SYNTHESIS OF HETEROCYCLIC COMPOUNDS AS POTENTIAL ANTICANCER AGENTS

A thesis presented in part fulfilment of the requirements for the Degree of Doctor of Philosophy

by

Lesley Ann Stewart

Department of Chemistry
University of Glasgow
Glasgow

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In memory of my Mum and Granny

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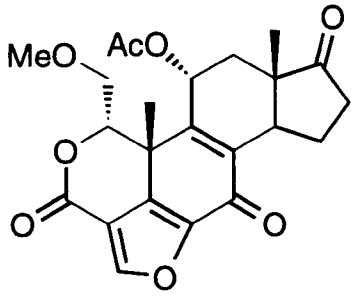
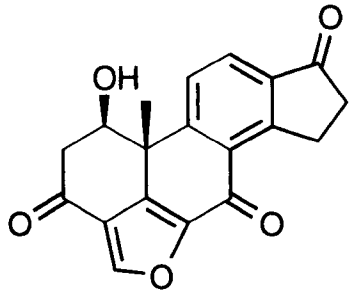
ABSTRACT

Cancer is one of the leading causes of death in the western world today. This work looks at first the development of modern anticancer drugs and their drawbacks. The need for research into new and more efficient drugs is highlighted. Traditional anticancer drugs such as alkylating agents have targeted cell DNA causing cell death. Our approach however was to target a key enzyme, phospholipase D (PLD), in the cell signalling transduction pathway thus inhibiting cell division.

The natural products wortmannin **I** and demethoxyviridin **II** have been shown to inhibit PLD and so provide a basis for the development of novel anticancer drugs. A series of furan and thiophene derivatives modelled on the suspected pharmacophore have therefore been synthesised.

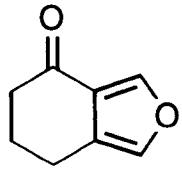


I



II

A number of routes towards the synthesis of fused systems **III** and **IV** with carbonyls in conjugation with a furan ring were investigated.



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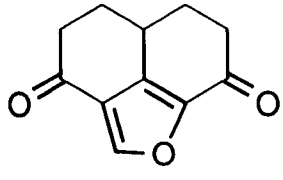
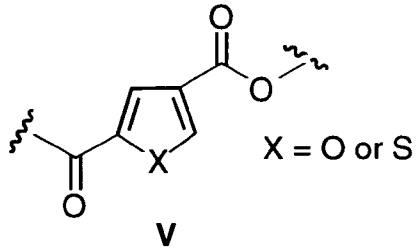


IV

Subsequent to this several 3,5-disubstituted furan and thiophene derivatives **V** were synthesised from 3-furoic acid and thiophene-3-carboxylic acid.



V

Various esters were made and a carbonyl group added at the 5-position using Friedel-Crafts acylation and Vilsmeier-Haack formylation. This basic structure represents the simplest form of the active component of wortmannin **I**. Further elaboration of the formyl group by reaction with vinylmagnesium bromide and oxidation with manganese dioxide introduced α,β-unsaturation analogous to that found in wortmannin **I**. Diels-Alder cyclisation with various dienes then gave a number of compounds with bulky side chains. These novel heterocyclic compounds are now undergoing biological evaluation for inhibition of phospholipase D.

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"The Truth is Out There"

CHAPTER 1

This chapter describes the background of cancer and the development of treatments. Problems associated with current chemotherapy are discussed in detail highlighting the need for new and better anticancer drugs.

1.1 THE CANCER PROBLEM

Cancer is an ancient disease dating as far back as the dinosaurs (paleopathologists have found cancerous lesions on dinosaur bones). Egyptians also drew examples of breast cancer in their hieroglyphics on papyrus, and by the 4th century B.C. many types of tumours such as stomach and uterine cancer had been described.

In 1775 Percivall Pott, a London physician, linked the incidence of scrotal cancer in men to their jobs as chimney sweeps when they were young boys. It was not, however, until the 19th century that scientists began to study cancer systematically, looking at what causes cancer and how it can be cured.[1]

Today, cancer is one of the leading causes of death in the western world. Although commonly associated with ageing it affects people of all ages and all parts of the body.

1.2 CAUSES OF CANCER

Causes of cancer are many and varied. Tobacco and bad diet (including alcohol) are believed to be the two top causes accounting for almost two thirds of all deaths from cancer.[2] Ironically these are the most avoidable. Enviromental carcinogens include industrial pollutants, sunlight and other sources of radiation. Exposure to carcinogens

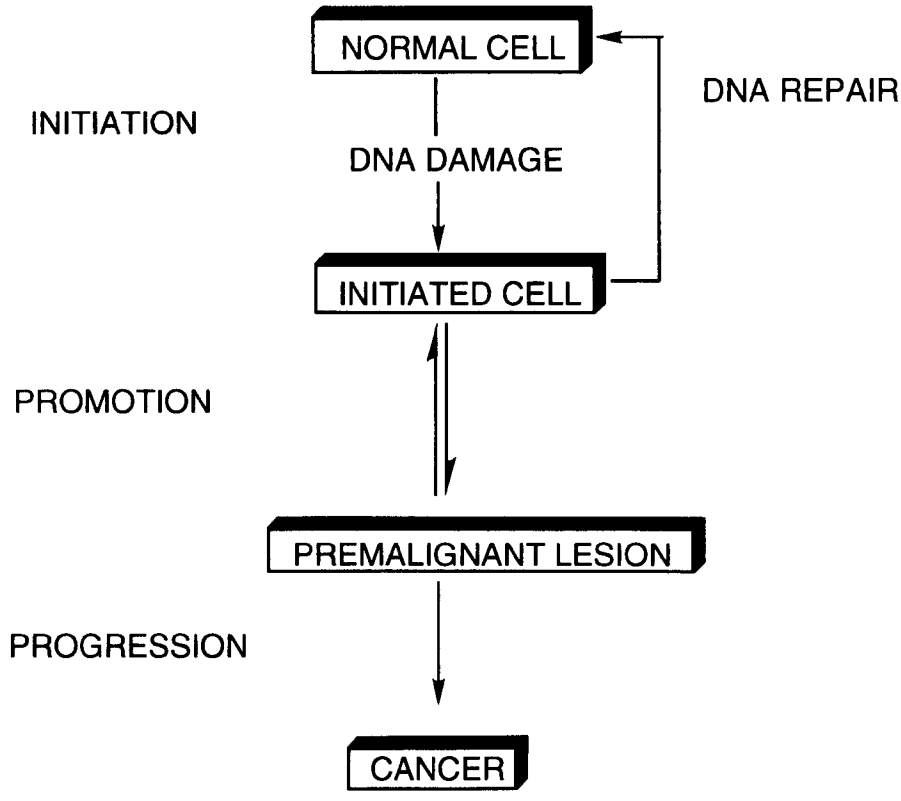
can also vary according to occupation e.g. painters have a high exposure to benzene, a known human carcinogen. Inherited genetic defects may also give a person a predisposition towards developing cancer. This does not mean that an individual will definitely develop cancer but it does mean that the chances of developing cancer are increased. There is, however, considerable research into the identification of faulty genes to allow early detection and thus prevention of cancer.[3]

1.3 DEVELOPMENT OF CANCER IN THE BODY

When a cell mutates it does not form a tumour instantaneously. The cell must go through a variety of other transformations which will result in further changes. This section deals with how a cell can become damaged to initially give a mutated cell and then further how a mutated cell progresses to give a tumour.

The development and invasion of cancer in the body can be broken down into three main areas - initiation, promotion and progression (scheme 1.1)[4,5]

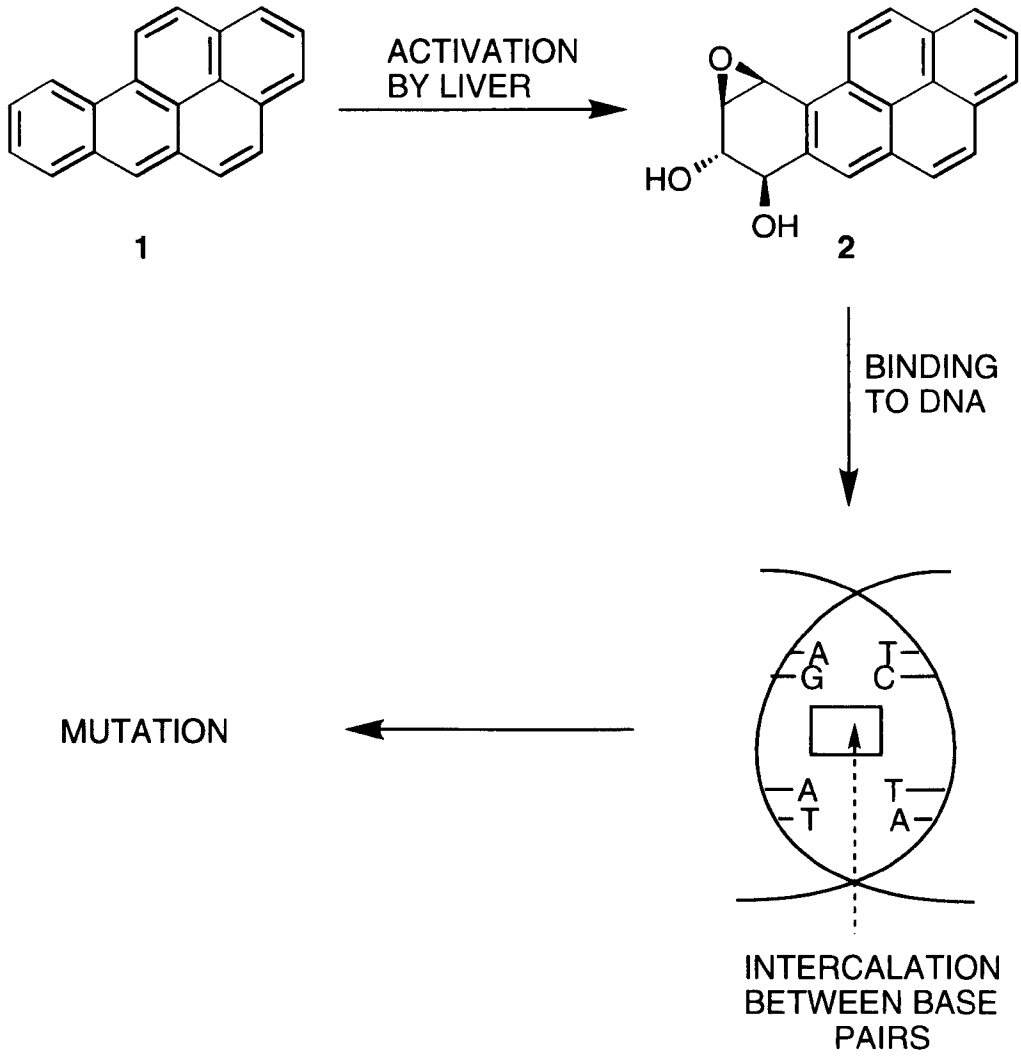
When a carcinogen is introduced into the body a cancerous cell will not immediately result. This is due to the "latency effect" where a period of time elapses before there is growth of the tumour. The initial application of a carcinogen will result in the formation of an irreversible initiated cell. Time may then elapse before a second agent, known as the promoter, will act reversibly on the initiated cell giving a premalignant lesion. Changes in the premalignant lesion, such as increased growth rate, increased invasiveness and metastases, result from the third stage of this process known as progression. These changes are usually associated with a change in the number and arrangement of genes which encode for various proteins.



Scheme 1.1: Development of Cancer in the Body

Several animal experiments have been carried out to demonstrate this sequence of events.[1] The first experiments started over 40 years ago with a single application of a carcinogen to the skin of a mouse. No effect was observed until a second agent was chronically applied to the same site. Even when the application of the secondary agent was one year after the initial application 100% incidence of tumour formation occurred. Animal experiments also demonstrated that promotion was reversible. Removal of the secondary agent before the appearance of neoplastic lesions caused the delay or prevention of the lesions appearing. A human example of this process would be in the development of lung cancer in smokers. Smoking produces benz[a]pyrene **1**, a polycyclic hydrocarbon, which is a chemical carcinogen and an initiating agent. Activation of polycyclic hydrocarbons e.g. **1** by the liver will form the epoxydiol **2** which will bind to the base pairs in DNA by intercalation, leading to mutation.

Prolonged or repeated exposure to this chemical carcinogen or the application of a secondary agent (a promoter) may indeed induce a tumour.



Scheme 1.2: ***Interaction Between Polycyclic Hydrocarbons and DNA***

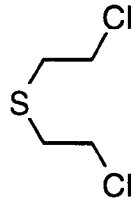
However, by stopping smoking the risk of former smokers developing lung cancer reduces each year after having stopped.

1.4 ANTICANCER DRUG DEVELOPMENT

Cancer treatment involving chemicals dates back over 500 years when preparations involving zinc, silver and mercury were used. However, the first documented case of a drug being used to treat cancer was in 1865 when Lissauer gave potassium arsenite (Fowlers' solution) to a patient with leukaemia and noted a positive effect[6]. It was not however until 80 years later that the first effective anticancer drug was developed by Adair and Bagg.[7] Since then, time, money and manpower have been invested by pharmaceutical companies and universities into the discovery of new and more effective drugs.

1.4.1 ALKYLATING AGENTS

The development of nitrogen mustards as potential anticancer agents dates back to 1917 when sulfur mustard bis(β-chloroethyl)sulfide **3**, was used as a tool in chemical warfare.[8] Although side effects of sulfur mustard were known to be burning in the eyes, skin and respiratory tract, other toxic side effects,[9] such as damage to the bone marrow and lymphoid tissue were not observed until World War I was over.



3

Figure 1.1: Bis(β-chloroethyl)sulfide

In 1931 Adair and Bagg[7] examined the effect of sulfur mustard on humans when injected directly into tumours. Although initially good signs were observed, such as the shrinkage of tumours, the bad side effects previously mentioned prevailed and the drug was considered to be too toxic for further use.

Attention was then turned to the nitrogen analogues of the sulfur mustards. Animal studies during World War II demonstrated that heavy exposure to the nitrogen analogues, bis(β-chloroethyl)amino compounds, destroyed lymphoid tissue. In the late 1930's Gilman and co-workers, knowing the effect that sulfur mustard had on tumours, investigated the effect of nitrogen mustard on mice with lymphosarcoma. A positive effect was observed and in 1942 the first clinical trial involving the administration of a nitrogen mustard to a patient with lymphosarcoma was carried out. Results of this trial were not made public until 1946 when Gilman and Philips published a review[10] on its success. Although highly successful in shrinking tumours of patients with lymphosarcoma and Hodgkin's disease the drugs were found to damage the bone marrow so this damage became a limiting factor in their use.

One of the first nitrogen mustards shown to be effective as an anticancer drug is the bifunctional alkylating agent mechloroethamine **4** also known as mustine. It is still in use today as part of a 4-drug cocktail for Hodgkin's disease.[11]

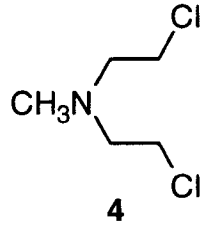


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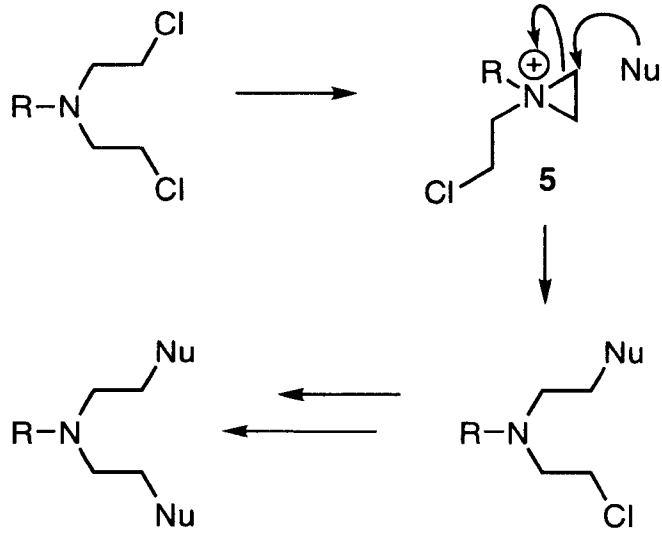
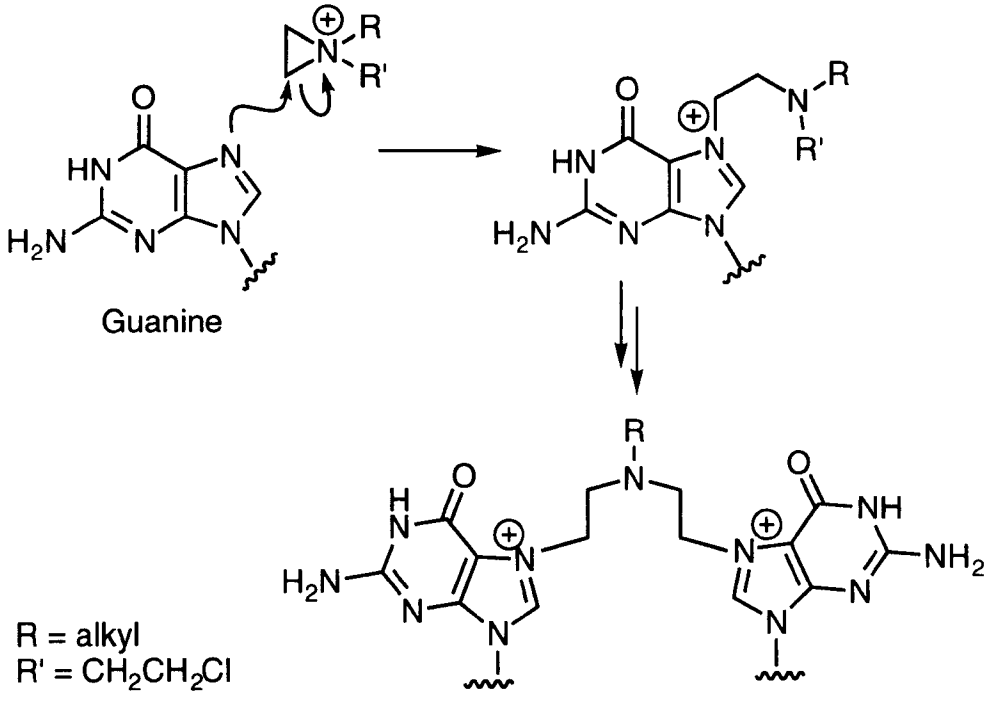
Figure 1.2: Mechloroethamine

Alkylating agents generally function by chemically interfering with DNA replication. First the nitrogen on the alkylating agent attacks the electropositive carbon next to the chlorine to form the highly reactive aziridinium ion **5**. This will now be very susceptible to nucleophilic attack as shown in scheme 1.3.



Scheme1.3: Attack of Nucleophile on Bifunctional Alkylating Agent

In cells nucleophilic attack will usually be from the N^7 of guanine (or in some cases attack occurs from the N^3 of adenine) and a process of de-purination may occur. This means that the guanine base will detach itself from the DNA strand. However, the more usual mode of action of a bifunctional alkylating agent is to cause cross-linking between two separate strands of DNA. This renders the DNA unable to twist apart and separate for replication which results in cell death (see scheme 1.4).



Scheme 1.4:Cross Linking of two DNA Guanine Units

The mode of action of mechloroethamine **4** is as described in scheme 1.3. Mechloroethamine **4** has a major problem, however. It is "too" reactive as it very readily forms the aziridinium ion. It can only be administered intravenously and its high reactivity causes irritation at the site of injection.[11] However, since its introduction there has been considerable work done on the area of alkylating agents and nitrogen mustards. Melphalan **6** and Chlorambucil **7** (see figure 1.3) are nitrogen mustards in wide use today. They are not as reactive as mechloroethamine **4** because of the aromatic ring adjacent to the nitrogen.[12] The aziridinium ion will therefore not form so readily and this reduced activity allows time for wide distribution throughout the body before they exert their effect.

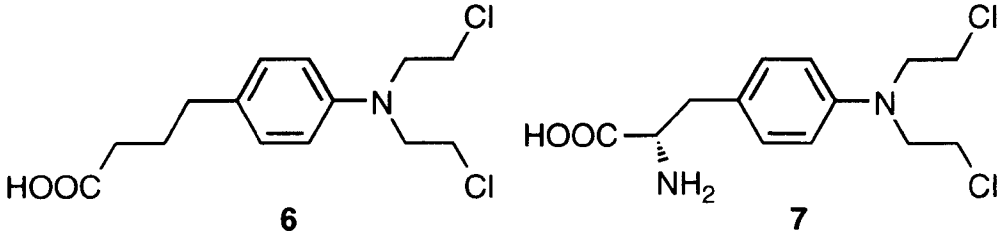


Figure 1.3: Chlorambucil and Melphalan (L-PAM)

One of the most widely used alkylating agents to emerge is the pro-drug cyclophosphamide **8**.[13]

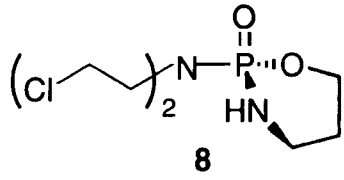
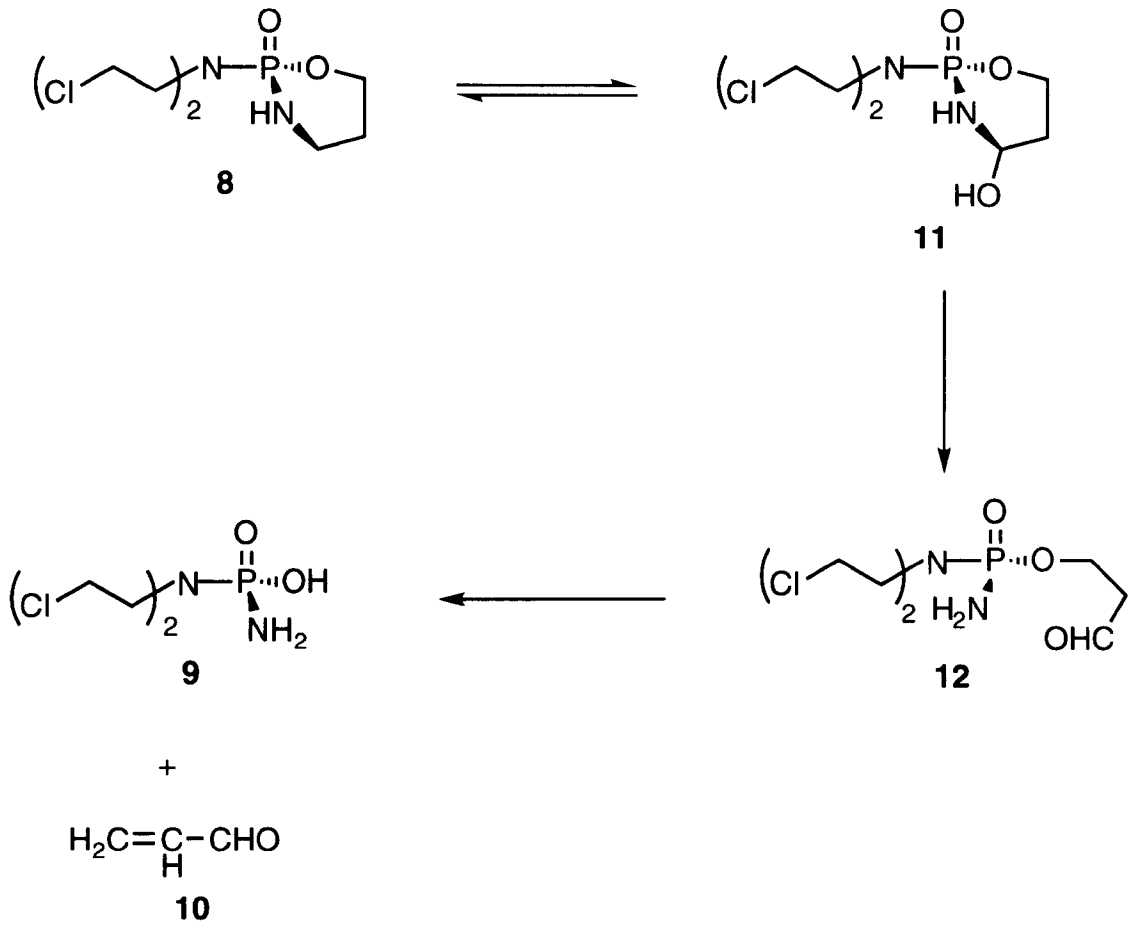


Figure 1.4 Cyclophosphamide

Cyclophosphamide **8** was synthesised with the hope that it would be inactive in the body until the ring structure was broken down by an enzyme more commonly found in cancer cells than in normal cells therefore becoming active only in the cancer cell.

Although not converted in the cancer cells to its active form, cyclophosphamide is converted to its active phosphoramide mustard **9** in the liver as shown in scheme 1.5. In addition to the cytotoxic metabolites **9** and **10** there are a number of non-cytotoxic metabolites which arise from enzymatic oxidation of the non-cytotoxic intermediates 4-hydroxycyclophosphamide **11** and aldophosphamide **12**.



Scheme 1.5: Generation of Phosphoramide Mustard from Cyclophosphamide

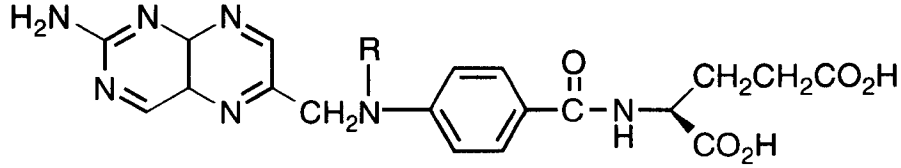
Cyclophosphamide is superior to the other alkylating agents and is used in treatment of lymphosarcoma, Hodgkin's disease, breast, ovarian and lung cancers.

1.4.2 ANTIMETABOLITES

Antimetabolites resemble the structure of natural metabolites necessary for nucleic acid synthesis required for cell division and therefore interfere with the normal utilisation. The antimetabolite blocks the normal enzyme from doing its natural job. The three classes of compounds under the category of antimetabolites are antifolates, antipurines and antipyrimidines.

ANTIFOLATES

Following a report that folic acid concentrate inhibited sarcoma in mice Sidney Farber investigated the effect of folic acid derivatives in leukaemic children. In 1947 he gave 16 children with leukaemia the drug aminopterin **13** and noted that temporary remissions occurred in 10 out of the 16 children[14]. The search for more powerful but less toxic antifolates thus began. In 1949 a breakthrough occurred when an analogue of aminopterin methotrexate **14** was developed by Seegar[15].

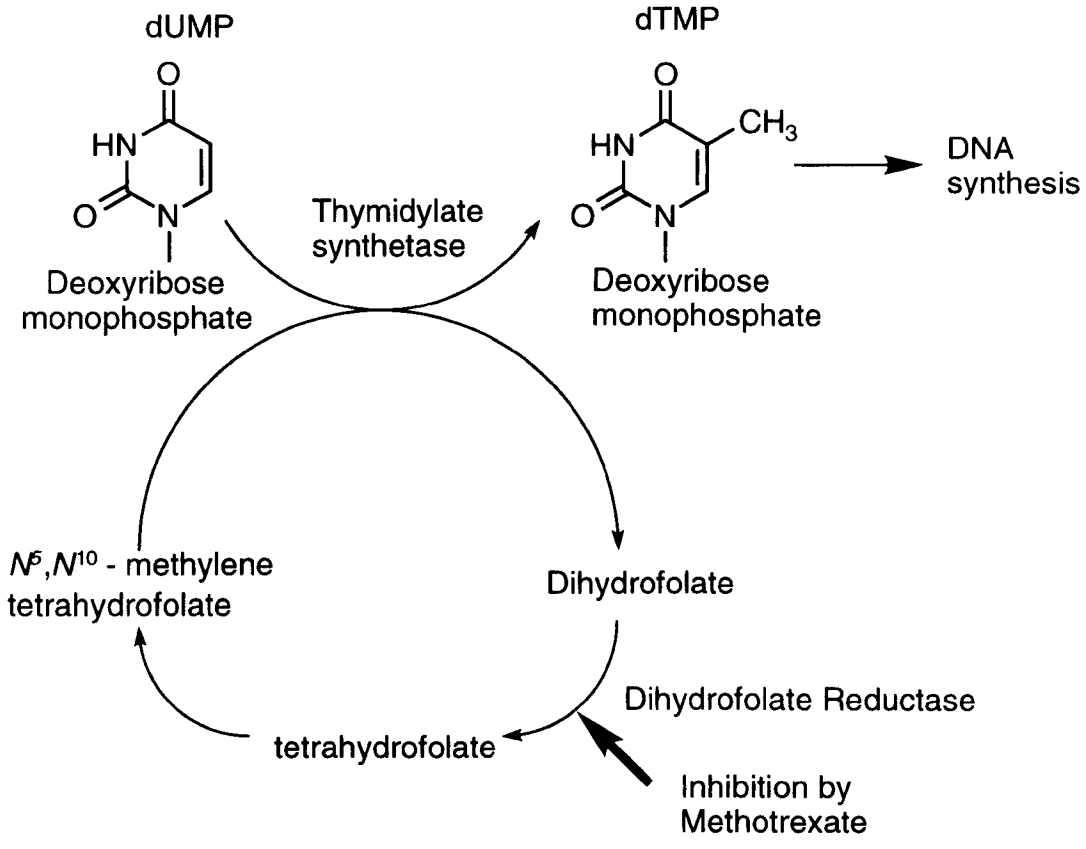


13 R = H
14 R = Me

Figure 1.5: Aminopterin and Methotrexate

Methotrexate **14** is an analogue of the vitamin folic acid. Reduced folate is required for the transfer of methyl groups in the biosynthesis of purines and in the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) which are processes necessary for cell division (see scheme 1.6). The latter of these

reactions is dependent upon reduced folate being available. Methotrexate **14** is a competitive inhibitor of dihydrofolate reductase, an enzyme essential for the generation of the reduced folate. Without the reduced folate dTMP production is inhibited and the cells cannot divide, resulting in cell death.



Scheme 1.6: Inhibition of Cell Division by Methotrexate

Currently methotrexate **14** is one of the best drugs of this class to be developed and is still widely in use for the treatment of cancer of the uteris. After several treatments the tumour is completely destroyed and the patient is restored to full health.

More recently Fernandez and co-workers[16] have developed a number of new methotrexate analogues which have shown strong anticancer activity. The prototype for these compounds is IAHQ **15** which, like methotrexate **14,** has been shown to compete with dihydrofolate reductase and is active against colon cancer.

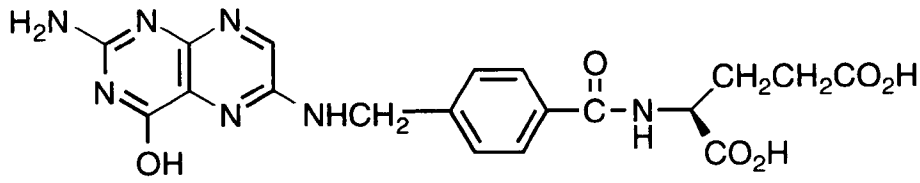


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Figure 1.6: IAHQ

ANTIPYRIMIDINES

Antipyrimidines were developed as potential anticancer compounds by Heidelberger and co-workers[17]. Previously it had been reported that abnormal cells in tumours utilised an abnormally high quantity of uracil which is essential for nucleic acid synthesis and cell division. Heidelberger postulated that if a compound were structurally similar to that of uracil it may then compete with it and a potential anticancer compound may consequently be found. This hypothesis led to the discovery of 5-fluorouracil **16**, a compound differing from uracil only by the fluorine at position 5.

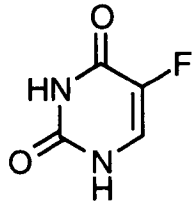

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Figure 1.7 5-Fluorouracil

5-Fluorouracil **16** blocks the formation of thymidine nucleotides from uracil nucleotides by inhibiting the enzyme thymidylate synthetase (see scheme 1.6). Methylation is prevented because of the fluorine at position 5. 5-Fluorouracil **16** was the first effective antipyrimidine to be found and is useful in the treatment of certain forms of breast cancer and gastrointestinal cancer. Since the introduction of 5-fluorouracil **16** other antipyrimidines have been developed for other cancers. For

example, cytosine arabinoside **17** is an antipyrimidine which was first used in patients in the early 1960's and is still one of the main drugs used for antileukemic therapy today[18].

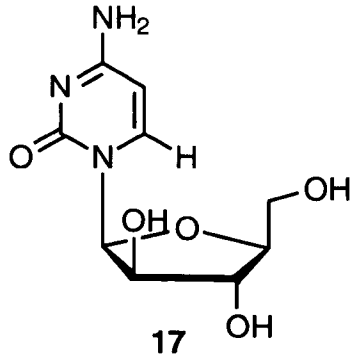

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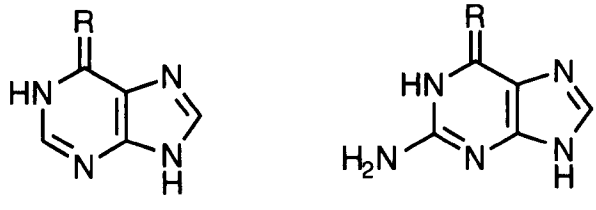
Figure 1.8: Cytosine Arabinoside

ANTIPURINES

The development of antipurines as potential anticancer and antiviral compounds dates back to the early 1940s to the work of George Hitchings and Gertrude Elion at the Wellcome Research Laboratories.[19] In 1944 Hitchings postulated that it might be possible to prevent cell division by the inhibition of nucleic acid synthesis by a purine analogue. Elion was given the task of synthesising hundreds of purine and pyrimidine analogues. By 1951 they had synthesised and tested over one hundred compounds and amongst the most active were 6-mercaptopurine **18** and 6-thioguanine **19** which are the sulfur analogues of hypoxanthine **20** and guanine **21** respectively. Both were shown to be very active against rodent tumours and leukaemia[20].



18 R = S
20 R = O

19 R = S
21 R = O

Figure 1.9: 6-Mercaptopurine and 6-Thioguanine

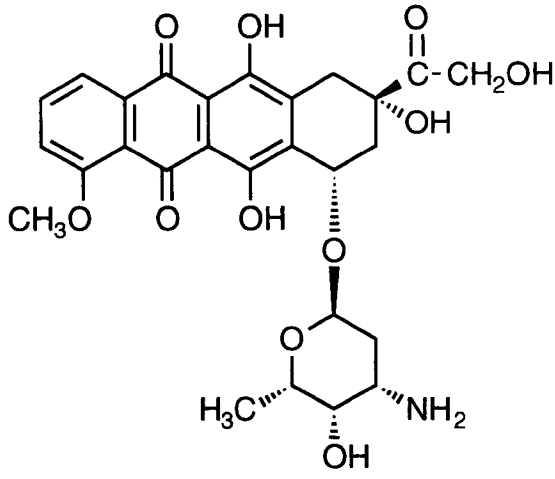
Their mode of action is complicated but believed to be through incorporation of their nucleotide metabolites into DNA. The cytotoxicity of 6-thioguanine **19** probably results from its mistaken incorporation during DNA synthesis resulting in functionally changed polynucleotides *i.e.* altered DNA. In contrast 6-mercaptopurine probably affects a number of enzyme activities.

Clinical trials began involving children with leukaemia and it was observed that 6-mercaptopurine caused the initial remission of cancer. 6-Thioguanine **19** was shown to be more effective against rat tumours but was more toxic. Today, 6-mercaptopurine **18** is used in combination with other drugs to cure almost 80% of children with acute lymphocytic leukaemia and 6-thioguanine is used to treat acute myelocytic leukaemia.

As well as anticancer drugs Hitchings and Elion also discovered several other clinically useful drugs such as allopurinol for treatment of gout, acyclovir for treatment of the herpes virus and azathiopurine, an immunosuppressive drug used in kidney transplants. In 1988 Hitchings and Elion received the Nobel prize for their contributions to the development of effective drugs for the treatment of cancer and other diseases.

1.4.3 NONCOVALENT DNA BINDING DRUGS[21]

The binding of drugs to DNA is complex involving interactions with sugars, phosphates, bases and base stacks. The foremost type of physical interaction is intercalation between the drug and the DNA double helix. Doxorubicin **22**, an anthracycline molecule linked to the sugar daunosamine is an example of such an intercalator.

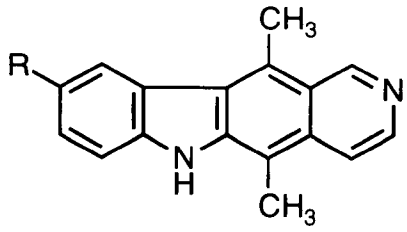


22

Figure 1.10: Doxorubicin

To permit intercalation, the DNA double helix must stretch along the strand length to allow insertion of the drug between, and parallel to, the stacked adjacent base pairs without disturbing the overall stacking of the bases. The result of this is that the backbone of the DNA becomes distorted leading to partial unwinding of the helix. However, much of the DNA is packed in such a way as to be protected from this type of drug. Doxorubicin **22** must therefore operate by other mechanisms to explain its toxicity. The quinone ring may undergo metabolism to produce a semiquinone radical which in turn reacts rapidly with oxygen to give the superoxide O_2^{-}.[22] This superoxide will then undergo several reactions which ultimately lead to cell death. In hypoxic conditions *i.e.* where the cell is starved of oxygen doxorubicin **22** still leads to cell death so the previous two mechanisms cannot be the only ones acting. A mechanism involving the generation of free radicals can be used to explain this, but in reality the exact mode of action of doxorubicin **22** is not fully understood. Doxorubicin has a variety of clinical uses for many types of solid tumours and leukaemia.

Other intercalators include ellipticine **23** which is an alkaloid first isolated in 1959 by Horning and co-workers[23] from the leaves of *Ochrosia elliptica* (Apocynaceae). Ellipticine **23** and its analogue 9-methoxyellipticine **24** have been shown to possess anticancer activity against experimental tumours and leukaemias.



23 R = H
24 R = OMe

Figure 1.11: Ellipticine and 9-Methoxyellipticine

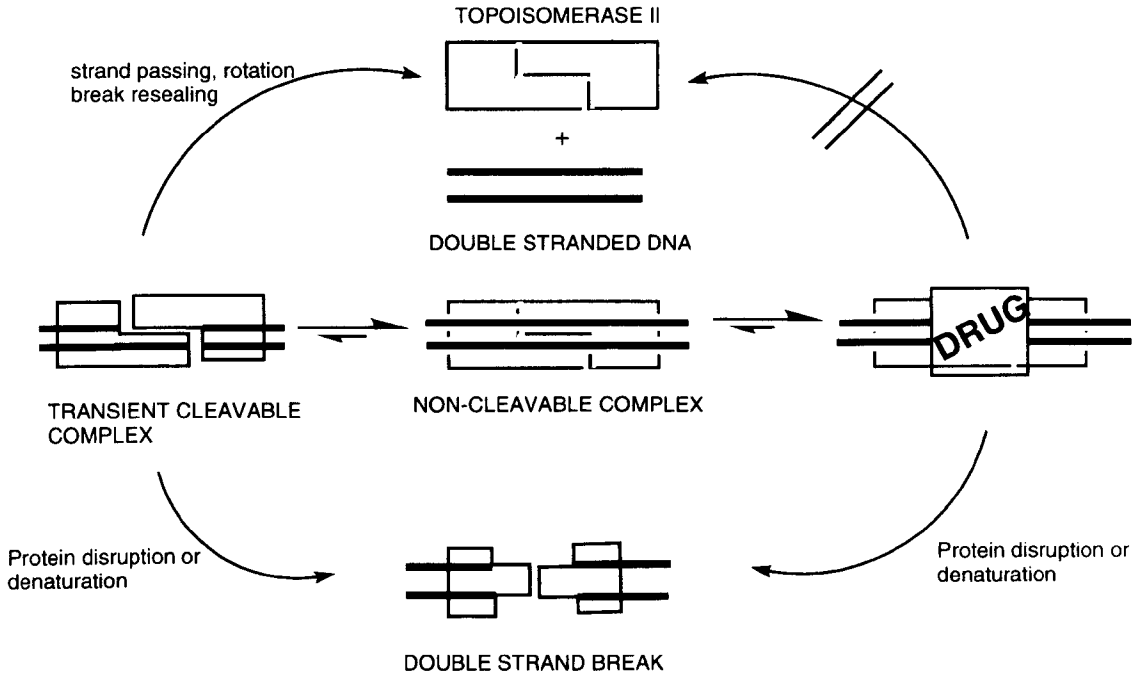
1.2.4 INHIBITION OF CHROMATIN FUNCTION

Chromosomes are packed tightly in the nucleus of the cell and undergo many changes with regard to intracellular positioning and conformation. There are several proteins and enzymes in the cell which will control the way in which the DNA replicates and agents have been developed which interfere with these processes. Two main classes of such compounds are topoisomerase inhibitors and microtubule inhibitors.

TOPOISOMERASE INHIBITORS[24]

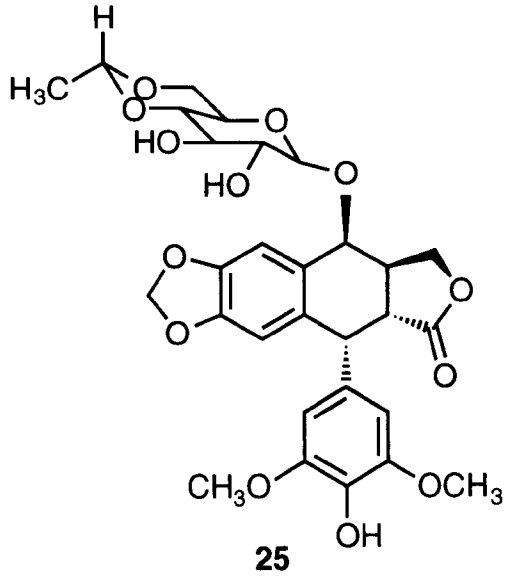
Prior to cell division DNA must unwind and untangle for processes such as replication and transcription to occur. Topoisomerases are enzymes which selectively relax and break parts of the DNA strand so that replication can occur. Topoisomerase II interacts with the DNA strand to form a complex which is termed "non-cleavable" as shown in scheme 1.7. The enzyme then cuts both strands giving a transient cleavable complex. The DNA is then free to undergo the required conformational

change. The break then reseals and the topoisomerase dissociates from the DNA double strand. The cleavable complex is however vulnerable to protein disruption or denaturation as shown which results in permanently cleaved DNA.



Scheme 1.7: Inhibition of Topoisomerase II Enzyme

Drugs such as etoposide **25** stabilise the cleavable complex such that the chances of double strand breakage are much higher. This destruction of the DNA therefore results in cell death.

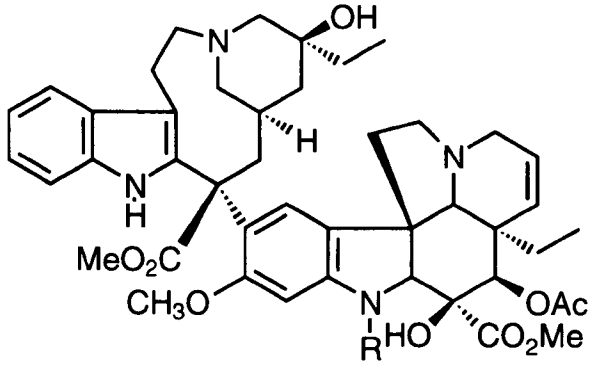


25

Figure 1.12: Etoposide

MICROTUBULE INHIBITORS

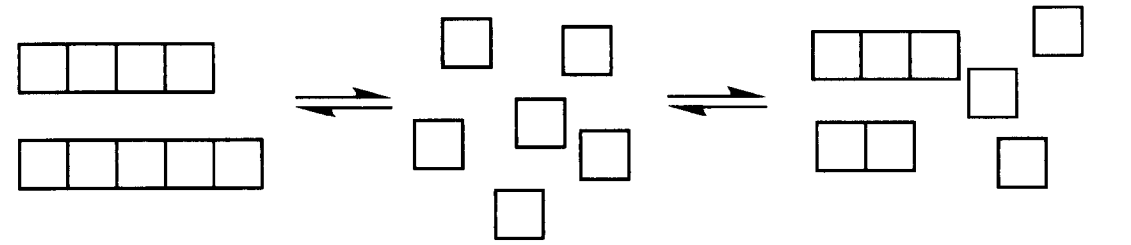
Serendipity played a part in the discovery of the vinca alkaloids, the first microtubule inhibitors to be found. In the late 1950's Noble and fellow workers[25] examined the claim that vinca alkaloids extracted from the periwinkle plant could produce hypoglycaemia. Although the claims could not be substantiated, bone marrow suppression was observed in experimental rats. Later Johnson and co-workers[26] elaborated on this work by demonstrating that certain alkaloid fractions possessed antileukaemic activity. Of the 4 alkaloids tested only two, vincristine **26** and vinblastine **27**, were used to treat cancer in humans.



26 R = CHO
27 R = CH_3

Figure 1.13: Vincristine and Vinblastine

Vincristine **26** and vinblastine **27** are inhibitors of microtubule formation. Microtubules are protein polymers that are responsible for various aspects of cellular morphology and movement such as formation of the mitotic spindle which is necessary for the separation of chromosomes during cell division. Their major component is tubulin and they exist in a state of dynamic equilibrium with continuous formation and degradation from cytoplasmic tubulin. Indeed, they can be thought of as growing and shrinking polymers as shown in scheme 1.8.



Scheme 1.8: Dynamic Equilibrium Between Microtubule Growing and Shrinking Polymers

The tubulin released from a microtubule when it depolymerises would normally attach itself to a growing polymer. The vinca alkaloids vinblastine **27** and vincristine **26** attach themselves to the tubulin rendering them useless for the growing microtubule. The shrinking polymer will then release more tubulin which again will be bound to the vinca alkaloid. Two shrinking polymers are thus formed with the result that there are no effective microtubules in action. Note that although structurally similar vinblastine **27** and vincristine **26** display very different toxicities. Vinblastine **27** is used in combination chemotherapy of testicular cancer whereas vincristine **26** is used for the treatment of childhood leukaemia

Taxol® (paclitaxel) **28** is also a microtubule inhibitor and is one of the most promising drugs for the treatment of breast or colon cancer. It is extracted from the pacific yew but it takes one mature tree to provide enough Taxol® to treat one patient. The tree is a slow growing evergreen and is becoming rare. A synthetic approach to Taxol® from more readily available precursors is therefore desirable. Although total synthesis of Taxol® has been successfully carried out, is not suitable for commercial production due to low yields in multi-step syntheses.[27,28,29]

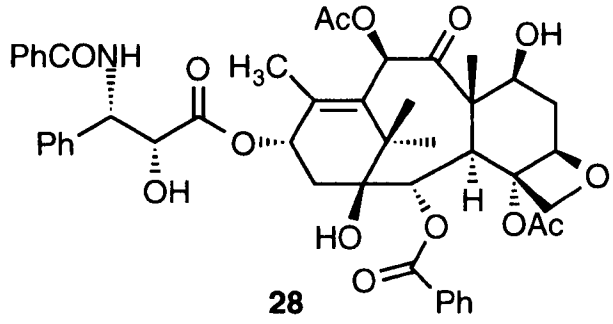


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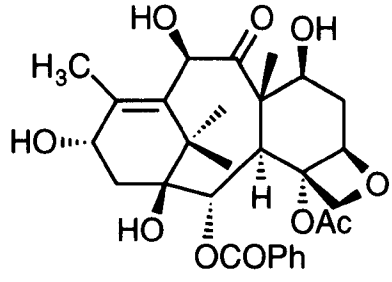
Figure 1.14: Taxol®

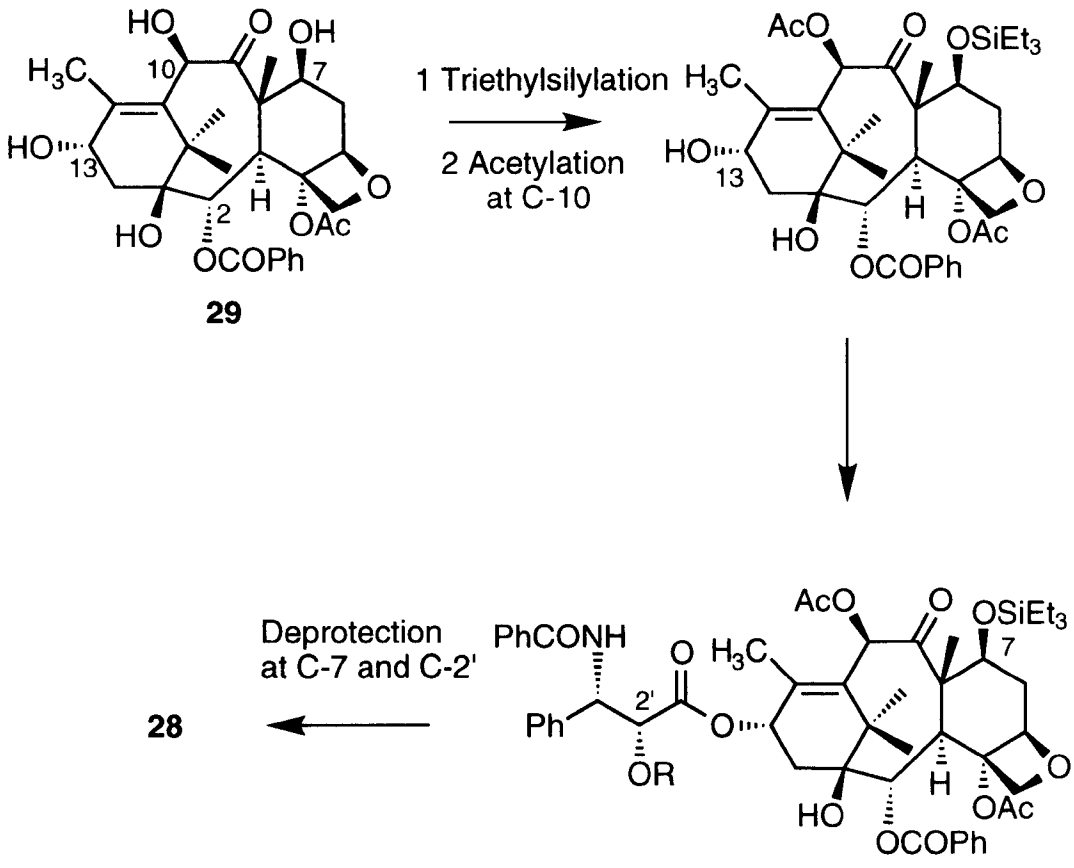
Several companies are however investigating tissue cultures of the Pacific yew bark cells to make Taxol® **28**. Another approach to the problem is to use a tissue-culture approach in plants which synthesise compounds which are structurally similar to Taxol® **28**. Pierre Potier[30] found that 10-deacetylbaccatin III **29**, a compound structurally similar to Taxol® **28** could be isolated from *Taxus baccata* .



29

Figure 1.15: 10-Deacetylbaccatin III

Semi synthesis of Taxol® **28** from this precursor can easily be achieved *via* several simple steps as shown in scheme 1.9. 10-Deacetylbaccatin III **29** is first protected at the carbon-7 position using triethylsilylation and acetylated at the carbon-10 position. Acylation at carbon-13 by *O*-protected *N*-benzoyl phenylisoserine followed by deprotection of both carbon-7 and carbon 2' affords Taxol® **28**.



Scheme 1.19: Synthesis of Taxol® from 10-Deacetylbaccatin III

The mode of action of Taxol® **28** is to promote the assembly of microtubules by causing the stabilisation of the polymers. There will therefore be no free tubulin for other microtubules to form and without the necessary microtubules the cells cannot function properly resulting in cell death.

A compound which has recently been shown to possess the same inhibitory action on cancer cells as Taxol® **28** is discodermolide **30**. Discodermolide **30** was isolated from *Discodermia dissoluta*, a sponge that grows at a depth of around 200 metres in the Caribbean.[31] Pre-clinical tests have shown that discodermolide **30** is at least as potent as Taxol® **28** against breast cancer cells and eighty times as potent against leukaemia cells. Since its discovery almost a decade ago there have been several

research groups looking at its synthesis and to date there are at least three methods underway for total synthesis.[32,33,34]

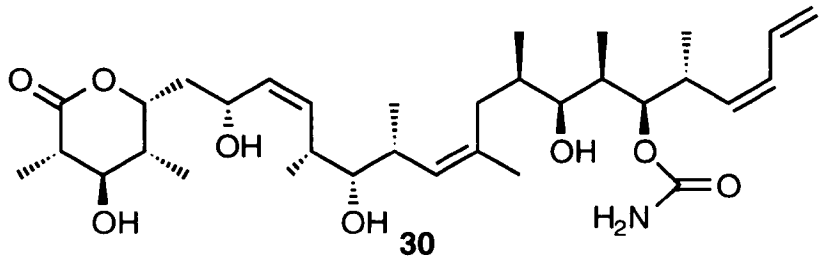


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Figure 1.16: Discodermolide

1.5 PRESENT DAY CANCER THERAPY

Surgery and radiotherapy can be used to eradicate small primary tumours but the main problem with these treatments are that they are "local". This means that they are only useful for the treatment of a tumour in one specific site and are therefore of no use as a single therapy when the cancer has spread to sites distant from its origin. Chemotherapy is a more wide reaching therapy and is therefore an acceptable alternative for secondary tumours.

Clinical results have shown that when single drugs are administered to tumours they do not give an optimum cure because of the resistance some tumours display to certain drugs. Therefore if there is more than one drug present within the system then there is a chance that the tumour will not show resistance to the second drug. Combination chemotherapy involving the administration of several drugs at the same time or the combination of chemotherapy with surgery and/or radiotherapy often provides the best treatment. A summary of these treatments is given below.

1.5.1 COMBINATION CHEMOTHERAPY[35]

Combination chemotherapy involves the utilisation of several anticancer drugs in the same treatment. In selecting drugs for use in this therapy there are several restrictions which must be considered. Only drugs which have been shown to display excellent anticancer activity and whose toxic effects either do not overlap or produce their side effects at different times during or after treatment can be used. The drugs must also have different modes of action and/or do not display cross-resistance. By using combination chemotherapy patients with leukaemia will be free from the disease 5 years after treatment and many will go on to be completely cured.[36]

1.5.2 MULTIDISCIPLINARY CHEMOTHERAPY

Adjuvant chemotherapy involves the application of chemotherapy to tumours which have previously been reduced in size or eradicated either by surgery, radiotherapy or by a combination of both. An application of this therapy is to women who have stage II breast cancer[37] and whose primary tumour has successfully been eradicated. Without the treatment these women have a 40% chance of dying due to residual cancer cells still present. Adjuvant chemotherapy reduces this chance to 20%. However the main drawback is that women who would normally be cured by the surgery and/or radiotherapy alone risk the toxicities associated with the chemotherapy. Before this therapy is used the risk: benefit considerations must be evaluated.

As well as applying chemotherapy after surgery there are advantages to applying it before surgery.[38] This method is commonly used for treating osteogenic sarcoma (a bone cancer found in young women).[39,40] Amputation achieves only a 20% cure rate because in addition to the bone cancer there are small pockets of cancer cells in the lungs that are too small to be detected when the amputation is carried out. However if

chemotherapy is given before and after surgery the small pockets of cancer cells in the lungs will be destroyed and the chances of survival will be vastly improved, completely curing 70 - 80%.

1.6 PROBLEMS WITH PRESENT DAY CHEMOTHERAPY

One of the main limiting factors with chemotherapy is that it is best used to treat small tumours. Anticancer drugs can only penetrate and kill so much of a tumour in one dose. Therefore in a large tumour only 99% of cancer cells may be eradicated whereas in a small tumour all the cancer cells will be eradicated. The remaining cancer cells in the large tumour although present in small quantities will quickly multiply and replicate again producing a large tumour.[41]

Anticancer drugs also kill healthy dividing cells particularly those with a high rate of proliferation such as hair follicles, gastrointestinal tract, bone marrow and lymphocytes involved in the immune defence mechanism. It is their destruction which causes the side effects commonly associated with chemotherapy such as hair loss, nausea/vomiting and an increase in susceptibility to infection. This can cause distress and embarrassment for the patient. In addition to the anticancer drugs, other medication is often given to the patient for pain relief. However, this too can be problamatic as the additional medication can interfere with the normal functioning of the anticancer drug. For example if aspirin is given for pain relief it will inhibit the normal excretion of methotrexate.[42]

1.6.1 THE THERAPEUTIC INDEX AND TUMOUR RESPONSE

Current anticancer drugs are said to have a low therapeutic index (TI).

$$TI = \frac{\text{Dose producing toxicity in 50\% of the population}}{\text{Dose producing effectiveness in 50\% of the population}}$$

This means that the doses which effect a good response in comparison to those which give bad responses are only separated by a fine line - this is clearly seen in figure 1.17.[43] It is not always possible, therefore, to increase the response by simply increasing the dosage. To overcome this, combination chemotherapy can be employed. Although this will bring about a reduction in tumour size it may also bring about an increase in side effects for the patient mainly because the effect the drugs have on one another is unknown.

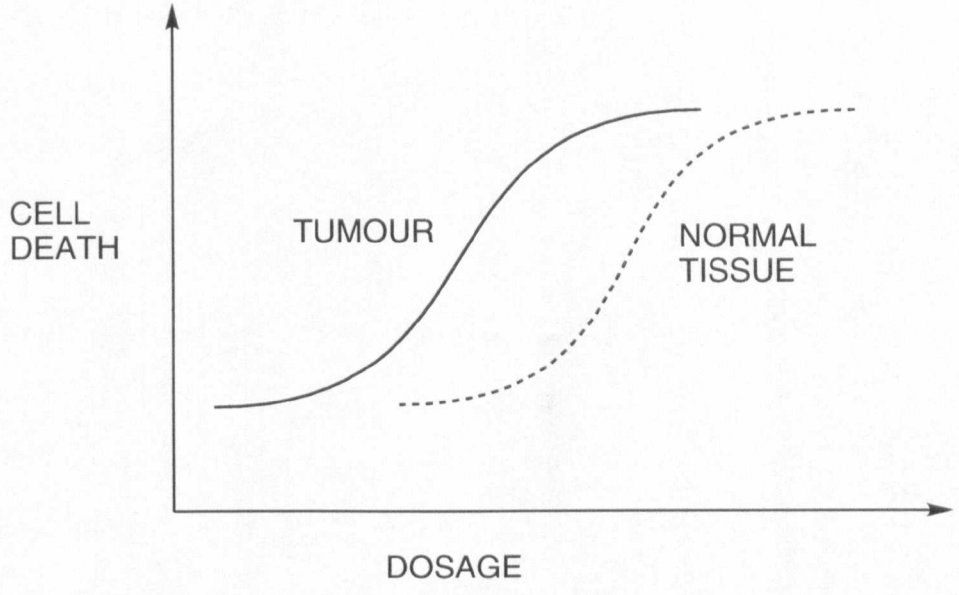


Figure 1.17: Effect of Drug Dosage on Cell Death

1.6.2 TUMOUR RESISTANCE[44]

A major problem encountered when treating tumours is that they may show resistance. This resistance can be divided into two types - intrinsic or acquired.

A tumour is instrinsically resistant if it does not initially respond to the the anticancer drug. This could be due to the poor uptake of the drug by the cell or an inability of the patient to convert the drug into its active form. The overall effect is that the tumour does not receive the drug.

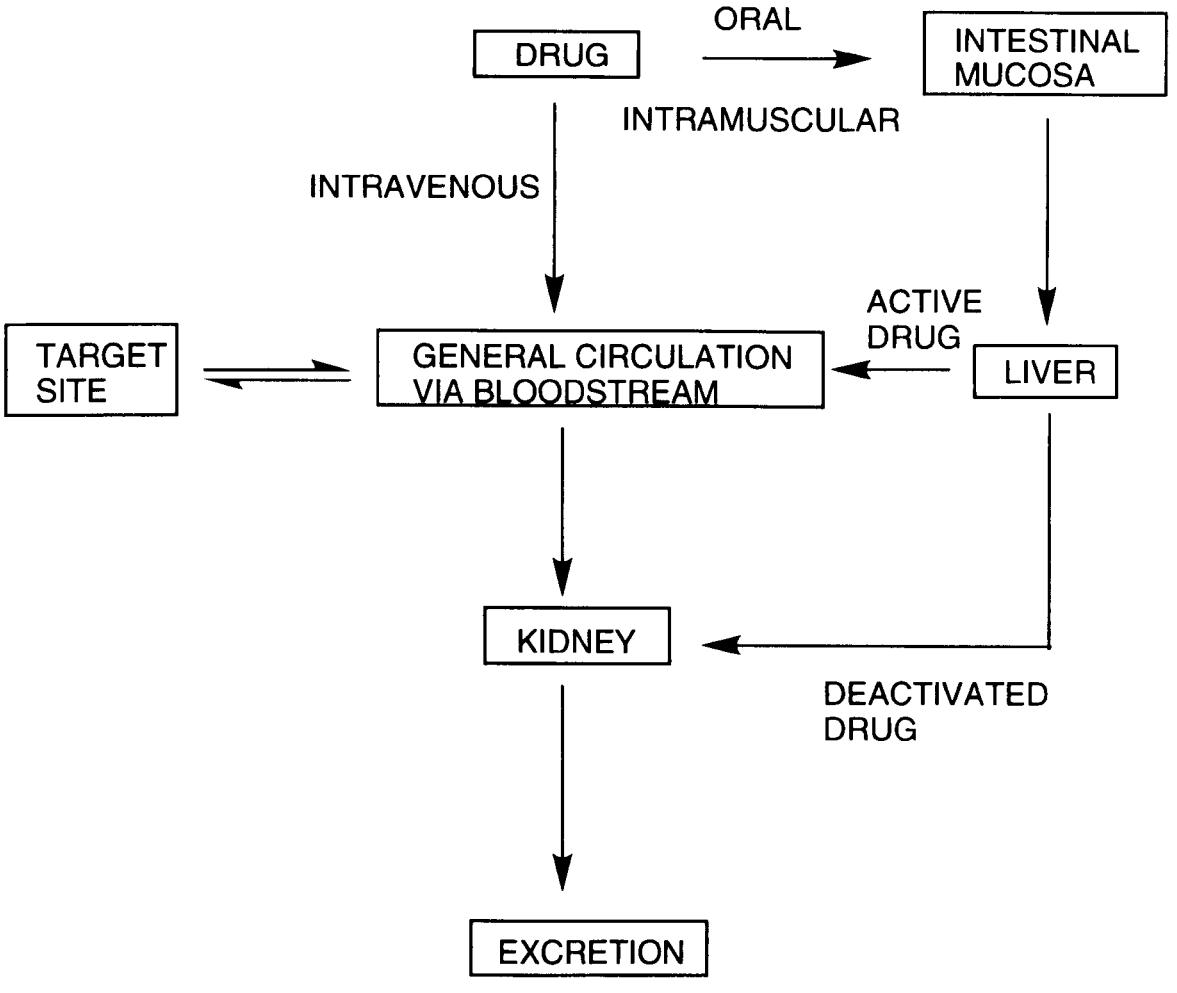
Acquired resistance results when there are many different types of cells arising from mutations within a tumour. Present within a single tumour can be those cells which do respond to treatment and those which simply do not respond. This means that a tumour which has initially shown a good response may seem to develop resistance as the proportion of non-resistant cells decreases.

It is however not fully understood why some cells display good responses to drugs whilst others are non-responsive.

1.6.3 ABSORPTION, DISTRIBUTION AND EXCRETION[45]

The proportion of drug available for potential therapeutic effect is dependent on the amount absorbed and delivered into circulation. This is usually called the bioavailability of a drug and is dependent upon several factors. Physical administration of the drug is important. If the drug is administered intravenously then it is assumed that the drug has been absorbed completely. On the other hand if the drug is administered by some other means such as oral or intramuscular then it may be assumed that only partial absorption has taken place. This is because the drug has

several "barriers" to penetrate before general circulation. The drug must first dissolve and pass through the gastrointestinal mucosa in order to reach the intestinal capillaries. From there the drug must be transported through the liver to allow metabolism followed by general circulation. Bioavailability will decrease in each of these steps and metabolism will often render many drugs inactive. The pathway of an anticancer drug is shown in scheme 1.10.



Scheme 1.10: Pathway of Anticancer Drug

Excretion of the drugs also poses a problem. Many have to be excreted *via* the kidney in the urine. The problem is that many drugs such as methotrexate and *cis*-platin are potentially toxic to the kidney. It may therefore be necessary to stimulate drug excretion by maintaining an alkaline pH for methotrexate or by producing a rapid

urinary flow of cis-platin. This type of excretion unfortunately cannot be tolerated in patients who have problems with their renal function.

Existing anticancer drugs are therefore not effective enough and new targets and new drugs must still be found.

1.7 RECENT DEVELOPMENTS IN THE SEARCH FOR NEW ANTICANCER THERAPIES

The anticancer drugs previously described are concerned with inhibition of cell replication by interfering with the DNA. There are however a number of new approaches which look at tackling the problem of cancer from a different angle. This section deals with a few of these approaches.

1.7.1 ANGIOGENESIS INHIBITORS[46,47]

Like any other growing tissue in the body, tumours require nourishment in the form of nutrients and oxygen, as well as efficient elimination of waste material such as carbon dioxide and lactic acid to survive. Tumours have therefore developed the ability to release specific growth factors called angiogenic factors which induce blood vessel formation. The formation and proliferation of these blood vessels is called "angiogenesis". This, process however is not limited to tumours as angiogenesis occurs naturally in the body when a wound heals.

Having recognised that tumour growth is angiogenesis-dependent, a new potential cancer therapy has been proposed on the basis that if proliferation of blood vessels could be halted then the cancer cells would die. A new class of compounds called "angiostatic steroids" is emerging with tetrahydrocortisol as one of the most

promising drugs in this area. Tetrahydrocortisol **31** is the breakdown product of cortisone, a hormone responsible for regulating blood pressure and blood sugar particularly when the body has experienced stress or an injury and has been shown to inhibit capillary growth. When administered in combination with heparin, normally used to prevent clotting, the inhibition is increased.

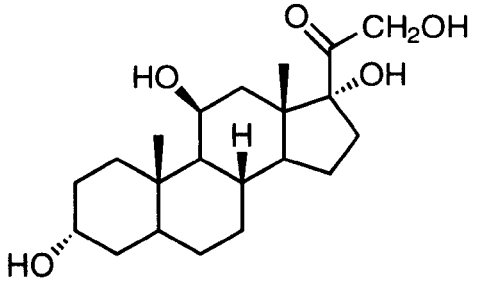


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Figure 1.18: Tetrahydrocortisol

Angiostatic steroids have not yet been approved to treat cancer and along with many other types of angiogenesis inhibitors are now being investigated for use.[48,49]

1.7.2 GENE THERAPY

Gene therapy is the replacement of genes such as tumour suppressor genes which have become inactivated during malignant tumour development. The simplest strategy to insert the gene is to infect the cancer cell with a virus carrying a normal copy of the gene. It would be hoped that normal cells already carrying 2 copies of the gene would tolerate additonal copies. Once the gene has been inserted the cancer cells should revert back to their normal pattern of growth.

Although it is virtually impossible to deliver the missing gene to all the tumour cells this does not pose a problem. Studies have shown that by replacing one tumour suppressor gene in cells which have multiple genetic defects the tumour can be

reversed and a normal growth pattern resumes. Gene therapy would be most suited to those cancers which are genetically inherited and to those which are caused by genetic defects. One gene which is being studied extensively for replacement gene therapy is the p53 gene. This encodes the protein p53 which is involved in the control of DNA replication in mutated cells. It is not expressed in normal undamaged cells but more than half of human tumours have been found to react with antibody to p53. After mutation of the DNA p53 is activated halting DNA synthesis until the damaged DNA has been repaired. However, if p53 is unable to switch off the replication, which happens in mutated cells, then the cell will replicate in the uncontrolled and undifferentiated manner associated with cancer cells. Recently there have been successful trials in the US by Roth and co-workers at the M. D Anderson Cancer Centre in Houston, Texas[50]. They managed to replace defective p53 genes with normal copies in lung cancer patients using gene therapy and succeeded in either shrinking tumours or halting their growth. However, all the patients subsequently died from other tumours which had resulted from metastasis. This illustrates the problem mentioned earlier of getting the normal copy of the p53 gene either into all the lesions or into the primary tumour before it has had a chance to spread.

1.7.3 BORON-NEUTRON CAPTURE THERAPY[51]

An alternative treatment for cancer, although not yet in use, is Boron Neutron Capture Therapy (BNCT) involving the capture of a slow moving neutron by a ^{10}B nucleus. The main application of this treatment would be where tumours are inaccessible by other methods.

$$^{10}B + {}^{1}n \longrightarrow {}^{11}B \longrightarrow {}^{4}He^{2+} + {}^{7}Li^{2+} + 2.4MeV + gamma$$

The ^{11}B which is consequently formed undergoes nuclear fission to produce the cytotoxins $^{4}He^{2+}$ and $^{7}Li^{2+}$ accompanied by 2.4 MeV of kinetic energy and weak gamma radiation. These are short lived species which can travel only a small distance to the surrounding cells. Thus, if the ^{10}B can be selectively placed in cancer cells then the toxins produced will kill only the malignant cells whilst leaving the healthy cells intact. This sequence of events is summarised in scheme 1.11.

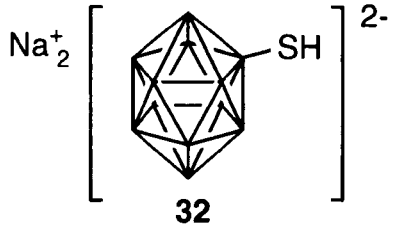
^{1}n + CELL ⟶ NO REACTION

^{10}B + CELL ⟶ ^{10}B • CELL (INTERACTION SPECIFIC TO CANCER CELL)

^{10}B • CELL + ^{1}n ⟶ ($^{4}He^{2+}$ + $^{7}Li^{2+}$) CELL (CELL DEATH)

Scheme 1.11 Cell Death Resulting from BNCT

The ^{10}B is administered in the form of an enriched ^{10}B compound although an efficient mechanism of drug delivery has yet to be developed. Once administered a beam of slow moving neutrons is then applied to the tumour resulting in cell death. Currently $B_{12}H_{11}SH^{2-}$ (BSH) **32** (injected intraveneously in the form of its sodium salt) and 4-(dihydroxyboryl)phenylalanine (BPA) **33** are undergoing clinical trials against primary melanoma lesions and brain tumours.



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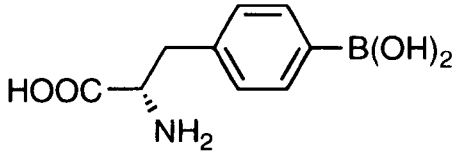

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Figure 1.19: BSH and BPA

1.8 THE INTRACELLULAR SIGNAL TRANSDUCTION PATHWAY

In order to investigate new anticancer drugs one must first look at how the cell divides and what triggers a cancer cell to divide in an uncontrollable and undifferentiated fashion.

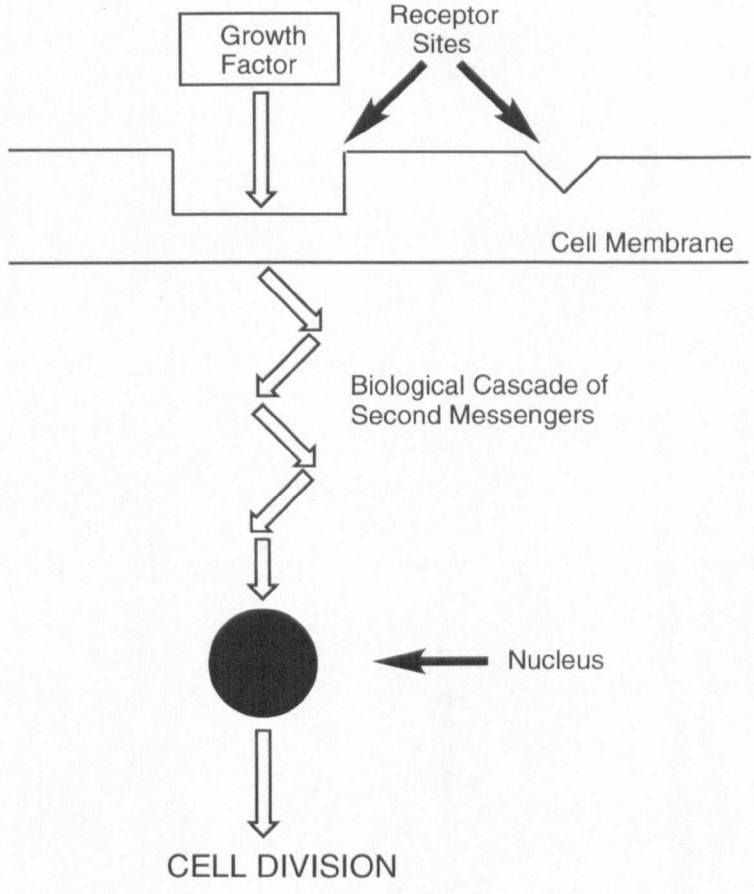
In healthy cells proto-oncogenes are genes which normally encode proteins that are components of signalling pathways. The products of these genes fall into 5 main categories as shown:[52]

1 Growth Factors:	secreted by cells and stimulate cell growth eg platelet-derived growth factor (PDGF).
2 Cell-Surface Receptors:	receives and encodes growth factor.
3 Tyrosine Kinase:	responsible for intracellular signalling and regulates protein function.
4 GTP-binding proteins:	involved in activation of several hormone and growth factor mediated signalling pathways.
5 DNA-binding proteins:	involved in regulation of gene expression in the nucleus and in transcription.

The over expression of a proto-oncogene to give an oncogene can lead to the overactivation of the signalling pathway and the cell will receive a signal for unrestrained growth. If a drug could be found which would inhibit only the signal

transduction pathway activated by an oncogene whilst leaving the other pathways untouched then a route to reversing cancer will have been dicovered.

Cell division begins when a growth factor, a proto-oncogene as previously described, binds to its specific cell receptor site on the cell membrane activating a cascade of intracellular signalling reactions. These cascades involve small effector molecules called second messengers and the overall result of this process is that the cell will receive a signal to divide.



Scheme 1.12 Pathway leading to Cell Division

However in cancerous cells the process of cell division is over-exaggerated. This can be due to several factors. Over production of the growth factor or mutation of the cell receptor site in such a way that it accepts any growth factor are specific examples of abnormal expression of proto-oncogenes. In both cases the signalling pathway will

be over expressed and the cell will receive a signal to divide uncontrollably. Possible targets for anticancer drugs can therefore be to prevent the overproduction of the growth factor, blockage of the cell surface receptor site, blockage of components in the signalling pathway or by direct inhibition of DNA replication in the nucleus.

As well as the over-expression of the oncogenes the inactivation of tumour suppressor genes can also play a part in tumour growth. This was explained in more detail in section 1.7.2 which dealt with gene therapy.

The area of anticancer drug therapy in which this project deals with is the inhibition of the intracellular signal transduction pathway.

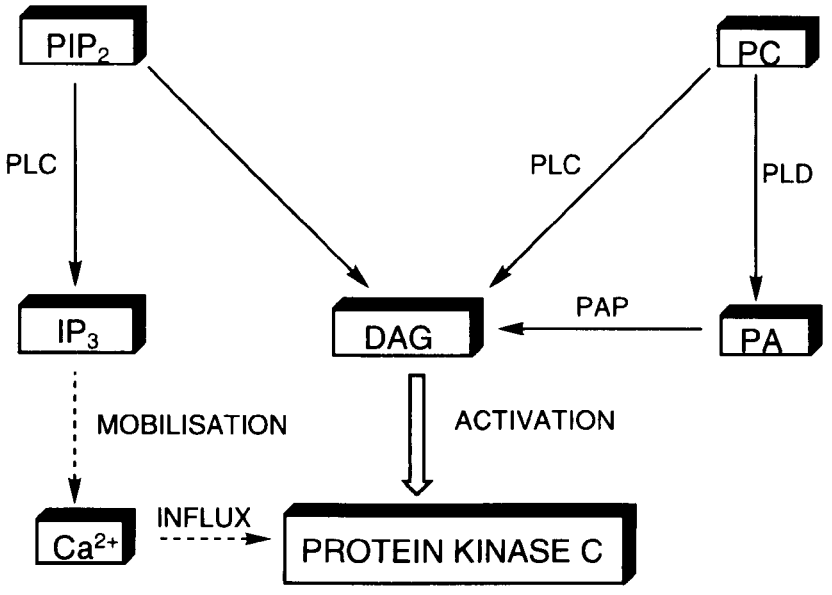
1.8.1 SIGNALLING PATHWAYS - WHICH ONE TO INHIBIT?

In cells there are many different signalling pathways involving secondary messengers which initiate the various processes such as hair growth, cell division and other regulatory functions which occur within the cell.[53] In cancerous cells it has been observed that levels of one of the intracellular second messengers diacylglycerol have been phenominally high.[54] Presumably this is due to the over activation of the signalling pathway leading to the formation of the diacylglycerol. Diacylglycerol has been implicated in several cellular processes including regulation of cell growth, differentiation and regulation of gene expression. In particular it activates protein kinase C which initiates cell division.[55] The role of diacylglycerol is therefore essential. Without it cells cannot divide, whilst too much will cause over activation of protein kinase C which results in overproliferation. In light of this evidence many research groups have chosen to inhibit protein kinase C as a target for a potential anticancer compound. This project deals with the inhibition of phospholipase D, a key enzyme in the production of diacylglycerol. If the levels of diacylglycerol can be

controlled, so too can protein kinase C activity and ultimately so too can cell division. It is also hoped that inhibition of this signalling pathway would be selective enough to leave all the other necessary pathways required for normal cell growth and function intact.

1.8.2 SOURCES OF DIACYLGLYCEROL[56]

There are several routes to the production of diacyglycerol as shown in scheme 1.13. Initially it was thought that one of the main sources of diacylglycerol was by the phospholipase C catalysed breakdown of phosphatidyl inositol-4,5-bisphospate (PIP_2) to give inositol-1,4,5-trisphospate (IP_3) and diacylglycerol. IP_3 is believed to mobilise intracellular Ca^{2+} from the endoplasmic reticulum while diacylglycerol increases the affinity that protein kinase C has for Ca^{2+}. The result is an overall increase in the activity of protein kinase C and the cell divides.

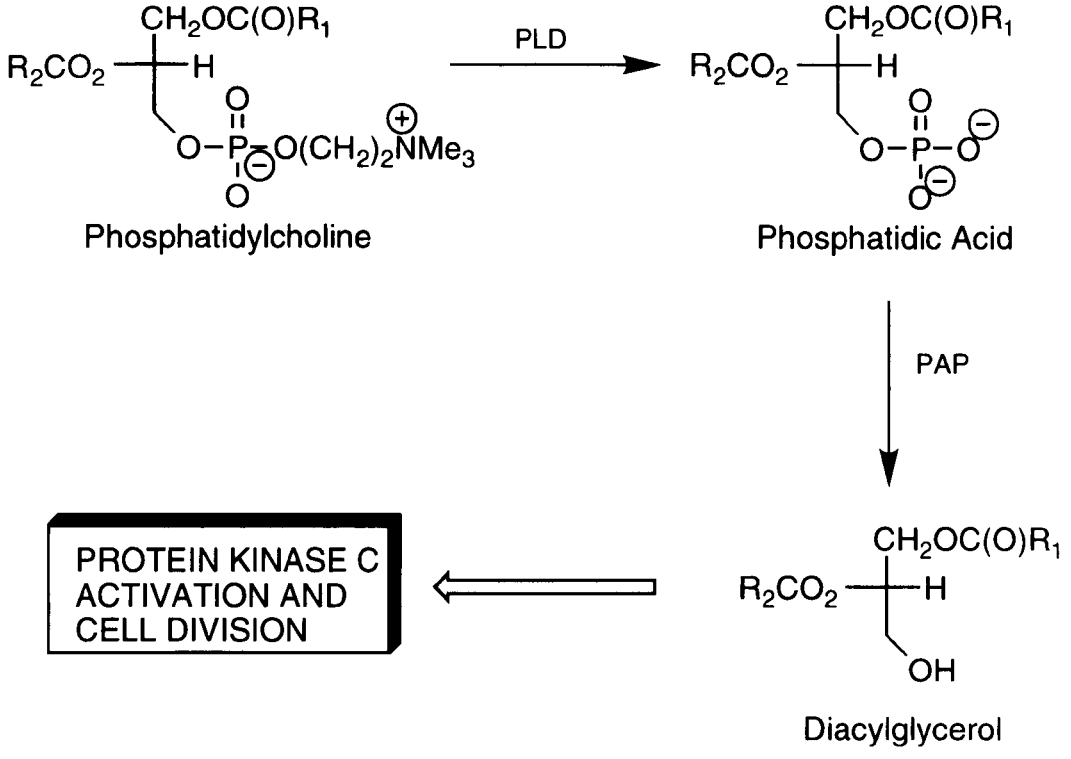


DAG - Diacylglycerol
PIP_2 - Phospatidylinositol-4,5-bisphosphate
IP_3 - Inositol-1,4,5-trisphosphate
PC - Phosphatidylcholine
PA - Phosphatidic acid
PLD - Phospholipase D
PLC - Phospholipase C
PAP - Phosphatidic acid phosphohydrolase

Scheme 1.13: Pathways Leading to Production of Diacylglycerol and Protein Kinase C Activation

The general belief now, however, is that the main source of diacylglycerol comes from the breakdown of phosphatidyl choline found in the cell membrane. This breakdown can occur via two different pathways as can be seen from scheme 1.13.

Phospholipase C catalysed breakdown involves a direct pathway to give diacylglycerol and choline. The phospholipase D catalysed breakdown goes *via* an indirect pathway giving first phosphatidic acid which is broken down into diacylglycerol by phosphatidic acid phosphohydrolase. This route is shown in more detail in scheme 1.14.



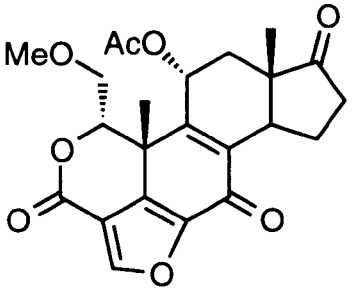
Scheme 1.14 Direct Production of Diacylglycerol from Phosphatidyl Choline

It is now widely believed that the indirect route to diacylglycerol involving phospholipase D is the main route to the formation of diacylglycerol.[56]

1.8.3 INHIBITION OF PHOSPHOLIPASE D BY WORTMANNIN AND RELATED COMPOUNDS

Reinhold and co-workers [57] carried out a series of experiments to deduce the mode of activation of phospholipase D. Their experiments primarily involved the investigation of a phospholipase D catalysed phosphatidylation reaction which converted ethanol to phosphatidylethanol. The amount of phosphatidylethanol generated was then used as a measure of the activation of phospholipase D. From their findings they concluded that there were 3 separable but interacting mechanisms for phospholipase D activation. In particular, one of these mechanisms was found to be inhibited by wortmannin.

In 1991 Bonser and co-workers[58] also demonstrated that wortmannin **34** and its related compound demethoxyviridin **35** blocked both phospholipase C and phospholipase D activation in the human neutrophil.



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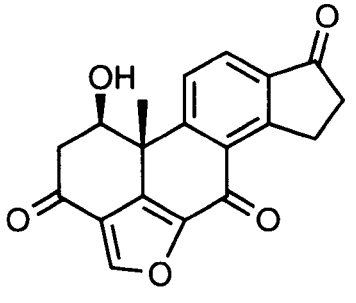

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Figure 1.20: Wortmannin and Demethoxyviridin

In light of this evidence therefore it would seem appropriate that wortmannin **34**, demethoxyviridin **35** and their related compounds provide a starting point for the synthesis of new anticancer drugs.

CHAPTER 2

2.1 LEAD COMPOUNDS

Steroids belonging to the viridin series possess the common backbone **36** and share the common feature of a furan ring fused between C-4 and C-6 of the steroidal framework. The viridins differ only in the oxidation pattern of ring A.

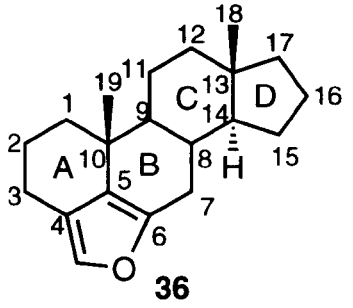

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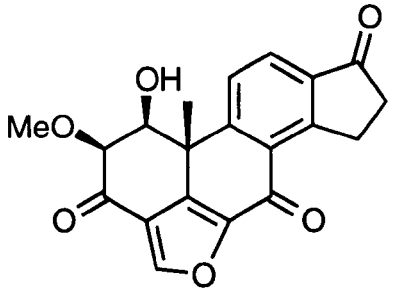
Figure 2.1: Common Backbone of the Viridin Steroidal Family

Many of these compounds possess selective antifungal activity and more recently they have attracted interest in their ability to inhibit steps in the cell signalling process making them attractive potential anticancer drugs.

2.2 VIRIDIN AND DERIVATIVES

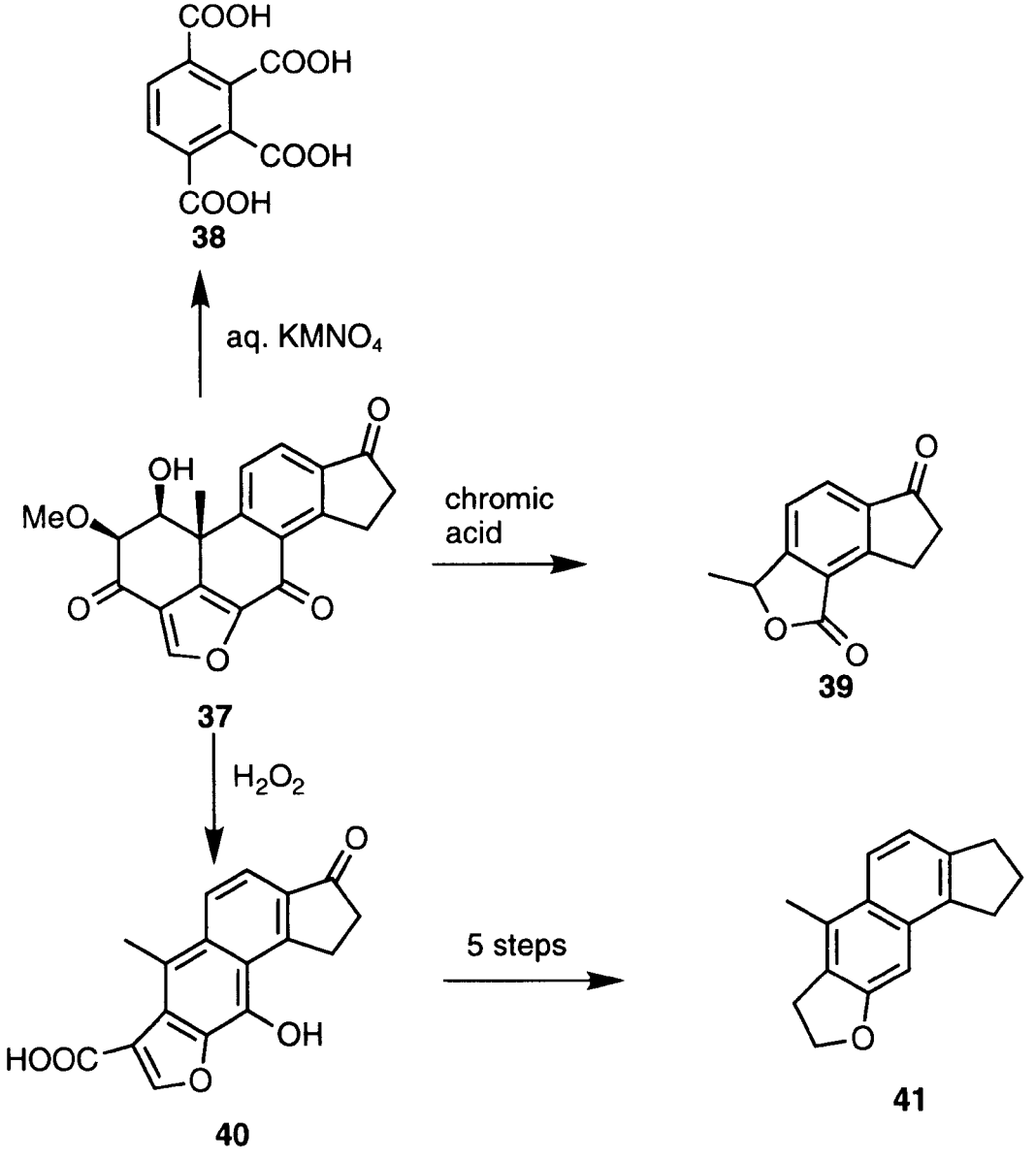
Viridin **37** was first described in 1945 as an antifungal metabolite of *Gliocladium virens*.[59]



37

Figure 2.2: Viridin

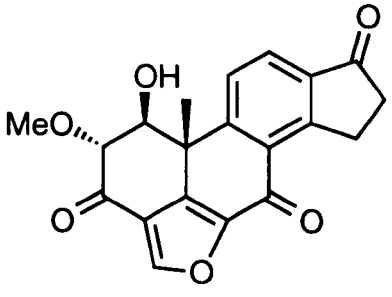
Its structure was determined by oxidative degradation. When treated with hot aqueous potassium permanganate viridin gave benzene-1,2,3,4-tetracarboxylic acid[60,61] **38** from the aromatic C ring. Milder oxidation with chromic acid gave the phthalide **39**, the structure of which was confirmed by synthesis. This degradation confirmed the relationship of both the carbonyl at position 7 and of the methyl group at position 10. The carbon skeleton of rings B, C and D and the position of the furan ring were elucidated by the transformation of **40**[62,63] (which is the product of hydrogen peroxide oxidation of viridin) into the methylcyclopentanaphtho[2,3-*b*]furan **41**. Like the phthalide the structure of this compound has also been confirmed by synthesis[64].



Scheme 2.1: Structure Elucidation of Viridin

Finally the overall structure was confirmed by ^{1}H nmr studies of viridin and its derivatives[65] and by X-ray analysis[66]. The absolute stereochemistry followed from biosynthetic studies[67].

Care must be taken when purifying viridin as it readily undergoes isomerisation at C-2 to give the epimer β-viridin **42**. To avoid this happening when isolating viridin **37** or its derivatives acidic alumina must be used for purfication.

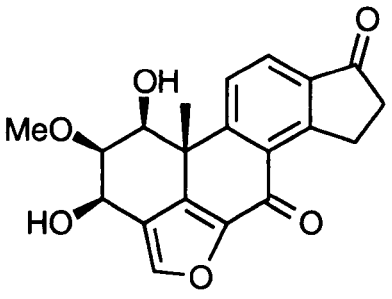


42

Figure 2.3: β-viridin

Viridiol **43** is a dihydroderivative of viridin **37** and studies by Jones and co-workers[68] have shown that it is formed irreversibly from the liquid culture of viridin **37** in the presence of *G. virens*, a viridin-producing fungus. Viridin **37** labelled with ^{14}C at the methoxy group was taken up by the mycelium of *G. virens* and reduced to radiolabelled viridiol **43**.

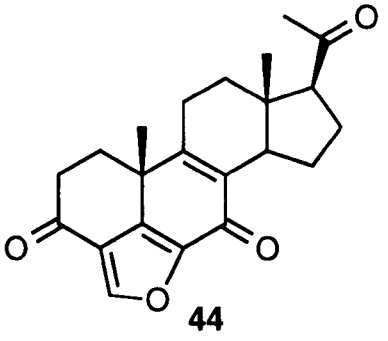
Viridiol **43** is ineffective as an antibiotic but is a potent phytotoxin.[69] As the reduction to viridiol **43** is independent of culture pH, carbon source and nitrogen source this transformation is therefore seen to have potential herbicidal applications.



43

Figure 2.4: Viridiol

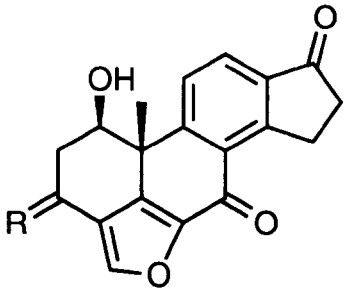
Other viridin-producing fungi include *Trichoderma viride* where it is produced in the surface culture of Raulin Thom medium at 25°C.[70] If, however, fermentation is carried out at 32°C viridin **37** is produced in a much lower yield but is accompanied by a less polar metabolite virone **44** which is not produced at all at 25°C. Its structure was deduced by Blight and co-workers[71] .



44

Figure 2.5: Virone

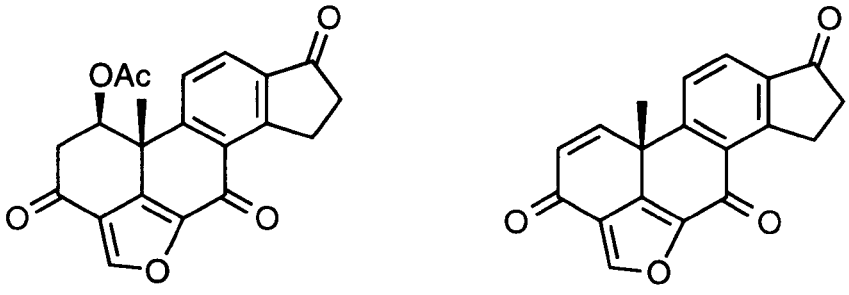
Demethoxyviridiol **45** and demethoxyviridin **35** have been isolated from *Nodulisporium hinnuleum*. Both structures (see figure 2.6) were elucidated by X-ray crystallography[72] and extensive chemistry has been carried out on the latter derivative.



35 R = O
45 R = α-H, β-OH

Figure 2.6: Demethoxyviridin and Demethoxyviridiol

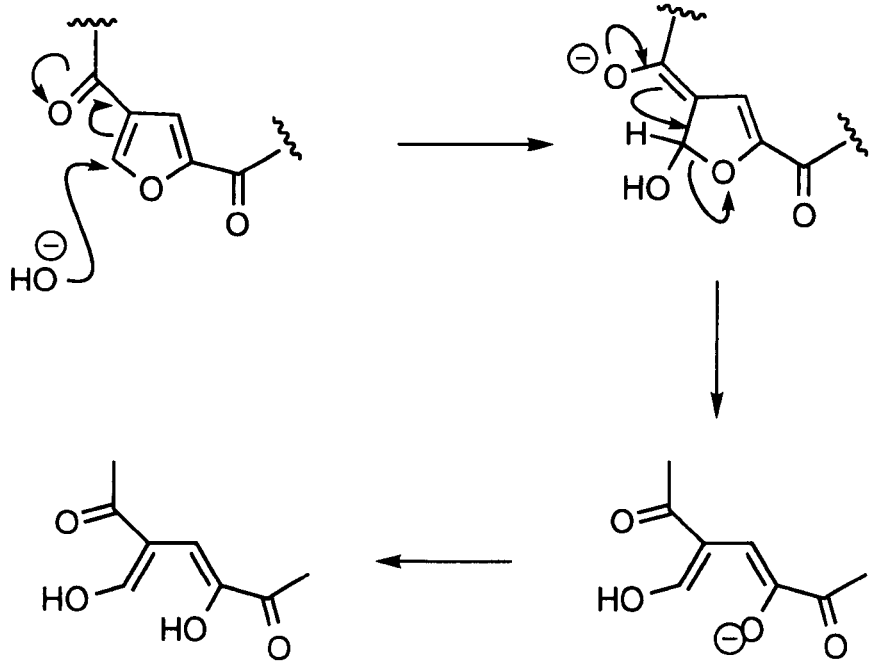
Like viridin **37**, demethoxyviridin **35** is relatively unstable in alkaline conditions and is handled in an acidic medium wherever possible. It readily gives its monoacetate **46** when treated with acetic anhydride and pyridine.[73] Treatment with methanesulfonyl chloride gives the monomethanesulfonate[73] which undergoes facile elimination to afford the α,β-unsaturated ketone **47** (see figure 2.8).



46 **47**

Figure 2.7 Derivatives of Demethoxyviridin

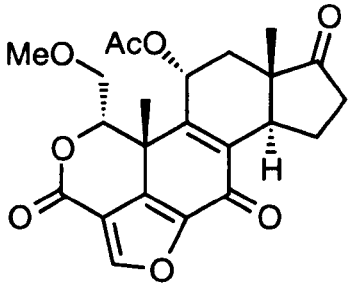
The lability to alkali shown by demethoxyviridin **37** and its derivatives may in part be due to facile conjugate addition to the furan ring at C-20 under the influence of the carbonyls at C-3 and C-7.[74] (see scheme 2.2)



Scheme 2.2: Lability of Furan System to Base

2.4 WORTMANNIN AND DERIVATIVES

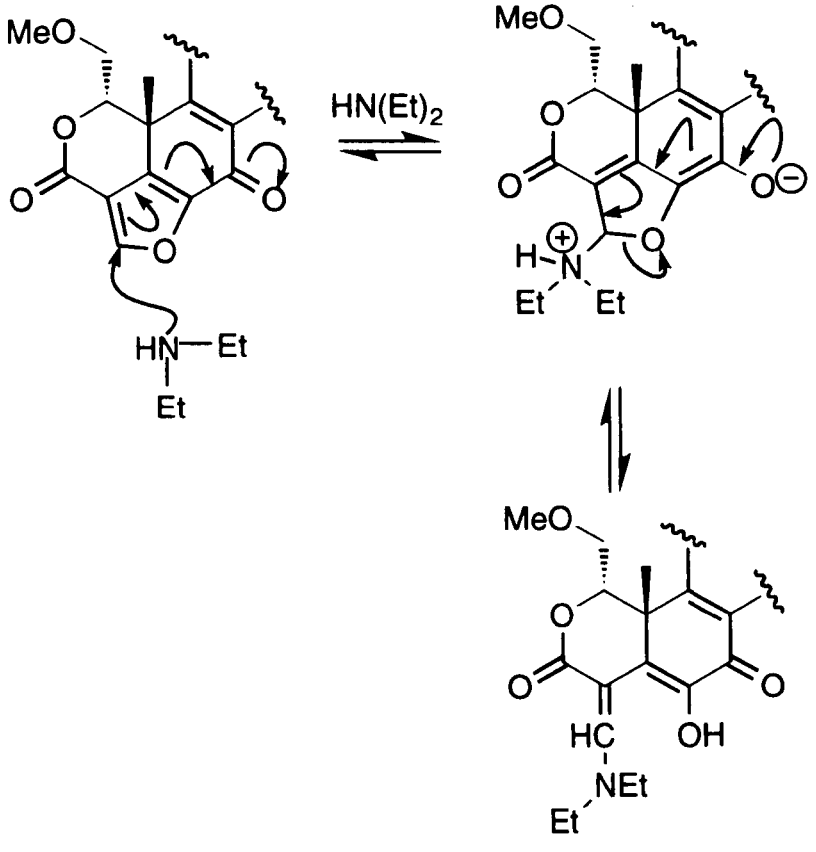
Wortmannin **34** was first isolated from *Penicillium wortmannii* in 1946 by Brian and co-workers[70]. The structure was elucidated both by chemical analysis[75] and by X-ray crystallography[76].



34

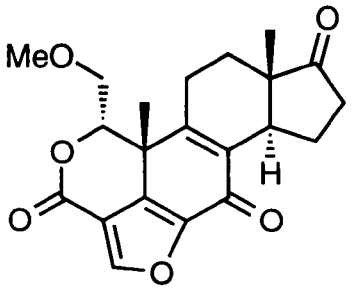
Figure 2.8: Wortmannin

Due to the sensitive nature of the furan system Haefliger and co-workers[77] looked at protecting the furan nucleus with secondary amines. This would allow manipulation of the rest of the molecule (see scheme 2.3 for the protection).



Scheme 2.3: Protection of the Furan Nucleus

The same group of workers isolated 11-desacetoxywortmannin **48** as a new metabolite from the culture filtrate of *Penicillium funiculosum* Thom.[78]



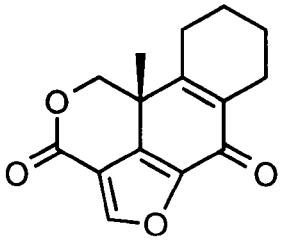
48

Figure 2.9 11-Desacetoxywortmannin

Although possessing weak antifungal activity 11-desacetoxywortmannin **48** is highly active as an antiinflammatory agent. Owing to this interesting property, steps were taken to further derivatise both wortmannin **34** and 11-desacetoxywortmannin **48** with the introducton of a corticoid side chain at position 17 and to transform the acetoxy group at C-11 into an alcohol. The antiinflammatory potency of the parent compounds and their derivatives were then compared. When given to rhesus monkeys, a single dose of 1 or 3 mg/kg caused weakness, decreased motility, uncoordinated behaviour and anorexia. When given to rats, 11-desacetoxy-wortmannin **48** exhibited a dose-dependent inhibition of primary and secondary arthritis by improving the grip function. However upon repeated application of the compounds toxic side-effects were observed. Introduction of the corticoid side-chain caused complete loss of activity.

Although these compounds were shown initially to have interesting and important properties, their high toxicities prevented further development into useful drugs. The chemistry then lay dormant for almost two decades but interest in these steroids continued to grow. Interest grew particularly in their importance as inhibitors of enzymes involved in the signalling pathways leading to cell division.

Broka was the first to synthesise the furanocyclohexadienone lactone subunit **49** of both wortmannin **34** and 11-desacetoxywortmannin **48**.[79] The subunit was tested for biological activity to block fMet-Leu-Phe stimulated generation of superoxide by neutrophils but was shown to be inactive under conditions where wortmannin **34** had an IC_{50} of 0.1 μM.

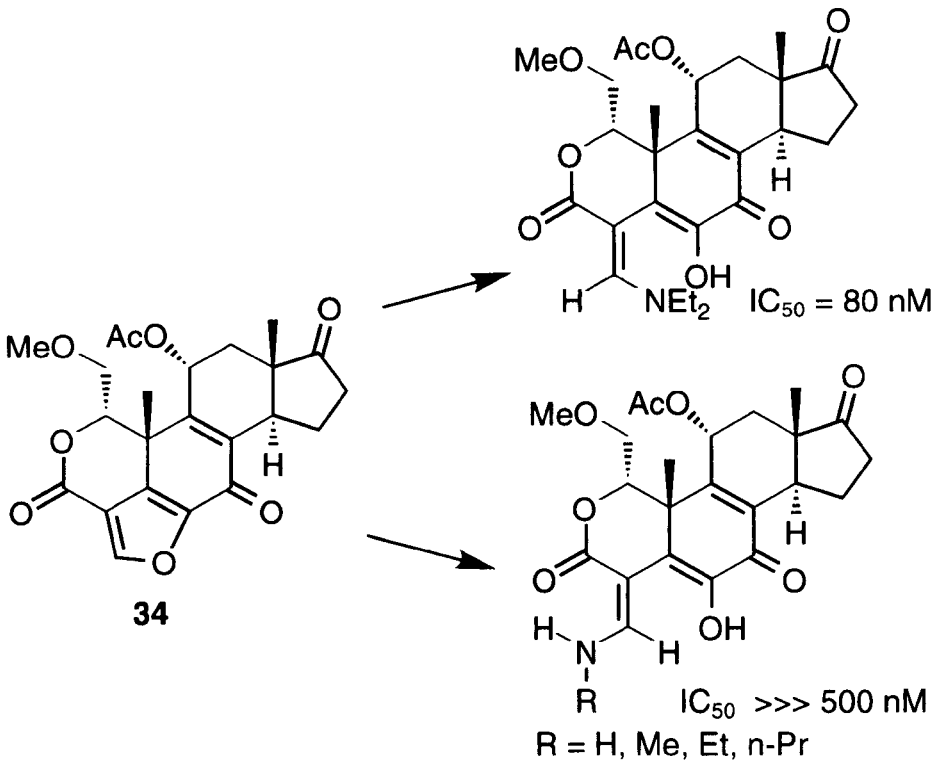


49

Figure 2.10: Furanocyclohexadienone unit of Wortmannin

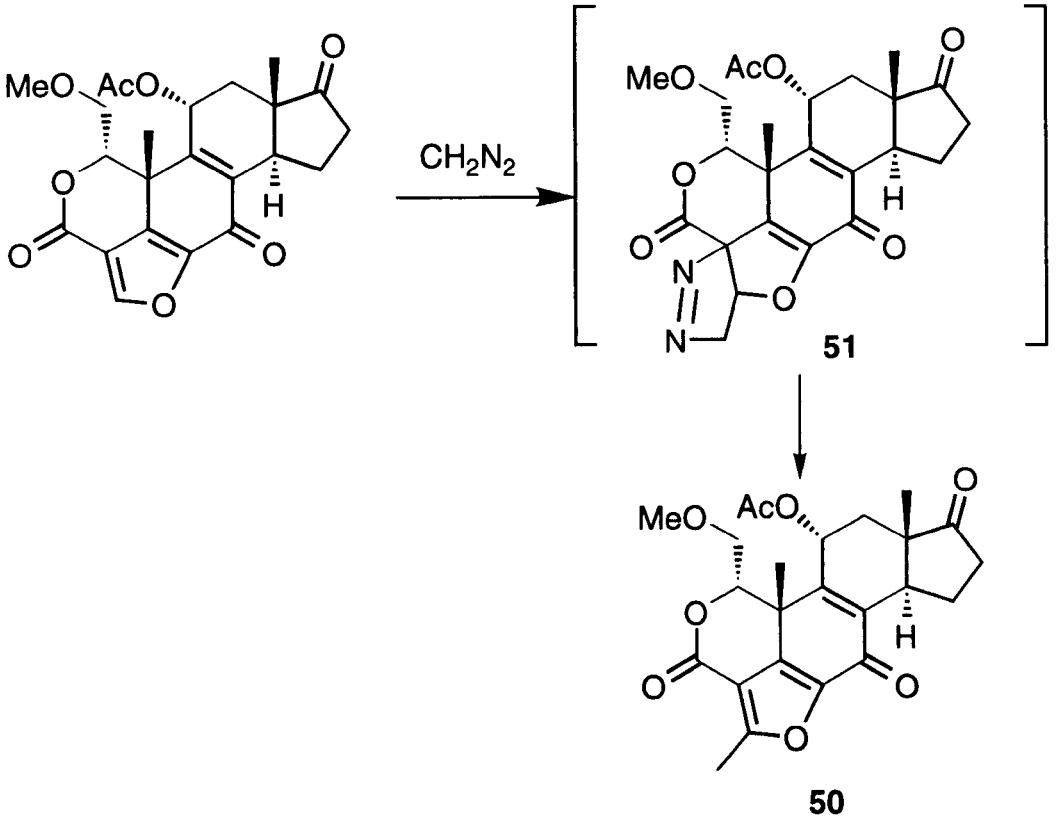
In 1994 wortmannin **34** was reported to be a potent (4.2 nM) and selective inhibitor of phosphatidylinositol-3'-kinase.[80] This kinase has been identified as an important enzyme in a number of signalling pathways leading to cell transformation. Wortmannin **34** therefore became an attractive new compound for leads for new anticancer compounds.

Researchers at Lilly in Indiana were interested in making synthetic modifications to the furan portion of the molecule since the highly electrophilic C-20 position may be responsible for much of its biological activity[81]. Studies on the configuration of the double bond on ring opening with amines showed that secondary and primary amines give the *E*- and *Z*-geometries respectively. This can possibly explain the marked differences in activity (see scheme 2.4). The compound with *Z*-geometry displays hydrogen bonding to the carbonyl at position 3 which will "lock" these molecules into this position.



Scheme 2.4 Primary and Secondary Amine Adducts of Wortmannin

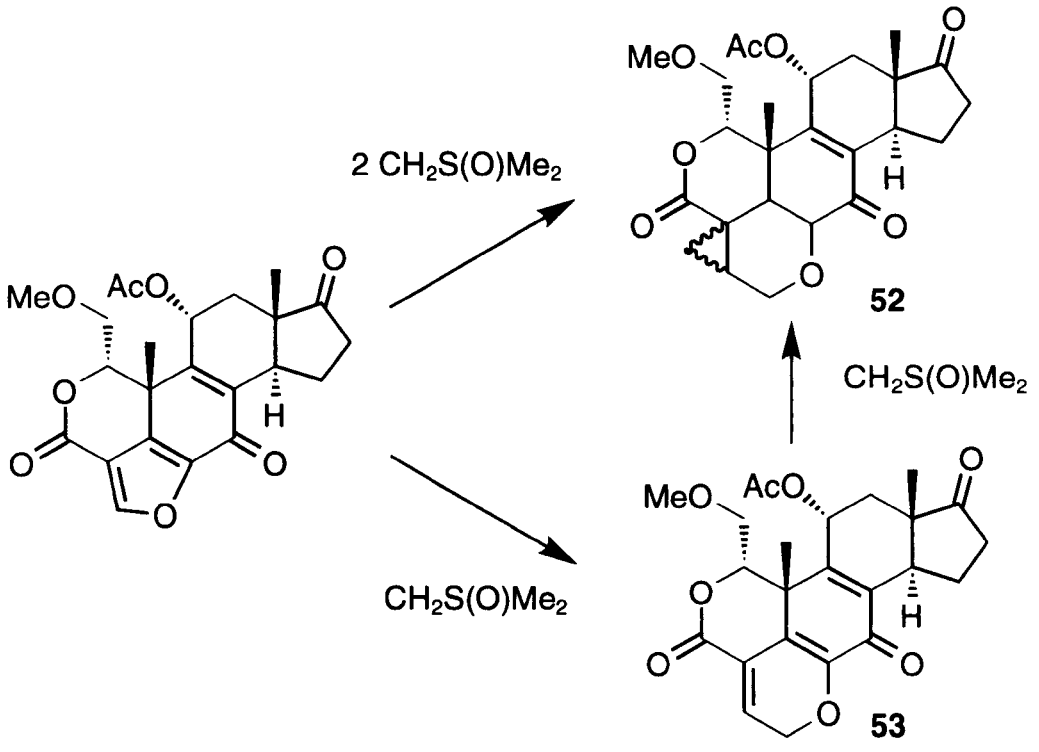
To explore further the chemistry of the furan and specifically the functionality at C-20, wortmannin **34** was treated with diazomethane (see scheme 2.5).



Scheme 2.5: Formation of 20-Methylwortmannin

This gives the 20-methylwortmannin derivative **50** rather than the expected cyclopropane or pyrazoline derivatives. Although the pyrazoline **51** was not detected it is assumed that this is an intermediate which loses nitrogen to give the 20-methylwortmannin **50**. The addition of a methyl group the position 20 destroys the PI-3 kinase activity.

Unique ring expansions using trimethylsulfoxonium ylides were observed giving **52** and **53** and which product formed dependent on the number of equivalents of ylide used. Results have shown that if two equivalents were used together then the derivative **52** with the cyclopropane on the tetrahydropyran was made. However, if wortmannin **34** was first treated with one equivalent of the ylide then a pyrone type system was formed. Subsequent treatment of this with a second equivalent of the ylide affords the tetrahydropyran/ cyclopropane system. This is summarised in scheme 2.6.



Scheme 2.6: Unique Ring Expansions using Trimethylsulfoxonium Ylides

Although both products shown in scheme 2.6 displayed lower activity than wortmannin **34** the cyclopropane adduct **52** (without the efficient C-20 Michael acceptor site) showed the greatest loss of activity. Norman and co-workers[81] concluded that the C-20 position in the furan ring is an important site in the molecule and that changes at that position have a dramatic consequence on the PI-3 kinase inhibitory potency.

2.4 HALENAQUINONE AND RELATED COMPOUNDS

Halenaquinone **53**, halenaquinol **54** and xestoquinone **55** were isolated as the major components from the dichloromethane partition fraction of *Xestospongia c. f. carbonaria*. [82] Halenaquinone **53** and halenaquinol **54** are two of only four natural marine products found to inhibit protein kinase C.

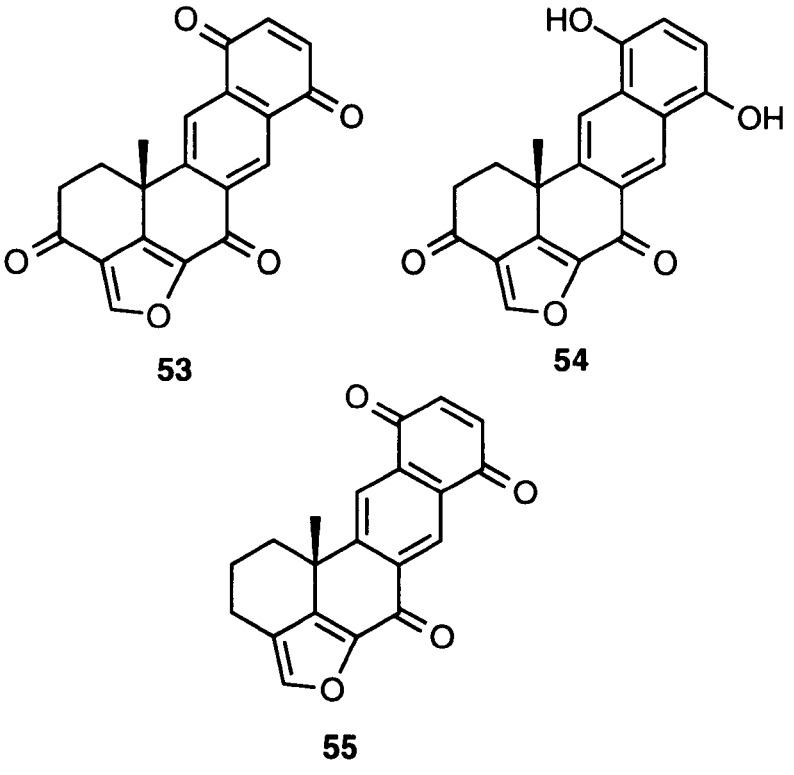
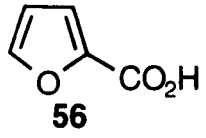


Figure 2.11 Halenaquinone, Halenaquinol and Xestoquinone

Both halenaquinone **53** and halenaquinol **54** have been shown to be effective against epidermal growth factor receptor protein tyrosine kinases. The potency of the halenaquinol **54** is easily explained because it oxidises readily to halenaquinone **53**. As enhanced protein tyrosine kinase activity has been associated with proliferative diseases such as cancer, the inhibition by this family of compounds shows potential for the discovery of new chemotherapeutic agents. Due to the activity of halenaquinone **53** and halenaquinol **54**, other structurally similar compounds including Xestoquinone **55** were tested for biological activity against protein kinase C but all proved to be inactive. This supports the suggestion that the furan ring in conjugation with the two carbonyl groups is essential for biological activity.

2.5 INTRODUCTION TO FURANS

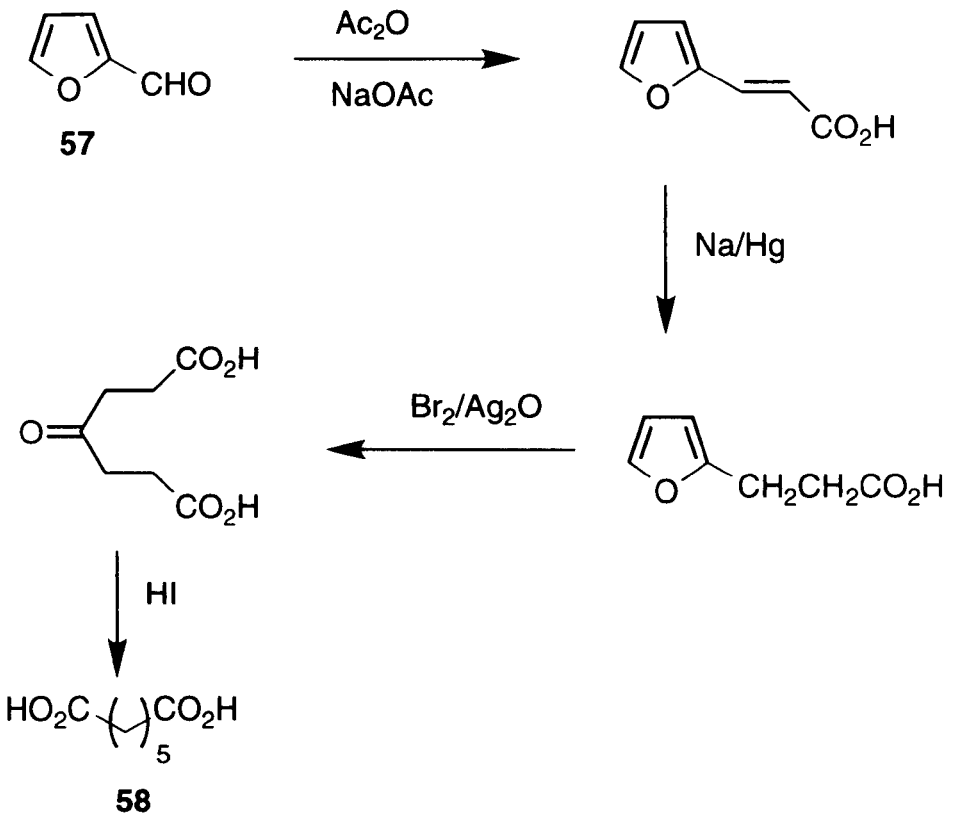
Furans are volatile, fairly stable compounds with pleasant odours. The earliest furan compound isolated was pyromucic acid **56**, usually known as furoic or furan-2-carboxylic acid which was obtained by Scheele in 1780 by the dry distillation of mucic acid.[83]



56

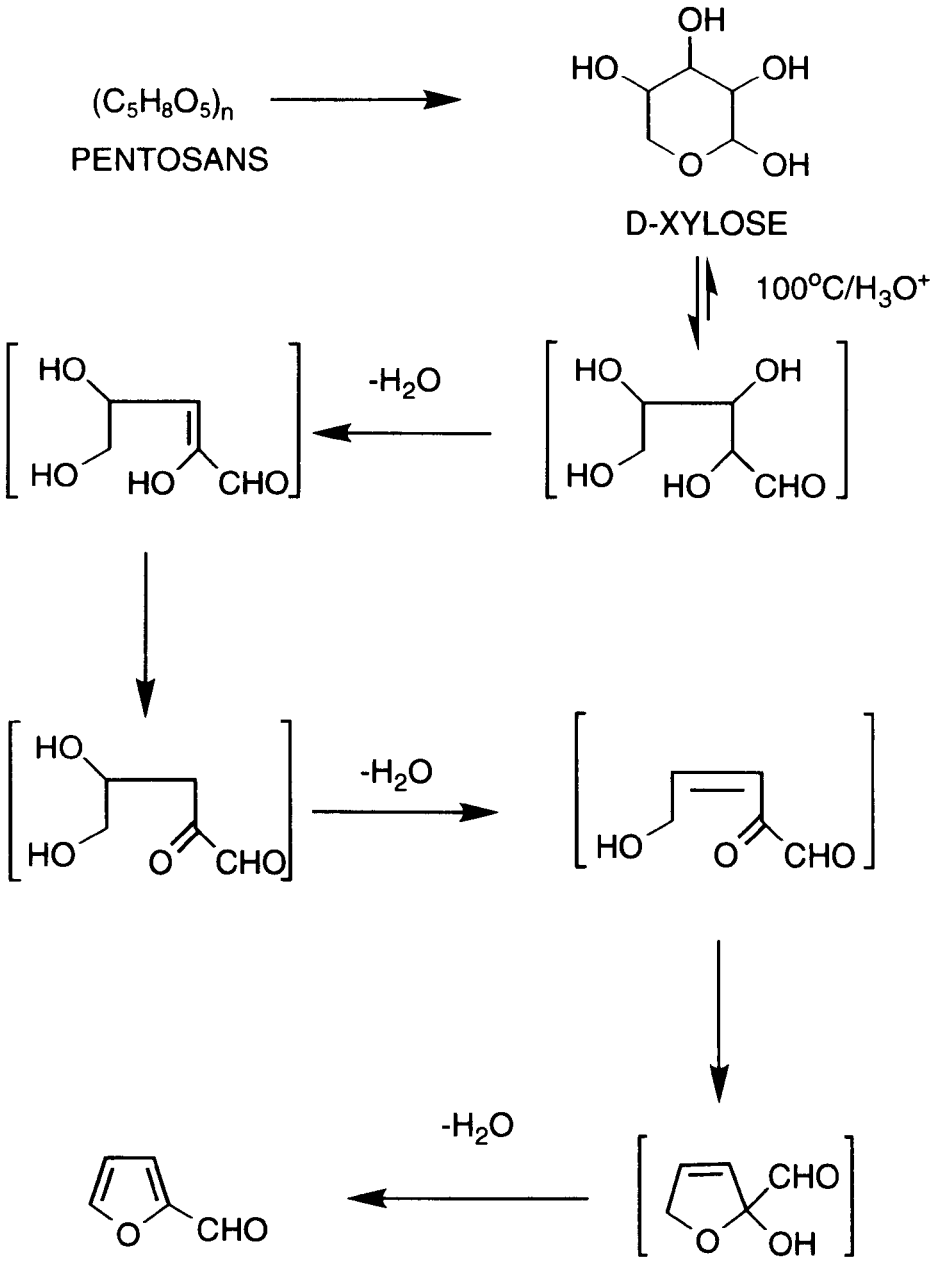
Figure 2.12: Pyromucic Acid

Furan itself was first obtained in 1870 by treating barium furoate with soda lime. Nowadays it is readily available and its commercial importance is mainly due to its role as the precursor of the widely used solvent tetrahydrofuran. The arrangement of atoms in furan was not established until 1877 when Baeyer treated furfural **57** with acetic anhydride and sodium acetate followed by reduction and ring opening to give pimelic acid **58**.[83]



Scheme 2.7: ***Formation of Pimelic Acid***

The furfural or furan-2-carbaldehyde used by Baeyer previously was first obtained in 1832 by the action of sulfuric acid and manganese dioxide on sugar. Incidentally the name furfural is derived from *furfur* which is latin for bran. It was not however until 1920 that furfural became commercially available cheaply and in large quantities from the acid catalysed ring-opening of xylose, obtained from pentosans which are polysaccharides extracted from plants such as oat husks. As dehydrating agents such as phosphorus pentoxide or zinc chloride do not bring about the formation of the furan the transformation is not a simple dehydration. Similar treatment of erythritol with dilute mineral acid fails to produce any furfural suggesting that the presence of a β-hydroxyaldehyde is a necessary condition for the reaction.[84] The mechanism shown is consistent with acid hydrolysis with the acid catalysing the overall loss of three moles of water from the D-xylose.

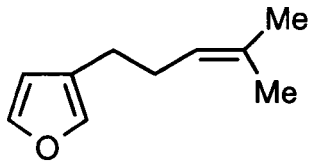


Scheme 2.8:Formation of Furfural through dehydration D-Xylose by Sulphuric Acid.

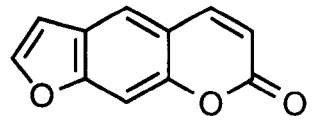
Other examples of the formation of furans from carbohydrates include the formation of 5-hydroxymethylfurfural from the treatment of sucrose[85] with oxalic acid at 125-145°C.

2.6 NATURALLY OCCURRING FURANS AND COMPOUNDS OF INTEREST

The aromatic furan ring system, although not found in higher animal metabolism occurs widely in secondary plant metabolites especially in terpenoids such as perillene **59** and the furocoumarin pimpenelin **60**:[86]



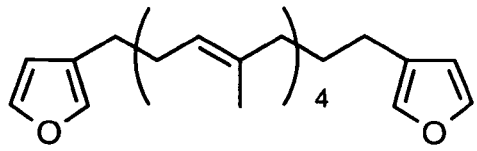
59



60

Figure 2.13: ***Perillene and Pimpenelin***

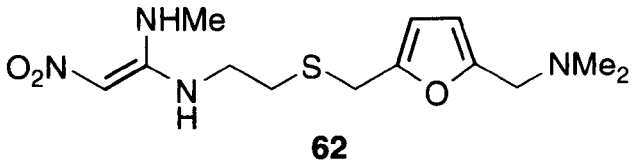
It is common for plants to construct furans by modifying one end of a terpenoid chain giving 3-monosubstituted furans although disubstituted furans have also been well documented.[87] Recent interest in marine natural products has shown several terpenoids in which both ends of the system terminate in furan rings. An excellent example of this is difurospinulosin **61**.



61

Figure 2.14: ***Difurospinulosin***

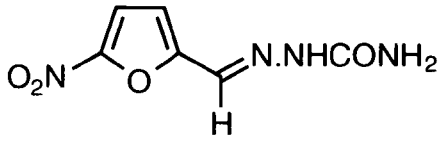
Interest is also growing in the pharmaceutical industry into the importance and use of compounds containing furan rings. One of the most important furan containing compounds is Zantac **62**, which reduces gastric acid secretion and is important in the treatment of ulcers.



62

Figure 2.15: Zantac

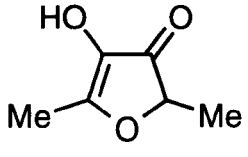
There are a number of 5-nitrofurfural derivatives which are important chemotherapeutic agents such as the bactericide 'Furacin' **63** being an example.[88]



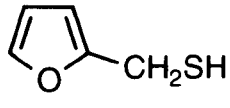
63

Figure 2.16 Furacin

Amongst furan compounds are several which are of great importance in fragrances and flavours. Compounds like the 3-furanone derivative furaneol **64** are particularly interesting because their odours depend on concentration. Indeed furaneol **64** can seem to resemble pineapple, caramel or burnt toast. In low concentrations the odour of furfuryl mercaptan **65** resembles that of roasted coffee which is only formed during the roasting process of the coffee beans and is not present in the fresh beans.



64



65

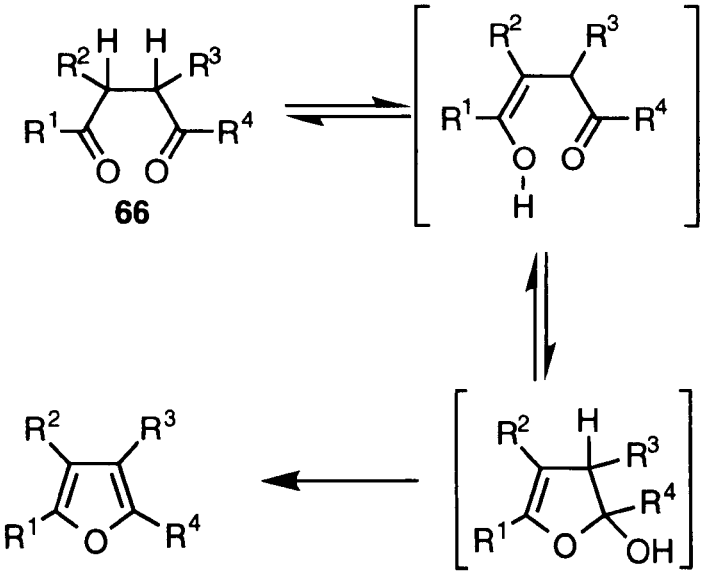
Figure 2.17: Furaneol and Furfuryl Mercaptan

2.7 SYNTHESIS OF FURANS[86]

There are several ways of synthesising furan compounds starting with non-heterocyclic precursors, the most common involving ring closure with elimination of water between the dienolic forms of 1,4-dicarbonyl compunds. Two of the most common methods are the Paal-Knorr synthesis and the Feist-Benary synthesis.

2.7.1 THE PAAL-KNORR SYNTHESIS[89]

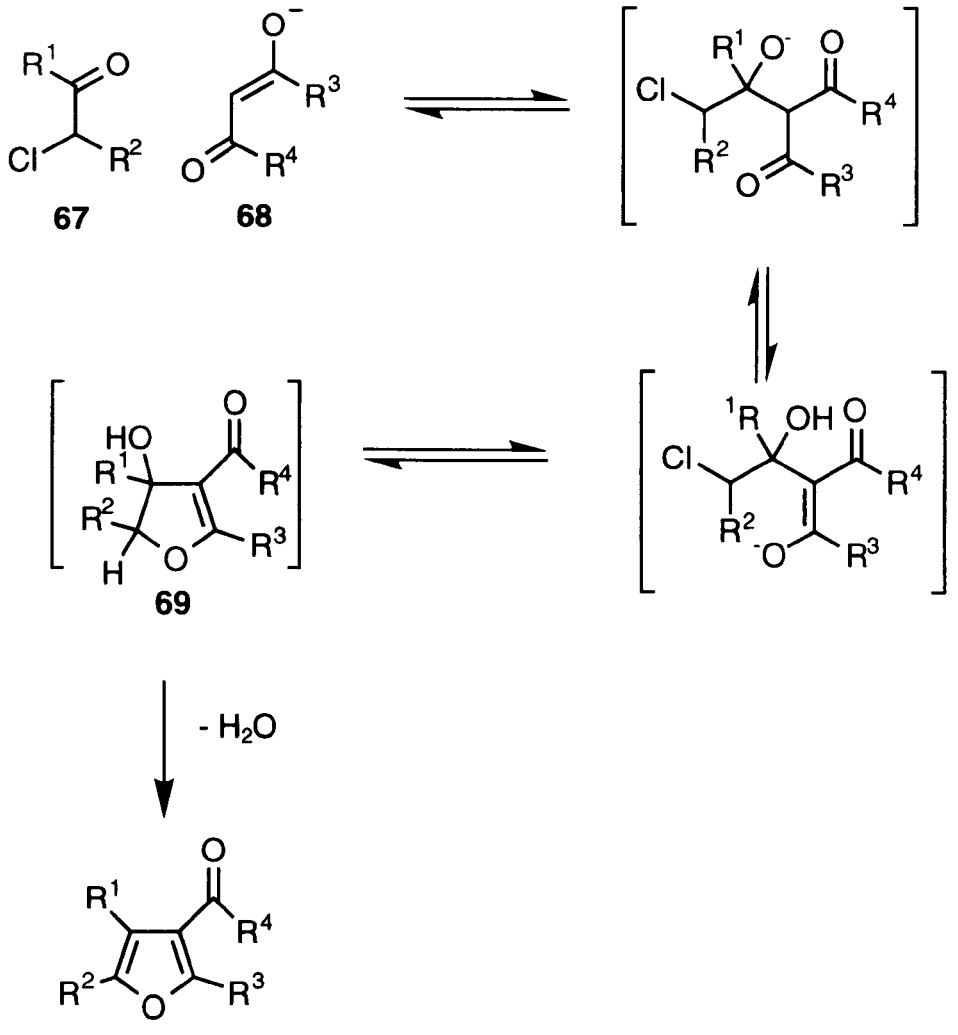
This synthesis involves the cyclodehydration of 1,4-dicarbonyl compounds **66**. The main limitation on the generality of this approach is the availability of an appropriate 1,4-dicarbonyl compound. Once obtained, the cyclisation of such precursors, which provide all of the carbon atoms and the oxygen atom necessary for the furan, generally proceeds in high yield. Usually non-aqueous acid conditions are employed to encourage the required loss of water. The process involves the oxygen of the enol form of one of the carbonyl groups adding to the carbon of the other carbonyl group. Elimination of water then completes the process. This sequence of events is shown in scheme 2.9.



Scheme 2.9: ***The Paal-Knorr Synthesis***

2.7.2 THE FEIST-BENARY SYNTHESIS[90,91]

The Feist-Benary synthesis involves the intermolecular pyridine catalysed aldol condensation of an α-haloketone **67** with a 1,3-dicarbonyl **68** followed by ring closure and elimination of water (scheme 2.10).



Scheme 2.10: The Feist-Benary Synthesis

The synthesis usually proceeds as shown but in a few instances the reaction stops short of the final dehydrative step giving the 3-hydroxy-2,3-dihydro furan **69**.

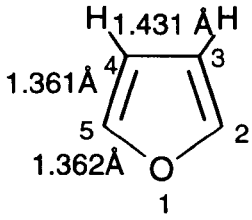
2.8 PHYSICAL PROPERTIES OF FURANS

Furan itself is a colourless liquid with a boiling point 31-32°C with a chloroform-like smell. It is only slightly soluble in water but is miscible with most organic solvents. Microwave studies have shown it to be a planar molecule.[92] Calculation of the molecular parameters for a number of furan derivatives has found the following:

a the carbon - oxygen bonds in furan are shorter than those of reduced derivatives such as THF

b the carbon - oxygen - carbon angle has contracted slightly in furan

The bond lengths and angles[91] are shown in figure 2.18:



C_5-O-C_2 = 106.6°
O-C_2-C_3 = 110.7°
C_2-C_3-C_4 = 106.0°

Figure 2.18: Bond Lengths and Bond Angles of Furan

Comparing furan to benzene, the distance between carbon atoms 3 and 4 is slightly longer than that of the aromatic carbon-carbon bond. Also the bond lengths between carbons 2 and 3 and carbons 4 and 5 are very close to that of an olefin. These results show that furan cannot be fully represented by classical formula **A** but it is best considered as a resonance hybrid of structures **A** to **E**. The furan molecule is far from a regular pentagon in shape, and the bond lengths suggest that structure **A** is the major contributor to the resonance hybrid.[93]

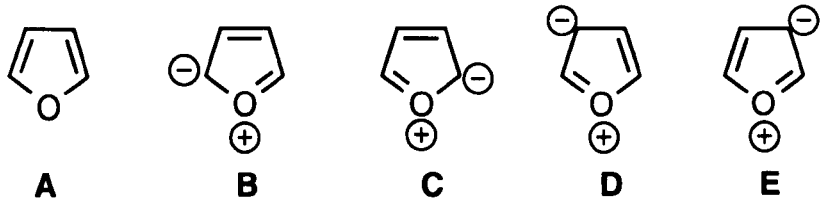


Figure 2.19: Resonance Structures of Furan

Of the other resonance structures, **B** and **C** are expected to be the most important for several reasons. The energy required to separate the charges is lower in these cases than in other charged structures as the distance involved is less. **B** and **C** are also completely conjugated and are more stable than 4 and 5 which are considered to be cross-conjugated. However calculation of the π-electron densities for furan gives the result shown in figure 2.20 which is the reverse of what we might have expected from the above argument. Electrophilic attack greatly favours substitution at positions 2 and 5 in agreement with resonance structures.

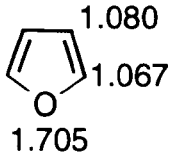


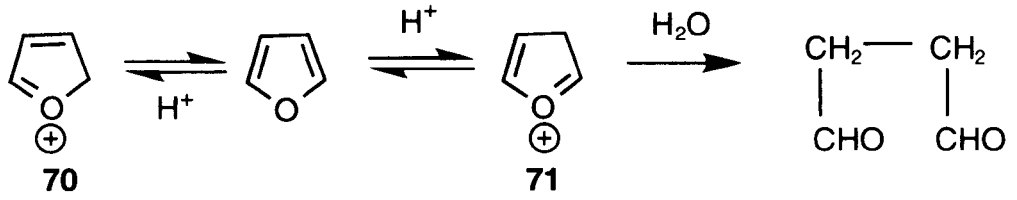
Figure 2.20 Electron distribution on Furan

In order for the furan ring to behave as an aromatic structure it must have six π-electrons in the ring. The oxygen atom must provide 2 electrons but since oxygen is more electronegative than, say, nitrogen it will provide the 2 electrons less easily and therefore furan is less aromatic than pyrrole. The physical data suggest therefore that furan should behave as a diene ether.

2.9 CHEMICAL PROPERTIES OF FURANS

Furans undergo ring opening relatively easily under dilute acid conditions and this has been compared to the hydrolysis of enol ethers.[94] This hydrolysis however is not as facile as that of enol ethers because the initial attack of the proton involves the electrons of the oxygen atom. These electrons as previously discussed contribute to the π-electrons required for the aromaticity. The withdrawal reduces the resonance energy of the ring and converts the "aromatic" furan into the very much less stabilised cation. Deuterium exchange experiments[95] showed that cation **70** is formed 10^3

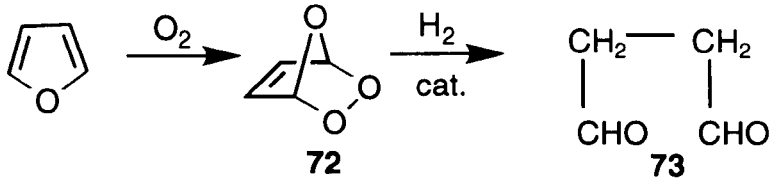
times as rapidly as **71** but hydrolysis to succindialdehyde presumably takes place through the latter.



Scheme 2.10: Hydrolysis of Furan to Succindialdehyde

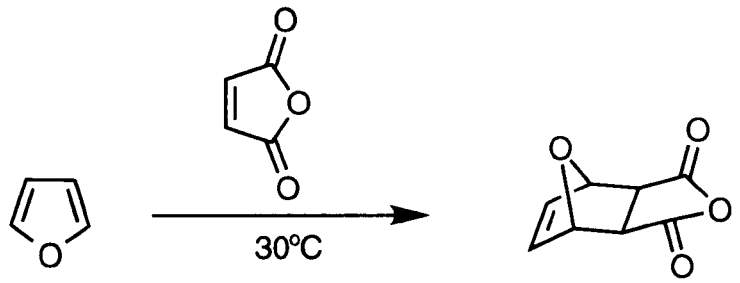
The mildest conditions necessary to effect this hydrolysis are such that polymerisaton of succindialdehyde occurs to a major extent.

Furan itself is not stable in the presence of air or oxygen and is usually stabilized by the addition of small quantities of hydroquinone. Aerial oxidation usually takes place by a 2,5-addition similar to addition to a 1,3 diene, leading to a peroxide **72** which has been isolated and then through a free radical polymerisation to a resin. Hydrogenation of the peroxide gives succindialdehyde **73**.



Scheme 2.11: 2,5-Addition by Aerial Oxidation leading to Succindialdehyde

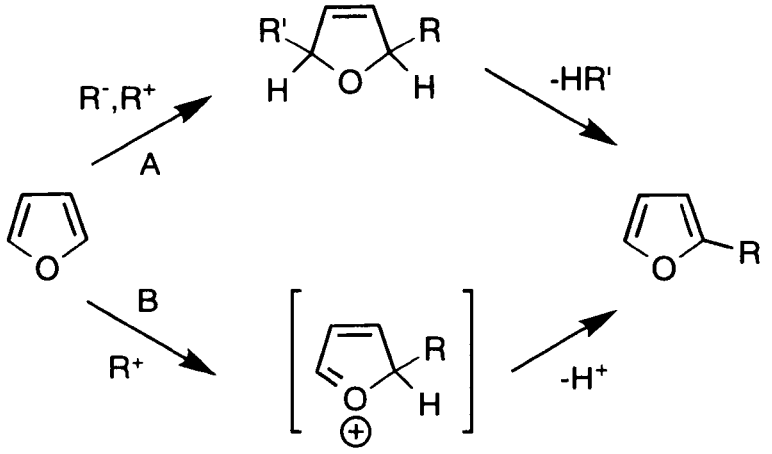
Furans also participate in a variety of cycloaddition reactions.[96] In particular they behave as 1,3-dienes in Diels-Alder type reactions. Its cycloaddition reaction with maleic anhydride is outlined in scheme 2.12.[97].



Scheme 2.12: Cycloaddition of Furan with Maleic Anhydride

The *exo* adduct **74** is formed twice as fast as the less stable *endo* isomer. The *endo* form changes to the *exo* form *via* disassociation then recombination.

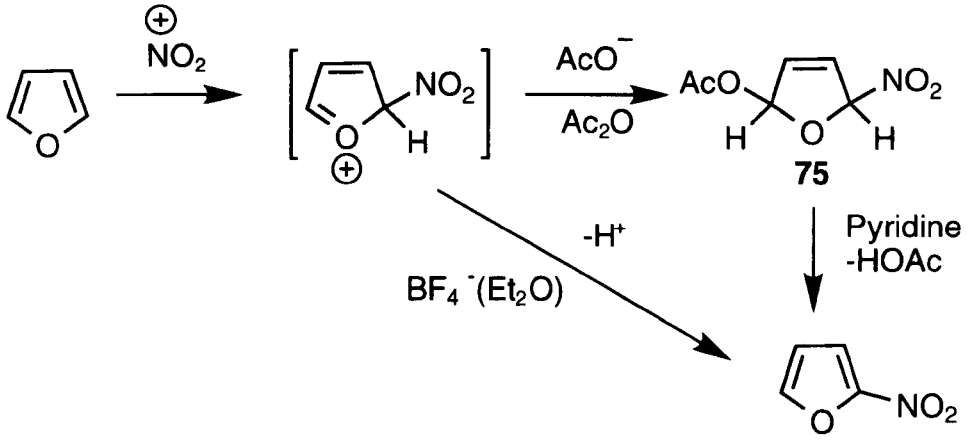
Substitution of the hydrogen atoms of the furan ring can also take place readily with substitutions usually taking place at positions 2 and 5. The substitutions can go by two different mechanisms as shown in scheme 2.13.[98,99] The first mechanism involves 1,4- addition followed by elimination as shown in pathway A. Alternatively, substitution can occur by electrophilic attack followed by proton loss as shown in the pathway B which is analagous to substitutions in benzene.



Scheme 2.13: Substitution of Furan

As the intermediates from 1,4-addition are unstable they are often unable to be isolated and subsequently can be mistaken for an electrophilic reaction. The nitration of furan

gives a good example of where the two mechanisms operate under different reaction conditions. With fuming nitric acid, acetic anhydride and pyridine 1,4- addition with isolation of intermediate **75** as evidence of this pathway. However with nitronium tetrafluoroborate where the BF_4^- counterion is non-nucleophilic, 2-nitrofuran is produced by the electrophilic mechanism[100].

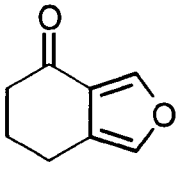


Scheme 2.14: Nitration of Furan

This project is concerned with the application of furan chemistry to the formation of potential anticancer drugs based on the active component of wortmannin and related compounds. In particular structures with the furan in conjugation with the two carbonyl groups are examined.

CHAPTER 3

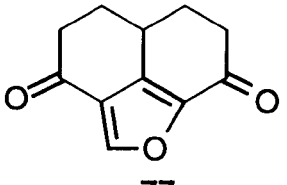
This chapter describes the synthetic approaches to the ketofuran **76**. This was chosen as a target because it possesses the furan in conjugation with one carbonyl group which would hopefully mimic the pharmacophore of the lead compounds - wortmannin and demethoxyviridin. Two general approaches were taken, the first involving the assembly of the furan nucleus on a cyclohexane ring base (sections 3.1 and 3.2) and the second starting with the furan ring intact and building the cyclohexane ring onto it by applying a wide range of synthetic methodology (section 3.3).



76

Figure 3.1: Target Ketofuran

Synthetic approaches are also described to the diketofuran **77**. In a similar fashion to ketofuran **76** the diketofuran contains a furan ring in conjugation with two carbonyl groups. It was expected that this would more accurately mimic the active component of the lead compounds.

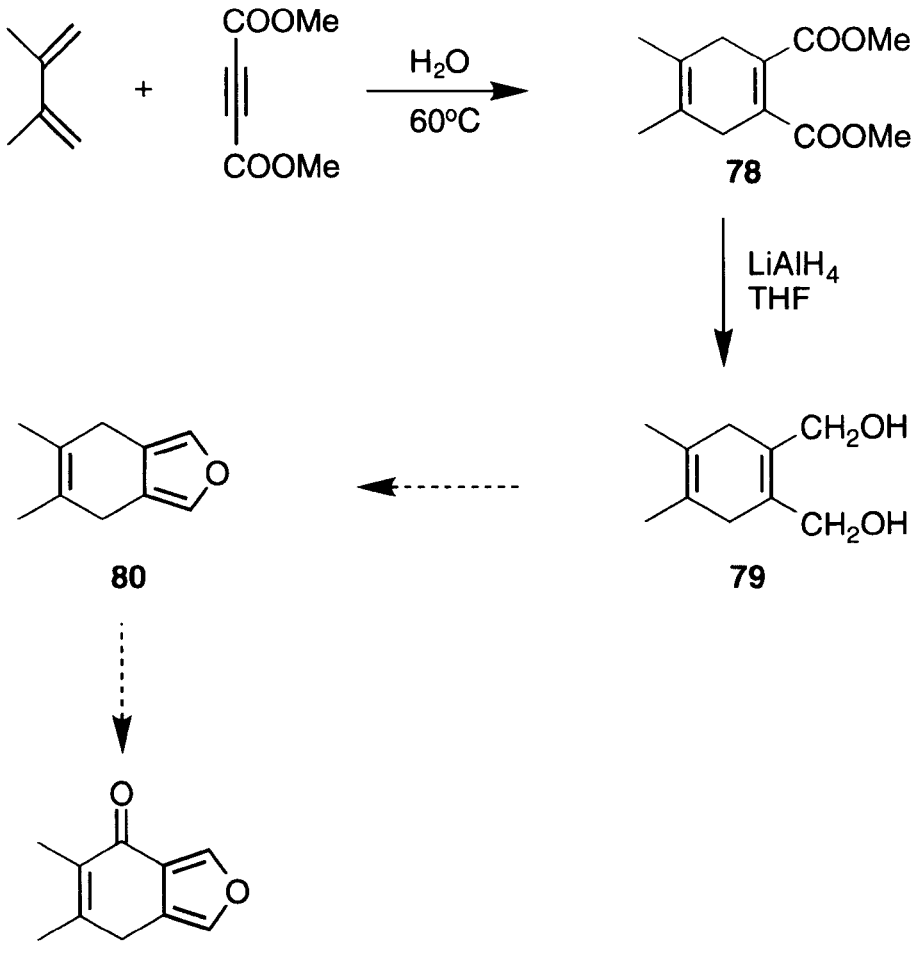


77

Figure 3.2: Target Diketofuran

3.1 ATTEMPTED SYNTHESIS OF FURAN *VIA* DIOL OXIDATION

The target furan in scheme 3.1 was chosen as it possesses the same carbon skeleton as ketofuran **76**. The synthesis involves a Diels-Alder reaction of dimethyl acetylenedicarboxylate and 2,3-dimethyl-1,3-butadiene followed by reduction of the resulting dimethyl 4,5-dimethyl-1,4-cyclohexadiene-1,2-dicarboxylate **78**. Cyclisation followed by allylic oxidation would give a compound suitable for biological testing against phospholipase D inhibition. Although there was literature precedence for the feasibility of this scheme, problems were encountered which are explained in the following text.



Scheme 3.1: Synthesis via Diol Oxidation

3.1.1 DIELS-ALDER BETWEEN 2,3-DIMETHYL-1,3-BUTADIENE AND DIMETHYLACETYLENE DICARBOXYLATE

The Diels-Alder ($4\pi + 2\pi$) cycloaddition between 2,3-dimethyl-1,3-butadiene (the diene) and dimethyl acetylenedicarboxylate (the dienophile) gave dimethyl 4,5-dimethyl-1,4-cyclohexadiene-1,2-dicarboxylate in 55% yield. The reaction proceeds well for a number of reasons. Both the diene and the dienophile possess the necessary characteristics required for a successful Diels-Alder reaction. The diene has electron donating methyl groups which increase the energy of the HOMO π-orbital and the dienophile has methyl ester withdrawing groups which lower the energy of the LUMO π-orbital.[101] The energy gap between the HOMO and LUMO orbitals is therefore decreased leading to an overall faster reaction. The effect of the substituents is shown diagramatically in scheme 3.2

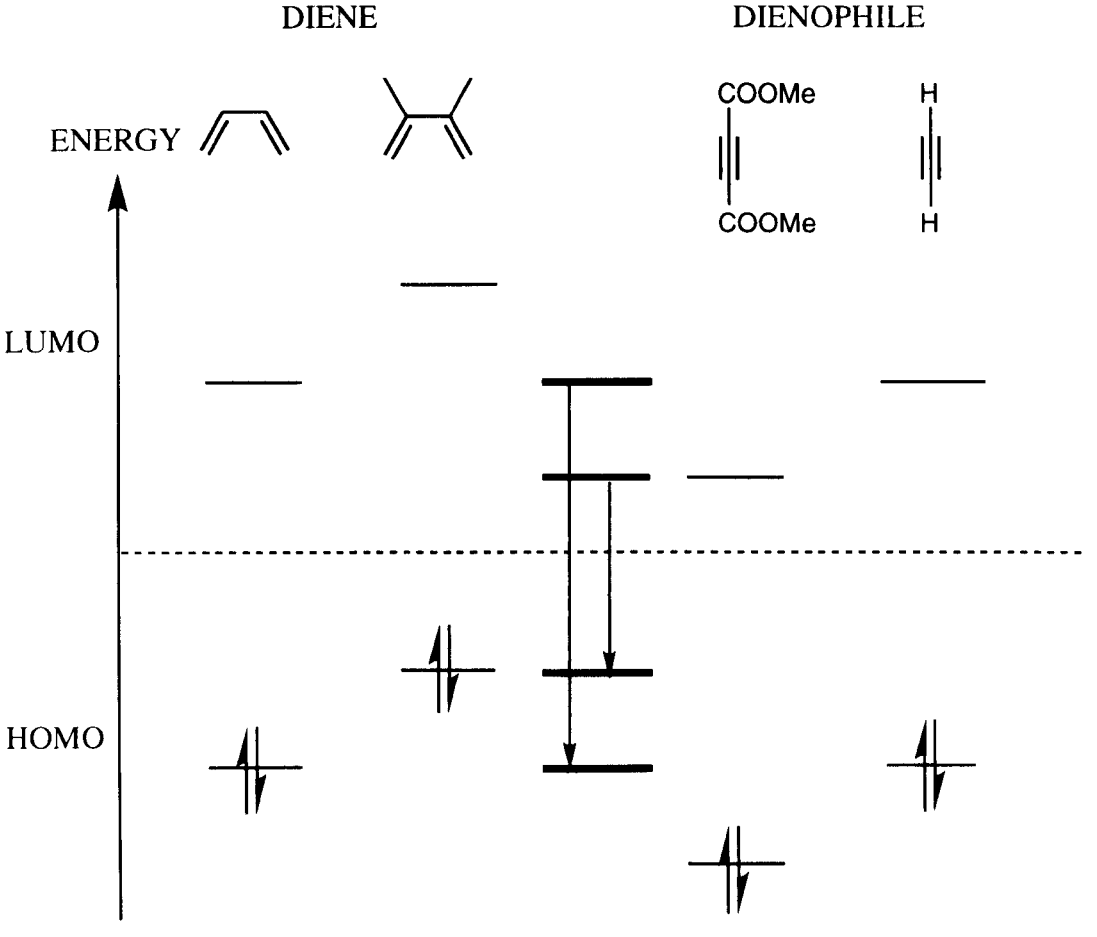
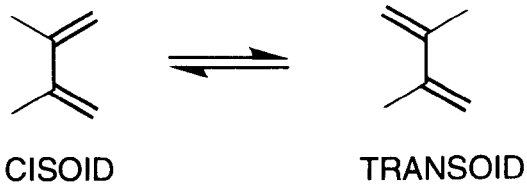


Figure 3.2: Electronic Substituent effects on orbital energies

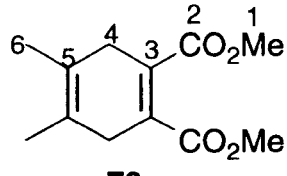
Water is a good solvent for Diels-Alder reactions involving substances with non-polar regions.[102] This is due to the "hydrophobic effect" where a polar solvent, in this case water, pushes two non-polar reactants close together thus accelerating the reaction.

However, the diene can exist in either a cisoid or a transoid state. If the methyl groups were replaced by larger groups then the transoid state would be favoured and since Diels-Alder reactions prefer the cisoid state the reaction would proceed less efficiently. In this case, however, the cisoid and transoid states are present in almost equal amounts. The reaction therefore proceeds quickly as the transoid equilibriates to the cisoid when the latter is consumed (see scheme 3.3)



Scheme 3.3: Equilibrium Between Cisoid and Transoid States of 1,4-Dimethylbutadiene

The structure identification of dimethyl 4,5-dimethyl-1,4-cyclohexadiene-1,2-dicarboxylate **78** in figure 3.4 was confirmed by ^{1}H and ^{13}C nmr.



78

Figure 3.4: Dimethyl 4,5-dimethyl-1,4-cyclohexadiene-1,2-dicarboxylate

^{1}H Nmr indicated the presence of the methoxy groups at δ3.76, the methyl groups at δ1.7 and the methylenes at position 4 at δ2.29. The ^{13}C nmr spectrum showed peaks at 133.3, 34.05 and 121.47 corresponding to C-3, 4 and 5 respectively of the cyclohexadiene. The signal corresponding to C-3 is shifted significantly downfield because it is in conjugation with the carbonyl of the ester.

3.1.2 REDUCTION OF THE DI-ESTER TO 1,2-BIS(HYDROXY-METHYL)-4,5-DIMETHYL-1,4-CYCLOHEXADIENE (79)

The diol **79** was obtained by reduction with lithium aluminium hydride in a poor yield (18%). The ^{1}H nmr spectrum showed three peaks at δ4.22, δ3.8 and δ2.74 corresponding to the carbon adjacent to the alcohol, and to the methylene and methyl groups respectively. The ^{13}C nmr spectrum showed the absence of the ester groups. This together with mass spectral data helped to confirm the structure **79**. However, due to the low yield from this method other ways of reducing dimethyl 4,5-dimethyl-1,4-cyclohexadiene-1,2-dicarboxylate **78** were looked at.

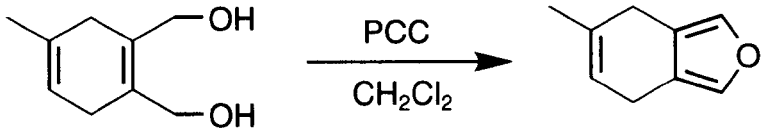
Reduction of the ester **78** was attempted using sodium borohydride.[103] This proved unsuccessful and although starting material was consumed and several products were observed, none were isolated. Consultation with the literature revealed that esters can be reduced by sodium borohydride in the presence of iodine[104]. This method generates borane *in situ*:

$$2NaBH_4 + I_2 \xrightarrow{THF} 2NaI + H_2 + 2BH_3.THF$$

The sodium borohydride was used in excess and the iodine added slowly to it. No identifiable products were obtained from this reaction.

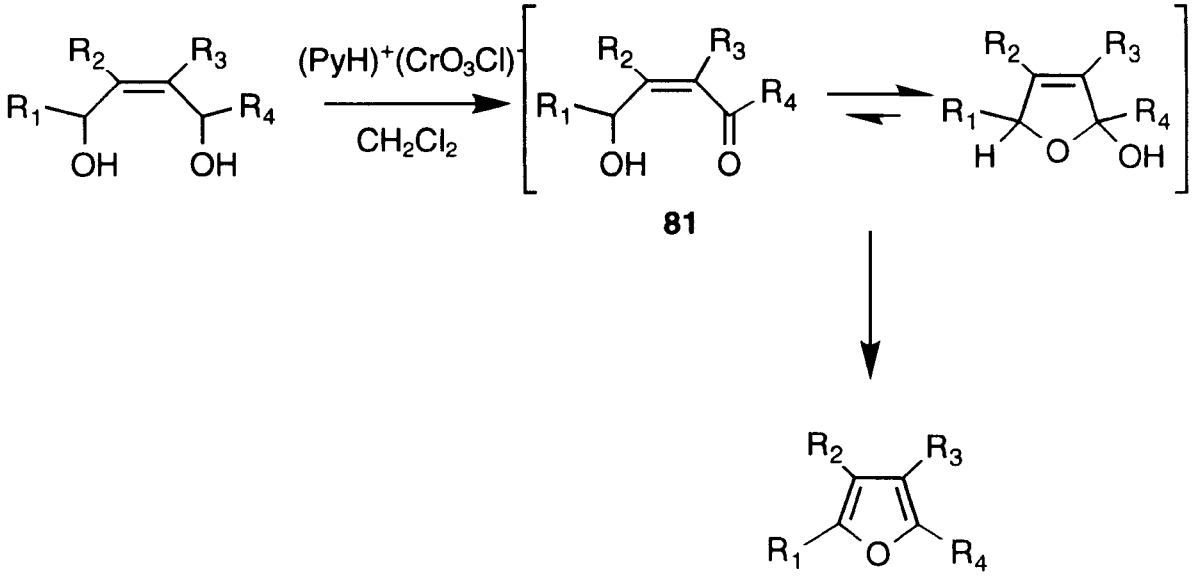
3.1.3 CYCLISATION OF 1,2-DIHYDROXYMETHYL-4,5-DIMETHYL-1,4-CYCLOHEXADIENE TO FURAN 80

1,2-Dihydoxymethyl-4,5-dimethyl-1,4-cyclohexadiene **79** was treated with pyridinium chlorochromate in dichloromethane and gave no cyclised product **80** (see scheme 3.1). This was disappointing because Nishiyama and co-workers[105] had reported the effective transformation of (Z)-2-butene-1,4-diols to substituted furans by this method (see scheme 3.4).



Scheme 3.4: ***Pyridinium chlorochromate cyclisation of (Z)-2-Butene-1,4-diol***

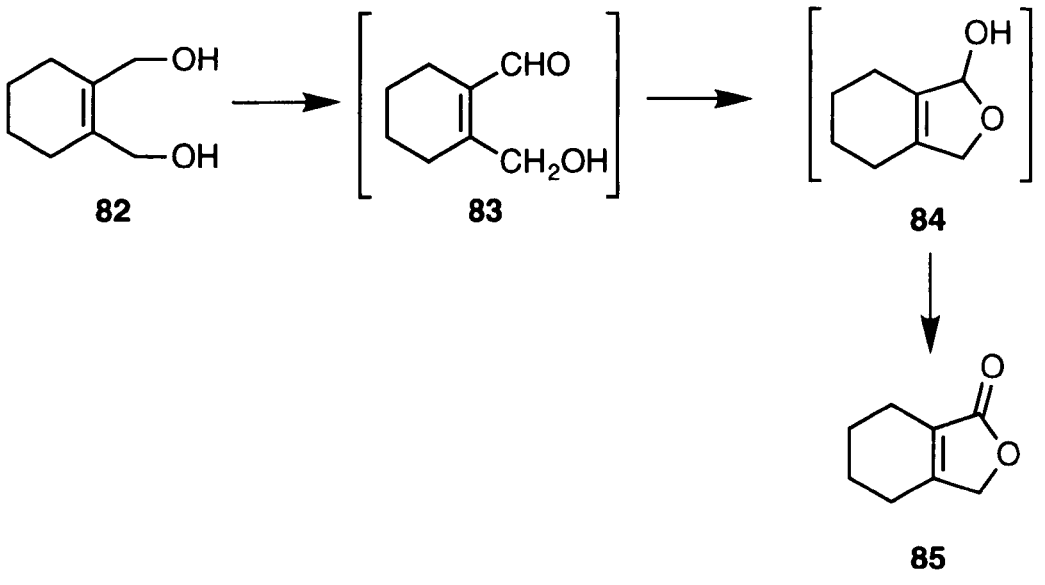
The pyridinium chlorochromate oxidises only one of the alcohol groups to give the intermediate **81** which cyclises to give the hemiacetal and dehydrates to give the furan.



Scheme 3.5: Transformation of (Z)-2-Butene-1,4-Diol to Furan via Pyridinium Chlorochromate.

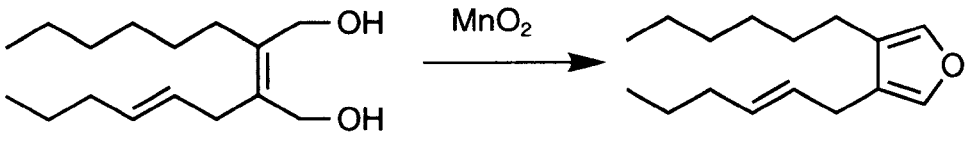
This is similar to the Paal-Knorr intermediate (see section 2.7.1). The intermediate from pyridinium chlorochromate involves one carbonyl and one alcohol and a 1,4-elimination whereas the Paal-Knorr intermediate involves two carbonyls and a 1,2-elimination of water.

Since the pyridinium chlorochromate route of cyclisation was not successful, attempts were made using manganese dioxide as the oxidant . An early paper by Butina and co-workers[106] showed that oxidation of the analogous diol **82** initially gave the monoaldehyde **83** which then cyclised to the 5-membered lactol **84**. Butina found, however, that rather than eliminating water to give the furan, the lactol underwent a second oxidation to the lactone **85.**



Scheme 3.6: Oxidation to Lactone

However, Nishiyama reported that cyclisation of diol **86** to the corresponding furan can be achieved using manganese dioxide.



86

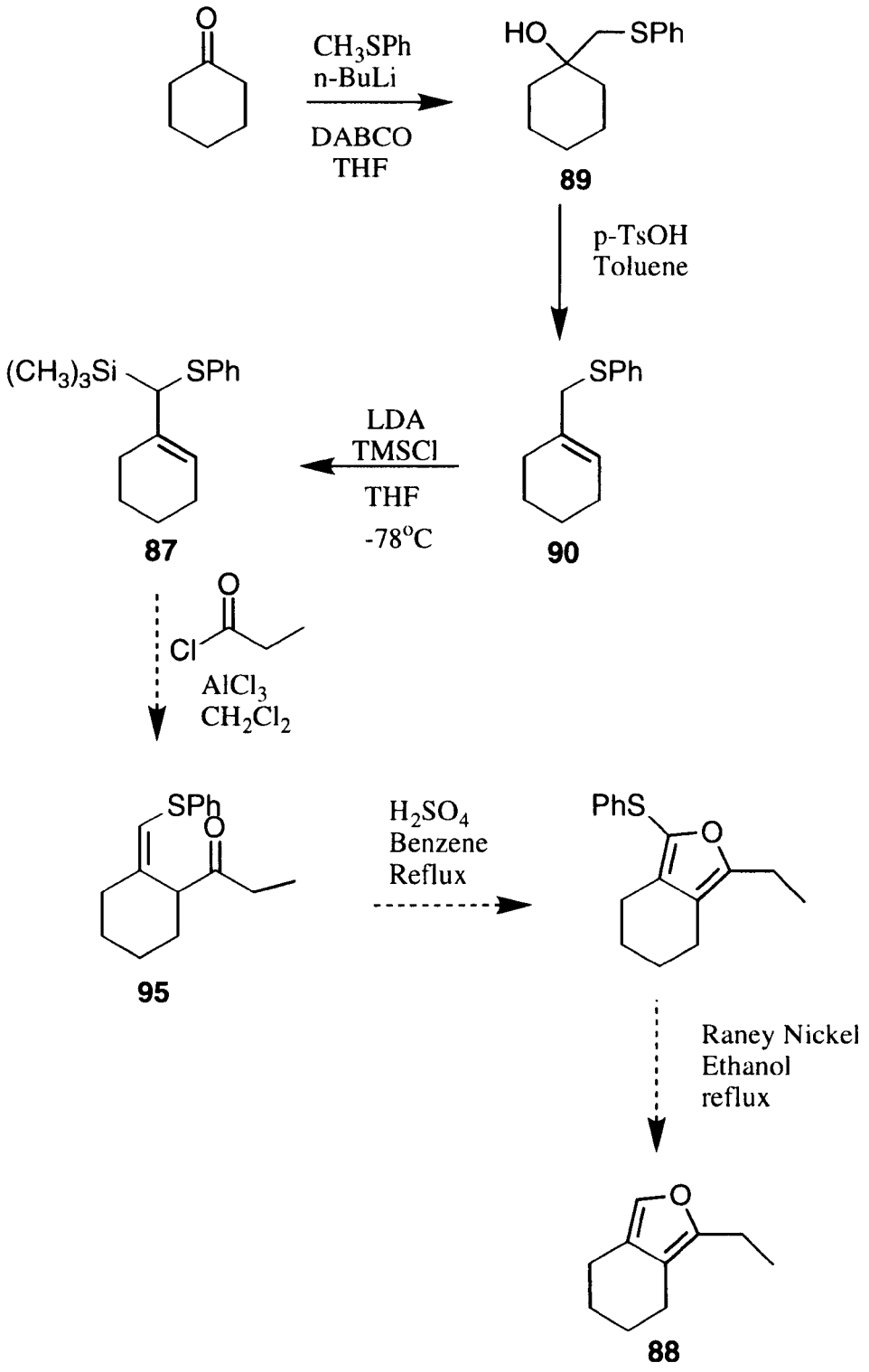
Scheme 3.7: Oxidation of (Z)-2-Butene-1,4-diol* via *Manganese Dioxide

Despite using 10 equivalents of manganese freshly prepared dioxide from manganous sulfate and potassium permanganate, diol **79** failed to cyclise to give the desired furan. The scheme was therefore abandoned.

3.2 SYNTHESIS *VIA* ALLYLIC SULPHIDES

An alternative route to fused furans was set out by Hiroi and Sato[107] and is outlined in scheme 3.7.

Furan annulation occurred *via* the aluminium chloride catalysed acylation of allylic phenyl sulfide **87** followed by refluxing with sulfuric acid and benzene. Finally reductive desulfurisation with Raney Nickel removed the unwanted α-phenylthio group from the furan to give the desired furan **88**. We therefore proceeded to follow Hiroi and Sato's work in detail below.



Scheme 3.8: Furan Annelation* via *Allylic Sulphides

3.2.1 THIOANISOLE ADDITION TO CYCLOHEXANONE

Cyclohexanone was treated with the anion generated by *n*-butyl lithium and thioanisole at 0°C to give the cyclohexanol **89**. Hiroi and Sato used diazabicyclo[2.2.2]octane (DABCO) in their system. In our hands, however good yields (81%) and fast reactions occurred both with and without the addition of DABCO.

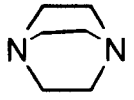


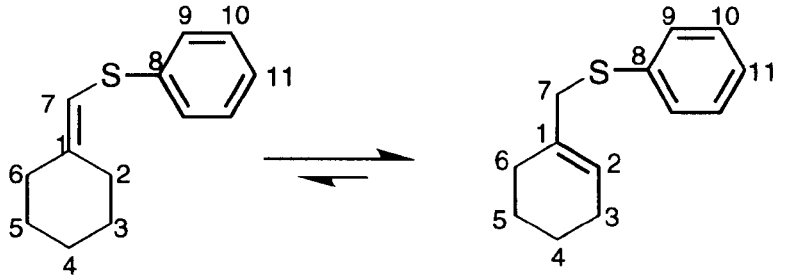
Figure 3.5: Diazabicyclo[2.2.2]octane

DABCO is a strong electron donor possessing two lone pairs and therefore co-ordinates strongly to the lithium. In THF *n*-butyl lithium exists in both trimeric and dimeric forms so this co-ordination helps to break up these clusters thus accelerating the reaction.

The ^1H nmr spectrum of cyclohexanol **89** showed a broad singlet at $\delta 1.98$ corresponding to the hydroxyl group. In addition to the peaks at $\delta 7.07$ for the phenyl and the multiple at $\delta 1.3$ for the cyclohexane ring there was a singlet at $\delta 2.89$ integrating for 2 protons which corresponds to the CH_2 group adjacent to the sulfur. This data together with the notable absence of the carbonyl stretch and the appearance of the hydroxyl at 3400 cm^{-1} confirmed that the expected product **89** had been formed.

3.2.2 DEHYDRATION OF 1-(PHENYLTHIOMETHYL)-CYCLOHEXANOL

Dehydration was effected using Dean and Stark conditions with toluene and *p*-toluenesulfonic acid. During the dehydration there can be seen to be two possible routes for water elimination, giving the double bond either *endo* or *exo* to the cyclohexane ring. Hiroi reported that only 1-(phenylthiomethyl)cyclohexene **90** was formed whereas we also managed to isolate phenylthiomethylidenecyclohexane **91**, the *exo* isomer, as a minor product.



91 **90**

EXO ENDO

Scheme 3.8: Equilibrium Between Major and Minor Isomers

This regioselectively occurs because under acidic conditions the *endo* **90** and the *exo* **91** isomers will be in equilibrium, with the more thermodynamically stable *endo*-isomer being predominant[108]. The two nmr spectra of these compounds are quite different from one another as shown in table 3.1.

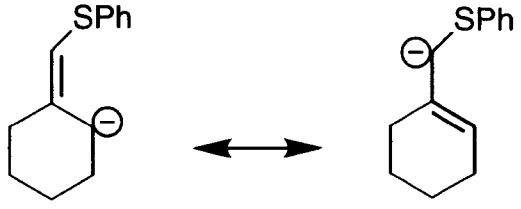
H	*ENDO* **90** δ ppm	*EXO* **91** δ ppm
2	5.51	2.5
3,4,5,6	1.1	2.5
7	3.46	5.78
9,10,11	7.12	7.2

Table3.1: Nmr Constants for the Exo and Endo Isomers

The most notable change is H-7 and H-2 arising from the different *exo* and *endo* positions of the double bond. The olefinic proton in each case is found further downfield at approximately δ5.5. This can be attributed to the anisotropy of the double bond.

3.2.3 SILYLATION OF 1-(PHENYLTHIO(TRIMETHYLSILYL)-METHYL)CYCLOHEXENE

Treatment of the mixture of 1-(phenylthiomethyl)cyclohexene **90** and its isomer **91** with lithium diisopropylamide (LDA) and trimethylsilyl chloride afforded 1-(phenylthio(trimethylsilyl)methyl)cyclohexene **87** in 38% yield. Separation of the *endo* and *exo* isomers was not essential as when treated with LDA both isomers generate the same allylic anion as shown in scheme 3.9.



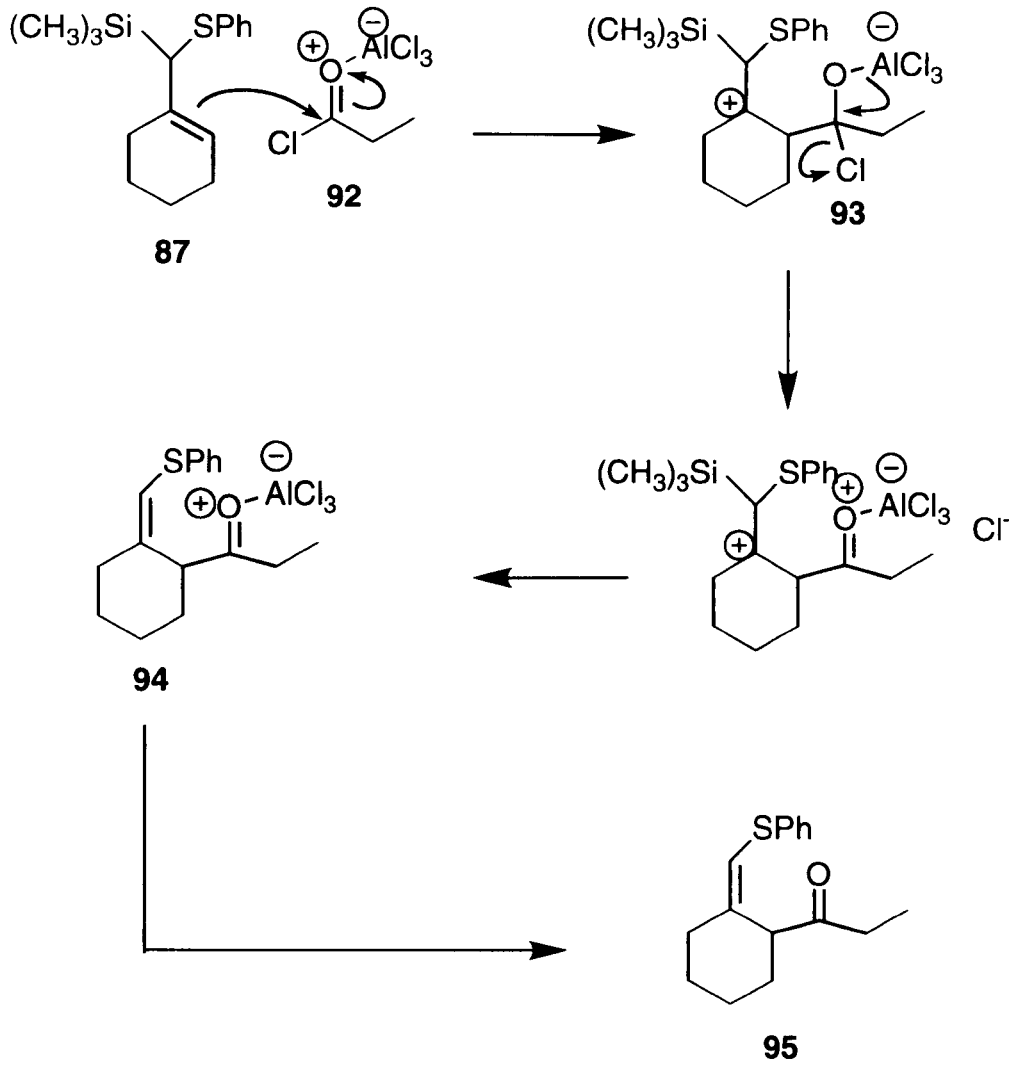
Scheme 3.9: Common Allylic Anion Through Resonance

The nmr for the silylated compound **87** (see scheme 3.8) is similar to the *endo* compound with a large singlet at δ0.15 corresponding to the TMS group. Addition of the TMS group does not cause a significant change in the chemical shift of the neighbouring proton.

3.2.4 ALUMINIUM CHLORIDE CATALYSED ACYLATION

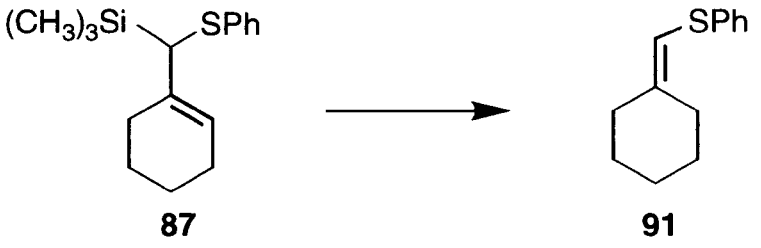
Several attempts at acylation of 1-(phenylthio(trimethylsilyl)methyl)cyclohexene **87** to give 2-propanoyl-1-phenylthiomethylenecyclohexane **95** were made. The mechanism

of the desired reaction involves the formation of adduct **92** between the propanoyl chloride and the aluminium chloride. The double bond of the cyclohex-1-ene ring attacks the adduct at the carbonyl to form the stabilised β-silyl cation **93**. Overall loss of trimethylsilylchloride gives **94** and aqueous work up would then give 2-propanoyl-1-phenylthiomethylene cyclohexane **95**



Scheme 3.10: Proposed Acylation to give 2-Propanoyl-1-Phenylmethylene cyclohexane

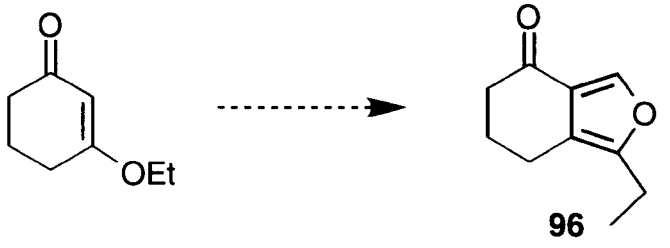
In all cases despite careful drying of reagents the desired compound **95** was not isolated. Instead the procedure produced only the the exocyclic olefin **91** (scheme 3.11):



87 91

Scheme 3.11:Transformation to Exocyclic Olefin

Attempts using titanium tetrachloride as an alternative Lewis acid were made but again the exocyclic olefin was obtained. If this method of furan annulation had been successful the route would have been repeated using the protected form of cyclohexa-1,3-dione which would have given the target **96**. This transformation is shown in scheme 3.12:

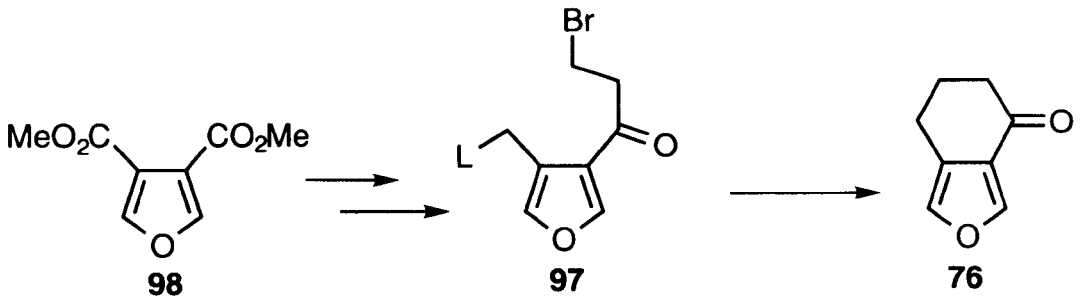


96

Scheme 3.12: Proposed Furan Annulation via Allylic Sulphide Route using Cyclohexa-1,3-dione

3.3 ATTEMPTED SYNTHESIS OF FURAN (76)*VIA* AN INTRAMOLECULAR GRIGNARD - METHOD ONE

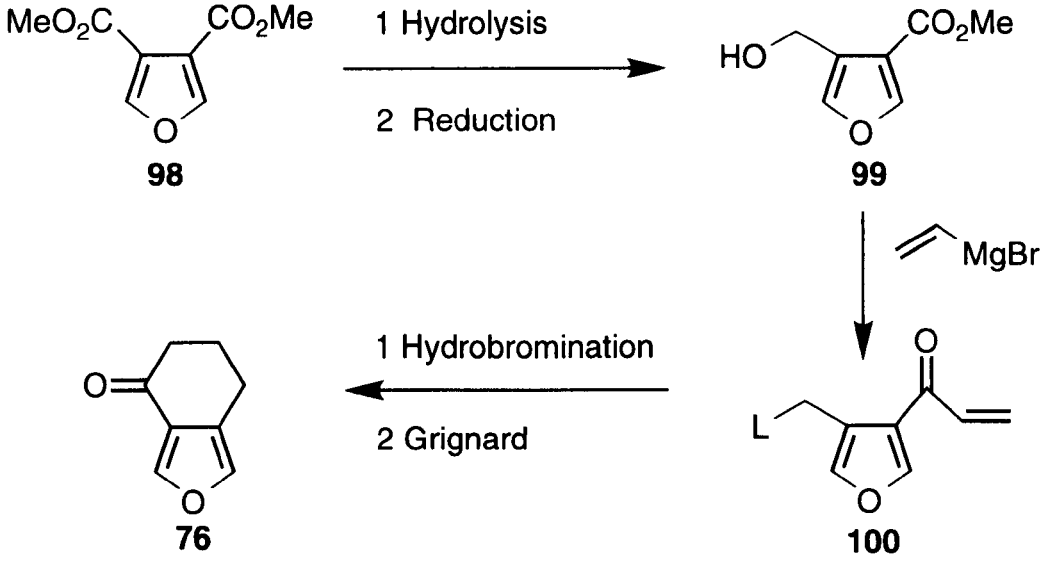
Given the difficulties encountered in assembling the furan ring it was decided to start with an intact furan nucleus and build on the cyclohexane portion. This approach involves the cyclisation *via* an intramolecular Grignard. Ideally an intermediate of general structure **97** is desired in order to allow ring closure.



where L = good leaving group

Scheme 3.13: Proposed Synthesis to Target Furan via Intramolecular Grignard

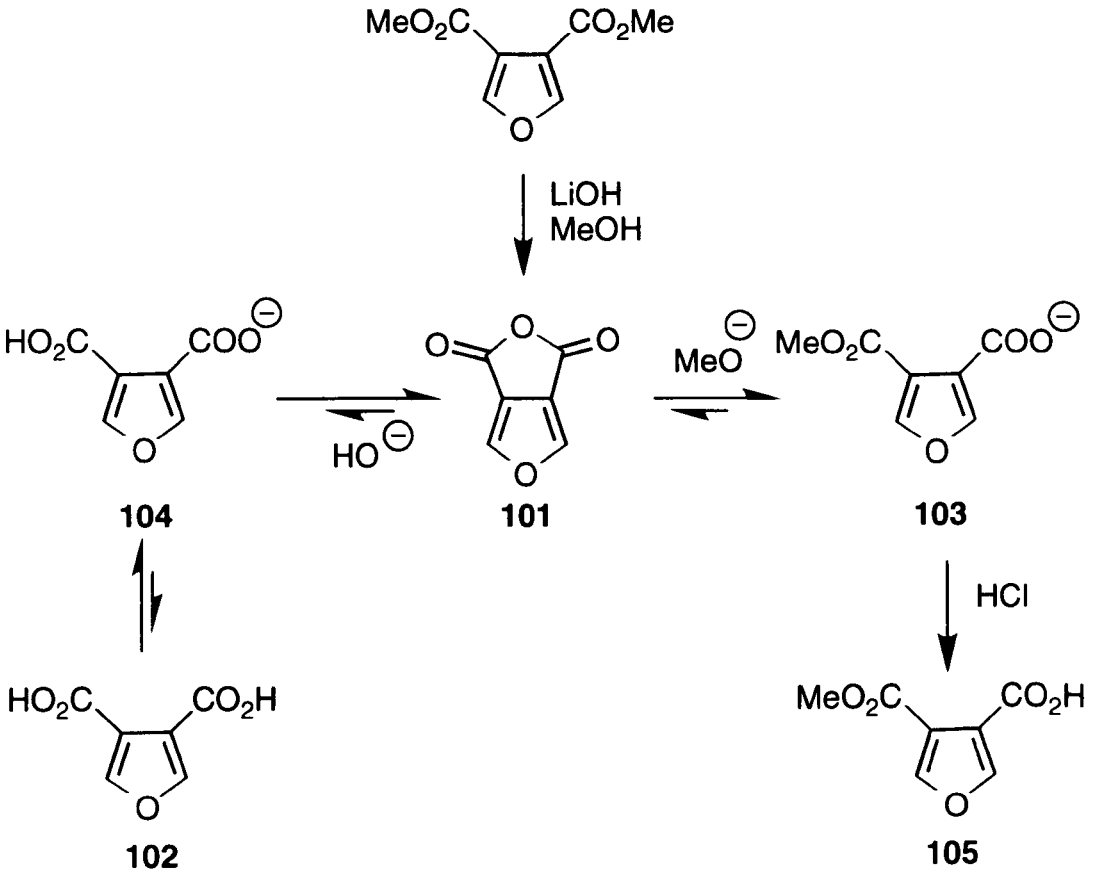
The first attempt considered was to mono hydrolyse selectively dimethyl furan-3,4-dicarboxylate **98**. Once obtained the acid could then be selectively reduced to the alcohol **99**. Attack with vinylmagnesium bromide at the ester and the conversion of the hydroxyl group into a better leaving group would give the desired intermediate **100**. Hydrobromination followed by the intramolecular Grignard would give the desired furan **76**.



Scheme 3.14: Proposed Synthesis to Target Furan 76 via Mono-hydrolysis of Di-ester

3.3.1 SELECTIVE HYDROLYSIS OF ESTER FUNCTION

Initial attempts to differentiate between the two methyl groups were made by forming the cyclic anhydride **101**. The first attempt used the mild base lithium hydroxide in methanol. The main assumption of this mechanism is that under basic conditions the anhydride **101** will predominate and not the unwanted *bis*-acid product **102**. This is shown more clearly in scheme 3.15:

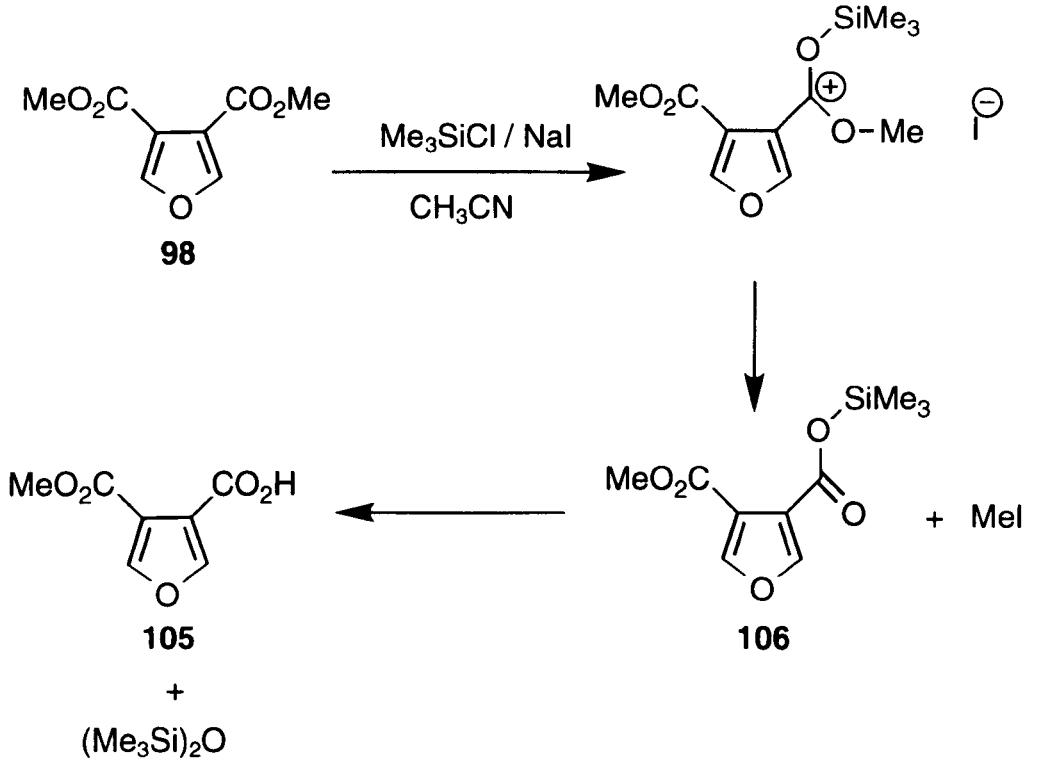


Scheme 3.15: Proposed Selective Mono-hydrolysis via Lithium Hydroxide

The hydroxide anion is a better leaving group than the methoxide anion and therefore there will be a drive to form intermediate **103** rather than **104**. Acidic work up would then give the desired product **105**. This method however proved to be

unsuccessful and a second attempt to form the anhydride using concentrated sulfuric acid was tried. Again product **105** was not formed.

A final attempt using trimethylsilyl iodide was tried and was found to be successful (see scheme 3.16).



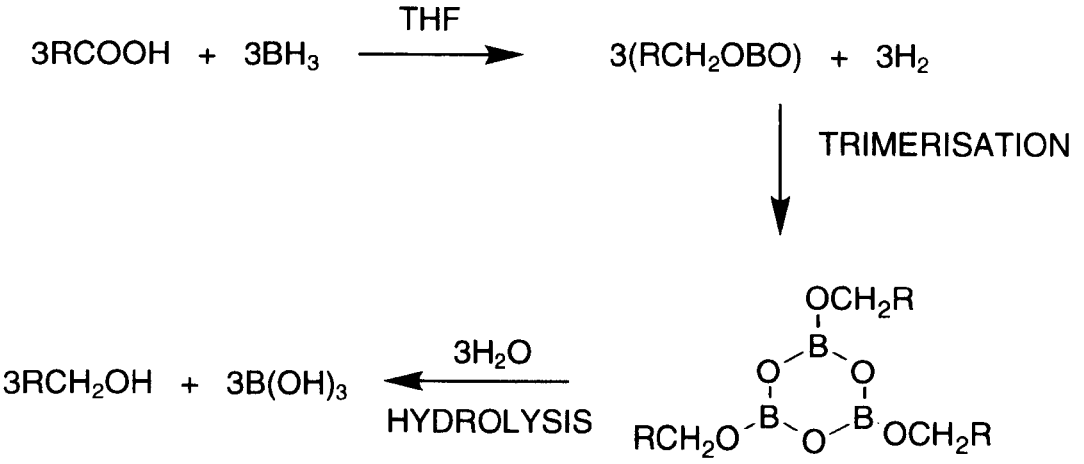
Scheme 3.16: Selective Mono-Hydrolysis via Trimethylsilyl iodide

Trimethylsilyl iodide was made *in situ* by refluxing trimethylsilyl chloride and sodium iodide in acetonitrile. Addition of the dimethyl furan-3,4-dicarboxylate **98** gave the silyl ester **106** *via* the intermediate iodide salt. The main driving force for this is the formation of the strong silicon-oxygen bond. Hydrolysis of the silyl ester **106** with aqueous work up afforded the product which was isolated as the sodium salt by extraction into sodium bicarbonate. Acidification of the aqueous layer gave the product **105**. The molecular ion of 170.0205 corresponding to $C_7H_5O_5$ combined

with ^{1}H and ^{13}C nmr spectra showing an unsymmetrical furan confirmed the structure of the product.

3.3.2 ATTEMPTED SELECTIVE REDUCTION OF ACID GROUP IN PRESENCE OF ESTER

Carboxylic acids can be reduced to the corresponding alcohol by a variety of methods including metal hydrides such as lithium aluminium hydride.[109] The problem with these reducing agents is they will reduce the ester function as well as the acid. Reports by Yoon and fellow workers[110] indicated that it was possible to reduce acids in the presence of other functional groups including esters using a borane.THF complex in mild conditions. The acid **105** was therefore treated with BH_3.THF to attempt to form the trialkoxyboroxine intermediate as shown in scheme 3.17. On hydrolysis this should have given the alcohol and boric acid.



Scheme 3.17: Reduction of Acid with BH3.THF

However this reaction was not successful and alcohol **99** was not isolated.

As an attempt to reduce the acid group with sodium borohydride also failed, other methods were looked at. Kim and co-workers[111] indicated that it was possible to

reduce acid chlorides in the presence of other functional groups such as acid anhydrides, acids and esters. Reduction of the acid in the form of its acid chloride using two different forms of zinc-modified cyanoborohydride prepared by two different methods was attempted.

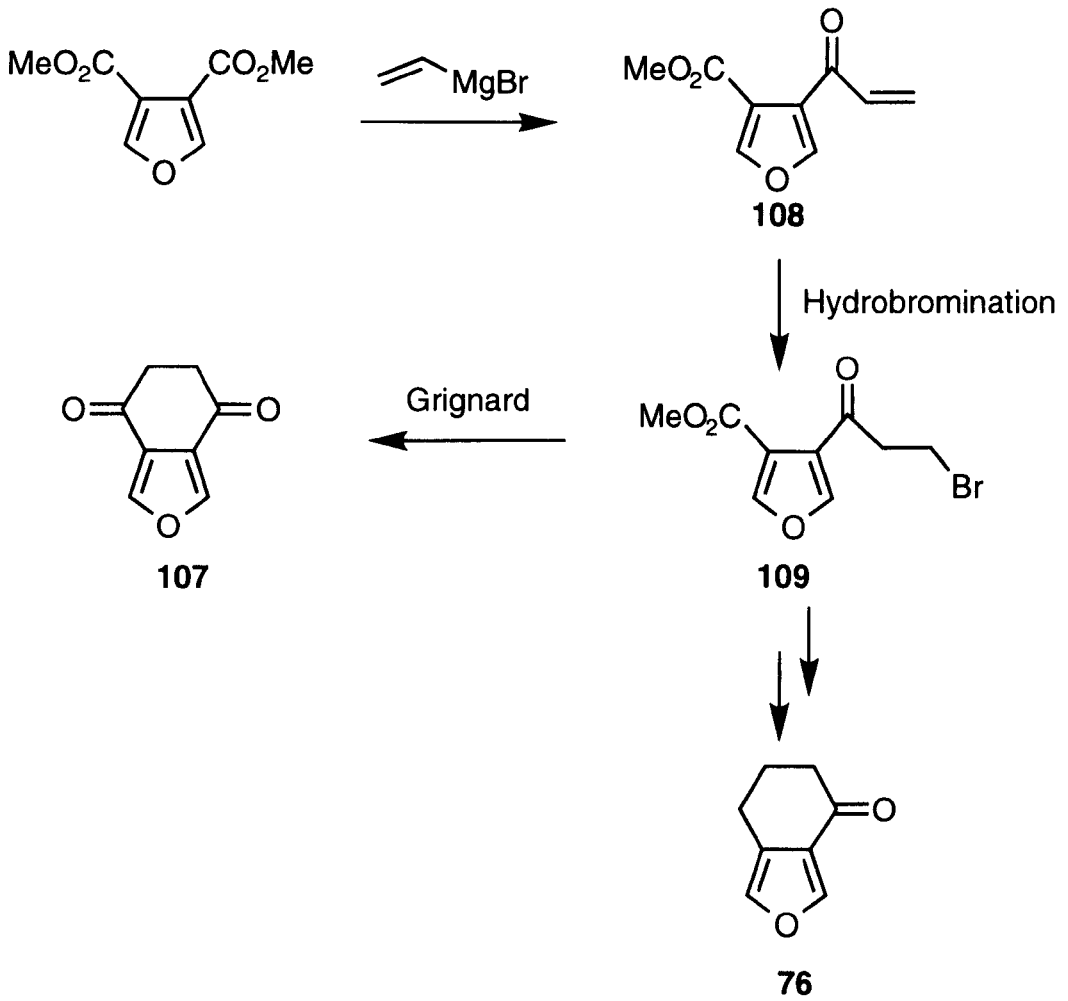
First the acid chloride was prepared by refluxing the acid in THF and a large excess of thionyl chloride for 4 hours. The zinc-modified cyanoborohydride was prepared using a 2:1 mixture of sodium cyanoborohydride and zinc choride in THF. A white precipitate was formed which according to Kim did not contain much of the reducing power. The reducing agent was soluble in THF so the supernatant solution was transferred from the reaction flask into the acid chloride. The resulting solution was stirred for 48 hours after which time no reaction had occurred.

A second attempt at preparing the zinc-modified cyanoborohydride was made. This time diethyl ether was used as the reaction medium. The reagent was prepared in the same way as previous attempt and a white slurry was again observed. This time according to Kim this slurry should contain 90% of the reducing power and very little contained in the diethyl ether. At first Kim believed that the slurry formed was sodium chloride but when the reagent was prepared in methanol no slurry was obtained. From this Kim drew the conclusion that the zinc-modified cyanoborohydride was the white slurry and that this reagent was made up of a mixture of $Na[ZnCl(BH_3CN)_2]$, $Na_2[ZnCl_2(BH_3CN)_2]$, $Na[Zn(BH_3CN)_3]$ and $Zn(BH_3CN)_2$ rather than pure $Zn(BH_3CN)_2$ as the reducing species.

In light of this the acid chloride prepared was syringed into the flask containing the slurry of zinc-modified cyanoborohydride in diethyl ether. Unfortuntely again no reaction was observed and so this reaction was abandoned.

3.4 ATTEMPTED SYNTHESIS OF FURAN (76) *VIA* AN INTRAMOLECULAR GRIGNARD- METHOD 2

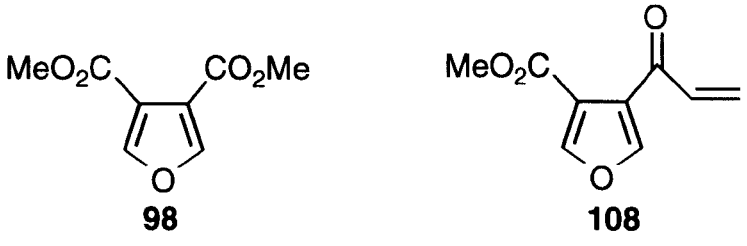
An alternative synthesis to structure **76**, and the similar compound **107**, follows the methodology shown in scheme 3.18. Since only one of the ester groups was selectively hydrolysed as described in section 3.3.1 it was thought that dimethyl furan-3,4-dicarboxylate could be selectively attacked at only one ester group by vinylmagnesium bromide to give the intermediate **108**. Hydrobromination of **108** followed by an intramolecular Grignard reaction would give **107.** Alternatively conversion of the ester moiety to a good leaving group would allow a Grignard cyclisation similar to that in scheme 3.14 to give **76**.



Scheme 3.18: Alternative Synthesis to Ketofuran 76 via an Intramolecular Grignard

3.4.1 GRIGNARD ATTACK USING VINYLMAGNESIUM BROMIDE

A solution of dimethyl furan-3,4-dicarboxylate in THF was treated with vinyl-magnesium bromide and as expected the desired mono-ester **108** was isolated as a yellow oil. Structure identification by ^{1}H nmr showed clearly the signals due to the vinyl protons at δ5.16 and δ6.06 (showing the expected coupling pattern). The ^{13}C nmr spectrum showed the presence of two distinct carbonyls with peaks at δ165.5 and δ178.1 for the ester and the ketone repectively. Signals due to olefinic carbons at δ114.8 and δ129.3 were also observed. Even when the furan was treated with an excess of Grignard reagent still there was attack at only one ester site. This can be explained by the relative electron-withdrawing properties of the ester and ketone functions.



98 **108**

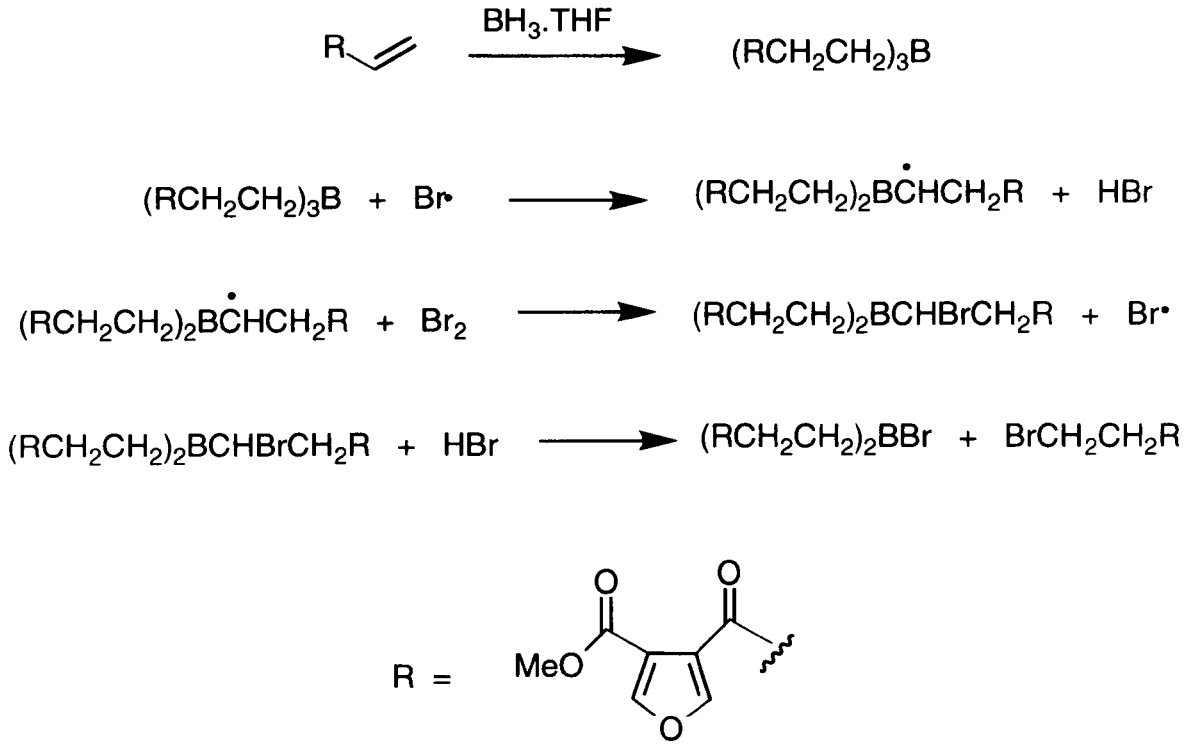
Figure 3.7: Comparison of Ester and Enone

The ketone fragment in product **108** is less electron withdrawing than the corresponding ester in starting material **98**. The ester group in the product is therefore less vulnerable to nucleophilic attack.

3.4.2 ATTEMPTED HYDROBROMINATIONS

Hydroboration followed by bromination should provide an excellent route to the anti-Markovnikov hydrobromination of the double bond. The first hydroborating agent to be considered was borane (used as a 1M solution in THF).[112] An excess of this

reagent was added to the ketone **108**. The reaction was then wrapped in aluminium foil to exclude light and the bromine added. Tlc indicated that many products had been formed as well as a considerable amount of baseline material. The mechanism involves free-radical bromination as shown in scheme 3.19 and does not involve the simple rupture of the carbon-boron bond by bromine.

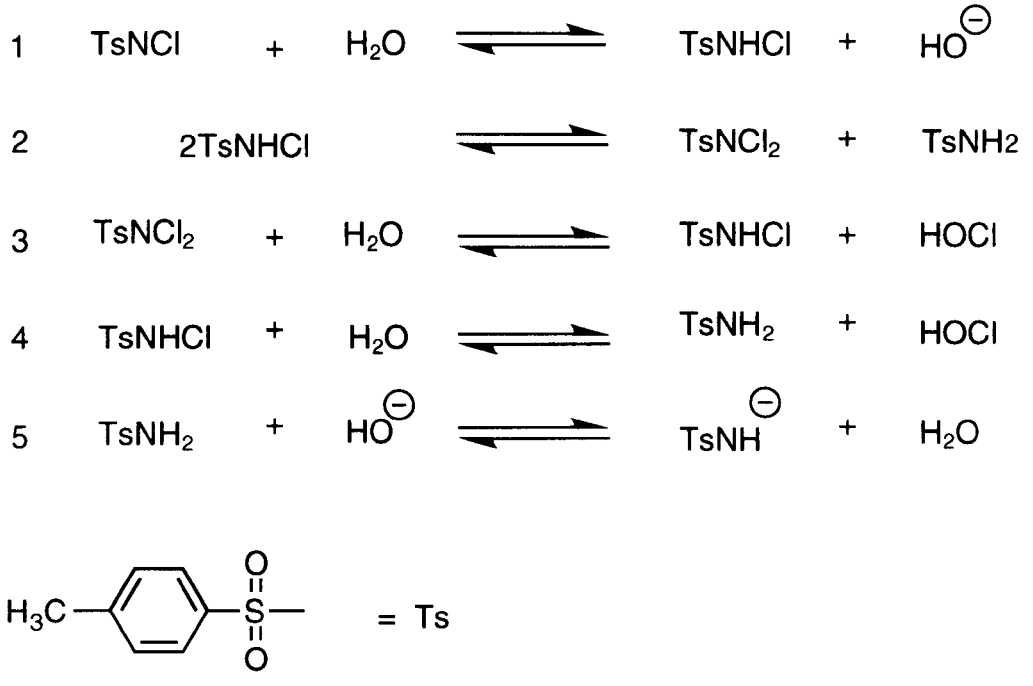


Scheme 3.19: Mechanism of Anti-Markovnikov Hydrobromination

As this reaction proved to be unsuccessful the same reaction was repeated using dicyclohexylborane as the hydroborating species.[113] Dicyclohexylborane is normally used in systems where there are more than one double bond present. Because of its large steric bulk dicyclohexylborane will selectively hydroborate the less sterically hindered double bond. However, in our case we simply wanted to hydroborate the only double bond present in the molecule. Two different methods were used for dicyclohexylborane. The first involved addition of the alkene solution to the preformed dicycohexylborane solution. After allowing to stir for 2 hours light was excluded and a solution of bromine was added and stirred for a further 1 hour at O°C

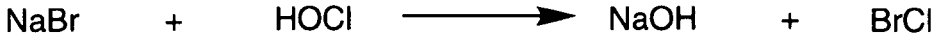
before being quenched with water. Tlc indicated that no product had been formed. This method was repeated but light was not excluded and the reaction worked up using sodium methoxide in methanol. Again no product was formed.

As the brominations using molecular bromine were proving troublesome a different brominating species was used. Bromine chloride was generated *in situ* from the reaction between chloramine-T and sodium bromide.[114] The first stage of the reaction involves the reaction between chloramine-T and water to generate hypochlorous acid as shown in scheme 3.20.



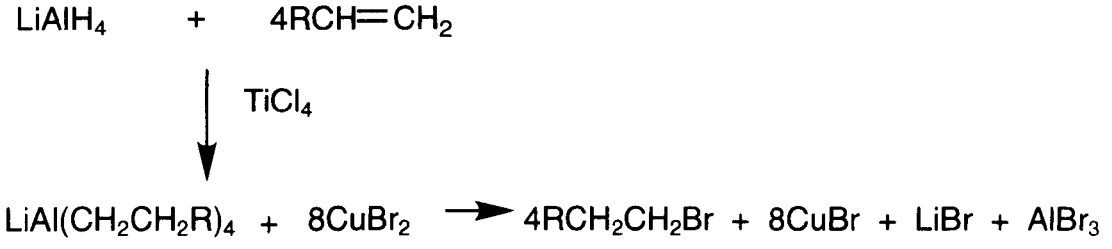
Scheme 3.20: Generation of Hypochlorous Acid via Chloramine-T

As can be seen hypochlorous acid is generated in steps 3 and 4. This is an excellent source of positive chlorine which will react with sodium bromide to give bromine chloride as shown below:



Hydrochloric acid was added to neutralise the excess sodium hydroxide generated. However, this method failed to produce the desired brominated product **109**.

As the brominations *via* hydroboration were not proceeding as expected attention was turned to different methods of anti-Markovnikov hydrobromination. Hydroalumination involving lithium aluminium hydride was looked at.[115] The overall reaction equation is shown in scheme 3.21:



Scheme 3.21: Reduction of Alkene via Hydroalumination

No mechanistic investigation has been carried out but it has been assumed that the reaction proceeds by two separate steps:

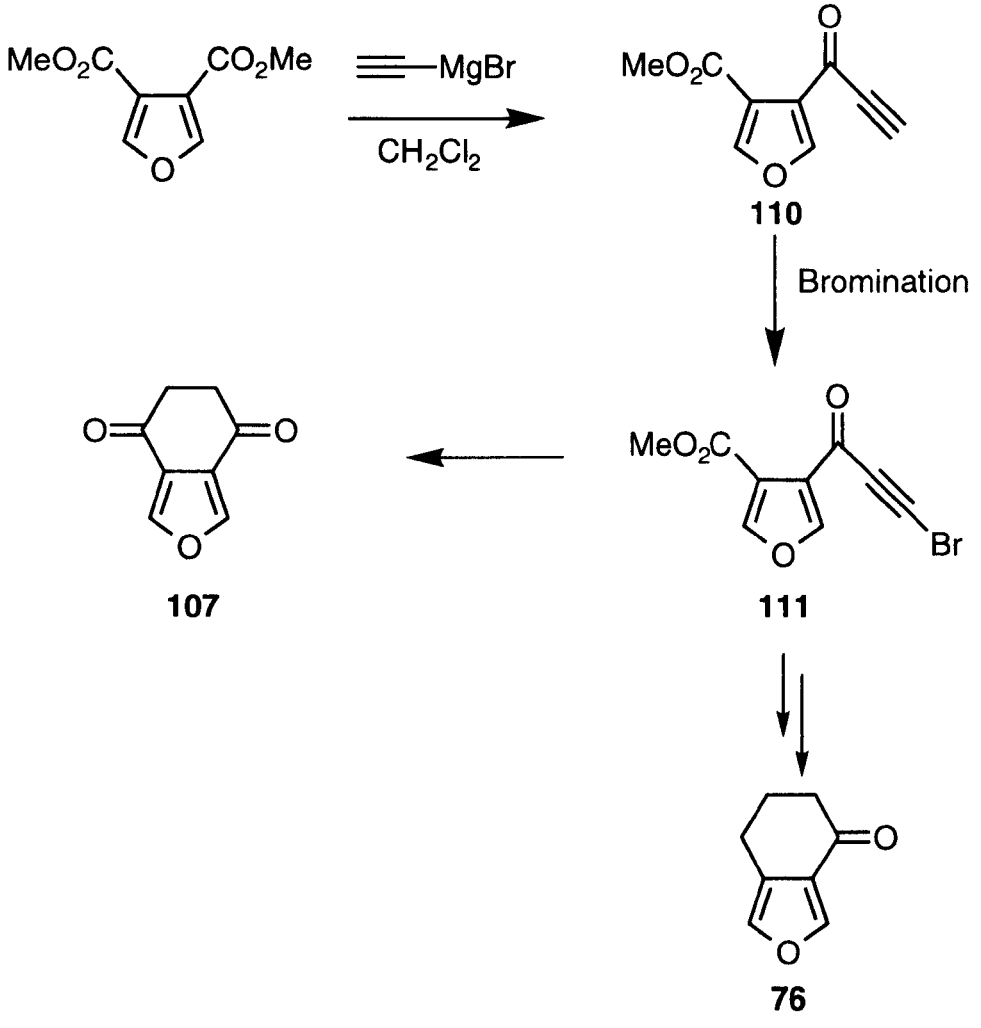
1 formation of an alkyl radical either by direct electron transfer oxidation of a carbon-aluminium bond by the copper(II)halide or via homolytic decomposition of the alkyl copper intermediate produced by the reaction of the alkylaluminium with copper(II)halide.

2 alkyl radical then reacts with a second equivalent of the copper (II) halide by a ligand transfer process.

When we tried to hydrobrominate **108** using this method it failed to give us our desired hydrobrominated compound **109**. Due to the unsuccessful nature of this reaction scheme it was subsequently abandoned.

3.5 ATTEMPTED SYNTHESIS OF KETOFURAN (76) VIA AN INTRAMOLECULAR GRIGNARD - METHOD THREE

The methodology for this route follows that of the vinyl route as described in section 3.4. An outline of this is shown in scheme 3.22.



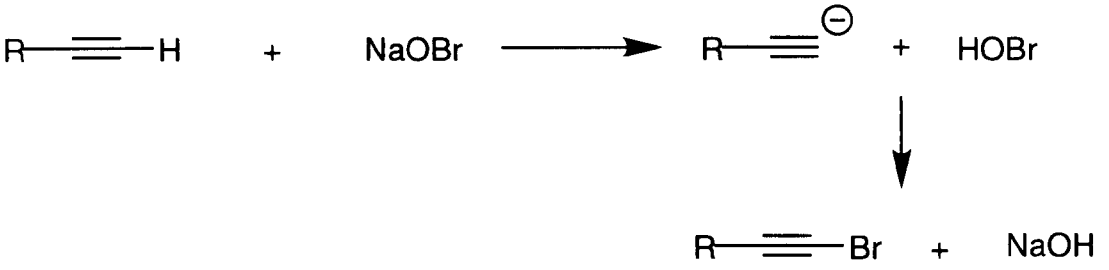
Scheme 3.22: Route to Target Furan via Acetylene

3.5.1 GRIGNARD ATTACK USING ETHYNYLMAGNESIUM CHLORIDE

Dimethyl furan-3,4-dicarboxylate **98** was treated with ethynyl magnesium chloride giving the mono-ketone **110**. Despite using several equivalents of ethynyl magnesium chloride the reaction did not go to completion and a mixture of the product **110** and starting material **98** was isolated. The ^1H nmr spectrum showed a singlet for the ethynyl proton at δ1.7 and peaks at δ7.2 and δ7.6 for the two furan protons. In addtion to these, there were also peaks corresponding to the starting material. Several attempts were made to purify the mixture by column chromatography but all gave inadequate separations and therfore futher characterisation was not attempted It was therefore decided to carry the mixture through to the bromination stage in the hope that the brominated product would be sufficiently more polar than the starting material allowing satisfactory separation, purification and characterisation.

3.5.2 ATTEMPTED BROMINATIONS OF ACETYLENIC KETONE

Early literature has shown that terminal acetylenes can be brominated using hypobromite solutions.[116,117] The sodium hypobromite solution was prepared by adding bromine to an aqueous solution of sodium hydroxide. The acetylene **110** was then added to the hypobromite solution and the hypobromite ion should have abstracted a proton to leave the sodium salt of the acetylene. The anion of the acetylene should then have attacked the bromine of the hypobromous acid to give the brominated acetylene **111** and sodium hydroxide. This is shown in scheme 3.23.



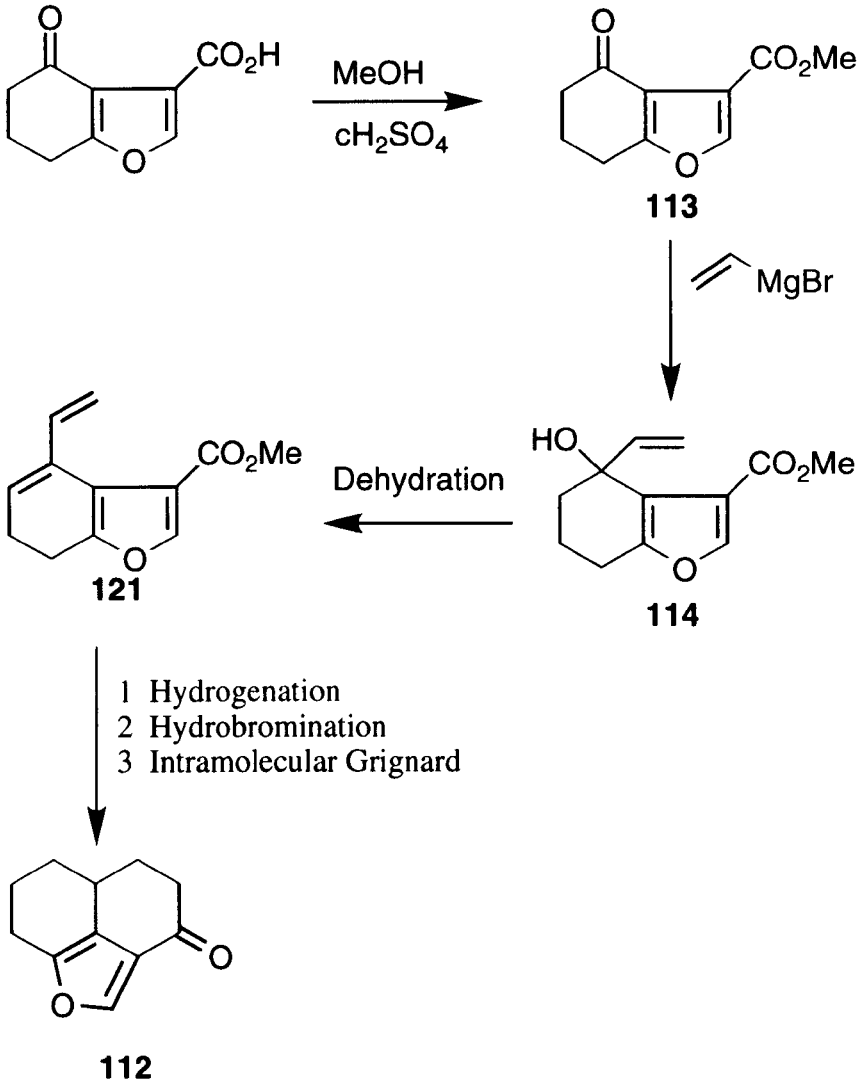
Scheme 3.23: Bromination of Acetylene via Sodium Hypobromite

However this reaction proved to be unsuccessful in our system.

Attention was therefore turned towards the possibility of brominating the acetylene *via* the lithium acetlylide which had previously been well documented.[118] Deprotonation of our acetylene was carried out in THF at -78°C using *n*-butyl lithium. Treatment of this lithium acetylide with molecular bromine as the bromination agent would have been expected to give the desired bromoacetylene **111**. However, careful addition of the bromine at -20°C with the exclusion of light did not give the desired product. Instead a complex mixture of products were formed which could not be isolated. This attempt using lithium acetylide was repeated using *N*-bromosuccinimide (NBS) as the source of bromine. NBS releases bromine steadily but still no desired brominated product was formed.

3.6 ATTEMPTED SYNTHESIS OF FURAN (112)

This section describes the attempted synthesis of target molecule **112** which is structurally similar to the target diketofuran **77**. Esterification of 4,5,6,7-tetrahydro-4-oxobenzo[*b*]furan-3-carboxylic acid will protect the acid during the attack by vinylmagnesium bromide on the ketone. This also provides a better leaving group for the anticipated intramolecular Grignard later in the synthesis (see scheme 3.24).



Scheme 3.24: Synthesis to Target Furan via Dehydration

3.6.1 ESTERIFICATION AND GRIGNARD ATTACK

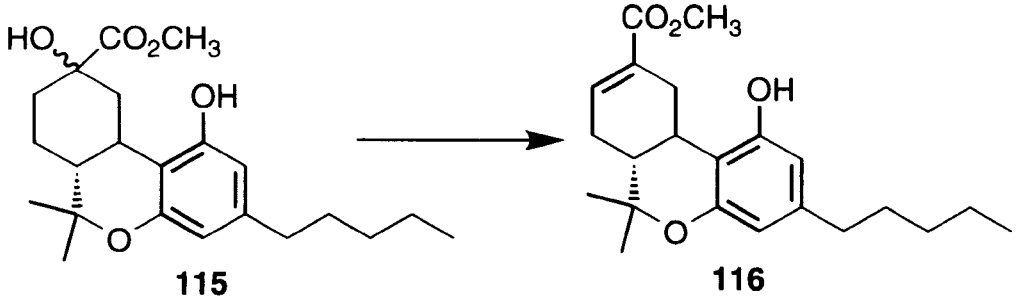
Esterification of 4,5,6,7-tetrahydro-4-oxobenzo[*b*]furan-3-carboxylic acid was successfully achieved using a catalytic amount of concentrated sulfuric acid in methanol. Identification of the methyl ester **113** was by primarily by nmr and mass spectroscopy. The most notable feature in ^{1}H nmr spectrum was the singlet at δ3.78 corresponding to the methyl ester. The ^{13}C nmr spectrum showed the presence of two carbonyls with peaks at δ161.4 and δ192.0 corresponding to the ester and ketone

respectively. These data together with accurate mass and elemental analysis confirmed the structure of the ester.

Grignard attack with vinylmagnesium bromide successfully gave **114**. The attack was exclusively at the ketone and not at the ester group as expected since ketones are, in general, more reactive towards nucleophiles than esters. The structure of the alcohol was confirmed by both infra-red and nmr spectroscopy. Infra-red showed the presence of only one carbonyl with a signal at 1714 cm^{-1} corresponding to the ester. Each of the olefinic protons was observed as a doublet of doublets occurring at δ4.7, δ5.07 and δ6.08.

3.6.2 ATTEMPTED DEHYDRATION OF TERTIARY ALCOHOL

The alcohol was first treated with thionyl chloride in the presence of pyridine in an attempt to effect the dehydration. This method is known to be effective for dehydrating tertiary alcohols. Schwartz and Madam[119] demonstrated its use in dehydrating the hindered alcohol **115** to give cyclohexene **116** as shown in scheme 3.25.

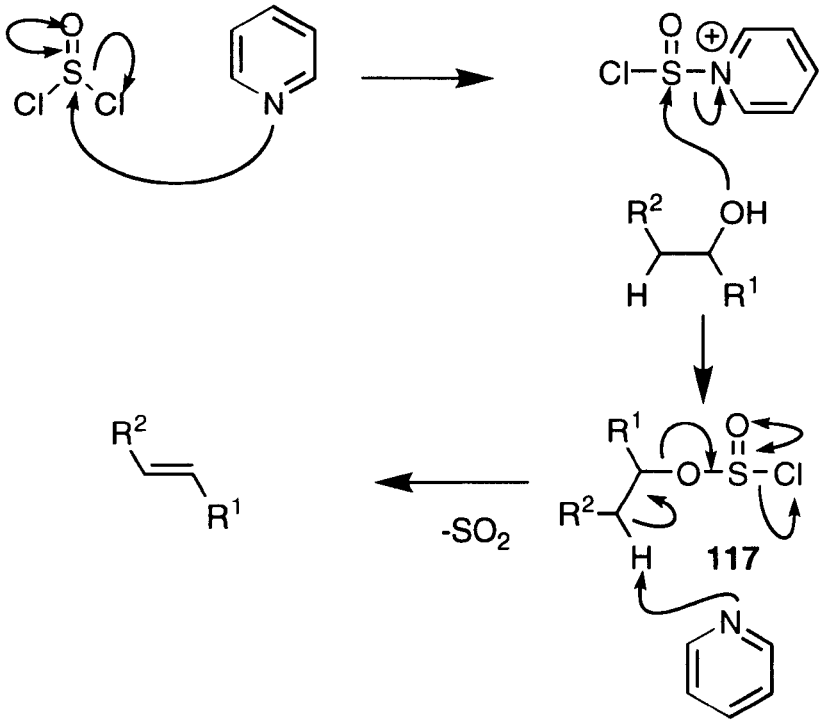


115 **116**

Scheme 3.25: Dehydration of Hindered Alcohol via $SOCl_2$ and Pyridine

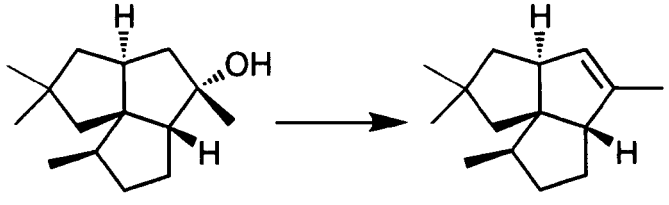
The mechanism for this dehydration is fairly simple with the thionyl chloride-pyridine complex reacting with the alcohol to form an alkyl chlorosulfate **117** (scheme 3.26).

Removal of the proton β– to the alcohol by pyridine leading to the elimination of sulfur dioxide and the chloride ion gives the desired olefin. Unfortunately, however, this was not effective for our system.



Scheme 3.26: Chlorination of alcohol via $SOCl_2$ and Pyridine

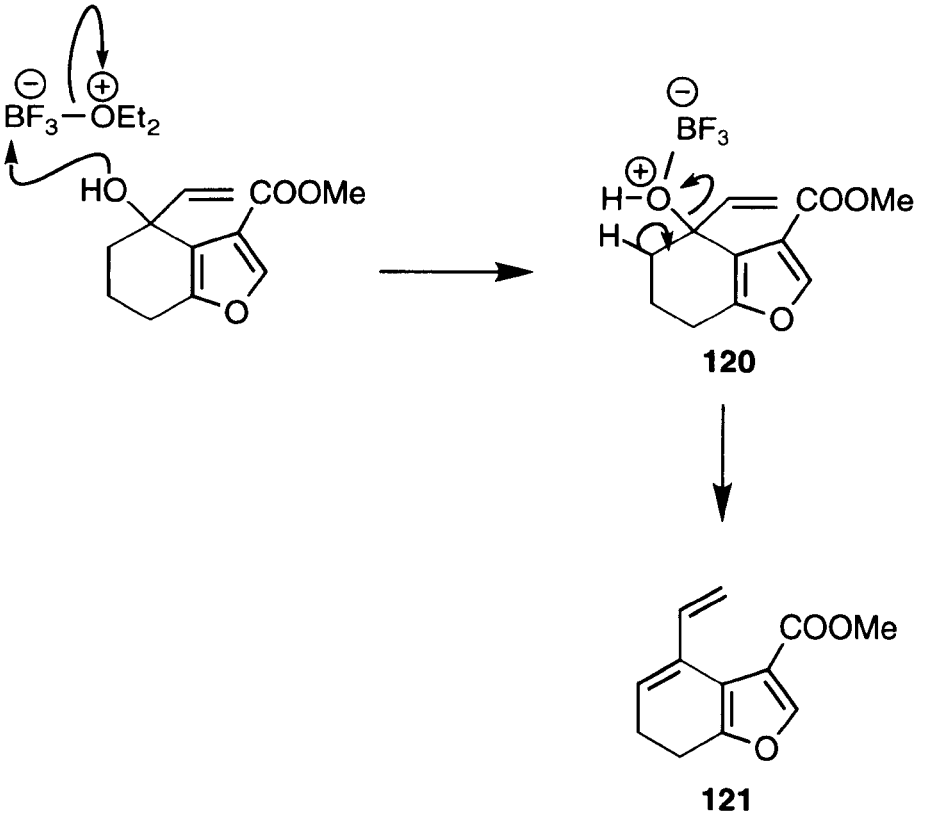
Traditional methods of dehydration were also tried including acid catalysis using *para*-toluene sulfonic acid and concentrated sulfuric acid, but these all proved to be ineffective despite literature precedence[120]. Boron trifluoride was then tried as Hua[121] had previously used this to dehydrate the alcohol **118** to give (+) pentalenene **119**.



118 **119**

Scheme 3.27: Synthesis of (+)Pentalenene via Dehydration using BF_3OEt_2

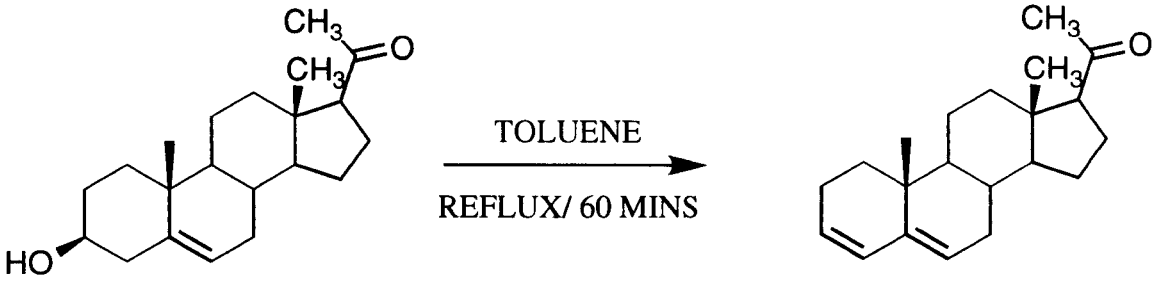
As boron trifluoride is a Lewis acid it accepts electrons and readily forms a complex **120** which will readily eliminate to form the olefinic product **121**.



Scheme 3.28: Mechanism of Dehydration via $BF_3.OEt_2$

However all attempts using this reagent was proved to be unsuccessful and starting material was recovered in all cases.

Copper (II) sulfate adsorbed onto silica gel was tried as a final attempt at dehydration. Although it is widely known that anhydrous Copper (II) sulfate can be used to dehydrate alcohols under fairly drastic conditions,[122,123] a paper by Nishiguchi and co-workers[124] demonstrated that dehydration of alcohols can occur under mild conditions through a silica-supported copper(II)sulfate catalyst. An example of the use of this is shown in scheme 3.29.

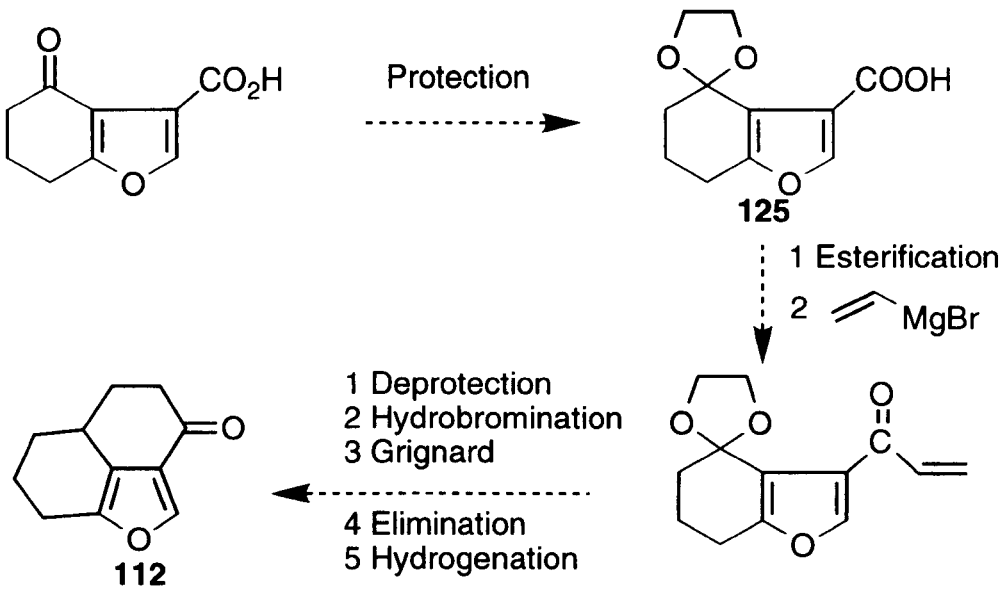


Scheme 3.29: Example of Dehydration via Silica Supported Copper(II) Catalyst.

A solution of copper sulfate in water was pre-adsorbed onto silica by removal of the water *in vacuo*. Activation of the catalyst was achieved by heating in an oven at 150°C for 2 hours. This catalyst was then added to a solution of the alcohol in cyclohexane and stirred for 1 hour. Tlc unfortunately indicated the presence of baseline material. Using potassium hydrogen sulfate gave a product which was possibly the desired alkene **121** but this could not be identified as it readily decomposed on standing. This backed the growing suspicion that this compound was highly unstable and subject to polymerisation. This route was therefore abandoned.

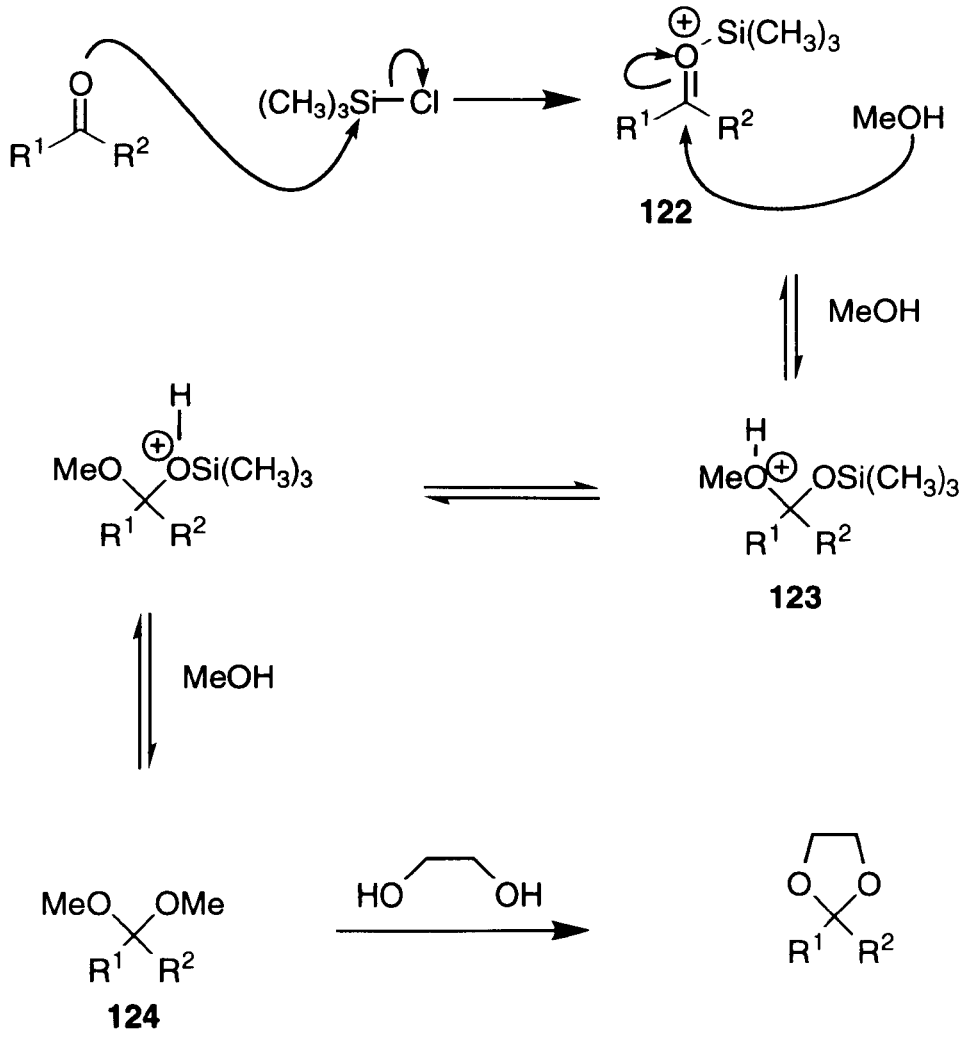
3.7 ALTERNATIVE SYNTHESIS TO TARGET FURAN(112)

The final attempt in this series was based on similar methodology as outlined in section 3.6. Attempts at protecting the carbonyl were therefore made in the hope that if this were successful then the Grignard vinyl magnesium bromide could selectively attack only the methyl ester. This would then allow bromination followed by an intramolecular Grignard to give the target **112** as seen in scheme 3.30.



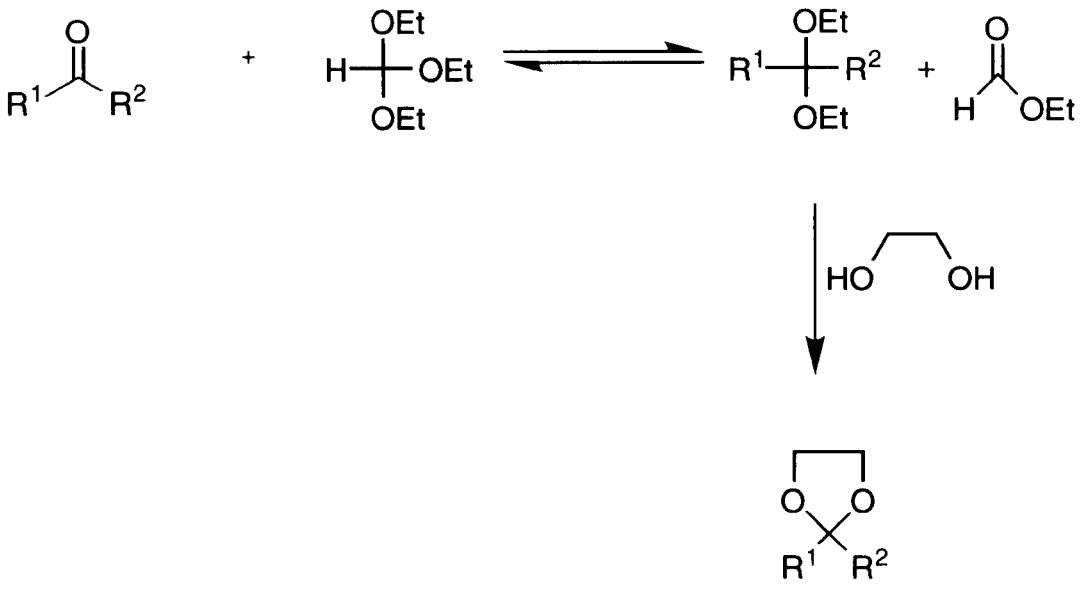
Scheme 3.30: Ketal Protection in Attempted Synthesis to Furan 112

Attempts at protecting the ketone carbonyl were first made using trimethylsilyl chloride, ethylene glycol and methanol.[125] As can be seen in the mechanism (scheme 3.31) the ketone carbonyl should first attack the silicon with expulsion of a chloride ion to form the intermediate **122**. This intermediate has a strong silicon-oxygen bond with a stabilised carbocation β to the silicon. Methanol then attacks the oxonium ion to give **123** which undergoes proton transfer followed by a second methanol attack to give the dimethyl ketal **124**. Transacetalation with ethylene glycol would give the desired protected ketone **125**. However only starting material was recovered. Changing to neat ethylene glycol or an ethylene glycol/dichloromethane mixture showed no improvement and starting material was still recovered.



Scheme 3.31: Ketal Protection via TMSCl and Ethylene Glycol

Due to the unsuccesful nature of the trimethylsilylchloride and ethylene glycol system a different approach was tried using triethyl orthoformate[126]. In this case the ketone was treated with the triethyl orthoformate and should have given the diethyl ketal **126** and ethyl formate as shown in scheme 3.32. Again transacetalation with ethylene glycol should have given the desired protected ketone but in all attempts using this method only starting material was recovered.



Scheme 3.32: Ketal Protection via Trimethylorthoformate and Ethylene Glycol

A final attempt using ethylene glycol and oxalic acid was tried but again no product was formed. Since the formation of the acetal was proving to be troublesome this scheme was abandoned.

3.8 CONCLUSION

Athough several attempts were made to make the target furans (such as **76**) all were unsuccessful. Attention was therefore turned to making a simpler compound but with the active component of the lead compounds still intact. This strategy is examined in chapter 4.

CHAPTER 4

As attempts to make the 3,4-disubstituted furans as described in chapter 3 were unsuccessful we decided to investigate routes to making the 3,5-disubstituted furans with the backbone shown in figure 4.1.

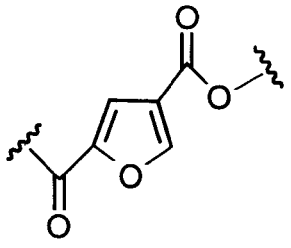
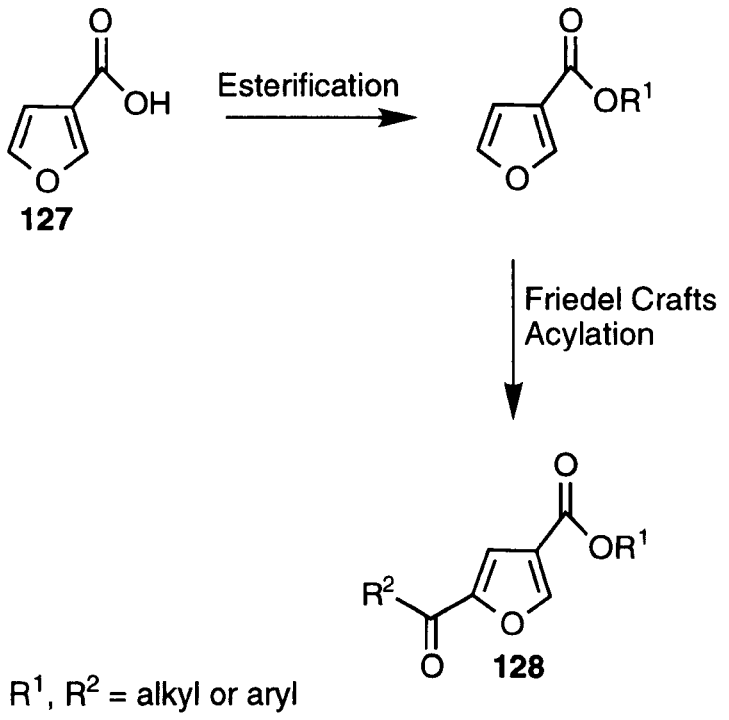


Figure 4.1: Target 3,5-Disubstituted Furan

These compounds which contain the pharmacophore of the lead natural products could then undergo biological testing.

4.1 SYNTHESIS OF 3,5-DISUBSTITUTED FURANS VIA FRIEDEL-CRAFTS ACYLATION

A simple approach to forming 3,5-disubstituted furans is to start with the commercially available 3-furoic acid **127**. Esterification followed by Friedel-Crafts acylation would provide access to compounds with the desired 3,5-dicarbonyl arrangement **128** as shown in scheme 4.1.



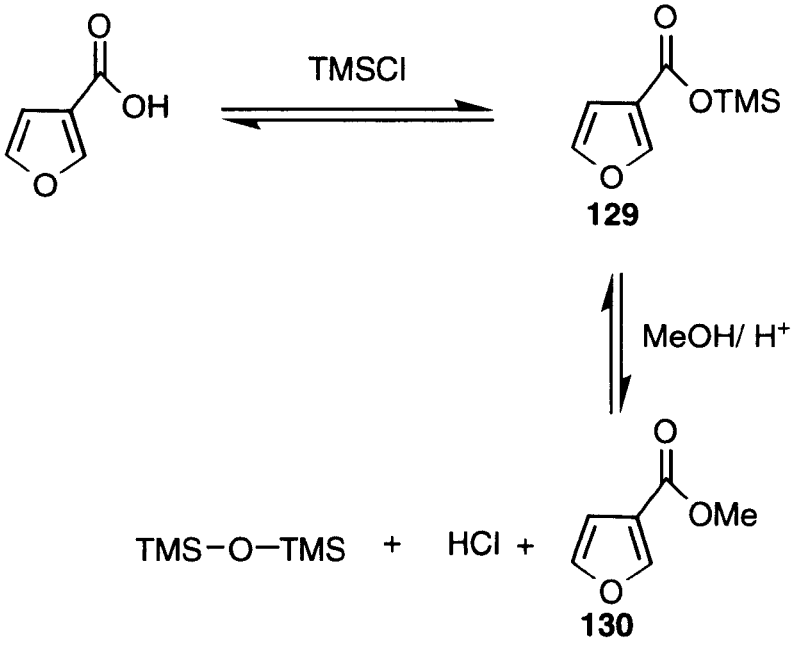
Scheme 4.1: Esterification and Friedel-Crafts Acylation Leading to Target 3,5-Disubstituted furan

4.1.1 ESTERIFICATION OF 3-FUROIC ACID

METHYL 3-FUROATE

Two methods to make methyl 3-furoate **130** were used. The traditional way of forming esters using methanol and concentrated sulfuric acid gave the desired methyl ester but in a poor 38% yield. An unusual approach utilising the mild conditions set out by Brook and Chan[127] involving the generation of a silyl ester intermediate proved to be more successful. Thus, chlorotrimethylsilane reacted with the 3-furoic acid to give the silyl ester **129** and hydrochloric acid. Displacement of the silanol group with methanol then afforded methyl 3-furoate **130**. The 57% yield obtained was higher than that obtained with the traditional method. Methyl 3-furoate was isolated as a colourless oil which exhibited the expected sharp singlet in the ^{1}H nmr

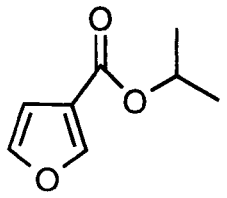
spectrum at δ 3.74 for the methyl ester and a carbonyl peak at 1728 cm^{-1} in the infra-red spectrum.



Scheme 4.2: ***Esterification*** **via** ***Silyl Ester***

ISOPROPYL 3-FUROATE

Formation of isopropyl 3-furoate was first attempted *via* the silyl ester. Exactly the same conditions as for the preparation of methyl 3-furoate were used but when the resulting mixture was analysed by tlc no ester was present. The more traditional, harsher conditions of concentrated sulfuric acid in isopropanol were therefore resorted to. Isopropyl 3-furoate **131** was successfully obtained as a colourless oil in 60% yield by this method. ^1H nmr showed the distinctive septet at δ 5.07 for the single proton and a doublet at δ1.20 for the terminal methyl groups of the isopropyl group.

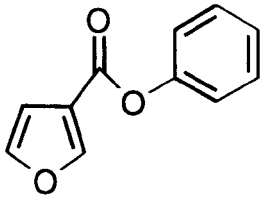


131

Figure 4.2: Isopropyl 3-furoate

PHENYL 3-FUROATE

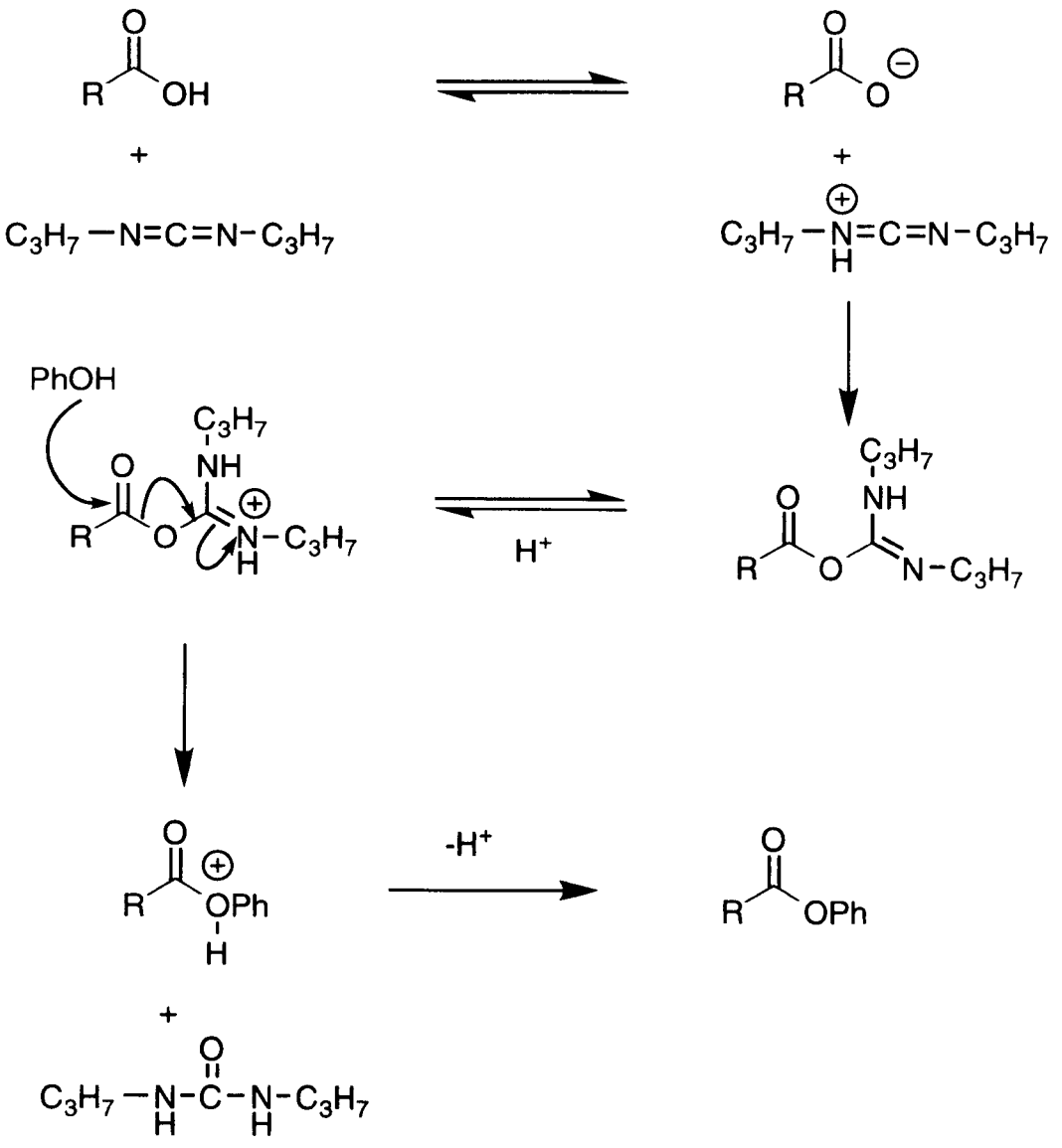
Phenyl 3-furoate **132** was formed using two different coupling agents, the first being dicyclohexylcarbodiimide[128] (DCC) which gave the product but in a very poor 38% yield. However when diisopropylcarbodiimide (DIC) was used a much better yield of 68% was acheived. Phenyl 3-furoate **132** was isolated as white crystals with a low melting point of 38°C. Usually, when isolated, it was at first in the form of a colourless oil which gradually formed white crystals on standing.



132

4.3: Phenyl-3-furoate

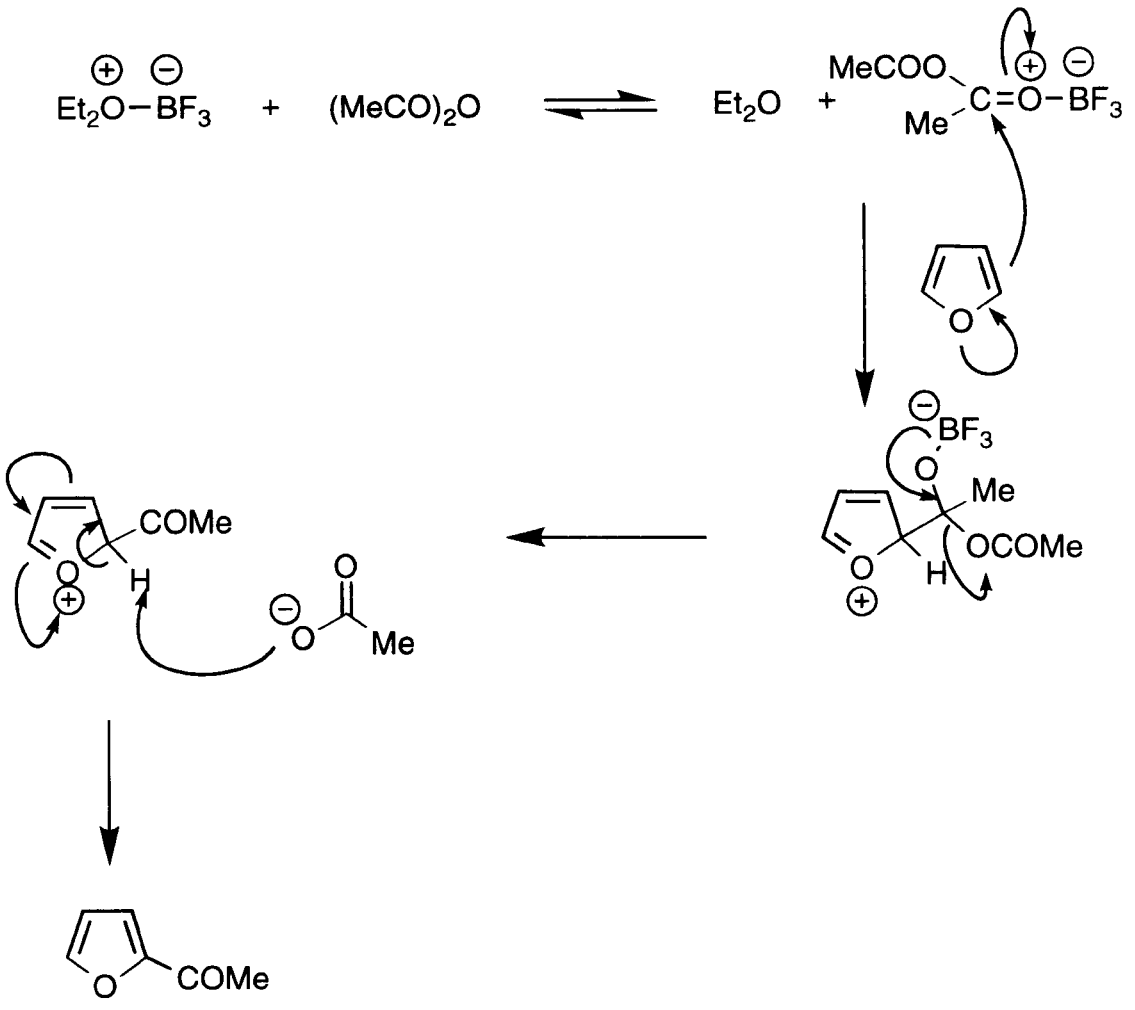
An advantage of using DIC over DCC is that with the DCC method the insoluble dicyclohexylurea is formed but using DIC the more soluble diisopropylurea is formed. The mechanism for the coupling using DIC is shown in scheme 4.2.



Scheme 4.2: Mechanism of Diisopropylcarbodiimide Esterification.

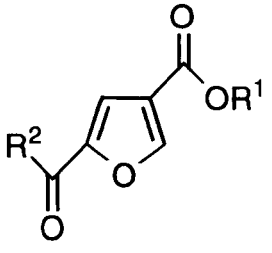
4.1.2 FRIEDEL-CRAFTS ACYLATIONS ON 3-FUROATE ESTERS

Having formed the desired 3-furoate esters a Friedel-Crafts acylation would put in place a carbonyl group at position 5 giving the desired target compounds **128**. This type of reaction has been documented extensively for the acetylation of furan at 0°C with acetic anhydride and boron trifluoride etherate.[129] The mechanism is shown in scheme 4.3.



Scheme 4.3: General Mechanism for Friedel-Crafts Acetylation

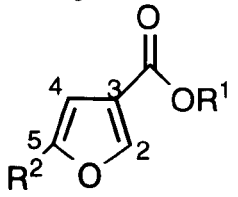
This reaction system was applied to the furoate esters but heat was required to effect the transformation. Although acetic anhydride was used to give the 5-acetyl ester derivatives, acid chlorides were used to put in other groups. The acid chlorides used were isobutyryl chloride and cyclohexylcarbonyl chloride. Table 4.1 shows the range of Friedel-Crafts derivatives made with their yields and conditions used.



	R^1	R^2	TIME HR	TEMP°C	YIELD%
133	Me	Me	0.1	50	46
134	^iPr	Me	0.1	50	32
135	Ph	Me	0.1	50	65
136	Me	^iPr	0.5	50	21
137	^iPr	^iPr	1	90	63
138	Ph	^iPr	1.5	60	52
139	Me	C_6H_{11}	1	100	60
140	^iPr	C_6H_{11}	2	90	32

Table 4.1: Reaction Conditions and Yields for 3,5 Disubstituted Furans

^1H nmr spectra in each case showed the disappearance of one of the furan signals and a change in the coupling pattern and coupling constants. Table 4.2 shows these changes for methyl 3-furoate and its respective Friedel-Crafts derivatives.



	R^1	R^2	2-H	4-H	Coupling pattern and constants (Hz)
130	Me	H	8.02	6.74	dd $J_{4,5}$ 1.88 $J_{4,2}$ 0.68 $J_{2,5}$ 1.5
133	Me	COMe	8.13	7.46	d $J_{4,2}$ 0.64
136	Me	CO^iPr	8.06	7.39	d $J_{4,2}$ 0.59
139	Me	COC_6H_{11}	7.99	7.32	Unresolved

Table 4.2: Coupling Constants and Shift Patterns for H-4 and H-2 for Methyl ester and its Friedel Craft Derivatives

As can be seen there is a downfield shift for proton 4 caused by the effect of the carbonyl at position 5 pulling away electron density from H-4 . It is consequently deshielded and shifted downfield. Additionally two carbonyl absorptions were observed at around 1650 cm^{-1} and 1720 cm^{-1} in the infra-red spectrum corresponding to the acid and ester respectively. In a normal unsubstituted furan, the coupling constants are $J_{2,3}$ 1.8, $J_{3,4}$ 3.4, $J_{2,5}$ 1.5 and $J_{2,4}$ 0.9. Comparison of these coupling constants and those of methyl 3-furoate with those in table 4.2 led us to the conclusion that the derivatives were substituted at the 5 position.

These data with the ^{1}H nmr, ^{13}C nmr and accurate mass spectra helped to confirm the identity of the various Friedel-Crafts derivatives.

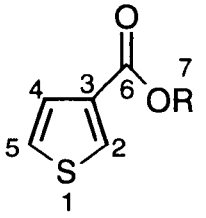
4.2 SYNTHESIS OF 3,5-DISUBSTITUTED THIOPHENES VIA FRIEDEL-CRAFTS ACYLATION

As the synthesis of the 3,5-disubstituted furan derivatives was successful the thiophene analogues were also synthesised. Once made they could then undergo biological testing to establish whether the sulfur in place of the oxygen would have any significant effect on biological activity.

4.2.1 SYNTHESIS OF THIOPHENE ESTERS

The methyl, isopropyl and phenyl esters of thiophene-3-carboxylic acid were successfully prepared using the procedures described for the esterification for 3-furoic acid. Thus, methyl 3-thiophene carboxylate **141a** was prepared in 60% yield using chlorotrimethylsilane and methanol, isopropyl 3-thiophenecarboxylate **141b** was prepared in 63% yield with isopropanol and a catalytic quantity of concentrated

sulfuric acid and finally phenyl 3-thiophenecarboxylate **141b** was prepared in 60% yield using diisopropylcarbodiimide and phenol in THF.



141a R = Me
141b R = ^{i}Pr
141c R = Ph

Figure 4.4: General Structures for Thiophene-3-carboxylate Esters

Table 4.3 shows the ^{1}H nmr details for the methyl ester for both furan and thiophene methyl esters.

H	Methyl 3-thiophenecarboxylate **141a**		Methyl 3-furoate **130**	
2	8.00	dd $J_{2,4}$ 1.08 and $J_{2,5}$ 3.02	8.02	dd $J_{2,4}$ 0.73 and $J_{2,5}$ 1.48
4	7.42	dd $J_{4,2}$ 1.01 $J_{4,5}$ 5.05	6.74	dd $J_{4,2}$ 0.68 and $J_{4,5}$ 1.88
5	7.19	dd $J_{5,2}$ 3.02 and $J_{5,4}$ 5.05	7.43	dd $J_{5,4}$ 1.72and $J_{5,2}$ 1.52
7	3.75	s	3.79	s

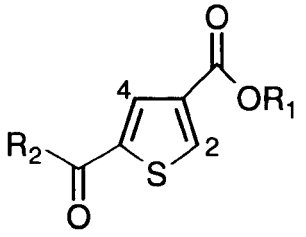
Table 4.3: Comparison of ^{1}H nmr values for Methyl 3-thiophene carboxylate with Methyl 3-furoate

The biggest difference in the spectra is the chemical shift for H-4. H-4 of methyl 3-thiophene carboxylate is shifted considerably more downfield than its H-4 in the furan analogue. This can be attributed to the relative aromaticities of the furan and the thiophene. Since the sulfur is more electropositive than oxygen it will give up its electrons more readily and will therefore contribute to the π-aromatic sextet more readily. Thiophene is therefore more aromatic than furan and so due to the increased anisotropy effect its protons are deshielded and are consequently shifted more downfield (ie higher δ). However, oxygen will inductively pull electrons away from

protons in positions 2 and 5 causing them to appear at similar shifts to those in thiophene.

4.2.2 SYNTHESIS OF THIOPHENE FRIEDEL-CRAFTS DERIVATIVES

The methyl, isopropyl and phenyl 3-thiophene carboxylate esters were treated with acetic anhydride and isobutyryl chloride in the presence of $BF_3.OEt_2$ to give the respective disubstituted Friedel-Crafts derivatives. Table 4.4 shows these derivatives with the reaction conditions and yields.



	R_1	R_2	TIME (HR)	TEMP °C	YIELD %
142	Me	Me	0.1	50	79
143	iPr	Me	2.0	70	38
144	Ph	Me	1.5	50	55
145	Me	^{i}Pr	4.0	50	57
146	iPr	^{i}Pr	2.0	90	51
147	Ph	^{i}Pr	1.5	90	20

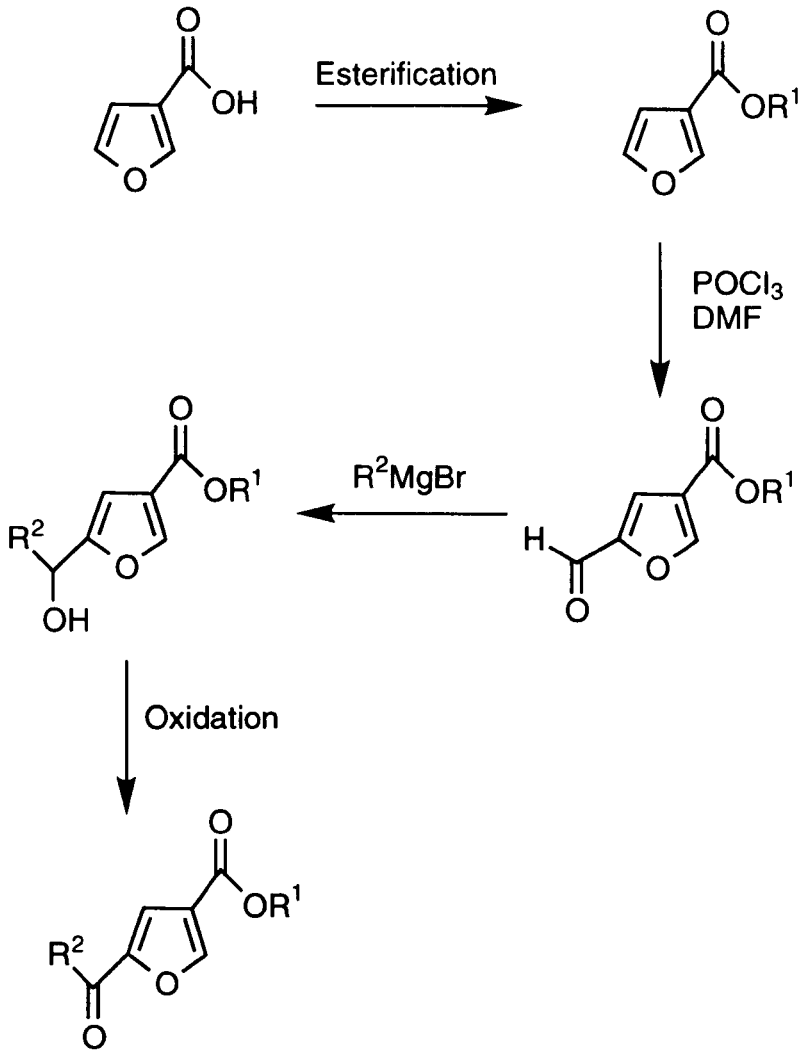
Table 4.4: Reaction Conditions for Acylation of 3-Thiophenecarboxylate Esters

Structure identification was carried out by infra-red, ^{1}H nmr and ^{13}C nmr spectroscopy. Infra-red first helped to identify the presence of two carbonyl peaks for

each of the derivatives at 1660 and 1720 cm^{-1} . The ^1H nmr spectra also showed that there were peaks present at approximately δ8.0 and δ8.4 corresponding to two thiophene protons. The coupling constants of 1.2 Hz between these thiophene signals helped to identify which isomer had been isolated. In a normal unsubstituted thiophene the coupling constants are $J_{2,3}$ 4.8 $J_{2,4}$ 1.0 $J_{2,5}$ 2.8 and $J_{3,4}$ 3.5 Hz. If, therefore, substitution had occurred at the 2 position then we would have expected to see a coupling constant of around 4.8 Hz. The coupling constant we obtained was 1.2 Hz confirming that substitution had occurred at the 5 position.

4.3 SYNTHESIS OF 3,5-DISUBSTITUTED FURANS VIA FORMYLATION

Formylation would provide an excellent starting point for a variety of 3,5 disubstituted furans which would have the two carbonyl groups in the correct positions as the target molecule. It was envisaged that these formyl derivatives could then undergo nucleophilic attack from a variety of nucleophilic reagents such as Grignard reagents to give the corresponding alcohol. Oxidation of this would give the desired 3,5-disubstituted compounds. This is summarised in scheme 4.4.

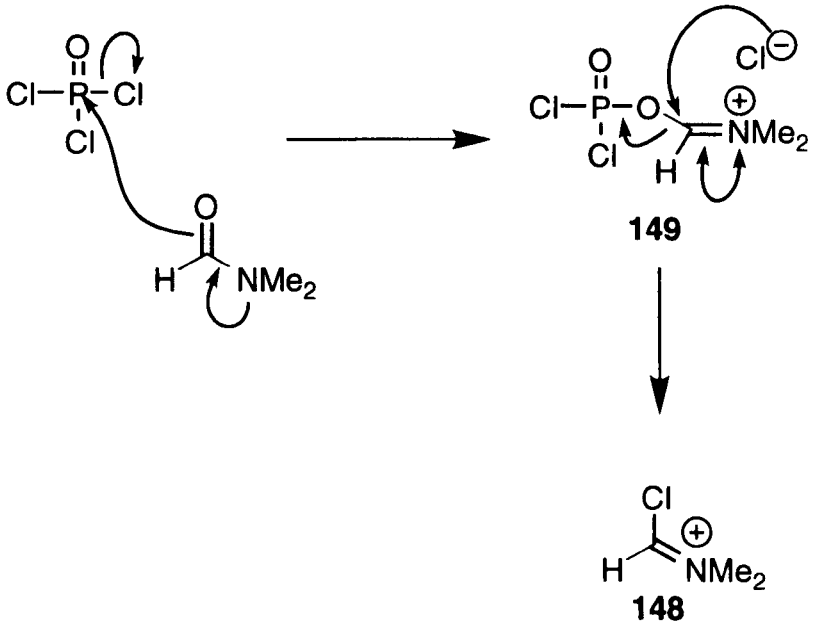


Scheme 4.4: Generation of 3,5-Disubstituted Furans* via *Formylation and Nucleophilic attack.

In the scheme, the Grignard reagent vinylmagnesium bromide was used. The secondary alcohol when oxidised would provide access to an allylic ketone which mimics the active component and the α,β-unsaturation in wortmannin giving highly-desirable compounds for biological testing.

4.3.1 VILSMEIER-HAACK FORMYLATION

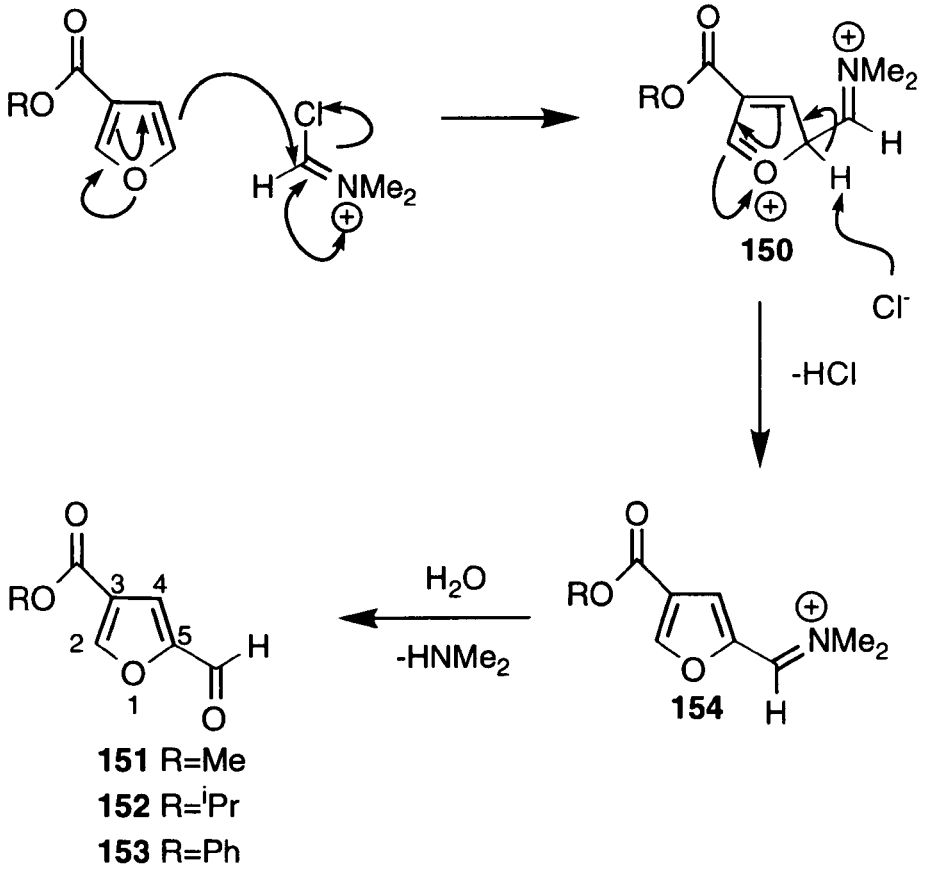
In order to introduce a formyl group at position 5 a Vilsmeier-Haack reaction[130,131] was carried out using dimethylformamide and phosphorus oxychloride to form the electrophile **148** (see scheme 4.5). Electrons from the lone pair of the dimethylamine feed in to the carbon-nitrogen bond encouraging the attack by the carbonyl oxygen on the electropositive phosphorus atom. Expulsion of a chloride ion gives intermediate **149**. Chloride attack then gives **148** as the electrophile.



Scheme 4.5: Generation of Electrophile for Vilsmeier-Haack Formylation

In our system an accurate 1:1 molar ratio of dimethylformamide and phosphorus oxychloride was required to make the yellow solid of the Vilsmeier salt. If a 1:1 molar ratio was not used then the solid did not form and on reacting the resulting yellow oil with the appropriate furoate ester no formylation was observed. However when the yellow Vilsmeier salt was efficiently formed and reacted with the appropriate furan the desired 5-formyl-3-furoate ester was obtained. The mechanism involves the initial attack from the furan on the electrophile. Deprotonation by the chloride ion

results in formation of intermediate **150** which will hydrolyse to give the desired aldehyde upon aqueous work up.

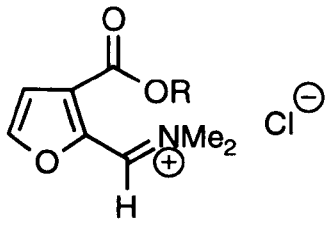


Scheme 4.6: Electrophilic attack to give 5-Formyl-3-Furoate Ester

Nmr of the 5-formyl-3-furoate esters (**151, 152, 153**) clearly indicated the presence of two compounds for substitution at the 2- and 5- positions. At this stage they could not be separated by column chromatography on silica. The ratios of the respective isomers were obtained from the nmr spectra and then confirmed by the isolation of the allylic alcohol derivatives (see table 4.5). The ratios are, however, not directly comparable with each other because of the different reaction conditions used in each case.

Attack was found to be preferentially at position 5 as expected. The intermediate **154** derived from substitution at position 5 has greater delocalisation of the positive charge than the intermediate formed on substitution at position 4. The electron withdrawing

ester groups also disfavour attack at position 2 as this would result in a positive charge at the 3 position. Steric hindrance also plays a part in the selectivity since substitution at position 2 would form the intermediate **155** in which there would be a significant steric interaction.

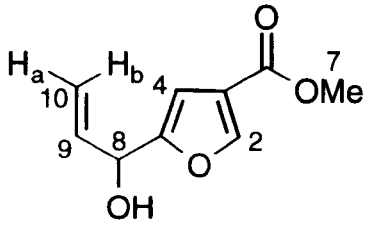


155

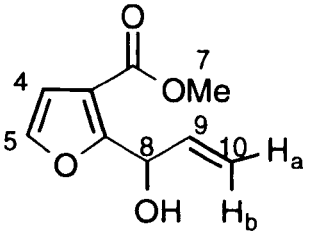
Figure 4.5: Adduct from Electrophilic Attack at Position 2

4.3.2 GRIGNARD ATTACK BY VINYLMAGNESIUM BROMIDE ON 5- AND 2-FORMYL-3-FUROATE ESTERS

Mixtures of the 2- and 5-formyl-3-furoate esters were treated with the Grignard reagent vinylmagnesium bromide to give the respective allylic alcohols. Purification by column chromatography successfully separated the two isomers at this stage.



156 R = Me
157 R = ^{i}Pr
158 R = Ph



159 R = Me
160 R = ^{i}Pr
161 R = Ph

Table 4.5 shows the yields of the various isomers isolated.

R	5- isomer	2- isomer	RATIO
Me	53	5	10:1
^{i}Pr	41	8	5:1
Ph	46	-	-

Table 4.5: Relative Yields of 2- and 5- Isomers

The results shown in table 4.5 are surprising as we would have expected the proportion of 2- substitution to decrease with increasing steric bulk of the ester. Although the tlc of the allylic phenyl ester did show the presence of two species, only the 5- substituted isomer could be successfully isolated.

There are marked differences observed in the ^{1}H nmr spectrum for the two allylic alcohols. The most notable difference is the change in the shift and coupling patterns of the furan signals. Table 4.5 shows these differences for methyl 5-(1-hydroxy-2-propenyl)-3-furoate and methyl 2-(1-hydroxy-2-propenyl)-3-furoate. The other allylic alcohols isolated showed similar coupling patterns. The assignment of the substitution pattern was done by comparing the coupling constants for the allylic alcohols with that of unsubstituted furan as described previously in 4.1.2.

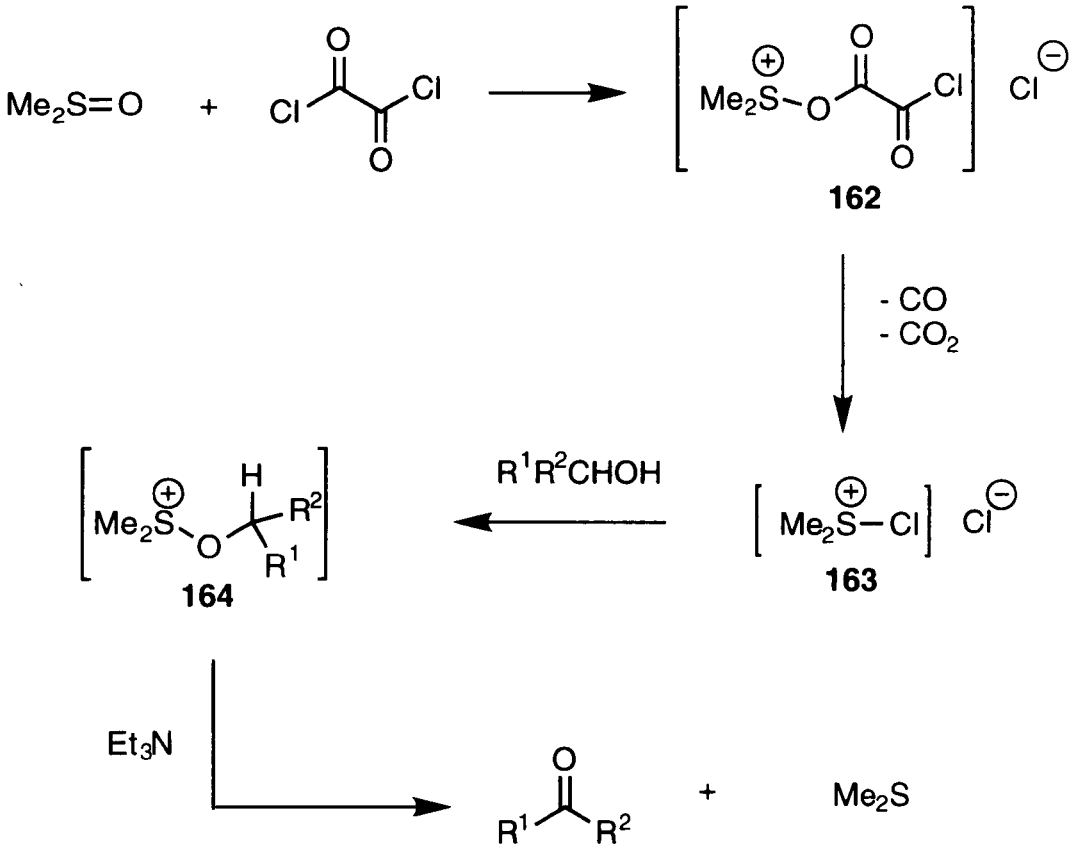
	Methyl 5-(1 hydroxy-2-propenyl)-3-furoate **156**		Methyl 2-(1 hydroxy-2-propenyl)-3-furoate **159**	
H	δ	Coupling pattern	δ	Coupling pattern
2	7.83	d, $J_{2,4}$ 0.84	NOT APPLICABLE	
4	6.45	d, $J_{4,2}$ 0.84	7.22	d, $J_{4,5}$ 1.94
5	NOT APPLICABLE		6.59	d.$J_{5,4}$ 1.93
7	3.72	s	3.72	s
8	5.05	br d, $J_{8,9}$ 5.82	4.74	br d, $J_{8,9}$ 5.31
9	5.95	ddd, $J_{9,8}$ 5.81, $J_{9,10b}$ 16.15, $J_{9,10a}$ 10.33	6.01	ddd, $J_{9,8}$ 5.63, $J_{9,10a}$ 10.32, $J_{9,10b}$ 15.9,
10a, 10b	5.35	unresolved	5.35	unresolved

Table 4.6: Comparison of ^1H nmr spectra for Allylic Alcohols

4.3.3 OXIDATION TO ALLYLIC KETONES

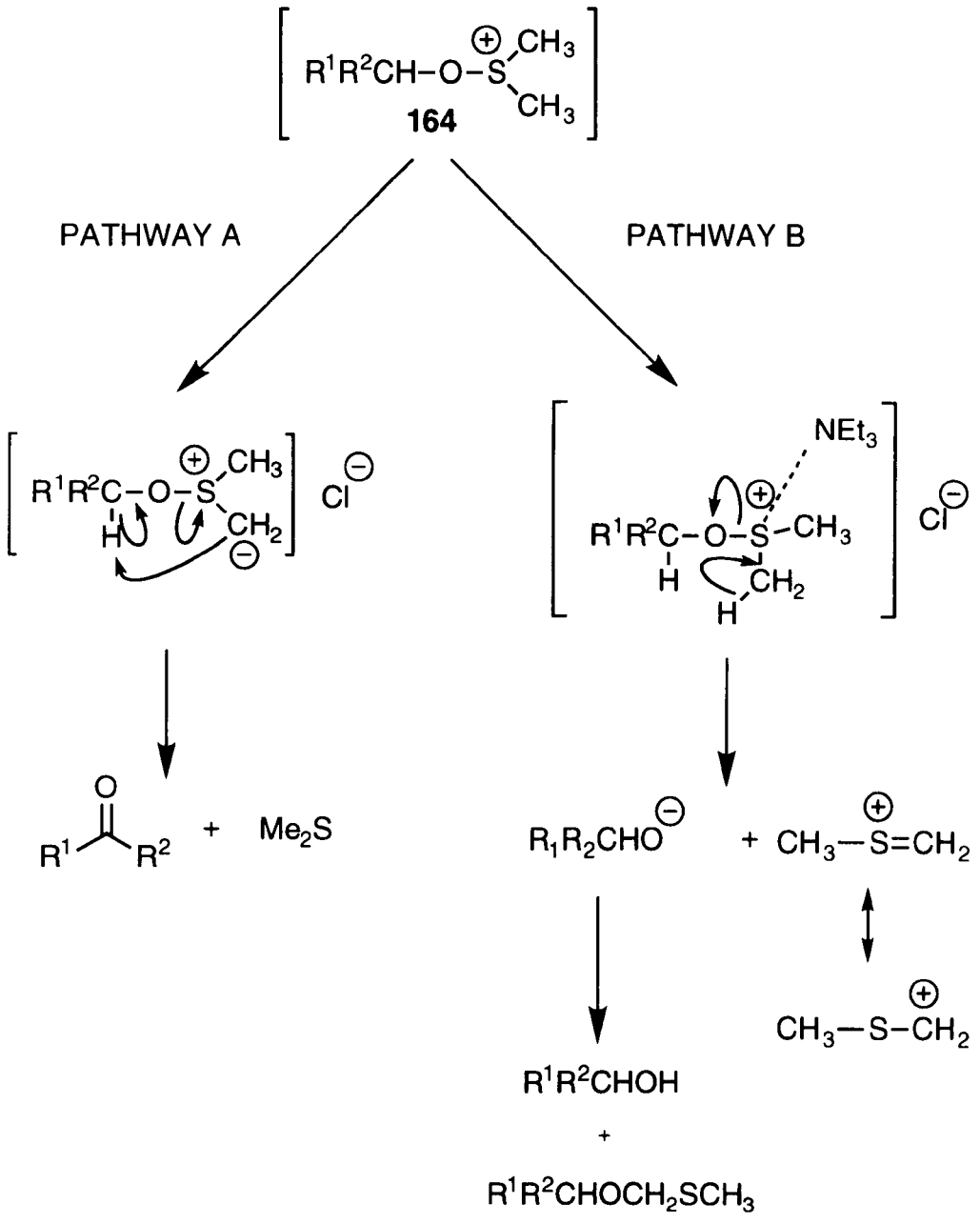
SWERN OXIDATION

The first attempt to oxidise the allylic alcohols to their respective ketones used Swern conditions.[132] Oxalyl chloride was treated with dimethylsulfoxide in dichloromethane at very low temperatures. The procedure recommends -60 °C but for practical reasons we chose -78 °C using an acetone/dry ice bath. This low temperature is important as this initial reaction to form intermediate **162** is highly exothermic and can be explosive. This intermediate breaks down releasing carbon dioxide and carbon monoxide giving the salt **163.** Upon reaction of the alcohol to be oxidised with the salt **163** an alkoxysulfonium salt **164** is formed[133,134] which breaks down on treatment with triethylamine to give the ketone and dimethylsulfide. The latter reaction has been well documented.[135,136]



Scheme 4.7: Mechanism of Swern Oxidation

Our system failed to produce the ketone and the starting alcohol was recovered. There are several reasons why the alcohol may not have been oxidised including of course failure of the initial alkoxysulfonium salt to form. Steric hindrance of the alcohol and the mechanism of the breakdown of the alkoxysulfonium salt by the triethylamine may give another possible explanation. As shown in scheme 4.8 there are two possible breakdown pathways of the salt **164**. Path A shows proton abstraction by the CH_2^- to give the desired ketone and dimethylsulfide. However path B provides an alternative pathway regenerating the alcohol. Rather than deprotonating the methyl group triethylamine in this case has attacked the electropositive sulfur. Proton elimination and sulfur-oxygen bond fission then generates the alkoxide which in turn regenerates the alcohol.



Scheme 4.8 Two Possible Pathways for Swern Oxidation

The size of the R groups is important in determining which pathway is followed. As bulk and steric hindrance are increased the sulfur becomes less accessible for nucleophilic attack from the triethylamine and pathway A will be favoured. Small R groups on the other hand will favour pathway B. Comparing our substrate **165** to other substrates (**166, 167**) which have undergone successful oxidation under

Swern conditions it can be seen that ours is less sterically hindered than the others which could explain the observed lack of oxidation.

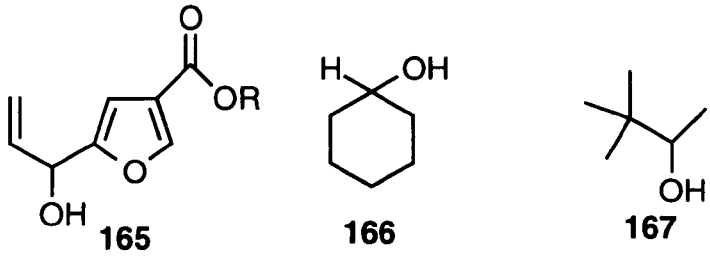
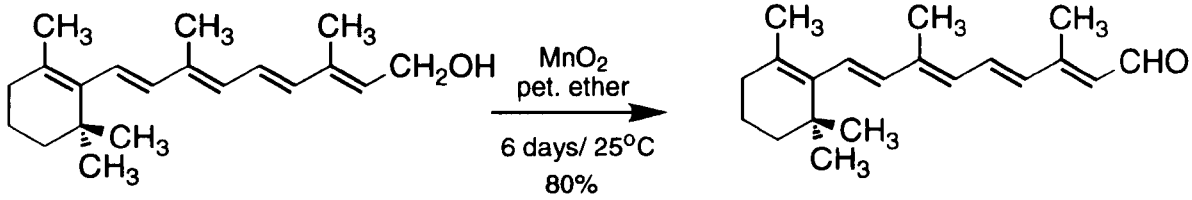


Figure 4.6: Comparison of Allylic Alcohol with known Substrates for Swern Oxidation

MANGANESE DIOXIDE

Since the Swern oxidation was proving to be difficult, manganese dioxide was considered as an alternative oxidant. It is a heterogeneous oxidative reagent similar to oxidants such as copper oxide, silver oxide and manganese (III) acetate[137]. Its potential as an oxidant was first documented by Goodwin, Ball and Morton[138] for its use in the oxidation of vitamin A_1 into retinal.



Scheme 4.9: Oxidation of Vitamin A_1 to Retinal

Since then it has been used extensively in the selective oxidation of α,β–unsaturated alcohols, saturated alcohols, phenols, hydrazines, hydrocarbons and others. There are commercial sources of active maganese dioxide with Backson and Winthrop Laboratories in New York and E. Merck in Darmstadt in Germany as the main suppliers but we decided to make our own, following the procedure laid out by

Mancera, Rosenkranz and Sondheimer[139]. The reagent was precipitated from a warm solution of manganese sulfate and potassium permanganate. The pH of the solution is important in defining how active the precipitated manganese dioxide is. The procedure we followed gave "active" manganese dioxide from an acidic medium. Preparation of the reagent by the method of Attenburrow, Cameron and Chapman[140] gives active manganese dioxide from alkaline conditions whilst that prepared by the original Ball, Goodwin and Morton procedure gives manganese dioxide from neutral conditions and is reportedly[141] less active than the other two. Once prepared, the manganese dioxide was dried in the oven at 110°C for 24 hours in order to activate it. It was in fact stored in the oven until it was required. Pratt and Van de Castle[142] showed that heating at 125°C for a longer time gives a more active material.

There are several forms of manganese dioxide and their various reactivities were compared by Vereschagin and co-workers[143] who concluded that the order of reactivity for the oxidation of benzyl alcohol was:

$$\gamma\text{-}MnO_2 > \text{active } MnO_2 > \alpha\text{–}MnO_2$$

Additionally they concluded that the oxidisng power of active manganese dioxide was dependent upon the content of γ-manganese dioxide.

The structure of active manganse dioxide was determined by various physical methods including thermogravimetric analysis (TGA) which showed that there were three distinct areas of weight loss as shown:

TEMPERATURE	ELIMINATION OF
20 - 200 °C	non bonded water molecules
200 - 500 °C	bonded water molecules *i.e.* hydroxy ligands
500 - 525 °C	labile oxygen ligands

On the basis of the above information as well as ESR studies it was proposed that the structure of active manganese dioxide **168** was as shown in figure 4.7.

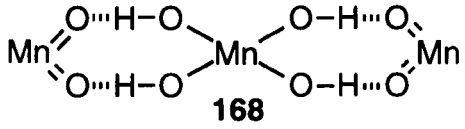


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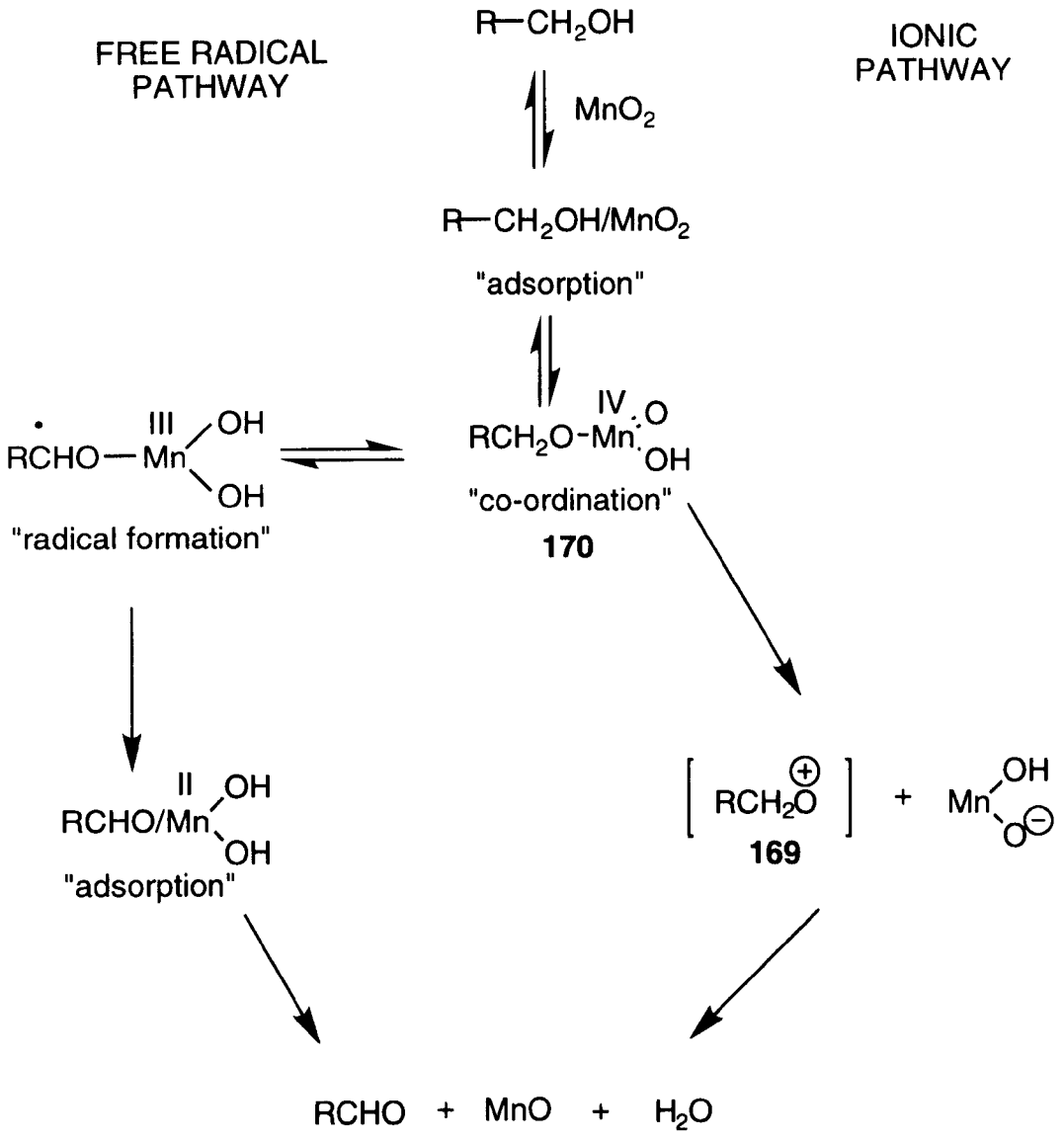
Figure 4.7: Proposed structure of Manganese Dioxide

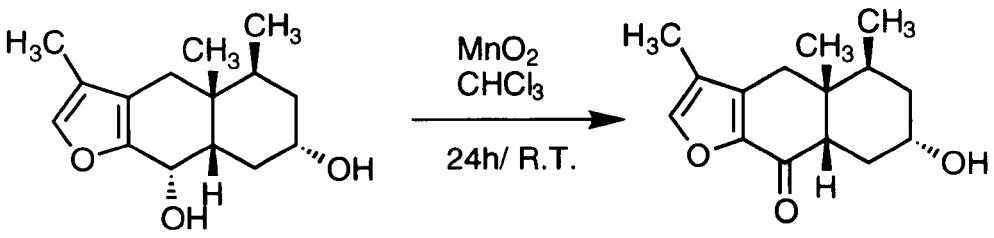
The mechanism of oxidation by manganese dioxide is unclear. Based on the observation that the rate of oxidation of various benzyl alcohols by manganese dioxide is relatively independent of the nature of benzyl substituents, Pratt and co-workers[144,145,146] proposed a free radical mechanism. Later, in 1967, Hall and Story[147] re-interpreted these results in terms of a formally ionic mechanism with the positive charge on the oxygen **169** and not the benzylic carbon as expected.

Both the free radical and the ionic mechanisms begin with the adsorption of the alcohol onto the manganese dioxide *via* an allylic or aromatic π-bond or *via* manganese ions and alcohol oxygen co-ordination[148] to give the co-ordination complex **170**. In the free radical mechanism a hydrogen atom is then transferred which gives the stablilised radical which undergoes intramolecular electron transfer to give the products. In the ionic mechanism the co-ordinated complex loses the manganese fragment to form the transition state **169** which loses a proton to give the oxidised product.



Scheme 4.10: Two possible pathways for Manganese Dioxide Oxidation

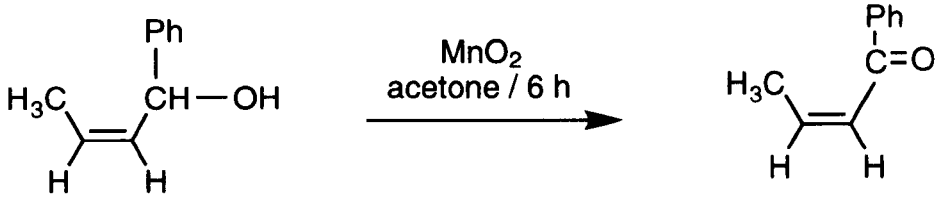
There was considerable literature precedence for the successful oxidation of our compounds. Brooks and Draffan[149] showed the oxidation of an alcohol next to a furan **171** which gave the cis fused keto alcohol **172**



171 172

Scheme 4.11: Oxidation of Sesquiterpenoid Furanopentasol 171 by Manganese Dioxide

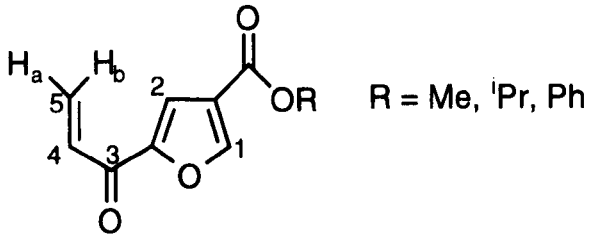
Similarly, oxidation of allylic alcohols has been well documented[150,151]. Scheme 4.12 shows the transformation of the both aromatic and allylic alcohol *cis*-1-phenyl-2-buten-1-ol **173** to the corresponding *cis* ketone **174**.[152]



173 174

Scheme 4.12: Oxidation of Allylic Alcohol *cis*-1-Phenyl-2-buten-1-ol.

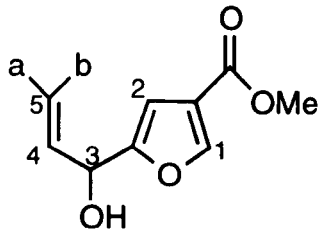
In view of the literature precedence we treated our alcohols with 10 equivalents of manganese dioxide in light petroleum (40:60). Purification afforded the methyl, isopropyl and phenyl 5-(2-propenoyl)-3-furoates. Table 4.7 shows a comparison of the ^1H nmr shift values of the propenoyl fragment showing that there is little change irrespective of which ester is present.



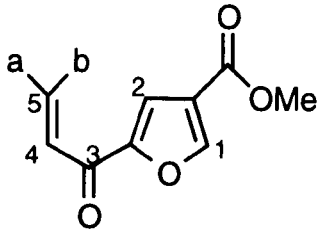
		H				
		1	2	4	5a	5b
175	Me	8.06	7.46	6.96	5.85	6.48
176	iPr	8.08	7.47	6.9	5.86	6.51
177	Ph	8.28	7.60	6.98	5.91	6.55

Table 4.7: Comparison of ^1H nmr data for ketones

Large changes were oberved when comparing the ^1H shifts for 5-(2-propenoyl)-3-furoates with their corresponding alcohols. The changes shown in table 4.8 are for methyl 5-(2-propenoyl)-3-furoate and its corresponding alcohol but the shift pattern is typical for both the isopropyl and phenyl esters.



156



175

H	1	2	3	4	5a	5b
156	7.83	6.45	5.05	5.95	5.35	
175	8.06	7.46	N/A	6.96	5.85	6.48

Table 4.8: Comparison of ^1H Nmr Values of Allylic Alcohol 156 with Enone 175

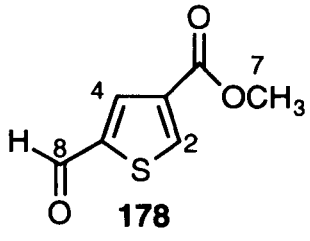
The changes in the ^1H nmr spectrum between the allylic alcohol **156** and the allylic ketone **175** can be attributed to the change in electron delocalisation between the two molecules. The ketone is electron withdrawing and deshields the protons in the double bond and in the furan causing a downfield shift (i e higher δ values).

4.4 SYNTHESIS OF 3,5-DISUBSTITUTED THIOPHENES VIA FORMYLATION

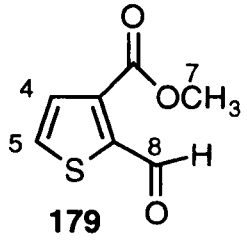
The synthesis of 3,5-disubstituted thiophenes following parallel methodology to the synthesis of 3,5-disubstituted furans described in section 4.3 is detailed below.

4.4.1 FORMYLATION OF METHYL 3-THIOPHENECARBOXYLATE

Methyl 3-thiophene carboxylate was added to the yellow Vilsmeier salt formed from phosphorus oxychloride and dimethylformamide. The reaction mixture was warmed to 100 °C and held at this temperature for one hour. Tlc indicated that two products had been formed - methyl 5-formyl-3-thiophenecarboxylate **178** and methyl 2-formyl 3-thiophenecarboxylate **179**. Unlike the two formyl isomers of methyl 3-furoate these thiophene isomers were separated and isolated at this stage in a ratio of 4:1 respectively by column chromatography. Table 4.9 shows the comparison between the nmr spectra of the two different isomers.



178



179

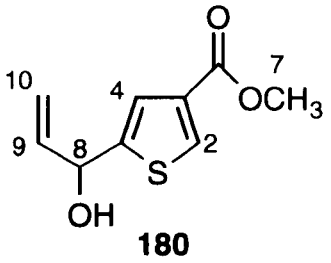
H	Methyl-5-formyl-3-thiophenecarboxylate **178**		Methyl-2-formyl-3-thiophenecarboxylate **179**	
2	8.36	d $J_{2,4}$ 1.29	NOT APPLICABLE	
4	8.08	d $J_{4,2}$ 1.29	7.57	br. s
5	NOT APPLICABLE		7.59	br. s
7	3.87	s	3.90	s
8	9.85	dd $J_{8,4}$ 1.34 and $J_{8,2}$ 2.59	10.53	s

Table 4.9: Comparison of ^1H nmr Values Methyl 5-Formyl-3-thiophenecarboxylate with Methyl 2-Formyl-3-thiophenecarboxylate

The protons at position 4 are markedly different due to this proton in the 5-formyl isomer being in conjugation with the aldehyde. Electron withdrawal by the aldehyde causes H-4 to be deshielded and so it appears more downfield. This does not occur in the 2- isomer. H-2 is more downfield in methyl 5-formyl-3-thiophenecarboxylate than H-5 in methyl 2-formyl-3-thiophenecarboxylate due to it being in conjugation with the carbonyl of the ester. H-5 however has moved slightly downfield from δ7.19 in the starting ester to δ7.59 in the 2- isomer because it is slightly deshielded by the formyl group. The carbonyls in the IR spectra are found at similar frequencies for the two isomers at 1670 and 1720 cm^{-1}. This, although confirming the introduction of the formyl group does not help distinguish the two isomers.

4.4.2 GRIGNARD ATTACK ON FORMYL ESTER

Addition of vinylmagnesium bromide to a solution of methyl 5-formyl-3-thiophenecarboxylate in THF gave methyl 5-(1-hydroxy-2-propenyl)-3-thiophenecarboxylate **180** in 57% yield.



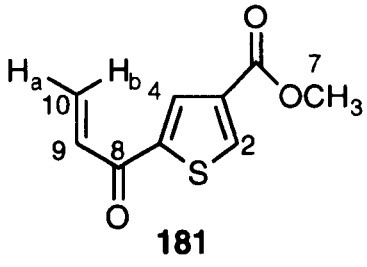
180

Figure 4.8: Methyl 5-(1-Hydroxy-2-propenoyl)-3-thiophenecarboxylate

The ^1H nmr spectrum of the allylic alcohol **180** shows clearly the doublet of doublet of doublets at δ6.01 for proton 9. Infra-red detected the presence of only one carbonyl at 1720 cm^{-1} corresponding to the ester.

4.4.3 OXIDATION OF METHYL 5-(1-HYDROXY-2-PROPENYL)-3-THIOPHENECARBOXYLATE

Methyl 5-(1-hydroxy-2-propenyl)-3-thiophenecarboxylate was stirred at room temperature with 10 equivalents of freshly prepared manganese dioxide to give methyl 5-(2-propenoyl)-3-thiophenecarboxylate **181** in 60% yield



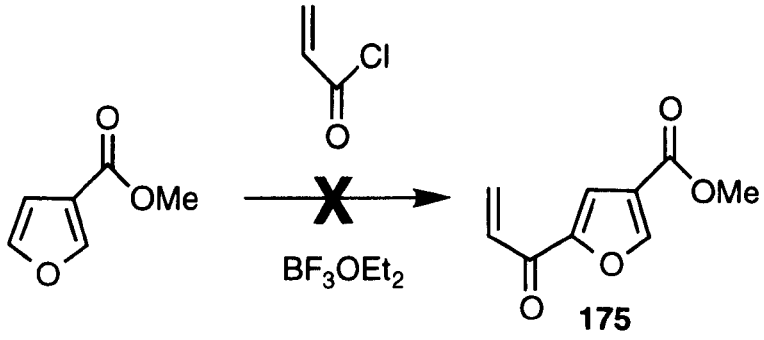
181

Figure 4.9: Methyl 5-(2-propenoyl)-3-thiophenecarboxylate

The ^1H nmr spectrum showed clearly the doublet of doublets for H-10a at δ5.87 and for H-10b at δ6.46. H-9 is found more downfield at δ7.02 due to the deshielding effect of the carbonyl. Infra-red helped confirm the structure by showing the presence of two carbonyls - 1660 cm^{-1} for the allylic ketone and 1720 cm^{-1} for the ester.

4.5 ALTERNATIVE SYNTHESIS TO KETONE 175

Although the route to formation of methyl 5-(2-propenoyl)-3-furoate **175** was successful it is lengthy and involved. Therefore, a different approach was taken using the methodology behind the successful Friedel-Crafts reactions in section 4.1. In light of this attempts were made to couple methyl 3-furoate with acryloyl chloride in the presence of boron trifluoride etherate as the Lewis acid. All attempts were unsuccessful and baseline material was isolated.

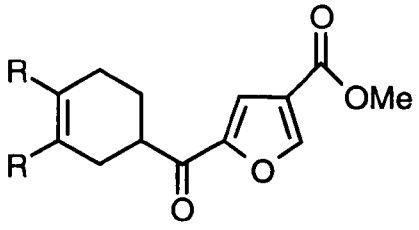


Scheme 4.13: Alternative Pathway to Methyl 5-(2-propenoyl)-3-furoate via Friedel-Crafts Acylation

4.6 FORMATION OF DIELS-ALDER ADDUCTS

Once the allylic ketone was formed it seemed appropriate to make Diels-Alder adducts as this would provide more derivatives for biological testing with greater steric bulk at the 5-position of the molecule. Methyl 5-(2-propenoyl)-3-furoate was refluxed with 2,3-dimethyl-1,3-butadiene, 2,3-dimethoxy-1,3-butadiene and cyclohexa-1,3-diene in

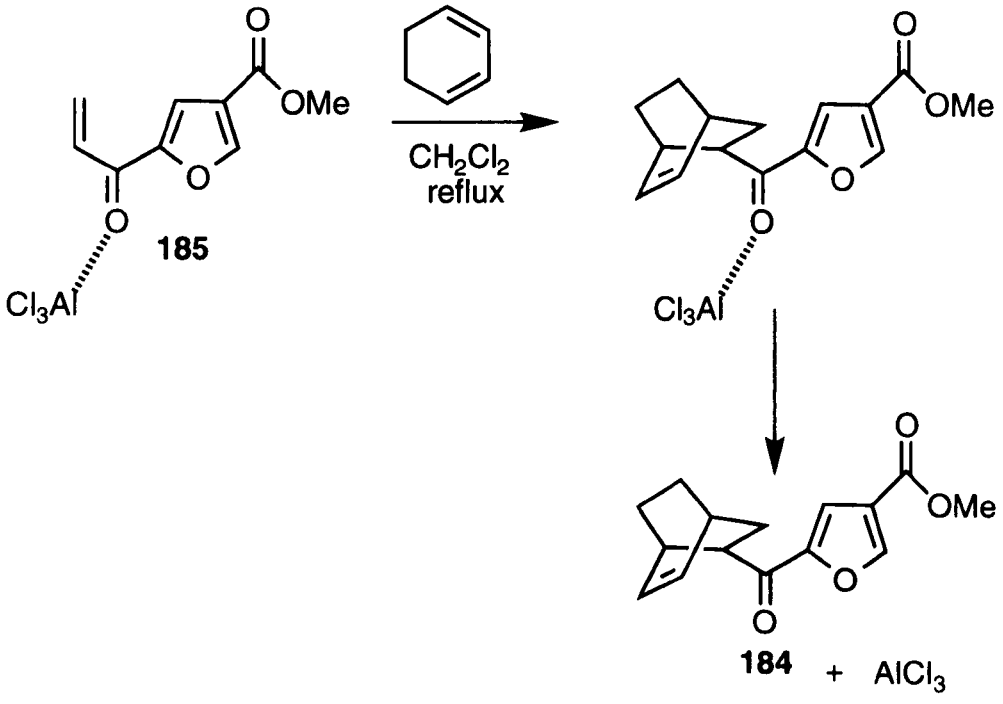
dichloromethane solution. Successful reactions were obtained under these conditions with the first two forming adducts **182** and **183**.



182 R = Me
183 R = OMe

Figure 4.10: ***Cycloadducts from Diels-Alder Reactions***

On treatment with cyclohexa-1,3-diene no reaction was observed and starting material was recovered. This was surprising because cyclohexa-1,3-diene is locked into the cisoid conformation which implies that this should be a fast reaction. The adduct **184** was successfully made, however, when the Lewis acid aluminium chloride was added.

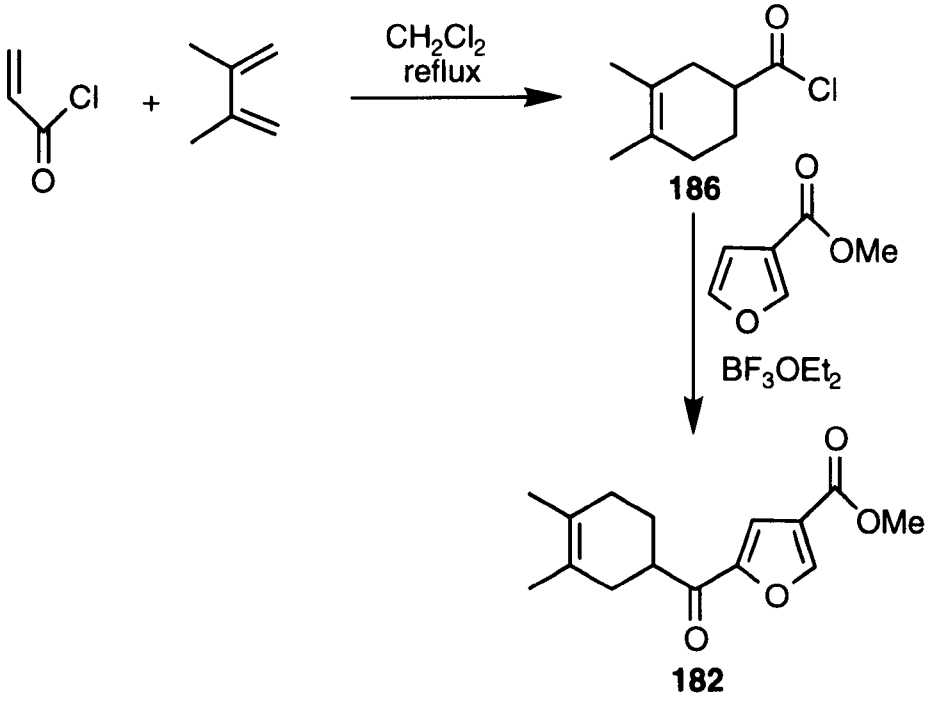


Scheme 4.14: ***Formation of Lewis Acid Accelerated Diels-Alder Adduct***

Yates and Eaton[153] in the early 1960's first reported accelerated Diels-Alder [4+2] cycloadditions of maleic anhydride, dimethylfumarate and *p*-benzoquinone to anthracene. Since then there have been many other Lewis acid accelerated Diels-Alder reactions reported.[154,155] The aluminium co-ordinates to the oxygen of the ketone forming complex **185**. Electrons therefore are pulled away from the allylic double bond (as seen in scheme 4.14). The effect of the electron withdrawing property is to decrease in the energy difference between the HOMO and LUMO orbitals of the diene and dienophile resulting in a faster reaction. (see Figure 3.3 in Chapter 3)

4.7 ALTERNATIVE SYNTHESIS TO DIELS-ALDER ADDUCT

An alternative convergent synthesis to the Diels-Alder adduct **182** would be the Friedel-Crafts reaction between the furoate ester and the appropriate acid chloride (see scheme 4.15).



Scheme 4.15: Convergent Synthesis of Diels-Alder Adduct

Acryloyl chloride was refluxed with 2,3-dimethybutadiene to form the desired acid chloride **186** *via* a Diels-Alder reaction as shown in scheme 4.14. The dichloromethane solvent was then removed *in vacuo* to leave the acid chloride as a colourless oil. Methyl 3-furoate and boron trifluoride etherate were then added and the resulting mixture refluxed. The ^{1}H nmr spectrum of the isolated material was consistent with the product isolated from the Diels-Alder reaction between methyl 5-(2-propenoyl)-furoate and 2,3-dimethylbutadiene. However, the yield was low (23%) but in comparison to the overall yield *via* formylation (4.8% - based on methyl 3-furoate) this is obviously preferable. The conditions would be further optimised if this method were to be used again.

Attempts to form the isopropyl ester adduct following this method proved to be unsuccessful. However it is envisaged that transesterification of the methyl ester prepared above would give access to other desired compounds.

4.8 BIOLOGICAL TESTING

Several of the compounds made (**133** - **140**) have been sent away for testing of their ability to inhibit phospholipase D. We are still waiting on the results of this biological testing.

CHAPTER 5

5.1 ISOLATION AND DERIVATISATION OF WORTMANNIN

Wortmannin **34** was isolated from the freeze dried culture of *Talaromyces wortmanii* which was incubated on Raulin and Thom still culture. Since wortmannin **34** has been shown to exhibit phospholipase D inhibition it therefore seemed appropriate to derivatise it in order to test the biological activity. Functionalisation centred around the carbonyl at position 17 since it had been previously been shown that derivatisation of the furan or of the two carbonyls in conjugation with it destroyed any biological activity it possessed.

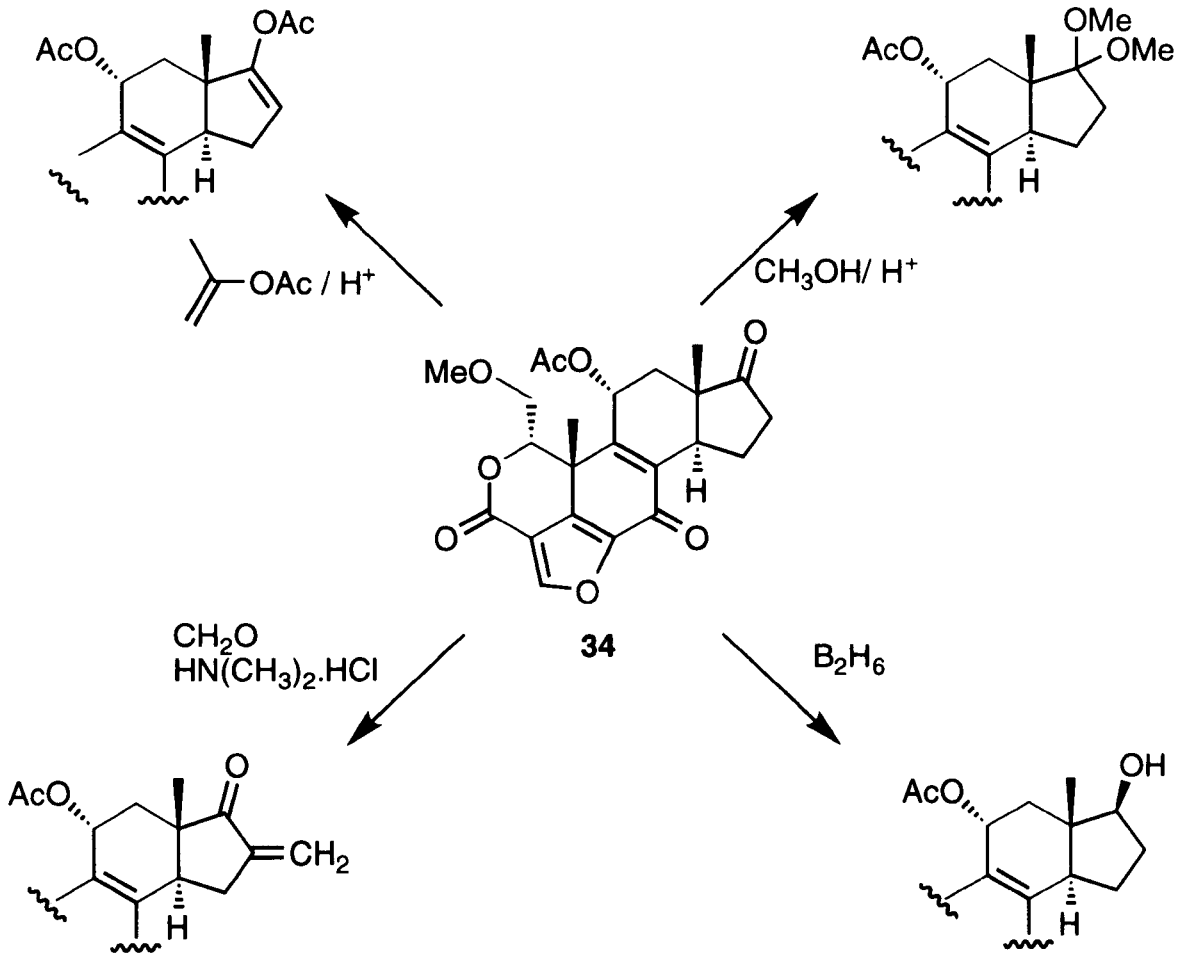
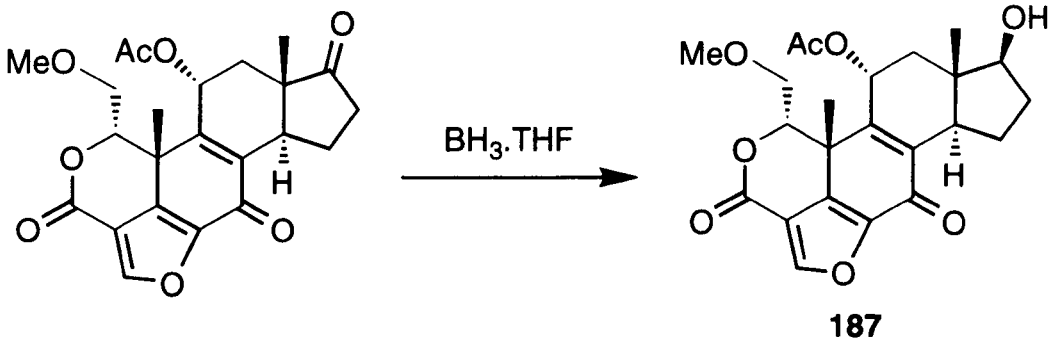


Figure 5.1: Functionalisation at C-17 of Wortmannin

The main chemistry centred around work by Haefliger and co-workers[77] who derivatised wortmannin as shown in scheme 5.1. As the compounds they prepared were not tested for phospholipase D inhibition they provided a suitable starting point.

5.1.1 SYNTHESIS OF WORTMAN-17β-OL

Wortmannin was reduced to wortman-17β-ol **187** by using the BH_3.THF complex as shown in scheme 5.2.



Scheme 5.2: Reduction of Wortmannin to Wortmannin-17β-ol

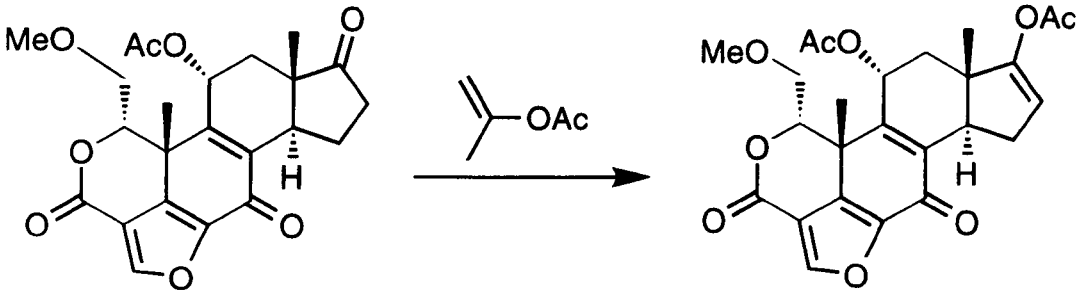
There are 4 carbonyls in wortmannin **34** and therefore 4 possible sites for reduction. The carbonyl at C-3 and the acetyl ester were not reduced because the former is a lactone and the latter an ester neither of which are easily reduced by borane. The carbonyl at C-7 is α,β unsaturated and once again such systems are not reduced by borane. The ketone carbonyl at C-17 was found to be reduced. These general observations can be explained by the relative nucleophilic nature of the various carbonyls. Borane is an electrophile (i.e. a Lewis Acid)[156,157] and will therefore attack the oxygen and not the carbon of the carbonyl functional group unlike hydride reagents such as lithium aluminium hydride. The selectivity is consequently different and the most nucleophilic carbonyl will be reduced preferentially. In this case it is the ketone carbonyl since in both the ester and the lactone the nucleophilicity is reduced

by the oxygen neighbouring the carbonyl. Likewise for the α,β-unsaturated ketone resonance delocalisation reduces the nucleophilicity.

When the ketone is reduced the alcohol forms selectively on the same face as the neighbouring methyl group as the incoming BH_3.THF complex will prefer to attack the side of the ring with the smallest group - in this case the side opposite the methyl. Hydrogen delivery will therefore be on the α face and the alcohol will be on the β face.

5.1.2 SYNTHESIS OF WORTMANNIN ENOL ACETATE

Wortmannin **34** was treated with isopropenyl acetate and catalytic *para*-toluenesulfonic acid to give the expected wortmannin enol acetate **188** in 58% yield. This transformation is seen in scheme 5.3.



188

Scheme 5.3: Transformation to Wortmannin Enol Acetate

The mechanism involves firstly protonation of the isopropenyl acetate which is then attacked by the oxygen of the carbonyl displacing isopropenol. The isopropenol is in equilibrium with the more stable acetone and it is the formation of this which is the driving force for the reaction. Like the previous reduction formation of this derivative on the C-17 carbonyl is dependent upon the nucleophilicity of the oxygen. Following

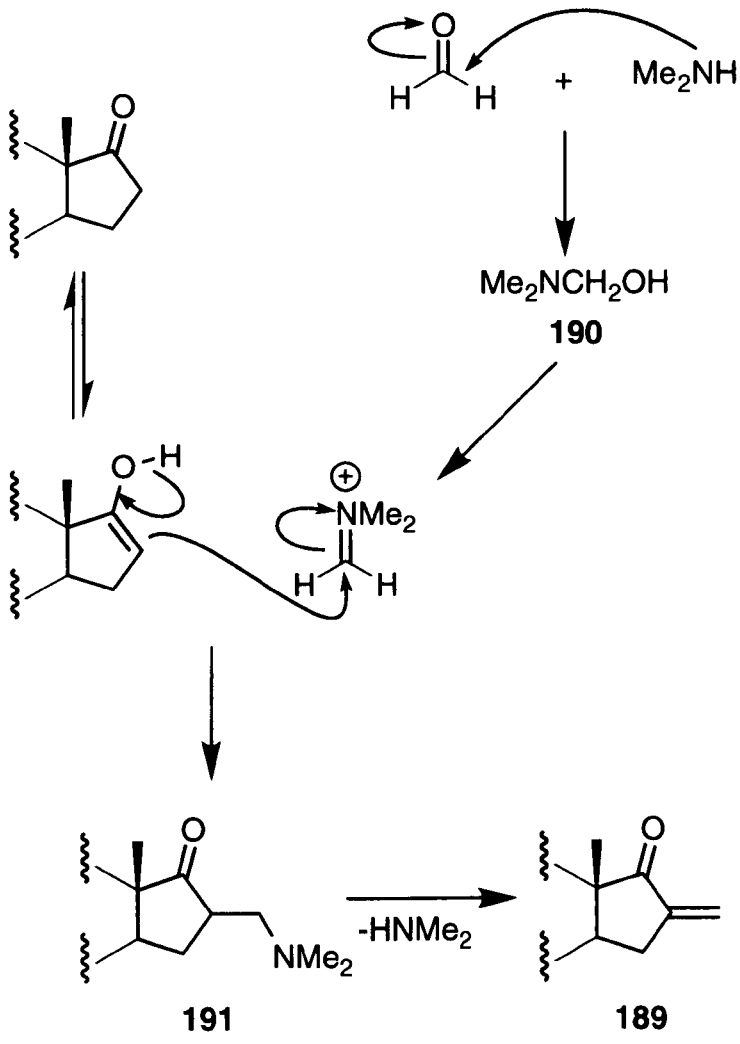
the same arguments as previously C-17 has the most nucleophilic oxygen and will therefore react preferentially over the other carbonyl groups.

5.1.3 SYNTHESIS OF 16-METHYLIDENEWORTMANNIN

Formation of 16-methylidenewortmannin **189** was done using the Mannich reaction. Usual Mannich conditions[158] involve condensation of formaldehyde with ammonium chloride and a compound containing an active hydrogen. The system used to generate 16-methylidenewortmannin **189** used dimethylamine hydrochloride, the salt of the secondary amine. The use of primary or secondary amines or even amides have been well documented.[159] The dimethylamine reacts with the formaldehyde to give Me_2NCH_2OH **190** which then reacts with the enol form of the ketone giving **191**, which is called the Mannich Base.

The Mannich reaction can either be base or acid catalysed and kinetic studies have led to proposals for the mechanism. Scheme 5.4 shows the proposed mechanism for the acid catalysed reaction.[160]

This Mannich base can have several different fates dependent upon whether the amine is primary, secondary or tertiary. In the case of shown tertiary amine no further condensation with either the aldehyde or the ketone takes place. The amino group is β to the carbonyl and so dimethylamine is easily eliminated providing an easy route to the α,β-unsaturated ketone.



Scheme 5.4: Mechanism of Mannich Reaction

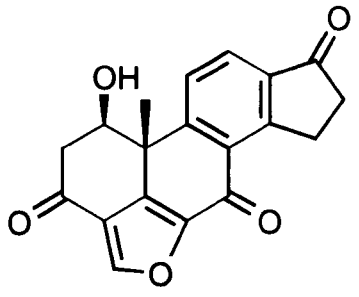
5.1.4 ATTEMPTED KETAL FORMATION AND ATTEMPTED HYDROGENATION OF 16-METHYLIDENEWORTMANNIN

An attempt was made to form the ketal at carbonyl-17 by reacting wortmannin **34** with methanol in the presence of acid. A white precipitate was observed which was in agreement with literature but when isolated this proved to be starting material. This was repeated on several occcasions but no ketal was isolated.

An attempt was also made to hydrogenate 16-methylidenewortmannin **189** using hydrogen and a palladium/carbon catalyst. This was unsuccessful and resulted in baseline material being formed.

5.2 ISOLATION OF DEMETHOXYVIRIDIN AND DERIVATISATION

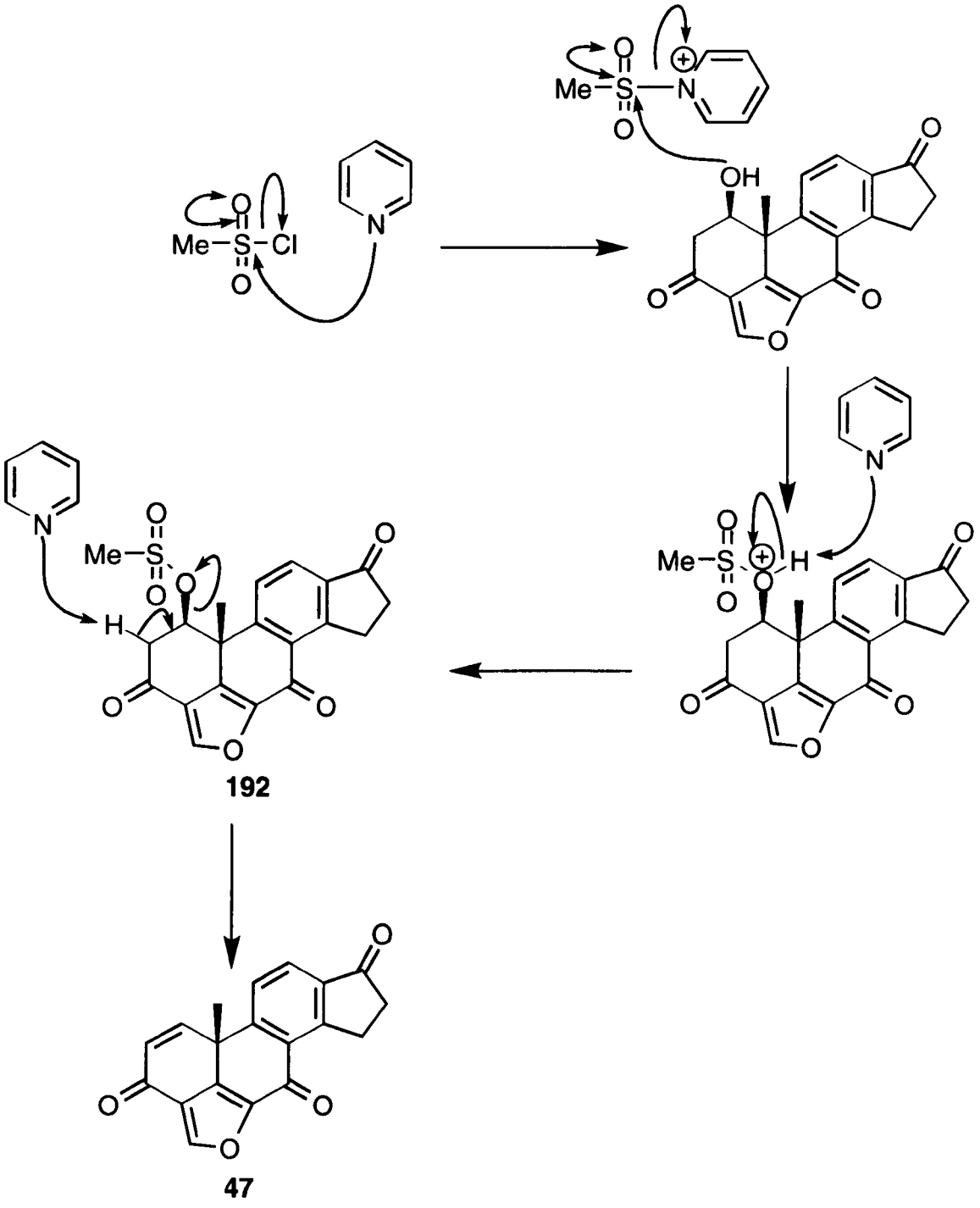
Demethoxyviridin **35** was isolated from *Nodulisporium hinnuleum* grown on Rhaulin and Thom culture medium.



35

Figure 5.1: Demethoxyviridin

Demethoxyviridin **35** was treated with methanesulfonyl chloride in the presence of pyridine to give first the methanesulfonate ester **192** which undergoes further elimination to give the α,β-unsaturated derivative PLD-7 **47**. This compound has since been sent for biological testing and we are awaiting results.



Scheme 5.5: Formation of PLD-7

CHAPTER 6

6.1 GENERAL NOTES

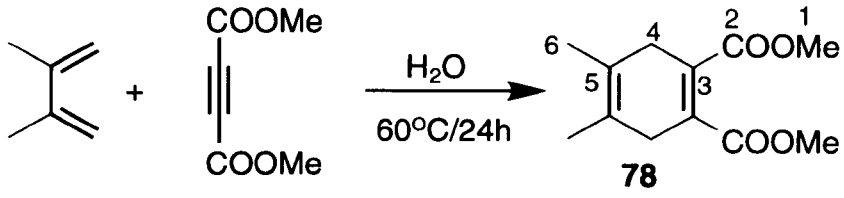
Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded with a Perkin Elmer R32 spectrophotometer operating at 90 MHz (δ_H) or a Bruker AM200 or WP200-SY spectrophotometer operating at 200 MHz (δ_H) and 50 MHz (δ_C). Tetramethylsilane (TMS) was used as an internal standard in deuterated solvents. The numbering schemes used are to aid identification in the ^1H and ^{13}C spectra. Infra red (IR) spectra were obtained on either a Perkin Elmer 983 spectrophotometer or a Philips PU 9800 FTIR spectrophotometer. Elemental analyses were performed using a Carlo-Erba 1106 elemental analyser. Mass spectra (MS) were recorded on AEI MS12 or MS902 spectrometers. Only major peaks are quoted.

Thin layer chromatography (TLC) was carried out on glass backed silica plates of 0.25 mm thickness. Compounds were visualised using UV light and by staining with vanillin solution with heat development. Column chromatography was carried out on silica gel, 70-230 mesh with solvent systems described.

All solvents were purified by standard techniques as described in Perrin and Armarego.[161]

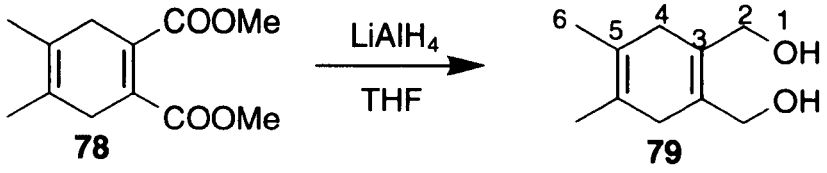
6.2 SYNTHESIS OF TARGET FURAN VIA DIOL OXIDATION

DIMETHYL 4,5-DIMETHYL-1,4-CYCLOHEXADIENE-1,2-DICARBOXYLATE (78)



Dimethyl acetylenedicarboxylate (6 g: 42 mmol) and 2,3-dimethyl-1,3-butadiene (4.14 g: 50.4 mmol) were added dropwise to water (40 ml). The resulting solution was stirred for 24 h at 60°C and on cooling to room temperature a white precipitate formed which was filtered, dried and recrystallised from methanol yielding dimethyl 4,5-dimethyl-1,4-cyclohexadiene-1,2-dicarboxylate **78** (5.14 g, 54.6%); m.p. 69-70°C IR ν_{max} 1720 and 1658 cm^{-1}; δ_H (200 MHz : $CDCl_3$) 1.71 (6H, s, H-6), 2.29 (4H, s, H-4) and 3.76 (6H, s, H-1); δ_C (50 MHz): 17.90 (C-6), 34.05 (C-4), 52.12 (C-1), 121.47 (C-5), 133.30 (C-3) and 168.5 (C-2). *m/z* 224 (M^+, 2.6), 193 (M^+-OMe,14.7) and 177 (100.%) (Found M^+, 224.1058: C 64.86 and H 6.41%, $C_{12}H_{16}O_4$ requires M, 224.1048; C 64.86 and H 6.30%)

REDUCTION OF DIMETHYL 4,5-DIMETHYL-1,4-CYCLOHEXADIENE-1,2-DICARBOXYLATE (79)



METHOD 1: *VIA* LITHIUM ALUMINIUM HYDRIDE

To a flame dried flask under nitrogen was charged lithium aluminium hydride (167mg: 4.41 mmol) at 0°C followed by THF (10 ml). Whilst the temperature was

maintained at 0°C the ester (500 mg: 2.21 mmol).was slowly added dropwise and the resulting solution stirred for 1.5 h. The reaction was quenched with a solution of sodium sulfate decahydrate. Hydrochloric acid (1M) was slowly added until the solution became acidic (pH 3). The solution was extracted with ethyl acetate (3 x 30ml) and the organic extracts combined, washed with sodium bicarbonate (3 x 25ml), brine (3 x 25 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give the residual oil as the crude product. Purification *via* column chromatography eluting with hexane: ethyl acetate (1:1) afforded 1,2-dihydroxymethyl-4,5-dimethyl-1,4-cyclohexadiene **79** (676 mg: 4 mmol: 18%) m.p. 70°C; δ_H ($CDCl_3$: 200 MHz): 2.74 (6H, s, H-6), 3.8 (2H, s, H-4) and 4.22 (4H, s, H-2). δ_C ($CDCl_3$: 50 MHz):17.38 (C-6), 34.5 (C-4), 61.3 (C-2), 121.0 (C-5) and 129.9 (C-3). *m/z*: 168 (M^+, 1.7), 150 (15.3) and 121 (32%) (Found M, 168.1159 $C_{10}H_{16}O_2$ requires 168.1150).

METHOD 2: USING SODIUM BOROHYDRIDE

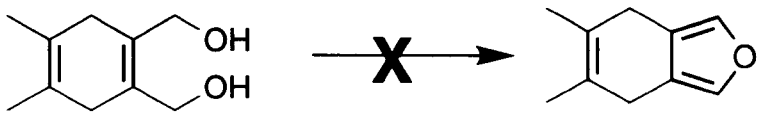
To a stirring solution of dimethyl 4,5-dimethyl-1,4-cyclohexadiene-1,2-dicarboxylate (200 mg: 0.89 mmol) in methanol (15 ml) was added sodium borohydride (130 mg: 3.57 mmol). After the initial effervescence the resulting solution was stirred for 3 h. Tlc eluted with hexane: ethyl acetate (2:1) indicated that no reaction had occurred. A further portion of sodium borohydride (130 mg: 3.57 mmol) was added and the resulting solution stirred overnight. Tlc indicated again the presence of starting material only.

METHOD 2: USING *IN SITU* FORMATION OF BORANE

Sodium borohydride (240 mg: 6.63 mmol) was aded to a dry flask in a nitrogen atmsphere followed by THF (15 ml). The solution was cooled to 0°C and iodine (560 mg: 2.2 mmol) was slowly added. dimethyl 1,4-cyclohexadiene-4,5-dimethyl-1,2-dicarboxylate (500 mg: 2.2 mmol) in THF (5 ml) was added and the mixture

brought to reflux for 0.5 h. Tlc indicated the presence of only starting material and low running baseline material.

ATTEMPTED CYCLISATION TO FURAN (80)



79 80

METHOD 1: USING PYRIDINIUM CHLOROCHROMATE

Pyridinium chlorochromate (380 mg: 1.78 mmol) was added portionwise to a solution of 1,2-dihydroxymethyl-4,5-dimethyl-1,4-cyclohexadiene (200 mg: 1.19 mmol) in CH_2Cl_2 (25 ml) and stirred at room temperature for 0.5 h. The resulting solution was then extracted with diethyl ether (3 x 25 ml) and the organics washed with sodium bicarbonate (2 x 20 ml), brine (2 x 20 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and tlc indicated that there was a mixture of products.

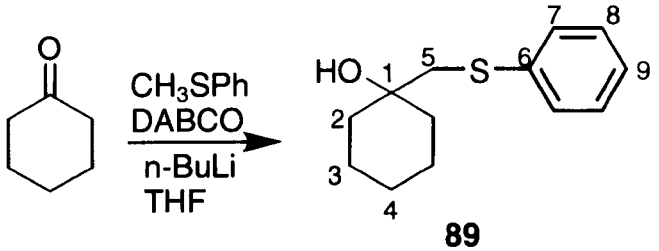
METHOD 2: USING MANGANESE DIOXIDE

Manganese dioxide was first prepared as follows: a solution of manganous sulfate (7.16 g: 47 mmol) in water (400 ml) was warmed to 90°C and potassium permanganate (6 g: 37 mmol) in water (20 ml) was slowly added. Brown solid manganese dioxide precipitated immediately and the resulting slurry was heated at 90°C for 1 h. The solution was then filtered to give manganese dioxide which was washed with hot water (200 ml), methanol (200 ml) and diethyl ether (200 ml). Drying overnight afforded active manganese dioxide (6.09 g : 90.4%).

To a stirred solution of the diol **79** (200 mg: 1.19 mmol) in CH_2Cl_2 (25 ml) was added 10 equivalents of manganese dioxide (10.2 g: 11.9 mmol). The resulting slurry was stirred at room temperature for 24 h. Tlc indicated the presence of only starting material.

6.3 SYNTHESIS*VIA* ALLYLIC SULPHIDES

1-(PHENYLTHIOMETHYL)-1-CYCLOHEXANOL (89)

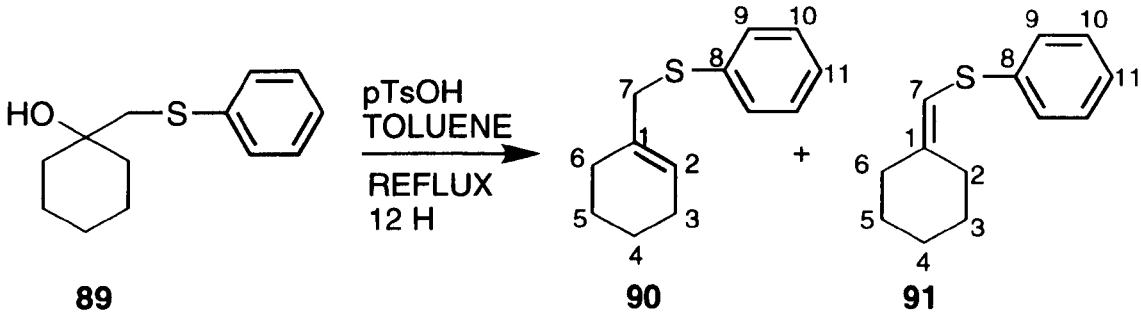


89

A dry 3 neck flask in a nitrogen atmosphere was charged with diazabicyclo[2.2.2]octane (2.24 g: 20 mmol), THF (20 ml), thioanisole (2.34 ml: 2.48 g: 20 mmol) and cooled to 0°C. *n*-Butyllithium (12.7 ml: 1.5M, 20 mmol) was slowly added and the resulting solution stirred for 1.5 h Cyclohexanone (2.1 ml: 1.86 g: 20 mmol) was added and the mixture stirred for 1 h at 0°C then 1 h at room temperature. The reaction was quenched with ammonium chloride solution and the solution extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed with sodium bicarbonate (3 x 30 ml), brine (3 x 30 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give the crude product as a yellow oil. Purification using column chromatography eluting with light petroleum/ethyl acetate (10:1) afforded 1-(phenylthiomethyl)cyclohexanol **89** as a yellow oil (3.59 g: 16.2 mmol: 81%); IR (neat) ν_{max} ; 1580 and 3400 cm^{-1}; δ_H (200 MHz ; $CDCl_3$); 1.1- 1.5 (10H, m, H-2,3 and 4), 1.98 (1H, br s, OH), 2.89 (2H, s, H-5) and 7.07 (5H, m, H-7,8 and 9).

δ_C (50 MHz) 22.04 (C-4), 25.57 (C-3), 33.74 (C-2), 47.71 (C-5), 71.22 (C-1), 126.07 (C-9), 128.89 (C-7) and 129.47 (C-8) and 137.2 (C-6). *m/z* 222(M^+, 7.7), 124 (100) and 99 (22.5%).

1-(PHENYLTHIOMETHYL)CYCLOHEXENE (90)



89 **90** **91**

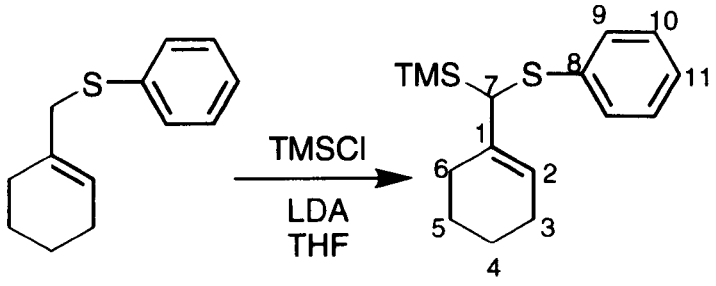
A solution of 1-(phenylthiomethyl)-1-cyclohexanol (1.54 g: 6.9 mmol) in 30 ml toluene and a catalytic amount of para-toluene sulfonic acid was allowed to reflux under Dean and Stark conditions for 12 h. The solution was cooled and was extracted with ether (3 x 20 ml). The combined organic extracts were washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml) and dried over magnesium sulfate. The solvent was removed *in vacuo* giving the crude product. Purification by column chromatography eluting with cyclohexane) afforded the two isomers 1-(phenylthiomethyl)cyclohexene **90** (566 mg: 2.77 mmol: 40%) and phenylthiomethylidenecyclohexane **91** (119 mg:0.58 mmol: 8%) as yellow oils in a ratio of 5:1:

Data for 1-(phenylthiomethyl)cyclohexene **90**: IR ($CDCl_3$ solution); 1580 and 1660 cm^{-1}. δ_H (200 MHz ; $CDCl_3$); 1.1-1.2 (10H, m, H-3,4,5 and 6), 3.46 (2H, s, H-7); 5.51 (1H, m, H-2) and 7.12-7.47 (5H, m, H-9,10 and 11). δ_C (50 MHz); 22.69(C-4),25.25 (C-5), 27.21 (C-3) 29.69 (C-6), 42.3 (C-7), 125.59(C-11), 126.00 (C-9), 128.58 (C-10), 130.06 (C-2), 133.00 (C-1) 136.85 (C-8). *m/z* 204

(M+, 42.6), 110(39.7) and 95 (100%) (Found M, 204.0977 $C_{13}H_{16}S$ requires 204.0972)

Data for phenylthiomethylidenecyclohexane **91**: δ_H (200 MHz : $CDCl_3$); 1-2.5 (10H, m, H-2-6), 5.78 (1H, s, H-7) and 7.02-7.23 (5H, m, H-9, 10 and 11). δ_C(50 MHz) 26.44 (C-4), 28.37 (C-3), 30.41 (C-2), 125.42 (C-7), 127.68 (C-9), 128.82 (C-10), 129.06 (C-1), 137.68 (C-8) and 148.26 (C-7). *m/z* 204 (M^+, 95.1), 147 (17.5), 141 (10.5) and 129 (20.3%) (Found M^+, 204.0976 $C_{13}H_{16}S$ requires M, 204.0972)

1-(PHENYLTHIO(TRIMETHYLSILYL)METHYL)-CYCLOHEXENE (87)

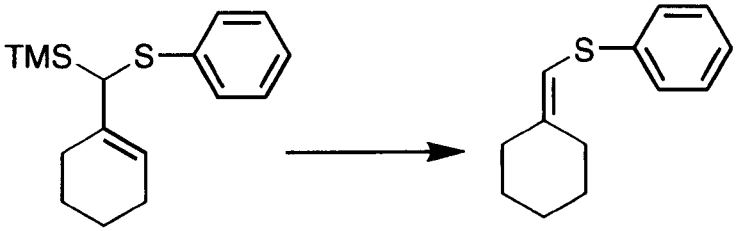


90 **87**

To a solution of 1-(phenylthiomethyl)cyclohexene (1.35 g: 66.2 mmol) in 10 ml THF held at -78°C was added dropwise LDA (6.61 ml: 100 mmol). The resulting solution was stirred for 2 h maintaining the temperature at -78°C. A solution of trimethylsilylchloride (1.26 ml: 1.08 g: 100 mmol) was then slowly added and the mixture stirred at -78°C for 4 h. The reaction was quenched with a saturated solution of ammonium chloride and extracted with ether. The organic extracts were washed with 10% aqueous hydrochloric acid (2 x 20 ml), sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml) and dried over magnesium sulfate. The ether was then removed under reduced pressure to give the crude product as the residue. Purification *via*

column chromatography eluting with petroleum ether afforded 1-(phenylthio(trimethylsilyl)methyl)cyclohexene **87** as a yellow oil (698 mg: 2.52 mmol: 38%); IR (neat) ν_{max}1590 and 1650 cm^{-1}. δ_H (200 MHz: $CDCl_3$): 0.15 (9H, s, TMS), 1.4 - 2.1 (8H, m, H-3,4,5 and 6), 3.14 (1H, s, H-7), 5.45 (1H, m, H-2) and 7.03 - 7.30 (5H, m, H-9,10 and 11) δ_C (50 MHz): -1.86 (TMS), 22.57, 23.08, 26.44, 29.72, 123.05 (C-11), 125.05 (C-9), 127.47 (C-10), 129.04 (C-2), 138.46 (C-8) and 148.22 (C-1) *m/z*: 276 (M^+, 9.3), 199 (7.9), 167 (6.3) and 109 (35%) (Found M^+, 276.1369 $C_{16}H_{24}SSi$ requires M, 276.1598)

ATTEMPTED PREPARATION OF 2-PROPANOYL-1-PHENYLTHIO-METHYLENE)CYCLOHEXANE (95)

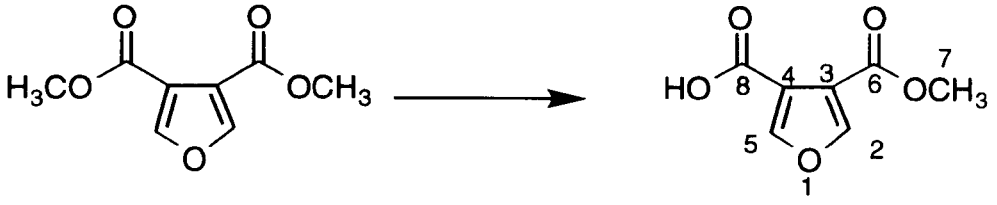


87 **91**

A dry flask held in a nitrogen atmosphere was cooled to -78°C and aluminium chloride (72 mg : 0.54 mmol) and CH_2Cl_2 (10 ml) were added. A solution of propionyl chloride (0.05 ml: 0.54 mmol) in CH_2Cl_2 (4 ml) was then slowly added followed by 1- (phenylthio(trimethylsilyl)methyl)cyclohexene **87** (10 mg: 0.36 mmol) and the resulting solution was stirred for 6 h with the temperature maintained at -78°C. The reaction was quenched with ammonium chloride (4 ml: 1M solution) and warmed to room temperature. The reaction was diluted with diethyl ether (10 ml) and washed with brine (2 x 20 ml), sodium bicrbonate (2 x 20 ml) and dried over magnesium sulfate. Tlc indicated that a product had been made and nmr was consistent with phenylthiomethylidenecyclohexane.

6.4 ATTEMPTED SYNTHESIS OF FURAN (76) *VIA* AN INTRAMOLECULAR GRIGNARD - METHOD ONE

4-CARBOMETHOXY-3-FUROIC ACID (105)



98 **105**

ATTEMPT 1: USING LITHIUM HYDROXIDE

A stirring solution of dimethyl 3,4-furan dicarboxylate (200 mg: 1.08 mmol) in methanol (9 ml) and water (3 ml) was cooled to 0°C and lithium hydroxide (228 mg: 5.4 mmol) slowly added. The resulting solution was stirred for 24 h. Water (10 ml) was then added and the solution brought to pH 5 with 1M HCl. The solution was extracted with ethyl acetate (3 x 10 ml) but tlc of this extract indicated the presence of starting material only.

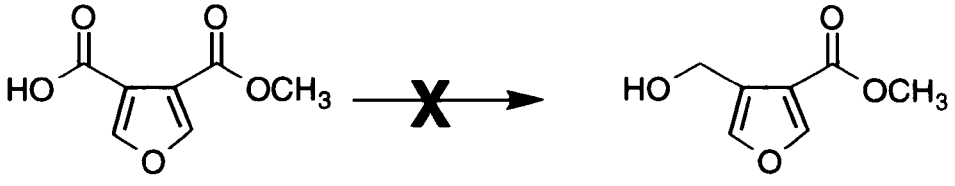
ATTEMPT 2: USING CYCLIC ANHYDRIDE WITH ACID CATALYST

Dimethyl 3,4-furan dicarboxylate **98** (115 mg: 0.62 mmol) was dissolved in THF (10 ml) and a catalytic amount of conc. sulfuric acid added. The resulting solution was then refluxed for 4 h. Tlc indicated starting material only.

ATTEMPT 3 USING *IN SITU* SILYL ESTER FORMATION

To a flame dried flask, flushed with nitrogen, was charged dimethyl 3,4-furan dicarboxylate **98** (500 mg: 2.7 mmol), acetonitrile (10 ml) and sodium iodide (1.22 g: 8.14 mmol). To this stirring solution was added dropwise a solution of trimethylsilylchloride (1.027 ml: 0.88 g: 8.09 mmol) in acetonitrile (25 ml) and the resulting solution refluxed for 4 h. The solution was cooled and water (50 ml) added to hydrolyse the silyl ester. The solution was extracted with diethyl ether (3 x 20 ml). The organic extracts were combined and washed with sodium thiosulfate and sodium bicarbonate (3 x 20 ml). The sodium bicarbonate washings were cooled to 0°C and acidified with 1M HCl. The resulting aqueous solution was then extracted with ethyl acetate (3 x 20 ml) and the combined organic extracts washed with brine (3 x 20 ml). The solvent was removed *in vacuo* and purification *via* column chromatogaphy, eluting with light petroleum/ ethyl acetate (1:1) afforded 3-carbomethoxy-4-furoic acid **105** (218 mg: 1.28 mmol: 47%) δ_H (200 MHz: $CDCl_3$): 3.93 (3H, s, H-7), 8.07 (1H, d,$J_{2,5}$ 1.78 Hz, H-2), 8.17 (1H, d, $J_{5,2}$ 1.77 Hz H-5) δ_C (50 MHz): 53.57 (C-7), 114.99 (C-4), 116.66 (C-3), 150.72 (C-5), 152.54 (C-2), 161.14 (C-6) and 167.09 (C-8); *m/z*: 170 (M^+, 15.5), 139 (95.5) and 111 (3.5%) (Found M^+, 170.0205, $C_7H_6O_5$ requires 170.0.215).

ATTEMPTED SELECTIVE REDUCTION OF ACID GROUP IN PRESENCE OF ESTER



METHOD 1: USING BORANE REDUCTION

To a flame dried flask flushed with nitrogen was added THF (10 ml) followed by the acid **105** (272 mg: 1.6 mmol) and the flask was cooled to -20°C. Borane-THF

adduct (1.6 ml: 1.0 M solution in THF: 1.6 mmol) was slowly added and the solution allowed to warm slowly to room temperature. The resulting solution was stirred overnight but tlc indicated the presence of starting material only.

METHOD 2: USING REDUCTION OF *IN SITU* ACID CHLORIDE (IN THF)

Preparation of Acid Chloride: To a flask containing THF (20 ml) was added the acid **105** (147 mg: 0.86 mmol) followed by thionyl chloride (1.88 ml: 3.0 g: 2.58 mmol) and the solution refluxed for 4 h.

Preparation of zinc modified sodium cyanoborohydride solution: A flame dried flask held in a nitrogen atmosphere was charged with sodium cyanoborohydride (108 mg: 1.7 mmol), zinc chloride (118 mg: 0.86 mmol) and THF (20 ml). The resulting mixture was stirred at room temperature for 3 h.

The THF solution of the zinc modified sodium cyanoborohydride, which contains most of the reducing power was syringed out of the flask and slowly added to the acid chloride. The solution was then stirred for 48 h at room temperature. Methanol (5 ml) was then added followed by potassium iodate (20 ml: 0.1 M). Tlc of the solution indicated that only starting material was present.

METHOD 3:USING REDUCTION OF *IN SITU* ACID CHLORIDE (IN DIETHYL ETHER)

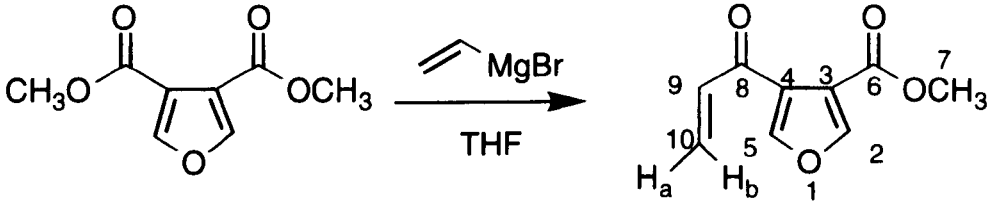
Preparation of Acid Chloride: To a flask containing the acid **105** (150 mg: 0.8 mmol) was charged diethyl ether (10 ml) followed by thionyl chloride (0.12 ml: 1.99 mg: 1.68 mmol) and the resulting solution stirred for 1 h then brought to reflux for 3 h.

Preparation of zinc modified sodium cyanoborohydride: A flame dried flask held in a nitrogen atmosphere was charged with sodium cyanoborohydride (92 mg: 1.46 mmol), zinc chloride (200 mg: 1.5 mmol) and diethyl ether (20 ml). Thr resulting slurry was stirred for 1 h.

The acid chloride was then syringed into the flask containing the zinc modified sodium cyanoborohydride and the resulting solution stirred for 24 h. Methanol (5 ml) was then added followed by potassium iodate (20 ml: 0.1 M). Tlc of the resulting solution indicated that only starting material was present.

6.5 ATTEMPTED SYNTHESIS OF FURAN (76) *VIA* AN INTRAMOLECULAR GRIGNARD - METHOD TWO

METHYL 4-(2-PROPENOYL)-3-FUROATE

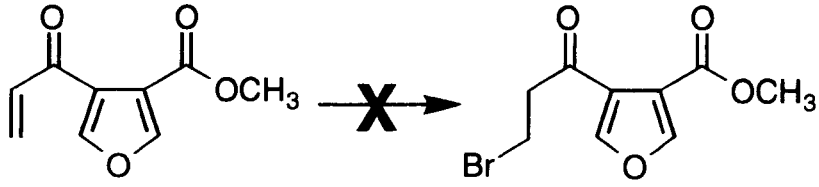


98 **108**

To a solution of dimethyl 3,4-furan dicarboxylate **98** (5 g: 27.15 mmol) in THF (30 ml) was added vinylmagnesium bromide (30 ml: 1.0 M solution in THF; 35 mmol) dropwise. The resulting solution was stirred at room temperature for 12 h before being quenched with water and the solution extracted with ethyl acetate (3 x 25 ml). The organic extracts were combined, washed with sodium bicarbonate (3 x 25 ml), brine (3 x 25 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure to leave the crude product as an oil. Purification *via*

column chromatography eluting with light petroleum/ethyl acetate (5:1) afforded methyl-4(2-propenoyl)-3-furoate **108** as a yellow oil (1.8 g: 10 mmol: 37%) δ_H(200 MHz; $CDCl_3$) 3.85 (3H, s, H- 7), 5.16 (1H, dd,$J_{10a,10b}$ 1.18 Hz, $J_{10a,9}$ 10.43,Hz H-10a), 5.24 (1H, m, H-10b), 6.06 (1H, dd,$J_{9,10a}$ 11.70 Hz, $J_{9,10b}$ 16.08 Hz, H-9), 7.27 (1H, d,$J_{2,5}$ 1.7 Hz H-2), 8.03 (1H, d,$J_{5,2}$ 1.72 Hz H-5); δ_C(50 MHz) 52.29 (C-7), 114.78 (C-10), 117.16 (C-4), 116.2 (C-3), 129.36 (C-9), 141.61 (C-2), 150.62 (C-5), 165.52 (C-6) and 178.1 (C-8). *m/z*: 180 (M^+, 100), 153 (M^+-C_2H_3, 32) and 121 (M^+-COOMe, 44%) (Found M^+, 180.1614; $C_9H_8O_4$ requires M, 180.1617).

ATTEMPTED HYDROBROMINATION OF METHYL 4-(2-PROPENOYL)-3-FUROATE



108 **109**

METHOD 1: USING HYDROBORATION WITH BORANE

A solution of the alkene **108** (179 mg: 0.99 mmol) in THF (5 ml) was added to a dry flask held in a nitrogen atmosphere followed by THF (15 ml). The flask was cooled to 0°C and BH_3.THF (3.0 ml: 1.0 M solution in THF; 3.0 mmol) was added dropwise. The resulting solution was stirred for 1 h and the temperature was maintained at 0°C. Light was then excluded from the reaction by wrapping the reaction vessel in aluminium foil and a solution of Br_2 (0.15 ml ; 467 mg: 0.46 mmol) in THF (2 ml) was added. The resulting solution was stirred at room temperature for 2 h before being quenched with water and the solution extracted with

ethyl acetate (2 x 20 ml). Tlc of the extract indicated that only starting material was present.

METHOD 2: USING HYDROBORATION WITH DICYCLOHEXYL-BORANE AND EXCLUSION OF LIGHT

To a dry flask at 0°C in a nitrogen atmosphere was added cyclohexene (0.3 ml: 243 mg: 2.8 mmol), THF (5 ml), borane-THF adduct (1.44 ml: 1.0 M solution in THF; 1.44 mmol) and the solution stirred for 1.5 h. A solution of the alkene **108** (200 mg: 1.11 mmol) in THF (5 ml) was added and the resulting solution stirred for 2 h. The flask was shielded from light and water (10 ml) followed by bromine (0.1 ml: 311 mg: 1.95 mmol) was added and the resulting solution was stirred at 0°C for 1 h before being quenched with water and the solution extracted with ethyl acetate (2 x 20 ml). Tlc of the extract indicated that no product had been formed and the starting material remained.

METHOD 3: USING HYDROBORATION WITH DICYCLOHEXYL-BORANE

To a dry flask flushed with nitrogen and and cooled to 0°C was added cyclohexene (0.3 mmol: 243 mg: 2.8 ml), THF (5 ml) and borane-THF (1.44 ml: 1.0 M solution in THF: 1.44mmol). The resulting solution was then stirred for 1 h. The alkene **108** (200mg: 1.11 mmol) was then slowly added and the resulting solution was stirred for 0.75 h. Without sheilding from light and without quenching the borane a solution of bromine (0.1 ml: 312 mg: 1.95 mmol) in THF (2 ml) was slowly added followed by a solution of sodium methoxide in methanol. The resulting solution was alowed to stir for 12 h at room temperature . Tlc indicated that no product had been formed.

METHOD 4: USING *IN SITU* FORMATION OF BrCl

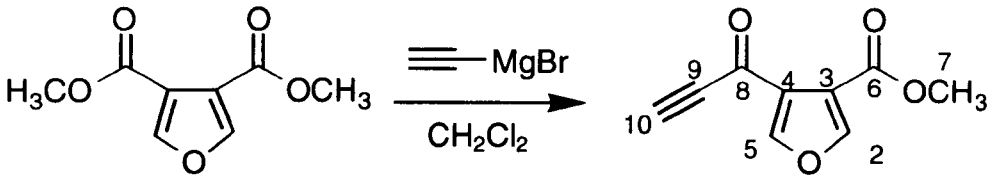
To a dry flask flushed with nitrogen and cooled to O°C was charged the alkene **108** (200mg; 1.11 mmol), THF (10 ml), borane.THF adduct (1.66 ml; 1.0M solution in THF; 1.66 mmol) and the reaction stirred for 2h. Sodium bromide (171 mg: 1.66 mmol) in water (10 ml) was added and the reaction cooled to 0°C and sheilded from light. Chloramine-T (758 mg: 3.7 mmol) was dissolved in a mixture of THF (7.5 ml) and water (7.5 ml) and then added to the solution. The mixture was then treated with a 10% HCl solution saturated with sodium chloride (10 ml) and the resulting solution was stirred for 15 minutes. The resulting solution was quenched with ammonium chloride. Tlc indicated the presence of only starting material.

METHOD 5:USING HYDROALUMINATION WITH LITHIUM ALUMINIUM HYDRIDE

To a dry flask flushed with nitrogen was added the alkene **108** (200 mg: 1.11 mmol), THF (10 ml), lithium aluminium hydride (0.3 ml: 1.0 M solution in THF; 0.3 mmol), and a catalytic amount of titanium tetrachloride and the resulting solution stirred for 3 h. The solution was cooled to -78°C and copper (II) bromide (0.59 g: 2.6 mmol) added before stirring the solution overnight and allowing to warm gradually to room temperature. The reaction was quenched with water and the solution was extracted with diethyl ether. Hydrochloric acid (1M) was added in order to solubilise the green precipitate which had formed. The combined extracts were then washed with sodium bicarbonate and brine and dried over magnesium sulfate. The solvent was reduced *in vacuo*. Tlc indicated a mixture of products which could not be separated.

6.6 ATTEMPTED SYNTHESIS OF FURAN (76) *VIA* AN INTRAMOLECULAR GRIGNARD - METHOD THREE

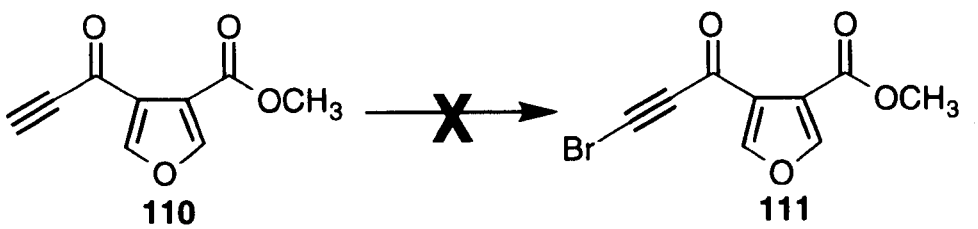
GRIGNARD ATTACK USING ETHYNYLMAGNESIUM BROMIDE



98 **110**

To a flame dried flask held in a nitrogen atmosphere was added the dimethyl 3,4-furan dicarboxylate **98** (200 mg: 1 mmol) followed by CH_2Cl_2 and the solution cooled to 0°C. Ethynylmagnesium bromide (2.6 ml: 1.5 M solution in THF: 1.73 mmol) was added to the stirring solution before stirring for for 6 h. The solution was diluted with water (50 ml) and then extracted with diethyl ether (3 x 25 ml). The combined organic extracts were washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml), dried over magnesium sulfate and the organics removed *in vacuo*. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (5:1) afforded a mixture of starting material **98** and product **110**, which could not be separated further by this method. δ_H ($CDCl_3$: 90 MHz): 1.7 (1H, s, H-10), 3.5 (3H, s, H-7), 7.4 (1H, s, H-2) and 7.6 (1H, s, H-5)

ATTEMPTED BROMINATIONS



110 **111**

METHOD 1: USING HYPOBROMITE SOLUTION

Sodium hydroxide (5 g) was dissolved in ice (20 g), and to the resulting slurry bromine (3.2 ml: 9.98 g: 62 mmol) was added. The alkyne **110** (150 mg: 0.78 mmol)was added to the hypobromite solution formed and the mixture stirred overnight. A saturated solution of ammonium chloride (20 ml) was then added and the solution extracted with diethyl ether (2 x 15 ml). The combined organic extracts were washed with water (2 x 10 ml) and dried over magnesium sulfate. Tlc of the resulting organics indicated that no product had been formed. Starting material was reclaimed.

METHOD 2 : USING *n*-BUTYL LITHIUM / BROMINE

A solution of the alkyne **110** (161 mg: 0.9 mmol) in THF (10 ml) was cooled to -78°C and shielded from light. *n*-Butyl lithium (0.85 ml: 1.6 M solution in THF; 1.3 mmol) was slowly added and the reaction vessel temperature raised to -20°C. A solution of bromine (0.1 ml: 312 mg: 1.95 mmol) in THF (5 ml) was added. The solution was then warmed to room temperature and stirred for 24 h before quenching with a saturated solution of ammonium chloride (10 ml). Tlc indicated a complex mixture of unisolable products.

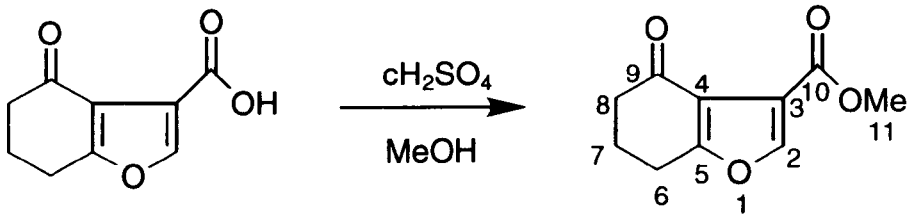
METHOD 3: USING *n*-BUTYL LITHIUM / *N*-BROMOSUCCINIMIDE

A solution of the alkyne **110** (134 mg: 0.7 mmol) in THF (10 ml) was cooled to -70°C and *n*-butyl lithium (0.8 ml: 1.6 M solution in THF; 1.3 mmol) added. *N*-bromosuccinimide (224 mg: 1.26 mmol) was added and the resulting solution stirred

at 0°C for 1 h. Tlc indicated no product so the reaction was warmed to room temperature and stirred overnight. Tlc indicated no reaction.

6.7 ATTEMPTED SYNTHESIS TO FURAN (112)

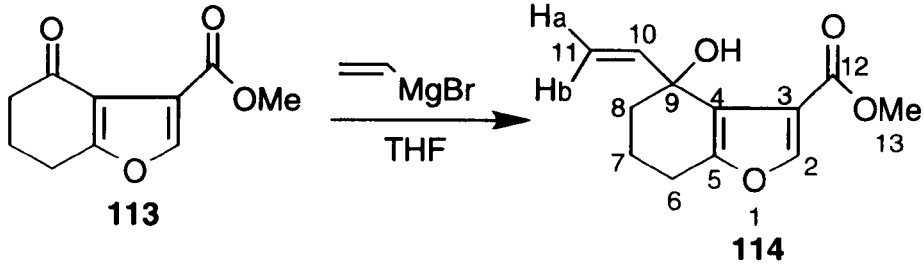
METHYL 4,5,6,7-TETRAHYDRO-4-OXO-BENZO[*b*]FURAN-3-CARBOXYLATE



113

A solution of 4,5,6,7-tetrahydro-4-oxo-benzo[*b*]furan-3-carboxylic acid (190 mg: 1.05 mmol) in methanol (15 ml) and a catalytic amount of sulfuric acid was refluxed for 12 h. The mixture was then cooled, water was added and the solution was extracted with ethyl acetate (3 x 20 ml), washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml), dried over magnesium sulfate and the solvent removed under reduced pressure. Purification using column chromatography afforded **113** as a yellow powder (89.3 mg: 0.46 mmol: 47%) m.p. 103°C: δ_H(200 MHz: $CDCl_3$): 2.11 (2H, m, H-7), 2.48 (2H, m, H-6), 2.84 (2H, m, H-8), 3.78 (3H, s, H-11) and 7.81 (1H, s, H-2); δ_C (50 MHz): 22.06 (C-7), 23.5 (C-6), 38.59 (C-8), 51.92 (C-11), 115.96 (C-4), 117.61 (C-3), 147.95 (C-2), 161.30 (C-10), 168.42 (C-5) and 192.04 (C-9). *m/z*: M^+, 194 (37.3), 166 (100) and 108 (42.8%) (Found M^+, 194.0586; C 61.72 and H 5.14%, $C_{10}H_{10}O_4$ requires M, 194.0579: C 61.85 and 5.15%)

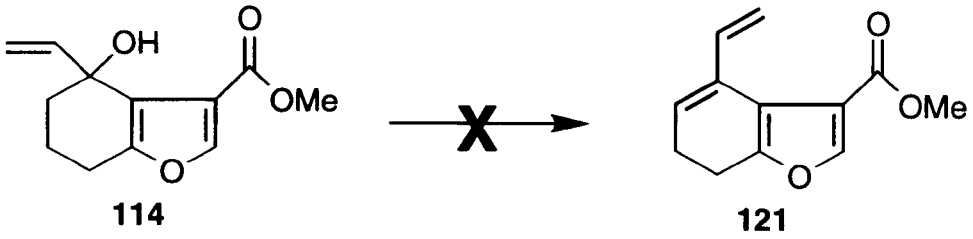
GRIGNARD ATTACK ON ESTER 113



113 **114**

To a solution of ester **113** (1.93 g: 9.99 mmol) in THF 20 ml in a flame dried flask held in a nitrogen atmosphere and cooled to 0°Cwas added vinylmagnesium bromide (11.5 ml: 1.0 M in THF: 11.5 mmol) and the resulting solution stirred for 12 h. The reaction was then quenched with a saturated solution of ammonium chloride and the solution extracted with ethyl acetate (3 x 25 ml). The combined extracts were washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml), dried over magnesium sulfate and the solvent removed *in vacuo* to give the crude product as the residual oil. Purification using column chromatography eluting light petroleum; ethyl acetate (4:1) afforded the desired compound **114** as a yellow powder; 1.23 g (5.54 mmol: 55%) m.p. 66°C IR ν_{max} (nujol mull): 3128 and 1714 cm^{-1}. δ_H (200 MHz; $CDCl_3$): 1.6-1.9 (6H, m, H-6,7 and 8), 3.83 (3H, s, H-13), 4.7 (1H, dd,$J_{11b,11a}$ 1.22 Hz ,$J_{11b,10}$ 17.23 Hz, H-11b), 5.07 (1H, dd,$J_{11a,11b}$ 1.22 Hz, $J_{11a,10}$ 10.45 Hz, H-11a), 6.08 (1H, dd,$J_{10,11b}$ 10.44 Hz, $J_{10,11a}$ 17.26 Hz, H-10) and 7.87 (1H, s, H-10); δ_C (50 MHz): 19.59 (C-7), 22.77 (C-6), 36.07 (C-8), 52.03 (C-13), 71.93 (C-9), 113.99 (C-11), 117.19 (C-4), 120.66 (C-3), 143.92 (C-10), 147.54 (C-2), 153.91 (C-5) and 165.49 (C-12). *m/z*: 222 (M^+, 18.9), 191 (M^+-OMe, 6.9) and 163.9(M^+-COOMe, 100%) (Found M, 222.0893, $C_{12}H_{14}O_4$ requires 222.0892)

6.6 ATTEMPTED DEHYDRATION OF TERTIARY ALCOHOL (114)



114 **121**

METHOD 1: USING $SOCl_2$ / PYRIDINE

To a flame dried flask held in a nitrogen atmosphere were charged the alcohol **114** (100 mg: 0.45 mmol), pyridine (1 ml) and thionyl chloride (2 ml). The resulting solution was stirred for 1 h before being poured into an ice-water mixture.(20 g) The solution was then extracted with ethyl acetate (2 x 15 ml). Tlc indicated that only baseline material was present and the reaction was abandoned.

METHOD 2: USING p-TsOH / BENZENE

A catalytic amount of para-toluenesulfonic acid was added to a solution of the alcohol **114** (100 mg: 0.45 mmol) in benzene (25 ml) and the resulting solution was refluxed under Dean and Stark conditions. The solution turned black and tlc indicated that mainly baseline material was present. The reaction was abandoned.

METHOD 3: USING $BF_3.OEt_2$

To a solution of the alcohol **114** (100 mg: 0.45 mmol) in CH_2Cl_2 (20 ml) was added slowly dropwise $BF_3.OEt_2$ (0.06 ml: 71.4 mg: 0.50 mmol). The solution

turned a deep purple colour and tlc indicated that all the starting material had been converted to baseline. The reaction was abandoned.

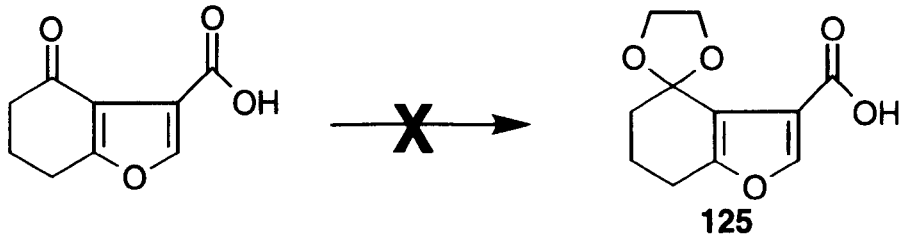
METHOD 4: USING $CuSO_4$ SUPPORTED CATALYST

The catalyst was first prepared by adding silica (1 g) to a solution of copper sulfate (390 mg: 2.45 mmol) in water (10 ml). The water was removed under reduced pressure and the resulting powder was heated at 150°C for 2 h. The catalyst (0.56 g) was then added to a solution of the alcohol **114** (100mg: 0.45 mmol) in cyclohexane (10 ml) and stirred for 1 h. Tlc indicated that there were several unisolable products present.

METHOD 5: USING $KHSO_4$

To a flame dried flask held in a nitrogen atmosphere was added the alcohol **114** (100 mg: 0.45 mmol), THF (10 ml) and a catalytic amount of $KHSO_4$. The resulting solution was allowed to reflux for 3 h. Tlc indicated that there was a less polar product and this was attempted to be isolated by column chromatoraphy eluting with light petroleum: ethyl acetate but decomposition occurred and product was never recovered.

6.8 ALTERNATIVE SYNTHESIS TO TARGET FURAN (112) *VIA* PROTECTED KETOFURAN (125)



125

METHOD 1: USING ETHYLENE GLYCOL AND TMSCl

Ethylene glycol (4 ml: 4.45 g: 72 mmol), methanol (10 ml), ketone (120 mg: 0.61 mmol) and trimethylsilyl chloride (153 mg: 0.18 ml: 1.4 mmol) were stirred at room temperature for 50 hours. The reaction was monitored by tlc but after this time only starting material was present.

METHOD 2: USING ETHYLENE GLYCOL AND TMSCl (CONCENTRATED)

A solution of ketone (120 mg: 0.6 mmol), ethylene glycol (10 ml) and trimethylsilyl chloride (0.334ml: 285 mg: 2.64 mmol) was stirred at room temperature for 24 h. Tlc revealed that no product had been formed.

METHOD 3:USING ETHYLENE GLYCOL AND TRIETHYL-ORTHOFORMATE

Ethylene glycol (5 ml: 5.56 g: 89 mmol), triethyl orthoformate (0.1 ml), ketone (120 mg: 0.61 mmol) and a catalytic amount of *p*-TsOH was stirred for 24 h. Tlc analysis indicated that no product had been formed.

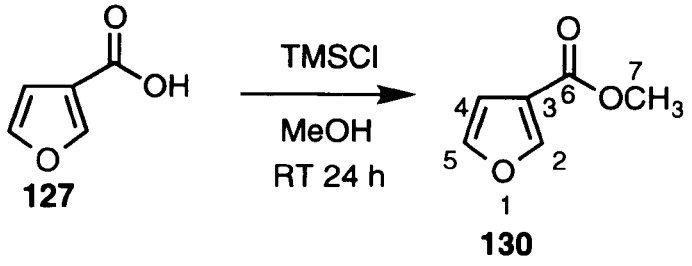
METHOD 4: USING ETHYLENE GLYCOL AND OXALIC ACID

A solution of ethylene glycol (5 ml), oxalic acid (100mg: 0.7 mmol) and ketone (120 mg: 0.61 mmol) in CH_3CN (15ml) was allowed to stand at room temperature for 1 h before cold water (10 ml) was poured onto the mixture. The organics were extracted with diethyl ether. Tlc analysis of this revealed that no product had been formed.

6.9 SYNTHESIS OF 3,5 DISUBSTITUTED FURANS VIA FRIEDEL-CRAFTS ACYLATION

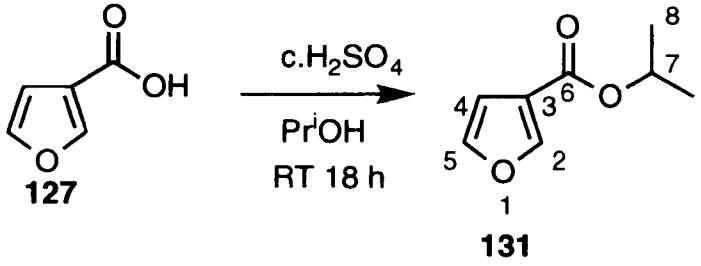
ESTERIFICATION OF FUROIC ACID

METHYL 3-FUROATE (130)



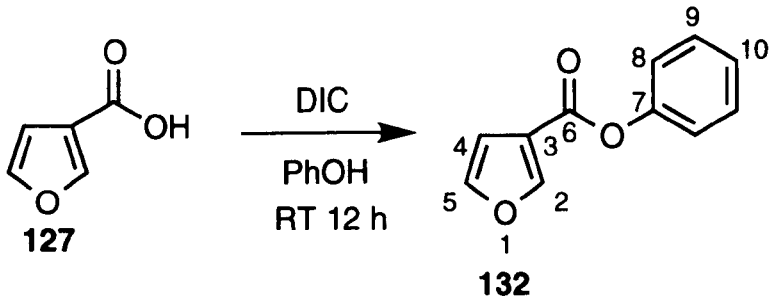
Chlorotrimethylsilane (4.97 ml: 4.25 g: 39.16 mmol) was added dropwise to a stirred solution of 3-furoic acid (2 g: 17.8 mmol) in dry methanol (20 ml) in a nitrogen atmosphere. The resulting solution was stirred at room temperature for 24 h. Water (25 ml) was added and the solution extracted with ethyl acetate (3 x 35 ml). The combined extracts were then washed with sodium bicarbonate (3 x 30 ml), brine (3 x 25 ml), dried over magnesium sulfate and the solvent removed *in vacuo* to give the crude product. Purification *via* column chromatography eluting with light petroleum/ethyl acetate (4:1) afforded methyl 3-furoate **130** as a colourless oil (1.3 g: 10 mmol: 57%). IR ν_{max}($CHCl_3$ soln) 1728, 3024 and 3156 cm^{-1}; δ_H (200MHz: $CDCl_3$) 3.79 (3H, s, H-7) 6.74 (1H, dd, $J_{4,2}$ 0.68 Hz, $J_{4,5}$ 1.88 Hz, H-4), 7.43 (1H, dd, $J_{5,4}$ 1.72 and $J_{5,2}$ 1.52 Hz, H-5) and 8.02 (1H, dd, $J_{2,4}$ 0.73 Hz, $J_{2,5}$ 1.48Hz, H-2);δ_c (50 MHz) 51.2 (C-7), 109.5 (C-4), 119.0 (C-3), 143.5 (C-5), 147.5 (C-2) and 161.3 (C-6)`; *m/z* 126 (M^+, 45.7) and 95 (M^+-OMe100%) (Found M 126.0317: $C_6H_6O_3$ requires 126.0316)

ISOPROPYL 3-FUROATE (131)



To a stirred solution of 3-furoic acid **127** (10 g, 89 mmol) in isopropanol (75 ml) was added dropwise a catalytic amount of concentrated sulfuric acid. The resulting mixture was then stirred at room temperature for 18 h. Water (100 ml) was added and the solution extracted with ethyl acetate (3 x 25 ml). The organic layers were combined, washed with sodium bicarbonate (3 x 25 ml), brine (3 x 25 ml) and dried over magnesium sulfate. The solvent was then removed under reduced pressure and the residual oil purified by column chromatography with light petroleum: ethyl acetate (4:1) as the eluent to yield isopropyl 3-furoate **131** (8.25 g: 53 mmol: 60%), IR ν_{max}(film) 1722 cm^{-1}). δ_H(200MHz; film) 1.20 (6H, d, $J_{8,7}$ 6.27, H-8)), 5.07 (1H, septet, $J_{7,8}$ 6.6 Hz, H-7), 6.62 (1H, dd, $J_{4,5}$ 1.87 Hz, $J_{4,2}$ 0.72 Hz, H-4), 7.30 (1H, dd, $J_{5,4}$ 1.72 Hz $J_{5,2}$ 1.44 Hz, H-5), 7.89 (1H, dd, $J_{2,4}$ 0.7 Hz, $J_{2,5}$ 1.48 Hz, H-2); δ_C(50 MHz; $CDCl_3$) 21.64 (C-8), 67.57 (C-7), 109.66 (C-4) 119.84 (C-3), 143.41 (C-5), 147.31 (C-2), 162.40 (C-6); *m/z*: 154 ($M^{+\cdot}$ 10.1), 112 (33.2) and 95 (100.0%) (Found M^+, 154.0624 $C_8H_{10}O_3$ requires M 154.0629).

PHENYL 3-FUROATE (132)

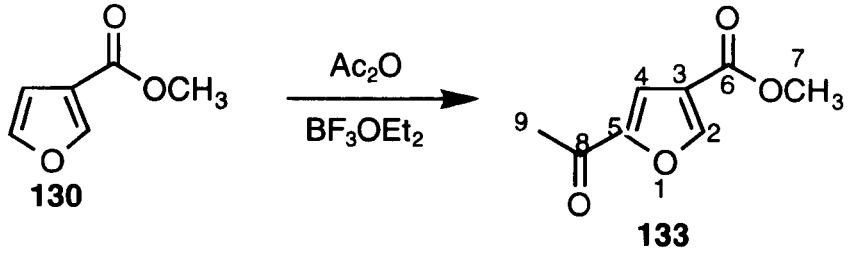


To a stirring solution of furoic acid **127** (1 g: 8.9 mmol) and phenol (1.25 g: 13.35 mmol) held in a nitrogen atmosphere was added diisopropylcarbodiimide (2.09 ml: 1.68 g: 13.3 mmol) dropwise. The resulting solution was stirred at room temperature for 12 h before being quenched with water (50 ml) and the solution extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give the crude product as a residual oil. Purification by column chromatography eluting with light petroleum/ethyl acetate (10:1) afforded phenyl 3-furoate **132** as white crystals (1.13 g: 6.01 mmol: 68%) m.p. 36-38°C IR ν_{max} ($CHCl_3$ solution): 1739, 3013, 3029 and 3154 cm^{-1}. δ_H (200 MHz): 6.88 (1H, d, $J_{4,5}$ 1.21 Hz, H-4), 6.97 - 7.50 (6H, m, H-5,8,9 and 10) and 8.20 (1H, d, $J_{2,4}$ 0.63 Hz, H-2); δ_C (50 MHz): 110.03 (C-4), 118.84 (C-3), 121.67 (C-8), 125.90 (C-10), 129.46 (C-9), 144.04 (C-5), 148.65 (C-2), 150.41 (C-7) and 161.38 (C-6). *m/z*: 188 (M^+, 21.6) and 95 (M^+-OPh, 100%) (Found M^+, 188.0474 $C_{11}H_8O_3$ requires 188.0473).

GENERAL PROCEDURE FOR FRIEDEL-CRAFTS REACTIONS

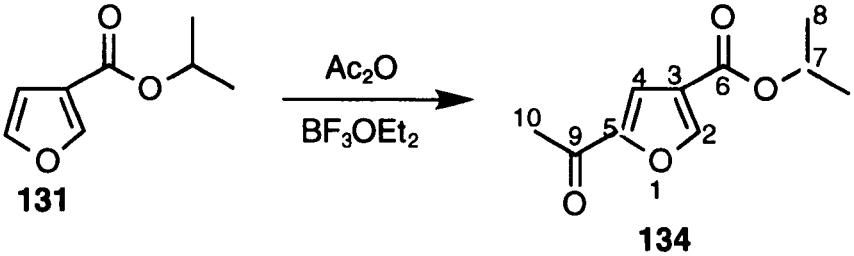
A solution of the appropriate ester and either acetic anhydride or the appropriate acid chloride (2 ml) was heated to the desired temperature before $BF_3.OEt_2$ was added dropwise. The reaction was monitored by tlc and quenched with water when complete. The solution was extracted with ethyl acetate (3 x 25 ml) and the combined organic extracts washed with sodium bicarbonate, brine and dried over magnesium sulfate. The solvent was reduced *in vacuo* to leave the crude product as a black residual oil. Purification procedures are described followed by the data for each compound.

METHYL 5-ACETYL-3-FUROATE (133)



The general procedure was followed using methyl 3-furoate (200 mg; 1.58 mmol), acetic anhydride (2 ml), and $BF_3.OEt_2$ (0.48 ml: 0.57 g: 4.08 mmol). The temperature of the reaction was 50°C and the time taken for completion was 5 minutes. Purification by column chromatography eluting with light petrolum/ ethyl acetate (4:1) afforded methyl 5-acetyl-3-furoate **133** (122 mg: 5.8 mmol: 46%) IR ν_{max}(KBr disc); 1721 and 1673.9 cm^{-1}; δ_H(200 MHz: $CDCl_3$) 2.50 (3H, s, H-9), 3.90 (3H, s, H-7), 7.46 (1H, d, $J_{4,2}$ 0.63 Hz, H-4) and 8.13 (1H, d, $J_{2,4}$ 0.64 Hz, H-2); δ_C(50MHz); 26.101 (C-9), 52.032 (C-7), 114.41 (C-4), 116.305 (C-3), 150.197 (C-2), 153.214 (C-5), 162.397 (C-6) and 186.52 (C-8). *m/z*168 (M^+, 48.0), 153 (100), 121 (25.3) and 95 (29.8%); (Found M^+ 168.0414; C 57.29 H 4.72%; $C_8H_8O_4$ requires M^+, 168.0421 C 57.14, H 4.76%)

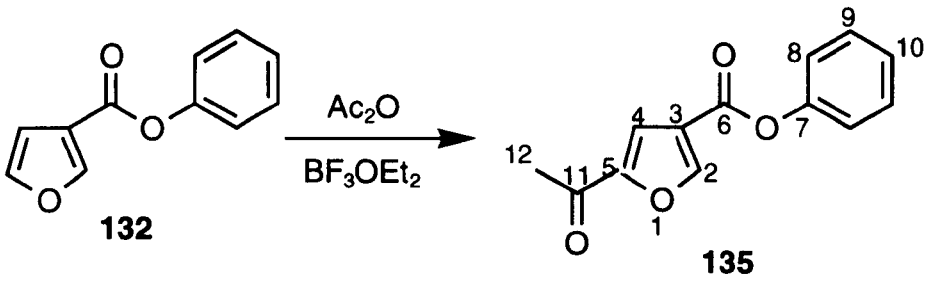
ISOPROPYL 5-ACETYL-3-FUROATE (134)



The general procedure was followed using isopropyl 3-furoate **131** (260 mg: 1.68 mmol), acetic anhydride and $BF_3.OEt_2$ (0.2 ml: 238 mg: 1.7 mmol). The

temperature was 50°C and the time for completion was 5 minutes. Purification by column chromatography eluting with light petroleum/ethyl acetate (5:1) afforded isopropyl 5-acetyl-3-furoate **134** as a yellow solid; 105 mg (0.535 mmol: 32%); IR ν_{max} ($CHCl_3$ solution); 3147, 3030, 3011, 1719.4 and 1683.2 cm^{-1}; δ_H(200 MHz: $CDCl_3$):1.34 (6H, d, $J_{8,7}$ 6.24 Hz, H-8), 2.5 (3H, s, H-10), 5.17 (1H, septet, $J_{7,8}$ 6.25 Hz, H-7), 7.46 (1H, d, $J_{4,2}$ 0.62 Hz, H-4) and 8.1 (1H, d, $J_{2,4}$ 0.62 Hz, H-2) δ_C (50 MHz): 21.87 (C-8), 36.96 (C-10), 68.72 (C-7), 116.56 (C-4), 128.94 (C-3), 150.09 (C-2), 153.2 (C-5)152.9 (C-6) 186.5 (C-9). *m/z*: 196 (M^+, 25.5), 180 (23.5),153 (37.3), 139 (100) and 124 (29.8%); (Found M^+, 196.0723: $C_{10}H_{12}O_4$ requires 196.0735.

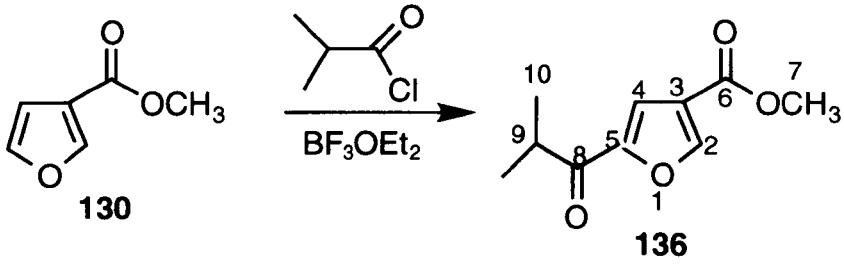
PHENYL 5-ACETYL-3-FUROATE (135)



The general procedure was followed using phenyl 3-furoate **132** (320 mg: 1.7 mmol), acetic anhydride (3 ml) and $BF_3.OEt_2$ (0.4 ml: 0.476 g: 3.4 mmol). The temperature was 50°C and the time taken for completion was 5 minutes. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (5:1) afforded phenyl 5-acetyl-3-furoate **135** as a yellow solid (255 mg: 1.1 mmol: 65%); IR ν_{max}(KBr disc): 1678, 1738, 3067 and 3134 cm^{-1}. δ_H (200 MHz; $CDCl_3$): 2.53 (3H, s, H-12), 7.16-7.54 (5H, m, H-8,9 and 10), 7.58 (1H, d, $J_{4,2}$ 0.68 Hz, H-4) and 8.29 (1H, d, $J_{2,4}$ 0.70 Hz, H-2) δ_C (50 MHz): 26.11 (C-12), 116.34 (C-4), 121.43 (C-8), 126.19 (C-10), 129.54 (C-9), 150.89 (C-2), 151.32

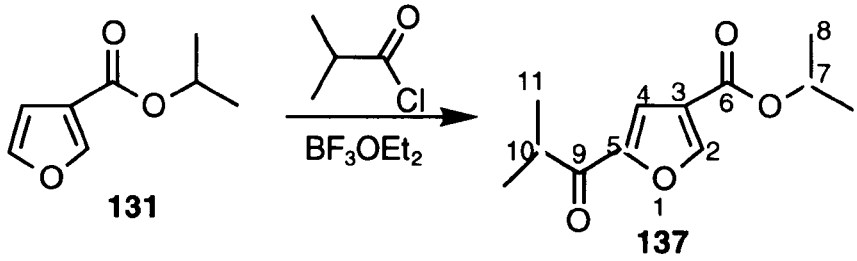
(C-7)153.2(C-7),160.1 (C-6) and 190.8 (C-11) *m/z*: 230 (M^+, 24.7) and 137 (100%) (Found 230.0577 $C_{13}H_{10}O_4$ requires 230.0579)

METHYL 5-ISOBUTYRYL-3-FUROATE (136)



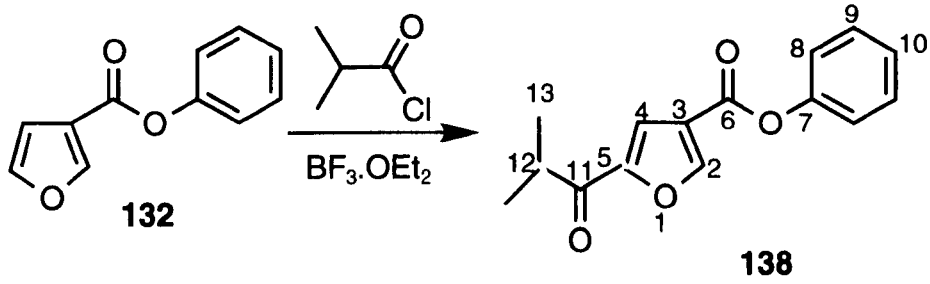
The general procedure was followed using methyl 3-furoate **130** (300 mg: 2.38 mmol), isobutyryl chloride (3 ml), $BF_3.OEt_2$ (0.5 ml: 0.595 g: 4.25 mmol). The temperature for the reaction was 50°C and the solution was stirred for 0.5 h. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (10:1) afforded methyl 5-isobutyryl-3-furoate **136** (98 mg: 0.5 mmol: 21%); m.p. 48-50°C IR ν_{max} (CH_2Cl_2 solution): 1682, 1729, 3062 and 3144 cm^{-1}. δ_H (200MHz; $CDCl_3$): 1.14 (6H, d, $J_{10,9}$ 6.86 Hz, H-10),3.26 (1H, septet, $J_{9,10}$ 6.94 Hz, H-9), 3.78 (1H, s, H-7), 7.39 (1H, d, $J_{4,2}$ 0.59 Hz, H-4), 8.06 (1H, d, $J_{2,4}$ 0.59 Hz, H-2) δ_C (50 MHz): 18.71 (C-10), 36.25 (C-9), 51.77 (C-7), 109.01 (C-3), 115.98 (C-4), 149.96(C-2), 152.36(C-5), 162.25(C-6) 190.42 (C-8) *m/z*: 196 (M^+, 21.6), 165 (M^+-OCH_3, 9.7), 153 (M^+-C_3H_7, 100%) (Found 196.0714 $C_{10}H_{12}O_4$ requires 196.0735).

ISOPROPYL 5-ISOBUTYRYL-3-FUROATE (137)



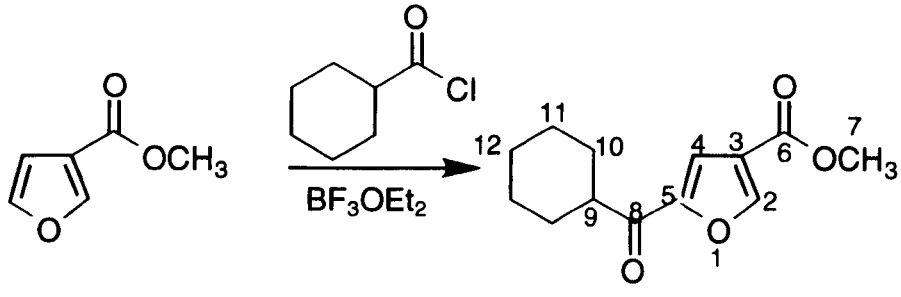
The general procedure was followed using isopropyl 3-furoate **131** (300 mg: 1.9 mmol), isobutyryl chloride and $BF_3.OEt_2$ (0.46 ml: 0.54 g: 3.89 mmol). The temperature was 90°C and the time for completion was 1h. Purification by column chromatography eluting with light petroleum/ethyl acetate (5:1) afforded isopropyl 5-isobutyryl-3-furoate **137** as a yellow solid (277 mg: 1.32 mmol: 63%); IR ν_{max} (CH_2Cl_2 soln); 1682, 1706 and 3062 cm^{-1}; δ_H (200 MHz; CDCl3); 1.19 (6H, d, $J_{10,11}$ 7.02 Hz, H-10), 1.34 (6H, d, $J_{11,10}$ 6.24 Hz, H-11), 3.32 (1H, septet, $J_{7,8}$.6.3 Hz, H-7), 5.16 (6H, septet, $J_{8,7}$ 6.26 Hz, H-8), 7.49 (1H, d, $J_{4,2}$ 0.7 Hz, H-4) and 8.13 (1H, d, $J_{2,4}$ 0.66 Hz, H-2); δ_C(50MHz); 18.61 (C-11), 21.71 (C-8), 36.29 (C-10), 68.62 (C-7), 116.30(C-4),120.2 (C-3) 149.98(C-5), 152.7 (C-2), 161.59 (C-6), and 193.41 (C-9); *m/z* 224 (M^+, 9.7), 181 (27.6) and 139 (37.1%); (Found M^+, 209.0834 : $C_{11}H_{16}O_4$ requires 209.0813)

PHENYL 5-ISOPROPYL-3-FUROATE (138)



The general procedure was followed using phenyl 3-furoate **132** (90 mg: 0.46 mmol), isobutyryl chloride and $BF_3.OEt_2$ (0.1 ml: 119 mg: 0.85 mmol). The temperature was 60°C and the time taken for completion was 1.5 h. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (10:1) afforded phenyl 5-isopropyl 3-furoate **138** as a yellow oil (64 mg: 0.248 mmol: 52%;); m.p. 94°C; IR ν_{max}(CH_2Cl_2 solution): 1705, 1744, 2979 and 3063 cm^{-1}; δ_H (200 MHz; $CDCl_3$): 1.22 (6H, d, $J_{13,12}$ 6.83 Hz, H-13), 2.64 (1H, septet, $J_{12,13}$ 6.88 Hz, H-12), 7.07-7.21 (6H, m, H-8, 9 and 10), 7.53 (1H, s, H-4) and 8.21 (1H, d, $J_{2,4}$ 0.39 Hz, H-2); δ_C (50 MHz): 18.662 (C-13), 33.755 (C-12), 116.22 (C-4), 120.60 (C-3), 121.44 (C-8), 126.15 (C-10), 129.50 (C-9), 150.09 (C-2), 152 (C-5), 160.32 (C-6) and 183.63 (C-11); *m/z*: 258 (M^+, 14.0), 165 (M^+-OPh, 100) and 137 (M^+-COOPh, 1.3%): Found 258.0877 $C_{15}H_{14}O_4$ requires 258.0892.

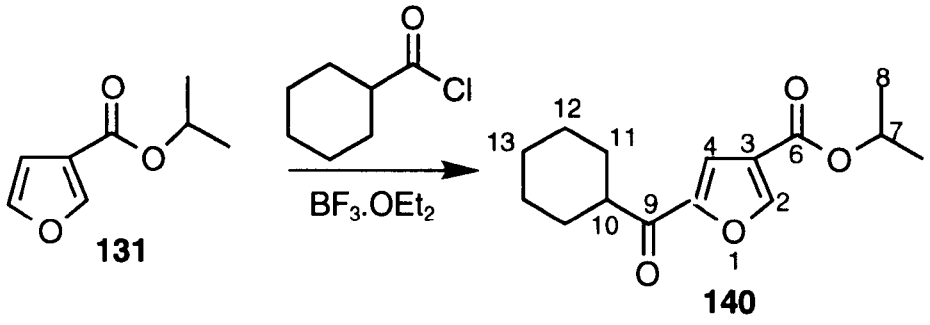
METHYL 5-CYCLOHEXYLCARBONYL-3-FUROATE (139)



The general procedure was followed using methyl 3-furoate **130** (350 mg: 2.77 mmol), cyclohexylcarbonyl chloride (3 ml) and $BF_3.OEt_2$ (0.66 ml: 0.785 g: 5.61 mmol). The temperature for the reaction was 100°C and the time taken for completion was 1 h. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (10:1) afforded methyl 5-cyclohexylcarbonyl-3-furoate **139** (387 mg: 1.64 mmol: 60%) IR ν_{max} ($CHCl_3$ solution) 3145, 3027, 3013, 1702 and 1728 cm^{-1}. δ_H(200 MHz: $CDCl_3$) 1.51 (11H, m, H-9,10,11 and 12), 3.71 (3H, s, H-7), 7.32 (1H, s, H-4) and 7.99 (1H, s, H-2); δ_C (50 MHz); 24.62 (C-12), 25.55

(C-11), 28.56 (C-10), 46.22 (C-9), 51.72 (C-7), 115.86 (C-4), 120.79 (C-3), 149.95 (C-2), 152.49 (C-5), 162.26 (C-8) and 182.1 (C-6). *m/z* 236 (M^+, 24.6), 206(1.7), 181(50.9) and 168 (96.4%); (Found M^+ 236.1042; $C_{13}H_{16}O_4$ requires M^+, 236.1047).

ISOPROPYL 5-CYCLOHEXYL-3-FUROATE (140)

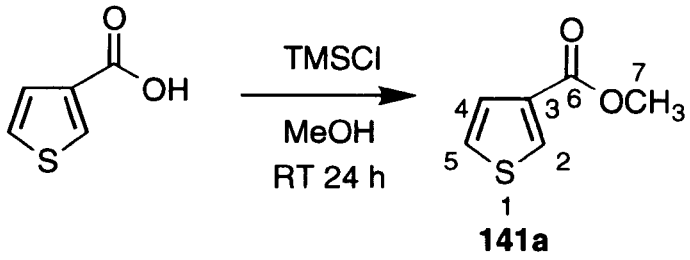


The general procedure was followed using isopropyl 3-furoate **131** (200 mg: 1.58 mmol), cyclohexylcarbonyl chloride (3 ml) and $BF_3.OEt_2$ (0.28 ml: 333 mg: 2.25 mmol). The temperature was 90°C and the time for completionwas 2 h. Purification *via* column chromatography eluting with light Petroleum/ ethyl acetate (10:1) afforded isopropyl 5-cyclohexyl-3-furoate **140** (134 mg: 0.5 mmol: 32%) ; IR ν_{max} ($CHCl_3$ soln.): 3146, 2984, 1720 and 1678 cm^{-1}; δ_H (200 MHz; $CDCl_3$): 1.14-1.97 (13H, m, H-8,10,11,12 and 13), 5.16 (1H, septet, $J_{7,8}$ 5.77 Hz, H-7), 7.38 (1H, s, H-4) and 8.03 (1H, s, H-2). δ_C (50 MHz): 20.67 (C-8), 21.79 (C-8), 25.57 (C-13), 25.65 (C-12) (C-28.8 (C-11), 46.39 (C-10), 68.57 (C-7), 116.17 (C-4), 121.70 (C-3), 149.87 (C-2), 152.3 (C-5), 161.5 (C-6) and 192.62 (C-9). *m/z*: 264 (M^+, 2.6), 221 (M^+-C_3H_7, 3.4) and 205 (M^+-OC_3H_7, 5.0%) (Found M^+, 264.1354 $C_{15}H_{20}O_4$ requires M, 264.1361).

6.10 SYNTHESIS OF 3,5-DISUBSTITUTED THIOPHENES VIA FRIEDEL-CRAFTS ACYLATION

ESTERIFICATION OF THIOPHENE-3-CARBOXYLIC ACID

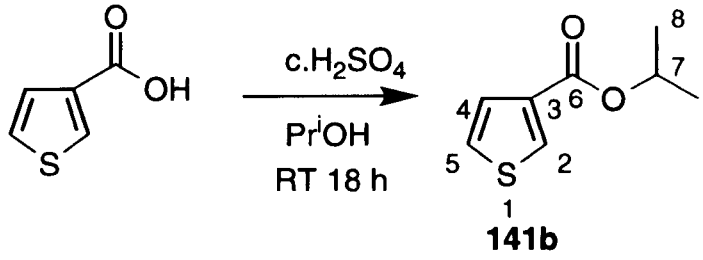
METHYL 3-THIOPHENECARBOXYLATE (141a)



141a

Chlorotrimethylsilane (5.9 ml: 5.05 g: 46.4 mmol) was added dropwise to a flask containing thiophene-3-carboxylic acid (3 g ; 23.4 mmol) in methanol (10 ml). The resulting solution was stirred at room temperature before being quenched with water (50 ml) and the solution extacted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine (3 x 20 ml) and sodium bicarbonate (3 x 20 ml) and before drying over magnesium sulfate. The solvent was removed under reduced pressure giving the crude product as the residual oil. Purification *via* column chromatography eluting with light petroleum/ethyl acetate (5:1) afforded methyl-3-thiophenecarboxylate **141a** as a colourless oil 2.2 g (15 mmol: 60%); IR ν_{max} ($CHCl_3$): 1717, 3020 and 3117 cm^{-1}. δ_H(200 MHz; $CDCl_3$): 3.75 (1H, s, H-7), 7.19 (1H, dd, $J_{5,2}$ 3.02 Hz, $J_{5,4}$ 5.05 Hz, H-5), 7.42 (1H, dd, $J_{4,2}$ 1.01 Hz, $J_{4,5}$ 5.05 Hz, H-4) and 8.00 (1H, dd, $J_{2,4}$ 1.08, $J_{2,5}$ 3.02 Hz, H-2). δ_C(50 MHz): 51.58 (C-7), 125.94 (C-5), 127.75 (C-4), 132.54 (C-2), 133.42 (C-3) and 162.99 (C-6). *m/z* 142 (41.7) and 111 (M^+-OMe, 100%) (Found 142.0081 $C_6H_6O_2S$ requires 142.0088).

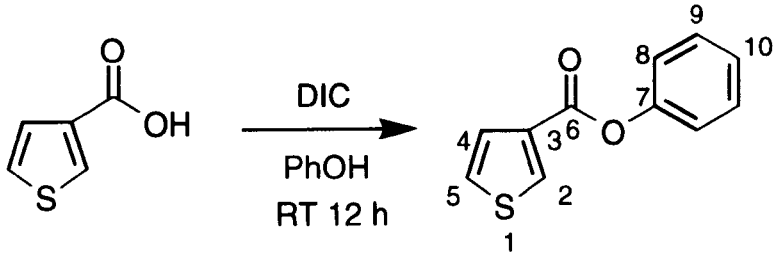
ISOPROPYL 3-THIOPHENECARBOXYLATE (141b)



141b

A catalytic amount of concentrated sulfuric acid was added to a stirring solution of thiophene-3-carboxylic acid (5 g: 39 mmol) in isopropanol (50 ml). The resulting solution was stirred for 12 h at room temperature. The solution was then poured into water (50 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with sodium bicarbonate (3 x 25 ml), brine (3 x 20 ml) and dried over magnesium sulfate. The solvent was removed *in vacuo* giving the ester as the residual oil. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (5:1) afforded isopropyl-3-thiophenecarboxylate **141b** as a colourless oil (4.2 g: 24 mmol: 63%); δ_H (200 MHz; $CDCl_3$); 1.34 (6H, d, $J_{8,7}$ 6.27 Hz, H-8), 5.20 (1H, septet, $J_{7,8}$ 6.27 Hz, H-7), 7.28 (1H, dd, $J_{5,2}$ 3.03 Hz $J_{5,4}$ 5.03 Hz, H-5), 7.51 (1H, dd, $J_{4,2}$ 1.14 Hz, $J_{4,5}$ 5.05 Hz, H-4) and 8.08 (1H, dd, $J_{2,4}$ 1.16 Hz, $J_{2,5}$ 3.05 Hz, H-2). δ_C (50 MHz); 21.88 (C-8), 67.96 (C-7), 125.75 (C-5), 127.87 (C-4), 132.25 (C-2), 134.37 (C-3) and 162.25 (C-6) *m/z* 170 (M^+, 17.1), 128 (36.4) and 111 (100%) (Found M^+, 170.0406 $C_{11}H_7O_2S$ requires 170.0401).

PHENYL-3-THIOPHENECARBOXYLATE (141c)

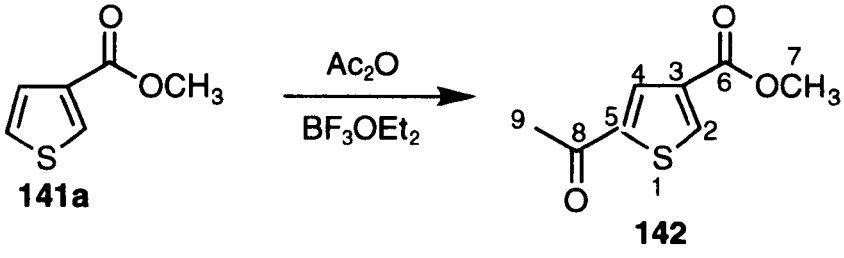


141c

Diisopropylcarbodiimide (2.09 ml: 1.68 g: 13.3 mmol) was added dropwise to a solution of thiophene-3-carboxylic acid (1.00 g: 8.9 mmol) and phenol (1.25 g: 13.3 mmol) in THF (20 ml). The resulting solution was stirred overnight at room temperature. Water (50 ml) was added and the solution extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were combined and washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml) and dried over magnesium sulfate. The ethyl acetate was then removed *in vacuo* to leave the crude ester as a white solid. Purification by column chromatography eluting light petroleum/ethyl acetate (10:1) afforded phenyl-3-thiophenecarboxylate **141c** as a white solid (1.02 g: 4.9 mmol: 60%); m.p. 63-65°C; IR $\nu_{max}(CHCl_3)$; 3117, 3028, 3013 and 1733 cm^{-1}. δ_H (200 MHz; $CDCl_3$); 7.16-7.4 (6H, m, H-Ph and H-5), 7.64 (1H, dd, $J_{4,2}$ 1.18 Hz, $J_{4,5}$ 5.08 Hz, H-4) and 8.29 (1H, dd, $J_{2,5}$ 1.2 Hz, $J_{2,4}$ 3.06 Hz, H-2). δ_C (50 MHz); 121.21 (C-8), 125.89 (C-4), 126.4 (C-10), 128.21 (C-5), 129.48 (C-9), 132.1 (C-3), 134.03 (C-2), 150.66 (C-7) and 161.05 (C-6); *m/z* 204 (M^+, 11.1) and 111 (M^+-OPh, 100%) (Found M^+, 204.0244 $C_{11}H_8O_2S$ requires 204.0245).

SYNTHESIS OF THIOPHENE FRIEDEL-CRAFTS DERIVATIVES

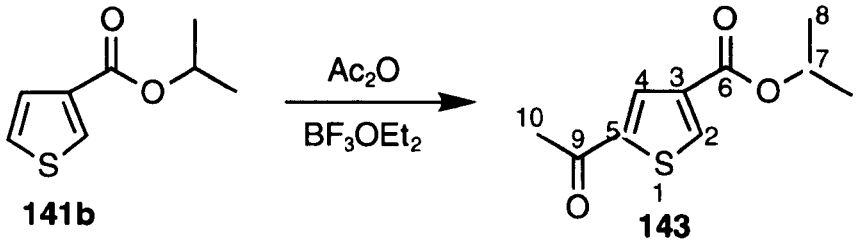
METHYL 5-ACETYL-3-THIOPHENECARBOXYLATE (142)



The general procedure for Friedel-Crafts reactions was followed using methyl 3-thiophenecarboxylate **141a** (200 mg: 1.4 mmol), acetic anhydride, $BF_3.OEt_2$ (0.08 ml: 95 mg: 0.7 mmol). The temperature for the reaction was 50°C and the

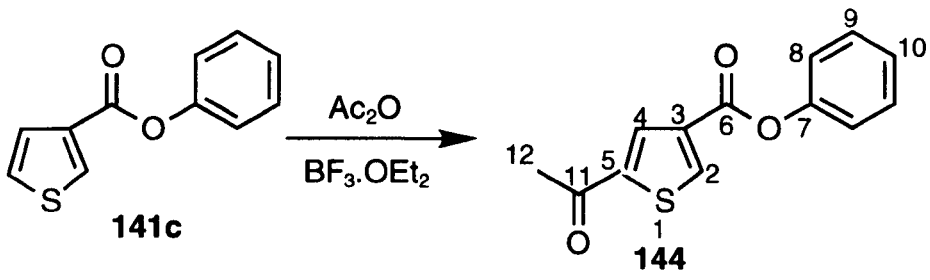
time taken for reaction to go to completion was 5 minutes. Purification by column chromatography eluting with light petroleum/ ethyl acetate 5:1) afforded methyl 5-acetyl-3-thiophenecarboxylate **142** (204 mg: 1.11 mmol: 79%) IR ν_{max}($CHCl_3$ solution); 1671, 1720, 3009 and 3026 cm^{-1}. δ_H (200 MHz: $CDCl_3$): 2.57 (3H, s, H-9), 3.88 (3H, s, H-7), 8.04 (1H, d, $J_{4,2}$ 1.27 Hz, H-4) and 8.31 (1H, d, $J_{2,4}$ 1.24 Hz, H-2). δ_C (50 MHz): 26.62 (C-9), 52.14 (C-7), 132.49 (C-4), 134.08 (C-2), 139.45 (C-3), 145.16 (C-5), 162.47 (C-6), 190.61 (C-8); *m/z*: 184 (M^+, 37.6), 169 (M^+-Me, 100) and 153 (M^+-OMe, 25.1) (Found 184.0200 $C_8H_8O_3S$ requires 184.0194)

ISOPROPYL 5-ACETYL-3-THIOPHENECARBOXYLATE (143)



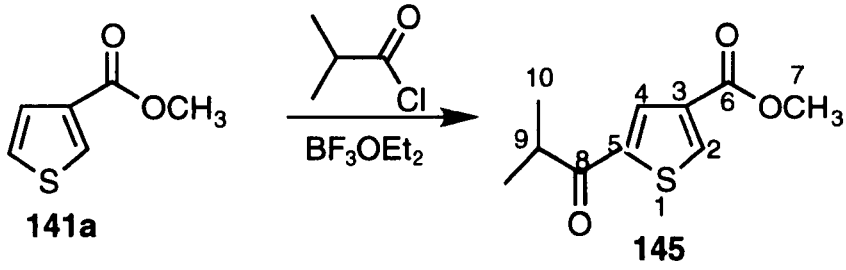
The general procedure was followed using isopropyl thiophene-3-carboxylate **141b** (200 mg: 1.17 mmol), acetic anhydride (3 ml) and $BF_3.OEt_2$ (0.28 ml: 333 mg: 2.35 mmol). The temperature was 70°C and the time taken for completion was 2 h. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (3:1) afforded the isopropyl 5-acetyl-3-thiophenecarboxylate **143** (94 mg: 0.38 mmol 38%) IR ν_{max}($CHCl_3$ solution): 1670, 1712, 3026 and 3111 cm^{-1}. δ_H (200 MHz; $CDCl_3$): 1.34 (6H, d, $J_{8,7}$ 6.25 Hz, H-8), 2.57 (3H, s, H-10), 5.20 (1H, septet, $J_{7,8}$ 6.28 Hz, H-7), 8.03 (1H, d, $J_{4,2}$ 1.24 Hz, H-4) and 8.30 (1H, d, $J_{2,4}$ 1.24 Hz, H-2). δ_C (50 MHz): 21.67 (C-8), 26.63 (C-10), 68.72 (C-7), 130.05 (C-4), 132.48 (C-2), 135.00 (C-3), 139.17 (C-5), 161.5 (C-6) and 190.66 (C-9). *m/z*: 212 (M^+, 26.9), 169 (M^+-C_3H_7, 2.5) and 153 (M^+-OC_3H_7, 71.3) (Found 212.0481 $C_{10}H_{12}O_3S$ requires 212.0507)

PHENYL 5-ACETYL-3-THIOPHENECARBOXYLATE (144)



The general procedure was followed using phenyl thiophene-3-carboxylate **141c** (200 mg: 1 mmol), acetic anhydride (3 ml) and $BF_3.OEt_2$ (0.2 ml: 238 mg: 2 mmol). The temperature was raised to 50°C and the time taken for completion was 1.5 h. Purification *via* column chromatography eluting light petroleum/ ethyl acetate (5:1) afforded the phenyl 5-acetyl-3-thiophenecarboxylate **144** as white crystals (132 mg: 0.53 mmol: 55%) IR ν_{max} ($CHCl_3$ solution): 31672, 1737, 3026 and 3110 cm^{-1}. δ_H (200 MHz; $CDCl_3$): 2.54 (3H, s, H-12), 7.1-7.46 (5H, m, PhH), 8.12 (1H, d, $J_{4,2}$ 1.21 Hz, H-4) and 8.54 (1H, d, $J_{2,4}$ 1.20 Hz, H-2). δ_C (50 MHz): 26.67 (C-12), 121.51 (C-8), 126.16 (C-4), 129.56 (C-10), 132.68 (C-9), 133.45 (C-2), 140.61 (C-3), 145.8 (C-5), 150.34 (C-7), 160.32 (C-6) and 190.58 (C-11); *m/z*: 246 (M^+, 9.5), 153 (100) and 111 (21.6) (Found 246.0355 $C_{13}H_{10}O_3S$ requires 246.0350)

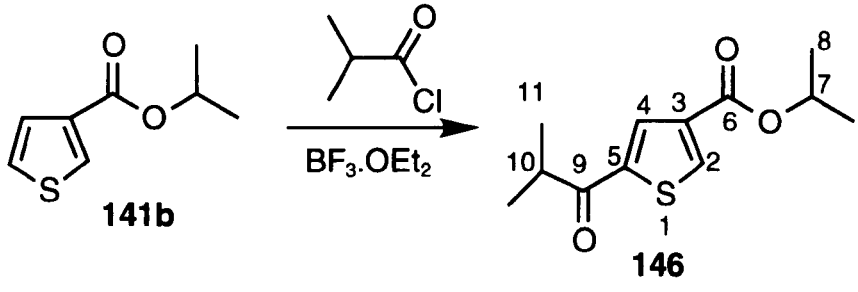
METHYL 5-ISOPROPYL-3-THIOPHENE-CARBOXYLATE (145)



The general procedure was followed using methyl thiophene-3-carboxylate **141a** (110 mg: 0.7 mmol), isobutyryl chloride (3 ml) and $BF_3.OEt_2$ (0.04 ml: 47.6 mg:

0.33 mmol). The temperature for the reaction was 50°C and the time taken for completion was 4 h. Purification by column chromatography eluting with light petroleum/ ethyl acetate, (5:1) afforded methyl 5-isopropyl-3-thiophenecarboxylate **145** (122 mg: 0.57 mmol: 57%) IR ν_{max} ($CHCl_3$ soln.): 1664, 1720, 3026 and 3111 cm^{-1}. δ_H (200 MHz: $CDCl_3$): 1.04 (6H, d, $J_{10,9}$ 6.84 Hz, H-10), 3.21 (1H, septet, $J_{9,10}$ 6.63 Hz, H-9), 3.68 (3H, s, H-7), 7.87 (1H, d, $J_{4,2}$ 1.17 Hz, H-4), 8.12 (1H, d, $J_{2,4}$ 1.18 Hz, H-2); δ_C (50 MHz): 20.57 (C-10), 36.73 (C-9), 51.95 (C-7), 131.38 (C-4), 133.98 (C-3), 139.118 (C-2), 144.22 (C-5), 162.30 (C-6), 190.24 (C-8) *m/z*: 212 (M^+, 14.3), 169 (M^+-C_3H_7,100) and 181 (M^+-OMe,4.3%) (Found M^+, 212.0494 C 56.56 and H 5.60% $C_{10}H_{12}O_3S$ requires M 212.0507 C 56.60 and H 5.80 %).

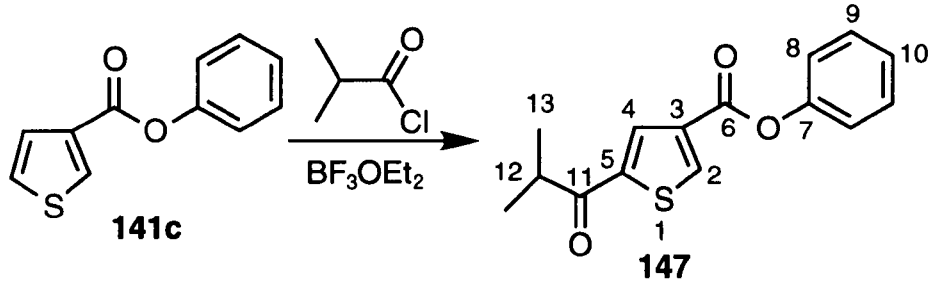
ISOPROPYL 5-ISOBUTYRYL-3-THIOPHENECARBOXYLATE (146)



The general procedure was followed using isopropyl thiophene-3-carboxylate **141b** (500 mg: 2.94 mmol), isobutyryl chloride (3 ml) and $BF_3.OEt_2$ (0.7 ml: 83.3 mg: 5.88 mmol). The temperature was 90°C and the time taken for completion was 2 h. Purification by column chromatography eluting with light petroleum/ ethyl acetate, (5:1) afforded isopropyl 5-isobutyryl-3-thiophenecarboxylate **146** (365 mg: 1.52 mmol: 51%) IR ν_{max}(CH_2Cl_2 solution): 1713, 1732, 3062 and 3111 cm^{-1}. δ_H (200 MHz: $CDCl_3$): 1.15 (6H, d, $J_{11,10}$ 6.84 Hz, H-11), 1.27 (6H, d, $J_{8,9}$ 6.24 Hz, H-8), 3.34 (1H, septet, $J_{10,11}$ 6.85 Hz, H-10), 5.10 (1H, septet, $J_{7,8}$ 6.28 Hz, H-7), 7.98 (1H, d, $J_{4,2}$ 1.21 Hz, H-4) and 8.23 (1H, d, $J_{2,4}$ 1.22 Hz, H-2). δ_C (50 MHz):

19.19 (C-11), 21.81 (C-8), 36.75 (C-10), 68.57 (C-7), 131.6 (C-4), 134.92 (C-3), 138.88 (C-2), 144.1 (C-5), 161.49 (C-6) and 197.23 (C-9); *m/z* 240 (M^+, 29.8), 197 (M^+-C_3H_7, 91.0), 181 (M^+-OC_3H_7, 17.2), 155 (100%) (Found 240.0818, $C_{12}H_{16}O_3S$ requires 240.0820)

PHENYL 5-ISOBUTYRYL-3-THIOPHENECARBOXYLATE (147)



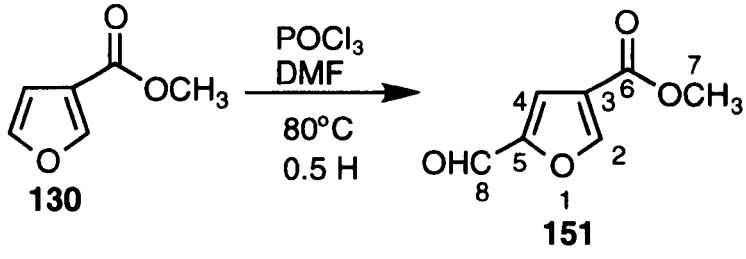
The general procedure was followed using phenyl 3-furoate **141c** (380 mg: 1.86 mmol), isobutyryl chloride (3 ml) and $BF_3.OEt_2$ (0.44 ml: 523 mg: 3.72 mmol). The temperature was 90°C and the time taken for completion was 1.5 h. Purification by column chromatography eluting with light petroleum/ ethyl acetate (10:1) afforded phenyl 5-isobutyryl-3-thiophenecarboxylate **147** as a yellow oil (100 mg: 19.6%); IR ν_{max}($CDCl_3$ soln.): 1167, 1735, 3019 and 3112 cm^{-1}. δ_H (200 MHz: $CDCl_3$): 1.27 (6H, d, $J_{13,12}$ 6.86 Hz, H-13), 3.44 (1H, septet, $J_{12,13}$ 6.84 Hz, H-12), 7.17-7.47 (5H, m, H-8,9 and 10), 8.20 (1H, d, $J_{4,2}$ 1.12 Hz, H-4) and 8.51 (1H, d, $J_{2,4}$ 1.2, H-2). δ_C (50 MHz): 18.78 (C-13), 36.91 (C-12), 121.51 (C-8), 126.3 (C-4), 129.42 (C-10), 132.23 (C-9), 133.42 (C-2), 134.2 (C-3), 146.9 (C-7), 150.39 (C-5) 162.3 (C-6)and 197.33 (C-11). *m/z*: 274 (M+, 13.7) and 181 (M^+-OPh, 100%) (Found 274.0647 $C_{15}H_{14}O_3S$ requires 274.0664)

6.11 SYNTHESIS OF 3,5-DISUBSTITUTED FURANS VIA FORMYLATION

GENERAL PROCEDURE FOR FORMYLATION OF FUROATE ESTERS

To a flask, cooled to 0°C, were added phosphorus oxychloride (1.2 equivalents) and dimethylformamide (1.2 equivalents). The resulting mixture was allowed to stand for 20 min. A yellow solid formed and the appropriate ester (1 equivalent) was added to the flask. The temperature was raised to 80°C and the resulting mixture was stirred for the appropriate length of time specified in the individual procedures before being cooled and poured into a mixture of ice/water. An aqueous solution of potassium carbonate was added dropwise and the solution extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were then washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml) and dried over magnesium sulfate. The solvent was removed *in vacuo* to leave the crude products as black oils. Purification *via* column chromatography eluting with light petroleum/ethyl acetate (5:1) afforded the respective formylated furoates.

METHYL 5-FORMYL-3-FUROATE (151)



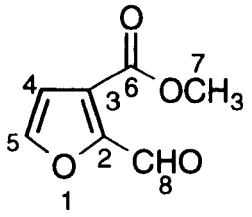
The general procedure for formylation of the furoate esters was followed using methyl 3-furoate **130** (900 mg: 7.14 mmol), phosphorus oxychloride (1.46 g: 9 mmol)

and DMF (0.74 ml: 0.7 g: 9 mmol). The reaction mixture was heated for 0.5 h. Purification afforded a mixture of methyl 5-formyl-3-furoate **151** and methyl 2-formyl-3-furoate in a 10:1 ratio. Total mass isolated was 760 mg (4.9 mmol: 38%).

Data for methyl 5-formyl-3-furoate **151**:

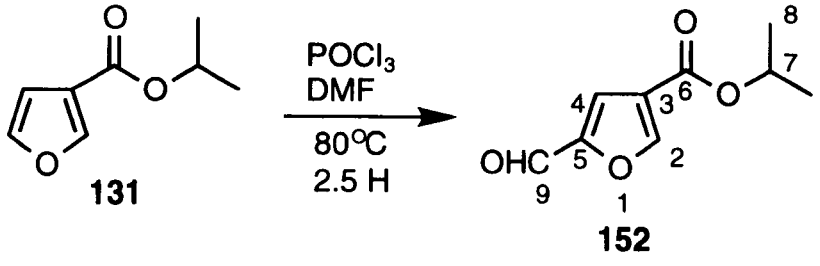
IR ν_{max}(KBr disc); 1722, 1697, 3140 and 3084 cm^{-1}. δ_H(200 MHz; $CDCl_3$); 3.86 (1H, s, H-7), 7.51 (1H, d, $J_{4,2}$ 0.7 Hz, H-4), 8.19 (1H, d, $J_{2,4}$ 0.62 Hz, H-2) and 9.66 (1H, d, $J_{8,4}$ 0.24 Hz, H-8). δ_C(50 MHz); 51.96 (C-7), 119.57 (C-4), 121.36 (C-3), 151.41 (C-2), 153.1 (C-5), 161.91 (C-6) and 177.76 (C-8). *m/z*: 154 (M^+, 49.5) and 123 (M^+-OMe, 100%)(Found M^+, 154.0261; $C_7H_6O_4$ requires 154.0265).

Data for methyl 2-formyl-3-furoate:



δ_H(200 MHz; $CDCl_3$); 3.92 (3H, s, H-7), 6.86 (1H, d, $J_{4,5}$ 1.80 Hz, H-4), 7.25 (1H, s, H-5) and 10.20 (1H, d, $J_{8,4}$ 0.78 Hz, H-8)

ISOPROPYL 5-FORMYL-3-FUROATE (152)



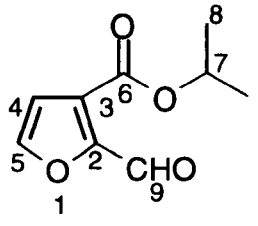
The general procedure for formylating furoate esters was followed using isopropyl 3-furoate **131** (1.01 g: 655 mmol), phosphorus oxychloride (0.76 mg: 1.26 g:

8.2 mmol) and dimethylformamide (0.63 ml: 0.6 g: 8.2 mmol). The reaction was warmed for 2.5 h before work up in the usual manner. Purification *via* column chromatography afforded a mixture of isopropyl 5-formyl-3-furoate **152** and isopropyl 2-formyl-3-furoate in a ratio of 4:1.

Data for isopropyl 5-formyl-3-furoate:

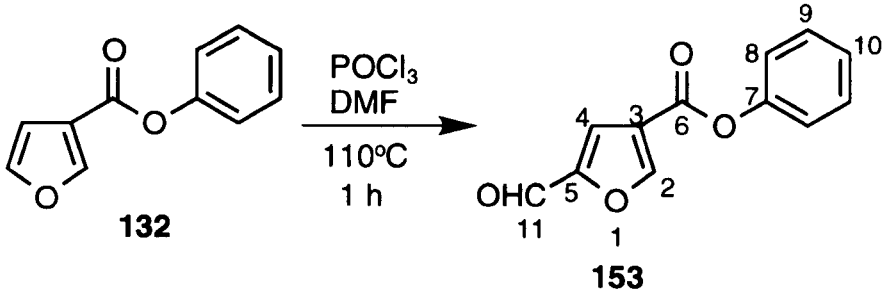
Yield 678 mg (3.72 mmol: 28.7%); IR $\nu_{max}(CHCl_3)$: 1686, 1722, 3032 and 3146 cm-1. δ_H (200 MHz; $CDCl_3$): 0.97 (6H, d, $J_{8,7}$ 6.24 Hz, H-8), 4.83 (1H, septet, $J_{7,8}$ 6.24 Hz, H-7), 7.19 (1H, s, H-4), 7.87 (1H, s, H-2) and 9.32 (1H, d, $J_{9,4}$ 0.55 Hz , H-9). δ_c (50 MHz): 21.57 (C-8), 68.6 (C-7), 112.78 (C-3), 119.73 (C-4), 151.23 (C-2), 152.98 (C-5), 160.91 (C-6) and 177.68 (C-9). *m/z*: 182 (M^+,14.0), 139 (M^+-C_3H_7, 41.2) and 123 (M^+-OC_3H_7, 93.4). (Found 182.0585 $C_9H_{10}O_4$ requires 182.0579).

Data for isopropyl 2-formyl-3-furoate:



δ_H ($CDCl_3$: 200 MHz:): 6.52 (1H, d, $J_{4,5}$ 1.76 Hz, H-4), 7.32 (1H, dd, $J_{5,9}$ 0.9 Hz, $J_{5,4}$ 1.63 Hz, H-5) and 9.85 (1H, d, *J*0.81. H-9).

PHENYL 5-FORMYL-3-FUROATE (153)



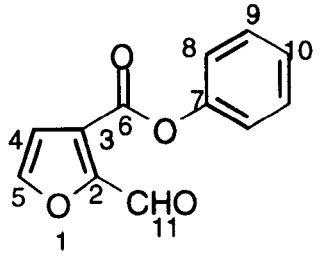
132 **153**

The general procedure for formylating furoate esters was followed using phenyl 3-furoate **132** (3.8 g: 20 mmol), phosphorus oxychloride (4.66 ml: 7.66 g: 50 mmol) and DMF (3.86 ml: 3.64 g: 50 mmol). The temperature was raised from 80°C to 100°C and the time taken for completion of the reaction was 1h. Purification *via* column chromatography afforded phenyl 5-formyl-3-furoate **153** and phenyl 2-formyl-3-furoate 2.04 g (38% : 9.4 mmol).

Data for phenyl 5-formyl-3-furoate **153**:

IR ν_{max}($CHCl_3$ solution): 1696, 1746, 2836 and 3146 cm^{-1}. δ_H (200 MHz: $CDCl_3$): 6.73-7.25 (5H, m, H-8, 9 and 10), 7.58 (1H, s, H-4), 8.32 (1H, s, H-2) and 9.62 (1H, s, H-11). δ_C (50 MHz): 119.92 (C-4), 120.95 (C-3), 121.44 (C-8), 126.48 (C-10), 129.63 (C-9), 150.03 (C-7), 152.31 (C-2), 153.29 (C-5), 159.96 (C-6) and 177.86 (C-11). *m/z*: 216 (9.1) and 123 (M^+-OPh, 83.3%) (Found M^+, 216.0414 C 66.42, H 3.80% $C_{12}H_8O_4$ requires M, 216.0.422 C 66.66, H 3.70%)

Data for phenyl 2-formyl-3-furoate:

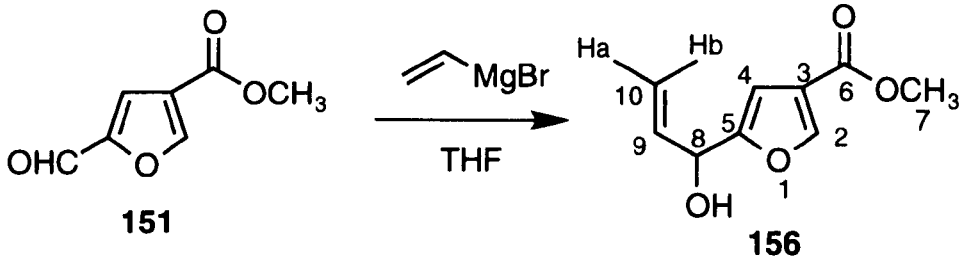


δ_H ($CDCl_3$; 200 MHz): 7.0 (1H, s, H-4), 7.3-7.4 (10H, m, H-8,9 and 10), 7.6 (1H, s, H-5) and 10.4 (1H, s, H-11)

GENERAL PROCEDURE FOR VINYLMAGNESIUM BROMIDE ATTACK ON FORMYL FUROATE ESTERS

To a solution of the appropriate formylated furoate ester (1 equivalent) in 30 ml THF held under nitrogen was added vinylmagnesium bromide (1.2 equivalent) at 0°C. The solution was warmed to room temperature and stirred for 12 h. Water (50 ml) was added and the solution extracted with ethyl acetate (3 x 25 ml). The organic extracts were combined, washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml) and dried over magnesium sulfate. Solvent was removed under reduced pressure to give the crude product. Purification *via* column chromatography eluting with hexane/ethyl acetate (2:1) afforded the respective alkylated isomers.

METHYL 5-(1-HYDROXY-2-PROPENYL)-3-FUROATE (156)



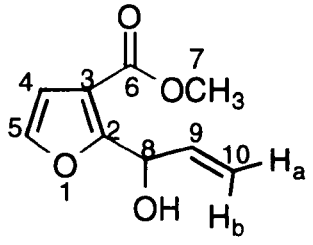
151 **156**

The general procedure was followed using a mixture of methyl 5-formyl-3-furoate **151** and methyl 2-formyl-3-furoate (2.89 g: 18.7 mmol) and vinylmagnesium bromide (22.5 ml: 1.0 M in THF; 22.5 mmol). Purification afforded methyl 5-(1-hydroxy-2-propenyl)-3-furoate **156** (1.8 g: 9.8 mmol: 53%) and methyl-2-(1-hydroxy-2-propenyl)-3-furoate **159** (180 mg: 0.98 mmol: 5%) as colourless oils.

Data for methyl 5-(1-hydroxy-2-propenyl)-3-furoate **156**:

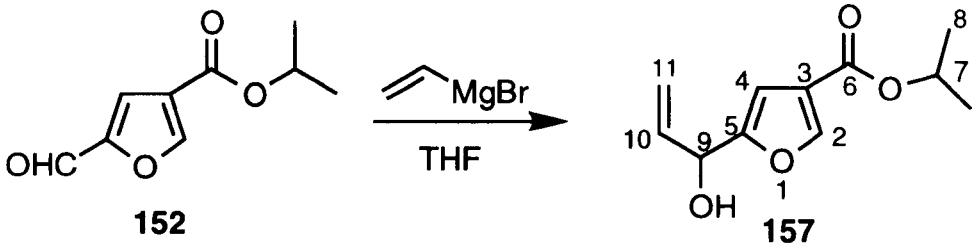
IR: $\nu_{max}(CHCl_3)$; 1725 and 3149 cm^{-1}. δ_H (200 MHz; $CDCl_3$); 3.72 (1H, s, H-7), 5.05 (1H, br d, $J_{8,9}$ 5.82 Hz, H-8), 5.35 (2H, m, H-10), 5.95 (1H, ddd, $J_{9,8}$ 5.81 Hz, $J_{9,10a}$ 10.33 Hz $J_{9,10b}$ 16.15 Hz, H-9), 6.45 (1H, d, $J_{4,2}$ 0.84 Hz, H-4) and 7.83 (1H, $J_{2,4}$ 0.84 Hz, H-2). δ_C(50 MHz); 51.53 (C-7), 67.97 (C-8), 106.29 (C-4), 116.73 (C-10), 119.35 (C-3), 136.21 (C-9), 147.33 (C-2), 156.76 (C-5) and 163.66 (C-6). *m/z*; 182 (M^+, 100), 155 (71.5), 139 (25.7) and 126 (70.2%) (Found M^+, 182.0571 $C_9H_{10}O_4$ requires M, 182.0578).

Data for methyl 2-(1-hydroxy-2-propenyl)-3-furoate **159**:



IR: $\nu_{max}(CHCl_3)$; 1720, 3088, 3136 cm^{-1}. δ_H (200 MHz; $CDCl_3$); 3.78 (1H, s, H-7), 4.74 (1H, br d, $J_{8,9}$ 5.31 Hz, H-8), 5.25 -5.45 (2H, m, H-10), 6.01 (1H, ddd, $J_{9,8}$ 5.63 Hz, $J_{9,10a}$ 10.32 Hz, $J_{9,10b}$ 15.9 Hz, H-9), 6.59 (1H, d, $J_{4,5}$ 1.93 Hz, H-4) and 7.22 (1H, d, $J_{5,4}$ 1.94 Hz, H-5). δ_C (50 MHz); 52.03 (C-7), 68.79 (C-8), 110.881 (C-4), 113.84 (C-3), 116.14 (C-10), 136.13 (C-9), 141.18 (C-5), 162.1 (C-2) and 165.18 (C-6). *m/z*; 182 (M^+, 22.5), 155 (13.9), 150 (90.7) and 123 (100%) (Found M^+, 182.0576 $C_9H_{10}O_4$ requires M, 182.0578).

ISOPROPYL 5-(1-HYDROXY-2-PROPENYL)-3-FUROATE (157)



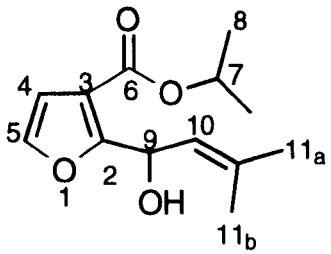
152 **157**

The procedure was followed using a mixture of isopropyl 5-formyl-3-furoate and isopropyl 2-formyl-3-furoate (1.05 g; 5 mmol) and vinylmagnesium bromide (10.0 ml: 1.0 M solution in THF: 10.0 mmol). Purification afforded isopropyl 5-(1-hydroxy-2-propenyl)-3-furoate **157** (472 mg: 2.24 mmol: 41%) and isopropyl 2-(1-hydroxy-2-propenyl)-3-furoate **160** (100 mg: 0.476 mmol: 8%) as colourless oils.

Data for isopropyl 5-(1-hydroxy-3-propenyl)-3-furoate **157**:

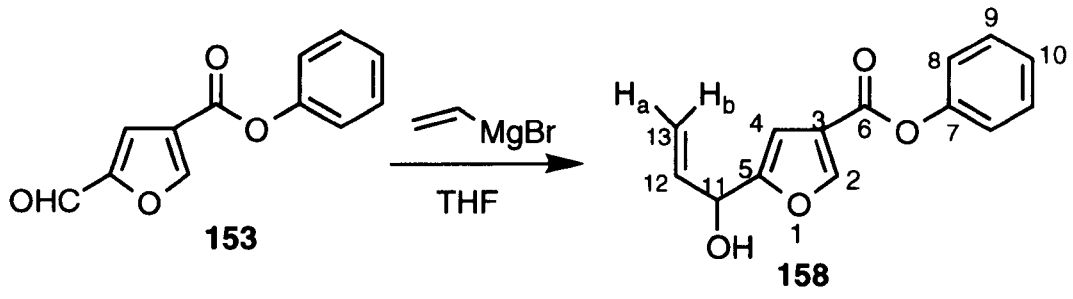
IR ν_{max} ($CHCl_3$): 1144, 1712, 3034 and 3156 cm^{-1}. δ_H (200 MHz) ($CDCl_3$): 1.22 (6H, d, $J_{8,7}$ 6.27 Hz , H-8), 4.86 (1H, septet, $J_{7,8}$ 6.23 Hz , H-7), 5.05 (1H, br d, H-9), 5.89 (2H, m, H-11), 6.48 (1H, s, H-4) and 7.65 (1H, d, $J_{2,4}$ 0.77 Hz , H-2). δ_C (50 MHz): 21.79 (C-8), 68.05 (C-9), 68.1 (C-7), 106.47 (C-4), 116.79 (C-11), 120.22 (C-3), 136.33 (C-10), 147.25 (C-2), 156.68 (C-5) and 162.92 (C-6). *m/z*: 210 (M+, 25.7), 168 (38.9), 151 (67.6), 141 (45.9) and 122 (43.9%) (Found 210.0886 $C_{11}H_{14}O_4$ requires 210.0891)

Data for isopropyl 2-(1-hydroxy-3-propenyl)-3-furoate **160**:



IR ν_{max} ($CHCl_3$); 1724, 2984 and 3264 cm^{-1} δ_H (200 MHz; $CDCl_3$); 1.08 (6H, d, $J_{8,7}$ 6.23 Hz, H-8), 4.92 (1H, septet, $J_{7,8}$ 6.34 Hz, H-7), 5.12 (2H, m, H-11), 5.69 (1H, br d, $J_{9,10}$ 5.42 Hz, H-9), 5.88 (1H, ddd, $J_{10,9}$ 5.89 Hz, $J_{10,11a}$ 10.23 Hz $J_{10,11b}$ 17.05 Hz, H-10), 6.51 (1H, s, H-4) and 7.73 (1H, s, H-5). *m/z*; 210 (M^+, 43.2), 151 (100) and 139 (66.5%) (Found 210.0882 $C_{11}H_{14}O_4$ requires 210.0891)

PHENYL 5-(1-HYDROXY-2-PROPENYL)-3-FUROATE (158)

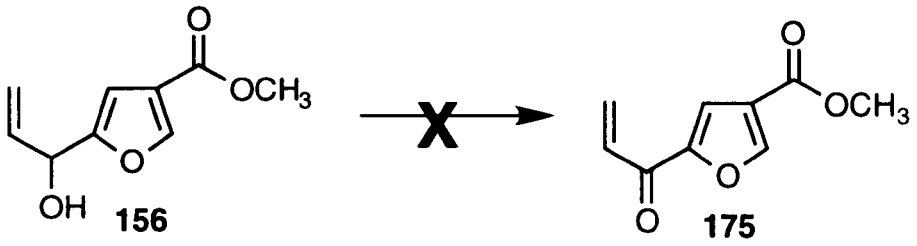


153 158

The general procedure was followed using a mixture of phenyl 5-formyl-3-furoate and phenyl 5-formyl-3-furoate (2.0 g; 9.25 mmol) and vinylmagnesium bromide (10 ml: 1.0 M in THF; 10 mmol). Purification afforded phenyl 5-(1-hydroxy-2-propenyl)-3-furoate **158** as a colourless oil; (1.05 g: 4.3 mmol: 46%) IR ν_{max} (CH_2Cl_2 solution): 1740, 3024, 3082 and 3154 cm^{-1}. δ_H(200 MHz): 4.26 (1H, br d, $J_{11,12}$ 5.8 Hz, H-11), 5.28 (1H, dd, $J_{13a,13b}$ 1.07 Hz $J_{13a,12}$ 13.49 Hz, H-13a), 5.38 (1H, dd, $J_{13b,13a}$ 1.10 Hz and $J_{13b,12}$ 10.77 Hz, H-13b), 6.13 (1H, ddd, $J_{12,11}$ 5.38 Hz, $J_{12,13a}$ 10.31 Hz and $J_{12,13b}$ 16.24 Hz, H-12), 6.74 (1H, $J_{4,2}$ 0.58 Hz, H-4), 7.10-7.42 (5H, m, H-8,9 and 10) and 8.16 (1H, d, $J_{2,4}$ 0.56 Hz, H-2) δ_C(50 MHz): 68.22 (C-11), 106.78(C-4), 117.27(C-13), 119.19 (C-3), 121.61 (C-8), 125.98 (C-10), 129.47 (C-9), 136.02 (C-12), 148.45 (C-2), 150.96 (C-7), 156.97 (C-5), 161.8 (C-6) *m/z*: 244 (M^+, 8.8) and 151 (100%) (Found M, 244.0742, $C_{14}H_{12}O_4$ requires 244.0735).

OXIDATION TO KETONES

SWERN OXIDATION



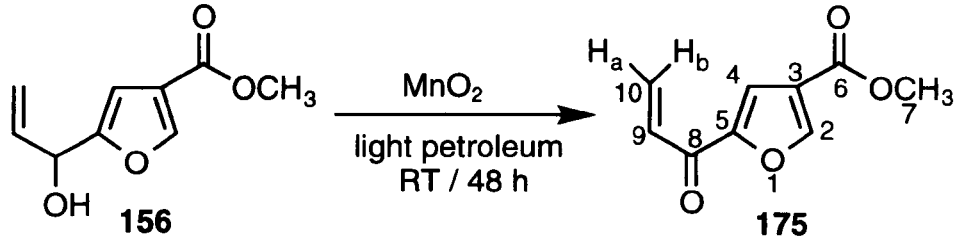
To a flask cooled to -78°C and flushed with nitrogen was added oxalyl chloride (0.1 ml: 145 mg: 1.14 mmol) followed by CH_2Cl_2 (5 ml). Dimethylsulfoxide (0.16 ml: 176 mg: 2.25 mmol) in CH_2Cl_2 (2 ml) was slowly added and stirred for 5 minutes before methyl 5-(1-hydroxy-2-propenyl)-3-furoate **156** (135 mg: 0.7 mmol) dissolved in CH_2Cl_2 was added dropwise. The solution turned a murky grey colour and after 15 minutes triethylamine (0.5 ml: 363 mg: 3.6 mmol) was added and the solution slowly warmed to room temperature. The resulting mixture was stirred for 15 minutes and the solution turned purple. On addition of water (25 ml) an exotherm was observed. The aqueous layer was separated from the organic layer and was then back extracted with CH_2Cl_2 (2 x 10 ml). The organic extracts were combined, washed with brine and the solvent removed under reduced pressure to give an orange solid identified as starting material.

GENERAL PROCEDURE FOR OXIDATION USING MANGANESE DIOXIDE

Manganese dioxide (10 equivalents) was added to a solution of the appropriate 5-(1-hydroxy-2-propenyl)-3-furoate ester (1 equivalent) in light petroleum (10 ml) and stirred for 48 h. The resulting mixture was then filtered through a pad of Celite® to

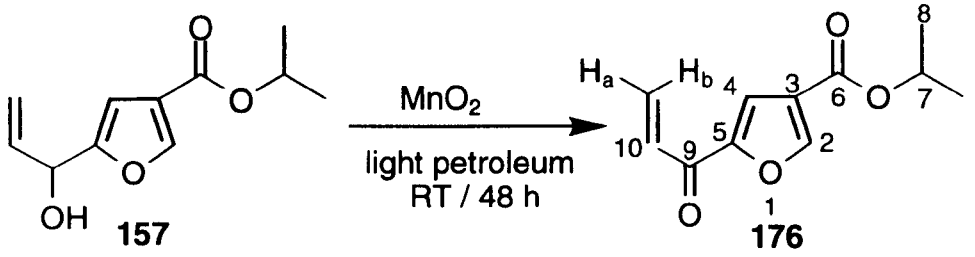
remove the residual manganese dioxide. The solvent was removed *in vacuo* to leave the crude product. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (4:1) afforded the respective oxidised furoates.

METHYL 5-(2-PROPENOYL)-3-FUROATE (175)



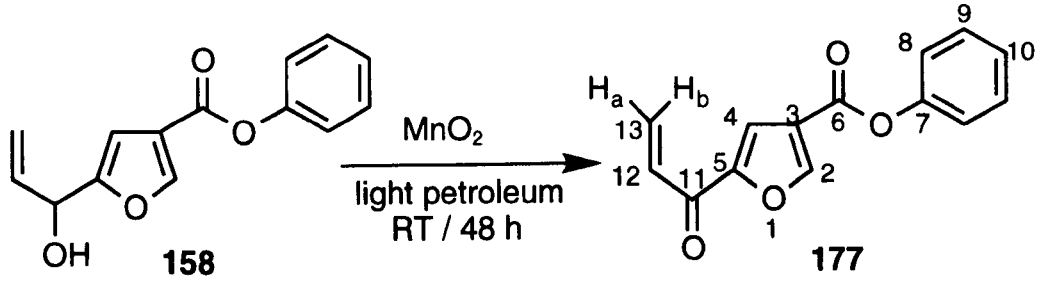
The general procedure for oxidation was followed using methyl 5-(1-hydroxy-2-propenyl)-3-furoate **156** (100 mg: 0.55 mmol) and manganese dioxide (478 mg: 5.55 mmol). Purification *via* column chromatography afforded methyl 5-(2-propenoyl)-3-furoate **175** as a white solid (24 mg: 0.13 mmol: 24%); IR $\nu_{max}(CH_2Cl_2)$ 1672, 1728, 3064 and 3144 cm^{-1}. δ_H (200 MHz; $CDCl_3$); 3.79 (1H, s, H-7), 5.85 (1H, dd, $J_{10a,10b}$ 1.56 Hz, $J_{10a,9}$ 10.44 Hz, H-10a), 6.48 (1H, dd, $J_{10b,10a}$ 1.54 Hz, $J_{10b,9}$ 17.1 Hz, H-10b), 6.96 (1H, dd, $J_{9,10a}$ 10.45 Hz, $J_{9,10b}$ 17.13 Hz, H-9), 7.46 (1H, s, H-4) and 8.09 (1H, s, H-2). δ_c (50 MHz); 51.9 (C-7), 116.97 (C-4), 121.22 (C-3), 130.42 (C-10), 130.69 (C-9), 150.48 (C-2), 153.21 (C-5), 162.16 (C-6) and 177.79 (C-8). *m/z*; 180 (M^+, 100), 153 (M^+-C_2H_3, 89.9), 149 (M^+-OMe, 78) and 121 (M^+-COOMe, 43.8) (Found M^+ 180.0420, C 59.9 and H 4.42% ; $C_9H_8O_4$ requires M^+, 180.0426 C 60.0 and H 4.44%).

ISOPROPYL 5-(2-PROPENOYL)-3-FUROATE (176)



The general procedure was followed using isopropyl 5-(1-hydroxy-2-propenyl)-3-furoate **157** (200 mg: 0.95 mmol) and manganese dioxide (826 mg: 9.5 mmol). Purification afforded isopropyl 5-(2-propenoyl)-3-furoate **176** as a white solid (55 mg: 3.75 mmol: 28%) m.p. 42-44°C; IR $\nu_{max}(CH_2Cl_2)$: 1670, 1720, 3018 and 3154 cm^{-1} δ_H (200 MHz: $CDCl_3$) 1.27 (6H, d, $J_{8,7}$ 6.26 Hz , H-8), 5.14 (1H, septet, $J_{7,8}$ 6.27 Hz, H-7), 5.866 (1H, dd, $J_{11a,11b}$ 1.58 Hz, $J_{11a,10}$ 10.42 Hz, H-11a), 6.51 (1H, dd, $J_{11b,11a}$ 1.57 Hz, $J_{11b,10}$ 17.13 Hz, H-11b), 6.9 (1H, dd, $J_{10,11a}$ 9.75 Hz, $J_{10,11b}$ 17.12 Hz , H-10), 7.47 (1H, d, $J_{4,2}$ 0.69 Hz , H-4) and 8.08 (1H, d, $J_{2,4}$ 0.69 Hz , H-2). δ_C (50 MHz): 21.81 (C-8), 68.7 (C-7), 117.24 (C-4), 122.07 (C-3), 130.44 (C-11), 130.77 (C-10), 152.41 (C-2), 153.15 (C-5), 161.4 (C-6) and 177.92 (C-9). *m/z*: 208 (M^+, 26.5), 166 (36.7), 149 (100) and 139 (78.4%).(Found 208.0738 $C_{11}H_{12}O_4$ requires 208.0735).

PHENYL 5-(2-PROPENOYL)-3-FUROATE (177)

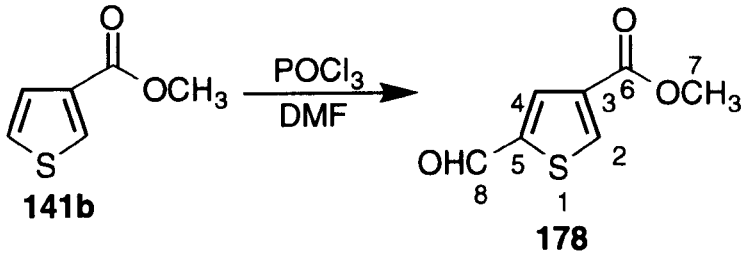


The general procedure was followed using phenyl 5-(1-hydroxy-2-propenyl)-3-furoate **158** (100 mg: 0.41 mmol) and manganese dioxide (356 mg: 4.1 mmol).

Purification afforded phenyl 5-(2-propenoyl)-3-furoate **177** (20 mg: 0.082 mmol: 20%); IR ν_{max} ($CDCl_3$ solution): 1672, 1744 and 3020 cm^{-1}. δ_H (200 MHz): 5.91 (1H, dd, H-13a), 6.55 (1H, dd, H-13b), 6.98 (1H, dd, H-12), 7.07-7.40 (5H, m, H-8, 9 and 10), 7.60 (1H, s, H-4) and 8.28 (1H, s, H-2) *m/z*; 242 (16.6) and 149 (100); (Found 242.0583 $C_{14}H_{10}O_4$ requires 242.0579)

6.12 SYNTHESIS OF 3,5-DISUBSTITUTED THIOPHENES *VIA* FORMYLATION

METHYL 5-FORMYL-3-THIOPHENECARBOXYLATE

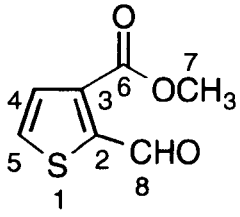


To a flask cooled to 0°C was added phosphorus oxychloride (2.16 ml: 3.55 g: 23 mmol) and dimethylformamide (1.79 ml: 1.69 g: 23 mmol). The yellow Vilsmeier salt formed which was allowed to stand for 20 minutes. Methyl 3-thiophenecarboxylate (1.32 g: 9.2 mmol) was added and the solution warmed to 100°C for 6 h. The mixture was cooled to room temperature and poured onto an ice/water mixture (15 g) and potassium carbonate (5 g) added. The solution was then extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml) and dried *in vacuo* to give the crude ester. Purification of the residual oil *via* column chromatography eluting with light petroleum/ ethyl acetate (4:1) afforded methyl 5-formyl-3-thiophenecaboxylate (300 mg: 1.76 mmol: 19%) and methyl 2-formyl-3-thiophene-carboxylate (71 mg: 4.18 mmol: 4.1%) in a ratio of 4.2:1.

Data for methyl 5-formyl-3-thiophenecarboxylate **178**:

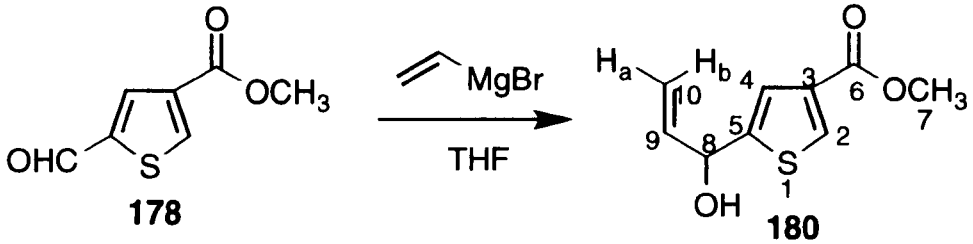
IR ν_{max} ($CDCl_3$): 1671, 1720, 3042 and 3138 cm^{-1} δ_H (200 MHz: $CDCl_3$); 3.83 (3H, s, H-7), 8.08 (1H, d, $J_{4,2}$ 1.29 Hz, H-4), 8.36 (1H, d $J_{2,4}$ 1.29 Hz, H-2) and 9.85 (1H, dd, $J_{8,4}$ 1.34 Hz, $J_{8,2}$ 2.59 Hz, H-8). δ_C(50 MHz); 52.16 (C-7), 134.42 (C-3), 136.28 (C-4), 140.31(C-2), 144.2(C-5), 162.08 (C-6) and 183.5 (C-8). *m/z*; 170 (M^+, 52.1), 139 (M^+-OMe, 100) and 111 (M^+-COOMe, 22.1%) (Found M^+, 170.0011; $C_7H_6O_3S$ requires M, 170.0037).

Data for methyl 2-formyl-3-thiophenecarboxylate **179**:



Yield, IR ν_{max} ($CDCl_3$): 1666, 1724, 3052 and 3114 cm^{-1}.δ_H(200MHz: $CDCl_3$); 3.9 (3H, s, H-7), 7.57 (1H, br s, H-4), 7.59 (1H, d, br s, H-5) and 10.53 (1H, s, H-8). *m/z*; 170 (M^+, 43.3), 155 (M^+-Me, 32.9), 139 (M^+-OMe, 39.2) and 111 (M^+-COOMe, 100%) (Found 170.0024 $C_7H_6O_3S$ requires 170.0037).

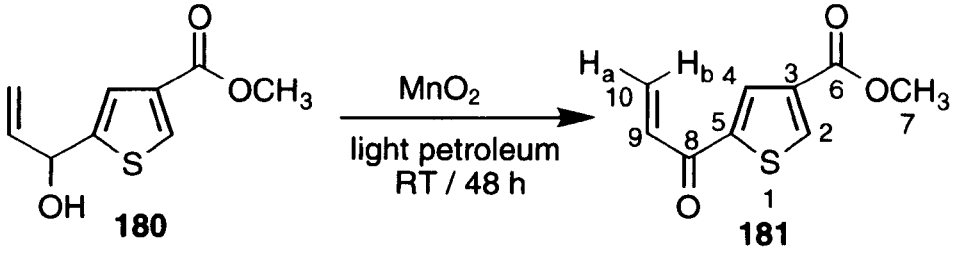
METHYL 5- (1-HYDROXY-2-PROPENYL)3-THIOPHENE-CARBOXYLATE (180)



A dry flask was charged with methyl 5-formyl-3-thiophenecarboxylate **178** (500 mg: 3.4 mmol) and THF (20 ml) and cooled to 0°C. Vinylmagnesium bromide (3.4 ml: 1.0 M in THF: 3.4 mmol) was added dropwise and the resulting solution warmed to

room temperature and stirred for 12 h. Water (50 ml) was added and the resulting solution extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml) and dried over magnesium sulfate. The solvent was then removed under reduced pressure and the residual oil purified by column chromatography eluting with light petroleum/ ethyl acetate (4:1) affording methyl 5-(1-hydroxy-2-propenyl)-3-thiophene carboxylate **180** (331 mg: 1.67 mmol: 57%) IR ν_{max} ($CDCl_3$ soln.); 1678, 1720, 3054 and 3112 cm^{-1}. δ_H (200 MHz: $CDCl_3$): 3.77 (3H, s, H-1), 5.10(2H, m, H-10), 6.01 (1H, ddd, $J_{9,8}$ 6.15 Hz, $J_{9,10a}$ 10.23 Hz, $J_{9,10b}$ 16.05 Hz, H-9), 7.26 (1H, d, $J_{4,2}$ 0.74 Hz, H-4) and 7.94 (1H, $J_{2,4}$ 1.35 Hz, H-2); δ_C (50 MHz): 51.8(C-7), 70.69 (C-8), 114.53 (C-4), 116.19 (C-10), 124.41 (C-3), 132.62 (C-2), 138.80 (C-9), 147.97 (C-5) and 163.3 (C-6) *m/z*; 198 (M^+, 44.9), 183 (M^+-Me, 16.5), 167 (M^+-OMe, 52.9) and 139 (M^+-COOMe, 81.8) : Found 198.0353 $C_9H_{10}O_3S$ requires M, 198.0350.

METHYL 5-(2-PROPENOYL)-3-THIOPHENECARBOXYLATE (181)

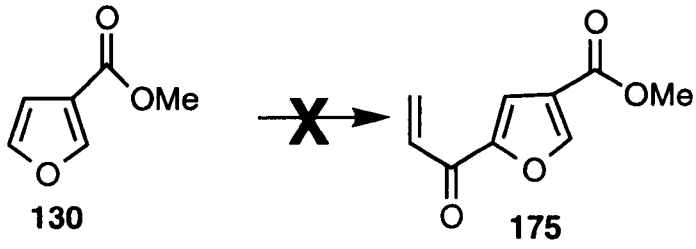


To a solution of methyl 5-(1-hydroxy-2-propenyl)-3-thiophene carboxylate (200 mg: 1 mmol) in light petroleum (10 ml) was added manganese dioxide (860 mg: 10 mmol) and the resulting slurry stirred for 24 h. The mixture was then filtered through a pad of Celite® to remove the residual manganese diioxide. The solvent was removed *in vacuo* to leave the crude product. Tlc indicated that there was only one compound present therfore further purification was not necessary. This gave methyl 5-(2-

propenoyl)-3-thiophenecarboxylate as a white solid (106mg: 0.5 mmol:53%); m.p. 59-60°C; IR ν_{max} ($CDCl_3$ solution): 1660, 1720, 3112 and 3310 cm^{-1}. δ_H (200 MHz): 3.5 (3H, s, H-7), 5.87 (1H, dd, $J_{10a,10b}$ 1.53 Hz, $J_{10a,9}$ 10.42 Hz, H-10a), 6.46 (1H, dd, $J_{10a,10b}$ 1.53 Hz, $J_{9,10b}$ 17.0 Hz, H-10b), 7.02 (1H, dd, $J_{9,10a}$ 10.42 Hz, $J_{9,10b}$17.01 Hz, H-9), 8.06 (1H, d, $J_{4,2}$ 1.20 Hz, H-4) and 8.30 (1H, d, $J_{2,4}$ 1.21 Hz, H-2); δ_C (50 MHz): 52.12 (C-7), 129.9 (C-10), 130.97 (C-4), 132.26 (C-2), 134.20 (C-3), 139.86 (C-9), 145.2 (C-5), 162.36 (C-6) and 182.25 (C-8); *m/z*; 196 (M^+,15.7), 165 (M^+-OMe, 11.5) and 137 (M^+-COOMe,11.3%) (Found 196.0198 $C_9H_8O_3S$ requires 196.0194).

6.13 ALTERNATIVE SYNTHESIS TO KETONE (175)

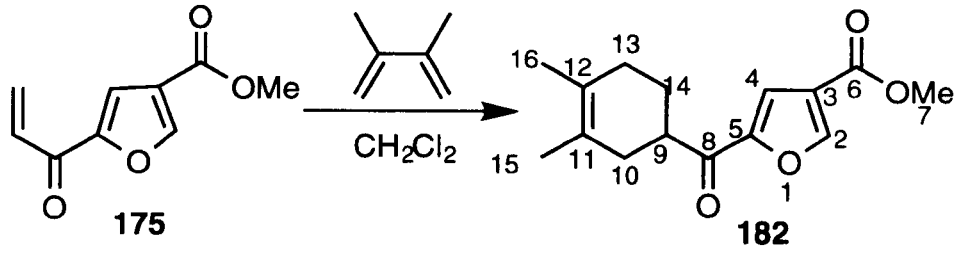
ATTEMPTED FRIEDEL-CRAFTS REACTION USING ACRYLOYL CHLORIDE



Methyl 3-furoate **130** (500 mg: 3.9 mmol) was added to a stirring solution of acryloyl chloride (2 ml) and the resulting solution warmed to 70°C. $BF_3.OEt_2$ (1.0 ml: 1.19 g: 8.45 mmol) was then slowly added and the solution turned black. Tlc using light petroleum/ ethyl acetate (5:1) as the eluent indicated that a complex mixture of products had been formed.

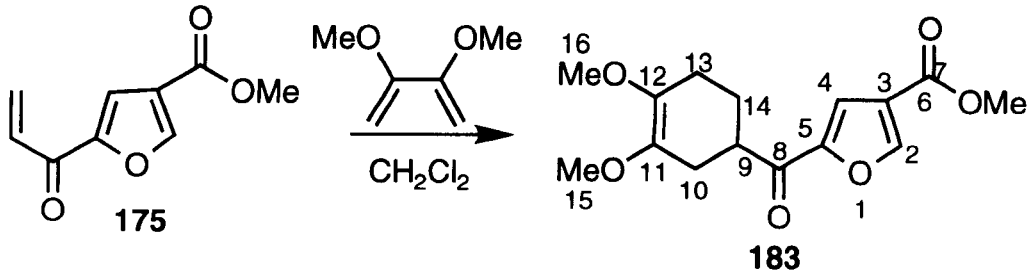
6.14 SYNTHESIS OF DIELS-ALDER ADDUCTS

DIELS-ALDER USING 2,3-DIMETHYLBUTADIENE AND METHYL 5-(2-PROPENOYL)-3-FUROATE



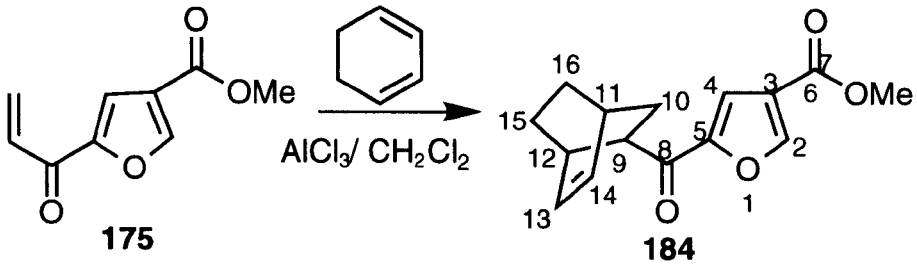
To a solution of methyl 5-(2-propenoyl)-3-furoate **175** (150 mg: 0.83 mmol) in CH_2Cl_2 (5 ml) in a flame dried flask under a nitrogen atmosphere was added 2,3-dimethyl-1,3-butadiene (0.14 ml: 101 mg: 1.25 mmol). The resulting solution was refluxed overnight. The solution was cooled before being diluted with water and extracted with ethyl acetate (3 x 20 ml). The organic extracts were combined, washed with sodium bicarbonate (3 x 20 ml), brine (3 x 20 ml) and the solvent reduced *in vacuo* to leave the crude product as the residual oil. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (3:1) afforded the Diels-Alder adduct; 82 mg (0.31 mmol: 37%): IR ν_{max}(CH_2Cl_2 solution): 1705, 1729, 2915 and 3066 cm^{-1}. δ_H (200MHz, $CDCl_3$): 1.62 (6H, s, H-15 and 16), 1.84 (6H, m, H-10,13 and 14), 3.18 (1H, tt, H-9), 3.90 (3H, s, H-7), 7.40 (1H, d, $J_{4,2}$ 0.69 Hz, H-4) and 8.05 (1H, d, $J_{2,4}$ 0.69 Hz, H-2). δ_C (50 MHz): 18.78 (C-15), 18.95 (C-16), 25.92 (C-14), 31.20 (C-13), 33.51 (C-10), 43.42 (C-9), 51.95 (C-7), 116.15 (C-4), 120.96 (C-3), 123.94 (C-12), 125.29 (C-11), 150.05 (C-2), 152.6 (C-5), 162.41 (C-6) and 192.37 (C-8). *m/z*: 262 (M^+, 33.1), 231 (6.8) and 203 (1.3%). (Found M^+, 262.1198 $C_{15}H_{18}O_4$ requires 262.1205).

DIELS-ALDER ADDUCT FORMATION WITH 2,3-DIMETHOXY-BUTADIENE



To a solution of methyl 5-(2 propenoyl)-3-furoate (150 mg: 0.83 mmol) in CH_2Cl_2 was slowly added 2,3-dimethoxybutadiene (0.15 ml: 141 mg: 1.23 mmol). The resulting solution was refluxed overnight and then cooled, diluted with water (20 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic extracts were then washed with brine (3 x 20 ml), sodium bicarbonate (3 x 20 ml) and the solvent removed *in vacuo*. Purification *via* column chromatography eluting with light petroleum/ethyl acetate (5:1) afforded the title compound (64 mg: 0.22 mmol: 26%); δ_H (200MHz, $CDCl_3$): 2.36 (6H, m, H-10, 13 and 14), 3.18 (1H, m, H-9), 3.55 (3H, s, H-16), 3.57 (3H, s, H-15), 3.90 (3H, s, H-7), 7.40 (1H, d, $J_{4,2}$ 0,69 Hz, H-4) and 8.06 (1H, d, $J_{2,4}$ 0.69 Hz, H-2). δ_C (50 MHz): 23.35 (C-13), 24.53 (C-14), 24.66 (C-10), 42.66 (C-9), 51.98 (C-7), 57.21,57.33 (C-15 and 16), 116.47 (C-4), 117.03, 121.16 (C-3), 130.77 (C-12), 137.76 (C-11), 150.49 (C-2), 162.25 (C-5), 177.89 (C-6) and 190.00 (C-8). *m/z* 294 (M^+, 11.5), 263 (2.6) and 235 (1.5%) (Found M^+, 294.1069 $C_{15}H_{18}O_6$ requires M, 294.1102).

LEWIS ACID ACCELERATED DIELS-ALDER ADDUCT FORMATION

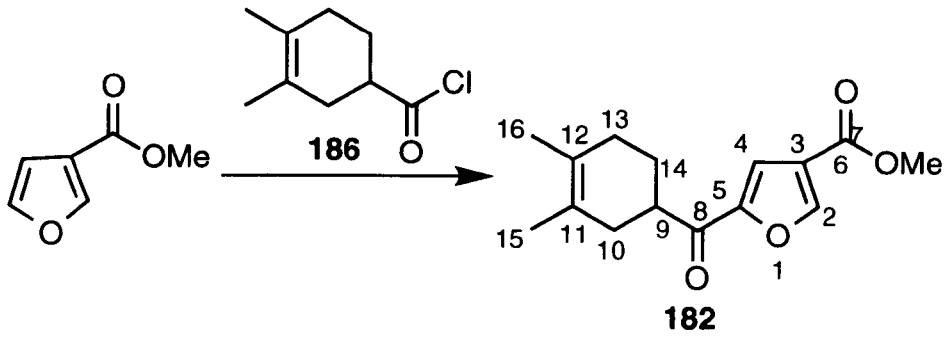


175 **184**

To a solution of methyl 5-(2-propenoyl)-3-furoate (90 mg: 0.5 mmol) in CH_2Cl_2 (10 ml) was added 1,3-cyclohexadiene (0.1 ml: 84.1 mg:1 mmol) and $AlCl_3$ (100 mg: 0.75 mmol). The resulting mixture was refluxed overnight before being cooled and diluted with water. The solution was then extracted with ethyl acetate (3 x 20 ml) and the combined organic extracts washed with brine (3 x 20 ml) and sodium bicarbonate (3 x 20 ml). Solvent was removed under reduced pressure and purification *via* column chromatography eluting with light petroleum/ ethyl acetate (4:1) afforded the desired Diels-Alder adduct **184** (43 mg: 0.16 mmol: 33%) IR ν_{max}($CHCl_3$ solution): 1681, 1728, 3026 and 3145 cm^{-1}. δ_H ($CDCl_3$; 200MHz) 1.7 (4H, m, H-14, and 15), 2.58 (1H, m, H-13), 2.85 (1H, m, H-16), 3.31 (1H, m, H-10), 3.79 (3H, s, H-7), 4.06 (1H, m, H-9), 6.21 (1H, m, H-11), 6.31 (1H, m, H-12), 7.34 (1H, d, $J_{4,2}$ 0.69 Hz, H-4) and 8.02 (1H, d, $J_{2,4}$ 0.7 Hz, H-2); δ_C (50MHz) 24.18 (C-16) , 25.95 (C-15), 29.33 (C-11), 32.77 (C-10), 46.45 (C-12) , 49.23 (C-9), 51.90 (C-7), 115.61 (C-4), 120.87 (C-3), 130.90 (C-14) , 134.85 (C-13), 149.64 (C-2), 152.94 (C-5), 162.43 (C-6) and 194.60 (C-8). *m/z*: 260 (5.1), 229 (4.1) and 169 (5.4%) (Found M^+, 260.1048 $C_{15}H_{16}O_4$ requires M, 260.1048)

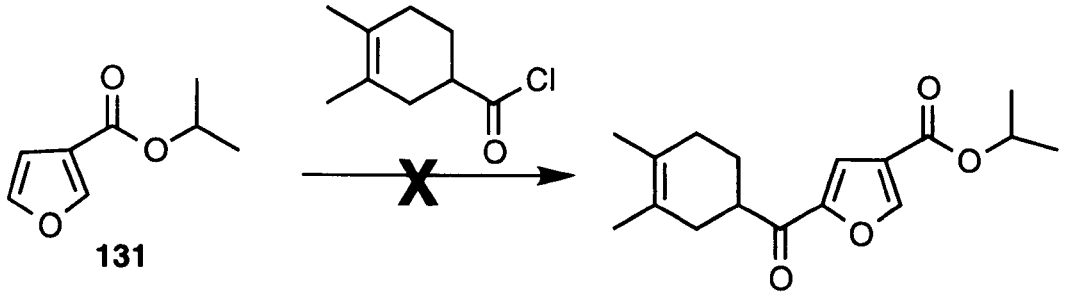
6.15 ALTERNATIVE SYNTHETIC ROUTE TO DIELS-ALDER ADDUCTS

FRIEDEL-CRAFTS USING METHYL 3-FUROATE



To a stirring solution of 2,3-dimethylbutadiene (0.68 ml: 500 mg: 6 mmol) in CH_2Cl_2 (10 ml) was slowly added acryloyl chloride (2.02 ml: 550 mg: 6 mmol) and the resulting solution heated to 40°C for 1 h. The CH_2Cl_2 was then removed *in vacuo* to leave the acid chloride as a colourless oil. To the oil was added methyl 3-furoate (250 mg: 1.98 mmol) and the solution warmed to 80°C. $BF_3.OEt_2$ (0.47 ml: 0.55 g: 3.93 mmol) was slowly added and the solution turned a black colour. Tlc indicated that product had been formed. Purification by column chromatography eluting with light petroleum / ethyl acetate (5:1) afforded the desired product **182** (121 mg: 0.46 mmol: 23%). Spectroscopic analysis was consistent with the data obtained for the product **182** obtained previously.

ATTEMPTED FRIEDEL-CRAFTS USING ISOPROPYL 3-FUROATE

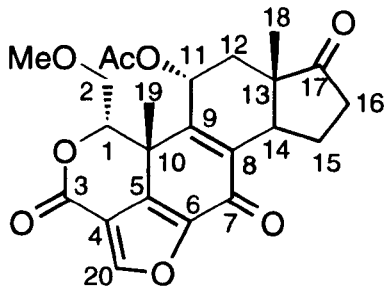


The method used for generation of the acid chloride between 2,3-dimethybutadiene and acryloyl chloride was identical to the preceeding reaction. To the resultant oil

isopropyl 3-furoate (200 mg: 1.3 mmol) was added and the solution warmed to 80°C. $BF_3.OEt_2$ (0.4 ml: 0.46 g: 3.34 mmol) was slowly added and the solution turned black. Tlc indicated that no product had been formed. The reaction temperature was increased to 100°C but Tlc showed again that no product had been formed and only low running baseline material.

6.16 SYNTHESIS OF WORTMANNIN DERIVATIVES

ISOLATION OF WORTMANNIN 34



34

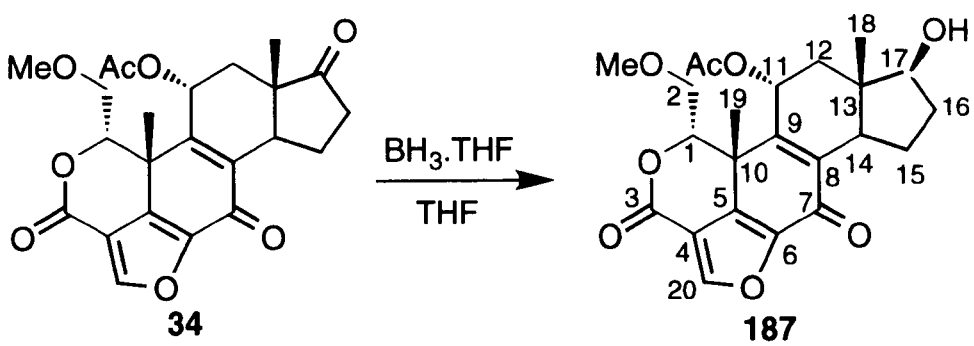
Wortmannin was obtained from *Talaromyces wortmanii* CBS Baarn-Delft (CBS 387.67) as a freeze dried culture. The culture was maintained on 2% malt agar slants and transferred to Raulin and Thom (+ 5% extra glucose) still culture (5 l) separated into roux bottles. Table 6.1 shows the ingedients for the still culture.

INGREDIENT	WT (g)
De-ionised water	1 L
Glucose	52.5
Tartaric Acid	2.66
Ammonium tartrate	2.66
Di-ammonium hydrogenorthophosphate	0.4
Potassium carbonate	0.4
Magnesium carbonate	0.27
Ammonium sulfate	0.17
Zinc sulfate	0.05
Ferrous sulfate	0.09

Table 6.1: Ingredients for still culture

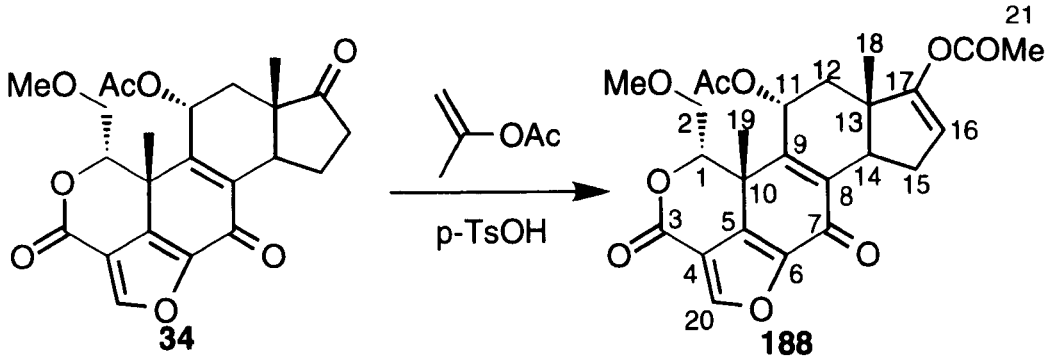
The roux bottles were transferred to a room in subdued light for 264 h at 25°C maintaining a pH of 3.9. The contents of the roux bottles were filtered, the broth collected and the organics isolated by continuous extraction for 24 h with ethyl acetate. The ethyl acetate extracts were dried over magnesium sulfate and evaporation of the solvent *in vacuo* left the crude wortmannin as a solid. Purification *via* column chromatography eluting with light petroleum/ ethyl acetate (1:1) afforded wortmannin **34** as a green solid (2.1 g: 0.46g l^{-1}) mp 238-240°C IR $\nu_{max}(CH_2Cl_2$ solution): 1648, 1748, 3140 cm^{-1}. δ_H(200 MHz: $CDCl_3$): 0.84 (3H, s, H-18), 1.67 (3H, s, H-19), 2.15 (3H, s, OAc), 2.51 (2H, m, H-16), 2.70 (1H, m, H-14), 2.85 (2H, m, H-12), 2.90 (2H, m, H-15), 3.28 (3H, s, OMe), 3.37 (2H, dd, *J* 1.77 and *J* 11.15 Hz, H-2), 4.72 (1H, dd, *J* 1.74 and *J* 7.00 Hz, H-1), 6.09 (1H, ddd, *J* 2.65, *J* 7.55 and *J* 8.67, H-11) and 8.21 (1H,s, H-20). δ_C (50 MHz); 14.5 (C-18), 20.97 (CH_3CO), 22.86 (C-15), 26.41 (C-19), 35.65 (C-16), 40.67 (C-10), 43.98 (C-14), 49.12 (C-13), 59.12 (MeO), 70.03 (C-11), 72.78 (C-2), 88.46 (C-1), 114.15 (C-4), 140.29 (C-5), 142.81 (C-9), 144.69 (C-6), 149.50 (C-8), 150.07 (C-20), 157.60 (C-3), 169.49 (CH_3CO), 172.59 (C-7) and 216.30 (C-17).*m/z* 385 (M^+-OAc, 1.5) and 266 (11.8%) (Found M^+, C 64.24, H 5.57 $C_{23}H_{24}O_8$ requires M, C 64.48, H 5.57%).

WORTMANNIN-17β-OL (187)



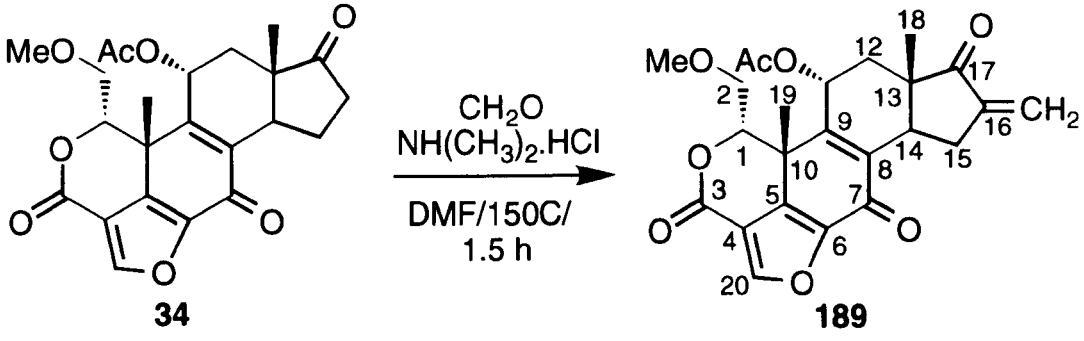
To a flame dried flask flushed with nitrogen were charged Wortmannin **34** (150 mg: 0.37 mmol) and 10 ml THF before being cooled to 0°C. BH_3.THF (0.74 ml: 1.0 M solution in THF: 0.74 mmol) was added slowly dropwise and the resulting solution kept at 0°C for 5 hr. A colour change from orange to yellow was observed. Water was added and organics were extracted with ethyl acetate (3 x 25 ml), washed with sodium bicarbonate (3 x 20 ml) and brine (3 x 20 ml). The organic layer was then dried over magnesium sulfate and the solvent removed under reduced pressure to give the crude product. Purification by column chromatography eluting with light petroleum / ethyl acetate (1:2) afforded the desired product **187** as a yellow solid (72 mg;: 0.1 mmol: 48%); IR ν_{max} ($CHCl_3$ solution); 1647, 1680, 1750, 3026 and 3143 cm^{-1}. δ_H (200 MHz); 0.79 (3H, s, H-19), 1.74 (3H, s, H-18), 2.07 (3H, s, OAc), 2.23 (1H, m, H-16), 2.51 (1H, m, H-16), 2.71 (1H, m, H-14), 2.91 (1H, dd, *J*7.32 and *J*11.11 Hz, H-2), 3.12 (3H, s, CH_3O), 3.37 (1H, dd, *J*1.75 and *J* 11.11 Hz, H-2), 3.80 (1H, t, *J* 7.84 Hz, H-14), 4.29 (1H, m, H-17), 4.69 (1H, dd, *J*1.72 and *J*7.26 Hz, H-1), 6.04 (1H, m, H-11) and 8.17 (1H, s, H-20)· δ_C (50 MHz: $CDCl_3$); 11.76(C-18), 21.07(C-19), 24.58(C-15), 26.46(C-22), 30.35(C-12), 39.98(C-13), 40.63(C-10), 44.09(C-16), 45.2(C-14), 59.33(CH_3O), 70.75(C-11), 72.82(C-2), 78.9(C-17), 88.91(C-1), 114.11(C-4), 141.94(C-5), 142.62(C-9), 144.94(C-6), 148.39(C-8), 149.82(C-20), 157.75(C-3), 169.63(C-21) and 172.96(C-7)

WORTMANNIN ENOL ACETATE (188)



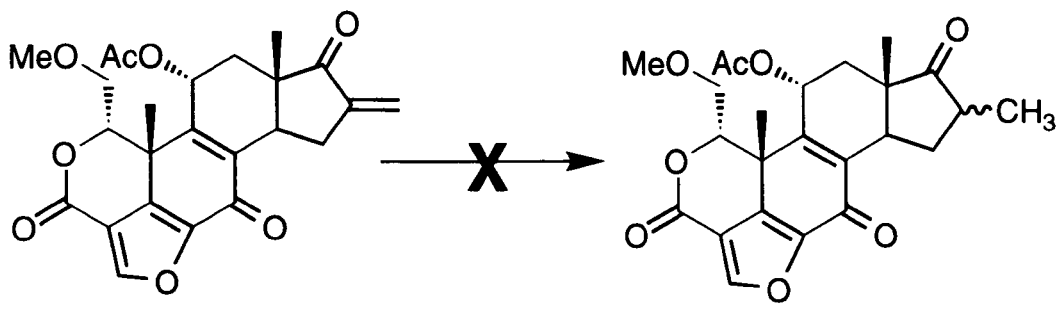
To a flame dried flask flushed with nitrogen were charged wortmannin **34** (158 mg: 0.39 mmol), isopropenyl acetate (5 ml) and a catalytic amount of para-toluenesulfonic acid. The resulting mixture was allowed to stir for 24 h at 100°C. The resulting solution was then extracted with ethyl acetate (3 x 25 ml), washed with sodium bicarbonate (3 x 10ml), brine (3 x 10 ml) and dried over magnesium sulfate. The residual solvent was then removed under reduced pressure to give the crude product. Purification was achieved *via* column chromatography eluting with light petroleum/ ethyl acetate (1:5) to give wortmannin enol acetate **188** (100 mg: 0.2 mmol: 58%) IR ν_{max} ($CHCl_3$ solution): 1646, 1680, 1752, 2970 and 3144 cm^{-1}. δ_H (200 MHz; $CDCl_3$): 0.86 (3H, s, H-18), 1.60 (1H, m, H-12), 1.66 (3H, s, H-19), 2.06 (3H, s, H-21), 2.11 (3H, s, OAc), 2.43 (2H, m, H-15), 2.60 (1H, m, H-12), 2.85 (1H, m, H-14), 2.98 (1H, m, H-2), 3.13 (3H, s, OMe), 3.39 (1H, m, H-2), 4.61 (1H, m, H-1), 5.54 (2H, m, H-16), 6.03 (1H, m, H-11) and 8.19 (1H, s, H-20). δ_C (50 MHz): 16.27 (C-18), 20.998 (C-21), 21.04 ($\mathbf{C}H_3CO$), 26.175 (C-19), 30.28 (C-12), 39.25 (C-15), 40.25 (C-10), 46.07 (C-14), 47.75 (C-13), 59.32 (MeO), 70.10 (C-11),72.87 (C-2), 88.52 (C-1), 113 (C-16), 114.11 (C-4), 132 (C-17), 141.44 (C-5), 144.5 (C-6), 142.51 (C-9), 148.03 (C-8), 149.83 (C-20), 155.66 (C-3), 168.67 ($CH_3\mathbf{C}O$), 169.95 (C-21) and 172.5 (C-7).

16-METHYLIDENEWORTMANNIN (189)



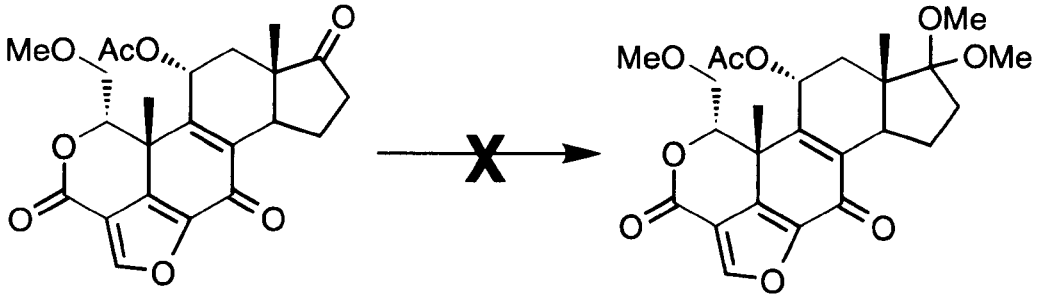
To a flame dried flask under a nitrogen atmosphere was added wortmannin **34** (150 mg: 0.35 mmol), dimethylamine hydrochloride (38 mg: 0.47 mmol), a catalytic amount of paraformaldehyde and 10 ml DMF. The resulting solution was stirred at 150°C for 0.5 h after which it gradually turned black . The solution was then cooled to 0°C and dilute HCl was added dropwise until an acidic pH was acheived. The solution was then extracted with ethyl acetate (3 x 20ml) and the extracts combined and washed with water (3 x 10 ml), brine (3 x 10 ml) and dried over magnesium sulfate. The solvent was then removed under reduced pressure to give the crude product as the residue. Purification by column chromatography eluting with ethyl acetate/ light petroleum (5:3) gave 16-methylidenewortmannin **189** (106 mg: 0.24 mmol: 69%); IR ν_{max} ($CDCl_3$ solution): 1644, 1748, 3020 and 3144 cm^{-1}. δ_H (200 MHz); 0.92 (3H, s, H-18), 1.68 (3H, s, H-19), 2.07 (3H, s, OAc), 2.92 (1H, dd, *J* 7.00 and 11.13 Hz, H-2), 3.11 (3H, s, OMe), 3.37 (1H, m, H-2), 4.70 (1H, dd, H-1), 5.5 (1H, s, H-21), 6.12 (2H, m, H-11) and 8.19 (1H, s, H-20). δ_C (50 MHz); 14.93 (C-18), 20.98 (CH_3CO), 26.45 (C-19), 34.05 (C-15) ,36.25(C-12), 40.78 (C-10),41.51(C-14),49.45 (C-13), 59.39 (MeO),69.93 (C-11),72.82 (C-2), 88.43 (C-1), 114.23 (C-4), 120.71 (C-23), 139.96 (C-5), 142.3 (C-9), 143.96 (C-16), 144.66 (C-6), 149.75 (C-8), 150.00 (C-20), 157.522 (C-3), 169.49 (CH_3CO), 172.5 (C-7) and 204.17 (C-17). *m/z*: 440 (M^+, 3.1), 381 (6.2) and 366 (63.4%) (Found M, 440.1472 $C_{24}H_{24}O_8$ requires 440.1471)

ATTEMPTED HYDROGENATION OF 16-METHYLIDENE-WORTMANNIN



A flask was charged with wortmannin **34** (20 mg: 0.04 mmol) followed by 15 ml ethyl acetate and a catalytic amount of palladium/carbon catalyst before being flushed with hydrogen. The resulting solution was allowed to stir for 12 h. The catalyst was then filtered through a pad of Celite® and the solvent removed under reduced pressure. Tlc indicated that although all starting material was consumed a complex mixture had been made. The reaction was therefore abandoned.

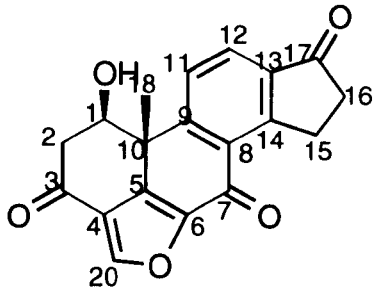
ATTEMPTED SYNTHESIS OF 17,17-DIMETHYLACETAL WORTMANNIN



Wortmannin **34** (150mg 0.35 mmol), a catalytic amount of concentrated sulfuric acid and 20 ml dry methanol were charged to a flame dried flask held under nitrogen. The mixture was stirred for 60 h at room temperature. A white precipitate formed and water (10 ml) was added. The resulting solution was extracted with ethyl acetate (3 x 20 ml) and the combined organic extracts were washed with sodium bicarbonate (3 x 10 ml), brine (3x 10 ml) and dried over magnesium sulfate. The solvent was removed in vacuo to leave an orange solid as the product. This orange solid was identified as the starting material.

6.17 ISOLATION OF DEMETHOXYVIRIDIN AND SYNTHESIS OF PLD-7

ISOLATION OF DEMETHOXYVIRIDIN (35)

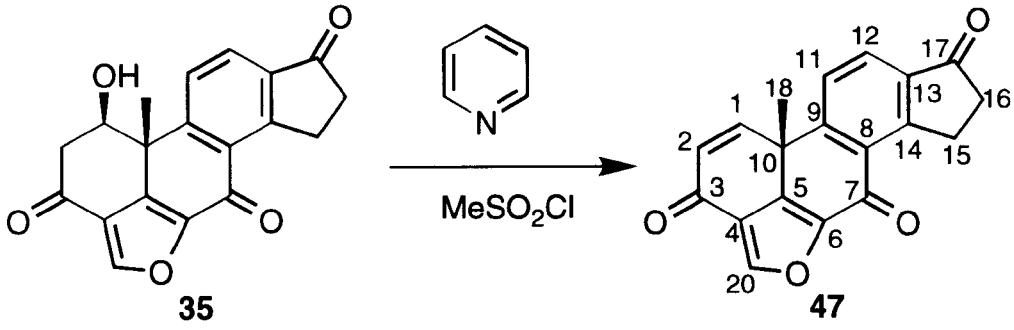


35

Nodulisporium hinnuleum (IMI catalogue number 214826) was maintained on 2% malt agar slants at 25°C. Raulin and Thom culture medium (with 5% extra glucose - see Table 6.1) was prepared and transferred to roux bottles and sterilised in an autoclave. The *Nodulisporium hinnuleum* was then transferred to the sterile culture medium and the bottles were tranferred to a room with artificial lighting at 25°C for 350 h. The broth was then decanted from the myceleum. The broth was then continuously extracted for 24 h with ethyl acetate and the myceleum was soxhlet extracted for 24 h with ethyl acetate after being freeze dried. As tlc indicated that demethoxyviridin was present in both the extracts of the broth and the myceleum they were combined and the solvent removed *in vacuo*. Crude demethoxyviridin was obtained as the residual oil. Purification *via* column chromatography eluting with ethyl acetate/ light petroleum (1:1) followed by recrystallisation from ethyl acetate gave demethoxyviridin **35** as white crystals. M.p. 149-152°C ; IR ν_{max} (KBr disc): 1530, 1586, 1624, 1673, 1702 and 3439 cm^{-1}. δ_H (200 MHz: DMSO): 1.55 (3H, m, H-18), 2.61 (2H, m, H-16), 2.72 (1H, dd, *J* 5.3 and *J* 18.3 Hz, H-2), 3.09 (1H, dd, *J* 10.07 and 18.3 Hz H-2), 3.54 (2H, m, H-15), 4.33 (1H, m, H-1), 6.09 (1H, br d, *J* 5.8 Hz, OH), 7.84 (1H, d, *J* 8.2 Hz, H-11), 8.59 (1H, d, *J* 8.2 Hz, H-12) and 8.80

(1H, s, H-20). δ_C(50 MHz: DMSO): 26 (C-18), 29 (C-16), 36 (C-2), 47 (C-15), 71 (C-1), 127, 129 (C-11, 12), 123 (C-4), 130, 137 (C-8.9), 145, 146 (C-13,14), 156 (C-5), 158 (C-6), 173 (C-7), 190 (C-3) and 206 (C-17); *m/z*: 322. 278, 250, 222, 165, 125 (Found M^+, 322.0837; C 69.9 and H 4.53% $C_{19}H_{14}O_5.1/3H_2O$ requires M^+, 32.0879; C 69.7 and H 4.5%)

SYNTHESIS OF PLD 7 (47)



Demethoxyviridin **35** (400 mg: 1.24 mmol) and methanesulfonyl chloride (427 mg: 3.72 mmol) were added to a 250 ml round bottom flask followed by pyridine (20 ml). The resulting solution was stirred for 72 h at room temperature. Water (200 ml) was added to quench the reaction and the aqueous phase extracted with diethyl ether (3 x 50 ml). The organic extracts were combined and washed with dilute hydrochloric acid (50 ml) and dried over magnesium sulfate. The residual solvent was removed *in vacuo* giving PLD 7 **47** (174 mg: 0.57 mmol: 46%) M.p. 147-153°C ; IR ν_{max}(KBr disc): 1528, 1586, 1632, 1665 and 1713 cm^{-1}. δ_H(200 MHz: $CDCl_3$): 1.8 (3H, s, H-18), 2.8 (2H, m, H-16), 3.70 (2H, t, *J* 5.9 Hz, H-15), 6.4 (1H,d, *J* 10.1 Hz, H-1), 7.7 (1H, d, *J* 10.1 Hz, H-2), 7.8 and 8.1 (2 x 1H, d, *J* 8.0 Hz, H-11 and 12) and 8.3 (1H, s, H-20); δ_C (50 MHz: $CDCl_3$); 29 (C-16), 36 (C-15), 41 (C-18), 122 (C-4), 124 (C-11) 128 (C-12), 131 (C 9), 132 (C-2), 145, 146 (C-13 and 8), 148 (C-1), 149 (C-20), 152 (C-5), 159 (C-6), 173 (C-7), 180 (C-

3) and 207 (C-17); *m/z*: 304, 289, 261, 176, 97 and 84. (Found M^+, 304.0734 $C_{19}H_{12}O_4$ requires 304.0718.

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