

Some Novel Reactions Of Cyclic Sulphones.

A Thesis Presented by

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Abstract

This thesis is divided into three chapters.

The first chapter is comprised of two sections. In the first of these an introduction to the trichothecene family of fungal metabolites is described. Selected reports concerning the biosynthesis, structure-activity relationships and total synthesis of the simple trichothecenes are discussed. In the second section two synthetic approaches toward ($\pm$)-trichodiene, an important biosynthetic precursor to the trichothecenes are described. The first approach employs a bicyclo[3.3.0]sulphone as the key intermediate, whilst the second utilises a bicyclo[4.3.0]sulphone in a similar rôle. Both of these intermediates are derived from a novel cyclic sulphone-enone isoprenoid building block, and the potential of this compound toward terpene synthesis is explored.

The second chapter is also divided into two sections. The first of these gives an introduction to the synthesis, properties and reactions of thiophene-1,1-dioxides, using selected examples from the literature. The second section describes attempts to exploit the reactive nature of thiophene-1,1-dioxides in a methodology directed towards the one step formation of multiple carbon-carbon bonds. Several approaches toward the generation and intramolecular trapping of appropriate thiophene-1,1-dioxides are described; a thiophene oxidation process proving most promising. On a similar line, the chemistry and electrochemical properties of η_4 -(3,4-dimethylthiophene)-1,1-dioxidetricarbonyliron are also described.

Chapter three provides a formal description of experimental results and procedures.

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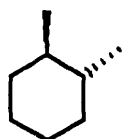
Abbreviations

Ac	Acetyl
AIBN	α,α' -Azoisobutyronitrile
Ar	Aromatic
Bn	Benzyl
Bz	Benzoyl
b	Broad
bpt.	Boiling point
Δ	Heat
DDO	Dimethyldioxirane
d	double
DCM	Dichloromethane
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
DPMS	Diphenylmethylsilyl
EtOAc	Ethyl Acetate
Ether	Diethyl ether
h ν	Light
HMPA	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m-CPBA	meta-Chloroperbenzoic acid

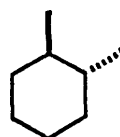
MoOPH	Oxidiperoxymolybdenum(pyridine)hexamethylphosphoramidate
mpt.	Melting point
Me	Methyl
MeM	Methoxymethyl
Ms	Methanesulphonyl
NBS	N-Bromosuccinimide
nmr	Nuclear magnetic resonance
OPP	Pyrophosphate
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl
PPTS	Pyridinium p-toluenesulphonate
q	Quartet
s	Singlet
t	Triplet
TBDMS	tertiarybutyldimethylsilyl
Tf	Trifluoromethanesulphonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
tlc	Thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	p-Toluenesulphonyl

Stereochemical Notation and Numbering.

Throughout this thesis, the graphical representation of stereochemistry is in accord with the conventions proposed by Maehr.¹³⁶ Thus, solid and broken wedges denote absolute configuration and solid and broken lines denote racemates. For the former, greater narrowing of both solid and broken wedges indicates increasing distance from the viewer.

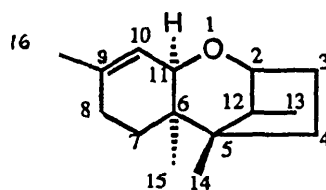


single enantiomer



racemic

In Chapter One compounds adopt the systematic (IUPAC) numbering system unless close analogy to the trichothecene basic skeleton exists, in which case the natural product numbering is applied. This numbering system is indicated below.



In Chapters 2 and 3 systematic (IUPAC) numbering is used throughout.

Chapter One

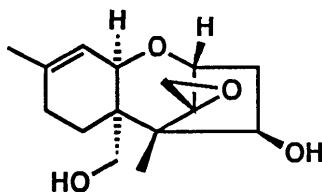
Synthetic Approaches Toward (±)-Trichodiene

1.1 Introduction.

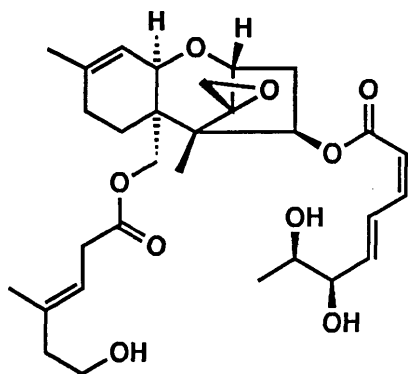
1.1.1 Background

The trichothecenes are a series of secondary metabolites produced by various members of the *Fungi Imperfecti* family of ground moulds. These compounds display a diverse spectrum of biological activity, ranging through antifungal, antiviral and antibacterial to antitumour properties. It is this latter aspect, combined with their high degree of cytotoxicity that makes these compounds attractive synthetic targets. It is not surprising therefore, that these compounds have been the subject of intense biological study and several total syntheses¹ of various trichothecenes have been reported. A general review of all the literature concerning trichothecenes is far beyond the scope of this dissertation, which aims to give a general outline of the properties and reported synthesis of trichothecenes using selected examples from the literature.

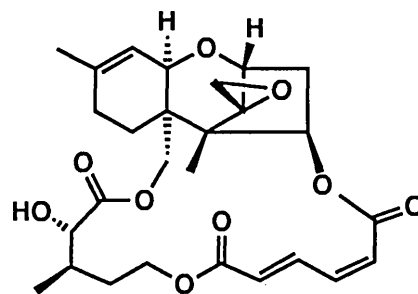
The trichothecenes also display profound toxicity toward mammalian systems, which limits their potential as therapeutic agents. For example, deoxynivalenol (vomitoxin) (1) has been identified as the 'vomiting factor' in farm animals when fed *fusarium* infected mouldy corn;² diacetoxyscirpenol (2) and deoxynivalenol (1) occur in feedstuffs implicated in the mycotoxicosis of swine³ and cattle,⁴ whilst T-2 toxin (3) is produced by *F. Poae* and *F. Spiarotrichioides* isolated from over wintered cereal associated with alimentary toxic aleukia in the USSR.⁵ Even more indicative of the potent toxicity of these compounds is the report that T-2 toxin (3) and diacetoxyscirpenol (2) are the active 'ingredients' of yellow rain, a deadly concoction reportedly used in chemical warfare in South East Asia.⁶ (Figure 1)



(4)



(5)

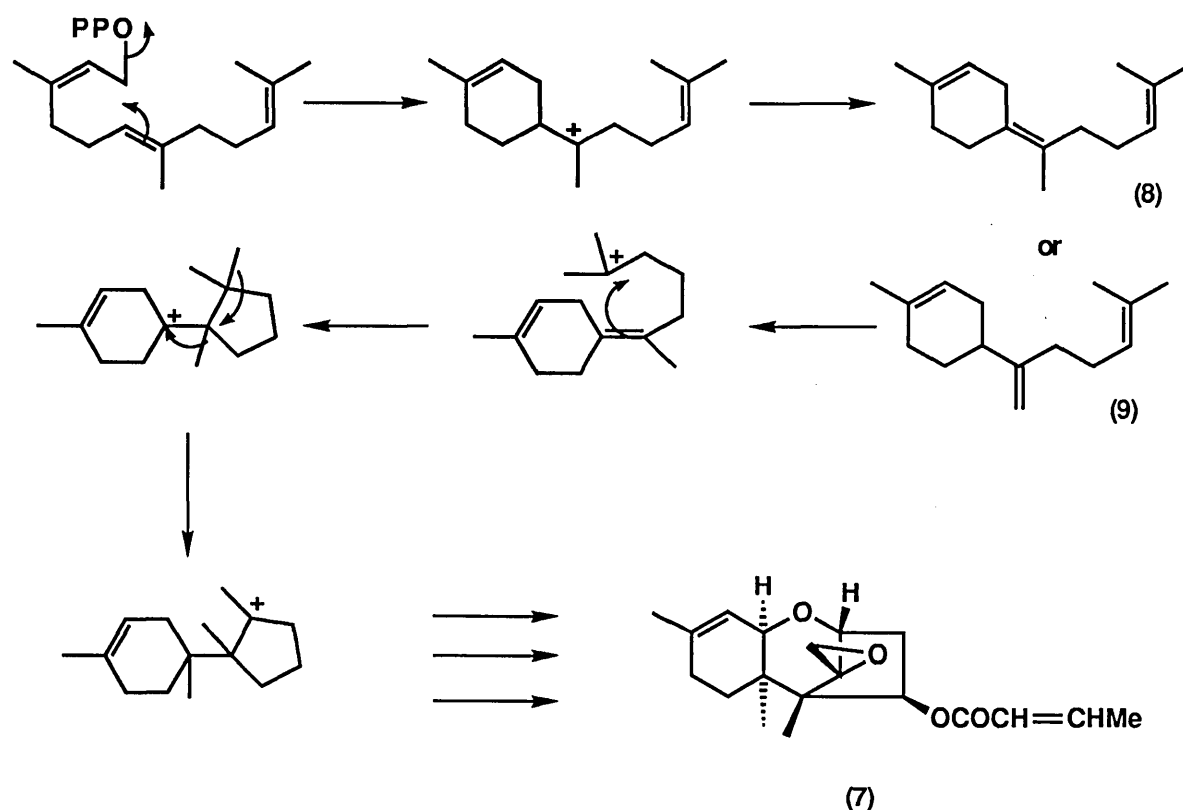


(6)

figure 2

1.1.2 Biosynthesis of the Trichothecene Nucleus.

Early work⁷ involving feeding experiments using [2-¹⁴C] mevalonate clearly indicated that the trichothecene nucleus of trichothecin (7) was sesquiterpenoid in nature, three mole equivalents of [2-¹⁴C] mevalonate being incorporated. Unfortunately, at the time this work was carried out the proposed structure of trichothecin was incorrect, thus degradative studies to ascertain the labelling pattern were in vain. A reinterpretation of these results⁸ on the basis of the correct structure led to the conclusion that C-2 of mevalonate translated to C-4, C-10 and C-14 of basic trichothecene skeleton. This labelling pattern also strongly suggested that a double 1,2 methyl shift occurred during biosynthesis, a result further validated by Dawkins,⁹ whose studies led to the formulation of the biosynthetic route shown in scheme 1; the key intermediate being either a γ or β bisabolene, (8) or (9) respectively.



Scheme 1

Cyclisation of *Z,E*-farnesyl pyrophosphate and subsequent deprotonation would lead to the formation of a bisabolene intermediate (8) or (9). Cyclisation and two 1,2-methyl shifts would then give the trichothecene hydrocarbon skeleton, which could then be selectively oxygenated and cyclised to yield trichothecin (7).

Two interesting factors arise from this proposed mechanism:

- i. The starting alicyclic sesquiterpene has a *Z*-double bond, so a *E* to *Z* isomerisation of *E,E*-farnesyl pyrophosphate must occur at some stage prior to cyclisation.
- ii. 'A' ring rearrangement must occur to establish the correct labelling position.

Further studies upon biosynthesis of the basic trichothecene skeleton have been carried out. Tamm,¹⁰ investigating the initially conceived idea that C-2 in mevalonate leads to incorporation at C-10 in the trichothecene skeleton, found that this observation was erroneous, and demonstrated that C-8 was in fact involved, thus

lending further support to the proposed biosynthetic route.

Hanson, however, revised this route by the use of double labelling experiments, and suggested an alternative pathway.¹¹ By the use of various tritium and ^{14}C labelled mevalonate pyrophosphates of known tritium to ^{14}C ratios, it was possible to ascertain the positions of these tritium labels and the number of labels lost during biosynthesis. The experiments consisted of feeding experiments utilising *Trichoderma spirulosum* and *Trichothecum Roseum* with $[2\text{-}^3\text{H}, 2\text{-}^{14}\text{C}]$, $(4R)$ $[4\text{-}^3\text{H}, 2\text{-}^{14}\text{C}]$ and $[5\text{-}^3\text{H}_2, 2\text{-}^{14}\text{C}]$ mevalonic acids, and also with $[2\text{-}^3\text{H}, 2\text{-}^{14}\text{C}]$ geranyl pyrophosphate. From the study of the labelling patterns in the isolated trichothecenes, it was concluded that:

i. From the number of $[2\text{-}^3\text{H}_2]$ mevalonate labels incorporated in trichodermol, and the $(4R)$ $[4\text{-}^3\text{H}]$ labelling pattern the initial farnesyl chain folds in manner (a) rather than (b) in figure 3, these observations being further substantiated by the work of Tamm.¹⁰

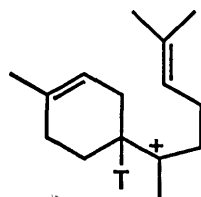


figure 3

ii. The absence of a $[2\text{-}^3\text{H}]$ mevalonoid label in the final spiro epoxide group showed that the initial methyl groups in farnesyl pyrophosphate retain their individuality during the biosynthetic pathway.

iii. The incorporation of a $[2\text{-}^3\text{H}]$ geranyl pyrophosphate indicated that the 4-pro-R mevalonoid hydrogen atom is retained. This was an important observation since

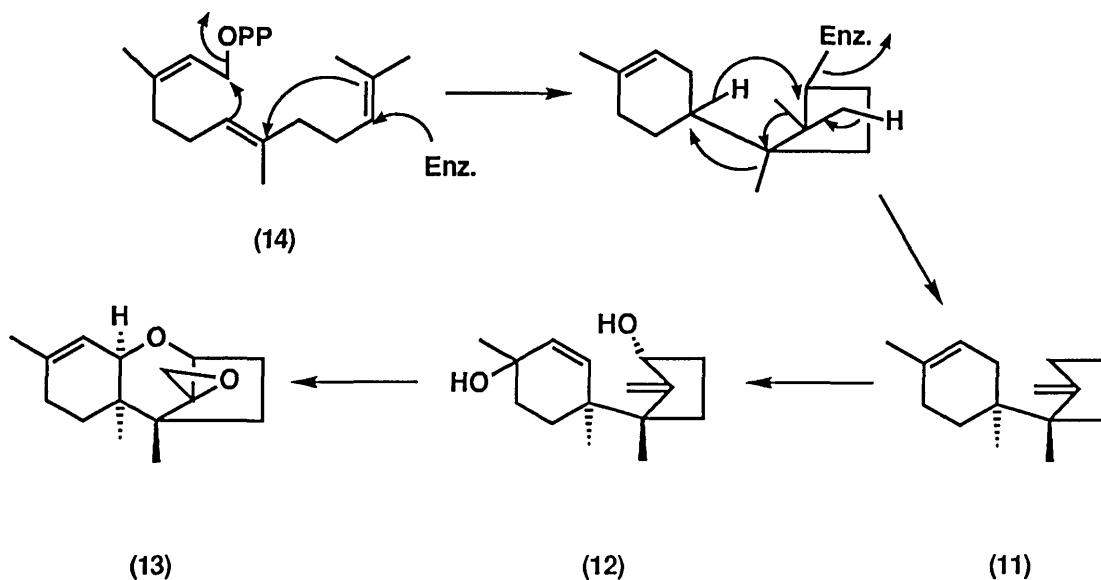
it discredits the intermediacy of a γ -bisabolene. Since the precursor to a γ -bisabolene intermediate would be the bisabolyl cationic species (10) in figure 4, formation of a γ -bisabolene by deprotonation would involve loss of tritium label, which was not the case.



(10)

figure 4

Degradation studies showed that the 4-pro-*R* mevalonoid hydrogen atom becomes the C-10 and C-2 hydrogen atoms in trichothecin (7), and this indicates that a hydride shift occurs at some stage during biosynthesis. As the C-10 hydrogen atom is derived from the terminal isoprenoid unit in farnesyl pyrophosphate, hydride transfer must occur between C-6 and C-2 of trichothecin (7) during biosynthesis. These results led to a revision of the previously proposed pathway to that shown in scheme 2.



scheme 2

Cyclisation occurs in concerted fashion, being initiated by enzymic attack at C-10 of *Z,E*-farnesyl pyrophosphate (14). Subsequent hydride transfer, two 1,2-methyl shifts and dissociation of the enzyme leads to trichodiene (11) a key intermediate in the pathway. Oxygenation of trichodiene then gives trichodiol (12) which can cyclise in an intramolecular S_N2' displacement reaction to give 12,13-epoxytrichothec-9-ene (13), the basic natural product skeleton. This compound is then capable of further biosynthetic elaboration to the diverse range of trichothecenes already isolated.

Since this pathway was first suggested, trichodiene (11), trichodiol (12) and 12,13-epoxytrichothec-9-ene (13)^{12,13,14} have all been isolated as minor metabolites from *Trichothecium Roseum*. Furthermore, tritium labelled trichodiene was prepared and administered to a culture of *Trichothecium Roseum*,¹⁵ where incorporation in trichothecin (7), as well as the other two minor metabolites, was observed.

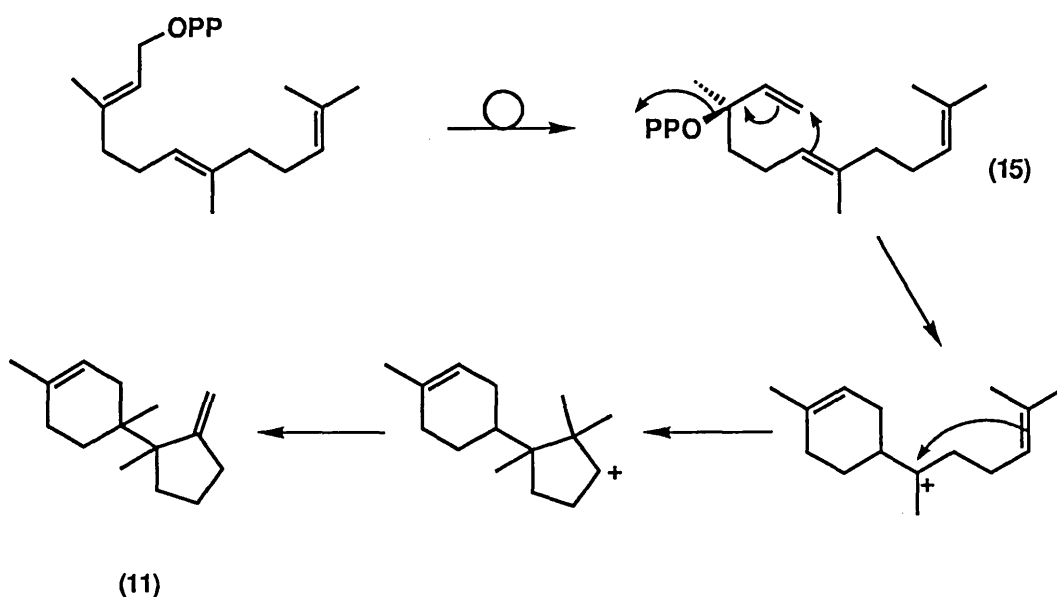
Therefore, trichodiene (11) may be considered a biosynthetic precursor of trichodiol (12), 12,13-epoxytrichothec-9-ene (13) and trichothecin (7). These observations were further validated by Hanson¹⁶ in 1976, again by the use of labelled trichodiene.

The intermediacy of γ -bisabolene (8) and β -bisabolene (9) has also been totally disproved, tritium incorporation of labelled γ - and β -bisabolenes into trichothecin (7) by *Trichothecium Roseum* being very low and non specific.²¹

Extensive studies have also been carried out upon the initial *E* to *Z* isomerisation of farnesyl pyrophosphate prior to cyclisation. Further details of the mechanism of this transformation were obtained by the incubation of several specifically labelled farnesyl pyrophosphates.²² The introduction of *E,E*-[4,8,12-¹⁴C₃] farnesyl pyrophosphate to *Trichothecium Roseum* gave trichodiene containing three tritium labels, clearly showing that the initial biosynthetic starting point was farnesyl pyrophosphate. Incubation of doubly labelled [1,5,9-³H₆, 4,8,12-¹⁴C₃]

farnesyl pyrophosphate was reported to give all *E,E*-farnesol containing 6 labels along with *Z,E*-farnesol and trichodiene (11) containing five. Thus, it appeared that the farnesyl isomerisation occurred *via* loss of one hydrogen atom. Further work indicated this hydrogen to be the pro-1(*S*)-hydrogen atom of *E,E*-farnesyl pyrophosphate,

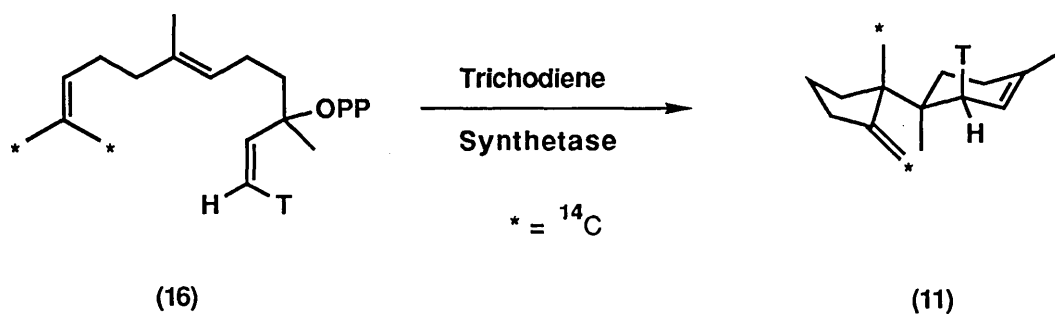
However, more recently the results of Cane *et al.*²³ have contradicted this earlier work. From incubation studies upon *E,E*-[1-³H₂, 12, 13-¹⁴C] farnesyl pyrophosphate, they came to the conclusion that both the C-1 hydrogen atoms were retained during the biosynthetic pathway, and postulated isomeric nerolidyl pyrophosphate (15) as the final acyclic intermediate during the biosynthesis of trichodiene (11). (Scheme 3).



scheme 3

Isomerisation occurs *via* a π -allyl cationic intermediate to give nerolidyl pyrophosphate (15). Consequent cyclisation generates a bisabolyl cation which can then undergo the previously described hydride and methyl shifts to give trichodiene

(11). This pathway was further validated by labelling studies²⁴ involving *Z,E*-[1-³H, 12, 13-¹⁴C] nerolidyl pyrophosphate (16) which gave trichodiene (11) labelled exclusively in the 11-β position. (Scheme 4). Scheme 3 thus represents the currently accepted biosynthetic transformation of *E,E*-farnesyl pyrophosphate to trichodiene (11).



scheme 4

The intimate details of the post-trichodiene stages of the biosynthesis of trichothecenes are still in some doubt. As already mentioned, trichodiol (12) and 12,13-epoxytrichothec-9-ene (13) have been observed to be minor metabolites present in trichothecene producing fungi, but their actual positions upon to biosynthetic pathway are as yet undetermined. The isolation of verrucarin K (17)¹⁷ and deoxytrichodermadiene (18)¹⁸ seems to suggest that epoxidation of the 12–13 double bond is not an immediate post-trichodiene step. Also, the recent isolation of isotrichodiol (19)¹⁹ from *Fusarium Calmorum* and related compounds 11-α-hydroxytrichodiene (20) and triol (21) from *Fusarium sporotrichioides*²⁰ (figure 5) suggests that metabolic 'grids', i.e. a combination of several not just one pathway, are operating in the post-trichodiene stages.

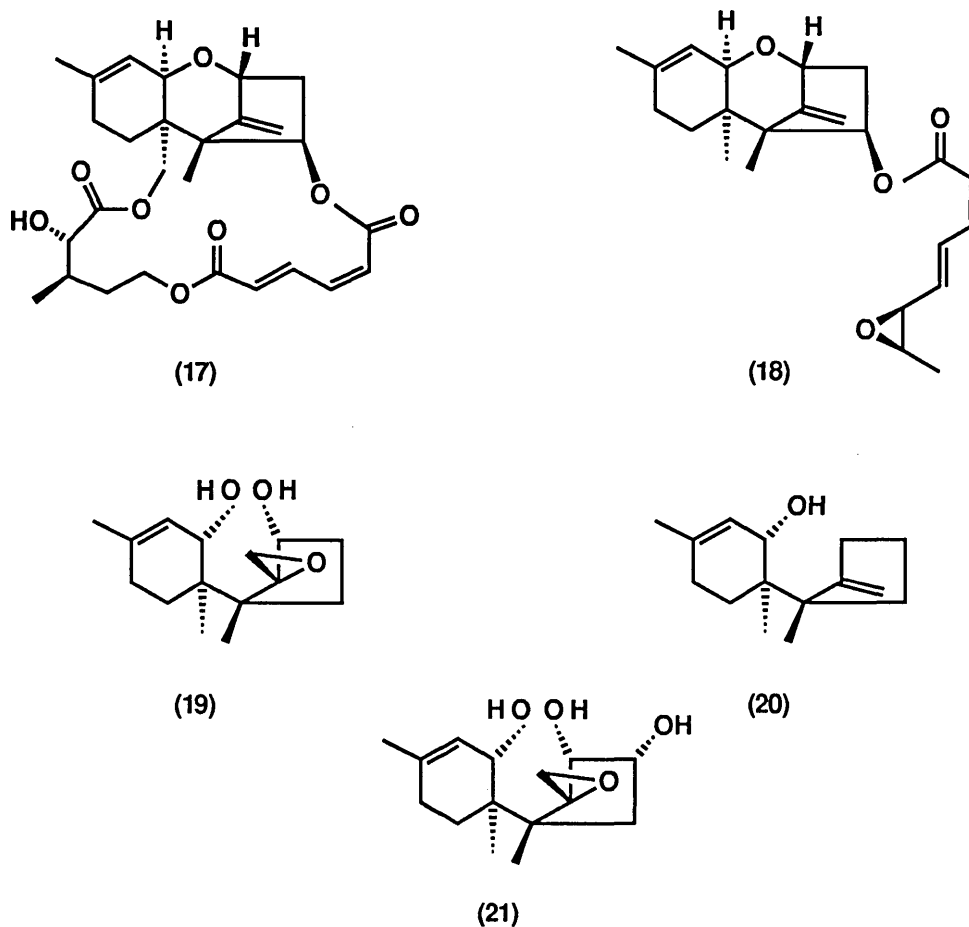


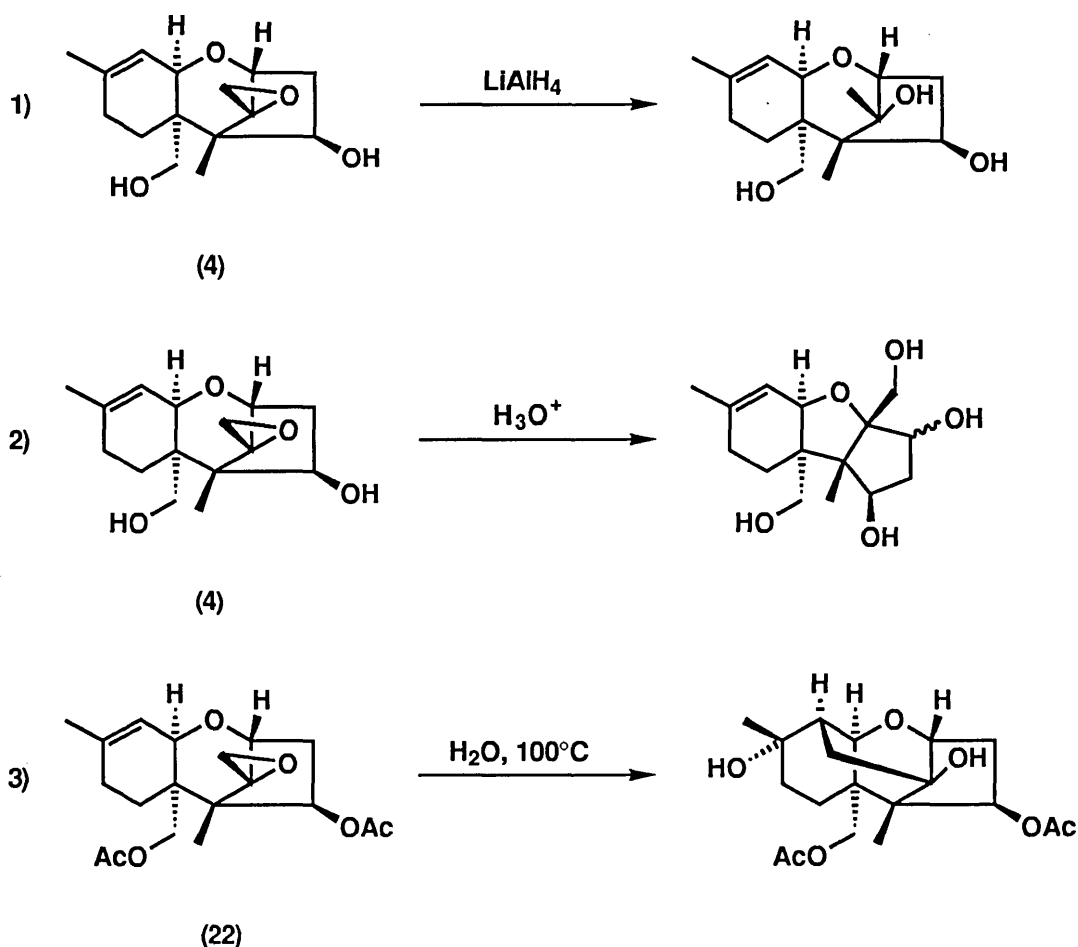
figure 5

1.1.3 Structure-Activity Relationships.

The remarkable bioactivity of trichothecenes arises from their ability to inhibit protein and / or DNA biosynthesis. The stage at which inhibition occurs is generally dependent on the size of the trichothecene; the larger (macrocyclic) trichothecenes tend to suppress biosynthesis at the initial stages, whilst the smaller ones affect the termination stages. Although the actual details of the inhibition process are still unclear, the rôle of the central 12,13-spiroepoxide group is often considered to be important. However, it is not vital, as verrucarin K (17) does show marked bioactivity, but generally loss of the spiroepoxide group reduces activity.²⁵

The epoxide group is known to be a trigger of chemical reactivity in three distinct ways,²⁶ as illustrated in scheme 5 by reactions of verrucarol (4) and verrucaroldiacetate (22): viz.

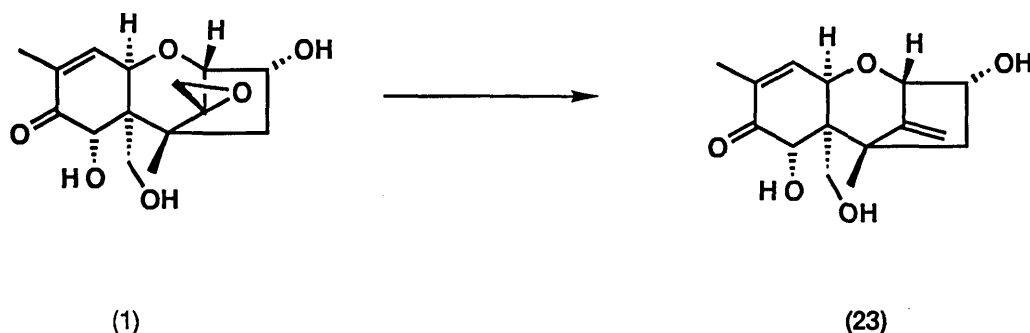
1. Attack at C-13
2. Rearrangement to the apotrichothecene skeleton
3. Participation of the 9,10 double bond.



scheme 5

Evidence exists for all three modes of reactivity participating in biochemical transformations. Although the 12,13 epoxide moiety is known to be quite sterically shielded towards external nucleophiles,²⁷ studies have shown that the predominant transformation of deoxynivalenol (1) is the deoxygenation of the spiroepoxide

group,²⁸ to form the 9,12-diene (23). This observation indicates that the key to biological activity is the ability of the epoxide group to act as an electrophile. (Scheme 6)



scheme 6

A variant of this theory is a mechanism involving apotrichothecene rearrangement; (ii) in scheme 5. The rearrangement of the basic trichothecene skeleton upon treatment with acid is well documented,²⁶ and involves protonation of the epoxide oxygen atom, followed by attack by the tetrahydropyranyl oxygen atom at C-12. Nucleophilic capture at C-2 then leads to the apotrichothecene skeleton, which may prove to be the vital step for biological activity. Further evidence connecting apotrichothecene rearrangement and bioactivity is found in the strict stereochemical requirements of the epoxide group that are necessary for biological activity. Screening studies against P388 leukemia involving the stereoisomeric dimethyltetrahydropyranylspiroepoxide model compounds (24) and (25), found that compound (24), possessing the 'correct' stereochemistry at the spiro-centre, showed greater activity. (figure 6).



figure 6

However, it is worth noting that trichotriol (26) (figure 7) has recently been isolated from *Fusarium sporotrichiodes*³⁴ and shows similar toxicity to T-2 toxin, although it is incapable of apotrichothecene rearrangement. This then suggests that toxicity and apotrichothecene rearrangement are not related.

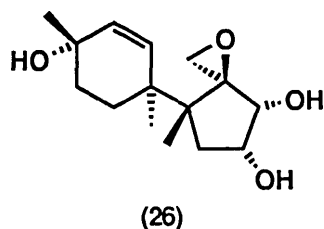


figure 7

Although there is strong evidence both for and against apotrichothecene rearrangement being a contributory factor in the bioactivity of the trichothecenes, the C9-C10 double bond does also appear to play a rôle in biological activity. For example, simple hydrogenation of the C9-C10 double bond to give the saturated A-ring derivative greatly reduces the activity,³⁰ although this effect may be on account of conformational changes in the tetrahydropyran B ring disfavoured by the aforementioned apotrichothecene rearrangement pathway. Intramolecular participation by the C9-C10 double bond in reactions of the C12-C13 epoxide group is known. Thus, when verrucarol diacetate (22) is heated to reflux in water at reflux (*cf.* pathway (iii) in scheme 5) reaction clearly occurs *via* intramolecular attack on the epoxide group. Epoxidation of the 9,10-double bond on the β -face generally improves biological

activity,³¹ and it is interesting to note that only one fungal metabolite,³² roritoxin C (27) (figure 8) and the plant derived baccarinoids³³ have an A ring 9,10- β -epoxide. All of these metabolites show very high toxicity and antileukæmic properties.

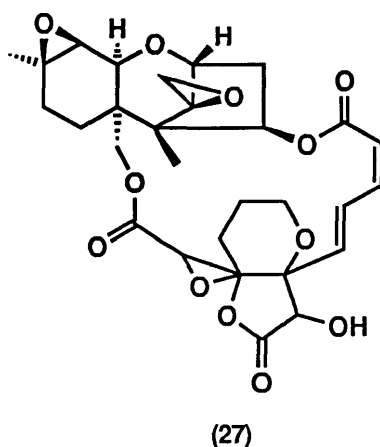


figure 8

As can be seen from the above summary, the structure-activity relationships of the basic trichothecene nucleus are particularly challenging to unravel. An additional twist in this already complex tale is in the structure activity relationships associated with the complex and macrocyclic esters, as subtle changes in the nature of the unsaturated chains in these higher metabolites also greatly affects their biological activity. Much further work is necessary in order to ascertain the key structural elements of the trichothecenes with regard to their bioactivity, so that production of analogues with 'tuned' bioactivity will be possible, thus enabling the elusive goal of using these compounds as effective therapeutic agents to be realised.

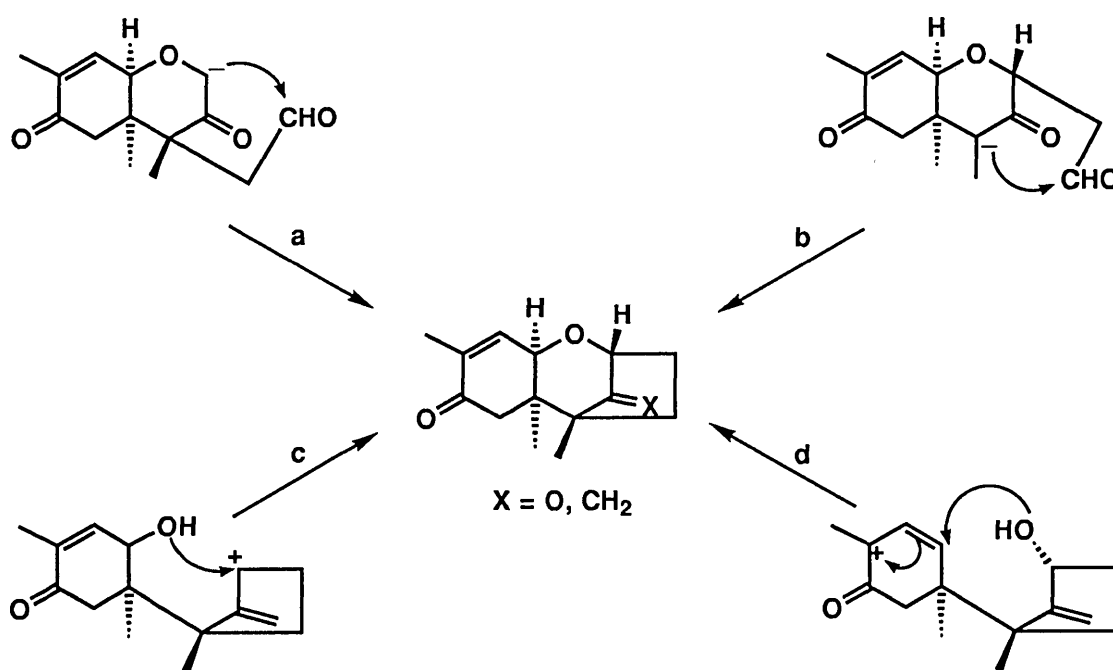
1.1.4 Synthesis of the central Trichothecene Nucleus.

.As reviews of both the biosynthesis³⁵ and synthesis³⁶ of the macrocyclic trichothecenes are available, attention will again be focused upon aspects relating to the

construction of the trichothecene nucleus

Synthetic approaches towards the trichothecenes have been extremely diverse in their conception. However, the selection and mode involved in the closure of the final ring provides an appropriate means of classifying the literature. Two main synthetic routes have been utilised, as first recognised by McDougal *et al.*³⁷ viz.

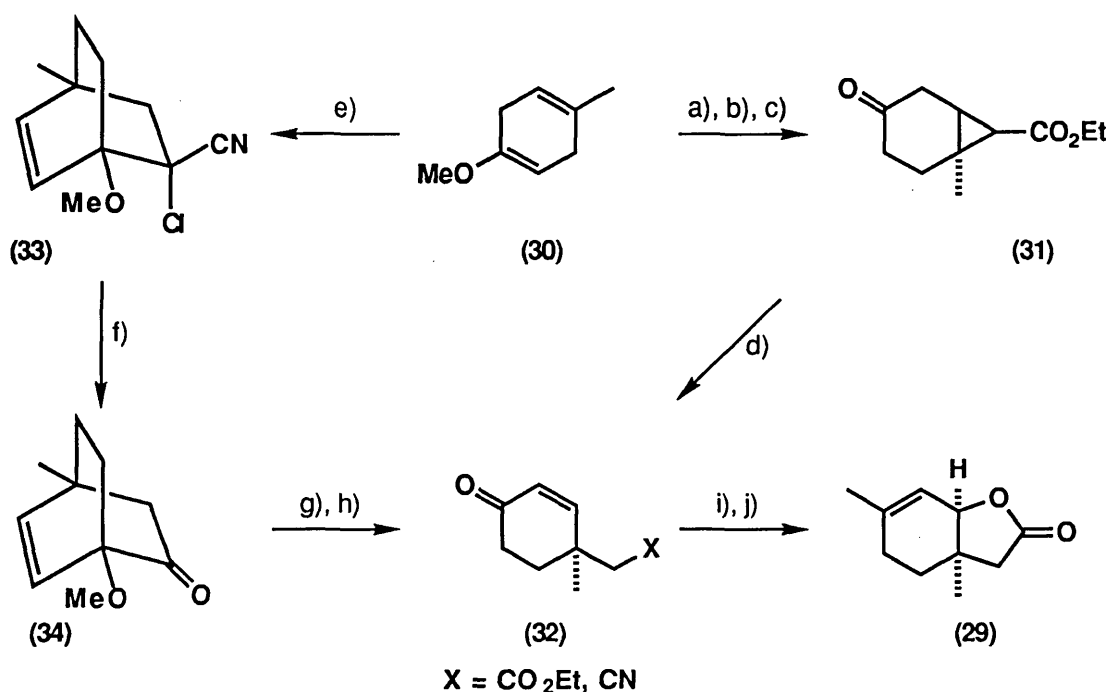
1. Aldol ring closure: path a,b, scheme 7
2. Biomimetic ring closure: path c,d: scheme 7



scheme 7

Whereas in the aldol and related approaches final ring closure takes place between C-2 and C-3 or C-4 and C-5 of a suitably functionalised C ring precursor (a,b in scheme 7), the biomimetic approach uses an oxygenated trichodiene derivative as the precursor (c,d in scheme 7).

The first synthesis of a trichothecene, trichodermin (28) was reported by Raphael *et al.* in 1973.^{1a} The key intermediate in the synthesis was the cis-fused γ -lactone (29), which was available from two independent routes, as shown in scheme 8.



a) MeOH, H₃O⁺, b) EtO₂CCHN₂, c) H₃O⁺, acetone d) NaOAc, AcOH,
 e) α -chloroacrylonitrile, f) Na₂S, H₂O, g) NH₃OH⁺Cl⁻, NaOAc, h) NaH, TsCl,
 i) MeMgCl, j) NaOH or HCl, MeOH.

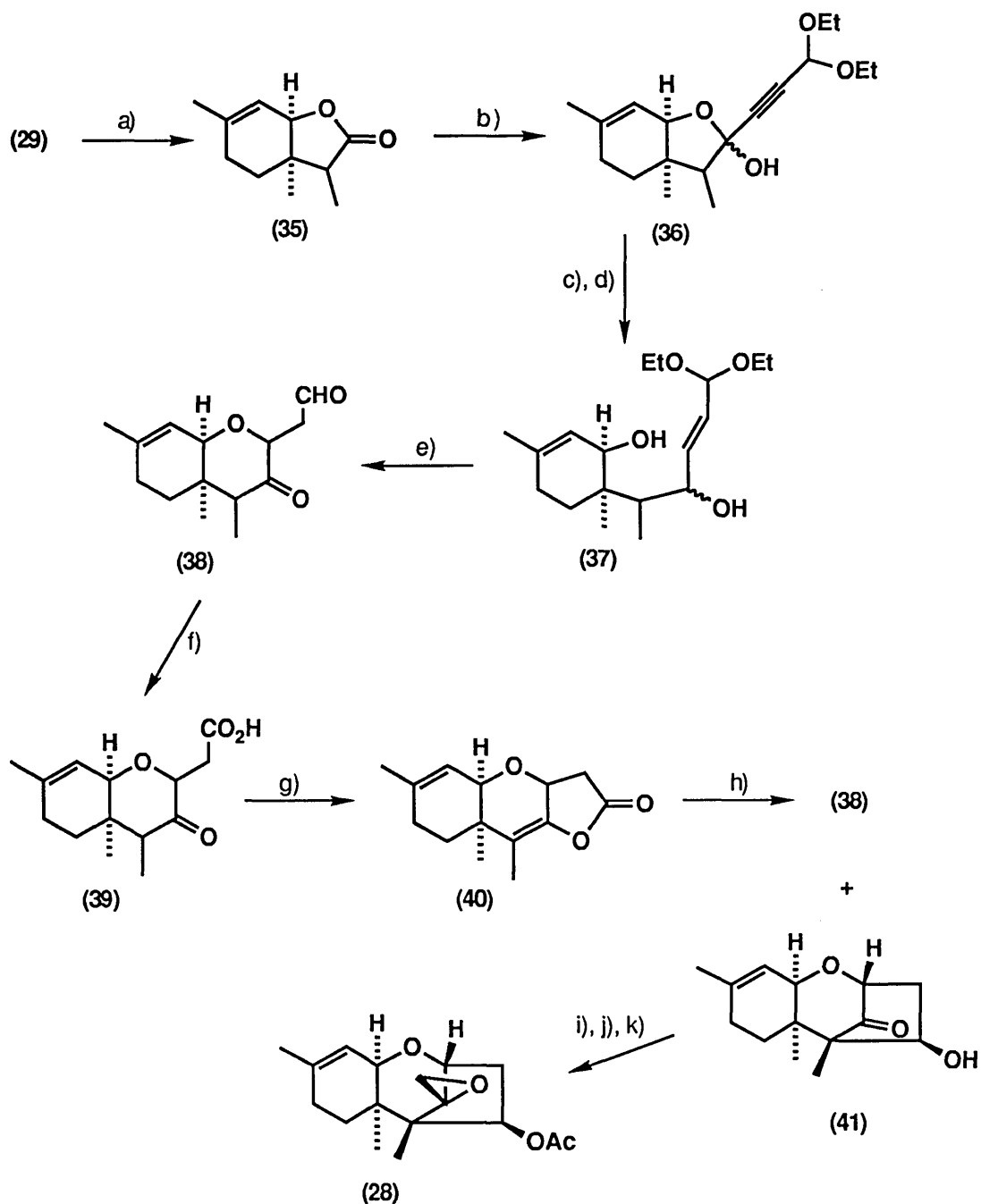
scheme 8

The starting point for both syntheses is the cyclohexadiene (30), obtained by Birch reduction of *para*-methoxytoluene. In the first, acid catalysed addition of methanol to the double bond of (30) gave the dimethyl ketal, subsequent treatment of which with ethyl diazoacetate yielded the cyclopropyl ester acetal. This ketal was then converted to the ketone (31) by trans-acetalisation using acidic acetone. Treatment of (31) with sodium acetate then gave the fragmented cyclohexanone (32, X=CO₂Et). The second approach utilised a low temperature Diels-Alder reaction between cyclohexadiene (30) and α -chloroacrylonitrile giving the adduct (33), isomerisation of (30) to the conjugated 1,3-diene presumably occurring prior to cyclisation. Reaction of (33) with sodium sulphide then led to the bicyclic ketone (34). Ketone (34) was then elaborated into cyclohexenone (27, X=CN) in high yield *via* an abnormal

Beckmann fragmentation process. Treatment of either the ester or nitrile variant of (27) with methylmagnesium chloride, followed by base or acid respectively, yielded the key γ -lactone (29) in high yield. This γ -lactone was then elaborated into trichodermin (28) as shown below. (Scheme 9).

Methylation of (29) using LDA followed by methyl iodide gave lactone (35). Treatment of (35) with 1-lithio-3,3-diethoxypropyne gave the acetylenic lactol (36). Reduction of this lactol using sodium borohydride followed by conversion of the alkyne moiety to the *E*-alkene by sodium and liquid ammonia reduction, then set the stage for an elegantly conceived operation, whereby treatment of (37) with acid released the masked aldehyde, and also induced nucleophilic attack of the tertiary alcohol upon the α,β -unsaturated aldehyde, forming the tetrahydropyran B ring. Chromium trioxide oxidation then furnished the aldol precursor (38). Despite intensive effort however, (38) could not be induced to undergo intramolecular aldol reaction. Instead, a different route was undertaken where the keto-aldehyde (38) was oxidised to the keto acid (39) and this acid cyclised to the enol lactone (40) using acetic anhydride. Fujimoto-Belleau reduction of (40) using lithium aluminium tri-*tert*-butoxy hydride then yielded the keto aldehyde (38) and the trichodermin precursor (41), albeit in only 7% yield.

The keto alcohol (41) was then elaborated to trichodermin (28) by Wittig olefination of the C-12 ketone, epoxidation of the resultant double bond using *m*-CPBA, then acetylation of the C-4 hydroxy group. Interestingly, the C-9,C-10 double bond was untouched during the epoxidation step, as the C-4 hydroxy group acted as an 'anchor' for the incoming peracid by hydrogen bonding, thereby increasing the rate and controlling the stereochemistry



a) LDA, MeI, b) 1-lithio-3,3-diethoxypropyne, c) NaBH_4 ,
d) Na , NH_3 , e) H_3O^+ , f) CrO_3 , g) $(\text{CH}_3\text{CO})_2\text{O}$, h) $\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}$,
i) $\text{CH}_2\text{P}(\text{Ph})_3$, j) m-CPBA, k) $(\text{CH}_3\text{CO})_2\text{O}$, pyridine

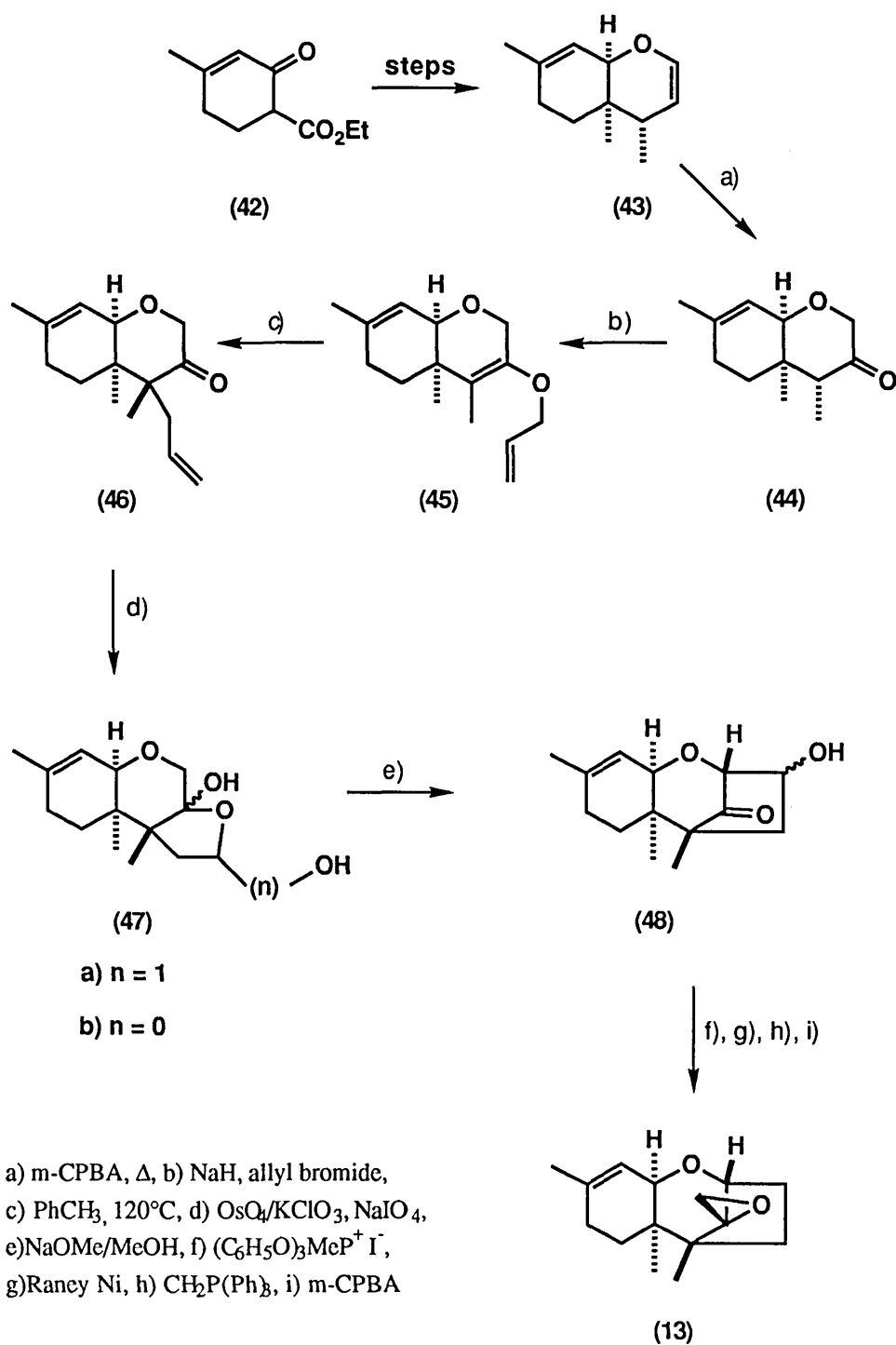
scheme 9

Following this synthesis of trichodermin (28), a variety of papers were

published concerning the synthesis of trichothecenes, many synthetic strategies being based on that of Raphael *et al.*^{1a} In 1974, Fujimoto^{1b} reported a total synthesis of (±)-12,13-epoxytrichothec-9-ene (13), and although C ring formation again took an aldol ring closure strategy, this time the aldol reaction formed the C-2,C-3 bond rather than the C-4,C-5 bond, as in the previous approach. This proved to be a crucial factor, the aldol reaction occurring in 90% yield. (Scheme 10).

The *cis*-fused bicyclic tetrahydropyran derivative (43) was prepared from the β-keto ester (42) by 1,4-addition to crotonaldehyde, Meerwein-Ponndorf reduction of the derived acetyl and lithium aluminium hydride reduction of the ester group. Treatment of (43) with m-CPBA and pyrolysis of the intermediate hydroxy ester yielded the *cis* fused lactone (44). Reaction of (44) with sodium hydride followed by allyl bromide then unexpectedly led to the O-alkylated derivative (45), which was fortuitously converted to the desired C-alkylated species (46) by Claisen rearrangement. Oxidation of the acyclic double bond then led to the tricyclic intermediate (47a), which was degraded by one carbon unit to the desired aldol precursor (47b) by oxidative periodate cleavage. Simple treatment of (47b) with sodium methoxide in methanol then gave the tricyclic species (48) in high yield. The synthesis was completed *via* conversion of the 3-hydroxy group to the corresponding iodide then reduction using Raney nickel. Finally, the C-12,C-13 epoxide group was introduced by the Wittig-peracid oxidation sequence of Raphael *et al.*^{1a}

Interestingly, the absence of a proximal hydroxy group 'anchor' for the oxidation meant only a 30% yield of 12,13-epoxytrichothec-9-ene (13) was obtained, the majority of the remaining material being the diepoxidised compound, the C9-C10 double bond also being attacked.

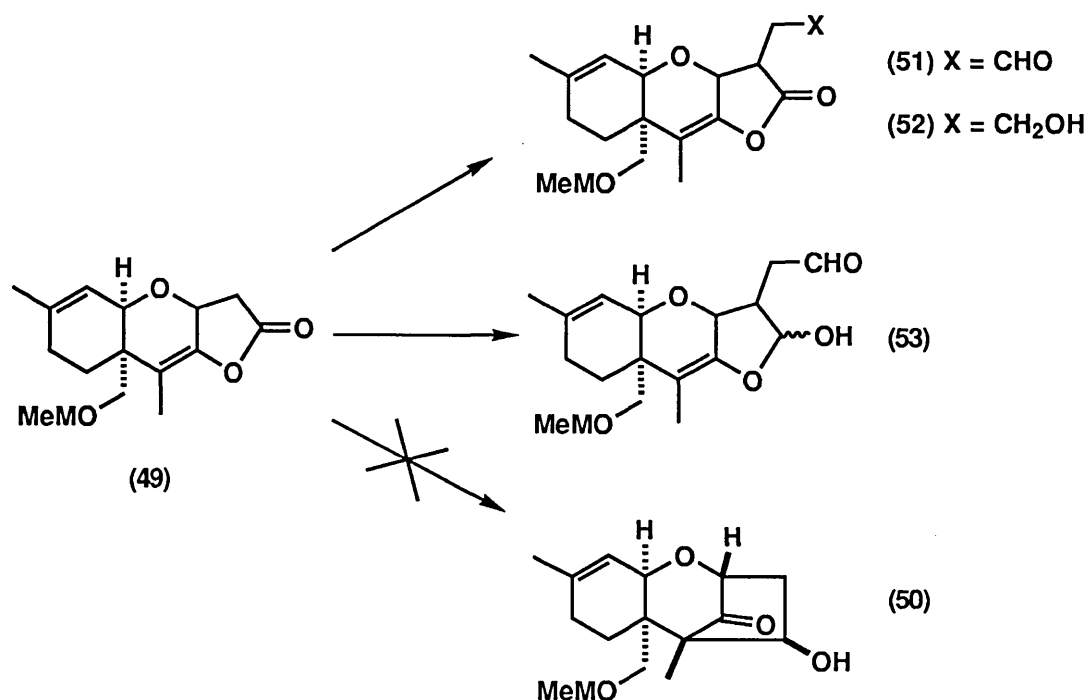


scheme 10

The superiority of the C2-C3 aldol approach was further demonstrated by

Raphael *et al.*³⁸ in which attempts were made to synthesise verrucarol (4) using the trichodermin synthetic methodology. The key step involved treatment of the lactone (49) (scheme 11) with lithium aluminium tri-*tert*-butoxy hydride in an attempt to produce the verrucarol derivative (50).

In the event, reduction only gave the keto-aldehyde (51), hydroxyketone (52) and hydroxyaldehyde (53).

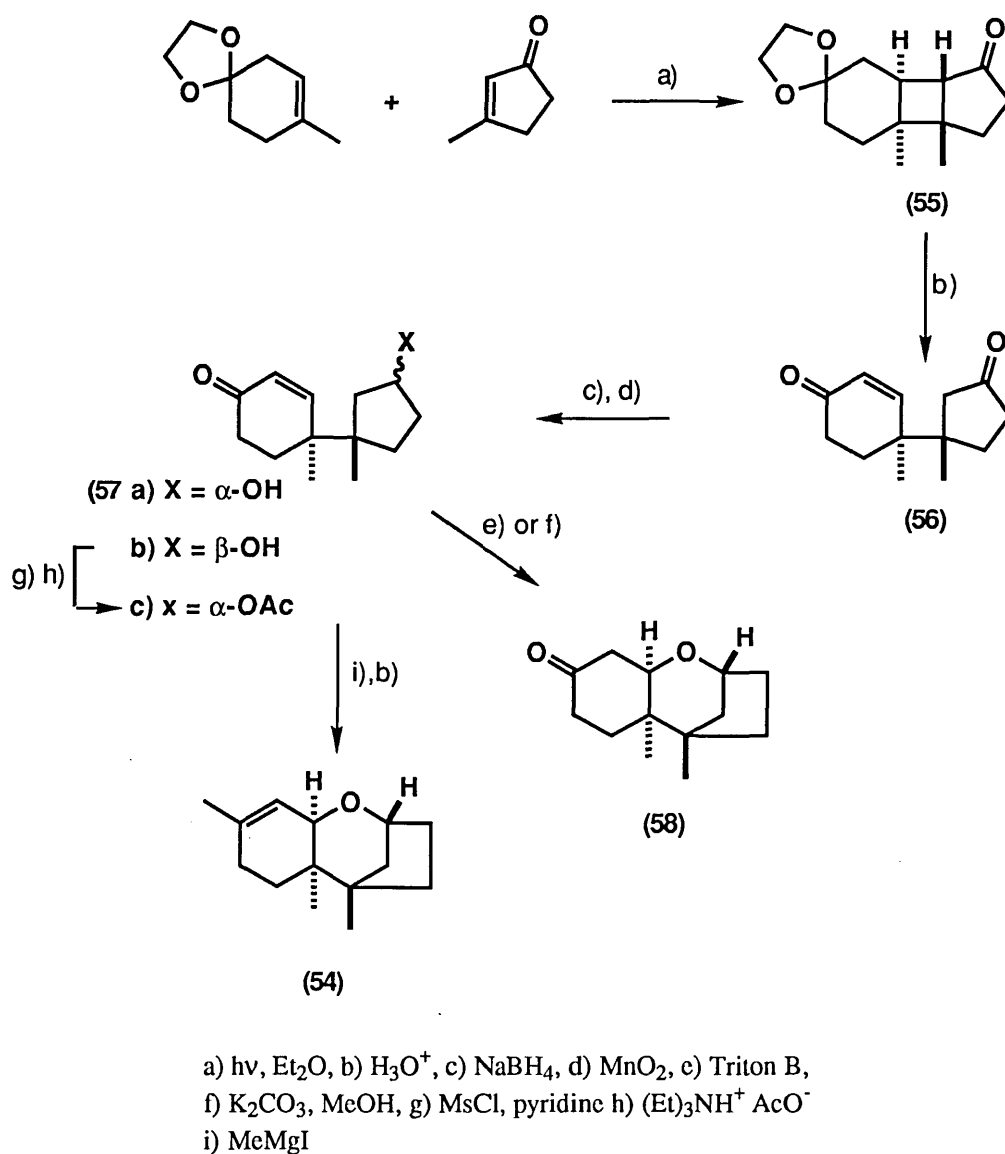


scheme 11

Subsequent syntheses of calonectrin,^{1c} an approach to deoxynivalenol (1)³⁹ and T-2 tetraol^{1d} have all been based on the aldol C-2,C-3 bond formation methodology.

Despite the success of the aldol approach towards trichothecene synthesis, the majority of pathways have utilised the biomimetic approach towards C ring formation (paths c,d, scheme 7). The first trichothecene synthesis that employed this strategy was that of a model compound (±)-13-nortrichothec-9(10)-ene (54) reported

by Kamikawa *et al.*^{1e} (Scheme 12).



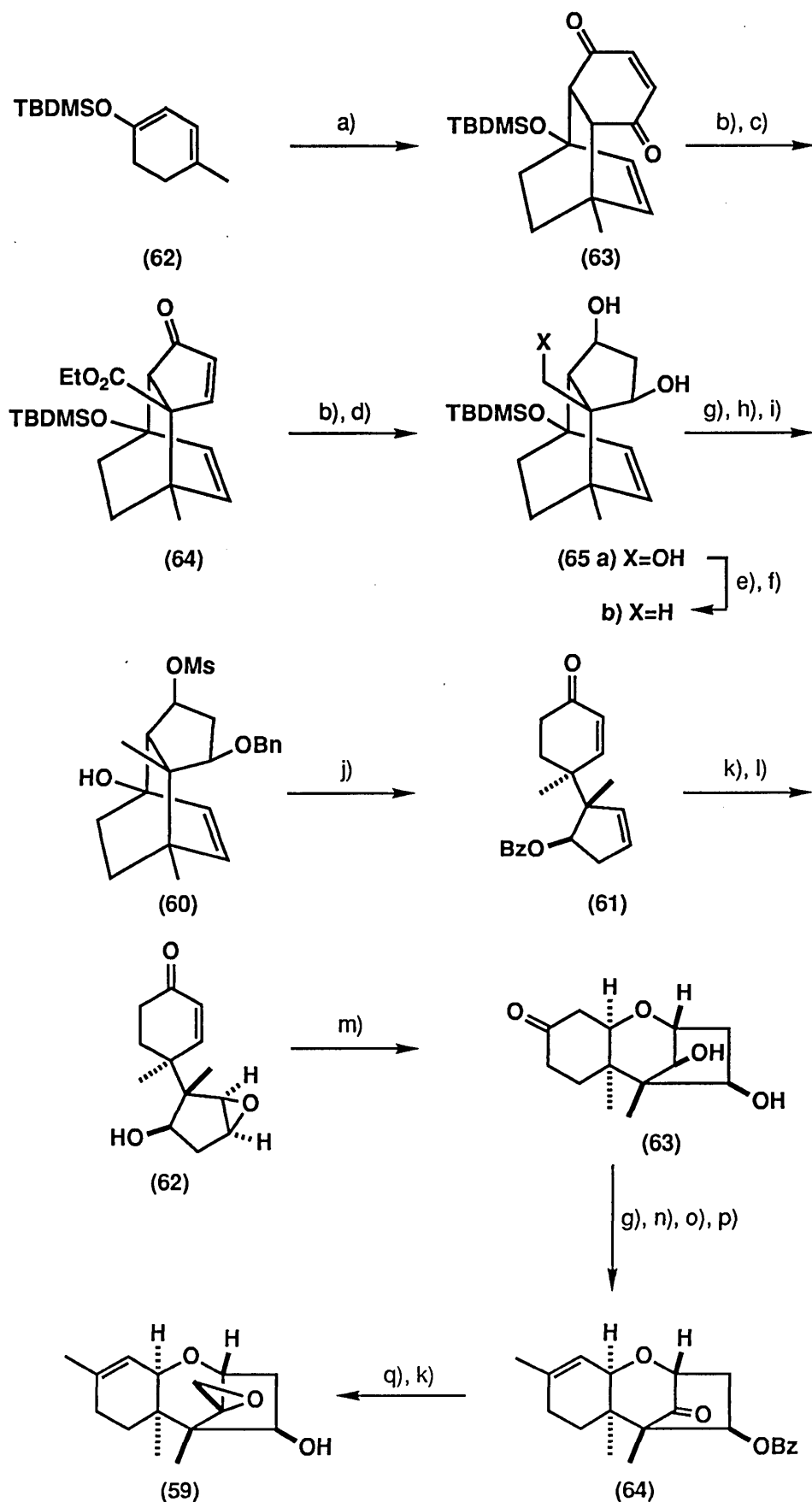
Scheme 12

Photolysis of a mixture of 3-methylcyclopent-2-en-1-one in the presence of an excess of 4-methylcyclohex-3-en-1-one ethylene ketal gave the [2+2] photoadduct (55) in poor yield. Acid-induced fragmentation of the cyclobutane ring afforded the α,β -unsaturated ketone (56), which was then reduced to the corresponding diol. The allylic hydroxy group was then selectively reoxidised back to the ketone using manganese dioxide, furnishing the stereoisomeric hydroxy ketones

(57a) and (57b). Preliminary attempts to cyclise this mixture using triton B only resulted in low yields of the tricyclic ketone (58), since only the minor stereoisomer (57a) possessed the correct orientation of the hydroxy group for cyclisation to occur. Inversion of the stereochemistry at the C-2 position of the major stereoisomer (57b) was achieved by S_N2 displacement of the tosylate derivative of (57b) with tetraethylammonium acetate giving keto ester (57c).. Saponification of this ester and subsequent cyclisation gave compound (58) in high yield, whereas treatment of acetate (57c) with methylmagnesium iodide followed by exposure to acid gave (±)-13-nortrichothec-9(10)-ene (54), *via* a biomimetic cyclisation procedure, again in high yield.

Six years later, Still^{1f} reported a total synthesis of (±)-trichodermol (59) in an elegant display of synthetic craftsmanship. The key step in the sequence is the Grob fragmentation of hydroxymesylate (60), establishing the correct *trans* stereochemical relationship between the two quaternary centres. (Scheme 13)

Diels-Alder reaction between the siloxyhexadiene (62) and hydroquinone gave adduct (63). Subsequent epoxidation and Hertz-Favorskii ring contraction proceeded stereospecifically affording unsaturated ester (64). Epoxidation of this ester followed by dissolving metal reduction yielded triol (65a), which was selectively deoxygenated to diol (65b) by an interesting photochemical reaction. Protecting group manipulation then set up the fragmentation precursor (60) which, upon treatment with sodium hydride, smoothly led to bicyclic intermediate (61). Alcohol directed epoxidation *via* debenzoylation of (61) gave (62) which, upon treatment with 2% aqueous H₂SO₄, afforded precursor (63). Elaboration into trichodermol (59) was then reasonably straightforward. The C-9 methyl group and double bond were introduced by use of methyllithium and subsequent dehydration of the tertiary alcohol, which fortuitously gave the correct regioisomeric olefin. Oxidation at C-12 and esterification at C-4 gave (64) which was elaborated to the 12,13-epoxide *via* the method of Raphael *et al.*^{1a} Final debenzoylation gave trichodermol (59).

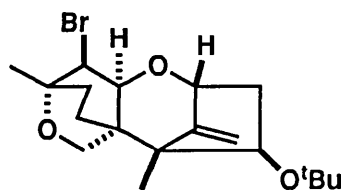


a) hydroquinone, b) *tert*-BuOOH, Triton B, c) NaOH, EtOH, d) Li, NH₃, e) Ac₂O
 f) HMPT-H₂O, hv, g) PhCOCl, h) TBAF, i) MsCl, K₂CO₃, MeOH, j) NaH, THF
 k) K₂CO₃, MeOH, l) *tert*-BuOOH, VO(acac)₂, m) H₂SO₄-H₂O, n) CrO₃, pyridine
 o) MeLi, p) POCl₃, pyridine, q) (Ph)₃PCH₂, DMSO, m-CPBA

scheme 13

Schlessinger and Nugent^{1g} also utilised a biomimetic B ring closure approach in their total synthesis of verrucarol (4). The stereochemical lynch-pin of the synthesis is the bicyclic lactone (65) which underwent a stereospecific Diels-Alder reaction, attack of the diene coming from the less hindered face, to form the A ring of verrucarol and also afford the correct *trans* stereochemical relationship between the C-5 and C-6 substituents (Scheme 14).

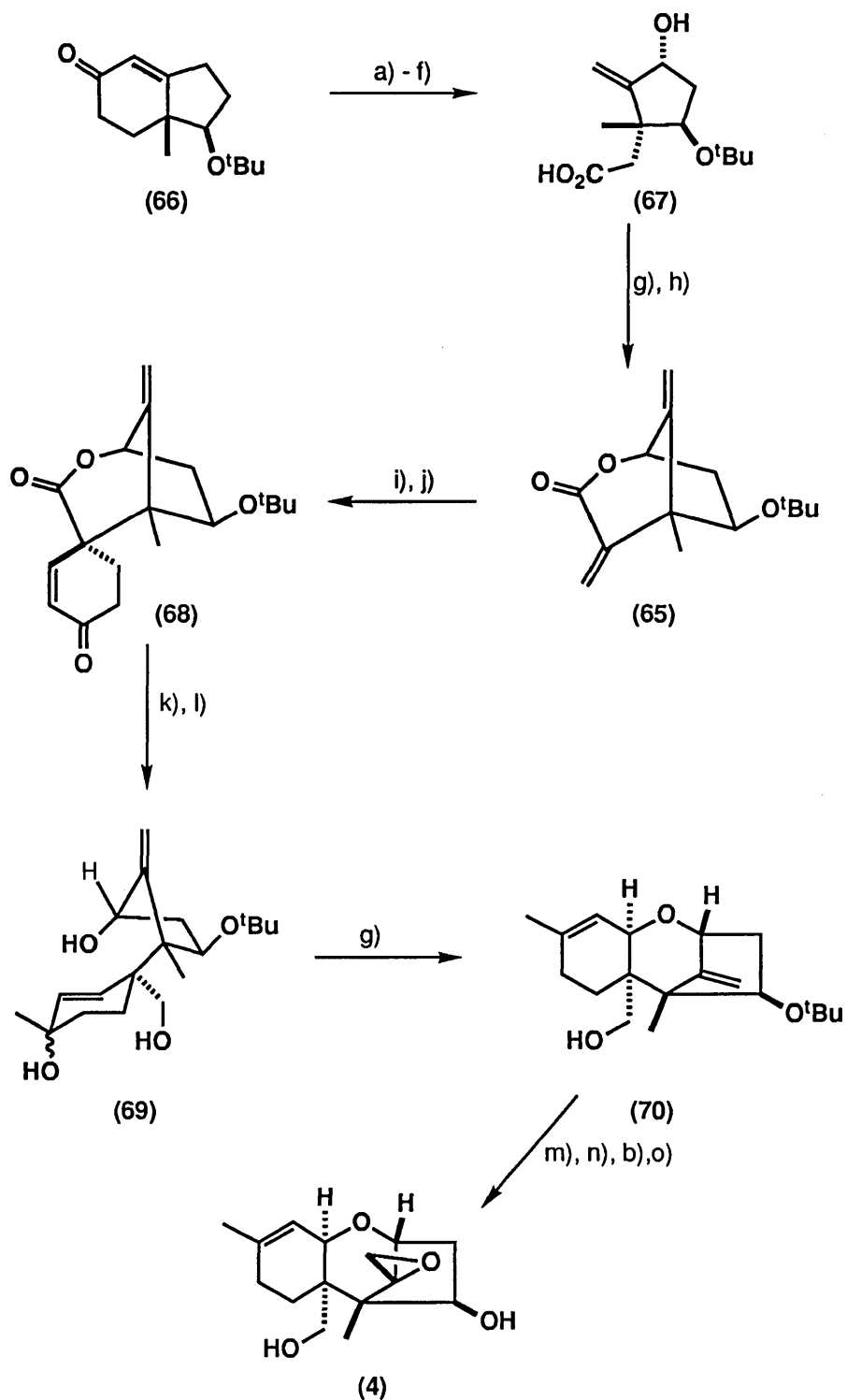
The starting point of the synthesis was bicyclic ketone (66), which was converted to the bicyclic lactone (65) *via* the highly substituted cyclopentane (67), as shown above. Diels-Alder reaction between (65) and 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (Danishefsky's diene) then yielded the spirocyclic lactone (68) after acidic work up. Reaction of (68) with methyllithium followed by reduction of the lactone using lithium aluminium hydride then gave the cyclisation precursor (69). Subsequent treatment of the crude reaction mixture with catalytic p-toluenesulphonic acid furnished the trichothecene derivative (70) with loss of the tertiary hydroxy group. Again elaboration of (70) to verrucarol (4) was based upon literature precedent, but in this case Raphael C-4 'anchored' epoxidation failed, as the C-15 hydroxy group tended to promote C-9,C-10 double bond epoxidation. An ingenious solution was found by protecting the double bond as the α -bromoether (71) (figure 9) using N-bromosuccinimide.



(71)

figure 9

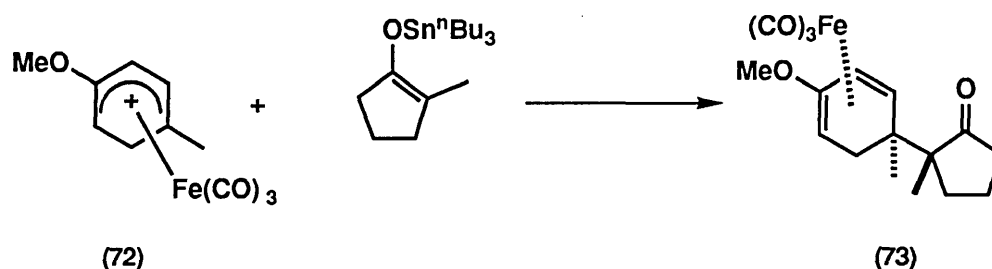
Subsequent deprotection of the C-4 hydroxy group, directed epoxidation of the C-12-C-13 double bond and treatment of the product with sodium metal in the presence of ethylamine gave verrucarol (4) in an overall 3.4% yield.



a) LDA, TMSCl, b) m-CPBA, c) O_3 , H_3O^+ , d) NaIO_4 , CrO_3 , e) $(\text{Ph})_3\text{PCH}_2$,
 f) SeO_2 , g) *p*-TSA, DCM, h) LDA, CH_2O , i) Danishefsky diene, j) Amberlite-IR20,
 k) MeLi, l) LiAlH_4 , m) NBS, acetone, n) TiCl_4 , o) Na, EtNH_2

scheme 14

Several other total syntheses have utilised the biomimetic ring closure approach, including two further syntheses of verrucarol (4),^{1h,1i} and anguidine^{1j} The methodology of Pearson^{1k} has led to the reported synthesis of trichodermol (59), trichodiene (11) and 12,13-epoxytrichothec-9-ene (13). The Pearson approach is worthy of further mention as it is possibly the shortest method reported for constructing the trichothecene nucleus. The basic strategy is centred around the observation that η_5 -iron tricarbonyl cationic complexes of the type (72) in scheme 15 undergo stereoselective nucleophilic addition exclusively at the methyl terminus by stabilised carbanions; the use of tin enolates has been reported particularly effective.

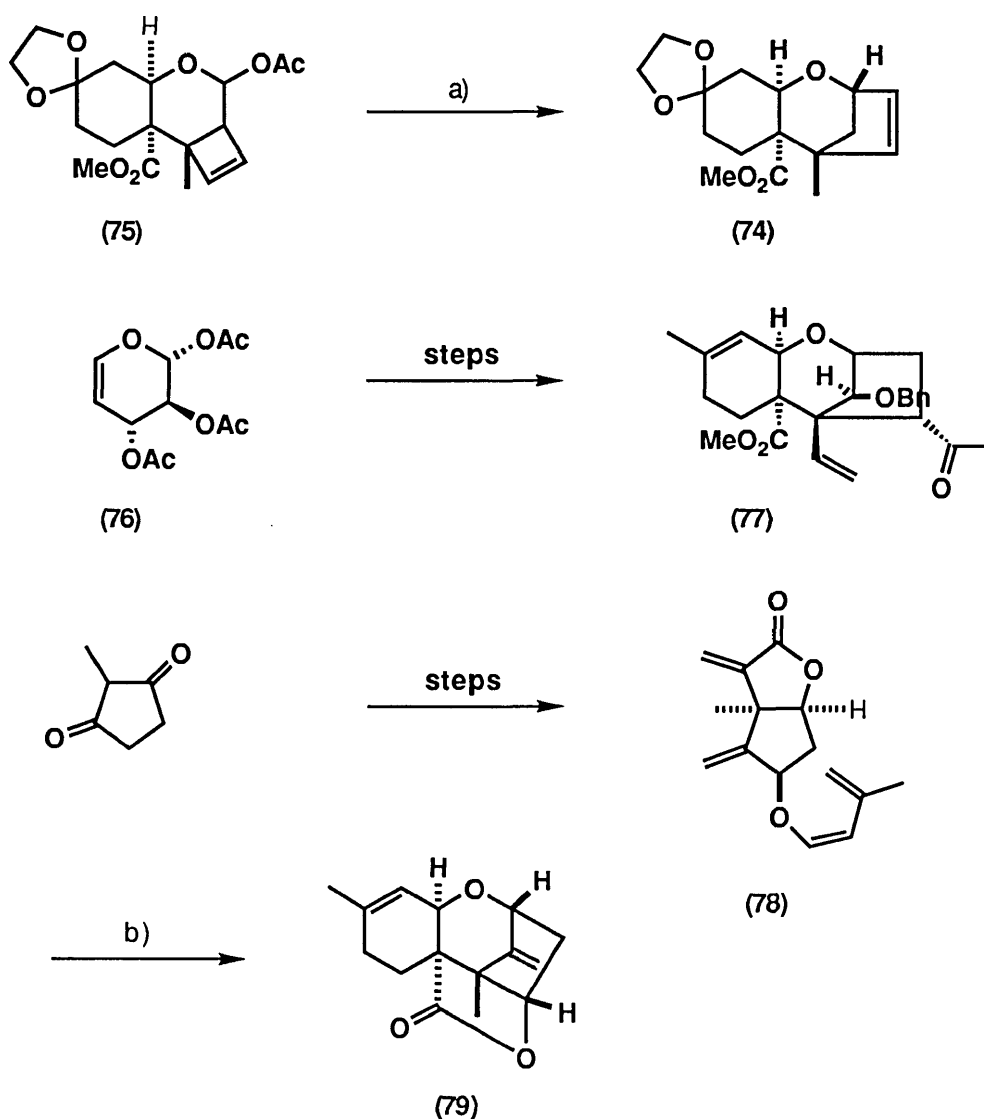


scheme 15

Consequently the resulting product (73) already possesses the trichothecene A and C rings, and also, on account of the high stereoselectivity of the reaction, the correct stereochemical relationship between the eventual C-5 and C-6 centres. This methodology has led to the total synthesis of trichodiene (11) in 5 steps, 12,13-epoxytrichothec-9-ene (13) in 10 steps and trichodermol (59) in 25 steps, each from the complex (72), the latter syntheses both using biomimetic B ring closure.

Although the aldol and biomimetic approaches constitute the majority of strategies applied to trichothecene synthesis, several 'alternative' approaches have been reported using novel transformations for ring formation. White *et al.*⁴⁰ constructed the tricyclic precursor (74) by making use of a cationic ring expansion of cyclobutene (75). Fraser-Reid⁴¹ converted D-glucose into the triacetate (76) which in turn was

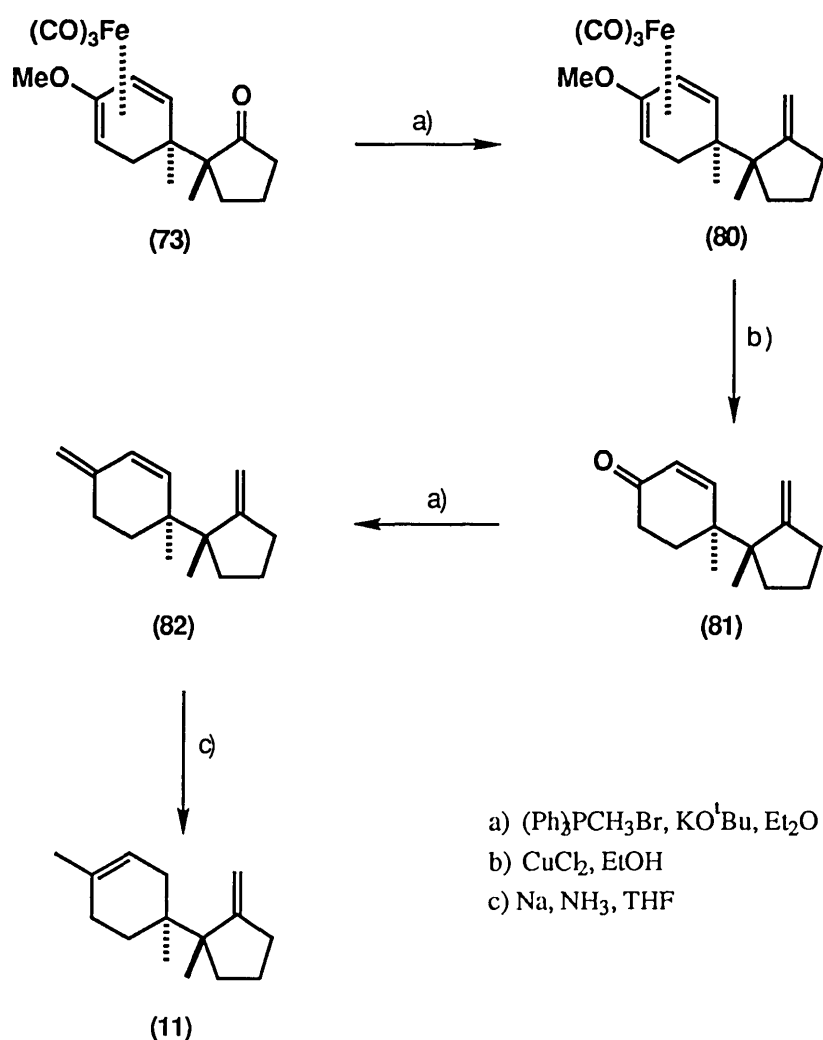
transformed into the trichothecene analogue (77), the sugar pyranoside ring forming the tetrahydropyran B ring. Perhaps one of the most remarkable approaches recently reported⁴² uses an intramolecular Diels-Alder reaction to simultaneously form both the A and B rings. The Diels-Alder precursor (78) was obtained in several steps from 2-methyl-1,3-cyclopentanedione. Attempts to purify (78) by chromatography on neutral alumina yielded an 83% yield of the desired Diels-Alder product (79), which was first reported by Trost^{1h} as an advanced intermediate in his synthesis of verrucarol (4). (Scheme 16)



a) *p*-TsOH, PhH, AcOH
b) Alumina, room temperature

scheme 16

Due to continued interest in its biological properties and potential as biosynthetic probe, the metabolic precursor to the oxygenated trichothecenes, trichodiene (11) has been the subject of much synthetic study.^{43,1k} Since this compound is relatively unfunctionalised compared to the oxygenated trichothecenes, achieving the correct stereochemical relationship between the two quaternary centres in the molecule becomes a particularly testing synthetic challenge. Indeed, of the 14 reported syntheses of trichodiene (11) 7 have resorted to separation of diastereomeric mixtures at some stage. Pearson^{1k} however, has successfully employed his organometallic approach toward a short diastereoselective synthesis of trichodiene (11), outlined in scheme (17).

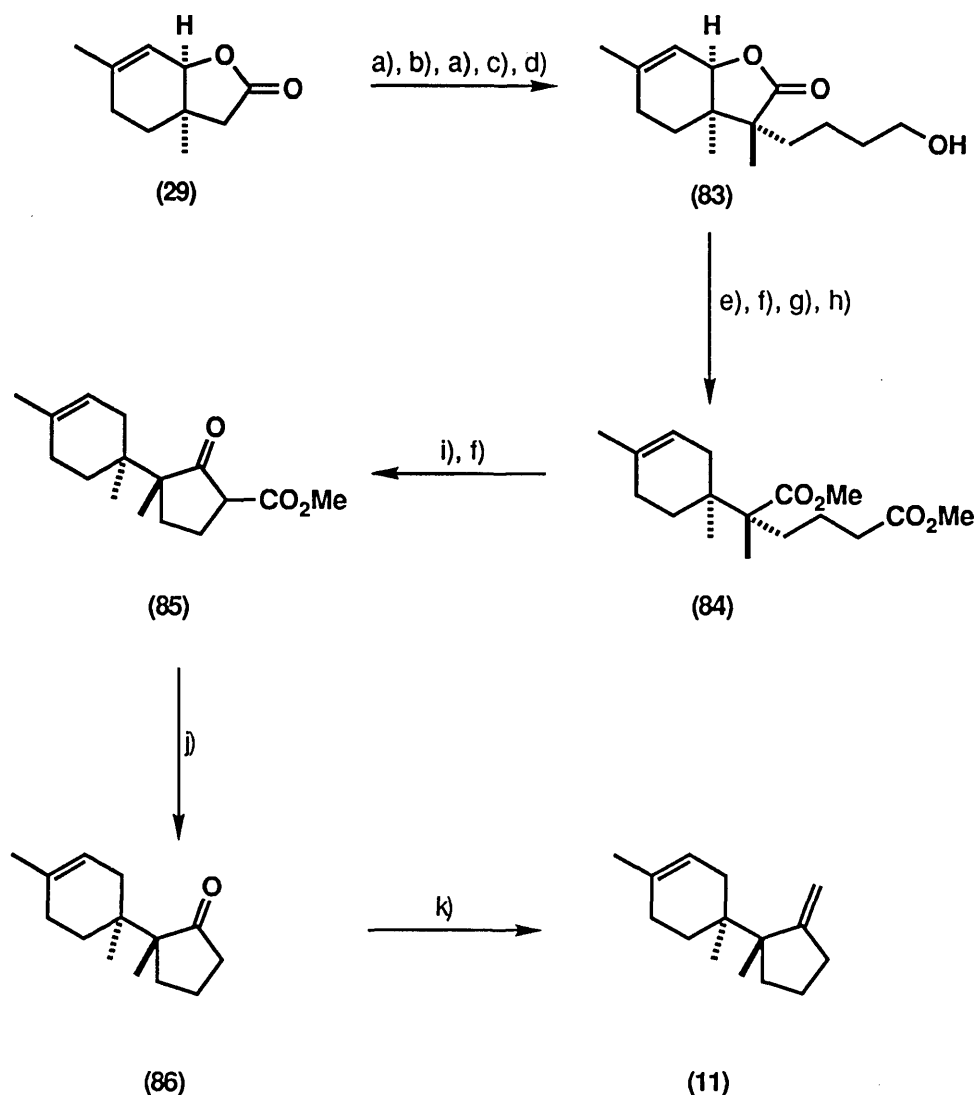


scheme17

η_4 Diene complex (73) was prepared from η_5 -dienylium iron complex (72) as shown in scheme 15. Wittig olefination of this complex gave (80), which underwent oxidative decomplexation using copper(II) chloride giving enone (81). A further Wittig reaction gave triene (82), which was subsequently reduced using sodium and ammonia to give trichodiene (11) in a short and highly stereoselective synthesis.

Welch *et al.*^{43a} solved the stereochemical problems associated with trichodiene (11) by stereoselective alkylation of the bicyclic lactone (29), first used by Raphael *et al.*^{1a} in their total synthesis of trichodermin.⁽²⁸⁾ (Scheme 18).

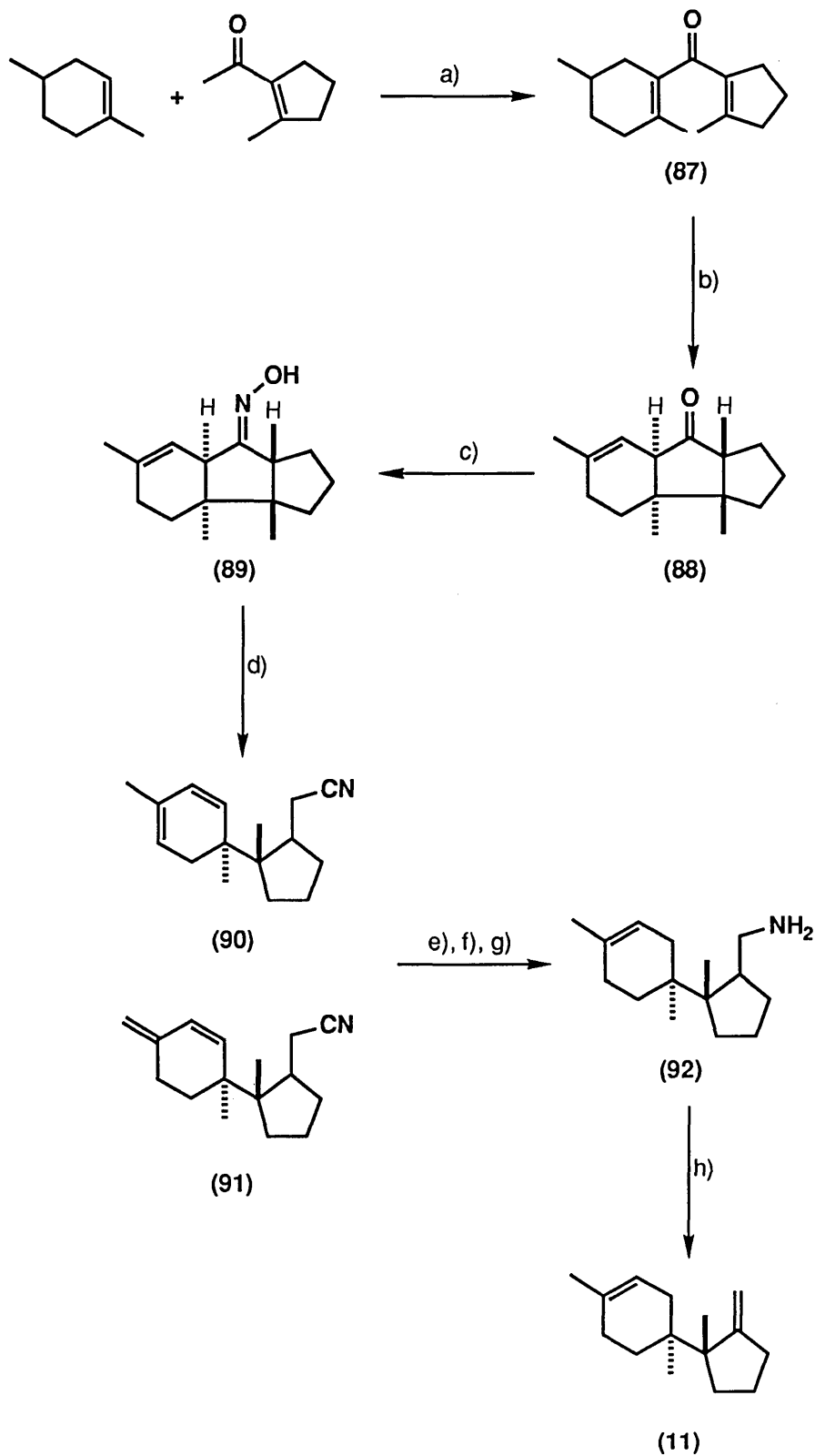
Carrying out the methylation, alkylation sequence depicted in scheme 18 upon (29) afforded the lactone alcohol (83), approach of the electrophilic species occurring *via* the least hindered convex face of bicyclic lactone (29). Transformation of (83) to the diester (84) and subsequent Dieckmann condensation furnished β -ketoester (85). Decarboxylation of (85) followed by Wittig olefination of the resultant ketone (86) then gave the trichodiene (11), as shown below.



a) LDA, b) MeI, c) Br (CH₂)₄OTHP, d) *p*-TsOH, MeOH, e) Ca, NH₃,
 f) H₃O⁺, g) NaCr₂O₇, H₂SO₄, h) CH₂N₂, i) NaN(TMS)₂, j) DBU,
 xylene, Δ, k) (Ph)₃PCH₂, DMSO, Δ

scheme 18

Harding and Clement ^{43b} have also reported a diastereoselective synthesis of trichodiene (11). The key reaction in their approach is a Nazarov cyclisation which not only establishes the correct stereochemical relationship between the eventual C-5 and C-6 centres but also introduces the C-9, C-10 double bond. (Scheme 19)



a) SnCl_4 , NaOMe , MeOH , b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DCM , 5 days, c) NH_2OH ,
d) $(\text{CF}_3\text{CO})_2\text{O}$, e) LiAlH_4 , f) NaCNBH_4 , g) Li , NH_3 , h) $m\text{-CPBA}$,
1.5mmHg Δ

scheme 19

Tin (IV) mediated coupling of 1,4-dimethylcyclohexene and 2-methyl-1-cyclopentenecarboxylic acid chloride gave the cyclisation precursor (87). Stirring a DCM solution of (87) and boron trifluoride etherate for 5 days at room temperature then yielded the Nazarov cyclisation product (88). Formation of the oxime (89) and subsequent Beckmann fragmentation then afforded a mixture of the two isomeric dienes (90) and (91) which were directly reduced to the amine (92). Oxidation of this amine followed by reduced pressure distillation then afforded trichodiene (11) by an elimination process. The spectroscopic data obtained for this compound indicated the total absence of the diastereisomeric product ($\pm$) bazzanene.

From the introductory section of this chapter it is apparent that much more study is necessary before any conclusions can be drawn concerning the structure-activity relationships of the trichothecenes. Thus, a concise yet flexible synthetic strategy, allowing the formation of both natural and unnatural products, is required. By systematic study, identification of the key structural elements with regard to the biological activity of these molecules should be possible. Therefore, the main aim of our studies in the trichothecene area was the formulation of such a strategy, and our attempts toward this synthetic goal are described in the next section.

1.2. Results and Discussion

From the previous section it is clear that a short, generally applicable route towards the synthesis of trichothecenes is still highly desirable. It was felt that a suitable initial target for study was trichodiene (11), and if a successful approach to this compound could be realised then simple modification of the methodology would lead to the synthesis of a diverse range of trichothecenes. It was also hoped that by basing our approach around the cyclic sulphone-enone (93) we would be able to demonstrate the potential of the molecule as a isoprenoid synthetic equivalent and a suitable building block for terpene synthesis. (Figure 10)

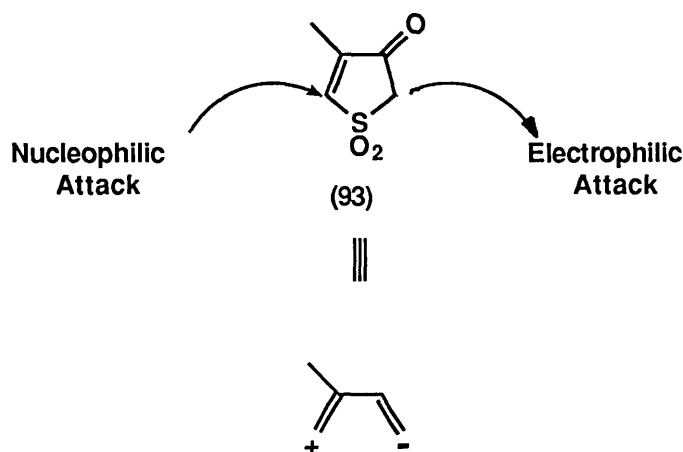
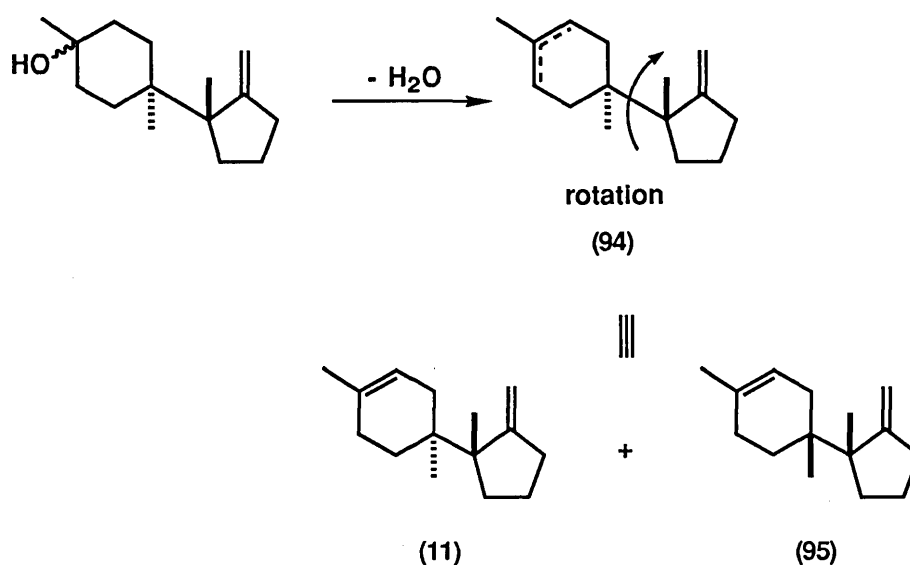


figure 10

Isoprenoid synthetic equivalents are much ^{sought} ~~seen~~ after, and a detailed review has been published concerning the nature and reactions of these species.⁴⁴ One can envisage that the molecule (93) has excellent potential as such, being able to undergo nucleophilic attack at C-2 and electrophilic attack at C-5. In fact, all five carbon atoms in (93) are available for further chemical elaboration.

The central problem in any synthesis of trichodiene lies in establishing the correct geometry of the two quaternary carbon atoms linking the A and C rings relative to the regiospecific placement of the C-9,C-10 double bond in the cyclohexene A ring. Several total syntheses have involved a dehydration strategy to introduce unsaturation, and although stereocontrol is implied in structures such as (94), the actual end result is the formation of a mixture of two natural products, trichodiene (11) and bazzanene (95), shown in scheme 20.



scheme 20

The essence of our strategy therefore lay in the introduction of a central sulphonyl group which would prevent free rotation and allow construction of a rigid framework, thereby creating a means for stereochemical control. A retrosynthetic analysis of our proposed route to trichodiene is depicted in figure 11.

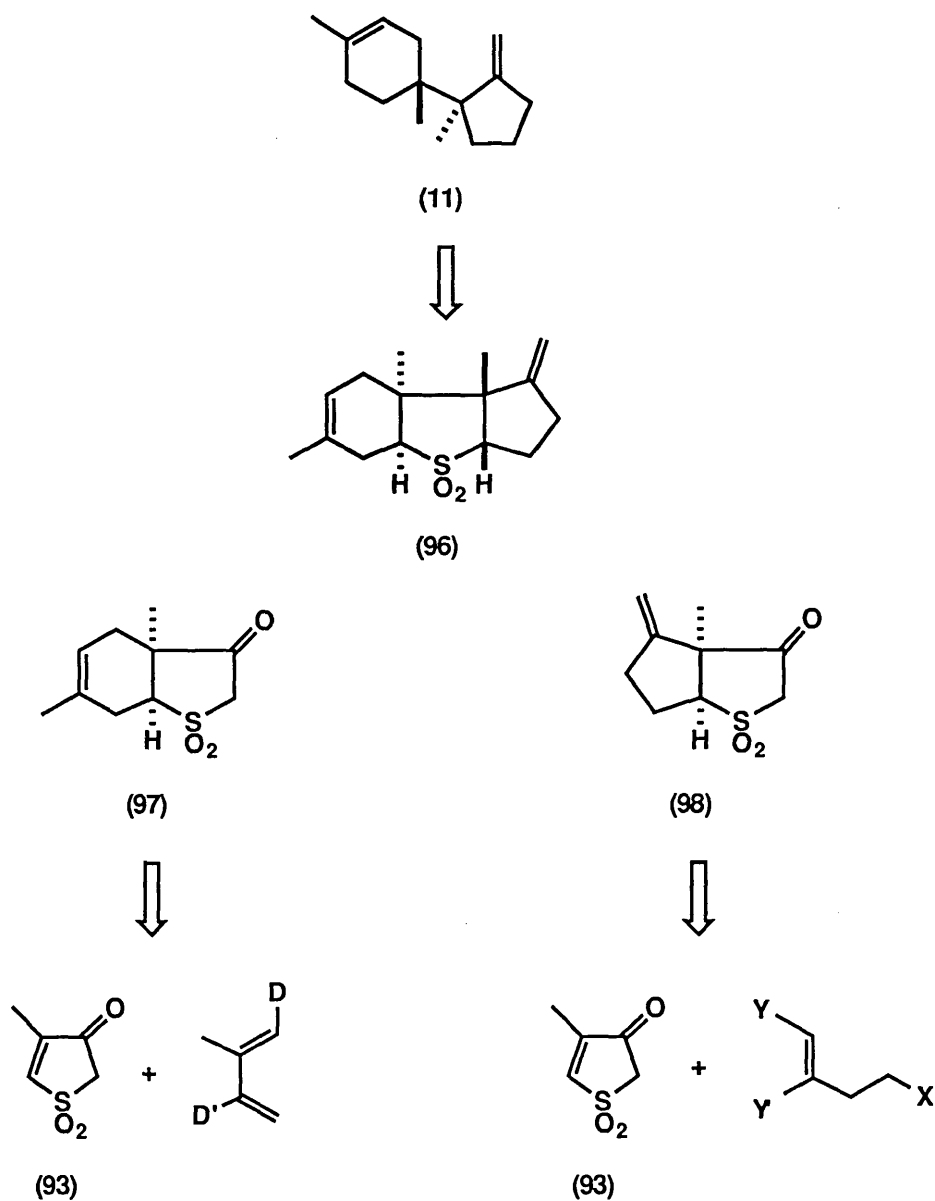


figure 11

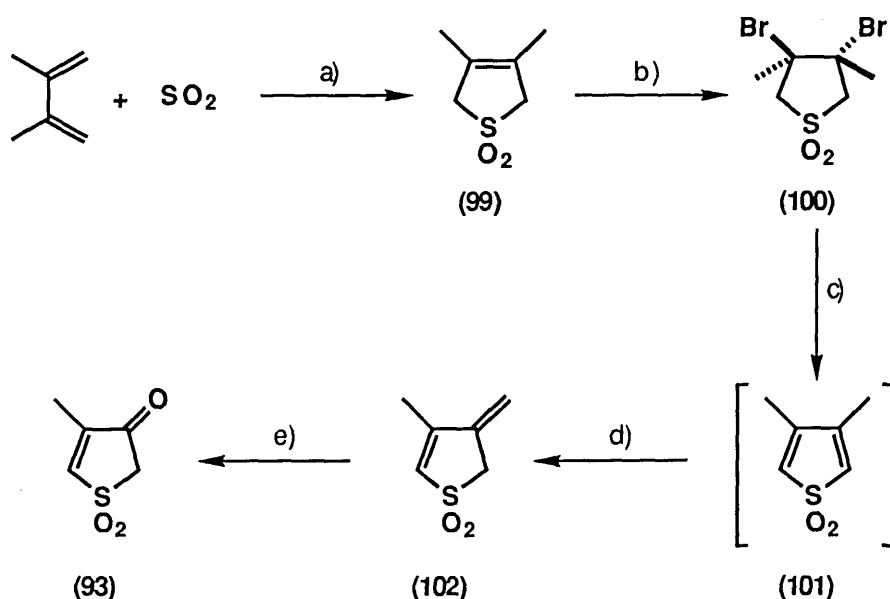
Reductive removal of sulphur dioxide was therefore envisaged as the final step of the overall sequence. The tricyclic precursor (96) could in turn be potentially derived from two distinct bicyclic precursors. One of these (97), already possesses the correctly orientated cyclohexene ring, and thereby requires a cyclopentannulation procedure, while the other, (98), featuring a heterobicyclo[3. 3. 0] system necessitates construction of the A ring. Such rigid, *cis*-fused bicyclic systems enable absolute

stereochemical control by virtue of their 'V' shaped nature, which permits stereospecific attack only from the convex face of the molecule.

Finally, it was considered that either of the bicyclic species (97) or (98) could be prepared from the monocyclic sulphone (93). Essentially, this molecule was to serve as a highly functionalised, rigid building block for annulation procedures.

1.2.1 Synthesis of Cyclic Sulphone Building Block (93)

Synthesis of sulphone starting material (93) was fairly routine, employing a slightly modified literature procedure.⁴⁵ The preparation was applicable to large scale (10g+), and purification of the various intermediates was adequately achieved by recrystallisation. (Scheme 21).



a) MeOH, pressure bottle, 100°C, b) Br_2 , PhH, Δ ,
c) NaOH, H_2O , d) 100°C, 1hr, e) O_3 , DMS

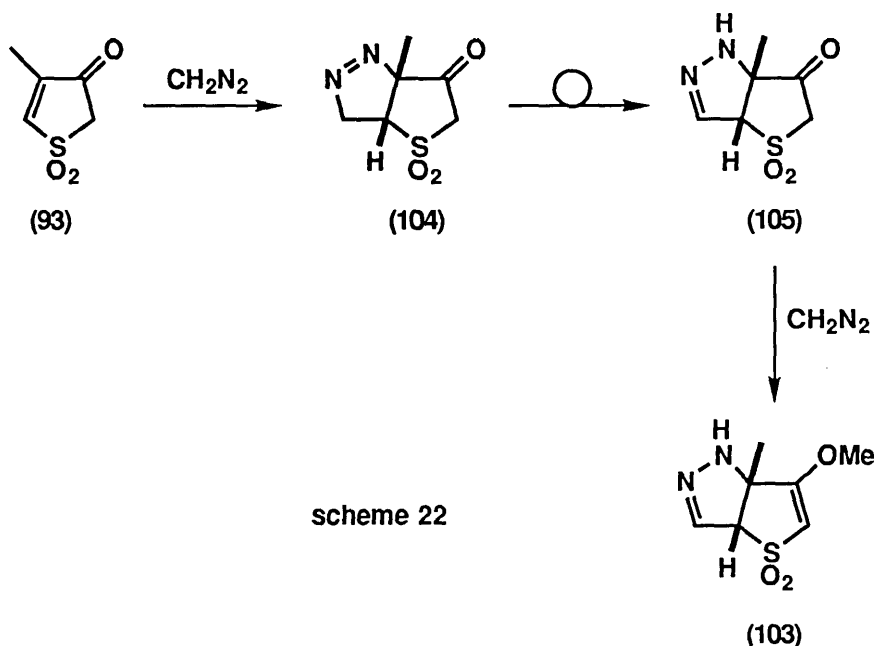
scheme 21

Thus, cheletropic addition of sulphur dioxide to 2,3-dimethylbuta-1,3-diene gave the cyclic sulphone (99) in 66% yield. Addition of excess bromine to a solution of (99) in refluxing benzene then afforded the dibromide (100), which was readily converted to the intermediate thiophene dioxide (101) in virtually quantitative yield by treatment with aqueous sodium hydroxide. Compound (101) is of great interest as it is a member of the highly elusive thiophene dioxide family, a more detailed discussion of which is given in Chapter Two. Normally, the aqueous suspension of (101) that was obtained from dibromide (100) was briefly refluxed, causing isomerisation to the thermodynamically more stable diene (102) again in an excellent 96% yield. Regioselective ozonolysis of the more electron rich double bond in (102) followed by a reductive work-up using dimethylsulphide then gave the cyclic keto sulphone (93) in 74% yield.

1.2.2 Preliminary Studies

Previous work within our group have already demonstrated some interesting chemistry of cyclic sulphone (93).⁴⁵ It is an excellent cycloaddition partner, undergoing Diels-Alder reactions with a variety of dienes, and also reacting as a dipolarophile upon treatment with diazomethane, yielding the bicyclic moiety (103) (Scheme 22)

The initial step in this reaction is a 1,3 dipolar cycloaddition reaction between diazomethane and (93) to form the intermediate heterobicyclo[3.3.0]ketone (104). This then rearranges to the more thermodynamically stable isomer (105), which reacts with a further equivalent of diazomethane to give the final bicyclic product (103).



The regiochemistry of the products obtained from Diels-Alder and diazomethane cycloaddition reactions, clearly show that the mesomeric effect of the carbonyl group wins out over the inductive effect of the sulphone in the competition for electron withdrawal from the double bond. This is a highly important observation as it allows the prediction of the regiochemical outcome of a whole host of reactions which the molecule can undergo. The formation of the methyl-enol-ether (103) from the β -ketosulphone (105) is also a useful transformation, as it represents a mild method for the conversion of β -ketosulphones of the type (79) to methyl-enol-ethers. The facile formation of the methyl-enol-ether moiety also demonstrates a further important property of (93); the high acidity of the C-5 protons. Truce *et al.*⁴⁶ have measured the acidity constants of a variety of cyclic β -ketosulphones and found the structurally similar species (106) to have a $\text{pK}_a = 5.83 \pm 0.04$. (Figure 12).

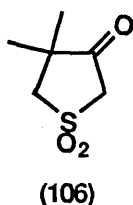
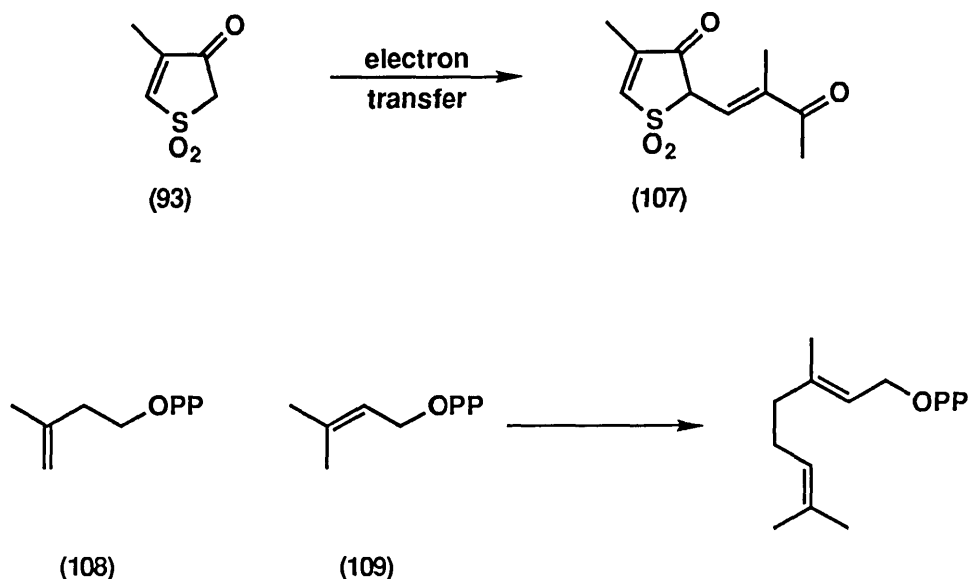


figure 12

The marked acidity of the C-5 protons of sulphone (93) is easily demonstrated by treatment with aqueous sodium bicarbonate, the immediate formation of a deep orange solution of the highly stabilised α -carbanion being observed. Furthermore, deprotonation of (93) using half an equivalent of LDA promotes a self condensation reaction which appears to occur by intermolecular nucleophilic 1,4-addition of the C-5 anion to the enone to give (107). This 'head to tail' coupling is analogous to the enzymic coupling of isopentenylpyrophosphate (108) and dimethylallylpyrophosphate (109), a key transformation in terpene biosynthesis. (Scheme 23).



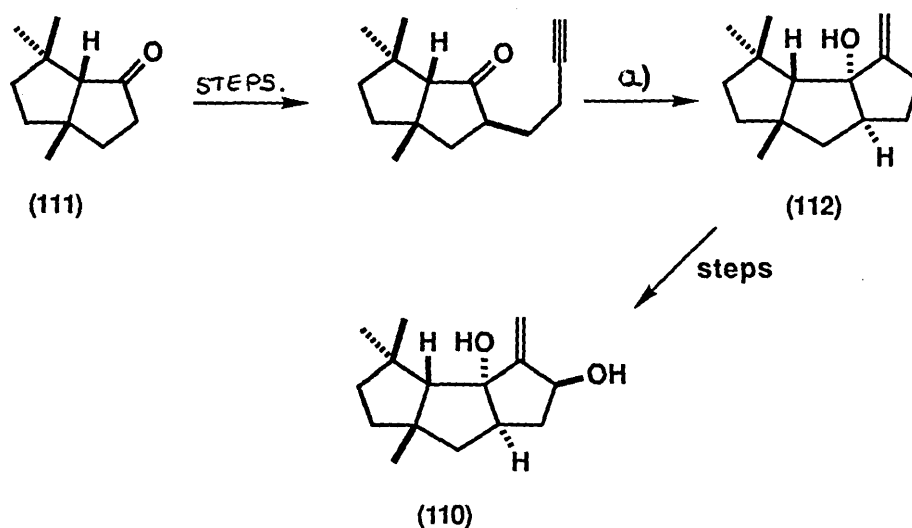
scheme 23

The actual mechanism of this sulphone-enone coupling reaction is thought to involve electron transfer, wherein LDA acts as an electron transfer reagent rather than as a base, and has good literature precedent.⁴⁷ The fact that the reaction is totally retarded in the presence of radical scavengers and coupling does not occur with bases that lack electron donating abilities lends further support to such a process.

The ability of cyclic sulphone (93) to mimic the biological coupling of isopentenylpyrophosphate (108) and dimethylallylpyrophosphate (109) demonstrates the potential of the compound for terpene synthesis. To this end it was decided to attempt a total synthesis of trichodiene (11) using (93) as the cornerstone of the synthetic methodology.

1.2.3 Approach via Bicyclo [3.3.0] Sulphone (98).

The first step in our approach toward trichodiene was the formation of the heterobicyclo[3.3.0] species (98), and it was thought that a radical addition-ring closure sequence would provide an appropriate means for the cyclopentannulation of (93). Pattenden *et al.*⁴⁸ utilised a similar radical ring closure strategy in their total synthesis of Capnellene-8 β -10 α -diol (110). In this synthesis it was necessary to alkylate the bicyclic ketone (111) by an indirect route, direct alkylation not being possible due to problems associated with competing elimination reactions of the homopropargyl unit, affording an enyne type systems. Sodium naphthalenide mediated radical ring closure then gave the tricyclic alcohol (112) which was further elaborated into Capnellene-8 β -10 α -diol (110). (Scheme 24).

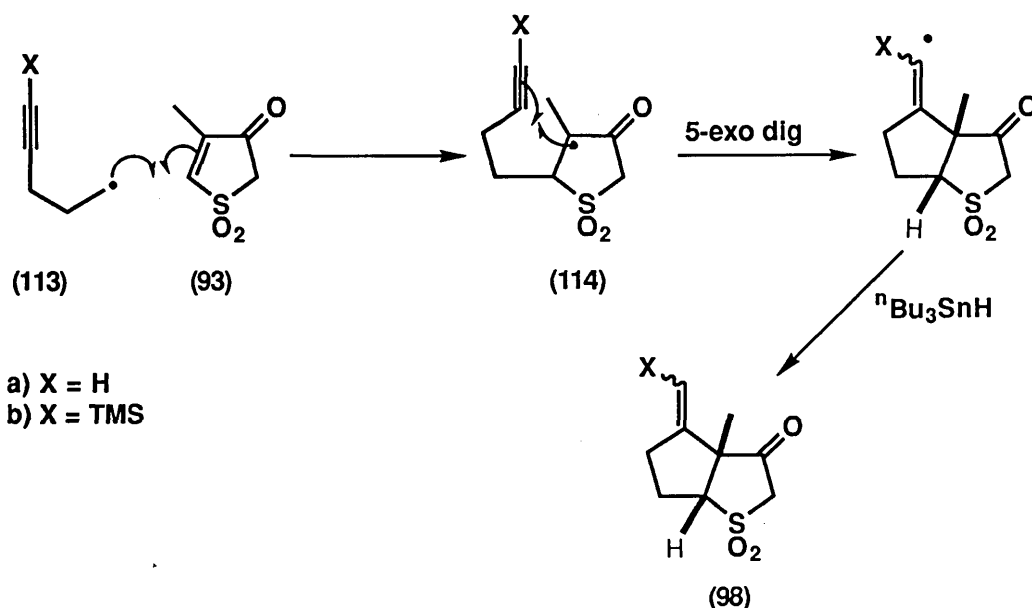


a) Sodium naphthalenide.

scheme 24

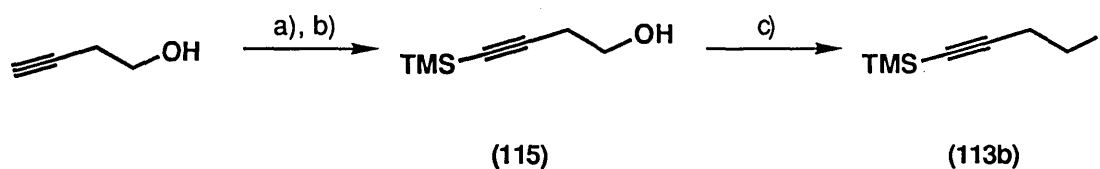
Rather than use the iodide as an electrophilic centre, it was envisaged that the alkylation-cyclisation process could be carried out in one step, by a tandem radical addition cyclisation-process, wherein nucleophilic addition of the alkyl radical derived from homopropargyl iodide to the electron deficient double bond of (93) is followed by 5-exo-dig cyclisation. (Scheme 25).

However, treatment of a refluxing toluene solution of sulphone (93) and homopropargyl iodide (113a) with 1.1 equivalents of tributyltinhydride and catalytic AIBN under standard free radical conditions, only led to reasonable recovery of the sulphone (93) and a very small amount of a material that was tentatively assigned structure (98a). However, the starting iodide appeared to be totally consumed in the reaction.



scheme 25

Homopropargyl iodide proved to be a highly volatile liquid in our hands, and it was this property of the compound that was thought to be the reason for the failure of this initial reaction. Since prolonged heating, typically 120°C for 18 hours, was employed in this reaction and preparations were always carried out on a small scale, significant losses of this reagent during the course of the reaction would be experienced. Subsequently, the silylated acetylene (113b) was synthesised by a modified literature⁴⁸ route. Double deprotonation of 3-butyne-1-ol and treatment of the resultant dianion with excess chlorotrimethylsilane gave the silylacetylenic alcohol (115) in 90% yield, after exposure of the crude reaction mixture to aqueous acid. Treatment of (115) with iodine in the presence of triphenylphosphine and imidazole then afforded an 85% yield of the acetylenic iodide (113b). (Scheme 26)



a) n-butyllithium (2eq.), excess TMSCl,
 b) H_3O^+ , c) $\text{P}(\text{Ph})_3$, I_2 , imidazole

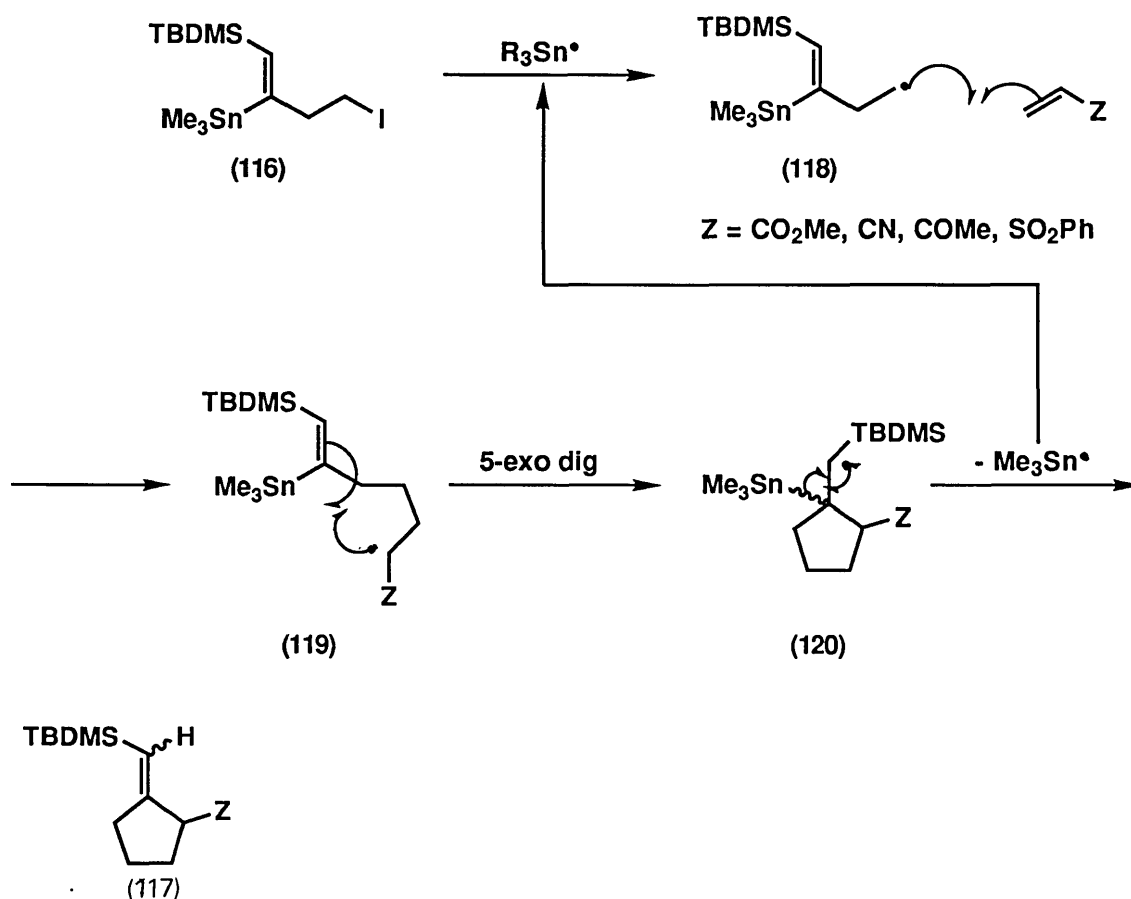
scheme 26

It was envisaged that the trimethylsilyl substituent would decrease the volatility of the compound and thus increase the yield of the cyclopentannulated product. This proved to be the case, as reaction of the silylacetylene (113b) and sulphone (93) with tributyltin hydride led to a 45% yield of the required bicyclo[3.3.0]sulphone (98). Benzoyl peroxide was the preferred catalytic initiator as use of AIBN gave products derived from direct addition to (93).

Several problems were still experienced with this reaction, the major difficulty being the effect of concentration upon the reaction yield. In order to achieve acceptable yields, the reaction medium had to be dilute, typically in the concentration range of 0.001-0.002 molar, and large scale preparation was not feasible. Moreover, purification of the product proved to be arduous and time consuming. Application of standard work-up conditions for tin reactions was not possible, as treatment of the crude reaction mixture with fluoride always led to appreciable product decomposition, presumably *via* deprotonation at the sulphone α -position. Pure samples of the bicyclo[3.3.0]sulphone (98b) could only be obtained was extensive column chromatography. Nevertheless, despite its tedious nature, this purification was considered acceptable if the reaction could be applied to larger scales.

At this stage Curran *et al.*⁴⁹ reported the use of a novel radical cyclopentannulating reagent (116), in which treatment of a mixture of (116) and an electron deficient olefin with an additional 0.7-2.0 equivalents of tributyltin hydride

afforded the corresponding vinylcyclopentane (117). The proposed mechanism for this transformation is outlined in scheme 27.

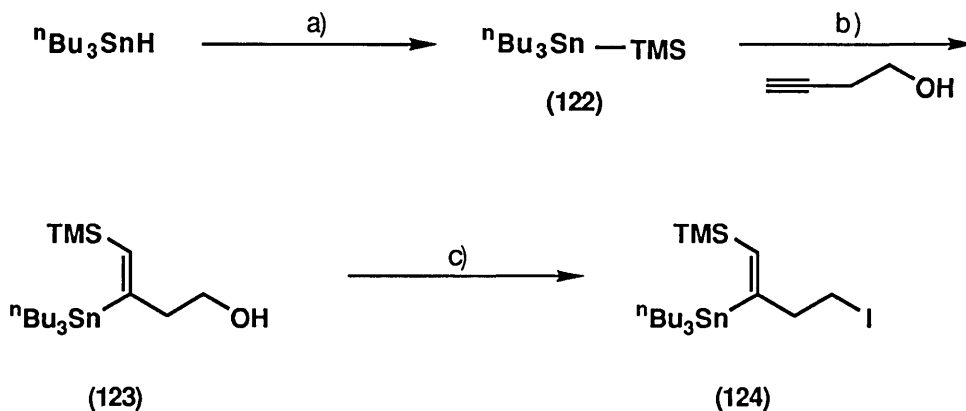


scheme 27

Abstraction of an iodine atom from (116) by $R_3Sn^\bullet$ gives the nucleophilic radical (118). Addition of this radical to the electron deficient alkene generates intermediate radical (119). Subsequent 5-exo-trig ring closure and β -scission of the resulting cyclopentyl radical (120) affords the vinylcyclopentane product (117) and a trimethylstannyl chain carrier radical.

A striking experimental observation in this reaction is the necessity for the use of a large excess of tri-*n*-butyltin hydride, despite the fact that the proposed mechanism implies that only catalytic quantities should be required. Due to the aforementioned problems associated with purification, and the requirement that the reaction be applicable to large scale operation, the Curran methodology in such a

format was not of great use to us. Nevertheless, if modification of the reaction were possible, such that only catalytic quantities of tri-*n*-butyltin hydride were necessary, then a possible solution to the problems associated with the synthesis of (98) would be realised. To this end, the analogous vinylstannane (124) was prepared as shown. (Scheme 28).



a) LDA, TMSCl, b) Pd (PPh₃)₄, THF, Δ, c) PPh₃, I₂, imidazole

scheme 28

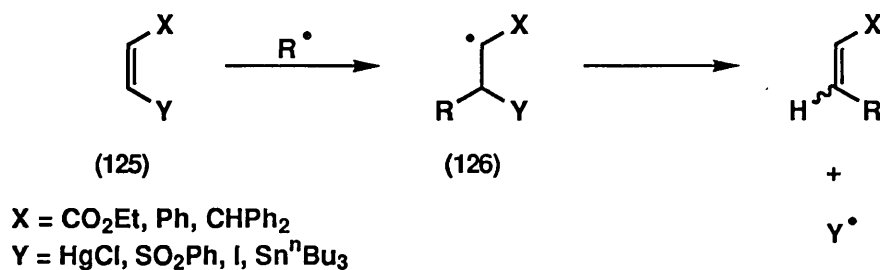
Deprotonation of tri-*n*-butyltinhydride with LDA gave the lithiotin species, which was then quenched with chlorotrimethylsilane giving silylstannane (122). Palladium(0) mediated addition of (122) across the triple bond of homopropargyl alcohol afforded the olefinic alcohol (123). This in turn was converted in acceptable yield to the required iodide (124) by reaction with triphenylphosphine and iodine in the presence of imidazole.

It was hoped that the desired reaction would occur simply by carrying the reaction out under conditions where hydrogen atom transfer from the stannane was not possible. Since the Curran procedure employs a large excess of tri-*n*-butyltin hydride, preferential reduction of any of the intermediate radicals in scheme 27 could be one of

the reasons for the poor chain length. Initially, it was postulated that the addition of a small amount of hexaphenylditin to the reaction followed by a short period of photolysis would achieve this transformation. Hence, to a Pyrex flask containing a toluene solution of the sulphone (93) and the iodide (124) was added 16 mol% of hexaphenylditin, and the reaction irradiated using a medium pressure mercury lamp for 30 minutes. T.l.c analysis of the reaction after this time showed only the presence of the starting materials. Despite extensive experimentation, only the starting sulphone (93) was recovered. This result indicates that the actual rate of addition and/or cyclisation is slow, hence the radical chain is rapidly terminated. Therefore a low, constantly generated source of tin initiator radicals within the reaction mixture is required, in order to compensate for the very short chain length. In an effort to achieve this objective, the reaction was repeated, but 27 mol% of hexa-*n*-butylditin was slowly added over 6 hours, with constant irradiation. Once again, no appreciable amounts of the previously prepared product were observed.

The failure of the two above reactions correlates with the observation of Curran that the chain process in the reaction is very short. Indeed, since an equal ratio of initiator to reactant is required, the classification of the reaction as radical chain process is at best dubious.

Several factors may contribute to the reason for the poor radical turnover of this procedure, but worthy of note is work by Baldwin,⁵⁰ who has studied the radical addition-elimination reactions of β -stannyl acrylates of the type (125, $X=CO_2Et$, $Y=Sn^nBu_3$) in scheme 29. As with the Curran procedure, the chain length in this process is short, acceptable yields only being obtained when the reaction was periodically reinitiated using in total 0.5 molar equivalents of AIBN.



scheme 29

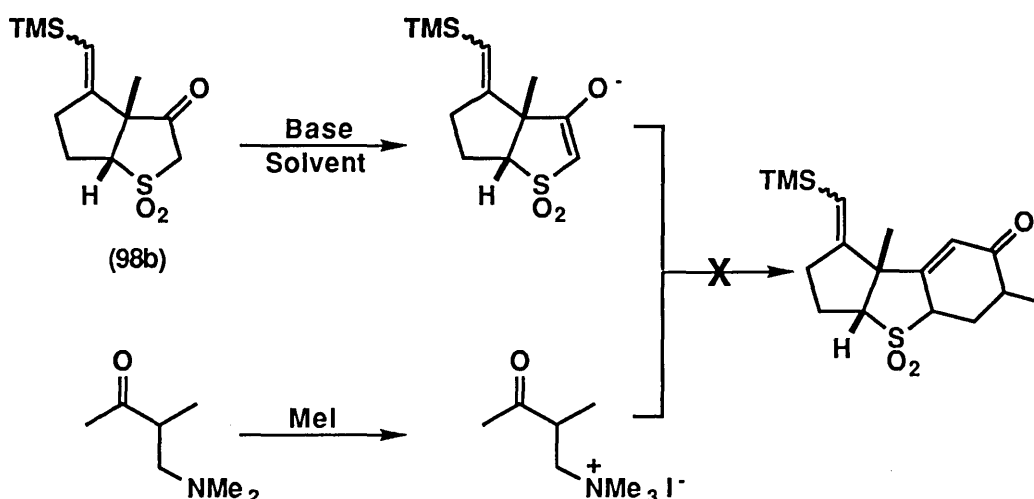
Similar studies by Russel⁵¹ concluded that β -elimination from systems of the type (125, $\text{X}=\text{Ph}$, CHPh_2 , $\text{Y}=\text{HgCl}$, SO_2Ph , I , Sn^nBu_3) is particularly slow for the vinylstannane analogue, the poorest yields of the addition-elimination product being obtained when $\text{Y} = \text{Sn}^n\text{Bu}_3$.

From these observations it is apparent that β -elimination is a relatively slow process for intermediate radical tin species of the type (126, $\text{Y}=\text{Sn}^n\text{Bu}_3$) in scheme 29. This could then explain the inefficiency of the radical chain in the Curran annulation sequence. Steric factors may also contribute, as the 5-exo-trig ring closure step involves the intramolecular attack of a tertiary radical on a trisubstituted double bond, interactions will occur between the quite bulky tin substituent and the electron withdrawing group of the olefinic acceptor. Further complications exist in the case of sulphone (93), as the compound exhibits a strong, broad absorption centred at 360nm in its u.v. spectrum. Thus, the possibility of competitive absorption in the reaction medium arises, which would in turn diminish the formation of initiator radicals thereby retarding the radical chain reaction.

Despite the problematic nature of the initial radical annulation reaction attempts to elaborate intermediate bicyclo[3.3.0]sulphone (98b) to the tricyclic precursor (96) were made. As cyclohexenannulation of (98b) was required, the classical Robinson annulation methodology⁵² was selected as a possible means of

achieving this transformation.

Several variations of the Robinson annulation procedure have been reported in the literature and extensive reviews of the subject exist.⁵³ A survey of the literature revealed that the Mannich base methiodide variant⁵⁴ was particularly suited to our needs, as this method works particularly well for highly stabilised enolate anions. The methiodide salt required for this reaction was readily obtained from the commercially available Mannich base by treatment with methyl iodide. (Scheme 30)



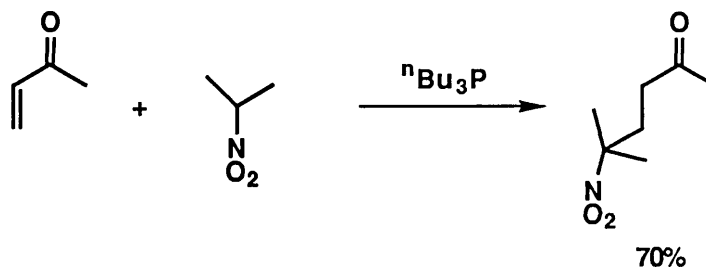
scheme 30

Base	Solvent
NaH	THF
^t BuOK	DME
NaOH	MeOH

Unfortunately, all attempts to cyclohexenannulate (98b) were to no avail, only low recovery of the starting sulphone being observed. The highly hygroscopic nature of the methiodide salt employed in these reactions was of particular concern, especially since in general small scale preparation was employed. Further attempts to annulate (98b) were made employing but-3-en-2-one as a model Michael acceptor, but again only starting material (98b) was recovered.

Further consultation of the literature revealed that trialkylphosphines have

been reported to be excellent catalysts for promoting 1,4 addition reactions of 2-nitropropane to α,β -unsaturated carbonyl compounds.⁵⁵ For example, treatment of an equimolar mixture of but-3-en-2-one and 2-nitropropane with 1 mol% of tri-*n*-butylphosphine led to the formation of the 1,4 addition product in 70% yield. (Scheme 31)



scheme 31

All attempts to engage sulphone (98b) and but-3-en-2-one in a similar reaction were unsuccessful. Carrying out the reaction at room temperature simply resulted in the rapid polymerisation of the enone. Pre-cooling the reaction mixture to -10°C did retard the rate of this polymerisation reaction, but after several hours at this temperature again only the sulphone starting material (98b) and polymeric material were obtained.

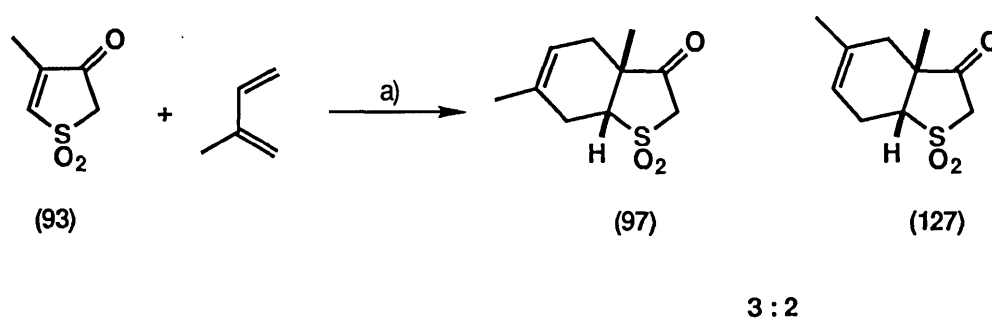
The reason for the failure of the enolate anion derived from (98b) to undergo 1,4 addition reactions is unclear. Although the lack of reactivity of the anion of β -ketosulphone (98b) may be due to the highly stabilised nature of the anion, this is the case with many Michael donors. Finally, in view of the fact that fluoride anion work-up of the successful radical cyclopentannulation reaction led to considerable reduction in yield (*vide supra*) the β -ketosulphone moiety in these systems may be inherently prone to base induced decomposition. This is further supported by the observation that recovery of (98b) from attempted Robinson annulation procedures was always fairly low.

The problematic nature of the initial radical cyclopentannulation sequence not only limited the extent to which Robinson annulation of (98b) could be explored,

but was also a weak link in our proposed synthetic chain. Thus, a second synthetic pathway toward trichodiene (11) was examined.

1.2.4 Approach via Heterohydrindane (97)

The primary step in our second approach taken toward trichodiene (11) consisted of a Diels-Alder reaction to construct the intermediate heterohydrindane (97). The highly reactive nature of sulphone (93) toward cycloaddition reactions has already been commented on, and it was envisaged that the compound would undergo a facile Diels-Alder reaction with isoprene itself, in which the electron releasing inductive effect of the methyl group should create a predominance of the required regioisomer (97). This proved to be the case, heating a thoroughly degassed, benzene solution of sulphone (93), isoprene and catalytic hydroquinone in a sealed tube at 125°C for 72 hours gave a 76% yield of two regioisomers (97) and (127) in a 3:2 ratio respectively. (Scheme 32)

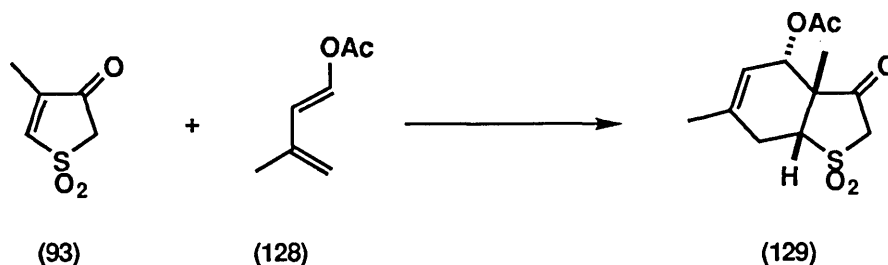


a) PhH, catalytic hydroquinone, sealed tube, 120°C

scheme 32

As expected the predominant isomer was (97), but separation of the two regioisomers proved to be surprisingly difficult, the two compounds being totally

inseparable by column chromatography. H.P.L.C. provided a possible answer, as a degree of separation had been observed using this method, but instead it was decided to use a modified isoprene, capable of directing the regiochemistry of the cycloaddition reaction toward the desired regioisomer. Further study⁴⁵ of the Diels-Alder reactions of sulphone (93) using 1-acetoxyisoprene (128) had shown that the presence of an electron donating group at the 1-position of the diene totally directed the stereochemistry toward one regioisomer, the 5-acetoxy compound (129) shown in scheme 33. This compound itself might be envisaged to possess synthetic potential in studies toward the higher oxygenated trichothecenes. For example, formation of the π -allyl palladium complex of (128) would create an potential electrophile for for B ring formation *via* attack by hydroxyl oxygen.

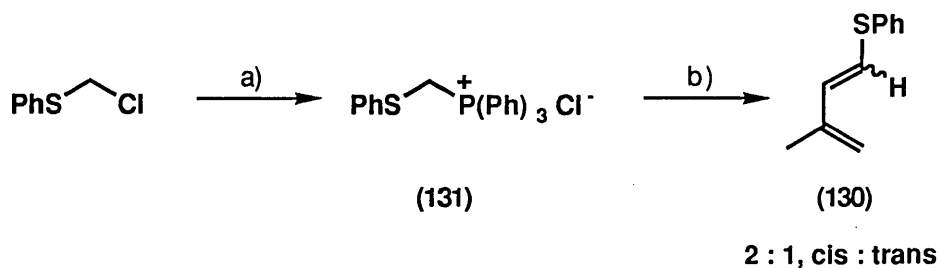


scheme 33

Hence, a strong electron donating, yet easily cleaved isoprene substituent was required and after some consideration it was decided to use 1-phenylthio-3-methylbuta-1,3-diene (130), as the phenylthio group would be strongly electron donating and direct the regiochemistry of the reaction toward the required regioisomer. This group could then be easily removed after the cycloaddition reaction by treatment with Raney nickel.

Initially the Wittig olefination procedure⁵⁶ was utilised in the synthesis of 1-phenylthio-3-methylbuta-1,3-diene (130), as shown below. Treatment of

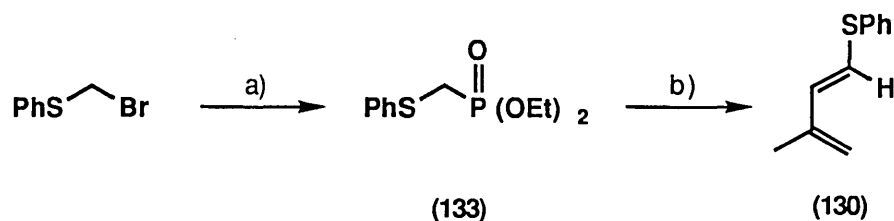
phenylthiochloromethane with triphenylphosphine gave the phosphonium salt (131) which in turn was employed in a Wittig reaction with methacrolein to give the requisite diene (130) as a 2:1 mixture of *cis* and *trans* isomers respectively. (Scheme 34)



a) P(Ph)_3 , PhCH_3 , Δ , b) $^n\text{BuLi}$, methacrolein

scheme 34

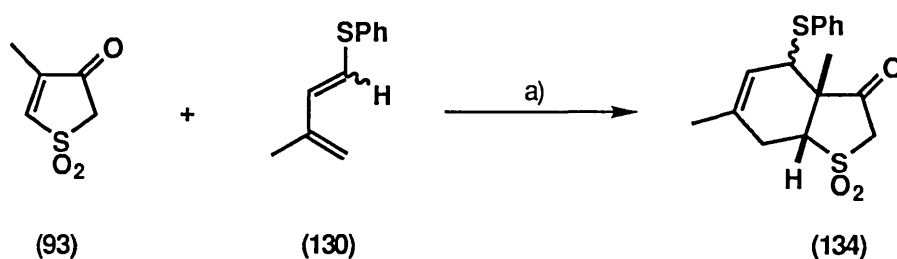
Removal of the phosphorous residues from the final product of this reaction proved to be quite difficult, distillation not being possible since extensive polymerisation of the product occurred even in the presence of hydroquinone. An alternative route to (130) was therefore employed, and, as is often the case with problematic Wittig reactions, use of Wadsworth-Emmons⁵⁷ methodology proved more successful. Thus, the phenylthiomethylphosphonate (133) was prepared by Arbuzov^{57b} reaction between phenylthiobromomethane and triethylphosphite, which then underwent Wadsworth-Emmons reaction with methacrolein. In this instance (130) was obtained exclusively as the *E*-isomer. (Scheme 35)



a) P(OEt)_3 , Δ , b) $n\text{BuLi}$, methacrolein

scheme 35

Subsequent studies upon the Diels-Alder reaction between sulphur diene (130) and sulphone (93) revealed that, after some experimentation, acceptable yields could be obtained using refluxing benzene as the solvent under stringently anaerobic conditions, a sonication procedure being used to render the reaction mixture oxygen free. Although yields tended to be lower than expected due to polymerisation of the diene, typically in the range of 40-50%, the reaction was regiospecific, only the required heterohydrindane regioisomer (134) being obtained as a 5:1 ratio of stereoisomers. (Scheme 36).



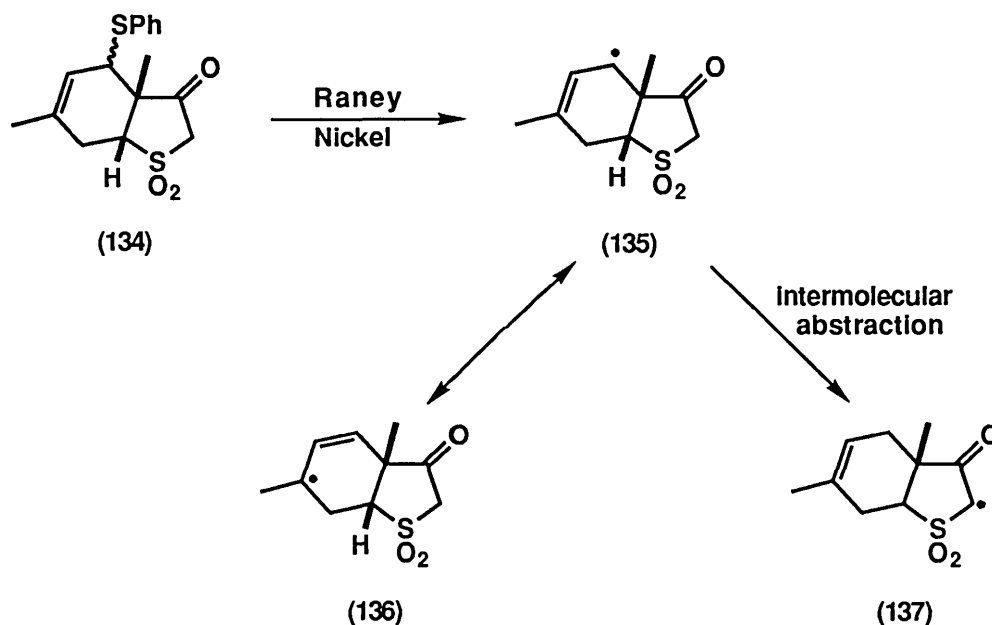
a) PhH , catalytic hydroquinone, 80°C

scheme 36

Removal of the sulphide moiety was then attempted by refluxing a methanolic solution of (134) in the presence of Raney nickel. Unfortunately,

subjecting heterohydrindane (134) to these reaction conditions led to the formation of several products, some of which appeared to be double bond regioisomers of the required product (97)

Although the actual mechanism of Raney nickel reduction is still in some doubt, it is generally accepted that reaction is free radical in nature⁵⁸. The formation of a free radical at C-5, as in (135) in scheme 37 could explain the failure of this step. As the radical (135) $\leftrightarrow$ (136) is allylic, hydrogen atom capture can occur at either terminus of the system, although on strain energy grounds the desired adduct (97) should be favoured. Alternatively, intermolecular hydrogen atom abstraction from the activated C-8 position leading to an intermediate such as (137) is also possible.



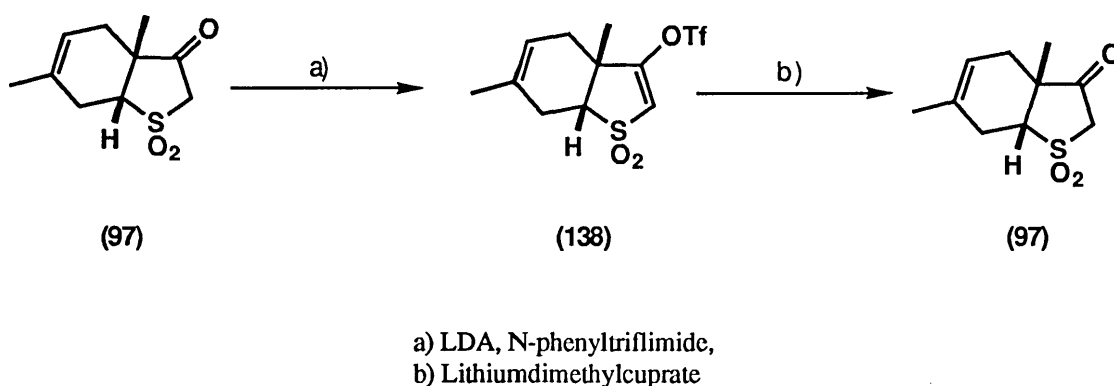
scheme 37

As this attempt to achieve regiospecific placement of the C-3 methyl group was unsuccessful, we decided to revert to the regioselective reaction with isoprene itself. For the purposes of preliminary exploratory chemistry, it was decided to use the isomeric mixture of adducts (97) and (127). This decision was taken in view of the fact that if significant advances were made the potential for HPLC separation existed,

and also by the fact that the ^1H nmr spectra of the two regioisomers were sufficiently distinct in terms of analysis. For the sake of clarity however, only the major isomer (97) will be shown in future reaction schemes.

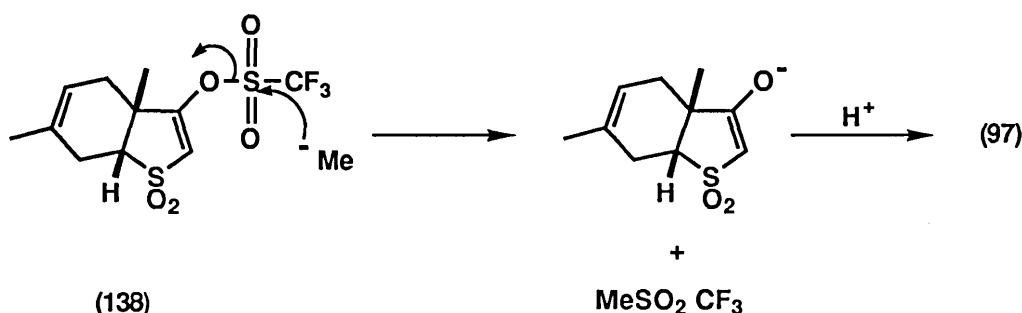
The next step in our proposed route was the introduction of a methyl group at C-7 of (97) which would eventually become the C-14 quaternary centre of trichodiene. This involved the transformation of a ketone group to a substituted olefin, a process usually achieved *via* attack of an appropriate nucleophile, such as a Grignard or lithio species, upon the carbonyl group followed by dehydration. In the case of heterohydrindane (97) this did not appear possible, the high acidity of the C-8 protons promoting the organometallic reagent to react preferentially as a base. As expected, and unlike simple carboxylic acids, treatment of (97) with excess methyllithium gave the β -ketosulphonyl anion which proved resistant to further attack.

Alternatively, one of the better known methods for the synthesis of substituted olefins from ketones is displacement of the corresponding vinyl triflate with a lithiumdialkylcuprate⁵⁹ Thus, the vinyltriflate (138) was prepared in 61% yield from the heterohydrindane (97) by a literature procedure.⁶⁰ (Scheme 38). N-phenyltriflimide was preferred as the triflating agent, as opposed to triflic anhydride, as it is much more easily handled, being a fairly air stable crystalline solid. Furthermore, C-sulphonation has been reported to be less of a problem with this reagent, unlike triflic anhydride⁶¹.



scheme 38

Surprisingly, treatment of the triflate (138) with lithiumdimethylcuprate led to the heterohydrindane precursor (97). Clearly, attack of the cuprate was occurring at the sulphur atom of the triflate rather than the sp^2 carbon centre, which was followed by elimination of the enolate anion of (97). (Scheme 39)

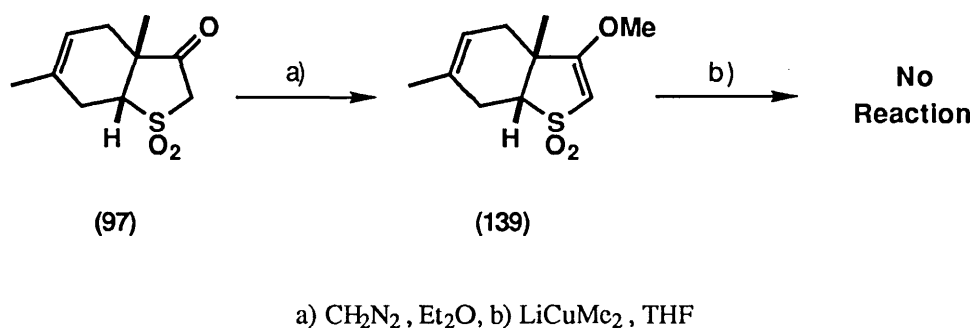


scheme 39

Attack at the sulphur atom of triflates is extremely rare, carbon-oxygen bond cleavage usually being preferred. This result suggested that unfavourable steric factors prevented the desired reaction, despite the reported observation⁶² that cuprate displacement of vinyl triflates is generally compatible to considerable steric congestion around both nucleophile and electrophile.

Attempts were then made to introduce the methyl group by Michael

addition of lithiumdimethylcuprate into α,β -unsaturated sulphone (139), readily available from treatment of heterohydrindane (97) with diazomethane. This compound should be an excellent Michael acceptor, the electron donating nature of the methoxy group combined with the electron withdrawing nature of the sulphone, creating a 'push-pull' system. Moreover, the steric congestion around the C-7 centre should be much less than in the case of triflate (138), and only one potentially reactive site exists in the molecule. However, treatment of (139) with large excesses of lithiumdimethylcuprate led only to the recovery of starting material, as shown below. (Scheme 40)

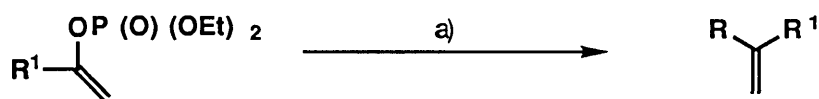


scheme 40

The failure of (139) to react with lithiumdimethylcuprate species clearly indicated that strong steric interactions prevented the reaction occurring. Organocopper species are known to be polymeric in their nature⁶³, and this factor, combined with the presence of a quaternary centre at the C-6 position could explain the deleterious reactivity of triflate (138) and α,β -unsaturated sulphone (139) toward cuprates.

These observations were further validated by attempts to introduce the C-7 methyl group by a palladium mediated cross coupling reaction. Oshima *et al.*⁶⁴ have reported that alanes also undergo palladium (0) mediated cross coupling reactions with enol phosphates, reaction yields being comparable to those observed for triflate-

stannane cross couplings. (Scheme 41).



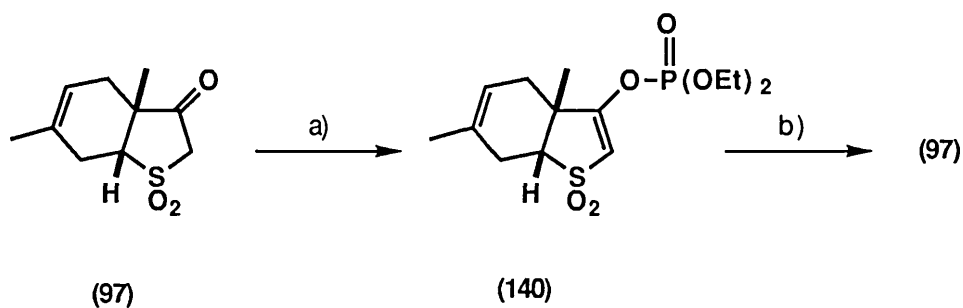
R^1 = aliphatic, aromatic

R = aliphatic

a) R_3Al , $\text{Pd(PPh}_3)_4$, 1,2-dichloroethane, Δ

scheme 41

Deprotonation of heterohydrindane (97) with LDA and subsequent treatment of the lithium enolate with diethylchlorophosphite gave the enol phosphate (140). All attempts to cross couple this compound, even in the presence of up to 50 mol% of tetrakis(triphenylphosphine)palladium(0), again led to formation of the heterohydrindane (97). (Scheme 42).



a) LDA, ClP(O)(OEt)_2 , b) AlMe_3 , $\text{Pd(PPh}_3)_4$, 1,2-dichloroethane, 80°C

scheme 42

Although the mechanism of this reaction involves insertion of the reactive

palladium species in the vinylic C-7, oxygen bond, as opposed to the perpendicular approach required for conjugate addition, it must once again experience great steric repulsion, such that the preferred mode of reaction is nucleophilic attack of the alane upon the phosphorous centre. The ketone product would then be formed by a similar mechanism to that shown in scheme 39.

To further investigate the theory that steric repulsion is in fact the reason for the lack of reactivity of the above compounds, the lowest energy conformations of the triflate (138) and the phosphate (140) were calculated, using the C.A.C.H.E. molecular modelling system.

As can be seen in figures 13 and 14 in both cases the C-6 quaternary methyl group points almost directly above the convex face of the sp^2 hybrid C-7 centre. Since attack of any reagent at the C-7 centre will occur via the least hindered convex face, concave face attack being too sterically hindered, this centre is effectively shielded from any incoming reagent. Thus, nucleophilic attack upon this centre is not sterically viable, and introduction of the eventual C-14 methyl group of trichodiene would have to be achieved by a different approach.

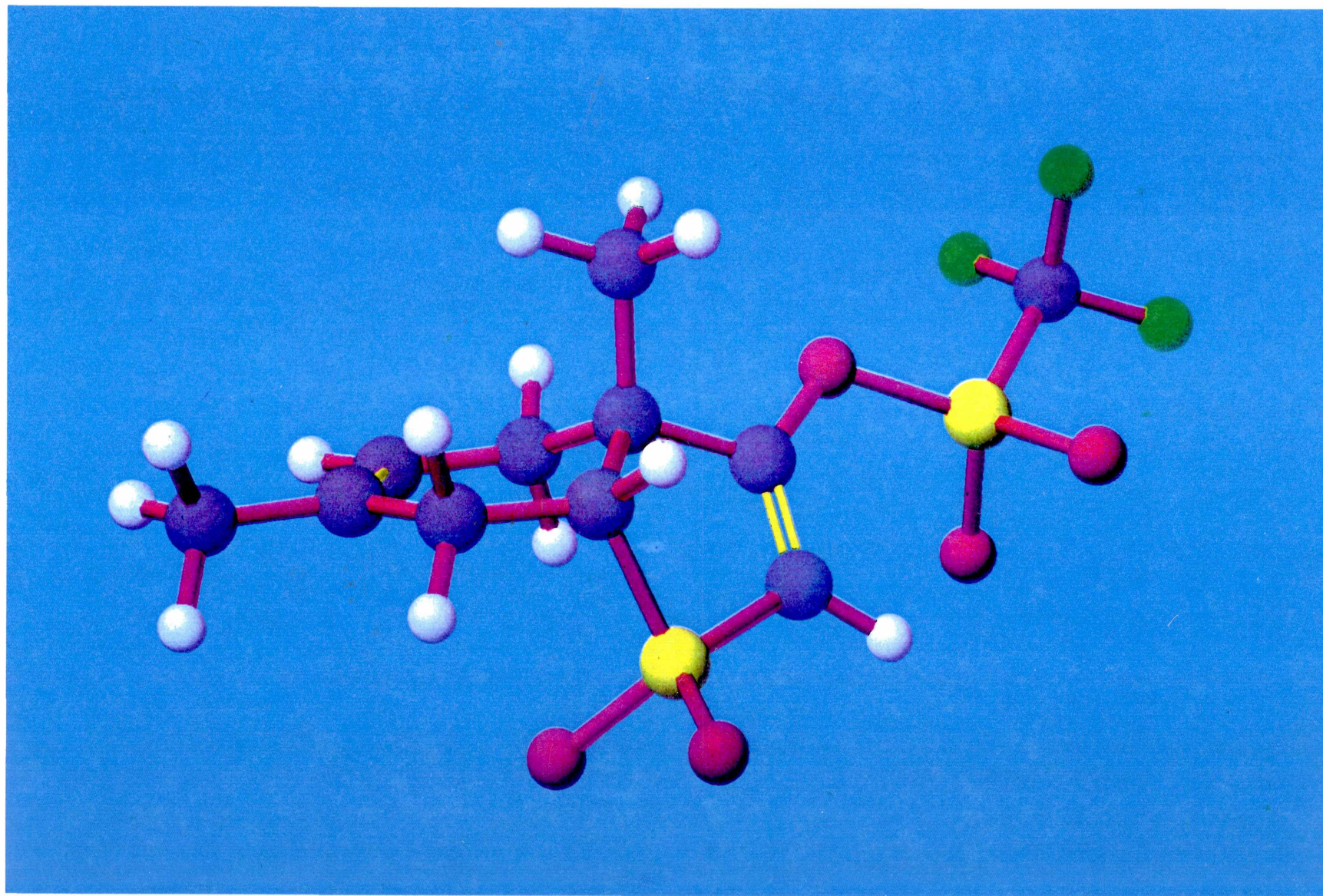


figure 13

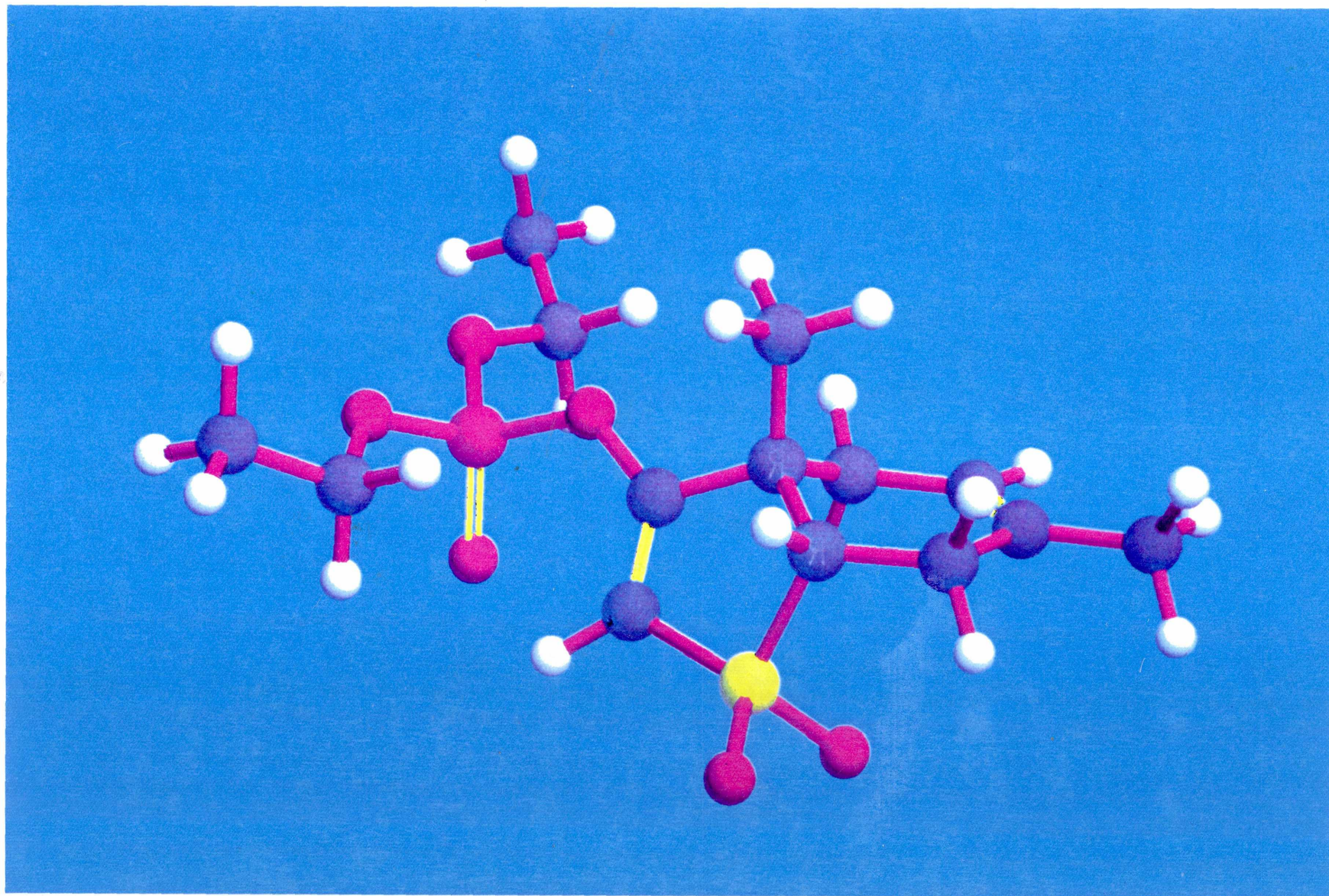
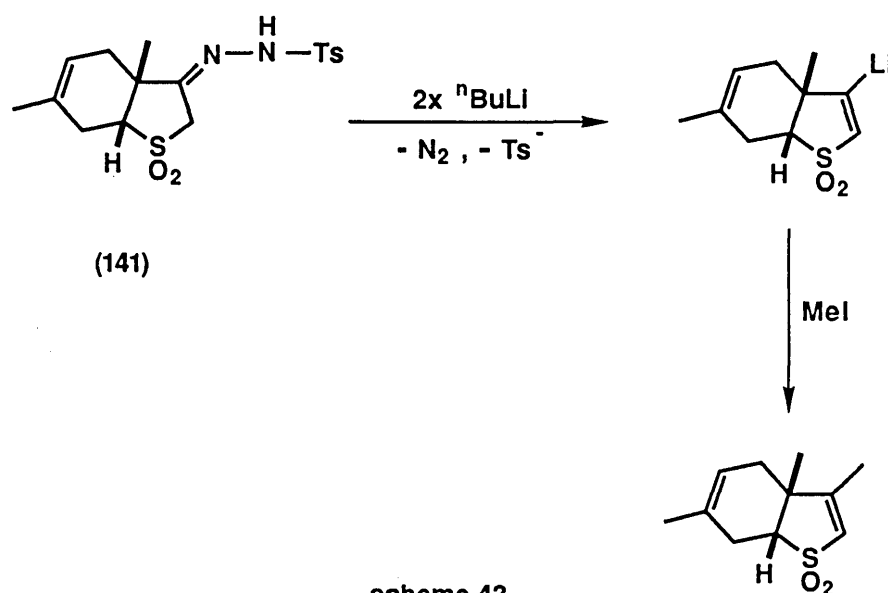


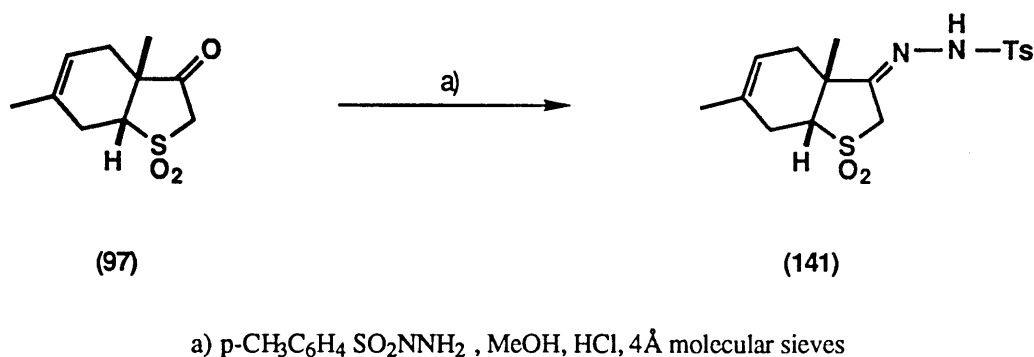
figure 14

In this respect we were particularly attracted to the potential of the Shapiro reaction,⁶⁵ which has been extensively⁶⁶ used in the literature to convert carbonyl groups into substituted olefins. As indicated in scheme 43 formation of the tosylhydrazone (141) and subsequent dilithiation of this compound should lead, after loss of nitrogen and tosyl anion, to a vinyl lithium species that would be capable of reacting as nucleophile toward iodomethane; reversing the electronic rôles of the reacting species with respect to previously attempted methylation reactions.



In the event, the formation of tosylhydrazone (141) proved to be quite challenging, the application of standard methods for the formation of hydrazones were to no avail. After much experimentation, it was discovered that quite forcing reaction conditions were necessary to carry out the transformation, typical conditions being a refluxing solvent system of 5:1 methanol : concentrated hydrochloric acid in the presence of crushed 3Å molecular sieves, which gave the desired product in 98% yield. The necessity for such forcing conditions again demonstrates the hindered nature of the C-7 position. Also, only one regioisomer of the tosylhydrazone (141) was formed,

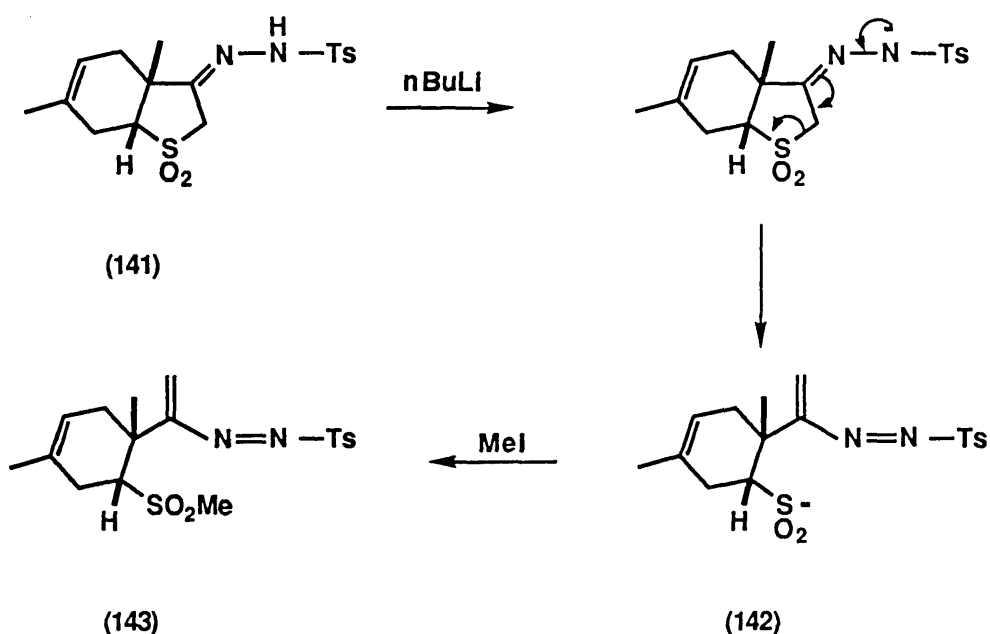
presumably unfavourable steric interactions between the adjacent methyl group and the tosyl group prevented the formation of the other possible regioisomer. (Scheme 44).



scheme 44

Exposure of the hydrazone (141) to the standard elimination conditions followed by use of iodomethane as the electrophile did not result in the formation of the expected product. The spectroscopic data so far collected for the product appear to be consistent with the structure (143) shown below. Unfortunately the non-crystalline nature of the material obtained from this reaction prevented the total elucidation of its structure by X-ray analysis. The proposed mechanism for the formation of this product is shown in scheme 45

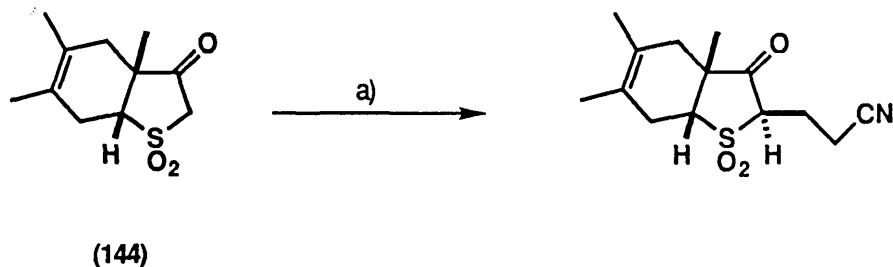
Deprotonation of the hydrazone nitrogen atom and subsequent fragmentation of the thiocyclopentane ring results in the sulphonyl anion (142), which upon treatment with methyl iodide gives the methyl sulphone product (143). The driving force for this fragmentation reaction is the ability of an alkyl sulphinylate to function as a leaving group, though reduction in steric strain of the system may also be a contributing factor. However, it must be stressed that this structure remains to be rigorously established.



scheme 45

1.3 Conclusions and Perspectives

The major objective of this section of our research programme was to explore the chemistry of 3-methyl-4-thiacyclopent-2-ene-1,1-dioxide (93) in terms of its application as an isoprenoid synthetic equivalent toward the synthesis of trichothecenes. Despite the fact that our synthetic target, trichodiene (11) was not successfully completed, the foregoing discussion has hopefully demonstrated that the sulphone-enone building block (93) is unusually versatile, and capable of participating in free radical, ionic and cycloaddition reactions, all of which are formidable weapons in the arsenal of the synthetic organic chemist. Furthermore, associated studies carried out in the latter stages of this project revealed that in the presence of HMPA the enolate anion derived from heterohydrindane (144), a Diels-Alder product obtained from cyclic sulphone (93) and 2,3-dimethylbuta-1,3-diene, undergoes 1,4-additions to appropriate Michael acceptors in good yield. (Scheme 46)



a) ⁿ Butyllithium, HMPA, THF, -78°C, acrylonitrile

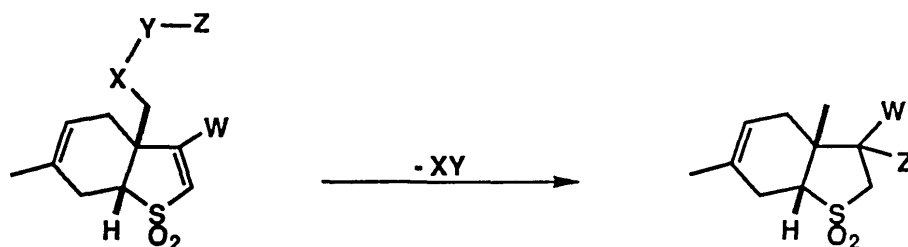
scheme 46

Spectral data obtained for this compound suggested that addition was stereoselective, presumably the electrophile approaching heterohydrindane (144) from the least hindered convex face, and so our initial strategy of utilising the sulphone functional group as a means of directing the stereochemical outcome of chemical transformations of compounds such as (144) appears to hold.

This observation may hold key to success in future Robinson annulation procedures.

Also, as shown by molecular modelling, the proximate nature of the C-6 quaternary methyl group in heterohydrindanes of the type (141) and (142) creates a severe steric hinderance around the C-7 position of these systems, making chemical elaboration of this centre difficult.. However, the very nature of the close proximity of this quaternary group could be in fact exploited by introduction a C-6 substituent that is capable either of 'anchoring' an external reagent or promoting intramolecular functionalisation of the C-7 position itself, as shown for a general case in scheme 47. Thus in theory, the proximate nature of the C-6 substititnt has the potential to direct a reagent to the C-7 position, thus giving rise to the possibility of regioselective

transformations.



scheme 47

This approach may therefore provide a means of circumventing the problems associated with intermolecular attack upon the C-7 position of such derivatives.

In summary, although further work is required to totally ascertain the full potential of 3-methyl-4-thiacyclopent-2-ene-1,1-dioxide (93) as a terpenoid building block, and hence toward a general route to the trichothecenes, the range and scope of reactivity exhibited thus far by (93) suggests that this molecule possesses definite qualities as an isoprenoid synthon.

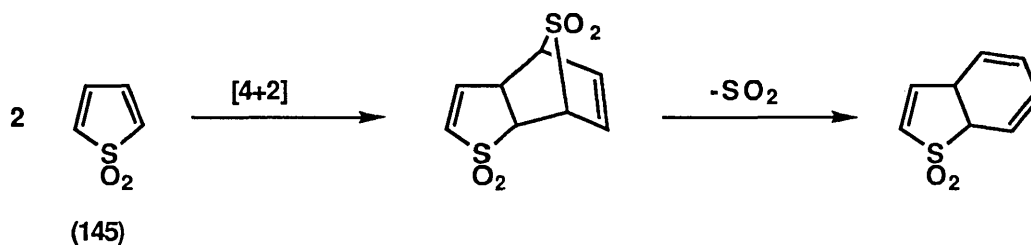
Chapter Two

The Synthesis and Reactions of Thiophene-1,1-dioxides.

2.1. Introduction.

2.1.1 Background

Thiophene-1,1-dioxide (145) is a thermally unstable compound that has never been isolated in the free state. Upon formation, the molecule rapidly dimerises by a [4+2] cycloaddition reaction which affords dihydrobenzo(b)thiophene-1,1-dioxide with the loss of sulphur dioxide⁶⁷, as in scheme 48.



scheme 48

Fortunately, not all thiophene-1,1-dioxides are unstable at ambient temperatures, substitution around the ring tends to create a steric barrier to the dimerisation and thereby increases the thermal stability of these compounds. 3,4-Dimethyl-(101), 2,5-di-*tert*-butyl-(146) and tetrachlorothiophene-1,1-dioxide (147) all have been isolated in the free state. (Figure 15).

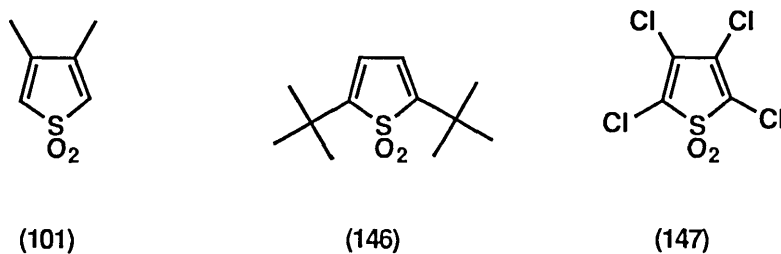


figure 15

3,4-Dimethyl-thiophene-1,1-dioxide (101) was an intermediate in our synthesis of the cyclic sulphone (93), (See scheme 21) and it was the marked stability of this compound that first raised our interest in these molecules.

Theoretical and structural studies have been carried out on various thiophene-1,1-dioxides in attempts to elucidate the structural and electronic properties of these compounds. Schweig *et al.*⁶⁸ recorded the photoelectron spectrum of 2,5-di-*tert*-butylthiophene-1,1-dioxide (146) and concluded that the presence of the sulphone group stabilised the HOMO of the compound by 0.85eV relative to 2,5-di-*tert*-butylcyclopentadiene. X-ray diffraction studies have also been carried out on 2,5-di-*tert*-butylthiophene-1,1-dioxide⁶⁸ (146), and oxidation of the sulphur atom was found to cause an elongation of the carbon-sulphur bond by 0.04Å relative to 2,5-di-*tert*-butylthiophene, as in figure 16.

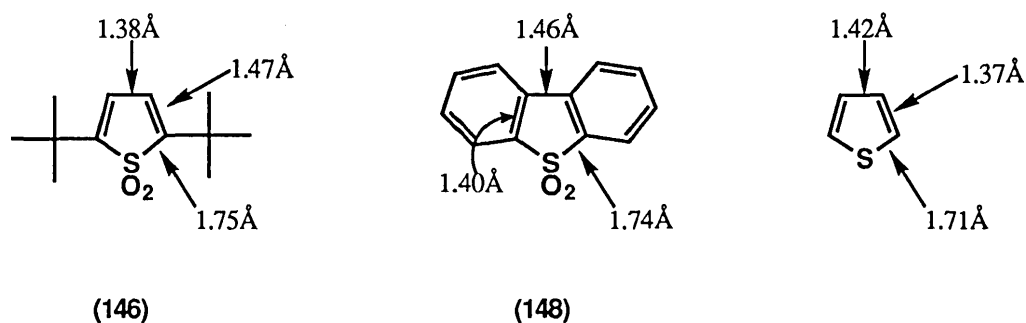


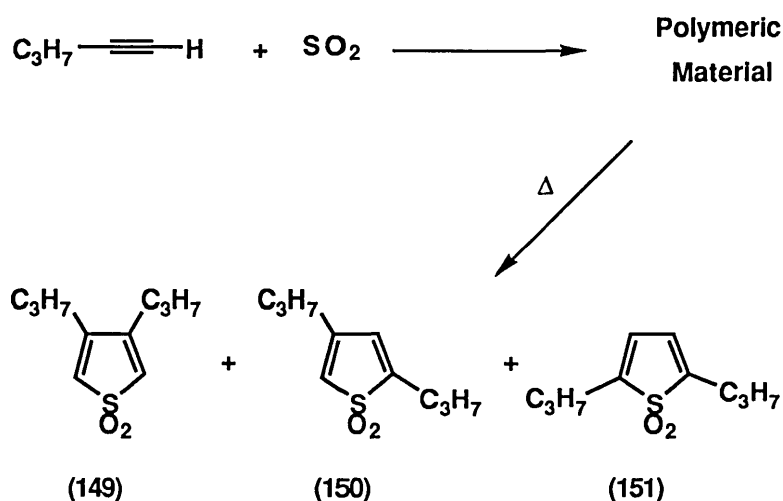
figure 16

A more striking observation from figure 16 is the large elongation of the carbon-carbon double bond of (146); 0.1eV relative to 2,5-di-*tert*-butylthiophene. Studies upon dibenzothiophene dioxide (148) by Kronfeld⁷⁰ disclosed a similar elongation of the carbon-sulphur bond and a small elongation of the carbon-carbon double bond. The lengthening of the double bond in (148) will obviously be less pronounced than in (146) as distortion of a highly stable aromatic ring system would be involved. From the above observations it is apparent that electron withdrawal by

the sulphone group destabilises the carbon-carbon diene system. Whether this electron withdrawal is purely inductive in its nature or a combination of inductive and other effects is still unclear. Whatever the nature of the electronic effects the sulphone group has upon the diene system in the compounds, the resulting set of energy levels certainly promote thiophene-1,1-dioxide cycloaddition reactions.

2.1.2 Synthesis of Thiophene-1,1-dioxides

The existence of thiophene-1,1-dioxides was first suggested by Marvin and Williams⁷¹ who proposed the regioisomeric di-*n*-propylthiophene-1,1-dioxides (149), (150) and (151) as the products obtained from the pyrolysis of the polymer formed between sulphur dioxide and pent-1-yne. (Scheme 49).



scheme 49

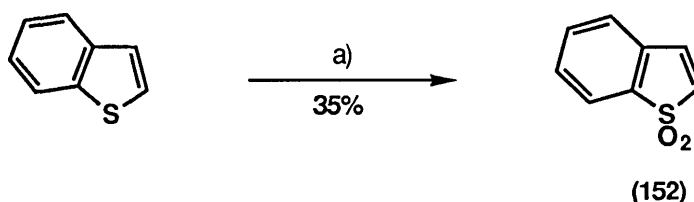
Chemical degradation studies established the presence of α,β -unsaturated sulphone functionality, but total characterisation of the products obtained was not possible.

Generally, the methods for the synthesis of thiophene-1,1-dioxides involve

either the oxidation of an appropriate thiophene or a double elimination reaction to establish the diene system of the final product. Hence, it is appropriate to discuss these two approaches and other methods for the formation of these compounds separately.

2.1.2.1 Approaches Involving Oxidation of Thiophenes.

Several oxidising agents have been utilised for the transformation of thiophenes to the corresponding thiophene-1,1-dioxides, although until recently the method was quite capricious in its nature. Initially acidic hydrogen peroxide was employed as the oxidising reagent, Lanfry⁷² reporting the preparation of benzo(b)thiophene-1,1-dioxide (152) by the oxidation of benzo(b)thiophene with this reagent. (Scheme 50).



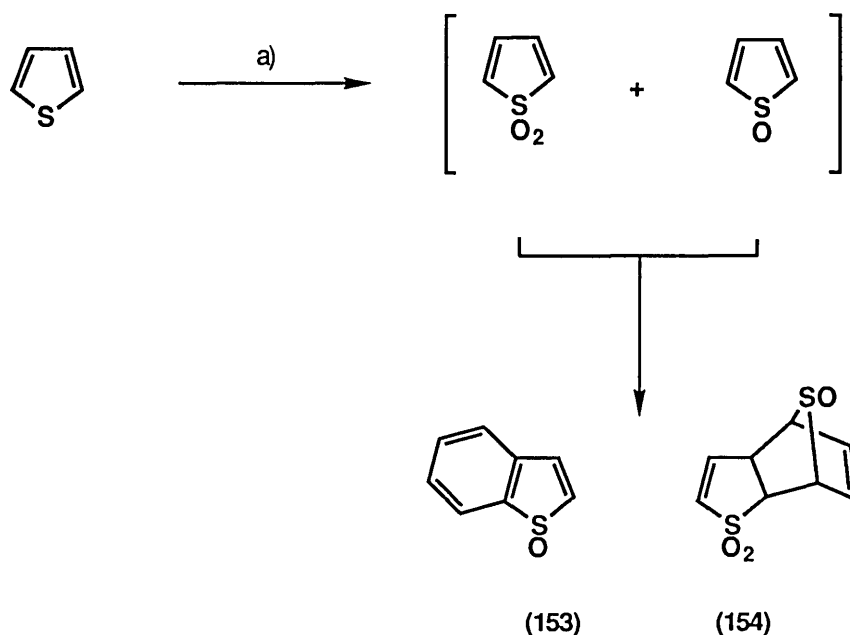
a) H_2O_2 , $\text{CH}_3\text{CO}_2\text{H}$

scheme 50

Only a slight excess of oxidising agent was employed in this reaction and the yield was a fairly poor 35%. The procedure was modified by Lampert⁷³ and Davies⁷⁴ who both independently reported that the use of a three fold excess of peroxide reagent and briefly refluxing the reaction mixture greatly improved yields to a much more acceptable 90%.

Despite the initial success of peroxide oxidations, the appearance of more easily handled and stored peracid reagents, especially *meta*-chloroperbenzoic acid

(*m*-CPBA), led to the general demise of the acidic hydrogen peroxide reagent. Lampert had already noted that peracetic acid oxidised benzo(b)thiophene to its dioxide in comparable yield to that obtained with acidic hydrogen peroxide, whilst Melles and Backer⁷⁵ reported that various polysubstituted phenyl and methyl thiophenes could be oxidised to their corresponding dioxides by treatment with perbenzoic or peracetic acid. They also noted that the presence of electron withdrawing groups upon the ring retarded the reaction, for example, 2-acetylthiophene was totally unreactive despite prolonged heating of the reaction mixture. Furthermore, independent attempts to oxidise thiophene itself^{76,77} resulted in the proposed formation of the bicyclic sulfoxide (153) and sulphone (154), although total determination of these structures was not possible. These products were presumably formed by [4+2] cycloaddition between the two intermediates shown. (Scheme 51).

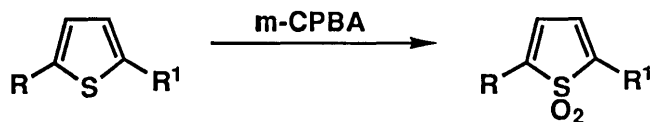


a) PhCO_3H or $\text{CH}_3\text{CO}_3\text{H}$

scheme 51

Similar results were obtained with various monosubstituted thiophenes, although again the exact structural assignments of these compounds were never resolved.

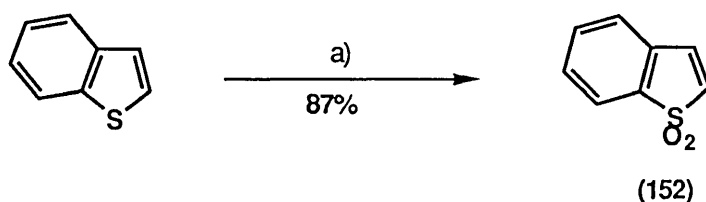
With the emergence of m-CPBA as a potent oxidising agent, several papers concerning the application of this reagent to the oxidation of thiophenes appeared. Initially, yields tended to vary considerably, and undesired side reactions such as polymerisation and acid catalysed decomposition often caused diminished reaction yields. In general, acceptable yields were only obtained with polysubstituted thiophenes. Van Tilborg⁷⁸ introduced a modified procedure for this transformation in which three mole equivalents of m-CPBA were employed and the residual acid in the reaction mixture was frozen out. The solids were then removed by treatment with tertiary amino substituted molecular resins. A further advantage of these resins was that they decomposed, then removed, any residual peracid present in the reaction mixture, thus preventing product over oxidation and degradation. This modification allowed the preparation of several disubstituted thiophene-1,1-dioxides in acceptable yields, the technique being clearly superior to previous methods, as can be seen in table 1



	Yield (%)	
R , R ¹	Me	Ph
Van Tilborg	52	74
Melles	14	47

table 1

More recently several other oxidising agents have been employed to convert thiophenes to their corresponding thiophene-1,1-dioxides. Oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH), a reagent often utilised in the oxidation of enolates⁷⁹, quite smoothly oxidises 2,5 diphenylthiophene and benzo(b)thiophene to their dioxides⁸⁰. Conditions are very mild, but long reaction times are necessary. Hence, stirring a DCM solution of benzo(b)thiophene with 1.1 equivalents of MoOPH for one week at room temperature gave benzo(b)thiophene-1,1-dioxide (152) in 87% yield. (Scheme 52).



a) MoO₅ , HMPA, DCM, 6 days

scheme 52

Sodium perborate has also been utilised in this transformation⁸¹ and several thiophenes have been oxidised by this reagent. Unfortunately, the reaction requires a highly acidic medium, glacial acetic acid often being employed as the solvent, thus precluding acid sensitive functionality and restricting the applicability of the process. However, yields do tend to be better than those obtained with m-CPBA.

Finally, the versatile oxidising agent dimethyldioxirane (DDO) has also been employed.⁸² Conditions are very mild, reaction occurring at room temperature in virtually neutral conditions. The reaction is also very selective, high yields being obtained and side reactions not being a significant problem. 2,5-Dimethylthiophene, for example, is cleanly oxidised to its dioxide in high yield, in almost twice the yield obtained with m-CPBA using the method of Van Tilborg, as shown in table 2.



Thiophene		Yield (%)	
R	R ¹	m-CPBA	DDO
Me	Me	52	93
PhCH ₂	PhCH ₂	48	93
Et	COMe	0	53

table 2

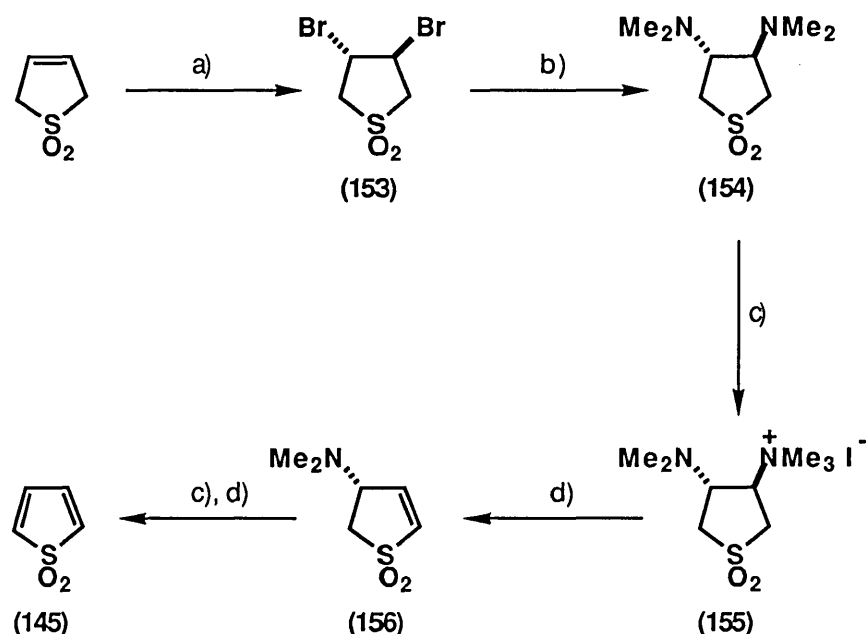
Of greater interest is the third entry in table 2 where a deactivated thiophene, 2-acetyl-5-ethyl-thiophene, is oxidised in 53% yield, despite the fact that the compound has been reported to be totally unreactive towards m-CPBA.

The remarkably facile, yet selective nature of this reagent makes it, at

present, the best reported oxidising agent for the formation of thiophene-1,1-dioxides from thiophene precursors.

2.1.2.2 Double Elimination Approaches

The majority of other approaches taken toward thiophene-1,1-dioxides involve elimination reactions to establish the diene system of the compound. The first of these, which was also the first attempted synthesis of the parent compound thiophene-1,1-dioxide, was reported by Bailey and Cummins⁸³ in 1954. The six step synthetic pathway is shown. (Scheme 53).



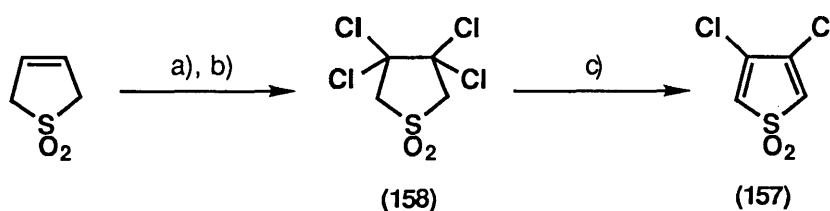
a) Br_2 , CHCl_3 , Δ , b) Me_2NH (excess), 3 days,
c) MeI , d) Ag_2O , H_2O

scheme 53

2,5-Dihydrothiophene-1,1-dioxide was brominated to afford the dibromide (153). Treatment of this dibromide with dimethylamine gave the diamine (154), by an elimination-addition sequence, a large excess of dimethylamine being present in the reaction mixture. Formation of the methiodide salt (155) and its subsequent

Hoffman degradation gave the vinyl sulphone (156) which was again subjected to the degradation sequence to give the required thiophene-1,1-dioxide (145). The product was reported to be stable in dilute solution at low temperature, but rapidly dimerised upon concentration or warming.

A similar route has been used by Mandel *et al.*⁸⁴ in their preparation of 3,4-dichlorothiophene-1,1-dioxide (157). Again a double elimination reaction was utilised to form the thiophene-1,1-dioxide product. The elimination precursor was the tetrachloro species (158) obtained from extensive chlorination of 2,5-dihydrothiophene-1,1-dioxide. (Scheme 54).



a) Cl₂, CCl₄, b) Cl₂, CCl₄, hν, Δ, c) MeOH, NH₃, H₂O

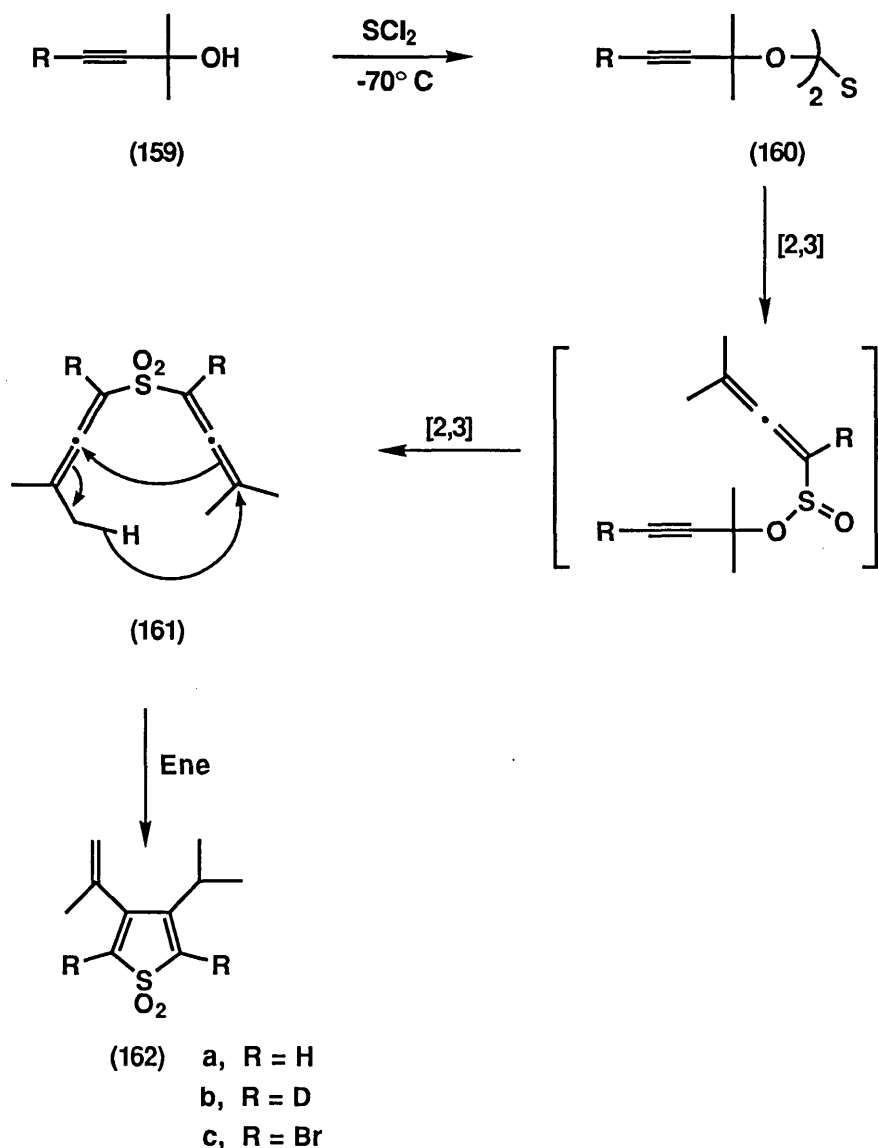
scheme 54

Base induced elimination from suitable precursors is a facile method for the formation of thiophene-1,1-dioxides. 3,4-Dihalothiacyclopentane-1,1-dioxides are often the reagents of choice as the elimination reaction is very facile, especially in the 3,4 dibromo species. This allows the generation of potentially unstable thiophene-1,1-dioxides at low temperatures, obviously a favourable process. Also, these precursors are readily available *via* halogenation of the appropriate 2,5-thiacyclopent-3-ene-1,1-dioxide.

2.1.2.3 Other Methods of Generation.

Very few other methods for the preparation of thiophene-1,1-dioxides have

been reported in the literature, but of particular note is the synthesis of 3-isopropenyl-4-isopropyl-thiophene-1,1-dioxide (162a) from dimethylpropargyl alcohol (159).⁸⁵ (Scheme 55).



scheme 55

Treatment of propargyl alcohol (159) with sulphur dichloride gives the intermediate sulfoxylate (160) which then undergoes two sequential 2,3 sigmatropic shifts to afford the diallenyl sulphone (161). Upon further heating the thiophene-1,1-dioxides (162) are formed via an intramolecular ene reaction. To demonstrate the applicability of this methodology, 2,5-dideuterio (162b) and 2,5-dibromothiophene-

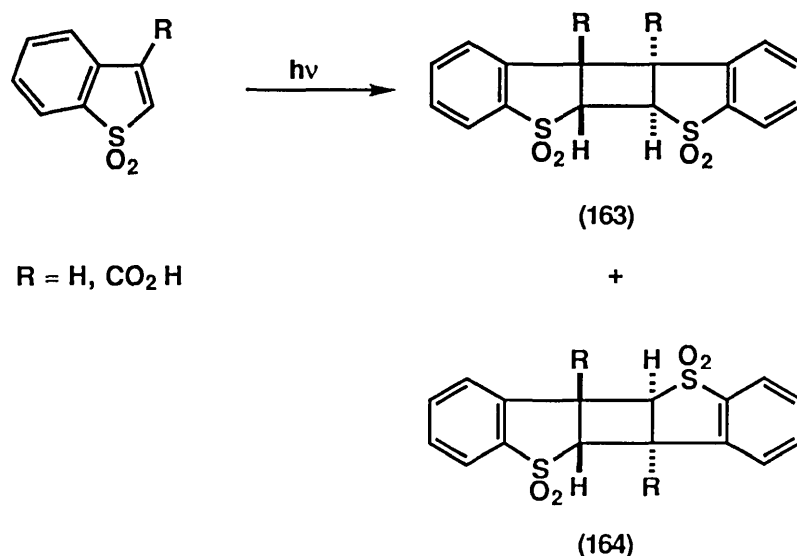
1,1-dioxides (162c) were prepared in an analogous fashion.

2.1.3 Reactions of Thiophene-1,1-dioxides

Not surprisingly cycloaddition reactions take a major rôle in the range of reactivity displayed by thiophene-1,1-dioxides, though other reactions have been reported. The compounds tend to react as 4π components, although cycloadditions where they behave as 2π components are known. Since the range and nature of these reactions is quite diverse it is appropriate to consider each mode of cycloaddition separately, for clarity.

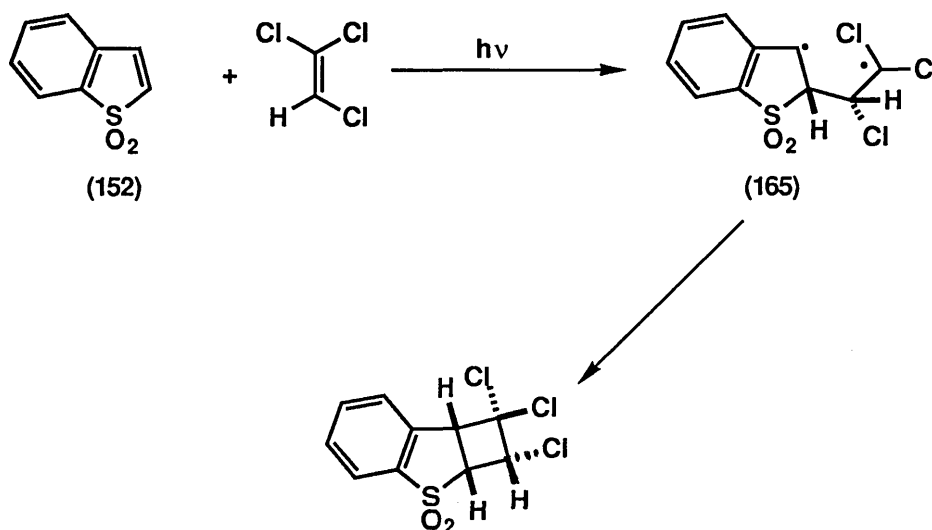
2.1.3.1 Photochemical [2+2] Cycloaddition

Benzo(b)thiophene-1,1-dioxides readily undergo photochemical dimerisation by a [2+2] cycloaddition process. Photolysis of benzo(b)thiophene-1,1-dioxides of the type shown in scheme 56 affords both the head to head and head to tail dimers (163) and (164) respectively.⁸⁶



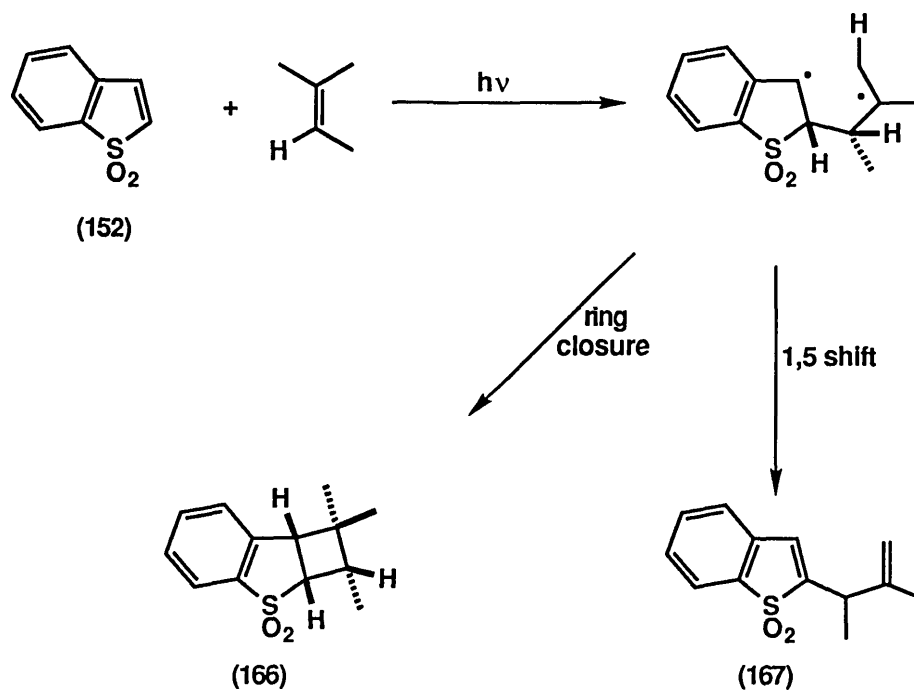
scheme 56

The stereochemistry of the reaction is predominantly anti as shown. Alkenes also undergo [2+2] cycloaddition reactions with benzo(b)thiophene-1,1-dioxide (152), and in unsymmetrically substituted olefins, such as 1,1,2-trichloroethene, the cycloaddition is regioselective. Initial bond formation occurs between the 2-position of the benzo(b)thiophene-1,1-dioxide and the least substituted end of the olefin acceptor, giving the biradical intermediate (165).⁸⁷ (Scheme 57).



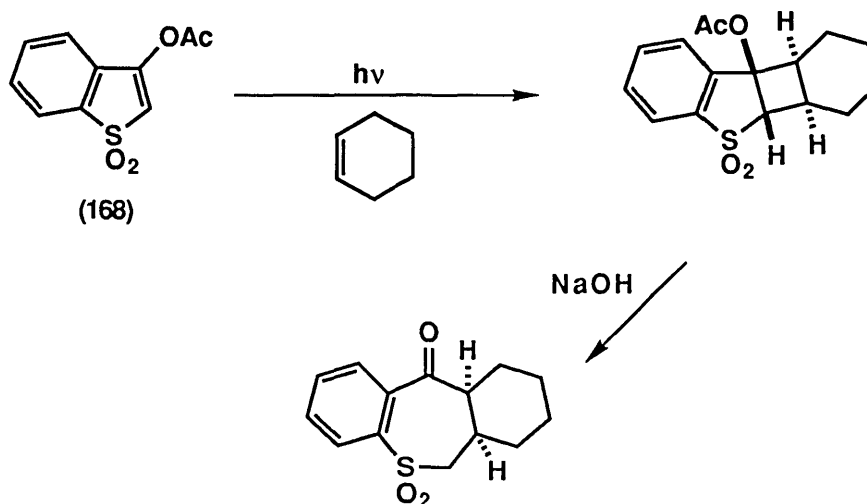
scheme 57

The intermediacy of the biradical intermediate (165) was proved by studies involving 2-methylbut-2-ene. Two products were obtained from the reaction between this olefin and benzo(b)thiophene-1,1-dioxide (152), the expected [2+2] cycloadduct (166) and also the isopentenylbenzo(b)thiophene-1,1-dioxide (167), the latter product being obtained *via* a 1,5 hydrogen shift of the intermediate biradical (165). (Scheme 58).



scheme 58

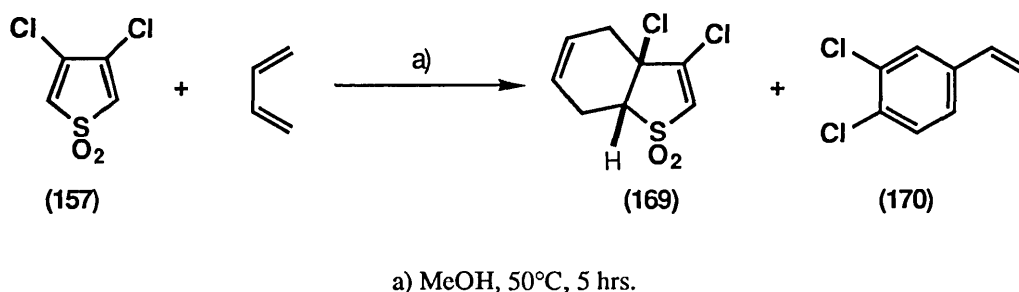
3-Acetoxybenzo(b)thiophene-1,1-dioxide (168) also undergoes cycloaddition reactions with cycloalkenes.⁸⁸ The acetoxycyclobutane product, when treated with base, undergoes a ring expansion reaction to give novel seven membered tricyclic γ -keto sulphones, as shown for cyclohexene. (Scheme 59).



scheme 59

2.1.3.2 Thermal [2+4] Cycloaddition Reactions

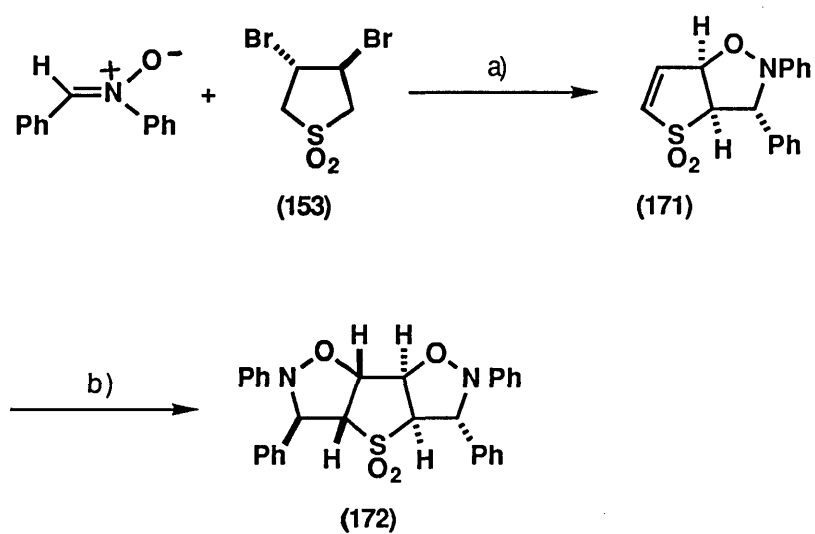
As already seen in its dimerisation reaction, thiophene-1,1-dioxide is capable of reacting as the 2π component in Diels-Alder reactions. Furthermore, heating a mixture of 3,4-dichlorothiophene-1,1-dioxide and buta-1,3-diene leads to the formation of two products⁸⁹, (169) and (170). The former arises from the thiophene-1,1-dioxide reacting as the 2π -component, whilst the latter arises from reaction as the 4π component followed by extrusion of sulphur dioxide. (Scheme 60).



scheme 60

2.1.3.3 1,3 Dipolar Cycloaddition Reactions.

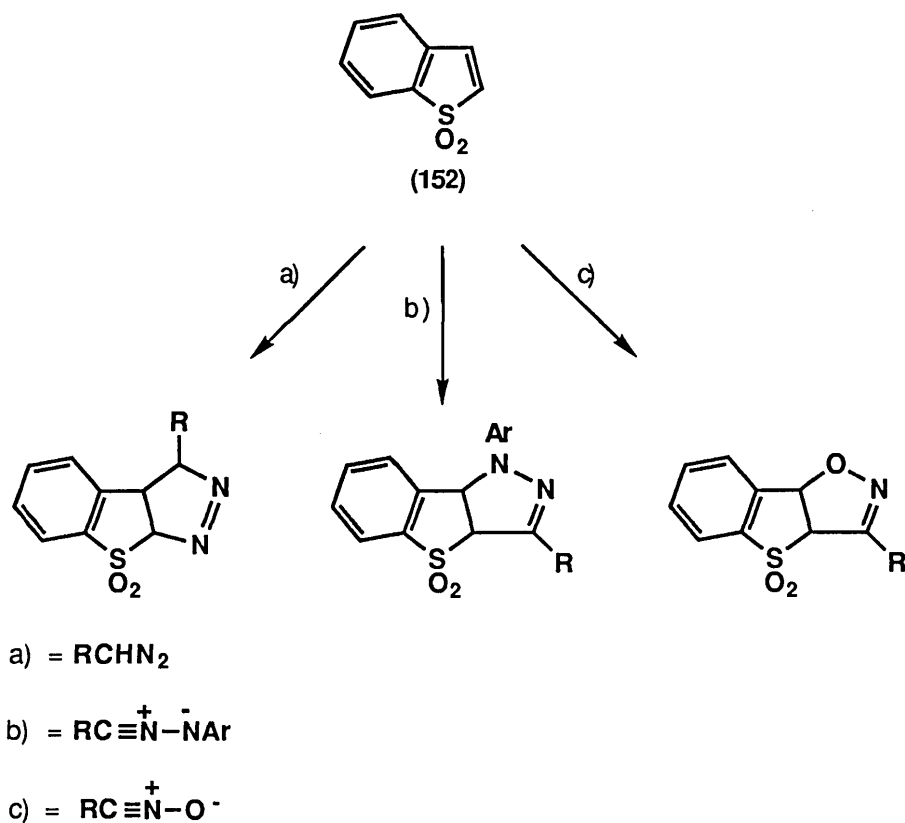
Thiophene-1,1-dioxide, generated *in situ* by the action of base upon the dibromide (153), undergoes a 1,3 dipolar cycloaddition reaction with N, α -diphenylnitrone.⁹⁰ The reaction is regioselective, giving the isooxazoline (171) as the sole product. Use of excess nitrone leads to the bis adduct (172) where the two isooxazoline rings have an anti arrangement, X-ray studies elucidating the stereochemical relationship between the two rings. (Scheme 61).



a) Pyridine, CHCl₃, b) excess N,α-diphenylnitronium ion.

scheme 61

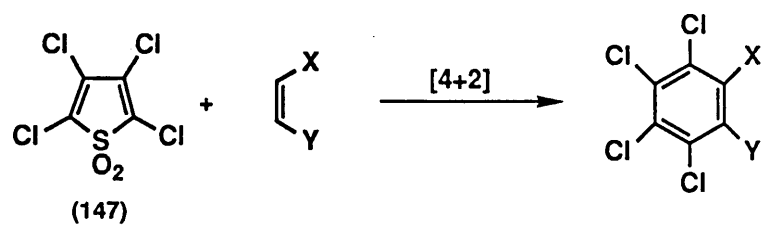
Benzo(b)thiophene-1,1-dioxide (152) also undergo 1,3 dipolar cycloaddition reactions with a variety of 1,3 dipoles; dipolar cycloaddition reactions with diazoalkanes⁹¹, nitrilimines⁹² and nitrile oxides⁹³ have all been reported. (Scheme 62).



scheme 62

2.1.2.4 Thermal [4+2] Cycloaddition

A vast array of thermal [4+2] cycloaddition reactions of thiophene-1,1-dioxides have been reported in the literature and a comprehensive discussion of these reports is beyond the scope of this dissertation. However, the wide range of alkenes that will undergo [4+2] cycloadditions with thiophene-1,1-dioxides is aptly demonstrated by studies of Raasch⁹⁴ involving 2,3,4,5-tetrachlorothiophene-1,1-dioxide (147). Selected examples from this report are shown in table (3).

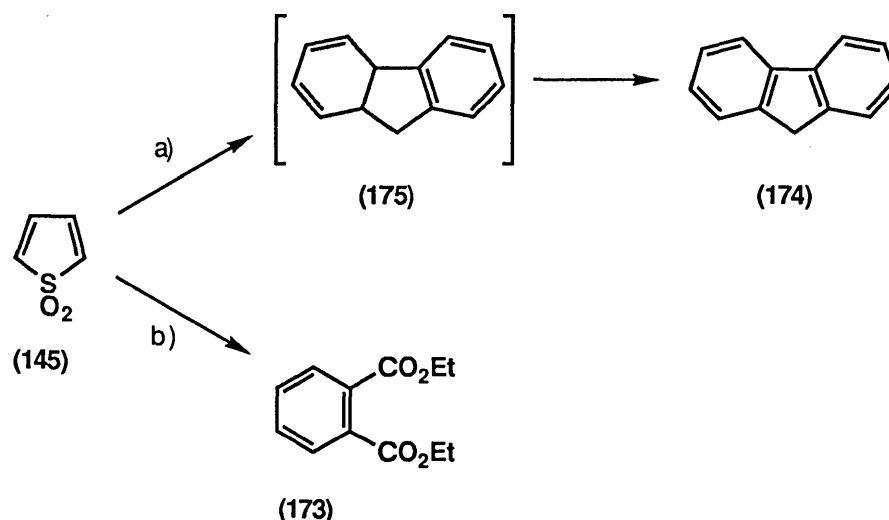


Alkene	Product	Yield (%)
		89
		92
1-Dodecene		88
		73
		83
		91

table 3

The above results demonstrate the potent reactivity of thiophene-1,1-dioxides toward Diels-Alder cycloaddition reactions. Reaction conditions tend to be mild and often exothermic in their nature, with both electron deficient and electron rich dieneophiles reacting in high yield.

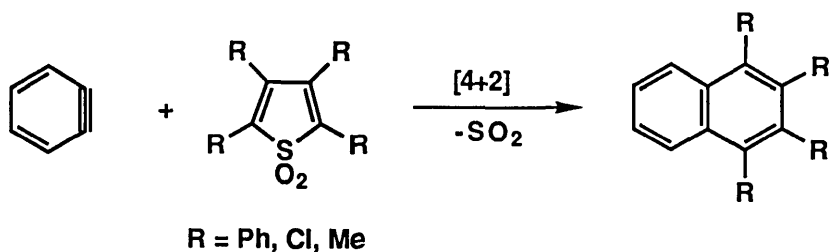
The cycloaddition reaction is not limited to the formation of cyclohexadienes, aromatic systems can also be formed by the use of acetylenes as the dienophile as demonstrated by the formation of diethylphthalate⁹⁵ (173). Furthermore, the use of indene results in the formation of fluorene (174), following aerial oxidation of the Diels-Alder adduct (175). (Scheme 63).



a) Indene, CHCl_3 , room temperature, 2 days
 b) diethylacetylenedicarboxylate, CHCl_3 , room temperature, 87 hours.

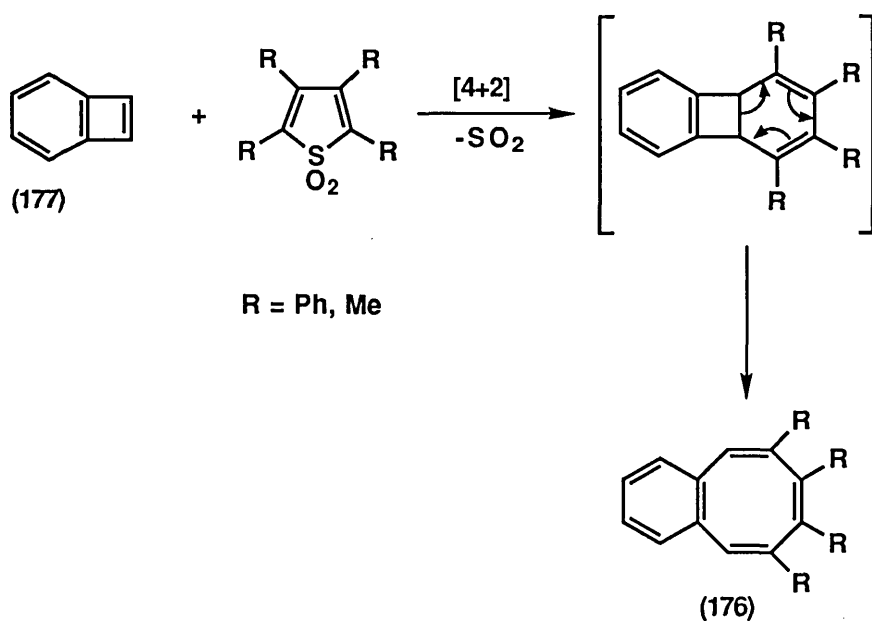
scheme 63

Benzyne can also be trapped by thiophene-1,1-dioxides⁹⁶ giving substituted naphthalenes as the products in good yields, as in scheme (64).



scheme 64

The synthetically challenging molecule benzocyclooctene (176) has been synthesised by treating benzocyclobutene (177) with tetrasubstituted thiophene-1,1-dioxides.⁹⁷ (Scheme 65).

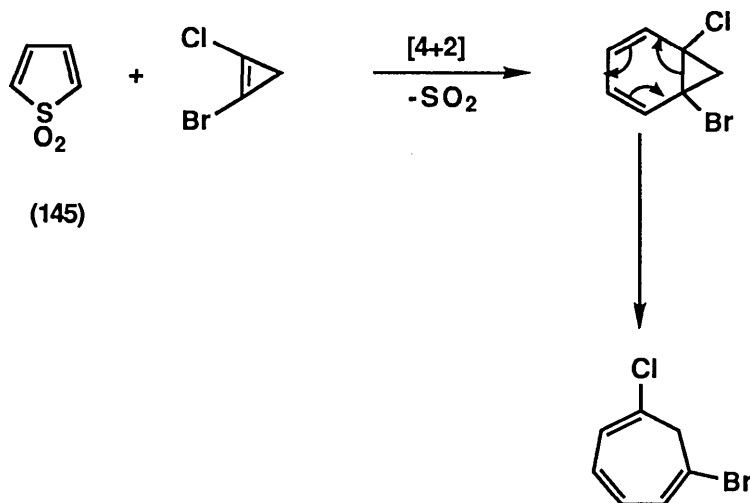


scheme 65

Initial [4+2] cycloaddition followed by the extrusion of sulphur dioxide generates an intermediate cyclobutane derivative, which undergoes electrocyclic ring opening under the reaction conditions to give the observed product (176).

In a similar manner cycloheptatrienes have also been synthesised from cyclopropenes and thiophene-1,1-dioxides again by a cycloaddition-ring expansion

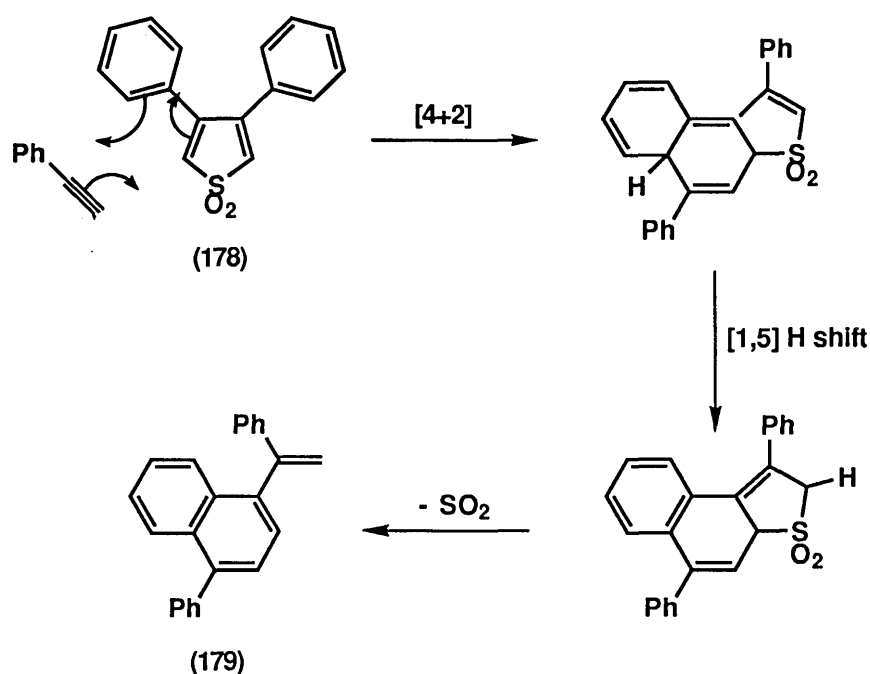
protocol.⁹⁸ (Scheme 66).



Not all [4+2] cycloaddition reactions occur across the terminal-positions of the π -system of the thiophene-1,1-dioxide. Treatment of the 3,4-diphenylthiophene-1,1-dioxide (178) with phenylacetylene does not give the expected tetraphenylbenzene product in appreciable yield. Instead the major product obtained is the disubstituted naphthalene (179), which results from addition to a diene system comprising one of the double bonds of the thiophene-1,1-dioxide unit, and one of the Kekulé double bonds of the aromatic ring. A subsequent 1,5 hydrogen shift followed by extrusion of sulphur dioxide restores the aromaticity of the system.⁹⁹ (Scheme 67).

The authors explained this preferred mode of addition by assuming the reaction to be an inverse electron demand Diels-Alder reaction. Electron withdrawal by the sulphone group lowers the HOMO of the thiophene-1,1-dioxide to the point where the weak electron donating effect of the phenyl group upon the acetylene is insufficient for reaction to occur. Obviously, the energetically preferred HOMO-LUMO interaction of the reacting system is between the styrene unit and phenylacetylene but the electronic nature of this interaction is not apparent. A

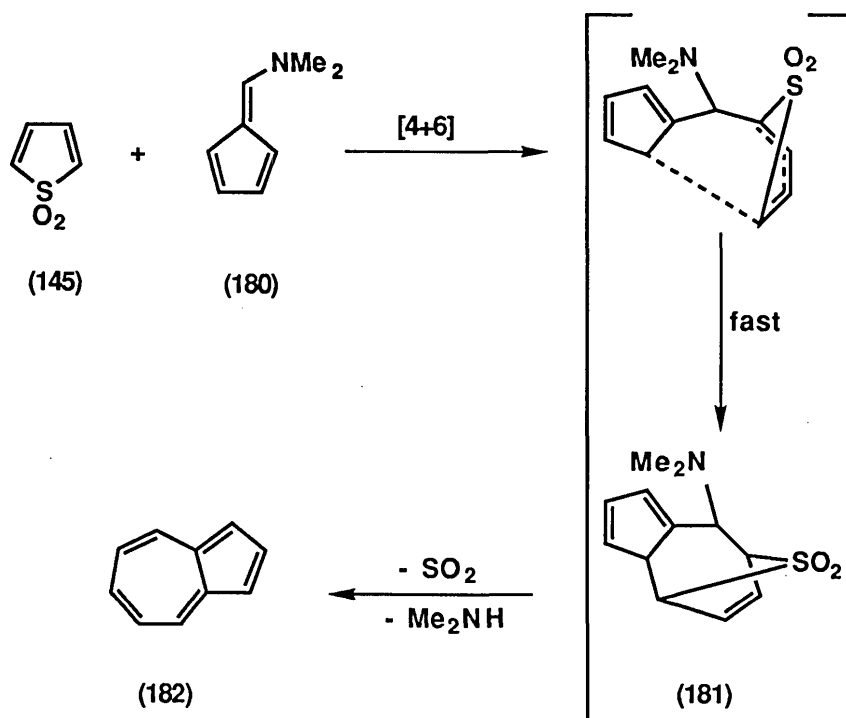
complete analysis of the energy levels of the frontier molecular orbitals and the positions of the largest orbital coefficients of both molecules is necessary before any explanation for the preferred regiochemistry of the cycloaddition reaction can be drawn.



scheme 67

2.1.2.5 Thermal [4+6] Cycloaddition

Thermal [4+6] cycloaddition reactions between thiophene-1,1-dioxide (145) and 6-aminofulvene (180) have led to a regioselective synthesis of azulene.¹⁰⁰ Following cycloaddition, the intermediate of the type (181) in scheme 68 extrudes sulphur dioxide followed by dimethylamine to give azulene (182).

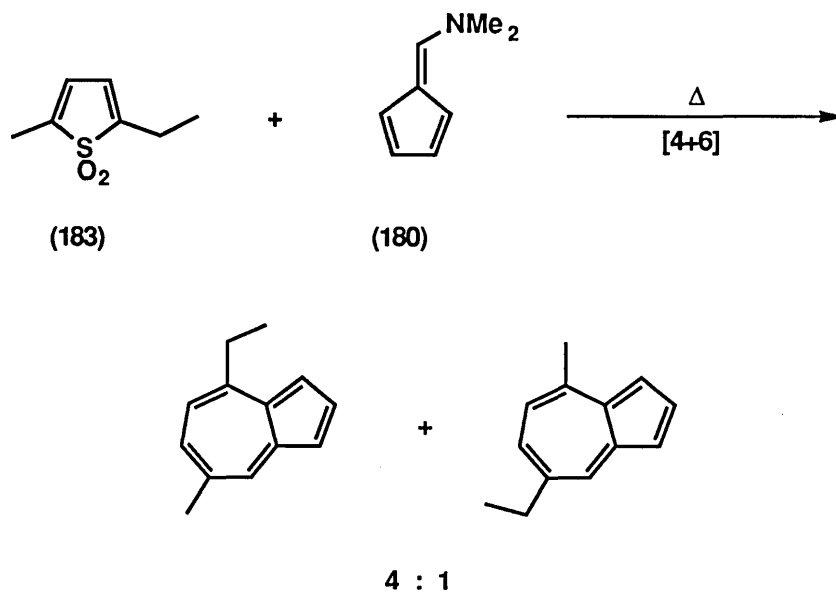


scheme 68

Since the rate of the reaction is independent of solvent polarity, with the reaction occurring at a similar rate in either benzene or methanol, it is highly likely that both bonds are formed in rapid succession. However, since the C-2 position is highly nucleophilic in fulvenes, it is probable that initial formation of a C-2 fulvene C-2 thiophene-1,1-dioxide bond occurs and is followed by the formation of the second C-6 fulvene C-5 thiophene-1,1-dioxide bond in an asynchronous manner.

Attempts have been made to explain the regiochemistry of fulvene cycloaddition reactions by Frontier Molecular Orbital Theory¹⁰¹ but in some cases the reasoning fails. Instead, the consideration of steric factors is sufficient to explain the regiochemical outcome of the above reaction. If initial bond formation is between the C-2 fulvene position and the thiophene-1,1-dioxide, the least hindered sulphone α -position will be attacked, as least steric repulsion will occur at this position. Thus, the regiochemical outcome of the reaction can be predicted by the application of a

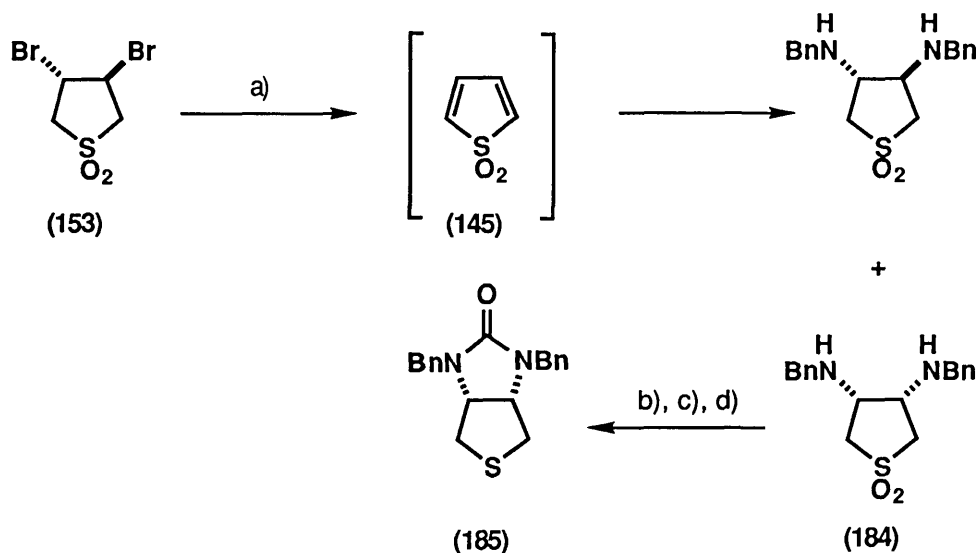
simple steric argument, as appears to be the case for the reaction between 2-ethyl-5-methylthiophene-1,1-dioxide (183) and 6-aminofulvene (180). (Scheme 69).



scheme 69

2.1.2.6 Other Reactions.

Thiophene-1,1-dioxides undergo a variety of other reactions that do not involve cycloaddition processes. They react with several reagents and have been utilised as synthetic building blocks. For example, a formal synthesis of ($\pm$)-biotin has been reported by Bates *et al.*¹⁰², in which thiophene-1,1-dioxide is the key intermediate. The basic strategy is shown below. (Scheme 70).

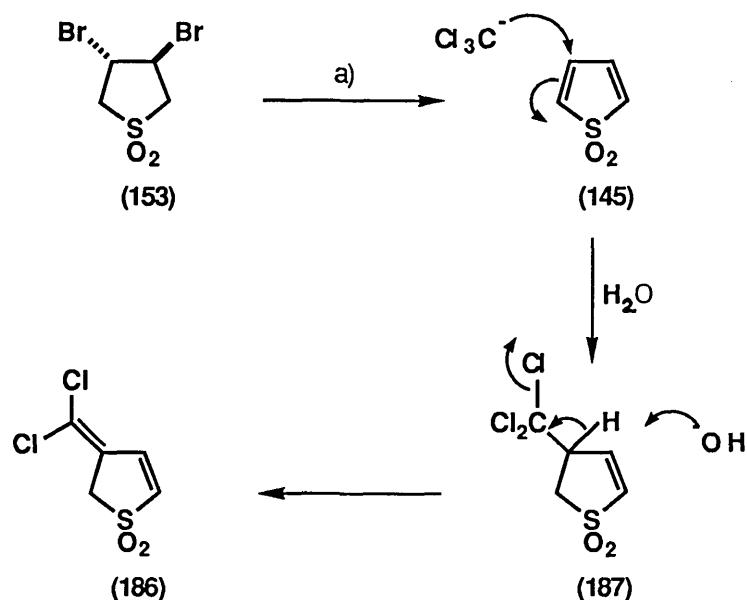


a) excess BnNH₂, MeOH, b) COCl₂, c) separate, d) LiAlH₄, Et₂O

scheme 70

Treatment of the dibromide (153) with excess benzylamine gave a mixture of the *cis*- and *trans*-diamines (184), in a similar reaction to that reported by Bailey and Cummins.⁸³ Treatment of these diamines with phosgene then afforded the corresponding bicyclic ureas which were separated by careful recrystallisation. Reduction of the sulphone moiety of the desired *cis* isomer using lithium aluminiumhydride then gave the bicyclic sulphide (185). Since the elaboration of this compound to (±)-biotin had been previously described, this then represented a formal total synthesis of the molecule.

Thiophene-1,1-dioxides have also been reported to react as α,β -unsaturated sulphones and undergo Michael addition. Treatment of a solution of the dibromide precursor (153) in chloroform with aqueous sodium hydroxide, under phase transfer conditions, led to the formation of the 3-dichloromethylene-thiacyclopent-2-ene-1,1-dioxide (186).¹⁰³ (Scheme 71).



a) NaOH , H_2O , CHCl_3 , $\text{BnEt}_3\text{N}^+ \text{Cl}^-$

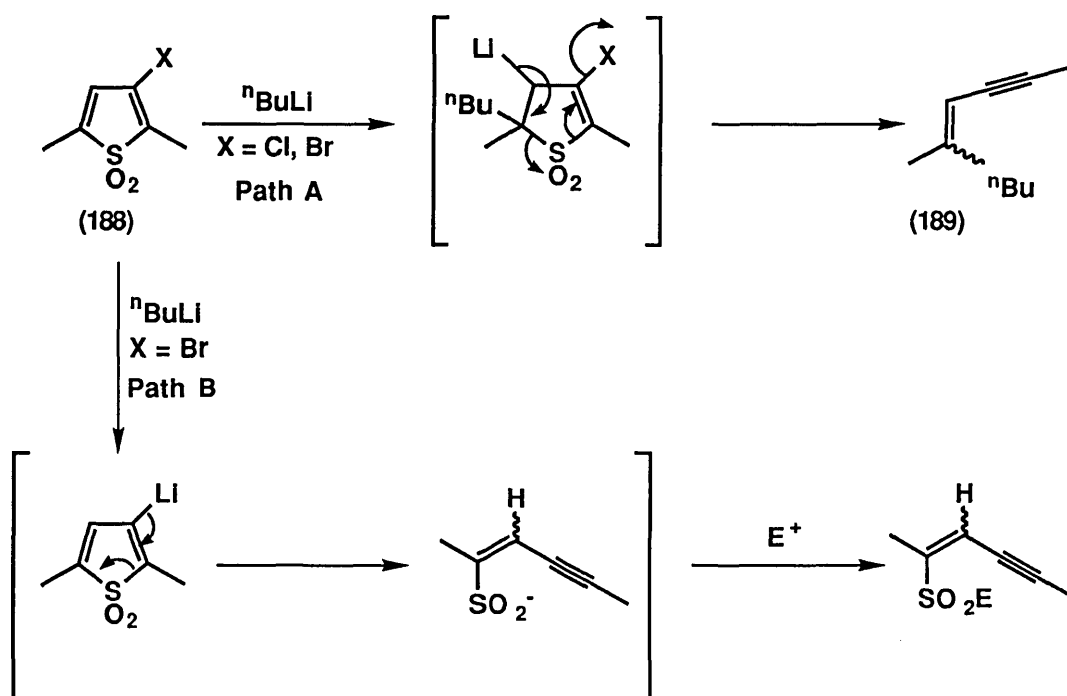
scheme 71

Michael addition of trichloromethyl anion to thiophene-1,1-dioxide (145) and protonation of the resulting α -sulfonyl anion intermediate afforded (187). Subsequent dehydrohalogenation of (187) then furnished 3-dichloromethylene-thiacyclopent-2-ene-1,1-dioxide (186). Similar results were obtained using bromoform as the solvent; the structures of the products were elucidated by X-ray crystallography.

The addition of the trichloromethyl anions to thiophene-1,1-dioxide must be very rapid, demonstrating the high reactivity of this compound. Since trichloromethyl anions undergo very rapid fragmentation reactions affording dichlorocarbene and a chloride anion and no products derived from carbene addition to thiophene-1,1-dioxide were observed, thiophene-1,1-dioxide must act as a very efficient trap for trichloromethyl anions.

Aryl and alkyl lithium reagents also add to halogenated thiophene-1,1-

dioxides though the nature of the product obtained is dependent upon the halogen substituent as shown.¹⁰⁴ (Scheme 72).

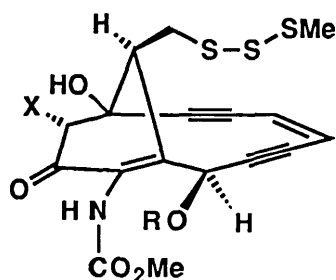


scheme 72

In the reaction between 3-chloro-2,5-dimethylthiophene-1,1-dioxide (188, $X=\text{Cl}$) and n -butyllithium only nucleophilic addition to the C-5 position of the thiophene-1,1-dioxide is observed (Path A). Subsequent ring opening and loss of sulphur dioxide as shown then gives the enyne (189). Although 3-bromo-2,5-dimethylthiophene-1,1-dioxide (188, $X=\text{Br}$) also undergoes an analogous reaction, a competing reaction, namely metal-halogen exchange, also occurs due to the weaker nature of the carbon-halogen bond. (Path B). Again ring opening occurs this time giving a sulphonyl anion which can undergo further reaction with an appropriate electrophile. Thus, a mixture of two products is obtained in the case of the brominated analogue.

This reaction of halogenated thiophene-1,1-dioxides represents a facile route to enyne systems. Recently much attention¹⁰⁶ has been focused upon the

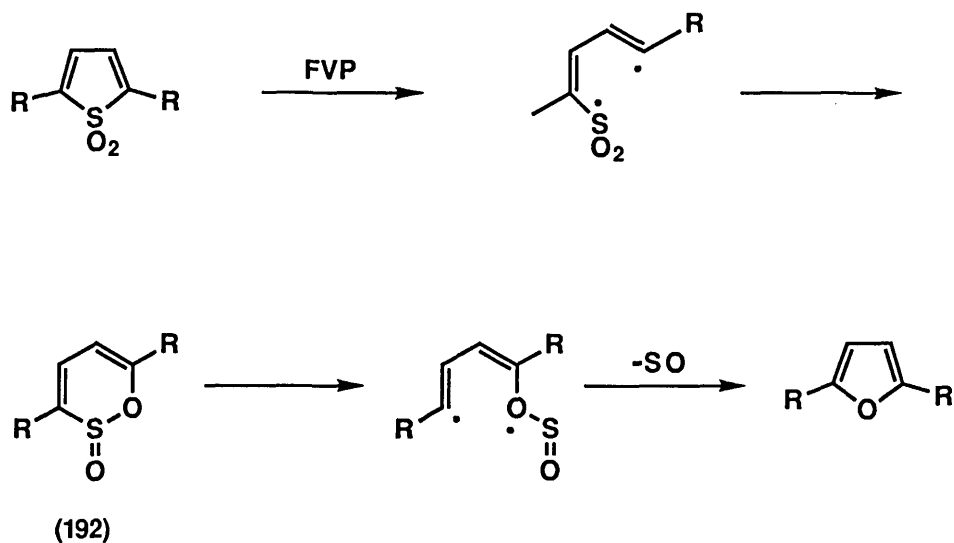
synthesis of such units as they are the key structural element of the so called enediyne antibiotics, two examples of which are esperamycin (190) and calcheamycin (191), as the compounds show a range of biological activity. (Figure 17). The above reaction clearly demonstrates the synthetic potential of thiophene-1,1-dioxides, as one could predict that treating thiophene-1,1-dioxides of the type (188) with lithium acetylides represents a potential route to these novel systems.



$X = OR^1$ Esperamycin (190)
 $X = H$ Calicheamycin (191)
 $R, R^1 = \text{complex sugar units}$

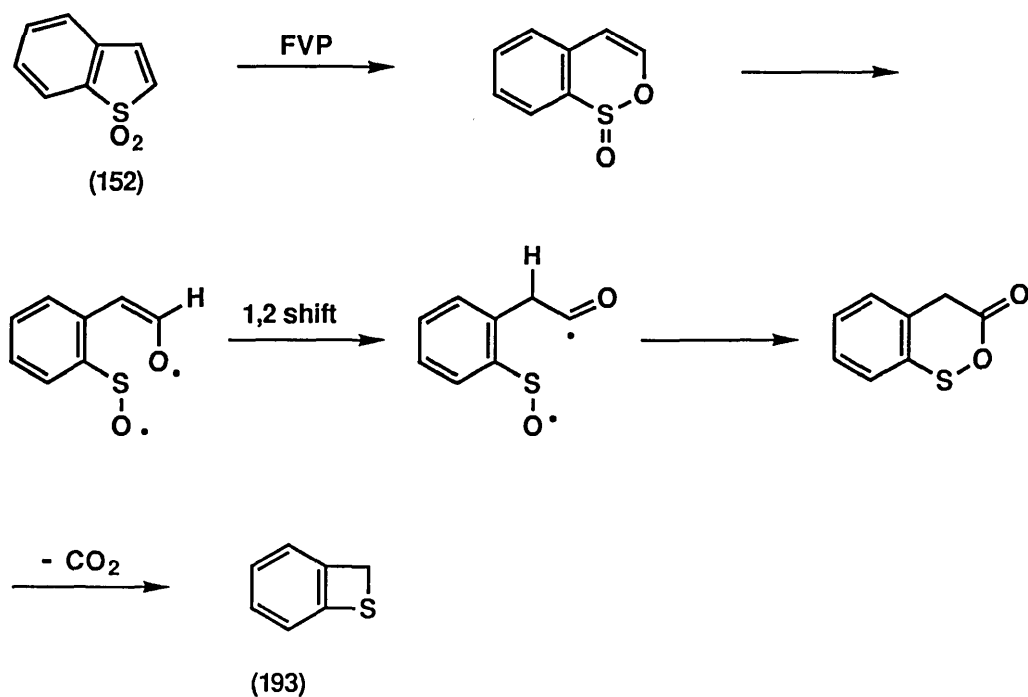
figure 17

Flash vacuum pyrolysis of thiophene-1,1-dioxides usually affords furans,¹⁰⁵ though the nature of the substituents does dictate the reaction pathway. Furans are formed *via* the cyclic sulphinate ester (192) which rapidly extrudes sulphur monoxide to give the furan product. (Scheme 73).



scheme 73

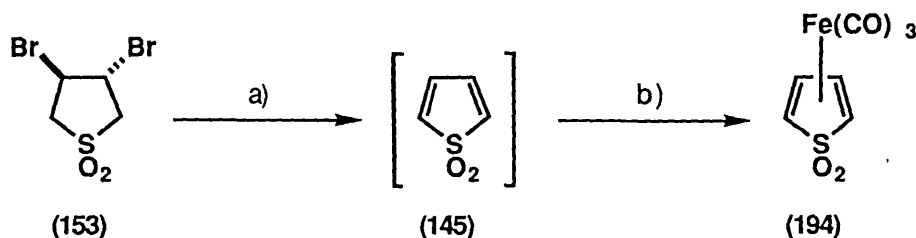
Benzo(b)thiophene-1,1-dioxide (152) when submitted to flash vacuum pyrolysis gives benzothiete (193) in 45% yield.¹⁰⁵ The postulated mechanism, depicted in scheme 74 involves a novel 1,2 hydride shift as shown.



scheme 74

2.1.2.7 Formation of η_4 (Diene)Tricarbonyl Iron Complexes

Tricarbonyl iron complexes of a range of thiophene-1,1-dioxides, both stable and unstable, have been prepared by photolysis of the compound in the presence of iron pentacarbonyl.¹⁰⁷ The complex of the parent, thiophene-1,1-dioxide (145) has been prepared in this manner, and is reported to be quite stable at ambient temperatures. Thiophene-1,1-dioxide was prepared by treatment of a cold benzene solution of the dibromide precursor (153) with sodium hydroxide, the resulting solution of thiophene-1,1-dioxide (145) being irradiated in the presence of iron pentacarbonyl to form the complex (194). (Scheme 75).



a) NaOH, PhH, 0°C, b) $\text{Fe}(\text{CO})_5$, PhH, $h\nu$

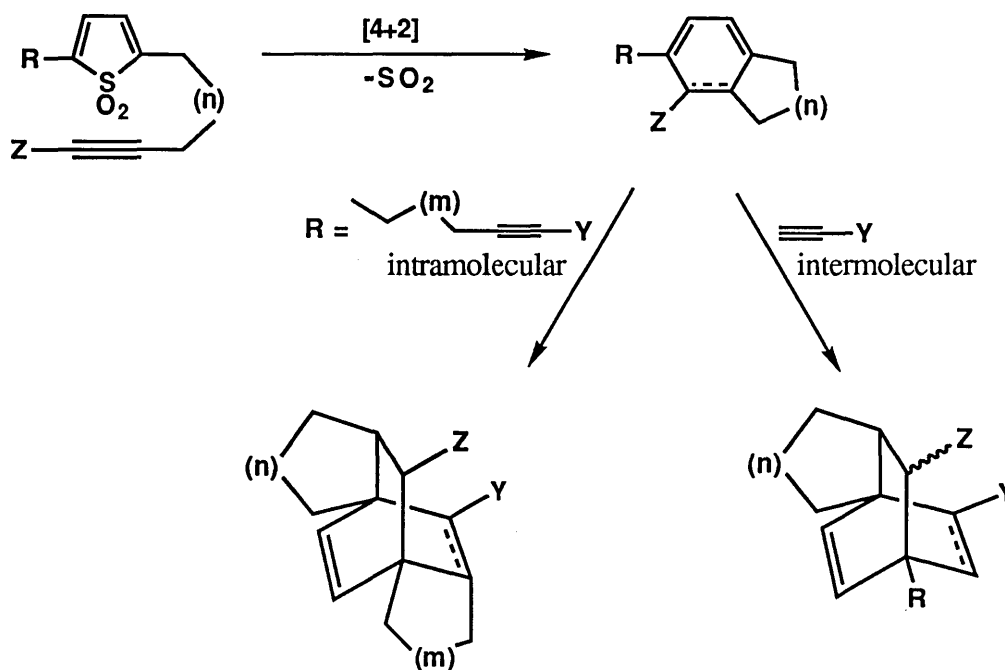
scheme 75

Complexes of 2,5-dimethyl and 3,4-diphenylthiophene-1,1-dioxide have been prepared in a similar fashion.

The ability to prepare these complexes and their high stability once formed offers an excellent method for the synthesis of stable precursors to otherwise unobtainable thiophene-1,1-dioxides. Also, since decomplexation of η_4 (diene)tricarbonyl iron complexes is a well documented and generally facile process, conditions for the generation of the free thiophene-1,1-dioxide should be very mild.

2.2 Results and Discussion

From the previous section of this chapter it is apparent that thiophene-1,1-dioxides undergo [4+2] cycloaddition reactions with a vast range of dienophilic partners, the parent compound thiophene-1,1-dioxide and its monosubstituted derivatives being particularly reactive. Unfortunately, this potent reactivity can be very problematic: as self-dimerisation reactions are always a potential side reaction. It was envisaged that this reactivity could be harnessed however, by generating the thiophene-1,1-dioxide in the presence of an intramolecular dienophilic trap. Since intramolecular reactions have an entropic gain relative to their intermolecular counterparts, the so called 'hinge effect', self dimerisation reactions would be accordingly minimised. Also, as thiophene-1,1-dioxides react with both electron deficient and electron rich olefins, a diverse range of dienophiles would be applicable to this procedure. Moreover, the products derived from cycloaddition with olefinic partners would be dienes themselves, capable of further elaboration, again in either an intramolecular or intermolecular sense, thereby providing a rapid entry in to complex polycyclic systems. Acetylenic partners provide a potential route into highly substituted aromatic systems. These facets are encapsulated in scheme 76, which demonstrates a potential methodology for the stereo and regioselective formation of four carbon-carbon σ bonds in a single reaction.



Accordingly, the construction of suitable precursors for intramolecular Diels-Alder reactions of thiophene-1,1-dioxides required a flexible approach to be developed which involved two interrelated objectives; *viz*

- a) the formation of a carbon-carbon bond between the latent diene and dienophile
- b) mild methods for the generation or release of the thiophene-1,1-dioxide *in situ*, prior to cyclisation.

While the following discussion describes a variety of approaches toward this synthetic goal, it should be appreciated that several of these were under simultaneous investigation, and that the results obtained are not necessarily in chronological order.

Before any synthetic studies were carried out, it was decided to try to obtain a clearer picture of the reasons for the highly reactive nature of simple thiophene-1,1-dioxides. To this end, the HOMO and LUMO energy levels of both thiophene-1,1-

dioxide and buta-1,3-diene were calculated and comparisons made between the values obtained.

2.2.1 Theoretical Studies

The values of the HOMO and LUMO energy levels of thiophene-1,1-dioxide and buta-1,3-diene were calculated using the PM3 method upon the C.A.C.H.E. molecular modelling system. (Figure 18)

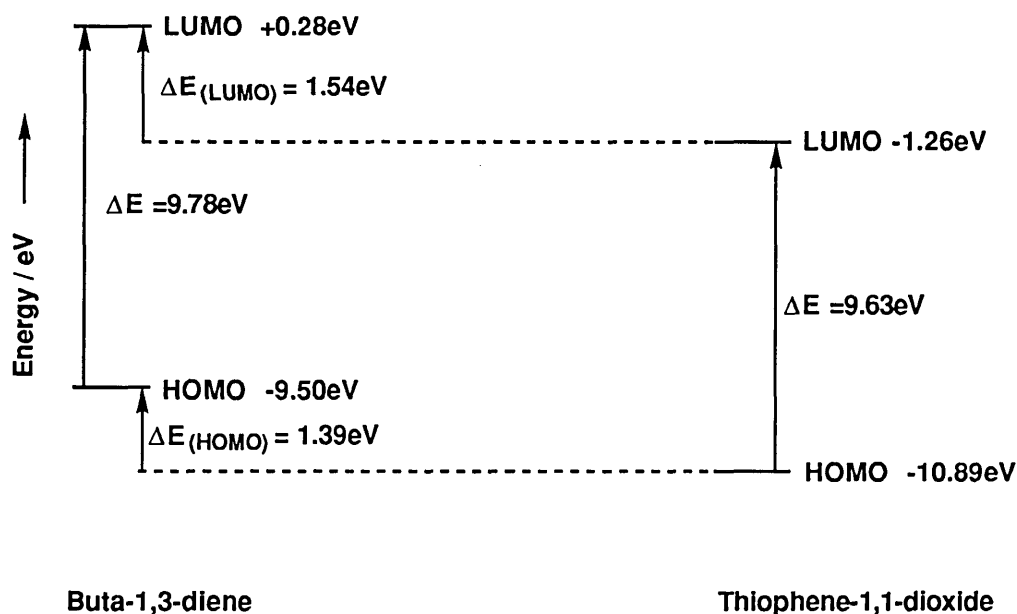


figure 18

As expected, the presence of the sulphone moiety lowers both the HOMO and LUMO of thiophene-1,1-dioxide relative to buta-1,3-diene. Interestingly, the LUMO is lowered to a greater extent than the HOMO, thus the HOMO-LUMO energy difference in thiophene-1,1-dioxide is smaller than that in buta-1,3-diene. This then explains the greater tendency of thiophene-1,1-dioxide to undergo dimerisation by a [4+2] cycloaddition process, under conditions where buta-1,3-diene would be quite stable.

Clearly the LUMO of thiophene-1,1-dioxide is low lying, so the compound would be expected to be an excellent inverse electron demand Diels-Alder diene, as is the case. As the prominent interaction in these processes is a $\text{HOMO}_{(\text{dienophile})} - \text{LUMO}_{(\text{diene})}$ interaction, lowering the LUMO of the diene by electron withdrawal and raising the HOMO of the dienophile, relative to ethene, by electron donation promotes the reaction.¹⁰⁸ However, thiophene-1,1-dioxide also reacts quite readily with electron deficient olefins⁹⁴, a situation in which the energy levels of both reactants are lowered by electron withdrawal. The explanation for this ability of thiophene-1,1-dioxide to undergo cycloaddition reactions with electron deficient olefins is less clear. Obviously, since cycloaddition reactions do occur a HOMO-LUMO interaction between the two species must be energetically feasible. It is tempting to suggest that thiophene-1,1-dioxide does indeed have antiaromatic character, and some form of mesomeric electron withdrawal lowers the energy levels of the compound to the extent that these reactions may occur. Such a scenario would have to involve the empty d-orbitals upon the sulphur atom, and although evidence does exist for a through conjugative effect of the sulphone group in thiophene-1,1-dioxides,⁶⁸ the energetic accessibility of these orbitals is still under debate.

In conclusion, although the exact nature of the orbital interactions in thiophene-1,1-dioxide is unclear, a pronounced lowering of the HOMO and LUMO energy levels occurs upon introduction of the sulphone moiety, making the molecules excellent Diels-Alder substrates. Moreover, the HOMO-LUMO energy difference is reduced relative to buta-1,3-diene, explaining the tendency of simple thiophene-1,1-dioxides to dimerise.

2.2.2 Synthesis of Thiophene-1,1-Dioxides

The strategy undertaken toward the generation of thiophene-1,1-dioxides was initially based on the cyclic sulphone-enone (93). As already seen in the previous chapter, the highly functionalised molecule is a flexible motif capable of diverse elaboration. (Figure 19)

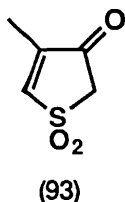
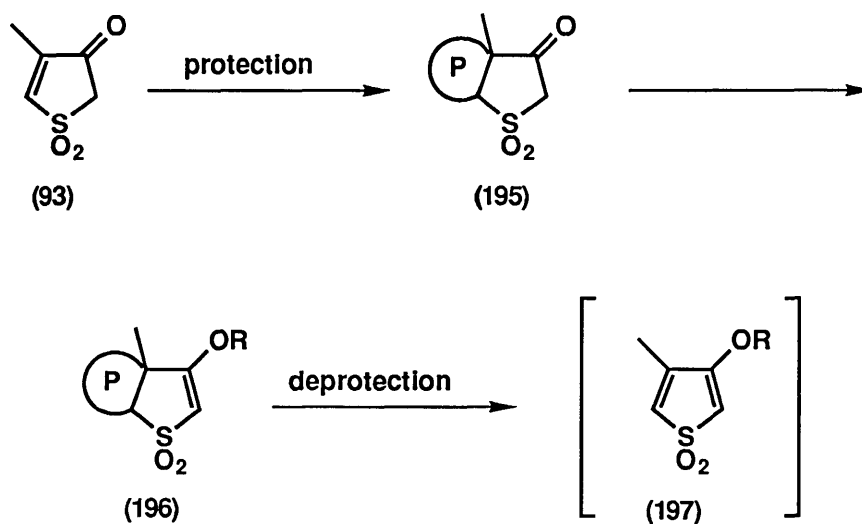


figure 19

At first inspection it may seem that a direct conversion of the β -ketosulphone unit to an enol-ether derivative would be the obvious choice, particularly in view of the acidity of the C-2 protons. However, previous studies⁴⁵ ascertained that such a stratagem was entirely unsuccessful; various attempts to construct silyl enol ethers, enol ethers and enol acetates failed to yield any evidence either for the thiophene-1,1-dioxide or for a dimeric Diels-Alder adduct.

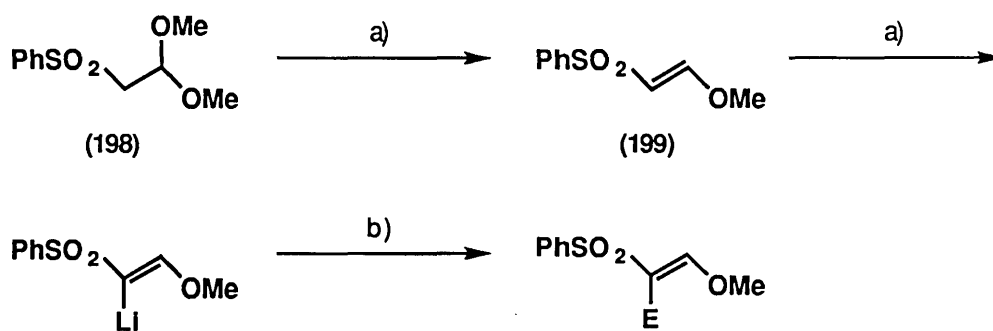
Accordingly, the synthetic pathway for the elaboration of (93) into a suitable thiophene-1,1-dioxide precursor is outlined in scheme 77.



scheme 77

Protection of the double bond of compound (93) would afford a cyclic β -ketosulphone of the type (195). Conversion of the ketone group into enol-ether (196) as shown above, and subsequent deprotection of the double bond would then provide a route to the disubstituted thiophene-1,1-dioxide (197).

A recent publication by Simpkins,¹⁰⁹ describing the transformation of sulphone- β -dimethylacetals to substituted vinyl sulphones by the route shown below, was of particular interest, as the methodology provided a potential means for the introduction of a dienophilic unit into the latent thiophene-1,1-dioxide (196). (Scheme 78).



a) n-butyllithium, THF, -78°C, b) E⁺, Δ

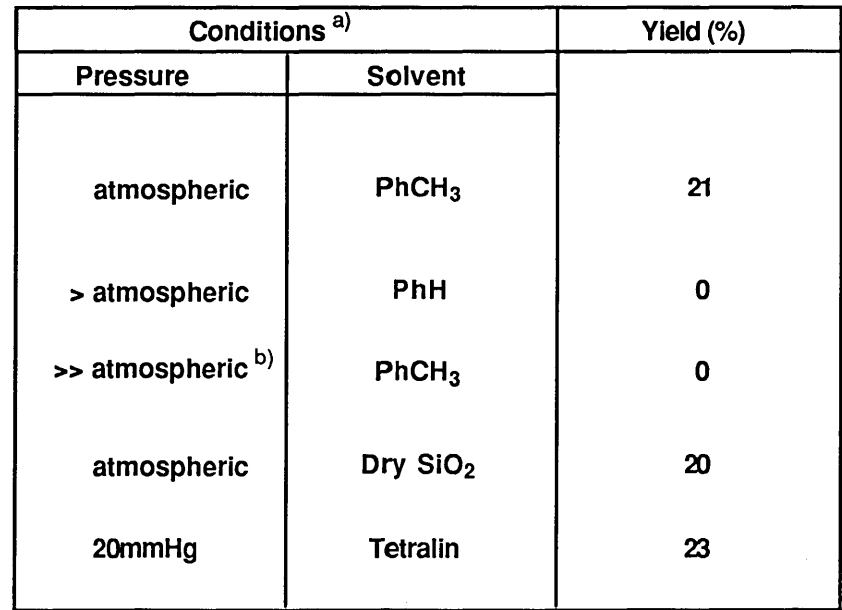
scheme 78

Treatment of dimethylacetal (198) with two equivalents of n-butyllithium resulted in the initial formation of the vinylsulphone (199) by elimination of lithium methoxide. The ability to deprotonate (199) with a second equivalent of n-butyllithium was of great interest, as obvious analogies existed between species (199) in the Simpkins procedure and intermediate (196) in scheme 77. Thus treatment of a species of the type (196, R = Me) with n-butyllithium should result in the formation of a similar α-lithio anion. Subsequent addition of an appropriate electrophilic species to this anion then provides a suitable means for the introduction of dienophilic substituents to thiophene-1,1-dioxide precursor (196). Moreover, previous studies upon the chemistry of the cyclic sulphone (93) suggested that the formation of the methyl enol ether (196, R = Me) could be achieved under mild conditions by treatment of cyclic β-ketosulphone (195) with diazomethane. Furthermore, the presence of the methoxy group would create a 'push-pull' system, thus further facilitating the thiophene-1,1-dioxide toward cycloaddition reactions.

2.2.2.1 Retro Diels-Alder Approach

The first investigations toward the generation of 3-methoxy-4-methylthiophene-1,1-dioxides involved a retro Diels-Alder strategy. Thus, an suitable diene was sought which would undergo a cycloaddition reaction with the sulphone enone (93), function as a protecting group during subsequent transformations, and then undergo a facile retro Diels-Alder reaction to liberate the free thiophene-1,1-dioxide. Anthracene appeared to fulfill these criteria, the molecule being an excellent Diels-Alder substrate, undergoing cycloaddition reactions with various electron deficient olefins, and the retro Diels-Alder reactions of its adducts are well documented.¹¹⁰ It was expected from previous observations that cycloaddition between sulphone enone (93) and anthracene would be a facile process and occur in high yield. Despite extensive experimentation, this proved not to be the case, yields for the process being quite poor and variation of the reaction conditions gave results inconsistent with a bimolecular Diels-Alder cycloaddition mechanism (table 4).

Heating a toluene solution of sulphone enone (93) and anthracene to 120°C for 48 hours gave the desired Diels-Alder adduct (200) in 21% yield. Since this yield was rather disappointing the reaction was repeated but the internal pressure of the system was increased. Remarkably this change in pressure totally retarded the reaction, none of the desired product being observed under these conditions. Similar results were obtained when the reaction was carried out in a continuous flow apparatus under very high pressures.



b) Continuous flow reactor employed at a temperature of 120°C.

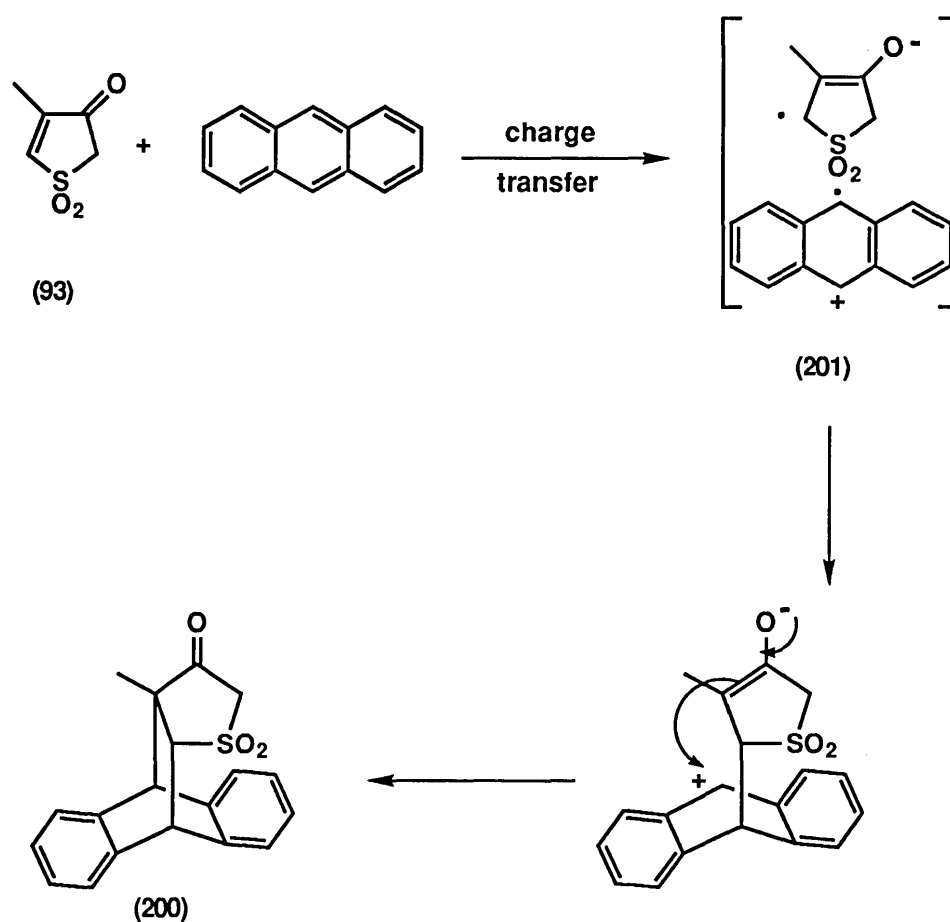
Around this time Smit *et al.*¹¹¹ reported that the rates of Diels-Alder reactions could be accelerated by preadsorption of the reactants on chromatographic standard silica, and carrying the reaction out under solvent free conditions. Indeed, performing the above reaction under these conditions led to a low but comparable yield of adduct (200). Considering the restricted mobility of the reagents within the

reaction medium, the fact that a similar yield was obtained here to that when solvent was employed demonstrates the high activating effect of the silica. Possibly the most surprising result was obtained when the reaction was repeated at a reduced pressure employing tetralin as the solvent. Again the yield of the Diels-Alder adduct (200) was low, but slightly better than when the reaction was carried out at atmospheric pressure, a result that is totally opposed to that expected for a bimolecular Diels-Alder reaction.

From the above observations, it is clear that the above reaction does not exhibit the expected behaviour for a classical bimolecular cycloaddition pathway.

One possible explanation for the somewhat adverse affect of pressure upon this reaction is that the mechanism of this reaction involves a charge transfer process. The observation that anthracene is capable of forming a charge transfer complex with tetracyanoethylene,¹¹² an olefin that possesses powerful one electron acceptor properties,^{113a} and the fact that sulphone enone (93) has also been observed to display charge transfer abilities,⁴⁵ suggests this may be the case. A feasible mechanism for this process is depicted below. (Scheme 79).

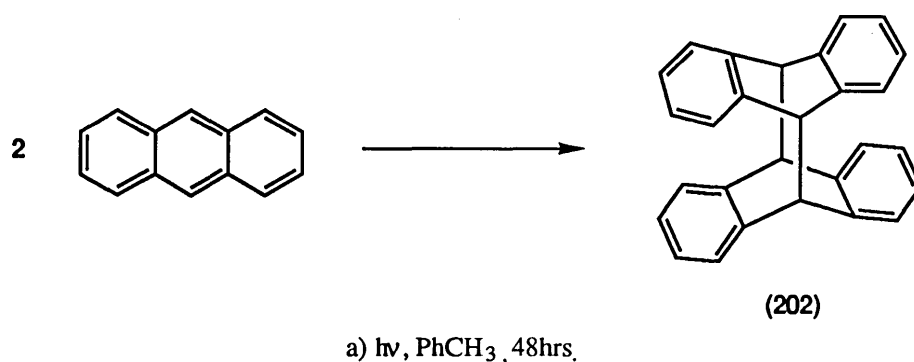
The formation of an intermediate complex of the type (201) in scheme 79 could potentially explain the adverse affect of pressure upon the reaction. If the molecular volume of the intermediate charge transfer complex (201) was greater than the combined volume of the two starting materials, then increasing the pressure of the system would retard the formation of this intermediate and hence the reaction.



scheme 79

Attempts to detect the charge transfer complex by UV spectroscopy were to no avail; intense absorptions by the two starting materials creating a broad and generally featureless spectrum.

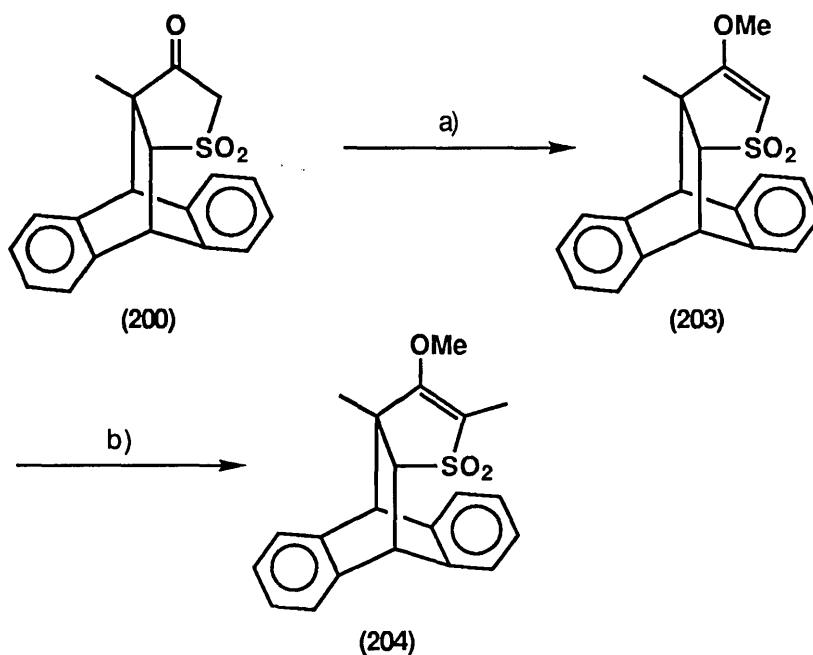
In a further attempt to elucidate the mechanism of this reaction, photochemical preparation of adduct (200) was attempted. Irradiation of a toluene solution of the two starting materials in a standard photolysis well resulted in the formation of the anthracene dimer (202) via a [4+4] cycloaddition procedure.^{113b} (Scheme 80).



scheme 80

Although these results tend to negate the charge transfer process proposed in scheme (79), it is clear that the reaction is not occurring by a formal cycloaddition process. The exact explanation for these observations is as yet unresolved.

Despite the poor yields obtained with the initial Diels-Alder reaction it was decided to pursue this methodological line. Treatment of (200) with diazomethane afforded the enol-ether (203). in 58% yield. Encouraging results were also obtained when the deprotonation reactions of this enol-ether (203) were studied. Preliminary deprotonation studies upon (203) with one equivalent of *n*-butyllithium, in an analogous fashion to that of Simpkins,¹⁰⁹ followed by treatment of the resulting anion with iodomethane resulted in the formation of the α -methylated product (204) in 60% yield by ^1H nmr. (Scheme 81).



a) Diazomethane, EtOAc, b) n-butyllithium, THF, -78°C, MeI

scheme 81

Since a formal pathway for the formation of thiophene-1,1-dioxide precursors had been established, attempts to discover the optimum conditions for the final retro Diels-Alder reaction were made. Simple decomposition studies involving a standard melting point apparatus showed that compound (203) was stable up to 185°C, but disappointingly, all initial attempts to retro Diels-Alder (203), in the presence of an intermolecular trap for the thiophene-1,1-dioxide thus formed, simply resulted in the recovery of starting material. Only when the reaction was heated to 250°C, employing sulpholane as the solvent, did any appreciable reaction occur. At this temperature an extensive transmigration of the reaction mixture resulted in the formation of several products, none of which could be identified as deriving directly from the thiophene-1,1-dioxide precursor (203).

Interestingly, when dimethyl acetylenedicarboxylate (DMAD) was employed as the intermolecular trap for the liberated thiophene-1,1-dioxide, an alternative product

to that reported¹¹⁴ in the literature was obtained. The spectral properties of this compound suggested it was a trimer of DMAD as opposed to the reported tetrameric species obtained from prolonged heating of DMAD.

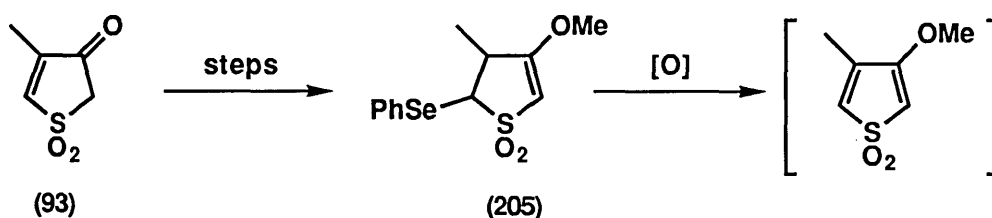
Inconsistencies in the collected spectral data for this compound obtained have prevented a determination of its structure.

Attempts to carry out a retro Diels-Alder reaction photochemically also failed; photolysis of a benzene solution of (203) and excess DMAD resulted in a high recovery of the starting materials.

The reluctance of the adduct (203) to undergo a retro Diels-Alder reaction is indicative of the high energy nature of the thiophene-1,1-dioxide produced. The inability to achieve this final reaction implied that the retro Diels-Alder approach to thiophene-1,1-dioxides was not feasible.

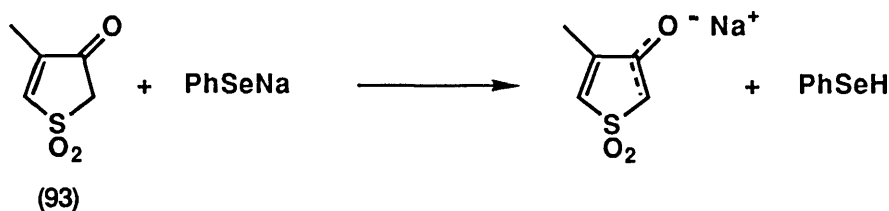
2.2.2.2 Selenoxide Elimination Approach

From the previous section it is apparent that formation of substituted 3-methoxy-4-methylthiophene-1,1-dioxides *via* final introduction of the C-4,C-5 double bond would require a particularly facile process. Possibly one of the mildest methods for the introduction of double bonds in molecular frameworks is the selenoxide elimination approach, introduced by Sharpless¹¹⁵ and now regarded a routine synthetic operation in organic chemistry.¹¹⁶ Our attention was therefore directed toward the oxidation of a selenide of the form (205) in scheme 82 which could prove a mild method for the formation of 3-methoxy-4-methylthiophene-1,1-dioxides as shown.



scheme 82

Initial attempts to form selenide (205) involved conjugate addition of sodium phenylselenide to sulphone (93), followed by treatment of the resulting selenide with diazomethane, to form the precursor (205). However, treatment of (93) with sodium phenylselenide, formed by the method of Ley *et al.*¹¹⁷, resulted in almost instantaneous formation of phenylselenol *via* deprotonation of (93) to give the anion of the β -keto-sulphone, the characteristic deep orange colour of the anion being observed. (Scheme 83).

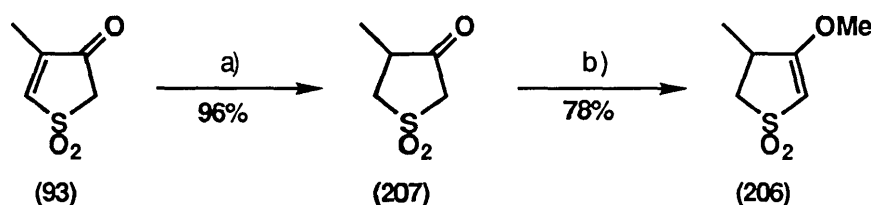


scheme 83

The formation of phenylselenol in the above reaction again demonstrates the highly acidic nature of (93). Despite the fact that sodium phenylselenide is not generally a basic reagent, deprotonation of (93) was very rapid. Due to this result, an alternative approach to the requisite selenide (205) was undertaken. This involved an electronic rôle reversal in which attempts were made to form (205) by treatment of the sulphonyl anion (206) with phenylselenenyl chloride.

The α,β -unsaturated sulphone (206) was readily available from the

sulphone enone (93) by catalytic hydrogenation followed by treatment of the resulting saturated β -ketosulphone (207) with diazomethane. This then generated the required compound in high yield. (Scheme 84)



a) H_2 , 10%Pd / C, b) diazomethane, EtOAc

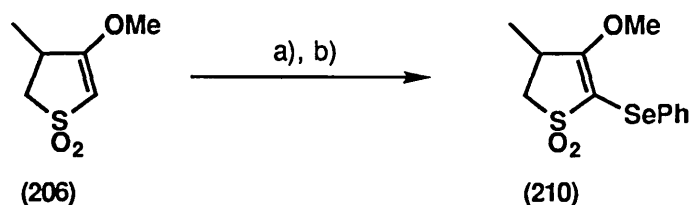
scheme 84

Although the site of kinetic deprotonation of (206), as evidenced by the work of Simpkins *vide supra*, should involve formation of a vinylic anion (208), we considered that some thermodynamic tendency toward the formation of the desired regioisomeric anion (209) might be possible in this case. (Figure 20)



figure 20

In the event, efforts under a variety of experimental conditions yielded only the vinyl selenide (210). (Scheme 85). In retrospect, the greater s character of the C-2 position, and the possibility of chelation *via* the ether oxygen atom at C-3 probably combine to dominate the situation from both a thermodynamic and kinetic standpoint.



a) n-butyllithium, THF, room temperature, 3hours, b) PhSeCl, THF

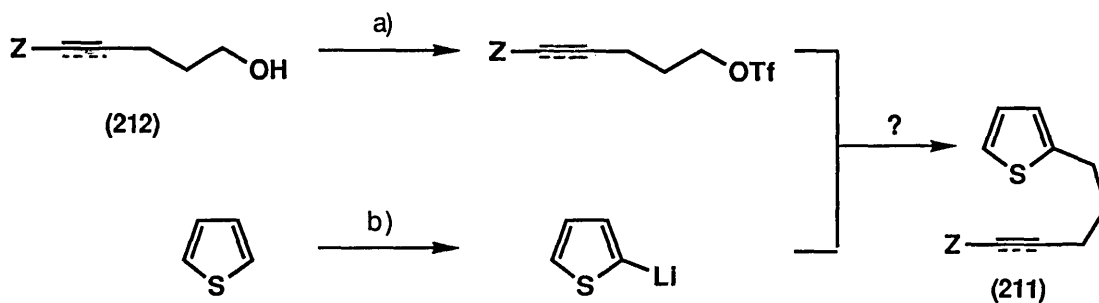
scheme 85

In theory, carbon alkylation of the vinylic anion (208) with the dienophilic sidechain could then have been followed by efforts to introduce the phenyseleno moiety at C-5 utilising anion chemistry, this approach was not further pursued.

2.2.2.3 Thiophene Oxidation Approach

The final 'classical' approach taken toward the synthesis of thiophene-1,1-dioxides and their subsequent cycloaddition reactions involved a significant change in direction. It was decided to return to an established method for the formation of thiophene-1,1-dioxides; oxidation of the corresponding thiophene. Initially this method was disregarded as the procedure tended to be quite capricious in its nature. However, the disclosure that thiophenes could be oxidised to their dioxides in a facile yet highly selective manner by dimethyldioxirane⁸², led to a reevaluation of this strategy.

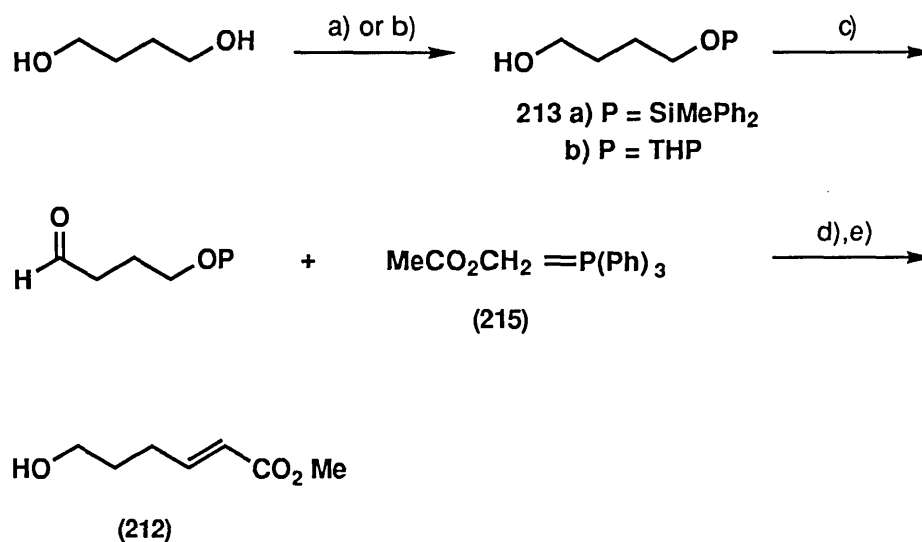
Preliminary studies were directed toward establishing a general synthesis of substituted thiophenes of the type (211) in scheme 86. It was envisaged that these compounds could be readily obtained by treatment of an appropriate triflate, derived from the corresponding alcohol (212), with 2-lithiothiophene. (Scheme 86).



a) Triflic anhydride, pyridine, DCM, b) n-butyllithium, TMEDA, thiophene

scheme 86

To this end the olefinic ester (212, Z = CO₂Me) was synthesised from butane-1,4-diol by the route shown in scheme 87.

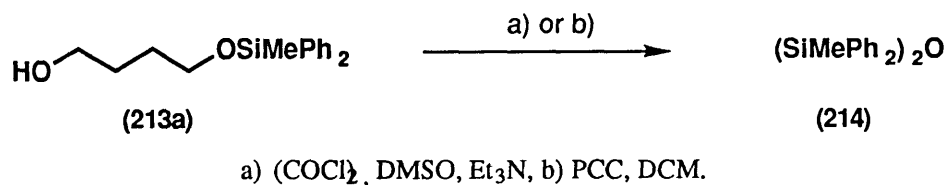


a) Ph₂MeSiCl, imidazole, DMF, b) dihydropyran, PPTS, DCM
c) PCC, DCM, d) MeCN, reflux., e) TsOH, MeOH, 1 hour.

scheme 87

Surprisingly, attempts to oxidise the monoprotected diol (213a) using

either pyridinium chlorochromate¹¹⁸ or Swern¹¹⁹ conditions led to the formation of diphenylmethyldisiloxane (214) in 84% and 80% yield respectively. (Scheme 88).



scheme 88

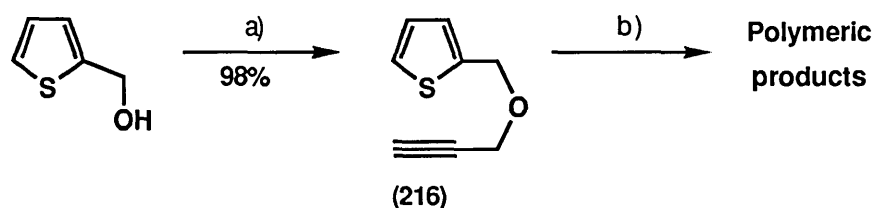
The exact mechanism of this reaction is as yet unclear.

This problem was easily overcome by changing the nature of the alcohol protecting group. Thus, butane-1,4-diol was monoprotected as the tetrahydropyranyl (THP) ether to give (213b). Oxidation of (213b) again using PCC this time afforded the desired aldehyde in 54% yield. This aldehyde then underwent a Wittig reaction with the stabilised phosphorane (215) which, after brief exposure of the crude reaction mixture to *para*-toluenesulphonic acid in methanol, gave α,β -unsaturated ester (212) in an excellent 94% yield

Unfortunately, all attempts to transform alcohol (212) to its corresponding triflate by treatment with pyridine and triflic anhydride¹²⁰ were to no avail, the compound appearing to decompose upon warming. Likewise, efforts were made to convert 4-pentyn-1-ol to its corresponding triflate, and again the isolation of this triflate proved very difficult. Purification of these compounds by chromatography also resulted in apparent rapid decomposition. Attempts were also made to react the triflate *in situ* with 2-lithiothiophene, but none of the desired substituted thiophene was obtained.

However, a variation of this approach enabled the formation of a suitably substituted model thiophene. This employed commercially available 2-thiophenemethanol as the starting material, the acetylenic moiety being introduced by

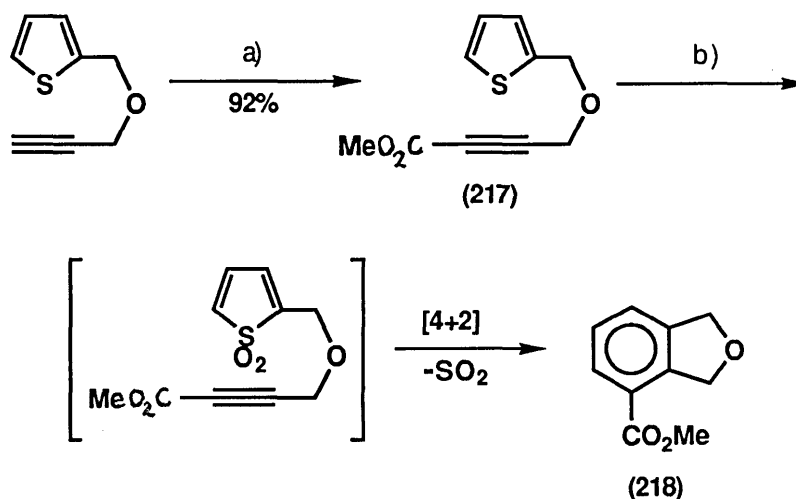
a Williamson etherification process.¹²¹ Thus, deprotonation of 2-thiophenemethanol with sodium hydride and subsequent reaction of the resulting sodium alkoxide with homopropargyl bromide resulted in a 98% yield of the acetylenic ether (216) as shown. (Scheme 89)



a) NaH, DME, propargyl bromide, b) dimethyldioxirane (3eq.), DCM

scheme 89

All efforts to oxidise this primary acetylene with dimethyldioxirane resulted in polymerisation of the starting material, presumably due to concomitant attack of the oxidising agent upon the acetylene functional group. Since dimethyldioxirane can be considered to be electrophilic oxidising agent, introduction of a carbomethoxy substituent upon the acetylene group should prevent attack by the oxidising agent. The acetylenic ester (217) was prepared in high yield by deprotonation at the terminal acetylene position of (216) with *n*-butyllithium followed by quenching of the resultant anion with methylchloroformate. (Scheme 90).



a) n-butyllithium, THF, MeCO_2Cl , b) dimethyldioxirane (3eq.), DCM

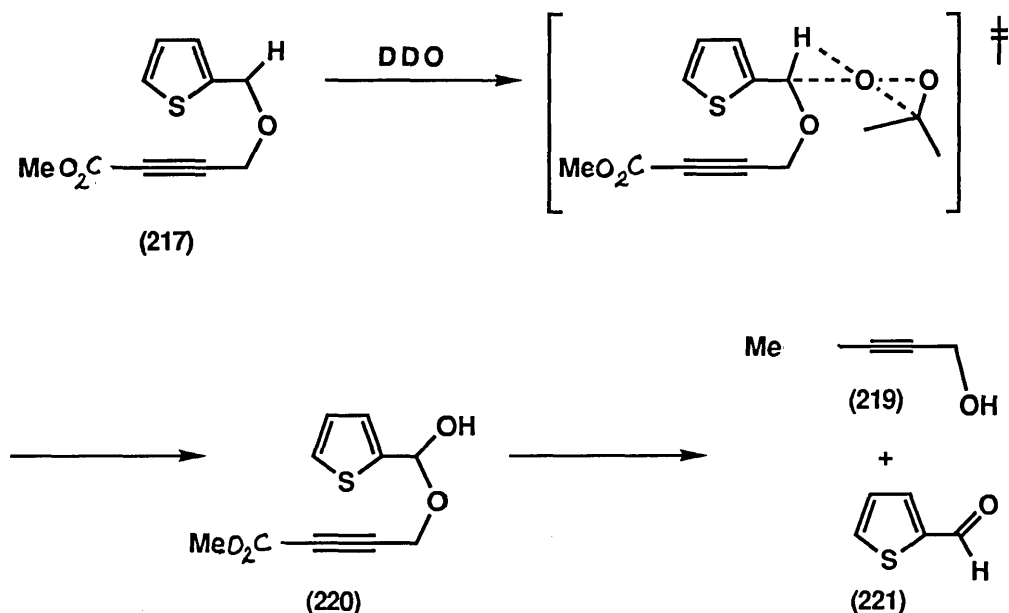
scheme 90

Oxidation of the above acetylenic ether (217) with three equivalents of dimethyldioxirane resulted in the clean formation of two products. One of these products was found to be the expected dihydroisobenzofuran (218), obtained by oxidation of (217) to its corresponding dioxide and subsequent cyclisation and extrusion of sulphur dioxide as shown. Unfortunately the yield of this product was only 13%, and the majority of the starting material was converted to a second product. The spectral properties of this second product indicated that heterobenzylic oxidation had occurred furnishing the acetylenic alcohol (219).

The formation of acetylenic alcohol (219) may be considered to result from insertion of dimethyldioxirane into the heterobenzylic carbon-hydrogen bond. Murray *et al.*¹²² have reported that dimethyldioxirane is capable of oxidising the benzylic position of an array of suitable arenes. For example, toluene, ethylbenzene and isopropylbenzene have all been oxidised to their respective aldehydes or alcohol using this reagent.

The exact mechanism for this insertion reaction is still unclear although the transition state depicted in scheme 91 featuring the so called 'butterfly' mechanism is

widely accepted.



scheme 91

Heterobenzylic oxidation of the acetylenic ether (217) gives the hemiacetal (220) which breaks down to give the observed alcohol (219) and 2-thiophenecarboxaldehyde (221). Thus, oxidation of the heterobenzylic position competes with sulphur oxidation in the above process.

Since both 2,5-dibenzyl and 2-acetyl-5-ethylthiophene have both been oxidised to their corresponding dioxides in high yield by dimethyldioxirane,⁸² the presence of the ether oxygen atom must in some way facilitate the present heterobenzylic oxidation process. One might envisage that electron donation by the oxygen atom lone pair could drive the transition state depicted in scheme 91 over to the product side of the reaction coordinate. (Figure 21).

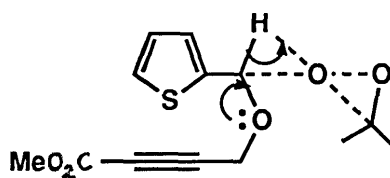


figure 21

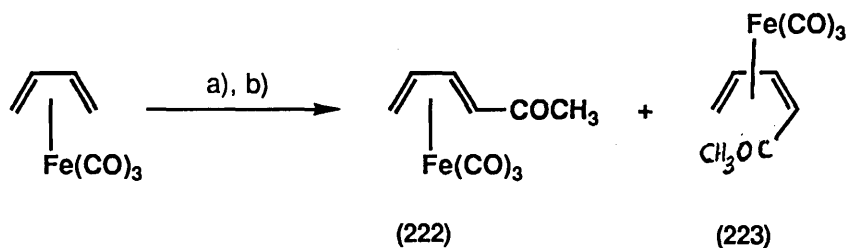
Further study of this oxidation-cyclisation procedure is required in order to establish the full potential of this methodology. The preliminary results outlined above, combined with the published literature, suggest that the presence of a heteroatom substituent upon the heterobenzyl position promotes oxidation of this position. In theory, substitution of the oxygen atom in molecule (217) by a methylene group should totally inhibit this undesired process leading to high yields of the derived cycloaddition product.

2.2.3 Preparation and Reactions of η_4 -(thiophene-1,1-dioxide)tricarbonyliron Complexes

As previously discussed, photolysis of thiophene-1,1-dioxides in the presence of iron pentacarbonyl affords η_4 -(thiophene-1,1-dioxide)tricarbonyliron complexes.¹⁰⁷ Whilst still keeping the original aim of utilising thiophene-1,1-dioxides in the one step formation of multiple carbon bonds firmly in mind, it was decided to study the general chemistry of these complexes, as very little literature precedent existed. Therefore, the reactivity of these complexes toward electrophiles, nucleophiles and bases was explored, in attempts to discover new reactions of these compounds which could prove a means of realising controlled carbon-carbon bond formation, and hence provide access to suitably protected precursors for intramolecular Diels-Alder reactions.

2.2.3.1 Reaction With Electrophiles

η_4 -(Diene)tricarbonyliron complexes have been reported to undergo acylation reactions under standard Friedel-Crafts conditions,¹²³ affording *E* and *Z* dienone tricarbonyliron complexes of the type (222) and (223). (Scheme 92).



a) AlCl_3 , CH_3COCl , DCM, b) H_2O

scheme 92

The rôle of the iron unit in this reaction is thought to be stabilising rather than activating. Since Friedel-Crafts are excellent polymerisation catalysts for 1,3-dienes, it is thought that the ability of the metal to stabilise the intermediate cationic species by formation of a π -allyl complex of the type depicted in figure 22 prevents this polymerisation reaction taking place.

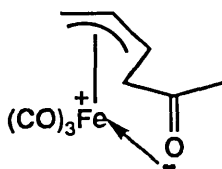
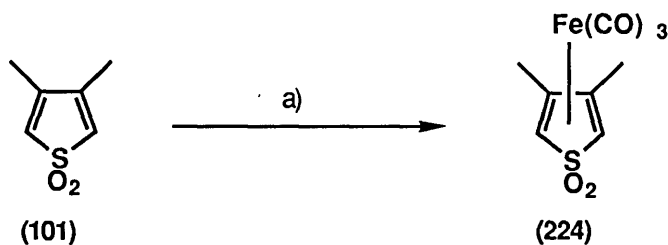


figure 22

It was of interest to investigate whether similar η_4 -(thiophene-1,1-

dioxide)tricarbonyliron complexes would undergo a similar reaction, as the process offered an excellent method for the introduction of substituents on the thiophene-1,1-dioxide ring. To this end, the complex η_4 -(3,4-dimethylthiophene-1,1-dioxide)tricarbonyliron (224) was prepared by a slight modification of the published procedure¹⁰⁷. (Scheme 93).

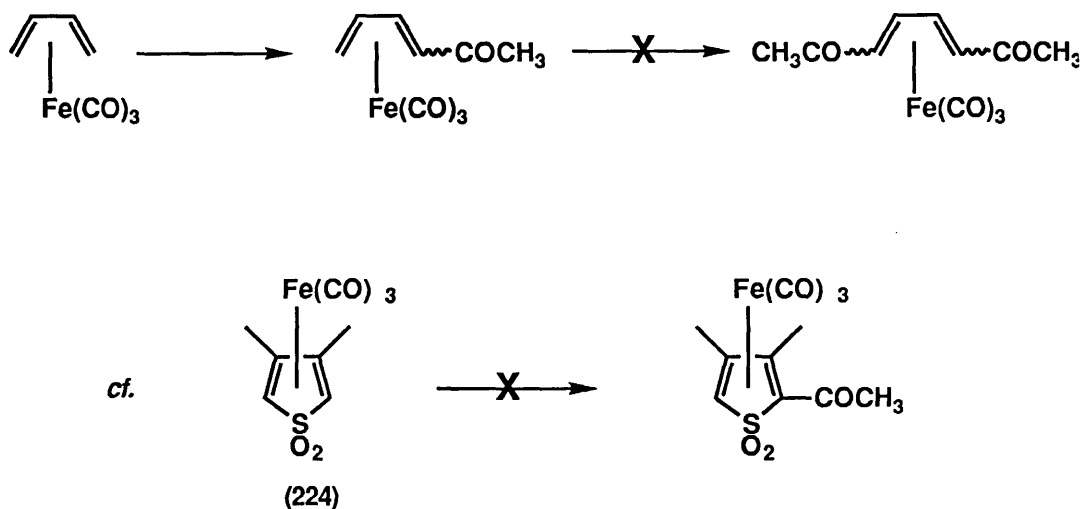


a) $\text{Fe}_2(\text{CO})_9$, THF, reflux.

scheme 93

Refluxing a 2:1 mixture of 3,4-dimethylthiophene-1,1-dioxide (101) and diironnonacarbonyl in THF led to the formation of the complex (224) in 60% yield. The yields obtained in this process were less than those reported in the literature, but the use of highly toxic iron pentacarbonyl was avoided. However, all efforts to acylate this complex were to no avail, despite the use of elevated reaction temperatures and a large excess of the acylating reagent. (Scheme 94).

This result is readily explained when the deactivating nature of the sulphone group is considered. It is pertinent to note that when η_4 -(buta-1,3-diene)tricarbonyliron was subjected to Friedel-Crafts acylation, only the monoacylated product was obtained, even in the presence of a large excess of the acylating reagent.¹²³ Thus, a ketone group is quite capable of deactivating a diene complex toward acylation reactions. Since a sulphone has comparable, if not stronger, withdrawing abilities, the inert nature of complex (224) toward Friedel-Crafts acylation is not at all suprising.



scheme 94

2.2.3.2 Reaction With Nucleophiles

Neutral η_4 -(diene)tricarbonyliron complexes are capable of undergoing nucleophilic attack by both stabilised and unstabilised carbanions, and the regioselectivity of attack is dependent on the nature of the nucleophilic species.

Three possible sites of attack exist within these complexes:

1. at the diene terminal positions.
2. at the diene internal positions.
- 3 upon a coordinated carbon monoxide ligand

All three possible reactive centres are depicted in figure 23.

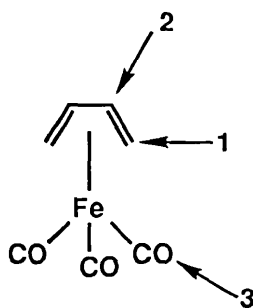
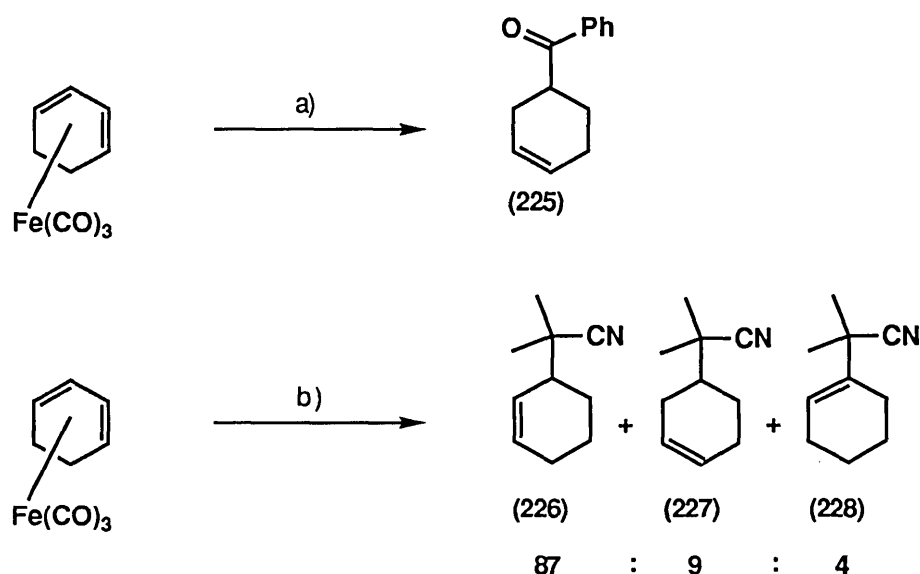


figure 23

Extensive studies by Semmelhack and co-workers¹²⁴ have revealed the conditions that favour each mode of attack. Initial studies revealed that stabilised carbanions preferentially attack the diene ligand, whilst higher energy carbanions prefer attack at carbon monoxide ligands. For example, treatment of η_4 -(cyclohexa-1,3-diene)tricarbonyliron with phenylmagnesium bromide led to a 15% yield of the phenyl ketone (225); reacting the same complex with 2-lithio-2-methyl-propionitrile in the presence of HMPA gave the three regioisomeric cyclohexenes (226), (227) and (228) in a combined 98% yield upon acidic workup. (Scheme 95).



a) PhMgBr , THF, b) $\text{LiC}(\text{CH}_3)_2\text{CN}$, THF, HMPA

scheme 95

Compounds (226) and (227) derive from the direct protonation of the intermediate π -allyl anionic complex (229) in figure 24, whilst the third product is presumed to derive from (229) by a hydride elimination-readdition sequence.

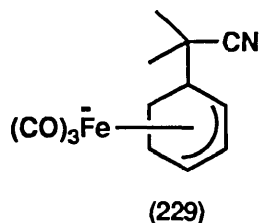
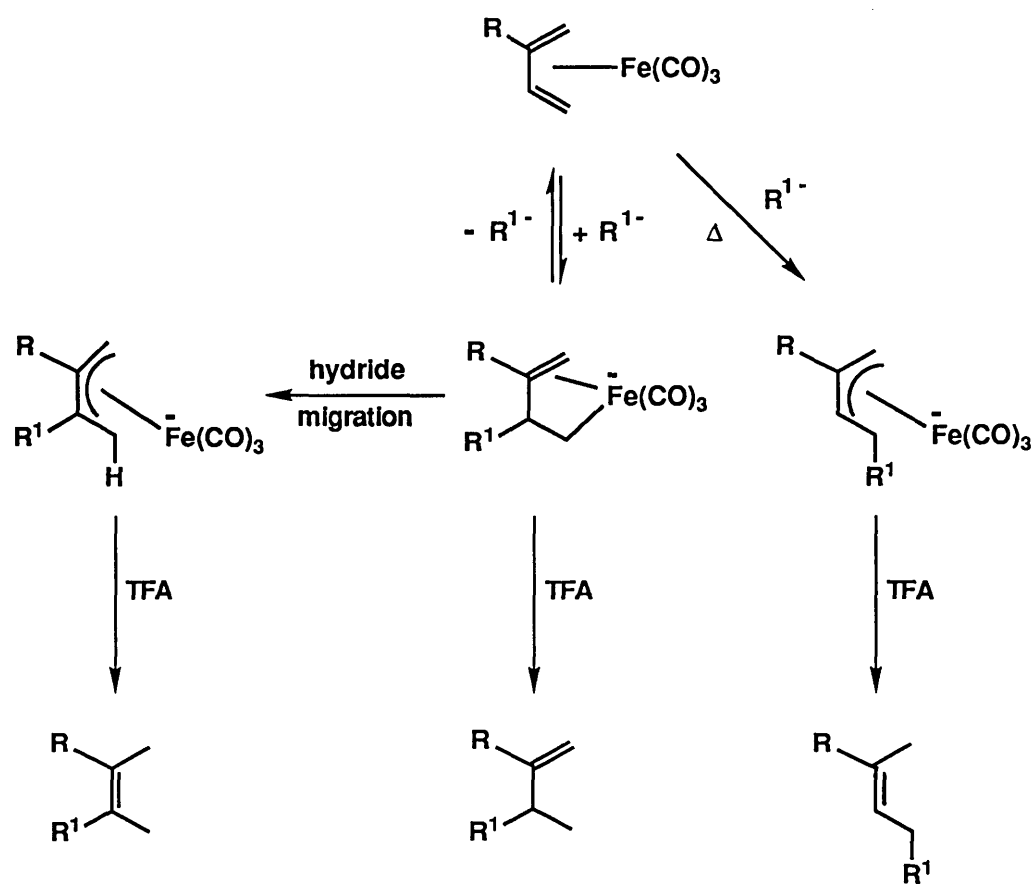


figure 24

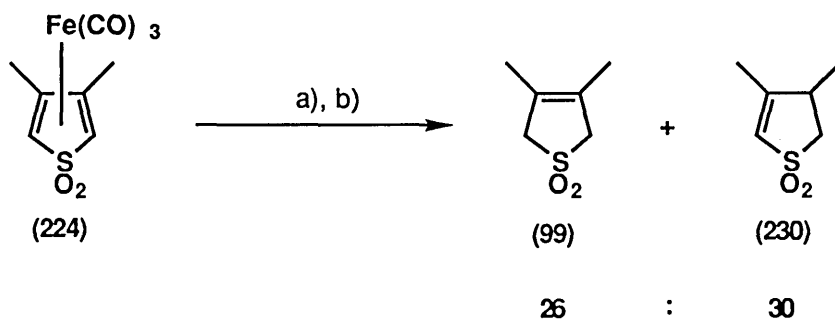
Further studies by Semmelhack¹²⁵ have concluded that initial nucleophilic attack occurs exclusively at the diene internal position. Upon warming the reaction mixture, facile rearrangement occurs to give a thermodynamically more stable η^3 -allyl anionic complex of the type (229) above. Formation of this species is postulated to occur by a reversal of the initial addition reaction followed by readdition at the terminal position, or in some cases by hydride migration. Treatment of the intermediate complexes with trifluoroacetic acid (TFA) then affords the alkene products. The proposed mechanism for these transformations is shown below for a general η^4 -(diene)tricarbonyliron complex. (Scheme 96).

Since the sulphone group in thiophene-1,1-dioxides has been found to exert a strong electron withdrawing effect upon the diene system, the η^4 -(diene)tricarbonyliron complexes of these compounds should be highly activated toward nucleophilic attack. Moreover, the effect of the presence of the sulphone group upon the regiochemistry of attack of external nucleophiles upon the thiophene dioxide ligand would also be of great interest.



scheme 96

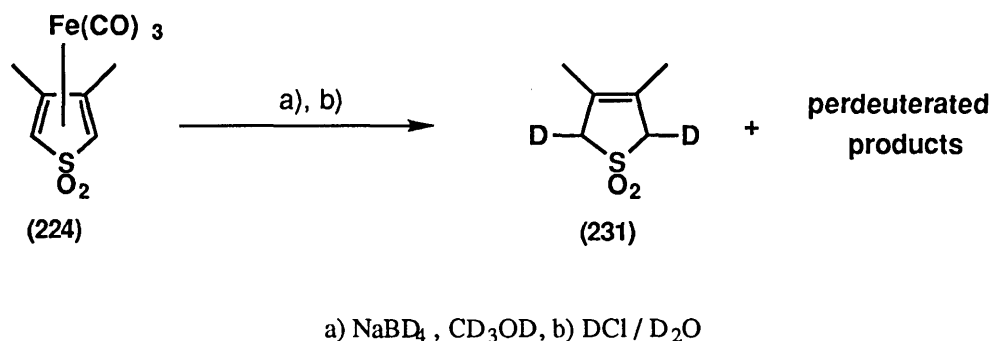
Preliminary studies involving hydride as the incoming nucleophile proved very promising, η_4 -(3,4-dimethylthiophene-1,1-dioxide)tricarbonyliron being smoothly reduced to the two regioisomeric thiacyclopentenedioxides (230) and (99) by sodium borohydride in a combined 56% yield. (Scheme 97).



a) $NaBH_4$, MeOH, b) 10% HCl / H_2O

scheme 97

Sodium borodeuteride also reduced complex (224), though the reaction was less clean than in the case with borohydride. The use of deuterated solvents gave polydeuterated products, presumably due to exchange phenomena, only one of which was totally characterisable as 2,5-dideuterio-3,4-dimethylthiophene-1,1-dioxide (231). (Scheme 98).



scheme 98

Unexpectedly, complex (224) proved inert towards nucleophilic attack by stabilised carbanions similar to those utilised by Semmelhack. The complex did appear to react with unstabilised carbanions such as methyllithium and *n*-butyllithium, with a rapid darkening of the reaction mixture occurring upon addition of the alkyllithium species. Protic workup of these reactions resulted in a high recovery of the starting complex, no products derived from nucleophilic addition were observed. It was postulated that deprotonation was occurring during these reactions which was verified by further studies.

A possible reason for this lack of reactivity displayed by η_4 -(3,4-dimethylthiophene-1,1-dioxide)tricarbonyliron is due to steric hindrance experienced by the incoming reactant. A crystal structure of this complex¹²⁶ has been obtained that shows the sulphur atom to be distorted approximately 27° out of the plane of the diene system, due to unfavourable steric interaction with the carbon monoxide ligands. This distortion means that one of the sulphone oxygen atoms points

virtually perpendicular to the diene system as shown in figure 25.

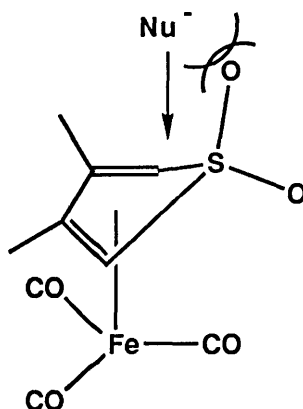
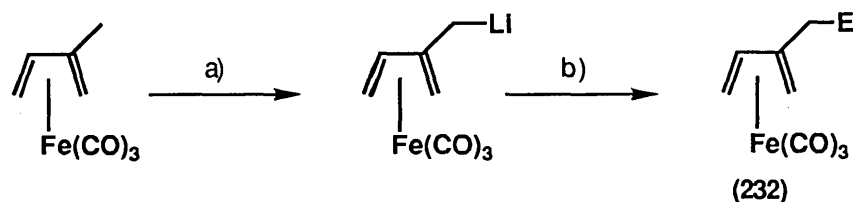


figure 25

Any incoming species will experience a strong steric interaction with this oxygen atom. In the case of nucleophile an additional electronic repulsion between the oxygen atom lone pairs and the negatively charged species would add to the steric interactions, thus preventing the reactant reaching the reactive site. Presumably, hydride reduction occurs as the incoming species in this reaction is much smaller and less prone to steric repulsion.

2.2.3.3 Deprotonation Reactions

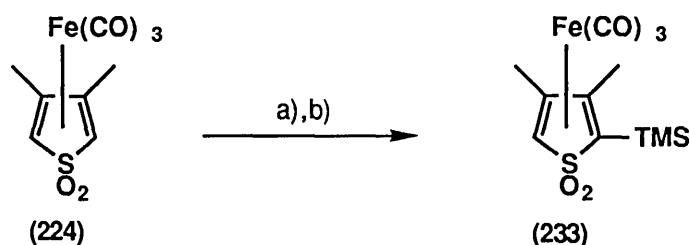
During studies upon nucleophilic addition to η_4 -(3,4-dimethylthiophene-1,1-dioxide)tricarbonyliron, it was postulated that treatment of this complex with simple organolithium reagents resulted in deprotonation rather than addition. A survey of the literature indicated that this was indeed the case; Semmelhack *et al.*¹²⁷ has reported that η_4 -(isoprene)tricarbonyliron is readily deprotonated by LDA. Subsequent treatment of the lithioanion with an electrophile afforded substituted complexes of the type (232). (Scheme 99).



a) THF, -78°C , LDA (2hr. addition), b) E^+ ,

scheme 99

In an analogous fashion, η_4 -(3,4-dimethylthiophene-1,1-dioxide)tricarbonyliron was deprotonated with LDA followed by treatment with chlorotrimethylsilane (TMSCl), to give the α -silylated product (233) in 12% yield. Several attempts were made to improve this yield, including slow addition of the base which was reported by Semmelhack to be a superior deprotonation process, but yields of the silylated complex (233) remained disappointingly low. (Scheme 100).

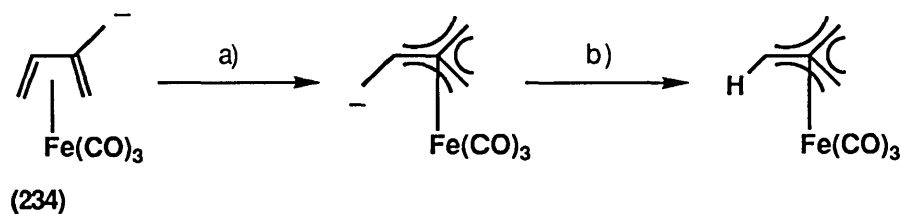


a) LDA, THF, -78°C , b) TMSCl

scheme 100

The striking feature of this reaction is the fact that the regiochemistry of the reaction differs to that reported. Similar efforts to deprotonate the parent complex η_4 -(thiophene-1,1-dioxide)tricarbonyliron were unsuccessful, which suggests that initial deprotonation was occurring at the allylic position, an observation which was in agreement with those of the Semmelhack group. They reported that the anionic

complex (234) was thermally unstable above -30°C , rearranging to a trimethylenemethane type complex which had been isolated as the neutral species after a protic workup. (Scheme101).



a) THF, -78°C , LDA (2hr. addition), b) 0°C , 24hrs, $\text{NH}_4^+\text{Cl}^-_{(\text{aq})}$

scheme 101

Attempted formation of an analogous complex using a deuterium chloride quench was to no avail; in fact no deuterium incorporation was observed at all, despite stirring the complex (224) for several hours at 0°C in the presence of LDA. This result indicated that the actual deprotonation reaction was slow, and a series of experiments soon ascertained that the product yield was solely dependent upon the time interval before a protic workup was performed. From these studies it became apparent that TMSCl was acting as an *in situ*. electrophile and deprotonation was indeed a slow process.

Also, in all of the above deprotonation reactions, products directly derived from a trimethylenemethane species were never observed. This suggested that an intermediate of this type was not involved, and that deprotonation was occurring at the sulphone α -position, despite the apparent inert nature of η_4 -(thiophene-1,1-dioxide)tricarbonyliron to deprotonation.

Alternatively, as in the α -alkylation of anions derived from allylic sulphones, it can be envisaged that deprotonation at the methyl group leads to a species in which the η_4 -character of the complex is lost, and the resultant anion is best represented by a structure such as (235) in which the anionic iron complex undergoes α -silylation

with chlorotrimethylsilane as observed. (Figure 26).

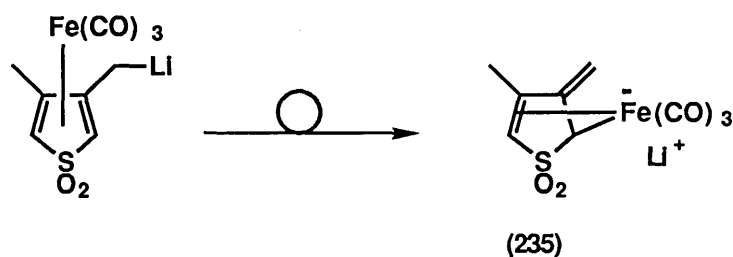
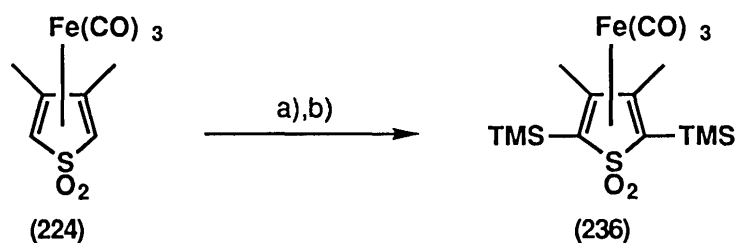


figure 26

In an attempt to facilitate deprotonation HMPA was employed as a co-solvent with THF. Repeating the initial reaction in the presence of HMPA surprisingly resulted in the formation of a totally different complex, with none of the silylated complex (233) being observed. This new product was found to be the *bis* silylated complex (236), obtained in a similar yield to the monosilylated complex (233). (Scheme102).



a) LDA, THF, HMPA, -78°C, b) TMSCl

scheme 102

The crystalline nature of the bis silylated complex allowed X-ray analysis to be carried out, giving complete structural information. The crystal structure of is indicated in figure 27.

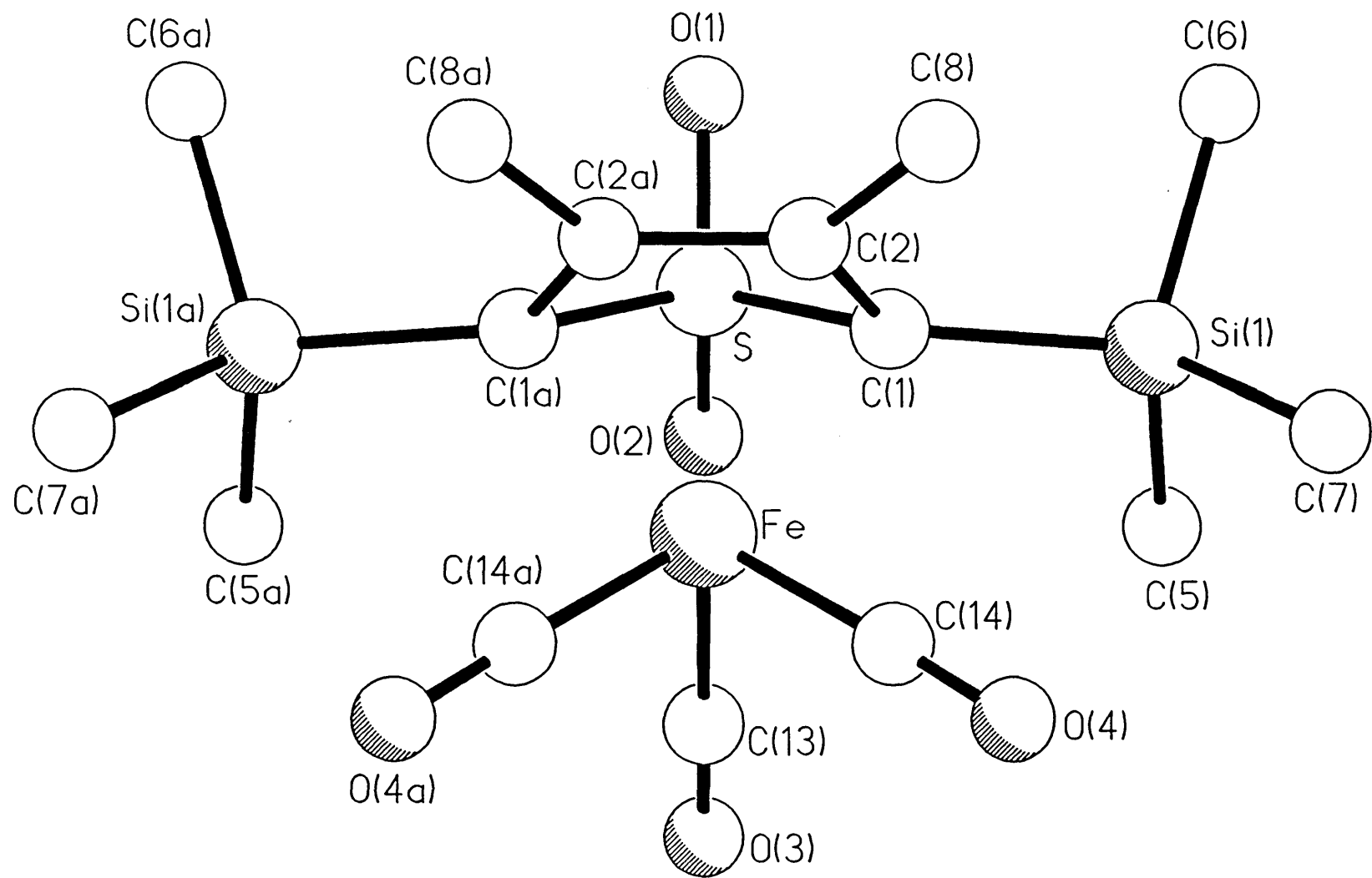


figure 27

From figure 27 it can be seen that the molecule possesses a plane of symmetry that passes directly through both the sulphur and iron atoms. Thus, as is the case with η_4 -(3,4-dimethylthiophene-1,1-dioxide)irontricarbonyl (224),¹²⁶ the sulphone group and one of the carbonyl ligands are in an eclipsed conformation. Unfavourable steric interactions between the oxygen atoms of the sulphone group and the carbonyl ligand causes the sulphur atom to move out of the plane of the diene system. The eclipsed nature of these two groups can be more easily visualised in the plan view of the complex shown in figure 28.

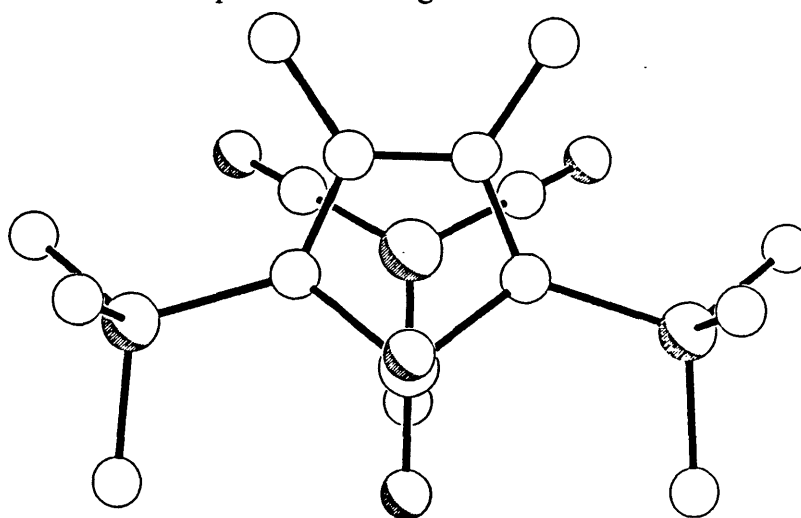


figure 28

Plan view of complex (236) showing the eclipsed nature of the sulphone group and carbonyl ligand.

The presence of the trimethylsilyl substituents upon the thiophene-1,1-dioxide ring causes a slight elongation of the C-1, C-2 double bond relative to the unsubstituted complex. This elongation is due to electron withdrawal by the silicon group *via* d-p orbital overlap, a phenomena that could also explain the proposed higher acidity of the monosilylated complex (233) compared to unsubstituted complex (224).

Finally the iron carbon bond lengths of the two equivalent carbonyl ligands in (236) were found to be shorter than that of the eclipsed ligand; a difference of

0.03Å being observed. This observation is thought to be due the steric interactions between this ligand and the sulphone moiety, causing a slight elongation of the metal-ligand bond.

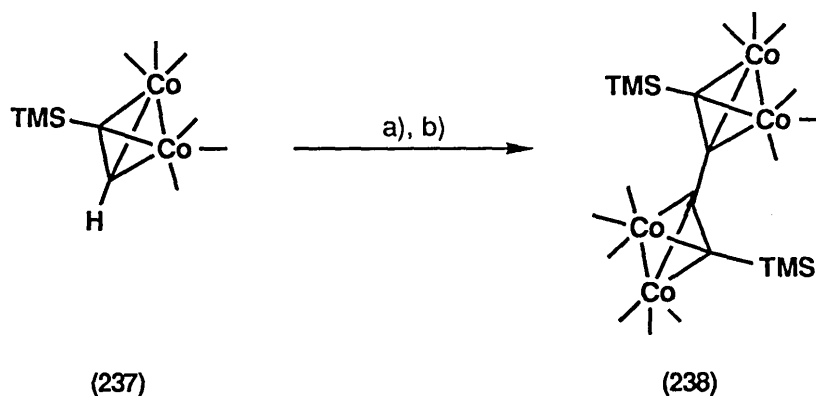
The total absence of the monosilylated complex (233) from the reaction mixture when HMPA was employed suggests that this latter complex is preferentially deprotonated in the presence of the starting material. As the yield of *bis* silylated complex was comparable to that obtained of monosilylated complex when the reaction was run in the absence of HMPA, despite very similar reaction conditions, this deprotonation reaction must be more facile. Indeed, repeating the reaction using three equivalents of base increased the yield of the *bis* silylated adduct (236) to 22%, again none of the monosilylated product being observed.

Although the yields in the above reactions are poor, the ability to deprotonate η_4 -(thiophene-1,1-dioxide)tricarbonyliron complexes and react their resulting anions with electrophiles represents a potential methodology for achieving the original goal of the systematic 'one pot' formation of multiple carbon bonds. More work is necessary in order to discover the optimum conditions for this deprotonation reaction, and also to ascertain the range of electrophiles that are capable of reacting with the anion formed.

2.2.3.4 Cyclic Voltammetry Studies

During the course of our studies on the deprotonation reactions of η_4 -(3,4-dimethylthiophene-1,1-dioxide)tricarbonyliron (224), often several products were often observed when HMPA was included in the reaction mixture, albeit in very small amounts. Since solvents such as HMPA are well known to promote electron transfer reactions¹²⁸, it was postulated that a single electron transfer reaction was taking place. Moreover, Magnus⁴⁷ has already reported that attempts to deprotonate hexacarbonyl(trimethylsilyl)ethyne)dicolbalt (237) using LDA resulted in the

formation of the dimeric species (238), a transformation which appeared to occur *via* a single electron transfer mechanism. (Scheme 103).



a) LDA, ether, -78°C - 0°C, b) H₂O or D₂O

scheme 103

In order to obtain more information upon the redox chemistry of (224) cyclic voltammetry studies were carried out to ascertain whether single electron transfer was indeed taking place. The cyclic voltammogram of (224) is shown in figure 29, ferrocene being included as an internal standard.

The voltammogram obtained took the form of an irreversible wave, i.e. the redox system exhibited non-Nernstein behaviour. However, it was possible to establish the peak reduction and oxidation potentials for the complex, which were found to be -2.68 and 1.69V respectively, relative to an Ag / Ag⁺ reference electrode. The large negative value of the peak reduction potential for (224) implied that single electron transfer was not occurring during the deprotonation studies described above and LDA was in fact acting solely as a base. Despite the fact that several other products were observed by t.l.c during our deprotonation studies, the isolation of appreciable amounts of these compounds proved difficult, implying that they were in fact minor side products of the reaction.

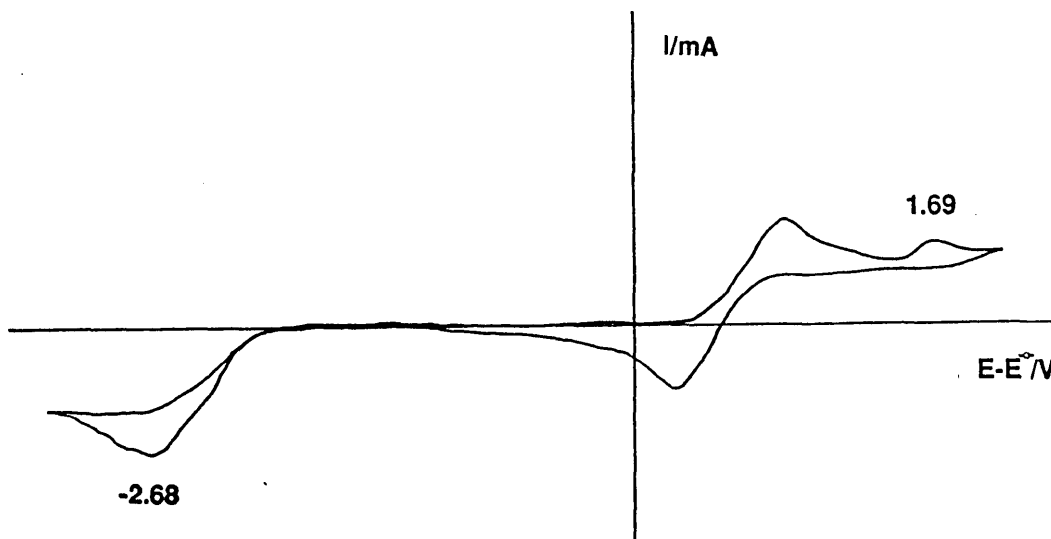


figure 29

Cyclic voltammogram of
 η_4 -(3,4-dimethylthiophene-1,1-dioxide)tricarbonyliron
 using 0.1M $\text{Bu}_4\text{N}^+\text{PF}_6^-$ in THF as base electrolyte, silver
 reference electrode, platinum working and counter electrodes.

2.3 Conclusions and Perspectives

In summary, the foregoing chapter has demonstrated, albeit on a limited scale, that the possibility of effecting intramolecular Diels-Alder reactions involving a thiophene dioxide partner is a viable approach. Of those methods examined, the most straightforward obviously lies in elaboration of suitable thiophene derivatives and *in situ* oxidation. Initial study of the preparative organometallic chemistry of iron tricarbonyl thiophene dioxide complexes has indicated that while direct addition of nucleophiles cannot be achieved, deprotonation reactions are certainly feasible and further efforts in this area using 2-alkyl substituted derivatives as precursors of heterobenzylic anions should certainly be pursued.

In essence, this introductory study has provided avenues for further research through which the chemistry of thiophene dioxides may be tamed.

Chapter Three

Experimental

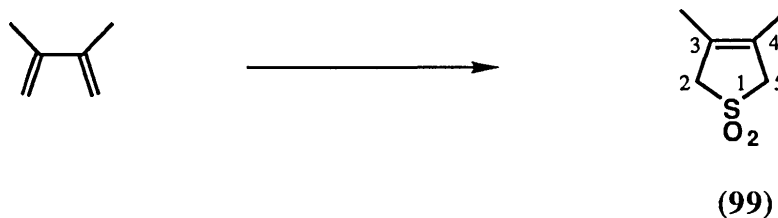
^1H and ^{13}C nmr spectra were recorded at 90MHz on a Jeol FX 90Q instrument, at 250 MHz and 62.9MHz respectively on a Bruker WM-250 instrument, at 270 MHz on a Jeol GSX 270 instrument and at 500 MHz and 125.8 MHz respectively on a Bruker AM-500 instrument, with residual protic solvent as the internal standard. Spectra were recorded in d-chloroform and d_6 -benzene as specified. Infrared spectra were recorded on a Perkin Elmer 983G spectrometer. Mass spectra were recorded on a VG 7070B instrument under E.I. conditions. Microanalyses were performed in the Imperial College Chemistry Department microanalytical laboratory. Sonication was performed using a Sonicor SC-52 cleaning bath. Melting points were determined on a Reichert hot-stage and are uncorrected..

Petrol refers to petroleum ether b.p. 40-60°C which was distilled prior to use. Diethyl ether, dimethoxyethane and tetrahydrofuran were distilled from sodium - benzophenone ketyl under argon immediately prior to use. Toluene was distilled from sodium under an atmosphere of argon immediately prior to use. Dichloromethane was distilled from phosphorus pentoxide under an atmosphere of argon again immediately prior to use. Dimethyl formamide and hexamethylphosphoramide were distilled from calcium hydride at reduced pressure, and stored over 4Å molecular sieves under argon. Pyridine, diisopropylamine and N,N,N'N'-tetramethylethylenediamine were distilled from potassium hydroxide and stored over 4Å molecular sieves under argon. Chlorotrimethylsilane was freshly distilled from calcium hydride and residual acid removed by treatment with sodium metal. All other solvents and reagents were purified by standard means.

All reactions were performed using oven dried glassware under an atmosphere of dry argon unless otherwise stated. Analytical thin layer chromatography was performed on pre-coated glass backed plates (Merck Kieselgel 60 F₂₅₄) and visualised using ultra violet light, iodine, potassium permanganate and acidic ammonium molybdate (IV) as appropriate. Preparative column chromatography was performed at low positive pressure on Merck Kieselgel 60 (230 - 400 mesh).

Chapter One

Preparation of 3,4-dimethylthiacyclopent-3-ene-1,1-dioxide (99)



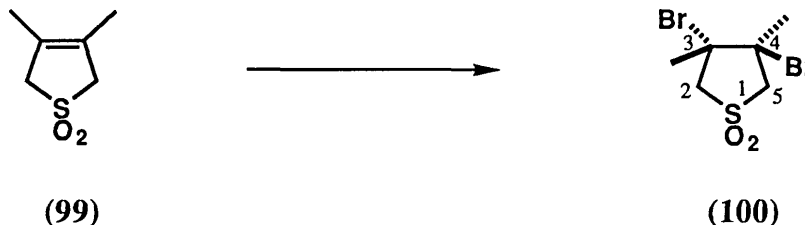
A pressure bottle, pre-cooled to -78°C , was charged with 2,3-dimethylbuta-1,3-diene (24.6g, 0.30mol), liquid sulphur dioxide (13.8ml, 0.3mol), hydroquinone (0.68g, 0.062mol) and methanol (15ml). The bottle was then sealed and heated at 100°C for 4 hours. After cooling, the bottle was opened and the resulting yellow solution removed. Evaporation of the solvent *in vacuo* and recrystallisation of the yellow solid from methanol gave **3,4-dimethylthiacyclopent-3-ene-1,1-dioxide (99)** as white crystals, (28.42g, 66%).

Mpt = 136°C

ν_{max} (film) 2920, 2853, 1444, 1294, 1109, 821cm^{-1}

δ_{H} (90MHz, CDCl_3) 3.75 (4H, s, 2xH-2, 2xH-5), 1.79ppm (6H, s, 2xCH₃)

Preparation of *trans*-3,4-dibromo-3,4-dimethylthiacyclopentane-1,1-dioxide (100)



To a refluxing solution of 3,4-dimethylthiacyclopent-3-ene-1,1-dioxide (99) (11.56g, 79.2mmol) in benzene (50ml) was added bromine (8ml, 156mmol) in benzene (10ml), dropwise so as to maintain a steady reflux. The reaction mixture was then refluxed for a further 10 minutes, before being cooled to room temperature. The resulting precipitate was filtered off, washed with cold benzene, and dried *in vacuo* to give *trans*-3,4-dibromo-3,4-dimethyl-2,4-thiacyclopentane-1,1-dioxide (100) (20.33g, 84%) as a white solid.

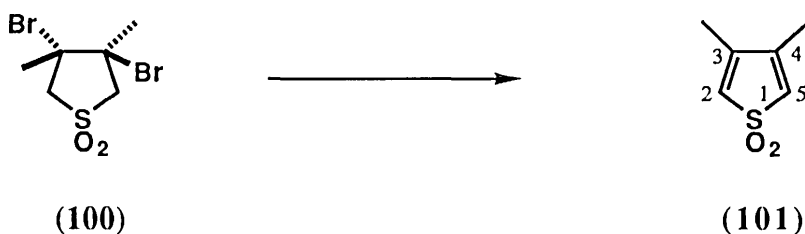
Mpt = 195-196°C

ν_{max} (mull) 1311, 1274, 1154, 1142, 1099cm⁻¹

δ_H (90MHz, CDCl₃) 4.05 (2H, d, 14.8Hz, H-2, H-5), 3.70 (2H, d, 14.8Hz, H-2, H-5), 2.15ppm (6H, s, 2xCH₃)

m/z 290, 278, 276 (M⁺), 215, 213, 211, 135, 133

Preparation of 3,4-dimethylthiophene-1,1-dioxide (101)



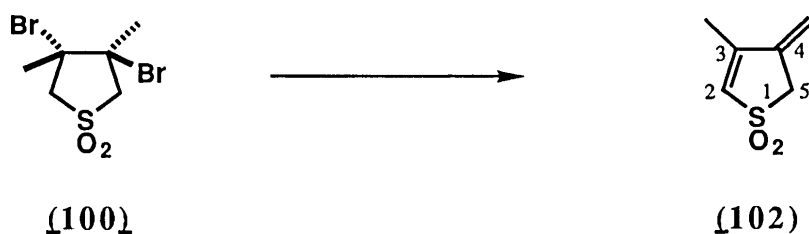
To a solution of sodium hydroxide (0.45g, 11.25mmol) in water (20ml) was added *trans*-3,4-dibromo-3,4-dimethylthiacyclopentane-1,1-dioxide (100) (1.63g, 5.02mmol). The resulting suspension was stirred at room temperature for 3 hours, after which time the reaction mixture was neutralised using 10% aqueous hydrochloric acid, and then extracted using EtOAc (3x10ml). The organic extracts were combined, washed with saturated sodium hydrogen carbonate solution (10ml), water (10ml), and finally dried (MgSO_4). Removal of the solvent *in vacuo* gave **3,4-dimethylthiophene-1,1-dioxide (101)** (0.737g, 96%) as a white solid.

Mpt = 103-105°C

ν_{max} (mull) 3073, 2922, 1561, 1387, 1287, 1176, 1095 cm^{-1}

δ_{H} (270MHz, CDCl_3) 6.32 (2H, d, 0.8Hz, H-2, H-5), 2.05ppm (6H, d, 0.8Hz, 2x CH_3),

Preparation of 3-methyl-4-methylenethiacyclopent-2-ene-1,1-dioxide (102)



A suspension of 3,4-dibromo-3,4-dimethylthiacyclopentane-1,1-dioxide (100) (31.90g, 104mmol), and sodium hydroxide (8.80g, 220mmol) in water (220ml) was stirred at room temperature for 3 hours, then heated at reflux for 1 hour. Upon cooling fine white crystals precipitated from the reaction mixture, which were collected by

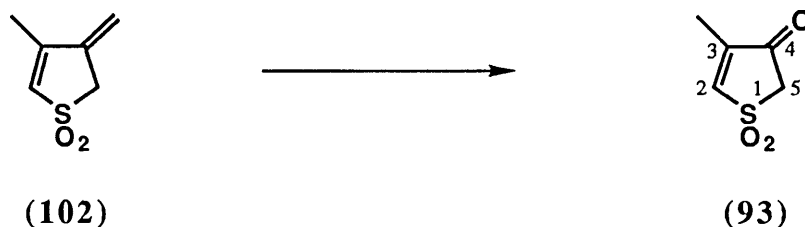
filtration. The solid was then washed with water, and dried *in vacuo* over CaCl_2 to give **3-methyl-4-methylenethiacyclopent-2-ene-1,1-dioxide (102)** (14.13g, 96%).

Mpt = 103-104°C

ν_{max} (mull) 3069, 2924, 1589, 1282, 1129 cm^{-1}

δ_{H} (90MHz, CDCl_3) 6.50 (1H, bs, H-2), 5.55 (1H, bs, $\text{C}=\text{CH}_2$), 5.40 (1H, bs, $\text{C}=\text{CH}_2$), 3.45 (2H, s, 2xH-5), 2.10ppm (3H, d, 1.0Hz, CH_3).

Preparation of 3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (93)



A solution of 3-methyl-4-methylenethiacyclopent-2-ene-1,1-dioxide (102) (6.40g, 44.3mmol) in DCM (200ml), at room temperature, was treated with ozone until the reaction was complete as indicated by tlc (SiO_2 , 25% EtOAc in petrol). Dimethylsulphide (40ml) was then added and the reaction mixture stirred at room temperature overnight. The solvent and excess dimethylsulphide were removed *in vacuo*, and the resulting solid dissolved in EtOAc (20ml). This solution was washed thoroughly with water, dried (MgSO_4) and the solvent removed *in vacuo*. Subsequent recrystallisation from aqueous methanol gave **3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (93)** (4.80g, 74%) as a white solid.

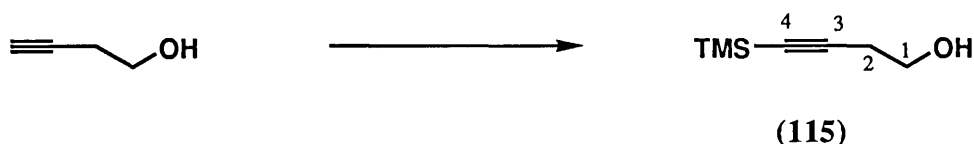
Mpt = 166-167°C

ν_{max} (mull) 3065, 2999, 1729, 1616, 1325, 1118 cm^{-1}

δ_{H} (270MHz, CDCl_3) 7.46 (1H, q, 1.5Hz, H-2), 3.91 (2H, s, 2xH-5), 2.05ppm (3H,

d, 1.5Hz, CH₃)

Preparation of 4-trimethylsilylbut-3-yn-1-ol (115)⁴⁸



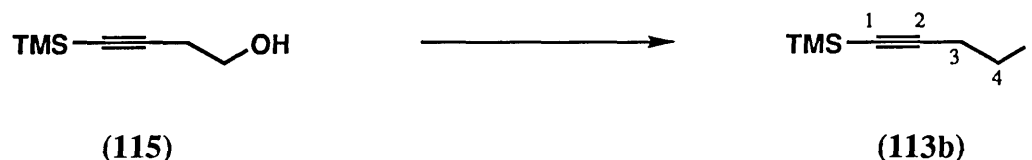
To a solution of n-butyllithium in hexane (35ml of a 2.5M solution in hexanes, 87.5mmol) in anhydrous THF (80ml) at -78°C was added 3-butyne-1-ol (3.02g, 43.1mmol) dropwise over 15 minutes. After stirring for a further 20 minutes, freshly distilled chlorotrimethylsilane (15ml) was added, the reaction mixture stirred for 15 minutes, then warmed to room temperature. A 20% solution of hydrochloric acid in THF (100ml) was added and the reaction stirred for a further 1.5 hours. Following neutralisation using solid sodium hydrogen carbonate the mixture was diluted with water (50ml) then extracted with ether and the combined organic extracts dried (MgSO₄). Removal of the solvents *in vacuo* and distillation of the resulting yellow oil gave **4-trimethylsilylbut-3-yn-1-ol (115)**. (5.52g, 90%) as a clear oil.

Bpt = 60°C at 0.3mmHg, lit = 86-88°C at 0.4mmHg

ν_{max} (film) 3346, 2956, 2177, 1249, 1054, 843cm⁻¹

δ_H (270MHz, CDCl₃) 3.75 (1H, bs, OH), 3.68 (2H, bt, 9.8Hz, 2xH-1), 2.51 (2H, t, 9.8Hz, 2xH-2), 0.16ppm (9H, s, Si(CH₃)₃).

Preparation of 4-iodo-1-trimethylsilylbut-1-yne.(113b)⁴⁸



To a solution of 4-trimethylsilylbut-3-yn-1-ol (115) (6.00g, 42.2mmol), in ether and acetonitrile (200ml, 4:1) was added triphenylphosphine (15.2g, 58.1mmol) and imidazole (5.02g, 73.7mmol), and the reaction mixture stirred for 10 minutes. Iodine (11.25g, 88.6mmol) in ether (50ml) was then added *via* cannula, and the reaction mixture was stirred for a further 8 hours. The resulting precipitate was filtered off, the filtrate washed with saturated sodium thiosulphate solution (10ml), water (10ml) then dried (MgSO_4). Removal of the solvents *in vacuo* and Kügelrohr distillation gave the required 4-iodo-1-trimethylsilylbut-1-yne.(113b)

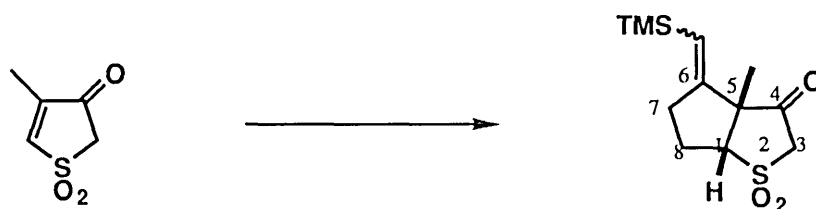
(8.74g, 85%), as a clear oil.

Bpt = 85°C at 0.8mmHg, lit = 40°C at 0.1mmHg

ν_{max} (film) 2959, 2177, 1250, 843 cm^{-1}

δ_{H} (270MHz, CDCl_3) 3.22 (2H, t, 9.8Hz, 2xH-4), 2.78 (2H, t, 9.8Hz, 2xH-3), 0.17ppm (9H, s, $\text{Si}(\text{CH}_3)_3$).

Preparation of *E*- and *Z*-5-methyl-4-oxo-2-thia-6-(trimethylsilylmethylene)bicyclo[3.3.0]octane-2,2-dioxide.(98)



(93)

(98)

To a refluxing solution of 3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (93) (100.1mg, 0.68mmol) and 4-iodo-1-trimethylsilylbut-1-yne.(115) (500mg, 2.01mmol) in toluene (20ml), was added a solution of tributyltin hydride (222.8mg, 0.77mmol) and benzoyl peroxide (25.5mg, 0.11mmol) in toluene (5ml) over 18 hours *via* a syringe pump. When addition was complete, the reaction mixture was cooled and the solvent removed *in vacuo*. The residual yellow oil was then purified by extensive column chromatography (5-25% EtOAc in petrol). This gave *E*- and *Z*-5-methyl-4-oxo-6-(trimethylsilylmethylene)-2-thiabicyclo[3.3.0]octane-2,2-dioxide (98) (78.4mg, 44%) as an inseparable 4:1 mixture of isomers.

Mpt = 75-76°C.

ν_{max} (mull) 2956, 2929, 1741, 1603, 1378, 1317, 1129, 1247, 846cm⁻¹

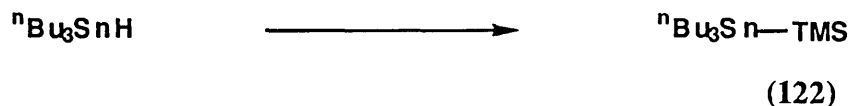
δ_H (270MHz, CDCl₃) *major*:- 5.71 (1H, bs, C=CH), 3.96 (1H, d, J=16.6Hz, H-3b), 3.70 (1H, bd, 2.9Hz, H-1), 3.64 (1H, dd, 16.6Hz, 1.0Hz, H-3a), 2.89 (1H, ddd, 14.7Hz, 8.7Hz, 2.3Hz, H-8b), 2.72 (1H, ddd, 9.7Hz, 4.3Hz, 2.3Hz, H-7a), 2.47 (1H, ddd, 8.7Hz, 4.3Hz, 1.5Hz, H-7b), 1.50 (3H, s, CH₃), 0.12ppm (9H, s, Si(CH₃)₃)

minor:- 5.65 (1H, bs, C=CH), 3.96 (1H, d, J=16.6Hz, H-3b), 3.70 (1H, bd, 2.9Hz, H-1), 3.64 (1H, dd, 16.6Hz, 1.0Hz, H-3a), 2.89 (1H, ddd, 14.7Hz, 8.7Hz, 2.3Hz, H-8b), 2.64 (1H, ddd, 9.7Hz, 4.3Hz, 2.3Hz, H-7a), 2.52 (1H, ddd, 8.7Hz, 4.3Hz, 1.5Hz, H-7b), 1.54 (3H, s, CH₃), 0.12ppm (9H, s, Si(CH₃)₃).

m/z 272 (M⁺), 257, 166, 151, 120, 73.

Accurate mass (M-Me) Observed 257.0673 C₁₁H₁₇O₃SSi requires 257.0667

Preparation of tributyl(trimethylsilyl)stannane (122)¹³²



To a solution of diisopropylamine (1.64g, 16.2mmol) in THF (20ml) at -10°C was added n-butyllithium (7.22ml of a 2.5M solution in hexanes, 16.2mmol) dropwise over 20 minutes. The solution was then stirred for 5 minutes, re-cooled to -10°C then tributyltin hydride (4.22g, 14.5mmol) was added dropwise over 10 minutes. After stirring for a further 45 minutes at 0°C chlorotrimethylsilane (10ml, excess) was added. The reaction mixture was then stirred at room temperature overnight and a fine white precipitate formed. Removal of the solvent *in vacuo* and vacuum distillation of the residue at reduced pressure gave tributyl(trimethylsilyl)stannane (122) (2.52g, 48%) as a clear oil.

Bpt = 90°C at 0.3mmHg, lit = 87°C at 0.5mmHg

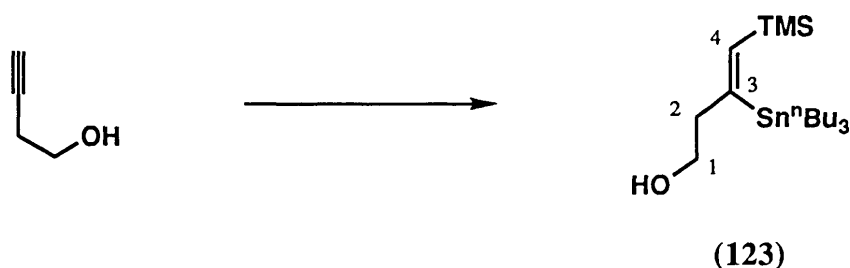
ν_{max} (neat) 1416, 1375, 1338, 1291, 1244, 1180, 1148, 836 cm^{-1}

δ_{H} (270MHz, CDCl_3) 1.69-0.87 (27H, m, 3xBu), 0.33ppm (9H, quin, 26.9Hz, 25.9Hz, $\text{Si}(\text{CH}_3)_3$)

m/z 364, 362, 360, (M^+), 307, 291, 177, 73.

Accurate mass (M^+) Observed 364.1608, $\text{C}_{15}\text{H}_{36}\text{SnSi}$ requires 364.1595

Preparation of 3-(tributylstannyl)-4-(trimethylsilyl)-but-3-en-1-ol (123)



A solution of 3-butyn-1-ol (235mg, 3.36mmol), tributyl(trimethylsilyl)stannane (122) (1.22g, 3.36mmol) and tetrakis(triphenylphosphine)palladium(0) (20.5mg, 0.017mmol) in THF (5ml) was refluxed for 2 hours. After this time the reaction mixture was cooled, filtered through celite and the solvents removed under reduced pressure. Distillation of the residue gave **3-(tributylstannyl)-4-(trimethylsilyl)-but-3-en-1-ol (123)** (1.041g, 72%).

Bpt = 118°C at 0.5mmHg.

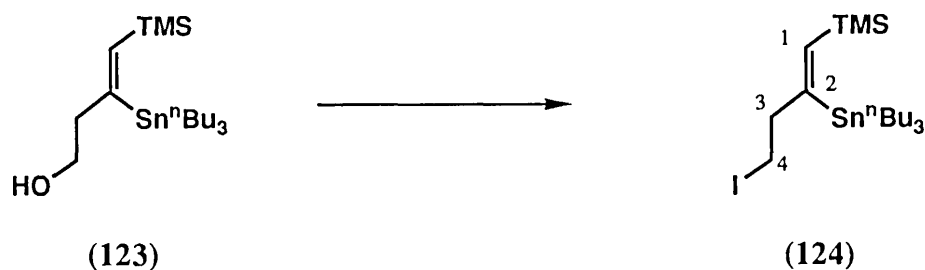
ν_{max} (neat) 3382, 2955, 2922, 1635, 1457, 1375, 1338, 1292, 1247, 1179, 839 cm^{-1}

δ_H (270MHz, CDCl_3) 6.62 (1H, d, 1Hz, H-4), 3.57 (1H, bs, OH), 3.30 (2H, m, 2xH-1), 2.62 (2H, m, 2xH-2), 1.74-0.87 (27H, m, 3xBu), 0.22ppm (s, 9H, $\text{Si}(\text{CH}_3)_3$)

m/z 419, 377, 291, 177, 73, 57.

Accurate mass ($\text{M}-\text{Me}^+$) Observed 419.1806, $\text{C}_{18}\text{H}_{39}\text{OSiSn}$ requires 419.1792

Preparation of 4-iodo-2-(tributylstannyl)-1-(trimethylsilyl)-but-1-ene (124)



To a solution of 3-(tributylstannyl)-4-(trimethylsilyl)-but-3-en-1-ol (123) (1041mg, 2.46mmol) in a 4:1 mixture of ether:acetonitrile (20ml) was added triphenylphosphine (890mg, 3.43mmol) and imidazole (280mg, 4.12mmol). After stirring for 15 minutes at room temperature iodine, (1415mg, 5.57mmol) in ether (10ml) was added slowly until a persistent brown colour remained. The reaction mixture was then stirred for a further 2 hours and filtered. Then the residue was washed with aqueous sodium thiosulphate solution (10ml), and water (10ml). After drying (Na_2SO_4), the residue was then concentrated *in vacuo* and the resulting yellow oil distilled at reduced pressure to give 4-iodo-2-(tributylstannyl)-1-(trimethylsilyl)-but-1-ene (124) (520mg, 40%).

Bpt = 85°C at 0.6mmHg.

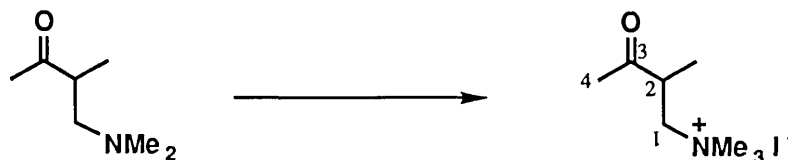
ν_{max} (neat) 2955, 2920, 1630, 1455, 1370 cm^{-1}

δ_{H} (270MHz, CDCl_3) 6.44 (1H, s, H-1), 2.95 (2H, m, 2xH-4), 2.85 (2H, m, 2xH-3), 1.71-1.05 (27H, m, 3xBu), 0.89ppm (s, 9H, $\text{Si}(\text{CH}_3)_3$)

m/z 487, 485, 483, 415, 253, 73, 57.

Accurate mass (M-Bu^+) Observed 487.0340, $\text{C}_{15}\text{H}_{32}\text{ISiSn}$ requires 487.0347

Preparation of (2-methyl-3-oxobutyl)trimethylammonium iodide



4-Dimethylamino-3-methylbutan-2-one (500mg, 3.87mmol) and iodomethane (1140mg, 8.03mmol) were carefully mixed at room temperature, and the reaction mixture was allowed to stand at room temperature for 5 minutes, in which time it set solid. The

resultant yellow solid was then recrystallised from ethanol to give **(2-methyl-3-oxobutyl)trimethylammonium iodide** (737mg, 72%) as a highly hygroscopic white solid.

ν_{max} (neat) 1707, 1490, 1272, 1242, 1046 cm^{-1}

δ_{H} (270MHz, CDCl_3) 4.05 (1H, m, H-2), 3.48 (2H, d, 13.5Hz, 2xH-1), 3.43 (9H, s, $\text{N}^+(\text{CH}_3)_3$), 2.45 (3H, s, 3xH-4), 1.36ppm (3H, d, 9.5Hz, CH_3),

m/z 361 ($\text{M}^+ \cdot 5\text{H}_2\text{O}$), 142, 127, 58, 45, 31.

Preparation of phenylthiomethyltriphenylphosphonium chloride (131) ¹³³



A solution of 1-chloromethylphenylsulphide (4.99g, 31.5mmol) and triphenylphosphine (8.25g, 31.5mmol) in toluene (10ml) was heated to 70°C for 18 hours. The reaction mixture was filtered and the residue dried *in vacuo*. Subsequent recrystallisation from an ether / petrol mixture afforded **phenylthiomethyltriphenylphosphonium chloride (131)** (6.69g, 51%) as needle like crystals.

Mpt = 120-122°C, lit = 118°C

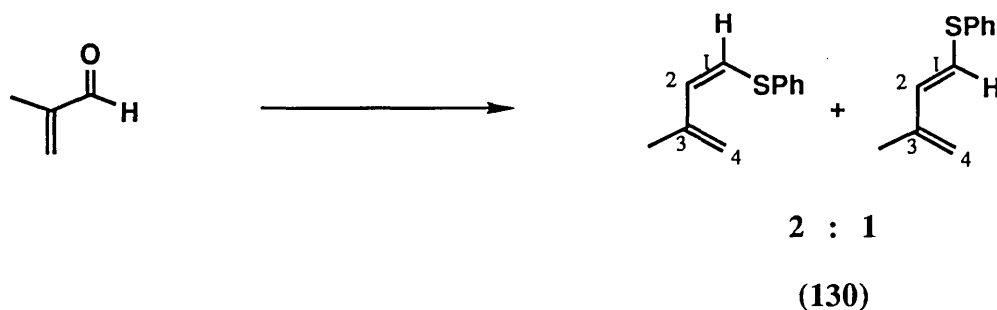
ν_{max} (mull) 3052, 3013, 2851, 2743, 1112, 744. cm^{-1}

δ_{H} (90MHz, CDCl_3) 7.92-7.05 (20H, m, 4xPh), 5.65 ppm (2H, d, 9.2Hz, PhSCH_2)

m/z 384 ($\text{M}-\text{HCl}$)⁺, 307, 262.

Accurate mass ($\text{M}-\text{HCl}$)⁺ Observed 384.1096, $\text{C}_{25}\text{H}_{21}\text{PS}$ requires 384.1101

Preparation of *E*- and *Z*- 1-phenylthio-3-methyl-buta-1,3-diene (130)¹³⁴



A suspension of (phenylthiomethyl)triphenylphosphonium chloride (131) (500mg, 1.07mmol) in THF (5ml) at 0°C, was treated with *n*-butyllithium (452μl of a 2.5M solution in hexanes, 1.13mmol) and the reaction stirred at 0°C for 10 minutes. The resulting red solution was then cooled to -78°C and freshly distilled methacrolein (350mg, 4.99mmol) added. The reaction mixture was warmed to room temperature over 15 minutes and then stirred at room temperature for 1 hour. Water (1ml) was then added and the mixture was extracted with ether. Subsequent purification by flash chromatography (SiO₂, 5% ether in petrol) yielded *E*- and *Z*-1-phenylthio-3-methyl-buta-1,3-diene (130) (128mg, 68%) in a 2:1 ratio of *Z*:*E* isomers as viscous clear oils.

ν_{max} (neat) 3076, 2969, 1610, 1561, 1478, 1437, 690 cm⁻¹

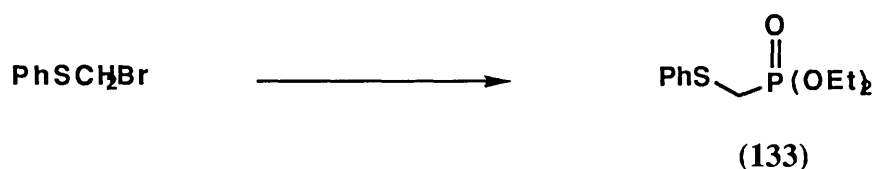
δ_H (270MHz, CDCl₃) *Z* isomer:- 7.49-7.12 (5H, m, Ph), 6.28 (1H, d, 10.7Hz, H-1) 6.10 (1H, d, 10.7Hz, H-2) 5.14 (1H, bs, H-4a or H-4b) 5.01 (1H, bs, H-4a or H-4b) 2.06ppm (3H, dd, 1.2Hz, 0.8Hz, CH₃)

E isomer:- 7.49-7.12 (5H, m, Ph), 6.49 (1H, d, 15.4Hz, H-1) 6.36 (1H, d, 15.4Hz, H-2) 4.96 (1H, bs, H-4a or H-4b) 4.94 (1H, bs, H-4a or H-4b) 1.89ppm (3H, dd, 1.5Hz, 0.8Hz, CH₃)

m/z 176, 161, 109, 99.

Accurate mass (*M*⁺) Observed 176.0657 C₁₁H₁₂S requires 176.0659

Preparation of diethyl(phenylthiomethyl)phosphonate (133)



To phenylthiobromomethane (2.50g, 12.3mmol) was added triethylphosphite (2.04g, 12.3mmol) cautiously with stirring. After approximately one quarter of the phosphite had been added the reaction mixture was gently warmed until reaction was indicated by gentle reflux. The remaining phosphite was then added at a rate which maintained gentle reflux. When all the phosphite had been added, the reaction mixture was heated to 100°C for one hour then cooled. The residual oil was then passed through a short plug of silica using EtOAc as eluant and subsequent removal of the solvent *in vacuo*. afforded **diethyl(phenylthiomethyl)phosphonate (133)** (2.77g, 86%)

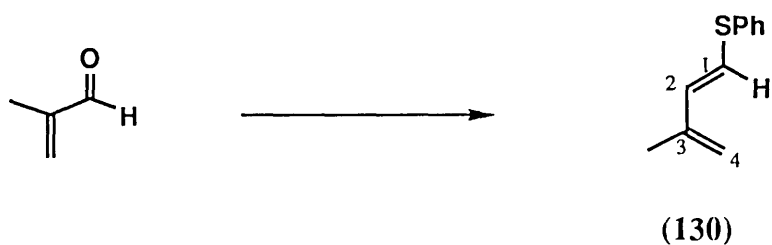
ν_{max} (neat) 3056, 2980, 1232, 1051, 1024, 968 cm^{-1}

δ_{H} (90MHz, CDCl_3) 7.55-7.20 (5H, m, Ph), 4.15 (4H, q, 7.7Hz, $2\times\text{OCH}_2$), 3.22 (2H, d, 14.2Hz, PhSCH_2), 1.31ppm (6H, t, 7.7Hz, $2\times\text{OCH}_2\text{CH}_3$).

m/z 260, 232, 204, 123, 109, 77.

Accurate mass (M^+) Observed 260.0636, $\text{C}_{11}\text{H}_{17}\text{O}_3\text{PS}$ requires 260.0642.

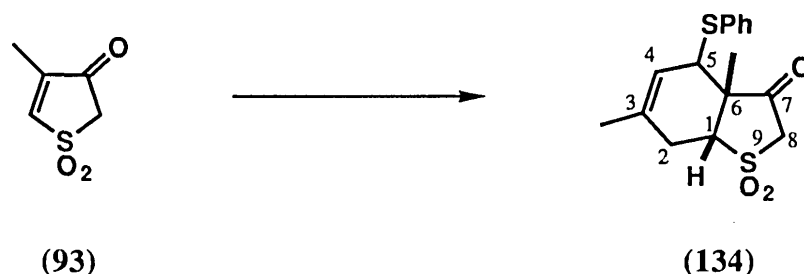
Preparation of *E*-1-phenylthio-3-methyl-buta-1,3-diene (130)



A solution of diethyl(phenylthiomethyl)phosphonate (133) (2.00g, 7.68mmol) in THF (10ml) was cooled to -78°C and n-butyllithium (3.69ml of a 2.5M solution in hexanes, 9.22mmol) was added dropwise. When addition was complete the mixture was stirred for an additional 30 minutes before methacrolein (3.00g, 42.8mmol) was added. The reaction mixture immediately turned a deep turquoise colour which slowly dissipated upon warming to room temperature. After washing vigorously with water (3x10ml) and drying (MgSO₄), the resulting oil was passed through a short plug of silica using 30-40°C petrol as eluant to give *E*-1-phenylthio-3-methyl-buta-1,3-diene (130) (866mg, 64%) as a clear oil.

All data recorded were identical to that described above for the same compound.

Preparation of 3,6-dimethyl-7-oxo-5-phenylthio-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (134).



A mixture of *E*- and *Z*-1-phenylthio-3-methyl-buta-1,3-diene (130) (80.2mg, 0.45mmol) and 3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (93) (66.4mg, 0.45mmol) were dissolved in benzene (2ml) and the reaction mixture thoroughly degassed by a sonication/bubbling cycle. Typically, the solution was sonicated using a standard cleaning bath for ten minutes, then argon was bubbled through the mixture for a further 10 minutes; the whole process being repeated a further three or four times. After

degassing the reaction mixture was heated at reflux under an argon atmosphere for 12 hours. The reaction was then cooled, the volatiles removed *in vacuo.*, and the resulting yellow oil purified by column chromatography (SiO₂, 20% EtOAc in petrol). This gave **3,6-dimethyl-7-oxo-5-phenylthio-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (134)** (66.3mg, 46%) as two stereoisomers in a 5:1 ratio both as clear oils.

ν_{max} (film) 3064, 2922, 1745, 1617, 1324, 1130, 690 cm⁻¹

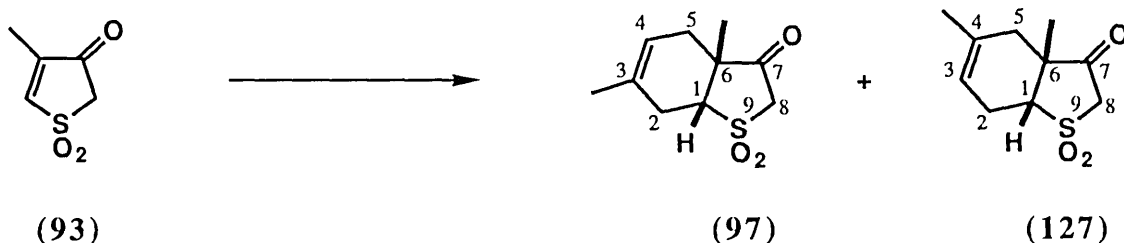
δ_H (270MHz, CDCl₃) *major*:-7.43-7.17 (5H, m, Ar), 5.71 (1H, m, H-4), 4.10 (1H, d, 18.0Hz, H-8b), 3.70 (1H, dd, 18.0Hz, 1.0Hz, H-8a), 3.49-3.45 (2H, m, H-5 and H-1), 2.77 (1H, ddd, 18.5Hz, 1.5Hz, 0.7Hz, H-2b), 2.33 (1H, ddd, 18.5Hz, 8.5Hz, 1.0Hz, H-2a), 1.79 (3H, s, allylic CH₃), 1.42ppm (3H, s, CH₃).

minor:-7.43-7.21 (5H, m, Ar), 5.70 (1H, m, H-4), 4.17 (1H, m, H-5), 3.70 (1H, dd, 17.8Hz, 1.7Hz, H-8a), 3.52 (1H, m, H-1), 3.50 (1H, d, 17.8Hz, H-8b), 2.71 (1H, ddd, 18.5Hz, 1.5Hz, 0.7Hz, H-2b), 2.42 (1H, ddd, 18.5Hz, 9.5Hz, 1.3Hz, H-2a), 1.74 (3H, s, allylic CH₃), 1.54ppm (3H, s, CH₃).

m/z 322 (M⁺), 146, 109

Purification problems associated with this compound and instability to conditions associated with mass spectrometry prevented total characterisation.

Preparation of 3,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (97) and 4,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (127).



A pressure bottle was charged with isoprene (3.41g, 50.0mmol), benzene (5ml), 3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (93) (1.05g, 7.18mmol) and hydroquinone (100mg, 0.91mmol). The reaction mixture was then thoroughly degassed by the sonication/bubbling cycle described above. The bottle was then sealed and heated at 125°C for 72 hours. Subsequent removal of the solvent *in vacuo* and purification by column chromatography (SiO₂, 20% EtOAc in petrol), afforded **3,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (97)** and **4,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (127)** (1.21g, 78%) as an inseparable 3:2 mixture of (97) and (127) respectively as a clear oil.

ν_{max} (film) 2923, 2852, 1741, 1608, 1317, 1189.cm⁻¹

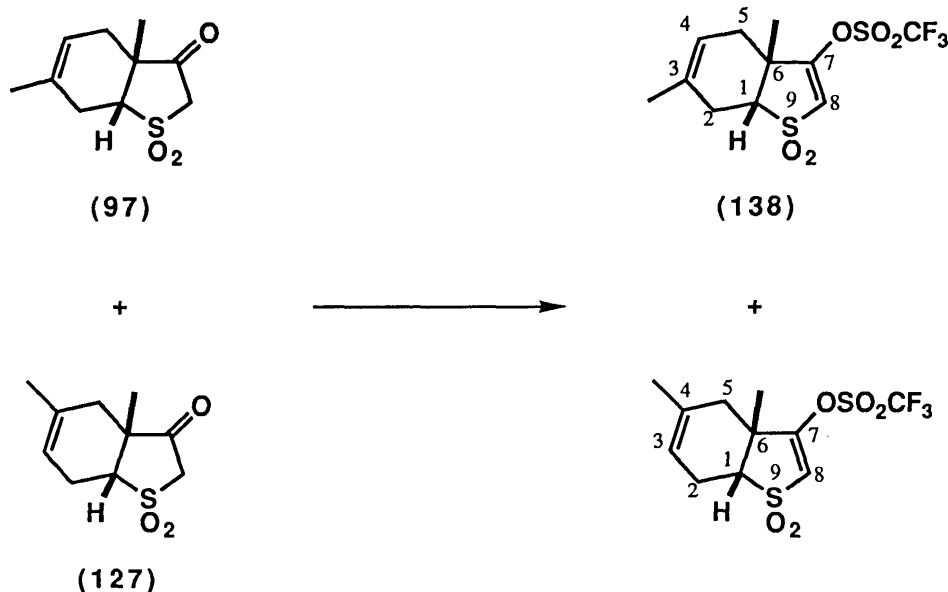
δ_H (500MHz, CDCl₃) *major*:- 5.47 (1H, m, H-4), 3.83 (1H, d, 18.0Hz, H-8a), 3.69 (1H, dd, 18.0Hz, 0.7Hz, H-8b), 3.50 (1H, dd, 8.4Hz, 0.7Hz, H-1), 2.81 (1H, d, 16.8Hz, H-5b), 2.70 (1H, d, 19.0Hz, H-2b), 2.36 (1H, dd, 19.0Hz, 8.4Hz, H-2a), 1.90 (1H, dd, 16.8Hz, 5.2Hz, H-5a), 1.76 (3H, bs, allylic CH₃), 1.31ppm (3H, s, CH₃).

minor:- 5.46 (1H, m, H-3), 3.81 (1H, d, 18.0Hz, H-8a), 3.71 (1H, dd, 18.0Hz, 0.7Hz, H-8b), 3.42 (1H, dd, 7.5Hz, 0.7Hz, H-1), 2.55-2.46 (4H, m, 2xH-2 and 2xH-5), 1.70 (3H, bs, allylic CH₃), 1.32ppm (3H, s, CH₃).

m/z 214 (M⁺), 150, 149, 107.

Found C=56.19%, H=6.71%, C₁₀H₁₄S₀₃ requires C=56.05%, H=6.58%

Preparation of 3,6-dimethyl-9-thia-7-(trifluoromethanesulphonyl)bicyclo[4.3.0]nona-3,7-diene-9,9-dioxide (138) and 4,6-dimethyl-9-thia-7-(trifluoromethanesulphonyl)bicyclo[4.3.0]nona-3,7-diene-9,9-dioxide.



To a solution of lithiumdiisopropylamide in DME (1ml) at -78°C , prepared from diisopropylamine (26.7mg, 0.26mmol) and n-butyllithium (116 μl of a 2.5m solution in hexanes, 0.28mmol), was added a mixture of 3,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (97) and 4,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (44.3mg, 0.21mmol) in DME (1ml). The mixture was stirred at -78°C for 20 minutes before N-phenyltriflimide (125.4mg, 0.35mmol) in DME (1ml) was added dropwise. After stirring at -78°C for a further 10 minutes the reaction was warmed to room temperature and quenched with saturated ammonium chloride solution (2 drops). Removal of the solvents *in vacuo* and purification by column chromatography (SiO₂, 20% EtOAc in petrol) gave an inseparable 3:2 mixture of 3,6-dimethyl-9-thia-7-(trifluoromethanesulphonyl)bicyclo[4.3.0]nona-3,7-diene-9,9-dioxide (138) and 4,6-dimethyl-9-thia-

7-(trifluoromethanesulphonyl)bicyclo[4.3.0] nona-3,7-diene-9,9-dioxide
(41.6mg, 61%) respectively as a clear oil.

ν_{max} (film) 2972, 1627, 1596, 1429, 1375, 1370, 1208, 1141 cm^{-1}

δ_{H} (270MHz, CDCl_3) *major*:- 6.66 (1H, s, H-8), 5.54 (1H, m, H-4), 3.42 (1H, dd, 7.7Hz, 3.1Hz, H-1), 2.73-2.65 (2H, m, H-2 and H-5), 2.40-1.97 (2H, m, H-2 and H-5), 1.83 (3H, bs, allylic CH_3), 1.44ppm (3H, s, CH_3).

minor:- 6.67 (1H, s, H-8), 5.62 (1H, m, H-3), 3.34 (1H, dd, 8.1Hz, 3.6Hz, H-1), 2.73-2.65 (2H, m, H-2 and H-5), 2.40-1.97 (2H, m, H-2 and H-5), 1.76 (3H, bs, allylic CH_3), 1.42ppm (3H, s, CH_3).

m/z 346 (M^+), 331, 281, 225, 149.

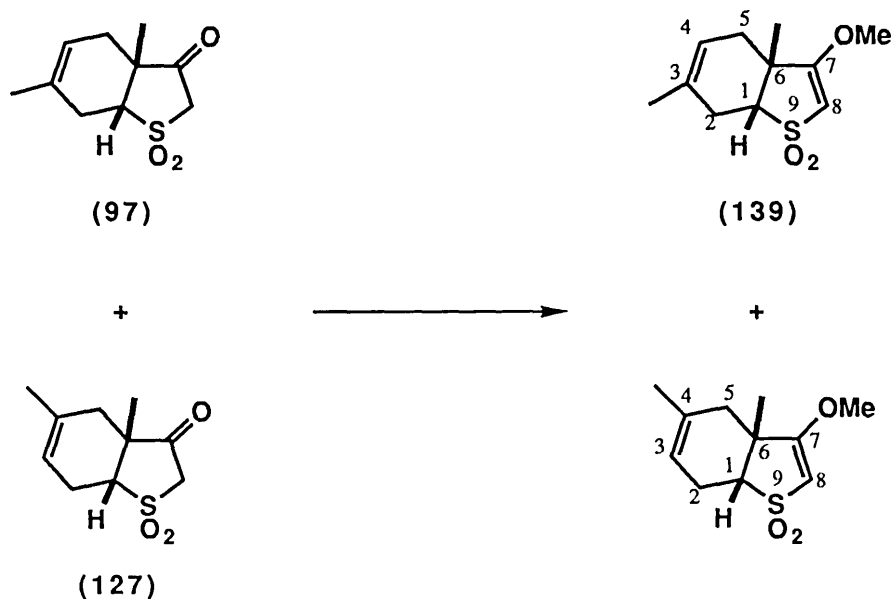
Accurate mass (M^+) Observed 346.0163, $\text{C}_{11}\text{H}_{13}\text{F}_3\text{S}_2\text{O}_5$ requires 346.0156.

Attempted Displacement of 3,6-dimethyl-9-thia-7-(trifluoromethanesulphonyl)bicyclo[4.3.0]nona-3,7-diene-9,9-dioxide (138) and 4,6-dimethyl-9-thia-7-(trifluoromethanesulphonyl)bicyclo[4.3.0] nona-3,7-diene-9,9-dioxide with lithiumdimethylcuprate

To a slurry of copper (I) iodide (39.6mg, 0.21mmol) in THF (1ml) at 0°C was added methyllithium in ether (0.246ml of a 1.4M solution in ether, 0.34mmol) and the reaction stirred at this temperature for 20 minutes. After this time all the solid had disappeared yielding a bright yellow solution. This solution was then cooled to -15°C and the mixture of the two vinyl triflates (47.6mg, 0.137mmol) was added as a solution in THF (1ml) dropwise *via* cannula. Stirring was continued for a further 15 minutes after which time tlc analysis (SiO_2 , 20% EtOAc in petrol) showed all the starting material

to have disappeared. The reaction was then quenched with saturated ammonium chloride solution (1ml) and extracted several times with EtOAc. The combined extracts were dried (MgSO_4) and the solvent removed *in vacuo*. Subsequent column chromatography (SiO_2 , 25% EtOAc in petrol) afforded a 3:2 mixture of **3,6-dimethyl-7-oxo-9-thiabicyclo [4.3.0]non-3-ene-9,9-dioxide (97)** and **4,6-dimethyl-7-oxo-9-thiabicyclo [4.3.0]non-3-ene-9,9-dioxide (127)** (16.2mg, 52% recovery). All data recorded for these two products closely matched those already given.

Preparation of 3,6-dimethyl-7-methoxy-9-thiabicyclo[4.3.0]nona-3,7-diene-9,9-dioxide (139) and 4,6-dimethyl-7-methoxy-9-thiabicyclo [4.3.0]nona-3,7-diene-9,9-dioxide.



A solution of 3,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (97) and 4,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (127) (63.3mg, 0.29mmol) in EtOAc (1ml) was treated with a solution of diazomethane in ether (

prepared from Dizald[®] by reaction with sodium hydroxide in ethanol), until reaction was indicated to be complete by tlc (SiO₂, 25% EtOAc in petrol). The solvents were removed *in vacuo* and the resulting yellow solid purified by column chromatography (SiO₂, 20% EtOAc in petrol), which gave an inseparable mixture of **3,6-dimethyl-7-methoxy-9-thiabicyclo[4.3.0]nona-3,7-diene-9,9-dioxide (139)** and **4,6-dimethyl-7-methoxy-9-thiabicyclo[4.3.0]nona-3,7-diene-9,9-dioxide** (51.6mg, 77%).

ν_{max} (mull) 2922, 2852, 1599, 1459, 1377, 1290, 1108 cm⁻¹

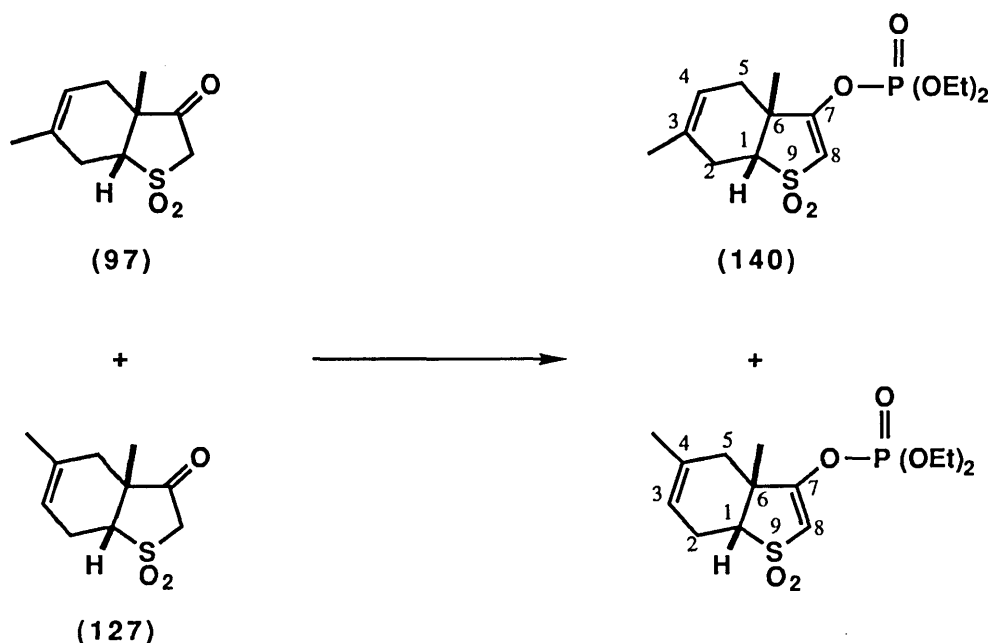
δ_H (270MHz, CDCl₃) *major*:- 5.56 (1H, s, H-4), 5.47 (1H, m, H-8), 3.71 (3H, s, OCH₃), 3.29 (1H, dd, 8.1Hz, 3.2Hz, H-1), 2.67-2.58 (2H, m, H-2 and H-5), 2.36-1.87 (2H, m, H-2 and H-5), 1.78 (3H, bs, allylic CH₃), 1.31ppm (3H, s, CH₃).

minor:-5.55 (1H, s, H-3), 5.52 (1H, m, H-8), 3.72 (3H, s, OCH₃), 3.21 (1H, dd, 8.1Hz, 3.4Hz, H-1), 2.67-2.58 (2H, m, H-2 and H-5), 2.36-1.87 (2H, m, H-2 and H-5), 1.77 (3H, bs, allylic CH₃), 1.31ppm (3H, s, CH₃).

m/z 228 (M⁺), 213, 196, 164, 163.

Found C=57.80%, H=7.06%, C₁₁H₁₆SO₃ requires C=57.81%, H=7.17%

Preparation of 7-(diethylphosphonyltrioxy)-3,6-dimethyl-9-thiabicyclo[4.3.0]nona-3,7-diene-9,9-dioxide (140) and 7-(diethylphosphonyltrioxy)-4,6-dimethyl-9-thiabicyclo[4.3.0]nona-3,7-diene-9,9-dioxide.



A mixture of 3,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (97) and 4,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (127) (18.8mg, 0.09mmol) was dissolved in DME (1ml) and the solution cooled to -78°C . n-Butyllithium (39 μl of 2.5M in hexanes, 0.01mmol) was then added dropwise and the resulting yellow solution stirred at -78°C for a further 45 minutes. After this time diethylchlorophosphate (31.5mg, 0.182mmol) was added and the reaction mixture slowly warmed to room temperature. 1 Drop of saturated ammonium chloride solution was then added and the volatiles removed under reduced pressure. Column chromatography of the residue (SiO_2 , 50% EtOAc in petrol) gave 7-(diethylphosphonyltrioxy)-3,6-dimethyl-9-thiabicyclo[4.3.0]nona-3,7-diene-9,9-dioxide (140) and 7-(diethylphosphonyltrioxy)-4,6-dimethyl-9-thiabicyclo[4.3.0]nona-3,7-diene-9,9-dioxide (14.5mg, 48%) as inseparable viscous oils.

ν_{max} (mull) 2922, 1624, 1459, 1294, 1106, 1029 cm^{-1}

δ_{H} (270MHz, CDCl_3) *major*:- 6.41 (1H, s, H-8), 5.51 (1H, m, H-4), 4.23 (4H, m,

OCH₂CH₃), 3.31 (1H, dd, 7.8Hz, 3.2Hz, H-1), 2.66 (1H, m, H-2 or H-5), 2.42-2.25 (2H, m, H-2 and H-5), 1.97 (1H, m, H-2 or H-5), 1.81 (3H, bs, allylic CH₃), 1.38 (3H, s, CH₃), 1.35ppm (6H, m, OCH₂CH₃).

minor:-6.41 (1H, s, H-8), 5.58 (1H, m, H-3), 4.23 (2H, s, OCH₂CH₃), 3.23 (1H, dd, 8.1, 3.6, H-1), 2.66 (1H, m, H-2 or H-5), 2.42-2.25 (2H, m, H-5 and H-8), 1.97 (1H, m, H-2 or H-5), 1.71 (3H, bs, allylic CH₃), 1.37 (3H, s, CH₃), 1.35ppm (6H, m, OCH₂CH₃).

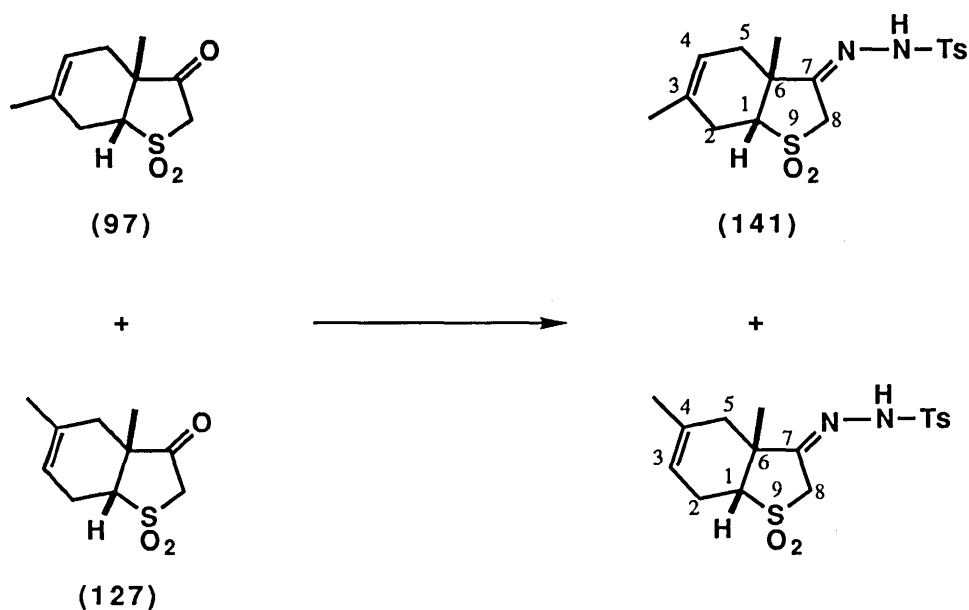
m/z 350 (M⁺), 332, 179, 44, 28.

Accurate mass (M⁺) Observed 350.0952, C₁₄H₂₃SO₆P requires 350.0961

Attempted palladium catalysed cross coupling reaction of 7-(diethylphosphonyltrioxy)-3,6-dimethyl-9-thiabicyclo[4.3.0]nona-3,7-diene-9,9-dioxide (140) and 7-(diethylphosphonyltrioxy)-4,6-dimethyl-9-thiabicyclo[4.3.0]nona-3,7-diene-9,9-dioxide.

To a solution of the above phosphonates (14.5mg, 0.041mmol) in 1,2-dichloroethane (1ml) was added tetrakis(triphenylphosphine)palladium(0) (4.8mg, 0.004mmol) and the reaction stirred at room temperature for 10 minutes. Trimethylaluminium (46µl of a 2.0M solution in toluene, 0.092mmol) was then added dropwise and the reaction mixture refluxed for 3 hours. After cooling, water (1 drop) was cautiously added and the volatiles removed under reduced pressure. Purification by column chromatography (SiO₂, 25% EtOAc in petrol) yielded a mixture of **3,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (97)** and **4,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (127)** (6.5mg, 74%). All spectral data recorded were in agreement with given above.

Preparation of *trans*-3,6-dimethyl-7-(4-methylbenzenesulphonylhydrazono)-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (141) and *trans*-4,6-dimethyl-7-(4-methylbenzenesulphonylhydrazono)-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide.



To a solution of a mixture of 3,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (97), and 4,6-dimethyl-7-oxo-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (127) (200mg, 0.932mmol) in methanol (5ml) was added 4-methylbenzenesulphonylhydrazide (866mg, 4.66mmol), concentrated hydrochloric acid (1ml), and pre-dried powdered 3Å molecular sieves (300mg). The reaction mixture was then heated at reflux for 48 hours. After this time the reaction was diluted with water and neutralised by addition of solid sodium hydrogen carbonate (caution). Water (1ml) was then added and the mixture exhaustively extracted with EtOAc. The combined extracts were washed with saturated sodium chloride solution, water, and then dried (MgSO₄). Removal of the solvent at reduced pressure and purification by column chromatography (SiO₂, 25-40% EtOAc in petrol) afforded a 3:2 mixture of *E*-3,6-dimethyl-7-(4-

methylbenzenesulphonylhydrazono)-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (141) and *E*-4,6-dimethyl-7-(4-methylbenzenesulphonylhydrazono)-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (289mg, 98%).

ν_{max} (mull) 3259, 2918, 1596, 1448, 1306, 1164, 1120, 814 cm^{-1}

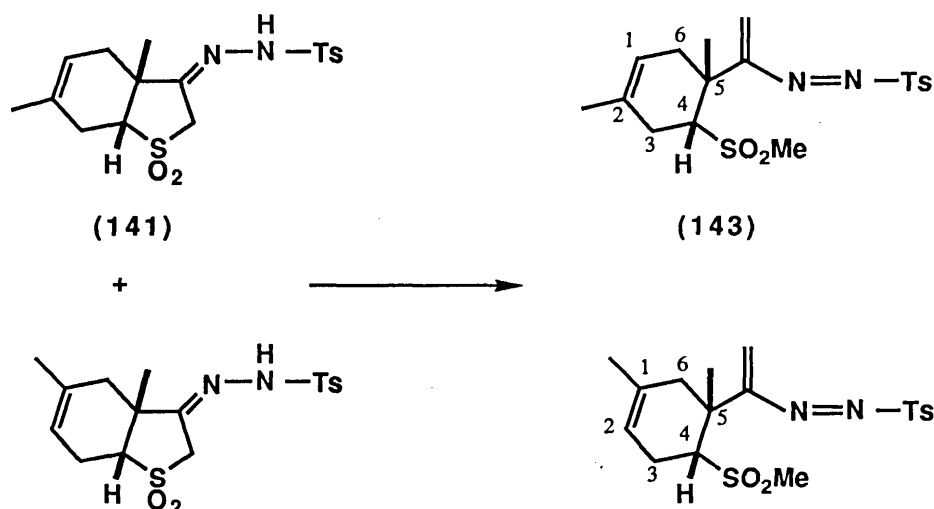
δ_H (270MHz, CDCl_3) *major*:- 8.35 (1H, bs, NH), 7.78 (2H, d, 8.2Hz, Ar) 7.27 (2H, d, 8.2Hz, Ar), 5.30 (1H, m, H-4), 3.85 (2H, bs, 2xH-8), 3.22 (1H, bd, 8.1Hz, H-1), 2.72-2.55 (2H, m, H-2 and H-5), 2.48-2.18 (2H, m, H-2 and H-5), 2.40 (3H, s, ArCH_3) 1.68 (3H, bs, allylic CH_3), 1.25ppm (3H, s, CH_3).

minor- 8.35 (1H, bs, NH), 7.78 (2H, d, 8.2Hz, Ar) 7.27 (2H, d, 8.2Hz, Ar), 5.30 (1H, m, H-3), 3.85 (2H, s, 2xH-8), 3.15 (1H, bd, 8.12Hz, H-1), 2.72-2.55 (2H, m, H-2 and H-5), 2.48-2.18 (2H, m, H-2 and H-5), 2.40 (3H, s, ArCH_3) 1.57 (3H, bs, allylic CH_3), 1.23ppm (3H, s, CH_3).

m/z 383, $(\text{MH})^+$, 227, 172, 156, 92

Accurate mass $(\text{MH})^+$ Observed 383.1100 requires 383.1101

Attempted Shapiro reaction upon *trans*-3,6-dimethyl-7-(4-methylbenzenesulphonylhydrazono)-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide (141) and *trans*-4,6-dimethyl-7-(4-methylbenzenesulphonylhydrazono)-9-thiabicyclo[4.3.0]non-3-ene-9,9-dioxide.



To a solution of the above hydrazones (212mg, 0.66mmol) in TMEDA (2ml) at -78°C was added n-butyllithium (666 μl of a 2.5M solution in hexanes, 1.67mmol) and the reaction mixture stirred at this temperature for 30 minutes. Then the flask was warmed to room temperature and stirring continued for a further hour. The reaction mixture was then re-cooled to 0°C and iodomethane (2.28g, 16.1mmol) added dropwise. The reaction was stirred for a further 30 minutes, after which time water (10ml) was added and the mixture extracted with EtOAc (3x10ml). The organic extracts were then dried (MgSO_4) and the volatiles removed at reduced pressure to give a pale yellow oil, which was purified by column chromatography (SiO_2 , 0-20% EtOAc in petrol) to give a product tentatively assigned the structure (143) above, as a clear oil (47.1mg, 22%).

ν_{max} (mull) 3259, 2918, 1596, 1448, 1306, 1164, 1120, 814cm^{-1}

δ_{H} (270MHz, CDCl_3) *major*- 7.81 (2H, d, 8.0Hz, Ar), 7.30 (2H, d, 8.0Hz, ArH), 5.33 (1H, bs, H-1), 4.95 (2H, bs, $\text{C}=\text{CH}_2$), 3.17 (1H, d, 8.9Hz, H-4), 2.82-2.20 (4H, m, 2xH-3 and 2xH-6), 2.45 (3H, s, SO_2CH_3), 2.40 (3H, s, ArCH_3), 1.60 (3H, d, 3.9Hz, allylic CH_3), 1.22ppm (3H, s, CH_3).

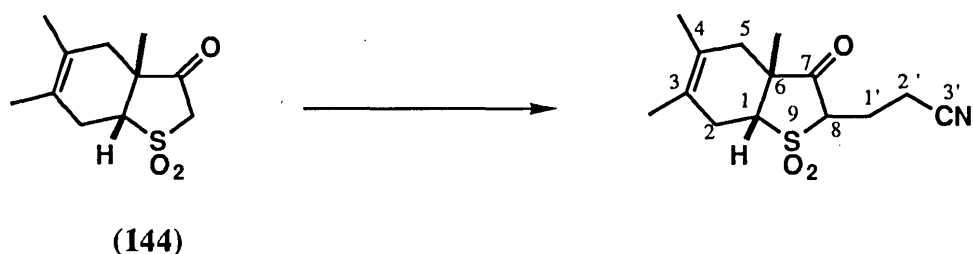
minor- 7.81 (2H, d, 8.0Hz, Ar), 7.30 (2H, d, 8.0Hz, Ar), 5.33 (1H, bs, H-2), 4.95 (2H, bs, $\text{C}=\text{CH}_2$), 3.08 (1H, d, 8.9Hz, H-4), 2.82-2.20 (4H, m, 2xH-3 and 2xH-6),

2.45 (3H, s, SO₂CH₃), 2.40 (3H, s, ArCH₃), 1.53 (3H, d, 2.9Hz, allylic CH₃), 1.20ppm (3H, s, CH₃).

m/z 246, 171, 155, 124, 107, 91.

Found C=54.46%, H=5.92%. N=7.06%; C₁₈H₂₄N₂S₂O₄ requires C=54.52%, H=6.10%, N=6.84%

Preparation of 8-(2-cyanoethyl)-7-oxo-9-thia-3,4,6-trimethylbicyclo[4.3.0]non-3-ene-9,9-dioxide



n-Butyllithium (100μl of a 2.5M solution in hexanes, 0.25mmol), was added dropwise to a solution of 7-oxo-9-thia-3,4,6-trimethylbicyclo[4.3.0]non-3-ene-9,9-dioxide (144) (50.4mg, 0.22mmol) in THF (1ml) and HMPA (90.5mg, 0.51mmol) at -78°C. After 30 minutes acrylonitrile (117.2mg, 2.21mmol) was added and the reaction mixture warmed to room temperature over a further 30 minutes then stirred for a further 18 hours. The reaction was quenched with water (2 drops) and the volatiles removed *in vacuo*. Column chromatography (SiO₂, 20% EtOAc in petrol) then gave 8-(2-cyanoethyl)-7-oxo-9-thia-3,4,6-trimethylbicyclo[4.3.0]non-3-ene-9,9-dioxide (40.8mg, 65%) as a clear oil.

ν_{max} (film) 2918, 2280, 1739, 1312, 1131.cm⁻¹

δ_H (270MHz, CDCl₃) 3.37 (1H, dd, 10.0Hz, 3.4Hz, H-8), 3.25 (1H, dd, 12.0Hz,

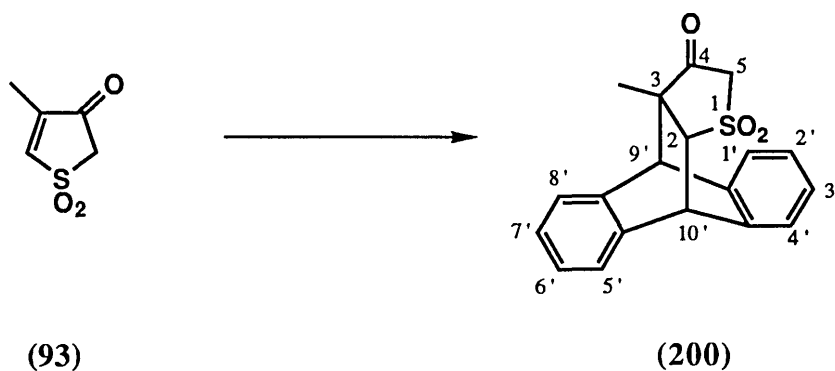
5.1Hz, H-1), 2.76-2.68 (4H, m, 2xH-2', H-5, H-2), 2.38-2.18 (4H, m, 2xH-1', H-5, H-2), 1.85 (3H, d, 0.5Hz, allylic CH_3) 1.77 (3H, bs, 0.5Hz, allylic CH_3), 1.35ppm (3H, s, CH_3).

m/z 281 (M^+), 228, 217, 121.

Accurate mass (M^+) Observed 281.1088, $\text{C}_{14}\text{H}_{19}\text{NO}_3\text{S}$ requires 281.1086

Chapter Two

Preparation of 2,3-(9,10-dihydro-9,10-anthra)-3-methyl-4-oxothiacyclopentane-1,1-dioxide (200).



a) At Atmospheric Pressure

To a solution of 3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (93) (250mg, 1.71mmol) in toluene (5ml) was added anthracene (625mg, 3.51mmol) and the reaction mixture heated to reflux for 48 hours. After this time the reaction was cooled, the solvent removed *in vacuo* and the crude material purified by column chromatography (SiO₂, 20% EtOAc in petrol), This gave 2,3-(9,10-dihydro-9,10-anthra)-3-methyl-4-oxothiacyclopentane-1,1-dioxide (200) (112mg, 21%) as a white solid.

Mpt =194-196°C decomposes.

ν_{max} (film) 2922, 2853, 1734, 1376, 1130cm⁻¹

δ_H (270MHz, CDCl₃) 7.45-7.15 (8H, m, ArH), 4.98 (1H, d, 2.4Hz, H-10'), 4.33 (1H, s, H-9'), 3.35 (1H, bd, 2.4Hz, H-2), 3.23 (1H, dd, 17.0Hz, 1.7Hz, H-5a), 1.76 (1H, dd, 17.0Hz, H-5b), 1.32ppm (3H, s, CH₃).

m/z 324 (M⁺), 215, 202, 178.

Found C=70.60%, H=5.14%, C₁₉H₁₆SO₃ requires C=70.35%, H=4.97%

b) At Reduced Pressure

A solution of 3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (93) (500mg, 3.42mmol) and anthracene (1.25g, 7.01mmol) in tetralin (20ml) was heated at 120°C for 48 hours at a reduced pressure of 30mmHg. The solvent was removed *in vacuo* and the product purified as described above, giving **2,3-(9,10-dihydro-9,10-anthra)-3-methyl-4-oxothiacyclopentane-1,1-dioxide (200)** (255mg, 23%).

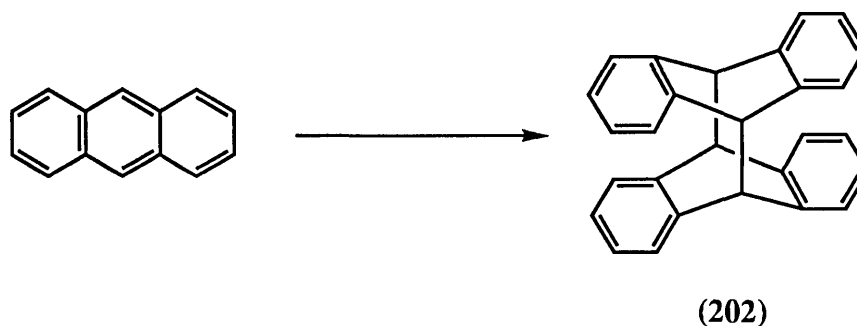
All data recorded was identical to that previously stated.

c) Dry Silica Conditions

3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (93) (500mg, 3.42mmol) and anthracene (1.25g, 7.01mmol) were added to chromatography standard silica (1:15 w/w) that had been pre-dried at 180°C for 12 hours. The mixture was thoroughly shaken and then heated at 75°C for 2.5 hours. After this time the temperature was raised to 120°C and heating continued for a further 48 hours. The resulting pink solid was washed with EtOAc and the solvent removed *in vacuo*. Purification by column chromatography as described then yielded slightly impure product which was recrystallised from aqueous ethanol to give **2,3-(9,10-Dihydro-9,10-anthra)-3-methyl-4-oxothiacyclopentane-1,1-dioxide (200)** (196mg, 19%)

All data was consistent with that described above.

d) Attempted Photochemical Preparation



A solution of 3-methyl-4-oxothiacyclopent-2-ene-1,1-dioxide (93) (250mg, 1.71mmol) and anthracene (1.25g, 3.51mmol) in EtOAc (30ml) was placed in a quartz photolysis well and the mixture purged with argon for several minutes before being irradiated using a medium pressure mercury lamp. After 24 hours tlc analysis (SiO_2 , 20% EtOAc in petrol) indicated that all the anthracene had been consumed, but the sulphone starting material was still present. Filtration of the reaction mixture and subsequent recrystallisation of the residue from chloroform gave **anthracenophotodimer (202)**^{113b} as a white solid (276mg, 46%).

Mpt = 255-258°C lit. = 260°C.

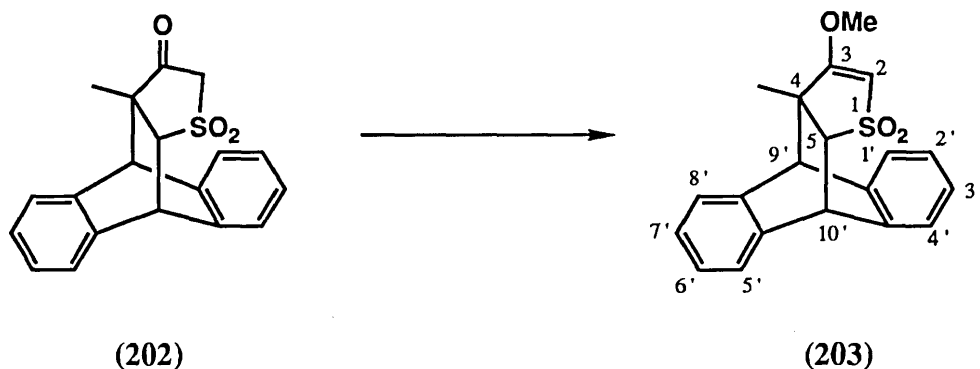
ν_{max} (mull) 3037, 3014, 2922, 2853, 1450, 1375, 1292, 1220, 1160, 1102 cm^{-1}

δ_{H} (270MHz, CDCl_3) 6.92 (8H, q, 5.8Hz, 3.4Hz, Ar), 6.81 (8H, q, 5.8Hz, 3.4Hz, Ar),

4.54 (4H, s, 4xArCH)

m/z 350, 179, 178.

Preparation of 4,5-(9,10-dihydro-9,10-anthra)-3-methoxy-4-methylthiacyclopent-2-ene-1,1-dioxide (203)



A solution of 2,3-(9,10-dihydro-9,10-anthra)-3-methyl-4-oxothiacyclopentane-1,1-dioxide (200) (60.1mg, 0.19mmol) in ether (20ml) was treated with diazomethane until the reaction was judged complete by t.l.c. (SiO_2 , 20% EtOAc in petrol). The solvent was then removed *in vacuo* and the residue purified by column chromatography (SiO_2 , 20% EtOAc in petrol), to give **4,5-(9,10-dihydro-9,10-anthra)-3-methoxy-4-methylthiacyclopent-2-ene-1,1-dioxide (203)** as white solid (35.5mg, 58%).

Mpt= 185°C decomposes.

ν_{max} (mull) 3000, 2922, 1610, 1375, 1215, 1101 cm^{-1}

δ_{H} (270MHz, CDCl_3) 7.45-7.15 (8H, m, ArH), 5.15 (1H, s, H-2), 4.83 (1H, d, 2.7Hz, H-10'), 4.31 (1H, s, H-9'), 3.51 (3H, s, OCH_3), 3.17 (1H, d, 2.7Hz, H-5), 1.33ppm (3H, s, CH_3)

m/z 338 (M^+), 307, 291, 273, 178.

Found C=70.68%, H=5.46%, $\text{C}_{20}\text{H}_{18}\text{SO}_3$ requires C=70.98%, H=5.36

Attempted Thermal Retro Diels-Alder Reaction of 4,5-(9,10-Dihydro-9,10-anthra)-3-methoxy-4-methylthiacyclopent-2-ene-1,1-dioxide (203)

4,5-(9,10-dihydro-9,10-anthra)-3-methoxy-4-methylthiacyclopent-2-ene-1,1-dioxide (203) (100.2mg, 0.296mmol) and dimethylacetylenedicarboxylate (426mg, 3.00mmol) were dissolved in *tert*-butylbenzene (1ml) and the reaction mixture thoroughly degassed by the sonication technique described above. Subsequently the reaction was heated to reflux in a Woods metal bath for 14 hours, then cooled. The solvent was removed under reduced pressure and the solid residue purified by column chromatography (SiO₂, 0-20% EtOAc in petrol) affording 4,5-(9,10-dihydro-9,10-anthra)-3-methoxy-4-methylthiacyclopent-2-ene-1,1-dioxide (203) (82.3mg, 82% recovery) and an as of yet unidentified product (47.6mg) which appeared to be a trimer of dimethylacetylenedicarboxylate.

Mpt=113-115°C

$\nu_{\max}$ (mull) 2953, 2922, 1745, 1726, 1707, 1600, 1579, 1242, 1103cm⁻¹

δ_{H} (270MHz, CDCl₃) 4.24 (3H, s), 3.92 (3H, s), 3.85 (3H, s), 3.78ppm (3H, s).

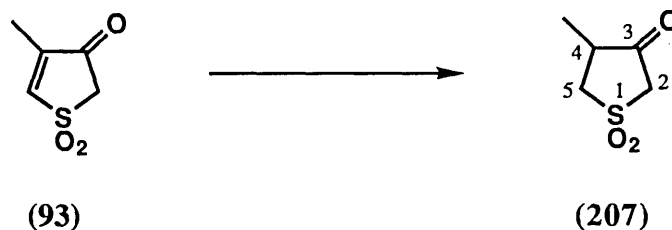
$\delta_{\text{C}}\{^1\text{H}\}$ (125.8MHz, CDCl₃) 163.13, 162.11, 161.22, 157.29, 130.26, 128.15, 92.80, 58.77, 53.13, 52.35, 51.93ppm.

m/z 367 (M-CO₂Me⁺), 337, 308, 291, 272, 241.

Accurate mass (M-CO₂Me⁺) Observed 367.0665, C₁₆H₁₅O₁₀ requires 367.0678

All data obtained for 4,5-(9,10-dihydro-9,10-anthra)-3-methoxy-4-methylthiacyclopent-2-ene-1,1-dioxide (203) was identical that already stated above.

Preparation of 4-methyl-3-oxo-thiacyclopentane-1,1-dioxide (207)



A solution of 4-methyl-3-oxothiacyclopent-2-ene-1,1-dioxide (93) (500mg, 3.42mmol) in EtOAc (10ml) containing 10% palladium on charcoal (100mg) was stirred over a positive pressure of hydrogen for 1.5 hours. After this time the catalyst was removed by filtration through celite and the solvent removed *in vacuo*. The crude product was recrystallised from aqueous methanol to give **4-methyl-3-oxo-thiacyclopentane-1,1-dioxide (207)** (486mg, 96%), as a white solid.

Mpt = 75-76°C

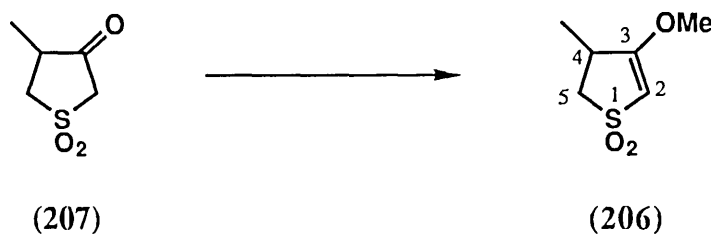
ν_{max} (mull) 3000, 2922, 2852, 1741, 1362, 1141 cm^{-1}

δ_H (500MHz, CDCl_3) 3.75-3.71 (3H, m), 3.30-3.20 (2H, m), 1.37ppm (3H, d, 6.6Hz, CH_3)

m/z 148 (M^+), 56, 42.

Found C=40.51%, H=5.40%, $\text{C}_5\text{H}_8\text{SO}_3$ requires C=40.53%, H=5.40%

Preparation of 3-methoxy-4-methyl-thiacyclopent-2-ene-1,1-dioxide (206)



A solution of 4-methyl-3-oxo-thiacyclopentane-1,1-dioxide (207) (104mg, 0.675mmol) in ether (10ml) was treated with diazomethane until the reaction was judged complete by t.l.c. (SiO₂, 25% EtOAc in petrol). Removal of the solvent *in vacuo* followed by column chromatography (SiO₂, 25% EtOAc in petrol) gave **3-methoxy-4-methyl-thiacyclopent-2-ene-1,1-dioxide (206)** (96.2mg, 84%) as a clear oil, which upon storage at 4°C formed a colourless solid.

Mpt = 45-48°C

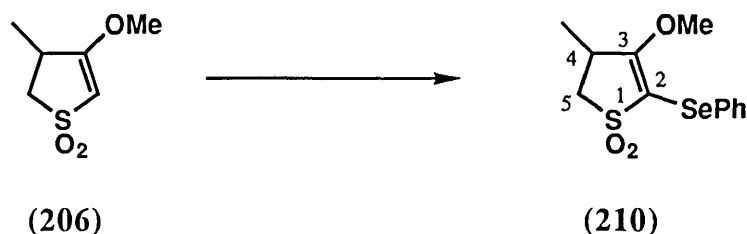
ν_{max} (mull) 3077, 1604, 1219, 1342, 1101 cm⁻¹

δ_H (270MHz, CDCl₃) 5.63 (1H, s, H-2), 3.75 (3H, s, OCH₃), 3.58 (1H, dd, 12.9Hz, 8.3Hz, H-5a), 3.14 (1H, m, H-4), 3.05 (1H, dd, 12.9Hz, 4.4Hz, H-5b), 1.33ppm (3H, d, 7.1Hz, CH₃).

m/z 162 (M⁺), 131, 96, 83, 39.

Found C=44.54%, H=6.07%, C₆H₁₀SO₃ requires C=44.43%, H=6.21%

Preparation of 3-methoxy-4-methyl-2-phenylselenothiacyclopent-2-ene-1,1-dioxide (210).



To a stirred solution of 3-methoxy-4-methyl-thiacyclopent-2-ene-1,1-dioxide (206) (189.6mg, 1.16mmol) in THF (1ml) at -78°C was added n-butyllithium (510μl of 2.5M solution in hexanes, 1.28mmol). The reaction mixture was then stirred at -78°C for 1 hour then warmed to room temperature and stirred for a further 3 hours. After this time

phenylselenenylchloride (287.3mg, 1.50mmol) in THF (1ml) was added *via* cannula. The reaction mixture was then warmed to room temperature over 30 minutes and saturated ammonium chloride solution (1ml) added. After extraction with EtOAc (2x5ml), drying (MgSO_4) and removal of the solvent under reduced pressure, the crude reaction mixture was purified by column chromatography (SiO_2 , DCM). This gave **3-methoxy-4-methyl-2-phenylselenothiacyclopent-2-ene-1,1-dioxide (210)** (80.6mg, 22%) as a crystalline white solid, and the starting material (50.4mg, 27%) as a clear oil.

Mpt = 130°C

ν_{max} (mull) 1593, 1285, 1216, 1124, 1057 cm^{-1}

δ_{H} (270MHz, CDCl_3) 7.51 (2H, m, Ar), 7.24 (3H, m, Ar), 4.22 (3H, s, OCH_3), 3.56 (1H, dd, 12.9Hz, 8.1Hz, H-5a), 3.09 (1H, m, H-4), 3.01 (1H, dd, 12.4Hz, 4.4Hz, H-5b), 1.32ppm (3H, d, 6.9Hz, CH_3)

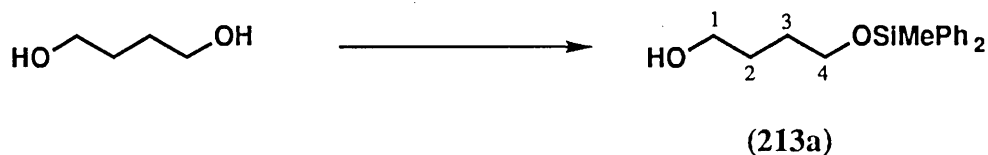
m/z 318 (M^+), 239, 157, 77.

Found C=45.46%, H=4.26%, $\text{C}_{12}\text{H}_{14}\text{SSeO}_3$ requires C=45.43%, H=4.26%

Accurate mass (M^+) Observed 317.9833, $\text{C}_{12}\text{H}_{14}\text{SSeO}_3$ requires 317.9828

All data obtained for the starting material corresponded exactly to that already given.

Preparation of 4-(diphenylmethoxysiloxy)butan-1-ol (213a)



A solution of imidazole (0.50g, 7.34mmol) and chlorodiphenylmethoxysilane (0.835g, 3.58mmol) in DMF (5ml) was added to a solution of butane-1,4-diol (3.22g, 35.8mmol)

in DMF (10ml), slowly over 3 hours. The reaction mixture was stirred overnight before being poured into water (50ml). The organic layer was separated and the aqueous layer further extracted with ether. The extracts were combined, dried (MgSO_4) and the solvents removed *in vacuo*. The resulting yellow oil was purified by column chromatography (SiO_2 , 20% ether in petrol) to give **4-(diphenylmethyloxy)butan-1-ol (213a)** (0.540g, 53%) as a clear oil.

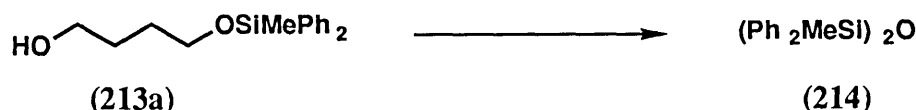
ν_{max} (film) 3385, 3046, 3018, 1427, 1253, 1118, 753 cm^{-1}

δ_{H} (270MHz, CDCl_3) 7.59-7.39 (10H, m, 2xAr), 3.74 (2H, t, 5.8Hz, 2xH-4), 3.63 (2H, bs, 2xH-1), 1.92 (1H, bs, OH), 1.65 (4H, m, 2xH-2, 2xH-3), 0.65ppm (3H, s, Si-CH₃).

m/z 257, (M-CHO⁺), 227, 214, 199, 137, 77.

Accurate mass (M-C₄H₈O⁺) Observed 214.0810, C₁₃H₁₄SiO₂ requires 214.0813.

Preparation of methyldiphenyldisiloxane (214)¹²⁹



(a) Pyridiniumchlorochromate Oxidation.

To a suspension of pyridiniumchlorochromate (38.4mg, 0.177mmol) in DCM (2ml) was added diphenylmethyloxybutan-1-ol (213a) (25.5mg, 0.089mmol) and the reaction mixture stirred at room temperature overnight. The dark brown slurry formed was then filtered through a small plug of silica using ether and the resulting yellow solution concentrated under reduced pressure. Column chromatography (SiO_2 , 10% ether in petrol) gave **methyldiphenyldisiloxane (214)** (15.2mg, 84%) as a clear oil which slowly solidified on storage at 4°C.

Mpt = 47-48°C, (lit = 47-48°C).

$\nu_{\max}$ (film) 3063, 2924, 1260, 1118, 1038, 1023, 792 cm^{-1}

δ_{H} (270MHz, CDCl_3) 7.55-7.28 (20H, m, 4xPh), 1.55ppm (6H, s, CH_3)

m/z 410 (M^+), 395, 317, 256, 241, 125, 77.

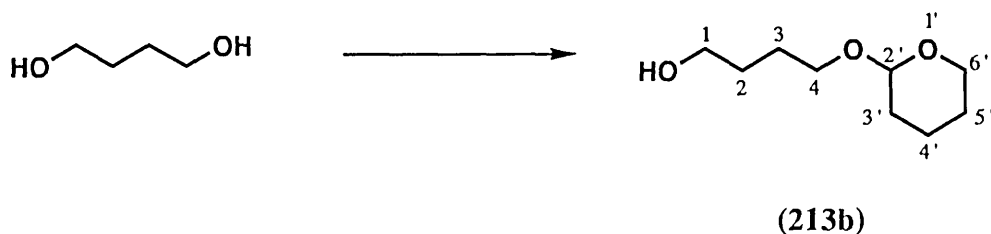
Found C=76.11%, H=6.40%, $\text{C}_{26}\text{H}_{26}\text{SiO}_2$ requires C=76.04%, H=6.38%

b) Swern Oxidation

To a stirred solution of oxalylchloride (106mg, 0.84mmol) in dry DCM (2ml) at -78°C was added DMSO (132mg, 1.68mmol) dropwise. The solution was stirred for 10 minutes then 4-diphenylmethyloxybutan-1-ol (213a) (87.2mg, 0.305mmol) was added dropwise. After stirring for 20 minutes at -78°C a thick white precipitate had formed. Triethylamine (353mg, 3.45mmol) was added and the reaction mixture brought to room temperature overnight. Water (10ml) was then added and the mixture extracted several times with ether. The extracts were combined, dried (MgSO_4) and subsequent solvent removal *in vacuo* afforded a yellow oil. Column chromatography (SiO_2 , 5%EtOAc in petrol) gave **methyldiphenyldisiloxane (214)** (49.8mg, 80%) as a clear oil.

All data collected was consistent with that stated above

Preparation of 4-tetrahydro-2H-pyran-2-yloxy-butan-1-ol (213b)¹³⁰



To butane-1,4-diol (10.0g, 111mmol) was added pyridinium-*para*-

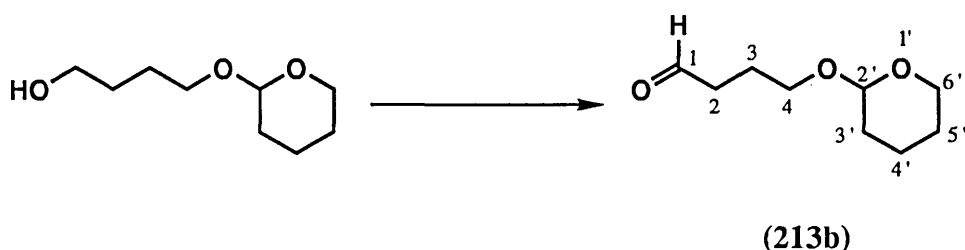
toluenesulphonate (1.39g, 5.54mmol) and the reaction mixture stirred at room temperature whilst dihydropyran (9.33g, 111mmol) was added slowly over 3 hours. After this time water (10ml) was added and then the mixture extracted several times with ether. The organic extracts were combined, washed thoroughly with water (2x10ml) then dried (Na_2SO_4). Removal of the volatiles *in vacuo* and column chromatography (SiO_2 , neat ether) afforded **4-tetrahydro-2H-pyran-2-yloxy-butan-1-ol (213b)** (10.63g, 55%) as a clear oil.

ν_{max} (film) 3410, 2948, 2720, 1366, 1257, 1121, 1065, 1034. cm^{-1}

δ_{H} (270MHz, CDCl_3) 4.49 (1H, t, 3.2Hz, 2.9Hz, H-2'), 3.71 (1H, t, 9.8Hz, H-4), 3.70 (1H, m, H-6'), 3.56 (2H, bt, 2xH-1), 3.36 (1H, m, H-6'), 3.34 (1H, t, 9.8Hz, H-4) 2.09 (1H, bs, OH), 1.72-1.38ppm (10H, m, 2xH-2, 2xH-3, 2xH-3', 2xH-4', 2xH-5').

m/z 175 (MH^+), 101, 91, 85, 73.

Preparation of 4-tetrahydro-2H-pyran-2-yloxy-butan-1-ol¹³⁰



A solution of 4-tetrahydro-2H-pyran-2-yloxy-butan-1-ol (213b) (2.00g, 11.5mmol) in DCM (10ml) was added dropwise to a suspension of pyridiniumdichromate (4.78g, 12.6mmol) and activated crushed 4Å molecular sieves (5.00g) in DCM (120ml), and the reaction mixture stirred at room temperature for 4 hours. After this time the reaction mixture was decanted from the residual black gum and the solid washed several times with

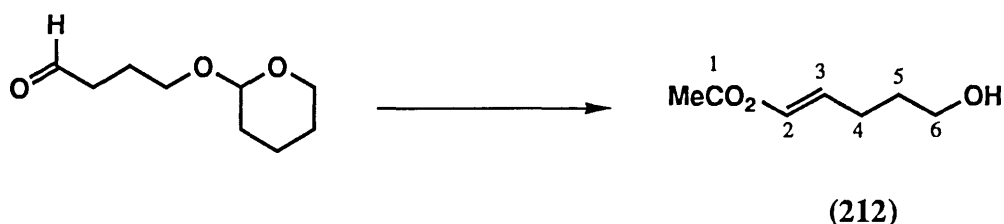
ether. Removal of the solvents *in vacuo*. and purification by dry flash chromatography (SiO₂, neat ether) furnished **4-tetrahydro-2H-pyran-2-yloxy-butanal** (1.12g, 54%) as a clear oil.

ν_{max} (film) , 2941, 2721, 1732, 1439, 1351, 1258, 1121.cm⁻¹

δ_H (270MHz, CDCl₃) 9.77 (1H, t, 1.7Hz, H-1), 4.58 (1H, t, 3.2Hz, H-2'), 3.82 (1H, m, H-6'), 3.80 (1H, t, 7.8Hz, H-4), 3.49 (1H, t, 7.8Hz, H-4), 3.36 (1H, m, H-6'), 2.52 (2H, dt, 7.1Hz, 1.7Hz, 2xH-2), 1.98-1.49ppm (8H, m, 2xH-3, 2xH-3', 2xH-4', 2xH-5').

m/z 143 (M-HCO⁺), 101, 85, 71.

Preparation of *E*-methyl-6-hydroxyhex-2-enoate (212)¹³⁰



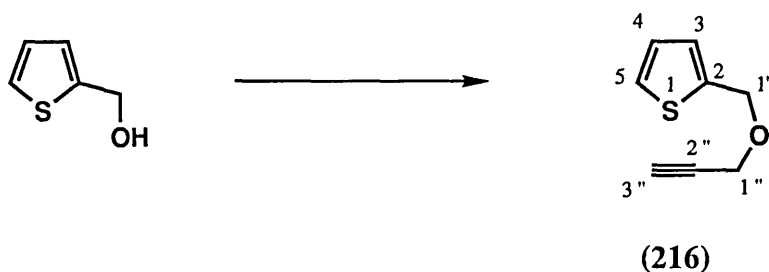
To a solution of 4-tetrahydro-2H-pyran-2-yloxy-butanal (280mg, 1.63mmol) in acetonitrile (5ml) was added carbomethoxymethylidenetriphenylphosphorane (712mg, 2.04mmol) and the reaction mixture heated to reflux for 12 hours. The reaction was then cooled and the solvent removed under reduced pressure. The resulting oily solid was dissolved in THF (5ml) and an equal volume of 10% aqueous hydrochloric acid added, and the solution stirred until deprotection was complete as judged by t.l.c. (SiO₂, neat ether). Subsequently, the reaction was poured into aqueous saturated sodium hydrogen carbonate, and the mixture extracted several times with EtOAc. Purification by column chromatography (SiO₂, 75-100% ether in petrol), then gave *E*-methyl-6-hydroxyhex-2-enoate (**212**) (222.2mg, 94%) as colourless oil.

ν_{max} (film) 3410, 2934, 1722, 1655, 1439, 1275, 1022. cm^{-1}

δ_H (270MHz, CDCl_3) 6.95 (1H, dt, 15.9Hz., 6.8Hz, H-3), 5.84 (1H, dt, 15.9Hz., 1.6Hz, H-2), 3.70 (3H, s, OCH_3), 3.64 (2H, bt, 5.8Hz, 2xH-6), 2.26 (2H, ddt, 7.1Hz, 6.8Hz, 1.6Hz, 2xH-4), 1.85-1.70ppm (3H, m, 2xH-5, OH).

m/z 144 (M^+), 126, 113, 85, 59, 31.

Preparation of 2-(2-propynoxymethyl)thiophene (216)



Sodium hydride (44.0mg of a 60% dispersion in mineral oil, 1.1mmol) was washed with THF (1ml) under argon then suspended in dry THF (1ml). After cooling to 0°C 2-thiophenemethanol (1.14g, 1.0mmol) was added dropwise and the reaction mixture stirred at 0°C for 30 minutes. Propargyl bromide (2.22ml of an 80% solution in toluene, 2.0mmol) was added and the reaction stirred for a further hour. After this time water (2ml) was added and the reaction mixture extracted with ether. The combined extracts were dried (MgSO_4) and the solvent removed *in vacuo*. Reduced pressure distillation then furnished 2-(2-propynoxymethyl)thiophene (216) (1.48g, 98%) as a colourless oil.

Bpt = 160°C at 20mmHg

ν_{max} (film) 3288, 3104, 2854, 2115, 1074, 703 cm^{-1}

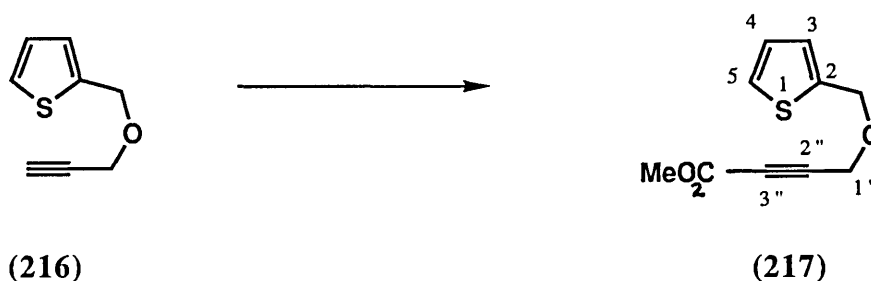
δ_H (270MHz, CDCl_3) 7.35 (1H, dd, 3.2Hz, 1.1Hz, H-5), 7.08 (1H, d, 3.5Hz, 1.1Hz, H-

3), 6.95 (1H, dd, 3.5, 3.2Hz, H-4), 4.80 (2H, s, 2xH-1'), 4.18 (2H, d, 1.6Hz, 2xH-1''), 2.44ppm (1H, d, 1.6Hz, H-3'')

m/z 152 (M^+), 122, 113, 97.

Accurate mass (M^+) Observed 152.0298, C_8H_8SO requires 152.0295

Preparation of 2-(3-carbomethoxy-2-propynoxymethyl)thiophene (217)



To a solution of 2-(2-propynoxymethyl)thiophene (216) (500mg, 3.27mmol) in THF (1ml) at $-78^{\circ}C$ was added n-butyllithium (1.44ml of 2.5M solution in hexanes, 3.59mmol) and the reaction stirred at this temperature for 1 hour. Methylchloroformate (370.9mg, 3.92mmol) was then added and the reaction mixture slowly warmed to room temperature. The solution was poured into water and extracted several times with ether. The organic extracts were then combined and dried ($MgSO_4$). Removal of the solvent *in vacuo* and subsequent flash column chromatography (SiO_2 , 50% ether in petrol) gave 2-(3-carbomethoxy-2-propynoxymethyl)thiophene (217) (636.1mg, 92%) as a viscous oil.

ν_{max} (film) 3002, 2952, 2237, 1712, 1432, 1256, 1089, 1057, 707 cm^{-1}

δ_H (270MHz, $CDCl_3$) 7.32 (1H, dd, 3.1Hz, 1.2Hz, H-5), 7.05 (1H, dd, 3.4Hz, 1.2Hz, H-3), 6.98 (1H, dd, 3.4, 3.1Hz, H-4), 4.78 (2H, s, 2xH-1'), 4.28 (2H, s, 2xH-1''), 3.79ppm (3H, s, CO_2CH_3).

m/z 210 (M^+), 195, 151, 97, 59.

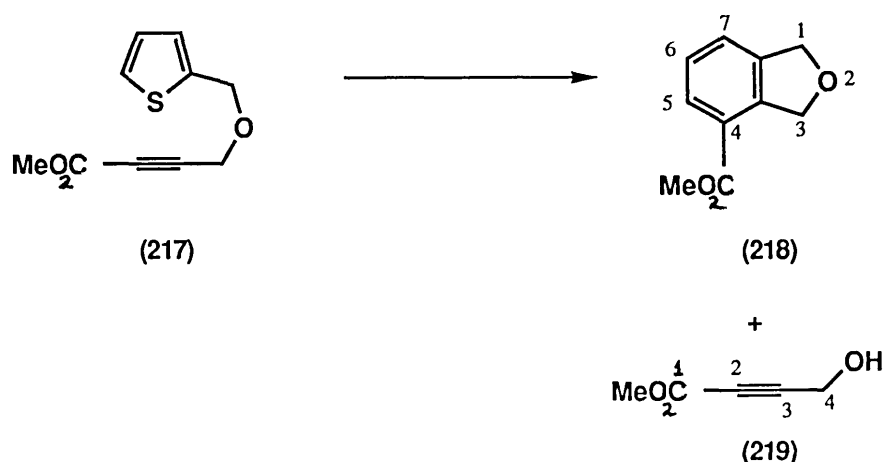
Accurate mass (M^+) Observed 210.0350, $C_{10}H_{10}O_3S$ requires 210.0351

Oxidation of 2-(3-carbomethoxy-2-propynoxymethyl)thiophene (217)

a) Preparation of Dimethyldioxirane

To a 500ml pyrex round bottomed flask was added water (24ml), acetone (16ml) and sodium hydrogen carbonate (14.4g, 0.171mol). Oxone[®] (30.0g, 0.049mol) was then added in approximately 10g portions. After each addition the reaction was put under reduced pressure so as to maintain steady distillation of the reaction mixture. Cooling the receiver flask to -78°C greatly reduced losses of the product due to evaporation or decomposition. When reaction was complete the resulting yellow distillate was passed through a short pad of $MgSO_4$ to remove any residual water and used without further purification. Excess reagent was stored in a commercial freezer at -10°C .

b) Oxidation of 2-(3-carbomethoxy-2-propynoxymethyl)thiophene (217)



A solution of 2-(3-carbomethoxy-2-propynoxymethyl)thiophene (217) (82.8mg,

0.394mmol) in DCM (1ml) was treated with freshly prepared dimethyldioxirane (14.8ml of an approximately 80mmolar solution in acetone, 1.84mmol) and the reaction mixture stirred at room temperature for 18 hours. The volatiles were then removed *in vacuo* and the resulting yellow oil purified by flash column chromatography (SiO₂, 0-50% ether in petrol). This afforded two products methyl-4-(1,3-dihydroisobenzofuran)carboxylate (218) (7.5mg, 13%) and methyl-4-hydroxybut-2-ynoate¹³¹ (219) (15.7mg, 35%) as a white solid and a yellow oil respectively.

methyl-4-(1,3-dihydroisobenzofuran)carboxylate (218)

Mpt. = 56-57°C

ν_{max} (film) 2918, 2850, 1715, 1440, 1280, 1143, 752 cm⁻¹

δ_H (270MHz, CDCl₃) 7.32 (1H, dd, 3.1Hz, 1.2Hz, H-5), 7.05 (1H, d, 3.4Hz, H-7), 6.98 (1H, dd, 3.4, 3.1Hz, H-6), 4.78 (2H, s, 2xH-3), 4.28 (2H, s, 2xH-1), 3.79ppm (3H, s, CO₂CH₃).

m/z 210 (M⁺), 195, 151, 97, 59.

Accurate mass (M⁺) Observed 178.0632, C₁₀H₁₀O₃ requires 178.0630.

methyl-4-hydroxybut-2-ynoate (219)¹³¹

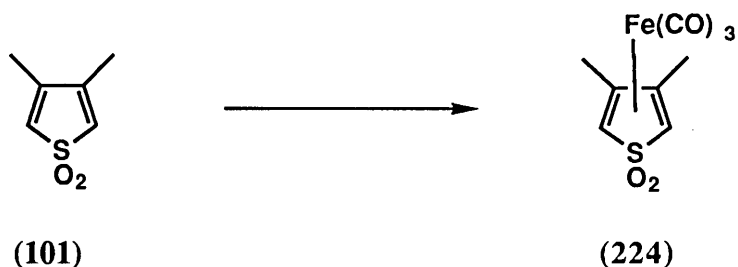
ν_{max} (film) 3410, 2956, 2240, 1712, 1264, 1023.cm⁻¹

δ_H (270MHz, CDCl₃) 4.38 (2H, d, 4.2Hz, CH₂), 3.76 (3H, s, CO₂CH₃), 2.80ppm (1H, bs, OH).

m/z 114 (M⁺), 83, 59, 55.

Accurate mass (M⁺) Observed 114.0319, C₅H₆O₃ requires 114.0317

Preparation of η_4 -(3,4-dimethyl-thiophene-1,1-dioxide)tricarbonyliron(0)
(224)¹²⁶



To a solution of 3,4-dimethyl-thiophene-1,1-dioxide (500mg, 3.47mmol) in THF (10ml) was added diironnonacarbonyl (2.52g, 6.92mmol) and the reaction mixture refluxed for 15 hours. The volatiles were then removed under reduced pressure and the resulting black residue passed through a silica/celite pad using EtOAc as eluant. Column chromatography (SiO₂, 20% EtOAc in petrol) then gave η_4 -(3,4-dimethyl-thiophene-1,1-dioxide)tricarbonyliron(0) (224) as a pale yellow solid (490mg, 50%).

Mpt = 146-148°C

$\nu_{\max}$ (mull) 3082, 2922, 2852, 2070, 2015, 1267, 1191 cm⁻¹

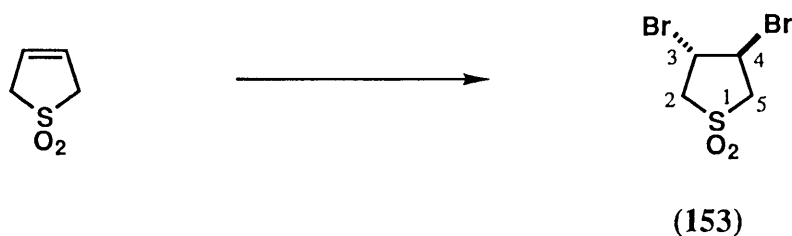
δ_{H} (250MHz, C₆D₆) 3.41 (2H, s, H-5 and H-2), 1.32 (6H, s, 2xMe)

$\delta_{\text{C}} \{^1\text{H}\}$ (125.8MHz, CDCl₃) 207.5 (CO), 96.7 (C-2), 70.4 (C-3), 13.5ppm (CH₃)

m/z 284 (M⁺), 256, 228, 200, 144, 136.

Found C=38.33%, H=2.80%, C₉H₈FeO₅S requires C=38.07%, H=2.80%

Preparation of *trans*-3,4-dibromothiacyclopentane-1,1-dioxide.(153)⁸³



1-Thiacyclopent-3-ene-1,1-dioxide (5.00g, 42.3mmol) was dissolved in benzene (10ml) and the reaction mixture heated to reflux. Bromine (5ml, 97.5mmol) was then added dropwise so as to maintain steady reflux. After addition was complete heating was continued for a further 5 hours then the reaction was cooled to room temperature. The resulting precipitate was filtered off, washed with cold benzene, and dried *in vacuo* to give ***trans*-3,4-dibromo-thiacyclopentane-1,1-dioxide (153)** (11.19g, 95%) as a white solid.

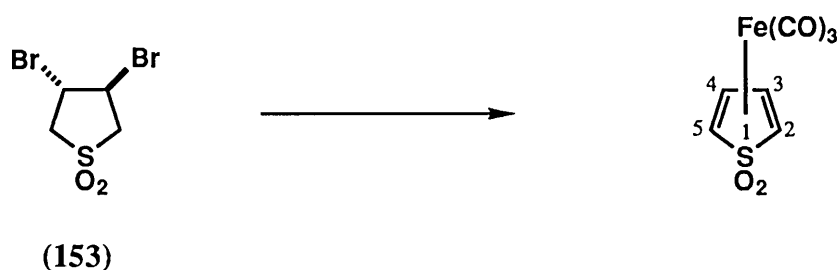
Mpt = 140-142°C, lit = 141-142°C

ν_{max} (mull) 1314, 1290, 1143, 1124, 1116, 1099, 907 cm^{-1}

δ_{H} (270MHz, CDCl_3) 4.74 (2H, dd, 6.3Hz, 4.7Hz, H-3, H-4), 4.02 (2H, dd, 14.2Hz, 6.3Hz, H-2b, H-5a), 3.51ppm (2H, dd, 14.2Hz, 6.3Hz, H-2a, H-5b).

m/z 290, 278, 276 (M^+), 215, 213, 211, 135, 133

Preparation of η_4 -(thiophene-1,1-dioxide)tricarbonyliron(0)¹⁰⁷



A rapidly stirred suspension of sodium hydroxide (60.4mg, 1.51mmol) in benzene (10ml) was cooled to 0°C and *trans*-3,4-dibromothiacyclopentane-1,1-dioxide.(153) (200mg, 0.72mmol) was added in one portion. The reaction mixture was then stirred for 1.5 hours before being transferred *via* lagged cannula to a pre-stirred suspension of diironnonacarbonyl (745mg, 2.04mmol) in THF (10ml) also at 0°C. Stirring was

continued for a further 1.5 hours before the reaction mixture was filtered through a silica/celite pad, using EtOAc as eluant. The solvents were then removed *in vacuo* and the resulting green solid purified by column chromatography (SiO₂, 20-40% EtOAc in petrol) affording η_4 -(thiophene-1,1-dioxide)tricarbonyliron (72.5mg, 40%).

Mpt = 188-190°C, lit = 189-190°C

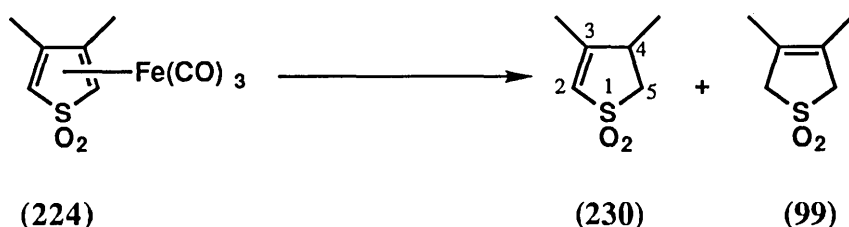
ν_{max} (mull) 2078, 2016, 1257, 1191, 1096 cm⁻¹

δ_H (250MHz, CDCl₃) 3.41 (2H, d, 0.7Hz, H-5 and H-2), 1.32ppm (2H, d, 0.7Hz, H-3 and H-4)

m/z 256 (M⁺), 228, 200, 172, 108.

Found C=32.74%, H=1.45%, C₇H₄FeS₂O₅ requires C=32.83%, H=1.57%

Reduction of η_4 -(3,4-dimethyl-thiophene-1,1-dioxide)tricarbonyliron(0) (224)



A solution of η_4 -(3,4-dimethyl-thiophene-1,1-dioxide)tricarbonyliron (224) (185mg, 0.66mmol) in methanol (5ml) was treated with sodium borohydride (89.0mg, 2.36mmol in total) until no starting material was present by tlc. (SiO₂, ether). 10% aqueous hydrochloric acid (1ml) was added and the reaction mixture stirred for a further 30 minutes. The reaction mixture was then neutralised by addition of solid sodium hydrogen carbonate, poured into water, and extracted several times with EtOAc. The organic extracts were combined, dried (MgSO₄) and the solvent removed *in vacuo*. Column chromatography (SiO₂, 20% EtOAc in petrol) gave 3,4-dimethylthiacyclopent-2-ene-1,1-

dioxide (230) (32.3mg, 33%)¹³⁵ and 3,4-dimethylthiacyclopent-3-ene-1,1-dioxide (99) (19.4mg, 20%) as a viscous oil and a white crystalline solid respectively.

3,4-dimethylthiacyclopent-2-ene-1,1 dioxide (230):-

ν_{max} (film) 3055, 2924, 1592, 1280, 1131cm⁻¹

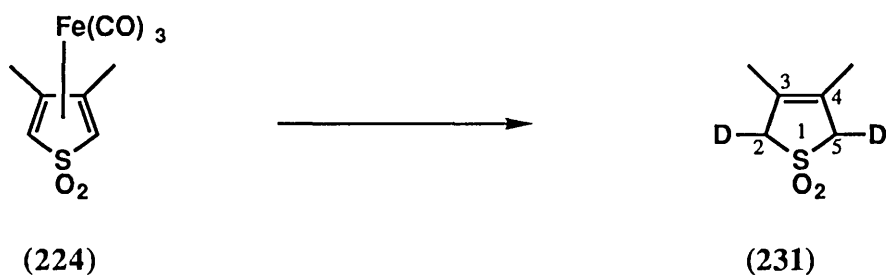
δ_H (270MHz, CDCl₃) 6.28 (1H, m, H-2), 3.50 (1H, dd, 13.2Hz, 7.9Hz, H-5a), 3.04 (1H, m, H-4), 2.96 (1H, dd, 13.2Hz, 3.9Hz, H-5b), 2.22 (3H, s, allylic CH₃), 1.32ppm (3H, d, 7.0Hz, CH₃)

m/z 146 (M⁺), 131, 82, 67.

Accurate mass (M⁺) Observed 146.0402 C₆H₁₀SO₂ requires 146.0402.

All data for 3,4-dimethylthiacyclopent-3-ene-1,1-dioxide.(99) was as previously stated.

Preparation of 2,5-dideuterio-3,4-dimethylthiacyclopent-3-ene-1,1-dioxide (231).



To a solution of η_4 -(3,4-dimethyl-thiophene-1,1-dioxide)tricarbonyliron (224) (50.1mg, 0.176mmol) in d₄-methanol (1ml) was added sodium borodeuteride (36.8mg, 0.88mmol in total) in approximately 10mg portions, until all the starting material had disappeared by tlc. (SiO₂, ether). 10% DCl in D₂O (1ml) was added and the reaction mixture stirred for a further 30 minutes. After this time the reaction was neutralised with solid sodium hydrogen carbonate and poured into water (1ml). Extraction with EtOAc, drying of the combined organic extracts (MgSO₄), and column chromatography (25%

EtOAc in petrol) gave **2,5-dideuterio-3,4-dimethylthiacyclopent-3-ene-1,1-dioxide (231)** (5.26mg, 20%) as a clear oil.

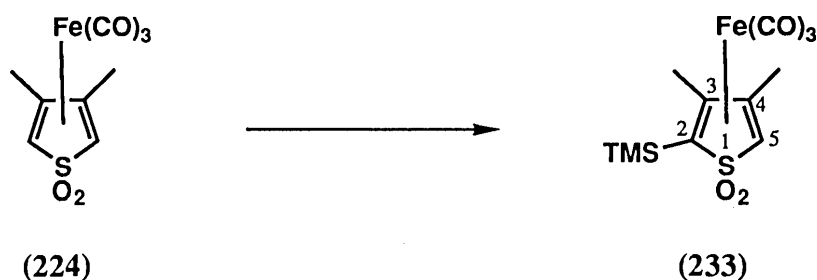
ν_{max} (film) 2920, 2853, 1444, 1287, 1145, 1173 cm^{-1}

δ_H (90MHz, CDCl_3) 3.70 (2H, s, H-2, H-5) , 1.78 ppm (6H, s, 2x CH_3)

m/z 148 (M^+), 94, 84, 69.

Accurate mass (M^+) Observed 148.0527, $\text{C}_6\text{H}_8\text{D}_2\text{S}\text{O}_2$ requires 148.0529.

Preparation of η_4 -[3,4-dimethyl-2-(trimethylsilyl)-thiophene-1,1-dioxide]tricarbonyliron(0) (233)



n-Butyllithium (240 μl of a 2.5M solution in hexanes, 0.60mmol), was added to diisopropylamine (60.7mg, 0.60mmol) and reaction mixture stirred at 0°C for 10 minutes. THF (1ml) was added and the reaction cooled to -78°C. A solution of (η_4 -3,4-dimethylthiophene-1,1-dioxide)tricarbonyliron(0) (224) (150mg, 0.528mmol) in THF (1ml) was added *via* cannula, and the mixture stirred at -78°C for a further 30 minutes before chlorotrimethylsilane (2ml, large excess) was added dropwise. After reaching room temperature overnight, the reaction mixture was stirred for a further 24 hours then quenched with 10% aqueous hydrochloric acid. (1ml). Water (1ml) was added followed by solid sodium hydrogen carbonate until the reaction reached the neutral point. Extraction with EtOAc, drying the organic extracts (MgSO_4) and removal of the solvent

in vacuo gave a crude yellow oil. Purification by flash column chromatography (SiO₂, 25% EtOAc in petrol) gave the starting complex (224) (75.3mg, 50% recovery) and η_4 -(3,4-dimethyl-2-(trimethylsilyl)-thiophene-1,1-dioxide)tricarbonyliron(0) (231) (22.0mg, 12%) as a yellow oil.

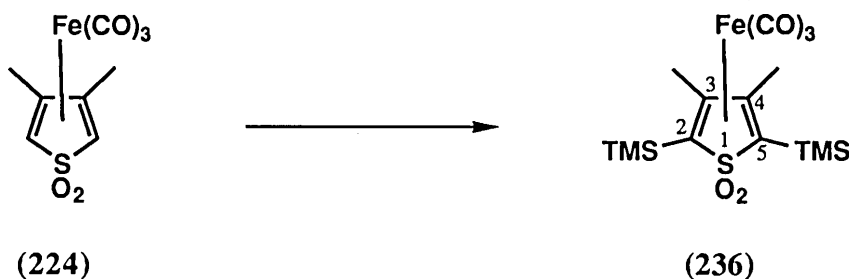
ν_{max} (film) , 2952, 2073, 2014, 1251, 1138, 853 cm⁻¹

δ_H (250MHz, CDCl₃) 3.35 (1H, s, H-5), 1.35 (3H, s, CH₃), 0.97 (3H, s, CH₃), 0.32 (9H, s, Si(CH₃)₃)

m/z 356 (M⁺), 328, 300, 272, 208.

Accurate mass (M-CO)⁺ Observed 327.9886, C₁₁H₁₆FeO₄SSi requires 327.9887.

Preparation of η_4 -[2,5-bis(trimethylsilyl)-3,4-dimethylthiophene-1,1-dioxide]tricarbonyliron(0) (236)



To a solution of lithium diisopropylamide (64.3mg, 0.60mmol) in THF (1ml), prepared from diisopropylamine and n-butyllithium as described above, cooled to -78°C, was added HMPA (1ml). After 15 minutes η_4 -(3,4-dimethyl-thiophene-1,1-dioxide)tricarbonyliron (224) (150mg, 0.528mmol) in THF (1ml) was added dropwise *via* cannula and the reaction mixture stirred for 1 hour at -78°C. Chlorotrimethylsilane (2ml, large excess) was then added dropwise and the reaction warmed to room temperature overnight. After treatment of the reaction mixture with 10% aqueous

hydrochloric acid. (1ml) and neutralisation using solid sodium hydrogen carbonate, the mixture was extracted with EtOAc and the combined organic extracts dried (MgSO_4). Purification by flash column chromatography (SiO_2 , 25-30% EtOAc in petrol) then yielded the starting complex (224) (12.5mg, 8% recovery) and η_4 -[2,5-bis(trimethylsilyl)-3,4-dimethylthiophene-1,1-dioxide]tricarbonyliron(0) (24.1mg, 11%) both as crystalline yellow solids.

mpt = 135°C decomposes.

ν_{max} (film) 2020, 2008, 2014, 1252, 1118, 857. cm^{-1}

δ_{H} (250MHz, C_6D_6) 2.27 (6H, s, 2x CH_3), 0.38 (18H, s, 2x $\text{Si}(\text{CH}_3)_3$)

$\delta_{\text{C}}\{^1\text{H}\}$ (125.8MHz, CDCl_3) 207.6 (CO), 102.5 (C-2), 73.7 (C-3), 14.6 (CH_3) 0.47ppm ($\text{Si}(\text{CH}_3)_3$)

m/z 400 (M-CO), 372, 344, 280, 73.

Accurate mass (M-CO)⁺ Observed 400.0284, $\text{C}_{14}\text{H}_{24}\text{FeO}_4\text{SSi}_2$ requires 400.0283.

Appendix

Single Crystal X-ray Data for structure 236.

Crystal data: $C_{15}H_{24}FeO_5SSi$ = 428.4, orthorhombic, $a = 13.914(6)$, $b = 7.515(2)$, $c = 20.316(11)\text{\AA}$. Volume = $2124.3\text{\AA}^3$, space group = Pnam, $Z = 4$, $D_c = 1.340\text{ Mg/m}^3$, $CuK\alpha$ radiation $\lambda = 1.54178\text{\AA}$, $F(000) = 896$, (graphite monochromator), using ω -scans. Data were collected on a Nicolet R3m/E diffractometer. A crystal of dimensions $0.1 \times 0.1 \times 0.43\text{mm}$ was used. 1383 Independent reflections ($2\theta \leq 116^\circ$) were measured, of which 958 had $|F_o| > 3.0\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarisation factors; a numerical absorption correction was applied; maximum and minimum transmission factors 0.5195 and 0.3125 respectively. The structure was resolved by direct methods. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were Riding model assigned with fixed isotropic U value. Refinement was by block cascade, full matrix least squares to $R = 0.058$, $R_w = 0.064$ [$w^{-1} = \sigma^2(F) + 0.0010F^2$]. Computations were carried out upon an Eclipse S140 using the SHELXTL PLUS program system.

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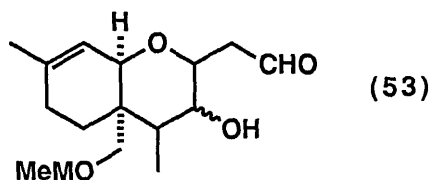
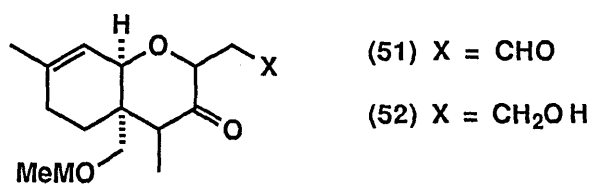
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Corrigenda

Page 31, scheme 11, structures (51), (52) and (53) should read:-



Page 38, scheme 16, structure (76) should read:-

