UNIVERSITY OF SOUTHAMPTON

THE DEVELOPMENT OF NEW SYNTHETIC METHODS FOR CHROMONE AND ERGOCHROME CONSTRUCTION

A thesis submitted for the degree of

Doctor of Philosophy

by

Roger Swinford Brown

July 1986

DEDICATED

TO MY PARENTS

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

THE DEVELOPMENT OF NEW SYNTHETIC METHODS FOR CHROMONE AND ERGOCHROME CONSTRUCTION

by Roger Swinford Brown

The ergochromes possess useful anti-tumour properties whilst chromones are useful drugs for the treatment of allergic asthma. The aim of the project was to synthesise ergoflavin or an analogue for the first time, and to this end novel synthetic methods for α,β-unsaturated ketones and oxygenated dienes were developed.

Two major routes are described:
The first uses aliphatic starting materials and allows the construction of highly substituted chromones by an intramolecular Diels-Alder reaction. To achieve this a synthetic method to novel phenylthio substituted α,β-unsaturated ketone equivalents (α'-phenylthio-β-amidoketones) was developed. It consisted of nitrile oxide additions to 1-phenylthioprop-2-ene, whilst additions to 1-phenylsulphinyl-1,2-propadiene were also investigated.

The second route involved the use of a preformed aromatic ring and; (a) an intramolecular Diels-Alder reaction to form a pyrone ring or - (b) an intermolecular Diels-Alder reaction and subsequent Friedel-Crafts cyclisation to give a pyrone ring.

For this, a selenium diene protection, alkylation and deprotection methodology was developed. Depending upon the substrate and oxidative conditions α,β-unsaturated ketones, allylic alcohols, dienes and lactones were obtained. A second route to 4-oxygenated-1,3-butadienes provided the impetus to develop a titanium reagent for the olefination of 4-substituted-3-buten-2-ones.

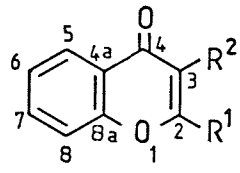
Finally, an investigation into radical cyclisations of allylically substituted phenylseleno substrates was made.

CHAPTER 1

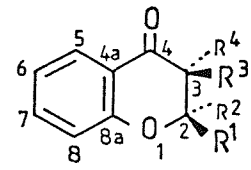
INTRODUCTION

1:1 GENERAL INTRODUCTION AND AIMS OF THE PROJECT

Chromones (1) and 4-chromanones (2) contain the pyrone unit which is a widely distributed unit in nature. It is found predominantly in innumerable flavanoid compounds and the naturally occurring chromones are a relatively small subset, and number approximately fifty five[1]. One of the best known of these is euginin (3) obtained from the wild clove and responsible for its characteristic aroma. It was once thought that all naturally occurring chromones possessed a 2-methyl or a 2-hydroxymethyl group, but subsequently a series of 2-alkyl-5,7-dihydroxy-6-methyl chromones have been isolated from *Dianella revoluta* and *Styandra grandis*. The alkyl groups are saturated C_{27}, C_{29} and C_{31} chains[2] (4).

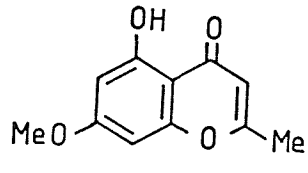


(1)

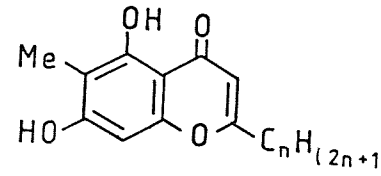


(2)

If R^1 = R-C_6H_4 Compound (1)
is a flavone



(3)



(4)

The aim of the project was to develop novel routes to oxygen heterocycles, for although many routes presently exist (see Section 2.1), few exist for chromones with highly substituted aromatic systems or complex chromanones such as the biologically active ergochromes.

1:2 AN INTRODUCTION TO THE BIOLOGICALLY ACTIVE CHROMONES AND CHROMANONES.

1:2:1 The Ergochromes.

The ergochromes[3] are a series of dimeric compounds which form the pigments found in the fungus *Claviceps purpurea*. They are present in the permanent mycelium of the filamentous fungus which grows on rye grasses. The fungus, commonly known as "Ergot", has become associated with the "disease" ergotism and the contamination of rye by this dark purple fungus has lead to mass poisonings right up to this century due to the presence of ergot alkaloids[4] such as ergotamine.

Although the first ergochrome preparations were isolated by Dragendorff[5] around 1877, the structure of the ergochromes was only elucidated in the 1960's[6-8]. The investigation of these compounds was hindered both by their great sensitivity to hydrolysis and their inherent similarity to each other. Since many differ only in configuration of a few of the many centres of chirality it was not possible to obtain them in the pure and homogeneous state by classical separation methods. Table 1.1 provides a summary of the ergochromes obtained from ergot by chromatography with the exception of secalonic acid D. Secalonic acid D is not found in the ergot extractions but has been isolated from *Penicillium oxalicum* by Steyn[9]. It has been shown to be the optical enantiomer of secalonic acid A.

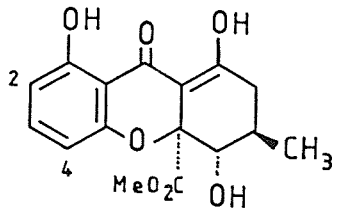
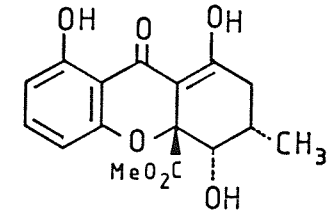
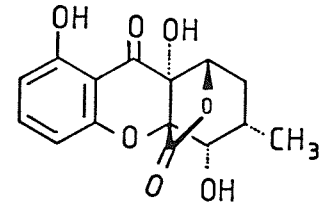
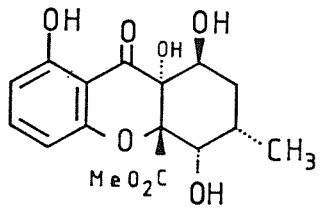
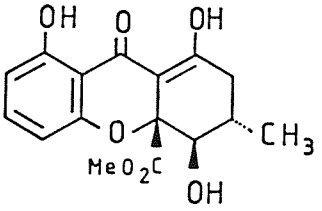
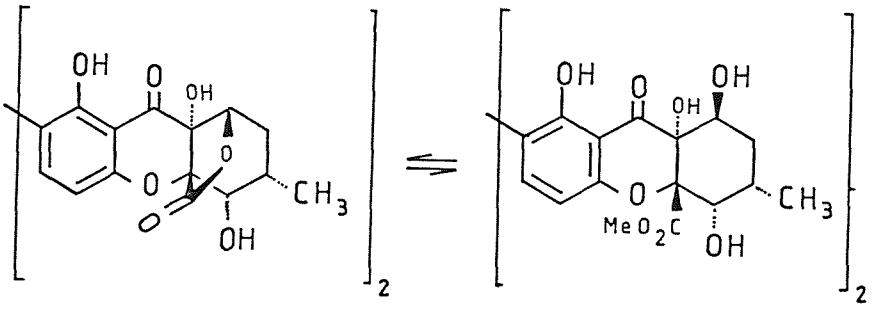
		Linkages	Name
A		A - A	ergochrome AA [2,2'] (secalonic acid A)
B		B - B	ergochrome BB [2,2'] (secalonic acid B)
		C - C	ergochrome CC [2,2'] (ergoflavin)
C		A - B	ergochrome AB [2,2'] (secalonic acid C)
		A - C	ergochrome AC [2,2] (ergochrysin A)
		B - C	ergochrome BC [2,2'] (ergochrysin B)
D		A - D	ergochrome AD [2,2']
		B - D	ergochrome BD [2,2']
E		C - D	ergochrome CD [2,2']
		D - D	ergochrome DD [2,2']
		E - E	ergochome AA [2,2'] (secalonic acid D)

Table 1.1

Franck *et al.*[10] have demonstrated that the monomeric compound D (table 1.1) can be converted into monomeric compound C by heating in hot acetic acid, this results in elimination of methanol and closure of the lactone. Thus some of the ergochromes are interconvertable:-

A-D ⟶ A-C
B-D ⟶ B-C (ergochrysin B)
C-D ⟶ C-C (ergoflavin)
D-D ⟶ C-C (ergoflavin)

The structural relationship between C and D ergochromes has been confirmed by the reverse transformation. Saponification of the lactone followed by treatment with diazomethane converts ergoflavin to ergochrome DD (scheme 1.1).



(5) (6)

(Scheme 1.1)

The structures and absolute configurations have been determined for all the ergochromes. The configurations have been assigned for not less than 80 centres of chirality, giving as a result an unusually complete group of natural products which contains all ten possible combinations of two of the four xanthene derivatives A,B,C and D and hence the simple nomenclature has been adopted.

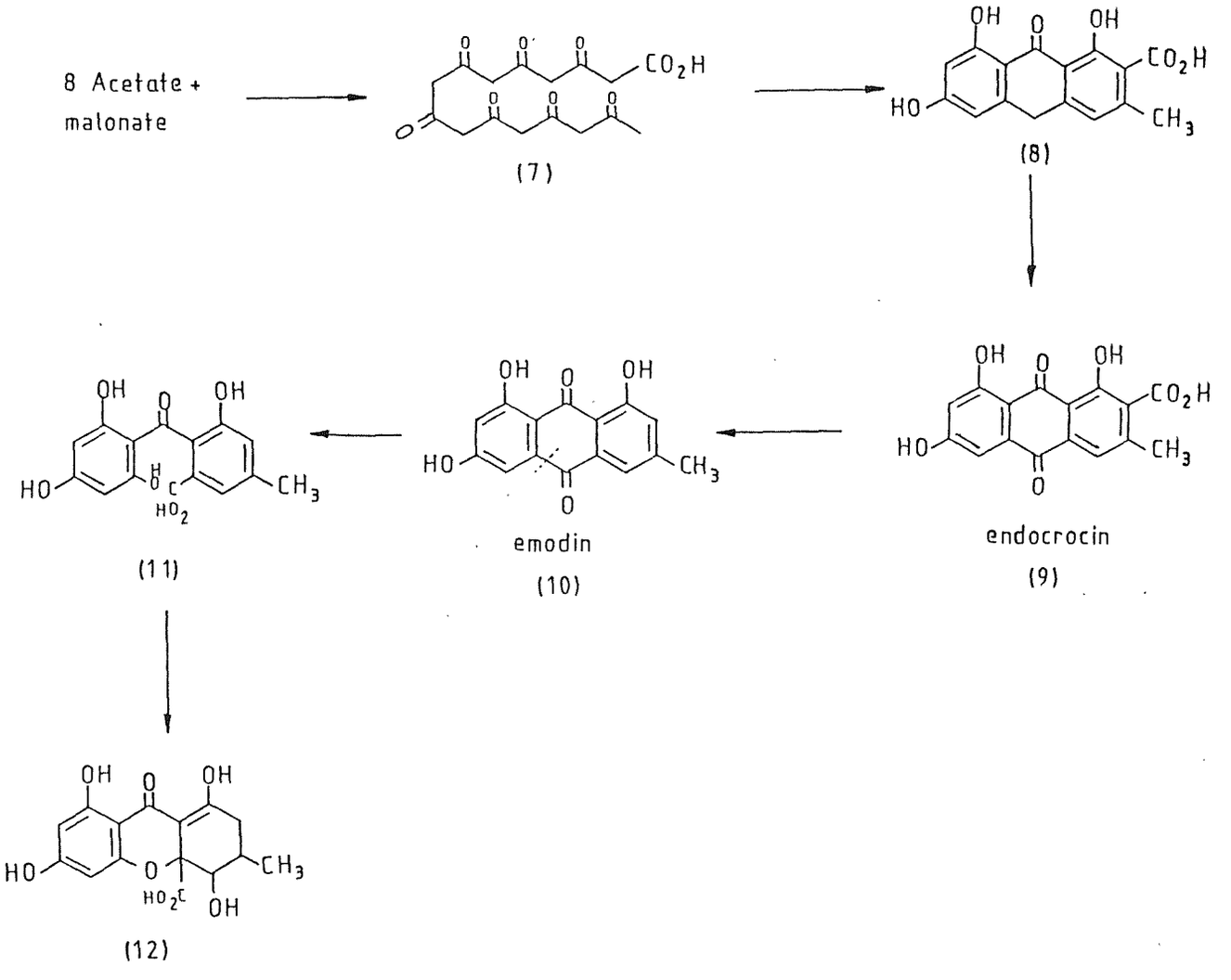
In 1971 Whalley *et al.*[6] corrected the original structural assignments

of the ergochromes. They deduced by nuclear magnetic resonance spectroscopy (n.m.r.) and chemical studies that the two halves of the dimeric molecules were linked at the [2,2'] positions and not the [4,4'] as previously suggested. The erroneous assignments of [4,4'] linkages demonstrates the doubt often associated with the Gibbs test used in many of the earlier structural investigations.

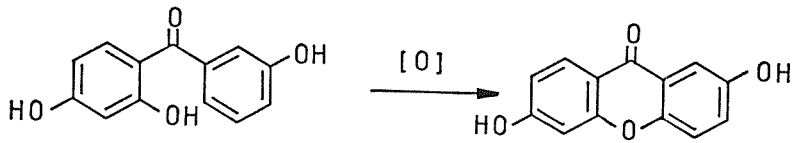
1:2:2 Biosynthesis of the Ergochromes.

The biosynthesis of the ergot compounds was suggested by the fact that they all contain a tricyclic C_{15} system with similar arrangement of the substituents. Gatenbeck[11] proved that the biosynthesis of endocrocin (9) involves the condensation of eight molecules of acetic acid *via* acetyl and malonyl coenzyme A, and that emodin (10) is formed from the decarboxylation of endocrocin (9). Heptaoxopalmitic acid (7) and emodinanthane (8) may occur as intermediates (scheme 1.2).

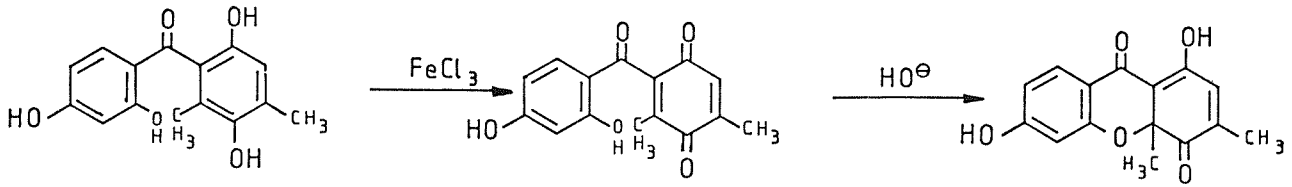
It has been proved by biosynthetic studies that tritiated emodin when administered to *Claviceps pupurea* results in incorporation of radioactivity into the ergochromes, whilst [^{14}C] labelled shikimic acid fed to the fungus did not[12-13]. The oxidative ring cleavage of emodin (10) under Baeyer-Villiger conditions with peracids has been systematically studied, and the anthraquinones investigated were found to be inert. Thus a reaction of this type seems unlikely for the conversion of an anthraquinone to a xanthone *in vivo*[14]. Model studies have verified the validity of proposing an oxidative phenolic coupling. Lewis and Warrington[15] have obtained 2,6-dihydroxyxanthone (14) in high yield by the oxidation of (13) with potassium hexacyanoferrate(III). Similarly scheme 1.3 shows an application of this procedure for the formation of a secalonic acid model. This lends credibility to the proposed biosynthetic pathway for the ergochromes[16].



(Scheme 1. 2)



(13) (14)



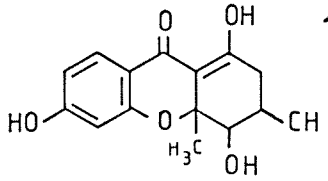
(15) (16) (17)

REAGENTS

(i) $NaBH_4$

(ii) H_2 / Pd - C

(i), (ii)



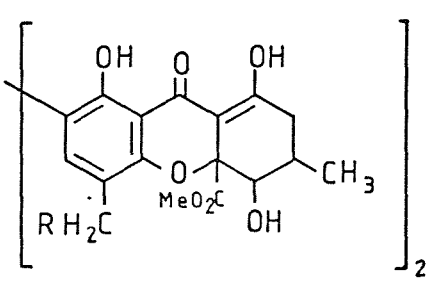
(18)

(Scheme 1.3)

1:2:3 Biological activity of the secalonic acids and their derivatives.

Secalonic acid D obtained from *Penicillium oxalicum*, a toxigenic fungus, has been found to be the major toxic metabolite present[9]. The fungus causes acute toxicoses in rats, mice and ducklings. The isolated secalonic acid D has been shown to have an LD_{50} value of 42 mg/kg on male and female white mice as determined by Weil's method[17], which involves dosing the compound intraperitonally to the mice. Likewise secalonic acid A obtained from *Aspergillus ochraceus* has an oral toxicity LD_{50} of greater than 250 mg/kg in mice, but an intraperitonal LD_{50} of less than 50 mg/kg on the same species[18]. A comparative idea of the toxicity[19] of these compounds can be obtained if we consider the LC_{50} values for *Artemia salina* larvae (brine shrimps); secalonic acid D had an LC_{50} of 32.85 mg/ml versus 0.31 mg/ml for the notorious yellow rain T-2 toxin[20].

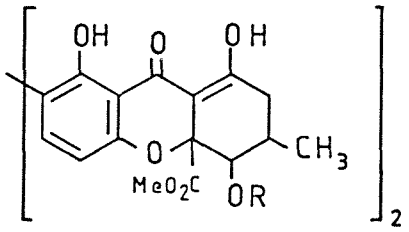
The Asahi Chemical Company have obtained secalonic acids by culturing *Aspergillus aculeatus* on rice powder[21]. They found that derivatives of secalonic acid (19), where R is a nitrogen containing ring or chain, gave compounds with antitumour properties[22].



(19)

The reaction of the appropriate secalonic acid with an N-methylol derivative of an N containing ring, or an appropriate *bis*-carbamate, in the presence of various dehydrating agents or catalysts afforded

them compounds of the type (19). Alternatively these may be prepared by reacting 4,4'-*bis*(aminomethyl)-secalonic acid with any number of chloroformic acids.



R = H, 2'-tetrahydrofuranyl or 2'-tetrahydropyranyl.

(20)

Their studies demonstrated that when mice bearing the Ehrlich tumour were treated with 400 mg/kg of 4,4'-*bis*(phthalimidomethyl)-secalonic acid D on the second and fourth day after tumour inoculation, they lived 311% longer than the controls[22]. Similarly it has been demonstrated that an antitumour agent for local application to humans contains as its main component a compound of formula (20) and or its pharmaceutically acceptable salt (Na^+, K^+ or NH_4^+ salts).

Direct application of the agent to the tumour portion potentiates the immunity, the lymphocyte is infiltrated and the tumour brought into necrosis. This agent has been found to be partially effective against bladder cancer in doses of 50-100 mg/day[23].

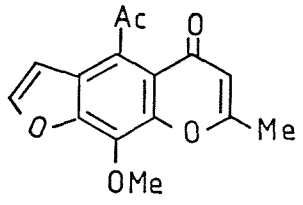
1:3 Chromones and anti-allergy activity.

Asthma is a distressing respiratory disease which can restrict a normal lifestyle and can in severe cases be fatal[24]. Narrowing of the airways in the lung is symptomatic of the disease and this can be brought about by three main mechanisms; spasm of the circular muscle fibres (bronchoconstriction), inflammation with resultant swelling of the airway lining (mucosal oedema), or excessive secretion of mucus

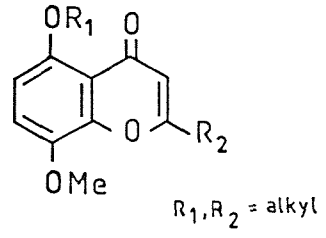
(mucus plugging). Its incidence is high, with about five percent of the U.K. population suffering its symptoms at sometime, and up to thirty percent of the population of the islanders of Tristan da Cunha[25].

Allergic asthma is brought about by the development of a sensitivity to commonly encountered air-borne proteins. Examples of such allergens (antigens) are grass pollens, moulds, the common house-dust mite and the hair and skin of various animals. Exposure to an allergen results in the release of substances (mediators of anaphylaxis) that induce the asthmatic attack. Many of these mediators have now been identified. Some, histamine and certain prostaglandins, act directly on the lung muscle to cause bronchoconstriction, whereas the chemotactic factors cause infiltration of cells (eosinophils and neutrophils) and give rise to the inflammatory processes. In addition the slow reacting substance of anaphylaxisis (SRS-A) identified as a mediator for nearly fifty years is both a potent bronchoconstriction and chemotactic agent. SRS-A is now known to be a mixture of several components belonging to the family of compounds known as the leukotrienes, namely LTD_4 and LTB_4[26].

Prior to 1965 asthma was treated by the use of bronchodilatory drugs, and in severe asthmatics corticosteroids were used to control mucosal oedema by reducing inflammation. In the 1950's Bengers Laboratories initiated research to try and discover new bronchodilator drugs. They started by investigating the furanochromone[27], khellin (21), the active constituent of the plant *Ammi visnaga* which has been known to possess bronchodilating properties since biblical times. A number of analogues were synthesised (22) and although several potent bronchodilators were identified their unpleasant side effects of nausea and vomiting could not be eliminated.

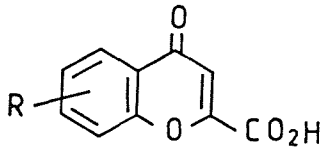


(21)



(22)

In 1956 Dr. Altounyan, a chest physcian involved with the testing of chromones for activity, discovered that compounds of the type (23) with a carboxylic function in the 2-position of the benzopyran ring (conferring water solubility to the compounds, enabling aerosol administration) though inactive as bronchodilators possessed prophylactic activity. Sodium salts of compounds (23), when administered as aqueous aerosolised solutions, inhibited the effect of allergen challenge, but they were ineffective if administered after allergen attack. The most active compounds were those possessing a 5-alkoxy substituent, for example R= 5-$OCH_2CH(OH)CH_3$.



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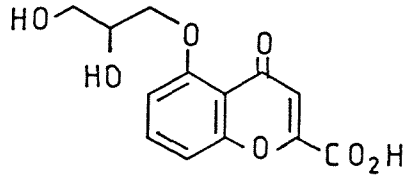
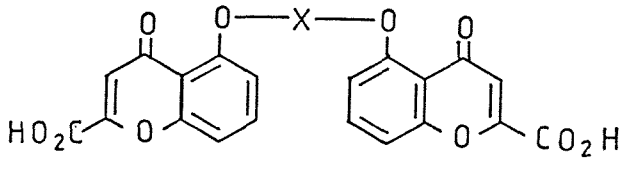


(24)

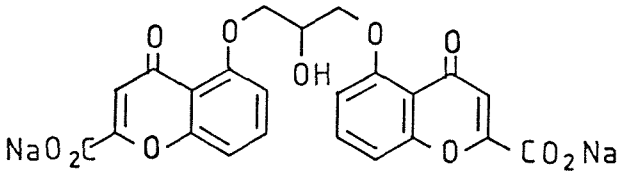
The major problem was that the drugs hitherto synthesised were effective for only 10 minutes prior to allergen challenge. Subsequently a compound (24) was synthesised and it appeared to possess the much sought after long term activity. It was then

discovered that new batches of the compound were inactive. The only conclusion which could be drawn was that the earlier batches of compound were analytically impure.

It was postulated that the contaminant might be a *bis*-chromone of the general structure (25). Compounds with this *bis*-structure were found to have a longer duration of activity and 1965 marked the year when a *bis*-chromone, sodium cromoglycate (26), was synthesised with a 4-6 hour efficacy after administration. Very rapidly new problems arose due to the method of administration. The drug was shown to have poor absorption in the gastrointestinal tract and therefore oral administration was ineffective . Hence it was necessary to facilitate inhalation of the drug, and as several milligrams were required the "Spinhaler" was developed; a device capable of delivering 20 mg of sodium cromoglycate to the lung. The compound was finally marketed as "INTAL" by Fisons Pharmaceuticals in 1968.



(25)



(26)

Much research has been devoted to the discovery of a second generation drug which might have longer activity and be effective on a larger range of asthmatics (Intal is only effective on the sub-group of allergen induced asthma patients). However to this end no effective replacement has been found.

CHAPTER 2

ESTABLISHED ROUTES TO CHROMONES

2:1 CLASSICAL ROUTES TO CHROMONES.

An excellent review of classical routes which have a wide applicability to the synthesis of the benzopyran ring can be found in the book by Ellis[1]. Although many routes are available, those involving highly substituted aromatic systems often fail to give satisfactory results.

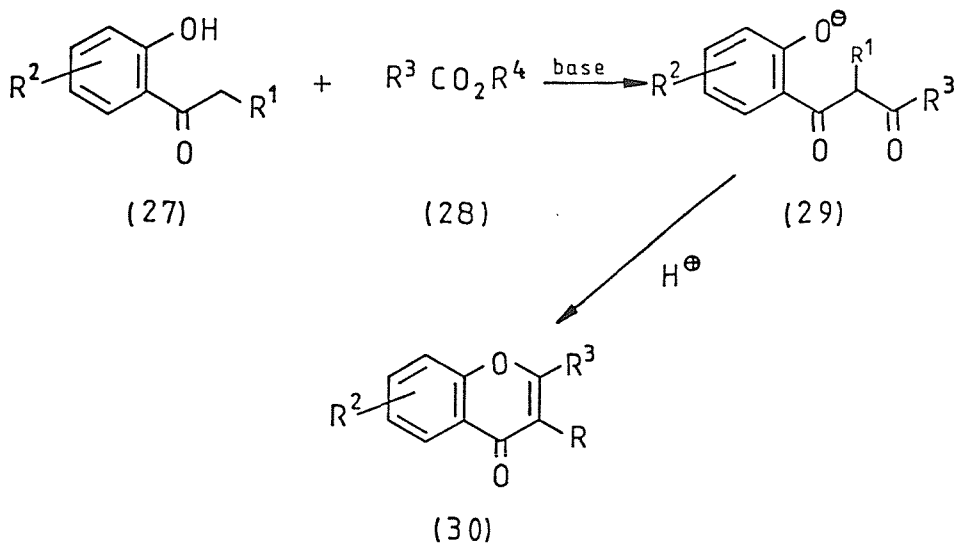
Routes roughly fall into two wide categories where the chromones are formed from; (a) those compounds not containing a pyran ring or (b) those compounds containing a reduced pyran ring.

A brief summary of the more important chromone forming reactions is described in the next few sections.

2:2 ROUTES NOT INVOLVING A PRE-FORMED PYRAN RING.

2:2:1 Claisen condensation of *o*-hydroxyaryl alkyl ketones with carboxylic esters.

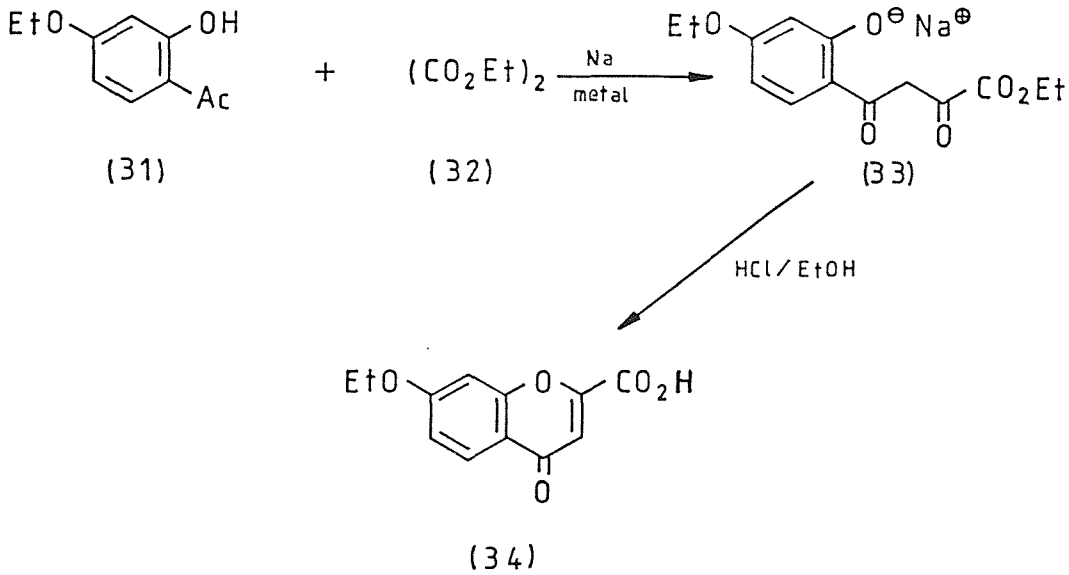
This is one of the most frequently employed methods for the synthesis of chromones. Claisen condensation of an *o*-hydroxyaryl alkyl ketone (27) with a carboxylic ester (28), in the presence of a strong base, gives a 1,3-dioxophenol (29) which is also the key intermediate in the Baker-Venkataraman rearrangement. The 1,3-dioxophenol (29) is then cyclised on acid treatment[1,28] (scheme 2.1). Experimentally the 1,3-dioxophenol often precipitates out as a yellow or orange sodium salt, although purification is rarely performed at this stage.



(27) (28) (29) (30)

(Scheme 2.1)

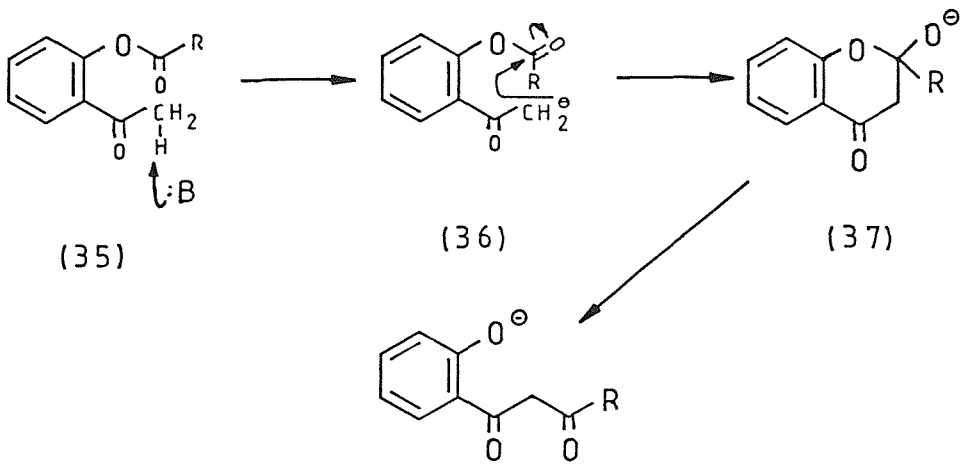
Using the Claisen approach a wide variety of chromones can be synthesised, usually in good yields. It was first described by Kostanecki, Paul and Tambor[29] in their synthesis of 7-ethoxy-4H-1-benzopyran-2-carboxylic acid (34) (scheme 2.2).



(31) (32) (33) (34)

(Scheme 2.2)

The Baker-Venkataraman[30-31] rearrangement is essentially a different method for obtaining the 1,3-dioxophenol intermediate (38). It is derived from the rearrangement of *o*-acyloxyacylbenzenes[32] (35) by heating with a base. Scheme 2.3 illustrates the route and shows the postulated mechanism.

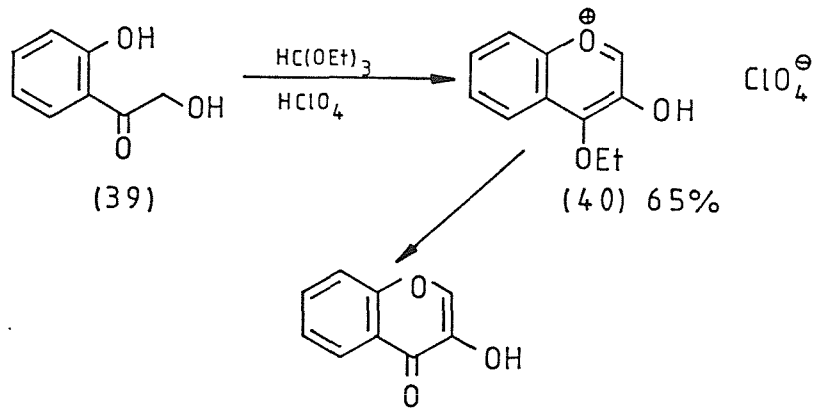


(35) (36) (37) (38)

(Scheme 2.3)

2:2:2 Condensation of *o*-hydroxyaryl alkyl ketones under acidic conditions.

Electron rich 2-hydroxyacetophenones (39) have been successfully converted into benzopyrylium salts (40) by treatment with triethyl orthoformate and a strong acid. The benzopyrylium salt can then be converted to the chromone on warming with water[33-34]. This methodology has been extended to the synthesis of 3-hydroxychromones[35] (41) and compares well with existing published syntheses[36] (scheme 2.4).

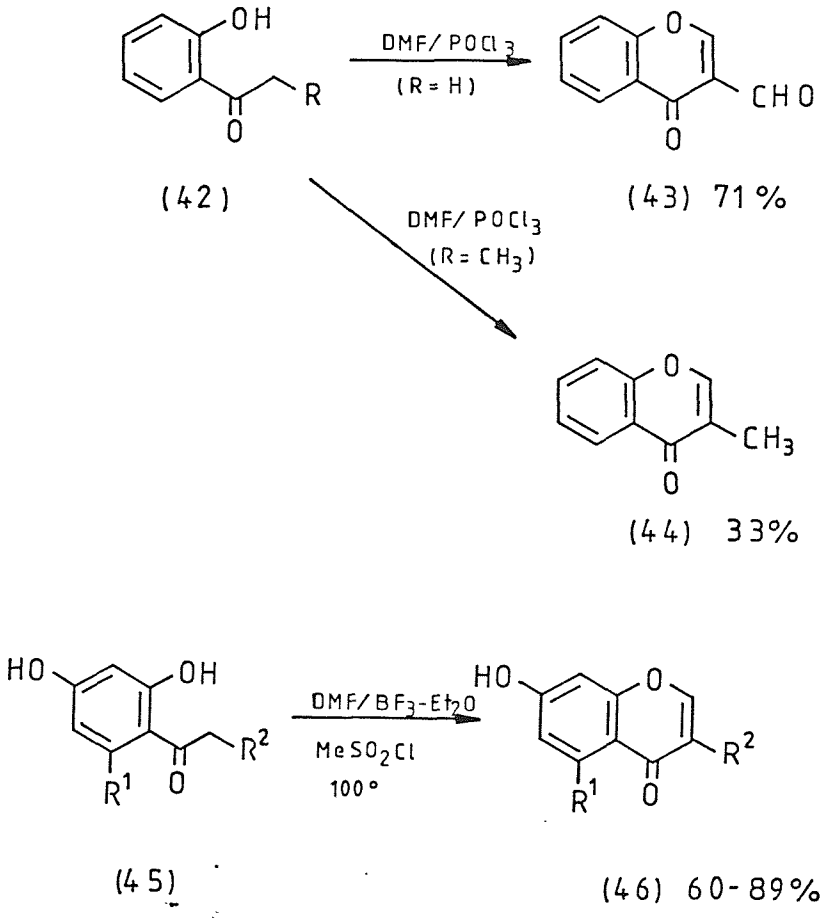


(39) (40) 65% (41) 100%

(41) 100%

This condensation is very useful for the preparation of 2-unsubstituted chromones[37] and can be accomplished by a number of means all based on the Vilsmeier[38-39] type of reagent. An illustration of the basic methodology is shown below (scheme 2.5).

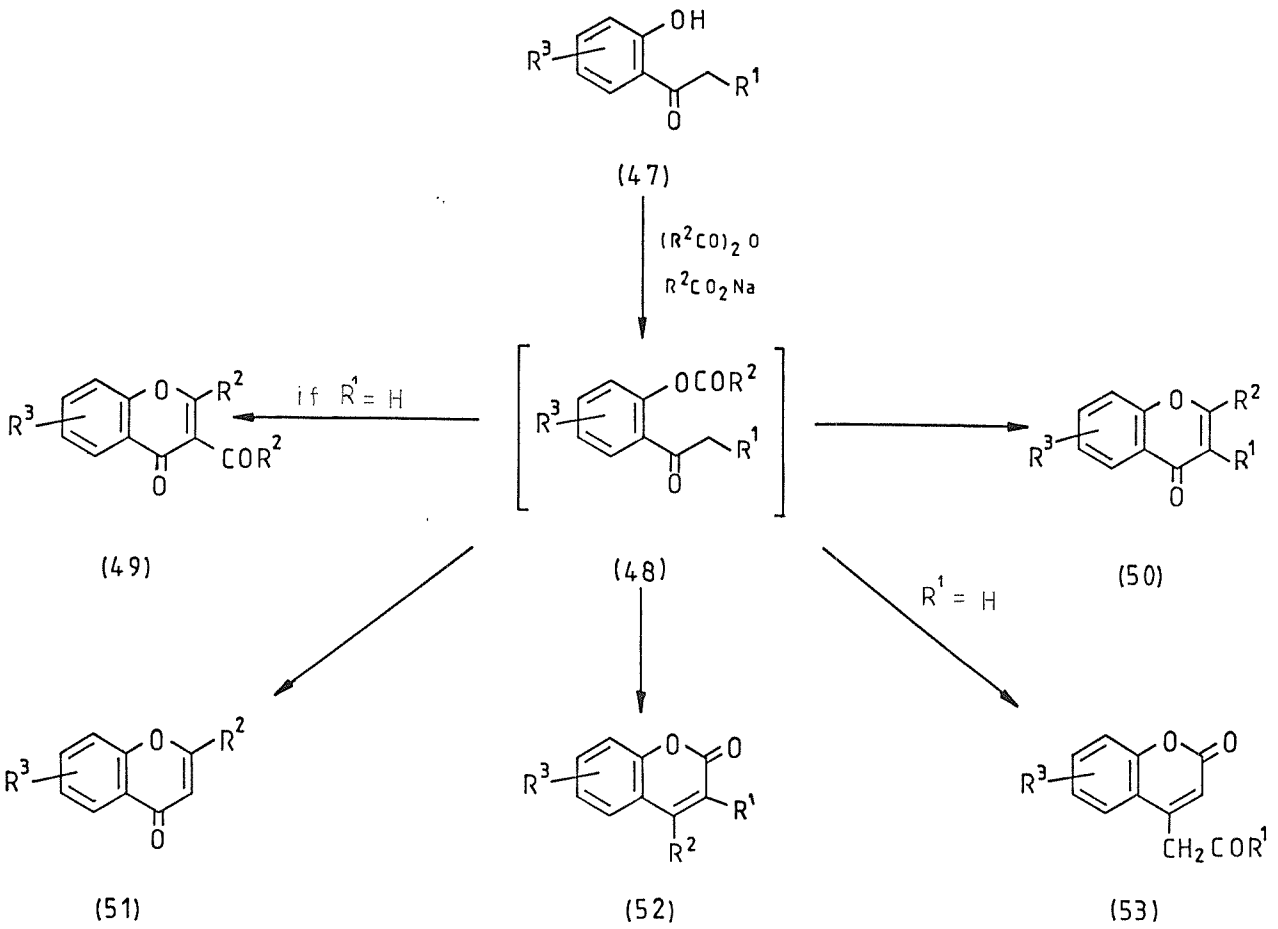
Compound (43) is the result of a double Vilsmeier reaction, whilst compounds (44) and (45) are more classical ring closure reactions.



(Scheme 2.5)

2:2:4 The Kostanecki-Robinson reaction.[40-41]

When an *o*-hydroxyacetophenone is boiled with acetic acid containing sodium acetate a number of products can be obtained[1] (scheme 2.6). An *o*-acyloxyphenylalkanone (48) is the most likely initial product; it can then undergo a Baker-Venkataraman rearrangement (see section 2:2:1) to yield an *o*-hydroxydiketone which eliminates water to give chromones (49) and (50). When R^1 is a substituent other than hydrogen, chromone (50) is formed but when R^1= H either (49), (51), or a mixture of both are formed. An alternative reaction is an intramolecular aldol condensation followed by dehydration which gives the coumarins (52) and (53).

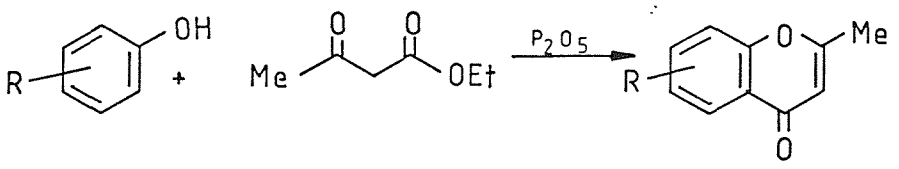

OH
R3
R1
O
(47)
(R2CO)2O
R2CO2Na
OCOR2
R3
R1
O
(48)
if R1 = H
R3
O
R2
COR2
O
(49)
R3
O
R2
R1
O
(50)
R1 = H
R3
O
R2
O
(51)
R3
O
O
R1
R2
(52)
R3
O
O
CH2COR1
(53)

(Scheme 2.6)

Despite the limitations imposed by the number of possible products, this method has been successful in the synthesis of a large number of chromones. This can be attributed to the number of substituents which are chemically inert to the reaction conditions *e.g.* alkyl[42], alkoxy[43], halogen[44], acyl[45], nitro[46], alkoxycarbonyl[47], cyano[48], cyanomethyl[49] and acetamido[50].

2:2:5 The Simonis reaction.

The Simonis reaction[51] involves the reaction of a phenol with 3-oxoesters in the presence of phosphorus pentoxide to give chromones and coumarins. The Simonis reaction is illustrated in scheme 2.7.

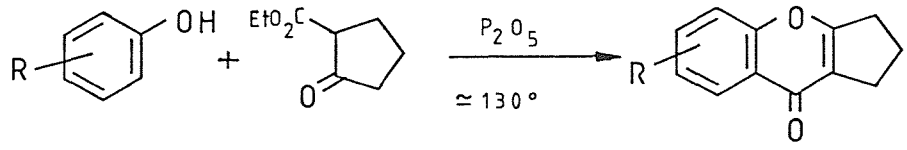


(54) (55) (56)

R = o-cresol, 2,4-Me_2phenol, m-NO_2phenol, 4-Cl-2-Me-phenol or 2-Cl-4-Me-phenol.

(Scheme 2.7)

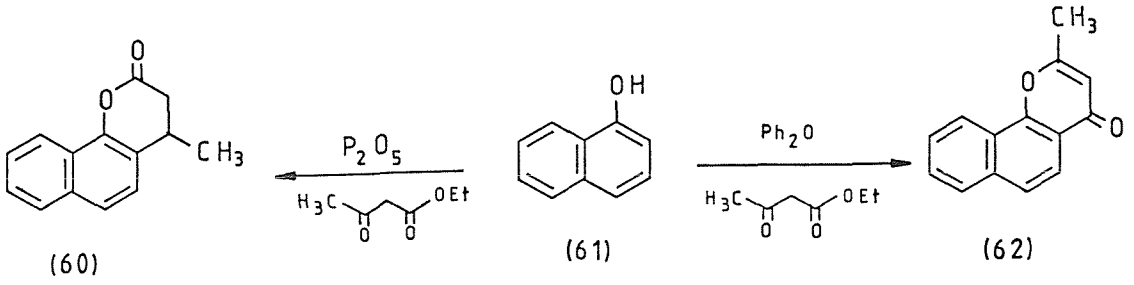
Cyclic oxoesters have also been utilised to give tricyclic chromones[52] (59)(scheme 2.8).



(57) (58) (59)

(Scheme 2.8)

Other condensing agents that have been used in this reaction are phosphoryl chloride[53] and polyphosphoric acid[54]. Sulphuric acid, however, gives rise to a coumarin *via* the Pechmann[55] reaction. This reaction can also be conducted thermally, and sometimes gives chromones[56] (62) which are otherwise unobtainable if using phosphorus pentoxide (scheme 2.9).



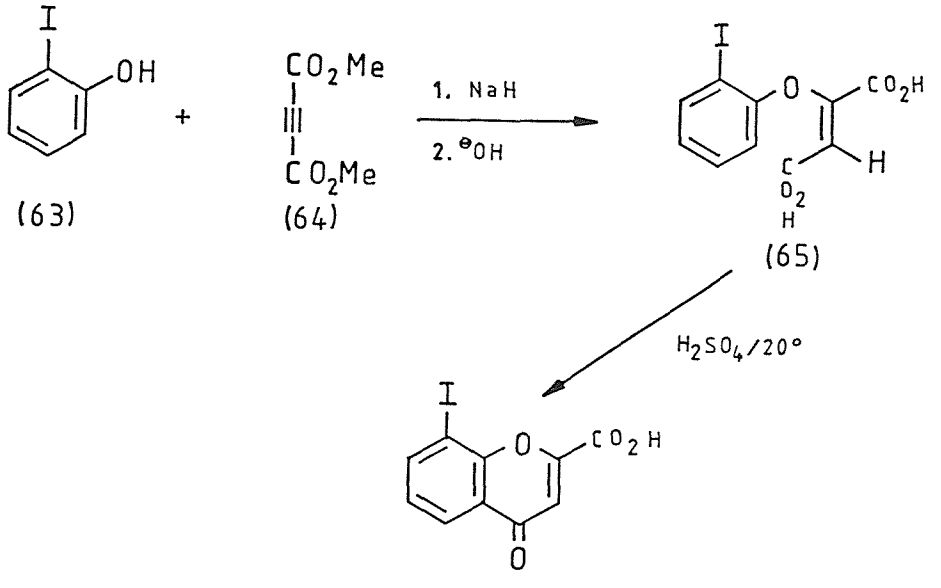
(Scheme 2.9)

The major restriction to the thermal reaction is the reactivity of the phenol, for instance *p*-cresol[57] and *p*-hydroxybenzoic acid[58] do not undergo the Simonis reaction, whilst 2,4,6-trihydroxyacetophenone[59] and 2-methylresorcinol[60] do.

2:2:6 Condensation of a phenol with an unsaturated acid or ester.

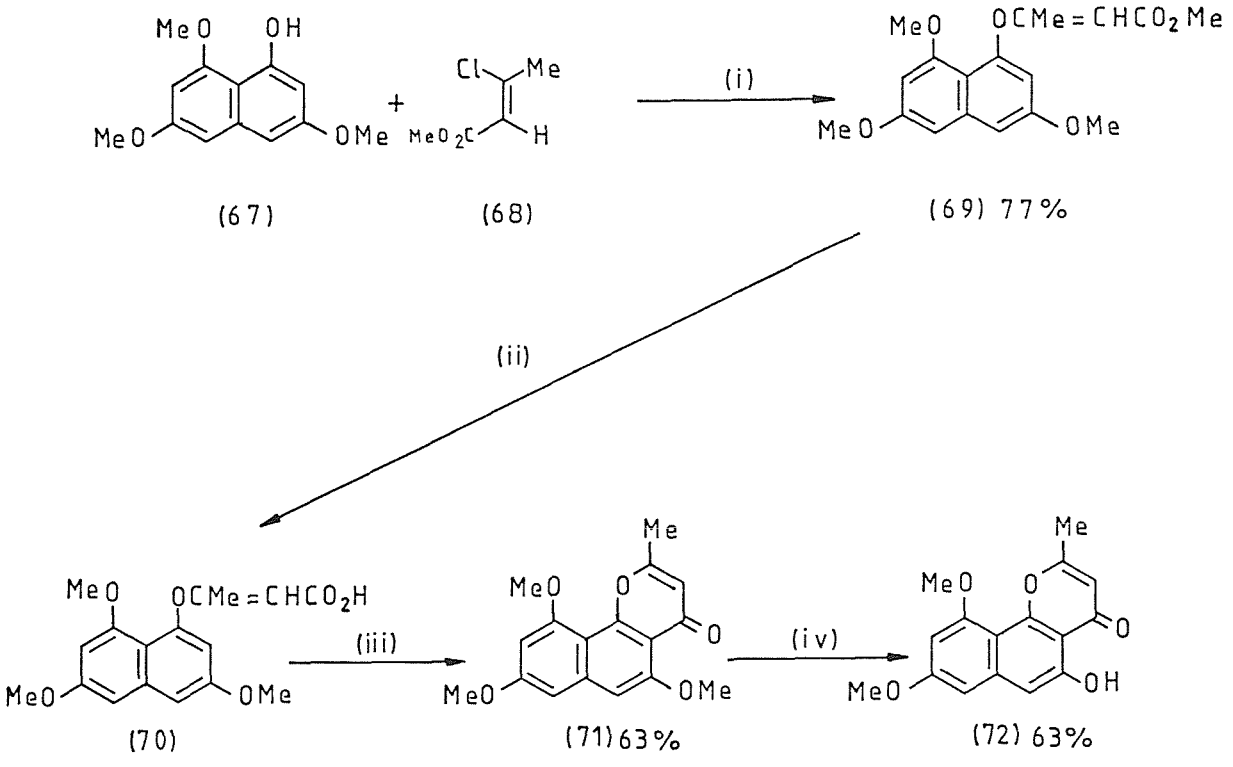
The condensation of a phenol with an unsaturated acid or its ester is another method commonly employed in the synthesis of chromones. This can be accomplished under a variety of conditions as with many of the methods described in the preceding sections . A number of bases may be employed where necessary; sodium metal[61], potassium carbonate[62] *etc*, and the resulting intermediate cyclised using acid; sulphuric acid[63], perchloric acid[62] or hydrogen fluoride[64]. An example of the reaction is shown in scheme 2.10. *o*-Iodophenol is converted into the corresponding chromone (66) in an overall yield[65] of 33%. The reaction

proceeds by Michael addition of the phenoxide anion to the unsaturated ester, saponification of the diester and cyclisation of the diacid (65) with sulphuric acid.



(Scheme 2.10)

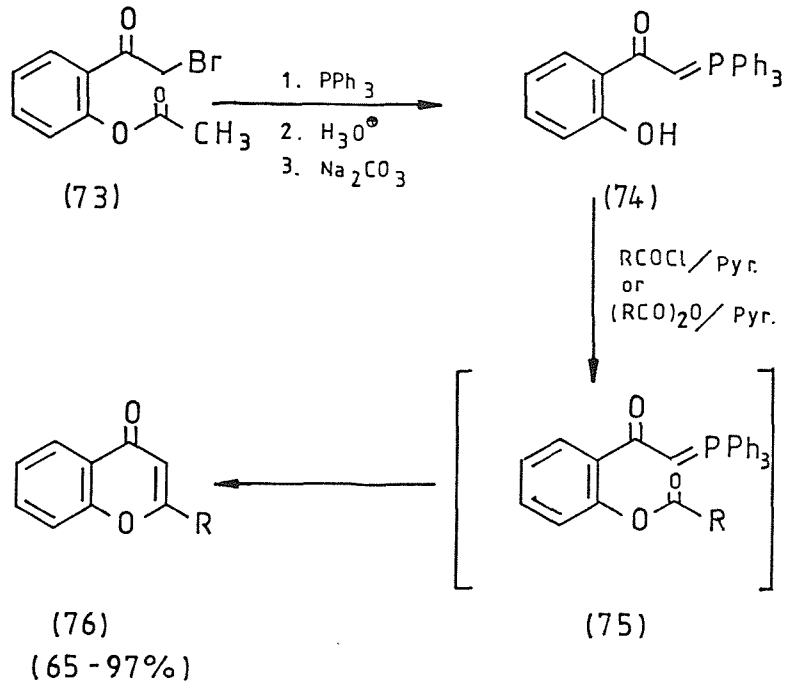
Equally successful is the use of 3-chlorobutenoic acid esters (68) which has found application in the synthesis of the naturally occurring naphthopyranone, flavasperone[62] (72) (scheme 2.11).



(Scheme 2.11)

2:2:7 An intramolecular Wittig ring closure methodology.

A simple method to produce chromones has been reported by Le Corre[66] *et al.* This route involved the reaction of *o*-acetylphenylacyl bromide with triphenylphosphine and gave an *o*-hydroxyphenylacylidenetriphenylphosphine (74) which on heating with carboxylic acid chlorides or anhydrides, in boiling toluene with pyridine, yielded the unstable phosphorane (75). This phosphorane intermediate underwent spontaneous intramolecular olefination of the ester carbonyl function to give the desired chromone (76)(scheme 2.12).



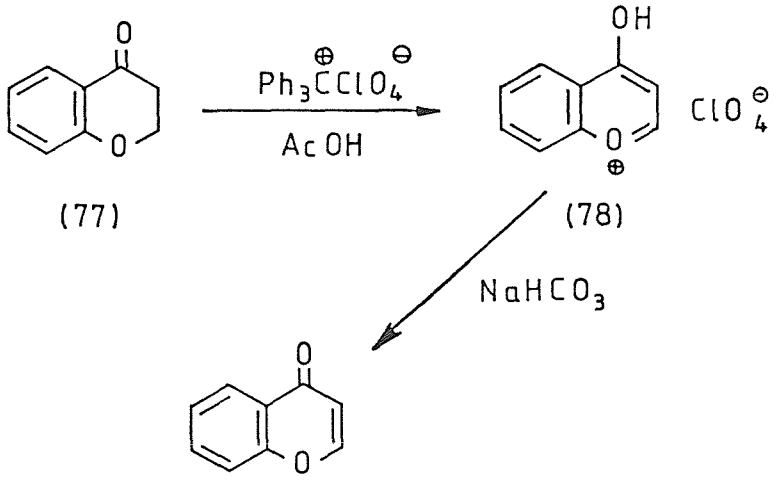
(73) (74) (75) (76) (65-97%)

(Scheme 2.12)

2:3 ROUTES INVOLVING A PRE-FORMED PYRAN RING.

2:3:1 Conversion of chromanones to chromones.

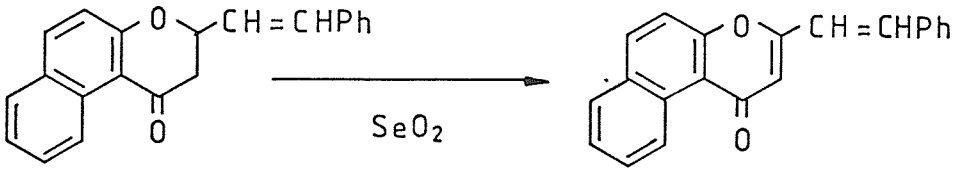
In general these methods are not of any great preparative value, in that chromanones are not readily available and the yields are often low. Various reagents have been employed, for example; triphenylmethyl perchlorate in acetic acid can be used to convert a chromanone into a 4-hydroxybenzopyrylium perchlorate (78), this on treatment with sodium bicarbonate gives the chromone[67] (79) (scheme 2.13).



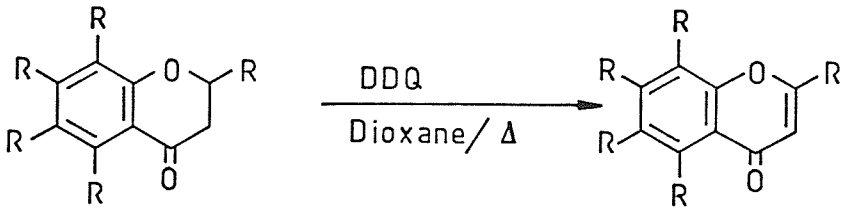
(Scheme 2.13)

Oxidative methods have involved selenium dioxide[68], 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[69] (DDQ) (scheme 2.14), catalytic dehydrogenation on charcoal[70], thallium trinitrate[71] and many other variations.

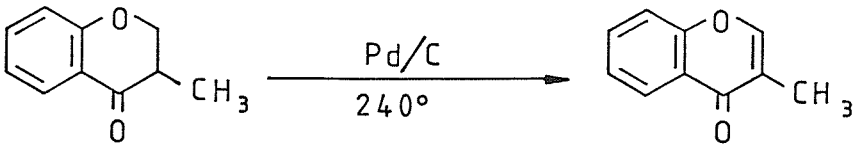
Other methodologies have utilised dehydration of 2-hydroxychromones[72] and dehydrobromination[73] (scheme 2.15).



(80) (81) 33%

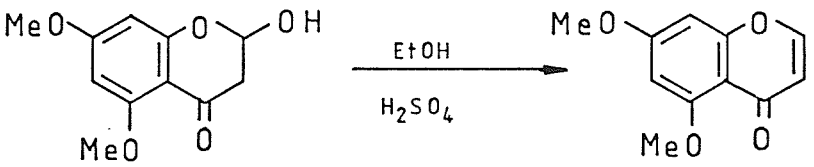


(82) (83) 50-75%

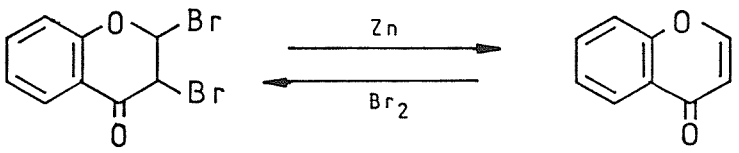


(84) (85)

(Scheme 2.14)



(86) (87)



(88) (89)

(Scheme 2.15)

2:4 CONCLUSION.

The preceding sections provide a brief overview of the routes presently available for the synthesis of chromones. In contrast we decided to opt for two basic approaches. The first was to set up a complete benzopyran system from aliphatic starting materials and adjust the oxidation levels of the rings at a later stage. In this way a variety of substitution patterns in the benzene ring would be obtained. This flexibility would be eminently suitable for the provision of compounds for biological testing.

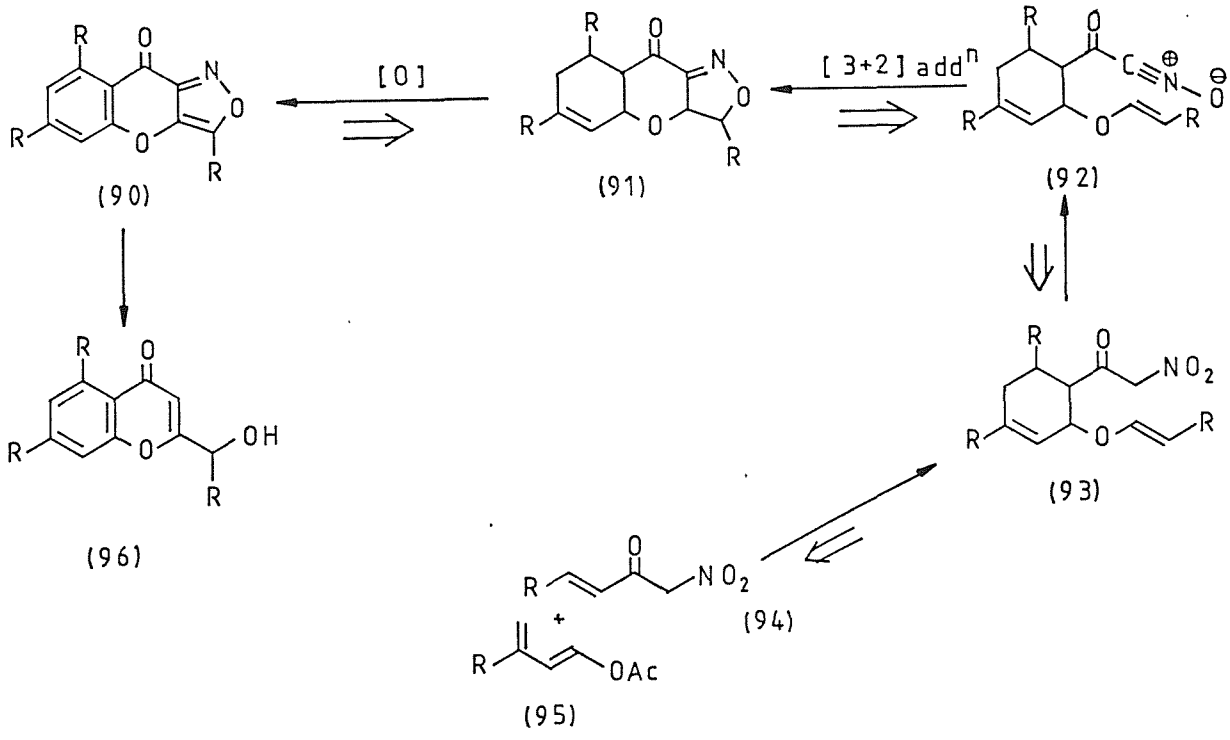
The second basic approach was to use a preformed phenyl ring and to form a chromanone either by an intramolecular Diels-Alder reaction, or by a two step procedure using an intermolecular Diels-Alder reaction followed by a Friedel-Crafts cyclisation. The resulting chromanones could then be oxidised to give a chromone, or form a route into the ergochrome series of compounds. These approaches will be described fully in the following chapters.

CHAPTER 3

ROUTES TO THE CARBOCYCLIC SKELETON OF OXYGEN HETEROCYCLES

3:1 ROUTES INVOLVING NITRILE OXIDE CYCLOADDITIONS TO ALLENES.

Our desire to synthesise ergoflavin and novel chromones led us to consider the development of several new synthetic methods. We proposed to investigate a route to oxygen containing 6,6-bicyclic ring systems and to adjust the oxidation level of the rings at a later stage. Illustrated below (scheme 3.1) is one of the initial routes involving an isoxazole chromanone (90) a useful intermediate molecule.

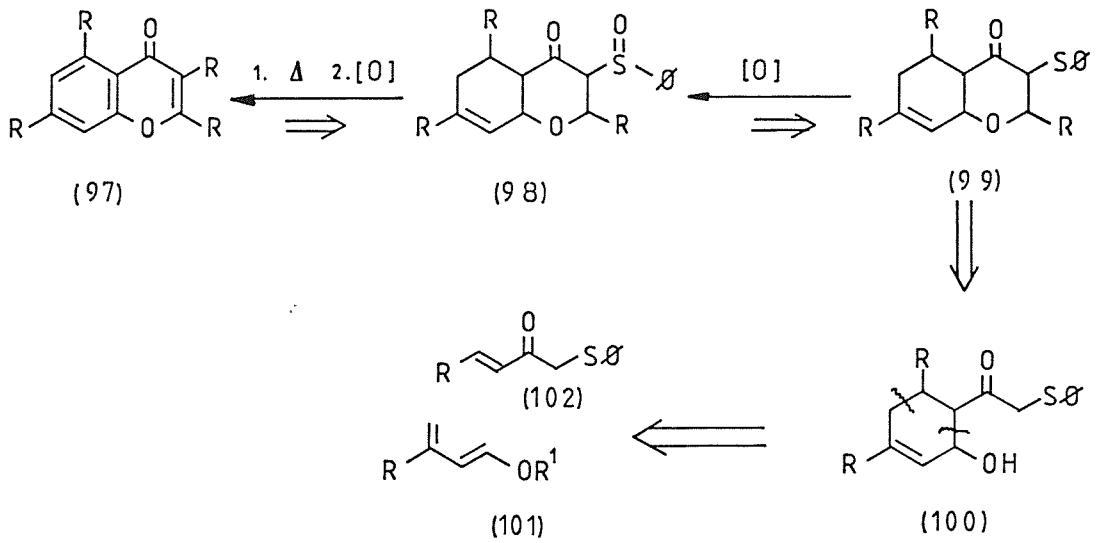


(Scheme 3·1)

This route initiated research into synthesising the α'-nitroenones (94), that could be converted by a Diels-Alder reaction with functional group modification into the nitrile oxide precursors (93). The nitro compound (93) could be dehydrated to the nitrile oxide which

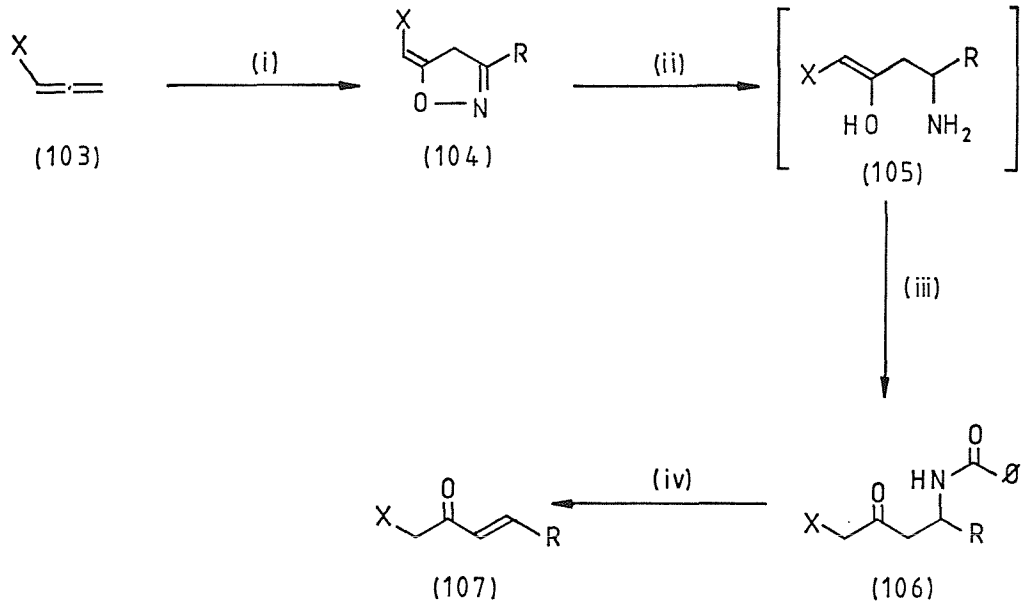
on intramolecular [3+2] cycloaddition, would give the tetrahydro-isoxazoline chromanone (91). Oxidation of this would lead to the isoxazole chromanone (90) series, and a useful entry to 2-hydroxymethyl (96) or other 2-substituted chromones.

Subsequently we decided to look at classic Claisen type condensations of the hitherto unknown α'-phenylthioenones. A retrosynthetic route is described in scheme 3.2. It outlines how, by relatively classic chemistry, compounds of the tetrahydro-chromanonic structure (99) could be synthesised. Elimination of the phenylsulphinyl group, and aromatisation of the rings would give access to a series of highly substituted chromone compounds.



(Scheme 3.2)

The two routes described both involve formation of α'-substituted enones as *bis*-annulating agents. To enable the synthesis of these enones a nitrile oxide approach was adopted. With the anticipation that a nitrile oxide [3+2] cycloaddition would proceed with substituted allenes. A nitrile oxide cycloaddition with phenylsulphonyl-1,2-propadiene was subsequently reported by Guilford and Turner[74] and we decided to implement the general routes illustrated by scheme 3.3.



X = (a) NO_2 (b) PhS (c) PhSO

Reagents

(i) $R\text{-}C\equiv\overset{\oplus}{N}\text{-}\overset{\ominus}{O}$

(ii) $H^{\ominus}$

(iii) ØCOCl/NEt_3/Et_2O

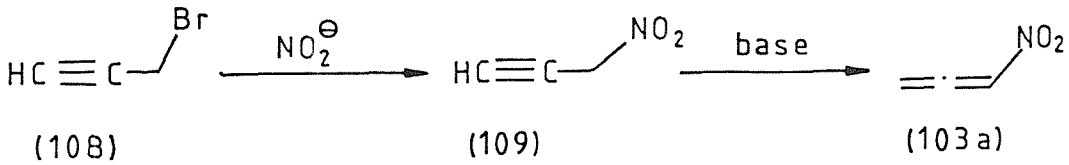
(iv) elimination

(Scheme 3.3)

We envisaged that reductive cleavage of the N-O bond of the novel *exo*-methylene isoxazolines (104) would yield the γ-aminoenol (105), which is the tautomer of the β-aminoketone. We planned to derivatise the amine as an amide to prevent intermolecular reaction of the β-aminoketone, and finally eliminate the amine/amide to give an α,β-unsaturated ketone (107).

The 1-nitro-1,2-propadiene was a novel compound and a synthetic strategy had to be adopted using acetylenic chemistry[75] (scheme 3.4). We believed that the displacement of bromide anion from propargyl bromide by nitrite anion would facilitate access to 3-nitropropyne

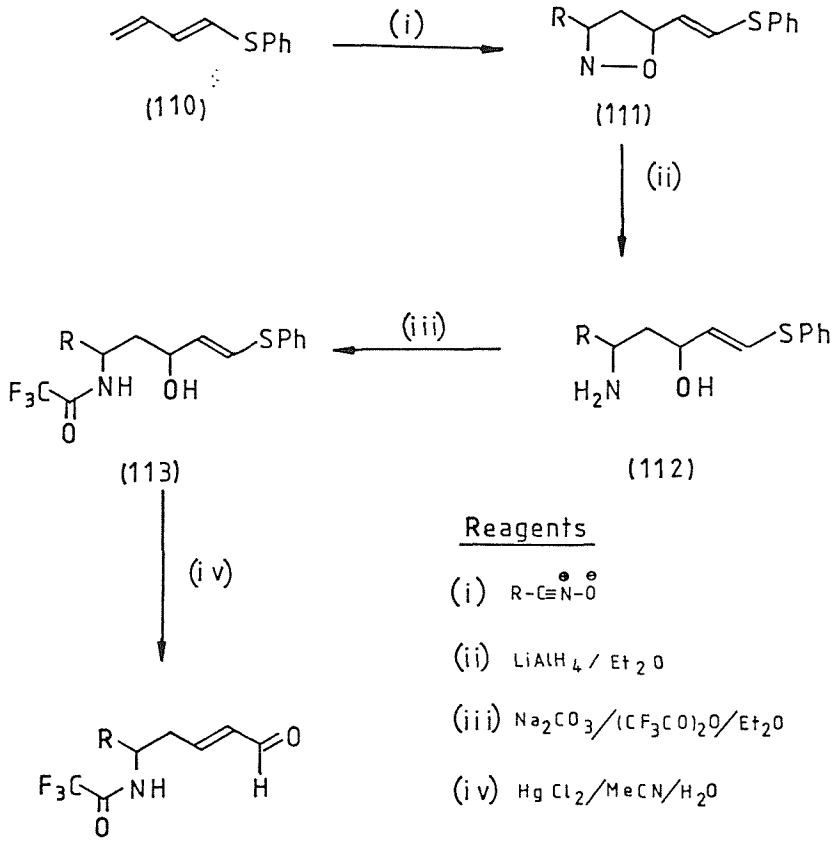
(109), and that base treatment[75] would provide us with the desired nitroallene (103a).



(108) (109) (103a)

(Scheme 3.4)

The 1-phenylsulphinyl-1,2-propadiene (103c) molecule was a literature compound[76], and the nitrile oxide additions could easily be embarked upon. This was a novel route and a continuation of the nitrile oxide additions carried out by Parsons and Lathbury[77] to unsaturated dienes. Their work utilised nitrile oxide additions to 1-phenylthio-1,3-butadiene (110) and yielded products from 1,3-dipolar cycloadditions to the terminal double bond (scheme 3.5).



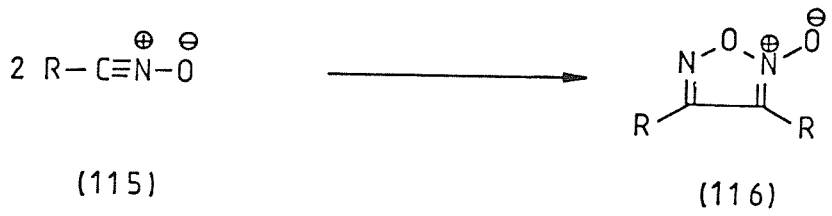
(114) 31 - 33 % overall

(Scheme 3.5)

3:1:1 Nitrile oxide cycloadditions.

3:1:2 Physical properties of nitrile oxides.

Nitrile oxides[78] (115) are white crystalline solids. The lower homologues of the aliphatic series melt below room temperature and only those few members which are prevented from dimerisation by steric hindrance are stable liquids. The large majority dimerise readily to give 1,2,5-oxadiazole-2-oxides (furoxans (116)) (scheme 3.6).



(115) (116)

(Scheme 3.6)

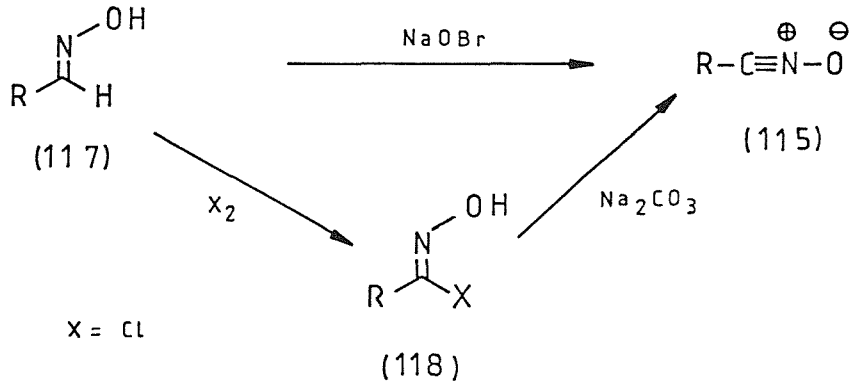
Benzonitrile oxide has a melting point of 15°C and is stable for 30 to 60 minutes at room temperature, whereas acetonitrile oxide melts at -5°C and has a stability of less than a minute at room temperature. Higher aromatic nitrile oxides, such as 2,6-dimethyl-benzonitrile oxide, melt at 80°C and are infinitely stable at room temperature.

3:1:3 Preparation of nitrile oxides.

Nitrile oxides may be prepared by a plethora of different procedures all of which involve the use of preformed C-N-O bonds in the substrate. The most widely adopted method is the formal dehydrogenation of aldoximes[79]. This may be accomplished in one step by the treatment of the aldoxime (117) with alkaline hypobromite[80]. The disadvantage of this route is that most polyfunctional nitrile oxides are obtained in low yields. A more selective method involves the reaction of N-bromosuccinimide with aldoximes in the presence of

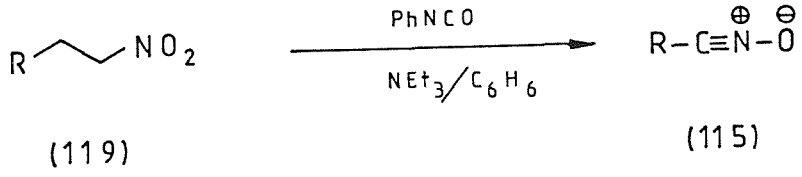
alkali metal alkoxides or tertiary amine bases[81]. This allows the preparation of amino substituted aromatic, heterocyclic and polyfunctional nitrile oxides in satisfactory to good yields.

A two step methodology from aldoximes can be implemented by chlorination of the aldoxime to give a hydroximic acid chloride[82] (118), which on treatment with a variety of bases undergoes facile dehydrohalogenation to give the nitrile oxide (scheme 3.7).



(Scheme 3.7)

A popular method involves dehydration of primary nitro compounds using typically phenyl isocyanate and triethylamine (Mukaiyama[83] dehydration) or phosphorus pentoxide[84] as dehydrating agents (scheme 3.8).

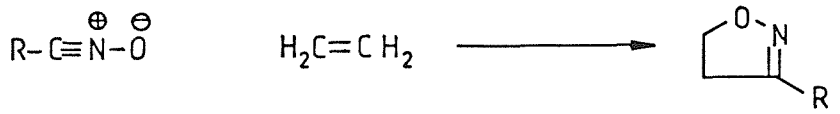


(Scheme 3.8)

Various other methods exist but they have found less applicability to organic synthesis[85].

3:1:4 Dipolar additions of nitrile oxides.

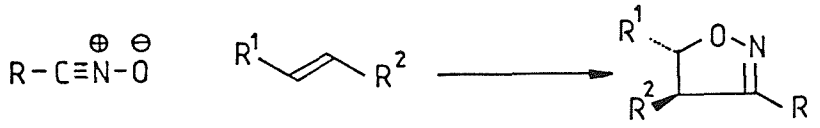
As already described in our proposed chromone routes, nitrile oxides can be added to olefins to give 2-isoxazolines[78] (121) (scheme 3.9).



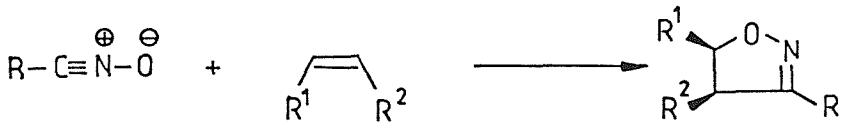
(115) (120) (121)

(Scheme 3.9)

The 1,3-dipolar cycloaddition reaction follows a concerted four centre mechanism[86] and experimentally this results in retention of the configuration of the olefinic substrate in the 2-isoxazoline product (scheme 3.10). *Syn* addition of the nitrile oxide is always observed and predictably of pericyclic processes, the rate of reaction is almost solvent independent[87-88].



(115) (122) (123)



(115) (124) (125)

(Scheme 3.10)

Nitrile oxides add to both electron rich and electron deficient olefins. Terminal and conjugated olefins react readily, but increasing alkyl substitution decreases the reactivity of the olefinic substrate. Tri- and tetra-alkyl substituted olefins give poor yields of adducts except with the most stable aromatic nitrile oxides[89].

The addition of nitrile oxides to unsymmetrical olefins can in general give rise to one of two regioisomers, or a mixture of both, depending on the electronic nature of R and R^1 (scheme 3.11). However, in many cases we see not only stereoselectivity but also regiospecificity.

(126)

(127)

(Scheme 3.11)

The ratio of the products can be understood if we apply frontier molecular orbital (FMO) theory[90] which will be discussed later (section 3:2:3).

3:2 RESULTS AND DISCUSSION.

3:2:1 Approaches to 3-nitropropyne.

Our initial thoughts focused on the preparation of 1-nitro-1,2-propadiene (scheme 3.4) so that the retrosynthetic pathway to

isoxazoline chromanones (scheme 3.1) could be converted into a synthetic reality. As our methodology has already been outlined elsewhere (section 3:1), a brief resume is all that we require here. We envisaged that conversion of propargyl bromide to 3-nitropropyne would be a straight forward functional group interchange[91], followed by isomerisation to the allene.

Halide-nitrite exchange reactions[92-94] by an S_N2 displacement are well documented. The common overriding problem with these reactions is the solubility of the nitrite anion in organic solvents. Kornblum[95] has performed these reactions using urea and DMF as a solvent system in order to maximise the solubility of the sodium nitrite.

Other methods include the use of crown ethers[96-97], primarily to complex the metal cation and produce a "naked anion" with inherently greater nucleophilicity. They are oxygen coordinating templates which have cavity sizes that can be tailored to fit specific metal cations. 18-crown-6 selectively coordinates potassium ions (ionic radius 1.33 Å)[98] whilst 15-crown-5 selectively coordinates sodium ions (ionic radius 0.97Å)[98] but not vice versa.

An alternative to crown ether complexation is the use of a metal to increase the leaving ability of the halide anion. Silver nitrite[94,99,100] has several advantages in the classical halide-nitrite displacements. It not only forms an insoluble precipitate of silver halide, but alleviates the other problem of ambidentate nucleophilicity of the nitrite anion due to the softness of the silver cation. The result is to reduce the amount of O- in favour of N-alkylation of the nitrite anion in primary halide cases.

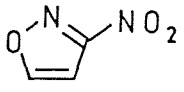
A problem we did not consider initially with silver was its ability to coordinate with unsaturation within the molecule (utilised in silver chromatography[101-102]) and its ability to react with terminal acetylenes[103].

Over the years ion exchange resins[104] have been used successfully in Sn2 displacements. This is due to their ability to allow close association of the substrate with the anion which is held on a support. They are particularly useful for continuous processes.

All the methods described were attempted, with varying degrees of success. Table 3.1 summarises the conditions and results. Kornblum observed that solvent systems other than DMF favoured formation of nitrite esters rather than the corresponding nitro compounds. The reaction of sodium nitrite with propargyl bromide has been investigated by Rossi *et al.*[105] They observed that the reaction in DMF alone as solvent gave a 33% yield of 3-nitroisoxazole (128). This result was confirmed by our research but with lower yields (entry 1). Although traces of the desired 3-nitropropyne may have been observed, mainly starting material and 3-nitroisoxazole were obtained.

Crown ether complexation of the alkali metal cations did not improve the situation and only starting material was recovered from these experiments (entries 2 and 3). Similar results were obtained from the anionic exchange resin procedure (entry 7).

The most encouraging results were obtained from the use of silver nitrite (entries 4 and 5). It was postulated that a one electron transfer mechanism[106] was operating in this transformation as brown fumes were evolved, tentatively identified as nitrogen dioxide. These reactions were observed by n.m.r. and i.r. spectroscopy to afford mixtures of propargyl bromide, 3-nitropropyne, 3-nitroisoxazole and the nitrite ester. Separation of these products could not be achieved chromatographically, nor was distillation appropriate due to the explosive instability of these mixtures.



(128)

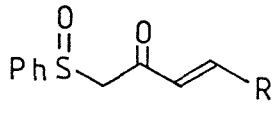
entry no.	reagent Ref.	solvent	additives	temp. (°C)	time (hr)	Result
1	$NaNO_2$ [94]	DMF	urea	-30	12	SM + 3-nitroisoxazole
2	$NaNO_2$	MeCN	18-crown-6	RT	24	SM
3	$NaNO_2$	CH_2Cl_2	15-crown-5	RT	12	SM
4	$AgNO_2$ [99]	Et_2O	—	0	36	SM 3 nitropropyne nitrite ester
5	$AgNO_2$	CH_2Cl_2	—	-5	24	3 nitropropyne 3 nitroisoxazole
6	$AgNO_2$	CH_2Cl_2	—	RT	24	Complex mixuture
7	IRA-900 [104] ($NO_2^{\ominus}$)	C_6H_6	—	RT	24	SM

TABLE 3.1

The preceding approach was deemed inadvisable due to the explosive nature of the products, so an alternative route involving nitrile oxide additions to 1-phenylsulphinyl-1,2-propadiene was investigated.

3:2:2 Nitrile oxide additions to 1-phenylsulphinyl-1,2-propadiene.

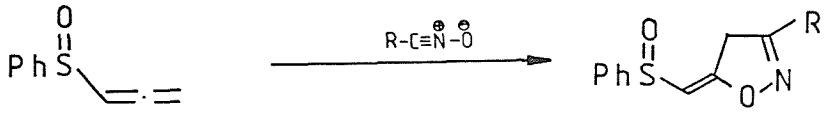
The strategy behind this route was outlined in schemes 3.2 and 3.3 and hinges upon the ability to synthesise a *bis*-annulating agent (107c).



(107c)

We anticipated this reagent would find application in Diels-Alder and intramolecular anionic cyclisations.

Nitrile oxide [3+2] cycloadditions to 1-phenylsulphinyl-1,2-propadiene successfully afforded the desired adducts[107] (129), table 3.2.



(103c) (129)

R	No. (129)	Yield(%)	Method
CH_3	a	44	A
C_2H_5	b	64	A
Ph	c	0	B
Ph	c	69	A
CO_2Et	d	0	B
CO_2Et	d	9	A
CH_2OTHP	e	32	A

A) Nitrile oxide generated by dehydration of a primary nitro compound.

B) Nitrile oxide generated by dehydrochlorination of a hydroximic acid chloride.

TABLE 3.2

The subsequent observations were made about the reaction conditions and products:-

a) The adducts only were obtained when using the Mukaiyama dehydration methodology for nitrile oxide production, and none could be obtained from dehydrochlorination of hydroximic acid chlorides.

b) Reaction occurred exclusively with the terminal double bond giving the site selectivity shown (table 3.2).

c) Molecules with the regiochemistry depicted (129) were exclusive products.

d) Where the nitrile oxide contained a chiral centre, *e.g.* $R=CH_2OTHP$, diastereoisomeric mixtures were formed not resolvable by chromatography on silica,

and

e) we believe that only the (*E*)-isomer of the isoxazole was formed, showing the reaction to be stereoselective.

We postulate that the dehydration of a primary nitro compound is a slower reaction than the corresponding dehydrochlorination of hydroximic acid chlorides. Thus in the former the nitrile oxide concentration is limited by its rate of formation, rather than by its sluggish reaction with the allene substrate. This minimises the dimerisation to furoxans. The cases where dehydrochlorination was employed resulted in furoxan formation, suggesting that cycloaddition was a kinetically limiting step, and that the fast dimerisation step became a preferential route once the nitrile oxide had been formed.

The (*E*)-geometry of the *exo* double bond was postulated on the basis of the high field proton n.m.r. spectrum (400 MHz) and nuclear Overhauser effect (nOe) studies. The molecule showed no spin-spin coupling of the protons, nor was there any observable nOe enhancements between the *endo*-cyclic methylene and vinylic proton. This suggests that we have an (*E*)-geometry. To verify this we would need to obtain the corresponding (*Z*)-molecule to ascertain if it indeed would exhibit the nOe phenomenon; this was clearly not possible by this methodology.

The diastereoisomeric mixtures can be explained by the chirality associated with the phenylsulphinyl group due to the tetrahedral arrangement of the lone pair of electrons and groups about the sulphur atom.

3:2:3 Nitrile oxide products: A frontier orbital approach.

The site selectivity and regiochemistry observed in these reactions can be rationalised using a frontier molecular orbital approach[90]. The site selectivity is difficult to predict on the basis of qualitative FMO theory. It is necessary to consider the interaction energy, ΔE, gained and lost when the orbitals of one reactant overlap with those of another. Thus where two possible sites exist the favourable reaction site is the one which maximises ΔE (equation 1).

FMO theory is an approximation of perturbation molecular orbital theory and the energy ΔE is related to a number of variables[108-109] (equation 1).

$$\Delta E = \underbrace{-\sum_{ab} (q_a + q_b)\beta_{ab}S_{ab}}_{\text{first term}} + \underbrace{\sum_{k<1} \frac{Q_k Q_l}{\varepsilon R_{kl}}}_{\text{second term}} + \underbrace{\sum_{r}^{occ.}\sum_{s}^{unocc.} - \sum_{s}^{occ.}\sum_{r}^{unocc.} \frac{2(\Sigma_{ab} c_{ra} c_{sb} \beta_{ab})^2}{E_r - E_s}}_{\text{third term}} \qquad \text{Eq. 1}$$

q_a, q_b: Electron populations in atomic orbitals a and b.

β, S : Resonance and overlap integrals respectively.

Q_k, Q_l: Total charges on atoms k and l.

ε : Local dielectric constant.

R_{kl} : Distance between atoms k and l.

c_{ra} : Atomic orbital coefficient of orbital a in molecular orbital r, where r refers to the molecular orbitals on one molecule and s refers to those on the other.

E_r : Energy of molecular orbital r.

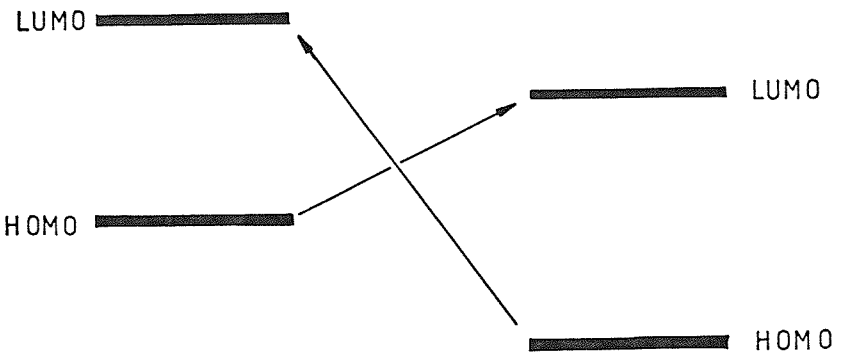
The first term in the above equation describes the first order closed repulsion term and is similar for several pathways or sites. The second term is a mathematical representation of the coulombic repulsion (or attraction) contribution when ions or polar molecules react together. The final term in equation 1 is a representation of the interaction of the occupied orbitals (highest occupied molecular orbitals, HOMO) of one of the reactants with the unoccupied orbitals (lowest unoccupied molecular orbitals, LUMO) of the other reactant. It is this third term which forms the basis of FMO theory.

In cycloaddition reactions the frontier orbital interactions are almost always between orbitals well separated in energy. They are dependant upon this third term.

For any two sites, E_r-E_s in any particular pair of reactants is always

the same. Likewise the β^2 term remains a constant so it is only the Σc^2 term of the equation which determines the site selectivity. The site which will maximise the ΔE is the major site of reaction. However as FMO is only an approximation, exceptions do occur.

Regiochemistry is determined by the interaction energies of the molecular orbitals. First it is necessary to ascertain whether a reaction is HOMO dipole or LUMO dipole controlled. For example, which is the major interaction; the HOMO orbitals of the substrate with the LUMO of the reagent, or vice versa (scheme 3.12)?



1,3-Dipole (A) Dipolarophile (B)

(Scheme 3-12)

The major interaction energies are determined by equation 2, a derivation from the third term of equation 1.

$$\Delta E = \frac{(c_{ij}c_{ji}\gamma)^2}{E^A_{HO}-E^B_{LU}} - \frac{(c_{ji}c_{ij}\gamma)^2}{E^B_{HO}-E^A_{LU}} \qquad \text{Eq. 2}$$

c_{ij} : Coefficients of the interacting FMO's on the atoms i and j.

γ : An overlap integral.

E : The energy of the molecular orbital in question.

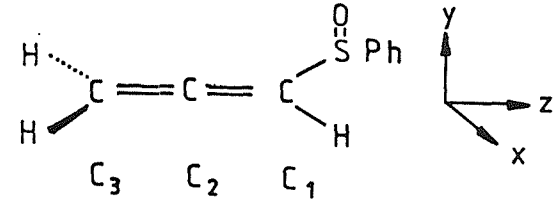
The closer the energy of the HOMO and LUMO orbitals of the two systems the greater the domination of that interaction. If the HOMO of A and the LUMO of B are close together then $E^A_{HO}-E^B_{LU}$ is small and the first term of equation 2 dominates. Thus the reaction will be HOMO dipole controlled.

Once the controlling HOMO and LUMO orbitals have been deduced we must look at the best way of achieving maximum overlap of the orbitals[110]. The regiochemistry is predicted by the atoms with the largest orbital coefficients interacting with each other to give maximum overlap of the orbitals overall. These atomic orbital coefficients have been calculated using a CNDO[111] program. Methylsulphinyl-1,2-propadiene was used as a model for phenylsulphinyl-1,2-propadiene to simplify the CNDO calculations. This implementation of the program allows a conformational adjustment of the molecule in question, and the atomic orbital coefficients obtained in table 3.3 were the result of varying the conformation of the molecule until its total energy was minimised[112]. The coordinates for this conformation can be found in appendix 1.

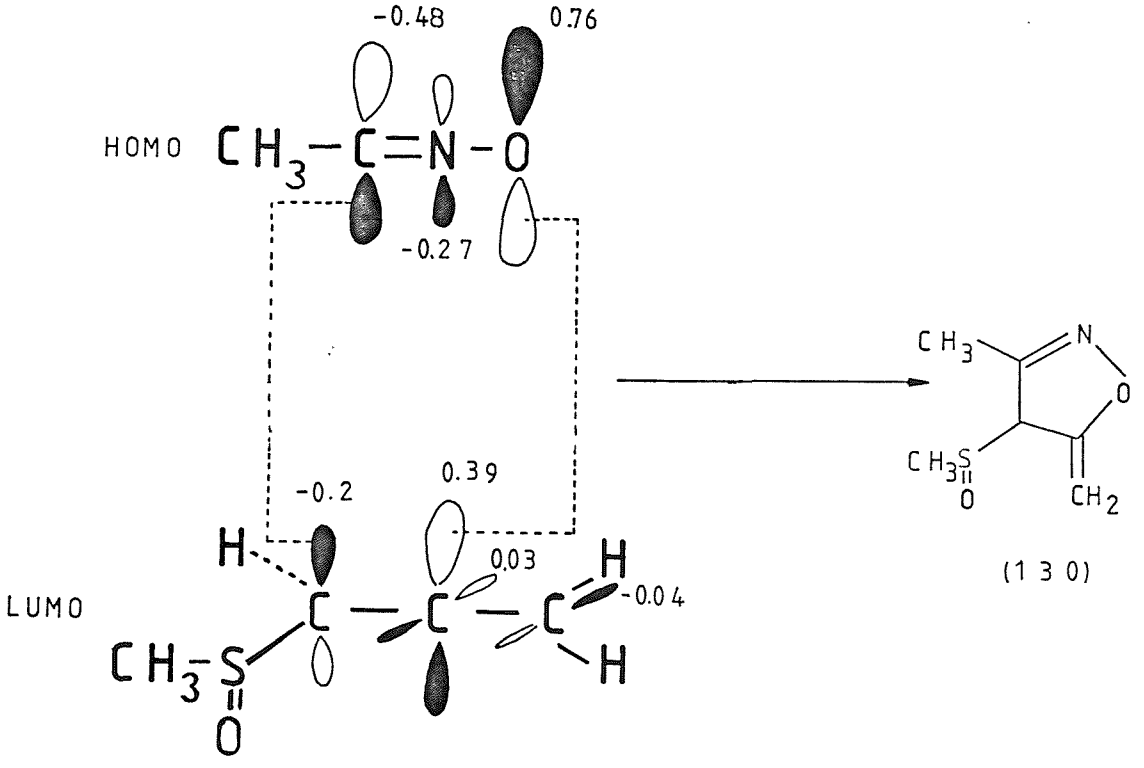
Molecule	HO/LU	Energy[a] (eV)	Orbital coefficients[a]			
			C_C	C_N	C_O	
Dipole	HO	-11.5 (-12.0)	-0.48 (0.52)	-0.27 (0.26)	0.76 (-0.76)	
	LU	4.1 (4.1)	0.52 (0.60)	-0.59 (-0.63)	0.27 (0.28)	
			C_{1px}	C_{2px}	C_{2py}	C_{3py}
Dipolarophile	HO	-12.2	0.09	0.08	0.21	0.42
	LU	2.1	-0.20	0.39	0.03	-0.04

a. Figures in parenthesis are literature values[113]

TABLE 3.3

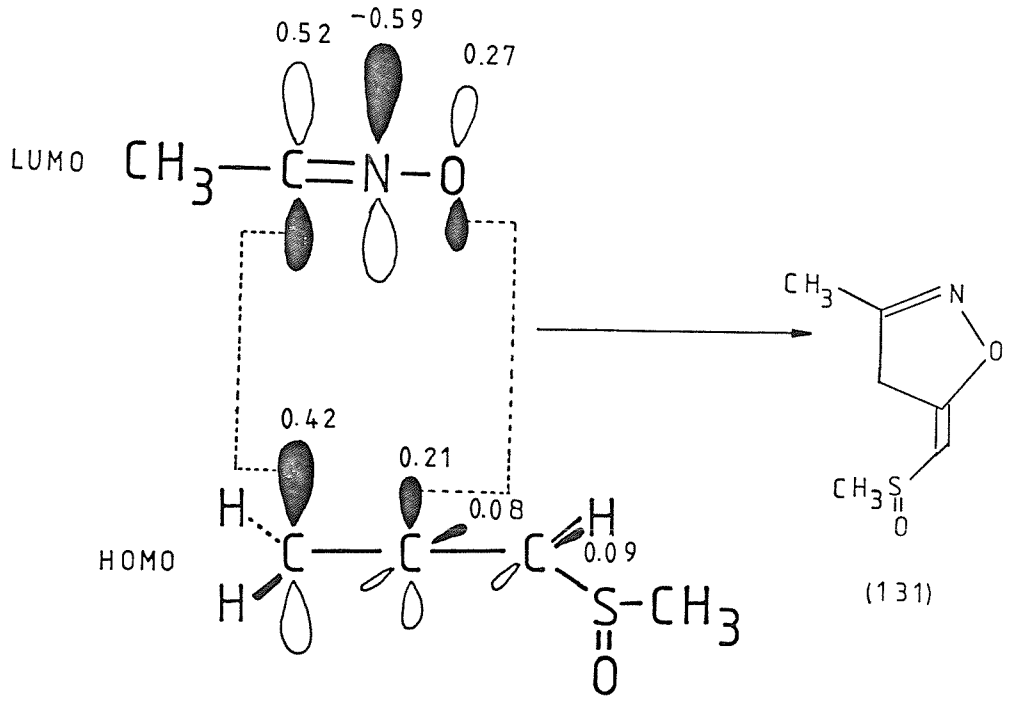


The calculated values for the atomic orbital coefficients of the relevant frontier molecular orbitals for the dipole and dipolarophile are given in table 3.3. Inspection of the table reveals that the HOMO dipole interaction with the LUMO dipolarophile should be the major interaction (energy difference of these orbitals is 13.6 eV versus the other possible interaction which is 16.3 eV). Scheme 3.13 illustrates the result of such an interaction. Although favourable on the HOMO dipole and LUMO dipolarophile energy basis, this outcome does not take into account the steric hindrance of the sulphinyl group with the methyl group of the acetonitrile oxide, which would be significant in the transition state of the reaction. This may be the reason why we do not see the products from this interaction.



(Scheme 3.13)

Although the LUMO dipole/HOMO dipolarophile interaction is not energetically favourable, the atomic orbital coefficients do in fact predict our observed products (scheme 3.14). This is also the pathway of minimum steric hindrance in the transition state.

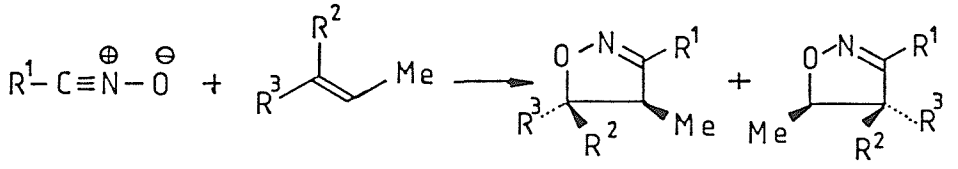


(Scheme 3.14)

Thus if the calculation was made more realistic by taking into account van der Waals repulsions for the reaction transition state, rather than the simple FMO treatment, this LUMO dipole controlled pathway might well be energetically favourable. It has already been described by Houk[110] that the reaction of nitrile oxides with electron rich dipolarophiles are LUMO dipole controlled reactions.

3:2:4 Nitrile oxide products: A steric approach.

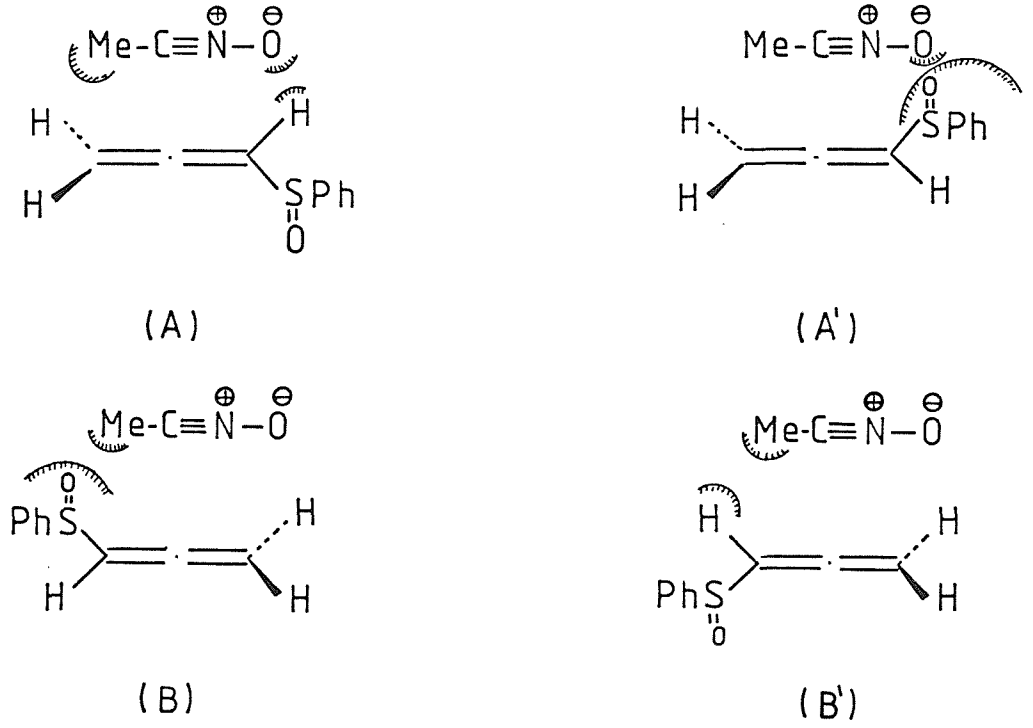
A steric approach to the 1,3-dipolar cycloadditions of nitrile oxides to unactivated unsymmetrical olefins has been investigated by Martin and Dupre[89]. They generalised that nitrile oxides react with (*Z*)-disubstituted olefins (132a) to afford 4,5-dialkyl-isoxazolines (133a) exclusively, whilst (*E*)-disubstituted olefins (132b) give a mixture of (133b) and (134b) where the 4,5-dialkyl-isoxazoline (133b) is the major regioisomer (scheme 3.15).



	(115)	(132)	(133)	(134)
(a)	R^2 = alkyl , R^3 = H		100%	0 %
(b)	R^2 = H , R^3 = alkyl		major	minor

(Scheme 3.15)

The results of our experiments confirm that a steric approach may be extended to predict the outcome of nitrile oxide additions to phenylsulphinyl-1,2-propadiene. Scheme 3.16 depicts the four possible nitrile oxide approaches to the substrate. Approach A evidently leads to a low energy early transition state by minimising steric interaction of the reactants. This steric steering leads to the transition state which results in our observed products.

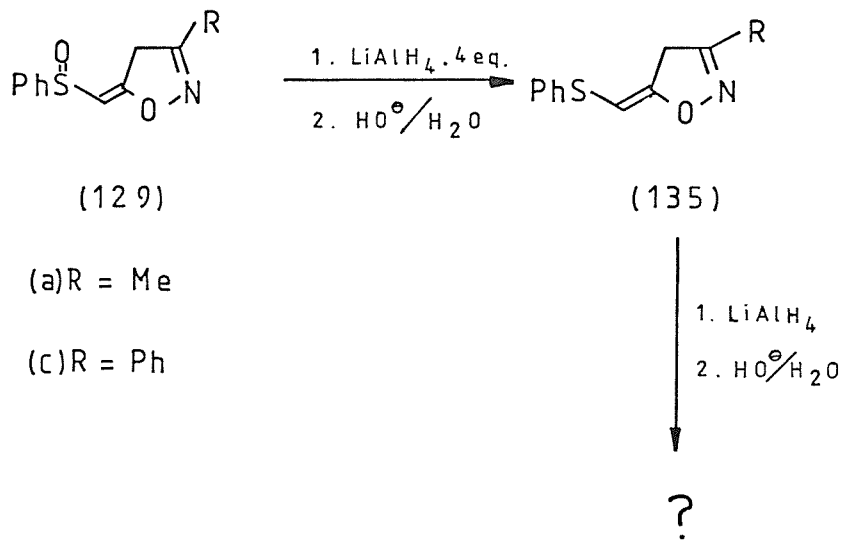


(Scheme 3.16)

3:2:5 Attempted reduction of the isoxazoline N-O bond.

A good precedent[114] exists for the reduction of the N-O bond of 2-isoxazolines to produce γ-aminoalcohols. Jäger[115-116] has used the technique extensively in the synthesis of polyols and sugars, and it has been employed to obtain the key intermediate in the Smith[117] synthesis of milbemycin β_3. All these syntheses differ from our isoxazoline in that ours would yield a β-aminoketone.

The action of lithium aluminium hydride ($LiAlH_4$, 4 equivalents) reduced the sulphoxides (129) to the corresponding sulphides (135) scheme 3.17).



(Scheme 3.17)

Treatment with a further four equivalents of $LiAlH_4$ gave a product of at that time unknown structure.

It was reported at this time that samarium diiodide[118] was an effective reducing agent for isoxazoles[119] *via* a single electron transfer (SET) mechanism. We decided to investigate the use of this cheap reagent for the reduction of our isoxazoline adducts. The

reagent was prepared using commercially available samarium metal, rather than ultra high purity Samarium metal, by a novel ultrasonic technique[120] (scheme 3.18).

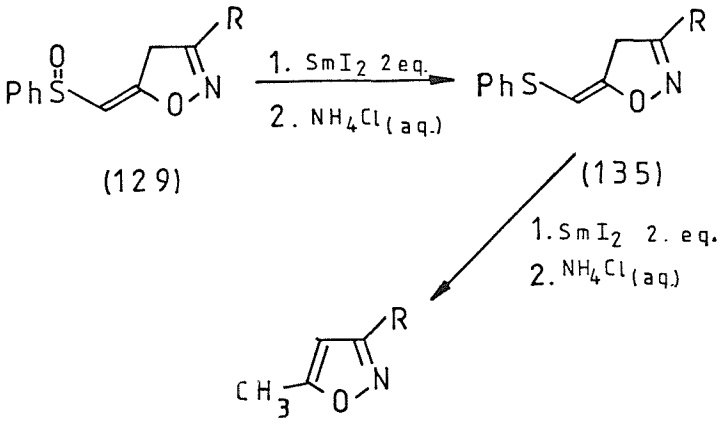
$$Sm + ICH_2CH_2I \xrightarrow[THF/RT]{Ultrasound} SmI_2 + CH_2=CH_2$$

(136) (137) (138) (120)

100 %

(Scheme 3.18)

Treatment of the cycloadducts (129) with samarium diiodide (SmI_2) reduced the sulphoxide initially to the sulphide[121], which on further treatment with another aliquot of SmI_2 afforded the 3-methyl-5-substituted-isoxazoles (139) (scheme 3.19).



(139) (a) = 60 %

(c) = 60 %

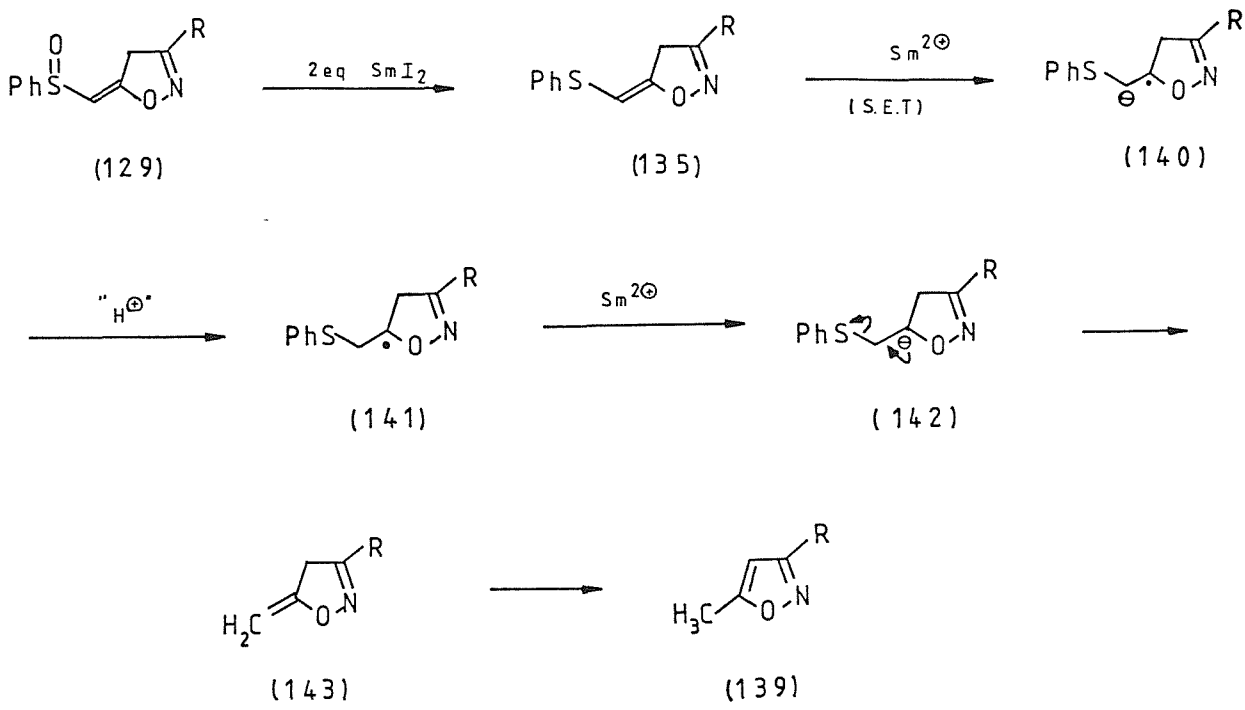
(a) R = Me

(c) R = Ph

(Scheme 3.19)

The products of this reaction were found to be identical with those

observed with the $LiAlH_4$ procedure but yields were much improved and by-products minimised. We have postulated an SET mechanism for the transformation (scheme 3.20).



(129) (135) (140) (141) (142) (143) (139)

(Scheme 3.20)

In this mechanism we suggest that initial elimination of the sulphide occurs to provide an *exo*-methylene species (143) and a thiophenolate anion (thiophenol is a discernible by-product). The *exo*-methylene intermediate then isomerises rapidly to the thermodynamically more stable aromatic isoxazole (139).

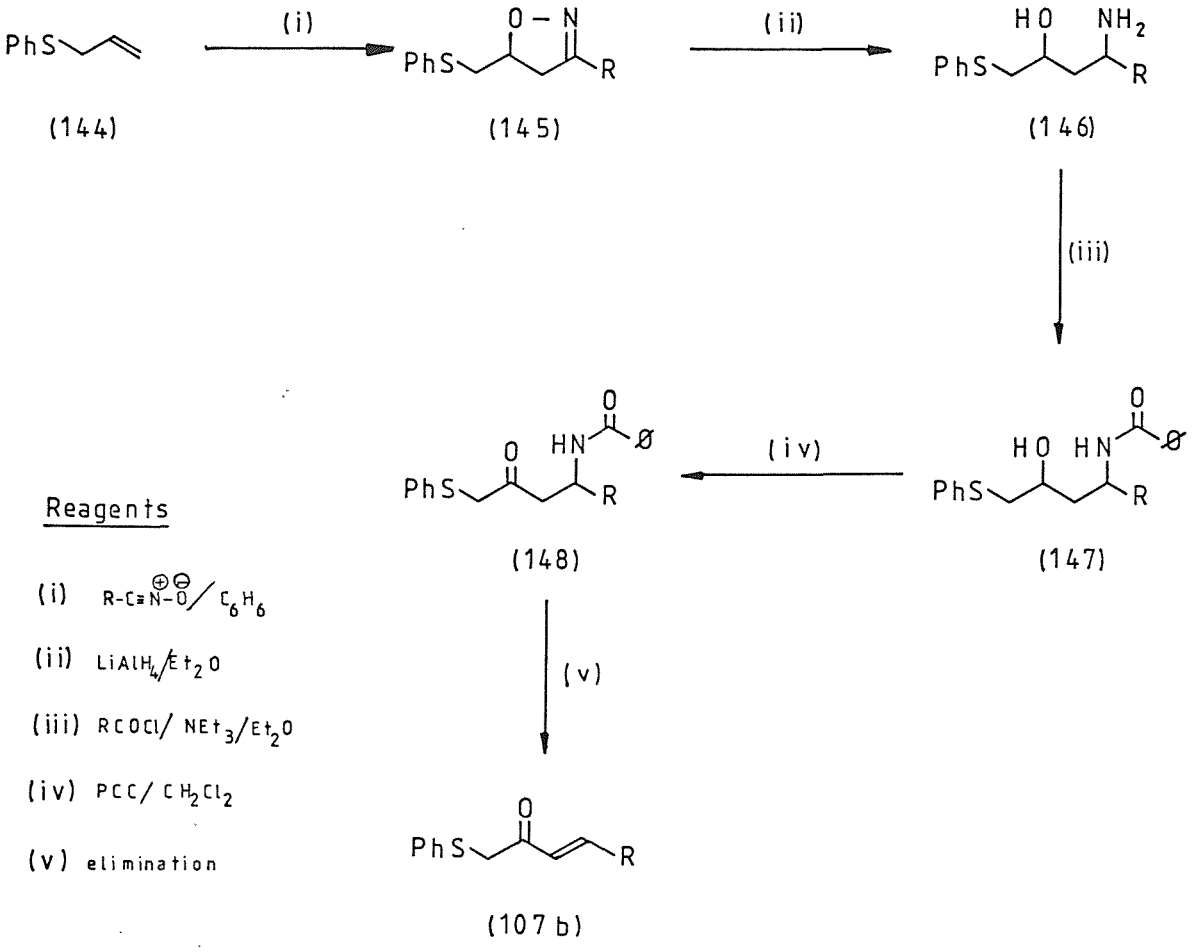
3:2:6 Conclusion.

In view of the difficulty observed in reducing the N-O bond of the novel isoxazolines and the problem of the instability we might have

encountered with β-aminoketones, we decided to investigate another cycloaddition route involving addition of nitrile oxides to 1-phenylthioprop-2-ene. This would lengthen our route by one step as we would have to adjust the oxidation level of the γ-aminoalcohol to the corresponding ketone.

3:3 A 1-PHENYLTHIOPROP-2-ENE ROUTE TO α,β-UNSATURATED KETONES.

A similar but more traditional approach to the problem of the synthesis of α,β-unsaturated ketones (107b) was adopted (scheme 3.21).



(Scheme 3.21)

The route above involves a nitrile oxide addition to 1-phenylthioprop-2-ene (144), followed by reduction of the isoxazoline N-O bond (145)

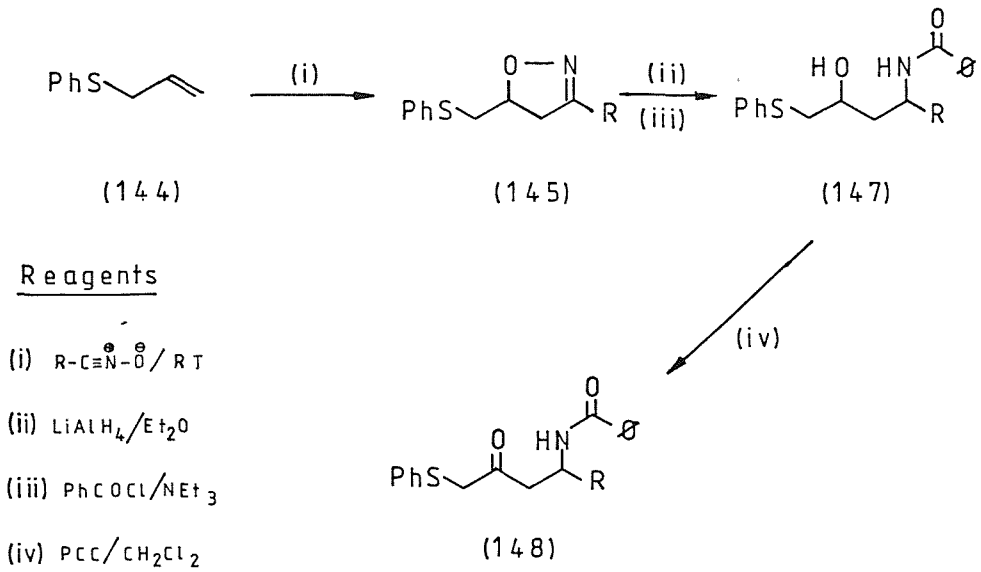
to yield a γ-aminoalcohol (146), protection of the amine as an amide (147), followed by oxidation of the alcohol to afford a β-amidoketone (148). The final step requires elimination of the amide to give us our substituted α,β-unsaturated ketones (107b). We envisaged that this route, although not particularly short, would be relatively facile to implement. It has the advantage that both ends of the α,β-unsaturated ketone can easily be modified.

3:3:1 Results and Discussion.

Nitrile oxide additions were performed on 1-phenylthioprop-2-ene with considerable success to produce a single regioisomeric isoxazoline (145) in fair to good yields. Reduction with lithium aluminium hydride gave the γ-aminoalcohols (146), which were trapped *in situ* with benzoyl chloride[122] to give the corresponding γ-amidoalcohols (147), which were then isolated. Oxidation using pyridinium chlorochromate (PCC)[123] proceeded smoothly affording the enone equivalents (148). Table 3.4 summarises the results of these experiments.

The theories of FMO and steric hindrance already outlined apply equally to these cycloadditions (section 3:2:3 *et seq.*). It will be noted once again that only additions performed using the Mukaiyama dehydration of primary nitro compounds were efficacious.

In a desire to widen the scope of this synthetic method we extended this approach to the synthesis of α,β,γ,δ-unsaturated ketones. The unsaturated nitro-alkanes (149) were dehydrated as before, and the resulting nitrile oxides added smoothly to 1-phenylthioprop-2-ene. The resulting adducts (150) were reduced with $LiAlH_4$ or di-*iso*butylaluminium hydride (DIBAL-H) in hexane[124] (Table 3.5). Reduction of the N-O bond with $LiAlH_4$ gave the totally saturated amidoalcohols (151) as the major product through 1,4-hydride addition, and to a much lesser extent the desired unsaturated amidoalcohols



Reagents

(i) $R-C\equiv\overset{\oplus}{N}-\overset{\ominus}{O}$ / RT

(ii) $LiAlH_4/Et_2O$

(iii) $PhCOCl/NEt_3$

(iv) PCC/CH_2Cl_2

Compound	R	Yield (%) (145)	Yield (%) (147)	Yield (%) (148)
a	Me[A]	60	80	40
b	Et[A]	45	76	54
c	Ph[A]	54	66	32
d	CH_2OTHP[A]	32	54	32
e	$COEt$[B]	0	—	—
c	Ph[B]	0	—	—

Method of nitrile oxide generation

A : Dehydration of primary nitro compounds.

B : Dehydrohalogenation of hydroximic acid chlorides.

(TABLE 3.4)

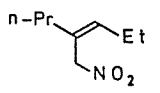
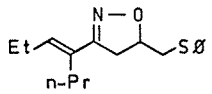
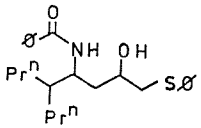
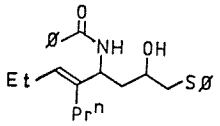
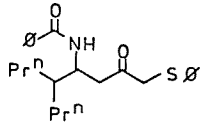
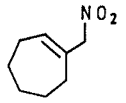
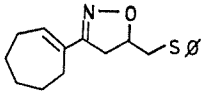
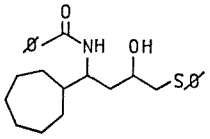
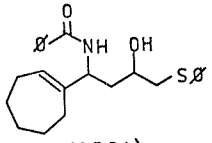
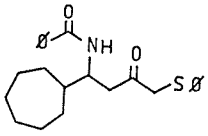
Nitro-Compounds	Adducts Yield (%)	Reduction Products Yield (%)		PCC Oxidation Yield (%)
 (149a)	 (150a) 61%	 (151a)	 (152a)	 (153a) 15%
		$LiAlH_4$ 30%	3%	
		DiBAL-H 93%	0%	
 (149b)	 (150b) 67%	 (151b)	 (152b)	 (153b) 25%
		$LiAlH_4$ 33%	15%	
		DiBAL-H 87%	0%	

TABLE 3.5

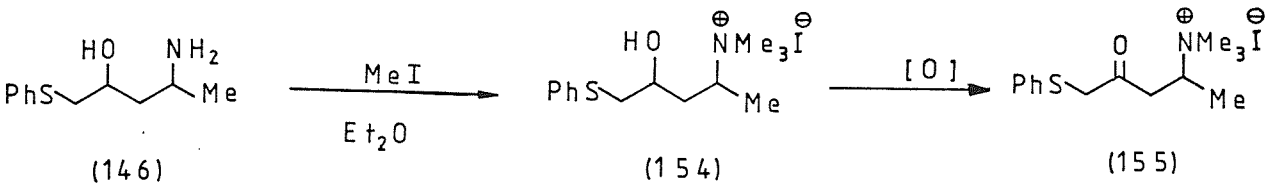
(152) by 1,2-hydride addition. DIBAL-H however gave exclusive 1,4-hydride addition affording the saturated compounds (151). Subsequent PCC oxidation of the major products gave us more examples of the desired enone equivalents (153), table 3.5.

3:3:2 Attempts to prepare 4-substituted-1-phenylthio-3-buten-2-ones

To complete our synthesis of substituted α,β-unsaturated ketones it was necessary to eliminate the benzoyl amide function. The literature methodology[125] for this transformation is to pyrolyse the amide so that it undergoes a *syn* elimination *via* a cyclic transition state analogous to Cope or acetate elimination. The range of conditions undertaken to effect this transformation is shown in table (3.6).

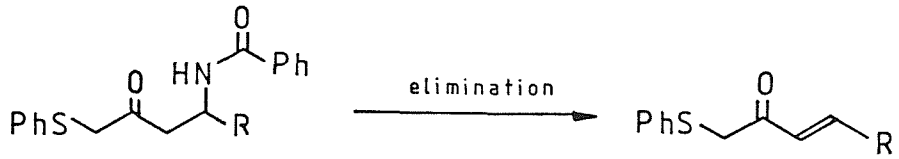
Pyrolysis was found to give complex mixtures, whilst acidic hydrolysis[126] with *p*-toluenesulphonic acid (*p*TSA) or glacial acetic acid gave either starting material, or complex mixtures depending on the temperatures. The amides were found to be inert to base hydrolysis[127].

Hofmann elimination of the quaternary ammonium salt[128] of the γ-aminoalcohol (154) was also investigated. However treatment of the crude γ-aminoalcohol (146) with methyl iodide gave a brown gum and PCC oxidation of this material gave an inseparable mixture of compounds (scheme 3.22).



(146) (154) (155)

(Scheme 3.22)



(148) (107b)

R	Conditions	Results
Me Ph	Pyrolysis in a melting point tube.	Fast moving 2,4-DNP and $KMnO_4$ active spot appeared t.l.c.
Me Ph	Heated under reflux in C_6H_6 and *p*TSA for 5 hrs.	Complex mixture.
Me Ph	Glacial acetic acid at R.T. for 24 hrs.	SM
Me Ph	Glacial acetic acid at 100°C for 5 hrs.	Complex mixture
Me Ph	K_2CO_3 in DMF at 50°C for 24 hrs.	SM
Me Ph	K_2CO_3 in ether at 35°C for 24 hrs.	SM
Me Ph	Vacuum pyrolysis 10^{-2} mm Hg down a 10 cm quartz packed column	Complex mixture.

TABLE 3.6

3:3:3 Conclusion

This route has provided some interesting and synthetically useful results, but failed to give the desired α,β-unsaturated ketones due to the difficulty in eliminating the amide or handling the quaternary ammonium salt. It may be possible to protect the amine as another derivative which is more amenable to elimination. The *exo*-methylene isoxazoline adducts may still be useful as masked β-aminoketones and it only requires a suitably mild deprotection method to be developed to utilise these synthons.

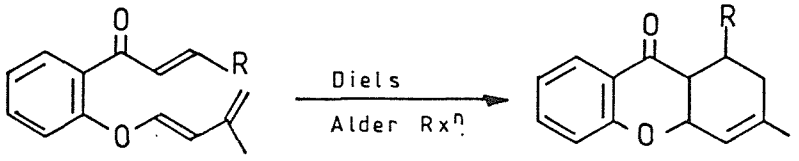
CHAPTER 4

ROUTES TO OXYGEN HETEROCYCLES UTILISING PRE-FORMED AROMATIC RINGS

4:1 INTRODUCTION TO AN INTRAMOLECULAR DIELS-ALDER APPROACH.

This area of research was entered into with the intent to perform an intramolecular Diels-Alder reaction and hence continue our theme of Diels-Alder reactions (intermolecular approach Chapter 3), with the significant difference being that we would use a preformed benzene ring system and utilise the Diels-Alder reaction to set up the pyrone system.

We believed that (157) would be a useful molecule to allow entry to the ergochrome series of compounds. One of the key steps we proposed is illustrated in scheme 4.1.

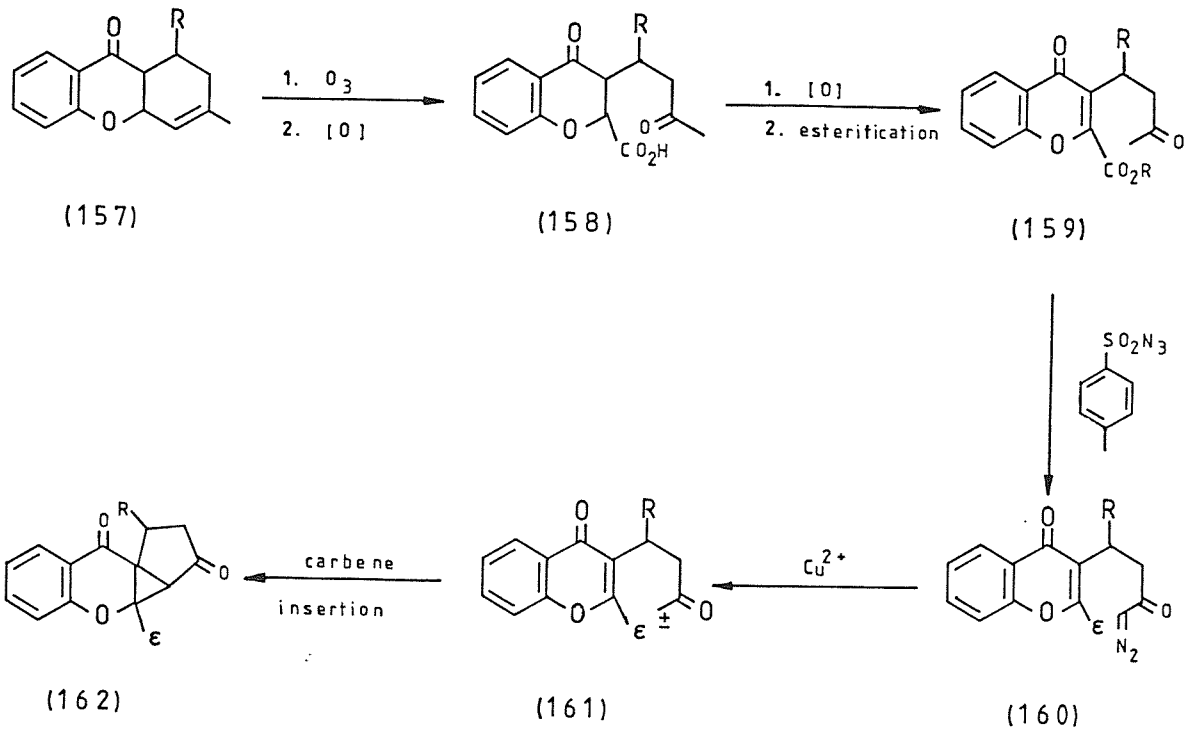


(156) (157)

(Scheme 4.1)

The forward strategy from compound (157) to the natural product series is shown in schemes 4.2 and 4.3. They employ a key tetracyclic compound (162). The keto-acid (158) can be obtained by the ozonolysis and oxidative work up of the tricyclic chromanone (157). Oxidation to the corresponding chromone and protection of the acid affords the keto-ester (159), which on treatment with p-toluenesulphonyl azide[129] allows access to the diazo-ketone (160). The diazo-ketone could be treated with a variety of metal salts[130] or photolysed to eliminate

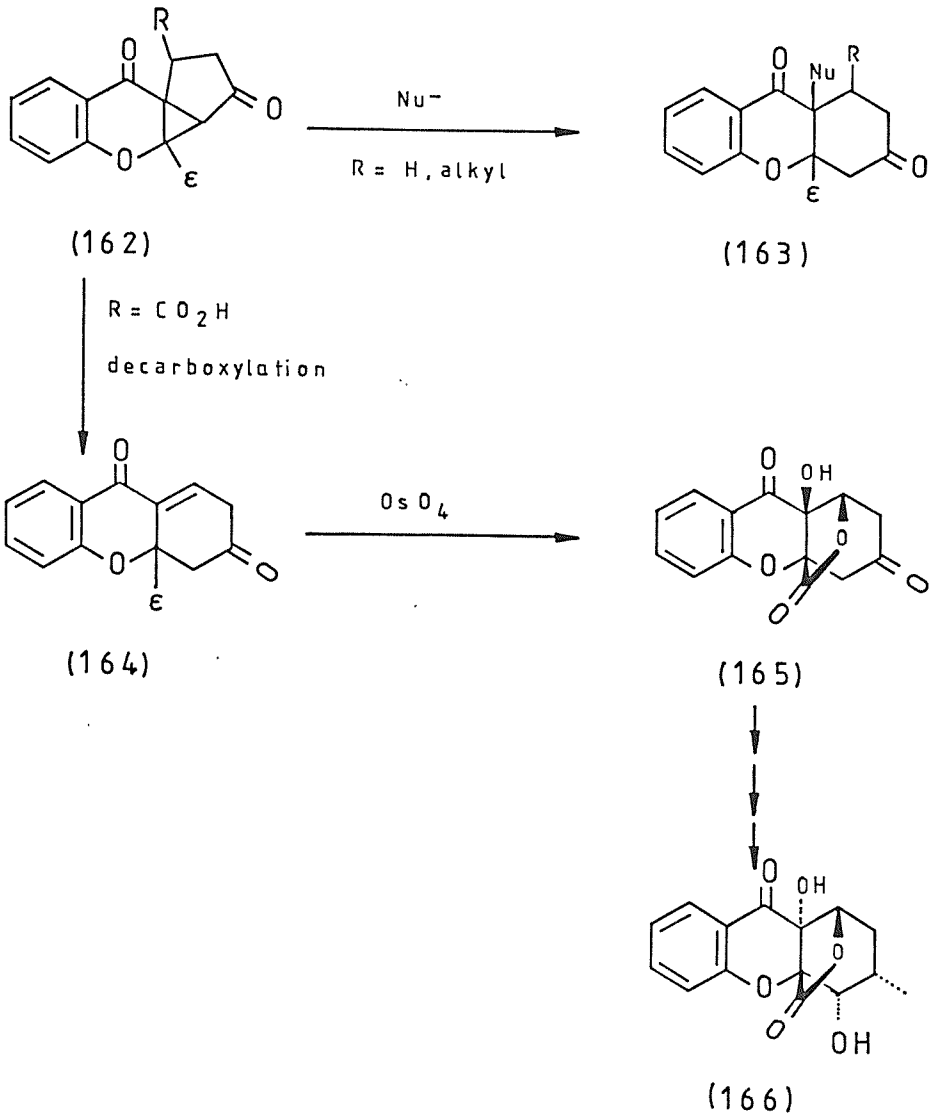
nitrogen gas and afford the carbene[131] (161) which would, we anticipated, easily insert into the carbon carbon double bond of the chromone to yield the tetracyclic cyclopropyl compound (162) (scheme 4.2).



(Scheme 4.2)

The resulting compound, depending upon the substitution of the cylopentanone ring, could be opened up to allow entry to chromanones or ergochrome model compounds either by decarboxylative or nucleophilic ring opening strategies[132] (scheme 4.3).

To summarise, the key step of these approaches involves the ring opening of the novel tetracyclic cyclopropyl compound (162).



(162) (163) (164) (165) (166)

(Scheme 4.3)

We have used this synthetic pathway as a vehicle for the development of new synthetic methods for the alkylative protection and deprotection of dienes, as the strategy involves the use of hitherto unknown oxygenated dienes (156) in an intramolecular Diels-Alder reaction (scheme 4.1). To this end we investigated an organo-selenium approach.

4:2 A SELENIUM APPROACH.

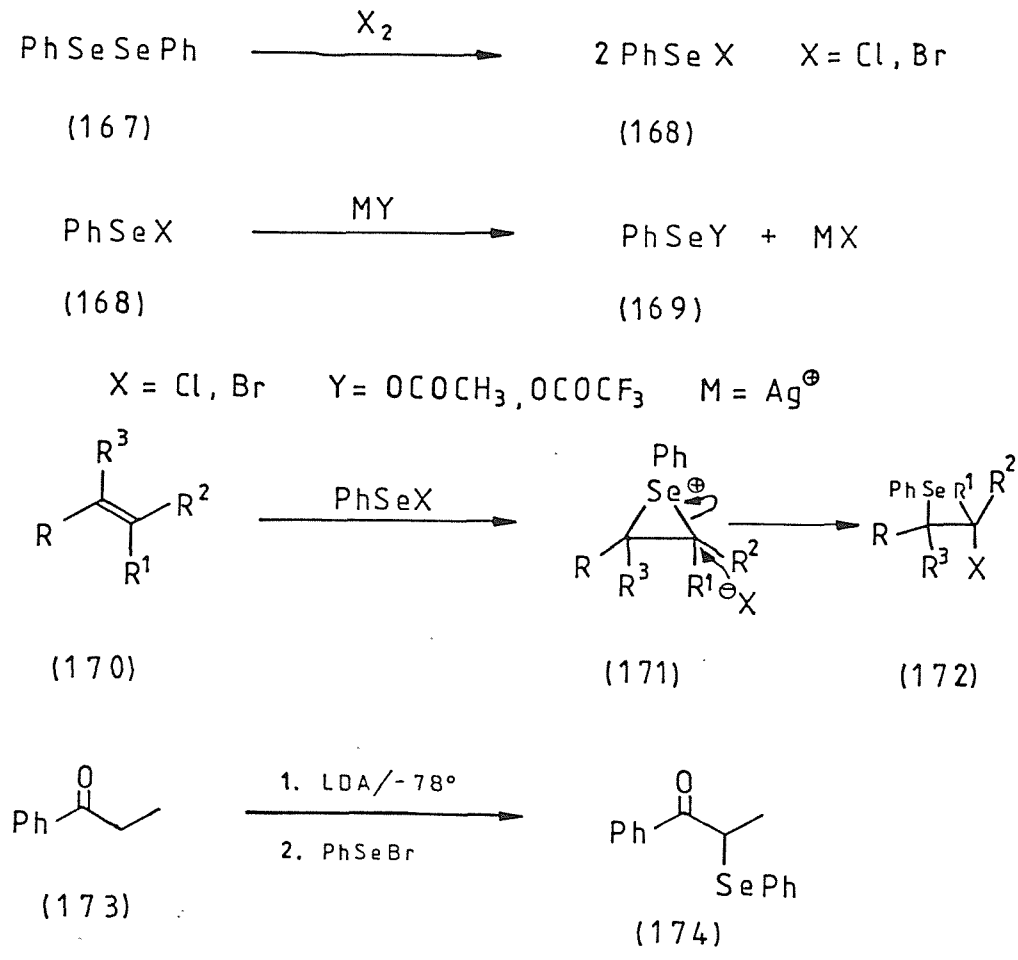
4:2:1 An Introduction to Organo-Selenium Chemistry.

The period since 1970 has seen a great renaissance in organo-selenium chemistry. This is notably due to the discovery and development of new types of selenium reagents which have proved to be useful and versatile tools in organic synthesis.

Unsaturation can easily be introduced to a molecule using the elimination of an organo-selenium species and this has placed organo-selenium reagents in a position of prominence in today's organic chemistry.

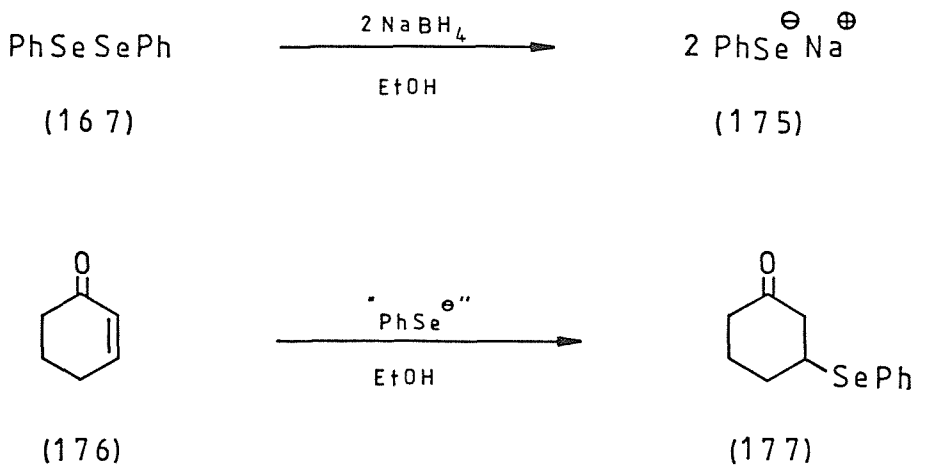
Considerable effort has been expended both on the electrophilic addition of "$PhSe^{+}$" to carbon carbon double bonds (and other electron rich species) and the nucleophilic addition of "$PhSe^{-}$" to electrophilic substrates[133] (scheme 4.4).

The usual electrophilic selenium species is generated from PhSeSePh either by oxidation, or by treatment with chlorine[134] or bromine[135] to generate PhSeCl or PhSeBr respectively (scheme 4.4). These reagents can then be converted to the trifluoroacetate or acetate compounds depending upon their desired application.



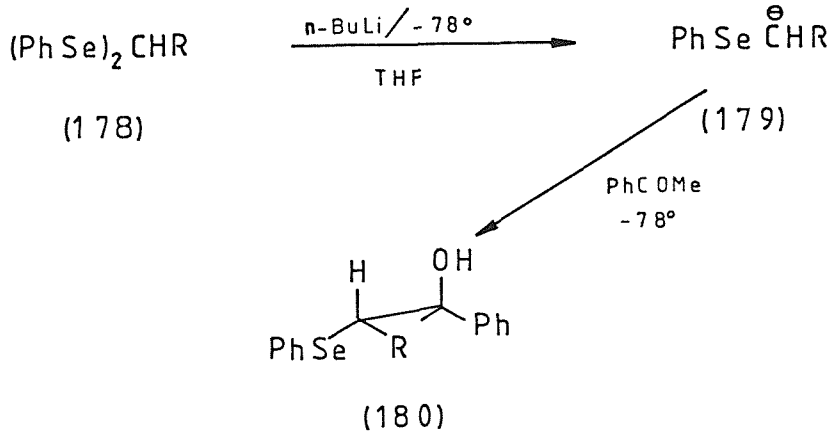
(Scheme 4.4)

The nucleophilic "$PhSe^-$" species is usually generated by the reduction of PhSeSePh with sodium borohydride[136-138] to give the sodium selenoate. This can then be reacted with epoxides[136], α,β-unsaturated systems[139], or used in displacement reactions of halides[140] and sulphonates[141](scheme 4.5).



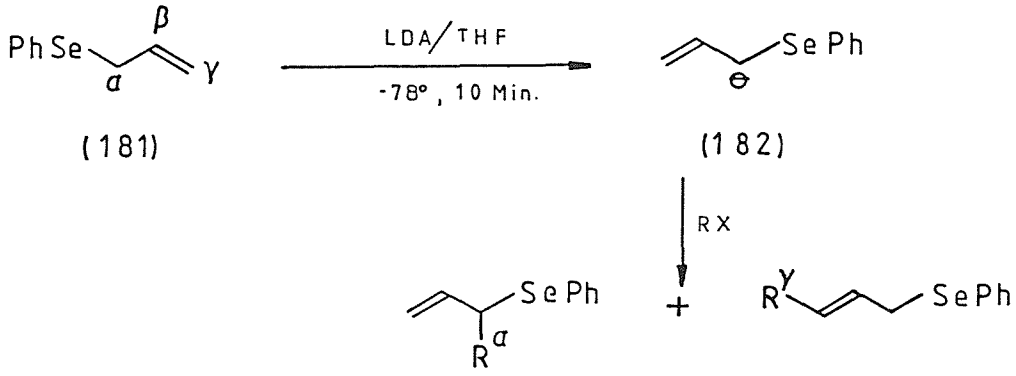
(Scheme 4.5)

Once an organo-selenide has been generated, it can be used to stabilise carbanions. $(PhSe)_2CH_2$ has a pKa 35 compared with a pKa 32-33 for the corresponding sulphur analogue[142]. They can be reacted with ketones or aldehydes with considerable success. Selenium stabilised carbanions are best generated by the Se-C bond cleavage of selenoketals[143] (scheme 4.6).



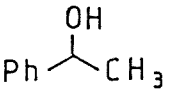
(Scheme 4.6)

Alternatively allylic selenides can be deprotonated at the α-position, to give a stabilised carbanion, and reacted with alkyl halides, epoxides, ketones etc. The reaction of allylically stabilised anions involve a competition at α and γ sites and the product ratio depends on the nature of the electrophile[144-145]. Where γ addition occurs, a 1:1 ratio of (*E*)- and (*Z*)-isomers is obtained (scheme 4.7).



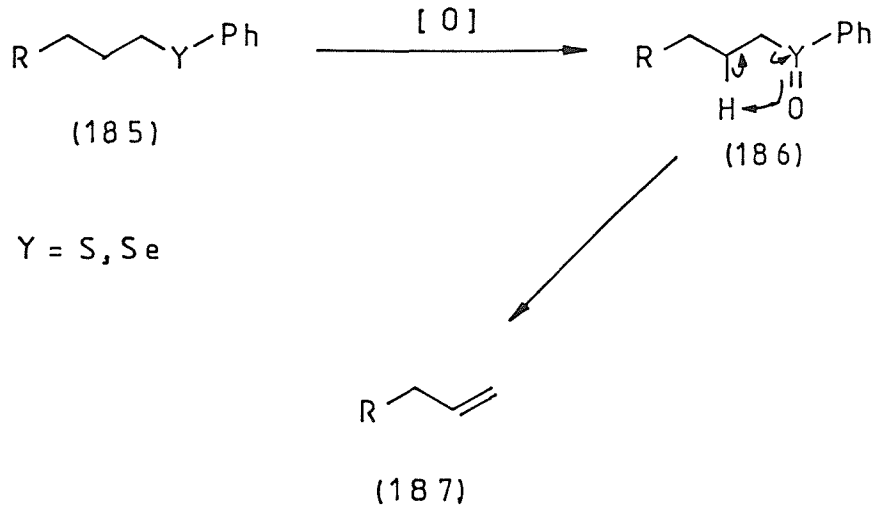
(181) (182)

(183) (184)

	α	Ratio	γ
R = Me_3Si	82		18
R = $PhMe_2Si$	41		59
R = 	15		85

(Scheme 4.7)

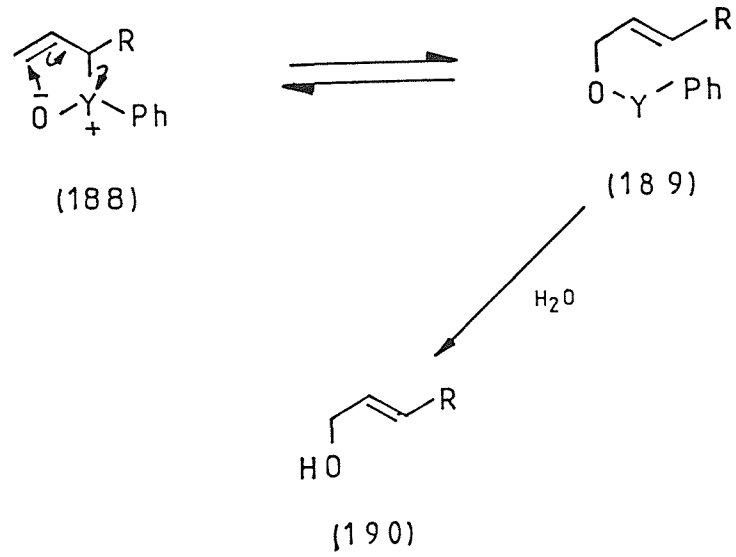
As already mentioned, the major use of alkyl phenyl selenides is to form olefins from the alkyl portion using mild conditions. This is achieved by oxidation of the selenide to the corresponding selenoxide and subsequent *syn*-elimination of phenylselenenic acid[146]. Many analogies can be drawn from the corresponding sulphur compounds where the alkyl sulphoxide produced by oxidation of the alkyl sulphide also undergoes *syn*-elimination to afford an olefin[147-148] (scheme 4.8).



(Scheme 4.8)

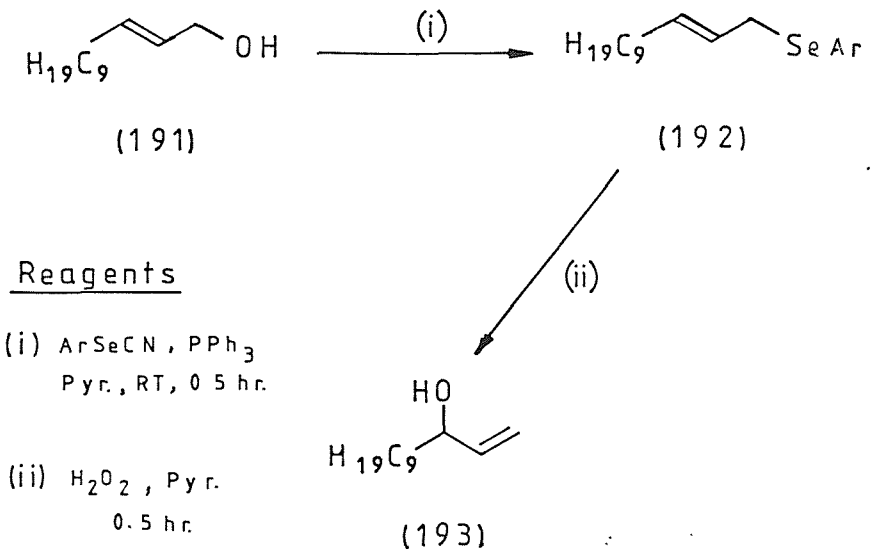
The selenium version of this reaction can be performed using a variety of oxidising agents and a multitude of conditions for the elimination step which typically occurs at temperatures of 50 to 120°C lower than their sulphur counterparts[133].

Allylic selenoxides either eliminate or undergo facile [2,3] sigmatropic rearrangement to give allylic alcohols in an analogous way to allylic sulphoxides. This process is reversible, but in contrast to the sulphur situation, the equilibrium for the reaction lies predominantly to the right[149], and the selenenic esters can be readily hydrolysed to the corresponding allylic alcohols (scheme 4.9).



(Scheme 4.9)

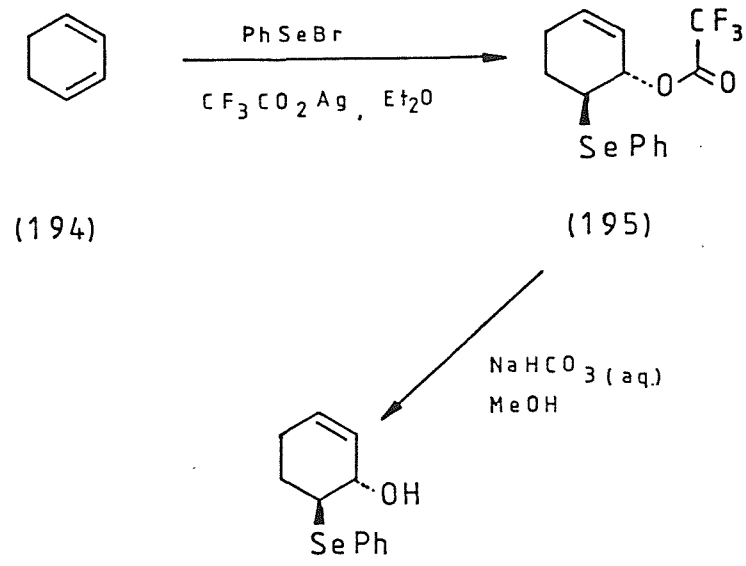
This rearrangement has been used in the 1,3-transposition of allylic alcohols[150] illustrated in scheme 4.10.



(Scheme 4.10)

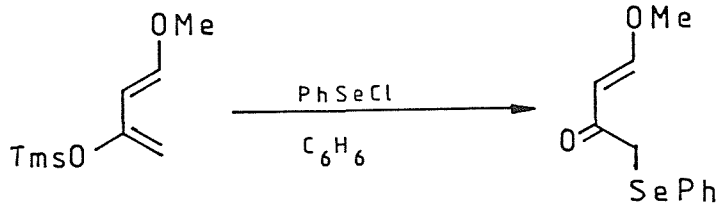
The intermediate allylic selenoxide rearranges and the resulting selenenic ester is hydrolysed *in situ* in the reaction medium[145].

Surprisingly little attention has been devoted to the addition of electrophilic arylselenenic reagents to dienes. The cases reported involve addition of PhSeBr in the presence of silver trifluoroacetate to give 1,2-hydroxyselenation[151] (scheme 4.11), or the addition of phenylselenenyl chloride to Danishefsky's diene, not a typical diene being a silyl enol ether and gives 4-methoxy-1-phenylseleno-buten-2-one (198) as the product[152] (scheme 4.12).



(194) (195)

(Scheme 4.11)



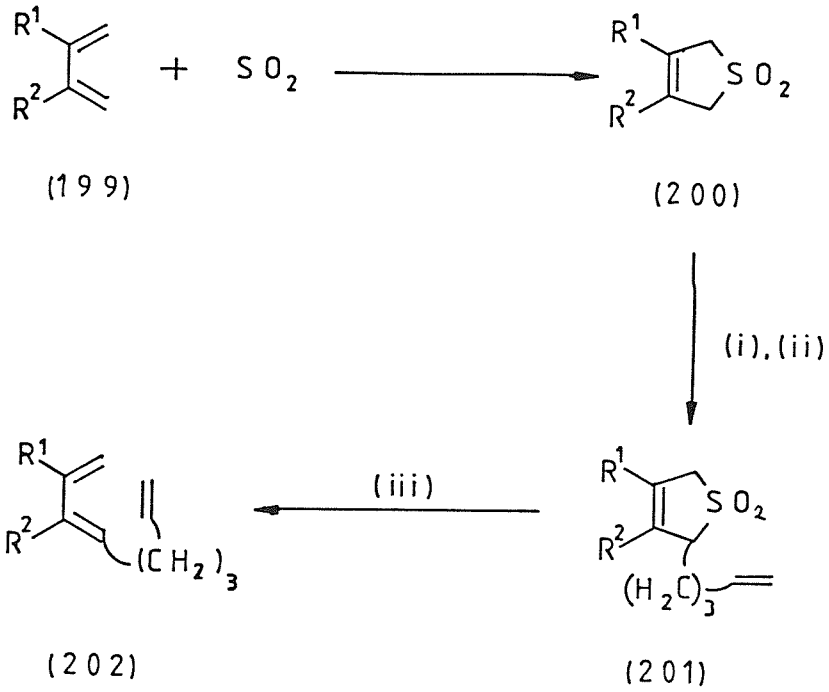
(197) (198)

(Scheme 4.12)

Thus we decided to study the addition of phenylselenenyl chloride to dienes, and investigate if a protective, alkylative deprotection methodology could be developed.

4:2:2 <u>Diene protection and deprotection : Proposed route.</u>

Few acceptable diene protection methods exist, and all suffer from either low yields or reagents which are difficult to handle. The best protection methodologies employ either iron pentacarbonyl complexes[153], or sulphur dioxide addition to give sulpholenes followed by alkylation and deprotection to give alkylated dienes[154-156](scheme 4.13).

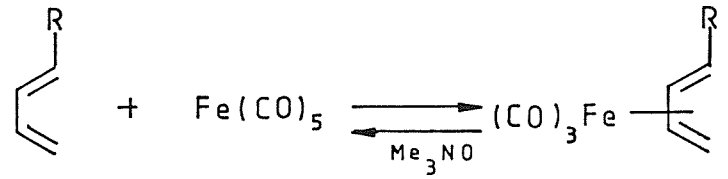


Reagents

(i) $LiN(SiMe_3)_2$, THF

(ii) $CH_2=CH(CH_2)_3I$

(iii) 240°

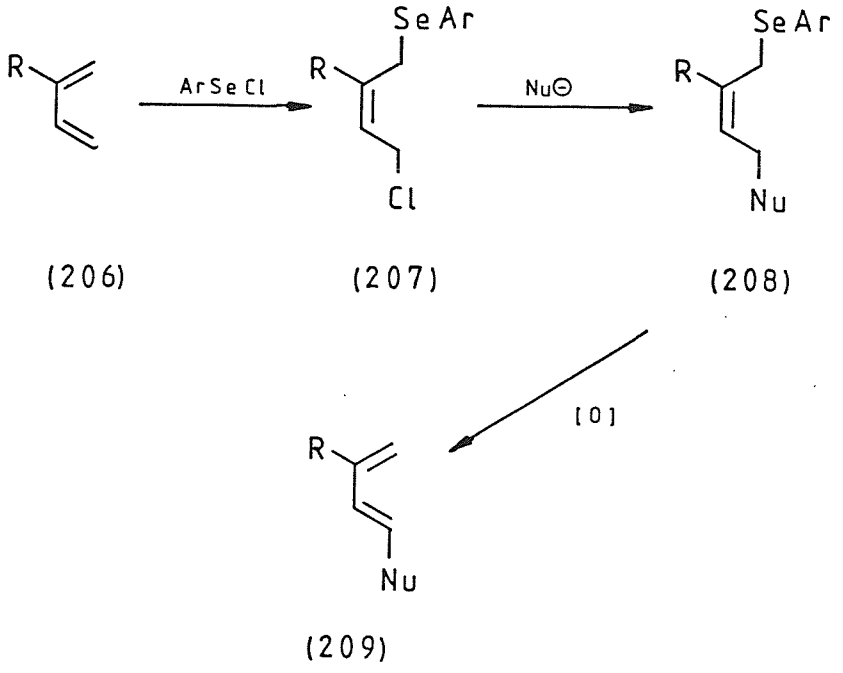


(Scheme 4.13)

Deprotection of iron carbonyl complexes can prove difficult, whilst in the latter, thermal extrusion of SO_2 to regenerate the diene can be

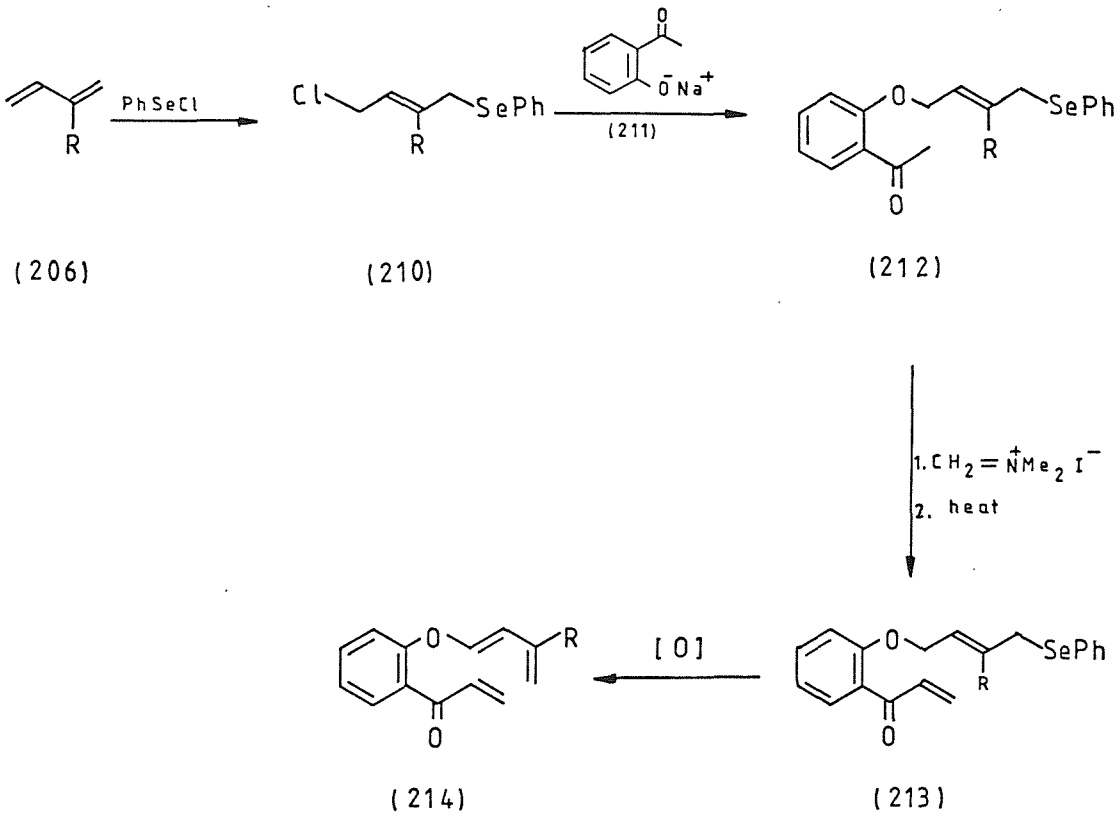
awkward with thermally labile dienes, leading to low yields.

In contrast to the above methods, we decided to investigate the addition of phenylselenenyl chloride to dienes, and see if a new route to substituted dienes could be developed (scheme 4.14).



(Scheme 4.14)

This methodology would allow us access to our oxygenated dienes (scheme 4.1); such a strategy can be found in scheme 4.15. It uses a substituted *o*-hydroxyacetophenone as the nucleophile, and generates (212) as a "latent diene". Treatment with Eschenmoser's salt[157] and elimination of the quaternary ammonium salt would afford the α,β-unsaturated ketone (213). Subsequent oxidation of the selenide would, if our synthetic proposal was sound , yield the Diels-Alder precursor (214) required for the ergochrome routes.



(206) (210) (212) (214) (213)

(Scheme 4.15)

Therefore this route to the ergochrome series relies on our ability to bring a new selenium synthetic method for substituted dienes to fruition.

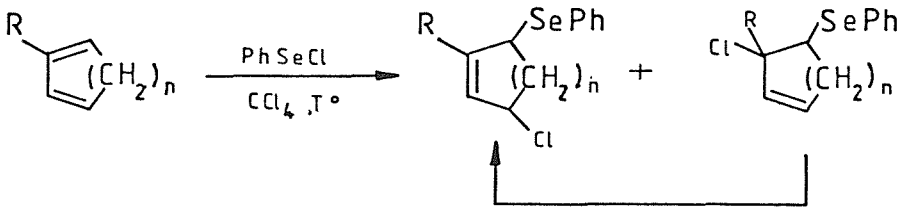
4:3 RESULTS AND DISCUSSION

4:3:1 Addition of phenylselenenyl chloride to dienes: The protection step

We began our research into the protection and alkylative deprotection of dienes by looking at the reaction of phenylselenenyl chloride with isoprene, and later extended this to other dienes; *i.e.* butadiene, cyclohexadiene and cyclopentadiene.

A summary of our results is shown in table 4.1, and they demonstrate the difference that reaction temperature can make to the products. At higher temperatures the isoprene derived phenylselenenyl chloride

adducts show the 1,2- Markovnikov product as the major product, whilst at lower temperatures the 1,2- and 1,4-addition products are present in equal amounts.



Cmpd no.	n	R	T°C	Yield (%) (216)+(217)	Ratio (216):(217)
a	–[2]	Me	0	77	1 : 1
a	–[2]	Me	60	69	2 : 5
b	–[2]	H	-10	90	2 : 3
b	–[2]	H	0	82	1 : 1
c	1	H	-15	90	—[1]
d	2	H	-15	95	—[1]

(1) Exclusive 1,2-addition

(2) Acyclic 1,3-butadiene

TABLE 4.1

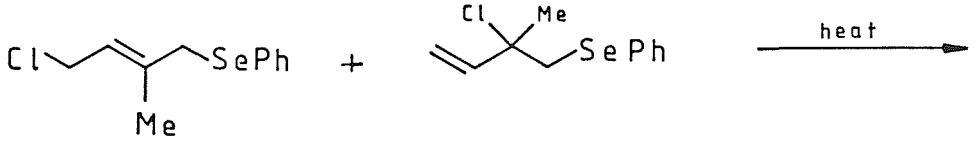
In contrast, for the butadiene derived compounds the 1,2- Markovnikov adduct predominates at lower temperatures, suggesting that this is the kinetic product.

In the acyclic cases we evidenced mixtures of the (*E*)- and (*Z*)-isomers of the 1,4-adducts, but we were unable to deduce the relative proportions of (*E*)- and (*Z*)- by n.m.r. spectroscopy.

In all the examples, separation of the mixtures of adducts was impossible either by chromatography or distillation due to the sensitivity of the compounds.

We deduced the relative proportions of 1,2- to 1,4- in the isoprene adduct from low field ^{1}H n.m.r. (60MHz) on the basis of the signal at δ4.4 for proton $\underline{H}C=CH_2$ in the 1,2-adduct and the δ5.2 signal for the $\underline{H}CCH_2Cl$ in the 1,4 adduct. For the butadiene products the ratio of the 1,2- and 1,4-adducts were deduced on the basis of the protons adjacent to the chloro group in the 1,4- and 1,2-adducts giving signals at δ3.9 ($C\underline{H}_2Cl$) and δ4.4 ($C\underline{H}$-Cl) respectively.

All the mixtures were thermally unstable; heating the butadiene or isoprene derived adducts at 40-60°C under reduced pressure (0.4 mm Hg) resulted in regeneration of the starting diene, diphenyl diselenide and dark resinous residues (scheme 4.16).



(216a) · (217a)

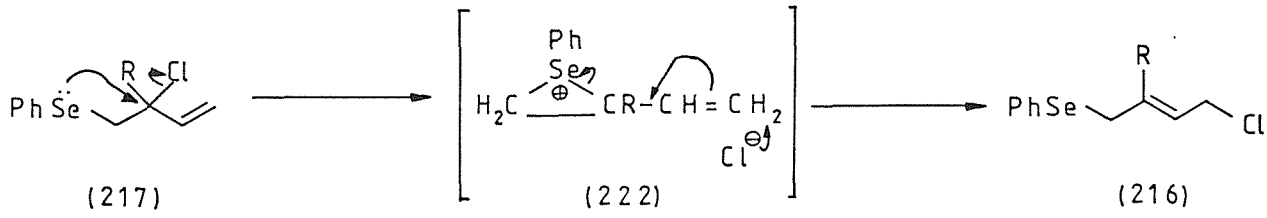
PhSeSePh + resin

(Scheme 4.16)

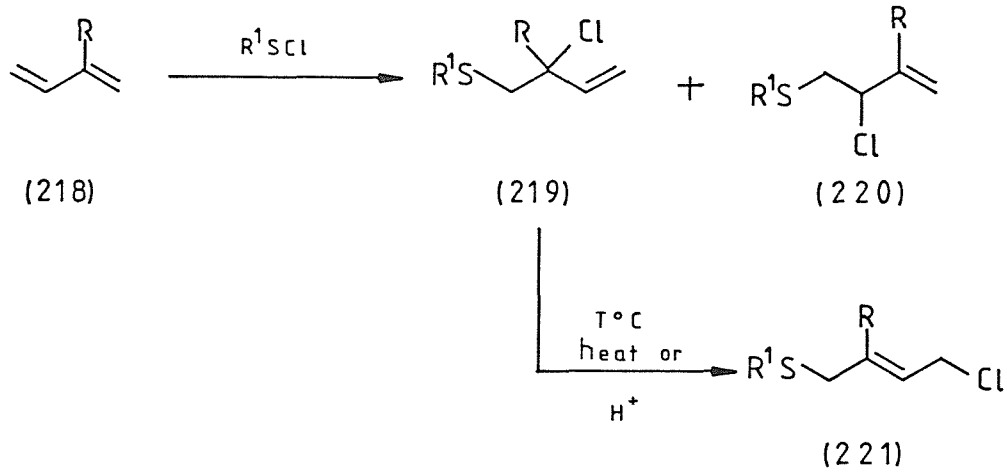
Further research disclosed that post-isomerisation occurred in the cyclic cases transforming the 1,2-adducts into 1,4-adducts. The 1,2-adducts of the cyclic cases isomerised on standing in the fridge at 4°C for a period of 2 weeks to give predominantly the 1,4-adduct. We postulate that this occurs in the butadiene adduct in subsequent reactions although there is no evidence for this occurring in the fridge (+4°C). This postulate was made to explain the results of later reactions. In contrast the isoprene adducts were completely stable to isomerisation at room temperature.

We can compare these results with those of the corresponding sulphur analogues[158]. The major difference is that the exclusive products from the addition of benzenesulphenyl chloride to butadiene, or isoprene are 1,2-adducts. The 1,2-Markovnikov addition products of benzenesulphenyl chloride are stable to post-isomerisation at room temperature, but elevated temperatures (60°C) and acid catalysis (cat. H_2SO_4) can initiate isomerisation to the 1,4-adducts. The 1,2-adduct between methanesulphenyl chloride and isoprene undergoes facile isomerisation to the 1,4-adducts at room temperature, whilst butadiene derived compounds undergo isomerisation at 60°C or with acid catalysis (see table 4.2).

In conclusion it was observed that the isomerisation of the 1,2-phenylselenenyl chloride adducts occurred more readily than in the corresponding sulphur analogues. This is because selenium is more electropositive than sulphur, and hence the positive charge developed in the episelenonium ion intermediate (scheme 4.17) is tolerated more readily.



(Scheme 4.17)



(218) (219) (220)

(221)

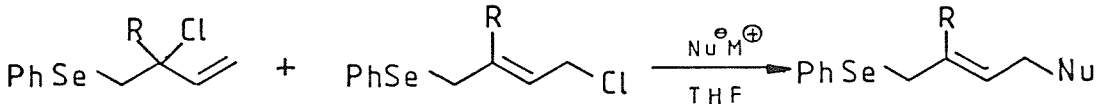
No.	R	R^1	Yield (219) (%)	Yield (220) (%)	T°C	Yield (221) (%)
a	H	Me	95	0	60	Partial[1] conversion
b	H	C_6H_5	98	0	60	Partial[1]
c	Me	Me	57	43	RT	>90
d	Me	C_6H_5	60	40	60	partial[1]

(1) Yields Not Quoted in the Lit.

TABLE 4.2

4:3:2 Products of nucleophilic attack on monoadducts of phenylselenenyl chloride and dienes: The alkylation step.

As already described we needed to add nucleophiles to the phenylselenenyl chloride diene adducts to prepare 1,4-substituted compounds, either by S_N2' or direct S_N2 mechanism (for the 1,2- and 1,4-adducts respectively (scheme 4.18).



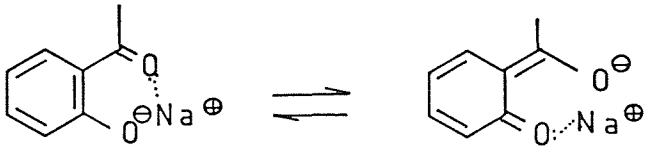
(217) (216) (223)

(Scheme 4.18)

Various nucleophiles were successfully added to the adducts derived from butadiene or isoprene and the results are presented in table 4.3.

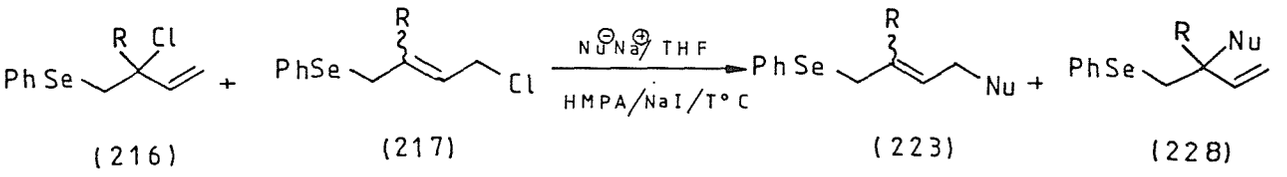
With the exception of the addition of sodio dimethyl malonate to (216h), most proceeded smoothly giving exclusive 1,4-addition products by S_N2 or S_N2' attack of the substrate.

Addition of the sodium salt of *o*-hydroxyacetophenone to the isoprene adducts was found to be ineffective due to the stability of the sodium chelate and its tautomers (scheme 4.19).

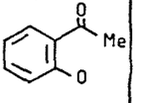
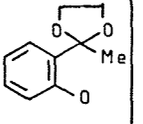


(224) (225)

(Scheme 4.19)



(216) (217) (223) (228)

No.	R	Nu	T°C	Yield (%) (223)	Yield (%) (228)
a	Me	$(MeO_2C)_2CH$ [1]	67	60	—
b	Me	PhO [2]	67	70	—
c	Me	o-allyl-C_6H_4O	67	36	—
d	Me	Ac(Ph)N	67	14	—
e	Me	PhS	67	60	—
f	Me		67	0	—
g	Me		67	27	—
h	H	$(MeO_2C)_2CH$ [3]	RT	32	32
i	H	EtS	0	60	—

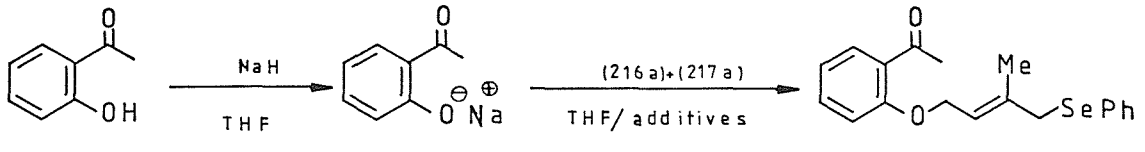
1. HMPA and NaI were not required in this case

2. 10 eq. of sodium phenoxide were used to obtain good yields

3. irreproducible result.

TABLE 4.3

Various reaction modifications were employed to try to achieve reaction of the nucleophile, as can be seen in the summary given in table 4.4.



(226) (223f)

entry no.	eq. of NaH	additives	eq. of phenoxide	temp(T) (°C)	time (hr)	Result
1	1.1	HMPA/NaI	1	67	12	Decomposition of (216a)+(217a) occurred in each case.
2	2.2	HMPA/NaI	10	67	12	
3	1.1	HMPA/NaI	1	RT	48	
4	2.2	HMPA/NaI	10	RT	48	
5	1.1	—	1	67	12	
6	2.2	—	10	67	12	

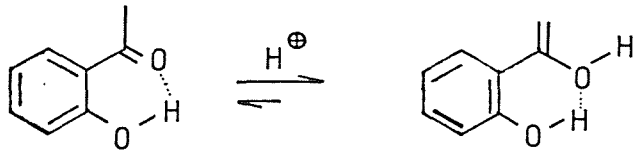
TABLE 4.4

It was decided that a better option would be to ketalise the *o*-hydroxyacetophenone with ethylene glycol. Under the classical conditions of Dean and Stark reflux with pTSA this gave irreproducible yields of 5%, or less, of the desired ketal. We explained this by invoking the hydrogen bonded nature of the *o*-hydroxyacetophenone (scheme 4.20). It is further complicated as under acid conditions the enol form of the ketone will also exist giving a hydrogen bonded six

membered system (scheme 4.21). The hydrogen bonded nature of the parent compound is substantiated by its infrared spectrum which shows a low intensity C=C stretch at 1640 cm^{-1} and no C=O stretch at all.

(226) (227)

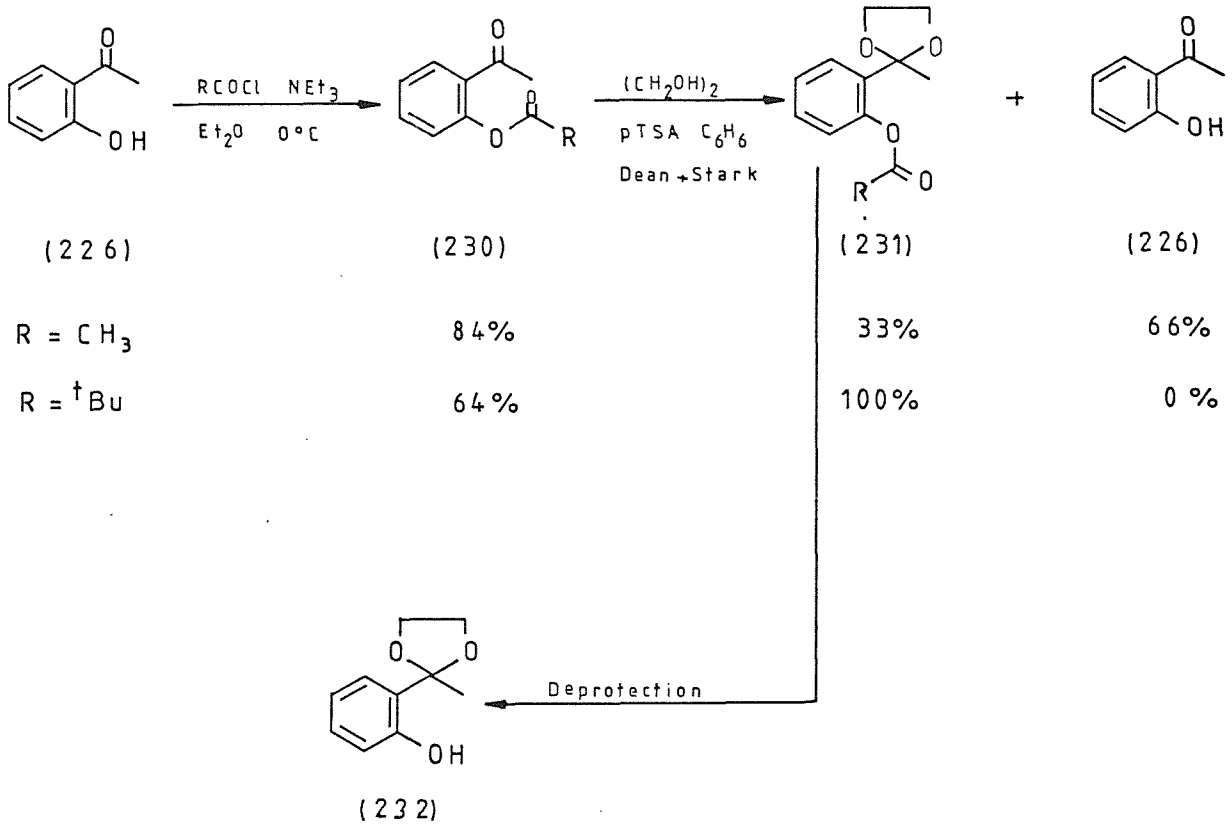
(Scheme 4.20)



(226) (229)

(Scheme 4.21)

Thus it was decided to protect the phenol as an ester, ketalise and deprotect the phenol (scheme 4.22).



		(226)	(230)	(231)	(226)
(a)	R = CH_3		84%	33%	66%
(b)	R = ^tBu		64%	100%	0 %

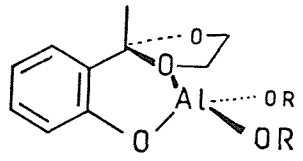
(232)

(Scheme 4.22)

The low yield (33%) of the acetoxy ketal (231a) is because the catalytic amount of pTSA leads to hydrolysis of the acetate so giving 66% of (226a). Thus the more hydrolysis stable pivaloyl derivative was employed as a protecting group.

The deprotection of the phenol, by removal of the pivaloyl group, is not a trivial transformation. Saponification with aqueous NaOH was found to be ineffective, and the most suitable rationale was to use lithium aluminium hydride; this proved highly effective giving yields of up to 75% on scales of 1-2g, but was found difficult to scale up due to the formation of a stable insoluble aluminate. This was

presumably due to the ready chelating ability of the oxygen functionality (233).



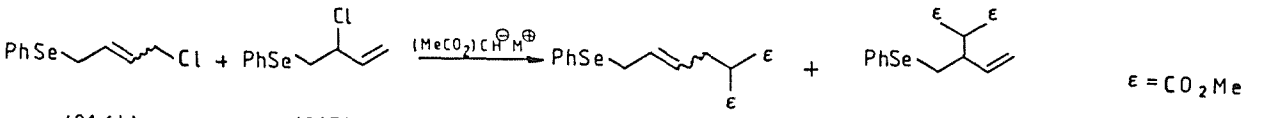
(233)

A much more effective route was to employ six equivalents of methyllithium in THF, and although once again an insoluble chelate was formed, it could more easily be destroyed by the addition of brine. This resulted in yields of approx. 80-90% on an 10-15g scale, without undue difficulty.

This ketalised *o*-hydroxyacetophenone proved to be a more effective nucleophile than its parent ketone, but at best gave yields of only 27% (table 4.3), although a variety of conditions were researched. The low yields were again attributed to the good chelating abilities of the anion, already experienced in its formation, and in all of the reactions it became evident that the thermal instability of the chloroselenides was a limiting factor. This was a serious constraint as the reaction required heating for all but the most powerful nucleophiles.

The thermal instability proved even more of a hindrance in the addition of nucleophiles to the butadiene derived chloroselenides (216b) and (217b). The addition of sodio dimethyl malonate gave very irreproducible results. Table 4.5 summarises the experiments investigated. Various postulates were made during this study :-

i) That the reaction was susceptible to light causing radical decomposition. To test this the reaction was performed under photolytic and dark conditions.



(216b) (217b) (223h) (228h)

Eq. of DMM	Time (hr)	Temp (°C)	Solvent	Additives	Cation M^+	Yields (%)	Ratio (223h):(228h)	Observations
1.5	4	67	THF	——	Na^+	17	1 : 1	
1.5	18	67	THF		Na^+	0		
1.5	18	67	THF	NaI	Na^+	0		
1.5	4	67	THF	NaI	Na^+	10	2 : 1	
1.0	18	67	THF	NaI	Na^+	0		chloro-selenides heated with NaI and anion of DMM added
2.0	144	RT	THF	HMPA	Na^+	67	1 : 1	
2.0	144	RT	THF	HMPA	Na^+	5	1 : 1	above reaction scaled up 2X
2.0	12	RT	DMF	——	Na^+	10	1 : 1	
2.0	48	RT	THF	15-crown-5	Na^+	15	1 : 1	
2.0	144	RT	THF	HMPA	Na^+	27	1 : 1	irradiation with a 150W tungsten lamp.
2.0	144	RT	THF	HMPA	Na^+	26	@	reaction performed in the dark.
1.0	12	RT	THF	HMPA/NaI	Na^+	27	2 : 3	
2.0	48	RT	THF	HMPA	K^+	0		anion was insoluble in THF.
1.0	18	RT	THF	——	$BrMg^+$	0		anion of DMM formed, confirmed by work-up with D_2O.
1.0	12	67	THF	$Pd(PPh_3)_4$	Na^+	30	2 : 3	

@ Only (223h) was formed.

(TABLE 4.5)

ii) That the reaction was influenced by the hardness and softness of the countercation, and thus various countercations (K^+ and $MgBr^+$ cations) were investigated for the nucleophile.

iii) That the nucleophilicity of the anion could be enhanced by the use of crown ethers[96-97] or HMPA[159], either by complexation of the cation or by increasing the solubility of the sodium salt of dimethyl malonate respectively.

iv) That Pd° would complex with the allylic chloride, and that the Pd° π-allyl complex[160] would be attacked by the nucleophile, to give the required products.

The eventual conclusion drawn from these many reactions was that the butadiene derived adducts were thermally unstable, and that the salt of dimethyl malonate was an insufficiently powerful nucleophile. This conclusion was substantiated in that the sodium salt of ethanethiol gave reproducible results with reasonable yields. This was because the reaction could be performed at 0°C due to the powerful nature of the nucleophile. The other interesting observation was the S_N2 attack of the dimethyl malonate at the tertiary centre giving rise, for the first time, to a 1,2-product.

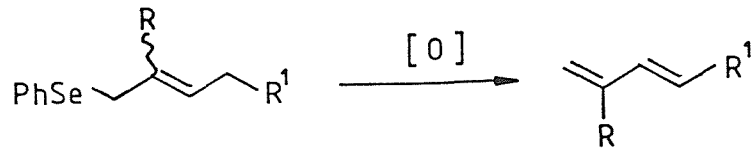
To summarise, we were now able to synthesise 1-phenylseleno-4-substituted-but-2-enes (208), consistent with our proposal to create a new diene protection and alkylative deprotection methodology. We had established an alkylative strategy and our investigation now relied on a method to remove the phenylseleno group and regenerate a diene.

4:3:3 Oxidations of 1-phenylseleno-4-substituted-but-2-enes : The deprotection step.

4:3:3:A Oxidation by aqueous hydrogen peroxide

Our synthetic methodology required an efficient removal of the

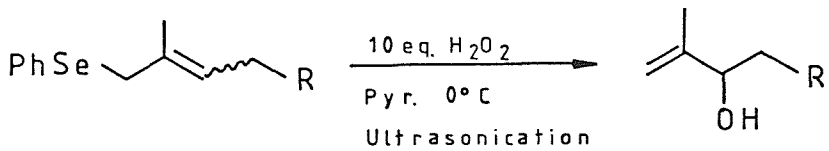
protecting group, in our case the phenylseleno group, and generation of the modified diene (scheme 4.23).



(234) (235)

(Scheme 4.23)

To bring about this hitherto unknown transformation we began by investigating the use of aqueous hydrogen peroxide and pyridine as an oxidising agent[135,161]. This reagent resulted in oxidation of the seleno group to a selenoxide which underwent a [2,3] sigmatropic rearrangement (see section 4:2:1) to give a selenenic ester as an intermediate. This selenenic ester was readily hydrolysed to the allylic alcohol. The pyridine was present to "mop-up" the phenylselenenic acid produced as a by-product. It was observed that ultrasonication accelerated the two-phase reaction from approximately 40 minutes to 5 minutes (table 4.6).

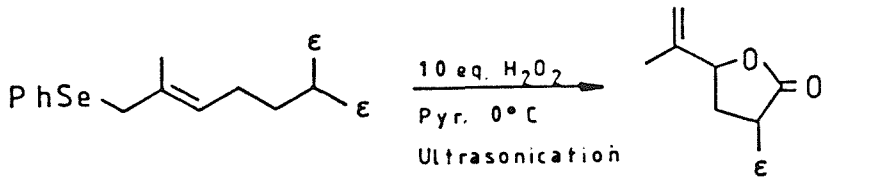


(223) (236)

Compound NO.	R	(236) Yield (%)
b	PhO	60
c	o-allyl-C_6H_4O	50
d	Ac(Ph)N	55
e	PhS	20

TABLE 4.6

The only exception to these results was for the compound where R = $CH(CO_2Me)_2$, here the lactone (237) was formed in high (80%) yield (scheme 4.24).

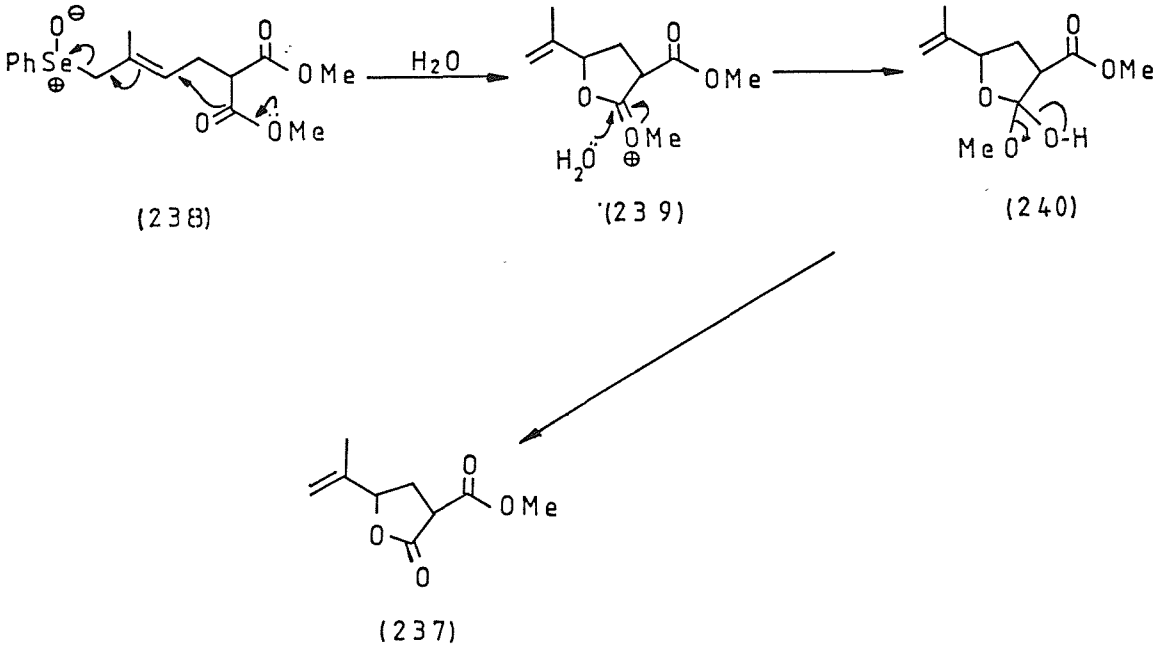


(223a) (237) 80%

ε = CO_2Me

(Scheme 4.24)

Several mechanisms may be postulated for the formation of the lactone. There was no evidence for the allylic alcohol (241) as an intermediate so we can postulate a mechanism involving a neighbouring group participation (scheme 4.25).



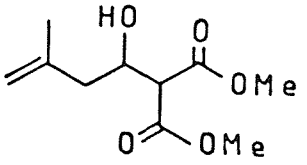
(238) (239) (240)

(237)

(Scheme 4.25)

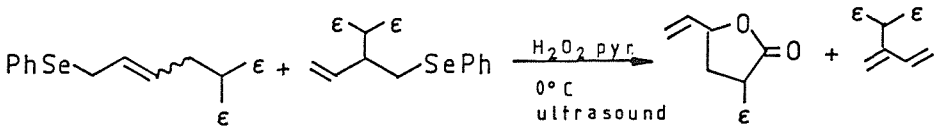
An alternative mechanism would involve a [2,3] sigmatropic

rearrangement of the selenoxide, as already described, but if this was the case we must assume that intramolecular lactonisation was extremely rapid, as none of the intermediate allylic alcohol (241) could be isolated.



(241)

The butadiene derived malonate compound gave a mixture of products (scheme 4.26).



	(223h)		(228h)	60%	(242)		(243)
ratio	2	:	3		5	:	1

$\varepsilon = CO_2Me$

pyr = pyridine

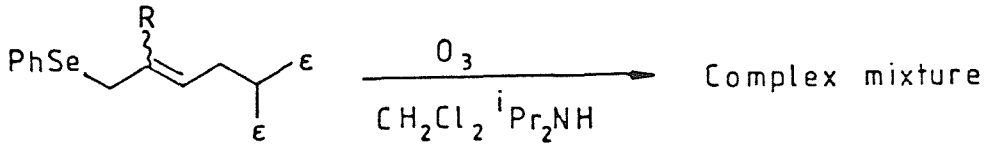
(Scheme 4.26)

The formation of the lactone (242) was perfectly predictable in view of our earlier results, whilst the diene (243) is the product we expect from a classical, 1,2-elimination mechanism (see section 4:2:1). Further investigation of these results revealed that an excess of the lactone had been formed, more than would have been predicted on the basis of the 1,4 starting adduct and a 60% overall conversion. This it appeared that under the oxidative conditions compound (228h) could be interconverted to compound (223h) probably *via* a radical mechanism.

Thus although some of the results had been fully predictable, we were unable to form the desired 4-substituted-1,3-butadienes (209) using hydrogen peroxide as the oxidising agent. We propose that the intermediate selenenic ester was being hydrolysed by the aqueous medium, and this led us to investigate non-aqueous oxidising agents.

4:3:3:B Oxidation by *m*-Chloroperoxybenzoic acid (*m*CPBA)

In our desire to form butadiene type compounds we decided to investigate non aqueous oxidising agents. Initially we decided to adopt ozone[162-163] as the oxidising agent, but this gave a complex mixture of products which could not be identified (scheme 4.27).



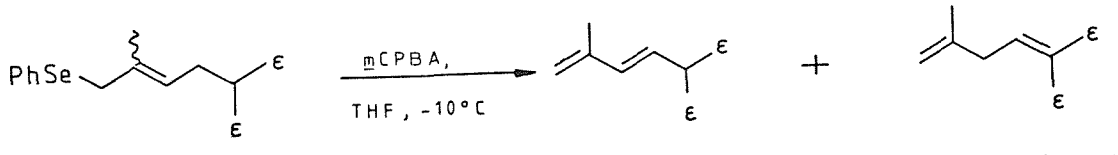
(223 a)

R = Me ε = CO_2Me

(Scheme 4.27)

It had already been noted by Clive[133] that ozone is not the reagent of choice where the substrate contains C=C bonds or other groups, which may be subject to ozonolysis. A more selective alternative was to employ *m*-chloroperbenzoic acid[133] (*m*CPBA) as the oxidising agent.

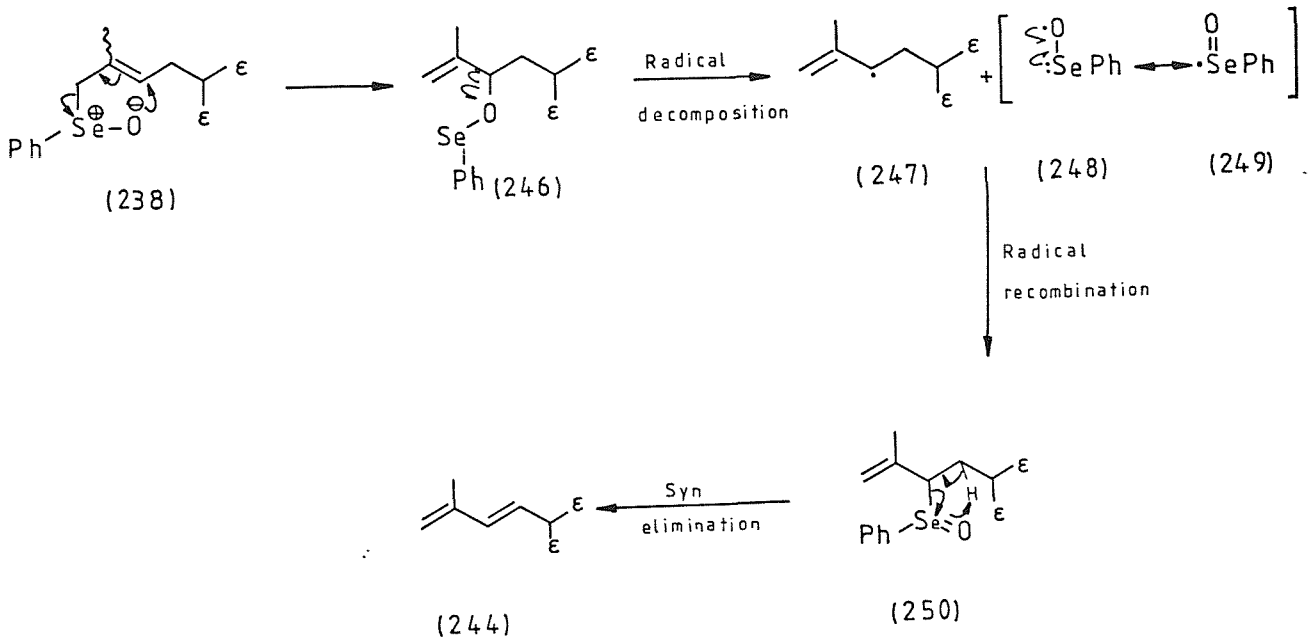
We modified our research by using *m*CPBA on the malonate compounds which gave us our desired product (244) and the de-conjugated diene (245) (scheme 4.28).



(223 a) (244) 13% (245) 61%

(Scheme 4.28)

The formation of the diene (244) is unlikely to have occurred by a pericyclic mechanism, as it would be an eight electron anti-aromatic process. More likely is a [2,3] sigmatropic rearrangement of selenoxide followed by radical decomposition[164], recombination and final 1,2-elimination of the selenoxide (scheme 4.29).



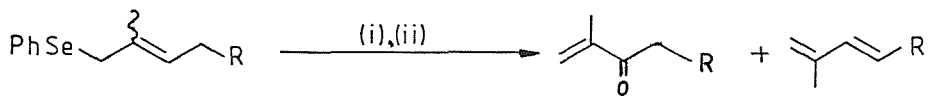
(238) (246) (247) (248) (249) (244) (250)

(Scheme 4.29)

The propensity of selenium species to participate in radical reactions has already been well documented[164], as have 1,2-eliminations of the selenoxide, so this mechanism would explain our apparently disallowed pericyclic process. The deconjugated diene results from the isomerisation of the 1,3-butadiene to a preferential 1,5-diene which allows further conjugation with the ester functionality.

With this successful result we pursued the oxidation of our other compounds (223a-d) (table 4.3) with *m*CPBA . This was again successful in the preparation of some 1,3-butadienes (252), however other major

products were observed, namely the 1-substituted-3-methyl-3-buten-2-one compounds (251) (table 4.7).



(223) (251) (252)

Reagents

(i) N eq. of mCPBA/THF, -15°C.

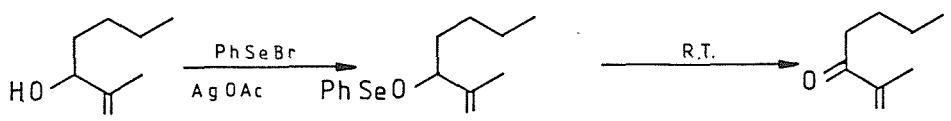
(ii) Add reaction to boiling CCl_4

Compound	R	N eq. of mCPBA	Yield (%) (251)	Yield (%) (252)
b	PhO	1	25	25
		2	44	—
c	o-allyl-C_6H_4O	1	12	—
		2	25	—
d	Ac(Ph)N	1	40	58

TABLE 4.7

Formation of the ketones was an unexpected observation, for whilst allylic alcohols are well documented products of the [2,3] rearrangement of allylic selenides, the formation of ketones has rarely been observed and then only in specific cases. Sharpless & Lauer[149] investigated the reaction of linalool with phenylselenenyl bromide, and found that in the presence of silver acetate the ketone

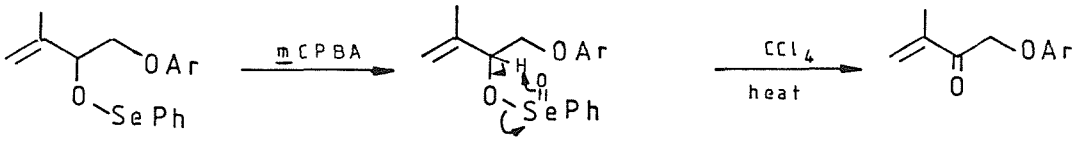
compound could be formed from the selenate ester (scheme 4.30).



(253) (254) (255)

(Scheme 4.30)

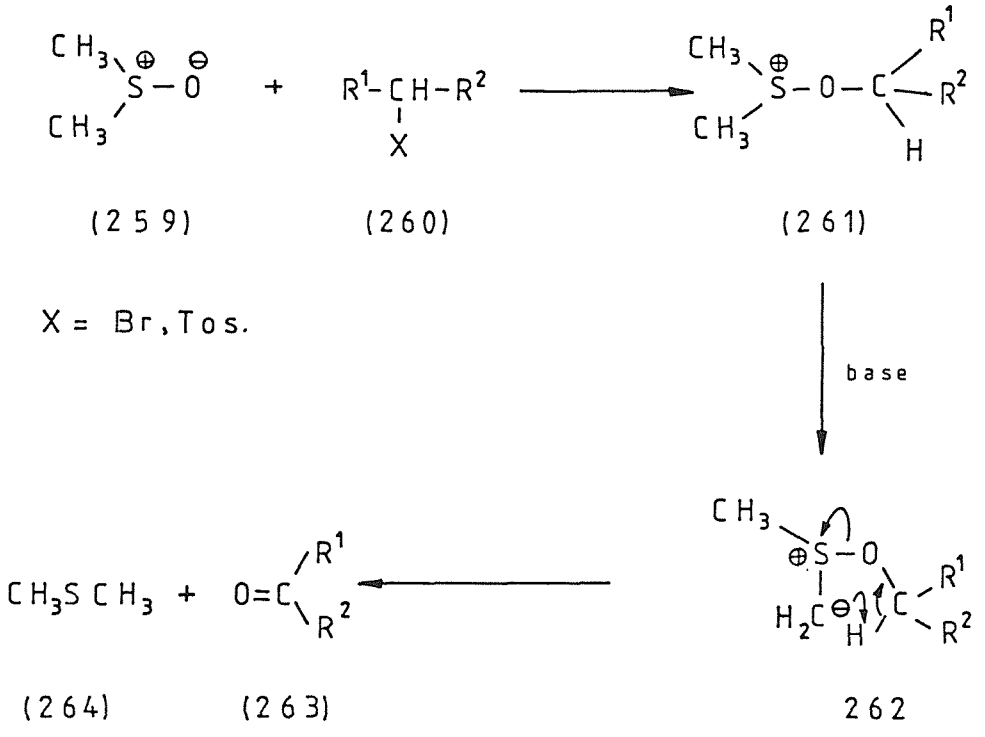
This result, exactly analogous to our observations, implies that the carbonyl products may in part arise directly from the (Se(II)) ester. However the fact that two equivalents of *m*CPBA leads to formation of the ketone (251) in higher yields, suggests that further oxidation of the selenenic esters (Se(II)) to seleninic esters (Se(IV)), improves the decomposition to the ketone (scheme 4.31).



(256) (257) (258)

(Scheme 4.31)

The decomposition of the intermediate (256) or (257) is analogous to the mechanism observed in the Swern oxidation[165], and its many variants (scheme 4.32).



(Scheme 4.32)

To conclude, the investigation of our organic selenium methodology to dienes did not result in the development of a universal diene synthesis, however several meritorious results have been unearthed :-

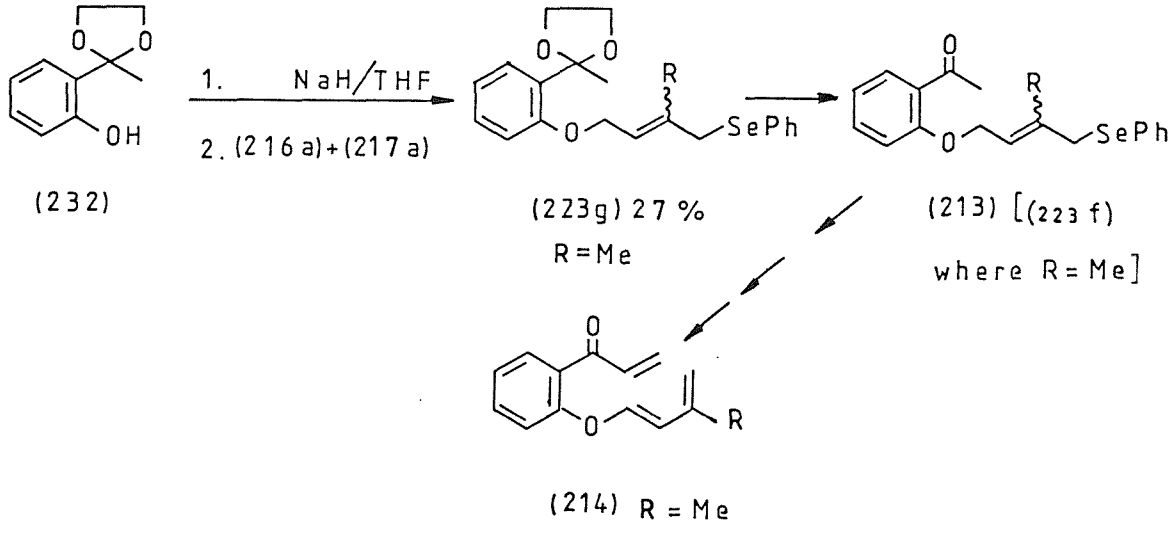
(i) Phenylselenenyl chloride can be added in a 1,4- and 1,2-fashion to give useful chloroselenides.

(ii) The chloroselenides may be reacted with various nucleophiles to displace the chloro group and produce novel allylically substituted phenylselenides.

(iii) The allylically substituted phenylseleno group may be removed *via* [2,3] sigmatropic rearrangement to give either alcohols, ketones or dienes depending both upon the oxidation conditions and the substrate.

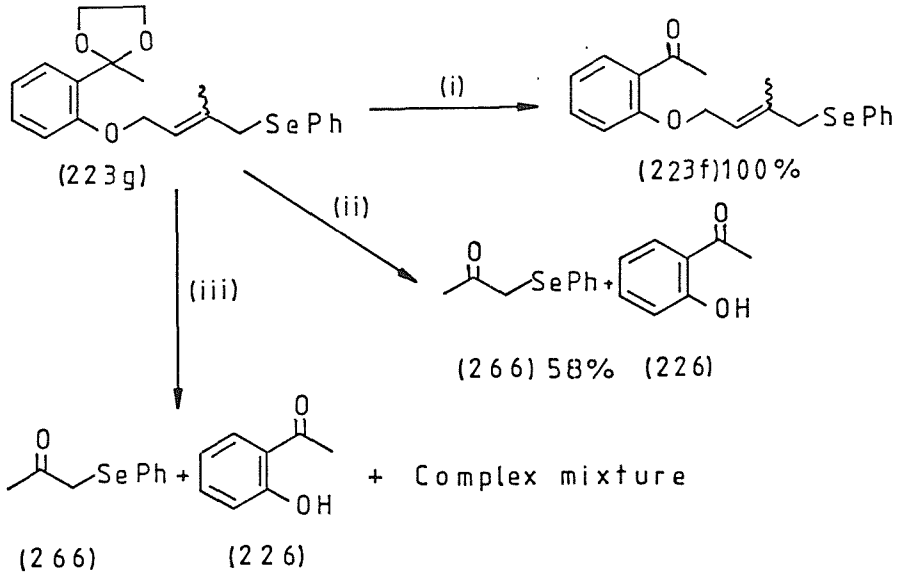
4:4 APPLICATION OF THE METHODOLOGY TO THE SYNTHESIS OF ERGOCHROMES

We wanted to synthesise oxygenated dienes (214) so that we could implement our synthetic route to the ergochrome series of compounds, as already explained (section 4:1). A route to a potential Diels-Alder precursor essential for this route was outlined in scheme 4.15, and to this end we have already described a synthesis of (214) see below (scheme 4.33).



(Scheme 4.33)

We had envisaged it to be a simple task to prepare (223g) but despite much research the yield of (223g) from the ketalised *o*-hydroxyacetophenone could not be improved above 27%. We attempted to remove the ketal under a variety of conditions, but the best reagent was found to be pyridinium tosylate in acetone[166] (scheme 4.34) giving a quantitative yield of the desired ketone (223f). Scheme 4.34 illustrates the use of other reagents but most afforded complex mixtures of products due to a novel fragmentation of (223g).



(Scheme 4.34)

Reagents

(i) $pyr^{\oplus}\ Tos^{\ominus}$ acetone/80°C/2hr.

(ii) HCl acetone/80°C/3hr.

(iii) pTSA acetone/ 80°C/12 hr.

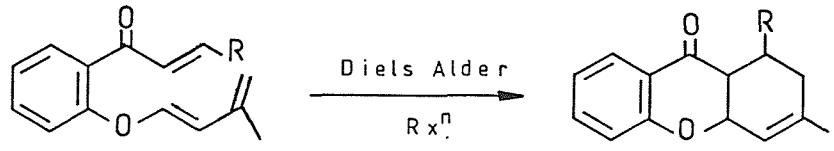
In view of the low yield (27%) and irreproducibility of the nucleophilic displacement step to form (223g) and our inability to produce high yields of 1,3-butadienes we decided to turn our attention to other avenues of investigation.

CHAPTER 5

A WITTIG REACTION APPROACH TO OXYGEN HETEROCYCLES

5:1 AN INTRODUCTION TO WITTIG APPROACHES TO HETEROCYCLES

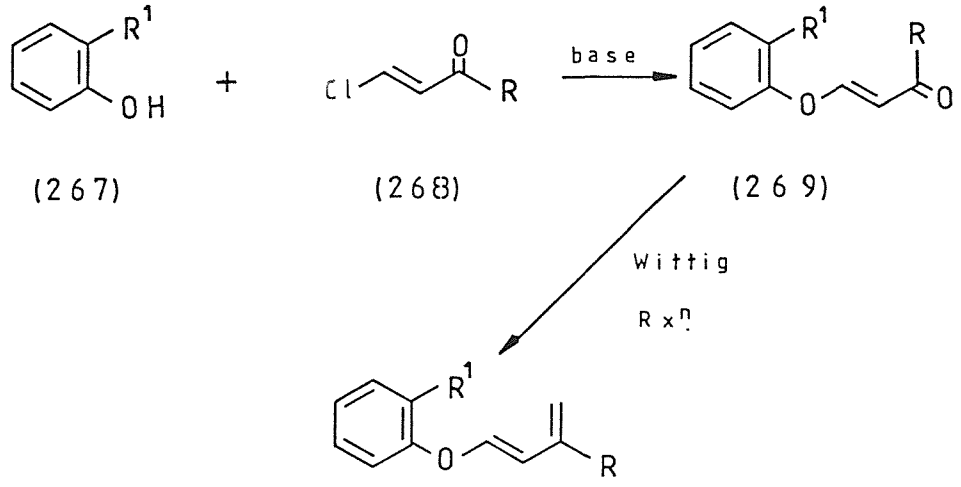
In chapter 4 we described a synthetic strategy which utilised, as a key step, the intramolecular Diels-Alder reaction to set up a chromanone tricycle (scheme 5.1). We continued our work on this strategy by investigating a retrosynthetic analysis of compound (156) different to that described in section 4:1 and scheme 4.15, which employed a selenium protection/deprotection methodology[167].



(156) (157)

(Scheme 5.1)

Our new retrosynthesis was to involve ketovinylation of a phenol to yield the vinylogous ester (269) which when subjected to olefination would afford the diene (270) (scheme 5.2).



(267) (268) (269)

(270)

(Scheme 5.2)

If R^1 =  then we would quickly obtain our desired intermediate (156).

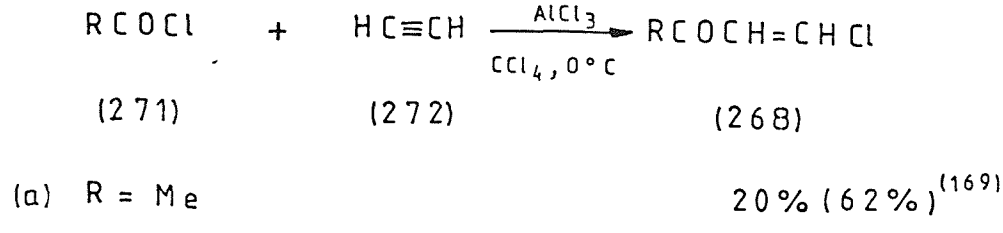
The reaction of nucleophiles and methyl-β-chlorovinyl ketones (268) is well documented under a variety of conditions[168], whilst the Wittig reaction we postulated would olefinate the vinylogous ester (269), and lead us into hitherto unknown 1-aryloxy-3-alkyl-1,3-butadienes (270).

The advantage of this route over other possible strategies was its brevity and the ease with which modification of substitution patterns in the molecule (270) could be achieved, either by varying the substitution of the starting phenol (267) or else at the Wittig reaction stage.

5:2 RESULTS AND DISCUSSION

5:2:1 Preparation of 4-chloro-3-buten-2-one (268a)

4-Chloro-3-buten-2-one (268a), a noted skin irritant and lachrymator, may be prepared by a variety of methods[168]. The easiest route, however, involves the reaction of acetyl chloride with acetylene in the presence of a Friedel-Crafts catalyst[169] (scheme 5.3).



(Scheme 5.3)

In our hands, we discovered this reaction to be somewhat capricious, giving irreproducible results depending upon the history of both the acetylene and the aluminium trichloride ($AlCl_3$). Finely powdered and sublimed $AlCl_3$ was found to be essential and on reaction work-up and

distillation the best yields were no better than 63%. N.m.r. analysis revealed that in fact we had isolated a co-distillate of 4-chloro-3-buten-2-one and acetic acid. Extraction with cold aqueous sodium carbonate solution removed the acid, but reduced the overall yield to 20%.

The instability of the 4-chloro-3-buten-2-one may be a limiting factor as it decomposes at room temperature within a day, and darkens visibly in a freezer at -20°C over a period of weeks, although redistillation will give the colourless ketone once more. It follows that the exothermic destruction of excess acetyl chloride during work up may cause the demise of some of the desired product. Another factor which may be implicated in the low yielding reaction is the coagulation of the aluminium trichloride, which is insoluble in the carbon tetrachloride and acetyl chloride, so limiting the available surface area of the catalyst.

The low yield at this stage did not deter us as the reagents are cheap and the reaction relatively easy to perform on a multi-gram scale.

A comprehensive range of R groups may be incorporated in the β-chlorovinyl ketone (268) by varying the acid chloride employed in the Friedel-Crafts reaction, as reviewed by Pohland and Benson[168]. The higher homologues are reported to possess greater stability and hence are easier to handle.

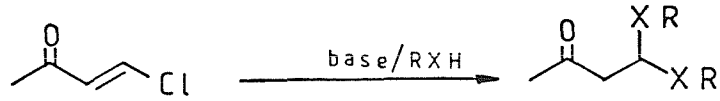
5:2:2 The nucleophilic displacement of the chlorine atom from 4-chloro-3-buten-2-one.

The vinylogous acid chlorides (268) may be reacted with a variety of nucleophiles[168] *e.g.* :- ammonia[170]; primary[171], secondary[172], and tertiary amines[173]; thiophenols[174]; phenols[175] and organic anions (malonates[176], alkyl-acetoacetates[177] *etc.*). All these reagents displace the β-chlorine atom, yielding 4-substituted-3-buten-2-ones (273) (scheme 5.4).

(268a) (273)

(Scheme 5.4)

However, aliphatic alcohols and thiols react with vinylogous acid chlorides to give acetals[178] and thioacetals[179] (scheme 5.5).



(268a) (274)

X = O, S

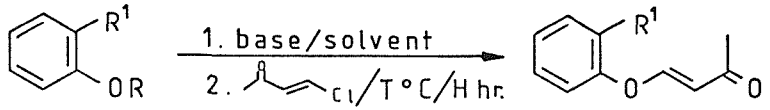
R = alkyl

(Scheme 5.5)

The conditions employed for the displacement of the β-chlorine atom by an alkoxide, phenoxide or thiophenoxide usually involve aqueous solutions of sodium or potassium hydroxide as the base[175].

We began our research using these conditions and then turned to a variety of others (table 5.1).

Initially we tried the literature conditions[175] of 10% sodium hydroxide with *o*-hydroxyacetophenone (entry 1), but on work-up only obtained the starting phenol, presumably due to the chelation properties of this phenol described in section 4:3:2.



(275) (269)

entry no.	base	eq. of base	solvent	T°C	H hrs.	Substrate	R^1	R	Result
1	10% aq. NaOH	1.1	H_2O	R.T.	5	a	$CH_3\overset{O}{\overset{\|}{C}}-$	H	S.M.
2	10% aq. NaOH	2.2	H_2O	R.T.	72	b			S.M.
3	^{n}BuLi	1.1	THF	-78– R.T.	24	c		H	Polymer
4	K_2CO_3	1.1	DMF	R.T.	78	a	$CH_3\overset{O}{\overset{\|}{C}}-$	H	S.M.
5	K_2CO_3	1.1	DMF	R T	24	c		H	(269c) 97%

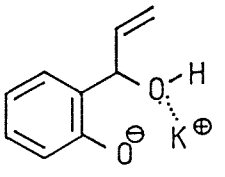
TABLE 5.1

Attempts to hydrolyse the pivaloyl ester (entry 2) and trap the phenoxide as it was formed with the vinylogous acid chloride failed, giving a 95% recovery of the starting pivalate. Under aprotic conditions, treatment of the protected *o*-hydroxyacetophenone with *n*-butyllithium (entry 3) followed by the vinylogous acid chloride (268a) resulted in polymerisation of the starting material, whilst potassium carbonate in DMF with *o*-hydroxyacetophenone gave back the starting phenol (entry 4).

Treatment of the protected *o*-hydroxyacetophenone with potassium carbonate in DMF, followed by the vinylogous acid chloride at room temperature did, however, result in 97% yields of the desired vinylogous ester (269a) (entry 5).

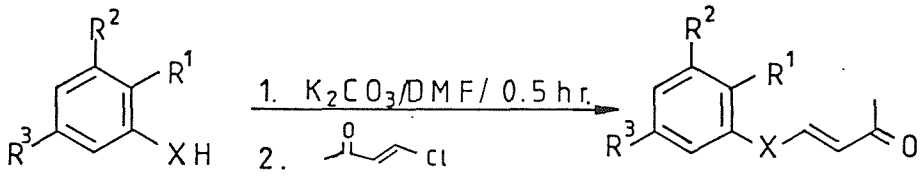
This encouraged us to expand the scope of this mild reaction to include a variety of phenols; phenol, the simplest case gave higher yields than recorded in the literature methods (80-87%)[168].

A summary of the ketovinylation of some phenols and thiophenol can be found in table 5.2. The reaction of phenols (276f) and (276g) with 4-chloro-3-but-2-ene failed and we postulate that the problem of anion chelation (277) already described is the limiting factor, as it effectively destroys the nucleophilic character of the phenoxide anion (scheme 5.6).



(277)

(Scheme 5.6)

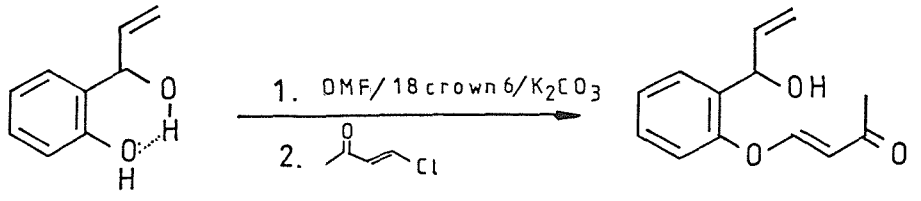


(276) (269)

(269)	R^1	R^2	R^3	X	Yield (%) (lit. yield)
a	H	H	H	O	98 (80)[175.]
b	CO_2Me	H	H	O	50
c		H	H	O	97
d	H	OMe	OMe	O	80
e	H	H	H	S	98 (55)[174.]
f		H	H	O	0
g		H	H	O	0

TABLE 5.2

If this was the case, 18-crown-6, a selective chelation agent for potassium ions[96-97], might alleviate the problem by removing the potassium countercation and release the phenoxide as a "Naked Anion". In practice the experiment gave back the starting phenol (scheme 5.7).



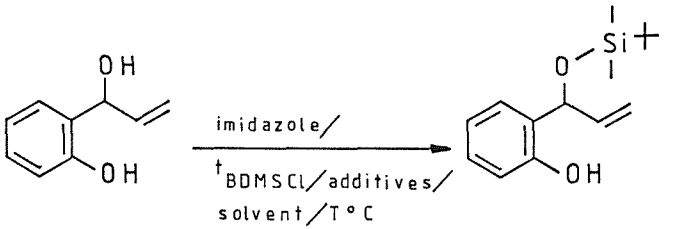
(276f) (269f)

(Scheme 5.7)

The use of caesium carbonate in DMF as a base[106] gave the same results, although we had hoped that the larger cation would be less strongly bound within the chelate. In an attempt to eliminate the problem of hydrogen bonding we attempted to protect the secondary alcohol (276f) as a *t*-butyldimethylsilyl ether. This group, being large, might force the molecule to adopt a conformation which would disfavour H-bonding or chelation, so leaving the phenoxide free to act as a nucleophile (table 5.3).

As can be seen from table 5.3, we were unable to achieve this protection, probably due to the lability of the silyl group, enhanced by the the presence of the phenolic -OH group. This lability would lead to silyl migration and easy hydrolysis of any silyl ether formed.

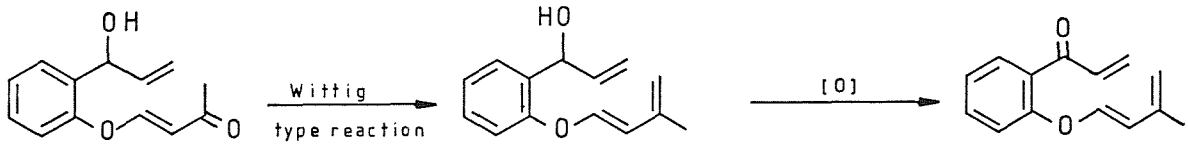
Numerous conditions were tried to form this silyl ether; an *in situ* formation of TBDMSI[180], (entry 5) (successfully used in the formation of silyl enol ethers[181]) was tried but no positive results could be achieved. This was unfortunate as the compound (269f) would have been a useful intermediate for the synthesis of our Diels-Alder precursor (scheme 5.8).



(276f) (278)

Entry No.	Solvent	Additives	T°C	Reaction time (hrs)	Result
1	DMF	none	RT	24	SM
2	DMF	none	50	24	SM
3	DMF[182]	DMAP	RT	24	SM
4	DMF	DMAP	50	24	SM
5	DMF	MeCN/NaI DMAP	RT	24	SM
6	DMF	MeCN/NaI DMAP	60	24	SM

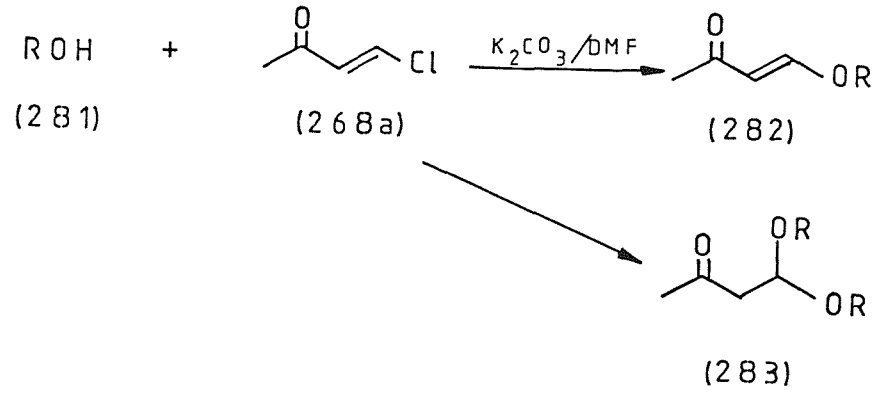
TABLE 5.3



(269f) (279) (280)

(Scheme 5.8)

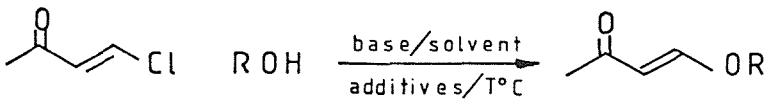
We decided to investigate the reaction of alcohols with 4-chloro-3-buten-2-one under potassium carbonate/DMF conditions to see if clean formation of the corresponding 4-alkoxy-3-buten-2-one could be achieved. We noted earlier that previous workers synthesised ketals whilst attempting to form 4-alkoxy-3-buten-2-ones (scheme 5.9).



(281) (268a) (282) (283)

(Scheme 5.9)

In our efforts to try to add *d*-2-octanol to 4-chloro-3-buten-2-one, various conditions were tried, with little success. Table 5.4 tabulates the various basic conditions employed.



(268a) (284) (285)

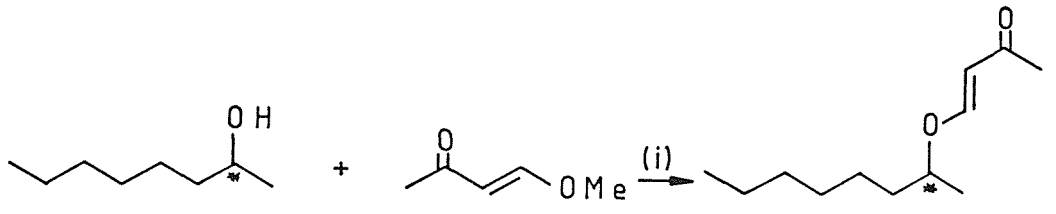
R = d-2-octyl

Base	Solvent	Temp. for base addition (°C)	Temp for alkoxide addition (°C)	RX^n time (hrs)	Result
K_2CO_3	DMF	0	RT	36	SM
^nBuLi	THF	-78	RT	18	SM
^nBuLi	THF-HMPA	-78	RT	18	SM
^nBuLi	Et_2O	-78	RT	18	SM
^nBuLi	Et_2O-HMPA	-78	RT	18	SM
K_2CO_3	DMF-DMAP	RT	RT	18	SM

TABLE 5.4

An inspection of the literature had already revealed that vinylogous transesterification[183] was a viable alternative. Reaction of 4-methoxy-3-buten-2-ene (286) with *d*-2-octanol in benzene with a catalytic amount of pyridinium tosylate (*p*-toluene sulphonate)

afforded the chiral 4-(*d*-2-octyloxy)-3-buten-2-one (285) in 46% yield after distillation (scheme 5.10).



(284) (286) (285) 46%

Reagents

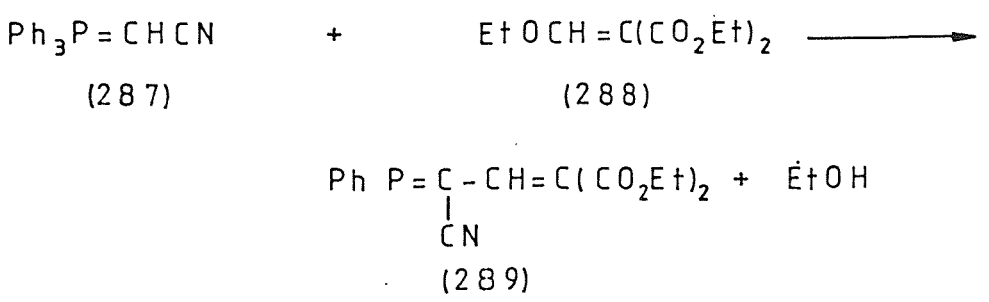
(i) $Pyr^{\oplus}Tos^{\ominus}/C_6H_6$/4a Molecular sieve/heat 18 hrs.

(Scheme 5.10)

It was now possible to investigate the olefination of various vinylogous esters as suggested in scheme 5.2. If this proved successful we would have a route to novel 1-aryloxy-3-substituted-1,3-butadienes and chiral dienes.

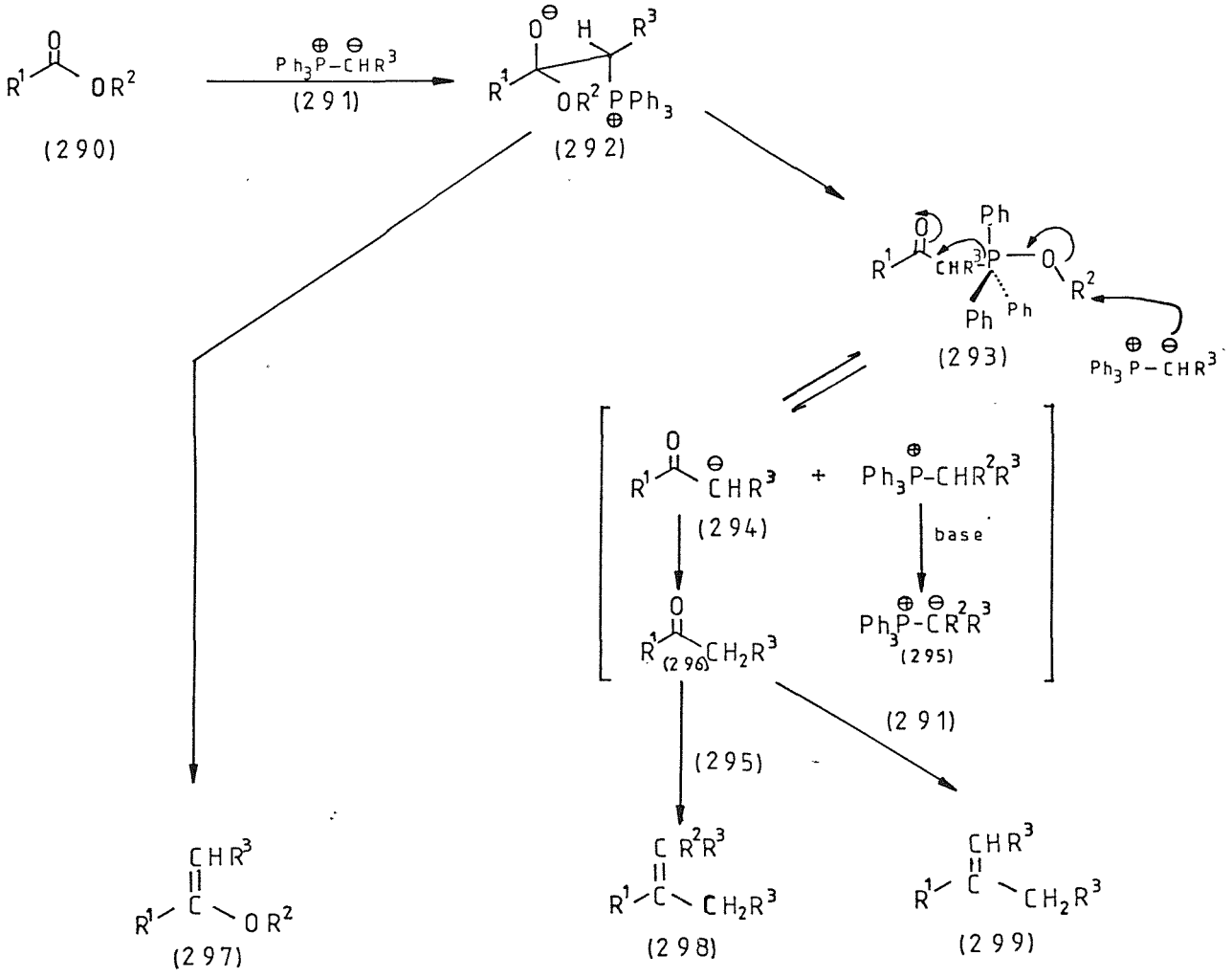
5:2:3 The reaction of methylenetriphenylphosphorane with 4-aryloxy--3-buten-2-ones

The reaction of methylenetriphenylphosphorane[184-185] with vinylogous esters was to prove a difficult step. The literature demonstrates that Wittig reagents add in a Michael fashion to vinylogous compounds and if a substituent capable of forming a stable anion is present (such as ethoxide or cyanide) a new phosphorane (289) is formed[186] (scheme 5.11).



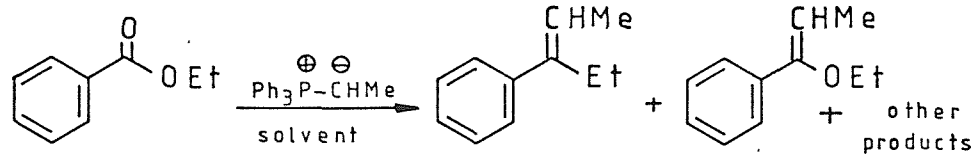
(Scheme 5.11)

Similarly, it has been noted that Wittig reagents do not usually olefinate esters to give enol ethers efficiently, but tend to give complex phosphoranes which then react further to give branched olefins[187] (scheme 5.12).



(Scheme 5.12)

The reaction of ethylidenetriphenylphosphorane with ethylbenzoate is a good example, and demonstrates the mixtures that can be obtained from this reaction. The exact product ratios depend upon the solvent employed. Table 5.5 illustrates the range of products obtained and the effect that solvent can have on the product ratios[187].



(300) (301) (302)

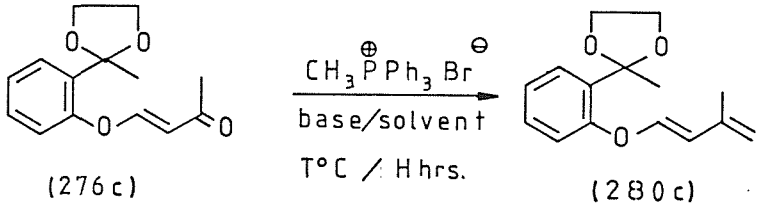
(301): (Z) a + (E) b; (302): (Z) c + (E) d; e

Solvent	Yield(%) overall	product distribution (%) (a + b)	a	b	(c + d)	e
benzene	96	83	71	12	17	—
THF	77	73	57	16	20	7
DMSO	68	77	60	16	20	4
HMPA	89	29	23	6	65	4
^{t}BuOH	36	100	57	43	—	—

TABLE 5.5

We anticipated problems, both in view of these results and from the similarity of vinylogous esters to carboxylic esters. A range of

experimental conditions were investigated (table 5.6), which in general confirmed the results noted by previous workers in the field.

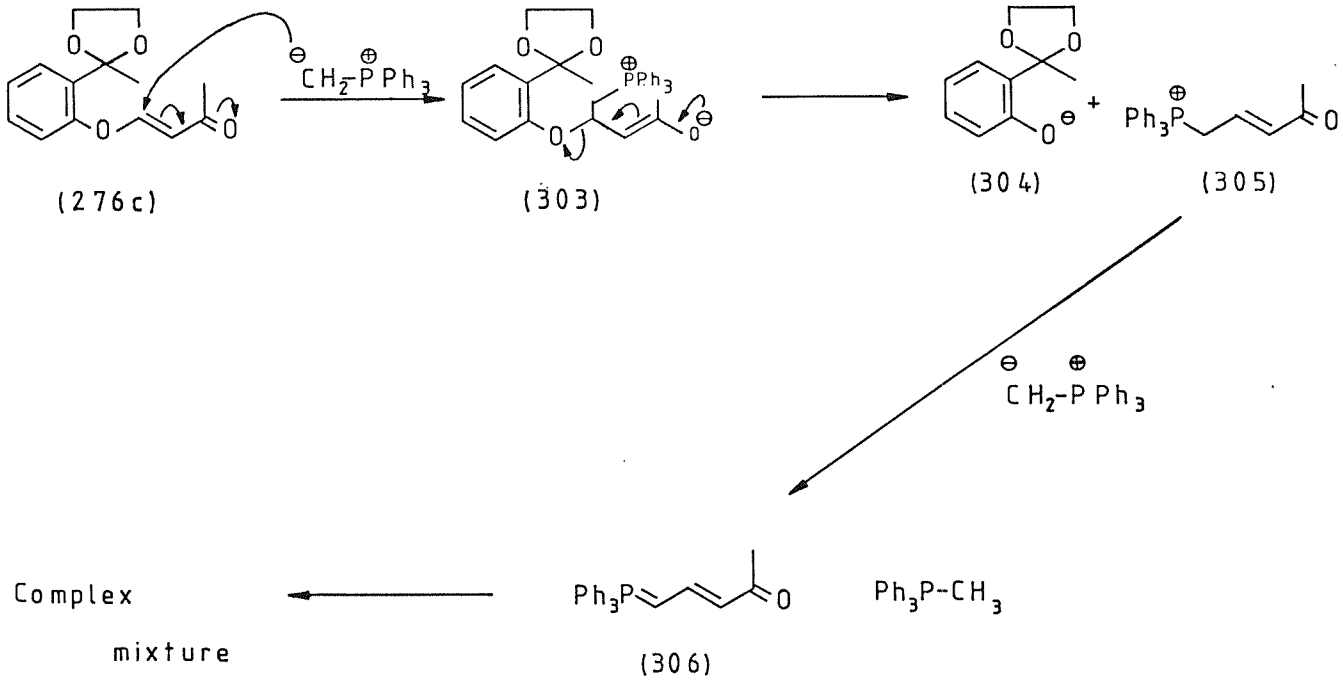


(276c) (280c)

Entry No.	Base	Solvent	T °C	Hours H hrs.	Result
1	^{n}BuLi [184.]	Et_2O	-78°–RT	4	Recovered phenol, SM and other unidentified products.
2	^{n}BuLi	THF	-78 – RT	5	The Phenol+ SM and other products.
3	NaH [188.]	DMSO	0	60	SM+slight traces of phenol.
4	$NaNH_2$ [189]	NH_3/Et_2O	80	12	Phenol+ other unidentified products.

TABLE 5.6

We concluded that Michael addition of the phosphorus ylid (methylenetriphenylphosphorane) was occurring, in effect giving us displacement of the phenol and transylidation (scheme 5.13). The new phosphorane (306) then reacts intermolecularly with itself to give complex mixtures of products.

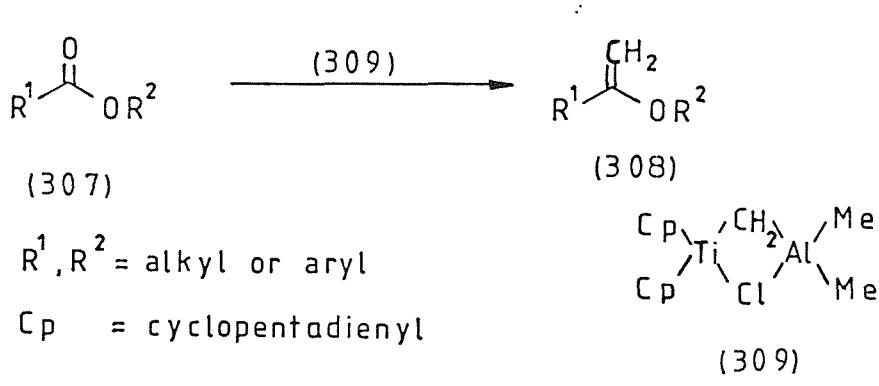


(Scheme 5.13)

The problems associated with the Wittig reagent have prompted the search for suitable alternatives to achieve the olefination both of esters and readily enolisable ketones. The similarity of esters to vinylogous esters led us to investigate some of these alternatives.

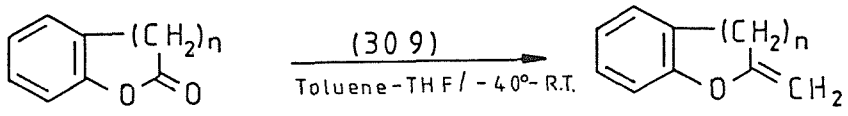
5:3 THE DEVELOPMENT OF A TITANIUM WITTIG REAGENT.

As we have already described, the direct methylenation of esters, or vinylogous esters by phosphorus ylids is generally not a viable synthetic operation. Recent studies by Tebbe[190-191] and other workers[192] have shown that the more electrophilic "transition metal ylids" such as (309) can be used to olefinate carboxylic acid derivatives (scheme 5.14).



(Scheme 5.14)

Evans and co-workers[193] found that a wide range of ester and lactone methylenations could be achieved using the "Tebbe reagent" (scheme 5.15).



(310)

(a) n = 1

(b) n = 2

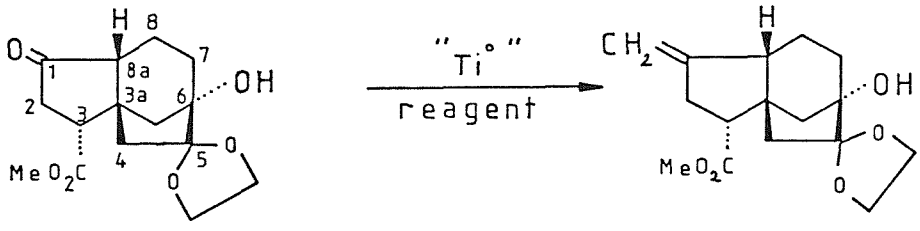
(311)

(a) 85%

(b) 85%

(Scheme 5.15)

The success of this reagent prompted us to investigate if any Ti° had been employed for the olefination of vinylogous esters. No such examples existed but a simple (and less hazardous to prepare) reagent came to light. Lombardo[194] successfully methylenated (312) and aldehydes using a Ti° reagent. One carbon homologation with ylids $Ph_3P=CH_2$ or $Me_2S(O)=CH_2$[195] had led to epimerisation of the 8a-hydrogen in the molecule, even though the latter reagent had been reported[196] not to enolise ketones (scheme 5.16).



(312)

(313) 90%

(Scheme 5.16)

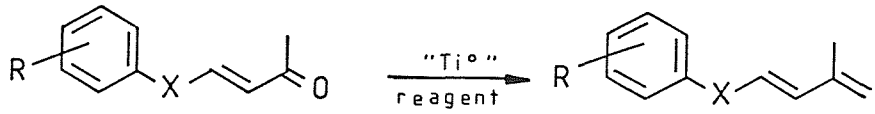
Lombardo initially utilised a $Zn/CH_2Br_2/TiCl_4$ reagent (developed by Oshima[197]) with little success, destroying the starting material (312). Modification of the Oshima procedure so that the reagent was prepared at -40°C and stirred for 3 days at 5°C, rather than preparation at room temperature as described by Oshima, gave 90% isolated yield with no evidence of epimerisation and left the ester

intact. In view of these results we were intrigued as to whether a vinylogous ester could be methylenated.

The use of CD_2Br_2 is shown[194] to give CD_2 incorporation into the molecule, so confirming that the methylene group is derived from the methylene bromide and not from the methylene chloride used as solvent for the methylenation.

5:3:1 Results and discussion

Investigation of the Lombardo reagent ($Zn/TiCl_4/CH_2Br_2$) confirmed its use as a methylenating agent, and further dilution with tetrahydrofuran (20 ml) during its preparation gave an easily syringeable slurry. Treatment of a range of vinylogous esters with the reagent gave, in an almost instantaneous reaction, the desired dienes in high yield (scheme 5.17). There was no evidence of the free phenol being liberated and acceptably pure dienes were obtained after work-up.

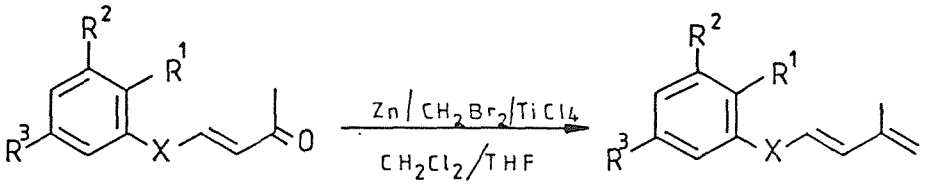


X = O,S

(269) (280)

(Scheme 5.17)

The results obtained using our modified reagent are given in table 5.7. In each case the *trans*-diene was formed, with no evidence for the *cis* in the ^1H n.m.r. spectrum.



(269) (280)

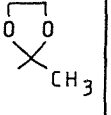
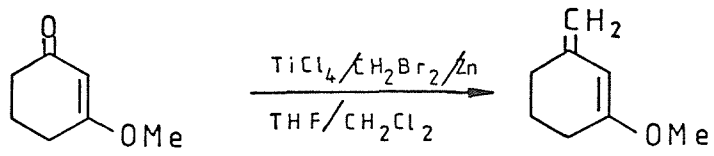
(280)	R^1	R^2	R^3	X	Yield (%)
a	H	H	H	O	92
b	CO_2Me	H	H	O	88
c		H	H	O	85
d	H	OMe	OMe	O	80
e	H	H	H	S	91

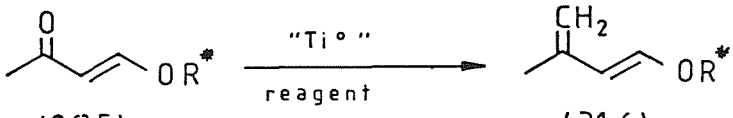
TABLE 5.7

This new diene synthesis was applied to 3-methoxycyclohexanone (314) and 4-(*d*-2-octyloxy)-3-buten-2-one (285) providing in the former case a high yield (70%) of pure 1-methoxy-3-methylene-1-cyclohexene (315) for the first time[198] and in the latter the chiral diene (316) in 67% yield (scheme 5.18). This clearly demonstrates the generality of this

process and its use in both formation of 1-aryloxy-, 1-alkoxy- and 1-arylthio-1,3-butadienes and the synthesis of chiral 1-alkoxy-dienes.



(314) (315)

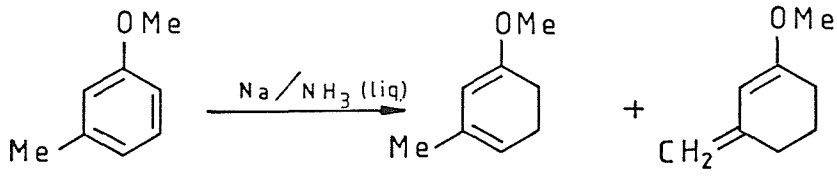


(285) (316)

$R^* =$ d-2-octyl

(Scheme 5.18)

Prior to the use of this reagent, compound (315) had been synthesised[198] by a "Birch reduction" of the corresponding anisoles (317) (scheme 5.19).



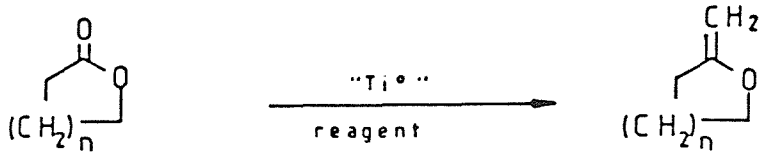
(317) (318) (315)

ratio 1 : 1

(Scheme 5.19)

The only other compound cited in the literature was the 3-methyl-1-phenylthio-1,3-butadiene (280e) which may be synthesised by a number of methods[199-203], with yields ranging from 29% to 92%. Our route is of comparable value and in general, it is easier to perform. Our spectral data was in full agreement with that given in the literature.

Investigation of the reaction of lactones (319) with our reagent showed it to be selective for ketones and vinylogous esters; lactones and esters are recovered unchanged (scheme 5.20).



(319) (320)

(a) n = 1 0%

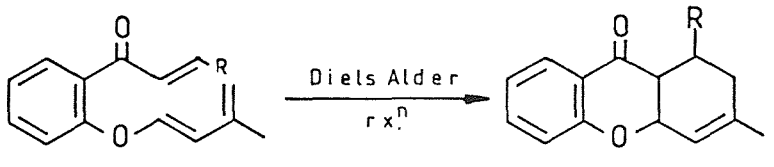
(b) n = 2 0%

(Scheme 5.20)

To summarise we have developed a general high yielding mild procedure for the preparation of 1-substituted-oxy-1,3-dienes from low cost reagents which are easy to handle and readily available.

5:4 APPLICATIONS OF 1-ARYLOXY-3-METHYL-1,3-BUTADIENES TO THE SYNTHESIS OF CHROMANONES USING AN INTRAMOLECULAR DIELS-ALDER REACTION.

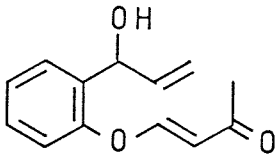
In section 5:1 we outlined a procedure to synthesise the necessary Diels-Alder precursor (156) for use in the synthesis of compound (157) (scheme 5.21).



(156) (157)

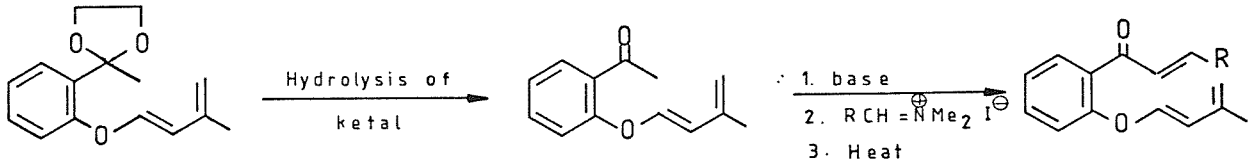
(Scheme 5.21)

We have already described the problems encountered with the synthesis of (269f) (section 5:2:2), which would have been a useful intermediate in the synthesis of compound (157).



(269f)

As a result, we focused our attention on one of our other readily available compounds (280c) which we hoped to convert into compound (156)(scheme 5.22).



(280c) (321) (156)

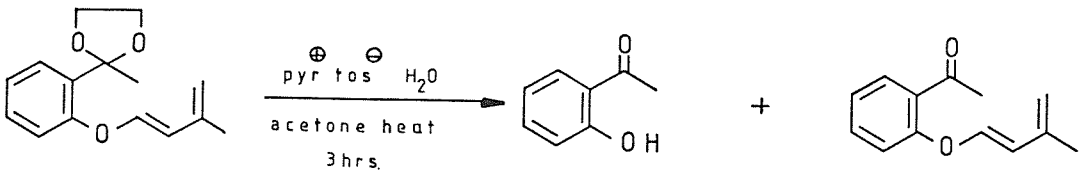
(Scheme 5.22)

In order to implement this strategy it was necessary to hydrolyse the ketal and liberate the ketone, usually a facile transformation.

5:4:1 Results and discussion

5:4:2 Hydrolysis of a dienol-ketal (280c)

The deprotection of the ketone (321) by hydrolysis of the ketal (280c) is usually a trivial step, but we quickly encountered problems. Boiling the ketal (280c) with pyridinium tosylate[166] in acetone and water for 3 hours resulted in a mixture of compounds (scheme 5.23).



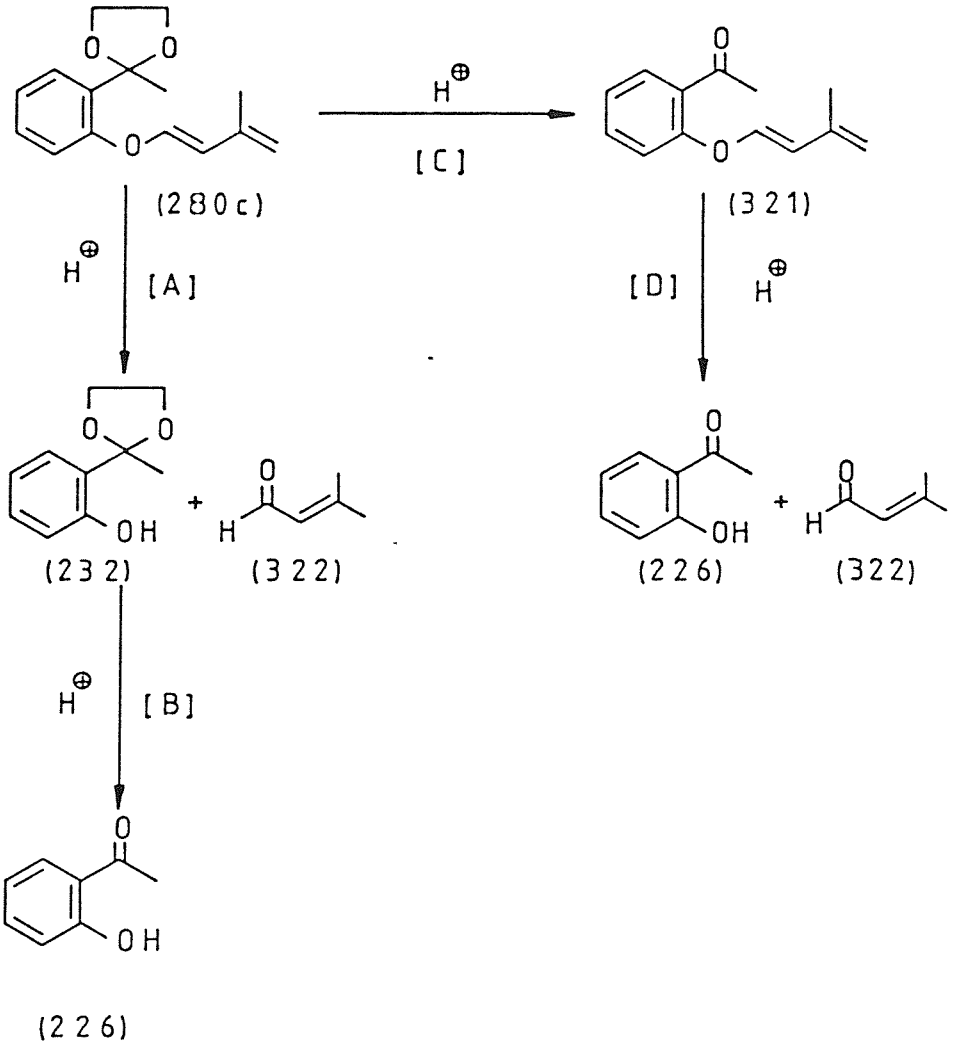
(280c) (226) + (321)

Yield 80%

ratio 2 : 1

(Scheme 5.23)

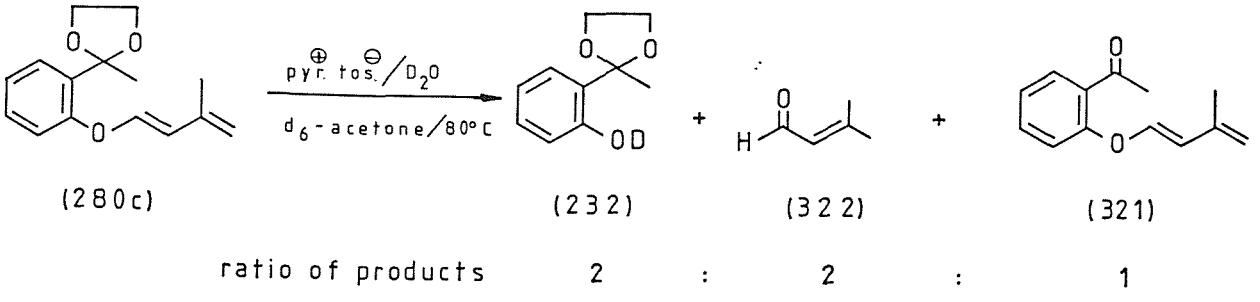
The ratio of products was determined by 60 MHz ^1H n.m.r. We postulated two possible routes for the observed products (scheme 5.24).



(Scheme 5.24)

Scheme 5.24 shows two possible pathways to account for our observed products. Either we are encountering route (C) to our desired product, which then undergoes further hydrolysis (route D) to give *o*-hydroxyacetophenone, or the *o*-hydroxyacetophenone observed is formed by route (A), and hence pathways (A) and (B) are in competition with the desired route (C).

To investigate the reaction further, it was performed at varying temperatures in a sealed n.m.r. tube. The reaction was conducted in d_6-acetone, D_2O and catalysed by pyridinium tosylate. At 80°C the reaction was complete within 30 minutes as judged by 100 MHz ^1H n.m.r. giving a mixture of products (scheme 5.25).



(280c) (232) (322) (321)

ratio of products 2 : 2 : 1

(Scheme 5.25)

N.m.r. revealed that no *o*-hydroxyacetophenone had formed during this time, hence the products (321) and (232) were obtained by the competition of pathways (A) and (C) respectively (scheme 5.24). We conclude that any *o*-hydroxyacetophenone formed is by further hydrolysis of (232) (path (B) rather than *via* path (D) which does not participate in this reaction at all. Compound (321) once formed appears to be stable under hydrolytic conditions).

We continued the investigation of this reaction at room temperature to see if temperature affected the relative rates of reaction paths (A) and (C) and hopefully promote the required pathway (C).

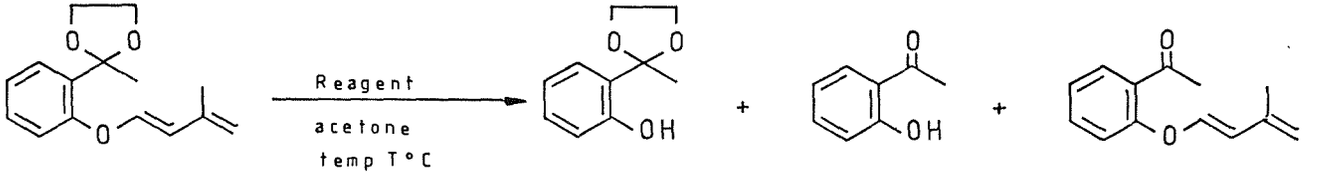
The n.m.r. study of this hydrolysis at room temperature is summarised in table 5.8.

Time (hrs)	Reaction Yield (%)	Ratio of o-hydroxyacetophenone : (321)
1	0	——
5	33	2 : 1
14	60	2 : 1
20	65	2 : 1
48	80	2 : 1
72	81	2 : 1

TABLE 5.8

The effect of temperature was found not to affect the relative rates of pathways (A) and (C); they remain in a 2:1 ratio; lowering the temperature does, however, affect the relative rates of pathways (A) and (B), and path (A) becomes rate determining. At higher temperature (80°C) path (B) must be the slowest, and hence the rate determining step.

In view of these results we investigated other deprotection methods :- e.g. *p*-toluenesulphonic acid[204], lithium tetrafluoroborate[205] and Amberlyst-15[206] (table 5.9).



(280c) (232) (226) (321)

Entry No.	Reagent	T°C	Time(hr)	Yield (%)	Ratio (232) : (226) : (321)
1	pTSA	80	3	70	— 2 : 1
2	pyr.$^{\oplus}$ tos.$^{\ominus}$	80	3	80	— 2 : 1
3	pyr.$^{\oplus}$ tos.$^{\ominus}$	RT	72	81	— 2 : 1
4	Amberlyst-15	RT	2	85	1 : 1 —
5	$LiBF_4$	RT	3·5	62	2 : 1 —

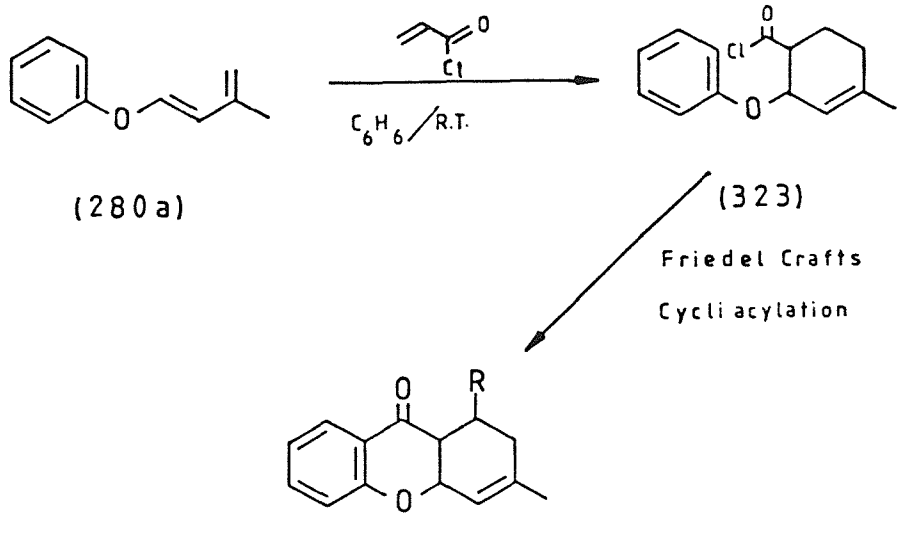
TABLE 5.9

p-Toluenesulphonic acid (entry 1) gave similar results to the pyridinium tosylate already described. Amberlyst-15 (entry 4) and lithium tetrafluoroborate (entry 5) selectively hydrolysed the dienol ether first, and we saw no signs of the desired product in either case.

In view of these results we abandoned this intramolecular Diels-Alder approach to (157) and decided to investigate an intermolecular approach.

5:5 INTERMOLECULAR APPROACHES TO CHROMONES UTILISING 1-ARYLOXY-3--METHYL-1,3-BUTADIENES

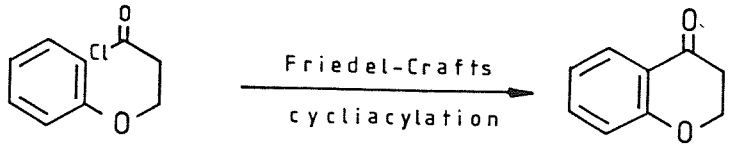
In accordance with our desire to synthesise chromones and ergochromes using the strategies outlined in Chapter 4 (scheme 4.2. and 4.3), we were required to synthesise the tricyclic chromanone (157). The previous sections have outlined various routes involving an intramolecular Diels-Alder step. The following sections deal with an intermolecular Diels-Alder approach, and a subsequent Friedel-Crafts cyclisation[207] (scheme 5.26).



(157) R = H

(Scheme 5.26)

The precedent[208] for this cyclisation comes from the simple acid chloride (324) which was successfully cyclised to give chromanone (325) (scheme 5.27).



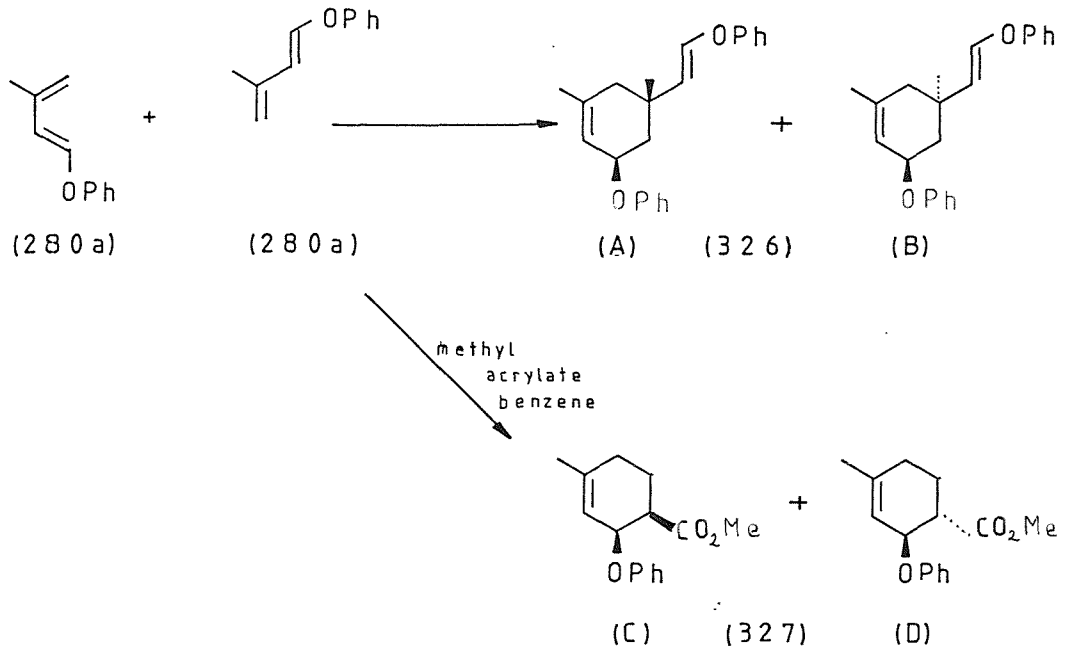
(324) (325)

(Scheme 5.27)

5:5:1 Results and discussion

To implement our cyclisation we required the compound (323); the easiest method of preparation was to perform an intermolecular Diels-Alder reaction between 1-phenoxy-3-methyl-1,3-butadiene (280a) and acryloyl chloride to give the adduct (323) (scheme 5.26).

To achieve this the reactants were stirred in benzene at room temperature but the reaction gave a complex mixture of products. The major product obtained was phenol and we postulate that this was due to the acidity associated with acryloyl chloride (due to dissolved HCl). In order to circumvent this problem we looked instead at the Diels-Alder reaction of methyl acrylate with 1-phenoxy-1,3-butadiene; this gave promising results, except that our desired product was the minor component. We obtained a mixture of dimeric products and required products in the ratio 2:1 respectively (scheme 5.28).



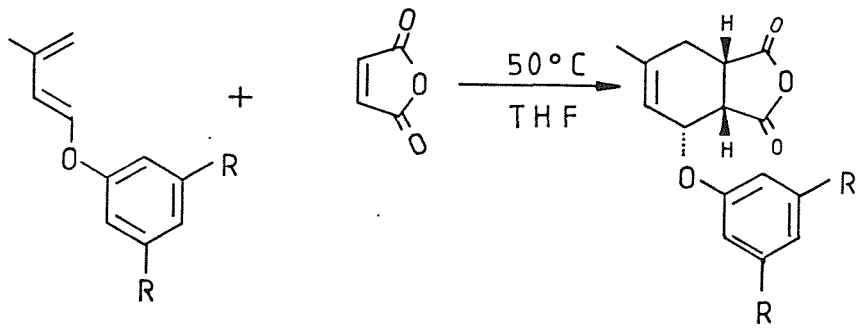
ratio of product (A + B) : (C + D) = 2 : 1 (by n.m.r.)

Yield (A + B + C + D) based upon (280a) = 60%

(Scheme 5.28)

The dimerisation was a very facile process, and so we decided that a more reactive dieneophile should be employed.

The reaction of sublimed maleic anhydride with dienes (280a) and (280d) gave 80% and 50% yields of the respective *endo*-adducts (329) (scheme 5.29).



(280)

(a) R = H

(d) R = OMe

(329)

80 %

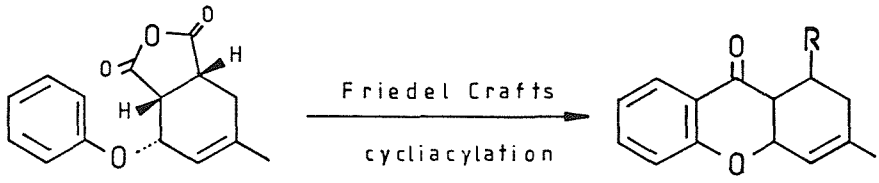
50 %

(Scheme 5.29)

The adducts (329) were suitable substrates for us to investigate the possibility of an intramolecular Friedel-Crafts reaction, and hence entry to the tricyclic chromanone (157) and analogues (scheme 4.3).

5:5:2 <u>The intramolecular Friedel-Crafts cycliacylation of (329)</u>

The Friedel-Crafts cycliacylation[207] of (329a) shown in scheme 5.30 would yield one of the desired tricycles.

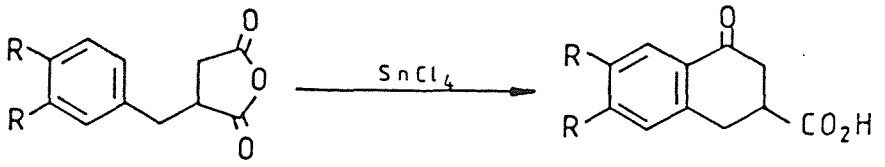


(329a)

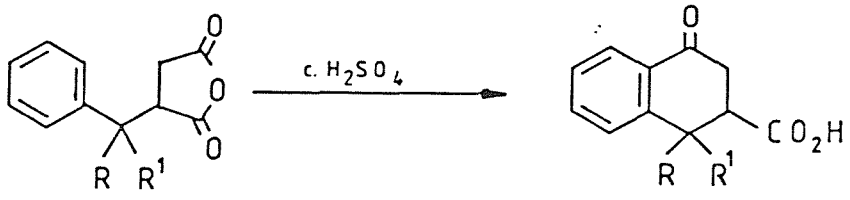
(157) R = CO_2H

(Scheme 5.30)

Several examples of simple intramolecular anhydride cyclisations already existed; the all carbon version having been used in the synthesis of 3-carboxy-1-tetralones[209-210] (331) under a variety of conditions (scheme 5.31).



(330) R = OMe (331)

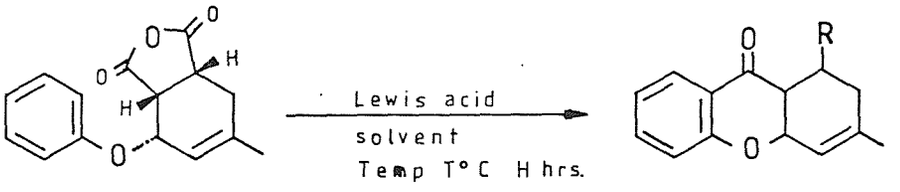


(332) R,R¹ = H, alkyl (333)

(Scheme 5.31)

With these examples in mind we were encouraged to look at the intramolecular cycliacylation of (329a).

Polyphosphoric acid has been successfully utilised in the cyclisation of acids[211-212] and anhydrides[213] (scheme 5.32). A number of variants of this cyclisation were implemented, and the results tabulated in table 5.10.

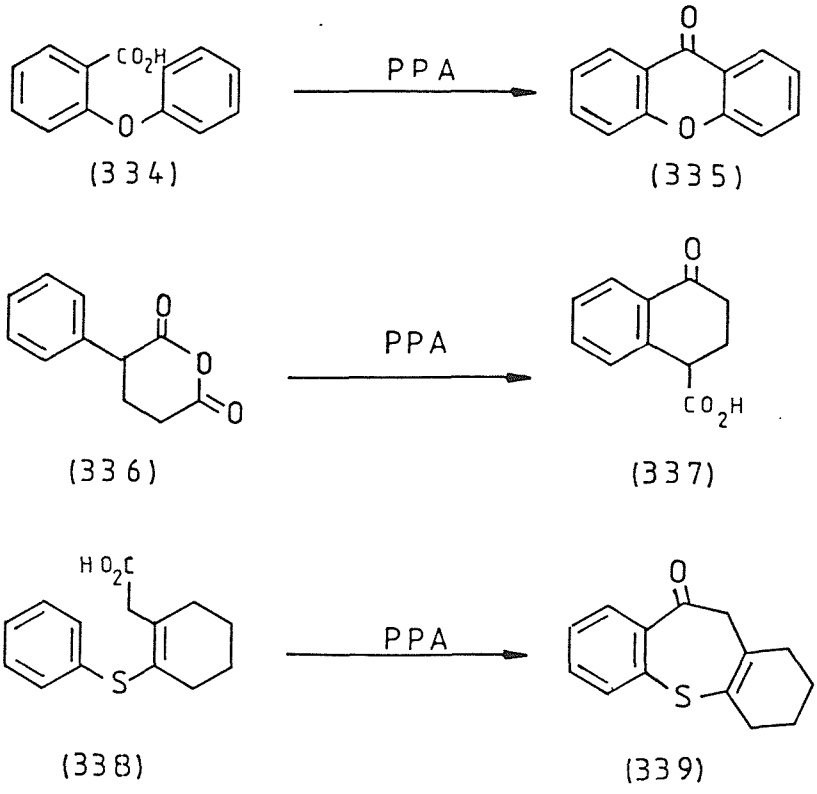


(329a) (157)

R = CO_2H

entry no.	Solvent	Lewis acid	T°C	H hrs.	Result
1	PPA.	—	50-60	2	SM
2	PPA	—	80	2	Complex mixture
3	PPA	—	70	4	SM
4	CH_3NO_2	$AlCl_3$	RT	5	SM
			101	1	Complex mixture
5	CH_2Cl_2	$AlCl_3$	-78	1.5	SM
			-30	1	SM
			RT	5	Complex mixture
6	CH_2Cl_2	$TiCl_4$	-78	2	SM
			-30	2	Complex mixture
7	CH_2Cl_2	$SnCl_4$	-78	4	SM
			-30	2	Complex mixture
8	CH_2Cl_2	BF_3OEt_2	-78	4	SM
			-30	24	Complex mixture

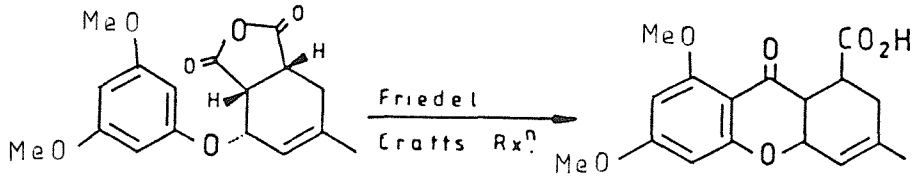
TABLE 5 10



(Scheme 5.32)

In our example only inseparable complex mixtures or starting material were obtained (entries 1, 2 and 3). Nitromethane has often been cited[214] as a useful solvent for Friedel-Craft reactions, but the results were found to be disappointing (entry 4) in our case. In an effort to achieve this cyclisation a range of Lewis acids[215] were tried in methylene chloride as the solvent (entries 5, 6, 7, 8). Various temperatures were employed whilst the reaction was monitored by t.l.c. In each case the starting material disappeared and was replaced by a very slow moving spot. N.m.r. and i.r. spectra showed that a complex mixture of products were obtained, with little evidence of our desired product (157).

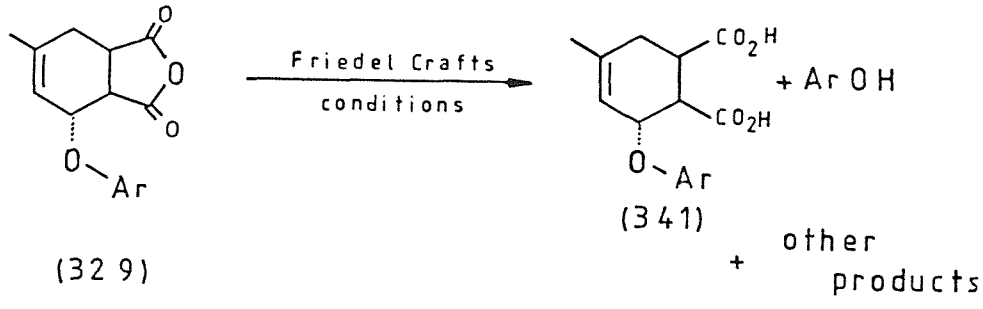
To facilitate the cyclisation we decided to investigate the Friedel-Crafts cycliacylation of the more electrophilic substrate (329d) (scheme 5.33).



(329d) (340)

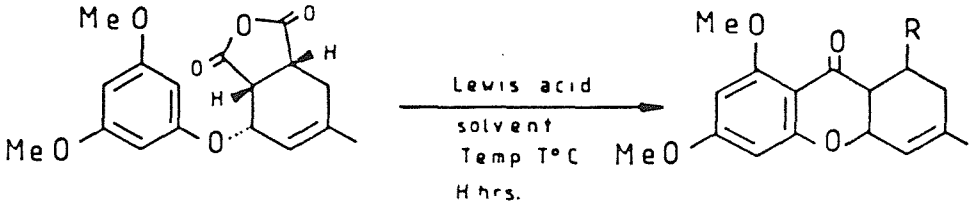
(Scheme 5.33)

Since this had an activated phenyl ring, we hoped that this would readily cyclise to give a tricycle (340). A similar variety of conditions to that employed with the unactivated substrate were tried, but in each case complex mixtures were obtained (table 5.11). One of the compounds of this mixture was the corresponding phenol (276d) and possibly the diacid (341) from the opening of the anhydride (scheme 5.34).



(329)

(Scheme 5.34)



(329d) (340)

$R = CO_2H$

Entry no.	Solvent	Lewis acid	T°C	H hrs.	Result
1	PPA		55	2	SM
2	PPA		80	2	Complex mixture
3	PPA		65	4	
4	CH_3NO_2	$AlCl_3$	RT 101	5 1	SM
5	CH_2Cl_2	$AlCl_3$	-78 -30 RT	2 1 6	SM Complex mixture
6	CH_2Cl_2	$TiCl_4$	-78 -30	2 2	SM Complex mixture
7	CH_2Cl_2	$SnCl_4$	-78 -30	5 3	Complex mixture
8	CH_2Cl_2	$BF_3.OEt_2$	-78	1	Complex mixture

TABLE 5.11

5:6 CONCLUSION

In the first half of this chapter we successfully developed a synthetic methodology to synthesise 1-aryloxy- and 1-alkoxy-3-methyl-1,3-butadienes using a simple Ti° methylenating reagent, having been unable to achieve this using the simple Wittig reagent (methylenetriphenylphosphorane).

The hitherto unknown dienes were utilised in synthetic approaches to chromanonic tricycles (157) and (340), and to this end the competitive hydrolysis of a ketal versus a dienol-ether was investigated by n.m.r. spectroscopy. The intramolecular Diels-Alder approach central to Chapter 4 was abandoned, in favour of an intermolecular approach and a study was made of the next step, an intramolecular Friedel-Crafts cycliacylation.

Further research in this area is required, and a suitable set of conditions may still exist to bring this strategy to a successful conclusion.

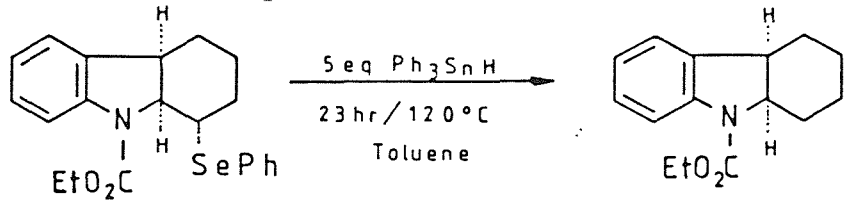
CHAPTER 6

A SELENIUM RADICAL INVESTIGATION

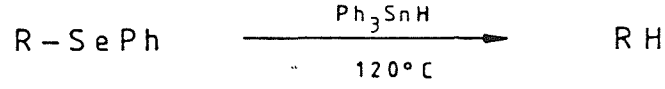
6:1 RADICAL CYCLISATIONS : AN INTERIM STUDY

6:1:1 Introduction to selenium radical chemistry

Investigations by Clive *et al.*[164] have revealed that homolytic fission of the C-Se bond is a useful reaction leading either to reduction or cyclisation (where possible). Their research concentrated on the reduction of phenylselenides using triphenyltin hydride (scheme 6.1).



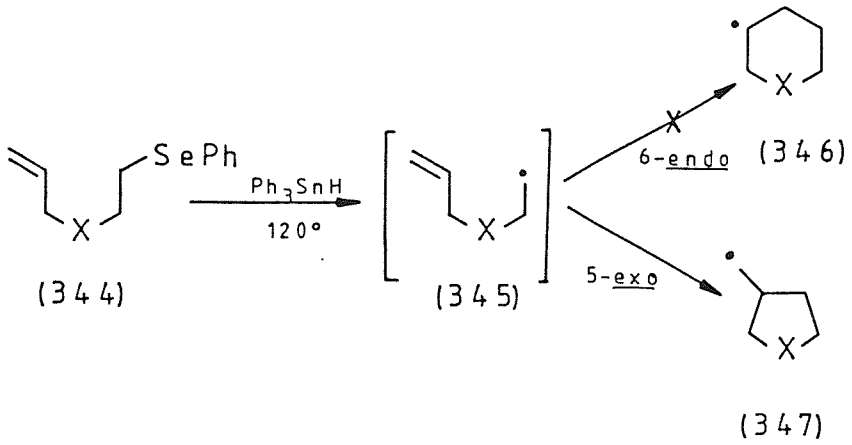
(342) (343)



R = $C_{12}H_{25}$-, PhCH(Me)-

(Scheme 6.1)

Further research[164] by Clive involved the reduction of dodecylselenobenzene in the presence and absence of catalytic amounts of AIBN (5 mol%). This revealed that initially the rate is higher in the presence of the radical initiator. Olefinic radicals such as (345) (X = CH_2 or O) are well known to undergo 5-*exo* rather than 6-*endo* closure[216-218], and this fact was utilised by these researchers as a probe in these studies (scheme 6.2).



(Scheme 6.2)

In view of these results they concluded that carbon radicals were involved in C-Se reduction by tin hydrides and that C-Se homolytic scission was a facile process.

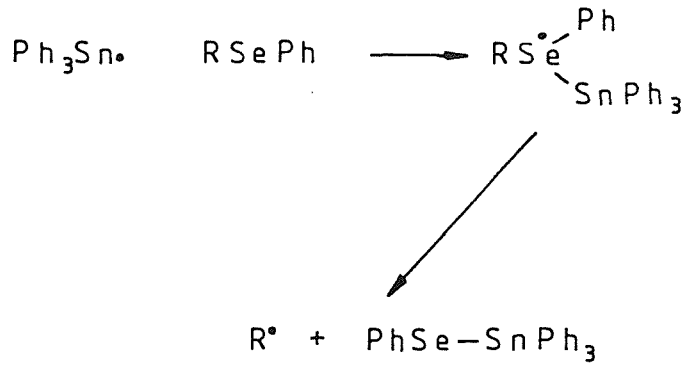
Various mechanisms[219] are postulated for tin hydride reductions and two likely ones are shown in schemes 6.3 and 6.4.

$$Ph_3Sn-H \xrightarrow{h\nu} Ph_3Sn\cdot$$

$$Ph_3Sn\cdot + RSePh \longrightarrow R^{\bullet} + Ph_3Sn-SePh$$

$$R^{\bullet} + Ph_3SnH \longrightarrow RH + Ph_3Sn\cdot$$

(Scheme 6.3)



(Scheme 6.4)

6:1:2 Approaches to 5,5-bicyclo ring systems

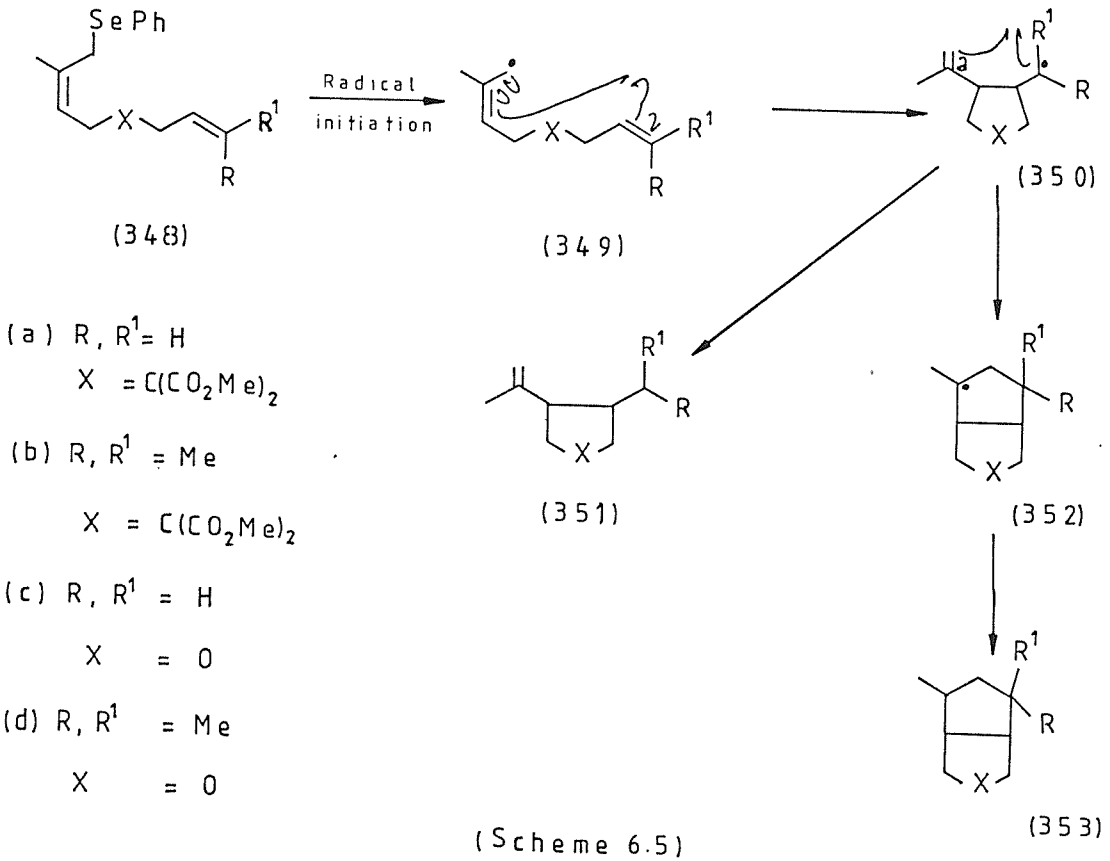
In chapter 4 we described novel routes to allylic selenides and postulated radical mechanisms to account for some of the anomalous results obtained (section 4.3.3).

On consideration of our previous results and Clive's work, we initiated research into the possible use of our allylic selenides for the preparation of 5,5-bicyclo systems and simple five membered rings (scheme 6.5).

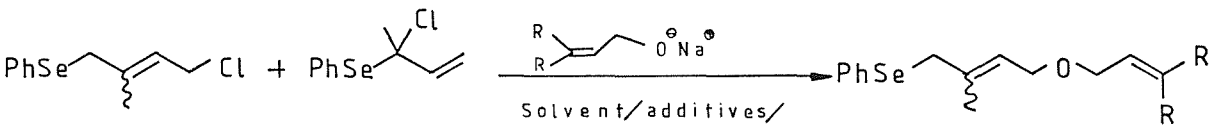
6:2 RESULTS AND DISCUSSION

6:2:1 The synthesis of suitable radical substrates (348)

Chapter 4 dealt in depth with the thermal instability of 4-chloro-1-phenylselenenyl-2-butenes (217) and 2-chloro-1-phenylselenenyl-2-butenes (216) and the difficulty of achieving S_N2 or S_N2' displacement


SePh
Radical
initiation
(348)
(349)
(350)
(351)
(352)
(353)
(a) R, R¹= H
X = C(CO₂Me)₂
(b) R, R¹ = Me
X = C(CO₂Me)₂
(c) R, R¹ = H
X = O
(d) R, R¹ = Me
X = O

(Scheme 6.5)



(217a) (216a) (348)

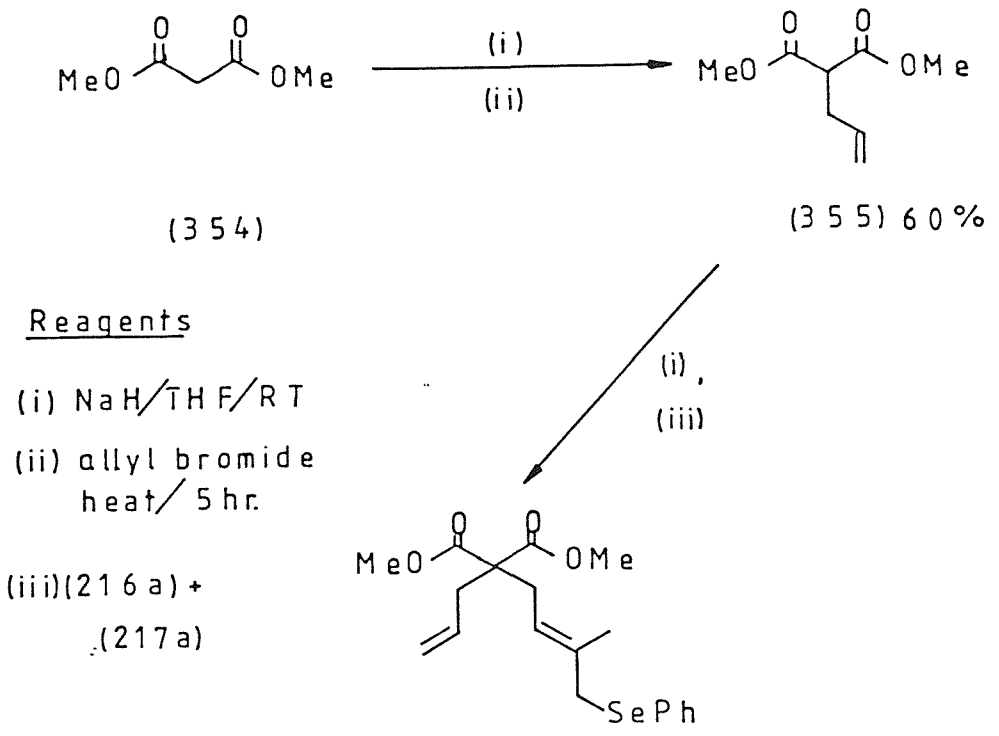
sodium hydride was employed in the formation of the alkoxide in each case.

entry no.	R	Solvent	additives	Temp(°C)	Rx^{n} Time (hr)	Result
1	Me	THF	HMPA	66	20	Starting alcohol
2	Me	THF	HMPA/NaI	66	20	recovered
3	Me	THF	—	66	20	in each
4	H	THF	HMPA/NaI	66	18	experiment
5	H	THF	HMPA	66	18	
6	H	THF	—	66	18	
7	H	Et_2O	—	35	18	

(TABLE 6.1)

of the halogen by nucleophiles. Once again we experienced considerable problems in the displacement by the oxy-anions of prenol or allyl alcohol and failed to synthesise the desired products (Table 6.1).

The difficulty in reacting the anion of allylic alcohols with the chloro-selenides forced us to investigate the all carbon analogue. Alkylation of dimethylmalonate with allyl bromide gave a 60% yield of the substituted malonate (355), and further alkylation with the mixture of chloro-selenides (216a) and (217a) gave the desired quaternary compound (348a) in 38% yield (scheme 6.6).



(Scheme 6.6)

With compound (348a) available it was possible to investigate

homolytic C-Se bond fission and the likelihood of a radical cyclisation.

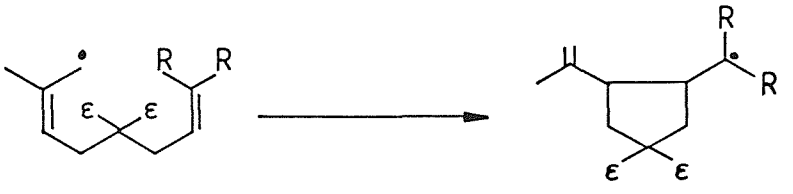
6:2:2 Investigations into radical cyclisations

We decided to approach the problem of homolytic C-Se bond cleavage from several angles. Fission of the bond was studied under photolytic conditions either in the presence or absence of tin hydrides.

Table 6.2 illustrates clearly the need for the presence of tin hydrides to propagate the reaction, as absence resulted in almost quantitative recovery of starting material (entries 1 and 5). All other variants of this reaction produced mixtures of starting material and products which were unidentifiable at the time.

We were encouraged by these results because starting material was clearly being consumed, presumably through C-Se bond fission.

We postulated that the cyclopentanoid compound (350) was formed and that further cyclisation was not occurring due to the instability of the methylene radical (R=H, scheme 6.7) or the possibility of a *trans* relationship between the alkene and the newly formed radical centre.



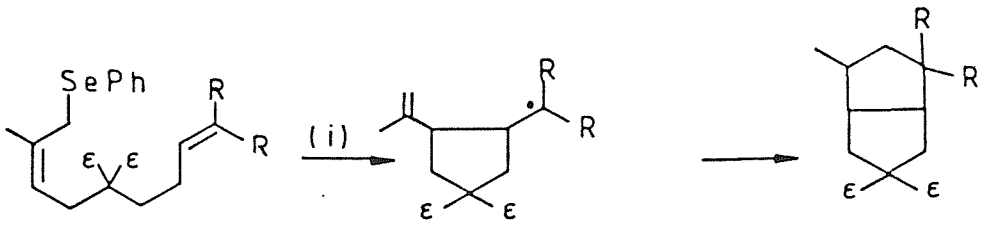
(349) (350)

(a) R = H

(b) R = Me

ε = CO_2Me

(Scheme 6.7)



(348 a or b) (350) (353)

Reagents

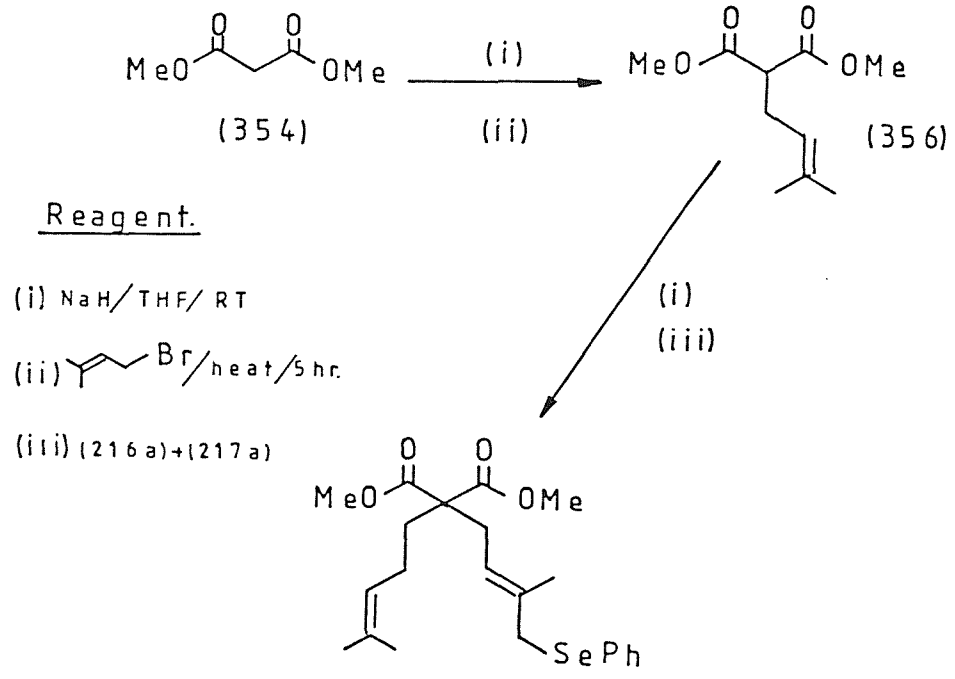
(i) radical source/ initiator/ benzene

entry no.	R	radical source	initiator	temp (°C)	time (hr)	Result
1	H	$h\nu^1$	AIBN	RT	12	SM
2	H	$h\nu^1$ $^nBu_3SnH$	AIBN	RT	5	SM + complex mixture
3	H	$h\nu^2$ $^nBu_3SnH$	AIBN	RT	5	
4	H	$^nBu_3SnH$	AIBN	80	5	
5	H	——	AIBN	80	12	SM
6	H	$h\nu^1$ Ph_3SnH	AIBN	RT	12	complex mixture

1. medium pressure mercury vapour lamp + pyrex filter
2. 150W tungsten lamp.

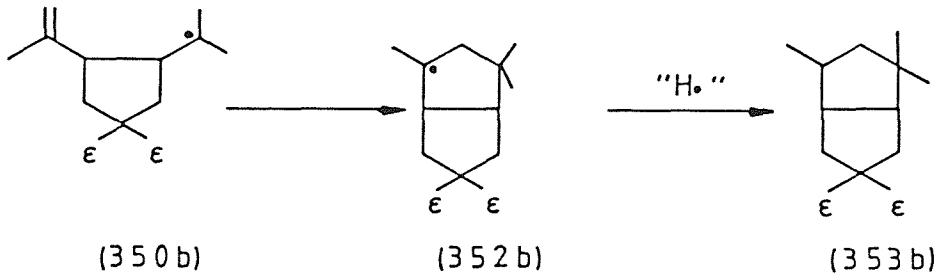
TABLE 6.2

In order to test this postulate we synthesised (348b) by alkylating dimethylmalonate under the same conditions as before (scheme 6.8).



(Scheme 6.8)

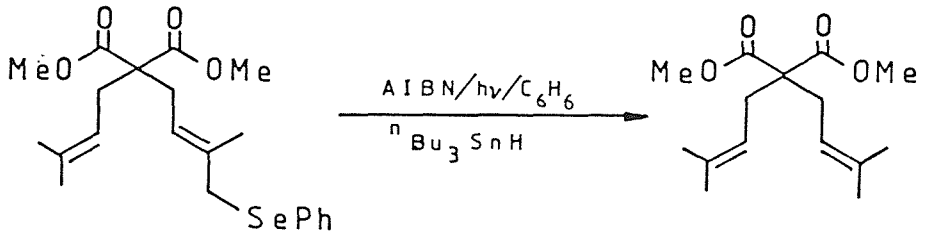
The intermediate (350b) which was formed after the first cyclisation would now be the more stable tertiary radical, which might either be quenched or else undergo the second cyclisation to (353b) (scheme 6.9).



ε = CO_2Me

(Scheme 6.9)

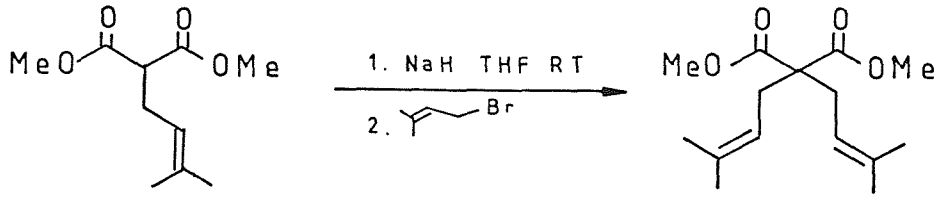
We used the same conditions as previously described (see table 6.2) and isolated the reduced compound (357) as the major product (scheme 6.10).



(348b) (357)

(Scheme 6.10)

To ensure that we had in fact obtained the reduced product we synthesised compound (357) by further alkylation with the allylic bromide (scheme 6.11).

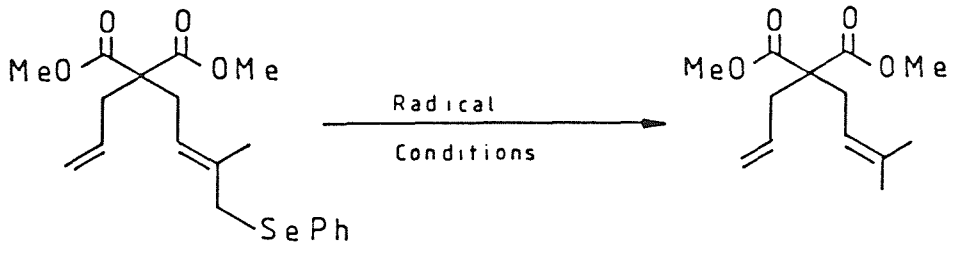


(356) (357)

(Scheme 6.11)

Comparison of the n.m.r., m.s. and i.r. spectra confirmed that the product had been obtained by reduction of the C-Se bond to give (357). Reinterpretation of our previous results in table 6.2 also revealed

that the major product in each case has been that due to reduction of the C-Se bond (scheme 6.12).



(348a) (358)

(Scheme 6.12)

These results are in agreement with those observed by Clive[164] in his studies on non allylic selenides.

6:3 CONCLUSION

To summarise, we found that homolytic fission of the C-Se bond readily occurs under a variety of radical conditions, giving simple reduction of the selenide (*i.e.* formation of C-H bond). If the allylic radical (358) could be produced in any appreciable concentration it may be possible in other cases to achieve cyclisation.

(349) (358)

(Scheme 6.13)

Once this radical (358) has formed it should be possible to achieve the first 5-*exo* cyclisation, especially if high dilution techniques were employed in the reaction. This would lower the hydride concentration and encourage the cyclisation rather than the observed reduction of starting material. Further work in this area would be required, but the validity of such a cyclisation has been strengthened by our research. Lack of time precluded us from pursuing further studies.

CHAPTER 7

EXPERIMENTAL

7:1 GENERAL PROCEDURES AND INSTRUMENTATION

Proton nuclear magnetic resonance spectra (^{1}H n.m.r.) were recorded at 60 MHz on Perkin Elmer R12 or R24B spectrometers, at 100 MHz on a Varian Associates XL-100/12 spectrometer and at 360 MHz on a Bruker AM-360 spectrometer. Except where otherwise stated, ^{1}H n.m.r. spectra were recorded at 60 MHz for solutions using tetramethylsilane (T.M.S. $\delta = 0$) as internal or, for silicon containing compounds, external standard. Carbon-13 nuclear magnetic resonance spectra (^{13}C n.m.r.) were recorded at 25.15 MHz on a Varian Associates XL-100/12 spectrometer, or at 90.56 MHz on a Brucker AM-360 spectrometer. Infrared spectra (i.r.) were determined using a Perkin-Elmer 157G infrared spectrophotometer; absorption bands are given in wave numbers (cm^{-1}) relative to a polystyrene standard. Ultraviolet spectra (u.v.) were recorded on a Pye Unicam SP800 spectrophotometer for solutions; maximum absorptions (λ_{max}) are given in nanometers (nm). Mass spectra (m.s.) were determined on a Kratos-AEI MS30 with a Digispec DS55 data system, using electron impact and an ionising voltage of 70eV, or chemical ionisation with ammonia gas as the ioniser. The mass to charge ratios of the major ion fragments are quoted with their intensities (expressed as a percentage of the base peak intensity) in parentheses.

Abbreviations used in the descriptions of spectra are shown in table 7.1.

Spectrum	Abbreviations
^{1}H n.m.r.	s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad,
i.r.	w = weak, m = medium, s = strong, br = broad
u.v.	sh = shoulder
m.s.	M^+ = molecular ion

TABLE 7.1

Analytical thin layer chromatography (t.l.c.) was carried out using glass plates coated with Merck silica gel HF_{254} (0.5 mm thickness). Spots were visualised either by observation under ultraviolet radiation (254 nm), exposure to iodine vapour or spraying with neutral aqueous potassium permanganate, or acidic 2,4-dinitrophenylhydrazine. "Flash" chromatography refers to the separation technique developed by Still *et al.*[220] and was carried out using Machery-Nagel silica gel 60 (0.04-0.063 nm).

n-Butyllithium was used as a 15% solution in hexane, methyllithium as a 1.4 M solution in diethyl ether, and di*iso*butylaluminium hydride as a 1.1 M solution in hexane; all these reagents were standardised before use.

Melting points were determined using an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed by the Microanalysis Laboratory, University College, London.

Except where otherwise stated, organic solutions were dried over anhydrous magnesium sulphate, filtered and concentrated by removal of the solvent using a rotary evaporator. Petroleum ether refers to the fraction of boiling range 40 - 60°C and "ether" to diethyl ether.

Where necessary solvents were dried according to the published procedures[221-223] shown in table 7.2.

All reactions were performed under an inert atmosphere of nitrogen unless otherwise stated.

Solvent	Drying Method
Benzene Toluene Acetonitrile Dichloromethane Petroleum ether Triethylamine Pyridine Di*iso*propylamine Dimethyl sulphoxide	Distilled from calcium hydride
Chloroform Carbon tetrachloride N,N-Dimethylformamide	Distilled from phosphorus pentoxide
Tetrahydrofuran Ether	Distilled from sodium in the presence of benzophenone
Methanol	Distilled from magnesium methoxide
Ethanol	Distilled from magnesium ethoxide

TABLE 7.2

The experimental procedures contain the use of widely accepted abbreviations, table 7.3 summarises the conventions adopted.

List of abbreviations used

AIBN	- 2,2'-Azobis-(2-methylpropionitrile) (azobisisobutyronitrile)
DIBAL-H	- Di*iso*butylaluminium hydride
DHP	- Dihydropyranyl
DMAP	- 4-Dimethylaminopyridine
DMF	- N,N-Dimethylformamide
DMM	- Dimethyl malonate
DMSO	- Dimethylsulphoxide
HMPA	- Hexamethylphosphoric triamide
LDA	- Lithium di*iso*propylamide
*m*CPBA	- *m*-Chloroperoxybenzoic acid
PCC	- Pyridinium chlorochromate
PDC	- Pyridinium dichromate
pyr.	- Pyridine
pyr. Tos.	- Pyridinium tosylate
TBDMS	- *t*-Butyldimethylsilyl
THF	- Tetrahydrofuran
THP	- Tetrahydropyranyl
TMS	- Trimethylsilyl
Tos	- Tosylate
*p*TSA	- *p*-Toluenesulphonic acid
n.m.r.	- nuclear magnetic resonance spectroscopy
i.r.	- infrared spectroscopy
m.s.	- mass spectroscopy
u.v.	- ultraviolet-visible spectroscopy
g.l.c.	- gas liquid chromatography
E.I.	- electron impact
C.I.	- chemical ionisation

TABLE 7.3

7.2 EXPERIMENTAL PROCEDURES

3-Nitropropyne (109).

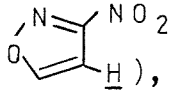
A solution of 3-bromopropyne (4.05g, 0.034 mol) in methylene chloride (10 ml) was added dropwise over 15 minutes to a stirred solution of silver nitrite[99] (7.8g, 0.05 mol) in methylene chloride (20 ml) at -5°C. The reaction was maintained at -5°C for 12 hours, and then at room temperature for a further 6 hours. T.l.c.(ether) indicated that there were three components in the reaction mixture.

The solvent was removed *in vacuo* Proton n.m.r. revealed 3-nitropropyne (109), 3-nitritopropyne and 3-nitroisoxazole (128). This was fractionally distilled, to afford a mixture of 3-nitropropyne (109) and 3-nitritopropyne.
(Yield : 0.1g, 3% b.p. : 102-104°C)

CAUTION This fraction subsequently detonated.

Crude reaction mixture :

^{1}H n.m.r. δ (CCl_4): 2.50(m, 1H, HC≡C-CH_2-X), 3.90(m superimposed doublets, 2H, CH_2-X), 5.00 (m, 2H, CH_2-X), 7.00(d, J=2 Hz, 1H,



), 8.80(d, J=2 Hz, 1H, O-CH= of 3-nitroisoxazole).

X = $-NO_2$, -ONO

i.r. ν_{max} (thin film): 3300(m, C-H), 3000(w, C-H), 2950(w, C-H), 2120(m, C≡C), 1660(s, -O-N=O), 1650(s, -O-N=O), 1560(s,$-NO_2$), 1350(s, $-NO_2$).

3-Methyl-5-phenylsulphinylmethylene-2-isoxazoline (129a)[107].

iso-Cyanatobenzene (0.71g, 6 mmol) and 1-sulphinyl-1,2-propadiene (0.5g, 3 mmol) in benzene (15 ml) was treated dropwise with a solution

of nitroethane (0.225g, 3 mmol) and triethylamine (0.061g, 0.6 mmol) in benzene (2 ml) at 0°C. The reaction was allowed to warm to room temperature and stirred for 24 hours.

The reaction mixture was filtered, the filtrate concentrated *in vacuo* and chromatographed on silica to afford 3-methyl-5-phenylsulphinylmethylene-2-isoxazoline as a pale yellow solid.
(Yield : 0.29g, 44 % m.p. : 66-69°C)
(t.l.c. (1:1 petroleum ether:ether) r_f = 0.13)

^{1}H n.m.r. δ ($CDCl_3$) 400 MHz: 2.20(s, 3H, $C\underline{H}_3$-C=N), 4.18(s, 2H, -N=C-$C\underline{H}_2$-C-O), 6.02(s, 1H, C=C$\underline{H}$-S(O)), 7.50(s, 5H, $C_6\underline{H}_5$).

^{13}C n.m.r. δ ($CDCl_3$): 11.3(q, $\underline{C}H_3$), 53.8(t, $\underline{C}H_2$), 106.3(d, =$\underline{C}$H(S)), 124.0, 129.3, 131.8, 142.0($\underline{C}_6H_5$-), 160.0(s, =$\underline{C}$(O)-CH_2), 161.2(s, CH_3-$\underline{C}$=N).

i.r. ν_{max} ($CHCl_3$): 3040(w), 3000(m), 2900(s), 2850(s), 1600(s, aryl C=C), 1410(s), 1040(s, -S=O).

m.s.: 221(M^+, 13%), 125(50), 96(100), 77(21), 51(14), 39(7).

$C_{11}H_{11}NO_2S$ requires : %C 59.71; %H 5.01; %N 6.33
found : %C 59.59; %H 5.14; %N 6.14

3-Ethyl-5-phenylsulphinylmethylene-2-isoxazoline (129b)[107].

The method employed was similar to that used for the preparation of 3-methyl-5-phenylsulphinylmethylene-2-isoxazoline (129a).
(Yield : 0.18g, 64% m.p. : 58-59°C)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.12)

^{1}H n.m.r. δ ($CDCl_3$): 1.20(t, J=8 Hz, 3H, $C\underline{H}_3$-CH_2), 2.60(q, J=8 Hz, 2H, CH_3-$C\underline{H}_2$), 4.20(s, 2H,

-N=C-C$\underline{H}_2$-C-O), 6.04(s, 1H, C=C$\underline{H}$-S(O)), 7.50(s, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3030(w), 1600(s, aryl C=C), 1440(s), 1410(s), 1050(s, -S=O).

m.s.: 235(M^+, 11%), 125(34), 110(100), 77(23), 51(18), 39(10).

$C_{12}H_{13}NO_2S$ requires M : 235.0667
found : 235.0597

3-Phenyl-5-phenylsulphinylmethylene-2-isoxazoline (129c)[107].

The method employed was similar to that used for the preparation of 3-methyl-5-phenylsulphinylmethylene-2-isoxazoline (129a).
(Yield : 0.35g, 69% m.p. : 90-97°C)
(t.l.c. (1:1 petroleum ether:ether) r_f = 0.20)

^{1}H n.m.r. δ ($CDCl_3$): 4.25(s, 2H, -N=C-C$\underline{H}_2$-C-O), 6.50(s, 1H, C=C$\underline{H}$-S(O)), 7.50(m, 10H, 2x $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3040(w), 1603(m), 1580(m), 1050(s), 700(s), 660(s).

m.s.: 283(M^+, 15%), 158(100), 125(39), 77(47), 51(19).

$C_{16}H_{13}NO_2S$ requires M : 283.0667
found : 283.0780

3-Ethoxycarbonyl-5-phenylsulphinylmethylene-2-isoxazoline (129d)[107].

The method employed was similar to that used for the preparation of 3-methyl-5-phenylsulphinylmethylene-2-isoxazoline (129a).

(Yield : 0.07g, 9%)
(t.l.c. (1:1 petroleum ether:ether) r_f = 0.25)

^{1}H n.m.r. δ ($CDCl_3$):	1.4(t, J=6 Hz, 3H, $C\underline{H}_3$-CH_2), 4.2(s, 2H, -N=C-$C\underline{H}_2$-C-O), 4.4(q, J=6 Hz, 2H, CH_3-$C\underline{H}_2$-O), 6.6(s, 1H, C=C$\underline{H}$-S(O)), 7.5(s, 5H, $C_6\underline{H}_5$).
i.r. ν_{max} ($CHCl_3$):	3040(w), 3000(m), 1740(s), 1600(m), 1580(m), 1040(s).
m.s.:	279(M^+, 6%), 154(11), 125(100), 109(9), 77(20), 51(11).
$C_{13}H_{13}NO_4S$ requires *M* :	279.0565
found :	279.0569

<u>3-[(Tetrahydro-2H-pyran-2-yl)-oxy]-methyl-5-phenylsulphinylmethylene-2-isoxazoline</u> (129e)[107].

The method employed was similar to that used for the preparation of 3-methyl-5-phenylsulphinylmethylene-2-isoxazoline (129a).
(Yield: 0.18g, 31%)
(t.l.c. (1:1 petroleum ether:ether) r_f = 0.17)

^{1}H n.m.r. δ ($CDCl_3$):	1.5(m, 12H, 2x(3x$C\underline{H}_2$), two diastereoisomers), 3.5(m, 6H, 2x($C\underline{H}_2$-O-C$\underline{H}$), 4.2(s, 4H, 2x(-N=C-$C\underline{H}_2$-C-O)), 4.7(s, 4H, 2x(N=C-$C\underline{H}_2$-O), 6.2(s, 2H, 2x(C=C$\underline{H}$-SO)), 7.3-7.5(m, 10H, 2 x $C_6\underline{H}_5$).
i.r. ν_{max} ($CHCl_3$):	1600(m), 1580(w), 1450(m), 1040(s).
m.s.:	321(M^+, 3%), 236(8), 196(100), 125(30), 85(30), 77(40).

$C_{16}H_{19}NO_4S$ requires *M* : 321.1035
found : 321.1085

3-Methyl-5-(phenylthiomethyl)-2-isoxazoline (145a)[107].

iso-Cyanatobenzene (0.71g, 6 mmol) and 1-phenylthio-2-propene (0.45g, 3 mmol) in benzene (15 ml) were treated dropwise with a solution of nitroethane (0.225g, 3 mmol) and triethylamine (0.061g, 0.6 mmol) in benzene (2 ml) at 0°C. The reaction was allowed to warm to room temperature and stirred for 24 hours.

The reaction mixture was filtered, concentrated *in vacuo* and chromatographed on silica to afford 3-methyl-5-(phenylthiomethyl)-2-isoxazoline as a pale yellow solid.
(Yield : 0.38g, 61% m.p. : 35-37°C)
(t.l.c. (2:1 petroleum ether:ether) r_f= 0.01)

^{1}H n.m.r. δ ($CDCl_3$): 1.90(s, 3H, $C\underline{H}_3$-C=N), 3.00(m, 4H, PhS-$C\underline{H}_2$-CH and HC-$C\underline{H}_2$-C=N), 4.75(m, 1H, CH_2-$C\underline{H}$(O)-CH_2), 7.25(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3022(m), 2980(s), 2920(s), 1620(m), 1580(s), 1480(s), 1029(s), 690(s).

m.s.: 207(M^+, 21%), 124(88), 123(100), 109(13), 84(67).

$C_{11}H_{13}NOS$ requires *M* : 207.0714
found : 207.0565

3-Ethyl-5-(phenylthiomethyl)-2-isoxazoline (145b)[107].

The method employed was similar to that used for the preparation of 3-methyl-5-(phenylthiomethyl)-2-isoxazoline (145a).
(Yield : 0.86g, 45%)
(t.l.c. (2:1 petroleum ether:ether) r_f= 0.22)

^{1}H n.m.r. δ ($CDCl_3$): 1.10(t, 3H, J=7Hz, $C\underline{H}_3$-CH_2), 2.30(q, 2H, J=7Hz, $C\underline{H}_2$-CH_3), 3.05(m, 4H, PhS-$C\underline{H}_2$-CH and HC-$C\underline{H}_2$-C=N), 4.65(m, 1H, CH_2-$C\underline{H}$(O)-CH_2), 7.25(m, 5H, $C_6\underline{H}_5$).

^{13}C n.m.r. δ ($CDCl_3$): 10.8(q, $\underline{C}H_3$-), 21.2(t, CH_3-$\underline{C}H_2$), 37.7(t, =C-$\underline{C}H_2$-CH), 41.4(t, S-$\underline{C}H_2$-), 78.2(d, S-CH_2-$\underline{C}H$(O)-), 126.6, 129.1, 129.8, 135.5($\underline{C}_6H_5$-), 159(s, -$\underline{C}$=N).

i.r. ν_{max} (thin film): 3022(m), 2980(s), 2920(s), 1620(m), 1480(s), 1460(s), 1440(s), 1029(m), 1090(m), 690(s).

m.s.: 221(M^+, 4%), 125(11), 124(75), 123(100), 109(5), 98(56), 77(21), 70(51), 45(54), 32(64).

$C_{12}H_{15}NOS$ requires *M* : 221.0874
found : 221.1203

<u>3-Phenyl-5-(phenylthiomethyl)-2-isoxazoline</u> (145c)[107].

The method employed was similar to that used for the preparation of 3-methyl-5-(phenylthiomethyl)-2-isoxazoline (145a).
(Yield : 0.72g, 54% m.p. : 74-75°C)
(t.l.c. (1:1 petroleum ether:ether) r_f=0.46)

^{1}H n.m.r. δ ($CDCl_3$): 2.85-3.60(m, 4H, PhS-$C\underline{H}_2$-CH and HC-$C\underline{H}_2$-C=N), 4.90(m, 1H, CH_2-$C\underline{H}$(O)-CH_2), 7.40(m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3060(w), 3030(w), 3000(s), 2980(s), 2910(m), 1600(w), 1580(m), 1480(s), 1440(s), 1360(s), 1200-1230(m), 910(s).

m.s.: 269(M^+, 21%), 146(100), 124(84), 123(60), 118(35), 109(8), 77(15).

$C_{16}H_{15}NOS$ requires M : 269.1820
found : 269.0721

3-[(Tetrahydro-2H-pyran-2-yl)-oxy]-methyl-5-(phenylthiomethyl)-2-isoxazoline (145d)[107].

The method employed was similar to that used for the preparation of 3-methyl-5-(phenylthiomethyl)-2-isoxazoline (145a).
(Yield : 0.23g, 32%)
(t.l.c. (ether) r_f=0.48)

^1H n.m.r. δ ($CDCl_3$): 1.30-2.00(br s, 6H, 3x$C\underline{H}_2$ of THP ring), 2.85-4.10(m, 6H, PhS-$C\underline{H}_2$-CH, HC-$C\underline{H}_2$-C=N and CH_2-$C\underline{H}_2$-O), 4.35(m, 2H, N=C-$C\underline{H}_2$-O), 4.40-5.10(m, 2H, O-$C\underline{H}$(O)-CH_2 and CH_2-$C\underline{H}$(O)-CH_2), 7.35(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3010(m), 2950(s), 2850(m), 1620(w), 1600(w), 1580(w), 1480(m), 1440(s), 1080(m), 1029(m).

m.s.: 307(M^+, 6%), 223(3), 184(4), 137(10), 125(7), 123(49), 109(8), 100(25), 85(100).

$C_{16}H_{21}NO_3S$ requires M : 307.1242
found : 307.1120

5-(Phenylthiomethyl)-3-(1-propylbutenyl)-2-isoxazoline (150a)[107].

The method employed was similar to that used for the preparation of 3-methyl-5-(phenylthiomethyl)-2-isoxazoline (145a).
(Yield : 1.2g, 61%)
(t.l.c. (1:1 petroleum ether:ether) r_f=0.51)

^{1}H n.m.r. δ ($CDCl_3$): 1.0(m,6H, 2x $C\underline{H}_3$-), 1.5(m, 2H, CH_3-$C\underline{H}_2$-CH_2) 2.3(m, 4H, -$C\underline{H}_2$-C=CH-$C\underline{H}_2$), 3.1(m, 4H, PhS-$C\underline{H}_2$-CH and HC-$C\underline{H}_2$-C=N), 4.7(m, 1H, CH_2-$C\underline{H}$(O)-CH_2), 5.7(m, 1H, CH_2-$C\underline{H}$=C mixture of (*E*)- and (*Z*)-isomers), 7.4(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3000(m), 2960(s), 2920(m), 2870(m) 1580(m), 1480(m), 1460(m), 1440(m).

m.s.: 289(M^+, 10%), 166(25), 124(28), 123(35), 55(100), 44(16), 41(27).

$C_{17}H_{23}NOS$ requires *M* : 289.1500
found : 289.1530

3-(Cycloheptenyl)-5-(phenylthiomethyl)-2-isoxazoline (150b)[107].

The method employed was similar to that used for the preparation of 3-methyl-5-(phenylthiomethyl)-2-isoxazoline (145a).
(Yield : 1.16g, 67%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.57)

^{1}H n.m.r. δ ($CDCl_3$): 1.20-2.00(br m, 6H, -($C\underline{H}_2$)$_3$-)), 2.12-2.50 (m, 2H, CH_2-$C\underline{H}_2$-C(-C=N)=), 2.50-2.80 (m, =C-$C\underline{H}_2$-CH_2), 2.91-3.50(m, 4H, PhS-$C\underline{H}_2$-CH and HC-$C\underline{H}_2$-C=N), 4.50-5.00(m, 1H, CH_2-$C\underline{H}$(O)-CH_2), 6.15(t, J=6Hz, 1H, -C=$C\underline{H}$-CH_2), 7.35(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3005(m), 2940(s), 2851(m), 1595(m), 1500(s), 1460(m), 1450(s), 1350(m), 1029(m), 700(s).

m.s.: 287(M^+, 22%), 164(74), 125(11), 124(79), 123(67), 95(100), 77(24), 67(44), 55(40), 53(14), 45(31), 41(47), 39(21), 32(18).

$C_{17}H_{21}NOS$ requires M : 287.1343
found : 287.1210

4-Amino-1-phenylthiopentan-2-ol (146a)[107].

A solution of the isoxazoline (145a) (0.1g, 0.48 mmol) in ether (15 ml) was added to a stirred ethereal (15 ml) suspension of lithium aluminium hydride (0.06g, 1.6 mmol). The reaction was stirred at room temperature for 2 hours until all the starting material had disappeared as judged by t.l.c. Aqueous sodium hydroxide solution (1 ml, 2 mmol, 2M) was added carefully and the reaction mixture filtered under suction. The solid residue was washed with brine (3 x 15 ml) and the combined aqueous washings extracted with ether (4 x 20 ml). The organic extracts were combined, dried and the solvent was removed *in vacuo* to yield the crude 4-amino-1-phenylthiopentan-2-ol (146a).
(Yield : 0.096g, 95%, colourless oil)
(t.l.c. (ether) r_f= baseline)

^1H n.m.r. δ ($CDCl_3$): 1.20(d, J=6Hz, 3H, $C\underline{H}_3$-CH(NH_2)-), 1.75 (m, 2H, CH-$C\underline{H}_2$-CH), 2.65(br m, 3H, -$N\underline{H}_2$, D_2O exchangeable, CH_3-$C\underline{H}$(NH_2)-CH_2), 3.00(m, 3H, PhS-$C\underline{H}_2$- and -CH_2-$C\underline{H}$(OH)-CH_2), 4.00(m, 1H, -OH, D_2O exchangeable), 7.4(m, 5H, $C_6\underline{H}_5$).

The crude 4-amino-1-phenylthiopentan-2-ol (146a) was used without

further purification in the following step. In subsequent analogues the intermediate γ-aminoalcohols were not isolated.

4-Benzoylamino-1-phenylthiopentan-2-ol (147a).

The crude 4-amino-1-phenylthiopentan-2-ol (146a) (0.096g, 0.46 mmol) was treated with benzoyl chloride (0.06g, 0.5 mmol) and triethylamine (0.1g, 1 mmol) in ether (10 ml). The white precipitate which formed was filtered off, and the ether removed *in vacuo*. The residue was chromatographed on silica to give 4-benzoylamino-1-phenylthiopentan-2-ol (147a), as a pale yellow oil.
(Yield : 0.12g, 85%)
(t.l.c. (ether) r_f= 0.29)

^{1}H n.m.r. δ ($CDCl_3$): 1.25(d, J=5Hz, 3H, $C\underline{H}_3$-CH(NH)-), 1.80(m, 2H, CH-$C\underline{H}_2$-CH), 2.80-3.40(m, 3H, PhS-$C\underline{H}_2$- and CH_3-$C\underline{H}$(NH)-CH_2-), 3.80(br s, 1H, -O$\underline{H}$), 4.25(m, 1H, CH_2-$C\underline{H}$(OH)-CH_2), 6.65(br s, 1H, -N$\underline{H}$), 7.30(m, 10H, 2 x aryl $C_6\underline{H}_5$).

^{13}C n.m.r. δ ($CDCl_3$): 21(q, $\underline{C}H_3$), 41, 42(t, S-$\underline{C}H_2$ and CH-$\underline{C}H_2$-CH), 44(d, $\underline{C}$H-NH), 68(d, $\underline{C}$H-OH), 126-135(8C, 2 x $\underline{C}_6H_5$), 167(s, $\underline{C}$=O).

i.r. ν_{max} ($CHCl_3$): 3400(br s), 3050(s), 1650(s), 1600(m), 1580(m), 1490(m).

m.s.: 316(M^++1, 41%), 298(67), 192(16), 188(32), 177(29), 176(100), 105(90), 77(21).

$C_{18}H_{21}NO_2S$ requires M+1 : 316.1366
found : 316.1369

4-Benzoylamino-1-phenylthiohexan-2-ol (147b).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-ol (147a).
(Yield : 0.45g, 76%, Colourless oil)
(t.l.c. (ether) r_f= 0.32)

^{1}H n.m.r. δ ($CDCl_3$): 0.9(t, J=7Hz, 3H, $C\underline{H}_3$-CH_2), 1.7(m, 4H, CH-$C\underline{H}_2$-CH and CH(NH)-$C\underline{H}_2$-CH_3), 3.1(m, 2H, PhS-$C\underline{H}_2$-), 3.4-4.3(m, 3H, CH_3-$C\underline{H}$(NH)-CH_2-, CH_2-$C\underline{H}$(OH)-CH_2 and -O$\underline{H}$), 6.7(br d, J=6Hz, 1H HC-N$\underline{H}$), 7.0-7.9(m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3420(br m), 3030(w), 3000(s), 2960(s), 2920(m), 2865(m), 1650(s), 1600(w), 1560(m), 1520(s), 1490(s), 1220(s), 910(s).

m.s.: 311(M^+-18, 0.1%), 282(5), 206(5), 190(22), 122(13), 105(100), 77(27).

4-Benzoylamino-4-phenyl-1-phenylthiobutan-2-ol (147c)

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-ol (147a).
(Yield : 0.28g, 66%, pale yellow oil)
(t.l.c. (ether) r_f= 0.41)

^{1}H n.m.r. δ ($CDCl_3$): 2.1(m, 2H, CH-$C\underline{H}_2$-CH), 2.7-3.2(m, 2H, PhS-$C\underline{H}_2$-CH(OH)), 3.4(br s, 1H, -O$\underline{H}$), 3.7(m, 1H, CH_2-$C\underline{H}$(OH)-CH_2), 5.2(m, 1H, Ph-$C\underline{H}$(NH)-CH_2-), 7.0-8.0(m, 16H, 3 x $C_6\underline{H}_5$- and -N$\underline{H}$).

i.r. ν_{max} ($CHCl_3$): 3400(br s), 3030(m), 3000(s), 2920(m), 1670-1650(s), 1600(m), 1580(s), 1530(s), 1500(s), 1450(m).

m.s.: 254(M^+-CH_2-SPh, 1.3%), 210(10), 146(11), 124(16), 123(12), 105(100), 77(47).

$C_{16}H_{16}NO_2$ requires M : 254.1181
found : 254.1397

4-Benzoylamino-1-phenylthio-5-(tetrahydro-2H-pyran-2-yl)-oxypentan-2-ol (147d).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-ol (147a).
(Yield : 0.23g, 54%, pale yellow oil)
(t.l.c. (ether) r_f= 0.20)

^1H n.m.r. δ ($CDCl_3$): 1.2-2.1(m, 8H, -($C\underline{H}_2$)$_3$- and CH-$C\underline{H}_2$-CH), 3.1(m, 2H, PhS-$C\underline{H}_2$-CH), 3.3-4.0(m, 6H, CH(NH)-$C\underline{H}_2$-O, CH_2-$C\underline{H}_2$-O, -O$\underline{H}$, and CH_2-C$\underline{H}$(OH)-CH_2), 4.1-5.0(m, 2H, CH_2-C$\underline{H}$(O)-O and CH_2-C$\underline{H}$(NH)-CH_2-), 6.9-7.0(br d, 1H, -CH(N$\underline{H}$)), 7.1-7.9(m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} (thin film): 3400(br s), 3060(m), 1670-1650(s), 1600(m), 1580(m), 1490(s), 1350(m) 1029(m), 910(s).

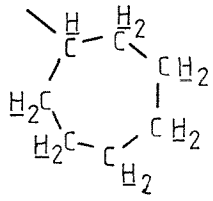
m.s.(EI): 208(0.4%), 205(0.4), 204(2.2), 192(9.1), 123(3.4), 122(10.6), 110(4.7), 105(100), 85(49.6), 77(35).

m.s.(CI/NH_3): 416(M^++1, 5%), 332(22), 167(11), 166(100), 105(8), 85(6).

$C_{23}H_{29}NO_4S$ requires M^++1 : 416.1895
found : 416.1875

4-Benzoylamino-4-cycloheptyl-1-phenylthiobutan-2-ol (151b).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-ol (147a).
(Yield : 0.22g, 33%, colourless oil)
(t.l.c. (ether) r_f= 0.57)

^{1}H n.m.r. δ ($CDCl_3$): 1.20-1.90(m, 13H, ),
1.95-2.20(m, 2H, CH-C<u>H</u>$_2$-CH), 3.00-3.50(m, 2H, PhS-C<u>H</u>$_2$-CH), 3.80-4.62(m, 3H, CH_2-C<u>H</u>(NH)-CH-, CH_2-C<u>H</u>(OH)-CH_2 and -O<u>H</u>), 6.80-8.00(m, 11H, 2 x C_6<u>H</u>$_5$ and -N<u>H</u>).

i.r. ν_{max} ($CHCl_3$): 3600-3200(s), 3060(m), 3000(s), 2920(s), 2850(s), 1650(br s), 1600(m), 1580(s), 1530(s), 1490(s), 1360(s), 1330(s), 1300(s).

m.s.: 396(M^+-1, 0.2%), 274(12), 174(23), 105(100), 77(32), 32(11).

$C_{24}H_{31}NO_2S$ requires M^+-1 : 396.1997
found : 396.2198

4-Benzoylamino-4-cycloheptenyl-1-phenylthio-butan-2-ol (152b).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-ol (147a).
(Yield : 0.045g, 15%, yellow oil)
(t.l.c. (ether) r_f= 0.42)

^{1}H n.m.r. δ ($CDCl_3$): 1.20-2.00(m, 8H, $-(C\underline{H}_2)_3-$ and $CH-C\underline{H}_2-CH$), 2.05-2.30(m, 4H, $\underline{H}_2C-C=CH-C\underline{H}_2$), 3.00-3.20 (m, 2H, $PhS-C\underline{H}_2-CH$), 3.65-3.90(m, 1H, $CH_2-C\underline{H}(OH)-CH_2$), 4.40-4.70(m, 2H, $CH_2-C\underline{H}(NH)-CH-$ and $-O\underline{H}$), 5.85(t, J=6Hz, $C=C\underline{H}-CH_2$), 6.73(br d, 1H, $-N\underline{H}$), 7.10-7.80 (m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3500-3200(m), 3060(m), 3000(s), 2920(s), 2855(s), 1650(s), 1600(m), 1580(s), 1530(s), 1490(s), 1450(s), 1440(s).

m.s.: 395(M^+, 0.1%), 228(22), 122(14), 105(100), 77(25).

$C_{24}H_{29}NO_2S$ requires *M* : 395.1919
found : 395.1901

4-Benzoylamino-1-phenylthio-5-propyl-5-octen-2-ol (152a).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-ol (147a).
(Yield : 0.04g, 3%, yellow oil)
(t.l.c. (ether) r_f= 0.58)

^{1}H n.m.r. δ ($CDCl_3$): 0.9-1.2(m, 6H, 2 x $C\underline{H}_3$), 1.3-2.2(m, 8H, $CH-C\underline{H}_2-CH$ and $C\underline{H}_2-C=CH-C\underline{H}_2-C\underline{H}_2$), 3.1(m, 2H, $PhS-C\underline{H}_2-CH$), 4.0-5.0(m, 3H, $CH_2-C\underline{H}(NH)-C=$, $CH_2-C\underline{H}(OH)-CH_2$ and $-O\underline{H}$), 5.5(t, J=6Hz, 1H, $CH_2-C\underline{H}=C$), 6.7(br s, 1H, $-N\underline{H}$), 7.1-7.8(m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3400-3200(br m), 3060(m), 3000(s), 2960(s), 2920(s), 2870(s), 1650(s), 1600(m), 1580(s)

1480(s), 1470(m), 1450(m), 1440(m), 1380(m), 1360(s), 1320(s).

m.s.: 397(M^+, 0%), 105(100), 85(12), 77(24), 55(10).

$C_{24}H_{31}NO_2S$ requires M : 397.2075
found : 397.2091

4-Benzoylamino-1-phenylthio-5-propyloctan-2-ol (153a).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-ol (147a).
(Yield : 0.4g, 30%, yellow oil)
(t.l.c. (ether) r_f= 0.66)

^{1}H n.m.r. δ ($CDCl_3$): 0.8-1.1(m, 6H, 2 x C$\underline{H}_3$), 1.2-1.8(m, 11H, CH-C$\underline{H}_2$-CH, and C$\underline{H}$(C$\underline{H}_2$-C$\underline{H}_2$)C$\underline{H}_2$-C$\underline{H}_2$), 3.2(m, 2H, PhS-C$\underline{H}_2$-CH), 4.2-4.8(m, 3H, CH_2-C$\underline{H}$(NH)-CH, CH_2-C$\underline{H}$(OH)-CH_2 and -O$\underline{H}$), 7.0(br s, 1H, -N$\underline{H}$), 7.1-8.3(m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3500-3250(m), 3060(s), 3000(s), 2960(s), 2880(s), 1650(s), 1600(m), 1580(s), 1480(s), 1440(m).

m.s.: 398(M^+-1, 1%), 174(17), 105(100), 77(25), 55(10).

$C_{24}H_{33}NO_2S$ requires M-1 : 398.2153
found : 398.2165

4-Benzoylamino-1-phenylthiopentan-2-one (148a).

Pyridinium chlorochromate (0.1g, 0.45 mmol) was added to a solution 4-4-benzoylamino-1-phenylthiopentan-2-ol (147a) (0.035g, 0.11 mmol) in methylene chloride (10 ml) at room temperature. The reaction was stirred for 2hr until all the starting material had disappeared as judged by t.l.c.

The reaction mixture was filtered, and the black gum washed with ether (3 x 5 ml) until granular in appearance. The organic washings were combined, dried and the solvent removed *in vacuo*. The residue was chromatographed on silica, to afford 4-benzoylamino-1-phenylthiopentan-2-one (148a) as a creamy crystalline solid.

(Yield : 0.014g, 40% m.p. : 122-3°C)
(t.l.c. (ether) r_f= 0.43)

^{1}H n.m.r. δ ($CDCl_3$): 1.25(d, 3H, J=6Hz, $C\underline{H}_3$-CH), 2.90(d, 2H, J=5Hz, O=C-$C\underline{H}_2$-CH), 3.70(s, 2H, PhS-$C\underline{H}_2$-C=O), 4.40(m, 1H, CH_3-C$\underline{H}$(NH)-CH_2), 6.70(m, 1H, N$\underline{H}$), 7.50(m, 10, 2x $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3430(br m), 3360(br m), 3040(m), 1720(s), 1660(s), 1600(m), 1580(m), 700(s).

m.s.(EI): 313(M^+, 0.4%), 149(26), 105(17), 94(100), 85(5), 43(27).

m.s.(CI/NH_3): 314(M^++1, 100%), 206(47), 178(73), 122(43), 105(42).

$C_{18}H_{19}NO_2S$ requires *M* : 313.1137
found : 313.1007

4-Benzoylamino-1-phenylthiohexan-2-one (148b).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-one (148a).
(Yield : 0.053g, 54% m.p. : 87-9°C)
(t.l.c. (ether) r_f= 0.41)

^{1}H n.m.r. δ ($CDCl_3$): 0.90(t, J=6Hz, 3H, $C\underline{H}_3$-CH_2), 1.55(qd, J=6Hz, J'=2Hz, 2H , CH_3-$C\underline{H}_2$-CH), 2.90(d, J=5Hz, 2H, O=C-$C\underline{H}_2$-CH), 3.68(s, 2H, PhS-$C\underline{H}_2$-C=O), 4.30 (m, 1H, CH_3-$C\underline{H}$(NH)-CH_2), 6.60(m, 1H, N$\underline{H}$), 7.50(m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3450(br m), 3160(m), 3080(w), 3040(m), 3010(w), 2980(s), 2940(s), 1720(s), 1660(s), 1600(w), 1580(m), 1520(s), 1500(s), 1390(m).

m.s.: 327(M^+, 4%), 206(14), 162(17), 123(10), 109(8), 105(100), 83(38), 77(44), 57(18), 55(15), 43(13).

$C_{19}H_{21}NO_2S$ requires *M* : 327.1293
found : 327.1384

4-Benzoylamino-4-phenyl-1-phenylthiobutan-2-one (148c).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-one (148a).
(Yield : 0.063g, 32%, m.p. : 108-114°C)
(t.l.c. (ether) r_f= 0.52)

^{1}H n.m.r. δ ($CDCl_3$): 3.30(dd, J=12Hz, J'=4Hz, 2H, O=C-$C\underline{H}_2$-CH), 3.60(s, 2H, PhS-$C\underline{H}_2$-C=O), 5.65(m, 1H, C_6H_5-$C\underline{H}$(NH)-CH_2)), 7.00-7.80(m, 15H, 3 x $C_6\underline{H}_5$), 8.20(m, 1H, N$\underline{H}$).

i.r. ν_{max} ($CHCl_3$): 3410(br m), 3060(m), 3000(s), 2980(s), 2920(s), 1720(s), 1660(s), 1600(m), 1580(s), 1510(s), 1490(s), 1029(m), 1070(m).

m.s.: 269(M^+-PhCOH, 1.1%), 210(1.2), 166(3), 146(8), 125(9), 124(9), 123(8), 109(9), 105(100), 77(55), 57(9).

$C_{23}H_{21}NO_2S$ requires *M*-PhCOH : 269.0874
found : 269.0882

4-Benzoylamino-1-phenylthio-5-(tetrahydro-2H-pyran-2-yl)--oxypentan-2-one (148d).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-one (148a).
(Yield : 0.032g, 32%, light yellow oil)
(t.l.c. (ether) r_f= 0.39)

^1H n.m.r. δ ($CDCl_3$): 1.30-1.90(m, 6H, $-(C\underline{H}_2)_3-$), 3.05(m, 2H, $O=C-C\underline{H}_2-CH$), 3.20-4.00(m, 7H, $PhS-C\underline{H}_2-C=O$, $CH_2-C\underline{H}(O)-O$, $CH_2C\underline{H}_2-O$ and $CH-C\underline{H}_2-O$), 4.53 (m, 1H, $CH_2-C\underline{H}(NH)-CH_2$), 7.05(m, 1H, $N\underline{H}$), 7.10-7.82(m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3420(br m), 3060(m), 3000(s), 2960(s), 2850(m), 1710(s), 1650(s), 1600(m), 1580(s), 1520(s), 1490(s), 1440(m), 1029(s), 1070(s), 910(s).

m.s.(EI): 329(M^+-DHP, 3%), 312(1), 206(8), 190(12), 105(100), 85(95), 109(4), 123(9), 122(15), 94(10), 77(10).

m.s.(CI/NH_3): 414(M^++1, 36%), 386(12), 332(11), 331(20), 330(100), 329(22), 312(29), 236(55), 235(29), 218(31), 105(29), 85(39).

$C_{23}H_{27}NO_4S$ requires *M*-DHP : 329.1086
found : 329.1062

4-Benzoylamino-1-phenylthio-5-propyloctan-2-one (153a).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-one (148a).
(Yield : 0.04g, 25%, colourless oil)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.42)

^1H n.m.r. δ ($CDCl_3$): 0.7-1.2(m, 6H, 2 x C$\underline{H}_3$), 1.3-2.0(m, 9H, C$\underline{H}$(C$\underline{H}_2$-C$\underline{H}_2$)C$\underline{H}_2$-C$\underline{H}_2$), 2.9(m, 2H, O=C-C$\underline{H}_2$-CH), 3.2(s, 2H, PhS-C$\underline{H}_2$-C=O), 4.4(m, 1H, CH_2-C$\underline{H}$(NH)-CH), 6.9-7.8 (m, 11H, N$\underline{H}$ and 2x 5 aryl C$\underline{H}$).

i.r. ν_{max} ($CHCl_3$): 3420(br m), 3300(br m), 3040(m), 3000(s), 2950(s), 2920(s), 2850(m), 1720(s), 1650(s), 1600(m), 1580(s), 1510(m), 1480(m), 1350(s).

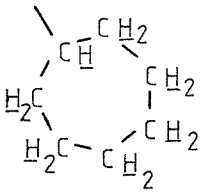
m.s.: 397(M^+, 0.4%), 296(14), 123(10), 109(8), 105(100), 77(44), 57(18).

$C_{24}H_{31}NO_2S$ requires *M* : 397.2075
found : 397.2075

4-Benzoylamino-4-cycloheptyl-1-phenylthiobutan-2-one (153b).

The method employed was similar to that used for the preparation of 4-benzoylamino-1-phenylthiopentan-2-one (148a).

(Yield : 0.020g, 15%, colourless oil)
(t.l.c. (ether) r_f= 0.63)

^{1}H n.m.r. δ ($CDCl_3$): 1.2-2.0(m, 13H, ),

2.3-3.5(m, 4H, PhS-C<u>H</u>$_2$-C=O and O=C-C<u>H</u>$_2$-CH),
4.1-4.2(m, 1H, CH_2-C<u>H</u>(NH)-CH),
6.9(m, 1H, N<u>H</u>), 7.0-8.1(m, 10H, 2 x 5 C_6<u>H</u>$_5$).

i.r. ν_{max} ($CHCl_3$): 3420(br w), 3300(br w), 3040(m), 3000(s), 2910(s), 2850(m), 1720(s), 1650(s), 1600(m), 1580(m), 1510(s), 1480(s), 1350(m).

m.s.(CI/NH_3): 396(M^++1, 13%), 286(15), 244(60), 105(100).

$C_{24}H_{29}NO_2S$ requires M+1 : 396.1997
found : 396.2211

<u>4-Benzoylamino-4-cycloheptenyl-1-phenylthiobutan-2-ol</u> (151b).

Di-*iso*-butylaluminium hydride in hexane (5.5 ml, 5.5 mmol, 1M) was added dropwise to a solution of 3-cycloheptenyl-5-phenylthiomethyl-2-isoxazoline (150b) (0.25g, 0.87 mmol) in ether (30 ml) at room temperature. The reaction was stirred for 2 hrs. until all the starting material had disappeared as judged by t.l.c.

Aqueous sodium hydroxide (1 ml, 2 mmol, 2M) was cautiously added to the reaction mixture, the resulting precipitate filtered and washed with aqueous saturated sodium potassium tartrate (5 ml) and ether (50 ml). The organic filtrate was separated and the aqueous phase extracted with ether (3 x 50 ml). The organic extracts were combined, dried and the solvent removed *in vacuo*. This crude material was

redissolved in ether (30 ml), treated with triethylamine (0.18g, 1.7 mmol) followed by benzoyl chloride (0.12g, 0.85 mmol). The white precipitate which formed was filtered off and the filtrate concentrated *in vacuo*. The residue was chromatographed on silica with 1:1 petroleum ether:ether as eluant to yield 4-benzoylamino-4-cycloheptenyl-1-phenylthiobutan-2-ol (151b) as a colourless oil.

(Yield : 0.3g, 87%)

Spectral data was consistent with the compound prepared *via* reduction with lithium aluminium hydride previously described.

4-Benzoylamino-1-phenylthio-5-propyloctan-2-ol (151a).

Prepared using the procedure described above. The spectral data was consistent with the compound previously described.

(Yield : 0.31g, 93%, colourless oil)

4-Chloro-2-methyl-1-phenylseleno-2-butene (216a) and 2-chloro-2-methyl-1-phenylseleno-3-butene (217a).

A solution of isoprene (10 ml) in CCl_4 (10 ml) was added to a solution of phenylselenenyl chloride (1.92g, 10 mmol) in CCl_4 (10 ml) at 0°C and stirred, during the addition a change from a dark red to a light yellow colour occurred. The reaction was allowed to warm up to ambient temperature and the solvent removed *in vacuo*. The yellow oil was chromatographed on silica using petroleum ether:ether (4:1) as eluant to afford an inseparable mixture of 4-chloro-2-methyl-1-phenylseleno-2-butene (216a) and 2-chloro-2-methyl-1-phenylseleno-3-butene (217a) as a yellow oil.
(Yield : 2g, 78%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.61)

Spectral data for the mixture:

^{1}H n.m.r. δ (CCl_4):	1.2-2.0(m, 6H, $C\underline{H}_3$-), 3.2-4.2(m, 6H, -$C\underline{H}_2$-Cl -$C\underline{H}_2$-Se & -$C\underline{H}_2$-Se), 4.5(m, 1H, $\underline{H}C{=}CH_2$), 5.0(m, 2H, $C\underline{H}_2{=}CH$), 5.1-5.8(m, 1H, CH_2-$C\underline{H}$=C(Me)-CH_2), 7.1-7.5(m, 10H, 2 x $C_6\underline{H}_5$).
i.r. ν_{max} (thin film):	3040(s), 3020(s), 2965(s), 2920(s), 1690(w), 1650(m), 1580(s), 1480(s), 1380(s), 1300(m), 1250(s), 1180(s), 1070(s), 1000(s), 740-750(s).
m.s.:	316(Ph_2Se_2, 20%), 315(6), 313(9), 312(36), 311(21), 310(25), 309(9), 308(11), 260(M^+, 2%), 234(21), 159(14), 158(24), 157(100), 156(22), 155(54), 154(37), 117(10), 78(31), 77(64), 75(13), 67(13), 65(14), 51(35), 50(19), 41(12), 39(17).
$C_{11}H_{13}{}^{35}Cl^{80}Se$ requires *M* :	260.0622
found :	260.0621

4-Chloro-1-phenylseleno-2-butene (216b) and 2-chloro-1-phenylseleno-3-butene (217b).

Phenylselenenyl chloride (4.73g, 24.6 mmol) in CCl_4 (30 ml) was stirred at ambient temperature for 15 minutes and the solution was cooled to -10°C. Butadiene was slowly bubbled through the solution over a period of 5-10 minutes until the dark red colour of the phenylselenenyl chloride was replaced by a light yellow colour. The solvent was removed *in vacuo* and the orange oil filtered through a glass filter paper to give a mixture of 4-chloro-1-phenylseleno-2-butene (216b) and 2-chloro-1-phenylseleno-3-butene (217b) in the ratio 2:3.
(Yield : 5.39g, 90%)

Spectral data for the mixture:

^{1}H n.m.r. δ (CCl_4): 3.30(m, >2H, -C<u>H</u>$_2$-SePh), 3.90(d, <2H, =CH-C<u>H</u>$_2$-Cl), 4.45(m, <1H, =CH-C<u>H</u>(CH_2)-Cl), 5.00-6.20(m, <3H, CH_2-C<u>H</u>=C<u>H</u>-CH_2 and <u>H</u>$_2$C=C<u>H</u>-CHCl-), 7.10-7.60(m, 5H, C_6<u>H</u>$_5$).

The ratio of 1,2- or 1,4-addition of phenylselenenyl chloride based on the δ3.90 and δ4.45 proton signals showed that the n.m.r. was consistent with a ratio of 3:2.

i.r. ν_{max} (CCl_4): 3060(m), 1580(s), 1480(s), 1440(s), 930(s), 690(s).

m.s.: 256(M^+, 11%), 211(11), 209(6), 159(11) 158(35), 157(53), 156(22), 155(34), 154(30), 153(15), 130(14), 129(13), 117(10), 91(34), 89(41), 78(66), 77(100), 75(21), 53(56), 50(25), 39(31).

$C_{10}H_{11}{}^{35}Cl^{80}Se$ requires M : 245.9714
found : 245.9718

<u>2-Chloro-1-phenylseleno-3-cyclopentene</u> **(217c).**

Phenylselenenyl chloride (5g, 26 mmol) in CCl_4 (30 ml) was stirred at room temperature for 15 minutes. The solution was cooled to -10°C and cyclopentadiene (2.57g, 39 mmol) was added dropwise over a period of 10 minutes so that the temperature was maintained at 0°C or below. The reaction was stirred for a further 30 minutes, during which time the deep red colour changed to a light yellow colour. The solvent and excess cyclopentadiene was removed *in vacuo*, and the yellow oil filtered through a glass fibre filter paper to give <u>2-chloro-1-phenylseleno-3-cyclopentene</u> (217c) and traces of <u>4-chloro-1-phenylseleno-2-cyclopentene</u> (216c).

(Yield : 6.00g, 90 %)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.68)

Spectral data for the mixture:

^{1}H n.m.r. δ ($CDCl_3$): 1.50(m, CH-C<u>H</u>$_2$-CH), 2.10-3.10(m, C<u>H</u>-Se, <u>H</u>C-C= and C<u>H</u>$_2$-C=), 3.80-4.90(m, C<u>H</u>-Cl), 5.50-6.00(m, HC-<u>H</u>C=C<u>H</u>-CH and CH_2-C<u>H</u>=C<u>H</u>-CH), The combined integrals for the above signals is 6H.
7.00-7.70(m, 5H, C$_6$<u>H</u>$_5$).

After 2 weeks at -4°C isomerisation occurred to give mainly the 1,4-product <u>4-chloro-1-phenylseleno-2-cyclopentene</u> (216c); the ^{1}H n.m.r. changed with the increase of signals at δ5.80 and δ6.00 and disappearance of the signals at δ5.90 (*i.e.* changes in vinylic protons).

i.r. ν_{max} (thin film): 3060(s), 2980(m), 1580(s), 1480(s), 1440(s), 1350(s), 1300(m), 1230(m), 1190(m), 1150(m), 1070(m), 1025(s), 1000(m), 920(m), 900(m), 785(m), 740(s), 695(s), 670(m).

m.s.: 314($(PhSe)_2$, 24%), 312(22), 260(13), 258(M^+, 25%), 256(11), 234(11), 158(100), 157(61), 156(49), 155(37), 154(44), 103(27), 101(73), 78(42), 77(60), 66(51), 65(71), 51(22), 43(26), 39(29).

$C_{11}H_{11}{}^{35}Cl^{80}Se$ requires *M* : 257.9714
found : 257.9872

2-Chloro-1-phenylseleno-3-cyclohexene (217d).

Phenylselenenyl chloride (1.5g, 7.8 mmol) in CCl_4 (10 ml) was stirred at room temperature for 15 minutes. The solution was cooled to -10°C and 1,3-cyclohexadiene (1g, 12.5 mmol) in CCl_4 was added dropwise over a period of 10 minutes so that the temperature was maintained at 0°C or below. The reaction was stirred for a further 30 minutes, during which time the deep red colour changed to a light yellow colour. The solvent and excess 1,3-cyclohexadiene was removed *in vacuo*, and the orange oil filtered through a glass fibre filter paper to give 2-chloro-1-phenylseleno-3-cyclohexene (217d).
(Yield : 2.0g, 95 %)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.65)

^1H n.m.r. δ ($CDCl_3$): 2.10(m, 4H, CH-($C\underline{H}_2$)$_2$-CH), 3.65(m, 1,H, C$\underline{H}$-Se), 4.50(m, 1H, C$\underline{H}$-Cl), 5.70(m, 2H, CH_2-C$\underline{H}$=C$\underline{H}$-CH), 7.00-7.70(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} (thin film): 3080(m), 3040(m), 2960(m), 2920(m), 1480(s), 1440(s), 1225(s), 700(s).

m.s.: 314($(PhSe)_2$, 8%), 272(M^+, 6%), 158(14), 157(15), 79(100), 78(17), 77(37).

$C_{12}H_{13}{}^{35}Cl^{80}Se$ requires M : 271.9868
found : 271.9842

Methyl-(2-methoxycarbonyl-5-methyl-6-phenylseleno)-4-hexenoate (223a).

A solution of dimethyl malonate (0.38g, 2.8 mmol) in THF (2 ml) was added dropwise to a suspension of sodium hydride (0.1g, 4.1 mmol) in THF (10 ml) at room temperature. The reaction mixture was stirred for 10 minutes. To this was added a solution of (216a) and (217a) (0.68g, 2.6 mmol) in THF (10 ml). The reaction was heated under reflux for 4

hrs until all the starting material had disappeared as judged by t.l.c. Water (1 ml) was added carefully followed by saturated sodium chloride solution (5 ml). The aqueous phase was separated and extracted with ether (3 x 50 ml). The organic extracts were combined, dried and concentrated *in vacuo*. The residue was chromatographed on silica to afford methyl-(2-methoxycarbonyl-5-methyl-6-phenylseleno)-4-hexenoate (223a) as a yellow oil.
(Yield : 0.56g, 60%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.39)

^{1}H n.m.r. δ ($CDCl_3$): 1.79(br s, 3H, $\underline{H}_3C-C(CH_2)=CH$), 2.40(m, 2H, $=C-C\underline{H}_2-CH$), 3.20(m, 1H, $CH_2-C\underline{H}(CO_2Me)_2$), 3.55(m, 2H, $PhSe-C\underline{H}_2-C(CH_3)=$), 3.70(s, 6H, 2 x $OC\underline{H}_3$), 5.10(m, 1H, $CH_2-C\underline{H}=C(CH_3)CH_2$), 7.40(m, 5H, $C_6\underline{H}_5$).

The ^{1}H n.m.r. was confirmed by proton decoupling experiments.

i.r. ν_{max} (thin film): 3060(m), 3040(m), 2980(m), 2825(m), 1760-1740(s), 1580(m), 1480(s), 1440(s), 1340(m), 740(s), 690(s).

m.s.: 356(M^+, 2.5%), 354(1.5), 199(91), 157(15), 139(75), 111(13), 107(50), 81(15), 80(18), 79(100), 77(31), 59(48), 55(21), 53(21), 41(27), 39(22).

$C_{16}H_{20}O_4{}^{80}Se$ requires *M* : 356.0526
found : 356.0600

Methyl-(2-methoxycarbonyl-6-phenylseleno)-4-hexenoate (223h).

A solution of dimethyl malonate (1.07g, 8 mmol) in THF (2 ml) was added to a suspension of sodium hydride (0.2g, 8.3 mmol) in THF (20 ml). HMPA (0.5 ml) was added, and then the mixture of chloroselenides (216b) and

(217b) (1g, 4 mmol) in THF (2 ml). The reaction was stirred for 6 days at room temperature. Water (1 ml) was added carefully followed by saturated sodium chloride solution (3 ml). The aqueous phase was separated and extracted with ether (3 x 20 ml). The organic extracts were combined, dried and concentrated *in vacuo*. The residue was chromatographed on silica to afford a mixture of methyl-(2-methoxycarbonyl-6-phenylseleno)-4-hexenoate (223h) and methyl-(2-methoxycarbonyl-3-phenylselenomethyl)-4-pentenoate (228h) in the ratio 1:1.

Physical data for methyl-(2-methoxycarbonyl-6-phenylseleno)-4--hexenoate (223h) (*E*)- and (*Z*)- isomers:
(Yield : 0.47g, 34%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.24)

^{1}H n.m.r. δ ($CDCl_3$) 360 MHz: 2.52(m, 2H, =C-C$\underline{H}_2$-CH$(CO_2Me)_2$), 3.30 (m, 1H, $CH_2C\underline{H}(CO_2Me)_2$), 3.41(m, 2H, =CH-C$\underline{H}_2$Se), 3.81(s, 3H, O$C\underline{H}_3$), 3.82 (s, 3H, O$C\underline{H}_3$), 5.20(m, 1H, $\underline{H}C$-CH_2-CH), 5.71(m, 1H, =C$\underline{H}CH_2$Se), 7.20-7.90(m, 5H, $C_6\underline{H}_5$).

^{13}C n.m.r. δ ($CDCl_3$) 90.56 MHz: 29.56($\underline{C}H_2$Se), 31.45($\underline{C}H_2$Se), 41.1($\underline{C}H_2$CH=CH), 45.8($\underline{C}H_2$CH=CH), 52.29, 52.40, 52.50, 52.9 (O$\underline{C}H_3$), 55.6($\underline{C}H(CO_2Me)_2$), 126.0-137.0 (very complex due to PhSeSePh contamination $\underline{C}_6H_5$ and $\underline{C}H$=$\underline{C}H$), 166.9, 167.5, 167.6, 168.1 ($\underline{C}$=O).

i.r. ν_{max} (thin film): 3080(w), 3005(m), 2960(m), 2850(w), 1765(s), 1750(s), 1585(m), 1482(m), 1440(s).

m.s.: 342(M^+, 1.9%), 288(10), 185(80), 157(25), 155(14), 125(80), 121(23), 109(19), 93(53), 85(18), 78(29), 77(45), 67(22), 65(32),

59(100), 51(32).

$C_{15}H_{18}O_4{}^{80}Se$ requires *M* : 342.0370
found : 342.0401

Physical data for methyl-(2-methoxycarbonyl-3-phenylselenomethyl)-4--pentenoate (228h):

(Yield : 0.45g, 34%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.26)

^{1}H n.m.r. δ ($CDCl_3$) 360 MHz: 3.15(m, 3H, $SeC\underline{H}_2$, and $C\underline{H}$-C=CH_2), 3.74 (m, 6H, 2 x $OC\underline{H}_3$), 3.81(m, 1H, $C\underline{H}(CO_2Me)_2$), 5.11(m, 2H, C=$C\underline{H}_2$), 5.82(m, 1H, $\underline{H}C$=CH_2), 7.20-7.60(m, 5H, $C_6\underline{H}_5$).

^{13}C n.m.r. δ ($CDCl_3$) 90.56 MHz: 30.9($\underline{C}H_2Se$), 44.15($H\underline{C}$-CH=CH_2), 52.29, 52.40 (2x $O\underline{C}H_3$), 55.74($H\underline{C}(CO_2Me)_2$), 118.2($H_2\underline{C}$=), 127.11, 129.12, 130.16, 133.02, 136.83($\underline{C}_6H_5$ and $H\underline{C}$=CH_2), 168.14, 168.42(2 x $\underline{C}$=O).

i.r. ν_{max} (CCl_4): 3080(w), 3010(w), 2980(w), 2860(w), 1765(s), 1745(s), 1650(w), 1580(w), 1480(m), 1440(s).

m.s.: 185(M^+-SePh, 18%), 125(30), 121(17), 93(27), 91(46), 85(64), 77(37), 67(27), 59(100), 53(37).

1-Ethylthio-4-phenylseleno-2-butene (223i)

Ethanethiol (0.47g, 0.6 ml, 8 mmol) was added dropwise to a stirred suspension of sodium hydride (0.2g, 8.3 mmol) in THF (10 ml) at room temperature. The reaction mixture was stirred for 30 min. and the chloroselenides (216b) and (217b) (1g, 4 mmol) added slowly. The reaction mixture was stirred for a further 3 hours. Water (1 ml) was added carefully followed by saturated sodium chloride solution (3 ml).

The aqueous phase was separated and extracted with ether (3 x 20 ml). The organic extracts were combined, dried and concentrated *in vacuo*. The residue was chromatographed on silica to afford 1-ethylthio-4-phenylseleno-2-butene (223i) as a yellow oil.
(Yield : 0.6g, 55%)
(t.l.c. (9:1 petroleum ether:acetone) r_f= 0.51)

^{1}H n.m.r. δ (CCl_4): 1.20(t, J=8Hz, 3H, $C\underline{H}_3CH_2$), 2.25(q, J=8Hz, 2H, $CH_3C\underline{H}_2$), 2.95(d, J=6Hz, 2H, S-$C\underline{H}_2$-CH=), 3.45(m, 2H, Se-$C\underline{H}_2$-CH=), 5.45(m, 2H, $\underline{H}C=C\underline{H}$), 7.00-7.60(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} (CCl_4): 3080(m), 3020(w), 2980(m), 2940(m), 2880(w), 1580(s), 1480(s), 1025(m), 965(s), 700(s).

m.s.: 272(M^+, 1.5%), 157(100), 77(20), 122(10).

$C_{12}H_{16}S^{80}Se$ requires *M* : 272.0138
found : 272.0111

3-Methyl-1-phenoxy-4-phenylseleno-2-butene (223b)

Phenol (0.60g, 6.3 mmol) in THF (13 ml) was added dropwise to a stirred suspension of sodium hydride (0.15g, 6.25 mmol) in THF (10 ml) at room temperature. HMPA (0.25 ml, 1.38 mmol) and sodium iodide (0.02g, 0.13 mmol) were added and the reaction mixture stirred for 30 min. The chloroselenides (216a) and (217a) (0.25g, 0.96 mmol) in THF (5 ml) were added dropwise and the reaction mixture heated under reflux for 4 hours. The aqueous work up described in the preceding experiment was used to afford after chromatography on silica 3-methyl-1-phenoxy-4-phenylseleno-2-butene (223b) as a yellow oil.
(Yield : 0.21, 70%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.62)

^{1}H n.m.r. δ ($CDCl_3$): 1.85(br s,3H, $\underline{H}_3C$-C=), 3.45(m, 2H, PhSe-C$\underline{H}_2$), 4.40(d, J=6Hz, 2H, =CH-C$\underline{H}_2$OPh), 5.40(t, J=6Hz, 1H, =C$\underline{H}$-CH_2OPh), 6.70-7.70(m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} (CCl_4): 3080(s), 3000(w), 2980(w), 2930(m), 1680(m), 1660(m), 1600(s), 1590(s), 1580(s), 1500(s), 1480(s), 1440(s).

m.s.: 318(M^+, 1.2%), 227(19), 226(16), 225(100), 223(44), 222(19), 221(18), 161(31), 160(46), 159(21), 158(15), 157(60), 155(31), 154(16), 153(16), 147(10), 144(29), 143(27), 107(13), 94(39), 77(75).

$C_{17}H_{18}O^{80}Se$ requires M : 318.0523
found : 318.0594

<u>3-Methyl-1-(2-allyl)-phenoxy-4-phenylseleno-2-butene</u> (223c)

A similar procedure as described for the preparation of 3-methyl-1-phenoxy-4-phenylseleno-2-butene (223b) was applied.
(Yield : 0.25g, 36%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.63)

^{1}H n.m.r. δ (CCl_4): 1.90(m, 3H, $\underline{H}_3C$-C=), 3.40(m, 4H, Se$\underline{CH}_2$- and H_2C=CH-C$\underline{H}_2$), 4.0-4.8(m, 2H, O-C$\underline{H}_2$), 4.9-5.3 (m, 2H, $\underline{H}_2C$=CH), 5.4-6.3(m, 2H, =C$\underline{H}$-CH_2O and $\underline{H}C$=CH_2), 6.5-7.7(m, 9H, $C_6\underline{H}_5$ and $C_6\underline{H}_4$).

i.r. ν_{max} (CCl_4): 3080(s), 3040(m), 2910(s), 2860(m), 1645(s), 1600(s), 1580(s), 1500(s), 1480(s), 1455(s), 1440(s).

m.s.: 225(M^+-OAr, 10%), 157(15), 145(16), 144(15), 143(15), 107(29), 105(15), 78(32), 77(61),

67(51), 55(48), 53(40), 51(46), 43(46), 41(100), 39(64).

3-Methyl-4-phenylseleno-1-phenylthio-2-butene (223e)

A similar procedure as described for the preparation of 3-methyl-1-phenoxy-4-phenylseleno-2-butene (223b) was applied.
(Yield : 0.59g, 60%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.61)

^{1}H n.m.r. δ (CCl_4): 1.85(br s, 3H, $\underline{H}_3C$-C=), 3.35(m, 4H, PhSe$C\underline{H}_2$ and PhS$C\underline{H}_2$), 5.40(m, 1H, $CH_2C\underline{H}$=), 7.50(m, 10H, 2 x $C_6\underline{H}_5$).

i.r. ν_{max} (thin film): 3040(s), 3010(m), 3000(m), 2990(m), 2920(m), 1580(s), 1480(s), 1440(s), 1380(m), 1300(m), 1180(m), 1075(s), 1029(s), 1010(m), 905(m), 750(s), 700(s).

m.s.: 334(M^+, 1%), 257(10), 225(50), 157(100), 155(33), 154(26), 153(16), 148(20), 147(15), 144(29), 143(37), 107(23), 94(19), 77(75), 68(12).

$C_{17}H_{18}S^{80}Se$ requires *M* : 334.0290
found : 334.0322

1-Acetylphenylamino-3-methyl-4-phenylseleno-2-butene (223d)

A similar procedure as described for the preparation of 3-methyl-1-phenoxy-4-phenylseleno-2-butene (223b) was applied.
(Yield : 0.091g, 14%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.09)

^{1}H n.m.r. δ (CCl_4): 1.65(br s, 3H, $\underline{H}_3C$-C=), 1.80(s, 3H, $C\underline{H}_3C$=O), 3.50-4.40(m, 4H, $SeC\underline{H}_2$ and $NC\underline{H}_2$), 5.30(m, 1H, $\underline{H}C(CH_2)$=C), 7.00-7.60(m, 10H, 2x $C_6\underline{H}_5$).

i.r. ν_{max} (CCl_4): 3060(w), 2980(w), 2920(m), 2850(w), 1670(s), 1600(s), 1580(w), 1500(m), 1480(m), 1440(s), 1395(s).

m.s.: 314(0.1%), 225(0.2), 202(100), 160(73), 157(7), 104(38), 93(16), 78(10), 77(25), 43(35), 41(6).

m.s.(CI/NH_3): 360(M^++1, 13%), 202(100), 160(73), 157(7), 104(37), 93(16), 78(9), 77(25), 43(32), 41(8).

$C_{19}H_{21}ON^{80}Se$ requires M+1 : 360.0866
found : 360.0799

3-Methyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)-phenoxy]-4-phenylseleno-2-butene (223g).

A similar procedure as described for the preparation of 3-methyl-1-phenoxy-4-phenylseleno-2-butene (223b) was used.
(Yield : 0.25g, 27%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.42)

^{1}H n.m.r. δ (CCl_4): 1.70(s, 3H, $C\underline{H}_3$-CO_2), 1.85(br s, 3H, $\underline{H}_3C$-C=), 3.50(m, 2H, $SeC\underline{H}_2$), 3.70(m, 4H, O-$(C\underline{H}_2)_2$-O), 4.45(d, J=6Hz, 2H, O-$C\underline{H}_2$-CH=), 5.45(t, J=6Hz, 1H, O-CH_2-$C\underline{H}$=), 6.60-7.70(m, 9H, $C_6\underline{H}_5$ and $C_6\underline{H}_4$).

i.r. ν_{max} (CCl_4): 3080(m), 3060(m), 2980(s), 2940(m), 2880(s), 1680(m), 1600(s), 1580(s), 1490(s), 1480(s), 1370(s).

m.s.: 404(M^+, 0.3%), 225(100), 223(51), 157(29), 144(25), 121(22), 87(25), 67(28), 43(37),

$C_{21}H_{24}O_3{}^{80}Se$ requires M : 404.0890
found : 404.0863

4-Isopropenyl-2-methoxycarbonyl-4-butanolide (237).

Methyl-(2-methoxycarbonyl-5-methyl-6-phenylseleno)-4-hexenoate (223a) (0.1g, 0.28 mmol) in CCl_4 (10 ml) and pyridine (0.02g, 0.28 mmol) was treated dropwise with hydrogen peroxide (0.5 ml, 30%) at 0°C. The reaction was ultrasonicated in an ultrasonic bath for 5 minutes or until all the starting material had been consumed as judged by t.l.c. Aqueous saturated sodium bisulphite solution was added carefully (approx. 1 ml or until effervescence had ceased). The organic phase was separated and the aqueous layer extracted with ether (3 x 25 ml). The organic extracts were combined, dried and concentrated *in vacuo*. Chromatography on silica afforded 4-isopropenyl-2-methoxycarbonyl-4-butanolide (237) as a colourless oil.
(Yield : 0.04g, 80%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.19)

^{1}H n.m.r. δ (CCl_4): 1.80(br s, 3H, $\underline{H}_3C$-C=), 2.45(m, 2H, CH-C$\underline{H}_2$-CH), 3.40(m, 1H, O=C-C$\underline{H}$), 3.70(m, 1H, O-C$\underline{H}$-CH_2), 3.80(s, 3H, OC$\underline{H}_3$) 4.95, 5.05(br s, 2H, $\underline{H}_2$C=).

i.r. ν_{max} (CCl_4): 3080(w), 2980(m), 2950(s), 2920(m), 2840(m), 1780(s), 1740(s), 1650(w), 1550(m), 1450(s), 1440(s), 1380(m), 1350(m).

m.s.: 184(M^+, 3%), 169(11), 152(21), 139(15), 137(34), 125(46), 124(17), 114(12), 109(15), 98(10), 87(34), 81(66), 79(33), 41(31), 39(35), 55(100).

$C_9H_{12}O_4$ requires *M* : 184.0735
found : 184.0809

$C_9H_{12}O_4$ requires : %C 58.69: %H 6.57: %O 34.74
found : %C 58.51: %H 6.41: %O 34.61

2-Methoxycarbonyl-4-vinyl-4-butanolide (242) and methyl-(2-methoxycarbonyl-3-methylene)-4-pentenoate (243).

The same procedure as described for the preparation of 4-isopropenyl-2-methoxycarbonyl-4-butanolide (237) was applied to a mixture of methyl-(2-methoxycarbonyl-6-phenylseleno)-4-hexenoate (223h) and methyl-(2-methoxycarbonyl-3-phenylselenomethyl)-4-pentenoate (228h) in the ratio 2:3.

The procedure yielded a mixture of products 2-methoxycarbonyl-4-vinyl-4-butanolide (242) and methyl-(2-methoxycarbonyl-3-methylene)-4-pentenoate (243) as oils in the ratio of 5:1 respectively.

Spectral data for 2-methoxycarbonyl-4-vinyl-4-butanolide (242):

(Yield : 0.39g, 51%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.40)

^{1}H n.m.r. δ (CCl_4): 2.00-3.00(m, 2H, CH-C<u>H</u>$_2$-CH), 3.40 and 3.45 (two s, 1H, O=C-C<u>H</u> diastereoisomers) 3.70 and 3.78(two s, 3H, OC<u>H</u>$_3$ diastereoisomers), 4.05(m, 1H, O-C<u>H</u>), 4.90-6.10(m, 3H, <u>H</u>C=C<u>H</u>$_2$).

i.r. ν_{max} (CCl_4): 3000(w), 2950(w), 1800(s), 1750(s), 1450(m).

m.s.: 170(*M*$^+$, 2%), 138(26), 132(17), 125(20), 114(75), 111(68), 110(27), 100(18), 69(17), 67(42), 55(100).

$C_8H_{10}O_4$ requires *M* : 170.0579
found : 170.0540

Spectral data for methyl-(2-carboxymethyl-3-methylene)-4-pentenoate (243):

(Yield : 0.008g, 9.4%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.65)

^{1}H n.m.r. δ (CCl_4): 3.70(s, 6H, 2x $OC\underline{H}_3$), 4.25(s, 1H, $C\underline{H}(CO_2Me)_2$) 5.00-5.30(m, 4H, $HC=C\underline{H}_2$ and $C=C\underline{H}_2$), 6.3(m, 1H, $\underline{H}C=CH_2$).

i.r. ν_{max} (CCl_4): 3000(w), 2950(w), 1770(s), 1745(s), 1600(w), 1440(m).

u.v. λ_{max} (EtOH): 269(919), 262(1104), 216(10488).

m.s.: Too thermally labile to obtain a mass spectrum, sample decomposed on probe.

3-Methyl-1-phenoxy-3-buten-2-ol (236b).

The same procedure as described for the preparation of 4-isopropenyl-2-methoxycarbonyl-4-butanolide (237) was applied to 3-methyl-1-phenoxy-4-phenylseleno-2-butene (223b).
(Yield : 0.034g, 60%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.40)

^{1}H n.m.r. δ (CCl_4): 1.82(d, J=1Hz, 3H, $\underline{H}_3C-C=CH_2$), 2.60(s, 1H, -O$\underline{H}$), 3.90(m, 2H, PhO-$C\underline{H}_2$), 4.40(m, 1H, HO-C$\underline{H}$), 4.90, 5.10(two br s, 2H, $=C\underline{H}_2$), 6.80-7.30(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} (CCl_4): 3500(m), 3080(m), 3040(m), 2980(m), 2920(s), 2880(m), 1600(s), 1590(s), 1500(s), 1490(s), 1455(s), 1300(s), 900(s).

m.s.: 178(M^+, 1%), 171(13), 167(11), 161(25) 160(19), 159(16), 157(15), 149(29), 107(19), 94(48), 91(33), 78(21), 77(38), 71(26), 69(17), 67(20), 65(22), 57(30), 55(30), 43(100), 41(35), 39(17).

$C_{11}H_{14}O_2$ requires M : 178.0994
found : 178.0981

<u>3-Methyl-1-(2-allyl)-phenoxy-3-buten-2-ol</u> (236c).

The same procedure as described for the preparation of 4-isopropenyl-2-methoxycarbonyl-4-butanolide (237) was applied to 3-methyl-1-(2-allyl)-phenoxy-4-phenylseleno-2-butene (223c).
(Yield : 0.03g, 50%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.40)

^{1}H n.m.r. δ (CCl_4): 1.80(br s, 3H, $\underline{H}_3C-C=CH_2$), 2.40(s, 1H, -O$\underline{H}$), 3.40(br d, J=6Hz, 2H, $C\underline{H}_2-CH=CH_2$), 3.90(m, 2H, ArO-$C\underline{H}_2$), 4.40(m, 1H, HO-C$\underline{H}$), 5.00(m, 4H, 2 x =$C\underline{H}_2$), 6.00(m, 1H, C$\underline{H}$=CH_2), 7.00(m, 4H, $C_6\underline{H}_4$).

i.r. ν_{max} (CCl_4): 3400(w), 3080(m), 2980(m), 2920(m), 2880(w), 1650(s), 1640(m), 1602(m), 1580(m), 1500(s), 1450(s), 1250(s).

m.s.: 218(M^+, 20%), 148(23), 147(12), 133(46), 134(100), 132(22), 131(16), 119(42), 117(13), 115(20), 107(22), 92(12),

91(35), 78(11), 77(19), 71(48), 43(22), 41(20), 39(21).

$C_{14}H_{18}O_2$ requires *M* : 218.1302
found : 218.1190

1-Acetylphenylamino-3-methyl-3-buten-2-ol (236d).

The same procedure as described for the preparation of 4-isopropenyl-2-methoxycarbonyl-4-butanolide (237) was applied to 1-acetylphenylamino-3-methyl-4-phenylseleno-2-butene (223d).
(Yield : 0.03g, 55%)
(t.l.c. (ether) r_f= 0.20)

^{1}H n.m.r. δ (CCl_4): 1.65(br s, 3H, $\underline{H}_3C-C=CH_2$), 1.80(s, 3H, $C\underline{H}_3-C=O$), 3.30-4.10(m, 4H, -O$\underline{H}$, HO-C$\underline{H}$ and N-C$\underline{H}_2$), 4.80, 5.00(two br s, 2H, =C$\underline{H}_2$), 7.20-7.60(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} (CCl_4): 3400(br m), 3060(w), 2980(w), 2920(m), 1660(s), 1600(s), 1500(s), 1440(m), 1300(m).

m.s.: 202(M^+-OH, 1.3%), 136(19), 107(13), 106(100), 93(15), 77(10), 43(22).

m.s. (CI/NH_3): 238(M^++NH_4, 3.1%), 220(M^++1, 44%), 106(100).

$C_{13}H_{17}NO_2$ requires *M*+1 : 220.1337
found : 220.1301

3-Methyl-1-phenylthio-3-buten-2-ol (236e).

The same procedure as described for the preparation of 4-isopropenyl-2-methoxycarbonyl-4-butanolide (237) was applied to 3-methyl-4-

phenylseleno-1-phenylthio-2-butene (223e).
(Yield : 0.2g, 20%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.20)

^{1}H n.m.r. δ (CCl_4):	1.70(br s, 3H, $\underline{H}_3C$-C=CH_2), 2.80(s, 1H, -O$\underline{H}$), 3.05(m, 2H, PhS-$C\underline{H}_2$), 4.00(m, 1H, HO-C$\underline{H}$), 4.90, 5.10(two br s, 2H, =$C\underline{H}_2$), 7.30(m, 5H, $C_6\underline{H}_5$).
i.r. ν_{max} (thin film):	3400(s), 3070(w), 3060(w), 2990(m), 2920(m), 1580(s), 1480(s), 1030(s), 900(m).
m.s.:	194(M^+, 8.5%), 124(98), 123(58), 110(23), 109(16), 91(12), 78(15), 77(21), 71(47), 51(15), 39(17), 32(100).
$C_{11}H_{14}OS$ requires *M* :	194.0762
found :	194.0810

3-Methyl-1-phenoxy-3-buten-2-one (251b) and 3-methyl-1-phenoxy-1,3-butadiene (252b)

3-Methyl-1-phenoxy-4-phenylseleno-2-butene (223b) (0.28g, 0.88 mmol) in THF (10 ml) was treated with a solution of *m*-chloroperbenzoic acid (90%, 0.17g, 0.88 mmol) in THF (5 ml) at -10°C. The reaction was stirred for 30 minutes or until all the starting material had disappeared as judged by t.l.c. The reaction mixture was then added to boiling CCl_4 (20 ml) and heated under reflux for 10 minutes. The reaction mixture was concentrated *in vacuo* and chromatographed on silica to afford a mixture of 3-methyl-1-phenoxy-3-buten-2-one (251b) and 3-methyl-1-phenoxy-1,3-butadiene (252b) as oils.

Spectral data for 3-methyl-1-phenoxy-3-buten-2-one (251b):
(Yield : 0.019g, 25%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.42)

^{1}H n.m.r. δ (CCl_4):	1.90(d, J=2Hz, $\underline{H}_3C-C=CH_2$), 4.80(s, 2H, $O=C-C\underline{H}_2-O$), 5.80-6.05(m, 2H, $=C\underline{H}_2$), 6.65-7.30(m, 5H, $C_6\underline{H}_5$).
i.r. ν_{max} ($CHCl_3$):	3500(w, enol), 3100(w), 3050(m), 3020(s), 3000(s), 2960(m), 2920(s), 1690(s), 1640(m), 1600(s), 1580(s), 1500(s), 1460(m), 1440(m), 1380(m), 1250(s).
m.s.:	176(M^+, 100%), 133(32), 107(55), 94(49), 83(30), 77(73), 69(89).
$C_{11}H_{12}O_2$ requires *M* :	176.0837
found :	176.0801

Spectral data for 3-methyl-1-phenoxy-1,3-butadiene (252b):
(Yield : 0,018g, 25%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.58)

^{1}H n.m.r. δ (CCl_4):	1.80(br s, 3H, $\underline{H}_3C-C=CH_2$), 4.42-4.60(m, 4H, $=C\underline{H}_2$ and $\underline{H}C=C\underline{H}-O$), 6.50-7.50(m, 5H, $C_6\underline{H}_5$).
i.r. ν_{max} ($CHCl_3$):	3010(s), 2980(m), 2915(m), 1600(s), 1590(m), 1580(m), 1495(s), 1480(s), 1440(s), 1220(s).
m.s.:	160(M^+, 29%), 94(24), 78(32), 77(100), 67(22), 65(30), 51(32), 50(23), 41(20), 39(23).

$C_{11}H_{12}O$ requires *M* : 160.0888
found : 160.0853

Selective preparation of 1-phenoxy-3-buten-2-one (251b).

The same procedure for the preparation of a mixture of 1-phenoxy-3-buten-2-one (251b) and 3-methyl-1-phenoxy-1,3-butadiene (252b) was used except that 2 mole equivalents of *m*CPBA (0.24g, 90%, 1.3 mmol) was used to afford 1-phenoxy-3-buten-2-one (251b).
(Yield : 0.049g, 44%)
Spectral data was consistent with the earlier preparation.

3-Methyl-1-(2-allyl)-phenoxy-3-buten-2-one (251c).

The same procedure was used as for the selective preparation of 3-methyl-1- phenoxy-3-buten-2-one (251b) to afford 3-methyl-1-(2-allyl)-phenoxy-3-buten-2-one (251c) as an oil.
(Yield : 0.03g, 25%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.40)

^{1}H n.m.r. δ (CCl_4): 1.90(br s, 3H, $\underline{H}_3C-C=CH_2$), 3.40(m, 2H, $C\underline{H}_2-CH=CH_2$), 4.90(s, 2H, $O=C-C\underline{H}_2-O$), 5.00(m, 2H, $HC=C\underline{H}_2$), 5.95(m, 3H, $H_3C-C=C\underline{H}_2$ and $\underline{H}C=CH_2$), 7.00(m, 4H, $C_6\underline{H}_4$).

i.r. ν_{max} (CCl_4): 3080(w), 2980(w), 2920(m), 1705(s), 1660(m), 1685(m), 1650(m), 1600(w), 1580(w), 1490(s), 1440(m).

m.s.: 216(M^+, 9.5%), 134(33), 133(100), 131(36), 119(31), 115(21), 107(27), 105(24), 91(57), 83(30), 78(21), 77(32), 69(91), 55(34), 43(43), 41(55), 39(23).

$C_{14}H_{16}O_2$ requires *M* : 216.1150
found : 216.1101

1-Acetylphenylamino-3-methyl-3-buten-2-one (251d) and 1-acetylphenylamino--3-methyl-1,3-butadiene (252d).

A similar procedure as that used in the preparation of 1-phenoxy-3-buten-2-one (251b) and 3-methyl-1-phenoxy-1,3-butadiene (252b) was applied and afforded 1-acetylphenylamino-3-methyl-3-buten-2-one (251d) and 1-acetylphenylamino-3-methyl-1,3-butadiene (252d) as oils in the ratio of 3:2 respectively.

Spectral data for 1-acetylphenylamino-3-methyl-3-buten-2-one (251d):
(Yield : 0.11g, 60%)
(t.l.c. (ether) r_f= 0.40)

^{1}H n.m.r. δ ($CDCl_3$): 1.68(br s, 3H, $\underline{H}_3C-C=CH_2$), 1.90(s, 3H, $C\underline{H}_3-C=O$), 3.50(m, 2H, $N-C\underline{H}_2$), 5.00-5.50(m, 2H, $\underline{H}_2C=C(CH_3)$), 7.50(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3060(m), 3000(s), 2920(m), 1695(m), 1650(s), 1600(s), 1590(s), 1580(m), 1500(m).

m.s.: 217(M^+, 1.5%), 202(100), 160(56), 106(52), 104(30), 77(28), 43(18).

$C_{13}H_{15}NO_2$ requires M : 217.1102
found : 217.1072

Spectral data for 1-acetylphenylamino-3-methyl-1,3-butadiene (252d):
(Yield : 0.062g, 40%)
(t.l.c. (ether) r_f= 0.25)

^{1}H n.m.r. δ ($CDCl_3$): 1.65(br s, 3H, $\underline{H}_3C-C=CH_2$), 1.90(s, 3H, $C\underline{H}_3-C=O$), 4.10(m, 1H, $C-C\underline{H}=CH-N$), 5.00(m, 2H, $\underline{H}_2C=C(CH_3)$), 5.90(d, J=9Hz, 1H, $CH=C\underline{H}-N$), 7.40(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3050(w), 2995(m), 2920(m), 1640(s), 1600(s), 1580(w), 1500(m), 1440(w), 1430(w), 1405(s).

m.s.: 201(M^+, 0.2%), 149(11), 106(100), 43(12),

$C_{13}H_{15}NO$ requires M : 201.1154
found : 201.1102

2-(4-Methyl-1-oxa-5-phenylseleno-3-pentenyl)-acetophenone (223f).

A solution of 3-methyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)-phenoxy]-4-phenylseleno-2-butene (223g) (0.048g, 0.118 mmol) and pyridinium tosylate (0.009g, 0.035 mmol) in acetone(1.75 ml) and water (0.05 ml) was heated under reflux for 3 hours. The reaction mixture was concentrated *in vacuo*, diluted with ether (10 ml), and washed first with saturated aqueous sodium bicarbonate solution (2x25 ml) and then saturated sodium chloride solution (10 ml). The organic phase was separated, dried, and the solvent removed to give 2-(4-methyl-1-oxa-5-phenylseleno-3-pentenyl)-acetophenone (223f) as an oil after chromatography on silica.
(Yield : 0.042g, 99%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.52)

^1H n.m.r. δ (CCl_4): 1.90(br s, 3H, $C\underline{H}_3$-C=), 2.40(s, 3H, $C\underline{H}_3$-C=O), 3.50(br s, 2H, $C\underline{H}_2Se$), 4.10 and 4.40(br s, 2H overall, $C\underline{H}_2$-O (*E*)- and (*Z*)- isomers in a 2:1 ratio), 5.40(m, 1H, OCH_2-C$\underline{H}$=C), 6.50-7.70(m, 9H, $C_6\underline{H}_5$ and $C_6\underline{H}_4$).

i.r. ν_{max} ($CHCl_3$): 3080(s), 3000(s), 2920(s), 2860(m), 1680(s), 1675(s), 1600(s), 1580(s), 1490(s), 1450(s), 1440(s), 1390(m), 1360(s), 1300(s), 1240(s), 1165(s), 1130(s), 1000(s), 700(s).

m.s.: 360(M^+, 0.3%), 225(71), 223(37), 203(100), 183(31), 159(23), 157(69), 155(34), 145(51), 144(41), 143(35), 121(32), 91(23), 78(23), 77(42), 68(27) 67(74), 65(29), 43(76), 41(33), 39(23).

$C_{19}H_{20}O_2{}^{80}Se$ requires M : 360.0628
found : 360.0578

2-Acetylphenylpivalate (230b).

Trimethylacetyl chloride (36.15g, 36.9 ml, 0.3 mol), was added dropwise to a solution of *o*-hydroxyacetophenone (27.2g, 24 ml, 0.2 mol) and triethylamine (30.3g, 41.6 ml, 0.3 mol) in ether (100 ml) at 0°C, the reaction mixture was stirred vigorously, and the temperature maintained at 10-15°C using an ice bath, the reaction was then stirred for one hour at room temperature. Water (100 ml) was added and the ethereal layer separated. The aqueous layer was extracted with ether (4 x 150 ml) and the ethereal extracts were combined and washed with a saturated aqueous solution of sodium carbonate (3 x 50 ml), dried and the solvent removed *in vacuo*. Distillation under reduced pressure gave 2-acetylphenylpivalate (230b) as an oil.
(Yield : 28g, 64% b.p. : 115°C/1mmHg)

^{1}H n.m.r. δ (CCl_4): 1.30(s, 9H, $(C\underline{H}_3)_3C$), 2.40(s, 3H, $C\underline{H}_3$-C=O), 7.4(m, 4H, $C_6\underline{H}_4$).

i.r. ν_{max} (thin film): 3080(w), 2990(s), 2940(m), 2880(m), 1750(s), 1695(s), 1600(s), 1580(m), 1480(s), 1450(s), 1400(s), 1360(s), 1200-1240(s).

m.s.: 220(M^+, 10%), 136(61), 121(100), 85(21) 57(40).

$C_{13}H_{16}O_3$ requires *M* : 220.1099
found : 220.1094

2-(2-Methyl-1,3-dioxolan-2-yl)-phenylacetate (231a).

A mixture of 2-acetylphenylacetate (230a) (5g, 0.028 mol), *p*TSA (0.10g, 0.6 mmol), ethylene glycol (2.60g, 0.042 mol) and benzene (50 ml) was heated under reflux in a Dean and Stark apparatus overnight. The reaction was allowed to cool, washed with saturated aqueous sodium carbonate solution (3 x 20 ml) and the organic phase separated. The aqueous layer was extracted with ether (3 x 20 ml) and the organic extracts combined, dried and concentrated *in vacuo* to give a 2:1 mixture of *o*-hydroxyacetophenone and 2-(2-methyl-1,3-dioxolan-2-yl)-phenylacetate (231a) as oils, reduced pressure distillation gave pure 2-(2-methyl-1,3-dioxolan-2-yl)-phenylacetate (231a) as a waxy solid.
(Yield : 2.06g, 33% m.p. : 45-49°C)

^{1}H n.m.r. δ (CCl_4): 1.70(s, 3H, $\underline{H}_3C$-C(O)O), 2.30(s, 3H, $C\underline{H}_3$C=O), 3.75(m, 4H, (O-$C\underline{H}_2)_2$)), 7.30(m, 4H, $C_6\underline{H}_4$).

i.r. ν_{max} ($CHCl_3$): 3010(m), 3000(m), 2900(m), 1760(s), 1650(s), 1580(m), 1490(m), 1450(m), 1380(s), 1310(s).

m.s.: 222(M^+, 0.5%), 155(39), 91(53), 87(100), 43(58).

$C_{12}H_{14}O_4$ requires *M* : 222.0892
found : 222.0923

2-(2-Methyl-1,3-dioxolan-2-yl)-phenylpivalate (231b).

2-Acetylphenylpivalate (230b) (10g, 0.046 mol), pTSA (0.15g, 0.8 mmol) in ethylene glycol (4.28g, 0.069 mol) and benzene (100 ml) was heated under reflux in a Dean and Stark apparatus overnight. The reaction was allowed to cool, washed with saturated aqueous sodium carbonate

solution (3x40 ml) and the organic phase separated. The aqueous layer was extracted with ether (3x 20 ml) and the organic extracts combined, dried and concentrated *in vacuo* to give 2-(2-methyl-1,3-dioxolan-2-yl)-phenylpivalate (231b) as a white crystalline solid after freeze-drying.

(Yield : 12g, 100% m.p. : 59-62°C)

^{1}H n.m.r. δ (CCl_4): 1.35(s, 9H, $(C\underline{H}_3)_3C$), 1.65(s, 3H, $\underline{H}_3C$-C(O)O), 3.80(m, 4H, $(O\text{-}C\underline{H}_2)_2$)), 7.40(m, 4H, $C_6\underline{H}_4$).

i.r. ν_{max} (CCl_4): 3080(w), 2990(s), 2940(m), 2900(s), 1750(s), 1610(m), 1580(m), 1480(s), 1460(m), 1450(m), 1400(m), 1370(s), 1280(s), 1235(s), 1200(s), 1130(s).

m.s.: 264(M^+, 0.1%), 249(11), 172(10), 129(33), 91(20), 57(100), 87(8).

$C_{15}H_{20}O_4$ requires M : 264.1362
found : 264.1473

2-(2-Methyl-1,3-dioxolan-2-yl)-phenol (232).

Methyllithium (63ml, 0.9M, 0.057 mol) was added quickly to a solution of 2-(2-methyl-1,3-dioxolan-2-yl)-phenylpivalate (231b) (5g, 0.019 mol) in ether (25 ml) at 0°C under an atmosphere of argon. The reaction was allowed to warm up to room temperature and was stirred for a further 3 hours. Water (150 ml) was added and a heavy white precipitate formed. A further aliquot of water was added (100 ml) and the solution gently warmed until the precipitate dissolved. The solution was extracted with methylene chloride (4 x 100 ml), the extracts were combined, dried and the solvent removed *in vacuo*. The oil was distilled (90°C/2 mmHg) and the resulting sticky white crystalline material dissolved in ether (15 ml) and the solvent

removed *in vacuo* to afford 2-(2-methyl-1,3-dioxolan-2-yl)-phenol (232) as a powdery white crystalline solid.
(Yield : 2.5g, 73% m.p. : 57-58°C)

^{1}H n.m.r. δ (CCl_4): 1.65(s, 3H, H_3C-C(O)O), 3.90(m, 4H, (O-CH_2)$_2$)), 7.00(m, 4H, C_6H_4), 7.90(br s, 1H, -OH, D_2O exchangeable).

i.r. ν_{max} (nujol mull): 3300(br s), 3020(m), 2980(m), 2880(m), 1640(s), 1620(m), 1580(s).

m.s.: 180(M^+, 23%), 165(27), 137(13), 121(100), 43(49), 39(21).

$C_{10}H_{12}O_3$ requires *M* : 180.0786
found : 180.0782

2-(1-Hydroxy-2-propenyl)-phenol (276f).

Magnesium turnings (2.9g, 0.12 mol) and sufficient THF (5 ml) to cover them were placed in a 200 ml round bottom flask equipped with a dry ice condenser. A crystal of iodine was added and vinyl bromide (0.5g, 4 mmol) added dropwise to the stirred suspension, once the reaction had initiated further THF (35 ml) was added. A solution of vinyl bromide (14g, 9.2 ml, 0.13 mol) in THF (12 ml) was added at a rate sufficient to maintain the reaction under reflux. When the addition was complete the reaction was heated under reflux for 30 min., and the Grignard reagent allowed to cool to room temperature. Salicaldehyde (6.68g, 0.05 mol) was added dropwise (a transitory yellow colour appeared at each addition), the reaction was stirred at room temperature for 30 min., and then heated under reflux for 10 min. The reaction mixture was allowed to cool and saturated aqueous ammonium chloride solution (100 ml) added. The reaction mixture then was extracted with ether (4 x 100 ml), the extracts combined, dried and concentrated *in vacuo*. Distillation under reduced pressure gave 2-(1-hydroxy-2-propenyl)-

phenol (276f) as a yellow oil.
(Yield : 4.0g, 53% b.p. : 70-72°C/3 mmHg)

^{1}H n.m.r. δ ($CDCl_3$) 100MHz : 4.82(m, 2H, =C$\underline{H}_2$), 5.76(m, 1H, CHC$\underline{H}$=CH_2), 6.42(br d, J=10Hz, C$\underline{H}$(OH)CH=), 6.88(m, 5H, $C_6\underline{H}_4$ and -O$\underline{H}$).

i.r. ν_{max} (thin film): 3400(br m), 3050(s), 2980(m), 2840(s), 1650(s), 1610(s), 1580(s), 1490(s), 1460(s), 1450(m), 1400(s), 1370(s), 1240(s), 1200(s), 1160(s), 1120(s), 1050(s), 1020(s), 940(s), 930(s), 870(w), 850(w), 790(s), 760(s), 740(s), 690(s).

m.s.: 150(M^+, 0.6%), 149(1), 131(100), 103(10), 77(17), 51(18), 44(21).

$C_9H_{10}O_2$ requires M : 150.0681
found : 150.0702

4-Phenoxy-3-buten-2-one (269a)[175].

To a stirred suspension of potassium carbonate (0.17g, 1.3 mmol) in DMF (1 ml), at room temperature, was added phenol (0.10g, 1.1 mmol). The reaction was stirred for 30 minutes, during which time a light yellow colour formed.

On rapid addition of 4-chloro-3-buten-2-one (1.5 mmol) the reaction mixture became a deep red colour. The stirring was continued until all the starting phenol had disappeared as judged by t.l.c.

The reaction mixture was diluted with water (10 ml) and extracted with ether (3 x 5 ml). The ethereal extracts were combined, washed with a further aliquot of water (10 ml), dried and the solvent removed *in vacuo*, to yield 4-phenoxy-3-buten-2-one (269a) as a light yellow oil.

(Yield : 0.17g, 98% b.p. : 113-114°C/ 2 mm Hg)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.33)

^{1}H n.m.r. δ ($CDCl_3$) 100MHz: 2.20(s, 3H, $\underline{H}_3C$-C=O), 5.88(d, J_{trans}= 12 Hz, 1H, HC=C$\underline{H}$-CO), 7.00-7.50(m, 5H, $C_6\underline{H}_5$), 7.76(d, J_{trans}=12 Hz, $\underline{H}$C=CH-CO).

i.r. ν_{max} (thin film): 3080(m), 1705(s), 1670(s), 1630(s), 1220(s), 960(m), 800(m), 700(m).

m.s.: 162(M^+, 9.8%), 147(57), 94(13), 91(44), 78(48), 77(61), 68(31), 65(29), 51(48), 50(22), 43(100), 39(53).

$C_{10}H_{10}O_2$ requires *M* : 162.0681
found : 162.0684

<u>4-(2-Methoxycarbonyl)-phenoxy-3-buten-2-one</u> (269b).

The method employed was similar to that used for the preparation of 4-phenoxy-3-buten-2-one (269a).
(Yield : 0.2g, 50%)
t.l.c. (1:1 petroleum ether:ether) r_f= 0.18)

^{1}H n.m.r. δ (CCl_4): 2.10(s, 3H, $\underline{H}_3C$-CO), 3.85(s, 3H, $\underline{H}_3C$-O), 5.65 (d, J_{trans}=13 Hz, 1H, HC=C$\underline{H}$-CO), 6.60-7.80(m, 4H, $C_6\underline{H}_4$), 7.65(d, J_{trans}=13 Hz, 1H, $\underline{H}$C=CH-CO).

i.r. ν_{max} ($CHCl_3$): 3010(m), 2960(m), 1730(s), 1680(s), 1620(s), 1600(s), 1580(s), 1490(s), 1450(s), 1440(s), 1310(s), 1200-1250(br s), 1160(s), 1090(s), 960(s), 850(s), 700(s).

m.s.: 220(M^+, 1%), 177(20), 161(75), 147(25), 85(100), 43(31).

$C_{12}H_{12}O_4$ requires M-CH_3CO : 177.0552
found : 177.0473

4-[2-(2-Methyl-1,3-dioxolan-2-yl)-phenoxy]-3-buten-2-one (269c).

The method employed was similar to that used for the preparation of 4-phenoxy-3-buten-2-one (269a).
(Yield : 0.2g, 97%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.20)

^1H n.m.r. δ (CCl_4): 1.70(s, 3H, $\underline{H}_3C$-C(O)O), 2.15(s, 3H, $\underline{H}_3C$-CO), 3.75-3.95 (m, 4H, O-($C\underline{H}_2)_2$-O), 5.80(d, J_{trans}=12 Hz, 1H, HC=C$\underline{H}$-CO), 7.00-7.60(m, 4H, $C_6\underline{H}_4$), 7.65(d, J_{trans}=12 Hz, 1H, $\underline{H}$C=CH-CO).

i.r. ν_{max} (thin film): 3080(m), 3000(s), 2950(m), 2900(s), 1700(s), 1650(s), 1610(s), 1600(s), 1580(s), 1490(s), 1450(s), 1370(s), 1210(s), 1150(m), 1070(s), 1050(s), 955(s), 900(m), 870(m), 780(s), 765(s), 665(m), 620(s).

m.s.: 248(M^+, 1%), 233(65), 186(29), 147(94), 87(86), 43(100).

$C_{14}H_{16}O_4$ requires M : 248.1049
found : 248.1040

4-[(3,5-Dimethoxy)-phenoxy]-3-buten-2-one (269d).

The method employed was similar to that used for the preparation of 4-phenoxy-3-buten-2-one (269a).
(Yield : 0.19g, 80%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.25)

^{1}H n.m.r. δ ($CDCl_3$) 100MHz: 2.22(s, 3H, $\underline{H}_3C$-CO), 3.78(s, 6H, 2 x O$C\underline{H}_3$), 5.95(d, J_{trans}=13 Hz, 1H, HC=C$\underline{H}$-CO), 6.00-6.40(m, 3H, $C_6\underline{H}_3$), 7.75(d, J_{trans}=13 Hz, 1H, $\underline{H}$C=CH-CO).

i.r. ν_{max} (thin film): 3100(w), 3010(m), 2980(m), 2860(m), 1690(s), 1650(m), 1600(s), 1480(m), 1440(m), 1210(s), 1200(s), 1180(s), 1070(s), 1060(s), 950(w), 840(w), 740(m), 680(m).

m.s.: 222(M^+, 61%), 221(10), 207(70), 205(18), 191(24), 179(16), 154(32), 151(12), 139(12), 125(14), 122(13), 94(16), 69(20), 44(23), 43(72).

$C_{12}H_{14}O_4$ requires M : 222.0892
found : 222.0894

4-Phenylthio-3-buten-2-one (269e)[174].

The method employed was similar to that used for the preparation of 4-phenoxy-3-buten-2-one (269a).
(Yield : 98% b.p. : 126-129°C/ 2 mm Hg)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.37)

^{1}H n.m.r. δ ($CDCl_3$) 100MHz: 2.20(s, 3H, $\underline{H}_3C$-CO), 6.00(d, J_{trans}=16 Hz, 1H, HC=C$\underline{H}$-CO), 7.20-7.60(m, 5H, $C_6\underline{H}_5$), 7.72 (d, J_{trans}= 16 Hz, 1H, $\underline{H}$C=CH-CO).

i.r. ν_{max} (thin film): 3080(s), 3020(m), 1730(s), 1660(br s), 1560(br s), 1480(s), 1450(s), 1360(s), 1250(s), 1165(s), 1090(s), 1070(s), 1030(s), 950(s), 900(s), 850(s), 830(s), 750(s).

m.s.: 178(M^+, 85%), 163(100), 135(40), 109(35), 101(20), 91(30), 43(35).

$C_{10}H_{10}OS$ requires *M* : 178.0452
found : 178.0450

4-(*d*-2-Octyloxy)-3-buten-2-one (285)[183].

d-2-Octanol (2.6g, 3.1 ml, 0.02 mol), pyridinium tosylate (0.05g, 0.2 mmol) and 4-methoxy-3-buten-2-one (1g, 0.01 mol) in benzene (12 ml) were heated under Dean and Stark conditions for 18 hours. 4A Molecular sieves were used to remove methanol continuously. The reaction was allowed to cool, concentrated *in vacuo* and the residue distilled under reduced pressure to afford 4-(*d*-2-octyloxy)-3-buten-2-one (285) as a colourless oil.
(Yield : 0.9g, 46% b.p. : 65-70°C/ 0.33mm Hg)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.49)

^{1}H n.m.r. δ ($CDCl_3$) 100MHz: 0.90(m, 3H, $\underline{H}_3C$-$(CH_2)_5$), 1.20-1.70(m, 13H, $(C\underline{H}_2)_5$-CH-$C\underline{H}_3$), 2.18(s, 3H, $\underline{H}_3C$-CO), 4.08(br m, 1H, CH_3-C$\underline{H}$(O)), 5.65(d, J_{trans}=12 Hz, 1H, HC=C$\underline{H}$-CO), 7.52(d, J_{trans}=12 Hz, 1H, $\underline{H}$C=CH-CO).

i.r. ν_{max} (thin film): 2980(s), 2950(s), 2880(s), 1690(s), 1660(s), 1640(s), 1620(s), 1600(s),

	1470(m), 1460(s), 1390(s), 1365(s), 1250(s), 1210(s), 1150(s), 1120(s), 960(s), 850(w), 820(w).
m.s.:	198(M^+, 0.5%), 87(34), 71(61), 57(75), 55(18), 43(100), 41(32).
$C_{12}H_{22}O_2$ requires *M* :	198.1620
found :	198.1658

$[\alpha]_D^{22}$ ($CHCl_3$) = 11° (±2°)

Preparation of Titanium Methylenating Reagent.[194]

Titanium tetrachloride (2.3 ml) was added dropwise over 5 minutes to a stirred suspension of zinc dust (5.75g) in THF (50 ml) and methylene bromide (2.02 ml) at -40°C, under an atmosphere of argon. The mixture was allowed to warm to room temperature and stirred for an hour, then a further portion of THF (20 ml) was added. The reagent was stirred for three days at this temperature to give a thick grey slurry of the active species, which could be syringed.

3-Methyl-1-phenoxy-1,3-butadiene (280a).

The titanium zero slurry (2 ml) was added to the 4-phenoxy-3-buten-2-one (269a) (0.1g, 0.61 mmol) in dry methylene chloride (1 ml); further aliquots of the slurry were added if necessary until all the starting material had disappeared as judged by t.l.c.

Saturated sodium bicarbonate solution (4 ml) was added and the resulting thick emulsion extracted with ether (4 x 10 ml). The extracts were combined, dried, and concentrated *in vacuo*, to afford 3-methyl-1-phenoxy-1,3-butadiene (280a) as a yellow oil.
(Yield : 0.09g, 92%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.71)

^{1}H n.m.r. δ ($CDCl_3$) 100MHz: 1.87(s, 3H, $\underline{H}_3C$-C=C), 4.82-4.90(m, 2H, $\underline{H}_2C$=C), 6.10(d, J_{trans}=14 Hz, 1H, C=C$\underline{H}$-C(CH_3), 6.75(d, J_{trans}=14 Hz, 1H, O-C$\underline{H}$=CH), 6.80-7.40(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} (thin film): 3080(br w), 2980(m), 2930(w), 1650(s), 1590(s), 1490(s), 1230(br s), 1170(s), 1120(s), 930(m), 880(m), 800(m), 760(s), 700(s).

m.s.: 160(M^+, 67%), 159(75), 145(85), 94(100), 77(48), 67(35), 43(60).

$C_{11}H_{12}O$ requires M-CH_3 : 145.0653
found : 145.0797

<u>1-(2-Methoxycarbonyl)-phenoxy-3-methyl-1,3-butadiene</u> (280b).

The method employed was similar to that used for the preparation of 3-methyl-1-phenoxy-1,3-butadiene (280a).
(Yield : 0.088g, 88%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.65)

^{1}H n.m.r. δ ($CDCl_3$): 1.84(s, 3H, $\underline{H}_3C$-C=C), 3.84(s, 3H, O-C$\underline{H}_3$), 4.84-4.90 (m, 2H, $\underline{H}_2C$=C(CH_3), 6.11(d, J_{trans}=15 Hz, 1H, C=C$\underline{H}$-C(CH_3)), 6.68 (d, J_{trans}=15 Hz, 1H, O-C$\underline{H}$=CH)), 6.60-7.90(m, 4H, $C_6\underline{H}_4$).

i.r. ν_{max} ($CHCl_3$): 3080(w), 3010(s), 2980(s), 1730(s), 1650(s), 1620(s), 1600(s), 1580(s), 1490(s), 1440(s), 1360(s), 1200-1280(br s), 1170(s), 1140(s), 1100(s), 970(s), 940(s), 850(s), 700(s).

m.s.: 218(M^+, 10%), 152(42), 121(40), 120(100), 98(52), 92(32), 83(40).

$C_{13}H_{14}O_3$ requires M : 218.0932
found : 218.0942

1-[2-(2-Methyl-1,3-dioxolan-2-yl)-phenoxy]-3-methyl-1,3-butadiene (280c).

The method employed was similar to that used for the preparation of 3-methyl-1-phenoxy-1,3-butadiene (280a).
(Yield : 0.084g, 85%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.64)

^1H n.m.r. δ ($CDCl_3$) 100MHz: 1.80(s,3H, $\underline{H}_3C$-C(O)O), 1.88(s, 3H, $\underline{H}_3C$-C=C), 3.95(m, 4H, O-($C\underline{H}_2$)$_2$-O), 4.82-4.89(m, 2H, $\underline{H}_2C$=C(CH_3), 6.14(d, J_{trans}=13 Hz, 1H, C=C$\underline{H}$-C(CH_3)), 6.70 (d, J_{trans}=13 Hz, 1H, O-C$\underline{H}$=CH)), 6.90-7.65(m, 4H, $C_6\underline{H}_4$).

i.r. ν_{max} (thin film): 3080(s), 3000(s), 2940(s), 2900(s), 1650(s), 1600(s), 1580(s), 1480(s), 1450(s), 1370(s), 1230(br s), 870(s), 810(s) , 740(m) , 760(s).

m.s.: 246(M^+, 5%), 165(57), 121(46), 91(18), 87(39), 67(12), 43(100), 41(22).

$C_{15}H_{18}O_3$ requires M : 246.1256
found : 246.1244

1-[(3,5,-Dimethoxy)-phenoxy]-3-methyl-1,3-butadiene (280d).

The method employed was similar to that used for the preparation of 3-methyl-1-phenoxy-1,3-butadiene (280a).
(Yield : 0.091g, 80%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.60)

^{1}H n.m.r. δ ($CDCl_3$) 100MHz: 1.88(s, 3H, $\underline{H}_3C$-C=C), 3.75(s, 6H, 2 x O$C\underline{H}_3$), 4.80-4.85(m, 2H, $\underline{H}_2C$=C), 6.05(m, 4H, C=C$\underline{H}$-C(CH_3 and $C_6\underline{H}_3$), 6.65(d, J_{trans}=14 Hz, 1H, O-C$\underline{H}$=CH).

i.r. ν_{max} (thin film): 3080(br w), 2980(w), 2960(w), 1610(s), 1500(m), 1480(m), 1460(m), 1450(m), 1210(s), 1200(s), 1160(s), 1060(m), 930(w), 820(m).

m.s.: 220(M^+, 72%), 205(31), 191(20), 171(18), 154(100), 153(11), 125(56), 95(10), 94(17), 68(28), 41(16).

$C_{13}H_{16}O_3$ requires *M* : 220.1099
found : 220.1123

3-Methyl-1-phenylthio-1,3-butadiene (280e)[199].

The method employed was similar to that used for the preparation of 3-methyl-1-phenoxy-1,3-butadiene (280a).
(Yield : 0.09g, 91%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.73)

^{1}H n.m.r. δ ($CDCl_3$) 100MHz: 1.85(s, 3H, $\underline{H}_3C$-C=C), 4.90(m, 2H, $\underline{H}_2C$=C(CH_3), 6.30,6.50(ABq, J_{trans}=15 Hz, 2H, $\underline{H}$C=C$\underline{H}$-S), 7.15-7.60(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} (thin film): 3070(m), 1640(m), 1590(s), 950(s), 890(s), 690(s).

m.s.: 176(M^+, 35%), 143(30), 99(100), 65(20).

1-Methoxy-3-methylenecyclo-1-hexene (315)[198].

The method employed was similar to that used for the preparation of 3-methyl-1-phenoxy-1,3-butadiene (280a).
(Yield : 0.07g, 70%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.64)

^{1}H n.m.r. δ ($CDCl_3$) 100MHz: 1.70-2.50(m, 6H, =C-($C\underline{H}_2$)$_3$-C=), 3.60 (s, 3H, $\underline{H}_3C$-O), 4.55-4.60(m, 2H, $\underline{H}_2C$=C), 5.35(br s, 1H, =C-C($\underline{H}$)=).

i.r. ν_{max} (thin film): 2940(s), 2840(m), 1680(s), 1650(s), 1610(s), 1480(s), 1220(s), 1180(s), 1170(s), 1145(s), 740(m).

m.s.: 220(polymerisation on probe), 205(55), 125(M^++1, 100%), 111(30), 91(30), 55(30).

Spectral data consistent with literature[198].

3-Methyl-1-(*d*-2-octyloxy)-1,3-butadiene (316).

The method employed was similar to that used for the preparation of 3-methyl-1-phenoxy-1,3-butadiene (280a).
(Yield : 0.1g, 67%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.88)

^{1}H n.m.r. δ ($CDCl_3$): 0.90(m, 3H, $\underline{H}_3C-(CH_2)_5$), 1.20-1.70(m, 13H, $(C\underline{H}_2)_5-CH-C\underline{H}_3$), 1.78(br s, 3H, $\underline{H}_3C-C=C$), 3.84(m, 1H, $CH_3-C\underline{H}(O)$), 4.65-4.75((m, 2H, $\underline{H}_2C=C$), 5.74(d, J_{trans}=13 Hz, 1H, $C=C\underline{H}-C(CH_3)$), 6.40(d, J_{trans}=13 Hz, 1H, $O-C\underline{H}=CH$)).

i.r. ν_{max} ($CHCl_3$): 2980(s), 2940(s), 2870(s), 1650(s), 1640(s), 1460(s), 1380(s), 1260(m), 1180(s), 1120(s), 920(s), 870(m), 820(w).

m.s.: 197(M^++1, 0.1%), 116(17), 113(19), 112(13), 99(32), 98(13), 97(22), 83(18), 71(33), 70(32), 57(40), 55(40), 45(100), 43(66).

$C_{13}H_{24}O$ requires M+1 : 197.1905
found : 197.1950

$[\alpha]_D^{24}$ ($CHCl_3$) = 74° (±2°)

<u>5-Methyl-3-phenoxy-1,2-cyclohex-4-enedicarboxylic anhydride</u> (329a).

Sublimed maleic anhydride (0.067g, 0.69 mmol) in THF (0.5 ml) was added to 3-methyl-1-phenoxy-1,3-butadiene (0.1g, 0.625 mmol) in THF (0.5 ml). The reaction mixture was stirred at 50°C for 5 hours and then allowed to cool to room temperature and concentrated *in vacuo*. The residue was dissolved in ether (5 ml), washed quickly with ice-cold water (3x 2 ml), decolourised with charcoal concentrated and dried *in vacuo* to afford <u>5-methyl-3-phenoxy-1,2-cyclohex-4-enedicarboxylic anhydride</u> (329a) as a brown oil.
(Yield : 0.13g, 80%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.22)

^{1}H n.m.r. δ (acetone-d_6) 100 MHz: 1.90(br s, 3H, $C\underline{H}_3-C(CH_2)=CH$), 2.76(m, 2H, $CH-C\underline{H}_2-C(CH_3)$), 3.65(dd, J=10Hz,

J=6Hz, 1H, OCH-C<u>H</u>(CH)-C=O), 3.85(m, 1H, CH_2-C<u>H</u>(CH)-C=O), 5.34(m, 1H, CH-C<u>H</u>(O)-CH), 6.13(m, 1H, C=C<u>H</u>-CH), 6.80-7.50(m, 5H, $C_6\underline{H}_5$).

^{13}C n.m.r. δ ($CDCl_3$) 90.56 MHz: 23.43(<u>C</u>H_3), 27.24(<u>C</u>H_2-C=), 37.88 (<u>C</u>H-C=O), 46.44(OCH-<u>C</u>H-C=O), 70.15(<u>C</u>HOPh), 116.91, 121.12, 122.43, 157.80($\underline{C}_6H_5$), 130.27(<u>C</u>H=C), 142.30 (Me-<u>C</u>(CH_2)=), 171.73, 175.61(<u>C</u>=O).

i.r. ν_{max} ($CHCl_3$): 3060(w), 2940(w), 1860(w), 1800(s), 1720(m), 1605(m), 1600(w), 1500(m), 1240(br m), 1030(w), 945(w), 910(w), 840(w), 700(m), 680(m).

m.s.: 258(M^+, 0.4%), 94(100), 93(10), 43(15), 39(13).

$C_{15}H_{14}O_4$ requires *M* : 258.0892
found : 258.0896

<u>5-Methyl-3-(3,5-dimethoxy)-phenoxy-1,2-cyclohex-4-enedicarboxylic anhydride</u> **(329d).**

A similar procedure was applied as described for the preparation of 5-methyl-3-phenoxy-1,2-cyclohex-4-enedicarboxylic anhydride (329a).
(Yield : 0.06g, 50%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.35)

^1H n.m.r. δ (acetone-d_6) 100MHz: 1.98(br s, 3H, C<u>H</u>$_3$-C(CH_2)=CH), 2.75(m, 2H, CH-C<u>H</u>$_2$-C(CH_3)), 3.60-4.10(m, 8H, CH-C<u>H</u>(CH)-C=O, CH_2-C<u>H</u>(CH)-C=O and 2x C<u>H</u>$_3$O), 5.40(m, 1H, CH-C<u>H</u>(O)-CH), 6.25(m, 4H, C=C<u>H</u>-CH and $C_6\underline{H}_3$).

i.r. ν_{max} (thin film):	3100(m), 3020(m), 2980(s), 2860(s), 1850(m), 1780(s), 1650(s), 1600(s), 1500(m), 1440(br s), 1200(m), 1150(s), 1050(s), 930(br s), 840(br s), 700(s).
m.s.:	318(M^+, 2%), 154(100), 125(50), 94(19), 93(58), 91(27), 77(25), 68(47), 55(14), 51(13), 43(31), 39(20).
$C_{17}H_{18}O_6$ requires *M* :	318.1103
found :	318.1156

Methyl 2-allyl-2-methoxycarbonyl-5-methyl-6-phenylseleno-4-hexenoate (348c).

Methyl 2-methoxycarbonyl-4-pentenoate (355) (0.172g, 1 mmol) was added dropwise to a stirred suspension of sodium hydride (0.04g, 57% dispersion in oil, 1.1 mmol) in THF (5 ml) at room temperature. The reaction mixture was stirred for 10 minutes at this temperature and then a 1:1 mixture of 4-chloro-2-methyl-1-phenylseleno-2-butene (217a) and 2-chloro-2-methyl-1-phenylseleno-3-butene (216a) (0.4g, 1.5 mmol) was added and the reaction mixture heated under reflux for 5 hours. The reaction mixture was allowed to cool and water (3 ml) was added. The organic layer was separated and the aqueous phase extracted with ether (3 x 10 ml), the organic extracts were combined, dried and the solvent removed *in vacuo*. Chromatography on silica afforded methyl 2-allyl-2-methoxycarbonyl-5-methyl-6-phenylseleno-4-hexenoate (348c) as a colourless oil.
(Yield : 0.146g, 37%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.31)

^{1}H n.m.r. δ (CCl_4):	1.75(br s, 3H, $C\underline{H}_3$-C=), 2.50(m, 4H, $C\underline{H}_2$-CH=CH_2 and $C\underline{H}_2$-CH=C), 3.40(m, 2H, $C\underline{H}_2$Se), 3.60(s, 6H, 2x $C\underline{H}_3O$), 4.90-6.00(m, 4H, $\underline{H}C$=$C\underline{H}_2$ and $C\underline{H}$=CCH_3), 7.2(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} ($CHCl_3$): 3040(m), 3000(s), 2960(s), 1750(br s), 1650(m), 1580(m), 1480(m), 1440(s), 1300-1180(br s), 1020(w), 1000(w), 930(m), 690(s).

m.s.: 396(M^+, 0.5%), 239(29), 179(50), 157(30), 155(17), 147(31), 139(35), 137(23), 119(75), 107(16), 91(31), 77(43), 59(58), 41(100).

$C_{19}H_{24}O_4{}^{80}Se$ requires M : 396.0840
found : 396.0808

Methyl 2-methoxycarbonyl-2-(3-methyl-2-butenyl)-5-methyl-6-phenylseleno-4-hexenoate (348b).

A similar procedure was applied as for the preparation of methyl 2-allyl-2-methoxycarbonyl-5-methyl-6-phenylseleno-4-hexenoate (348c).
(Yield : 0.9g, 43%)
(t.l.c. (1:1 petroleum ether:ether) r_f= 0.52)

^1H n.m.r. δ ($CDCl_3$) 100 MHz: 1.58(br s, 3H, $C\underline{H}_3$-C(CH_2)=), 1.62(br s, 3H, $C\underline{H}_3$-C(CH_3)=), 1.72(br s, 3H, $C\underline{H}_3$-C(CH_3)=), 2.28-2.58(m, 4H, 2 x CH-$C\underline{H}_2$-CH=), 3.50 (m, 2H, $C\underline{H}_2$Se), 3.70(s, 6H, 2 x O$C\underline{H}_3$), 4.80-5.50(m, 2H, 2 x C=C$\underline{H}$-CH_2), 7.32(m, 5H, $C_6\underline{H}_5$).

i.r. ν_{max} (thin film): 3040(w), 3000(m), 2960(s), 2920(m), 2860(m), 1750(br s), 1580(w), 1480(m), 1440(s), 1380(w), 1300-1180(br s), 745(s), 700(s).

m.s.: 356(3%), 267(4), 255(13), 199(19), 167(100), 165(13), 135(21), 69(19), 43(18), 41(18).

$C_{21}H_{28}O_4{}^{80}Se$ requires $M^+-{}^{80}SePh$: 267.1596
found : 267.1553

Methyl 2-methoxycarbonyl-5-methyl-2-(3-methyl-2-butenyl)-4-hexenoate (357).

Methyl 2-methoxycarbonyl-5-methyl-4-hexenoate (356) (0.2g, 1 mmol) was added dropwise to a suspension of sodium hydride (0.04g, 57% dispersion in oil, 1 mmol), in THF (5 ml) at room temperature. The reaction mixture was stirred for 10 min. 1-Bromo-3-methyl-2-butene (0.22g, 1.5 mmol) was added and the reaction heated under reflux for 2 hours. Excess bromide was removed *in vacuo* to afford methyl 2-methoxycarbonyl-5-methyl-2-(3-methyl-2-butenyl)-4-hexenoate (357) as an oil.
(Yield : 0.21g, 80%)

^{1}H n.m.r. δ (CCl_4): 1.70(br s, 12H, 4 x $C\underline{H}_3$), 2.50(br d, J=9Hz, 4H, 2 x $C\underline{H}_2$-CH=), 3.70(s, 6H, 2 x $OC\underline{H}_3$), 4.90(m, 2H, 2 x $CH_2C\underline{H}$=C).

i.r. ν_{max} (thin film): 2960(m), 2915(m), 2870(m), 1750(br s), 1440(m), 1290(m), 1230(m), 1200(m), 1170(m), 1070(m), 1060(m).

m.s.: 268(M^+, 0.7%), 167(29), 135(42), 69(73), 57(50), 43(56), 41(100).

$C_{15}H_{24}O_4$ requires M : 268.1674
found : 268.1623

Methyl 2-methoxycarbonyl-5-methyl-2-(3-methyl-2-butenyl)-4-hexenoate (357).

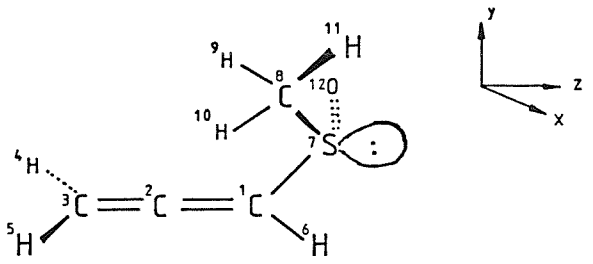
A solution of methyl 2-methoxycarbonyl-2-(3-methyl-2-butenyl)-5-methyl-

6-phenylseleno-4-hexenoate (348b) (0.1g, 0.24 mmol) in benzene (50 ml) with AIBN (0.004g, 10 mol%) and tri-*n*-butyltin hydride (0.073g, 0.067ml, 0.25 mmol) was irradiated for 6 hours with a medium pressure mercury vapour lamp (450W). The lamp was extinguished, the solvent removed *in vacuo* and the residue dissolved in acetonitrile (5 ml) and washed with hexane (3 x 2 ml) to remove the tin residues. The solvent was removed *in vacuo* and the residue chromatographed on silica to give methyl 2-methoxycarbonyl-5-methyl-2-(3-methyl-2-butenyl)-4-hexenoate (357) as an oil.

Spectral data was consistent with an authentic sample (see above).

APPENDIX 1

The co-ordinates for the total miniumum energy of methylsulphinyl-1,2-propadiene were obtained by rotation of the methyl group about the S_7-C_8 bond by 30° increments and then by the rotation of the CH_3SO-functionality about the C_1-S_7 bond by 60° increments. The co-ordinates recorded below correspond to the molecule with its total energy minimised.



ATOM	X(Å)	Y(Å)	Z(Å)
1	0.00	0.00	0.00
2	0.00	0.00	-1.31
3	0.00	0.00	-2.62
4	-0.93	0.00	-3.15
5	0.93	0.00	-3.15
6	0.00	-0.93	0.53
7	0.00	1.58	0.93
8	1.55	2.22	0.26
9	1.35	3.18	-0.26
10	1.98	1.49	-0.45
11	2 27	2 39	1.08
12	-1.12	2.41	0.59

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