THE CARBAMATE GROUP: MIGRATIONAL AND LEAVING PROPERTIES : TOWARDS THE SYNTHESIS OF FLAVENES

by

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Pietermaritzburg
January 1996.

DEDICATED TO ARTHI

DECLARATION

I hereby certify that this research is a result of my own investigation which has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed : ....

S. Mahabir

I hereby certify that this statement is correct.

Signed : ....

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CONTENTS.

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ABBREVIATIONS

aq	aqueous
Ar	aryl
b.p	boiling point
br	broard
BuLi	butyllithium
°C	degrees Celsius
COSY	correlation spectroscopy
d	doublet
DABCO	1,4-diazobycyclo-[2,2,2]-octane
E^+	Electrophile
EI	electron impact
Et	ethyl
ether	diethyl ether
GC/MS	gas chromatography/mass spectroscopy
Δ	Heat
HETCOR	heteronuclear chemical shift correlation
hep	heptet
iPr	isopropyl
LDA	lithium diisopropylamine
MHz	megahertz
M^+	molecular ion
m	multiplet
Me	methyl
ml	millilitre/s
m.p.	melting point
min	minute
NaH	sodium hydride
NMR	nuclear magnetic resonance spectroscopy
Nu	nucleophile

PG	protecting group
Ph	phenyl
p.n.d.	proton noise decoupled
q	quartet
rt	room temperature
s	singlet
t	triplet
THF	tetrahyhrofuran
TLC	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine

SUMMARY

The carbamate functionality has been primarily associated with a major class of insecticides, *e.g.*, Baygon and Carbofuran. However, in recent years, the carbamate group has enjoyed much success as an intermediate in organic synthesis. Its migratory and leaving group capability has enabled the development of synthetic procedure for the synthesis of natural products intermediates[35].

The research herein, describes three main properties of the carbamate group and their utilisation in the synthesis of a flavonoid derivative, flav-3-ene (i).
These properties of the carbamate are:

1) The migrational capability of the amide portion of the carbamate from vinylic to allylic alcohols.

2) The leaving group capability of the carbamate.

3) The carbamate as a directing metalation group in directed *ortho-*metalation reactions.

A fairly simple, good-yielding and short procedure, utilising the migratory and leaving group capability of the carbamate, for the synthesis of flav-3-ene (i), is reported herein. A low-yielding one-pot synthesis for the flav-3-ene (i), utilising the carbamate as a directing metaltion group is also reported.

In an attempt to synthesize naturally-occurring flavan-3-ols, tetramethoxy-substituted flav-3-ene (ii) was synthesised using the migrational and leaving-group capability of the carbamate.

Attempts to form flavan-3-ol (iii) from flav-3-ene (i) led to the isolation of the flavan-3,4-diol (iv) and flavone (v) which are also important intermediates in the synthesis of natural products.

(i)

(ii)

(iii)

(iv)

(v)
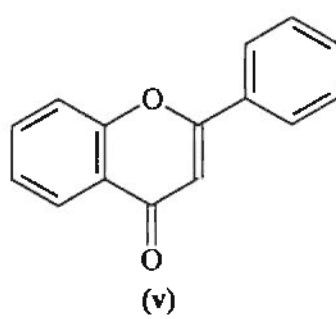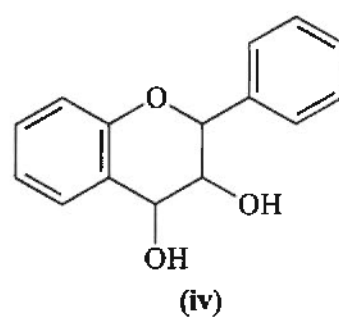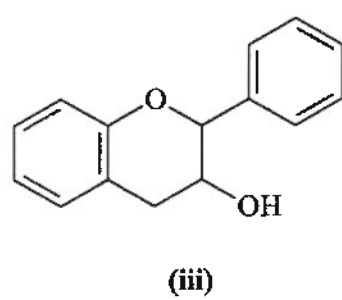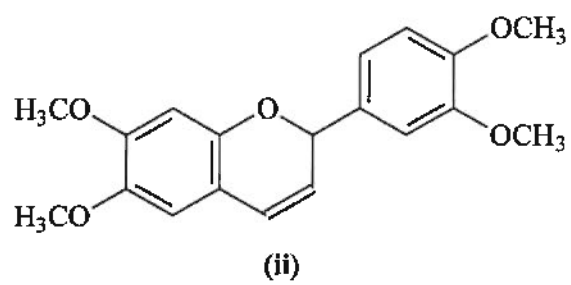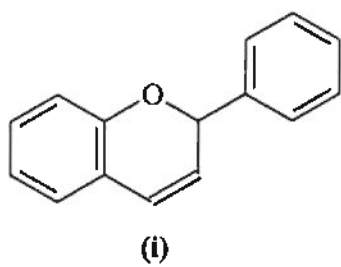
CHAPTER 1 : INTRODUCTION

PART A

1.0   THE CARBAMATE MOIETY

The aim of this project was to investigate the reactivity of the carbamate functionality (1), in particular its migrational ability from vinylic to allylic alcohol's, as well as its leaving-group ability.
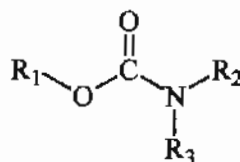
(1)

As part of the ongoing research in this department, the carbamate functionality has been widely studied and exploited as a useful intermediate in organic synthesis. Our intention was to exploit the leaving and migrational ability of the carbamate group in the synthesis of natural products such as flavonoids.

1.1   Nomenclature

Carbamic acid, NH_2COOH, an unstable compound which in acid solution decomposes to form carbon dioxide and ammonia[1], forms the basis for the systematic naming of carbamates. Esters of carbamic acid are then referred to as carbamates. Substituents bonded to the nitrogen atom are termed N-alkyl N-aryl or N,N-dialkyl or N,N-diaryl, while those attached to the oxygen are referred to by their usual IUPAC names. Carbamate **(2)** would then be systematically named as 1-phenyl-N,N-diethyl carbamate.

(2)
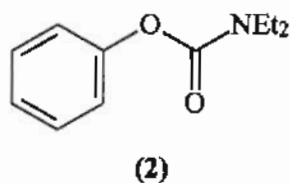
1.2   USES OF CARBAMATES.

1.2.1   AGRICULTURAL USES

In order to maximise agricultural crop production, the application of pesticides becomes very necessary. Carbamates have found extensive application in pest control as insecticides, herbicides nematocides and fungicides; both as *o*-carbamates and as thio- and dithio-carbamates.[2, 3, 4, 5, 6]

Other pesticides such as DDT and Dieldrin, although cheap and effective, are non-specific and have long-lasting damaging effects on the environment. These pesticides not only affect terrestrial flora and fauna, but also damage aquatic habitats when washed into rivers and streams by rain water. Carbamate pesticides on the other hand are more selective and do not remain active in the soil for extended periods of time, and hence are favoured over organochlorines.

Some of the most successful carbamate insecticides used today are carbaryl **(3)**, baygon **(4)**, carbofuran **(5)**, and propoxur **(6)**.
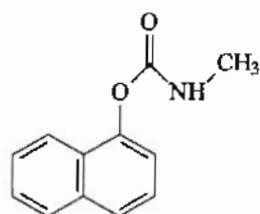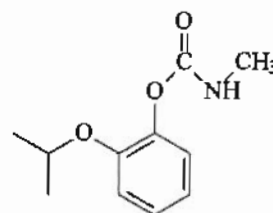
(3) (4)
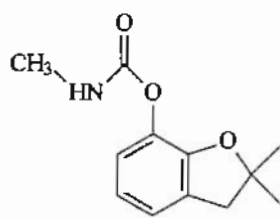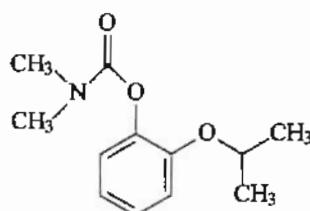
(5) (6)

The mode of action of these compounds appears to be as inhibitors of the insect enzyme acetylcholinesterease.

Transmission of nerve impulses of the synapses depends upon the successful and rapid equilibrium between acetylcholine and choline being maintained in the synapse. Subsequent to the transfer of the "nerve message" to the receptor in the post synapse membrane, the acetyl choline is hydrolysed to choline by acetylcholinesterase and so the equilibrium is maintained.

By inhibiting the action of acetylcholinesterase, the nervous system is impeded by the slow hydrolysis of the carbamoylated intermediate, causing an undesirable accumulation of acetylcholine in the synapse, and unless treated, results in the death of the affected organism.[7]

1.2.2   THE PHARMACOLOGY OF CARBAMATES.

The oldest known biologically-active carbamate physostigmine (7) was isolated from the calabar bean *Physostigma bebebosum* in 1864.[8]
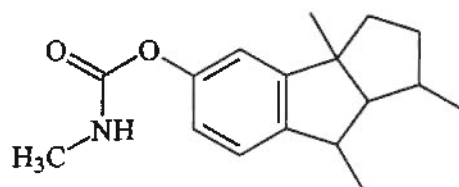
(7)

The application of physostigmine (7) dates back to the 17tb century, when West African tribes used it for capital punishment. The person found guilty, was forced to swallow the milky potion of the calabar bean seeds. The accused would then develop shakes, froth at the mouth and die.[9] Physostigmine has recently been found to be useful in the treatment of Alzheimer's disease.[10, 11, 12]

Mitomycin C (8), a highly toxic antitumor antibiotic extracted from *Streptomyces caespitoscus*, contains three recognised carcinostatic groups, an aziridine, a carbamate and a quinone. Mitomycin C is clinically administered for the treatment of carcinomas of the breast, lung, colon and stomach.[13]
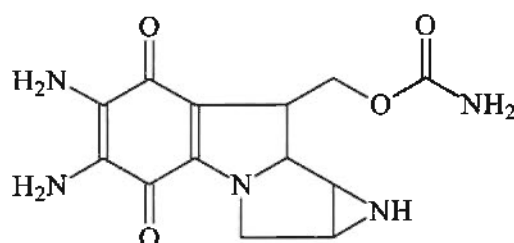
(8)

Carbamates are also being used as antiseptics,[14] local anaesthetics[15] and anti-leukaemia agents.[14]

1.2.3 INDUSTRIAL USES.

An important use of carbamates is as insulators (polyurethane based) in the refrigeration industry and they have been shown to be a better insulators than most polystyrenes.[16] An ethyl carbamate/formaldehyde mixture has been used in the textile industry to produce a crease-resistant fabric.[17] Carbamates have also been used in hair conditioners,[18] as plasticizers (softeners) for rubber,[19] and as fuel additives.[20]

1.3 SYNTHETIC ROUTES TO CARBAMATES

Many synthetic routes have been developed for carbamates, with few having commercial significance. This is mainly due to the use of the toxic phosgene (9). By virtue of the fact that phosgene is a gas at room temperature, makes handling and measuring difficult.

$$
\begin{array}{c}
O \\
\parallel \\
Cl - C - Cl
\end{array}
$$

(9)
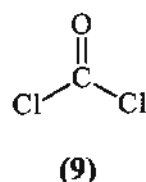
1.3.1 REACTION OF β-ALKOXYETHYL CHLOROCARBONATES WITH AQUEOUS AMMONIA (Scheme 1)

This method affords β-alkoxyethyl carbamates in average yields.[21] The β-alkoxyethyl chlorocarbonates (10) are obtained by the action of phosgene upon various β-alkoxyethanols. The β-alkoxyethanols are prepared by treating ethylene oxide with the desired alcohol in the presence of a small amount of sulphuric acid as a catalyst. The β-alkoxyethyl carbamates are prepared from the corresponding chlorocarbonates by treating them with aqueous ammonia.
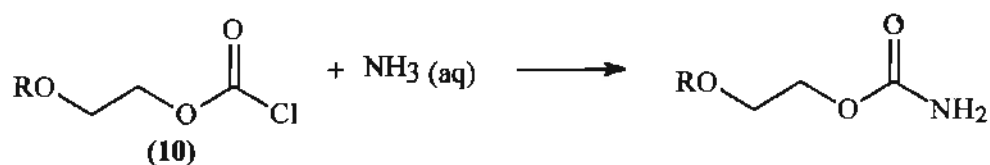
Scheme 1

The disadvantage of this reaction is the need to use highly toxic phosgene gas. Recently, two alternatives to phosgene have been introduced, namely, trichloromethyl carbonate ("diphosgene") **(11)** and Bis(trichloromethyl) carbonate ("triphosgene") **(12)**. Due to triphosgene being a non-toxic solid (mp 80°C), this reagent is safer, easier, more practical to handle and hence can be more accurately measured than gaseous phosgene. Both these reagents have proven to be suitable substitutes for phosgene.
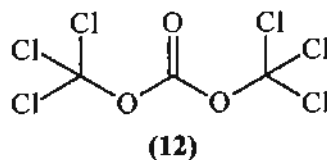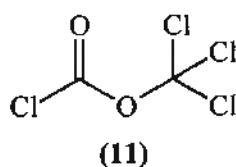
1.3.2   REACTIONS OF CARBAMOYL CHLORIDES WITH ALCOHOLS

N,N-disubstituted carbamates are prepared by the reaction of N,N-disubstituted carbamoyl chlorides with alcohols **(Scheme 2)**. Two possible mechanisms are possible for this reaction **(Scheme 2)**:

i) An addition-elimination, *i.e.*, a concerted displacement of the halide ion by the alkoxy nucleophile (path A) or

ii) unimolcular loss of the halide ion (path B).
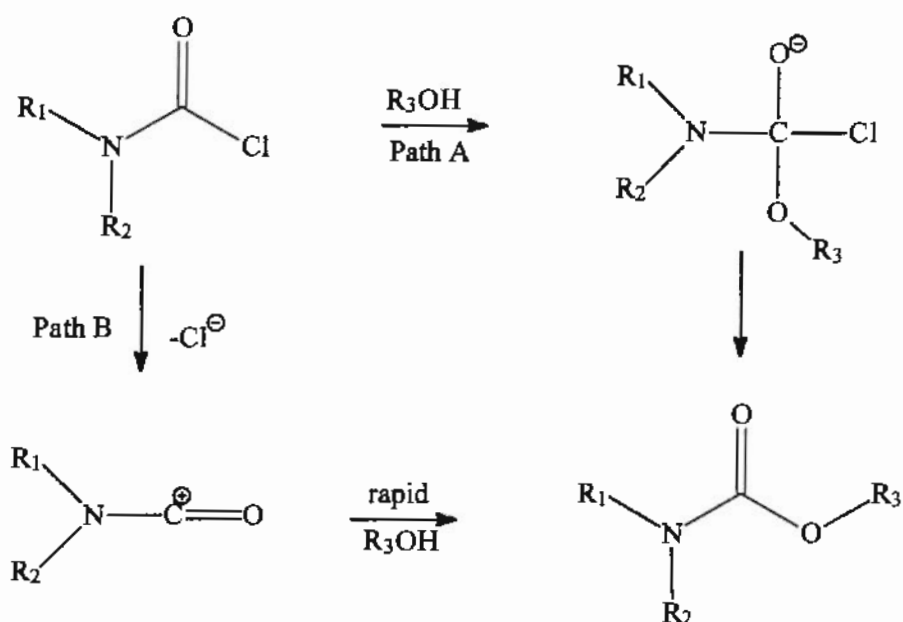
Scheme 2

This provides a good general method for the preparation of carbamates on a laboratory scale. The process is not industrially viable due to the use of phosgene gas in the preparation of the carbamoyl chlorides.[14]

1.3.3 REACTION OF ALCOHOLS WITH UREA.

Of all preparative methods in carbamate chemistry, the reaction of urea with alcohol is one of the most favoured routes to carbamates on a commercial scale. Ethyl carbamate was first prepared by Wohler in 1840 from urea and ethanol.[14] The general reaction involves heating the alcohol with urea under pressure **(Scheme 3)**.
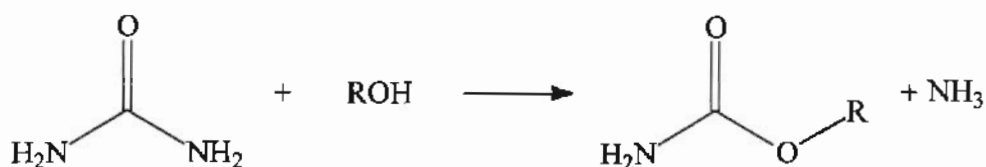
Scheme 3

In 1946 Paquin[14] reported the catalytic effect of various metal salts upon the rate of reaction of an alcohol with ureas. The use of these catalysts led to higher yields of the alkyl carbamates with much shorter heating cycles.

1.3.4   REACTION OF ISOCYANATES WITH ALCOHOLS.

All types of alcohols - primary, secondary, tertiary and polyhydric-react with isocyanates to give N-substituted carbamates[22] **(Scheme 4)**. The reaction is rapid and quantitative, being accelerated by the presence of a tertiary amine.[23]

$$R_1\!-\!N\!=\!C\!=\!O \;+\; R_2OH \longrightarrow$$
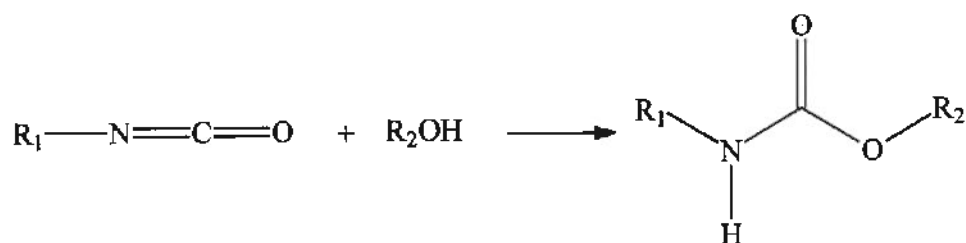
Scheme 4

1.3.5   THE HOFMANN REACTION

The reaction of amides, in particular long chain-alkyl amides and amides of α,β-unsaturates, *via* the Hofmann degradation, yield in a dry state, isocyanates which in alcoholic solution are converted to the corresponding carbamate[24] **(Scheme 5)**.

$$R_1 , R_2 = \text{alkyl} \quad ; \quad X = \text{halide}$$
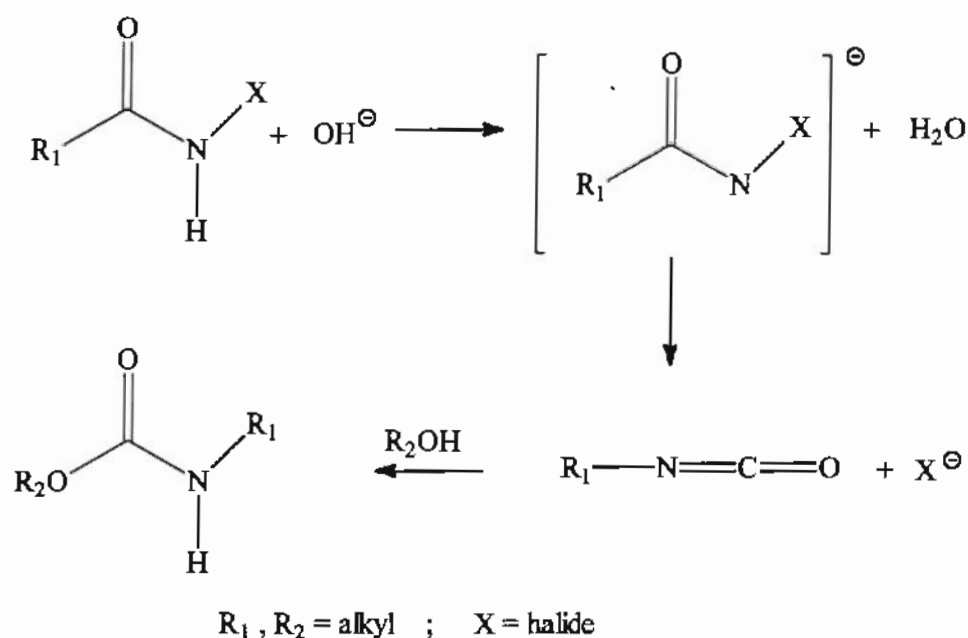
Scheme 5

1.3.6 REACTIONS OF AMINES WITH CARBONATES

Interest has been shown in acetylenic carbinols as central nervous system depressants.[25] Many simple methods, however, for preparing carbamates from carbinols fail, owing mainly to the ease of dehydration. Highly unsaturated carbinols lead to additional complications, hence it is not surprising that many methods have been carried out unsuccessfully. This problem is overcome by forming the carbamate *via* the phenyl carbonate of the carbinol.[26]

Treatment of methyl vinyl ethynyl carbinol (13) with pyridine and phenylchloroformate results in the carbonate. Reaction of the carbonate with liquid ammonia result in the carbamate in good yields (Scheme 6).
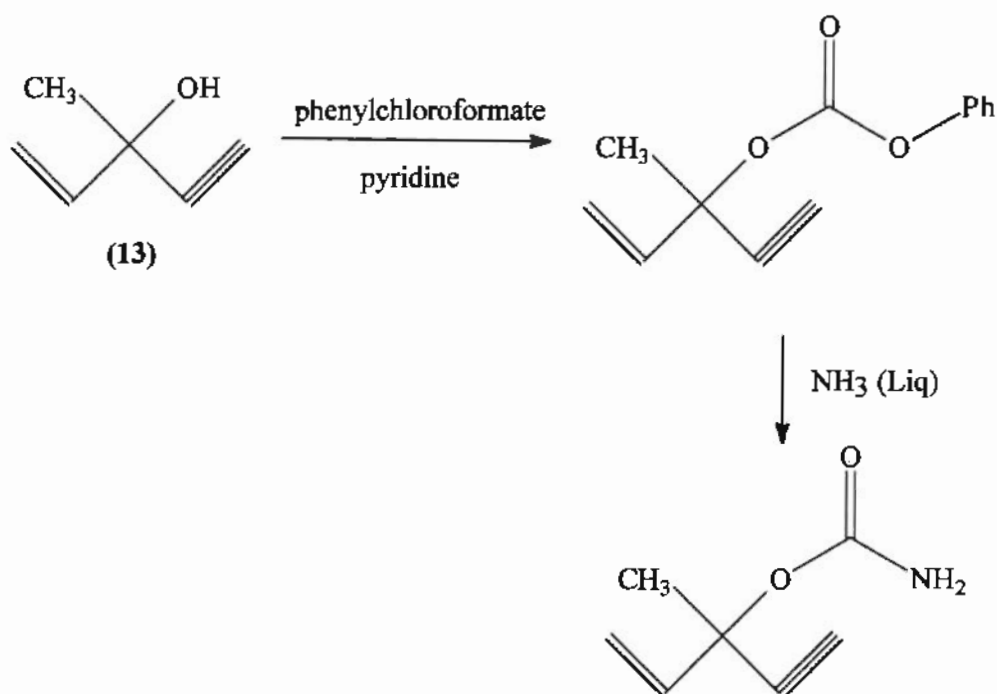
Scheme 6

In recent years considerable interest has been shown in the development of milder and more reactive alkoxy - carbonylation reagents. Among these are di-(2-pyridyl)-carbonate (14)[27] and N,N-disuccinimidyl carbonate (15).[28]
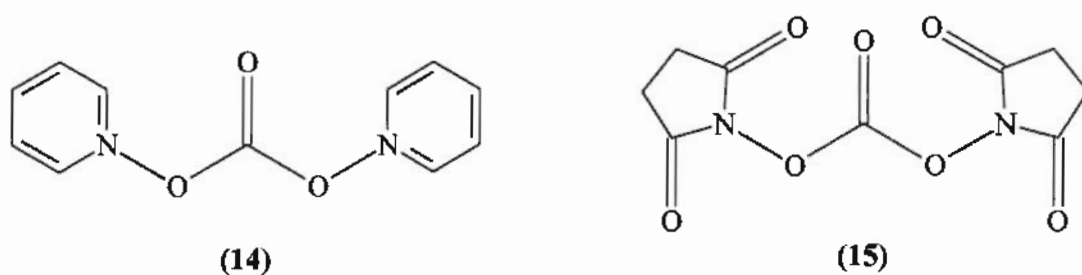
Both these reagents have been used in the preparation of mixed carbonates under mild condition (0°C) which, when treated with amines, yield the corresponding carbamates. This reaction is particularly useful for carbamates of sterically-hindered amines and alcohols.

1.4 REACTIONS OF CARBAMATES

1.4.1 HYDROLYSIS OF CARBAMATES

1.4.1.1 Base catalysed Hydrolysis

Carbamates generally decompose rapidly under alkaline conditions. Alkaline hydrolysis of carbamates proceed *via* two different pathways depending on the nature of the carbamate group.

Unsubstituted, monosubstituted and disubstituted carbamates, derived from aliphatic alcohols are hydrolysed in alkaline solution to an amine, water and carbonate ions[14] **(Scheme 7)**.

(16)

$$(16) \longrightarrow R_1OH + R_2R_3NCOO^{\ominus}$$

$$R_2R_3NCOO^{\ominus} + H_2O \rightleftharpoons R_2R_3NCOOH + OH^{\ominus}$$

$$R_2R_3NCOOH \longrightarrow R_2R_3NH + CO_2$$

$$CO_2 + 2OH^{\ominus} \longrightarrow CO_3{}^{2\ominus} + H_2O$$
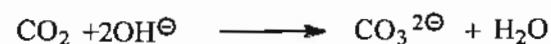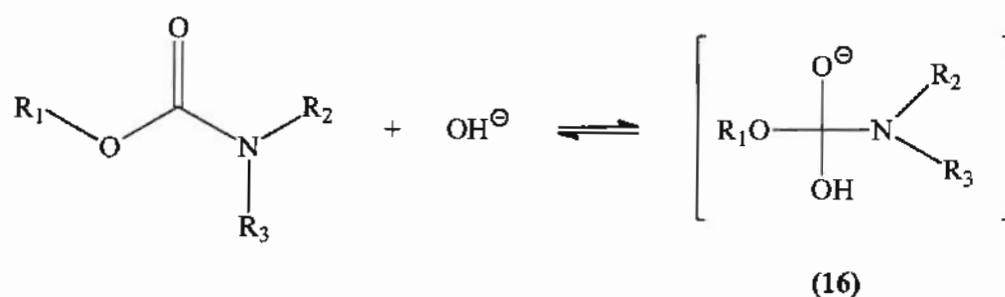
$$R_1 = \text{alkyl}$$
$$R_2, R_3 = \text{H, alkyl, aryl}$$

Scheme 7

The hydroxyl anion reacts with the ester carbonyl to yield an unstable tetrahedral intermediate (16), which decomposes to an alcohol and a carboxylate ion. The carboxylate anion readily picks up a proton from water and spontaneously decomposes into an amine and carbon dioxide.

Carbamates derived from phenol hydrolyse more rapidly than aliphatic carbamates and by a different mechanism. The ease of departure of the phenoxide ion is a driving force of this fast reaction (Scheme 8).

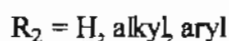$$R_2N=C=O + H_2O \longrightarrow R_2NHCOOH$$

$$R_2NHCOOH \longrightarrow R_2NH_2 + CO_2$$

$$CO_2 + 2OH^\ominus \longrightarrow CO_3{}^{2\ominus} + H_2O$$

$$R_2 = H, \text{ alkyl, aryl}$$
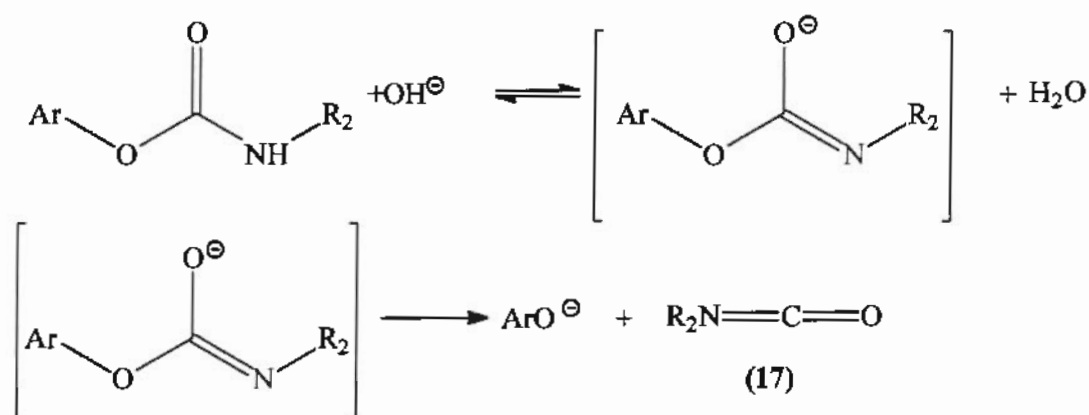
Scheme 8

This mechanism involves the removal of an N-proton by the hydroxide ion to produce an unstable intermediate which in turn forms an isocyanate (17) and a phenoxide ion. The isocyanate reacts instantaneously with water to give a carbamic acid derivative which decomposes to an amine and carbon dioxide.

However, N,N-disubstituted aromatic carbamates cannot form an isocyanate intermediate (17) and the carbamates hydrolyse rather slowly *via* the mechanism outlined in **Scheme 7** above.

1.4.1.2 Acid catalysed Hydrolysis

Treatment of carbamates with HCl or HBr in the presence of glacial acetic acid leads to the formation of CO_2, an ammonium halide and an alkyl halide[14] (**Scheme 9**).
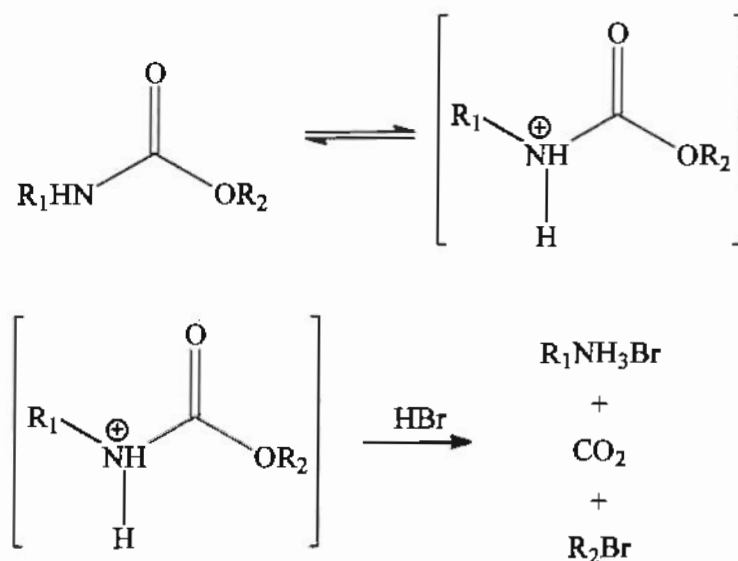
Scheme 9

The N-group of the carbamate is initially protonated and its alkoxy group then attacked by the halide ion.

Carbamates, however, are quite stable to acids under many other conditions, *e.g.*, anhydrous HCl or BF_3 do not decompose carbamates.

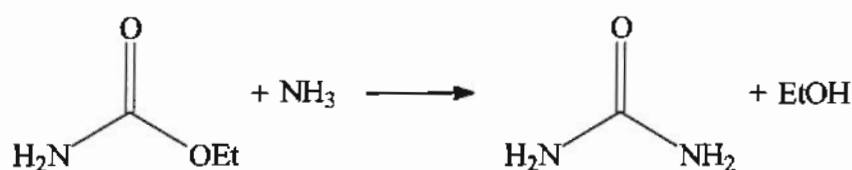## 1.4.2 REACTIONS AT THE ESTER GROUP

The reaction of nucleophiles with carbamates is quite similar to that of ordinary esters. The reaction involves the nucleophilic displacement of the alkoxy or aryloxy group from the carbamate. Werner[29] has demonstrated the formation of urea from the heating, at 150°C, of ethyl carbamate with ammonia **(Scheme 10)**.

Scheme 10

N,N-dialkylureas are formed by heating N-alkyl carbamates with the corresponding amine, *e.g.*, diphenylurea was formed when aniline and ethyl carbamate were heated together **(Scheme 11)**.

Scheme 11

An example of a reaction of an amine with a carbamate to yield a monosubstituted urea derivative **(18)** is outlined below. **(Scheme 12)**, i.e., the reaction of ethyl carbamate with dicyandiamide to form ameline **(19)**.
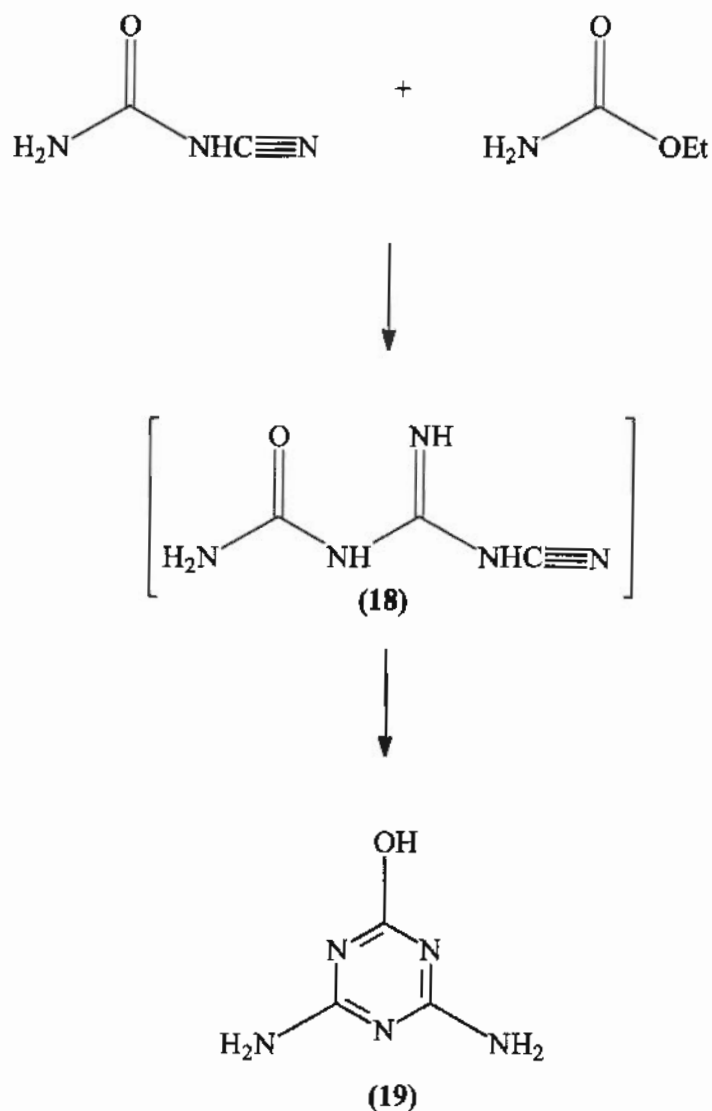
Scheme 12

1.4.3 REACTION OF THE AMIDO GROUP

Carbamates can be acylated by various carboxylic esters, anhydrides, or acid halides.[14] Certain carbamates are acylated by isocyanates. In general, carbamates are more readily acylated than ordinary amides.

N-acylcarbamates are formed from the reaction of carboxylic acid esters with carhamates to give substituted eneamines. It is noteworthy that the keto carbonyl rather than the ester carbonyl reacts with ethyl carbamate to give the substituted eneamine (**Scheme 13**).
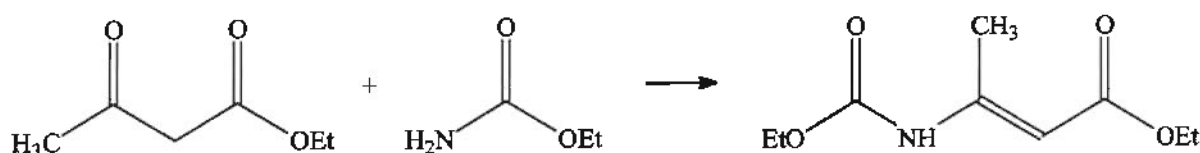
Scheme 13

The reaction of acid halides with carbamates has been utilised in the preparation of 3-(3,4-dichlorophenyl)oxazolidinetrione **(20)**.[30] Treatment of isopropyl 3,4-dichlorocarbanilate with a slight excess of oxalyl chloride give the oxazolidinetrione **(20)** **(Scheme 14)**.

R = alkyl

(20)
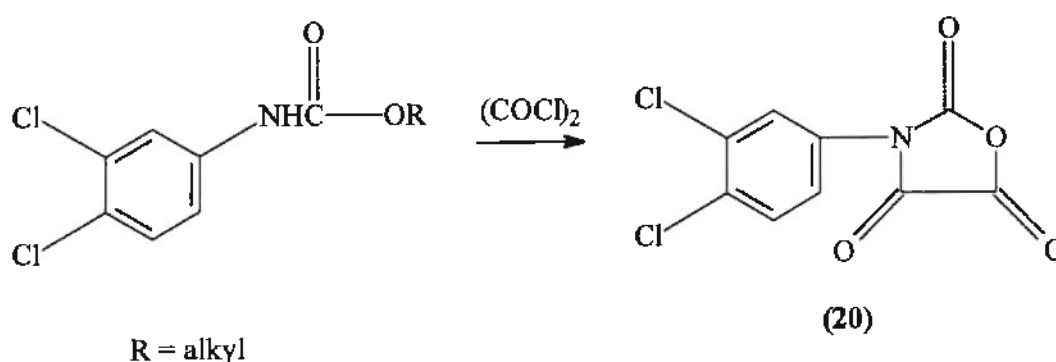
Scheme 14

1.4.4   REACTIONS OF CARBONYL COMPOUNDS WITH CARBAMATES.

The advent of formaldehyde-urea condensates for coatings and formaldehyde-fatty acid amide condensates for textile agents, had greatly stimulated interest in this field through the 1950's.

The type of products obtained when aldehydes are treated with carbamate esters depends upon the pH of the reaction. **Scheme 15** below outlines the mode of reaction of three primary condensation products between aldehydes and carbamate esters.[14]

$$RCHO \ + \ H_2NCOOR_1 \ \xrightarrow[\text{alkali}]{\text{trace}} \ \overset{\displaystyle OH}{\underset{\displaystyle}{RCHNHCOOR_1}}$$

$$RCHO \ + \ 2H_2NCOOR_1 \ \xrightarrow[\text{acid}]{\text{trace}} \ RCH(NHCOOR_1)_2 \ + \ H_2O$$

$$RCHO \ + \ H_2NCOOR_1 \ \xrightarrow[\text{acidic}]{\text{strongly}} \ (RCH\!-\!NCOOR_1)_3 \ + \ H_2O$$
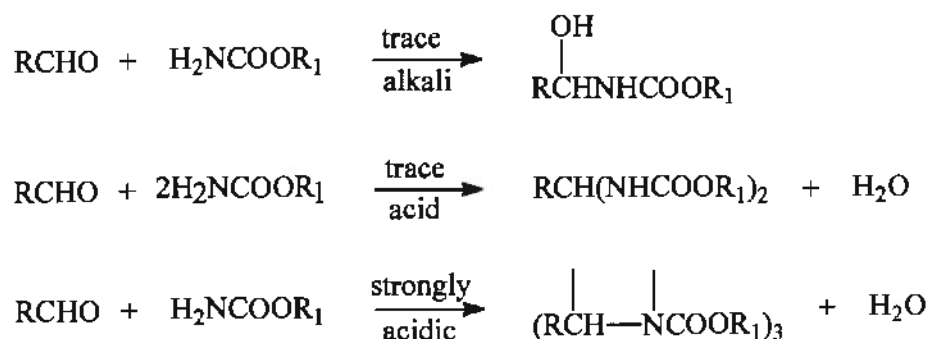
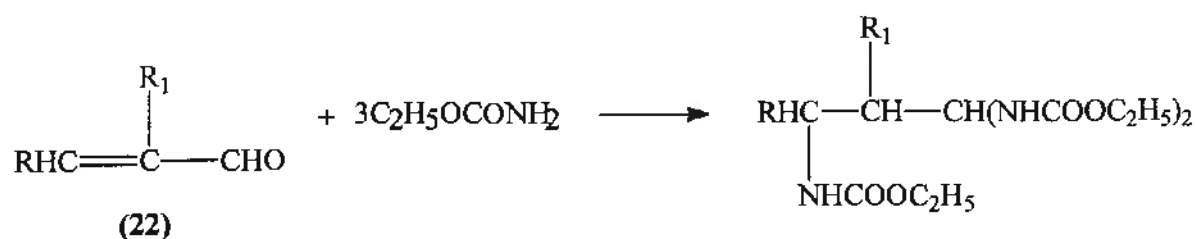**Scheme 15**

The preparation of methylenebis(ethylcarbamate) **(21)** by the reaction of two moles of ethyl carbamate and one mole of formaldehyde **(Scheme 16)** in the presence of trace amounts of mineral acids, was described by Conrad [31] in 1903.

$$CH_2O \ + \ H_2NCOOC_2H_5 \ \longrightarrow \ HOCH_2NHCOOC_2H_5$$

$$\Big\downarrow -H_2O$$

$$\underset{\textbf{(21)}}{CH_2(NHCOOC_2H_5)_2} \ \longleftarrow \ H_2C\!\!=\!\!NCOOC_2H_5 \ + \ H_2NCOOC_2H_5$$
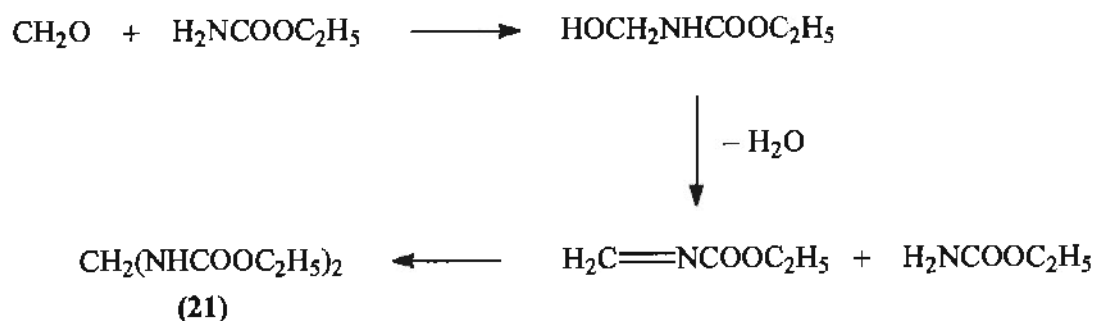
Scheme 16

Substituted acroleins **(22)** have been treated with three moles of ethyl carbamate in a combination of a Michael-type reaction and a normal 1,2 aldehyde condensation **(Scheme 17)**.

$$\underset{\textbf{(22)}}{RHC\!\!=\!\!\overset{\displaystyle R_1}{\underset{\displaystyle}{C}}\!-\!CHO} \ + \ 3C_2H_5OCONH_2 \ \longrightarrow \ RHC\!-\!\overset{\displaystyle R_1}{\underset{\displaystyle NHCOOC_2H_5}{CH}}\!-\!CH(NHCOOC_2H_5)_2$$
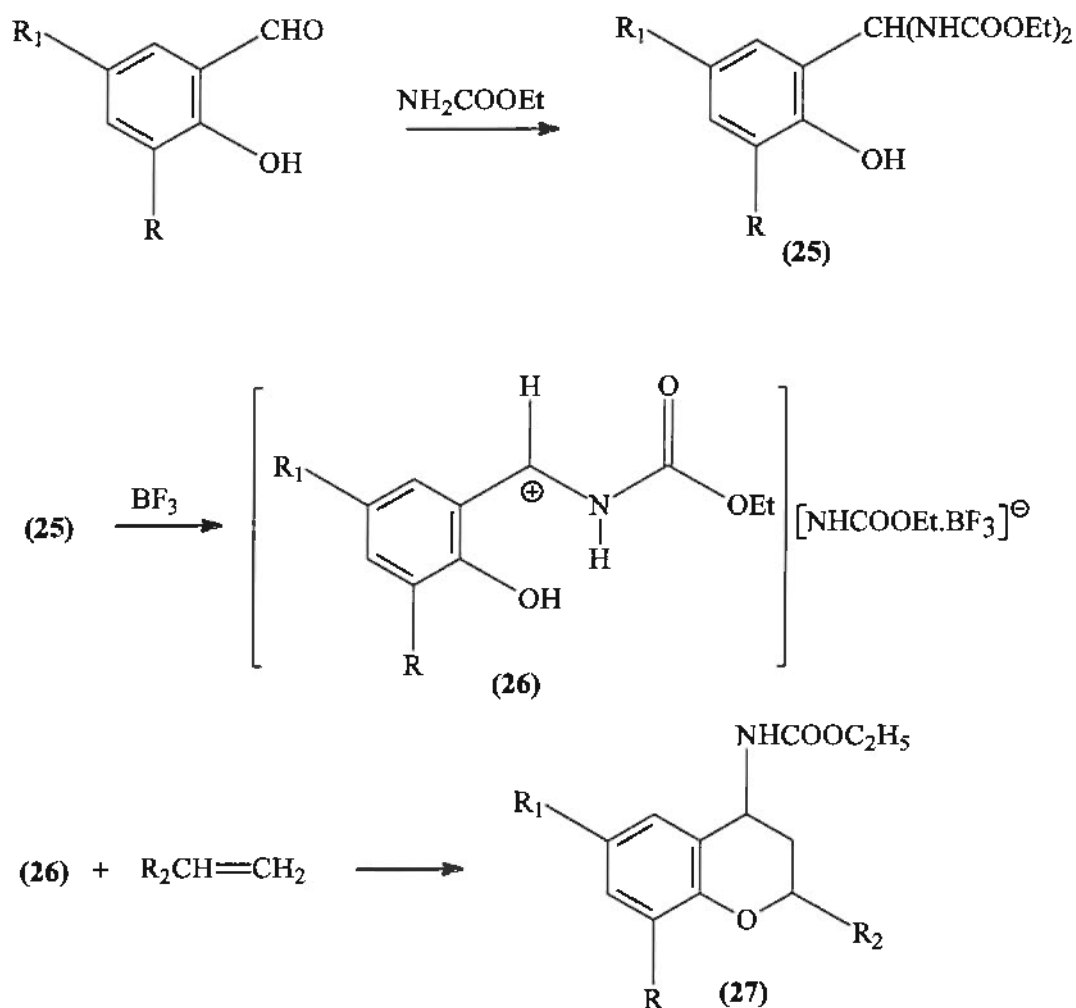
Scheme 17

Cinnamaldehyde condenses with two moles of ethyl carbamate to form cinnamylidenebis(ethyl carbamate), similar to (21) above. No addition across the double bond is observed. Kraft[32] made a peculiar observation that α-ethylcinnamaldehyde (23) reacted with only one mole of carbamate. The product was unaffected by refluxing for several hours in dilute or concentrated mineral acid. This reaction led to the synthesis of substituted indanone derivatives (24) (Scheme 18).


R = Et, CH₂Ph
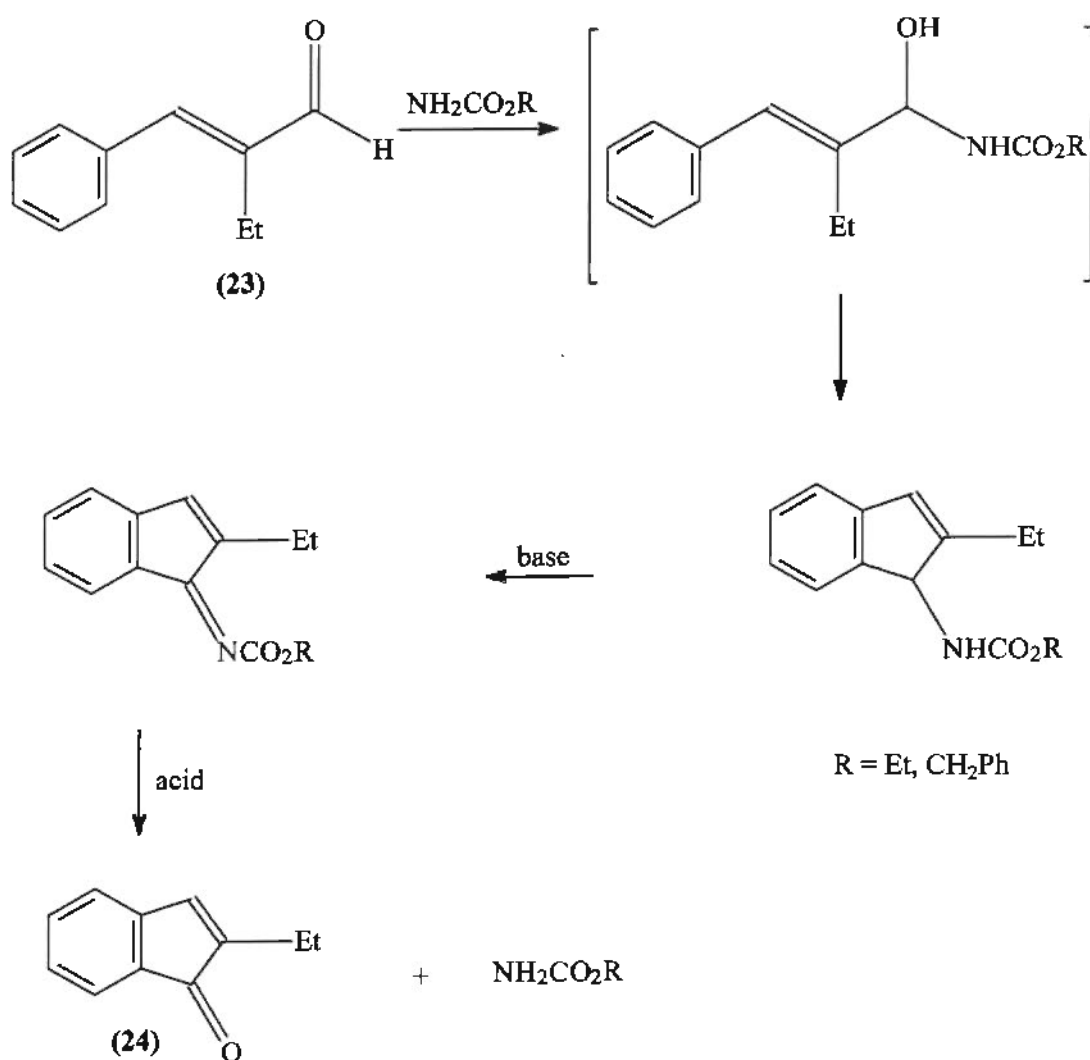
Scheme 18

The work of Merten[14] and coworkers using BF_3 catalysis has expanded the chemistry of methylenebis carbamate esters to an exciting degree.

Merten and Muller found that biscarbamates (25) of o-hydroxybenzaldehydes react with olefins in the presence of BF_3 to form chromans (27) (Scheme 19). The reaction occurs via the intermediate (26).
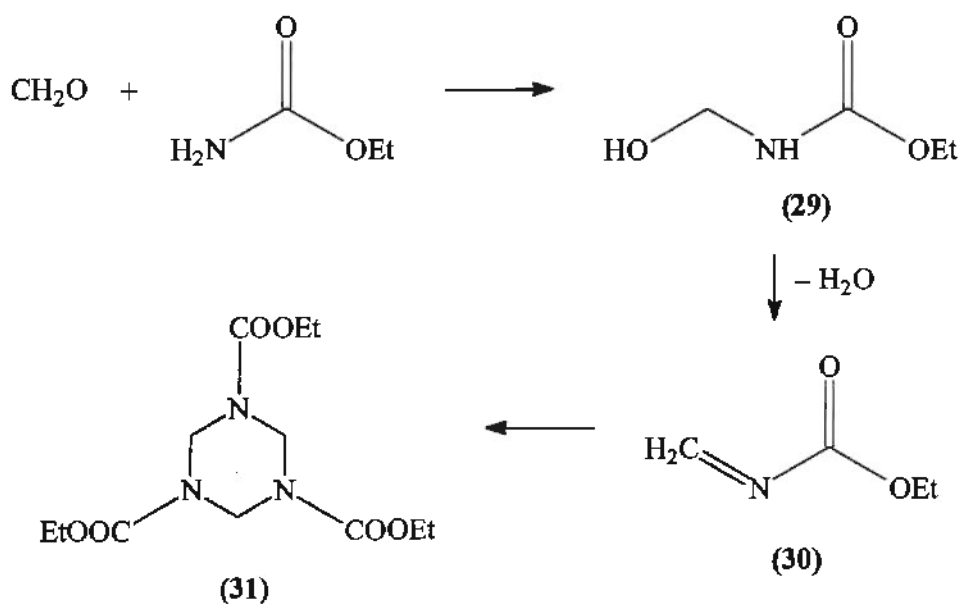

Scheme 19

Similarly benzoflavans (28) were obtained when 2-hydroxynaphthaldehyde was condensed with styrene and ethyl carbamate (Scheme 20).
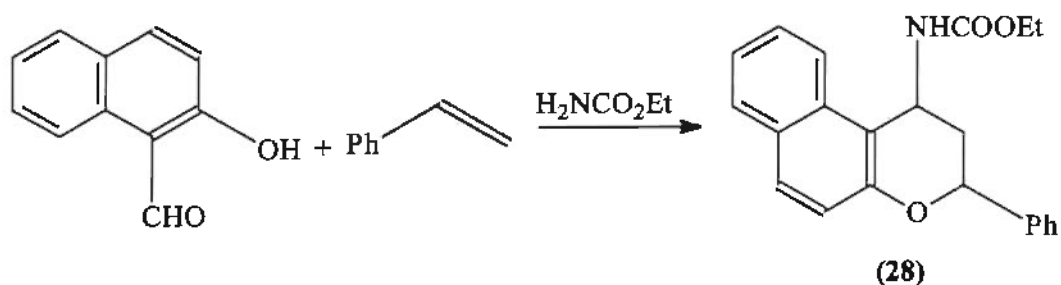
Scheme 20

The reaction between formaldehyde and ethyl carbamate results in the formation of N-hydroxymethylcarbamate **(29)**, which dehydrates to form a methylene imine **(30)**. The methylene imine trimerizes to form tricarbethoxyhexahydrotriazine **(31)** **(Scheme 21)**.
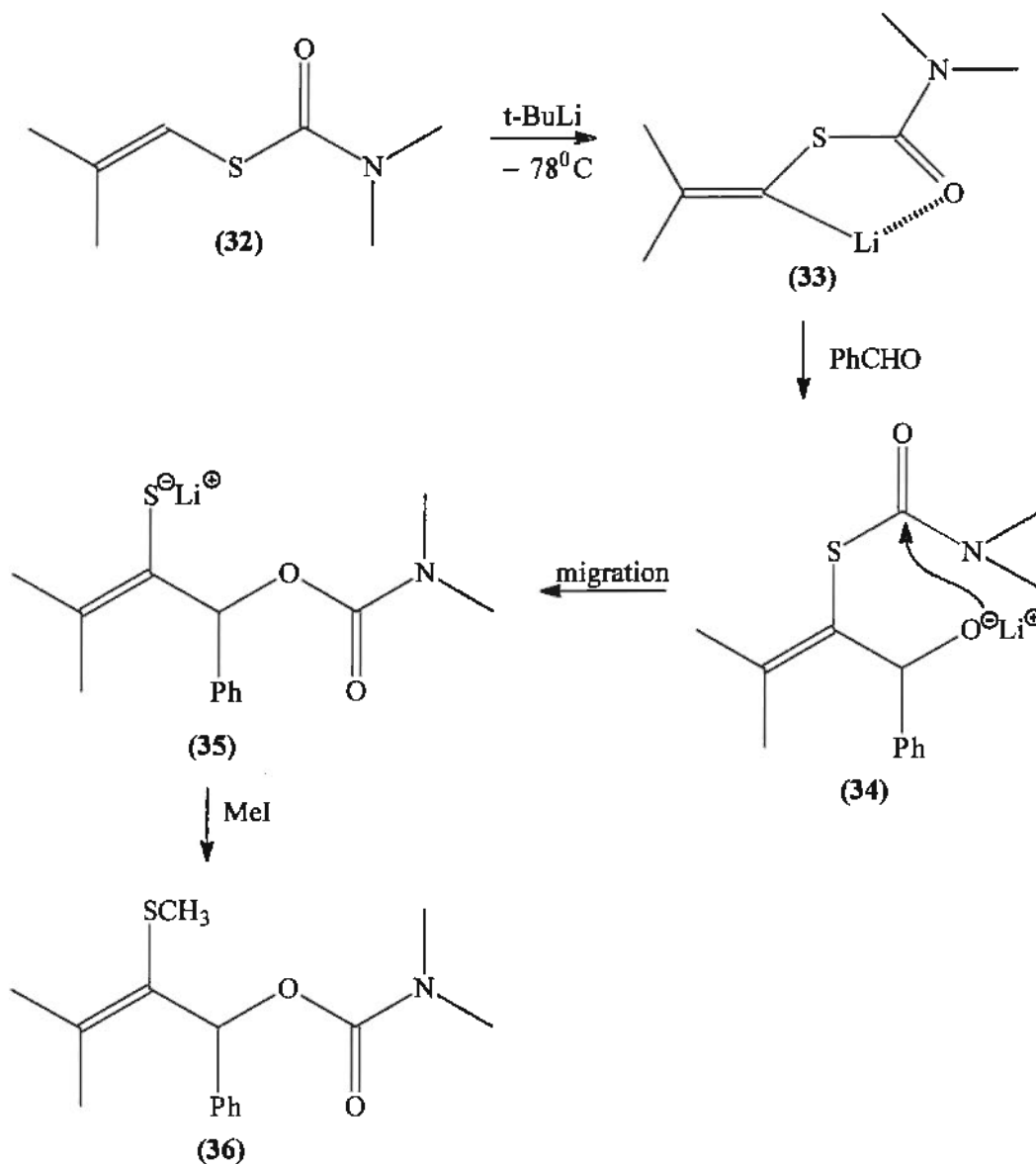

Scheme 21

1.5   CARBAMATES AS SYNTHETIC INTERMEDIATES

1.5.1   ACTIVATING-STABILISING ABILITY OF THE CARBAMATE GROUP.

1.5.1.1 The Migrational and leaving-group ability of the carbamate.

Hoppe[33] and co-workers were the first to report the migration of the carbamate in 1980. This involved the intramolecular transfer of the amide portion of the carbamate from a sulphur atom to an oxygen atom **(Scheme 22)**

Scheme 22

S-vinyl thio carbamate (32) was treated with tert-butyllithium at -78 °C resulting in deprotonation at the α-position. This gives rise to a carbamate-stabilised lithium complex (33). Reaction of (33) with benzaldehyde followed by the amide migration resulted in the lithium enethiolate (35) *via* the intermediate (34). The lithium enethiolate (35) was trapped as the methyl vinyl thioether (36).

A more recent report on the migrational ability of the carbamate by Snieckus[34] describes the migration of the amide portion of the carbamate intramolecularly from a vinylic

oxygen to an allylic oxygen. N,N-diethyl vinyl carbamate was deprotonated in the α-position giving a lithium stabilised lithium complex, similar to **(33) (Scheme 22)** above. Reaction with aldehydes provided an allylic alkoxide for migration of the amide portion of the carbamate, the driving force being the formation of the thermodynamically more stable enolate. Reaction with alkyl halides led to normal α-substituted carbamates.

Van Rensburg[35] exploited the migrational ability as well as the leaving-group capability of the carbamate in the synthesis of chromenes **(40)** and coumarins **(42) (Scheme23)**.
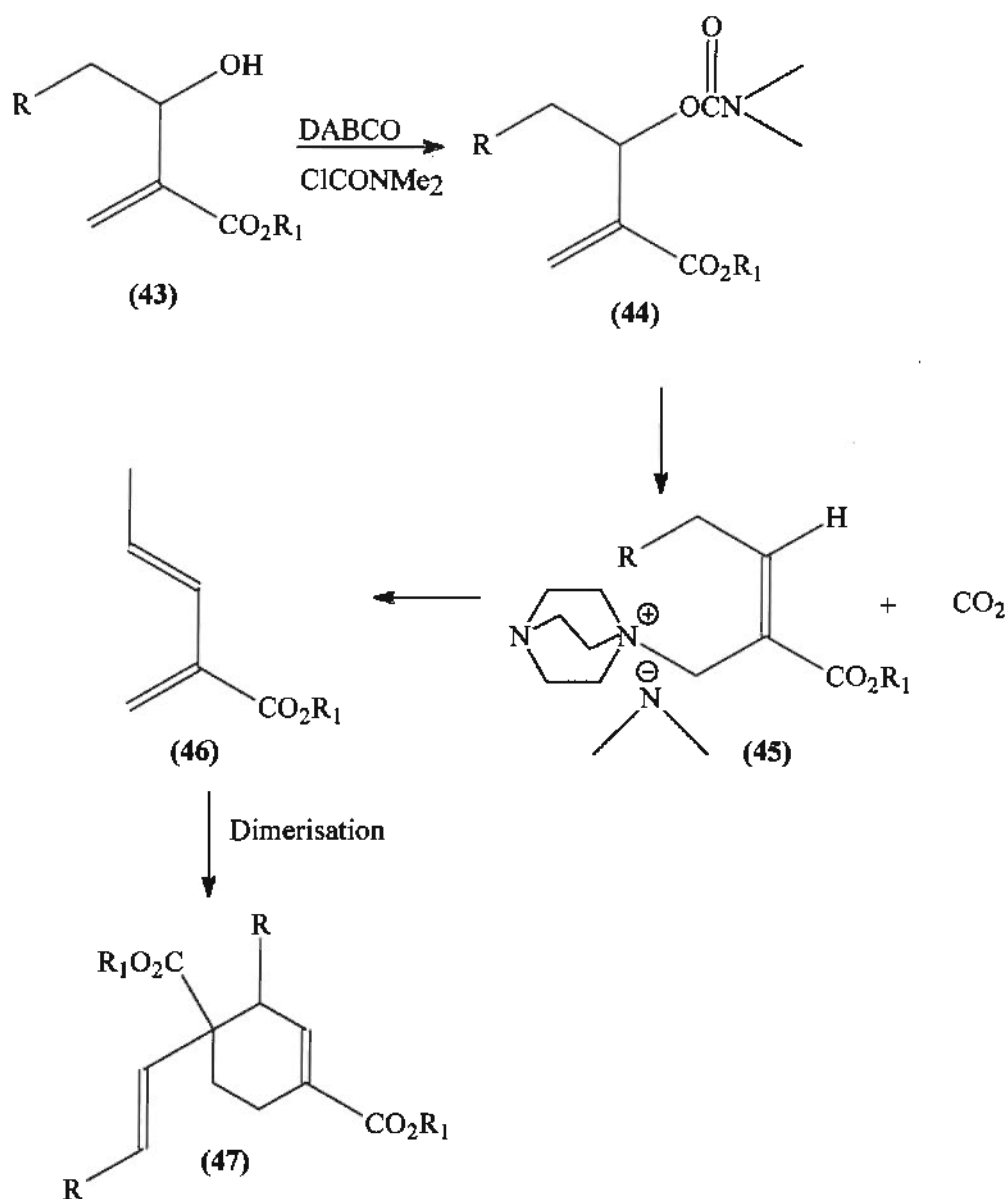
Scheme 23
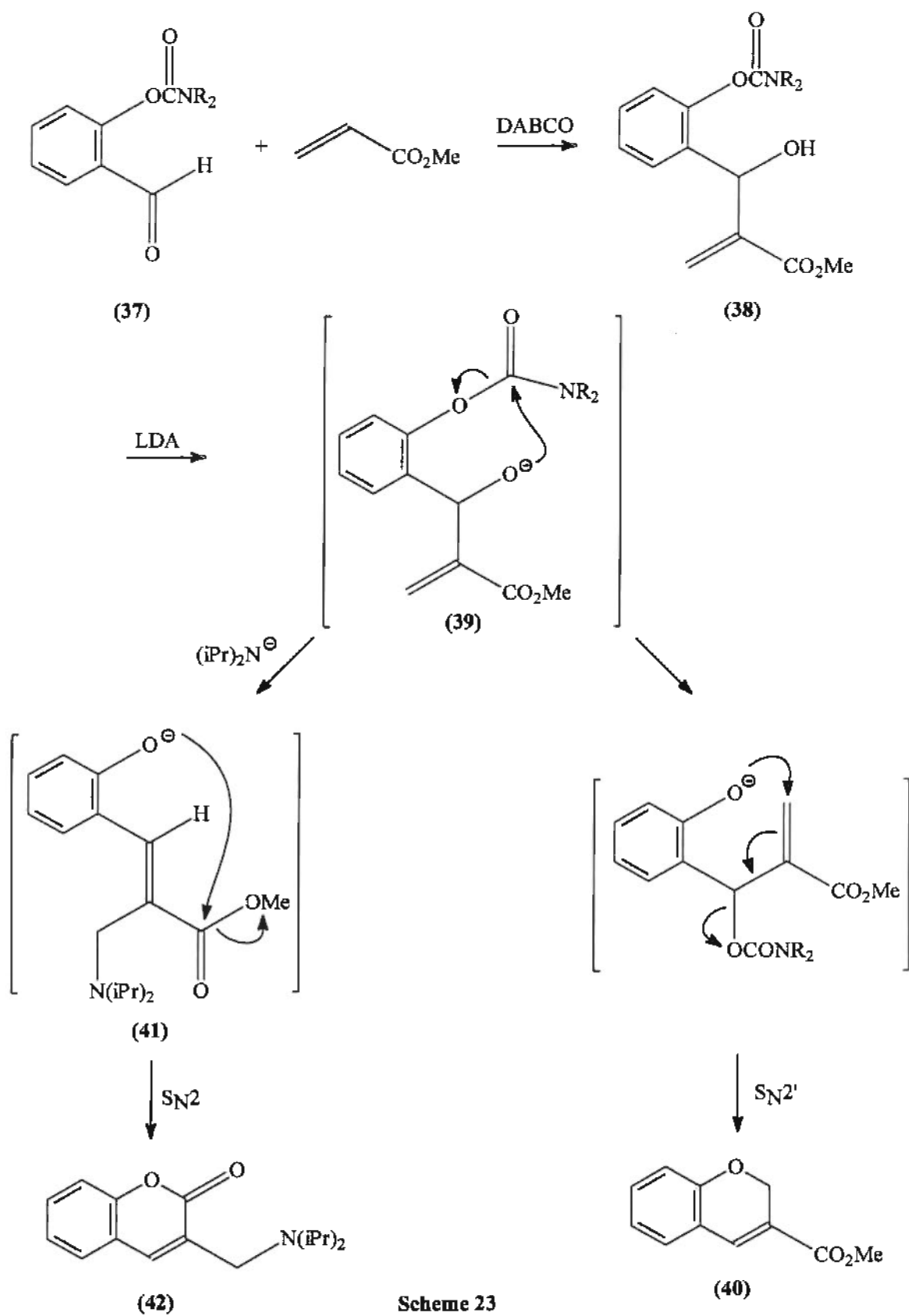
The allylic alcohol **(38)** is formed when aldehyde **(37)** reacts with methyl acrylate and DABCO in the Baylis Hillman reaction. The mechanism then involves the usual migration of the amide portion of the carbamate to the allylic position *via* a favoured six-membered transition state **(39)** giving the allylic carbamate. From this point two competing reactions are evident.

    a) Cyclisation *via* the intramolecular S_N2' rection pathway giving the chromene adduct **(40)**.

    b) An S_N2' reaction between LDA and the allylic carbamate giving the intermediate **(41)**.

Intermediate **(41)** then undergoes cyclisation *via* an intramolecular S_N2 pathway yielding coumarin **(42)**. This intramolecular S_N2 reaction occurs as a consequence of the original β-position being masked by diisopropylamine.

Van Rensburg further extended the migrational and leaving group capability of the carbamate as an effective tool in the synthesis of substituted cyclohexenes **(47)** **(Scheme 24)**.
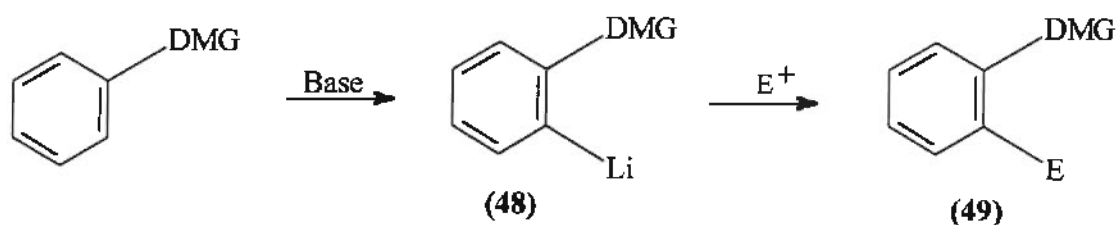
Scheme 24

The mechanism outlined above **(Scheme 24)** involves the formation of an allylic carbamate intermediate **(44)** from the allylic alcohol **(43)** (Baylis-Hillman adduct). The allylic carbamate **(44)** then reacts with DABCO in an S_N2' reaction giving the ammonium salt **(45)**. The formation of the dimethylamine anion and carbon dioxide is a result of the spontaneous decomposition of the carbamate leaving group. Concerted elimination of the DABCO results in the formation of the diene ester **(46)** which dimerizes *via* a Diels-Alder type reaction affording the substituted cyclohexene **(47)**.

1.5.1.2 Beta-Metalations

The directed *ortho*-metalation (DoM) reaction was discovered independently by Gilman[36] and Wittig.[37]

The directed *ortho* metalation reaction **(Scheme 25)** involves deprotonation of a site ortho to a heteroatom-containing substituent {directed metalation group (DMG)} by a strong base. The product of this deprotonation is usually a DMG-stabilised *ortho*-lithiated complex **(48)**.

Scheme 25

Treatment of the lithiated complex **(48)** with suitable electrophiles (E^+) results in 1,2-disubstituted aromatic adducts **(49)**.

Of the many DMG's that exist the carbamate proves to be one of the most successful and powerful of these groups used. This is due to the fact that that the carbonyl provides a good site for effective co-ordination with the lithium metal, and is a poor electrophile for nucleophilic attack by strong alkyllithium bases.[38] These factors result in products of high regioselectivity.[39] An example of such a complex is the *ortho*-lithiated *o*-phenyl carbamate **(50)**.
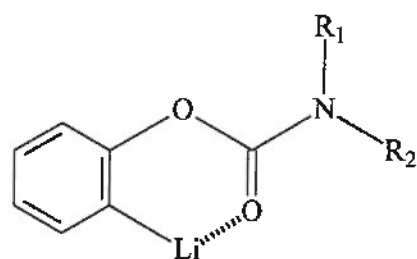
R_1, R_2 = alkyl, aryl

(50)

In their discussion on *ortho*-lithiations, Snieckus and co-workers[39] refer to and make use of the migration of the amide portion of the carbamate from the oxygen atom to the *ortho* carbon atom (**Scheme 26**).

(51)

(52)

(54)

1) RLi

2) E^+

(53)
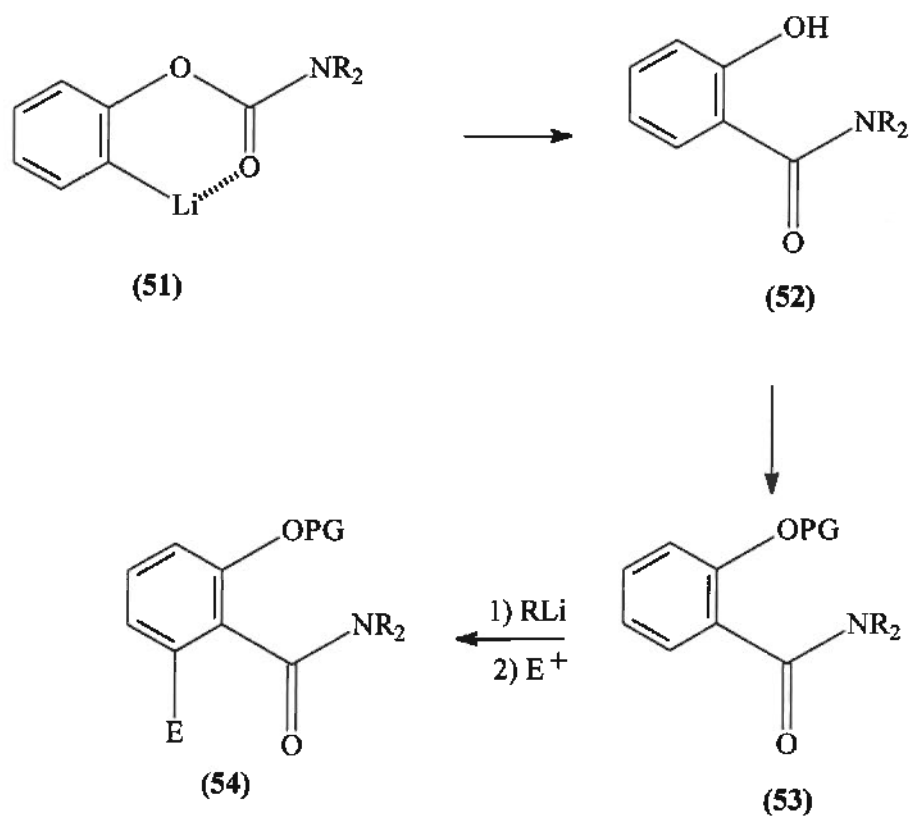
Scheme 26

This rearrangement takes place on allowing the *ortho*-lithiated complex (**51**) to warm to room temperature from -78°C, without the addition of any electrophiles, to give the

salicylamide **(52)**. In this anionic equivalent of the *ortho*-Fries rearrangement, the carbamate serves as a "carrier" of the amide into an *ortho* site**(52)** from which, after suitable phenol protection, it may ohlige further DoM chemistry, leading to 1,2,3-trisubstituted aromatics **(54)**.

1.5.1.3 Alpha-Metalation.

The α-metalation reaction involves deprotonation of a site α to a heteroatom by a strong base. The product of this deprotonation is usually a heteroatom-stabilised α-metalated complex which can in turn be reacted with electrophiles.[40]

O-substituted oxy-allyl anions[41] **(55)** serve as synthetic equivalents of homoenolate ions[42] **(56)**.


(55)

(56)

(57)

$R_5 = NR_2$, OR, SR, SiR_3
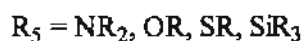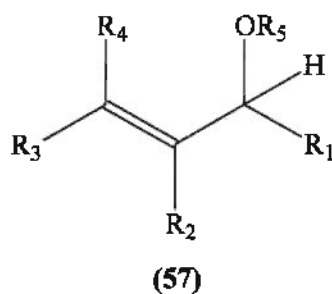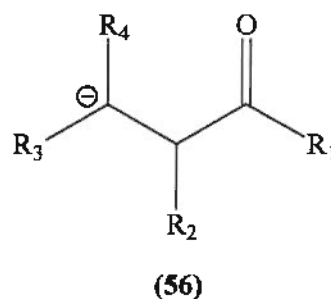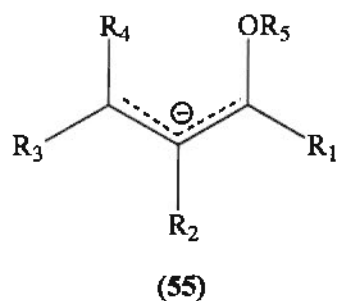
The allyl anions (55) are generated directly from their corresponding allyl ethers (57). These anions have previously been used, but their scope of application as homoenolate reagents is very limited.

There are two main reasons for their limited use. Firstly, the stability of anion (55) is drastically reduced by alkyl groups R^1 and R^3 in the electron-rich α- and β-positions. Regioselectivity of substitution of anion (55) is the second limitation in that substitution can occur at either the γ-position (58) or at the α-position (59).
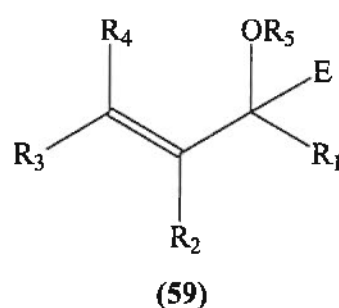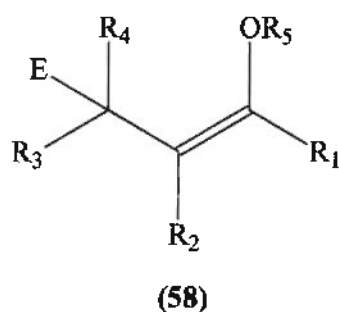

In 1980 Hoppe[43] reported the use of an allylic N,N-dialkylcarbamoyl ester (60) as an effective homoenolate equivalent which overcame the above discussed limitations of allyl ethers (57). Hoppe found that the presence of this N,N-dialkylcarbamoyl group as the allylic ester (60) gave a highly stabilized allylic carbamate lithium complex (61) upon deprotonation with LDA (Scheme 27).
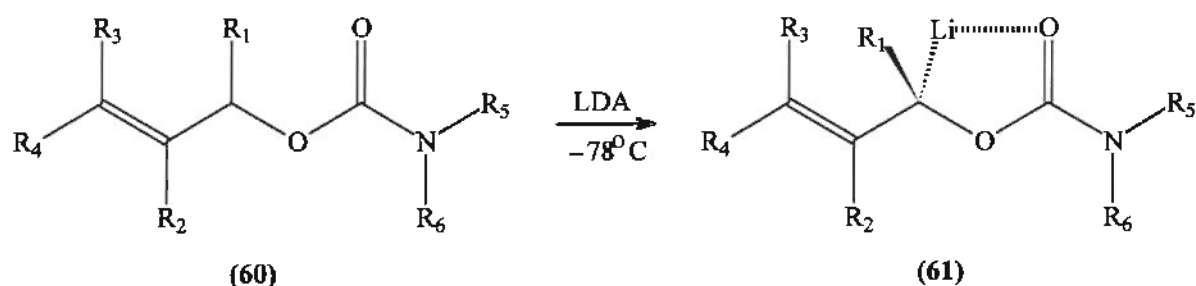
Scheme 27

The allylic carbamate lithium complex (61) has been termed a "tight-ion pair" in which the lithium cation is held at the α-carbon atom by the complexing carbonyl oxygen of the carbamate ester.[44]

The N,N-dialkyl carbamoyl group in the ester increases the kinetic acidity of the α-protons, by chelation, to an extent that alkyl-substituted allyl derivatives can also be deprotonated. This group also overcomes the problem of regioselectivity in that reliable γ-substitution (62) is generally observed (Scheme 28).
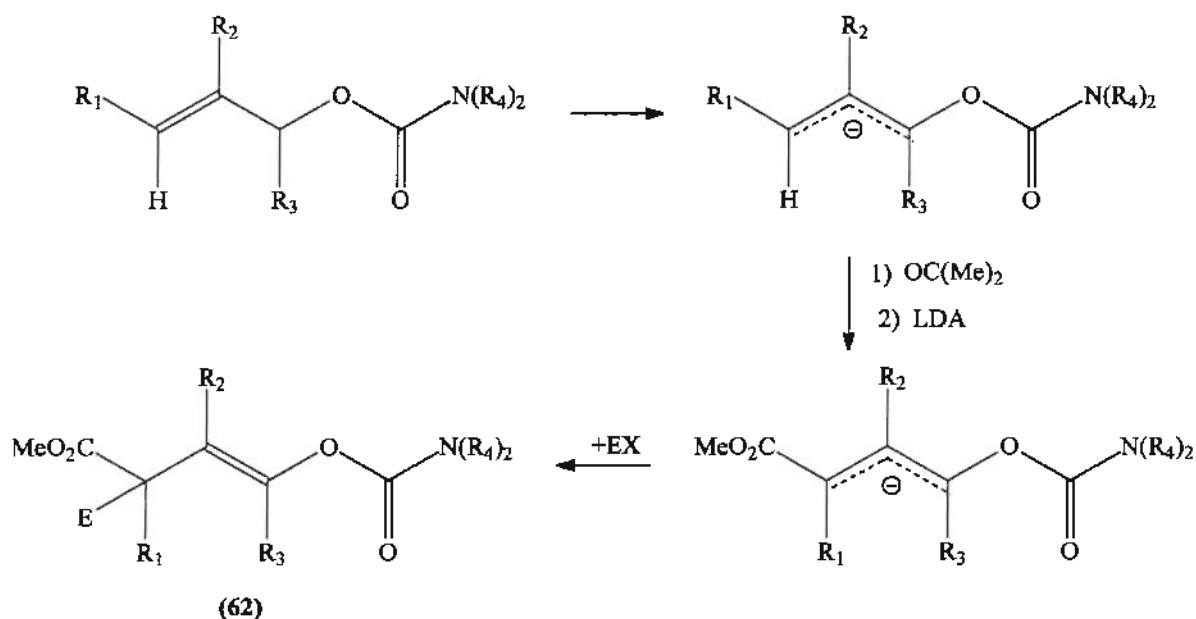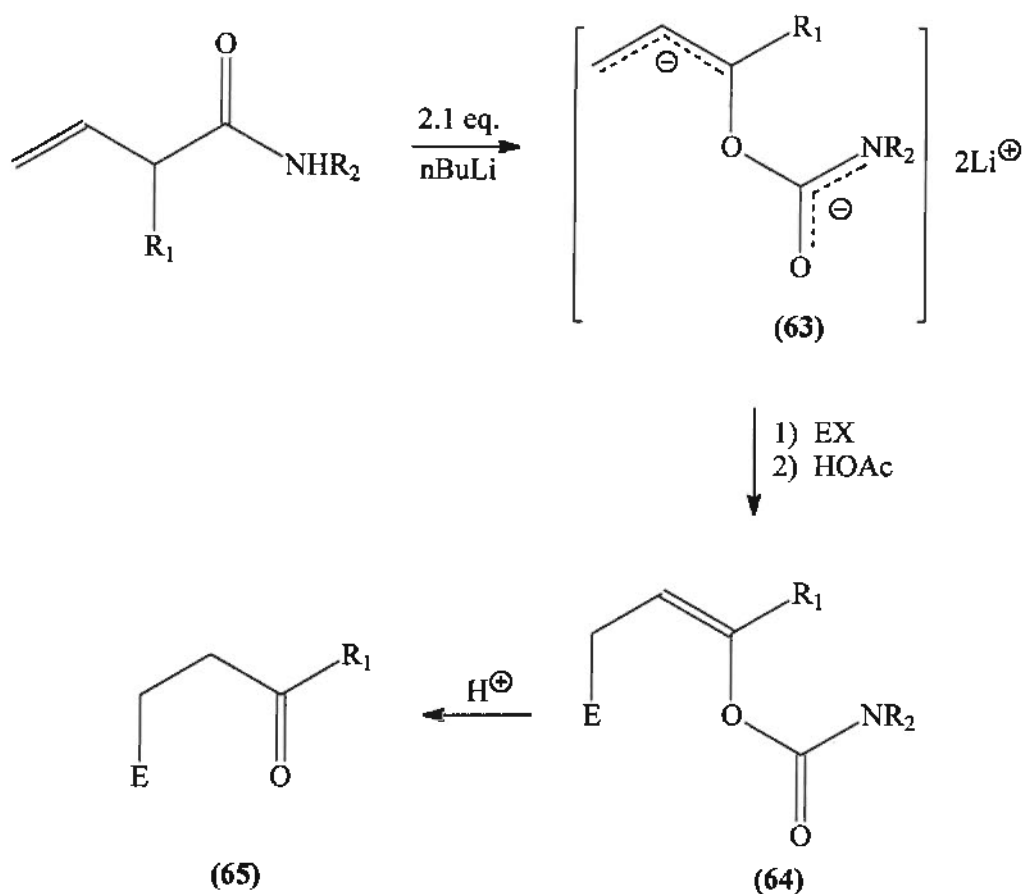

Scheme 28

An envisaged problem with the reaction outlined above (Scheme 28) is the susceptibility of the carbonyl group of the ester to nucleophilic attack, when strongly nucleophilic alkyllithium bases are used for the metalation.

The carbonyl group of the ester can be protected either by using sterically-demanding N-alkyl moieties or by reducing its electrophilicity, i.e., electronic protection.

Hoppe[45] reduced the electrophilicity of the carbonyl group by double deprotonation of allyl N-alkyl or N-aryl carbamates with strongly nucleophilic n-BuLi **(Scheme 29)** to give double lithium salts **(63)**.
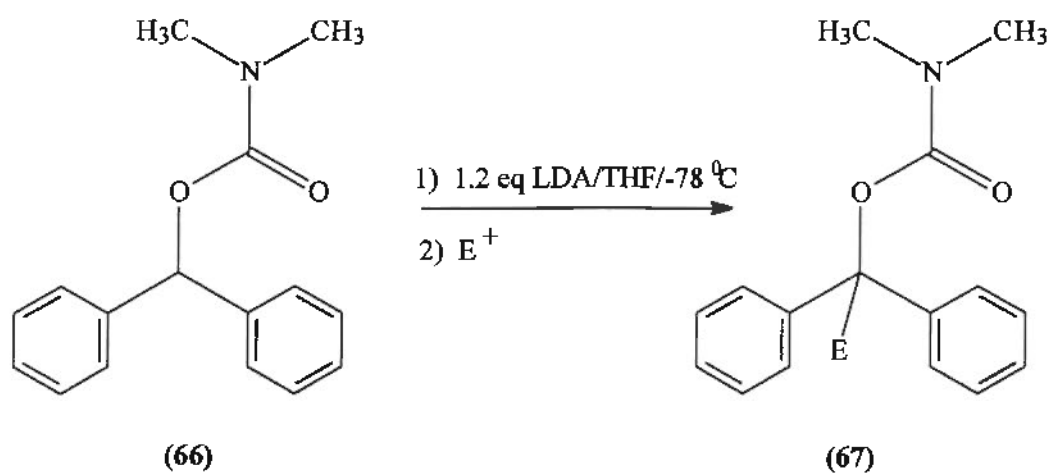

Scheme 29

On treatment of **(63)** with electrophile (EX) predominantly Z-configured γ-adducts **(64)** are obtained, along with small amounts of α-allyl esters. The enol esters **(64)** were then hydrolysed under acidic conditions to yield β-substituted carbonyl compounds **(65)**.

As a variation to Hoppes work, Longley[46] carried out α-metalation reactions on the highly hindered 1-(N,N-dimethylcarbamoyloxy)-1,1-diphenylmethane **(66)**. Longley used a range of electrophiles to produce α-substituted carbamates **(67)** **(Scheme 30)**. The

success of the reaction is governed principally by the bulk of the incoming electrophile and its steric interaction with the carbamate.

(66) → (67)

1) 1.2 eq LDA/THF/-78 °C

2) E⁺

E = Me , PhCH$_2$M , TMS , PhCH=CHCH(OH)

Scheme 30

PART B

1.6 THE FLAVONOIDS

The flavonoids constitute one of the most numerous and widespread groups of compounds in the plant kingdom. The chemical structures are based on a C_6-C_3-C_6 skeleton with a chroman ring bearing a second aromatic ring in position 2, 3 or 4 (**Fig.1**). In a few cases, the six-membered heterocyclic ring occurs in an isomeric open form or is replaced by a five-membered ring.
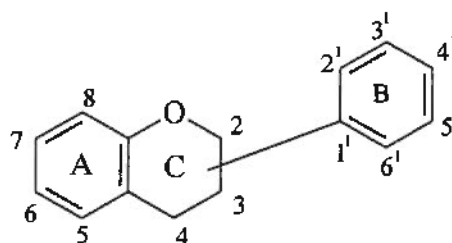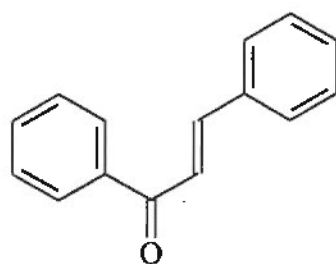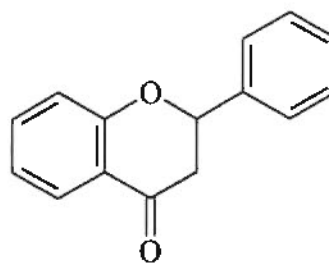

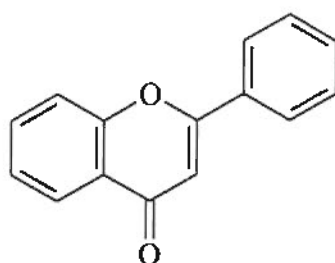**Fig. 1. The basic structure of most flavonoids.**

The flavonoids are divided into a number of classes based on the degree of oxidation of the C-ring and the position of the B-ring. Some of these are shown below.

Chalcone   **Flavanone**

Flavone
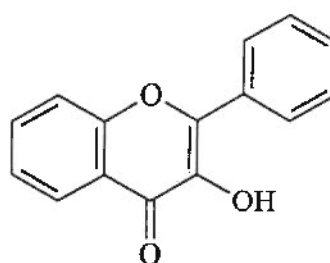
Flavonol
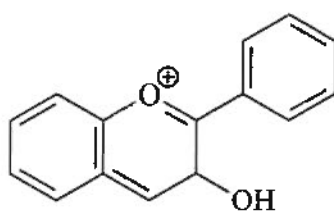
Anthocyanidin
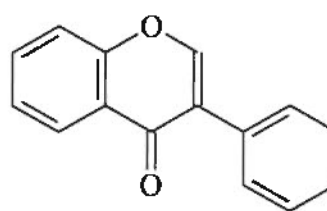
isoflavone
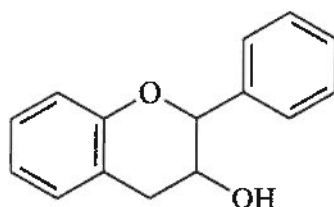
Flavan-3-ol
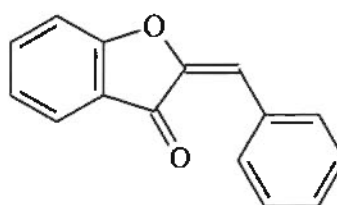
Aurone
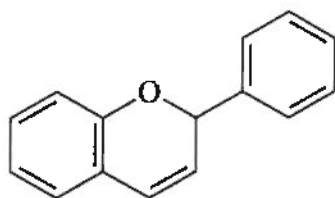
Flav-3-ene
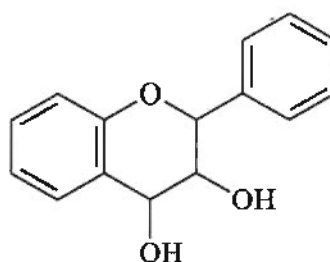
Flavan-3,4-diol

Variations in substitution patterns, stereochemistry and in the nature of the substituents, result in an extensive range of compounds within each class of flavonoids.   A

comprehensive list of all known flavonoids by Harborne[47] totalling over 4000 structures bears testament to the diversity of this unique class of compounds.

1.7   THE BIOLOGICAL FUNCTION OF THE FLAVONOIDS.

The reason why plants produce these compounds in such vast quantities, and with such structural variation, has been the focus of a great deal of attention in recent years. It is clear that the role of the flavonoids is multifunctional. They exhibit a wide variety of biochemical, physiological and ecological activities which enable plants to survive the various challenges of their environment.

A major function of the flavonoids is in imparting colour to flowers and fruit in order to attract animals (mainly bees and other insects), for the purpose of pollination and seed dispersal. Flower colour has recently been reviewed.[48] Anthocyanins provide most of the pink, orange, red, violet and blue colours to flowers. The chalcone, aurones and yellow flavonols sometimes contribute to yellow flower colour and these, together with the colourless flavone and flavonol glycosides, are frequently responsible for u.v. patterns which guide insects, especially bees, in their search for nectar and hence pollination of the flowers.

The flavonoids are conjugated aromatic compounds and as such may act as potent screening agents against harmful u.v. radiation. The u.v.-induced activity of a number of enzymes involved in flavonoid biosynthesis has been demonstrated,[49,50] and may serve to confirm this theory. The flavonoids are typical phenolic compounds and therefore act as potent antioxidants and metal chelators.

Flavonoids play a role in plant defence against microbial attacks. The antimicrobial properties of the proanthocyanidins have been discussed in a recent review.[51] A number of flavonoid phytoalexins have been identified. Phytoalexins are antimicrobial (especially antifungal) compounds produced by plants as part of a plant's natural defence

against micro-organisms. Most of the flavonoid phytoalexins are isoflavonoids although other classes of flavonoids have been demonstrated. For example, four dihydroflavonols, including (68) have been identified as phytoalexins of the legume *Shuteria vestita.*[52]
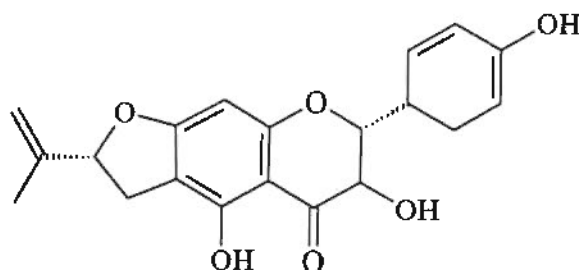
(68)

In another example, three flavans (69), (70) and (71) were isolated as phytoalexins of *Narcissus pseudonarcissus* after inoculation with *Botrytis cinerea.*[53]
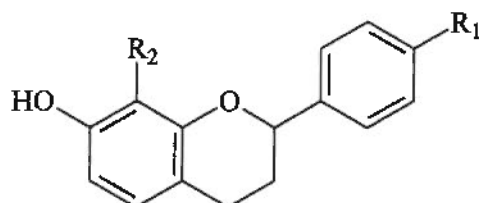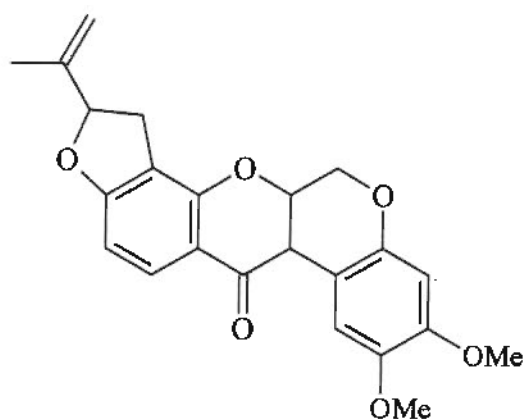

(69) $R_1=R_2=H$

(70) $R_1=OH$, $R_2=H$

(71) $R_1=OH$, $R_2=Me$

Plant flavonoids affect insect behaviour, development and growth. The insecticidal activity of rotenoids, which may be traced to an inhibition of the mitochondrial electron transport system, has been discussed by McClure.[54] Rotenone (72) appears to be one of the most active of the naturally-occurring rotenoids.

(72)

Besides the insecticidal activity of the rotenoids, the roles of flavonoids as feeding stimulants, feeding deterrents and larval growth inhibitors have been demonstrated in a variety of plant species. For example, a flavan-2-ol glycoside **(73)** isolated from *Ulmus americana* is believed to act as a feeding stimulant for the smaller European elm bark beetle *Scolytus multistratus* (Marsham).[55, 56] The feeding deterrent activity of a number of naturally-occurring flavonoids against the aphids *Schizaphis graminum* and *Myzus persrede* have been demonstrated.[57] Many of these, including the dihydrochalcone phlorizin **(74)** and the flavanone errodictyol **(75)** showed strong deterrency at concentrations well within the range often found in plants. Finally, the cotton leaf anthocyanin, cyanidin 3-glucoside **(76)** has been shown to be particularly inhibitory to the larval growth in the tobacco budworm *Heliothis viriscens*.[58]

(73)

(74)

(75)

(76)
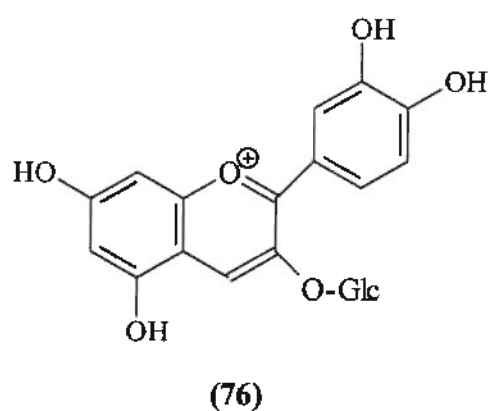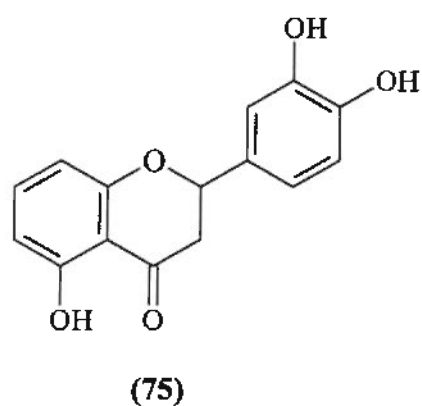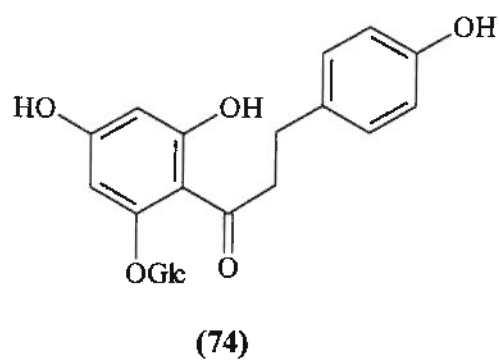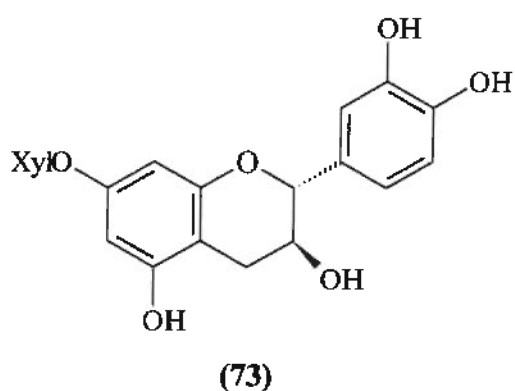
The oestrogenic activity of simple isoflavones such as daidzein **(77)** and of coumestans such as coumestrol **(78)** have long since been established and extensively discussed by McClure.[54] These compounds are structurally related to the synthetic oestrogen, diethylstilbestrol **(79)**.

(77)

(78)

(79)
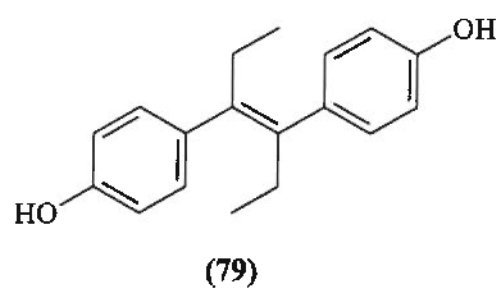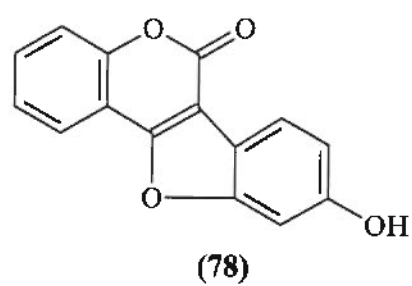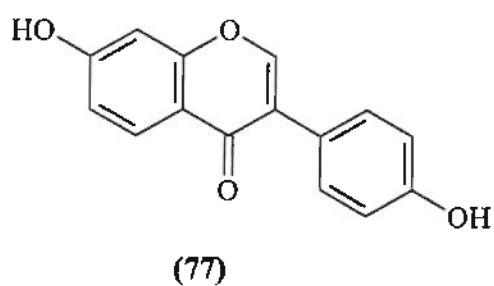
Although not as potent, they nevertheless approach sufficient levels in forage crops such as clovers (*Trifolium* spp.) and lucerne (*Medicosofiva*) to exert definite physiological effects when eaten in quantity.[59]

1.8 PHARMACOLOGY OF THE FLAVONOIDS.

In recent years interest in traditional remedies and plant-derived drugs have witnessed a spectacular revival. The flavonoids in particular have received renewed interest. Their widespread occurrence in flowering plants, and therefore availability, as well as their overall uniformity in chemical structure, so that structure-activity relationships are easily established, makes this class of compounds ideal for pharmacological screening. It is therefore not surprising that a wide variety of pharmacological activities such as anti-inflammatory, anti-ulcer, anti-anginal, anti-hepatoxic, anti-allergic, antimicrobial, antiviral *etc.* have been attributed to the flavonoids in recent years. A thorough review of the pharmacological activity of the flavonoids has been published under the editorship of Cody, Middleton and Harborne.[60] Some of the pharmacological activities displayed by the flavonoids are perhaps best illustrated with a few examples.

An aqueous alcoholic extract of the root of a South American plant called *"Cabeca de Negra"* is available to plantation workers in the Amazon jungle as an oral antidote against snake and spider venoms. Two pterocarpans, cabenegrin A-1 **(80)** and cabenegrin A-2 **(81)** were isolated as the active principle.[61] Both of these have been shown to possess potent snake antivenom properties.

(80)   (81)
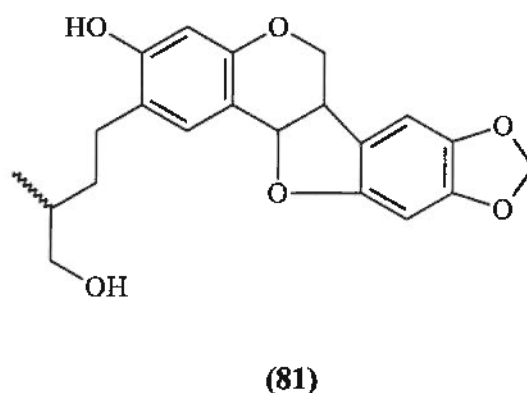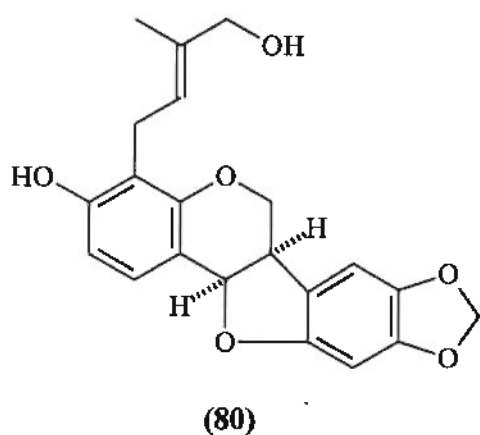
A number of flavonoids with anti-inflammatory properties have been isolated in recent years.[62] Of these, hypolaetin-8-glycoside **(82)** isolated[63] from *Sderitis magronensis* is

interesting in that it displays both anti-inflammatory and anti-ulcer properties.[64] The authors suggest that this compound may provide a useful alternative to anti-inflammatory drugs of the aspirin type.
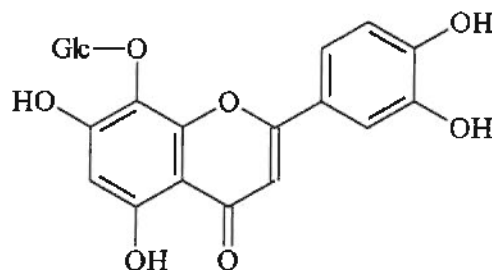
(82)

Various flavan-3-ols and proanthocyanidins have been isolated from *Citus incanus* subspecies.[65] *Citus* species, indigenous to the Mediterranean area are used as an antidiarrhoic and as a general remedy for the treatment of various skin diseases in folk medicine.

The rhizomes of the fern *Polypodium glycyrrhiza* exhibit a bittersweet taste, and have a history of human consumption both for the use as a food and medicinal agent. From a 1-butanol extract of this plant part a bitter flavonoid glycoside, (+)-afzelechin-7-0-β-D-apioside) **(83)** was isolated.[66]
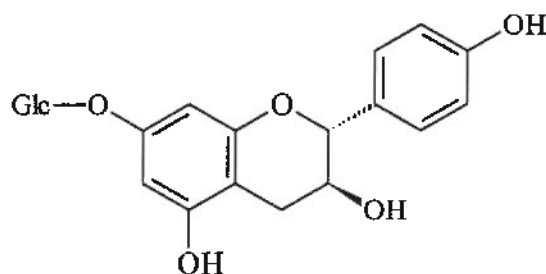
(83)

In recent years, considerable effort has been made to identify and characterise molecules capable of mediating nucleic acid strand scission. Hecht[67] and co-workers reported two flavonoid-type compounds that mediate DNA strand scission, *i.e.* (-)-epicatechin **(84)** and procyanidin B2 **(85)**.

3,4 Diol **(86)** serves as an intermediate in the biosynthesis of di- **(85)**, tri-, tetra- and poly-meric flavonoids.
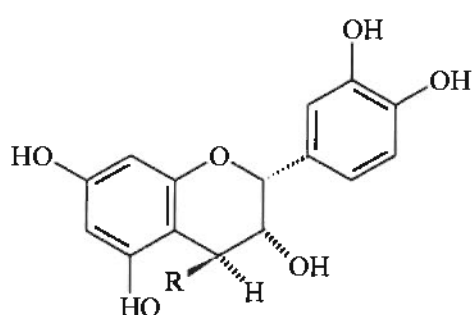
(84) R=H
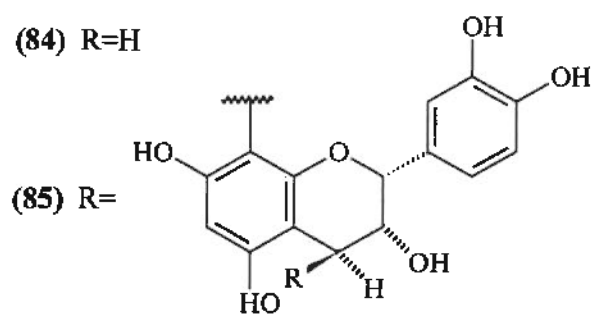
(85) R=

(86) R=OH

1.9 SYNTHESIS OF SOME FLAVONOIDS.

1.9.1 BASIC APPROACHES

Theoretically, there are at least four ways of forming the C_6-C_3-C_6 flavonoid skeleton from simple starting materials, but only two have achieved importance for the laboratory synthesis.[70]

i) Condensation of a C_6-C_2 unit (2-hydroxyacetophenone) with a C_6-C_1 unit (aromatic aldehyde) according to **Scheme A**; and

ii) Acylation of a C_6 unit (phenols) with a C_6-C_3 unit (α-cinnamic acid derivatives) according to **Scheme B**.
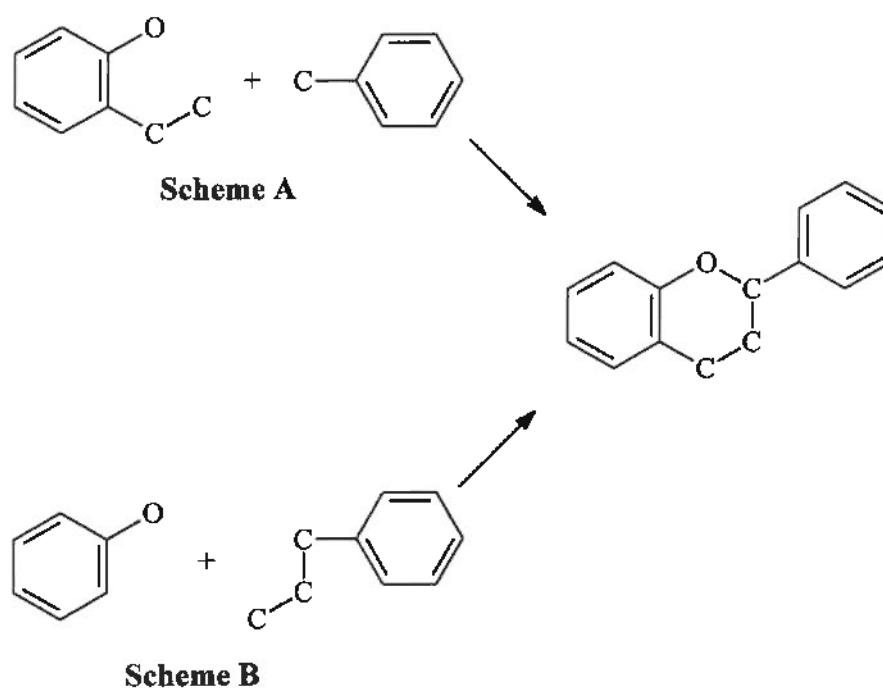
Scheme A

Scheme B

The work reported herein involves both approaches with an emphasis on the former approach.

1.9.2 SYNTHESIS OF Δ^3-FLAVENE

Descotes and Missos[68] have reported an elegant synthesis of Δ^3-flavene (91) from Δ^2-chromene (87) in excellent yield (Scheme 31).

Scheme 31

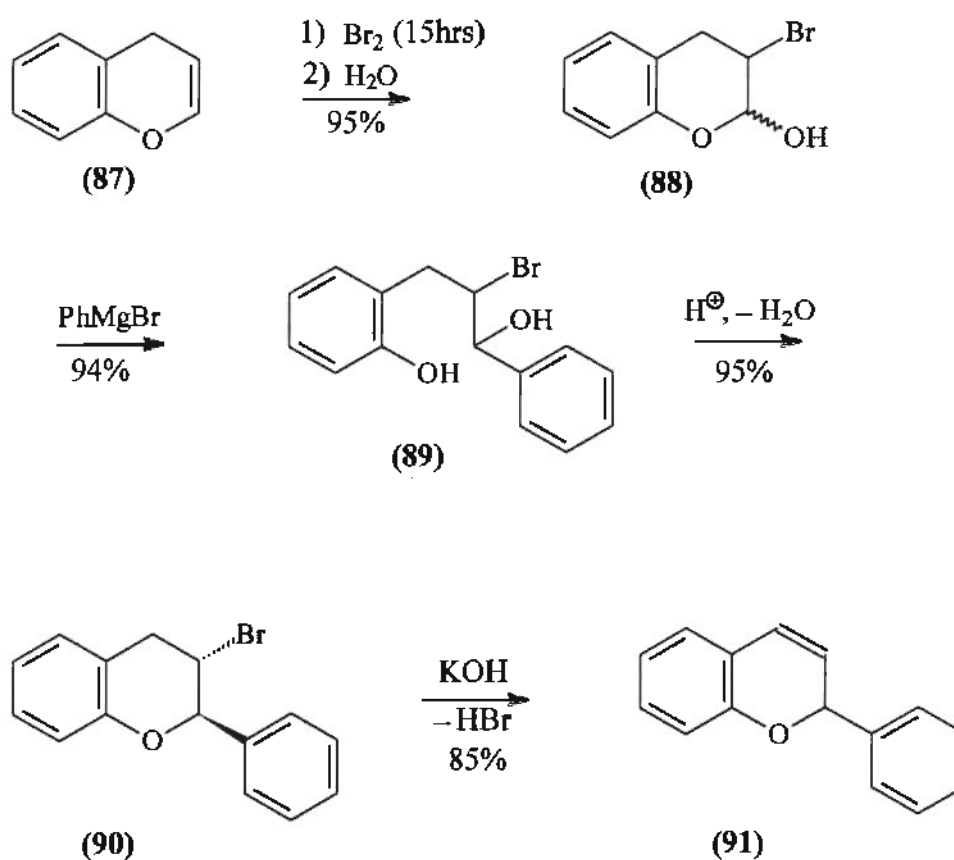Compound (87) is readily prepared by Maitte's procedure.[69] The mixture of isomeric bromohydrin (88) obtained from (87), reacts with phenyl magnesium bromide to give 2-bromo-1-hydroxy-3-(2-hydroxyphenyl)-1-phenylpropane (89) in good yield.

Heating of (89) with p-toluene sulphonic acid in toluene produces *trans*-3-bromoflavan (90), which is converted into the Δ^3-flavene (91) by treatment with methanolic potassium hydroxide.

Scheme 31 depicts a convenient preparative route to various substituted Δ^3-flavenes starting from Δ^2-chromene and substituted arylmagnesium halides.

Other methods for the preparation of flave-3-ene (**24**), include

i) the dehydration of o-cinnamoyl-phenol with 2,3-dichloro-5,6,dicyanobenzoquinone[71] and

ii) NaBH$_4$ reduction of 2'-hydroxychalcones[72] and subsequent treatment with formic acid.

1.9.3   SYNTHESIS OF FLAVANONES

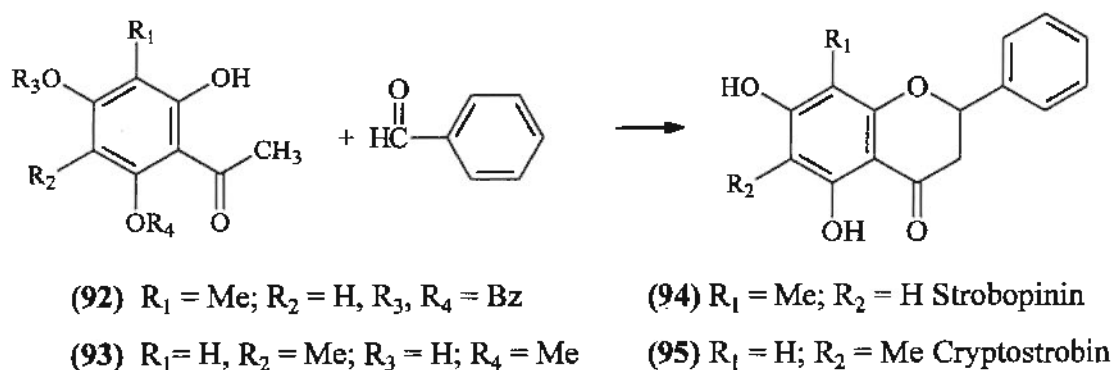Flavanones are obtained from chalcones by acid- or alkali-catalysed ring closure.

Ring closure is favoured by an OH group in position 6' of the chalcone and generally by the presence of a phloroglucinol structure. Zemplen *et al.*[73] reported a spontaneous cyclisation of 2',6'-dihydroxy-3',4'-dimethoxychalcone to dimethylisocarthamidin simply by the adjusting of the solution to pH=2. On the other hand, flavanones substituted at position 8 are difficult to prepare and require more harsh reaction conditions; e.g. the preparation of 5,6,7,8,4'-pentamethoxyflavanone from 2'-hydroxy-3,4,5,6,4'-pentamethoxychalcone required 30 hrs boiling with concentrated sulphuric acid. In most cases, however, the isomerization requires 1-2% acid or alkali with or without heating.

Debenzylation and partial demethylation may be achieved during the cyclization process with hydrobromic acid in glacial acetic acid as shown in **Scheme 32**.
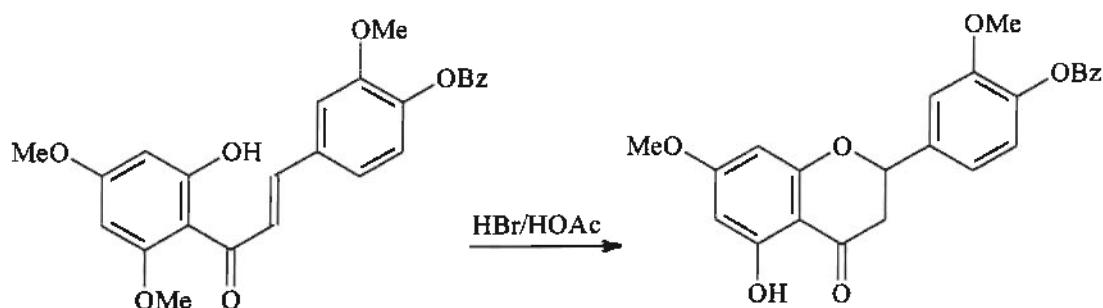
Scheme 32

The C-methylflavanones,[27] strobopinin(**94**) and cryptostrobin(**95**) are synthesised in one step (**Scheme 33**) by condensation of 2-hydroxy acetophenone derivatives (**92**) and (**93**) with benzaldehyde in ethanolic potassium hydroxide, followed by cleavage of the protecting groups.


(**92**) R_1 = Me; R_2 = H, R_3, R_4 = Bz   (**94**) R_1 = Me; R_2 = H Strobopinin

(**93**) R_1= H, R_2 = Me; R_3 = H; R_4 = Me   (**95**) R_1 = H; R_2 = Me Cryptostrobin

1.9.4 SYNTHESIS OF FLAVONES.

### 1.9.4.1 By Dehydrogenation of Chalcones and Flavanones.

The conversion of a chalcone into a flavone involves the addition of bromine across the double bond, followed by treating with alcoholic potash.[74] This procedure has undergone many modifications. For example in the synthesis of cirsimaritin[74](**99**), chalcone (**96**) is brominated to produce the α,β-dibromochalcone (**97**), which is then boiled with

methanol to produce the β-methoxy-α-bromochalcone **(98)**. **(98)** is converted into cirsimaritin **(99)** by thermal cyclization with simultaneous partial demethylation. **(Scheme 34)**.

(96)   **(97)**

(99) Cirsimartin   **(98)**
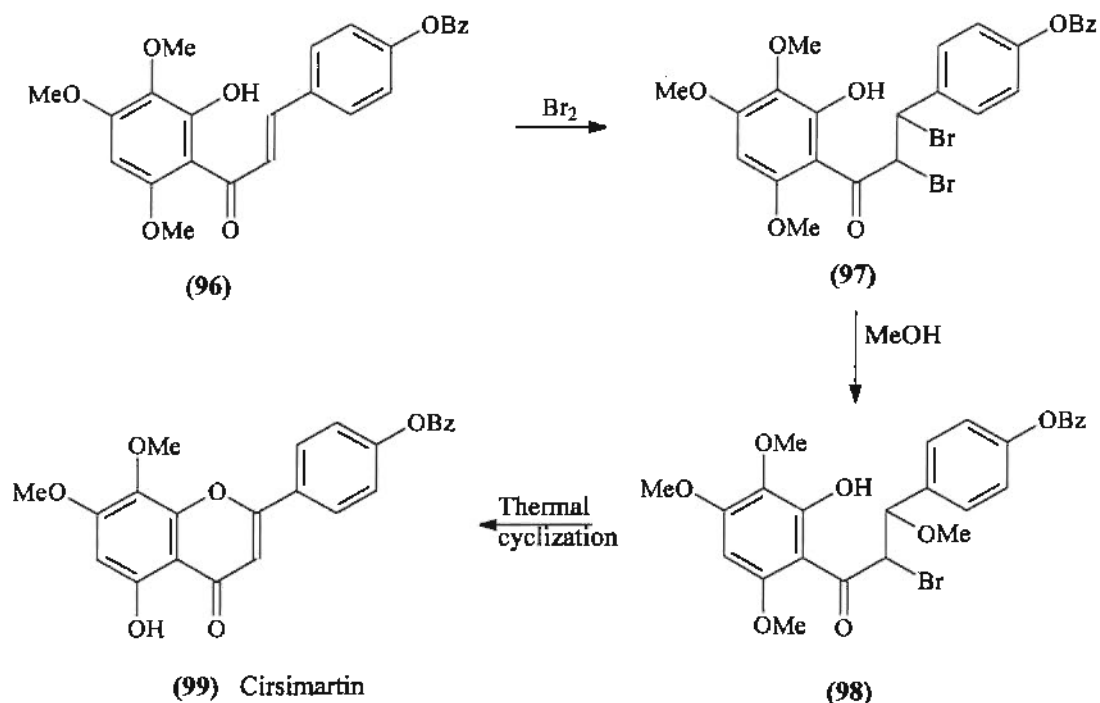
Scheme 34

The flavone Apigenin **(101)** is formed by dehydrogenation of the Havanone naringenin **(100)**[74] **(Scheme 5)**. The dehydrogenation involves a benzoyl peroxide-catalysed bromination of the flavanone **(100)** with 1 mol of N-bromosuccinimide in carbon tetrachloride, followed by acid hydrolysis.


(100) naringenin   **(101)** Apigenin
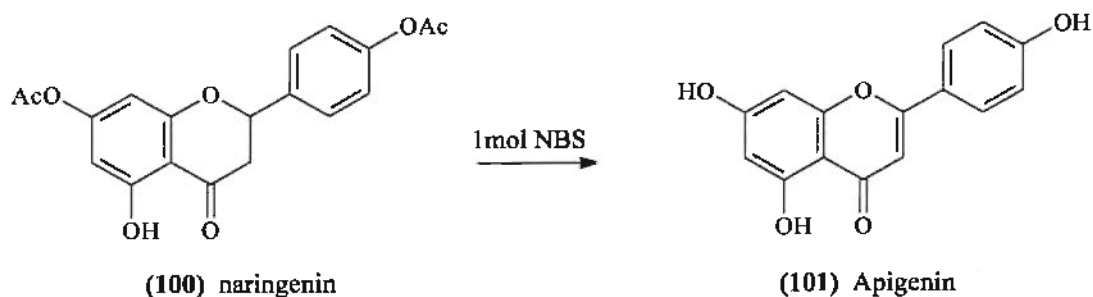
Scheme 35

Dehydration with selenium dioxide[74] has also been used for the synthesis of a number of flavones from their corresponding flavanones.

1.9.4.2 By Baker-Venkataraman Rearrangement.[74]

This method involves acylation of o-hydroxyacetophenones (102) with aromatic acid chlorides in acetone-potassium carbonate or pyridine. The resulting esters (103) are converted into diketones (105) with potassium hydroxide in pyridine. Ring closure is performed by treatment of the diketones (105) with acid which affords a 2-hydroxy-flavanone (106) which dehydrates to the flavone (107) (Scheme 36).
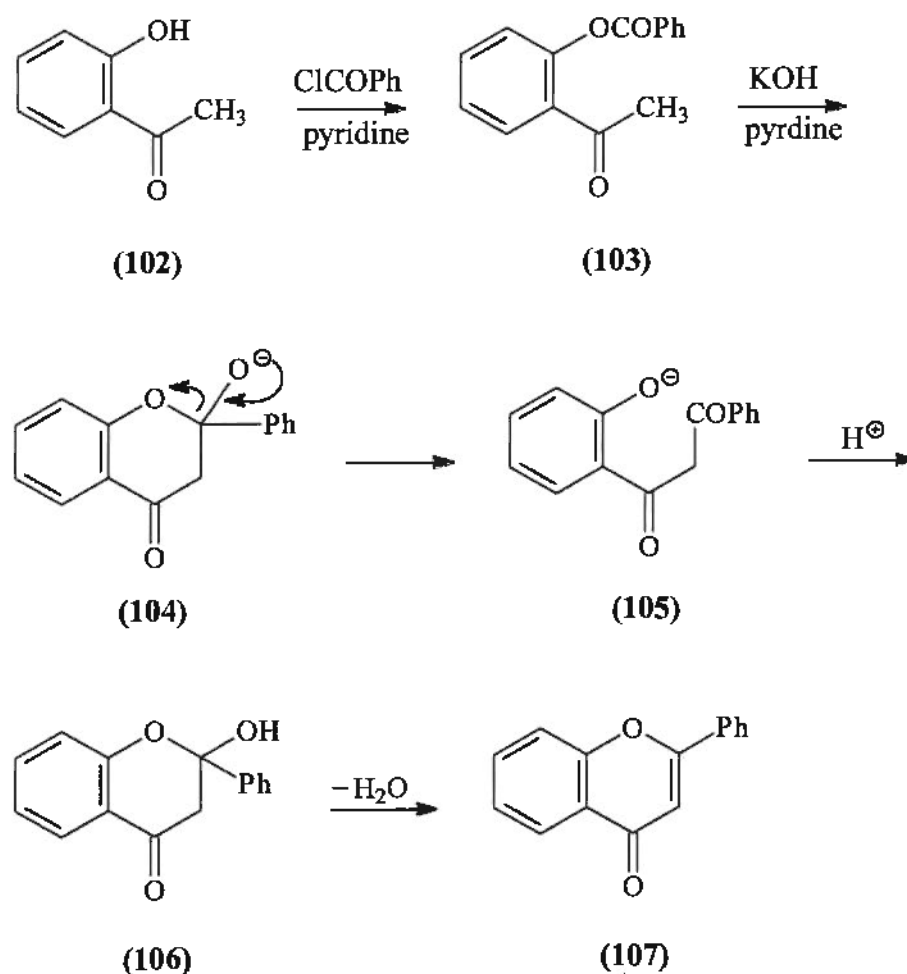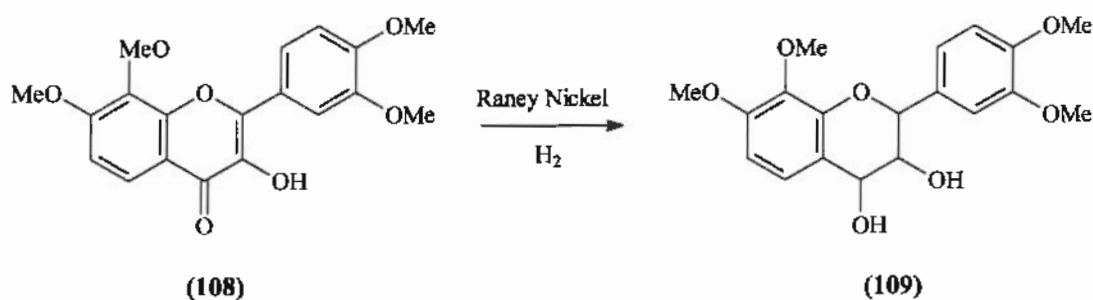

Scheme 36

1.9.5 SYNTHESIS OF FLAVAN-3,4-DIOL[75] LEUCOANTHOCYANIDINS

These compounds are sometimes accessible by reduction of flavonols, and can usually be obtained from dihydroflavonols as these are more easily reduced than the flavonols. The former method provides a route to 2,3-*cis*-3,4-cis diols, whereas the latter can yield both 3,4-*cis*- and 3,4-*trans*-diols which will usually be 2,3-*trans* compounds because this is the more stable configuration of the dihydroflavonols.

1.9.5.1 Flavan-3,4-diols from flavonols.

The synthesis of (1)-melocacidintetramethylether **(109)** involves the catalytic hydrogenation of 7:8:3':4'-tetramethoxyflavonol **(108)** in ethanol of Raney nickel at 100°C and 100 atm. **(Scheme 7)**. This gave the first crystalline synthetic leucoanthocyanidin, 7,8,3',4'-tetramethoxyflavan-3,4-diol **(109)**, a methoxylated derivative of the parent flavan-3,4 diol. This leucoanthocyanidin **(109)** was shown to be a 2,3-*cis*-3,4-*cis* racemate.

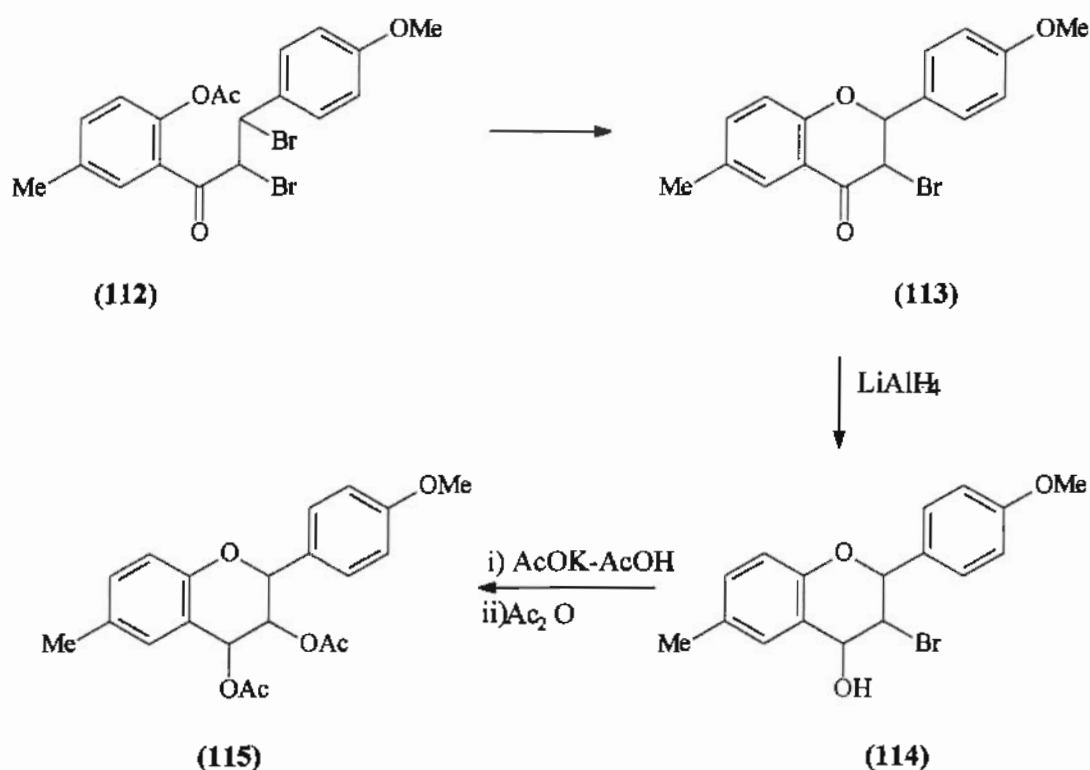**Scheme 7**

1.9.5.2 Flavon-3,4-diols from Dihydroflavonols

Dihydroquercetin **(110)** was converted by sodium borohydride into amorphous leucocyanidin **(111) (Scheme 8).**

(110)　　　　　　　　　　　　　　　**(111)**
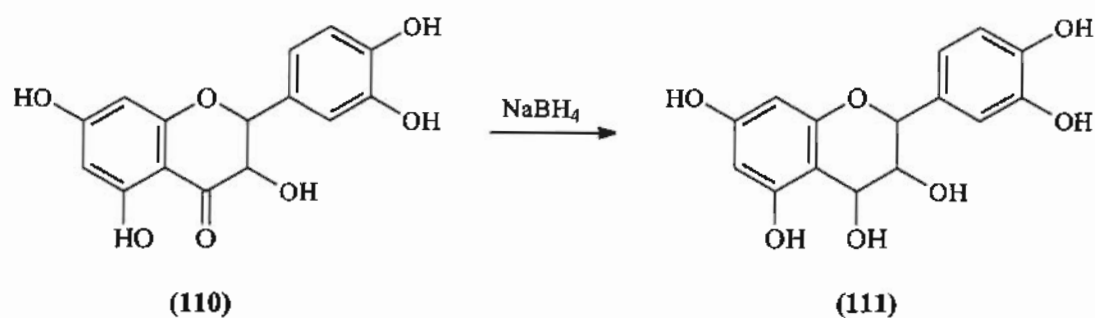
Scheme 38

1.9.5.3 Flavan-3,4-diols from 3-Bromoflavanones.

This method has been applied, to the synthesis of 4'-methoxy-6-methylflavan-3,4-diol. Cyclisation of the chalcone dibromide **(112)** in acetic acid gives the 3-bromoflavanone **(113)**, which is reduced with lithium aluminium hydride to the bromoflavonol **(114)** and this is converted with acetic anhydride-potassium acetate into 4'-methoxy-6-methylflavan-3,4 diol diacetate **(115) (Scheme 39).**
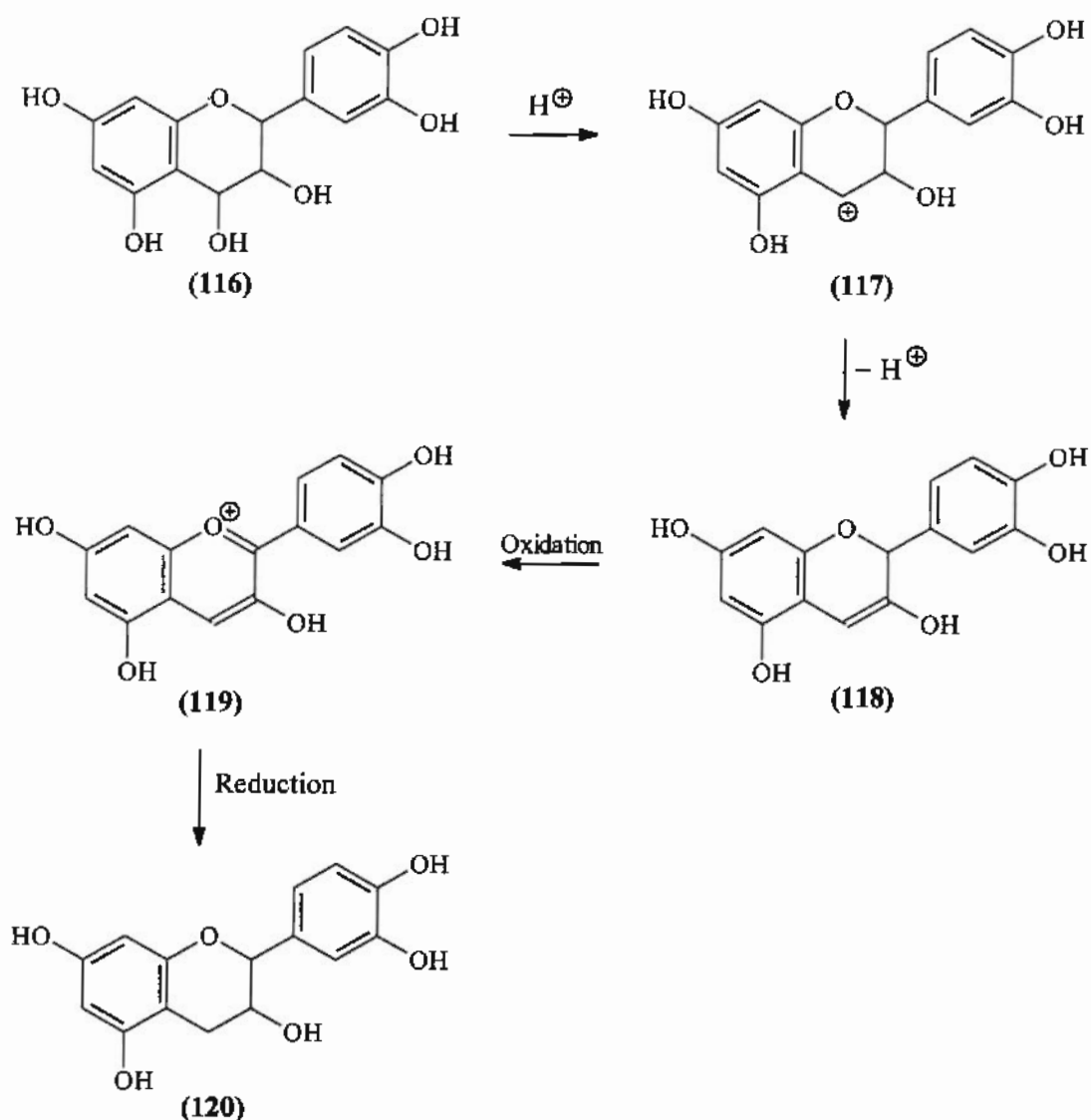
Scheme 39

1.9.6 SYNTHESIS OF FLAVAN-3-OLS[76] *VIA* FLAVAN 3,4 DIOLS.

1.9.6.1 Solvolysis of leucoanthocyanidins (flavan-3,4-diols).

The most characteristic chemical reaction of flavan-3,4 diols **(116)** is their partial (up to 50%) conversion with hot acid to the corresponding anthocyanidin **(119)**. The flavan-3,4-diol under acidic conditions is readily solvolysed to give the corresponding resonance-stabilised benzyl carbocation **(117)**. A dehydration then occurs to give the flav-3-ene-3-ol **(118)**, followed by aerial oxidation to give the anthocyanidin **(119)**. The anthocyanidin **(119)** can then be reduced[77] to the flavan-3-ol (catechin) **(120)** **(Scheme 40)**.

Scheme 40

An alternative synthesis is that of Weinges[78] which depends upon the reducibility first of dihydroflavonols to diols, then the diols to catechins. Flavonol **(121)** is reduced/hydrogenated to the 3,4-diol **(123)** via the dihydroflavonol **(122)**. The diol **(123)** is then hydrogenated in dioxane with Pd as the catalyst. This results in cleavage of the hydroxyl group to yield the flavan-3-ol **(124)** (catechin) **(Scheme 41).**
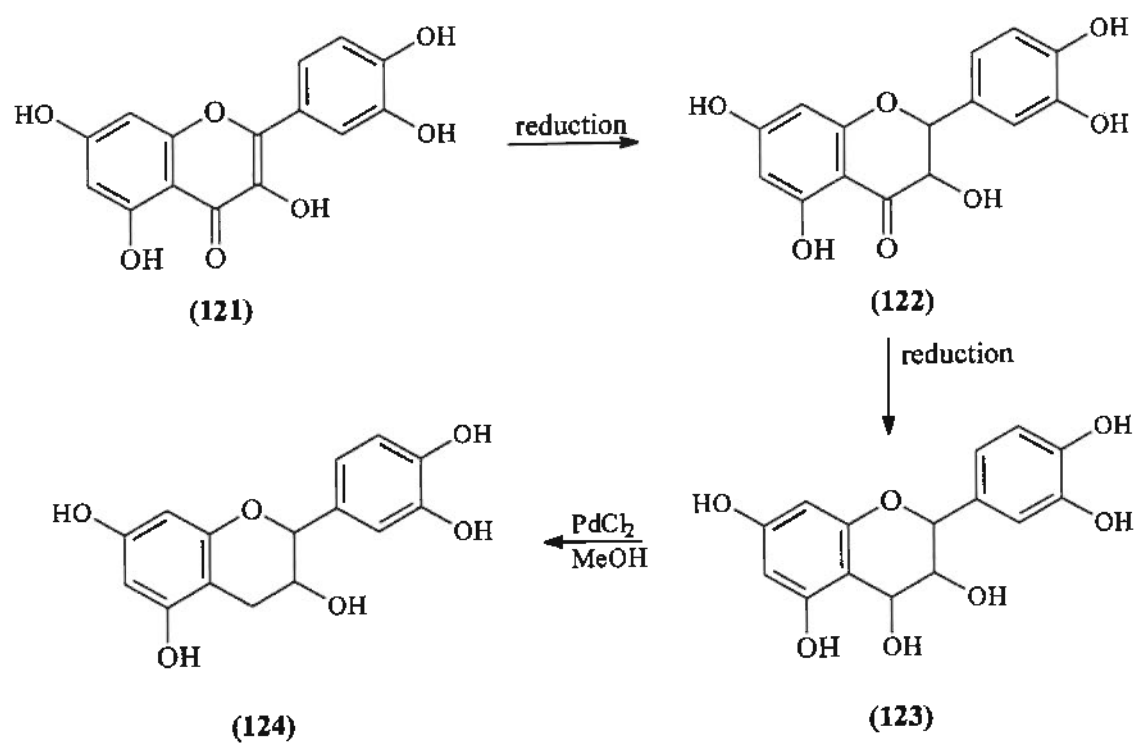
Scheme 41

CHAPTER 2 : DISCUSSION

In recent years research in our laboratories has been concentrated on the use of the carbamate functionality as a synthetic intermediate in organic synthesis. The carbamate moiety has enjoyed much success over the past few years in this field of organic chemistry. As pointed out earlier on, Van Rensberg[35] utilised the carbamate as an effective intermediate in the synthesis of chromenes and coumarins **(Scheme 23)** above.

The work reported herein describes and exemplifies three important and very effective properties of the carbamate functionality, which are described in detail in section 1.5:

1. The migrational ability of carbamates from vinylic to allylic alcohols.
2. The leaving-group ability of carbamates
3. The carbamate as a directing metalation group in directed *ortho*-metalation reactions.

Each of these properties by their individual standards deserve credit as effective tools in organic synthesis. However, when two or even all three of these properties are incorporated into a synthetic strategy, and operate consecutively in a single reaction, the combination proves to be a highly potent one, providing simpler and shorter methods towards the target molecules.

The primary aim of the project was to extend van Rensburg's work on the synthesis of chromenes and coumarins **(Scheme 23)** to the synthesis of the flav-3-ene **(91)**, utilising the migrational and leaving-group capability of the carbamate functionality.

As mentioned in section 1.9.1, there are two basic approaches employed to form a flavonoid skeleton. The approach described here **(Scheme 42)** involves the condensation of a C_6-C_2 unit (2-hydroxyacetophenone) with a C_6C_1 unit (aromatic aldehyde) (*i.e.*, Scheme A of section 1.9.1). The synthetic strategy set forward, incoporating the migrational and leaving group capability of the carbamate functionality for the synthesis of flav-3-ene **(91)** is shown in below **(Scheme 42)**
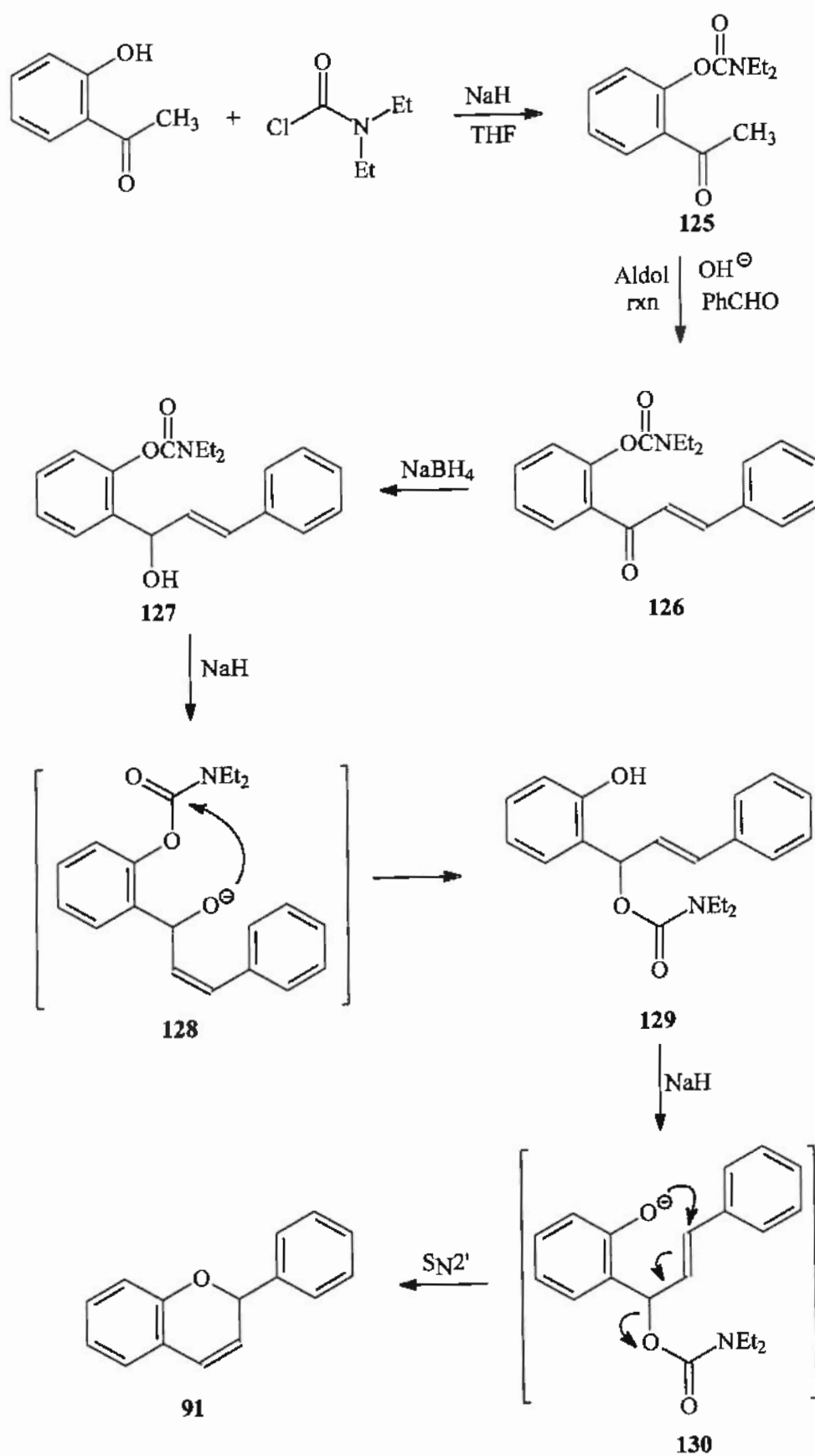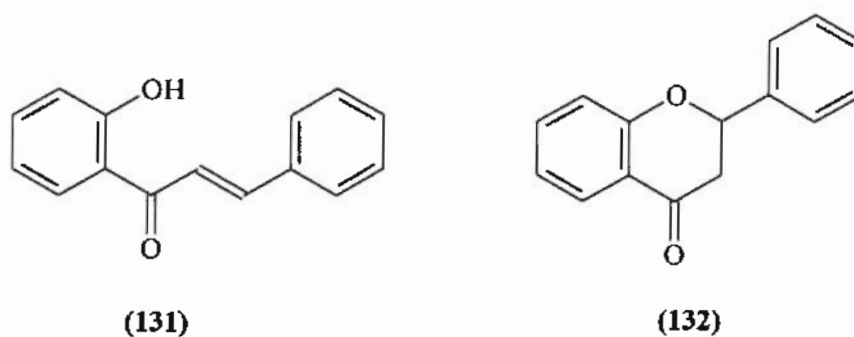
Scheme 42

2-Hydroxyacetophenone provides a suitable vinylic alcohol to form the carbamate (125) by reacting it under basic conditions with N,N-diethylcarbamoylchloride. The carbonyl of the acyl group is also ideally positioned for a potential allylic alcohol for the carbamate to migrate to. We envisaged that the allylic alcohol (127) could be obtained by reducing the carbonyl of the α,β-unsaturated system (126) which could be obtained by an aldol reaction on carbamate (125) with benzaldehyle under basic condition. Deliberate abstraction of the hydroxyl proton of the allylic alcohol (127) using a suitable base would result in the intramolecular migration of the amide portion of the carbamate *via* a favourable six-membered transition state (128). This would afford the allylic carbamate (129), where abstraction of the acidic phenol proton would provide a phenoxide anion (130) which would attack the olefinic system and eliminate the carbamate in an S_N2' reaction to afford the flav-3-ene (91).

The reason for choosing the N,N-diethyl substituted carbamoylchloride can be rationalised in terms of its favourable properties. Hoppe[43] reported that N,N-diethyl carbamate esters are not attacked by n-BuLi as a result of the carbonyl group being sufficiently sterically blocked. Also the greater inductive effect of the ethyl groups compared to methyl groups, would render the carbonyl less electrophilic and hence less susceptible to attack by n-BuLi.

2.1   SYNTHESIS OF FLAV-3-ENE (91)

2-Hydroxyacetophenone was treated with NaH and diethylcarbamoyl chloride in THF to yield the carbamate (125) (Scheme 42) in a good yield (78%). In an attempt to prepare (126), the carbamate (125) was treated with potassium hydroxide and benzaldehyde in ethanol. This, however, did not result in the expected product (126). Instead, this reaction yielded the chalcone (131) and the flavanone (132).

(131)   **(132)**

From the formation of these products it is clear that the carbamate is not stable to potassium hydroxide. It is evident that the aldol condensation does proceed, but so does the base hydrolysis of the carbamate **(Scheme 43)**. It is not known whether the carbamate is cleaved prior to the alcohol condensation or *vice versa*.


(133)

$$Et_2NCOO^{\ominus} \xrightarrow{H_2O} CO_2 + Et_2NH$$
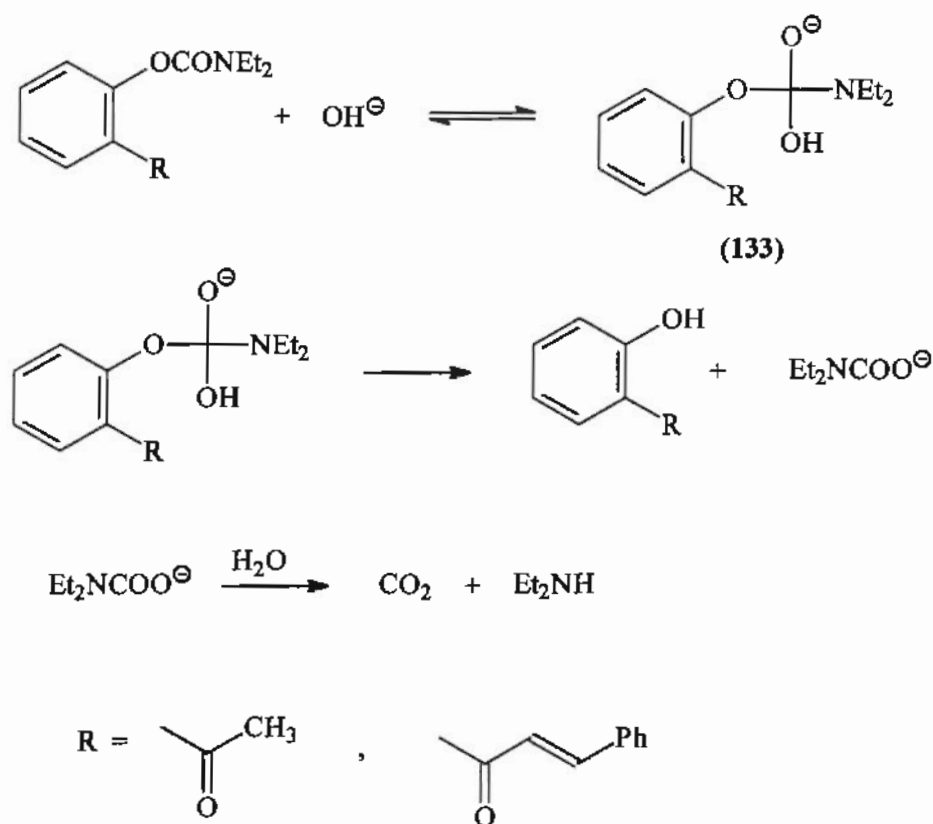
Scheme 43

The hydroxide ion attacks the carbonyl carbon of the carbamate to yield an unstable tetrahedral intermediate **(133)** which collapses to an alcohol and a carbamate ion, which

picks up a proton from water and spontaneously decomposes to diethylamine and carbon dioxide.

The flavanone **(132)** forms by cyclisation of the chalcone **(131)** when the acidic hydroxyl proton is deprotonated by the potassium hydroxide present in the reaction mixture as shown below **(Scheme 44)**


(131)

KOH

1,4 addition

(132)
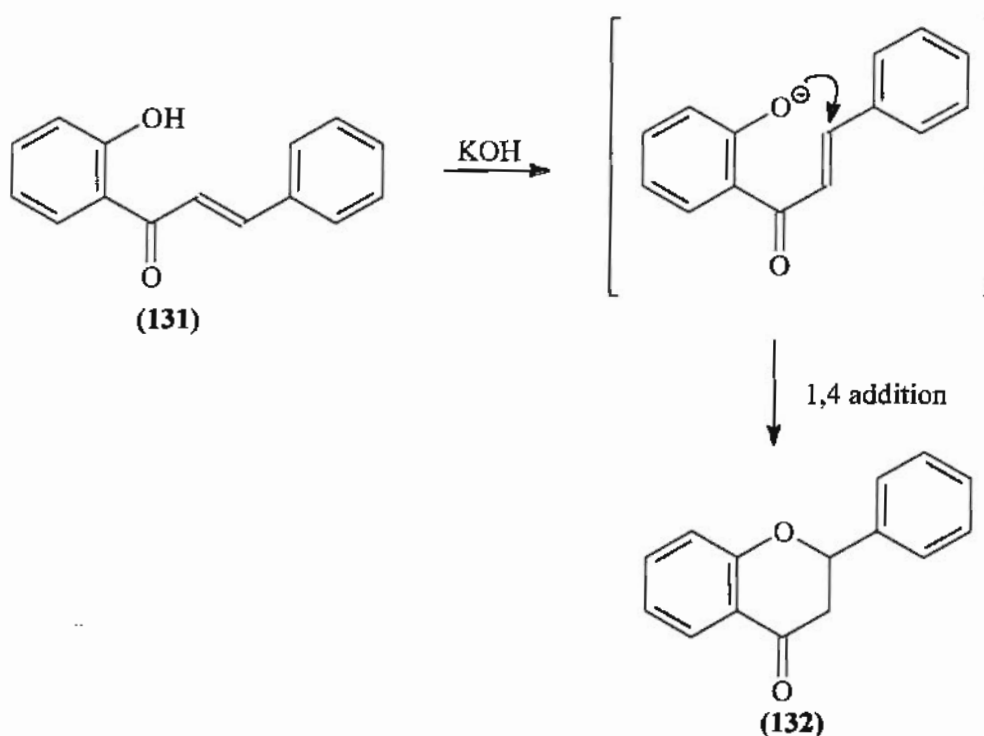
Scheme 44

When 2-hydroxyacetophenone was treated with potassium hydroxide and benzaldehyde a considerably higher yield (22%) of the flavanone **(132)** was obtained.

Since the carbamate is not stable under basic conditions it then seemed logical to attempt an acid-catalysed aldol condensation. Carbamates have been known to be more stable and hydrolyse only very slowly in acid solution.

Carbamate (125) was then treated with hydrochloric acid gas and benzaldehyde and the carbamate (126) was obtained in good yield (Scheme 45). The carbamate functionality was hydrolysed, but only to a very small extent, resulting in the isolation of a mere 1,2% of the hydrolysed product, chalcone (131).
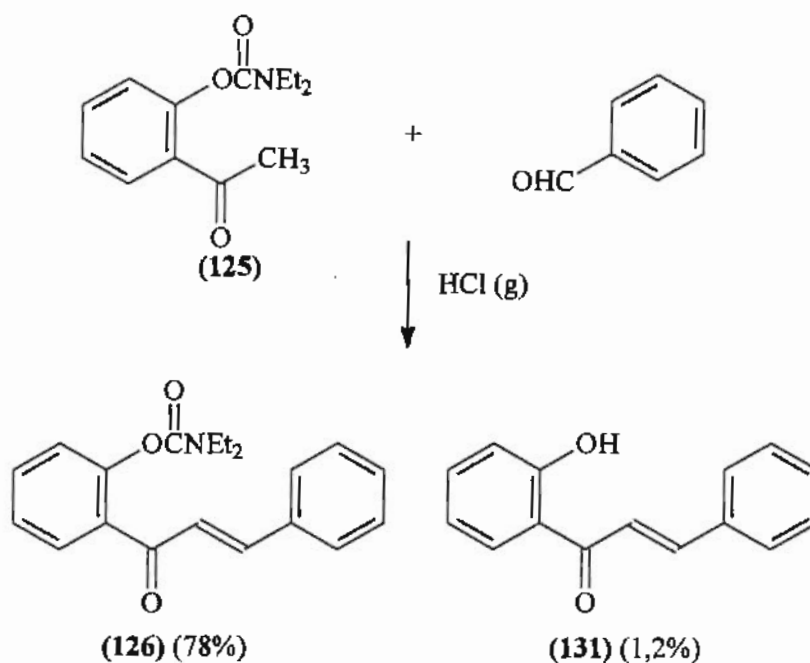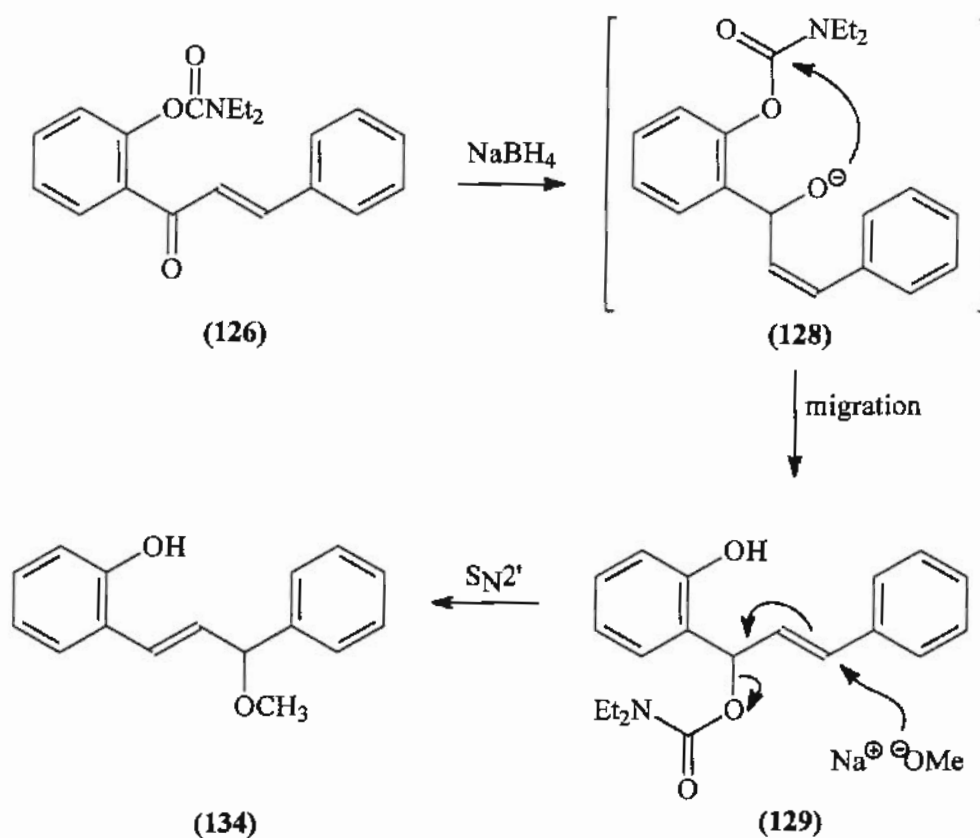

Scheme 45

The next step in the synthesis involved the reduction of the α,β-unsaturated ketone (126) to the allylic alcohol (127). The reducing agent chosen was NaBH₄, due to its mediocre reducing power to avoid reduction of the double bond. Ketone (126) was thus treated with NaBH₄ in methanol and the reaction quenched with sodium hydroxide to afford two compounds, allylic alcohol (127) and a methoxy-substituted product (134) (Scheme 46).
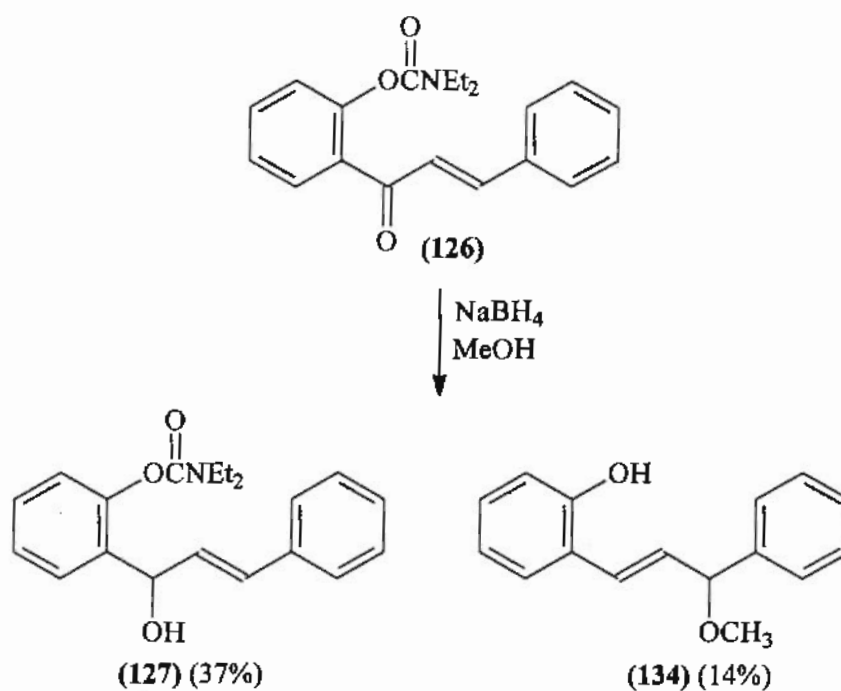
Scheme 46

The experimental procedure provided an insight into the formation of the methoxy-substituted product **(134)**. The course of the reaction was monitored using TLC. This showed the formation of only a single product (the allylic alcohol **(127)**) until all of the ketone **(126)** was consumed. After the reaction was quenched with sodium hydroxide and worked-up, TLC revealed the formation of a second product, *i.e.*, **(134)**. A mechanism for the formation of **(134)** is outlined below **(Scheme 47)**

Scheme 47

It seems that once the ketone **(126)** has been reduced to the allylic alcohol, the amide portion of the carbamate migrates to the allylic position *via* the favourable six-membered transition state **(128)** to form the allylic carbamate **(129)**. The driving force could be the formation of the thermodynamically more stable phenoxide anion. This could have been expected since the reaction was carried out 0 °C and migrations of carbamates have been reported at temperatures as low as -28 °C.[35] The addition of sodium hydroxide resulted in the formation of sodium methoxide by deprotonation of the methanol. The sodium methoxide then attacked the benzyl carbon of the olefin, eliminating the carbamate in an S_N2' reaction to afford the methoxy-substituted product **(134)**.

The final step in the synthesis involved the deprotonation of the allylic alcohol **(127)**, with NaH which resulted in an average yield (53%) of the flav-3-ene **(91)**. The mechanism of the reaction is shown below **(Scheme 48)**
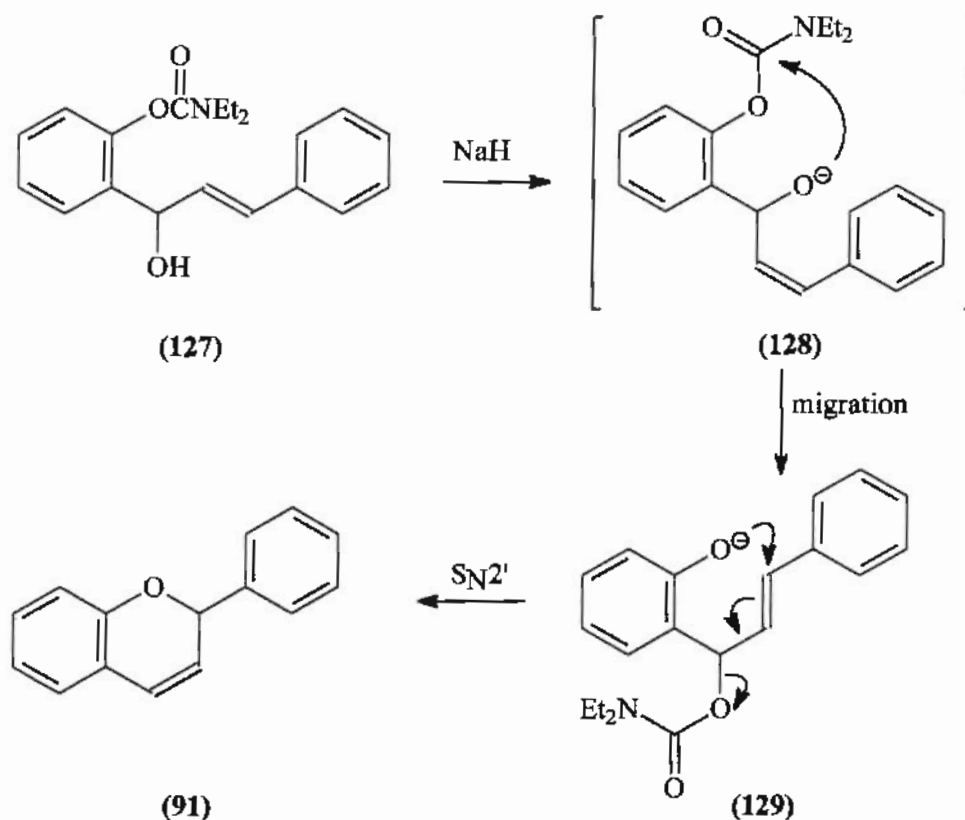
Scheme 48

As expected, deprotonation of the acidic hydroxyl proton of the allylic alcohol **(127)** resulted in the migration of the amide portion of the carbonate *via* the favourable six-membered transition state **(128)** to afford the allylic carbamate **(129)**. The isolation of the allylic carbamate **(129)** was not necessary since the phenoxide ion spontaneously attacks the benzylic carbon of the double bond and eliminates the carbamate in an S_N2' reaction to afford the flav-3-ene **(91)**.

2.1.1   THE SHORTENED SYNTHESIS OF THE FLAV-3-ENE (91).

A side reaction, such as the one observed in the reduction of ketone **(126)** to the allylic alcohol **(127)** **(Scheme 46)**, (*i.e.*, the formation of the methoxy-substituted product **(134)**), is often perceived as being a negative factor in a reaction.

The isolation of the methoxy substituted product **(134)** in this reaction, however, proved to be a positive factor, in the sense that it gave insight into an idea to provide a shorter, more effective synthesis towards the flav-3-ene **(91)**. The formation of the methoxy-substituted product **(134)** suggests that the amide portion of the carbamate does in fact migrate during the reduction step, and provided that the reaction mixture is subjected to harsher reaction conditions, the phenoxide ion rather than methoxide ion would attack the benzylic carbon of the double bond and eliminate the carbamate in an S_N2' fashion to afford the flav-3-ene **(91)** without the isolation of the allylic alcohol. This would shorten the synthesis by a single step and also eliminate isolating the unstable allylic alcohol **(127)**.

The reduction was then attempted in the usual way at 0^0C without isolation of the allylic alcohol **(127)**. Instead the reaction mixture was refluxed for 12 hrs and this did indeed result in the formation of the flav-3-ene in a good yield (68%) **(Scheme 49)** This method resulted in only a small yield of the methoxy-substituted product **(134)**.
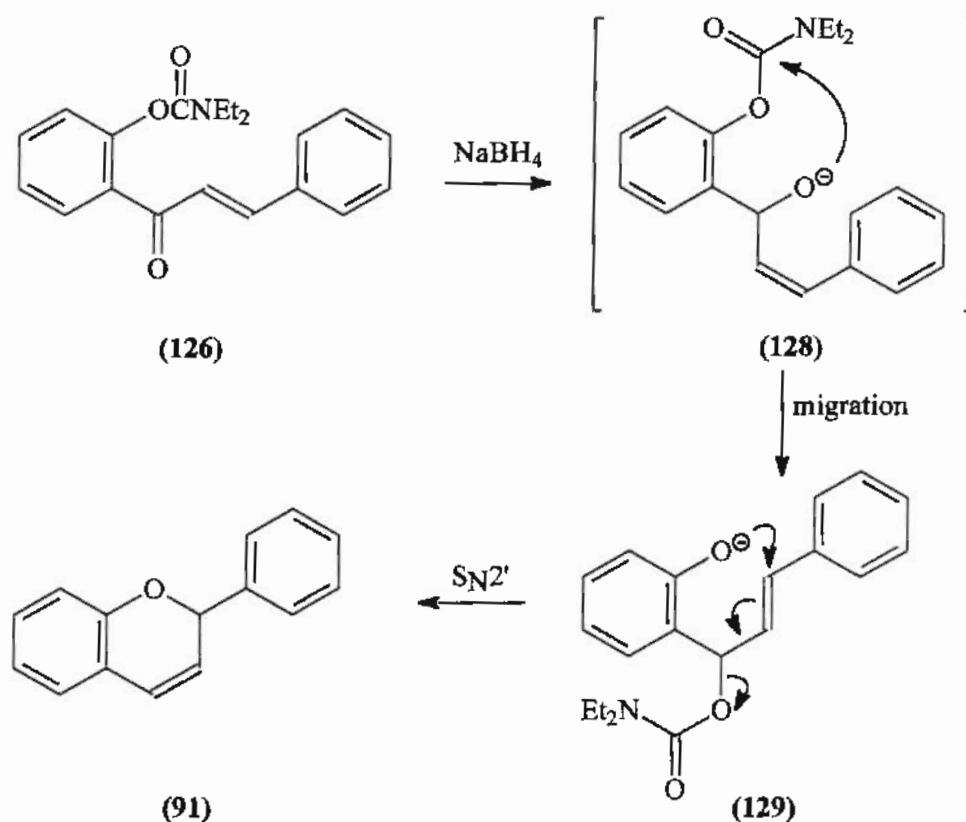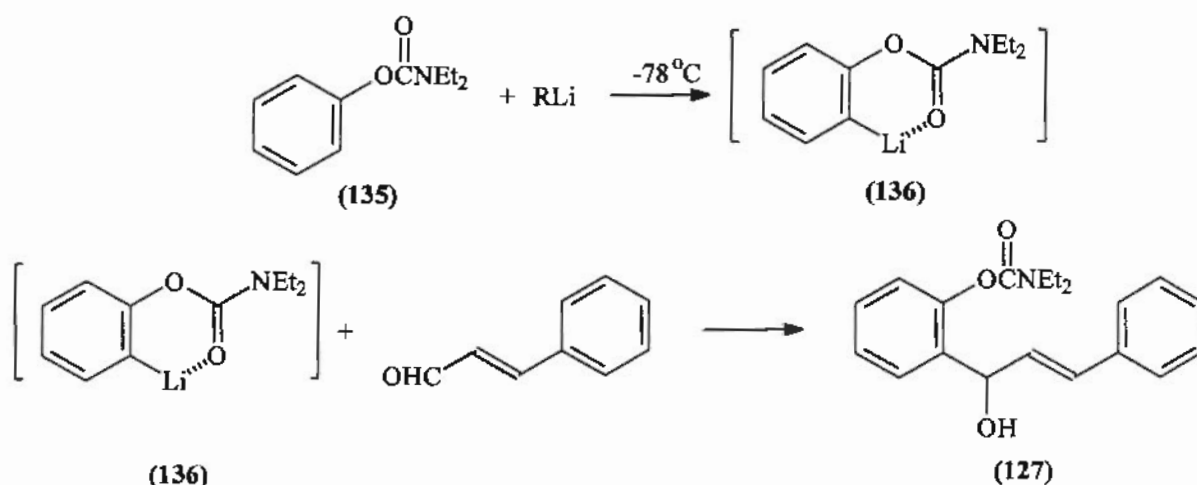
Scheme 49

The method provided an overall higher yield of the flav-3-ene (91). In going from the ketone (126) via the isolation of the allylic alcohol (127) the flav-3-en was obtained in an overall (30%) yield. However, the direct method outlined above (**Scheme 49**) yielded 68% of the flav-3-ene (91).

This reaction (**Scheme 49**) exemplifies the power of the carbamate as an intermediate in organic synthesis. The reaction depicts two properties of the carbamate, *i.e.*, the migrational and the leaving ability of the carbamate, being incoporated into a single reaction, providing a shorter method with a higher yield of the product.

2.1.2 A ONE-POT SYNTHESIS OF THE FLAV-3-ENE (91)

In an attempt to provide an even shorter synthesis of the flav-3-ene (91) than the one outlined in section 2.1.1, we envisaged that the exploitation of the carbamate moiety as a good directing metalation group would assist us in accomplishing this task. We envisaged that the treatment of 1-phenyl-N,N-diethyl carbamate (135) with an alkyllithium base followed by treatment with cinnamaldehyde would result in the formation of the allylic alcohol (127) in a single step (Scheme 50).

The reaction would proceed *via* the carbamate-stabilised *ortho*-lithiated complex (136).

Scheme 50

Since the allylic alcohol (127) would exist as the lithium salt in solution prior to quenching, it would be possible that the amide portion of the carbonate would migrate and the product even cyclise to form the flav-3-ene (91) in a single step.

The carbamate (135) was thus treated with sec-butyllithium at -78 °C, followed by the addition of cinnamaldehyde. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The reaction did indeed result in the isolation of the flav-3-ene (91), unfortunately in a low yield of 10%, while cinnamyl alcohol (67%) was isolated as the major product. (Scheme 51)
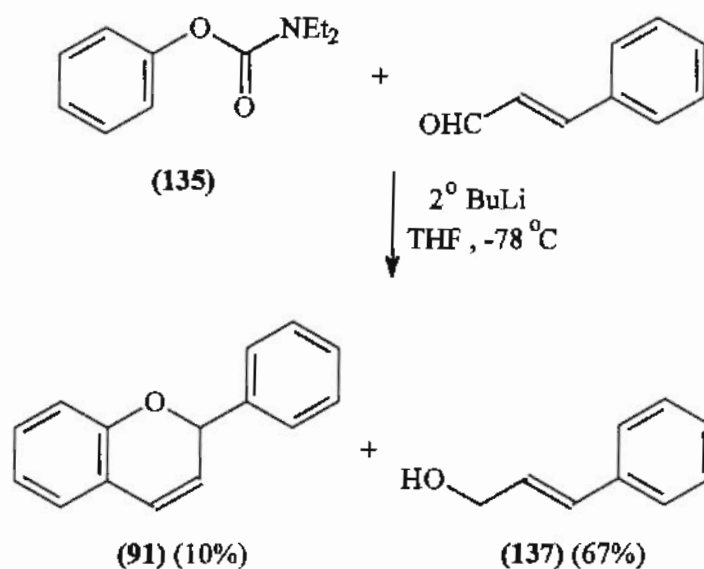
Scheme 51

The reaction classically demonstrates the incoporation of all three properties of the carbamate, *i.e.*, the migration, the leaving group as well as ortho-directing ability of the carbamate functionality, operating simultaneously to provide a convenient one-pot synthesis of the flav-3-ene **(91)**, albeit in poor yield.

The formation of the cinnamyl alcohol is rationalised below **(Scheme 52)**.
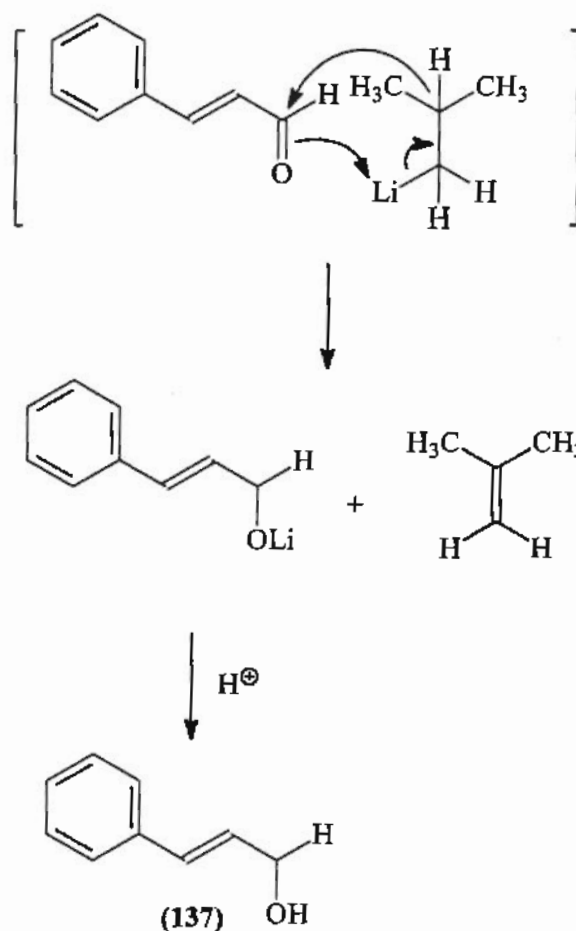
Scheme 52

The carbonyl group of the cinnamaldehyde is attacked by the sec-butyllithium in a concerted way, resulting in the formation of 2-methyl-prop-1-ene and the lithium salt of cinnamyl alcohol which is quenched to form the cinnamyl alcohol (137). It is not known why the sec-butyllithium does not react with the cinnamaldehyde in a 1,2- or 1,4-addition reaction, since neither of these electrophilic centres is sterically hindered.

Due to the poor yield obtained for the flav-3-ene (91), this approach was no longer pursued.

2.1.3 THE SYNTHESIS OF 2-CINNAMYL- 2H-1-BENZOPYRAN.

The approach outlined in section 2.1.1 was pursued and repeated using cinnamaldehyde instead of benzaldehyde in the aldol condensation (**Scheme 53**).
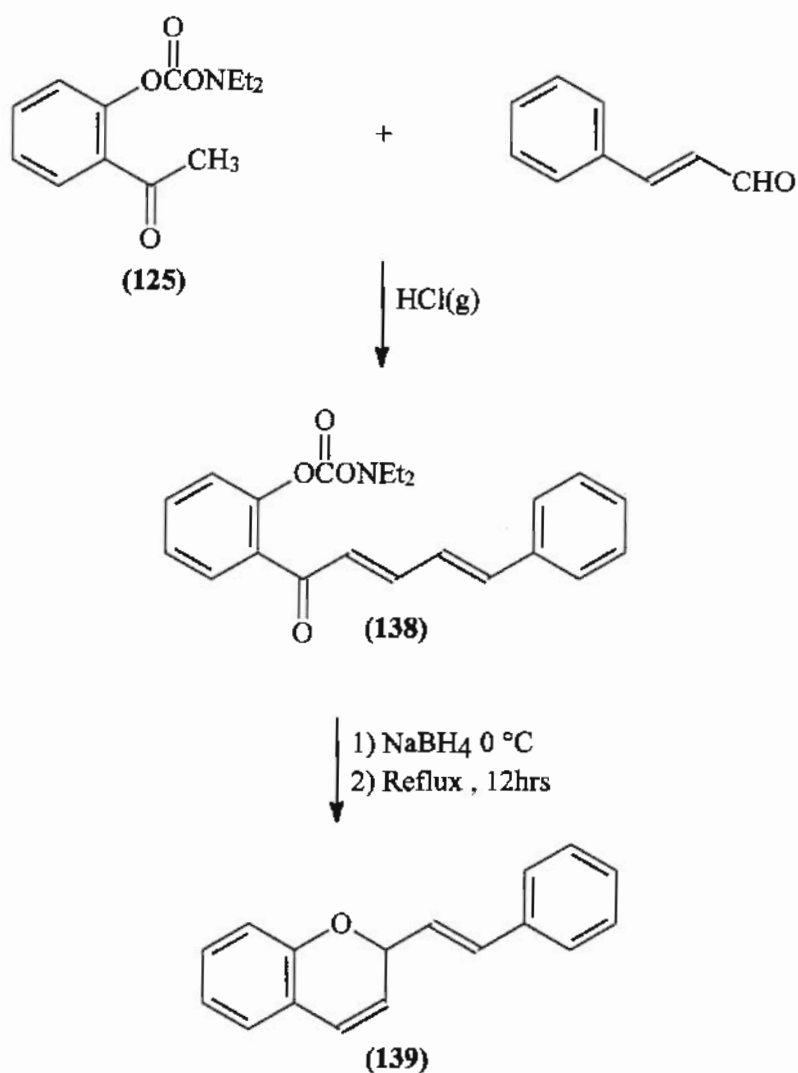
Scheme 53

Carbamate (125) was thus treated with cinnamaldehyde and gaseous HCl to afford the ketone (138). The ketone (138) was treated with NaBH₄ followed by reflux to afford the "flavonoid" type compound (139) with the extended conjugated side chain.

2.1.3.1 The "identification" of 1-(*o*-N,N-diethylcarbamoyloxyphenyl)-5-phenyl-2,4-pentadiene-1-one **(138)**.

(138)
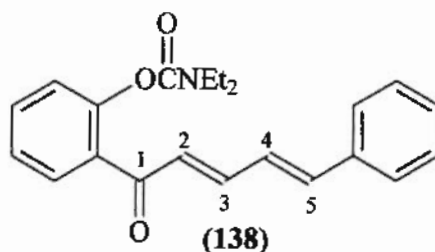
^{1}H NMR, ^{13}C NMR, HETCOR and COSY spectra were obtained for the compound **(138)** in $CDCl_3$ as well as C_6D_6. A large variation in proton shifts, carbon shifts and splitting patterns were observed in moving from $CDCl_3$ to C_6D_6. The spectra obtained in d-chloroform revealed inconclusive proton correlations in the COSY spectrum. One of the vinyl protons was also located beneath the clump of aromatic protons which provided further difficulties in the assignment. The spectra obtained in d-benzene however showed explicit splitting patterns of the vinyl protons as well as the removal of the vinyl proton from beneath the aromatic region, that was observed in the spectrum in d-chloroform. The ^{13}C spectrum (in d-benzene) however, resulted in a large change in shift of a vinyl carbon from what was observed in the spectrum in d-chloroform. This as well seems inconclusive since one would expect the d-benzene to have an effect on the proton and not to any great extent on the carbons, at least not as great as the one observed in this instance. These findings are discussed below.

The spectrum obtained in d-chloroform **(Spectrum 1)**

(Spectrum 1) shows the enlarged region where the aromatic and vinylic protons are found. NOE experiments confirmed that the upfield doublet at 6.6ppm-6.7ppm belongs to the benzylic-vinylic proton H_5. The COSY spectrum clearly showed coupling of this doublet to the vinylic proton beneath the aromatic region marked **z**, which logically is assigned to H_4. This then leaves the assignment of protons H_2 and H_3 to either of the signals marked **x** or **y**. One would expect the other terminal proton of the diene chain, *i.e* H_2 to be a doublet similar to H_5 or perhaps a doublet with some fine long-range splitting.

H_2 cannot be assigned to either **x** or **y** since **x** is an overlapping doublet of doublets with large coupling constants and **y** is also a doublet of doublets with large coupling constants. These coupling constants are not consistent with long range coupling, hence H_2 could not be assigned with any certainty using these spectra.

The spectrum obtained in d-benzene **(Spectrum 2)**

It is noteworthy that the resolution is increased to such a great extent in moving from d-chloroform to d-benzene. It is also worth mentioning that the vinylic proton that was hidden in the aromatic region is now far enough removed from the aromatic clump, which enables a more concise assignment to the proton.

It was assumed that the doublet at 6.5ppm-6.6ppm corresponds to H_5, as was observed in the spectrum with d-chloroform. The COSY spectrum now clearly shows correlation of this doublet with the doublet of doublets (J=15.63 Hz, J=10.74 Hz) (with fine long range splitting J=0.73 Hz) marked **(x)**. **(x)** would then be assigned to H_4. The doublet (J=15.36 Hz) (with long range splitting J=0.68 Hz) marked **(y)** would then be assigned to the terminal proton H_2. This is consistent with the splitting pattern that one would expect to find for the proton H_2. Finally H_3 is assigned to the doublet of doublets (J=15.30 Hz, J=10.35 Hz) downfield marked **(z)**. This proton (H_3) clearly shows correlation, in the COSY to protons H_2 and H_3 marked **(y)** and **(x)** respectively.

The only shortcoming concerning the spectrum in d-benzene is the great change in chemical shift observed for the carbon correlating with H_5. The carbon correlating to H_5 in the spectrum in d-chloroform occurs at a shift of 129.30ppm, whereas, in d-benzene the shift changes to 141.81ppm. This large discrepancy in the carbon shift created much doubt about the assignment of carbon correlating to H_5. A possible explanation for this is that the up-field doublet in spectrum **2**, is not proton H_5, but perhaps H_2. Further experiments are being conducted to investigate the effect of the benzene on the carbon shifts. The compound **(138)** has at this stage not been fully characterised.
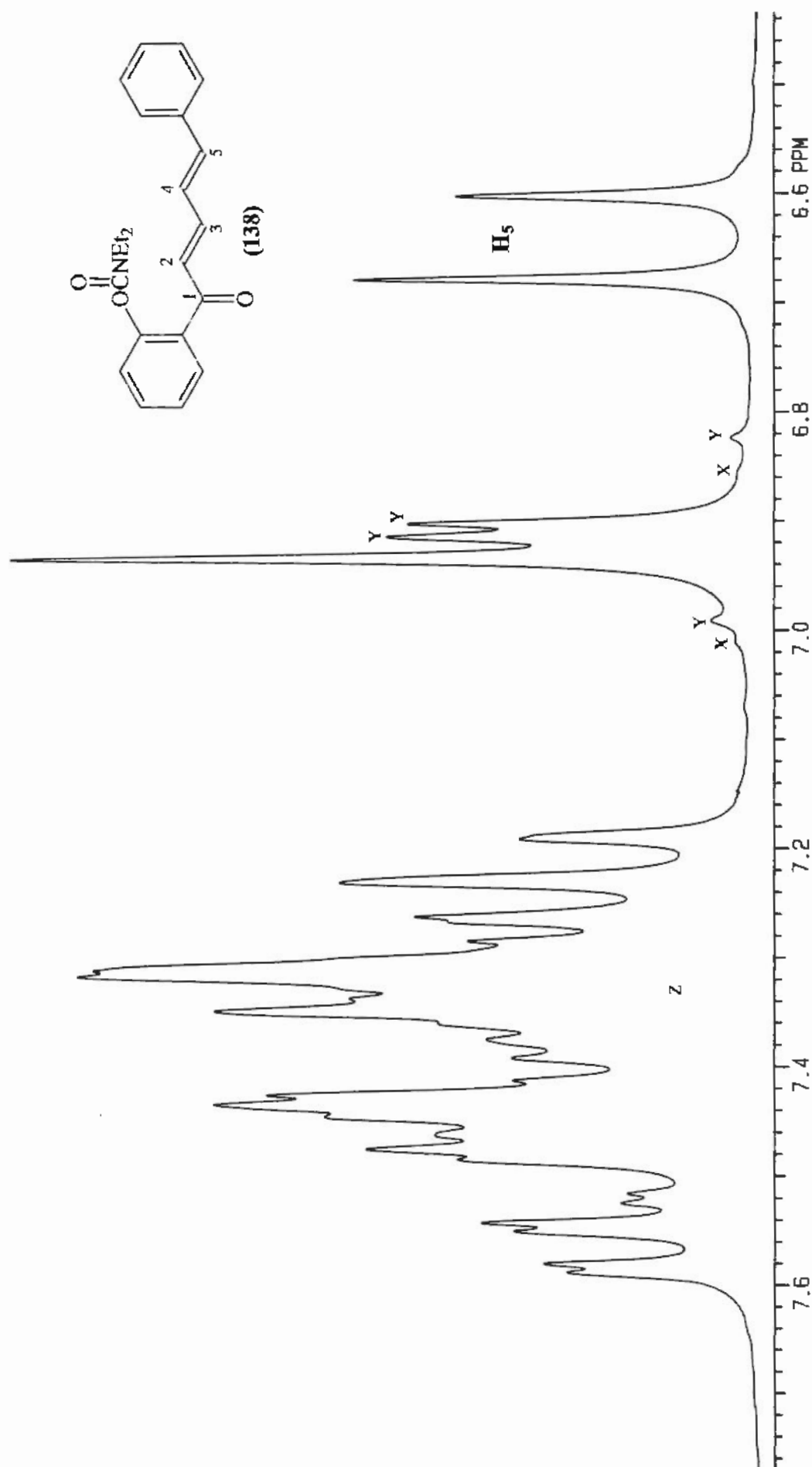
Spectrum 1. (138) in d-Chloroform

Spectrum 2. (138) in d-Benzene
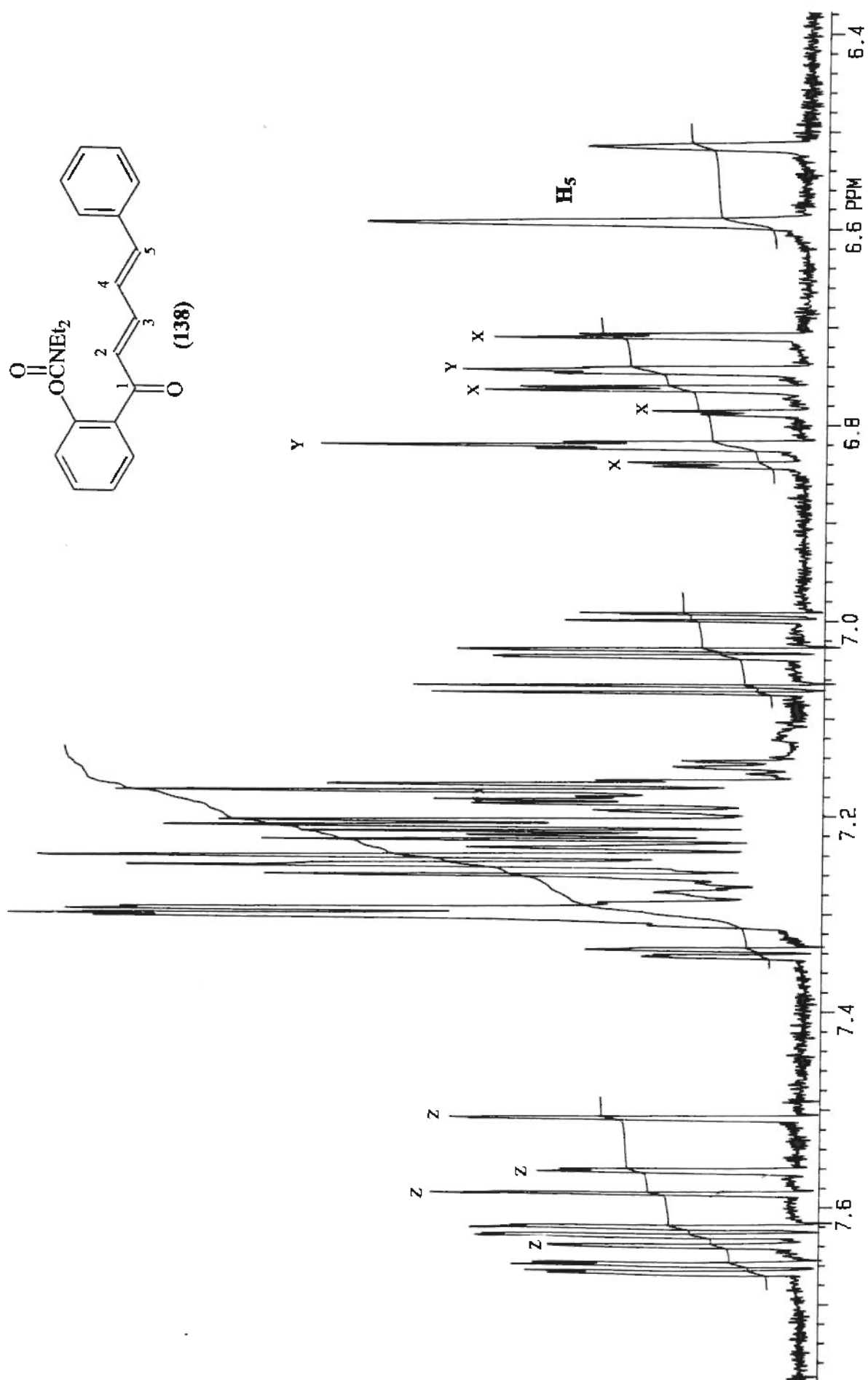
2.2 THE SYNTHETIC STRATEGY TOWARDS THE SYNTHESIS OF NATURALLY-OCCURRING FLAVAN-3-OL.

The next aim of the project was to incoporate the migrational and leaving group capability of the carbamate functionality in the synthesis of the flavan-3-ol compound **(140)**.


(140)
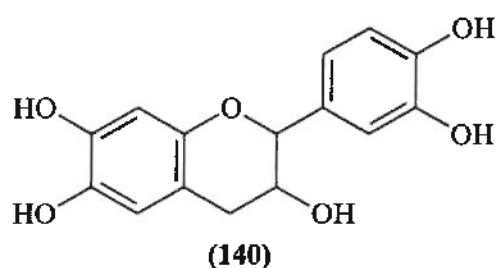
This compound does not exist naturally, but does have a close resemblance to the naturally-occurring flavan-3-ol, catechin **(120)**.

(120)
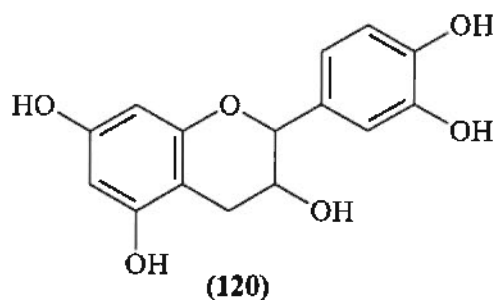
The synthesis of the flavan-3-ol **(140)** would thus lay the foundation for the synthesis of naturally-occurring flavonols, such as catechin **(120)**, by choosing suitably hydroxy-substituted starting materials.

The retrosynthesis of the flavan-3-ol **(140)** is outlined below **Scheme 54**
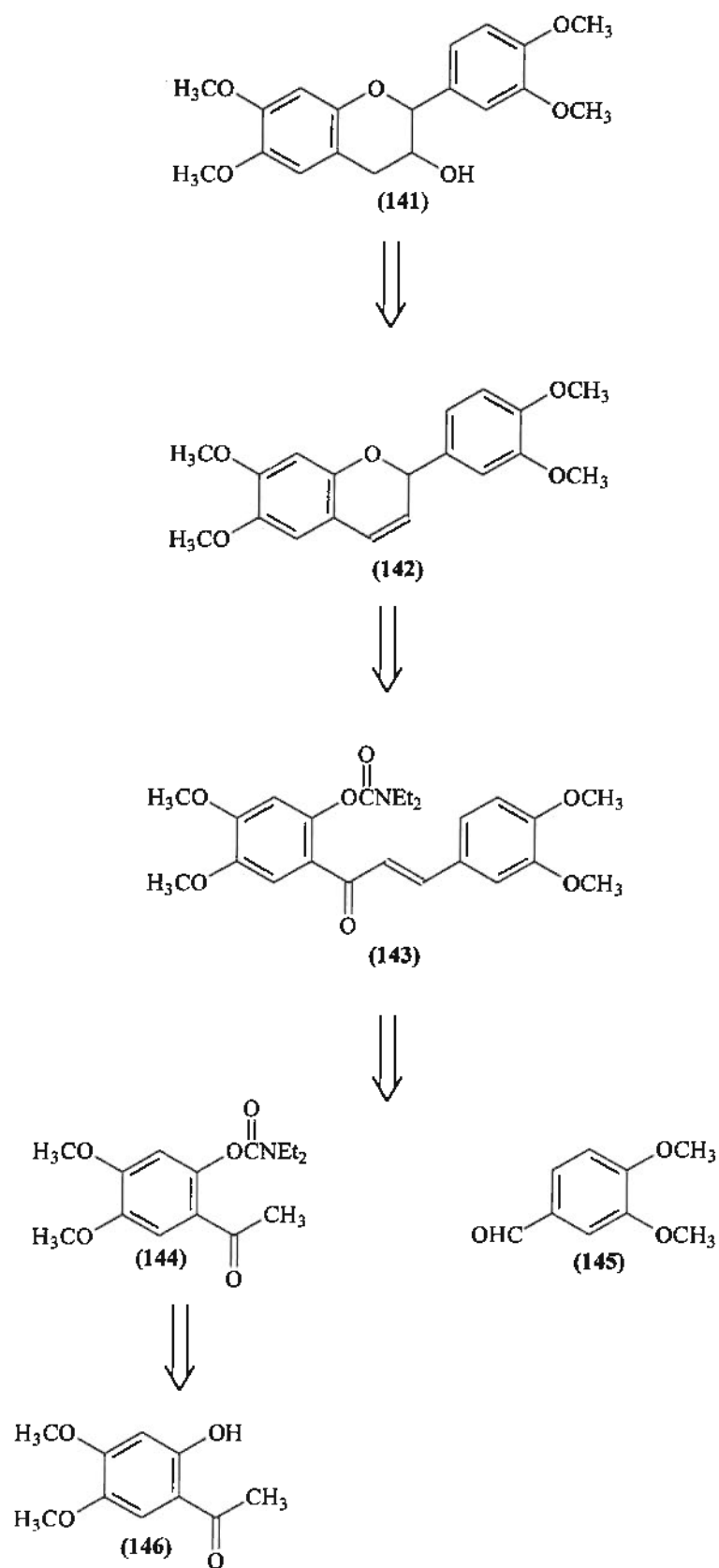
Scheme 54

We envisaged that the four hydroxyl substituents on the aromatic A and B rings of the flavan-3-ol (140) would require protection during the reaction, hence the methylated derivative (141). An aldol condensation of the carbamate (144), derived from its alcohol precursor (146), with the benzaldehyde derivative (145), would result in the α,β-unsaturated derivative (143). Reduction of the carbonyl functionality of compound (143) with NaBH$_4$ followed by reflux, would result in the formation of flav-3-ene derivative (142). Hydration of the olefin of (142) would afford the tetramethoxy-substituted flav-3-ene (141) which on demethylation would result in the tetrahydroxy-substituted flavan-3-ol (140).

2.2.1 THE SYNTHESIS OF 4',5',6,7-TETRAMETHOXY-FLAV-3-ENE DERIVATIVE (142).

2.2.1.1 The Synthesis of 2-Hydroxy-4,5-dimethoxyacetophenone (146).

A method for the synthesis of (146) was obtained from the literature[79]. Although quite long, the reaction procedures are fairly simple and products are obtained in good to excellent yield. The procedure also gives one a good insight into a wide variety of chemistry and chemical procedures. The synthesis of 4,5-dimethoxy-2-hydroxy acetophenone (146) is outlined below (Scheme 55).
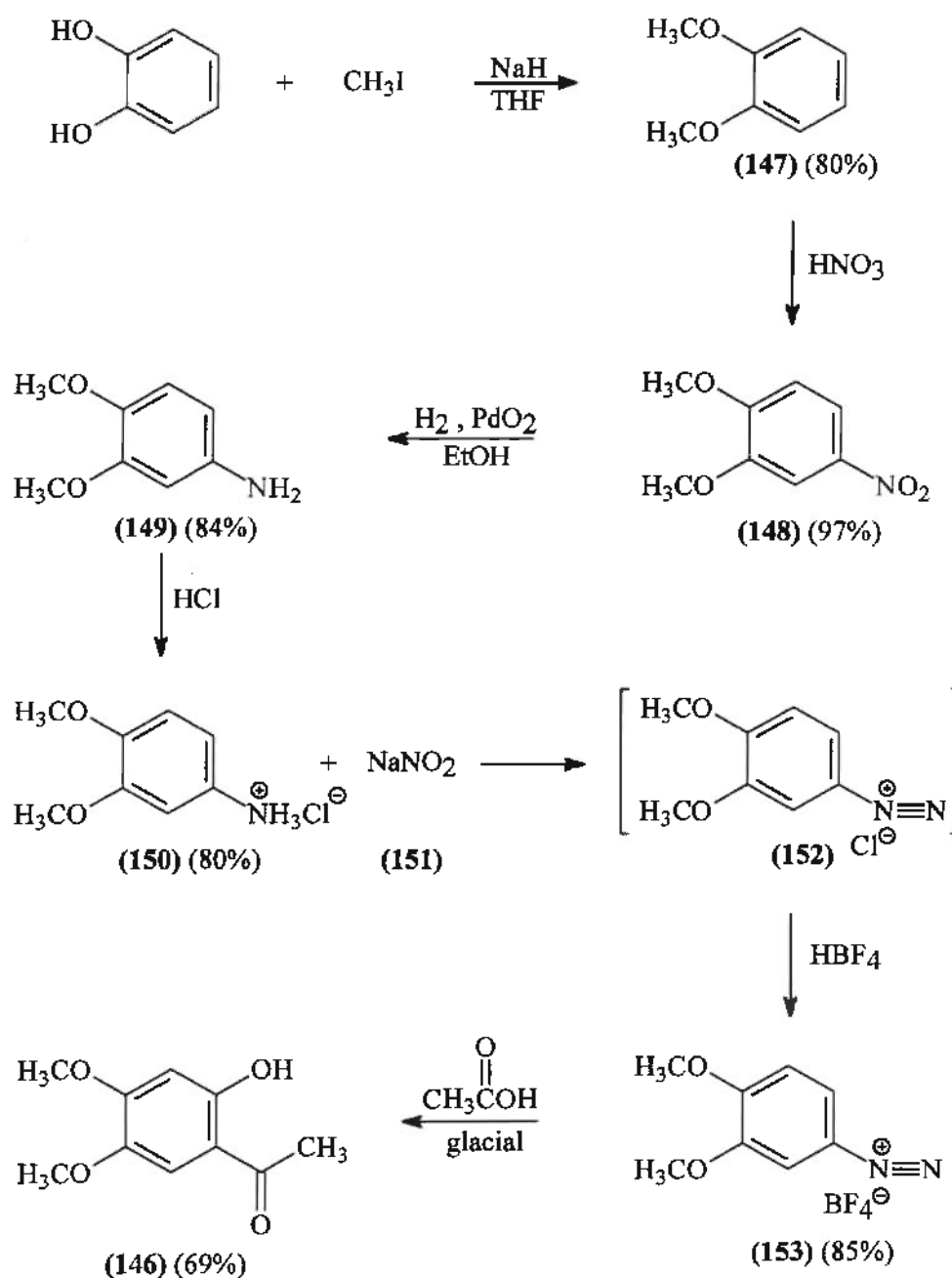
Scheme 55

Catechol was treated with NaH in THF to afford varatrole (147) in excellent yield. Veratrole (147) was then treated with nitric acid which resulted in nitroveratrole[80] (148). The nitro-group was then reduced, by hydrogenation in an autoclave, using PdO_2 as a catalyst, to the corresponding 3,4-dimethoxyaniline (149). The hydrochloride salt (150) of the amine was formed by treating it with HCl. The hydrochloride salt (150) was then

reacted with sodium nitrite **(151)** to yield the intermediate diazonium salt **(152)**, which was reacted with fluoroboric acid to afford 3,4-dimethoxyphenyldiazonium fluoborate **(153)**. This compound **(153)** was then reacted with glacial acetic acid to yield the target molecule **(146)** in good yield **(Scheme 55)**.

The next task in the synthesis was to protect the phenolic group of **(146)** as the N,N-diethyl carbamate, which was done quite simply. Acetophenone derivative **(146)** was reacted with NaH and diethyl carbamoyl chloride to afford the carbamate **(144)** in excellent yield **(Scheme 56)**.
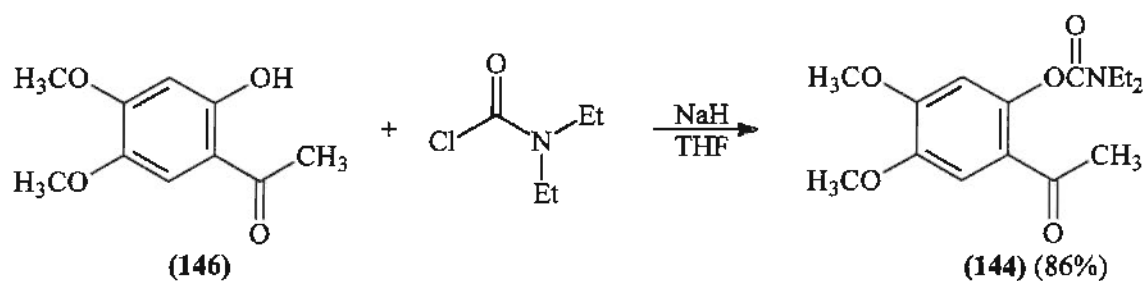
Scheme 56

This completed the formation of the first synthon that would be used in the aldol condensation. The next step would be to synthesise the aldehyde, *i.e.*, 3,4-dimethoxy benzaldehyde **(145)**, which would be the second synthon for the aldol condensation.

2.2.1.2 Synthesis of 3,4-Dimethoxybenzaldehyde **(145)**[81]

An obvious precursor to this synthon **(145)** would be vanillin **(153)**. Vanillin **(153)** was treated with potassium hydroxide and dimethyl sulphate to afford veratraldehyde **(145)** in excellent yield **(Scheme 57)**.
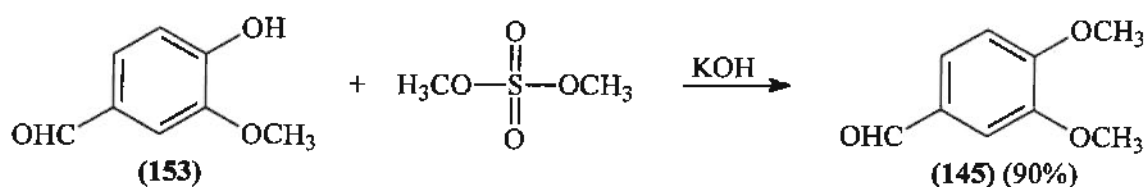
Scheme 57

The next step was to condense the two synthons, *i.e.*, carbamate **(144)** and 3,4-dimethoxybenzaldehyde **(145)** in the acid-catalysed (gaseous HCl) aldol reaction **(Scheme 58)**. As noted previously, the carbamate was cleaved to a small extent **(154)**. The desired product was obtained in an average yield of 55%, while the carbamate **(144)** was recovered in a 27% yield.
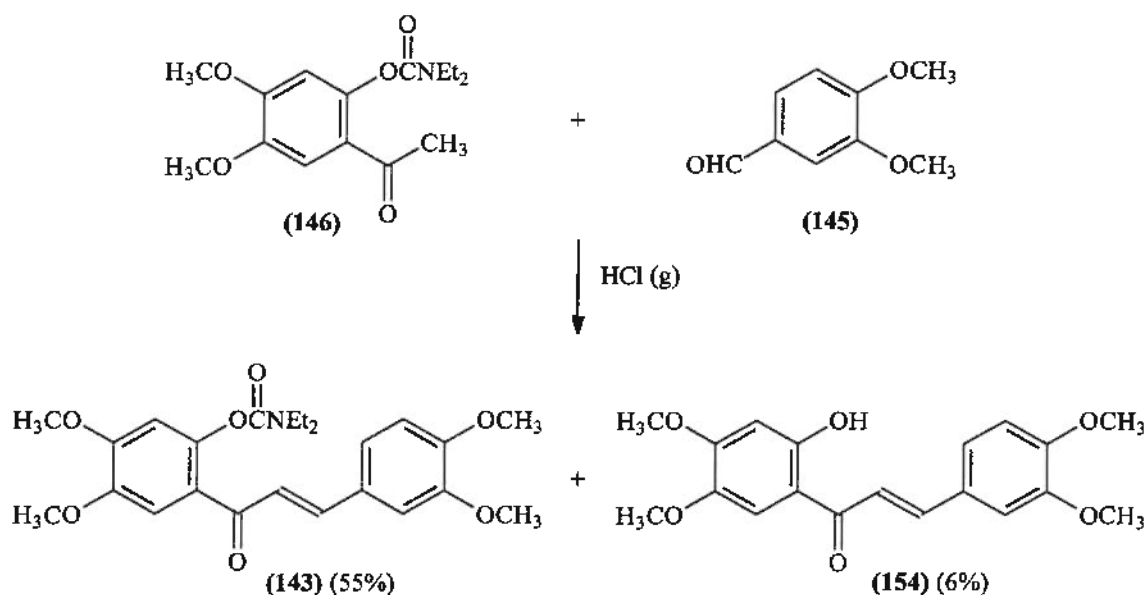
Scheme 58

The next step was to treat the aldol product **(143)** with NaBH₄. The compound **(143)** was reduced with NaBH₄ at 0°C and refluxed for 12hrs, which resulted in the isolation of the desired product **(142)** in a 47% yield, while 41% of the ketone **(143)** was recovered **(Scheme 59)**.
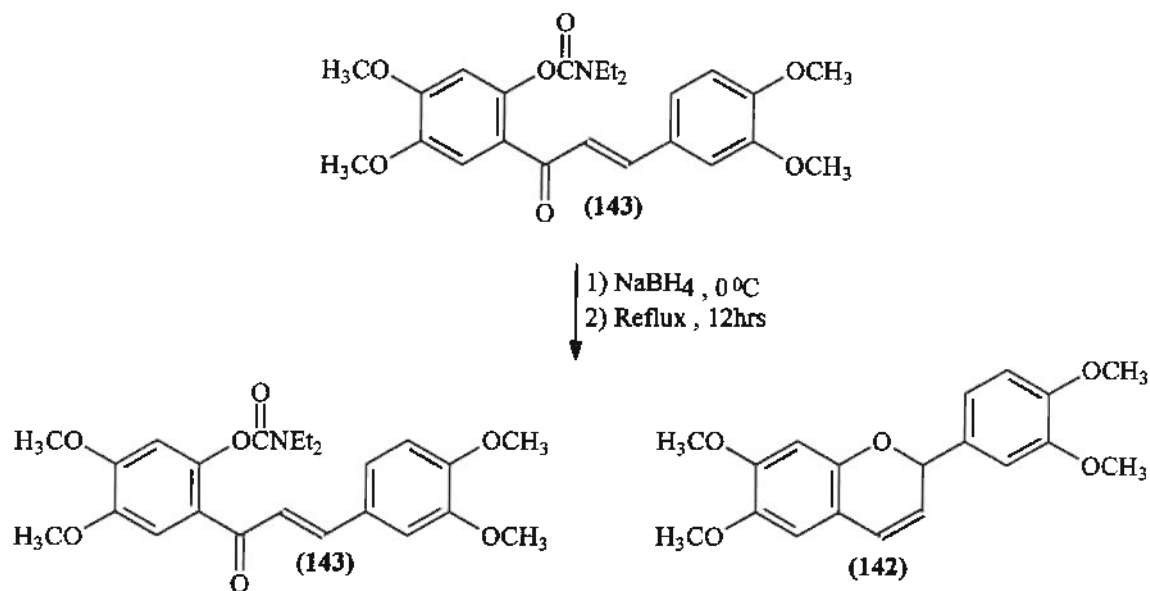
Scheme 59

At this stage only two steps were left to complete the synthesis of the tetrahydroxy substituted flavan-3-ol **(140)**, *i.e.*:

1)   The introduction of a hydroxyl group in the 3-position by hydration of the alkene, and

2)   Deprotection of the methylated hydroxy groups to afford the tetrahydroxy-substituted flavan-3-ol **(140)**.

2.3   ATTEMPTED SYNTHESIS OF FLAVAN-3-OL

Due to the availability of flav-3-ene **(91)**, this compound was used as a model to introduce the hydroxy group into position three **(Scheme 60)** and once perfected, the method would then be applied to the tetramethoxy-substituted derivative **(142)**.
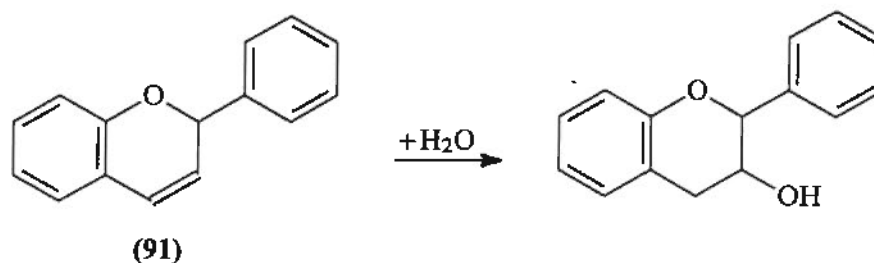
Scheme 60

As the heading above (2.3) suggests, this task was not accomplished. The attempts, however, provided exciting challenges and gave rise to synthetic methods to other flavonoid derivatives.

2.3.1 BY A DIRECT HYDROXYLATION.

We envisaged this method to be troublesome, since neither position of the olefin, in the flav-3-ene **(91)**, is more substituted than the other and hence the hydroxy group could be introduced in either position-3 or position-4. Despite this envisaged shortcoming, a hydroxylation was attempted using boranemethyl sulphide (BMS) as the hydroxylating agent **(Scheme 61)**
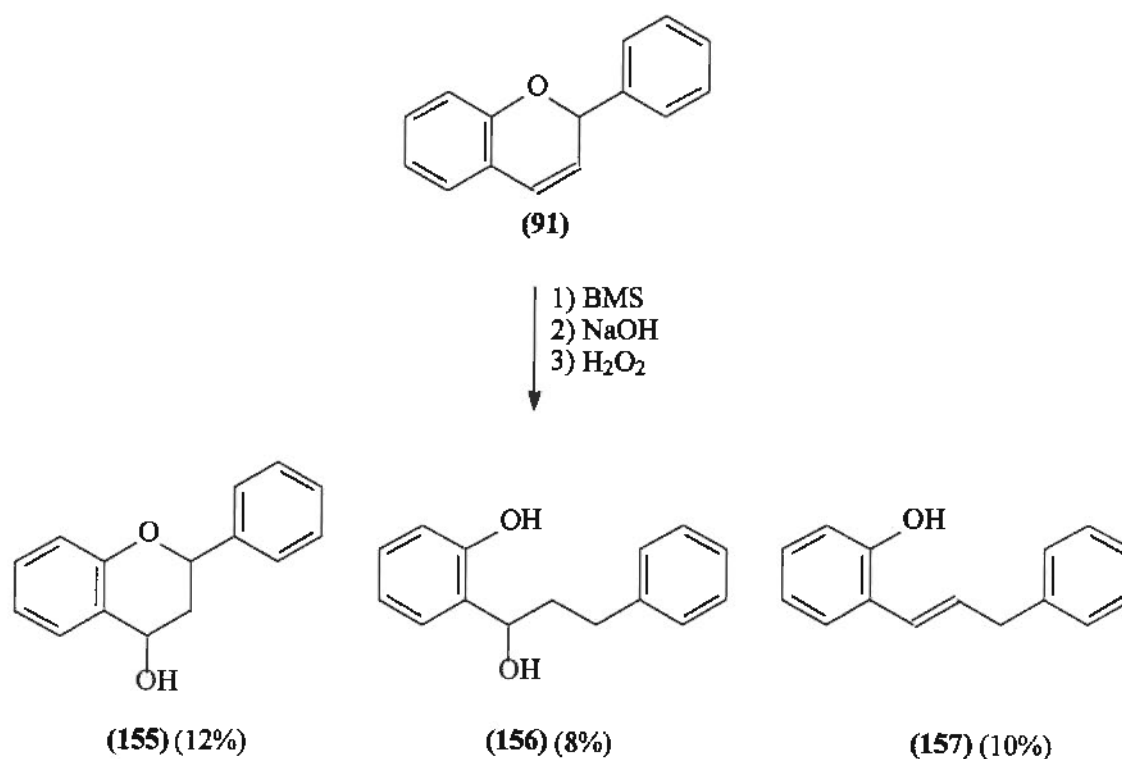
Scheme 61

As can be seen from the nature of the products and the yields, this method proved to be highly undesirable. The flavan-4-ol **(155)** was isolated as an inseparable mixture of two diastereomers and demonstrates the incorrect introduction of the hydroxyl group into the 4-position.

The isolation of compounds **(156)** and **(157)** shows the instability of the flav-3-ene **(91)** towards the reagents used, resulting in cleavage of the pyran ring.

2.3.1.1 The identification of 1-(*o*-hydroxyphenyl)-3-phenylprop-1-ene **(157)**.

When 1-(*o*-hydroxyphenyl)-3-phenyl-prop-1-ene **(157)** was first isolated the position of the double bond was not known. The other possibility was 3-(*o*-hydroxyphenyl)-1-phenylprop-1-ene **(157a)**, shown below.
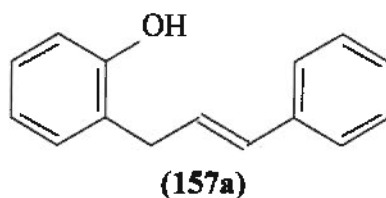
(157a)

^{1}H NMR, ^{13}C NMR, HETCOR, and COSY spectra were obtained for this compound and neither could, with any degree of certainty, be correlated with one of the two possible compounds **(157)** or **(157a)**. It was expected however, that mass spectrometry would aid in the identification, since one would expect different fragmentation patterns for **(157)** and **(157a)**. The expected fragmentations of the two copounds are shown below(**Fig2**).
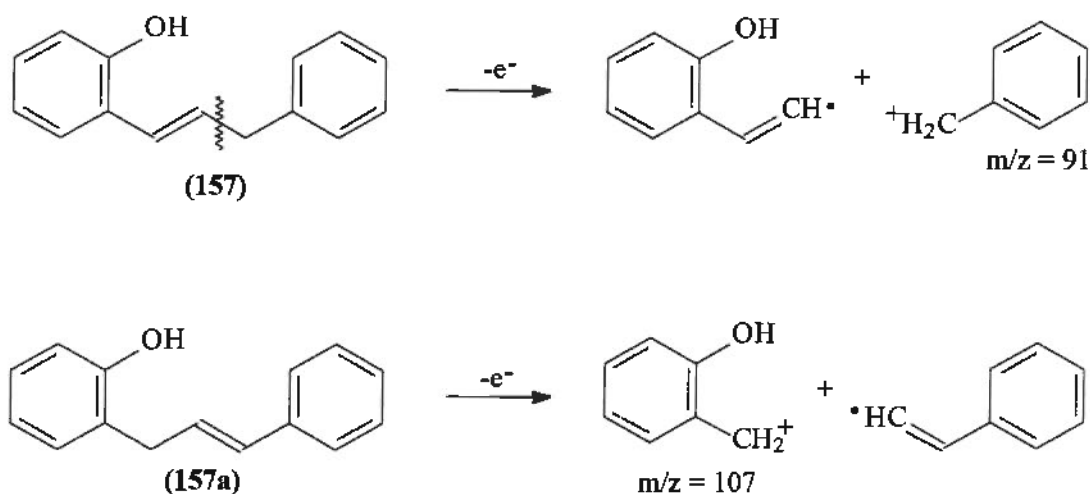
Fig2 Expected Fragmentatios

It would be expected that the fragmentation of **(157)** would produce the benzyl cation (m/z=91) as the most stable fragment and **(157a)**, the o-hydroxybenzyl cation (m/z=107) as the most stable fragment. Mass spectrometry of the compound isolated revealed a peak at 91 with a relative abundance of a 100%. This suggests that the compound is consistent with the structure denoted by **(157)**, *i.e.*, 1-(*o*-hydroxyphenyl)-3-phenyl-prop-1-ene.

2.3.2 *VIA* THE FORMATION OF AN AN EPOXIDE

Due to the short comings experienced in the direct hydroxylation method **(Scheme 61)**, it was decided to form the flavan-3-ol *via* an epoxide, since the epoxide can be selectively cleaved to introduce the hydroxyl group correctly into the 3-position. **(Scheme 62)**
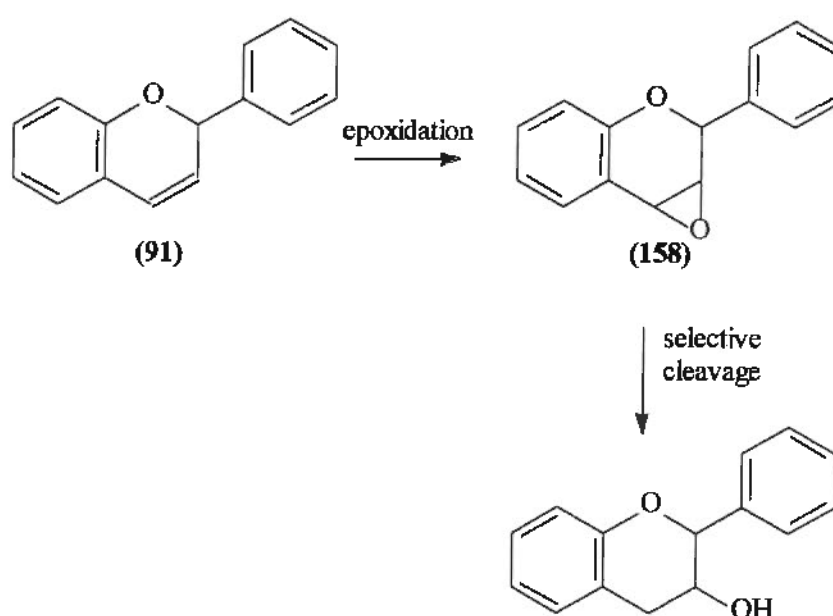
Scheme 62

2.3.2.1 Epoxidation using magnesium monoperphthalate hexahydrate (MMPP)

The first epoxidation method tried was the treatment of flav-3-ene **(91)** in isopropyl alcohol with an aqueous solution of magnesium monoperphthalate hexahydrate. The epoxide **(158, Scheme 62** above) was not isolated, but three other compounds were isolated including a flavan-3,4-diol, which is the skeleton structure of numerous naturally-occurring flavan-3,4-diols. The nature of the products isolated is depicted below **(Scheme 63)**
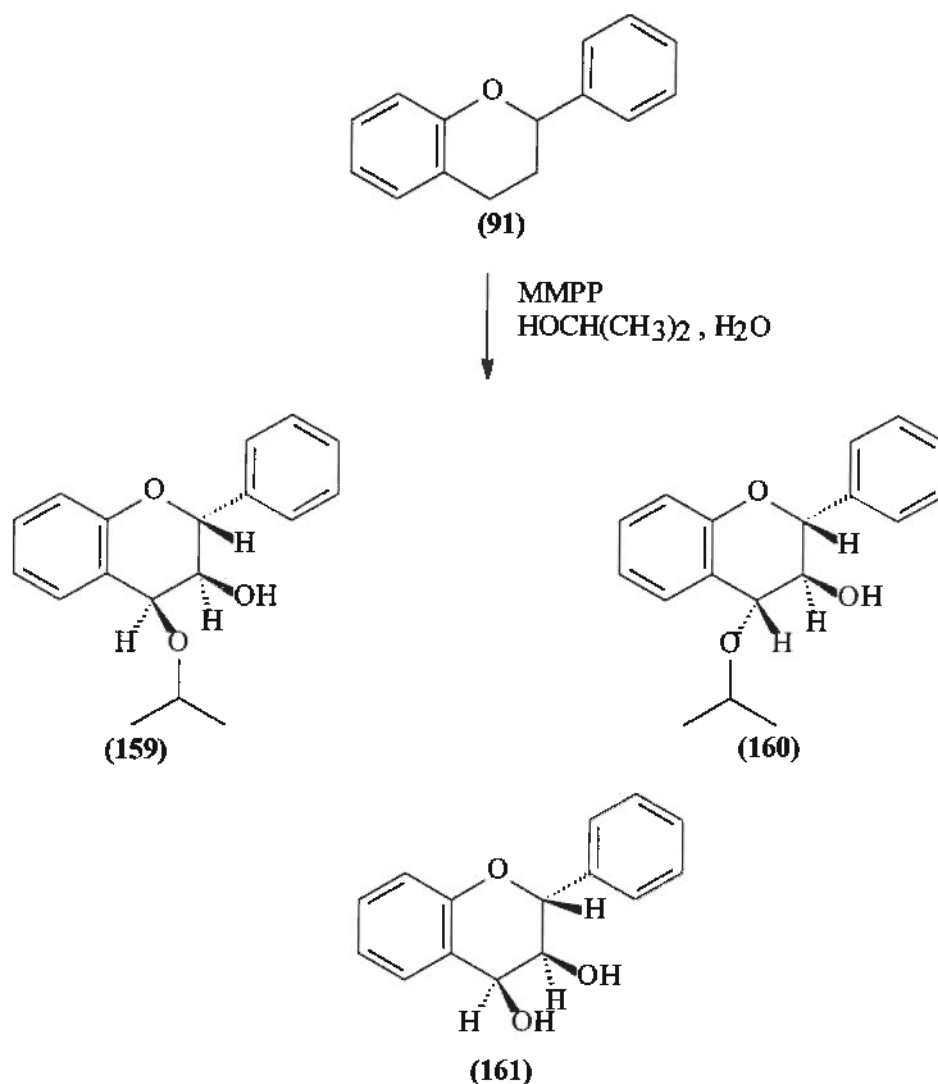
Scheme 63

Isomers **159** and **160** were separated using centrifugal chromatography with a 45:1 hexane:ethyl acetate eluant mixture. Each of the isomers were characterised using ^{1}H NMR, ^{13}C NMR, HETCOR and COSY spectra. The relative stereochemistry was determined using coupling constants and nuclear Overhauser effects (NOE) and is discussed below.

(159)
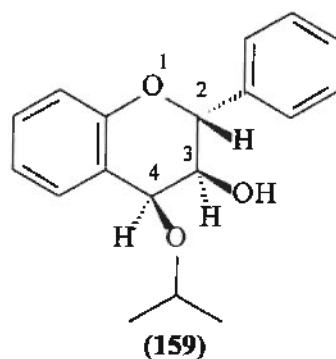
$$J(H_2) = 8.53Hz$$

$$J(H_4) = 3.59Hz$$

A large coupling constant between H_2 and H_3 (J=8,53 Hz) implies that these hydrogens are trans to each other. A smaller coupling constant between H_4 and H_3 (J=3.59 Hz), implies that these hydrogens are cis to each other. NOE studies confirmed these findings.

(160)
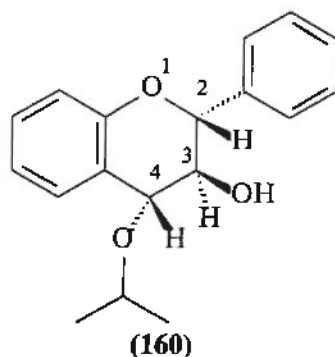
$$J(H_2) = 9.79Hz$$

$$J(H_4) = 8.71Hz$$

The large coupling constant in the NMR signals of H_2 and H_3 (J=9.79 Hz) implies a trans stereochemistry between these hydrogens. A large coupling constant between H_4 and H_3 (J=8.17) also implies a trans stereochemistry between these two protons, hence the relative stereochemistry of compound **(160)** is as shown above. NOE results confirmed these findings.

The separation of the cis-diol **(161)** also posed problems due to another compound (X) moving at the same R_f on the TLC plate as **(161)**. Mass spectrometry of the mixture indicated that compound X has the same mass as the cis-diol **(161)**, which led us to believe that X may be an isomer of the cis-diol **(161)**, perhaps the trans-diol (X').

(X')
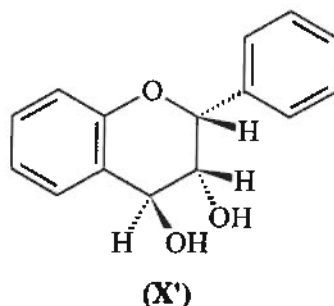
An attempt to separate the two "isomers" using centrifugal chromatography with a 6:2 mixture of hexane:ethyl acetate resulted in the purification of the cis-diol **(161)** only, compound X not being obtained in sufficient purity to be identified.

The cis-diol was characterised using ^{1}H NMR, ^{13}C NMR , HETCOR and COSY spectra. The relative stereochemistry was determined by coupling constants and is discussed below.
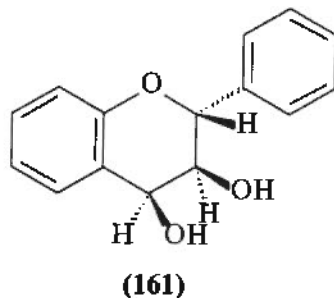

$J(H_2) = 9.16 \text{ Hz}$

$J(H_4) = 3.57 \text{ Hz}$

(161)

The large coupling constant between H_2 and H_3 (J=9.16 Hz) implies a trans-stereochemistry between these two protons. The small coupling between H_4 and H_3 (J=3.57 Hz) implies as a cis stereochemistry between these two protons, resulting in the cis-diol **(161)**.

Compound X was eventually separated from the cis-diol **(161)** using preparative TLC with a 6:2 hexane:ethyl acetate eluent mixture. This revealed that compound X was not an isomer of the cis-diol **(161)**. Mass spectroscopy indicated that X had the same mass as diol **(161)**. However ^{1}H and ^{13}C NMR spectrometry revealed otherwise. Compound X was not characterised.

Due to the lengthy times and practical difficulties associated with preparative TLC, another method was used for the separation of the diol **(161)** from compound X, *i.e.*, a trans-ketalisation reaction. A mixture of the diol **(161)** and X was treated with 2,2-dimethoxy propane in dichloromethane using p-toluene sulphonic acid as a catalyst. This resulted in the formation of the cis-acetal **(162)**, formed from the cis-diol **(161)** which was isolated with little difficulty **(Scheme 64)**.

(161)

(162)
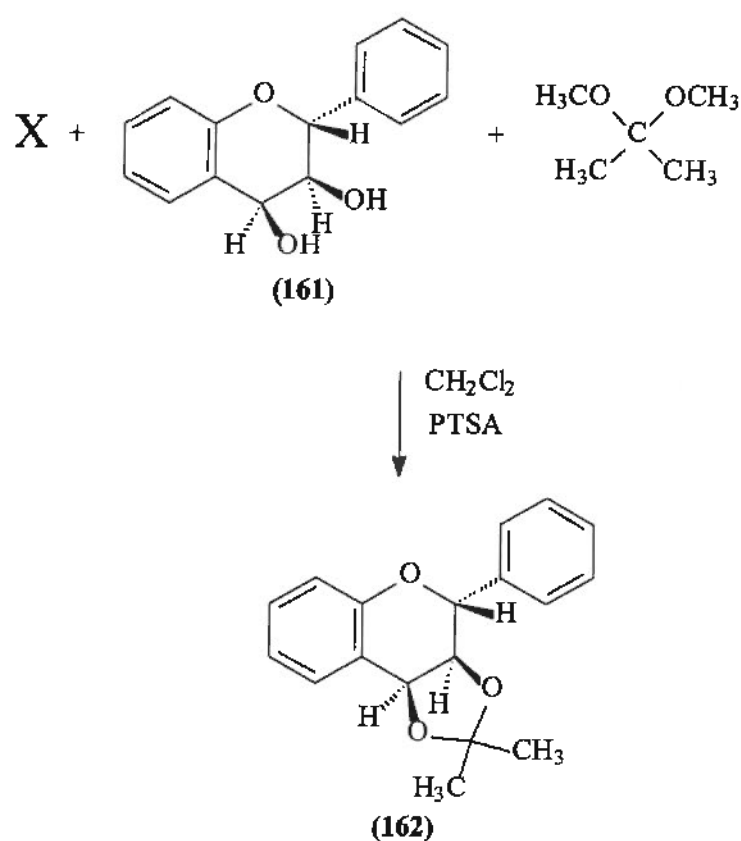
Scheme 64

The acetal structure **(162)** was determined using ^{1}H NMR, ^{13}C NMR, HETCOR and COSY spectroscopy. The relative stereochemistry of **(162)** was determined using coupling constants and is discussed below.
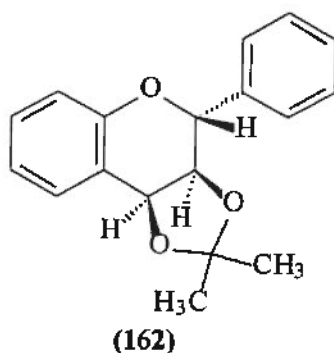
$J(H_2) = 9.80$ Hz

$J(H_4) = 5.56$ Hz

(162)

The large coupling constant between H_2 and H_3 ($J = 9.80$ Hz) implies a trans-stereochemistry between these two protons. The small coupling between H_4 and H_3 ($J = 5.56$) implies as a cis-stereochemistry between these two protons, resulting in the cis-acetal **(162)**.

Assuming that compound X was the trans-diol (X'), one would expect the acetal to form only with the cis-diol due to the lower energy associated with its formation. Drewes *et al.*[76], however, reported that the acetal would form from both the cis-diol and the trans diol. This reaction thus implies that the ketalisation reaction does not serve as an effective tool for separating or differentiating between cis and trans 1,2-diols.

The formation of the products outlined in **Scheme 63** is rationalised by the mechanism outlined below **(Scheme 65)**.
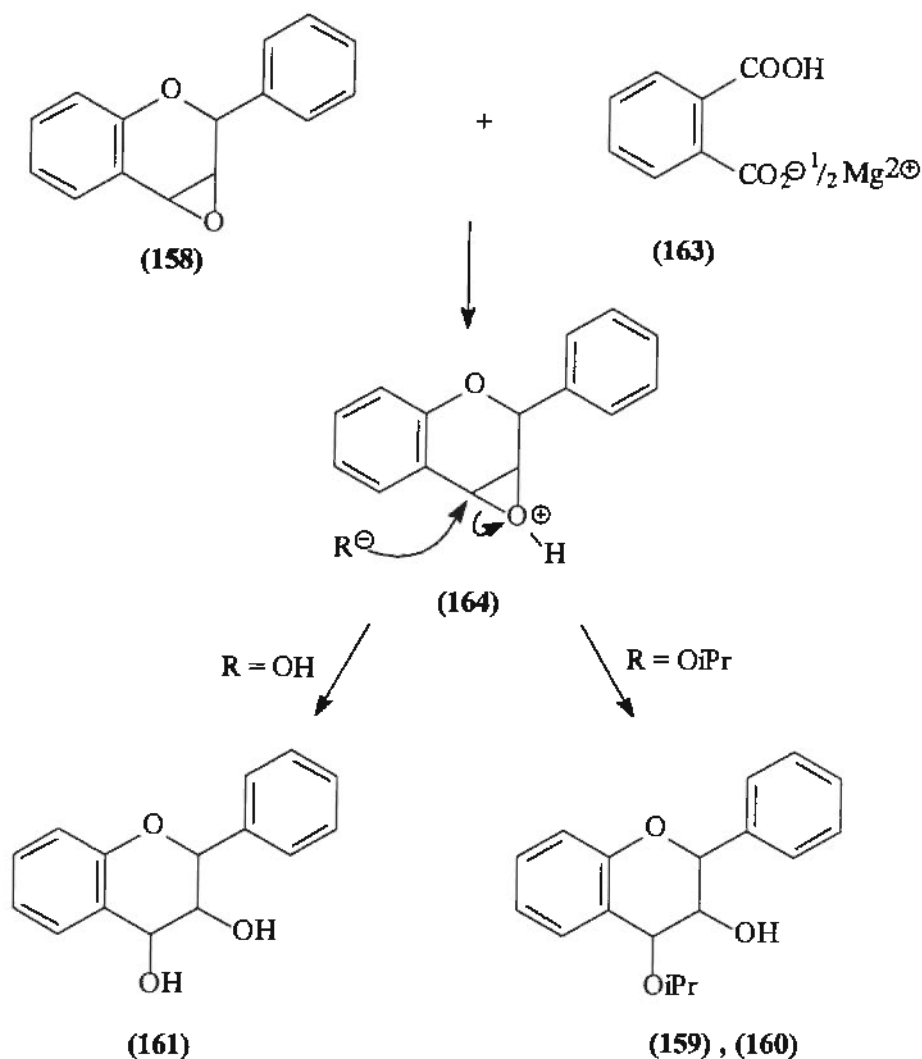
Scheme 65

It can be assumed that the epoxidation does in fact take place to form (**158**). However, due to the formation of the phthalic acid derivative (**163**) as a by-product of the epoxidation, the epoxide is easily protonated to form the unstable intermediate (**164**). This intermediate, being susceptible to nucleophilic attack, can be attacked either by the water to form the diol (**154**) or by isopropyl alcohol to form compounds (**159**) and (**160**).

The epoxidation was also attempted in a reaction medium buffered at pH=11. This did not affect the nature of the products, obtained, which seems to suggest that the epoxide may be attacked without the formation of the intermediate (**164**).

2.3.2.2 Epoxidation *via* the Bromohydrin.

An alternate method for the epoxidation is *via* the bromohydrin (165). The flavene (91) was reacted with 1.1 equivalents of NBS in water to afford the bromohydrin (165) in a 50% yield. (**Scheme 66**)

(91)   (165)
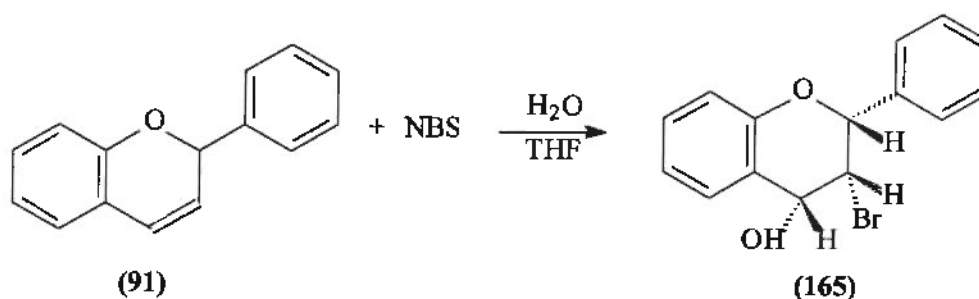
Scheme 66

When the reaction was first carried out, the substitution pattern was not known, *i.e.* whether the hydroxy and the bromine groups are as shown above or swapped around. This problem was solved by reducing the bromohydrin with $LiAlH_4$ which afforded a diastereomeric mixture of the flavan-4-ol (155) below, which indicated that the bromine is in position-3.

(155)
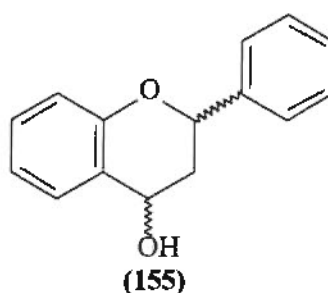
The bromohydrin (165) was characterised using ^{1}H NMR, ^{13}C NMR, HETCOR and COSY spectroscopy. The relative stereochemistry was determined using coupling constants as shown below.
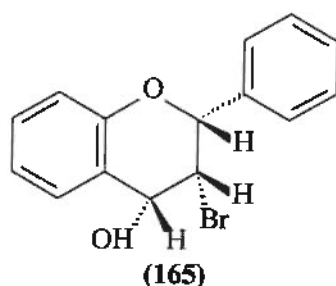
$J(H_2) = 0.91$ Hz

$J(H_3) = 2.20$ Hz

(165)

The small coupling constants of both H_2 and H_4, indicate that these protons are cis to H_3, hence the stereochemistry of bromohydrin **(165)** is as shown above.

Once the substitution pattern and the stereochemistry was determined the bromohydrin **(165)** was treated with NaH in THF **(Scheme 67)**. This afforded the expected epoxide **(158)** in a small yield and an unexpected flavone **(166)**.

(165)

NaH
THF

(166) (38%)   +   **(158)** (10%)
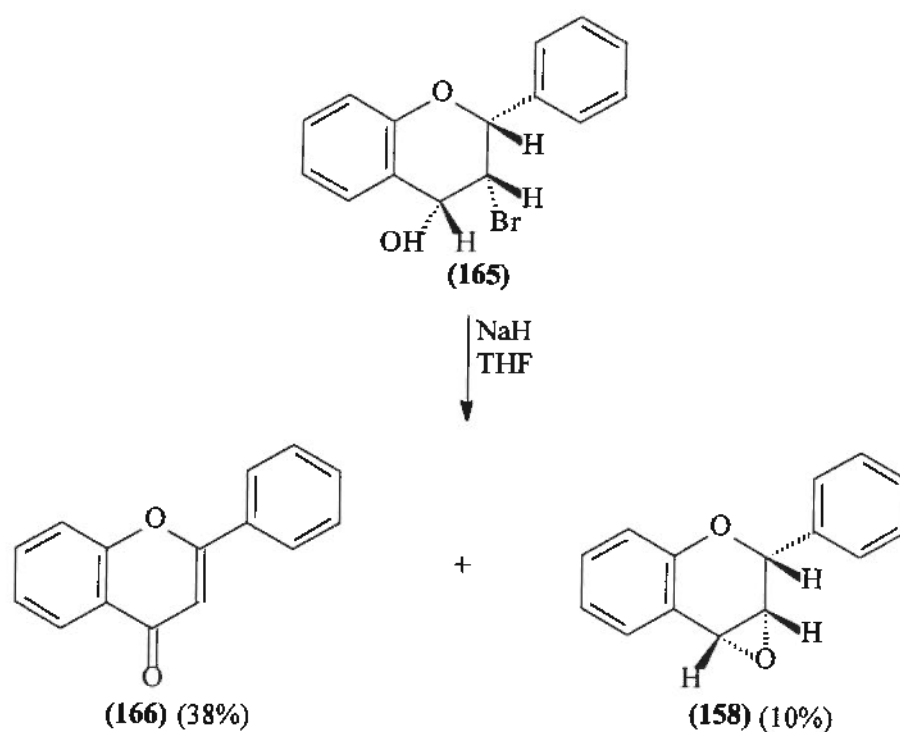
Scheme 67

The epoxide **(158)** was characterised using ^{1}H NMR, ^{13}C NMR, HETCOR and COSY spectroscopy. The relative stereochemistry was determined using coupling constants as shown below.

$J(H_2) = 1.05$ Hz

$J(H_2) = 1.35$ Hz

(158)
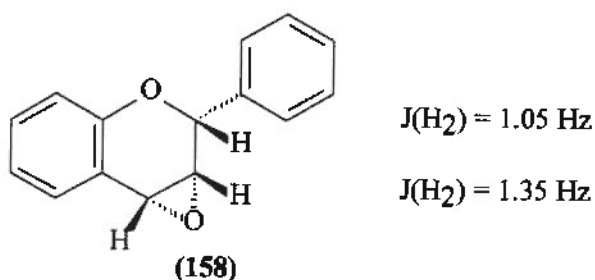
The small coupling constants of both H_2 and H_4, indicate that these protons are cis to H_3, hence the stereochemistry of epoxide **(158)** is as shown above.

The poor yield of the epoxide can be attributed to the unfavourable stereochemistry of the bromine and the hydroxyl group. Due to the fact that the bromine and the hydroxyl group are on the same side of the ring, upon deprotonation the bromine would hinder the oxy ion from attacking the C_3 position and eliminating the bromine.

The formation of flavone **(166)** is rationalised below **(Scheme 68)**.
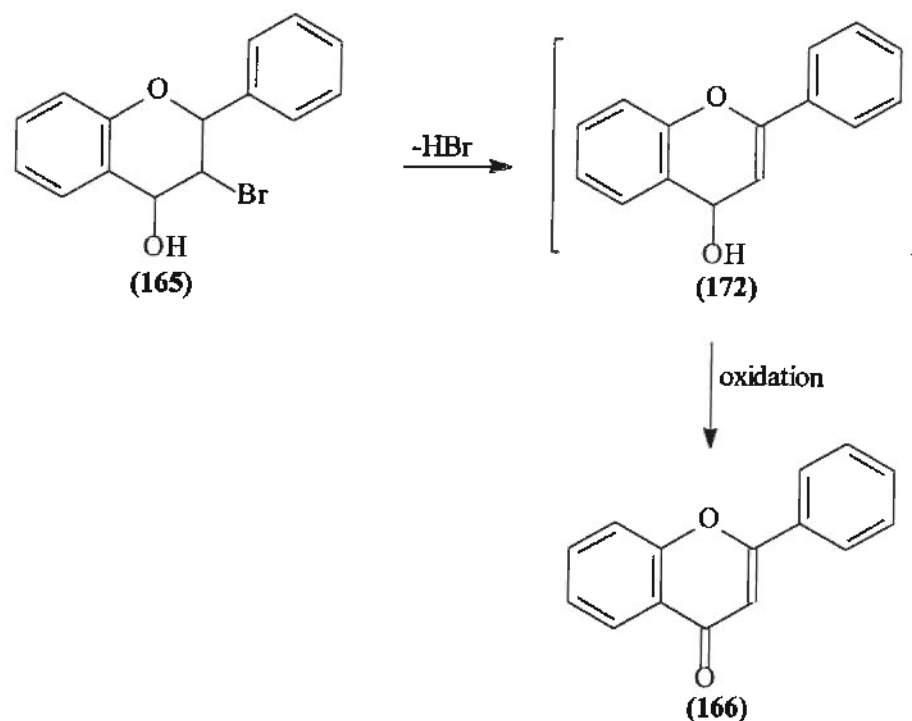
Scheme 68

The removal of HBr from the bromohydrin **(165)** results in the flavanol intermediate **(172)** which upon oxidation affords the flavone **(166)**.

In an effort to increase the 50% yield of bromohydrin obtained from the reaction with NBS **(Scheme 66)**, an alternative method was used. Flav-3-ene **(91)** was treated with Br_2 and H_2O. This reaction however, did not result in expected bromohydrin, but instead ketone **(167)** was formed in a 30% yield **(Scheme 69)**.
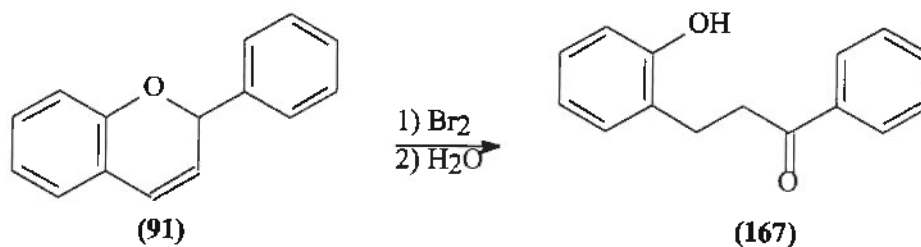
Scheme 69

A mechanism for the formation of the ketone (167) is outlined below (Scheme 70).
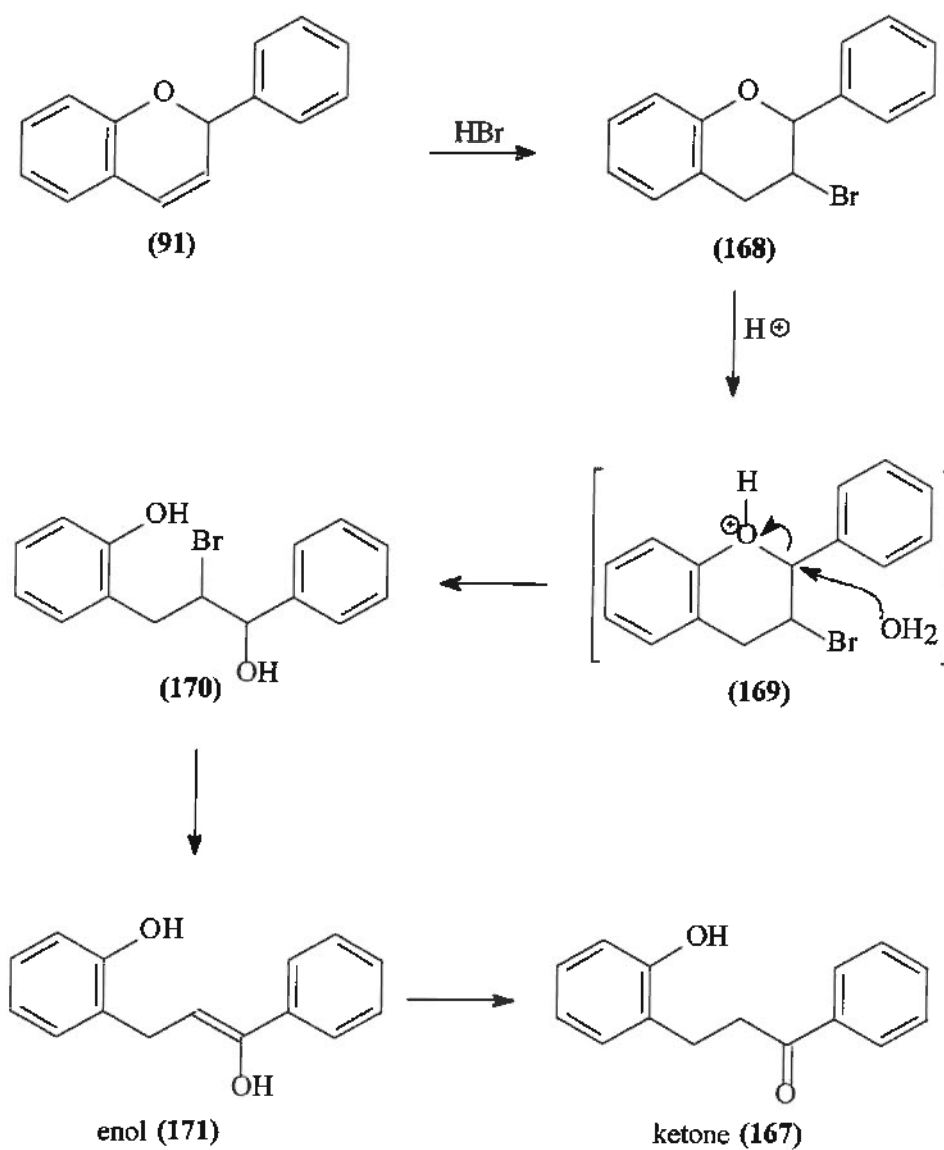
Scheme 70

The formation of the ketone (167) can be rationalised by assuming that HBr was present in the bromine that was used in the reaction. The HBr would then add across the double bond of the flav-3-ene (91) to yield the 3-bromoflavan (168). The presence of acid would

result in the protonation of the oxygen of the pyran ring, which would render the C_2 position susceptible to nucleophilic attack. This would cleave the pyran ring in by water attacking C_2 (intermediate(169)) or perhaps *via* the formation of a stabilised benzylic carbocation on C_2, to yield the bromohydrin (170). Removal of HBr from the bromohydrin (170) results in the formation of the enol (171) which tautomerises to the ketone (167).

At this stage, time did not permit the exploration of other avenues for the formation of the flavan-3-ol. However, other possible approaches are discussed in the section that follows.

2.4   POSSIBLE ROUTES TO THE FORMATION OF FLAVAN-3-OL.

Most naturally-occurring compounds such as flavan-3-ols, exist as optically pure compounds. In the synthesis therefore of naturally-occurring compounds, one would have to consider the stereochemistry of the chiral centres on the molecule, *i.e.* asymmetric synthesis.

2.4.1 BY AN ASYMMETRIC EPOXIDATION

Jacobson[82] reported the use of salen Mn(III) catalysts (172) for the asymmetric epoxidation of unfunctionalised olefins similar to flav-3-ene (91). The epoxide may then be cleaved to an optically-pure flavan-3-ol.

(172)
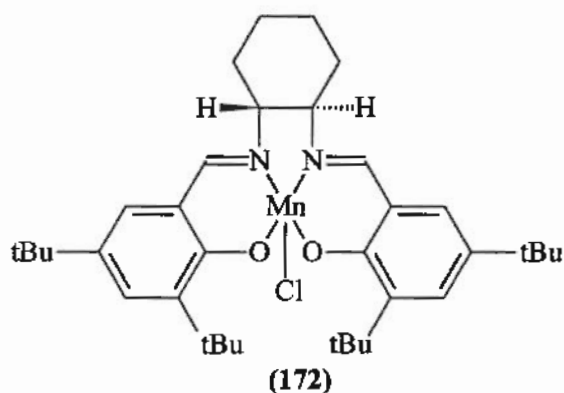
The catalytic utility of an asymmetric method is closely tied to the accessibility of the catalyst and can be severely undermined if the process for the preparation of the catalyst proves costly or technically difficult for large scale preparation. Jacobson[83] outlined an efficient, highly optimised procedure for the preparation of both enantiomers of (172) which is practical for both large-scale and laboratory-scale preparation (Scheme 71).

A.

dl + meso

B.

C.

(172)
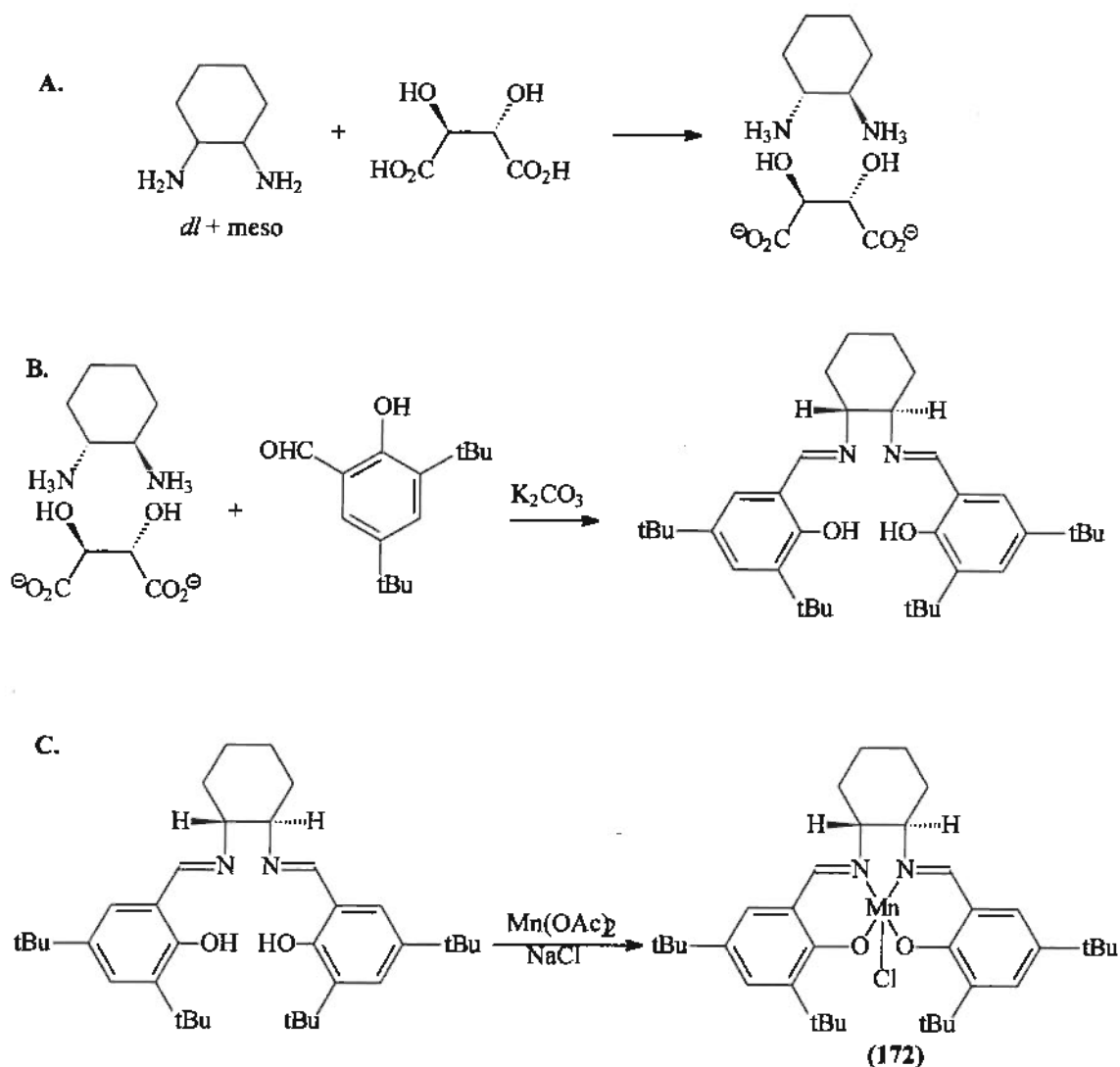
Scheme 71

2.4.2 BY AN ASYMMETRIC DIHYDROXYLATION

Optically-pure flavan-3-ols may also be prepared *via* optically-pure flavan-3,4-diols. The asymmetric dihydroxylation is one of the simplest catalytic asymmetric processes to perform.[84] The essential components for the process are osmium tetroxide and an ester of either of the alkaloids - dihydroquinidine or dihydroquinine. N-methylmorpholine N-oxide, generally serves as an oxidant. The cis-diol **(173)** obtained from the asymmetric dihydroxylation may then be converted to the flavan-3-ol **(177)** **(Scheme 72)**.
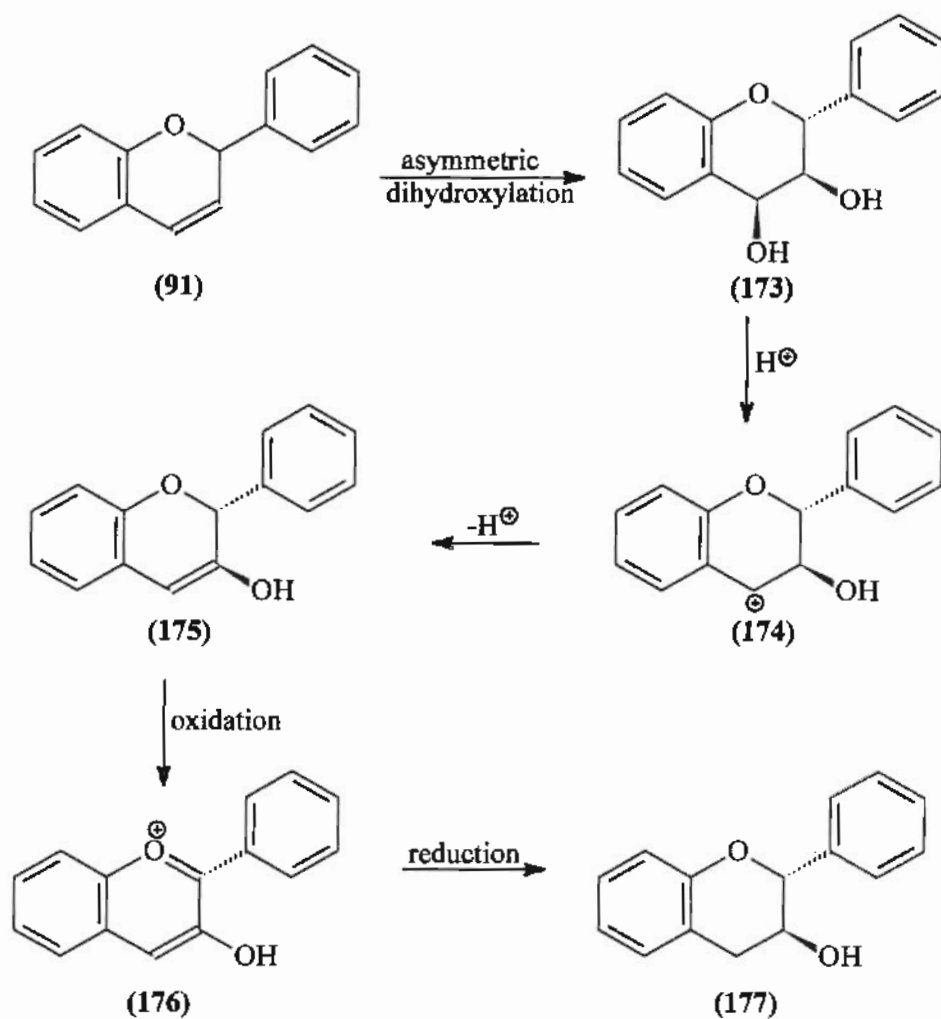
Scheme 72

The cis-flavan-3,4-diol **(173)** can be solvolysed under acidic conditions to give the corresponding resonance-stabilised benzyl carbocation **(174)**. A dehydration may then occur to give the flav-3-en-3-ol **(175)**, followed by aerial oxidation to give the anthocyanidin **(176)**. The anthocyanidin **(176)** can then be reduced to the optically-pure flavan-3-ol **(177)**.

CHAPTER 3 : EXPERIMENTAL

3.1 CHEMICALS AND INTSRUMENTATION

All solvents were distilled according to standard procedures before use.[85] Flash column chromatography was performed using Merck silica gel (200-400 mesh) by the technique of Still et al.[86] Pre-coated Kieselgel 60 F_{254} Merck plastic sheets were used for thin-layer chromatography. Centrifugal chromatography was carried out using a Harrison Research Chromatotron Model 7934T on 4mm Merck silica gel (200-400 mesh) coated glass plates. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR spectra ([1]H 200 MHz and [13]C 50 MHz) were recorded on a Varian Gemini 200 instrument. All chemical shifts are reported in ppm downfield from teramethylsilane as an internal standard, using d-chloroform as a solvent, unless otherwise stated. Mass spectra were recorded on a Hewlett-Packard mass spectrometer (HP5988A).

Compounds that have the basic flavonoid skeleton are numbered as shown below. Spectral data recorded for these compounds, coincide with this numbering. Certain compounds have their own numbering and this numbering is shown below the data recorded. J-values are quoted in hertz.
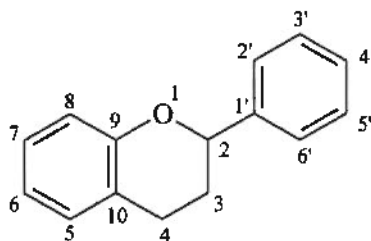
Numbering for Flavonoids

3.2   SYNTHESIS OF FLAV-3-ENE (91)

o-N,N-diethylcarbamoyloxyacetophenone (125)

NaH (60% in paraffin), (1.45g, 36.7 mmol) was added in small portions to a solution of 2-hydroxyacetophenone (5.00 g; 36.7 mmol) in THF (20 ml) at 0°C (ice bath). The addition of NaH resulted in a yellow-green solution which was stirred for 0.5h at room temperature. N,N-diethylcarbamoyl chloride (4.98 g; 36.7 mmol) in THF (10 ml) was then added dropwise at room temperature. The mixture was then refluxed for 10 hrs, resulting in a yellow-brown solution which was quenched with saturated ammonium chloride (20 ml). The THF was removed on a rotary evaporator and the aqueous phase extracted with ether. The combined ether layers were dried with anhydrous $MgSO_4$ and filtered. The ether was removed under vacuum to afford a yellow oil which was purified by chromatography on silica gel with a 5:1 hexane:ethyl acetate mixture to afford o-N,N-diethylcarbamoyloxyacetophenone (125) (6.56 g , 76%). The crude material could also be distilled, collecting the fraction boiling at 180-182°C (0.51 mmHg) to afford (125), as a clear oil.

δ_H **(200 MHz)** 1.15-1.30 (6H, 2xt, N(CH$_2$CH_3)$_2$); 2.53 (3H, s, CHCH_3); 3.31-3.53 (4H, 2xq, N(CH_2CH$_3$)$_2$); 7.09-7.13 (1H, dd, Ar-H); 7.19-7.27 (1H, m, Ar-H); 7.42-7.51 (1H, m, Ar-H); 7.70-7.75 (1H, dd, Ar-H)

δ_C **(50 MHz)** 13.31 and 14.14 (2xq, N(CH$_2$CH$_3$)$_2$; 29.496 (q, COCCH_3); 41.95 and 42.28 (2xt, N(CH_2CH$_3$)$_2$); 123.77(d, Ar-C); 125.28(d, Ar-C); 129.61(d, Ar-C); 132.936 (d, Ar-C); 131.97 (s, CCOCH$_3$); 149.82(s, COCON); 153.676 (s, OCON); 198.03 (s, COCH$_3$)

m/z (EI) 235 (M$^+$, <1%), 163 (4), 121 (10), 100 (100), 72 (29).
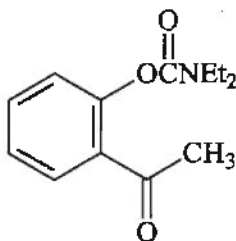
(125)

1-(*o*-Hydroxyphenyl)-3-phenyl-2-propene-1-one (131) and

2-Phenyl-2,3-dihydro-4H-benzopyran (Flavanone) (132)

To a suspension of *o*-N,N-diethylcarbamoyloxyacetophenone **(125)** (1.00 g, 4.26 mmol) in ethanol (5 ml) was added 50% aqueous potassium hydroxide (0.4 ml) which resulted in a yellow solution. Distilled benzaldehyde (0.54 g; 5.11 mmol) was then added dropwise and the solution stirred for 12 h. This formed an intense red solution which was quenched with water (15 ml) and extracted with ether. The ether layer was separated and dried with anhydrous MgSO$_4$. The MgSO$_4$ was filtered off and the ether reduced under vacuum. The crude mixture was separated using flash chromatography with a 12:1 ratio of hexane:ethyl acetate to afford yellow crystals of 1-(*o*-hydroxyphenyl)-3-phenyl-2-propen-1-one **(131)** (0.65 g; 68%); mp=79°C and white crystals of flavanone **(132)** (0.086 g, 9%) mp =66°C .

Data for 1-(*o*-hydroxyphenyl)-3-phenyl-2-propen-1-one **(131)**:

δ_H **(200 MHz)** 6.91-7.05 (2H, m, Ar-*H*); 7.41-7.54 (4H, m, Ar-*H*); 7.64-7.68 (2H, m, Ar-*H*); 7.90-7.97 (1H, m, Ar-*H*); 7.62-7.69 (1H, d, Ar-C*H*=CH, *J*=15.47); 7.88-7.97 (1H, d, O=C-C*H*, *J*=15.47); 12.84 (1H, s, -O*H*).

δ_C **(50 MHz)** 118.61 (d, Ar-*C*); 118.85 (d, Ar-*C*); 120.04 (d, O=C-CH=CH); 128.85 (2xd. Ar-*C*); 129.02 (2xd, Ar-*C*); 129.64 (d, Ar-*C*); 130.93 (d, Ar-*C*); 136.41 (d, Ar-*C*); 145.46 (d, Ar-CH=CH); 119.97(s, *C*-COCH); 134.64 (s, *C*-CH=CH); 163.56(s, *C*-OH); 193.70 (s, Ar-*C*=O).

m/z 224 (M$^+$, 42%), 147 (100), 120 (70), 103 (53), 77 (5).

(131)
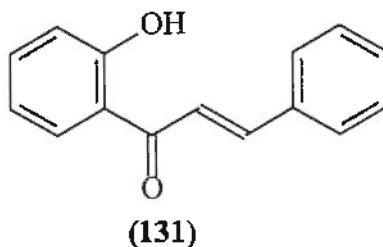
Data for flavanone **(132)**:

δ_H **(200 MHz)** 2.80-2.90 (1H, dd, *H*CH, *J*=3.27, *J*=16.86); 2.98-3.13 (1H, dd, -HC*H*-, *J*=13.00, *J*=16.92); 5.40-5.48 (1H, dd, OC*H*, *J*=3.27, *J*=13.00); 6.98-7.07 (2H, m, Ar-*H*); 7.23-7.52 (6H, m, Ar-*H*); 7.89-7.94 (1H, m, Ar-*H*).

δ_C **(50 MHz)** 44.58 (t, *C*H$_2$); 79.50 (d, O-*C*H); 118.06 (d, Ar-*C*), 121.55 (d, Ar-*C*); 126.10 (2xd, Ar-*C*), 126.98 (d, Ar-*C*); 128.71 (d, Ar-*C*); 128.78 (2xd, Ar-*C*); 136.14 (d, Ar-*C*); 120.85 (s, *C*-C=O); 138.68 (s, *C*-CH-O); 161.47 (s, *C*-O); 191.86 (s, *C*=O).

m/z 224 (M$^+$, 43%), 147 (47), 120 (100), 104 (42), 51 (9).

(132)
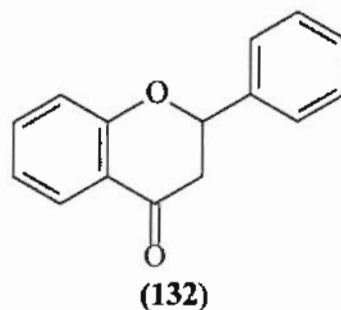
1-(*o*-N,N-diethylcarbamoyloxyphenyl)-3-phenyl-2-propene-1-one (126)

HCl(g) was generated using a Kipps apparatus by adding concentrated sulphuric acid dropwise to a slurry of sodium chloride and 33% hydrochloric acid. *o*-N,N-diethylcarbamoyloxyacetophenone(125) (1.5 g, 6.38 mmol) and distilled benzaldehyde (0.81 g, 7.65 mmol) were placed in a round-bottomed flask with a stirrer bar. The HCl(g) generated, was then bubbled into the mixture for 15 min. The flask was then closed and sealed with parafilm and left to stir for 12 hrs, which afforded an intense red solution. The reaction was quenched with saturated NaHCO$_3$ (10 ml) and extracted with ether. The ether layer was dried with anhydrous MgSO$_4$, filtered and reduced. The crude material was chromatographed on a column using 4:1 ratio of hexane:ethyl acetate to afford 1-(*o*-N,N-diethylcarbamoyloxyphenyl)-3-phenyl-2-propene-1-one (126) (78%) as a yellow viscous oil.

δ_H (200MHz) 1.00-1.16 (6H , 2xt , N(CH$_2$C*H*$_3$)$_2$; 3.21-3.38 (4H, 2xq N(C*H*$_2$CH$_3$)$_2$; 7.08-7.16(1H, d, O=C-C*H*=CH, *J*=16.04); 7.54-7.65(1H, d, O=C-CH=C*H*-Ph, *J*=16.21); 7.20-7.65(9H, m, Ar-H).

δ_C (50 MHz) 12.96 and 13.82 (2xq, N(CH2*C*H$_3$)$_2$; 41.62 and 42.00 (2xt, N(*C*H$_2$CH$_3$)$_2$; 123.36(d, O=C-*C*H=CH); 125.13 (d, Ar-*C*), 125.67 (d, Ar-*C*); 128.19 (2xd, Ar-*C*); 128.65 (2xd, Ar-*C*); 129.25 (d, Ar-*C*); 130.36 (d, Ar-*C*); 131.85 (d, Ar-*C*); 144.83(d, CH=*C*H-Ph); 134.33 (s, *C*-C=O); 134.33 (s, *C*-CH=CH); 149.10 (s, *C*-OC=O); 153.26(S, O=*C*-N); 192.36(s, O=*C*-CH=CH)

m/z (EI) 323 (M$^+$, 3%), 100 (100), 77 (19), 72 (80), 44 (30).

(126)
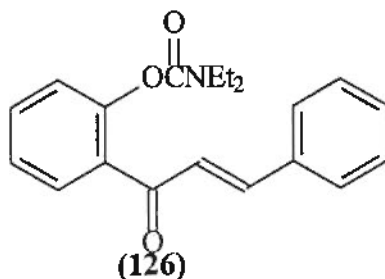
1-(o-N,N, diethylcarbamoyloxyphenyl)-3-phenyl-1-hydroxyprop-2-ene (127)

3-(o-hydroxyphenyl)-1-phenyl-1-methoxyprop-2-ene (134)

NaBH$_4$ (0.11 g 2.86 mmol) was added portionwise to a yellow solution of 1-(o-N,N-diethylcarbamoyloxyphenyl)-3-phenyl-2-propene-1-one **(126)** (0.5 g, 1.55 mmol) in MeOH (15 ml) at 0°C. The reaction was stirred for 45 min after which the reaction mixture turned nearly colourless. TLC showed complete disappearance of the starting material after this time. The reaction was allowed to warm to ambient temperature and stirred for a further 15 mins. The reaction was then quenched with 1M NaOH (12 ml) and the methanol removed under vacuum. The aqueous layer was extracted with ether, dried with anhydrous magnesium sulphate, filtered and reduced under vacuum. The crude mixture was separated on a column using a 4:1 hexane:ethyl acetate mixture to afford 1-(o-N,N,diethylcarbamoyloxyphenyl)-3-phenyl-1-hydroxyprop-2-ene **(127)** (0.26, 53%) and 3-(o-hydroxyphenyl)-1-phenyl-1-methoxyprop-2-ene **(134)** (0.95 g, 14%).

Data for 1-(o-N,N-diethylcarbamoyloxyphenyl)-3-phenyl-1-hydroxyprop-2-ene (127)

δ_H **(200 MHz)** 1.05-1.19 (6H, 2xt, N(CH$_2$CH_3)$_2$; 3.20-3.42 (4H, 2xq, N(CH_2CH$_3$)$_2$; 3.85-3.86 (1H, brs, -OH); 5.43-5.46 (1H, brs, CH-OH); 6.29-6.39 (1H, dd, HO-CH-CH=CH, J=5.06, J=15.86); 6.64-6.72 (1H, dd, CH=CH-Ph, J=1.46, J=15.93); 7.01-7.06 (1H, dd, Ar-H); 7.12-7,35 (7H, m, Ar-H); 7.47-7.52 (H, dd, Ar-H)

δ_C **(50 MHz)** 13.00 and 13.96 (txq, N(CH2CH$_3$)$_2$; 41.66 and 42.07 (2x6, N(CH$_2$CH$_3$)$_2$; 68.76 (d, CH-OH); 122.33 (d, H0-CH=CH), 125.77 (d, CH=CH-Ph); 126.21 (2xd, Ar-C), 127.14 (d, Ar-C); 127.99 (d, Ar-C); 128.16 (2xd, Ar-C); 128.37 (d, Ar-C); 129.38 (d, Ar-C); 129.38 (d, Ar-C); 130.05 (d, Ar-C); 135.27 (s, C-CH-OH); 136.55 (s, C-CH=CH); 148 (s, C-OC=O); 154.33 (s, O=C-N)

m/z (no satisfactory result obtained)

(127)
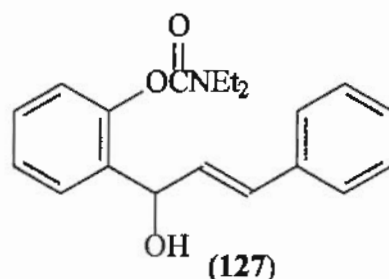
Data for 3-(*o*-hydroxyphenyl)-1-phenyl-1-methoxyprop-2-ene **(134)**:

δ_H **(200 MHz)** 3.45 (3H, s, -OCH_3); 4.95-4.98 (1H, d, CH-OCH$_3$, J=7.03); 6.29-6.40 (1H, dd, CH-CH-OCH$_3$, J=7.03, J=15.91); 6.55-6.63 (1H, d, CH=CHCH, J=15.99); 6.80-6.93 (2H, m, Ar-H); 7.01-7.06 (1H, dd, Ar-H); 7.16-7.39 (6H, m, Ar-H)

δ_C **(50 MHz)** 56.57 (q, -OCH_3); 85.65 (d, CH-OCH$_3$); 117.10 (d, Ar-C); 119.92 (d, Ar-C); 126.72 (2xd, Ar-C); 127.16 (d, CH-CH-OCH$_3$); 128.24 (d, Ar-C); 128.55 (2xd, Ar-C); 129.39 (d, Ar-C); 132.93 (d, CH=CH-CH); 123.93 (s, C-CH=CH); 135.99 (s, C-CHOCH$_3$); 155.42 (s, C-OH)

m/z (EI) 240 (M$^+$, 0%); 207 (100), 178 (17), 131 (46), 89 (7)

(134)
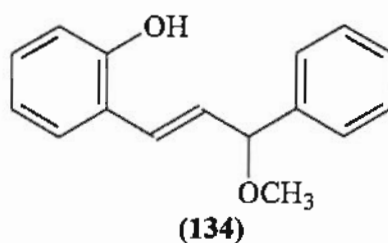
2-Phenyl-2H-1-benzopyran (flav-3-ene) (91)

1-(o-N,N-diethylcarbamoyloxyphenyl)-3-phenyl-prop-2-ene-1-ol (127) (0.180 g, 0.55 mmol) in THF (3 ml) was added dropwise to a suspension of THF (5 ml) and NaH (0.024 g, 1.00 mmol) at 0°C in a round-bottomed flask fitted with a drying tube. After stirring the reaction for 15 min at 0°C it was allowed to warm to room temperature and stirred for a further 12 h (overnight). The reaction was quenched with saturated NH₄Cl. The THF was removed on a rotary evaporator and the aqueous layer extracted with ether. The combined ether layers were dried with anhydrous MgSO₄, filtered and reduced under vacuum. The crude mixture was separated using chromatography with a 4:1 hexane:ethyl acetate mixture to afford 2-phenyl-2H-1-benzopyran (flav-3-ene) (91) (0.061 g, 53%) as a clear liquid.

δ_H (200 MHz) 5.73-5.80 (1H, dd, H_3, J=3.38, J=9.81); 5.88-5.91 (1H, dd, H_2, J=1.87, J=3.33); 6.48-6.54 (1H, ddd, H_4, J=0.55, J=1.89, J=9.85); 6.75-6.81 (1H, m, Ar-H); 6.84-6.88 (1H, dd, Ar-H); 6.97-7.01 (1H, dd, Ar-H); 7.05-7.14 (1H, m, Ar-H); 7.29-7.46 (5H, m, Ar-H).

δ_C (50 MHz) 77.10 (d, C_2); 115.94 (d, Ar-C); 121.13 (d, Ar-C); 123.92 (d, C_4), 124.80 (d, C_3); 126.54 (d, Ar-C); 126.96 (d, Ar-C); 128.31 (d, Ar-C); 128.61 (d, Ar-C); 129.42 (d, Ar-C), 121.25 (s, C_{10}); 140.762 (s, C_1); 153.096 (s, C_9)

m/z (EI) 208 (M⁺, 68%); 207 (95); 178 (21); 131 (100); 89 (25)

(91)
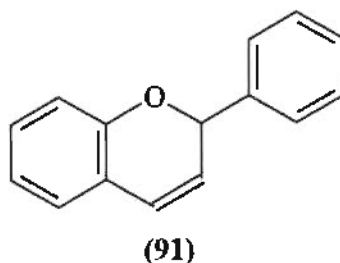
3.2.1 THE SHORTENED SYNTHESIS OF 2-PHENYL-2H-1-BENZOPYRAN (FLAV-3-ENE) (91)

NaBH$_4$ (0.186 g, 4.9 mmol) was added portionwise to a yellow solution of 1-(o-N,N-diethylcarbamoyloxyphenyl)-3-phenyl-2-propene-1-one **(126)** (0.86 g, 2.7 mmol) in MeOH (40 ml), at 0°C. The reaction was stirred at 0°C for a further 1 hour which resulted in pale yellow solution. The reaction mixture was allowed to warm up to room temperature and then refluxed for 16 h. After this time the solution turned an orange-brown and the MeOH was removed under vacuum, affording an orange precipitate. NH$_4$Cl (20ml) was added to the precipitate and extracted with ether. The combined ether layers were dried with anhydrous MgSO$_4$, filtered and concentrated under vacuum. The crude mixture was separated on a column using a 4:1 ratio of hexane:ethyl acetate to afford flav-3-ene **(91)** (0.335 g, 68%) and 3-(o-hydroxyphenyl)-1-phenyl-1-methoxyprop-2-ene **(134)** (0.023 g, 4%).

1-Phenyl-N,N-diethylcarbamate (135)

Phenol (10g, 0.11mol) in THF (10ml) was added dropwise to a suspension of NaH (60% in paraffin) (4.68g, 0.20mol) in THF (30ml) at 0°C. The reaction was allowed to warm to room temperature and then stirred for 0.5h. After cooling to 0°C again N,N-diethylcarbamoyl chloride (15.87g, 0.12mol) in THF (10ml) was added dropwise. The reaction mixture was allowed to warm to room temperature and then stirred for 4hrs. The reaction was quenched with saturated ammonium chloride and the THF removed under vacuum. The aqueous layer was extracted with ether, dried with anhydrous $MgSO_4$, filtered and reduced under vacuum. The crude mixture was distilled to afford the 1-phenyl-N,N-diethylcarbamate (135) as a clear liquid. (19.71g, 96%)

δ_H (200 MHz) 1.12-1.22 (6H, 2xt, $N(CH_2CH_3)_2$); 3.29-3.38 (4H, 2xq, $N(CH_2CH_3)_2$); 7.06-7.17 (3H, m, Ar-H); 7.26-7.35 (3H, Ar-H).

δ_C (50 MHz) 12.67 and 12.84 (2xq, $N(CH_2CH_3)_2$); 41.67 and 41.74 (2xt, $N(CH_2CH_3)_2$; 121.219 (2xd, Ar-C); 124.454 (d, Ar-C); 128.60 (2xd, Ar-C); 151.05 (s, C-OC=O); 153.59 (s, C=O)

m/z (EI) 193 (M^+, 21%); 100 (100), 94 (22), 72 (90), 56 (17)

(135)
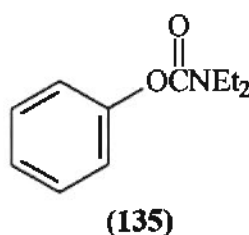
3.2.2 A ONE-POT SYNTHESIS OF FLAV-3-ENE (91)

One-pot synthesis of flav-3-ene (91) and the formation of cinnamyl alcohol (137).

Sec-butyllithium {2.1 ml (1.42M), 3.11 mmol} was added dropwise to a solution of TMEDA (0.361 g, 3.11 mmol) in anhydrous THF (5 ml) at -78°C under a nitrogen atmosphere. 1-Phenyl-N,N-diethylcarbamate (135) (0.50 g, 2,60 mmol) in THF (2 ml) was added, and the solution stirred for 1 h, resulting in a yellow-brown mixture. Distilled cinnamaldehyde (0.48 g, 3.63 mmol) in THF (2 ml) was added and the reaction allowed to warm to room temperature and stirred for 12 h (overnight). The reaction was quenched with NH$_4$Cl and the THF removed under reduced pressure. The aqueous layer was extracted with ether, dried with anhydrous MgSO$_4$, filtered and reduced under vacuum. The crude mixture was separated on a column to afford flav-3-ene (91) (0.054 g, 10%) and cinnamyl alcohol (137) (0.234 g, 67%).

Data for cinnamyl alcohol (137)

δ_H(200MHz) 3.00 (1H, brs, -OH); 4.22-4.25 (2H, dd, -CH_2, J=1.33, J=5.52); 6.22-6.36 (1H dt, CH=CH-CH$_2$, J=15.91, J=5.57); 6.51-6.59 (1H, dt, Ph-CH=CH-CH$_2$, J=15.93, J=1.38); 7.19-7.53 (5H, Ar-H).

δ_C(50MHz) 63.26 (t, CH_2); 126.40 (2xd, Ar-C); 127.53 (d, CH=CH-CH$_2$); 128.51 (3xd, Ar-C); 130.75 (d, Ph-CH=CH); 136.65 (s, C-CH=CH).

m/z (EI) 134 (M$^+$, 75%), 105 (47), 92 (100), 91 (76), 48 (55).
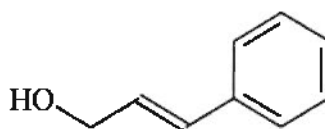
(137)

3.2 SYNTHESIS OF 2-CINNAMYL-2H-1-BENZOPYRAN.

1-(*o*-N,N-diethylcarbamoyloxyphenyl)-5-phenyl-2,4-pentadien-1-one (138)

HCl (g) was generated in the same way as outlined for the synthesis of (126). When HCl (g) was bubbled into a mixture of *o*-N,N-diethylcarbamoyloxyacetophenone (125) (1.5 g, 6.4 mmol) and distilled cinnamaldehyde (1.01 g, 7.66 mmol), the solution turned an intense red and then an intense blue colour. HCl (g) was bubbled into the mixture for a total of 15 min. The reaction vessel was stoppered and sealed with parafilm, stirred for 12 h and quenched with NaHCO₃ and extracted with ether. The combined ether layers were dried with anhydrous MgSO₄, filtered and reduced under vacuum to afford a crude mixture, black in colour. This was passed through an ether plug of silica gel. The eluant was reduced under vacuum and the crude mixture separated on a column, using 4:1 ratio of hexane: ethyl acetate. This afforded yellow crystals of 1-(*O*-N,N-diethylcarbamoyloxyphenyl)-5-phenyl-2,4-pentadien-1-one (138) (1.24 g, 56%), mp=88°C. *o*-N,N-diethylcarbamoyloxyacetophenone (125) was recovered in a 27% yield.

N.B The data documented below is not conclusive (see page 71)

δ_H **(200 MHz)** (in CDCl₃) 1.10-1.28 (6H, 2xq, N(CH₂C*H₃*)₂); 3.26-3.4 (4H, 2xq, N(C*H₂*CH₃)₂); 6.60-6.68 (1H, d, *H₅*, *J*=15.22); 6.82-6.99 (1H, dd, *H₂* *J*=17.9, *J*=15.5); 6.86-7.02 (1H, *H₃*, overlapping dd (triplet) *J*=15.6); 7.23-7.59 (10H, m, 9xAr-*H*, *H₄*).

δ_C **(50 MHz)** 13.34 and 14.6 (2xq, N(CH₂*C*H₃)₂); 41.90 and 42.28 (2xt, N(*C*H₂CH₃)₂); 123.47 (d, Ar-*C*); 125.23 (d, Ar-*C*); 126.63 (d, *C₂*); 127.24 (2xd, Ar-*C*); 128.84 (2xd, Ar-*C*); 129.23 (d, Ar-*C*); 129.30 (d, *C₅*); 129.36 (d, Ar-*C*); 131.81 (d, Ar-*C*); 141.91 (d, *C₃*); 145.48 (d, C4); 132.92 (s, *C*-C=O); 135.98 (s, *C*-CH=CH); 149.15 (s, *C*-OC=O); 153.49 (s, N-*C*=O); 192.77 (s, O=*C*-CH=CH).

m/z (EI) (M=351) 349 (M⁺, <1%), 128 (4), 115 (3), 100 (100), 72 (38).

(138)
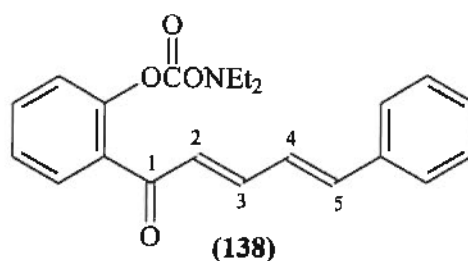
2-Cinnamyl-2H-1-benzopyran (139)

1-(*o*-N,N-diethylcarbamoyloxyphenyl)-5-phenyl-2,4-pentadien-1-one   **(138)**   (0.58g, 1.67mmol) and NaBH$_4$ (0.12g, 3.10mmol) was reacted in the same way as for the synthesis of **(91)**. Centrifugal chromatography using a 4:1 ratio of hexane:ethyl acetate afforded 2-cinnamyl-2H-1-benzopyran **(139)** as a red oil (0.25g, 58%)

δ_H **(200 MHz)** 5.36-5.4 (1H, dddd, H_3); 5.60-5.68 (1H, dd, H_4, J=3.85, J=9.80); 6.25-6.36 (1H, dd, H_2 J=6.88, J=15.84); 6.37-6.43 (1H, dd, H_5, J=1.56, J=9.78); 6.55-6.64 (1H, dd, H_1 J=0.72, J=15.90); 6.77-7.33 (9H, m, Ar-H).

δ_C**(50MHz)** 75.52 (d, C_3); 116.04 (d, Ar-C); 121.11 (d, Ar-C); 123.73 (d, C_4); 124.07 (d, C_5); 126.56 (d, Ar-C); 126.65 (2xd, Ar-C); 126.95 (d, C_2); 127.93 (d, Ar-C); 128.44(2xd, Ar-C); 129.27(d, Ar-C); 131.95(d, C_1); 121.44(s, C_6); 136.12(s, C_0); 152.89(s, C_7).

m/z (EI) 353 (M$^+$, 6%), 236 (13), 117 (4), 100 (100), 72 (22).

(139)
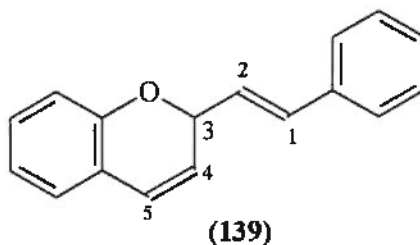
3.3 THE SYNTHESIS OF 4',5'.6',7-TETRAMETHOXYFLAV-3-ENE.

1,2-Dimethoxybenzene (147) (veratole)

NaH (60% in paraffin) (4.58 g, 0.32 mol) was added to a solution of catechol (7 g, 0.064 mol) and methyl iodide (40 g, 0.29 mmol) in anhydrous THF (350 ml) at room temperature. On addition of NaH the solution turned grey and then blue. The flask was stoppered with a drying tube and stirred for 24 h. The THF was removed and the residue was distributed between water (100 ml) and ether (150 ml). The ether layer was washed twice with water, dried over anhydrous MgSO$_4$, filtered and removed under vacuum. The residue was distilled (67°C) to afford 1,2-dimethoxybenzene (147) (7.30 g, 80%).

δ_H (200 MHz) 3.818 (6H, s, -OCH_3); 6.80 - 6.91 (4H, m, Ar-H)

δ_C (50 MHz) 55.68 (2xq, -OCH$_3$); 111.26 (2xd, Ar-C); 120.81 (2xd, Ar-C); 148.96 (2xs, C-OCH$_3$)

m/z (EI) 138 (M$^+$, 100%), 123 (38), 95(37), 77 (84), 65 (56)

(147)
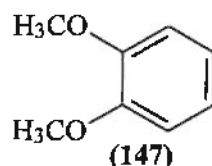
3,4-Dimethoxynitrobenzene (Nitroveratrole) (148)

1,2-Dimethoxybenzene (147) (4.81 g, 0.035 mol) was placed in a round bottom flask and cooled to 0°C in an ice bath. Nitric acid (14.5 ml of a 55% aqeous solution), was added dropwise to the 1,2-dimethoxybenzene, which resulted in the formation of a yellow precipitate. The reaction is highly exothermic. After 10 min the reaction was quenched with saturated NaHCO$_3$ and extracted with chloroform. The combined chloroform layers were dried with anhydrous MgSO$_4$, filtered and reduced to afford 3,4-dimethoxynitrobenzene (148) (5.70g, 97%) as yellow crystals.

δ_H **(200 MHz)** 3.97 (3H, s, -OCH_3); 4.00 (3H, s,OCH_3); 6.91-6.96 (1H, d, H_5, J=8.91); 7.71-7.73 (1H, d, H_2, J=2.56); 7.87-7.93 (1H, dd, H_6, J=2.64, J=8.94).

δ_C **(50 MHz)** 56.29 and 56.48 (2xq, OCH_3); 106.30 (d, C_5); 109.85 (d, C_6); 117.79 (d, C_2); 141.38 (s, C_3); 148.80 (s, C_4); 154.51 (s, C_1).

m/z (EI) 183 (M$^+$, 100%), 137 (16), 107 (10), 79 (54), 77 (35).

(148)
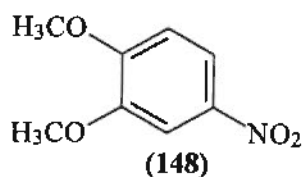
3,4-Dimethoxyaniline (149) (veratrylamine)

Nitroveratrole **(148)** (5 g, 0.027 mol) was suspended in ethanol (50 ml) and placed in an autoclave at 50°C. Palladium oxide was used as a catalyst. Hydrogen (0.8 MPa) was applied to the reaction mixture for 2 h. The palladium oxide was then filtered off and the ethanol was removed under vacuum to afford the 3,4-dimethoxyaniline **(149)** (3.34 g, 84%) as a yellow oil which goes black when exposed to the atmosphere.

δ_H **(200 MHz)** 3.40 (2H, brs, NH_2); 3.79 (3H, s, -OCH_3); 3.81 (3H, s, -OCH_3); 6.19-6.25 (1H, dd, H_6, J=2.58, J=8.35); 6.29-6.30 (1H, d, H_2, J=2.56); 6.67-6.72 (1H, d, H$_5$, J=8.4)

δ_C **(50 MHz)** 55.66 and 56.54 (2xq, OCH_3); 100.62 (d, C_2); 106.29 (d, C_6); 112.96 (d, C_5); 140.68 (s, C_4); 142.02 (s, C_1); 149.76 (s, C_3)

m/z (EI) 153 (M$^+$, 68%), 138 (100), 110 (71), 95 (42), 67 (34)

(149)
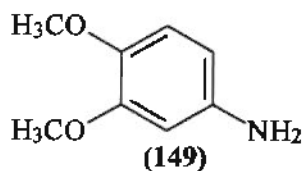
3,4-Dimethoxyphenyldiazonium Fluoborate (153)

Ethanol was saturated with HCl (g) (generated using a Kipps apparatus) to which veratrylamine (149) (3.2 g, 0.029 mol) in ethanol was added. The ethanol was reduced to a small volume under vacuum, ether was added and the amine hydrochloride was filtered off and dried. The yield was quantitative. Sodium nitrite (1.69 g, 0.023 mol) was dissolved in a minimum amount of water and added to a solution of the amine hydrochloride (3.84 g, 0.020 mol) and concentrated HCl (10 ml) at 0°C. The reaction was stirred for 15 min after being allowed to warm up to room temperature. Fluoroboric acid (4.3 ml, 0.026 mol) of a 54% diethyl ether solution was added which resulted in the formation of a precipitate. The salt was filtered off under suction and washed consecutively with fluoroboric acid (HBF$_4$), ethanol and ether. The yield of this crude fluoborate salt (153) was (4.34 g, 85%). It was recrystallized from acetone and benzene which resulted in a considerable decrease in yield. mp = 122°C.

δ_H (200 Mhz) (in d-Acetone) 3.97 (3H, s, OCH_3); 4.15 (3H, s, OCH_3); 7.51-7.56 (1H, d, H_5, J=9.16); 8.16-8.18 (1H, d, H_2, J=2.55); 8.47-8.53 (1H, dd, H_6, J=2.56, J=9.16)
δ_C (50 MHz) 57.24 (q, -OCH$_3$); 58.08 (q, -OCH$_3$); 113.26 (d, Ar-C); 114.27 (d, Ar-C); 131.81 (d, Ar-C); 103.10 (s, C_4); 150.97 (s,C_1); 161.57 (s, C$_3$).
m/z - no satisfactory result obtained.

(153)
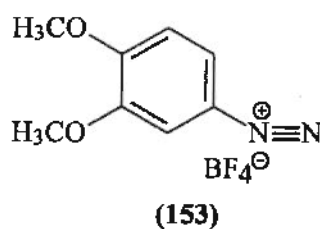
2-Hydroxy-4,5-dimethoxyacetophenone (146)

3,4-dimethoxyphenyldiazonium fluoborate (153) (5.89 g, 0.023 mol) was placed in a round-bottomed flask with glacial acetic acid (30 ml) and heated under reflux until nitrogen evolution was evident. The fluoborate went into solution, and after the vigorous reaction which took place had subsided, the solution was refluxed for ten minutes. It was then cooled and the product which separated was filtered off. The crude product was dissolved by heating it in 75 ml of 15% potassium hydroxide solution, with activated charcoal. The charcoal was filtered off and the solution acidified with hydrochloric acid. The resultant precipitate was filtered off and washed with H_2O and dried. The yield of 2-hydroxy-4,5-dimethoxyacetophenone (146) was 3.20 g; 71%, which was recrystallized from ethanol and H_2O, mp=112°C.

δ_H (200 MHz) 2.55 (3H, s, O=C-CH_3); 3.79 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 6.45 (1H, s, H_3); 7.26 (1H, s, H_6); 12.67 (1H, s, Ph-OH)

δ_C (50 MHz) 26.53 (q, O=C-CH$_3$); 56.28 and 56.81 (2xq, OCH$_3$); 100.99 (d, C_3); 113.51 (d, C_6); 112.32 (s, C_1); 113.58 (s, C_5); 142.99 (s, C_2); 160.78 (s, C_4); 203.49 (s, C=O).

m/z (EI) 192 (M^+, 70%), 181 (100), 135 (11), 95 (9), 69 (13)
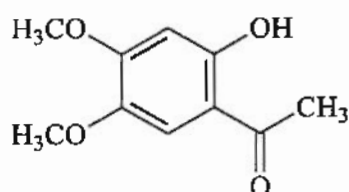
(146)

4,5-Dimethoxy-2-N,N-diethylcarbamoyloxyacetophenone (144)

NaH (60% in paraffin) (0.27g, 6.7 mmol) was added portionwise to a solution of 2-hydroxy-4,5-dimethoxyacetophenone (146) (1.10 g, 5.61 mmol) and THF (30 ml) at 0°C. This resulted in the precipitation of a green salt. The reaction mixture was allowed to warm up to room temperature and stirred for 0.5 hr. Diethylcarbamoyl chloride (0.913 g, 6.74 mmol) in THF (10 ml) was added dropwise and the solution refluxed for 48 hrs. The reaction was quenched with saturated NH_4Cl, the THF removed under vacuum and the aqueous layer extracted with ether. The ether layers were dried over anhydrous $MgSO_4$, filtered, and reduced under vacuum. The crude mixture was separated on a column to afford 4,5-dimethoxy-2-N,N-diethylcarbamoyloxyacetophenone (144) (1.42 g, 86%), mp=53°C. The alcohol, 2-hydroxy-4,5-dimethoxyacetophenone (146) was recovered in a 10% yield.

δ_H (200 MHz) 1.18-1.33 (6H, 2xt, $N(CH_2CH_3)_2$); 2.53 (3H, s, $O=C-CH_3$); 3.36-3.58 (4H, 2xq, $N(CH_2CH_3)$; 3.91 (3H, s, OCH_3); 3.92 (3H, s, OCH_3); 6.60 (1H, s, H_6); 7.36 (1H, s, H_3).

δ_C (50 MHz) 13.33 and 14.23 (2xq, $N(CH_2CH_3)_2$; 41.81 and 42.21 (2xt, $N(CH_2CH_3)_2$); 56.21 (2xq, 2x -OCH_3); 106.92 (d, C_3); 111,45 (d, C_6); 123.26 (s, C_1); 145.76 (s, C_5); 146.22 (s, C_2); 152.99 (s, C_4); 153.84 (s, $N-C=O$); 195.71 (s, $CH_3C=O$).

m/z (EI) 295 (M^+, 8%), 181 (3), 167 (1), 100 (100), 72 (65).

(144)
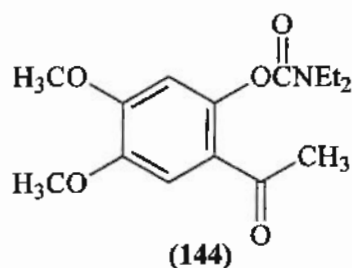
3,4-Dimethoxybenzaldehyde (145) (veratric aldehyde)

In a three-neck round-bottomed flask fitted with a stirrer bar, a reflux condenser and two separating funnels, vanillin (10 g, 0.066 mol) was melted using an oil bath. With vigorous stirring a solution of potassium hydroxide (6.51g 0.07 mol) in ml H_2O (10.61) was added dropwise. Just after this was started, the addition of dimethyl sulphate (10.79 g, 8.1 ml, 0.085 mol) was begun. Before use, the dimethyl sulphate was washed with ice water and a cold saturated sodium bicarbonate solution. The external heat was stopped after a minute and the mixture continued to reflux from the heat of the reaction. A turbidity soon developed and separation into two layers occurred. After the addition of both reagents a final yellow colour was permanent and the reaction mixture was alkaline to litmus. The product was extracted with ether and the ether layer washed with water. The ether layer was then dried over anhydrous $MgSO_4$, filtered and reduced under vacuum to afford veratric aldehyde (16) (9.82 g, 90%) mp=41°C.

δ_H (200 MHz) 3.92 (3H, s, -OCH_2); 3.95 (3H, s, -OCH_3); 6.96 - 6.99 (1H, d, H_5, J=8.15); 7.38-7.39 (1H, d, H_2, J=1.9); 7.42 - 7.47 (1H, dd, H_6, J=1.9, J=8.2); 9.84 (1H, s, CHO).

δ_C (50 MHz) 55.88 (q, -OCH_3); 56.11 (q, -OCH_3); 108.83 (d, C_5); 110.39 (d, C_2); 126.78 (d, C_6); 130.05 (s, C_1); 149.51 (s, C_3); 154.39 (s, C_4); 190.82 (d, HC=O).

m/z (EI) 166 (M^+, 100%); 165 (60), 95 (18), 77 (16).

(145)
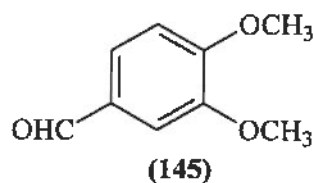
1-(2-N,N-Diethylcarbamoyloxy-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-ene-1-one (143) and

1-(2-hydroxy-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)prop-2-ene-1-one (154)

4,5-Dimethoxy-2-N,N-diethylcarbamoyloxyacetophenone **(144)** (1.2 g, 4.33 mmol) and 3,4-dimethoxybenzaldehyde **(145)** (0.86 g, 5.20 mmol) were dissolved in a minimum amount of THF and treated in the same way as for the synthesis of 1-(o-N,N-diethylcarbomoyloxyphenyl)-3-phenyl-2-propene-1-one **(126)** After work-up the crude mixture was separated on a column using 1:1 mixture of hexane:ethyl acetate, to afford **(143)** (1.06 g, 55%) as yellow crystals (mp=110°C) and **(154)** (0.09 g, 5%). 4,5-Dimethoxy-(o-N,N-diethylcarbamoyloxy)acetophenone **(144)** was recovered in a 27% yield (0.34 g).

Data for **(143)**

δ_H **(200 MHz)** 1.01-1.13 (6H, 2xt, N(CH$_2$CH_3)$_2$; 3.23-3.32 (4H, 2xq, N(CH_2CH$_3$)$_2$); 3.91 (3H, s, -OCH_3); 3.92 (6H, s, (-OCH_3)$_2$); 3.94 (3H, s, -OCH_3); 6.71 (1H, s, H_a); 6.85-6.89 (1H, d, H_g, J=8.34); 6.99-7.07 (1H, d, H_d, J=15.84); 7.08-7.09 (1H, d, H_e, J=2.01); 7.14-7.19 (1H, dd, H_f, J=1.93, J=8.24); 7.18 (1H, s, H_b); 7.52-7.60 (1H, s, H_e, J=15.86)

δ_C **(50 MHz)** 13.18 and 14.06 (2xq, N(CH$_2$CH$_3$)$_2$); 41.68 and 42.13 (2xt, N(CH$_2$CH$_3$)$_2$); 55.89, 55.97, 56.24, 56.32 (4xq, -OCH$_3$); 106.75 (d, Ar-C); 110.11 (d, Ar-C); 110.98 (d, Ar-C); 111.38 (d, Ar-C); 122.82 (d, O=C-CH=C); 124.13 (d, Ar-C); 144.16 (d, Ar-C); 144.16 (d, O=C-CH=CH); 124.89 (s, C-C=O); 127.78 (s, C-CH=CH); 149.08 (C-O-C=O); 146.41, 151.19.96 (4xq, -OCH$_3$); 153.73 (s, N-C=O); 191.12 (s, O=C-CH=CH).

m/z (EI) 4.44 (M$^+$, 2%); 343 (2), 207 (3), 100 (100), 72 (48).

(143)
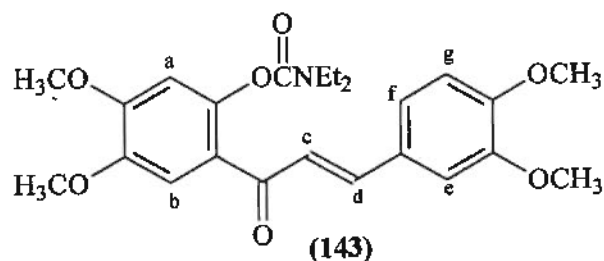
Data for **(154)**.

δ_H (200 MHz) 3.92, 3.93, 3.94, 3.97 (12H, 4xs, -OCH_3); 6.51 (1H, s, H_a); 6.89-6.94 (1H, d, H_g, J=8.35); 7.14 - 7.16 (1H, d, H_e, J=2.04); 7.25 - 7.31 (1H, dd, H_f, J=1.74, J=1.74, J=8.27); 7.27 (1H, s, H_b); 7.33-7.41 (1H, d, J=15.4, H_c); 7.82-7.89 (1H, d, H_d, J=15.36); 13.48 (1H, s, -OH).

δ_C **(50 MHz)** 56.02, 56.18, 57.16 (4xq. -OCH_3); 100.8 (d, Ar-C); 110.67 (d, Ar-C); 111.15 (d, Ar-C); 111.44 (d, Ar-C); 118.96 (d, Ar-C); 123.02 (d, O=C-CH); 144.717 (d, 0=C-CH=CH); 112.03 (s, C-C=O); 127.75 (s, C-CH=CH); 141.82, 149.23, 151.57, 156.99 (4xs, C-OCH$_3$); 161.73 (s, C-OH); 191.43 (s, C=O)

m/z (EI) (no satisfactory result obtained)

(154)
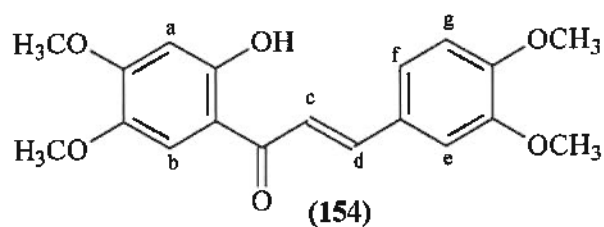
2-(4'5'-Dimethoxyphenyl)-2H-1-(6,7-dimethoxybenzopyran) (142)

(143) (0.96 g, 2.20 mmol) in MeOH (20 ml) was treated in the same way as outlined for the synthesis of flav-3-ene (91). The crude mixture was separated on a column with a 1:1 ratio of hexane:ethyl acetate to afford a red foam of 2-(4'5'-dimethoxyphenyl)-2H-1-(6,7-dimethoxybenzopyran) (142) (0.33 g, 47%).

δ_H (200 MHz) 3.77, 3.80, 3.83, 3.85 (12H, 4xs, -O-CH_3); 5.61-5.68 (1H, dd, H_3, J=3.36, J=9.7); 5.75-5.78 (1H, dd, H_2, J=2.04, J=3.28); 6.41 (1H, s, H_8); 6.43-6.49 (1H, dd, H_4, J=1.76, J=9.75); 6.56 (1H, s, H_5); 6.79-6.84 (1H, d, H_3, J=7.89); 6.95-7.01 (1H, dd, H_2 J=1.94, J=10.33); 7.00 (1H, d, H_6, J=1.93)

δ_C (50 MHz) 55.75, 55.80, 56.39 (4xq, -OCH$_3$); 77.01 (d, C_2); 100.69 (d, Ar-C); 110.38 (d, Ar-C); 110.87 (d, Ar-C); 119.77 (d, Ar-C); 122.31 (d, C_4); 124.04 (d, C_3); 113.24 (s, C_{10}); 133.13 (s, $C_{1'}$); 143.3, 147.48, 148.98, 149.07 (4xs, C-OCH$_3$); 149.78 (s, C_7)

m/z (EI) 328 (M$^+$, 100%); 327 (80); 313 (26); 164 (15), 57 (9).

(142)
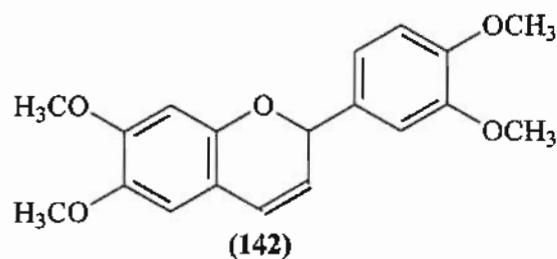
2-Phenyl-4-hydroxy-1-benzopyran (flavan-4-ol)(155)

1-(*O*-Hydroxyphenyl)-3-phenyl-1-propanol (156)

1-(*O*-Hydroxyphenyl)-3-phenyl-1-propene (157)

A dry round-bottomed flask, equipped with a magnetic stirrer bar, pressure-equalising dropping funnel, and a reflux condenser was flushed with dry nitrogen and maintained under a positive nitrogen pressure. The flask was then charged with flav-3-ene (**91**) (1 g, 4.80 mmol) and THF (2 ml) and cooled to 0-5°C with an ice bath. Borane-dimethyl sulphide (BMS) (1.8 ml of a 2M solution, 3.21 mmol) was then added dropwise and the solution stirred for 3 hrs at ambient temperature. Ethanol (1.6 mls) was then added, followed by 0.6 mls of 3M sodium hydroxide. After cooling to 0°C in the ice bath, hydrogen peroxide (0.6 ml of a 30% aqueous solution) was added dropwise. The cooling bath was removed and the reaction mixture was heated at reflux for 1 h. The reaction was then poured into ice water (20 ml) and extracted with ether. The ether was washed with saturated aqueous sodium chloride, dried over anhydrous $MgSO_4$, filtered and concentrated on a rotary evaporator. The crude mixture was separated using centrifugal chromatography repeatedly. This afforded a diastereomeric mixture of flavan-4-ol (**155**) (0.13 g, 12%), mp=99°C; 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanol (**156**) (0.08 g, 8%), mp=57°C; and 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (**157**) (0.120 g, 10%) as a clear liquid.

Data for the of diastereomeric mixture of flavan-4-ol (**155**). (M=major , N=minor)

δ_H (**200MHz**) 1.96-2.46 (4H, m, H_3(M,N)); 4.72-4.75 (1H, t, H_4(M)); 4.92-5.01 (1H, m, H_4(N)); 5.06-5.13 (1H, dd, H_2(N), *J*=1.92, *J*=11.63); 5.19-5.26 (1H, dd, H_2(M), *J*=2.66, *J*=11.62); 6.84-7.48 (18H, m, Ar-*H*(M,N)).

δ_C (**50MHz**) 38.12 (t, C_3(M)); 39.82 (t, C_3(N)); 63.65 (d, C_4(M)); 65.60 (d, C_4(M)) 72.94 (d, C_2(M)); 76.78 (d, C_2(N)); 116.60 (d, Ar-*C*(N)); 117.3 6(d, Ar-*C*(N)); 120.71 (d, Ar-*C*(M)); 120.85 (d, Ar-*C*(N)); 126.01 (2xd; Ar-*C*(N)); 126.17 (2xd; Ar-*C*(M)); 126.90 (d, Ar-*C*(N); 127.96 (d, Ar-*C*(M)); 128.14 (2xd; Ar-*C*(N)); 128.49 (d, Ar-*C*(M)); 128.56 (d, Ar-*C*(M)); 129.03 (d, Ar-*C*(N)); 129.91 (d, Ar-*C*(M)); 129.99 (d,

Ar-C(N)); 123.28 (s, C_{10}(M)); 125.64 (s, C_{10}(N)); 140.37 (s, C_1(N)); 140.81 (s, C_1(M)); 154.35 (s, C_9(N)); 154.75 (s, C_9(M)).

m/z (EI) 226 (M^+ (major), 6%), 207 (10), 121 (47), 104 (100),77 (19); 226 (M^+ (minor), 8%), 207 (13), 121 (52), 104 (100), 77 (16).

(155)
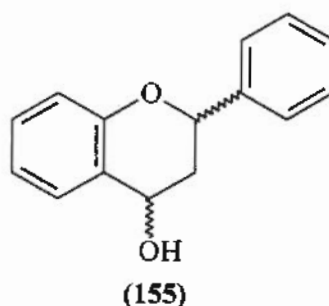
Data for 1-(o-hydroxyphenyl)-3-phenyl-1-propanol **(156)**.

δ_H **(200 MHz)** 1.82-2.15 (2H, m, Ph-CH_2); 2.63-2.75 (1H, m, HO-CH-CH_2); 2.81-2.97 (1H, m, HO-CH-CH_2); 3.0-3.9 (1H, brs, CH-OH); 4.53-4.59 (1H, dd, CH-OH, J=3.98, J=10.2); 6.78-6.82 (2H, m, Ar-H); 7.04-7.13 (2H, m, Ar-H); 7.18-7.33 (5H, m, Ar-H); 7.20-7.80 (1H, brs, Ph-OH).

δ_C **(50 MHz)** 25.84 (t, HOCH-CH$_2$-); 39.32 (t, Ph-CH$_2$); 116.10 (d, Ar-C); 120.74 (d, Ar-C); 125.73 (d, Ar-**C**); 127.58 (2xd, Ar-C); 127.67 (d, Ar-C); 128.44 (2xd, Ar-C); 130.54 (d, Ar-C); 127.22 (s, C-CH-OH); 143.74 (s, C-CH$_2$); 154.29 (s, C-OH).

m/z (EI) 228 (M^+, 91%), 104 (72), 91 (64), 79 (71), 77 (100).

(156)
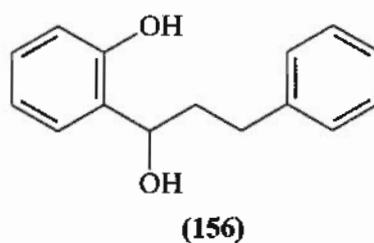
Data for 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene **(157)**.

δ_H **(200 MHz)** 3.54-3.57 (2H, d, PhCH_2, *J*=5.75); 4.91-4.976 (1H, brs, Ar-OH); 6.28-6.42 (1H, dt, CH=CH-CH$_2$, *J*=15.86, *J*=5.68); 6.45-6.53 (1H, d, CH=CH-CH$_2$, *J*=16.03); 6.76-6.80 (1H, dd, Ar-*H*); 6.83-6.91 (1H, m, Ar-*H*); 7.07-7.36 (7H, m, Ar-*H*)

δ_C **(50 MHz)** 34.02 (t, CH_2); 115.61 (d, Ar-*C*); 120.87 (d, Ar-*C*); 126.09 (2xd, Ar-*C*); 127.18 (d, CH=CH-CH); 127.78 (d, Ar-*C*); 128.38 (2xd, Ar-*C*); 130.32 (d, Ar-*C*); 131.42 (d, CH=CH-CH); 125.48 (s, *C*-CH=CH); 136.94 (s, *C*-CH$_2$); 15389 (s, *C*-OH)

m/z (EI) 210 (M$^+$, 90%), 115 (54), 104 (60), 91 (100), 77 (58).
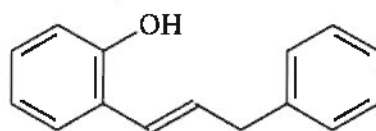
(157)

2-Phenyl-3-hydroxy-4-isopropoxy-1-benzopyrans (159) and (160)

2-Phenyl-3,4-dihydroxy-1-benzopyran (flavan-3,4-diol) (161)

A solution of magnesium monoperphthalate hexahydrate (MMPP) (1.66 g, 3.37 mmol) in a minimum amount of water (~13 ml) was added to a solution of flav-3-ene (91) (0.7 g, 3.37 mmol) in isopropyl alcohol (10 ml). The mixture was then refluxed for 12 hrs. After this time, the isopropanol was removed under vacuum. The aqueous layer was saturated with NaCl and extracted with $CHCl_3$. The combined $CHCl_3$ layers were washed twice more with H_2O, dried over anhydrous magnesium sulfate, filtered and reduced under vacuum. Centrifugal chromatography using a 6:2 hexane:ethyl acetate mixture afforded a diastereomeric mixture of the 2-phenyl-3-hydroxy-4-isopropoxy-1-benzopyrans (159) and (160) (0.57 g, 6%) and mixture of the flavan-3,4 diol (161) and the compound that was not characterised. The diastereomeric mixture of (159) and (160) was separated using centrifugal chromatography with a 45:1 mixture of hexane:ethyl acetate to afford a 1:3 ratio of (159) : (160). The flavan-3,4-diol (161) was separated as white crystals, from the unidentifiable compound using preparative TLC with a 6:2 mixture of hexane to ethyl acetate. The diol (161) can also be separated using flash chromatography with a 6:2 mixture of hexane:ethyl acetate. The yield of (161) was 0.31 g (38%), mp=138°C

Data for 2-Phenyl-3-hydroxy-4-isopropoxy-1-benzopyran (159)

δ_H **(200 MHz)** 1.17-1.20 (3H, d, -CH-CH_3); 1.28-1.31 (3H, d, -CHCH_3); 2.59-2.63 (1H, d, -OH, J=8.06); 3.95-4.07 (1H, hep, CH_3CHCH_3); 4.05-4.16 (1H, ddd, H_3, J=8.45); 4.49-4.51 (1H, d, H_4, J=3.59); 5.18-5.22 (1H, d, H_2), J=8.53); 6.91-6.99 (2H, m, Ar-H); 7.23-7.31 (2H, m, Ar-H); 7.32-7.48 (5H, m, Ar-H).

δ_C **(50 MHz)** 22.04 (q, CH-CH_3); 23.30 (q, CH-CH_3); 69.48 (d, C_3); 69.79 (d, $CHCH_3$); 70.31 (d, C_4); 77.52 (d, C_2); 116.79 (d,Ar-C); 120.37(d, Ar-C); 127.21 (2xd, Ar-C); 128.35 (d, Ar-C); 128.53 (2xd, Ar-C); 130.09 (2xd, Ar-C); 120.84 (s, C_{10}); 138.59 (s, C_1); 154.15 (s, C_9)

m/z (EI) 284 (M^+, 1%); 165 (40), 123 (100), 122 (95), 91 (36)

(159)
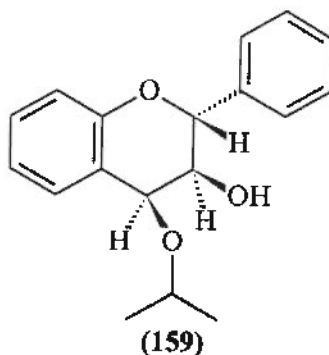
Data for **2-Phenyl-3-hydroxy-4-isopropoxy-1-benzopyrans (160)**.

δ_H **(200 MHz)** 1.25-1.28 (3H, d, CH-CCH_3, $J = 6.14$); 1.44-1.37 (3H, d, CH-CH_3, J=6.11); 1.87 - 1.89 (1H, d, -OH, J=3.02); 3.98-4.08 (1H, ddd, H_3, J=3.02, J=8.17, J=9.87); 4.69-4.73 (1H, d, H_4, J=8.17); 4.05-4.90 (1H, d, H_2, J=9.79); 6.83-6.84 (1H, d, Ar-H); 6.87-7/04 (1H, m, Ar-H); 7.14-7.25 (1H, m, Ar-H); 7.37-7.25 (6H, m, Ar-H).

δ_C **(50 MHz)** 22.49 (q, -CHCH_3); 23.33 (q, -CHCH_3); 73.06 (d, H_3CCHCH$_3$); 73.45 (d, C_3); 76.53 (d, C_4); 81.14 (d, C_2); 116.22 (d, Ar-C); 121.37 (d, Ar-C); 127.64 (2xd, Ar-C); 127.96 (d, Ar-C); 128.77 (2xd, Ar-C); 128.96 (d, Ar-C); 128.99 (d, Ar-C); 123.67 (s, C_{10}); 137.33 (s, C_1) 154.06 (s, C_9)

m/z (EI) 284 (M$^+$, 4%); 165 (51), 123 (100), 122 (92), 91 (27)

(160)
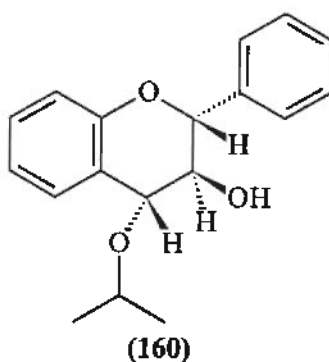
Data for flavan-3,4-diol **(161)**.

δ_H **(200 MHz)** (in d-pyridine) 4.26-4.33 (1H, dd, H_3, J=3.57, J=9.18; 5.01-5.03 (1H, d, H_4, J=3.53); 5.54-5.58 (1H, d, H_2, J=9.16); 6.87-7.06(2H, m, Ar-H) 7.13-7.29 (4H, m, Ar-H); 7.50-8.57 (3H, m, Ar-H).

δ_C **(50 MHz)** 67.72 (d, C_4); 72.19 (d, C_3); 78.75 (d, C_2); 117.25 (d, Ar-C) 121.51 (d, Ar-C); 125.97 (d, Ar-C); 128.80 (d, Ar-C); 128.94 (2xd, Ar-C); 129.08 (2xd, Ar-C); 130.31 (d, Ar-C); 132.04 (d, Ar-C); 125.97 (s, C_{10}); 140.95 (s, C_1·); 155.51 (s, C_9).

m/z (EI) 242 (M$^+$, 10%), 141 (55), 120 (100), 91 (51), 57 (39).

(161)
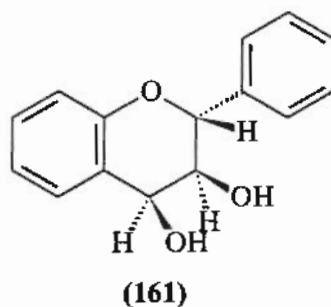
2-Phenyl-3,4-isopropylidenedioxy-1-benzopyran (Acetal) (162)

Flavan-3,4-diol **(161)** and compound X (0.17g, 0.70mmol) were dissolved in dichloromethane, to which 2,2-dimethoxypropane (0.09g, 0.82mmol) was added. A spatula tip of p-toluene sulphonic acid was added and the reaction stirred for 24h. The reaction was quenched with saturated ammonium chloride and the aqueous layer extracted with chloroform. The combined chloroform layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The crude mixture was then separated using centrifugal chromatography with a 6:2 mixture of hexane:ethyl acetate to afford white crtstals (mp=76°C) of the acetal **(162)** (0.032g, 18%).

δ_H **(200 MHz)** 1.49 (3H, s, C-CH_3); 1.58 (3H, s, C-CH_3); 4.30-4.38 (1H, dd, H_3, J=5.59, J=9.8); 4.56-4.61 (1H, d, H_2, J=9.8); 5.12-5.15 (1H, d, H_4, J=5.56); 6.99-7.10 (2H, m, Ar-H); 7.25-7.53 (7H, m, Ar-H).

δ_C **(50 MHz)** 25.86 (q, CH_3); 28.43 (q, CH_3) 71.28 (d, C_4); 75.86 (d, C_3); 77.88 (d, C_2); 117.35 (d, Ar-C); 121.90 (d, Ar-C); 127 (2xd, Ar-C); 128.52 (d, Ar-C); 128.56 (2xd, Ar-C); 129.94 (d, Ar-C); 130.83 (d, Ar-C); 109.21 (s, H_3C-C-CH_3); 120.21 (s, C_{10}); 137.84 (s, C_1); 155.22 (s, C_9).

m/z (EI) 282 (M$^+$, 32%), 197 (100), 161 (66), 103 (66), 77 (46)

(162)
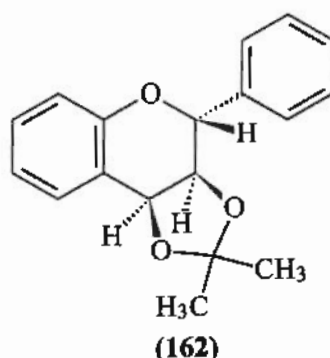
3-Bromo-4-hydroxy-2-phenyl-1-benzopyran (165)

N-bromosuccinimide (NBS) (0.47 g, 2.6 mmol) was added to a solution of flav-3-ene **(91)** (0.5 g, 2.4 mmol) in THF (2 ml) and H_2O (1.53 ml). The reaction mixture was stirred at room temperature for 5 hrs. Brine (10 ml) was added to the reaction mixture and the THF was removed under vacuum. The aqueous layer was extracted with ether. The combined ether layers were washed three times with 15 ml portions of brine, dried over anhydrous $MgSO_4$, filtered and reduced under vacuum. The crude mixture was purified using centrifugal chromatography with an 8:1 hexane:ethyl acetate mixture to afford 3-bromo-4-hydroxy-2-phenyl-1-benzopyran **(165)** (0.37 g, 50%) as a yellow liquid which blackens when exposed to the atmosphere.

δ_H **(200 MHz)** 3.84 (1H, s, -OH); 4.12 - 4.14 (1H, dd, H_3, J=0.93, J=2.38); 4.73-4.74 (1H, d, H_4, J=2.2); 5.16 (1H, d. H_2, J=0.91); 6.87-7.06 (2H, m, Ar-H); 7.15-7.24 (2H, m, Ar-H); 7.28-7.46 (5H, m, Ar-H)

δ_C **(50 MHz)** 53.73 (d, C_3); 69.29 (d, C_4); 72.38 (d, C_2); 117.24 (d, Ar-C); 121.57 (d, Ar-C); 125.99 (2xd, Ar-C); 128.06 (d, Ar-C); 128.13 (2xd, Ar-C); 130.38 (d, Ar-C); 130.79 (ol, Ar-C); 119.68 (s, C_{10}); 137.63 (s, $C_{1'}$); 183.39 (s, C_9)

m/z (EI) (M$^+$, 304 (Br^{79}), 26%), 306 (Br$^{81)}$(26%), 207 (70), 184 (93) , 182 (100) , 122 (71).

(165)
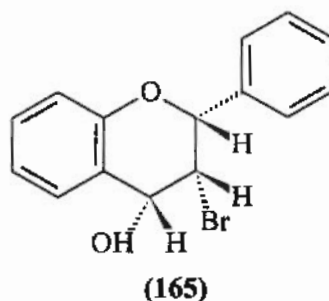
Reduction of 3-Bromo-4-hydroxy-2-phenyl-1-benzopyran (165)

A solution of LiAlH$_4$ (0.10g , 2.62mmol) in THF (2.7ml) was placed in a round bottomed flask under an atmosphere of nitrogen. 3-Bromo-4-hydroxy-2-phenyl-1-benzopyran (165) (0.20g , 6.56mmol) in THF (1ml) was added dropwise to the solution which was then stirred for 12h. The reaction was cooled in an ice bath and the excess hydride destroyed by injecting a 1:1 mixture of THF and water dropwise. The THF was removed under vacuum and the aqueous layer extracted with ether. The combined ether layers were dried over anhydrous MgSO$_4$, filtered and reduced under vacuum. The crude mixture was then separated using centrifugal chromatography with a 7:1 mixture of hexane:ethyl acetate to afford a diastereomeric mixture of the flavan-3-ol (155) (0.03g , 20%). (See above for characterisation)

(155)
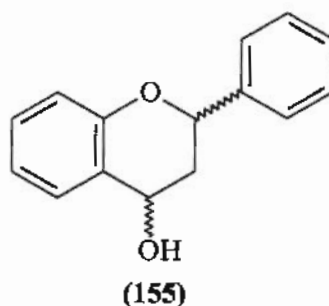
3,4-Oxide-2-phenyl-1-benzopyran (epoxide) (158) and
2-Phenyl-4H-1-benzopyran (Flavone) (166)

3-Bromo-4-hydroxy-2-phenyl-1-benzopyran (165) (0.47g , 1.54mmol), in THF (4ml) was added dropwise to a solution of NaH (60% in paraffin) (0.08g , 3.34mmol) in THF (5ml) at 0°C. The reaction mixture was stirred for 0.5hr at 0°C and allowed to warm to room temperature and stirred for a further 12h. The reaction was quenched with saturated NH$_4$Cl and the THF removed under vacuum and the aqueous layer extracted with ether. The combined ether layers were then dried over anhydrous MgSO$_4$, filtered and reduced under vacuum. The crude mixture was then separated using centrifugal chromatography with an 8:1 mixture of hexane:ethyl acetate to afford epoxide (158) (0.035g , 10%) and white crystals (mp.=93°C) of flavone (166) (0.11g , 32%).

Data for epoxide (158)

δ_H(200MHz) 3.87-3.901 (1H, dd, H_3, J=1.35, J=4.37); 4.02-4.04 (1H, d, H_4, J=1.35); 5.62-5.63 (1H, d, H_2,, J=4.37) 6.81-7.00 (2H, m, Ar-H); 7.21-7.43 (7H, m, Ar-H).
δ_C(50MHz) 49.61 (d, C_4); 58.82 (d, C_3); 74.24 (d, C_2); 121.52 (d, Ar-C); 127.06 (2xd, Ar-H); 128.66 (d, Ar-H); 128.82 (2xd, Ar-C); 129.93 (d, Ar-C); 130.77 (d ,Ar-C); 120.01 (d, C_{10}); 137.35 (d, C_1·); 152.18 (d, C_9).
m/z (EI) 224 (M$^+$, 34%), 196 (100), 167 (25), 118 (42), 89 (98).

(158)
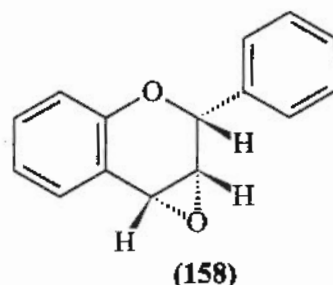
Data for flavone **(166)**.

δ_H**(200MHz)** 6.80 (1H, s, H_3); 7.28-7.55 (5H, m, Ar-*H*); 7.62-7.71 (1H, m, Ar-*H*); 7.86-7.9 (1H, m, Ar-*H*); 8.18-8.23 (2H, m, Ar-*H*)

δ_C**(50MHz)** 107.43 (d, Ar-*C*); 118.05 (d, Ar-*C*); 125.18 (d, Ar-*C*); 125.58 (d, Ar-*C*); 126.20 (2xd, Ar-*C*); 128.98 (2xd, Ar-*C*); 131.58 (d, Ar-*C*); 133.75 (d, Ar-*C*); 123.83 (s, $C_{1'}$); 131.58 (s, C_2); 156.13 (s, C_9); 163.29 (s, C_{10}); 178.39 (s, C_4).

m/z (EI) 222 (M$^+$, 38%), 194 (18), 165 (7), 120 (100), 92 (54).

(166)
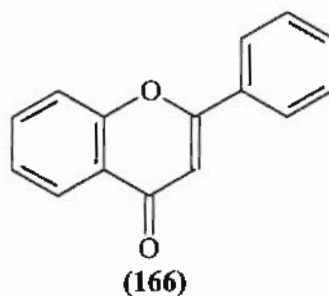
3-(*o*-Hydroxypheny)-1-phenyl-1-propanone (167)

Flav-3-ene **(91)** (0.3g, 1.44mmol) was placed in a round-bottomed flask, to which bromine (0.30g, 1.59mmol) was added. The reaction stood unstirred for two days, which resulted in an intense red solution. Water (1ml) was added and the reaction stirred for 6h. The reaction mixture was then extracted with ether. The combined ether layers were then dried over anhydrous $MgSO_4$, filtered and reduced under vacuum. The crude mixture was then separated using centrifugal chromatography with a 8:1 mixture of hexane:ethyl acetate to afford propanone **(167)** (0.11g, 34%).

δ_H(**200MHz**) 2.98-3.05 (2H, t, CH_2-C=O); 3.37-3.43 (2H, dd, CH_2-Ar); 6.80-6.93 (2H, m, Ar-*H*); 7.05-7.13 (2H, m, Ar-*H*) 7.35-7.56 (3H, m, Ar-*H*); 7.91-7.97 (2H, m, Ar-*H*); 8.07 (1H, brs, -O*H*).

δ_C(**50MHz**) 23.72 (t, CH_2-C=O); 40.26 (t, CH_2-Ar); 117.23(d, Ar-*C*) 120.71(d, Ar-*C*); 127.97(d, Ar-*C*); 128.35 (2xd, Ar-*C*) 128.67 (2xd, Ar-*C*); 130.64 (d, Ar-*C*); 133.77 (d, Ar-*C*); 127.87 (s ,*C*-C=O); 136.06 (s, *C*-OH); 154.48 (s, *C*-CH$_2$CH$_2$); 202.10 (s, CH$_2$*C*=O)

m/z (EI) 226(M$^+$, 33%) ,207 (15) , 121 (8) , 105 (100) , 77 (70).

(167)
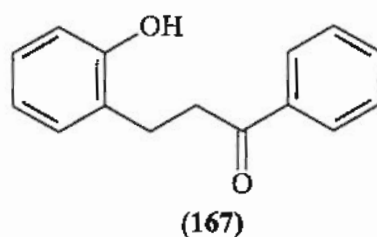
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APPENDIX : ^{1}H AND ^{13}C NMR SPECTRA

(125)

The structure shows a benzene ring with an acetyl group (C(=O)CH₃) and an OC(=O)NEt₂ carbamate substituent in ortho positions.

O=CNEt₂
| (as OCNEt₂)

CH₃

O

(125)

(131)

(131)

(132)

(132)

(126)

0 PPM

(126)

(127)

OH

OCH₃

(134)

OH

OCH₃

(134)

180   160   140   120   100   80   60   40   20 PPM   0

(91)

(91)

(135)

(135)

HO—CH=CH—C₆H₅

(137)

(137)

(138)

(138)

(138)

in d-Chloroform

(138)

in d-Chloroform

(138)

in d-Benzene

(138)
in d-Benzene

(139)

(139)

H3CO

H3CO

(147)

H_3CO

H_3CO

(147)

H₃CO

H₃CO

NO₂

(148)

H_3CO

H_3CO —NO$_2$

(148)

H$_3$CO

H$_3$CO — NH$_2$

(149)

H₃CO

H₃CO

NH₂

(149)

H₃CO—, H₃CO— benzene ring with N≡N⁺ group, BF₄⁻

(153)

H3CO— / H3CO— phenyl ring with $\overset{\oplus}{N}{\equiv}N$, $BF_4^{\ominus}$

(153)

H₃CO — OH

H₃CO — CH₃

(146)   O

H₃CO, OH

H₃CO, CH₃

(146) O

(144)

(144)

OHC — (benzene ring with OCH₃ at position adjacent and OCH₃ below)

(145)

(145)

(142)

(142)

(143)

H_3CO —OH —OCH₃

H_3CO —OCH₃

O (154)

(155)

(155)

OH

OH (156)

1 PPM

OH

OH **(156)**

40 PPM

60

80

100

120

140

(157)

(157)

(159)

(159)

(160)

(160)

(161)

(161)

(162)

(162)

(165)

(165)

(158)

(158)

(166)

(166)

(167)

(167)