SYNTHETIC AND SPECTROSCOPIC STUDIES OF ISOPSORALEN DERIVATIVES

Submitted in fulfilment of the requirements

for the degree of

MASTER OF SCIENCE

By

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September 2001

School of Chemical and

Physical Sciences

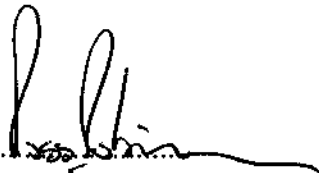University of Natal

Pietermaritzburg

DECLARATION

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

Signed.................................

Dino Justin Clarke

I hereby certify that this statement is correct.

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ABSTRACT

The biological and photochemical properties associated with psoralens and isopsoralens have resulted in this class of compounds being widely investigated. Much emphasis has been placed on the synthesis of different analogues of these compounds as a means to fine tune these properties and therefore enhance their value to the medical community. Synthetic approaches carried out have concentrated on the preparation of various substituted derivatives, as well as the synthesis of heteroanalogues of these compounds, where one or both of the intracyclic oxygen atoms have been replaced with sulfur, nitrogen and even in some cases, selenium.

In this project, the synthesis of a number of alkyl substituted isopsoralen analogues were investigated, utilising the reductive ozonolysis of *o*-allyl hydroxycoumarins as a key synthetic step. This approach led to the preparation of a number of novel 8-alkyl substituted 8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-ones in good yields.

This approach was subsequently extended in order to achieved the synthesis of sulfur analogues of isopsoralen, with the sulfur atom replacing the oxygen atom of the furan ring. Conversion of the hydroxy group of the *o*-allyl hydroxycoumarin into the protected thiol, followed by reductive ozonolysis and deprotection of the thiol, afforded 8-methoxy-8,9-dihydro-2*H*-thieno[2,3-*h*] chromen-2-one.

Preliminary investigations into the inclusion of selenium into the benzofuran ring system have indicated great potential for future synthetic approaches towards a range of seleno-isopsoralen derivatives.

CONTENTS

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my supervisor Dr. Ross Robinson for all his assistance and support during this project. Thanks must also go to my co-supervisor, Dr. David Gravestock for all his help and encouragement throughout the course of this project.

I would also like to thank the following people for technical assistance:

•Dr. Orde Munro for the X-ray crystallographic analysis he carried out, as well as for his assistance in the computational work performed.

•Prof. P. Boshoff (of the Cape Technikon Mass Spectrometry Unit) for all the high resolution mass spectrometry he carried out.

•Mr. Martin Watson for his assistance in the running and interpreting of NMR spectra.

•Mr. James Ryan for always being on hand to mend any mechanical problems.

•Mr. Paul Forder the glass blower, for providing the necessary glassware.

•The lab technicians Mr. Raj Somaru and Mr. Wilson Zondi, for always being ready to assist when needed.

Thanks also to my friends and colleagues in the Warren laboratory, for all their support and comradery, and for making the laboratory a pleasant place to work. Finally, I would like to thank Prof. S.E. Drewes and Mr. Martin Dovey for assisting in the final proof-reading of my thesis.

1. INTRODUCTION

1.1 BACKGROUND

The family of furocoumarin derivatives, known as psoralens, belong to an important class of natural and synthetic heterocyclic compounds which have been widely utilised both as drugs for the photo chemotherapeutic treatment of a range of topical skin diseases, as well as useful probes for the DNA and RNA structure and function of viral, bacterial and mammalian systems.[1,2,3]

Structurally, psoralens are tricyclic ring systems formed by the fusion of a furan ring with a coumarin. A linear fusion of these two structures affords a psoralen, while an angular fusion leads to an isopsoralen, also known as angelicin. **Figure 1** shows the structure of psoralen, angelicin, and some psoralen derivatives, as well as the numbering system typically used for these types of compounds. Both psoralens and isopsoralens have been isolated and characterised from natural sources,[4,5] most notably in the *Rutacae, Umbelliferae* and *Leguminosae* families.

Psoralen

Isosporalen
(Angelicin)

8-Methoxypsoralen
(8-MOP)

4,5',8-Trimethylpsoralen
(TMP)
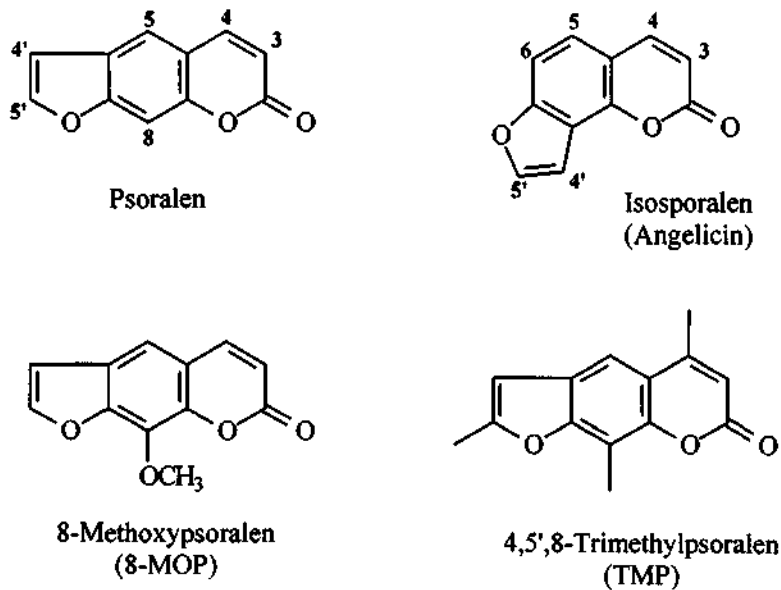
Figure 1

1.1.1 Uses of Psoralens

Clinically, psoralen derivatives are used in PUVA (psoralen plus UV-A) therapy and as such are used to treat a variety of topical skin diseases such as psoriasis and vitiligo.[3, 6] More recently, psoralens have also found use in extracorporeal photochemotherapy as a treatment of cutaneous T-cell lymphomas and other autoimmune diseases,[7] and they are also now recognised as effective virucidal agents, especially against enveloped viruses such as the herpes simplex virus and the human immunodefiency virus type 1 (HIV-1).[8] Psoralens have also proved to be a useful tool for the elucidation of the structure and function of nucleic acid in living systems,[1] as well as useful model compounds for mutagenesis and repair studies.[9]

1.2 INTERACTION WITH DNA

The biological activity of psoralens is essentially due to the photochemical reaction that occurs between psoralens and nucleic acids, especially DNA.[1] The primary site of this photo reaction is Thymine,[10] a pyrimidine base found in DNA, and the process follows three distinct steps. The first step involves intercalation of the planar psoralen between the base pairs of a DNA double helix (**Figure 2**).
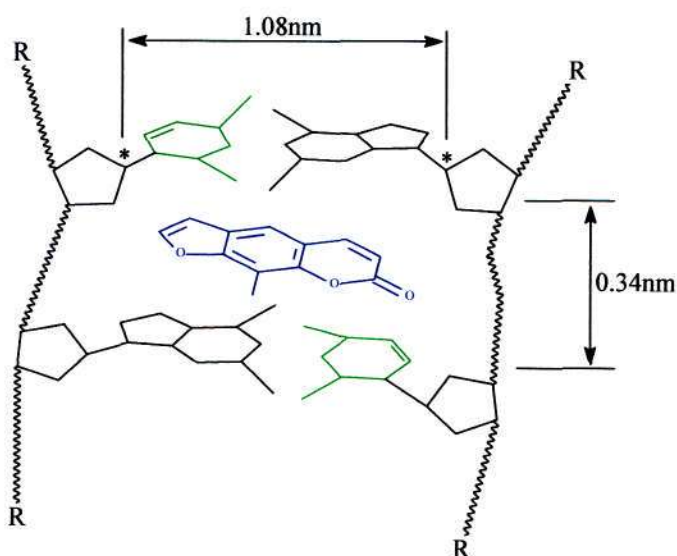
Figure 2: A schematic representation of the intercalation of 8-MOP between the base pairs of a DNA double helix.

In **Figure 2**, the intercalation of 8-MOP is clearly visible. It can be seen that the planar psoralen is optimally sized to fit into the geometric constraints[11] provided by the positioning of the bases. The structures of the bases have been simplified in order to provide a clearer and more concise representation of the intercalation step.

The subsequent step involves absorption of a long wave UV light photon (320-410 nm), inducing the intercalated psoralen to undergo a [2,2] cycloaddition reaction with the adjacent pyrimidine base. This reaction takes place between the 3,4 or 4',5' double bonds of the psoralen and the 5,6 double bond of the pyrimidine base to form either a furan-side or a pyrone-side monoadduct. Looking at **Figure 2**, the bases displayed in green are those with which cycloaddition can occur. Absorption of a second photon by some properly positioned monoadducts can then lead to the formation of a diadduct, resulting in interstrand cross-linking of the DNA double helix (**Scheme 1**). These adducts interfere with the unwinding of the DNA helix during replication, thus preventing replication and leading to the subsequent death of the cell.
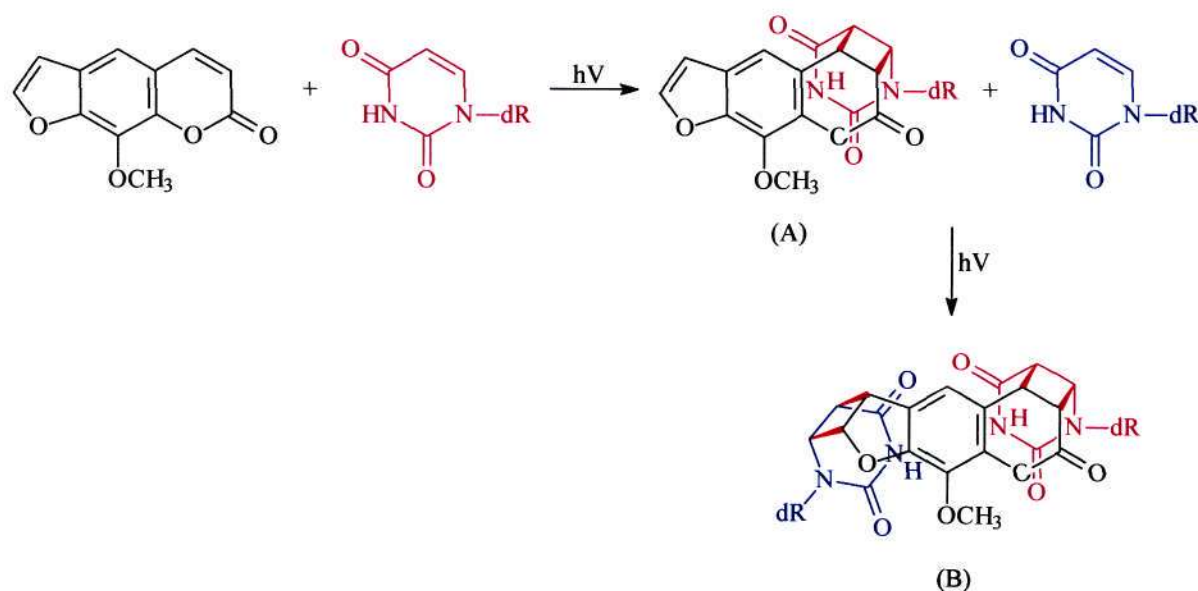
Scheme 1: The formation and structures of (A) the pyrone-side 8-MOP-pyrimidine monoadduct and (B), the 8-MOP-pyrimidine diadduct.

There has been extensive investigation of the photochemical addition products that are formed between psoralens and the pyrimidine bases of DNA and RNA, with the detailed structure of both monoadducts and diadducts formed with several psoralen derivatives having been reported.[2,12,13,14] Studies have also been conducted on sequence specificity[10] and thermal properties[15] of selected psoralen crosslinks, and the excited states of some psoralen derivatives have also been studied using luminescence and photoselection measurements.[16] Recent research in Italy has resulted in the development of a computational molecular modelling tool of DNA-psoralen complexes in order to help in the design of new furocoumarins.[17]

The versatility of psoralen chemistry arises from the degree of control that can be achieved within the reaction, by controlled timing of the delivery of the light. Furthermore, the monoadducts and diadducts (crosslinks) formed between psoralens and pyrimidines can be reversed with short wavelength ultraviolet light, a property used to great advantage in the determination of nucleic acid secondary structure using psoralens.[1]

1.2.1 Bifunctionality versus Monofuctionality

In spite of the success of the traditionally used psoralen derivatives 8-MOP and TMP in PUVA therapy, there have been a number of undesirable side effects associated with such treatment,[3] including skin phototoxicity, mutation and skin carcinogenesis. These side effects are generally attributed largely to the formation of interstrand crosslinks in the DNA double helix. As a result of protracted debates in the clinical community over the relative mutagenicity and/or carcinogenicity of monoadducts versus crosslinks, there has been increased interest in the synthesis of monofunctional psoralen derivatives which only add once to DNA, in the hope of overcoming the side effects experienced in traditional PUVA therapy.[3]

Isopsoralens, due to their angular geometry, do not crosslink to DNA. Their geometry is such that once a monoadduct has been formed, further reaction with a pyrimidine residue on the adjacent nucleic acid strand to form a crosslink is not possible due to a misalignment of the two reactive double bonds. There has thus been extensive interest in the synthesis of various isopsoralen derivatives in order to determine the extent of their reactivity towards DNA as an application in photochemotherapy, in comparison to the traditionally used 8-MOP and TMP. In fact, several

methylangelicin derivatives such as 6,4'-dimethyl and 4,6,4'-trimethylangelicin have been shown to have a much lower mutagenic activity and genotoxicity than 8-MOP. While they lacked any skin erythemogenic activity, they still showed a high antiproliferative activity; proving to be more effective than 8-MOP in the clearing of psoriatic lesions.[18]

Another way of blocking the bifunctionality of psoralens is to introduce steric hindrance or electron-withdrawing groups into the active sites. This type of research has led to the preparation and photobiological testing of derivatives such as pyridopsoralens[19] and carbethoxypsoralens.[20] Certain pyrrolocoumarins have also been found to be monofunctional and thus lacking in any skin phototoxicity.[21]

1.2.2 Effects of Substituents

The ability of the psoralen ring sytem to intercalate into and photobind to DNA and RNA is greatly influenced by the steric, position and electronic characteristics of the different substituents that are present on the parent compound. There have been many correlations made towards the extent of the effects that different substituents have on the photochemistry of psoralen derivatives. Some of the general trends known are the following:

(i) The photochemical effects of methylated psoralens and isopsoralens are much quicker than the unsubstituted analogues, with 6-methylangelicins showing an extremely high antiproliferative activity;[18]

(ii) Methyl substitution also seems to have an effect on pyrone versus furan photoaddition. Thus 8- MOP, with a methyl in the 4-position shows an overwhelming preference for addition to the furan double bond (*ca.* 98 %), attributed to steric interference between this methyl group and the 5-methyl group of thymine in the DNA. Those without this group show a much higher proportion of pyrone double bond addition (*ca.* 18 %);[22]

(iii) A methoxy group at the 8-position slows the photochemistry, for example, 8-MOP reacts much more slowly with DNA and also has a much greater half-life in solution than TMP;[23] and

(iv) Other strong electron withdrawing or donating groups such as hydroxy, amino, and nitro groups either drastically reduce or completely eliminate the ability of the psoralen to

undergo photocycloaddition with nucleic acids. For example, 8-MOP substituted at the 5- position with an amino or nitro group shows no reactivity with DNA.[23]

1.3 SYNTHETIC ROUTES TOWARDS PSORALEN DERIVATIVES

The synthetic strategies which have been developed largely involve the preparation of the psoralen tricyclic ring system from either a coumarin or a benzofuran and subsequently extending the synthetic procedure to the third ring (i.e. the furan or pyrone ring) respectively. These two systems were originally prepared from resorcinol or a derivative (**Scheme 2**), in this case the substituents at the 5 and 8 positions of the final psoralen were those present in the resorcinol derivative used in the initial step.

Less utilised methods involve the exocyclic modification of the intact psoralen nucleus. Some recent approaches involve the use of a single ring system other than resorcinol from which to build on the furan and pyrone rings using various synthetic procedures. All these techniques are able to lead to a large range of psoralen derivatives containing many different functionalities.

Resorcinol   Coumarin   Benzofuran
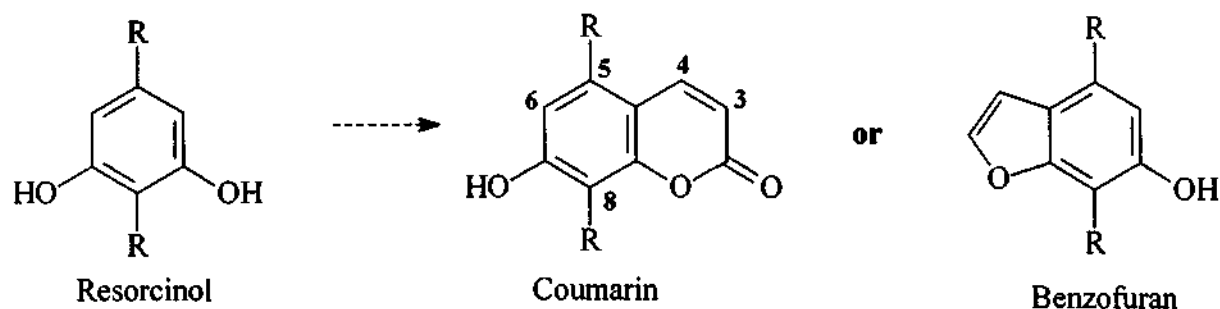
Scheme 2

1.3.1 General Psoralen Synthesis

1.3.1.1 Using *o*-allyl-7-hydroxycoumarins

One of the more common methods utilised for psoralen synthesis involves the use of *o*-allyl

hydroxy coumarins as a starting material, with attention being directed towards the synthesis of the furan ring in order to complete the system. Kaufman[24] reported the synthesis of methyl-substituted psoralens and isopsoralens *via* this starting material using a method involving Claisen rearrangement, acetylation, bromination and cyclisation in a basic medium (**Schemes 3 and 4**).
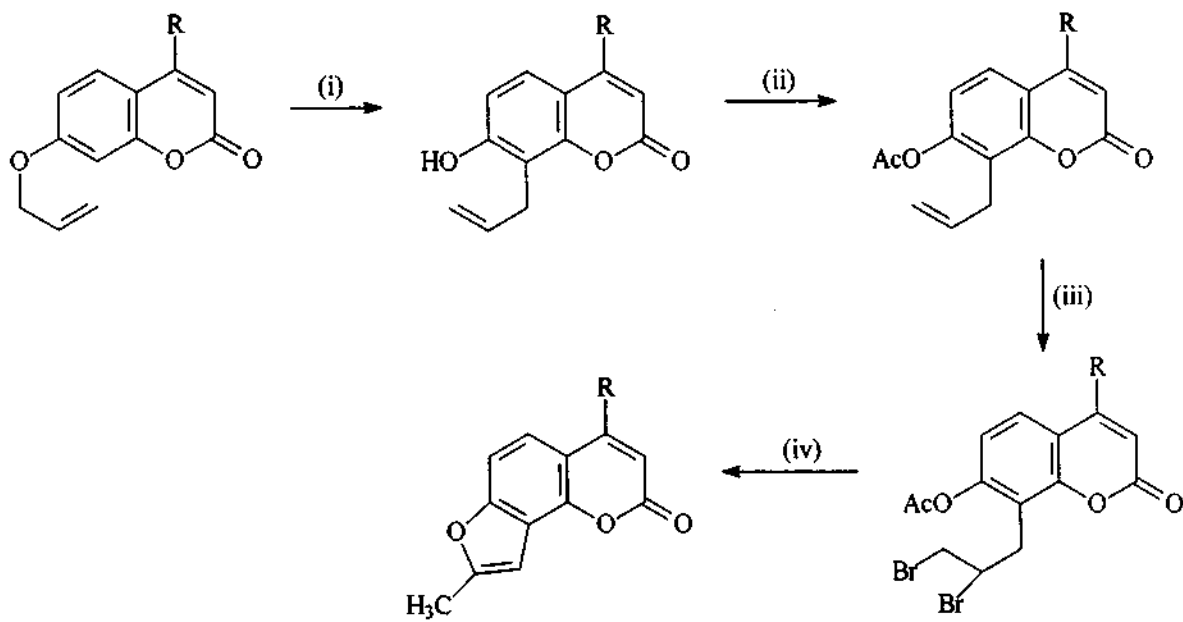
(i) 220°C; (ii) Ac$_2$O, NaOAc; (iii) Br$_2$; (iv) KOH, C$_2$H$_5$OH

Scheme 3
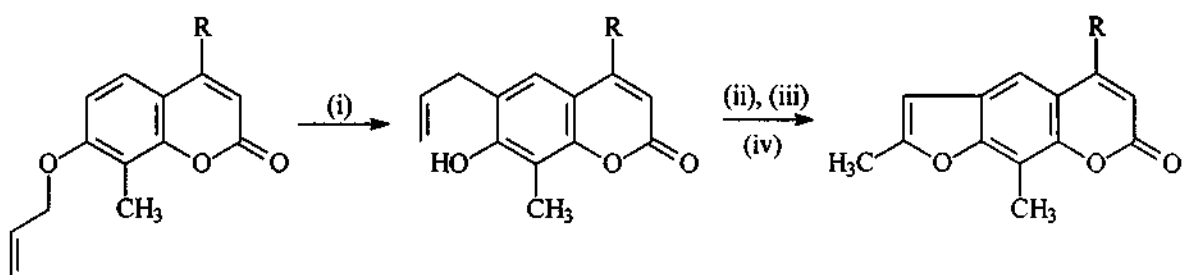
(i) 220°C; (ii) Ac$_2$O, NaOAc; (iii) Br$_2$; (iv) KOH, C$_2$H$_5$OH

Scheme 4

Kaufman utilised this method in later work for the synthesis of 8-amino-4,5'-dimethyl psoralen,[25] where 4-methylcoumarin was nitrated to give an amino group in the 8-position. Acetylation,

bromination and cyclisation as previously achieved then afforded the desired psoralen. This method was a novel approach towards these types of derivatives at the time. Previous methods had mostly consisted of the preparation of these types of compounds from *o*-formyl or *o*-acyl-7-hydroxycoumarins in three or four steps. However, the former compounds were generally prepared in low yield, while the latter coumarins were produced by Fries rearrangements, which frequently led to mixtures of isomeric compounds. The work reported by Kaufman was thus one of the first to demonstrate the value of *o*-allyl-hydroxycoumarins as intermediates in the synthesis of furocoumarin derivatives.

Research reported by Roy and Sen[26] describe the use of 6-allyl-5-hydroxycoumarin, as well as 6-acetyl-5-hydroxycoumarin in the preparation of two, methyl-substituted allopsoralens (4a,b). 6-Allyl-5-hydroxycoumarin (2), on cyclisation with hydrobromic acid in glacial acetic acid gave 2,3-dihydro-2-methyl allopsoralen (3). This subsequently led to the isopsoralen derivative 4a on dehydrogenation over Pd/C in boiling diphenyl oxide (Scheme 5). The synthesis of the isopsoralen derivative 4b was achieved *via* condensation of 6-acetyl-5-hydroxycoumarin with ethyl bromoacetate to yield 5, the corresponding acid of which gave the psoralen derivative 4b on heating with acetic anhydride and sodium acetate (Scheme 5).
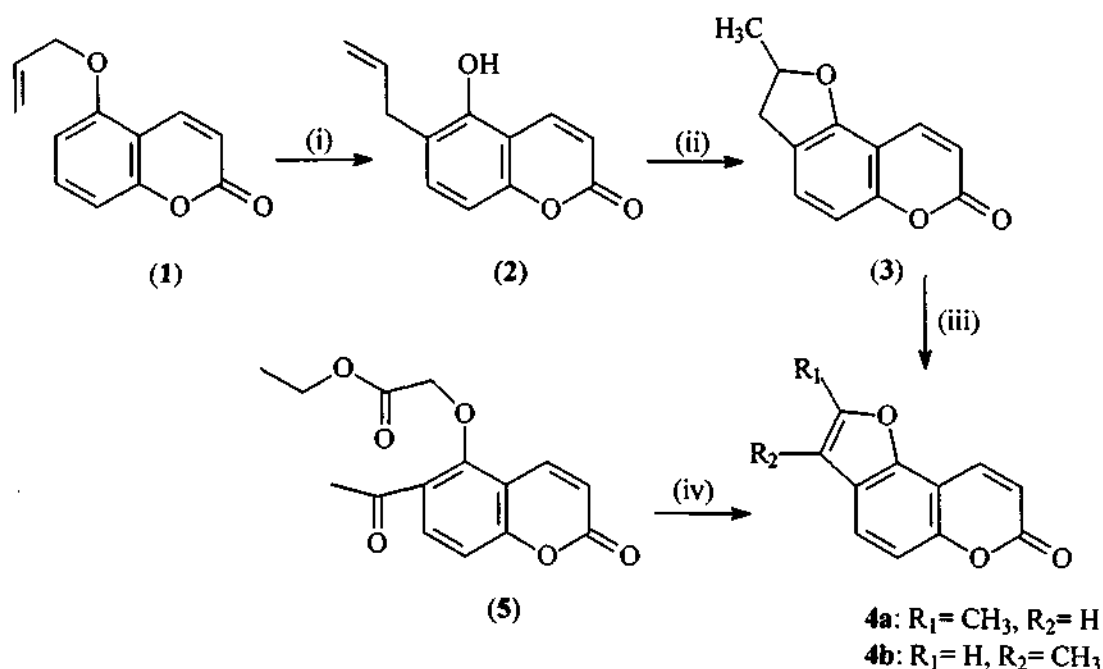
(i) Dimethylaniline, reflux; (ii) HBr/ CH₃COOH, reflux;
(iii) Diphenyl oxide, 10% Pd/C; (iv) Acetic anhydride, sodium acetate

Scheme 5

6-Allyl-7-hydroxycoumarins have also been applied to the synthesis of a range of 8-acetyl-psoralens.[27] The introduction of the acetyl into the 8-position was achieved *via* a Fries rearrangement[28] of the acetate of coumarin **6** to produce **7** (**Scheme 6**). The corresponding allyl ethers were obtained by reaction with either allyl bromide or 2,3-dichloro-1-propene in 1:1 DMF and benzene mixture together with potassium carbonate at 80°C to yield the allylaryl ether **8**. Claisen rearrangement then led to the 6-allyl-8-acetyl hydroxycoumarin analogues (**9**). Acetyl migration to give 6-acetyl-8-allyl hydroxycoumarins proved to be a problematic side reaction. Treatment of **9** (X= Cl) with 70% sulfuric acid mixture afforded the 8-acetylpsoralens (**10**) (**Scheme 6**). This procedure was also utilised in the synthesis of 4,5',8-trimethylpsoralen.[29] These compounds proved to be very versatile, with the acetyl group being converted to the amino methyl, α- and β-hydroxyethyl, α-aminoethyl and 8-methoxypsoralens. Ozonolysis of **9** (X= H) in formic acid also led to the corresponding aldehydes, which on treatment with a variety of acids, resulted in furan formation to give the acetylpsoralen derivatives **11**.
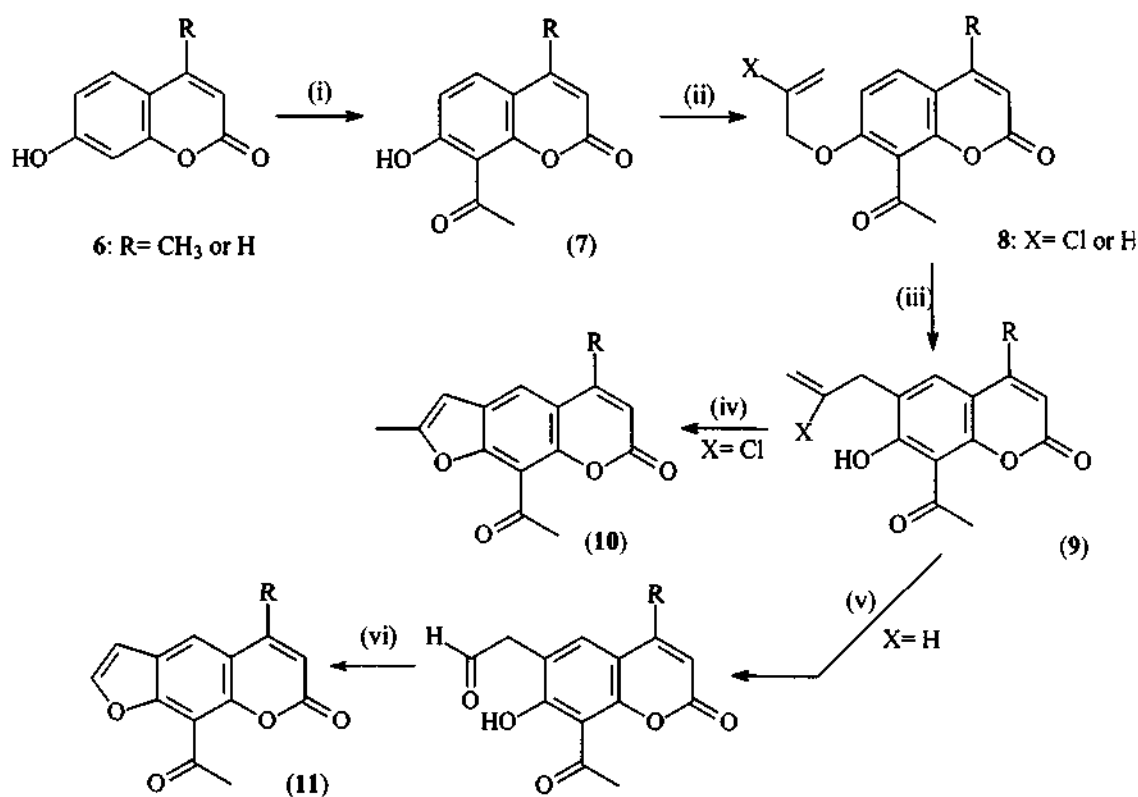
(i) Hexamethylenetetramine, CH₃COOH, 95°C;
(ii) DMF, potassium fluoride, allyl bromide or 2,3-dichloro-1-propene;
(iii) Diisopropylbenzene, reflux; (iv) 70% H₂SO₄, H₂O; (v) Formic acid, O₃, (CH₃)₂S;
(vi) 85% H₃PO₄ / 70% H₂SO₄ / polyphosphoric acid or methanesulfonic acid

Scheme 6

Syntheses carried out by Guiotto et al.[18,30] resulted in the preparation of various, new methyl-substituted isopsoralens. A number of these derivatives were synthesised using the same procedures as described by Kaufman[24] and Roy and Sen,[26] however starting with 5- and 7-hydroxycoumarins substituted in various positions with methyl groups. These starting materials afforded a range of novel isopsoralen derivatives 12 - 14 (Scheme 7).

12: R_1, R_2, R_3= CH_3 or H

(13)

14: R_1, R_2= CH_3 or H
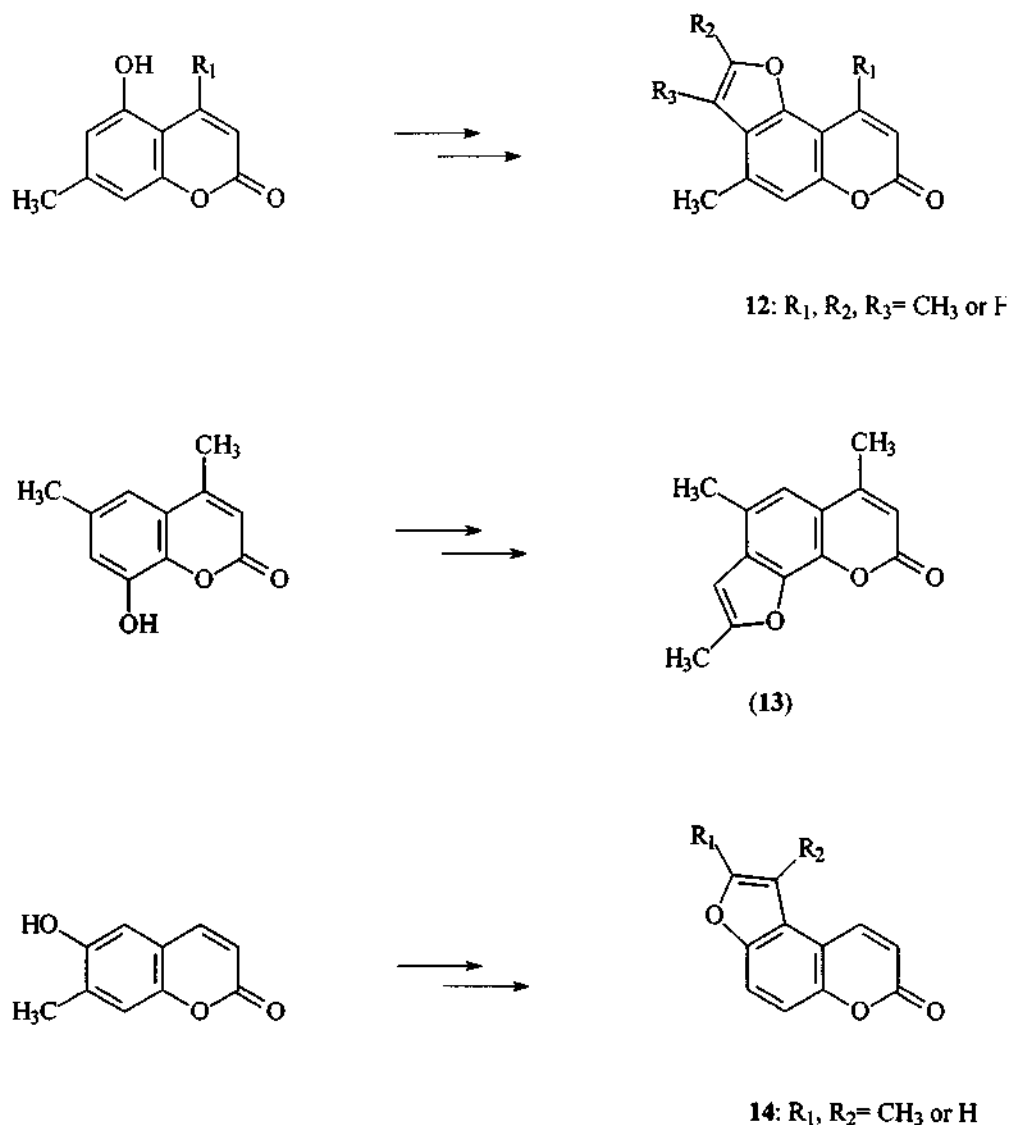
Scheme 7

Additional work by Guiotto et al. made use of a different approach (Scheme 8) in which the synthesis of a range of methylated isopsoralens without any substitution in the furan ring was achieved. Ozonolysis of the o-allyl hydroxycoumarins (15, 18, and 21) then afforded the

corresponding *o*-hydroxy coumarinylacetaldehydes (**16, 19,** and **22**) which were cyclised in the presence of phosphoric acid to afford the methyl substituted isopsoralens (**17, 20,** and **23**) in *ca.* 30-40 % yield (**Scheme 8**).
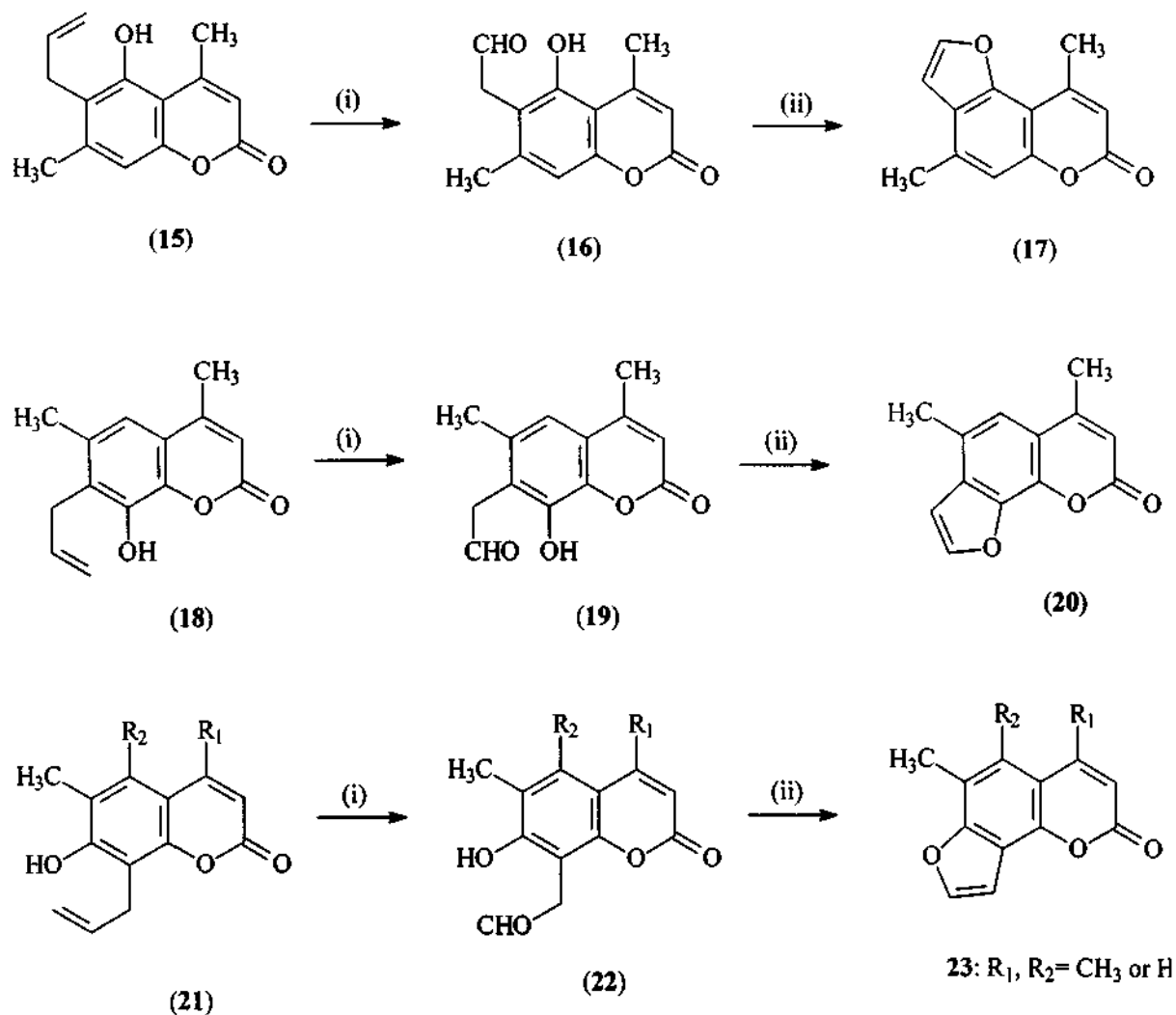
(i) O_3, H_2/ Pd 10% on $CaCO_3$; (ii) 85% H_3PO_4, 100°C

Scheme 8

1.3.1.2 Other Synthetic Routes Towards Psoralen Derivatives

There have been various other synthetic routes towards psoralen derivatives that do not make use of *o*-allyl hydroxycoumarins. MacLeod and Worth[31] reported the synthesis of a range of psoralen derivatives utilising an intramolecular aldol condensation reaction (**Scheme 9**). This was

achieved *via* condensation of chloroacetone or phenacyl bromide with 7-hydroxy coumarin (or its 4-methyl derivative) to yield compounds **25**, which, when refluxed in 0.1N aqueous KOH followed by cooling and acidification, afforded the respective psoralens (**26**). It was found that cyclisation occurred so as to afford the linear psoralens only.

24: R_1 = CH$_3$ or H   25: R_1= CH$_3$ or H   (26)
                                         R_2= CH$_3$ or C$_6$H$_5$
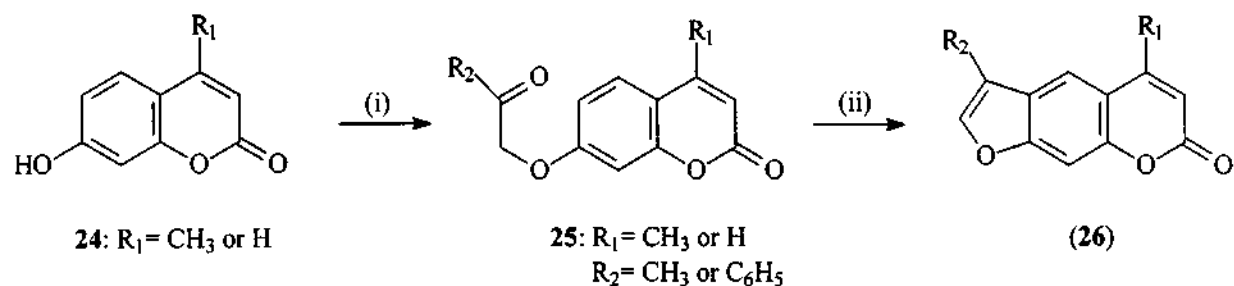
(i) CH$_3$COCH$_2$Cl or C$_6$H$_5$COCH$_2$Br, K$_2$CO$_3$; (ii) KOH/6 hours, H$^+$

Scheme 9

In the search for monofunctional psoralen derivatives, as discussed before, a few pyridopsoralens have also been prepared.[19] Those derivatives with a fused pyridine ring on the pyran of the psoralen were accessed *via* the condensation of 1-benzyl-3-ethoxycarbonyl-piperidin-4-one with 6-hydroxy-2,3-dihydrobenzofuran acetates **27** according to the von Pechmann reaction. Aromatisation of the subsequent products using palladium on charcoal afforded the pyropsoralens (**29**) (**Scheme 10**).

27: R= CH$_3$ or H   (28)   (29)

(i) Palladium/Charcoal
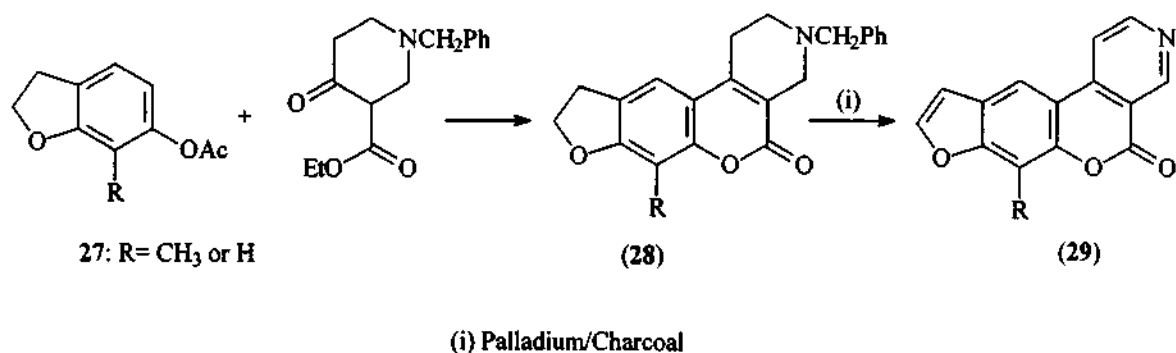
Scheme 10

Psoralens with a pyridine ring fused to the furan ring were prepared using a different route. The diaryl ether (**32a**) was synthesised by condensation of the nitropyridine **30** with the phenol **31** (**Scheme 11**). This compound, after reduction to the amine and diazotisation to **32b**, decomposed in the presence of cupric chloride to give the benzofuro-pyridine (**33**). Demethylation in boiling pyridine hydrochloride and formylation at the 8-position with hexamethylenetetra-amine in boiling acetic acid then afforded the aldehyde **34**. Condensation with diethyl malonate gave the ethoxycarbonyl-pyridopsoralen (**35**), which, following decarboxylation and hydrolysis, yielded the final pyridopsoralen (**36**) in 49% yield. Analogous compounds, with a benzene ring fused to the furan ring have also been prepared using similar chemistry.[32]

(**30**)   (**31**)   **32a**: R= NO₂,
32b: R= N₂⁺Cl⁻

(**34**)   (**33**)

35: R= CO₂Et,
36: R= H
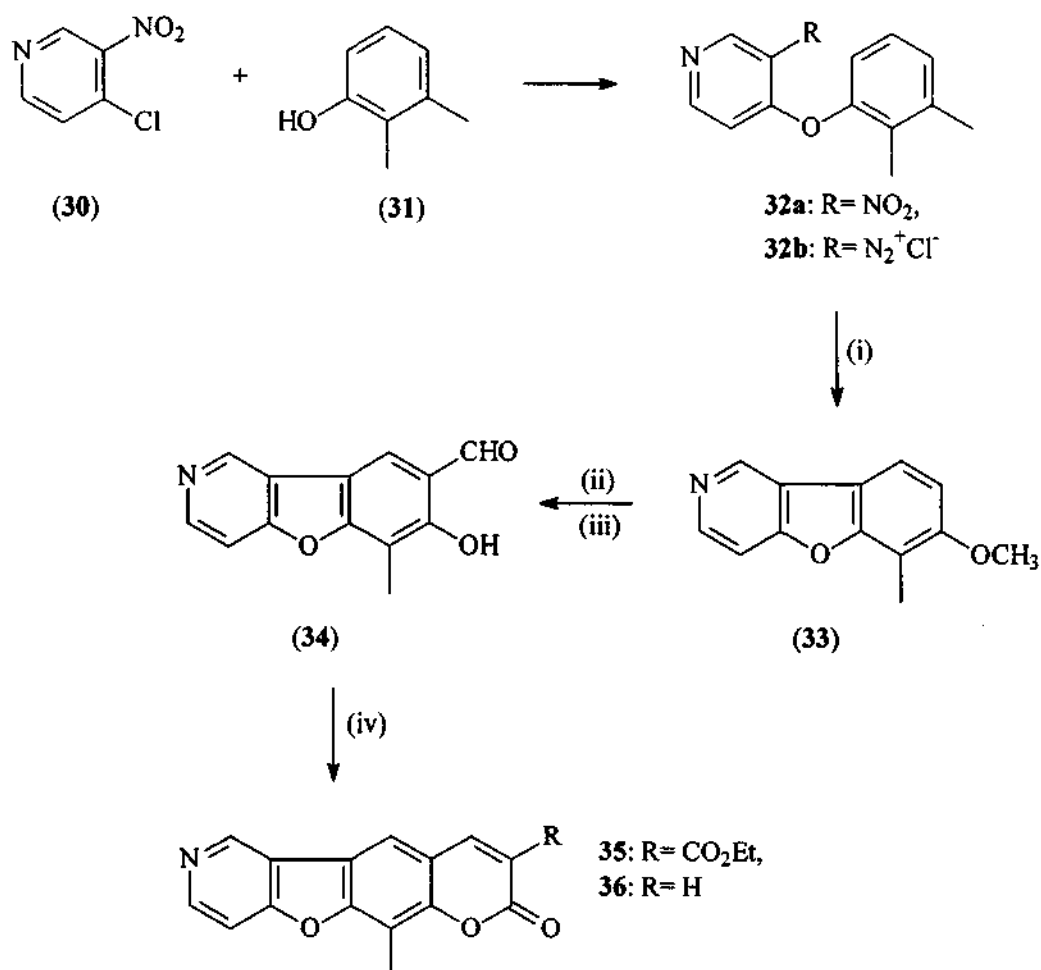
(i) Cupric chloride, acetone H₂O, 35°C then reflux; (ii) Pyridine hydrochloride, 220-230°C;
(iii) Hexamethylenetetra-amine, acetic acid; (iv) Ethanol, diethylmalonate, piperidine, reflux

Scheme 11

A different approach towards the synthesis of angular furanocoumarins was reported by Wulff and co-workers.[33] They described the synthesis of the isopsoralen derivatives sphondin (**42a**) and heratomin (**42b**), by utilising the benzannulation reaction of furylcarbene complexes of chromium (**Scheme 12**). Sphondin was prepared by the benzannulation of the 2-furyl complex **40** with methyl 4-pentynoate **38**, by heating in THF for 18 hours. The complex was obtained from the ammonium metal acylate **37** (prepared in two steps from furan and chromium hexacarbonyl). The product from the reaction (**41a**), was then dehydrogenated using 2,3-dichloro-5,6-dicyano quinone (DDQ) to afford sphondin (**42a**). The synthesis of heratomin was achieved using the same methodology from the carbene complex **39**. The final dehydrogenation, however, did prove problematic and gave a much lower yield of the final psoralen, **42b**.
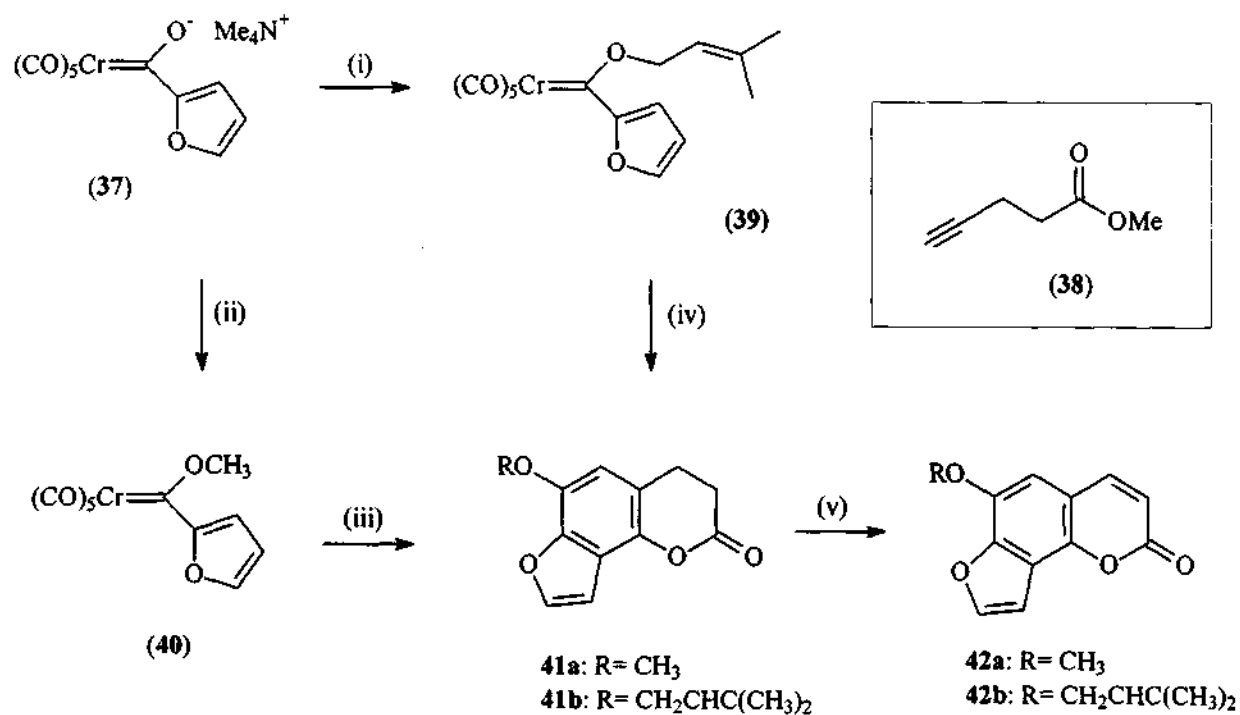
(i) $(CH_3)_2C=CHCH_2Br$, $20^\circ C$; (ii) AcCl, CH_3OH; (iii) **38**, $85^\circ C$/ air, silica gel;
(iv) **38**, CH_3OH, $85^\circ C$/ Cl_3CO_2H, PhH, reflux; (v) 4eq. DDQ, $PhCH_3$, reflux

Scheme 12

Also reported recently has been the use of a photochemical aromatic annulation strategy in the synthesis of the psoralen bergapten (47).[34] In this procedure, the aromatic annulation of ketone 43 with the siloxyalkyne (44) was achieved by irradiating a degassed solution of the two for 3.5 hours, followed by refluxing for a further 2 hours (Scheme 13). The resulting silylated product (45) was then methylated with methyl iodide and the two silyl ethers cleaved with tetra-n-butylammonium floride to give the diol (46). Oxidative cylcisation was then achieved using a ruthenium complex catalyst. This was followed by dehydrogenation with DDQ, to afford the desired 5-methoxy psoralen (47) in 86% yield.

(43) (44) (i) → (45)

(ii)
(iii)

(47) (iv) ← (v) (46)
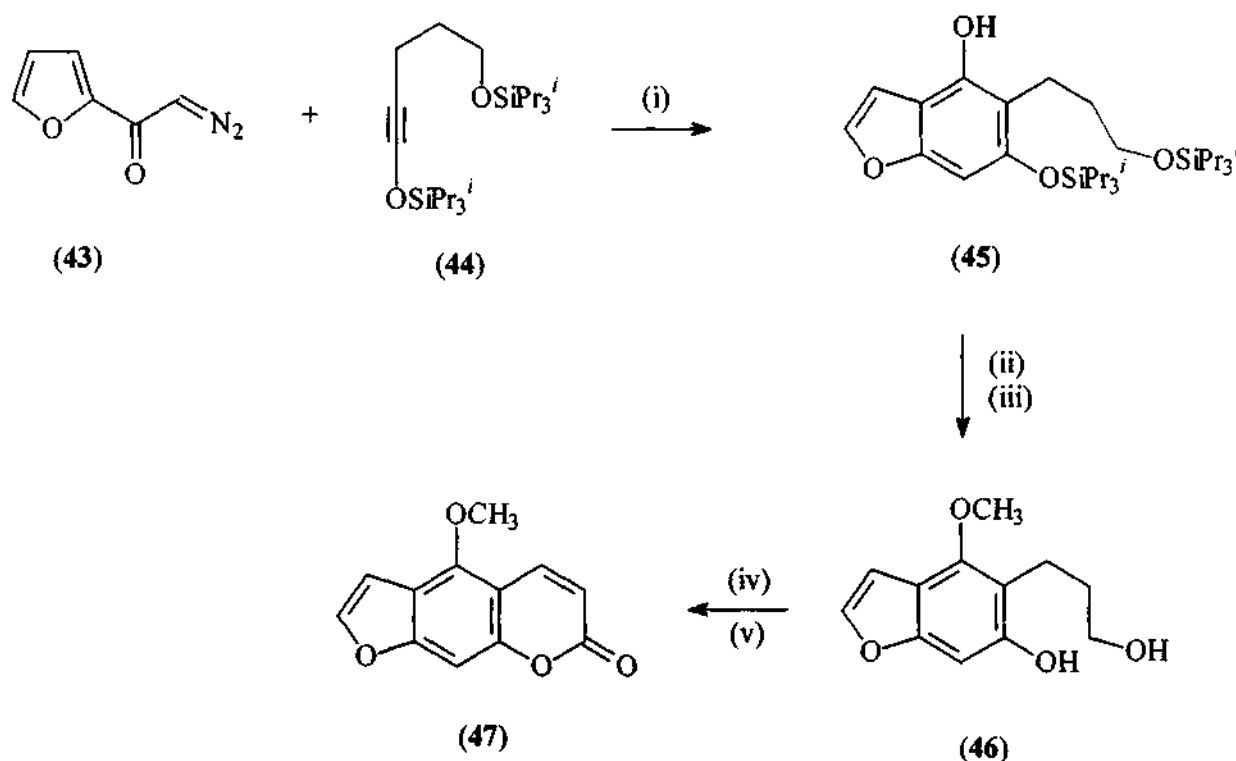
(i) hν, ClCH$_2$CH$_2$Cl, heat; (ii) K$_2$CO$_3$, CH$_3$I, acetone, heat;
(iii) n-Bu$_4$NF, THF, 0°C to R.T.; (iv) cat. H$_2$Ru(PPh$_3$)$_4$, acetone-toluene, 185°C;
(v) DDQ, benzene, cat. p-nitrophenol, heat

Scheme 13

The utilisation of anionic [4+2] cycloaddition strategy towards the synthesis of 8-MOP and its isoster has been reported by Murty and Datta.[35, 36] The preparation involved the annulation of methyl 3-(phenylsulfinylmethyl)-2-furoate (48) with enone 49 to give the desired product 50a,

which was subsequently methylated to give **50b** (**Scheme 14**). Flash vacuum thermolytic conditions (500°C, 0.1 mmHg)[37] afforded the enone 8-methoxy-1-oxa-*s*-indacen-7-one (**51**). Treatment of this product with thiophenol in the presence of triethylamine provided the keto sulfide **52**. This, when exposed to $H_2O_2/(CH_3CO)_2O/$ H_2SO_4 yielded the desired 8-methoxy psoralen (**53**), along with ketosulfone **54**.

(48)   (49)   50a: R= H
                                                                              50b: R= CH$_3$

(53)   (52)   (51)

(54)
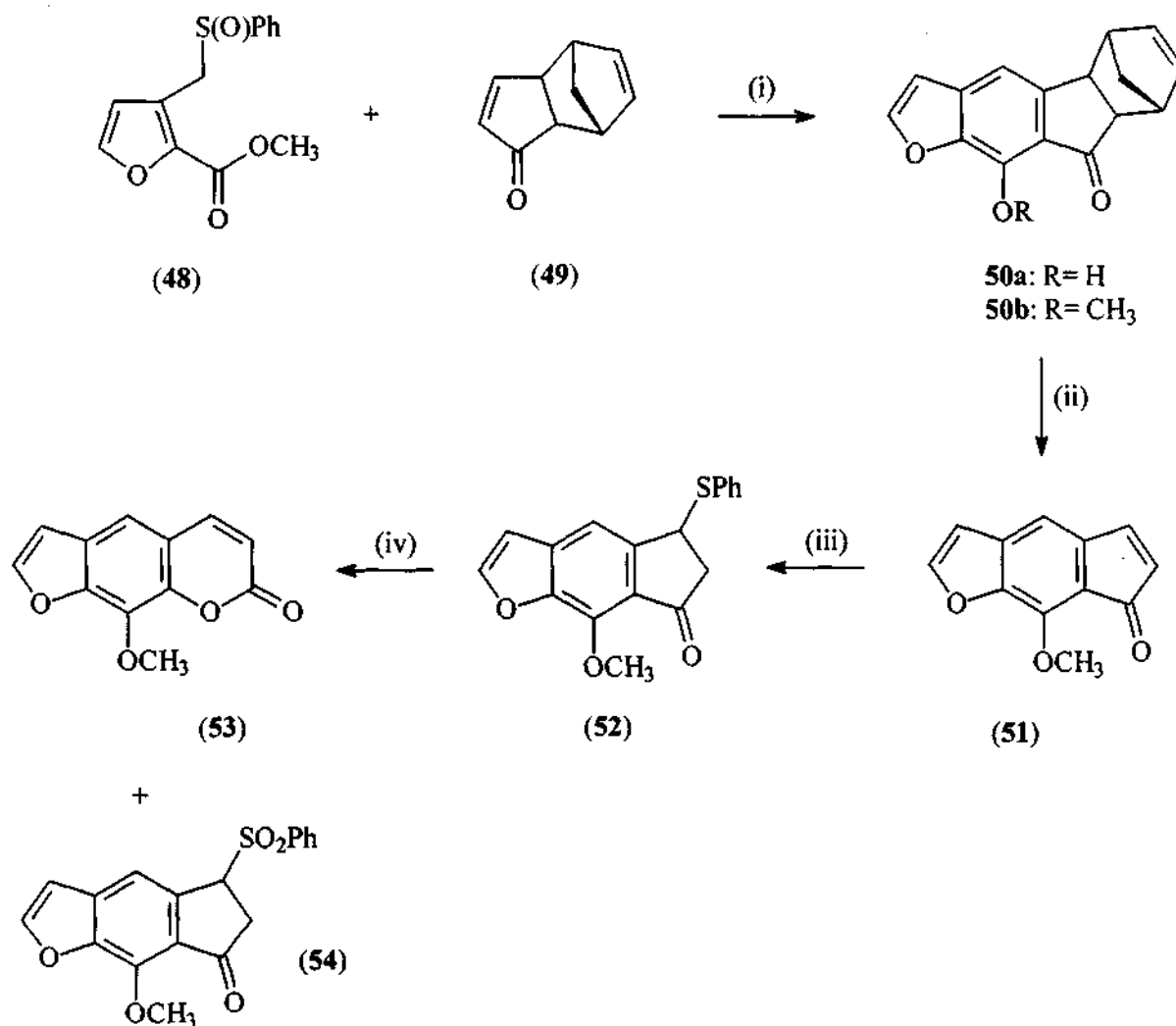
(i) ^{t}BuOLi, -60°C; (ii) FVP (500°C, 0.1 mmHg);
(iii) PhSH, Et$_3$N; (iv) H_2O_2, Ac$_2$O, H_2SO_4

Scheme 14

The chemistry that has been described thus far represents the main areas of research towards the synthesis of psoralen derivatives. There have also been a few other synthetic pathways towards these types of compounds. These involve the recent biosynthsesis of some psoralen

derivatives,[38,39,40] and also the synthesis of some analogues of, for example 8-MOP[41] and 4,5',8-TMP[42] *via* exocyclic modification of the intact parent ring system.

1.3.2 Synthesis of psoralen heteroanalogues

A popular area of interest in the synthesis of organic molecules with biological activity often lies with the synthesis of heteroanalogues of these compounds i.e. replacement of oxygen atoms in the molecule with heteroatoms like nitrogen and sulfur. This has also been of great interest in the area of psoralen chemistry, with a vast range of heteroanalogues being synthesised in order to prepare psoralen derivatives with a more efficient photochemistry than those traditionally used in photochemotherapy. So far the literature reveals that a number of nitrogen, sulfur, and even some selenium analogues of psoralen and isopsoralen have been synthesised, and some of these new derivatives have been tested with regard to their photophysical, photochemical, and photobiological properties.

1.3.2.1 Synthesis of Nitrogen Analogues

In the search for heteroanalogues of psoralens with a more efficient photochemistry, there has been much work reported on the synthesis of psoralen derivatives containing nitrogen in the tricyclic ring system. A novel approach towards the construction of azapsoralen, in which one of the ring oxygen atoms was replaced by nitrogen, made use of an intramolecular Diels-Alder reaction[43] (**Scheme 15**). In this procedure, the required starting material **55** was prepared in seven steps and in good yield from ethyl acetoacetate. The acid-catalysed reaction of this with furan gave **56**, from which the acetal **57** was prepared. This acetal, on heating with Pd/C, underwent cycloaddition with aromatisation to give **58**, which was subsequently deprotected to the tricyclic ketone **59**. A number of treatments: oximation, mesylation, Beckman rearrangement[44] and dehydrogenation then afforded azapsoralen **61** in a low overall yield.

The tricyclic ketone **59** could also be converted into psoralen *via* a Baeyer-Villiger[45] oxidation reaction, demonstrating the potential value of utilising the Diels-Alder approach as a means of synthesising a range of psoralens and their heteroanalogues. A number of substituted azapsoralens with a pyridine ring substituting the central benzene ring of the psoralen nucleus

have also been synthesised recently.[46]
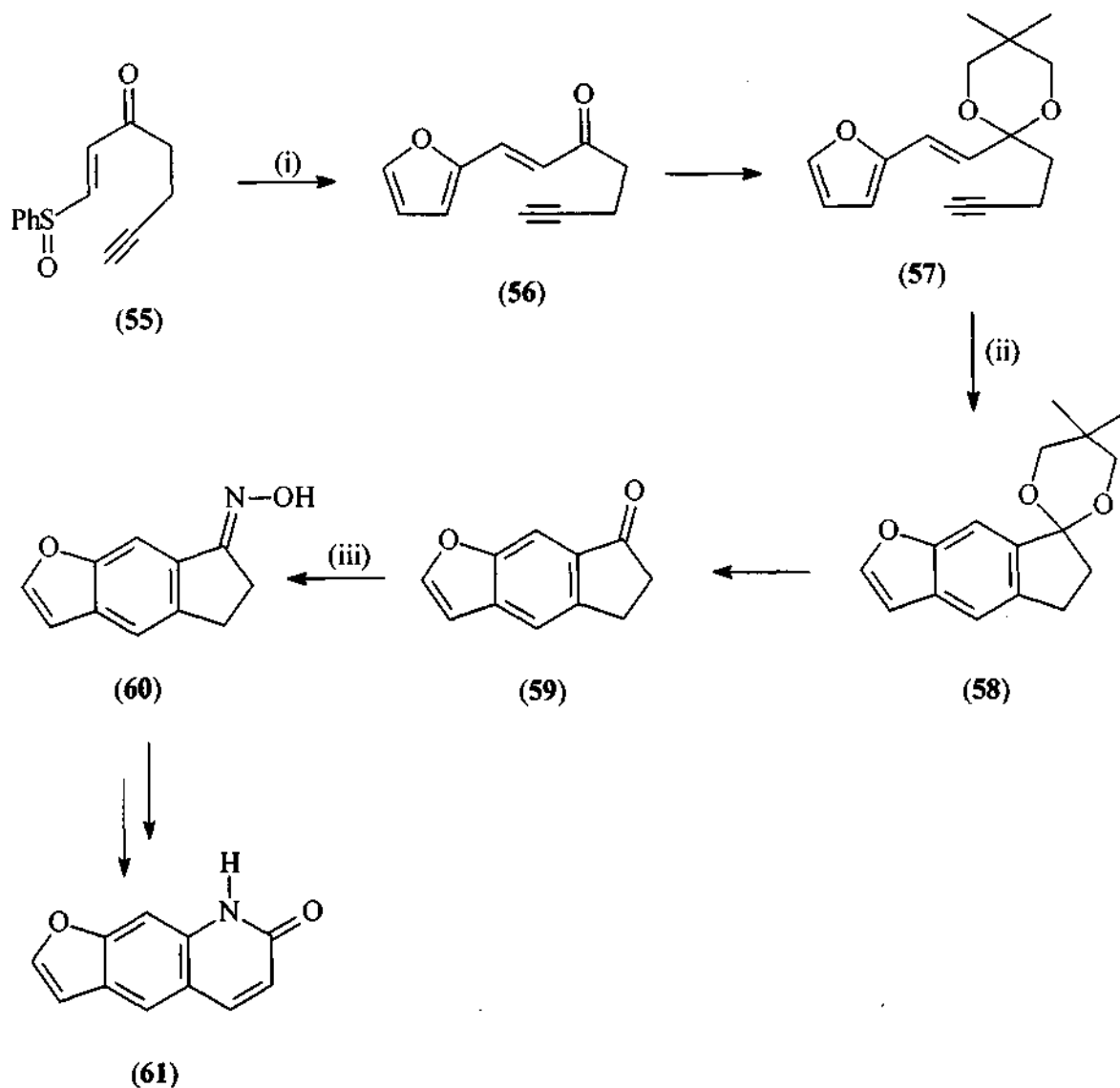
(i) 10eq. furan, *p*-TSOH; (ii) 10% Pd/C, xylene, 200°C;
(iii) H₂NOH.HCl, NaOAc, ethanol, reflux

Scheme 15

A new range of pyrrolocoumarin derivatives reported by Quanten *et al.*,[47] were synthesised from
m-anisidine (**62**) (**Scheme 16**). The first step involved formylation or acetylation with formic acid
or acetic anhydride to give the substituted amine products **63a** and **63b** respectively. Reduction
with LiAlH₄ followed by treatment with chloroacetyl chloride, then ring closure with AlCl₃
afforded the alkylated amines (**66a,b**). These *N*-alkyl-6-hydroxyoxindoles were then reduced in

the presence of LiAlH$_4$ and isolated as the hydrochloride. Pechman condensation with ethyl acetoacetate, followed by dehydrogenation then afforded the desired pyrrolocoumarins (**69a,b**). These derivatives, as well as some others tested, have been found to exhibit potential photochemotherapeutic properties.[48, 49]
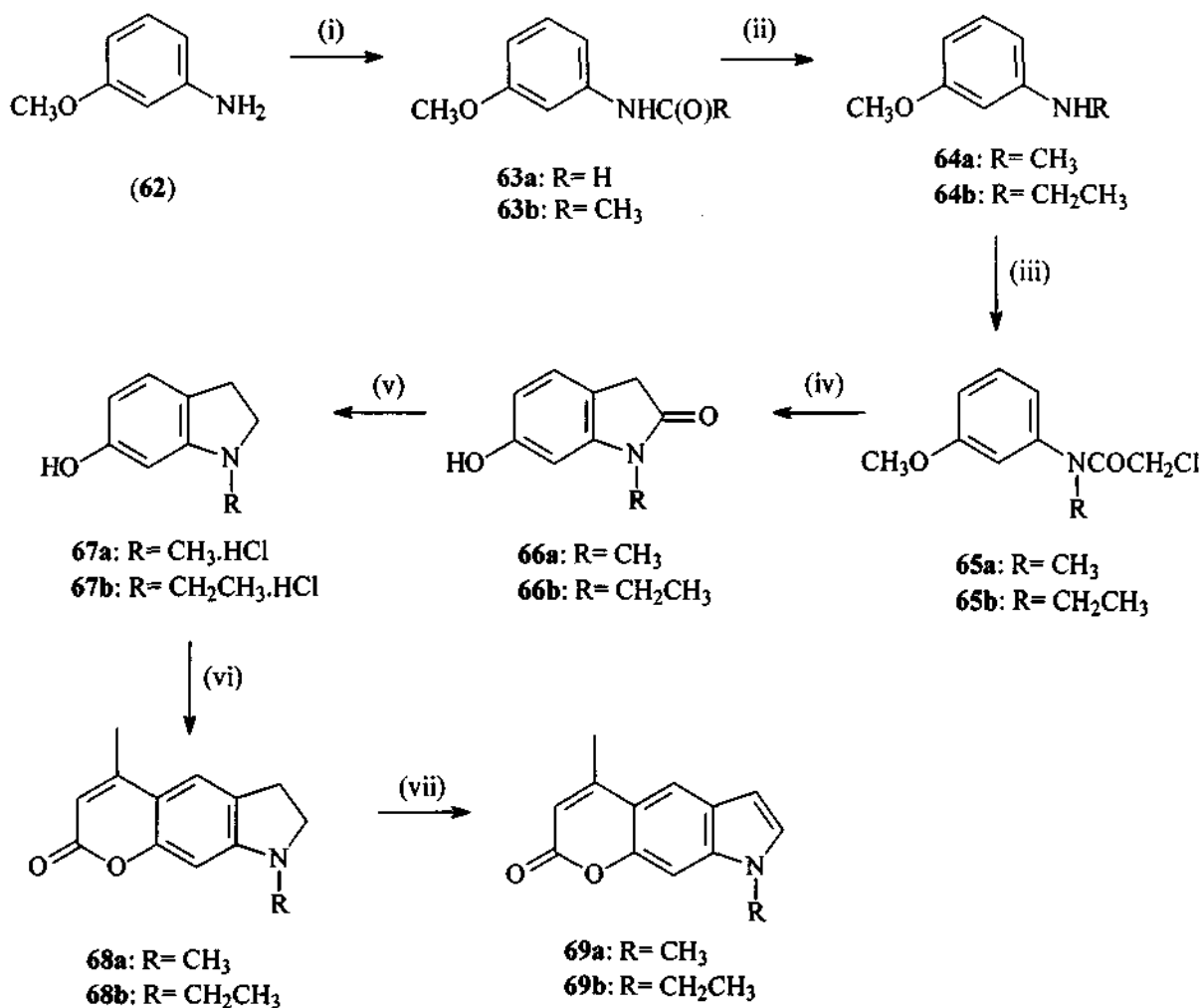
(i) HCOOH or HOAc,(CH$_3$CO)$_2$O, (ii) LiAlH$_4$; (iii) ClCH$_2$COCl; (iv) AlCl$_3$;
(v) LiAlH$_4$.NaBH$_4$; (vi) ethyl acetoacetate, triethylamine, ZnCl$_2$; (vii) Pd/C

Scheme 16

A range of methylfuroquinolinones, with nitrogen replacing oxygen in the pyrone ring, have been

synthesised by Guiotto *et al.*[50] Their procedure involved condensation of 2,6-diaminotoluene (70) (Scheme 17) with ethylacetoacetate or ethyl methylacetoacetate to give the 7-amino quinolin-2-ones (71). Formation of the diazonium salts followed by hydrolysis then afforded the 7-hydroxy derivatives (72). The formation of the furan ring was accomplished using the approach established by Kaufman, which involved allylation, rearrangement, acetylation, bromination and cyclisation to afford the methylated furo[3,2-g]quinolin-7(8*H*)-ones (74).

(70)   71: R= H or CH₃   (72)

74: R and R₁= H or CH₃   73: R₁= H or CH₃
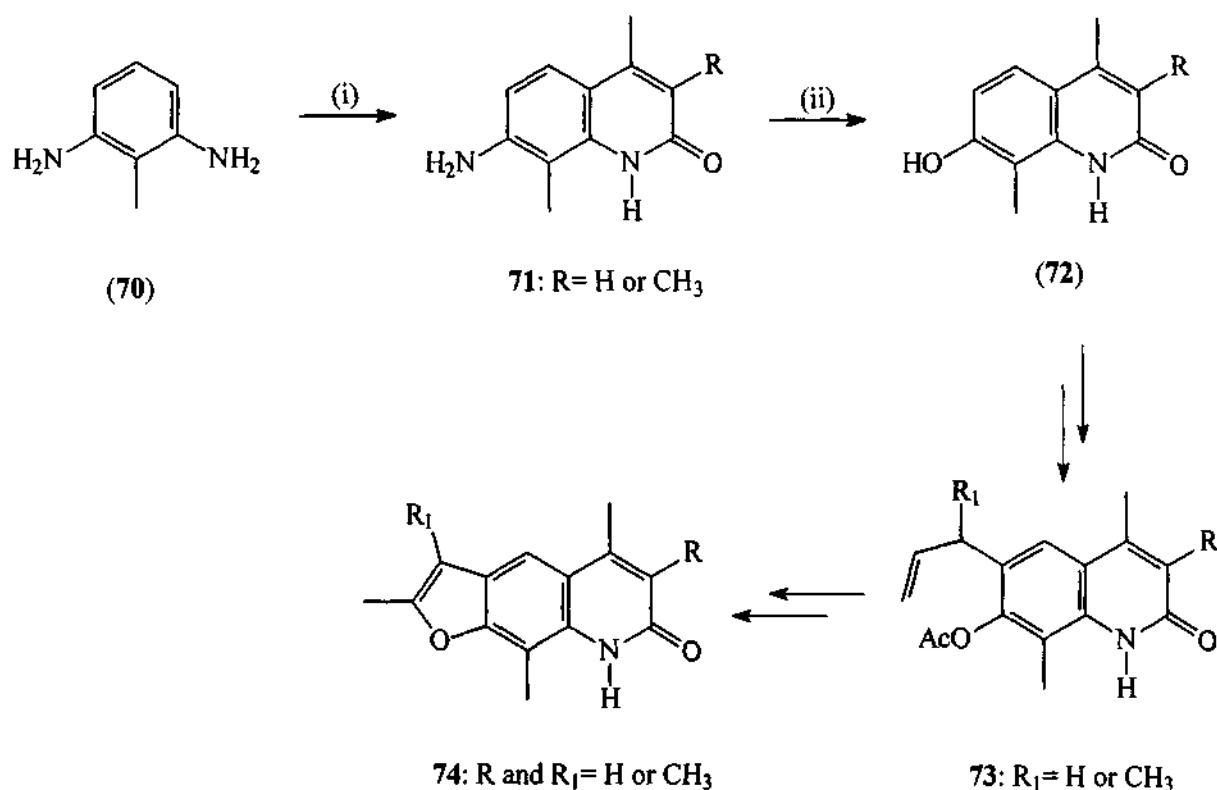
(i) Ethylacetoacetate, 150°C;
(ii) H₂O, conc. H₂SO₄, sodium nitrite, 0°C then boiling H₂SO₄

Scheme 17

Recently a large range of psoralen derivatives with nitrogen substituted at various positions in the psoralen nucleus were reported, again by Guiotto and co-workers.[51] Making use of variations in methodology already discussed, they synthesised a range of various, differently substituted psoralen analogues 75 to 82 (**Figure 3**, R= H or CH₃). The antiproliferative activity of these analogues was also tested, and some of the compounds synthsesised were found to possess very

promising biological activity. In fact, the pyrrolocoumarins were found to exhibit significant photoreactivity towards nucleic acids, and the largely predominant formation of a 3,4 photoadduct, (indicated by HPLC and spectroscopic studies), provides strong evidence for the monofunctionality of these compounds.

(75)   (76)   (77)

(78)   (79)   (80)

(81)   (82)
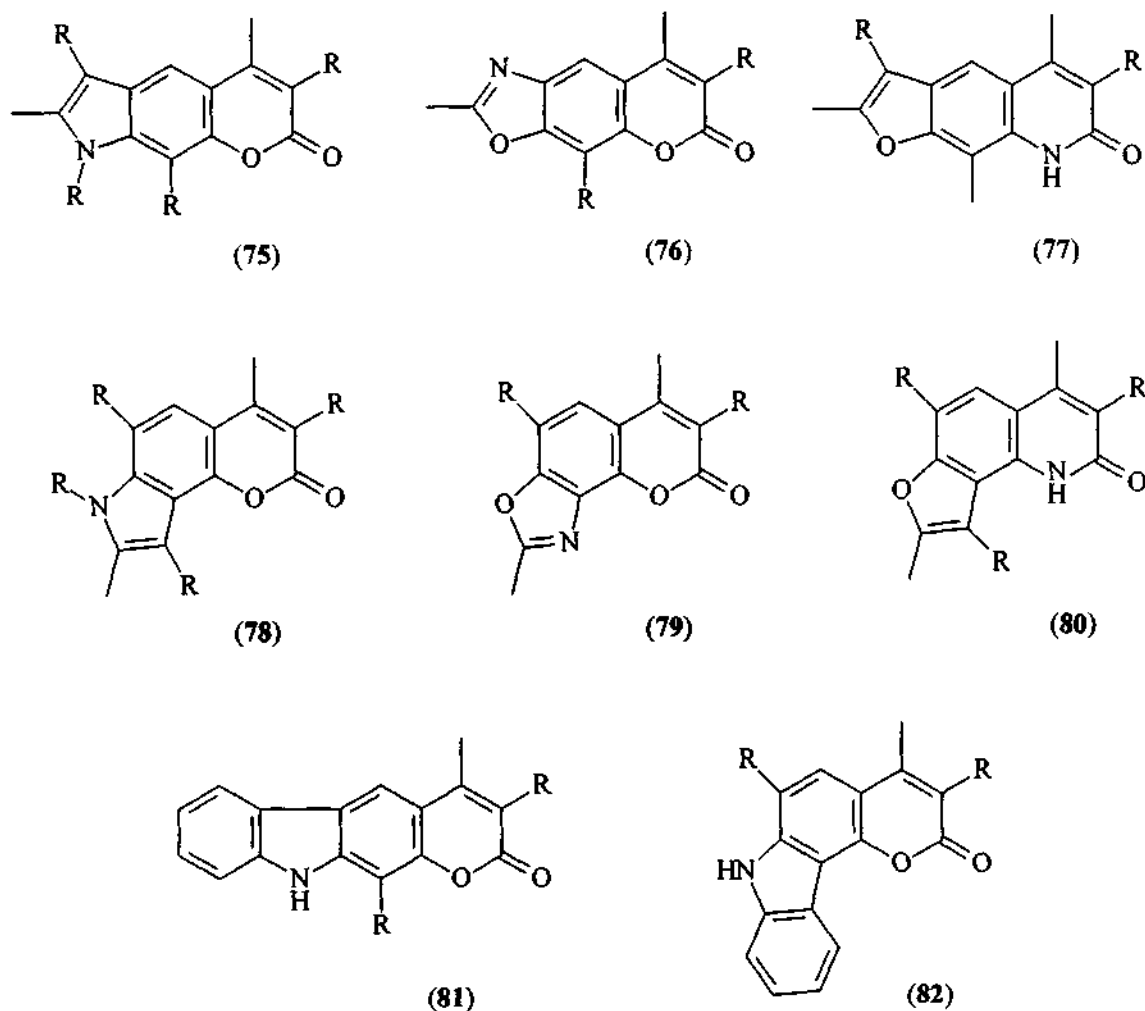
Figure 3

1.3.2.2 Synthesis of Sulfur Analogues

The synthesis of psoralen derivatives containing sulfur has not received as much attention as that of the nitrogen derivatives. However interest in these compounds has increased in recent years, with some derivatives proving to be very efficient DNA photoinactivating agents with great promise in photochemotherapy.[52] One of the first reported syntheses of a thio-psoralen was by

Wellman[53] in 1980, who synthesised the sulfur analogue of 4,5',8-TMP, utilising an unusual thio-Claisen rearrangement as a key step (**Scheme 18**). The procedure involved conversion of the phenol group of 4,8-dimethyl-7-hydroxycoumarin (**83**) into a thiol in three steps to give the 7-thio substituted coumarin (**86**). Allylation with 2,3-dibromo-1-propene followed by Claisen rearrangement then led directly to the psoralen analogue **88** *via* spontaneous reaction of the newly formed thiol with the terminal alkene of the rearranged allyl group.
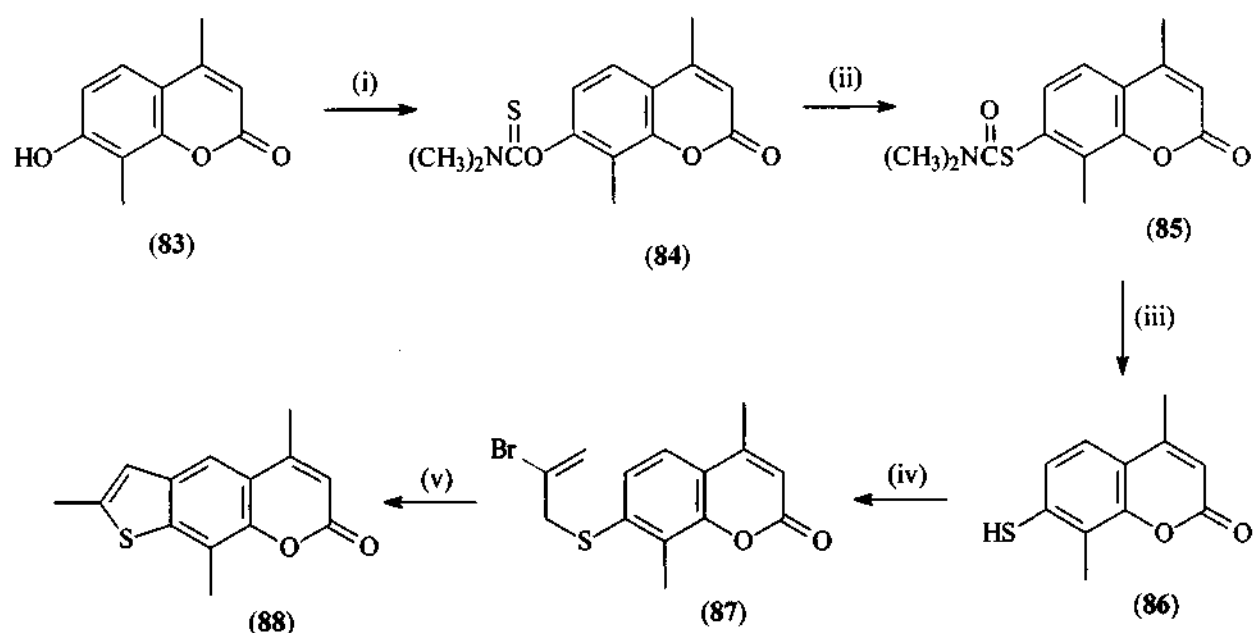
(i) NaH,DMF/ (CH₃)₂NCSCl;   (ii) 240-250°C, 40min;   (iii) KOH/ HCl;
(iv) KOH, 2,3-dibromo-1-propene;   (v) refluxing dimethylaniline, 48h

Scheme 18

Wulff *et al.*[33] also reported the synthesis of the sulfur derivative of sphondin, utilising the same benzannulation approach that they used for the synthesis of sphondin (**42a**) itself (**Scheme 12**, page 14). The synthesis involved the benzannulation of the thio-2-furyl complex (**89**) with methyl 4-pentanoate (**38**) to give the benzannulated thiolactone (**Scheme 19**). Oxidation of this thiolactone (**90**) with DDQ as previously described then afforded thiosphondin (**91**) in 69% yield.

(38) O

(CO)₅Cr=<OMe ... (89)
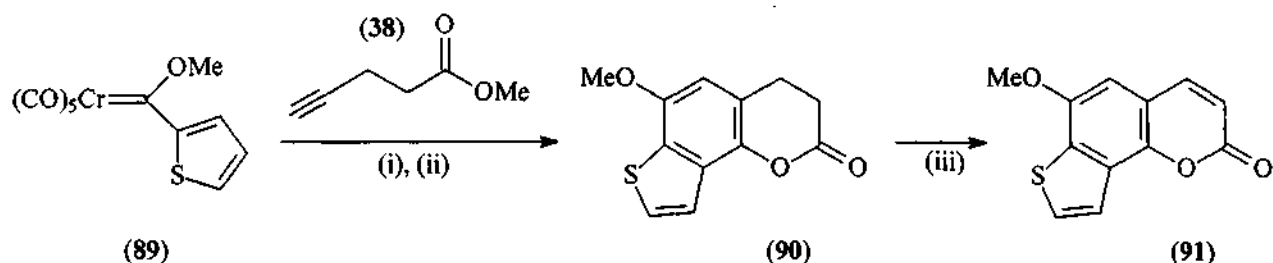
(i) THF, 85°C, 18h; (ii) SiO₂, air; (iii) 2eq. DDQ, toluene, reflux, 4h

Scheme 19

Jakobs *et al.*[54] recently reported the synthesis of various sulfur analogues of psoralen using a completely different route. Their approach led to the formation of the thio derivative **96**, where sulfur had replaced *both* the intracyclic oxygen atoms of psoralen. This compound was synthesised using a route which employed 4,6-dibromoisophthalaldehyde (**92**) as a starting material (**Scheme 20**). Reaction of this compound with one equivalent of potassium ethanethiolate yielded the thio alkylated compound **93** which, after reaction with ethyl 2-mercaptoacetate in basic medium, gave product **94a** in 75% yield.

This compound, after saponification and decarboxylation yielded 6-ethylthio-5-formylbenzo[*b*]-thiophene (**94b**). A Wittig-Horner reaction[55] using triethyl phosphonoacetate transformed this compound into the ester **95**, which was hydrolysed and then cyclised in polyphosphoric acid silyl ether (PPSE) to give the psoralen analogue, 7*H*-thieno[3,2-*g*][1]benzothiopyran-7-one (**96**) in 42% yield.

(92)   (93)   94a: R= COOC$_2$H$_5$
                        94b: R= H

(96)   (95)
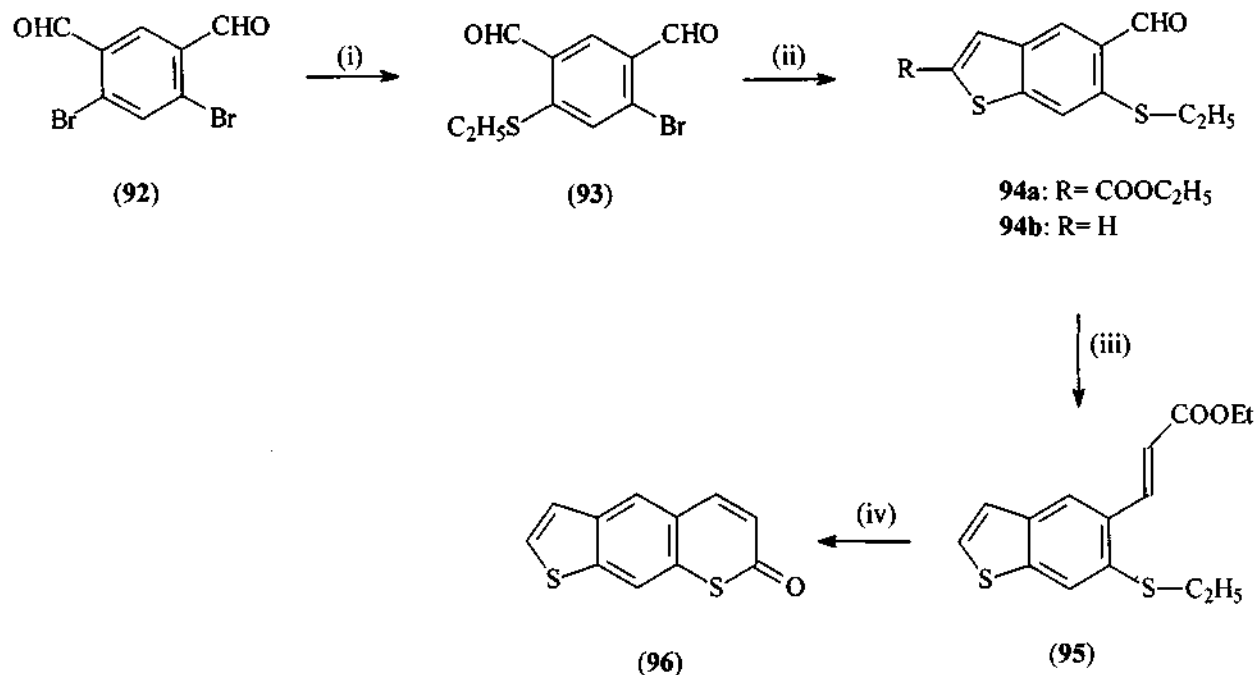
(i) C$_2$H$_5$SH, K$_2$CO$_3$; (ii) ethyl mercaptoacetate;

(iii) THF, triethyl phosphonoacetate, Ba(OH)$_2$.0,8H$_2$O; (iv) PPSE, 100°C

Scheme 20

Later work by the same group reported the preparation of two more thio-psoralens, in which the sulfur atom replaced only one of the two oxygen atoms of psoralen.[56] The starting material for this work was the same as used before, the dibromo compound **92**. The synthesis of the first analogue 7H-thiopyrano[3,2-f][1]benzofuran-7-one (**101**) was achieved by first converting one of the bromines of 4,6-dibromoisophthalaldehyde (**92**) into a phenol (**97**) by reaction with KOH in DMSO (**Scheme 21**). This phenol was then converted into the benzofuran derivative **98a** by reaction with ethylbromoacetate. Subsequent hydrolysis of the ester followed by decarboxylation then led to **98b**. Nucleophilic substitution of the bromine atom by ethanethiolate afforded the thioether **99**, which was transformed into **100** as before. Hydrolysis and cyclisation of the acid in the presence of PPSE then afforded the desired product 7H-thiopyrano[3,2-f][1]benzofuran-7-one (**101**) in 43% yield.
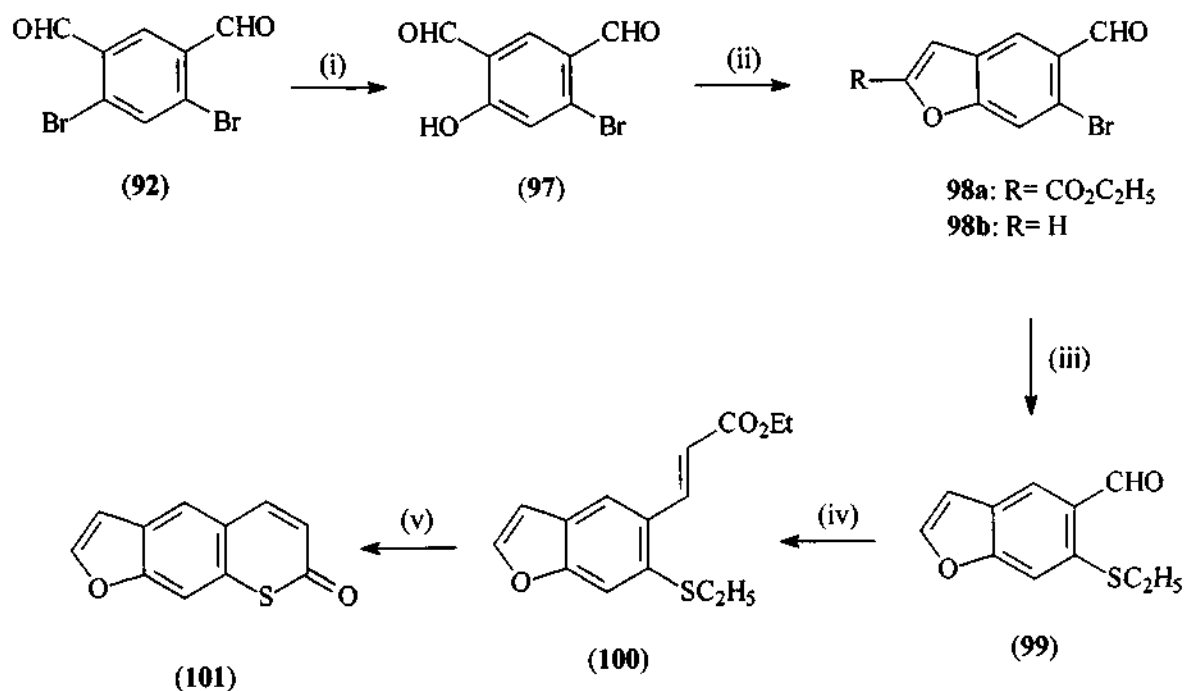
(i) KOH, DMSO, 90°C; (ii) Ethylbromoacetate, DMF; (iii) K$_2$CO$_3$, ethanethiol;
(iv) THF, triethyl phosphonoacetate, Ba(OH)$_2$.0,8H$_2$O; (v) PPSE, 120°C

Scheme 21

The second analogue, 2H-thieno[3,2-g][1]benzopyran-2-one (**105**), where sulfur replaces the oxygen of the furan ring (**Scheme 22**), was prepared by reacting **92** with lithium methanolate in methanol to give the required intermediate **102** . This was reacted with potassium ethylthio glycolate to afford **103a**. Saponification and decarboxylation consequently afforded **103b**, which was converted to the vinylogous acid **104** *via* a Knoevenagel reaction.[57] Cyclisation in the presence of PPSE afforded the desired analogue 2H-thieno[3,2-g][1]benzopyran-2-one (**105**) in 60% yield.

(92)   (102)   103a: R= CO₂C₂H₅
                             103b: R= H

(105)   (104)
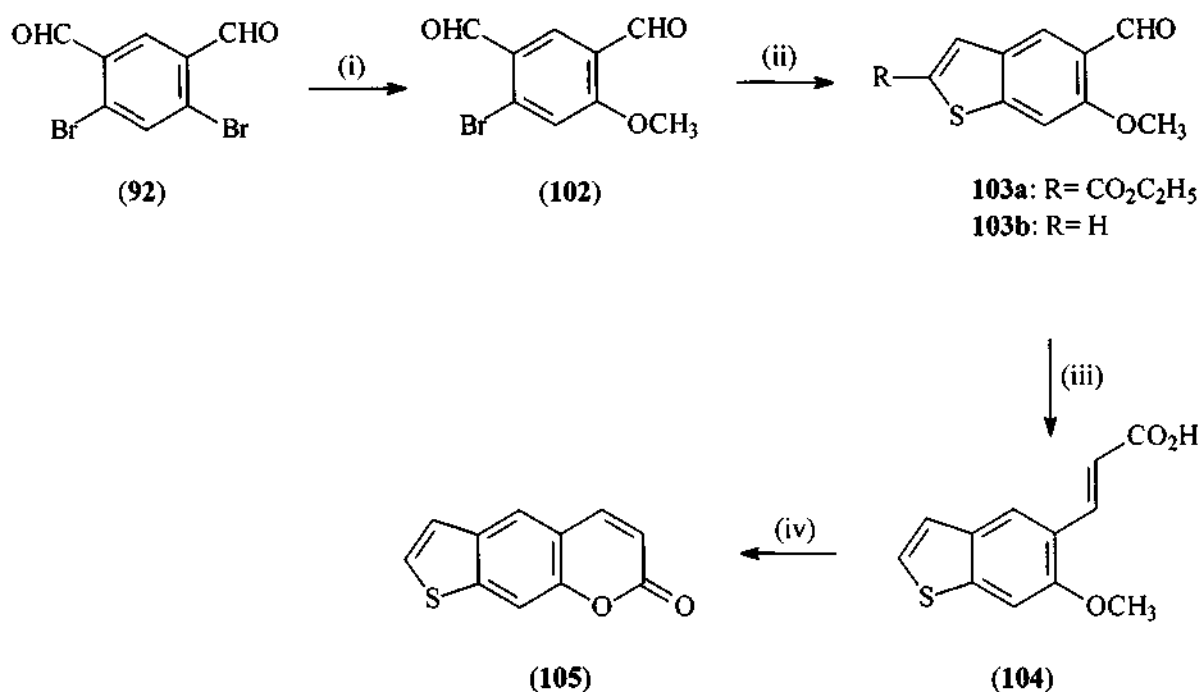
(i) Li, methanol, reflux; (ii) K₂CO₃, ethyl mercaptoacetate;
(iii) Pyridine, piperidine, malonic acid; (iv) PPSE, 170°C

Scheme 22

Further research by Jakobs and Christiaens[58] also led to the synthesis of a new analogue of isopsoralen using a different route (**Scheme 23**). The known ketone, tetrahydro-4,5,6,7-benzofuran-4-one (**106**) was converted *via* the Vilsmeier-Haack reaction[59,60] into the chloroformyl product **107**. Nucleophilic substitution of the chlorine atom by the ethanethiolate anion yielded a thioether (**108**), which was aromatised with 2,3-dichloro-5,6-dicyano quinone (DDQ) to give **109**. Preparation of the ester, followed by saponification and cyclisation in PPSE afforded the desired isopsoralen analogue 4*H*-thiopyrano[2,3-*e*]benzofuran-4-one (**111**) in 84% yield.
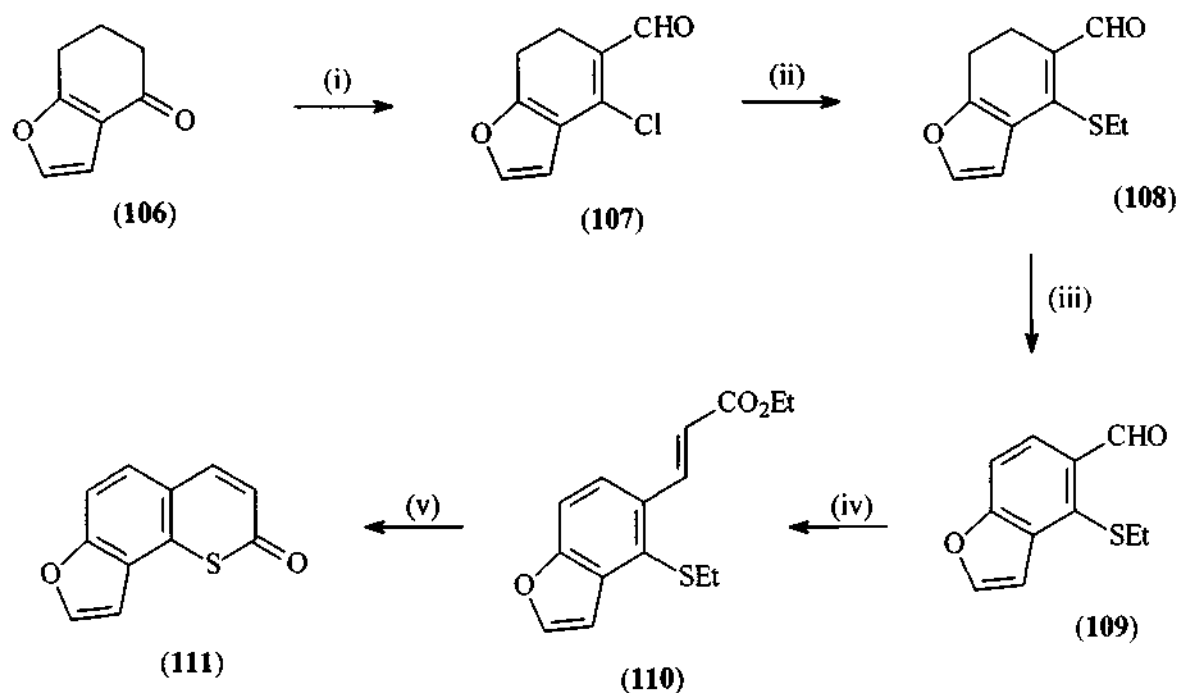
(i) DMF, 1,1,2-trichloroethane, phosphorus oxychloride; (ii) K$_2$CO$_3$, ethanethiol;
(iii) DDQ; (iv) Triethyl phosphonoacetate, Ba(OH)$_2$.0,8H$_2$O;
(v) PPSE, 100°C

Scheme 23

Mosti and co-workers[61] have also recently reported the synthesis of a thio-isopsoralen analogue *via* a method in which the thio-furan ring was present in the starting material and subsequent synthesis of the pyrone ring completed the isopsoralen (**Scheme 24**). In this procedure the precursor **112** (obtained by refluxing the available ketone in *N,N*-dimethylformamide dimethylacetal) was reacted with dimethyl malonate to give **113**. This was then aromatised in the presence of DDQ. The ester (**114**) was converted to the corresponding carboxylic acid and decarboxylated by refluxing in quinoline containing a catalytic amount of copper powder to afford the thio-isopsoralen analogue **116** in 70% yield. Photobiological testing of this analogue showed a strong inhibition of T2 bacteriophage infectivity as well as significant repression of DNA synthesis in *Ehrlich ascites* cells. The analogue also appeared to be free of any of the known phototoxicity of furocoumarins on the skin.[61]
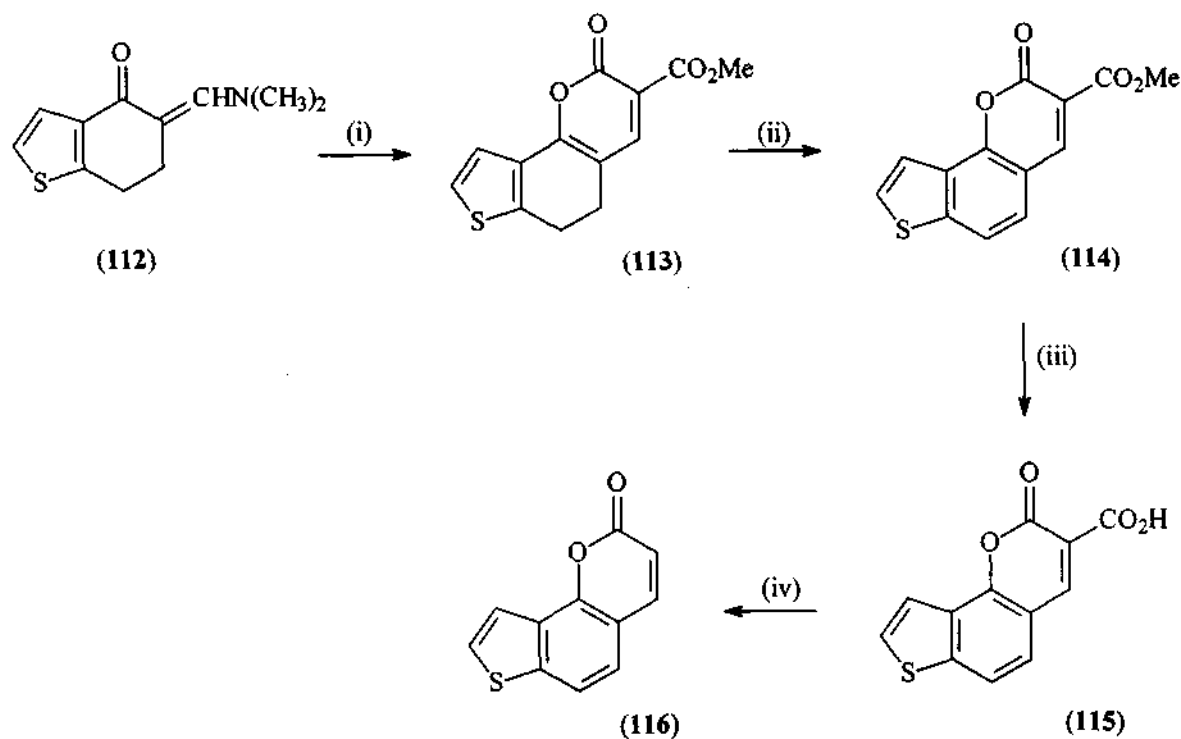
(i) $MeO_2CCH_2CO_2Me$; (ii) DDQ; (iii) HCl/ CH_3CO_2H; (iv) Quinoline, Cu

Scheme 24

A novel approach to sulfide derivatives of psoralens, where sulfur is incorporated as a substituent in the 5'-position instead of in the psoralen nucleus, has recently been reported in the literature.[62] The introduction of the acetyl group into the 8-position was achieved *via* a Fries rearrangement of the acetate of 7-hydroxycoumarin to give **117** (**Scheme 25**). The ethyl carbazone of this compound was converted using the Hurd-Mori synthesis[63] into the 1,2,3-thiadiazole **118**.

The tandem decomposition/cyclisation reaction was achieved using the system potassium carbonate/tetrabutylammonium bromide/acetone, and quenching with methyl iodide. This afforded the isopsoralen derivatives **119** in *ca*. 30-35% yields. The linear psoralen could also be obtained analogously using a coumarin blocked at the 8-position with a methyl group.
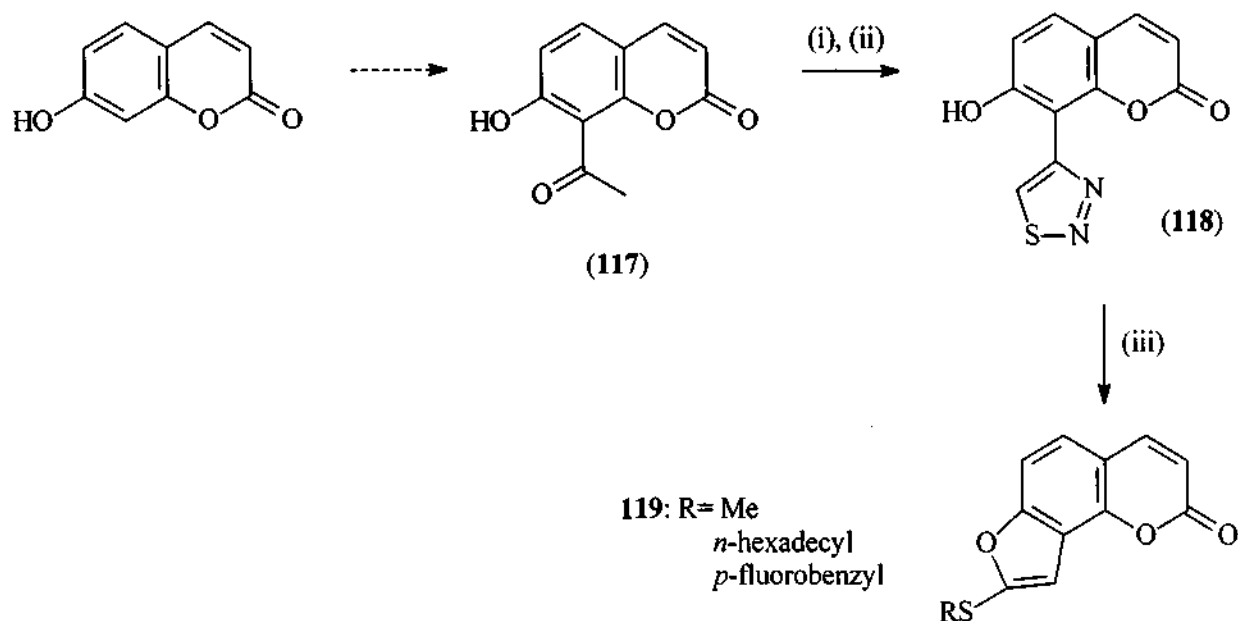
(i) NH₂NHCOOEt;   (ii) SOCl₂, 25°C;   (iii) base, RX, 25°C

Scheme 25

The synthesis of sulfur analogues of psoralens and isopsoralens has become an important area in the field of psoralen chemstry, with an increased interest in recent years towards the synthesis of these types of compounds. The fact that some of these compounds have exhibited potent photobioligical activity means that there is still a lot of work to be done in this area, with the synthesis of a greater variety of analogues for biological testing a definite domain of interest.

1.3.2.3 Synthesis of Selenium Analogues

Until recently, no study on the effect of a heavy atom like selenium on psoralen photo- reactivity had been reported. One of the first reported syntheses of a seleno-psoralen derivative was made in 1992 by Jakobs, Christiaens and Renson.[54] They reported on the synthesis of three possible hetero-psoralens where selenium, along with sulfur, replaced the two intracyclic oxygen atoms of psoralen.

The basic starting compound for their work was 4,6-dibromoisophthalaldehyde (92). This compound was found to be a very versatile starting material for the synthesis of all sulfur and

selenium analogues of psoralen, as has already been seen in the section on sulfur analogues. The synthetic procedure is very similar to that used for the synthesis of the sulfur analogues already discussed (namely compounds **96, 101, 105**).

Reaction of the starting material 4,6-dibromoisophthalaldehyde (**92**) with one equivalent of potassium ethanethiolate yielded compound **93** (as for the sulfur analogue synthesis, see **Scheme 20**, page 24) which was converted into the product **120a** (**Scheme 26**). This compound, after saponification and hydrolysis yielded 6-bromo-5-formylbenzo[*b*]thiophene (**120b**). The bromine atom of **92** was then substituted by methaneselenolate to afford the selenoether (**121**) in 69% yield. Reaction of aldehyde **121** with triethyl phosphonoacetate yielded the ester **122**. Saponification to the corresponding acid, followed by cyclisation then afforded the desired product 7*H*-seleno- pyrano[3,2-f][*1*]benzothiophen-7-one (**123**) in 44% yield.

(**92**)   (**93**)   **120a**: R= CH$_2$COOC$_2$H$_5$
                                                                                                                        120b: R= H

(**123**)   (**122**)   (**121**)
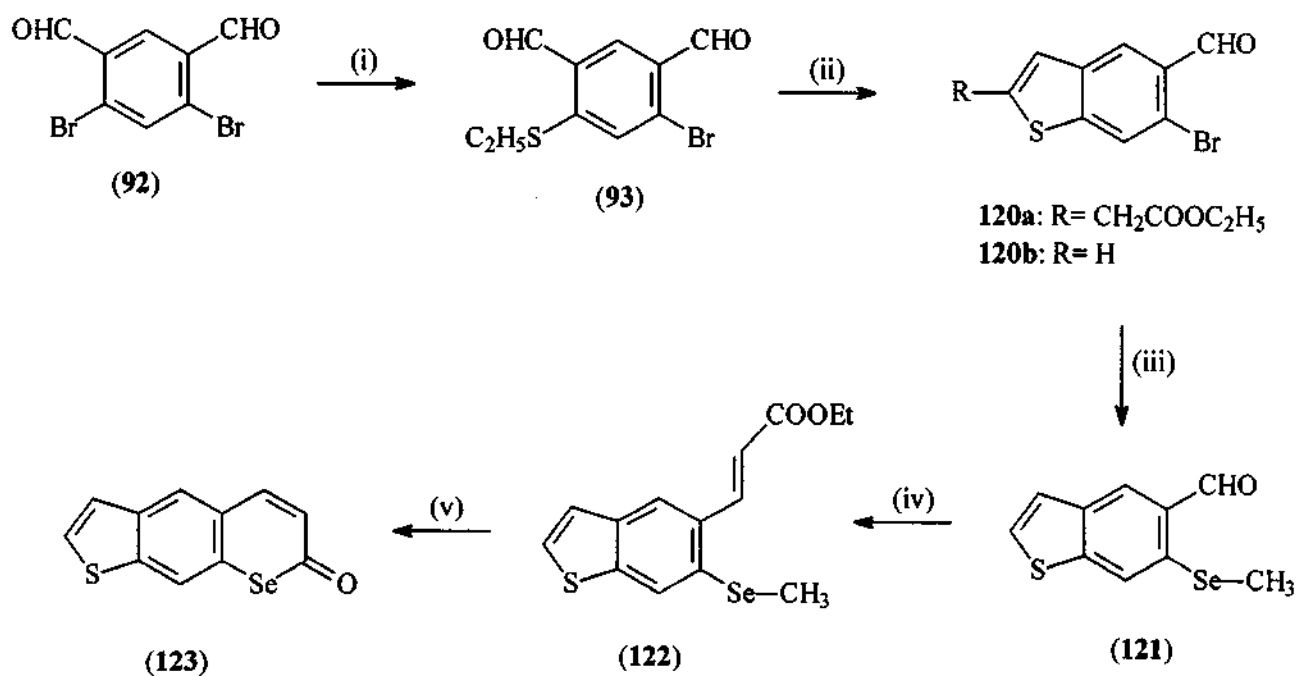
(i) K$_2$CO$_3$, C$_2$H$_5$SH; (ii) DMF, ethyl mercaptoacetate; (iii) K$_2$CO$_3$, acetonitrile, methaneselenol; (iv) THF, triethyl phosphonoacetate, Ba(OH)$_2$.0,8H$_2$O; (v) PPSE, 100°C

Scheme 26

The seleno-psoralen analogue **127** was also synthesised by successively reacting the dibromo starting compound (**92**) with one equivalent of potassium ethanethiolate and one equivalent of potassium methaneselenolate (**Scheme 27**) to afford 4-ethylthio-6-methylselenoiso phthalaldehyde (**124**). This was then refluxed in ethyl bromoacetate and the seleno ether obtained cyclised to the benzofuran derivative **125**. The ester was saponified and decarboxylated. The aldehyde **125** was then transformed into ester **126** as before; hydrolysis and cyclisation of this compound then afforded the desired product 2*H*-selenolo[3,2-*g*][*1*]benzothiopyran-2-one (**127**) in 57% yield.
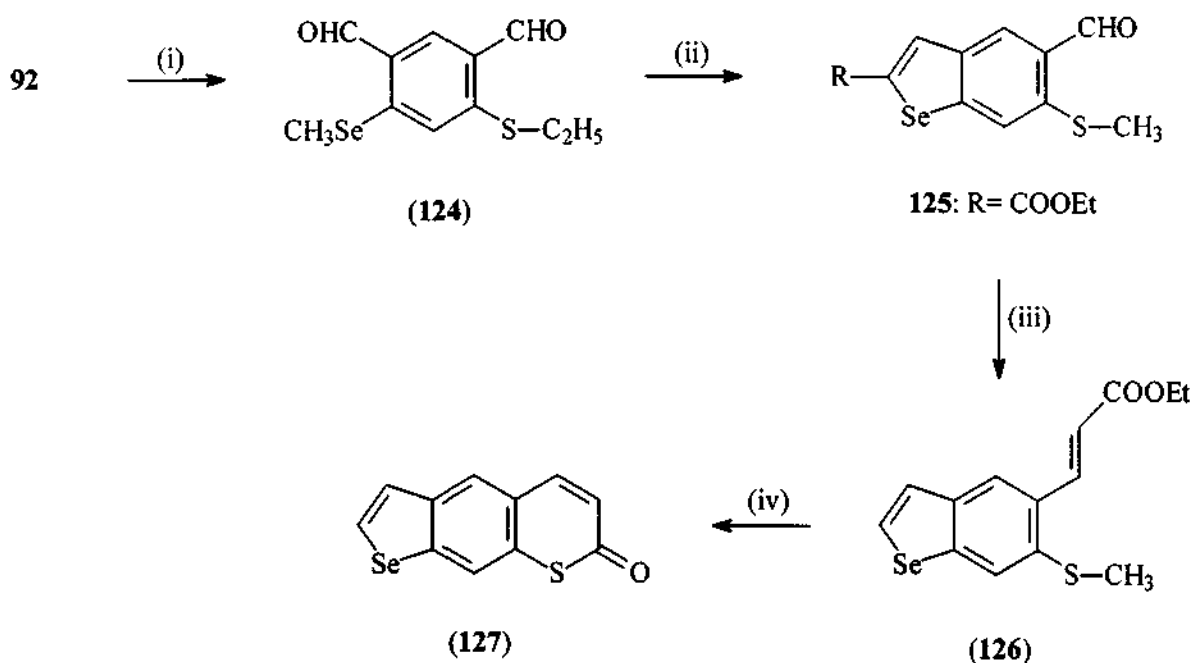
(i)K$_2$CO$_3$, DMF, ethanethiol, 24hrs, then methaneselenol; (ii) Ethylbromoacetate, reflux; (iii) THF, triethyl phosphonoacetate, Ba(OH)$_2$.0,8H$_2$O; (iv) PPSE, 100°C

Scheme 27

The third compound, in which selenium replaced both oxygen atoms (**Scheme 28**) was accessed by reacting 4,6-dibromoisophthalaldehyde (**92**) with one equivalent of potassium methane selenolate. The product was refluxed in ethyl bromoacetate to afford the precyclic selenoether (**128**) which was cyclised using K$_2$CO$_3$. The resulting benzoselenofuran (**129**) was reacted with

potassium methaneselenolate to afford the selenoether (**130a**), which was then saponified and decarboxylated to afford **130b**. From this compound was prepared the vinylogous ester *via* a Wittig-Horner type reaction. It was subsequently saponified and cyclised in PPSE to afford the final product, 7*H*-selenolo[3,2-g][*1*]benzo-selenopyran-7-one (**132**) in 34% yield.
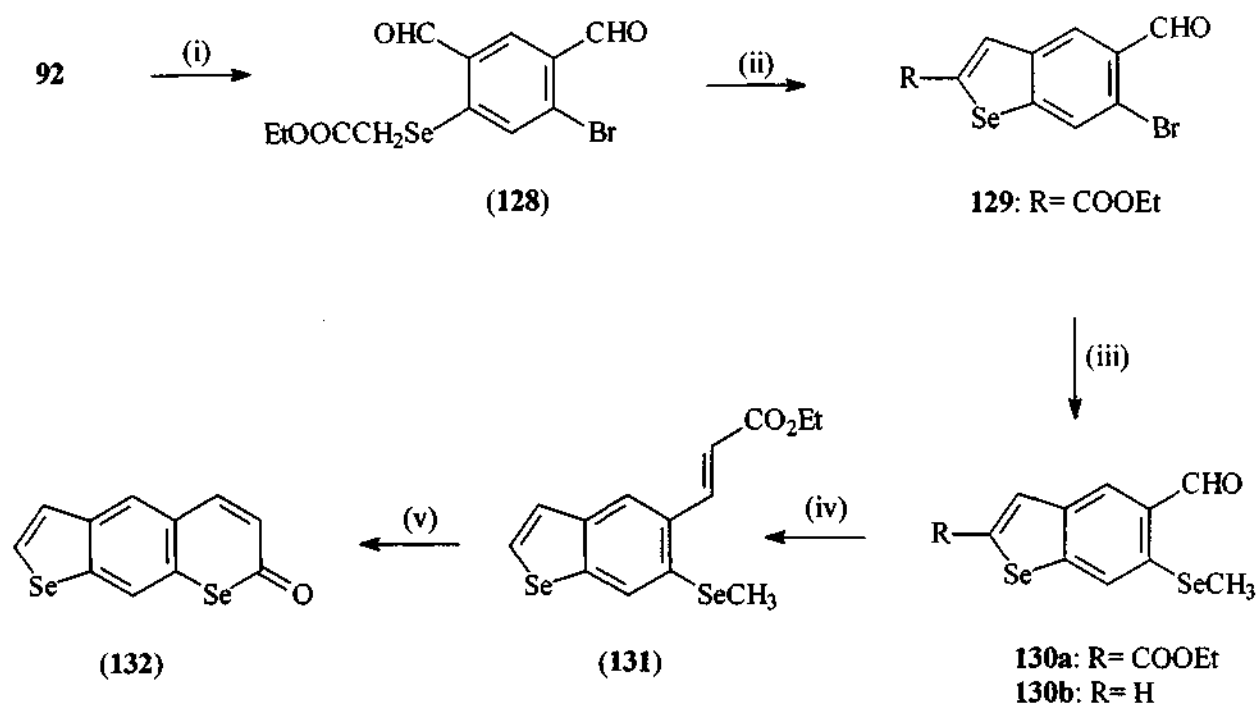
(i)K_2CO_3, acetonitrile, methaneselenol; (ii) Ethylbromoacetate, reflux, K_2CO_3;
(iii) K_2CO_3, acetonitrile, methaneselenol; (iv) THF, triethyl phosphonoacetate, $Ba(OH)_2.0,8H_2O$;
(v) PPSE, 100°C

Scheme 28

Some work published a few years later by the same research group[56] involved the synthesis of a further range of seleno-psoralen analogues, but where the selenium atom replaced only one of the two endocyclic oxygen atoms of psoralen.

The synthesis involved using the same dibromo starting material (**92**). The synthesis of the first analogue 7*H*-selenopyrano[3,2-*f*][*1*]benzofuran-7-one (**135**) was achieved by first converting 4,6-dibromoisophthalaldehyde (**92**) into the phenol (**97**) (**Scheme 29**) by reaction with KOH in DMSO as described before. The phenol was then transformed into the benzofuran derivative

(98a) by reaction with ethylbromoacetate; hydrolysis and decarboxylation of the ester then led to 98b. Nucleophilic substitution of the bromine atom by methaneselenolate then afforded the selenoether (133), which was transformed into the ester (134) as before. Hydrolysis and cyclisation of the acid in the presence of PPSE afforded the desired product 7*H*-selenopyrano[3,2-*f*][*1*]benzofuran-7-one (135) in 43% yield.
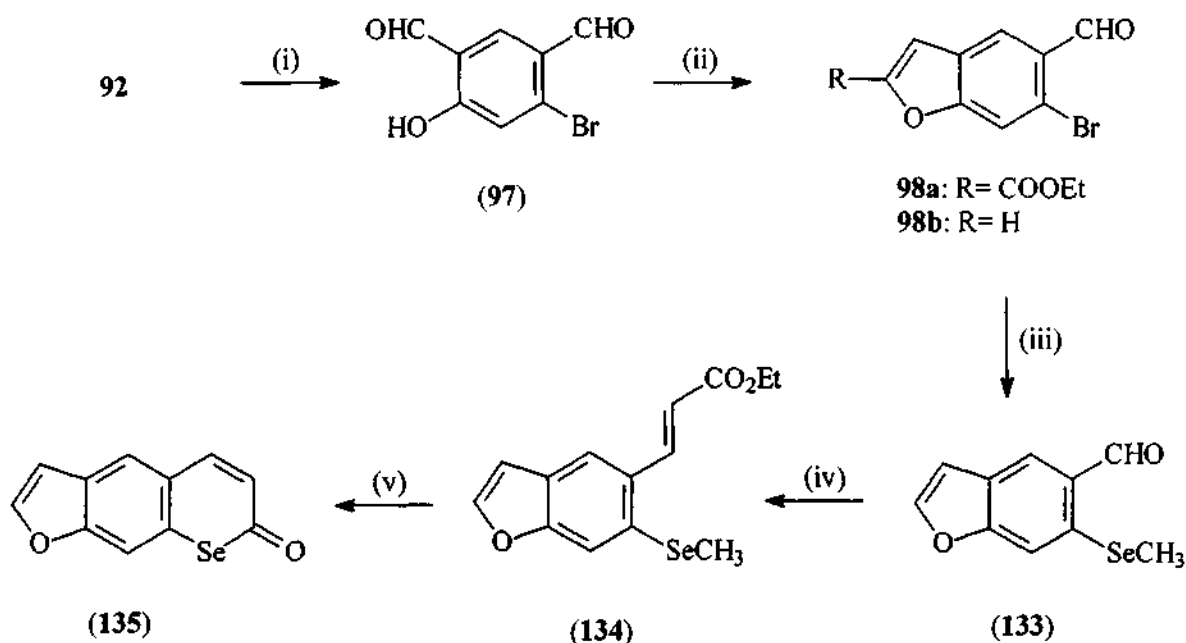
(i) KOH, DMSO, 90°C; (ii) K_2CO_3, DMF, ethylbromoacetate, reflux;
(iii) K_2CO_3, DMF, methaneselenol; (iv) THF, triethyl phosphonoacetate, $Ba(OH)_2.0,8H_2O$;
(v) PPSE, 150°C

Scheme 29

The final psoralen analogue synthesised (139) consisted of a selenium atom in place of the oxygen atom of the furan ring. This was accessed by initially reacting 4,6-dibromoiso phthalaldehyde (92) with one equivalent of lithium methanolate in methanol to yield the ether 102 (Scheme 30). The bromine was replaced by selenium as before to afford the seleno ether (136a). Reaction with ethylbromoacetate then afforded 136b, which was subsequently cyclised in basic medium to afford the selenophene derivative (137a). The ester was hydrolysed and decarboxylated to give 137b, which was converted into the ester (138) and cyclised using the

same methods previously mentioned. This afforded the final product 2H-selenolo[3,2-g][l]benzo- pyran-2-one (**139**). However, the yield of the final reaction was found to be only 19 % owing to polymer formation; a higher yield was obtained by first demethylating **137b** into the benzofuran (**137c**) with lithium chloride. The phenol was then transformed into the final product in 32% yield by a classical Perkin reaction.[64,65]

92 $\xrightarrow{\text{(i)}}$

(**102**)

$\xrightarrow{\text{(ii)}}$

136a: R_1= CH_3
136b: R_1= CH_2COOEt

$\downarrow$ (iii)

137a: R_2= COOEt, R_3= CH_3
137b: R_2= H, R_3= CH_3
137c: R_2= R_3= H

$\xleftarrow{\text{(iv)}}$

(**138**)

$\xleftarrow{\text{(v)}}$

(**139**)
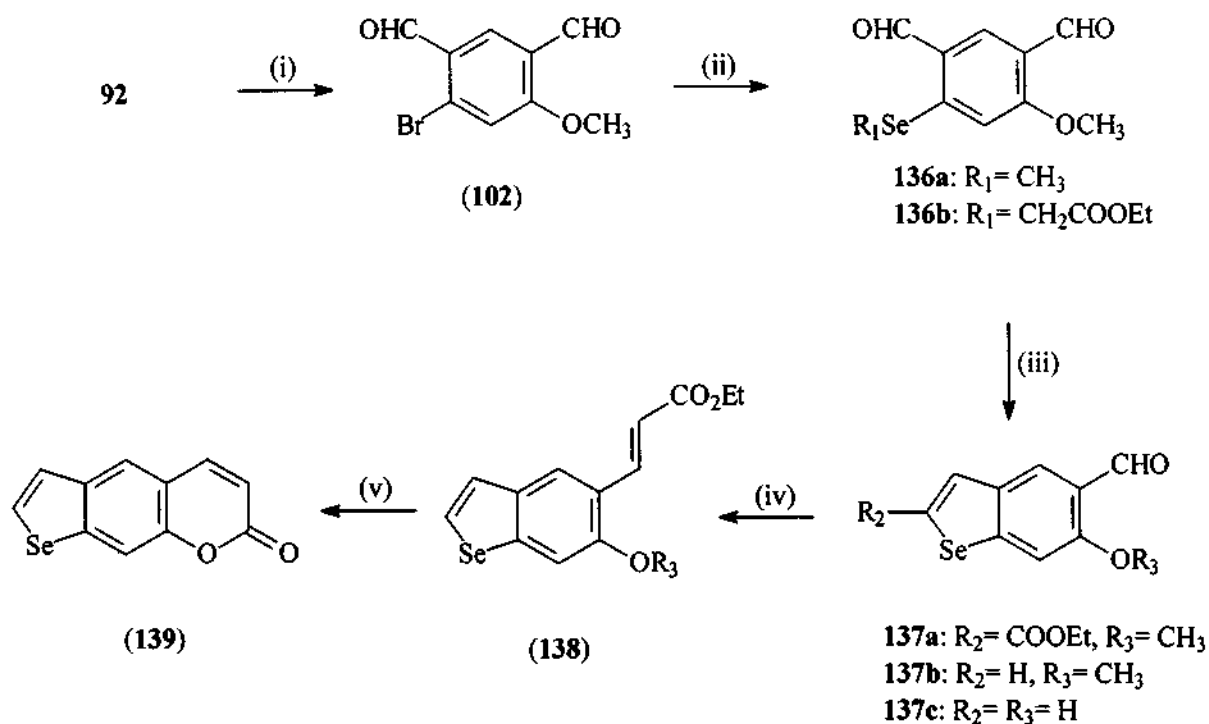
(i) Lithium, methanol, reflux; (ii) K_2CO_3, DMF, methaneselenol; (iii) K_2CO_3, DMF; (iv) THF, triethyl phosphonoacetate, Ba(OH)$_2$.0,8H$_2$O; (v) PPSE, 150°C

Scheme 30

To date, these methodologies have been the only reported synthesis of selenium analogues of psoralen, and photobiological[52] and other testing (spin trapping and electron spin resonance spectroscopy)[66] have revealed that these analogues show great promise in the use of photochemotherapy. Up to now there has been no reported synthesis of analogues of isopsoralen, so the synthesis and photobiological testing of these types of compounds will be of great interest in this field of research.

1.4 AIMS OF THIS RESEARCH PROJECT

As has already been demonstrated, the synthesis of the wide range of furocoumarin derivatives known as psoralens and isopsoralens is an important area of research in the improvement of the biological activity of these important compounds. It has already been shown that two of the most important areas in this field involve the synthesis of the monofunctional isopsoralen derivatives, as well as the preparation of any possible hetero analogues, as these have been shown, in some cases, to possess potent photobiological activity. The aim of this project was thus to attempt to develop and optimise methodology that could lead to the preparation of a range of new isopsoralen derivatives incorporating both oxygen, sulfur, and hopefully even selenium atoms in the parent isopsoralen nucleus.

2. DISCUSSION

This project has been concerned with the development of a synthetic route towards the preparation of a number of isopsoralen derivatives. In the discussion which follows, attention will be focussed on the synthetic steps which led towards the final compounds synthesised. The mechanistic detail of some of these transformations will be discussed in order to afford a greater understanding of the processes involved. Selected proton and carbon NMR spectra for some of the compounds synthesised will be discussed.

2.1 PREPARATION OF OXYGEN ANALOGUES

2.1.1 Synthesis of *o*-allyl hydroxycoumarins

The allyl aryl ether (141) was synthesised by reaction of the substituted phenol (140)with an alkyl halide, in this case, allyl bromide in the presence of a base (K_2CO_3).The reaction afforded the allyl aryl ether, 7-(allyloxy)-2*H*-chromen-2-one (141) in *ca*. 90% yield (Scheme 31). The ether was subsequently subjected to a thermal Claisen rearrangement reaction,[67,68] affording the 8-allyl-7-hydroxy-2*H*-chromen-2-one (142) in *ca*. 80% yield.
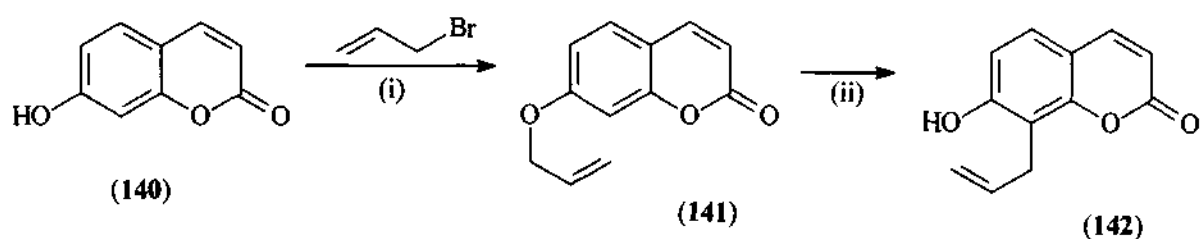
(i) K_2CO_3, acetone, reflux; (ii) *N,N*-diethylaniline, 220°C

Scheme 31

2.1.1.1 The Claisen Rearrangement Reaction

The Claisen rearrangement[67,68] is a thermally induced rearrangement of an allylic aryl ether into the corresponding o-allylphenol. If both *ortho* positions are filled, the allyl group migrates to the *para* position. Migration to the *meta* position has not been observed, and if both the *ortho* and *para* groups are filled, the reaction has been shown to not take place at all. The mechanism for this reaction is a concerted pericyclic [3,3] sigmatropic rearrangement (Scheme 32), with the σ bond migrating over 3 atoms. As Scheme 32 shows, the first step involves the slow, rate determining migration of the allyl group to the ortho position of the corresponding ketone product (141a). Subsequent keto-enol tautomerisation then takes place to afford the alcohol 142, this reaction is the fast step and is driven forward by the regaining of aromaticity.
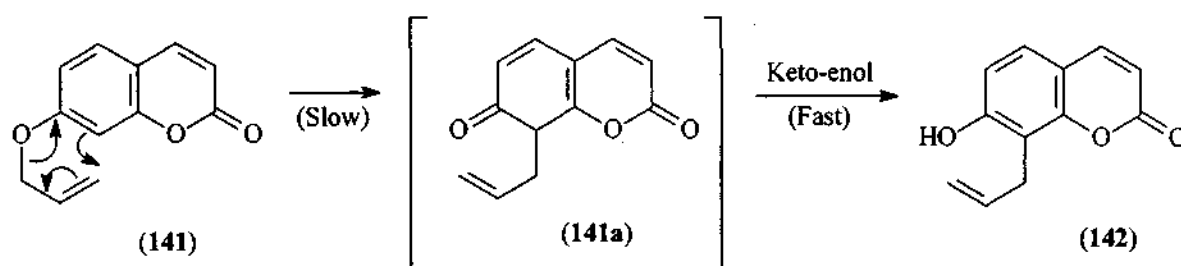
Scheme 32

Evidence for this type of mechanism has been supported by the absence of crossover products when mixtures are heated, the fact that the reaction is first order in ether, and the presence of the allylic shift (demonstrated by ^{14}C labelling experiments), which is required by this mechanism. Since the mechanism does not involve ions, it is not greatly dependant on the presence or absence of substituent groups on the ring. However, the rate of the reaction has been shown to be greatly influenced by the choice of solvent in which it is run.[69]

The allyloxy coumarin (141, Scheme 32) contains two vacant ortho positions to the hydroxyl group, it would therefore be expected that rearrangement would afford a mixture of the two possible regioisomers i.e. the allyl group migrated to both the 6- and 8-positions. However this is not the case, instead there is total regioselectivity in the reaction affording the 8-allyl isomer (142) exclusively. This occurrence has also been noted previously in the literature,[24] where it was

shown that the 8-position is the most reactive during the Claisen rearrangement. This is somewhat surprising due to the fact that the mechanism has been shown to be independant of substituents on the aromatic ring. Rearrangement to the 6-position (leading to the synthesis of psoralens) is only possible when there is a group blocking the 8-position.

The position of the allyl group in the 8-position was confirmed by Correlation Spectroscopy (COSY) of 8-allyl-7-hydroxy-2H-chromen-2-one (142) (Figure 3).[†] The coupling between protons H-5 and H-6 in this spectrum clearly indicates that the allyl group did, in fact, migrate to the 8-position as expected, leaving the 3,4 and 5,6 protons to couple with each other.
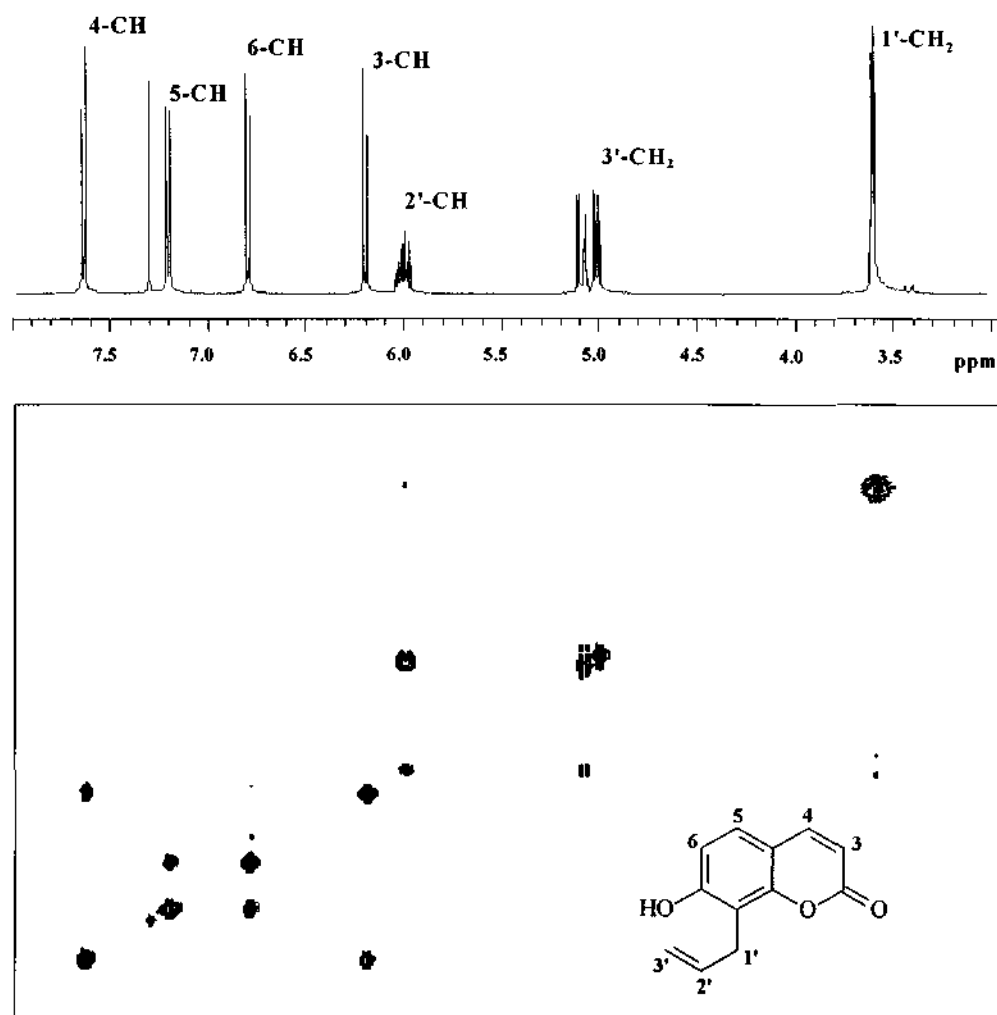
Figure 3: 500 MHz COSY Spectrum of 8-allyl-7-hydroxy-2H-chromen-2-one (142) in CDCl₃.

[†]IUPAC numbering will be used when discussing NMR spectra.

Nowhere in the literature could an explanation for the observed regioselectivity be found, there seems to be only an acceptance and utilisation of this fact but no attempt to propose any possible explanation for it. In order to account for the regioselectivity of this reaction, some molecular mechanics (MM2) and electronic structure theory (AM1) calculations were performed on the coumarin systems studied. The calculations were performed using Hyperchem[70] and revealed some interesting results which seem to coincide with the observations for the rearrangement reaction. It must be noted that in order for the Claisen rearrangement (as with most pericyclic reactions) to take place there must be an overlap of an electronically occupied molecular orbital (usually the HOMO or Highest Occupied Molecular Orbital) with an unoccupied molecular orbital (this is usually the LUMO, or Lowest Unoccupied Molecular Orbital). Only in this way can there be the donation of electrons from one carbon atom to another as is required for the formation of a new carbon-carbon bond, as shown by the mechanism for the reaction.

The calculated molecular orbitals for the coumarin systems examined (**Figure 4**) revealed the following:-

(i) the HOMO -2 orbital [**Figure 4 (A)**] is of π-symmetry and has non vanishing amplitude on the allyl group, suggesting that the terminal alkene in fact acts as the electron-donor; the electron-acceptor is thus carbon 8 of the aromatic ring of the coumarin.

(ii) a plot of the LUMO for the coumarin system, [**Figure 4 (B)**] reveals that this molecular orbital does *not* lie over the carbon 6 atom which, remembering that this molecular orbital is an indication of the area in which any donated electrons can be placed (since it is unoccupied by any electrons), accordingly suggests that this carbon cannot act as the electron acceptor for the reaction. This consequently provided a tentative explanation for the observed regioselectivity in this reaction.

These results together with our observations clearly indicate that there *must* be a significant influence by substituent groups on the mechanism of this reaction.
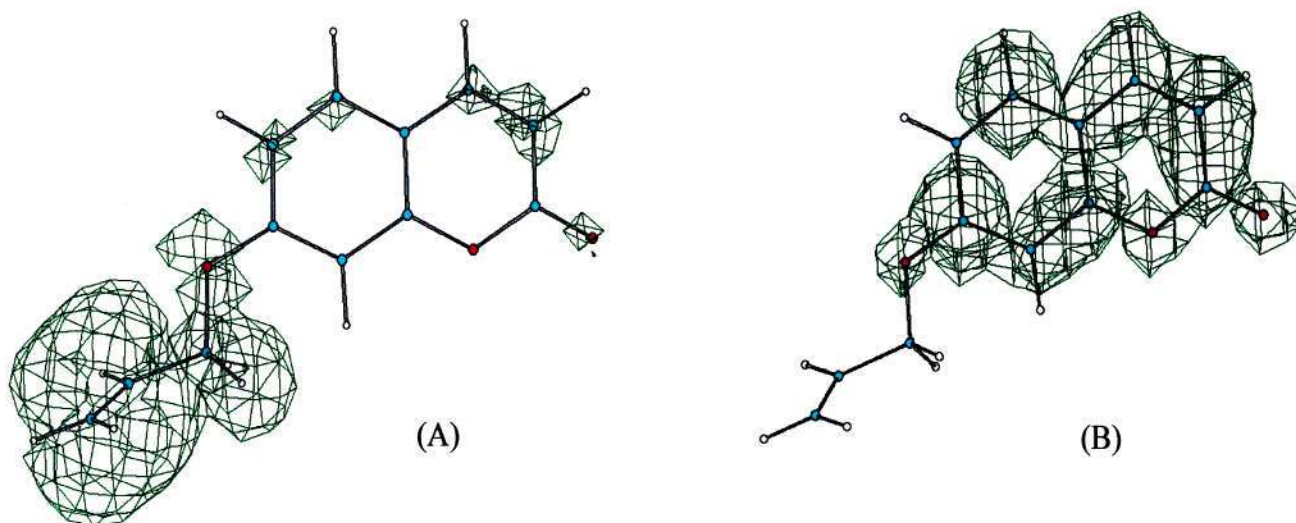
Figure 4: Figure of the Squares of the Electron Probability plots for the HOMO -2 (A) and the LUMO (B) molecular orbitals for 7-(allyloxy)-2*H*-chromen-2-one (**141**).

2.1.2 Synthesis of Isopsoralen Analogues

2.1.2.1 Synthesis of 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**150a**)

In order to complete the formation of the furan ring, 8-allyl-7-hydroxy-2*H*-chromen-2-one (**142**) was subjected to ozonolysis in order to cleave the terminal alkene of the allyl group and subsequently generate an aldehyde (**Scheme 33**).

The oxidative cleavage of olefins by ozonolysis is a well established transformation in organic chemistry[45] and is used widely for synthetic purposes. The process results in the cleavage of a double bond, usually under extremely mild conditions (at or below -78°C),¶ the products of this cleavage being aldehydes/ketones or their peroxidic products (in the case of aldehydes, their oxidative products, the carboxylic acids).

¶ Ozonolysis carried out at higher temperatures resulted in degradation of the product.
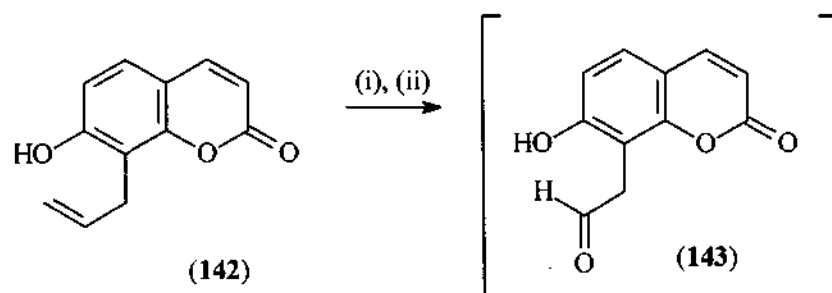
(i) O$_3$, THF, -78°C, 1.5 hrs;

(ii) Dimethylsulfide, -10°C to 0°C

Scheme 33

The mechanism of ozonolysis has been extensively investigated in the literature. Criegee[71] proposed a mechanism (**Scheme 34**), which has been widely accepted, and has been substantiated by subsequent ^{17}O NMR spectroscopic experiments.[72] The mechanism is believed to involve the addition of the ozone molecule to the alkene to form a molozonide (**144**), (**Scheme 34**). This is a highly unstable system and immediately decomposes into a carbonyl compound (**146**) and a 'carbonyl oxide' (**145**) which themselves immediately condense again to form the more stable ozonide (**147**). Hydrolysis or (preferably) reduction of this ozonide affords the two carbonyl products, in the cases where an aldehyde would be formed, the equivalent of peroxide generated by the hydrolysis produces a carboxylic acid instead, it is thus preferable to use the reductive work up to reduce the peroxy link.

Reducing agents such as Zn/AcOH, Me$_2$S, Ph$_3$P and Me$_3$P have all been used,[45] however in this project Me$_2$S was the reagent of choice. There are a number of advantages to using this reagent;[73] it is highly selective, the reduction is performed under neutral conditions, excess dimethylsulfide is easily removed by evaporation and the by-products, methanol and dimethyl sulfoxide, induce no problems with regards to subsequent purification.
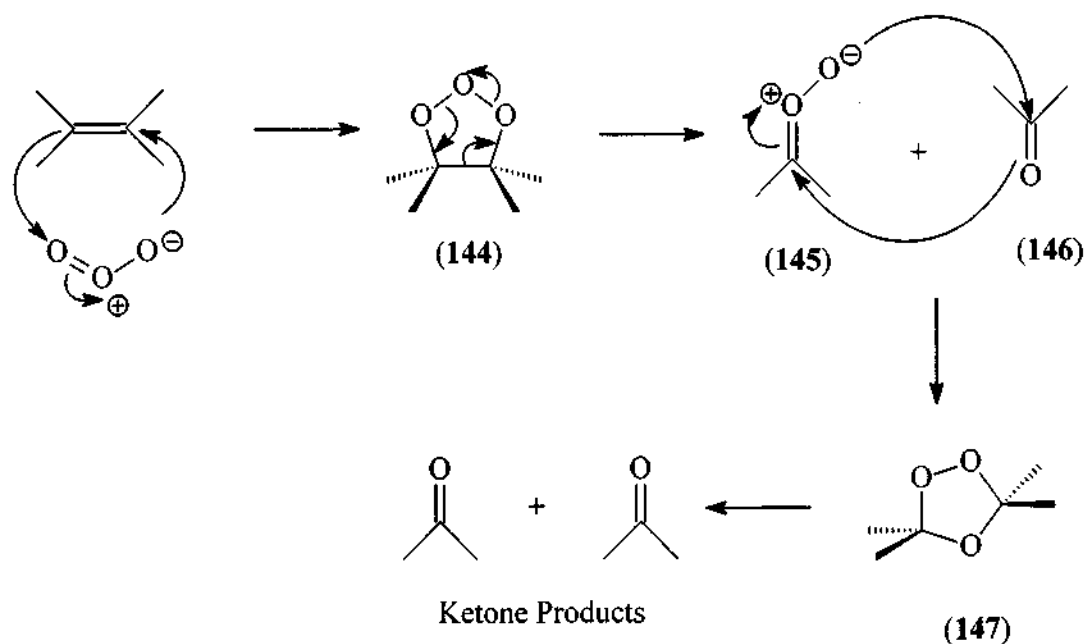
Scheme 34

2.1.2.1.1 Formation of the Hemiacetal and Subsequent Nucleophilic Substitution

The aldehyde (143) was, as expected, never isolated, and instead cyclisation took place between the phenol moiety and the carbonyl carbon resulting in the formation of a hemiacetal (149) (Scheme 35), the mechanism of this reaction involves attack by the lone pair of electrons on the oxygen atom of the hydroxyl group onto the δ^+ carbonyl carbon, followed by protonation of the negative carbonyl oxygen to form the cyclised product (148). The positively charged oxygen atom subsequently loses its proton to form the hemiacetal (149).

This hemiacetal, in the presence of methanol, underwent subsequent nucleophilic substitution of the hydroxyl group with the methoxy nucleophile of the methanol, resulting in the formation of the novel 5'-methoxy isopsoralen derivative, 8-methoxy-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (150a) as a racemic mixture of the R and S enantiomers.The hemiacetal (149) was able to be isolated from reactions carried out in THF without the addition of any alcohol, and was shown to be relatively stable.
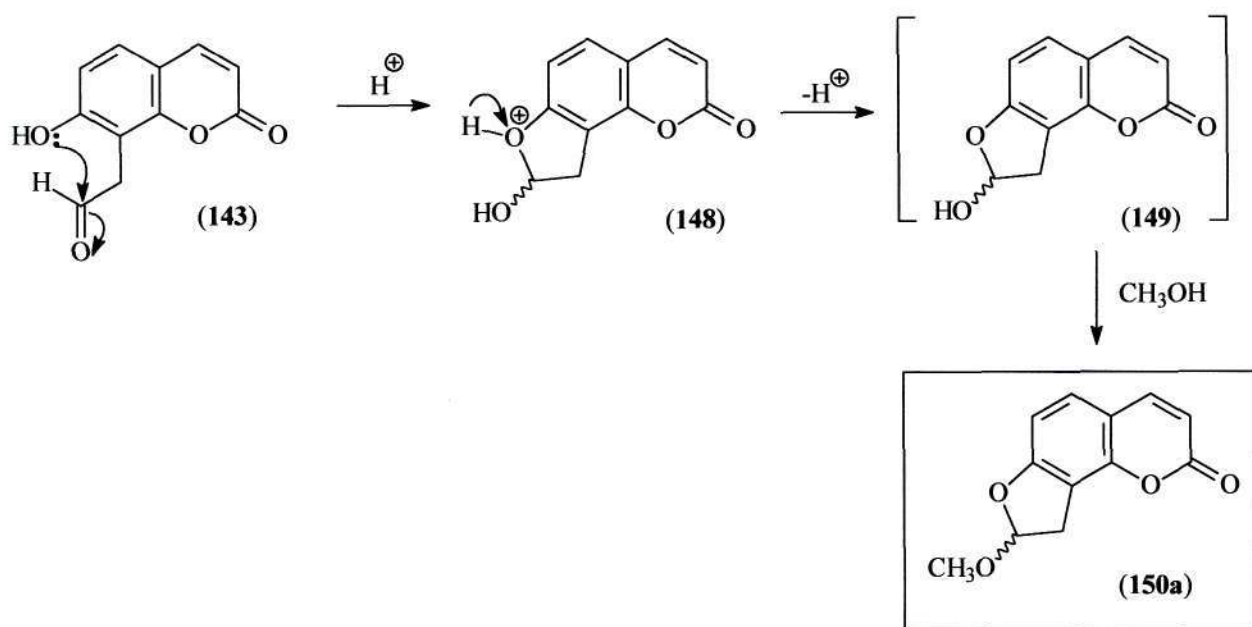
Scheme 35

Compound **150a** was characterised by X-Ray Crystallography (**Figures 5** and **6**) and NMR spectroscopy (**Figures 7** and **8**). From the Crystal structure it can be observed that the isopsoralen derivative lies in the Monoclinic crystal system with the space group being $P2_1/a$. The two enantiomers are related by a centre of inversion in the space group. The crystal structure also shows the expected planarity of the molecule, and in the solid state the molecules are shown to be packed tightly together in the unit cell, indicating the potential for π-stacking of these compounds and hence the potential for intercalation into the DNA double helix.
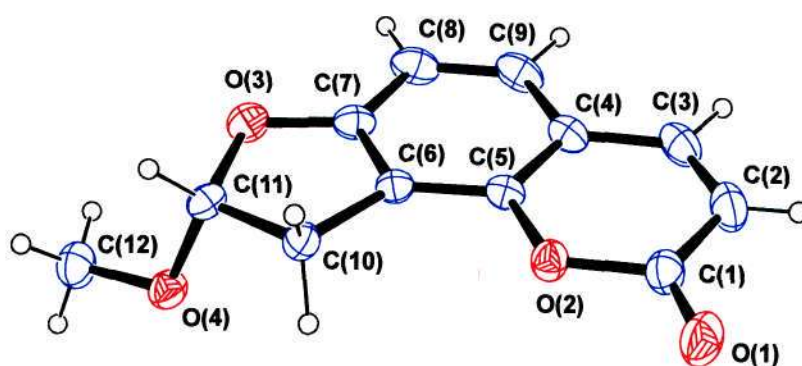
Figure 5: X-ray crystal structure, showing crystallographic numbering, of 8-methoxy-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (**150a**).
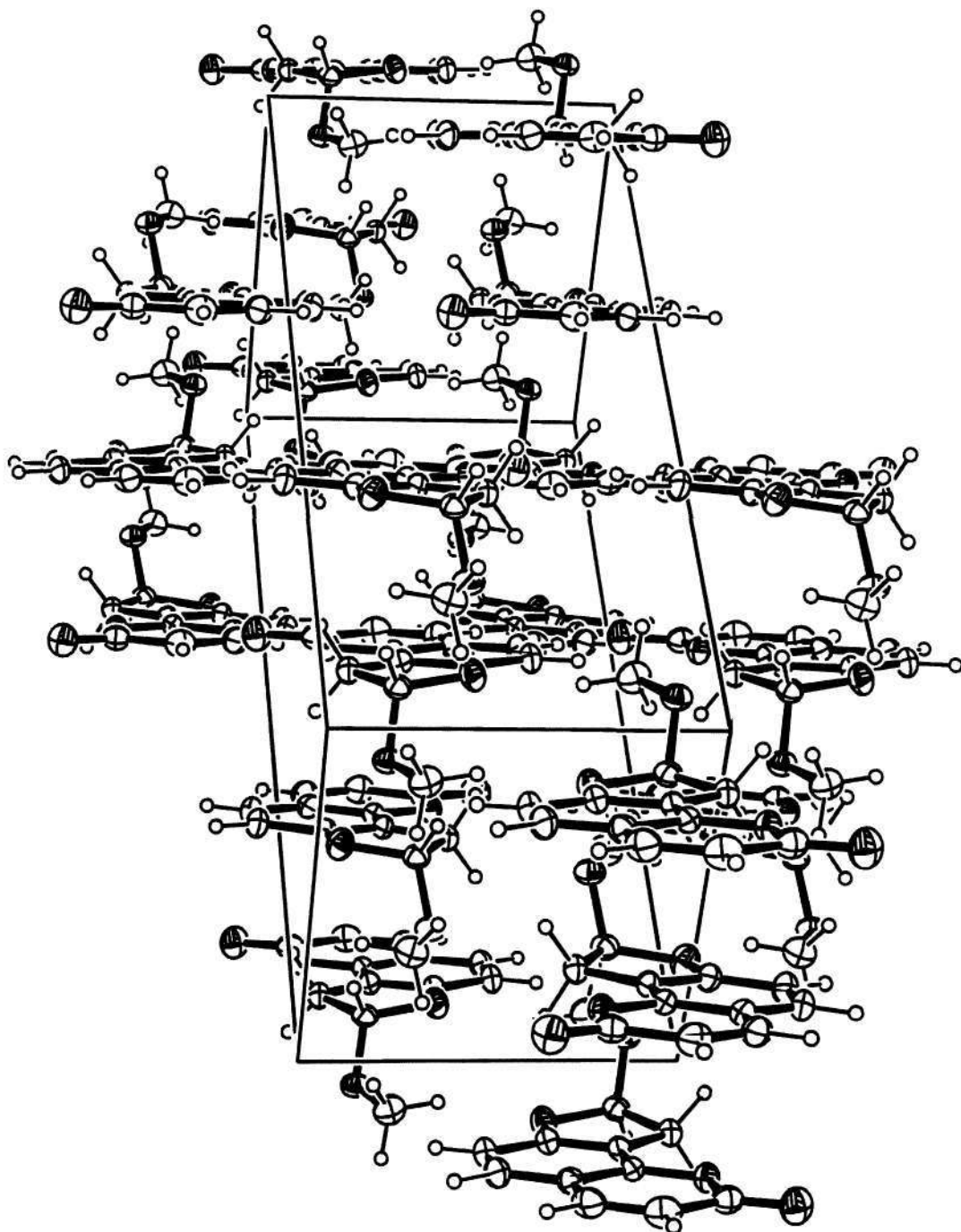
Figure 6: Diagram showing the packing of 8-methoxy-2*H*-furo-[2,3*h*]chromene-2-one

(**150a**) in the unit cell.
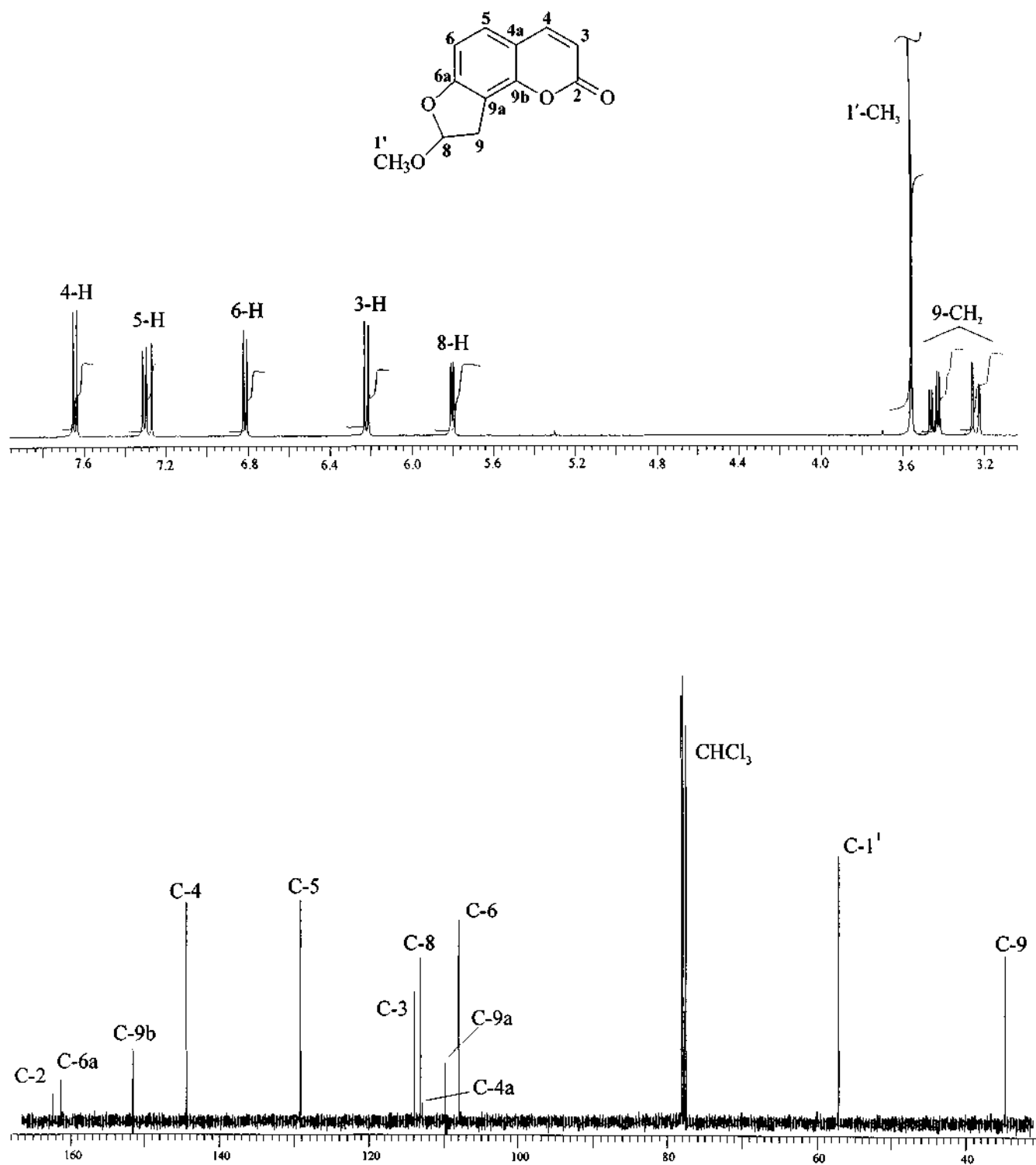
Figure 7: 500 MHz ^{1}H and 125 MHz ^{13}C Spectra of 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*] chromen-2-one (**150a**) in CDCl$_3$.

The proton NMR spectrum for 8-methoxy-8,9-dihydro-2H-furo[2,3-h]chromen-2-one **150a** (**Figure 7**) shows clearly the presence of the methoxy methyl (a singlet at 3.5 ppm) and also the four aromatic protons (four doublets between 6.2 and 7.6 ppm). There is also an interesting coupling effect between the 9-CH$_2$ and the proton on the stereogenic carbon (C-8). The two protons of the CH$_2$ are diastereotopic and thus are split into two separate signals for each proton. A magnification of the spectrum (**Figure 8**) show the geminal coupling between these two protons at 17.1 Hz, resulting in a pair of doublets. Further coupling to the 8-H proton further splits each of these signals into a doublet of doublets, with the magnetic non-equivalence of Ha and Hb giving rise to different coupling constants for these two signals.

This coupling effect has been rationalized by the work of Karplus.[74,75,76] He stated, on the basis of calculations, the dependance of the vicinal coupling constant on the dihedral angle Φ. From these calculations, he determined that the vicinal coupling constant can be *approximated* by the equation:

$$J_{H,H'} = 4.22 + (-0.5) \cos \Phi + 4.5 \cos \Phi$$

Using Hyperchem, an energy minimised structure of (**150a**) was calculated. This structure computed a dihedral angle of 132.5° for Ha, and a much smaller one of only 7.8° for Hb. Both the R and S enantiomers revealed similar calculated dihedral angles. Subsequent analysis of the ^{1}H NMR spectrum then showed a coupling constant of 2.3 Hz for Ha, and a larger coupling constant of 6.6Hz for Hb. These values compare favourably with those obtained using the Karplus equation, which equates J values of 4.2 Hz and 8.1 Hz for Ha and Hb respectively.
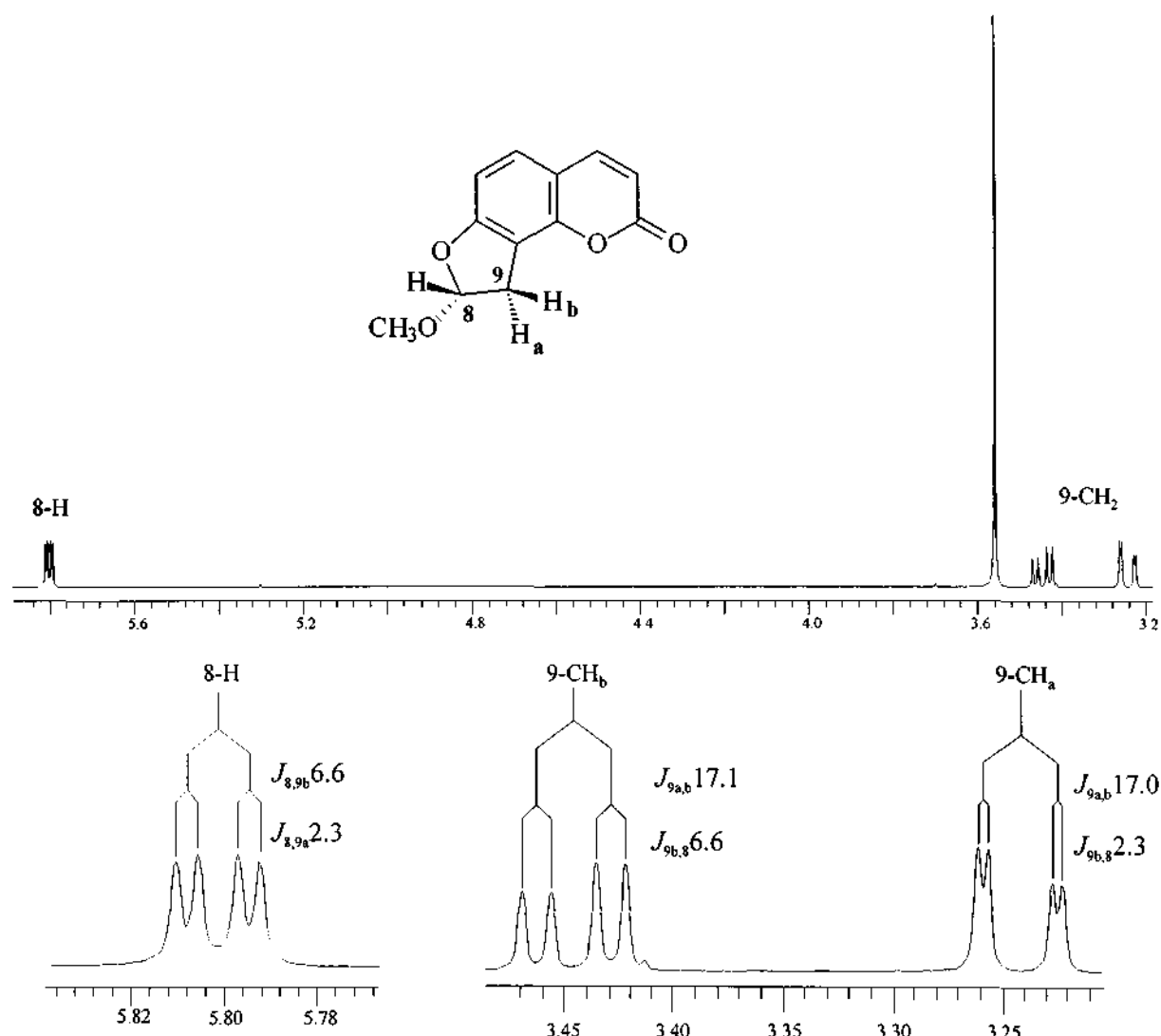
Figure 8: Partial 500 MHz ^{1}H NMR spectrum for 8-methoxy-8,9-dihydro-$2H$-furo[2,3- h] chromen-2-one(**150a**) showing the splitting of the 9-CH_2 and the 8-CH protons.

2.1.2.2 Investigation of Other Nucleophiles

Due to the interest in these compounds, extension of this approach to include other nucleophiles was examined. Ethanol, isopropanol and *tert*-butanol were all successful in producing the subsequent 5'-substituted isopsoralen derivatives (**150b-d**) in *ca.* 65-75% yields. Purification of these types of compounds on silica proved problematic.[§] Fortunately, however, these compounds are crystalline and hence, in most cases the need for chromatography proved unnecessary.

[§]Degradation was observed on prolonged exposure to silica gel.

(142)   (149)   150b: R= CH₃CH₂
                                                                        150c: R= (CH₃)₂CH
                                                                        150d: R= (CH₃)₃C

(i) THF, -78°C, O₃, then dimethylsulfide, -10°C to R.T.

Scheme 36

The NMR spectrum of 8-ethoxy-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (**150b, Figure 9**) revealed some interesting splitting patterns for the methylene protons of the ethoxy group. The splitting patterns for the 9-CH₂ and 8-CH protons are similar to those seen for 8-methoxy-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (**150a, Figure 8**), with the two protons on carbon 9 each being split into a doublet of doublets with different coupling constants due to the magnetic non-equivalence of these two protons.

However, in addition to these signals there was also a splitting of the two C-H protons attached to the 1'-carbon. This was displayed as two multiplets between 3.2 and 3.5 ppm (**Figure 9**), and comes about because these two protons are in fact diastereotopic and hence have different chemical shifts. The fact that these protons are diastereotopic despite the absence of a stereogenic centre is well known in this type of system and has been documented before.[75] The expanded section clearly shows the multiplets as a doublet of quartets, which arise from the geminal coupling of the two protons Ha and Hb (9.4 Hz), followed by independent coupling with the terminal methyl group (J = 7.1 Hz). The methyl signal is, as expected, a clear triplet showing a coupling of 7.1 Hz.

Figure 9: 500 MHz ¹H NMR spectrum of 8-ethoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**150b**) showing splitting patterns for the 1'-CH₂ protons.

A range of other nucleophiles including ethanethiol, acetic acid and phenol were also utilised in order to explore the potential of this reaction, however it was observed that in fact, no subsequent nucleophilic substitution took place, with the hemiacetal being isolated instead. This may be attributed to the fact that these compounds are not as strongly nucleophilic as those used previously, and thus were not able to induce the nucleophilic substitution that had previously been achieved.

A recent report by Roels and Metz[77] describe the use of the Dess-Martin periodinane (DMP),[78,79] (which is a widely used reagent for the oxidation of primary and secondary alcohols to aldehydes and ketones), as a crucial co-reagent for the acylation of the hemiacetal tetrahydro-$2H$-pyran-2-ol (151) (Scheme 37). They found that when 151 was stirred in acetic acid no conversion of the hemiacetal took place, however in the presence of DMP there was complete transformation of hemiacetal 151 into 154 in 15 minutes at room temperature.

Their proposed mechanism for the reaction first depicts a ligand exchange between one of the acetoxy groups of DMP and the hemiacetal (151) to afford the intermediate (152). This intermediate then generates an oxonium ion (153) which reacts with the acids to form the acylated lactols (154, R= Me, Et).

Conducting an approach such as that carried out by Roels and Metz may allow for the inclusion of other nucleophiles into the hemiacetal system (149) and could hopefully lead to the preparation of further analogues of isopsoralen 150.
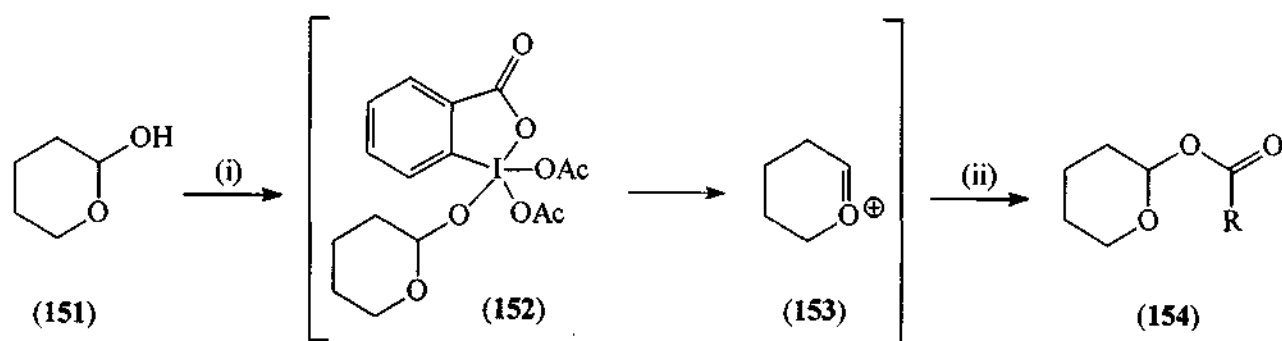
(i) DMP, HOAc, CH$_2$Cl$_2$, 15min R.T.;
(ii) R-CO$_2$H (R=Me, Et)

Scheme 37

2.1.2.3 Synthesis of 2*H*-furo[2,3-*h*]chromen-2-one (**156**)

The hemiacetal (**149**) was transformed into the known isopsoralen 2*H*-furo[2,3-*h*]chromen-2-one (**156**)[33] by performing a dehydration reaction (**Scheme 38**) on the hemiacetal. The starting compound was dissolved in toluene containing a catalytic amount of *p*-toluenesulfonic acid as a dehydrating agent. In the dehydration reaction, the hydroxyl group is protonated by the catalyst to form the protonated intermediate **155**, subsequent loss of water results in the formation of a new double bond in the furan ring, affording 2*H*-furo[2,3-*h*]chromen-2-one (**156**) in quantitative yield. A Dean and Stark apparatus was used to facilitate the removal of water, which is crucial in order for this reaction to succeed.
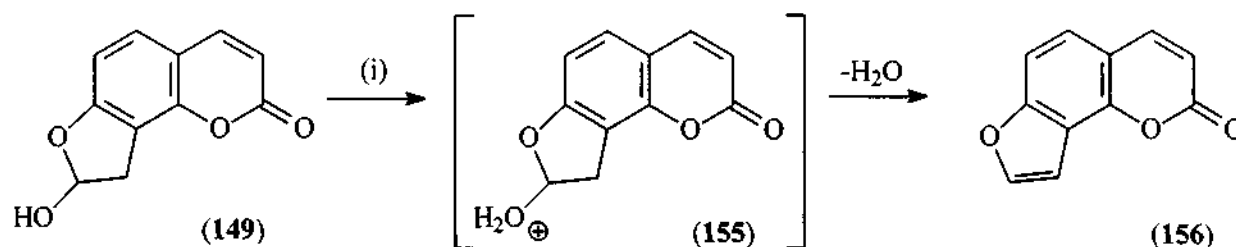
(i) Toluene, *p*-toluenesulfonic acid, reflux

Scheme 38

2.1.2.4 Investigation of Substituted Allyl Groups

Once the synthetic route to synthesise the range of 5'-substituted isopsoralen derivatives (**150a-d**) had been established, it was decided to extend the scope of this approach by using different, substituted allyl groups in order to include other functionality in the furan ring system and to investigate the possible effects such a substituent might have on the subsequent nucleophilic substitution (**Scheme 39**). The use of two substituted allyl groups was proposed, namely a methyl- and a methyl ester-substituted allyl group.

R= CH₃, CO₂CH₃
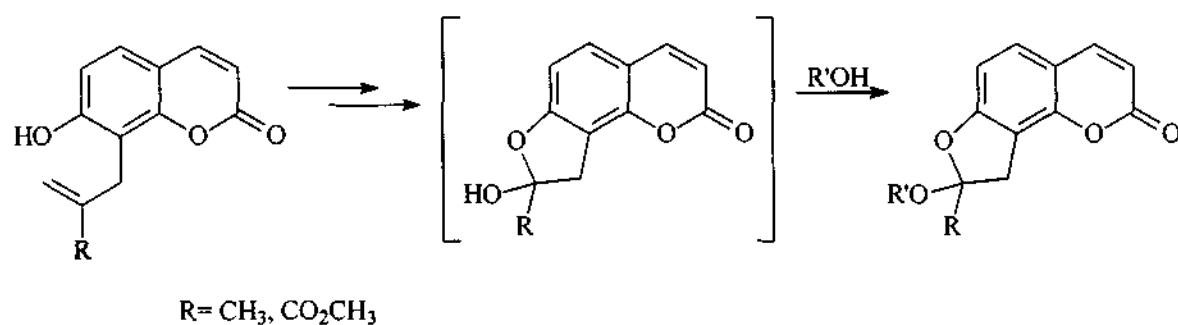
Scheme 39

2.1.2.4.1 Synthesis of 8-methoxy-8-methyl-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (**163**)

In order to introduce the R-functionality, 3-bromo-2-methyl-1-propene was reacted with the 7-hydroxycoumarin (**140**) to afford the allyl aryl ether **157** (**Scheme 40**). Subsequent Claisen rearrangement led to its rearranged product **158**, which, when subjected to ozonolysis and treatment with methanol afforded a compound which at first was thought to be the equivalent hemiacetal as had been isolated previously. However, on closer inspection of the ^{13}C NMR data, it was found to be the ketone derivative, 7-hydroxy-8-(2-oxopropyl)-2H-chromen-2-one (**159**) obtained after reductive workup following the ozonolysis reaction. Thus, in this instance, cyclisation did *not* take place between the hydroxyl group and the carbonyl carbon.
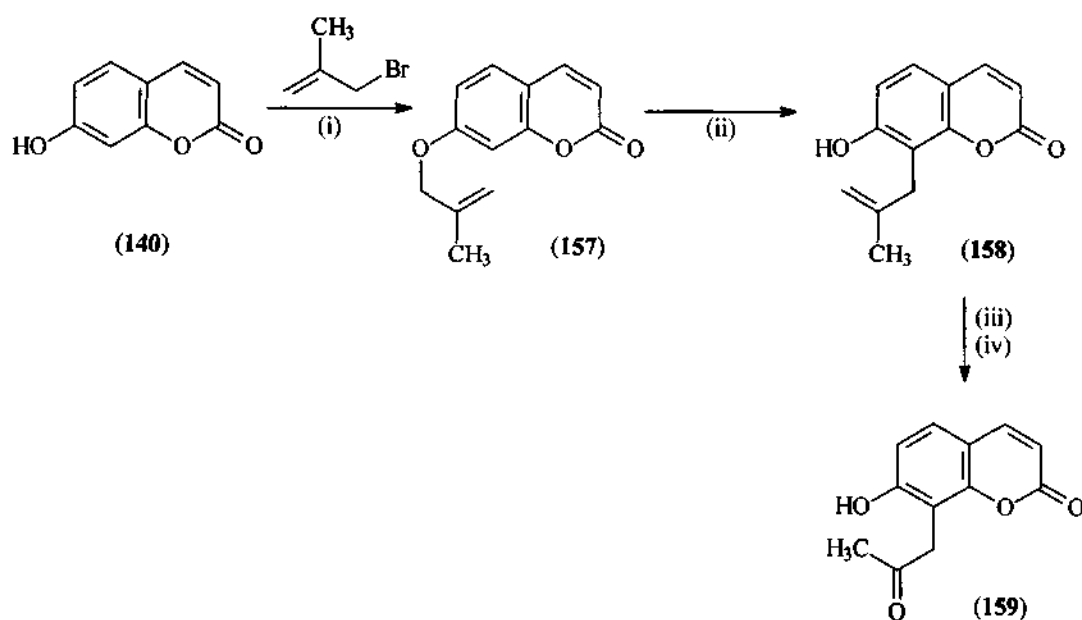
(i) K₂CO₃, acetone, reflux, (ii) N,N-diethylaniline, reflux;
(iii) O₃, THF,-78°C, then dimethylsulfide,-10°C to R.T.; (iv) CH₃OH, heat

Scheme 40

There are two possible explanations for the failure of the cyclisation. Firstly, the methyl group of the ketone would have a positive inductive effect of electron density towards the carbonyl carbon. This would subsequently result in this carbon being less electrophilic when compared with the carbonyl carbon of the aldehyde (143), and therefore decreasing the susceptibility for attack by the lone pair on the oxygen of the hydroxyl group toward the carbonyl carbon. Another reason for the lack of cyclisation could be due to the steric bulk of the methyl group itself, with steric interactions between the methyl and hydroxyl groups preventing nucleophilic attack from occurring at the optimum Burgi-Dunitz trajectory[80,81] and thus hindering the reaction.

In order to obviate the problems associated with the cyclisation step, p-toluenesulfonic acid was utilised as a catalyst (**Scheme 41**) in order to induce cyclisation. In this approach, the catalyst would protonate the carbonyl oxygen of **159**, leading to the formation of the carbocation (**160**), this will then force the lone pair of electrons on the hydroxyl oxygen to attack this carbon and thus cyclisation occurs. This indeed occurred and the hemiacetal (**161**) obtained from this cyclisation then underwent a dehydration reaction in the presence of the catalyst in the same manner as shown before (**Scheme 38**, page 51) and afforded the known isopsoralen derivative 8-methyl-2H-furo[2,3-h] chromen-2-one (**162**)[24] in quantitative yield.
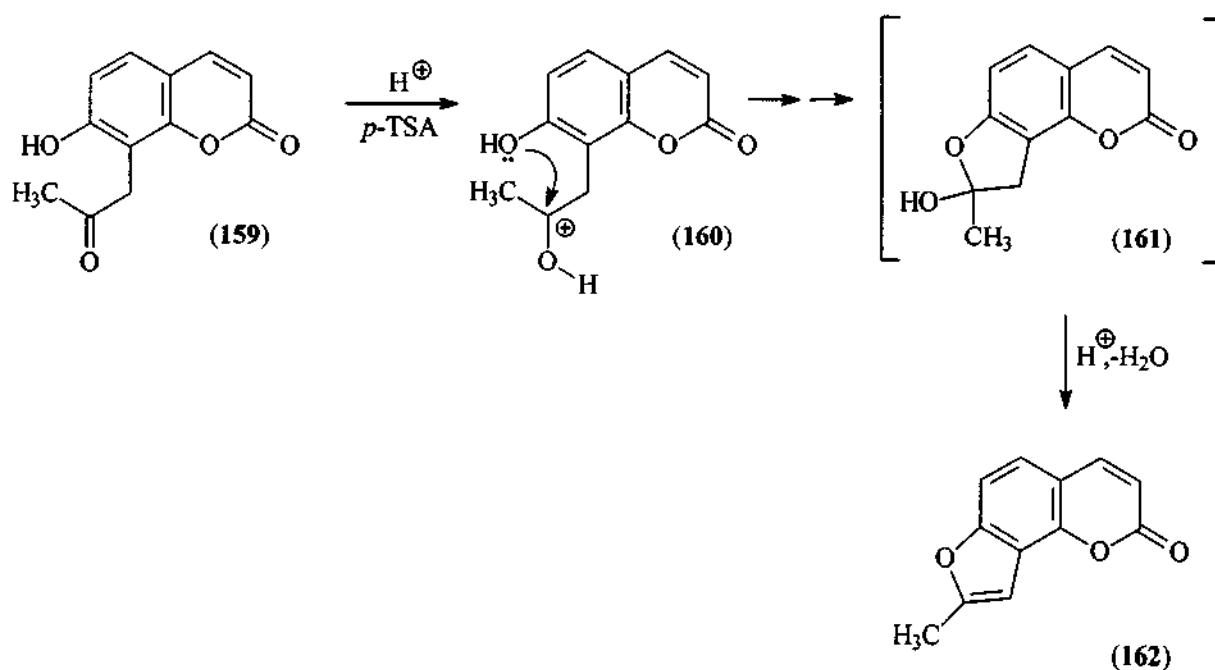
Scheme 41

The success of this procedure then prompted the speculation that if this same technique was repeated using methanol as a solvent, nucleophilic substitution of the hydroxyl group with the methoxy nucleophile should occur in preference to dehydration, to give the expected substituted isopsoralen derivative. This approach was attempted (**Scheme 42**) and the reaction did, in fact, afford the expected isopsoralen derivative, 8-methoxy-8-methyl-8,9-dihydro-2*H*-furo[2,3-*h*] chromen-2-one (**163**) in quantitative yield as a racemic mixture. This compound was characterised by NMR spectroscopy (**Figure 10**).

(i) CH₃OH, *p*-TSA, 4Å molecular sieve, reflux
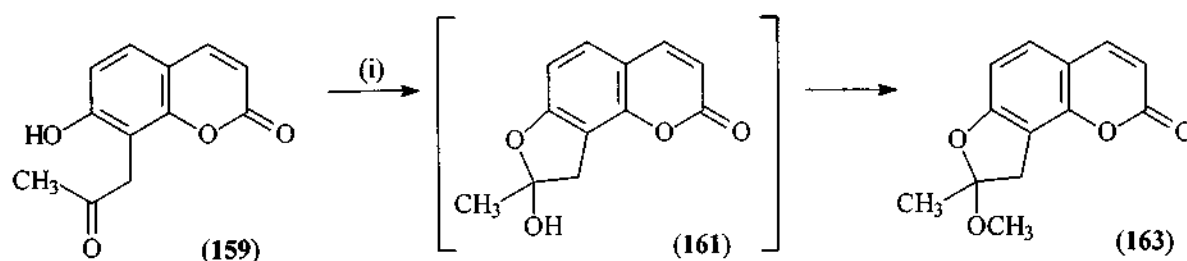
Scheme 42
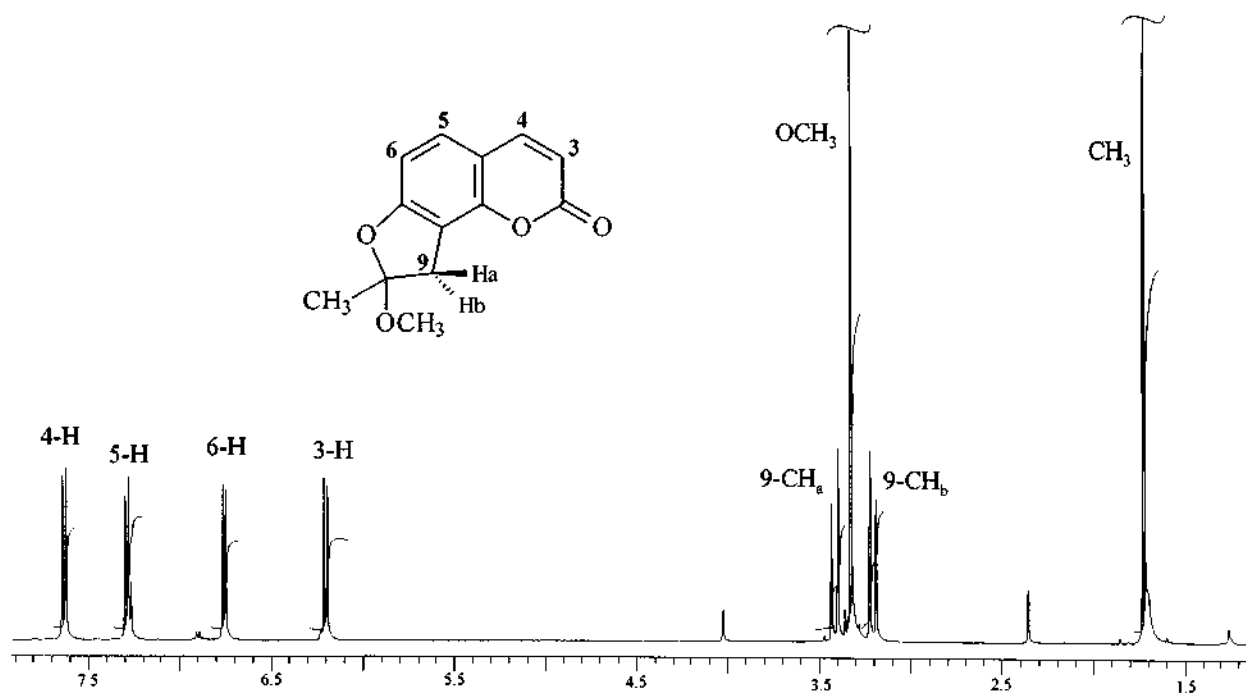
Figure 10: 500 MHz ¹H NMR spectrum of 8-methoxy-8-methyl-8,9-dihydro-2*H*-furo[2,3-*h*] chromen-2-one (**163**) in CDCl₃.

2.1.2.4.2 Synthesis of methyl 2-{[(2-oxo-2*H*-chromen-7-yl)oxy]methyl}acrylate (**169**)

The methyl 2-(chloromethyl)acrylate (**168**) required in order to introduce an ester functionality into the system (**Scheme 45**) was synthesised using the Baylis-Hillmann reaction.[82] The Baylis-Hillmann reaction involves the coupling of an aldehyde and an acrylate ester (**Scheme 43**), catalysed by a tertiary amine base, usually 1,4-diazabicyclo[2.2.2]octane (DABCO). The reaction, which tends to be rather slow (sometimes taking 4-7 days or longer, for completion) has found wide application in the synthesis of a large range of natural products including necic acids.[83]
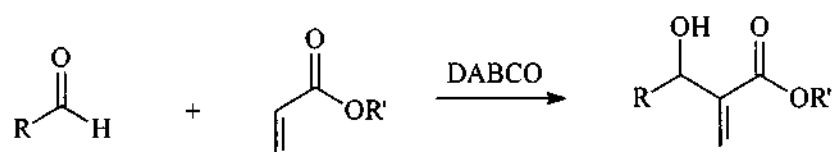
Scheme 43

A kinetic and mechanistic study undertaken by Bode and Kaye,[84] led to the proposal of a mechanism for the reaction which was consistent with the experimentally determined data and also with earlier suggestions put forward in a review of the Baylis-Hillman reaction by Drewes and Roos.[82] The mechanism, as applied to the reaction carried out in this project (**Scheme 44**), involves an addition-elimination sequence initiated by nucleophilic attack of the tertiary amine on methyl acrylate (**164**) to form the transient zwitterionic enolate species which subsequently attacks the electrophilic paraformaldehyde to afford the intermediate adduct (**165**). The formation of this intermediate is thought to be the rate-determining step. Proton transfer and elimination of the amine catalyst then affords the coupled product (**166**) as well as its dimer, the symmetrical ether **167**.
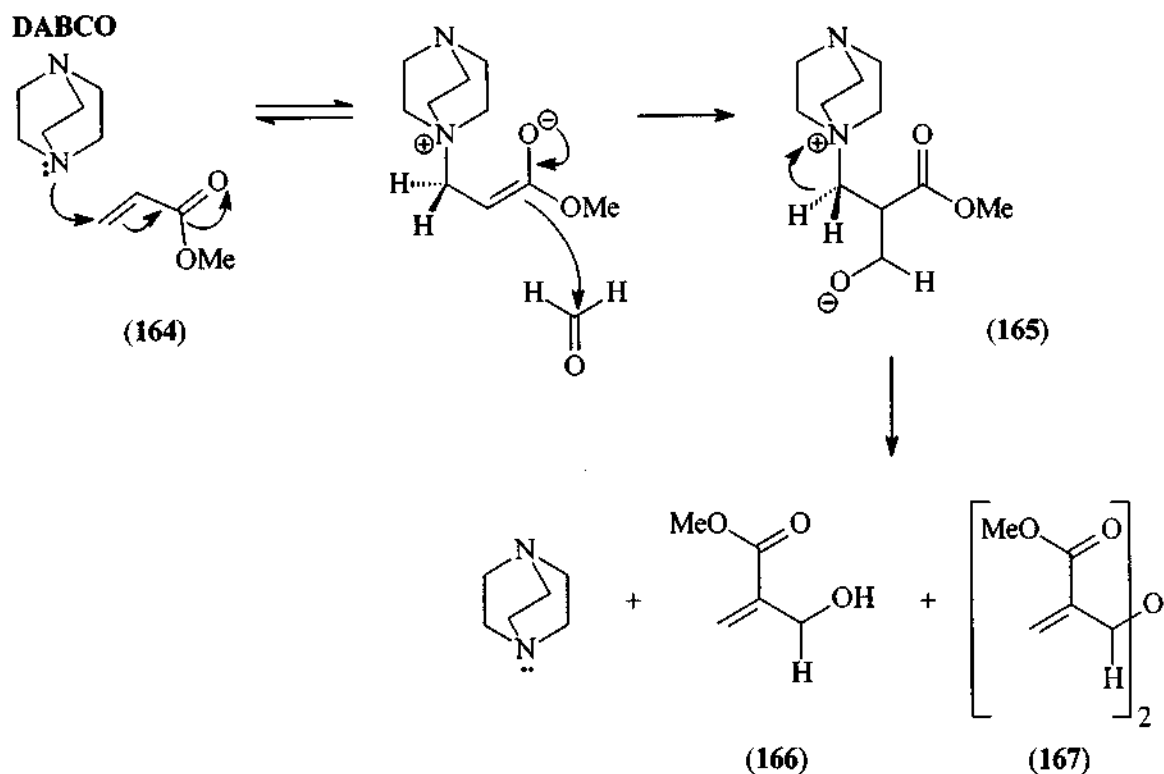
Scheme 44

The next step involved the activation of **166** to facilitate the reaction with 7-hydroxycoumarin (**140**), achieved by replacing the hydroxyl group with a halide atom. One advantage found here is that there is no need to separate out the coupled product (**166**) and the ether (**167**) since this ether is also converted into the halide under the same conditions.[85] Thus the crude mixture of products **166** and **167** can be used for the subsequent halogenation step. Initial attempts to convert the hydroxyl into a bromide using HBr were unsuccessful, however conversion to the chloride was achieved by reaction with thionyl chloride to afford 2-chloromethylacrylate (**168**) in *ca.* 60% yield (**Scheme 45**).
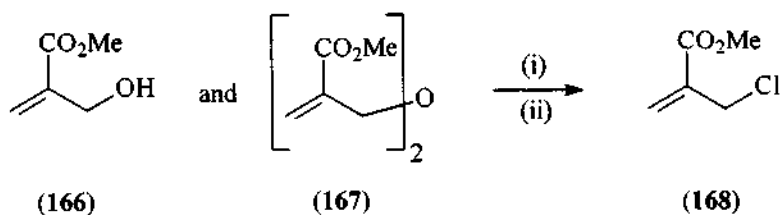
(i) DMF, benzene, thionyl chloride, 60°C;
(ii) H₂O(s)

Scheme 45

Once the 2-chloromethylacrylate (168) was synthesised, it was treated with 7-hydroxy coumarin (140) in the presence of potassium carbonate to afford the allyl aryl ether (169) in 95% yield (Scheme 46). The next intended step was to perform the Claisen rearrangement on methyl 2-{[(2-oxo-2H-chromen-7-yl)oxy]methyl} acrylate (169) so as to obtain the rearranged product (170). However, this step proved to be surprisingly difficult despite previous literature precedence to support this reaction.[86]
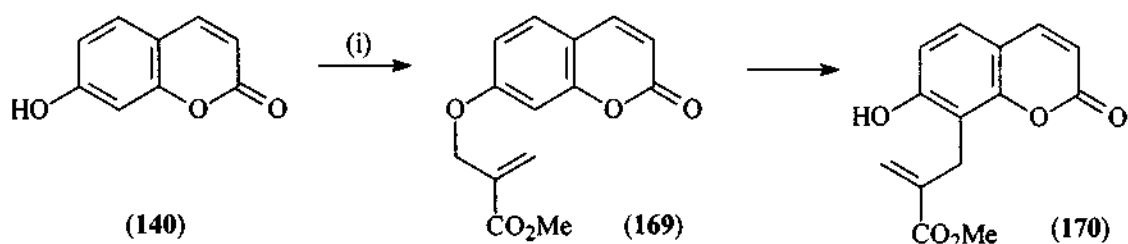
(i) THF, NaH, then 168, reflux, 3hrs.

Scheme 46

Unfortunately, normal thermal conditions (refluxing N,N-diethylaniline) had no effect when trying to perform the Claisen rearrangement on the coumarin 169, and hence the reaction was repeated using a variety of other conditions,[45,87] namely:-

(i) Refluxing N,N-diethylaniline containing AlCl₃ as a catalyst;

(ii) Refluxing trifluoroacetic acid; and

(iii) Refluxing toluene containing p-toluenesulfonic acid as a catalyst.

None of these conditions, however, were successful in inducing the rearrangement to occur. A probable explanation for the failure of the rearrangement may be the competing delocalisation within the system (**Scheme 47**), resulting in the formation of the enolate of the α,β-unsaturated ester. This has the effect of creating the system displayed by compound **171**, where the negative charge has been delocalised over the entire ester functionality. It will be noticed that the resonance structure formed by pathway **b** can still undergo rearrangement since the allyl group is still in place. However, a predominance of the resonance structure formed by pathway **a** would definitely hinder rearrangement since this structure is unable to undergo rearrangement.

The enolate species is stabilised by the presence of protons in solution, thus carrying out the reaction in an aprotic solvent may lead to the formulation of reaction conditions which facilitate the desired rearrangement reaction.
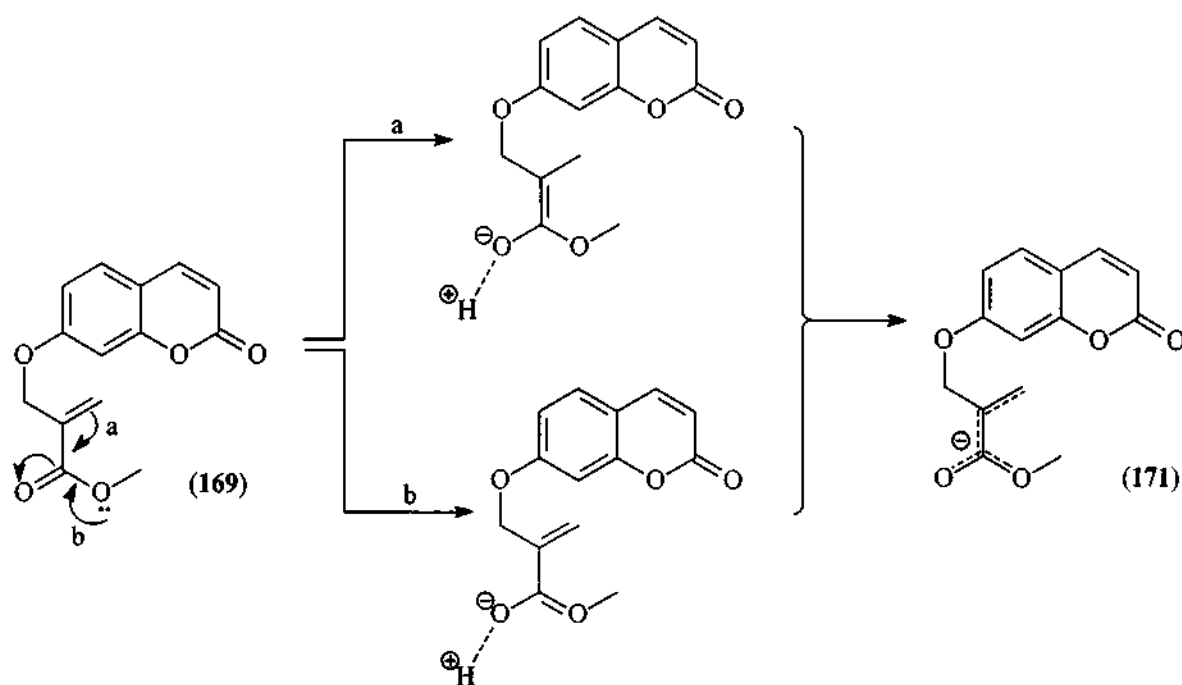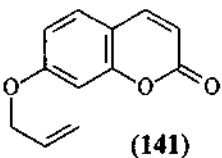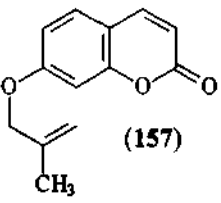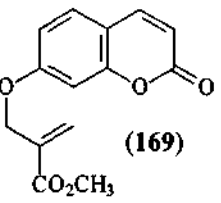
Scheme 47

The presence of the system displayed by coumarin **171** has been corroborated by calculations performed on the coumarin **169** using Hyperchem. These calculations, as were performed on the previous allyloxy coumarin systems, revealed similar HOMO-LUMO plots as before, (*cf.* **Figure 4**, page 40) suggesting that the reaction could occur and should afford the same

regioselectivity as noted before. However, inspection of the charge distribution on each atom for all three systems showed that the charge on the terminal vinyl carbon of coumarin **169** was less negative than that of the same carbons on the other two coumarin systems (**Table 2**). This is indicative of the representation shown in **Scheme 47** where the negative charge has been delocalised, thus making the alkene a substantially less efficient electron donor and consequently lowering the probability of overlap between the occupied and unoccupied molecular orbitals.

A subsequent examination of the energy gap between the HOMO -2 and the LUMO for the system revealed, as expected, a slightly larger energy gap as for the previous systems (**Table 2**), suggesting that the reaction would require a larger input of energy in order for cyclisation to take place.

Table 2: Comparison of terminal carbon charges and HOMO/LUMO energy gaps for different substituted allyloxy coumarins.

Coumarin System	(141)	(157) CH_3	(169) CO_2CH_3
Charge on terminal vinyl carbon[a]	-0.19	-0.19	-0.08
Energy gap (eV)	9.55	9.15	9.90

[a] Measured in Electron Units

2.2 PREPARATION OF SULFUR ANALOGUES

Due to the success of the synthetic pathway towards the range of oxo-isopsoralens, attention was focussed on exploring the feasibility of extending this methodology to incorporate a sulfur heteroatom in the isopsoralen ring system. The rationalisation for doing this has already been discussed in the introduction, namely that the synthesis of thio-analogues of psoralens have found increased application in recent years. Some of these analogues have in fact been shown to possess significant biological activity with markedly less phototoxicity when compared to the traditionally used oxygenated systems.[52,61]

2.2.1 Synthetic pathway towards thio-isopsoralen derivatives

It was decided that the most feasible way to approach the synthesis of thio-analogues of isopsoralen would be to make use of the coumarin parent compound 7-hydroxycoumarin (140), which had been used previously and to subsequently convert the phenolic moiety at the 7-position into a thiol. The thiol group is expected to have similar properties to the phenol, the 7-thiocoumarin would therefore be expected to undergo nucleophilic attack with an aldehyde, in the same manner as observed previously to afford the thio-furan ring system. The question arose as to where in the synthetic pathway it would be most advantageous to conduct the functional group conversion to the thiol.

2.2.1.1 The Thio-Claisen rearrangement

The Thio-Claisen rearrangement[68] of allyl phenyl sulfides is different from that observed in the oxygen systems. Although the sulfur analogues show high thermal stability, they do undergo cleavage at 300°C. However, in solution, preferably in quinoline or diethylaniline, rearrangement does occur, but the obtained products are unexpectedly different from the oxygen systems. It has been documented in the literature that allyl phenyl sulfide (172) in refluxing quinoline is transformed into a mixture of 2-methylthiacoumaran (174) and thiachroman (175) (Scheme 48).[68]

It has been accepted that o-allylthiophenol (173) is, in fact, the initial product of the

rearrangement reaction, but that this product cyclises rapidly under the rearrangement conditions into the observed products (174) and (175). It has been shown that the independently prepared thiophenol 173 affords the same products in refluxing quinoline.[88] The formation of these products is thought to be due to the competitive ionic and radical additions of the thiol function to the allylic double bond of 173.

(172)   (173)   (174)   (175)
                                                   40%   37%
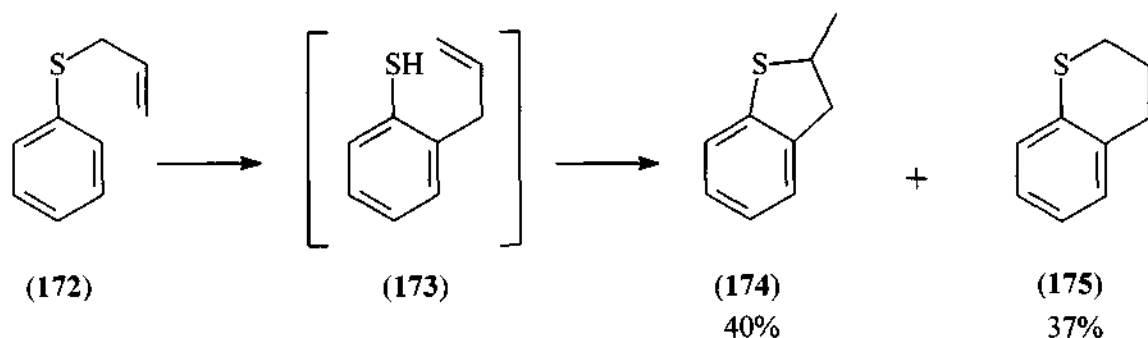
Scheme 48

It is clear from this information that, in our case, direct conversion to the thiol would not be a feasible scenario as the Claisen rearrangement would result in the formation of these undesired products. In fact, even conversion to the thiol after rearrangement but prior to ozonolysis would not be desirable. It was therefore decided to achieve the conversion to the thiol using the reagent, dimethylthiocarbamoyl chloride,[53] so as to afford a protected thiol which could then be deprotected only after the allyl group had been transformed *via* reductive ozonolysis. This reagent would be advantageous as it would act as both a protecting group and mediator of functional group interconversion. Furthermore, the dimethylthiocarbamoyl protecting group is stable to ozonolysis.

2.2.1.2 Synthesis of S-(8-allyl-2-oxo-2H-chromen-7-yl)N,N-dimethylcarbamothioate (177)

The first two steps in the sequence towards the incorporation of a sulfur atom in the furan ring thus involved the reaction of the coumarin 142 with dimethylthiocarbamoyl chloride to afford the dimethylcarbamothioate derivative (176). This compound was then subjected to a thermal rearrangement reaction, in which there is an interconversion between the sulfur and oxygen atoms to give the protected thiol (177) in 86% yield (Scheme 49). It can be seen that use of this approach has introduced a sulfur atom into the position previously occupied by the hydroxyl

group.

(142)   **(176)**   **(177)**
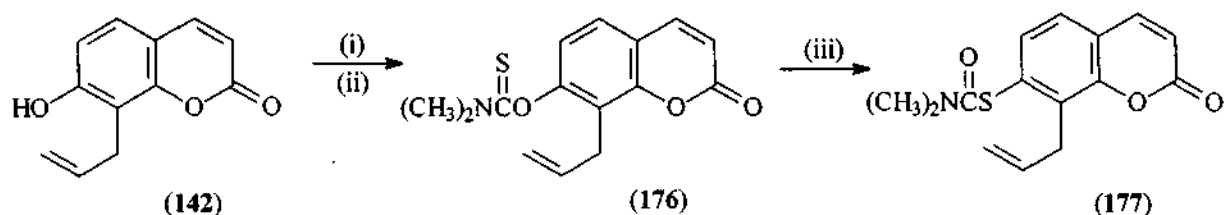
(i) DMF, NaH; (ii) (CH₃)₂NCSCl, 60°C;

(iii) N₂, 220-240°C, 40 min.

Scheme 49

2.2.1.3 Synthesis of 8-methoxy-8,9-dihydro-2*H*-thieno[2,3-*h*]chromen-2-one (185)

The successful synthesis of the protected thiol (177) precipitated some thought towards what measure should be taken next. Under normal circumstances, in order to generate the thiol, the ensuing step would be to cleave off the protecting group by treatment with base and then acid, leaving the thiol (178), however, this would presumably undergo rapid cyclisation, as discussed earlier in **Scheme 47**, to afford a mixture of compounds 179 and 180 (**Scheme 50**), which was undesirable, even though one of the products (179) is, in fact, an isopsoralen derivative.

(177)   **(178)**

(179)   +   **(180)**
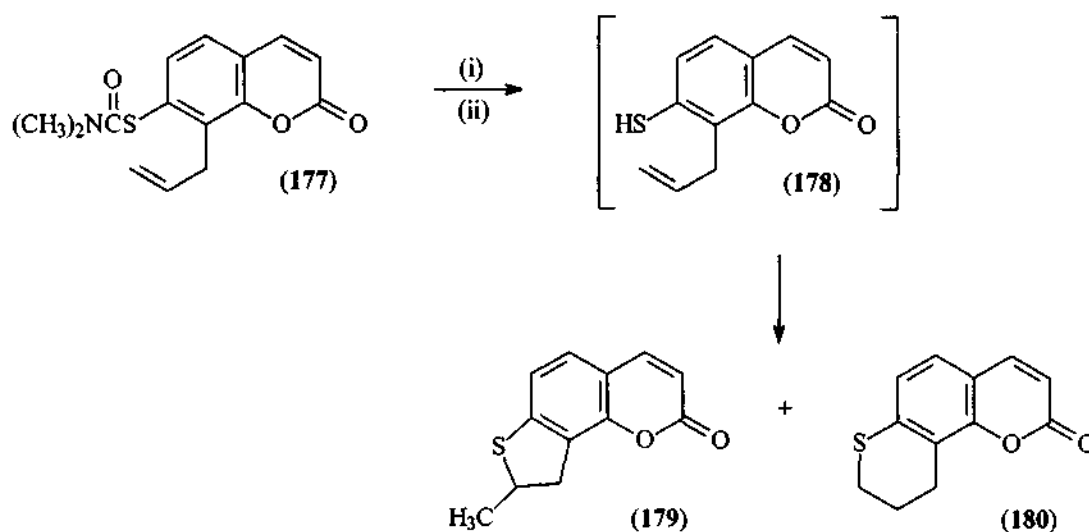
(i) CH₃OH, KOH; (ii) H⁺, H₂O

Scheme 50

It was consequently decided to leave the protected thiol intact until after the aldehyde had been generated. The coumarin (177) was therefore subjected to reductive ozonolysis (Scheme 51) to afford the aldehyde (181) after workup. This aldehyde, generated in the reaction, was subsequently protected as an acetal using the standard procedure,[45] and resulted in formation of S-[8-(2,2-dimethoxyethyl)-2-oxo-2H-chromen-7-yl]N,N-dimethylcarbamothioate (182), which was characterised by NMR spectroscopy (Figure 11). The protection step was performed in order to prevent any possible reaction of the aldehyde in the basic conditions needed to cleave off the dimethylthiocarbamate protecting group.

(i) THF, -78°C, O$_3$, then dimethylsulfide, -10°C to R.T.;
(ii) CH$_3$OH, 4Å molecular sieve, reflux
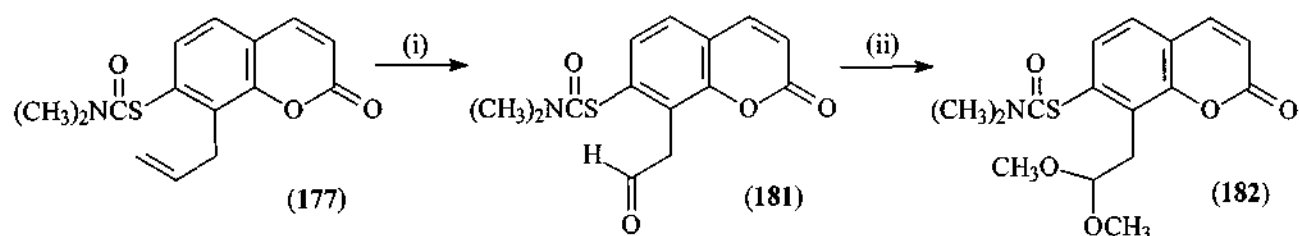
Scheme 51
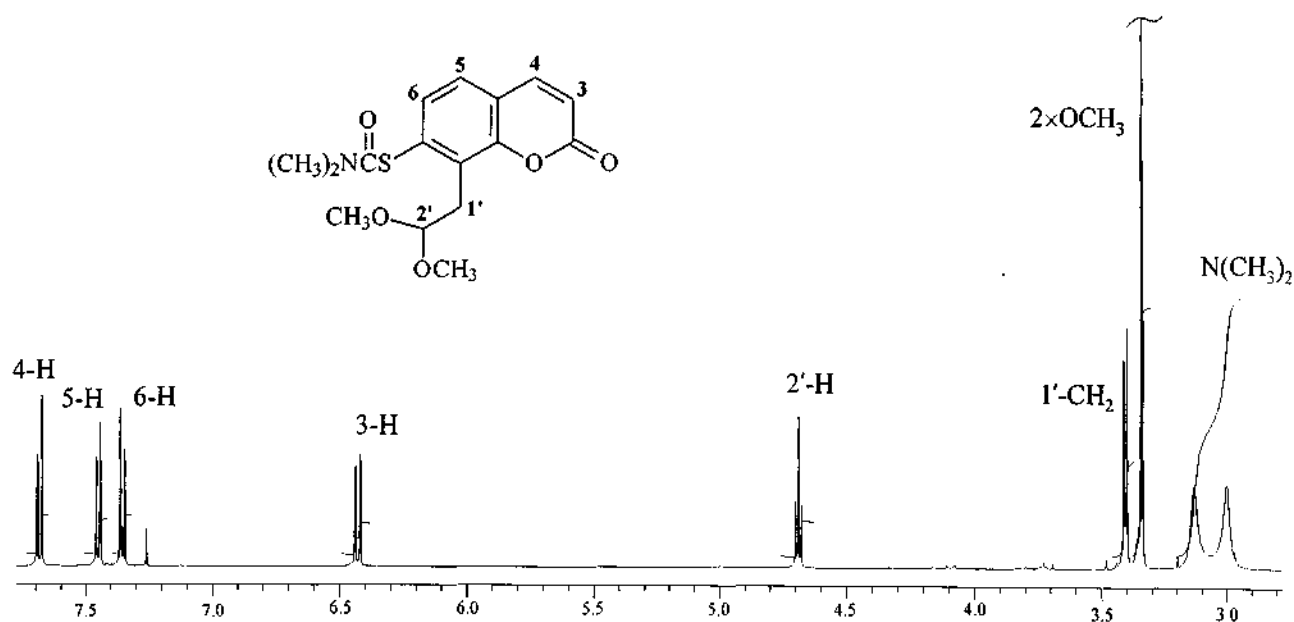
Figure 11: 500 MHz ^{1}H NMR spectrum of S-[8-(2,2-dimethoxyethyl)-2-oxo-2H-chromen-7-yl]N,N-dimethylcarbamothioate (182) in CDCl$_3$.

Synthesis of the isopsoralen analogue (185) was then completed by reaction of the acetal (182) with KOH, followed by treatment with aqueous acid (Scheme 52). The treatment with acid simultaneously cleaved the carbamate group and deprotected the acetal to regenerate the aldehyde (183). This compound would presumably undergo rapid nucleophilic attack as was seen with the oxygen analogues, resulting in the formation of the hemiacetal (184), this intermediate was in fact not isolated.

This hemiacetal underwent nucleophilic substitution of the hydroxyl group in the presence of methanol, affording the desired isopsoralen, 8-methoxy-8,9-dihydro-2H-thieno[2,3-h]chromen-2-one (185). This reaction did not proceed as cleanly as with the oxygenated systems, with a number of unidentifiable side products being formed, and a significantly lower yield of 29% when compared to the yields of $ca.$ 65-75% for the oxo-isopsoralen derivatives.

(i) CH₃OH, KOH, reflux; (ii) H⁺, H₂O
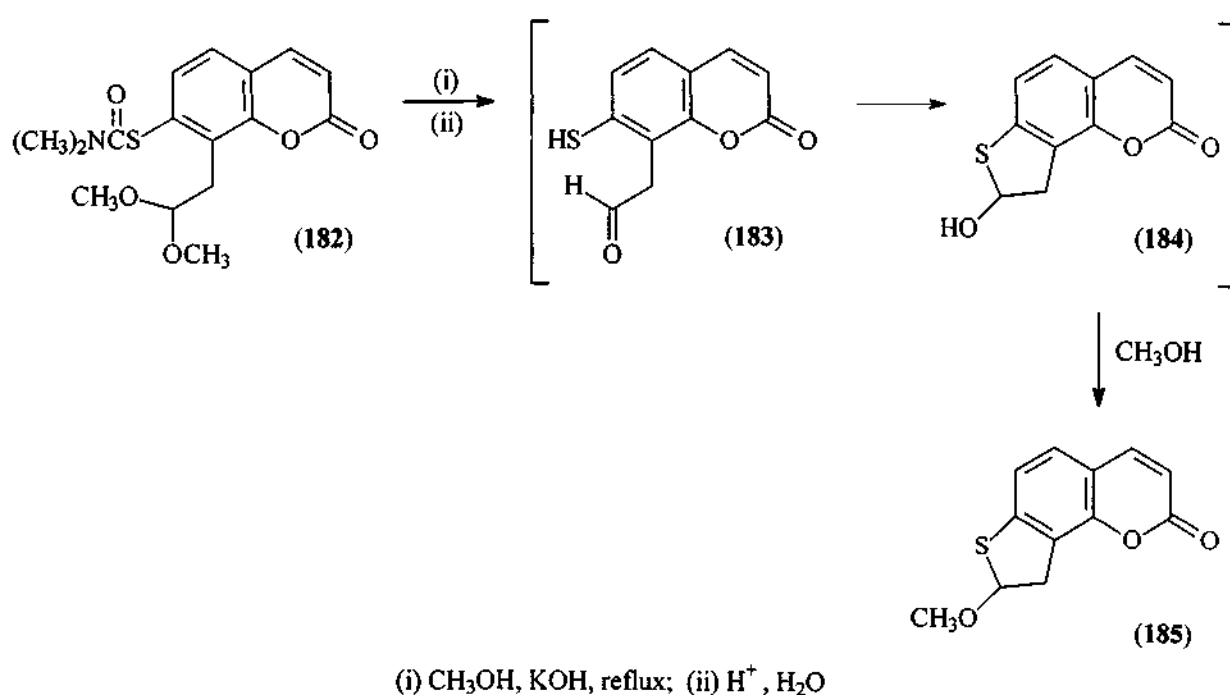
Scheme 52

2.2.1.4 Attempted synthesis of 8-ethoxy-8,9-dihydro-2H-thieno[2,3-h]chromen-2-one (186)

This same approach was then attempted using ethanol as a solvent (Scheme 53). This was in order to accomplish the synthesis of the ethoxy substituted derivative (186). The synthetic procedure was essentially the same, except that in this case there was no protection of the aldehyde functionality (181) since this was now thought to be both unnecessary and also a possible contributing factor towards the presence of undesirable side products found earlier. Unfortunately the approach outlined in Scheme 53 failed to provide any conclusive evidence of the desired isopsoralen derivative (186).

Initial GC-MS analysis of the mixture provided evidence for the presence of the hemiacetal derivative (184), but crude NMR spectroscopic analysis failed to provide any additional proof due to the presence of some impurities. The only conclusive signals observed were those for the four aromatic protons of the coumarin system. Preparative layer chromatography also failed to purify the reaction mixture, with NMR spectroscopy of the bands proving to be very similar to the original sample. NMR spectrscopic analysis did however show the absence of the dimethylcarbamothioate group, which along with the GC-MS data would tentatively suggest that the hemiacetal was, in fact, obtained as a major product.

High resolution mass spectrometry of the sample provided evidence for the presence of the charged species (187) (M$^+$, 203), suggesting once again that the hemiacetal was in fact, a major component of the original reaction mixture. No explanation could be given for the failure of this reaction,[#] and due to time constraints further attempts at this reaction were not examined.

[#] Failure was not due to use of the unprotected aldehyde since repetition of the reaction using the acetal protected species produced similar results.

(i) CH_3CH_2OH, KOH, reflux; (ii) H^+, H_2O
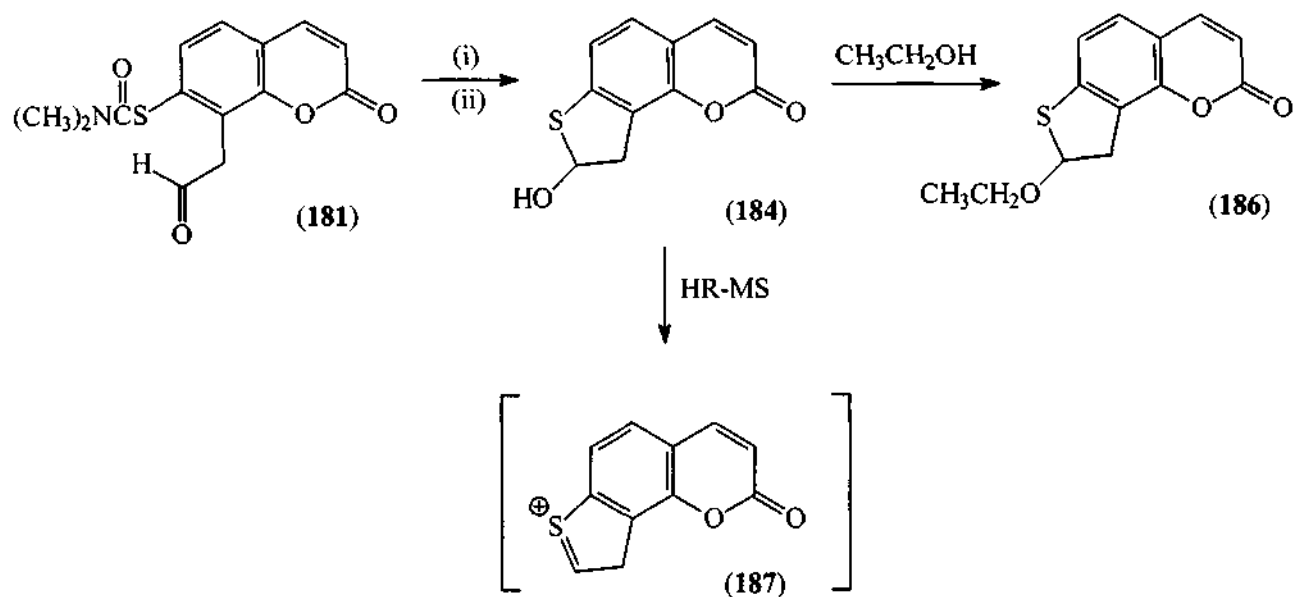
Scheme 53

2.2.2 Variable Temperature NMR Spectroscopic Studies

An interesting observation was made when studying the proton NMR spectra of compounds **176** and **177**. The signals for the two *N*-methyl groups of the dimethylcarbamothioate group of **177** (**Figure 13**), which are completely resolved at low temperatures, begin to approach coalescence as the temperature is increased to room temperature. The dependance on temperature of these rotameric systems is well known and has been extensively documented in the literature.[75,89,90,91]

The C-N bond has a high proportion of double bond character [**Figure 12 (B)**], which hinders rotation and subsequently results in the two methyl groups being magnetically non-equivalent. At low temperature, the energy of the system is lower than the rotational barrier of the C-N double bond, resulting in two separate singlets for the these two methyl groups.

At higher temperatures, however, the rotational barrier is overcome. Exchange between the two methyl groups now occurs at a rate fast enough to cause them to be indistinguishable by NMR spectroscopy, resulting in coalescence of the two singlets into one broad signal.

(A)   (B)
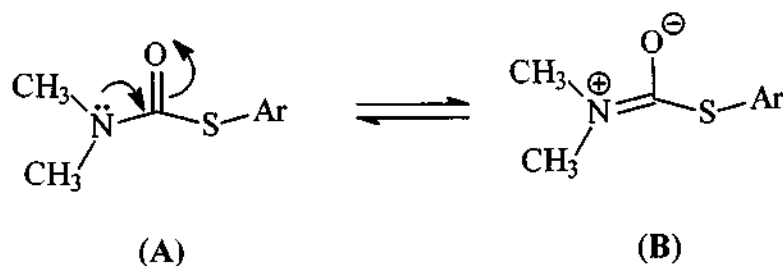
Figure 12

Figure 13 shows the 500 MHz ^{1}H NMR signals for the methyl protons of the dimethyl carbamothioate group of coumarin derivative **177**, in deuterated 1,1,2,2-tetrachloro ethane $(C_2D_2Cl_4)$.[†] The NMR signals are recorded at different temperatures, and exhibit the coalescence of the two singlets into one broad band as the rate of exchange of the two methyl groups is increased with increasing temperature. The coalescence temperature T_c, was found to be 43.0°C (316K).

The free energy of activation for the process, ΔG^* was calculated using the equation:[75]

$$\Delta G^* = 2.303 \; RT_c (\log k_b T_c/h - \log 2.22 \; \Delta v)$$

where R= gas constant

T_c= coalescence temperature in K

k_b= Boltzmann's constant

h= Planck's constant

Δv= difference in chemical shift when signals are completely resolved

This method equates ΔG^* as 64.3 kJ.mol^{-1}, which is comparable to other reported values[90] of 64-72 kJ.mol^{-1} for these types of systems. Another reported method by Smith *et al.*[92] for determining ΔG^*, making use of Δv_c, the estimated difference in chemical shift at the coalescence point, provided a similar value of 66.5 kJ.mol^{-1} for ΔG^*.

[†]1,1,2,2-tetrachloroethane was chosen due to its large working temperature range (*ca.* -35 to 135°C).

268K
Δν = 69.3Hz

298K
Δν = 68.1Hz

308K
Δν = 57.4Hz

315K
Δν =31.1Hz

316K (T_c)
$Δν_c$ = 27.0Hz

358K
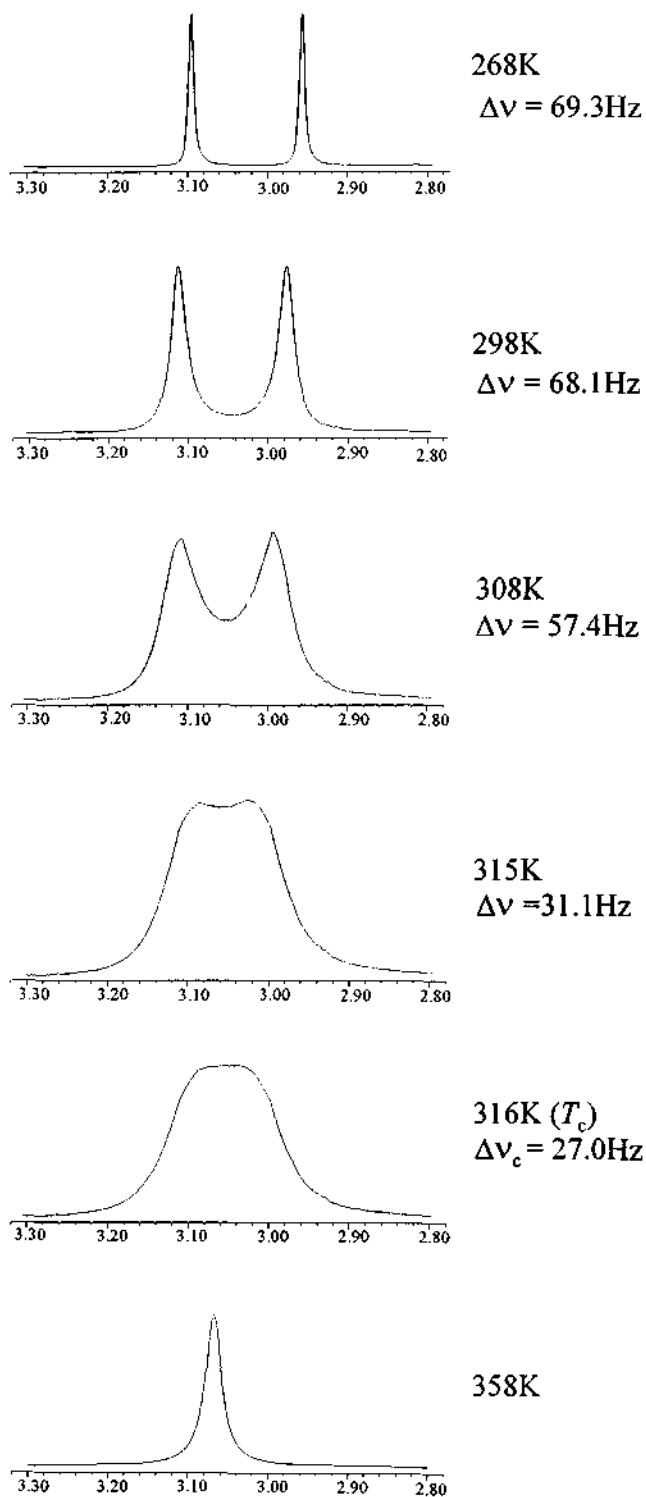
Figure 13: Partial 500 MHz ^{1}H NMR spectra showing the coalescence of the two methyl peaks of the dimethylcarbamothioate group of S-(8-allyl-2-oxo-2H-chromen-7-yl)N,N-dimethycarbamothioate (**177**). The coalescence temperature was found to be 316K.

The rotameric signals for the dimethylcarbamothioate group for compound **176** show a significantly different temperature dependance for the two methyl groups. In this system coalescence was *only* reached at 118°C (391K), over 2.5 times greater than that observed for the former system. The corresponding rotational barrier for the process was calculated to be 80.6 kJ.mol⁻¹, significantly higher than that of the previous system. This indicates that isomer **D** of **176** (**Figure 14**) is much more prevalent than isomer **C** of **176**, i.e. the rotation about the C-N bond is significantly more hindered.

$$CH_3 \underset{CH_3}{\overset{S}{\diagdown N}} \diagdown O - Ar \quad \rightleftharpoons \quad CH_3 \underset{CH_3}{\overset{S^{\ominus}}{\diagdown N^{\oplus}}} = \diagdown O - Ar$$

(C)   (D)
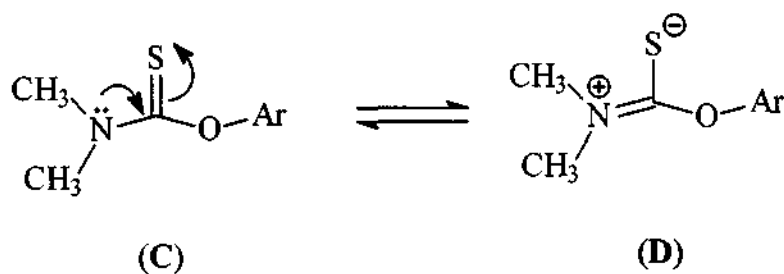
Figure 14

Another factor to consider for these two systems is the presence of the heteroatom adjacent to the carbonyl or thiocarbonyl group. These have a conflicting action, as shown in **Figure 15**, which would affect double bond character of the C-N bond, and would thus also have a lowering influence on the rotational barrier of the C-N bond and subsequently on the temperature at which coalescence occurs. However, since calculated rotational barriers compare favourably with reported values[90] for similar systems without the adjacent heteroatom, it can be concluded that this effect is minimal. Future work could involve looking at similar systems, but without the adjacent heteroatoms, in order to determine to what extent the presence of these atoms influence the rotational barrier energies.

$$CH_3 \underset{CH_3}{\overset{S}{\diagdown N}} \diagdown O - Ar \qquad CH_3 \underset{CH_3}{\overset{O}{\diagdown N}} \diagdown S - Ar$$

(E)   (F)
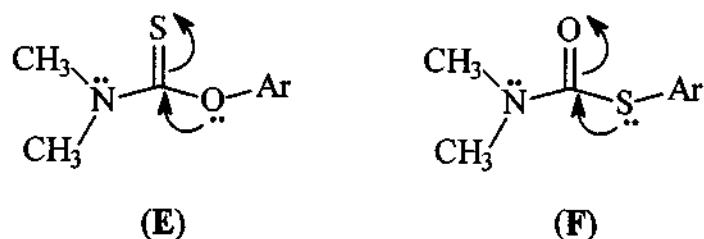
Figure 15

2.3 SELENIUM ISOPSORALEN ANALOGUES

Attention was subsequently directed towards utilising the type of chemistry already established as a possible route towards the synthesis of some selenium analogues of isopsoralen. As has already been mentioned, photobiological[52] and other testing (spin trapping and electron spin resonance spectroscopy)[66] has revealed that some selenium analogues of psoralen are more effective than their oxygen analogues in regard to their biological activity. Selenium analogues of psoralens thus show great promise in the use of photochemotherapy. However, despite this fact very little research has been published on analogues which contain selenium, with only 4 papers discovered so far detailing the synthesis and study of these types of analogues. There has also been no report in the literature on the synthesis of selenium analogues of the angular isopsoralens, so any progress made in this regard would obviously be of great importance towards the further study of these types of systems.

2.3.1 Proposed Route to Selenium Isopsoralens

There has been no report in the literature to date on a method by which an aromatic hydroxyl group may be directly converted into a selenyl group. However methods do exist whereby bromine can be replaced by selenium in a nucleophilic substitution process, these methods have already been used in order to synthesise various selenium analogues of psoralen, as has been discussed in the introduction (Section 1.3.2.3).

Our proposal, outlined in **Scheme 54**, involved the conversion of the hydroxyl group of 7-hydroxy-8-allyl coumarin (**142**) into bromine to afford the 7-bromo derivative (**188**). This could then be subjected to ozonolysis and protection of the aldehyde, as had been previously achieved, to afford the acetal (**189**). The ozonolysis needed to be performed prior to substitution with selenium since selenides are known to be oxidised to selenoxides in the presence of ozone.[93] The acetal (**189**) could then be reacted with methaneselenol in a similar procedure to that used by Jacobs et al.[54,56] to afford the seleno product (**190**). Deprotection of this and subsequent cyclisation between the selenyl residue and the aldehyde, catalysed by polyphosphoric acid silyl ether (PPSE), should then afford the seleno isopsoralen derivative **191**.
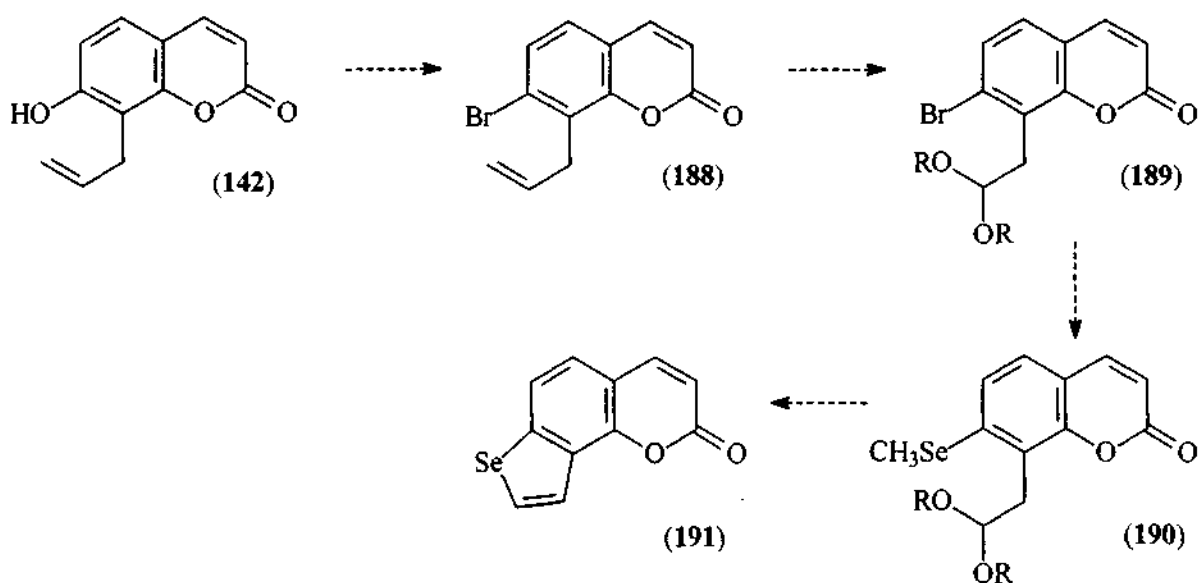
Scheme 54

2.3.1.1 Attempted Preparation of 8-allyl-7-bromo-2H-chromen-2-one (188)

One of the few methods for converting an aromatic hydroxyl group into a bromine involves the use of triphenylphosphine dibromide. This reagent has been successfully used in both aryl and aromatic alcoholic systems,[94] and a report by Bandin et al.[95] describes the conversion of 2,7-dihydroxynaphthalene (192) into 7-bromo-2-hydroxynaphthalene (193) in 35% yield using this approach (Scheme 55).
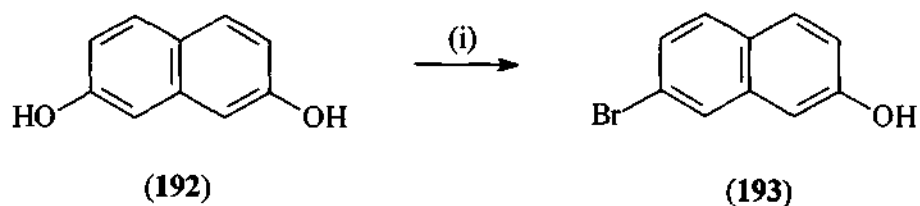
(i) CH₃CN, Ph₃PBr₂

Scheme 55

This procedure was thus attempted in order to convert the coumarin (142) into the bromine substituted derivative 8-allyl-7-bromo-2H-chromen-2-one (188) (Scheme 56). However, this approach proved unsuccessful, with several attempts resulting only in the regaining of starting material with no evidence for the presence of any desired product.
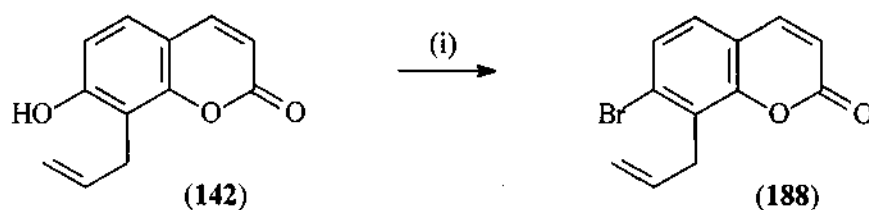
(i) DMF, Ph₃PBr₂

Scheme 56

Due to the failure of triphenylphosphine dibromide in introducing bromine, attention was focussed on utilising a triflate in order to bring about the desired transformation. In a recent publication, a method was reported in which substitution of an aromatic hydroxyl group with a bromide atom was achieved. This method involved the conversion of the hydroxyl to the triflate using trifluoromethanesulfonic anhydride, followed by treatment with tetrabutylammonium bromide. This method has been used successfully by Makosza and Podraza in hydroxyazulene systems[96] (Scheme 57), with the 6-hydroxyazulene derivative 194 being converted into the triflate (195) in high yield. Subsequent reaction with various alkyl ammonium halides afforded the substituted azulene derivatives (196) in *ca.* 90% yields.
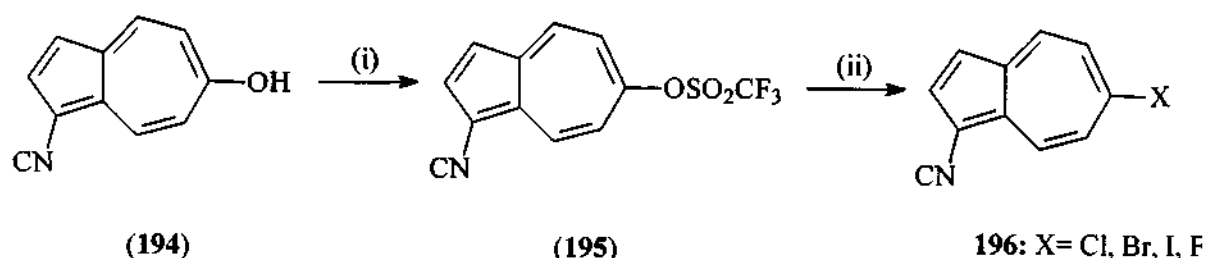
(i) THF, Et₃N, (CF₃SO₂)₂O;
(ii) R₄N⁺X⁻

Scheme 57

Unfortunately, this method also proved unsuccessful when attempted on our coumarin system (**Scheme 58**). The initial reaction did afford the triflate (**197**) as expected, but subsequent treatment with Bu_4NBr failed to produce the expected bromide (**188**), with only the starting triflate being isolated from the reaction mixture after several attempts at the reaction.

(**142**)   (**197**)   (**188**)

(i) THF, $(CF_3SO_2)_2O$, Et_3N, $-70^{\circ}C$;
(ii) Acetonitrile, Bu_4NBr, reflux
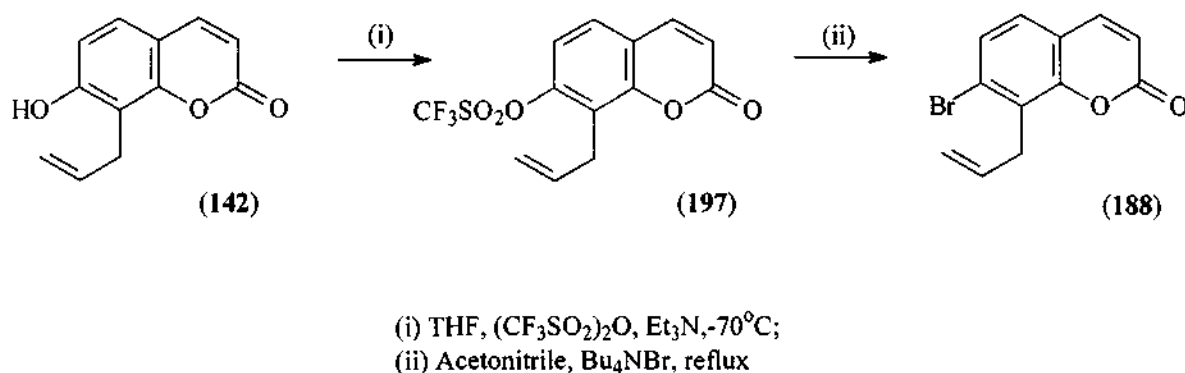
Scheme 58

2.3.2 Revised Synthetic Route

The lack of success in synthesising the coumarin **188** led to a new proposed synthetic route utilising bromophenol (**198**) as a potential starting point. Allylation and Claisen rearrangement of this compound should afford the phenol (**200a**), along with its other *ortho*-rearranged product as outlined in **Scheme 59**. The desired phenol, once isolated, could then be converted into the corresponding coumarin (**201**) *via* the Pechmann Condensation Reaction.[97] Once the substituted coumarin **200** had been prepared, subsequent substitution with selenium, ozonolysis and cyclisation could be achieved as previously discussed in **Scheme 54** (see page 71).
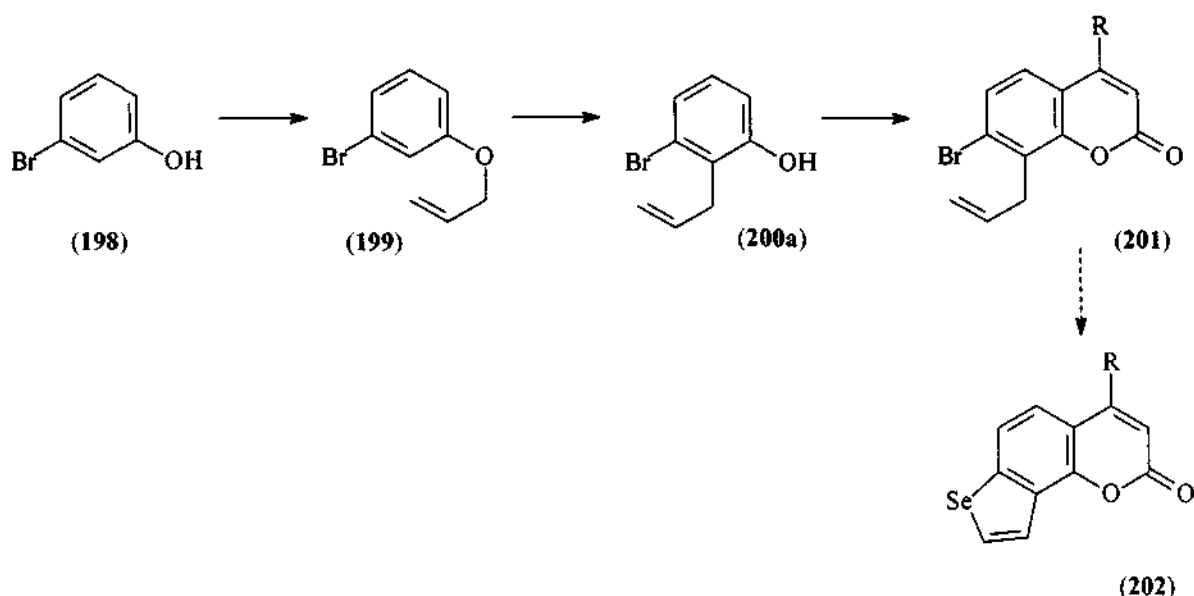
Scheme 59

2.3.2.1 Synthesis of 2-allyl-3-bromophenol (200a)

The first step in the new proposed synthetic route (**Scheme 60**) involved the allylation of bromophenol using the same procedure as had previously been performed during the earlier synthesis of 7-allyloxy coumarin (**141**). This afforded the allyl phenyl ether (**199**) which, upon Claisen rearrangement gave the two expected regioismers, 2-allyl-3-bromophenol (**200a**) and 2-allyl-5-bromophenol (**200b**). These were then separated using column chromatography.
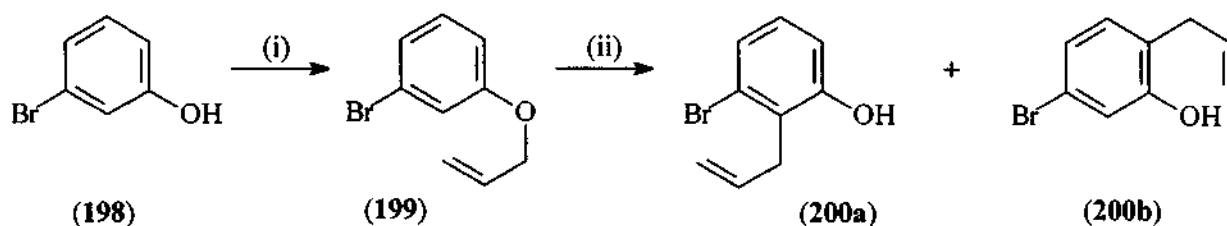
(i) K_2CO_3, allylbromide, acetone, reflux;

(ii) N_2, 220°C, 40min.

Scheme 60

Separation of the two isomers was difficult due to the similar retention times of the two on silica gel, but separation was achieved using a relatively non-polar solvent system (5:95 ethyl acetate/hexane) to give the two isomers in a ratio of 53% of (200a) to 41% of (200b). This ratio differs somewhat from those obtained by White and Slater,[98] who determined experimentally a yield of *ca.* 36% for (200a) and a ratio of 0.56 for the two isomers.

2.3.2.2 Attempted Synthesis of Coumarin System *via* Pechmann Condensation

Once the desired regioisomer had been isolated, the preparation of the coumarin ring system was attempted using the well known Pechmann Condensation reaction.[97] This reaction, widely used for the synthesis of coumarin systems, generally involves the coupling of a β-ketoester with a phenol (Scheme 61) to give access to a variety of 4-substituted coumarins. In this project, using 2-allyl-3-bromophenol (200a), this reaction should afford the desired coumarin (201). The advantage of using this reaction is, of course, the possibility of accessing extra functionality at the 4-position of the coumarin if so desired.
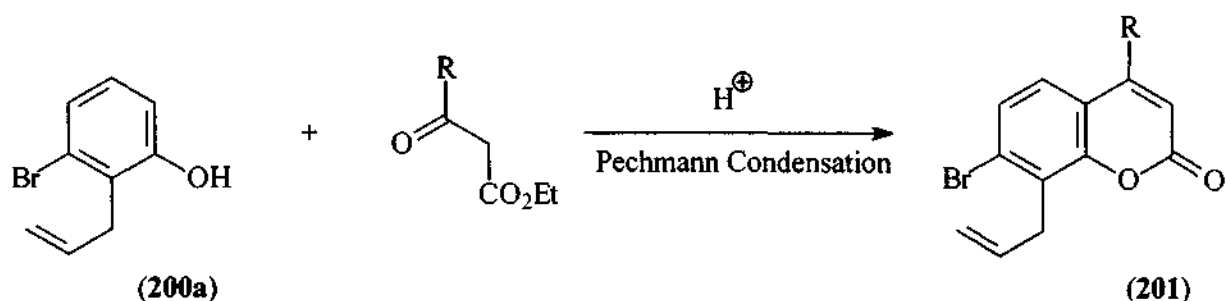
Scheme 61

The first attempt at the Pechmann Condensation proposed the use of ethylacetoacetate as the β-ketoester, which should have led to the formation of the equivalent 4-methyl substituted coumarin derivative (201, R=CH$_3$). This reaction was repeatedly attempted using three different catalysts: concentrated sulfuric acid, aluminium trichloride and phosphoric acid. All these are known condensing agents for the Pechmann reaction and have been used successfully in different systems, however all three failed to induce the Pechmann Condensation to occur, with GC-MS and NMR analysis of the reaction mixtures revealing the presence of starting material only. It was then decided to utilise another approach which had been reported for the synthesis

of the 4-hydroxycoumarin derivative (203). The method (Scheme 62) involves the use of malonic acid, with an equimolar mixture of anhydrous zinc chloride and phosphorous oxychloride as the condensing agents.[99] However, this approach also proved unsuccessful and once again only starting material was obtained from the reaction mixture.
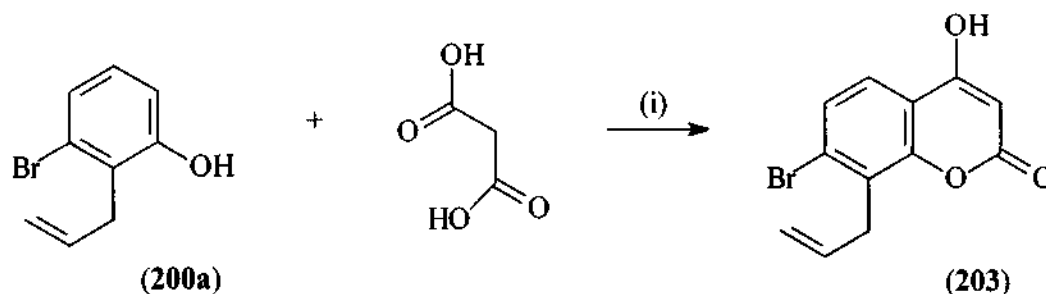
(i) ZnCl$_2$, POCl$_3$, 65°C, 35hrs.

Scheme 62

2.3.2.3 Attempted synthesis of the selenium substituted benzofuran ring

Due to the lack of success with the formation of the benzopyran ring system, and time constraints, it was decided to focus attention on one key aspect, namely the inclusion of selenium into the furan ring. Once this had been achieved one could then look at the construction of the benzopyran ring. To this end it was proposed to protect the hydroxyl group of 200a with a suitable protecting group and proceed with the rest of the synthesis of the benzofuran system.

The 2-allyl-3-bromophenol (200a) was thus reacted with *tert*-butyldimethylsilyl chloride,[100] a versatile protecting agent for the hydroxyl group, (Scheme 63) to afford the protected phenol (204).This compound, upon treatment with ozone followed by reductive workup, and subsequent protection of the aldehyde, afforded the acetal, [3-bromo-2-(2,2-dimethoxyethyl)phenoxy](*tert*-butyl)dimethylsilane (205) in 84% yield.

(i) THF, NaH, (CH$_3$)$_3$C(CH$_3$)$_2$SiCl;

(ii) THF, O$_3$, -78°C, then dimethylsulfide, -10°C to R.T.;

(iii) CH$_3$OH, p-TSA, 4Å molecular sieve, reflux
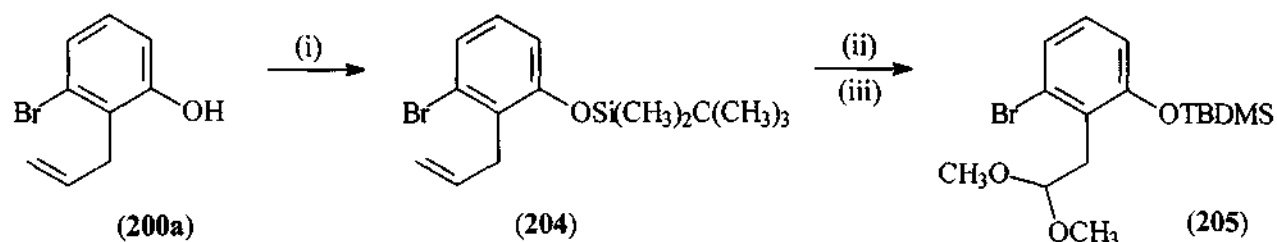
Scheme 63

Following the successful synthesis of the acetal (205), the nucleophilic subtitution of the bromine atom with methaneselenol was attempted in order to synthesise the seleno-ether (206), and thereby introduce the selenium residue into the correct position for the synthesis of the desired seleno-isopsoralen derivative (Scheme 64). However, this reaction was unsuccessful, GC-MS and NMR analysis of the products obtained suggest that instead of the nucleophilic substitution of the bromine atom taking place, the methaneselenol deprotected the silyl group of (205) to afford its corresponding phenol.

(i) K$_2$CO$_3$, acetonitrile, methaneselenol
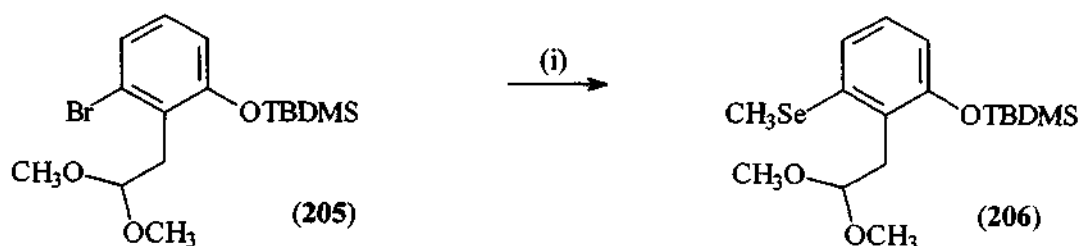
Scheme 64

Lack of success with this prompted looking at the original bromophenol (**200a**) and determining if just the substitution was in fact possible before any of the other synthetic work had been achieved on this compound. The reaction was attempted using two separate methods in order to prepare the substituted phenol (**207**). Both methaneselenol and lithium methyl selenide[101,102] (which should hopefully act as a more powerful nucleophile) were used in order to induce the substitution of the bromine (**Scheme 65**), but both these approaches failed and only starting material was isolated from both these reaction mixtures.

(**200a**)   (**207**)

(i) K_2CO_3, acetonitrile, methaneselenol
(ii) MeSeLi
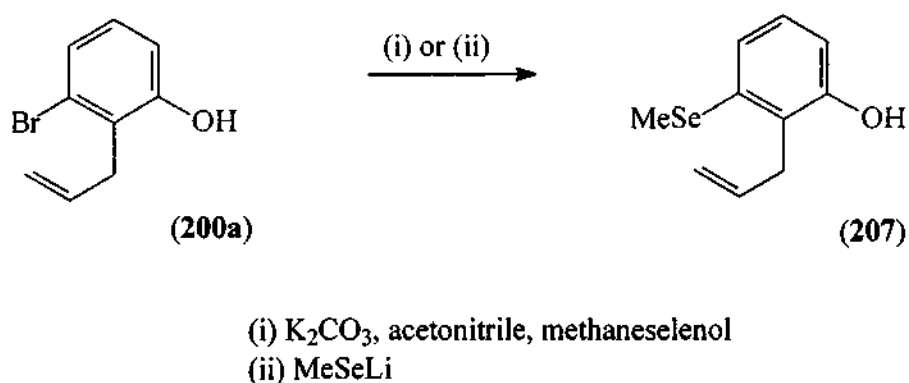
Scheme 65

The synthetic work attempted towards the range of selenium analogues of ispsoralen proved unsuccessful in synthesising these types of compounds. However, it is still judged that this is a highly feasible area of research and therefore should not be discontinued without further endeavours. The following argument provides a feasible explanation for the lack of success in this area, and also attempts to put forward ideas towards the successful synthesis of selenium analogues of isopsoralen. The novelty of this work demands that this area of research be continued.

A possible reason for the failure of all attempts to substitute the bromine atom with a selenyl group can be found when looking at the systems used in this project. The selenyl group is coming in as a nucleophile. However, the benzene ring of, for example, **200a** is already electron rich, which would hinder any nucleophilic substitution from taking place. Added to this is the fact the aromatic ring contains two groups, a phenol and an allyl chain, which are both,

themselves, electron donating. This would subsequently make the aromatic ring even more electron rich, further diminishing the chance of any nucleophilic substitution taking place.

In order to induce nucleophilic substitution, we therefore need to pull electron density out of the aromatic ring using suitable groups. One such compound is 4,6-dibromoisophthalaldehyde (92), which has been used successfully by Jacobs et al[54,56] when substituting bromine with selenium. This compound, as was shown in the introduction, has been utilised as a starting material in the synthesis of a number of selenium analogues of psoralen (see Schemes 26 to 30, pages 30 to 34). The difference in this compound is, of course, the presence of two aldehyde substituents. These aldehydes are electron withdrawing, and would therefore pull electron density out of the phenyl ring. This has the effect of making the phenyl ring less electron rich, and thereby facilitating the nucleophilic substitution process.

Future work on this project would therefore make use of this or similar compounds as a means to the preparation of selenium-substituted isopsoralen analogues. The proposed approach towards this synthesis is outlined in Schemes 66 and 67. Starting with 4,6-dibromoisophthalaldehyde (92), and converting one of the bromine atoms into a hydroxyl group would afford the phenol derivative (97). This phenol could then be subjected to the usual treatment carried out in this project. Allylation of the hydroxyl group would afford the allyl aryl ether (208), which at this stage could be reaction with methaneselenol to give the substituted derivative 4-(allyloxy)-6-(methylselenyl) isophthalaldehyde (209). A recently discovered report by Clive and Postema[103] describe conditions whereby ozonolysis can be performed on olefinic phenyl selenides with preservation of the selenium unit, thus substitution with selenium before attempting ozonolysis is proposed. Claisen rearrangement of 209 would then afford the rearranged product (210). Another option would be to do the Claisen rearrangement first before attempting the nucleophilic substitution.
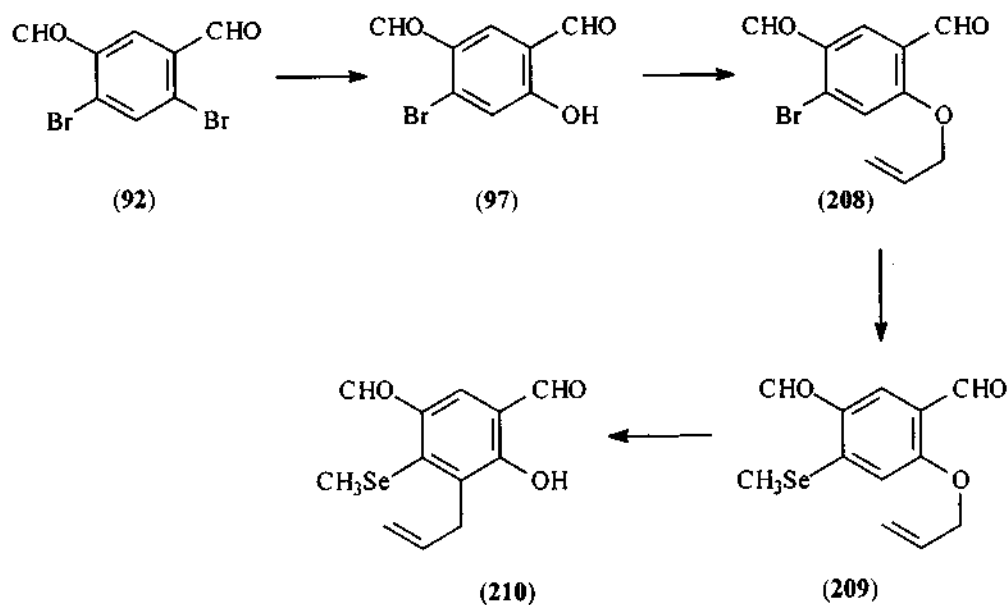
Scheme 66

Once the phenol (**210**) is obtained, the synthesis of the selenium substituted furan ring can be attempted (**Scheme 67**). First the hydroxyl group needs to be protect as before, by reaction with *tert*-butyl dimethylsilylchloride to afford the protect phenol (**211**). This, after ozonolysis and reduction to the aldehyde (**212**), could then be cyclised in the presence of polyphosphoric acid silyl ether (PPSE) to give the selenofuran (**213**). Synthesis of the pyrone ring using known procedures would then afford the seleno-isopsoralen 2-oxo-2*H*-seleno[2,3-*h*]chromene-6-carbaldehyde (**214**).
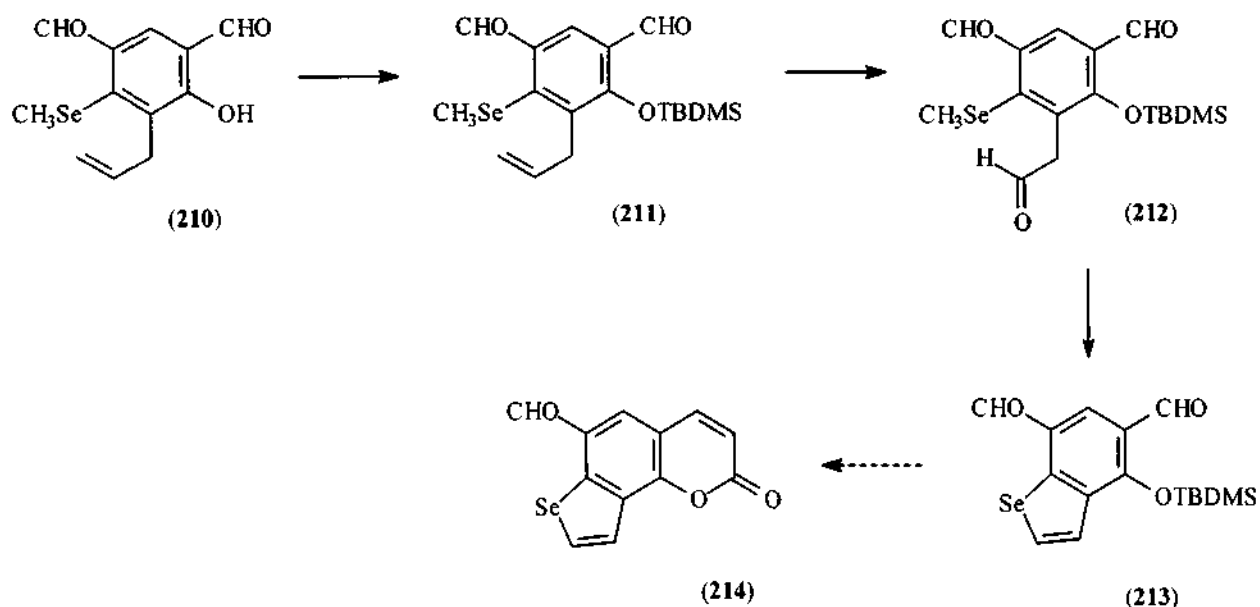
Scheme 67

If successful, this procedure could hopefully be further modified in an effort to lead to a diverse range of other seleno-isopsoralen derivatives. Some possibilities include modification of the aldehyde functionality of **214**, and extension of this approach to include selenium or sulfur in place of the oxygen atom in the pyrone ring.

2.4 CONCLUSION

The initial aims of this project, to develop a synthetic approach towards a range of new isopsoralen derivatives, and to extend this approach to include sulfur in place of oxygen in the benzofuran ring, have all been achieved.

The synthesis of a range of 8-alkyl substituted 8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-ones in good yields was achieved, utilising the reductive ozonolysis of *o*-allyl hydroxycoumarins as a key synthetic step. A computational examination of the coumarin systems studied have led to a better understanding for the regioselectivity observed for the Claisen rearrangement. Extension of this approach to include sulfur led to the synthesis of the thio-isopsoralen derivative, 8-methoxy-8,9-dihydro-2*H*-thieno[2,3-*h*]chromen-2-one, *via* conversion of the hydroxyl group into a thiol using the known reagent dimethylthiocarbamoyl chloride. An intriguing ^{1}H NMR spectroscopic study was also performed on the *N,N*-dimethylcarbamothioate moiety of the protected thiol.

A further aim of this project was to develop a synthetic route which would provide access towards isopsoralen derivatives containing selenium in the benzofuran ring system. Initial investigations in this regard have indicated great potential for this type of approach, and have laid the foundations for the future synthesis of seleno-isopsoralen derivatives.

This project has thus identified various possibilities for future research; these include the following:-

(i) use of more highly substituted allyl groups as a means of accessing further substituted isopsoralen derivatives.

(ii) a more complete computational study towards understanding the regioselectivity of the Claisen reaction, using the variously substituted allyl groups.

(iii) work towards the synthesis of additional substituted thio-isopsoralen analogues.

(iv) a more complete NMR spectroscopy study of the *N,N*-dimethylcarbamothioate groups, with or without heteroatoms adjacent to the carbonyl or thiocarbonyl group.

(v) further work towards developing a synthetic route towards a range of seleno-
isopsoralen derivatives.

3. EXPERIMENTAL

3.1 GENERAL

All ^1H, ^{13}C and 2D NMR spectra were run on a Varian Unity-Inova 500 MHz spectrometer, and were referenced using the solvent signals. Spectra recorded in $CDCl_3$ were calibrated using the solvent signal at 7.26 ppm for ^1H and 77.0 ppm for ^{13}C, while ^1H and ^{13}C spectra run in CD_3OD were calibrated using the solvent signals. All coupling constants (J) are given in Hz, and the atom numbering used in quoting the NMR data follows IUPAC nomenclature.[104,105]Low resolution mass spectra were recorded on a Hewlett Packard 5890 using a quadrupole mass analyzer, while high resolution mass spectra were obtained on a double-focusing Kratos MS 80RF mass spectrometer (Cape Technikon Mass Spectrometry Unit). Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

All solvents used were distilled and dried prior to use.[106] When reactions were carried out using air- or moisture-sensitive reagents, such as NaH, triflic anhydride, methyllithium, phosphorus reagents and ethyl malonyl chloride, the glassware was flame dried under dry nitrogen (previously flushed through a 3Å molecular sieve drying column) before use. All other reactions were carried out using semi-dry conditions i.e. using oven-dried glassware under an inert (dry nitrogen) atmosphere. Anhydrous solvents were obtained as follows:

(i) THF (tetrahydrofuran) was dried by boiling under reflux over sodium wire, in the presence of benzophenone, then distilled.

(ii) Xylene and triethylamine (Et_3N) were boiled under reflux over CaH_2, distilled and collected over 3Å molecular sieves.

(iii) Methanol and ethanol were boiled under reflux over calcium carbonate, then distilled.

(iv) Acetone was dried by storing over 4Å molecular sieve overnight.

(v) Dimethylformamide (DMF) was dried by boiling under reflux over 4Å molecular sieve,[107] then distilled and collected over 4Å molecular sieve.

Flash chromatography was performed using either column chromatography with Merck silica gel 60 (230-400 mesh; particle size 0.040-0.063 nm) or by radial chromatography on a chromatotron using Merck silica gel 60 PF_{264} containing gypsum for Preparative Layer Chromatography. Thin Layer Chromatography (TLC) was performed on Merck Aluminium Sheets containing Silica Gel 60 F_{254} (layer thickness, 0.2 mm), with visualization of the compounds by inspection under UV light (254/365 nm) and/or by exposure to iodine vapour.

Ozone required for the ozonolysis reactions was generated using a Fischer Ozone Generator (Model 500), with a current setting of *ca.* 200mA and a flow rate of *ca.* 1 ml/min.

3.2 PREPARATIVE PROCEDURES

3.2.1 Synthetic work towards oxygen analogues

Preparation of 7-(allyloxy)-2H-chromen-2-one (141)

3-bromo-1-propene (5.71 ml, 66 mmol) was added dropwise under dry nitrogen, using a pressure equalising dropping funnel, to a stirred mixture of 7-hydroxy-2H-chromen-2-one (140) (5.0 g, 30 mmol) and anhydrous K_2CO_3 (5.8 g, 41 mmol) in dry acetone (*ca.* 150 ml).The resulting mixture was then boiled under reflux for 5 hours, following which it was allowed to cool, and the K_2CO_3 filtered off using a sintered glass funnel. The filtrate and washings were removed *in vacuo* and the residue recrystallised from methanol to afford, as pale yellow crystals, 7-(allyloxy)-2H-chromen-2-one (141) (5.62 g, 92%), m.p. 78-79°C (from methanol) (lit.,[24] 93-93.5°C); v_{max}(KBr)/cm^{-1} 1614, 1723 and 3082; δ_H(500 MHz; CDCl$_3$) 4.60 (2H, d, $J_{1',2'}$ 5.3, 1'-CH$_2$), 5.34 (1H, dd, J_{cis} 10.4 and J_{gem} 1.2, C=CH) and 5.44 (1H, dd, J_{trans} 17.2 and J_{gem} 1.2, C=CH), 6.05 (1H, ddt, J_{trans} 17.3, J_{cis} 10.5 and $J_{2',1'}$ 5.3, 2'-H), 6.26 (1H, d, $J_{3,4}$ 9.5, 3-H), 6.83 (1H, d, $J_{8,6}$ 2.3, 8-H), 6.87 (1H, dd, $J_{6,8}$ 2.3 and $J_{6,5}$ 8.5, 6-H), 7.38(1H, d, $J_{5,6}$ 8.6, 5-H) and 7.64 (1H, d, $J_{4,3}$ 9.3, 4-H); δ_C(125 MHz; CDCl$_3$) 69.9 (C-1'), 102.4 (C-8), 113.2 (C-4a), 113.80 (C-3), 113.86 (C-6), 119.2 (C-3'), 129.4 (C-5), 132.8 (C-2'), 114.0 (C-4), 156.5 (C-8a), 161.8 (C-7) and 162.4 (C-2); *m/z* 202 (M$^+$, 100%) and 187 (71).

Preparation of 8-allyl-7-hydroxy-2H-chromen-2-one (142)

7-(allyloxy)-2H-chromen-2-one (141) (5.0 g, 24.7 mmol) was dissolved in N,N-diethylaniline (*ca.* 50 ml) in a two-necked flask attached to a nitrogen line and a condenser, and boiled under reflux at *ca.* 220 °C for 3 hours. The reaction mixture was then cooled, during which time precipitation of some of the product occurred, hexane (40 ml) was then added in order to precipitate out the remaining product. The precipitate was filtered, washed with hexane, dried by vacuum filtration, and recrystallised from ethyl acetate to afford, as cream crystals, 8-allyl-7-hydroxy-2H-chromen-2-one (142) (4.2 g, 84%), m.p. 151-153°C (from ethyl acetate) (lit.,[24] 165-166°C); v_{max}(KBr)/cm^{-1} 1600, 1699 and 3332; δ_H(500 MHz; CDCl$_3$) 2.81 (1H, s, OH), 3.61 (2H, d, $J_{1',2'}$ 6.2, 1'-CH$_2$), 5.0 (1H, dd, J_{cis} 10.1 and J_{gem} 1.8, C=CH) and 5.12 (1H, dd, J_{trans} 17.2 and J_{gem} 1.8, C=CH), 6.01 (1H, ddt, J_{trans} 17.2, J_{cis} 10.1 and $J_{2',1'}$ 6.2, 2'-H), 6.20 (1H, d, $J_{3,4}$ 9.6, 3-H), 6.80

(1H, d, $J_{6,5}$ 8.5, 6-H), 7.21 (1H, d, $J_{5,6}$ 8.5, 5-H) and 7.64 (1H, d, $J_{4,3}$ 9.4, 4-H); δ_C(125 MHz; CDCl$_3$) 27.3 (C-1'), 112.2 (C-3), 112.7 (C-4a), 113.2 (C-6), 114.7 (C-8), 115.9 (C-3'), 127.2 (C-5), 135.69 (C-2'), 145.1 (C-4), 154.2 (C-8a), 159.5 (C-7) and 162.9 (C-2); m/z 202 (M$^+$, 100%), 187 (75), 173 (28) and 159 (26).

Preparation of 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (150a)

8-allyl-7-hydroxy-2*H*-chromen-2-one (142) (2.0 g, 9.9 mmol) was dissolved in dry THF (60 ml) in a three-necked flask fitted with a reflux condenser and attached to an ozone generator. Two traps containing an acidified 1.1 M KI solution (110 ml acidified with 10 ml glacial acetic acid) were connected to the outlet of the three-necked flask in order to mop up any unreacted ozone. The flask was cooled to -78°C using a solid CO$_2$/acetone bath. Ozone was then bubbled through the stirred mixture for 100 minutes at a rate of *ca.*1ml/min, after which analysis by TLC showed the disappearance of starting material. Dimethyl sulfide (0.9 ml, 12.4 mmol) was added, the reaction mixture warmed to -10°C (salt/ice bath), and stirred for a further 3 hours, allowing the mixture to slowly warm to room temperature. Methanol (30 ml) was then added, and the mixture was boiled under reflux for 3 hours and left stirring overnight under nitrogen. The solvent was then removed *in vacuo* to leave a dark orange oil, from which the product crystallized out as orange crystals. Recrystallisation from methanol afforded *8-methoxy-8,9-dihydro-2H-furo[2,3-h]chromen-2-one* (150a) (1.43 g, 66%), m.p. 144-145°C (from methanol) (Found: M$^+$, 218.05846. C$_{12}$H$_{10}$O$_4$ requires *M*, 218.05791); v_{max}(KBr)/cm^{-1} 1615, 1724 and 3442; δ_H(500 MHz; CDCl$_3$) 3.24 (1H, dd, J_{gem} 17.1 and $J_{9a,8}$ 2.3, 9-CH$_a$) and 3.45 (1H, dd, J_{gem} 17.1 and $J_{9b,8}$ 6.6, 9-CH$_b$), 3.56 (3H, s, CH$_3$), 5.80 (1H, dd, $J_{8,9a}$ 2.3 and $J_{8,9b}$ 6.6, 8-H), 6.22 (1H, d, $J_{3,4}$ 9.6, 3-H), 6.81 (1H, d, $J_{6,5}$ 8.2, 6-H), 7.30 (1H, d, $J_{5,6}$ 8.2, 5-H) and 7.64 (1H, d, $J_{4,3}$ 9.5, 4-H); δ_C(125 MHz; CDCl$_3$) 34.3 (9-CH$_2$), 56.9 (1'-CH$_3$), 107.9 (C-6), 109.7 (C-8), 113.08 (C-9a), 113.2 (C-3), 114.05 (C-4a), 129.4 (C-5), 144.9 (C-4), 151.9 (C-9b), 161.7 (C-6a) and 162.9 (C-2); m/z 218 (M$^+$, 100%), 187 (60), 175 (43) and 147 (22).

Preparation of 8-ethoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (150b)

Following the procedure used for the synthesis of 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*] chromen-2-one (150a), 8-allyl-7-hydroxy-2*H*-chromen-2-one (142) (0.80 g, 3.96 mmol) was dissolved in dry THF (40 ml) in a three-necked flask, cooled to -78°C, and ozone was bubbled

through the system for *ca.* 80 minutes. Dimethyl sulfide (0.4 ml, 5.5 mmol) was then added, and following workup of the reaction afforded *8-ethoxy-8,9-dihydro-2H-furo[2,3-h]chromen-2-one* (**150b**), as pale yellow crystals, (0.62 g, 67%), m.p. 107-109°C (from ethanol) (Found: M^+ 232.07441, $C_{13}H_{12}O_4$ requires M, 232.07356); v_{max}(KBr)/cm^{-1} 1613, 1726 and 3320; δ_H(500 MHz; CDCl$_3$) 1.26 (3H, t, $J_{2',1'}$ 7.1, 2'-CH$_3$), 3.23 (1H, dd, J_{gem} 16.9 and $J_{9a,8}$ 2.5, 9-CH$_a$) and 3.45 (1H, dd, J_{gem} 16.9 and $J_{9b,8}$ 6.7, 9-CH$_b$), 3.69 and 3.95 (2H, 2×dq, J_{gem} 9.4 and $J_{1',2'}$ 7.1, 1'-CH$_2$), 5.91 (1H, dd, $J_{8,9a}$ 2.5 and $J_{8,9b}$ 6.6, 8-H), 6.21 (1H, d, $J_{3,4}$ 9.4, 3-H), 6.79 (1H, d, $J_{6,5}$ 8.2, 6-H), 7.29 (1H, d, $J_{5,6}$ 8.2, 5-H) and 7.64 (1H, d, $J_{4,3}$ 9.4, 4-H); δ_C(125 MHz; CDCl$_3$) 15.7 (2'-CH$_3$), 34.4 (9-CH$_2$), 65.5 (1'-CH$_2$), 107.9 (C-6), 108.7 (C-8), 113.08 (C-3), 113.1 (C-9a), 113.9 (C-4a), 129.4 (C-5), 144.7 (C-4),151.9 (C-9b), 161.7 (C-6a) and 162.8 (C-2); *m/z* 232 (M^+, 79%), 175 (100), 148 (25) and 187 (20).

Preparation of 8-isopropoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (150c)

Following the procedure used for the synthesis of 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*] chromen-2-one (**150a**), 8-allyl-7-hydroxy-2*H*-chromen-2-one (**142**) (0.80 g, 3.96 mmol) was dissolved in dry THF (40 ml) in a three-necked flask, cooled to -78°C, and ozone was bubbled through the system for *ca.* 80 minutes. Dimethyl sulfide (0.4 ml, 5.5 mmol) was then added, and following workup of the reaction afforded *8-isopropoxy-8,9-dihydro-2H-furo[2,3-h]chromen-2-one* (**150c**), as an orange oil from which the product crystallised out as pale yellow crystals, (0.73 g, 75%), m.p. 117-119°C (from isopropanol) (Found: M^+ 246.08952, $C_{14}H_{14}O_4$ requires M, 246.08921); v_{max}(KBr)/cm^{-1} 1625, 1715 and 3419; δ_H(500 MHz; CDCl$_3$) 1.20-1.25 [6H, 2×d, J 6.1, CH(CH_3)$_2$], 3.23 (1H, dd, J_{gem} 16.9 and $J_{9a,8}$ 2.4, 9-CH$_a$) and 3.45 (1H, dd, J_{gem} 16.9 and $J_{9b,8}$ 6.9, 9-CH$_b$), 4.08 (1H, heptet, J 6.2, 1'-H), 6.01 (1H, dd, $J_{8,9a}$ 2.5 and $J_{8,9b}$ 6.9, 8-H), 6.23 (1H, d, $J_{3,4}$ 9.4, 3-H), 6.79 (1H, d, $J_{6,5}$ 8.2, 6-H), 7.29 (1H, d, $J_{5,6}$ 8.1, 5-H) and 7.64 (1H, d, $J_{4,3}$ 9.4, 4-H); δ_C(125 MHz; CDCl$_3$) 22.0 and 23.6 [CH(CH$_3$)$_2$], 34.2 (9-CH$_2$), 71.8 (C-1'), 106.2 (C-8), 107.4 (C-6), 107.6 (C-4a), 112.5 (C-3), 112.8 (C-9a), 128.9 (C-5), 144.3 (C-4), 151.6 (C-9b), 160.8 (C-6a) and 162.4 (C-2); *m/z* 246 (M^+, 53%), 204 (44) and 175 (100).

Preparation of 8-(*tert*-butoxy)-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (150d)

Following the procedure used for the synthesis of 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*] chromen-2-one (**150a**), 8-allyl-7-hydroxy-2*H*-chromen-2-one (**142**) (0.80 g, 3.96 mmol) was

dissolved in dry THF (40 ml) in a three-necked flask, cooled to -78°C, and ozone was bubbled through the system for *ca.* 80 minutes. Dimethyl sulfide (0.4 ml, 5.5 mmol) was then added, and following workup of the reaction afforded *8-(tert-butoxy)-8,9-dihydro-2H-furo[2,3-h]chromen-2-one* (**150d**), as an orange oil from which the product crystallised out as yellowish crystals, (0.74 g, 71%), m.p. 119-122°C (from *tert*-butanol) (Found: M^+-$C(CH_3)_3$, 204.04375, $C_{15}H_{16}O_4$ requires *M*, 260.104859); v_{max}(KBr)/cm^{-1} 1621, 1729 and 3385; δ_H(500 MHz; CDCl$_3$) 1.25 [9H, s, C(CH$_3$)$_3$], 3.24 (1H, dd, J_{gem} 17.0 and $J_{9a,8}$ 2.3, 9-CH$_a$) and 3.43 (1H, dd, J_{gem} 17.1 and $J_{9b,8}$ 6.6, 9-CH$_b$), 5.79 (1H, dd, $J_{8,9a}$ 2.3 and $J_{8,9b}$ 6.6, 8-H), 6.21 (1H, d, $J_{3,4}$ 9.6, 3-H), 6.80 (1H, d, $J_{6,5}$ 8.2, 6-H), 7.29 (1H, d, $J_{5,6}$ 8.2, 5-H) and 7.64 (1H, d, $J_{4,3}$ 9.4, 4-H); δ_C(125 MHz; CDCl$_3$) 29.9 [C(CH$_3$)$_3$], 33.8 (9-CH$_2$), 102.7 (C-1'), 107.5 (C-6), 109.3 (C-8), 112.7 (C-3), 113.6 (C-4a), 125.1 (C-9a), 129.0 (C-5), 144.3 (C-4), 151.5 (C-9b), 161.3 (C-6a) and 162.3 (C-2); *m/z* 260 (M$^+$, 16%), 176 (100), 204 (67) and 148 (28).

Preparation of 8-hydroxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (149)

8-allyl-7-hydroxy-2*H*-chromen-2-one (**142**) (1.0 g, 4.95 mmol) was dissolved in dry THF (40 ml) in a three-necked flask which was connected to an ozone generator. Two KI traps (acidified 1.1 M solution) were also connected to the three-necked flask in order to neutralize any unreacted ozone. The reaction mixture was then cooled to -78°C, and ozone was bubbled through the system for *ca.* 80 minutes. Dimethyl sulfide (0.45 ml, 6.2 mmol) was then added, the reaction mixture warmed to -10°C (salt/ice bath) and stirred overnight, allowing the mixture to warm to room temperature. The solvent was then removed *in vacuo* and the resulting residue was passed through a column (50:50 ethyl acetate/hexane as a running solvent) to afford, as white crystals, 8-hydroxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**149**) (0.52 g, 51%), m.p. 137-139 °C (from ethyl acetate) (Found: M$^+$, 204.0426, $C_{11}H_8O_4$ requires *M*, 204.04226); v_{max}(KBr)/cm^{-1} 1614, 1689 and 3302; δ_H(500 MHz; CD$_3$OD)[1] 3.19 (2H, d, $J_{9,8}$ 5.3, 9-CH$_2$), 4.89 (1H, t, $J_{8,9}$ 5.2, 8-H), 6.21 (1H, d, $J_{3,4}$ 9.4, 3-H), 6.88 (1H, d, $J_{6,5}$ 8.5, 6-H), 7.31 (1H, d, $J_{5,6}$ 8.5, 5-H) and 7.78 (1H, d, $J_{4,3}$ 9.4, 4-H); δ_C(125 MHz; CD$_3$OD) 30.9 (9-CH$_2$), 98.2 (C-8), 111.5 (C-3), 111.9 (C-4a), 112.7 (C-9a), 113.8 (C-6), 127.7 (C-5), 145.9 (C-4), 154.4 (C-9b), 160.5 (C-6a) and 163.5 (C-2); *m/z* 204 (M$^+$, 34%), 174 (100), 146 (75) and 118 (29).

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[1] OH signal suppressed due to ^{2}D exchange.

Preparation of 2*H*-furo[2,3-*h*]chromen-2-one (156)

8-hydroxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (149) (0.03 g, 0.15 mmol) was placed in a two-necked flask containing THF (20 ml) and connected to a reflux condenser and a nitrogen line. *p*-Toluenesulfonic acid (0.01 g) and some 3Å molecular sieve were added to the flask and the reaction mixture was boiled under reflux for 2 hours. The mixture was then passed through a plug of silica gel to remove the catalyst, and the solvent removed *in vacuo* to afford, as colourless crystals, 2*H*-furo[2,3-*h*]chromen-2-one (156) (0.028 g, 100%), m.p. 132-133 °C (from methanol) (lit.,[33] 137-137.5°C); v_{max}(KBr)/cm^{-1} 1620, 1709 and 3385; δ_H(500 MHz; CD$_3$OD) 6.35 (1H, d, $J_{3,4}$ 9.4, 3-H), 6.59 (1H, d, $J_{9,8}$ 2.2, 9-H), 6.98 (1H, d, $J_{8,9}$ 2.1, 8-H), 7.21 (1H, d, $J_{5,6}$ 8.3, 5-H), 7.39 (1H, d, $J_{6,5}$ 8.3, 6-H) and 8.06 (1H, d, $J_{4,3}$ 9.5, 4-H); δ_C(125 MHz; CD$_3$OD) 98.4 (C-9), 106.8 (C-6), 113.2 (C-3), 114.1 (C-4a), 117.6 (C-9a), 125.2 (C-5), 146.1 (C-4), 146.2 (C-8), 147.9 (C-9b), 156.8 (C-6a) and 161.2 (C-2); *m/z* 186 (M$^+$, 100%), 158 (94) and 102 (28).

Preparation of 7-[(2-methyl-2-propenyl)oxy]-2*H*-chromen-2-one (157)

3-bromo-2-methyl-1-propene[§] (5.0 ml, 49.6 mmol) was added dropwise under nitrogen to a stirred mixture of 7-hydroxy-2*H*-chromen-2-one (140) (4.02 g, 24.3 mmol) and K$_2$CO$_3$ (4.66 g, 32.9 mmol) in dry acetone (*ca.*130 ml). The mixture was then boiled under reflux for 5 hours, allowed to cool, and the K$_2$CO$_3$ filtered and washed with fresh acetone. The solvent was then removed *in vacuo* and the residue recrystallised from methanol to afford 7-[(2-methyl-2-propenyl)oxy]-2*H*-chromen-2-one (157), as cream crystals (4.55 g, 86%), m.p. 59-60°C (from methanol); v_{max}(KBr)/cm^{-1} 1609, 1734 and 3454; δ_H(500 MHz; CDCl$_3$) 1.82 (3H, s, CH$_3$), 4.49 (2H, s, 1'-CH$_2$), 5.02 and 5.09 (2H, 2×s, 3'-CH$_2$), 6.24 (1H, d, $J_{3,4}$ 9.6, 3-H), 6.81 (1H, d, $J_{8,6}$ 2.4, 8-H), 6.86 (1H, d, $J_{6,5}$ 8.7 and $J_{6,8}$ 2.3, 6-H), 7.36 (1H, d, $J_{5,6}$ 8.7, 5-H) and 7.63 (1H, d, $J_{4,3}$ 9.4, 4-H); δ_C(125 MHz; CDCl$_3$) 19.9 (CH$_3$), 72.9 (1'-CH$_2$), 102.4 (C-8), 113.3 (C-4a), 113.7 (C-6), 113.8 (C-3), 114.2 (3'-CH$_2$), 129.4 (C-5), 140.4 (C-2'), 144.1 (C-4), 156.5 (C-8a), 161.9 (C-7) and 162.6 (C-2); *m/z* 216 (M$^+$, 100%), 201 (61) and 134 (37).

[§]3-chloro-2-methyl-1-propene (3.60 g, 40 mmol) was also used, affording the required product 7-[(2-methyl-2-propenyl)oxy]-2*H*-chromen-2-one (157) (4.21 g, 80%).

Preparation of 7-hydroxy-8-(2-methyl-2-propenyl)-2*H*-chromen-2-one (158)

7-[(2-methyl-2-propenyl)oxy]-2*H*-chromen-2-one (157) (3.80 g, 17.6 mmol) was dissolved in *N,N*-diethylaniline (40 ml) in a one-necked flask fitted with a reflux condenser and nitrogen line, and boiled under reflux for 3 hours. The reaction mixture was then left to cool and hexane (*ca.*40 ml) was added to precipitate out the product, which was then recrystallized from ethyl acetate to afford 7-hydroxy-8-(2-methyl-2-propenyl)-2*H*-chromen-2-one (158), as cream crystals (2.95 g, 77%), m.p. 123-125°C (from ethyl acetate); v_{max}(KBr)/cm^{-1} 1603, 1684 and 3442; δ_H(500 MHz; CDCl$_3$) 1.77 (3H, s, CH$_3$), 3.64 (2H, s, 1'-CH$_2$), 4.81 and 4.90 (2H, 2×s, 3'-CH$_2$), 6.25 (1H, d, $J_{3,4}$ 9.4, 3-H), 6.56 (1H, br. s, OH), 8.86 (1H, d, $J_{6,5}$ 8.5, 6-H), 7.27 (1H, d, $J_{5,6}$ 8.5, 5-H) and 7.66 (1H, d, $J_{4,3}$ 9.6, 4-H); δ_C(125 MHz; CDCl$_3$) 22.5 (CH$_3$), 31.4 (1'-CH$_2$), 112.5 (3'-CH$_2$), 112.6 (C-3), 112.8 (C-4a), 113.2 (C-8), 113.5 (C-6), 127.4 (C-5), 143.6 (C-2'), 144.6 (C-4), 153.7 (C-8a), 159.1 (C-7) and 162.1 (C-2); *m/z* 216 (M$^+$, 87%), 201 (100) and 173 (48).

Preparation of 7-hydroxy-8-(2-oxopropyl)-2*H*-chromen-2-one (159)

7-hydroxy-8-(2-methyl-2-propenyl)-2*H*-chromen-2-one (158) (0.8 g, 3.7 mmol) was dissolved in methanol (40 ml) in a three-necked flask, cooled to -78°C (solid CO$_2$/acetone) and ozone was passed through the system for *ca.* 80 minutes. Dimethyl sulfide (0.33 ml, 4.57 mmol) was then added and the reaction mixture stirred overnight under nitrogen while allowing to gradually warm to room temperature. The solvent was removed *in vacuo* to leave an orange oil from which the final product crystallised out. Recrystallisation from methanol afforded 7-hydroxy-8-(2-oxopropyl)-2*H*-chromen-2-one (159), as pale orange crystals (0.56 g, 68%), m.p. 188-190°C (from methanol) (Found: M$^+$, 218.05768, C$_{12}$H$_{10}$O$_4$ requires *M*, 218.05791); v_{max}(KBr)/cm^{-1} 1614, 1729 and 3317; δ_H(500 MHz; CD$_3$OD)$^\#$ 2.29 (3H, s, 3'-CH$_3$), 3.99 (2H, s, 1'-CH$_2$), 6.19 (1H, d, $J_{3,4}$ 9.4, 3-H), 6.85 (1H, d, $J_{6,5}$ 8.5, 6-H), 7.33 (1H, d, $J_{5,6}$ 8.5, 5-H) and 7.75 (1H, d, $J_{4,3}$ 9.4, 4-H); δ_C(125 MHz; CD$_3$OD) 29.4 (3'-CH$_3$), 37.8 (2'-CH$_2$), 109.5 (C-8), 111.3 (C-3), 112 (C-4a), 112.6 (C-6), 127.9 (C-5), 145.2 (C-4), 153.8 (C-8a), 159.9 (C-2), 162.7 (C-7) and 207.5 (C-2'); *m/z* 218 (M$^+$, 100%) and 187 (52).

$^\#$OH signal suppressed due to ^{2}D exchange.

Preparation of 8-methyl-2H-furo[2,3-h]chromen-2-one (162)

A mixture of 7-hydroxy-8-(2-oxopropyl)-2H-chromen-2-one (159) (0.25 g, 1.25 mmol), and p-toluenesulfonic acid (0.05 g) in dry toluene (20 ml) was placed in a two-necked flask fitted with a Dean and Stark apparatus containing 4Å molecular sieve, and connected to a nitrogen line. The mixture was then boiled under reflux for 4 hours, cooled, and then passed through a plug of silica gel. Removal of the solvent *in vacuo* afforded, as white crystals, 8-methyl-2H-furo[2,3-h] chromen-2-one (162) (0.24 g, 98%), m.p. 124-126°C (from toluene) (lit.,[24] 153-154°C); ν_{max}(KBr)/cm^{-1} 1614, 1706 and 3317; δ_H(500 MHz; CD$_3$OD) 2.38 (3H, s, 1'-CH$_3$), 6.39 (1H, d, $J_{3,4}$ 9.1, 3-H), 6.78 (1H, s, 9-H), 7.40 (1H, d, $J_{6,5}$ 8.5, 6-H), 7.43 (1H, d, $J_{5,6}$ 8.3, 5-H) and 8.04 (1H, d, $J_{4,3}$ 9.2, 4-H); δ_C(125 MHz; CD$_3$OD) 20.1 (1'-CH$_3$), 99.2 (C-9), 108.2 (C-6), 113.1 (C-3), 113.8 (C-4a), 118.1 (C-9a), 123.2 (C-5), 145.8 (C-4), 147.4 (C-9b), 157.4 (C-8), 157.5 (C-6a) and 161.9 (C-2); m/z 200 (M$^+$, 100%) and 171 (73).

Preparation of 8-methoxy-8-methyl-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (163)

7-hydroxy-8-(2-oxopropyl)-2H-chromen-2-one (159) (0.25 g, 1.25 mmol), and p-toluenesulfonic acid (0.02 g) were dissolved in methanol in a two-necked flask fitted with a condenser and containing 4Å molecular sieve. The mixture was boiled under reflux for 5 hours under an atmosphere of dry nitrogen, the mixture was then passed through a plug of silica gel to remove the catalyst, and the solvent *in vacuo* to afford, as white crystals, 8-methoxy-8-methyl-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (163) (0.29 g, 100%), m.p. 121-122°C (from methanol) (Found: M$^+$ 232.07352, C$_{13}$H$_{12}$O$_4$ requires M, 232.073562); ν_{max}(KBr)/cm^{-1} 1615, 1728 and 2941; δ_H(500 MHz; CDCl$_3$) 1.73 (3H, s, CH$_3$), 3.20 and 3.42 (2H, 2×d, J_{gem} 17.1, 9-CH$_2$), 3.32 (3H, s, OCH$_3$), 6.20 (1H, d, $J_{3,4}$ 9.6, 3-H), 6.75 (1H, d, $J_{6,5}$ 8.2, 6-H), 7.28 (1H, d, $J_{5,6}$ 8.2, 5-H) and 7.63 (1H, d, $J_{4,3}$ 9.6, 4-H); δ_C(125 MHz; CDCl$_3$) 24.2 (CH$_3$), 37.1 (9-CH$_2$), 50.2 (OCH$_3$), 106.8 (C-6), 112.3 (C-3), 112.9 (C-8), 113.0 (C-4a), 114.2 (C-9a), 128.8 (C-5), 144.1 (C-4), 151.1 (C-9b), 160.9 (C-6a) and 162.1 (C-2); m/z 232 (M$^+$, 100%), 201 (68), 171 (52) and 115 (24).

Preparation of methyl 2-(hydroxymethyl)acrylate (166) and dimethyl 4-oxahept-1,6-diene-2,6-dicarboxylate (167)[85]

Methyl acrylate (18.0 ml, 0.20 mol), paraformaldehyde (9.04 g, 0.30 mol) and DABCO (1.12 g, 10 mmol) were stirred at 95°C for 4 hours in an autoclave to afford, on cooling, a mixture of the

product and its ether (23 g). This was used in the subsequent halogenation step without further purification, however separation of the two components could be achieved by column chromatography (30:70 ethyl acetate/hexane). Chromatography on a 2.0 g sample afforded first the ether, dimethyl 4-oxahept-1,6-diene-2,6-dicarboxylate (167) as a colourless oil (1.2 g, 56%); v_{max}(thin film)/cm^{-1} 1638, 1722 and 2953; δ_H(500 MHz; CDCl$_3$) 3.72 (6H, s, 2×OCH$_3$), 4.20 and 4.26 (4H, 2×s, 2×CH$_2$), 5.85 and 6.26 (4H, 2×m, 2×C=CH_2); δ_C(125 MHz; CDCl$_3$) 52.4 (2×OCH$_3$), 66.4 and 69.4 (2×CH$_2$), 126.5 and 126.9 (2×C=CH$_2$), 137.4 (2×C=CH$_2$) and 166.7 (2×C=O); m/z 214 (M$^+$, <1%), 115 (100), 83 (82) and 99 (30). This was followed by methyl 2-(hydroxymethyl)acrylate (166), also a colourless oil, (0.51 g, 44%); v_{max}(thin film)/cm^{-1} 1636, 1718 and 3422; δ_H(500 MHz; CDCl$_3$) 3.76 (3H, s, OCH_3), 4.31 (2H, m, CH_2), 4.81 (1H, s, OH), 5.82 and 6.28 (2H, 2×s, C=CH_2); δ_C(125 MHz; CDCl$_3$) 52.5 (OCH$_3$), 62.9 (CH$_2$), 126.4 (C=CH$_2$), 139.9 (C=CH$_2$) and 167.4 (C=O); m/z 116 (M$^+$, 6%), 87 (100), 84 (74) and 55 (58).

Attempted preparation of methyl 2-(bromomethyl)acrylate

A solution of methyl 2-(hydroxymethyl)acrylate (166) (10 g, 86 mmol) in conc. HBr (47% aq solution, 24 ml) was stirred in a two-necked round bottomed flask at 0°C. Dilute H$_2$SO$_4$ (8% solution, 22 ml) was added dropwise to this solution, and the reaction mixture was then stirred at room temperature for a further 16 hours. The reaction mixture was then extracted with diethyl ether (80 ml), washed with saturated aqueous NaHCO$_3$ (3×50 ml) and with brine (50 ml). The organic phase was then dried (anhydrous MgSO$_4$) and the solvent removed under vacuum to afford a colourless oil, which, through GC-MS and NMR analysis was shown to consist only of starting material.

Preparation of methyl 2-(chloromethyl)acrylate (168)

A mixture of methyl 2-(hydroxymethyl)acrylate (166) (5.0 g, 43 mmol), DMF (0.14 ml) and dry benzene (2 ml) were stirred at 0°C in three-necked flask fitted with a thermometer, pressure-equalizing addition funnel and a reflux condenser attached to an aqueous NaOH scrubber. Thionyl chloride (5.75 ml, 80 mmol) was added dropwise under dry nitrogen, the resulting mixture was then heated at 60°C for 5 hours. The reaction was then quenched via the slow addition of crushed ice and the mixture obtained extracted with diethyl ether. The organic layer was washed with brine (30 ml), dried (anhydrous MgSO$_4$), and the solvent removed in vacuo to

afford, as a colourless oil, methyl 2-(chloromethyl)acrylate[85] (168) (3.42 g, 60%); v_{max}(thin film)/cm^{-1} 1738, 2957 and 3459; δ_H(500 MHz;CDCl$_3$) 3.68 (3H, s, OCH$_3$), 4.16 (2H, s, CH$_2$), 5.83 and 6.22 (2H, 2×s, C=CH$_2$); δ_C(125 MHz; CDCl$_3$) 42.1 (CH$_2$), 51.9 (OCH$_3$), 125.9 (C=CH$_2$), 136.6 (C=CH$_2$) and 165.9 (C=O); m/z 134 (M$^+$, 14%), 103 (100), 99 (85) and 105 (34).

Preparation of methyl 2-{[(2-oxo-2H-chromen-7-yl)oxy]methyl}acrylate (169)

Into a 50 ml two-necked round bottomed flask fitted to a condenser, nitrogen line and pressure-equalizing addition funnel, was placed NaH (0.312 g of a 50% oil dispersion, 6.5 mmol)† in dry THF (25 ml). 7-hydroxy-2H-chromen-2-one (140) (1.0 g, 6.17 mmol) in dry THF (15 ml) was added dropwise and the mixture allowed to stir until the evolution of hydrogen gas had ceased. Methyl 2-(chloromethyl)acrylate (168) (1.01 g, 7.0 mmol) was then added and the mixture boiled under reflux for 6 hours until TLC showed the disappearance of starting material. The solvent was then removed under vacuum and the residue recrystallised from methanol to afford, as pale yellow crystals, methyl 2-{[(2-oxo-2H-chromen-7-yl)oxy]methyl}acrylate (169) (1.53 g, 95%), m.p. 95-97°C (from methanol); v_{max}(KBr)/cm^{-1} 1615, 1710 and 3423; δ_H(500 MHz; CDCl$_3$) 3.83 (3H, s, CO$_2$CH$_3$), 4.82 (1H, s, 1'-CH$_2$), 6.00 and 6.44 (2H, 2×s, 3'-CH$_2$), 6.26 (1H, d, $J_{3,4}$ 9.4, 3-H), 6.86 (1H, s, 8-H), 6.88 (1H, d, $J_{6,5}$ 8.5, 6-H), 7.39 (1H, d, $J_{5,6}$ 8.6, 5-H) and 7.64 (1H, d, $J_{4,3}$ 9.4, 4-H); δ_C(125 MHz; CDCl$_3$) 52.4 (CO$_2$CH$_3$), 66.8 (1'-CH$_2$), 102.3 (C-8),113.1 (C-3), 113.2 (C-4a), 113.7 (C-6), 127.6 (3'-CH$_2$), 129.1 (C-5), 135.1 (C-2'), 143.6 (C-4), 156.0 (C-8a), 161.4 (C-7), 161.6 (C-2) and 165.9 (CO$_2$CH$_3$); m/z 260 (M$^+$, 18%), 228 (100), 171 (51), 199 (45) and 115 (23).

Attempted preparation of methyl 2-[(7-hydroxy-2-oxo-2H-chromen-8-yl) methyl]acrylate (170)

Method 1.-

Methyl 2-{[(2-oxo-2H-chromen-7-yl)oxy]methyl}acrylate (169) (0.40 g, 1.54 mmol) was dissolved in N,N-diethylaniline (30 ml) in a 50 ml round bottomed flask fitted with a reflux condenser and nitrogen line. The reaction mixture was then boiled under reflux for 10 hours after which time the absence of product was confirmed by ^{1}H NMR spectroscopy.

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†NaH was washed twice with dry THF prior to use.

Method 2.-

Methyl 2-{[(2-oxo-2*H*-chromen-7-yl)oxy]methyl}acrylate (**169**) (0.40 g, 1.54 mmol) was dissolved in a suspension of *N,N*-diethylaniline (30 ml) containing aluminium chloride (0.10 g, 0.75 mmol) in a 50 ml round bottomed flask fitted with a reflux condenser and nitrogen line. The reaction mixture was then boiled under reflux, and analysis of the reaction mixture after 4, 8 and 12 hours revealed that no product had formed.

Method 3.-

Methyl 2-{[(2-oxo-2*H*-chromen-7-yl)oxy]methyl}acrylate (**169**) (0.40 g, 1.54 mmol) was dissolved in trifluoroacetic acid (40 ml) in a 100 ml round bottomed flask. The reaction mixture was then boiled under reflux for 24 hours, after which time the absence of any product was confirmed by GC-MS and NMR spectroscopy.

Method 4.-

Methyl 2-{[(2-oxo-2*H*-chromen-7-yl)oxy]methyl}acrylate (**169**) (0.30 g, 1.15 mmol) was dissolved in toluene containing *p*-toluenesulfonic acid (0.05 g) as a catalyst. The reaction mixture was then boiled under reflux, and analysis after 8, 12 and 16 hours revealed the absence of any desired product.

3.2.2 Synthetic work towards sulfur analogues

Preparation of *O*-(8-allyl-2-oxo-2*H*-chromen-7-yl)*N,N*-dimethylcarbamothioate (176)
8-allyl-7-hydroxy-2*H*-chromen-2-one (**142**) (2.0 g, 9.9 mmol) was dissolved in dry DMF (20 ml) in a two-necked flask fitted with a thermometer, reflux condenser and nitrogen line. NaH (0.53 g of a 50% oil dispersion, 11.0 mmol)[1] was then added. Once the evolution of hydrogen gas had ceased, dimethylthiocarbamoyl chloride (1.29 g, 10.5 mmol) was added and the reaction mixture was heated at 60°C for 30 minutes. The reaction mixture was then poured into 50 ml of cold water and the precipitate obtained was filtered, dried, and recrystallised from ethanol to afford, as cream crystals, *O*-(8-allyl-2-oxo-2*H*-chromen-7-yl)*N,N*-dimethylcarbamothioate (**176**) (2.71

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[1]NaH was washed twice with dry THF prior to use.

g, 96%), m.p. 103-104°C (from ethanol) (Found: M^+ 289.07775, $C_{15}H_{15}O_3SN$ requires M, 289.07727); ν_{max}(KBr)/cm^{-1} 1595, 1671, 1723 and 2925; δ_H(500 MHz; CDCl$_3$) 3.38 and 3.47 [6H, 2×s, N(CH_3)$_2$], 3.54 (2H, d, $J_{1',2'}$ 6.3, 1'-CH$_2$), 5.03 (1H, dd, J_{cis} 10 and J_{gem} 1.5, C=CH) and 5.08 (1H, dd, J_{trans} 17.1 and J_{gem} 1.6, C=CH), 5.95 (1H, ddt, J_{trans} 17.1, J_{cis} 10.0 and $J_{2',1'}$ 6.3, 2'-H), 6.40 (1H, d, $J_{3,4}$ 9.6, 3-H), 7.03 (1H, d, $J_{6,5}$ 8.4, 6-H), 7.38 (1H, d, $J_{5,6}$ 8.4 5-H) and 7.69 (1H, d, $J_{4,3}$ 9.6, 4-H); δ_C(125 MHz; CDCl$_3$) 28.7 (C-1'), 39.5 and 44.1 [N(CH$_3$)$_2$], 116.5 (C-3), 116.8 (C-3'), 117.5 (C-4a), 121.1 (C-6), 122.4 (C-8), 126.5 (C-5), 135.1 (C-2'), 144.1 (C-4), 153.5 (C-8a), 155.4 (C-7), 161.2 (C-2) and 187.1 (C=S); m/z 289 (M^+, 24%) and 217 (100).

Preparation of S-(8-allyl-2-oxo-2H-chromen-7-yl)N,N-dimethylcarbamothioate (177)

O-(8-allyl-2-oxo-2H-chromen-7-yl)N,N-dimethylcarbamothioate (176) (2.70 g, 9.34 mmol) was heated neat under nitrogen in a two-necked flask containing a thermometer at *ca.* 230°C for 40 minutes, cooled, and the residue recrystallised from ethanol to afford the rearranged product, S-(8-allyl-2-oxo-2H-chromen-7-yl)N,N-dimethylcarbamothioate (177) (2.32 g, 86%), m.p. 101-105°C (from ethanol) (Found: M^+ 289.07765, $C_{15}H_{15}O_3SN$ requires M, 289.07727); ν_{max}(KBr)/cm^{-1} 1543, 1603 and 1723; δ_H(500 MHz; CDCl$_3$) 3.02 and 3.14 [6H, 2×s, N(CH_3)$_2$], 3.81 (2H, d, $J_{1',2'}$ 6.2, 1'-CH$_2$), 5.01-5.04 (2H, m, 3'-CH$_2$), 5.97 (1H, ddt, J_{trans} 17.6, J_{cis} 9.8 and $J_{2',1'}$ 6.2, 2'-H), 6.44 (1H, d, $J_{3,4}$ 9.6, 3-H), 7.36 (1H, d, $J_{6,5}$ 8.2, 6-H), 7.46 (1H, d, $J_{5,6}$ 8.0, 5-H) and 7.69 (1H, d, $J_{4,3}$ 9.6, 4-H); δ_C(125 MHz; CDCl$_3$) 32.1 (1'-CH$_2$), 37.3 [N(CH$_3$)$_2$], 116.5 (3'-CH$_2$), 117.5 (C-3), 119.8 (C-4a), 125.8 (C-6), 132.8 (C-8), 133.4 (C-5), 133.5 (C-7), 135.1 (C-2'), 143.6 (C-4), 152.3 (C-8a), 160.6 (C-1) and 165.7 [NC(O)S]; m/z 289 (M^+, 30%) and 217 (100).

Preparation of S-[8-(2,2-dimethoxyethyl)-2-oxo-2H-chromen-7-yl]N,N-dimethyl carbamothioate (182)

S-(8-allyl-2-oxo-2H-chromen-7-yl)N,N-dimethylcarbamothioate (177) (1.0 g, 3.46 mmol), was dissolved in dry THF in a three-necked round bottomed flask connected to an ozonator and two traps containing acidified KI (1.1 M solution). The reaction flask was cooled to -78°C using a solid CO$_2$/acetone slurry and ozone was bubbled through the mixture for *ca.* 80 minutes until analysis by TLC showed the disappearance of starting material. Dimethyl sulfide (0.3 ml, 4.15 mmol) was then added and the mixture stirred at -10°C for a further 3 hours while allowing the temperature to warm to room temperature. Methanol (20 ml), *p*-toluenesulfonic acid (0.02 g) and

4Å molecular sieve (*ca.* 0.5 g) were then added and the reaction mixture boiled under reflux for 4 hours until TLC showed there was no starting material left. The volatile components were removed *in vacuo* and the final product purified *via* radial chromatography (50:50 ethyl acetate/hexane) to afford S-[8-(2,2-dimethoxyethyl)-2-oxo-2H-chromen-7-yl]N,N-dimethyl carbamothioate (**182**) (0.99 g, 84%), m.p. 96-99°C (from methanol) (Found: M$^+$ 337.09877, $C_{16}H_{19}O_5SN$ requires M, 337.09839); v_{max}(KBr)/cm^{-1} 1654, 1727 and 2948; δ_H(500 MHz; CDCl$_3$) 3.00 and 3.12 [6H, 2×s, N(CH_3)$_2$], 3.34 (6H, s, 2×OCH_3), 3.40 (2H, d, $J_{1',2'}$ 5.7, 1'-CH$_2$), 4.69 (1H, t, $J_{2',1'}$ 5.7, 2'-H), 6.43 (1H, d, $J_{3,4}$ 9.4, 3-H), 7.35 (1H, d, $J_{6,5}$ 8.2, 6-H), 7.45 (1H, d, $J_{5,6}$ 8.2, 5-H) and 7.68 (1H, d, $J_{4,3}$ 9.6, 4-H); δ_C(125 MHz; CDCl$_3$) 31.9 (1'-CH$_2$), 36.9 [N(CH$_3$)$_2$], 53.9 (2×OCH$_3$), 104 (C-2'), 117 (C-3), 119.2 (C-4a), 125.6 (C-6), 129.8 (C-8), 133.2 (C-5), 134.5 (C-7), 143.3 (C-4), 152.3 (C-8a), 160.1 (C-2) and 165.5 [NC(O)S]; m/z 337 (M$^+$,28%), 203 (100) and 234 (28).

Preparation of 8-methoxy-8,9-dihydro-2H-thieno[2,3-h]chromen-2-one (185)

S-[8-(2,2-dimethoxyethyl)-2-oxo-2H-chromen-7-yl]N,N-dimethylcarbamothioate (**182**) (0.80 g, 2.3 mmol) was added to a stirred mixture of dry methanol containing KOH (0.168 g, 3.0 mmol) in a round bottomed flask fitted with a condenser and heated under reflux for *ca.* 4 hours. The reaction mixture was then acidified (HCl) and boiled under reflux for a further 2 hours. Water (5 ml) was then added and the product extracted with ether (3×30 ml). The organic layer was dried (anhydrous MgSO$_4$) and the solvent removed *in vacuo* to yield, as an orange oil from which the product crystallised out as orange crystals, 8-methoxy-8,9-dihydro-2H-thieno[2,3-h]chromen-2-one (**185**) (0.156 g, 29%), m.p. 141-143°C (from methanol) (Found: M$^+$ 234.03381, $C_{12}H_{10}O_3S$ requires M, 234.03507); v_{max}(KBr)/cm^{-1} 1600, 1717 and 3452; δ_H(500 MHz; CDCl$_3$) 3.38 (3H, s, CH$_3$), 3.51 (1H, dd, J_{gem} 17.3, $J_{9a,8}$ 5.5, 9-CH$_a$) and 3.78 (1H, d, J_{gem} 17.3, 9-CH$_b$), 5.54 (1H, d, $J_{8,9a}$ 5.5, 8-H), 6.30 (1H, d, $J_{3,4}$ 9.6, 3-H), 7.18 (1H, d, $J_{6,5}$ 8.0, 6-H), 7.29 (1H, d, $J_{5,6}$ 8.0, 5-H) and 7.66 (1H, d, $J_{4,3}$ 9.6, 4-H); δ_C(125 MHz; CDCl$_3$) 40.1 (9-CH$_2$), 56.3 (1'-CH$_3$), 92.7 (C-8), 114.5 (C-3), 115.9 (C-9a), 118.8 (C-6), 125.3 (C-4a), 127.6 (C-5), 143.6 (C-4), 145.7 (C-6a), 150.6 (C-9b) and 160.6 (C-2); m/z 234 (M$^+$, 92%), 203 (100), 147 (60) and 174 (21).

Attempted preparation of 8-ethoxy-8,9-dihydro-2*H*-thieno[2,3-*h*]chromen-2-one (186)

S-[8-(2,2-dimethoxyethyl)-2-oxo-2*H*-chromen-7-yl]*N*,*N*-dimethylcarbamothioate (182) (0.80 g, 2.3 mmol) was added to a mixture of dry ethanol containing KOH (0.168 g, 3.0 mmol) and heated under reflux for *ca.* 4 hours. The reaction mixture was then acidified (HCl) and boiled under reflux for a further 2 hours. Water (5 ml) was then added and the product extracted with ether (3×30 ml). The organic layer was dried (anhydrous MgSO$_4$) and removed *in vacuo* to yield an orange oil. GC-MS and NMR spectroscopic analysis of this oil could neither confirm nor disprove the presence of the desired product. ^{1}H NMR spectroscopy proved inconclusive due to the presence of impurities, only the aromatic proton signals could be observed with any clarity, and attempts to purify the oil using chromatography were unsuccessful, with ^{1}H NMR spectroscopic analysis of the bands being similar to that of the original sample. GC-MS analysis did provide evidence for the presence of the hemiacetal (184), and high resolution mass spectrometry analysis the presence of the charged species 187 (possibly formed from the hemiacetal losing water to form a positively charged sulfur atom, see **scheme 53**, page 66) providing further evidence for the presence of the hemiacetal in the original reaction mixture.

3.2.3 Synthetic work towards selenium analogues

Attempted Preparation of 8-allyl-7-bromo-2*H*-chromen-2-one (188)

Method 1.-

8-allyl-7-hydroxy-2*H*-chromen-2-one (142) (0.50 g, 2.47 mmol) and triphenylphosphine dibromide (1.10 g, 2.60 mmol) were dissolved in dry DMF (30 ml) in a 50 ml two-necked round bottomed flask fitted with a reflux condenser and a nitrogen line. The reaction mixture was boiled under reflux for 3 hours, where the absence of any formation of product was confirmed by TLC and GC-MS analysis. The reaction mixture was then boiled under reflux for a further 4 hours, and NMR spectroscopic analysis of the mixture confirmed the failure of the reaction.

Method 2.-

Part A:

Preparation of 8-allyl-2-oxo-2*H*-chromen-7-yl trifluoromethanesulfonate (197)

8-allyl-7-hydroxy-2*H*-chromen-2-one (142) (0.50 g, 2.47 mmol) was dissolved in dry THF (15 ml) in a 25 ml two-necked round bottomed flask fitted with a nitrogen line. The reaction mixture was cooled to -70°C and freshly distilled triethylamine (1.08 ml, 7.72 mmol) was added *via* a cannula, followed by triflic anhydride (0.50 ml, 2.97 mmol). The mixture was stirred for 15 minutes after which the organic solvents were removed under vacuum. Water (10 ml) was added, and the product extracted with ether (2×20 ml) and dried (anhydrous $MgSO_4$). Removal of the solvent afforded, as a pale yellow oil, 8-allyl-2-oxo-2*H*-chromen-7-yl trifluoromethanesulfonate (197) (0.78 g, 94%); v_{max}(KBr)/cm^{-1} 1421, 1601, 1743 and 3431; δ_H(500 MHz; $CDCl_3$) 3.65 (2H, d, $J_{1',2'}$ 5.9, 1'-CH_2), 4.93 (1H, dd, J_{cis} 10.0 and J_{gem} 1.8, C=C*H*) and 5.21 (1H, dd, J_{trans} 16.9 and J_{gem} 1.8, C=C*H*), 5.94 (1H, ddt, J_{trans} 16.9, J_{cis} 10.0 and $J_{2',1'}$ 5.9, 2'-H), 6.45 (1H, d, $J_{3,4}$ 9.1, 3-H), 7.22 (1H, d, $J_{6,5}$ 8.3, 6-H), 7.45 (1H, d, $J_{5,6}$ 8.5, 5-H) and 7.70 (1H, d, $J_{4,3}$ 9.3, 4-H); δ_C(125 MHz; $CDCl_3$) 28.1 (1'-CH_2), 117.6 (3'-CH_2, C-3 and C-6), 118.6 (q, J_{CF} 320, CF_3), 118.8 (C-4a), 122.4 (C-8), 127.2 (C-5), 132.9 (C-2'), 142.9 (C-4), 149.5 (C-7), 153.2 (C-8a), 159.6 (C-2); *m/z* 334 (M$^+$, 44%), 173 (100), 201 (76) and 128 (41).

Part B:

Attempted Preparation of 8-allyl-7-bromo-2*H*-chromen-2-one (188)

8-allyl-2-oxo-2*H*-chromen-7-yl trifluoromethanesulfonate (197) (0.40 g, 1.24 mmol) was dissolved in acetonitrile (30 ml) in a 50 ml round bottomed flask fitted with a reflux condenser attached to a nitrogen line. Tetrabutylammonium bromide (0.46 g, 1.44 mmol) was then added, and the reaction mixture boiled under reflux for 16 hours. Analysis of the sample using GC-MS and ^{13}C NMR spectroscopy confirmed the absence of any product.

Preparation of 1-(allyloxy)-3-bromobenzene (199)

K_2CO_3(5.59 g, 40.5 mmol) was added to a solution of 3-bromophenol (198) (5.00 g, 28.9 mmol) in acetone (120 ml) contained in a 250 ml two-necked flask fitted with a reflux condenser and a nitrogen line. 3-bromo-1-propene (5.50 ml, 63.5 mmol) was then added and the reaction mixture boiled under reflux for 5 hours, after which the K_2CO_3 was filtered off using a scintered

glass filter funnel. The filtrate and washings were then reduced *in vacuo* to leave a brown oil, 1-(allyloxy)-3-bromobenzene (**199**) (6.08 g, 98%); v_{max}(thin film)/cm^{-1} 1474, 1590 and 3426; δ_H(500 MHz; CDCl$_3$) 4.52 (2H, d, $J_{1',2'}$ 5.3, 1'-CH$_2$), 5.32 (1H, dd, J_{cis} 10.5 and J_{gem} 1.4, C=CH) and 5.43 (1H, dd, J_{trans} 17.2 and J_{gem} 1.4, C=CH), 6.04 (1H, ddt, J_{trans} 17.1, J_{cis} 10.5 and $J_{2',1'}$ 5.4, 2'-H), 6.85 (1H, d, $J_{6,5}$ 8.0, 6-H) and 7.08-7.16 (3H, m, Ar-H); δ_C(125 MHz; CDCl$_3$) 68.8 (1'-CH$_2$), 113.7 (C-6), 117.8 (3'-CH$_2$), 117.9 (C-2), 122.7 (C-3), 123.9 (C-4), 130.5 (C-5), 132.6 (C-2') and 159.3 (C-1); *m/z* 214 [M$^+$(^{81}Br), 73%], 105 (100), 133 (89), 145 (30), 174 (22) and 199 (22).

Preparation of 2-allyl-3-bromophenol (200a) and 2-allyl-5-bromophenol (200b)

1-(allyloxy)-3-bromobenzene (**199**) (6.08 g, 28.5 mmol) was heated neat under nitrogen to *ca.* 200°C for 4 hours until analysis by TLC showed that the starting product had disappeared. The two possible regioisomers for the rearrangement reaction were then separated using column chromatography (5:95 ethyl acetate/hexane as eluant) on some of the reaction mixture (1.0 g, 4.69 mmol). This afforded first, as an orange oil, 2-allyl-5-bromophenol (**200b**) (0.41 g, 41%); v_{max}(thin film)/cm^{-1} 1408, 1495, 1589 and 3444; δ_H(500 MHz; CDCl$_3$) 3.36 (2H, d, $J_{1',2'}$ 6.4, 1'-CH$_2$), 5.15 (2H, m, 3'-CH$_2$), 5.37 (1H, br. s, OH), 5.98 (1H, ddt, J_{trans} 17.1, J_{cis} 10.3 and $J_{2',1'}$ 6.4, 2'-H) and 6.99 (3H, m, Ar-H); δ_C(125 MHz; CDCl$_3$) 34.9 (1'-CH$_2$), 117.1 (3'-CH$_2$), 118.9 (C-2), 120.8 (C-3), 122.2 (C-4), 122.8 (C-6), 131.9 (C-5), 135.7 (C-2') and 155.2 (C-1); *m/z* 214 [M$^+$(^{81}Br), 100%], 105 (81), 133 (76), 174 (33) and 145 (23). The second fraction to be eluted, also an orange oil, was 2-allyl-3-bromophenol (**200a**) (0.53 g, 53%); v_{max}(thin film)/cm^{-1} 1446, 1579 and 3448; δ_H(500 MHz; CDCl$_3$) 3.61 (2H, d, $J_{1',2'}$ 5.9, 1'-CH$_2$), 5.08 (3H, m, 3'-CH$_2$ and -OH), 5.96 (1H, ddt, J_{trans} 16.9, J_{cis} 10.3 and $J_{2',1'}$ 5.9, 2'-H), 6.73 (1H, d, $J_{6,5}$ 8.0, 6-H), 6.94 (1H, t, $J_{5,6}$ 8.0 and $J_{5,4}$ 8.0, 5-H) and 7.14 (1H, d, $J_{4,5}$ 8.0, 4-H); δ_C(125 MHz; CDCl$_3$) 34.3 (1'-CH$_2$), 114.9 (C-6), 116.2 (3'-CH$_2$), 125.3 (C-4), 125.6 (C-3), 125.7 (C-2), 128.4 (C-5), 134.5 (C-2') and 154.8 (C-1); *m/z* 214 [M$^+$(^{81}Br), 65%], 105 (100), 133 (89) and 187 (14).

Attempted preparation of 8-allyl-7-bromo-4-methyl-2*H*-chromen-2-one (201)

Method 1.-

Concentrated sulfuric acid (0.71 ml) was added to a two-necked round bottomed flask, fitted with a pressure-equalizing dropping funnel and nitrogen line, and cooled to 5°C using an ice bath. A mixture of 2-allyl-3-bromophenol (200a) (0.20 g, 0.94 mmol) and ethyl acetoacetate (0.12 ml, 0.94 mmol) was then added dropwise, ensuring the temperature did not rise above 10°C. When the addition was complete, the mixture was warmed to room temperature, and stirred overnight. Ice water (10 ml) was then added to the solution, and the precipitate was filtered off under vacuum and washed with water. Analysis by GC-MS and NMR spectroscopy revealed the absence of the formation of any product.

Method 2.-

In a two-necked round bottomed flask fitted with a pressure-equalizing dropping funnel and a nitrogen line, 2-allyl-3-bromophenol (200a) (0.20 g, 0.94 mmol) and ethyl acetoacetate (0.12 ml, 0.94 mmol) were dissolved in dry nitrobenzene. A mixture of anhydrous aluminium chloride (0.25 g, 1.88 mmol) in hot dry nitrobenzene (10 ml) was added, and the mixture heated at 125-130°C for 2 hours under nitrogen. The mixture was then cooled, and ice and concentrated HCl (0.1 ml) was added. A small aliquot was removed, the nitrobenzene removed under high vacuum, and a GC-MS and NMR sample prepared. The sample was found to consist only of starting material, with no desired product evident.

Method 3.-

Hypophosphoric acid (2 ml) was added to a two-necked round bottomed flask, fitted with a pressure-equalizing dropping funnel and nitrogen line and cooled to 5°C using an ice bath. A mixture of 2-allyl-3-bromophenol (200a) (0.20 g, 0.94 mmol) and ethyl acetoacetate (0.12 ml, 0.94 mmol) was then added dropwise, after which the reaction mixture was heated at 80°C for 12 hours. The reaction mixture was found to contain only starting material, with no trace of the desired product.

Method 4.-

2-allyl-3-bromophenol (**200a**) (1.0 g, 4.69 mmol) was dissolved in THF (30 ml) in a two-necked round bottomed flask fitted with a nitrogen line. NaHCO$_3$ (0.39 g, 4.69 mmol) was then added and the mixture stirred for 10 minutes. Ethyl malonyl chloride (0.721 ml, 5.6 mmol) was then added using a cannula and the mixture was stirred overnight. Analysis using GC-MS and NMR spectroscopy showed that no desired product had formed, with only starting material being present in the reaction mixture.

Attempted preparation of 8-allyl-7-bromo-4-hydroxy-2*H*-chromen-2-one (203)

THF (10 ml) was added to a two-necked flask fitted with a nitrogen line. 2-allyl-3-bromophenol (**200a**) (0.13 g, 0.61 mmol), malonic acid (0.07 g, 0.67 mmol), anhydrous zinc chloride (0.25 g, 1.83 mmol) and phosphorus oxychloride (0.17 ml, 1.83 mmol) were then added and the mixture was boiled under reflux for a total of 40 hours. Analysis by GC-MS and NMR spectroscopy revealed only the presence of starting material, with no evidence of the desired product.

Preparation of 2-allyl-3-bromophenyl *tert*-butyl(dimethyl)silyl ether (204)

Method 1.-

2-allyl-3-bromophenol (**200a**) (1.0 g, 4.69 mmol) was dissolved in THF (20 ml) in a two-necked flask fitted with a nitrogen line. *Tert*-butyl dimethylsilyl chloride (0.86 g, 5.7 mmol) and imidazole (0.80 g, 11.7 mmol) were added to the flask and the reaction mixture stirred overnight. Analysis by GC-MS and NMR spectroscopy revealed that no reaction had occurred, and only the starting material was present.

Method 2.-

NaH (0.15 g of a 50% oil dispersion, 3.1 mmol)§ was added to dry THF (20 ml) in a 50 ml two-necked flask under nitrogen. 2-allyl-3-bromophenol (**200a**) (0.5 g, 2.34 mmol) was then added and the reaction mixture was stirred until the evolution of hydrogen gas had ceased (*ca*. 30 min). *tert*-Butyl dimethylsilyl chloride (0.42 g, 2.8 mmol) was added and the mixture stirred overnight under an atmosphere of dry nitrogen. The reaction mixture was then diluted with ether (20 ml),

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§NaH was washed twice with dry THF prior to use.

washed with *aq.* 10% $NaHCO_3$ solution (20 ml) and then with brine solution (15 ml). The organic layer was separated, dried (anhydrous $MgSO_4$) and the solvent removed under vacuum to afford, as a yellow oil, 2-allyl-3-bromophenyl *tert*-butyl(dimethyl)silyl ether (**204**) (0.73 g, 95%); v_{max}(thin film)/cm^{-1} 1273, 1456, 2930 and 2957; δ_H(500 MHz; $CDCl_3$) 0.25 [6H, s, Si(CH_3)$_2$], 1.02 [9H, s, C(CH_3)$_3$], 3.57 (2H, d, $J_{1',2'}$ 6.3, 1'-CH_2), 5.01 (2H, m, 3'-CH_2), 5.92 (1H, ddt, J_{trans} 17.4, J_{cis} 10.1 and $J_{2',1'}$ 6.4, 2'-H), 6.76 (1H, d, $J_{6,5}$ 8.0, 6-H), 6.95 (1H, t, $J_{5,6}$ 8.0 and $J_{5,4}$ 8.1, 5-H) and 7.16 (1H, d, $J_{4,5}$ 8.1, 4-H); δ_C(125 MHz; $CDCl_3$) -4.2 [Si(CH_3)$_2$], 18.2 [C(CH$_3$)$_3$], 25.7 [C(CH$_3$)$_3$], 34.2 (1'-CH$_2$), 115.3 (3'-CH$_2$), 117.3 (C-6), 125.4 (C-4), 125.8 (C-3), 127.7 (C-5), 130.5 (C-2), 134.9 (C-2') and 154.5 (C-1); *m/z* 328 [M$^+$(^{81}Br), 5%] 271 (100), 243 (78), 175 (43), 190 (41) and 229 (26).

Preparation of [3-bromo-2-(2,2-dimethoxyethyl)phenoxy](*tert*-butyl)dimethylsilane (205)

2-allyl-3-bromophenyl *tert*-butyl(dimethyl)silyl ether (**204**) (0.70 g, 2.14 mmol) was dissolved in THF (50 ml) in a three-necked round bottomed flask connected to an ozonator and two traps containing acidified KI (1.1 M solution). The reaction flask was cooled to -78°C using a solid CO_2/acetone slurry and ozone was bubbled through the mixture for *ca.* 80 minutes until analysis by TLC showed the disappearance of starting material. Dimethyl sulfide (0.19 ml, 2.60 mmol) was added and the mixture stirred at -10°C for a further 3 hours while allowing the temperature to warm to room temperature. Half the THF (*ca.* 25 ml) was then removed under vacuum, and methanol (20 ml) and *p*-toluenesulfonic acid (0.05 g) added, as well as 3Å molecular sieve (0.5 g). The mixture was then boiled under reflux for 3 hours. Removal of the solvent under vacuum, and the catalyst by passage through a plug of silica gel, afforded, as a yellow oil, [3-bromo-2-(2,2-dimethoxyethyl)phenoxy](*tert*-butyl) dimethylsilane (**205**) (0.67 g, 84%); v_{max}(thin film)/cm^{-1} 1451, 1588, 2930 and 2955; δ_H(500 MHz; $CDCl_3$) 0.23 [6H, s, Si(CH_3)$_2$], 0.98 [9H, s, C(CH_3)$_3$], 3.13 (2H, d, $J_{1',2'}$ 5.7, 1'-CH_2), 3.47 (6H, s, 2×OCH_3), 4.72 (1H, t, $J_{2',1'}$ 5.7, 2'-H), 6.80 (1H, d, $J_{6,5}$ 8.0, 6-H), 6.93 (1H, t, $J_{5,6}$ 8.0 and $J_{5,4}$ 8.2, 5-H) and 7.18 (1H, d, $J_{4,5}$ 8.2, 4-H); δ_C(125 MHz; $CDCl_3$) -4.1 [Si(CH_3)$_2$], 18.3 [C(CH$_3$)$_3$], 25.9 [C(CH$_3$)$_3$], 34.6 (1'-CH$_2$), 53.8 (2×OCH$_3$), 104.2 (C-2'), 117.8 (C-6), 124.9 (C-3), 125.8 (C-4), 126.3 (C-2), 128.7 (C-5) and 155.3 (C-1); *m/z* 376 [M$^+$(^{81}Br), 3%], 214 (100), 118 (24) and 199 (21).

Attempted preparation of *tert*-butyl[2-(2,2-dimethoxyethyl)-3-(methylselenyl) phenoxy]dimethylsilane (206)

[3-bromo-2-(2,2-dimethoxyethyl)phenoxy](*tert*-butyl)dimethylsilane (**205**) (0.60 g, 1.60 mmol) and K_2CO_3 (0.25 g, 1.70 mmol) were suspended in acetonitrile (7 ml) in a 20 ml round bottomed flask fitted to a nitrogen line. The slurry was then cooled to -5°C using a salt/ice bath and methaneselenol (162 µl, 1.70 mmol) was added. The mixture was then stirred at 25°C for 24 hours and then poured onto water (10 ml). The organic layer was extracted with ether, dried with $MgSO_4$, and evaporated to dryness under vacuum. Analysis of the brown oil remaining confirmed the absence of the desired product, but from GC-MS evidence, and the disappearance of the *tert*-butyl dimethylsilyl peaks in the ^{1}H NMR spectrum, it was concluded that this protecting group was cleaved off during the reaction period.

Attempted preparation of 2-allyl-3-(methylselenyl)phenol (207)

Method 1.-

2-allyl-3-bromophenol (**200a**) (0.4 g, 1.88 mmol) and K_2CO_3 (0.28 g, 2.02 mmol) were suspended in acetonitrile (10 ml) in a 50 ml round bottomed flask fitted with a nitrogen line. The slurry was cooled to -5°C using a salt/ice bath, methaneselenol (200 µl, 2.10 mmol) was added, and the mixture stirred at 25°C for 24 hours, after which it was poured onto water (10 ml). Analysis of the organic phase established the absence of any reaction.

Method 2.-

Powdered selenium metal (0.176 g, 2.23 mmol) was suspended in dry THF (5 ml) in a 20 ml two-necked flask fitted with a nitrogen line. Methyllithium (1.53 ml of a 1.6 M commercial solution, 2.44 mmol) was then added dropwise *via* a syringe to the stirred suspension at room temperature. After *ca.* 20 min all the grey selenium had disappeared and a white suspension was obtained. A solution of 2-allyl-3-bromophenol (**200a**) (0.30 g, 1.40 mmol) in dry DMF (10 ml) was then added to this suspension. The flask was then heated so as to allow the THF and ether to distill off under nitrogen. The reaction mixture was then stirred at 120°C for a total of 36 hours. Analysis of the reaction mixture after this time by GC-MS and NMR spectroscopy revealed the absence of any reaction.

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5. APPENDIX

CRYSTALLOGRAPHIC DATA FOR 8-METHOXY-8,9-DIHYDRO-2*H*-FURO[2,3-*h*] CHROMEN-2-ONE (150a).

Table 2. Crystal data and structure refinement for 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*] chromen-2-one (**150a**).

Identification code	dino1
Empirical formula	C12 H10 O4
Formula weight	218.20
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P21/a
Unit cell dimensions	a = 7.902(3) A alpha = 90.031(19) deg.
	b = 7.2686(14) A beta = 99.44(3) deg.
	c = 17.500(5) A gamma = 90.00(3) deg.
Volume	991.6(5) A^3
Z, Calculated density	4, 1.462 Mg/m^3
Absorption coefficient	0.111 mm^{-1}
F(000)	456
Crystal size	1.40 x 0.80 x 0.25 mm
Theta range for data collection	2.36 to 27.96 deg.
Index ranges	-10<=h<=10, -3<=k<=9, -4<=l<=23
Reflections collected / unique	3555 / 2339 [R(int) = 0.0221]
Completeness to 2theta = 27.96	97.9%
Max. and min. transmission	0.9729 and 0.8605
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2339 / 0 / 152
Goodness-of-fit on F^2	1.209
Final R indices [I>2sigma(I)]	R1 = 0.0812, wR2 = 0.3114
R indices (all data)	R1 = 0.0931, wR2 = 0.3211
Largest diff. peak and hole	0.594 and -0.419 $e.A^{-3}$

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters
(A^2 x 10^3) for 8-methoxy-8,9-dihydro-2H-furo[2,3-h]chromen-2-one (**150a**).[‡] U(eq)
is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(2)	9405(3)	5901(3)	3313(1)	38(1)
O(3)	6088(3)	8980(3)	1274(2)	48(1)
O(4)	6847(3)	6735(3)	444(1)	43(1)
O(1)	10895(4)	4274(4)	4252(2)	58(1)
C(1)	10506(4)	5794(5)	4017(2)	43(1)
C(2)	11069(5)	7518(5)	4387(2)	52(1)
C(3)	10552(5)	9134(5)	4071(2)	50(1)
C(4)	9401(4)	9229(4)	3349(2)	40(1)
C(5)	8872(4)	7557(4)	2987(2)	34(1)
C(6)	7765(4)	7531(4)	2290(2)	33(1)
C(7)	7187(4)	9186(4)	1959(2)	40(1)
C(8)	7660(6)	10884(4)	2295(2)	51(1)
C(9)	8778(6)	10873(5)	2993(2)	51(1)
C(10)	6991(4)	5997(4)	1776(2)	36(1)
C(11)	6037(4)	7038(4)	1076(2)	38(1)
C(12)	5939(5)	7450(5)	-268(2)	52(1)

[‡]For atom numbering see **Figure 5**, page 43.

Table 4. Bond lengths [A] and angles [deg] for 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*] chromen-2-one (**150a**).

O(2)-C(5)	1.368(3)
O(2)-C(1)	1.390(4)
O(3)-C(7)	1.368(4)
O(3)-C(11)	1.452(4)
O(4)-C(11)	1.383(4)
O(4)-C(12)	1.430(4)
O(1)-C(1)	1.201(4)
C(1)-C(2)	1.446(5)
C(2)-C(3)	1.333(6)
C(3)-C(4)	1.432(5)
C(4)-C(9)	1.400(5)
C(4)-C(5)	1.403(4)
C(5)-C(6)	1.380(4)
C(6)-C(7)	1.381(4)
C(6)-C(10)	1.499(4)
C(7)-C(8)	1.391(5)
C(8)-C(9)	1.385(6)
C(10)-C(11)	1.530(4)
C(5)-O(2)-C(1)	121.6(2)
C(7)-O(3)-C(11)	107.7(2)
C(11)-O(4)-C(12)	114.0(3)
O(1)-C(1)-O(2)	116.3(3)
O(1)-C(1)-C(2)	127.0(3)
O(2)-C(1)-C(2)	116.7(3)
C(3)-C(2)-C(1)	121.8(4)
C(2)-C(3)-C(4)	121.1(3)
C(9)-C(4)-C(5)	118.8(3)
C(9)-C(4)-C(3)	124.2(3)
C(5)-C(4)-C(3)	117.1(3)
O(2)-C(5)-C(6)	117.6(2)
O(2)-C(5)-C(4)	121.7(3)
C(6)-C(5)-C(4)	120.6(3)
C(5)-C(6)-C(7)	118.6(3)
C(5)-C(6)-C(10)	132.7(3)
C(7)-C(6)-C(10)	108.7(3)
O(3)-C(7)-C(6)	113.1(3)
O(3)-C(7)-C(8)	123.7(3)

Table 4. Continued..

C(6)-C(7)-C(8)	123.2(3)
C(9)-C(8)-C(7)	117.1(3)
C(8)-C(9)-C(4)	121.7(3)
C(6)-C(10)-C(11)	102.2(2)
O(4)-C(11)-O(3)	110.3(3)
O(4)-C(11)-C(10)	109.2(2)
O(3)-C(11)-C(10)	107.4(2)

Table 5. Anisotropic displacement parameters (A^2 x 10^3) for 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-one (**150a**). The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^{2} U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(2)	40(1)	34(1)	37(1)	2(1)	1(1)	1(1)
O(3)	51(1)	41(1)	51(2)	5(1)	3(1)	13(1)
O(4)	35(1)	53(1)	39(1)	4(1)	8(1)	4(1)
O(1)	64(2)	58(2)	48(2)	11(1)	-4(1)	9(1)
C(1)	41(2)	53(2)	37(2)	2(1)	6(1)	1(1)
C(2)	49(2)	66(2)	38(2)	-9(2)	1(1)	-9(2)
C(3)	55(2)	52(2)	44(2)	-16(2)	12(2)	-14(2)
C(4)	46(2)	37(2)	40(2)	-7(1)	13(1)	-5(1)
C(5)	37(1)	29(1)	37(2)	-2(1)	12(1)	-1(1)
C(6)	33(1)	29(1)	39(2)	1(1)	9(1)	2(1)
C(7)	44(2)	32(2)	46(2)	4(1)	14(1)	7(1)
C(8)	69(2)	29(2)	59(2)	1(1)	23(2)	6(1)
C(9)	71(2)	31(2)	55(2)	-10(1)	24(2)	-7(1)
C(10)	35(1)	32(1)	40(2)	0(1)	4(1)	0(1)
C(11)	28(1)	43(2)	44(2)	2(1)	9(1)	2(1)
C(12)	50(2)	63(2)	42(2)	5(2)	3(2)	-1(2)

Table 6. Hydrogen coordinates (x 10^4) and isotropic
displacement parameters (A^2 x 10^3) for 8-methoxy-8,9-dihydro-2H-furo[2,3-h]
chromen-2-one (**150a**).

	x	y	z	U(eq)
H(2)	11750(4)	7501(5)	4820(3)	62
H(3)	10960(2)	10240(6)	4330(13)	60
H(8)	7230(2)	12030(6)	2050(13)	61
H(9)	9130(19)	12010(6)	3235(13)	61
H(10A)	6200(2)	5260(2)	2027(7)	43
H(10B)	7880(2)	5190(2)	1628(4)	43
H(11)	4870(5)	6625(19)	963(5)	46
H(12A)	6550(2)	7207(9)	-664(13)	78
H(12B)	5805(7)	8710(4)	-222(2)	78
H(12C)	4870(4)	6897(19)	-378(4)	78

Table 7. Torsion angles [deg] for 8-methoxy-8,9-dihydro-2*H*-furo[2,3-*h*]chromen-2-
one (**150a**).

C(5)-O(2)-C(1)-O(1)	-180.0(3)
C(5)-O(2)-C(1)-C(2)	-0.4(5)
O(1)-C(1)-C(2)-C(3)	179.9(4)
O(2)-C(1)-C(2)-C(3)	0.4(6)
C(1)-C(2)-C(3)-C(4)	0.4(6)
C(2)-C(3)-C(4)-C(9)	178.6(4)
C(2)-C(3)-C(4)-C(5)	-1.1(5)
C(1)-O(2)-C(5)-C(6)	-179.4(3)
C(1)-O(2)-C(5)-C(4)	-0.3(5)
C(9)-C(4)-C(5)-O(2)	-178.6(3)
C(3)-C(4)-C(5)-O(2)	1.1(5)
C(9)-C(4)-C(5)-C(6)	0.4(5)
C(3)-C(4)-C(5)-C(6)	-179.9(3)
O(2)-C(5)-C(6)-C(7)	178.8(3)
C(4)-C(5)-C(6)-C(7)	-0.2(5)
O(2)-C(5)-C(6)-C(10)	-1.0(5)
C(4)-C(5)-C(6)-C(10)	180.0(3)
C(11)-O(3)-C(7)-C(6)	-6.2(4)
C(11)-O(3)-C(7)-C(8)	174.6(3)
C(5)-C(6)-C(7)-O(3)	-179.4(3)
C(10)-C(6)-C(7)-O(3)	0.4(4)
C(5)-C(6)-C(7)-C(8)	-0.2(5)
C(10)-C(6)-C(7)-C(8)	179.6(3)
O(3)-C(7)-C(8)-C(9)	179.6(3)
C(6)-C(7)-C(8)-C(9)	0.5(6)
C(7)-C(8)-C(9)-C(4)	-0.3(6)
C(5)-C(4)-C(9)-C(8)	-0.1(5)
C(3)-C(4)-C(9)-C(8)	-179.8(3)
C(5)-C(6)-C(10)-C(11)	-175.1(3)
C(7)-C(6)-C(10)-C(11)	5.1(3)
C(12)-O(4)-C(11)-O(3)	-69.7(3)
C(12)-O(4)-C(11)-C(10)	172.4(3)
C(7)-O(3)-C(11)-O(4)	-109.7(3)
C(7)-O(3)-C(11)-C(10)	9.2(3)
C(6)-C(10)-C(11)-O(4)	111.1(3)
C(6)-C(10)-C(11)-O(3)	-8.6(3)