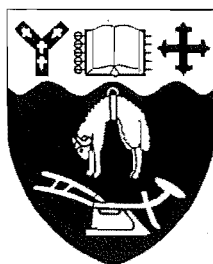# The preparation of possible prodrugs for cancer chemotherapy

A thesis submitted in partial fulfilment

of the requirements for the Degree of

Doctor of Philosophy in Chemistry

in the

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by

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ACKNOWLEDGMENTS

ABSTRACT

This thesis concerns the design and preparation of compounds which are relevant to a new strategy for the selective chemotherapeutic treatment of tumour cells. These bridged polycyclic compounds are prepared by Diels-Alder chemistry involving cyclic dienes. The bridge is to be cleaved at the cancer site by tumour-selective chemistry acting on an appropriate trigger. This activation of a low toxicity 'prodrug' results in the formation of a planar, aromatic structure which is a characteristic of known anti-cancer drugs (intercalating agents).

The crucial step in the organic synthesis of these potential prodrugs is a Diels-Alder reaction involving two classes of diene, 1-(methylthio)isobenzofurans and pyranones, with various dienophiles. Examination of this step started with the reaction of 1,1-bis(methylthio)ethene with various pyranones. Stable adducts were isolated from its reaction with methyl coumalate and a benzopyranone; but only substituted carbazoles were observed from the reaction with pyrano[3,4-*b*]indol-3-ones. An investigation into the thermal stability of the isolated adducts resulted in the observation of an unusual [1,5]-methylthio migration. In comparison to 1,1-bis(methylthio)ethene, 1-(methylthio)-1-(*p*-tolylsulfonyl)ethene was observed to have lower reactivity and regioselectivity upon reaction with electron-deficient pyranones. The resulting adducts were unstable due to the facile elimination of *p*-toluenesulfinic acid and only aromatic products were isolated. Diels-Alder adducts were isolated from the reaction of 1-(methylthio)-1-(*p*-tolylsulfonyl)ethene with 1-(methylthio)isobenzofurans, but they were of low stability and of mixed regio- and stereo- chemistries. The reaction of arynes with 1-(methylthio)isobenzofurans was also investigated. The Diels-Alder reaction between 3,4-didehydropyridine and a protected 1-(methylthio)isobenzofuran resulted in the preparation of a precursor of a tricyclic hetero-aromatic compound, namely the known biologically active compound, 2-azaanthraquinone.

ABBREVIATIONS:

Ar .... aromatic

18-Crown-6 .... 1,4,7,10,13,16-hexaoxacyclooctadecane,

COSY 2D-NMR .... correlation spectroscopy, 2-dimensional NMR, ^{1}H by ^{1}H

DNA .... deoxyribonucleic acid

ESR................................. electron-spin resonance

Et .... ethyl, $-CH_2CH_3$

HOMO .... highest occupied molecular orbital

Lawesson's Reagent .... 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-

2,4-disulfide, $(p\text{-}CH_3OC_6H_4\text{-}PS_2)_2$

LDA .... lithium diisopropylamide, $[(CH_3)_2CH]_2NLi$

LUMO .... lowest unoccupied molecular orbital

MTT................................ 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-

2H-tetrazolium bromide,

NBS .... N-bromosuccinimide,

NMR .... nuclear magnetic resonance

nOe .... nuclear Overhauser effect

Nu .... nucleophile

Ph.................................... phenyl, $-C_6H_5$

RNA................................ ribonucleic acid

TBAF.............................. tetrabutylammonium fluoride, $[CH_3(CH_2)_3]_4N^+F^-$

TFA .... trifluoroacetic acid, CF_3COOH

Tol .... tolyl, $-C_6H_4CH_3$

X .... halogen

INTRODUCTION

This thesis concerns the design and synthesis of molecules which may be relevant to the treatment of cancer. This introduction will start with a description of cancer and some of the conventional methods for the treatment of this disease and their shortcomings. New approaches of selectively targeting drugs at tumours will be described. This will lead on to a proposed design of a class of potential anti-cancer drugs and a description of how such molecules can be synthesised using Diels-Alder cycloaddition chemistry.

1.1. Cancer -A description of the disease and its treatment

1.1.1. The disease [1]

The replication of mammalian cells is normally carefully regulated by growth control mechanisms. Cancer arises when mutations in the cell's DNA cause this mechanism to break down, allowing the cell to replicate uncontrollably. Eventually a mass of cells, called a *tumour*, can form. Most tumours provide little risk to the host animal because they are localised and contained. These are termed *benign*. However, tumours can be *malignant*. These tumours begin to invade surrounding tissue, eventually allowing cells to separate from the tumour and spread around the body via the blood stream and lymphatic system. These cells can set up other sites of cancerous growth. This spread of tumour cells and establishment of sites of secondary growth is called *metastasis* and is often fatal.

1.1.2. Conventional treatment of cancer [2,3]

There are several accepted methods for the treatment of cancer. If a tumour is benign or yet to metastasise, it can be removed by surgical methods; that is, physically cutting out the cancerous growth. Another possible treatment is radiotherapy which involves bombarding the tumour with a focused beam of ionising radiation. The resulting formation of radicals is *cytotoxic* to the cells because of the eventual formation of lethal double strand breaks in the DNA. Both of these forms of treatment involve a localised attack on the tumour. The other major area of the treatment of cancer is the use of *chemotherapy*. Often these approaches are combined in the battle against this disease.

Chemotherapy is the treatment of a disease by a chemical substance that has detrimental effects to the component that causes the disease. Cancer chemotherapy involves the application of a chemical or mixture of chemicals to tumour cells, with the aim of killing, or aiding the body in killing those cells. These chemicals, or drugs are usually administered orally or intravenously and therefore much of the victim is potentially exposed to the drug. These drugs therefore require several properties to be successful:

- they must be amenable to successful transport around the body, that is, from the point of administration through to the tumour or cancerous cells

- the active form of the drug must be stable to degradation by the body's metabolic processes

- the drug must be of maximal toxicity to the tumour cells but of minimal toxicity to normal cells, in other words, the side effects of the drug must be inconsequential or, preferably, non-existent.

The last point of selective toxicity to cancerous cells is a major challenge in cancer chemotherapy. The only major characteristic that differentiates most tumour

cells from normal cells is that they divide more often due to the loss of growth control mechanisms. Rapid cell replication is therefore a main target in cancer chemotherapeutic methods. Drugs that act by targeting this characteristic are termed *anti-proliferatives*.

Sugar-Phosphate backbone

Base pairs

B-DNA strand
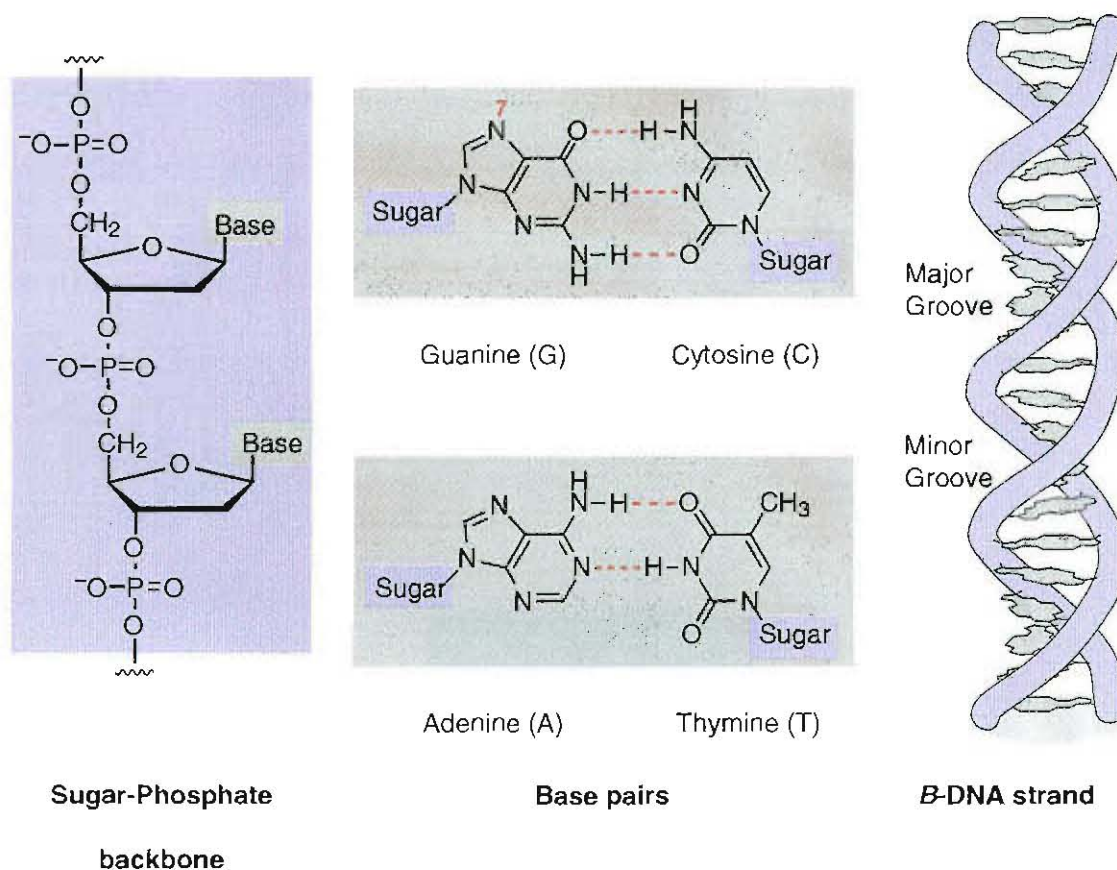
Figure 1.1: The structure of deoxyribonucleic acid (DNA)

(with major and minor grooves shown for one observed conformation, *B*-DNA)

Most of these drugs target processes involving deoxyribonucleic acid (DNA), the information carrying molecule in the cell. The structure of DNA is outlined in **Figure 1.1**. Disruption in the biochemistry of this molecule is often sufficient to induce death of the cell. Most cancer chemotherapeutic regimes today involve a combination of drugs. This combination usually contains an antimetabolite[4] and an agent that directly interacts with the DNA[5]. The mode of action of these drugs is as follows:

- *Antimetabolites:*

These inhibit enzymes involved in the synthesis of DNA. They are therefore only lethal to cells which are in the DNA synthesis stage of their cycle, resulting in a fairly selective toxicity to rapidly dividing cells.

- *Agents that interact directly with DNA:*

Molecules that interact directly with DNA and affect its biochemistry may be cytotoxic.

Some anti-tumour agents act by covalently binding to the DNA. The N-7 position of guanine (indicated in **Figure 1.1**) is one of the more nucleophilic sites and hence is susceptible to electrophilic attack. However, the reactivity of sites on DNA is strongly controlled by steric, electronic and hydrogen-bonding interactions between the drug and the DNA.

Some anti-tumour agents do not covalently bind with DNA but are shaped such that they fit snugly into a specific part of the DNA molecule. They are held in place by various interactions such as van der Waals' forces and hydrogen-bonding. Some are thought to bind in the major or minor grooves of the double helix (see **Figure 1.1**). Others are planar, aromatic molecules that slot (*intercalate*) between the base pairs of the DNA, distorting the helical backbone (see Section 1.1.7).

If any of the above modifications are drastic enough, the biochemistry of the DNA is disrupted, leading to cell death.

1.1.3.   Limitations of conventional cancer chemotherapy

A limitation of anti-proliferatives is that they do not target one of the basic changes which define cancer cells, but a later consequence of these changes. Thus they are not 'cancer-cell specific' so much as 'dividing-cell specific'. Rapid cell replication is also a characteristic of the normal cells in bone marrow, the gut, skin epithelium, and mucosa of the mouth. Therefore, common side-effects involved in cancer

chemotherapy are nausea, vomiting, irritation to skin and mucous membranes, and the long term delayed side-effect of bone marrow depression. In some forms of cancer (those associated with solid tumours) there is a population of slow growing cells which are not affected by conventional chemotherapeutic drugs. In these cases, treatment is not curative and regrowth can occur.

Regrowth can also occur if a certain population of the mutant tumour cells is unaffected by a particular drug. After the rest of the tumour is killed off, this resistant strain of cells remains to replicate. The resulting secondary tumour will be immune to treatment by this drug. Hence a combination of drugs and treatments is often used. If this combination involves treatments with different mechanisms of action then there is an increased chance of killing all the cells and preventing the development of drug resistance.

1.1.4. Hypoxic cells as a target for chemotherapy [6,7,8]

Some of the above short-comings of conventional cancer chemotherapy could be overcome if a property that is more selectively characteristic of tumours is found. This should limit drug side-effects and increase drug toxicity. One such characteristic found in solid tumours is chronic *hypoxia*. The majority of human cancers are slow growing solid tumours[9]. For a tumour to reach a diameter of a few millimetres, it must induce development of additional blood supply. This cancer cell vasculature is not efficient and cells in the tumour can end up a long way from the nearest blood vessel. In the body, the oxygen needed by the cells for respiration is carried over long distances in the blood stream complexed with haemoglobin. However, the oxygen has to get from the blood stream to the cells by diffusion. It is consumed by living cells so its concentration drops as a function of distance from the nearest blood vessel. At about 150 μm (about ten cells) from a vessel, the oxygen concentration falls essentially to zero. Cells further than this from a blood vessel suffer oxygen deprivation and are termed *hypoxic*. Such hypoxia has been termed *diffusion limited* and often surrounds a

zone of *necrosis* where the oxygen starved cells have died (**Figure 1.2**). Another transient type of hypoxia has been observed in animal tumours caused by the spasmodic closing off of a blood vessel, possibly because of the high fluid pressure in a tumour. This is termed *perfusion hypoxia*. A combination of these factors means that solid tumours contain a variable but significant proportion of cells in the hypoxic state.
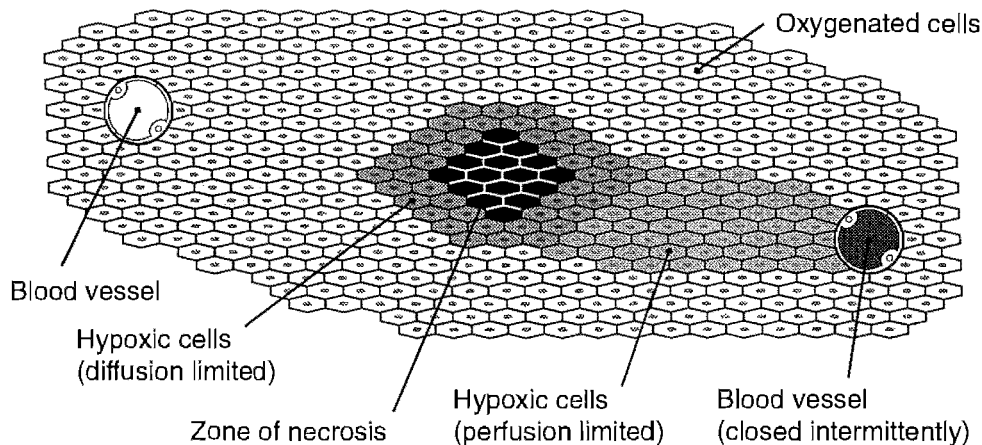
Figure 1.2: Hypoxic cells and the zone of necrosis in a solid tumour

Hypoxic cells only replicate occasionally because they are starved of nutrients and hence they are not susceptible to conventional anti-proliferative drugs. In fact, once the rapidly replicating cells around the hypoxic cells have been killed off, the hypoxic cell's blood supply is replenished, allowing them to start rapidly proliferating. These cells have already been exposed to the drug and so may have mutated to resist that treatment. Hypoxic cells also have an increased resistance to the lethal effects of ionising radiation. The DNA radical, produced by the encounter of this radiation with normal cells, reacts with molecular oxygen to form the peroxy-DNA radical, DNA-OO•. This relatively stable radical can ultimately result in lethal DNA strand breaks. In hypoxic cells, this stabilisation cannot occur. Species such as thiols, acting as free radical scavengers, chemically restore the DNA radical to undamaged DNA, making hypoxic cells more resistant to radiotherapy. A few drugs, such as the radical generator bleomycin rely on a reaction with oxygen to cause DNA breaks and so this

treatment is also of lower toxicity to hypoxic cells. The very distance of these cells from blood vessels makes it difficult to get a reasonable concentration of the drug into these cells; especially if it has a high binding efficiency and so gets 'caught up' on the way.

Hypoxic cells therefore present a major challenge in cancer chemotherapy and much effort has been put into overcoming these problems; for example drugs called *sensitisers* can be administered before radiotherapy; these take place of the oxygen in the formation of stabilised DNA radicals. The hypoxic property of solid tumours can however be used to the advantage of cancer chemotherapy. Here is a unique and consistent characteristic of a portion of tumour cells that differentiates them from normal cells. This property can be used by drugs to selectively target tumours, potentially decreasing side-effects and allowing an increase in toxicity.

1.1.5. Drugs for the treatment of hypoxic cells [6,8,10]

One way to target hypoxic cells selectively is by the use of *prodrug* methodology. A prodrug is a precursor of a drug molecule that is of lower toxicity and may have improved delivery properties when compared to the active drug. The prodrug must undergo spontaneous or enzymatic transformation within the body near, or at, the required site in order to release the active drug. As prodrugs are converted to an active form at the targeted site, the prodrug has the added advantage that it is always moving down a concentration gradient. The requirements of a hypoxic cell prodrug are as follows:

- *Effective distribution:*

  The prodrug form must be of low toxicity, or preferably non-toxic, and stable to normal metabolic processes. It must be able to efficiently migrate from the blood vessel to the isolated hypoxic cells. Solid tumours, because of their poor blood supply, have difficulty in removing cell waste products and

the mutant cells can often be 'leaky'. Both of these factors result in a large amount of extracellular fluid in tumours[11]. Nutrients and drugs often rely on pressure gradients to allow them to migrate out of the blood vessel. In tumours this gradient can be close to non-existent meaning that the only mode of distribution available is diffusion. Efficient diffusion is favoured for 'small' molecules with low binding affinities.

• *Activation in hypoxic conditions:*

The prodrug must undergo rapid and selective metabolism to the active drug in hypoxic environments. Hypoxic cells, being oxygen deficient, encourage irreversible reductive chemistry. Bioreductive activation is possible in all cells, but is readily reversed by molecular oxygen in well-oxygenated cells. Therefore a prodrug would ideally be activated by a reduction process with a reversible component, preferably occurring with a reduction potential in the 'window' of -450 to -300 mV. A reduction potential less than this means that cellular reduction is not sufficiently rapid; a potential greater than this means that the scavenging reaction by molecular oxygen in normal cells is too slow allowing premature activation. An example of a type of *bioreductive trigger* that fulfils these criteria is nitro-aromatics. The reduction of the nitro group to an amine involves several steps (**Figure 1.3**). The first step can be reversed by molecular oxygen. The change from an electron-withdrawing nitro group (Hammett σ value = +0.78) to an electron-donating amine group (σ = -0.66) can be utilised in the activation of a prodrug.
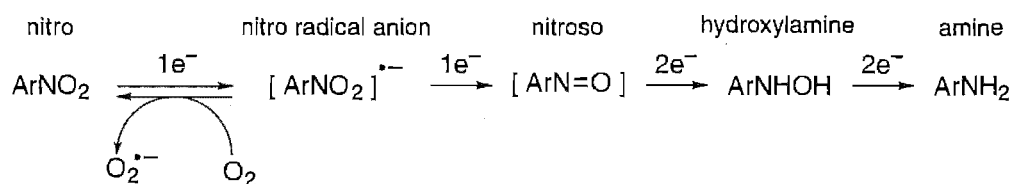
Figure 1.3: The reduction of nitro-aromatics

• *Suitable properties of the active form:*

The non-replicating property of hypoxic cells requires that the active form of the drug must be toxic to all phases of a cell's cycle. A high differential between the toxicity of the prodrug and the active form allows the use of larger doses. Another preferable property of the active form is a long half life and the ability to diffuse to neighbouring cells. The high interstitial pressure of tumours compared to normal cells is thought to encourage the flow of the activated drug from the hypoxic core to the surrounding oxygenated tumour cells. This allows the drug to be toxic to a greater portion of the tumour than just the hypoxic region.

1.1.6.   Some examples of hypoxia-selective cytotoxins [6,12]

A few selected examples of hypoxia-selective cytotoxins that fulfil some of the above criteria are as follows:

• *Mitomycin C*[13]

Mitomycin C, **1a**, is one of a series of hypoxia-selective cytotoxins that is activated by the reduction of a quinone functionality. A nitrogen in mitomycin C (coloured red in **Figure 1.4**) is amide-like in that its lone pair is conjugated, through the quinone double bond, to a carbonyl group. Reduction converts this nitrogen to a nucleophilic tertiary amine which promotes the E1 elimination of methanol. This causes activation of the drug, as shown, encouraging DNA alkylation. Subsequent reaction with the DNA produces lethal cross-links. Mitomycin C is the only drug currently used clinically that is thought to be a hypoxia-selective cytotoxin. Porfiromycin, **1b**, has superior selectivity *in vitro* and *in vivo* and is now in clinical trial.

Quinones are reduced in a two step process, firstly to the semiquinone radical anion and then to the hydroquinone. The first step is reversible which was a postulated requirement for successful prodrugs. However, many
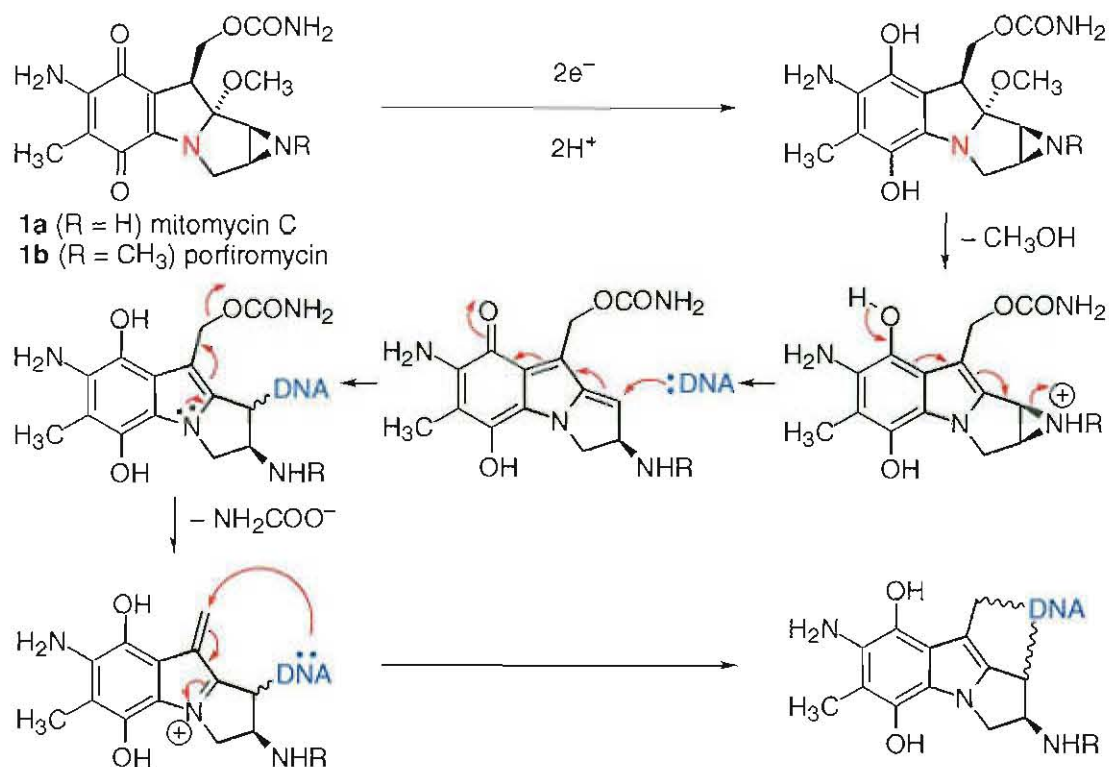
Figure 1.4: The bioreductive activation of mitomycin C, **1a**, and porfiromycin, **1b**, and subsequent cross-linking of DNA

quinones, including mitomycin C, are good substrates for enzymes that are capable of reducing them in a single two-electron transfer, a step that is not reversible by molecular oxygen. Thus, mitomycin C can be toxic to oxygenated cells.

- *Nitrobenzyl quaternary mustards*[14,15]

SN 25246, **2**, is one of a series of nitrobenzyl quaternary mustards designed specifically to be hypoxia-selective cytotoxins. In hypoxic cells the nitro radical anion produced (see **Figure 1.3**) fragments to generate a benzyl radical and a nitrogen mustard, **3** (the clinical drug mechlorethamine) (**Figure 1.5**). *In vitro*, **2** is several thousand-fold more toxic towards hypoxic tumour cells than normal oxygenated ones. Mechlorethamine shows activity against non-replicating cells and shows results suggesting that it is capable of
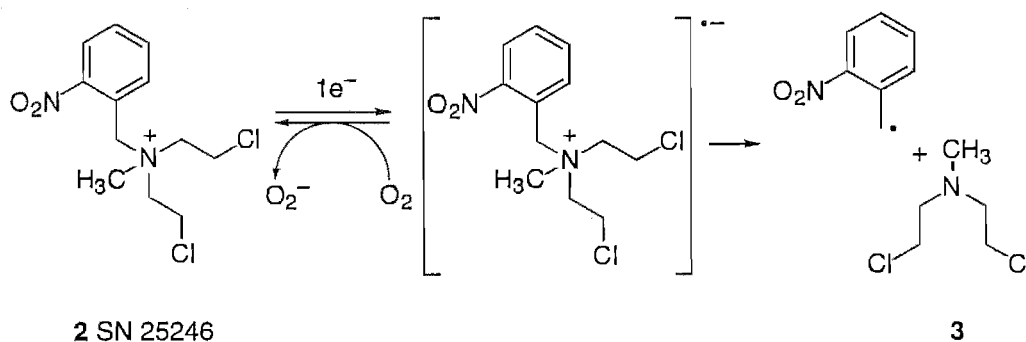
2 SN 25246   **3**

Figure 1.5: The bioreductive activation of SN 25246

migrating from the hypoxic site of formation and killing surrounding oxygenated cells. The reduction potential of SN 25246 is -350 mV. These results fulfil the criteria laid down in Section 1.1.5 for hypoxia-selective cytotoxins.

- *Nitracrine*[16]

The 1-nitroacridine derivative nitracrine, **4** (R = NO$_2$), has been used clinically as an anti-cancer drug and has been shown to have potent hypoxia-selective cytotoxicity against tumour cells in culture.
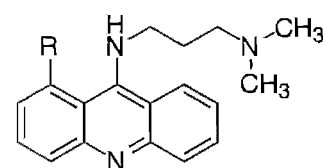
4 nitracrine

Toxicity maybe caused by reduction to give **4** (R = NHOH or NH$_2$) which could subsequently *intercalate* DNA and form cross-links via nucleophilic attack of the hydroxylamine or amine group. However, **4** did not show significant activity against hypoxic cells *in vivo*, probably because of its rapid metabolism and relatively high level of DNA-binding which would be expected to markedly slow its rate of diffusion into areas of hypoxia.

1.1.7. Intercalating agents [12,17,18,19]

An intercalating agent (such as nitracrine, 4) is a non-covalently binding drug which reversibly slots (*intercalates*) in between the base pairs of helical DNA. The intercalating components of such compounds are planar and usually polycyclic and aromatic in nature. For optimal intercalation, this planar component must possess a minimum surface area of 28 $Å^2$, that is, three or four appropriately arranged 5- to 6-membered rings. Intercalation of the chromophore forces the base pairs apart vertically, from an original distance of 3.4 Å to a separation of 7–8 Å. This causes puckering and unwinding of the sugar-phosphate backbone to accommodate the intercalating agent. This is shown diagrammatically for *B*-DNA in **Figure 1.6**. The principal driving forces for intercalation of an intercalating agent are:

- favourable van der Waals forces between the base pairs and the intercalated molecule

- a decrease in hydrophobic interactions by the removal of an aromatic molecule from an aqueous medium

- favourable electrostatic and hydrogen bonding interactions between substituents on the intercalating agent and the DNA.

Many intercalating agents show potent anti-tumour activity and hence have been used in cancer chemotherapy. It was thought that the presence of the intercalating agent directly interfered with DNA or RNA synthesis; however, the anti-tumour activity of an intercalating agent does not necessarily correspond to its DNA-binding strength. Ethidium bromide, for example, is a strong intercalator, but is only weakly cytotoxic. Also, the concentration of intercalating drug required to block replication and transcription of DNA is many times greater than that necessary for clinical activity. It is now known that many intercalating agents cause cell death by stimulating strand breaks in the DNA. It is thought, and in some cases has been shown, that this is due to
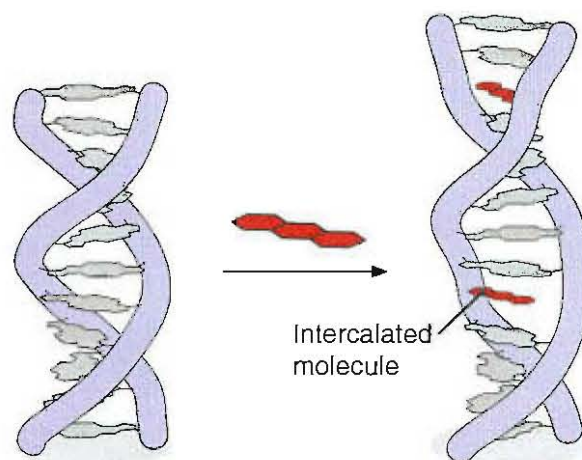
Figure 1.6: Intercalation of a planar aromatic molecule into *B*-DNA causing unwinding and

elongation of the helix

an interaction involving topoisomerase II. Topoisomerase II is a homodimeric protein that helps regulate the torsional strain and controls the conformation of super-coiled DNA. This enzyme cuts both strands of the DNA, with a four base pair stagger between the nicks, and then allows another DNA duplex to pass through the break before resealing the strands, changing the amount of super-coiling in the DNA. This is shown diagrammatically in **Figure 1.7**.

Many potent intercalating agents form a stable ternary complex with the topoisomerase II and the DNA. The intercalating agent seems to stabilise the cleaved
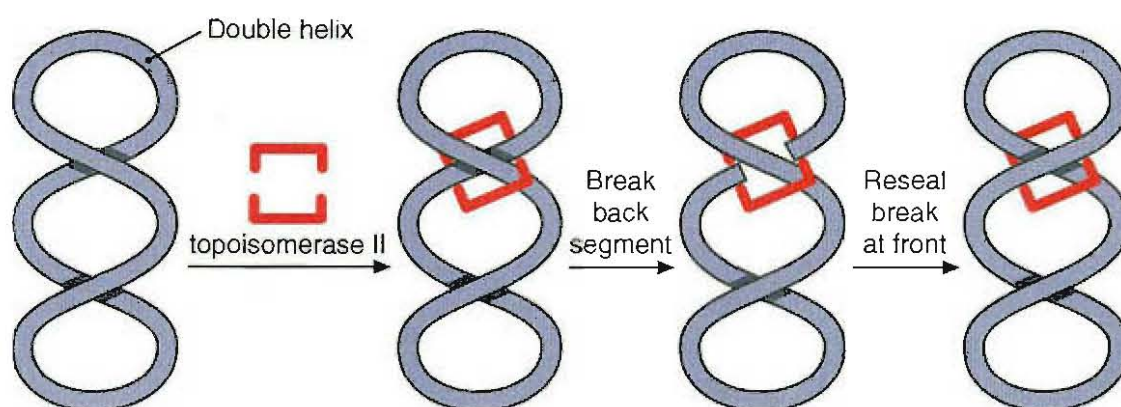
Figure 1.7: The breaking and resealing of a segment of circular DNA by topoisomerase II

DNA complex and hence interferes with the resealing step, keeping the DNA in the broken state. Topoisomerase II is in greater concentrations in replicating cells explaining the selective toxicity of intercalating agents towards tumour cells. Cytotoxic intercalating agents therefore seem to require two components, a planar aromatic system and a substituent that can affect the biochemistry of DNA.

1.1.8. Some examples of intercalating agents[17]

A few selective examples of intercalating agents are as follows:

- *Amsacrine*[16]

CH3O — NHSO2CH3

HN

H2N — N — NH2
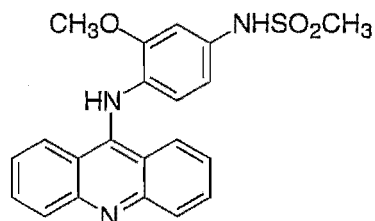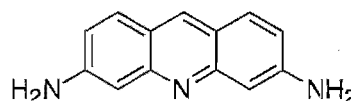
5 amsacrine   **6** proflavine

The phenomenon of intercalation was first used to describe the interaction of proflavine, **6**, with DNA. The first acridine to reach clinical use was amsacrine, **5**. It is postulated that the acridine ring system intercalates the DNA with the anilino substituent lying at an angle to the acridine plane in the minor groove (see **Figure 1.1**) with the $NHSO_2CH_3$ substituent pointing tangentially away from the helix in a position to interact with a second macromolecule. The mode of action was found to involve an enzyme mediated cleavage of DNA and subsequently the topoisomerase II-intercalator-DNA complex was first described for amsacrine. Amsacrine however has poor drug distribution properties and so analogues are being investigated with improved aqueous solubility and lower pK_a.

• *Ellipticine*[20]
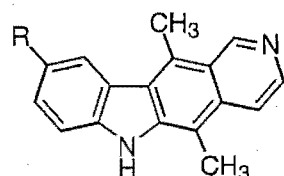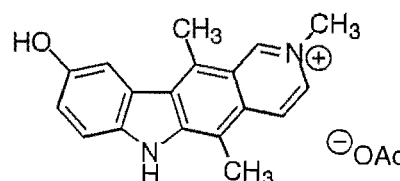
7 ellipticine (R = H)   **8** NMHE

Ellipticine, **7** (R = H), and 9-methoxyellipticine, **7** (R = OCH_3), were originally isolated from the leaves of *Ochrosia elliptica* Labill. A derivative, **7** (R = OH), was found to have improved anti-cancer activity, but low solubility was still a problem which led to the preparation of NMHE (or elliptinium), **8**. Ellipticine and NMHE are strong intercalating DNA-binders and cause double DNA strand breaks as expected for a DNA-topoisomerase II targeting agent. Ellipticine and its derivatives have not been used widely as anti-tumour drugs because of toxicity problems. They decrease heart rate and can cause irreversible respiratory depression.

• *Anthracyclines*[21]
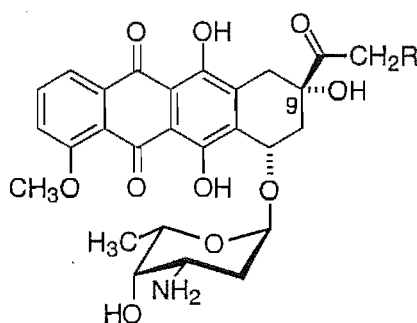
9 (R = H) daunorubicin (Daunomycin)

10 (R = OH) doxorubicin (Adriamycin)

Daunorubicin, **9**, and doxorubicin, **10**, were the first anthracycline drugs introduced into clinical use for the treatment of malignant tumours. Their success caused the production of several hundred analogues. At present, doxorubicin has the widest spectrum of anti-tumour activity of all such anti-cancer drugs and is the most used anti-tumour drug worldwide. These intercalating agents differ from others in that they intercalate 'head first'. A crystal structure of the daunorubicin/d(CGTACG)$_2$ complex shows the planar

chromophore to be at right angles to the base pair's axis rather than parallel to it, with the amino-sugar lying in the minor groove. Strong evidence exists that both daunorubicin and doxorubicin can generate protein-associated strand breaks in DNA that correlate well with the anti-tumour activity of the drugs, suggesting that these intercalating agents are able to form a complex with topoisomerase II and DNA. Doxorubicin is also an effective iron-chelator and the resulting complex is very reactive in catalysing free radical reactions, notably the conversion of hydrogen peroxide to the lethal hydroxyl radical. This property, as well as providing an alternative mode of action against some forms of human cancer cells, also causes the cardiac toxicity observed for doxorubicin.

• *Actinomycin D*[18,22]
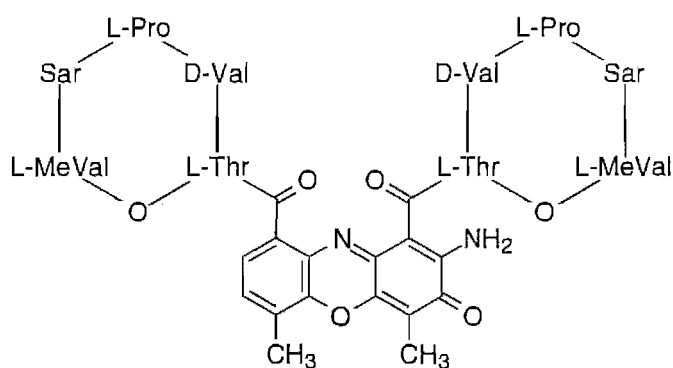
11 actinomycin D

An X-ray crystal structure of a deoxyguanosine/actinomycin D complex confirms that the planar chromophore of actinomycin D, **11**, intercalates DNA, with the two identical cyclo-peptides binding along the minor groove, holding the chromophore in place. The resulting slow dissociation of actinomycin D is thought to account for its superior biological activity. The ability of actinomycin D to intercalate DNA and to inhibit DNA-dependent RNA synthesis is widely accepted as its major mode of action. Actinomycin D has been used clinically, but only against a narrow range of tumours and toxicity is a problem.

1.2. The proposed design of an anti-cancer prodrug

The aim of this research is to investigate the preparation of a prodrug precursor of an intercalating agent. Placing a bridge over one of the aromatic rings of a potential intercalating agent will block intercalation, not only because of the steric interactions of the bridge, but also because of the resulting loss of planarity. This prodrug will be selectively activated in the vicinity of the cancer site to release, upon bridge removal, the planar intercalating drug (shown diagrammatically in **Figure 1.8**). A bioreductive trigger attached to the bridged area could encourage bridge opening upon its activation, allowing selective production of a cytotoxic intercalating agent in hypoxic cells. The active form of the hypoxia-selective cytotoxin, nitracrine (Section 1.1.6), is an intercalating agent, but the prodrug form still has the planar chromophore moiety intact. This inactivated form therefore still has reasonable DNA-binding affinity, affecting the delivery of the drug. A 'small', bridged molecule should have low or no DNA-binding properties allowing ease of diffusion throughout the body, including into the isolated hypoxic core of a solid tumour.
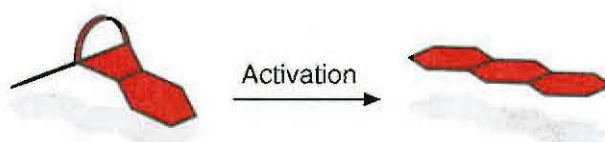
Figure 1.8: The activation of the proposed bridged prodrug to form an intercalating agent

Because the intercalating form is only produced at the target site, there is no need to limit its DNA-binding affinity. This drug, with high DNA-binding affinity, may therefore have very limited diffusion properties, preventing ejection of the compound from the hypoxic cell; a common defence mechanism of tumour cells. Interactions between the DNA and substituents on the intercalating component will disrupt the DNA function, leading to cell death. The cytotoxicity of these substituents can be comparatively low, allowing the prodrug to be of low toxicity. However, upon activation of the prodrug and intercalation of the active form, the cytotoxic substituent

will be held in prolonged proximity to the DNA, encouraging interaction with the strand or associated molecules. This cytotoxic interaction, upon intercalation, effectively becomes an intramolecular reaction rather than a less favoured bimolecular one.

The cytotoxic substituent could, for example, be a mild alkylating agent. Upon intercalation, subsequent pseudo-intramolecular alkylation will covalently bind the active drug to the DNA strand, resulting in superior biological activity, comparable to the strong DNA-binding actinomycin D (Section 1.1.8). Another possible substituent could interact with one of the many enzymes associated with DNA, such as topoisomerase II (Section 1.1.7). This disruption in the biochemistry of DNA could lead to cell death.

To summarise: the postulated prodrug will be selectively activated at the centre of a solid tumour by bioreductively triggered bridge opening. The high DNA-binding affinity of the resulting intercalating agent will target it to the hypoxic cell's DNA and selectively hold the DNA destructive component for a prolonged time in the immediate vicinity of this cell's DNA, where it can undergo its cytotoxic mode of action. This high selectivity should keep any side effects to a minimum. This prodrug will be a small, metabolically stable, organic molecule that will therefore be able to diffuse through solid tumours to the isolated hypoxic core. This envisaged prodrug could be used in conjunction with conventional anti-proliferative drugs to totally eradicate solid tumours.

1.3.   The strategy for the synthesis of a prodrug precursor of an intercalating agent

A direct method for the preparation of bridged polycyclic systems is a Diels-Alder reaction involving a cyclic diene. The following sections will introduce the

Diels-Alder reaction and outline the requirements of the resulting bridged adducts. The bridge must be chosen such that stable adducts can be easily synthesised. It must also be possible to attach an appropriate trigger to the prodrug form which, upon activation, causes cleavage of the bridge and formation of a planar polycyclic system.

1.3.1.   The Diels-Alder reaction[23]

The Diels-Alder reaction is a $[_\pi 4_s + _\pi 2_s]$ cycloaddition. It is a very useful reaction in synthetic organic chemistry and its discovery earned Otto Diels and Kurt Alder the 1950 Nobel Prize in Chemistry.

diene   dienophile   cyclohexene ring

a: A concerted, synchronous mechanism

b: A two-step mechanism
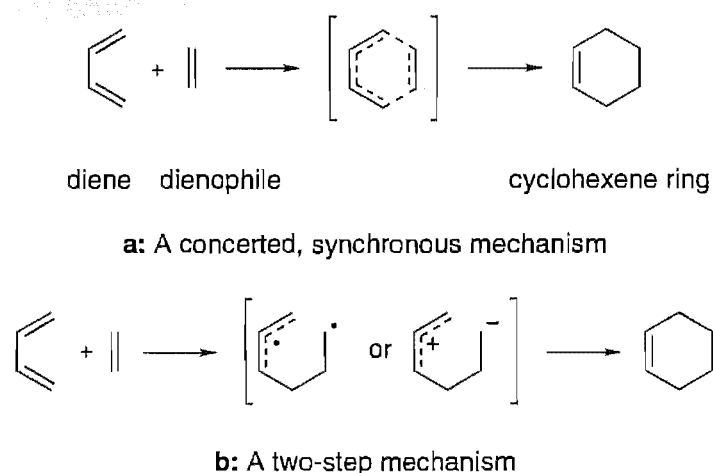
Figure 1.9: The Diels-Alder reaction

Most Diels-Alder reactions can be described by a bimolecular, one-step mechanism. Support for this concerted mechanism can be seen in the *syn* stereospecificity of the reaction and in the rate acceleration that occurs when pressure is applied to the reaction; the latter observation resulting from the large negative (-30 to -40 cm^3 mol^{-1})[24] volume of activation required to achieve the transition state. In the case of a *synchronous* mechanism, where the bond-forming and bond-breaking processes occur simultaneously, this transition state can be represented as shown in **Figure 1.9a**. Substituents on the *diene* and *dienophile* can cause the rate of formation of one σ-bond to exceed the second one. The reaction mechanism is now termed *non-*

synchronous, the extreme case being a two-step mechanism involving a biradical or zwitterion intermediate (**Figure 1.9b**).

Normal electron-demand   Inverse electron-demand
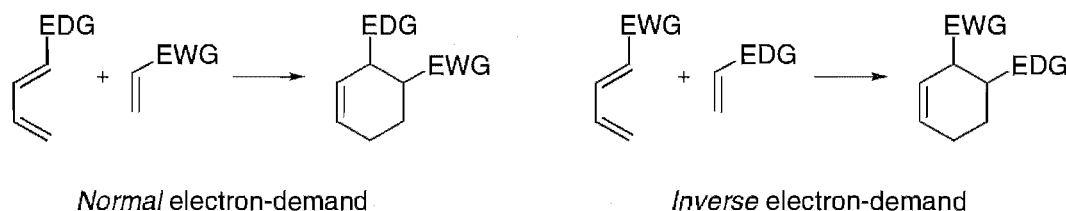
Figure 1.10: The Diels-Alder reaction

(EDG = electron-donating group, EWG = electron-withdrawing group)

For a Diels-Alder reaction to be facile, the reagents require substituents with complementary electronic properties. By convention, a *normal* electron-demand Diels-Alder reaction is characterised by the reaction of an electron-deficient dienophile with an electron-rich diene. This is the most commonly observed situation in efficient Diels-Alder reactions. Consequently, a Diels-Alder reaction with the opposite electronic demands is termed an *inverse* electron-demand reaction (**Figure 1.10**). The reaction is reversible and the reverse process is termed a *retro*-Diels-Alder reaction. Frontier molecular orbital theory describes the Diels-Alder reaction as the interaction of the highest occupied molecular orbital (HOMO) of one component with the lowest unoccupied molecular orbital (LUMO) of the other one. The dominating orbital interaction is between the two orbitals closest in energy. Electron-donating (alkyl, alkoxy or amine) groups raise the energy of molecular orbitals; whereas electron-withdrawing (nitrile, nitro, carbonyl or sulfone) groups lower their energy. Therefore the dominating orbital interaction in a *normal* electron-demand reaction is the diene HOMO with the dienophile LUMO (**Figure 1.11**).

1.3.2. The bridge of the adduct

The bridge of the polycyclic compound could realistically be either one or two atoms long. Some possible two-membered bridges include $-CH_2-CH_2-$, $-CO-O-$, $-CO-NH-$ and $-N=N-$. Dinitrogen bridges undergo facile elimination, whereas alkyl-
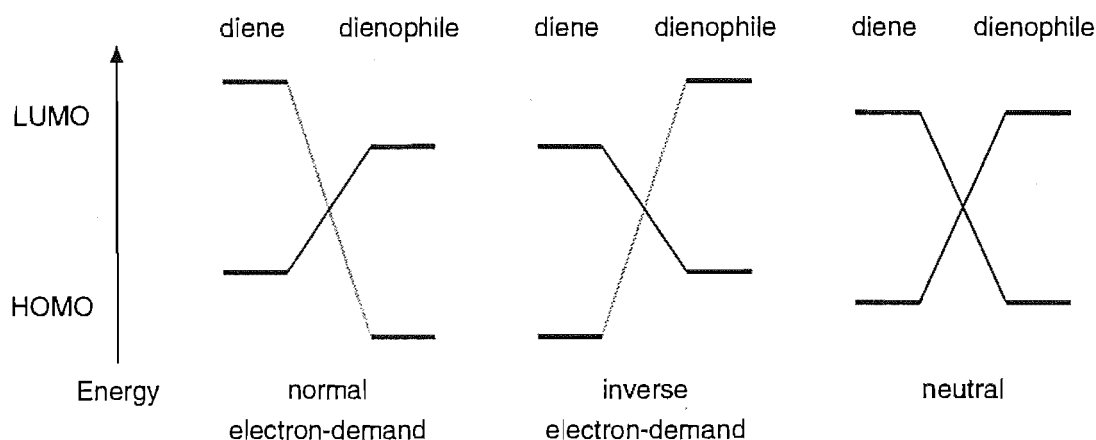
Figure 1.11: HOMO-LUMO arrangements for various types of Diels-Alder reactions

or amide- bridges are relatively stable, making subsequent drug activation difficult. Some possible one-membered bridges include $-CH_2-$, $-O-$, and $-NH-$. Again, the alkyl- and amine- bridges would probably be too stable for our purposes. Carboxy- and oxygen- bridged compounds are isolable and the Diels-Alder chemistry of the associated cyclic dienes is well documented. These bridges also have the potential to be selectively cleaved upon activation of the prodrug and so will form the basis of the work in this thesis.

1.3.3. Attachment of the trigger

The trigger requires an appropriate linkage for ease of attachment and successful action. Attachment of the trigger to the prodrug using a sulfide unit has several advantages. A thiolate anion is a good nucleophile that can be alkylated with a wide variety of substituents, allowing attachment of a great range of triggers with synthetic ease. Thiols are reasonable leaving groups allowing cleavage of the trigger-sulfur bond upon activation. Delocalisation of the sulfur electrons can then initiate cleavage of the prodrug's bridge. There are several well-documented benzyl-based protecting groups of thiols that can be cleaved by reduction[25] (for example, see **Figure 1.12**). The activation of such a prodrug in hypoxic conditions would be similar to the activation of hypoxia-selective cytotoxin, **2** (**Figure 1.5**).

A sulfide linkage has also been reported for a cancer prodrug that is activated by an enzyme attached to the tumour cell by way of an antibody-enzyme conjugate[26]. The antibody selectively binds to an antigen on the tumour cell surface and the attached enzyme metabolises the prodrug in direct vicinity of the tumour cell, releasing the thiol substituted active drug (**Figure 1.13**).
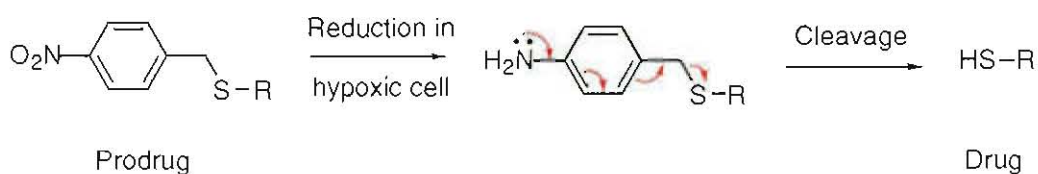
Figure 1.12: An example of selective cleavage of a trigger-sulfur bond in the reducing conditions of a hypoxic cell to produce a thiol substituted drug
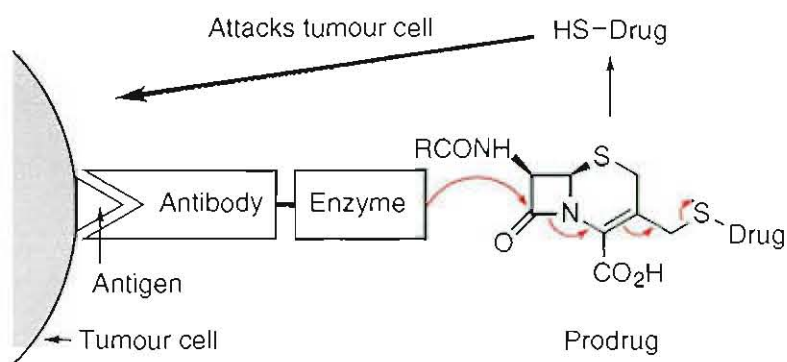
Figure 1.13: An example of antibody-directed enzymatic cleavage of a trigger-sulfur bond in the vicinity of a tumour cell to produce a thiol substituted drug

1.4.   Synthetic work in this thesis

1.4.1.   Carboxy-bridge

Carboxy-bridged compounds can be prepared by the reaction of pyranones with alkenes. Diels-Alder reactions of this type have been known to give stable bridged adducts[24]. However, the reactions of alkynes with pyranones give highly strained, and
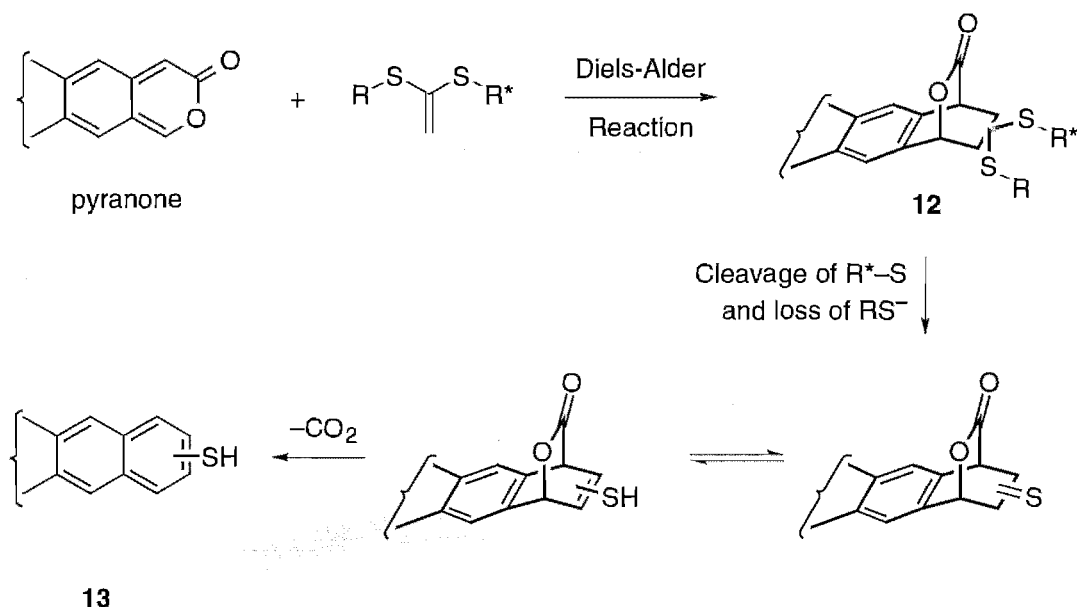
Figure 1.14: The preparation of a carboxy-bridged polycyclic compound and the subsequent transformation to a planar, aromatic compound

hence unstable, bridged cyclohexadienes. These adducts spontaneously lose carbon dioxide to give the aromatic product. This, therefore, is a way of triggering the transformation of a non-planar, polycyclic compound to a planar aromatic one. If a thiol protecting group (R*) is cleaved from a Diels-Alder adduct such as **12** (**Figure 1.14**) then subsequent loss of a thiolate anion followed by tautomerisation will produce a carboxy-bridged cyclohexadiene which will spontaneously aromatise to give **13**.

The adduct, **12**, can be prepared from the Diels-Alder reaction of a pyranone with an appropriately substituted dienophile (**Figure 1.14**). *Chapter 2* of this thesis describes an investigation into the preparation of such adducts by the reaction of a model dienophile, 1,1-bis(methylthio)ethene, with various pyranones. *Chapter 3* deals with the thermally induced decarboxylation of two of the adducts prepared in *Chapter 2* and an unusual rearrangement observed during this decomposition. *Chapter 4* describes an attempt to improve the reactivity of the dienophile by replacing one of the sulfides with a sulfonyl group. The reaction of this new dienophile with various pyranones is reported.

1.4.2. Oxygen-bridge

Oxygen-bridged polycyclic compounds can be prepared from Diels-Alder reactions involving the well-known isobenzofuran diene system[27]. These dienes have been used in the synthesis of several polycyclic aromatic compounds[28], such as a derivative of daunorubicin (Section 1.1.8)[29]. The oxygen-bridge in the initial Diels-Alder adduct is cleaved to reveal an aromatic ring. This provides another strategy for the preparation of prodrugs of intercalating agents. If a thiol protecting group (R*) is cleaved from adducts such as **14** or **16** (**Figure 1.15**) then this should induce bridge cleavage (and in the case of **14**, elimination of water) to give the planar aromatics, **15** and **17** respectively.
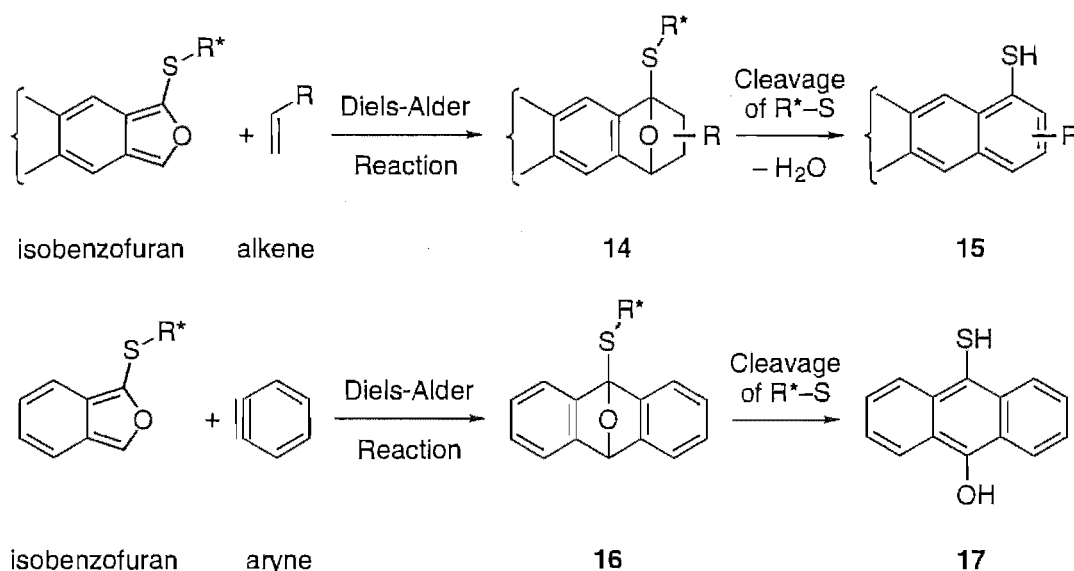
Figure 1.15: Two possible preparations of oxygen-bridged polycyclic compounds and the subsequent transformation to planar, aromatic compounds

The preparation of **14** and **16** involves the Diels-Alder reactions of isobenzofurans with alkenes and arynes respectively (**Figure 1.15**). *Chapter 5* of this thesis describes the preparation of models of **14** by the reaction of 1-(methylthio)isobenzofurans with the sulfonyl substituted dienophile (mentioned in Section 1.4.1). *Chapter 6* describes the reaction of these same dienes with arynes with

the aim of isolating adducts comparable to **16**. The formation of planar compounds from these adducts is also investigated.

1.5.   Conclusion

Cancer accounts for about 20% of deaths in Western countries[15]. Despite substantial research, there is still much to be learned about the successful treatment of the disease. The major difficulty facing cancer chemotherapy is the similarity of cancerous cells to normal cells. The structure and suggested mode of action of some conventional anti-proliferative drugs have been described. A majority of human cancers are solid tumours with hypoxic cores. The development of drug resistance and the side effects observed for the above drugs have lead to the investigation of hypoxia-selective cytotoxins. The aim of this project is to investigate the preparation of bridged polycyclic compounds with the impetus of preparing prodrugs of intercalating agents. These prodrugs could be activated by hypoxic conditions or by antibody-directed enzyme catalysis. This could provide a method for the selective delivery of a DNA damaging component to the desired target, namely the DNA in tumour cells.

This thesis describes the synthesis of such compounds which involves the Diels-Alder reactions of pyranones and isobenzofurans with various dienophiles. The inclusion of an appropriately positioned sulfide moiety is required for the later addition of a trigger functionality. The ability of these bridged adducts to form planar aromatic compounds, a characteristic of intercalating agents, is also investigated.

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1,1-BIS(METHYLTHIO)ETHENE AS A DIENOPHILE

2.1. Introduction

There have been only a few, specialised reports of bis(alkylthio)ethenes acting as dienophiles in Diels-Alder reactions[1,2]. Bis(alkylthio)ethenes, with conjugated substituents, have however occasionally been used as successful dienes[1,3]. 1,1-Bis(methylthio)ethene, **19**, could be considered to be a moderately electron-rich dienophile and therefore it was proposed that it could participate in *inverse* electron-demand Diels-Alder reactions. The few reports of **19** participating in [4+2] cycloaddition reactions involve hetero-atom dienes as shown in **Figure 2.1**.
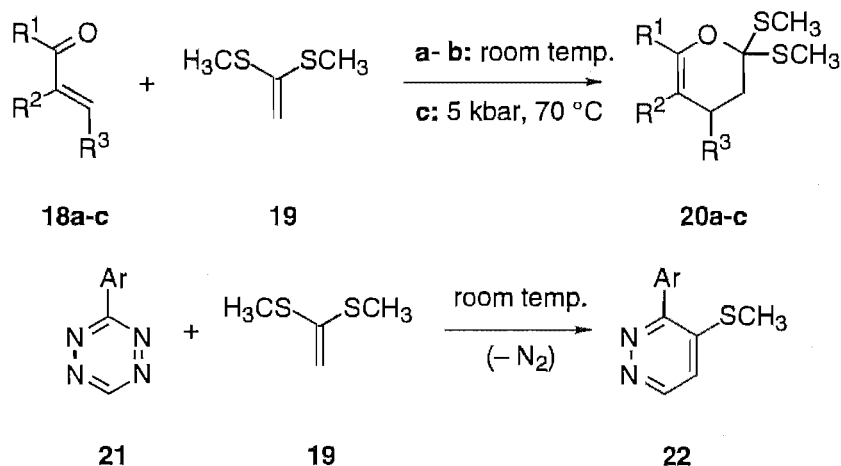
Figure 2.1: The reaction of 1,1-bis(methylthio)ethene with hetero-atom dienes

a: $R^1 = H$ $R^2 = CHO$ $R^3 = $ 2-thienyl;

b: $R^1 = H$ $R^2 = CHO$ $R^3 = $ 4-ClC$_6$H$_4$;

c: $R^1 = CH_3$ $R^2 = SPh$ $R^3 = $ (CH$_2$)$_3$CO$_2$CH$_3$

The reaction of **19** with **18a** and **b** occurred at room temperature to give **20a** and **b** in 84% and 67% yield respectively[4,5]. The reaction of **19** with **18c** was carried out at 5 kbar pressure and gave **20c** in 72% yield[6]. The diene, **21**, was reacted with various dienophiles; **19** was the least reactive example given. The Diels-Alder reaction, followed by extrusion of nitrogen, gave exclusively the *ortho* aromatic product, **22**[7].

We are unaware of any reports of Diels-Alder reactions between simple 1,1-bis(alkylthio)ethenes and all-carbon dienes. The dienes of interest in this work are pyran-2-ones (**23**, see **Figure 2.2**), a class of all-carbon dienes. Because of their partial aromatic character, pyranones undergo Diels-Alder reactions less easily than most cyclic conjugated dienes. Nevertheless, many successful cycloadditions have been reported[8,9]. Pyranones can participate in *normal* or *inverse* electron-demand Diels-Alder reactions providing that the electronic properties of their substituents are complementary to those of the dienophile.

The possible products from a cycloaddition between a pyranone and 1,1-bis(methylthio)ethene, **19**, are outlined in **Figure 2.2**. Two regioisomeric adducts are possible, **A** and **B**. Isolation of these adducts may be complicated by subsequent decomposition. The adducts could extrude carbon dioxide to give the corresponding, unstable dihydrobenzene. This retro-Diels-Alder will be encouraged by the gain in entropy obtained by the production of a gas. It is expected that the dihydrobenzene formed would immediately eliminate methanethiol to give the corresponding stable aromatic compounds (**C** or **D**). It is possible that the elimination of methanethiol could occur first, resulting in the formation of a bridged diene. This product is equivalent to the adduct expected from the reaction of an alkyne with a pyranone. There have been no reported isolations of such adducts[8]. Therefore the bridged diene would be expected to spontaneously lose carbon dioxide to give a substituted benzene.

A study was initiated to ascertain whether 1,1-bis(methylthio)ethene reacts with pyranones. The products from successful reactions were examined to see if the
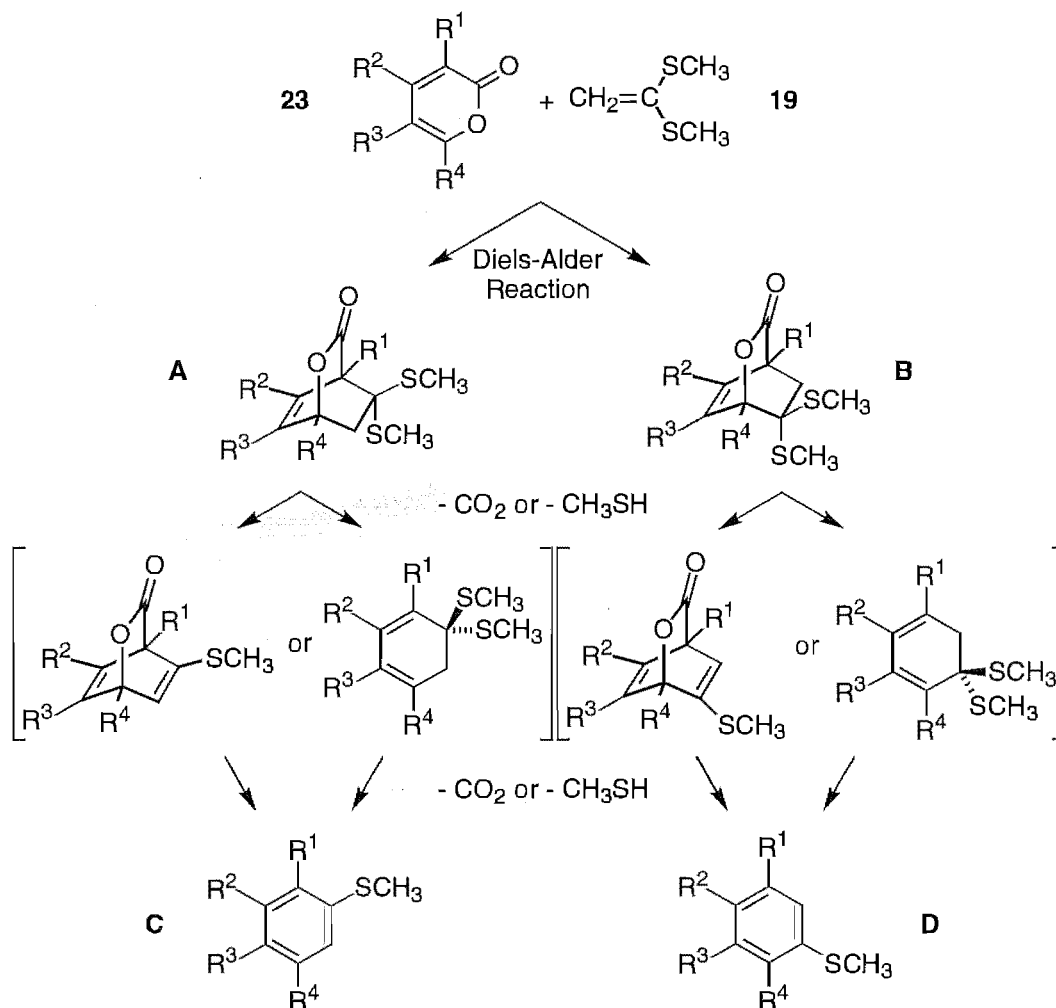
Figure 2.2: The Diels-Alder reaction between a pyran-2-one and 1,1-bis(methylthio)ethene

resulting Diels-Alder adducts were stable enough to be isolated, or whether they spontaneously eliminated methanethiol or carbon dioxide. The bridged products **A** or **B** are of interest in this research because of their potential use as prodrugs for cancer chemotherapy.

This chapter starts with the preparation of the dienophile, **19**. It then describes the preparation of simple monocyclic pyranones through to hetero-polycyclic examples. Each preparation is followed by a discussion of the Diels-Alder reaction of the diene with **19** and the products observed.

2.2.   The preparation of 1,1-bis(methylthio)ethene

$$CH_3I \xrightarrow[\text{3) NH}_4\text{OH}]{\substack{\text{1) Mg/ether} \\ \text{2) CS}_2}} CH_3-C\overset{S}{\underset{S^- NH_4^+}{\diagup}} \xrightarrow{\text{4) (CH}_3\text{O)}_2\text{SO}_2} CH_3-C\overset{S}{\underset{SCH_3}{\diagup}} \xrightarrow[\text{6) CH}_3\text{I}]{\text{5) LDA}} CH_2=C\overset{SCH_3}{\underset{SCH_3}{\diagup}}$$

24   **19**
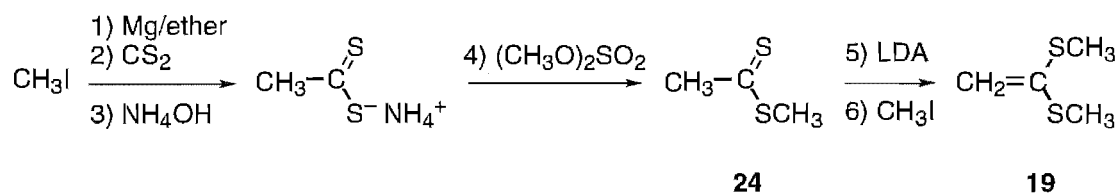
Figure 2.3: The preparation of 1,1-bis(methylthio)ethene

There are many methods for the synthesis of 1,1-bis(alkylthio)alkenes[1,10]. The method chosen for the preparation of 1,1-bis(methylthio)ethene, **19**, was the methylation of methyl dithioacetate, **24** (**Figure 2.3**). This has the advantage that one of the sulfide linkages is formed by an alkylation in the last step allowing a late introduction of a possible functionalised trigger. Methylmagnesium iodide, prepared in the usual way from iodomethane, was reacted with carbon disulfide, which, after the addition of aqueous ammonia, gave the dithioacetate salt[11]. This salt was methylated with dimethyl sulfate to give **24**. This is a low yielding reaction, but the availability and low cost of the reagents make it the most convenient method. (A more efficient method utilises methylmagnesium chloride[12], but this reagent is technically more difficult to prepare.) **24** was deprotonated with lithium diisopropylamide and alkylated with iodomethane to give the required alkene, **19**.

2.3.   The reaction of 1,1-bis(methylthio)ethene with two simple pyran-2-ones

The preparations of two simple pyran-2-ones are shown in **Figure 2.4**. Methyl coumalate, **25**, was prepared via dimerisation of malic acid in fuming sulfuric acid[13]. The 4,6-dimethyl substituted analogue, **26**, was similarly prepared from methyl acetoacetate[14].
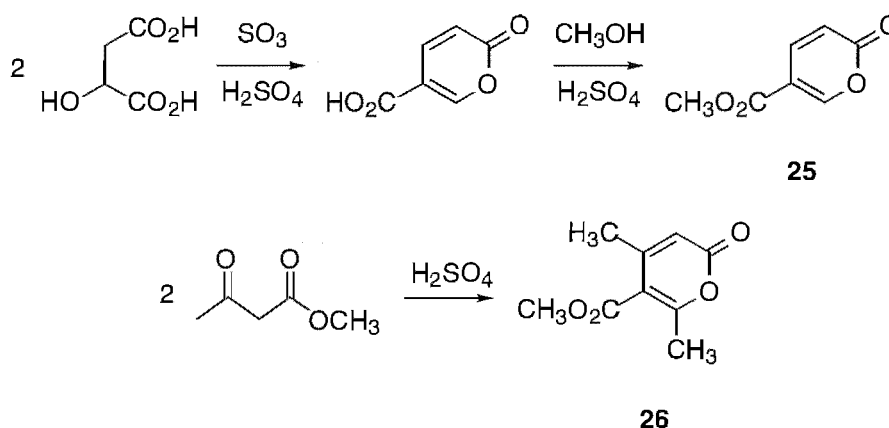
Figure 2.4: Preparation of methyl coumalate and methyl 4,6-dimethylcoumalate

The Diels-Alder reaction of **25** with 1,1-bis(methoxy)ethene, **27**, has been reported by Behringer and Heckmaier[15]. The only product they observed was **29a** (**Figure 2.5**). The other regioisomer was not observed; neither was the loss of methanol nor carbon dioxide. When I carried out the corresponding reaction of the sulfur analogue (**19** with **25**), the only product observed was the bridged adduct, **28**. The regiochemistry was confirmed by comparing the coupling constants in the proton NMR spectrum with those reported for a similar compound, **29b** (R = Et)[15] (**Figure 2.6**). This data is also consistent with the generalisations made by Afarinkia *et al.*[8] for the Diels-

25   19 X = S, 27 X = O   28 X = S, 29a X = O (R = CH₃)

26   19 X = S, 27 X = O   30 X = O   31 X = S, 32 X = O
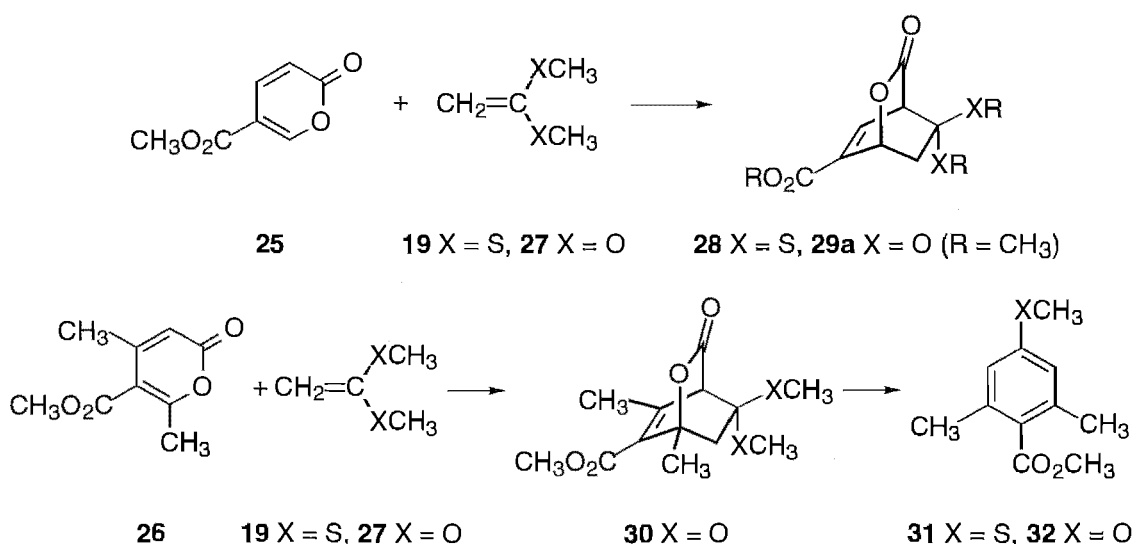
Figure 2.5: The reaction of 1,1-bis(methylthio)ethene, **19**, and 1,1-bis(methoxy)ethene, **27**, with methyl coumalates
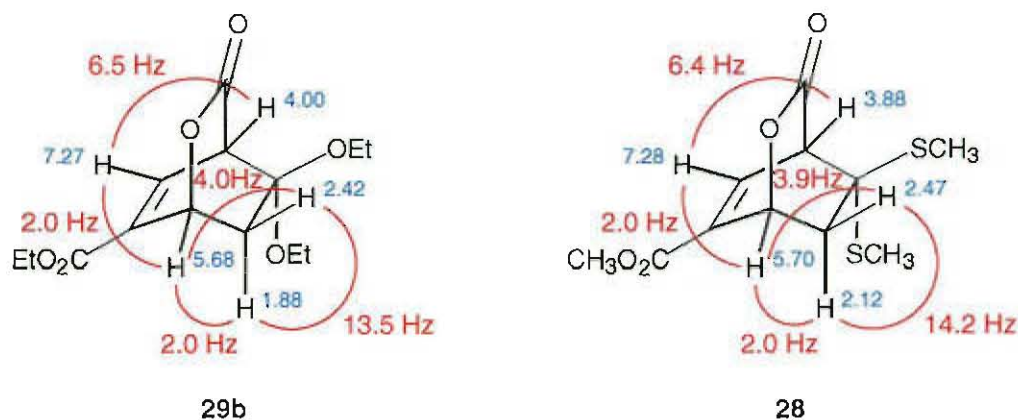
Figure 2.6: A comparison of the proton NMR chemical shifts (ppm) and coupling constants (Hz) observed for **29b**[15] and for **28**

Alder adducts of pyran-2-ones and pyrid-2-ones. *Exo* protons appear down-field of *endo* ones and have a larger coupling constant with the bridge-head hydrogen. Regiochemistry was also confirmed by the analysis of subsequent thermal decomposition products (described in Section 3.2).

The reaction of **27** with the dimethyl substituted coumalate, **26**, was examined by Jung and Hagenah[14]. They found that the reaction gave mostly the aromatic product, **32**, in refluxing benzene, but that the conditions could be optimised to favour the isolation of the bridged adduct, **30**. These conditions are outlined in **Table 2.1**.

Temperature	30	32
82 °C	10%	63%
78 °C	62%	–
< 75 °C	very slow reaction	

Table 2.1

The reaction of **26** with the sulfur analogue, **19**, in refluxing toluene gave only the substituted benzene, **31**. The bridged adduct was not isolated and no attempt was made to optimise the conditions to favour the isolation of this adduct.

In both cases the dimethyl substituted coumalate is less reactive than the non-substituted analogue. This difference could be due to steric demands and/or the slight electron-donating ability of the methyl groups; the latter causing **26** to be a less suitable diene for *inverse* electron-demand Diels-Alder reactions. This property would also make **30** more reactive towards a *normal* electron-demand retro-Diels-Alder reaction. That is, the loss of carbon dioxide, triggering aromatisation, as observed. This observation suggests that the loss of carbon dioxide is the rate determining step towards aromatisation rather than the loss of methanol/methanethiol. Jung and Hagenah attribute the low thermal stability of **30** to the alkyl substituent at the bridge-head position.

Behringer *et al.*[15] and Jung *et al.*[14] suggest that the above examples are not concerted cycloadditions, but rather a nucleophilic addition of the electron-rich dienophile to the pyran-2-one to give a zwitterionic intermediate **33**, followed by carbon-carbon bond formation to produce the observed bridged product. They support this notion by isolating **35** (in 92% yield) from the reaction of **25** with the very electron-rich dienophile, **34**.

33   **34**   **35**

Ar = p-$(CH_3)_2NC_6H_4$–
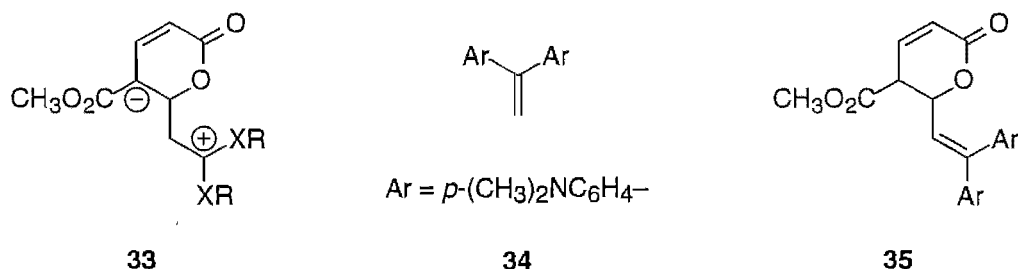
A similar dienophile to **19**, ethylthioethene, has since been reported by Markó and Evans to be unreactive with 3-carbomethoxypyran-2-one under thermal conditions[16]. Lewis acids are often used to catalyse Diels-Alder reactions[17] but it was stated that this type of catalyst, *eg.* $TiCl_4$, $AlCl_3$, $ZnBr_2$, SnX_4, $BF_3.Et_2O$ and Et_2AlCl proved unsuitable for the reaction of alkyl vinyl ethers with electron-deficient pyran-2-ones[16]. They led to either polymerisation of the enol ether or decarboxylation of the adducts formed. It has been found that reactions of alkoxy and alkylthio ethenes with

3-carbomethoxypyran-2-one can occur at room temperature when catalysed by lanthanide complexes to give the Diels-Alder adduct in excellent yields[16,18,19].

2.4. The reaction of 1,1-bis(methylthio)ethene with a benzopyranone

The above Diels-Alder chemistry must be applied to the synthesis of bridged polycyclic compounds if it is to be of use in the preparation of potential prodrugs (as described in Section 1.2). Removal of the bridge must give a planar, aromatic compound. As a step towards this type of system, the reaction of 1,1-bis(methylthio)ethene with a benzopyranone was examined.
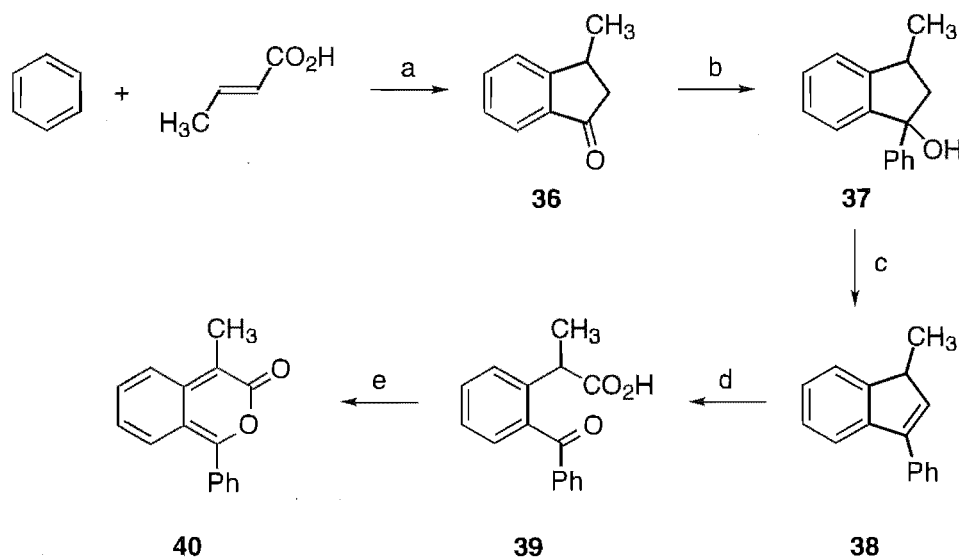
Figure 2.7: Preparation of 4-methyl-1-phenyl-3*H*-2-benzopyran-3-one, **40**

Reagents and conditions: (a) AlCl₃, benzene, reflux; (b) (i) PhMgBr, ether, reflux, (ii) 10% H₂SO₄; (c) P₂O₅, toluene, reflux; (d) NaIO₄, RuCl₃, CCl₄, CH₃CN, water, room temperature; (e) conc. H₂SO₄, gentle warming

The benzopyranone, **40**, was prepared as previously described[20] (**Figure 2.7**). The indanone, **36**, was prepared by a Friedel-Crafts acylation involving crotonic acid and benzene followed by ring closure. Reaction of **36** with the phenylmagnesium

bromide gave **37**. Dehydration by phosphorus pentoxide gave the indene, **38**, which underwent a ruthenium tetraoxide catalysed oxidative cleavage[21] to give the keto acid, **39**. (The catalyst was prepared *in situ* from ruthenium trichloride and sodium metaperiodate.) Treatment of **39** with concentrated sulfuric acid gave the bright red benzopyranone, **40**. This diene is relatively unstable due to the loss of benzenoid aromaticity and so was immediately trapped with the dienophile of interest. Verification of diene formation involved the reaction of the dehydration product with maleic anhydride[20] (**Figure 2.8**); the disappearance of the red colour serving as an indicator of the end-point of the reaction. The single adduct isolated, **41**, is expected to be the *endo* stereoisomer due to stabilising secondary orbital interactions in the transition state[22].

40   **41**
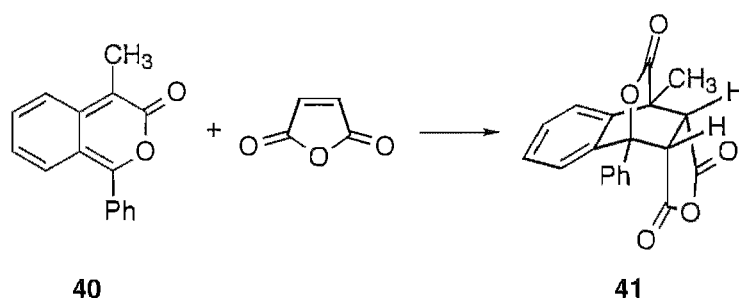
Figure 2.8: The reaction of maleic anhydride with 4-methyl-1-phenylbenzopyran-3-one

Benzopyranones are very reactive dienes because of the gain of benzenoid aromaticity when they undergo Diels-Alder reactions. The reaction of **19** and **27** with 4-methyl-1-phenylbenzopyran-3-one, **40**, has been reported to occur at similar rates in refluxing toluene[20]. Both dienophiles gave a single bridged adduct, **42** and **43**

40   **19 X = S, 27 X = O**   **42 X = S, 43 X = O**
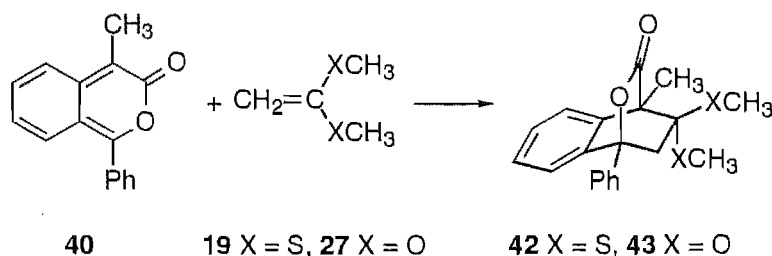
Figure 2.9: The reaction of 1,1-bis(methylthio)ethene and 1,1-bis(methoxy)ethene with

4-methyl-1-phenylbenzopyran-3-one

respectively (**Figure 2.9**). The cycloaddition of **40** and **19** was also carried out under high pressure conditions, 19 kbar at 20 °C. The activation of this reaction by increasing the pressure strongly suggests a concerted mechanism. The sole product from these reactions was incompletely characterised and so the thermal cycloaddition of **40** with **19** was repeated. A X-ray crystal structure of this regioisomer was obtained, confirming its identity (**Figure 2.10**). The regiochemistry of this reaction is the same as that observed for the coumalate case.
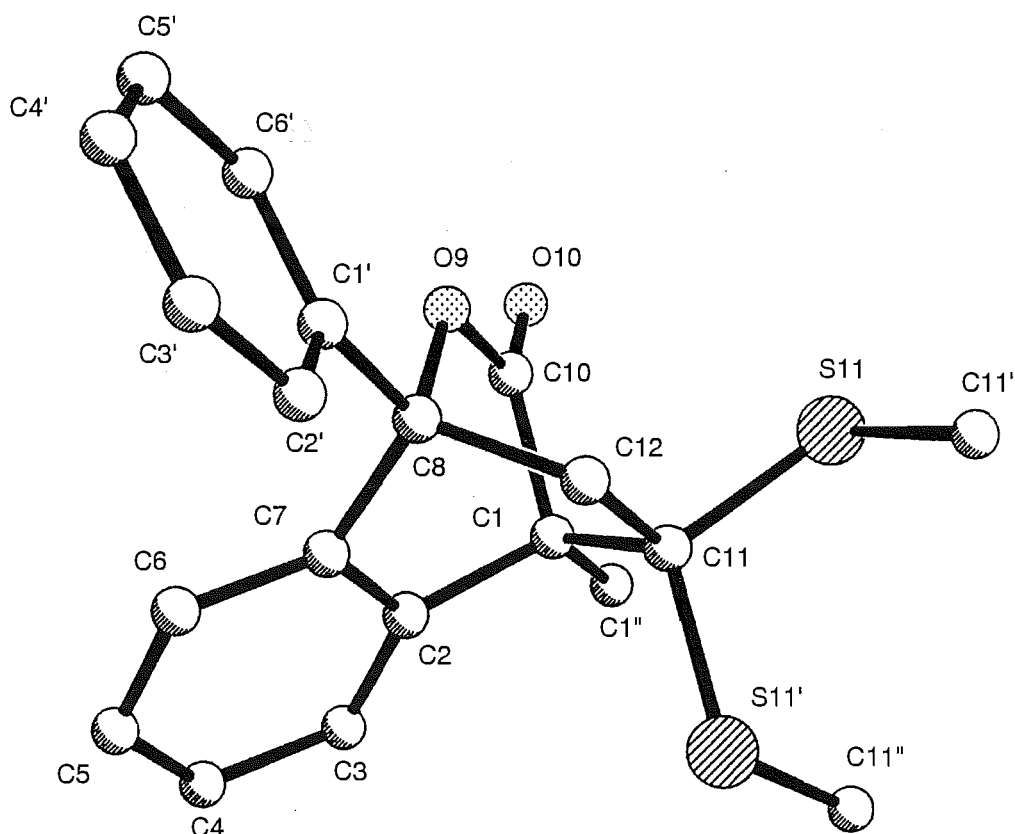
Figure 2.10: The X-ray crystal structure of **42**

(For tables of structural data see Appendix A.1)

40   **44a**   **44b**
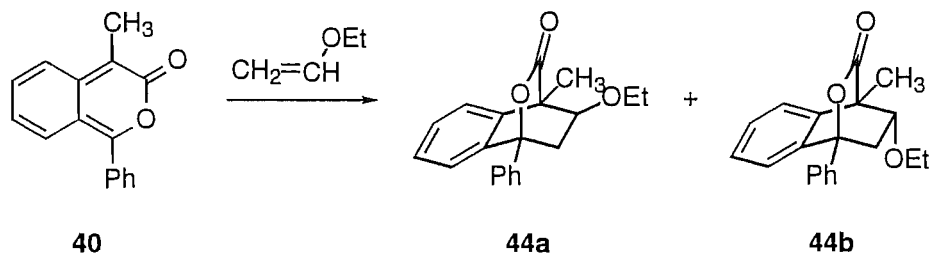
Figure 2.11: The reaction of ethyl vinyl ether with 4-methyl-1-phenylbenzopyran-3-one

The reaction of **40** with ethyl vinyl ether (**Figure 2.11**) gave a pair of stereoisomers in the ratio of 78:22. Formation of the other pair of isomers with the alternate regiochemistry was not observed. The isomers formed were separated by fractional crystallisation. The regio- and stereo- chemistry of the major isomer, **44b**, was determined by X-ray crystallography to be the *endo* isomer (**Figure 2.12**). These crystals had the unusual property of cracking when cooled to low temperatures and so the X-ray data collection was carried out at room temperature. The methyl group of the ethoxy side chain was disordered over two positions, C11A and C11". As described
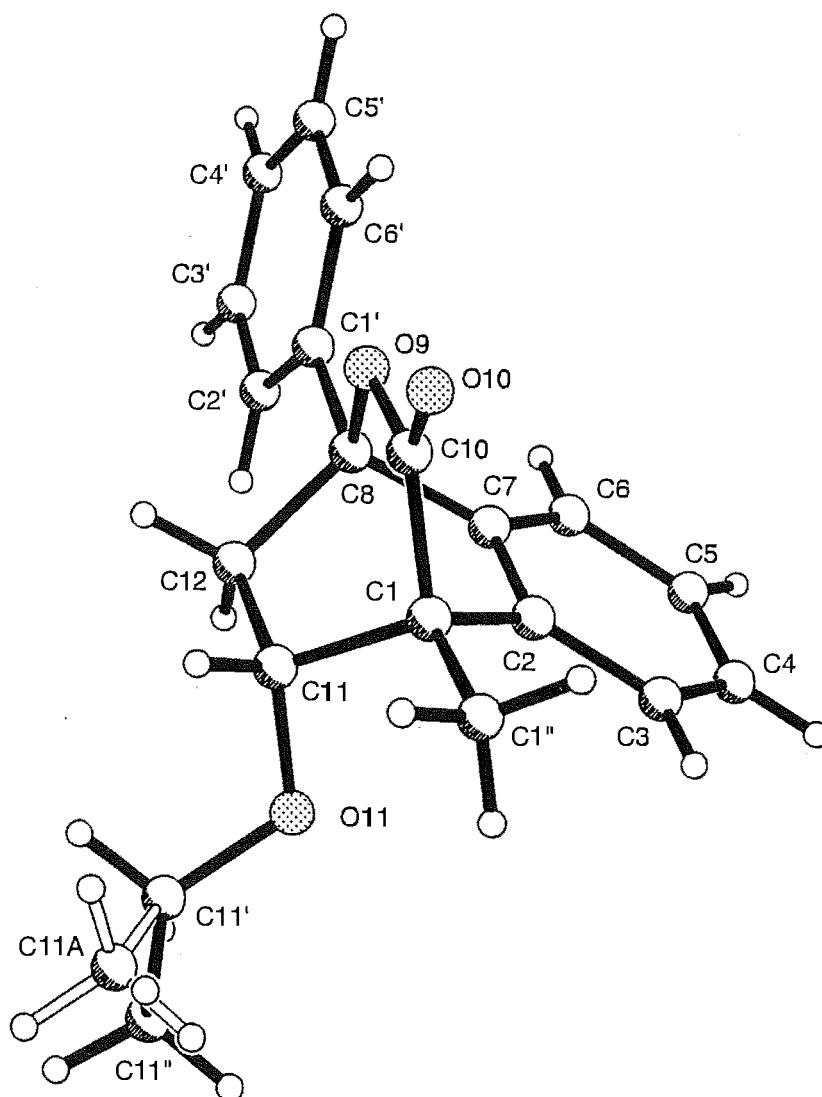
Figure 2.12: The X-ray crystal structure of **44b**

(For tables of structural data see Appendix A.2)

earlier, the predominance of the *endo* isomer is to be expected due to secondary orbital effects. This is also consistent with other examples of Diels-Alder reactions of alkoxy ethenes with pyran-2-ones[8,23].

The high regioselectivity of the reaction of **19** and ethyl vinyl ether with **40** can be attributed to steric and/or electronic factors. The methylthio/ethoxy substituents would probably prefer sterically to be oriented towards the methyl rather than the phenyl substituent. The favourable electronic interactions between these electron-donating substituents and the electron-withdrawing carbonyl of the diene could also influence the regiochemistry.

2.5.   The attempted preparation of pyrano[3,4-*b*]quinol-3-ones

The success of the Diels-Alder reactions involving the benzopyranone led us to extend this work to polycyclic heterocycles. These systems are expected to be more suited as successful prodrugs. The addition of the nitrogen and an extra ring will produce a tricycle which, after drug activation, is similar in structure to some conventional intercalating agents (see Section 1.1.8). The proposed synthesis for pyrano[3,4-*b*]quinol-3-ones, **50**, is outlined in **Figure 2.13**. It is based on a previously described preparation by Gray *et al.* of 2-carboxy-3-quinolineacetic acid (**49a**, Ph = OH)[24]. However, results from the benzopyranone work[20] show that a methyl substituted pyrone is more stable and hence more amenable to synthetic study. The preparation of **50b** was therefore investigated in parallel with a repetition of the known R = H series.

The initial quinoline, **45**, was prepared by a Friëdlander synthesis between 2-aminobenzaldehyde[25] and the appropriate 2-oxocarboxylic acid[26]. The bromination of **45** gave **46**. Gray *et al.* used dibenzoyl peroxide as the radical initiator and achieved a yield of 22%. Lehn *et al.*[27] used a 100 W tungsten light bulb as a radical initiator for

CO_2Et
CO_2Et + $RCH_2CH_2CO_2Et$ —— a, b ——

CHO
NO$_2$ —— c ——

CHO
NH$_2$

O CO$_2$H R —— d ——

45 R / CO$_2$CH$_3$ N

e

46 R / Br N CO$_2$CH$_3$

f

47 R / CN N CO$_2$CH$_3$

g

48 R / CN N O Ph

H$_3$O$^+$ / Δ

49 R / CO$_2$H N O Ph

—H$_2$O

50 R / O N O Ph
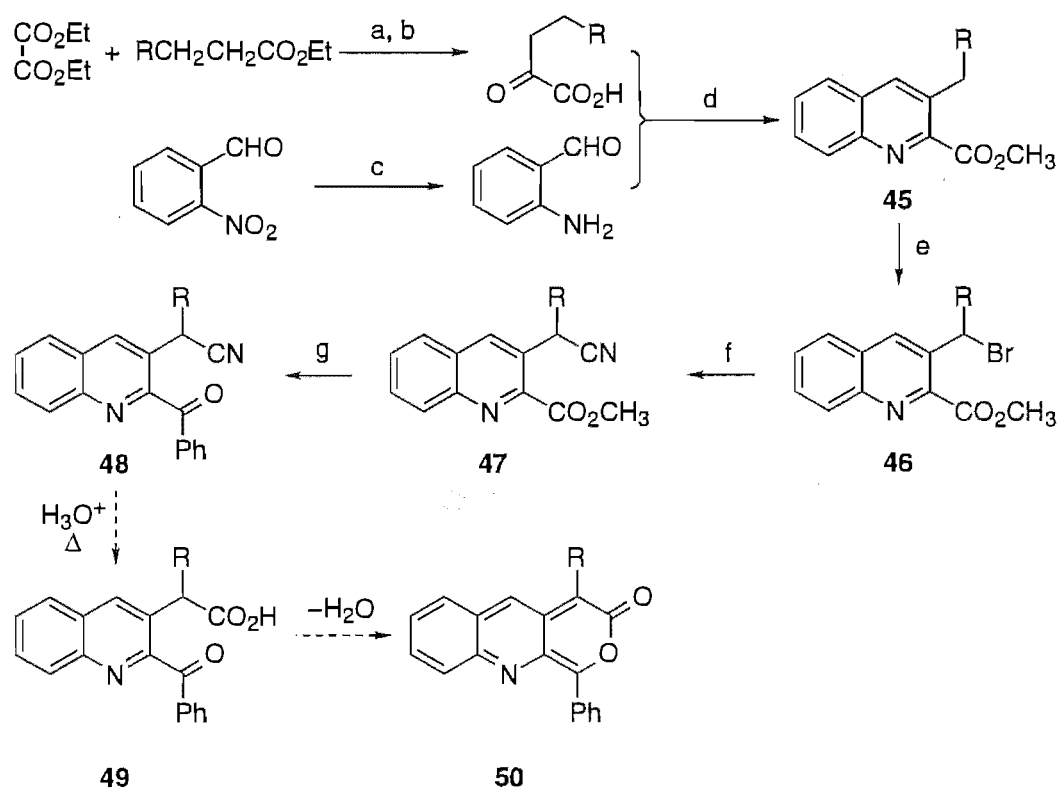
Figure 2.13: The proposed synthesis of pyrano[3,4-*b*]quinol-3-ones (a: R = H; b: R = CH$_3$)

Reagents and conditions: (a) NaOEt, ether, room temperature; (b) 10% H$_2$SO$_4$, reflux; (c) FeSO$_4$.7H$_2$O, H$_2$O, heat, then add NH$_4$OH; (d) NaOCH$_3$, CH$_3$OH, reflux, then conc. H$_2$SO$_4$ added, reflux; (e) *N*-bromosuccinimide, *hv*, CCl$_4$, reflux; (f) R = H: KCN, CH$_3$OH, reflux; R = CH$_3$: KCN, 18-crown-6, CH$_3$CN; (g) PhMgBr

the bromination of a similar heterocycle and thereby avoided poly-bromination which plagued the dibenzoyl peroxide method. The latter method, but using a 200 W bulb, was applied to **45**. A yield of 80% was achieved in the preparation of **46b**.

The cyanide substitution reaction of **46a** proceeded readily using potassium cyanide in refluxing methanol as previously described[24]. When these conditions where applied to the more sterically hindered **46b**, the major product was **51**. The weakly basic conditions have resulted in methoxide ions acting as the nucleophile. The reaction was repeated using acetonitrile as the solvent with a catalytic amount of a macrocyclic

polyether (18-crown-6) present. 18-Crown-6 chelates the cation of potassium cyanide, causing it to dissolve in acetonitrile, resulting in a "naked" cyanide ion that is a potent nucleophile[28]. These reaction conditions were examined at a range of temperatures. Under reflux, intramolecular nucleophilic substitution occurred to give the lactone, **52**, as the major product. At room temperature, the required nitrile, **47b**, was formed. It was found that intramolecular substitution was still competitive if the suggested 0.08 molar equivalents[28] of 18-crown-6 were used. To achieve an acceptable yield of product 0.25 molar equivalents of 18-crown-6 were required.
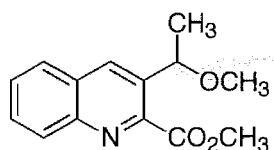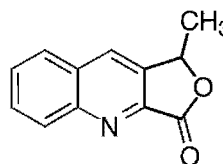
51   **52**

The reaction of the ester functionality of **47** with an aryl Grignard reagent required caution to avoid the formation of the disubstituted tertiary alcohol. One molar equivalent of phenyl magnesium bromide added to **47a** and **b** at low temperatures (-78 °C) gave the required product, **48a** and **b**, without complications in both cases. Hydrolysis of the nitrile substituent involved refluxing **48a** in 6 mol L^{-1} HCl[29]. The product had a proton NMR spectrum consistent with the expected product **49a**. The small amount of product obtained was lost in the attempt to purify it. The R = H series had by this stage served its purpose as a model synthesis and so preparation of **49a** was not investigated any further.

When **48b** was refluxed in 6 mol L^{-1} HCl, the product obtained in over 50% yield was **53**. This benzo[b][1,7]naphthyridine showed moderate activity in the *in vitro* P388 anti-tumour assay, corresponding to an ID_{50} of 3400 ng/mL (see Section A.5). The formation of **53** corresponds to protonation of the carbonyl oxygen followed by internal attack of the nitrile on the resulting electrophilic centre and interception of an intermediate cation by a chloride ion. Dehydration, promoted by the gain in
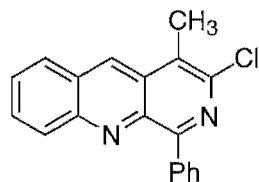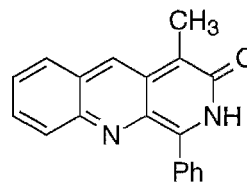
53   **54**

aromaticity, would result in the formation of **53**. To alleviate this problem, the reaction was repeated using an acid with a relatively non-nucleophilic counter-ion. Refluxing 40% sulfuric acid was used. The only product isolated was the lactam, **54**, corresponding to cyclization as described above, but where the cation has been intercepted by an oxygen containing nucleophile. Using refluxing 10% sulfuric acid, a different product was obtained and purified. This product had infra-red, proton and carbon-13 NMR and mass spectra consistent with the desired product, **49b**, with one exception. The mass spectrum contained an extra peak at m/z = 336.1. This corresponds to a molecular formula of $C_{20}H_{20}N_2O_3$ (Compound **49b** has m/z = 305.1 and a molecular formula of $C_{19}H_{15}NO_3$). The 305.1 ion has been shown not to be a 'daughter' of the 336.1 ion. Several unsuccessful attempts were made to obtain crystals of this product suitable for X-ray crystallographic analysis. An attempt was also made to dehydrate the product using the conditions described for the preparation of benzopyranones[20]. If **49b** had been prepared, then the formation of the pyrano[3,4-*b*]quinol-3-one, **50b**, was expected. This should undergo a Diels-Alder reaction with maleic anhydride to give a bridged adduct. This was not observed. Basic catalysed hydrolysis of the nitrile was attempted, without success, and so this route was abandoned.

A further, more direct, synthesis was attempted with the aim of preparing a possible pyrano[3,4-*b*]quinol-3-one precursor, **55** (**Figure 2.14**). This involved the reaction of 2-oxopentane-1,5-dioic acid[30] or its dimethyl ester with 2-aminobenzaldehyde[25]. Both reactions gave a complicated mixture of products that were

examined with proton NMR, UV and mass spectrometry. The required product, **55**, was

not observed in either case. No further attempts were made to prepare pyrano[3,4-

b]quinol-3-ones.

55
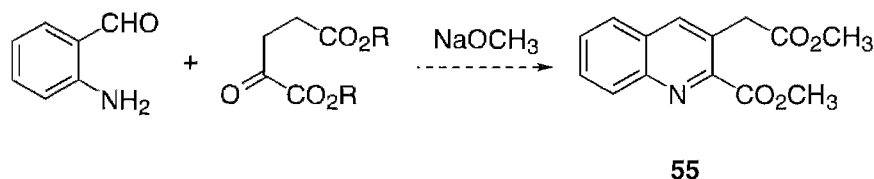
Figure 2.14: The attempted Friedlander synthesis to prepare **55** (R = H or CH$_3$)

2.6.   The reaction of 1,1-bis(methylthio)ethene with pyrano[3,4-*b*]indol-3-ones

Pyrano[3,4-*b*]indol-3-ones were first used as Diels-Alder dienes by Plieninger *et al.* in 1964[31]. It was not until 1985 that they where again used in synthesis, by Moody[32]. However, this class of compounds has now

7
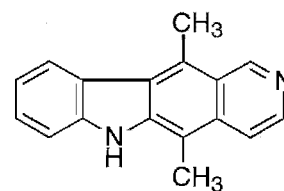
been extensively investigated and their Diels-Alder reactivity reviewed[33]. They have

been reacted with many electron-deficient dienophiles[33], but show little or no reactivity

with electron-rich alkynes[34]. Van Broeck *et al.*[35] report that the reaction of various

electron-rich alkenes with pyrano[3,4-*b*]indol-3-ones required heating at 80-120 °C in a

sealed tube for several days. In this and other reports the bridged Diels-Alder adducts

have not been isolated. The loss of bridging carbon dioxide is too facile in the

conditions required for reaction. The product formed, after decarboxylation, is a

carbazole, derivatives of which are known to show anti-tumour activity. For example,

ellipticine, **7**, is a potent intercalating agent[36,37,38] (see Section 1.1.8). Pyrano[3,4-

b]indol-3-ones are easily prepared, stable pyranones and therefore have the potential of

providing a quick, simple route to a cancer chemotherapeutic prodrug; providing a

stable bridged adduct can be isolated.
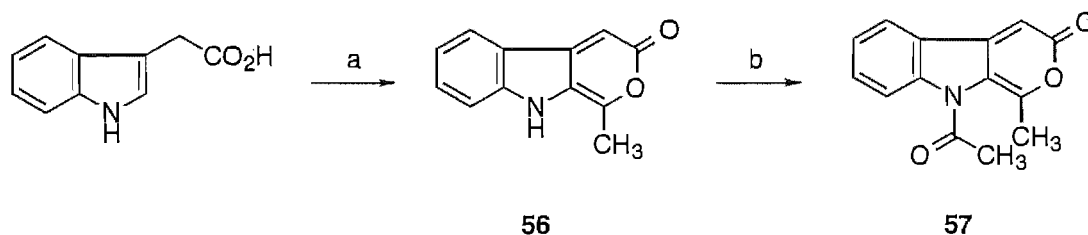
Figure 2.15: Preparation of 1-methylpyrano[3,4-*b*]indol-3-one and

9-acetyl-1-methylpyrano[3,4-*b*]indol-3-one

Reagents and conditions: (a) acetic anhydride, $BF_3.Et_2O$, room temperature; (b) NaH, acetic

anhydride, dimethylformamide, 0 °C

The pyrano[3,4-*b*]indol-3-one[32], **56**, was prepared from commercially

available indole-3-acetic acid by treatment of an acetic anhydride solution with boron

trifluoride etherate (**Figure 2.15**). This is analogous to the preparation of the 1-ethyl

substituted analogue[34]. **56** was then treated with sodium hydride followed by addition

of acetic anhydride to give the *N*-acylated pyrano[3,4-*b*]indol-3-one, **57**[39]. This last step

uses *N*,*N*-dimethylformamide (DMF) as a solvent because of the low solubility of **56** in

more volatile solvents. This made the work up difficult due to the high boiling point

and water solubility of DMF, contributing to a low yielding reaction.

The reaction of **56** with **19** was carried out in bromobenzene because of the

low solubility of **56** in toluene. The isolated product was identified as the substituted

carbazole, **58** (**Figure 2.16**). The other regioisomer was not observed. It is intriguing

that this is the same regiochemistry as observed for electron-deficient

dienophiles[39,40,41,42]. Retro-Diels-Alder loss of carbon dioxide to form the aromatic

product will be encouraged by the electron-donating nitrogen attached to the pyranone

ring. It was therefore postulated that attaching an acyl group to the nitrogen should

decrease its electron-donating properties, and hence make the bridged adduct more

stable. This should also cause the diene to be more reactive towards *inverse* electron-

demand Diels-Alder reactions. (Acylation of **56** has been observed to cause a drop of
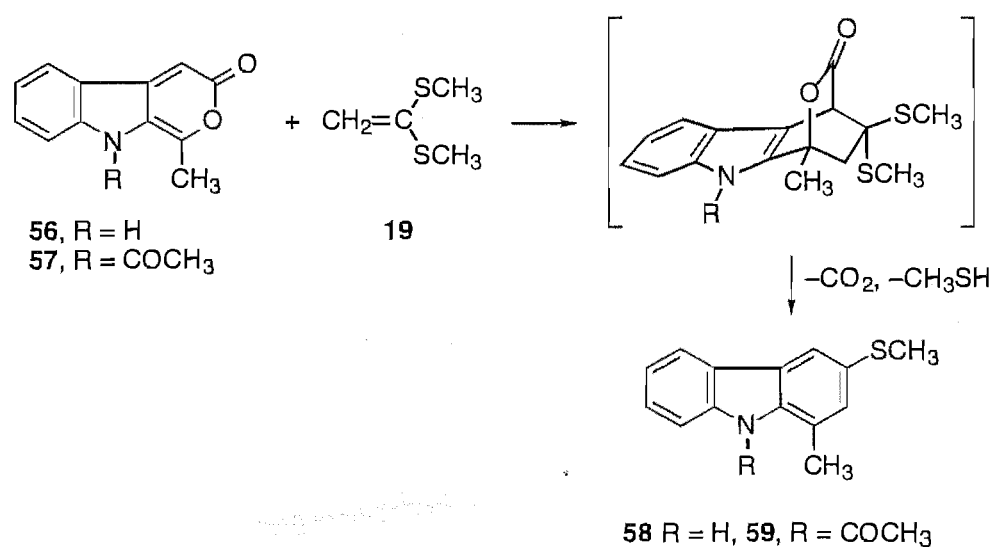
Figure 2.16: The reaction of 1,1-bis(methylthio)ethene with pyrano[3,4-*b*]indol-3-ones

reactivity and change in regiochemistry for *normal* electron-demand reactions; the electron-deficient dienophiles involved were $HC\equiv CO_2Et$[34] and $CH_2=CHCO_2CH_3$[39]).

The *N*-acylated pyrano[3,4-*b*]indol-3-one, **57**, was therefore reacted with **19**. The reaction was much slower than the non-*N*-acylated case and still gave the corresponding aromatic product, **59**. The less electron-rich diene was not as reactive, which was counter to expectation. There was also no change in the regiochemistry of the reaction. The lone pair on the nitrogen makes **56** a rather electron-rich pyranone and these results suggest that **19** may be reacting in a *normal* electron-demand sense with this diene. This electron donation will be decreased by *N*-acylation, making **57** less reactive. To see if it was possible for **19** to undergo *normal* electron-demand Diels-Alder reactions; it was mixed with cyclopentadiene, a reactive electron-rich diene. The reaction was monitored by proton NMR. After six days at 55 °C, dimerisation of cyclopentadiene was complete. No other product was observed.

The low reactivity of this system and the low stability of the bridged Diels-Alder adduct make this system unsuitable for the preparation of prodrugs, but has led to a simple synthesis of methylthio substituted carbazoles. These results could be

applicable to the synthesis of hyellazole, **60**. This alkaloid could not be prepared from a simple Diels-Alder reaction of 1-phenylpyrano[3,4-*b*]indol-3-one with 1-methoxypropyne because of the lack of reactivity of electron-rich alkynes with pyrano[3,4-*b*]indol-3-ones. An elaborate (5 steps) sequence had to be used[43]. The above results suggest that the reaction of 1,1-bis(methoxy)propene with the appropriate pyrano[3,4-*b*]indol-3-one and the subsequent loss of methanol may be a suitable strategy for the preparation of **60**.
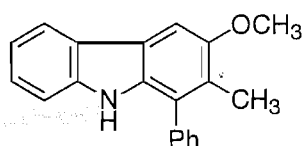
60

2.7. Conclusion

The Diels-Alder reaction of several pyranones with 1,1-bis(methylthio)ethene has been investigated. A summary of these results is given in **Table 2.2**, along with a comparison with the oxygen analogue, where available.

With the dienes tried, 1,1-bis(methylthio)ethene is a less reactive dienophile than its oxygen analogue, 1,1-bis(methoxy)ethene. The similar size of carbon and oxygen atoms cause oxygen to have strong π-donor properties. Therefore methoxy substituents have a stronger electron-donating resonance effect than methylthio groups. This high electron density raises the energy of the HOMO orbital of the methoxy substituted dienophile, making it a more reactive diene in *inverse* electron-demand Diels-Alder reactions.

In all cases only one product was observed, either the bridged adduct or the aromatic product. The product that formed was generally the same for the sulfur and oxygen case for each diene. It appears that the more reactive the diene, the more likely

Pyranone	1,1-Bis(methylthio)ethene **19**			1,1-Bis(methoxy)ethene **27**			
	Conditions	Product‡	% rxn.	Conditions	Product‡	% rxn.	Ref.
25	toluene reflux, 22 hrs	**28** (A)	74%	benzene reflux, 2 hrs	**29** (A)	65%	15
26	toluene reflux, 9 days	**31** (C)	21%	benzene reflux, 24 hrs	**30** (A) **32** (C)	10% 63%	14
40	toluene reflux, 24 hrs	**42** (A)	78%	toluene reflux, 12 hrs	**43** (A)	60%	20
56	bromobenzene 120°C, 4.5 days	**58** (C)	24%				
57	bromobenzene 120 °C, 14 days	**59**(C)	14%				

‡ As described in **Figure 2.2**; A = bridged Diels-Alder adduct, C = aromatic product

Table 2.2: Summary of the Diels-Alder reactions between 1,1-bis(methylthio)ethene and its oxygen analogue with various pyranones

the bridged Diels-Alder adduct can be isolated. Dienes that are less reactive in *inverse* electron-demand situations are likely to form an adduct that is more susceptible to the *normal* electron-demand retro-Diels-Alder, that is, the extrusion of carbon dioxide.

The pyrano[3,4-*b*]indol-3-one case suggests that 1,1-bis(methylthio)ethene is capable of undergoing *normal* electron-demand Diels-Alder reactions with electron-rich dienes. The ability of sulfur to stabilise an adjacent negative charge in a dipolar

transition state, probably by polarisation, could cause 1,1-bis(methylthio)ethene to react as a *normal* electron-demand dienophile.

These are probably concerted, non-synchronous Diels-Alder reactions: the high regioselectivity observed suggests a non-synchronous mechanism; however, the lowering of the activation energy by increasing the pressure (for the reaction with the benzopyranone) suggests that this is a concerted process.

The previously unreported potential of 1,1-bis(methylthio)ethene as a dienophile with several all-carbon, neutral dienes has hence been examined. The failure to prepared a stable bridged adduct which, upon bridge cleavage, would give tricyclic hetero-aromatic compound means that this chemistry may be of limited utility in the preparation of the envisaged cancer chemotherapeutic prodrugs.

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Chapter 3

THERMAL DECOMPOSITION OF THE DIELS-ALDER ADDUCTS

3.1. Introduction

The thermal stability of the two bridged Diels-Alder adducts successfully prepared in *Chapter 2* was investigated. The durability of the benzopyranone, 1,1-bis(methylthio)ethene adduct, with respect to bridge cleavage, is of interest because it models an envisaged prodrug. A certain level of adduct stability is required so that premature decarboxylation does not occur *in vivo*. This would have the unfavourable consequence of producing the active drug prior to tumour-selective activation. Upon exposure to thermal conditions, the adducts were expected to decompose by eliminating carbon dioxide and/or methanethiol; eventually resulting in the formation of aromatic products (as outlined in **Figure 2.2**).

3.2. Decomposition of the methyl coumalate, 1,1-bis(methylthio)ethene Diels-Alder adduct

The methyl coumalate, 1,1-bis(methylthio)ethene adduct, **28**, was heated neat at 145 °C and the reaction monitored by proton NMR. This thermally induced decomposition gave a clean mixture of three products. These products were separated by radial silica chromatography. One product was methyl coumalate, **25** (**Figure 3.1**). This must result from a reversal of the reaction used to prepare this adduct. It is surprising that this retro-Diels-Alder reaction can successfully compete with decarboxylation. The expected substituted benzene compound, **63**, was also present.
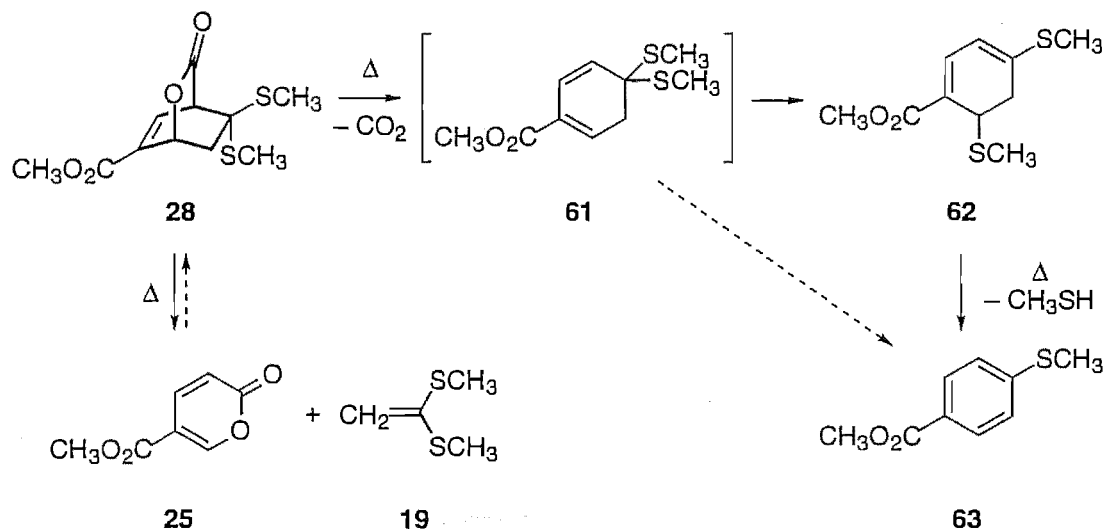
Figure 3.1: The thermal decomposition of the methyl coumalate, 1,1-bis(methylthio)ethene
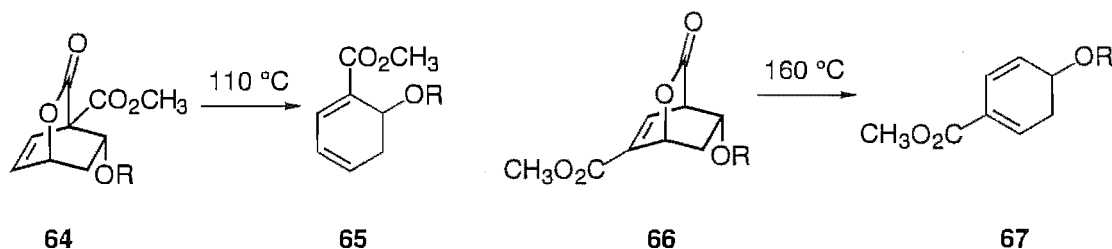
Diels-Alder adduct

Figure 3.2: The thermal decomposition of 3- and 5-carboxymethylpyran-2-one, enol ether

Diels-Alder adducts

This is formed when the initial adduct loses carbon dioxide and methanethiol. The other product isolated was an unexpected cyclohexadiene, **62**. This is presumedly due to decarboxylation of **28** followed by rearrangement. The diene, **61**, was not observed.

The driving force of this rearrangement appears to be the resonance stabilisation available to **62** due to the conjugation of the ester carbonyl, the diene and possibly the sulfur's outer shell electrons. This conjugation does not occur to the same extent in the intermediate, **61**. An insight into the relative stabilities of dienes **61** and **62** can be gleaned from the reported thermal decarboxylations of **64** and **66**[1] (**Figure 3.2**). In this report Markó and Evans isolated the resulting dienes, **65** and **67**, by rapid

chromatography. They noted that the conjugated dienes, **65**, were more stable than their analogues, **67**. The conjugated diene, **62**, was also formed if the Diels-Alder reaction of **25** with **19** was left for a longer period.

The cyclohexadiene, **62**, was stable enough to be isolated and examined with standard spectroscopic methods. However it eliminated methanethiol within a few days to give **63**. **62** had a strong infra-red absorption at 1700 cm^{-1} characteristic of a conjugated carbonyl group and an ultra-violet maximum absorption at 342 nm (ε = 9610) which is consistent with a conjugated diene, carbonyl system. The chemical shifts and coupling constants observed in the proton NMR spectrum for **62** are shown in **Figure 3.3** and these correlations were confirmed by a COSY (COrrelation SpectroscopY) 2D-NMR experiment. To verify the structure of **62**, the Diels-Alder reaction of it with maleic anhydride was attempted. After 2 hours at room temperature in ethyl acetate there was no reaction. After 2 hours at reflux, the major product was **63**, the result of methanethiol elimination. The reaction mixture was examined with proton NMR and mass spectrometry, but there was no indication of the presence of the Diels-Alder adduct or subsequent decomposition products.

Figure 3.4 shows the progress for one particular decomposition. The rate of decomposition was not reproducible in the conditions used, but the general reaction profile was similar in each case. This change in rates could be due to the presence of residual impurities and/or it could be an artefact of a radical driven process. The initial adduct, **28**, can undergo two possible retro-Diels-Alder reactions. The first is the reverse of the reaction that formed the adduct originally. This results in the formation of methyl coumalate, **25**, and 1,1-bis(methylthio)ethene, **19**. The gradual build up of the pyranone can be seen in **Figure 3.4**. The build up of **19** is not observed. This could be due to it being lost from the system as a result of its volatility. The second possible retro-Diels-Alder reaction is the extrusion of carbon dioxide to form the diene, **61**. As this compound was not observed, it must rapidly lose methanethiol to give the

substituted benzene, **63**; or rearrange by way of a [1,5]-methylthio shift to give **62**. The greater build up of **62** and **63** compared to **25** suggests that the latter is the more favourable reaction.
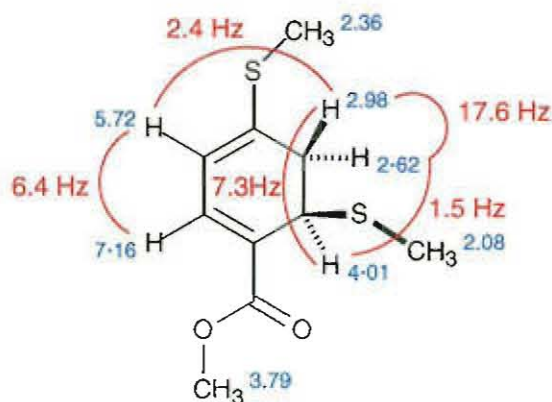
Figure 3.3: The proton NMR chemical shifts (ppm) and coupling constants (Hz) observed for

62
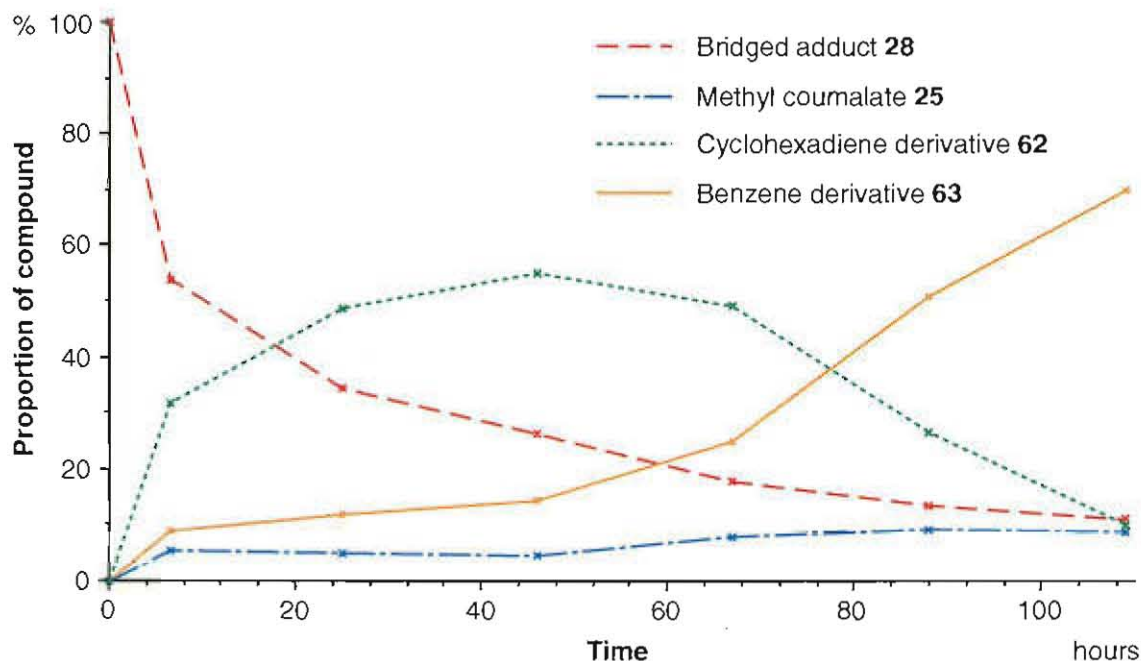
Figure 3.4: The methyl coumalate, 1,1-bis(methylthio)ethene Diels-Alder adduct was heated neat at 145 °C in a nitrogen atmosphere. The proportion of each compound present (as described in **Figure 3.1**) is plotted as a function of time. The formation of the decomposition products was monitored by proton NMR. The measurements were made by comparing the integration of the methyl ester peak corresponding to each compound.

As both dienophiles from these two retro-Diels-Alder reactions appear to be lost from the system, the reverse reaction to form **28** again cannot occur. Under these conditions it is an irreversible reaction. The cyclohexadiene derivative, **62**, builds up to become the major component of the mixture (**Figure 3.4**), suggesting that for **61**, the [1,5]-methylthio migration is more facile than the elimination of methanethiol. It is only after this point that the aromatic compound, **63**, is formed at an appreciable rate. This suggests that **63** is formed predominantly via the [1,5]-methylthio migration pathway rather than directly from **61**.

3.3.   [1,5]-Methylthio migrations

Many migrations of arylthio and alkylthio groups have been observed previously[2], although only a few are related to the one described above. The most common migrations are [1,3] in nature and, in the case of arylthio groups, are thought to involve a

68

trigonal bipyramidal intermediate, **68**. This is stabilised by the ability of sulfur to expand its octet, encouraged by the shrinking of the sulfur's d-orbitals by the electron-withdrawing aryl substituent. The rearrangement can also occur bimolecularly[3]: ionic if acid or base catalysed, or radical if exposed to light[4,5]. For the cases where a mixture of allyl sulfides has been examined, a combination of all the possible cross-over products has been obtained[3,6,7,8] indicating an intermolecular mechanism. Alkylthio groups cannot rearrange by a concerted mechanism because they are not able to stabilise an intermediate of type **68**. A radical process can be initiated by the presence of an alkylthio radical, formed *in situ* by the irradiation of the appropriate disulfide[9] or alkylthiol[10]. The radical mechanism then occurs as shown in **Figure 3.5**. The symmetrical radical intermediate, **69** (R = H), has been detected by ESR spectroscopy[9].

69
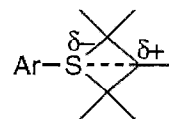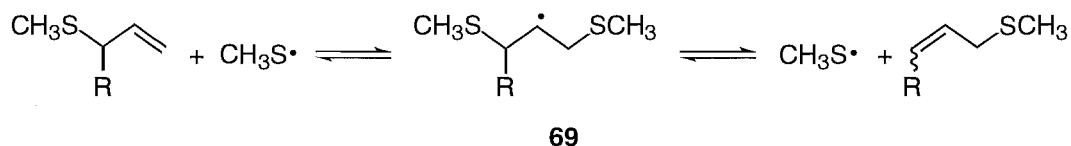
Figure 3.5: The radical rearrangement of allylic methyl sulfides (R = H or CH₃)

A [1,3]-methylthio shift has also been observed in acidic conditions[11]. In the preparation of dimethylthio substituted pyridines, a methylthio group migrated to form a more stable carbocation. It was not established whether this was an inter- or intra-molecular process. The possible pathway given is outlined in **Figure 3.6**.

The [1,5]-methylthio shift postulated in this work could be concerted or bimolecular in mechanism. The latter could either occur in a radical or ionic sense. There have been several reports of [1,5]-*aryl*thio shifts (or two successive [1,3] shifts) in acid catalysed[8,12,13] or photo-initiated[5] processes; however, reports of [1,5]-*alkyl*thio shifts are comparatively rare. Vishwakarma *et al.* observed that upon heating **70** with dimethyl acetylenedicarboxylate in xylene in a sealed tube at 160-170 °C, **74** was obtained in 16% yield[14]. The explanation given for this reaction involves a [1,5]-methylthio shift (**Figure 3.7**). The first step in this mechanism is the formation of the cyclobutane, **71**, *via* a [2+2] cycloaddition. This is followed by ring opening and then electrocyclic ring closure to give **72**. This intermediate appears to undergo a [1,5]-methylthio shift to give **73**. It is postulated that this then undergoes electrocyclic ring opening to give the *S*-methyl ester, which on intramolecular ring closure and elimination of dimethyl sulfide yields the isolated product, **74**. This rearrangement occurs in thermal, neutral conditions, similar to those present when **62** was formed.

Apparao *et al.*[7] observed that the reaction of **75** (R = CH₃, or CH₂CH₃) with sodium hydride at 40-45 °C gave the stereochemically pure diene **77** as the result of a base catalysed [1,3]-proton shift followed by a [1,5]-alkylthio shift (**Figure 3.8**).
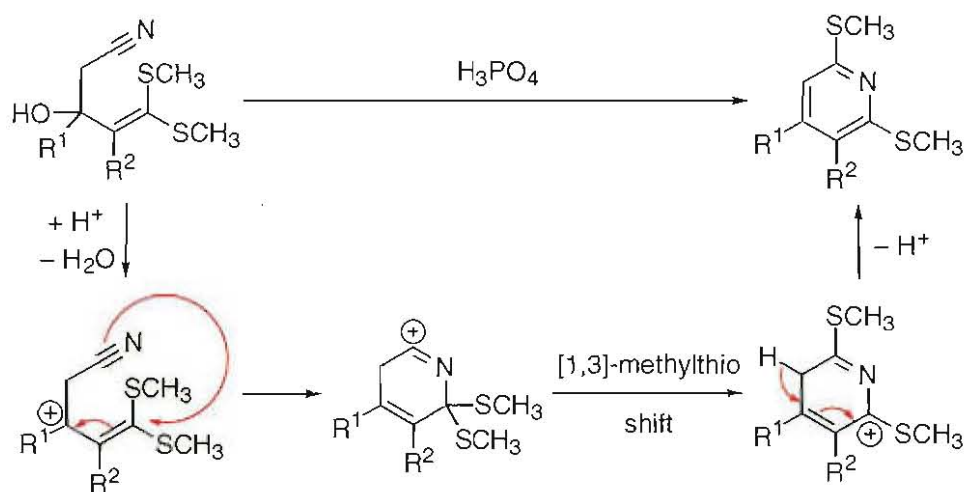
Figure 3.6: A preparation of substituted pyridine involving a [1,3]-methylthio shift
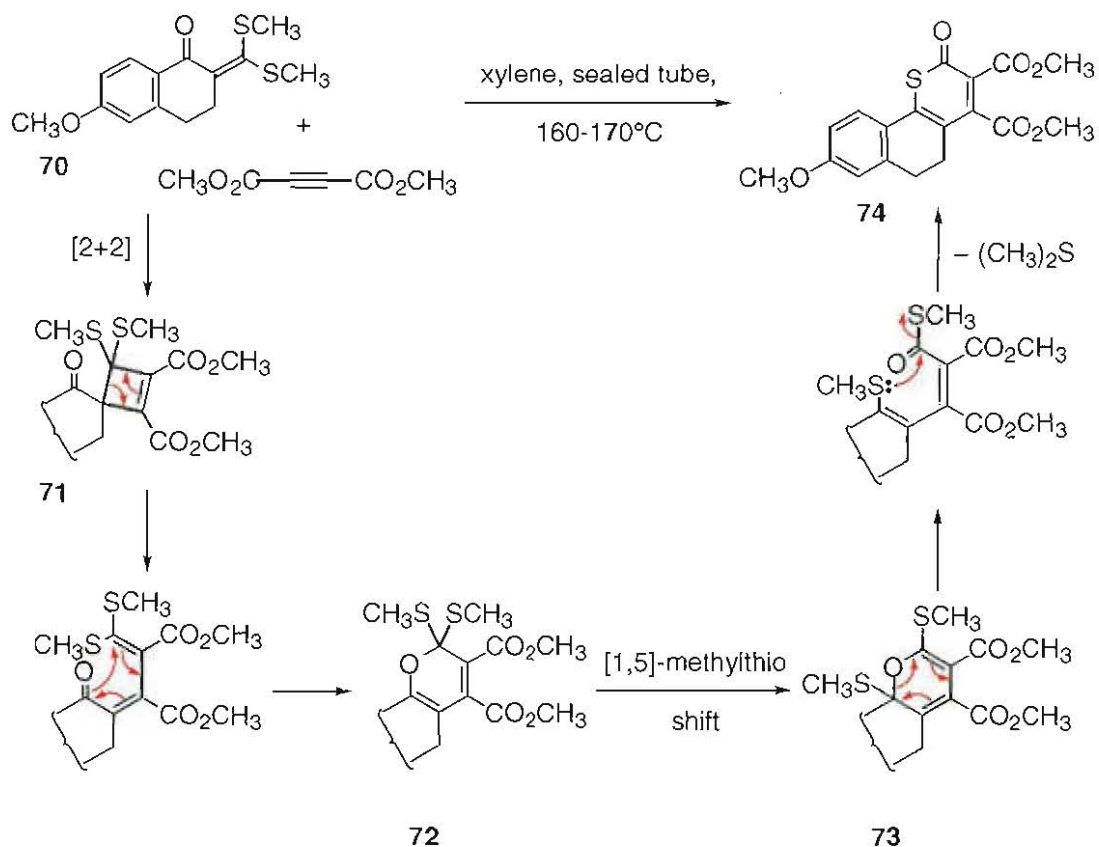
Figure 3.7: The suggested mechanism for the reaction of **70** with dimethyl

acetylenedicarboxylate and subsequent decomposition to give **74**
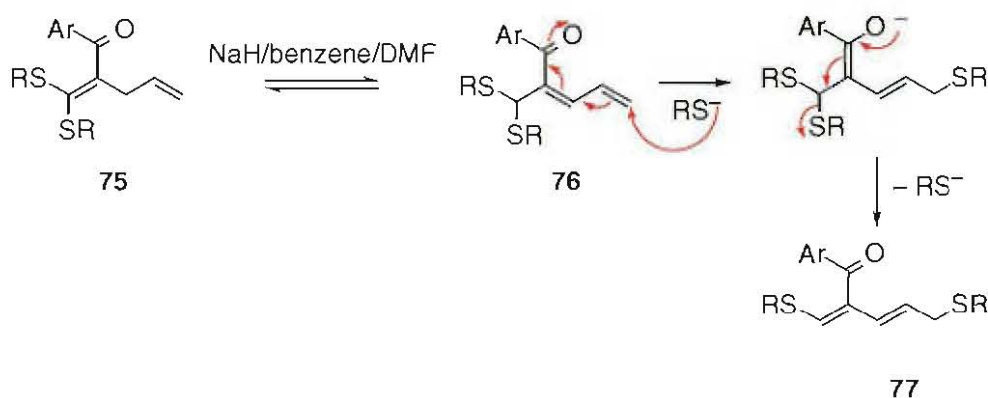
Figure 3.8: The mechanism for the rearrangement of **75** to give **77**, involving a [1,5]-alkylthio

shift

Attempts to isolate the intermediate, **76**, were unsuccessful. Mechanistic studies suggested that this was an ionic intermolecular rearrangement. The reaction was unaffected by the presence of radical inhibitors. When a mixture of **75** (Ar = Ph, R = CH$_3$) and **75** (Ar = p-CH$_3$OC$_6$H$_4$, R = CH$_2$CH$_3$) was exposed to the same conditions, the nine possible products resulting from intermolecular rearrangements were observed. Apparao *et al.* noted that these results do not eliminate the possibility of a thermal concerted process for the rearrangement, but that the ionic pathway appears to predominate in the presence of base.
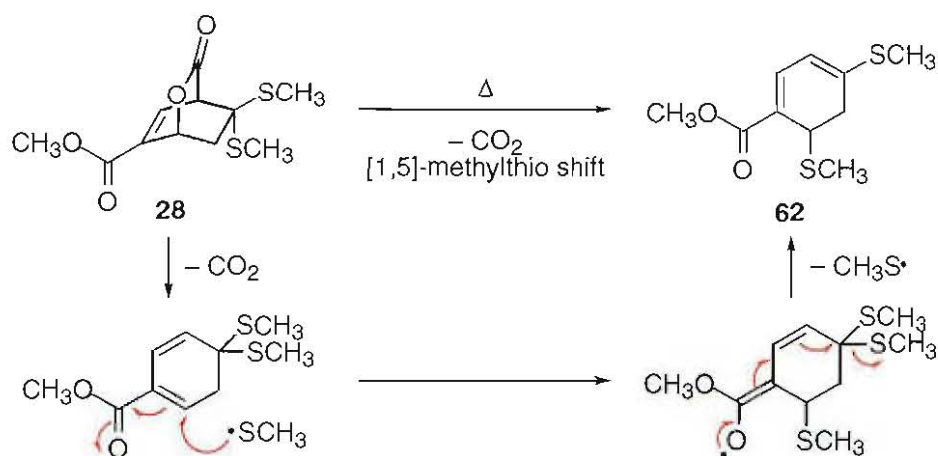
Figure 3.9: The suggested radical mechanism for the [1,5]-methylthio shift observed in the

thermal decomposition of **28**

It is difficult to obtain further information on the [1,5]-rearrangement observed in this work due to the transitory nature of the suggested precursor and the instability of the product. This rearrangement and the one proposed in the formation of **74** (**Figure 3.7**) both occurred in neutral conditions suggesting that in these cases the mechanism is not ionic in nature. Because we are dealing with a migrating alkylthio group instead of a stabilised arylthio one, this is probably a radical process rather than a concerted one. All three cases described above have a carbonyl functionality conjugated with the diene system. This would allow delocalisation in both radical and ionic intermediates. The nature of the stabilisation is shown for the ionic case in **Figure 3.8** and the radical case in **Figure 3.9**. It appears that the presence of an appropriately positioned carbonyl-like moiety may be crucial for the observance of a [1,5]-alkylthio shift. To test this hypothesis it was decided to replace the carbomethoxy substituent with an aromatic entity. The initial aim was to prepare 5-phenyl-2-pyranone and react this with 1,1-bis(methylthio)ethene. The resulting Diels-Alder adduct could then be subjected to the same conditions as for the methyl coumalate case, that is, heating neat at 145 °C. Examination of the thermal decomposition products may reveal whether a [1,5]-methylthio shift has occurred.

3.4. Preparation of phenylpyran-2-ones

The preparation of pyran-2-ones has recently been reviewed[15]. There are a number of methods for the synthesis of 5-phenylpyran-2-one, **79**[16,17] (**Figure 3.10** and **3.11**). The synthesis outlined in **Figure 3.10** was attempted first. The radical addition of carbon tetrachloride to ethyl vinyl ether gave the tetrachlorinated ether[18]. Subsequent thermally induced, regiospecific elimination of HCl[19] was implemented without complications. However, the ensuing acid-catalysed, aldol-like reaction with phenylacetaldehyde[16] proved more difficult. Only a very small yield of **78** was
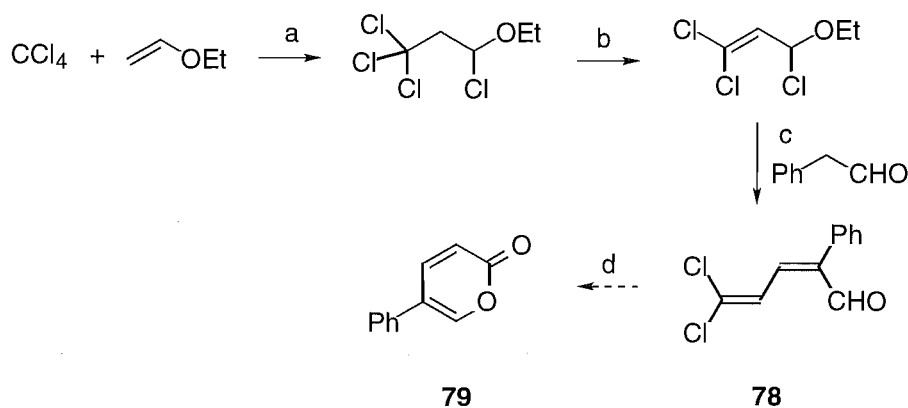
Figure 3.10: A synthesis of 5-phenylpyran-2-one

Reagents and conditions: (a) benzoyl peroxide, pyridine, reflux; (b) 130-150 °C, neat; (c) CH_3CO_2H, water, 0 °C; (d) CH_3CO_2H, reflux

achieved. This could not be improved on and so this strategy for the preparation of 5-phenylpyran-2-one was abandoned.

The synthesis outlined in **Figure 3.11**[17] was then attempted. This strategy has the advantage that it produces four phenylpyran-2-ones for which the Diels-Alder chemistry and the thermal decomposition of the subsequent adducts could be studied. The disadvantage is that **79** is the minor product. Methyl (Z)-3-chloropropenoate, **80**, was prepared as outlined in **Figure 3.11**. This involves the addition of bromine to fumaric acid to give dibromosuccinic acid[20]. Base induced double elimination of HBr gave the alkyne which upon decarboxylation, gave propynoic acid[21]. Copper(I) chloride catalysed addition of HCl selectively gave (Z)-3-chloropropenoic acid[22]. The methyl ester, **80**[23], was prepared and then used in the synthesis of phenyl-2-pyranones as described by Boulanger and Katzenellenbogen[17]. The triester resulting from the reaction of **80** with the sodium salt of diethyl phenylmalonate, was saponified and decarboxylated to give the two geometrical isomers of 2-phenylglutaconic acid, **81**. In my hands, the decarboxylation was spontaneous upon acidification of the saponification mixture; the reported procedure involved refluxing the triacid in 1 mol L^{-1} HCl for an hour.
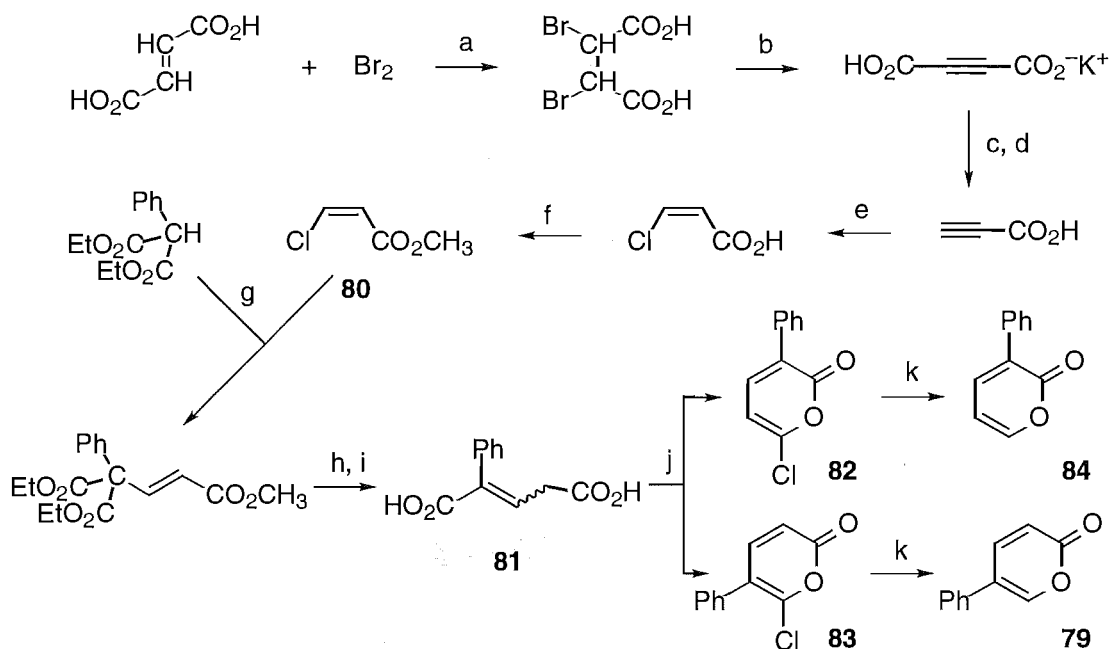
Figure 3.11: A synthesis of 5-phenylpyran-2-one

Reagents and conditions: (a) H_2O, reflux; (b) KOH, ethanol (– 2HBr); (c) 3 mol L^{-1} H_2SO_4;

(d) H_2O, Δ; (e) HCl, CuCl; (f) methanol, H_2SO_4; (g) NaH, tetrahydrofuran, reflux; (h) NaOH,

reflux; (i) HCl; (j) acetyl chloride, sealed tube, 100 °C; (k) Zn, CH_3CO_2H, tetrahydrofuran, room

temperature

Cyclization was achieved by heating the 2-phenylglutaconic acid in acetyl chloride in a sealed tube at 100 °C overnight. This reaction gives a messy mixture of products. A proton NMR spectrum of the crude reaction mixture showed that both of the chlorophenylpyran-2-ones, **82** and **83**, were present; **83** in much lower yield. Purification of these two products using radial chromatography only gave **82**, the unwanted pyranone. This could then be cleanly reduced to **84**. Reduction of a small amount of the crude cyclization mixture gave both **79** and **84**. This mixture was more conducive to separation by chromatographic techniques.

This complex, low yielding synthesis of 5-phenylpyran-2-one, **79**, was not investigated any further. Even if the preparation of 5-phenylpyran-2-one had been more successful, it was not at all certain that a stable 1,1-bis(methylthio)ethene Diels-Alder

adduct could be prepared, let alone whether the presence or absence of a [1,5]-methylthio shift could be precisely observed.

3.5. Decomposition of the benzopyranone, 1,1-bis(methylthio)ethene Diels-Alder adduct

Thermal decomposition of the methyl coumalate, 1,1-bis(methylthio)ethene adduct proved to be complex with two competing retro-Diels-Alder reactions and a methylthio migration observed. The thermal decomposition of the benzopyranone, 1,1-bis(methylthio)ethene Diels-Alder adduct, **42**, was then examined. The decomposition chemistry was much more simple for this adduct, with only one product being isolated; the substituted naphthalene, **86** (**Figure 3.12**). No intermediates resulting from methylthio migration or just decarboxylation (**85**) were observed. **42** was expected to be more stable than **28** due to the initial loss of benzenoid aromaticity upon decarboxylation. This was found to be the case: 97% of **42** remained after 25 hours of heating neat at 145 °C, compared with 35% of **28**. The stability of the benzopyranone adduct is as desired for the preparation of prodrugs that are stable *in vivo*.

42   **85**   **86**
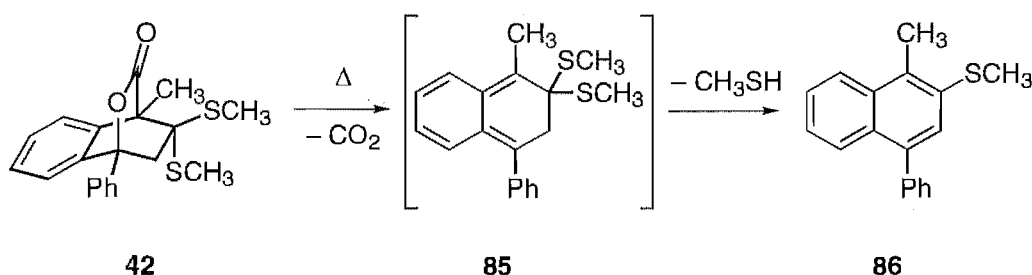
Figure 3.12: The thermal decomposition of the benzopyranone, 1,1-bis(methylthio)ethene

Diels-Alder adduct

3.6. Conclusion

During the thermal decomposition of the methyl coumalate, 1,1-bis(methylthio)ethene Diels-Alder adduct, a [1,5]-methylthio shift was observed. This type of migration has little precedent. It was suggested that this occurs by way of a radical process and that the carboxy substituent was crucial for the rearrangement to take place. An attempt was made to synthesise 5-phenylpyran-2-one in an effort to clarify the mechanistic details. Difficulty experienced in this synthesis and the transitory nature of the precursor and product of this rearrangement thwarted this investigation.

As predicted, the benzopyranone, 1,1-bis(methylthio)ethene Diels-Alder adduct has a greater thermal stability than the equivalent methyl coumalate adduct. This has been attributed to the initial loss of aromaticity required by **42** upon decarboxylation. This observation bodes well for the preparation of stable bridged adducts, similar to **42**, required for the synthesis of potential prodrugs.

3.7.   References

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REACTION OF 1-METHYLTHIO-1-(*p*-TOLYLSULFONYL)ETHENE WITH PYRANONES

4.1. Introduction

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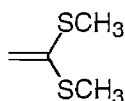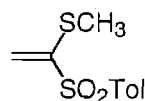
SCH$_3$	SCH$_3$
SCH$_3$	SO$_2$Tol
19	**87**

1,1-Bis(methylthio)ethene, **19**, has proved to be a fairly unreactive *inverse* electron-demand dienophile, and upon reaction with pyrano[3,4-*b*]indol-3-ones, may even have been reacting in a *normal* electron-demand sense (Section 2.6). It was postulated therefore, that oxidising one of the sulfides to a sulfone would provide an electron-deficient dienophile that would be more reactive in *normal* electron-demand reactions. That is, the electron-withdrawing capabilities of the sulfone should cause the dienophile to react favourably in Diels-Alder reactions involving electron-rich dienes. Increased reactivity would lead to cycloaddition reactions occurring under milder conditions, increasing the likelihood of isolating the resulting bridged Diels-Alder adducts. Spontaneous decarboxylation may cease to be a problem.

Vinyl sulfones have received much attention as useful intermediates in organic synthesis; both as Michael acceptors and in cycloaddition reactions[1]. Sulfonyl substituents have proved to be suitable electron-withdrawing groups for the activation of Diels-Alder reactions. They have been used in this capacity to replace carbomethoxy substituents on pyranones[2] and there have been occasional reports of the reaction of

vinyl sulfones with electron-rich pyranones and pyridones[3]. This chapter describes the preparation of 1-methylthio-1-(_p_-tolylsulfonyl)ethene, **87**, and its reaction with various pyranones.

4.2. The preparation of 1-methylthio-1-(_p_-tolylsulfonyl)ethene
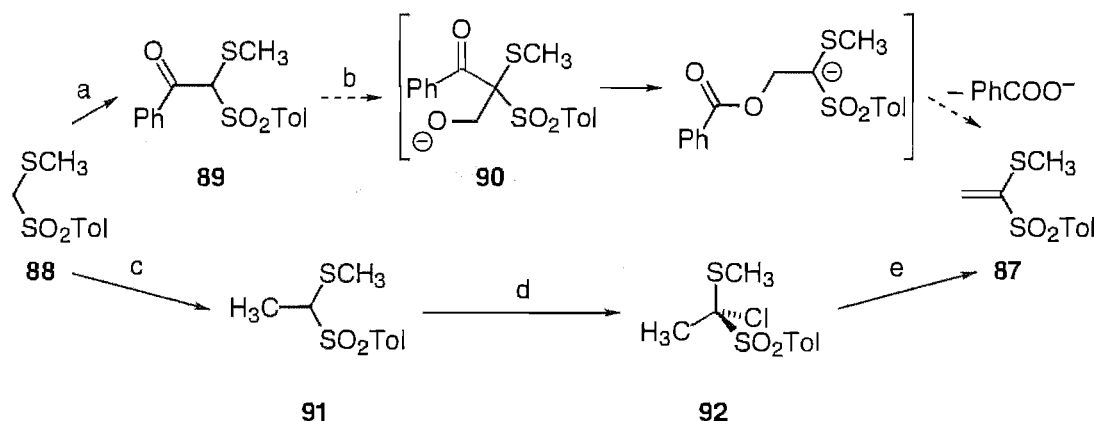
Figure 4.1: Two methods for the synthesis of 1-methylthio-1-(_p_-tolylsulfonyl)ethene

Reagents and conditions: (a) (i) NaH, tetrahydrofuran, 0 °C, (ii) Phenyl benzoate, reflux; (b) (i) NaH, tetrahydrofuran, 0 °C, (ii) paraformaldehyde, reflux; (c) (i) _n_-BuLi, tetrahydrofuran, -78 °C, (ii) CH₃I, room temperature; (d) SO₂Cl₂, chloroform, room temperature; (e) 90 °C, neat

Two methods for the synthesis of **87** are outlined in **Figure 4.1**. The first strategy begins with the acylation of methylthiomethyl _p_-tolyl sulfone, **88**. Reaction of the product, **89**, with formaldehyde should give the intermediate, **90**, which will then undergo a benzoyl transfer, from carbon to oxygen, followed by elimination of the benzoate anion to give the required alkene, **87**. The precedent for this rearrangement is described for various compounds with alkyl groups instead of the methylthio substituent[4]. The second strategy involves the methylation of the same starting material, **88**, to give **91**. Chlorination of this product followed by elimination of HCl has been reported to give **87**[5].

Methylthiomethyl *p*-tolyl sulfone, **88**, is a readily available compound which can be efficiently prepared from dimethyl sulfoxide, acetic anhydride and sodium *p*-toluenesulfinate[6], or it can be purchased. This starting material, **88**, was acylated with phenyl benzoate, using sodium hydride as the base, to give **89**[7]. However, the subsequent reaction of the anion of **89** with formaldehyde was not successful. The alternative method was therefore investigated.

There are several conditions reported for the methylation of **88**[6,8,9]. The formation of the anion of **88** using *n*-butyllithium as the base and subsequent reaction with iodomethane gave **91** in excellent yield. This product was chlorinated using sulfuryl chloride to give **92**[9,10]. The elimination of HCl from **92** has been reported by Katsuyuki and Takeo[10]. It involved refluxing **92** in chloroform for 32 hours. In my hands, these conditions gave about 20% reaction, whereas heating **92** at 90 °C neat for 5 hours gave 90% reaction (although the yield of isolated pure product was considerably less than this). The use of triethylamine in benzene at room temperature[11] to eliminate HCl was not successful.

1-Methylthio-1-(*p*-tolylsulfonyl)ethene, **87**, was then reacted with the pyranones described earlier (*Chapter 2*) and its reactivity and regioselectivity compared to that of 1,1-bis(methylthio)ethene, **19**.

4.3. The reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with two simple pyran-2-ones

1-Methylthio-1-(*p*-tolylsulfonyl)ethene, **87**, was reacted with methyl coumalate, **25**, and methyl 4,6-dimethylcoumalate, **26**. The conditions were the same as for the 1,1-bis(methylthio)ethene case; however in this case, even after longer reaction times, the yield of products was low. The products were the same substituted aromatics, **63** and **31**, seen previously (**Figure 4.2**). The bridged Diels-Alder adducts were not

25 R = H, 26 R = CH₃   87   63 R = H, 31 R = CH₃
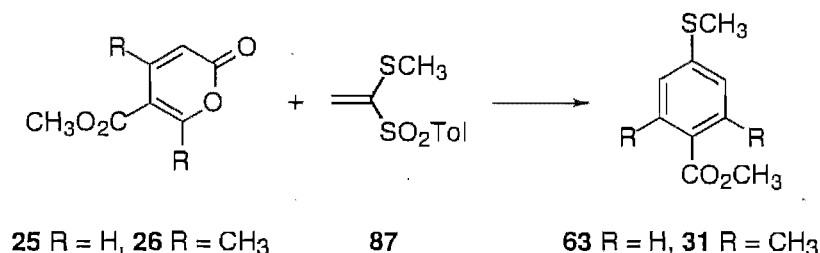
Figure 4.2: The reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with methyl coumalates

observed and therefore no information on the stereochemistry of the cycloaddition was obtained. The regioselectivity was the same as for the 1,1-bis(methylthio)ethene case.

The lower reactivity of **87** with methyl coumalates is expected because this involves the reaction of a less electron-rich dienophile with electron-deficient dienes. Elimination of *p*-toluenesulfinic acid may be rather facile for this type of adduct. This elimination, happening first, would trigger decarboxylation due to the unstable nature of bridged cyclohexadienes.

4.4. The reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with a benzopyranone

40   87   86   93
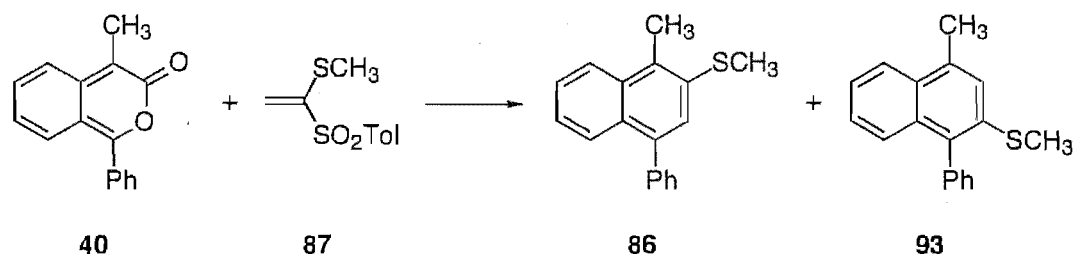
Figure 4.3: The reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with

4-methyl-1-phenylbenzopyran-3-one

1-Methylthio-1-(*p*-tolylsulfonyl)ethene, **87**, was reacted with 4-methyl-1-phenylbenzopyran-3-one, **40**. The rate of reaction was comparable to the reaction of 1,1-bis(methylthio)ethene with the same diene. However, in this case, no bridged

adduct was obtained, again suggesting that a facile *p*-toluenesulfinic acid elimination has triggered decarboxylation. The high regioselectivity observed for **19** was not observed for **87**. The two regioisomers, **86** and **93** (**Figure 4.3**), were obtained in a ratio of 2:5 respectively.

4.5. The reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with a pyrano[3,4-*b*]indol-3-one

56 R = H, **94** R = CH₃ **95** **96** R = H, **97** R = CH₃
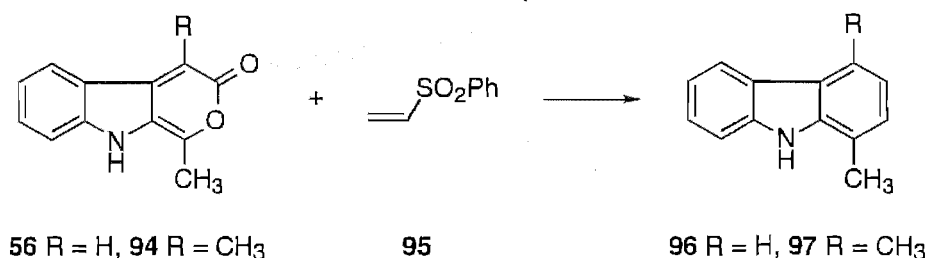
Figure 4.4: A previously reported reaction of a vinyl sulfone with pyrano[3,4-*b*]indol-3-ones

The reaction of vinyl sulfones with pyrano[3,4-*b*]indol-3-ones has been reported previously[12,13]. For example, the reaction of **56** and **94** with **95** gave **96** and **97** respectively (**Figure 4.4**). This was the only product observed in each case; that is, the substituted carbazole resulting from a Diels-Alder reaction followed by decarboxylation and elimination of benzenesulfinic acid.

1-Methylthio-1-(*p*-tolylsulfonyl)ethene, **87**, was reacted with 1-methylpyrano-[3,4-*b*]indol-3-one, **56**. The two aromatic regioisomers, **58** and **98**, were isolated (**Figure 4.5**). No adducts were observed. The addition of a methylthio group to the dienophile (**87** compared to **95**) has resulted in a decrease in regioselectivity. **87** appeared to be more reactive with the pyrano[3,4-*b*]indol-3-one than **19** was, as would be expected for this electron-rich diene. However the yield of products was low due to the decomposition of the diene. The pyrano ring appeared to have been hydrolysed to

the keto-acid even though the reactions were preformed under anhydrous conditions. This decomposition was not observed in the 1,1-bis(methylthio)ethene case.
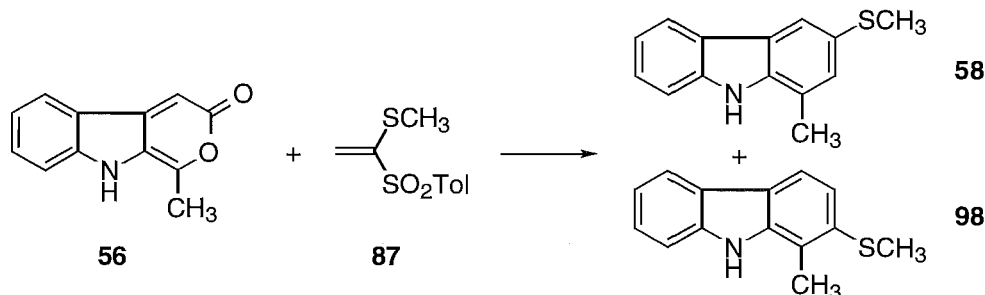
Figure 4.5: The reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with

1-methylpyrano[3,4-*b*]indol-3-one

4.6. A summary of the reactions of 1-methylthio-1-(*p*-tolyl-sulfonyl)ethene and 1,1-bis(methylthio)ethene with pyranones

A summary of the results of the Diels-Alder reactions of 1-methylthio-1-(*p*-tolylsulfonyl)ethene and 1,1-bis(methylthio)ethene with pyranones is shown in **Table 4.1**. Hemi-sulfone, **87**, is less reactive than the thioether, **19**, with electron-poor pyranones, such as the coumalates, but has an increased reactivity with electron-rich dienes, such as 1-methylpyrano[3,4-*b*]indol-3-one. This is attributed to the electron-withdrawing capacity of the sulfonyl substituent. The conditions required for reaction are such that no bridged adducts were isolated. The elimination of *p*-toluenesulfinic acid appears to be too facile. This elimination, occurring at a greater rate then the elimination of methanethiol, results in the isolation of methylthio substituted aromatic compounds only.

1-Methylthio-1-(*p*-tolylsulfonyl)ethene appears to be a fairly unreactive dienophile. The electron-withdrawing capacities of the sulfonyl substituent may have, to some extent, been cancelled out by the electron-donating methylthio substituent.

This could also explain the loss of regioselectivity shown by the dienophile, **87** (compared to **19**). The 1,1-bis(methylthio)- dienophile, **19**, having an electron-rich end gives high regioselectivity; whereas **87**, having two electronically conflicting substituents, yields a mixture of regioisomers.

Pyranone	1,1-Bis(methylthio)ethene 19			1-Methylthio-1-(*p*-tolylsulfonyl)ethene 87		
	Conditions	Products‡	% rxn	Conditions	Products‡	% rxn
25	toluene reflux, 22 hrs	28 (A)	74%	toluene reflux, 136 hrs	63 (C)	7%
26	toluene reflux, 9 days	31 (C)	21%	toluene reflux, 9 days	31 (C)	1%
40	toluene reflux, 24 hrs	42 (A)	78%	toluene reflux, 20 hrs	86 (C) 93 (D)	12% 30%
56	bromobenzene 120°C, 4.5 days	58 (C)	24%	bromobenzene 120 °C, 4 hrs	58 (C) 98 (D)	3% 4%
57	bromobenzene 120°C, 14 days	59 (C)	15%	–	–	–

‡ As described in **Figure 2.2**; A = bridged Diels-Alder adduct, C and D = aromatic products

Table 4.1: Summary of the Diels-Alder reactions of 1,1-bis(methylthio)ethene and 1-methylthio-1-(*p*-tolylsulfonyl)ethene with various pyranones

4.7. Conclusion

The reaction of a 1-alkylthio-1-(arylsulfonyl)ethene with various pyranones has been investigated. This slightly electron-deficient alkene has low reactivity as a Diels-Alder dienophile. The elimination of *p*-toluenesulfinic acid proved to be too facile, under the conditions required for cycloaddition, to allow the isolation of the bridged adducts. A drop in regioselectivity was observed for this dienophile compared with 1,1-bis(methylthio)ethene. This type of system appears to be unsuitable for the preparation of bridged prodrugs.

4.8. References

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REACTION OF 1-METHYLTHIO-1-(*p*-TOLYLSULFONYL)ETHENE WITH 1-(METHYLTHIO)-ISOBENZOFURANS

5.1. Introduction

The lack of reactivity of 1-methylthio-1-(*p*-tolylsulfonyl)ethene, **87**, towards pyranones makes this an unsuitable class of Diels-Alder reactions for the production of bridged adducts. The conditions required for cycloaddition are such that elimination of *p*-toluenesulfinic acid is facile. Isobenzofurans are highly reactive dienes[1,2] and hence may compensate for the low reactivity of **87**. This could allow the use of milder conditions; increasing the possibility of isolating bridged adducts. The Diels-Alder reactions of 1-(alkylthio)isobenzofurans with several electron-deficient dienophiles give stable, isolable bridged adducts. The bridge can be cleaved when exposed to
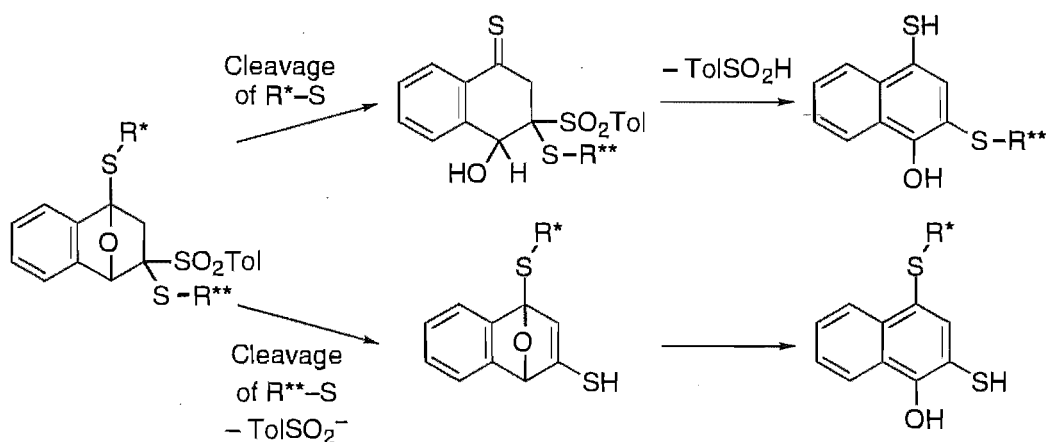
Figure 5.1: Two possible methods of activation of a 1-(alkylthio)isobenzofuran, 1-alkylthio-1-(*p*-tolylsulfonyl)ethene adduct (either R* or R** could be a trigger)

appropriate conditions[3]. 1-(Methylthio)isobenzofuran Diels-Alder adducts have already

been investigated as possible models of prodrugs of intercalating agents[3a]. The prodrug

form of this model system could have an appropriate trigger attached to either the

bridgehead sulfur or the 'dienophile' sulfur. Activation of either trigger will result in

the opening of the oxygen-bridge and the production of an extended planar aromatic

system (**Figure 5.1**).

5.2.   The preparation of 1-(methylthio)isobenzofurans

| (R = H) | 100 | 102 | 104 |
| (R = Ph) | 101 | 103 | 105 |
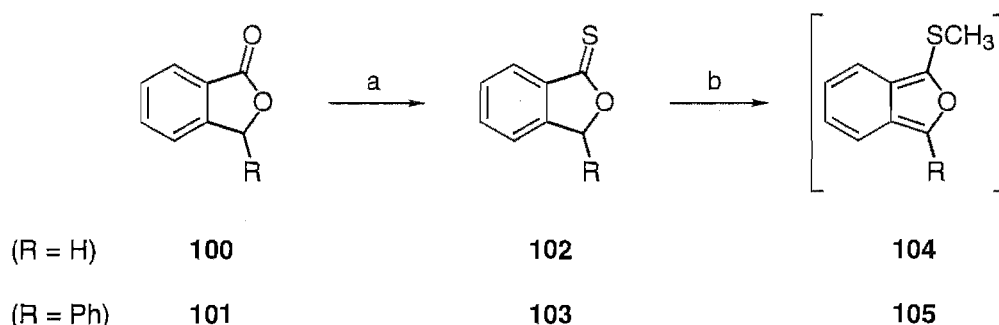
Figure 5.2: Preparation of 1-(methylthio)isobenzofurans, 104 and 105

Reagents and conditions: (a) Lawesson's reagent ((p-CH$_3$OC$_6$H$_4$-PS$_2$)$_2$), toluene, reflux;

(b) (i) lithium diisopropylamide, tetrahydrofuran, -78 °C, (ii) iodomethane, room temperature

Two isobenzofurans were prepared as shown in **Figure 5.2**[3a]. The phthalides,

100 and **101**, were reacted with Lawesson's reagent to give the respective 1,3-

dihydroisobenzofuran-1-thiones, **102** and **103**. These compounds were deprotonated

with stoichiometric amounts of anhydrous base (lithium diisopropylamide) and

alkylated with iodomethane to give the isobenzofurans, **104** and **105**. Isobenzofurans,

with a few exceptions, are too unstable to be isolated[2] and so in this case they were

trapped *in situ* with the dienophile of interest. This therefore becomes a 'one-pot'

procedure, from the thionolactones through to the final Diels-Alder adduct.

5.3.   The reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with 1-(methylthio)isobenzofuran
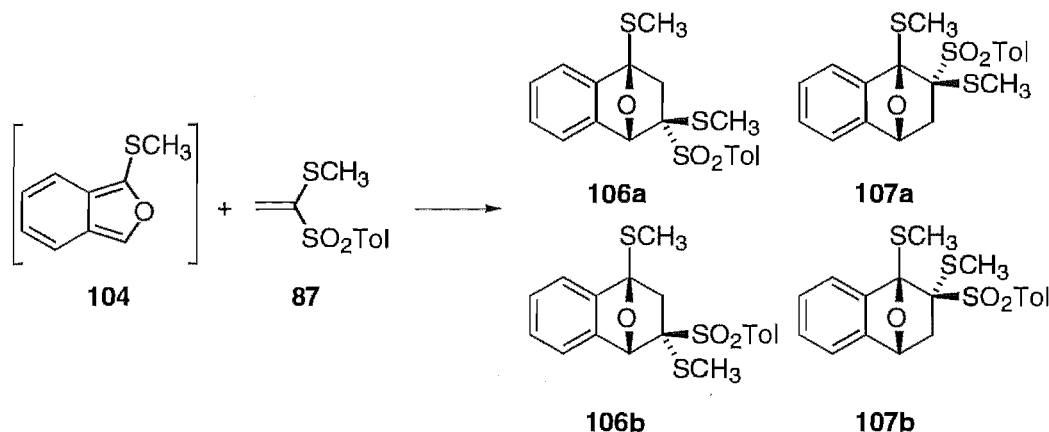
Figure 5.3: The Diels-Alder reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with

1-(methylthio)isobenzofuran

The Diels-Alder reaction of **87** with **104** gave all the four possible regio- and stereo- isomers, **106a, 106b, 107a** and **107b** (**Figure 5.3**). A proton NMR of crude reaction mixtures showed the ratio of the isomers **106a:106b:107a:107b** to be 12:49:13:26 respectively. The slight preference for the formation of the isomers **106b** and **107b** can be attributed to steric effects. An *exo* *p*-tolylsulfonyl group avoids unfavourable steric interactions that would otherwise raise the energy of the Diels-Alder transition state. Only three of the isomers could be isolated by chromatography; **106a** decomposed on the silica. The regio- and stereo- chemistries of the other isomers were proposed on the basis of proton NMR chemical shifts, coupling constants and nOe (Nuclear Overhauser Effect) measurements. The three resonances corresponding to the protons of the methyl groups of each isolated isomer were irradiated. The positive nOes observed in difference spectra are shown in **Figure 5.4**.
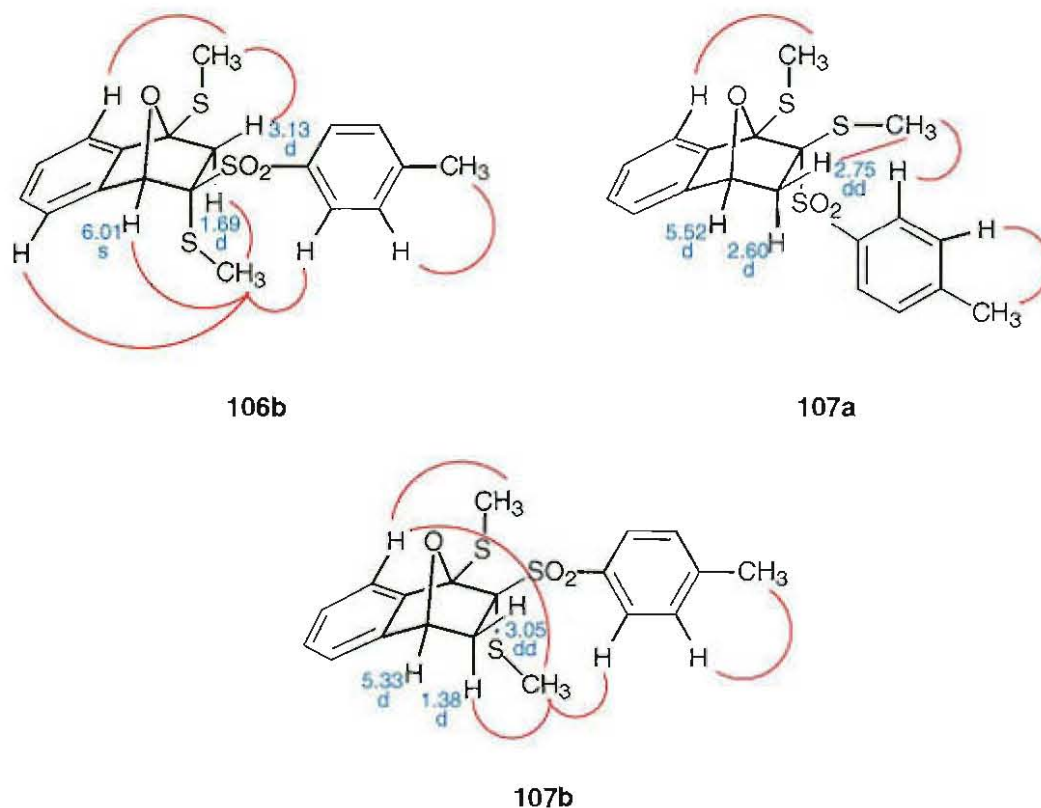
106b   **107a**

107b

Figure 5.4: The nOes observed (when the signals corresponding to the methyl protons were

irradiated) and some chemical shifts and multiplicities observed in the proton NMR of **106b**,

107a and **107b** (s = singlet, d = doublet, dd = doublet of doublets)

Isomer **106b**, underwent elimination of p-toluenesulfinic acid and bridge

opening within a few hours in the NMR solvent (d-chloroform) to give the previously

reported naphthol, **108**[4]. This product slowly oxidised in air to give the

naphthoquinone, **109**[5,6], which showed moderate activity against the *in vitro* P388 anti-

tumour assay, corresponding to an ID_{50} of 196 ng/mL (see Section A.5). This

compound, **109**, and many other substituted naphthaquinones, have been screened

108   **109**
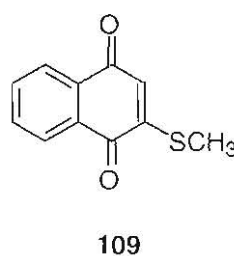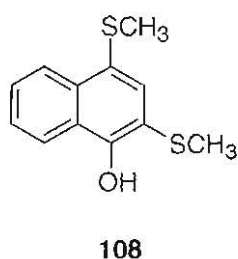
previously for *in vivo* anti-tumour activity in mice[7]. It showed slight to moderate

activity. The adducts with an *ortho* regiochemistry, **107a** and **107b**, appear to have

greater stability.

5.4. The reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with 1-methylthio-3-phenylisobenzofuran

105   **87**   **110**   **111**
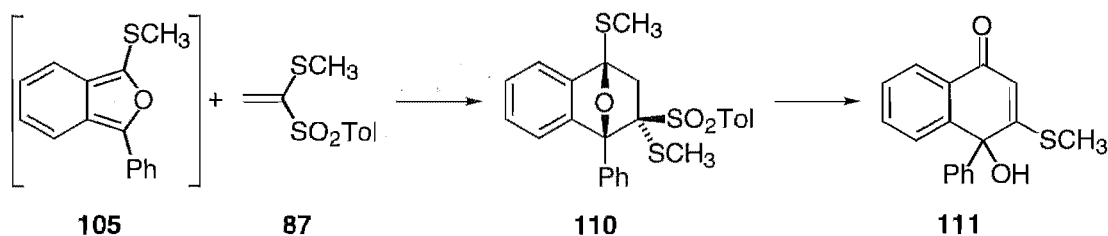
Figure 5.5: The Diels-Alder reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with

1-(methylthio)-3-phenylisobenzofuran and the subsequent decomposition of the adduct formed

When **105** was reacted with **87**, only one adduct, of the four possible isomers,

was observed (**Figure 5.5**). This compound decomposed rapidly in most solvents

making elucidation of regio- and stereo- chemistry by NMR very difficult. The product

of this decomposition was **111**. A nOe was not observed when the methyl protons were

irradiated. Despite this, an X-ray crystal structure demonstrated the regiochemistry to

be that shown (**Figure 5.6**). A strong hydrogen bond was observed between the alcohol

and the carbonyl of a neighbouring molecule in the crystal. This is outlined in **Figure

5.7**. The position of the methylthio substituent in **111** implies that the two methylthio

groups of the initial adduct were orientated *meta*. From steric arguments and the results

of the Diels-Alder reaction between **104** and **87**, it is suspected that the *p*-tolylsulfonyl

group is *exo*. This stereochemistry of **110** is assumed in **Figure 5.5**.
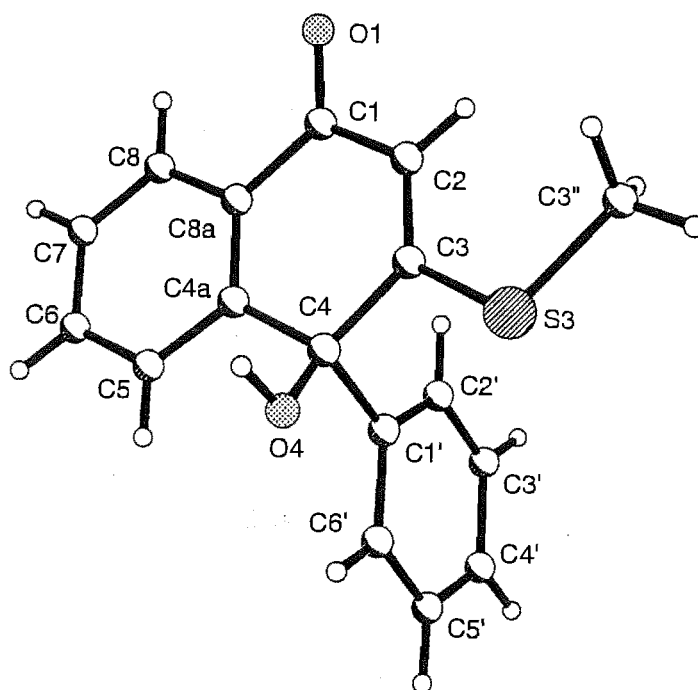
Figure 5.6: The X-ray crystal structure of **111**

(For tables of structural data see Appendix A.3)
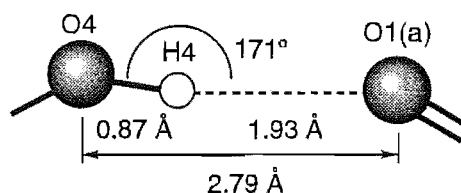
Figure 5.7: Details of the hydrogen bonding observed in the X-ray crystal structure of **111**

The reaction of **105** with **87** was comparatively slow and a major product did not involve reaction with the vinyl sulfone. This product was found to be the keto-*S*-methyl ester, **112**. This structure was confirmed by X-ray crystallography. (**Figure 5.8**). The formation of this type of compound has been observed before in Diels-Alder reactions of isobenzofurans with poor dienophiles[8] and as the product of prolonged exposure of isobenzofuran solutions to the atmosphere[9]. In the case of **112**, it was probably formed by the oxidation of unreacted diene during work-up.
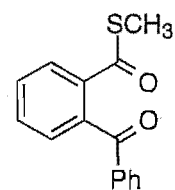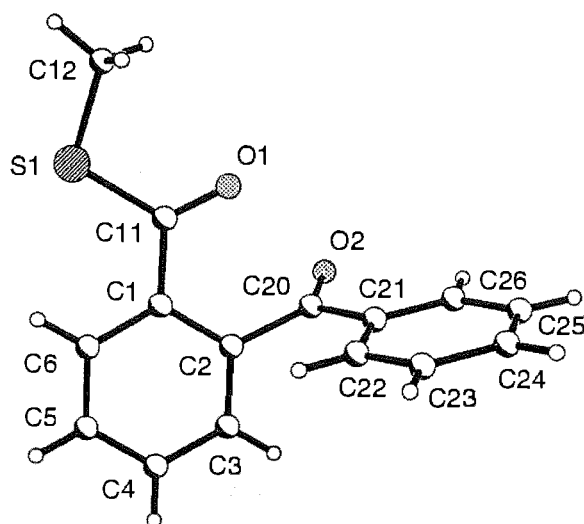
Figure 5.8: The X-ray crystal structure of **112**

(For tables of structural data see Appendix A.4)

5.5. Mechanism of degradation

A proposed mechanism for the formation of **108** and **111** is given in **Figure 5.9**. Following the elimination of *p*-toluenesulfinic acid, the lone pair of electrons on the bridgehead sulfur facilitates opening of the bridge. When R is a hydrogen, elimination of this group leads to the stable aromatic, **108**. However when R is a phenyl substituent, this elimination is no longer facile. The sulfonium cation is hence susceptible to nucleophilic attack by water in the NMR solvent. The resulting 1,4-diol, **113**, eliminates methanethiol to give the observed product **111**.

A similar mechanism has been used to explain the products of Diels-Alder reactions of carbomethoxy alkynes with 1-(ethylthio)-3-phenylisobenzofuran[3b,9] (**Figure 5.10**). The Diels-Alder adduct was not isolated, but underwent a rearrangement that includes an unusual [1,2]-phenyl shift. In the degradation of **110** (described in
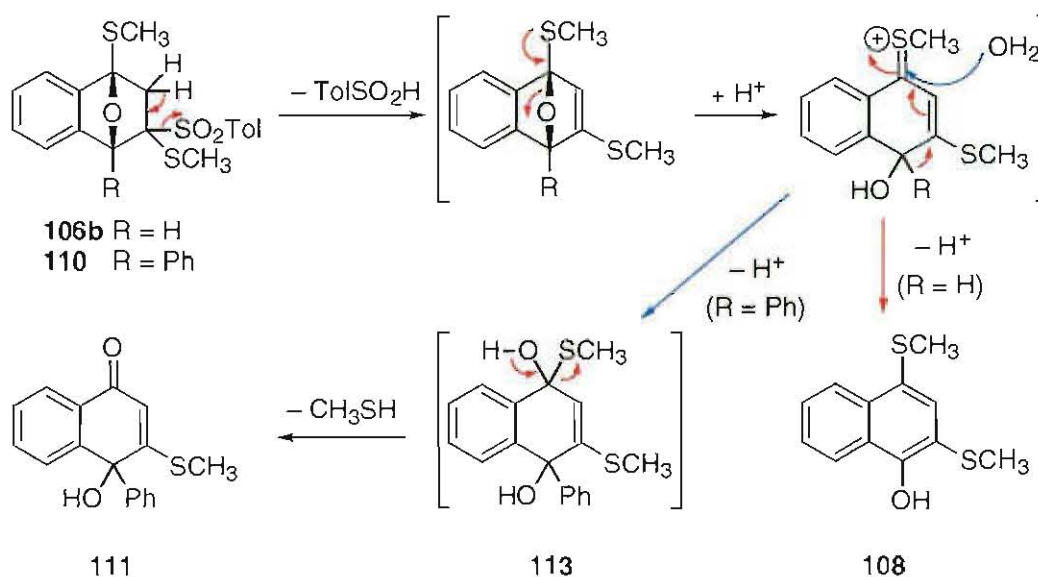
Figure 5.9: A possible mechanism for the degradation of adducts **106b** and **110**
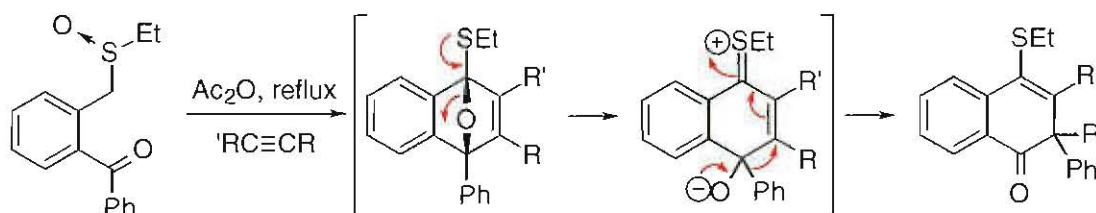
Figure 5.10: The proposed mechanism for the rearrangement of the adduct from the Diels-

Alder reaction of carbomethoxy alkynes (R = CO$_2$CH$_3$, R' = H or CO$_2$CH$_3$) with 1-(ethylthio)-3-

phenylisobenzofuran

Figure 5.9), the sulfonium cation has been trapped by water before a comparable shift

can occur, although the phenyl would also be migrating to a less electrophilic centre.

5.6. Conclusion

1-(Methylthio)isobenzofurans have proved to be sufficiently reactive dienes to

allow the isolation of bridged Diels-Alder adducts upon reaction with 1-methylthio-

1-(*p*-tolylsulfonyl)ethene. However, the reaction involving 1-(methylthio)-isobenzofuran, **104**, occurred with low regio- and stereo- selectivity and the adducts formed were of low stability. The reaction of 1-methylthio-3-phenylisobenzofuran, **105**, with the same dienophile gave only one of the four possible isomers, but this adduct was also relatively unstable. 1-Methylthio-1-(*p*-tolylsulfonyl)ethene has again (see *Chapter 4*) been shown to be an unsuitable diene for the preparation of stable Diels-Alder adducts due to the facile elimination of *p*-toluenesulfinic acid.

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REACTION OF ARYNES WITH 1-(METHYLTHIO)ISOBENZO-FURANS

6.1. Introduction

The preparation of the type of prodrugs described in *Chapter 1* requires the synthesis of stable bridged adducts with an appropriately attached thio substituent. Cleavage of this bridge must result in the formation of an intercalating agent. That is, a planar compound with at least three rings, preferably heterocyclic. The reaction of 1,1-bis(methylthio)ethene with pyranones did provide stable adducts (*Chapter 2*). However, due to difficulties encountered in the preparation of an appropriate diene, the extension of this system to the preparation of adducts capable of producing polycyclic hetero-aromatics was not successful. The Diels-Alder adducts from the reaction of pyranones with 1-methylthio-1-(*p*-tolylsulfonyl)ethene were not isolated (*Chapter 4*). The low reactivity of this system meant that, under the conditions required for reaction, the elimination of *p*-toluenesulfinic acid was facile, triggering aromatisation. This property and the loss in regioselectivity made this dienophile unsatisfactory. To this point, the envisaged prodrugs would have had the trigger attached to the dienophile component of the adduct. The adducts resulting from the reaction of 1-methylthio-1-(*p*-tolylsulfonyl)ethene with 1-(methylthio)isobenzofurans (*Chapter 5*) could have the trigger attached to either the diene or the dienophile component. Some adducts obtained from this more reactive system were isolated, but were unstable and there was still the problem of low regioselectivity. The diene would also require modification if, upon

cleaving the bridge of the adduct, planar, tricyclic compounds containing hetero-atoms were to be obtained.

This chapter reports the preparation of adducts where the envisaged attachment of the trigger is to the diene component only. Using the same dienes as in *Chapter 5*, the Diels-Alder chemistry involving arynes was investigated. The arynes used were benzyne (1,2-didehydrobenzene) and pyridyne (3,4-didehydropyridine). Cleaving the bridge of the resulting adducts provides a route to tricyclic compounds and the use of 3,4-didehydropyridine provides a synthetically simple method for the introduction of a nitrogen ring-atom. This therefore provides a simple, direct method for the preparation of bridged precursors of three-ring, heterocyclic compounds similar in structure to some conventional intercalating agents (Section 1.1.8).

6.2.   Arynes as dienophiles

Arynes are very reactive dienophiles. This presents the potential problem of preparing both the dienophile and the isobenzofuran *in situ*. The method required for the preparation of the arynes must be compatible with the isobenzofuran chemistry. The method chosen was the base promoted elimination of HX from a haloarene (**Figure 6.1**). Arynes are susceptible to nucleophilic attack and therefore the bulky base, lithium 2,2,6,6-tetramethylpiperidide, was used[1]. Literature precedent for this preparation of arynes in the presence of isobenzofurans involves alkoxy substituted isobenzofurans[2,3].
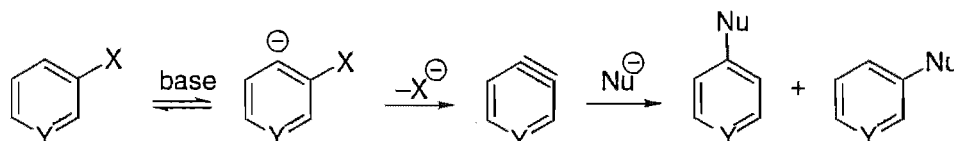
Figure 6.1: The preparation of an aryne (Y = CH or N) by base promoted elimination of a haloarene (X = Cl or Br) and the subsequent potential for nucleophilic attack

The preparation of pyridyne involving the reaction of 3-halopyridines with a strong base has been observed to produce 3,4-didehydropyridine rather than the regioisomer, 2,3-didehydropyridine[4]. This has been explained using the results of D/H exchange studies of pyridine with $NaND_2$ in ND_3. The relative rates of exchange of the 2-, 3- and 4- hydrogen atoms of pyridine are in the ratio 1:100:1000 respectively. Moreover, theoretical calculations have showed 3,4-didehydropyridine to be the most stable class of didehydropyridines.

6.3. The reaction of 1,2-didehydrobenzene with 1-methylthio-3-phenylisobenzofuran

The Diels-Alder reaction of 1,2-didehydrobenzene with **105** gave one product, **115** (**Figure 6.2**). This product has been reported previously from unrelated chemistry[5]. The central ring of the transient Diels-Alder adduct, **114**, is a similar oxygen-bridged cyclohexadiene to that obtained when p-toluenesulfinic acid is eliminated from the 1-methylthio-1-(p-tolylsulfonyl)ethene Diels-Alder adduct, **110** (*Chapter 5*). Consequently **114** has degraded in a similar manner to **110**, resulting in the anthrone, **115**; a product analogous to **111**. This could have occurred during work-up or chromatography.

105   **114**   **115**
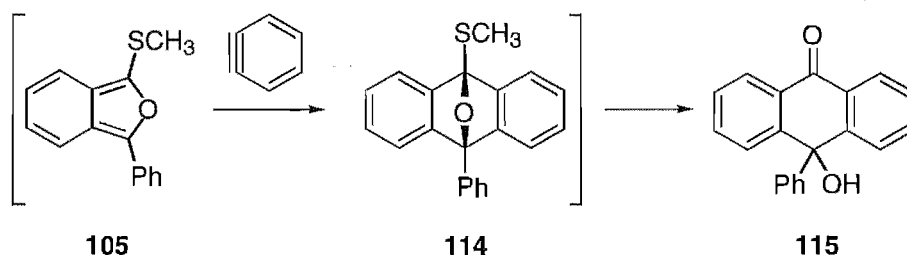
Figure 6.2: The Diels-Alder reaction of 1,2-didehydrobenzene with 1-methylthio-3-phenyl-isobenzofuran and the subsequent decomposition of the adduct formed

6.4. The reaction of 3,4-didehydropyridine with 1-methylthio-3-phenylisobenzofuran

The reaction of the nitrogen-containing dienophile, 3,4-didehydropyridine, was then investigated. The dienophile was formed from 3-bromopyridine and upon reaction with **105** gave equal amounts of the two possible bridged adducts, **116a** and **b** (**Figure 6.3**). The lack of regioselectivity of this dienophile is consistent with previous results[3]. In an attempt to separate these two isomers by chromatography, **116a** was isolated; **116b** had decomposed to **117b**, the product analogous to **115**. Similar decomposition of **116a** eventually occurred on storage, even under nitrogen at 0 °C, to give **117a**.
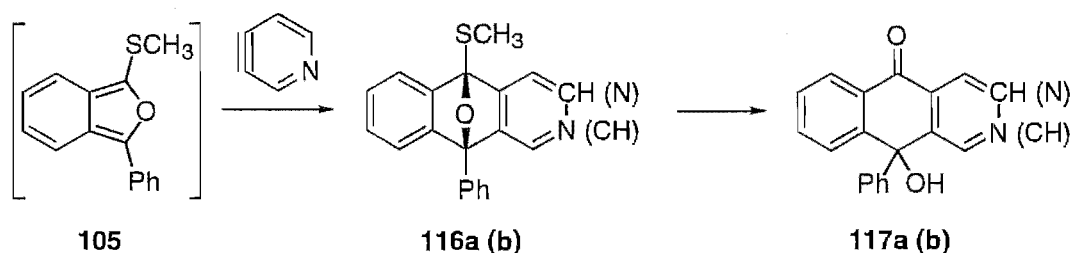
Figure 6.3: The Diels-Alder reaction of 3,4-didehydropyridine with 1-methylthio-3-phenyl-isobenzofuran and the subsequent decomposition of the adducts formed

6.5. The reaction of 3,4-didehydropyridine with 1-(methylthio)isobenzofuran

The isolation of bridged adducts which, upon bridge cleavage, produced tricycles containing hetero-atoms was encouraging for the successful preparation of a prodrug of an intercalating agent. This preparation was a 'one-pot' synthesis involving readily available starting materials. However, it is difficult for the resulting adducts to achieve planarity, as is seen in the formation of the non-planar compounds: **115**, **117a** and **117b**. Even if planarity was achieved, the bulky aromatic substituent is not likely to
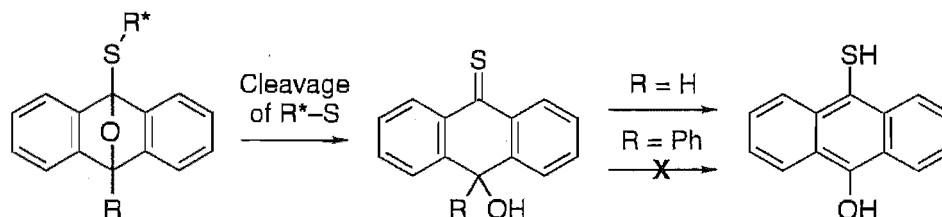
Figure 6.4: The transformation of abridged adduct to a planar, aromatic compound upon cleavage of a trigger (R*)

assist the binding of the resulting intercalating agent. Therefore it preferable to remove the phenyl group from the isobenzofuran. An adduct resulting from a Diels-Alder reaction involving a 3-unsubstituted-isobenzofuran is more likely to achieve planarity upon bridge-cleavage (**Figure 6.4**).

The reaction of 3,4-didehydropyridine with 1-(methylthio)isobenzofuran was attempted. A proton NMR of the crude reaction mixture showed the presence of the expected Diels-Alder adducts, **118a** and **b** (**Figure 6.5**). These isomers were identified using data from subsequent reactions (see Section 6.6). An attempt to purify and separate these isomers by chromatography gave a complex mixture of products. One product was isolated and identified as the known compound, 2-azaanthraquinone, **119**[6,7].

104   **118a (b)**   **119**
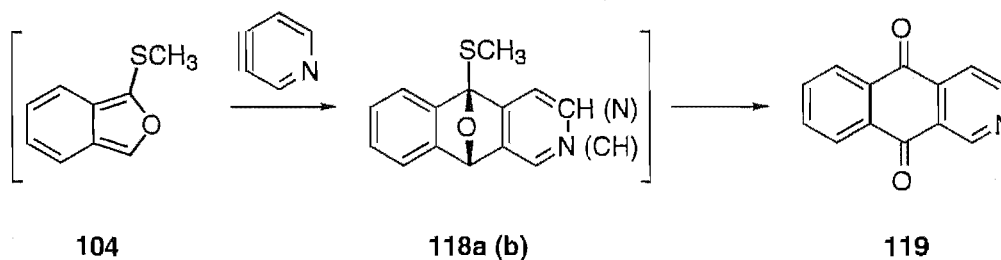
Figure 6.5: The Diels-Alder reaction of 1-(methylthio)isobenzofuran with 3,4-didehydropyridine

Azaanthraquinones are known physiologically active compounds[8]. 2-Azaanthraquinone has specifically been noted as an insect teratogen; application to insect eggs causing mutation[7,9]. Some 3-substituted-1-azaanthraquinones, **120**, have

shown potent anti-tumour activity against human cancer cell

lines[10]. The substituents (R) are thought to be capable of

alkylating the DNA, increasing the residence time of the

intercalating agent. The reported cytotoxic activity of this type

of compound is encouraging for the preparation of successful

cancer prodrugs by the reaction of 3,4-didehydropyridines

with 1-(alkylthio)isobenzofurans.
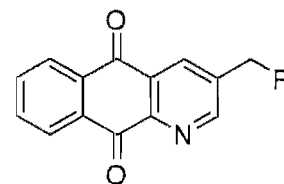
120

6.6.   The reaction of 3,4-didehydropyridine with 1-methylthio-3-(trimethylsilyl)isobenzofuran

The method for the preparation of **118a** and **b** requires refinement to allow

their isolation in reasonable yields. The reaction of 3,4-didehydropyridine with **104** has

the complication that the addition of lithium 2,2,6,6-tetramethylpiperidide to induce the

formation of the aryne, could lithiate the unsubstituted site of the furan ring. The

protection of this position has been described previously for the reaction of alkoxy

substituted isobenzofurans with arynes[2,3]. In these reports protection was achieved by

the addition of a trimethylsilyl substituent. Therefore **121** was prepared by the lithiation

of **104** and subsequent reaction with trimethylsilyl chloride (**Figure 6.6**). The resulting

104   **121**   **122a (b)**
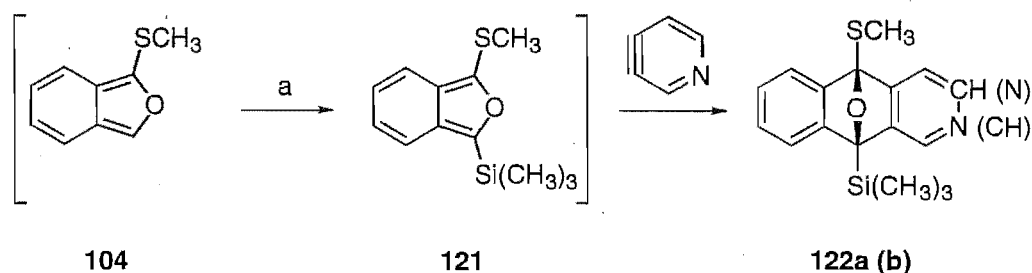
Figure 6.6: The preparation and Diels-Alder reaction of 1-methylthio-3-(trimethylsilyl)-

isobenzofuran with 3,4-didehydropyridine

Reagents and conditions: (a) (i) lithium diisopropylamide, tetrahydrofuran, -78 °C,

(ii) trimethylsilyl chloride, room temperature

disubstituted isobenzofuran was reacted with 3,4-didehydropyridine in the usual manner. This was a 'one-pot' synthesis; from the thionolactone, **102**, through to the Diels-Alder reaction. The sequence of reactions starts with deprotonation of the thionolactone followed by methylation, lithiation of the isobenzofuran, followed by silylation, addition of bromopyridine and finally the formation of 3,4-didehydropyridine *in situ* by the addition of lithium 2,2,6,6-tetramethylpiperidide. This process was successful in allowing the isolation and characterisation of the Diels-Alder adducts, **122a** and **b** (**Figure 6.6**). These two isomers were formed in equal amounts. Removal of the protecting group is required to give the desired adducts, **118a** and **b**.

Deprotection of the mixture of adducts was carried out using tetrabutylammonium fluoride (TBAF) in tetrahydrofuran; a source of 'naked' fluoride ions. The removal of the trimethylsilyl substituent is driven by the formation of the strong silicon-fluorine bond. These conditions brought about clean deprotection of **122a** and **b** to give the corresponding mixture of isomers, **118a** and **b** (**Figure 6.7**). A successful preparation of a bridged precursor of a tricyclic hetero-aromatic compound has been found. No attempt was made to separate the two regioisomers.

122a (b)   **118a (b)**
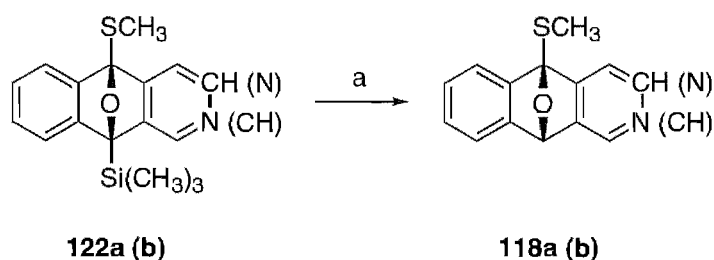
Figure 6.7: The deprotection of the 1-methylthio-3-(trimethylsilyl)isobenzofuran,

3,4-didehydropyridine Diels-Alder adduct

Reagent and conditions: (a) TBAF, tetrahydrofuran, 0 °C

Cleavage of the bridge of **118a** and **b** was achieved by the addition of a catalytic amount of trifluoroacetic acid (TFA). These conditions gave a similar complex
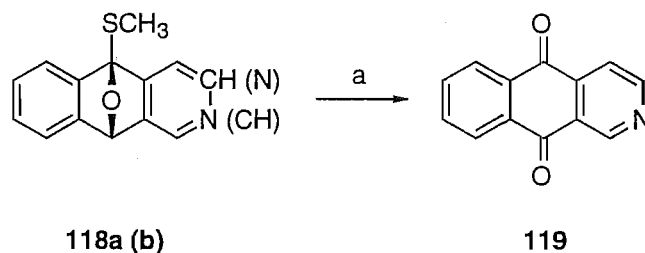
Figure 6.8: Cleavage of the bridge of the deprotected Diels-Alder adduct

Reagent and conditions: (a) TFA, CDCl₃, room temperature

mixture of products to that obtained from the direct Diels-Alder reaction of 1-(methylthio)isobenzofuran with 3,4-didehydropyridine (Section 6.5), including the azaanthraquinone, **119** (**Figure 6.8**).

The protection of the unsubstituted site of the furan ring of **104** with a trimethylsilyl group has allowed the isolation of the Diels-Alder adducts resulting from reaction with 3,4-didehydropyridine. Deprotection of this isomeric pair of adducts allowed the preparation of the required Diels-Alder adducts, **118a** and **b**. Cleavage of the oxygen-bridge gave, amongst other products, 2-azaanthraquinone, a known biologically active compound.

6.7. Conclusion

Reaction of 1-(methylthio)isobenzofurans with arynes was successful, and in some cases the bridged adducts formed were stable enough to be isolated. The use of 3,4-didehydropyridine allowed the straightforward preparation of bridged tricycles containing a nitrogen atom. The reaction involving the 3-unsubstituted isobenzofuran required the protection of this position to allow adduct isolation. The adducts prepared were precursors to a planar tricyclic compound containing a nitrogen ring-atom. Polycyclic, hetero-aromatic structures are characteristic of known intercalating agents.

Moreover, the chromophore obtained is known to have significant effects on the biochemistry of DNA, a regioisomer of which is a potent intercalating agent against human cancer cell lines.

Major inroads have been made into achieving the aim of this thesis. Chemistry relevant to the preparation of compounds which are possible cancer chemotherapeutic prodrugs has been investigated. A bridged precursor of a known biologically active compound has been isolated and this latent activity released upon cleavage of the bridge.

6.8.   References

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EXPERIMENTAL

7.1. General

Radial chromatography was performed using a 1, 2 or 4 mm silica plate. The silica was gradient eluted with the stated solvents. Gradient eluting involves eluting the silica with 0 to 100% of the more polar solvent combined with the less polar solvent. The plate was washed and reactivated using methanol.

Melting points (m.p.) were determined on a Reichert Hotstage microscope and are uncorrected.

Infra-red (IR) spectra were scanned on a Shimadzu FTIR-8201PC or a Perkin-Elmer 1600-FTIR spectrophotometer. The sample was presented as a $CDCl_3$ solution in a 0.1 or 1.0 mm NaCl solution cell, as an oil or as a Nujol® mull on NaCl plates. Positions of maximum absorptions (υ_{max}) are recorded in wavenumbers (cm^{-1}) and relative intensities denoted as weak (w), medium (m) or strong (s).

Ultra-violet (UV) spectra were scanned on a Hewlett Packard 8452A diode array spectrometer and the wavelengths (nm) of maximum absorptions (λ_{max}) recorded. The intensities of the maxima are expressed as molar absorptivities (ε).

Proton nuclear magnetic resonance (^1H NMR) and two dimensional nuclear magnetic resonance spectra were performed on a Varian Unity 300 MHz Fourier transform spectrophotometer. Peaks are quoted in ppm (δ) relative to tetramethylsilane (TMS) and multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q), mutiplet (m) or broad (br). Coupling constants (J) are quoted in Hertz (Hz).

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were performed at 75 MHz on a Varian Unity 300 MHz or a Varian XL 300 MHz Fourier transform spectrophotometer. Peaks are quoted in ppm (δ) relative to TMS.

NMR spectra were referenced (to residual protonated solvent) as follows:

Deuterated Solvent	Abbreviation	^{1}H NMR (δ)	^{13}C NMR (δ)
Chloroform	CDCl$_3$	7.24	77.00
Acetone	d$_6$-acetone	2.17	29.20 (methyl)
Benzene	C$_6$D$_6$	7.27	128.40
Dimethylsulfoxide	d$_6$-DMSO	2.60	39.60
Methanol	CD$_3$OD	3.30 (methyl)	49.30
Water	D$_2$O	4.70	–

Electron ionisation mass spectra (m/z) were performed on a Kratos MS80RFA operating at 4 kV and electron impact at 70 e V ([EI(70)]). Where possible, the high resolution mass of the parent ion is compared with the expected calculated value. The relative intensities of the fragment ions are quoted as a percentage.

Elemental microanalyses of crystalline samples were performed at the Chemistry Department, University of Otago, New Zealand.

X-ray crystallographic data were collected as follows: The unit cell parameters were obtained by least-squares refinement of the setting angles of reflections from a Siemens P4 diffractometer. A unique data set was measured (ω scans). The unique reflections obtained were used in the full-matrix least-squares refinement [SHELXL-93][1]. The intensities of 3 standard reflections were measured every 97 reflections throughout the data collection to check for decay. The structure was solved by direct methods [SHELXS-86][2]. Hydrogen atoms were fixed in idealised positions. All non-hydrogen atom parameters were refined using anisotropic atomic displacement

parameters. Neutral scattering factors and anomalous dispersion corrections for non-hydrogen atoms were taken from Ibers and Hamilton[3].

Solvents were purified as follows:

- *Acetonitrile* was pre-dried over potassium carbonate and distilled from phosphorus pentoxide.

- *Dichloromethane* was pre-dried over calcium chloride and distilled from calcium hydride.

- *Carbon tetrachloride* and *chloroform* were distilled from phosphorus pentoxide.

- *Dimethylformamide* was pre-dried over calcium hydride and distilled *in vacuo*.

- *Ethanol* and *methanol* were distilled from the appropriate magnesium alkoxide.

- *Ether (diethyl ether)* was pre-dried over calcium chloride and distilled from conc. sulfuric acid. Especially dry ether was further distilled from sodium wire using benzophenone as an indicator.

- *Ethyl acetate* was pre-dried over calcium chloride and distilled from calcium hydride.

- *Petroleum ether* was distilled from phosphorus pentoxide; the fraction distilling between 50 and 70 °C was collected.

- *Tetrahydrofuran* was pre-dried over calcium chloride and distilled from sodium wire using benzophenone as an indicator.

- *Toluene* and *benzene* were pre-dried over calcium chloride and distilled from calcium hydride.

Reagents:

These were purified in accordance with the recommendations collected in Perrin and Armarego[4] or used as obtained from commercial sources.

7.2. Preparation of 1,1-bis(methylthio)ethene (19)

Methyl dithioacetate (24)[5]

$$CH_3I \quad \begin{array}{c} 1)\ Mg/ether \\ 2)\ CS_2 \\ \hline 3)\ NH_4OH \end{array} \quad CH_3-C\overset{S}{\underset{S^- NH_4^+}{\diagdown}} \quad \begin{array}{c} 4)\ (CH_3O)_2SO_2 \\ \hline \end{array} \quad CH_3-C\overset{S}{\underset{SCH_3}{\diagdown}}$$
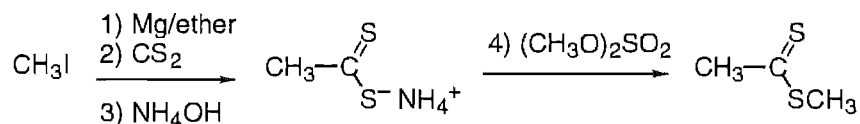
A few drops of iodomethane and a crystal of iodine were added to dry ether (300 mL) and magnesium turnings (17.2 g, 0.71 mol, 1.0 eq.). The mixture, in a dry nitrogen atmosphere, was gently warmed until reaction started. The rest of the iodomethane (44 mL, 0.70 mol, 1.0 eq.) was added slowly. The solution was left refluxing, with stirring, for a further 25 mins. The solution was cooled in ice, and carbon disulfide (50 mL, 0.83 mol, 1.2 eq.) was added slowly. The solution was left stirring in ice overnight. (CAUTION: very strong odour present throughout the rest of this experiment.) The ice cold solution was then poured slowly onto crushed ice (400 mL) and aqueous ammonia (sp.gr. = 0.880, 50 mL) was added. The precipitate formed was filtered off through fluted filter paper. The aqueous layer was separated and the organic layer extracted with water (2 x 50 mL). Dimethyl sulfate (30 mL, 0.24 mol, 0.34 eq.) was added to the combined aqueous extracts. This solution was left stirring under dry nitrogen over two days. The resulting biphasic solution was extracted with CH_2Cl_2 (6 x 50 mL). The combined organic extracts were dried (K_2CO_3) and filtered. The solvent was removed by distillation and the crude product purified by vacuum distillation.

Yield of **24**: 2.2 g, 20.7 mmol, 3%; yellow oil; b.p. 37-38 °C/12 mmHg; ^{1}H NMR (CDCl$_3$): δ 2.63 (3H, s), 2.87 (3H, s).

1,1-Bis(methylthio)ethene (ketene dimethyl thioacetal) (19)

$$CH_3-C\overset{S}{\underset{SCH_3}{\diagdown}} \quad \begin{array}{c} 1)\ LDA \\ \hline 2)\ CH_3I \end{array} \quad CH_2=C\overset{SCH_3}{\underset{SCH_3}{\diagdown}}$$
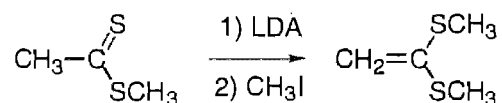
n-Butyllithium (4.2 mL of 1.6 mol L^{-1} solution in hexanes, 6.67 mmol, 1.25 eq.) was added dropwise to a stirred solution of diisopropylamine (0.9 mL, 6.41 mmol, 1.2 eq.) in tetrahydrofuran (6 mL) under dry nitrogen in an ice-salt bath. The solution was stirred for 20 minutes at this temperature and then cooled further in an acetone/dry ice bath. A solution of methyl dithioacetate (567 mg, 5.34 mmol, 1.0 eq.) in tetrahydrofuran (8 mL) was added dropwise. The solution was stirred under nitrogen at -78 °C for 2.5 hours. Iodomethane (0.84 mL, 13.3 mmol, 2.5 eq.) was added dropwise and the resulting mixture allowed to warm to room temperature and left stirring overnight. The tetrahydrofuran was removed by distilling through a Vigreux column at atmospheric pressure. Ether (6 mL) and water (6 mL) were added to the residue, the organic layer separated and the aqueous layer extracted with ether (2 x 4 mL). The combined organic layers were dried (MgSO4), filtered, and the ether removed by distillation through a Vigreux column at atmospheric pressure to give the crude product.

Yield of **19**: 610 mg, 5.07 mmol, 95%; yellow oil; ^{1}H NMR (CDCl3): δ 2.33 (6H, s), 5.21 (2H, s) (lit.[6] δ 2.28 (6H, s), 5.08 (2H, s)).

7.3.   Preparation of methyl coumalate (25)

Methyl 2-oxo-2*H*-pyran-5-ylcarboxylate (methyl coumalate) (25)[7]
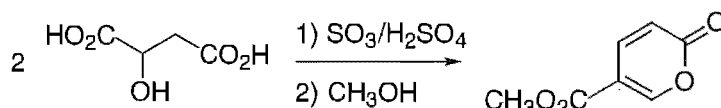
Concentrated sulfuric acid (8.5 mL) was added to malic acid (10.3 g, 0.077 mol, 2.0 eq.). To this suspension were added three 2.5 mL portions of 20% fuming sulfuric acid at 45 minute intervals. Once all the solid had dissolved the solution was heated on a steam bath for 1.5 hours. The reaction mixture was cooled,

methanol (15 mL, 0.37 mol, 10 eq.) was added, the mixture vigorously shaken to make it homogeneous., The solution was then heated on a steam bath for another hour, cooled and poured slowly onto crushed ice (40 g) with stirring. The solution was neutralised with sodium carbonate, filtered and the filtrate extracted with dichloromethane (4 x 20 mL). The combined organic extracts were washed with water, dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude product was recrystallised twice from petroleum ether/ethyl acetate.

Yield of **25**: 1.88 g, 12.2 mmol, 32%; pale yellow crystals; m.p. 68-69 °C; IR (CDCl$_3$): υ_{max} 1755 (s), 1728 (s), 1638 (w), 1558 (w), 1445 (m), 1303 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.89 (3H, s), 6.35 (1H, dd, J = 1.5, 9.8 Hz), 7.80 (1H, dd, J = 2.4, 9.8 Hz), 8.32 (1H, dd, J = 1.5, 2.4 Hz).

7.4. Preparation of methyl 4,6-dimethylcoumalate (26)

Methyl 4,6-dimethyl-2-oxo-2*H*-pyran-5-ylcarboxylate (methyl 4,6-dimethylcoumalate) (26)[8]
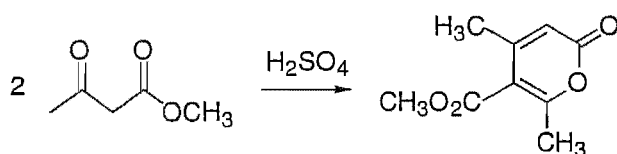
To concentrated sulfuric acid (5.1 mL), cooled to 10 °C, was added methyl acetoacetate (5.4 mL, 50 mmol) at such a rate that the temperature of the mixture remained below 15 °C. This solution was left standing at room temperature for 4 days with occasional stirring and was then poured onto ice (10 g). The product was extracted with ether (20 mL, 2 x 10 mL) and the combined organic extracts washed with aqueous NaHCO$_3$ (half saturated, 4 x 5 mL), brine (5 mL), dried (NaSO$_4$), filtered and concentrated *in vacuo*. The crude product was recrystallised from petroleum ether/ethyl acetate.

Yield of **26**: 830 mg, 4.56 mmol, 18%; white crystals; m.p. 62-64 °C; ^{1}H

NMR (CDCl$_3$): δ 2.22 (3H, d, *J* = 1.0 Hz), 2.40 (3H, s), 3.88 (3H, s), 6.03 (1H, s).

7.5. Diels-Alder reaction between 1,1-bis(methylthio)ethene (19) and methyl coumalate (25)

7,7-Bis(methylthio)-3-carbomethoxy-5-oxabicyclo[2.2.2]oct-2-en-6-one (28)
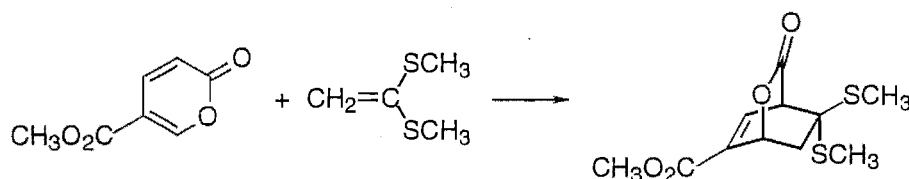
Methyl 2-oxo-2*H*-pyran-5-ylcarboxylate (40 mg, 0.26 mmol, 1.0 eq.) and

1,1-bis(methylthio)ethene (94 mg, 0.78 mmol, 3.0 eq.) were dissolved in toluene

(10 mL). The solution was refluxed under nitrogen for 22 hours and then concentrated

in vacuo. The crude product was purified using radial chromatography, eluting with

90% petroleum ether/10% ethyl acetate. The product can be recrystallised from

petroleum ether/ethyl acetate.

Yield of **28**: 53 mg, 0.19 mmol, 74%; white needles; m.p. 92-93.5 °C; IR

(CDCl$_3$): υ$_{max}$ 2955 (w), 2921 (w), 1758 (s), 1726 (s), 1635 (m) cm^{-1}; ^{1}H NMR

(CDCl$_3$): δ 2.10 (3H, s), 2.12 (1H, dd, *J* = 2.0, 14.2 Hz), 2.17 (3H, s), 2.47 (1H, dd, *J* =

3.9, 14.2 Hz), 3.83 (3H, s), 3.88 (1H, d, *J* = 6.4 Hz), 5.70 (1H, ddd, *J* = 2.0, 2.0, 3.9

Hz), 7.28 (1H, dd, *J* = 2.0, 6.4 Hz); ^{13}C NMR (CDCl$_3$): δ 12.41, 12.62, 40.56, 51.28,

52.35, 57.09, 73.05, 135.38, 139.07, 162.44, 168.87; m/z [EI (70)]: 274.0337 (found),

274.03335 (calcd.); 274 (M$^+$, 10%), 227 (M$^+$-SCH$_3$, 14%), 182 (M$^+$-CO$_2$, -SCH$_3$, -H,

100%), 124 (M$^+$-CO$_2$, -SCH$_3$, -CO$_2$CH$_3$, 88%).

Anal. Calcd. for C$_{11}$H$_{14}$O$_4$S$_2$: C, 48.16; H, 5.14; S, 23.37. Found: C, 47.98; H,

4.98; S, 23.23%.

7.6. Diels-Alder reaction between 1,1-bis(methylthio)ethene (19) and methyl 4,6-dimethylcoumalate (26)

Methyl 2,6-dimethyl-4-(methylthio)benzoate (31)
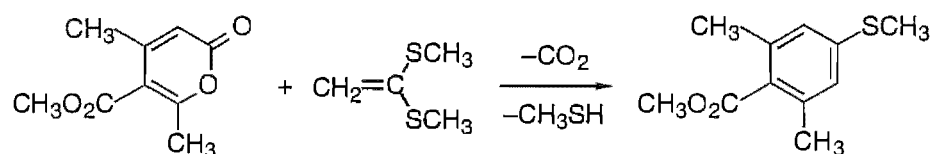
Methyl 4,6-dimethyl-2-oxo-2H-pyran-5-ylcarboxylate (45 mg, 0.25 mmol, 1.0 eq.) and 1,1-bis(methylthio)ethene (89 mg, 0.74 mmol, 3.0 eq.) were dissolved in toluene (10 mL). The solution was refluxed under nitrogen for 9 days and then concentrated *in vacuo*. A ^{1}H NMR spectrum of the crude reaction mixture showed that the reaction was 50% complete. The reaction was stopped at this stage and the product was purified using radial chromatography, eluting with petroleum ether. Some starting material (9 mg, 20%) was recovered.

Yield of **31**: 11 mg, 0.05 mmol, 21%; pale yellow oil; IR (CDCl₃): υ_{max} 2953 (w), 2926 (w), 1720 (s), 1590 (m), 1438 (m), 1273 (s) cm⁻¹; ^{1}H NMR (CDCl₃): δ 2.30 (6H, s), 2.46 (3H, s), 3.89 (3H, s), 6.90 (2H, s); ^{13}C NMR (CDCl₃): δ 15.21, 19.94, 51.82, 125.01, 130.28, 136.01, 140.19, 170.11; m/z [EI (70)]: 210.0716 (found), 210.07145 (calcd.); 210 (M⁺, 95%), 179 (M⁺-OCH₃, 100%).

7.7. Preparation of 2-(2-benzoylphenyl)propanoic acid (39)[9]

3-Methylindan-1-one (36)
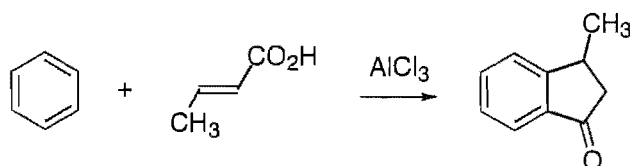
Anhydrous $AlCl_3$ (68 g, 0.51 mol, 3.2 eq.) was carefully added to crotonic acid (14.05 g, 0.16 mol, 1.0 eq.) in dry benzene (110 mL, 1.24 mol, 7.8 eq.). The resulting solution was refluxed for 5 hours and then the reaction quenched by pouring carefully into ice water (350 mL) in an ice bath. The resulting mixture was split in two and each half worked up as follows: Conc HCl (10 mL) and ethyl acetate (20 mL) was added. The aqueous layer was separated and extracted with ethyl acetate (2 x 30 mL). The organic layers were combined and washed with aqueous NaOH solution (4 mol L^{-1}, 2 x 50 mL) and water (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by vacuum distillation.

Yield of **36**: 9.18 g, 62.8 mmol, 38%; pale yellow oil; b.p. 70-74 °C/1 mmHg; ^{1}H NMR ($CDCl_3$): δ 1.41 (3H, d, J = 6.8 Hz), 2.28 (1H, dd, J = 3.4, 19.1 Hz), 2.94 (1H, dd, J = 7.3, 19.1 Hz), 3.45 (1H, m), 7.38 (1H, br t), 7.51 (1H, br d), 7.62 (1H, br t), 7.74 (1H, br d).

1-Methyl-3-phenyl-1*H*-indene (38)
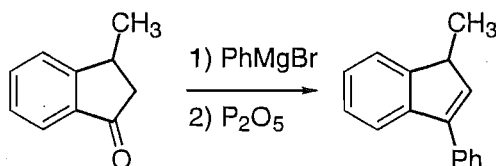
Magnesium turnings (1.10 g, 0.043 mol, 1.4 eq.) were stirred in freshly dried ether (24 mL). A few drops of bromobenzene solution (5.0 mL, 0.048 mol, 1.5 eq.; in 8 mL of ether) and a crystal of iodine were added to initiate the reaction. The remainder of the bromobenzene solution was added at such a rate as to maintain reflux. The solution was allowed to reflux for a further 10 minutes and then cooled to 0 °C. 3-Methylindan-1-one (4.50 g, 0.031 mol, 1.0 eq.) in ether (8 mL) was added slowly. The white precipitate formed was acidified with 10% sulfuric acid and the organic layer separated, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was taken up in toluene (30 mL) and refluxed over P_2O_5 (4.0 g, 0.028 mol, 0.9 eq.) for one hour.

After decantation of the organic solution and removal of the toluene, the residue was purified by vacuum distillation.

Yield of **38**: 3.64 g, 17.65 mmol, 57%; yellow oil; b.p. 116-120 °C/1 mmHg; ^{1}H NMR (CDCl$_3$): δ 1.39 (3H, d, J = 7.8 Hz), 3.59 (1H, dq, J = 2.0, 7.8 Hz), 6.52 (1H, d, J = 2.0 Hz), 7.24-7.62 (9H, m).

(2-Benzoylphenyl)propanoic acid (39)
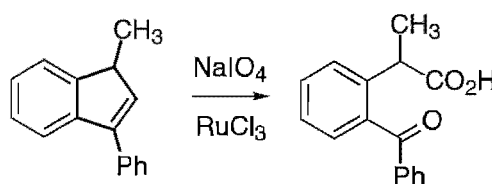
1-Methyl-3-phenyl-1H-indene (2.47 g, 11.9 mmol, 1.0 eq.) was added to a solution of sodium metaperiodate (10.45 g, 48.9 mmol, 4.1 eq.) in carbon tetrachloride (24 mL), acetonitrile (24 mL) and water (36 mL). To this biphasic solution, ruthenium trichloride hydrate (60 mg, 0.27 mmol, 0.02 eq.) was added, and the entire mixture stirred vigorously for 22 hours at room temperature. Dichloromethane (120 mL) and water (160 mL) were added, the organic layer removed, and the aqueous layer extracted with dichloromethane (3 x 20 mL). The combined organic extracts were extracted with aqueous sodium hydroxide solution (2 mol L^{-1}, 100 mL, 3 x 50 mL), the aqueous layer acidified with conc. HCl and the precipitate formed extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with water (50 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude product was recrystallised twice from benzene/petroleum ether.

Yield of **39**: 1.75 g, 6.87 mmol, 57%; white crystals; m.p. 85-86 °C; ^{1}H NMR (CDCl$_3$): δ 1.55 (3H, d, J = 6.8 Hz), 4.02 (1H, q, J = 6.8 Hz), 7.33-7.43 (2H, m), 7.50-7.71 (5H, m), 7.90 (2H, br d).

7.8. Diels-Alder reactions involving 4-methyl-1-phenyl-3*H*-2-benzopyran-3-one (40)

11,14-Dioxa-8-methyl-1-phenyltetracyclo[6.5.2.0^{2,7}.0^{9,13}]pentadec-2,4,6-trien-10,12,15-trione (41)[9]
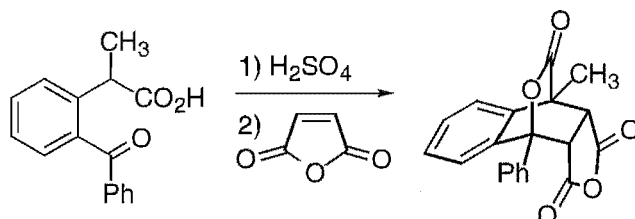
2-(2-Benzoylphenyl)propanoic acid (49 mg, 0.19 mmol, 1.0 eq.) was dissolved in conc. H$_2$SO$_4$ (0.16 mL) with gentle warming on a water bath to give an orange solution. Water (20 mL) was added to produce a deep red precipitate which was rapidly extracted with ethyl acetate (20 mL) containing maleic anhydride (95 mg, 0.97 mmol, 5.0 eq.). The aqueous layer was further extracted with ethyl acetate (10 mL). The solution was left standing for 3.5 hours after which time the red colour had faded to a pale orange. The solution was washed with saturated aqueous NaHCO$_3$ (10 mL), water (10 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*.

Yield of **41**: 46 mg, 0.14 mmol, 71%; white crystals; m.p. 218-220 °C (decomp. 205 °C); ^{1}H NMR (CDCl$_3$): δ 2.09 (3H, s), 3.66 (1H, d, *J* = 9.3 Hz), 4.68 (1H, d, *J* = 9.2 Hz), 6.99 (1H, d, *J* = 8.3 Hz), 7.36 (1H, br t), 7.45 (1H, br d), 7.51-7.59 (4H, m), 7.82 (2H, m).

11,11-Bis(methylthio)-1-methyl-9-oxa-8-phenyltricyclo[6.2.2.0^{2,7}]dodec-2,4,6-trien-10-one (42)[9]
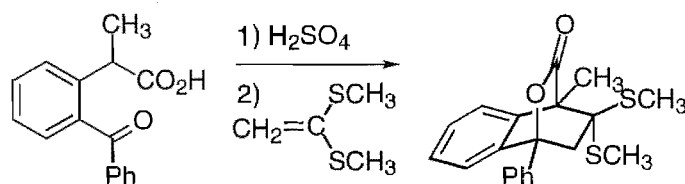
2-(2-Benzoylphenyl)propanoic acid (45 mg, 0.18 mmol, 1.0 eq.) was dissolved in conc. H_2SO_4 (0.18 mL) with gentle warming on a water bath to give an orange solution. Water (25 mL) was added to produce a deep red precipitate which was extracted with ethyl acetate (2 x 20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* (not to dryness). Toluene (20 mL) was added, and the solution concentrated *in vacuo* to remove any remaining ethyl acetate. Another 20 mL of toluene was added and the solution concentrated *in vacuo* to a final volume of 12 mL. 1,1-Bis(methylthio)ethene (54 mg, 0.45 mmol, 2.5 eq.) was added and the solution was refluxed under nitrogen for 24 hours, after which time the red colour had faded to a pale orange. The solvent was removed and the crude product purified using radial chromatography, eluting with 90% petroleum ether/10% ethyl acetate.

Yield of **42**: 49 mg, 0.14 mmol, 78%; white crystals; m.p. 138-141 °C; ^1H NMR ($CDCl_3$): δ 1.92 (6H, s), 2.24 (3H, s), 2.81 & 2.95 (2H, ABq, J = 14.6 Hz), 6.65 (1H, d, J = 7.3 Hz), 7.23 (1H, m), 7.40-7.59 (7H, m).

Crystal data and structure refinement for 42

$C_{20}H_{20}O_2S_2$, M 356.51, crystal dimensions 0.86 x 0.43 x 0.37 mm; orthorhombic, *a* 7.633(2), *b* 8.196(2), *c* 28.343(4) Å; α 90, β 90, γ 90 °; V 1773.0(7) $Å^3$, spacegroup $Pna2_1$, Z = 4, F(000) 752.0, $D_{calc.}$ 1.335 Mg m^{-3}, absorption coefficient 0.31 mm^{-1}, θ range for data collection 2.0 to 27.0, index ranges $0 \leq h \leq 9$, $0 \leq k \leq 10$, $0 \leq l \leq 36$; data/restraints/parameters 2273/1/220, goodness of fit on F^2 was 1.055, final R indices [$I>2\sigma(I)$] R_1 = 0.0249; R indices (all data) R_1 = 0.0285, wR_2 = 0.0672, largest difference peak and hole 0.23 and -0.22 e $Å^{-3}$.

The unit cell parameters were obtained by least-squares refinement of the setting angles of 22 reflections with $10.12 \leq 2\theta \leq 28.00$ °. A unique data set was measured at 130 K within $2\theta_{max.}$ = 54° limit (ω scans). Of the 2273 reflections obtained, 2081 were unique and were used in the full-matrix least-squares refinement.

The intensities of 3 standard reflections, measured every 97 reflections throughout the data collection, showed no significant decay.

The crystal structure data are reported in Appendix A.1.

11-Ethoxy-1-methyl-9-oxa-8-phenyltricyclo[6.2.2.0^{2,7}]dodec-2,4,6-trien-10-one (44)
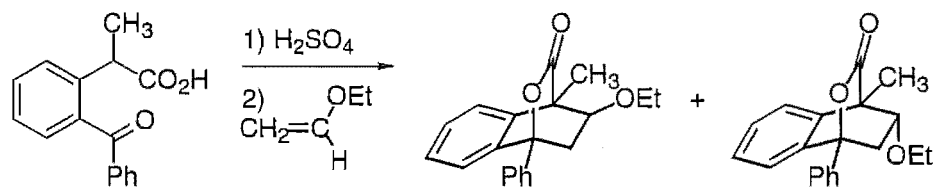
2-(2-Benzoylphenyl)propanoic acid (100 mg, 0.39 mmol, 1.0 eq.) was dissolved in conc. H_2SO_4 (0.33 mL) with gentle warming on a water bath to give an orange solution. Water (45 mL) was added to produce a deep red precipitate which was extracted with ethyl acetate (2 x 40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* (not to dryness). Toluene (25 mL) was added, and the solution concentrated *in vacuo* to 12 mL. Ethyl vinyl ether (0.39 mL, 4.08 mmol, 10.0 eq.) was added and the solution was refluxed under nitrogen for 3 hours after which time the red colour had disappeared. The solution was washed with saturated aqueous $NaHCO_3$ (12 mL), water (12 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. **44a** and **44b**[9] were formed in the ratio 22:78. The major of the two isomers was separated and purified by fractional recrystallisation from ethyl acetate/petroleum ether.

Combined yield of **44a** and **44b**: 98 mg, 0.32 mmol, 81%. **44b** *(endo)*: white crystals; m.p. 173-175 °C; ^{1}H NMR ($CDCl_3$): δ 1.11 (3H, t, J = 6.9 Hz), 1.83 (3H, s), 2.28 (1H, dd, J = 13.9, 2.2 Hz), 2.87 (1H, dd, J = 13.9, 8.1 Hz), 3.46 (1H, dq, J = 9.8, 7.0 Hz), 3.58 (1H, dq, J = 9.8, 7.0 Hz), 3.91 (1H, dd, J = 8.1, 2.2 Hz), 6.62 (1H, d, J = 7.4 Hz), 7.15-7.20 (1H, m), 7.35-7.38 (2H, m), 7.45-7.59 (5H, m). **44a** *(exo, not isolated)*: ^{1}H NMR ($CDCl_3$): δ 1.20 (3H, t, J = 6.8 Hz), 1.82 (3H, s), 2.42 (1H, dd, J = 13.7, 2.9 Hz), 2.79 (1H, dd, 13.7, 8.3 Hz), 3.44 (1H, dq, J = 9.3, 6.8 Hz), 3.61 (1H, dd,

J = 8.3, 2.9 Hz), 3.65 (1H, dq, J = 9.3, 6.8 Hz), 6.62 (1H, d, J = 7.8 Hz), 7.13-7.20 (1H, m), 7.34-7.60 (7H, m).

Crystal data and structure refinement for 44b (endo)

$C_{20}H_{20}O_3$, M 308.36, crystal dimensions 0.79 x 0.43 x 0.34 mm; monoclinic, a 8.509(3), b 8.564(2), c 22.247(5) Å; α 90, β 94.710(10), γ 90 °; V 1615.7(8) Å^3, spacegroup $P2_1/n$, Z = 4, F(000) 656, D_{calc} 1.268 Mg m^{-3}, absorption coefficient 0.084 mm^{-1}, θ range for data collection 2.50 to 25.00, index ranges $0 \leq h \leq 10$, $0 \leq k \leq$ 10, $-26 \leq l \leq 26$; data/restraints/parameters 2821/0/218, goodness of fit on F^2 was 1.057, final R indices [$I > 2\sigma(I)$] R_1 = 0.0505, wR_2 = 0.1189, R indices (all data) R_1 = 0.0834, wR_2 = 0.1398, largest difference peak and hole 0.243 and -0.334 e Å^{-3}.

The unit cell parameters were obtained by least-squares refinement of the setting angles of 38 reflections with $10 \leq 2\theta \leq 14$ °. A unique data set was measured at 302(2) K within $2\theta_{max}$ = 57° limit (ω scans). Of the 3026 reflections obtained, 2821 were unique (R_{int} = 0.0177) and were used in the full-matrix least-squares refinement. The intensities of 3 standard reflections, measured every 97 reflections throughout the data collection, showed < 2% decay.

Note: The reflections were obtained at room temperature because the crystals cracked if cooled to low temperatures.

The crystal structure data are reported in Appendix A.2.

7.9.   Attempted preparation of pyrano[3,4-*b*]quinolin-2-ones (50)

2-Aminobenzaldehyde[10]
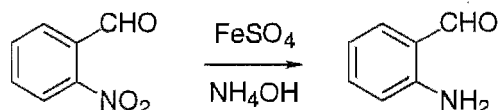
Water (350 mL), iron(II) sulfate heptahydrate (210 g, 0.76 mol, 9.5 eq.), conc. HCl (1.0 mL, 0.012 mol, 0.15 eq.) and 2-nitrobenzaldehyde (12 g, 0.08 mol, 1.0 eq.) were combined in that order. The mixture was stirred and heated to 90 °C. Aqueous ammonia (sp.gr. = 0.880, 50 mL) was added, and then three more portions (20 mL) of aqueous ammonia were added at 2 minute intervals. Immediately after the last portion was added, the mixture was steam distilled with the receiver cooled in ice. The distillation was stopped once 500 mL of distillate had been collected. Sodium chloride (150 g) was added to the distillate and the precipitate formed was collected by filtration. The product was dried under vacuum.

Yield of 2-aminobenzaldehyde: 7.9 g, 65.2 mmol, 82%; yellow needles; m.p. 38.5-41 °C; ^{1}H NMR (CDCl$_3$): δ 7.71-7.81 (2H, m), 7.93 (1H, dd, J = 6.9, 2.5 Hz), 8.09 (1H, dd, J = 6.9, 2.5 Hz), 10.39 (1H, s).

2-Oxobutanoic acid
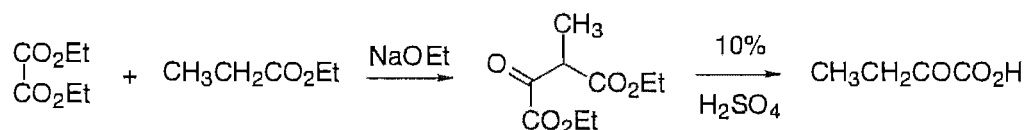
Sodium (2.28 g, 0.1 mol, 1.0 eq.) was added in small portions to freshly dried ethanol (35 mL, 0.6 mol, 6.0 eq.) at a rate sufficient to keep the ethanol refluxing. External heating was required to dissolve the last portions of sodium. The excess ethanol was removed by distillation. The remaining ethanol was removed by azeotropic distillation with toluene. After cooling the sodium ethoxide formed, freshly dried ether

(70 mL) and diethyl oxalate (13.6 mL, 0.1 mol, 1.0 eq.) were added. After 20 minutes stirring, ethyl propanoate (11.5 mL, 0.1 mol, 1.0 eq.) was added and the mixture stirred for 2.5 days, during which an orange precipitate formed.

The mixture was hydrolysed by the addition of water (70 mL), the layers separated and the ethereal layer washed with saturated $NaHCO_3$ solution (3 x 20 mL) and the ether layer discarded. The combined aqueous layers were acidified with conc. HCl (20 mL) and the layers separated. The aqueous layer was extracted with ether (3 x 20 mL), and the combined organic layers dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

10% sulfuric acid (100 mL) was added to the resulting oil and the mixture refluxed for 6 hours, becoming homogeneous. The solution was extracted with ether (4 x 30 mL) and the solvent removed *in vacuo* to give the crude product, purified by vacuum distillation.

Yield of 2-oxobutanoic acid: 3.82 g, 37.42 mmol, 37%; colourless oil; b.p. 80 °C/20 mmHg; IR ($CDCl_3$): υ_{max} 3419 (m), 2986 (m), 1783 (s), 1725 (s), 1602 (m), 1380 (m), 1330 (m), 1102 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.17 (3H, t, J = 7.1 Hz), 2.98 (2H, q, J = 7.1 Hz), 4.65 (1H, br s).

2-Carbomethoxy-3-methylquinoline (45a)[11]
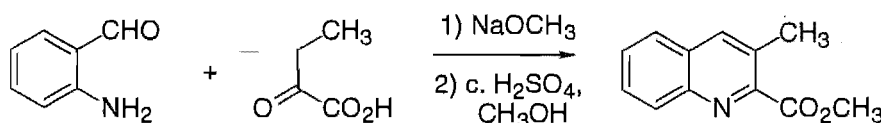
Sodium (1.46 g, 0.064 mol, 1.9 eq.) was added in small portions to dry methanol (150 mL). Once all of the sodium had reacted, 2-oxobutanoic acid (3.82 g, 0.037 mol, 1.1 eq.) and 2-aminobenzaldehyde (4.0 g, 0.033 mol, 1.0 eq.) were added and the solution heated under reflux for 16 hours. After cooling, conc. H_2SO_4 (3.2 mL, 0.058 mol) was cautiously added and the resultant solution heated under reflux for a

further 24 hours. The mixture was neutralised by the addition of saturated aqueous $NaHCO_3$ (50 mL), and then extracted with dichloromethane (150 mL, 6 x 50 mL). The combined organic extracts were dried ($NaSO_4$), filtered and concentrated *in vacuo*. The crude product was purified by short path vacuum distillation followed by further purification using radial chromatography, eluting with 67% petroleum ether/33% ethyl acetate.

Yield of **45a**: 1.91 g, 9.49 mmol, 29%; yellow oil; b.p. 165 °C/0.1 mmHg; ^{1}H NMR ($CDCl_3$): δ 2.70 (3H, d, $J = 0.9$ Hz), 4.06 (3H, s), 7.60 (1H, ddd, $J = 8.3, 6.8, 1.0$ Hz), 7.71 (1H, ddd, $J = 8.3, 6.8, 1.5$ Hz), 7.79 (1H, dd, $J = 8.3, 1.5$ Hz), 8.05 (1H, s), 8.20 (1H, dd, $J = 8.3, 1.0$ Hz).

3-Bromomethyl-2-carbomethoxyquinoline (46a)
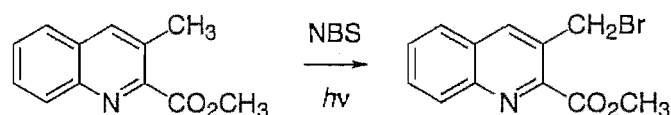
A mixture of 2-carbomethoxy-3-methylquinoline (650 mg, 3.23 mmol, 1.0 eq.) and *N*-bromosuccinimide (NBS) (575 mg, 3.23 mmol, 1.0 eq.) in refluxing carbon tetrachloride (175 mL) was irradiated overnight with a 200 W light bulb. The mixture was cooled, filtered and the filtrate washed with water (50 mL), aqueous NaOH solution (1.25 mol L^{-1}, 2 x 50 mL) and water (2 x 50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified using radial chromatography, eluting with 25% carbon tetrachloride/75% dichloromethane.

Yield of **46a**: 374 mg, 1.34 mmol, 41%; white crystals; m.p. 84-86 °C; ^{1}H NMR ($CDCl_3$): δ 4.11 (3H, s), 5.06 (2H, s), 7.67 (1H, ddd, $J = 8.3, 6.9, 1.4$ Hz), 7.80 (1H, ddd, $J = 8.3, 6.9, 1.4$ Hz), 7.86 (1H, dd $J = 8.3, 1.4$ Hz), 8.24 (1H, dd $J = 8.3, 1.4$ Hz), 8.30 (1H, s).

2-Carbomethoxy-3-cyanomethylquinoline (47a)[12]
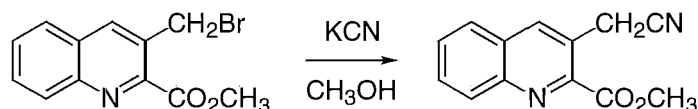
3-Bromomethyl-2-carbomethoxyquinoline (460 mg, 1.64 mmol) in methanol (16 mL) was added to dried potassium cyanide (174 mg, 2.46 mmol, 1.6 eq.) and the solution stirred overnight at room temperature. The solution was then refluxed for two hours, cooled and water (30 mL) added. The resulting solution was extracted with dichloromethane (4 x 18 mL). The combined organic layers washed with water (20 mL), dried ($MgSO_4$), filtered and the solution concentrated *in vacuo*. The crude product was recrystallised twice from methanol.

Yield of **47a**: 200 mg, 0.88 mmol, 54%; orange crystals; m.p. 128-130 °C; IR ($CDCl_3$): υ_{max} 3690 (w), 1724 (s), 1602 (w), 1458 (w), 1441 (w), 1327 (w), 1308 (m), 1292 (m), 1198 (m), 1172 (m), 1141 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.09 (3H, s), 4.39 (2H, s), 7.72 (1H, t, J = 7.7 Hz), 7.84 (1H, t, J = 7.7 Hz), 7.92 (1H, d, J = 7.7 Hz), 8.27 (1H, d, J = 7.7 Hz), 8.46 (1H, s); m/z [EI (70)]: 226.0743 (found), 226.0742 (calcd.); 226 (M$^+$, 73%), 194 (M$^+$-OCH$_3$, -H, 100%), 168 (M$^+$-C$_2$H$_2$O$_2$, 76%),166 (M$^+$ -CO$_2$CH$_3$, -H, 100%), 140 (M$^+$-CO$_2$CH$_3$, -H, -CN, 61%).

2-Benzoyl-3-cyanomethylquinoline (48a)
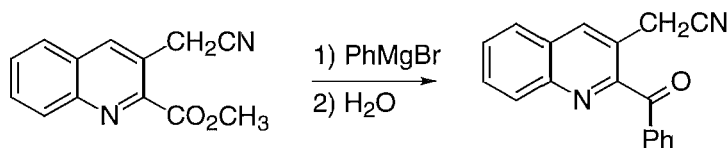
To 2-carbomethoxy-3-cyanomethylquinoline (47 mg, 0.21 mmol) stirring in anhydrous tetrahydrofuran (3 mL), at -78 °C, was added a PhMgBr/tetrahydrofuran solution (prepared in the usual way, 1.32 mol L^{-1}, 0.19 mL, 0.25 mmol, 1.2 eq.). The solution was allowed to warm to room temperature over 2.5 hours. Water (15 mL) was added and the mixture concentrated *in vacuo* to remove the tetrahydrofuran. The

aqueous layer was extracted with dichloromethane (10 mL). Aqueous HCl (2 mol L^{-1}, 0.2 mL) was added and the mixture extracted with dichloromethane (5 mL); this process was repeated. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Yield of **48a**: 47 mg, 0.17 mmol, 83%; pale yellow crystals; ^{1}H NMR ($CDCl_3$): δ 4.20 (2H, d, J = 1.0 Hz), 7.51 (2H, t, J = 7.3 Hz), 7.65 (1H, tt, J = 7.3, 1.4 Hz), 7.72 (1H, ddd, J = 7.8, 6.8, 1.0 Hz), 7.82 (1H, ddd, J = 8.3, 6.8, 1.4 Hz), 7.95 (1H, dd, J = 8.3, 1.4 Hz), 8.03 (2H, dd, J = 7.3, 1.4 Hz), 8.14 (1H, d, J = 8.8 Hz), 8.48 (1H, s); m/z [EI (70)]: 272 (M^+, 80%), 243 (M^+-CHO, 97%), 140 (M^+-HCN, $-COC_6H_5$, 23%), 105 ($COC_6H_5^+$, 100%), 77 ($C_6H_5^+$, 97%).

2-Oxopentanoic acid
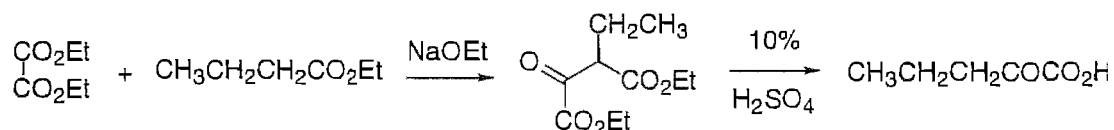
Sodium (9.2 g, 0.4 mol, 1.0 eq.) was added in small portions to freshly dried ethanol (120 mL, 2.0 mol, 5 eq.) at a rate sufficient to keep the ethanol refluxing. External heating was required to dissolve the last portions of sodium. The excess ethanol was then removed by distillation. The remaining ethanol was removed by azeotropic distillation with toluene. After cooling the sodium ethoxide formed, freshly dried ether (260 mL), diethyl oxalate (54 mL, 0.4 mol, 1.0 eq.) and ethyl butanoate (53 mL, 0.4 mol, 1.0 eq.) were added and the mixture stirred for 40 hours.

The mixture was hydrolysed by the addition of water (200 mL), the layers separated and the ethereal layer washed with water (3 x 50 mL) and the ether layer discarded. The combined aqueous layers were acidified with conc. HCl (40 mL) and the layers separated. The aqueous layer was extracted with ether (3 x 50 mL), and the combined organic layers dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

10% sulfuric acid (350 mL) was added to the resulting oil and the mixture refluxed for 5.5 hours, becoming homogeneous. The solution was extracted with ether (100 mL, 3 x 50 mL) and the solvent removed *in vacuo* to give the crude product, purified by vacuum distillation.

Yield of 2-oxopentanoic acid: 15.6 g, 134.4 mmol, 33%; colourless oil; b.p. 92-98 °C/20 mmHg; IR (CDCl$_3$): υ_{max} 3418 (m), 2969 (m), 1782 (s), 1723 (s), 1345 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 0.99 (3H, t, J = 7.6 Hz), 1.71 (2H, q, J = 7.3 Hz), 2.93 (2H, t, J = 7.1 Hz), 7.87 (1H, br s).

2-Carbomethoxy-3-ethylquinoline (45b)
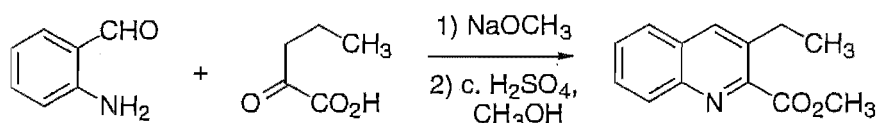
Sodium (0.91 g, 0.040 mol, 1.8 eq.) was added in small portions to dry methanol (100 mL). Once all of the sodium had reacted, 2-oxopentanoic acid (2.88 g, 0.025 mol, 1.1 eq.) and 2-aminobenzaldehyde (2.68 g, 0.022 mol, 1.0 eq.) were added and the solution heated under reflux for 16 hours. After cooling, conc. H$_2$SO$_4$ (2.2 mL, 1.8 eq.) was cautiously added and the resultant solution heated under reflux for a further 24 hours. The mixture was neutralised by the addition of saturated aqueous NaHCO$_3$ (30 mL), and then extracted with dichloromethane (100 mL, 3 x 50 mL). The combined organic extracts where dried (NaSO$_4$), filtered and concentrated *in vacuo*. The crude product was purified by vacuum distillation.

Yield of **45b**: 1.17 g, 5.44 mmol, 25%; brown oil; b.p. 126-128 °C/0.01 mmHg; ^{1}H NMR (CDCl$_3$): δ 1.35 (3H, t, J = 7.3 Hz), 3.06 (2H, q, J = 7.3 Hz), 4.06 (3H, s), 7.59 (1H, ddd, J = 8.3, 6.8, 1.0 Hz), 7.71 (1H, ddd, J = 8.3, 6.8, 1.5 Hz), 7.81 (1H, dd, J = 8.3, 1.5 Hz), 8.08 (1H, s), 8.18 (1H, dd, J = 8.3, 1.0 Hz).

(1-Bromoethyl)-2-carbomethoxyquinoline (46b)
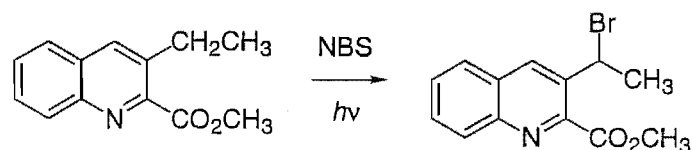
A mixture of 2-carbomethoxy-3-ethylquinoline (2.82 g, 0.013 mol, 1.0 eq.) and N-bromosuccinimide (NBS) (2.57 mg, 0.014 mol, 1.1 eq.) in refluxing carbon tetrachloride (710 mL) was irradiated overnight with a 200 W light bulb. The mixture was cooled, filtered and the filtrate washed with water (180 mL), aqueous NaOH solution (1.25 mol L^{-1}, 2 x 150 mL) and water (2 x 150 mL). The organic layer was dried (MgSO$_4$), filtered and concentrated *in vacuo*.

Yield of **46b**: 3.08 g, 10.47 mmol, 80%; brown oil; ^{1}H NMR (CDCl$_3$): δ 2.18 (3H, d, J = 6.9 Hz), 4.10 (3H, s), 6.18 (1H, q, J = 6.9 Hz), 7.66 (1H, ddd, J = 8.3, 6.9, 1.5 Hz), 7.79 (1H, ddd, J = 8.3, 6.9, 1.5 Hz), 7.89 (1H, dd J = 6.9, 1.5 Hz), 8.21 (1H, dd J = 6.9, 1.5 Hz), 8.54 (1H, s).

2-Carbomethoxy-3-(1-methoxyethyl)quinoline (51)
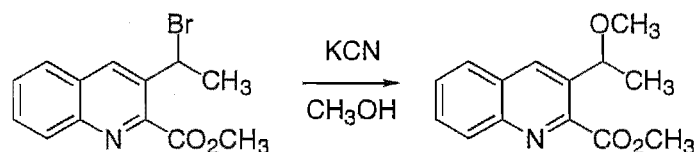
3-(1-Bromoethyl)-2-carbomethoxyquinoline (408 mg, 1.39 mmol) in methanol (12 mL) was added to dried potassium cyanide (144 mg, 2.21 mmol, 1.6 eq.) and the solution stirred overnight at room temperature. The solution was then refluxed for six hours, concentrated by distilling off the methanol, cooled and water (25 mL) added. The resulting solution was extracted with dichloromethane (4 x 15 mL). The combined organic layers were washed with water (15 mL), dried (MgSO$_4$), filtered and the solution concentrated *in vacuo*. The crude product was purified using radial chromatography, eluting with dichloromethane.

Yield of **51**: 177 mg, 0.72 mmol, 52%; white solid; m.p. 47 °C; IR (CDCl$_3$):

ν_{max} 2981 (w), 2934 (w), 1728 (s), 1456 (w), 1289 (m), 1208 (m), 1139 (s), 1111 (m)

cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.56 (3H, d, J = 6.3 Hz), 3.32 (3H, s), 4.07 (3H, s), 5.07

(1H, q, J = 6.3 Hz), 7.63 (1H, ddd, J = 9.3, 6.8, 1.0 Hz), 7.76 (1H, ddd, J = 8.3, 6.8, 1.4

Hz), 7.88 (1H, d, 8.3 Hz), 8.21 (1H, d, J = 9.3 Hz), 8.42 (1H, s); ^{13}C NMR (CDCl$_3$): δ

23.63, 53.02, 56.91, 75.40, 127.57, 128.33, 128.98, 129.80, 130.03, 134.42, 136.73,

146.30, 147.90, 166.72; m/z [EI (70)]: 245 (M$^+$, 62%), 230 (M$^+$-CH$_3$, 100%), 214 (M$^+$

-OCH$_3$, 18%), 198 (M$^+$-CH$_3$, -CH$_3$OH, 97%) 170 (M$^+$-COCH$_3$, -CH$_3$OH, 67%), 154

(M$^+$-CO$_2$CH$_3$, -CH$_3$OH, 69%).

Anal. Calcd. for C$_{14}$H$_{15}$NO$_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.34; H,

6.09; N, 5.54%.

1-Methylfuro[3,4-b]quinolin-3-one (52)
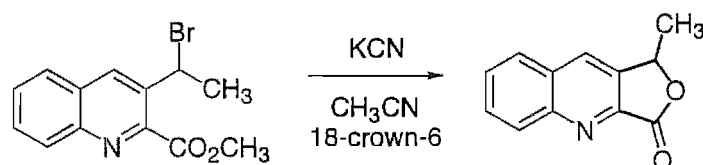
1,4,7,10,13,16-Hexaoxacyclooctadecane (18-crown-6) (9 mg, 0.03 mmol, 0.09

eq.) and 3-(1-bromoethyl)-2-carbomethoxyquinoline (108 mg, 0.37 mmol, 1.0 eq.)

were dissolved in acetonitrile (0.6 mL). This solution was added to dried potassium

cyanide (51 mg, 0.78 mmol, 2.1 eq.). The heterogeneous mixture was stirred under

reflux for 2.5 hours. The resulting mixture was filtered and the residue washed with

acetonitrile (0.5 mL). Water (2 mL) was added to the combined filtrates and the

mixture extracted with dichloromethane (3 x 2 mL). The combined organic layers were

dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude product was purified

using radial chromatography, eluting with 25% petroleum ether/75% dichloromethane.

The resulting product was recrystallised from methanol.

Yield of **52**: 20 mg, 0.1 mmol, 27%; white needles; m.p. 155-156 °C; IR (CDCl₃): υ_{max} 1778 (s), 1729 (w), 1580 (w), 1504 (m), 1377 (m), 1304 (m) cm⁻¹; ¹H NMR (CDCl₃): δ 1.71 (3H, d, *J* = 6.3 Hz), 5.75 (1H, q, *J* = 6.3 Hz), 7.66 (1H, ddd, *J* = 8.3, 6.8, 1.0 Hz), 7.79 (1H, ddd, *J* = 8.3, 6.8, 1.5 Hz), 7.91 (1H, d, *J* = 8.3 Hz), 8.24 (1H, s), 8.31 (1H, d, *J* = 8.3 Hz); ¹³C NMR (CDCl₃): δ 20.84, 76.23, 128.01, 129.10, 129.28, 130.05, 130.84, 130.91, 138.54, 144.78, 149.80, 167.91; m/z [EI (70)]: 199.0637 (found), 199.06332 (calcd.); 199 (M⁺, 76%), 184 (M⁺-CH₃, 32%), 156 (M⁺ -CO, -CH₃, 77%), 154 (M⁺-CO₂H, 32%), 128 (M⁺-CO₂, -C₂H₃, 100%).

Anal. Calcd. for C₁₂H₉NO₂: C, 72.35; H, 4.55; N, 7.03. Found: C, 72.13; H, 4.56; N, 7.02%.

2-Carbomethoxy-3-(1-cyanoethyl)quinoline (47b)
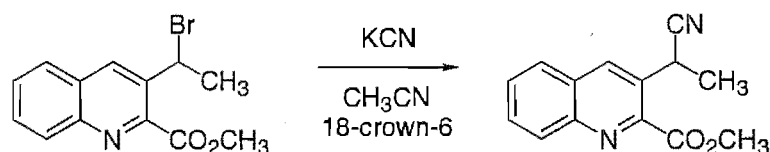
18-Crown-6 (60 mg, 0.23 mmol, 0.3 eq.) and 3-(1-bromoethyl)-2-carbomethoxyquinoline (249 mg, 0.85 mmol, 1.0 eq.) were dissolved in acetonitrile (1.8 mL). This solution was added to dried potassium cyanide (153 mg, 2.35 mmol, 2.8 eq.). The heterogeneous mixture was stirred at room temperature overnight. The resulting mixture was filtered and the residue washed with dichloromethane (2 x 1 mL). Water (5 mL) was added to the combined filtrates and the mixture extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. The crude product was purified using radial chromatography, eluting with 66% petroleum ether/34% ethyl acetate.

Yield of **47b**: 56 mg, 0.23 mmol, 28%; orange oil; IR (CDCl₃): υ_{max} 1724 (s), 1458 (m), 1382 (m), 1290 (m) cm⁻¹; ¹H NMR (CDCl₃): δ 1.73 (3H, d, *J* = 7.3 Hz), 4.07 (3H, s), 5.08 (1H, q, *J* = 7.3 Hz), 7.69 (1H, ddd, *J* = 7.8, 6.8, 1.4 Hz), 7.81 (1H, ddd, *J* = 8.3, 6.8, 1.4 Hz), 7.90 (1H, d, *J* = 7.8 Hz), 8.23 (1H, d, *J* = 8.3 Hz), 8.50 (1H, s); ¹³C

NMR (CDCl$_3$): δ 21.56, 27.90, 53.28, 121.20, 127.30, 128.48, 129.20, 129.81, 130.36, 130.79, 136.33, 145.44, 146.19, 165.86; m/z [EI (70)]: 240.0894 (found), 240.08987 (calcd.); 240 (M$^+$, 45%), 225 (M$^+$-CH$_3$, 7%), 208 (M$^+$-CH$_3$OH, 16%), 180 (M$^+$-H, -CO$_2$CH$_3$, 100%), 154 (M$^+$-CO$_2$CH$_3$, -HCN, 20%).

2-Benzoyl-3-(1-cyanoethyl)quinoline (48b)
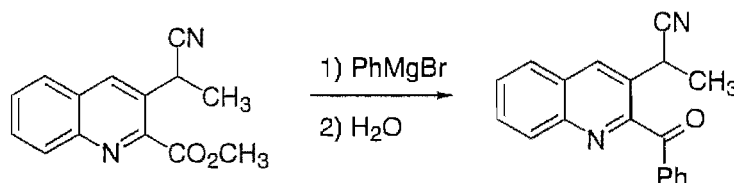
To 2-carbomethoxy-3-(1-cyanoethyl)quinoline (175 mg, 0.73 mmol) stirring in anhydrous tetrahydrofuran (8 mL), at -78 °C, was added a PhMgBr/tetrahydrofuran solution (prepared in the usual way, 1.15 mol L^{-1}, 0.76 mL, 0.87 mmol, 1.2 eq.). The solution was allowed to warm to room temperature and the mixture left stirring overnight. Water (40 mL) was added and the mixture concentrated *in vacuo* to remove the tetrahydrofuran. The aqueous layer was extracted with dichloromethane (10 mL). Aqueous HCl (2 mol L^{-1}) was added until the white precipitate dissolved. The mixture was extracted with dichloromethane (3 x 20 mL). The combined organic layers where dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude product was purified using radial chromatography, eluting with 80% petroleum ether/20% ethyl acetate.

Yield of **48b**: 151 mg, 0.53 mmol, 72%; yellow oil; IR (CDCl$_3$): υ$_{max}$ 2248 (m), 1667 (s), 1597 (m), 1455 (m), 1288 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.73 (3H, d, *J* = 6.9 Hz), 4.60 (1H, q, *J* = 6.9 Hz), 7.50 (2H, ddd, *J* = 7.8, 7.3, 1.5 Hz), 7.62-7.72 (2H, m), 7.80 (1H, ddd, *J* = 8.3, 6.8, 1.5 Hz), 7.95 (1H, dd, *J* = 8.3, 1.4 Hz), 8.00 (2H, dd, *J* = 8.8, 1.5 Hz), 8.12 (1H, d, *J* = 8.8 Hz), 8.54 (1H, s); ^{13}C NMR (CDCl$_3$): δ 21.74, 27.54, 121.06, 127.51, 127.95, 128.40, 128.55, 128.68, 129.58, 129.70, 130.67, 130.95, 133.92, 135.64, 135.79, 145.69, 194.06; m/z [EI (70)]: 286.11069 (found), 286.11061

(calcd.); 286 (M^+, 51%), 257 (M^+-CHO, 50%), 105 ($C_6H_5CO^+$, 100%), 77 ($C_6H_5^+$, 74%).

3-Chloro-4-methyl-1-phenylbenzo[*b*][1,7]naphthyridine (53)
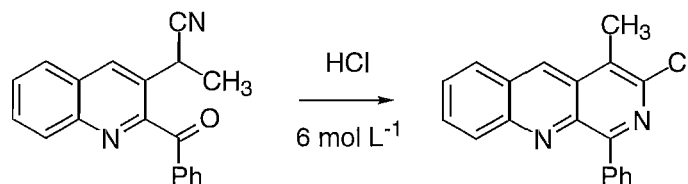
2-Benzoyl-3-(1-cyanoethyl)quinoline (142 mg, 0.50 mmol) was dissolved in 6 mol L^{-1} hydrochloric acid (40 mL) and the solution was refluxed for 4 hours. The resulting mixture was extracted with dichloromethane (2 x 10 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo* to give the crude product, which was recrystallised from methanol.

Yield of **53**: 80 mg, 0.26 mmol, 53%; yellow needles; m.p. 195-199 °C; IR (CDCl$_3$): υ_{max} 1562 (m), 1506 (m), 1444 (m), 1406 (m), 1344 (m), 1033 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.82 (3H, s), 7.53 (3H, m), 7.60 (1H, t, J = 7.8 Hz), 7.77 (1H, ddd, J = 8.3, 6.8, 1.5 Hz), 7.98 (1H, d, J = 8.3 Hz), 8.20 (1H, d, J = 8.8 Hz), 8.34 (2H, dd, J = 7.5, 1.6 Hz), 8.81 (1H, s); ^{13}C NMR (CDCl$_3$): δ 15.12, 123.46, 127.75, 127.86, 127.94, 128.18, 129.39, 130.01, 130.57, 130.71, 131.59, 131.71, 137.45, 140.79, 142.78, 148.67, 158.99; m/z [EI (70)]: 304.07690 (found), 304.07673 (calcd.); 304 (M^+, 74%), 303 (M^+-H, 59%), 268 (M^+-HCl, 8%), 143 (100%).

Attempted preparation of 2-benzoyl-3-(1-carboxyethyl)quinoline (49b)
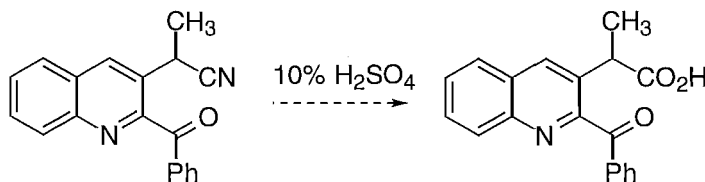
A 10% aqueous sulfuric acid solution (20 mL) was added to 2-benzoyl-3-(1-cyanoethyl)quinoline (114 mg, 0.40 mmol) and the mixture refluxed for 28 hours.

The resulting mixture was added to water (210 mL) and then extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified using radial chromatography, eluting with 50% petroleum ether/50% ethyl acetate and then recrystallised from benzene/petroleum ether.

Yield of unknown compound: 50 mg, 0.16 mmol, 41%; orange glass; m.p. 61-65 °C; IR ($CDCl_3$): υ_{max} δ 1756 (m), 1711 (s), 1671 (s), 1597 (m), 1454 (m), 1281 (m), 1177 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.60 (3H, d, J = 7.3 Hz), 4.16 (1H, q, J = 7.3 Hz), 7.41 (2H, t, J = 7.8 Hz), 7.55 (1H, t, J = 7.8 Hz), 7.62 (1H, ddd, J = 8.3, 6.8, 1.5 Hz), 7.73 (1H, ddd, J = 8.8, 6.8, 1.5 Hz), 7.86 (1H, dd, J = 8.3, 1.5 Hz), 7.95 (2H, d, J = 7.8 Hz), 8.07 (1H, d, J = 8.3 Hz), 8.29 (1H, s); ^{13}C NMR ($CDCl_3$): 18.00, 40.20, 127.47, 127.75, 127.95, 128.15, 128.84, 130.13, 130.77, 132.02, 133.68, 135.69, 135.77, 145.09, 155.18, 176.77, 195.06; m/z [EI (70)]: 305.10458 (found), 305.10519 (calcd.); 336 (28%), 305 (M$^+$, 40%), 277 (M$^+$-CO, 16%), 260 (M$^+$-CO_2H, 93%), 232 (M$^+$-CO_2H, -CO, 85%), 217 (M$^+$-CO_2H, -CO, -CH_3, 14%), 200 (M$^+$-C_6H_5CO, 13%), 154 (M$^+$-CO_2H, -C_6H_5CO, -H, 22%), 105 (C_6H_5CO$^+$, 79%), 77 ($C_6H_5{}^+$, 100%).

2-Oxopentane-1,5-dioic acid (α-ketoglutaric acid)[13]
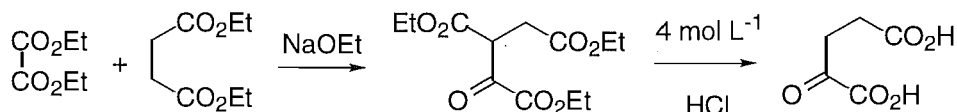
Sodium (9.27 g, 0.4 mol, 1.0 eq.) was added in small portions to freshly dried ethanol (141 mL, 2.4 mol, 6 eq.) at a rate sufficient to keep the ethanol refluxing. External heating was required to dissolve the last portions of sodium. The excess ethanol was removed by distillation. The remaining ethanol was removed by azeotropic distillation with toluene. After cooling the sodium ethoxide formed, freshly dried ether (260 mL), diethyl oxalate (54 mL, 0.4 mol, 1.0 eq.) and diethyl succinate (66.5 mL, 0.4 mol, 1.0 eq.) were added and the mixture stirred overnight.

The mixture was hydrolysed by the addition of water (200 mL), the layers separated and the ethereal layer washed with water (60 mL) and then discarded. The combined aqueous layers were acidified with conc. HCl (40 mL) and the layers separated. The aqueous layer was extracted with ether (2 x 60 mL), and the combined organic layers dried ($MgSO_4$), filtered, and concentrated *in vacuo.*

Water (400 mL) and conc. HCl (200 mL) were added to the resulting oil and the mixture refluxed for 4 hours, becoming homogeneous. The solution was concentrated *in vacuo* to give the crude product, which was recrystallised from toluene/acetone.

Yield of 2-oxopentane-1,5-dioic acid: 26.86 g, 184 mmol, 46%; white powder; m.p. 111-120 °C; IR (Nujol): υ_{max} 3506 (m), 2725 (m), 2660 (m), 1693 (br s), 1408 (m), 1310 (m), 1290 (m), 1252 (m), 1202 (m), 914 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.57 (2H, t, J = 6.3 Hz), 3.09 (2H, t, J = 6.3 Hz).

Attempted preparation of 2-carbomethoxy-3-(carbomethoxymethyl)quinoline (55)
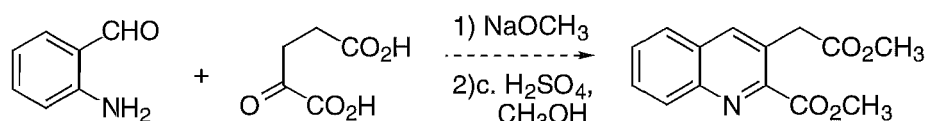
Sodium (920 mg, 0.040 mol, 3.0 eq.) was added in small portions to dry methanol (60 mL). Once all of the sodium had reacted, 2-oxopentane-1,5-dioic acid (2.13 g, 0.015 mol, 1.1 eq.) and 2-aminobenzaldehyde (1.61 g, 0.013 mol, 1.0 eq.) were added and the solution heated under reflux overnight. After cooling, conc. H_2SO_4 (2.2 mL, 0.040 mol) was cautiously added and the resultant solution heated under reflux for a further 24 hours. The mixture was neutralised by the addition of saturated aqueous $NaHCO_3$ (20 mL). Saturated aqueous NaCl (50 mL) was added and the mixture was extracted with dichloromethane (100 mL, 3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude mixture of products was separated into its components using radial silica

chromatography, gradient eluting with petroleum ether/ethyl acetate. The products were examined with ^{1}H NMR, UV and mass spectroscopy. These spectra were not consistent with those expected of the required product.

Dimethyl 2-oxopentane-1,5-dioate (dimethyl α-ketoglutarate)
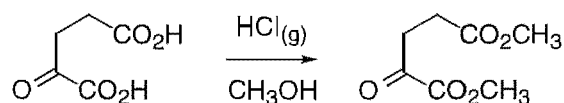
A solution of 2-oxopentane-1,5-dioic acid (524 mg, 3.6 mmol) in dry methanol (5 mL) was saturated with hydrogen chloride gas. The solution was refluxed overnight and then concentrated in vacuo. 50% $NaHCO_3$ solution (5 mL) was added to the residue and the product extracted with dichloromethane (3 x 3 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude product was purified using radial silica chromatography, eluting with 50% petroleum ether/50% ethyl acetate.

Yield of dimethyl 2-oxopentane-1,5-dioate: 101 mg, 0.58 mmol, 16%; colourless oil; ^{1}H NMR ($CDCl_3$): δ 2.66 (2H, t, J = 6.4 Hz), 3.15 (2H, t, J = 6.4 Hz), 3.67 (3H, s), 3.87 (3H, s) (lit.[14] (CCl_4): δ 2.43 (2H, t, J = 5 Hz), 2.92 (2H, t, J = 5 Hz), 3.42 (3H, s), 3.60 (3H, s)).

Attempted preparation of 2-carbomethoxy-3-(carbomethoxymethyl)quinoline (55)
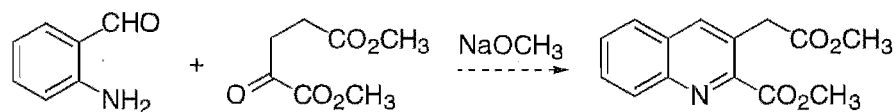
Sodium (25 mg, 1.09 mmol, 3.0 eq.) was added in small portions to dry methanol (2.5 mL). Once all of the sodium had reacted, dimethyl 2-oxopentane-1,5-dioate (79 mg, 0.45 mmol, 1.2 eq.) and 2-aminobenzaldehyde (46 mg, 0.38 mmol, 1.0 eq.) were added and the solution heated under reflux overnight. More 2-aminobenzaldehyde (46 mg, 0.38 mmol, 1.0 eq.) in methanol (0.5 mL) was added.

The solution was heated under reflux for another 24 hours. The mixture was poured into water (5 mL) and was extracted with dichloromethane (4 x 5 mL). The combined organic extracts were dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude mixture of products was separated into its components using radial silica chromatography, gradient eluting with petroleum ether/ethyl acetate. The products were examined with ^{1}H NMR, UV and mass spectroscopy. These spectra were not consistent with those expected of the required product.

7.10. Preparation of 1-methylpyrano[3,4-*b*]indol-3-one (56)[15]
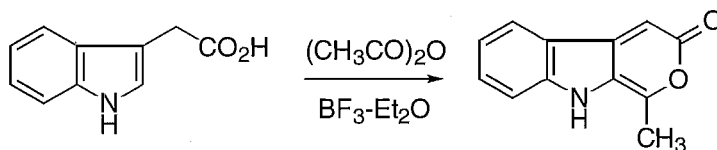
Freshly distilled boron trifluoride etherate (2 mL, 16.3 mmol, 1.4 eq.) was added in four portions over 1 hour to a stirred solution of indol-3-ylacetic acid (2.10 g, 12 mmol, 1.0 eq.) in acetic anhydride (4.6 mL, 48 mmol, 4 eq.) at 0 °C. The mixture was allowed to warm to room temperature and stirred for a further 30 minutes. Ether (50 mL) was added and the orange solid filtered off, washed with ether (50 mL), triturated with aqueous NaHCO$_3$ (half saturated, 2 x 50 mL), washed with water (3 x 40 mL) and dried *in vacuo*.

Yield of **56**: 1.49 g, 7.48 mmol, 62%; orange powder; m.p. 245 °C (d. 235 °C); ^{1}H NMR (d$_6$-DMSO): δ 2.60 (3H, s), 6.64 (1H, s), 7.11 (1H, t, *J* = 7.8 Hz), 7.32 (1H, d, *J* = 8.3 Hz), 7.62 (1H, t, *J* = 8.3 Hz), 8.08 (1H, d, *J* = 7.8 Hz), 10.57 (1H, br s).

7.11. Preparation of 9-acetyl-1-methylpyrano[3,4-*b*]indol-3-one (57)[16]
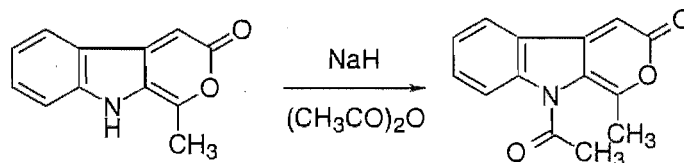
To a cooled suspension of sodium hydride (385 mg of a 50% mixture of sodium hydride in parafin oil, 8.0 mmol, 5 eq., washed three 3 times with petroleum ether) in dimethylformamide (14 mL) was added a suspension of 1-methylpyrano-[3,4-*b*]indol-3-one (308 mg, 1.6 mmol, 1.0 eq.) in dimethylformamide (19 mL). The mixture was stirred in an ice bath for 10 minutes and then freshly distilled acetic anhydride (0.35 mL, 3.7 mmol, 2.3 eq.) was added and the mixture stirred for a further 20 minutes. Water (25 mL) was slowly added, followed by saturated aqueous $NaHCO_3$ (25 mL). Brine (250 mL) and ether (50 mL) were added and the aqueous layer extracted with ether (5 x 50 mL). The combined organic layers were washed with brine (50 mL), dried ($NaSO_4$), filtered and concentrated *in vacuo*. The crude product was recrystallised from ethanol.

Yield of **57**: 119 mg, 0.49 mmol, 32%; orange crystals; m.p. 166-168 °C; ^{1}H NMR (CDCl$_3$): δ 2.51 (3H, s), 2.66 (3H, s), 6.44 (1H, d, J = 0.9 Hz), 7.37 (1H, t, J = 7.8 Hz), 7.63 (1H, t, J = 8.3 Hz), 7.74 (1H, d, 8.3 Hz), 7.84 (1H, d, 7.8 Hz).

7.12. Diels-Alder reaction between 1,1-bis(methylthio)ethene (19) and 1-methylpyrano[3,4-*b*]indol-3-one (56)

1-Methyl-3-methylthiocarbazole (58)
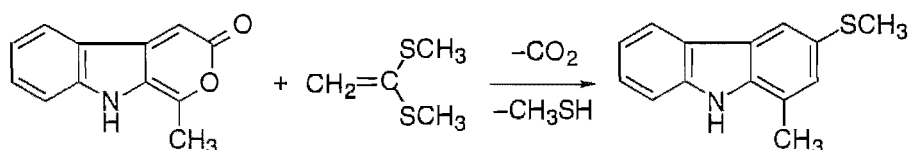
1-Methylpyrano[3,4-*b*]indol-3-one (40 mg, 0.20 mmol, 1.0 eq.) and 1,1-bis(methylthio)ethene (72 mg, 0.60 mmol, 3.0 eq.) were dissolved in bromobenzene (10 mL). The solution was heated at 120 °C under nitrogen for 4.5 days and then concentrated *in vacuo*. An ^{1}H NMR spectrum of the crude reaction mixture showed that the reaction was 50% complete. The reaction was stopped at this stage and the product purified using radial chromatography, eluting with ether. Some starting material (13 mg, 33%) was recovered.

Yield of **58**: 11 mg, 0.05 mmol, 24%; brown oil; IR (CDCl$_3$): υ_{max} 3473 (m), 2924 (w), 1603 (w), 1491 (m), 1478 (m), 1439 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.54 (3H, s), 2.56 (3H, s), 7.20-7.28 (2H, m), 7.38-7.47 (2H, m), 7.93 (1H, s), 8.04 (1H, d, *J* = 7.3 Hz), 8.08 (1H, br s); (d$_6$-DMSO): δ 2.62 (3H, s), 2.63 (3H, s), 7.24 (1H, ddd, *J* = 8.3, 7.8, 1.0 Hz), 7.30 (1H, dd, *J* = 1.0, 1.9 Hz), 7.47 (1H, ddd, *J* = 8.3, 7.3, 1.5 Hz), 7.59 (1H, d, *J* = 7.3 Hz), 8.04 (1H, d, *J* = 1.9 Hz), 8.20 (1H, d, 7.8 Hz), 11.31 (1H, br s); ^{13}C NMR (CDCl$_3$): δ 16.79, 18.98, 110.81, 118.93, 119.68, 120.41, 120.51, 123.19, 123.57, 126.00, 127.57, 128.28, 137.65, 139.66; m/z [EI (70)]: 227.0770 (found), 227.07687 (calcd.); 227 (M$^+$, 100%), 212 (M$^+$-CH$_3$, 83%), 180 (M$^+$-SCH$_3$, 9%), 167 (M$^+$-C$_2$H$_4$S, 20%).

7.13. Diels-Alder reaction between 1,1-bis(methylthio)ethene (19) and 9-acetyl-1-methylpyrano[3,4-*b*]indol-3-one (57)

9-Acetyl-1-methyl-3-methylthiocarbazole (59)
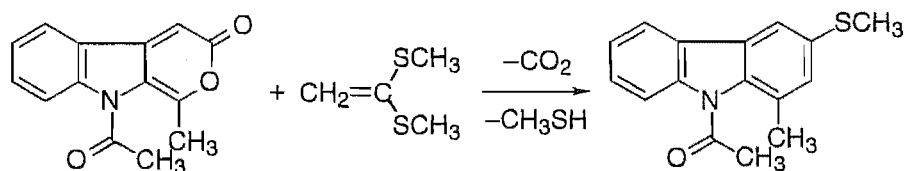
9-Acetyl-1-methylpyrano[3,4-*b*]indol-3-one (50 mg, 0.21 mmol, 1.0 eq.) and 1,1-bis(methylthio)ethene (62 mg, 0.52 mmol, 2.5 eq.) were dissolved in

bromobenzene (8 mL). The solution was heated at 120 °C under nitrogen for 14 days and then concentrated *in vacuo*. An ^{1}H NMR spectrum of the crude reaction mixture showed that the reaction was 15% complete. The reaction was stopped at this stage and the product purified using radial chromatography, eluting with 90% petroleum ether/10% ethyl acetate. Some starting material (40 mg, 80%) was recovered.

Yield of **59**: 8 mg, 0.03 mmol, 14%; yellow oil; IR (CDCl$_3$): υ_{max} 2926 (w), 1702 (s), 1478 (m), 1431 (m), 1366 (m), 1284 (s) cm^{-1}; ^{1}H NMR (d$_6$-acetone): δ 2.56 (3H, s), 2.71 (3H, s), 2.90 (3H, s), 7.38 (1H, dd, J = 1.9, 1.0 Hz), 7.50 (1H, ddd, J = 7.3, 7.3, 1.0 Hz), 7.62 (1H, ddd, J = 8.6, 7.3, 1.5 Hz), 8.03 (1H, d, J = 2.0 Hz), 8.10 (1H, dd, J = 8.3, 1.0 Hz), 8.26 (1H, dd, J = 8.1, 1.3 Hz); ^{13}C NMR (CDCl$_3$): δ 17.12, 21.29, 27.04, 114.48, 116.15, 120.11, 123.43, 125.29, 127.04, 127.37, 128.21, 129.03, 129.59, 133.69, 139.97, 170.57; m/z [EI (70)]: 269.0877 (found), 269.08743 (calcd.); 269 (M$^+$, 56%), 227 (M$^+$-COCH$_2$, 100%), 212 (M$^+$-COCH$_2$, -CH$_3$, 64%), 167 (M$^+$-COCH$_2$, -C$_2$H$_4$S, 19%).

7.14. Attempted Diels-Alder between 1,1-bis(methylthio)ethene (19) and cyclopentadiene
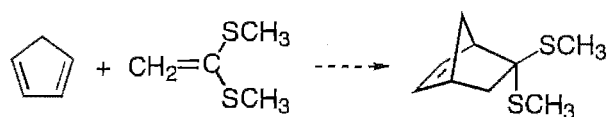
1,1-Bis(methylthio)ethene (1 drop) was added to freshly distilled cyclopentadiene (3 drops) in CDCl$_3$ (0.7 mL). The solution was heated at 55 °C and monitored by ^{1}H NMR. The dimerisation of cyclopentadiene was complete after six days, with no other product being observed.

7.15. Thermal decomposition of 1,1-bis(methylthio)ethene Diels-Alder adducts (28 and 42)

Methyl 4-(methylthio)benzoate (63), methyl 4,6-bis(methylthio)-1,3-cyclohexadienoate (62) and methyl 2-oxo-2*H*-pyran-5-ylcarboxylate (25)
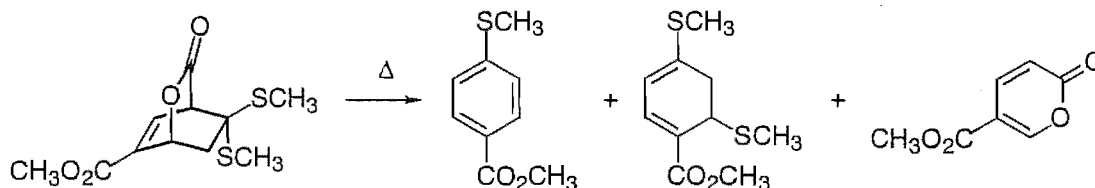
7,7-Bis(methylthio)-3-carbomethoxy-5-oxabicyclo[2.2.2]oct-2-en-6-one

(10 mg, 0.04 mmol) was heated neat under nitrogen at 145 °C for 17 hours. The resulting mixture was separated into its components using radial silica chromatography. **63** was obtained when the silica was eluted with 90% petroleum ether/10% ethyl acetate. **62** and **25** were obtained when the silica was eluted with 80% petroleum ether/20% ethyl acetate.

Yield of **63**: 1 mg, 0.01 mmol, 15%; white crystals; m.p. 78-80 °C; IR (CDCl$_3$): υ_{max} 1717 (s), 1596 (w), 1560 (w), 1437 (w), 1289 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.52 (3H, s), 3.90 (3H, s), 7.25 (2H, dd, J = 6.8, 1.9 Hz), 7.94 (2H, dd, J = 6.8, 1.9 Hz); ^{13}C NMR (CDCl$_3$): δ 14.82, 52.02, 124.90, 126.25, 129.87, 145.40, 166.86; m/z [EI (70)]: 182.0402 (found), 182.04015 (calcd.); 182 (M$^+$, 100%), 152 (M$^+$-OCH$_2$, 16%), 123 (M$^+$-CO$_2$CH$_3$, 17%), 108 (M$^+$-CO$_2$CH$_3$, -CH$_3$, 21%).

Yield of **62**: 2 mg, 0.01 mmol, 24%; yellow oil; IR (CDCl$_3$): υ_{max} 1700 (s), 1540 (s), 1437 (w), 1282 (m), 1243 (m), 1090 (m) cm^{-1}; UV (cyclohexane): λ_{max} 342 (ε = 9610) nm; ^{1}H NMR (CDCl$_3$): δ 2.08 (3H, s), 2.36 (3H, s), 2.62 (1H, dd, J = 17.6, 1.5 Hz), 2.98 (1H, ddd, J = 17.6, 7.3, 2.4 Hz), 3.79 (3H, s), 4.01 (1H, dd, J = 7.3, 1.5 Hz), 5.72 (1H, dd, J = 6.4, 2.4 Hz), 7.16 (1H, d, J = 6.4 Hz); ^{13}C NMR (CDCl$_3$): δ 13.72, 14.31, 36.06, 38.23, 51.76, 112.24, 122.42, 133.64, 145.39, 166.87; m/z [EI

(70)]: 230.0438 (found), 230.04352 (calcd.); 230 (M^+, 9%), 182 (M^+-CH_3SH, 100%), 152 (M^+-SCH_3, -OCH_3, 14%), 124 (M^+-SCH_3, -CO_2CH_3, 32%).

Yield of **25**: 0.4 mg, 0.003 mmol, 8%; The product had the same spectral properties as described previously (Section 7.3).

1-Methyl-2-methylthio-4-phenylnaphthalene (86)
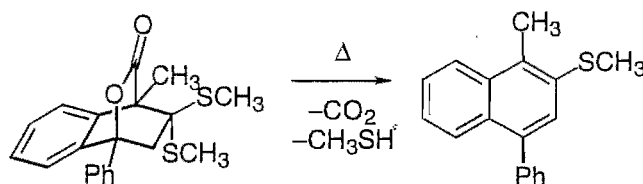
11,11-Bis(methylthio)-1-methyl-9-oxa-8-phenyltricyclo[6.2.2.0^{2,7}]dodec-2,4,6-trien-10-one (10 mg, 0.03 mmol) was heated neat under nitrogen at 145 °C for 20 days. The resulting mixture was purified using radial chromatography, eluting with 90% petroleum ether/10% ethyl acetate.

Yield of **86**: 5 mg, 0.02 mmol, 61%; colourless oil; IR (CDCl$_3$): υ_{max} 3676 (m), 3064 (w), 2926 (w), 1718 (m), 1602 (m), 1560 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.54 (3H, s, SCH$_3$), 2.81 (3H, s, Ar-CH$_3$), 7.35-7.56 (8H, m), 7.83 (1H, d, J = 7.8 Hz), 8.07 (1H, d, J = 7.3 Hz); ^{13}C NMR (CDCl$_3$): δ 15.64, 16.86, 124.04, 125.03, 125.74, 126.30, 126.67, 127.30, 128.26, 129.89, 130.13, 131.47, 132.96, 133.67, 138.92, 140.57; m/z [EI (70)]: 264.0975 (found), 264.09727 (calcd.); 264 (M^+, 100%), 249 (M^+-CH_3, 27%), 234 (M^+-CH_3, -CH_3, 20%), 217 (M^+-SCH_3, 16%), 215 (32%), 202 (M^+-SCH_3, -CH_3, 17%).

7.16. Attempted preparation of 5-phenyl-2-pyranone (79)

1,1,1,3-Tetrachloro-3-ethoxypropane[17]
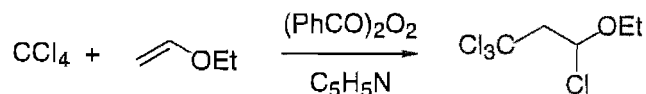
A solution of benzoyl peroxide (20 mg, 0.08 mmol, 0.002 eq.) and pyridine (10.6 µL, 0.13 mmol, 0.003 eq.) in dry ethyl vinyl ether (5 mL, 0.052 mol, 1.0 eq.) was added dropwise to a solution of pyridine (10.6 µL, 0.13 mmol, 0.003 eq.) in dry carbon tetrachloride (11.6 mL, 0.157 mol, 3.0 eq.) over two hours. The colourless solution was then refluxed for 1 hour. The excess carbon tetrachloride was removed under vacuum and the crude product was vacuum distilled.

Yield of 1,1,1,3-tetrachloro-3-ethoxypropane: 5.44 g, 24.08 mmol, 46%; colourless oil; b.p. 98-99 °C/19 mmHg; ^{1}H NMR (CDCl$_3$): δ 1.27 (3H, d, J = 7.3 Hz), 3.39 (1H, dd, J = 15.1, 2.6 Hz), 3.50 (1H, dd, J = 15.1, 7.3 Hz), 3.62 (1H, dq, J = 9.3, 7.3 Hz), 3.98 (1H, dq, J = 9.3, 7.3 Hz), 5.94 (1H, dd, J = 7.3, 2.5 Hz).

1,1,3-Trichloro-3-ethoxy-1-propene[18]
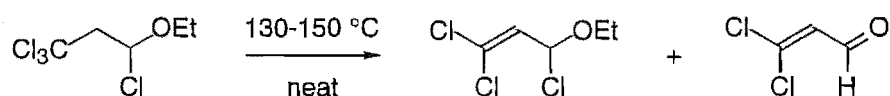
1,1,1,3-Tetrachloro-3-ethoxypropane (2.92 g, 12.9 mmol) was heated neat at 130-150 °C for 1.5 hours, by which stage the evolution of HCl had ceased. The reaction mixture was vacuum distilled resulting in a mixture of products, including 1,1,3-trichloro-3-ethoxy-1-propene and 3,3-dichloropropenal. This mixture was used in the following reaction without further purification.

Yield of product mixture: 2.3 g, 12.14 mmol, 94%; colourless oil; b.p. 100 °C/19 mmHg; *50% 1,1,3-Trichloro-3-ethoxy-1-propene:* ^{1}H NMR (CDCl$_3$): δ 1.25 (3H, t, J = 7.3 Hz), 3.53 (1H, dq, J = 8.7, 7.3 Hz), 3.61 (1H, dq, J = 8.7, 7.3 Hz), 6.20

(1H, d, J = 7.8 Hz), 6.25 (1H, d, J = 7.8 Hz); GCMS m/z [EI (70)]: 153 (M^+-Cl, 57%), 143 (M^+-OCH$_2$CH$_3$, 12%), 125 (M^+ H-CH$_2$CH$_3$, -Cl, 100%). *33% 3,3-Dichloropropenal:* ^{1}H NMR (CDCl$_3$): δ 6.42 (1H, d, J = 6.3 Hz), 9.85 (1H, d, J = 6.3 Hz); GCMS m/z [EI (70)]: 124 (M^+, 55%), 123 (M^+-H, 82%), 96 (M^+-CO, 38%), 61 ($C_2H_2Cl^+$, 84%), 60 (C_2HCl^+, 100%).

5,5-Dichloro-2-phenyl-2,4-pentadienal (78)[19]
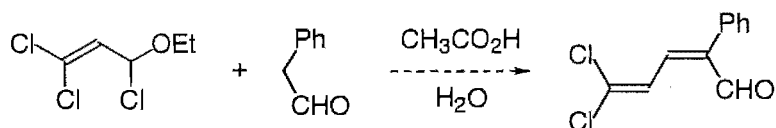
To an ice cold solution of phenylacetaldehyde (1.06 mL, 9.0 mmol, 1.0 eq.) in glacial acetic acid (1.5 mL) was added an ice cold solution of 1,1,3-trichloro-3-ethoxy-1-propene (2.05 g, 10.8 mmol, 1.2 eq.) in glacial acetic acid (2.2 mL). Water (0.24 mL) was added and two layers formed. The reaction mixture was kept in a refrigerator for 2.5 days. The reaction mixture was poured into ice water (40 mL). The oil that separated was removed and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ (2 x 20 mL), washed with water (10 mL), dried (NaSO$_4$) and filtered. The ether was removed by distillation at atmospheric pressure. Only a small amount of **78** was ever observed by ^{1}H NMR.

2,3-Dibromobutan-1,4-dioic acid (dibromosuccinic acid)[20]
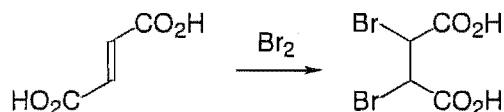
Water (200 mL) containing fumaric acid (100 g, 0.86 mol, 1.0 eq.) was heated to boiling in a flask connected to a double surface condenser, a dropping funnel and a mechanical stirrer. Bromine (45 mL, 0.87 mol, 1.01 eq.) was added slowly over 40 minutes. The mixture was refluxed for a further 20 minutes and cooled in an ice bath. The product was collected by vacuum filtration and washed with cold water until the

filtrate was colourless. The product was dried overnight at room temperature. No further purification was required.

Yield of 2,3-dibromobutan-1,4-dioic acid: 182.9 g, 0.66 mol, 77%; white crystals; m.p. 273-275 °C (sublimes); ^{1}H NMR (d$_6$-DMSO): δ 4.63 (2H, s).

Propynoic acid (propiolic acid)[21]
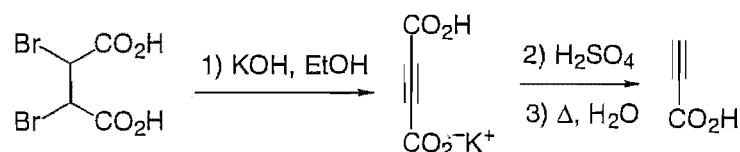
Dibromosuccinic acid (183 g, 0.66 mol, 1.0 eq.) was dissolved in hot ethanol (480 mL) and then allowed to cool. A solution of potassium hydroxide (85%, 200 g, 3.03 mol, 4.6 eq.) in ethanol (700 mL) was added slowly, keeping the temperature of the stirred solution less than 40 °C. The mixture was then refluxed for one hour, cooled in an ice bath and the precipitate formed filtered and washed twice with ethanol. The potassium salt was dissolved in water (700 mL) and cold 3 mol L^{-1} H$_2$SO$_4$ (165 mL) was added. The mixture was left stirring overnight and the precipitate formed filtered and heated in water (430 mL) at 95 °C for 1 hour. By this stage the precipitate had dissolved and the solution was refluxed for 1.5 hours, cooled, acidified (conc. HCl), saturated with ammonium chloride and extracted with ether (150 mL, 12 x 100 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude product was vacuum distilled.

Yield of propynoic acid: 11.17 g, 0.159 mol, 24%; colourless oil; b.p. 60-64 °C/20 mmHg; ^{1}H NMR (CDCl$_3$): δ 3.00 (1H, s).

(Z)-3-Chloropropenoic acid (*cis*-3-chloroacrylic acid)[22]
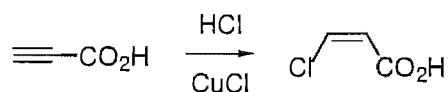
Propynoic acid (11.1 g, 0.158 mol, 1.0 eq.) was added over 25 minutes to a stirred solution of freshly prepared copper(I) chloride (1.0 g, 0.01 mol, 0.06 eq.) in concentrated HCl (27 mL). The solution was cooled in an ice bath during addition, keeping the temperature below 12 °C. The solution was stored overnight at 0 °C. The crystals formed were extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with 2 mol L^{-1} HCl (20 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo*.

Yield of (Z)-3-chloropropenoic acid: 11.11 g, 0.104 mol, 66%; white crystals; m.p. 58-60 °C; ^{1}H NMR (CDCl$_3$): δ 6.23 (1H, d, J = 8.3 Hz), 6.84 (1H, d, J = 8.3 Hz).

Methyl (Z)-3-chloropropenoate (methyl *cis*-3-chloroacrylate) (80)[23]
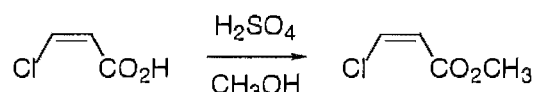
A solution of (Z)-3-chloropropenoic acid (11.1 g, 0.104 mol) and concentrated H$_2$SO$_4$ (2.2 mL) in freshly dried methanol (120 mL) was refluxed overnight. The solution was then poured into ice water (200 mL) and extracted with ether (100 mL, 4 x 50 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. The crude product was purified by vacuum distillation.

Yield of **80**: 6.76 g, 0.056 mol, 54%; colourless oil; b.p. 52-55 °C/20 mmHg; ^{1}H NMR (CDCl$_3$): δ 3.75 (3H, s), 6.19 (1H, d, J = 8.3 Hz), 6.70 (1H, d, J = 8.3 Hz).

Methyl 1,1-bis(carboethoxy)-1-phenyl-2-butenoate[24]
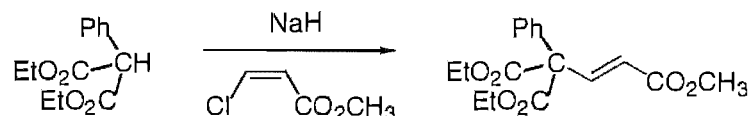
Sufficient sodium hydride (50% in oil) was washed with petroleum ether (3 x) to give 946 mg (39 mmol, 1.2 eq.) of clean reagent. Tetrahydrofuran (40 mL) was added and the mixture stirred under nitrogen. Diethyl phenyl malonate (7.09 mL,

33 mmol, 1.0 eq.) was slowly added. After gas evolution had ceased, the solution became homogeneous. Methyl (Z)-3-chloro-2-propenoate (3.4 mL, 33 mmol, 1.0 eq.) was added and the solution refluxed overnight. The mixture was cooled and quenched with water (80 mL) and extracted with ether (3 x 40 mL). The combined organic layers were washed with saturated sodium chloride (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

Yield of methyl 1,1-bis(carboethoxy)-1-phenyl-2-butenoate: 9.39 g, 0.029 mol, 89%; pale orange oil; ^{1}H NMR ($CDCl_3$): δ 1.22 (6H, t, J = 7.3 Hz), 3.58 (3H, s), 4.21 (4H, q, J = 7.3 Hz), 6.13 (1H, d, J = 12.2 Hz), 6.94 (1H, d, J = 12.2 Hz), 7.26-7.37 (3H, m), 7.49 (2H, dd, J = 8.3, 2.0 Hz).

2-Phenyl-2-penten-1,5-dioic acid (2-phenylglutaconic acid) (81)[24]
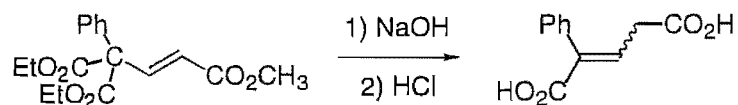
Sodium hydroxide (6.1 g, 0.152 mol, 5.2 eq.) in water (50 mL) was added to methyl 1,1-bis(carboethoxy)-1-phenyl-2-butenoate (9.39 g, 0.029 mol, 1.0 eq.) and the mixture refluxed overnight. The cooled solution was then washed with ether (20 mL) and acidified with conc. HCl causing the evolution of CO_2. The product was extracted with ether (40 mL, 2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the product as a mixture of stereoisomers.

Yield of **81**: 6.05 g, 29.34 mmol, 100%; cream coloured solid; m.p. 166-168 °C; ^{1}H NMR (d_6-DMSO) *E-isomer:* δ 3.17 (2H, d, J = 7.3 Hz), 7.19 (1H, t, J = 7.3 Hz), 7.26 (2H, dd, J = 7.8, 1.5 Hz), 7.36-7.51 (3H, m); *Z-isomer:* δ 3.56 (2H, d, J = 7.3 Hz), 6.43 (1H, t, J = 7.3 Hz), 7.36-7.51 (5H, m).

3-Phenyl-6-chloro-2-pyranone (82)[24]
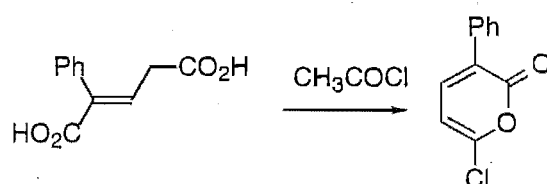
2-Phenylpent-2-en-1,5-dioic acid (6.05 g, 0.029 mol, 1.0 eq.) and acetyl chloride (41.9 mL, 0.588 mol, 20 eq.) were combined in a sealed tube and heated at 100 °C overnight. The tube was cooled, opened and the excess acetyl chloride removed *in vacuo*. The residue was quenched with water (80 mL), and extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. The product was separated from the crude mixture using radial chromatography eluted with 50% petroleum ether/50% dichloromethane. The product can be recrystallised from toluene/petroleum ether.

Yield of **82**: 402 mg, 1.95 mmol, 7%; orange needles; m.p. 101-102 °C; ^{1}H NMR (CDCl₃): δ 6.33 (1H, d, J = 6.8 Hz), 7.36-7.43 (3H, m), 7.42 (1H, d, J = 6.8 Hz), 7.60 (2H, dd, J = 8.3, 1.9 Hz).

3-Phenyl-2-pyranone (84)[24]
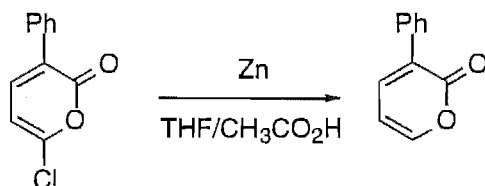
3-Phenyl-6-chloro-2-pyranone (65 mg, 0.32 mmol, 1.0 eq.) and zinc dust (310 mg, 4.7 mmol, 15.0 eq.) were dried under vacuum. Tetrahydrofuran (1.5 mL) and acetic acid (1.5 mL) were added and the mixture stirred overnight at room temperature under nitrogen. Ether (15 mL) was added and the resulting mixture was filtered followed by ether washings (2 x 2 mL). The filtrate was concentrated *in vacuo*. Water was added and the mixture extracted with dichloromethane (3 x 2 mL). The combined

organic layers where dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude product which can be recrystallised from toluene/petroleum ether.

Yield of **84**: 37 mg, 0.21 mmol, 68%; yellow needles; m.p. 102-105 °C; ^1H NMR ($CDCl_3$): δ 6.33 (1H, dd, J = 6.8, 4.9 Hz), 7.35-7.40 (3H, m), 7.42 (1H, dd, J = 6.8, 1.9 Hz), 7.49 (1H, dd, J = 5.4, 1.9 Hz), 7.63 (2H, dd, J = 7.8, 1.5 Hz).

7.17. Preparation of 1-methylthio-1-(*p*-tolylsulfonyl)ethene (87)

1-(Methylthio)phenacyl *p*-tolyl sulfone (89)[25]
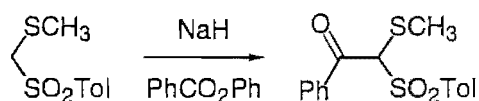
Sufficient sodium hydride (50% in oil) was washed with petroleum ether (3 times) to give 82 mg (3.42 mmol, 5.7 eq.) of clean reagent. Dry tetrahydrofuran (1 mL) was added and the mixture stirred under nitrogen at 0 °C. Methylthiomethyl *p*-tolyl sulfone (130 mg, 0.60 mmol, 1.0 eq.) in tetrahydrofuran (4 mL) was added and the mixture stirred for 15 minutes. Phenyl benzoate (179 mg, 0.90 mmol, 1.5 eq.) in tetrahydrofuran (2 mL) was added and the mixture stirred at the same temperature for 1 hour and then refluxed for 2 hours. The reaction was quenched by adding water (5 mL). The product was extracted with dichloromethane (3 x 5 mL) and the combined organic layers were washed with aqueous NaOH (2 mol L^{-1}, 4 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the product.

Yield of **89**: 82 mg, 0.26 mmol, 43%; yellow oil; ^1H NMR ($CDCl_3$): δ 2.26 (3H, s), 2.43 (3H, s), 5.48 (1H, s), 7.33 (2H, d, J = 7.9 Hz), 7.47 (2H, t, J = 7.8 Hz), 7.60 (1H, t, J = 7.3 Hz), 7.86 (2H, d, J = 8.3 Hz), 7.93 (2H, d, J = 8.7 Hz).

1-(Methylthio)ethyl *p*-tolyl sulfone (91)
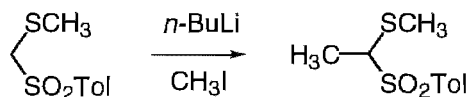
n-Butyllithium (17.6 mL of 1.6 mol L^{-1} solution in hexanes, 28.2 mmol, 1.15 eq.) was added to a solution (stirred under nitrogen) of methylthiomethyl *p*-tolyl sulfone (5.31 g, 24.5 mmol, 1.0 eq.) in dry tetrahydrofuran (60 mL) at -78 °C. The solution was stirred at -78 °C for 30 minutes then at room temperature for 3 hours. The solution was then cooled to -78 °C again and iodomethane (3.1 mL, 49 mmol, 2.0 eq.) was added. The solution was stirred for a further 30 minutes at -78 °C and then overnight at room temperature. Water (50 mL) was added and the mixture concentrated *in vacuo* to remove the tetrahydrofuran. The mixture was extracted with dichloromethane (50 mL, 2 x 25 mL) and the combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo* to give the crude product.

Yield of **91**: 5.53 g, 24.01 mmol, 98%; pale yellow oil; ^{1}H NMR (CDCl$_3$): δ 1.52 (3H, d, *J* = 7.3 Hz), 2.27 (3H, s), 2.44 (3H, s), 3.84 (1H, q, *J* = 7.3 Hz), 7.34 (2H, d, *J* = 8.3 Hz), 7.80 (2H, d, *J* = 8.3 Hz).

1-Chloro-1-(methylthio)ethyl *p*-tolyl sulfone (92)[26]
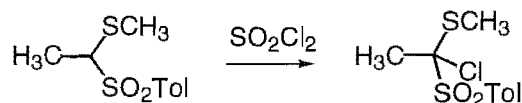
1-(Methylthio)ethyl *p*-tolyl sulfone (5.46 g, 23.7 mmol, 1.0 eq.) was dried under vacuum and dissolved in dry chloroform (60 mL). The solution was cooled to 0 °C and sulfuryl chloride (2.1 mL, 26.1 mmol, 1.1 eq.) added dropwise. The solution was stirred at this temperature for 2 hours and then at room temperature for a further 2 hours. The mixture was washed with water (50 mL, 25 mL) and the combined aqueous layers were extracted with dichloromethane (2 x 25 mL). The combined

organic layers where dried (MgSO$_4$), filtered and concentrated *in vacuo* to give the crude product.

Yield of **92**: 6.19 g, 23.38 mmol, 99%; pale yellow oil; ^{1}H NMR (CDCl$_3$): δ 1.99 (3H, s), 2.45 (3H, s), 2.47 (3H, s), 7.34 (2H, d, *J* = 8.3 Hz), 7.86 (2H, d, *J* = 8.3 Hz).

1-Methylthio-1-(*p*-tolylsulfonyl)ethene (87)
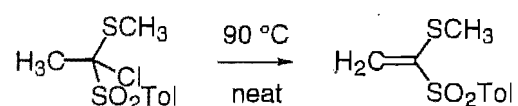
1-Chloro-1-(methylthio)ethyl *p*-tolyl sulfone (6.34 g, 23.9 mmol) was heated neat at 90 °C for 5 hours. The resulting crude product was purified by vacuum distillation (155 °C/0.5 mmHg). Ether (7 mL) was added to the distillate and the solution kept in a freezer overnight. The resulting crystals were collected by vacuum filtration.

Yield of **87**: 1.1 g, 4.84 mmol, 20%; white platelets; m.p. 82-85 °C; IR (CDCl$_3$): υ_{max} 1917 (w), 1597 (m), 1319 (s), 1157 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.27 (3H, s), 2.41 (3H, s), 5.64 (1H, d, *J* = 1.9 Hz), 6.53 (1H, d, *J* = 1.9 Hz), 7.31 (2H, d, *J* = 7.8 Hz), 7.80 (2H, d, *J* = 7.8 Hz); ^{13}C NMR (CDCl$_3$): δ 17.04, 21.61, 121.24, 128.44, 129.65, 135.76, 144.80, 150.06; m/z [EI (70)]: 228.02767 (found), 228.02788 (calcd.); 228 (M$^+$, 15%), 139 (Tol-SO$^+$, 33%), 91 (Tol$^+$, 39%), 73 (M$^+$-SO$_2$Tol, 100%).

Anal. Calcd. for C$_{10}$H$_{12}$O$_2$S$_2$: C, 52.60; H, 5.30; S, 28.08. Found: C, 52.37; H, 5.41; S, 27.78 %.

7.18. Diels-Alder reaction between 1-methylthio-1-(p-tolylsulfonyl)ethene (87) and methyl coumalate (25)

Methyl 4-(methylthio)benzoate (63)
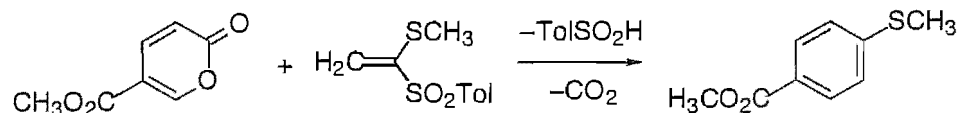
Methyl-2-oxo-2*H*-pyrano-5-carboxylate (46 mg, 0.30 mmol, 1.0 eq.) and 1-methylthio-1-(p-tolylsulfonyl)ethene (137 mg, 0.60 mmol, 2.0 eq.) were dissolved in toluene (12 mL). The solution was refluxed under nitrogen for 5.5 days and then concentrated *in vacuo*. The reaction mixture was separated into its components by radial silica chromatography.

Yield of **63**: 4 mg, 0.02 mmol, 7%; The product had the same spectral properties as described previously (Section 7.15).

7.19. Diels-Alder reaction between 1-methylthio-1-(p-tolylsulfonyl)ethene (87) and methyl 4,6-dimethylcoumalate (26)

Methyl 2,6-dimethyl-4-(methylthio)benzoate (31)
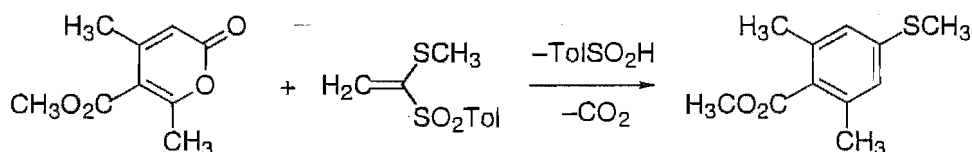
Methyl 4,6-dimethyl-2-oxo-2*H*-pyrano-5-carboxylate (55 mg, 0.30 mmol, 1.0 eq.) and 1-methylthio-1-(p-tolylsulfonyl)ethene (137 mg, 0.60 mmol, 2.0 eq.) were dissolved in toluene (12 mL). The solution was refluxed under nitrogen for 9 days and then concentrated *in vacuo*. The reaction mixture was separated into its components by radial silica chromatography.

Yield of **31**: 0.6 mg, 0.003 mmol, 1%; The product had the same spectral properties as described previously (Section 7.6).

7.20. Diels-Alder reaction between 1-methylthio-1-(*p*-tolylsulfonyl)ethene (87) and 4-methyl-1-phenyl-3*H*-2-benzopyran-3-one (40)

1-Methyl-2-methylthio-4-phenylnaphthalene (86) and 1-methyl-3-methylthio-4-phenylnaphthalene (93)
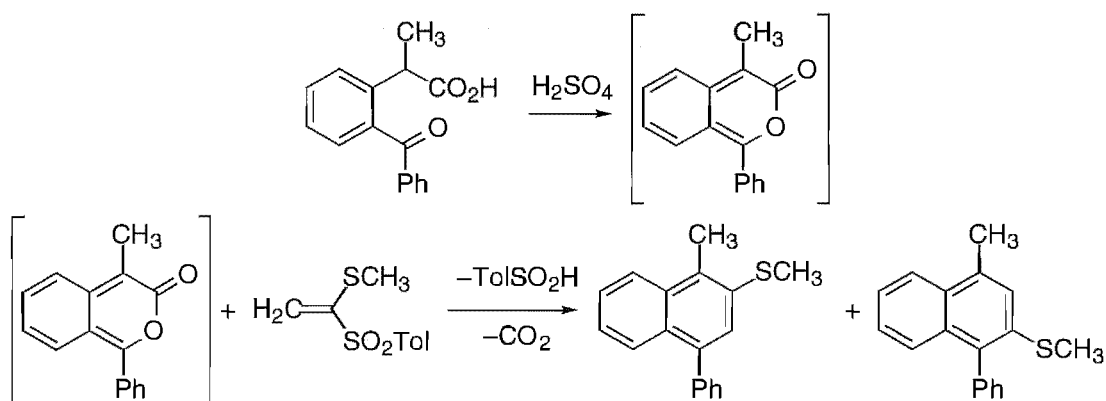
2-Benzoylphenylpropanoic acid (41 mg, 0.16 mmol, 1.0 eq.) was dissolved in conc. H_2SO_4 (0.16 mL) with gentle warming to give an orange solution. Water (20 mL) was added to produce a deep red precipitate which was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to about 10 mL. Toluene (15 mL) was added and the solution again concentrated to about 10 mL. This process was repeated to remove any remaining ethyl acetate. The final volume was 12 mL. 1-Methylthio-1-(*p*-tolylsulfonyl)ethene (110 mg, 0.48 mmol, 3.0 eq.) was added and the red solution was refluxed under nitrogen for 20 hours. By this stage the solution was pale yellow in colour and so was concentrated *in vacuo* and separated into its components by radial silica chromatography. The two regioisomers were collected when the silica was eluted with 90% petroleum ether/10% ethyl acetate.

Yield of **86**: 5 mg, 0.02 mmol, 12%; The product had the same spectral properties as described previously (Section 7.15).

Yield of **93**: 11 mg, 0.04 mmol, 26%; pale yellow oil; IR (CDCl$_3$): υ_{max} 3062 (m), 2982 (m), 2926 (m), 1717 (w), 1601 (m), 1587 (s), 1556(m), 1508 (m), 1443 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.45 (3H, s, SCH$_3$), 2.77 (3H, s, Ar-CH$_3$), 7.35 (1H, s), 7.31-7.56 (8H, m), 7.99 (1H, d, J = 8.3 Hz); ^{13}C NMR (CDCl$_3$): δ 16.29, 19.68, 123.94, 124.05, 124.82, 126.13, 126.24, 127.57, 128.42, 130.38, 130.63, 132.92, 134.04, 134.49, 135.63, 138.72; m/z [EI (70)]: 264.09713 (found), 264.09727 (calcd.); 264 (M$^+$, 100%), 249 (M$^+$-CH$_3$, 17%), 234 (M$^+$-CH$_3$, -CH$_3$, 83%), 215 (M$^+$-SCH$_5$, 30%), 202 (M$^+$-CH$_3$, -SCH$_3$, 23%).

7.21. Diels-Alder reaction between 1-methylthio-1-(*p*-tolylsulfonyl)ethene (87) and 1-methylpyrano-[3,4-*b*]indol-3-one (56)

1-Methyl-2-methylthiocarbazole (98) and 1-methyl-3-methylthiocarbazole (58)
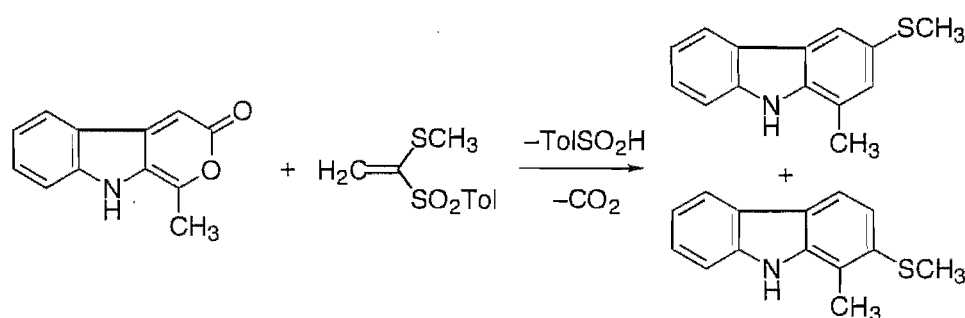
1-Methylpyrano[3,4-*b*]indol-3-one (58 mg, 0.29 mmol, 1.0 eq.) and 1-methylthio-1-(*p*-tolylsulfonyl)ethene (132 mg, 0.58 mmol, 2.0 eq.) were dissolved in bromobenzene (14 mL). The solution was heated at 120 °C under nitrogen. The reaction was monitored by ^{1}H NMR. After 4 hours there was no diene left. The reaction mixture was concentrated *in vacuo* and was separated into its components by radial

silica chromatography. The two regioisomers were collected when the silica was eluted with 80% petroleum ether/20% ethyl acetate. **98** was recrystallised from methanol.

Yield of **58**: 0.7 mg, 0.003 mmol, 1%; The product had the same spectral properties as described previously (Section 7.12).

Yield of **98**: 2 mg, 0.01 mmol, 3%; white platelets; m.p. 158-160 °C; ^{1}H NMR (CDCl$_3$): d 2.52 (3H, s), 2.59 (3H, s), 7.19 (2H, d, J = 7.9 Hz), 7.35-7.44 (2H, m), 7.87 (1H, d, J = 8.3 Hz), 7.91 (1H, br s), 8.00 (1H, d, J = 8.3 Hz); m/z [EI (70)]: 227.07661 (found), 227.07687 (calcd.); 227 (M$^+$, 100%), 212 (M$^+$-CH$_3$, 36%), 180 (M$^+$-SCH$_3$, 13%), 167 (M$^+$-C$_2$H$_4$S, 27%).

7.22. Preparation of 1,3-dihydroisobenzofuran-1-thione (102)[27]
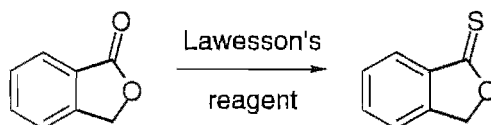
Phthalide (824 mg, 6.1 mmol, 1.0 eq.) in toluene (20 mL) was refluxed with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) (1.49 g, 3.7 mmol, 0.6 eq.) for 17 hours. The reaction solution was then concentrated *in vacuo* to give a yellow solid. This was then recrystallised twice from ether (15 mL) to give the pure product (filtering off the insoluble excess Lawesson's reagent). More product could be obtained by silica chromatography of the mother liquors, eluting with 80% petroleum ether/20% ethyl acetate.

Yield of **102**: 414 mg, 2.76 mmol, 45%; yellow needles; m.p. 111-114 °C; ^{1}H NMR (CDCl$_3$): δ 5.56 (2H, s), 7.47-7.53 (2H, m), 7.67 (1H, dt, J = 7.3, 1.0 Hz), 8.04 (1H, d, J = 7.3 Hz).

7.23. Preparation of 3-phenyl-1,3-dihydroisobenzofuran-1-thione (103)[27]
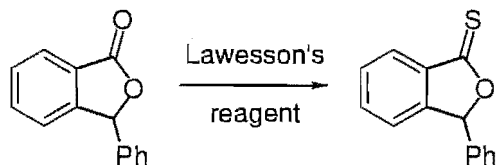
3-Phenylphthalide (1.03 g, 4.9 mmol, 1.0 eq.) in toluene (25 mL) was refluxed with Lawesson's reagent (1.18 g, 2.9 mmol, 0.6 eq.) for 17 hours. The reaction solution was then concentrated *in vacuo* to give a yellow oil. Excess Lawesson's reagent was removed by filtration after the addition of petroleum ether/ether. The mother liquor was concentrated *in vacuo* and the residue recrystallised twice from ether to give the pure product. More product could be obtained by silica chromatography of the mother liquors, eluting with 80% petroleum ether/20% ethyl acetate.

Yield of **103**: 623 mg, 2.75 mmol, 56%; yellow needles; m.p. 98-101 °C; ^{1}H NMR (CDCl$_3$): δ 6.62 (1H, s), 7.22-7.25 (2H, m), 7.30 (1H, dd, J = 7.3, 1.0 Hz), 7.33-7.37 (3H, m), 7.51 (1H, t, J = 7.3 Hz), 7.63 (1H, dt, J = 1.0, 7.3 Hz), 8.06 (1H, d, J = 7.3 Hz).

7.24. Diels-Alder reaction between 1-methylthio-1-(p-tolylsulfonyl)ethene (87) and 1-(methylthio)-isobenzofuran (104)

1,9-*endo*-Bis(methylthio)-11-oxa-9-*exo*-(p-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]-undeca-2,4,6-triene (106b),

1,10-*exo*-bis(methylthio)-11-oxa-10-*endo*-(p-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]-undeca-2,4,6-triene (107a) and

1,10-*endo*-bis(methylthio)-11-oxa-10-*exo*-(p-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]-undeca-2,4,6-triene (107b)
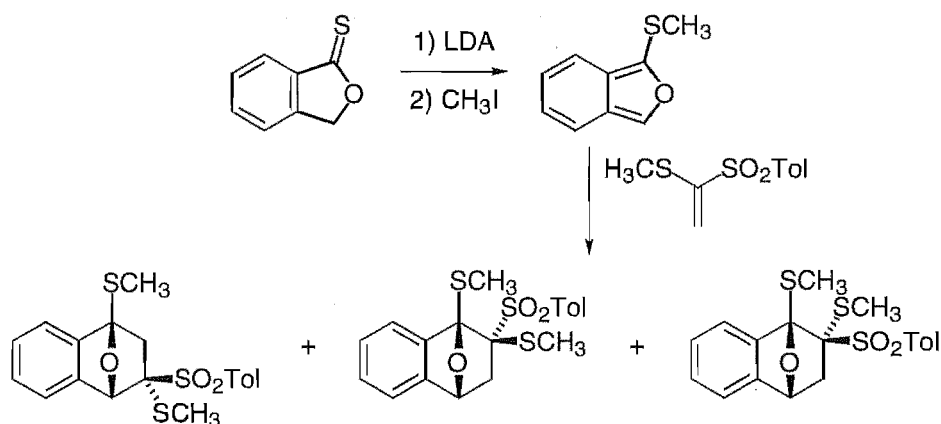
n-Butyllithium (0.24 mL of 1.6 mol L^{-1} solution in hexanes, 0.38 mmol, 1.2 eq.) was added dropwise to a stirred solution of diisopropylamine (49 μL, 0.35 mmol, 1.1 eq.) in tetrahydrofuran (3.3 mL) under dry nitrogen in an ice-salt bath. The solution was stirred for 20 minutes at this temperature and then cooled further in an acetone/dry ice bath. A solution of 1,3-dihydroisobenzofuran-1-thione (48 mg, 0.32 mmol, 1.0 eq.) in tetrahydrofuran (3.3 mL) was added dropwise. The solution was stirred under nitrogen at -78 °C for 1 hour. Iodomethane (24 μL, 0.38 mmol, 1.2 eq.) was added dropwise and the resulting mixture allowed to warm to room temperature over 2 hours. A solution of 1-methylthio-1-(p-tolylsulfonyl)ethene (87 mg, 0.38 mmol, 1.2 eq.) in tetrahydrofuran (0.9 mL) was added. The reaction solution was left stirring overnight under nitrogen at room temperature. The solution was then concentrated *in vacuo* to

remove excess tetrahydrofuran. The residue was partitioned between water (8 mL) and dichloromethane (8 mL). The aqueous layer was further extracted with dichloromethane (2 x 8 mL). The combined organic layers where dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was separated into its components by radial silica chromatography. **106b**, **107a** and **107b** were collected when the silica was eluted with 80% petroleum ether/20% ethyl acetate. **107b** could be recrystallised from ethanol.

Yield of **106b**: 75 mg, 0.19 mmol, 60%; white solid; m.p. 67.5-69 °C; ^{1}H NMR (C_6D_6): δ 1.69 (1H, d, J = 13.1 Hz, *endo* H), 1.84 (3H, s, CH_3S-CO), 1.96 (3H, s, CH_3-Ar), 2.15 (3H, s, $CH_3S-C-SO_2$), 3.13 (1H, d, J = 13.2 Hz, *exo* H), 6.01 (1H, s, H-CO), 6.92 (2H, d, J = 7.8 Hz), 6.99-7.09 (3H, m), 7.20 (1H, d, J = 5.9 Hz), 8.01 (2H, d, J = 8.3 Hz); m/z [EI (70)]: 236.03300 (found), 236.03296 (calcd.) *-for M^+-$TolSO_2H$ (the parent ion was not observed)*; 236 (M^+-$TolSO_2H$, 100%), 221 (M^+-$TolSO_2H$, -CH_3, 63%), 189 (M^+-$TolSO_2H$, -SCH_3, 16%), 177 ($C_{10}H_9OS^+$, 15%), 164 (M^+ -$TolSO_2(CH_3S)C=CH_2$, 23%), 139 (Tol-SO^+, 13%), 91 (Tol^+, 31%), 73 ($CH_3S-C=CH_2^+$, 12%).

Yield of **107a**: 6 mg, 0.02 mmol, 5%; white solid; m.p. 126-128 °C; ^{1}H NMR ($CDCl_3$): δ 2.05 (3H, s, CH_3S-CO), 2.10 (3H, s, CH_3-Ar), 2.43 (3H, s, $CH_3S-C-SO_2$), 2.60 (1H, d, J = 12.7 Hz, *endo* H), 2.75 (1H, dd, J = 12.7, 5.4 Hz, *exo* H), 5.52 (1H, d, J = 5.4 Hz, H-CO), 7.29-7.38 (5H, m), 7.54 (1H, d, J = 7.3 Hz), 7.78 (2H, d, J = 8.3 Hz).

Yield of **107b**: 25 mg, 0.06 mmol, 20%; white needles; m.p. 148-152 °C; IR ($CDCl_3$): $υ_{max}$ 2932 (m), 1597 (m), 1302 (m), 1142 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.38 (1H, d, J = 13.2 Hz, *endo* H), 2.11 (3H, s, CH_3S-CO), 2.42 (3H, s, CH_3-Ar), 2.48 (3H, s, $CH_3S-C-SO_2$), 3.05 (1H, dd, J = 13.2, 5.4 Hz, *exo* H), 5.33 (1H, d, J = 4.9 Hz, H-CO), 7.22-7.32 (5H, m), 7.49 (1H, d, J = 6.4 Hz), 7.99 (2H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$): δ 13.94, 15.83, 21.66, 43.64, 77.12, 78.96, 101.20, 119.39, 121.86, 126.94, 128.24, 128.90, 131.52, 135.30, 141.69, 144.56, 145.41; m/z [EI (70)]: 236.03293

(found), 236.03296 (calcd.) -*for M$^+$-TolSO$_2$H (the parent ion was not observed)*; 236 (M$^+$-TolSO$_2$H, 37%), 228 (TolSO$_2$(CH$_3$S)C=CH$_2$$^+$, 14%), 221 (M$^+$-TolSO$_2$H, -CH$_3$, 11%), 164 (M$^+$-TolSO$_2$(CH$_3$S)C=CH$_2$, 58%), 139 (Tol-SO$^+$, 40%), 121 (C$_7H_5S^+$, 32%), 91 (Tol$^+$, 27%), 73 (CH$_3$S-C=CH$_2$$^+$, 100%).

Anal. Calcd. for C$_{19}$H$_{20}$O$_3$S$_3$: C, 58.13; H, 5.14; S, 24.5. Found: C, 56.39; H, 4.67; S, 23.93 %.

2,4-Bis(methylthio)naphthalen-1-ol (108)
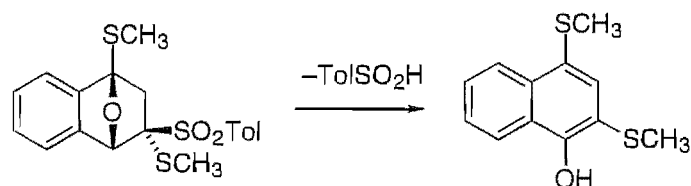
1,9-*endo*-Bis(methylthio)-11-oxa-9-*exo*-(*p*-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]-undeca-2,4,6-triene decomposed within hours upon standing in chloroform. The residue was purified by radial silica chromatography. **108** was collected when the silica was eluted with petroleum ether.

Yield of **108**: 6 mg, 0.03 mmol, 43%; white needles; m.p. 57-58 °C (lit.[28] 61-62 °C); IR (CDCl$_3$): υ_{max} 3398 (br m), 2926(m), 1578 (s), 1499 (m), 1437 (m), 1418 (m), 1366 (s), 1333 (s), 1238 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.36 (3H, s), 2.48 (3H, s), 7.24 (1H, s), 7.54 (1H, dd, *J* = 8.3, 1.4 Hz), 7.58 (1H, dd, *J* = 8.3, 1.4 Hz), 7.62 (1H, s), 8.28 (2H, t, *J* = 8.3 Hz); ^{13}C NMR (CDCl$_3$): δ 18.42, 19.98, 113.40, 123.51, 124.06, 125.03, 126.04, 126.11, 127.75, 132.87, 134.05, 152.88; m/z [EI (70)]: 236.03285 (found), 236.03296 (calcd.); 236 (M$^+$, 100%), 221 (M$^+$-CH$_3$, 68%), 177 (21%).

2-(Methylthio)naphthalen-1,4-dione (2-(methylthio)-1,4-naphthaquinone) (109)
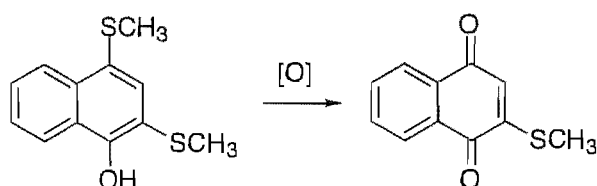
2,4-Bis(methylthio)naphthalen-1-ol slowly oxidised to the naphthoquinone upon exposure to air. This was separated from the naphthol by radial silica chromatography eluting with 90% petroleum ether/10% ethyl acetate. **109** was crystallised from ethanol.

Data for **109**: yellow needles; m.p. 161-163 °C (lit.[29] 165-166 °C); ^{1}H NMR (CDCl₃): δ 2.37 (3H, s), 6.56 (1H, s), 7.69 (1H, td, J = 7.3, 1.5 Hz), 7.74 (1H, td, J = 7.3, 2.0 Hz), 8.08 (1H, dd, J = 7.3, 2.0 Hz), 8.10 (1H, dd, J = 7.3, 1.5 Hz).

7.25. Diels-Alder reaction between 1-methylthio-1-(*p*-tolylsulfonyl)ethene (87) and 1-methylthio-3-phenylisobenzofuran (105)

1,9-Bis(methylthio)-11-oxa-8-phenyl-9-(*p*-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]undeca-2,4,6-triene (110)
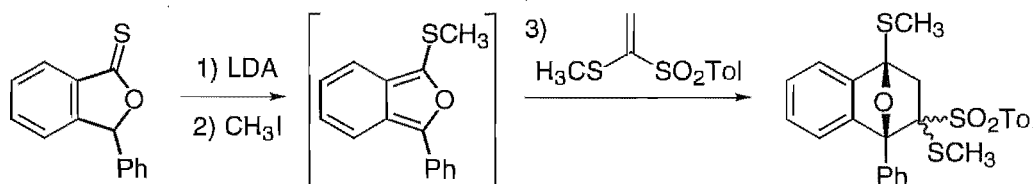
n-Butyllithium (0.27 mL of 1.6 mol L^{-1} solution in hexanes, 0.43 mmol, 1.25 eq.) was added dropwise to a stirred solution of diisopropylamine (58 μL, 0.41 mmol, 1.2 eq.) in tetrahydrofuran (3.5 mL) under dry nitrogen in an ice-salt bath. The solution was stirred for 35 minutes at this temperature and then cooled further in an acetone/dry ice bath. A solution of 3-phenyl-1,3-dihydroisobenzofuran-1-thione (78 mg, 0.34 mmol, 1.0 eq.) in tetrahydrofuran (3.5 mL) was added dropwise. The bright red solution was stirred under nitrogen at -78 °C for 1 hour. Iodomethane (28 μL, 0.45 mmol, 1.3 eq.) was added dropwise and the resulting mixture allowed to warm to room temperature over 2 hours. A solution of 1-methylthio-1-(*p*-tolylsulfonyl)ethene

(157 mg, 0.69 mmol, 2.0 eq.) in tetrahydrofuran (0.7 mL) was added. The reaction solution was left stirring overnight under nitrogen at room temperature. The solution was then concentrated *in vacuo* to remove excess tetrahydrofuran. The residue was partitioned between water (6 mL) and ethyl acetate (6 mL). The aqueous layer was further extracted with ethyl acetate (2 x 6 mL). The combined organic layers where dried (MgSO$_4$), filtered and concentrated *in vacuo*. The residue was separated into its components by radial silica chromatography. The only isomer isolated, **110**, was collected when the silica was eluted with 80% petroleum ether/20% ethyl acetate.

Yield of **110**: 80 mg, 0.17 mmol, 50%; yellow oil; IR (CDCl$_3$): υ_{max} 2978 (m), 2930 (m), 1761 (w), 1448 (m), 1439 (m), 1144 (s), 1113 (s) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.32 (3H, s), 2.23 (3H, s), 2.35 (1H, d, J = 12.7 Hz), 2.38 (3H, s), 2.87 (1H, d, J = 12.7 Hz), 7.21 (2H, d, J = Hz), 7.32-7.48 (6H, m), 7.61-7.67 (3H, m), 8.15 (2H, dd, J = 8.3, 1.5 Hz); ^{13}C NMR (CDCl$_3$): δ 12.14, 14.91, 21.41, 46.42, 83.07, 92.53, 119.53, 122.86, 127.63, 127.70, 128.13, 128.21, 129.12, 129.76, 133.76, 135.84, 143.24, 143.91; m/z [EI (70)]: 240.06105 (found), 240.06089 (calcd.) *-for M$^+$-TolSO$_2$(CH$_3$S)C=CH$_2$ (the parent ion was not observed)*; 266 (M$^+$-SO$_2$Tol, -SCH$_3$, 14%), 240 (M$^+$-TolSO$_2$(CH$_3$S)C=CH$_2$, 100%), 228 (TolSO$_2$(CH$_3$S)C=CH$_2$$^+$, 23%), 226 (MH$^+$ -TolSO$_2$(CH$_3$S)C=CH$_2$, -CH$_3$, 43%), 197 (M$^+$-TolSO$_2$(CH$_3$S)C=CH$_2$, -CH$_3$, -CO, 17%), 165 (C$_{13}$H$_9$$^+$, 41%), 139 (TolSO$^+$, 46%), 91 (Tol$^+$, 22%), 77 (Ph$^+$, 18%), 73 (CH$_3$SC=CH$_2$$^+$, 96%).

S-Methyl 2-(benzoyl)thiobenzoate (112)

Also isolated from the radial chromatography was thioester **112** when the silica was eluted with 90% petroleum ether/10% ethyl acetate. This product was recrystallised from petroleum ether.

Yield of **112**: 30 mg, 0.12 mmol, 41%; white needles; m.p. 60-61.5 °C; IR ($CDCl_3$): υ_{max} 3069 (w), 2932 (w), 1773 (m), 1668 (s), 1599 (m), 1450 (m), 1317 (m), 1279 (s), 1265 (s), 1211 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.29 (3H, s), 7.41 (3H, t, $J = 7.3$ Hz), 7.50-7.62 (3H, m), 7.75 (2H, dd, $J = 7.4$, 1.4 Hz), 7.99 (1H, dd, $J = 7.3$, 1.9 Hz); ^{13}C NMR ($CDCl_3$): δ 11.95, 128.10, 128.33, 129.39, 129.70, 132.15, 132.99, 133.04, 136.71, 136.80, 139.30, 192.27, 196.87; m/z [EI (70)]: 209 (M^+-SCH_3, 100%), 180 (MH^+-Ph, 22%), 152 (MH^+-Ph, -CO, 92%), 105 ($PhCO^+$, 59%), 77 (Ph^+, 80%).

Crystal data and structural refinement for 112

$C_{15}H_{12}O_2S$, M 256.31, crystal dimensions 0.79 x 0.33 x 0.03 mm; triclinic, *a* 7.9480(10), *b* 8.0680(10), *c* 11.0900(10) Å; α 74.490(10), β 88.250(10), γ 69.980(10) °; V 642.37(13) $Å^3$, spacegroup $P\bar{1}$, Z = 2, F(000) 268, D_{calc} 1.325 Mg m^{-3}, absorption coefficient 0.242 mm^{-1}, θ range for data collection 2.73 to 25.00, index ranges $0 \le h \le 9$, $-8 \le k \le 9$, $-13 \le l \le 13$; maximum and minimum transmissions 0.85 and 0.89, data/restraints/parameters 2231/0/163, goodness of fit on F^2 was 0.797, final R indices $[I>2\sigma(I)]$ $R_1 = 0.0353$, $wR_2 = 0.0661$, R indices (all data) $R_1 = 0.0671$, $wR_2 = 0.0733$, largest difference peak and hole 0.171 and -0.293 e $Å^{-3}$.

The unit cell parameters were obtained by least-squares refinement of the setting angles of 37 reflections with $8 \le 2\theta \le 14$ °. A unique data set was measured at 163(2) K within $2\theta_{max} = 50°$ limit (ω scans). Of the 2416 reflections obtained, 2235 were unique ($R_{int} = 0.0194$) and were used in the full-matrix least-squares refinement after being corrected for absorption by using the psi-scan method. The intensities of 3 standard reflections, measured every 97 reflections throughout the data collection, showed only 8% decay.

The crystal structure data are reported in Appendix A.3.

4-Hydroxy-3-methylthio-4-phenyl-4*H*-naphthalen-1-one (111)

1,9-Bis(methylthio)-11-oxa-8-phenyl-9-(*p*-tolylsulfonyl)tricyclo[6.2.1.0^{2,7}]-undeca-2,4,6-triene decomposed within a few hours in chloroform to give **111**, which was recrystallised from methanol.

Data for **111**: white prisms; m.p. 210 °C (sublimes); IR (CDCl$_3$): υ_{max} 3580 (w), 1645 (s), 1601 (m), 1589 (w), 1564 (m), 1448 (w), 1321 (s) 1256 (w), 1132 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.30 (3H, s), 3.02 (1H, br s), 6.24 (1H, s), 7.22-7.31 (3H, m), 7.36-7.49 (5H, m), 8.12 (1H, dd, J = 6.9, 1.5 Hz); (d$_6$-DMSO): δ 2.37 (3H, s), 6.33 (1H, s), 7.22 (1H, s), 7.26 (1H, ddd, J = 6.8, 4.4, 1.4 Hz), 7.35 (2H, t, J = 7.3 Hz), 7.42 (2H, dd, J = 8.8, 1.5 Hz), 7.49-7.53 (2H, m), 7.62 (1H, td, J = 7.3, 1.5 Hz), 8.06 (1H, dd, J = 8.3, 1.5 Hz); ^{13}C NMR (d$_6$-DMSO): δ 13.70, 74.03, 118.19, 124.66, 125.24, 127.18, 127.77, 127.86, 128.44, 129.07, 132.84, 144.81, 149.25, 173.18, 180.62; m/z [EI (70)]: 282.07161 (found), 282.07145 (calcd.); 282 (M$^+$, 21%), 266 (M$^+$-O, 6%), 235 (M$^+$-SCH$_3$, 100%), 209 (M$^+$-SCH$_3$, -C$_2$H$_2$, 66%), 181 (12%), 177 (M$^+$-PhCO, 12%), 152 (C$_{12}$H$_8$$^+$, 15%), 105 (PhCO$^+$, 37%), 77 (Ph$^+$, 22%).
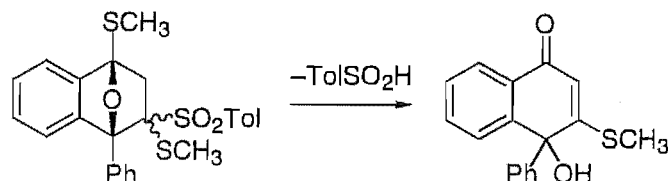
Crystal data and structural refinement for 111

C$_{17}$H$_{14}$O$_2$S, M 282.34, crystal dimensions 0.76 x 0.33 x 0.13 mm; monoclinic, *a* 7.216(2), *b* 22.708(5), *c* 8.544(2) Å; α 90, β 104.51(3) γ 90 °; V 1355.4(6) Å^3, spacegroup P2$_1$/c, Z = 4, F(000) 592, D$_{calc}$ 1.384 Mg m^{-3}, absorption coefficient 0.236 mm^{-1}, θ range for data collection 2.62 to 25.00, index ranges -8 ≤ h ≤ 0, 0 ≤ k ≤ 27, -9 ≤ l ≤ 10; data/restraints/parameters 2369/0/185, goodness of fit on F^2 was 0.877, final R

indices $[I>2\sigma(I)]$ $R_1 = 0.0720$, $wR_2 = 0.1699$, R indices (all data) $R_1 = 0.1249$, $wR_2 = 0.1999$, largest difference peak and hole 0.623 and -0.570 e Å^{-3}.

The unit cell parameters were obtained by least-squares refinement of the setting angles of 30 reflections with $13 \leq 2\theta \leq 7$ °. A unique data set was measured at 163(2) K within $2\theta_{max} = 57°$ limit (ω scans). Of the 2441 reflections obtained, 2372 were unique ($R_{int} = 0.0640$) and were used in the full-matrix least-squares refinement. The intensities of 3 standard reflections, measured every 97 reflections throughout the data collection, showed only 2% decay.

The crystal structure data are reported in Appendix A.4.

7.26. Diels-Alder reaction between 1,2-didehydrobenzene and 1-methylthio-3-phenylisobenzofuran (105)

10-Hydroxy-10-phenyl-10*H*-anthracen-9-one (10-Hydroxy-10-phenyl-9-anthrone) (115)
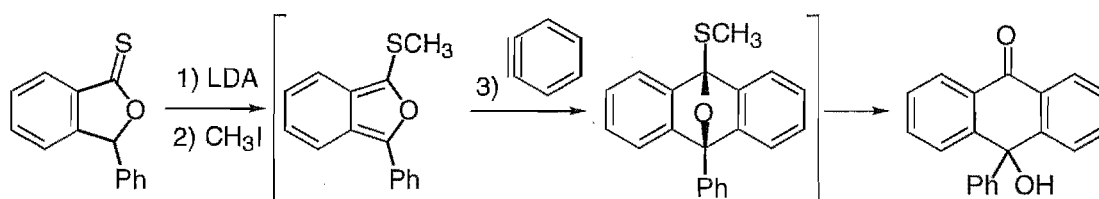
n-Butyllithium (0.36 mL of 1.6 mol L^{-1} solution in hexanes, 0.57 mmol, 1.25 eq.) was added dropwise to a stirred solution of diisopropylamine (76 µL, 0.55 mmol, 1.2 eq.) in tetrahydrofuran (4.5 mL) under dry nitrogen in an ice-salt bath. The solution was stirred for 20 minutes at this temperature and then cooled to -78 °C. A solution of 3-phenyl-1,3-dihydroisobenzofuran-1-thione (104 mg, 0.46 mmol, 1.0 eq.) in tetrahydrofuran (4 mL) was added dropwise. The resulting bright red solution was stirred under nitrogen at -78 °C for 1 hour. Iodomethane (35 µL, 0.55 mmol, 1.2 eq.) was added and the resulting mixture allowed to warm to room temperature over

2 hours, becoming pale yellow in colour. The reaction mixture was then cooled to 0 °C and bromobenzene (145 µL, 1.38 mmol, 3.0 eq.) was added, followed by the dropwise addition of a lithium tetramethylpiperidide solution. (The lithium tetramethylpiperidide solution was prepared by the addition of n-butyllithium (0.63 mL of a 1.6 mol L^{-1} solution in hexanes, 1.01 mmol, 2.2 eq.) to tetramethylpiperidine (155 µL, 0.92 mmol, 2.0 eq.) in tetrahydrofuran (2.3 mL) at 0 °C. The solution was stirred at this temperature for 30 minutes).

The reaction solution was stirred under nitrogen at 0 °C for 2 hours and then overnight at room temperature. The solution was then concentrated *in vacuo* to remove excess tetrahydrofuran. The residue was partitioned between water (25 mL) and dichloromethane (15 mL) and the aqueous layer further extracted with dichloromethane (2 × 10 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated *in vacuo*. The product was isolated by radial silica chromatography eluting with 80% petroleum ether/20% ethyl acetate. **115** was further purified by recrystallising from ethanol.

Yield of **115**: 42 mg, 0.15 mmol, 32%; white needles; m.p. 218-220 °C (lit.[30] 210-212 °C); IR (CDCl$_3$): υ_{max} 3589 (m), 3071 (w), 1665 (s), 1601 (s), 1493 (w), 1456 (m), 1448 (m), 1321 (s), 1302 (m), 1267 (s), 1159 (m) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.10 (1H, br s), 7.10-7.23 (3H, m), 7.31-7.41 (4H, m), 7.53 (2H, td, J = 7.8, 1.5 Hz), 7.59 (2H, dd, J = 8.8, 1.4 Hz), 8.19 (2H, dd, J = 7.8, 1.0 Hz); ^{13}C NMR (CDCl$_3$): δ 73.02, 125.39, 126.80, 126.85, 128.17, 128.33, 128.36, 129.69, 134.09, 145.90, 147.72, 183.76; m/z [EI (70)]: 286.09882 (found), 286.09938 (calcd.); 286 (M$^+$, 42%), 270 (MH$^+$-OH, 77%), 268 (M$^+$-H$_2$O, 20%), 241 (M$^+$-CO, -OH, 16%), 239 (C$_{19}$H$_{11}^+$, 17%), 209 (M$^+$-Ph, 100%), 193 (M$^+$-Ph, -O, 11%), 165 (M$^+$-Ph, -CO$_2$, 11%), 152 (C$_{12}$H$_8^+$, 16%), 105 (PhCO$^+$, 8%), 89 (18%), 77 (Ph$^+$, 15%).

7.27. Diels-Alder reaction between 3,4-didehydropyridine and 1-methylthio-3-phenylisobenzofuran (105)

5,10-Dihydro-5,10-epoxy-5-methylthio-10-phenylbenzo[*g*]isoquinoline (116a) and

5,10-dihydro-5,10-epoxy-10-methylthio-5-phenylbenzo[*g*]isoquinoline (116b)

(3-aza- and 2-aza- 9,10-epoxy-10-methylthio-9-phenylanthracene)
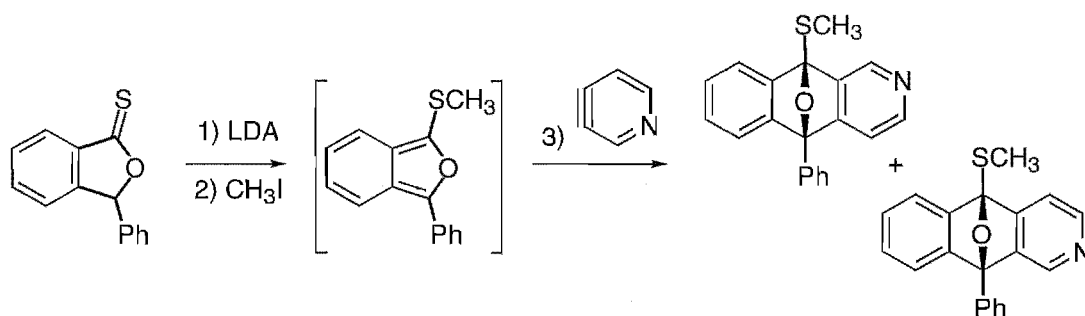
n-Butyllithium (0.32 mL of 1.6 mol L^{-1} solution in hexanes, 0.52 mmol, 1.25 eq.) was added dropwise to a stirred solution of diisopropylamine (70 µL, 0.50 mmol, 1.2 eq.) in tetrahydrofuran (4 mL) under dry nitrogen in an ice-salt bath. The solution was stirred for 20 minutes at this temperature and then cooled to -78 °C. A solution of 3-phenyl-1,3-dihydroisobenzofuran-1-thione (94 mg, 0.42 mmol, 1.0 eq.) in tetrahydrofuran (3.6 mL) was added dropwise. The resulting bright red solution was stirred under nitrogen at -78 °C for 1 hour. Iodomethane (31 µL, 0.50 mmol, 1.2 eq.) was added and the resulting mixture allowed to warm to room temperature over 2 hours, becoming pale yellow in colour. The reaction mixture was then cooled to 0 °C and 3-bromopyridine (120 µL, 1.25 mmol, 3.0 eq.) was added, followed by the dropwise addition of a lithium tetramethylpiperidide solution. (The lithium tetramethylpiperidide solution was prepared by the addition of *n*-butyllithium (0.57 mL of a 1.6 mol L^{-1} solution in hexanes, 0.91 mmol, 2.2 eq.) to tetramethylpiperidine (140 µL, 0.83 mmol, 2.0 eq.) in tetrahydrofuran (2.2 mL) at 0 °C. The solution was stirred at this temperature for 30 minutes.)

The reaction solution was stirred under nitrogen at 0 °C for 2 hours and then overnight at room temperature. The solution was then concentrated *in vacuo* to remove excess tetrahydrofuran. The residue was partitioned between water (20 mL) and dichloromethane (15 mL) and the aqueous layer further extracted with dichloromethane (2 x 10 mL). The combined organic layers where dried (MgSO$_4$), filtered and concentrated *in vacuo*. The pair of regioisomers were purified by radial silica chromatography eluting with 80% petroleum ether/20% ethyl acetate. **116a** was isolated by further radial silica chromatography. **116b** had decomposed to **117b** which was collected when the silica was eluted with 67% petroleum ether/33% ethyl acetate. **117b** was further purified by recrystallising from chloroform.

Yield of **116a** and **b**: 26 mg, 0.08 mmol, 20%; colourless oil; IR : (CDCl$_3$): υ_{max} 3069 (w), 3045 (w), 2224 (w), 1597 (m), 1450 (m), 1437 (w), 1414 (s), 1339 (w), 1321 (m), 1196 (s), 1022 (m) cm^{-1}; m/z [EI (70)]: 317.08710 (found), 317.08744 (calcd.); 317 (M$^+$, 91%), 302 (M$^+$-CH$_3$, 59%), 301 (M$^+$-O, 16%), 271 (MH$^+$-SCH$_3$, 100%), 270 (M$^+$-SCH$_3$, 90%), 269 (M$^+$-SCH$_3$, -H, 72%), 242 (M$^+$-SCH$_3$, -CO, 44%), 241 (M$^+$-C$_6$H$_4$, 49%), 240 (M$^+$-C$_5$H$_3$N, 37%), 214 (16%), 213 (26%), 149 (62%), 105 (PhCO$^+$, 33%), 77 (Ph$^+$, 24%).

^{1}H NMR (CDCl$_3$): δ *(116a)* 2.34 (3H, s), 7.05-7.14 (2H, m), 7.27-7.35 (3H, m), 7.49 (1H, tt, *J* = 7.3, 1.4 Hz), 7.57 (2H, td, *J* = 7.8, 1.5 Hz), 7.83 (2H, dd, *J* = 7.3, 1.5 Hz), 8.38 (1H, d, *J* = 4.9 Hz), 8.54 (1H, d, *J* = 1.0 Hz); *(116b, not isolated)* 2.37 (3H, s), 7.01-7.12 (2H, m), 7.25-7.38 (3H, m), 7.45-7.51 (1H, m), 7.53-7.59 (2H, m), 7.79 (2H, dd, *J* = 8.3, 1.5 Hz), 8.33 (1H, d, *J* = 4.4 Hz), 8.53 (1H, d, *J* = 1.0 Hz); ^{13}C NMR (CDCl$_3$): δ *(116a)* 11.63, 90.03, 95.23, 115.43, 120.95, 121.02, 126.65, 126.90, 126.98, 128.49, 128.90, 128.96, 133.29, 140.37, 146.58, 147.99, 149.31, 158.27.

5-Hydroxy-5-phenyl-5*H*-benzo[*g*]isoquinolin-10-one (117b)
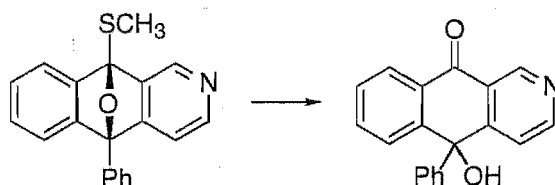
Data for **117b**: white crystals; m.p. 227-229 °C; IR (CDCl$_3$): υ_{max} 3690 (w), 3585 (w), 3069 (w), 1728 (w), 1701 (s), 1674 (s), 1601 (m), 1591 (m), 1448 (w), 1323 (m), 1265 (m), 1250 (s), 1155 (w), 1030 (w) cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 3.78 (1H, br s), 7.13-7.31 (5H, m), 7.43-7.47 (1H, m), 7.49 (1H, d, *J* = 5.9 Hz), 7.57-7.63 (2H, m), 8.22 (1H, dd, *J* = 8.3, 1.0 Hz), 8.56 (1H, d, *J* = 4.8 Hz), 9.24 (1H, s); (d$_6$-acetone): δ 7.30 (1H, tt, *J* = 7.3, 1.5 Hz), 7.40 (2H, tt, *J* = 7.3, 1.5 Hz), 7.51 (2H, dd, *J* = 7.3, 1.5 Hz), 7.63-7.69 (1H, m), 7.74 (1H, d, *J* = 5.3 Hz), 7.80 (2H, d, *J* = 3.9 Hz), 8.35 (1H, dd, *J* = 7.8, 1.0 Hz), 8.86 (1H, d, *J* = 5.4 Hz), 9.41 (1H, s); ^{13}C NMR *(protonated Cs only)* (d$_6$-acetone): δ 115.00, 125.60, 126.23, 127.21, 128.45, 128.71, 128.91, 134.61, 148.70, 153.86; m/z [EI (70)]: 287.09433 (found), 287.09463 (calcd.); 287 (M$^+$, 72%), 269 (M$^+$-H$_2$O, 24%), 210 (M$^+$-Ph, 100%), 127 (14%), 78 (PhH$^+$, 24%).

10-Hydroxy-10-phenyl-10*H*-benzo[*g*]isoquinolin-5-one (117a)
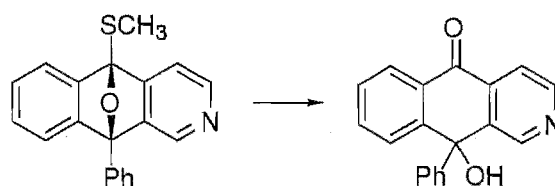
5,10-Dihydro-5,10-epoxy-5-methylthio-10-phenylbenzo[g]isoquinoline slowly underwent decomposition to give **117a**.

Data for **117a**: yellow oil; ^{1}H NMR (CDCl$_3$): δ 7.14-7.29 (5H, m), 7.39 (1H, td, *J* = 8.3, 1.5 Hz), 7.53-7.63 (2H, m), 7.80 (1H, d, *J* = 4.8 Hz), 8.13 (1H, d, *J* = 7.9 Hz), 8.34 (1H, dd, *J* = 4.9, 2.0 Hz), 8.68 (1H, s); (d$_6$-acetone): δ 7.31 (1H, tt, *J* = 7.3, 1.5 Hz), 7.41 (2H, t, *J* = 7.3 Hz), 7.55 (2H, dd, *J* = 7.8, 2.0 Hz), 7.66 (1H, ddd, *J* = 8.3, 5.4, 2.4 Hz), 7.81-7.83 (2H, m), 8.09 (1H, dd, *J* = 4.9, 1.0 Hz), 8.33 (1H, d, *J* = 7.4 Hz),

8.84 (1H, d, J = 5.3 Hz), 9.06 (1H, s); m/z [EI (70)]: 287.09459 (found), 287.09463

(calcd.); 287 (M^+, 44%), 269 (M^+-H$_2$O, 14%), 210 (M^+-Ph, 100%), 149 (27%), 127

(13%), 78 (PhH$^+$, 22%).

7.28. Diels-Alder reaction between 3,4-didehydropyridine and 1-(methylthio)isobenzofuran (104)

**Benzo[g]isoquinolin-5,10-dione (2-azaanthraquinone) (119)**
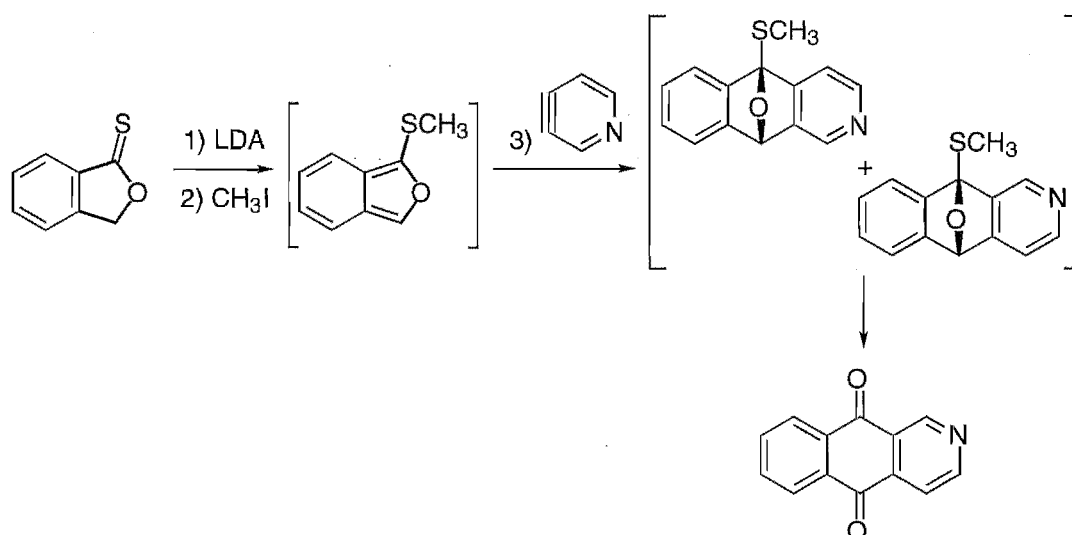
n-Butyllithium (0.38 mL of 1.6 mol L^{-1} solution in hexanes, 0.60 mmol,

1.2 eq.) was added dropwise to a stirred solution of diisopropylamine (77 µL,

0.55 mmol, 1.1 eq.) in tetrahydrofuran (5 mL) under dry nitrogen in an ice-salt bath.

The solution was stirred for 20 minutes at this temperature and then cooled to -78 °C. A

solution of 1,3-dihydroisobenzofuran-1-thione (75 mg, 0.50 mmol, 1.0 eq.) in

tetrahydrofuran (4 mL) was added dropwise. The resulting orange solution was stirred

under nitrogen at -78 °C for 1 hour. Iodomethane (37 µL, 0.60 mmol, 1.2 eq.) was

added and the resulting mixture allowed to warm to room temperature over 2 hours,

becoming dark green in colour. The reaction mixture was then cooled to 0 °C and

3-bromopyridine (240 µL, 2.50 mmol, 5.0 eq.) was added, followed by the dropwise

addition of a lithium tetramethylpiperidide solution. (The lithium tetramethylpiperidide solution was prepared by the addition of n-butyllithium (0.69 mL of a 1.6 mol L^{-1} solution in hexanes, 1.1 mmol, 2.2 eq.) to tetramethylpiperidine (169 µL, 1.0 mmol, 2.0 eq.) in tetrahydrofuran (2.4 mL) at 0 °C. The solution was stirred at this temperature for 30 minutes).

The reaction solution was stirred under nitrogen at 0 °C for 2 hours and then overnight at room temperature. The solution was then concentrated *in vacuo* to remove excess tetrahydrofuran. The residue was partitioned between water (20 mL) and ethyl acetate (20 mL). The aqueous layer was further extracted with ethyl acetate (2 x 15 mL). The combined organic layers where dried (MgSO$_4$), filtered and concentrated *in vacuo*. Many uncharacterised products were isolated by radial silica chromatography; **119** was obtained when the silica was eluted with 80% petroleum ether/20% ethyl acetate. It could be further purified by recrystallisation from chloroform.

Yield of **119**: 6 mg, 0.03 mmol, 6%; yellow needles; m.p. 178-181 °C (lit.[31] 179 °C (sublimes)); ^{1}H NMR (CDCl$_3$): δ 7.80-7.89 (2H, m), 8.05 (1H, dd, J = 4.8, 1.0 Hz), 8.27-8.33 (2H, m), 9.09 (1H, d, J = 4.9 Hz), 9.54 (1H, s); (d$_6$-DMSO): δ 8.04-8.12 (2H, m), 8.15 (1H, d, J = 5.4 Hz), 8.30-8.34 (2H, m), 9.25 (1H, d, J = 5.3 Hz), 9.49 (1H, s); ^{13}C NMR (CDCl$_3$): δ 102.91, 119.05, 126.75, 126.90, 132.91, 133.03, 134.90, 135.22, 138.70, 148.37, 155.23, 182.35, 182.37; m/z [EI (70)]: 209.04749 (found), 209.04768 (calcd.); 209 (M$^+$, 100%), 181 (M$^+$-CO, 37%), 153 (M$^+$-2CO, 47%), 126 (M$^+$-2CO, -CHN, 27%).

7.29. Diels-Alder reaction between 3,4-didehydropyridine and 1-methylthio-3-(trimethylsilyl)isobenzofuran (121)

5,10-Dihydro-5,10-epoxy-5-methylthio-10-(trimethylsilyl)benzo[g]isoquinoline

(122a) and

5,10-dihydro-5,10-epoxy-10-methylthio-5-(trimethylsilyl)benzo[g]isoquinoline

(122b)

(3-aza- and 2-aza- 9,10-epoxy-9-methylthio-10-(trimethylsilyl)anthracene)
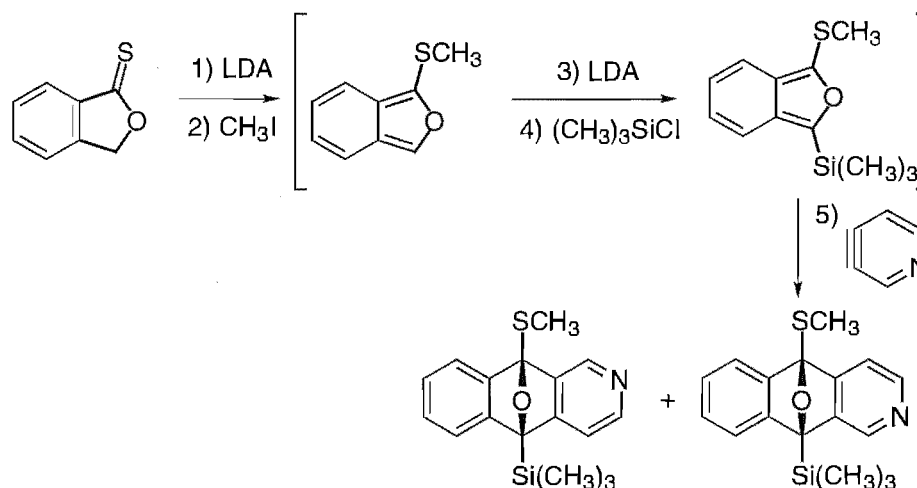
n-Butyllithium (0.34 mL of 1.6 mol L^{-1} solution in hexanes, 0.55 mmol, 1.1 eq.) was added dropwise to a stirred solution of diisopropylamine (70 µL, 0.50 mmol, 1.0 eq.) in tetrahydrofuran (5 mL) under dry nitrogen in an ice-salt bath. The solution was stirred for 30 minutes at this temperature and then cooled to -78 °C. A solution of 1,3-dihydroisobenzofuran-1-thione (75 mg, 0.50 mmol, 1.0 eq.) in tetrahydrofuran (4 mL) was added dropwise. The resulting orange solution was stirred under nitrogen at -78 °C for 1 hour. Iodomethane (34 µL, 0.55 mmol, 1.1 eq.) was added and the resulting mixture allowed to warm to room temperature over 1 hour, becoming dark green in colour. The reaction mixture was cooled to -78 °C and n-butyllithium (0.37 mL of 1.6 mol L^{-1} solution in hexanes, 0.60 mmol, 1.2 eq.) added dropwise. The mixture was left at -78 °C for 1 hour. Trimethylsilyl chloride (freshly distilled, 76 µL, 0.60 mmol, 1.2 eq.) was added and the resulting mixture allowed to

warm to room temperature over 1 hour, becoming dark red in colour. The reaction mixture was then cooled to 0 °C and 3-bromopyridine (144 μL, 1.50 mmol, 3.0 eq.) was added, followed by the dropwise addition of a lithium tetramethylpiperidide solution. (The lithium tetramethylpiperidide solution was prepared by the addition of n-butyllithium (0.69 mL of a 1.6 mol L^{-1} solution in hexanes, 1.1 mmol, 2.2 eq.) to tetramethylpiperidine (169 μL, 1.0 mmol, 2.0 eq.) in tetrahydrofuran (2.4 mL) at 0 °C. The solution was stirred at this temperature for 30 minutes).

The reaction solution was stirred under nitrogen at 0 °C for 4.5 hours and then overnight at room temperature. The solution was then concentrated *in vacuo* to remove excess tetrahydrofuran. The residue was partitioned between water (20 mL) and dichloromethane (20 mL) and the heterogeneous liquid filtered through a Celite bed. The layers were separated and the aqueous layer further extracted with dichloromethane (2 x 20 mL). The combined organic layers where dried ($MgSO_4$), filtered and concentrated *in vacuo*. **122a** and **b** were isolated by radial silica chromatography eluting with 89% petroleum ether/10% ethyl acetate/1% triethylamine. No further effort was made to separate the two regioisomers.

Yield of **122a** and **b**: 29 mg, 0.09 mmol, 18%; yellow oil; IR ($CDCl_3$): υ_{max} 2963 (m), 2934 (m), 1595 (m), 1578 (m), 1456 (m), 1439 (m), 1414 (m), 1267 (m), 1254 (s), 1219 (m), 1163 (m) cm^{-1}; ^{1}H NMR (C_6D_6): δ 0.35 (**a**, 9H, s), 0.36 (**b**, 9H, s), 2.07 (**a**, 3H, s), 2.07 (**b**, 3H, s), 6.85-6.90 (**a**, 2H, **b**, 2H, m), 6.90 (**b**, 1H, dd, J = 4.9, 1.0 Hz), 7.02 (**a**, 1H, dd, J = 4.9, 1.0 Hz), 7.17-7.22 (**a**, 1H, **b**, 1H, m), 7.29-7.34 (**a**, 1H, **b**, 1H, m), 8.33 (**b**, 1H, d, J = 4.9 Hz), 8.33 (**a**, 1H, d, J = 4.9 Hz), 8.78 (**a**, 1H, d, J = 1.0 Hz), 8.82 (**b**, 1H, s); ($CDCl_3$): δ 0.39 (**b**, 9H, s), 0.41 (**a**, 9H, s), 2.26 (**a**, 3H, s), 2.30 (**b**, 3H, s), 6.98-7.09 (**a**, 2H, **b**, 2H, m), 7.19 (**a**, 1H, **b**, 1H, ddd, J = 5.4, 4.4, 1.0 Hz), 7.25-7.29 (**a**, 2H, **b**, 2H, m), 8.27 (**b**, 1H, d, J = 4.8 Hz), 8.31 (**a**, 1H, d, J = 4.4 Hz), 8.42 (**b**, 1H, d, J = 1.0 Hz), 8.45 (**a**, 1H, d, J = 1.0 Hz); ^{13}C NMR (C_6D_6): δ -2.34, 11.68, 11.86, 83.47, 83.95, 97.10, 97.72, 116.22, 116.72, 121.30, 121.40, 121.51,

121.72, 126.51, 126.80, 126.88, 127.19, 141.19, 141.62, 144.86, 148.29, 148.62,

148.78, 148.90, 149.16, 151.90, 152.77, 158.84, 162.42; m/z [EI (70)]: 313.09573

(found), 313.09567 (calcd.); 313 (M^+, 27%), 298 (M^+-CH_3, 55%), 251 (M^+-CH_3,

-SCH_3, 9%),167 (MH_2^+-SCH_3, -$Si(CH_3)_3$, -CO, 11%), 73 ($Si(CH_3)_3^+$, 100%).

5,10-Dihydro-5,10-epoxy-5-methylthiobenzo[*g*]isoquinoline (118a) and

5,10-dihydro-5,10-epoxy-10-methylthiobenzo[*g*]isoquinoline (118b)

(3-aza- and 2-aza- 9,10-epoxy-9-methylthioanthracene)
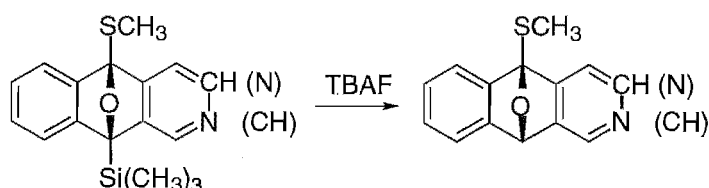
Tetrabutylammonium fluoride (TBAF) (81 μL of 1 mol L^{-1} solution in

tetrahydrofuran, 0.081 mmol, 1.1 eq.) was added dropwise to a solution of a mixture of

122a and **b** (23 mg, 0.073 mmol, 1.0 eq.) in tetrahydrofuran (1 mL) at 0 °C. The red

solution was stirred overnight. Ether (10 mL) was added and the organic layer washed

with brine (3 x 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a

mixture of **118a** and **b**. No further purification was attempted.

Yield of **118a** and **b**: 12 mg, 0.05 mmol, 68%; brown oil; ^{1}H NMR (C_6D_6): δ

2.06 (**a**, 3H, s), 2.08 (**b**, 3H, s), 5.60 (**b**, 1H, s), 5.67 (**a**, 1H, s), 6.66 (**b**, 1H, d, *J* = 4.9

Hz), 6.79-6.85 (**a**, 2H, **b**, 2H, m), 6.93-7.00 (**a**, 1H, **b**, 1H, m), 6.95 (**a**, 1H, d, *J* = 3.9

Hz), 7.25-7.30 (**a**, 1H, **b**, 1H, m), 8.30 (**b**, 1H, d, *J* = 4.4 Hz), 8.31 (**a**, 1H, d, *J* = 4.4

Hz), 8.49 (**a**, 1H, s), 8.81 (**b**, 1H, s); (CDCl$_3$): δ 2.27 (**a**, 3H, s), 2.31 (**b**, 3H, s), 6.04 (**b**,

1H, s), 6.13 (**a**, 1H, s), 7.02-7.12 (**a**, 2H, **b**, 3H, m), 7.21-7.34 (**a**, 3H, **b**, 2H, m), 8.32

(**b**, 1H, d, *J* = 4.9 Hz), 8.36 (**a**, 1H, d, *J* = 4.4 Hz), 8.45 (**b**, 1H, s), 8.51 (**a**, 1H, s); ^{13}C

NMR (C_6D_6): δ 11.74, 11.94, 79.86, 80.73, 96.87, 97.39, 115.90, 116.05, 121.21,

121.24, 121.33, 121.42, 126.99, 127.01, 127.36, 127.40, 141.29, 141.40, 145.23,

146.83, 147.73, 148.56, 149.01, 149.19, 149.43, 150.19, 157.23, 158.87; m/z [EI (70)]:

241.05612 (found), 241.05614 (calcd.); 241 (M^+, 28%), 226 (M^+-CH$_3$, 73%), 209

(16%), 194 (M^+-SCH$_3$, 100%), 166 (M^+-SCH$_3$, -CO, 44%), 139 (23%).

Benzo[*g*]isoquinolin-5,10-dione (2-azaanthraquinone) (119)
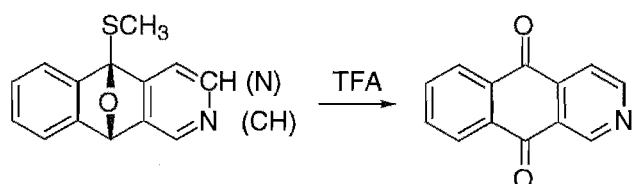
A drop of trifluoroacetic acid (TFA) was added to a solution of a mixture of

118a and **b** in CDCl$_3$. A ^{1}H NMR of the red solution 20 minutes later showed no

starting material was present and showed a mixture of products similar to those formed

from the reaction of 3,4-didehydropyridine with 1-(methylthio)isobenzofuran (Section

7.28), including **119**.

7.30. References

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A.1. X-ray crystal structure of 11,11-bis(methylthio)-1-methyl-9-oxa-8-phenyltricyclo[6.2.2.0^{2,7}]dodec-2,4,6-trien-10-one (42)

Figure A.1.1:
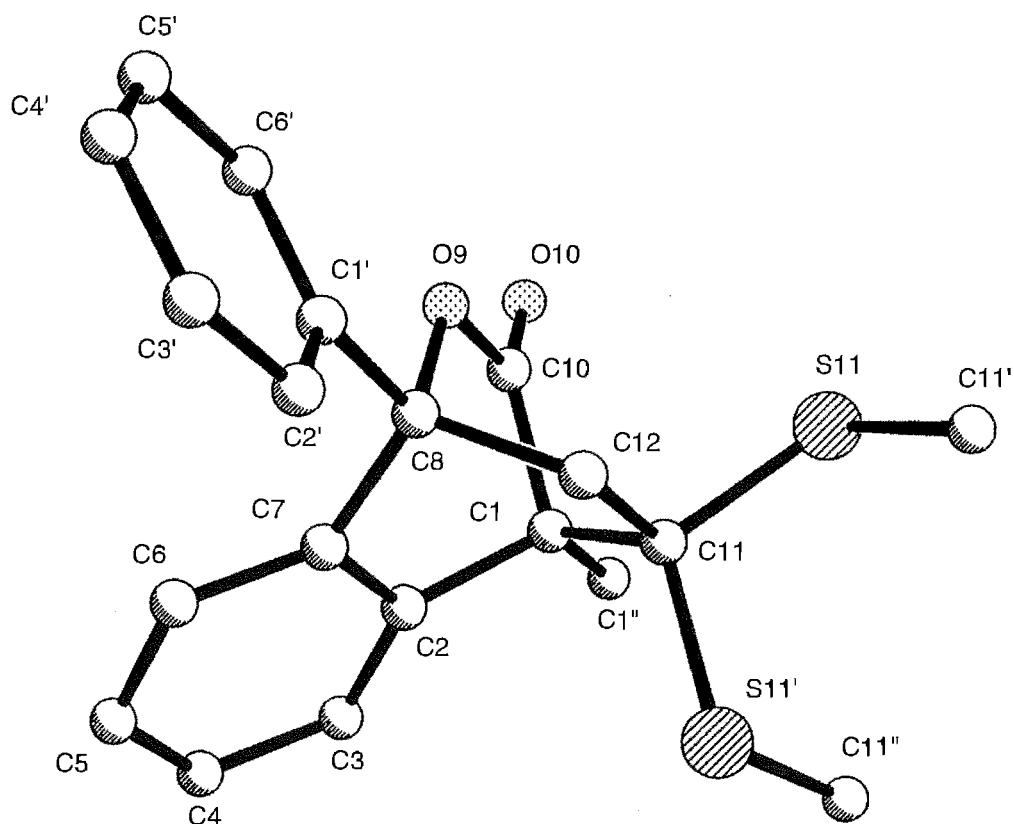
Table A.1.1: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **42**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

Atom	x	y	z	U(eq)
S11	8204.8(2)	4005.8(6)	9027.2(8)	18.17(12)
S11'	8515.3(2)	605.6(6)	7772.1(8)	20.35(13)
O10	7955.9(5)	3397(2)	13430(2)	18.1(3)
C1	8183.7(6)	1396(2)	11216(3)	14.8(4)
C2	8427.3(7)	-131(2)	11917(3)	15.3(4)
C3	8219.9(8)	-1653(3)	12125(3)	22.1(4)
C4	8480.0(8)	-2912(3)	12886(4)	27.3(5)
C5	8940.5(9)	-2652(3)	13419(3)	27.1(5)
C6	9151.9(8)	-1123(3)	13213(3)	21.6(5)
C7	8892.9(7)	127(2)	12459(3)	15.0(4)
C8	9056.5(6)	1867(2)	12148(3)	14.5(4)
O9	8719.8(5)	2935(2)	13079(2)	14.8(3)
C10	8260.7(6)	2667(2)	12664(3)	13.8(4)
C11	8479.5(7)	2044(2)	9600(3)	14.2(4)
C12	9002.5(6)	2270(3)	10193(3)	17.0(4)
C1"	7657.0(7)	1167(3)	10894(3)	19.5(4)
C11'	8572.4(8)	4729(3)	7264(3)	23.7(5)
C11"	7954.5(8)	677(3)	6649(3)	25.4(5)
C1'	9543.5(6)	2235(2)	12870(3)	17.3(4)
C2'	9938.1(8)	1656(3)	11987(3)	28.5(5)
C3'	10390.3(8)	1921(4)	12657(4)	35.3(6)
C4'	10449.8(8)	2750(3)	14217(4)	31.8(6)
C5'	10060.6(8)	3340(3)	15087(4)	33.9(6)
C6'	9607.0(8)	3075(3)	14426(3)	26.6(5)

Table A.1.2: Selected bond lengths (Å) for **42**

Atoms	Bond length	Atoms	Bond length
S11-C11	1.839(2)	S11-C11'	1.802(2)
S11'-C11	1.830(2)	S11'-C11"	1.807(2)
O10-C10	1.202(2)	C1-C2	1.526(3)
C1-C10	1.534(3)	C1-C11	1.583(3)
C1-C1"	1.524(3)	C2-C3	1.388(3)
C2-C7	1.399(3)	C3-C4	1.395(3)
C4-C5	1.384(3)	C5-C6	1.398(3)
C6-C7	1.385(3)	C7-C8	1.518(3)
C8-O9	1.477(2)	C8-C12	1.536(3)
C8-C1'	1.517(3)	O9-C10	1.357(2)
C11-C12	1.561(2)	C1'-C2'	1.390(3)
C1'-C6'	1.385(3)	C2'-C3'	1.397(3)
C3'-C4'	1.382(4)	C4'-C5'	1.375(4)
C5'-C6'	1.398(3)		

Table A.1.3: Selected bond angles (°) for **42**

Atoms	Bond angle	Atoms	Bond angle
C11-S11-C11'	102.74(10)	C11-S11'-C11"	106.99(10)
C2-C1-C10	103.89(16)	C2-C1-C11	107.97(15)
C2-C1-C1"	113.50(17)	C10-C1-C11	104.94(15)
C10-C1-C1"	109.82(16)	C11-C1-C1"	115.74(17)
C1-C2-C3	125.82(19)	C1-C2-C7	113.98(16)
C3-C2-C7	120.11(18)	C2-C3-C4	119.24(20)
C3-C4-C5	120.47(20)	C4-C5-C6	120.61(20)
C5-C6-C7	118.85(20)	C2-C7-C6	120.71(18)
C2-C7-C8	112.57(16)	C6-C7-C8	126.71(18)
C7-C8-O9	106.47(15)	C7-C8-C12	108.87(17)
C7-C8-C1'	114.06(16)	O9-C8-C12	106.00(15)
O9-C8-C1'	107.20(16)	C12-C8-C1'	113.65(17)
C8-O9-C10	114.31(15)	O10-C10-C1	125.85(17)
C1-C10-O9	114.47(16)	O10-C10-O9	119.67(19)
S11-C11-S11'	113.92(11)	S11-C11-C1	104.75(13)
S11-C11-C12	111.56(14)	S11'-C11-C1	114.03(13)
S11'-C11-C12	104.15(13)	C1-C11-C12	108.48(16)
C8-C12-C11	110.54(16)	C8-C1'-C2'	119.24(21)
C8-C1'-C6'	121.92(19)	C2'-C1'-C6'	118.78(19)
C1'-C2'-C3'	120.50(24)	C2'-C3'-C4'	120.29(23)
C3'-C4'-C5'	119.42(21)	C4'-C5'-C6'	120.58(24)
C1'-C6'-C5'	120.42(22)		

Symmetry transformations used to generate equivalent atoms

Table A.1.4: Anisotropic displacement parameters (Å^2 x 10^3) for **42**.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^*U_{12}]$$

Atom	U11	U22	U33	U23	U13	U12
S11	17.2(2)	17.1(2)	20.2(2)	4.3(2)	1.0(2)	2.2(2)
S11'	20.4(2)	23.0(2)	17.6(2)	-4.0(2)	0.1(2)	3.0(2)
O10	15.5(6)	18.0(7)	20.8(7)	0.0(6)	2.8(6)	3.3(5)
C1	13.6(9)	14.6(9)	16.3(10)	0.1(8)	2.0(8)	-1.2(7)
C2	19.7(9)	13.1(9)	13.0(10)	-0.3(8)	1.8(8)	0.7(7)
C3	26.5(11)	16.4(9)	23.5(11)	-3.0(9)	2.7(9)	-4.2(8)
C4	40.9(12)	12.4(9)	28.6(12)	1.2(10)	6.2(11)	-2.9(9)
C5	38.9(12)	16.2(10)	26.3(10)	6.7(9)	3.3(10)	8.4(9)
C6	22.7(10)	21.1(10)	21.0(11)	2.4(9)	0.0(8)	4.8(8)
C7	19.7(9)	11.4(8)	13.9(10)	-0.3(7)	3.1(7)	0.7(7)
C8	12.3(8)	12.4(8)	18.8(10)	0.1(8)	-0.3(8)	1.6(7)
O9	11.9(6)	14.8(6)	17.7(7)	-2.7(6)	-0.3(5)	0.7(5)
C10	14.7(8)	10.7(8)	16.0(9)	4.1(8)	-1.5(8)	-1.6(7)
C11	13.1(8)	13.1(9)	16.4(9)	0.8(7)	0.7(7)	-0.1(7)
C12	11.8(8)	19.9(10)	19.4(10)	3.0(8)	1.1(8)	-2.6(7)
C1"	13.1(9)	24.8(10)	20.1(11)	-0.3(9)	0.1(8)	-4.8(8)
C11'	25.2(11)	23.8(10)	22.0(11)	8.1(9)	-0.4(9)	-5.0(9)
C11"	24.2(11)	33.1(12)	19.0(11)	-1.1(10)	-4.0(9)	-7.6(9)
C1'	13.4(8)	16.9(9)	21.5(10)	4.9(9)	-3.3(9)	-1.4(7)
C2'	18.6(10)	44.3(13)	22.5(11)	-0.7(11)	1.0(9)	4.8(10)
C3'	14.8(9)	58.3(16)	32.8(13)	8.1(14)	1.8(10)	4.0(10)
C4'	16.6(10)	45.4(14)	33.4(13)	14.6(13)	-10.4(10)	-6.4(9)
C5'	26.7(12)	39.2(14)	35.9(14)	-6.5(12)	-11.9(11)	-2.5(10)
C6'	17.2(10)	31.6(11)	31.1(13)	-5.6(10)	-4.1(9)	1.7(9)

Table A.1.5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3)

for **42**

Atom	x	y	z	U(eq)
H3	7904.4(8)	-1835(3)	11753(3)	26.5
H4	8340.1(8)	-3956(3)	13038(4)	32.7
H5	9114.6(9)	-3520(3)	13931(3)	32.5
H6	9467.7(8)	-944(3)	13583(3)	25.9
H12A	9209.0(6)	1544(3)	9495(3)	20.4
H12B	9101.9(6)	3411(3)	9979(3)	20.4
H1"A	7524.2(13)	2174(7)	10041(20)	29.2
H1"B	7499.6(11)	910(20)	12003(4)	29.2
H1"C	7608.8(7)	271(13)	10060(20)	29.2
H11'A	8465(4)	5813(9)	6895(15)	35.5
H11'B	8552(5)	3972(11)	6273(9)	35.5
H11'C	8900.3(12)	4796(20)	7665(7)	35.5
H11"A	7988(2)	190(20)	5483(9)	38.1
H11"B	7853(3)	1815(3)	6530(20)	38.1
H11"C	7719(2)	70(20)	7322(12)	38.1
H2'	9900.2(8)	1076(3)	10918(3)	34.2
H3'	10658.0(8)	1528(4)	12038(4)	42.4
H4'	10756.9(8)	2912(3)	14685(4)	38.1
H5'	10100.3(8)	3933(3)	16147(4)	40.7
H6'	9340.6(8)	3473(3)	15049(3)	31.9

A.2.   **X-ray crystal structure of 11-*endo*-ethoxy-1-methyl-9-oxa-8-phenyltricyclo[6.2.2.0²,⁷]dodec-2,4,6-trien-10-one (44b)**

Figure A.2.1:
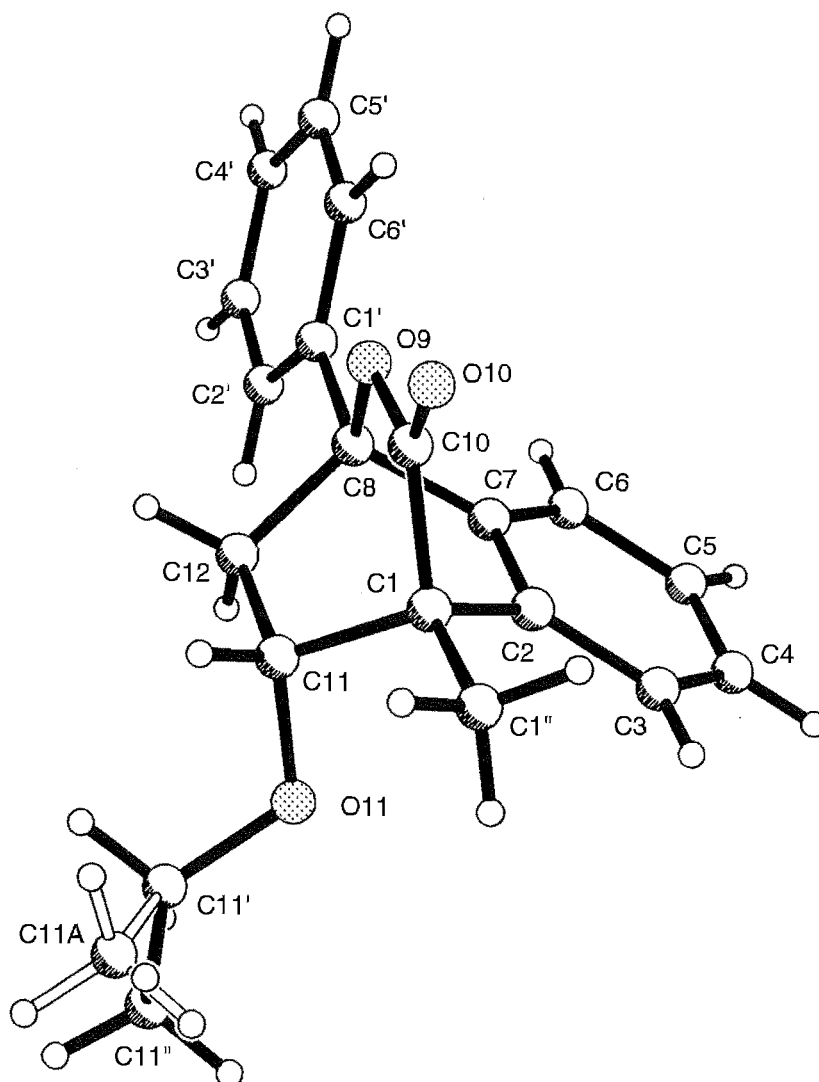
Table A.2.1: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **44b**. U(eq) is defined as one third of the trace of the orthogonalized U$_{ij}$ tensor

Atom	x	y	z	U(eq)
O10	2558(3)	5663(3)	8181(1)	94(1)
C1	986(3)	7923(3)	8373(1)	49(1)
C2	1778(3)	9240(3)	8726(1)	45(1)
C3	2225(3)	10655(3)	8501(1)	57(1)
C4	2961(3)	11735(3)	8883(1)	68(1)
C5	3261(3)	11418(3)	9481(1)	65(1)
C6	2820(3)	10002(3)	9717(1)	50(1)
C7	2067(2)	8925(2)	9336(1)	41(1)
C8	1476(3)	7345(2)	9506(1)	41(1)
O9	2221(2)	6215(2)	9122(1)	55(1)
C10	1982(3)	6506(3)	8529(1)	60(1)
C11	-593(3)	7611(3)	8649(1)	52(1)
C12	-283(3)	7252(3)	9321(1)	50(1)
C1"	766(4)	8168(4)	7698(1)	71(1)
C1'	1921(3)	6874(3)	10148(1)	43(1)
C2'	1088(4)	7423(3)	10604(1)	65(1)
C3'	1538(4)	7058(4)	11194(1)	75(1)
C4'	2817(4)	6146(3)	11336(1)	67(1)
C5'	3655(3)	5587(3)	10889(1)	65(1)
C6'	3211(3)	5943(3)	10297(1)	55(1)
O11	-1537(2)	8950(2)	8543(1)	70(1)
C11'	-3193(4)	8751(5)	8537(2)	105(1)
C11"	-4002(11)	9037(23)	8029(7)	210(10)
C11A	-3856(15)	8190(14)	7997(5)	109(4)

Table A.2.2: Selected bond lengths (Å) for **44b**

Atoms	Bond length	Atoms	Bond length
O10-C10	1.193(3)	C1-C2	1.502(3)
C1-C10	1.505(4)	C1-C1"	1.513(3)
C1-C11	1.545(3)	C2-C3	1.376(3)
C2-C7	1.386(3)	C3-C4	1.372(4)
C4-C5	1.362(4)	C5-C6	1.385(3)
C6-C7	1.374(3)	C7-C8	1.503(3)
C8-O9	1.468(3)	C8-C1'	1.501(3)
C8-C12	1.522(3)	O9-C10	1.342(3)
C11-O11	1.408(3)	C11-C12	1.528(3)
C1'-C2'	1.368(3)	C1'-C6'	1.376(3)
C2'-C3'	1.374(3)	C3'-C4'	1.356(4)
C4'-C5'	1.358(4)	C5'-C6'	1.373(3)
O11-C11'	1.418(4)	C11'-C11"	1.298(12)
C11'-C11A	1.372(10)		

Table A.2.3: Selected bond angles (°) for **44b**

Atoms	Bond angle	Atoms	Bond angle
C2-C1-C10	105.3(2)	C2-C1-C1"	115.4(2)
C10-C1-C1"	111.3(2)	C2-C1-C11	106.8(2)
C10-C1-C11	105.1(2)	C1"-C1-C11	112.2(2)
C3-C2-C7	119.7(2)	C3-C2-C1	126.6(2)
C7-C2-C1	113.7(2)	C4-C3-C2	119.6(2)
C5-C4-C3	120.7(2)	C4-C5-C6	120.6(3)
C7-C6-C5	118.8(2)	C6-C7-C2	120.6(2)
C6-C7-C8	126.7(2)	C2-C7-C8	112.7(2)
O9-C8-C1'	106.8(2)	O9-C8-C7	106.1(2)
C1'-C8-C7	114.7(2)	O9-C8-C12	105.7(2)
C1'-C8-C12	114.2(2)	C7-C8-C12	108.7(2)
C10-O9-C8	114.3(2)	O10-C10-O9	119.2(3)
O10-C10-C1	126.3(2)	O9-C10-C1	114.5(2)
O11-C11-C12	112.1(2)	O11-C11-C1	107.2(2)
C12-C11-C1	109.7(2)	C8-C12-C11	110.0(2)
C2'-C1'-C6'	118.1(2)	C2'-C1'-C8	120.5(2)
C6'-C1'-C8	121.3(2)	C1'-C2'-C3'	120.7(3)
C4'-C3'-C2'	120.6(3)	C3'-C4'-C5'	119.5(2)
C4'-C5'-C6'	120.3(3)	C5'-C6'-C1'	120.8(2)
C11-O11-C11'	117.2(3)	C11"-C11'-O11	116.2(6)
C11A-C11'-O11	112.8(6)		

Symmetry transformations used to generate equivalent atoms

Table A.2.4: Anisotropic displacement parameters ($\mathring{A}^2$ x 10^3) for **44b**.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^*U_{12}]$$

Atom	U11	U22	U33	U23	U13	U12
O10	144(2)	78(1)	61(1)	-13(1)	24(1)	33(1)
C1	60(2)	47(1)	40(1)	2(1)	3(1)	-4(1)
C2	41(1)	45(1)	49(1)	6(1)	7(1)	-1(1)
C3	58(2)	56(2)	58(2)	14(1)	6(1)	-8(1)
C4	73(2)	53(2)	78(2)	13(1)	8(2)	-18(1)
C5	66(2)	51(2)	78(2)	-5(1)	2(1)	-20(1)
C6	46(1)	50(1)	54(1)	-2(1)	-1(1)	-5(1)
C7	36(1)	40(1)	46(1)	2(1)	4(1)	1(1)
C8	45(1)	37(1)	43(1)	-1(1)	6(1)	2(1)
O9	72(1)	44(1)	49(1)	-2(1)	7(1)	13(1)
C10	80(2)	52(2)	47(2)	-5(1)	11(1)	2(1)
C11	55(2)	48(1)	51(1)	4(1)	-8(1)	-11(1)
C12	47(1)	52(1)	50(1)	3(1)	0(1)	-11(1)
C1"	93(2)	72(2)	46(2)	2(1)	2(1)	-7(2)
C1'	45(1)	37(1)	45(1)	3(1)	0(1)	-4(1)
C2'	78(2)	70(2)	46(2)	3(1)	2(1)	23(2)
C3'	97(2)	81(2)	46(2)	0(2)	3(2)	16(2)
C4'	81(2)	66(2)	49(2)	12(1)	-18(1)	-16(2)
C5'	48(2)	71(2)	72(2)	22(2)	-11(1)	-2(1)
C6'	42(1)	62(2)	61(2)	14(1)	4(1)	0(1)
O11	48(1)	77(1)	84(1)	21(1)	-7(1)	-1(1)
C11'	60(2)	138(3)	113(3)	23(3)	-6(2)	-11(2)
C11"	29(4)	413(30)	178(13)	125(16)	-46(5)	7(9)
C11A	145(10)	117(7)	66(6)	-26(6)	10(6)	-18(6)

Table A.2.5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($\mathring{A}^2$ x 10^3) for **44b**

Atom	x	y	z	U(eq)
H3	2028(3)	10878(3)	8092(1)	74
H4	3258(3)	12693(3)	8731(1)	88
H5	3766(3)	12160(3)	9734(1)	85
H6	3031(3)	9783(3)	10125(1)	65
H11	-1117(3)	6715(3)	8445(1)	68
H12A	-843(3)	7995(3)	9553(1)	65
H12B	-668(3)	6214(3)	9404(1)	65
H1"1	253(4)	7272(4)	7511(1)	92
H1"2	1776(4)	8309(4)	7543(1)	92
H1"3	129(4)	9078(4)	7611(1)	92
H2'	208(4)	8050(3)	10514(1)	84
H3'	961(4)	7440(4)	11500(1)	97
H4'	3119(4)	5904(3)	11737(1)	86
H5'	4534(3)	4961(3)	10983(1)	84
H6'	3790(3)	5550(3)	9994(1)	71
H11A	-3400(4)	7682(5)	8652(2)	136
H11B	-3576(4)	9426(5)	8843(2)	136
H11C	-5103(11)	8874(23)	8075(7)	272
H11D	-3669(11)	8348(23)	7724(7)	272
H11E	-3835(11)	10100(23)	7913(7)	272
H11F	-4973(15)	8076(14)	8017(5)	142
H11G	-3402(15)	7194(14)	7915(5)	142
H11H	-3658(15)	8909(14)	7681(5)	142

A.3. X-ray crystal structure of 4-hydroxy-3-methylthio-4-phenyl-4*H*-naphthalen-1-one (111)
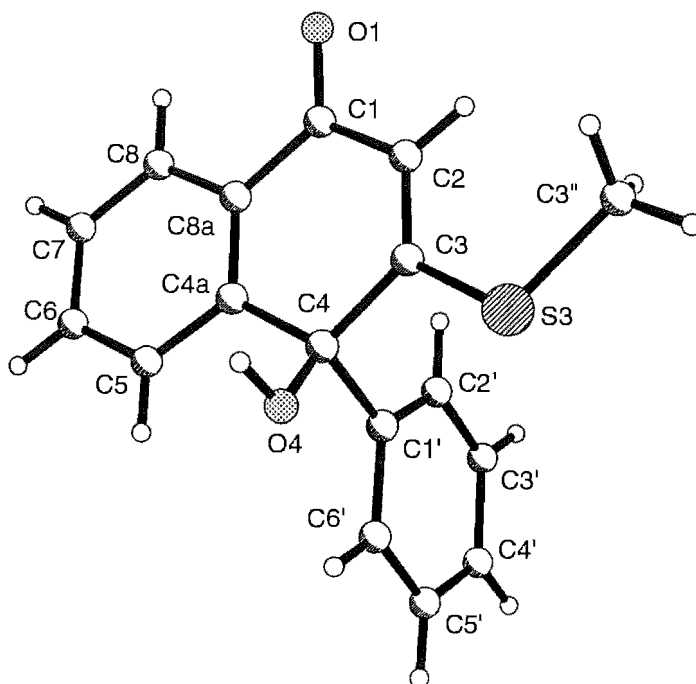
Figure A.3.1:

Table A.3.1: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **111**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

Atom	x	y	z	U(eq)
C1	-2560(6)	5100(2)	5207(5)	23(1)
C2	-1837(7)	5661(2)	5865(6)	26(1)
C3	-1222(7)	6077(2)	4967(6)	24(1)
C4	-1449(7)	6014(2)	3142(5)	24(1)
C4A	-2074(7)	5398(2)	2537(5)	23(1)
C5	-2076(7)	5251(2)	945(6)	28(1)
C6	-2726(8)	4704(2)	317(6)	35(1)
C7	-3404(7)	4300(2)	1246(6)	35(1)
C8	-3370(7)	4436(2)	2818(6)	30(1)
C8A	-2721(6)	4980(2)	3475(5)	23(1)
O1	-2951(5)	4712(1)	6102(4)	29(1)
S3	-114(2)	6735(1)	5719(2)	35(1)
C3"	-495(9)	6773(2)	7718(6)	44(1)
O4	287(5)	6178(1)	2767(4)	29(1)
C1'	-3002(7)	6452(2)	2290(6)	23(1)
C2'	-4801(7)	6460(2)	2593(6)	24(1)
C3'	-6168(7)	6853(2)	1824(6)	28(1)
C4'	-5783(7)	7252(2)	690(6)	32(1)
C5'	-4020(8)	7237(2)	362(7)	36(1)
C6'	-2605(7)	6846(2)	1151(6)	28(1)

Table A.3.2: Selected bond lengths (Å) for **111**

Atoms	Bond length	Atoms	Bond length
C1-O1	1.244(5)	C1-C2	1.438(6)
C1-C8A	1.481(6)	C2-C3	1.360(6)
C3-C4	1.533(6)	C3-S3	1.739(5)
C4-O4	1.418(5)	C4-C4A	1.519(6)
C4-C1'	1.539(6)	C4A-C8A	1.396(6)
C4A-C5	1.401(6)	C5-C6	1.388(7)
C6-C7	1.379(7)	C7-C8	1.373(7)
C8-C8A	1.389(7)	S3-C3"	1.798(5)
C1'-C2'	1.386(6)	C1'-C6'	1.403(6)
C2'-C3'	1.370(7)	C3'-C4'	1.404(7)
C4'-C5'	1.370(7)	C5'-C6'	1.393(7)

Table A.3.3: Selected bond angles (°) for **111**

Atoms	Bond angle	Atoms	Bond angle
O1-C1-C2	120.3(4)	O1-C1-C8A	120.8(4)
C2-C1-C8A	118.9(4)	C3-C2-C1	122.2(4)
C2-C3-C4	122.8(4)	C2-C3-S3	125.0(4)
C4-C3-S3	112.3(3)	O4-C4-C4A	111.7(4)
O4-C4-C3	109.2(4)	C4A-C4-C3	112.3(4)
O4-C4-C1'	107.6(4)	C4A-C4-C1'	108.4(4)
C3-C4-C1'	107.4(4)	C8A-C4A-C5	118.4(4)
C8A-C4A-C4	122.9(4)	C5-C4A-C4	118.6(4)
C6-C5-C4A	120.5(4)	C7-C6-C5	120.4(5)
C8-C7-C6	119.5(5)	C7-C8-C8A	121.1(5)
C8-C8A-C4A	120.0(4)	C8-C8A-C1	120.0(4)
C4A-C8A-C1	119.7(4)	C3-S3-C3"	103.1(3)
C2'-C1'-C6'	119.0(4)	C2'-C1'-C4	121.7(4)
C6'-C1'-C4	119.3(4)	C3'-C2'-C1'	120.9(4)
C2'-C3'-C4'	120.5(5)	C5'-C4'-C3'	118.7(5)
C4'-C5'-C6'	121.5(5)	C5'-C6'-C1'	119.3(4)

Symmetry transformations used to generate equivalent atoms

Table A.3.4: Anisotropic displacement parameters ($\mathring{A}^2 \times 10^3$) for **111**.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^*U_{12}]$$

Atom	U11	U22	U33	U23	U13	U12
C1	22(2)	25(2)	27(3)	3(2)	14(2)	0(2)
C2	29(3)	30(3)	24(3)	1(2)	13(2)	2(2)
C3	24(3)	21(2)	26(3)	1(2)	6(2)	0(2)
C4	26(2)	24(2)	23(3)	0(2)	8(2)	-4(2)
C4A	27(3)	22(2)	22(2)	2(2)	9(2)	4(2)
C5	35(3)	27(3)	27(3)	3(2)	15(2)	7(2)
C6	48(3)	36(3)	27(3)	-3(2)	18(3)	13(3)
C7	39(3)	27(3)	36(3)	-6(2)	7(3)	2(2)
C8	32(3)	28(3)	32(3)	1(2)	13(2)	0(2)
C8A	25(2)	22(2)	23(2)	1(2)	10(2)	0(2)
O1	34(2)	28(2)	30(2)	9(2)	16(2)	0(2)
S3	42(1)	27(1)	34(1)	-2(1)	7(1)	-5(1)
C3"	61(4)	39(3)	25(3)	-10(3)	3(3)	2(3)
O4	27(2)	28(2)	38(2)	8(2)	18(2)	1(2)
C1'	31(3)	18(2)	20(2)	-3(2)	5(2)	-1(2)
C2'	27(3)	23(2)	25(2)	-2(2)	11(2)	-3(2)
C3'	25(3)	30(3)	30(3)	-7(2)	11(2)	-1(2)
C4'	35(3)	20(2)	39(3)	0(2)	9(2)	2(2)
C5'	36(3)	33(3)	38(3)	11(2)	8(2)	-3(2)
C6'	29(3)	29(3)	32(3)	7(2)	17(2)	-3(2)

Table A.3.5: Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\mathring{A}^2 \times 10^3$) for **111**

Atom	x	y	z	U(eq)
H2	-1786(7)	5744(2)	6965(6)	32
H5	-1628(7)	5527(2)	290(6)	34
H6	-2705(8)	4606(2)	-760(6)	42
H7	-3890(7)	3932(2)	801(6)	41
H8	-3797(7)	4153(2)	3469(6)	36
H3"A	-102(51)	7161(6)	8186(19)	65
H3"B	265(43)	6467(11)	8398(14)	65
H3"C	-1855(12)	6711(17)	7659(8)	65
H4	1189(80)	5931(25)	3178(66)	40
H2'	-5090(7)	6188(2)	3344(6)	29
H3'	-7386(7)	6856(2)	2060(6)	33
H4'	-6726(7)	7527(2)	161(6)	38
H5'	-3756(8)	7500(2)	-420(7)	43
H6'	-1384(7)	6845(2)	919(6)	34

A.4. X-ray crystal structure of
S-methyl 2-(benzoyl)thiobenzoate (112)

Figure A.4.1:

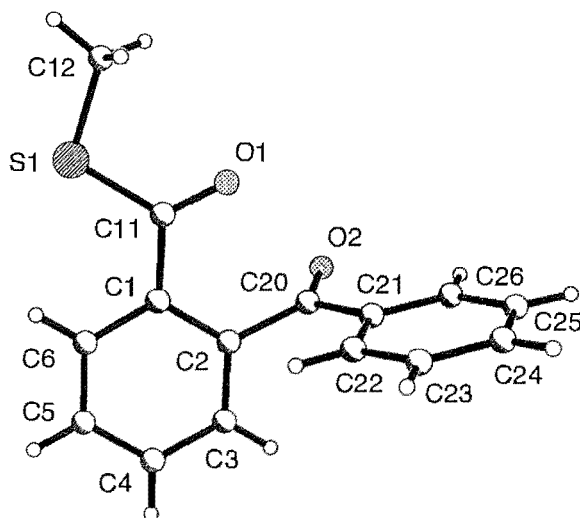**Table A.4.1:** Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($\mathring{A}^2$ x 10^3) for **112**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

Atom	x	y	z	U(eq)
S1	1986(1)	8647(1)	4062(1)	56(1)
O1	1352(2)	6202(2)	5924(1)	47(1)
O2	1665(2)	6401(2)	8629(1)	48(1)
C1	4086(2)	6626(3)	6247(2)	28(1)
C2	4296(2)	5707(2)	7525(2)	27(1)
C3	5916(3)	5270(3)	8184(2)	34(1)
C4	7306(3)	5744(3)	7596(2)	39(1)
C5	7102(3)	6658(3)	6338(2)	42(1)
C6	5508(3)	7090(3)	5673(2)	38(1)
C11	2390(3)	6982(3)	5529(2)	32(1)
C12	-71(3)	8568(4)	3510(2)	67(1)
C20	2811(3)	5227(3)	8253(2)	29(1)
C21	2898(2)	3291(3)	8602(2)	26(1)
C22	4038(3)	2034(3)	8036(2)	33(1)
C23	4070(3)	254(3)	8345(2)	41(1)
C24	2991(3)	-294(3)	9245(2)	45(1)
C25	1872(3)	936(3)	9837(2)	42(1)
C26	1807(3)	2732(3)	9514(2)	31(1)

Table A.4.2: Selected bond lengths (Å) for **112**.

Atoms	Bond length	Atoms	Bond length
S1-C11	1.766(2)	S1-C12	1.790(2)
O1-C11	1.206(2)	O2-C20	1.224(2)
C1-C6	1.393(3)	C1-C2	1.398(2)
C1-C11	1.488(3)	C2-C3	1.387(3)
C2-C20	1.510(3)	C3-C4	1.380(3)
C4-C5	1.378(3)	C5-C6	1.374(3)
C20-C21	1.483(3)	C21-C22	1.386(3)
C21-C26	1.396(3)	C22-C23	1.376(3)
C23-C24	1.378(3)	C24-C25	1.384(3)
C25-C26	1.380(3)		

Table A.4.3: Selected bond angles (°) for **112**

Atoms	Bond angle	Atoms	Bond angle
C11-S1-C12	100.69(11)	C6-C1-C2	119.0(2)
C6-C1-C11	122.0(2)	C2-C1-C11	118.9(2)
C3-C2-C1	119.2(2)	C3-C2-C20	117.5(2)
C1-C2-C20	123.3(2)	C4-C3-C2	120.8(2)
C5-C4-C3	120.2(2)	C6-C5-C4	119.5(2)
C5-C6-C1	121.2(2)	O1-C11-C1	122.4(2)
O1-C11-S1	122.2(2)	C1-C11-S1	115.4(2)
O2-C20-C21	121.8(2)	O2-C20-C2	119.4(2)
C21-C20-C2	118.5(2)	C22-C21-C26	119.6(2)
C22-C21-C20	121.1(2)	C26-C21-C20	119.3(2)
C23-C22-C21	120.5(2)	C22-C23-C24	119.8(2)
C23-C24-C25	120.4(2)	C26-C25-C24	120.1(2)
C25-C26-C21	119.6(2)		

Symmetry transformations used to generate equivalent atoms

Table A.4.4: Anisotropic displacement parameters ($\mathring{A}^2$ x 10^3) for **112**.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^*U_{12}]$$

Atom	U11	U22	U33	U23	U13	U12
S1	35(1)	87(1)	30(1)	2(1)	0(1)	-16(1)
O1	29(1)	57(1)	54(1)	-5(1)	-3(1)	-21(1)
O2	48(1)	37(1)	61(1)	-20(1)	29(1)	-15(1)
C1	25(1)	32(1)	28(1)	-9(1)	2(1)	-11(1)
C2	25(1)	28(1)	29(1)	-11(1)	5(1)	-8(1)
C3	30(1)	38(1)	31(1)	-9(1)	0(1)	-7(1)
C4	25(1)	48(2)	45(1)	-15(1)	-4(1)	-11(1)
C5	27(1)	56(2)	48(1)	-14(1)	10(1)	-22(1)
C6	31(1)	52(2)	30(1)	-7(1)	7(1)	-17(1)
C11	23(1)	40(1)	31(1)	-13(1)	5(1)	-7(1)
C12	39(1)	108(2)	40(1)	-17(1)	-10(1)	-9(2)
C20	28(1)	32(1)	26(1)	-10(1)	4(1)	-8(1)
C21	23(1)	30(1)	25(1)	-7(1)	1(1)	-10(1)
C22	30(1)	36(1)	33(1)	-11(1)	2(1)	-11(1)
C23	40(1)	34(1)	49(1)	-18(1)	-9(1)	-5(1)
C24	52(2)	30(1)	50(1)	-1(1)	-18(1)	-18(1)
C25	43(1)	47(2)	37(1)	1(1)	-4(1)	-26(1)
C26	28(1)	35(1)	29(1)	-6(1)	1(1)	-13(1)

Table A.4.5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($\mathring{A}^2$ x 10^3) for **112**

Atom	x	y	z	U(eq)
H3	6070(3)	4635(3)	9051(2)	41
H4	8406(3)	5440(3)	8060(2)	47
H5	8058(3)	6987(3)	5933(2)	50
H6	5372(3)	7716(3)	4805(2)	45
H12A	-461(3)	9448(4)	2682(2)	101
H12B	-994(3)	8884(4)	4098(2)	101
H12C	116(3)	7330(4)	3447(2)	101
H22	4804(3)	2404(3)	7431(2)	39
H23	4832(3)	-594(3)	7939(2)	49
H24	3015(3)	-1524(3)	9461(2)	54
H25	1147(3)	543(3)	10467(2)	50
H26	1024(3)	3584(3)	9909(2)	37

A.5. The P388 Anti-tumour Assay

This *in vitro* anti-tumour assay uses the P388 cell line (murine leukemia cells) and is up to a hundred times more sensitive to cytotoxic effects than the anti-viral BSC-1 cell line. The P388 assay is therefore a cytotoxic-based assay against a specific leukemia cell type. The IC_{50} result obtained from this assay represents the concentration of the test compound at which the number of viable cells is reduced by 50% relative to the control.

A two-fold dilution series of the sample of interest is incubated with P388 cells and MTT, a yellow tetrazolium salt, in small plastic wells. After seventy-two hours of incubation the concentration of the sample required to reduce the number of viable cells by 50% relative to a control (P388 cells, MTT, media and solvent) is calculated. The mitochondria of *viable* leukemia cells reduce the yellow dye MTT to a purple formazan derivative[1]. By measuring the light absorbance at 540 nm in each well, a direct quantification of formazan formation and therefore the number of viable cells is able to be determined. The absorbance is expressed as a percentage cell viability relative to the control, and is plotted against the logarithm of the sample concentration in the well to generate a sample concentration versus cell viability curve. The antilogarithm of the concentration producing a 50% reduction in the number of viable cells gives the IC_{50} result, which is expressed in the units of ng/mL.

The P388 cell line represents a rapidly dividing cell type, thus its efficacy in finding products with activity in the predominantly occurring slow growing solid tumours of humans such as lung, colon, breast, skin and kidney cancers is strictly limited[2]. However, it is important to consider that a P388-active compound may still display a selective activity against these types of tumours.

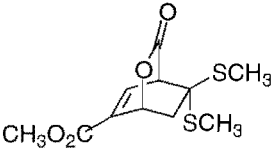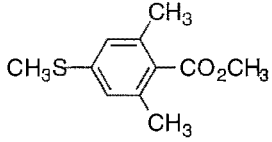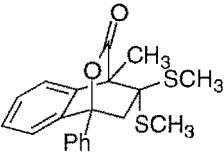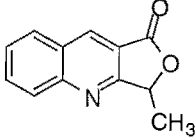**Table A.5.1:** The P388 results of some of the compounds prepared in this thesis
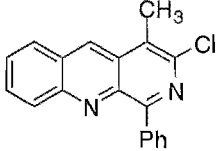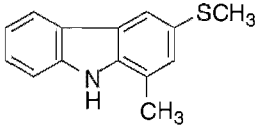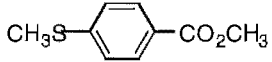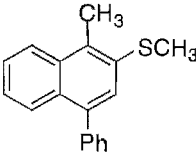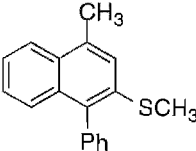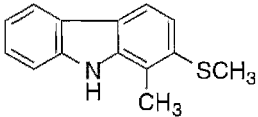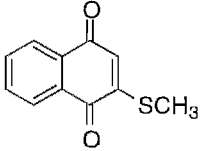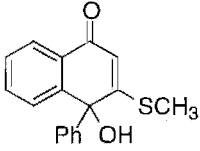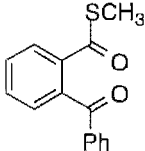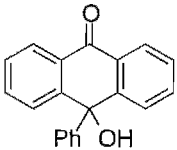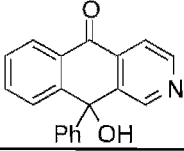
Compound	Code	Initial Solvent Concentration	ID_{50} (ng/mL)
	28	CH_3OH 5.0 mg/mL	823
	31	CH_3OH 5.0 mg/mL	> 62 500
	42	CH_3OH 5.0 mg/mL	> 62 500
	52	CH_3OH 5.0 mg/mL	> 62 500
	53	Dimethylsulfoxide 2.5 mg/mL	3 433
	58	CH_3OH 5.0 mg/mL	11 252
	63	CH_3OH 5.0 mg/mL	> 62 500
	86	CH_3OH 5.0 mg/mL	21 327
	93	CH_3OH/CH_2Cl_2 3:1 5.0 mg/mL	44 106

Table A.5.1: (continued)

SCH$_3$ / CH$_3$ (carbazole)	**98**	CH$_3$OH/CH$_2$Cl$_2$ 3:1 3.0 mg/mL	34 376
SCH$_3$ (naphthoquinone)	**109**	CH$_3$OH 2.5 mg/mL	196
Ph OH / SCH$_3$	**111**	CH$_3$OH 2.5 mg/mL	> 31 250
SCH$_3$ / O / Ph	**112**	CH$_3$OH 5.0 mg/mL	8 918
Ph OH	**115**	CH$_3$OH 5.0 mg/mL	54 058
Ph OH / N	**117a**	CH$_3$OH 5.0 mg/mL	35 986

A.6.   References

1.   Boyd, M.R. *Principles and Practice of Oncology* **1989**, *3*(10), 1-12.

2.   Marston, A.; Décosterd, L.A.; Hostettmann, K. *Cytoinhibitory compounds from higher plants* in: *Bioactive natural products: detection, isolation and structural determination*; Colegate, S.M.; Molyneux, R.J., Eds.; CRC Press Ltd.: Boca Ralton, 1993; p 221-240.