UNIVERSITY OF SOUTHAMPTON

A Synthetic Approach To Morphine

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UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

A SYNTHETIC APPROACH TO MORPHINE

by Charles Walter Ellwood

The synthesis of a putative intramolecular Diels-Alder reaction substrate, an intermediate in a synthetic approach to morphine, is described.

The condensation reactions of several *ortho*-bromophenols with allylic bromides are described. The *ortho*-bromophenyl allyl ethers thus produced were treated with a catalytic quantity of palladium acetate to give a series of benzofuran derivatives. Several 3,4,7-trisubstituted benzofurans were produced.

Two *ortho*-bromophenyl allyl ethers were subjected to radical cyclisation conditions. Two novel tetracyclic compounds were produced.

The condensation of nitromethane with several aromatic aldehydes is described. The β-nitroethenyl-aromatic compounds produced were reduced to give the corresponding β-nitroethyl-aromatic compounds.

The cycloaddition reactions of nitrones and silylnitronates to methyl E-2,4-pentadienoate are described. The isoxazole derivatives produced in these reactions were converted to dienyl or trienyl systems. The putative intramolecular Diels-Alder reaction substrate was produced using this methodology.

Acknowledgements.

I am indebted to my supervisor Dr. P. J. Parsons for his help and encouragement throughout my time in his research group. I would also like to thank Phil, and his wife Sue, for their friendship and support over the last three years.

My thanks are also due to my lab-mate of three years standing Steve Caddick. His enthusiasm for chemistry and cutting wit have fired me into action on many occasions. My other friends in the Chemistry Department are thanked for their help and encouragement.

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On a personal level my family are thanked for all the support they have given me both emotionally and materially. The friends with whom I have been priviledged to share a house have been of great support. Especially deserving of recognition is Helen Ebert who gave me a great deal of support when I plumbed the depths of depression and who since has helped me discover the joys of drinking wine.

Last, but by no means least, the S.E.R.C. and Glaxo Group Research (Ware) are acknowledged for providing financial support and Rob West is thanked for his diligence in proof-reading this script.

Abbreviations.

AIBN	Azobisisobut~~e~~yronitrile
DMF	Dimethylformamide
DMSO	Dimethyl Sulphoxide
24-DNP	2,4-Dinitrophenylhydrazine
Ether	(without any qualification) Diethyl Ether
FMO	Frontier Molecular Orbital
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
Petrol	Light Petroleum Ether (boiling range 40-60 °C)
PMO	Perturbational Molecular Orbital
Tf	Trifluoromethanesulphonyl
THF	Tetrahydrofuran

CHAPTER 1

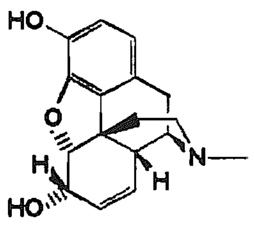
Section 1; The History of Morphine [1].

Since time immemorial *papaver somniferum*, the opium poppy, has been cultivated by man. The interest in this plant is far from purely aesthetic, for if the immature seed capsules are damaged a white juice is exuded. This juice turns brown as it dries to produce opium, a substance that has long been prized as a medicament because of its remarkable ability to relieve pain. The feeling of wellbeing that is also associated with the use of opium has almost certainly led to the abuse of the substance since the earliest of times.

For many centuries man used opium as a painkiller without worrying about the reasons for this activity, however by the beginning of the nineteenth century attempts to isolate the active constituents of opium were being made. Thus in 1803 Derosne reported that the extraction of opium with water and the subsequent precipitation of this extract with potassium carbonate yielded a crystalline solid which he called "salt of opium" [2]. Some two years later in 1805 Setürner reported the isolation of a pure alkaloidal base [3] which he named morphine (1) after Morpheus, an ancient Greek god of dreams and son of Somnus the god of sleep. The morphine isolated by Setürner was shown to have the same effect in dogs as did the opium from whence it came.

Further isolation work was performed on opium throughout the nineteenth century, this led to the isolation of noscapine (narcotine) (2) in 1817 [4], codeine (3) in 1832 [5], thebaine (4) in 1835 [6] and papaverine (5) in 1848 [7]. Many more opium alkaloids have been isolated in the intervening years. A total of 27 have been identified at the current time though many of these occur only in trace amounts. On average morphine is the most abundant of the opium alkaloids and is responsible for most of the biological activity of opium [8].

Once morphine had been isolated and its biological activity had been confirmed, attempts were made to characterise the compound more fully. The first satisfactory elemental analysis was performed in 1847 [9] and chemical studies were also undertaken from about this time. The intensity of study increased at the turn of the twentieth century and culminated in 1925 with Gulland and Robinson



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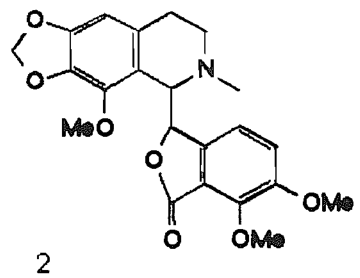

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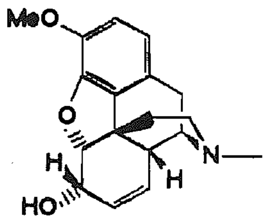

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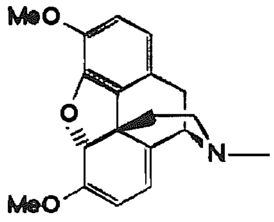

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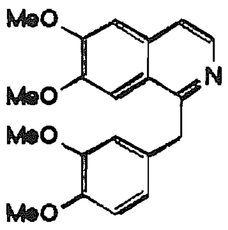

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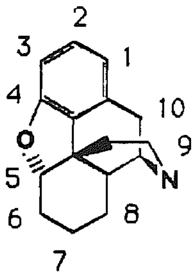
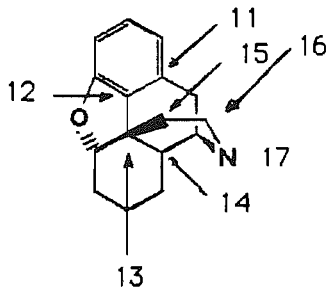




6. H-Tyr-Gly-Gly-Phe-Met-OH

7. H-Tyr-Gly-Gly-Phe-Leu-OH

proposing the now accepted structure for morphine (**1**) on the basis of their own work and also on that of Hesse, Vorgericten, Knorr and Pschorr [10,11].

A total synthesis was required in order to confirm that the proposed structure was indeed that of morphine. This task was completed by Gates and Tschudi who published details of the first total synthesis of morphine in 1952 [12]. X-ray crystallography and degradation studies provided the final proof of structure and absolute stereochemistry in 1955 [13,14] (the morphine produced by *papaver somniferum* is enantiomerically pure (-) morphine).

Section 2; The Clinical effects of Morphine [15,16].

In section 1 it has been noted that morphine, in the form of opium, has been abused for many years. The abuse potential of the drug and several undesirable side effects have limited the use of morphine as an analgesic. These problems have led to the manufacture of a large number of synthetic or semi-synthetic analogues of morphine in an attempt to find a "clean" analgesic.

A brief review of this work will be presented in due course, however first we will consider the activity of morphine in man.

The administration of morphine to man may cause some or all of the effects listed below;

a) Central effects are analgesia, euphoria, drowsiness, sleep, a raising of the pain threshold, a change of attitude and emotional responses.

b) Respiratory depression (this may be life threatening).

c) Cough suppression.

d) Nausea/vomiting.

e) Miosis (pupil contraction).

f) Constipation (due to effects on smooth muscle).

g) Hypotension (low blood pressure).

h) Histamine release (this can cause a rash or skin irritation).

i) Cyanosis (blue colouration of the skin).

j) Physical dependence on repeated administration with a withdrawal syndrome on cessation of use.

Many of these effects are also observed upon administration of analogues of morphine though the intensity of a given symptom varies from compound to compound. The ability of morphine and its analogues to produce these effects was thought to be due to the interaction of the drug with an opiate receptor. The possibility that more than one type of receptor may be involved in opiate binding was first suggested in the 1960's [17]. This theory was proven in 1975 with the discovery that at least three different opiate receptors could be identified in the mammalian body [18]. Subsequent studies suggest that up to five receptors may be involved in opiate binding [19].

Compounds which show a strong affinity for a particular opiate receptor produce effects characteristic of that receptor. Thus these observations encouraged the belief that a "clean" analgesic could be developed by tailoring the molecular affinity for the various receptor types. Unfortunately no detailed structural information about the receptor sites is available and thus rational drug design is difficult to achieve.

The existence of opiate receptors in the mammalian body was for many years an intriguing puzzle. It seemed unlikely that these receptors were supposed to interact with morphine from external sources and there was no evidence for morphine production in the mammalian body. The puzzle was at least partially solved with the discovery of the normal agonists of these receptors. The first of these agonists to be discovered were a pair of pentapeptides, methionine enkephalin (**6**) and leucine enkephalin (**7**), which were isolated and characterised in 1975 [20]. Several fragments of the peptidic hormone β-lipotropin have also been found to possess opiate style activity [21,22,23]. All of these endogenous peptidic opiates are now known as endorphins [24] and all show some structural similarity to the morphine molecule when they are folded in the correct manner.

Section 3; Analogues of Morphine Synthesised from Morphine, Codeine or Thebaine. [25]

The effects listed above show that morphine has both beneficial and detrimental actions in man. The most serious disadvantages of its clinical usage are respiratory depression and dependence liability. These dangers were realised from an early stage in the clinical usage of morphine and attempts to make "cleaner" analgesics were soon to follow. Thus by the last quarter of the nineteenth century chemical modifications to the morphine molecule were being made.

The first synthesis of heroin (**8**) (diacetyl morphine) was reported in 1874 [26] and this compound was brought into clinical use in 1898 [1]. It was claimed that heroin depressed respiration to a lesser degree than did morphine and that it had no dependence liability. Both these claims were soon disproven and the search for the ideal analgesic continued.

The early years of the twentieth century saw the introduction to clinical use of several compounds made by simple chemical modifications of morphine. Very little progress was made in producing "cleaner" analgesics.

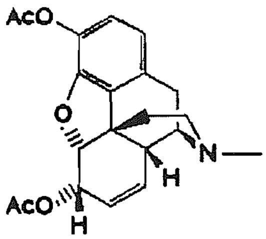
In 1915 Phol reported the synthesis of N-allylnorcodeine (**9**) which he claimed was antagonistic to the respiratory depression produced by morphine [27]. The corresponding morphine analogue N-allylnormorphine (**10**) (nalorphine) was prepared in 1941 and the antagonism to respiratory depression was confirmed [28]. Indeed nalorphine was found to be antagonistic to most of the effects of morphine in man. This compound however still retained an analgesic action similar to that of morphine and exhibited an ability to produce psychomimetic side effects. This latter characteristic precluded its use as an analgesic in man.

Some of the most important modifications to the basic morphine structure have been made using thebaine as a starting material. Thebaine is only a minor constituent of opium (though the scale of opium production ensures that a reasonable supply of this alkaloid is available) but is found in large quantities (up to 26% dry weight) in the latex of the poppy *papaver bracteatum* [29].

Treatment of thebaine (**4**) with acidic hydrogen peroxide gives 14-hydroxycodeinone (**11**) [30]. Catalytic hydrogenation of this material followed by treatment with hydrobromic acid gives 14-hydroxydihydromorphinone (**12**) [31] (oxymorphone) (scheme 1.1). This compound is a potent analgesic some ten times as active as morphine. The N-allyl analogue of this compound naloxone (**13**) [32] is a highly potent pure narcotic antagonist and has found clinical use in the treatment of opiate overdoses [1]. Care has to be exercised in the administration of this compound as it is antagonistic to all the effects of morphine. If the overdose victim is dependant on opiates the administration of naloxone rapidly precipitates the onset of the opiate withdrawal syndrome.

Bentley argued that a larger more rigid structure than morphine should bind more selectively to the opiate receptor and thus may give the "clean" analgesic that had been sought for so long. He decided to approach the compounds he desired using thebaine as a starting material.

The reaction of thebaine (**4**) with methylvinylketone gave the Diels Alder adduct (**14**). This was treated with n-propylmagnesium bromide and the intermediate was O-demethylated to give etorphine (**15**) (scheme 1.2). This compound is at least 2000 times more potent than morphine. The dihydro-derivative of etorphine (**16**) is reported to be some 12000 times as active as morphine! [33,34].



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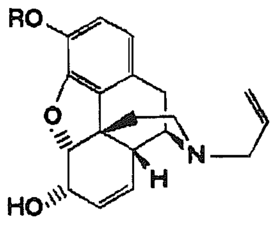
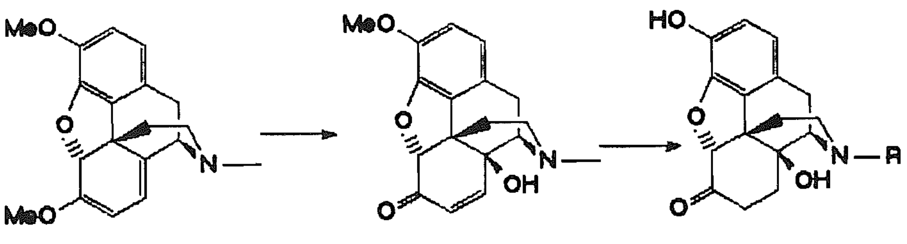


9 R=Me

10 R=H



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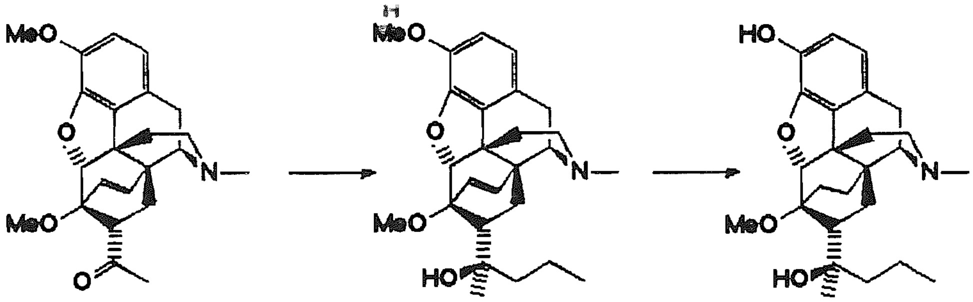
12 R=Me

13 R=Allyl

Scheme 1.1



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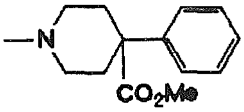
Scheme 1.2



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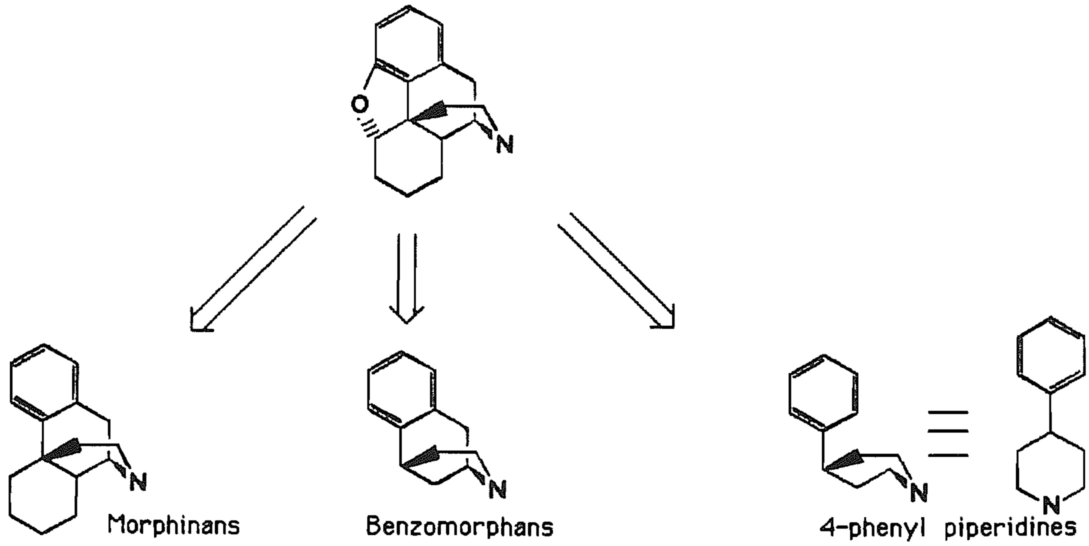
Section 4; Morphine fragments.

The discovery in 1939 of the opiate style analgesic activity of pethidine (**17**) [35], a 4-phenyl piperidine, was a major though (at the time) surprising advance in opiate research.

Several other classes of compound are now known to possess similar activity. Most of these compounds can be regarded as partial structures of morphine or as analogues thereof. The activity of these fragments has been attributed to three basic characteristics; a benzene ring, a quarternary carbon attached to this ring and a tertiary amino group two aliphatic carbons removed from the quarternary centre [1]. Morphine itself shows all of these characteristics as do almost all the compounds which exhibit opiate style activity. Scheme 1.3 shows the relationship between morphine and some of the more common fragments which retain opiate style biological activity.



Scheme 1.3

The Morphinans.

In this context the term morphinan refers to the morphine ring structure which lacks the C(4)-C(5) oxygen bridge found in morphine. It should be noted that the morphine ring system is named as a 4,5-epoxymorphinan.

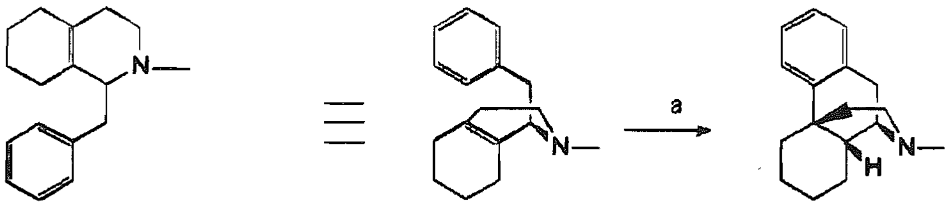
The morphinans are the most complex of the partial structures because they have the entire carbon skeleton of morphine and N(17) intact. The first synthetic morphinan (**18**) was reported in 1946 by Grewe [36]. His synthesis featured an intramolecular cyclisation of the 1-benzylisoquinoline derivative (**19**) to give the morphinan (**18**) [37] (scheme 1.4). This type of cyclisation reaction is now known as a Grewe cyclisation. The simple morphinan produced by Grewe showed some analgesic activity though it was less potent than morphine.

Schnider extended the work of Grewe; he added p-methoxybenzylmagnesium chloride to the tetrahydroisoquinoline derivative (**20**). Partial reduction of the intermediate (**21**) afforded the cyclisation precursor (**22**). Grewe cyclisation with concomitant methyl ether cleavage gave the 3-hydroxymorphinan (**23**) [38] (scheme 1.5). Chiral resolution afforded levorphanol (**24**) [39], a compound three to four times more active than morphine. The N-allyl analogue of levorphanol shows activity similar to that of nalorphine [25].

The Grewe cyclisation approach has also been used to make morphinans chirally [40] and has been used in four total syntheses of morphine [41,42,43,44]. These total syntheses will be reviewed later in this chapter.

A very different morphinan synthesis was reported by Monkovic *et al.* in 1973 [45]. The key steps in this approach were a Lewis acid catalysed Wagner-Meerwein ring expansion of (**25**) followed by a bromine-induced ring closure to give (**26**) (scheme 1.6). This approach gives rise to a C(8)-C(14)didehydromorphinan. This unsaturation allows the introduction of a hydroxyl group at C(14) giving access to simpler analogues of oxymorphone and naloxone.

These 14-hydroxymorphinans have also been approached from an early intermediate in the first synthesis of morphine [46].



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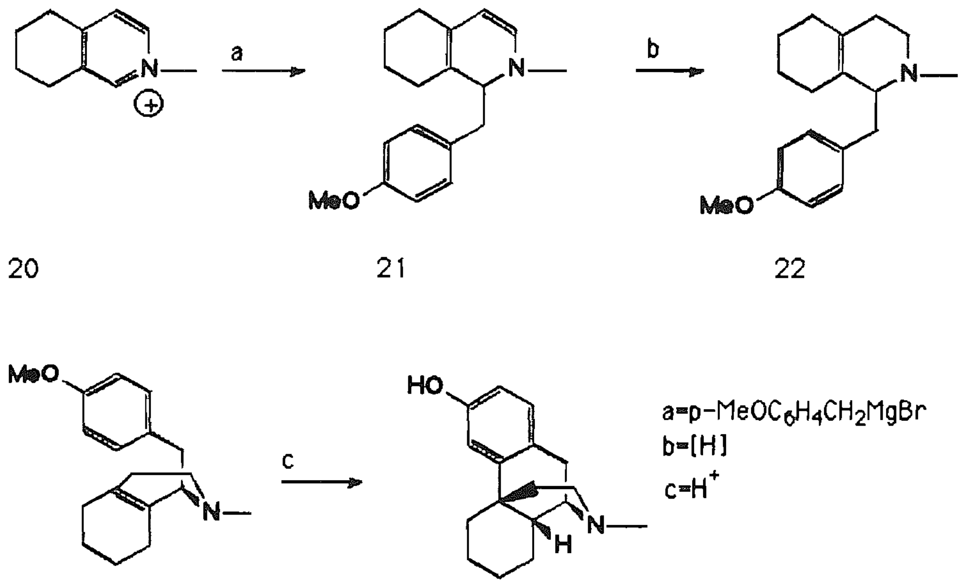
Scheme 1.4 a=H^+



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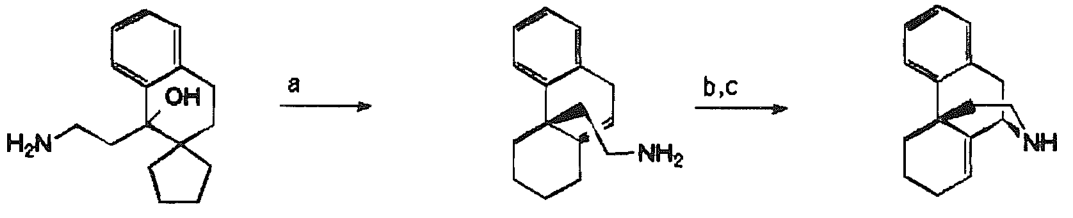
22

a=p-$MeOC_6H_4CH_2MgBr$
b=[H]
c=H^+

Scheme 1.5

23 (±) 24 (-)



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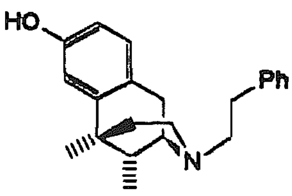
Scheme 1.6 a=HCl/Et_2O b=Br_2 c=$NaHCO_3$ / DMF.



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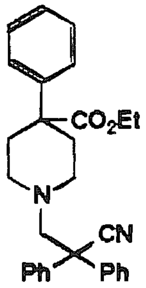

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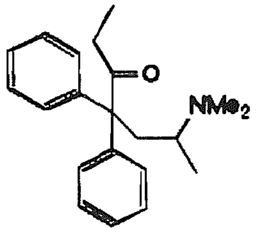

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The Benzomorphans.

The benzomorphans are an important class of compound in analgesic research. They differ from the morphinans that have just been discussed in that they have one less carbocyclic ring. Many benzomorphans show some analgesic activity and a few show some separation of analgesia from the other opiate-style activities in animals [1].

Only a few benzomorphans have found clinical use. One such is phenazocine (**27**) [1]. A thorough review of the benzomorphans is outside the scope of this thesis.

4-Phenyl Piperidines.

The first 4-phenyl piperidine to find clinical use as an analgesic was pethidine (**17**). The discovery of pethidine precipitated a large research effort. It led to the synthesis of a large number of 4-phenyl piperidines. No great separation of analgesia from the other opiate style activities was found in these compounds; however, some did show excellent separation of the effects on smooth muscle. Of these compounds some have been developed for clinical use as antidiarrhoeal agents, one such is diphenoxylate (**28**) [25].

The development of analogues of the 4-phenyl piperidines led to the introduction of methadone (**29**) and related compounds. Methadone has found clinical use in the treatment of opiate addiction. The withdrawal syndrome from methadone is slower, longer lasting and less intense than that from heroin or morphine. Methadone itself is an analgesic with a potency similar to that of morphine.

Several other classes of compound have also been shown to possess opiate style activity, but no great separation of analgesia from the other opiate activities has been found in these compounds.

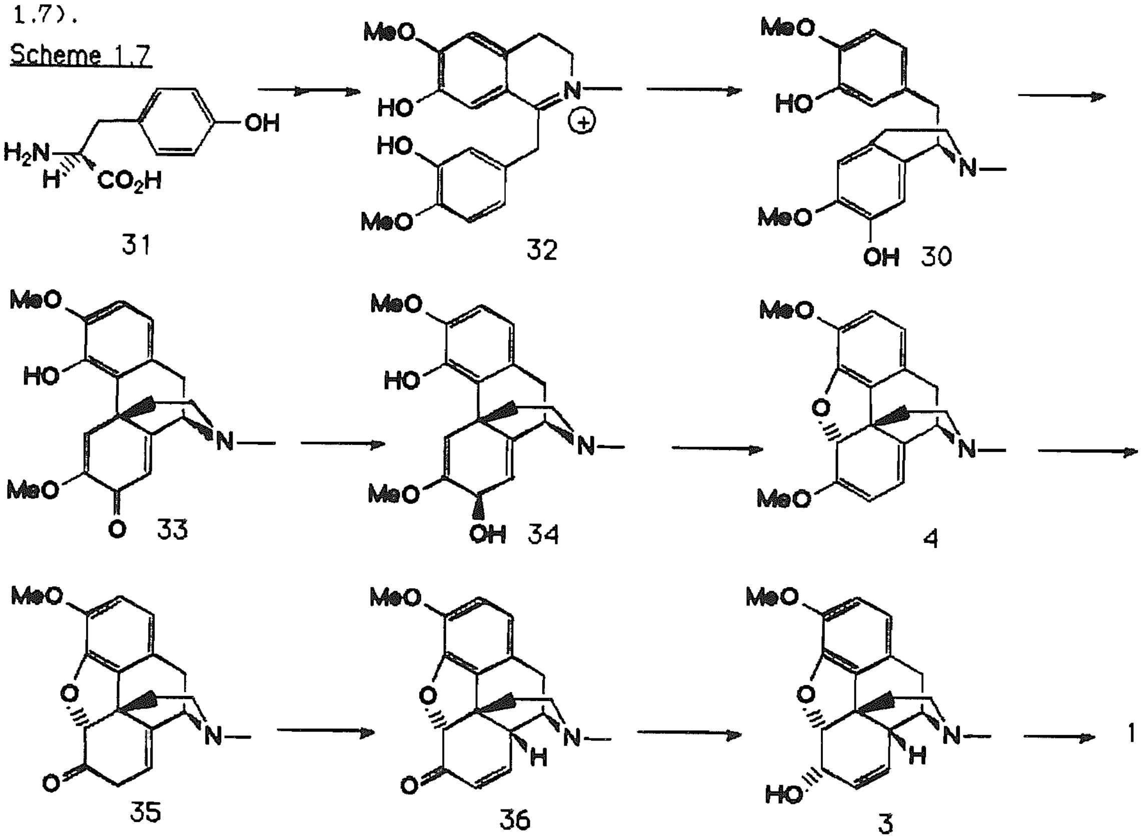
The brief overview of analgesic research presented above has taken us a long way away from morphine. This thesis will now concentrate on the synthesis of morphine and will start with a consideration of the biosynthesis of this important natural product.

Section 5; The Biosynthesis of Morphine.

The biosynthesis of morphine was studied predominantly in the 1960's by Barton, Battersby and their co-workers. They used ^{14}C and ^{3}H labelled substrates in many feeding experiments. More recent studies by Rapoport *et al.* have helped to confirm some of the later steps in the sequence.

In 1925 Robinson suggested that a biosynthetic relationship existed between morphine and a 1-benzyl isoquinoline precursor [10]. This relationship was confirmed in 1964 [47] with the identification of reticuline (**30**), itself made from two molecules of tyrosine (**31**) [48], as a precursor of morphine. The discovery in 1978 [49] that both R and S reticuline were converted to (-) morphine to the same extent by *papaver somniferum* was completely unexpected. Evidence exists to suggest that the dehydroreticulinium ion (**32**) is an intermediate in the epimerisation of S reticuline to R reticuline [49]. R reticuline then undergoes an intramolecular oxidative phenolic coupling reaction to produce salutaridine (**33**) [47]. Reduction of this material gives salutaridinol (**34**) [50] and thence thebaine (**4**) [51]. Morphine is produced from thebaine by way of neopinone (**35**) [52], codeinone (**36**) and codeine (**3**) [53,54] (scheme 1.7).

Scheme 1.7



Section 6; Previous Synthetic Approaches to Morphine.

The Early Syntheses of Morphine.

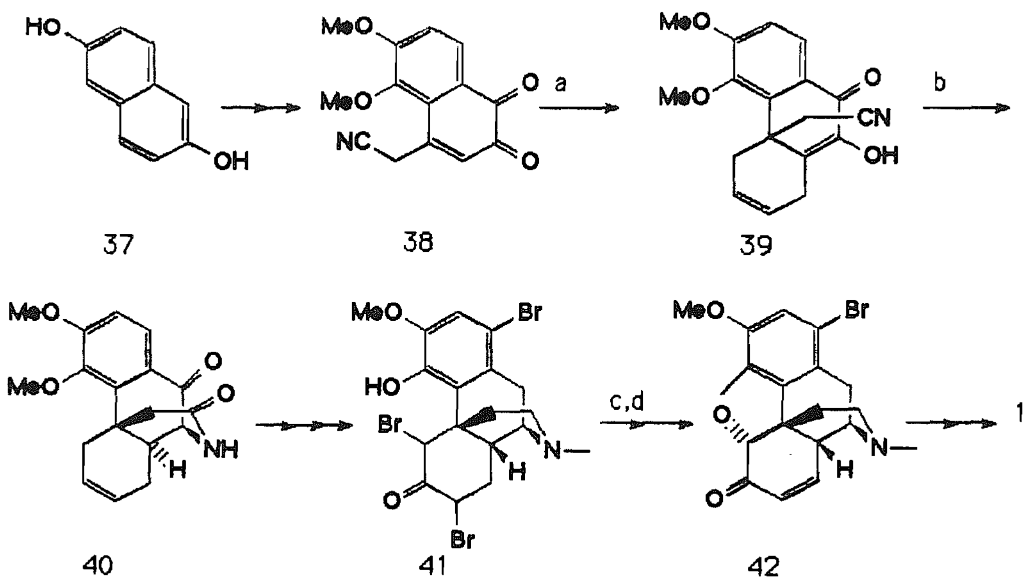
The first total synthesis of morphine was reported in 1952 by Gates and Tschudi [12]. By modern standards the synthesis was rather long but for the time it was reported it was a major and important achievement. The key steps in this approach are outlined in scheme 1.8.

2,6-Dihydroxynaphthalene (**37**) was converted in several steps to the nitrile (**38**). A Diels-Alder reaction of this compound with 1,3-butadiene gave (**39**) [55]. This compound has the three carbocyclic rings required for the morphine molecule already constructed. Catalytic hydrogenation of this molecule over a copper chromite catalyst gave the morphinan (**40**) which had the opposite stereochemistry at C(14) to that in morphine. The stereochemistry at this centre was inverted later in the synthesis by way of an α,β-unsaturated ketone.

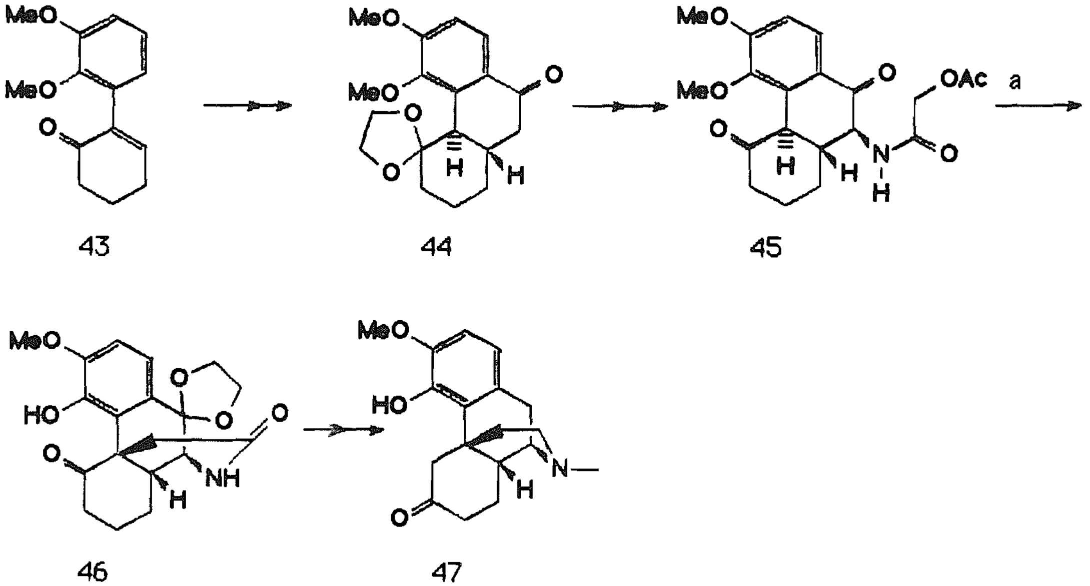
A long sequence of reactions led to the tribrominated intermediate (**41**).This intermediate loses two equivalents of hydrogen bromide upon treatment with 2,4-dinitrophenylhydrazine to give the codeinone derivative (**42**). This was converted to morphine in several steps [56].

Elad and Ginsburg reported their synthesis of morphine in 1954 [57]. They also approached the synthesis by building the carbocyclic rings first (scheme 1.9). Thus the bicyclic ketone (**43**) was converted in several steps to the monoprotected tricyclic diketone (**44**) [58]. The subsequent elaboration of this compound led to the ketone (**47**) which was an intermediate in the Gates and Tschudi morphine synthesis [55]. The manufacture of this material constituted a formal total synthesis of morphine.

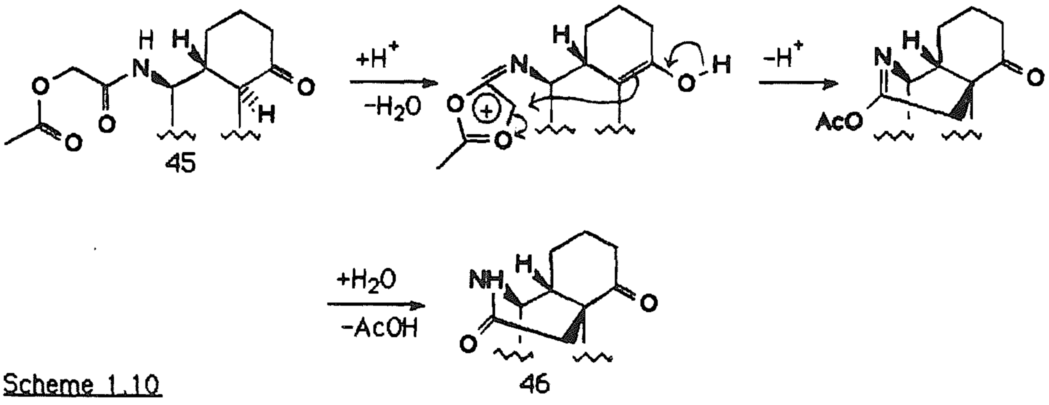
A possible mechanism for the key cyclisation reaction (**45**) to (**46**) was suggested by Stork and is shown in scheme 1.10 [59].



Scheme 1.8 a=butadiene, b=H_2/copper chromite, c=2,4-DNP d=H^+



Scheme 1.9 a=H^+



Scheme 1.10

The Grewe Cyclisation Approach.

The first synthetic morphinans were prepared using the approach developed by Grewe [36,37] which was discussed earlier. The extension of this work to give a formal total synthesis of morphine was completed in 1967 with both Grewe [41] and Morrison [42] reporting similar results.

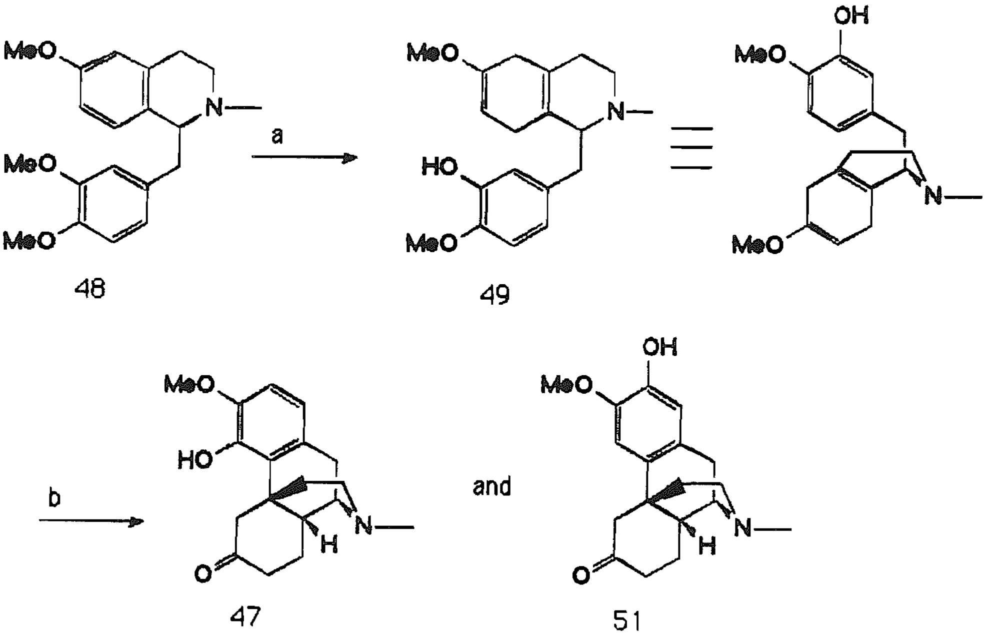
Morrisons work is illustrative of this approach. He made the 1-benzyltetrahydroisoquinoline (**48**) and performed a Birch reduction on it to obtain the cyclisation precursor (**49**). This was treated with aqueous hydrochloric acid to give a mixture of morphinans (**47**) and (**51**) in 3% and 37% yield respectively. Unfortunately the major product was the 2-hydroxymorphinan (**51**) which could not be used for morphine synthesis (scheme 1.11).

The Grewe cyclisation approach has been most successfully applied in systems where the undesirable cyclisation mode encountered by Grewe and Morrison is blocked with a group which is removed later in the synthesis. This strategy has been sucessfully applied in two total syntheses.

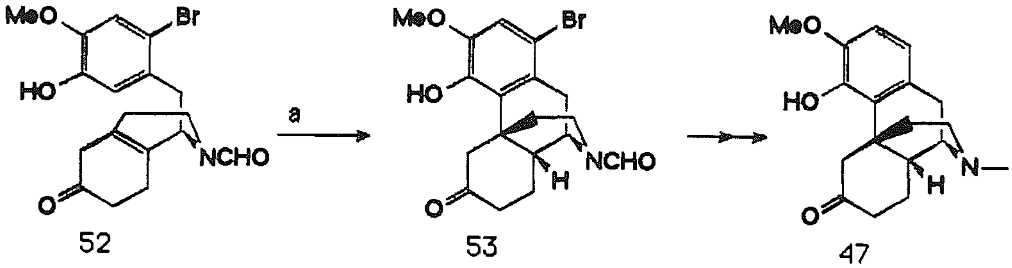
The work of Rice demonstrates the value of this approach [44]. He chose to use bromine as his blocking group. This approach is shown in scheme 1.12. The cyclisation precursor (**52**) was converted in 60% yield to the morphinan (**53**). The conversion of (**53**) to (**47**) completed a formal total synthesis of morphine.

The second of these approaches was that of Beyermann *et al.* [43]. They used a slightly different strategy. Their cyclisation substrate (**54**) contained two hydroxyl groups. This ensured the generation of the 2,4-dihydroxymorphinan (**55**). The hydroxyl group at C(2) was eventually removed by way of the tetrazole ether (**56**). Catalytic hydrogenation removed the tetrazole ether and also reduced the formamide to a methyl group to give (**47**) as is shown in scheme 1.13.

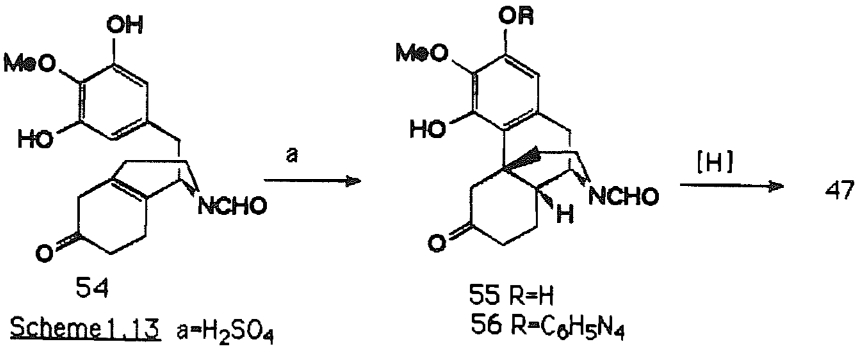
As well as the total syntheses discussed above this approach has been used to prepare 3-deoxy-7,8-dihydromorphinone [60].



<u>Scheme 1.11</u> a= Na/t-BuOH/NH$_3$ (l), b=HCl



<u>Scheme 1.12</u> a=NH$_4$F.HF/TfOH



<u>Scheme 1.13</u> a=H$_2$SO$_4$

The Biomimetic Approach.

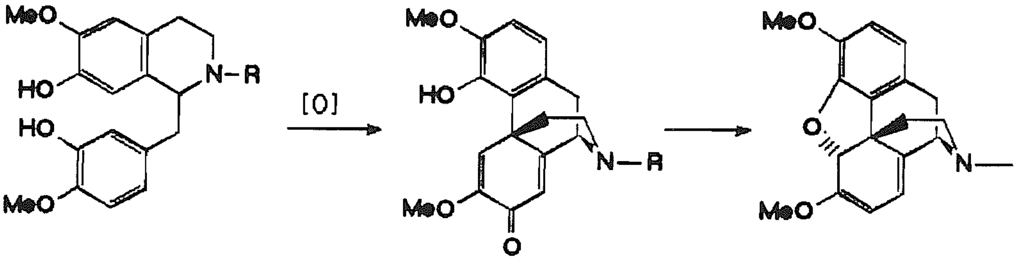
The oxidative phenolic coupling reaction which nature uses in the biosynthesis of morphine has proved to be much less successful in the laboratory.

All these approaches are summarised in scheme 1.14.

In 1967 Barton *et al.* reported a 0.03% yield of salutaridine (**33**) when reticuline (**30**) was oxidised with potassium ferricyanide. The other oxidising agents they tried were even less successful! [49]

Szántay *et al.* were somewhat more successful, using lead tetraacetate as the oxidising agent they converted (**30**) to (**33**) in 2.7% yield [61].

The most successful of these approaches was that of Schwartz and Mami [62]. They used (**57**) as substrate and thallium tristrifluoroacetate as the oxidising agent to obtain a 23% yield of the desired cyclisation product (**58**). This was reduced with lithium aluminium hydride and worked up with 1N hydrochloric acid to give thebaine (**4**). The conversions of salutaridine and thebaine to morphine are both known procedures, thus these approaches constitute formal total syntheses of morphine .



30 R=Me
57 R=CO_2Et

33 R=Me
58 R=CO_2Et

4

Scheme 1.14

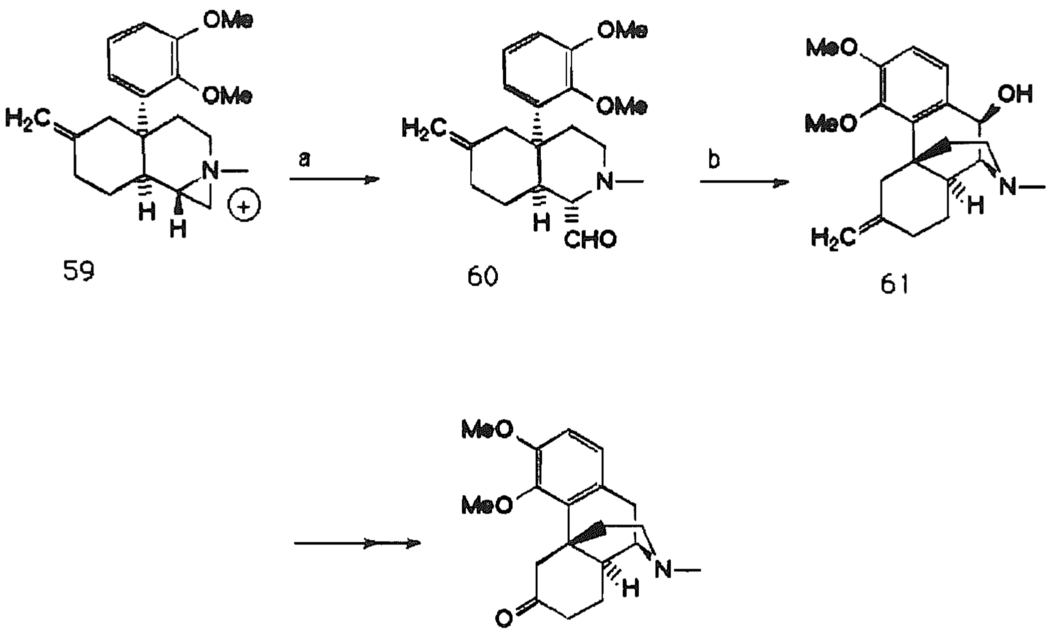
The Aziridinium Ion Approach.

Three similar approaches to the morphine structure were reported in the early 1980's [63,64,65]. These routes utilised an aziridinium ion as a key intermediate. The successful approach of Evans and Mitch is outlined in scheme 1.15 [63].

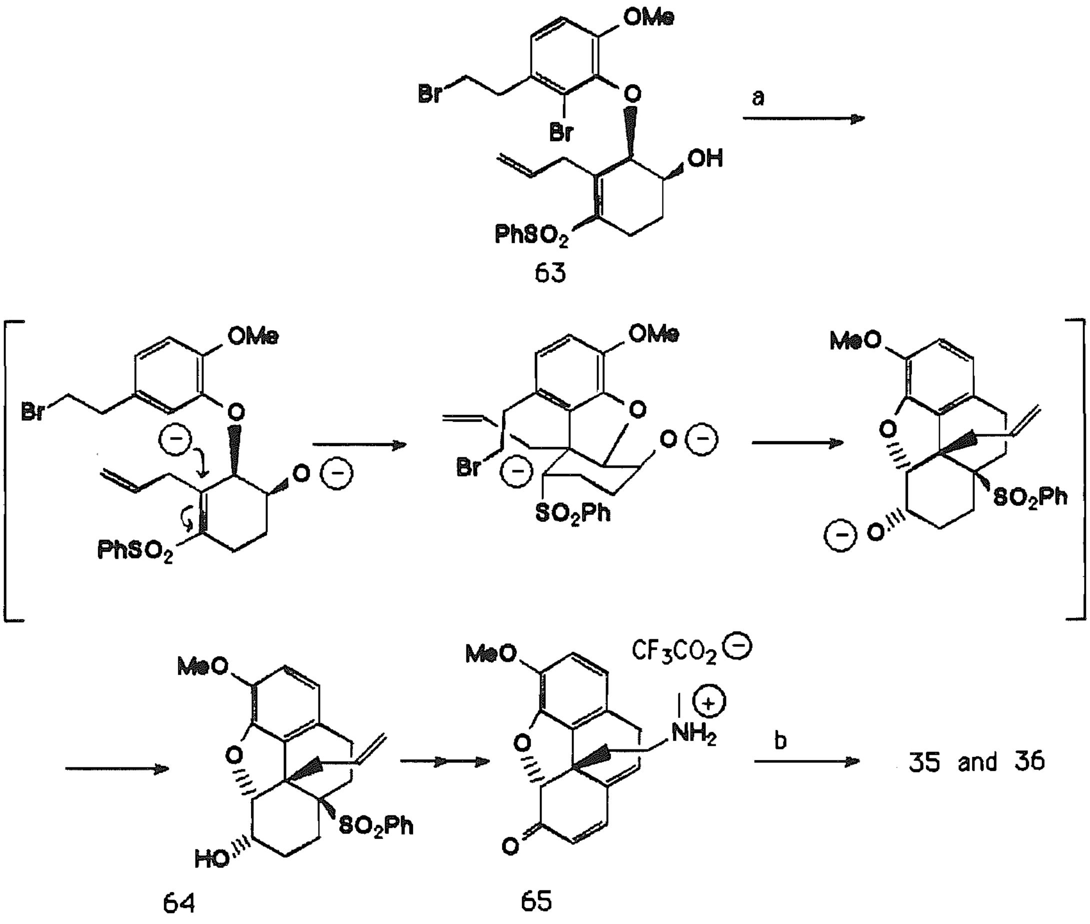
The key aziridinium ion (**59**) was prepared but was very reluctant to cyclise to give the morphinan skeleton. Treatment of (**59**) with dimethyl sulphoxide gave the aldehyde (**60**) which yielded the morphinan (**61**) on exposure to boron trifluoride etherate. A short series of simple modifications led to (**62**) which was an intermediate in the first synthesis of morphine.

The Vinyl Sulphone Approach.

Fuchs *et al.* used an intramolecular 1,4-addition of an organometallic species to a vinyl sulphone as a key step in their synthesis [66]. The anion generated as a result of this addition was then used in a second cyclisation reaction as shown in scheme 1.16 (the conversion of (**63**) to (**64**)). Further elaboration of (**64**) eventually gave the ammonium salt (**65**). This yielded a mixture of neopinone (**35**) and codeinone (**36**) on treatment with a mild base.



Scheme 1.15 a=Me_2SO, b=$BF_3.OEt_2$

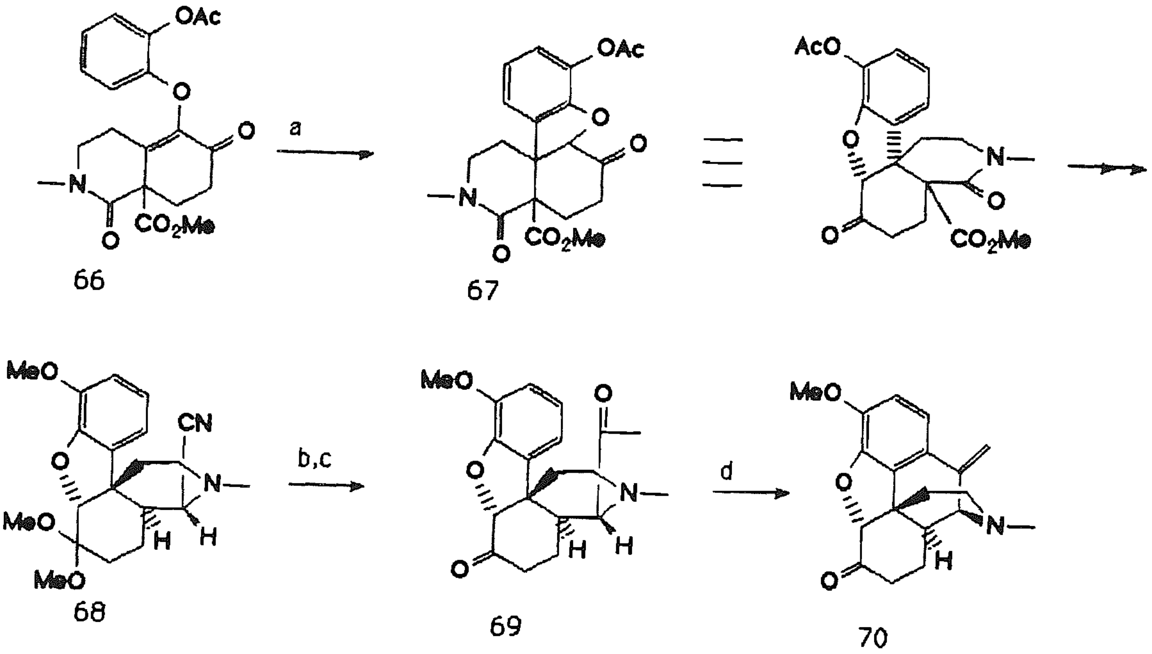


Scheme 1.16 a=n-BuLi, b=$NaHCO_3$

The Photochemical Approach.

A synthesis of the complete morphine skeleton which did not result in a total synthesis of morphine was reported by Schultz *et al.* in 1985 [67]. This approach is shown in scheme 1.17.

The photolysis of (**66**) gave the tetracyclic intermediate (**67**). Elaboration of this eventually gave the key nitrile (**68**). This was treated with methyl lithium and the intermediate imine was hydrolysed to give the ketone (**69**). Subsequent Friedel-Crafts ring closure and concomitant dehydration gave (**70**), a compound that possesses the entire morphine skeleton.



Scheme 1.17 a=hV, b=MeLi, c=H^+/H_2O, d=TfOH

Partial Structure Syntheses.

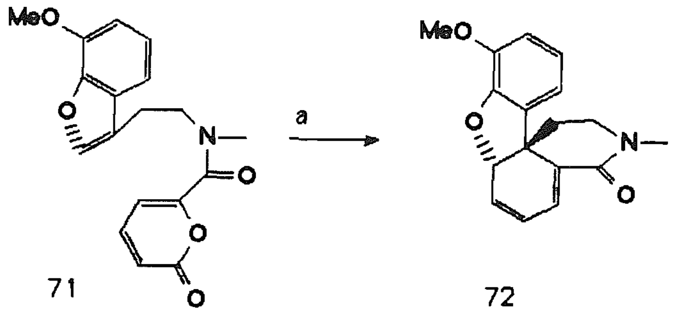
Several synthetic approaches to morphine which have resulted in the synthesis of morphine fragments have also been reported.

The intramolecular Diels-Alder reaction was utilised by Ciganek in his approach [68]. He heated the benzofuran derivative (**71**) to reflux in 1,2,4-trichlorobenzene for 10 hours. This gave the cyclisation product (**72**) in 53% yield (scheme 1.18).

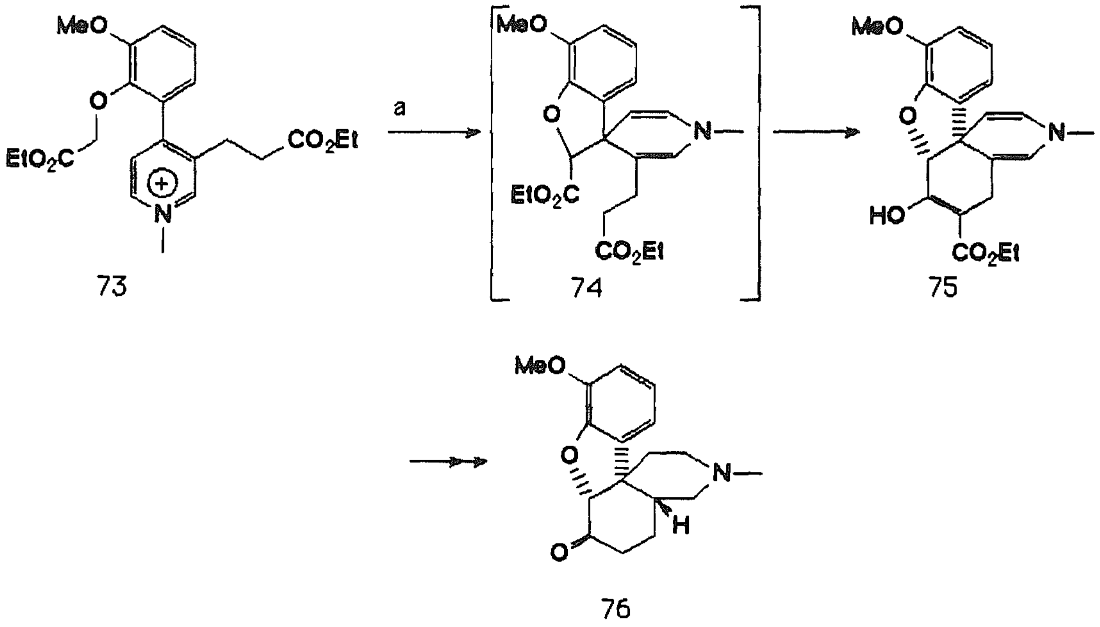
A similar fragment was prepared by Weller *et al.* [69]. They took the pyridinium ion (**73**) and generated an enolate anion. This cyclised in an intramolecular fashion to give the intermediate (**74**). A subsequent Dieckmann cyclisation gave the tetracyclic compound (**75**). Reduction and decarboxylation gave predominantly (**76**) (scheme 1.19).

Parker *et al.* reported a free radical approach to the carbocyclic skeleton [70]. Treatment of (**77**) with tributyltin hydride and a radical initiator gave (**78**) as a mixture of diastereomers (scheme 1.20).

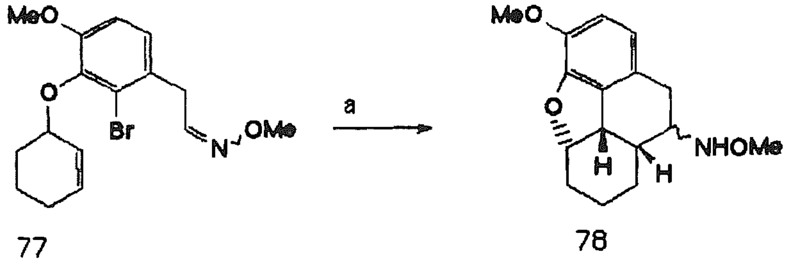
A free radical approach which resulted in the synthesis of the morphinan ring system was reported very recently by Harwood *et al.* [71].



Scheme 1.18 a= Heat



Scheme 1.19 a=NaOEt/DMF



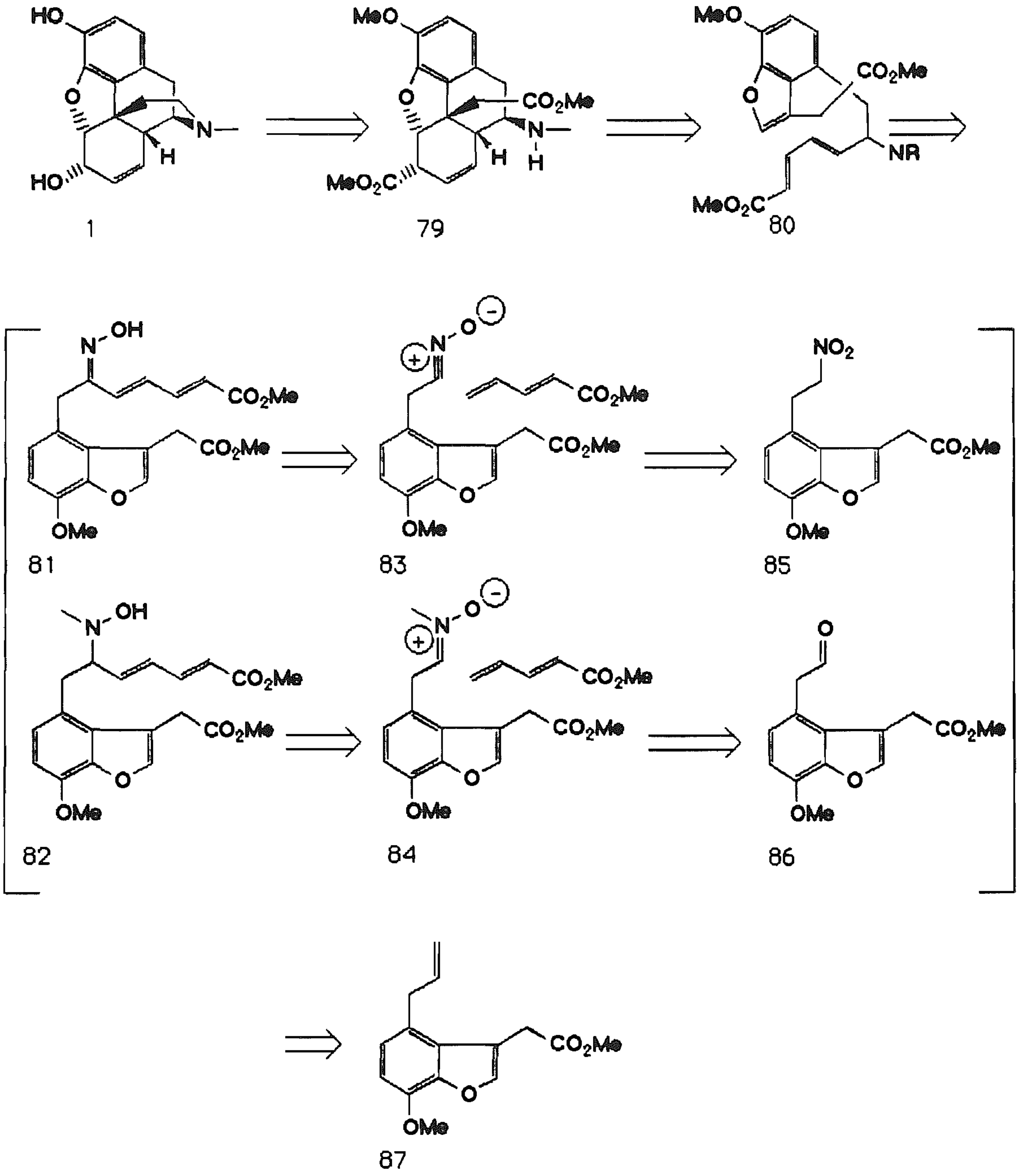
Scheme 1.20 a=Bu_3SnH and AIBN

Section 7; Our Retrosynthetic Analysis of Morphine.

The review of synthetic approaches to morphine presented above gives some idea of the variety of methodologies that have been used in order to produce morphine. Our retrosynthesis is shown in scheme 1.21. The initial disconnections and functional group interconversions revealed an inverse electron demand Diels-Alder reaction of a compound of general structure (**80**). The four centres of relative stereochemistry produced in such a reaction would be as required in a total synthesis of morphine if the reaction proceeded *via* an *endo* transition state.

Further disconnection revealed the addition of a 1,3-dipole such as (**83**) or (**84**) to a suitable diene. The 1,3-dipole would be generated from the nitro compound (**85**) or the aldehyde (**86**). The sensitivity of the functionality in (**86**) suggests that the compound (**87**) would be a suitable precursor in this series. The approach to this type of structure will be discussed at the start of the next chapter.

Our key step was similar in concept to that used by Ciganek to produce the fragment (**72**) (scheme 1.18), however the approach to our key step was radically different to that used by Ciganek and was designed to be as flexible as possible. If the approach proved successful this flexibility would be utilised in the synthesis of analogues of morphine.


HO
HO
O
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H
1
MeO
O
CO₂Me
N
H
H
MeO₂C
79
MeO
CO₂Me
O
NR
MeO₂C
80
N
OH
CO₂Me
CO₂Me
OMe
81
N
O
CO₂Me
CO₂Me
OMe
83
NO₂
CO₂Me
OMe
85
N
OH
CO₂Me
CO₂Me
OMe
82
N
O
CO₂Me
CO₂Me
OMe
84
O
CO₂Me
OMe
86
CO₂Me
OMe
87

Scheme 1.21

CHAPTER 2

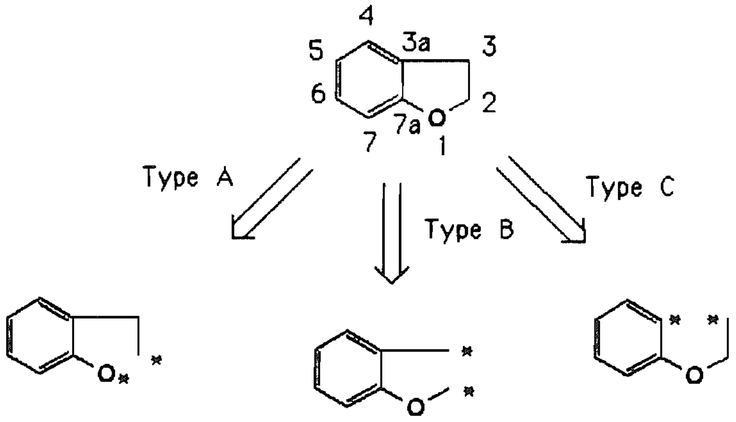
Section 1; Introduction.

Our retrosynthetic analysis for the construction of morphine was presented at the end of the previous chapter. The compound required for our approach was a 3,4,7-trisubstituted benzofuran. For a total synthesis of morphine such a compound should be easy to prepare on a large scale in good yield.

A survey of the literature showed that many approaches to the benzofuran ring system are known. Despite this variety, relatively few examples of 3,4,7-trisubstituted benzofurans were to be found. A brief review of syntheses of the benzofuran ring system is presented below.

Section 2; Synthetic Approaches to the Benzofuran Ring System.

Almost all the reported syntheses of the benzofuran ring system rely on the formation of the furan ring from a suitably substituted benzene ring. This review will consider only this type of benzofuran synthesis. Scheme 2.1 shows the disconnections that have been applied in this type of benzofuran ring system synthesis.



Scheme 2.1

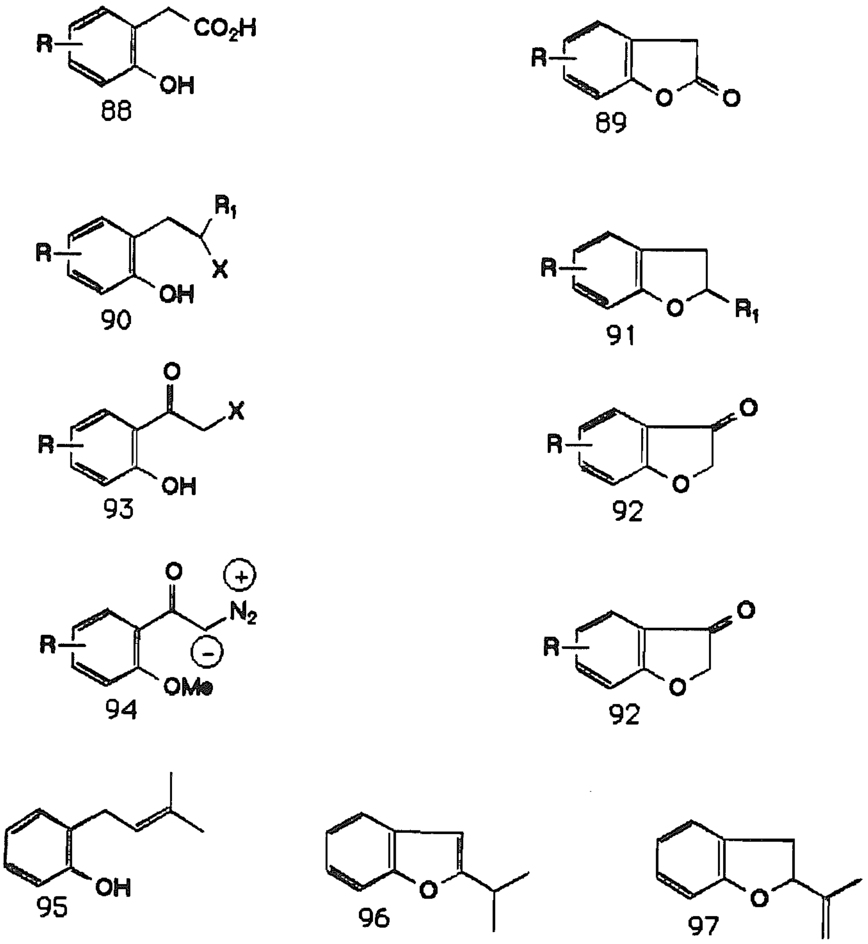
Type A approaches rely on the formation of the 1-2 bond in the key step. Several syntheses of the benzofuran ring system using this approach have been reported (scheme 2.2).

Ortho-hydroxyphenylacetic acids (**88**) cyclise spontaneously to give 2,(3H)-benzofuranones (**89**) [72].

Ortho-alkylphenols with suitable leaving groups β to the aromatic ring (**90**) cyclise readily to give benzofuran derivatives (**91**) [72].

3,(2H)-Benzofuranones (**92**) are prepared by the dehydrohalogenation of ω-halo-*ortho*-hydroxyacetophenones (**93**) [73] and by way of the ω-diazo-*ortho*-methoxyacetophenones (**94**) [74].

The *ortho*-allylic phenol (**95**) was oxidatively cyclised to give the benzofuran derivatives (**96**) and (**97**) upon treatment with palladium acetate [75]. A similar cyclisation of *ortho*-hydroxystyrenes has also been reported [76].



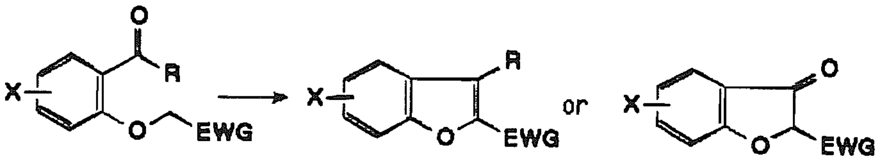
Scheme 2.2

Type B approaches rely on the formation of the 2-3 bond in the key step. These approaches tend to be condensation reactions related to the aldol reaction, the Perkin reaction or the Dieckmann cyclisation [77,78]. Scheme 2.3 shows this general approach.

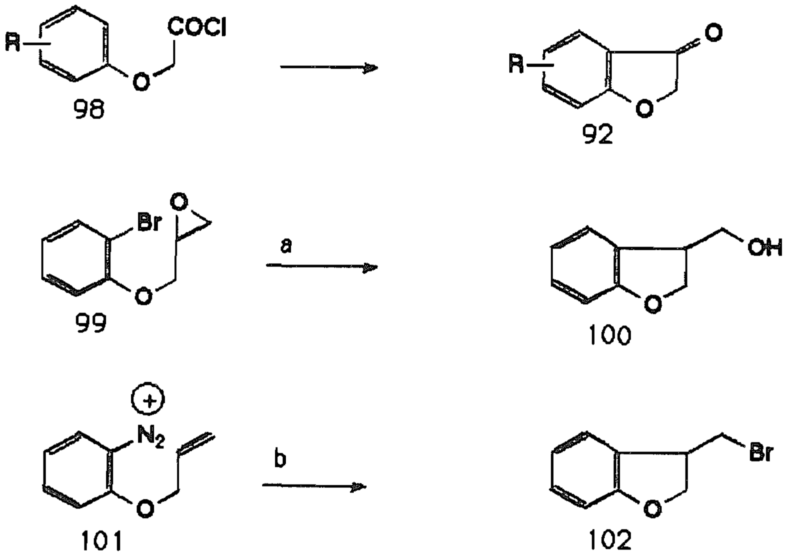
Type C approaches rely on the formation of the 3-3a bond in the key step. These approaches are shown in scheme 2.4.

Two distinctly different methods of forming the benzofuran ring system fit into this category. The first of these uses an intramolecular Friedel-Crafts alkylation or acylation as the key step. An example of this type of ring closure is the conversion of the phenoxyacetyl chlorides (**98**) to the 3,(2H)-benzofuranones (**92**) [79] (scheme 2.4).

The second of these approaches utilises the formation of a reactive centre ortho to the oxygen functionality. This then reacts to give the cyclisation product. The nature of the reactive intermediate may be anionic as in the conversion of (**99**) to (**100**) [80] or free radical as is thought to be the case in the conversion of (**101**) to (**102**) [81].



Scheme 2.3 R= H, Alkyl, OMe, etc., EWG= Ester, Nitro, etc.



Scheme 2.4 a=BuLi -100 C b=$CuBr_2$/DMSO.

Section 3; Our Approaches to the Benzofuran Ring System.

For our purposes we required a 4-substituted 7-methoxy-3-benzofuranacetate. We decided that our first synthetic target should be methyl 7-methoxy-4-(2-propenyl)-3-benzofuranacetate **(87)** (schemes 1.21 and 2.5).

The Intramolecular Friedel-Crafts Acylation Approach

Our first approach to this compound is shown in scheme 2.5. ~~t~~This utilises a type C approach with a Friedel Crafts style ring closure.

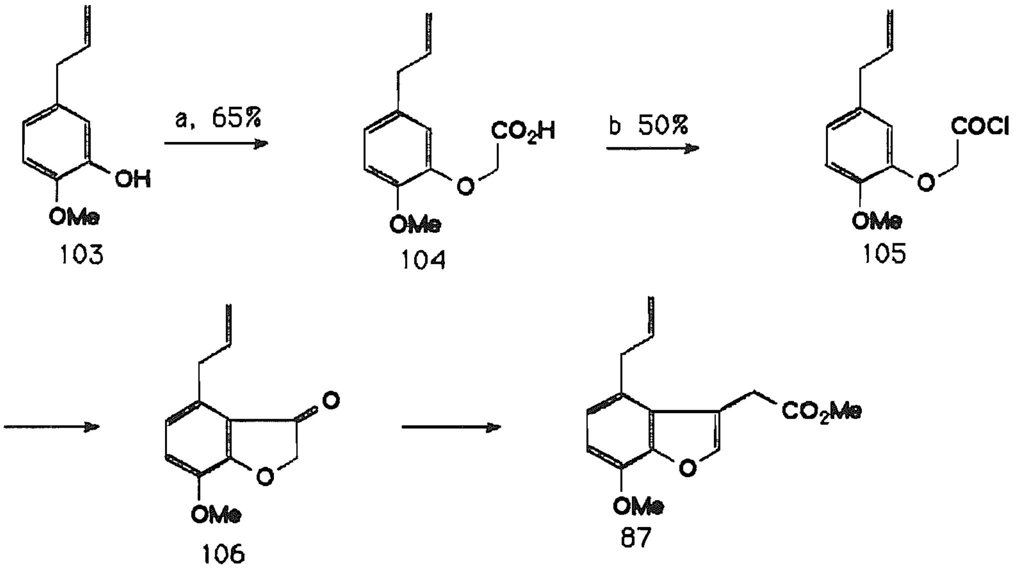
The phenol **(103)** was prepared using a modification of a published procedure [82]. Condensation of **(103)** with chloroacetic acid gave the expected phenoxyacetic acid **(104)**.

We hoped to effect the Friedel Crafts style ring closure using the free acid as the substrate (a dehydration reaction). Several dehydrating agents were used as we attempted to effect this conversion. These were polyphosphoric acid [83], polyphosphoric acid and phosphorus pentoxide, dry hydrogen fluoride [84] and trifluoroacetic anhydride. None of these reagents effected the desired cyclisation.

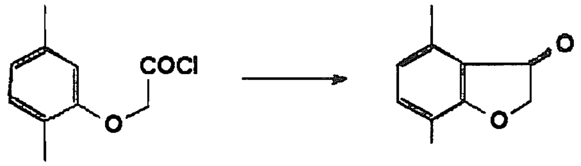
Our attention now turned to the acid chloride **(105)**. This compound was prepared from the carboxylic acid **(104)** and thionyl chloride [85]. Treatment of **(105)** with either aluminium trichloride [79] or polyphosphoric acid [86] did not result in the formation of the desired 3,(2H)-benzofuranone.

The reasons for the failure of these attempted intramolecular cyclisation reactions are not obvious. Palmer and Scollick [79] reported a 92% yield of 4,7-dimethyl-3,(2H)-benzofuranone when 2,5-dimethylphenoxyacetyl chloride was treated with aluminium trichloride (scheme 2.6). Thus the substitution pattern on the aromatic ring of **(105)** should not cause sufficient steric hindrance to prevent the cyclisation reaction occurring.

Our failure to produce the benzofuranone **(106)** led to the abandonment of the route outlined in scheme 2.5. Had **(106)** been prepared the elaboration to **(87)** would have been attempted using the Wittig methodology reported by Chan, Elix and Ferguson [87].



<u>Scheme 2.5</u> a=NaOH/$ClCH_2CO_2H$ b=$SOCl_2$



<u>Scheme 2.6</u>

Approaches Utilising *Ortho*-Bromophenols

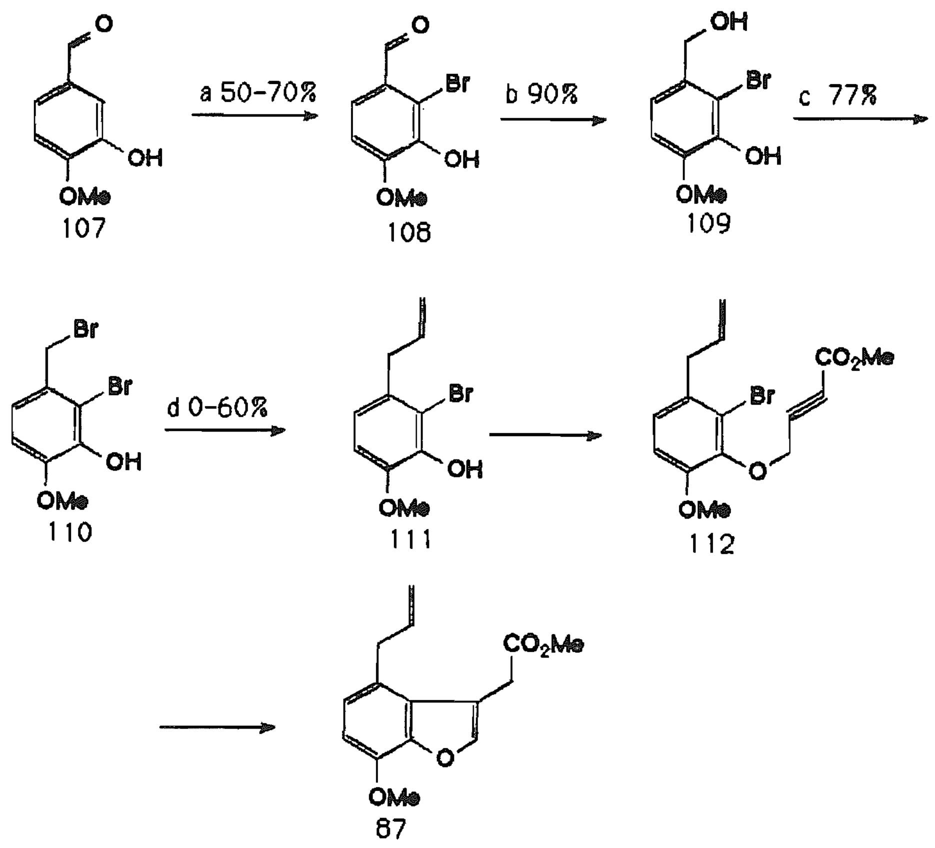
Our second approach to the compound (**87**) is shown in scheme 2.7. It is also a type C approach but in this case it is of the variety which relies on the formation of a reactive species *ortho* to the oxygen functionality.

The key phenol (**111**) in this approach was unknown at the commencement of this work. Our starting material for the synthesis of this compound was isovanillin (**107**). This was selectively brominated at the 2 position, to give the compound (**108**), using a variation of the procedure reported by Hazlet and Brotherton [88]. The conversion was effected by treating a vigorously stirred mixture of isovanillin, sodium acetate, acetic acid and a catalytic quantity of iron with a solution of bromine in acetic acid. The reasons for the selectivity of this bromination are unclear. The inclusion of a base (sodium acetate) in the reaction mixture appears to be important for the reaction selectivity and it is possible that the reaction occurs with the phenoxide ion as the active substrate.

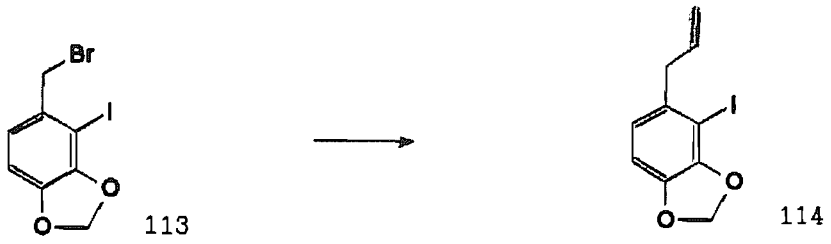
The reduction of this material with sodium borohydride gave the desired alchohol (**109**). This was converted to the benzylic bromide (**110**) and thence to the desired phenol (**111**) with a vinyl cuprate reagent. The cuprate reaction proved to be troublesome. The yield of the desired compound was variable and usually low (0-56%). This observation is in marked contrast to the work of Matthews [89] (scheme 2.8). He reported the conversion of the benzylic bromide (**113**) to the allylic compound (**114**) in 69% yield using conditions similar to those later employed by us.

We assumed that, in our case, the free phenol interfered with the organocuprate reaction despite the use of an excess of the the organometallic reagent. This should have generated the phenoxide ion and thus effectively have protected the phenol.

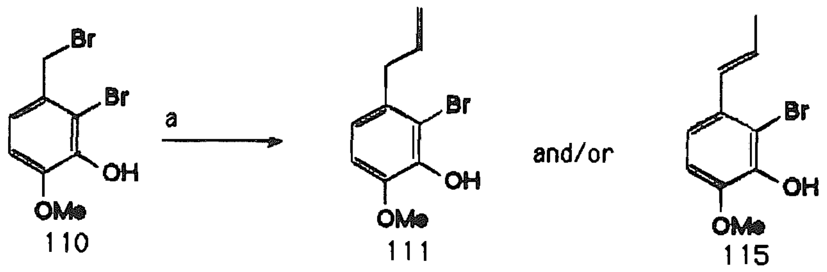
A colleague, Dr. P. G. Spoors, required the phenol (**111**) for his own purposes. He developed a synthesis of (**111**) from (**110**) using tri-n-butyl vinyltin and a catalytic quantity of tetrakis(triphenylphosphine)palladium(0) (scheme 2.9). This reaction gave good yields of phenolic products and usually gave the desired compound (**111**). Sometimes this material was contaminated with a small quantity of the isomeric phenol (**115**). Occasionally (**115**) was the predominant or even the only product of this reaction [90]. We repeated his conditions and confirmed these results.



Scheme 2.7 a=Br_2 b=$NaBH_4$ c=PBr_3 d=a vinyl cuprate



Scheme 2.8



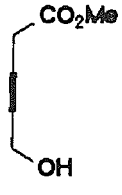
Scheme 2.9 a=$Bu_3SnCHCH_2/Pd(PPh_3)_4$

Despite the problems associated with its synthesis a sufficient quantity of the phenol (**111**) was prepared for us to pursue our goals. Thus our attention turned to the formation of the phenyl ether (**112**).

Our first approach to the construction of the ether (**112**) involved the coupling of the phenol (**111**) with a corresponding acetylenic unit. To this end we prepared methyl 4-hydroxy-2-butynoate (**116**) [91] (an extremely potent vesicant as I discovered the hard way!). We attempted the direct coupling of this alcohol with the phenol (**111**) and used either dicyclohexylcarbodiimide [92] or diethyl azodicarboxylate/triphenylphosphine [93] as the coupling reagent. The former gave no reaction and the latter gave an inseparable mixture of compounds.

Methyl 4-bromo-2-butynoate (**117**) was prepared using the method of Henbest *et al.* [94] but we were unable to effect the condensation of this compound with the phenol (**111**). We thus decided to try to prepare (**112**) using the two step methodology outlined in scheme 2.10. The condensation of propargyl bromide with the phenol (**111**) was accomplished using sodium hydride as base and cetyltrimethylammonium bromide as a catalyst. The adduct (**118**) was formed in 75% yield but was found to be unstable, even at -30°C, if it was not kept in solution.

We attempted to deprotonate the acetylene (**118**) using organic bases (n-butyl lithium or ethyl magnesium bromide) but were unable to form the desired anion (the reactions were attempted with the substrate in ethereal solution. The temperature of the reaction mixture was varied between -78°C and room temperature). The deprotonation was effected using sodium hydride as the base. The anion was quenched using deuterium oxide. This gave (**118a**), (**118**) with deuterium incorporated at the terminal position of the acetylene. The deprotonation of (**118**) proved to be a highly capricious reaction and we were unable to repeat the deprotonation reaction. We were thus unable to try to quench the anion with methyl chloroformate and the desired product (**112**) was never prepared.



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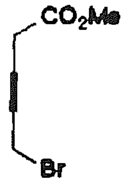

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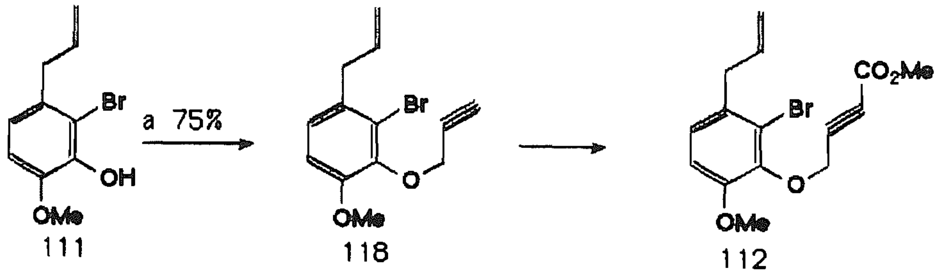
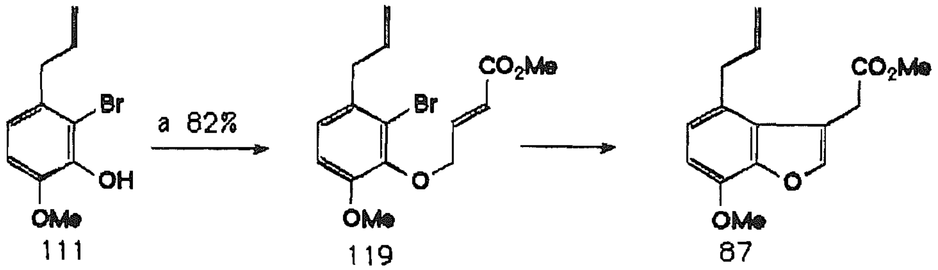


<u>Scheme 2.10</u> a=NaH/propargyl bromide



<u>Scheme 2.11</u> a=NaH/methyl 4-bromocrotonate

With the failure of this approach we turned our attention to the approach outlined in scheme 2.11. The phenol (**111**) and methyl 4-bromocrotonate condensed under conditions similar to those used to form the ether (**118**) to give the corresponding ether (**119**).

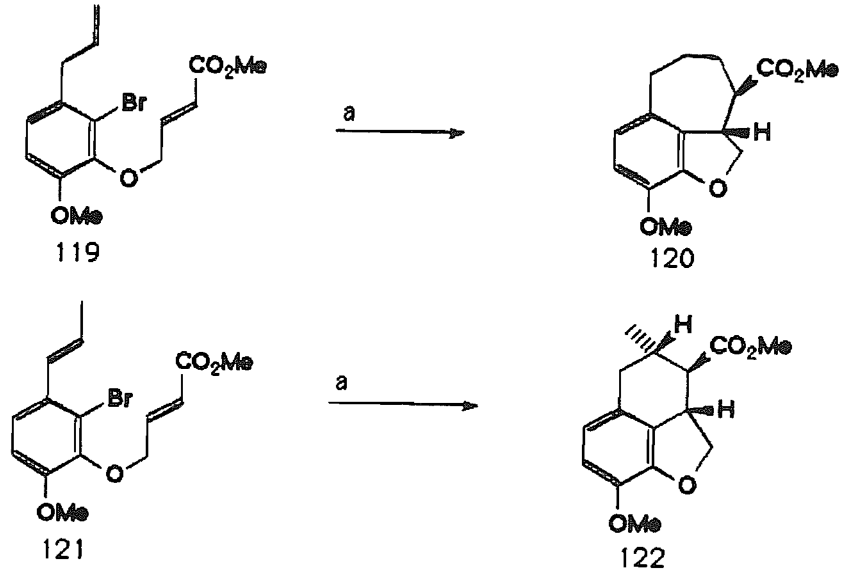
With the compound (**119**) in hand our attention turned to the formation of the benzofuran ring system. Two general methods of performing this type of ring closure appeared to be available to us, these being anion generation and free radical cyclisation. Both of these methods were mentioned in the review at the beginning of this chapter.

The Radical Cyclisation Approach

We decided to investigate the possibility of closing the furan ring using free radical methodology. The results of this investigation are shown in scheme 2.12.

The treatment of (**119**) with tri-n-butyltin hydride under standard radical cyclisation conditions [95] gave the 5-*exo*-trig-7-*endo*-trig tandem cyclisation product (**120**) as the only product.

We also prepared the ether (**121**) and subjected it to similar cyclisation conditions . It gave the 5-*exo*-trig-6-*endo*-trig tandem cyclisation product as the only product. This product would have been produced from (**119**) had a 5-*exo*-trig-6-*exo*-trig tandem cyclisation occurred.



Scheme 2.12 a=Bu_3SnH/AIBN

The selectivity for the 5-*exo*-trig-7-*endo*-trig tandem cyclisation in the conversion of (**119**) to (**120**) was an interesting observation. None of the alternative product (**122**) was found in the reaction mixture.

Both the 7-*endo*-trig and the 6-*exo*-trig cyclisation modes are favoured methods of ring closure [96], therefore it would not seem unreasonable to expect to observe a mixture of products from such a reaction.

The conversion of (**121**) to (**122**) showed that the lack of formation of (**122**) from (**119**) could not be explained by assuming that (**122**) was an unstable product. It also suggested that the possibility that the molecule (**119**) could not reach the right geometry to undergo a 5-*exo*-6-*exo* cyclisation was remote.

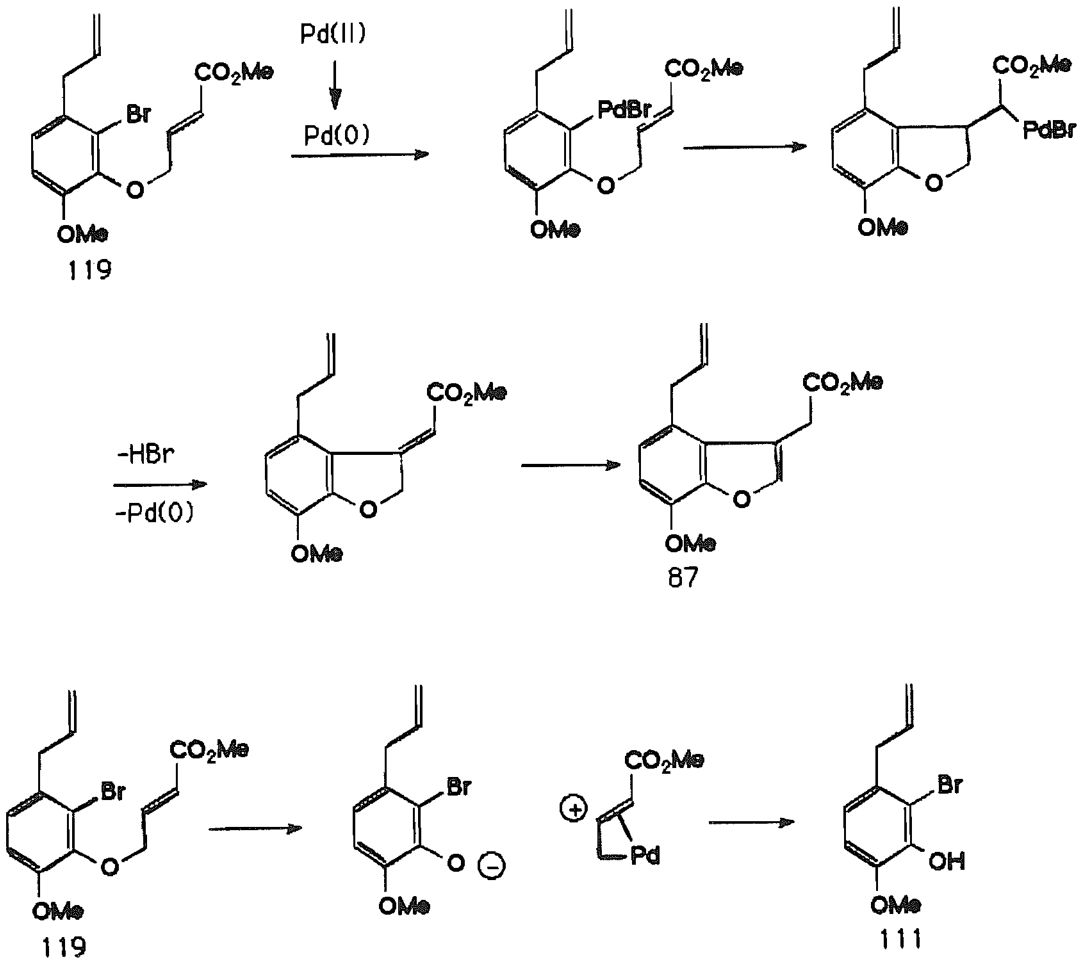
The formation of the tandem cyclisation product from the reaction of (**119**) with tri-n-butyltin hydride under radical generating conditions was not particularly surprising to us as tandem radical cyclisation reactions are frequently reported. From our point of view however, it was a disappointing result. In order to develop this route to give a benzofuran that we could use in our attempt to produce morphine, we would have to protect the allyl group of the phenol (**111**). We would also have the problem, inherent with this approach, of oxidising a dihyrobenzofuran to the corresponding benzofuran. For these reasons we decided not to pursue the radical cyclisation methodology.

The Palladium Catalysed Cyclisation Approach

Our attention turned to the possibility of forming the desired compound (**87**) from the ether (**119**) *via* a palladium-induced cyclisation. This route would utilise an intramolecular version of the Heck reaction [97]. An advantage of this procedure would be the generation of the benzofuran directly without the need for a separate oxidation step.

No report of this methodology having been applied to benzofuran synthesis could be found at the time we undertook this work. Examples of palladium catalysed syntheses of nitrogen containing heterocycles [98,99] and of carbocyclic rings [100,101] were easily found (for extra information on this type of chemistry see the references contained in [101], for reviews see [102,103,104]). A palladium-catalysed synthesis of dibenzofurans had also been reported [105]. We chose to investigate this reaction using the conditions reported by Grigg *et al.* in their work on carbocyclic ring closures [100].

Our initial results were encouraging. When a solution of (**119**), palladium acetate, triphenylphosphine and potassium carbonate in acetonitrile was heated to reflux for 18 hours two major products were produced. These were the desired benzofuran (**87**) and the phenol (**111**). Possible mechanisms for the formation of both these products are presented in scheme 2.13.

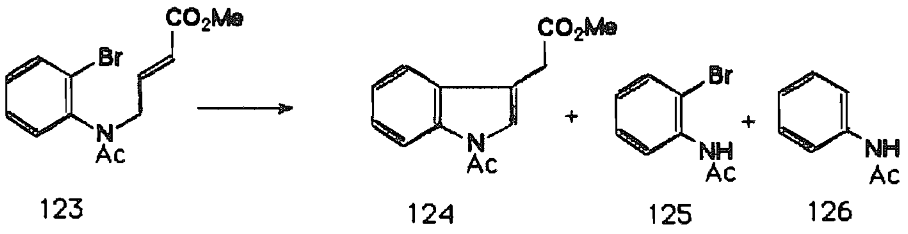


<u>Scheme 2.13</u>

The initial reduction of the palladium(II) species to a palladium(0) species is often invoked in this type of chemistry. The nature of the supposed reducing agent varies according to the nature of the reaction mixture. In reaction mixtures which incorporate formic acid (or the formate ion) the reduction is assumed to occur *via* a hydride transfer to the metal. In other cases the substrate, the base or even the solvent are invoked as the reducing agent.

The nature of the palladium(0) species supposedly formed in these reactions is uncertain. If the reaction mixture contains triphenylphosphine a complex such as tetrakis(triphenylphosphine) palladium(0) is assumed to be formed. It should be noted that tris(triphenylphosphine)palladium(0) has been shown to be formed in a catalytic hydratocarbonylation of alkenes where a palladium(II) catalyst was added at the start of the reaction [111] though no similar result has been recorded in cyclisation reactions. In the absence of any phosphine, either a tetrakis(solvent)palladium(0) complex or palladium metal is invoked as the reactive species.

The cleavage of the phenyl allyl ether under these reaction conditions was not particularly surprising as similar reactions have already been described. Tsuji *et al.* reported a method of preparing dienes from allylic ethers of phenol in 1978 [106]. They used palladium acetate/triphenylphosphine (1:10) as their catalyst. A year earlier Ban, Chiba and Mori reported a palladium catalysed approach to indoleacetic acid derivatives [98] (scheme 2.14). They also used a mixture of palladium acetate and triphenylphosphine as the catalyst in their reactions. They observed a mixture of ring closure and allylic cleavage products (**124**), (**125**) and (**126**) when they subjected their substrate (**123**) to the palladium reagent.



Scheme 2.14

Scheme 2.13 suggested that the formation of the phenol (**111**) occurred *via* the formation of a π-allyl palladium complex. The fate of this complex was not commented upon. In order for the reaction to remain catalytic in the use of palladium this complex must react further to regenerate the palladium(0) catalyst. The products of the decomposition of the π-allyl palladium complex were never identified or characterised.

We decided to investigate the palladium-catalysed reactions of (**119**) to try to find conditions which would allow us to selectively obtain the desired benzofuran (**87**). Changing the base from potassium carbonate to triethylamine or the solvent from acetonitrile to dimethylformamide had no noticeable effect. When tetrakis(triphenylphosphine)palladium(0) was used instead of the palladium acetate/triphenylphosphine mixture no cyclisation was observed, but the ether cleavage reaction proceeded as before. Eventually the reaction was attempted using acetonitrile as the solvent, potassium carbonate as the base and palladium acetate as the catalyst. No triphenylphosphine was added to the reaction mixture. We were gratified to observe the formation of the desired benzofuran (**87**) in 65% yield. None of the phenol (**111**) was observed in this reaction mixture.

In the light of these results we reconsidered the mechanisms of the reactions involved in these conversions.

The mechanisms presented in scheme 2.13 and the discussion above suggest that the active catalyst in this type of reaction is a palladium(0) species. In our original reactions this would be a compound related to tetrakis(triphenylphosphine)palladium(0). Such a species is almost certainly involved in the ether cleavage reaction. The mechanism of the cyclisation reaction is much less clear. There is literature precedent for the insertion of tetrakis(triphenylphosphine)palladium(0) into the carbon bromine bond [107]. We found no evidence of such a reaction occurring in our system (only the phenol (**111**) was produced when tetrakis(triphenylphosphine)palladium(0) was used as the catalyst).

Several palladium(0) species can be envisaged as being formed in the reaction mixture. We will only consider the possibility that palladium metal is generated in the reaction mixture. Two possible roles for palladium metal can be envisaged. One potential reaction of the metal would be the equivalent of a Grignard reaction. The organometallic intermediate created in such a reaction would then behave in a similar manner to that outlined in scheme 2.13. The elimination of "HPdBr" after cyclisation would result in the regeneration of the palladium metal. An alternative role for palladium metal can be envisaged. The metal could function as an active surface on which "surface bound radicals" are intermediates in the cyclisation reaction. Support for this scenario is found in the lability of arylbromides in palladium catalysed hydrogenation reactions [108] (hydrogen atoms bound to the metal surface are thought to be the active reducing agents in such reactions). However the lack of any tandem cyclisation products from these reactions brought into question the involvement of "radical" intermediates.

One further mechanism for the ring closure reaction will be considered. This is the possibility that the active catalyst for the ring closure is the palladium (II) species introduced to the reaction mixture at the start of the reaction. The mechanism of the cyclisation would be similar to that outlined in scheme 2.13 but the intermediate organopalladium species would be the palladium (IV) species analagous to the palladium (II) species shown.

Our success in forming the benzofuran (**87**) led us to investigate the scope of this method of benzofuran formation. The table 2.1 shows all the compounds we prepared and subjected to our cyclisation conditions (palladium acetate, potassium carbonate and acetonitrile at reflux). No attempt to present the results in chronological order is made in this table. As will become clear in the next chapter the precursor (**140**) was prepared at a much later date than the other cyclisation precursors.

We found the palladium catalysed cyclisation to be somewhat substrate dependent; the compounds (**119**), (**121**), (**128**), (**133**), (**140**) and (**142**) all gave good or very good yields of the corresponding benzofurans. The two substrates which contained nitro groups, (**131**) and (**132**), both failed to give any identifiable products upon similar treatment. The two simpler substrates, (**135**) and (**138**), both cyclised but were less predisposed to cyclisation than the more complex substrates that underwent cyclisation reactions. The substrate (**135**) gave the expected benzofuran (**136**) in approximately

30% yield along with the enol ether (**137**) also in about 30% yield. The ether (**138**) was even less readily cyclised under our reaction conditions and only small amounts of the desired furan were produced. The reluctance of these simpler substrates to cyclise led us to change the solvent from acetonitrile to dimethylformamide and to raise the reaction temperature to 120°C. Under these conditions (**135**) gave the benzofuran (**136**) in 57% yield and (**138**) gave the furan (**139**) in 50% yield.

Table 2.1

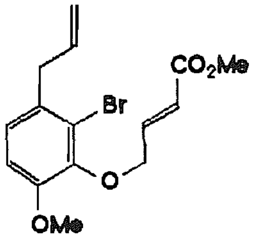
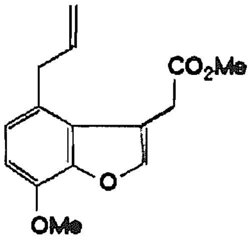
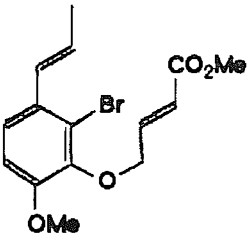
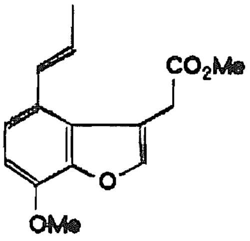
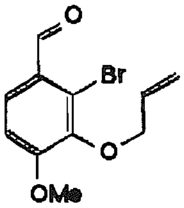
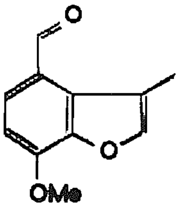
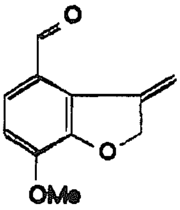
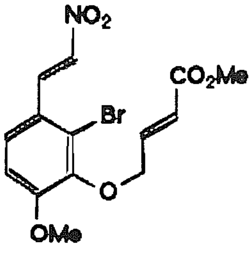
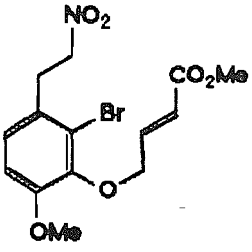
Substrate	Product(s)	Time/hrs	Yield/%
 119	 87	4	65
 121	 127	4	75
 128	 129  130	7	85 combined
 131	–	3	–
 132	–	2.5	–

Table 2.1

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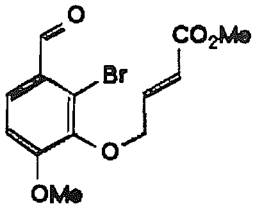
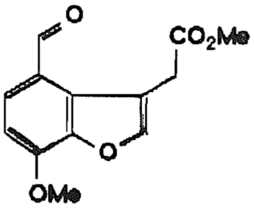
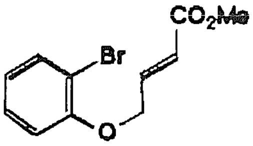
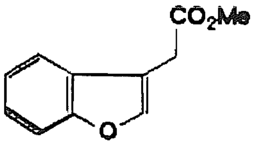
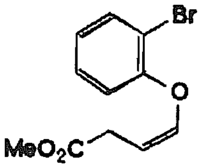
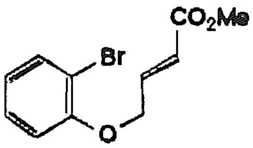
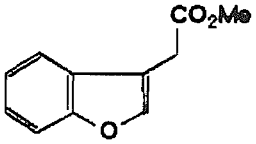
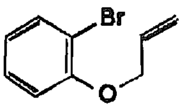
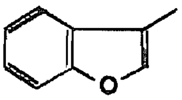
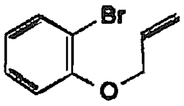
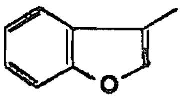
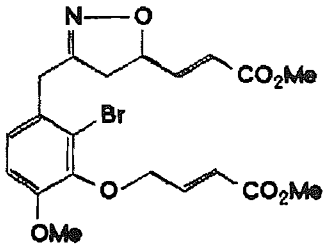
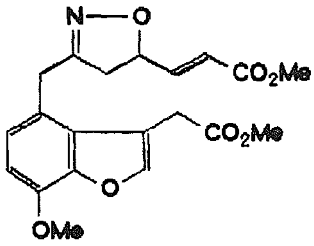
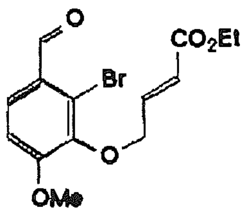
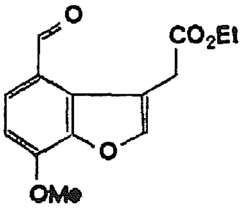
 133	 134	4	85
 135	 136	21	33
	 137		30
 135	 136	1*	57
 138	 139	18	trace
 138	 139	5*	50

Table 2.1

Substrate	Product(s)	Time/hrs	Yield/%
 140	 141	2	80
 142	 143	2	76

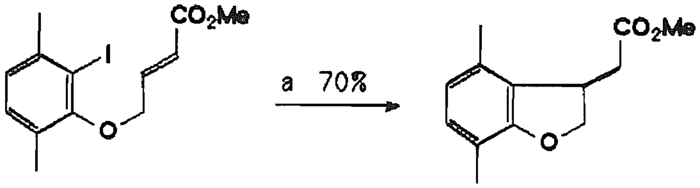
Reactions conducted in refluxing acetonitrile with 10% Pd(OAc)$_2$ and 200% K$_2$CO$_3$.

* Reactions conducted as above in dimethylformamide at 120 C.

As we were investigating our palladium catalysed cyclisation reactions we became aware of the work of Weeratunga *et al.* [109] (scheme 2.15). They took the precursor (**144**) and treated it with n-butyl lithium at -100°C. They obtained the cyclisation product (**145**) in 70% yield. The similarity between their substrate and many of our substrates was obvious. Their route was potentially an alternative method of benzofuran formation for us, should we have required it.

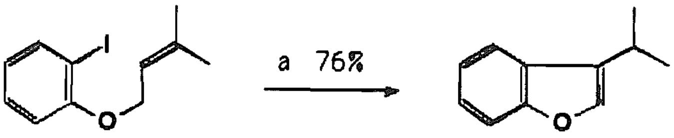
As our investigation of the palladium catalysed cyclisation drew to a close a similar cyclisation methodology was reported by Larock and Stinn [110]. They took a series of ortho-iodophenyl allyl ethers and effected their conversion to benzofurans using a complex mixture which included palladium acetate and sodium carbonate. Scheme 2.16 shows an example of their work. The ether (**146**) was cyclised to give the benzofuran (**147**) in good yield.

Our investigation of the palladium catalysed cyclisation reaction had served its purpose and had given us access to a variety of 4-substituted 7-methoxy-3-benzofuranacetates. The elaboration of these compounds will be discussed in the next chapter.



144 145

Scheme 2.15 a=BuLi -100 C



146 147

Scheme 2.16 a=$Pd(OAc)_2$ (cat.)

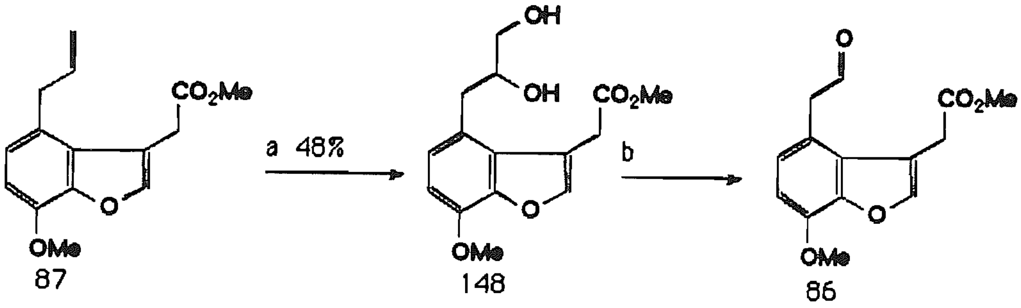
CHAPTER 3

Section 1; Introduction.

The previous chapter concluded with a discussion of the synthesis of a series of benzofurans. Amongst these was our key intermediate (**87**). This chapter will deal with the elaboration of this compound in accordance with the retrosynthetic analysis outlined in scheme 1.21. Some related work was performed and this work will also be discussed in this chapter.

Our key benzofuran (**87**) was subjected to an oxidation reaction with osmium tetroxide/trimethylamine-N-oxide [112]. This reaction afforded the vicinal diol (**148**) in a disappointing 50% isolated yield. Treatment of (**148**) with sodium metaperiodate gave the expected aldehyde (**86**) (Scheme 3.1).

With the aldehyde (**86**) in hand we were ready to try to form our key nitrone. This work will be described in due course but first the chemistry of nitrones will be considered in some detail.



Scheme 3.1 a=OsO_4/Me_3NO b=$NaIO_4$

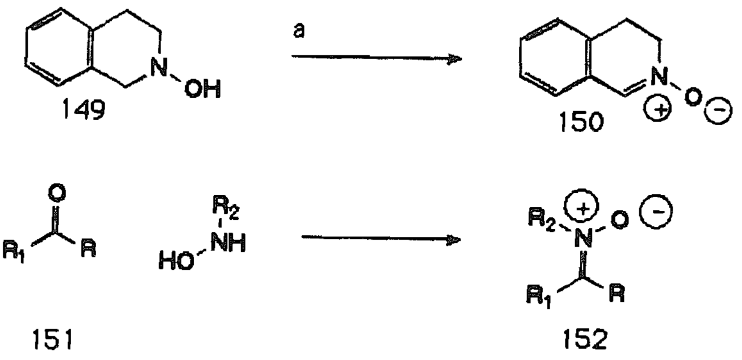
Section 2: The Formation and Cycloaddition Reactions of the Nitrones. [113]

The Formation of Nitrones.

Many methods of forming nitrones have been reported [114], but of these only two have found much employment in organic synthesis [113]. Scheme 3.2 shows the important methods of nitrone formation, they are the oxidation of N,N-disubstituted hydroxylamines and the condensation of aldehydes or ketones with N-substituted hydroxylamines.

The oxidation of N,N-disubstituted hydroxylamines with a variety of oxidising agents gives the corresponding nitrones, frequently in good yield. This method of nitrone formation is especially useful when the starting hydroxylamine is symmetrically substituted. If the hydroxylamine is not symmetrically substituted this method is useful in two situations. The first of these situations occurs when only one regioisomeric nitrone can be formed. The other situation occurs when the formation of one nitrone is greatly favoured over the formation of its regioisomer. The oxidation of (**149**) to give the nitrone (**150**) [115] is typical of this approach. The oxidising agent used in this case was mercuric oxide.

The condensation of aldehydes or ketones (**151**) with N-substituted hydroxylamines gives rise to the corresponding nitrones (**152**). This method of nitrone formation is especially useful for the formation of unhindered nitrones. Where the aldehyde or ketone is hindered nitrone formation tends to be slow or unobserved [114].



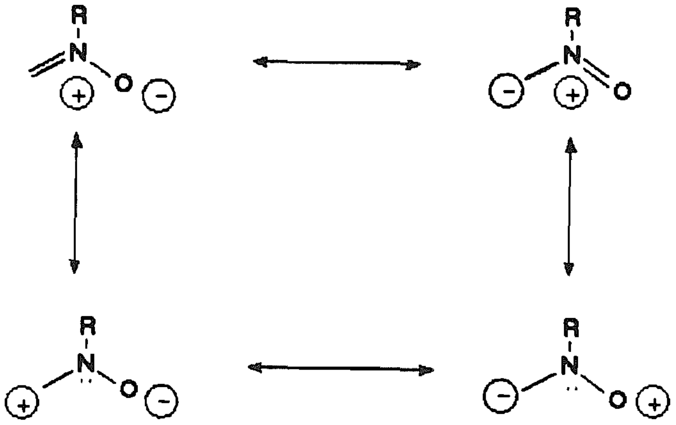
Scheme 3.2 a-HgO

It should be noted that very reactive nitrones are prone to dimerisation reactions [113]. This tendency can cause problems in the use of these nitrones in organic synthesis.

Also of note is the fact that many nitrones can exist as two geometrical isomers. This has been ignored in the discussion above and will be ignored from here on.

The Electronic Structure of Nitrones.

Nitrones carry no net charge but in terms of the valence bond theory they are zwitterionic species. Their electronic structure can be represented by a series of resonance structures. These are shown in scheme 3.3. From these structures it is obvious that predicting the reactivity of nitrones should be a non-trivial problem.



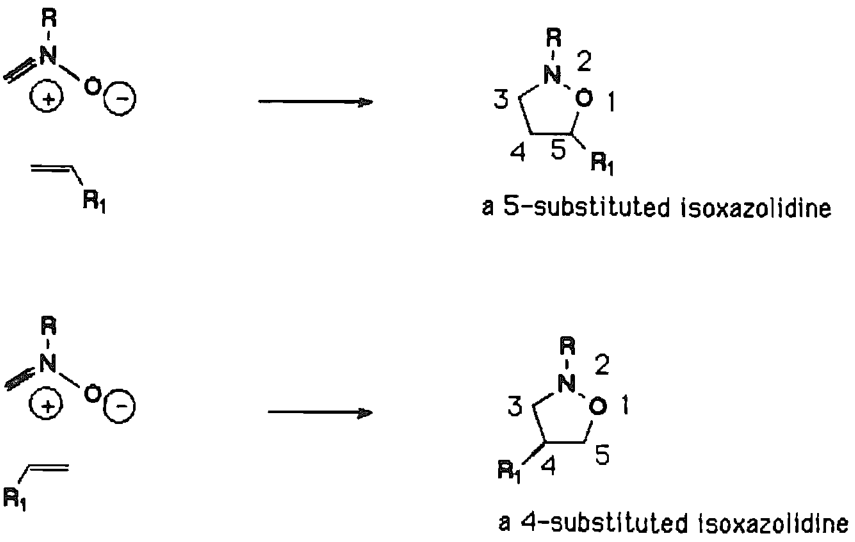
Scheme 3.3

The Intermolecular Cycloaddition of Nitrones to Alkenes.

The reaction of a nitrone with an alkene to give an isoxazolidine has been known for some time. The reaction is generally easy to perform and involves heating the nitrone and the alkene together in an inert solvent. The nitrone is classified as a 1,3-dipole and the alkene as a dipolarophile. The reaction is a [3+2] cycloaddition reaction involving six π electrons. Much of the early work on this type of reaction was performed by Huisgen *et al.* in the 1960's [116,117,118] and it was this pioneering work that generated the modern interest in this field of chemistry. The work of Huisgen and subsequent studies have lead to the understanding of the reactions of 1,3-dipoles as a class of compound. Part of this work has been a detailed study of the reaction of nitrones with alkenes. The results of these studies are summarised below in the form of a series of generalised observations and a discussion of the reaction mechanism. For the purposes of this discussion regiochemical considerations will be of paramount importance and stereochemical considerations will be, for the mostpart, ignored.

Regiochemical Considerations.

The reaction of a nitrone with ethene or a symmetrically 1,2-disubstituted alkene will proceed without regiochemical complication (though ethene itself tends to be unreactive toward nitrones [118]). The cycloaddition of a nitrone to a monosubstituted alkene can take one of two regiochemical courses. These are shown in scheme 3.4. If the nitrone oxygen adds to the most substituted end of the alkene the result of the reaction is a 5-substituted isoxazolidine; should the nitrone oxygen add to the least substituted end of the alkene the result of the reaction is a 4-substituted isoxazolidine.



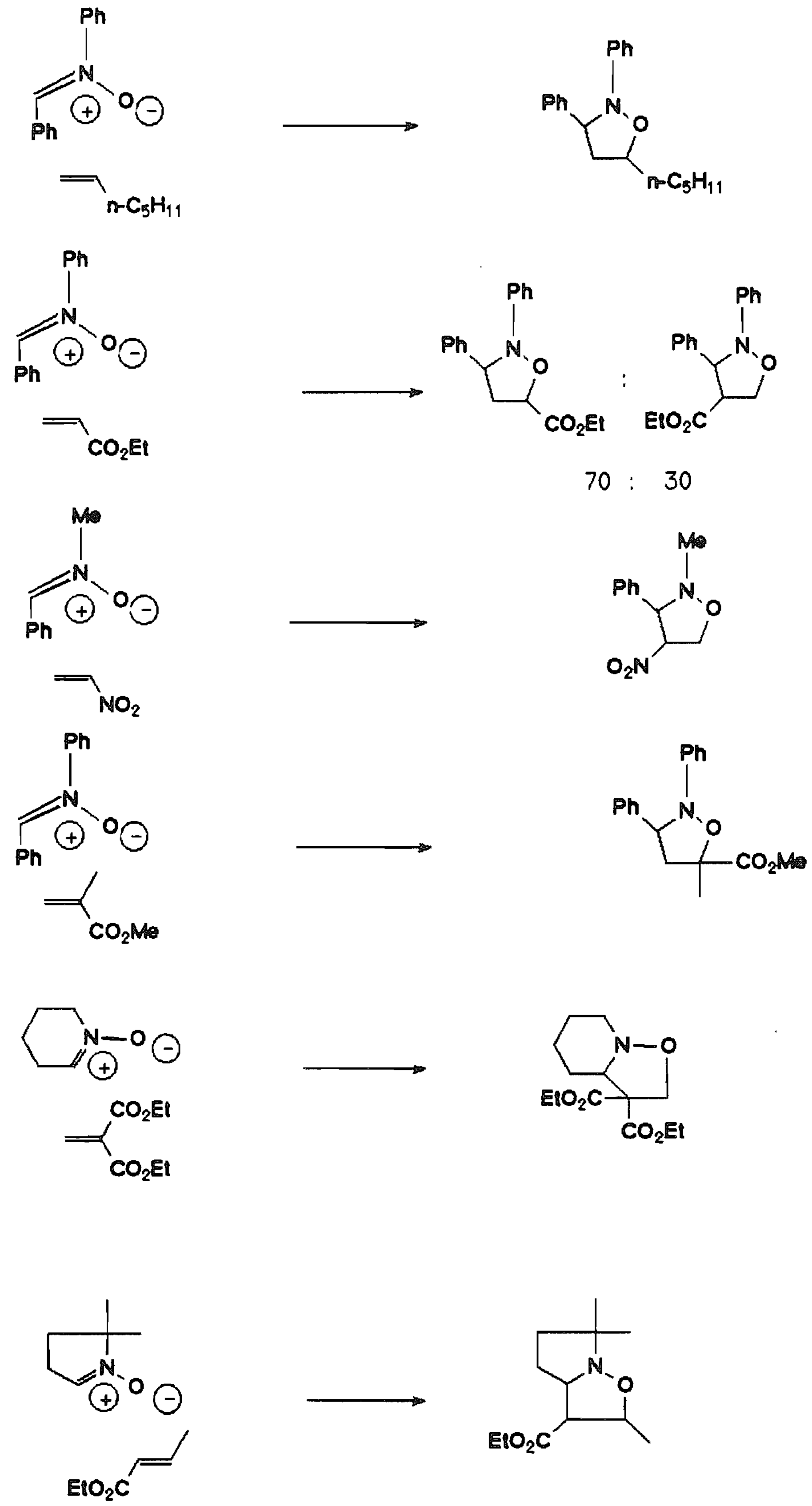
Scheme 3.4

The reactions of nitrones with electron rich monosubstituted alkenes (such as enol ethers) or "unactivated" monosubstituted alkenes (such as 1-heptene) tend to give 5-substituted isoxazolidines regioselectively. The reactions of nitrones with electron deficient monosubstituted alkenes more frequently give mixtures of both possible regioisomeric isoxazolidines. The more electron deficient the alkene the greater the quantity of the 4-substituted isoxazolidine. Thus ethyl acrylate and C,N-diphenylnitrone react to give a 70:30 mixture of 5-carboxyethyl and 4-carboxyethyl isoxazolidines [119] (scheme 3.5). The reaction of C-phenyl-N-methylnitrone and nitroethene gives the 4-nitroisoxazolidine as the only product [120] (scheme 3.5).

1,1-disubstituted alkenes react with nitrones to give 5,5-disubstituted isoxazolidines in most cases. Where both substituents on the alkene are electron withdrawing in nature, the product is the 4,4-disubstituted isoxazolidine [113] (scheme 3.5).

1,2-Disubstituted alkenes tend to react with nitrones to give mixtures of regioisomeric isoxazolidines. Where both groups on the alkene are similar in steric and electronic nature very little selectivity for one product over the other is observed. If one substituent is electron withdrawing in nature and the other is not, the electron withdrawing group tends to occupy the 4-position of the isoxazolidine product. The regioselectivity of the reaction increases with the greater differentiation in the nature of the substituents on the alkene. Thus the reaction of nitrones with crotonates tend to be regiospecific giving the 4-carboxylated product [113] (scheme 3.5).

Tri and tetra-substituted alkenes react with nitrones to give highly substituted isoxazolidines. Where the alkene has electron withdrawing substituents regioselectivity may be observed. The electron withdrawing groups tend to occupy the 4-position of the product isoxazolidine [113].



Scheme 3.5

The Rate of Nitrone Cycloaddition Reactions to Alkenes.

The relative rates of the cycloaddition of N-methyl-C-phenylnitrone to a variety of alkenes are shown in tables 3.1 and 3.2 [113]. Table 3.1 shows the effect on the rate of the cycloaddition reaction of altering the substituent on a series of monosubstituted alkenes. This table shows that the rate of the reaction is very substrate dependent. Simple alkenes (e.g. n-heptene) are relatively unreactive. When the alkene is substituted with an electron donating substituent a modest rate increase is observed in comparison to the simple alkene. When the alkene carries a potent electron withdrawing substituent (as is the case with acrylonitrile or methyl acrylate) the rate of the cycloaddition reaction increases dramatically over that with a simple alkene.

Table 3.2 shows the relative rates of addition of C-phenyl-N-methyl nitrone to a series of acrylic acid derivatives. The table shows that the intermolecular nitrone cycloaddition reaction is very sensitive to the amount of substitution on the alkene. The rate of addition of the nitrone to methyl acrylate is greater than that to a monosubstituted acrylate. Increasing the substitution further decreases the rate of the reaction. The table 3.2 shows that the rate of the cycloaddition of a nitrone to a monosubstituted alkene is some 3600 times that of the rate of addition of the same nitrone to a tetrasubstituted alkene of similar electronic character. These results suggest that the nitrone cycloaddition reaction is very sensitive to steric hindrance on the alkene.

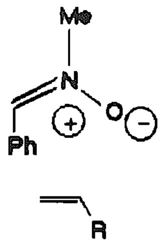


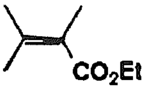
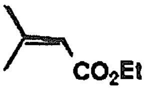
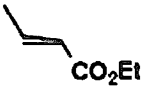
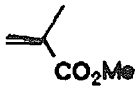
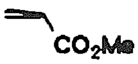
Table 3.1

The relative rate of addition of C-phenyl-N-methylnitrone to a series of dipolarophiles

Dipolarophile	K (rel) /toluene (120 C)
	1.0
	2.7
	2.8
	4.4
	106
	145

Table 3.2

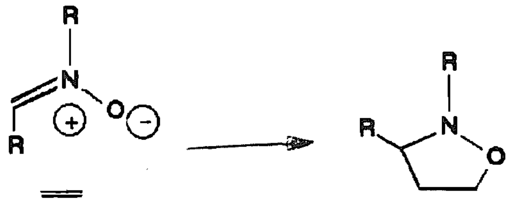
The relative rate of addition of C-phenyl-N-methylnitrone to acrylic acid derivatives

Dipolarophile	K(rel)/toluene (120 C)
	0.04
	1.0
	12
	49
	145

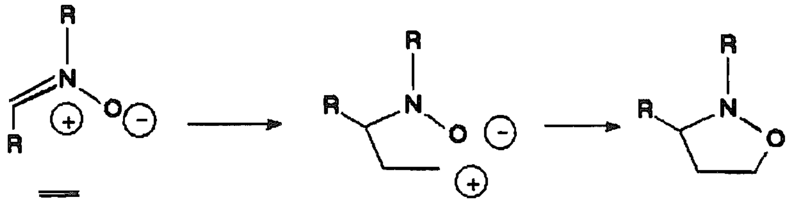
The Mechanism of the Cycloaddition of Nitrones to Alkenes.

Three basic mechanisms for the cycloaddition of nitrones to alkenes have been proposed. These are shown in scheme 3.6.

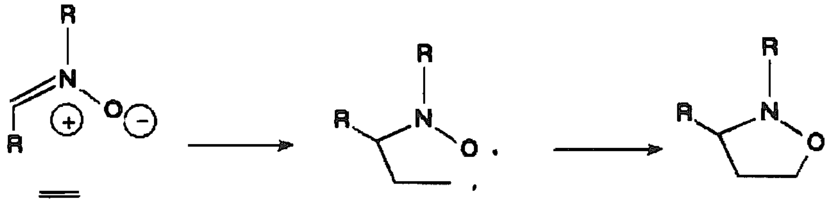
The mechanism involving a zwitterionic intermediate has been discounted due to the lack of a major effect on the rate of the reaction on changing the solvent from a non-polar to a highly polar solvent [113].



Zwitterionic Mechanism



Diradical Mechanism



Concerted Mechanism

Scheme 3.6

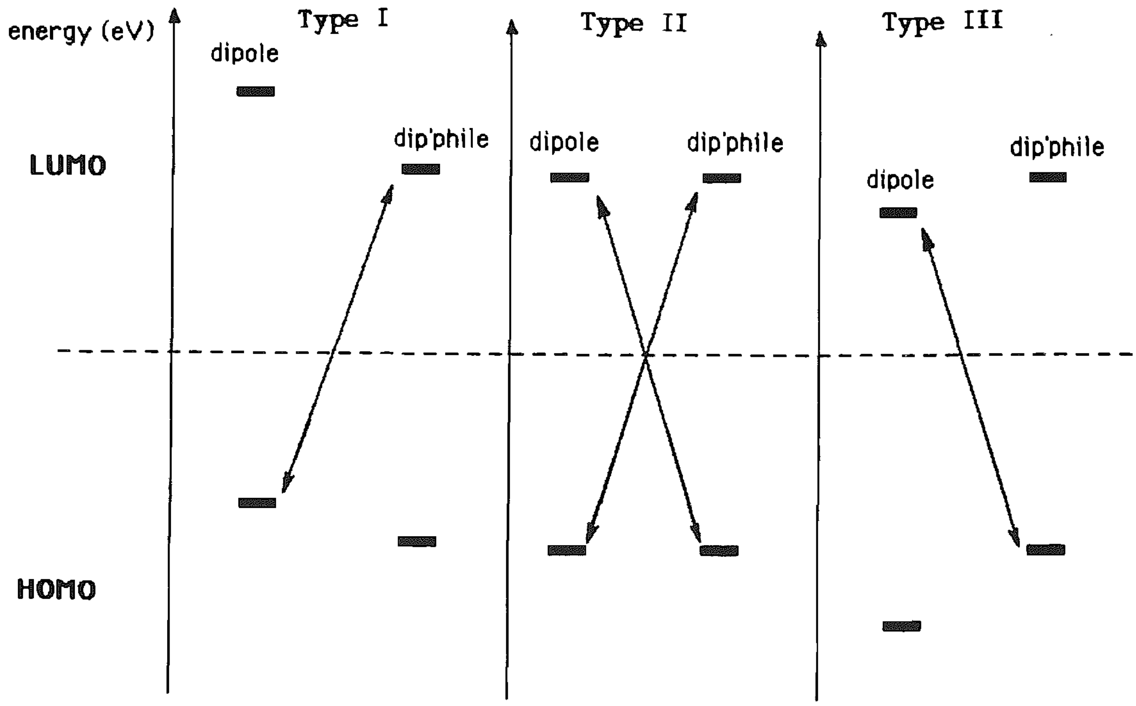
The two remaining mechanisms, the concerted cycloaddition reaction and the mechanism involving a diradical intermediate, are much harder to distinguish. The increase in rate of the cycloaddition reaction when either an electron donating or an electron withdrawing substituent is present on the alkene (dipolarophile) has already been noted. This observation has been interpreted by some as being due to the stabilisation of radical intermediates by the substituents on the alkene [121].

The major evidence in favour of the concerted mechanism is the observation that the geometry of 1,2-disubstituted alkenes is reflected in the stereochemistry of the product isoxazolidine. If the alkene has the Z geometry the substituents at positions 4 and 5 on the product isoxazolidine are invariably *cis* to each other. Similarly if the alkene has the E geometry the substituents at positions 4 and 5 on the product isoxazolidine are invariably *trans* to each other.

An explanation of the cycloaddition reactions of nitrones which appears to account for the observed regiochemistry of the reaction has been developed [113]. This explanation is found by the application of Fukui's frontier molecular orbital (FMO) theory [122,125] to this reaction. The theory considers the interactions of the highest occupied molecular orbital (HOMO) of one reacting component with the lowest unoccupied molecular orbital (LUMO) of the other reacting component (these are symmetry allowed interactions as will be discussed later). Before we can consider the frontier molecular orbital theory we need to consider the perturbational molecular orbital (PMO) theory from which it was developed [123]. If we consider the interaction of two molecular orbitals we find that the PMO theory predicts the lowering in energy of one molecular orbital (a stabilising effect) and an increasing in energy of the other molecular orbital (a destabilising effect). If the two interacting orbitals are both filled the overall effect is invariably destabilising. If the two interacting orbitals are empty no gain or loss of energy will occur. Only if one of the interacting orbitals is filled and the other is empty will the interaction lead to a net decrease in the energy of the system (stabilisation of the system). The PMO theory also states that the closer the interacting orbitals are in energy the greater the magnitude of the interaction. Thus the dominant interaction will be that in which the energy gap between the interacting orbitals is minimised. When considering the frontier orbitals this would be the interaction of the two HOMO's and would, of course, be destabilising. This type of destabilising interaction is reflected in the activation energy of the reaction.

The major stabilising effect would be the interaction of the HOMO of one component with the LUMO of the other component. The magnitude of this stabilisation will be much lower than the magnitude of the destabilisation caused by HOMO-HOMO interactions but it is this stabilising interaction that is important in FMO theory.

Consideration of HOMO-LUMO interactions led Sustmann to classify the reactions of 1,3-dipoles with dipolarophiles into three categories [124]. These are shown in pictorial form in scheme 3.7. Type I reactions are those in which the interaction between the dipole HOMO and the dipolarophile LUMO is dominant. Type III reactions are those where the reaction is controlled by the interaction of the dipole LUMO and the dipolarophile HOMO. In type II reactions the energy gap between the dipole HOMO and the dipolarophile LUMO is similar to that between the dipole LUMO and the dipolarophile HOMO. Thus the reaction could be controlled by either or both interactions. The reaction of nitrones with dipolarophiles are type II reactions.



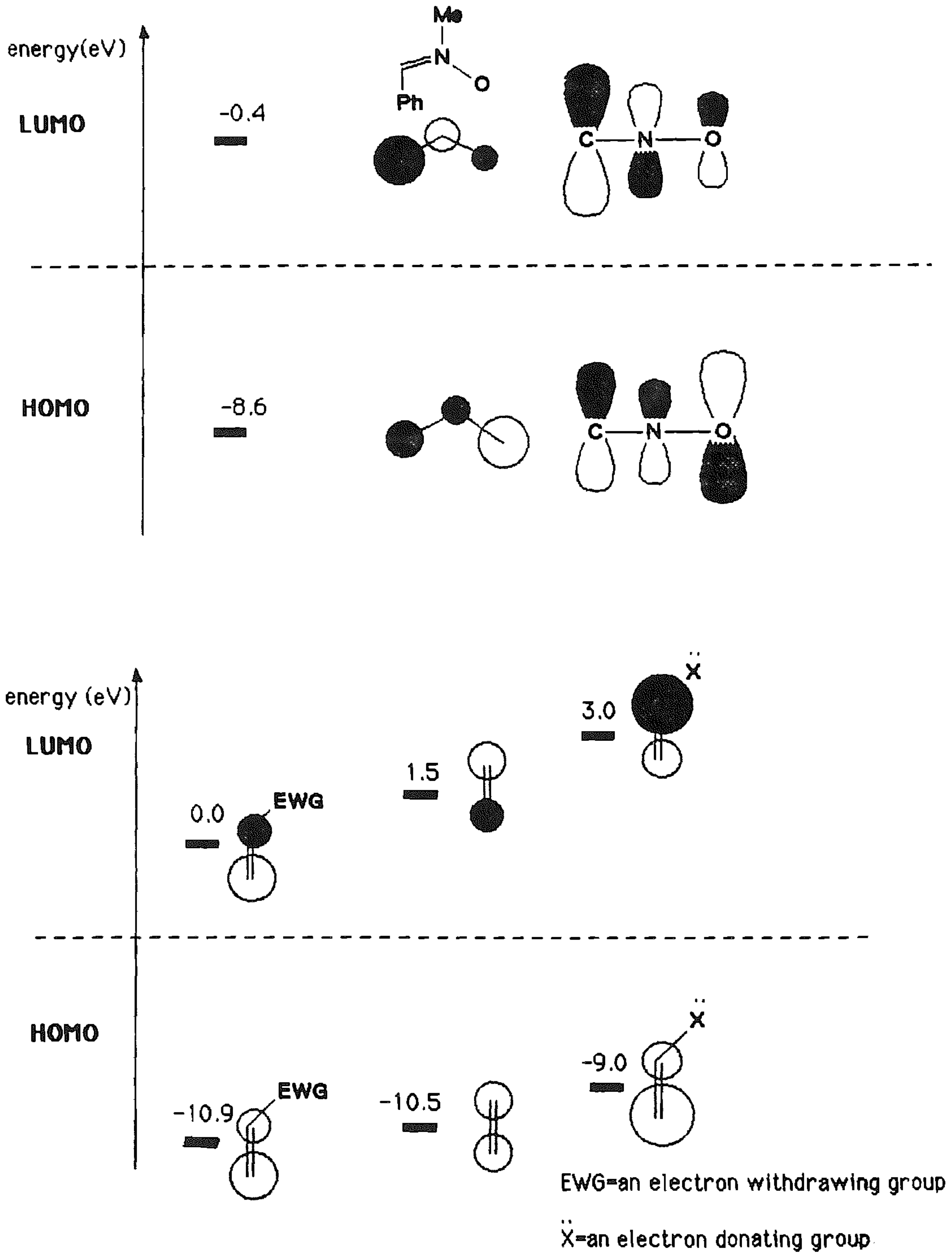
Scheme 3.7

Fukui's FMO theory states that "a majority of chemical reactions should take place at the position and in the direction of maximum overlapping of the HOMO and the LUMO of the reacting species" [122]. This means that the orbital amplitudes associated with the individual atoms involved in the dominant frontier molecular orbitals are instrumental in determining the regiochemistry of the reaction.

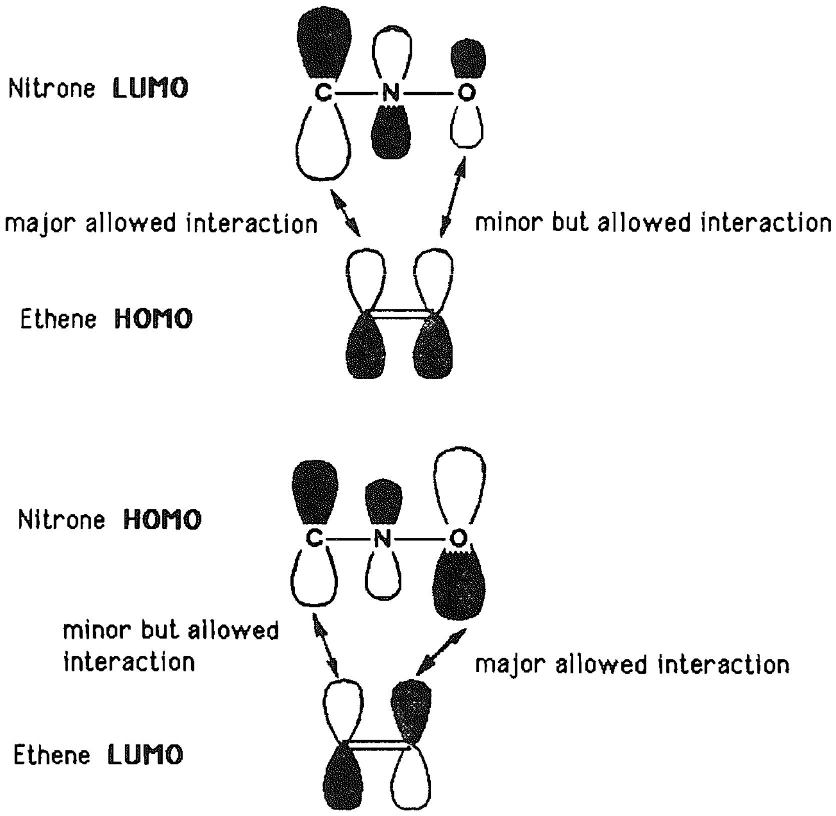
In order to apply this theory, a knowledge of the frontier orbital energies and amplitudes is required. Such data is available from a variety of sources. Some is obtained by experiment and some by calculation. The data which is used in the discussion below was obtained from [113,125,149] and its accuracy is taken on trust.

Scheme 3.8 shows the frontier orbitals of C-phenyl-N-methyl nitrone and a series of alkenes. The orbital amplitudes at given atoms are indicated, in relative terms, by the size of the "circles" drawn around each atom centre. A representation of the nitrone frontier orbitals in terms of individual p orbitals is also shown. This correlates directly with the "circles" method used to denote the rest of the orbitals in this (and the following) scheme. The "circles" can be regarded as the p orbitals seen from above rather than from the side.

The interaction of orbitals is allowed only where the orbitals are in phase. The phase of the orbital is indicated by the shading or otherwise of the circles drawn round the atoms. In order to decide whether an interaction is "allowed" by orbital symmetry the relative phases of the orbitals at the interacting terminals must be known. These orbital phases on the reacting centres determine whether the reaction is symmetry allowed. As has already been stated the interaction of a nitrone with a diplarophile is symmetry allowed (whether the reaction is nitrone HOMO or nitrone LUMO controlled). Scheme 3.9 shows the frontier orbital interactions for a nitrone and an alkene.


energy(eV)
LUMO
-0.4
Me
N
O
Ph
C
N
O
HOMO
-8.6
C
N
O
energy (eV)
LUMO
0.0
EWG
1.5
3.0
Ẍ
HOMO
-10.9
EWG
-10.5
-9.0
Ẍ
EWG=an electron withdrawing group
Ẍ=an electron donating group

Scheme 3.8


Nitrone **LUMO**
C
N
O
major allowed interaction
minor but allowed interaction
Ethene **HOMO**
Nitrone **HOMO**
C
N
O
minor but allowed interaction
major allowed interaction
Ethene **LUMO**

Scheme 3.9

As can be seen from the p orbital representation of the frontier orbitals (schemes 3.8 and 3.9) the phase of the orbitals is inverted on going through the plane of atoms. This is always true for orbitals which have some p character. This must be considered when deciding whether a reaction is or is not symmetry allowed (i.e. the relative phases of the orbitals at the termini of the dipole and the dipolarophile are important).

Now that we have armed ourselves with the information we need we can address the problem of the regiochemistry of nitrone cycloaddition reactions. The application of the rules laid out above to the interaction of the nitrone and the dipolarophiles shown in scheme 3.8 produces the following results. The interaction of the nitrone with an electron rich alkene would be controlled by the interaction of the nitrone LUMO with the alkene HOMO on the basis of the relative energies of the orbitals (for this interaction the energy gap is ca. 8.6 eV the alternative HOMO-LUMO interaction has an energy gap of ca. 11.6 eV). The orbital amplitudes associated with the nitrone LUMO and the alkene HOMO dictate the regiochemistry of the reaction. Application of the principle proposed by Fukui leads to the interaction of the atoms on the termini of the reacting species which are associated with the largest orbital amplitudes. Thus the nitrone carbon atom will interact with the unsubstituted end of the alkene. This dominant interaction will lead to the formation of the 5-substituted isoxazolidine, as is observed in such reactions. Simple monosubstituted alkenes behave as slightly electron rich alkenes. Again the regiochemistry of the reaction would be that for the highly electron rich alkenes just discussed. When the simplest alkene, ethene, is considered we find that the energy gap between the nitrone HOMO and the alkene LUMO is equivalent to that between the nitrone LUMO and the alkene HOMO (both about 10.1 eV). This represents a crossover point from nitrone LUMO to nitrone HOMO control. Thus when we consider the electron deficient alkene we find that the dominant interaction should be that between the nitrone HOMO and the alkene LUMO (an energy gap of ca. 8.6 eV for this interaction, the alternative HOMO-LUMO interaction has an energy gap of ca. 11.3 eV). With this in mind we would apply Fukui's postulate and predict that the regiochemical outcome of such a reaction would be an isoxazolidine with the electron withdrawing group on the 4-position. These predictions bear a striking similarity to the observed trends for such reactions. The crossover point from nitrone HOMO to nitrone LUMO control in such reactions will depend on the orbital energies of the individual nitrone. It should be noted that near the crossover point the interactions of the alkene FMO's with the nitrone HOMO and the nitrone LUMO will both be important and regiochemical control may well be lost.

There is also some correlation between the energy gap of the HOMO and the LUMO and the observed rate of the reaction. This relationship should not be relied upon too heavily. Many factors influence the rate of these reactions and the contribution of the frontier molecular orbitals is not necessarily dominant.

The FMO theory suggests that the addition of a nitrone to an alkene is probably best described as a concerted reaction. This does not neccessarily imply that the two σ-bonds which are being formed will be formed at the same rate, but merely that there will be some degree of σ-bond formation at both termini of the dipole at the same time.

Before we leave this discussion of frontier molecular orbital theory we will briefly consider the effect of frontier orbitals upon the stereochemistry of the isoxazolidine product(s). Some reactions of nitrones with alkenes produce isoxazolidines stereoselectively as well as regioselectively [113]. These results have been explained in terms of secondary orbital interactions of the frontier orbitals. A discussion of the stereochemical implications of this reaction is outside the scope of this thesis.

The discussion that has already been presented considers the intermolecular addition of a nitrone to an alkene. The intramolecular version of this reaction has also been studied in some detail. Regiochemical control in such reactions is often dictated by the geometry of the substrates rather than the frontier orbitals of the reacting components. A full discussion of the intramolecular nitrone cycloaddition reaction is beyond the scope of this thesis.

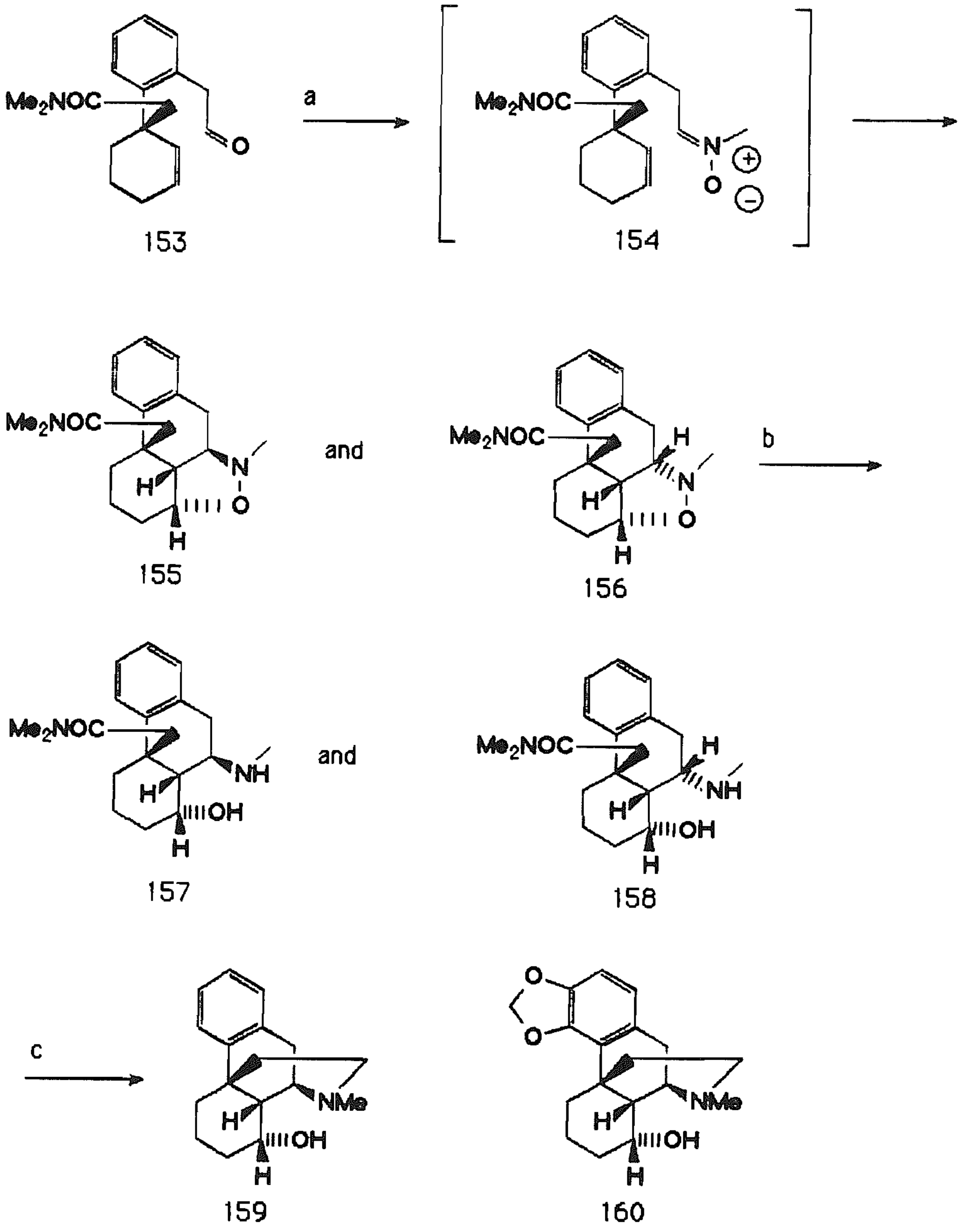
Organic Synthesis Using Nitrone Cycloaddition Chemistry.

The addition of a nitrone to a dipolarophile has been widely used by synthetic organic chemists in the last twenty years [113] and a particularly elegant synthesis of cocaine is numbered among the successful applications of such chemistry [126]. A review of such work is beyond the scope of this thesis. We will only consider the application of nitrone cycloaddition chemistry to the synthesis of morphine and the morphinans.

Chandler and Parsons reported a synthetic approach to the morphinans which utilised a nitrone cycloaddition as a key step [127]. This approach is shown in scheme 3.10. The aldehyde (**153**) was treated with N-methyl hydroxylamine to generate the nitrone (**154**). This underwent an intramolecular cycloaddition reaction to give an equimolar mixture of the tetracyclic products (**155**) and (**156**). The reduction of these materials gave (**157**) and (**158**). Treatment of (**157**) with hydrochloric acid gave the morphinan (**159**).

This work was extended by Matthews towards a total synthesis of morphine [128]. He produced the morphinan (**160**) in a manner similar to that used by Chandler and Parsons. He found that he could not transform (**160**) to any previously reported intermediate in morphine synthesis, nor could he transform this molecule to morphine itself.

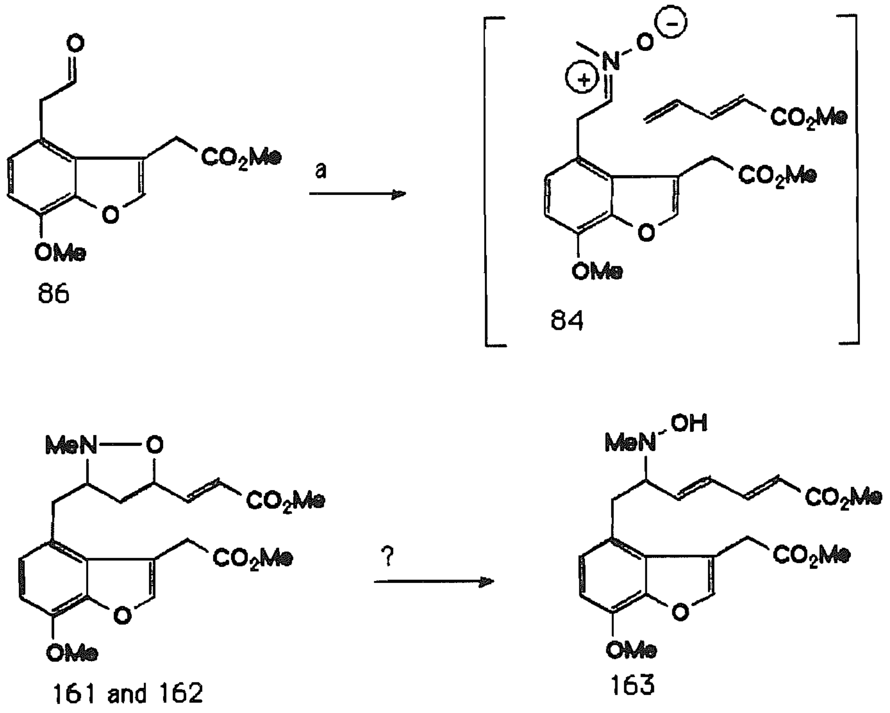
We could find no other reports of the nitrone cycloaddition methodology having been applied to the synthesis of morphine or the morphinans.



Scheme 3.10 a=MeNHOH b=H_2/raney nickel c=HCl

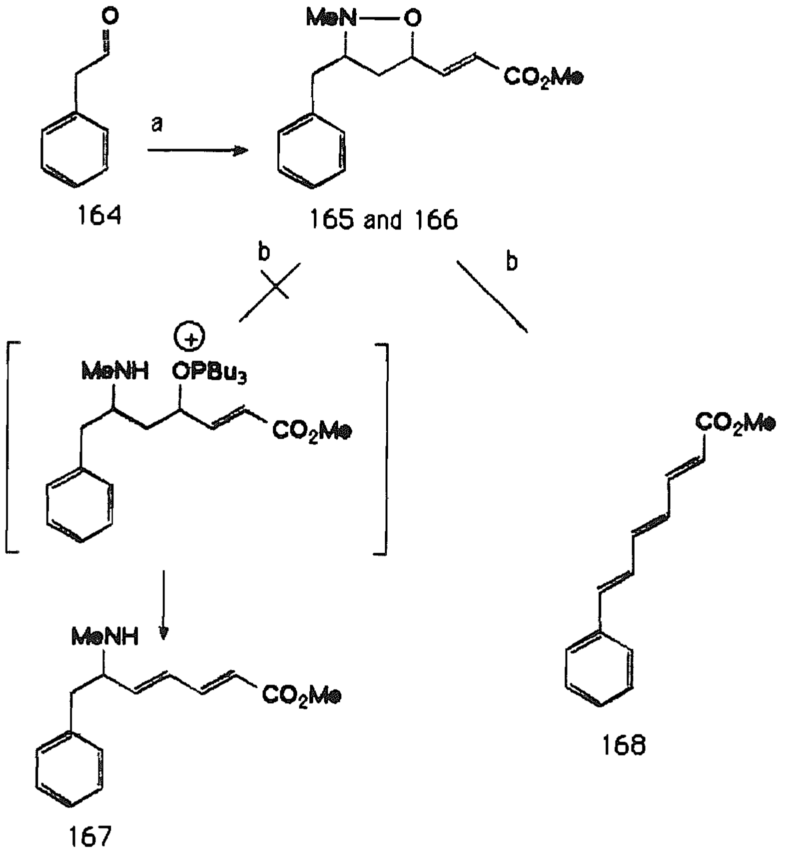
Section 3; Our Nitrone Cycloadditions and Related Reactions.

When we left our synthetic approach to morphine to consider the chemistry of the nitrone cycloaddition reaction our route had furnished us with the aldehyde (**86**) (scheme 3.11). In practice this aldehyde was not isolated. The crude aldehyde was mixed with toluene, methyl E-2,4-pentadienoate and N-methyl hydroxylamine. This mixture was heated to reflux for 3 hours, with water being removed from the reaction mixture by azeotropic distillation. These reaction conditions gave rise to the two diastereomeric isoxazolidines (**161**) and (**162**). Only the 5-substituted isoxazolidine was observed and the reaction occurred exclusively at the monosubstituted alkene. The site selectivity of this reaction reflects the sensitivity of nitrone cycloaddition reaction to steric hindrance. The regioselectivity of the reaction was that which we required but we considered ourselves fortunate to observe such excellent regioselectivity when we considered the electronic nature of the alkene.



Scheme 3.11 a=MeNHOH/ CO_2Me

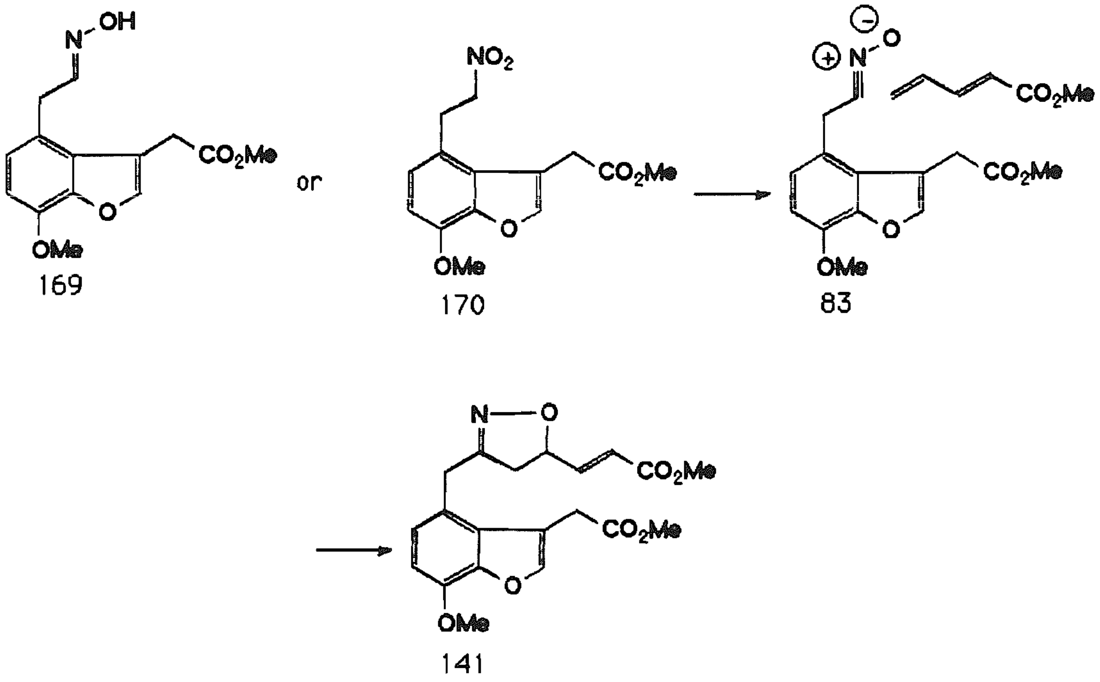
Our synthetic scheme required the cleavage of the N-O bond and the elimination of the oxygen functionality to generate the diene (**163**). Since (**161**) and (**162**) were available to us in very small quantities we decided to use a model compound to see if we could effect this transformation. Phenyl acetaldehyde (**164**), N-methyl hydroxylamine and methyl E-2,4-pentadienoate were heated to reflux in benzene solution with azeotropic removal of water to give a low yield of two diastereomeric isoxazolidines (**165**) and (**166**) (scheme 3.12). The yield of this reaction was not optimised as it was a model study.



<u>Scheme 3.12</u> a=MeNHOH/  CO_2Me b=H^+/PBu_3

The isoxazolidines were treated with tri-n-butylphosphine in the hope that the diene (**167**) would result. No product was formed from this reaction until 4-methylbenzoic acid was added to the mixture. The only product we observed was the triene (**168**) (scheme 3.12). This presumably arises by way of the elimination of methylamine from (**167**). This result was extremely disappointing for us. It suggested that dienes of the general structure represented by (**163**) and (**167**) would be unstable to the elimination of amines. When this result is viewed from the angle of our synthetic scheme the possibility that (**163**) (should it ever be prepared) would undergo a thermal intramolecular Diels -Alder reaction seemed remote. The generation of a *trans* double bond upon elimination of the amine functionality would also preclude the possibility of performing the intramolecular Diels-Alder reaction with the elimination product as substrate.

At this stage we decided to reconsider our synthetic approach to morphine. We decided to p~~e~~ursue the closely related strategy which was outlined in our retrosynthetic analysis (scheme 1.21). This involved the formation of a nitrile oxide rather than a nitrone. The nitrile oxide could be prepared from the oxime (**169**) of the aldehyde (**86**) (scheme 3.13). Alternatively the nitro-compound (**170**) could be used as the nitrile oxide precursor. We considered the approach to the aldehyde (**86**) and decided that, in view of the problems we had encountered in its synthesis, we should approach the synthesis *via* the nitro-compound (**170**).


N
OH
CO2Me
OMe
169
or
NO2
CO2Me
OMe
170
N
O
CO2Me
CO2Me
OMe
83
N
O
CO2Me
CO2Me
O
OMe
141

Scheme 3.13

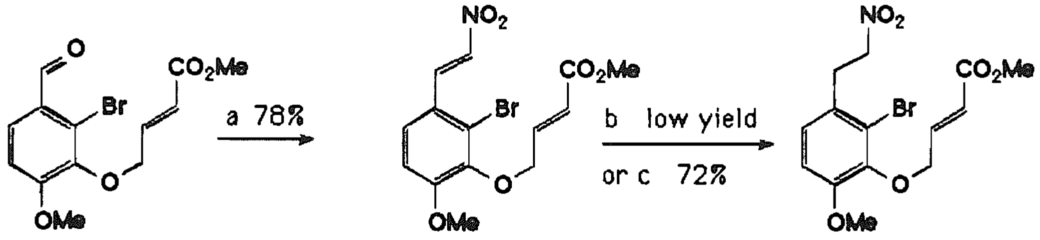
The Formation and Reduction of β-Nitrostyrenes.

We noted in chapter II that the compounds (**131**), (**132**) and (**133**) had been prepared and subjected to our palladium catalysed reaction conditions but we gave no indication of the conditions used to form these compounds. The ether (**133**) was prepared from brominated isovanillin and methyl 4-bromocrotonate (scheme 3.14). This was converted to the β-nitrostyrene (**131**) using a variation of the procedure reported by Wollenberg and Miller [129]. The reduction of this material to afford (**132**) was accomplished in low yield by treating a solution of (**131**) in tetrahydrofuran with sodium borohydride (scheme 3.14).

This work had been performed prior to the the choice of our new route. We hoped to take the benzofuran (**134**) and convert it to the nitro-compound (**170**) *via* the compounds (**171**) and (**172**). Our first attempt to effect this conversion relied upon our variation of the the procedure of Wollenberg and Miller which had been successfully applied by us to the synthesis of (**131**). The results of this reaction are shown in scheme 3.15.

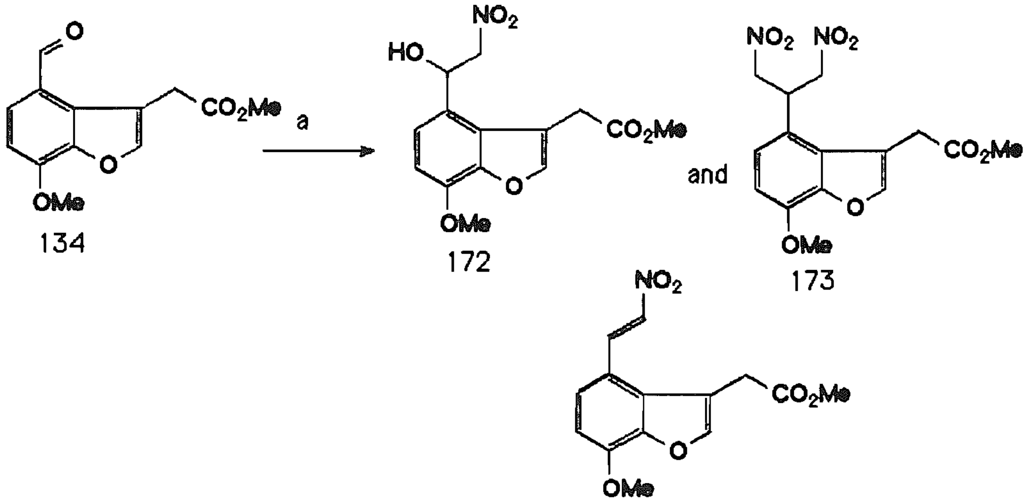
Nitromethane combined with (**134**) to give the nitroalcohol (**172**) as the initial product. Unfortunately starting material was not entirely consumed in this reaction. If the reaction mixture was stirred over a long period of time, a new product was observed. This was identified as the dinitro-compound (**173**), and was produced while starting material was present in the reaction mixture. We assume that this product is formed by way of the (unobserved) β-nitrostyrene (**171**).

A variety of conditions were employed in an attempt to effect the desired condensation. Treatment of (**134**) and the silylnitronate derived from nitromethane and trimethylsilyl chloride with a catalytic quantity of tetrabutylammonium fluoride [130] gave a similar mixture of products to those described above (this silylnitronate is unstable so it was prepared and used *in situ*). A similar mixture of products was also obtained from the reaction of (**134**) with the dianion of nitromethane [131,132].



133 131 132

Scheme 3.14 a= i) KF/MeOH/CH_2Cl_2/$MeNO_2$ b=$NaBH_4$/THF
ii) Ac_2O/Et_2O/CH_2Cl_2/DMAP c=$NaBH_4$/THF/AcOH

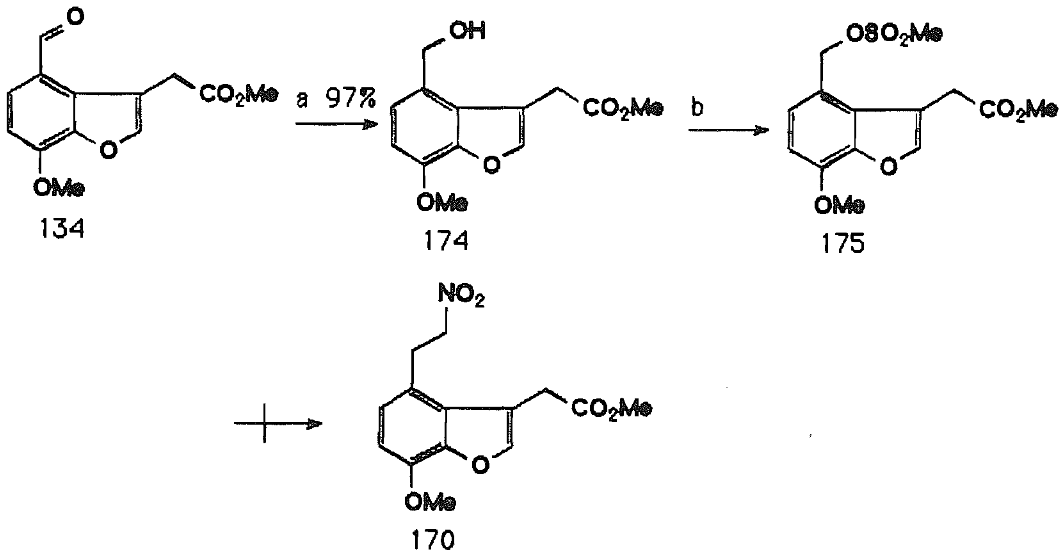


134 172 173 171

Scheme 3.15 a=KF/MeOH/CH_2Cl_2/$MeNO_2$

We rationalised our inability to form the desired adduct (**172**) quantitatively as being due to the highly electron rich nature of the benzofuran ring of the aldehyde (**134**). The electron richness of this ring system will make the aldehyde less susceptible to nucleophilic attack than most aldehydes and will facilitate the loss of water from the adduct (**172**). Three strategies to overcome these problems appeared to be available to us. These were an intramolecular trapping of the nitrostyrene (**172**), a reduction of the electron density in the aromatic ring system or a condenstion of nitromethane with a compound such as the mesylate (**175**) (scheme 3.16).

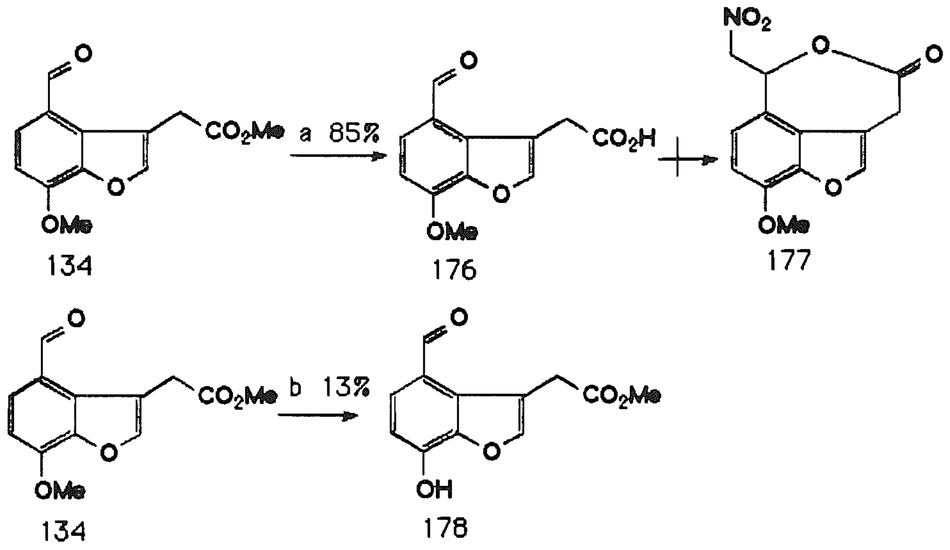
We chose to pursue the reaction of nitromethane with the compound (**175**) (scheme 3.16). The aldehyde (**134**) was treated with sodium borohydride in a mixture of tetrahydrofuran and methanol [133] to give the alcohol (**174**). This was treated with mesyl chloride and excess triethylamine [134] to give a compound assumed to be (**175**). Nitromethane was added to this solution in the hope that (**170**) would be produced. No identifiable material was isolated from the reaction mixture.



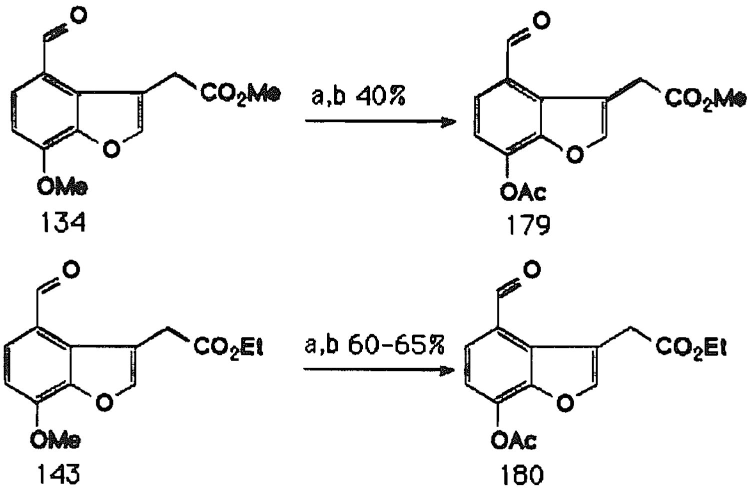
Scheme 3.16 a=$NaBH_4$/THF/MeOH b=$MeSO_2Cl$

Our attention returned to the aldehyde (**134**). This material was treated with lithium iodide in dimethyl formamide solution in the hopes of preparing the acid (**176**) [135] but we found that we had formed the phenol (**178**) instead (scheme 3.17). A solution of (**134**) in ethanol/dichloromethane was treated with potassium hydroxide. This gave the potassium salt of the acid (**176**). Nitromethane was added to the reaction mixture in the hope that it would condense with the aldehyde and that subsequent reactions would lead to the formation of the lactone (**177**). Nitromethane did condense with (**176**) but the lactone (**177**) was not formed. The reaction of the acid (**176**) with nitromethane appeared to parallel the reaction of the corresponding ester (**134**) with nitromethane. We were thus left with only one strategy to form the nitro-compound we required. This involved decreasing the electron density associated with the benzofuran ring in (134).

A colleague, Mr D. Hodgson, suggested that replacement of the 7-methoxy group of aldehyde (**134**) with an acetoxy group would boost the reactivity of the aldehyde. This was a suggestion that we decided to pursue. Our observation of the formation of the phenol (**178**) when we treated (**134**) with lithium iodide was utilised for this work. We decided to take (**134**) and cleave the methyl ether using a nucleophilic reagent. The procedure of Feutrill and Mirrington [136] was found to be the most efficient for our compound. Thus (**134**) was treated with the sodium salt of ethane thiol to give the corresponding phenoxide ion (scheme 3.18). This was then trapped with acetic anhydride to give the acetoxy derivative (**179**). The yield on this reaction was low (40%, presumably due to a competing ester cleavage reaction). The corresponding ethyl ester (**143**) was prepared and subjected to a similar procedure. This gave the corresponding acetoxy-aldehyde (**180**) in an acceptable yield (65%).



Scheme 3.17 a=KOH/EtOH/CH_2Cl_2 b=LiI/DMF

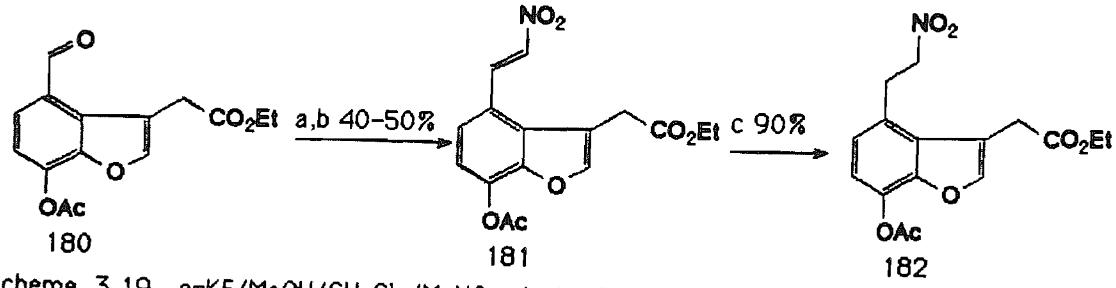


Scheme 3.18 a=NaSEt b=Ac_2O

With the compound (**180**) in hand our attention turned once again to the formation of the corresponding ß-nitrostyrene. We took (**180**) and subjected it to our variation of the procedure reported by Wollenberg and Miller. The results of this investigation were encouraging. The reaction of nitromethane with (**180**) did not result in the quantitative formation of the corresponding nitro-alcohol, however the formation of the dinitro-compound was suppressed. We found that we could obtain approximately a 50% yield of the nitrostyrene (**181**) from this reaction and could also recover 40% of the starting aldehyde (**180**) (scheme 3.19). We decided that this reaction was usable and that our attention should turn to the reduction of (**181**) to (**182**).

The treatment of a solution of (**181**) in tetrahydrofuran with sodium borohydride gave only a small quantity of the required product (**182**). It was obvious that the reduction of nitrostyrenes was a non-trivial problem. As such we decided to study the reaction using the readily accessible nitrostyrene (**131**) (scheme 3.14) as substrate.

A survey of the literature suggested that the reduction of vinylnitro compounds and especially of nitrostyrenes would be sensitive to the pH of the solution in which the reduction was performed [137]. The reduction we desired was reported to proceed most readily in acidic solution. This had been achieved by adding hydrochloric acid and sodium borohydride alternately to the reaction mixture [137] but such a procedure did not seem applicable on a small scale. We decided to search for an alternative, acidic, reducing mixture and observed that sodium borohydride had some stability in a mixture of tetrahydrofuran and acetic acid. The stability of this mixture was found to depend on the presence or absence of water. Addition of water to the mixture resulted in the vigorous evolution of hydrogen.



Scheme 3.19 a=KF/MeOH/CH_2Cl_2/$MeNO_2$ b=Ac_2O/Et_2O/CH_2Cl_2/DMAP c=$NaBH_4$/AcOH/THF

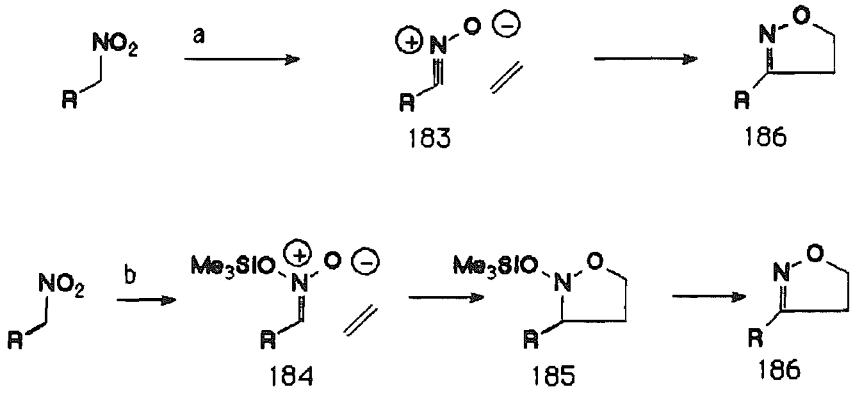
We found that we could effect the reduction of a solution of (**131**) in tetrahydrofuran with seven equivalents of sodium borohydride in the presence of seven equivalents of acetic acid. This procedure led to the formation of (**132**) in 72% yield when 8g of (**131**) was used. This procedure was also applied to the reduction of (**181**) and (**182**) was produced in 90% yield on a small scale.

Approaches to a Diels-Alder Reaction Substrate.

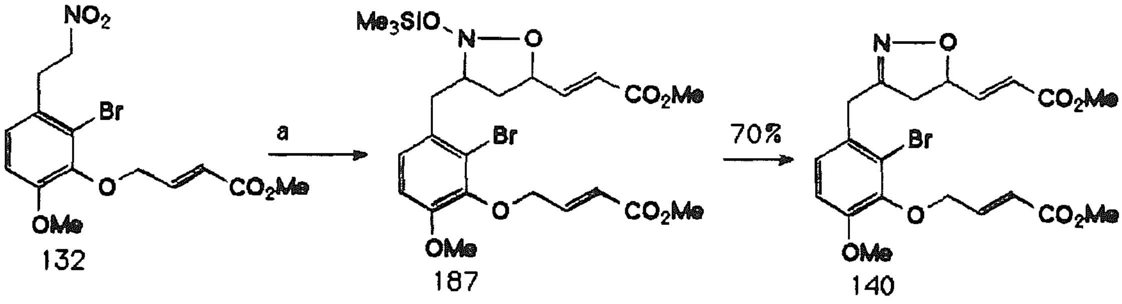
Our investigations had furnished us with the compounds (**132**) and (**182**). We could now investigate the conversion of these materials into isoxazolines. Two procedures appeared to be available to us for this conversion (scheme 3.20). The first of these procedures was developed by Mukaiyama and Hoshino [138]. They dehydrated primary nitro-compounds with a mixture of triethylamine and phenyl isocyanate in the presence of an alkene (dipolarophile). This generated a nitrile oxide (**183**) (a 1,3-dipole) which underwent addition to the alkene and produced an isoxazoline (**186**). A major disadvantage of this procedure is the generation of diphenyl urea as a side-product. This compound frequently makes the isolation of the isoxazolines difficult.

An alternative procedure for performing this conversion was reported by Torssell and Das [139]. They treated primary nitro-compounds with triethylamine and trimethylsilyl chloride to produce silyl nitronates (**184**) (compounds closely related to nitrones). These reacted with alkenes *in situ* to give the adducts (**185**). These compounds were found to eliminate trimethylsilyl alcohol on treatment with acid to generate the corresponding isoxazoline (**186**).

We chose to use the method developed by Torssell for our reactions, partially because of the problems associated with the Mukaiyama procedure and partially because of the similarity of the silylnitronates to the nitrones we had already used (from a theoretical viewpoint the silylnitronates and nitrones are very similar species). The reaction of (**132**) and methyl E-2,4-pentadienoate under the conditions described by Torssell gave the product (**140**) (scheme 3.21). We found that the intermediate (**187**) was formed in some reactions and could be converted to (**140**) by the addition of extra trimethylsilyl chloride.



Scheme 3.20 a=PhNCO/base b=Me$_3$SiCl/base

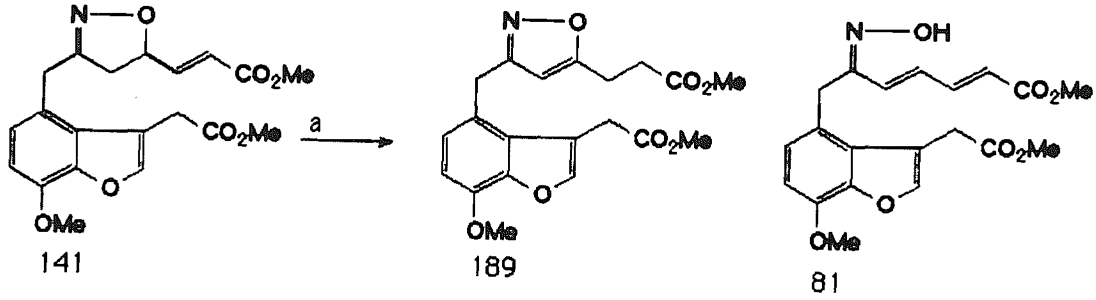


Scheme 3.21 a=Me$_3$SiCl/Et$_3$N

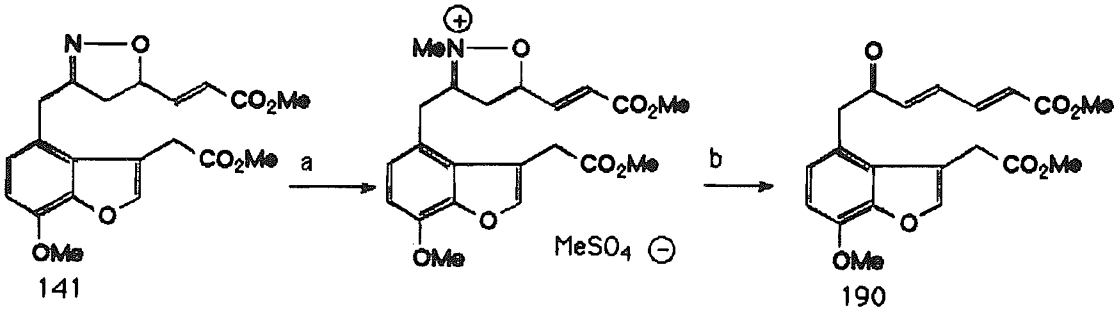
With compound (**140**) in hand we subjected it to our palladium catalysed cyclisation procedure. As was recorded in the previous chapter this reaction gave the corresponding benzofuran (**141**) in good yield (see table 2.1).

Our synthetic scheme required the formation of the diene (**81**) from the isoxazoline (**141**) (scheme 3.22). The work of Jäger suggested such a conversion may be possible using a strong base [140]. In our hands using our substrate (**141**) no identifiable products could be isolated from this reaction. A second method of converting (**141**) to (**81**) was envisaged. This involved heating (**141**), tetrakis-(triphenylphosphine)palladium(0), potassium carbonate and triethylamine to reflux in tetrahydrofuran solution in the hope of inducing an allylic elimination reaction similar in type to that we had observed as we investigated the synthesis of benzofurans. This did not occur but an unexpected isomerisation reaction gave us the isoxazole (**189**).

As time was running out for us we decided to perform a hydrolysis /elimination reaction on the isoxazoline (**141**). This was accomplished using a variation of the methodology of Kwiatkowski [141] and gave us the compound (**190**) (scheme 3.23).



Scheme 3.22 a=Pd(PPh$_3$)$_4$ /Et$_3$N/K$_2$CO$_3$



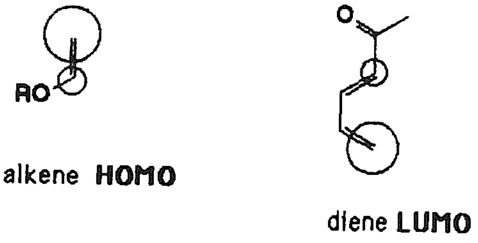
Scheme 3.23 a=Me$_2$SO$_4$ b=i) NaNO$_2$ /H$_2$O/CH$_2$Cl$_2$ ii) Et$_3$N/CH$_2$Cl$_2$

The compound (**190**) had all the functionality nec~~c~~essary for us to try our key reaction, an inverse electron demand intramolecular Diels-Alder reaction. Our first thought was to attempt this reaction as a thermal reaction. The conditions used as we tried to achieve this reaction are detailed in table 3.3. In no reaction could we find any evidence for the thermal Diels-Alder reaction having occurred. We turned our attention to the possibility of catalysing this reaction with Lewis acids. The only Lewis acid we tried was diethylaluminium chloride [142]. This reaction was unsuccessful and produced no recognisable product. Our last attempt to effect this reaction was to treat (**190**) with tris(p-bromophenyl)aminium hexachloroantimonate under conditions similar to those used by Bauld [143]. This reaction also failed to give us any recognisable product.

Table 3.3

Solvent	temp/°C	Time	Result
Xylene	140	3 days	Starting Material (S.M.)
Toluene	160	1 hour	S.M.
Toluene	180	1 hour	S.M.
Toluene	195	1 hour	S.M.
Toluene	190	14 hours	S.M.
Toluene	230	8 hours	S.M. and decomposition
Toluene	230	16 hours	S.M. and decomposition
o-dichloro-benzene	250	16 hours	S.M. and decomposition

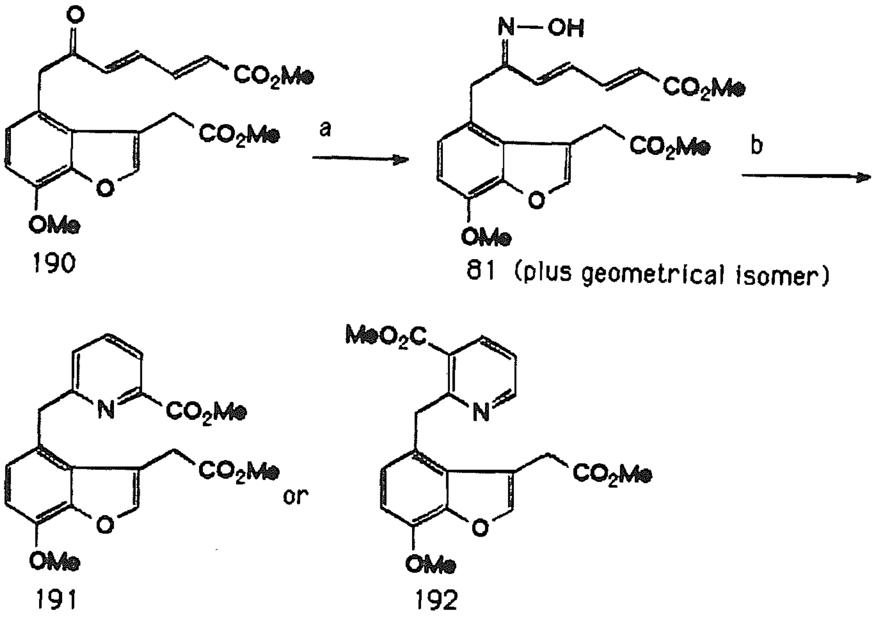
We decided to try to apply molecular orbital theory to this problem. The dienophilic unit is a furanyl double bond and we decided to approximate this by assuming it is electronically similar to an enol ether. The diene unit has an electron withdrawing group at each terminus and of these effects the effect of the ketone would be expected to be dominant. We approximated this unit with a simple terminally substituted electron deficient diene. While we were fully aware of the inadequecies of such approximations we felt that such an approach would at least give us a "feel" for the problems of such a reaction. The orbitals we considered are shown in scheme 3.24. We found that the interaction we required in order to effect the Diels-Alder reaction was not aided by the ketone group in conjugation with the diene unit. Equally we realised that the more electron withdrawing the group at the free terminus of the diene the more favourable the Diels-Alder reaction should be. From a frontier molecular orbital viewpoint we needed to get rid of the ketone functionality. However, from a synthetic viewpoint we needed to keep some heteroatom functionality at that position. We already knew that if we generated an sp^3 centre an elimination reaction would be very likely. Thus we needed to protect the ketone and maintain an sp^2 centre. We decided to form the oxime (**81**) (and its geometrical isomer) [144] (scheme 3.25). We subjected the mixture of isomers to the conditions of a thermal Diels-Alder reaction. We observed none of the desired adduct but we did isolate a quantity of material we tentatively identified as a pyridine. Two possible structures (**191**) and (**192**) fitted the data for this compound and these are also shown in scheme 3.25. At this juncture a shortage of time prevented us from investigating these reactions any further.



alkene **HOMO**

diene **LUMO**

Scheme 3.24



190

81 (plus geometrical isomer)

191

192

Scheme 3.25 a=$NH_3OHCl/MeOH/NaOAc$

CHAPTER 4

Conclusions and Suggestions for Further Work.

The first phase of our synthetic scheme, the synthesis of 3,4,7-trisubstituted benzofurans, was successfully concluded. The methodology that was developed appeared to be applicable to the synthesis of a reasonable variety of benzofurans. As such this constitutes a useful synthetic procedure.

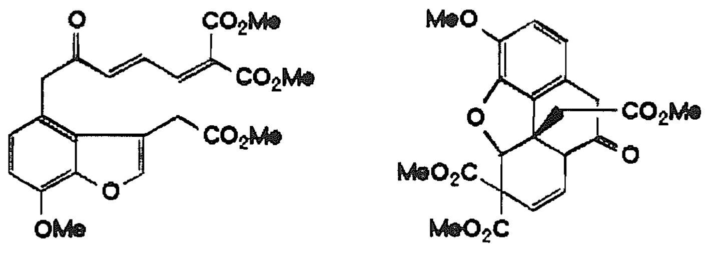
The detailed mechanism of this reaction is unclear (see chapter II). A study of the mechanism of this and related reactions should be both interesting and informative. If such a study were to be undertaken I would suggest the compound bis-(dibenzylideneacetone)palladium(0) [145] should be used as a source of complexed palladium(0). This species could be used in the absence of any phosphine to test the hypothesis that a palladium(0) species other than palladium metal or a palladium(0)/phosphine complex could be involved in the cyclisation reaction.

The second phase of our synthetic scheme was the formation of the diene portion of our Diels-Alder precursor. This was accomplished by way of a cycloaddition of a silylnitronate to an alkene (as was outlined in chapter III). While this is a literature procedure [139] it appears to be a much under-used synthetic methodology.

The third phase of our synthetic scheme, the intramolecular Diels-Alder reaction was tried but we could not form our desired adduct. The reasons for the failure of this reaction are not entirely clear. A contributing factor to the failure could be the choice of the diene unit. A similar diene unit has been reported to undergo an intramolecular Diels-Alder reaction onto an alkene [146]. A diene unit held in the s-*cis* configuration may well enable the reaction to occur. This may be achieved using the substrate (**190**) utilising a nickel(0) catalysed procedure reported recently by Wender [147]. An investigation of this reaction will have to await the arrival of a new researcher.

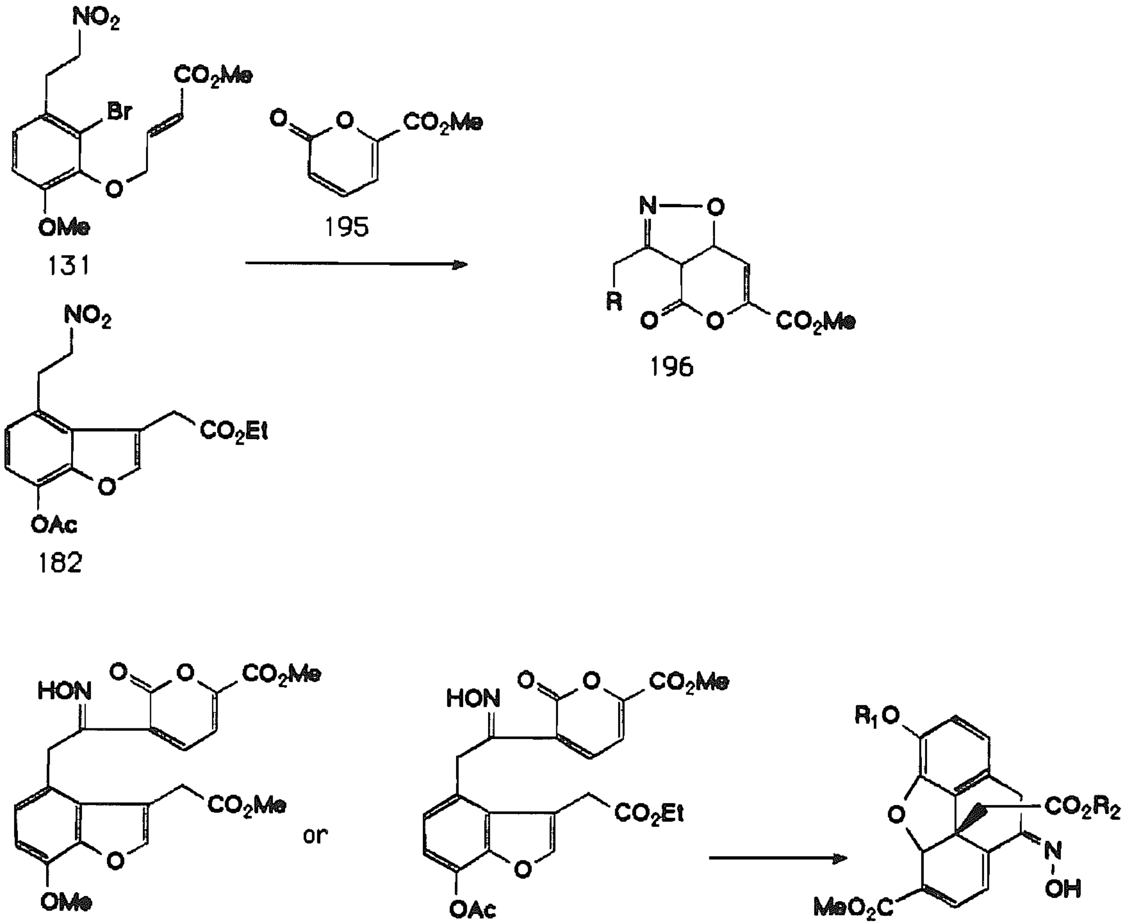
A brief consideration of the molecular orbitals involved in the Diels-Alder reaction was made in chapter III. The conclusion of this consideration was that the free terminus of the diene unit should be as electron withdrawing as possible. The compound (**193**) (scheme 4.1) would be a good starting substrate on which to test this hypothesis. It would be prepared in a similar manner to (**190**). The only problem that I would envisage in the approach to (**193**) concerns the regiochemistry of the addition of a silylnitronate to diene that is more electron deficient than methyl E-2,4-pentadienoate (the isoxazoline product may be substituted at the 4-position cf. the discussion in chapter III). Should (**193**) be prepared and the Diels-Alder reaction occur, (**194**) would result. The conversion of a *gem* diester to a ketone is a known procedure [148]. Such a reaction could be performed on a derivative of (**194**) to give the oxygen functionality required for a synthesis of morphine.

A more drastic change to the diene unit would be to ensure the s-*cis* configuration of the diene by restricting it in a ring (cf. Ciganek [68]). This is the approach I would recommend to any future worker on this chemistry. I suggest that the diene unit that should be employed is the pyrone (**195**) (scheme 4.2). This should react with a silylnitronate to give the product isoxazoline (**196**) with the most electron withdrawing group at the 4-position (cf. the nitrones see chapter III). The nitro-compound used in this reaction could be either (**132**) or (**182**). Using this approach it should be possible to generate either (**197**) or (**198**). Either of these compounds could undergo an intramolecular Diels-Alder with concomitant loss of carbon dioxide to produce a tetracyclic product (**199**).



193 194

Scheme 4.1



131 195 196 182

197 or 198 199

Scheme 4.2

CHAPTER 5

Section 1; General Experimental Procedures

All reactions were performed in vessels purged with nitrogen unless otherwise stated. Melting points were recorded on an *electrothermal* melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 298 infrared spectrophotometer.

Infrared spectral data are presented in the following manner:- V_{max} (solvent or phase) cm^{-1} and were referenced to the $1602cm^{-1}$ absorbance of polystyrene. The following abbreviations are used to suggest the intensity of a given absorbance:- s, strong; m, medium; w, weak; br, broad.

Proton nmr spectra were recorded on the following machines; 60MHz nmr spectra were recorded on a Perkin Elmer R 24 B nmr spectrometer, 250MHz nmr spectra were recorded on a Bruker 250MHz nmr spectrometer, 270MHz nmr spectra were recorded on a Jeol JNM GX 270 FT nmr spectrometer, 360MHz nmr spectra were recorded on a Bruker A M 360 nmr spectrometer, 500MHz nmr spectra were recorded on a Bruker VXR 500 nmr spectrometer.

Proton nmr data are presented in the following form:- δ_H(Frequency MHz, solvent, reference). The following abbreviations are used to show the multiplicity of a given signal:- d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants are denoted J= Hz. The abbreviations arom. and ald. denote aromatic and aldehydic protons respectively.

Carbon (13) nmr spectra were recorded at the following machines; 67.5 MHz spectra were recorded on a Jeol JNM GX 270 FT nmr spectrometer and 90.6 MHz spectra were recorded on a Bruker A M 360 nmr spectrometer.

Carbon (13) nmr data are presented in the following form:- δ_C(Frequency MHz, solvent, reference). H(1) C(13) correlations were determined using DEPT experiments. The following abbreviations show the results of these determinations:- q, qua~~r~~tenary; (CH), (CH_2) and (Me); self explanatory.

Elemental analyses were performed for us at University College London. These results are self explanatory.

Mass spectra were recorded on a VG analytical 70-250-8E normal geometry double focusing mass spectrometer. The ionisation mode used was electron impact. These data are presented in a form that is self explanatory. Where high resolution accurate masses were recorded these are presented after the normal (low resolution) spectral data.

Chromatographic separations were generally performed on silica, using the method of Still [150]. The silica used for these separations was sorbsil C 60. When alumina was used instead of silica this was Fluka type 507 C neutral alumina. The solvents used as eluents for the chromatography were used as supplied, with the exception of light petroleum ether, which was distilled from calcium hydride prior to use.

Thin layer chromatography was conducted using glass plates precoated with kieselgel SIL G-25 UV_{254}. The t.l.c. plates were visualised using UV light (254nm) then aqueous potassium permanganate.

The organic solvents used for reactions were generally purified and dried prior to use. This was accomplished by distillation of the solvent from a suitable drying agent in apparatus flushed with dry nitrogen. The drying agents used for specific solvents are listed below:

Ether	sodium in the presence of benzophenone
Tetrahydrofuran	sodium in the presence of benzophenone
Dimethyl formamide	calcium hydride (under reduced pressure)
Acetonitrile	calcium hydride
Dichloromethane	calcium hydride
Benzene	calcium hydride
Toluene	calcium hydride
Nitromethane	calcium chloride

Reagents were generally used as supplied. Methyl 4-bromocrotonate and ethyl 4-bromocrotonate were supplied as 90% pure mixtures. Initially we used them as supplied but eventually we distilled them and used them in the purified form. We indicate the reactions in which undistilled crotonates were used. The salts cetyl trimethylammonium bromide and potassium carbonate were dried by heating under reduced pressure for several hours. These salts were then kept in a desiccator until they were used. The purification of other materials are noted in the individual experimental details.

Aqueous solutions of inorganic materials were used either in the form of saturated solutions or as dilute (2 molar) solutions unless other dilutions are specified.

The nomenclature of the compounds in the following text is in accordance with that used by "chemical abstracts".

Section 2; Experimental Section.

Methyl 4-(E,E-6-methoxycarbonyl-2-hydroxyimino-3,5-hexadienyl)-7-methoxy-3-benzofuranacetate **(81)**. A solution of methyl 4-(E,E-6-methoxycarbonyl-2-oxo-3,5-hexadienyl)-7-methoxy-3-benzofuranacetate **(190)**(372mg, 1mmol), hydroxylamine hydrochloride (115mg, 1.67mmol) and sodium acetate (150mg, 1.83mmol) in methanol (20ml) was heated to reflux for 5 hours. The cold solution was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 2:1 petrol:ethyl acetate as eluent) to give the title compound as a mixture of geometrical isomers (160mg, 0.4mmol, 40%).

V_{max} (CH_2Cl_2) 3560 and 3300 (b,together OH), 1740 and 1715 (esters), 1630 (alkenes),1590 and 1510cm^{-1} (together aromatic ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.63 and 7.61 (1H,furans), 7.5-7.1 (2H,alkenes), 6.9-6.5 (4H,alkene and aromatic ring protons), 6.1 (d J=15.3Hz) and 5.9 (d J=15.5Hz) (1H,alkene), all other signals 4.2-3.6 (14H);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 171.8 (CO_2Me), 167.2 and 166.9 (CO_2Me), 157.5 and 154.4 (C=N for the E and Z oximes), 145.3 (q), 144.8 (q), 144.7 (q), 144.1 (q), 144.0 (CH), 143.96 (CH), 143.9 (CH), 143.7 (CH), 143.9 (CH), 143.7 (CH), 135.9 (CH), 133.8 (CH), 131.5 (CH), 127.3 (q), 127.1 (q), 126.3 (CH), 125.2 (CH), 124.2 (CH), 123.4 (CH), 122.0 (CH), 121.8 (q), 120.8 (q), 113.7 (q), 113.6 (q), 106.6 (CH), 106.5 (CH), 56.1 (OMe), 52.5 (CO_2Me), 52.4 (CO_2Me), 51.9 (CO_2Me), 51.8 (CO_2Me), 33.7 (CH_2), 30.8 (CH_2), 30.6 (CH_2), 26.7 (CH_2);

m/z 387 ($M^{+\cdot}$,15.7%), 370 ($M^{+\cdot}$-OH,34%), 310 ($M^{+\cdot}$-OH-HCO_2Me, 51.0%), 233 ($M^{+\cdot}$-$C_7H_8NO_3$,83.1%), 175 (100%).

Methyl 7-methoxy-4-(2-propenyl)-3-benzofuranacetate (**87**). Acetonitrile (10ml) was added to a mixture of methyl E-4-[2-bromo-6-methoxy-3-(2-propenyl)phenoxy]-2-butenoate (**119**) (510mg, 1.5mmol), potassium carbonate (390mg, 3mmol) and palladium acetate (30mg, 0.15mmol, 10mol%). The stirred mixture was heated to reflux for 5 hours. The cold mixture was filtered and the residue was washed with dichloromethane (50ml). The combined organic phase was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 10:1 petrol:ether as eluent) to give the title compound (248mg, 0.95mmol, 63%). A sample of this material was recrystallised (ether:petrol) to give white needles m.p. 72-74°C.

V_{max} (CH_2Cl_2) 1740 (ester), 1640 (alkene), 1600, 1580 and 1510cm^{-1} (together aromatic ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.6 (1H,s,furan), 6.9 (1H,d J=8.1Hz,arom.), 6.7 (1H,d J=8.1Hz,arom.), 6.1 (1H,m,$C\underline{H}=CH_2$), 5.1-4.9 (2H,m,$CH=C\underline{H_2}$), 4.0 (3H,s,OMe), 3.8 (2H,s,$C\underline{H_2}CO_2Me$), 3.7 (3H,s,CO_2Me), 3.6 (2H,d J=5.6Hz of t J=1.5Hz,$ArC\underline{H_2}CH=$);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 171.5 (ester), 145.0 (q), 144.3 (q), 143.5 (CH), 137.8 (CH), 127.2 (q), 124.8 (q), 124.2 (CH), 115.8 (q),113.6 (q), 106.3 (CH), 55.9 (OMe), 52.1 (CO_2Me), 36.0 ($Ar\underline{C}H_2CH=$), 30.3 ($\underline{C}H_2CO_2Me$);

m/z 260 (M^{+},100%), 201 ($M^{+}-CO_2Me$).

2-Methoxy-5-(2-propenyl)phenol (chavibetol) (**103**) [82]. Methyl iodide (15.6ml, 35.5g, 250mmol) was added dropwise with constant stirring to a mixture of magnesium turnings (6.1g, 250mmol) and a small crystal of iodine in dry ether (200ml). The rate of addition was such that the reaction mixture maintained at most a gentle reflux. Once the addition of methyl iodide was completed a solution of eugenol methyl ether (44.6g, 250mmol) in dry xylene (80ml) was added. As much volatile material as possible was distilled from the reaction mixture (b.p.40-60°C) then dry xylene (100ml) was added. This mixture was heated to reflux for 3 hours. The cold mixture was tipped cautiously into a mixture of ice-water (500ml) and glacial acetic acid (150ml). The resulting solution was washed with ether (3x300ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was dissolved in ether (100ml) and washed with 5% sodium hydroxide solution (3x70ml). The combined aqueous phase was acidified (dil. HCl) and washed with ether (3x200ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude phenolic product (34.6g).

This product was an equimolar mixture of chavibetol and the isomeric phenol, eugenol. Separation of this mixture was achieved as follows:-

The crude product (34.6g) was added to a solution of potassium hydroxide (16.3g) in ethanol (103ml). The mixture was heated to dissolve the salts formed. Slow cooling precipitated the sodium salt of eugenol preferentially and this was removed by filtration. Treatment of the residue with saturated ammonium chloride liberated a eugenol rich mixture of phenols. The phenols were isolated and subjected once again to the fractional crystallisation procedure described above.

The filtrate from the fractional crystallisation was concentrated *in vacuo* to give a chavibetol rich mixture of sodium phenoxides. This residue was treated with saturated ammonium chloride solution to liberate the free phenols. These were isolated and subjected to the fractional crystallisation procedure once again. This time the chavibetol fraction contained only a trace of eugenol and was thus kept.

Any fraction containing an appreciable amount of chavibetol was subjected to the fractional crystallisation procedure. By this methodology 17.2g of the crude compound was obtained. This was distilled *in vacuo* to give the title compound (15.5g, 95mmol, 38%).

The separation of the two phenols was visualised using glc (carbowax, 190°C).

V_{max} (liquid film) 3500 (OH), 1640 (w,alkene), 1600 and 1510cm^{-1} (together aromatic ring);

δ_H(60MHz, solvent $CDCl_3$, reference Me_4Si) 7.0-6.4 (3H,m,aromatics), 6.3-5.5 (1H,m,$C\underline{H}=CH_2$), 5.9 (1H,s,OH), 5.1 (1H,m) and 4.9 (1H,m) (together $=CH_2$), 3.6 (3H,s,OMe), 3.2 (2H,d J=6Hz,$C\underline{H}_2CH=$).

2-Methoxy-5-(2-propenyl)phenoxyacetic acid (**104**) [155]. Chloroacetic acid (10ml of a 50% aqueous solution) was added to a stirred solution of 2-methoxy-5-(2-propenyl)phenol (**103**) (3.90g, 24mmol) in aqueous sodium hydroxide (15ml of a 33% solution). The resulting solution was heated to 100°C for 1 hour.

The cold solution was diluted with water (40ml) and acidified to pH.3 (dil. HCl). The aqueous phase was washed with ether (3x120ml). The combined organic phase was washed with water (40ml) then extracted with 5% sodium carbonate solution (2x100ml). The combined aqueous phase was acidified to pH.3 (dil. HCl) and washed with ether (3x70ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product (3.44g, 15mmol, 65%) as a white solid m.p.84-86°C.

V_{max} (CH_2Cl_2) 3600-2500 (acid OH), 1775 and 1735 (acid carbonyl), 1640 (alkene) 1610, 1590 and 1500cm^{-1}) (together aromatic ring);
δ_H(60MHz, solvent $CDCl_3$, reference Me_4Si) 6.8-6.6 (3H,m,aromatics), 6.3-5.5 (1H,m,C$\underline{H}$=CH_2), 5.1 (1H,m) and 4.9 (1H,m) (together =CH_2), 4.6 (2H,s,OCH_2), 3.8 (3H,s,OMe), 3.2 (2H,d J=6Hz,benzylic).

2-Methoxy-5-(2-propenyl)phenoxyacetyl chloride (**105**). 2-Methoxy-5-(2-propenyl)phenoxyacetic acid (2.29g, 10.3mmol) was dissolved in freshly distilled thionyl chloride (20ml). The resulting solution was heated to reflux for 2 hours. Excess thionyl chloride was removed by distillation and the crude product was distilled *in vacuo* (140°C, 2mmHg) to give the title compound (1.24g, 5.16mmol, 50%) as a colourless liquid.

V_{max} (liquid film) 1810 (COCl), 1635 (alkene), 1605, 1595 and 1510cm^{-1} (together aromatic ring);
δ_H(60MHz, solvent $CDCl_3$, reference Me_4Si) 6.7 (3H,m,aromatic), 6.3-5.4 (1H,m,C$\underline{H}$=CH_2), 5.05 (1H,m,terminal alkene), 4.85 (3H,m,terminal alkene and OCH_2COCl), 3.7 (3H,s,OMe), 3.2 (2H,d J=6Hz,benzylic).

2-Bromo-3-hydroxy-4-methoxybenzaldehyde (**108**). A solution of bromine (6.9ml, 23.4g, 147mmol) in dry acetic acid (60ml) was added over a period of 20 minutes to a vigorously stirred mixture of 3-hydroxy-4-methoxybenzaldehyde (20.0g, 131.4mmol), anhydrous sodium acetate (21.6g, 264mmol) and powdered iron (approx. 0.5g) in dry acetic acid (100ml). The mixture was stirred for a further 60 minutes and was then tipped into a solution of sodium bisulphite (300ml of a 0.1 molar solution). This mixture was was kept at 5°C for 2 hours and the crude, solid product was recovered by filtration. The filtrate was concentrated *in vacuo* to approximately 30ml and the crude product precipitated was again collected by filtration.

The crude product was recrystallised (3:1 methanol:water) to give the title compound as white needles. The mother liquors were concentrated *in vacuo* and the residue was recrystallised to give more product (total yield 20.5g, 89mmol, 67.5%) m.p. 193-195°C.
ν_{max} (nujol mull) 3250 (b,OH), 1670 (s,aldehyde), 1600 and 1570cm^{-1} (together aromatic ring);
δ_H(60MHz, solvent $CDCl_3/(CD_3)_2SO$, reference Me_4Si) 10.2 (1H,s,aldehyde), 7.3 (1H,d J=6Hz) and 7.0 (1H,d J=6Hz) (aromatic ring protons), 3.9 (3H,s,OMe).

These data are in agreement with that reported for this compound [88].

2-Bromo-3-hydroxy-4-methoxybenzenemethanol (**109**) [151]. Solid 2-bromo-3-hydroxy-4-methoxybenzaldehyde (**108**) (7.0g, 30.3mmol) was added to a stirred solution of sodium hydroxide (24g, 0.6mol) and sodium borohydride (3.0g, 79mmol) in water (350ml). The resulting solution was stirred at room temperature for 1 hour. At the end of this time dilute hydrochloric acid was added cautiously with constant stirring to the solution. The addition was continued until the aqueous phase reached pH 3. The resulting suspension was filtered and the residue was recrystallised (water) to give the title compound (6.34g, 27.2mmol, 90%) m.p. 145-146°C as white needles.
ν_{max} (nujol mull) 3380 (b,OH), 1605 and 1500cm^{-1} (together aromatic ring);
δ_H(60MHz, solvent $CDCl_3/(CD_3)_2SO$, reference Me_4Si) 8.7 (1H,s,phenolic OH), 6.95 (1H,d J=8Hz,arom.), 6.8 (1H,d J=8Hz,arom.), 5.0 (1H,t J=5Hz,benzylic OH), 4.5 (2H,d J=5Hz,$\underline{CH_2}OH$), 3.8 (3H,s,OMe).

2-Bromo-3-bromomethyl-6-methoxyphenol (**110**). Phosphorus tribromide (4.0ml, 42.7mmol) was added dropwise to a cold (0°C) stirred suspension of 2-bromo-3-hydroxy-4-methoxybenzenemethanol (**109**) (6.34g, 27.2mmol) in dry dichloromethane (250ml). Once the addition was complete the cooling bath was removed. The mixture was stirred for 2 hours and was then tipped into a large vessel containing a saturated solution of sodium bicarbonate (250ml). The mixture was

stirred until the evolution of carbon dioxide had ceased and was then partitioned. The aqueous phase was washed with more dichloromethane (2x100ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was recrystallised (cyclohexane) to give the title compound (6.19g, 20.9mmol, 77%), m.p.93-94°C as white needles.
V_{max} (CH_2Cl_2) 3400 (br,OH), 1605 and 1490cm^{-1} (together arom. ring);
δ_H(360MHz, solvent $CDCl_3$, reference Me_4Si) 7.1 (1H,d,arom.), 6.8 (1H,d,arom.), 6.1 (1H,s,OH), 4.6 (2H,s,CH_2Br), 3.9 (3H,s,OMe);
δ_C(90.6MHz, solvent $CDCl_3$, reference Me_4Si) 147.3 (q), 143.8 (q), 122.1 (CH), 110.8 (q), 109.8 (CH), 56.5 (OMe), 34.1 (CH_2Br).

2-Bromo-6-methoxy-3-(2-propenyl)phenol (**111**). Vinylmagnesium bromide (50mmol, prepared from 1.24g of magnesium and 3.6ml of vinyl bromide in 50ml of tetrahydrofuran) was added rapidly to a cold (-15°C), stirred, solution of 2-bromo-3-bromomethyl-6-methoxyphenol (**110**) (3.0g, 10mmol), 2,2-dipyridyl (790mg, 5.1mmol) and copper (I) iodide (970mg, 5.1mmol) in tetrahydrofuran (50ml). The temperature of the solution reached a maximum of 20°C but rapidly dropped back to below 0°C. The solution was allowed to warm slowly to room temperature and stirring was continued overnight. The reaction mixture was then treated with ammonium chloride (3.25g) then wet ether (100ml) and finally aqueous acetic acid (100ml of a 50% V/V solution). The resulting mixture was opened to the atmosphere and was stirred vigorously until a blue aqueous phase was produced. The mixture was partitioned and the aqueous phase was washed with ether (2x50ml). The combined organic phase was concentrated *in vacuo* to a volume of approximately 30ml and was then diluted with ether (50ml). This solution was washed with sat. sodium bicarbonate solution (1x100ml) and solid sodium bicarbonate was added to the mixture until the evolution of gas ceased. The two phases were separated and the organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was subjected to column chromatography (silica, 4:1 petrol:ether as eluent) to give the title compound (1.16g, 4.8mmol, 48%) m.p. 56°C a white solid.
V_{max} (nujol mull) 3400 (br.,OH), 1630 (w, alkene), 1510 and 1500cm^{-1} (together arom. ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 6.8 (1H,d J=8.3Hz,arom.), 6.75 (1H,d J=8.3Hz,arom.), 6.1-5.9 (1H,m,$CH_2C\underline{H}=CH_2$), 6.0 (1H,s,OH), 5.1-5.0 (2H,m,$CH=CH_2$), 3.9 (3H,s,OMe), 3.5 (2H,d J=6.6Hz of t J=1.35Hz,$C\underline{H}_2CH=$);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 145.6 (q), 143.2 (q), 136.1 (CH), 132.6 (q), 120.6 (CH), 116.3 ($CH=\underline{C}H_2$), 111.0 (q), 109.7 (CH), 56.5 (OMe), 39.7 ($\underline{C}H_2CH=$);
m/z 242 (100%) and 244 (M^+), 227 (41%) and 229 (M^+-Me), 215 (21%) and 217 (M^+-CH_2=CH).

2-Bromo-6-methoxy-3-(1-propenyl)phenol (**115**). A solution of tri-n-butyl vinyl tin (26g, 80mmol), 2-bromo-3-bromomethyl-6-methoxyphenol (**110**) (18.9g, 64mmol) and tetrakis-(triphenylphosphine)palladium(0) (1.2g, 1.2mmol) in tetrahydrofuran (500ml) was heated to reflux for 18 hours. The cold solution was concentrated *in vacuo* and the residue was diluted with petrol (250ml) and partitioned with aqueous sodium hydroxide (2x250ml of a 10% solution). The combined aqueous phase was acidified (dil. HCl) and washed with dichloromethane (3x300ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was dissolved in ether and filtered through a plug of silica. The organic phase was concentrated *in vacuo* to give the title compound (12.47g, 51mmol, 80%) contaminated with the corresponding 2-(propenyl) isomer.
V_{max} (CH_2Cl_2) 3520 (OH), 1600 and 1490cm^{-1} (together aromatic ring);
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.0 (1H,d J=8.5Hz,arom.), 6.8 (1H,d J=8.5Hz,arom.), 6.6 (1H,d J=15.6Hz,$C\underline{H}=CHMe$), 6.05 (1H,d J=15.5Hz of q J=6.6Hz,$CH=C\underline{H}Me$), 6.0 (1H,s,OH), 3.7 (3H,s,OMe), 1.9 (3H,d J=6.6Hz of d J=1.7Hz,$=CH\underline{Me}$);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 145.9 (q), 142.9 (q), 131.4 (q), 129.5 (CH), 127.3 (CH), 117.4 (CH), 109.9 (CH), 109.7 (q), 56.4 (OMe), 18.6 ($=CH\underline{Me}$).
m/z 242 (100%) and 244 (M^+), 227 (47%) (M^+-Me), 91 (44%)

1-[2-Bromo-6-methoxy-3-(2-propenyl)phenoxy]-2-propyne (**118**). A solution of 2-bromo-6-methoxy-3-(2-propenyl)phenol (**111**) (1.50g, 6.25mmol) in tetrahydrofuran (15ml) was added slowly with constant stirring to a suspension of sodium hydride (150mg, 6.25mmol) in tetrahydrofuran (20ml). The resulting mixture was stirred for 15 minutes then propargyl bromide (1.66g, 12mmol, 1.83g of an 80% w/w solution of propargyl bromide in toluene) and cetyltrimethylammonium bromide (0.20g, 0.4mmol) were added. The mixture was heated to reflux for 15 hours. The cold solution was filtered and the filtrate was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 8:1 petrol:ether as eluent) to give the title compound (1.30g, 4.6mmol, 75%) m.p.$35^{\circ}C$ as a white solid.

This compound proved to be unstable when not in solution and was thus stored in ethereal solution at $-30^{\circ}C$.

V_{max}(nujol mull) 3300 (≡C-H), 2120 (C≡C), 1640 alkene, $1600cm^{-1}$ (aromatic ring);

δ_H(60MHz, solvent $CDCl_3$, reference Me_4Si) 6.9 (1H,d J=7Hz,arom.), 6.7 (1H,d J=7Hz,arom.), 6.2-5.6 (1H,m,$C\underline{H}=CH_2$), 5.1 (1H,s) and 4.9 (1H,m) (together $=CH_2$), 4.7 (2H,d J=3Hz,$OCH_2C\equiv$), 3.8 (3H,s,OMe), 3.4 (2H,d J=6Hz,benzylic), 2.4 (1H,t J=3Hz,≡CH).

1-[2-Bromo-6-methoxy-3-(2-propenyl)phenoxy]-3-^{2}H-2-propyne (**118a**). A solution of 1-[2-bromo-6-methoxy-3-(2-propenyl)phenoxy]-2-propyne (**118**) (450mg, 1.85mmol) in tetrahydrofuran (4ml) was added to a stirred suspension of sodium hydride (50mg, 2.1mmol) in tetrahydrofuran (5ml). The resulting mixture was stirred at room temperature for 3 days then deuterium oxide (0.1ml) was added. The reaction mixture was stirred for a further 60 minutes and was dried (Na_2SO_4). The solution was concentrated *in vacuo* to give the title compound. This reaction was very capricious and this result could not be repeated.

V_{max} (nujol mull) 2580 (≡C-D), 1990 (C≡C), 1640 ($CH=CH_2$), $1590cm^{-1}$ (aromatic ring);

δ_H(60MHz, solvent $CDCl_3$, reference Me_4Si) 6.9 (1H,d J=7Hz,arom.), 6.7 (1H,d J=7Hz,arom.), 6.3-5.5 (1H,m,$C\underline{H}=CH_2$), 5.1 (1H,s) and 4.9 (1H,m) (together $=CH_2$), 4.7 (2H,s,OCH_2), 3.8 (3H,s,OMe), 3.4 (2H,d J=6Hz,benzylic).

Methyl E-4-[2-bromo-6-methoxy-3-(2-propenyl)phenoxy]-2-butenoate (**119**). A solution of 2-bromo-6-methoxy-3-(2-propenyl)phenol (**111**)

(1.5g, 6.15mmol) in tetrahydrofuran (15ml) was added slowly to a stirred suspension of sodium hydride (150mg, 6.25mmol) in tetrahydrofuran (20ml). The mixture was stirred for 15 minutes then methyl 4-bromocrotonate (1.32g, 1.0ml of a 90% pure mixture supplied by the Aldrich chemical company) was added followed by cetyltrimethylammonium bromide (200mg, 0.4mmol). The mixture was heated to reflux for 15 hours. The cold mixture was filtered and the filtrate was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 8:1 petrol:ether as eluent) to give the title compound (1.73g, 5.1mmol, 82.5%), m.p.28-29°C as a white solid.

V_{max} (CH_2Cl_2) 1720 (ester), 1660 ($CH=CHCO_2Me$), 1600, 1500 and 1450 cm^{-1} (together arom. ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.1 (1H, d J=15.7 of t J=4.5,$\underline{H}$C=$CHCO_2Me$), 7.0 (1H,d J=8.5Hz,arom.), 6.8 (1H,d J=8.5Hz,arom.), 6.3 (1H,d J=15.7Hz of t J=2.2Hz,CH=C$\underline{H}$$CO_2Me$), 6.0 (1H,m,C$\underline{H}$=$CH_2$), 5.0 (2H,m,=$CH_2$), 4.7 (2H,d J=4.5Hz of d J=2.2Hz,OC$\underline{H}_2$CH=), 3.8 (3H,s,OMe), 3.75 (3H,s,CO_2Me), 3.5 (2H,d J=6.5Hz of t J=1.5Hz,ArC$\underline{H}_2$CH=);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 166.8 (ester), 151.8 (q), 145.1 (q), 143.4 ($\underline{C}$H=$CHCO_2Me$), 135.9 (CH), 132.7 (q), 125.3 (CH), 121.5 (CH=$\underline{C}$HCO_2Me), 120.3 (q), 116.3 (=CH_2), 111.4 (CH), 71.2 (O$\underline{C}H_2$CH=), 56.2 (OMe), 51.6 ($CO_2\underline{Me}$), 37.8 (Ar$\underline{C}H_2$CH=);

m/z 340 and 342 (M^+), 241 and 243 ($M^{+\cdot}-C_5H_7O_2$), 134 (100%);

M^+ $C_{15}H_{17}BrO_4$ requires: 340.03103 found: 340.0314.

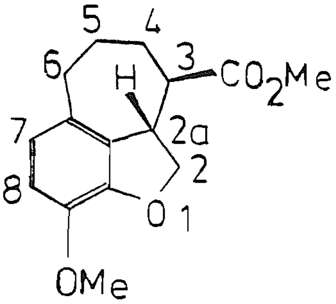
Methyl 2,2a,3,4,5,6-hexahydro-9-methoxycyclohepta[cd]benzofuran-3-carboxylate (**120**). A solution of methyl E-4-[2-bromo-6-methoxy-3-(2-propenyl)phenoxy]-2-butenoate (**119**) (290mg, 0,85mmol), tri-n-butyltin hydride (350mg, 0.32ml, 1.2mmol) and azo-*bis*-isobut~~e~~yronitrile (28mg, 0.16mmol) in benzene (30ml) was heated to reflux and irradiated with a desk lamp for 24 hours. The cold solution was concentrated *in vacuo* and the residue was dissolved in ether (20ml). Potassium fluoride dihydrate (300mg) and water (20ml) were added to the solution and this mixture was stirred for 18 hours at room temperature. The mixture was filtered and partitioned and the aqueous phase was washed with ether (2x20ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 4:1 petrol:ether as eluent) to give the title compound (approximately 190mg, 0.78mmol) m.p. 55-58°C contaminated with a trace of the starting material.

V_{max} (CH_2Cl_2) 1735 (ester), 1630, 1600 and 1510cm^{-1} (together aromatic ring);

δ_H(250MHz, solvent $CDCl_3$, reference Me_4Si) 6.6 (1H,d,arom.), 6.5 (1H,d,arom.), 4.85 (1H,t J=9.5Hz,2), 4.15 (1H,t J=9.0Hz,2), 3.9 (1H,d J=11Hz of t J=9.5Hz,2a), 3.85 (3H,s,OMe), 3.7 (3H,s,CO_2Me), 2.8-2.6 (2H,m,6), 2.55 (1H,d J=2.5Hz of t J=11.5Hz,3), 2.35 (1H,d J=14Hz of d J=6Hz of t J=2.5Hz), 2.1 (1H,m,5), 1.75 (1H,d J=14Hz of d J=2Hz of t J=12Hz,4), 1.5 (1H,m,5); The numbering used in the above assignments is that for this ring system. On the basis of these data the relative stereochemistry of this compound has been assigned as H(2a)β, H(3)α.

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 175.5 (ester), 148.2 (q), 143.0 (q), 133.2 (q), 128.1 (q), 120.5 (CH), 111.3 (CH), 76.6 (CH_2,2), 56.0 (OMe), 51.9 (CO_2Me), 50.7 (CH), 45.9 (CH), 35.2 (CH_2) and 27.6 (CH_2) (two signals for the three carbon atoms at positions 4, 5 and 6);

m/z 262 (M^+,100%), 203 (M^+-CO_2Me,58%), 161 (90%).



Methyl E-4-[2-bromo-6-methoxy-3-(1-propenyl)phenoxy]-2-butenoate (**121**). A solution of 2-bromo-6-methoxy-3-(1-propenyl)phenol (**115**) (5.0g, 20mmol) in tetrahydrofuran (40ml) was added over a period of 10 minutes to a suspension of sodium hydride (0.5g, 20mmol) in tetrahydrofuran (40ml). The mixture was stirred for 30 minutes then cetyltrimethylammonium bromide (0.4g, 0.8mmol) and methyl 4-bromocrotonate (4.2ml of a 90% pure mixture supplied by the Aldrich Chemical Company) were added. The mixture was heated to reflux for 18 hours, cooled and filtered. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography (silica, petrol:ether 9:1 as eluent) to give the title compound (5.43g, 16mmol, 78%), m.p.54-56°C as a white solid.

V_{max} (CH_2Cl_2) 1730 (ester), 1670 (w,alkene), 1600, 1500 and 1450cm^{-1} (together arom. ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.2 (1H,d J=8.7Hz, arom.), 7.1 (1H,d J=15.6Hz of t J=4.5Hz,CH=CHCO$_2$Me), 6.8 (1H,d J=8.7Hz,arom.), 6.6 (1H,d J=15.5Hz of q J=1.7Hz,MeCH=CH-), 6.3 (1H,d J=15.6Hz of t J=2Hz,CH=CHCO$_2$Me), 6.0 (1H,d J=15.6Hz of q J=6.6Hz,MeCH=CH-), 4.7 (2H,d J=4.5Hz of d J=2Hz,OCH$_2$CH=), 3.83 (3H,s,OMe), 3.76 (3H,s,CO$_2$Me), 1.9 (3H,d J=6.7Hz of d J=1.7Hz,MeCH=);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 166.8 (ester), 152.2 (q), 144.7 (q), 143.4 (CH=CHCO$_2$Me), 131.6 (q), 129.5 (CH), 127.4 (CH), 122.2, 121.5 (CH=CHCO$_2$Me), 118.9 (q), 111.5, 71.1 (OCH$_2$CH=), 56.2 (OMe), 51.7 (CO$_2$Me), 18.6 (MeCH=);

m/z 340 and 342 (M^+), 241 (100%) and 243 ($M^+-C_5H_7O_2$);

M^+ $C_{15}H_{17}BrO_4$ requires: 340.03103 found: 340.03241.

Methyl 8-methoxy-4-methyl-2a,3,4,5-tetrahydro-2H-naptho[1,8-bc]furan-3-carboxylate (**122**). A solution of methyl E-4-[2-bromo-6-methoxy-3-(1-propenyl)phenoxy)-2-butenoate (**121**) (300mg, 0.85mmol), tri-n-butyltin hydride (350mg, 1.2mmol) and azo-*bis*-isobutyronitrile (28mg, 0.17mmol) in benzene (40ml) was heated to reflux for 18 hours. The cold solution was concentrated *in vacuo* and ether (20ml), water (20ml) and potassium fluoride dihydrate (400mg, 4.2mmol) were added to the residue. This mixture was stirred for 24 hours. The resulting suspension was filtered and the filtrate was partitioned. The aqueous phase was washed with ether (2x20ml) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, petrol then petrol:ether 2:1 as eluent) to give the title compound (176mg, 0.68mmol, 80%), m.p.45-47°C as a white solid.

V_{max} (CH_2Cl_2) 1730 (ester), 1630, 1610 and 1500cm^{-1} (together arom. ring);

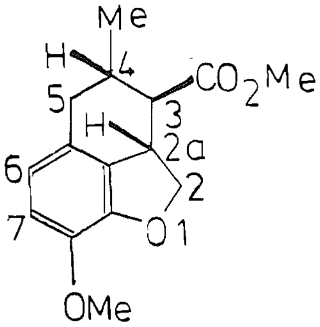
δ_H(360MHz, solvent $CDCl_3$, reference Me_4Si) 6.8 (1H,d,arom.), 6.6 (1H,d,arom.), 4.75 (1H,t J=8.4Hz,2), 4.1 (1H,d J=12.3Hz of d J=8.4Hz,2), 3.85 (3H,s,OMe), 3.75 (3H,s,CO$_2$Me), 3.75-3.6 (1H,m approx. q

J=10Hz,2a), 3.0 (1H,d J=16.7Hz of d J=5.5Hz,5), 2.35 (1H,d J=16.7Hz of d J=10.4Hz,5), 2.25 (1H,m,4), 2.15 (1H,t J=10.5Hz,3), 1.1 (3H,d J=6Hz,Me);

The numbering used in the above assignments is that for this ring system. On the basis of these data the relative stereochemistry of this compound was assigned as follows; H(2a) β, H(3)α, H(4)β.

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 174.9 (ester), 146.3 (q), 142.4 (q), 119.7 (CH), 113.6 (CH), 78.6 (2), 56.6 (OMe), 51.8 (CO_2Me), 50.8 (CH), 43.2 (CH), 34.6 (5), 33.6 (CH), 19.6 (Me);

m/z 262 (M^+,100%), 203 (M^+-CO_2Me,37%), 162 (60%).



Methyl 7-methoxy-4-(1-propenyl)-3-benzofuranacetate (127).

Acetonitrile (5ml) was added to a stirred mixture of methyl E-4-[2-bromo-6-methoxy-3-(1-propenyl)phenoxy]-2-butenoate (**121**) (341mg, 1mmol), potassium carbonate (280mg, 2mmol) and palladium acetate (22mg, 0.1mmol, 10mol%). The mixture was heated to reflux for 4 hours . The cold mixture was filtered and the residue was washed with dichloromethane (20ml). The combined organic phase was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 15:1 petrol:ether as eluent) to give the title compound (196mg, 0.75mmol, 75%), m.p.46-48°C as a white solid.

V_{max} (CH_2Cl_2) 1740 (ester), 1630 (alkene), 1580, 1510 and 1440cm^{-1} (together aromatic rings);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.6 (1H,s,furan), 7.1 (1H,d J=8.3Hz, arom.), 6.7 (1H,d J=8.3Hz,arom.), 6.7 (1H,d J=15.5Hz of m,C<u>H</u>=CHMe), 6.0 (1H,d J=15.5Hz of q J=6.8Hz,CH=C<u>H</u>Me), 3.9 (3H,s,OMe), 3.8 (2H,s,$C\underline{H}_2CO^2Me$), 3.7 (3H,s,CO_2Me), 1.9 (3H,d J=6.6Hz of d J=1.7Hz,CH=CH<u>Me</u>);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 171.3 ($\underline{C}O_2Me$), 144.7 (q), 144.5 (q), 143.5 (CH), 127.3 (CH), 127.0 (q), 125.5 (q), 120.6 (CH), 113.9 (q), 106.8 (CH), 56.0 (OMe), 52.1 ($CO_2\underline{Me}$), 31.0 ($\underline{C}H_2CO_2Me$), 18.6 (CH=$\underline{Me}$);

m/z 260 (M^{+}, 100%), 201 ($M^{+}-CO_2Me$).

2-Bromo-4-methoxy-3-(2-propenyloxy)benzaldehyde (**128**). Solid 2-bromo-3-hydroxy-4-methoxybenzaldehyde (**108**) (2.31g, 10mmol) was added in 5 portions to a stirred suspension of sodium hydride (0.24g, 10mmol) in tetrahydrofuran (30ml). The yellow solution formed was stirred for 15 minutes then cetyltrimethylammonium bromide (0.2g, o.4mmol) and allyl bromide (0.87ml, 10mmol) were added. The mixture was heated to reflux for 15 hours. The cold mixture was filtered and the filtrate was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 4:1 petrol:ether as eluent) to give the title compound (2.50g, 9.2mmol, 92%), m.p.74-76°C as a white solid.

V_{max} (liquid film) 1685 (ald.), 1580 and 1490cm^{-1} (together arom. ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 10.25 and 10.24 (1H,two s,together ald.), 7.7 (1H,d J=8.7Hz,arom.), 6.9 (1H,d J=8.7Hz,arom.), 6.2-6.1 (1H,m,$C\underline{H}=CH_2$), 5.4-5.2 (2H,m,$=CH_2$), 4.5 (2H,d J=6Hz of d J=1.2Hz,$OC\underline{H}_2CH=$), 4.0 (3H,s,OMe);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 191.1 and 191.05 (ald), 158.7 (q), 145.1 (q), 133.4 (CH), 127.3 (q), 126.5 (CH), 123.5 (q), 118.7 ($=CH_2$), 110.9 (CH), 74.1 ($O\underline{C}H_2CH=$), 56.3 (OMe);

m/z 270 and 272 (M^{+}), 229 (100%) and 231 ($M^{+}-(C_3H_5)$;

M^{+} $C_{11}H_{11}BrO_3$ requires: 269.98917 found: 269.98998.

7-Methoxy-3-methyl-4-benzofurancarboxaldehyde (**129**). Acetonitrile (5ml) was added to a stirred mixture of 2-bromo-4-methoxy-3-(2-propenyloxy)benzaldehyde (**128**) (272mg, 1mmol), potassium carbonate (280mg, 2mmol) and palladium acetate (22mg, 0.1mmol, 10mol%). The mixture was heated to reflux for 7 hours. The cold mixture was filtered and the residue was washed with dichloromethane (20ml). The combined organic phase was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 9:1 petrol:ether as eluent) to give the title compound (162mg, 0.85mmol, 85%), m.p.57-58°C.

V_{max} (CH_2Cl_2) 1690 (ald.), 1620 and 1570cm^{-1} (together arom. rings);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 10.23 (1H,s,ald.), 7.7 (1H,d J=8.5Hz,arom.), 7.5 (1H,s,furan), 6.8 (1H,d J=8.5Hz,arom), 4.06 (3H,s,OMe), 2.5 (3H,S,ArMe);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 189.4 (ald.), 150.0 (q), 145.3 (q), 144.5 (CH), 129.8 (q), 129.0 (CH), 124.7(q), 117.0 (q), 105.8 (CH), 56.3 (OMe), 12.1 (ArMe);

m/z 190 (M^+, 76%), 189 (M^+-H, 100%).

A small quantity of material which had spectral characteristics consistent with the corresponding 2(H)-3-*exo*methylene furan was also isolated. This material was more polar than the title compound on tlc (silica, 4:1 petrol:ether as eluent) and was not fully characterised.

Methyl E-4-[2-bromo-6-methoxy-3-E-(2-nitroethenyl)phenoxy]-2-butenoate (**131**). Solid methyl E-4-(2-bromo-6-methoxy-3-oxomethylphenoxy)-2-butenoate (**133**) (0.50g, 1.52mmol) was added to a stirred mixture of methanol (2ml), nitromethane (1ml), dichloromethane (0.5ml) and potassium fluoride dihydrate (0.03g, 0.32mmol). The resulting suspension was stirred for 18 hours at room temperature to give a solution of methyl E-4-[2-bromo-3-(1-hydroxy-2-nitroethyl)-6-methoxy-2-butenoate (by tlc on silica with dichloromethane as eluent a new spot R.F. 0.1). The solution was concentrated *in vacuo* and ether (4ml), dichloromethane (2ml) acetic anhydride (0.25ml, 2.6mmol) and 4-N,N-dimethylaminopyridine (0.01g, 0.1mmol) were added to the residue. This solution was heated to reflux for 18 hours. The cold solution was diluted with dichloromethane (20ml) and washed with water (20ml). The organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was recrystallised (cyclohexane/ethyl acetate) to give the title compound (0.45g, 1.2mmol, 78%) m.p. 127-128°C a yellow solid (found: C, 45.31;H, 3.54;N, 3.43;Br, 21.6. $C_{14}H_{14}NO_6Br$ requires C, 45.18;H, 3.79;N, 3.76;Br, 21.47%);

V_{max}(CH_2Cl_2) 1720 (ester),1660 (w), 1630 (alkene), 1585 and 1510 (aromatic ring), 1480 and 1320cm^{-1} (NO_2);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 8.4 (1H,d J=13.6Hz,$C\underline{H}=CHNO_2$), 7.5 (1H,d J=13.6Hz,$CH=C\underline{H}NO_2$), 7.1 (1H,d J=8.7Hz,arom.), 7.1 (1H,d J=15.6Hz of t J=4.5Hz,$OCH_2C\underline{H}=CH$), 6.9 (1H,d J=8.7Hz,arom.), 6.3 (1H,d J=15.6Hz of t J=1.9Hz, $OCH_2CH=C\underline{H}$), 4.7 (2H,d J=4.4Hz of d J=1.9Hz,OCH_2-), 3.9 (3H,s,OCH_3), 3.8 (3H,s,OCH_3);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 166.7 (ester), 156.2 (q), 145.8 (q), 142.6 ($OCH_2\underline{C}H=$), 137.8 (CH), 137.3 (CH), 124.8 (CH), 123.5 (q), 122.7 (q), 121.9 ($CH=\underline{C}HCO_2$), 111.6 (CH), 71.3 ($O\underline{C}H_2CH=$), 56.4 (OMe), 51.8 ($CO_2\underline{Me}$);

m/z 371 and 373 (M^+), 272 and 274 ($M^+-C_5H_7O_2$), 99 ($C_5H_7O_2$,100%).

Methyl E-4-[2-bromo-6-methoxy-3-(2-nitroethyl)phenoxy]-2-butenoate (**132**). Sodium borohydride (2.72g, 0.072mol) was added portionwise over a period of 2 hours to a cold (0°C), stirred solution of methyl E-4-[2-bromo-6-methoxy-3-E-(2-nitroethenyl)phenoxy]-2-butenoate (**131**) (8.0g, 0.021mol) in tetrahydrofuran (250ml) and acetic acid (8.1ml, 0.141mol). The cold mixture was stirred for 5 hours and was then allowed to warm to room temperature. Water (50ml) was added and stirring was continued for a further 15 minutes. The solution was concentrated *in vacuo* to remove the tetrahydrofuran and the aqueous residue was partitioned with dichloromethane (3x70ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was recrystallised (petrol:ether) to give the title compound (5.805g, 0.0155mol, 72%) m.p.65-67°C as white needles (found: C, 45.08; H, 4.33; N, 3.58; Br, 21.46. $C_{14}H_{16}NO_6Br$ requires C, 44.94; H, 4.31; N, 3.74; Br, 21.35%);

V_{max} (CH_2Cl_2) 1730 (ester), 1670 ($CH=CHCO_2Me$)), 1600, 1490 and 1440 (aromatic ring), 1550 and 1380cm^{-1} (NO_2);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.1 (1H,d J=15.8Hz of t J=4.4Hz, $C\underline{H}=CHCO_2$), 7.0, (1H,d J=8.5Hz,arom.), 6.8 (1H,d J=8.5Hz,arom.), 6.3 (1H,d J=15.8Hz of t J=1.9Hz,$CH=C\underline{H}CO_2$), 4.7 (2H,d J=4.4Hz of d J=1.9Hz,$OC\underline{H}_2CH=$), 4.6 (2H,t J=7.2Hz,CH_2NO_2), 3.84 (3H,s,OMe), 3.76 (3H,s,CO_2Me), 3.4 (2H,t J=7.2Hz,$C\underline{H}_2CH_2NO_2$

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 166.8 (ester), 155.9 (q), 145.3 (q), 143.1 ($\underline{C}H=CHCO_2Me$), 127.9 (q), 126.3 (CH), 121.6 ($CH=\underline{C}HCO_2Me$), 120.0 (q), 111.5 (CH), 74.7 (CH_2NO_2), 71.2 ($O\underline{C}H_2CH=$), 56.1 (OMe), 51.8 (CO_2Me), 33.6 ($ArCH_2$).

m/z 373 and 375 (M^+), 274 (100%) and 276 ($M^+-C_5H_7O_2$).

Methyl E-4-(2-bromo-6-methoxy-3-oxomethylphenoxy)-2-butenoate (**133**). Solid 2-bromo-3-hydroxy-4-methoxybenzaldehyde (**108**) (8.55g, 37mmol) was added portionwise to a stirred suspension of sodium hydride (0.91g, 38mmol) in tetrahydrofuran (60ml). The mixture was stirred for 15 minutes then cetyltrimethylammonium bromide (1.0g, 2mmol) and methyl 4-bromocrotonate (7.4ml of a 90% pure mixture supplied by the Aldrich Chemical Company) were added. The resulting mixture was heated to reflux for 18 hours. Water (40ml) was added to the cold mixture and stirring was continued for a further 30 minutes. The solid product obtained by this procedure was recovered by filtration. The filtrate was concentrated *in vacuo* to a volume of approximately 40ml and this aqueous phase was partitioned with dichloromethane (3x40ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give more of the crude product. All of the crude product was recrystallised (ethyl acetate:cyclohexane) to give the title compound (10.07g, 31mmol, 83%), m.p.120-121°C as a white solid (Found: C, 47.17; H, 3.96; Br, 24.57. $C_{13}H_{13}O_5Br$ requires C,47.44; H, 3.98; Br, 24.28%);
V_{max} (CH_2Cl_2) 1725 (ester), 1685 (ald.), 1500 and 1450cm^{-1} (together arom. ring);
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 10.24 (1H,s,ald.), 7.8 (1H,d J=8.7Hz,arom.), 7.1 (1H,d J=15.8Hz of t J=4.6Hz, $C\underline{H}=CHCO_2Me$), 7.0 (1H,d J=8.7Hz,arom.), 6.3 (1H,d J=15.8Hz of t J=1.9Hz,$CH=C\underline{H}CO_2Me$), 4.7 (2H,d J=4.5Hz of t J=1.9Hz,$OC\underline{H}_2CH=$), 3.95 (3H,s,OMe), 3.78 (3H,s,CO_2Me);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 190.8 (ald.), 166.6 (ester), 158.5 (q), 144.8 (q), 142.6 ($\underline{C}H=CHCO_2Me$), 127.4 (q), 126.9 (CH), 123.1 (q), 121.9 ($CH=\underline{C}HCO_2Me$), 111.0 (CH), 71.3 ($O\underline{C}H_2CH=$), 56.4 (OMe), 51.8 ($CO_2\underline{Me}$);
m/z 328 and 330 (M^+), 229 (100%) and 231 ($M^+-C_5H_7O_2$).
M^+ $C_{13}H_{13}BrO_5$ requires: 327.99465 found: 327.9933.

Methyl 7-Methoxy-4-oxomethyl-3-benzofuranacetate (**134**). Acetonitrile (10ml) was added to a stirred mixture of methyl E-4-(2-bromo-6-methoxy-3-oxomethylphenoxy)-2-butenoate (**133**) (658mg, 2mmol), potassium carbonate (560mg, 4mmol) and palladium acetate (44mg, 0.2mmol, 10mol%). The mixture was heated to reflux for 3 hours. The cold mixture was filtered and the filtrate was washed with dichloromethane (50ml). The combined organic phase was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, petrol:ethyl acetate 2:1 as eluent) to give the title compound (420mg, 1.69mmol, 85%), m.p.125-127°C as a white solid (Found: C, 62.77; H, 4.82. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.87%);

V_{max} (CH_2Cl_2) 1740 (ester), 1690 (ald.), 1620 and 1570cm^{-1} (arom. rings);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 9.8 (1H,s,ald), 7.63 (1H,s,furan), 7.62 (1H,d J=8.1Hz,arom.), 6.8 (1H,d J=8.1Hz,arom.), 4.0 (3H,s,OMe), 4.0 (2H,s,$C\underline{H}_2CO_2Me$), 3.7 (3H,s,CO_2Me);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 190.8 (ald.), 172.0 (ester), 150.3 (q), 146.1 (CH), 145.7 (q), 133.7 (CH), 127.7 (q), 124.6 (q), 115.3 (q), 105.6 (CH), 56.3 (OMe), 52.0 ($CO_2\underline{Me}$), 31.9 ($\underline{C}H_2CO_2Me$);

m/z 248 ($M^{+\cdot}$, 43.5%), 188 (100%).

Methyl E-4-(2-bromophenoxy)-2-butenoate (**135**). A solution of 2-bromophenol (1.73g, 10mmol) in tetrahydrofuran (5ml) was added over a period of 10 minutes to a suspension of sodium hydride (0.24g, 10mmol) in tetrahydrofuran (25ml). The mixture was stired for 15 minutes then cetyltrimethylammonium bromide (0.2g, 0.4mmol) and methyl 4-bromocrotonate (2.0ml, 17mmol) were added. The mixture was heated to reflux for 4 hours. The cold mixture was filtered and the filtrate was concentrated in vacuo to give the crude product. This was subjected to flash column chromatography (silica, 8:1 petrol:ether as eluent) to give the title compound (1.95g, 7.2mmol, 72%) as a colourless oil which solidified on cooling to give a white solid m.p.24-26°C.

V_{max}(CH_2Cl_2) 1730 (ester), 1670 (alkene), 1590, 1580, 1480 and 1440cm^{-1} (together arom. ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.5 (1H,m,arom.), 7.2 (1H,m,arom.), 7.1 (1H,d J=15.6Hz of tJ=3.7Hz,$C\underline{H}$=$CHCO_2Me$), 6.8 (2H,m,arom.), 6.3 (1H,d J=15.6Hz of t J=2.2Hz,CH=$C\underline{H}CO_2Me$), 4.7 (2H,d J=3.7Hz of d J=2.2Hz,$OC\underline{H}_2CH$=), 3.7 (3H,s,CO_2Me).

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 166.4 (ester), 154.2 (q), 141.9 ($\underline{C}H$=$CHCO_2Me$), 133.5 (CH), 128.5 (CH), 122.5 (CH), 121.7 (CH=$\underline{C}HCO_2Me$), 113.2 (CH), 112.2 (q), 67.2 ($O\underline{C}H_2CH$=), 51.7 ($CO_2\underline{Me}$);

m/z 270 and 272 (M^+), 99 ($C_5H_7O_2$, 100%).

Methyl 3-benzofuranacetate (**136**). A solution of methyl E-4-(2-bromophenoxy)-2-butenoate (**135**) (272mg, 1mmol) in dimethylformamide (5ml) was added to a stirred mixture of potassium carbonate (280mg, 2mmol) and palladium acetate (22mg, 0.1mmol, 10mol%). The mixture was heated to a temperature of 120°C for 1 hour. The cold mixtuure was filtered and the residue was washed with dichloromethane (20ml). The combined organic phase was partitioned with water (15ml) and the aqueous phase was washed with 1:1 petrol: dichloromethane (3x15ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 4:1 petrol:ether as eluent) to give the title compound (108mg, 0.57mmol,57%) as a colourless oil.

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.6 (1H,d J=1Hz,furan), 7.6-7.5 (1H,m), 7.5-7.45 (1H,m), 7.3-7.2 (2H,m), 3.7 (3H,s,CO_2Me), 3.7 (2H,d J=1Hz,$\underline{CH_2}CO_2Me$);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 171.3 (ester), 155.3 (q), 143.0 (CH), 127.7 (q), 124.6 (CH), 122.8 (CH), 119.7 (CH), 113.1 (q), 111.7 (CH), 52.3 (OMe), 29.7 ($\underline{C}H_2CO_2Me$).

These data are in agreement with that already published for this compound [152].

1-Bromo-2-(2-propenyloxy)benzene (**138**). A solution of 2-bromophenol (1.73g, 10mmol) in tetrahydrofuran (5ml) was added to a stirred suspension of sodium hydride (0.24g, 10mmol) in tetrahydrofuran (25ml). The mixture was stirred for 15 minutes then cetyltrimethylammonium bromide (0.2g, 0.4mmol) and allyl bromide (0.87ml, 10mmol) were added. The mixture was heated to reflux for 18 hours. The cold mixture was filtered and the filtrate was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 4:1 petrol:ether as eluent) to give the title compound (2.08g, 9.7mmol, 97%) as a colourless oil.

V_{max} (CH_2Cl_2) 1650 (w,alkene), 1590, 1580, 1480 and 1450cm^{-1} (together arom. ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.5 (1H,d J7.8Hz of d J=1.4Hz,arom.), 7.2 (1H,m,arom.), 6.9-6.7 (2H,m,arom.), 6.1-6.0

(1H,m,C$\underline{H}$=CH_2), 5.5 (1H,d J=17.3Hz of d J=1.4Hz,=CH_2), 5.3 (1H,d J=10.6Hz of d J=1.4Hz,=CH_2), 4.6 (2H,d J=4.5Hz,OCH_2-).
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 154.9 (q), 133.4 (CH), 132.6 (CH), 128.4 (CH), 122.0, 117.7 (=CH_2), 113.6 (CH), 112.3 (q), 69.6 (OCH_2).

These data are in agreement with that already published for this compound [153].

3-Methylbenzofuran (**139**). A solution of 1-bromo-2-(2-propenyloxy)-benzene (**138**) (213mg, 1mmol) in dimethylformamide (5ml) was added to a stirred mixture of potassium carbonate (280mg, 2mmol) and palladium acetate (22mg, 0.1mmol, 10mol%). The mixture was heated to a temperature of 120°C for 5 hours. The cold mixture was filtered and the residue was washed with dichloromethane (20ml). The combined organic phase was partitioned with water (15ml). The aqueous phase was washed with 1:1 petrol:dichloromethane (3x15ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, petrol as eluent) to give the title compound (68mg, 0.5mmol, 50%) a colourless oil.
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.5-7.2 (5H,m,arom.), 2.2 (3H,d J=1Hz,Me);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 155.4 (q), 141.4 (CH), 129.1 (q), 124.2 (CH), 122.3 (CH), 119.5 (CH), 115.7 (q), 111.4 (CH), 8.0 (Me).

These data are in agreement with that already published for this compound [154].

Methyl E-4-{2-bromo-3-[4,5-dihydro-5-(E-2-methoxycarbonylethenyl)-3-isoxazolemethyl]-7-methoxyphenoxy}-2-butenoate (**140**). Trimethylsilyl chloride (1.3ml, 10.3mmol), methyl E-2,4-pentadienoate (2.4ml, 21.4mmol) and triethylamine (1.6ml, 12.3mmol) were added to a cold (0°C), stirred solution of methyl E-4-[2-bromo-6-methoxy-3-(2-nitroethyl)phenoxy]-2-butenoate (**132**) (2.0g, 5.35mmol) in acetonitrile (40ml). The mixture was stirred at 0°C for 3 hours and then at room temperature for 3 days. The tlc of this mixture (silica, 1:1 petrol:ether as eluent) showed complete loss of starting material and two new spots (R.F.'s 0.58 and 0.54). This mixture was treated with trimethylsilyl chloride (0.3ml, 2.4mmol) and the mixture was stirred for a further 24 hours to give the reaction product (a new spot by tlc R.F. 0.25 with loss of the two spots at R.F.'s 0.58 and 0.54). The reaction mixture was partitioned between water (50ml) and dichloromethane (50ml) and the aqueous phase was washed with dichloromethane (3x50ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (neutral alumina deactivated with 3% w/w water, ether then ethyl acetate as eluents) to give the title compound (1.79g, 3.82mmol, 71%) m.p.83-85°C a white solid.

V_{max} (CH_2Cl_2) 1720 (esters), 1660 (alkene), 1600 (C=N), $1500cm^{-1}$) (aromatic ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.1 (1H,d J=15.6Hz of t J=4.5Hz,$CH_2C\underline{H}=CHCO_2Me$), 7.0 (1H,d J=8.5Hz,arom.), 6.9 (1H,d J=8.5Hz,arom.), 6.85 (1H,d J=15.6H of d J=5.6Hz,$C\underline{H}=CHCO_2Me$), 6.3 (1H,d J=15.6Hz of t J=1.9Hz,$CH_2CH=C\underline{H}CO_2Me$), 6.0 (1H,d J=15.6 of d J= 1.4Hz,$CH=C\underline{H}CO_2Me$, 5.1 (1H,m,isoxazole), 4.7 (2H,d J=4.5Hz of d J=1.9Hz,$C\underline{H}_2CH=CHCO_2Me$), 3.85 (3H,s,OMe), 3.8 (2H,s,benzylic), 3.76 (3H,s,CO_2Me), 3.73 (3H,s,CO_2Me), 3.1 (1H,d J=17Hz of d J=11Hz,isoxazole), 2.7 (1H,d J=17Hz of d J=7.5Hz,isoxazole);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 166.7 (q) and 166.3 (q) (esters), 156.3 (C=N), 152.6 (q), 145.1 (q), 144.7 ($\underline{C}H=CHCO_2Me$), 143.1 ($CH_2\underline{C}H=CHCO_2Me$), 128.1 (q), 126.0 (CH), 122.0 ($CH=\underline{C}HCO_2Me$), 121.6 ($CH_2CH=\underline{C}HCO_2Me$), 120.3 (q), 111.6 (CH), 78.5 (CH), 71.1 ($\underline{C}H_2CH=CHCO_2Me$), 56.1 (OMe), 51.8 ($CO_2Me$), 51.6 ($CO_2Me$), 42.2 ($CH_2$), 33.6 ($CH_2$);

m/z 467 (33.5%) and 469 (33.9%) (M^{+}), 368 (64.3%) and 370 (64.7%) ($M^{+}-C_5H_7O_2$), 289 (100%, $M^{+}-C_5H_7O_2-Br$).

Methyl 4-[4,5-dihydro-5-(E-2-methoxycarbonylethenyl)-3-isoxazolemethyl]-7-methoxybenzofuranacetate (**141**). Acetonitrile (23ml) was added to a stirred mixture of methyl E-4-{2-bromo-3-[4,5-dihydro-5-(E-2-methoxycarbonylethenyl)-3-isoxazolemethyl]-7-methoxyphenoxy}-2-butenoate (**140**) (2.55g, 5.4mmol), potassium carbonate (1.53g, 11.1mmol) and palladium acetate (93mg, 0.41mmol). The mixture was heated to reflux for 2 hours. The cold mixture was filtered and the filtrate was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 2:1 petrol:ethyl acetate as eluent) to give the title compound (1.75g, 4.53mmol, 84%) as a red oil which crystallised slowly when stored at -30°C.

V_{max} (CH_2Cl_2) 1730 (esters), 1660 (C=N), 1630 (alkene), 1580 and 1510cm^{-1} (together aromatic ring)

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.6 (1H,s,furan), 6.9 (1H,d J=8.1Hz,arom.), 6.7 (1H,d J=8.1Hz,arom.), 6.8 (1H,d J=15.6Hz of d J=5.4Hz,C<u>H</u>=CHCO$_2$Me), 6.0 (1H,d J=15.6Hz,CH=C<u>H</u>CO$_2$Me), 5.1 (1H,m,isoxazole), 3.97 (3H,s,OMe), 3.9 (4H,s,benzylic protons), 3.7 (6H,s,two CO_2Me), 3.0 (1H,d J=17Hz of d J=11Hz,isoxazole), 2.6 (1H,d J=17Hz of d J=7.7Hz,isoxazole);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 171.6 (CO_2Me), 166.3 (CO_2Me), 158.2 (C=N), 145.2 (q), 145.0 (q), 144.7 (<u>C</u>H=CHCO$_2$Me), 144.1 (CH), 127.4 (q), 124.7 (CH), 121.9 (CH=<u>C</u>HCO$_2$Me), 120.5 (q), 113.5 (q), 106.4 (CH), 78.4 (isoxazole), 56.0 (OMe), 52.2 (CO_2Me), 51.7 (CO_2Me), 42.1 (CH_2), 30.6 (CH_2), 30.4 (CH_2);

m/z 387 (M^{+},45%), 328 ($M^{+}-CO_2Me$,27.9%), 233 ($M^{+}-C_7H_8NO_3$,53%), 175 (100%).

Ethyl E-4-(2-bromo-6-methoxy-3-oxomethylphenoxy)-2-butenoate (**142**). Solid 2-bromo-3-hydroxy-4-methoxy-benzaldehyde (**108**) (9.24g, 40mmol) was added to, a stirred suspension of sodium hydride (0.96g, 40mmol) in tetrahydrofuran (120ml) over a period of 15 mins. The mixture was stirred until all the sodium hydride had reacted then cetyltrimethylammonium bromide (0.47g, 0.94mmol) and ethyl 4-bromocrotonate (8.27g, 6ml, 43mmol) were added . The mixture was heated to reflux for 2 hours and the cooled mixture was diluted with water (150 ml). The solution was concentrated *in vacuo* to remove the tetrahydrofuran. Sodium hydroxide (5ml of a 10% solution) was added to the resulting mixture which was then partitioned with dichloromethane (3x100 ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was recrystallised (ether: petrol) to give the title compound (7.27g). The mother liquors were concentrated *in vacuo* and the residue obtained was subjected to flash column chromatography (silica petrol: ether 4:1 to 1:1 as eluent) to give further crude product. This was recrystallised as before to give more of the

product (3.30g), (total yield 10.57g, 30.6 mmol, 77%), m.p. 61-62°C (found C,48.78; H,4.24; Br,23.14. $C_{14}H_{15}O_5Br$ requires C,49.00; H,4.41; Br,23.28%);
V_{max} (CH_2Cl_2) 1720 (s, ester), 1690 (s, ald), 1590cm^{-1} (alkene);
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 10.25 (1H,s,ald), 7.75 (1H,d J=8.7Hz, arom. ring), 7.1 (1H,d J=15.8Hz of t J=4.4Hz, $CH_2C\underline{H}=$), 7.0 (1H,d J=8.7Hz,arom), 6.3 (1H,d J=15.8Hz of t J=1.9Hz =$CHCO_2Et$), 4.7 (2H,d J=4.4Hz of d J=1.9Hz,$OC\underline{H_2}CH$), 4.2 (2H,q J=7.2Hz,ethyl), 3.95 (3H,s,Me), 1.3 (3H,t J=7.2Hz,ethyl);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 190.9 (ald), 166.3 (q,ester), 158.6 (q), 145.0 (q), 142.3 ($CH_2\underline{C}H=$), 127.5 (q), 126.9 (CH), 123.3 (q), 122.5 (=$\underline{C}HCO_2Et$), 111.1 (CH), 71.5 ($O\underline{C}H_2CH=$), 60.7 (OCH_2Me), 56.5 (OMe), 14.1 ($CH_2\underline{C}H_3$);
m/z 342 and 344 ($M^{+\cdot}$), 229 and 231 ($M^{+\cdot}-CH_2CO_2Et$, 100%).

Ethyl 7-methoxy-4-oxomethyl-3-benzofuranacetate (**143**). Acetonitrile (150ml) was added to a mixture of ethyl E-4-(2-bromo-6-methoxy-3-oxomethylphenoxy)-2-butenoate (**142**) (10.34g, 30mmol) potassium carbonate (5.0g, 60mmol) and palladium acetate (300mg, 1.33mmol, 4.4mol%). The stirred mixture was heated to reflux for 2 hours. The cooled mixture was filtered and the filtrate was concentrated *in vacuo* to give a black oil. This was subjected to flash column chromatography (silica, 1:1 petrol:ether as eluent) to give the crude product. Recrystallisation (petrol, ether) gave the title compound (6.03g, 23mmol, 77%), m.p.59-60°C as white needles.
V_{max} (CH_2Cl_2) 1740 (ester), 1690 (ald.), 1590cm^{-1} (alkene);
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 9.9 (1H,s,ald), 7.7 (2H,overlapping d J=8.3Hz (arom.) and s (furan), 6.9 (1H,d J=8.3Hz,arom.), 4.2 (2H,q J=7.2Hz,CH_2Me), 4.07 (3H,s,OMe), 4.04 (2H,s,CH_2CO_2Et), 1.3 (3H,t J=7.2Hz,CH_2CH_3);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 190.7 (ald.), 171.5 (ester), 150.3 (q), 146.1 (CH), 145.7 (q), 133.6 (CH), 127.8 (q), 124.7 (q), 115.5 (q), 105.6 (CH), 60.8 (OCH_2Me), 56.4 (OMe), 32.2 ($\underline{C}H_2CO_2Et$), 14.2 (CH_2CH_3);
m/z 262 (M^+), 216 (M^+-EtOH), 189 (M^+-CO_2Et, 100%);
M^+ $C_{14}H_{14}O_5$ requires: 262.08412 found: 262.0830.

Methyl 4-(2,3-dihydroxypropyl)-7-methoxy-3-benzofuranacetate (**148**). A catalytic quantity of osmium tetroxide was added to a stirred solution of methyl 7-methoxy-4-(2-propenyl)-3-benzofuranacetate (**87**) (120mg, 0.46mmol) and trimethylamine-N-oxide dihydrate (107mg, 0.96mmol) in a mixed solvent consisting of tetrahydrofuran:water:t-butanol 30:4:1 (35ml). The mixture was stirred at room temperature for 20 hours then a solution of sodium metabisulphite (600mg, 3mmol) in water (15ml) was added. After stirring for a further hour the solution was filtered and concentrated *in vacuo* to a volume of approximately 20ml. This aqueous phase was washed with dichloromethane (3x20ml). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, ethyl acetate as eluent) to give the title compound (60mg, 0.205mmol, 46%), m.p.68-70°C as a colourless oil which slowly solidified to give a white solid.

V_{max} (CH_2Cl_2) 3560 (OH), 1740 (ester), 1620, 1590 and 1510cm^{-1} (together arom. rings);

δ_H(360MHz, solvent $CDCl_3$, reference Me_4Si) 7.61 (1H,s,furan), 7.0 (1H,d J=8.1Hz,arom.), 6.7 (1H,d J=8.1HZ,arom.), 3.92 (3H,s,OMe), 3.85-3.75 (3H,overlapping m and s,$C\underline{H}_2CO_2Me$ and $C\underline{H}(OH)$), 3.67 (3H,s,CO_2Me), 3.62 (1H,d J=11.2Hz of d J=3.1Hz) and 3.45 (1H,d J=11.2Hz of d J=6.7Hz) together $C\underline{H}_2OH$, 3.1 (2H,b s,OH), 2.9 (2H,m,$ArC\underline{H}_2CH(OH)$);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 172.0 (ester), 145.1 (q), 144.4 (q), 143.7 (CH), 127.5 (q), 124.9 (CH), 123.4 (q), 113.5 (q), 106.4 (CH), 73.3 (CH(OH)), 65.8 (CH_2OH), 56.0 (OMe), 52.4 ($\underline{C}O_2Me$), 35.5 ($Ar\underline{C}H_2CH(OH)$), 30.7 ($\underline{C}H_2CO_2Me$),

m/z 294 (M^+), 276 (M^+-H_2O), 262 (M^+-MeOH,12%), 234 (M^+-HCO_2Me,98%), 175 (100%).

Methyl 4-[5-(E-2-methoxycarbonylethenyl)-2-methyl-3-isoxazolidinemethyl]-7-methoxy-3-benzofuranacetate (**161**) and (**162**). Sodium metaperiodate (50mg, 0.13mmol), trifluoroacetic acid (1 drop) and water (3ml) were added to a stirred solution of methyl 4-(2,3-dihydroxypropyl)-7-methoxy-3-benzofuranacetate (**148**) (37mg, 0.13mmol) in tetrahydrofuran (6ml). The mixture was stirred at room temperature for 30 minutes then water (3ml) was added. The mixture was partitioned with ether (3x30ml) and the combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give crude methyl 7-methoxy-4-(2-oxoethyl)-3-benzofuranacetate (an ^1H N.M.R. spectrum of this material showed a triplet at δ 9.7 indicating the formation of the aldehyde). The crude aldehyde was dissolved in toluene (60ml). Methyl E-2,4-pentadienoate (0.5g, 4.5mmol) and N-methylhydroxylamine (40mg, 0.85mmol) were added and the solution was brought to reflux. Azeotropic distillation removed water and allowed the solution volume to be reduced to approximately 20ml. The solution was maintained at reflux for 3 hours and the cold solution was concentrated *in vacuo* to give the crude product. Flash column chromatography (silica, 1:1 petrol:ether as eluent then silica, ether as eluent) gave the title compound as a mixture of diastereomers (major product 11mg, 0.03mmol, 21%, minor product 8mg, 0.02mmol, 15%). No assignment of relative stereochemistry could be made on the basis of ^1H N.M.R data.

δ_H(250MHz, solvent $CDCl_3$, reference Me_4Si) major product; 7.62 (1H,s,furan), 7.05-6.9 overlapping signals (1H,d,arom.) and (1H,d of d, alkene), 6.7 (1H,d,arom.), 6.05 (1H,d of d, alkene), 4.7 (1H,m,allylic), 3.99 (3H,s,OMe), 3.95 (1H,d) and 3.85 (1H,d) together $C\underline{H}_2CO_2Me$, 3.76 (3H,s,CO_2Me), 3.74 (3H,s,CO_2Me), 3.2 (1H,d of d,benzylic), 3.05 (1H,m,RR'CHN), 2.8 (1H,d of d,benzylic), 2.6 overlapping signals (3H,s,NCH_3) and (1H,m,isoxazolidine), 1.95 (1H,m,isoxazolidine);
minor product; 7.62 (1H,s,furan), 6.95 (1H,d,arom.), 6.9 (1H,d of d,alkene), 6.7 (1H,d,arom.), 6.0 (1H,d of d,alkene), 4.7 (1H,m,allylic), 3.99 (3H,s,OMe), 3.9 (1H,d) and 3.8 (1H,d) together $C\underline{H}_2CO_2Me$, 3.7 (6H,two s,CO_2Me, 3.2 (1H,d of d,benzylic), 3.0 (1H,m,RR'CHN), 2.9 (1H,d of d,benzylic), 2.6 (3H,s,NMe), 2.3 (1H,m) and 2.1 (1H,m) together isoxazolidine.
m/z (major product) 403 ($M^{+\cdot}$,0.36%), 275 ($M^{+\cdot}-C_6H_8O_3$,25%). 175 (36%), 170 (100%).

3-Benzenemethyl-5-(E-2-carboxymethylethenyl)-2-methylisoxazolidine (**165**) and (**166**). A mixture of freshly distilled phenylacetaldehyde (240mg, 2.0mmol), N-methylhydroxylamine (100mg, 2.1mmol) and methyl E-2,4-pentadienoate (560mg, 5mmol) in toluene (100ml) was heated to reflux for 4 hours. Water was removed from the solution by azeotropic distillation. The cold solution was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 2:1 petrol:ether as eluent) to give the title compound as a pair of diastereomers (major product 45mg, 0.17mmol, 9% and minor product 30mg, 0.11mmol, 6%) as colourless oils. Both diastereomers were contaminated with a small quantity of an impurity which appeared to be aromatic in nature. This impurity could not be visualised by tlc so the compounds were used with the impurity still present.

V_{max} (liquid film, both diastereomers showed similar spectra) 1720 (ester), 1660 (alkene), 1600, 1490 and 1450cm^{-1} (together aromatic ring);

δ_H(360MHz, solvent $CDCl_3$, reference Me_4Si) major product; 7.5-7.1 (arom.), 6.95 (1H,d J=15.6Hz of d J=5.7Hz,C<u>H</u>=$CHCO_2Me$), 6.0 (1H,d J=15.6Hz of d J=1.4Hz,CH=C<u>H</u>CO_2Me), 4.65 (1H,m,allylic), 3.75 (3H,s,OMe), 2.95 (2H,m), 2.67 (3H,s,NMe), 2.65 (1H,m), 2.55 (1H,m), 1.9 (1H,d J=12.5Hz of t J=7.3Hz);

minor product; 7.5-7.1 (arom.), 6.85 (1H,d J=15.6Hz of d J=5.8Hz,C<u>H</u>=$CHCO_2Me$), 6.05 (1H,d J=15.6Hz of d J=1.4Hz,CH=C<u>H</u>CO_2Me), 4.6 (1H,m,allylic), 3.7 (3H,s,OMe), 2.9 (2H,m), 2.7 (3H,s,NMe), 2.7 (1H,m), 2.3 (1H,m), 2.05 (1H,m)

m/z 261 (M^{+}), 230 (M^{+}-OMe), 170 (M^{+}-$PhCH_2$,100%), 91 ($PhCH_2$,29.9%).

Methyl 7-phenyl-2,4,6-heptatrienoate (**168**). A solution of 3-benzenemethyl-5-(E-2-methoxycarbonylethenyl)-2-methylisoxazolidine (187mg, a mixture of diastereomers (**165**) and (**166**) with an unidentified impurity, ca.0.76mmol), tributylphosphine (400mg, 2mmol) and 4-methylbenzoic acid (103mg, 0.76mmol) in benzene (4ml) was heated to reflux for 8 hours. The cold solution was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 4:1

petrol:ether as eluent) to give the title compound (24mg, 0.11mmol, ca.15%) m.p.96-99°C a white solid.
V_{max} (CH_2Cl_2) 1710 (ester), 1630 and 1610 (s) (alkenes), 1600, 1570, 1490 and 1430cm^{-1} (together aromatic ring);
δ_H(500 and 360MHz, solvent $CDCl_3$, reference Me_4Si) 7.5-7.2 (6H,m,aromatic ring protons and C$\underline{H}$=CHCO$_2$Me, the latter is seen at 7.38 as a d J=15.4Hz of d J=11.5Hz at 500MHz, at 360MHz each signal shows fine splitting into a further d J=0.7Hz), 6.88 (1H,d J=15.5Hz of d J=10.8Hz,C$\underline{H}$=CHPh), 6.74 (1H,d J=15.5Hz,CH=C$\underline{H}$Ph), 6.73 (1H,d J=15.0Hz of d J=10.8Hz the 360MHz spectrum shows each signal is split into a t J=0.65Hz,δ to CO$_2$Me), 6.45 (1H,d J=15.0Hz of d J=11.5Hz,γ to CO$_2$Me), 5.9 (1H,d J=15.4Hz,CH=C$\underline{H}$CO$_2$Me), 3.75 (3H,s,CO$_2$Me)
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 167.7 (ester), 144.7 (CH), 141.0 (CH), 136.9 (CH), 136.7 (q), 130.3 (CH), 128.9 (CH), 128.5 (CH), 128.0 (CH), 126.9 (CH), 120.5 (CH), 51.7 (OMe);
m/z 214 (M^+,28.3%), 155 (M^+-CO$_2$Me,100%).

Methyl 7-methoxy-4-[bis(nitromethyl)methyl]-3-benzofuranacetate (**173**). A solution of methyl 7-methoxy-4-oxomethyl-3-benzofuranacetate (**134**) (125mg, 0.5mmol), nitromethane (0.27ml, 5mmol) and potassium hydroxide (60mg, 1.1mmol) in methanol (1ml) and dichloromethane (1ml) was stirred for 18 hours at room temperature. Initially tlc (silica, CH_2Cl_2 as eluent) showed the formation of the expected β-hydroxynitro compound. As stirring was continued the loss of the aldehyde slowed and a new product, the title compound, was observed. Prolonged stirring did not cause the reaction to go to completion. A sample of the title compound was obtained by column chromatography (silica, CH_2Cl_2 as eluent) as a white solid m.p.129-130°C. This product cospotted (t.l.c.) with a product observed in the condensation of nitromethane with (**134**) using potassium fluoride as the base.
V_{max} (CH_2Cl_2) 1735 (ester), 1630, 1580 and 1510 (aromatic rings), 1560 and 1360cm^{-1} (together NO_2);
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.6 (1H,s,furan), 6.9 (1H,d J=8.3Hz,arom.), (1H,d J=8.3Hz,arom.), 4.9-4.6 (5H,m,CH(CH$_2$NO$_2$)$_2$), 4.0 (2H,s,C$\underline{H}_2$CO$_2$Me), 3.98 (3H,s,OMe), 3.7 (3H,s,CO$_2$Me);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 172.1 (ester), 146.0 (q), 145.6 (q), 144.9 (CH), 127.7 (q), 121.3 (CH), 119.5 (q), 113.2 (q), 107.0 (CH), 76.8 (CH_2NO_2), 56.2 (OMe), 52.6 (CO_2Me), 36.3 (CH), 30.4 ($\underline{C}H_2CO_2Me$);
m/z 352 (M^+,100%), 260 (M^+-2xNO_2).

Methyl 4-hydroxymethyl-7-methoxy-3-benzofuranacetate (**174**). Methyl 7-methoxy-4-oxomethyl-3-benzofuranacetate (**134**) (620mg, 2.5mmol) was dissolved in 10:1 a tetrahydrofuran:methanol mixture (15ml). The solution was cooled to 0°C and sodium borohydride (50mg, 1.4mmol) was added. The mixture was stirred for 30 minutes and was then poured into saturated ammonium chloride solution (20ml). The mixture was partitioned with dichloromethane (3x40ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (608mg, 2.43mmol, 97%), m.p.90°C a white solid.
V_{max} (CH_2Cl_2) 3600 (OH), 1740 (ester), 1630, 1590, and 1520cm^{-1} (arom. rings);
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.62 (1H,s,furan), 7.0 (1H,d J=8.1Hz,arom.), 6.7 (1H,d J=8.1Hz,arom.), 4.7 (2H,s,$C\underline{H}_2OH$), 3.96 (3H,s,OMe), 3.90 (2H,s,$C\underline{H}_2CO_2Me$), 3.7 (3H,s,CO_2Me), 2.5 (1H,s,OH);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 172.3 (ester), 145.6 (q), 145.2 (q), 143.9 (CH), 127.3 (q), 126.1 (q), 124.4 (CH), 113.7 (q), 105.8 (CH), 63.1 ($\underline{C}H_2OH$), 56.0 (OMe), 52.3 ($CO_2\underline{Me}$), 30.2 ($\underline{C}H_2CO_2Me$);
m/z 250 (M^+,100%), M^+ $C_{13}H_{14}BrO_5$ requires: 250.0841 found: 250.0836.

7-Methoxy-4-oxomethyl-3-benzofuranacetic acid (**176**). Methyl 7-methoxy-4-oxomethyl-3-benzofuranacetate (**134**) (248mg, 1mmol) was added to a stirred mixture of ethanol (1.5ml), dichloromethane (1.5ml) and potassium hydroxide (114mg, 2mmol). The mixture was stirred at ambient temperature for 30 mins. and was then added to water (20ml). The solution was concentrated *in vacuo* to remove the organic solvents and the aqueous phase thus obtained was washed with dichloromethane (1x10ml). This organic phase was discarded. The aqueous phase was acidified (dil. HCl) and

partitioned with ethyl acetate (3x20ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (200mg, 0.85mmol, 85%), m.p.180°C a white solid.
V_{max} (nujol mull) 1710 (acid), 1685cm^{-1} (ald.);
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 10.04 (1H,s,ald.), 8.1 (1H,s,furan), 7.9 (1H,d J=8.4Hz,arom.), 7.2 (1H,d J=8.4Hz,arom.), 4.13 (3H,s,OMe), 4.05 (2H,s,CH_2CO_2H), 3.5 (broad,acid);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 190.6 (ald.), 172.5 (acid), 150.0 (q), 146.9 (CH), 144.8 (q), 132.4 (CH), 127.9 (q), 124.3 (q), 115.6 (q), 106.4 (CH), 56.5 (OMe), 31.5 (CH_2CO_2H);
m/z 234 (M^+), 190 (M^+-CO_2,100%), 189 (M^+-CO_2H);
M^+ $C_{12}H_{10}O_5$ requires:234.0528 found:234.0530.

Methyl 7-hydroxy-4-oxomethyl-3-benzofuranacetate (**178**). A solution of methyl 7-methoxy-4-oxomethyl-3-benzofuranacetate (**134**) (248mg, 1mmol) and anhydrous lithium iodide (134mg, 1mmol) in dimethylformamide (5ml) was heated to reflux for 7 hours. The cooled solution was tipped into dilute hydrochloric acid (10ml) and the mixture was partitioned with dichloromethane (3x30ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 1:1 petrol:ethyl acetate as eluent) to give the starting material (127mg, 0.51mmol, 51%) and the title compound (30mg, 0.13mmol, 13%), m.p.142-144°C a white solid.
V_{max} (CH_2Cl_2) 1740 (ester), 1690cm^{-1} (ald.);
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 9.8 (1H,s,ald.), 7.66 (1H,s,furan), 7.5 (1H,d J=8.1Hz,arom.), 6.8 (1H,d J=8.1Hz,arom.), 3.97 (2H,s,CH_2CO_2Me), 3.58 (3H,s,OMe);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 189.9 (ald.), 171.3 (q,ester), 147.6 (q), 145.7 (CH), 144.6 (q), 133.0 (CH), 127.7 (q), 123.3 (q), 115.0 (q),109.7 (CH), 51.0 (OMe), 30.2 (CH_2CO_2Me);
m/z 234 (M^+,65%), 202 (M^+-MeOH,100%), 175 (M^+-CO_2Me,92%), 174 (M^+-HCO_2Me,94%).

Ethyl 7-Acetoxy-4-oxomethyl-3-benzofuranacetate (**180**). Ethane thiol (2.2ml, 2.0g, 32mmol) was added over a period of 10 mins.

to a stirred suspension of sodium hydride (1.55g, 32mmol) in dimethyl formamide (110ml). The mixture was stirred until all the sodium hydride had reacted. Ethyl 7-methoxy-4-oxomethyl-3-benzofuranacetate (**143**) (5.63g, 21.5mmol) was added and the stirred mixture was heated to reflux for 30 mins. Acetic anhydride (4.4ml, 46.6mmol) was added to the cold suspension and the mixture was stirred for 90 mins. The solution was concentrated *in vacuo* and the residue was partitioned between water (200ml) and ether (3x50ml). The combined organic phase was washed with water (1x20ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 2:1 petrol:ether as eluent) and the resulting product was recrystallised (ether, petrol) to give the title compound (3.75g, 12.9mmol, 60%), m.p.68-70°C as white flakes (Found: C, 61.73; H, 4.78. $C_{15}H_{14}O_6$ requires C, 62.07; H, 4.86%);

V_{max} (CH_2Cl_2) 1780 (AcO), 1740 (ester), 1700 (ald.), 1620 and 1580cm^{-1} together arom.;

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 10.03 (1H,s,ald.), 7.7 (1H,d J=8.1Hz,arom.), 7.68 (1H,s,furan), 7.2 (1H,d J=8.1Hz,arom.), 4.2 (2H,q J=7.1Hz,$C\underline{H}_2Me$), 2.4 (3H,s,$COC\underline{H}_3$), 1.3 (3H,t J=7.1Hz,$CH_2C\underline{H}_3$)

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 191.0 (ald.), 171.2 ($\underline{C}O_2Et$), 167.8 ($Me\underline{C}O_2$), 147.7 (q), 146.7 (CH), 140.1 (q), 131.2(CH), 129.0(q), 128.7 (q), 117.3 (CH), 115.5 (q), 60.9 ($O\underline{C}H_2Me$), 32.0 ($\underline{C}H_2CO_2Et$), 20.8 ($\underline{C}H_3CO_2$), 14.2 ($OCH_2\underline{C}H_3$)

m/z 290 (M^+), 248 ($M^+-C_2H_2O$), 202 ($M^+-CH_2CO_2Et-H$, 100%).

Ethyl 7-acetoxy-4-(E-2-nitroethenyl)-3-benzofuranacetate (**181**). Solid potassium fluoride dihydrate (35mg, 0.4mmol) was added to a stirred solution of ethyl 7-acetoxy-4-oxomethyl-3-benzofuranacetate (**180**) (0.875g, 3.01mmol) in nitromethane (2ml). The mixture was stirred at ambient temperature for 16 hours then the excess nitromethane was removed *in vacuo*. The residue was dissolved in a mixture of ether (10ml), dichloromethane (2ml) and acetic anhydride (0.5ml). 4-N,N-dimethylaminopyridine (30mg) was added and the mixture was stirred for 2 hours. Removal of the solvent *in vacuo* and flash column chromatography of the residue (silica, 1% ethyl acetate in dichloromethane as eluent) gave the title compound (0.435g, 1.3mmol, 44%) and recovery of the starting aldehyde (0.40g, 46%). A sample of the product was recrystallised (ether, petrol) to give the title compound as yellow needles m.p. 110-111°C (Found: C, 57.40; H, 4.47; N, 3.90. $C_{16}H_{15}NO_7$ requires C, 57.66; H, 4.54; N, 4.20%);

V_{max}(CH_2Cl_2) 1780 (AcO), 1740 (CO_2Et), 1620 (vinyl), 1520 (NO_2), 1350cm^{-1} (NO_2);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 8.5 (1H,d J=13.5Hz,$C\underline{H}=CHNO_2$), 7.7 (1H,s,furan), 7.5 (1H,d J=13.5Hz, $CH=C\underline{H}NO_2$), 7.4 (1H,d J=8.3Hz,arom.), 7.1 (1H,d J=8.3Hz,arom.), 4.2 (3H,q J=7.2Hz,$C\underline{H}_2Me$), 3.8 (2H,s,$C\underline{H}_2CO_2Et$), 2.4 (3H,s,$C\underline{H}_3CO_2$), 1.3 (3H,t J=7.2Hz,$OCH_2C\underline{H}_3$);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 170.2 (CO_2Et), 168.1 ($MeCO_2$), 147.0 (q), 146.0 (CH), 138.0 (q), 137.8 (CH), 135.1 (CH), 129.7 (q), 122.8 (CH), 121.6(q), 118.3 (CH), 114.0 (q), 61.7 (OCH_2Me), 30.7 ($\underline{C}H_2CO_2Et$), 20.7 ($\underline{C}H_3CO_2$), 14.0 ($CH_2\underline{C}H_3$);

m/z 333 (M^+), 291 ($M^+-C_2H_2O$, 100%).

Ethyl 7-acetoxy-4-nitroethyl-3-benzofuranacetate (**182**). Ethyl 7-acetoxy-4-(E-2-nitroethenyl)-3-benzofuranacetate (**181**) (167mg, 0.5mmol) was dissolved in a mixture of tetrahydrofuran (5ml) and acetic acid (0.14ml, 2.5mmol). The stirred solution was cooled (0°C) and sodium borohydride (76mg, 2mmol) was added in four portions over a period of 2 hours. The cold solution was stirred for a further 3 hours then water (10ml) was added. The mixture was tipped into water (10ml) and the aqueous phase was washed with dichloromethane (3x20ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 1:1 petrol: ether as eluent) to give the title compound (156mg, 0.46mmol, 92%) as a white solid. A sample of this material was recrystallised (ether:petrol) to give white flakes m.p. 86-88°C.

V_{max} (CH_2Cl_2) 1780 (AcO), 1740 (CO_2Et), 1560 and 1380cm^{-1} (together NO_2);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.61 (1H,s,furan), 7.0 (2H,s,arom.), 4.6 (2H,t J=7.9Hz,CH_2NO_2), 4.2 (2H,q J=7.2Hz,

$C\underline{H}_2Me$), 3.8 (2H,s,$C\underline{H}_2CO_2Et$), 3.6 (2H,t J=7.9Hz,$C\underline{H}_2CH_2NO_2$), 2.38 (3H,s,CH_3CO), 1.3 (3H,t J=7.2Hz,$CH_2C\underline{H}_3$);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 170.8 (CO_2Et), 168.6 ($MeCO_2$), 147.1 (q), 144.8 (CH), 135.1 (q), 128.0 (q), 126.6 (q), 124.0 (CH), 117.9 (CH), 113.5 (q), 75.7 (CH_2NO_2), 61.6 (OCH_2Me), 30.7 ($\underline{C}H_2CO_2Et$), 29.6 ($\underline{C}H_2CH_2NO_2$), 20.8 ($\underline{C}H_3CO$), 14.2 ($OCH_2\underline{C}H_3$);
m/z 335 (M^+), 293 ($M^+-C_2H_2O$), 246 (100%).

Methyl 4-[5-(2-methoxycarbonylethyl)-3-isoxazolemethyl]-7-methoxy-3-benzofuranacetate (**189**). A solution of methyl 4-[4,5-dihydro-5-(E-2-methoxycarbonylethenyl)-3-isoxazolemethyl]-7-methoxy-3-benzofuranacetate (**141**) (120mg, 0.3mmol), tetrakis(triphenylphosphine)palladium(0) (35mg, 0.03mmol), potassium carbonate (76mg, 0.55mmol) and triethylamine (0.1ml, 0.72mmol) in tetrahydrofuran (10ml) were heated to reflux for 5 days. By the end ofths period virtually all the solvent had been lost. The residue was dissolved in dichloromethane (10ml) and filtered. The filtrate was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, 1:1 petrol:ether as eluent) to give the title compound (50mg, 0.125mmol, 41.7%) m.p.55-58°C a white solid.
V_{max} (CH_2Cl_2) 1735 (esters), 1630, 1600, 1580 and 1510cm^{-1} (together aromatic rings);
δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.6 (1H,s,furan), 7.0 (1H,d J=8.1Hz,arom.), 6.75 (1H,d J=8.1Hz,arom.), 5.7 (1H,s,isoxazole), 4.2 (2H,s,benzylic), 3.98 (3H,s,OMe), 3.82 (2H,s,$C\underline{H}_2CO_2Me$), 3.71 (3H,s,CO_2Me), 3.63 (3H,s,CO_2Me), 3.0 (2H,t J=7.5Hz,CH_2), 2.7 (2H,t J=7.5Hz,CH_2);
δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 172.2 (q), 171.7 (q) and 171.5 (q) (two esters and one other C), 163.7 (q), 145.3 (q), 144.9 (q), 144.0 (CH), 127.4 (q), 124.8 (CH), 122.5 (q), 113.6 (q), 106.4 (CH), 101.3 (CH,isoxazole), 56.1 (OMe), 52.3 (CO_2Me), 52.0 (CO_2Me), 31.5 (CH_2), 30.5 (CH_2), 29.2 (CH_2), 22.2 (CH_2);
m/z 387 (M^+,100%), 328 (M^+-CO_2Me,50.7%), 233 ($M^+-C_7H_8NO_3$,54.3%), 175 (68.7%).

Methyl 4-(E,E-6-methoxycarbonyl-2-oxo-3,5-hexadienyl)-7-methoxy-3-benzofuranacetate (**190**). A stirred solution of methyl 4-[4,5-

dihydro-5-(E-2-methoxycarbonylethenyl)-3-isoxazolemethyl]-7-methoxy-3-benzofuranacetate (**141**) (1.75g, 4.53mmol) in dimethyl sulphate (0.55ml, 5.8mmol) was heated to 50°C for 6 hours. The cold mixture was dissolved in dichloromethane (10ml) and this solution was cooled to 0°C. A solution of sodium nitrite (320mg, 4.64mmol) in water (10ml) was added and the resulting mixture was stirred vigorously for 15 minutes. The mixture was partitioned and the aqueous phase was washed with dichloromethane (3x20ml). The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude product. The residue was dissolved in dichloromethane (30ml) and this solution was cooled to 0°C. Triethylamine (1.2ml, 8.6mmol) was added and the solution was stirred for 3 hours. The solution was allowed to warm to room temperature during this period. The mixture was concentrated *in vacuo* to give the crude product. This was subjected to flash column chromatography (silica, ether:petrol 2:1 as eluent, the mix was loaded onto the column as a dichloromethane solution) to give the title compound which precipitated from the chromatography solvent as pale yellow needles. The solid product was collected by filtration, the filtrate was concentrated and the residue was rechromatographed to give the title compound as before (total 0.822g, 2.2mmol, 49%) m.p.117°C (C, 63.67; H, 5.29. $C_{20}H_{20}O_7$ requires C, 64.51; H, 5.41%);

V_{max} (CH_2Cl_2) 1740 (sh) and 1720 (esters), 1690 (ketone), 1630 (alkenes), 1600 and 1510cm^{-1} (together aromatic ring);

δ_H(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.6 (1H,s,furan), 7.2 (2H,m,alkenes), 6.9 (1H,d J=8.1Hz,arom.), 6.7 (1H,d J=8.1Hz,arom.), 6.5 (1H,d J=14.5Hz of m) and 6.2 (1H,d J=14.3Hz of m) (together alkenes α to carbonyls), 4.1 (2H,s,benzylic), 3.98 (3H,s,OMe), 3.76 (3H,s,CO_2Me), 3.73 (2H,s,$C\underline{H}_2CO_2Me$), 3.69 (3H,s,CO_2Me);

δ_C(67.5MHz, solvent $CDCl_3$, reference Me_4Si) 197.4 (C=O), 171.6 (CO_2Me), 166.3 (CO_2Me), 145.3 (q), 145.1 (q), 144.1 (CH), 141.4 (CH), 139.1 (CH), 134.1 (CH), 128.9 (CH), 127.8 (q), 125.8 (CH), 118.9 (q), 113.5 (q), 106.6 (CH), 56.1 (OMe), 52.3 (CO_2Me), 52.0 (CO_2Me), 45.6 (CH_2,benzylic), 30.3 ($\underline{C}H_2CO_2Me$);

m/z 372 (M^+,15%), 233 ($M^+-C_7H_7O_3$,100%), 175 (24.6%).

The Thermolysis of Methyl 4-(E,E-6-methoxycarbonyl-2-hydroxyimino-3,5-hexadienyl)-7-methoxy-3-benzofuranacetate. A solution of methyl 4-(E,E-6-methoxycarbonyl-2-hydroxyimino-3,5-hexadienyl)-7-methoxy-3-benzofuranacetate (**81**) and its geometrical isomer (25mg, 0.06mmol) in toluene (2.5ml) was heated to 250°C in a sealed tube for 20 hours. None of the desired intramolecular Diels Alder reaction was observed. The only compound to be isolated and characterised was a 4-substituted methyl 7-methoxy-3-benzofuranacetate (5mg, 0.014mmol). The substituent at the 4-position was identified as a methoxycarbonyl substituted pyridinemethyl group. The splitting pattern for the aromatic protons of this grouping showed that the three CHs' were contiguous. This suggested that the product was a 2,3 (**192**) or a 2,6 (**191**) disubstituted pyridine. The spectral data could not be used to distinguish between these two possible products. δH(270MHz, solvent $CDCl_3$, reference Me_4Si) 7.95 (1H,d J=7.5Hz of d J=0.8Hz,pyridine), 7.66 (1H,t J=7.7Hz,pyridine), 7.62 1H,s,furan), 7.07 (1H,d J=7.9Hz of d J=0.8Hz, pyridine), 6.95 1H,d J=8.1Hz) and 6.75 (1H,d J=7.9Hz) (together benzene ring protons), 4.5 (2H,s,CH_2 at the 4-position on the benzofuran ring), 4.02 (3H,s,OMe), 3.99 (3H,s,OMe), 3.8 (2H,d J=1.15Hz, CH_2CO_2Me), 3.6 (3H,s,CO_2Me);
m/z 369 (M^+,100%), 337 (M^+-MeOH,57%), 309 (M^+-HCO_2Me,64%), 294 (M^+-CO_2Me-Me-H,87%), 175 (30%).

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