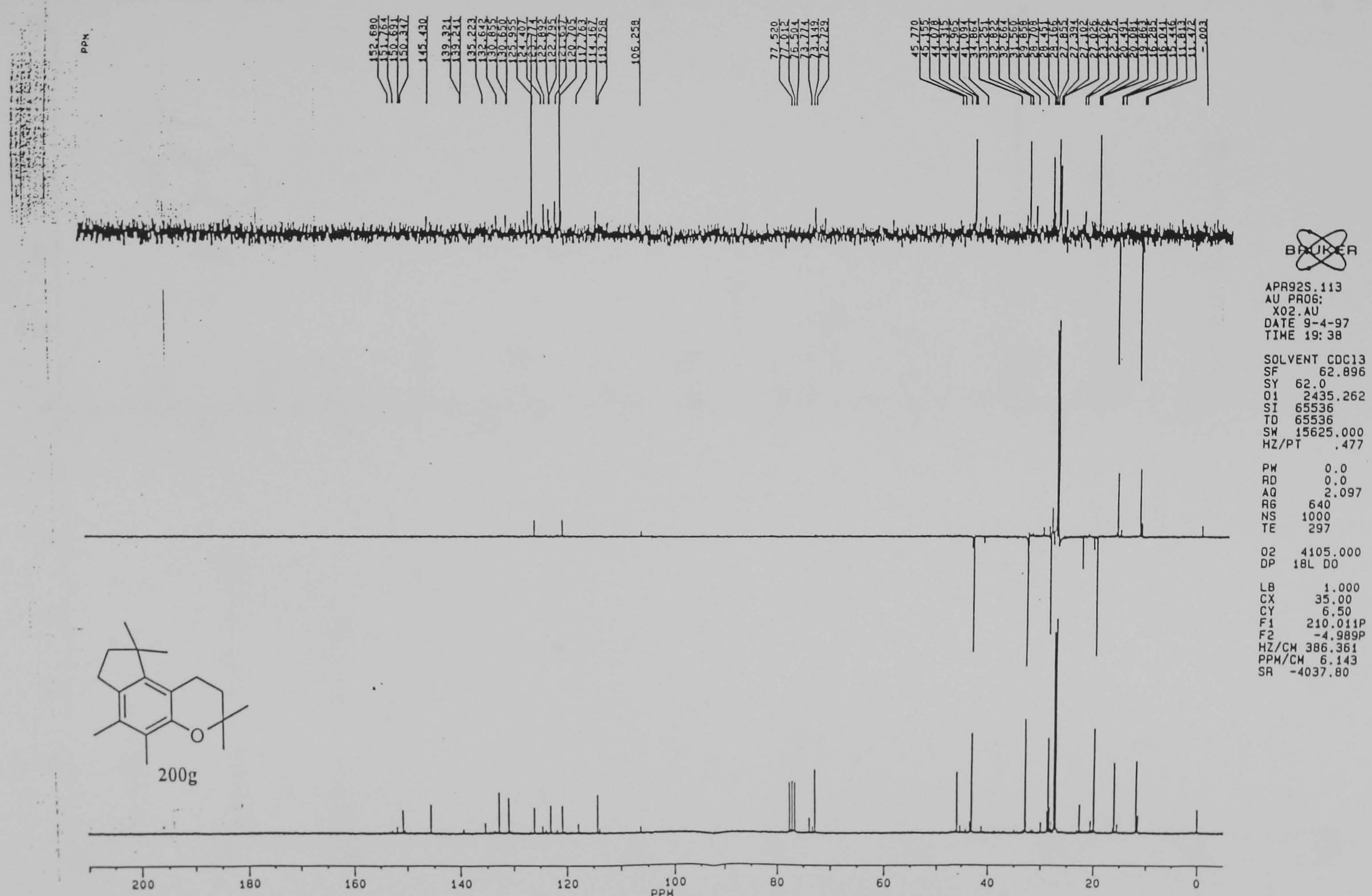
SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

O2 4105.000
DP 18L DO

LB 1.000
CX 35.00
CY 18.00
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4037.80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122.892
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76.504
73.774
73.149
72.729
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44.078
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41.094
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33.251
32.822
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28.708
28.451
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27.855
27.394
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27.026
23.026
22.572
20.491
20.081
19.863
16.285
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15.446
11.813
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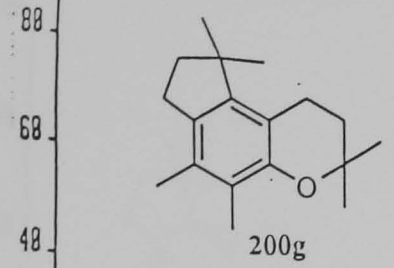
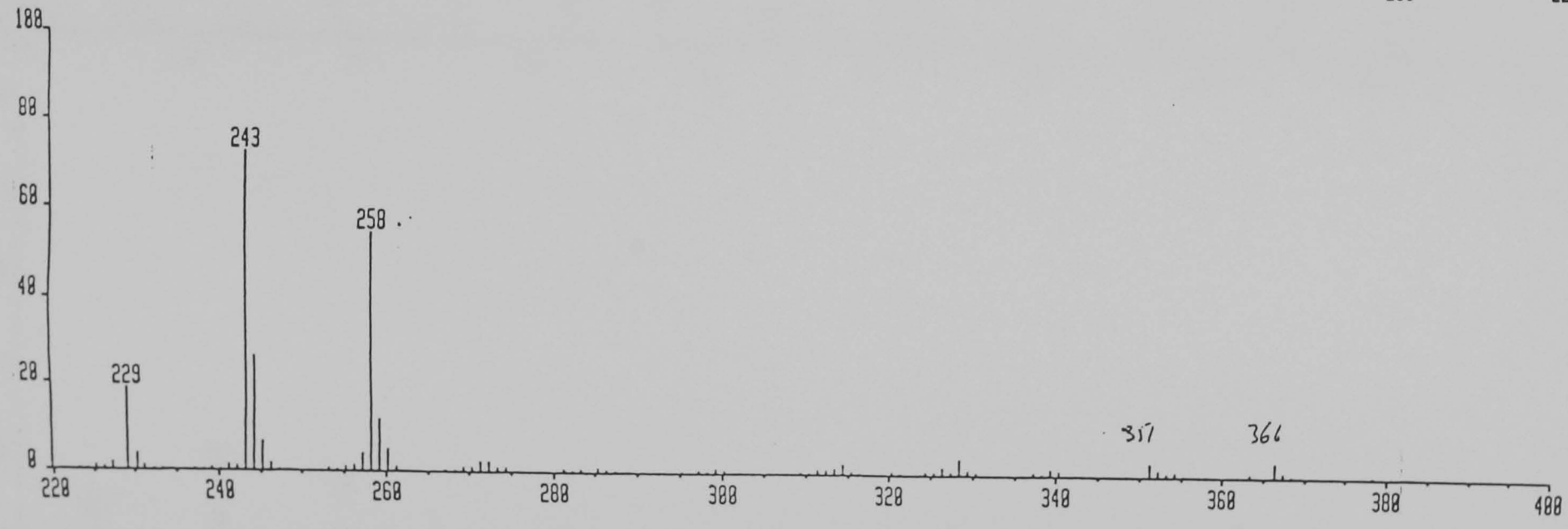
PPM
BRUKER
APR92S.113
AU PROG:
X02.AU
DATE 9-4-97
TIME 19:38
SOLVENT CDC13
SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477
PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297
O2 4105.000
DP 18L DO
LB 1.000
CX 35.00
CY 6.50
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4037.80
200g
200
180
160
140
120
100
PPM
80
60
40
20
0

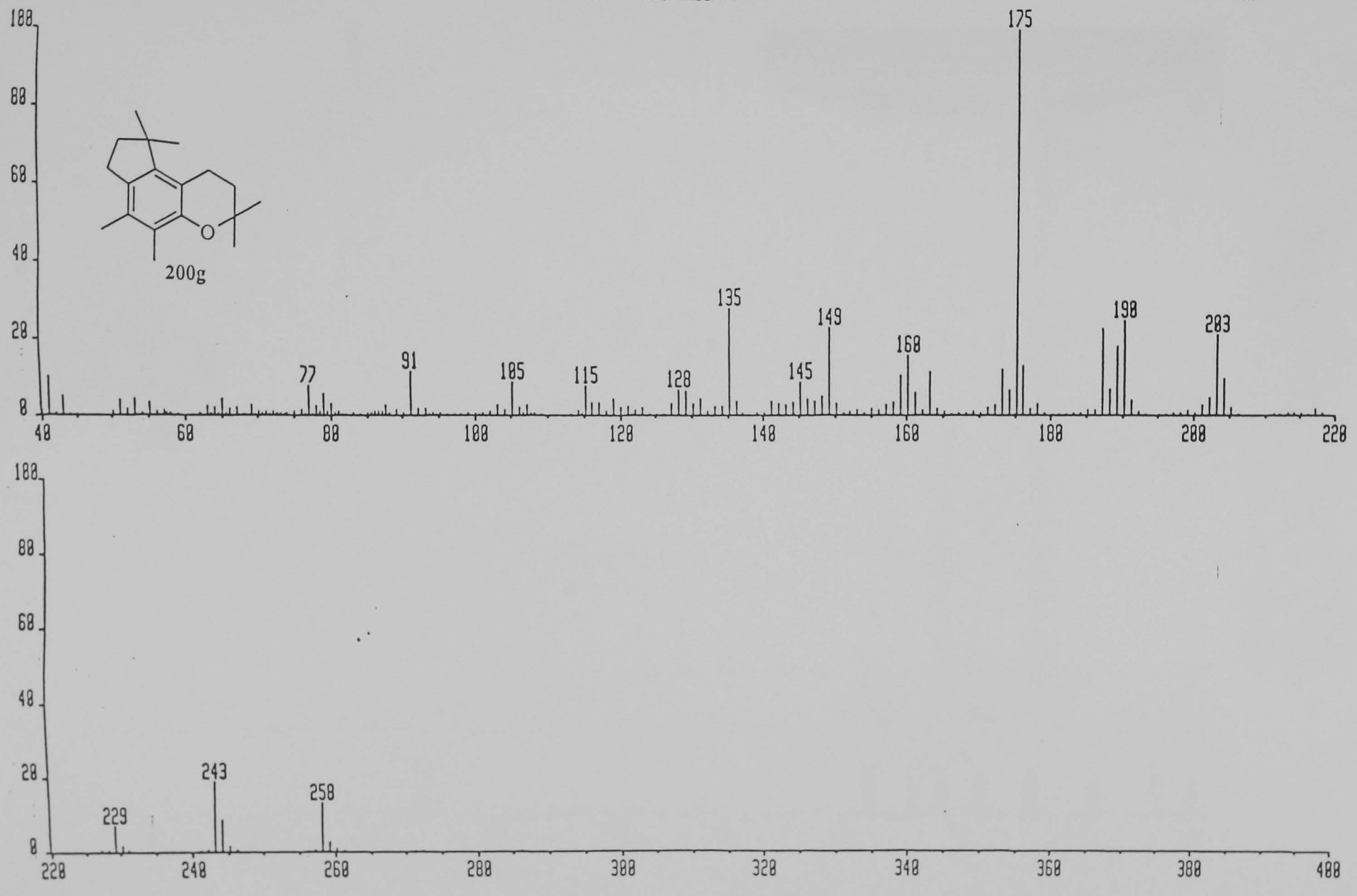
RES478#18♦ x1 Bgd=8 12-MAR-97 15:52♦8:81:15 78-258 EI♦
BpM=8 I=2.9v HM=8 TIC=214831088 Acnt: Sys:LRP
RUN NO.1898 SAMPLE: RM#139(C) PT= 8° Cal:CAL2782
HMR: 189338
MASS: 1

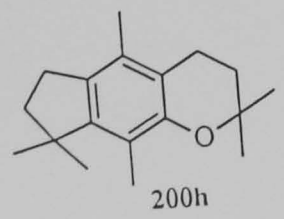


200g

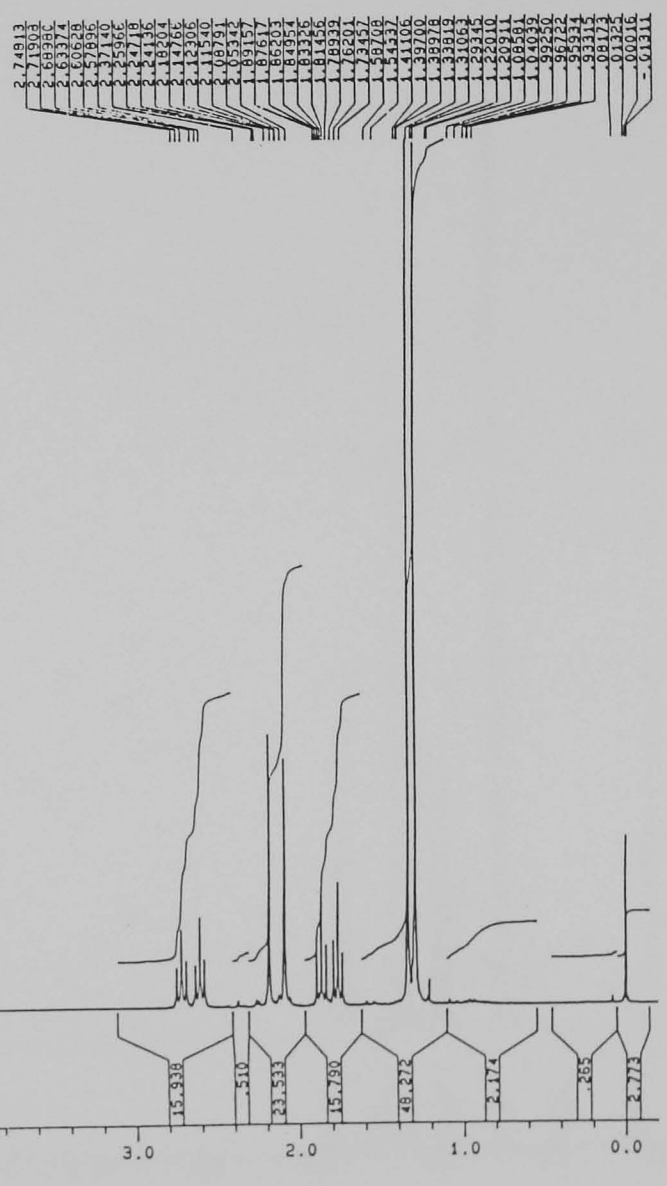


RES47812♦ x1 Bgd=1 12-MAR-97 15:52♦8:08:32 78-258 EI♦
BpM=8 I=4.4v Hm=8 TIC=191708888 Acnt: Sys:LRP HMR: 2864588
RUN NO.1898 SAMPLE: RM#139(C) PT= 8° Cal:CAL2782 MASS: 17





200h



BRUKER

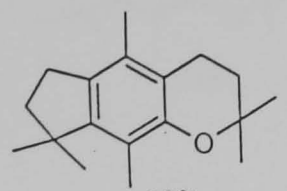
FE243S.210
AU PROG:
X00.AU
DATE 26-2-97
TIME 2:36

SOLVENT CDCl3
SF 250.133
SY 100.0
O1 4358.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 2
NS 96
TE 297

O2 0.0
DP 63L PO

LB .200
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SA 2884.61



200h

CDCL3

BRUKER

FE243S.210
AU PROG:
X00.AU
DATE 26-2-97
TIME 2:36

SOLVENT CDC13
SF 250.133
SY 100.0
O1 4358.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

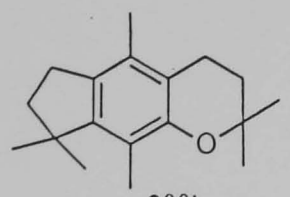
PW 0.0
RD 0.0
AQ 3.277
RG 2
NS 96
TE 297

O2 0.0
DP 63L PO

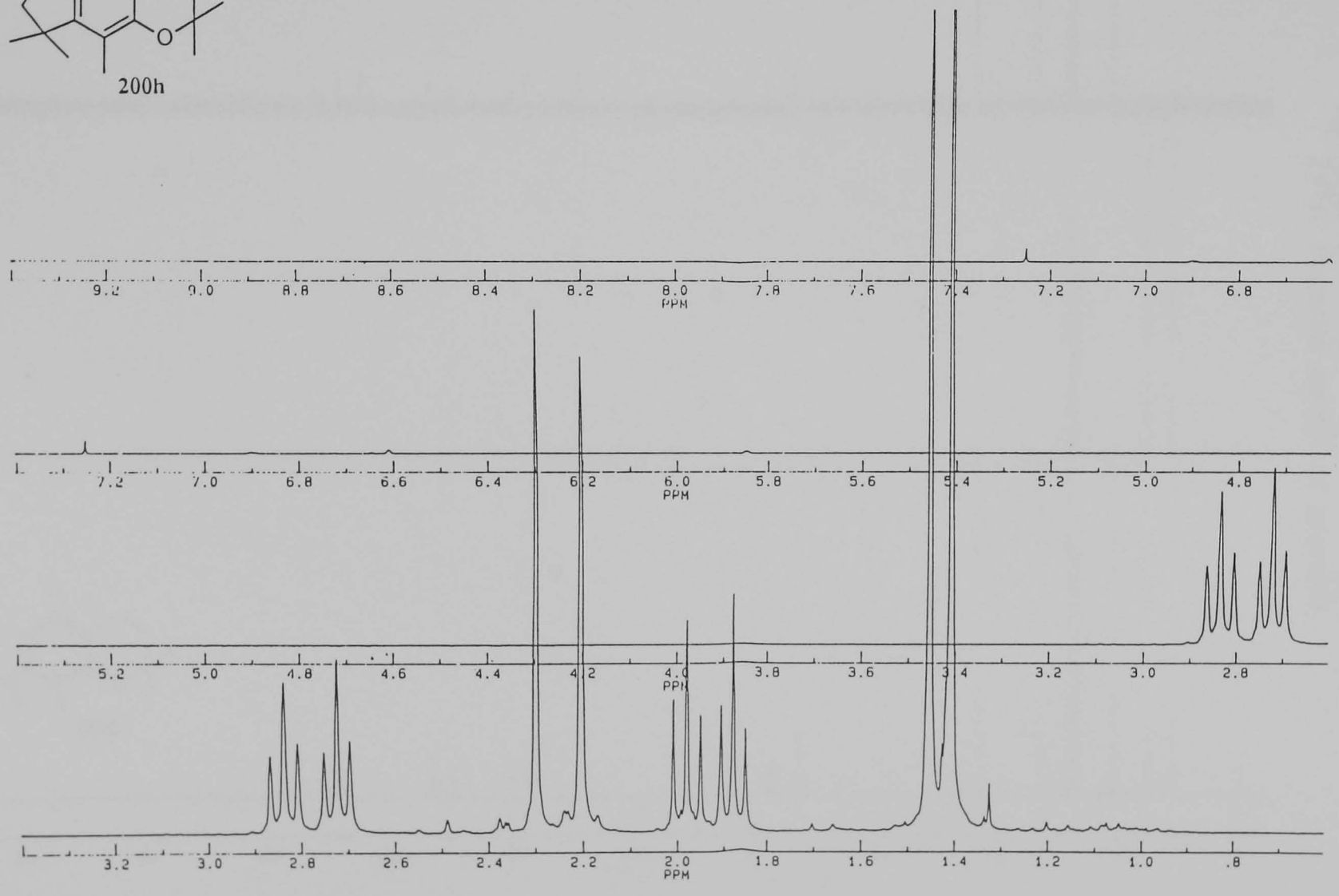
LB .200
CX 35.00
CY 0.0
F1 13.601P
F2 -.399P
HZ/CM 100.054
PPM/CM .400
SR 2855.92

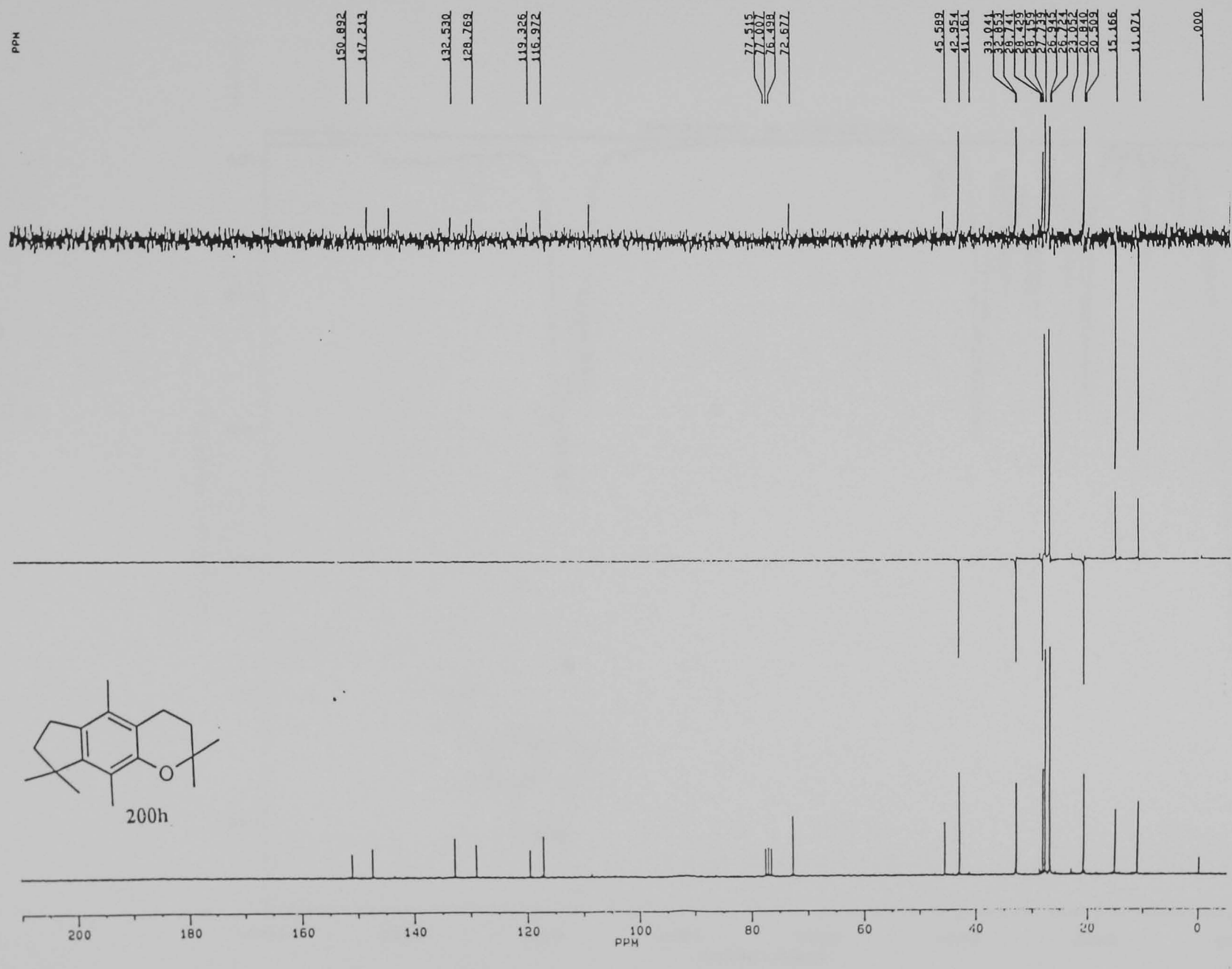
20Hz/cm Expansions

CDCL3



200h





200h

BRUKER

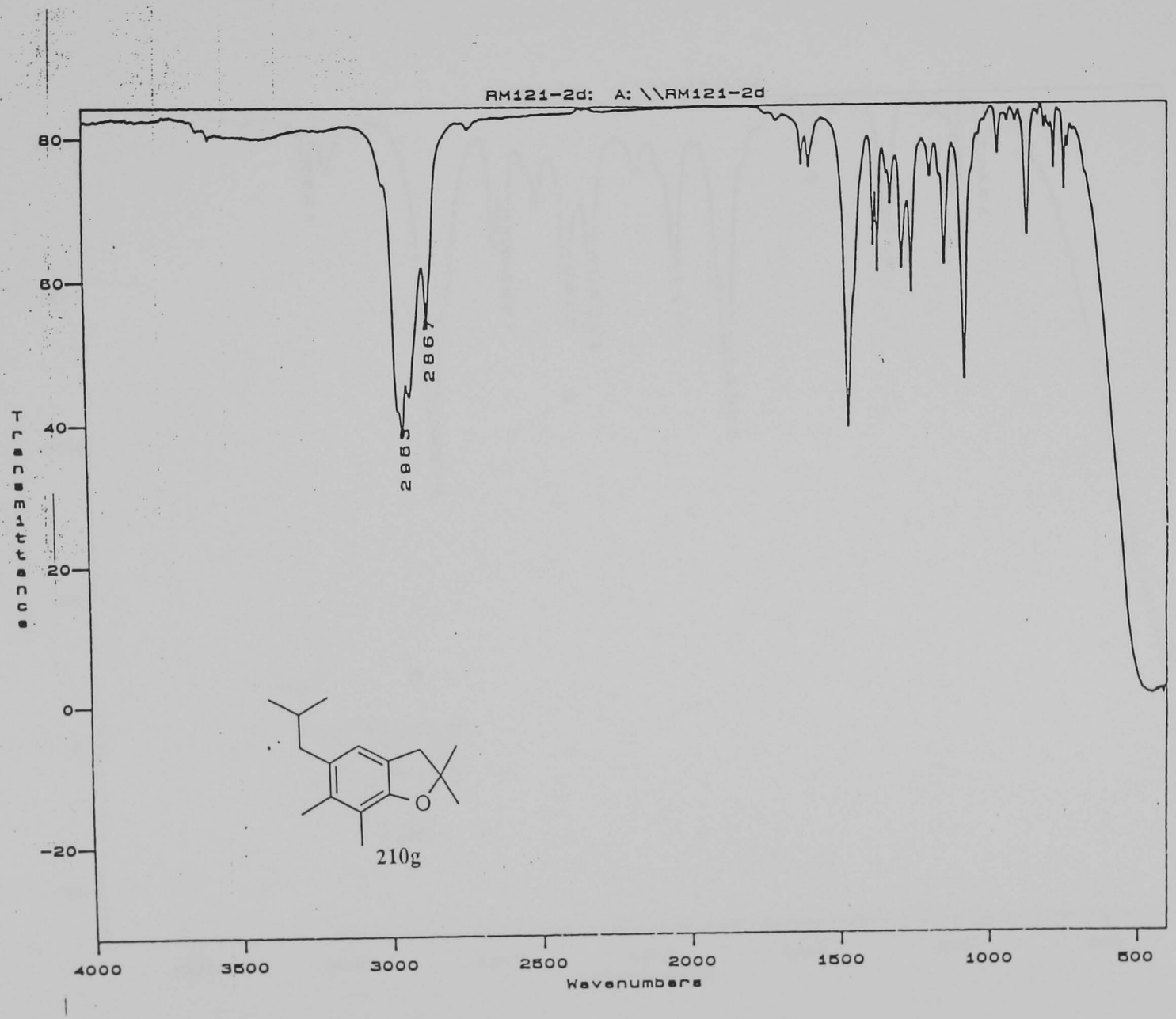
FE240S.210
AU PROG:
X02.AU
DATE 26-2-97
TIME 0:36

SOLVENT CDCl3
SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 400
NS 1000
TE 297

O2 4105.000
DP 18L D0

LB 1.000
CX 35.00
CY 6.50
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4037.80


RM121-2d: A:\\RM121-2d
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60
40
20
0
-20
%Transmittance
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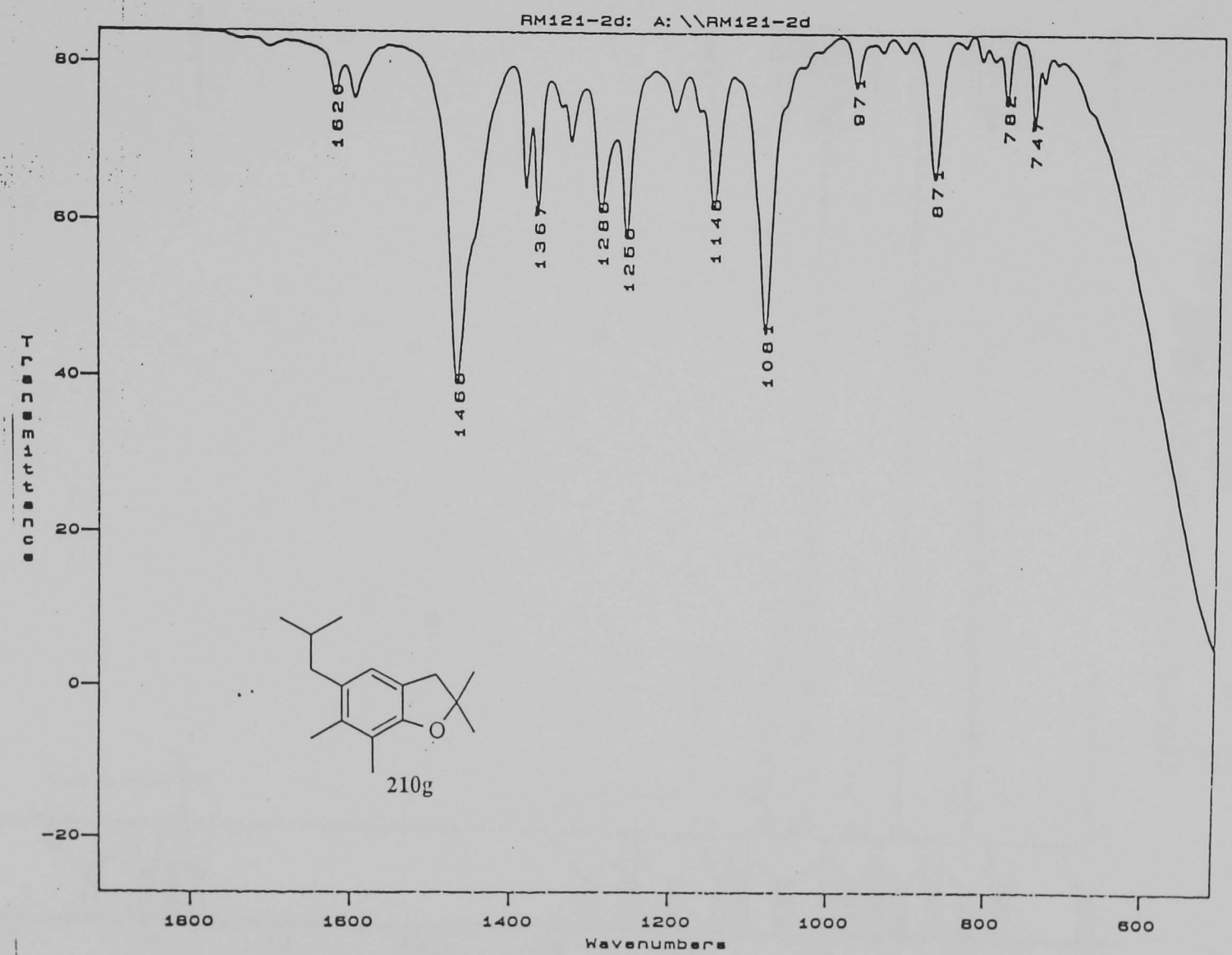
2865
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers
O

210g


RM121-2d: A: \\RM121-2d
%Transmittance
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60
40
20
0
-20
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1467
1367
1288
1256
1148
1081
871
871
782
747
1800
1600
1400
1200
1000
800
600
Wavenumbers
O

210g

6.71234
2.93915
2.41713
2.14807
2.12913
2.11818
2.09764
1.75031
1.43046
.93307
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BRUKER
OC200S.124
AU PROG:
X00.AU
DATE 20-10-98
TIME 14:29
SOLVENT CDCl3
SF 250.133
SY 100.0
O1 4358.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 0.0
RD 0.0
AQ 3.277
RG 1
NS 96
TE 297
O2 0.0
DP 63L PO
LB .200
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 2898.65
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.227
.137
7.793
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.275
34.546
.169
4.186
.140
23.032
.791
23.650
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3.193
9.0
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0
1.0
0.0

210g

210g

BRUKER

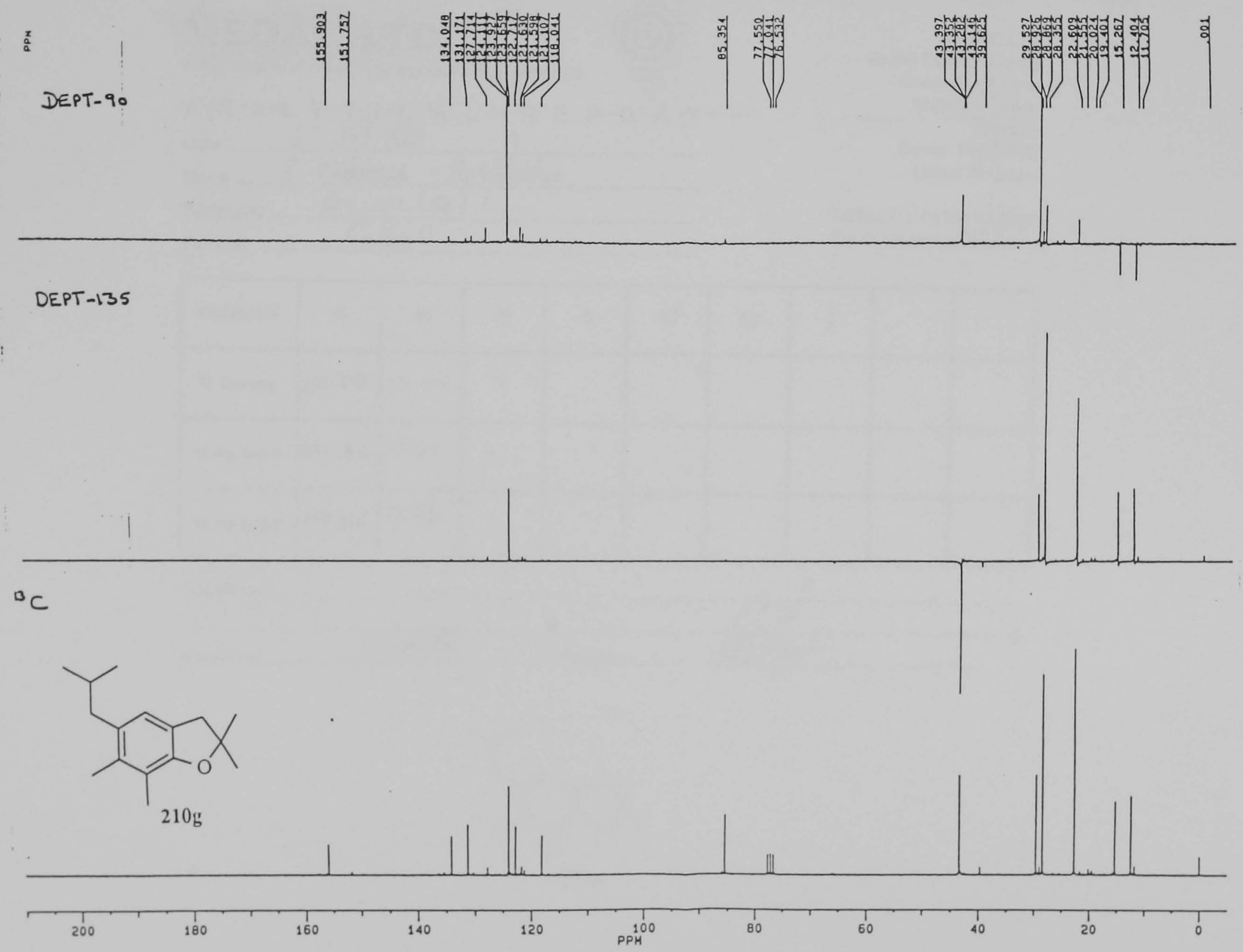
OC201S.124
AU PROG:
X02.AU
DATE 20-10-98
TIME 15:26

SOLVENT CDCl3
SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 400
NS 1000
TE 297

O2 4105.000
DP 18L DO

LB 1.000
CX 35.00
CY 18.00
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4034.94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29.537
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28.352
22.609
21.552
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15.267
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OC1805.124
AU PROG:
X02.AU
DATE 20-10-98
TIME 1:56
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SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477
PW 0.0
RD 0.0
AQ 2.097
RG 400
NS 1000
TE 297
O2 4105.000
DP 18L DO
LB 1.000
CX 35.00
CY 6.50
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4034.46
13C
O
210g
200
180
160
140
120
100
80
60
40
20
0
PPM

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United Kingdom

Tel/Fax No. 01784 434299
Email: MedacLtd@aol.com

ANALYTICAL REPORT

Date 31 JAN 2000

Name R. Mahmoud - Hertfordshire

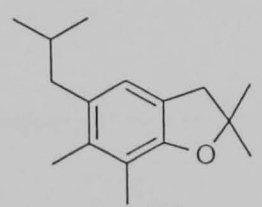
Sample ID RM 121 (2a)

Formula $C_{15}H_{24}O$

ELEMENT	C	H	N	S	Cl	Br	I		
% Theory	82.70	10.41	-						
% Found 1	79.32	9.51	-						
% Found 2	79.64	9.72	-						

Comments .....

Assay No 66589 Analyst .....



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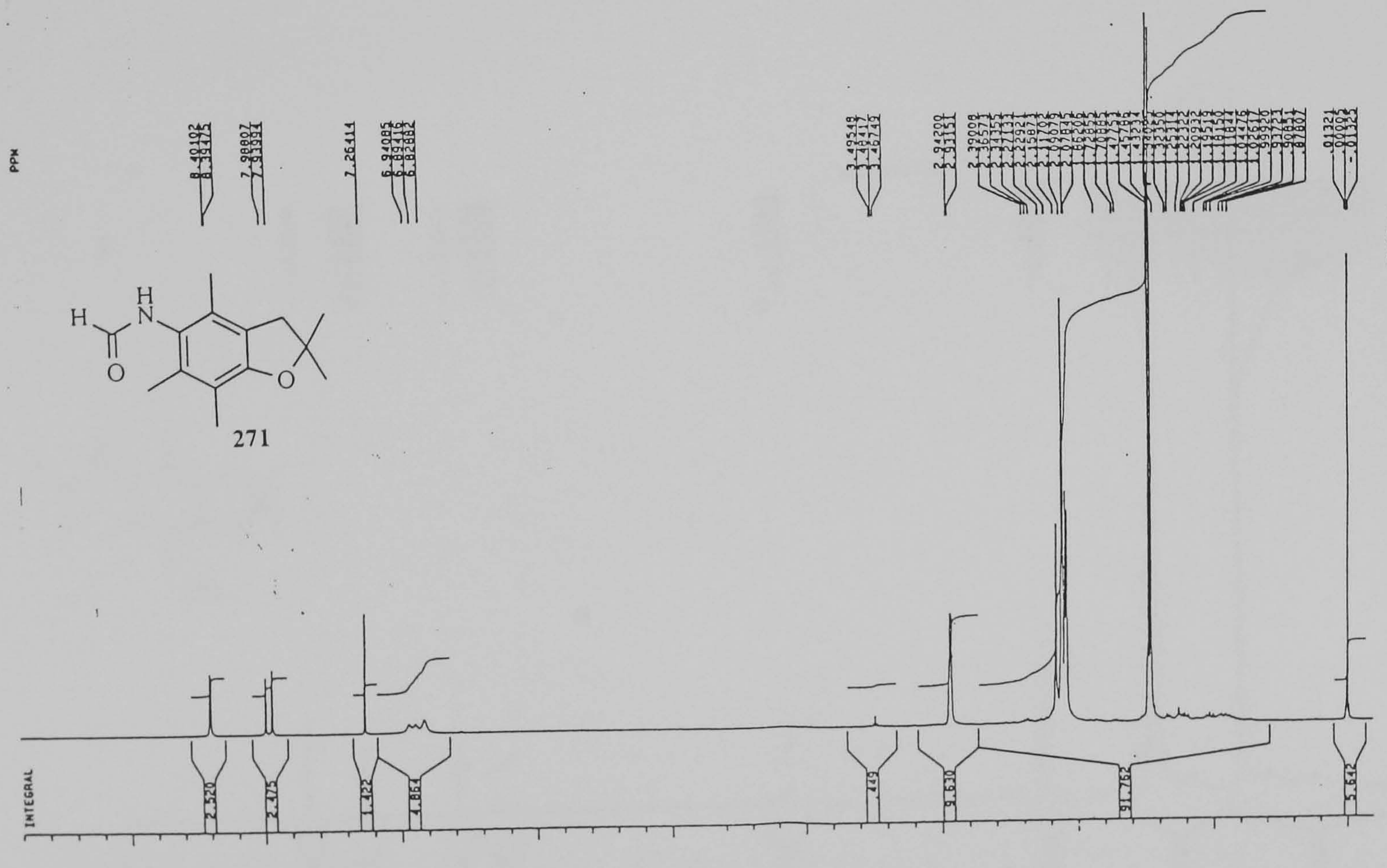
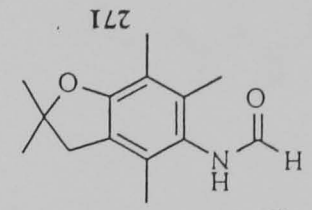


271

MY070S.154
AU PROG:
X00.AU
DATE 7-5-99

SOLVENT	CDCl3
SF	250.133
SY	100.0
O1	4358.000
SI	32768
TD	32768
SW	5000.000
HZ/PT	.305
PW	0.0
RD	0.0
AQ	3.277
RG	20
NS	96
TE	297
FW	6300
O2	0.0
DP	63L PO
LB	.200
GB	.100
CX	35.00
CY	18.00
F1	9.801P
F2	-.199P
HZ/CM	71.463
PPM/CM	.286
SR	2853.48

271

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MY0805.154
AU PROG:
     X00.AU
DATE 16-8-99
SOLVENT CDCl3
SF    250.133
SY  100.0
O1   4358.000
SI    32768
TD    32768
SW   5000.000
HZ/PT   .305

PW      0.0
RD      0.0
AQ      3.277
RG       20
NS       96
TE      297

FW     6300
O2      0.0
DP   63L PO

LB      .200
GB      .100
CX        35.00
CY        18.00
F1     9.801P
F2     -.199P
HZ/CM  71.463
PPM/CM   .285
SR    2852.57
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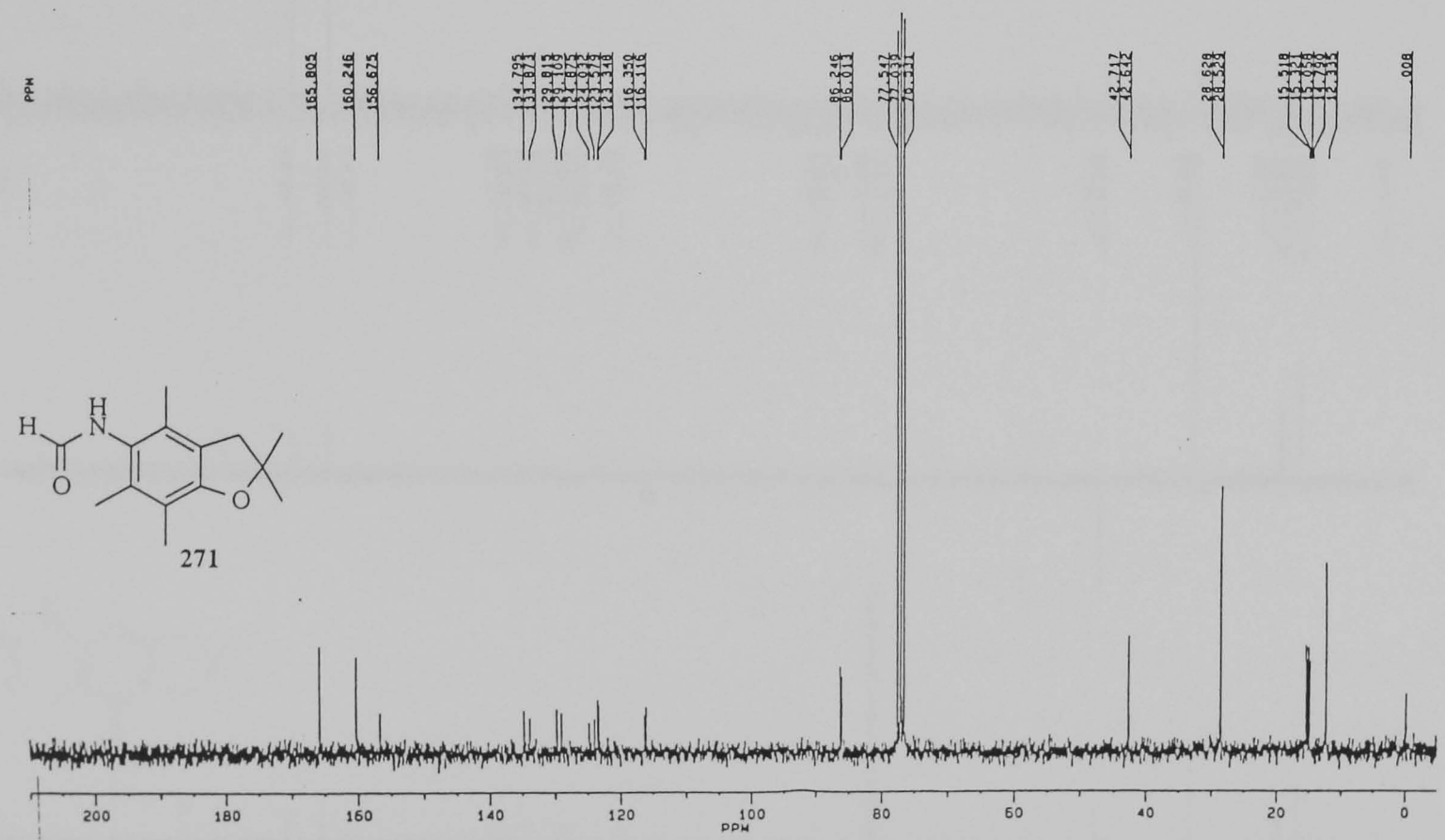


271

BRUKER

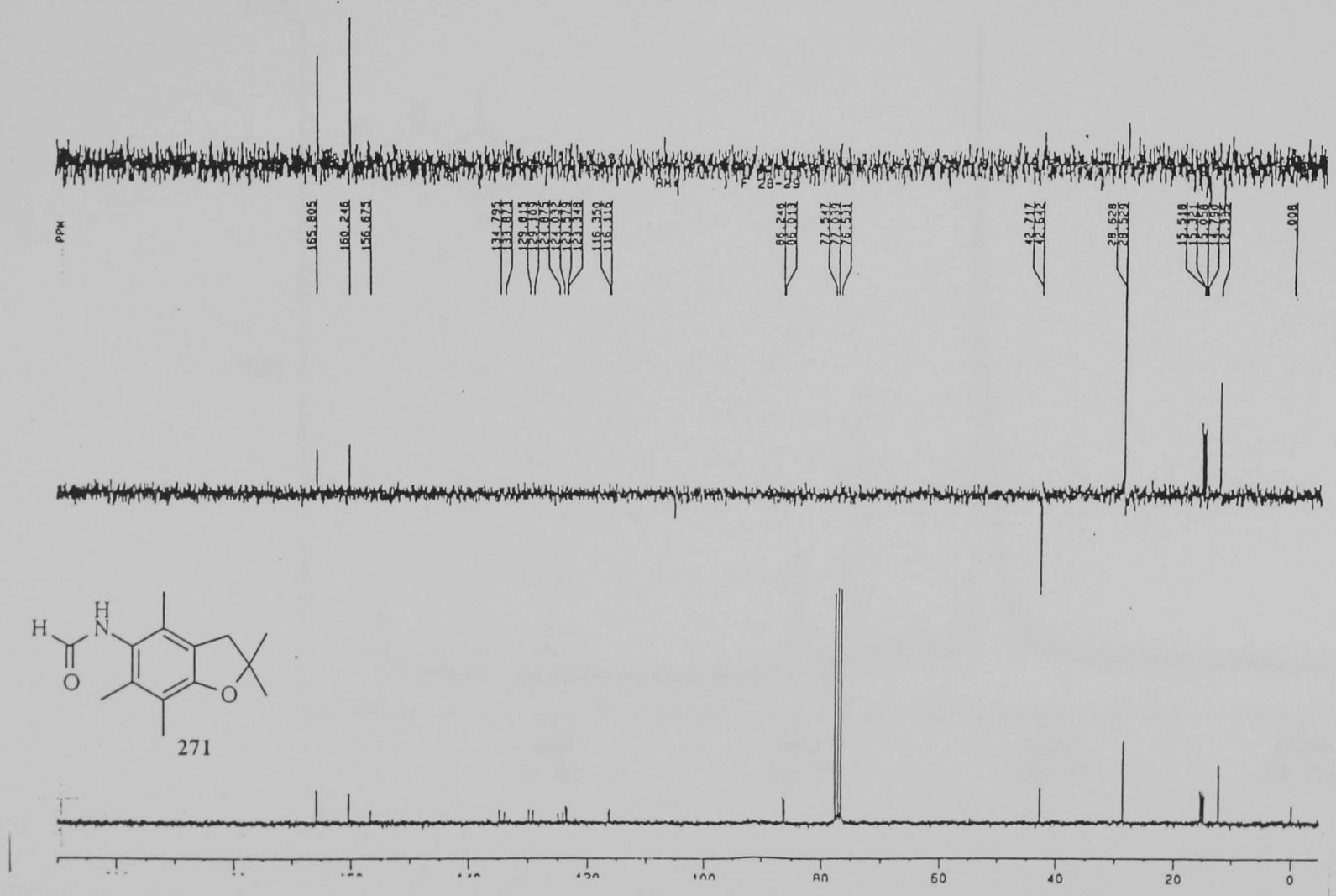
MY071S.154
AU PROG:
X02.AU
DATE 8-5-99

SOLVENT CDCl3
SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

FW 19600
O2 4105.000
DP 18H DO

LB 1.000
GB .100
CX 35.00
CY 18.00
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4044.96



MY071S.154
AU PROG:
X02.AU
DATE 8-5-99

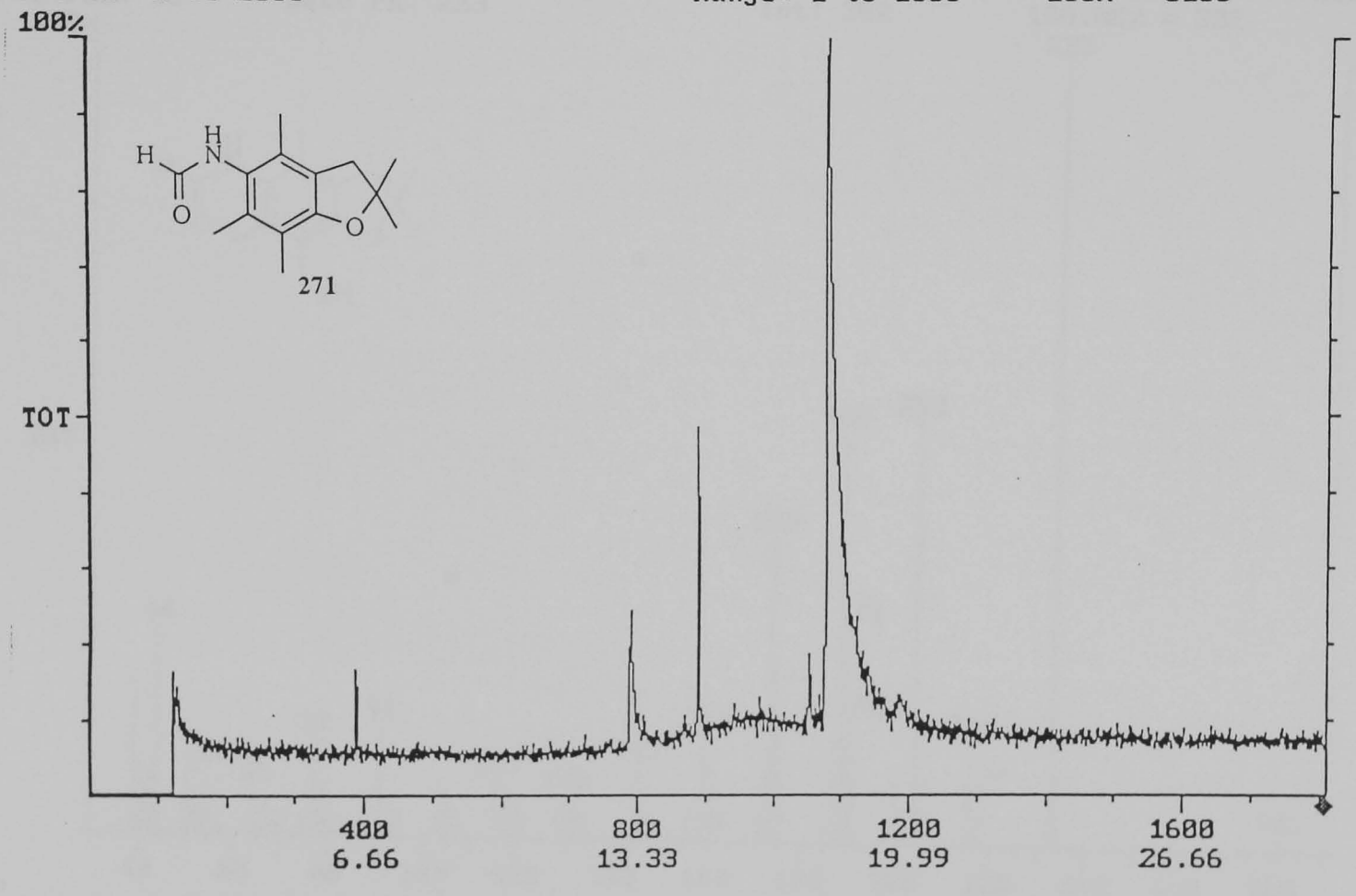
SOLVENT CDC13
SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

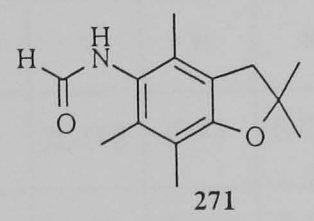
FW 19600
O2 4105.000
DP 18H DO

LB 1.000
GB .100
CX 35.00
CY 6.50
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4044.96

Chromatogram Plot C:\SATURN\DATA\RM28 Date: 01/26/99 14:03:30
Comment: RM156(3)-FRACTION 28-29
Scan: 1 Seg: 1 Group: 0 Retention: 0.01 RIC: 0 Masses: 0-0
Plotted: 1 to 2500 Range: 1 to 1806 100% = 3153



Spectrum Plot C:\SATURN\DATA\RM28 Date: 01/26/99 14:03:30
Comment: RM156(3)-FRACTION 28-29
Scan: 1080 Seg: -- Group: -- Retention: 17.99 RIC: 3153 Masses: 39-281
Pks: 95 Base Pk: 233 Int: 382 100.00% = 382
100%



271

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Email: MedacLtd@aol.com

ANALYTICAL REPORT

Date 3/1/00

Name R. Tahmood

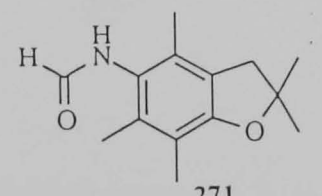
Sample ID RM 158 (3)

Formula $C_{14}H_{19}NO_2$

ELEMENT	C	H	N	S	Cl	Br	I		
% Theory	72.07	8.21	6.00						
% Found 1	72.29	8.45	5.22						
% Found 2	72.41	8.43	5.23						

Comments .....

Assay No 67668 Analyst .....



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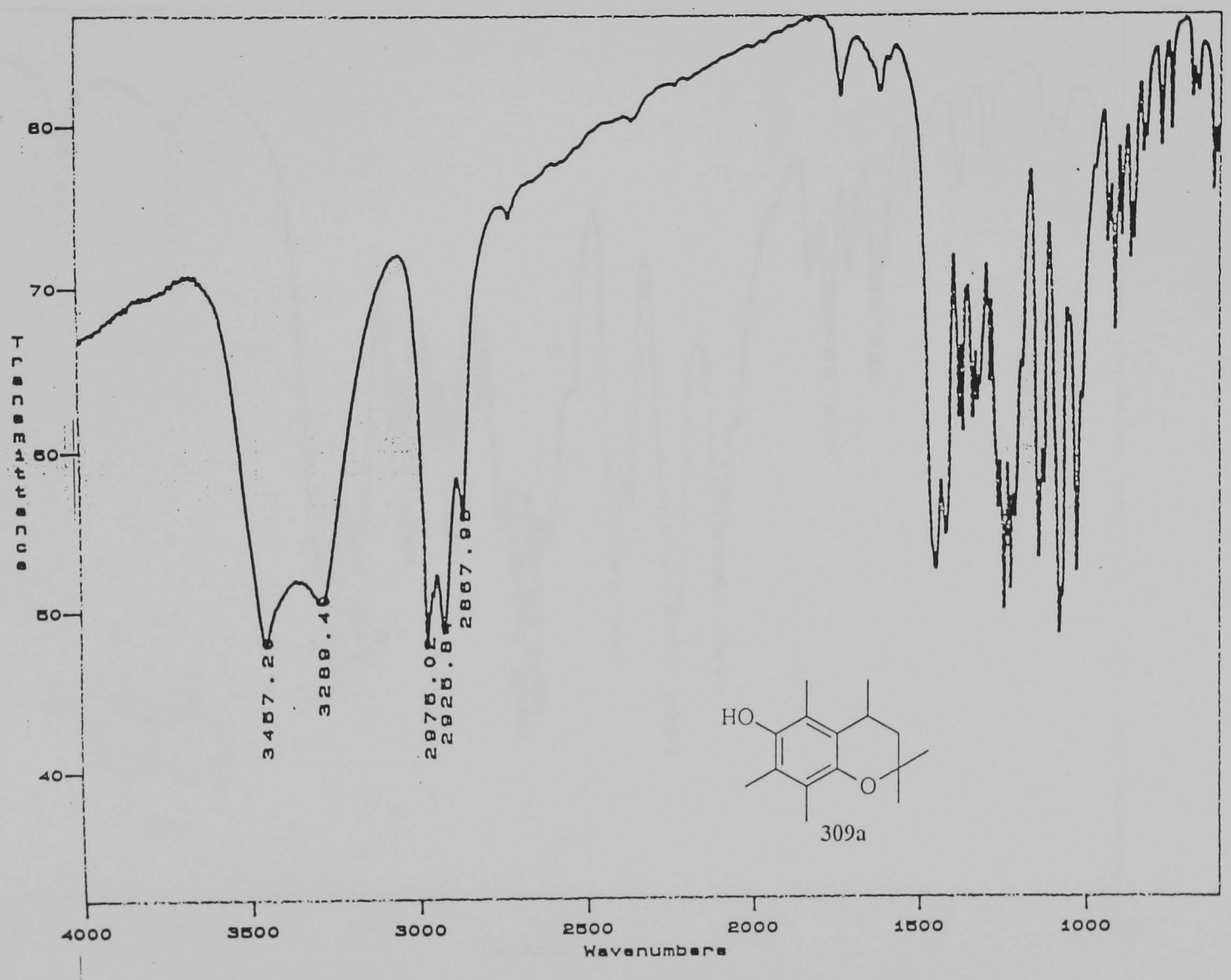
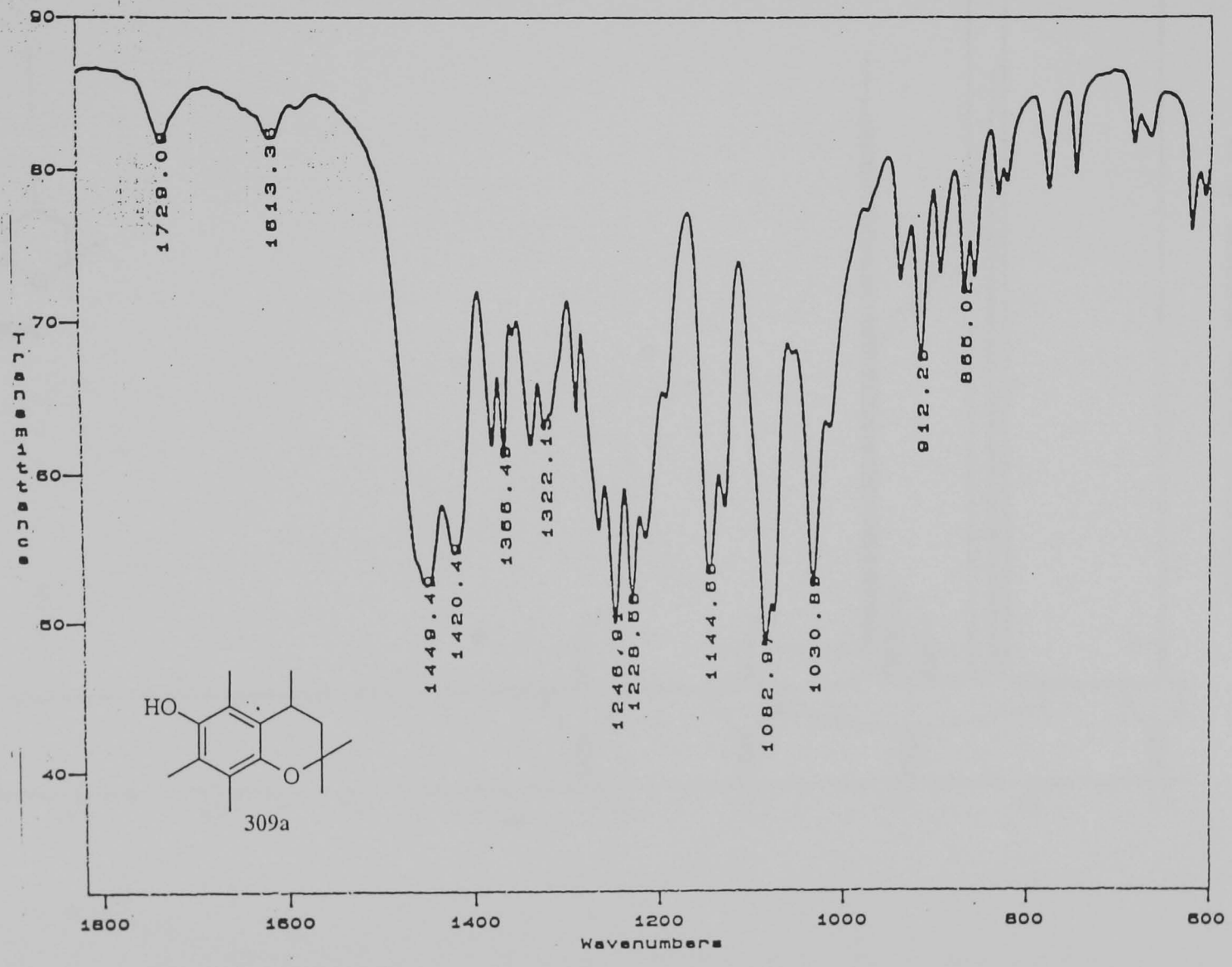

80
70
60
50
40
Transmittance
3457.26
3289.46
2975.05
2928.85
2867.95
4000
3500
3000
2500
2000
1500
1000
Wavenumbers
HO
O

309a


90
80
70
60
50
40
1728.0
1613.3
1448.4
1420.4
1366.4
1322.1
1246.9
1228.6
1144.6
1082.9
1030.8
912.2
865.0
HO
O
1800
1600
1400
1200
1000
800
600
Wavenumbers

309a

309a

BRUKER

```
JN250S.110
AU PROG:
 X00.AU
DATE 25-6-96
TIME 9: 43

SOLVENT CDCl3
SF     250.133
SY 100.0
O1    4358.000
SI   32768
TD   32768
SW    5000.000
HZ/PT    .305

PW       0.0
RD       0.0
AQ       3.277
RG         4
NS        96
TE       297

O2       0.0
DP   63L PO

LB        .200
CX      35.00
CY      18.00
F1       9.80:P
F2       -.:99P
HZ/CM   71.463
PPM/CM    .286
SR    2863.86
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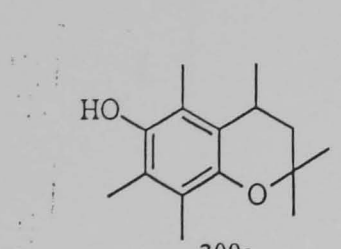
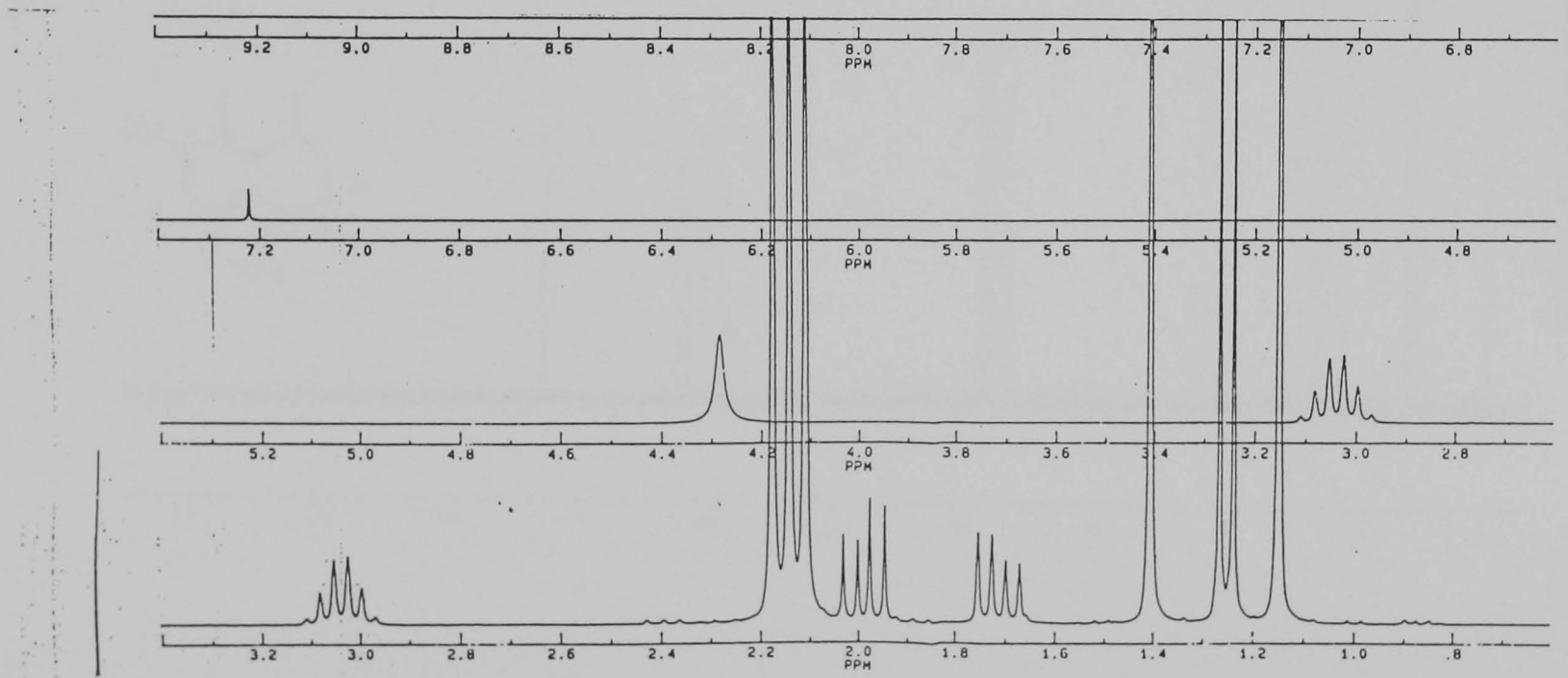
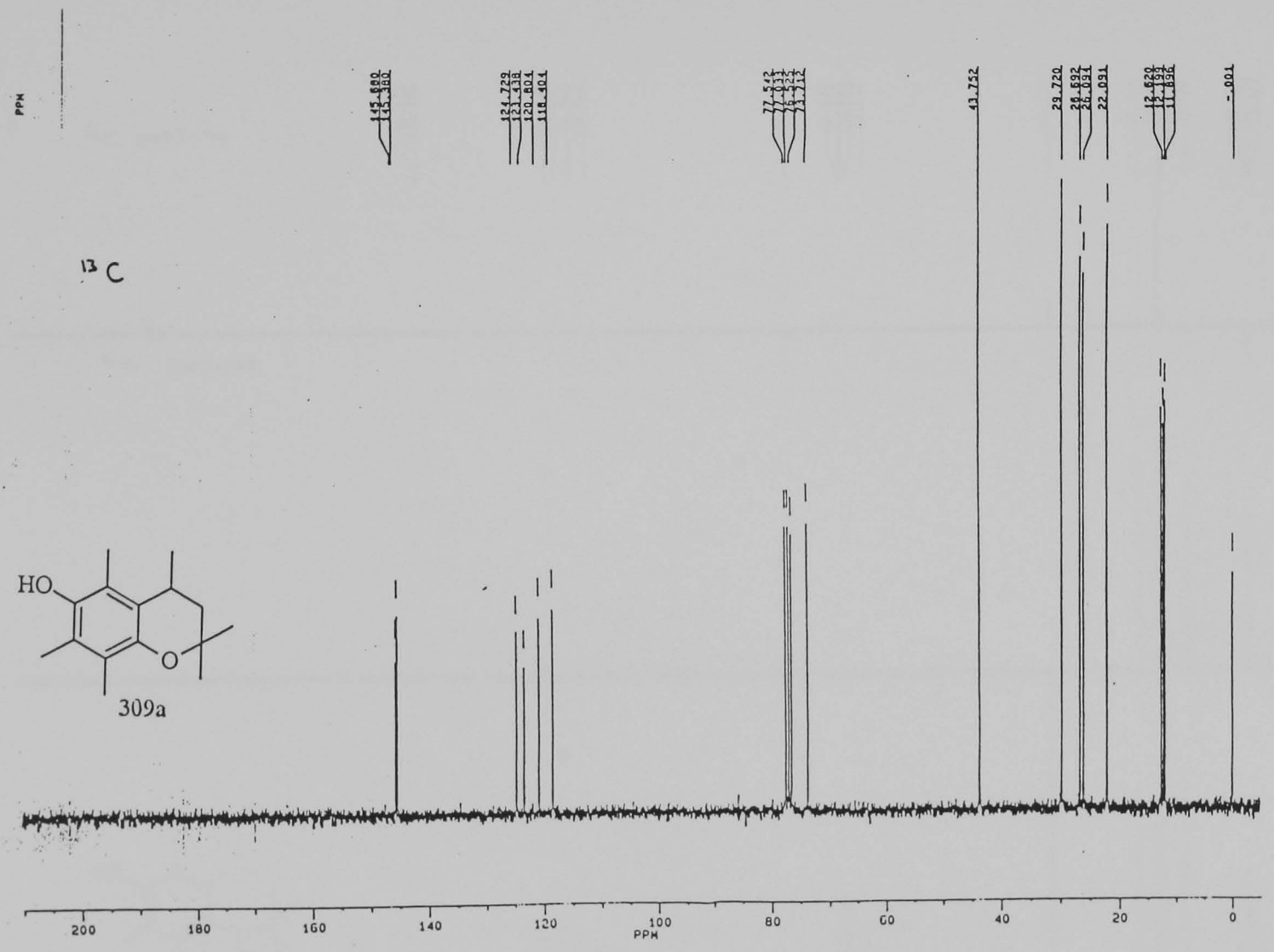

HO
O

309a

F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4043.05
200
180
160
140
120
100
PPM
80
60
40
20
0


9.2
9.0
8.8
8.6
8.4
8.2
8.0
PPM
7.8
7.6
7.4
7.2
7.0
6.8
7.2
7.0
6.8
6.6
6.4
6.2
6.0
PPM
5.8
5.6
5.4
5.2
5.0
4.8
5.2
5.0
4.8
4.6
4.4
4.2
4.0
PPM
3.8
3.6
3.4
3.2
3.0
2.8
3.2
3.0
2.8
2.6
2.4
2.2
2.0
PPM
1.8
1.6
1.4
1.2
1.0
.8



BRUKER

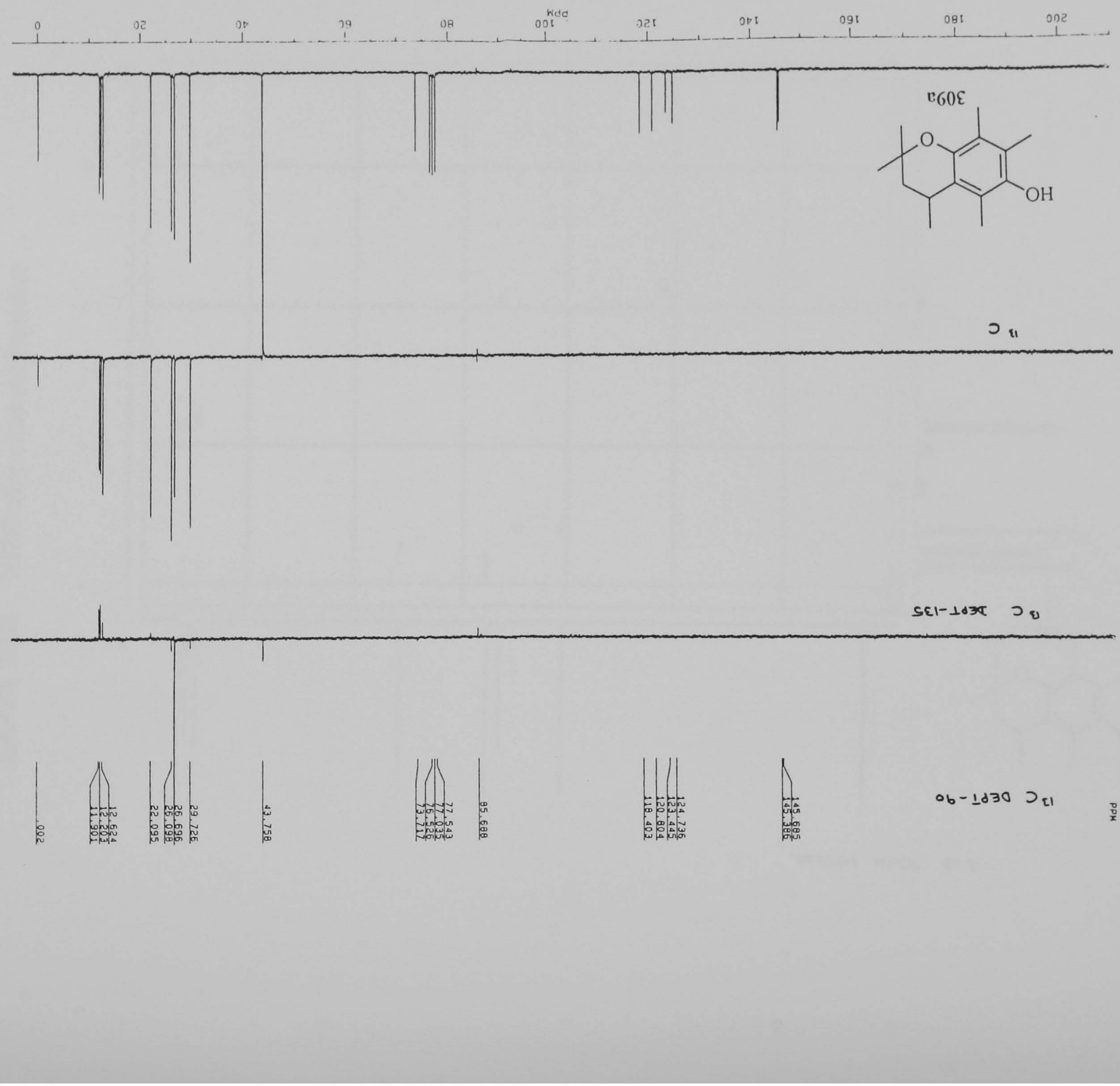
JN261S.140
AU PROG:
X02.AU
DATE 27-6-96
TIME 11:49

SOLVENT CDCl3
SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

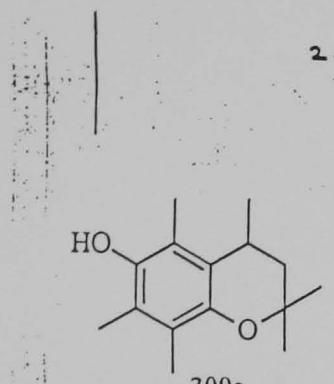
PW 0.0
RD 0.0
AQ 2.097
RG 800
NS 500
TE 297

O2 4105.000
DP 18L D0

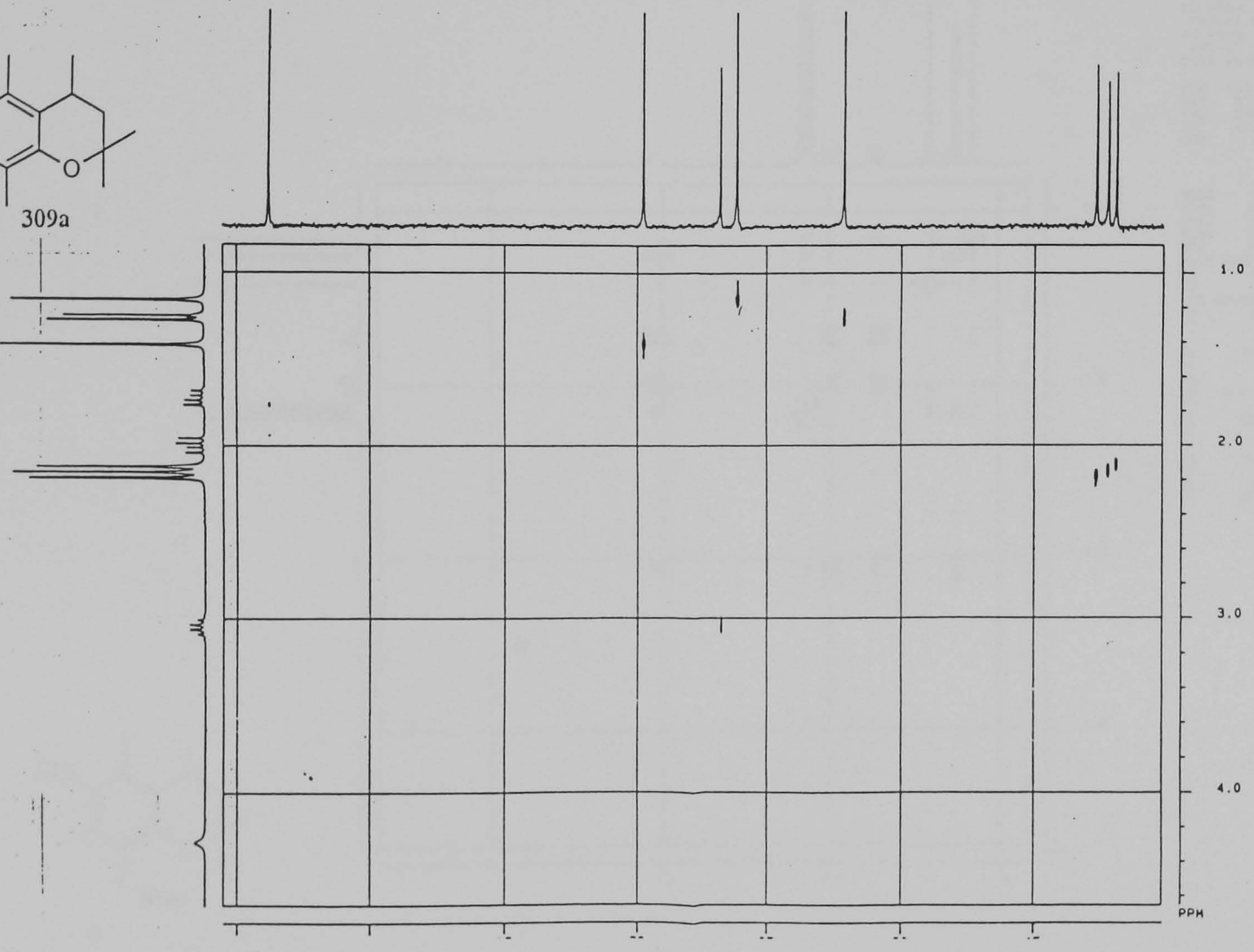
LB 1.000
CX 35.00
CY 18.00
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4042.57


309a
OH
O
13 C
13C DEPT-90
13C DEPT-135
PPM
0
20
40
60
80
100
120
140
160
180
200
145.685
145.380
124.736
123.445
120.804
118.403
95.688
77.643
77.032
76.526
73.717
43.758
39.726
26.696
26.098
22.095
12.624
12.203
11.901
.002
SOLVENT CDCl3
SF 62.896
SY 62.0
01 2435.262
SI 65536
TO 65536
SW 15625.000
HZ/PT .477
PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297
D2 4105.000
DP 18L 00
LB 1.000
CX 35.00
CY 6.50
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4043.05
BRUKER
UN251S.110
AU PR06:
X02.AU
DATE 25-6-96
TIME 10:40

2-D ^{13}C-^{1}H HETCOR



309a

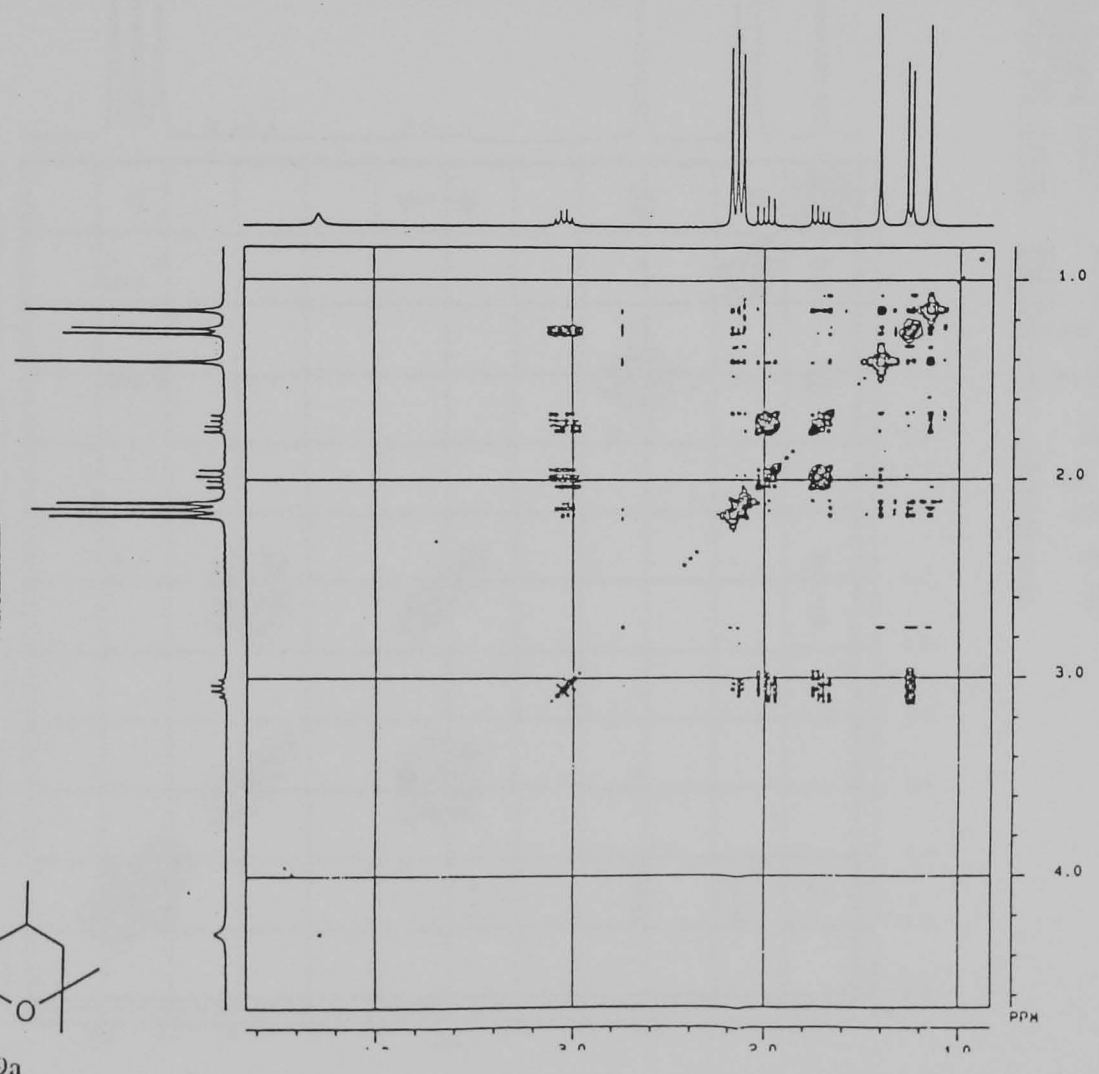


BRUKER

JN258110.SMX
F1 PROJ:
PROJH1.001
F2 PROJ:
PROJX.001
AU PROG:
Z28.AU
DATE 25-6-96

SI2	2048
SI1	512
SW2	2222.222
SW1	477.099
NDO	2
WDW2	0
WDW1	0
SSB2	4
SSB1	4
MC2	M
PLIM ROW:	
F1	45.497P
F2	10.165P
AND COLUMN:	
F1	4.649P
F2	.835P
D1	.6120000
S3	0H
P1	9.50
D0	.0000030
P6	10.60
D2	.0037000
P5	5.30
D4	.0018500
S2	18H
RGA	
RD	0.0
PW	0.0
DE	283.80
NS	32
DS	2
P9	85.00
NE	128
IN	.0005240

2-D COSY-45



BRUKER

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JN255110.SMX
F1 PROJ:
 PROJH1.001
F2 PROJ:
 PROJH1.001
AU PROG:
 Z27.AU
DATE 25-6-96

SI2   1024
SI1    512
SW2   956.023
SW1   478.469
ND0      1

WDW2     S
WDW1     S
SSB2     0
SSB1     0
MC2      M
PLIM ROW:
F1       4.654P
F2        .832P
AND COLUMN:
F1       4.658P
F2        .832P

D1     .6690000
P1        9.20
AGA
RD    0.0
PW        0.0
DE      656.00
NS           8
DS           2
D0     .0000030
P3        4.60
NE         128
IN     .0010450
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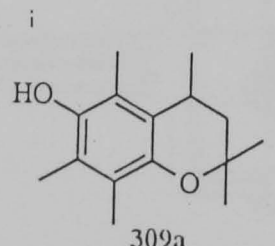
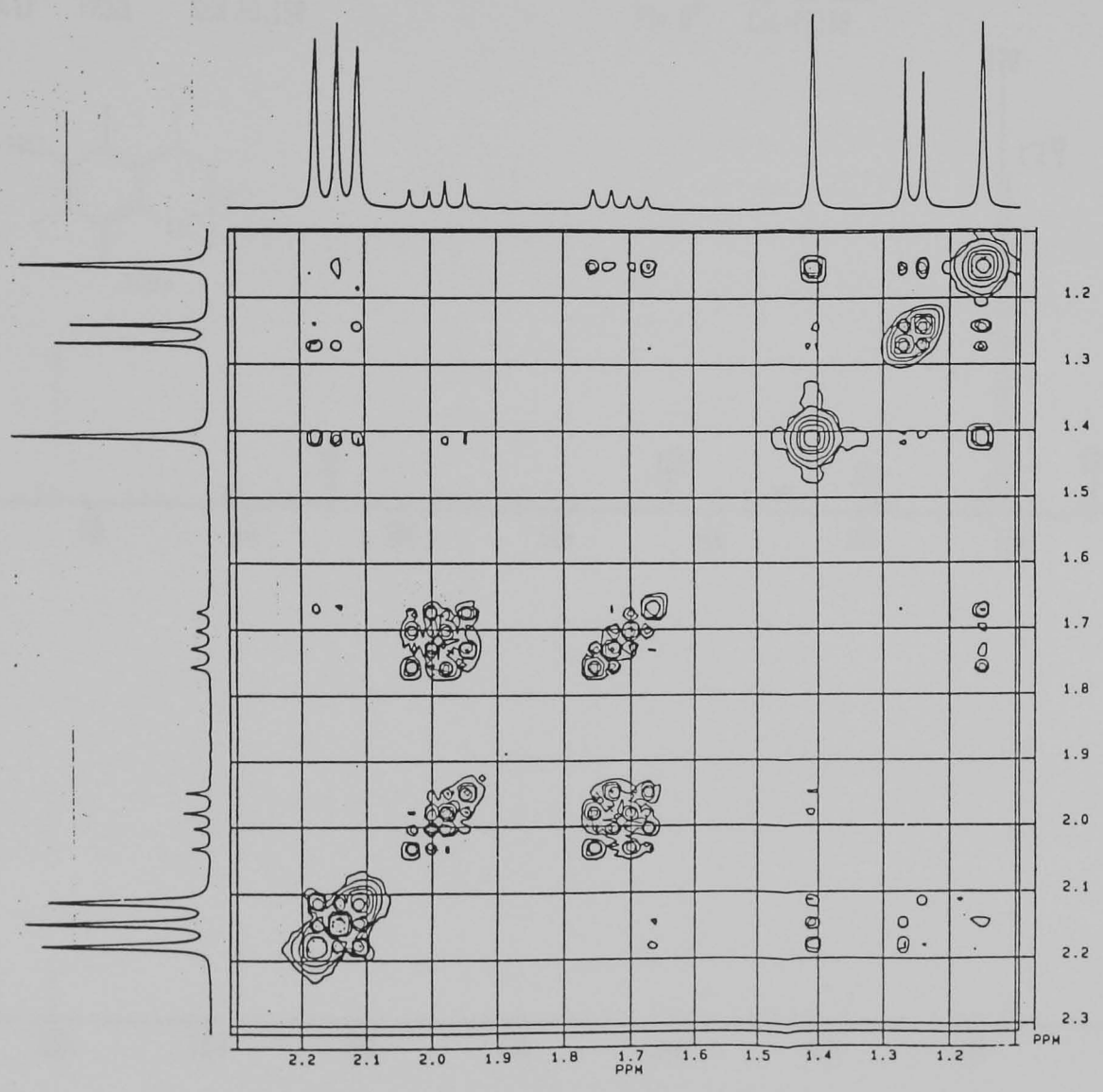


309a

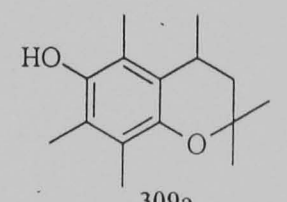
EXPANSION 2-D COSY-45



BRUKER

JN255110.SMX
F1 PROJ:
PROJH1.001
F2 PROJ:
PROJH1.001
AU PROG:
Z27.AU
DATE 25-6-96

SI2	1024
SI1	512
SW2	956.023
SW1	478.469
NDO	1
WDW2	S
WDW1	S
SSB2	0
SSB1	0
MC2	M
PLIM ROW:	
F1	2.310P
F2	1.094P
AND COLUMN:	
F1	2.312P
F2	1.094P
D1	.6690000
P1	9.20
RGA	
RD	0.0
PW	0.0
DE	656.00
NS	8
DS	2
DO	.0000030
P3	4.60
NE	128
IN	.0010450



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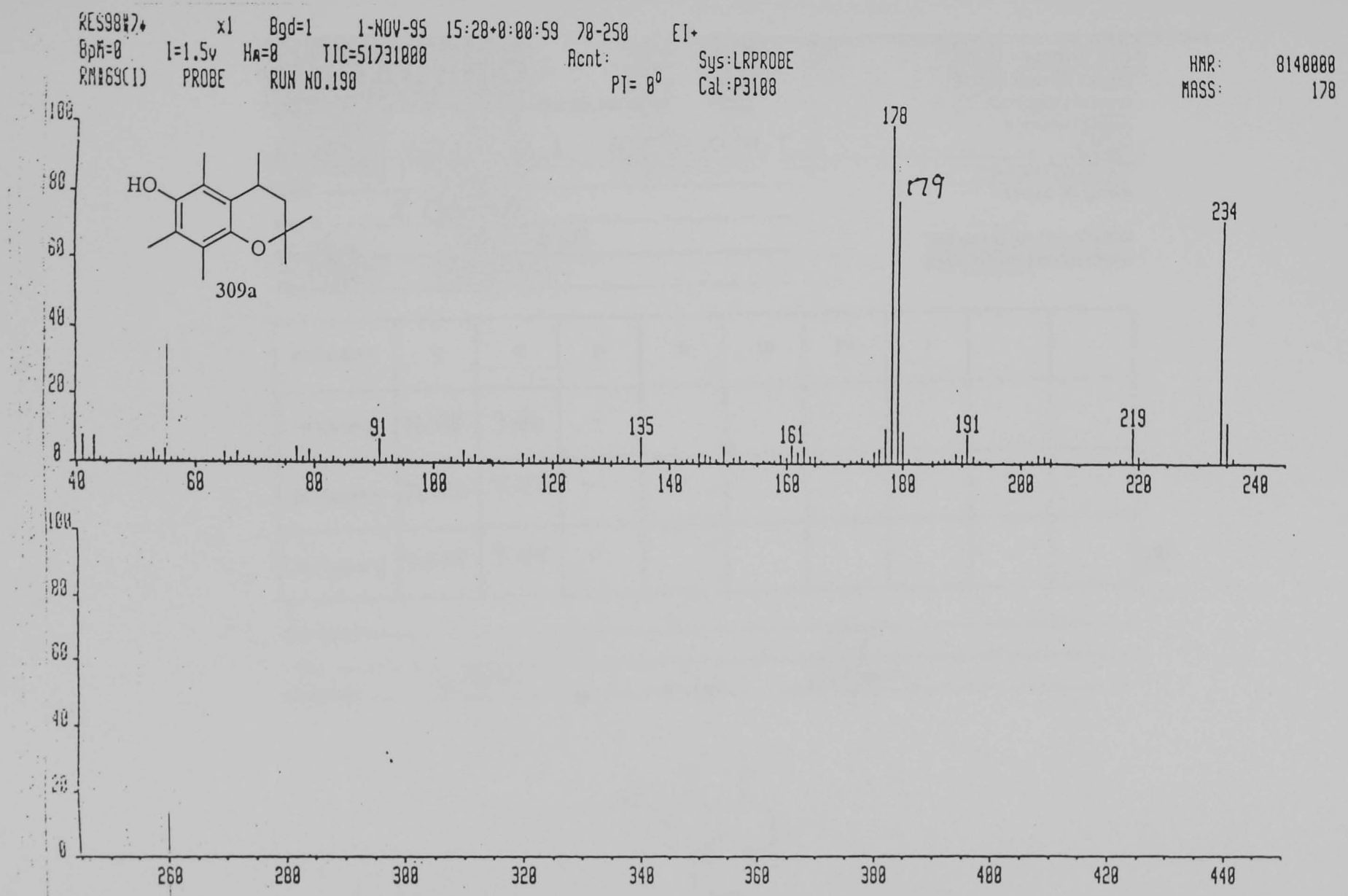
RES98#7◆ x1 Bgd=1 1-NOV-95 15:28+0:00:59 70-250 EI+
BpM=0 I=1.5v HA=0 TIC=51731000 Acnt: Sys:LRPROBE
RM169(1) PROBE RUN NO.190 PT= 0° Cal:P3108
HMR: 8140000
MASS: 178
HO
O
309a
178
179
234
91
135
161
191
219
100
80
60
40
20
0
40
60
80
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440

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ANALYTICAL REPORT

Date 31.1.00

Name R. Tahmood

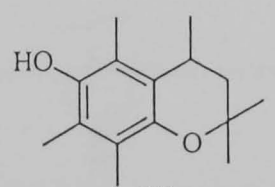
Sample ID RH #69

Formula $C_{13}H_{22}O_2$

ELEMENT	C	H	N	S	Cl	Br	I		
% Theory	76·88	9·46	-						
% Found 1	76·26	9·47	-						
% Found 2	76·15	9·44	-						

Comments .....

Assay No 67671 Analyst .....



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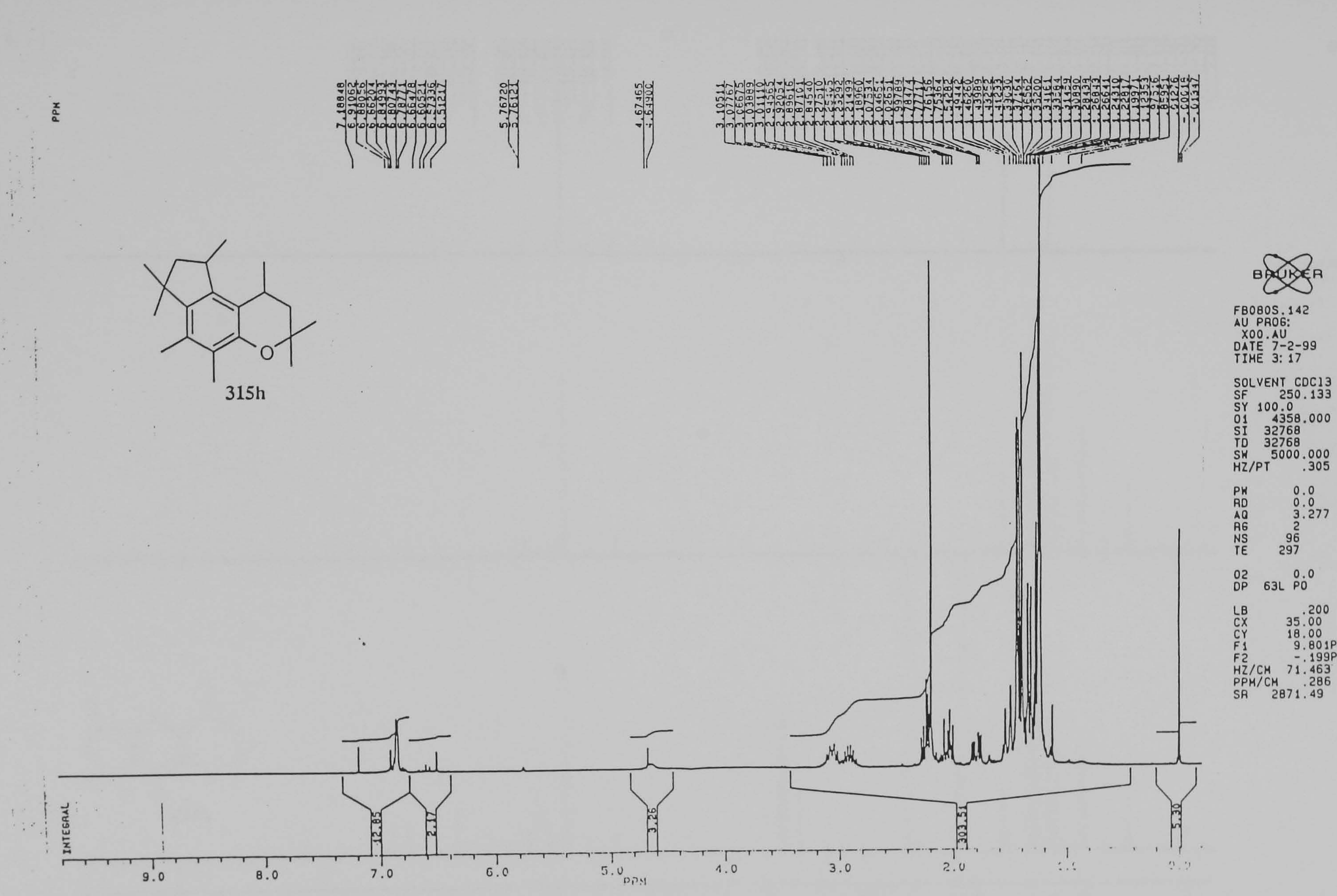
315h
BRUKER
FB080S.142
AU PROG:
X00.AU
DATE 7-2-99
TIME 3:17
SOLVENT CDCl3
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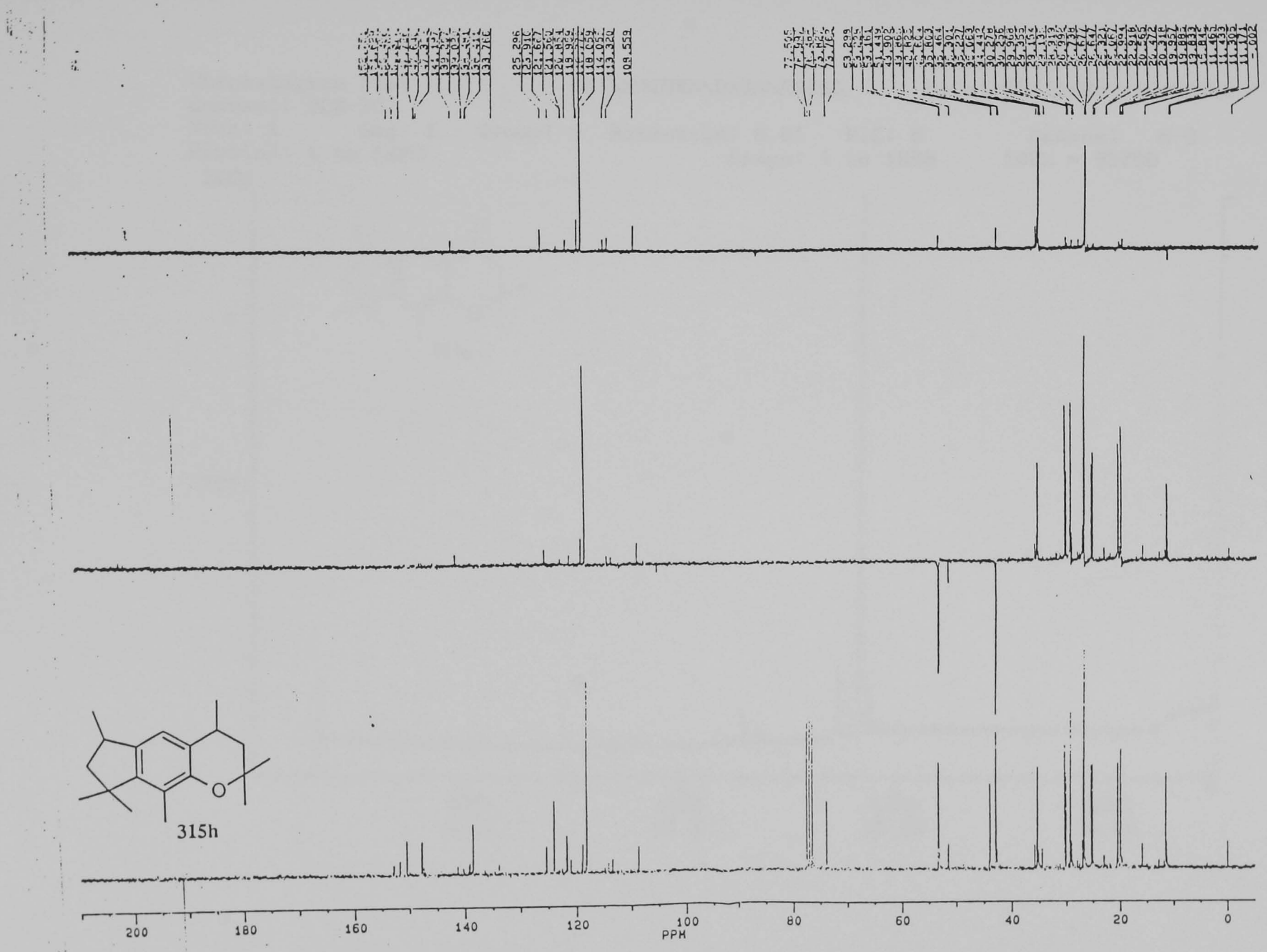
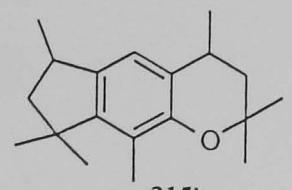
SY 100.0
O1 4358.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305
PW 0.0
RD 0.0
AQ 3.277
RG 2
NS 96
TE 297
O2 0.0
DP 63L PO
LB .200
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 2871.49
INTEGRAL
12.85
2.17
3.26
303.51
5.30
9.0
8.0
7.0
6.0
5.0
PPM
4.0
3.0
2.0

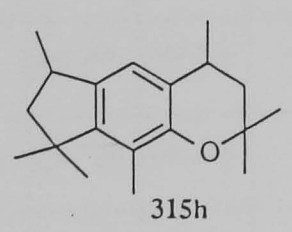

315h
200
180
160
140
120
100
80
60
40
20
0
PPM

Chromatogram Plot C:\SATURN\DATA\RAZ86 Date: 05/11/99 10:50:00
Comment: DCB-2C
Scan: 1 Seg: 1 Group: 0 Retention: 0.01 RIC: 0 Masses: 0-0
Plotted: 1 to 1800 Range: 1 to 1800 100% = 93798



315h

Spectrum Plot C:\SATURN\DATA\RAZ86 Date: 05/11/99 10:50:00
Comment: DC3-2C
Scan: 1134 Seg: 1 Group: 0 Retention: 18.89 RIC: 93798 Masses: 37-450
Pks: 230 Base Pk: 257 Int: 12556 100.00% = 12556



315h

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United Kingdom

Tel/Fax No. 01784 434299
Email: MedacLtd@aol.com

A N A L Y T I C A L R E P O R T

Date 31 Mar 00

Name R. Yahmood

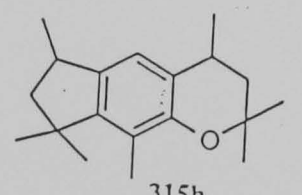
Sample ID DC-21c

Formula $C_{19}H_{28}O$

ELEMENT	C	H	N	S	Cl	Br	I		
% Theory	83.77	10.36	-						
% Found 1	82.98	10.34	-						
% Found 2	82.85	10.32	-						

Comments .....

Assay No 67669 Analyst .....



315h