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**Synthesis of α -Farnesene Autoxidation Products and
Cross-conjugated Polyenes.**

Presented in partial fulfilment of the requirements for the degree of

Doctor of Philosophy in Chemistry

**At
Massey University.**

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Synthesis of
 α -Farnesene Autoxidation Products
and Cross-conjugated Polyenes

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Abstract.

3-Sulfolenes (2,5-dihydrothiophene-1,1-dioxides) are well known as diene equivalents which are readily unmasked by the cheletropic elimination of sulfur dioxide under thermal conditions. This chemistry has been used in the synthesis of conjugated triene autoxidation products of α -farnesene and previously unknown cross-conjugated polyene hydrocarbons.

α -Farnesene (3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraene) is a sesquiterpene found in the surface coating of apples. The *in vivo* autoxidation of α -farnesene is believed to cause superficial scald, a serious post harvest disorder of the fruit. The principal α -farnesene autoxidation product, "Anet's Trienol" (**1.8a**), was prepared in five steps from geraniol. The isomeric 3*Z*-trienol (**1.8b**) was also observed as a minor component (*ca.* 5%). Key steps involved the use of TMEDA to effect the regioselective alkylation of 3-methyl-3-sulfolene and the cheletropic elimination of sulfur dioxide from the resultant 2,3-disubstituted-3-sulfolene. The acid catalysed hydroperoxidation of "Anet's Trienol" was achieved with anhydrous hydrogen peroxide in THF and gave the conjugated trienyl hydroperoxide (**1.7a**) as a single regioisomer in good yield (47%) together with traces of the stereoisomeric 3*Z*-trienyl hydroperoxide (**1.7b**) (*ca.* 4%). The trienyl hydroperoxides (**1.7a**) and (**1.7b**) (96:4) were cyclised efficiently under an oxygen atmosphere in the presence of "samarium peroxide" to afford a diastereoisomeric mixture (*ca.* 1:1.2) of endoperoxy hydroperoxides (**1.11a**) and (**1.11b**) (85:15). Selective reduction of the hydroperoxides (**1.11a**) and (**1.11b**) gave the corresponding endoperoxy alcohols (**1.12a**) and (**1.12b**) (85:15) again as a mixture of diastereoisomers (*ca.* 1:1.2).

Alternative syntheses of these α -farnesene autoxidation products were investigated. Three regioisomeric allylic alcohols (**2.1**), (**2.2**) and (**2.3a**) were prepared from geraniol and, when exposed to water or anhydrous hydrogen peroxide in the presence of an acid catalyst, underwent highly regioselective oxygen transposition reactions to give "Anet's Trienol" (**1.8**) and the corresponding trienyl hydroperoxide (**1.7**) respectively as mixtures of stereoisomers. The secondary allylic alcohol (**2.1**) gave only the 3*E*-isomeric trienes (**1.7a**) and (**1.8a**), while the tertiary alcohol (**2.2**) and primary alcohol (**2.3a**) gave mixtures of the isomeric 3*E* and 3*Z*-trienes (**1.7a**)/ (**1.7b**) and (**1.8a**)/ (**1.8b**) dependant upon on the regiochemistry of the allylic alcohol starting material. *E/Z*

isomeric ratios of transposition products indicated that intermediate carbocations did not interconvert under the reaction conditions. An analogous radical mechanism has been presented to explain the formation of minor 3*Z*-trienyl species formed under conditions consistent with the generation of farnesene peroxy radicals.

The Stille cross-coupling of simple iodinated and stannylated sulfolene derivatives was investigated as a route to *bis*-sulfolenes. 3-Iodo-3-sulfolene (**3.37**), prepared in 4 steps from 3-sulfolene, was coupled with 3-tributylstannyl-3-sulfolene (**3.33**) to give the *bis*-3-sulfolene (**3.26**) in excellent yield (95%). This constitutes the first synthesis of a *bis*-sulfolene. Molecules of this type represent masked cross-conjugated polyenes ([*n*]-dendralenes). In an effort to access the higher, unknown [*n*]-dendralenes, the Stille cross-coupling of 3-iodo-3-sulfolene (**3.37**) with a variety of *mono*- and *bis*-stannanes was investigated and *bis*-sulfolene precursors to [4]-, [5]-, [6]- and [8]-dendralene were prepared. The utility of 3-iodo-3-sulfolene (**3.37**) as a coupling partner in the Stille reaction was briefly investigated and a range of other, novel cross-conjugated polyene precursors were prepared. The carbonylative Stille cross-coupling of 3-iodo-3-sulfolene (**3.37**) was also achieved. 3,4-Diiodo-3-sulfolene (**4.15**) was prepared in four steps from 2-butyne-1,4-diol and coupling with 3-tributylstannyl-3-sulfolene (**3.33**) yielded the first example of a *tris*-3-sulfolene (**4.13**) in 43% yield.

Capillary pyrolysis (CP) was developed as a practical alternative to flash vacuum pyrolysis and proved a valuable technique for the cheletropic elimination of sulfur dioxide from the cross-conjugated polyene precursors prepared by the Stille coupling of iodo-3-sulfolenes. Using CP, [3]-, [4]-, [5]-, [6]- and [8]-dendralene were prepared (52-89%) and their spectral characterisation was achieved. This constitutes the first general strategy for the synthesis of this poorly represented class of fundamental hydrocarbons. The synthesis of other novel cross-conjugated polyenes was achieved using CP and further demonstrated the value of this technique.

The diene-transmissive Diels-Alder reaction of the [*n*]-dendralenes with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) was investigated briefly and evidence for the occurrence of the theoretical maximum number of diene-transmissive Diels-Alder reactions, *viz.* [*n*-1] was obtained.

To
Andrea, my wife
and
Frank, my granddad.

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Abbreviations.

AIBN	2,2'-azo- <i>bis</i> -isobutyronitrile
b.p.	boiling point
aq.	aqueous
br.	broad
Bu	butyl
BuLi	<i>n</i> -butyl lithium
°C	degrees Celsius
<i>ca.</i>	circa (approximately)
cat.	catalytic
<i>cf.</i>	confer (compare)
cm ⁻¹	wave number
<i>con</i> -	conrotatory
COSY	correlated spectroscopy
CP	capillary pyrolysis
d	doublet
dba	dibenzylidene acetone
DBPO	di- <i>t</i> -butylperoxylate
DBU	1,8-diazabicyclo-[5,4,0]-undec-7-ene
DEPT	distortionless enhancement by polarisation transfer
DIBALH	diisobutylaluminium hydride
<i>dis</i> -	disrotatory
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
DMSO	dimethyl sulfoxide
DPA	diphenylamine
DTDA	diene-transmissive Diels-Alder
δ	chemical shift
E	electrophile
EI	electron ionisation
eq.	equation
equiv.	molar equivalent(s)
Et	ethyl
eV	electron volts

ϵ	molar extinction coefficient
FAB	fast atom bombardment
FVP	flash vacuum pyrolysis
GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
GED	gas-phase electron diffraction
HETCOR	heteronuclear correlated spectroscopy
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum correlation
HPLC	high pressure liquid chromatography
hr(s)	hour(s)
Hz	Hertz
I.D.	internal diameter
<i>i</i> Pr	<i>isopropyl</i>
IR	infrared
J	coupling constant
K	degrees Kelvin
L	ligand
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
Lit.	literature
λ_{\max}	absorption maxima (UV)
m	multiplet
M	molar
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
MHz	megahertz
min(s)	minute(s)
mmHg	millimetres of mercury
mmol	millimole
mol	mole
m.p.	melting point
nm	nanometre
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance

Nu	nucleophile
ν_{\max}	absorption maxima (IR)
<i>o</i> -	<i>ortho</i> -
<i>p</i> -	<i>para</i> -
<i>p</i> TSA	<i>para</i> -toluensulfonic acid
Ph	phenyl
PhH	benzene
ppm	parts per million
PTAD	4-phenyl-1,2,4-triazoline-3,5-dione
pyr.	pyridine
q	quartet
quant.	quantitative
quint	quintet
rel. int.	relative intensity
rfx.	reflux
rt	room temperature
s	singlet
sat.	saturated
sext	sextet
sh.	shoulder
sol.	solution
t	triplet
<i>t</i> BHP	<i>tert</i> -butylhydroperoxide
THF	tetrahydrofuran
tlc	thin layer chromatography
TMEDA	N,N,N',N'-tetramethylethylenediamine
Tol	tolyl
<i>viz.</i>	<i>videlicet</i> (namely)
UHP	urea hydrogen peroxide complex
UV	ultraviolet

Chapter 1

Synthesis of α -Farnesene Autoxidation Products.

1.1 Introduction

α -Farnesene (3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraene) (1.1) (Figure 1.1) is a naturally occurring sesquiterpene hydrocarbon found in the surface coating of apples,¹ pears,² and quinces.³ It has been identified as a volatile emitted from bananas⁴ and in the berries of the genus *Vismia*.⁵ α -Farnesene (1.1) also occurs in the scent of many flower species⁶ where it imparts a subtle yet distinct apple-like aroma. It is also an important semiochemical and has been isolated from the Dufour's gland of at least two species of ant⁷ and identified as both an oviposition stimulant for the Codling moth⁸ and an attractant for its larvae.⁹

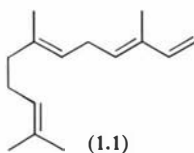


Figure 1.1

1.1.1 Superficial Scald.

Despite the widespread occurrence of this acyclic sesquiterpene, it is the presence of α -farnesene (1.1) in the surface coatings of many pome fruit (apples and pears) which has dominated scientific interest in this compound. Indeed, (1.1) has long been associated with the occurrence of superficial scald, a physiological disorder resulting in blackening of the fruit skin after cold storage.^{10,11} Also referred to as “storage scald”, “common scald” or just “scald”, this post harvest disorder is characterised by browning of the hypodermal cells. In mild cases, only the outer cell layers, or epidermis, are discoloured, but in more severe instances, the entire hypodermis, extending to five or six layers beneath the fruit surface may be affected. In extreme cases of scald, collapse of the damaged tissue is observed and the fruit appears black and pitted.¹² The flesh

beneath the scalded area however, remains unaffected and is quite edible. Nonetheless, the unsightly appearance of scalded fruit severely restricts their marketability.

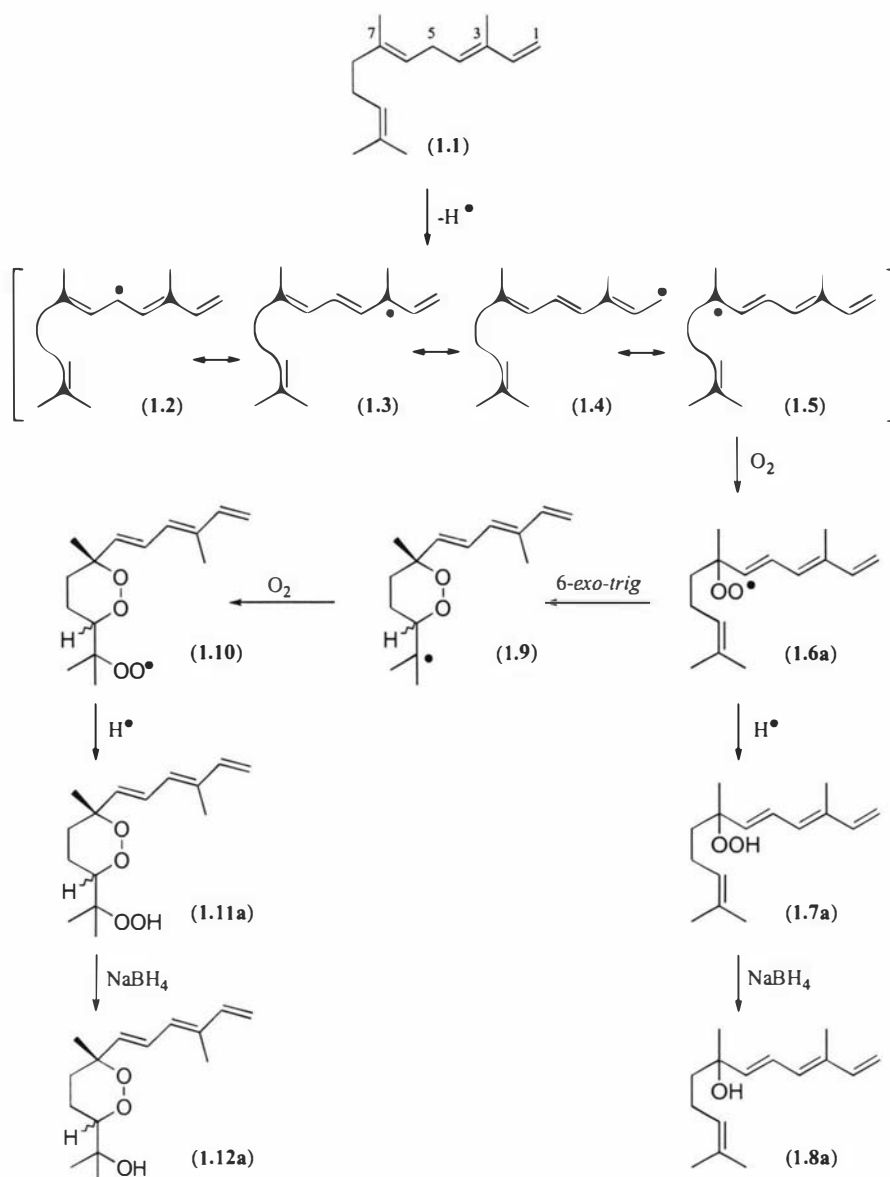
1.1.2 α -Farnesene Autoxidation.

α -Farnesene (1.1) accumulates in the surface coating of stored apples and its concentration in the skin has been shown in several studies to correlate with the extent and severity of superficial scald.¹³⁻¹⁶ Autoxidation products of α -farnesene, including hydroperoxides or intermediary free radicals, have been suggested as the actual causal agents for scald.¹⁷

In an early investigation into the *in vitro* autoxidation α -farnesene (1.1),¹⁸ Anet observed the formation of the hydroperoxides (1.7a) and (1.11a) by UV spectroscopy, but was unable to isolate or characterise these materials because of their instability. (Scheme 1.1) However, reduction of the autoxidation mixture with sodium borohydride allowed for the isolation and characterisation of the corresponding conjugated trienol (1.8a) and the endoperoxide (1.12a). Trienol (1.8a) is commonly referred to as "Anet's trienol".

Anet proposed a free radical mechanism to explain the formation of these products¹⁸ and was amongst the first researchers to conclude that cyclic peroxides, also known as endoperoxides, could be formed *via* polyene autoxidation.¹⁹ Autoxidation is initiated by hydrogen atom abstraction from the weakest C-H bond, i.e. at C5 of the methylene-interrupted triene. The resulting α -farnesene radical species can be drawn as a stabilised heptatrienyl radical, with four contributing canonical forms (1.2) - (1.5). (Scheme 1.1). At, or around ambient oxygen pressures, the rate of dioxygenation of carbon centred radicals approaches the diffusion control limit (*ca.* $10^9 \text{ l mol}^{-1} \text{ s}^{-1}$),²⁰ hence addition of molecular oxygen to the farnesene radical ((1.2)-(1.5)) is very rapid.

In principle, this process can generate four possible autoxidation products, i.e. through oxygenation at either C1, C3, C5 or C7, however, only C7 oxygenated species (**1.6a**) and products derived from it have been reported.[†]



Scheme 1.1

The peroxy radical (**1.6a**) is a common intermediate in the formation of both the conjugated trienylhydroperoxide (**1.7a**) and the endoperoxy hydroperoxide (**1.11a**). Hydrogen atom abstraction from another molecule of α -farnesene gives (**1.7a**) directly

[†] It has since been shown that polyenic peroxy radicals which retain the maximum degree of conjugation are favoured²¹ and the formation of (**1.6a**) is therefore fully consistent with these observations. Nonetheless, it must be noted that oxygenation at C1 also generates a peroxy radical species which retains maximum conjugation, i.e. through formal oxygen entrapment of canonical form (**1.4**). However, the 1-hydroperoxide was not observed. The possible mechanistic implications of this observation in relation to the autoxidation of α -farnesene are discussed in Chapter 2, section 2.4.

and serves to propagate the autoxidation process. Alternatively, cyclisation of the peroxy radical (**1.6a**) onto the pendant prenyl substituent generates a second carbon-centred radical species (**1.9**). Subsequent entrapment with molecular oxygen is again rapid and the resultant peroxy radical (**1.10**) can abstract an hydrogen atom from any suitable donor source, i.e. α -farnesene, to yield the hydroperoxide (**1.11a**) while simultaneously propagating the autoxidation process.

During the purification of the conjugated trienol (**1.8a**), Anet¹⁸ also observed (but was unable to separate chromatographically), a minor isomeric reduction product (*ca.* 13%). This he correctly assigned as the 3*Z*-conjugated trienol (**1.8b**),[†] which he suggested necessitated the existence of the corresponding 3*Z*-trienylhydroperoxide (**1.7b**) and its radical predecessor (**1.6b**). (Figure 1.2) The origin of this relatively high proportion of 3*Z*-isomer is unclear, especially when it is considered that naturally occurring α -farnesene, (as used by Anet) contains, at most, only *ca.* 3% of the 3*Z*-isomer.^{22,23}

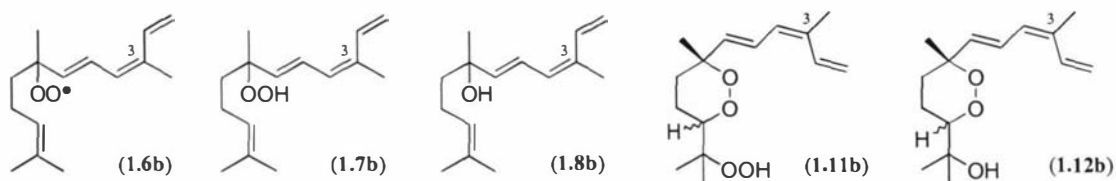


Figure 1.2

The endoperoxy alcohol (**1.12a**) was isolated by Anet¹⁸ as a 60:40 mixture of undetermined diastereoisomers and while the possible existence of "trace amounts" of isomeric 3*Z*-counterparts, i.e. (**1.11b**) and (**1.12b**), was considered likely by Anet, their presence could not be confirmed.

Until recently, it was assumed that the conjugated trienes which accumulate in the surface coating of stored apples were identical to the *in vitro* α -farnesene autoxidation products proposed by Anet, *viz.* hydroperoxides (**1.7a**) and (**1.11a**).¹⁸ (Scheme 1.1) Indeed, the characteristic UV absorption spectra of these trienes (λ_{max} 259, 269 and 281 nm) was used to estimate the concentration of "conjugated trienes" in the hexane skin washes of stored fruit.²⁴ However, using HPLC and GCMS techniques, it has since

[†] During this discussion all derivatives of α -farnesene are numbered as for the parent compound (**1.1**) (3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraene).

been demonstrated by Rowan *et al.*²⁵ that the bulk of the conjugated trienes produced *in vivo* are in fact the more stable trienols (1.8), with the 3*E*-isomer (1.8a) generally comprising up to 85% of the total “triene” content with the 3*Z*-isomer (1.8b) constituting most of the remainder. The hydroperoxides (1.7a) and (1.7b) were also identified, but only as minor contributors (typically < 5%).[†] The endoperoxy alcohol (1.12a) was tentatively identified, but again as a minor component (< 5%) of the triene content of the surface coating. Later work, by Whitaker *et al.*²⁷ reiterated these findings and confirmed that the “triene” component in the surface wax of stored apples is comprised mainly of the isomeric conjugated trienols (1.8a) and (1.8b), and not, as once was thought, the hydroperoxides (1.7a) and (1.11a).

1.1.3 The Treatment of Superficial Scald.

Conjugated trienes progressively accumulate on the surface of stored apples and concentrations of trienes, as measured by UV spectroscopy, correlate more closely with the occurrence and severity of superficial scald than does the concentration α -farnesene.^{2,14,16,26} Natural antioxidants are also present on the surface of apples^{16,28} and may retard the autoxidation of α -farnesene.^{29,30} A more complex hypothesis, relating scald development to the levels of various UV absorptions in hexane extracts from the apple skin, has been presented.³¹

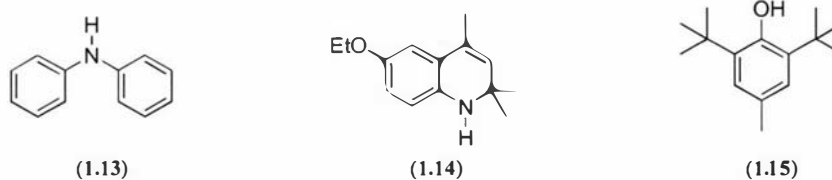


Figure 1.3

In view of the impact of superficial scald on fruit sales and wasted storage costs, considerable effort has been invested into understanding and controlling this disorder. Many of the measures currently employed to prevent scald also provide circumstantial evidence for the involvement of α -farnesene autoxidation products in its development. Indeed, scald can be effectively controlled by post harvest treatment of the fruit with

[†] An earlier report identified hydroperoxide (1.7) as the major triene component of apple wax, albeit as an unspecified stereoisomer characterised *after reduction* of the isolate with NaBH₄.²⁶

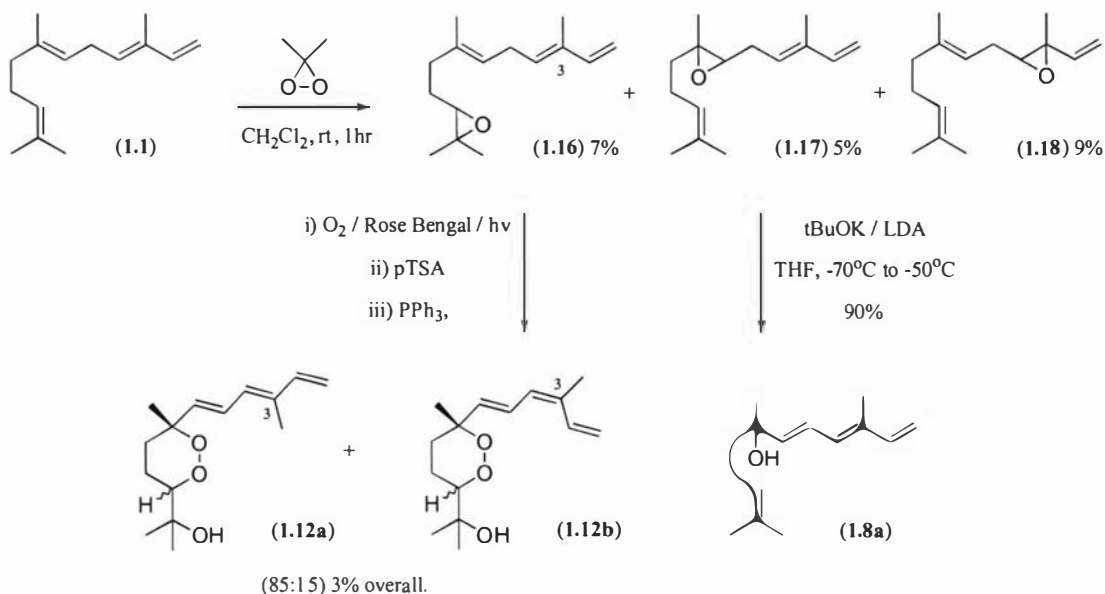
antioxidants such as diphenylamine (DPA) (1.13),^{13,14,30} 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline (ethoxyquin) (1.14)² or 2,6-di-*t*-butyl-4-methylphenol (BHT) (1.15).³² (Figure 1.3) Safety concerns surrounding the use of such postharvest treatments and the possibility of legislative changes threaten to marginalise the use of synthetic antioxidants and alternative chemical³³⁻³⁹ and environmental, “non-chemical” control measures continue to be sought.⁴⁰⁻⁵¹ Strategies for the control of superficial scald, prior to 1989, have been reviewed.⁵²

1.2 The Synthesis of α -Farnesene Autoxidation Products.

The rational development of alternative control strategies requires a better understanding of the role of α -farnesene in the initiation of superficial scald and of the significance of the α -farnesene oxidation products present or formed during the storage of apples. Access to α -farnesene autoxidation products is, therefore, of considerable importance.

1.2.1 Earlier Work.

The chemical oxidation of α -farnesene has been investigated as a source of synthetic autoxidation products and has led, albeit in low yield, to the first syntheses of Anet's conjugated trienol (1.8a) and endoperoxy alcohol (1.12a).⁵³⁻⁵⁶ Treatment of α -farnesene with either dimethyldioxirane or *m*CPBA gave a mixture of the isomeric farnesene *mono*-epoxides (1.16)-(1.18) in low yield which were readily separated by flash chromatography. (Scheme 1.2) Photosensitised oxidation of epoxide (1.16) in the presence of Rose Bengal, followed by acid catalysed hydroperoxide ring opening of the epoxide, gave the endoperoxy alcohol (1.12a) as a 4:1 mixture of unspecified diastereoisomers in 3% yield. This material contained *ca.* 15% of the isomeric 3*Z*-triene (1.12b). While the presence of (1.12b) was consistent with Anet's earlier observations,¹⁸ the origin of such a high proportion of the 3*Z*-isomer (1.12b), from a 3*E*-precursor (1.16), was again unclear. Treatment of epoxide (1.17) with the mixed base *t*BuOK/LDA⁵⁷ in THF at low temperature resulted in its clean rearrangement to the conjugated trienol (1.8a) as a single stereoisomer in excellent yield (90%).

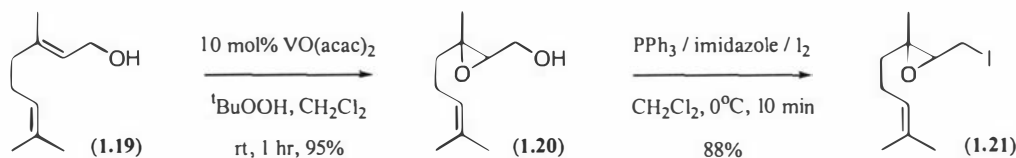


Scheme 1.2

The synthesis of the conjugated trienes (1.8a) and (1.12a) by this route, while low yielding, proved of significant value. The synthetic autoxidation products (1.8a) and (1.12a) were used as reference standards in the identification and quantification of naturally occurring trienes present in the skin of fresh and stored apples.²⁵ However, only small quantities of material were accessible by this approach and this strategy did not grant access to the unstable hydroperoxides (1.7) and (1.11) believed to be the actual causal agents of superficial scald.¹⁷ The aim of the work presented here was to improve upon the syntheses of (1.8a) and (1.12a) and to simultaneously develop viable syntheses of the trienyl hydroperoxides (1.7a) and (1.11a), granting access to synthetic α -farnesene autoxidation products in quantities suitable for biological evaluation.

1.2.2 A New Approach to “Anet’s Trienol”.

The epoxidation of α -farnesene is both poorly regioselective and low yielding.^{23,53} For these reasons the method of Spicer *et al.*^{53,54} (Scheme 1.2) is of limited value as a synthetic route to the conjugated trienol (1.8a), especially when quantities of material suitable for testing are required. Nonetheless, the facile and high yielding base catalysed rearrangement of the intermediate farnesene epoxide (1.17) suggested that an alternative route to *this* material was the most obvious way to prepare workable quantities of (1.8a). An improved synthesis of farnesene epoxide (1.17), from geraniol (1.19), is described below.⁵⁸

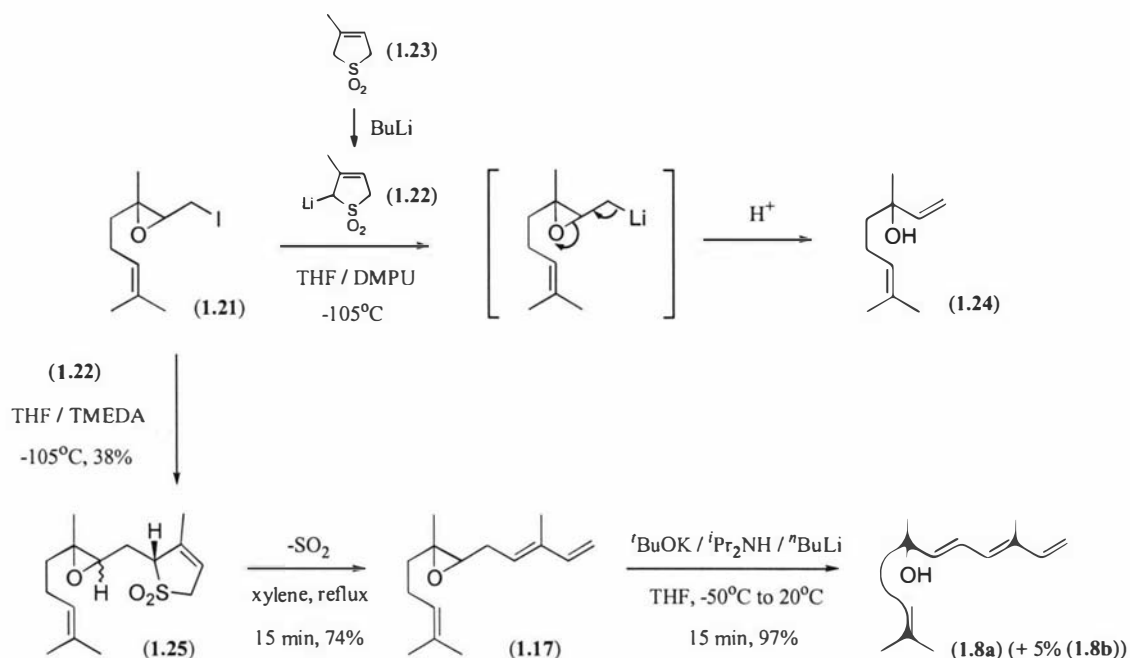


Scheme 1.3

Directed epoxidation of geraniol (**1.19**) with *t*-butyl hydroperoxide in the presence of catalytic vanadyl acetylacetonate⁵⁹ gave epoxy alcohol (**1.20**) in excellent yield after chromatography on silica gel. (Scheme 1.3) Conversion of (**1.20**) to the known iodoepoxide (**1.21**)⁶⁰ proceeded smoothly with triphenylphosphine, imidazole and elemental iodine in dichloromethane at room temperature.⁶¹ Attempted purification of iodoepoxide (**1.21**) by short path distillation (Kugelrohr), resulted in decomposition and ultimately this was abandoned in favour of chromatography on silica gel. It proved essential to store the purified material under argon at low temperature in the dark to avoid decomposition.

It was envisaged that the regioselective introduction of an isoprene (2-methyl-1,3-butadiene) moiety into (**1.21**) could be achieved through displacement of iodide with 2-lithio-3-methyl-3-sulfolene (**1.22**), followed by the cheletropic elimination of sulfur dioxide to unmask the protected 2-methyl-1,3-butadiene unit. (Scheme 1.4) The use of 3-sulfolene derivatives as diene equivalents is well known and is discussed further in **Chapter 3**. The regioselective metalation of 3-methyl-3-sulfolene (**1.23**) is also known and has proved a useful synthetic tool in the preparation of related farnesene derivatives.^{23,53-56}

The deprotonation of 3-methyl-3-sulfolene (**1.23**) must be carried out at low temperatures, typically below -90°C , and the presence of a suitable co-solvent such as HMPA is mandatory.⁶² It has been observed, however, that 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)^{23,53,54,56} and *N,N,N',N'*-tetramethylethylenediamine (TMEDA)²³ are also effective co-solvents for the regioselective metalation of 3-methyl-3-sulfolene (**1.23**) and are significantly less toxic than HMPA.⁶³



Scheme 1.4

Initial attempts to alkylate 2-lithio-3-methyl-3-sulfolene (1.22) with iodoepoxide (1.21) at low temperature in the presence of DMPU were unsuccessful and led to the exclusive formation of linalool (1.24), presumably as a result of initial metal-halogen exchange and β -fragmentation of the epoxide. (Scheme 1.4) A similar result was reported by Moody in attempts to alkylate the dianion of methylacetoacetate with iodoepoxide (1.21).⁶⁰ The reaction pathway, however, was successfully diverted to the requisite 2,3-disubstituted-3-sulfolene with the use of TMEDA as co-solvent, and (1.25) was isolated as a 1:1 mixture of diastereoisomers in 38% yield. Unreacted iodoepoxide (1.21) was also recovered in 55% yield, representing a corrected yield for (1.25) of 85% at 45% conversion.

Thermolysis of sulfolene (1.25) in refluxing, degassed xylene afforded the farnesene epoxide (1.17) in good yield (74%) after removal of solvent and purification by chromatography on silica gel. ¹H NMR analysis of (1.17) prepared in this manner demonstrated that no minor isomeric epoxides were present. This approach to epoxide (1.17) is, therefore, both highly regio- and stereoselective and represents a practical, higher yielding alternative to the direct epoxidation of α -farnesene reported earlier.

β -Fragmentation of (1.17) with the strong mixed base, ^tBuOK/LDA⁵⁷ was achieved in near quantitative yield after slightly modifying the conditions of Brimble *et al.*⁵⁶ and

carrying out the reaction at temperatures higher than those originally reported. ^1H NMR analysis of (1.8a) prepared in this manner indicated the presence of the minor isomeric tetraene (1.8b) (*ca.* 5%). (Figure 1.2) In all other ways, however, the conjugated trienol (1.8a) was identical to both the material isolated by Anet¹⁸ and to that prepared earlier by Spicer.^{54,56} The origin of trace amounts of (1.8b) was unclear.

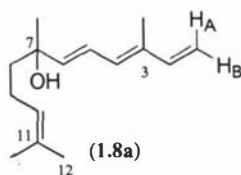


Table 1.1a ^1H NMR Data for (1.8a)

	1-H _A	1-H _B	2-H	4-H	5-H	6-H	8-H ₂	9-H ₂	10-H	12-H ₃	3-Me	7-Me	11-Me	7-OH
δ / ppm	5.21	5.03	6.41	6.08	6.58	5.80	1.60	2.03	5.12	1.68	1.88	1.33	1.60	1.71
	d	d	dd	d	dd	d	m	m	m	s	s	s	s	br.s
J / Hz	17.4	10.6	17.4 10.6	11.1	15.2 11.1	15.2	-	-	-	-	-	-	-	-

Table 1.1b ^{13}C NMR Data for (1.8a)

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	3-Me	7-Me	11-Me
δ / ppm	112.2	141.1	134.7	130.7	123.5	141.2	73.3	42.4	23.0	124.2	131.6	25.6	12.1	28.2	17.7
	t	d	s	d	d	d	s	t	t	d	s	q	q	q	q

^1H NMR analysis of (1.8a) (Table 1.1a) revealed four upfield three proton singlets, assigned as the methyl substituents 3-Me, 7-Me, 11-Me and the terminal methyl group at C12. The non-equivalent methylenes (8-CH₂ and 9-CH₂) appeared as broad multiplets, with the more upfield signal of the 8-CH₂ protons partly obscured by the signals of the 11-Me and C12-H₃ methyl groups. Of greater significance to the stereochemical assignment of (1.8a) was the alkenic region of the spectrum, which exhibited seven distinct proton resonances. Clearly visible was the ABX pattern associated with protons H_A, H_B and 2-H (the X component). From the magnitude of the coupling constants, H_A and H_B were readily assigned and analysis of the two upfield doublet of doublets present in the spectrum easily distinguished the 6.41 ppm multiplet as the 2-H resonance. The remaining upfield doublet of doublets was assigned, by

default, as the internal methine proton H-5. The magnitude of the coupling constant (15.2 Hz) established the geometry of the 5,6-double bond as *trans* and by association identified the 6-H resonance at 5.80 ppm. The remaining downfield doublet, at 6.08 ppm, was attributed to the 4-H proton. This alone, however, did not confirm the *E*-stereochemistry of the trisubstituted double bond between C3 and C4. This was achieved by comparison with the ^1H NMR spectra of 3-methyl-1,3*E*,5-hexatriene (**1.26a**) and 3-methyl-1,3*Z*,5-hexatriene (**1.26b**) (Figure 1.4) which confirmed the presence of the anticipated 3*E*-triene. The 4-H chemical shift of (**1.8a**) ($\delta_{4\text{-H}} = 6.08$ ppm) was in excellent agreement with 4-H shift observed in the *trans* model system (**1.26a**) ($\delta_{4\text{-H}} = 6.08$ ppm).⁶⁴



Figure 1.4

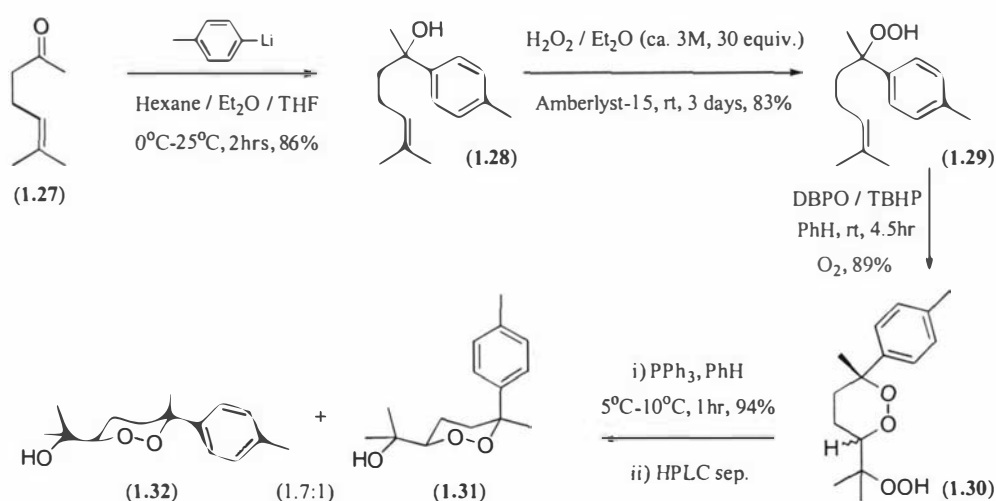
Of even greater diagnostic value was the large chemical shift difference observed between the 2-H proton resonances of 3-methyl-1,3*E*,5-hexatriene (**1.26a**) and 3-methyl-1,3*Z*,5-hexatriene (**1.26b**). For the 3*Z*-isomer, the distinctive 2-H doublet of doublets is shifted over 0.5 ppm downfield relative to its 3*E* isomer. This distinctive shift was used to identify the presence of the minor isomeric 3*Z*-triene (**1.8b**) and has since proved invaluable in the quantification of 3*Z*-methyltriene isomers formed in other product mixtures. An equally dramatic stereochemical dependency is observed in the ^{13}C NMR for the chemical shift of C2.⁶⁴

^{13}C NMR analysis of conjugated trienol (**1.8a**) confirmed the presence of one major stereoisomer, exhibiting 15 carbon resonances. (Table 1.1b) The appearance of eight alkenic signals; two quaternary, five methines and one methylene, was fully consistent with a structure containing four double bonds, two of which are trisubstituted. The C2 resonance at $\delta = 141.1$ ppm agreed well with the model system (**1.26a**) and supported the assignment of (**1.8a**) as the 3*E*-isomer. The oxygenated quaternary carbon (C7) appears at *ca.* 73 ppm. ^1H and ^{13}C NMR assignments were confirmed by COSY and HMQC experiments and comparison with reported data.^{54,56}

1.2.3 The Synthesis of Farnesene Hydroperoxides.

The acid-mediated conversion of alcohols into hydroperoxides is a particularly efficient process if the intermediate carbocation is stabilised by electron donating groups or resonance. As such, the formation of tertiary benzylic and tertiary allylic hydroperoxides from an alcoholic precursor has been well documented.¹⁹

This mode of reactivity has been utilised by Boukouvalas and co-workers in a recent racemic synthesis of the antimalarial agent yingzhaosu C (**1.31**).⁶⁵ (Scheme 1.5) The tertiary benzylic alcohol (**1.28**) was prepared by addition of *p*-tolyllithium to 6-methyl-5-hepten-2-one (**1.27**) which, in the presence of Amberlyst-15 (an acidic resin) and anhydrous hydrogen peroxide, was converted to the benzylic hydroperoxide (**1.29**) in an isolated yield of 83%.



Scheme 1.5

The formation of peroxy radicals from the benzylic hydroperoxide (**1.29**) and cyclisation onto the proximate alkene was crucial for the success of this approach and a variety of conditions for the formal homolysis of the hydroperoxide O-H bond were investigated. Peroxy radical formation was successfully achieved in the presence of di-*t*-butylperoxylate (DBPO) (0.5 equivalents) and *t*-butyl hydroperoxide (*t*BHP) (10 equivalents) at room temperature in benzene under an oxygen atmosphere. Cyclisation to generate an intermediate carbon centred radical ensued and rapid oxygen entrapment and hydrogen atom abstraction gave the endoperoxide hydroperoxides (**1.30**) as a mixture of diastereoisomers in good yield. Selective reduction of the hydroperoxide and

chromatographic separation gave the diastereomerically pure endoperoxy alcohols (1.31) and (1.32). Comparison with naturally occurring material confirmed the relative stereochemistry of yingzhaosu C as the *cis*-diastereoisomer (1.31).

Boukouvalas' synthesis of yingzhaosu C suggested that a similar strategy for the preparation of farnesene autoxidation products may prove equally effective. The conversion of the conjugated allylic trienol (1.8a) to its hydroperoxide (1.7a) was therefore investigated.

1.2.3.1 Anhydrous Hydrogen Peroxide.

The hydroperoxidation of tertiary alcohols in acidic medium is often achieved with anhydrous hydrogen peroxide in diethyl ether. This reagent is normally prepared by the laborious and potentially hazardous ethereal extraction of concentrated aqueous hydrogen peroxide solutions.⁶⁶ Alternative sources of hydrogen peroxide have been reported⁶⁷ and these include complexes with tertiary amines.⁶⁸ It has been noted, however, that some of these crystalline derivatives are explosively unstable.⁶⁹ In contrast, the urea-hydrogen peroxide adduct (UHP) has been shown to be a safe, alternative source of anhydrous hydrogen peroxide^{70,71} that is readily prepared from urea and 30% aqueous hydrogen peroxide.⁷² UHP prepared in this manner has been used as an oxidising agent in a wide range of organic reactions.⁷⁰

UHP was prepared in 36% yield from urea and 30% aqueous hydrogen peroxide according to the method of Lu *et al.*⁷² Iodometric analysis⁷³ of UHP, dried to constant weight over P₂O₅ under vacuum, indicated 34.4% available hydrogen peroxide from a theoretical maximum of 36.2%. The preparation of ethereal solutions of hydrogen peroxide from UHP was investigated. Vigorously stirred suspensions of anhydrous UHP in dry ether gave hydrogen peroxide concentrations of only 0.09 M (\pm 0.01 M) after 1 hour at room temperature as determined by iodometric analysis.⁷³ Extended stirring at room temperature (18 hours) saw no increase in the concentration of hydrogen peroxide. Under identical conditions, however, slurries of anhydrous UHP in dry THF gave hydrogen peroxide concentrations of 0.89 M (\pm 0.01 M) after one hour as determined by iodometric analysis.⁷³ Saturation at *ca.* 0.9 M was observed at room temperature and the resulting solution of hydrogen peroxide in THF could be easily

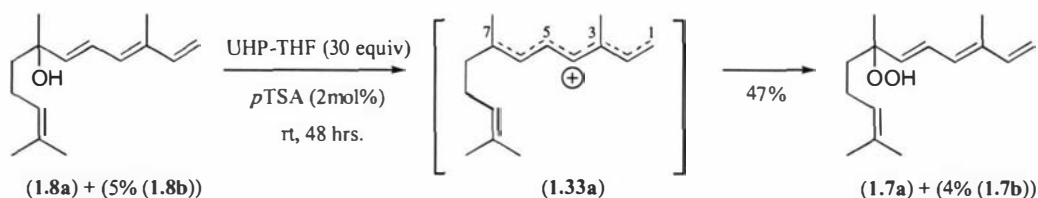
collected by syringe, leaving behind the dense insoluble deposit of urea and undissociated UHP. Other researchers have reported hydrogen peroxide saturation of THF (by UHP) at 0.256 M at room temperature after 40 minutes.⁶⁷ However, no experimental or analytical details were given and a more critical evaluation of this procedure was not possible.

It can be concluded that UHP is a convenient, alternative source of anhydrous hydrogen peroxide, that is both easy to handle and easy to use in the preparation of standard solutions. It should be noted, however, that while no problems were encountered with the use of this reagent, blast shields and appropriate safety equipment were always used when handling anhydrous solutions of H₂O₂.

1.2.3.2 Hydroperoxidation of “Anet’s Trienol”.

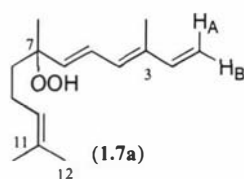
Treatment of conjugated trienol (**1.8a**) (containing *ca.* 5% (**1.8b**)) with anhydrous hydrogen peroxide in THF and Amberlyst-15 gave a complex mixture of products containing numerous peroxidic components, as judged by tlc.[†] In the presence of catalytic *p*-toluene sulfonic acid (*p*TSA) (2 mol%), however, the formation of a single, less polar hydroperoxidic compound was observed. (**Scheme 1.6**) This material exhibited intense UV activity on silica and was easily reduced (when co-spotted with triphenylphosphine) to give a product with the same tlc characteristics as the conjugated trienol (**1.8a**). After 48 hours at room temperature, traces of non-polar dehydration products were also observed so the reaction mixture was partitioned against water and ether and worked up in the usual way. Rapid preparative, centrifugal chromatography under argon afforded the conjugated trienyl hydroperoxide (**1.7a**) as a colourless oil in 47% yield, containing a trace amount of the 3*Z*-isomer (**1.7b**) (*ca.* 4%) as judged by ¹H NMR. Unreacted trienol (**1.8a**) (24%) was also recovered containing the same proportion of the 3*Z*-isomer (**1.8b**) observed in the starting material (*i.e.* *ca.* 5%). This represents the first synthesis of the conjugated trienyl hydroperoxide (**1.7a**).

[†] Many reagents have been reported for the selective detection of peroxides on tlc.⁷⁴ In our hands N,N-dimethyl-*p*-phenylenediamine dihydrochloride⁷⁵ [Reidel-de Haën] proved particularly useful for the selective identification of peroxidic farnesene products formed through either autoxidation or acid catalysed hydroperoxidation.



Scheme 1.6

^1H NMR data for (1.7a) (Table 1.2a) was similar to that obtained for the conjugated trienol (1.8a) and only small chemical shift differences were observed for the majority of signals. The C8-H₂ and C7-Me signals showed a small downfield shift of *ca.* 0.1 ppm relative to the trienol (1.8a). Of particular note, however, was the appearance of the hydroperoxide proton (-OOH) as a sharp singlet at 7.55 ppm.

Table 1.2a ^1H nmr Data for (1.7a)

	1-H _A	1-H _B	2-H	4-H	5-H	6-H	8-H ₂	9-H ₂	10-H	12-H ₃	3-Me	7-Me	11-Me	7-OOH
δ / ppm	5.25	5.08	6.42	6.09	6.59	5.77	1.72	2.02	5.12	1.69	1.90	1.41	1.62	7.55
	d	d	dd	d	dd	d	m	m	m	s	s	s	s	s
J / Hz	17.4	10.6	17.4	11.0	15.4	15.4	-	-	-	-	-	-	-	-

Table 1.2b ^{13}C nmr Data for (1.7a)

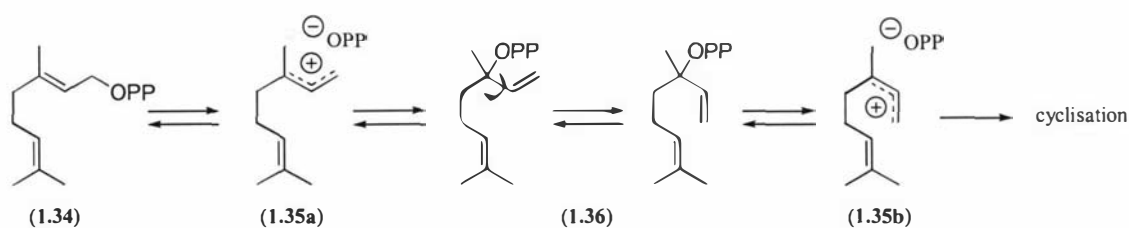
	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	3-Me	7-Me	11-Me
δ / ppm	113.0	140.9	135.9	130.5	127.0	136.6	84.6	37.7	27.5	124.0	132.0	25.7	12.2	21.8	17.7
	t	d	s	d	d	d	s	t	t	d	s	q	q	q	q

The ^{13}C NMR spectrum was fully consistent with structure (1.7a) (Table 1.2b) yet revealed significant differences when compared with the carbon data obtained for the conjugated trienol (1.8a). The oxygenated quaternary carbon (C7) appeared at 84.6 ppm, shifted over 11 ppm downfield relative to its C7 counterpart in (1.8a). Carbon resonances proximate to the hydroperoxide moiety were also shifted relative to the

alcohol, though none as dramatically as C7. Carbons α to C7, *viz.* C6, C8 and 7Me, were shifted upfield by *ca.* 5.5 ppm, while carbons C5 and C9 (β) were shifted downfield, although to a lesser degree (*ca.* 4 ppm). No effects γ to C7 were observed.

The chemo- and regioselectivity of the hydroperoxidation reaction outlined in **Scheme 1.6** was intriguing, as neither cyclised products nor regioisomeric hydroperoxides (*i.e.* oxygenation at C1, C3 or C5) were observed. Furthermore, the proportion of **(1.7b)** generated was similar to the proportion of **(1.8b)** present in the starting material.

To explain the lack of cyclised products, it is necessary to invoke an intermediate heptatrienyl carbocation with C6-C7 *transoid* configuration, *i.e.* **(1.33a)** (**Scheme 1.6**). A similar argument has been advanced to explain the lack of reactivity of linalool **(1.24)** and its derivatives towards cyclisation.⁷⁶ The stereochemical integrity of cations of this type is further highlighted in the biosynthetic conversion of geranyl diphosphate **(1.34)** into cyclic monoterpenes.^{77,78} (**Scheme 1.7**) This transformation takes place by a stepwise sequence of enzyme-assisted events, involving ionisation to a *transoid* carbocation **(1.35a)**, ion recombination to form linalyl diphosphate **(1.36)**, C-C single bond rotation and subsequent ionisation to form the *cisoid* cation **(1.35b)**; a species which can attain the necessary geometry for cyclisation. An analogous sequence of events has been proposed in the sesquiterpene series.⁷⁹

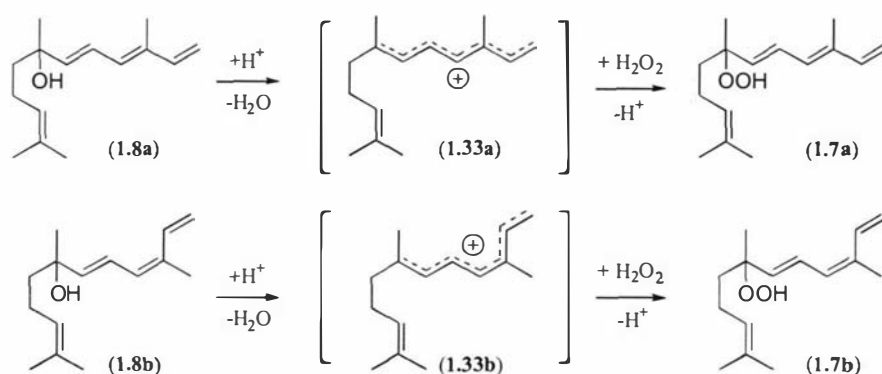


Scheme 1.7

Thus, for the conversion of **(1.8a)** into cyclic products, addition of the isolated, pendant C=C double bond to the heptatrienyl carbocation moiety would require a C6-C7 *cisoid* arrangement of the delocalised carbocation (*cf.* **(1.35b)**) which, in turn, necessitates the adoption of a much less favourable conformation of protonated alcohol **(1.8a)** during the departure of H₂O.

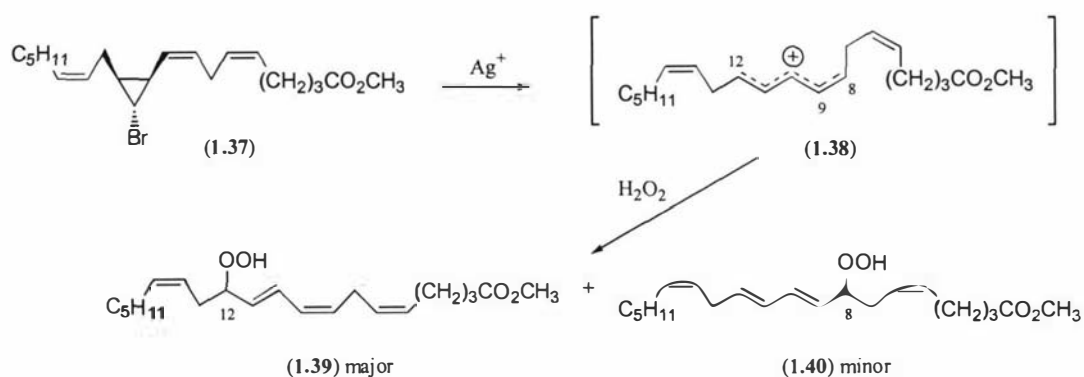
The absence of the three other possible regioisomeric hydroperoxide products in the reaction between (1.8a) and anhydrous hydrogen peroxide (Scheme 1.6) can also be rationalised. It is likely that the formation of an intermediate heptatrienyl carbocation (1.33a) which retains the maximum degree of conjugation is favoured in a fashion which is analogous to the formation of polyenic peroxy radicals noted earlier.²¹ Furthermore, steric effects notwithstanding, trapping of an intermediate cation with an appropriate nucleophile would be expected to occur at the terminus of the conjugated system which contributes the larger degree of carbocationic character. Hydroperoxidation at the tertiary centre C7 satisfies both these expectations. Nonetheless, this observation did raise the issue of whether regioisomers of trienol (1.8a), which might also serve as precursors to the heptatrienyl cation (1.33a), could also be transformed into the 7-hydroperoxide (1.7a) and thereby allow a more streamlined synthesis of this valuable α -farnesene autoxidation product. This hypothesis has been investigated and is discussed in Chapter 2.

To explain the apparent stereochemical integrity of the hydroperoxide mixture (1.7a) and (1.7b) with respect to the starting material (1.8a) and (1.8b), it is suggested that the formation of any intermediate heptatrienyl carbocation species involved in this transformation occurs stereospecifically. Thus, loss of water from protonated (1.8a) generates the C3-C4 *transoid* heptatrienyl carbocation (1.33a), while loss of water from protonated (1.8b) generates the isomeric C3-C4 *cisoid* heptatrienyl carbocation (1.33b). (Scheme 1.8) Moreover, trapping of these non-interconverting carbocations with H₂O₂ at C7 is also a stereospecific process. This is discussed more fully in Chapter 2.



Scheme 1.8

The formation of carbocations of specific geometry has been reported by Porter.^{19,80,81} The symmetry controlled, silver ion-mediated ring opening of the 2-vinyl-1-bromocyclopropane (1.37) gave the C8-C9 *cisoid* pentadienyl carbocation (1.38) which, in the presence of anhydrous ethereal hydrogen peroxide, gave a 2:1 mixture of the conjugated dienyl hydroperoxides (1.39) and (1.40). (Scheme 1.9) The absence of a tertiary position at the termini of Porter's conjugated carbocation (1.38) saw a reduction in the regioselectivity of the nucleophilic addition process and reaction at both ends of the cation (1.38) was observed. Nonetheless, trapping of the intermediate C8-C9 *cisoid* carbocation (1.38) at C12 occurred preferentially to give the 12-HPETE methyl ester (1.39) as the major product with 8*Z*-stereochemistry.



Scheme 1.9

With access to milligram quantities of the conjugated trienyl hydroperoxide (1.7a) (albeit containing *ca.* 4% of the stereoisomeric hydroperoxide (1.7b)) it was possible to explore the formation of the endoperoxy hydroperoxide (1.11a).

1.2.4 The Synthesis of Farnesene Endoperoxides.

The mechanism presented by Anet¹⁸ for the autoxidation of α -farnesene suggested the intermediacy of peroxy radical species such as (1.6a). (Scheme 1.1) Later work by Porter²¹ demonstrated the importance of peroxy radicals in all forms of autoxidation and, in particular, during the autoxidation of unsaturated lipids. The significance of this chemistry has spurred researchers to investigate ways to prepare peroxy radicals (ROO^*) by chemical means.^{19,82}

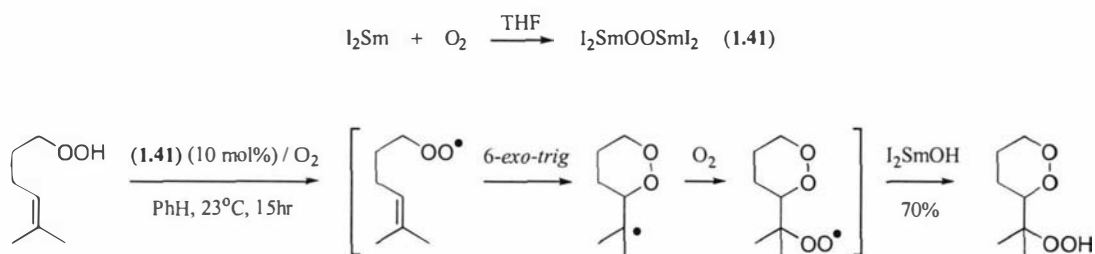
1.2.4.1 Formation of Farnesene Peroxy Radicals

It was anticipated that the formation of a peroxy farnesene radical (**1.6a**) through chemical means would, in the presence of molecular oxygen, mimic the radical cascade postulated by Anet in the autoxidation of α -farnesene. Control of this process would thus lead to a useful synthesis of the endoperoxy hydroperoxide (**1.11**).

The synthesis of the antimalarial agent yingzhaosu C (**1.31**) has been reported by Boukouvalas⁶⁵ and has been outlined in **Scheme 1.5**. (section 1.2.3) The success of this approach relied on the controlled formation of an intermediate peroxy radical from a hydroperoxide precursor with the radical initiator di-*t*-butylperoxylate (DBPO). As suggested earlier, the application of a similar strategy in the formation of farnesene radical species might be equally effective. In deference to the explosive nature of DBPO,^{65,83} however, an alternative, safer peroxy radical initiator was sought.

1.2.4.2 “Samarium Peroxide”.

Corey and Wang have reported a samarium-based protocol for the preparation of peroxy radicals.⁸² In the presence of a stoichiometric equivalent of molecular oxygen, samarium diiodide⁸⁴ (SmI_2) is instantly discoloured to give a pale yellow solution of “samarium peroxide” (**1.41**). (**Scheme 1.10**) Tentatively assigned the structure $\text{I}_2\text{SmOOSmI}_2$, Corey showed this material to be an effective catalyst for the formation of peroxy radicals from hydroperoxidic precursors. While the mechanism by which this reagent initiates peroxy radical formation is unknown, it has been suggested that $\text{I}_2\text{SmO}^\bullet$ radicals are responsible for the selective abstraction of H^\bullet from the hydroperoxide moiety.⁸²

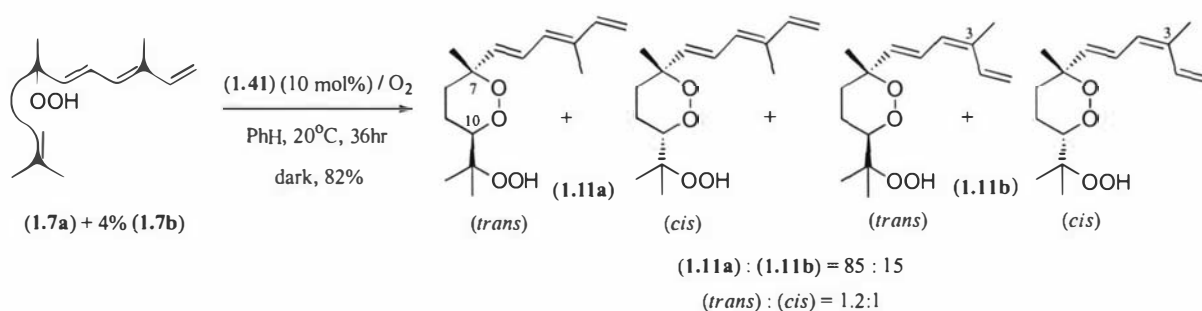


Scheme 1.10

Corey also demonstrated that under these conditions, peroxy radicals generated from hydroperoxides bearing suitably positioned alkenyl substituents undergo smooth *6-exo-trig* radical cyclisation to ultimately afforded endoperoxy hydroperoxides. (Scheme 1.10) Indeed, Boukouvalas⁶⁵ investigated the use of (1.41) in the synthesis of yingzhaosu C and, while it proved successful (79%), was abandoned in favour of the higher yielding (89%), yet more hazardous DBPO protocol. Nonetheless, “samarium peroxide” (1.41) was investigated as an initiator in the formation of farnesene peroxy radicals in the synthesis of the endoperoxy hydroperoxides (1.11).

1.2.4.3 Synthesis of Endoperoxy Hydroperoxides.

In the presence of 10 mol% “samarium peroxide” (1.41) under an oxygen atmosphere in benzene at room temperature, the conjugated trienyl hydroperoxide (1.7a) (containing *ca.* 4% of the 3*Z*-isomer, (1.7b)) was converted to the farnesene endoperoxy hydroperoxides (1.11a) and (1.11b) in a combined, isolated yield of 82%. (Scheme 1.11) An enrichment of the minor 3*Z*-triene component was observed (with respect to the starting material) with (1.11b) comprising 15% of the product mixture. Detailed ¹H NMR analysis of the chromatographed material indicated the isomeric trienes (1.11a) and (1.11b) were both present as a mixture of two undetermined diastereomers[†] in the ratio of 1.2:1.



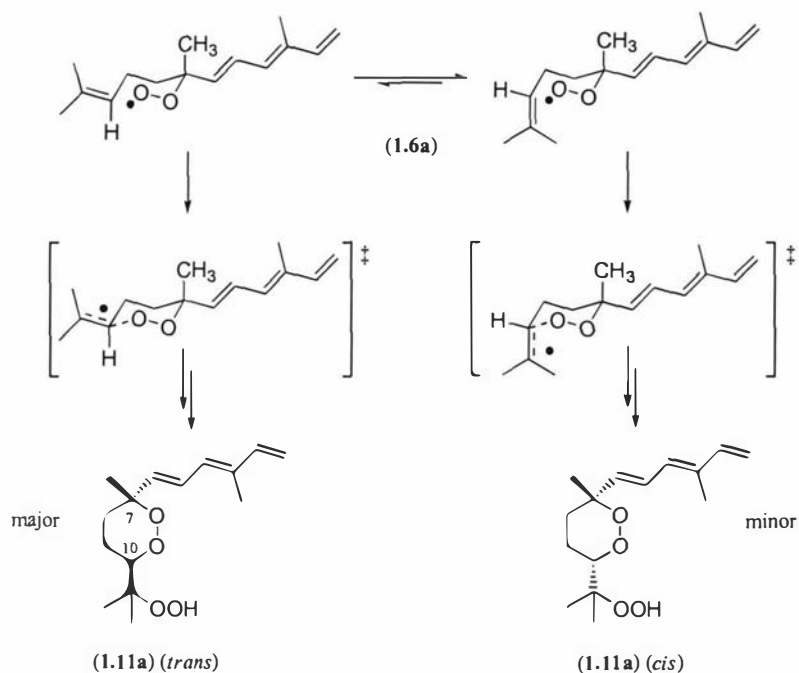
Scheme 1.11

The hydroperoxide (-OOH) and the alkenic signals of the major 3*E*-trienes (1.11a) were clearly resolved for both diastereoisomers. In contrast, however, most of the alkenic and all of the aliphatic signals of the minor 3*Z*-trienes (1.11b) were obscured by the major isomer (1.11a). Nonetheless, the hydroperoxide protons (-OOH) and the

[†] Due to the relative instability of the endoperoxy hydroperoxides (1.11a) and (1.11b) a detailed stereochemical analysis by ¹³C NMR was carried out using the endoperoxy alcohols (1.12a) and (1.12b). See section 1.2.4.4.

characteristic 2-H protons of the 3*Z*-trienes (**1.11b**) were well resolved for both diastereoisomers and the composition of the product mixture could therefore be determined.

Low levels of diastereoselectivity in peroxy radical cyclisations of this type have been reported by Porter.⁸⁵ Porter concluded that the observed diastereoselectivity could be best explained by assuming a chair-like transition state, where the bulkier substituents (in this instance destined for the C7- and C10-positions of the newly forming endoperoxide) preferentially adopt equatorial like orientations. Cyclisation of the peroxy radical (**1.6a**) through a chair-like transition state which places the bulky trienyl and isopropenyl “substituents” in a *trans* relationship is therefore expected to yield the major farnesene endoperoxide, i.e. (**1.11a trans**). (Scheme 1.12) Conversely, cyclisation *via* a more sterically encumbered transition state, where these “substituents” are *cis* to one another, is likely to be less favoured and lead to the minor isomer, i.e. (**1.11a cis**). A similar observation was reported by Boukouvalas during the synthesis of yingzhaosu C (**1.31**) (Scheme 1.5),⁶⁵ where peroxy radical cyclisation gave the *trans* isomer as the major product (*trans:cis* = 1.7:1).



Scheme 1.12

The difference in stereochemistry between the 3*E* and 3*Z*-triene moieties of (**1.7a**) and (**1.7b**) respectively appeared to have no effect on the diastereoselectivity of the radical

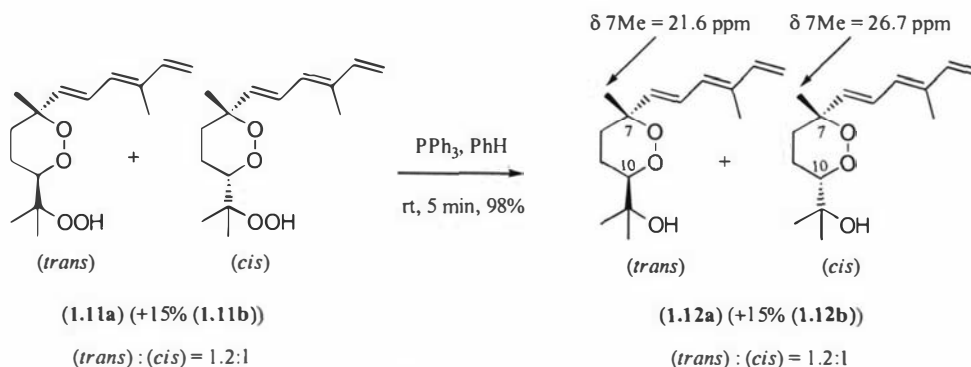
cyclisation and the product distribution of *cis* and *trans* isomers was the same in the minor 3*Z*-trienyl endoperoxide (**1.11b**) as in the 3*E*-triene (**1.11a**).

While it is possible to rationalise the observed diastereoselectivity of the radical cyclisation, it is more difficult to explain the enrichment of 3*Z*-trienes in the product mixture (15%) with respect to the starting material (4%). The selective loss of the 3*E*-triene species is unlikely, especially in view of the reaction's high yield (82%). The possible stereochemical consequences of peroxy radical formation are, however, discussed in section 2.4 and may offer an explanation for this observation.

1.2.4.4 Synthesis of Endoperoxy Alcohols.

The selective reduction of the endoperoxide mixture (**1.11a**) and (**1.11b**) was achieved with triphenylphosphine in benzene at room temperature. This transformation gave the endoperoxy alcohols (**1.12a**) and (**1.12b**) in near quantitative yield without affecting either the diastereomeric ratio (*trans*:*cis* = 1.2:1) or the 3*E*:3*Z* ratio (85:15). (Scheme 1.13)

It is known that in the chair conformation, the axial methyl substituent of *cis*-1,4-dimethylcyclohexane has a chemical shift (in the ¹³C NMR spectrum) that is *ca.* 4 ppm upfield of the chemical shift of the equatorial methyl substituents in the *trans*-1,4-dimethyl isomer.^{86,87} Furthermore, it is also known that six membered endoperoxides (1,2-dioxanes) exist in stable chair-like conformations that are similar to their carbocyclic analogues.⁸⁸ Thus, by analysis of substituent chemical shifts, it is possible to determine the relative stereochemistry of 1,4-disubstituted, six membered endoperoxides.⁸⁹ This technique has been used to assign the relative stereochemistry of numerous marine and other naturally occurring endoperoxides^{65,89-91} and can also be used to assign the relative stereochemistry of the endoperoxy alcohols (**1.12a**) and (**1.12b**).



Scheme 1.13

^{13}C NMR analysis of the relatively stable endoperoxy alcohols (1.12a) and (1.12b) indicated that the C7-methyl (7Me) resonance of the major isomer appeared *ca.* 5 ppm upfield of the minor component. It was therefore concluded that the C7-methyl substituent of the major isomer was axial and *cis* to the equatorially disposed bulky hydroxyisopropyl substituent at C10. It is important to note, however, that in defining the relative stereochemistry of the endoperoxides (1.12a) (and (1.12b)), the C7-methyltriene moiety takes preference over the smaller C7-methyl substituent. Hence, the major diastereoisomer has been assigned as the *trans*-isomer (1.12a), i.e. with a *trans*-relationship between the trienyl- and hydroxyisopropyl-substituents across the endoperoxide ring. These assignments are fully consistent with the predicted stereochemical outcome of the peroxy radical cyclisation suggested by Porter.⁸⁵

1.3 Biological Activity of α -Farnesene Autoxidation Products.

To assess the scald inducing properties of the synthetic α -farnesene autoxidation products prepared in the course of this study, samples of these materials were exposed to the surface coatings of various apple cultivars. Preliminary results suggest that either by direct application to the skin, or upon expose to the volatilised synthetic materials, the conjugated trienols (1.8a) and (1.8b) are the most effective agents for the induction of superficial scald. The conjugated trienyl hydroperoxides (1.7a) and (1.7b) also induce scald, but less efficiently than the trienols (1.8a) and (1.8b). These observations are consistent with earlier findings, which showed that the conjugated trienols (1.8a) and (1.8b) constitute the bulk of “trienes” found in apples^{25,27} and that the incidence of superficial scald correlates more closely with the concentration of these “trienes” (as measured by UV) than with the concentration of α -farnesene itself.^{2,14,16,26} Indeed, other preliminary results suggest that farnesene endoperoxides, *viz.* (1.11), which appear

only as minor components in the surface coatings of stored apples,²⁵ show little activity in the induction of superficial scald. A detailed analysis of scald induction and dose responses for the synthetic α -farnesene autoxidation products described above, together with other scald causing agents, is currently in preparation.⁹²

1.4 Conclusions.

Access to α -farnesene autoxidation products has previously been limited to the conjugated trienol (**1.8a**) and the endoperoxy alcohol (**1.12a**), both containing small yet varying proportions of the isomeric 3Z trienes (**1.8b**) and (**1.12b**) respectively. These materials were prepared from α -farnesene by either direct autoxidation¹⁸ (**Scheme 1.1**) or through low yielding and poorly regioselective chemical oxidation processes.⁵⁶ (**Scheme 1.2**) New methodology has been developed for the synthesis of the conjugated trienol (**1.8a**) (**Scheme 1.4**), granting access to quantities of material suitable for biological evaluation. Furthermore, the conjugated trienol (**1.8a**) has proved a key intermediate in the formation of the remaining α -farnesene autoxidation products identified by Anet¹⁸ and quantities of these materials sufficient for biological testing have also been prepared.

UHP has been utilised as a safe and practical source of anhydrous hydrogen peroxide and this reagent has been used in the acid-catalysed hydroperoxidation of trienol (**1.8a**). (**Scheme 1.6**) The trienyl hydroperoxide (**1.7a**) was isolated in good yield and represents the first synthesis of this highly labile α -farnesene autoxidation product. Corey's recently reported samarium-based protocol⁸² for the generation of peroxy radicals under mild conditions was effective in transforming the hydroperoxide (**1.7a**) into the endoperoxy hydroperoxides (**1.11a**) and (**1.11b**). (**Scheme 1.11**) This result demonstrated that the peroxy radical (**1.6a**), proposed originally by Anet as an intermediate in the autoxidation of α -farnesene,¹⁸ does indeed undergo smooth cyclisation in the presence of oxygen to ultimately afford farnesene endoperoxides. The selective reduction of the hydroperoxide moiety in the presence of the endoperoxide gave the more stable endoperoxy alcohols (**1.12a**) and (**1.12b**) thereby completing the synthesis of the required α -farnesene autoxidation products. (**Scheme 1.13**)

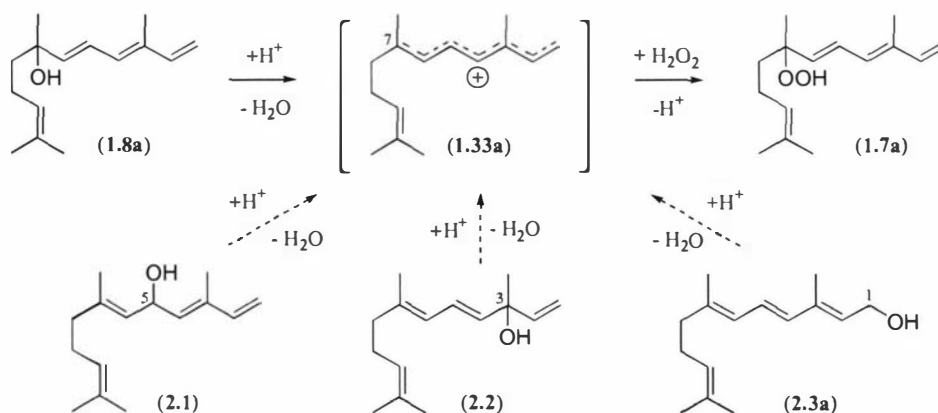
The appearance of minor isomeric 3*Z*-trienyl components was observed throughout the transformations described above. In general, the reactivity noted for the major 3*E*-isomers, was mirrored by the minor components. The enrichment of 3*Z*-trienes, however, under conditions of peroxy radical formation is anomalous and has yet to be explained.

Chapter 2

Oxygen Transposition Reactions in the Farnesene System.

2.1 Introduction

Transformation of Anet's trienol (**1.8a**) into the trienyl hydroperoxide (**1.7a**) was a remarkably selective process. (**Scheme 2.1**) Neither cyclised products nor regioisomeric hydroperoxides were observed. It was concluded that in the presence of anhydrous hydrogen peroxide and an acid catalyst, loss of water from the protonated alcohol (**1.8a**) generated a stabilised heptatrienyl carbocation intermediate (**1.33a**) that reacted only at C7. From this result it was suggested that formation of the same intermediate carbocation (**1.33a**) by other means would, in the presence of anhydrous hydrogen peroxide, also yield the hydroperoxy triene (**1.7a**) in what could potentially be a more streamlined approach to the α -farnesene autoxidation products discussed in **Chapter 1**.



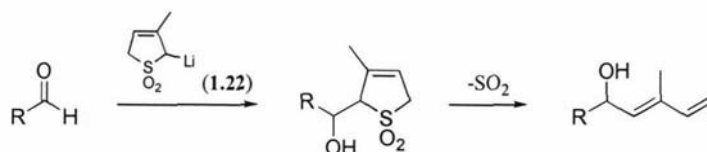
Scheme 2.1

The regioisomeric allylic alcohols (**2.1**), (**2.2**) and (**2.3a**) were considered likely precursors to the heptatrienyl carbocation (**1.33a**). (**Scheme 2.1**) Thus, alcohols (**2.1**) (**2.2**) and (**2.3a**) were synthesised and their reaction with anhydrous hydrogen peroxide under acidic conditions was investigated.

2.2 Carbocation Precursors.

2.2.1 Synthesis of the Secondary Allylic Alcohol (2.1).

In **Chapter 1** the farnesene epoxide (**1.17**) was prepared by the regioselective alkylation of 2-lithio-3-methyl-3-sulfolene (**1.22**) with the epoxyiodide (**1.21**) in the presence of TMEDA. Cheletropic elimination of sulfur dioxide from the resultant 2,3-disubstituted 3-sulfolene (**1.25**) furnished the epoxide (**1.17**). (**Scheme 1.4**) In an extension of this methodology, the 1,2-addition of 2-lithio-3-methyl-3-sulfolene (**1.22**) to geranial (**2.4**) would grant access to a 2,3-disubstituted sulfolene from which the allylic secondary alcohol (**2.1**) could be obtained. This general approach has been used by other workers and has proved to be a powerful synthetic method for the formation of 5-hydroxy-1,3-dienes.⁹³⁻⁹⁷ (**Scheme 2.2**)

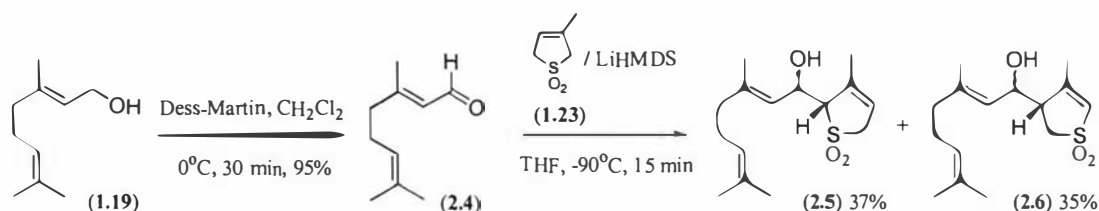


Scheme 2.2

While the alkylation of 2-lithio-3-methyl-3-sulfolene (**1.22**) with alkyl iodides is generally conducted at low temperature in the presence of a suitable co-solvent,⁶² the addition of sulfolene anions, *viz.* (**1.22**), to carbonyl compounds is best achieved under “Barbier” type conditions with⁹⁷ or without⁹⁴⁻⁹⁶ co-solvents. This involves the generation of a nucleophilic sulfolene anion in the presence of an electrophile (the aldehyde). Suitable bases used for this purpose include lithium hexamethyldisilazide (LiHMDS) and lithium diisopropylamide (LDA). This process is operationally easy to perform and does not require rigorously controlled low temperature conditions to prevent unwanted ring opening of the sulfolene anion. (See section 3.3.2, **Chapter 3**) This strategy was adopted for the synthesis of the secondary allylic alcohol (**2.1**).

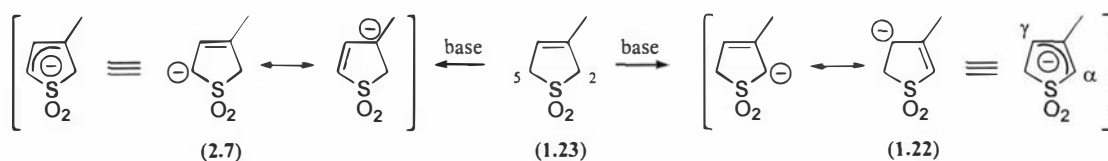
Oxidation of geraniol (**1.19**) with the Dess-Martin periodinane⁹⁸ gave geranial (**2.4**) in 95% yield after purification by short path distillation under reduced pressure (Kugelrohr). (**Scheme 2.3**) Generation of 2-lithio-3-methyl-3-sulfolene (**1.22**) (from 3-methyl-3-sulfolene (**1.23**)⁹⁹ and LiHMDS in THF at -90°C) in the presence of geranial

(**2.4**) gave a mixture of the two regioisomeric secondary allylic alcohols (**2.5**) and (**2.6**). Flash chromatography readily separated the isomers and ^1H NMR analysis revealed the desired 1,2-addition product (**2.5**) as a *ca.* 2:1 mixture of diastereoisomers. Separation of the diastereoisomers was not necessary as the cheletropic elimination of sulfur dioxide from (**2.5**) was expected to remove the stereocentre borne by the sulfolene ring. ^1H NMR analysis of the remaining isomer (**2.6**) revealed a *ca.* 1:1 mixture of diastereoisomers. No 5-alkylated 3-sulfolene products were observed.



Scheme 2.3

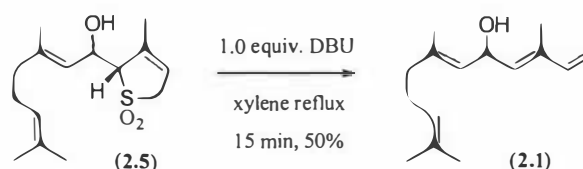
The reaction of 3-methyl-3-sulfolene (**1.23**) with other unsaturated aldehydes has been reported and under these conditions both α - and γ -alkylated products (*viz.* (**2.5**) and (**2.6**)) have been observed.^{94,96} Deprotonation of 3-methyl-3-sulfolene (**1.23**) at the 2-position generates the stabilised allylic carbanion (**1.22**), which can be drawn as two contributing canonical forms. (Scheme 2.4) Alkylation at either the α - or γ -termini of the allyl carbanion is possible, although α -alkylation is favoured at lower temperatures as a consequence of charge localisation.^{94,96} Comparable regioselectivity has also been observed in the reaction of acyclic allylic sulfone carbanions with unsaturated ketones at low temperature.¹⁰⁰



Scheme 2.4

As an aside, it is possible to rationalise the regioselective formation of 2-alkylated 3-methylsulfolene derivatives over their 5-alkylated analogues by considering the relative stability of the sulfolene carbanions (**1.22**) and (**2.7**) in terms of their contributing canonical forms. (Scheme 2.4) Deprotonation of 3-methyl-3-sulfolene (**1.23**) at the 2-position generates the carbanion (**1.22**) stabilised through resonance forms with

secondary carbanion character, whereas removal of a proton from the 5-position of (1.23) gives an allylic carbanion (2.7) that has significant tertiary character. It is likely that this tertiary character destabilises (2.7) with respect to (1.22), at least with electron donating substituents at the 3-position, and favours the regioselective deprotonation of 3-methyl-3-sulfolene at the 2-position. Indeed, it has been observed that 3-sulfolene derivatives bearing electron withdrawing substituents at the 3-position favour 5-alkylation.⁹⁷ Under these circumstances γ -alkylation is not observed, probably due to steric factors and charge localisation. (See section 3.3.2, Chapter 3)



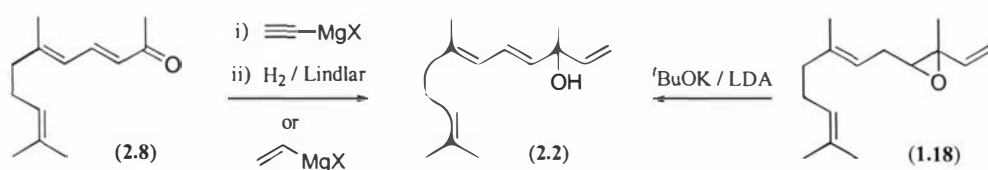
Scheme 2.5

Thermolysis of sulfolene (2.5) in refluxing, degassed xylene resulted in significant decomposition of the starting material and none of the desired alcohol (2.1) was isolated. However, in the presence of one molar equivalent of 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU), thermolysis of sulfolene (2.5) in refluxing xylene under argon gave the secondary allylic alcohol (2.1) in 50% yield. The thermolysis of sulfolene (2.5) in the presence of other bases (K_2CO_3 and $KHCO_3$) was unsuccessful. To prevent decomposition and uncontrolled rearrangement of (2.1), purification on silica was carried out with eluting solvents containing triethylamine (0.1% v/v). ^{13}C NMR analysis of the freshly chromatographed allylic alcohol (2.1) indicated the presence of only one isomeric diene ascribed, through symmetry considerations of the elimination process, as the 3*E*-diene.

The transformation of sulfolene (2.5) to the conjugated dienol (2.1) in the absence of any basic co-solvents has been reported, albeit in 13% yield.⁵⁶ In our hands, the presence of DBU proved essential. Pyridine⁹⁵ and pyridine/DBU mixtures⁹³ have also been employed to facilitate elimination from sulfolene derivatives in related systems and are believed to act as scavengers for SO_2 liberated during the course of the reaction.

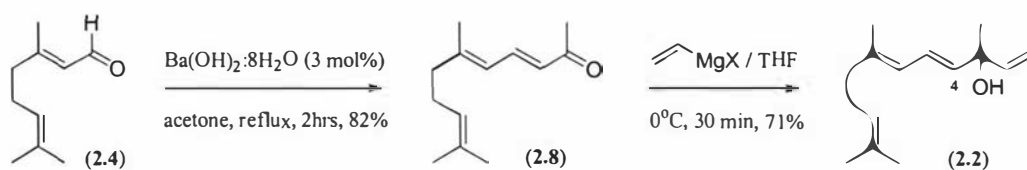
2.2.2 Synthesis of the Tertiary Allylic Alcohol (2.2).

The tertiary allylic alcohol (2.2) has received considerable synthetic interest as an important intermediate in the synthesis of carotenoids.^{101,102} It has also been identified as a constituent of *Brickellia californica* oil (Californian aster oil).¹⁰³ Several synthetic approaches to this material exist and the majority involve addition of a nucleophilic two carbon fragment to pseudoionone (2.8).^{101,104} (Scheme 2.6) Alcohol (2.2) has also been prepared by the base catalysed β -fragmentation of the farnesene epoxide (1.18),⁵⁶ however synthesis of this precursor is low yielding and poorly regioselective (section 1.2.1, Chapter 1). In light of the very low yielding route to (1.18) and no obvious means of improving the regioselectivity of α -farnesene oxidation, a modification of the pseudoionone approach to (2.2) was investigated.



Scheme 2.6

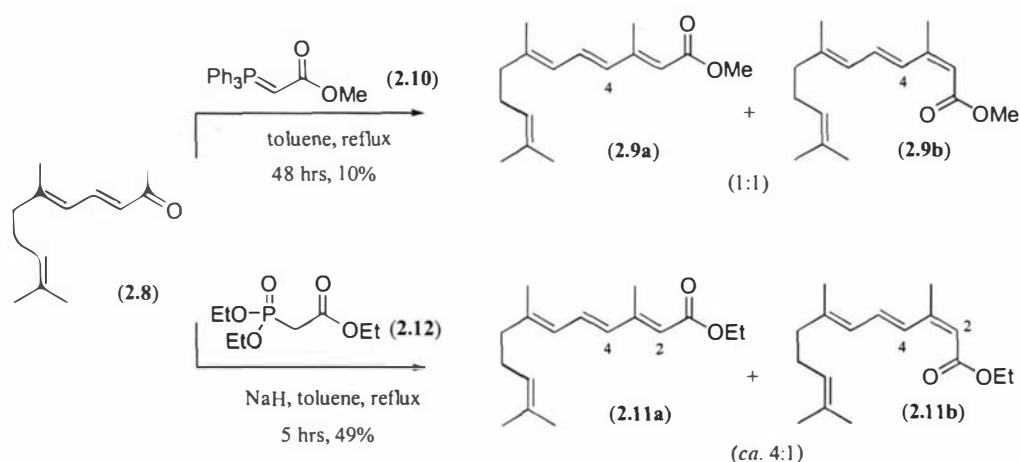
Pseudoionone (2.8) was prepared in 82% yield from geranial (2.4) and acetone. The use of 3 mol% $\text{Ba}(\text{OH})_2$ ¹⁰⁵ gave higher yields than previously reported procedures involving sodium ethoxide¹⁰⁶ and had the additional advantage of being operationally easier to perform. The stereochemistry of the newly formed double bond was confirmed as *trans* by the presence of a 15.4 Hz coupling constant in the ^1H NMR spectrum. The addition of vinyl magnesium bromide to pseudoionone (2.8) gave the desired tertiary allylic alcohol (2.2) in 71% yield after purification by chromatography. Allylic alcohol (2.2) prepared in this manner was obtained as a single isomer (4*E*, $J = 15.4$ Hz) and data for this compound was consistent with earlier reports.^{56,103}



Scheme 2.7

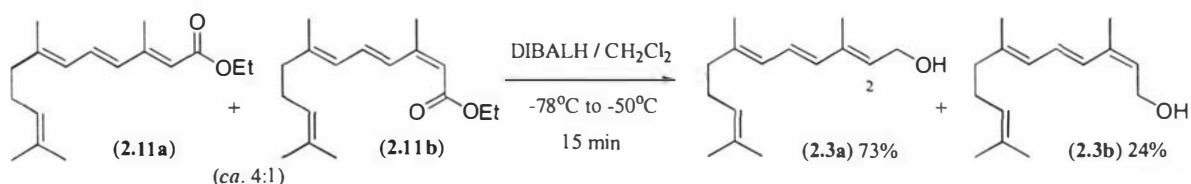
2.2.3 Synthesis of the Primary Allylic Alcohol (2.3a).

The primary allylic alcohol (**2.3a**) (*E,E,E*-4,5-dehydrofarnesol) has been identified as a biosynthetic precursor to the plant hormone abscisic acid and has therefore received some synthetic attention.¹⁰⁷ Alcohol (**2.3a**) was prepared by the diisobutylaluminium hydride (DIBALH) reduction of the all *trans*-methyl dehydrofarnesoate (**2.9a**). The synthesis and characterisation of isomeric dehydrofarnesoate esters, including (**2.9a**), has been studied extensively by Pattenden.^{108,109} This approach was adopted for the synthesis of the primary allylic alcohol (**2.3a**).



Scheme 2.8

The reaction of pseudoionone (**2.8**) with the stabilised ylid methyl (triphenylphosphoranylidene) acetate (**2.10**) in refluxing toluene was slow and showed no stereoselectivity. The methyl esters (**2.9a**) and (**2.9b**) were isolated as a 1:1 mixture in only 10% yield after 48 hours at reflux. However, the Horner-Emmons reaction of pseudoionone (**2.8**) with the anion prepared from triethylphosphonoacetate (**2.12**) and sodium hydride in toluene¹¹⁰ gave a ca. 4:1 mixture of the isomeric conjugated trienoate esters (**2.11a**) and (**2.11b**) respectively, in 49% yield after 5 hours at reflux. (Scheme 2.8) Characterisation and the assignment of stereochemistry for the ethyl ester mixture was readily achieved by comparison with ¹H NMR data for the known methyl esters (**2.9a**) and (**2.9b**).¹⁰⁹ The H-4 proton of the major *2E*-isomer (**2.11a**), appeared as a doublet ($\delta = 6.18$ ppm, $J = 15.2$ Hz) well upfield of the H-4 doublet of the minor *2Z*-isomer (**2.11b**) ($\delta = 7.65$ ppm, $J = 15.4$ Hz). This chemical shift difference was identical to that observed with the methyl esters (**2.9**) and has been well documented.¹⁰⁹



Scheme 2.9

Separation of the ethyl esters (2.11a) and (2.11b) could be achieved by chromatography on silica gel. It proved easier, however, to reduce the ester mixture with diisobutylaluminium hydride (97% yield) and separate the resulting *2E* and *2Z*-allylic alcohols (2.3a) and (2.3b). In this manner the all *trans* primary allylic alcohol (2.3a) was obtained as a single stereoisomer in 73% yield from the mixture of ethyl esters (2.11a) and (2.11b). (Scheme 2.9)

2.3 Transposition Reactions.

With access to workable quantities of the regioisomeric allylic alcohols (2.1), (2.2) and (2.3a) as pure stereoisomers, their oxygen transposition reactions were next investigated. It was anticipated that the acid catalysed elimination of water from the protonated alcohols would, in the presence of anhydrous hydrogen peroxide, yield the trienyl hydroperoxy (1.7a) *via* the regioselective oxygenation of the common extended carbocation intermediate (1.33a). (Scheme 2.1) Furthermore, formation of the intermediate carbocation (1.33a) in the presence of other nucleophiles (i.e. water) would allow access to other conjugated trienes including Anet's trienol (1.8a). The latter was suggested as a route to (1.8a) by Brimble *et al.*⁵⁶ but was not successful in their hands.⁵⁴

2.3.1 Regioselectivity.

Gratifyingly, exposure of the alcohols (2.1), (2.2) and (2.3a) to either anhydrous hydrogen peroxide (UHP-THF) or water, in the presence of *p*TSA at 20°C, resulted in the regioselective transposition of the oxygen functionality to the C7 position only. (Table 2.1) (Entry 1 represents the hydroperoxidation of trienol (1.8a) described in section 1.2.3.2, Chapter 1)

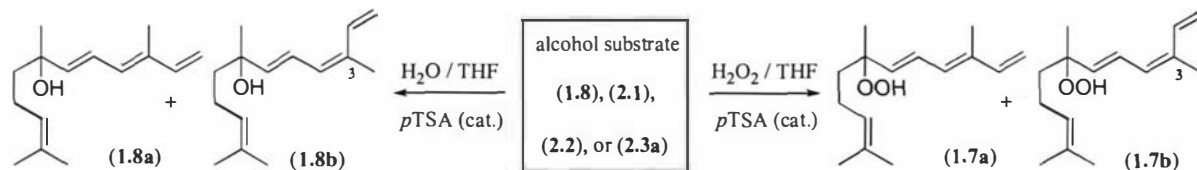


Table 2.1

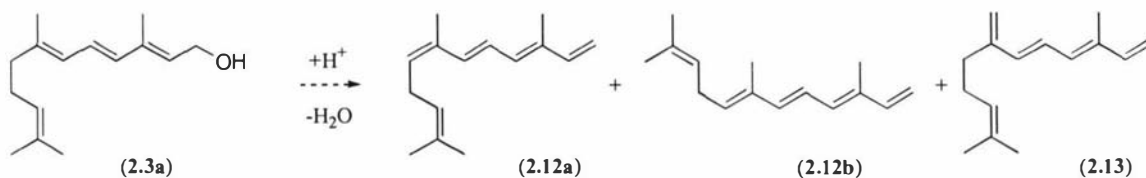
entry	substrate	reagent ^a	time	product	3E:3Z	yield (%)
1	(1.8) ^b	H ₂ O ₂	48 hr	(1.7)	96:4	47 ^c
2	(2.1)	H ₂ O ₂	5 min	(1.7)	>99:1	100
3	(2.1)	H ₂ O	5 min	(1.8)	>99:1	100
4	(2.2)	H ₂ O ₂	6 hr	(1.7)	73:27	100
5	(2.2)	H ₂ O	6 hr	(1.8)	72:28	96
6	(2.3a)	H ₂ O ₂	6 hr ^d	(1.7)	-	trace ^e
7	(2.3a)	H ₂ O	6 hr ^d	(1.8)	87:13	15 ^f
8	(1.8) ^g	H ₂ O ₂	48 hr	(1.7)	69:31	55 ^h

^a 75 equivs. ^b 3E:3Z ratio 95:5. ^c 30 equivs. H₂O₂ used, recovered (1.8) 24% (3E:3Z = 95:5). ^d 2.0 equivs. *p*TSA used. ^e 6-methyl-5-hepten-2-one (1.27) 23% was the major product (see Scheme 2.11). ^f recovered (2.3a) 56% and a mixture of dehydration products 8% were also isolated (see Scheme 2.10). ^g 3E:3Z = 72:28. ^h recovered (1.8) 26% (3E:3Z = 73:27).

For the secondary and tertiary allylic alcohols (2.1) and (2.2) respectively, the transposition reactions proceeded both efficiently and very cleanly (Table 2.1, entries 2 to 5) whereby a simple aqueous work-up afforded spectroscopically pure products. In contrast, the primary allylic alcohol (2.3a) proved unreactive under the standard conditions (2-6 mol% *p*TSA). Under more forcing conditions, however, (2.0 equivalents of *p*TSA) in the presence of water, the allylic alcohol (2.3a) did provide the trienol (1.8a), albeit in a yield of only 15%. (Table 2.1, entry 7) In addition, unreacted starting material (2.3a) (56%) and a mixture of unidentified dehydration products (8%) were also isolated.

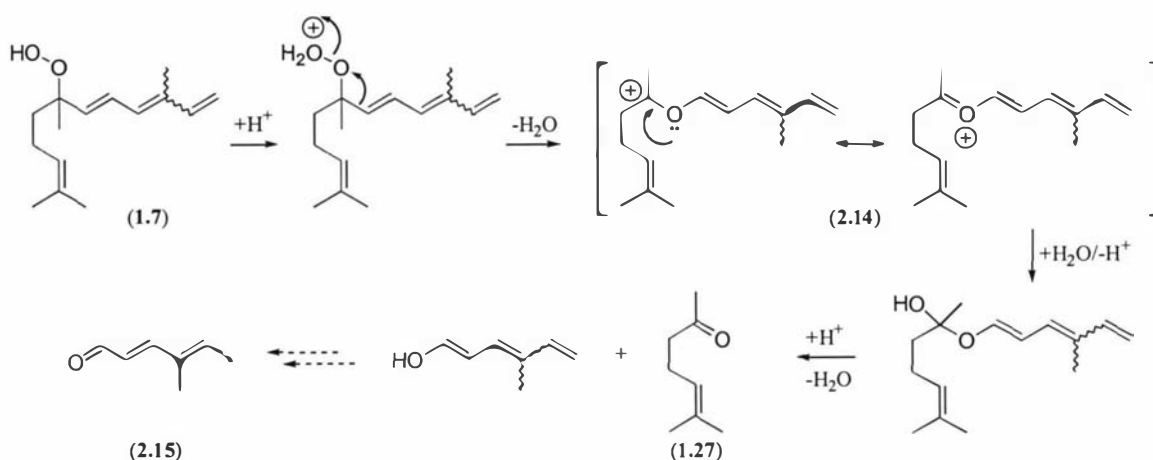
GCMS analysis of the dehydration product mixture indicated the presence of three isomeric hydrocarbons in equal proportions each formulating as C₁₅H₂₂. ¹H NMR analysis of the inseparable mixture, while complex, revealed a broadened quartet (δ = 2.86 ppm) consistent with a pair of overlapping doubly allylic methylene triplets, each similar in appearance to the C5 methylene triplet (δ = 2.82 ppm) observed in α -

famesene (**1.1**).⁵⁵ A complex upfield alkenic region ($\delta = 4.92\text{-}5.26$ ppm) was also observed, suggesting the presence of a 1,1-disubstituted alkene. ^{13}C NMR analysis revealed an equally complex pattern of signals and 44 discrete resonances (29 alkenic and 15 aliphatic) were observed. It is therefore likely that the dehydration products, obtained from (**2.3a**) under the more forcing conditions needed to effect oxygen transposition, are the conjugated tetraenes (**2.12a**), (**2.12b**) and (**2.13**). (Scheme 2.10) These assignments remain speculative.



Scheme 2.10

In the presence of 2.0 equivalents of *p*TSA and anhydrous hydrogen peroxide, alcohol (**2.3a**) gave a complex mixture of products containing only traces of the trienyl hydroperoxides (**1.7a**) and (**1.7b**) as judged by tlc (Table 2.1, entry 6). No reaction was observed with lesser quantities of *p*TSA. The attempted chromatographic isolation of the hydroperoxides (**1.7**) was, however, unsuccessful and only 6-methyl-5-hepten-2-one (**1.27**) was obtained (23%). The ketone (**1.27**) was identified by comparison with commercial material.



Scheme 2.11

The acid catalysed decomposition of hydroperoxides, or Hock cleavage, is well known¹⁹ and involves protonation of the hydroperoxide and C→O migration of an alkyl substituent with concomitant loss of water to generate an intermediate

oxocarocation, *cf.* (2.14). (Scheme 2.11) Hydration of (2.14) yields a hemiacetal, which upon acid catalysed hydrolysis generates a carbonyl compound and an alcohol fragment. The Hock cleavage of the allylic hydroperoxides (1.7) generates an enol, which is likely, under the reaction conditions, to tautomerise to the hexadienal (2.15). Hexadienal (2.15), however, was not observed, perhaps reflecting the volatility and reactivity of this compound.

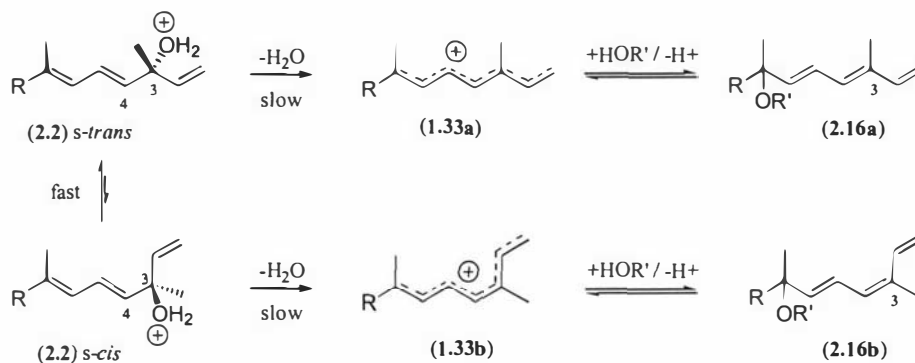
The relatively reactive nature of the allylic alcohols (2.1) and (2.2) towards substitution is due, most likely, to the formation of a significantly more delocalised π -system upon ionisation. From this perspective, the comparatively sluggish reactivity of the more stable conjugated trienols (1.8) and (2.3a) is to be expected. It was concluded that (2.3a) was of limited value as a precursor to α -farnesene autoxidation products as both Hock cleavage of the hydroperoxide (1.7a) and dehydration of the alcohol (1.8a) were competitive with oxygen transposition even when the reactions were quenched at low conversions.

2.3.2 Stereoselectivity.

It was intriguing to note that the transposition product stereochemistry was dependent upon the regiochemistry of the starting material. Thus, the tertiary allylic alcohol (1.8) retained its high stereoisomeric ratio upon hydroperoxidation (Table 2.1, entry 1) and the secondary allylic substrate (2.1) provided single stereoisomeric products with both hydrogen peroxide and water (Table 2.1, entries 2 and 3). In contrast, the tertiary and primary allylic alcohols, (2.2) and (2.3a) respectively, furnished mixtures of 3*E* and 3*Z*-isomers (Table 2.1, entries 4,5 and 6) with differing *E/Z* ratios for each substrate. In all cases 5*E*-alkenes were formed exclusively, as witnessed by a large *trans*-coupling constant (*ca.* 15 Hz) (*cf.* Tables 1.1a and 1.2a). Moreover, the stereochemistry of recovered starting materials from incomplete conversions (Table 2.1, entries 1 and 8) remained unchanged. It is also interesting to note that each substrate afforded the *same stereoisomeric ratio* with either water or anhydrous hydrogen peroxide.

Previously, it was suggested that the stereochemical integrity observed for the hydroperoxidation of (1.8), (i.e. *E/Z* (1.8) \cong *E/Z* (1.7), Table 2.1, entry 1), could be explained by the stereospecific formation and reaction of the intermediate heptatrienyl carbocations (1.33a) and (1.33b). (Scheme 1.8) The stereochemical outcome of the

other transposition reactions described in **Table 2.1** can also be explained by invoking the intermediacy of the same configurationally immobile heptatrienyl carbocationic intermediates (**1.33a**) and (**1.33b**). This is represented for the tertiary allylic alcohol (**2.2**) in **Scheme 2.12**, where $R = C_6H_{11}$ and $R' = H$ or OH .



Scheme 2.12

Free rotation about the C3-C4 carbon-carbon single bond in the alcohol (**2.2**) (and the protonated species derived from it) allows rapid interconversion of all possible conformations. However, to achieve the planar π system of an extended carbocation, loss of water from only two conformations is possible. Water loss from the protonated alcohol (**2.2**) in an *s-trans* conformation about the C3-C4 carbon-carbon single bond generates a carbocation with *transoid* geometry, i.e. (**1.33a**), while loss of water from the corresponding *s-cis* conformer leads to the carbocation with *cisoid* geometry (**1.33b**). Trapping at C7 with an oxygen nucleophile generates the two *3E* and *3Z* stereoisomeric products (**2.16a**) and (**2.16b**) respectively. The carbocations (**1.33a**) and (**1.33b**) are non-interconvertible under the reaction conditions since orbital overlap from C1 through C7 of the heptatrienyl cation precludes bond rotation. Furthermore, it can be argued that if (**1.33a**) and (**1.33b**) were interconvertible under the reaction conditions, the same *E:Z* product ratio would be obtained irrespective of either the starting material's regiochemistry (**Table 2.1**, entries 2-7) or stereoisomeric ratio (**Table 2.1**, entries 1,8).

Further evidence to support the existence of configurationally stable carbocationic intermediates was obtained by subjecting a mixture of the *3E* and *3Z*-isomeric trienols (**1.8a**) and (**1.8b**) (72:28) (obtained previously, *cf.* **Table 2.1**, entry 5) to the standard hydroperoxidation conditions (**Table 2.1**, entry 8). After work up and careful chromatographic separation, the *E/Z* ratios of the hydroperoxidic products (53%) and

recovered alcohol (26%) were found to be identical ($\pm 3\%$) to that of the starting material. This result confirmed that the stereoisomeric ratio of (1.8) was retained upon hydroperoxidation and reiterated our earlier findings (Table 2.1, entry 1). Furthermore, the unchanged *E/Z* ratio of the hydroperoxides (1.7) obtained under these conditions requires that addition of the nucleophile to the carbocations (1.33a) and (1.33b) *must occur exclusively at C7* since addition at C3, and the intermediacy of alcohol (2.2) or the equivalent hydroperoxide, would result in an altered *E/Z* ratio of the products (*cf.* Table 2.1, entries 4 and 5 and Scheme 2.12). The addition of an oxygen nucleophile (HOR') to a cationic intermediate (1.33) is therefore *effectively* irreversible for the alcohols (2.1), (2.2) and presumably (2.3a), since the formation of only one regioisomeric triene (C7 oxygenation) was ever observed.

Assuming that the interconversion between the *s-cis* and *s-trans* conformers is rapid and that loss of water from each conformer is both rate limiting and irreversible, then the *E/Z* product ratio obtained from alcohol (2.2) will depend upon the relative rates of formation of the carbocations (1.33a) and (1.33b). (Scheme 2.12) Hence, through manipulation of the Arrhenius equation (eq. 1),¹¹¹ the difference in activation energy (ΔE) for the formation of the carbocations (1.33a) and (1.33b) at 20°C can be calculated when the product ratio is known.

$$k = e^{-(\Delta E/RT)} \quad \text{eq.1}$$

Where $k = [s\text{-}cis]/[s\text{-}trans] = [(1.7b)]/[(1.7a)] = 27/73 = 0.37$

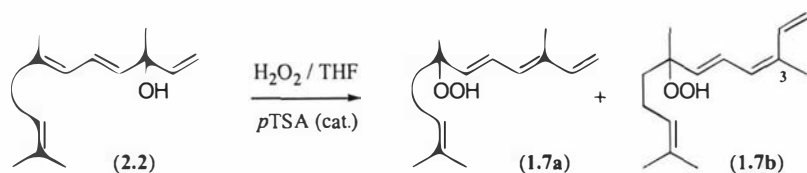
ΔE = difference in activation energy for the formation of (1.33a)/(1.33b)

R = gas constant = 8.31 JK⁻¹mol⁻¹

T = temperature K = °C + 273.15.

Hence $\Delta E = -RT \ln k = 2422 \text{ Jmol}^{-1}$ eq. 2

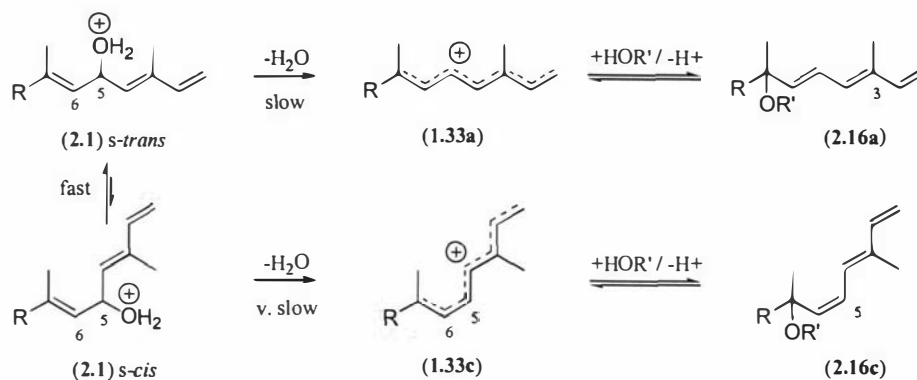
This result (eq. 2) suggests that the difference in activation energy for the formation of the carbocations (1.33a) and (1.33b) is small and that even dramatic variations in temperature will result in only minor changes in the *E/Z* product ratios, i.e. (1.7a):(1.7b). This was confirmed experimentally by conducting the hydroperoxidation of (2.2) at different temperatures. (Table 2.2)

**Table 2.2**

entry	temperature/ °C	time / hrs	yield (%)	3E:3Z ratio ((1.7a):(1.7b))	
				measured	calculated
1	20	6	100	73:27	-
2	60	1	100	71:29	70.6:29.4
3	-10	48	95	77:23	75.2:24.8

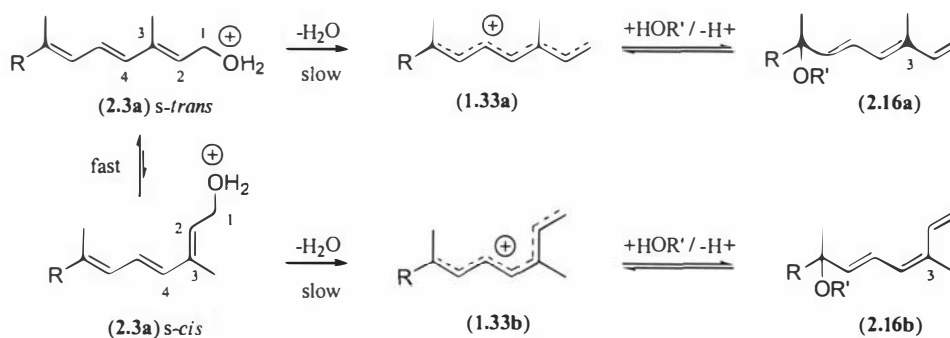
At 60°C (after 1 hour) an increased proportion of the 3Z-isomer (29%) was observed (Table 2.2, entry 2), while the reaction at -10°C (after 48 hours) gave a diminished proportion of the same 3Z-hydroperoxide (1.7b) (23%) (entry 3). Both ratios agreed well with the predicted isomeric ratios calculated from equation 1, and confirmed that the formation of the *cisoid* and *transoid* carbocations (1.33b) and (1.33a) is governed by Arrhenius type behaviour.¹¹¹

The high stereoselectivity observed for the transposition reactions of the secondary allylic alcohol (2.1) is notable, since this substrate offers a means of preparing Anet's trienol (1.8a) and the corresponding hydroperoxide (1.7a) as single stereoisomers in quantitative yield. Indeed, in the absence of basified eluting solvents, even chromatographic purification of (2.1) on silica resulted in its rearrangement to (1.8a). The high degree of stereoselectivity observed in these processes is consistent with the selective formation of a single carbocation intermediate (1.33a). An argument analogous to that presented in Scheme 2.12 can be used to explain these observations.



Scheme 2.13

Elimination of water from the protonated alcohol (2.1) is again possible *via* a pair of *s-cis* and *s-trans* conformers. (Scheme 2.13) For alcohol (2.1), these conformers are interchangeable by rotation about the C5-C6 single bond. In the *s-cis* form (which leads to the C5-C6 *cisoid* carbocation (1.33c)), the two bulky C5- and C6-substituents are positioned in a sterically demanding orientation which is likely to be significantly less favoured than the corresponding *s-trans* conformer, which leads to the *transoid* carbocation (1.33a). Despite these steric considerations, interconversion between the *s-cis* and *s-trans* conformers will still be rapid and it is the loss of water from each conformer that is rate limiting and irreversible. Hence, the stereoselectivity of this process (> 99:1) is again a consequence of the difference in rates of formation of the intermediate carbocations (1.33a) and (1.33c) generated through the loss of water from the respective *s-trans* and *s-cis* conformers. A stereoselectivity of > 99:1 corresponds to a difference in activation energy of *ca.* 11.2 KJmol⁻¹ for this process.



Scheme 2.14

A similar consideration of the primary allylic alcohol (2.3a) suggests that oxygen transposition should lead to a single stereoisomer since the possible conformers about the C1-C2 single bond are equivalent. (Scheme 2.14) Free rotation, however, about the

C3-C4 and C5-C6 single bonds is nonetheless still possible. It has been suggested, however, that the *s-trans* conformation of the C5-C6 single bond for alcohol (2.1) is favoured over the corresponding *s-cis* conformer. It is therefore likely that the C5-C6 *s-trans* conformation of (2.3a) is also favoured.[†] Thus, possible stereoisomeric cationic intermediates derived from (2.3a) are again likely to occur only through the elimination of water from a species comprised of *s-cis* and *s-trans* conformers about the C3-C4 single bond. (cf. Scheme 2.12 and Table 2.1, entries 4 and 5) The stereoselectivity of this process, however, is governed by the relative rates of water loss from protonated intermediates (C3-C4 conformers) which are different from the intermediates generated by protonation of the tertiary alcohol (2.2). It cannot be assumed that the rates of water loss from these different C3-C4 *s-cis* and C3-C4 *s-trans* conformers will be the same and, in turn, the ratio of *cisoid* and *transoid* carbocations (1.33a) and (1.33b) may also be different. The formation of only 13% of the minor isomeric triene (1.8b) from (2.3a) (Table 2.1, entry 7) suggested this was indeed the case; and while the isomeric ratio of the hydroperoxides (1.7) could not be measured, it is expected that this too would reflect this subtle change in the relative rates of cation formation. It is also interesting to note that the proportion of (1.8b) (13%) generated through the transposition of oxygen functionality from C1 to C7 appears very similar to the proportion of the minor 3*Z*-trienic species generated during farnesene peroxy radical formation (ca. 13-15%). (Schemes 1.1, 1.2 and 1.11)

2.3.3 Oxygen Transposition with Other Nucleophiles.

The generality of transposition reactions with other nucleophiles was examined briefly. The allylic alcohols (2.1) and (2.2) were exposed to *p*TSA (5 mol%) in the presence of methanol and anhydrous *tert*-butyl hydroperoxide (*t*BHP). (Table 2.3) With the secondary allylic alcohol (2.1), excellent stereoselectivity was again observed (> 99:1) with both methanol and *t*BHP (entries 1 and 2) although the presence of minor elimination products necessitated purification of the product mixtures by chromatography. The tertiary allylic alcohol (2.2) again furnished mixtures of the 3*E* and 3*Z*-isomeric transposed products, with the same *E:Z* ratio for both methanol and *t*BHP (entries 3 and 4). The stereoselectivity observed with both nucleophiles was identical to that obtained previously through either the alcohol transposition or

[†] This argument also explains why only 5*E*-transposition products were obtained from the tertiary allylic alcohol (2.2). (Table 2.1, entries 4 and 5)

hydroperoxidation of (2.1) and (2.2) (Table 2.1, entries 2-5) and suggests that carbocationic intermediates (1.33a) and (1.33b) are again involved. It was interesting to note, however, that both the methoxylation and *t*-butyl hydroperoxidation of (2.2) proceeded more swiftly (1 hr) than the corresponding transposition reactions reported in Table 2.1 (6hrs).

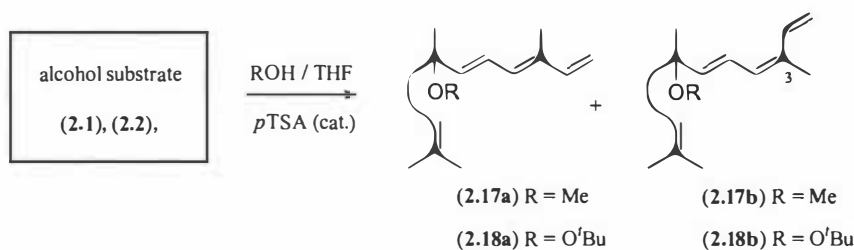


Table 2.3

entry	substrate	R ^a	time	product	3E:3Z	yield (%) ^b
1	(2.1)	Me	5 min	(2.17)	>99:1	82
2	(2.1)	O ^t Bu	5 min	(2.18)	>99:1	85
3	(2.2)	Me	1 hr	(2.17)	71:29	93
4	(2.2)	O ^t Bu	1 hr	(2.18)	71:29	96

^a 75 equivalents. ^b isolated yield after chromatography on silica gel.

2.3.4 Oxygen Transposition Reactions in Related Systems.

The mineral acid-catalysed transposition of allylic alcohols is a well known reaction and before the discovery of the Wittig reaction¹¹² was a common method for the preparation of conjugated polyenic systems.¹¹³ Nonetheless, oxygen transposition reactions continue to prove of synthetic interest and several, more recent syntheses of oxygenated conjugated polyenes have been reported.¹¹⁴⁻¹¹⁷ None of these reports, however, have investigated either hydroperoxide transposition or the stereochemical consequences of transposition reactions across polyene systems bearing substituents.

There is evidence that oxygen transposition reactions across substituted polyenes may occur in the formation of certain natural products. The tertiary allylic alcohol (2.17) was isolated as a constituent of the root of *Ageratum fastigiatum* (a flowering annual) together with mixtures of the 3E and 3Z-trienes (2.18a) and (2.18b), in an unspecified

isomeric ratio.^{118,119} (**Figure 2.1**) The regioisomeric trienols (**1.8a**) and (**1.8b**), together with the angelate derivatives (**2.19a**) and (**2.19b**), were also isolated from the same source. It is likely, in view of the isolation of (**2.17**), that both the tertiary allylic alcohol (**2.2**) and the angelate derivative (**2.20**) were also present in the root extract yet remained unobserved. Indeed, both (**2.2**) and (**2.20**), as potential precursors to (**1.8a**)/(**1.8b**) and (**2.19a**)/(**2.19b**) respectively, *have* been identified as natural products and isolated from plants of the genus *Brickellia*, which belongs to the same tribe (*Eupatorieae*) as *Ageratum*.¹⁰³

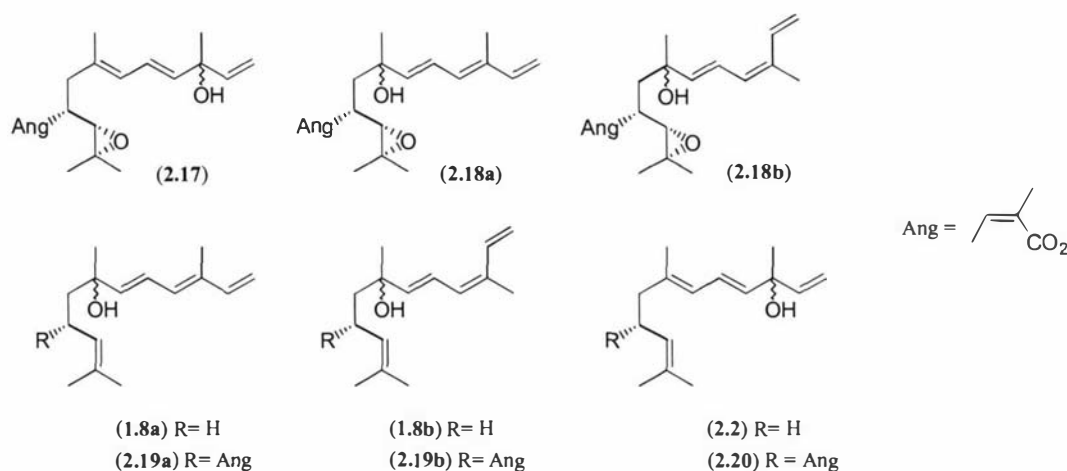


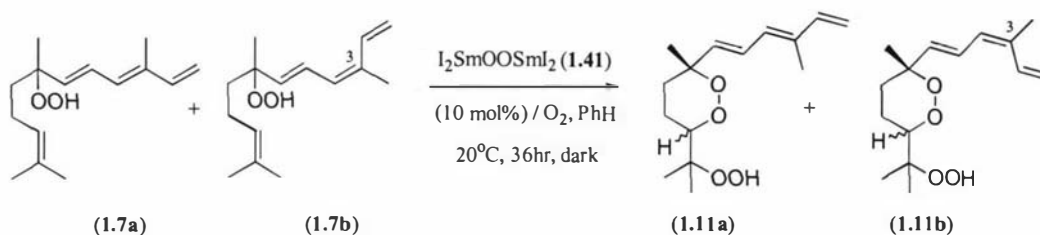
Figure 2.1

2.4 Stereoselectivity in the Formation of Farnesene Peroxy Radicals.

The hydration and hydroperoxidation of the allylic alcohols (**2.1**) and (**2.2**) has proved an effective method for the preparation of the C7-oxygenated conjugated trienes (**1.8**) and (**1.7**) respectively. Furthermore, this has been achieved on a scale where hundreds of milligrams of these materials were prepared and made available for biological testing. The availability of these materials also allowed for the synthesis of the remaining farnesene endoperoxides (**1.11**) and (**1.12**) on a comparable scale.

It was anticipated that conversion of the all *trans*-conjugated trienyl hydroperoxide (**1.7a**) (*E/Z* > 99:1, prepared from the secondary allylic alcohol (**2.1**), **Table 2.1**, entry 2) to the corresponding endoperoxy hydroperoxide (**1.11**), would furnish only one double bond stereoisomer, i.e. (**1.11a**) albeit still as a mixture of diastereoisomers (*cf.* **Scheme 1.11**). In the event, however, the hydroperoxide (**1.7a**), in the presence of the peroxy radical initiator “samarium peroxide” (**1.41**) under the conditions described

earlier (**Scheme 1.11**), generated essentially the same stereoisomeric mixture of 3*E* and 3*Z*-trienyl endoperoxy hydroperoxides as observed before. (**Table 2.4**, entry 2) Intrigued by this result, a mixture of the conjugated trienyl hydroperoxides (**1.7a**) and (**1.7b**) (73:27, prepared from the tertiary allylic alcohol (**2.2**), **Table 2.1**, entry 4) was subjected to the same conditions. After chromatography the endoperoxides (**1.11**) were again isolated as a 3*E*/3*Z* mixture in essentially the same ratio (81:19) as before (**Table 2.4**, entry 3). **Table 2.4**, entry 1, summarises the result obtained for the initial formation of the endoperoxide mixture (**1.11**), outlined in **Scheme 1.11**, obtained from a 96:4 mixture of 3*E* and 3*Z*-trienyl hydroperoxides (**1.7a**) and (**1.7b**). Together with entries 2 and 3 it is clear that the endoperoxides (**1.11**) are formed as essentially the same mixture of four isomeric compounds irrespective of the *E/Z* ratio of the starting hydroperoxide mixture (**1.7**).

**Table 2.4**

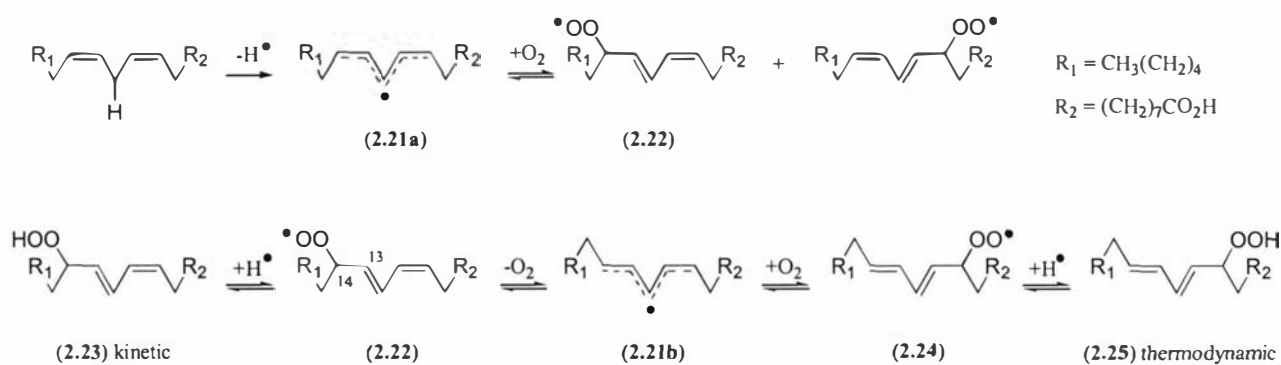
entry	(1.7a) : (1.7b)	<i>cis</i> : <i>trans</i>	(1.11a) : (1.11b)	yield (%)
1	96:4	1:1.2	82:18	83
2	>99:1	1:1.2	83:17	80
3	73:27	1:1.1	81:19	85

While the modest diastereoselectivity of peroxy radical cyclisations such as these has been rationalised⁸⁵ (section 1.2.4.3), the apparent equilibration of the conjugated triene moiety during this process has not. It is likely that this phenomenon is closely linked to the formation of conjugated trienyl peroxy radical species such as (**1.6a**) (**Scheme 1.1**)¹⁸ since similar double bond isomerisations, yielding comparable *E/Z* mixtures, have been observed whenever famesene peroxy radicals are involved, i.e. (**Scheme 1.1**)¹⁸ and (**Scheme 1.2**).^{54,56}

It is possible to rationalise the formation of 3*E*/3*Z* mixtures in the farnesene system by considering the mechanism of autoxidation in polyunsaturated lipids *and* the stereoselectivity of oxygen transposition reactions across substituted polyenes.

2.4.1 Lipid Autoxidation.

The mechanism of lipid autoxidation has been thoroughly investigated by Porter.²¹ It has been shown that hydrogen atom abstraction from methylene-interrupted dienes (linoleic acid derivatives) generates an extended pentadienyl radical (2.21a) with a *cisoid-transoid-transoid-cisoid* configuration.^{120,121} (Scheme 2.15)



Scheme 2.15

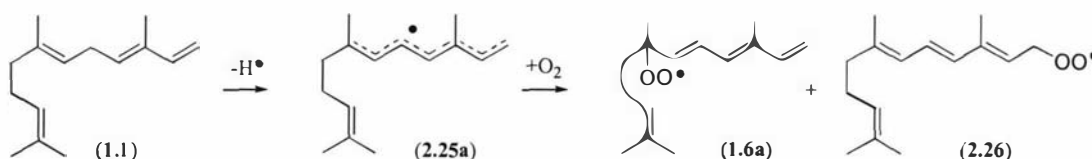
Coupling of carbon centred radicals with oxygen is very rapid (approaching the diffusion control limit²⁰) and can occur at either end of the pentadienyl radical (2.21a).[†] Considering only one of these possibilities for simplicity (Scheme 2.15), oxygenation of (2.21a) at the R₁ terminus will generate a peroxy radical species (2.22) where the stereochemistry of its carbon centred radical precursor (2.21a) is retained. In the presence of a hydrogen atom donor, entrapment of (2.22), before β-fragmentation, generates the kinetic hydroperoxide (2.23). However, the peroxy radical (2.22) is free to rotate about the C13-C14 single bond and if no good hydrogen atom donors are present, β-fragmentation will compete to generate the *transoid-transoid-transoid-cisoid* pentadienyl radical (2.21b). Oxygenation at either end of this species is also possible, however coupling at the end of (2.21b) remote from the site of β-fragmentation leads to the thermodynamically more stable peroxy radical (2.24) and ultimately to the all *trans*-dienyl hydroperoxide (2.25). A similar process is also possible through initial

[†] Coupling at the internal position of pentadienyl radicals has only been observed when both termini are sterically congested.¹²²

oxygenation of (2.21a) at the R₂ terminus, which leads to two other linoleate autoxidation products. Significantly, it is the relative rates of β-fragmentation from the peroxy radical pair (2.22) and (2.24) which determines the ratio of the thermodynamic and kinetic products. Assuming that abstraction of a hydrogen atom is fast for both the peroxy radicals (2.22) and (2.24), then it is the relatively slower β-fragmentation of the more stable all *trans* species (2.24) which determines the stereo- and regioselectivity of the autoxidation processes.¹²⁰

Peroxy radicals are readily formed from hydroperoxides in the presence of initiators.¹⁹ These include carbon centred radicals such as (2.21),¹²¹ as well as peroxy radicals themselves, i.e. (2.22) and (2.24).^{120,121} In the presence of molecular oxygen, kinetic hydroperoxides (2.23) are converted to their thermodynamically more stable regioisomeric counterparts (2.25) *via* transposition of dioxygen across carbon centred radical intermediates.¹²¹

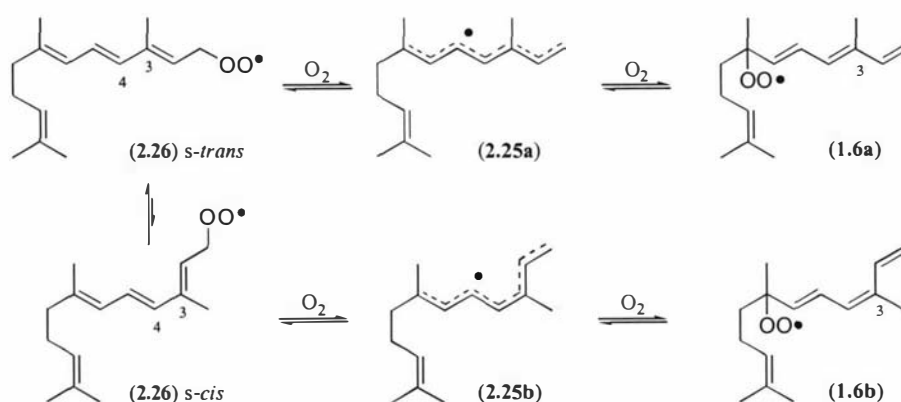
2.4.2 α-Farnesene Autoxidation



Scheme 2.16

The coupling of oxygen with carbon centred radicals is rapid and insensitive to structural features.^{20,122} Furthermore, the coupling of oxygen at the termini of extended polyenic carbon centred radicals is poorly regioselective.^{120,121} It is therefore reasonable to assume that the addition of oxygen to the farnesene radical (2.25a) will exhibit equally poor regioselectivity and that under autoxidative conditions, two kinetic peroxy radical species will be formed, i.e. (1.6a) and (2.26). (Scheme 2.16) While the familiar radical species (1.6a) will follow the autoxidative mechanism postulated by Anet (Scheme 1.1),¹⁸ it is suggested that the other primary kinetic peroxy radical species (2.26) will isomerise to give the thermodynamically more stable peroxy radical (1.6a). It is this isomerisation process which is likely to result in the formation of minor isomeric 3Z-triene species. (Scheme 2.17)

The β -elimination of oxygen from (2.26), to reform the farnesene radical (2.25a), is likely to be governed by stereochemical considerations similar to those observed in the formation of the extended heptatrienyl carbocations (1.33a) and (1.33b) from the primary allylic alcohol (2.3a). (Scheme 2.14) Hence, β -fragmentation of the peroxy radical species (2.26) in a C3-C4 *s-trans* conformation will generate the *transoid*-heptatrienyl radical (2.25a), while elimination from (2.26) in a C3-C4 *s-cis* conformation will give the isomeric *cisoid*-heptatrienyl radical (2.25b). (Scheme 2.17) Assuming that interconversion of conformers is rapid, then the relative rates of β -fragmentation from the *s-cis* and *s-trans* conformers of the C1 peroxy radical species (2.26) will control the stereoselectivity of this equilibration and hence the ratio of tertiary peroxy radicals (1.6a) and (1.6b) formed upon the re-oxygenation at C7 of their respective radical precursors (2.25a) and (2.25b).



Scheme 2.17

The stereoselectivity observed for the C1-C7 oxygen transposition of the primary allylic alcohol (2.3a) (Table 2.1, entry 7) under acidic conditions is therefore directly relevant. While this process involved the formation of charged intermediates and not neutral free radicals, it is likely that the conformational preferences and, more importantly, their relative rates of deoxygenation will be comparable. Indeed, it is suggested that the formation of the minor 3*Z*-trienyl endoperoxide species (1.11b) (17-19%) obtained from any mixture of the hydroperoxides (1.7a) and (1.7b) (Table 2.4) is a direct consequence of equilibration through peroxy radical formation, β -fragmentation, re-oxygenation to form (2.26) and secondary β -fragmentation with concomitant stereoisomerisation. (Scheme 2.17) Furthermore, it is suggested that under thermodynamic conditions, any process by which the extended heptatrienyl radical

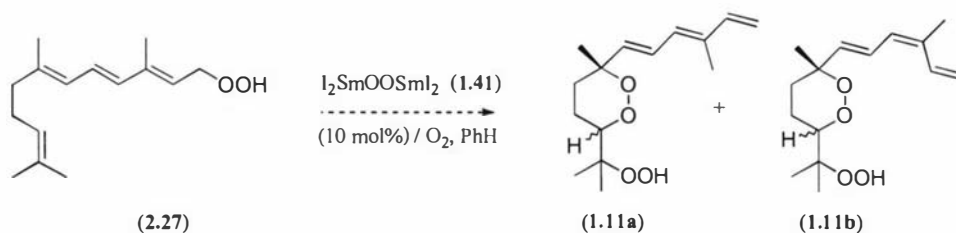
(2.25) is generated will result in a comparable mixture of 3*E* and 3*Z*-trienyl species, where ultimately formation of the thermodynamically more stable C7-regioisomeric hydroperoxy species (1.7a) and (1.7b) will dominate. This conclusion explains the origin of the relatively high proportion of 3*Z*-trienes (13%) obtained by the *in vitro* autoxidation of naturally occurring α -farnesene containing at most only 3% of 3*Z*-isomer.¹⁸ (Scheme 1.1) This conclusion also offers a rationale for the formation of the relatively high proportions of 3*Z*-trienes (15%) produced by the photosensitised oxidation of the farnesene epoxide (1.16) with essentially 100% 3*E* stereochemistry.^{54,56} (Scheme 1.2)

2.5 Conclusions.

The conjugated trienyl hydroperoxides (1.7a) and (1.7b) have been prepared from geraniol (1.19) via a series of concise synthetic routes, the shortest of which gave hydroperoxide (1.7a) as a single stereoisomer in only four steps.¹²³ During the course of this investigation the first examples of acid-catalysed hydroperoxidation of polyenic alcohols were carried out and, in general, these transformations proceeded cleanly and in high yield when anhydrous hydrogen peroxide in THF was used. Transposition reactions with other nucleophiles were equally efficient and granted access to, amongst others, the conjugated trienols (1.8a) and (1.8b). These reactions have been used to prepare α -farnesene autoxidation products on a scale suitable for testing and the biological evaluation of these materials is currently under way.⁹²

The unanticipated stereochemical outcome of oxygen transposition reactions across polyenes can be explained by invoking the formation of configurationally immobile acyclic carbocation intermediates, where it is believed their relative rates of formation determine the stereoselectivity of the transposition process. An analogous radical mechanism has been presented to account for the hitherto unexplained formation of minor 3*Z*-farnesene trienes observed originally by Anet¹⁸ and later by other workers.^{54,56,58,123} Based on precedent observed in the autoxidation of polyunsaturated lipids,²¹ it is anticipated that the dioxygenation of farnesene carbon centred radicals (2.25) (Scheme 2.16) generates both C7 and C1 intermediate peroxy radical species. β -Fragmentation of C1-peroxy radicals (2.26) generates configurationally immobile radical intermediates in a manner directly analogous to the

formation of cationic intermediates under acidic conditions. This process is believed to be subject similar stereochemical considerations.



Scheme 2.18

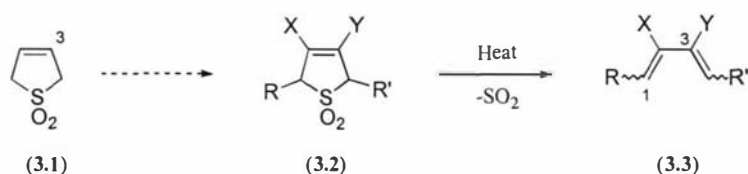
It may indeed be possible to explore this hypothesis through the formation and behaviour of the primary peroxy radical (2.26) prepared by other means. Thus, treatment of the primary hydroperoxide (2.27) with Corey's samarium peroxide radical initiator (1.41), in the presence of molecular oxygen, is expected to yield the same ratio of *cis* and *trans*-endoperoxy hydroperoxides (1.11a) and (1.11b) as previously observed. (Scheme 2.18)

Chapter 3

The Stille Cross-coupling of 3-Sulfolene Derivatives

3.1 Introduction.

The cyclic sulfone, 3-sulfolene (3.1)[†] is the parent compound of an important class of unsaturated, small ring heterocycles. The majority of synthetic effort directed toward 3-sulfolenes has focused on the preparation of more complex, substituted derivatives of the general structure (3.2) incorporating a diverse range of alkyl and heteroatom substitution.¹²⁴ (Scheme 3.1) Of enormous synthetic value is the role of 3-sulfolenes as masked 1,3-dienes. When heated, either in solution or as pure compounds, substituted 3-sulfolene derivatives of general structure (3.2) readily eliminate sulfur dioxide to furnish substituted 1,3-butadienes (3.3) with well defined regiochemistry and predictable stereochemistry. The value of 3-sulfolene derivatives as masked dienes has served as a major influence in the evolution of sulfolene chemistry. The syntheses and synthetic applications of these compounds have been reviewed by Chou¹²⁵ and more recently by Bhat.¹²⁶



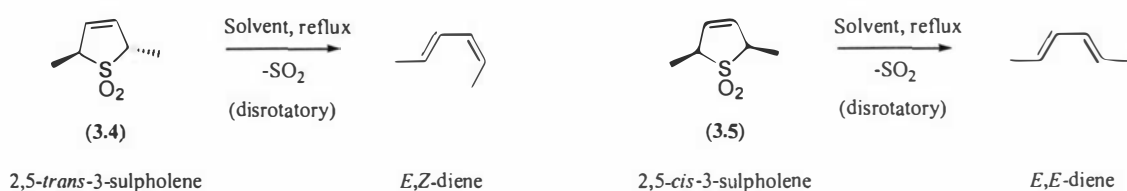
Scheme 3.1

3.2 3-Sulfolenes as Masked 1,3-Dienes.

Thermal extrusion of sulfur dioxide from 3-sulfolenes takes place at about 100-130°C and cleanly affords 1,3-dienes. This reaction can also be carried out at lower temperatures with the use of lithium aluminium hydride¹²⁷ or with ultrasonically dispersed potassium (UDK).¹²⁸ Of key importance to the value of 3-sulfolene derivatives as masked dienes is the stereocontrol which is possible with this process. The extrusion of sulfur dioxide from 3-sulfolenes proceeds *via* a cheletropic elimination and is a concerted, disrotatory process.^{129,130} The ring opening, or cycloreversion, is therefore stereospecific and governed by the rules of conservation of

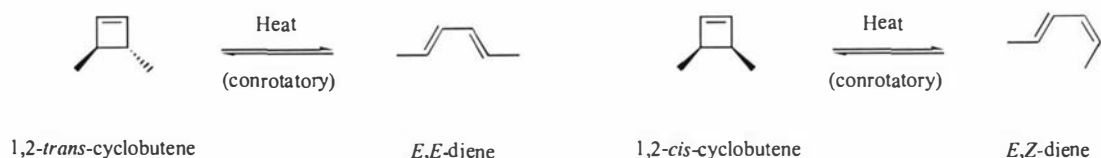
[†] The full IUPAC name for (3.1), 2,5-dihydrothiophene-1,1-dioxide is rarely used and for convenience the trivial name, 3-sulfolene, is commonly employed.

orbital symmetry.¹³¹ As with all disrotatory (and conrotatory) pericyclic processes there are two rotational modes and although one may dominate, both are symmetry allowed and each pathway must preserve orbital symmetry. Significantly, this means that the relative stereochemistry of substituents at the 2 and 5-positions of a 3-sulfolene derivative is translated into the geometry of the 1,3-diene upon extrusion of sulfur dioxide.¹²⁹ (Scheme 3.2) The reverse of this process (a 4+1 cycloaddition) is therefore, by necessity, also concerted and the diene geometry will determine the relative stereochemistry of any 3-sulfolene adduct derived from it by the addition of sulfur dioxide.¹³⁰



Scheme 3.2

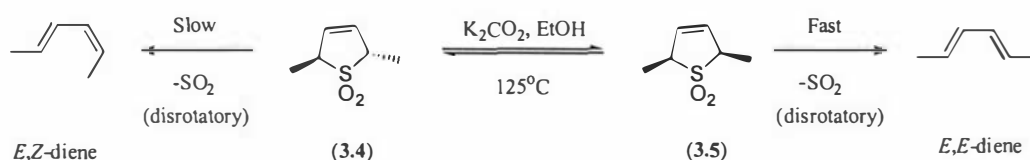
2,5-Trans-substituted 3-sulfolenes (**3.4**) afford *E,Z*-dienes, while *2,5-cis*-substituted 3-sulfolenes (**3.5**) afford all *trans* or *E,E*-dienes. It is interesting to note that this stereospecificity is the opposite to that observed for the electrocyclic ring opening of 1,2-dialkyl-cyclobut-3-enes, which proceed *via* concerted conrotatory processes under thermal conditions.¹³¹ (Scheme 3.3) This simple comparison may serve as a useful predictive tool for the analysis of the less intuitively obvious stereochemical consequences of cheletropic cycloreversions.



Scheme 3.3

The extrusion of sulfur dioxide from *cis*-3-sulfolenes (**3.5**) is faster than the extrusion from the *trans* isomer (**3.4**).¹³⁰ and this rate difference has been utilised in the stereoselective synthesis of *E,E*-1,3-dienes from diastereomeric mixtures of both *cis* and *trans*-2,5-disubstituted 3-sulfolenes.^{132,133} (Scheme 3.4) Under basic conditions (K_2CO_3 , EtOH sealed tube, 125°C), epimerisation of the *trans*-isomer (**3.4**) to the *cis*-

isomer (3.5) occurs faster than SO₂ extrusion from the *trans*-compound (3.4). Hence, SO₂ loss occurs predominantly from the *cis*-isomer (3.5), giving the *E,E*-diene selectively. With non-equivalent substituents at the 2 and 5-positions, this modification is particularly valuable. The theoretical possibility of two symmetry allowed disrotatory sulfur dioxide elimination processes from a mixture of *cis* and *trans*-2,5-disubstituted 3-sulfolenes can, in principle, yield a mixture of 4-isomeric dienes (i.e. 1*E*,3*Z*- 1*Z*,3*E*-, 1*E*,3*E*- and 1*Z*,3*Z*-). This modification has been used effectively in the synthesis of several natural products.^{132,133}



Scheme 3.4

With 3-sulfolenes bearing only one substituent at either the 2 or 5-position, the cheletropic elimination of sulfur dioxide produces 1-substituted-1*E*,3-dienes selectively. Although the formation of the corresponding 1*Z*-isomer is also possible (*via* the alternative symmetry allowed conrotatory process), the relatively high steric demands of this cycloreversion pathway preclude its formation.[†] (Scheme 3.5)



Scheme 3.5

Substituents at the 3-position have no effect on the stereochemistry of sulfur dioxide elimination, giving 2-substituted 1,3-butadienes. (Scheme 3.5)

3.3 The Synthesis of 3-Sulfolenes: An Overview.

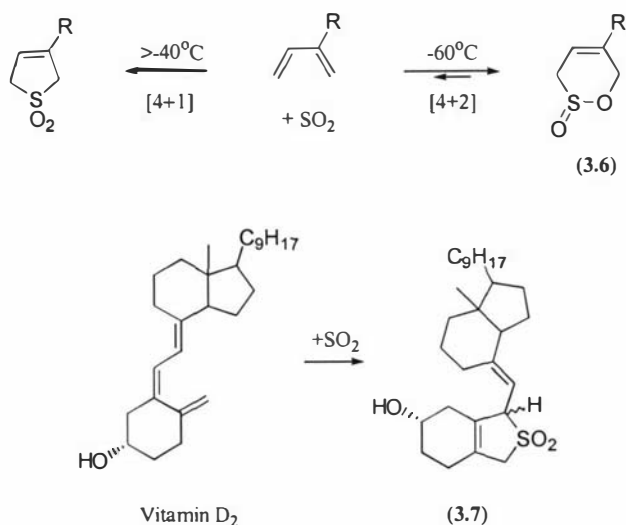
The value of 3-sulfolenes as masked 1,3-dienes has received considerable attention and has been the subject of two reviews^{125,126} and one book chapter.¹²⁴ It is in this context that most contemporary 3-sulfolene literature continues to appear. It is not our intention to extensively review the synthesis and utility of 3-sulfolenes again, but offer instead a more general overview of the synthetic approaches to 3-sulfolenes. There are

[†] This mode of reactivity was utilised extensively in the formation of α -farnesene derivatives discussed in Chapters 1 and 2.

five general methods for the preparation of 3-sulfolene derivatives. These are outlined in sections 3.3.1 to 3.3.5.

3.3.1 Cycloaddition Reactions.

1,3-Dienes undergo hetero-Diels-Alder additions with sulfur dioxide below -60°C to give the corresponding 3,6-dihydro-1,2-oxathiin-2-oxides (sultines) (3.6).¹³⁴ (Scheme 3.6) Sultines are unstable above -50°C and undergo cycloreversion, liberating the starting diene and sulfur dioxide which then undergo cheletropic additions¹³¹ above -40°C to give the corresponding 3-sulfolenes. As discussed above, sulfur dioxide addition is stereospecific and product stereochemistry is dependant upon diene geometry and substitution pattern.¹³⁰

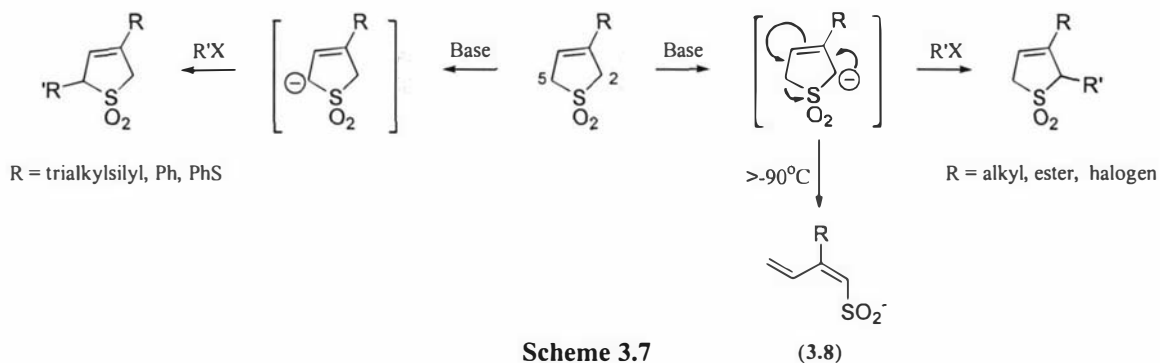


Scheme 3.6

This approach was used in some of the earliest examples of 3-sulfolene synthesis¹³⁵ but is not limited to the formation of simple 3-sulfolene derivatives. For example, the SO_2 adduct of vitamin D_2 (3.7) has been successfully prepared.¹³³ (Scheme 3.6) A limited number of alternative cycloaddition strategies have been used in the preparation of specialised 3-sulfolene derivatives,¹³⁶ however, most synthetic effort directed towards the synthesis of 3-sulfolenes has been expressly aimed at preparing functionalised 1,3-dienes *from* sulfolene precursors. As a direct consequence of this, the addition of sulfur dioxide to dienes has received little attention as a viable strategy for the synthesis of 3-sulfolenes other than for simple derivatives.⁹⁹

3.3.2 α -Substitution.

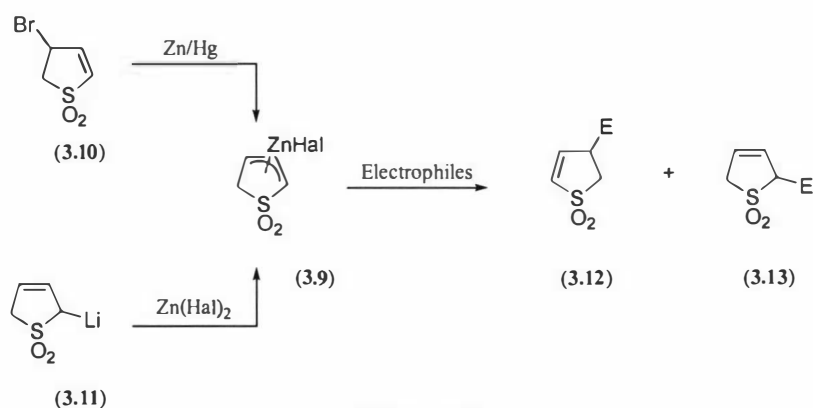
The 2- and 5-positions of 3-sulfolenes are α - to the sulfone moiety and, if unsubstituted, are easily deprotonated with a suitable base. It is the generation of the 2- and/or 5-anions of 3-sulfolenes, and their subsequent reaction with electrophiles, that constitutes the major part of the 3-sulfolene chemistry that is reported in the literature.¹²⁴⁻¹²⁶ (Scheme 3.7)



The troublesome formation of substituted dienyl sulfinic acids and their salts (3.8)^{137,138} by the facile, concerted ring fission of intermediate 3-sulfolene α -carbanions at temperatures above -90°C (shown for the 2-anion only) is a problem which has plagued the formation of 2/5-substituted-3-sulfolene derivatives.¹³⁹ The evolution of improved protocols for the regioselective alkylation of 3-sulfolenes, including low temperature⁶² and Barbier type reactions^{132,140,141} have, in some part, overcome this problem, greatly improving the utility of 3-sulfolenes as terminally substituted 1,3-diene precursors.¹²⁴⁻¹²⁶ Furthermore, with 3-substituted-3-sulfolenes, the regioselectivity of alkylation appears to be controlled by the electronic effects of the pre-existing substituent R. (Scheme 3.7) When R is alkyl, halogen¹⁴² or an ester,¹⁴³ selective alkylation is observed at the 2-position. When R = phenyl,⁹⁷ thiophenyl or trialkylsilyl,¹⁴⁴ the reverse regioselectivity is observed and 5-alkylation is dominant. It is also possible to reverse the regioselectivity of alkylation by generating a 2,5-dianion and selectively quenching with only one equivalent of alkylating agent.¹⁴⁵ Similarly, changing the concentration and nature of the solvent also affects the observed regioselectivity.²³ By these means, a range of 3-sulfolene and 1,3-butadiene

derivatives has been prepared and a battery of well-worked alkylation protocols has been established for the synthesis of α -substituted 3-sulfolenes.

In a departure from the normal mode of regioselectivity observed for α -substitution, zinc sulfolenylate (**3.9**), obtained by either the direct zincation of 4-bromo-2-sulfolene (**3.10**)¹⁴⁶ or by metal exchange between 2-lithio-3-sulfolenes (**3.11**) and zinc halides,¹³⁹ reacts with electrophiles to give mixtures of both 2-substitued-3-sulfolenes (**3.13**) and 4-substitued-2-sulfolenes (**3.12**). (Scheme 3.8)



Scheme 3.8

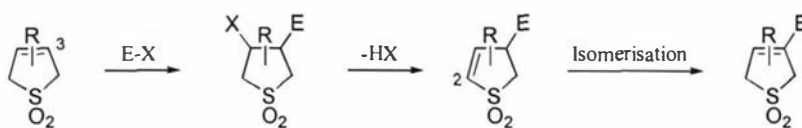
The product distribution is dependant upon the choice of electrophile and the nature of the counter ion used in the generation of the organozinc reagent.¹³⁹ Technically this method represents a modified alkylation procedure, although it is interesting to note that substitution in the 4-position is dominant with the majority of electrophiles. Zinc sulfolenylates react with elemental halogens to give 4-halogenated-2-sulfolenes (**3.12**, E = I, Br) exclusively,¹³⁹ and the formation of 2-halogenated-3-sulfolenes (**3.13**, E = I, Br, Cl) has not been reported.

Examples of the α -substitution of stannylated-3-sulfolenes have been achieved under Stille cross-coupling conditions and are discussed in detail in section 3.5.2.

3.3.3 β -Substitution.

This involves substitution of a group at the 3 (or 4) position of a 3-sulfolene, i.e. β to the sulfone moiety. There are two sub-categories to this general approach.

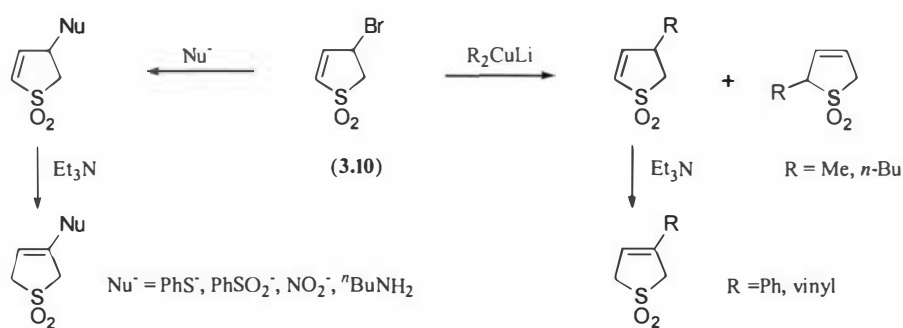
i) The more common approach involves addition of an electrophilic reagent (EX) to a 3-sulfolene, subsequent elimination of HX to give a 2-sulfolene intermediate and isomerisation under basic conditions to generate a new 3-sulfolene derivative. (**Scheme 3.9**) This three step process constitutes an overall β -substitution and has been used extensively in the formation of 3-thiolated 3-sulfolenes by the action of arylsulfenyl chlorides.¹⁴⁷



Scheme 3.9

Other electrophiles (EX) include N_2O_4 ,¹⁴⁸ Br_2 ,¹⁴⁹ acyl chlorides¹⁵⁰ and phenyl selenides.¹⁵¹ The palladium-mediated arylations of 3-sulfolenes (Heck reaction), belong to this category and are discussed in more detail in section 3.5.1.

ii) 4-Bromo-2-sulfolene (**3.10**)¹⁴⁹ represents one of the few electrophilic sources of the sulfolene moiety. This compound reacts with a range of heteroatom and carbon nucleophiles *via* a simple $\text{S}_{\text{N}}2$ mechanism to give 4-substituted-2-sulfolene derivatives.¹⁵² In the presence of base rearrangement occurs rapidly and in high yield to furnish the β -substituted 3-sulfolene derivatives. (**Scheme 3.10**)

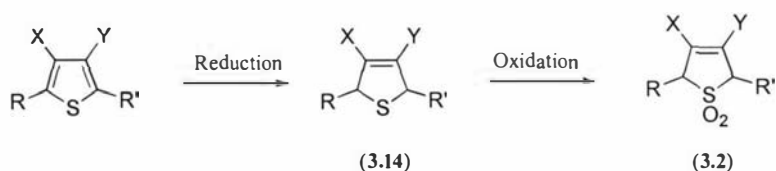


Scheme 3.10

With some organocuprates, substitution *via* an $\text{S}_{\text{N}}2'$ mechanism has also been observed.¹⁵²

3.3.4 2,5-Dihydrothiophene Precursors.

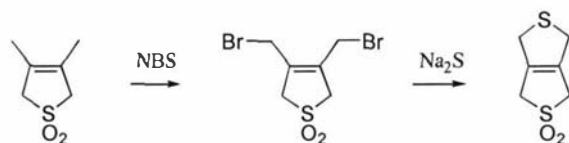
3-Sulfolenes can be prepared by the oxidation of 2,5-dihydrothiophenes (3.14).¹⁵³ (Scheme 3.11) This approach is used infrequently and is often disadvantaged by relatively lengthy *de novo* syntheses of the desired 2,5-dihydrothiophene precursor (3.14) when this is not obtainable directly by the reduction of an appropriately substituted thiophene.¹⁵⁴ The subsequent oxidation can, however, often be achieved in good yield under mild conditions. This approach eliminates the problem of unwanted ring fission and double bond migration¹⁵⁵ often encountered with strategies involving α -substitution.



Scheme 3.11

3.3.5 Functional Group Interconversion.

This synthetic approach to 3-sulfolenes involves only the manipulation of existing functional groups of the 3-sulfolene system (prepared by one or more of the above methods), but does not technically involve the formation of new bonds to the sulfolene nucleus.¹²⁴⁻¹²⁶ Scheme 3.12 outlines an example of functional group interconversion where successive manipulation of functionality around the sulfolene core generates a new sulfolene derivative.¹²⁵



Scheme 3.12

3-Sulfolenes are broadly tolerant to a wide range of reaction types, however, functional group manipulation involving strongly basic conditions (i.e. organolithium and Grignard reagents) are generally incompatible. This is due to the ready formation of 2-

and 5-anions of 3-sulfolenes and their competitive cycloreversion to give substituted dienyl sulfinic acids and their salts (3.8).^{137,138} (See section 3.3.2)

3.4 *Bis-3-sulfolenes.*

The majority of 3-sulfolene derivatives prepared by the methods described above are molecules that contain only one sulfolene unit.¹²⁴⁻¹²⁶ As *mono*-sulfolene derivatives these compounds are only *single* diene equivalents. The possibility of preparing sulfolene derivatives containing more than one masked diene unit offers the potential of extending this well established mode of reactivity and preparing molecules that contain many diene units. Despite the potential value of this strategy, there are remarkably few examples of *bis-3-sulfolenes* in the literature and *no* reports of higher, *oligo-3-sulfolenes*. The *bis-3-sulfolenes* currently known can be conveniently subdivided into two categories. (Figure 3.1)

- i) Pendant *bis-3-sulfolenes*, where two sulfolene units are linked at only one position of each ring by a group of atoms or tether.
- ii) Annulated *bis-3-sulfolenes*, where each sulfolene unit is annulated with a second ring as part of an extended polycyclic structure or as part of two tethered, remote polycyclic structures.

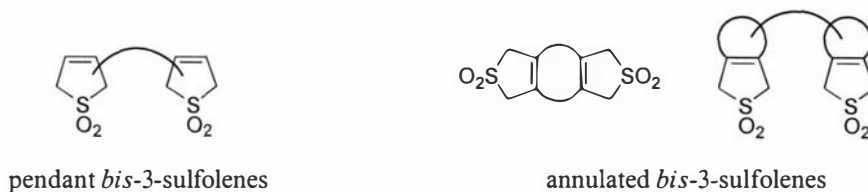


Figure 3.1

3.4.1 Pendant *Bis-3-sulfolenes.*

Several examples of pendant *bis-3-sulfolenes* that are linked with simple sulfur tethers (3.15), where $n = 0, 1$ and 2 ¹⁵⁶⁻¹⁵⁹ have been reported. (Figure 3.2) The sulfide (3.15, $n = 0$) was prepared by the reaction of sulfur dichloride with 3-sulfolene (3.1) (β -substitution). Subsequent oxidation with acidic hydrogen peroxide was used to prepare both the sulfoxide (3.15 $n = 1$)¹⁵⁹ and sulfone (3.15 $n = 2$).^{157,158} Pendant sulfolenes linked by saturated aliphatic tethers have also been reported. Sixteen examples of 2,2'-tethered *bis-3-sulfolenes* (3.16) have been prepared by the sequential alkylation (α -

substitution) of hetero-atom and alkyl-substituted 3-sulfolene derivatives with appropriate bifunctional alkylating agents.¹⁶⁰ A less obvious pendant *bis*-3-sulfolene is the intriguing 3,3'-tethered sulfolene derivative (3.17) elegantly prepared by a tandem $6\pi + 2\pi$ cycloaddition process.¹³⁶

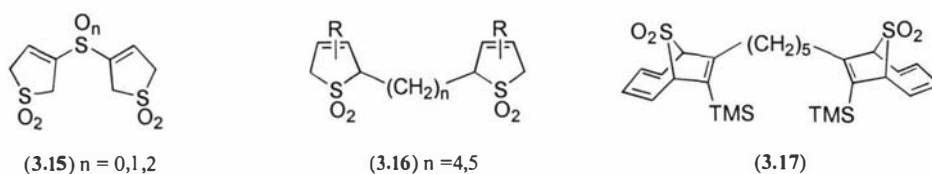


Figure 3.2

As pendant *bis*-3-sulfolenes, these compounds were prepared specifically as diene equivalents and under appropriate conditions all were effectively unmasked to give the desired polyenic products.

3.4.2 Annulated *Bis*-3-sulfolenes.

Examples of annulated *bis*-3-sulfolenes are more common than their pendant variants. The tetrahydroanthraquinone (3.18) (Figure 3.3) was constructed through a series of cycloaddition reactions and has been used in the synthesis of even longer linear cyclohexa-1,4-dienyl arrays.¹⁶¹

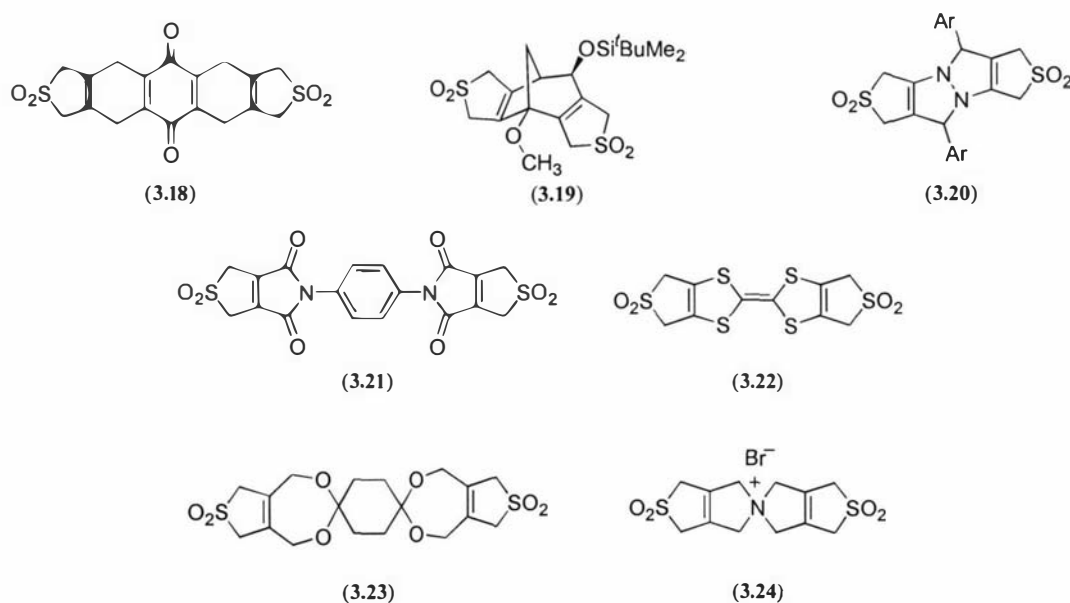


Figure 3.3

The bicyclooctane derivative (3.19) has been prepared and used to study the rate and regioselectivity of sultine-sulfolene interconversion.¹⁶² Other tetracyclic *bis*-3-sulfolenes have also been reported. The hydrazine (3.20) was prepared by the oxidation of a sulfolane precursor by workers in pursuit of “molecules of biological activity”¹⁶³ and is one of the few examples of a *bis*-3-sulfolene not specifically intended for use as a diene precursor.

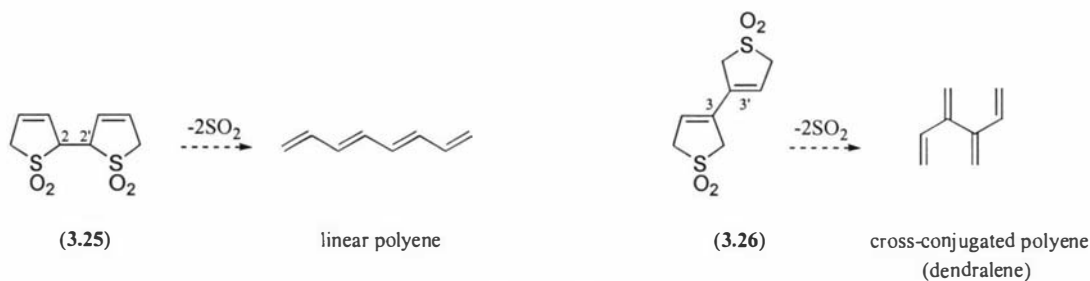
Bis-3-sulfolenes as tethered, remote polycyclic structures have been synthesised for use as Diels-Alder precursors to polymeric materials. In this context the *bis*-3-sulfolene (3.21) was thermally cleaved to reveal the corresponding *bis*-exocyclic diene and, in the presence of a suitable bifunctional dienophile, polymerisation occurred spontaneously to produce a well defined linear polymer.¹⁶⁴ Similarly, the tetrathiafulvalene adduct (3.22) was prepared as a monomeric precursor to organic semiconductors.¹⁶⁵ Diels-Alder polymerisation of the *bis*-diene prepared from the spiroketal sulfolene adduct (3.23) was the first example of this effective strategy.¹⁶⁶ Other spiro *bis*-3-sulfolene adducts have been reported. The ammonium salt (3.24) was obtained as a by-product in the formation of a pyrrole-annulated 3-sulfolene derivatives but was not investigated as a diene precursor.¹⁶⁷

The diverse range of chemical applications of these examples serves to demonstrate the value of *bis*-3-sulfolenes as polyene precursors. Perhaps more importantly, however, they are also strongly suggestive of a third class of potentially valuable *bis*-3-sulfolenes which have yet to receive *any* synthetic attention.

3.4.3 Fused *Bis*-3-sulfolenes.

As a sub-class of pendant *bis*-3-sulfolenes, it is possible to imagine two 3-sulfolene units coupled directly *without* a tethering group between the two ring systems. In the absence of a more suitable descriptor, it is suggested that molecules of this structural type be referred to as fused *bis*-3-sulfolenes. It is perhaps surprising to find this conceptually simple coupling variant has not been reported, particularly when there also exists the intriguing possibility of forming a variety of conjugated polyenic products through the simple cheletropic elimination of sulfur dioxide. Furthermore, by controlling the regioselectivity and stereoselectivity of any 3-sulfolene fusion, it is, in

principle, also possible to control the geometry and substitution of the polyene that is produced when the fused *bis*-sulfolene is unmasked. (**Scheme 3.13**)



Scheme 3.13

To this end 2,2'-fused *bis*-3-sulfolenes (**3.25**) represent masked linear tetraenes, while the regioisomeric 3,3'-*bis*-3-sulfolenes (**3.26**) are latent forms of cross conjugated π systems, known also as dendralenes.¹⁶⁸ The 2,3'- and 3,2'-combinations represent hybrid linear-cross conjugated variants. With additional sulfolene fusion (fused *oligo*-3-sulfolenes), the number of possible permutations and combinations for polyene synthesis increases accordingly.

It was our aim to investigate the formation and utility of fused *oligo*-3-sulfolenes as precursors to conjugated polyenes. Although no direct sulfolene coupling protocols have been reported, the regioselective palladium-mediated coupling of some sulfolene derivatives has been described (*vide infra*). It was believed that an adaptation of this strategy would be of value in the synthesis of fused *oligo*-3-sulfolenes.

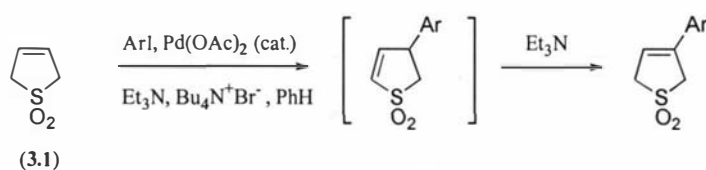
3.5 Palladium-Mediated Reactions in the Synthesis of 3-Sulfolenes.

While the general use and preparation of 3-sulfolene derivatives is of broad scope,¹²⁴⁻¹²⁶ the role of palladium-mediated carbon-carbon bond forming reactions¹⁶⁹ in the synthesis of sulfolene derivatives has received relatively little attention. The Heck and Stille coupling reactions of 3-sulfolenes that have been reported are reviewed below.

3.5.1 Heck Coupling.

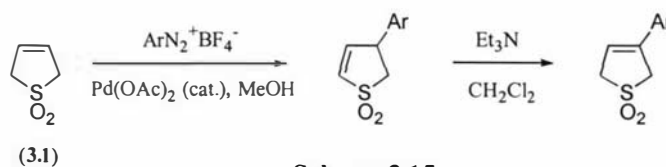
The first example of a palladium mediated carbon-carbon bond forming reaction in the synthesis of 3-sulfolene derivatives was reported by Harrington in 1987.¹⁷⁰ 3-

Sulfolene (3.1) was coupled with a range of simple aryl iodides in the presence of catalytic palladium acetate to yield the corresponding β -substituted 3-sulfolenes in good yield. (Scheme 3.14) 4-Substituted 2-sulfolenes were formed initially and, although not characterised, were smoothly converted under the reaction conditions into the reported products. No reaction was observed for substituted aryl iodides bearing strongly electron withdrawing *p*-nitro substituents and while the reaction was tolerant of sterically demanding *o*-substituted electrophiles, yields were modest and reaction times extended.



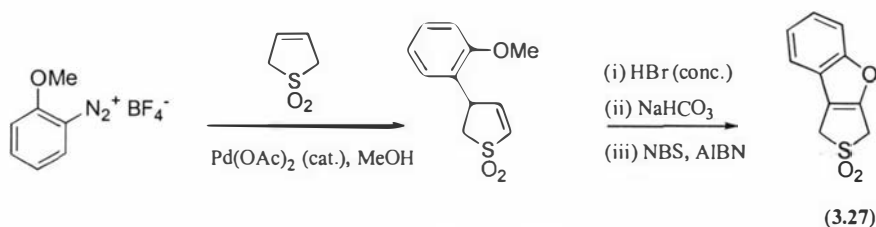
Scheme 3.14

The Heck reaction of 3-sulfolene with aryl diazonium salts has also been investigated.¹⁷¹ (Scheme 3.15) In refluxing methanol, again in the presence of catalytic palladium acetate, a range of 4-aryl-2-sulfolene derivatives were obtained in good yield.



Scheme 3.15

2-Sulfolene isomerisation did not occur under the reaction conditions, the corresponding 3-sulfolene derivatives being obtained quantitatively by the action of triethylamine in a subsequent step. No *o*-substituted or electron deficient aromatic electrophiles were surveyed.



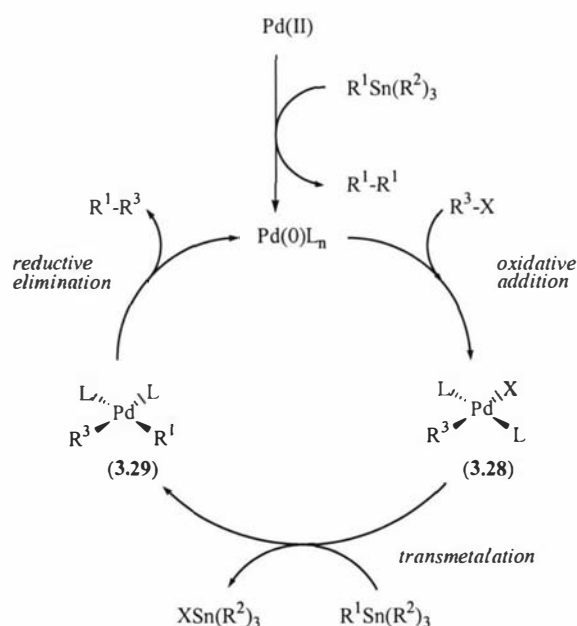
Scheme 3.16

In a direct application of this methodology, the tricyclic sulfolene derivative (3.27) was prepared by the Heck coupling of the aryl diazonium salt of *o*-anisidine with 3-sulfolene.¹⁷² (Scheme 3.16) Subsequent demethylation, base induced cyclisation and radical benzylic bromination/dehydrobromination were used to regenerate the desired 3-sulfolene moiety and complete the synthesis of (3.27).

From this limited number of sulfolene-based Heck reactions a consistent pattern of reactivity has emerged. The Heck arylation of the parent 3-sulfolene (3.1) yields 4-substituted-2-sulfolenes which, under basic conditions, are readily isomerised to the regioisomeric 3-sulfolene derivatives. The reactivity of vinylic and allylic coupling partners has not been investigated and similarly the reactivity of 2-sulfolenes and substituted sulfolenes in general also remains unexplored. Although a potentially fruitful area of research, the sulfolene Heck reaction was not pursued in the preparation of fused *oligo*-3-sulfolenes.

3.5.2 Stille Coupling.

Stille coupling has been defined as the palladium-catalysed coupling of unsaturated halides or sulfonates with organostannanes^{173,174} and has been extensively reviewed.^{173,175,176} A three step catalytic cycle has been proposed¹⁷³ and is represented below. (Scheme 3.17)

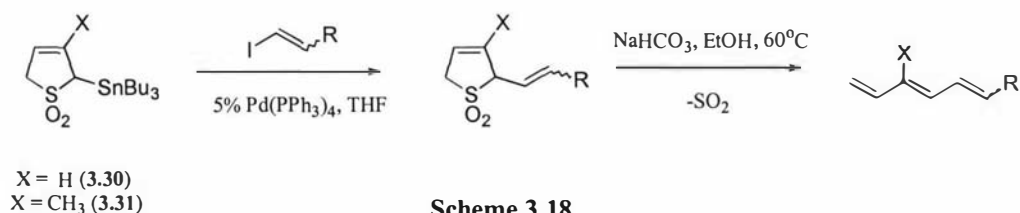


Scheme 3.17

While Pd(0) is the active catalytic species, many procedures utilise Pd(II) complexes. Under the reaction conditions, a Pd(0) species is generated *in situ* by an initial (fast) reduction process that results in concomitant oxidative coupling of two stannyl residues generating the homo-coupled product R^1-R^1 in a quantity equal to the amount of Pd(II) catalyst used. Once in the catalytic cycle, oxidative addition of an unsaturated halide or sulfonate (R^3-X) to a coordinatively unsaturated Pd(0) complex generates the intermediate complex (3.28). The intermediate (3.28) is generally formed as a *trans* square-planar complex, i.e., the ligands (L) are *trans* to one another, however, the intermediacy of the less stable *cis* complex has been postulated by Stille.¹⁷³ Transmetalation with an organostannane ($R^1Sn(R^2)_3$), involving the loss of tin halide or sulfonate ($XSn(R^2)_3$), leads to the substituted palladium complex (3.29) bearing both fragments of the final product. It has been shown that the transmetalation step is rate limiting and ligands (L) of lower donicity towards palladium than triphenylphosphine (i.e., tri(2-furyl)phosphine and triphenylarsine) exhibit major rate enhancements of up to 1000 fold.¹⁷⁷ With low donicity ligands many Stille coupling reactions, otherwise requiring forcing conditions, can be promoted effectively at room temperature. The final step of the process involves the reductive elimination of the coupled product (R^1-R^3) and the regeneration of a coordinatively unsaturated Pd(0) complex that re-enters the catalytic cycle.

The Stille coupling is of *very* broad scope and an impressive list of acyl, aryl, alkynyl, alkenyl and allyl halides and triflates have been successfully coupled with an equally comprehensive array of organostannanes.¹⁷⁵ Of equal significance to the synthetic utility of the Stille coupling reaction is the high degree of regiocontrol offered by the nature of the coupling partners. With *sp* and *sp*² substituted stannanes and halides alike, carbon-carbon bonds are formed regiospecifically at their respective substitution positions and the stereochemical integrity of the coupling partners is retained. For these reasons the Stille coupling reaction is a powerful synthetic tool and has been used extensively in synthesis.¹⁷⁸

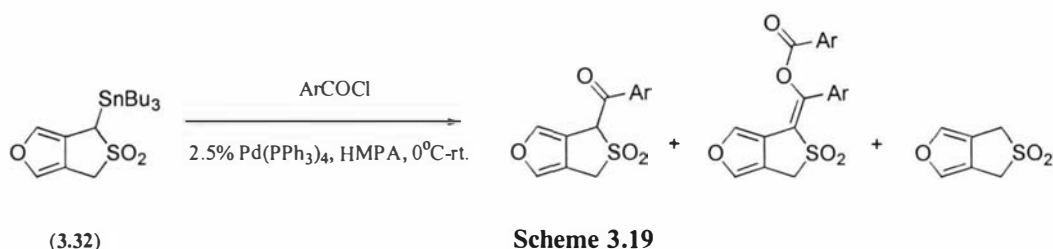
Like the Heck reaction, only a limited number of Stille coupling reactions involving sulfolenes have been reported. This may, in some part, be due to the relative obscurity of the requisite halogenated and stannylated sulfolene precursors. The three reported examples of the Stille reaction of sulfolenes all involve stannylated 3-sulfolenes.



Scheme 3.18

E- and *Z*-vinyl iodides have been coupled with 2-stannylated-3-sulfolenes (3.30, 3.31) in the presence of Pd(PPh₃)₄ in THF to give 2-vinyl-3-sulfolenes.¹⁷⁹ (Scheme 3.18) Yields were modest (*ca.* 30-40%) and no report of other regioisomeric coupled products was made (i.e. products resulting from allylic transposition). Thermal extrusion of sulfur dioxide under very mild, basic conditions furnished the expected conjugated trienes without isomerisation.

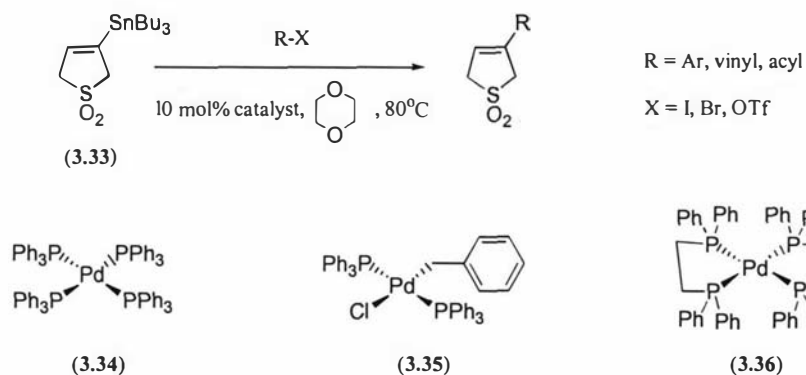
Coupling of the stannyl-sulfolene (3.32)¹⁸⁰ with a range of *p*-substituted benzoyl chlorides, in HMPA with catalytic Pd(PPh₃)₄, gave a mixture of acylated, doubly acylated and protiodestannylated products. (Scheme 3.19)



Scheme 3.19

The product distribution was variable and found to be dependent upon the electronic properties of the *p*-substituent of the acid chloride. Despite the mild reaction conditions, protiodestannylation could not be avoided and the reaction with other electrophilic coupling partners, including aryl and vinyl halides, was unsuccessful.

The Stille cross-coupling reaction of 3-stannylated-3-sulfolene (3.33), reported by Bew and Sweeney¹⁸¹ has been used to prepare a wide range of 3-substituted-3-sulfolenes. (Scheme 3.20)



Scheme 3.20

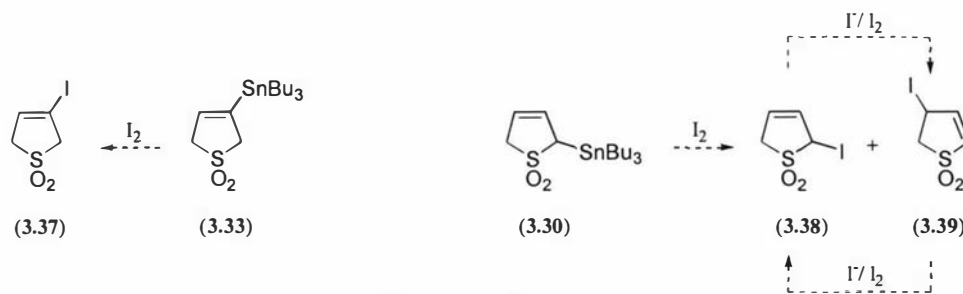
Reactions were carried out in 1,4-dioxane at 80°C and one of three catalyst systems were employed: *tetrakis*-(triphenylphosphine) palladium (0) (3.34), *trans*-benzyl(chloro)-*bis*-(triphenylphosphine) palladium (II) (3.35) (acyl chlorides only) and *bis*-[1,2-*bis*-(diphenylphosphino)] palladium (0) (3.36). Yields were variable, although generally good, and a diverse range of aryl and alkenyl iodides and bromides were successfully accommodated, as were acyl chlorides and cyclohexen-1-yl triflates, albeit in poorer yield. The reaction was tolerant of electron deficient and *o*-substituted arenes.

3.6 Research Aims.

The successful regioselective coupling of stannylated 3-sulfolenes with a range of electrophilic partners encouraged us to pursue the Stille cross-coupling reaction of 3-sulfolene derivatives as a possible synthetic route to fused *bis*-3-sulfolenes. This strategy required the synthesis of regiodefined stannylated and halogenated sulfolene coupling partners.

The stannylated 3-sulfolenes (3.30)¹⁸² and (3.33)¹⁸¹ have been prepared previously and it was envisaged that these methods could be easily adapted to provide workable quantities of the appropriate stannanes. However, while simple stannylated-3-sulfolenes were relatively accessible, iodinated 3-sulfolene derivatives have not been reported. It was anticipated, however, that tin-iodine exchange with the vinylic stannane (3.33) would yield 3-iodo-3-sulfolene (3.37), while exchange with the allylic stannane (3.30) would lead to either 2-iodo-3-sulfolene (3.38) by a simple S_E2 process, or to the known regioisomeric 4-iodo-2-sulfolene (3.39) by a competing S_E2' mechanism. (Scheme 3.21) The direct synthesis of 4-iodo-2-sulfolene (3.39) from 3-

sulfolene (3.1), according to Chou,¹³⁹ offered yet a further possible route to (3.39) and hence (3.38) through allylic transposition.



Scheme 3.21

With access to a range of iodo- and stannylated 3-sulfolene derivatives it would be possible to investigate the synthesis of fused *bis*-3-sulfolenes *via* the Stille cross-coupling reaction.

3.7 The Stille Cross-coupling of 3-Sulfolene Derivatives.

3.7.1 Synthesis of Coupling Partners.

3.7.1.1 4-Iodo-2-sulfolene.¹³⁹

Zinc sulfolenylates react with elemental halogens to give 4-halogenated-2-sulfolenes exclusively (3.12, E = I, Br, Scheme 3.8).¹³⁹ Attempts to reproduce this approach to 4-iodo-2-sulfolene were not immediately successful. Directions outlining the formation of zinc sulfolenylates reported by Chou¹³⁹ described the addition of a solution of anhydrous zinc halide in THF to a solution of lithium sulfolenylate generated in THF at -105°C from 3-sulfolene (3.1) and BuLi. After several unsuccessful attempts to reproduce this procedure (Table 3.1), a personal communication with the authors revealed that several crucial details had been omitted from the published work. It was necessary to fuse the zinc halide *in vacuo* and cool under argon prior to the addition of THF and, importantly, to add HMPA to the reaction mixture. In view of the toxicity of HMPA,⁶³ alternative co-solvents (or no co-solvent) were at first examined and variations in work-up (unspecified by Chou) were attempted. (Table 3.1, entries 1-4) However, the best results were indeed obtained when HMPA (11% in THF) was employed as co-solvent, whereupon 4-iodo-2-sulfolene (3.39) was isolated after

chromatography in 28% yield following a solid phase work-up of the reaction mixture on a silica gel pre-column, (entry 6).

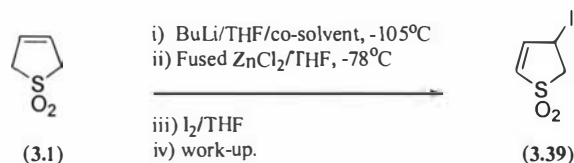


Table 3.1

entry	co-solvent (11%)	work-up	yield of (3.39) (%) / observations
1	none	NH ₄ Cl (aq)	0
2	none	Na ₂ S ₂ O ₃ (aq)	0
3	DMPU	NH ₄ Cl (aq)	Present in crude, not isolable
4	TMEDA	NH ₄ Cl (aq)	0
5	HMPA	NH ₄ Cl (aq)	Present in crude, not isolable
6	HMPA	silica gel	28

4-Iodo-2-sulfolene (3.39) prepared by this method was a mobile pale yellow oil that rapidly darkened on exposure to light and air. Solutions in benzene could be stored indefinitely at -18°C.

3.7.1.2 2-Iodo-3-sulfolene. Attempted Isomerisation of 4-iodo-2-sulfolene.

Solutions of 4-iodo-2-sulfolene in either CDCl₃ or CH₂Cl₂ became purple on exposure to light, indicating the liberation of elemental iodine. ¹H NMR analysis of this coloured solution revealed the formation of a new species, with signals consistent with the desired 2-iodo-3-sulfolene (3.38). This encouraged us to pursue the isomerisation of 4-iodo-2-sulfolene (3.39) to the regioisomeric 2-iodo-3-sulfolene (3.38) using iodine or iodide.

In the presence of one equivalent of elemental iodine in CDCl₃ at room temperature in the dark, partial isomerisation (23%) of (3.39) to (3.38) was observed by ¹H NMR over 24 hours. Careful tlc analysis revealed the isomeric allylic iodides were essentially inseparable on silica gel with most solvent systems, although a partial separation was

achievable with hexane-ethyl acetate-CH₂Cl₂ (2:1:1). Chromatographic separation of these compounds proved very difficult and gave, at best, an enrichment of only 50% of the 2-iodo compound (**3.38**). Light-induced decomposition of material during chromatography and silica gel-mediated isomerisation were suspected sources of difficulty. Attempts to effect the isomerisation of (**3.39**) to (**3.38**) in the presence of lithium iodide in d₆-acetone under identical conditions were unsuccessful and no reaction was observed. In view of the very labile nature of these iodides, additional attempts to prepare or further purify 2-iodo-3-sulfolene (**3.38**) were not pursued.

3.7.1.3 2-Tributylstannyl-3-sulfolene.¹⁸²

A convenient synthesis of 2-tributylstannyl-3-sulfolene (**3.30**) has been reported by Fraser-Reid and co-workers.¹⁸² Treatment of an excess of 3-sulfolene (**3.1**) with lithium hexamethydisilazide in the presence of tributyltin iodide (*as the limiting reagent*) at -78°C, gave 2-tributylstannyl-3-sulfolene (**3.30**) in a 50-55% isolated yield after chromatography. In our hands this procedure gave the desired product in 38% yield with significant quantities of an additional stannylated sulfolene not mentioned by the original workers. This material was shown to be the 2,5-*bis*-tributylstannyl-3-sulfolene (**3.40**) and was isolated after chromatography in 60% yield, (based on tin halide as the limiting reagent), as a 30:70 mixture of *cis* (**3.40b**) and *trans* (**3.40a**) diastereoisomers. (Table 3.2, entry 1) It is believed that the *bis*-stannylated sulfolenes (**3.40**) are formed by a second *in situ* stannylation of the preliminary product (**3.30**). The observed stereoselectivity is consistent with favoured abstraction (by a bulky base) of the least hindered and most acidic proton at the 5-position, located *trans* to the substituent at C-2, followed by rapid capture of the resulting α-carbanion before stereochemical inversion can occur. A similar observation has been made for the stereoselective alkylation of 2-substituted 3-sulfolenes, where the *trans*-2,5-dialkyl sulfolene adducts are also favoured.^{132,133} It was with reference to this precedent that the stereochemical assignment of (**3.40a**) and (**3.40b**) were made.

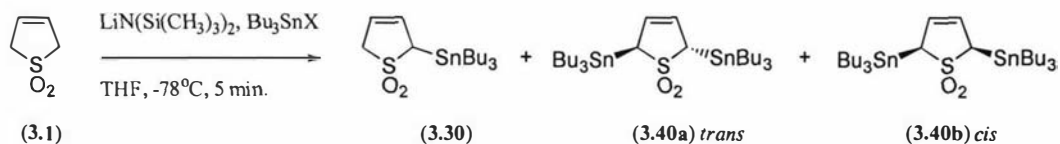


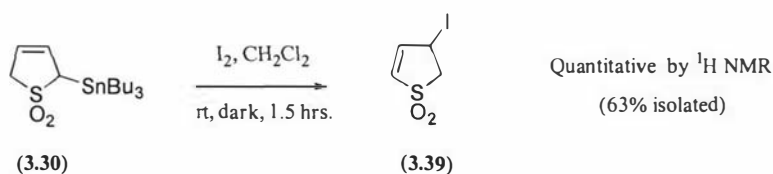
Table 3.2

entry	X	Yield %	
		(3.30)	(3.40a) / (3.40b)
1	I	38	60 (70:30)
2	Cl	48	31 (76:24)

On repeating the stannylation of 3-sulfolene, under otherwise identical reaction conditions with tributyltin chloride, the formation of the desired *mono*-stannylated sulfolene adduct was favoured (48%), as was expected with a less electrophilic stannylating agent. (Table 3.2, entry 2) The 2,5-*bis*-stannanes (3.40a) and (3.40b) were still formed, albeit in reduced yield (31%), again favouring the *trans* isomer. Attempted separation of the diastereomeric *bis*-stannylated sulfolenes (3.40a) and (3.40b) by column chromatography gave only small quantities of the major *trans*-stereoisomer (3.40a) and was not pursued further.

3.7.1.4 Tin-Iodine Exchange of 2-Tributylstannyl-3-sulfolene.

The treatment of 2-tributylstannyl-3-sulfolene (3.30) with one equivalent of elemental iodine in CH_2Cl_2 in the dark saw its smooth conversion, *via* an $\text{S}_{\text{E}}2'$ mechanism, to 4-iodo-2-sulfolene (3.39). (Scheme 3.22) This process was quantitative, as judged by ^1H NMR, and the product was identical to that prepared by the iodination of the zinc sulfolenylate (3.9).¹³⁹ Some isomerisation to the isomeric 2-iodo-3-sulfolene (3.38) was observed as before, however, this was minimal if the reaction was monitored closely by tlc and terminated when the last traces of stannane were consumed.

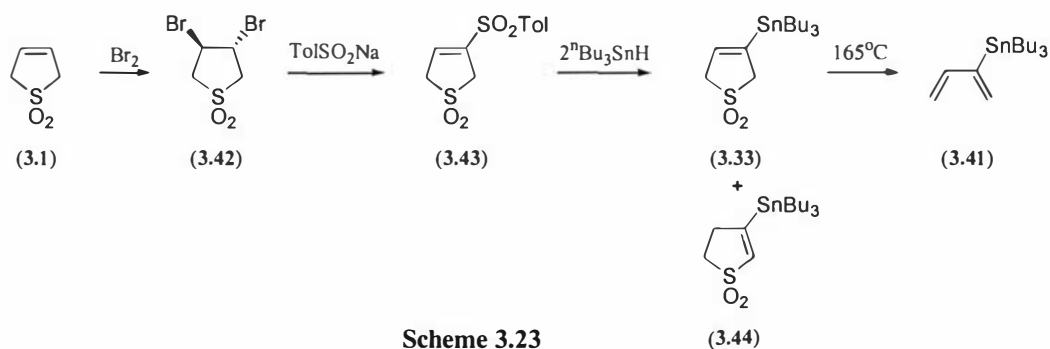


Scheme 3.22

After trituration with hexanes to remove the tin residues, the pure material was isolated in 63% yield and therefore represents a simple yet effective two step alternative route to 4-iodo-2-sulfolene (3.39), which does not involve the use of HMPA. In principle, the tributyltin iodide by-product can be recycled improving the potential efficiency of this process even further.

3.7.1.5 3-Tributylstannyl-3-sulfolene.¹⁸¹

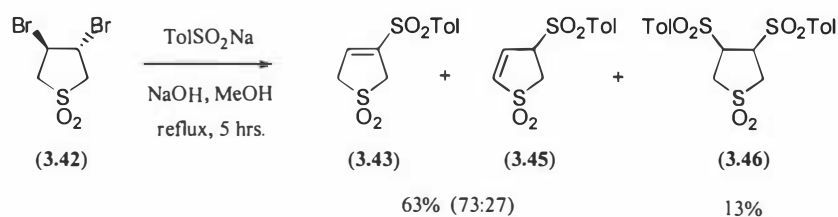
A three step synthesis of 3-tributylstannyl-3-sulfolene (3.33), as a stable precursor to 2-tributylstannyl-1,3-butadiene (3.41), has been developed by Bew and Sweeney from commercially available 3-sulfolene (3.1).¹⁸¹ (Scheme 3.23) Bromination of 3-sulfolene (3.1) gave *trans*-3,4-dibromosulfolane (3.42), which upon treatment with sodium *p*-toluenesulfinate tetrahydrate and sodium hydroxide in methanol yielded 3-(*p*-tolylsulfonyl)-3-sulfolene (3.43) as a single product. Radical desulfurative stannylation, according Ueno *et al.*,¹⁸³ with two equivalents of tributyltin hydride and a radical initiator, gave the desired stannane (3.33) in 72% isolated yield after chromatography. The formation of 5-20% of the regioisomeric 3-tributylstannyl-2-sulfolene (3.44) during chromatography was also noted. The unwanted appearance of this material was remedied by the use of neutral alumina, rather than silica gel, during the chromatographic purification. The thermal extrusion of sulfur dioxide to give 2-tributylstannyl-1,3-butadiene (3.41) was achieved by short path distillation under reduced pressure and the stannylated diene was isolated in gram quantities and good yield. The sulfolene itself, (3.33), could be stored indefinitely as a stable oil at 0°C.



Scheme 3.23

3.7.1.5.1 3-(*p*-Tolylsulfonyl)-3-sulfolene.¹⁸⁴

In our hands, 3,4-*trans*-dibromosulfolene (3.42) was readily prepared according to the method of Bailey and Cummins¹⁴⁹ with analytically pure material being obtained in 80-85% yield after recrystallisation from water-ethanol (2:1). The conversion of this material to 3-(*p*-tolylsulfonyl)-3-sulfolene (3.43), while omitted from Sweeney's original report, has been described by Inomata *et al.*¹⁸⁴ Inomata reported that treatment of dibromosulfolene (3.42) with a five fold excess of sodium *p*-toluenesulfinate and 1.1 equivalents of sodium hydroxide in refluxing methanol gave (3.43) as a single, analytically pure compound after recrystallisation from ethanol.



Scheme 3.24

On repeating Inomata's procedure (**Scheme 3.24**), the desired tosylsulfolene was obtained, but only as a mixture contaminated with the minor isomeric sulfolene (3.45) in the ratio of 73:27 (**Table 3.3**, entry 1). In addition, a small quantity of the 3,4-*bis*-tosylated sulfolene (3.46) (13%) was also isolated as an insoluble solid upon hot filtration prior to recrystallisation of the crude product. The isomeric sulfolenes (3.43) and (3.45) could not be separated on silica gel and the minor isomer proved impossible to remove by fractional crystallisation. ¹H NMR analysis of a mixture of (3.43) and (3.45) (CDCl₃), after recrystallisation, clearly showed signals consistent with (3.43) and identical to those reported by Inomata *et al.*¹⁸⁴ The identity of (3.45) was not, however, immediately apparent.

The appearance of signals attributable to a *p*-tolyl group strongly indicated the presence of a *p*-tolylsulfonyl moiety. Further analysis of the remaining integrational intensities confirmed the presence of five additional protons. The relatively simple spectrum consisted of a downfield, two proton doublet of quartets at 6.84 ppm; a single proton appearing as an intriguing triplet of triplets centred at 4.63 ppm; and a simple two proton doublet with a chemical shift of 3.47 ppm consistent with the expected chemical

shift of an α -sulfone methylene. It was assumed that the minor component (**3.45**) was the simple regioisomeric 4-(*p*-tolylsulfonyl)-2-sulfolene, but the spectral data did not appear entirely consistent with this assignment, particularly when comparison was made with the structurally related 4-iodo-2-sulfolene (**3.39**). (**Figure 3.4**)

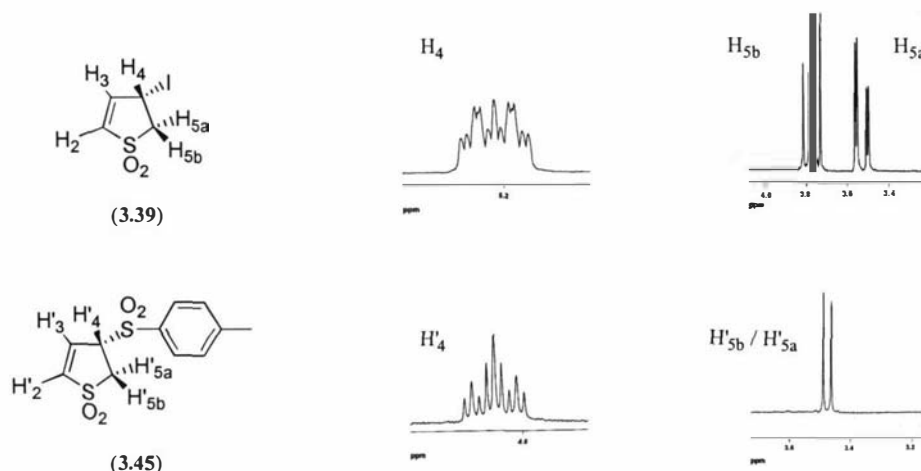


Figure 3.4

The ^1H NMR spectrum of (**3.39**) at room temperature in CDCl_3 shows the α -sulfone methylene as two distinct diastereotopic protons H_{5a} and H_{5b} , clearly resolved as a pair of doublets of doublets with a large geminal coupling constant (J_{5a-5b}) of 15.0 Hz and smaller vicinal couplings of 7.7 and 2.9 Hz for J_{4-5b} and J_{4-5a} respectively. The allylic methine proton H_4 appears as a complex, symmetrical multiplet, coupling with all other protons, while the alkenic protons H_3 and H_2 both appear as well resolved first order doublets of doublets (not shown in **Figure 3.4**). In short, the signals associated with (**3.45**), while exhibiting the appropriate integrational intensity and relative chemical shifts, did not demonstrate the expected multiplicities when compared with the iodide (**3.39**).

It is possible to rationalise this unexpected result by considering the potential origin of the magnetic non-equivalence of the diastereotopic protons H_{5a} and H_{5b} of the iodide (**3.39**). As a consequence of the steric bulk of the iodine substituent in (**3.39**), puckering, or ring oscillation, is slow with respect to the NMR time scale and the protons H_{5a} and H_{5b} are therefore neither chemically nor magnetically equivalent. The presence of a less sterically demanding 4-substituent (i.e. $-\text{SO}_2\text{Tol}$ in (**3.45**)) results in more rapid oscillation of the sulfolene ring. As the rate of ring oscillation increases, H'_{5a} and H'_{5b} will approach a time averaged magnetic equivalence and ultimately their

signals will coalesce, giving rise to a single line, split only by coupling to H'_4 . Hence the signal for protons H'_{5a}/H'_{5b} will appear as a simple doublet, while H'_4 will appear as a triplet split further by coupling to protons H'_2 and H'_3 . To account for the observed appearance of H'_4 as a triplet of triplets, it must be assumed that $J_{H'_4-H'_3}$ is of a equal magnitude to $J_{H'_4-H'_2}$. If the chemical shift difference ($\Delta\delta$) between protons H'_2 and H'_3 is small with respect to their mutual coupling, their appearance will tend towards an AB quartet; and, as a further consequence of assuming the value of $J_{H'_4-H'_3}$ is of a comparable magnitude to $J_{H'_4-H'_2}$, the signals for H'_2 and H'_3 will appear as a doublet of AB quartets. Long range COSY, optimised for 2.0 Hz, clearly indicated there was no additional coupling between the H'_5 protons and either H'_3 or H'_2 .

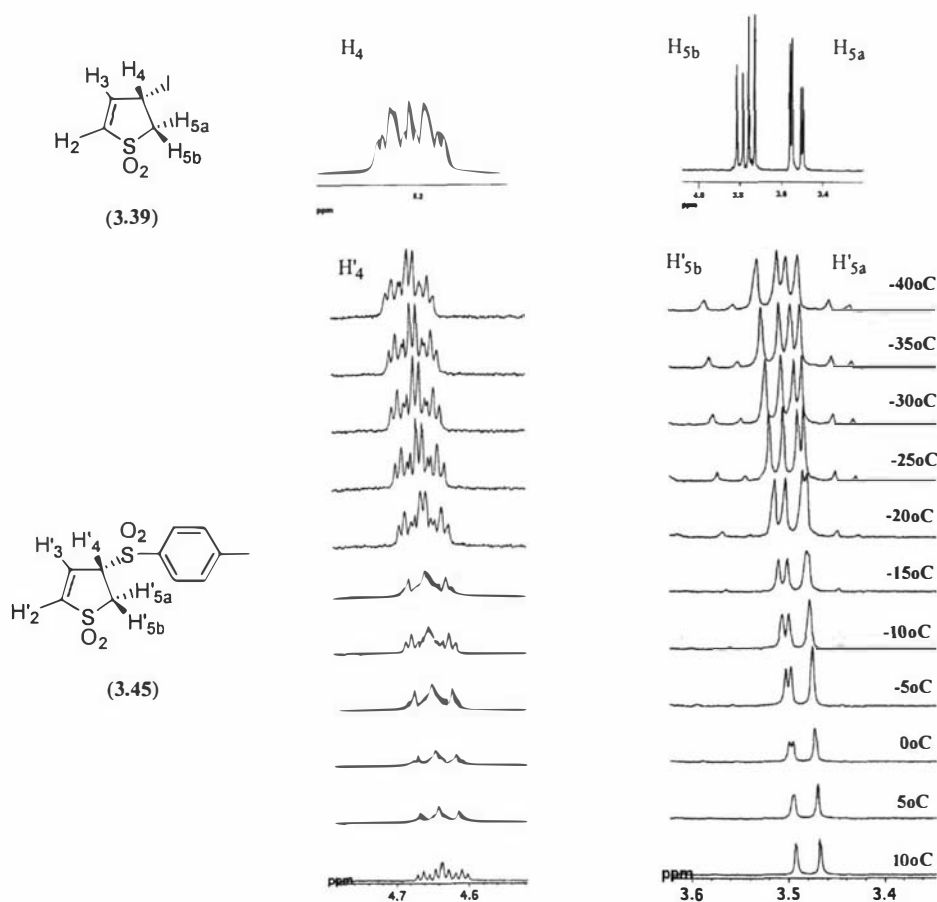
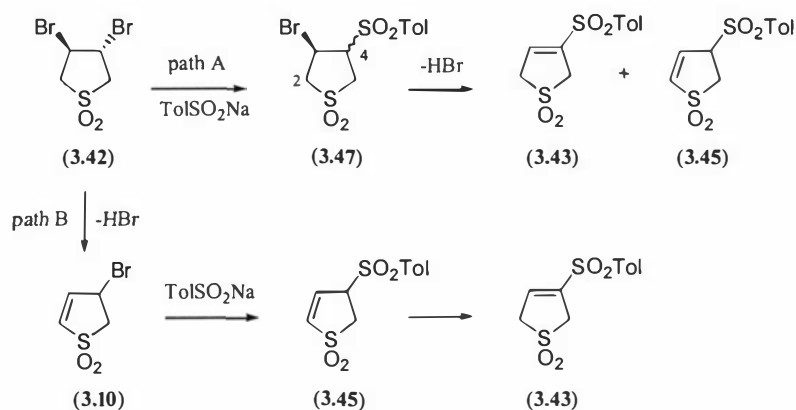


Figure 3.5

These assumptions were tested by observing the effect of reduced temperature on the ^1H NMR of (3.45). Spectra were recorded for the sulfolene mixture (3.43) and (3.45) at intervals of 5°C from 10°C to -40°C . (Figure 3.5) At 0°C , partial splitting of the H'_{5a}/H'_{5b} doublet was first observed. The magnitude of the apparent coupling increased smoothly as the temperature was reduced further and at -40°C a pair of well resolved

doublets ($J = 5.7, 3.5$ Hz) had evolved showing some evidence of additional second order complexity. Similarly the H'_4 triplet of triplets had collapsed, giving a more complex symmetrical multiplet comparable to that observed for H_4 in (3.39). Signals associated with H'_2 and H'_3 remained unchanged. From these observations it was concluded the unexpected 1H NMR of (3.45) was wholly consistent with the structural assignment of 4-(*p*-tolylsulfonyl)-2-sulfolene. Furthermore, the intuitive relationship between increased substituent size and reduced ring mobility was confirmed.

Two simple mechanistic possibilities exist for the formation of the sulfolene mixture (3.43) and (3.45) and one or both may be involved. Inomata¹⁸⁴ proposed that his one pot procedure proceeded *via* a substitution-elimination process. (Scheme 3.25, path A) This implies the existence of an intermediate 3-bromo-4-tosylsulfolane (3.47), formed by a direct S_N2 substitution reaction. Subsequent base catalysed dehydrobromination from either the 2- or 4-positions would give (3.45) and (3.43) respectively. In Inomata's hands, this elimination may have been regioselective, although it is more likely that both isomers were formed and subsequent base catalysed isomerisation of (3.45) to (3.43) occurred under the reaction conditions prior to isolation. The formation of small quantities of 3,4-*bis*-(*p*-tolylsulfonyl)-3-sulfolane (3.46) (Scheme 3.24) strongly suggests bromine substitution is indeed occurring before base induced dehydrobromination and therefore supports the mechanism proposed by Inomata.



Scheme 3.25

Alternatively, the formation of (3.45) and (3.43) may proceed *via* an elimination-substitution pathway. (Scheme 3.25, path B) Indeed, the base catalysed dehydrobromination of *trans*-3,4-dibromosulfolane (3.42) is well known and has long been used as a method to prepare 4-bromo-2-sulfolene (3.10).¹⁴⁹ Furthermore, (3.10)

has been shown to react with a variety nucleophiles, including phenylsulfinate, (Scheme 3.10) and this reaction occurs by an S_N2 pathway.¹⁵² However, under these conditions, spontaneous double bond isomerisation occurred rapidly and only 3-sulfolenes were isolated despite the intermediacy of the initially formed 2-sulfolenes.

The formation of an isomeric sulfolene mixture (3.43) and (3.45) was initially disappointing, although reasonable from a mechanistic viewpoint. Encouraged by the successful reports describing the formation of isomerically pure 3-arylsulfonyl-3-sulfolenes^{152,184} we re-investigated the formation of 3-(*p*-tolylsulfonyl)-3-sulfolene (3.43). (Table 3.3)

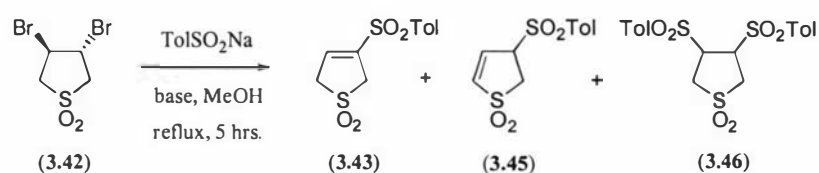


Table 3.3

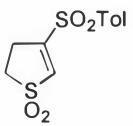
entry	NaSO ₂ Tol equivs	base (equivs)	yield (%)	
			(3.43):(3.45)	(3.46)
1	5.0	NaOH (1.1)	63 (73:27)	13
2	3.0	NaOH (1.1)	62 (72:28)	13
3	5.0	KOH (1.1)	58 (79:21)	10
4	5.0	KOH (2.0)	6 (100:0)	42
5	3.0	none	0	51

Reduction in the quantity of sodium *p*-toluenesulfinate (entry 2) saw essentially no change to the results obtained under Inomata's reported conditions¹⁸⁴ (entry 1). The use of potassium hydroxide saw a drop in yield, albeit small, and a marginal increase in the proportion of the desired 3-sulfolene (entry 3). The potential importance of base catalysed dehydrobromination was assessed by the use of 2 equivalents of potassium hydroxide (entry 4) whereupon it was found that (3.43) could be obtained as a single isomer although in very low yield. However, the surprising formation of the *bis*-tosyl-3-sulfolane (3.46) in significant quantities (42%) made this modification of little synthetic

use. No better conditions for the synthesis of isomerically pure (3.43) were found. In the absence of base (entry 5), *bis*-tosyl-3-sulfolene (3.46) was again obtained, but as the sole product, with no trace of the desired 3-sulfolene.

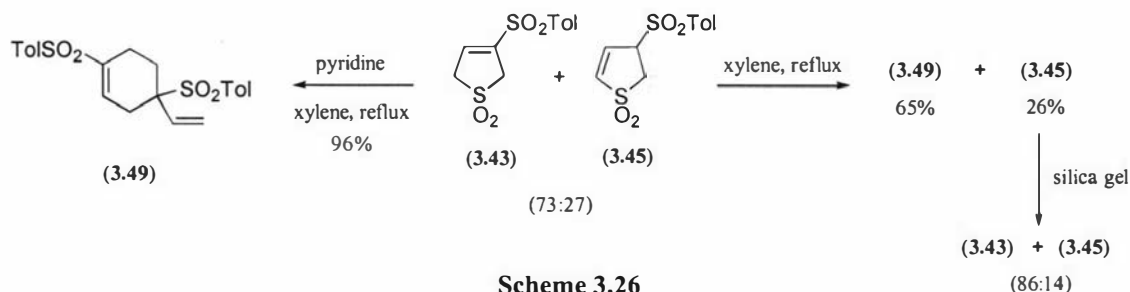
Some attempt to effect the base catalysed isomerisation of (3.45) to (3.43) was made. (Table 3.4) The addition of either excess triethylamine or excess pyridine to a chloroform solution of the sulfolene mixture (3.45) and (3.43) at room temperature showed some enrichment (11-18%) of the desired 3-sulfolene (3.43), Frustratingly, conversion remained incomplete despite extended reaction times. The addition of 0.1 equivalents of DBU saw the rapid formation of 3-(*p*-tolylsulfonyl)-2-sulfolene (3.48), as characterised by ^1H NMR, but no attempt to isolate this material was made.

Table 3.4

(3.43):(3.45) before	base	(3.43):(3.45) after
79:21	Et ₃ N	88:12
73:27	Pyridine	86:14
73:27	DBU	 (3.48)

Thermolysis of the 3-sulfolene (3.43) and subsequent regioselective Diels-Alder dimerisation of the resulting diene to give the cycloadduct (3.49) has been reported by Inomata *et al.*¹⁸⁴ (Scheme 3.26) When repeated, thermolysis of (3.43) and (3.45) (as a mixture) in the presence of excess pyridine did give the expected cycloadduct (3.49) in near quantitative yield, clearly indicating that the conversion of (3.45) to (3.43) was readily achievable under these conditions. In an attempt to isolate pure tosyl sulfolene (3.45) the thermolysis was carried out in the absence of base. The selective removal of (3.43) was indeed observed at 130°C in *d*₁₀-xylene leaving (3.45) untouched. However, when repeated preparatively, attempts to isolate and characterise (3.45) as a pure compound, by chromatography on silica gel, saw the unexpected regeneration of the original sulfolene mixture (86:14) as obtained after base catalysed isomerisation! It was concluded that separation through chromatography was not an effective method of

purifying either (3.45) or (3.43). Evidently, the pure 4-tosyl-2-sulfolene (3.45) isomerises to an equilibrium mixture upon chromatography.



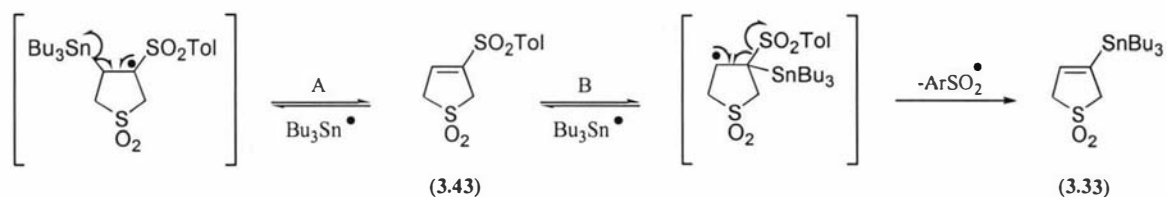
In view of the difficulties encountered in the formation and isomerisation of (3.43) and (3.45), coupled with a strong desire to pursue the preparation of the stannylated-3-sulfolene (3.33), no further optimisation of these processes were attempted.

3.7.1.5.2 Application of the Ueno Reaction.¹⁸³

Under normal conditions the Ueno reaction involves the substitution of an allylic aryl sulfone moiety with a trialkylstannane, where the overall allylic transposition proceeds *via* a radical addition-elimination process.¹⁸³ (Scheme 3.27)

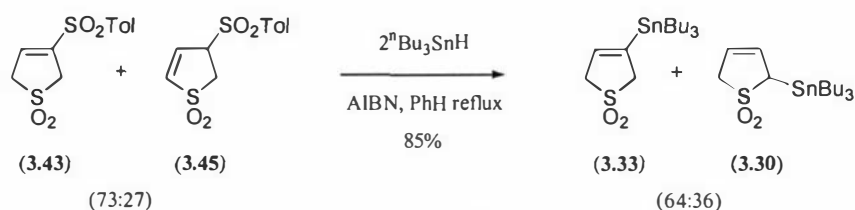


Under the conditions employed by Bew and Sweeney,¹⁸¹ however, the transformation of the vinylic aryl sulfone (3.43) to the vinylic stannane (3.33) (Scheme 3.22) must proceed *via* a different mechanism. The addition of a trialkyltin radical to the double bond of (3.43) can occur in one of two ways. (Scheme 3.28)



- A. "Michael type" addition to the 4-position of (3.43) generates an intermediate tertiary carbon centred radical, which cannot eliminate an aryl sulfone radical through a β -fragmentation process. Therefore, in the absence of ring fission or radical quenching, this species is compelled to eliminate the same tin radical thereby regenerating the starting material.
- B. Addition in the "anti-Michael" sense generates a secondary carbon centred radical intermediate, which is able to eliminate an aryl sulfone radical through a β -fragmentation process. Irreversibility in the C-S bond cleavage acts as the driving force for the reaction.

Considering the mechanistic implications of both the allylic and vinylic Ueno reactions it was expected that treatment of the arylsulfone mixture (3.43) and (3.45) with tributyltin hydride in the presence of a radical initiator in refluxing benzene would produce the desired 3-tributylstannylated-3-sulfolene (3.33) (vinylic Ueno reaction) and 2-tributylstannyl-3-sulfolene (3.30)¹⁸² (allylic Ueno reaction) respectively. (Scheme 3.29)



Scheme 3.29

According to the method of Bew and Sweeney,¹⁸¹ a solution of (3.43) and (3.45) in refluxing benzene, in the presence of two equivalents of freshly prepared tributyltin hydride¹⁸⁵ and a catalytic quantity of AIBN, were smoothly converted to the 3-tributylstannylated and 2-tributylstannylated 3-sulfolenes (3.33) and (3.30) respectively, in an 85% isolated yield. Prior to separation on silica gel, the ratio of isomers was estimated from the ^1H NMR spectrum of the crude reaction mixture. An initial sulfolene ratio of 73:27 ((3.43):(3.45)) gave a stannane ratio of 64:36 ((3.33):(3.30)), representing an effective enrichment of the allylic stannane over its vinylic regioisomer. The stannane (3.30), present in the mixture, exhibited identical spectral characteristics to the material prepared by the direct stannylation of 3-sulfolene (3.1) described earlier. (Table 3.2) The formation of 3-tributylstannyl-2-sulfolene (3.44) (Scheme 3.23), as reported by Bew and Sweeney, was not observed and, furthermore, neither (3.33) nor

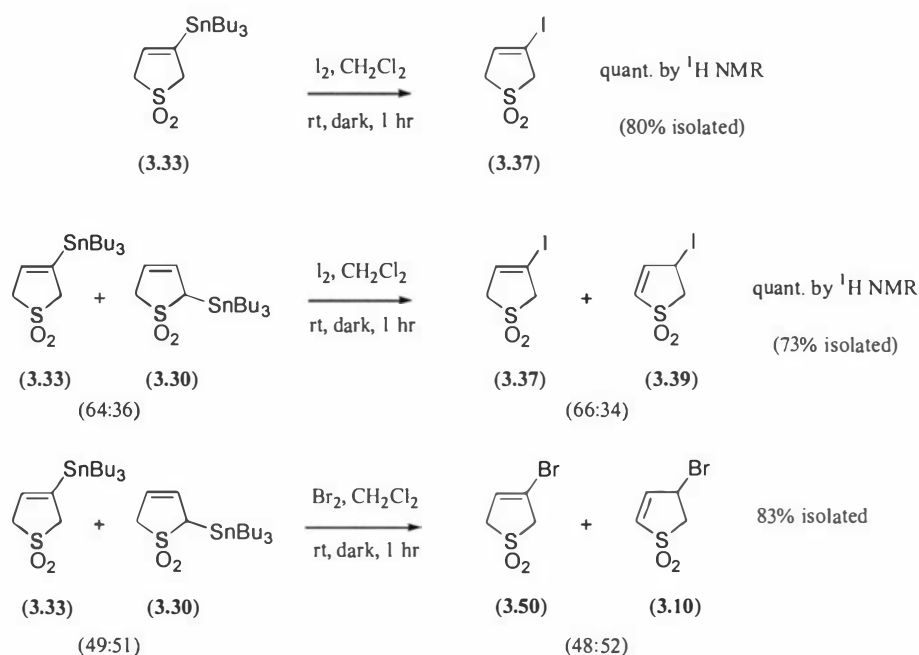
(3.30) suffered decomposition or isomerisation on silica gel during chromatographic separation as had been implied.¹⁸¹

A small quantity of isomerically pure 3-(*p*-tolylsulfonyl)-3-sulfolene (3.43) had been successfully prepared (Table 3.3, entry 4) and, to assess the regiochemical integrity of the Ueno reaction of the vinylic aryl sulfone (3.43), this material was subjected to the radical desulfurative stannylation conditions reported by Bew and Sweeney.¹⁸¹ The anticipated 3-tributylstannylated-3-sulfolene (3.33) was formed, but not, as anticipated, as a single product. The surprising formation of the isomeric 2-tributylstannylated 3-sulfolene (3.30) was again observed. ¹H NMR analysis of the crude reaction mixture revealed a product ratio of 73:27, favouring the vinylic stannane (3.33). Again the product ratio remained unchanged after chromatography giving the stannane mixture in a combined, isolated yield of 73%. In the absence of a plausible radical mechanism, formation of (3.33) can be most easily explained by invoking pre-equilibration of (3.43) to a mixture of both (3.43) and (3.45) prior to the radical desulfurative stannylation reaction. However, the surprising formation of (3.30) from isomerically pure 3-(*p*-tolylsulfonyl)-3-sulfolene (3.43) corroborates the observed enrichment of (3.30) over (3.33) in the Ueno reaction of the sulfolene mixture.

While it is impossible to say with certainty that the observations of Bew and Sweeney were incorrect, it is our belief that the formation of 3-tributylstannyl-2-sulfolene (3.44) as reported¹⁸¹ (Scheme 3.23) did not occur and a simple mis-assignment of the known stannane (3.30),¹⁸² as the true contaminant, was falsely reported. It is interesting to also note the omission of any reference relating to the preparation and composition of the key tosyl-3-sulfolene (3.43) in Sweeney's report. Nonetheless, in our hands multi-gram quantities of both 3-tributylstannyl-3-sulfolene (3.33) and 2-tributylstannyl-3-sulfolene (3.30) could be prepared easily and with careful chromatography isolated as pure compounds. Both stannanes were viscous colourless oils and proved to be stable indefinitely when stored under argon at low temperatures.

3.7.1.6 3-Halo-3-sulfolenes.

The conversion of *E*- and *Z*-vinyl stannanes to vinyliodides, with retention of configuration, has been achieved under mild conditions with elemental iodine.^{186,187} Treatment of 3-tributylstannyl-3-sulfolene (**3.33**) with 1.0 molar equivalent of iodine in CH₂Cl₂ at room temperature in the dark gave the vinyliodide (**3.37**) in quantitative yield as judged by ¹H NMR. (Scheme 3.30) Pure material, free of tin residues, was obtained in 80% yield after chromatography, trituration with hexanes and recrystallisation from diethyl ether-CH₂Cl₂. No reports of this light and air stable crystalline solid have been made in the literature.



Scheme 3.30

Mixtures of the regioisomeric stannanes (**3.33**) and (**3.30**) could be iodinated together and the resulting iodo-sulfolene adducts, (**3.37**) and (**3.39**) respectively, were readily separable by chromatography on silica gel. The formation of 4-iodo-2-sulfolene under these conditions confirmed the previous regioisomeric assignment of (**3.39**) and was wholly consistent with the earlier, independent synthesis and reactivity of 2-tributylstannyl-3-sulfolene (**3.30**) (Scheme 3.22) Analytically pure 3-iodo-3-sulfolene was obtained from this mixture after trituration with hexanes to remove tin residues and recrystallisation from ether-CH₂Cl₂. The isomeric ratio of this mixed tin-iodine exchange remained constant and on a large scale the iodides could be separated by

repeated fractional crystallisation without recourse to chromatography. In this manner gram quantities of both isomeric iodo-sulfolenes were readily available.

Bromination of the stannane mixture (3.33) and (3.30) could be achieved in good yield under equivalent conditions with elemental bromine. Again the regiochemical integrity of the tin-halogen exchange was preserved and the bromides (3.50) and (3.10) could be easily separated by chromatography on silica gel and purified by trituration with hexanes to remove traces of residual tributyltin bromide. Subsequent recrystallisation of (3.50), from ether-CH₂Cl₂, gave the vinylbromide as an analytically pure, air stable crystalline solid. The known allylic bromide (3.10),¹⁴⁹ an oil, was found to be more stable and easier to handle than the corresponding allyl iodide (3.39). As before, this route to 4-halogenated-2-sulfolene has distinct advantages over existing literature methods¹³⁹ and the direct regeneration and recycling of the stannylating agents as isolable by-products serves to improve the efficiency of the process and lessen the environmental impact of using organotin reagents.

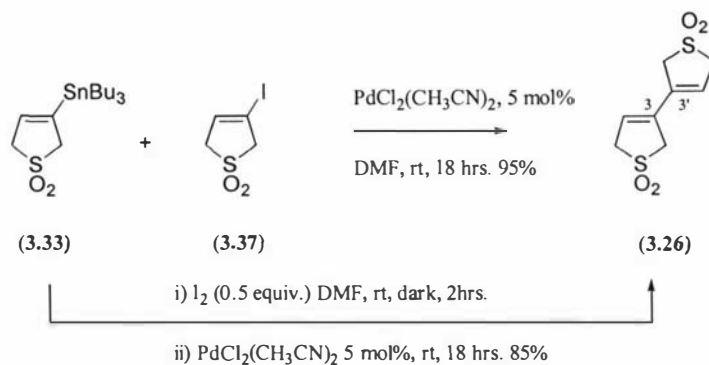
3.7.2 Preliminary Cross-coupling Experiments

With access to a range of stannylated and halogenated sulfolene derivatives the Stille cross-coupling reaction was investigated as a route to fused *bis*-sulfolenes.

3.7.2.1 Two Vinylic Partners.

With the Stille coupling of allylic electrophiles (halides), a regiochemical issue exists. These couplings proceed *via* η^3 -allylpalladium intermediates and substitution is therefore possible at either the α or γ positions.^{173,175} The same regiochemical question arises when considering the coupling of allylic stannanes. While substitution at the less hindered terminus of the electrophilic component is generally observed,^{173,175} the regioselectivity for the stannane partner is less well understood.¹⁷⁶ In recognition of these potential regiochemical complications, the preliminary Stille cross-coupling reactions were limited to the alkenyl iodide (3.37) and the alkenyl stannane (3.33).

It was anticipated that an initial survey of commonly used solvent and catalyst combinations would be necessary to find conditions suitable for the formation of fused *bis*-3-sulfolenes. While a detailed discussion of catalyst, ligand and solvent choice has been presented by Farina,¹⁷⁵ it was noted that many successful coupling reactions had been carried out in DMF with *bis*-(acetonitrile) palladium (II) dichloride. This simple combination appeared particularly valuable for the coupling of simple vinylic partners¹⁸⁸ and hence these conditions were the first solvent-catalyst combination to be investigated.



Scheme 3.31

When a degassed solution of iodo-sulfolene (3.37) and stannyl-sulfolene (3.33) was treated with a catalytic quantity of *bis*-(acetonitrile) palladium (II) dichloride in DMF, the reaction mixture darkened rapidly and both coupling partners were consumed over time, as judged by tlc. It was somewhat confusing, however, to see the characteristic streak of a tin halide on a silica tlc plate but no feature that could be attributed to the formation of any coupled product. Anticipating a failed reaction, the mixture was left overnight. After 18 hours at room temperature the solution had lightened in colour considerably; the starting materials had been consumed and, surprisingly, a heavy, off white precipitate had collected at the bottom of the flask. The supernatant was decanted off and the precipitate triturated with ether and hexane to remove residual DMF and tin halide respectively. The purified precipitate was found to be highly insoluble and d₆-DMSO proved to be the only solvent suitable for ¹H NMR analysis.

¹H NMR revealed a simple spectrum consisting of a single alkenic multiplet at 6.15 ppm and a pair of broadened α sulfone methylene multiplets at 4.11 and 4.04 ppm with an integrational intensity for all peaks of 1:2:2 respectively. Characteristically, the ¹H NMR spectra of most substituted 3-sulfolene derivatives show extensive long-range coupling and signals associated with this ring system are often broadened and poorly

resolved. As a consequence, proton NMR is often less diagnostic than the corresponding carbon spectra. ^{13}C NMR analysis showed only four signals; a quaternary alkenic carbon, an alkenic methine and two aliphatic methylenes. Comparison between the observed signals and ^{13}C chemical shifts of 3-methyl-3-sulfolene (1.23)⁹⁹ (Table 3.5) corroborated the presence of a 3-substituted 3-sulfolene moiety. High resolution mass spectrometry gave a weak molecular ion of 234 and a formulation of $\text{C}_8\text{H}_{10}\text{O}_4\text{S}_2$. Two sequential fragmentations ($m/z = 64$) were clearly visible in the mass spectrum: a result consistent with the loss of two molecules of sulfur dioxide. Sulfur dioxide loss under electron ionisation (EI) is a characteristic mass spectral fragmentation mode of most 3-sulfolene derivatives.

From these observations it was concluded that the precipitate isolated under these conditions was the desired 3,3'-*bis*-3-sulfolene (3.26). When repeated, this material was isolated in 95% yield. Recrystallisation was not successful, but analytically pure material could be obtained by trituration in refluxing acetone. This represents the first synthesis of any fused *bis*-sulfolene.

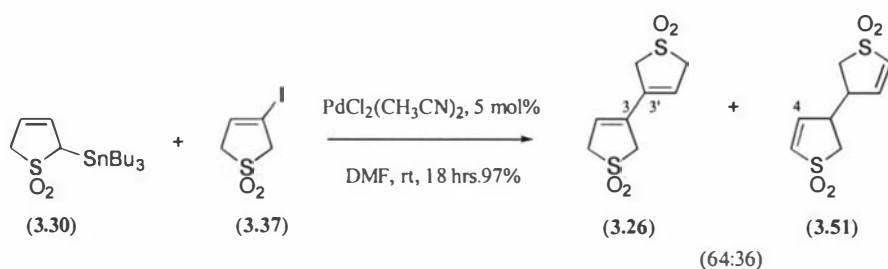
The direct formation of 3,3'-*bis*-3-sulfolene (3.26) could also be achieved by the *in situ* iodination of the vinyl stannane (3.33) and subsequent addition of catalyst. (Scheme 3.31) In this manner, (3.33) was converted to (3.26) in 85% isolated yield in a simple one pot procedure without the need to either prepare or isolate the intermediate iodosulfolene (3.37). This modification constitutes a efficient synthesis of a fused *bis*-3-sulfolene in only four steps from commercially available starting materials, *viz.* 3-sulfolene (3.1).

3.7.2.2 Coupling with One Allylic Partner.

3.7.2.2.1 Vinyl Iodide-Allylstannane.

It was anticipated that the coupling conditions successfully used to prepare 3,3'-*bis*-3-sulfolene (3.26) would prove of similar efficiency for the coupling of an allylic sulfolene partner (*i.e.* (3.30) or (3.39)) with either of the vinylic sulfolene derivatives (3.33) or (3.37).

Under the conditions employed above, vinyl iodide (3.37) and allyl stannane (3.30) coupled to give a near quantitative yield of an inseparable, 2:1 mixture of isomeric fused *bis*-sulfolenes as an amorphous off-white solid. (Scheme 3.32) By a simple comparison with earlier proton and carbon spectra, the major component was readily identified as 3,3'-*bis*-3-sulfolene (3.26) and after some deliberation the minor product was assigned as the regioisomeric 3,3'-*bis*-4-sulfolene (3.51) present as a single, unidentified diastereoisomer. This highly insoluble pair of compounds could not be separated and all spectral assignments were made by analysis of product mixtures.



Scheme 3.32

Of significant value to the structural assignment of (3.51) was the appearance of only four new signals in the ¹³C NMR spectrum. These signals consisted of two alkenic methines, one aliphatic methylene and an aliphatic methine. (Table 3.5) The presence of only four carbon signals strongly implied that the adduct was both symmetrical and coupled *via* an alkenic linkage, as observed for (3.26). However, the appearance of two alkenic methines and an olefinic AB system in the proton NMR indicated this could not be the case. Furthermore, the appearance of an aliphatic methine suggested coupling *via* a saturated carbon as the only possible structural variation that satisfied the observed carbon multiplicities obtained with the DEPT sequence. Three possible isomeric *bis*-sulfolene structures, *viz.* (3.51), (3.52) and (3.53), could be drawn which satisfied the constraints imposed by these observations. (Figure 3.5)

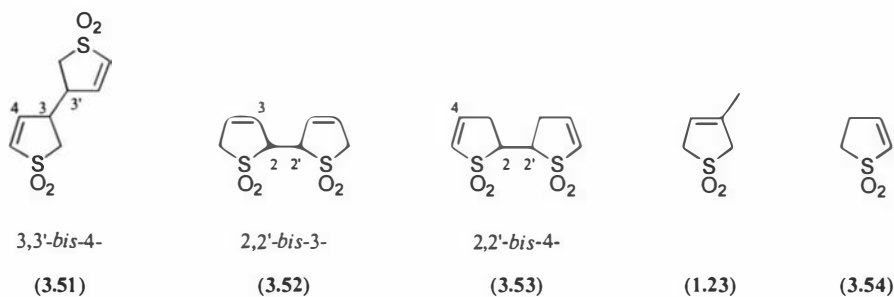
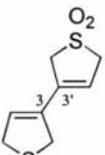
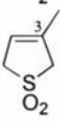

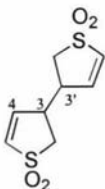
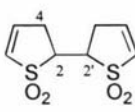


Figure 3.5

Although the conventional one dimensional proton spectrum yielded only limited information, HMQC analysis of the sulfolene mixture clearly demonstrated the diastereotopicity of the single methylene group with the α and β protons differentiated by a significant chemical shift difference (0.51 ppm).

Table 3.5 ^{13}C NMR chemical shifts (ppm) and multiplicities.

	C2	C3	C4	C5
 3,3'-bis-3- (3.26)	57.7 (t)	132.8 (s)	123.9 (d)	55.3 (t)
 (1.23)				
 (3.54)	131.9 (d)	138.8 (d)	26.5 (t)	47.5 (t)
minor <i>bis</i> -sulfolene component. (observed)	50.5 (t)	42.1 (d)	140.8 (d)	133.6 (d)
 3,3'-bis-4- (3.51) (<i>estimated</i>)	<i>56.5 (t)</i>	<i>35.5 (d)</i>	<i>138.8 (d)</i>	<i>131.9 (d)</i>
 2,2'-bis-4- (3.53) (<i>estimated</i>)	<i>56.5 (d)</i>	<i>35.5 (t)</i>	<i>138.8 (d)</i>	<i>131.9 (d)</i>

Shifts in italics indicate *estimated* values based on substituent effects ($\alpha = \beta = +9$ ppm).

Entries in bold represent **observed** chemical shifts of *bis*-sulfolene adducts.

Entries grouped by dashed lines indicate the major origin of structural assignments.

Although partly obscured by a coincident resonance with the lone methine proton, the appearance of such a dramatic diastereotopic differentiation strongly implied the methine and methylene carbons were in close proximity, i.e. adjacent to one another. This rationale, rather disappointingly, eliminated the exciting possibility of obtaining the 2,2'-*bis*-3-sulfolene (3.52) *via* this route. It *was* anticipated, however, that the coupling of a constrained vinylic sulfolene precursor would proceed regioselectively

and the use of 3-iodo-3-sulfolene (**3.37**) was therefore expected to yield 3-coupled products. On these grounds, structure (**3.53**) was also disfavoured. To justifiably eliminate this isomer it was necessary to make a comparison of the observed spectral features of the minor unknown component and the ^{13}C chemical shifts of 2-sulfolene (**3.54**).¹⁴⁹ (Table 3.5)

The alkenic signals of 2-sulfolene appear at 131.9 (C2) and 138.8 (C3) and compare favourably with the observed chemical shifts of 133.6 (C5) and 140.8 (C4) of the minor component.[†] While this conclusion corroborated the presence of a 4-sulfolene moiety and further justified the exclusion of (**3.52**), it shed no light on the regiochemistry of the *bis*-sulfolene fusion. It was possible, however, to estimate the ^{13}C chemical shifts of both a 3-substituted 4-sulfolene (**3.51**) and 2-substituted 4-sulfolene derivative (**3.53**) by considering the effects of substitution on the ^{13}C chemical shifts of the parent heterocycle, 2-sulfolene (**3.54**).

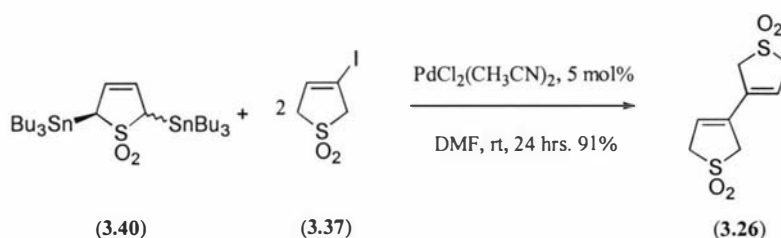
Typically, alkyl substitution at carbon results in a downfield shift of *ca.* 9 ppm (the α effect), while the adjacent carbon atom is also shifted downfield by a comparable although often smaller amount (the β effect).⁸⁷ While the magnitude of these shifts may vary, this phenomenon has been observed in cyclic systems⁸⁷ and can therefore be used to estimate the expected chemical shifts of the fused *bis*-sulfolenes (**3.51**) and (**3.53**). From this, it is expected that both the aliphatic methine and methylene signals of 2,2'-*bis*-4-sulfolene (**3.53**), would appear downfield relative to the C2 and C3 signals of 2-sulfolene at 56.5 ppm and 35.5 ppm respectively, assuming an α and β effect of 9 ppm for each carbon. For the *bis*-4-sulfolene (**3.51**), a similar treatment again estimates identical chemical shifts for the aliphatic methine and methylene (a consequence of assuming the same values for the α and β effects), but significantly requires the methylene (C2) to be the more downfield signal. This scenario is indeed observed and suggests the minor fused *bis*-sulfolene is (**3.51**). While the estimated chemical shifts may vary from those observed, it is the relative positioning of the methine and methylene signals which is important for the differentiation between the fused *bis*-sulfolenes (**3.53**) and (**3.51**).

[†] In the fused sulfolene system the position of substitution takes preference over the regiochemistry of the double bond; hence the origin of a 4-sulfolene substituent rather than a 2-sulfolene substituent.

The regiochemical assignment of the minor *bis*-sulfolene component could now be made, however, the issue of diastereoisomerism, and its spectral consequences, still remained. Excluding the occurrence of a coincidental resonance for *all* the signals of both diastereoisomers, it was concluded that the process, or processes, leading to (3.51) was highly diastereoselective. Indeed, the signal to noise ratio in the ^{13}C NMR spectrum of the product mixture was estimated at *ca.* 40:1 after an extended acquisition period, conservatively suggesting an actual diastereoselectivity of $> 20:1$, assuming a minimum detection threshold of twice the noise level for any minor signals.

Factors influencing the regiochemical outcome of non-symmetrical allyl stannane couplings are unclear and products of both α - and γ -substitution have been observed.^{173,175} Furthermore, it has been documented that allylstannanes exhibit a tendency to undergo double bond migration after coupling.¹⁸⁹ While these observations offer an explanation for the formation of the 3,3'-*bis*-3-sulfolene (3.26) they do not explain the origin of the diastereoselectivity observed in the formation of (3.51). To invoke palladium templated coupling of two π -allyl complexes is tempting, however there is no literature precedence upon which to base this conclusion and the reason for the diastereoselective formation of (3.51) remains unclear.

The efficient coupling of the vinyliodide (3.37) with the *mono*-stannylated allylic sulfolene (3.30) prompted us to investigate the reaction of (3.37) with the 2,5-*bis*-stannylated-3-sulfolene derivative (3.40), formed as a by-product in the stannylation of 3-sulfolene (3.1). (Table 3.2)



Scheme 3.33

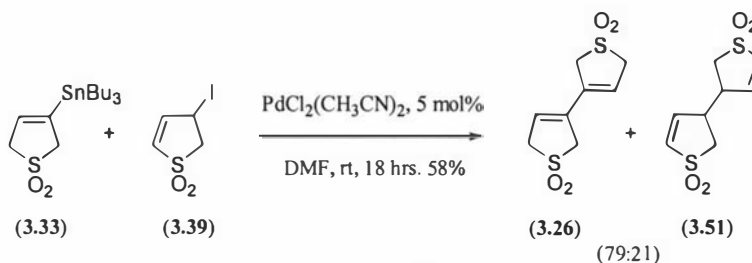
Under standard coupling conditions, two equivalents of iodide (3.37) and one of *bis*-stannane (3.40) were consumed over time, as judged by tlc, to yield an heavy, off white precipitate. (Scheme 3.33) After isolation and purification in the usual manner, ^1H and ^{13}C NMR identified the isolate as 3,3'-*bis*-3-sulfolene (3.26) containing no trace of

other isomeric sulfolenes. Based on iodide (3.37) the *bis*-3-sulfolene (3.26) was isolated in 91% yield. Tributyltin iodide was identifiable in the supernatant, but no trace of residual *bis*-stannane (3.40) was detected. The mass balance of isolated material suggested that 3,3'-*bis*-3-sulfolene (3.26) was derived solely from (3.37) through the formal homo-coupling of the vinyliodide. While the mechanism of this coupling is unclear, it is suggested that conversion of vinyliodide (3.37) to the vinylstannane (3.33) may occur under the reaction conditions with subsequent coupling of these vinylically constrained partners to yield 3,3'-*bis*-3-sulfolene (3.26). Tin-iodine exchange with the *bis*-stannane (3.40) to generate a stannylated iodo-sulfolene intermediate must therefore also occur. Elimination of tributyltin iodide or further tin-iodine exchange and loss of iodine from this intermediate may eventually lead to the formation of thiophene dioxide. Polymerisation of this unstable material is known to occur¹⁴⁹ and may account for the complete disappearance of (3.40) from the reaction mixture and formation of tributyltin iodide.

The homo-coupling of aryl iodides has been observed in transition metal catalysed cross-coupling reactions¹⁹⁰ and there is evidence for a mechanism involving the exchange of organic residues between palladium and tin.¹⁹¹ Further, unpublished results,^{192,193} however, suggest that the homo-coupling of vinyliodides under Stille cross-coupling conditions may be more common than is otherwise reported in the literature.

3.7.2.2.2 Allyl Halide-Vinylstannane.

The coupling of sulfolene derivatives with transposed allylic/vinylic functionality was next investigated. (Scheme 3.34) In degassed DMF, in the presence of catalytic *bis*-(acetonitrile) palladium (II) dichloride, the vinyl stannane (3.33) and allyl iodide (3.39) were coupled to again form an inseparable mixture of 3,3'-*bis*-3-sulfolene (3.26) and 3,3'-*bis*-4-sulfolene (3.51) (79:21) as an amorphous brown solid in 58% yield.



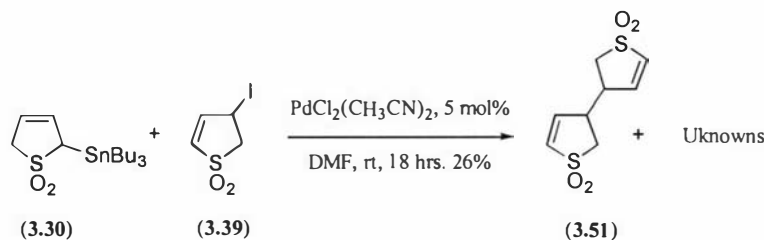
Scheme 3.34

The reduced yield may in part be due to the relative instability of the vinyl iodide (3.39) and certainly the isolation of a more intensely coloured product mixture was consistent with this observation. Again the selective formation of 3,3'-bis-3-sulfolene (3.26) was observed suggesting that coupling occurs preferentially at the terminus of the allyl moiety remote from sulfur. The isolation of only approximately half the expected mass balance of product made any mechanistic conclusions relating to changes in product ratio speculative. It is nonetheless interesting to note that no other products were observed and (3.51) was again formed as a single diastereoisomer as judged by ^{13}C NMR.

3.7.2.3 Coupling with Two Allylic Partners.

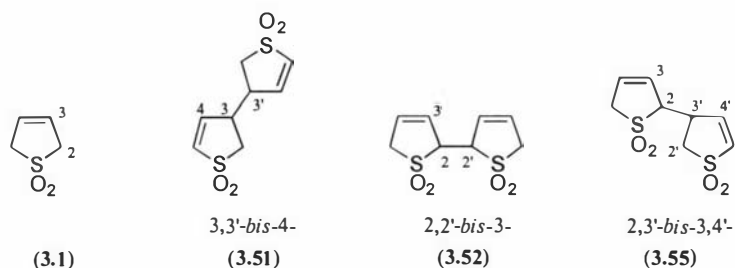
The Stille cross-coupling reaction of a vinylic sulfolene derivative and an allylic sulfolene counterpart has been shown to produce the 3,3'-bis-3-sulfolene (3.26) as the major product irrespective of the iodo- or stannyl-substituent regiochemistry. It was anticipated that the coupling of two allylicly-functionalised sulfolene derivatives would yield a similar result. This, however, was not the case.

Under standard conditions, coupling of the allylic stannane (3.30) and the allylic iodide (3.39) gave an inseparable mixture of compounds (26%) as a dark amorphous solid that did not contain 3,3'-bis-3-sulfolene (3.26), as judged by ^{13}C NMR. (Scheme 3.35) Clearly identified as the major reaction product, however, was the 3,3'-bis-4-sulfolene (3.51), again visible as a single diastereoisomer.



Scheme 3.35

^{13}C NMR and DEPT experiments showed the appearance of 12 signals in addition to those associated with 3,3'-bis-4-sulfolene (3.51). These signals (shown in bold in Table 3.6) consisted of nine methine, (six alkenic, three aliphatic) and three aliphatic methylenes.

Table 3.6 ^{13}C NMR chemical shifts (ppm) and multiplicities.

observed	C2	C3	C4	C5	C2'	C3'	C4'	C5'
(3.1)	55.6 (t)	124.7 (d)	124.7 (d)	55.6 (t)				
(3.51)	50.5 (t)	42.1 (d)	140.8 (d)	133.6 (d)	50.5 (t)	42.1 (d)	140.8 (d)	133.6 (d)
unknowns	67.3 (d)	142.7 (d)	126.3 (d)	56.7 (t)	51.2 (t)	38.9 (d)	139.6 (d)	132.6 (d)
	65.5 (d)	134.0 (d)	126.1 (d)	55.5 (t)				
<i>estimated</i>								
(3.55)	<i>64.6 (d)</i>	<i>133.7 (d)</i>	<i>124.7 (d)</i>	<i>55.6 (t)</i>	<i>56.5 (t)</i>	<i>35.5 (d)</i>	<i>138.8 (d)</i>	<i>131.9 (d)</i>
(3.52)	<i>64.6 (d)</i>	<i>133.7 (d)</i>	<i>124.7 (d)</i>	<i>55.6 (t)</i>	<i>64.6 (d)</i>	<i>133.7 (d)</i>	<i>124.7 (d)</i>	<i>55.6 (t)</i>

Shifts in italics indicate *estimated* values based on substituent effects ($\alpha = \beta = +9$ ppm).

Entries in bold represent **observed** chemical shifts of *bis*-sulfolene adducts.

Entries grouped by dashed lines indicate the major origin of structural assignments.

A good signal to noise ratio was obtained for the ^{13}C NMR spectrum of the product mixture and no quaternary carbons were present. From the multiplicities of the observed signals and their relative chemical shifts some structural inferences about the product mixture could be made.

The appearance of two alkenic methine signals ($\text{C4}'$, $\delta = 139.6$ ppm and $\text{C5}'$, $\delta = 132.6$ ppm) was reminiscent of the alkenic resonances observed for 3,3'-*bis*-4-sulfolene (**3.51**) and strongly suggested the presence of an additional 3-substituted-4-sulfolene moiety in the unknown product mixture. Further comparison indicated the presence of an aliphatic methylene ($\text{C2}'$, $\delta = 51.2$ ppm) and methine ($\text{C3}'$, $\delta = 38.9$ ppm) closely related to the expected chemical shifts of a 3-substituted-4-sulfolene moiety, yet different to those observed for the symmetrical *bis*-sulfolene (**3.51**).

The appearance of an aliphatic methine (C2 , $\delta = 65.5$ ppm) and methylene (C5 , $\delta = 55.5$ ppm) were consistent with the presence of a 2-coupled 3-sulfolene derivative. Invoking a 9 ppm α effect,⁸⁷ with reference to the parent 3-sulfolene (**3.1**), it is anticipated that the resonances of C2 and C5 of such a species will appear at or around 64.6 and 55.6 ppm respectively (estimated, italicised values in **Table 3.6**). The associated alkenic pair of this quartet of signals are expected to occur around 124.7 ppm (for C4), where the substitution at C2 (γ effect) is of lesser consequence; and within the range 128-134 ppm (for C3) where an allylic β effect of between 5-9 ppm⁸⁷ is anticipated to contribute more significantly. Signals with closely related chemical shifts ($\delta = 126.1, 134.0$ ppm) and appropriate multiplicities were observed in the carbon spectrum of the unknown mixture and substantiate the presence of a 2-coupled 3-sulfolene moiety.

From these observations it was concluded that, in addition to 3,3'-*bis*-4-sulfolene (**3.51**), the Stille cross-coupling of (**3.30**) and (**3.39**) gave a mixture of 2,2'-*bis*-3-sulfolene (**3.52**) and 2,3'-*bis*-3,4'-sulfolene (**3.55**) in approximately equal proportions. The tentative assignment of the observed spectral data (^{13}C NMR) for these putative structures is given in **Table 3.6**. Earlier precedent has suggested that coupling of an allylic sulfolene to generate the *bis*-sulfolene (**3.51**) proceeds diastereoselectively. It is likely similar selectivity is exhibited in the coupling of two allylic sulfolene partners

and as such it is suggested that (3.52) and (3.55) are also formed as single diastereoisomers.

In view of the poor yield of products, their difficult physical properties and the speculative nature of these structural assignments, no further attempt to investigate the Stille cross-coupling reaction of allylicly-functionalised sulfolene derivatives was made.

3.8 Conclusions.

The Stille cross-coupling reaction of appropriately functionalised sulfolene derivatives is an effective strategy for the synthesis of fused *bis*-sulfolenes. The coupling of two vinylic sulfolene partners proceeds in high yield under mild conditions to produce 3,3'-*bis*-3-sulfolene (3.26) as the first example of a fused *bis*-sulfolene derivative. Coupling of an allylic substrate with a vinylic partner, irrespective of the regiochemistry of the functionality, again yielded (3.26) as the major product with varying quantities of the regioisomeric *bis*-4-sulfolene (3.51) as a single diastereoisomer. Coupling of two allylic sulfolene partners gave a complex mixture of products, the exact nature of which remains uncertain. The formation of the symmetrical 3,3'-*bis*-3-sulfolene (3.26), seen in all other coupling combinations, was not observed under these conditions. Attempts to separate or purify any of the *bis*-sulfolene mixtures were unsuccessful.

Stille cross-coupling reactions utilising at least one allylic sulfolene substrate showed regioselective γ -coupling at the terminus of the π system, remote from the sulfone. Other workers have noted the selective coupling of vinyl iodides α to the sulfone of the allylic stannane (3.30).¹⁷⁹ This mode of reactivity was not observed here. With coupling between two allylic substrates, γ -regioselectivity again predominated, although there was some evidence to suggest that this did not occur exclusively. Farina¹⁷⁵ and Stille¹⁷³ have noted that allylstannanes and allylic halides have been under-utilised in the Stille cross-coupling reaction and that this is due primarily to a poor understanding of the issues effecting regiocontrol. This appears to be equally true for the cross-coupling of allylic sulfolenes. The high yielding and regioselective Stille cross-coupling of 3-iodo-3-sulfolene (3.37) suggested a general strategy for the preparation of 3-substituted-3-sulfolene derivatives as precursors to cross-conjugated polyenes. This is discussed in **Chapter 4**.

Chapter 4

The Synthesis of Bis-3-sulfolenes as Precursors to Cross-conjugated Polyenes.

4.1 Introduction.

Under the mild conditions of the Stille reaction, vinyl iodides couple readily with a wide range of stannanes to give substituted alkenes. Two general studies on the cross-coupling of simple vinyl iodides with alkenyl¹⁸⁸ and alkynyl stannanes¹⁹⁴ have been made and numerous examples of this reaction type with other classes of stannanes have subsequently been reported.¹⁷⁵ The “ligandless” catalyst *bis*-(acetonitrile) palladium (II) chloride¹⁹⁵ is commonly employed and when used in conjunction with DMF, forms an efficient catalyst-solvent combination that is stable, easily handled and compatible with a wide range of substrates.

Vinyl bromides have also been successfully coupled, albeit after extended reaction times and in reduced yields.¹⁸⁸ As with alkenyl chlorides, which have been used only rarely,¹⁷⁵ the observed reduction in rate of these coupling reactions has been attributed to a slow oxidative addition of the less reactive vinyl halides to the initial Pd(0) species formed in the preliminary stages of the catalytic cycle.¹⁷⁵ (Scheme 3.17) Although some of these problems have been overcome by working at elevated temperatures or by the addition of catalytic copper(I) iodide,^{196,197} vinyl iodides remain the most commonly used alkenyl halides employed in the Stille cross-coupling reaction.

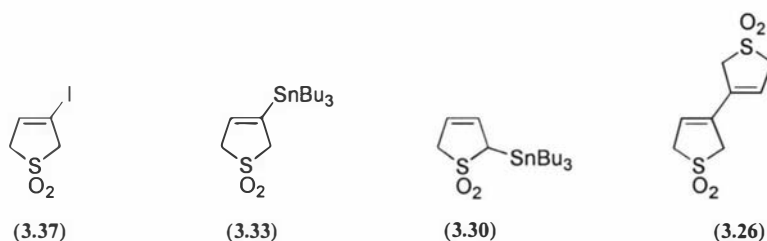


Figure 4.1

The vinyl iodide, 3-iodo-3-sulfolene (3.37) (Figure 4.1), has been successfully coupled with the stannyl sulfolenes (3.30) and (3.33) to give 3-fused *bis*-sulfolenes. (Chapter 3) In both instances, yields were excellent and when the stannyl-coupling partner was

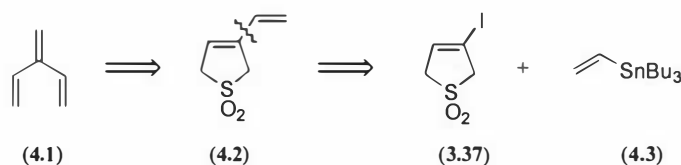
vinylically constrained, *viz.* (3.33), the 3-fused *bis*-3-sulfolene (3.26) was isolated as a single product.

The potential value of fused *bis*-3-sulfolenes as latent polyenes has been outlined in section 3.4.3 where it was noted that the regioselectivity of the sulfolene fusion would control the geometry and substitution of any masked polyene that was derived from it. The ready formation of fused *bis*-3-sulfolene (3.26) has established the feasibility of preparing compounds of this type and in principle represents a short and efficient synthesis of the cross-conjugated polyene [4]-dendralene. (See section 5.4.2, Chapter 5) It has also highlighted the value of 3-iodo-3-sulfolene (3.37) as a useful cross-coupling partner and, importantly, is suggestive of other latent forms of cross-conjugated polyenes (or dendralenes) (Scheme 3.13) which might also be accessible through a Stille cross-coupling approach. To date the preparation of dendralenes has received minimal synthetic attention¹⁶⁸ and therefore any general strategy aimed at the synthesis of this neglected class of simple hydrocarbons is of value. It was our aim to develop a general strategy for the synthesis of [n]-dendralenes based upon the Stille cross-coupling of 3-iodo-3-sulfolene (3.37).

4.2 A 3-Sulfolene Based Strategy for the Synthesis of [n]-Dendralene Precursors.

4.2.1 [3]-Dendralene Precursors.

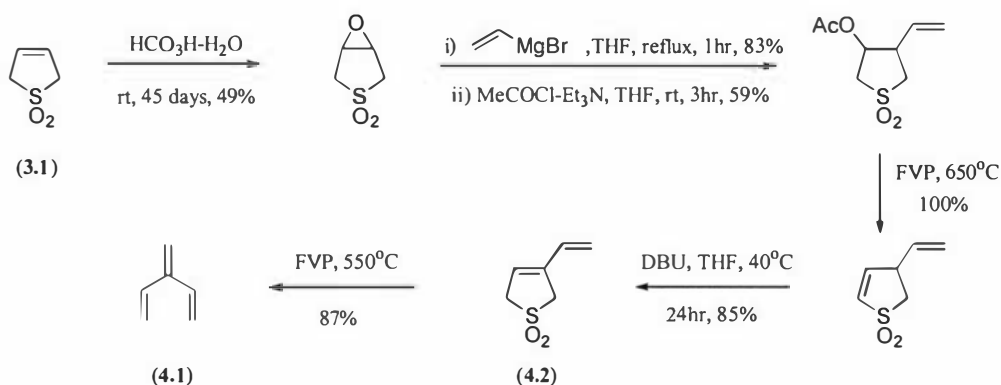
[3]-dendralene (4.1) is the simplest example of an unsubstituted cross-conjugated polyene and 3-vinyl-3-sulfolene (4.2) represents a possible precursor. Coupling of 3-iodo-3-sulfolene (3.37) with a simple vinyl stannane (4.3) therefore offers the potential of swift access to this compound. (Scheme 4.1)



Scheme 4.1

The value of (4.2) as a dendralene precursor has already been exploited by Cadogan and co-workers, where (4.2) was prepared in 5 steps from 3-sulfolene (3.1).¹⁹⁸ (Scheme

4.2) Subsequent cheletropic elimination of sulfur dioxide from the 3-sulfolene moiety by flash vacuum pyrolysis (FVP) unmasked the diene and gave [3]-dendralene (4.1) in 87% yield.

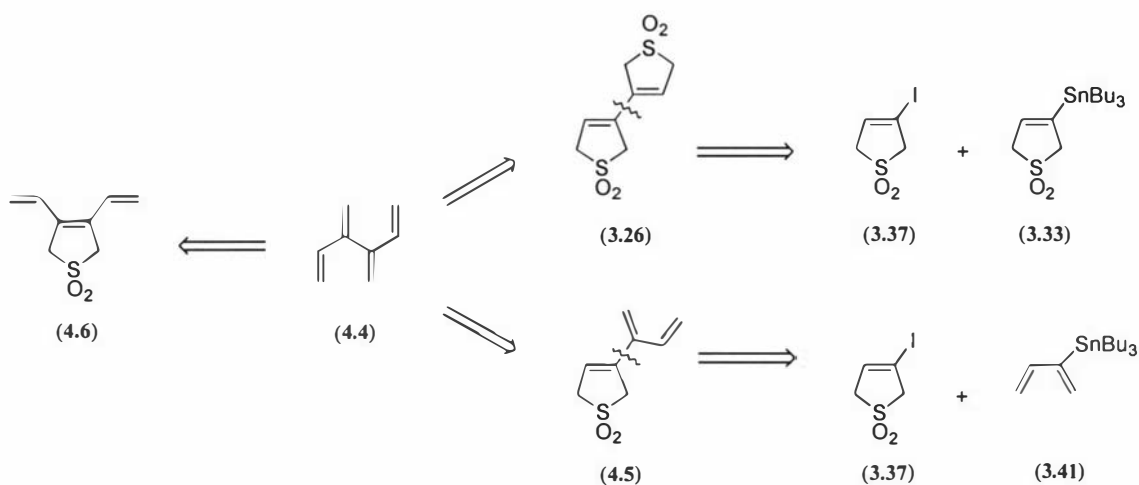


Scheme 4.2

Despite the time consuming nature of the reported synthesis (45 days for the initial transformation!) and recourse to two FVP steps, this report clearly demonstrates the value of 3-substituted 3-sulfolene derivatives as efficient dendralene precursors.

4.2.2 [4]-Dendralene Precursors.

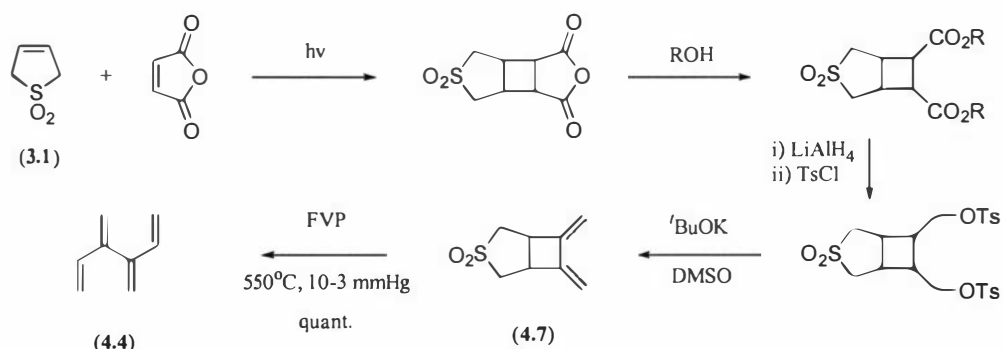
While the formation of fused *bis*-3-sulfolene (3.26) represents a short and efficient synthesis of a [4]-dendralene precursor, coupling of 3-iodo-3-sulfolene (3.37) with 2-tributylstannyl-1,3-butadiene (3.41) offers an alternative coupling strategy. (Scheme 4.3)



Scheme 4.3

The butadiene-substituted 3-sulfolene derivative (4.5) has been prepared previously by the direct addition of liquid sulfur dioxide to [4]-dendralene (4.4).¹⁹⁹ While this does not represent a viable synthesis of (4.5), the feasibility of performing the reverse reaction and generating [4]-dendralene from (4.5) (prepared by other means), would appear high. The divinylated sulfolene adduct (4.6) was also isolated from the sulfur dioxide addition reaction mixture¹⁹⁹ and represents a third [4]-dendralene equivalent.

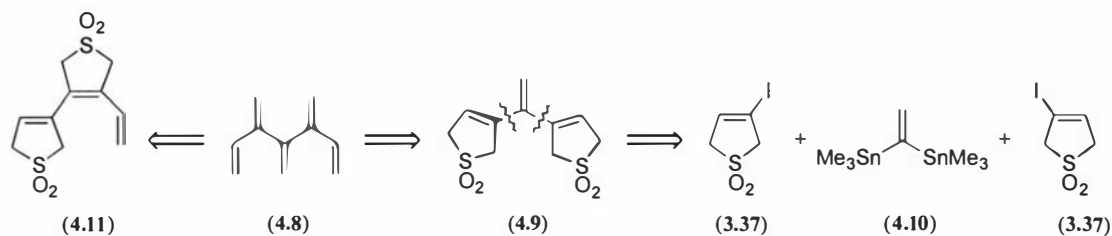
Cadogan and co-workers²⁰⁰ have reported a masked [4]-dendralene (4.7) derived from 3-sulfolene (3.1). (Scheme 4.4) This material was prepared in five steps and 25% overall yield from the photoadduct of 3-sulfolene (3.1) with maleic anhydride. Successive esterification, reduction to the diol, conversion to the *bis*-tosylate and elimination with potassium *t*-butoxide in DMSO gave (4.7) as a crystalline solid. Despite a tendency to polymerise on standing, this material underwent smooth elimination of sulfur dioxide under FVP conditions to give [4]-dendralene (4.4) in quantitative yield.



Scheme 4.4

4.2.3 [5]-Dendralene Precursors.

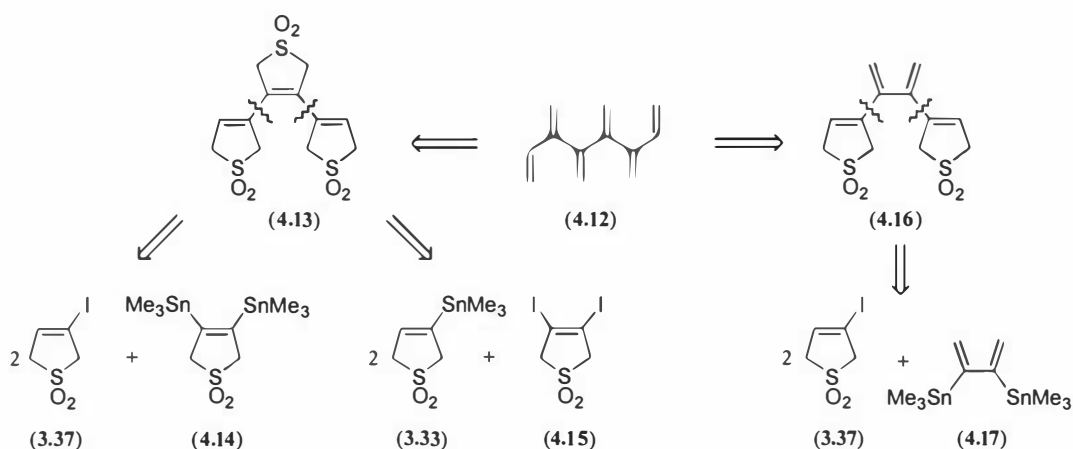
Excluding *mono*-sulfolene derivatives as precursors to [5]-dendralene (4.8) (these being substituted [3]-dendralenes or higher), two simple *bis*-3-sulfolenes can be considered as potential candidates. The symmetrical, pendant *bis*-3-sulfolene (4.9) represents a viable precursor, requiring the coupling of two 3-iodo-3-sulfolene units with a single 1,1-*bis*-stannylated ethylene derivative such as (4.10). (Scheme 4.5) The fused *bis*-3-sulfolene precursor (4.11), while also a viable [5]-dendralene precursor, would (as for synthesis of (4.6) (Scheme 4.3)) again require access to a bifunctional sulfolene coupling partner.



Scheme 4.5

4.2.4 [6]-Dendralene Precursors.

The fused *tris*-3-sulfolene (4.13) represents the ideal sulfolene-derived precursor to [6]-dendralene (4.12). However, disconnection of this molecule reveals that a bifunctional sulfolene coupling partner is again required. In the absence of an appropriate *bis*-stannylated sulfolene (4.14) or diiodo-sulfolene (4.15), a 3-iodo-3-sulfolene based strategy can be envisaged which suggests the substituted butadiene (4.16) as a potential [6]-dendralene equivalent. (Scheme 4.6) This approach requires a *bis*-alkenyl tin fragment supplied in the form of the *bis*-stannylated butadiene (4.17).

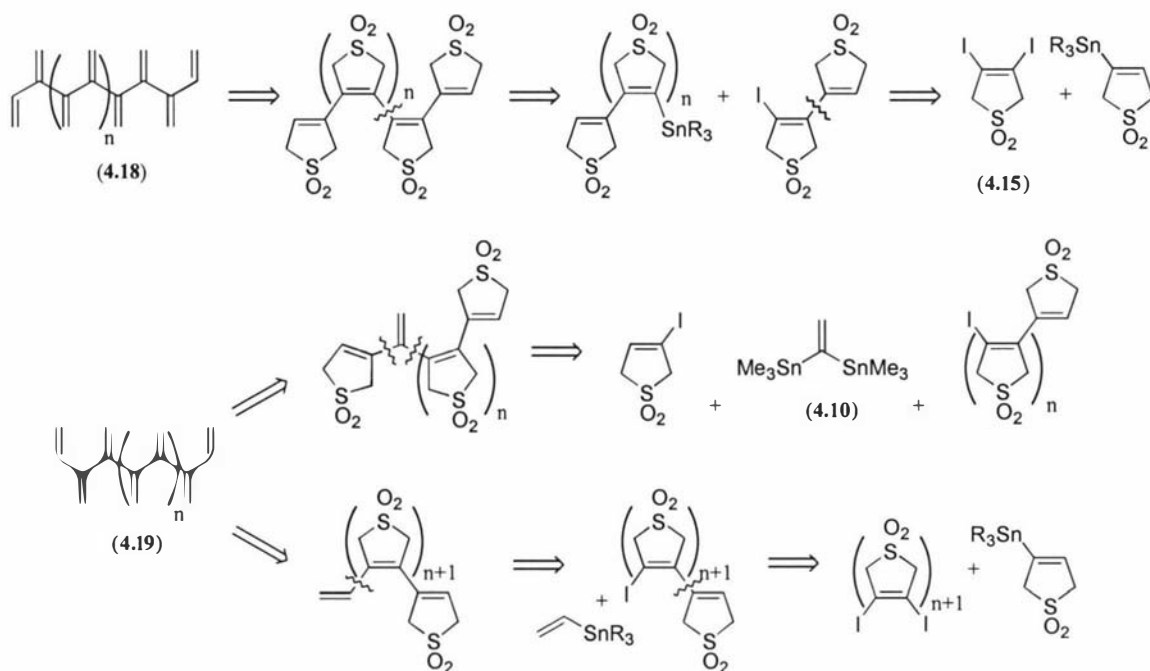


Scheme 4.6

4.2.5 Higher Dendralene Precursors.

To develop a general Stille cross-coupling based strategy for the synthesis to [6]-dendralene precursors and higher, access to 3,4-bifunctional 3-sulfolene derivatives appears desirable. With access to sulfolene derivatives of this nature, precursors to even numbered dendralenes (4.18) are, in principle, accessible by the stepwise coupling of smaller, appropriately functionalised sulfolene fragments in either a convergent or linear manner. (Scheme 4.7) Furthermore, at an appropriate juncture in the synthesis,

either insertion of a stannylated ethylene derivative, such as (4.10), or vinyl “capping” at the terminus of a sulfolene fragment, would grant access to precursors of higher, odd numbered dendralenes (4.19). In an attempt to prepare fused *oligo*-3-sulfolene derivatives as precursors to higher [n]-dendralene equivalents, the synthesis of the two putative, bifunctional sulfolene derivatives, 3,4-*bis*-stannylated-3-sulfolene (4.14) and 3,4-diido-3-sulfolene (4.15) were investigated.



4.2.6 Other Polyene Precursors.

To demonstrate the value of 3-iodo-3-sulfolene (3.37) as a general precursor to both 3-substituted 3-sulfolenes and novel, pendant *bis*-3-sulfolene derivatives, the Stille cross-coupling of 3-iodo-3-sulfolene (3.37) with a range of representative *mono*- and *bis*-stannanes was also investigated. The use of these sulfolene derivatives as masked 2-substituted 1,3-dienes is described in **Chapter 5**, together with the synthesis of [n]-dendralenes.

4.3 Preparation of Organotin Reagents

Many organotin reagents are commercially available. In this work, however, the majority of compounds used in cross-coupling reactions were either freshly prepared, according to established methods, or obtained by modified literature procedures.

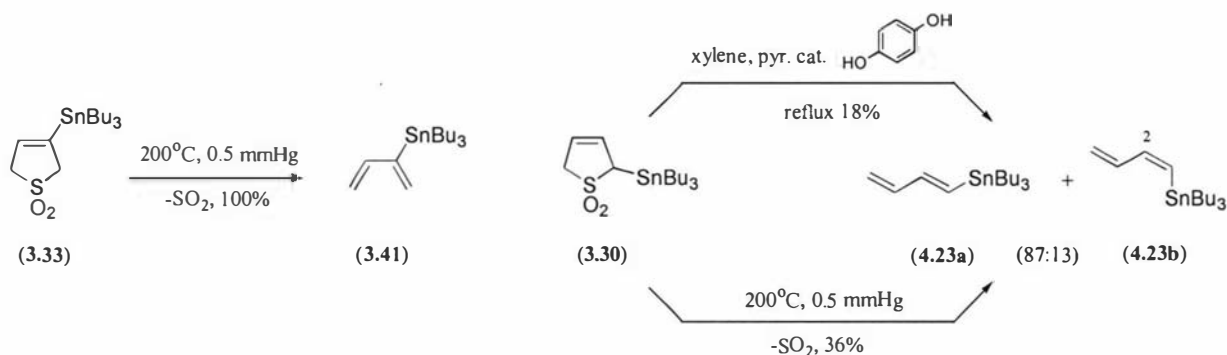
4.3.1 *Mono-stannanes.*

Tributylvinyl tin (4.3)²⁰¹ (Figure 4.2) was prepared by the action of vinylmagnesium bromide on tributyltin chloride to give the stannane in 78% yield after distillation. Tributylallyl tin (4.20)²⁰² was prepared in a similar manner from the allyl Grignard reagent to give the product in 63% yield after distillation. Tributylethynyl tin (4.21) was prepared according to the method of Renaldo *et al.*,²⁰³ by the reaction of lithium acetylide (ethylenediamine complex) with tributyltin chloride. Distillation of the crude reaction mixture gave the desired *mono*-stannylated reagent in 63% yield leaving a crude residue containing *bis*-(tributylstannyl) acetylene (4.22). Purification by flash vacuum filtration gave (4.22) in 6% yield that was used in coupling reactions without further purification.



Figure 4.2

Bew and Sweeney have reported the synthesis of 3-tributylstannyl-3-sulfolene (3.33)¹⁸¹ and this was discussed in detail in section 3.7.1.5. In our hands, destructive short path distillation of (3.33) under reduced pressure through a coiled, unpacked glass column gave 2-tributylstannyl-1,3-butadiene (3.41) in quantitative yield. (Scheme 4.8)



Scheme 4.8

The cheletropic elimination of sulfur dioxide from 2-tributylstannyl-3-sulfolene (3.30) in refluxing xylene containing pyridine and a small quantity of hydroquinone has been reported as an efficient means of preparing 1-tributylstannyl-1*E*,3-butadiene (4.23a).¹⁸² In our hands, this procedure gave a mixture of the isomeric dienes (4.23a)

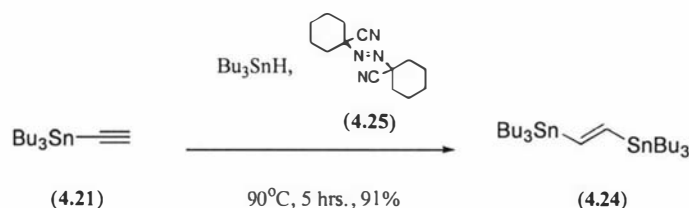
and (4.23b) (87:13) in modest yield (18%). (Scheme 4.8) Although complex, the ^1H NMR spectrum of the mixture clearly revealed the H-2 proton of the minor isomeric diene (4.23b) shifted downfield of the main alkenic region and exhibiting a *cis*-coupling constant of 12.7 Hz.

The destructive short path distillation of (3.30) was attempted as an alternative means of achieving the cheletropic desulfurisation. Under reduced pressure, through a coiled, unpacked glass column, a mixture of (4.23a) and (4.23b) were again isolated. The yield was improved (36%) but the same isomeric ratio was again observed. Separation of the stannylated dienes by chromatography could not be achieved and subsequent cross-coupling reactions were carried out on the stannane mixture.

4.3.2 *Bis-stannanes.*

4.3.2.1 *E-1,2-Bis-(tributylstannyl)ethene.*

E-1,2-Bis-(tributylstannyl)ethene (4.24) was prepared by the addition of tributyltin hydride¹⁸⁵ to tributylethynyl tin (4.21) in the presence of 1,1'-azo-bis-(cyclohexanecarbonitrile) (4.25) in a modification of the method according to Renaldo et al.²⁰³ (Scheme 4.9) Distillation gave the pure *bis*-stannane in 91% yield.

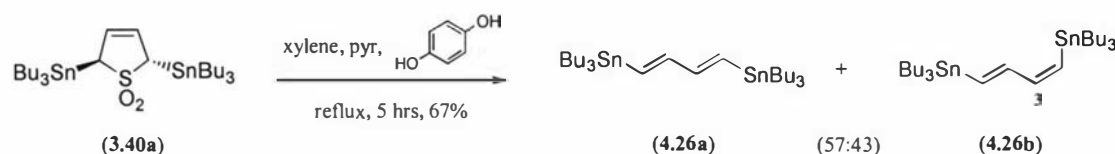


Scheme 4.9

4.3.2.2 *1,4-Bis-tributylstannyl-1,3-butadiene.*

The cheletropic elimination of sulfur dioxide from *mono*-stannylated 3-sulfolene derivatives is an effective method of preparing *mono*-stannylated butadienes. In an extension of this methodology, the elimination of sulfur dioxide from the novel 2,5-*bis*-stannylated 3-sulfolene (3.40) was briefly investigated as a new route to 1,4-*bis*-stannylated 1,3-butadienes (4.26).

Repeated column chromatography of the *bis*-stannylated sulfolene mixture (**3.40a**) and (**3.40b**) gave a sample of the major diastereoisomer, free of any isomeric material and assigned, by comparison with the known products of analogous alkylation procedures,¹³² as the *trans*-*bis*-stannylated-3-sulfolene (**3.40a**). Thermolysis of (**3.40a**), as a single diastereoisomer, in refluxing xylene containing pyridine and hydroquinone, saw its smooth conversion, over 5 hours as judged by tlc, to a single, non polar product. (Scheme 4.10) NMR analysis, however, revealed this material to be a mixture of 1,4-*bis*-tributylstannyl-1*E*,3*E*-butadiene (**4.26a**) and the 1*E*,3*Z* diene (**4.26b**), isolated in 67% yield in a ratio of 57:43 favouring the all *trans*-diene. The C3 methine proton of the minor *E,Z* isomer was clearly resolved as a well defined doublet of doublets ($J = 11.6$ and 9.7 Hz), shifted downfield of the remaining alkenic signals and away from the additional complexity brought to the spectrum by the tin-proton coupling. ¹³C NMR revealed the characteristic signals of the *n*-butyl carbons, plus six well resolved alkenic signals; two major (**4.26a**) and four minor (**4.26b**).

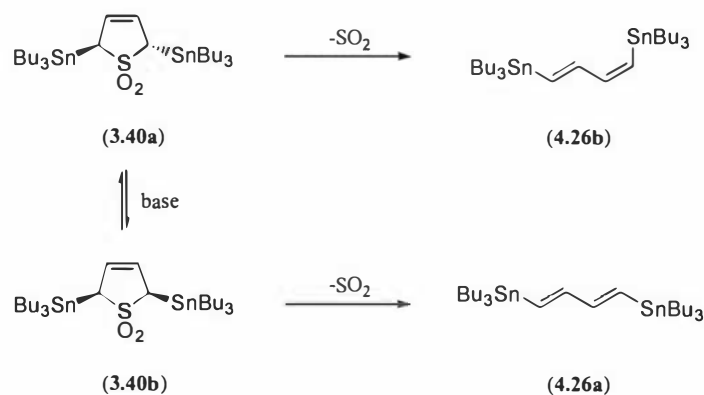


Scheme 4.10

Attempts to desulfurise (**3.40a**) by distillation under reduced pressure (Kugelrohr, > 250°C, 0.1 mmHg) proved unsuccessful. No products were collected and significant charring was observed in the hot zone of the oven. It is believed, however, that this method *is* viable and extensive decomposition occurred only because of the relatively poor vacuum that could be sustained by the distillation apparatus. With access to FVP, or a more efficient vacuum system, 2,5-*bis*-tributylstannyl-3-sulfolenes (**3.40**) are likely to prove efficient precursors to 1,4-*bis*-tributylstannyl-1,3-butadienes (**4.26**).

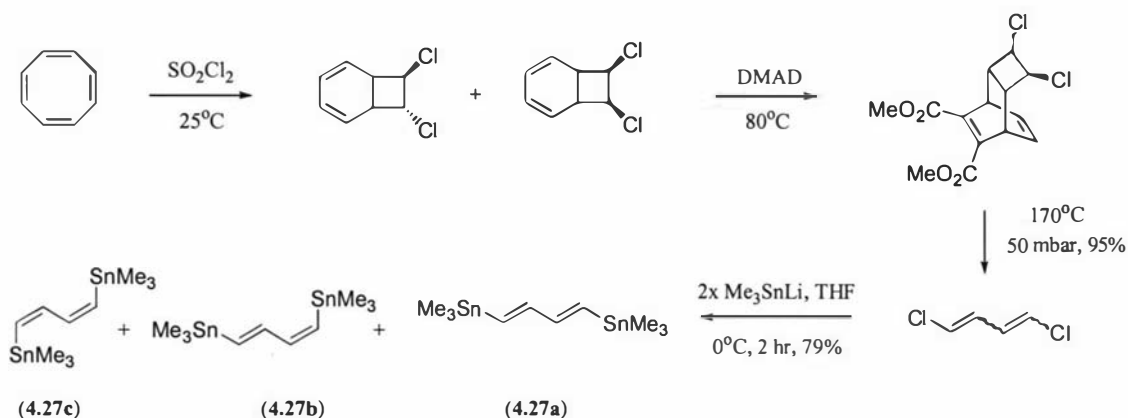
Thermolysis of 2,5-*trans*-disubstituted-3-sulfolene derivatives afford *E,Z*-dienes, while thermolysis of the isomeric 2,5-*cis*-disubstituted compounds give only *E,E*-dienes.^{129,130} (Scheme 3.2) The formation of both *E,E* and *E,Z*-stannyl dienes (**4.26**) from the pure *trans*-*bis*-stannylated sulfolene (**3.40a**) implied that isomerisation of the *trans* *bis*-stannane to a mixture containing its *cis* isomer (**3.40b**) occurred prior to thermolysis.^{132,133} (Scheme 4.11) Furthermore, the formation of a comparable

isomeric ratio of *E,E* (**4.26a**) and *E,Z*-stannyl dienes (**4.26b**) (57:43) implied that *trans-cis* isomerisation and subsequent cheletropic elimination (from the *cis*-isomer), occurred at a rate that was similar to the elimination of sulfur dioxide from the *trans* isomer alone. This implies that changing either the steric bulk of the tin residue, or the base, may alter the product ratio observed under thermolysis. Hence, it may be possible to develop conditions which significantly favour the formation of the *trans*-stannyl diene (**4.26a**) in a more stereoselective synthesis of 1,4-*bis*-stannylated-1,3-butadienes.



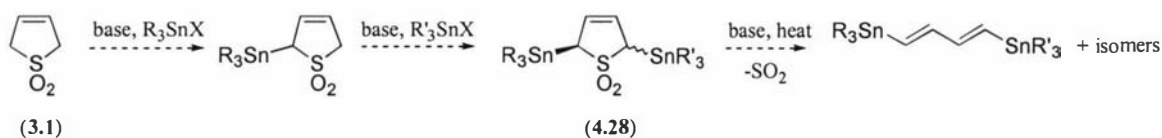
Scheme 4.11

The analogous 1,4-*bis*-(trimethylstannyl)-1,3-butadienes (**4.27a-c**) have been prepared by the direct stannylation of 1,4-dichloro-1,3-butadiene. (Scheme 4.12) They have been well characterised by ^1H NMR²⁰⁴ and ^{13}C NMR¹⁸⁷ and data for the *bis*-tributylstannylated dienes (**4.26**) compare favourably with that reported for the methyl analogues. 1,4-*Bis*-(trimethylstannyl)-1*E*,3*E*-butadiene (**4.27a**) has been used in the synthesis of linear polyenes as both a dianion equivalent^{204,205} and a Stille cross-coupling partner.^{187,206} Although a valuable diene synthon, the synthesis of (**4.27a**) is not trivial and utilises cyclooctatetraene as an expensive and unstable starting material.



Scheme 4.12

2,5-*Bis*-stannylated 3-sulfolenes (**3.40**) offer an alternative and potentially useful method of preparing 1,4-*bis*-stannylated 1,3-butadienes. Furthermore, they offer the possibility of preparing 1,4-*bis*-stannylated dienes which bear non-equivalent tin residues at the diene termini. (Scheme 4.13) Although speculative, the sequential stannylation of 3-sulfolene (**3.1**) with tin halides of differing substitution would grant access to diastereomeric mixtures of 2,5-*bis*-stannylated sulfolene derivatives (**4.28**). Stereoselective thermolysis, in a manner similar to that achieved for dialkyl sulfolenes^{132,133} (Scheme 3.4) and subsequent purification, represents a short alternative to the method currently employed



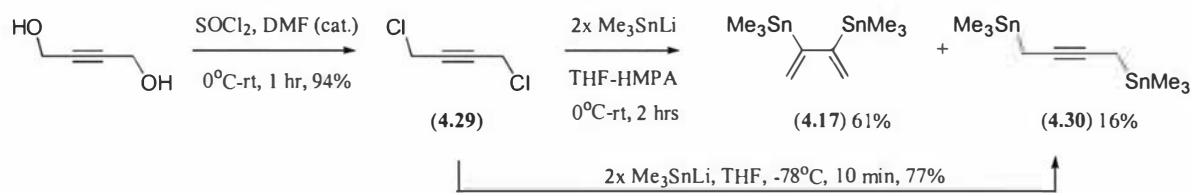
Scheme 4.13

Little time was available to investigate this approach and the *bis*-tributylstannyl dienes (**4.26a**) and (**4.26b**) were used in subsequent cross-coupling reactions with 3-iodo-3-sulfolene as a mixture of isomers.

4.3.2.3 2,3-*Bis*-trimethylstannyl-1,3-butadiene.

2,3-*Bis*-trimethylstannyl-1,3-butadiene (**4.17**) was identified as a potential coupling partner for the synthesis of higher dendralenes precursors containing “prematurely unmasked” diene units. *Bis*-stannane (**4.17**) has been prepared by the direct stannylation of 1,4-dichlorobut-2-yne (**4.29**) with two equivalents of trimethyltin

lithium in THF-HMPA at room temperature.^{207,208} At lower temperature, in the absence of the co-solvent HMPA, substitution without rearrangement is observed and the 1,4-*bis*-stannylated-but-2-yne (**4.30**) can be isolated.^{207,208}



Scheme 4.14

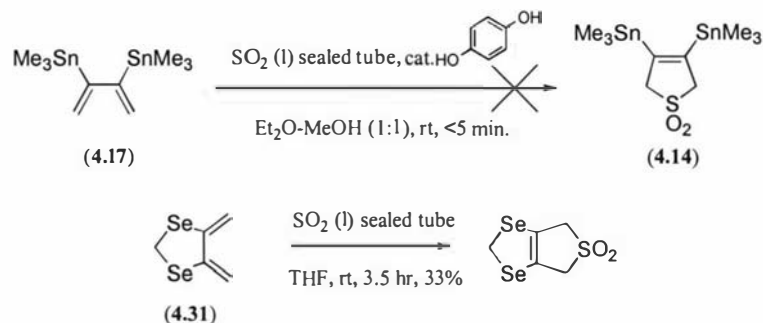
In our hands, chlorination of 1,4-dihydroxybut-2-yne with thionyl chloride and catalytic DMF gave 1,4-dichlorobut-2-yne (**4.29**) in excellent yield.²⁰⁹ The direct stannylation of dichloride (**4.29**) with two equivalents of trimethyltin lithium in THF-HMPA at room temperature gave satisfactory yields of the *bis*-stannane (**4.17**) (61%), however small quantities of (**4.30**) (*ca.* 16%) were consistently formed. (**Scheme 4.14**) Both compounds were readily separated by chromatography on silica gel and further purified by distillation. It was found that the preparation of trimethyltin lithium could be greatly improved by using lithium wire extruded into anhydrous THF while blanketed with an atmosphere of dry argon. Subsequent addition of tin halide, either as the bromide or chloride resulted in a rapid, exothermic reaction and formation of the characteristic dark green solution. Lithium clippings prepared in the conventional manner²¹⁰ reacted only slowly with trimethyltin bromide²¹¹ and not at all with the chloride.

1,4-*bis*-stannylated-but-2-yne (**4.30**) was prepared at low temperature but attempts to affect its rearrangement to the *bis*-stannane (**4.17**) with either catalytic trimethyltin lithium²⁰⁸ or methyl lithium²¹² offered no advantages over the room temperature reaction.

4.3.2.4 Attempted Synthesis of 3,4-*Bis*-trimethylstannyl-3-sulfolene.

3,4-Bifunctional-3-sulfolene coupling partners have been identified as important elements in a general strategy for the synthesis of higher dendralene precursors. (section 4.2.5) The addition of sulfur dioxide to *bis*-stannane (**4.17**) offered a short and potentially direct route to the 3,4-*bis*-stannylated 3-sulfolene derivative (**4.14**). (**Scheme 4.15**) The successful addition of sulfur dioxide to the diseleno-bridged

butadiene (4.31)²⁰⁸ set an encouraging precedent and a sealed tube reaction with SO₂ and (4.17) was attempted.

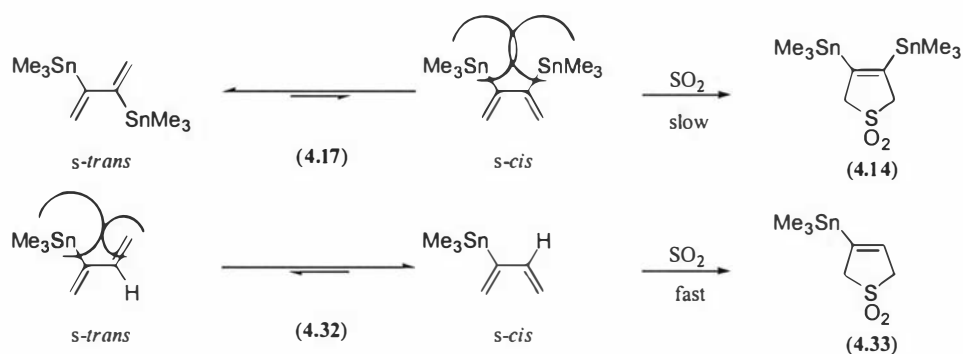


Scheme 4.15

The careful addition of liquid sulfur dioxide to a freshly prepared sample of (4.17) in ether-methanol containing a small quantity of hydroquinone saw the very rapid formation of a heavy white precipitate that was readily recovered by filtration. This material proved highly insoluble and NMR analysis could only be achieved on dilute solutions in d₆-DMSO. ¹H NMR analysis revealed a two proton singlet at *ca.* 3.0 ppm, suggestive of a methylene group adjacent to a sulfone and a nine proton methyl singlet at *ca.* 0.5 ppm showing the typical Sn-H coupling associated with a trimethyltin moiety. Some other minor features were also present but of negligible integrational intensity. While proton data initially appeared consistent with 3,4-*bis*-trimethylstannyl-3-sulfolene (4.14), ¹³C NMR analysis clearly indicated that no alkenic carbons were present, showing only two aliphatic signals at 78 and 53 ppm in addition to the characteristic "winged" signal of the trimethyltin fragment. It was concluded that the desired *bis*-stannylated 3-sulfolene (4.14) had not been formed. This was confirmed by elemental analysis, which established an empirical formula of C₁₀H₂₅O₄S₂Sn₂, indicating the inclusion of two molecules of sulfur dioxide. The high proportion of hydrogen was puzzling, however, the appearance of a broadened and intensified "water peak" in the ¹H NMR spectrum was suggestive of hidden exchangeable protons and, in the absence of any error in the combustion analysis, may offer some explanation for the increased proportion of hydrogen. Evidence to support the presence of an exchangeable proton species was granted by IR (KBr disc). This showed extensive hydrogen bonding around 3417 cm⁻¹ in addition to two strong bands at 1012 and 965 cm⁻¹ similar to, but slightly lower than those normally associated with the symmetric and asymmetric S=O stretches of a sulfinic acid.²¹³ Mass spectral analysis proved inconclusive. Under positive FAB mode, only a di-tin species of 671 mass units was evident. This showed

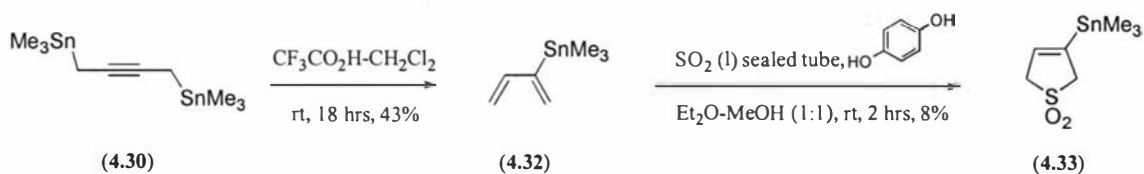
successive methyl fragmentation consistent with tin alkyl cleavage. Electron ionisation (EI) showed a high mass species (m/z 429), again with a characteristic di-tin isotope pattern. The appearance of a m/z 165 base fragment served to corroborate the presence of a trimethyltin residue. From this data no structural assignment could be made. It is believed, however, that the isolated material is a polymeric sulfinic acid containing a high proportion of trimethylated tin.

The ready formation of a sulfolene adduct from diene (4.31) contrasts markedly with the failure of *bis*-stannane (4.17) to undergo a similar reaction. (Scheme 4.15) It has been observed that simple exocyclic dienes, constrained to an *s-cis* conformation, i.e. (4.31), undergo much more rapid cycloaddition reactions than dienes that are free to adopt a less favourable *s-trans* form.²⁰⁸ Indeed, it is likely the presence of two bulky trimethyltin residues in (4.17) destabilise the requisite *s-cis* conformation, allowing unwanted reactions to compete with the desired cycloaddition of sulfur dioxide. (Scheme 4.16) It was anticipated, however, that the addition of sulfur dioxide to less sterically constrained dienes, bearing only one tin residue at C2, i.e. (4.32), would be more feasible and perhaps even favoured. As such this offered an alternative and potentially general synthesis of 3-stannylated-3-sulfolenes such as (4.33).



Scheme 4.16

Trifluoroacetic acid-promoted protiodestannylation of 1,4-*bis*-trimethylstannylbut-2-yne (4.30) has been shown to yield 2-trimethylstannyl-1,3-butadiene (4.32) in an efficient single step process.²⁰⁸ This literature procedure was repeated and the reaction of (4.32) with liquid sulfur dioxide under the conditions described above was investigated. (Scheme 4.17)



Scheme 4.17

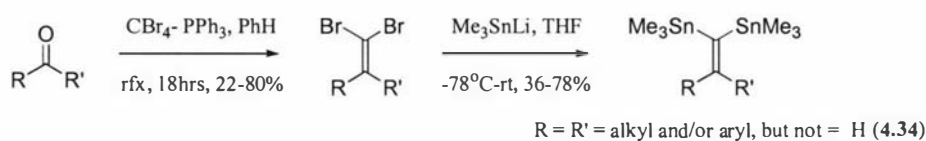
The addition of liquid sulfur dioxide to the trimethylstannane (4.32) again saw the formation of a heavy white precipitate, similar in appearance to that observed under identical conditions with the addition of SO_2 to the *bis*-stannane (4.17). Indeed, isolation and characterisation revealed this material to have identical physical and spectroscopic properties to the unknown compound isolated earlier. Elemental analysis, however, indicated a slight change in composition, giving an empirical formulation of $\text{C}_{10}\text{H}_{24}\text{O}_5\text{S}_2\text{Sn}_2$. It was assumed, however, that the two compounds were identical and that the observed differences were a result of cumulative errors expressed in the oxygen content. Nonetheless, the formation of a di-tin/di- SO_2 adduct from a *mono*-tin species is difficult to rationalise.

Tlc analysis of the supernatant from this reaction indicated the presence of a small quantity of unidentified product. After chromatographic purification, ^1H and ^{13}C NMR identified the isolate as 3-trimethylstannyl-3-sulfolene (4.33). This was later confirmed through mass spectral analysis. The yield, at 8%, was modest and the mass balance of total isolated material poor. Attempts to improve upon this with either shorter reaction times or lower temperatures were unsuccessful; results which indicate that the unknown reaction of sulfur dioxide with stannylated butadienes is strongly favoured over cycloaddition. The cross-coupling reactions of either 3-trimethylstannyl-3-sulfolene (4.33) or 3-trimethylstannyl-1,3-butadiene (4.32) were not investigated.

4.3.2.5 Attempted Synthesis of 1,1-Bis-trimethylstannylethene.

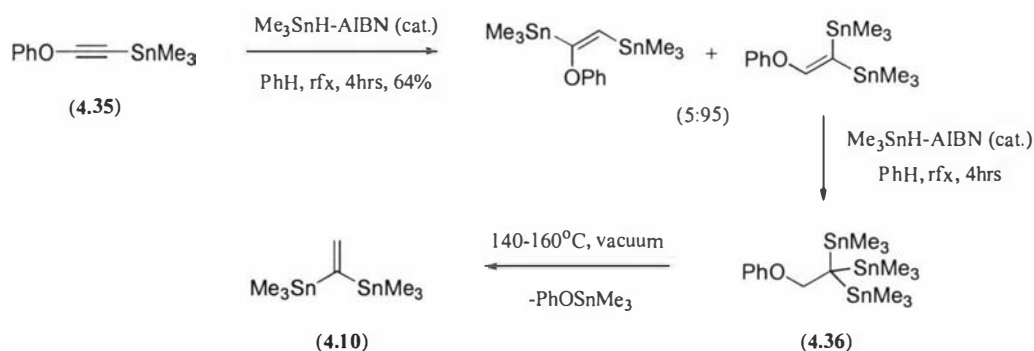
The retrosynthetic analysis of [5]-dendralene and higher, odd numbered dendralene precursors indicated the potential value of 1,1-*bis*-trimethylstannylethylene (4.10) as a cross-coupling partner with 3-iodo-3-sulfolene (3.37). Many 2-substituted and 2,2-disubstituted-1,1-*bis*-trimethylstannylethylene derivatives (4.34) have been prepared by the sequential dibromomethylenation and stannylation of aldehydes and ketones,²¹⁴ however, the synthesis of (4.10) from formaldehyde ($\text{R} = \text{R}' = \text{H}$, Scheme 4.18) by this

method has not been reported. Furthermore, competitive dehydrobromination during the second step of this sequence (metal-halogen exchange) is likely to make this approach to the parent *bis*-stannane (**4.10**) unworkable.



Scheme 4.18

Nonetheless, a synthesis of (**4.10**) has been reported by Mitchell.²¹⁵ This compound was prepared, in an undisclosed yield, by the destructive distillation of 1-phenoxy-2,2,2-*tris*-(trimethylstannyl)ethane (**4.36**), itself prepared by the double hydrostannylation of phenoxy-(trimethylstannyl)acetylene (**4.35**). (Scheme 4.19) Although neither experimental details nor the origin of acetylene (**4.35**) were described, the subsequent characterisation of (**4.10**) by ¹³C and ¹¹⁹Sn NMR^{215,216} suggested that pure material could be obtained by this method and on a useful synthetic scale.

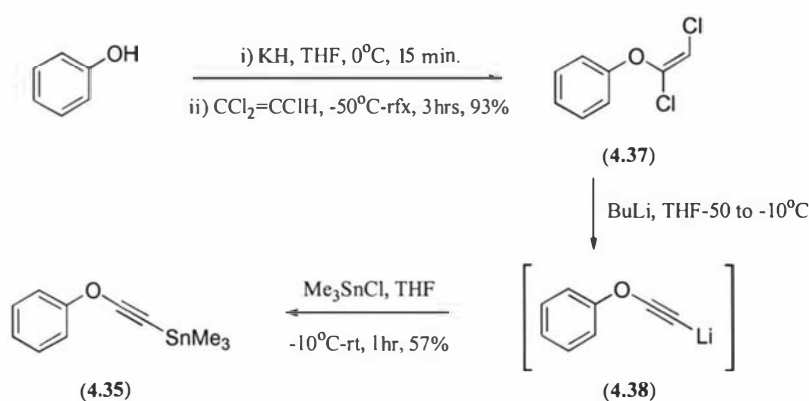


Scheme 4.19

While no synthesis of phenoxy-(trimethylstannyl) acetylene (**4.35**) has been reported, the conversion of naphthols to acetylenic ethers as described by Greene and co-workers²¹⁷ suggested a possible route.

Into a flask containing two equivalents of potassium hydride, the sequential introduction of phenol and trichloroethylene yielded dichloro-enol ether (**4.37**) as a single, undetermined stereoisomer. (Scheme 4.20) The stereochemistry (shown as *E*) proved to be unimportant as the addition of two equivalents of *n*-butyl lithium at low temperature effected an initial dehydrochlorination (removing any stereochemical

concerns) and subsequent metal-halogen exchange of the resultant chloroacetylene followed to give the intermediate lithium acetylide (**4.38**). Careful maintenance of the reaction mixture below -10°C and addition of trimethyltin chloride resulted in the formation of the desired phenoxy-(trimethylstannyl) acetylene, isolated in 57% yield after short path distillation. Quenching of the intermediate acetylide (**4.38**) with water gave only modest yields of phenoxyacetylene as an unstable, volatile oil⁷¹ and subsequent deprotonation followed by stannylation offered no advantages over the one pot process. Stannylacetylene (**4.35**) prepared by this method was a pale yellow oil. Upon storage at low temperature under argon, however, considerable polymerisation was observed. Attempts to redistill “old” samples were unsuccessful and no material could be re-isolated.



Scheme 4.20

The hydrostannylation of stannylacetylene (**4.35**) was investigated with trimethyltin hydride; prepared by the reduction of trimethyltin chloride with lithium aluminium hydride in tetraglyme.²¹⁸ In the presence of an excess of trimethyltin hydride (3 equivalents) and catalytic AIBN (10 mol%) in refluxing benzene, phenoxy-(trimethylstannyl) acetylene (**4.35**) was consumed over 5 hours as judged by tlc. With the exception of baseline material, no new features could be observed on silica plates. Removal of volatiles gave a yellow oil, ¹H NMR analysis of which revealed a complex aromatic region and an excess of trimethyltin protons but, significantly, no methylene signals consistent with 1-phenoxy-2,2,2-tris-(trimethylstannyl)ethane (**4.36**). Hydrostannylation of (**4.35**) with only a single molar equivalent of trimethyltin hydride gave a similar result with no discernible alkenic protons. Furthermore, the attempted destructive distillation of the crude isolate, obtained from the direct, double hydrostannylation of (**4.35**) yielded *no* identifiable volatile materials in a result clearly at odds with Mitchell's original report.²¹⁵ Personal communication with Mitchell

revealed the details of his original procedure had in fact been “lost” and he could offer no further comment on the process. It was acknowledged, with disappointment, that the instability of stannylacetylene (4.35), coupled with the hazardous nature of trimethyltin hydride and the scant experimental details available, made the synthesis of 1,1-*bis*-trimethylstannylethylene (4.10) non-trivial and it was therefore abandoned. The possibility of preparing related trialkylstannanes was considered briefly. While both the *bis*-triethylstannyl (4.39)²¹⁹ and *bis*-tributylstannyl ethylene derivatives (4.40)²²⁰ (Figure 4.3) are known, neither had been synthesised efficiently; both being observed only as minor components of complex reaction mixtures.

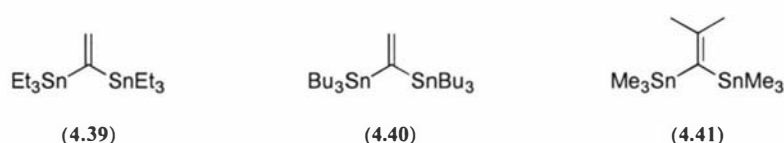
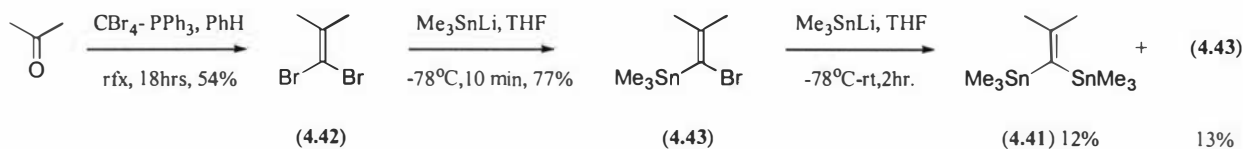


Figure 4.3

2-Substituted and 2,2-disubstituted-1,1-*bis*-trialkylstannylethylene derivatives (4.34) (Scheme 4.18) have been successfully coupled under Stille conditions to give *mono*-²²¹ and disubstituted products.²¹⁴ Furthermore, many of these stannanes are stable, easy to handle and obtained from simple starting materials. In view of this, and the unresolved difficulties encountered in the attempted synthesis of the *bis*-stannane (4.10), an alternative, model *bis*-stannane was sought. To this end the synthesis of the more readily accessible *gem*-dimethyl analogue (4.41) (Figure 4.3) was undertaken.

Corey-Fuchs dibromomethylenation²²² of acetone with carbon tetrabromide and triphenylphosphine in refluxing benzene gave the dibromide (4.42) in fair yield after distillation. (Scheme 4.21) Treatment of dibromide (4.42) with a two-fold excess of trimethyltin lithium in THF, at low temperature, saw its smooth conversion to the *mono*-substituted product (4.43). This material was readily isolated in good yield after short path distillation and characterised by ¹H and ¹³C NMR spectroscopy. ¹H NMR analysis revealed two non-equivalent allylic methyl signals, each showing Sn-H coupling of comparable magnitude (6.4 and 8.9 Hz). The ¹³C NMR spectrum was in good agreement with that published by Mitchell²¹⁴ and showed similar Sn-C coupling constants for both geminal methyl groups (28 and 29 Hz). Attempts to effect double bromine-tin substitution of (4.42) by allowing the reaction mixture to warm to room

temperature prior to quenching with water were unsuccessful and the bromostannane (4.43) was again formed as the major product, as judged by GCMS.



Scheme 4.21

Addition of excess trimethyltin lithium to bromostannane (4.43) at ambient temperature over an extended reaction period resulted in successful tin-halogen substitution. The desired *bis*-stannane (4.41) was isolated in modest yield (12%) after workup, column chromatography and purification by short path distillation. The unexpected isolation of unreacted bromostannane (4.43) (13%) indicated that tin-halogen exchange was slow even at room temperature and the use of elevated temperatures may be needed to improve yields further. Nonetheless, adequate quantities of (4.41) were now available to assess the Stille cross-coupling of 1,1-*bis*-stannylalkenes with 3-iodo-3-sulfolene (3.37).

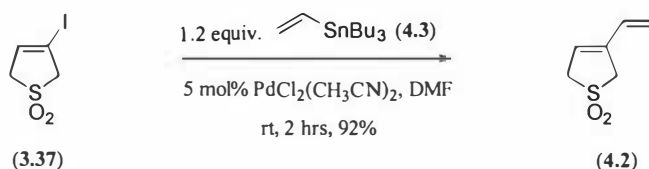
4.4 Cross-coupling Reactions of 3-Iodo-3-sulfolene.

The Stille cross-coupling of 3-iodo-3-sulfolene (3.37) with a variety of *mono*- and *bis*-stannanes was investigated as a method of preparing sulfolene-based [n]-dendralene precursors. The scope and limitations of this coupling strategy were investigated further through the synthesis of other, related 3-substituted 3-sulfolenes and pendant *bis*-3-sulfolene derivatives.

4.4.1 Coupling with *Mono*-stannanes.

4.4.1.1 3-Vinyl-3-sulfolene (4.2): A [3]-Dendralene Precursor.

The vinylation of alkenyl halides with tributylvinyl tin has been well documented.¹⁷⁵ Accordingly, treatment of 3-iodo-3-sulfolene (3.37) with a small excess of the freshly prepared tributylvinyl stannane (4.3) in the presence of 5 mol% *bis*-(acetonitrile) palladium (II) dichloride in degassed DMF at room temperature saw the rapid formation of 3-vinyl-3-sulfolene (4.2) as judged by tlc. (Scheme 4.22)



Scheme 4.22

Removal of solvent, chromatography on silica gel and recrystallisation gave the product as an air stable crystalline solid. The ¹H NMR spectrum was in good agreement with earlier reports¹⁹⁸ and showed the characteristic five protons of the 3-substituted 3-sulfolene moiety plus the three proton ABX system typical of a vinyl substituent. Mass spectral analysis showed a weak molecular ion (*m/z* 144, C₆H₈O₂S) and a more intense species corresponding to SO₂ loss (*m/z* 80) which confirmed the presence of the 3-sulfolene moiety. The remaining mass spectral fragmentation pattern was identical to that subsequently obtained for [3]-dendralene. (section 5.5.3, Chapter 5)

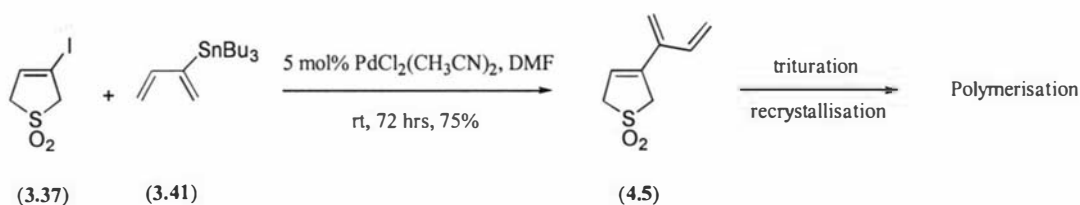
The Stille cross-coupling of the iodo-sulfolene (3.37) with tributylvinyl tin (4.3) represents a short, efficient and therefore viable alternative for the synthesis of the [3]-dendralene precursor (4.2) reported previously.¹⁹⁸ Furthermore, this synthesis can be achieved without recourse to specialised FVP equipment or lengthy reaction times (*cf.* Scheme 4.2).

4.4.1.2 2'-Butadienyl-3-sulfolene: A [4]-Dendralene Precursor.

The formation of fused *bis*-3-sulfolene (3.26) as a [4]-dendralene precursor has been discussed in detail in Chapter 3. Retrosynthetic analysis of [4]-dendralene (4.4), however, identified butadiene-substituted sulfolene derivative (4.5) as an alternative precursor. (Scheme 4.3)

It has been noted that alkenylstannanes which bear another substituent α - to tin appear difficult to couple, especially with internal alkenyliodides such as (3.37).¹⁷⁵ This difficulty has been attributed to steric hindrance. Hence, while it was expected that cross-coupling of the stannylated butadiene (3.41) with 3-iodo-3-sulfolene (3.37) would yield (4.5) successfully, it was also anticipated that this reaction would be slower than the corresponding formation of 3-vinyl-3-sulfolene (4.2). Indeed, in the presence of 5 mol% catalyst in DMF, coupling of stannylated butadiene (3.41) with 3-iodo-3-

sulfolene (**3.37**) was very sluggish and unreacted iodide (**3.37**) was still present even after 72 hours at room temperature. (Scheme 4.23) ^1H NMR analysis of the crude reaction mixture showed the presence of the butadiene-substituted sulfolene (**4.5**) which was isolated in 75% yield by chromatography, albeit contaminated with tin residues. Attempts to purify this material further by trituration with hexane and recrystallisation from ether resulted in extensive polymerisation.

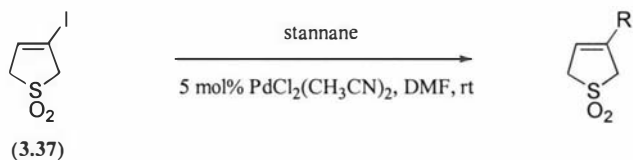


Scheme 4.23

Due to its problematic purification and tendency to undergo rapid polymerisation, it was concluded butadiene-substituted sulfolene (**4.5**) was unlikely to make a valuable [4]-dendralene precursor.

4.4.1.3 Related Cross-coupled Products. (A General to Route 3-Substituted-3-sulfolene Derivatives.)

Cross-coupling of 3-iodo-3-sulfolene (**3.37**) with the 1-tributylstannyl-1,3-butadienes (**4.23a** and **4.23b**) (as a mixture of isomers, *E:Z*, 87:13), gave the diene-substituted 3-sulfolene derivatives (**4.44a** and **4.44b**) with retention of the *E:Z* ratio (85:15). (Table 4.1, entry 1) Correcting for the presence of tributyltin iodide (still present in trace amounts after chromatography), a yield of > 90% was estimated for this reaction. Subsequent recrystallisation from dichloromethane-hexane gave the *E*-isomer (**4.44a**) as a single compound in 74% yield as an air stable crystalline solid. The minor *Z*-isomer (**4.44b**) could not be isolated as a pure compound. As observed earlier with the formation of 3-vinyl-3-sulfolene (**4.2**), terminal vinyl stannanes appear to couple rapidly with 3-iodo-3-sulfolene (**3.37**) at room temperature.

**Table 4.1**

entry	stannane	time / hrs	products	yield (% isolated)
1	 (4.23a) (87:13) (4.23b)	2	 (4.44a) (85:15) (4.44b)	(4.45a) 74
2	 ≡—SnBu ₃ (4.21)	2	 (4.45)	95
3	 C ₆ H ₅ —SnMe ₃	18	 (4.46)	68
4	 CH ₂ =CH—SnBu ₃ (4.20)	24	 (3.37)	34

Alkynylstannanes couple smoothly with a variety of electrophiles including alkenyl halides¹⁹⁴ and, according to Stille, represent the most reactive class of organotin reagents.¹⁷³ Although the coupling of unsubstituted terminal acetylenes with alkenyl halides can be achieved directly (Sonogashira coupling),¹⁷⁷ the Stille cross-coupling of alkynylstannanes nonetheless remains an important reaction.

The coupling of tributylethynyl tin (4.21) with 3-iodo-3-sulfolene (3.37), under standard conditions (5 mol% PdCl₂(CH₃CN)₃/DMF), gave 3-ethynyl-3-sulfolene (4.45) in excellent isolated yield as a stable crystalline solid. (Table 4.1, entry 2) Despite the enhanced reactivity of alkynyl tin reagents, when a similar coupling with 3-bromo-3-sulfolene (3.50) was attempted, the acetylenic sulfolene (4.45) was not detected even after extended reaction times (> 24 hrs) and elevated temperatures (80°C). The addition of catalytic copper (I) iodide^{196,197} proved equally ineffective. Failure to couple 3-bromo-3-sulfolene (3.50) with a reactive alkynylstannane, even under forcing conditions, clearly indicated this material was of limited value as a cross-coupling substrate and its use in cross-coupling reactions was not investigated further.

Arylstannanes couple readily with alkenyl iodides and many examples have been reported.¹⁷⁵ Under standard conditions trimethylphenyl tin coupled smoothly with 3-iodo-3-sulfolene to give 3-phenyl-3-sulfolene (**4.46**) in 68% yield. (**Table 4.1**, entry 3) Physical and spectroscopic characteristics of the recrystallised material were in good agreement with reported data.¹⁷⁰

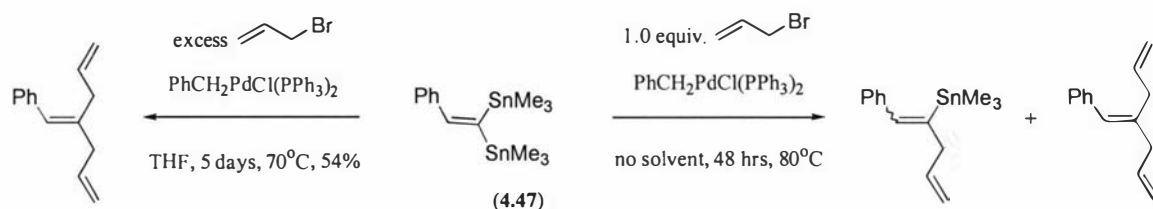
Many examples of cross-coupling reactions between allylstannanes and vinyl iodides have been reported and coupling at both the α and γ positions of the stannane have been observed.¹⁷⁵ Coupling of 3-iodo-3-sulfolene (**3.37**) with the symmetrical (unsubstituted) allyltributyl stannane (**4.20**) was therefore investigated since the formation of only a single product was anticipated. Under standard coupling conditions tlc analysis of the reaction mixture showed a gradual loss of stannane, however, no new products could be observed and workup and chromatography yielded only recovered 3-iodo-3-sulfolene (**3.37**). A similar result was obtained in the presence of catalytic copper (I) iodide,¹⁹⁷ where once again allyl stannane was consumed, but no coupled products were isolated. The reason for this unexpected behaviour remains unclear.

From this brief investigation, together with the successful synthesis of the [3]- and [4]-dendralene precursors (**4.2**) and (**4.5**), it was concluded that 3-iodo-3-sulfolene (**3.37**) is a valuable precursor to 3-substituted 3-sulfolenes. While cross-coupling with the allyl tin reagent (**4.20**) failed and coupling with the substituted alkenyl stannane (**3.41**) proved slow, it is likely that the use of alternative catalytic-solvent combinations will improve upon these apparent limitations.

4.4.2 Coupling with *Bis*-stannanes.

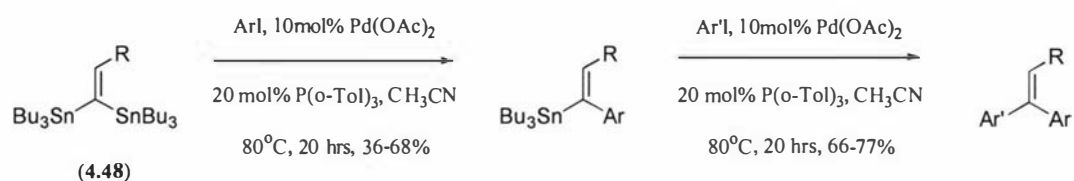
4.4.2.1 Synthesis of [5]-Dendralene Precursors.

The use of 1,1-*bis*-(trialkylstannyl) ethylenes as cross-coupling partners has received scant attention in the literature and only two reports exist. Mitchell,²¹⁴ in the earliest example of this reaction type, describes the formation of *mono*- and difunctionalised olefins by the palladium-catalysed allylation of the *gem*-dimetalated styrene (**4.47**). (**Scheme 4.24**) The ratio of products formed in these reactions was found to depend upon the reagent stoichiometry.



Scheme 4.24

Quayle,²²¹ in a later report further developed this coupling strategy through the regioselective *mono*-substitution of 1,1-*bis*-stannyl ethylenes (4.48) bearing a third, polar substituent (R) on the olefin. (Scheme 4.25) The successful coupling of aryl iodides with a series of *bis*-stannanes (4.48) is described and forms the basis of a general route to 1,1-*bis*-arylated ethylene derivatives. The regiocontrol of the arylation process was governed simply by the order in which the aryl iodides were coupled with the *bis*-stannane (4.48). It was observed, however, that cross-coupling reactions of this type were slow and, surprisingly, the rates of these reactions could not be improved by the addition of either copper (I) salts or rate-accelerating co-catalysts such as triphenylarsine.¹⁹⁶ The cross-coupling of aryl bromides was also investigated. In these cases it was found that the transfer of the “dummy” *n*-butyl ligands from tin to the electrophile¹⁷⁵ occurred in preference to the desired aryl substitution of (4.48). The scope of the electrophile was not surveyed further.



R = $-\text{CO}_2\text{Me}$, $-\text{CH}_2\text{OH}$, $-\text{CH}_2\text{OMOM}$

Scheme 4.25

The synthesis of pendant *bis*-3-sulfolene (4.9), as a precursor to [5]-dendralene, required access to 1,1-*bis*-trimethylstannyl ethylene (4.10). (Scheme 4.5) This compound could not be prepared, but its dimethyl analogue (4.41) was readily available from acetone. (Scheme 4.21) Hence the cross-coupling of (4.41) with two equivalents of 3-iodo-3-sulfolene (3.37) was investigated as a route to the putative dimethylated [5]-dendralene precursor (4.49). (Figure 4.4)

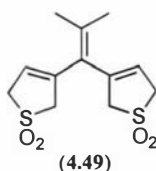
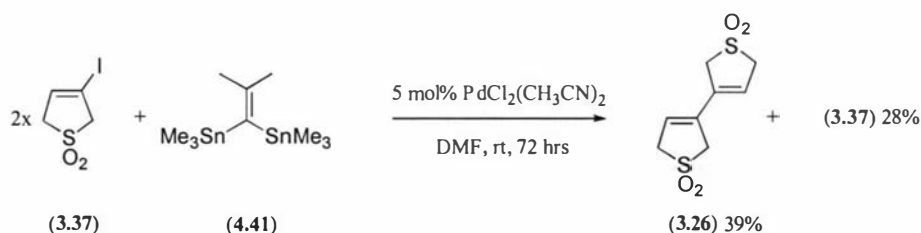


Figure 4.4

In the presence of 5 mol% *bis*-(acetonitrile) palladium (II) chloride in degassed DMF at room temperature, *bis*-stannane (4.41) was consumed over 72 hours to give a heavy white precipitate. Isolation of the precipitate in the usual manner and NMR analysis revealed this material to be the fused *bis*-3-sulfolene (3.26) and not the anticipated [5]-dendralene precursor (4.49) as expected. (Scheme 4.26) *Bis*-sulfolene (3.26) was obtained in 39% yield together with unreacted 3-iodo-3-sulfolene (3.37) (28%). No trace of unreacted *bis*-stannane (4.41) could be observed, but trimethyltin iodide was isolated from the reaction mixture. The isolation of *bis*-sulfolene (3.26) as the unexpected, yet major product is reminiscent of the reaction between 2,5-*bis*-tributylstannyl-3-sulfolene (3.40) and 3-iodo-3-sulfolene (3.37). (Scheme 3.33) These unusual outcomes point to a tin-iodine exchange occurring prior to coupling.

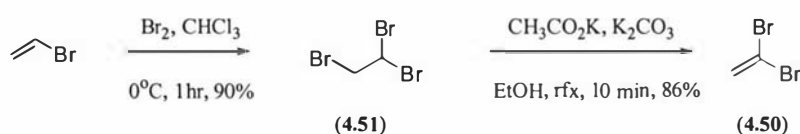


Scheme 4.26

In view of the difficulties encountered in the synthesis of [5]-dendralene precursors utilising a 1,1-*bis*-stannylated ethylene fragment, a simple reversal of functionality was investigated as an alternative approach. Thus, 1,1-dibromoethene (4.50) was prepared (Scheme 4.27) and its cross-coupling with 3-tributylstannyl-3-sulfolene (3.33) attempted. This adaptation offered the potential of gaining access to the parent [5]-dendralene precursor (4.9) bearing no superfluous alkyl substitution whilst still utilising a sulfolene-based Stille cross-coupling strategy.

Addition of elemental bromine to vinyl bromide in chloroform gave 1,1,2-tribromoethane (4.51) as a dense, colourless oil in 90% yield after distillation.²²³ (Scheme 4.27) Addition of neat 1,1,2-tribromoethane (4.51) to a refluxing suspension

of potassium acetate and potassium carbonate in ethanol, according to the method of Bergman,²²⁴ yielded 1,1-dibromoethylene (4.50) as an air sensitive colourless oil in 86% yield. On exposure to air, 1,1-dibromoethylene (4.50) became opaque and eventually polymerised to give a dense solid. Freshly prepared samples of 1,1-dibromoethylene (4.50) could be stored for several days over calcium chloride at low temperature without significant decomposition.



Scheme 4.27

In the presence of a catalytic quantity of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ in carefully degassed DMF at 40°C , two equivalents of the stannylsulfolene (3.33) were successfully coupled with the dibromide (4.50) to give the pendant *bis*-3-sulfolene (4.9) in a modest isolated yield of 11%. (Table 4.2, entry 1)

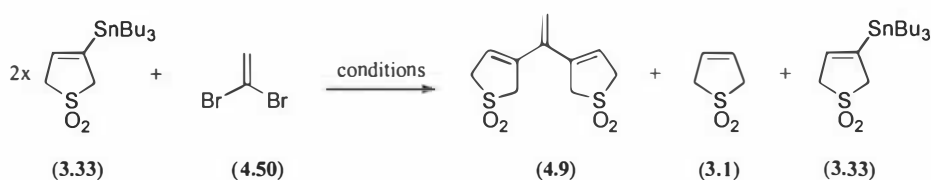


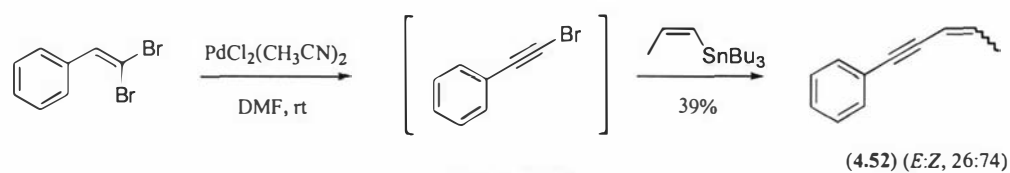
Table 4.2

entry	conditions	yield %		
		(4.9)	(3.1)	(3.33)
1	5 mol% $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ DMF, 40°C , 36 hrs.	11	19	-
2	2 mol% $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ 8 mol% Ph_3As , NMP, rt, 18 hrs.	3	25	38
3	5 mol% $\text{Pd}(\text{OAc})_2$, 10 mol% Ph_3P CH_3CN , 60°C , 18 hrs.	6	25	45

Bis-3-sulfolene (4.9) gave simple ^1H and ^{13}C NMR spectra consistent with its symmetrical structure, while high resolution mass spectrometry gave a moderately intense ($\text{M}^+ - \text{SO}_2$) ion which exhibited a further sulfur dioxide loss. A small quantity of

3-sulfolene (**3.1**) (19%), the product of protiodestannylation, was also isolated and identified by comparison with commercial material. Interestingly, no *mono*-coupled products were observed.

An isolated example of a *gem*-dibromomethylene cross-coupling reaction catalysed by $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ in DMF has been reported.²²⁵ (**Scheme 4.28**) In contrast to our findings, no *bis*-coupling was observed and preferential dehydrobromination of the dibromide to form an intermediate bromoacetylene was reported. Subsequent *in situ* coupling with 1-*Z*-propenyltributyl tin (> 95% *Z*) yielded the substituted enyne (**4.52**) as a mixture of isomers in moderate yield with no mention of protiodestannylation being made.



In an attempt to improve upon the efficiency of coupling between dibromide (**4.50**) and stannylsulfolene (**3.33**), alternative coupling conditions were investigated. Farina and co-workers¹⁷⁷ have observed large rate enhancements (up to a 1000 fold) in a range of representative Stille cross-coupling reactions, when triphenylphosphine ligands are replaced with either tri-2-furylphosphine (TFP) or triphenylarsine (TPA). Despite the “ligandless” conditions described in entry 1, it was anticipated that an enhancement in the rate of formation of (**4.9**) would be observed if Farina’s optimised conditions were employed. (**Table 4.2**, entry 2) However, in the presence of dipalladium *tris*-dibenzylideneacetone chloroform complex ($\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3$)²²⁶ and triphenylarsine in *N*-methylpyrrolidinone (NMP), *bis*-3-sulfolene (**4.9**) was formed in even lower yield with no apparent enhancement in rate over the existing conditions. Although the reaction was quenched after only 18 hours, a higher proportion of protiodestannylation was observed. Unreacted stannane (**3.33**) was also recovered.

The cross-coupling of *gem*-dibromomethylene compounds with alkynyl stannanes has been achieved in the presence of palladium acetate and triphenylphosphine in acetonitrile.²²⁷ Under these conditions (**Table 4.2**, entry 3) the pendant-*bis*-3-sulfolene (**4.9**) was obtained, but again in poor yield. 3-Sulfolene (**3.1**) and recovered stannane

(3.33) were the major components of the reaction mixture. Neither of the two modified procedures investigated offered any improvement over the original conditions employed and time constraints precluded any further optimisation. Nonetheless sufficient quantities of the sulfolene-based [5]-dendralene precursor (4.9) were available to assess the efficiency of a double cheletropic elimination process to prepare [5]-dendralene (4.8).

4.4.2.2 Synthesis of [6]-Dendralene Precursors.

The limited success of the Stille cross-coupling of 1,1-*bis*-stannylated ethylene derivatives with iodosulfolene coupling partners did not set an encouraging precedent. However, the coupling of *bis*-stannanes, where the tin residues are not borne by the same carbon atom has, in general, been accomplished with a greater degree of success.¹⁷⁵

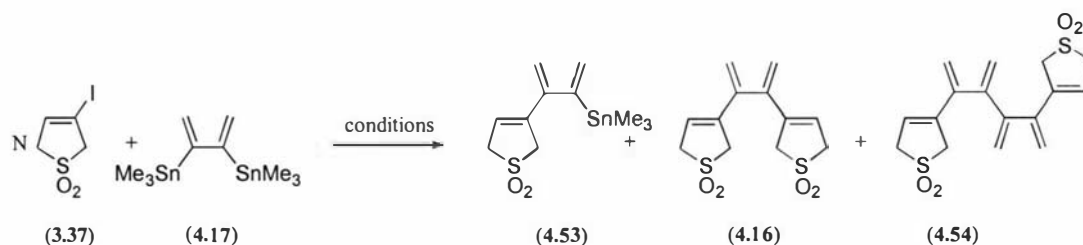


Table 4.3

entry	N	conditions	yield %			
			(4.53)	(4.16)	(4.54)	(3.26)
1	1.0	10 mol% PdCl ₂ (CH ₃ CN) ₂ DMF, 60°C, 72 hrs.	19	43	30	-
2	2.0	5 mol% PdCl ₂ (CH ₃ CN) ₂ DMF, 60°C, 72 hrs.	55	12	5	-
3	1.0	2.5 mol% Pd ₂ dba ₃ :CHCl ₃ 10 mol% Ph ₃ As, NMP, rt, 72 hrs.	10	19	-	^a
4	2.0	5 mol% Pd ₂ dba ₃ :CHCl ₃ 20 mol% Ph ₃ As, NMP, rt, 72 hrs.	^b	^b	-	83

^a An insoluble product (*bis*-sulfolene (3.26)) was observed but not isolated.

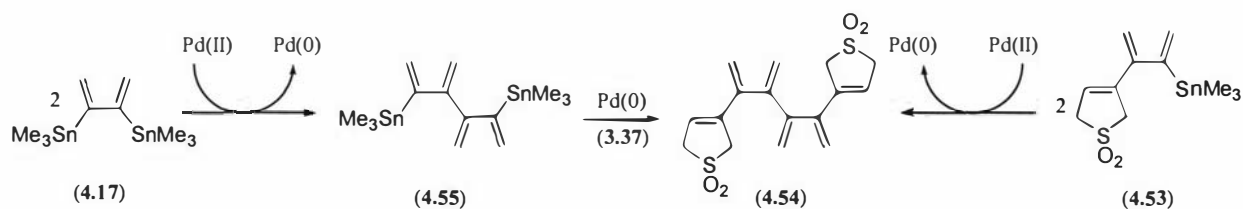
^b Observed on tlc but not isolated by chromatography.

It was therefore anticipated that the Stille cross-coupling of 3-iodo-3-sulfolene (**3.37**) with 2,3-*bis*-(trimethylstannyl)-1,3-butadiene (**4.17**) would yield a [6]-dendralene precursor. Furthermore, it was anticipated that control over the coupling could be achieved such that a *mono*-coupled species would also be obtained.

When a stoichiometric amount of *bis*-stannylated butadiene (**4.17**) and 3-iodo-3-sulfolene (**3.37**) were coupled at 60°C over 72 hours, a mixture of three products were observed on tlc and subsequently isolated by column chromatography. It should be noted that an error was made when calculating the mass of catalyst required and 10 mol% was inadvertently used instead of 5. (**Table 4.3**, entry 1) Nonetheless, the *mono*-coupled species (**4.53**) was isolated in 19% yield as an amorphous white solid and the expected *bis*-coupled product (**4.16**) was obtained in 43% yield, again as an amorphous solid. A third and unexpected 3-sulfolene adduct was also recovered in minor amounts. ¹H and ¹³C NMR in conjunction with mass spectrometry later showed this material to be the novel, pendant *bis*-sulfolene (**4.54**), itself a substituted [6]-dendralene. More importantly, however, was the significance of (**4.54**) as a potential [8]-dendralene precursor. Although unstable at room temperature, (**4.54**) was isolated in 30% yield.

There are two possible routes to the formation of *bis*-sulfolene (**4.54**), both requiring oxidative coupling of a stannylated butadiene. (**Scheme 4.29**)

- i. Reduction of palladium (II) to palladium (0) and concomitant oxidation of the *bis*-stannane (**4.17**) would yield a *bis*-stannylated [4]-dendralene (**4.55**). Subsequent coupling of this material with iodo-sulfolene (**3.37**) in the usual manner results in the observed product (**4.54**).
- ii. Alternatively (or simultaneously), the oxidative coupling of preformed *mono*-sulfolene species (**4.53**) will yield a similar result.



Scheme 4.29

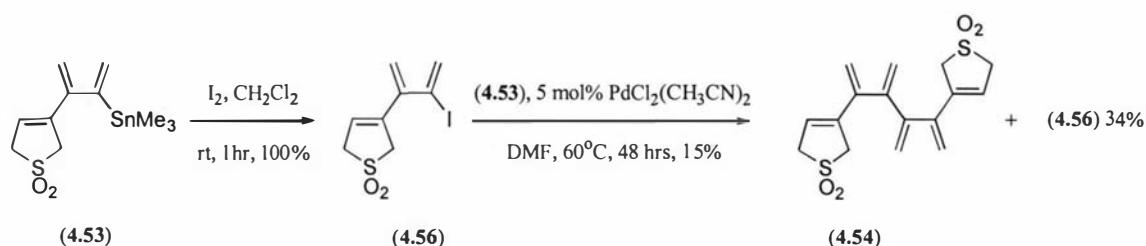
While there is little dispute over the potential origins of (4.54), an isolated yield of 30% is more difficult to explain. Despite the inadvertent use of 10 mol% of palladium (II) species as catalyst, it would be expected that at most a 20% yield of the [8]-dendralene precursor (4.54) could possibly be formed. This result is perhaps yet another example of tin-iodine exchange occurring under the reaction conditions leading to homo-coupled products in yields higher than expected.

It was also surprising to find that coupling of a stoichiometric ratio of *bis*-stannane (4.17) with the iodide (3.37) gave a higher proportion of the *bis*-coupled over *mono*-coupled products. From this it was reasonable to expect that coupling of two molar equivalents of 3-iodo-3-sulfolene (3.37) with one of the *bis*-stannane (4.17) would give an enhanced yield of the [6]-dendralene precursor (4.16). This was not the case. Under these conditions, albeit in the presence of only 5 mol% catalyst, a higher proportion of the *mono*-coupled adduct (4.53) was isolated over that of the expected *bis*-coupled product. (Table 4.3, entry 2) The [8]-dendralene precursor (4.55) was again observed, although in only 5% yield and unreacted 3-iodo-3-sulfolene (3.37) (16%) was also recovered.

This coupling process was also investigated under Farina's conditions.¹⁷⁷ With one equivalent of 3-iodo-3-sulfolene (3.37) (Table 4.3, entry 3) poor yields of both the *mono*-coupled and *bis*-coupled products, (4.53) and (4.16) respectively, were obtained, but the [8]-dendralene precursor (4.55) was not observed. A small quantity of insoluble material (believed to be the fused *bis*-3-sulfolene (3.26), see entry 4) was also observed, however, the recovery of this component proved difficult and it was not isolated. With two molar equivalents of iodide (3.37) (Table 4.3, entry 4), the fused *bis*-3-sulfolene (3.26) was formed as an insoluble solid and isolated in 83% yield as the major product. While traces of the *mono*-coupled and *bis*-coupled products, (4.53) and (4.16), but not (4.55), were observed (tlc), their isolation proved difficult and no characterisable material was obtained after column chromatography. The isolation of the *bis*-3-sulfolene (3.26) again suggests the occurrence of tin-iodine exchange under the reaction conditions, an unexpected outcome that is consistent with earlier observations. (Scheme 3.33 and Scheme 4.26)

The formation of the [8]-dendralene precursor (4.54) in such high yields was an unexpected bonus and suggested this compound could be synthesised directly by

coupling of stannane (**4.53**) with its corresponding iodide. (**Scheme 4.30**) Conversion of stannane (**4.53**) to the vinyl iodide (**4.56**) was achieved in quantitative yield with elemental iodine in dichloromethane. However, coupling at 60°C over 48 hours under standard conditions gave the desired [8]-dendralene precursor (**4.54**) in a disappointingly low yield of only 15%. The low yield and isolation of unreacted iodide (**4.56**) (34%) suggested this material might again have been formed as a product of Pd(II) reduction. However, the reason for the poor efficiency of the subsequent Stille cross-coupling reaction is unclear.



Scheme 4.30

Despite the general success of Farina's conditions when employed as a substitute for more conventional phosphine based catalysts, these conditions, when applied to the coupling of 3-iodo-3-sulfolene (**3.37**), offered no advantage over the "ligandless" catalyst PdCl₂(CH₃CN)₂ in DMF. Indeed, the higher boiling point of NMP, used as the solvent under Farina's conditions, made the isolation of sulfolene derivatives even more difficult and is not recommended.

4.4.2.3 Related Cross-coupled Products. (A General Route to Pendant *Bis*-3-sulfolenes.)

The cross-coupling of 3-iodo-3-sulfolene (**3.37**) with a range of unsaturated *bis*-stannanes was attempted as a preliminary investigation into the formation of pendant *bis*-3-sulfolenes containing conjugated tethers. (**Table 4.4**)

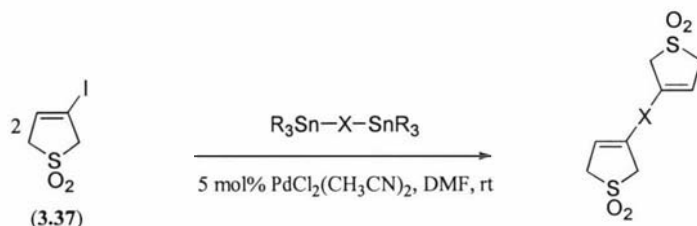


Table 4.4

entry	$\text{R}_3\text{Sn-X-SnR}_3$	time / hrs	product	yield % (isolated)
1	$\text{Bu}_3\text{Sn}-\text{C}\equiv\text{C}-\text{SnBu}_3$ (4.22)	2	(4.57)	93
2	$\text{Bu}_3\text{Sn}-\text{CH}=\text{CH}-\text{SnBu}_3$ (4.24)	3	(4.58)	95
3	$\text{Bu}_3\text{Sn}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{SnBu}_3$ (4.26a) + $\text{Bu}_3\text{Sn}-\text{CH}=\text{CH}-\text{CH}=\text{CH}-\text{SnBu}_3$ (4.26b) (57:43)	18	(4.59a) + (4.59b) (~1:1)	74

All coupling reactions were carried out under standard conditions with 5 mol% of catalyst with respect to the iodide (3.37). Two equivalents of iodide were used and no attempts were made to effect *mono*-coupling with a single equivalent of iodide (3.37). Somewhat surprisingly however, no evidence of any *mono*-coupled species was obtained during the monitoring of these reactions.

Coupling of the *bis*-stannylated acetylene (4.22) occurred smoothly and the ethynyl linked pendant *bis*-sulfolene (4.57) was isolated in 93% yield as a heavy white precipitate. (Table 4.4, entry 1) Attempts to recrystallise this material were unsuccessful as witnessed previously with other *bis*-sulfolene derivatives. However, near analytically pure material could be obtained from acetone as an amorphous solid.

Coupling of *trans*-*bis*-stannylated ethylene (4.24) occurred with similar efficiency and the alkenyl tethered *bis*-sulfolene (4.58) was isolated in excellent yield. (Table 4.4, entry 2) Again, while the insolubility of this material greatly aided its initial isolation, no subsequent purification could be achieved beyond trituration to remove tin residues.

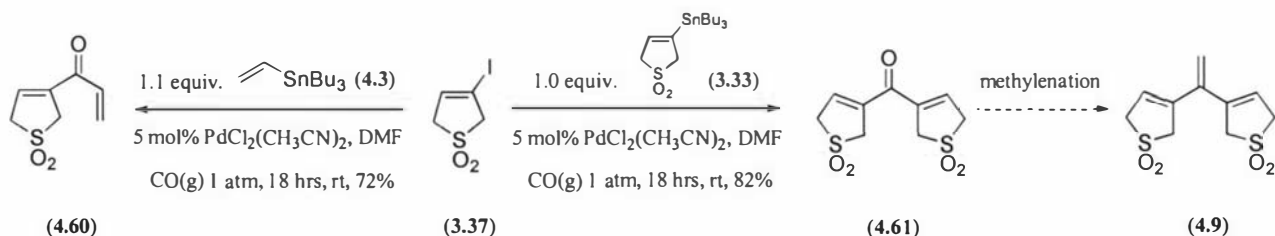
The formation of 1,4-*bis*-stannylated 1,3-butadienes (**4.26**) by the cheletropic elimination of sulfur dioxide from the novel 2,5-*bis*-stannylated 3-sulfolenes (**3.40**) has been described. (**Scheme 4.10**, section **4.3.2.2**) Although an inseparable mixture of *E,E*- and *E,Z*-dienes were obtained, their value as coupling partners in the sulfolene-Stille cross-coupling reaction was investigated and after 18 hours at room temperature under standard conditions a heavy, off white precipitate was isolated in the usual manner. NMR indicated this material to be the expected *bis*-coupled sulfolene derivative obtained as a mixture of *E,E*-(**4.59a**) and *E,Z*-isomers (**4.59b**). Determination of an accurate isomeric ratio from the ¹H NMR spectrum proved difficult due to the complexity of the alkenic region. A comparison of the relative peak heights of the carbon signals in the ¹³C NMR spectrum indicated the isomeric ratio of the distannanes (**4.26**) had been more or less retained in the products. (**Table 4.4**, entry 3)

4.4.3 Carbonylative Coupling.

When the Stille cross-coupling reaction is carried out under an atmosphere of carbon monoxide, carbonyl incorporation under catalytic conditions is possible. This reaction is general for alkenyl, aryl, heteroaryl and allylic electrophiles and an equally comprehensive array of organotin reagents have been successfully coupled.¹⁷⁵ Thus, the palladium-catalysed carbonylative coupling of alkenyl iodides with alkenylstannanes affords dialkenyl ketones and the reaction can be carried out under mild conditions at low carbon monoxide pressures. In general, any coupling partner compatible with standard non-carbonylative cross-coupling conditions is compatible with the carbonylative variant.

The nature and efficacy of the many catalyst-solvent combinations employed in the carbonylative cross-coupling reaction is as varied and diverse as the conditions employed in the non-carbonylative prototype. To assess the carbonylative cross-coupling of 3-iodo-3-sulfolene (**3.37**), the catalyst-solvent combination used successfully for all previous sulfolene cross-coupling reactions, i.e. Pd₂Cl₂(CH₃CN)₂/DMF, was retained. The reaction conditions developed for the non-carbonylative protocol were modified slightly, with the reaction mixtures being degassed and run under an atmosphere of carbon monoxide rather than argon.

Under these conditions, in the presence of a slight excess of tributylvinyl tin (**4.3**), 3-iodo-3-sulfolene (**3.37**) coupled smoothly to give the substituted vinyl ketone (**4.60**) in 72% yield. Only traces of 3-vinyl-3-sulfolene (**4.2**) were observed in the crude reaction mixture ($< 3\%$, as judged by ^1H NMR) and this material was not isolated. Chromatography and recrystallisation gave vinyl ketone (**4.60**) as an analytically pure, air stable crystalline solid. (Scheme 4.31) The ^1H NMR spectrum was fully consistent with structure (**4.60**) and the ^{13}C NMR spectrum exhibited the characteristic downfield carbon resonance of a cross-conjugated ketone ($\delta = 185.2$ ppm). IR confirmed the presence of an α,β -unsaturated ketone, showing absorptions at 1661 cm^{-1} ($\text{C}=\text{O}$) and 1607 cm^{-1} ($\text{C}=\text{C}$).



Scheme 4.31

The efficiency of the carbonylative coupling of 3-iodo-3-sulfolene (**3.37**) with the vinylstannane (**4.3**) suggested a possible alternative route to the [5]-dendralene precursor (**4.9**), prepared previously in only low yield from stannane (**3.33**). (Table 4.2) Unfortunately, while the carbonylative coupling of 3-iodo-3-sulfolene (**3.37**) with 3-tributylstannyl-3-sulfolene (**3.33**) proceeded with remarkable efficiency (Scheme 4.31), attempts to effect the subsequent methylenation of the ketone (**4.61**) were unsuccessful. It was fully anticipated that neither Wittig nor Peterson olefination would be compatible with the base-sensitive keto-sulfolene (**4.61**), however, the failure of both Tebbe's²²⁸ (**4.62**) and Petasis' reagents²²⁹ (**4.63**) (Figure 4.5) proved a disappointing result. Extensive decomposition of the keto-sulfolene (**4.61**) with both reagents was observed and no identifiable products isolated.

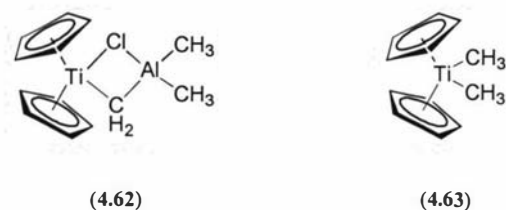


Figure 4.5

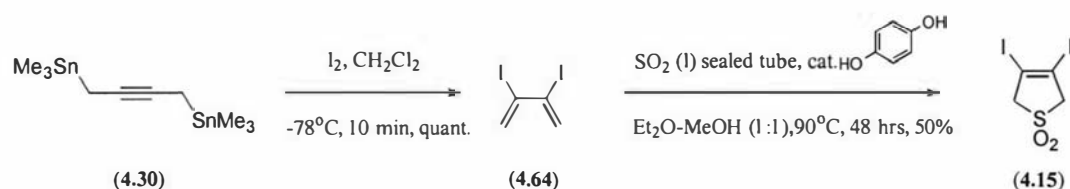
It was concluded that although the carbonylative cross-coupling of 3-iodo-3-sulfolene is an effective method for the preparation of 3-keto-3-sulfolene derivatives, subsequent methylenation is unlikely to prove useful as a general route to [n]-dendralene precursors.

4.5 Synthesis and Cross-coupling Reactions of 3,4-Diiodo-3-sulfolene.

Retrosynthetic analysis of higher dendralene precursors identified two potentially viable bifunctional 3-sulfolene derivatives as coupling partners in a general strategy for the synthesis of [n]-dendralenes. (Scheme 4.6) Unfortunately, attempts to prepare a *bis*-stannylated 3-sulfolene derivative (*viz.* 3,4-*bis*-trimethylstannyl-3-sulfolene (4.14)) were unsuccessful. (Scheme 4.15) The limitations imposed by this initial failure were overcome by the use of a “prematurely” unmasked *bis*-stannane (4.17) and precursors to both [6]- and [8]-dendralene were subsequently prepared. 3,4-Diiodo-3-sulfolene (4.15) was identified as the second bifunctional coupling partner and the synthesis and reactivity of this compound were therefore investigated.

4.5.1 Synthesis of 3,4-Diiodo-3-sulfolene.

The formation of simple 3-sulfolene derivatives by the addition of liquid sulfur dioxide to substituted 1,3-dienes has been discussed in section 3.3.1. It was envisaged that this reaction could be used for the formation of (4.15) by the addition of sulfur dioxide to the known diiododiene (4.64).²⁰⁸ (Scheme 4.32)



Scheme 4.32

Iodination of 1,4-*bis*-(trimethylstannyl)but-2-yne (4.30) in dichloromethane at low temperature, according to the method of Reich *et al.*,²⁰⁸ gave 2,3-diiodobutadiene (4.64) in excellent yield. Removal of excess iodine and trimethyltin iodide was achieved by successive washing of the crude reaction mixture with saturated sodium thiosulfate solution and water. While this workup provided spectroscopically

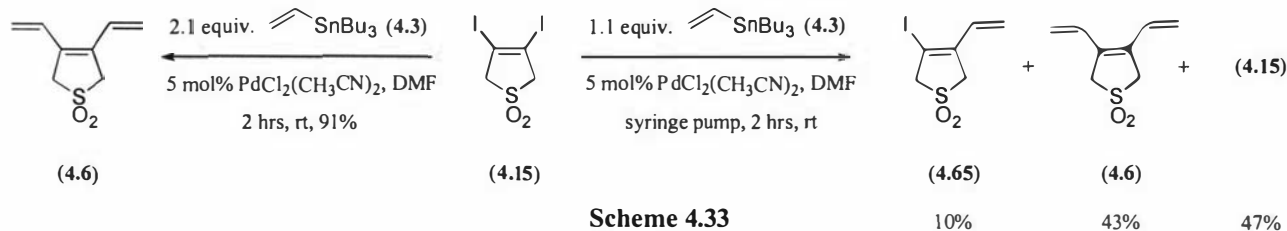
homogeneous material, product decomposition was rapid, especially in the presence of light, and 2,3-diiodobutadiene (**4.64**) was always obtained as a dark red oil. Nonetheless, even in an unpurified state, crude (**4.64**) reacted with liquid sulfur dioxide in a sealed tube at 90°C over 48 hours to give 3,4-diiodo-3-sulfolene (**4.15**) as a chromatographable solid in 50% yield over two steps from the stannane (**4.30**). Remarkably, unreacted diiodobutadiene (**4.64**) was also recovered (41%), however rapid polymerisation upon workup rendered this material impossible to recycle. Recrystallisation of chromatographed 3,4-diiodo-3-sulfolene (**4.15**) yielded analytically pure material as an air and light stable crystalline solid exhibiting very simple ^1H and ^{13}C NMR spectra. Mass spectral analysis showed an uncharacteristically intense molecular ion in addition to the expected sulfur dioxide fragmentation consistent with the presence of a 3-sulfolene moiety.

This short, yet efficient sequence represents the first synthesis of 3,4-diiodo-3-sulfolene (**4.15**) and although used to prepare only modest quantities of material (< 1g), it is likely to be amenable to the synthesis of (**4.15**) on a multi-gram scale.

4.5.2 Cross-coupling Reactions of 3,4-Diiodo-3-sulfolene.

4.5.2.1 Divinylation. Other [4]-Dendralene Precursors.

In the presence of 2.1 equivalents of tributylvinyl tin and a catalytic quantity of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ in DMF, diiodide (**4.15**) coupled smoothly to give the divinylated 3-sulfolene (**4.6**) in excellent yield as an air stable crystalline solid after chromatography and recrystallisation. (Scheme 4.33) ^1H NMR analysis was consistent with the symmetrical structure showing a well defined ABX system and a singlet for the α -sulfone methylenes. Other spectroscopic data, including mass spectra, were wholly consistent with the assigned structure and a sharp melting point of 115°C agreed closely with earlier literature reports of 113°C for (**4.6**) prepared by other means.¹⁹⁹



To assess the feasibility of preparing a *mono*-vinylated derivative of diiodide (4.15), coupling with one molar equivalent of tributylvinyl tin (4.3) was examined. Even with the slow syringe pump addition of the vinyl tin reagent, divinylsulfolene (4.6) was always formed preferentially over the *mono*-vinylated species (4.65). This surprising result was attributed to the steric inhibition offered by the diiodide towards oxidative addition to the reactive Pd(0) species. After replacement of one iodine atom by an alkenic residue, the sterically less encumbered *mono*-iodide (4.65) is free to react more readily giving a predominance of the *bis*-coupled product. The *mono*-coupled product was formed at best in only 10 % yield and isolation of this material was further complicated by an unfortunate co-elution with residual, unreacted diiodide (4.15). Chromatography with a variety of solvent systems was attempted, but no separation could be achieved. Consequently, the yields given are estimates based on ¹H NMR analysis of the crude reaction mixture and the iodovinylsulfolene (4.65) was never isolated as a pure compound.

4.5.2.2 *Tris*-3-sulfolene: A [6]-Dendralene Precursor.

While coupling of the simple alkenylstannane (4.3) with diiodide (4.15) gave a predominance of the *bis*-coupled adduct (4.6), it was anticipated that coupling with more sterically encumbered alkenylstannanes would be both slower and yield a more even mixture of *mono*- and *bis*-coupled products. Furthermore, the use of 3-tributylstannyl-3-sulfolene (3.33) offered the possibility of preparing the first example of a fused *tris*-3-sulfolene adduct.

Under standard conditions, diiodide (4.15), coupled with one equivalent of 3-tributylstannyl-3-sulfolene (3.33) to give a mixture of the *mono*- and *bis*-coupled products in modest yield after an extended reaction period together with a significant quantity (62%) of recovered diiodide. (Table 4.5, entry 1)

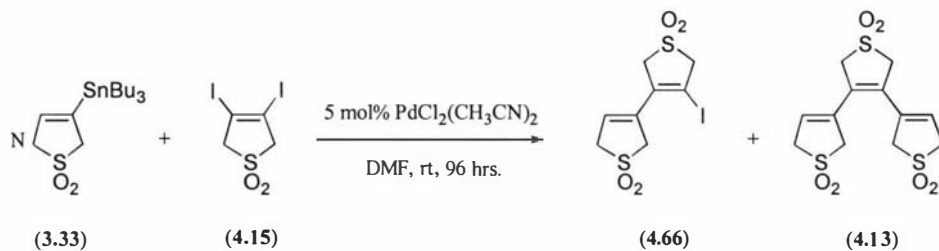


Table 4.5

entry	N	yield %			
		(4.66)	(4.13)	(4.15)	(3.33)
1	1.0	14	20	62	-
2	2.0	14	43	22	14

Whereas iodide (4.66) was soluble in organic media, the product of double coupling, i.e. *tris*-3-sulfolene (4.13), exhibited physical properties analogous to the *bis*-fused-3-sulfolene (3.26), and was therefore readily isolated from the reaction mixture as an insoluble amorphous solid. *Tris*-3-sulfolene (4.13) was purified by trituration (ether, then hexane) to remove tin residues. Subsequent attempts to recrystallise this material, however, were unsuccessful. For NMR analysis, solubility again proved to be a problem and all spectra were obtained from saturated, yet dilute solutions in d_6 -DMSO. The ^1H NMR spectrum exhibited characteristically broadened signals for all resonances and revealed a two proton alkenic methine singlet and the three chemically distinct α -sulfone methylene signals each integrating for four protons. The ^{13}C NMR spectrum showed only three alkenic and three aliphatic signals, with appropriate multiplicities, and was fully consistent with the symmetrical structure of (4.13). Traces of the fused *bis*-3-sulfolene (3.26) could be observed as an impurity (< 5%) in both the ^1H and ^{13}C NMR spectra. The presence of this minor component was attributed to the oxidative coupling of the stannylsulfolene (3.33) during the initial reduction of the palladium (II) catalyst. High resolution mass spectral analysis gave a molecular ion formulating for the tricyclic structure (4.13) and showed three successive sulfur dioxide losses.

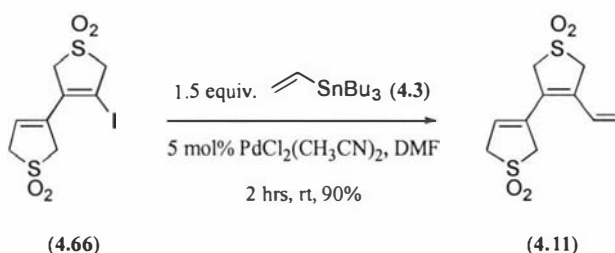
The *mono*-coupled species (4.66) was isolated after chromatography as an amorphous powder. Recrystallisation gave the iodide as a white crystalline solid which darkened rapidly on exposure to light. Spectroscopic data was fully consistent with structure

(4.66) and mass spectrometry gave a well formulated molecular ion which exhibited the loss of two sulfur dioxide fragments.

In an attempt to improve the overall yield and relative proportion of *tris*-3-sulfolene (4.13), the coupling of diiodide (4.15) with two molar equivalents of 3-tributylstannyl-3-sulfolene (3.33) was also investigated. (Table 4.5, entry 2) Under standard conditions, this modification improved the isolated yield of *tris*-3-sulfolene (4.13) significantly, but saw no change in the yield of *mono*-coupled species (4.66). In addition, small quantities of *both* unreacted diiodide (4.15) and stannane (3.33) were also recovered, indicating the reaction had yet to reach completion. Further improvements in yield could therefore be expected by either extending the reaction time, or more practically, by raising the reaction temperature.

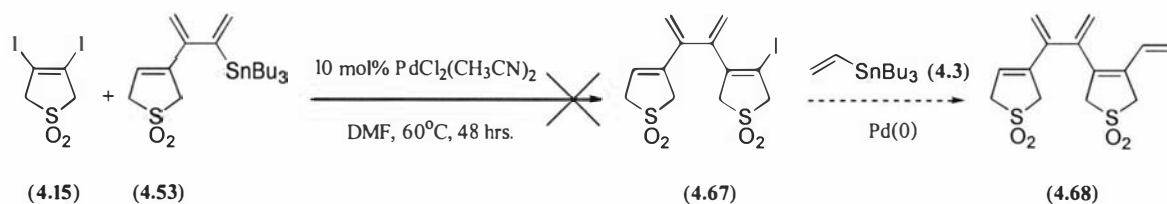
4.5.2.3 The Synthesis of Higher, Odd Numbered [n]-Dendralene Precursors.

The ready formation and relative stability of iodide (4.66) allowed for the synthesis of the second [5]-dendralene precursor (4.11). Thus, vinylation of iodide (4.66) under standard conditions with an excess of tributylvinyl tin (4.3) saw the rapid and smooth formation of the asymmetric [5]-dendralene precursor (4.11), which was isolated in 90% yield after trituration with hexane. (Scheme 4.34) While showing the characteristic polarity and general insolubility exhibited by most *bis*-3-sulfolene derivatives, recrystallisation of this material was achieved to give an air and light-stable crystalline solid.



Scheme 4.34

It was anticipated that the efficiency of this conversion (Scheme 4.34) would be reflected in the synthesis of the putative [7]-dendralene precursor (4.68). (Scheme 4.35) Unfortunately, attempts to prepare the necessary *tris*-3-sulfolene adduct (4.67) through *mono*-coupling of diiodo-3-sulfolene (4.15) with vinylstannane (4.53) under more forcing conditions proved unsuccessful.



Scheme 4.35

Indeed, while vinylstannane (**4.53**) was smoothly consumed over 48 hours at 60°C to give a single product (as judged by tlc), isolation and characterisation in the usual manner revealed this material to be the pendant *bis*-3-sulfolene (**4.54**). (**Figure 4.6**) *Bis*-sulfolene (**4.54**) was isolated in 16% yield and was again believed to be the product of oxidative homocoupling of the vinyl stannane (**4.53**). Unreacted diiodide (**4.15**) was also recovered (48%).

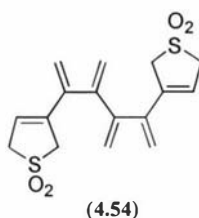


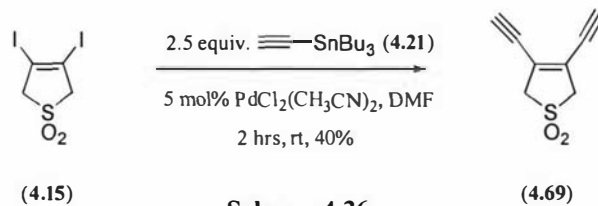
Figure 4.6

With limited time and little material to hand, the synthesis of a sulfolene-based [7]-dendralene precursor (**4.68**) was not investigated further.

4.5.2.4 Diethynylation: Synthesis of An Enediynes.

While the scope and limitations of 3,4-diiodo-3-sulfolene (**4.15**) as a Stille cross-coupling partner have not been fully investigated, the potential of (**4.15**) as a general precursor to 3,4-disubstituted-3-sulfolene derivatives was demonstrated through the synthesis of the enediyne (**4.69**).

Under standard cross-coupling conditions in the presence of an excess of tributylethynyl tin (**4.21**), 3,4-diiodo-3-sulfolene (**4.15**) coupled smoothly over two hours to give the enediyne (**4.69**) in a modest isolated yield of 40%. (**Scheme 4.36**) In light of the high yield of the alkynyl substituted 3-sulfolene (**4.45**) obtained through the coupling of (**4.21**) with *mono*-iodide (**3.37**) (**Table 4.1**, entry 2), it is proposed that polymerisation of a *mono*-coupled intermediate through a Sonogashira type process is occurring.



4.6 Conclusions.

Both 3-iodo- and 3,4-diiodo-3-sulfolene have been prepared and successfully coupled with a range of organostannanes. This Stille cross-coupling approach has formed the basis of a general strategy for the synthesis of sulfolene based [n]-dendralene precursors and has resulted in the synthesis of several, novel pendant *bis*-3-sulfolene derivatives. The synthesis of the *first* fused *tris*-3-sulfolene has also been accomplished. This, along with the successful formation of numerous sulfolene and *bis*-sulfolene adducts, has established the value of iodosulfolenes (3.37) and (4.15) as important coupling partners in the Stille cross-coupling reaction. It remains to explore the cheletropic elimination of sulfur dioxide from these sulfolene derivatives and hence establish their value as precursors to both [n]-dendralenes and other substituted 1,3-dienes. This is discussed in **Chapter 5**.

Chapter 5

The Synthesis of [n]-Dendralenes and Other Cross-conjugated Polyenes.

5.1 Introduction.

The dendralenes are a class of unsaturated hydrocarbons comprised solely of cross-conjugated carbon-carbon double bonds (C=C) or “etheno” units.¹⁶⁸ This simple, yet neglected class of alkenes derive their name from the Greek word “*dendron*”, meaning tree, indicating that each successive cross-conjugated etheno unit is added in a branching fashion thus creating an ever growing series of compounds. (Figure 5.1) The number of etheno units in each dendralene is used as a prefix and added to the name in a manner similar to the nomenclature used to describe the annulenes.

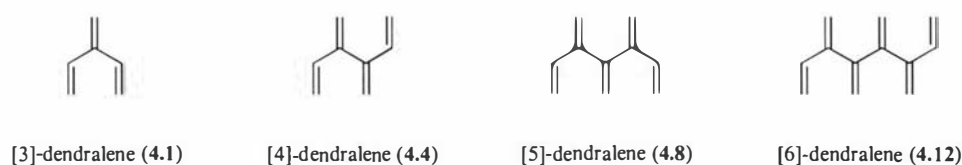
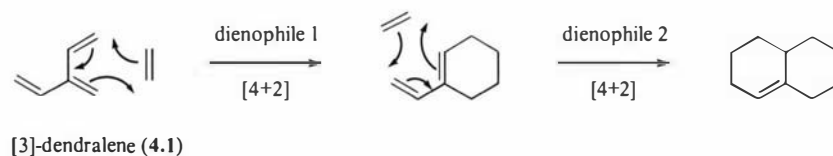


Figure 5.1

In recent years cross-conjugated molecules (including [3]-dendralenes) have received increasing attention.²³⁰ An important example includes the diene-transmissive Diels-Alder reaction (DTDA) of cross-conjugated polyenes.²³¹ The DTDA reaction involves the addition of a dienophile to a cross-conjugated polyene to generate a new 1,3-diene, which is itself able to undergo a further cycloaddition.²³² (Scheme 5.1) This strategy offers rapid access to complex polycyclic structures. To date, however, synthetically useful DTDA reactions have been limited mainly to the elaboration of hetero-atom substituted [3]-dendralene derivatives.²³³



Scheme 5.1

As the simplest examples of cross-conjugated molecules, [n]-dendralenes are also of theoretical and spectroscopic interest. Currently, linearly conjugated π -systems represent the most intensely studied class of conjugated molecules.²³⁴ The successful application of technology based on linearly conjugated π -systems has resulted in the development of numerous electronic devices²³⁵ and has spawned a growing interest in related cross-conjugated systems.²³⁶ There is also growing interest in cross-conjugated polyenes from a more theoretical point of view. Simple dendralenes appear to adopt twisted conformations and not, as might be expected, planar two-dimensional structures.²³⁷⁻²³⁹ Understanding conformational preferences such as these may yield important information for the development of future synthetic methodology and its ultimate application in new technology.

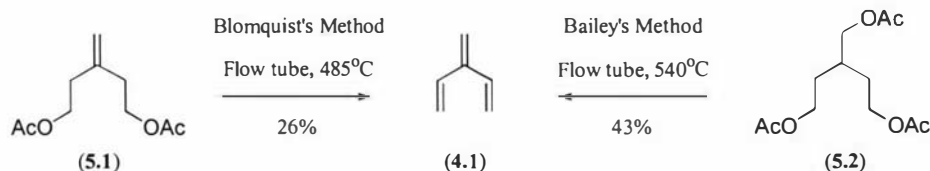
To study the chemical, spectroscopic and physical properties of the dendralenes, access to these compounds is required. To date only [3]- and [4]-dendralene have been prepared and the syntheses of higher analogues has not been reported. This chapter describes the cheletropic elimination of SO₂ from the novel 3-sulfolene precursors described in **Chapter 4** as a general strategy for the synthesis of [n]-dendralenes and related cross-conjugated polyenes.

5.2 Synthesis and Characterisation of [n]-Dendralenes: An Overview.

Despite a growing interest in the use of cross-conjugated polyenes as substrates for the diene-transmissive Diels-Alder reaction,²³¹ very few syntheses of the unsubstituted parent dendralenes have been reported. The synthesis and chemistry of the dendralenes (and their derivatives) prior to 1984 has been extensively reviewed by Hopf.¹⁶⁸ Since 1984, a limited number of new synthetic methods for the preparation of [3]- and [4]-dendralene have been reported, yet the higher dendralenes remain unknown. Furthermore, significant omissions and discrepancies in the spectroscopic characterisation of the known dendralenes have yet to be resolved. Sections **5.2.1** and **5.2.2** offer an overview of the synthesis and spectroscopic characterisation of the parent dendralenes known to date.

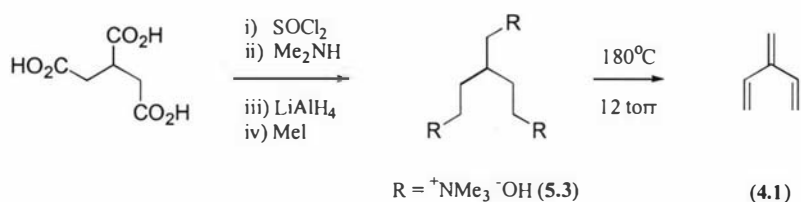
5.2.1 [3]-Dendralene.

[3]-Dendralene (**4.1**) was first prepared by Blomquist in 1955, by the flow tube pyrolysis of diacetate (**5.1**).²⁴⁰ (Scheme 5.2) This synthesis was closely followed by a related, yet independent report by Bailey, describing the pyrolysis of triacetate (**5.2**).²⁴¹



Scheme 5.2

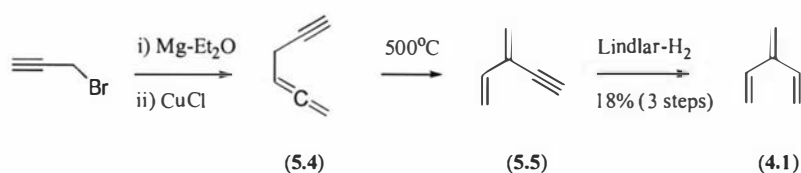
Despite some initial confusion by Bailey[†] over the UV characterisation of [3]-dendralene (**4.1**), both groups, using contemporary analytical techniques, reported similar data. In addition to UV, this included IR, boiling point, refractive indices, combustion analysis and chemical degradation studies. Not unexpectedly, no NMR or mass spectral data was reported in these early accounts. The availability of triacetate (**5.2**) established Bailey's pyrolysis as the preferred method for the synthesis of [3]-dendralene (**4.1**). [3]-dendralene (**4.1**) has also been prepared by the pyrolysis of the ammonium salt (**5.3**).²⁴³ (Scheme 5.3) While technically a new synthesis, the Hofmann degradation of (**5.3**) can be viewed as a variation of Blomquist's and Bailey's original pyrolysis techniques. Indeed, this new report contributed little to the synthetic development of [3]-dendralene. No yield was reported and the product was not characterised at all!



Scheme 5.3

[†] Bailey quotes an extinction coefficient (ϵ) of 205000,²⁴¹ but later corrects this figure quoting a new value ($\epsilon = 20500$).²⁴²

Hopf has prepared [3]-dendralene (**4.1**) by the reduction of dienyne (**5.5**).²⁴⁴ (Scheme 5.4) Dimerisation of propargyl magnesium bromide gave allene (**5.4**), the thermal rearrangement of which gave (**5.5**). Partial reduction of (**5.5**) with Lindlar's catalyst gave [3]-dendralene (**4.1**) in 18% yield over 3 steps. Spectroscopic data for [3]-dendralene prepared by this method was limited to the UV-visible spectrum only and the solvent used was not specified.



Scheme 5.4

A more comprehensive characterisation of [3]-dendralene was provided by Almenningen and co-workers in 1988.²³⁹ [3]-Dendralene (**4.1**) was prepared according to both Blomquist²⁴⁰ and Baileys' methods²⁴¹ and although no yields were given, extensive data for [3]-dendralene, purified by preparative GC, was reported. This included gas phase electron diffraction measurements, IR, Raman, UV and, importantly, ¹H and ¹³C NMR spectra (300 MHz in CD₂Cl₂ at 203 K) albeit of impure material. Mass spectral analysis was not included and, despite extensive electron diffraction measurements, the conformational implications of the solution state UV were not considered through the inclusion of a simple extinction coefficient.

A recent synthesis of [3]-dendralene by Cadogan,¹⁹⁸ entailing the cheletropic elimination of sulfur dioxide from 3-vinyl-3-sulfolene (**4.2**) has been discussed in section 4.2.1. (Scheme 4.2) Extensive vibrational data was reported for [3]-dendralene prepared by this method together with UV (unspecified solvent) and ¹H NMR in CDCl₃. Proton decoupled carbon data was not included, but the results of a DEPT experiment (*without* multiplicities) was reported. Again, no mass spectral data was given.

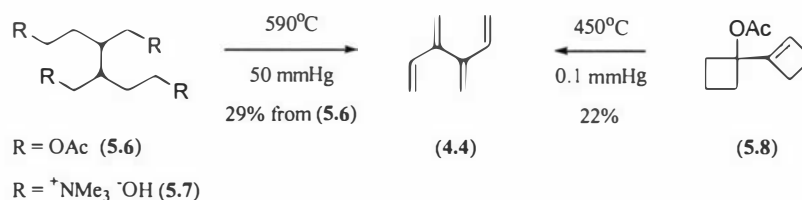
More recently (1992), Trahanovsky *et al.* investigated the thermal dimerisation of [3]-dendralene (**4.1**).²⁴⁵ Material for these experiments was prepared according to Bailey's original procedure²⁴¹ and mass spectral data was reported for the first time. ¹H NMR data (in d₆-benzene) was also given, together with proton decoupled ¹³C NMR spectra. Assignments were made through off resonance decoupling experiments,

however, the data obtained did not agree with earlier reports.^{198,239} This discrepancy was fully acknowledged by the authors, and the resulting confusion over the NMR characterisation of [3]-dendralene still remains.

In summary, despite the frequency with which [3]-dendralene (4.1) has been reported the characterisation of this material remains incomplete.

5.2.2 [4]-Dendralene.

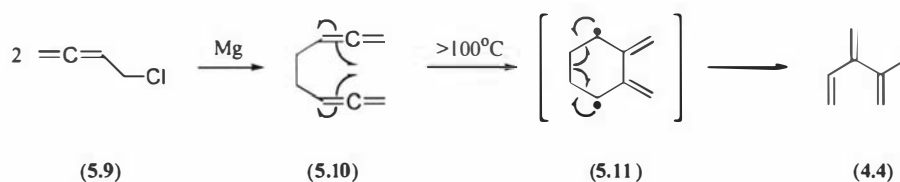
[4]-Dendralene (4.4) was first reported by Bailey in 1962.²⁴² Thermolysis techniques were again used and the tetraacetate (5.6) was subjected to flow tube pyrolysis at 590°C. [4]-Dendralene (4.4) was isolated in 24.7% yield after preparative GC of the pyrolysate mixture and at least 14 other components were detected but not characterised. (Scheme 5.5) This early report gave detailed UV, ¹H NMR (60 MHz) and gas phase IR data of the extensively purified material in addition to combustion analysis and molecular weight determinations. [4]-Dendralene (4.4) was further characterised by catalytic hydrogenation and comparison of the reduced product with 3,4-dimethylhexane.



Scheme 5.5

[4]-Dendralene (4.4) has also been prepared by other elimination methods. (Scheme 5.5) The Hofmann degradation of the tetraammonium salt (5.7) has been reviewed by Hopf¹⁶⁸ and actually predates Baileys original synthesis²⁴² by two years. However, work from this early German Ph. D. thesis²⁴⁶ has never been published. Small quantities of [4]-dendralene have also been prepared by the flow tube pyrolysis of the substituted cyclobutene (5.8).²⁴⁷ In this way, [4]-dendralene was isolated in 22% yield after purification by preparative GC. UV, solution IR and ¹H NMR (60 MHz, CDCl₃) spectral data were reported.

Wurtz coupling of the Grignard reagent prepared from 1-chloro-2,3-butadiene (**5.9**) and subsequent thermolysis has been reported in a patented synthesis of [4]-dendralene (**4.4**).²⁴⁸ Only scant experimental detail was given and no data was reported. The mechanism of this transformation is uncertain. While the Cope rearrangement of the putative *bis*-allene intermediate (**5.10**) would yield [4]-dendralene (**4.4**) directly, there also exists the possibility of forming [4]-dendralene (**4.4**) through the formation and rearrangement of the cyclohexyl diradical (**5.11**). (**Scheme 5.6**) Indeed the cyclohexyl diradical (**5.11**) prepared by alternative routes²⁴⁹ has been observed as a precursor to numerous products including [4]-dendralene (**4.4**). The syntheses of [4]-dendralene (**4.4**) by the thermal rearrangement of *bis*-allene (**5.10**), prepared by other means, has also been reported.^{199,250} Amazingly, no contribution to the characterisation of [4]-dendralene (**4.4**) was made through any of these methods.



Scheme 5.6

A recent synthesis of [4]-dendralene (**4.4**) by Cadogan and Gosney,²⁰⁰ involving the thermal elimination of SO₂ from the bicyclic sulfolane (**4.7**), has been described in section 4.2.2. (**Scheme 4.3**) While limited data for the crystalline precursor (**4.7**) was given, no data for the characterisation of [4]-dendralene (**4.4**) itself was reported despite claims of a “virtually quantitative yield”. Nonetheless, material prepared by this method was later subjected to gas phase electron diffraction measurements in an investigation into the molecular structure of [4]-dendralene.²³⁸ Low resolution ¹H NMR data and the results of DEPT experiments were reported. However, the ¹³C NMR data was still incomplete as the quaternary carbons of [4]-dendralene (**4.4**) were not observed and, incomprehensibly, the multiplicities of the remaining resonances were not listed.

The characterisation of [4]-dendralene (**4.4**) is far from complete. While (**4.4**) has been well characterised by UV and IR spectroscopy, only low field (60 MHz) ¹H NMR and incomplete ¹³C NMR data are available. Furthermore, no mass spectrometric analysis of [4]-dendralene (**4.4**) has been reported.

5.3 Thermolysis of Sulfolenes.

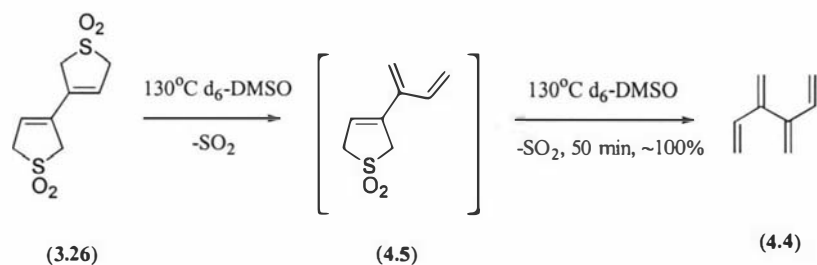
Chapters 3 and 4 of this thesis have described the synthesis of fused *bis* and *tris*-3-sulfolenes together with various novel pendant *bis*-3-sulfolene derivatives as putative [n]-dendralene precursors. In addition, other pendant *bis*-3-sulfolenes and simple substituted 3-sulfolene derivatives have also been prepared as potential precursors to other cross-conjugated polyenes. This chapter describes the cheletropic elimination of SO₂ from these compounds.

5.3.1 Solution State Thermolysis.

The cheletropic elimination of sulfur dioxide from 3-sulfolene derivatives has conventionally involved thermolysis under relatively mild conditions, for example in a refluxing solvent such as toluene or xylene (section 3.2). However, when considering this technique for the preparation of volatile and readily polymerisable polyenes such as the dendralenes, difficulties were anticipated in the isolation of these compounds. Indeed, recent syntheses of [3]-¹⁹⁸ and [4]-dendralene²⁰⁰ from stable crystalline precursors have employed “solventless” flash vacuum pyrolytic techniques, rather than solution thermolysis, hinting perhaps at the problems involved in the isolation of these unstable materials from high boiling point solvents. Nonetheless, the successful cheletropic elimination of SO₂ from various sulfolene based farnesene precursors (**Chapters 1 and 2**) encouraged us to pursue a conventional solvent-based thermolysis of *bis*-3-sulfolene (**3.26**) as a representative dendralene precursor.

Preliminary solvent-based thermolysis experiments were carried out in d₈-toluene and d₆-DMSO in sealed NMR tubes. The tubes were immersed in a thermostatically controlled oil bath and removed at regular intervals to record ¹H NMR spectra. While *bis*-sulfolene (**3.26**) was soluble in only DMSO, NMR analysis of a toluene suspension was also made to observe the liberation of any soluble thermolysis products.

Thermolysis of fused *bis*-3-sulfolene (**3.26**) as a suspension in d₈-toluene at 120°C over 18 hours saw no change in the sample composition. Indeed, subsequent thermolysis of (**3.26**) as a slurry in refluxing (undeuterated) xylene over 48 hours showed no decomposition and the starting material was recovered in essentially quantitative yield.



Scheme 5.7

Thermolysis of *bis*-sulfolene (3.26) as a dilute solution in d_6 -DMSO at 130°C , however, clearly indicated the formation of alkenic products. (Scheme 5.7) This process was observable directly by the thermolysis of a d_6 -DMSO solution of *bis*-sulfolene (3.26) in the heated probe of an NMR spectrometer. This is represented as a stack plot of successive ^1H NMR spectra recorded at 2 minute intervals at 130°C . (Figure 5.2)

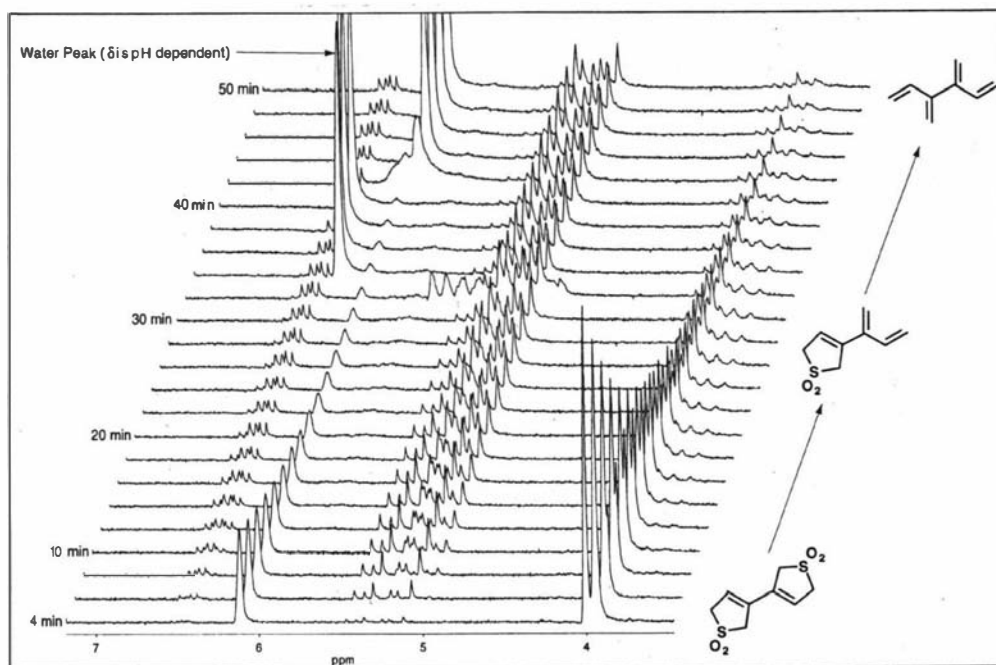


Figure 5.2

Plot 1 (4 minutes @ 130°C) revealed the ^1H NMR spectrum of essentially pure *bis*-sulfolene (3.26) (*cf.* section 3.7.2.1), although even after this short time, some additional alkenic signals between 5.0 and 6.5 ppm were just visible. Subsequent plots indicate a decrease in the intensity of signals associated with the *bis*-sulfolene (3.26) and an increase in the intensity of the alkenic features. After 8 minutes at 130°C , the formation of one major product was observed and comparison with the ^1H NMR of the 2'-butadiene-substituted 3-sulfolene (4.5), prepared earlier (section 4.4.1.2 and Scheme 4.23), confirmed the identity of this initial thermolysis product. Indeed, based on mass

spectral evidence, the formation of an intermediary *mono*-thermolysed product by the loss of one molar equivalent of SO₂ from (3.26) was fully anticipated. Continued heating saw the development of additional alkenic complexity with a second, yet distinct ABX spin system and pair of broadened singlets being observed. After 50 minutes, the reaction had reached completion and comparison with published ¹H NMR data of [4]-dendralene^{238,242,247} was made. The strong correlation with published ¹H NMR data indicated that the thermolysis of *bis*-3-sulfolene (3.26) in d₆-DMSO at 130°C had cleanly yielded [4]-dendralene (4.4) as a single compound. This represents the first synthesis of a cross-conjugated polyene through the cheletropic elimination of sulfur dioxide from a fused *bis*-3-sulfolene.

The appearance and surprising mobility of the residual water peak present in the DMSO used in the thermolysis of (3.26) (Figure 5.2) can be attributed to the formation of sulfurous acid (H₂SO₃), generated in increasing concentration over the course of the reaction by the hydration of liberated sulfur dioxide. Furthermore, the dramatic downfield shift in the position of the water (acid) peak after *ca.* 30 minutes coincided with a rupture in the NMR tube septum and presumably a change in the pH of the reaction medium.

All attempts to isolate [4]-dendralene (4.4) from a solution in DMSO were unsuccessful. Both solvent extraction and chromatography were investigated, but the volatility of (4.4) (122.5°C, 746 mmHg)²⁴² made its isolation even from pentane inefficient. Falling film evaporation and Kugelrohr distillation were equally ineffective and no characterisable material could be obtained. An alternative, solvent free thermolysis technique was evidently required.

5.3.2 Capillary Pyrolysis (CP).

The melting points of most *bis*-3-sulfolene derivatives have been found to be in excess of 300°C and, at atmospheric pressure, any visible change in composition occurred only when these materials were heated to around 450°C. Under vacuum, however, sublimation occurred readily at these temperatures and these observations strongly suggested the use of flash vacuum pyrolysis (FVP) as a means of preparing “solvent free” [n]-dendralenes from sulfolene precursors. Unfortunately, access to FVP apparatus was not available and a simple alternative had to be found. Apparatus made

from a modified, disposable glass pipette was developed to meet these requirements. (Figure 5.3)

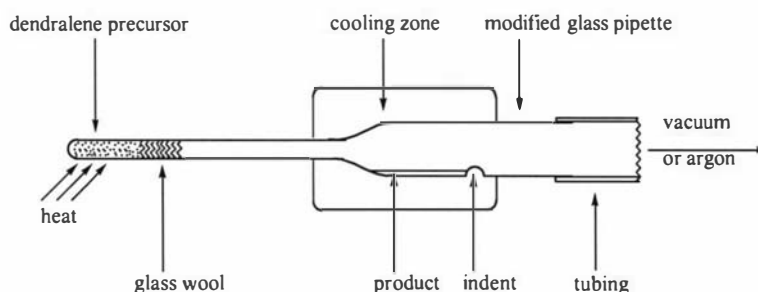


Figure 5.3

A long form Pasteur pipette (*ca.* 250 mm) was sealed at the tip and the body shortened to approximately 25 mm. A localised area of the pipette body was heated and a shallow indent pushed into the softened glass wall. This modification proved necessary for the localisation of volatilised products in the cooling zone. The dendralene precursor was placed into the sealed tip of the modified pipette, secured with a small wad of glass wool and the open end of the tube was connected to a conventional Schlenk line. The pipette was evacuated, its tip heated with a hot air gun and the volatile pyrolysis products condensed in the cooling zone (liquid nitrogen).

It was found that while sublimation and subsequent pyrolysis occurred readily under vacuum (*ca.* 0.1 mmHg), the small scale of the pyrolysis (*ca.* 10 mg) and volatility of the products resulted in the isolation of only minimal quantities of material at reduced pressures. However, when the pyrolysis was carried out under argon at ambient pressure, the thermolysed products, *including* sulfur dioxide could be efficiently trapped in the cooling zone. Furthermore, when warmed to room temperature under argon, the sulfur dioxide boiled off leaving only non-gaseous pyrolysates free of solvent.

While this simple method produced milligram quantities of clean isolate, the volatility of the products and the scale of the pyrolysis again caused problems. The calculation of a yield, based on mass, was not practical and further manipulations were extremely difficult to perform. Ultimately, it was found that transfer of the pipette contents into an NMR tube with a known volume of deuterated solvent gave a solution from which a yield could be easily calculated by reference to either an added internal standard (*tert*-butylmethyl ether) or, more practically, by comparison with the residual undeuterated

signal of the solvent, i.e. at 7.27 ppm for chloroform.[†] In this manner, a solution of known concentration could be either serially diluted for spectroscopic measurements (UV, solution cell IR, GCMS) or used in subsequent reactions. Hence CP proved ideally suited to the formation of small quantities of dendralenes and other polyenic products. Furthermore, this technique required only milligram quantities of precious precursor, was operationally simple to carry out, inexpensive and provided pure material in a form amenable to full characterisation.

5.4 [n]-Dendralene Synthesis.

The majority of dendralenes (and other polyenes) produced using capillary pyrolysis (CP) were either colourless oils at room temperature or waxy solids when frozen in liquid N₂. In the presence of liquid sulfur dioxide, however, these polyenes appeared as intensely coloured yellow oils. This simple observation proved a valuable indicator of the success (or failure) of each pyrolysis experiment.

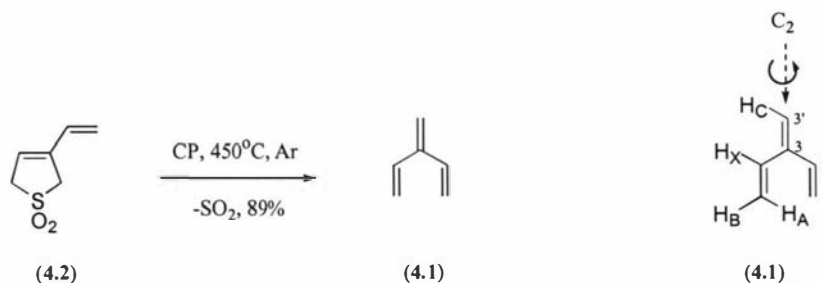
The synthesis and NMR characterisation[‡] of each member of the dendralene family is discussed independently. Proton identification, for the purpose of this discussion, has been made either alphabetically, i.e. H_C, H_D, H_E,...etc., or by reference to common spin systems where appropriate, e.g. H_X of an ABX system. Carbon atoms have been distinguished numerically, commencing at one end of the longest chain of the hydrocarbon. Methylene carbons along the chain have been denoted as prime carbons, for example C3'. This notation enables comparison of chemical shifts for similar carbons to be made between different members of the dendralene family. Each dendralene structure is symmetrical and, for simplicity, equivalent C and H atoms are labelled only once. It is nonetheless understood that during discussion this simple notation refers to both pairs of equivalent atoms.

[†] A variation of this method has been used to determine the yield of [3]-dendralene (4.1) prepared by the pyrolysis of triacetate (5.2), (Scheme 5.2)²⁴⁵ however, full experimental details were not given. A detailed procedure for the calculation of yield by the method described here is provided in Appendix 5.1.

[‡] Tables of ¹H and ¹³C NMR data for the dendralenes prepared by capillary pyrolysis of sulfolene precursors are given in Appendices 5.2 and 5.3. The ¹H and ¹³C NMR spectra are reproduced in Appendix 5.4.

5.4.1 [3]-Dendralene.

The capillary pyrolysis of 3-vinyl-3-sulfolene (**4.2**) under argon at 450°C cleanly afforded [3]-dendralene (**4.1**) as a colourless oil. Transfer from the pyrolysis apparatus, with a known volume of CDCl₃, indicated that this process had proceeded in 89% yield as determined by ¹H NMR. (Scheme 5.8) Furthermore, ¹H NMR analysis revealed a relatively simple spectrum, consistent with a C₂ symmetry axis through the central etheno fragment of [3]-dendralene. The spectrum shows a well resolved ABX spin system (H_A, H_B, H_X) for both equivalent vinyl groups and a broadened singlet for the internal methylene protons (H_C) with an integrational ratio of 3:1. Some additional, geminal coupling between H_A and H_B ($J_{AB} = ca. 1.5$ Hz) was also observed, but was resolved most clearly for the methylene protons H_A. These assignments were in good agreement with earlier reports.¹⁹⁸



Scheme 5.8

¹³C NMR analysis indicated the presence of 4 alkenic signals, consisting of a single downfield quaternary carbon (C3), a lone methine (C2) of intermediate chemical shift and a pair of upfield methylenes (C1 and C3'). Inverse gated ¹³C NMR, showing signal intensities proportional to the number of equivalent carbon atoms, established the internal methylene (C3') as the more upfield signal of this methylene pair. It should be noted, however, that the lower relative intensity of this signal (C3') in the conventional proton decoupled spectrum, proved equally diagnostic. (Appendix 5.4) This data was in good agreement with earlier reports^{198,239} and confirmed the assignment of the single quaternary carbon (C3), reported previously on only one occasion for a sample containing significant quantities of unidentified impurities.²³⁹

5.4.2 [4]-Dendralene.

Three different sulfolene-based [4]-dendralene precursors have been prepared through the Stille cross-coupling of iodo-3-sulfolenes. (**Figure 5.4**)

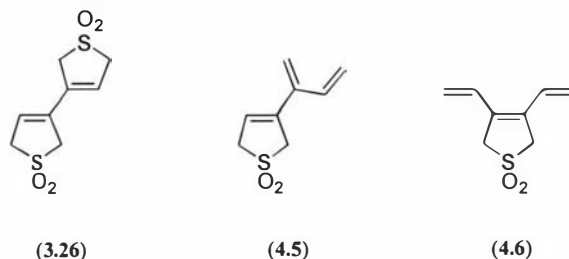
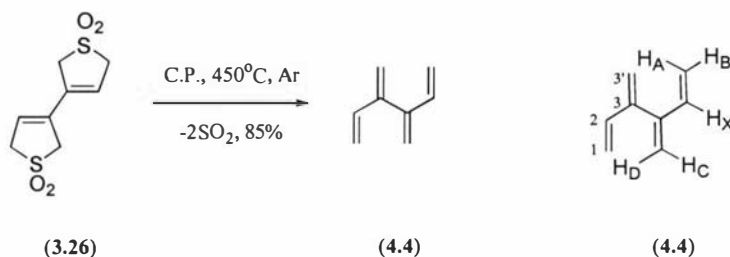


Figure 5.4

Butadiene-substituted 3-sulfolene (**4.5**) has proved to be an unstable precursor, readily undergoing polymerisation during isolation. Its use as a pyrolysis substrate for the preparation of [4]-dendralene was therefore not investigated. The formation of (**4.5**) as an intermediate in the solution state thermolysis of *bis*-3-sulfolene (**3.26**) in d_6 -DMSO (**Scheme 5.7**) has, however, formally demonstrated the value of (**4.5**) as a [4]-dendralene precursor.

In contrast to (**4.5**), the stable [4]-dendralene precursor (**3.26**), was ideally suited as a substrate for capillary pyrolysis. Indeed, under argon at 450°C , pyrolysis of *bis*-sulfolene (**3.26**) gave [4]-dendralene (**4.4**) as a colourless liquid in 85% yield as determined by ^1H NMR. (**Scheme 5.9**)



Scheme 5.9

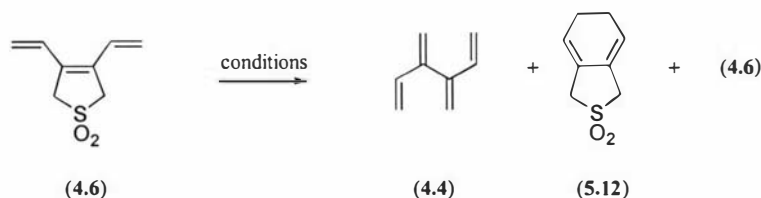
^1H NMR analysis again revealed a relatively simple spectrum, consistent with the C_2 symmetry of [4]-dendralene (**4.4**). In addition to the well resolved ABX spin system of the equivalent terminal vinyl groups (H_A , H_B , H_X) there appeared two non-equivalent methylene multiplets (H_C and H_D). As seen in the ^1H NMR spectrum of [3]-dendralene,

additional, geminal coupling between H_A and H_B could also be observed. Unfortunately, J_{AB} was not measurable directly due to the further complication of additional long range coupling and second order effects. Indeed, the appearance of H_C and H_D as multiplets corroborated the presence of these additional splittings, with their signals showing more than just the mutual, geminal coupling otherwise expected. Nonetheless, the 1H NMR data obtained by analysis of this [4]-dendralene sample agreed closely with data from earlier reports.^{238,242,247}

^{13}C NMR experiments yielded new data, giving the first fully proton decoupled ^{13}C NMR spectrum of [4]-dendralene (**4.4**). The quaternary carbon (C3), at 146.4 ppm, appeared as the most downfield signal of a group of four alkenic carbons. The positions of the methine (C2) and methylene carbons (C1, C3') were in close agreement with data from earlier DEPT experiments.²³⁸

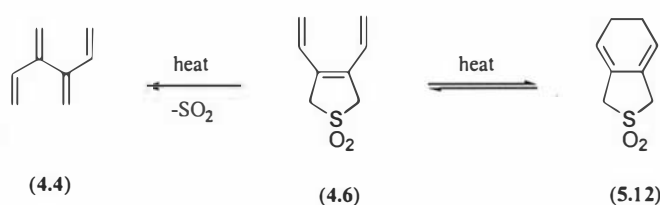
Having successfully prepared [4]-dendralene (**4.4**) from *bis*-sulfolene (**3.26**), attention was focused on the thermolysis of the remaining [4]-dendralene precursor, 3,4-divinyl-3-sulfolene (**4.6**). As an air stable crystalline solid, this material was again an ideal substrate for capillary pyrolysis. Its solubility in xylene, however, also offered the opportunity to examine its thermolysis in solution.

It was found that while divinyl-sulfolene (**4.6**) was smoothly consumed over 2.5 hours in refluxing xylene, [4]-dendralene (**4.4**) could not be detected by 1H NMR. Removal of the solvent and recrystallisation of the residue yielded the cyclic diene (**5.12**) formed *via* the thermally allowed 6π electrocycloisatation of (**4.6**) (a 1,3*Z*,5-hexatriene). Diene (**5.12**) was isolated in 91% yield. (**Table 5.1**, entry 1)

**Table 5.1**

entry	conditions	yield %		
		(4.4)	(5.12)	(4.6)
1	xylene, reflux, 2.5 hrs	-	91	-
2	CP, 450°C, Ar (1 atm.)	8	-	-
3	CP, 450°C, 0.8 mmHg	15	27	63

It was believed that while the 6π electrocycloislation of 3,4-divinyl-3-sulfolene (**4.6**) was favoured in refluxing xylene, equilibration between (**5.12**) and (**4.6**) would occur under the more forcing conditions of capillary pyrolysis through promotion of the 6π electrocyclic ring opening process. It was anticipated that under the reaction conditions, competition from the irreversible cheletropic elimination of sulfur dioxide from (**4.6**) would disrupt this equilibrium and ultimately favour the formation of [4]-dendralene (**4.4**). (Scheme 5.10) While this hypothesis appeared to hold true, yields were disappointingly low.

**Scheme 5.10**

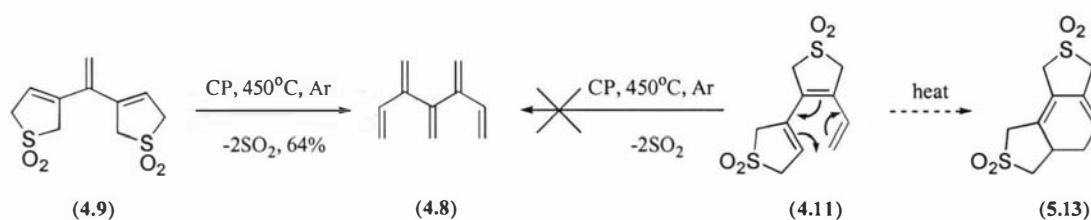
When subjected to capillary pyrolysis under argon at 450°C, 3,4-divinyl-3-sulfolene (**4.6**) gave [4]-dendralene (**4.4**) in only 8% yield as estimated by ^1H NMR. (Table 5.1, entry 2) It was concluded that electrocycloislation of (**4.6**) was rapid under these conditions and, in its molten state, the resultant cyclic diene (**5.12**) was more likely to undergo unwanted Diels-Alder reactions than the desired cycloreversion. Extensive charring and the isolation of only minimal quantities of volatile material certainly implied some form of polymerisation or decomposition had indeed occurred.

The capillary pyrolysis of 3,4-divinyl-3-sulfolene (4.6), under vacuum saw no such decomposition. However, while [4]-dendralene (4.4) was obtained in 15% yield, electrocyclic product (5.12) and unreacted starting material were also recovered in estimated yields of 27% and 63% respectively. (Table 5.1, entry 3) The separation of this mixture was not practical and the capillary pyrolysis of divinyl-sulfolene (4.6) was not investigated further.

The capillary pyrolysis of a pure sample of diene (5.12) was investigated briefly. Under argon, decomposition occurred and no volatile products were observed. Under vacuum, sublimation without pyrolysis dominated and unchanged starting material was isolated. It was concluded that insufficient contact with the “hot zone” in the apparatus was responsible for this failure. Nonetheless, it is believed that through recourse to genuine FVP the value of diene (5.12) as a [4]-dendralene precursor may yet be realised. If this is the case, then 3,4-divinyl-3-sulfolene (4.6) should also serve as a [4]-dendralene precursor.

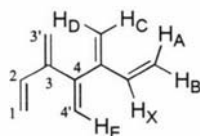
5.4.3 [5]-Dendralene.

Two [5]-dendralene precursors, (4.9) and (4.11), have been prepared through the Stille cross-coupling of sulfolene derivatives. Both were subjected to capillary pyrolysis. (Scheme 5.11)



Scheme 5.11

Pyrolysis of the symmetrical pendant *bis*-sulfolene (4.9), under argon at 450°C, resulted in the formation of a single, volatile product. On the basis of ¹H NMR analysis this material was readily assigned as [5]-dendralene (4.8) which was obtained in 64% yield in the first synthesis of this cross-conjugated hydrocarbon.



(4.8)

Figure 5.5

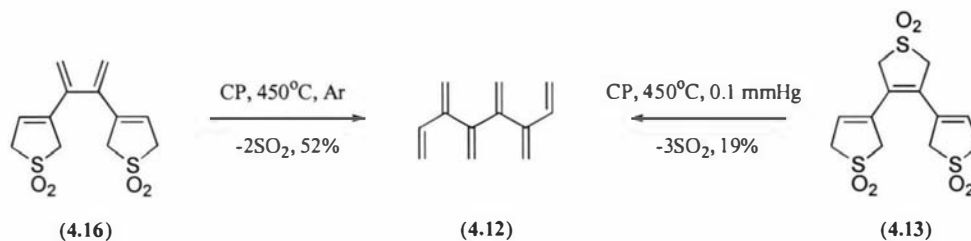
The ^1H NMR spectrum revealed the characteristic and well resolved ABX spin system of the terminal vinyl groups (H_A , H_B , H_X). (Figure 5.5) The upfield doublet (H_B) was partly obscured by the overpositioning of a narrow two proton multiplet, assigned as one of the internal methylene protons (H_C or H_D). In close proximity, appeared a sharp, two proton singlet and a second narrow, two proton multiplet. These features were attributed to the central methylene (H_E) and remaining, internal methylene protons (H_C or H_D) respectively. Geminal coupling between H_A and H_B ($J_{\text{AB}} = \text{ca. } 1.5 \text{ Hz}$) was again observed. This coupling was resolved most clearly for the terminal methylene protons (H_A).

The ^{13}C NMR spectrum revealed 6 alkenic signals. The appearance of a single methine carbon was readily assigned as C2. Two quaternary carbons (C3 and C4) were observed and, based on their relative peak heights, the lower intensity signal was readily attributable to the central methylene carbon C4. The remaining carbon atoms were all methylenic and by comparison with [3]- and [4]-dendralenes and consideration of their relative peak heights, it was possible to assign these signals to methylene carbons C1, C3' and C4'.

Attention was next focused on the capillary pyrolysis of the vinylated *bis*-sulfolene (4.11). It was found that under both argon at atmospheric pressure, or vacuum ($< 0.05 \text{ mmHg}$), no volatile materials could be isolated and extensive charring and decomposition of the starting material was observed. It is believed that a competitive 6π electrocyclisation pathway is again responsible for this disappointing result. Indeed, the attempted thermolysis of (4.11) in toluene saw the formation of a small quantity (*ca.* 20%, as judged by ^1H NMR) of a minor component consistent with structure (5.13). (Scheme 5.11) However, isolation of the cycloadduct (5.13) was not achieved and this observation remains speculative. Nonetheless, it is again believed that recourse to efficient FVP will establish the value of vinylated *bis*-sulfolene (4.11) as a [5]-dendralene precursor.

5.4.4 [6]-Dendralene.

The [6]-dendralene precursors (4.16) and (4.13) have been prepared through the Stille cross-coupling of sulfolene derivatives and both were subjected to capillary pyrolysis. (Scheme 5.12)



Scheme 5.12

Pyrolysis of the butadiene-tethered *bis*-sulfolene (4.16) under argon cleanly afforded [6]-dendralene (4.12) in 52% yield as judged by ¹H NMR, thus constituting the first synthesis of this simple cross-conjugated hydrocarbon. Visible in the ¹H NMR spectrum of this material was the characteristic and well resolved downfield doublet of doublets (H_x) of the ABX spin system. (Figure 5.6) The associated AB portion of this spin system (H_A and H_B) was less readily observed, being partly obscured by the overpositioning of four additional alkenic signals attributed to the remaining internal methylene protons (i.e. H_C, H_D, H_E and H_F).

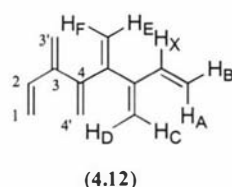
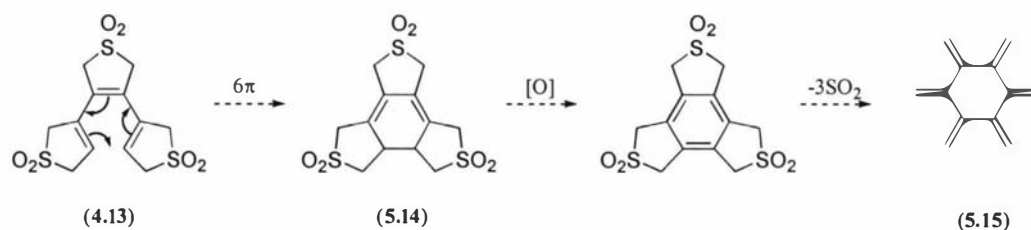


Figure 5.6

The ¹³C NMR spectrum revealed six alkenic signals and was otherwise very similar in appearance to the spectrum observed for [5]-dendralene. Two downfield quaternary signals were ascribed as the internal carbons C3 and C4 and, in the absence of any differentiation through signal intensity, were assigned simply by comparison with the lower vinylogue. A single methine carbon was unambiguously attributed to C2, while the remaining upfield trio of methylene signals (C1, C3' and C4') were again assigned by comparison with [5]-dendralene.

Capillary pyrolysis of the *tris*-sulfolene (**4.13**) was next investigated. (Scheme 5.12) Under argon, no volatile products were obtained and extensive charring was observed. However, under reduced pressure (*ca.* 0.1 mmHg), the capillary pyrolysis of *tris*-sulfolene (**4.13**) resulted in the isolation of [6]-dendralene, albeit in a modest yield of 19%.

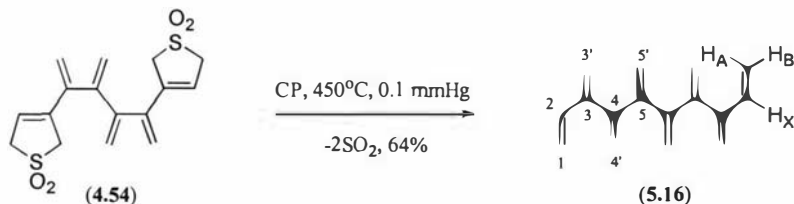


Scheme 5.13

The possibility of competitive 6π electrocyclic ring closure may offer some explanation for the relatively poor yield of [6]-dendralene obtained by the pyrolysis of *tris*-sulfolene (**4.13**). (Scheme 5.13) While no direct evidence for the formation of the cyclised product (**5.14**) exists, the symmetry-allowed 6π electrocyclic ring closure of other 3,4-disubstituted 3-sulfolenes i.e. 3,4-divinyl-3-sulfolene, has been observed and a similar mode of reactivity may therefore be possible with (**4.13**). While purely speculative in nature, the potential 6π electrocyclic ring closure of *tris*-sulfolene (**4.13**) offers the intriguing possibility of preparing the related cyclic cross-conjugated polyene, [6]-radialene (**5.15**).¹⁶⁸ Aromatisation of cyclohexadiene (**5.14**) and subsequent FVP mediated cheletropic elimination of sulfur dioxide from the resulting substituted aromatic may prove to be an efficient route to this compound.

5.4.5 [8]-Dendralene.

The capillary pyrolysis of the dendralene-tethered *bis*-sulfolene (**4.54**) was investigated as a route to [8]-dendralene (**5.16**). (Scheme 5.14) Under argon at atmospheric pressure, extensive decomposition was observed and no volatile products could be detected. It was concluded that the high boiling point of [8]-dendralene may be responsible for the failure of the argon blanketed pyrolysis. Indeed, under reduced pressure (0.1 mmHg), extrusion of sulfur dioxide proceeded smoothly and [8]-dendralene (**5.16**) was isolated in 64% yield as judged by ^1H NMR. This represents the first synthesis of [8]-dendralene.



Scheme 5.14

¹H NMR analysis revealed only alkenic signals, including a well resolved downfield doublet of doublets (H_x) of the ABX spin system. The remaining eight methylene protons, including the AB component of the terminal vinyl groups, appeared together as a complex multiplet. This confirmed the general trend observed previously for the lower dendralenes. Increasing chain length causes the internal methylenes to approach equivalence, resulting in an increasingly complex alkenic region upfield of an isolated H_x multiplet. The integrational intensities of these regions (H_x : methylene protons) was measured at 8:1 and was therefore fully consistent with the anticipated proton spectrum of [8]-dendralene.

The ¹³C NMR spectrum proved equally consistent with structure (5.16) and exhibited a pattern of signals similar to that established earlier for the lower dendralenes. A single methine carbon (C2) was flanked downfield by a trio of quaternary carbons (C3, C4 and C5) and upfield by a cluster of the remaining four methylene signals (C1, C3', C4' and C5'). Again, assignments were made by comparison with the lower dendralenes. It should be noted that while chemical shift differences across the series were slight, small differences, particularly for the internal methylene carbons, were always observed. Hence the full assignment of all signals could not be made unambiguously.

5.5 Further Spectral Characterisation of [n]-Dendralenes.

[n]-Dendralenes have been successfully prepared by the capillary pyrolysis of various sulfolene precursors. This simple technique yielded small quantities of dendralenes in a state of high purity in the cooling zone of the pyrolysis apparatus. Subsequent transfer with a deuterated solvent (typically CDCl₃) to an argon flushed NMR tube allowed both the calculation of a yield and the collection of ¹H and ¹³C NMR spectra of the product. When acid-free deuterated solvents were employed in this transfer, the resulting dendralene solution suffered minimal decomposition and could be used for further spectroscopic characterisation. In this manner the solution state IR and high resolution

GCMS of the undiluted [n]-dendralene solutions were performed and subsequent serial dilution with ethanol was carried out for quantitative UV spectral analysis.

5.5.1 Ultraviolet Spectra.

There has been considerable interest in the structure of cross-conjugated polyenes with particular attention being focused on the parent hydrocarbons [3]- and [4]-dendralene.¹⁶⁸ The molecular structure of [3]-dendralene has been investigated by gas-phase electron diffraction; a study which elucidated an *anti*, skew conformation.²³⁹ Hence, in the gas phase, [3]-dendralene (4.1) consists of an *anti*-butadiene fragment bearing a vinyl substituent at a subtended dihedral angle of *ca.* 40° to the diene plane. (Figure 5.7)

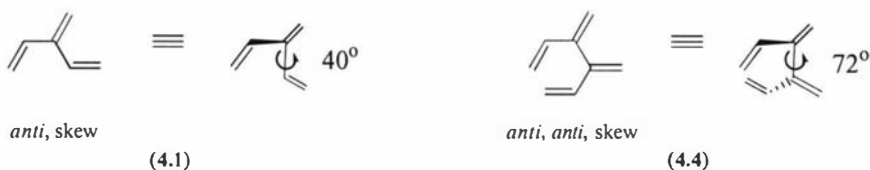


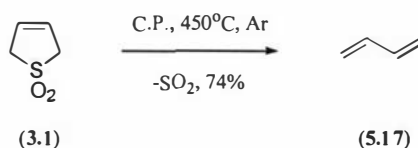
Figure 5.7

Similar measurements reveal that, in the gas phase, [4]-dendralene (4.4) prefers to adopt an *anti*, *anti*, skew conformation, where the plane of one *anti*-butadiene fragment subtends a dihedral angle of *ca.* 72° with the other.²³⁸ (Figure 5.7) In both instances it is clear that a planar cross-conjugated array is not favoured and that each diene moiety tends towards an isolated *anti*-1,3-butadiene fragment. This is reflected in the gas and solution phase UV of both species. The absorption maximum (λ_{\max}) of [3]-dendralene (4.1)[†] in ethanol has been observed at 223 nm ($\epsilon = 10230$),²⁴⁰ while for [4]-dendralene (4.4)[‡] in isooctane, a λ_{\max} of 217 nm ($\epsilon = 28500$) has been reported.²⁴² These values compare favourably with 1,3-butadiene (5.17), which in a stable *anti*-conformation, exhibits a λ_{\max} of 217 nm.²³⁷⁻²³⁹

[†] Other UV data for [3]-dendralene (4.1) has been reported: λ_{\max} 231 nm [no solvent specified], $\epsilon = 20500$;^{241,242} λ_{\max} 224 nm [no solvent specified], $\epsilon = 25100$;^{168,198,237,244} λ_{\max} 199 nm [gas phase], 206 nm [hexane].²³⁹

[‡] Other UV data for [4]-dendralene (4.4) has been reported: λ_{\max} 216 nm [no solvent specified], $\epsilon = 34000$;²⁵⁰ λ_{\max} 216 nm [no solvent specified].²⁴⁷

NMR solutions of [n]-dendralenes (of known concentration) were serially diluted with spectroscopic grade ethanol. The absorption spectra of the resulting solutions (typically containing 0.4% CDCl₃ by volume after dilution) were recorded against a reference solution of identical composition. The observed absorption maxima (λ_{\max}) and extinction coefficients (ϵ) of the dendralenes recorded in this manner are given in **Table 5.2**. To enable direct comparison with 1,3-butadiene (**5.17**) a small quantity of 3-sulfolene (**3.1**) was subjected to capillary pyrolysis (**Scheme 5.15**) and the product was manipulated in a manner identical to the dendralenes. This was necessary to eliminate unquantified solvent effects during the comparison of absorption maxima and extinction coefficients. Indeed, it was noted that λ_{\max} values for both [3]- and [4]-dendralene, when acquired in ethanol containing no chloroform, were blue shifted and agreed more closely with literature values (*vide supra*). An increase in the value of the extinction coefficients of [3]- and [4]-dendralene was also estimated when ethanol (100%) was employed as solvent.









Scheme 5.15

All dendralenes exhibited a single absorption maximum and, with the exception of [3]-dendralene, appeared at shorter wavelengths than 1,3-butadiene (**5.17**) ($\lambda_{\max} = 226.4$ nm).[†] From this it was concluded that the dendralenes do not behave as an extended cross-conjugated π system, but more as skewed *anti*-1,3-butadiene fragments with minimal electronic interaction.²³⁷⁻²³⁹ Indeed, a comparison of the molar extinction coefficients of the dendralenes with 1,3-butadiene (**5.17**) ($\epsilon_{\text{([n]-dendralene)}/\epsilon_{\text{(butadiene)}}$) (**Table 5.2**) more readily identified this as a general trend. Acknowledging potential errors in the calculation of concentrations, the extinction coefficient of each dendralene approximates to the sum of possible butadiene units it contains. This observation appears particularly relevant to the even numbered dendralenes, $n = 4$ (**4.4**) and $n = 8$ (**5.16**).

[†] The UV spectra of 1,3-butadiene (**5.17**) and the [n]-dendralenes (**Table 5.2**) prepared by capillary pyrolysis are reproduced in **Appendix 5.5**.

Table 5.2

n	[n]-dendralene	CP yield /%	λ_{\max} / nm	ϵ	$\frac{\epsilon \text{ ([n]-dendralene)}}{\epsilon \text{ (butadiene)}}$
2	 (5.17)	74	226.4	6450	1.00
3	 (4.1)	89	232.2	8160	1.27
4	 (4.4)	85	222.6	13500	2.09
5	 (4.8)	64	219.8	22200	3.44
6	 (4.12)	52	220.0	25050	3.88
8	 (5.16)	64	220.6	25160	3.90

It is interesting to speculate on the potential structure of the higher dendralenes based on their UV spectra. It is conceivable that if the skewed, alternating *anti*-butadiene fragments are neither interconverting nor staggered, i.e. not just a random combination of left and right handed twists, then the intriguing possibility of an helical secondary structure exists. The absorption maxima given in **Table 5.2** are presumably the result of absorption by several different conformers present at ambient temperature.

5.5.2 Infrared Spectra.

With access to only small quantities of dendralenes as dilute solutions in chloroform, infrared analysis was limited to solution phase techniques. Assignments of spectral features was made by reference to standard tables.²⁵¹

Characteristic features typical of unsaturated, alkenic hydrocarbons were observed for all dendralene species. These included strong C-H stretching above 3000 cm^{-1} and out

of plane C-H vibrations at around 990 cm^{-1} . Despite the use of carefully matched cell pairs, absorptions below *ca.* 950 cm^{-1} were obscured by solvent corrections and consequently the characteristic absorption of internal methylene groups (i.e. vinylidene C-H bending), seen normally around 890 cm^{-1} , were not observed. Asymmetric C=C stretching vibrations were evident in all samples and consistently appeared as relatively strong bands at around 1580 cm^{-1} . With higher members of the dendralene series, this characteristic absorption tended to lower frequencies, typically *ca.* 2 cm^{-1} per additional methylene, however, no change in signal intensity was observed.

From these observations, it was concluded that the solution state infrared analysis of the dendralenes, prepared through capillary pyrolysis, exhibited spectral features fully consistent with the important structural elements expected for this class of unsaturated hydrocarbons.

5.5.3 Mass Spectrometry.

In the few literature reports detailing the synthesis of [n]-dendralenes, the mass spectrometric analysis of these compounds has received only minimal attention. Significant effort was therefore made to characterise all the dendralenes and related polyenes prepared by capillary pyrolysis techniques.

The dimerisation of [3]-dendralene and other cross-conjugated polyenes has been well documented.²⁴⁵ In the present study, however, using conventional electron ionisation techniques (direct insertion probe), no evidence for the dimerisation of any dendralene species could be found. Nonetheless, to ensure the analysis of unimolecular species and avoid any potential contamination from dimeric and/or other oligomeric impurities, gas chromatographic mass spectral (GCMS) analysis of the dendralene solutions was performed.

All members of the dendralene family exhibited excellent thermal stability and gave clean GC traces consisting of only one peak. In addition, each dendralene gave a clean molecular ion (M^+), which under high resolution mode formulated well for the expected molecular species. The most intense ion of the molecular cluster for all the dendralenes arose from a simple proton loss, i.e. the $M-H^+$ species. With [3]- and [4]-dendralene an unusual M^+-3H species was also observed, but an analogous ion was not evident in the

spectra of the higher dendralenes. Fragmentation was generally characterised by a series of successive methylene losses, yet no common origin of the resultant base peaks could be discerned. Of particular note was the similarity between the spectra of the dendralenes and the sulfolene precursors from whence they came. In hindsight it was clear that the mass spectra observed for the sulfolene precursors were, with the exclusion of any sulfur dioxide containing fragments, essentially those of the dendralenes themselves.

5.6 Other Pyrolysis Products.

It has been shown that the Stille cross-coupling of iodo-sulfolenes with organostannanes is an effective method for the preparation of various substituted sulfolene derivatives. Furthermore, the development and application of capillary pyrolysis as a practicable pyrolysis technique has demonstrated the value of such sulfolene derivatives as precursors to [n]-dendralenes. To broaden the scope of this strategy the capillary pyrolysis of other sulfolene derivatives was investigated as a general route to 2-substituted 1,3-butadienes.

The capillary pyrolysis of 3-phenyl 3-sulfolene (**4.46**) and 3-ethynyl-3-sulfolene (**4.45**) gave the corresponding 2-substituted 1,3-butadienes in good yields as pure compounds. (**Table 5.3**, entries 1 and 2 respectively) 2-Phenyl-1,3-butadiene (**5.18**)²⁵² and 2-ethynyl-1,3-butadiene (**5.19**)²⁵³ have been prepared previously by other means. Pyrolysis of the *trans*-diene substituted sulfolene (**4.44a**) furnished a mixture of products in an estimated 58% yield. (**Table 5.3**, entry 3) GCMS analysis of this mixture indicated the presence of three isomeric C₈H₁₀ species (**5.20**) and a minor dimeric component formulating for C₁₆H₂₀. No further separation was attempted. The preparation of 3-methylene-1,4,6-heptatriene (**5.20**) from a different precursor through FVP techniques has been reported previously.²⁵⁴

Pyrolysis of the *trans*-ethylene tethered *bis*-sulfolene (**4.58**) under argon at ambient pressure gave no volatile products and considerable charring and decomposition of the starting material was observed. Under reduced pressure, however, pentaene (**5.21**) was obtained in 32 % yield as a single isomeric compound as judged by GCMS. (**Table 5.3**, entry 4) Pyrolysis of the ethynyl tether analogue (**4.57**) under argon yielded tetraenyne (**5.22**) in a modest 12% yield. This compound was prepared more efficiently (25%)

when the cheletropic elimination of sulfur dioxide from (4.57) was carried out under reduced pressure. (Table 5.3, entry 5)

Table 5.3

entry	sulfolene	polyene	yield ^a / %
1	(4.46)	(5.18)	79 ^b
2	(4.45)	(5.19)	63 ^b
3	(4.44a)	(5.20)	58 ^b
4	(4.58)	(5.21)	32 ^c
5	(4.57)	(5.22)	25 ^c
6	(4.69)	(5.23)	12 ^b
7	(3.50)	(5.24)	59 ^b
8	(3.37)	(5.25)	51 ^b

^a Yields were calculated from the ¹H NMR recorded in CDCl₃.

^b CP conducted at 450°C under an atmosphere of argon at ambient pressure.

^c CP conducted at 450°C under reduced pressure (ca. 0.1 mmHg).

The pyrolysis of 3,4-diethynyl-3-sulfolene (4.69) under argon at ambient pressure gave dienediyne (5.23) in low yield. (Table 5.3, entry 6) Significant decomposition of the starting material was observed, possibly due to competitive Bergman

cycloaromatisation.²⁵⁵ Indeed, the pyrolysis of (4.69) under vacuum saw a reduction in the degree of decomposition, but gave no improvement in yield. The reduction in yield under vacuum is more likely due to the volatility of the product than any change in the efficiency of sulfur dioxide elimination. Polyenes (5.21), (5.22) and (5.23) have not been reported previously. The capillary pyrolysis of the simple halogenated sulfolenes (3.50) and (3.37) was also achieved and the corresponding 2-halo-1,3-dienes, (5.24)¹⁹⁵ and (5.25)²⁶⁶ respectively, were obtained in fair yield. (Table 5.3, entry 7 and 8)

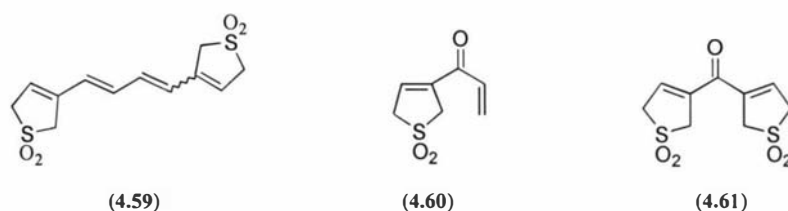


Figure 5.8

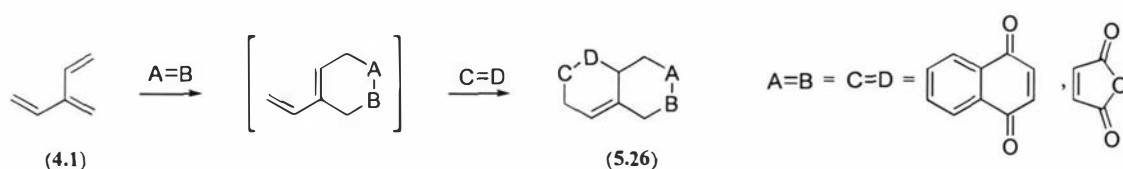
The capillary pyrolysis of 3-sulfolene precursors was not universally successful and a small number of derivatives would not undergo elimination of SO₂ under either argon at ambient pressure or under vacuum using this technique. Unsuccessful substrates included the two carbonylately coupled products (4.60) and (4.61) and the diene tethered *bis*-sulfolene (4.59) (as a mixture of isomers). (Figure 5.8) As suggested earlier, it is believed that recourse to efficient FVP is likely to establish the value of even these stubborn 3-sulfolene derivatives as viable polyene precursors.

5.7 Diene-Transmissive Diels-Alder (DTDA) Reactions of [n]-Dendralenes.

The diene-transmissive Diels-Alder (DTDA) reaction is a process that involves the $4\pi+2\pi$ cycloaddition of a dienophile to [3]-dendralene, to generate a new diene which is able to react with a second dienophile giving a polycyclic product.²³² (Scheme 5.1) In principle, the DTDA reaction can be applied to any [n]-dendralene giving a polycyclic product containing a maximum of [n-1] rings. This process is usually carried out on heteroatom substituted [3]-dendralenes, where the substitution pattern of the cross-conjugated triene is used to control the regioselectivity of the cycloaddition reactions.²³³ A limited number of DTDA reactions with non-heteroatom substituted [3]-dendralenes have also been reported.²⁵⁶⁻²⁵⁸ An important synthetic consideration of the DTDA reaction is that each diene/dienophile pair is constrained to react

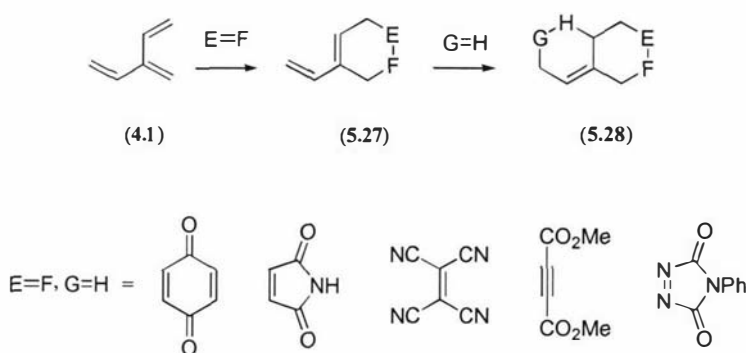
sequentially, and in this manner various polycyclic products have been successfully prepared.^{233,259-262} Relatively little attention, however, has been focused on the DTDA reactions of the unsubstituted, parent dendralenes.

[3]-dendralene (4.1) was independently prepared by Blomquist²⁴⁰ and Bailey²⁴¹ in 1955. Both authors reported the DTDA reaction of [3]-dendralene with various dienophiles and presented these results, together with spectroscopic data, as corroborative evidence for the hydrocarbon's cross-conjugated structure. These early reports described only *bis*-cycloadducts (5.26), prepared by the addition of two molar equivalents of the same dienophile, i.e. where "A=B" = "C=D". (Scheme 5.16)



Scheme 5.16

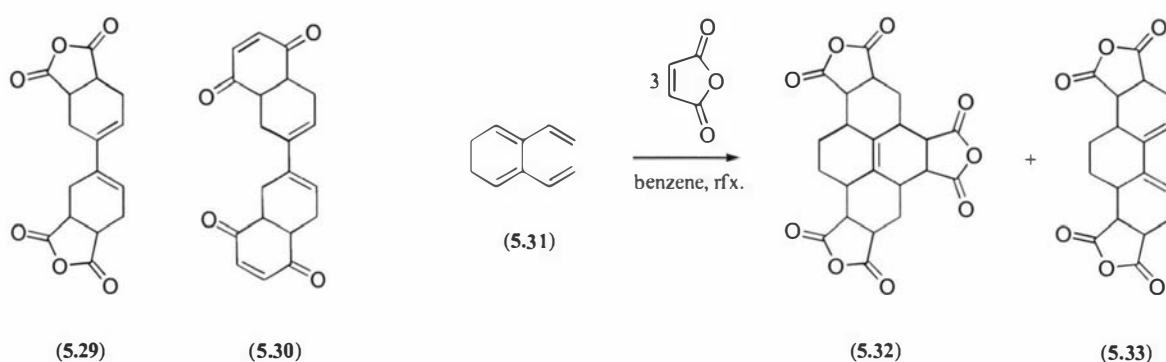
Later workers¹⁹⁸ were able to demonstrate that some selectivity towards *mono*-cycloaddition could be achieved by careful regulation of the reaction conditions. In this way certain *mono*-cycloadducts (5.27) and *bis*-cycloadducts (5.28), where "E=F" \neq "G=H", were prepared in modest yields. (Scheme 5.17)



Scheme 5.17

The DTDA reaction of [4]-dendralene has been studied less extensively. The first synthesis of [4]-dendralene (4.4) included reports of Diels-Alder adducts with maleic anhydride and benzoquinone and presented the *bis*-adducts (5.29) and (5.30) as corroborative evidence of the hydrocarbon's cross-conjugated structure.²⁴² (Scheme

5.18) While the formation of *bis*-adducts (5.29) and (5.30) is fully consistent with the *anti, anti*, skew conformation of [4]-dendralene, later deduced from UV and GED measurements,²³⁸ neither adduct was technically a DTDA product since the second dienophile did not add to a new diene created by the addition of the first. In contrast, a true DTDA reaction between maleic anhydride and the cyclic cross-conjugated polyene (5.31) has been reported. *Tris*-cycloadduct (5.32) was isolated, albeit in unspecified yield, together with a small quantity (unspecified) of the *bis*-adduct (5.33).²⁵⁰ (Scheme 5.18) This isolated report represents the only example of a [4]-dendralene DTDA reaction.



Scheme 5.18

5.7.1 DTDA Reactions of [4]-Dendralene.

It was our aim to briefly investigate the DTDA reaction of [4]-dendralene and attempt to prepare cycloadducts of the cross-conjugated hydrocarbon. For this study, 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (5.34) (Figure 5.9) was selected as an appropriate dienophile.

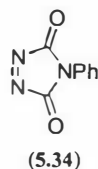
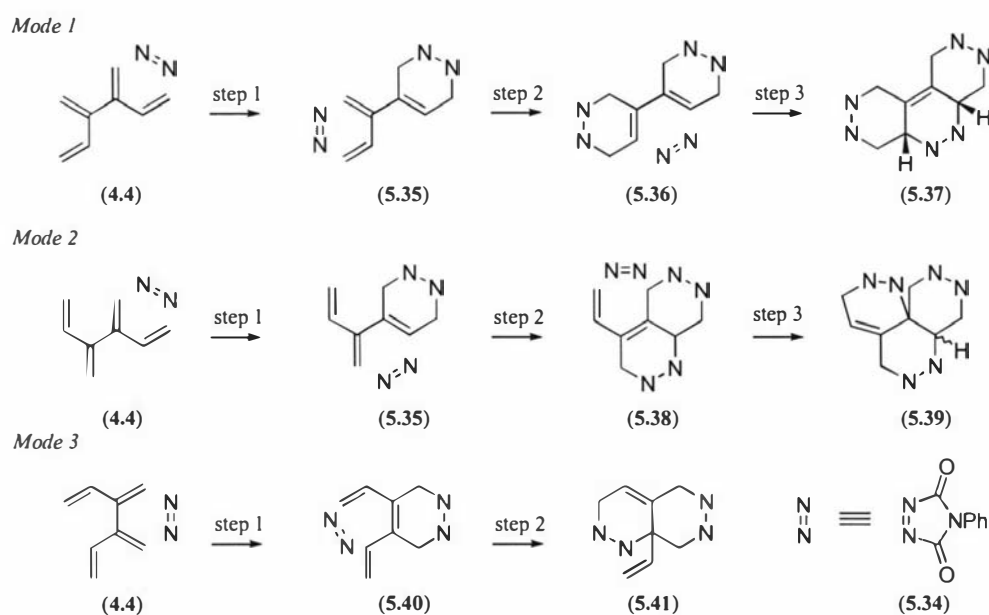


Figure 5.9

PTAD (5.34) is an azodicarbonyl compound. Such compounds are amongst the most reactive of dienophiles.²⁶³ Cycloadducts of PTAD are formed readily under mild conditions making it well suited to use with thermally labile dienes. Such cycloadducts are not intrinsically diastereomeric and selectivity issues are therefore limited to regiochemical considerations only. This greatly simplifies the NMR analysis of product

mixtures. Other practical considerations favouring the use of PTAD as a dienophile include its relative stability and ease of handling. Furthermore, solutions of PTAD are bright red, whereas cycloadducts are invariably colourless. Hence DTDA reactions involving this dienophile are potentially "auto-indicative" and offer a simple qualitative method for following the progress of a reaction.

It is possible to imagine three discrete modes for the DTDA reaction of [4]-dendralene with a dienophile. These are outlined in **Scheme 5.19**, where, for simplicity the dienophile (PTAD) (**5.34**) is represented as $N=N$.

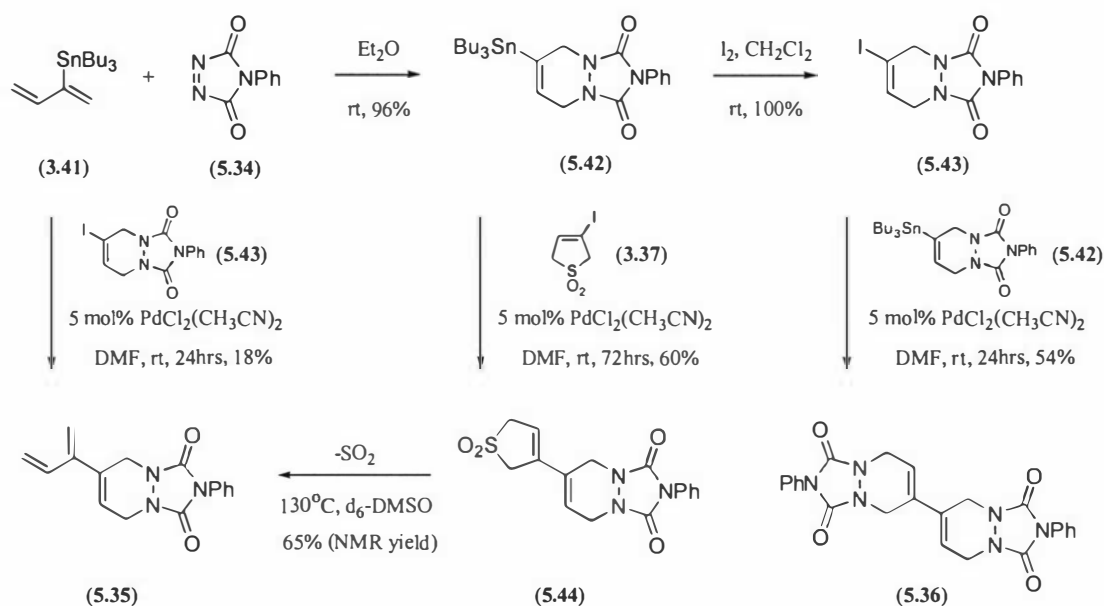


Scheme 5.19

- **Mode 1.** The cycloaddition of a dienophile at the dendralene terminus generates a preliminary terminal *mono*-cycloadduct (**5.35**). Addition of a second dienophile at the remaining diene terminus gives a symmetrical *bis*-cycloadduct (**5.36**). The resulting internal diene is able to undergo a third cycloaddition to generate the tricyclic *tris*-adduct (**5.37**). This mode of reactivity represents the only reported DTDA reaction of a [4]-dendralene.²⁵⁰ (**Scheme 5.18**)
- **Mode 2.** The preliminary formation of the terminal *mono*-cycloadduct (**5.35**) is followed by addition of a second dienophile at the newly generated internal diene to give an asymmetric *bis*-adduct (**5.38**). Addition of a third dienophile in a similar manner generates a tricyclic *tris*-adduct (**5.39**) as the product of a true diene transmissive cascade.

- *Mode 3*. Involves the preliminary addition of a dienophile across an internal diene to generate a symmetrical, linearly conjugated triene (5.40). This adduct is limited to only one more cycloaddition process, thereby generating an asymmetric vinylated *bis*-cycloadduct (5.41).

A priori, the reaction of PTAD with [4]-dendralene (4.4) was expected to yield the terminal *mono*-adduct (5.35) and the symmetrical *bis*-adduct (5.36). To aid in the identification and analysis of these and other potential products, cycloadducts (5.35) and (5.36) were prepared independently as reference materials. (Scheme 5.20)



The Diels-Alder reaction of stannylated 1,3-diene (3.41) with PTAD (5.34) proceeded smoothly at room temperature in ether to give the cycloadduct (5.42) as a low melting point solid in 96% yield.[†] Tin-iodine exchange under standard conditions gave vinyl iodide (5.43) as a white crystalline solid. The Stille cross-coupling of vinyl iodide (5.43) with stannylated 1,3-diene (3.41) gave the PTAD *mono*-adduct of [4]-dendralene (5.35) in low yield together with substantial quantities of unreacted starting materials (60-66%). While sufficient material for NMR analysis was obtained, an alternative route to the *mono*-cycloadduct (5.35) was also investigated. Stille cross-coupling of vinyl stannane (5.42) with 3-iodo-3-sulfolene (3.37) gave the substituted sulfolene (5.44) as the masked diene in good yield (60%). Sulfolene (5.44) was isolated as an

[†] The Diels-Alder reaction of (3.41) with other dienophiles has been reported earlier.²⁶⁴

amorphous solid and demonstrated physical properties akin to those of many of the *bis*-sulfolenes prepared earlier through a similar cross-coupling strategy. However, unlike many of these earlier derivatives, the capillary pyrolysis of (5.44) did not yield the desired thermolysis product and decomposition was always observed. Nonetheless, (5.44) was successfully unmasked as a dilute, yet saturated solution in d_6 -DMSO at 130°C to give triene (5.35) in 65% yield as judged by ^1H NMR analysis. Unfortunately the isolation of this product could not be achieved without significant decomposition and it was concluded that this route offered no advantages over the earlier, lower yielding sequence.

The symmetrical *bis*-adduct (5.36) was prepared in 54% yield by the Stille cross-coupling of stannane (5.42) with the corresponding iodide (5.43) under standard conditions. (Scheme 5.20) Again this material proved insoluble in all but the most polar solvents and NMR data for (5.36) could only be obtained from dilute, yet saturated solutions in d_6 -DMSO.

The DTDA reaction of [4]-dendralene (4.4) was investigated by the successive addition of stoichiometric equivalents of PTAD to standard solutions of the polyene in CDCl_3 at room temperature. It was anticipated that analysis by ^1H NMR would be possible. Unfortunately, the poor solubility of the products (also demonstrated by the putative cycloadducts (5.35) and (5.36)) necessitated the replacement of CDCl_3 by d_6 -DMSO prior to the analysis.

The addition of one molar equivalent of PTAD to a solution of [4]-dendralene (4.4) in CDCl_3 at room temperature saw the rapid consumption of the dienophile (as judged by the loss of colour) and, after 30 minutes, the formation of a turbid solution. No peaks attributable to [4]-dendralene were observed in the ^1H NMR spectrum. Anticipating the formation of insoluble *bis*-adducts, the solvent was exchanged. ^1H NMR analysis of the d_6 -DMSO solution revealed two products in a *ca.* 2:1 ratio. The major component was readily identified as the terminal *mono*-adduct (5.35), while the remaining material exhibited a clearly defined ABX spin system fully consistent with the symmetrical divinylated *mono*-cycloadduct (5.40). No attempt to isolate this material was made. The symmetrical *bis*-adduct (5.36) was not observed. It was concluded that, at room temperature in the presence of one equivalent of PTAD, no selectivity between cycloaddition modes (1, 2 or 3) was evident since the product ratio observed reflected a

purely statistical outcome. High resolution mass spectral analysis confirmed the presence of only *mono*-cycloadducts, giving a strong molecular ion (m/z 281) formulating for $C_{16}H_{15}N_3O_2$. No higher mass species were present in the FAB (+ve ion) mass spectrum.

The addition of two molar equivalents of PTAD to [4]-dendralene (**4.4**) in $CDCl_3$ resulted in an equally rapid discharge of the dienophile colour. This time the formation of a heavy white precipitate was observed. Every effort was made to obtain a representative, homogeneous sample of the reaction mixture for NMR analysis, but a significant proportion of the precipitated material remained insoluble even in the presence of a large volume of DMSO at 40°C. 1H NMR analysis of the DMSO-soluble fraction indicated the anticipated symmetrical *bis*-cycloadduct (**5.36**) was present only as a minor component (< 5%).

The DMSO-soluble fraction contained three additional components in a ratio of *ca.* 2:1:1. Of these, the major fraction was readily identified as the internal *mono*-cycloadduct (**5.40**). The isomeric terminal *mono*-adduct (**5.35**) was also present, however, the identity of the third component could not be established with certainty. The presence of a partly obscured, yet distinct, ABX spin system was consistent with either of the pendant vinyl *bis*-cycloadducts (**5.38**) and (**5.41**) and additional, corroborative signals were present around 4.8 and 4.0 ppm. While giving no structural information, mass spectral analysis of the product mixture confirmed the presence of a *bis*-cycloadduct (m/z 456) formulating well for $C_{24}H_{20}N_6O_4$. The presence of the *bis*-cycloadduct (**5.36**) (< 5%), however, must be remembered. Hence this result by no means confirms the presence of either (**5.38**) or (**5.41**).

The precipitation of insoluble cycloadducts also dogged the attempted formation and characterisation of *tris*-PTAD cycloadducts of [4]-dendralene (**4.4**). Indeed, after the addition of three equivalents of PTAD to the dendralene in chloroform, a heavy precipitate was again observed. Excess dienophile did not disperse over time (24 hours) and removal of the chloroform resulted in the formation of an amorphous red solid. Possible explanations for the presence of excess PTAD include:

- i. Unreacted dienes were prematurely removed from the reaction mixture by precipitation as insoluble *bis*-cycloadducts.
- ii. Cycloaddition of the third dienophile to generate *tris*-cycloadducts was slow.

- iii. The formation of “dead-end” *bis*-cycloadducts, i.e. (5.41) occurred significantly and only two equivalents of dienophile were consumed.
- iv. The initial concentration of [4]-dendralene (4.4) was reduced during the course of the reaction through competitive decomposition.

¹H NMR analysis of the reaction mixture's d₆-DMSO-soluble component revealed a complex mixture of products. Vinylic protons (ABX system) were again evident and as before were consistent with the presence of pendant vinyl *bis*-cycloadducts (5.38) and (5.41). Other features were less readily assigned and no further conclusions were drawn. Although NMR yielded little structural information, mass spectral analysis (+ve FAB), clearly indicated the presence of *bis*-cycloadducts and a high mass species (MH⁺) formulating well for a PTAD *tris*-adduct (C₃₂H₂₆N₉O₆, *m/z* 632).

The poor solubility of [4]-dendralene-PTAD cycloadducts was totally unexpected and this impacted significantly on the NMR analysis of the product mixtures during the course of this preliminary investigation. Nonetheless, from the limited data available together with important mass spectral evidence, some initial conclusions were drawn.

In the presence of a single molar equivalent of PTAD, no selectivity between terminal cycloaddition (modes 1 and 2) and internal cycloaddition (mode 3) was observed. While terminal cycloaddition (modes 1 and 2) has been observed previously,²⁴² internal cycloaddition (mode 3) has not. Subsequent addition of a second molar equivalent of dienophile resulted in the formation of the anticipated symmetrical *bis*-adduct (5.36) and was consistent with results of earlier workers investigating the DTDA reaction of less reactive dienophiles.²⁵⁰ While no conclusive NMR data could be presented to support the formation of a *tris*-cycloadduct by the addition of three molar equivalents of PTAD to [4]-dendralene, mass spectral analysis of the product mixture indicated the presence of one or both of the putative *tris*-cycloadducts (5.37) and (5.39). This observation constitutes the first evidence of a full DTDA reaction of [4]-dendralene (4.4).

5.7.2 PTAD Cycloadducts of Other [n]-Dendralenes.

The theoretical maximum number of cycloaddition reactions possible for a dendralene is one less than the number of cross-conjugated double bonds that it contains. Hence,

an [n]-dendralene can, in principle, undergo [n-1] possible cycloaddition reactions. To qualitatively assess the validity of this hypothesis, the DTDA reactions of the higher dendralenes with excess PTAD was briefly investigated. Acknowledging the potential insolubility of such cycloadducts, product mixtures obtained by the addition of excess PTAD to chloroform solutions of [n]-dendralenes were subjected to mass spectral analysis only.

Table 5.4

n	[n]-dendralene	molecular ions (MH) ⁺ / m/z (FAB)		formulation	PTAD equivalents	
		measured	calculated		observed	theoretical maximum
4	(4.4)	457.1615	457.1624	C ₂₄ H ₂₁ N ₆ O ₄	2*	
		632.1973	632.2006	C ₃₂ H ₂₆ N ₉ O ₆	3	3
5	(4.8)	658.2134	658.2163	C ₃₄ H ₂₈ N ₉ O ₆	3*	
		833.2530	833.2544	C ₄₂ H ₃₃ N ₁₂ O ₈	4	4
6	(4.12)	859.2672	859.2701	C ₄₄ H ₃₅ N ₁₂ O ₈	4*	
		1034.3024	1034.3083	C ₅₂ H ₄₀ N ₁₅ O ₁₀	5	5
8	(5.16)	911.2964	911.3014	C ₄₈ H ₃₉ N ₁₂ O ₈	4	
		1086.3408	1086.3396	C ₅₆ H ₄₄ N ₁₅ O ₁₀	5*	7

* Most intense molecular ion observed.

In the presence of excess PTAD, [4]-, [5]- and [6]-dendralenes underwent cycloaddition reactions to give the corresponding PTAD adducts containing a maximum of [n-1] equivalents of the dienophile. The protonated molecular ions (MH⁺) of these species formulated well for their expected molecular composition. Significant proportions of [n-2] cycloadducts were also observed in the product mixtures and again the protonated molecular ions of these species formulated well for the expected molecular composition. (**Table 5.4**)

The reactivity of [8]-dendralene (**5.16**), however, marked a clear departure from the trend observed in the lower dendralenes. After exposure to excess dienophile at room temperature for 8 days the incorporation of a maximum of only 5 PTAD molecules per

[8]-dendralene was observed. While no higher mass species were detected, a low mass cycloadduct containing 4 equivalents of dienophile was present as a minor component. It is likely that [n-1] cycloadducts of [8]-dendralene were not observed due to poor solubility and premature precipitation of lower mass cycloadducts.

5.8 Conclusions.

The conventional solution state elimination of SO₂ from 3-sulfolene derivatives proved of limited value for polyene precursors where the products were either too volatile or the precursors too insoluble. In response, capillary pyrolysis (CP) was developed as an alternative, “solventless” method to achieve the cheletropic elimination of sulfur dioxide from such polyene precursors. The successful application of this technique offered a simple, practical alternative to flash vacuum pyrolysis (FVP).

The capillary pyrolysis of *bis*- and *tris*-3-sulfolenes together with various pendant *bis*-3-sulfolene derivatives demonstrated the value of these derivatives as viable [n]-dendralene precursors. In this manner [5]-, [6]- and [8]-dendralene were prepared for the first time in good yield and, together with [3]- and [4]-dendralene, granted access to an otherwise “neglected group of highly unsaturated hydrocarbons”.¹⁶⁸ In addition to the spectroscopic characterisation of the dendralenes, a preliminary investigation into the diene-transmissive Diels-Alder (DTDA) reaction of these polyenes was made. It was concluded the dendralene DTDA reaction has significant potential as a synthetic tool and is worthy of further investigation.

Chapter 6

Experimental.

6.1 General Information.

Reactions were performed under an atmosphere of dry nitrogen in oven dried glassware, unless otherwise stated. Reagents (Aldrich Chemical Company, Inc) were generally used as received. Benzene, toluene, xylene, THF and diethyl ether (BDH) were purified by distillation from sodium benzophenone ketyl.²⁶⁵ Dichloromethane (BDH) was distilled from calcium hydride. DMF and NMP were distilled from calcium hydride under reduced pressure. Thin layer chromatography was carried out on aluminium backed Kieselgel 60 F₂₅₄ silica gel plates (Merck) with the solvents specified. Compounds were visualised under UV (365 and 254 nm) followed by treatment with either acidified ethanolic vanillin⁷⁴ or alkaline potassium permanganate,⁷⁴ unless otherwise specified. Flash column chromatography and rapid vacuum filtration were carried out using oven dried (150°C) silica gel (40-62 µm, Merck). Radial chromatography was performed on a 7924T Chromatotron (Harrison Research) using 230 mm diameter glass rotors coated with silica gel 60 HF₂₅₄ (63-200 µm, Merck)/calcium sulphate hemihydrate (BDH) (13%). Eluting solvents were freshly distilled laboratory grade. Short path distillation was carried out using a GKR-51 Kugelrohr (Büchi) at the temperatures and pressures described. When handling anhydrous solutions of H₂O₂, hydroperoxides and endoperoxides, protective (blast) shields were placed between the worker and the experiment and reactions were conducted on the minimum necessary scale. Slow addition of solutions or reagents to reaction mixtures was accomplished using a Cole Parmer 74900 series syringe pump.

NMR spectra were recorded on a Jeol GX270 spectrometer in CDCl₃ or d₆-DMSO at ambient temperature, unless specified. Chemical shifts (δ) are reported in parts per million (ppm) relative to chloroform at δ 7.27 and DMSO at δ 2.50 for ¹H (270 MHz) spectra and relative to chloroform at δ 77.0 and DMSO at δ 39.7 for ¹³C (68 MHz) spectra. Coupling constants (J) are given in Hertz (Hz). Tin coupling constants (J_{Sn-H}, J_{Sn-C}) are reported for ¹¹⁹Sn where these are resolved from ¹¹⁷Sn signals; otherwise the reported values represent an average. Where necessary, inverse gated, DEPT, COSY,

and HETCOR experiments were performed. The following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; m, multiplet; br., broad and obscured (where the multiplicity could not be determined due to the presence of a larger peak). Mass spectra were obtained with a VG70-250S double focusing magnetic sector mass spectrometer (VG Instruments) operating at either 40 eV or 70 eV. GCMS was carried out using an HP 5890 Series II gas chromatograph (Hewlett Packard) fitted with a 30 m x 0.25 mm I.D. DB1 column, 0.25 μ m film thickness (Alltech); temperature programmed for 5 min @ 40°C, 5°C/min, 20 min @ 280°C, with a 2 p.s.i. He head pressure coupled directly to the mass spectrometer. Ultraviolet-visible spectra were recorded on a UV-3101PC scanning spectrophotometer (Shimadzu) using spectroscopic grade solvents. Infrared measurements were carried out on a Paragon 1000 FT-IR spectrometer (Perkin-Elmer) with samples as either thin films between NaCl plates or as dispersions in KBr discs (1-3%) or as solutions in CDCl₃. Melting points were measured on a Reichert hot stage apparatus and are not corrected. Microanalysis was performed at the Chemistry Department, University of Otago (New Zealand).

6.2 Experimental for Chapter 1.

3,7-Dimethyl-2,3-epoxy-6-octen-1-ol (1.20).⁵⁹ (Scheme 1.3)



Anhydrous *t*-butyl hydroperoxide (2.03 g, 22.5 mmol) was added to a solution of geraniol (1.19) (2.667 g, 17.3 mmol) and vanadyl acetylacetonate (0.46 g, 1.73 mmol) in CH₂Cl₂ (50 ml) at rt under N₂. After 1hr, aqueous Na₂S₂O₃ (50% w/v, 50 ml) was added and the reaction mixture extracted with ether (3x50 ml). The combined organic phases were washed with water (2x50 ml) then sat. brine (50 ml), dried over MgSO₄, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (4:1) to yield the *title compound* (1.20) (2.8g, 95%) as a pale yellow oil (R_f = 0.29; hexane-ethyl acetate (4:1)): found M⁺ 170.1301, C₁₀H₁₈O₂ requires 170.1307; IR ν_{\max} (thin film) 3427, 2925,

1484, 1424, -1034 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.12-5.06 (1H, m, $(\text{CH}_3)_2\text{C}=\text{CH}-$), 3.84 (1H, dd, $J = 12.0, 4.3$ Hz, $-\text{CH}_2-\text{OH}$), 3.69 (1H, dd, $J = 12.0, 6.6$ Hz, $-\text{CH}_2-\text{OH}$), 2.98 (1H, dd, $J = 6.6, 4.3$ Hz, $-\text{C}(\text{O})\text{H}-\text{CH}_2\text{OH}-$), 2.10 (2H, q, $J = 7.5$ Hz, $=\text{CH}-\text{CH}_2-\text{CH}_2-$), 1.75-1.60 (2H, m, $-\text{CH}_2-\text{C}(\text{CH}_3)(\text{O})-$, $-\text{OH}$), 1.69 (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$), 1.62 (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$) 1.58-1.44 (1H, m, $-\text{CH}_2-\text{C}(\text{CH}_3)(\text{O})-$), 1.31 (3H, s, $\text{CH}_2-\text{C}(\text{CH}_3)(\text{O})-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 132.1, 123.3, 63.0, 61.4, 61.2, 38.4, 25.6, 23.6, 17.6, 16.7 ppm; MS m/z (rel. int. %) 170(1), 152(3), 149(3), 139(4), 121(7), 110(28), 109(77), 95(24), 82(49), 69(83), 67(48), 61(23), 55(37), 43(63), 41(100).

3,7-Dimethyl-2,3-epoxy-1-iodooct-6-ene (1.21).⁶⁰ (Scheme 1.3)



This compound has been made from the epoxyalcohol (1.20) *via* the tosylate.⁶⁰ We found (1.21) could be prepared directly from (1.20) according to the procedure of Lange and Gottardo.⁶¹ Iodine (0.363 g, 1.43 mmol) was added to a vigorously stirred solution of triphenylphosphine (0.406 g, 1.55 mmol), and imidazole (0.122 g, 1.79 mmol) in CH_2Cl_2 (10.0 ml) at 0°C under N_2 . After the iodine had completely reacted (*ca.* 5 min) the resulting pale yellow slurry was treated with a solution of 3,7-dimethyl-2,3-epoxy-6-octen-1-ol (1.20) (0.203 g, 1.19 mmol) in CH_2Cl_2 (1.0 ml) and the reaction mixture warmed to rt over 30 mins. The solvent was evaporated and the residue was triturated with hexane-ether (5:1, 20 ml). [The presence of a small quantity of silica gel (*ca.* 1-2 g) greatly improved the efficiency of this process.] The supernatant was filtered through a short plug of silica, rinsed with hexane-ether (5:1, 20 ml) and concentrated *in vacuo* to give a crude oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (10:1) to yield the *title compound* (1.21) (0.293 g, 88%) as a pale yellow oil that darkened on exposure to light ($R_f = 0.47$; hexane-ethyl acetate (10:1)): found M^+ 280.0331, $\text{C}_{10}\text{H}_{17}\text{IO}$ requires 280.0324; IR ν_{max} (thin film) 2925, 1450, 1384, 1174, 854 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.13-5.08 (1H, m, $(\text{CH}_3)_2\text{C}=\text{CH}-$), 3.36 (1H, dd, $J = 9.4, 5.5$ Hz, $-\text{C}(\text{O})\text{H}-\text{CH}_2\text{I}$), 3.10 (1H, dd, $J = 8.6,$

5.5Hz, $-CH_2I$), 2.99 (1H, dd, $J = 9.4, 8.6$ Hz, $-CH_2I$), 2.10 (2H, q, $J = 7.4$ Hz, $=CH-CH_2-CH_2-$), 1.77-1.67 (1H, m, $-CH_2-C(CH_3)(O)-$), 1.70 (3H, s, $=C(CH_3)CH_3$), 1.62 (3H, s, $=C(CH_3)CH_3$) 1.49-1.38 (1H, m, $-CH_2-C(CH_3)(O)-$), 1.30 (3H, s, $CH_2-C(CH_3)(O)-$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 132.2, 123.4, 63.9, 62.5, 38.4, 25.7, 23.8, 17.7, 15.7, 2.4 ppm; MS m/z (rel. int. %) 280(0.3), 153(9), 135(6), 125(7), 109(39), 95(13), 81(25), 69(84), 55(33), 43(100), 41(70).

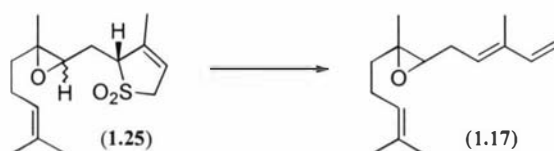
2-(2',3'-Epoxy-3',7'-dimethylocta-6'-en-1'-yl)-3-methyl-2,5-dihydrothiophene-1,1-dioxide (1.25). (Scheme 1.4)



BuLi (1.56 M [hexanes], 3.8 ml, 5.9 mmol) was added dropwise to a stirred solution of 3-methyl-2,5-dihydrothiophene-1,1-dioxide (1.23)⁹⁹ (0.75 g, 5.7 mmol) in THF (45.0 ml) and TMEDA (5.0 ml) at $-105^\circ C$ under N_2 , followed by, after 30 mins, a solution of 3,7-dimethyl-2,3-epoxy-1-iodooct-6-ene (1.21) (1.43 g, 5.1 mmol) in THF (2 ml). The reaction was maintained at $-105^\circ C$ and quenched after 1hr by the addition of sat. NH_4Cl solution (2 ml) and warmed to rt, whereupon water (50 ml) was added and the mixture was extracted with ether (2x50 ml). The combined ethereal extracts were washed with water (50 ml), then sat. brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (2:1) to yield recovered 3,7-dimethyl-2,3-epoxy-1-iodooct-6-ene (1.21) (0.78 g, 55%) followed by the *title compound* (1.25) (0.55 g, 38%) as a viscous oil as an inseparable *ca.* 1:1 mixture of diastereoisomers ($R_f = 0.27$; hexane-ethyl acetate (2:1)): found M^+ 284.1432, $C_{15}H_{24}O_3S$ requires 284.1446; IR ν_{max} (thin film) 2924, 1442, 1384, 1306, 1118, 915, 733 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 5.75 and 5.71 [each one diastereoisomer] (1H, br.s, $=CHCH_2SO_2R-$), 5.07 (1H, m, $C=CH-CH_2$), 3.82-3.60 (3H, m, $=CH-CH_2SO_2CHR-C(CH_3)=$), 3.02-2.94 (1H, m, $-C(O)H-CH_2-$), 2.32-2.21 and 1.84-1.72 [each one diastereoisomer] (2H, m, $-C(O)H-CH_2-CH(SO_2R)-$), 2.15-2.05 (2H m, $=CH-CH_2-CH_2-$), 1.91 and 1.88 [each one diastereoisomer] (3H, br.s, $-CH_2SO_2CHR-C(CH_3)=$), 1.68 (3H, s, $=C(CH_3)CH_3$), 1.53-

1.22 (2H, m, $-\text{CH}_2-\text{C}(\text{CH}_3)(\text{O})-$), 1.61 (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$), 1.31 (3H, s, $-\text{CH}_2\text{C}(\text{CH}_3)(\text{O})-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) [both diastereoisomers] δ 138.1, 137.9, 132.0, 123.3, 123.3, 117.5, 117.3, 65.2, 61.9, 60.8, 60.4, 59.2, 56.1, 55.6, 38.5, 27.9, 27.4, 25.7, 23.8, 23.7, 18.2, 18.1, 17.8, 16.8, 16.6 ppm; MS m/z (rel. int. %) 284(0.6), 266(0.7), 220(3), 201(10), 175(23), 161(7), 150(14), 137(25), 135(24), 119(12), 110(100), 95(59), 93(50), 81(46), 69(82), 55(31), 43(39), 41(61).

6,7-Epoxy-3,7,11-trimethyldodeca-1,3E,10-triene (1.17). (Scheme 1.4)



A solution of the 1:1 diastereoisomeric mixture of sulfolenes (**1.25**) (0.322 g, 1.13 mmol) in xylene (10 ml) was heated to reflux for 15 min under N_2 . The solvent was removed under reduced pressure to give a crude oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (20:1) to yield the *title compound* (**1.17**) (0.185 g, 74%) as a colourless oil ($R_f = 0.25$; hexane-ethyl acetate (20:1)): found M^+ 220.1816, $\text{C}_{15}\text{H}_{24}\text{O}$ requires 220.1827; IR ν_{max} (thin film) 3088, 2925, 1714, 16442, 1606, 1451, 1383, 1073, 988, 895 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.40 (1H, dd, $J = 17.4, 10.7$ Hz, $-\text{CH}=\text{CH}_2$), 5.51 (1H, m, $-\text{CH}=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2$), 5.14 (1H, d, $J = 17.4$ Hz, $-\text{CH}=\text{C}(\text{H})\text{H}$), 5.07 (1H, m, $(\text{CH}_3)_2\text{C}=\text{CH}-$), 4.99 (1H, d, $J = 10.7$ Hz, $-\text{CH}=\text{C}(\text{H})\text{H}$), 2.78 (1H, t, $J = 6.4$ Hz, $-\text{C}(\text{O})\text{H}-\text{CH}_2-$), 2.56-2.22 (2H, m, $-\text{C}(\text{O})\text{H}-\text{CH}_2-\text{CH}=\text{}$), 2.13-2.06 (2H, m, $=\text{CH}-\text{CH}_2-\text{CH}_2-$), 1.78 (3H, s, $-\text{CH}=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2$), 1.74-1.44 (2H, m, $-\text{CH}_2-\text{C}(\text{CH}_3)(\text{O})-$), 1.68 (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$), 1.61 (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$), 1.30 (3H, s, $\text{CH}_2-\text{C}(\text{CH}_3)(\text{O})-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 141.0, 136.0, 131.9, 126.9, 123.5, 111.5, 62.6, 60.7, 38.7, 28.3, 25.7, 23.9, 17.7, 16.6, 12.0 ppm; MS m/z (rel. int. %) 220(3), 205(7), 167(13), 149(28), 139(12), 134(18), 123(16), 119(12), 109(23), 95(30), 81(54), 79(52), 69(96), 57(50), 55(56), 43(48), 41(100).

3,7,11-Trimethyldodeca-1,3E,5E,10-tetraen-7-ol (1.8a). (Scheme 1.4)


This is a modification of the procedure by Brimble *et al.*⁵⁶ A solution of 6,7-epoxy-3,7,11-trimethyldodeca-1,3E,10-triene (1.17) (90.0 mg, 0.41 mmol) in THF (1.0 ml) was added to a mixture of *tert*-BuOK (0.183 g, 1.63 mmol), diisopropylamine (41.0 mg, 0.41 mmol) and BuLi (1.56 M [hexanes], 0.26 ml, 0.43 mmol) in THF (2.0 ml) at -50°C under N_2 . The reaction mixture was warmed to rt over 15 min and the solvent was removed under reduced pressure. The residue was dissolved in water (10 ml) and extracted with ether (2x20 ml). The combined ethereal extracts were washed with sat. brine (20 ml), dried over MgSO_4 , filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (4:1) to yield the *title compound* (1.8a) (87.0 mg, 97%) as a colourless oil ($R_f = 0.41$; hexane-ethyl acetate (4:1)): found M^+ 220.1824, $\text{C}_{15}\text{H}_{24}\text{O}$ requires 220.1827; λ_{max} (ϵ) (*n*-hexane) 251 sh. (21300), 260 (36500), 269 (48450), 280 (37600) nm; IR ν_{max} (thin film) 3363, 2922, 1608, 967, 889 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.58 (1H, dd, $J = 15.2, 11.1$ Hz, $-\text{CH}=\text{CH}-\text{CH}=\text{C}(\text{CH}_3)-$), 6.41 (1H, dd, $J = 17.4, 10.6$ Hz, $-\text{CH}=\text{CH}_2$), 6.08 (1H, d, $J = 11.1$ Hz, $=\text{CH}-\text{CH}=\text{C}(\text{CH}_3)-$), 5.80 (1H, d, $J = 15.2$ Hz, $-\text{C}(\text{OH})-\text{CH}=\text{CH}-$), 5.21 (1H, d, $J = 17.4$ Hz, $-\text{CH}=\text{C}(\text{H})\text{H}$), 5.15-5.09 (1H, m, $(\text{CH}_3)_2\text{C}=\text{CH}-$), 5.03 (1H, d, $J = 10.6$ Hz, $-\text{CH}=\text{C}(\text{H})\text{H}$), 2.08-1.98 (2H, m, $(\text{CH}_3)_2\text{C}=\text{CH}-\text{CH}_2-$), 1.88 (3H, s, $=\text{C}(\text{CH}_3)-\text{CH}=\text{CH}_2$), 1.71 (1H, s, $-\text{OH}$), 1.68 (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$), 1.66-1.54 (2H, m, $-\text{CH}_2-\text{C}(\text{OH})-$), 1.60 (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$), 1.31 (3H, s, $-\text{C}(\text{CH}_3)(\text{OH})-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 141.2 (C6), 141.1 (C2), 134.7 (C3), 131.6 (C11), 130.7 (C4), 124.2 (C10), 123.5 (C5), 112.2 (C1), 73.3 (C7), 42.4 (C8), 28.2 (C7- CH_3), 25.6 (C12), 23.0 (C9), 17.7 (C11- CH_3), 12.1 (C3- CH_3) ppm; MS m/z (rel. int. %) 220(6), 202(5), 187(3), 159(6), 147(3), 139(20), 138(21), 133(6), 121(34), 105(82), 95(50), 82(100), 81(64), 69(70), 67(51), 59(35), 55(34), 41(85).

Anhydrous Hydrogen Peroxide in THF. (Scheme 1.6)

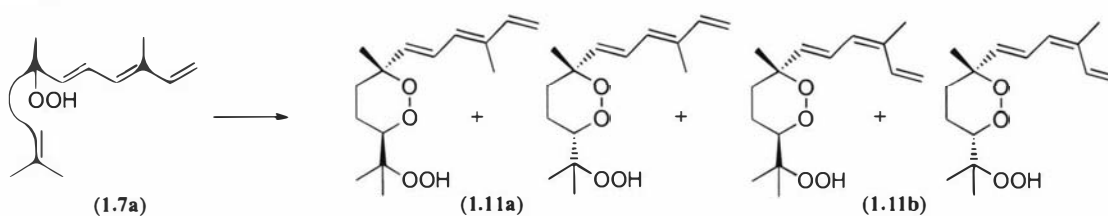
Urea hydrogen peroxide complex (UHP) was prepared according to the method of Lu *et al.*⁷² Urea (40.0 g, 0.67 mol) was dissolved in an aqueous solution of hydrogen peroxide (30% v/v, 102 ml) at 60°C. The solution was cooled to 0°C over 4 hrs and the crystals of UHP were filtered off and dried to constant weight (22.81 g, 36%) over P₂O₅ under vacuum: found⁷³ H₂O₂ 34.4%, CH₄N₂O:H₂O₂ requires H₂O₂ 36.2%. A slurry of dry UHP (3.5 g, 37.2 mmol) in THF (30 ml) was stirred at rt under argon for 1 hr. Iodometric analysis⁷³ of aliquots (1.0 ml) of the supernatant indicated available H₂O₂ = 0.89 M. Solutions of anhydrous hydrogen peroxide prepared in this manner were stable for several days at 0°C under argon.

7-Hydroperoxy-3,7,11-trimethyldodeca-1,3E,5E,10-tetraene (1.7a). (Scheme 1.6 and Table 2.1, entry 1)

p-Toluenesulfonic acid monohydrate (1.0 mg, 5.9x10⁻⁶ mol, 2 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,3E,5E,10-tetraen-7-ol (**1.8a**) (65.5 mg, 0.297 mmol, 3E:3Z = 95:5) in anhydrous H₂O₂/THF (0.89 M, 10 ml, 8.9 mmol, 30 equiv.) under an atmosphere of dry N₂ at rt. The solution was stirred for 48 hrs, diluted with water (20 ml) and extracted with ether (2x10 ml). The combined ethereal extracts were washed with water (2x10 ml) then sat. brine (10 ml), dried over MgSO₄, filtered and concentrated *in vacuo* to give an oil that was purified by preparative centrifugal chromatography on a silica rotor eluting with hexane-ethyl acetate (6:1) to yield recovered 3,7,11-trimethyldodeca-1,3,5E,10-tetraen-7-ol (**1.8a**) (15.4 mg, 24%, 3E:3Z = 95:5) and the *title compound* (**1.7a**) (32.3 mg, 47%, 3E:3Z = 96:4) as a colourless oil (R_f = 0.32; hexane-ethyl acetate (6:1)): found M⁺ 236.1775, C₁₅H₂₄O₂ requires 236.1776; λ_{max} (ε) (*n*-hexane) 251 sh. (20500), 262 (33200), 270 (43000), 280 (34100) nm; IR ν_{max} (thin film) 3398, 2927, 1616, 1445, 1376, 1105, 986, 967, 893 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 7.55 (1H, s, OOH), 6.59 (1H, dd, J = 15.4, 11.0 Hz, -

CH=CH-CH=C(CH₃-), 6.42 (1H, dd, J = 17.4, 10.6 Hz, -CH=CH₂), 6.09 (1H, d, J = 11.0 Hz, =CH-CH=C(CH₃-), 5.77 (1H, d, J = 15.4 Hz, C(OOH)-CH=CH-), 5.25 (1H, d, J = 17.4 Hz, -CH=C(H)H), 5.17-5.06 (1H, m, (CH₃)₂C=CH-), 5.08 (1H, d, J = 10.6 Hz, -CH=C(H)H), 2.04-1.98 (2H, m, (CH₃)₂C=CH-CH₂-), 1.90 (3H, s, =C(CH₃)-CH=CH₂), 1.77-1.66 (2H, m, -CH₂-C(OOH)), 1.69 (3H, s, =C(CH₃)CH₃), 1.62 (3H, s, =C(CH₃)CH₃), 1.41 (3H, s, -C(CH₃)(OOH)-) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 140.9 (C2), 136.6 (C6), 135.9 (C3), 132.0 (C11), 130.5 (C4), 127.0 (C5), 124.0 (C10), 113.0 (C1), 84.6 (C7), 37.7 (C8), 25.7 (C12), 22.5 (C9), 21.8 (C7-CH₃), 17.7 (C11-CH₃), 12.2 (C3-CH₃) ppm; MS *m/z* (rel. int. %) 236(1), 218(8), 202(19), 162(34), 159(34), 137(29), 119(31), 105(42), 93(55), 81(35), 69(89), 55(52), 43(100), 41(85).

1-Methyl-1-(6'-methyl-6'-(4''-methyl-1''*E*, 3''*E*, 5''-hexatrien-1''-yl)-1',2'-dioxan-3'-yl) ethyl hydroperoxide (1.11a) and 1-methyl-1-(6'-methyl-6'-(4''-methyl-1''*E*, 3''*Z*, 5''-hexatrien-1''-yl)-1',2'-dioxan-3'-yl) ethyl hydroperoxide (1.11b). (Scheme 1.11)

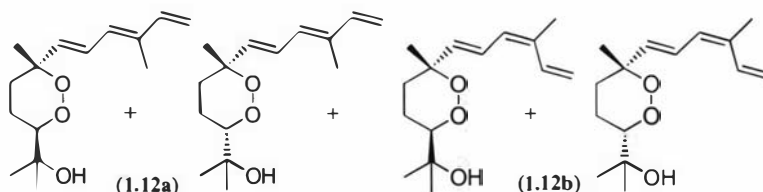


A solution of samarium (II) iodide (0.1 M [THF], 0.13 ml, 0.013 mmol [prepared according to the method of Inamoto and Ono⁸⁴]) was diluted with benzene (1.0 ml) and treated with dry oxygen (0.3 ml, 0.013 mmol). The resulting yellow solution was added dropwise over 2 hrs (syringe pump) to a stirred solution of the hydroperoxide (1.7a) (containing (1.7b) (4%)) (30.0 mg, 0.13 mmol) in benzene (12 ml) under an atmosphere of dry oxygen at 20°C in the dark. After 36 hrs, the solvent was removed under reduced pressure and the residue purified by preparative centrifugal chromatography on a silica rotor under an argon atmosphere, eluting with cold (0°C) hexane-ethyl acetate (4:1) to yield the *title compounds* (1.11a) and (1.11b) (28.2 mg, 82%, 3*E*:3*Z* = 85:15) as a colourless oil, each as an inseparable *ca.* 1:1.2 mixtures of diastereoisomers (*R_f* = 0.19; hexane-ethyl acetate (4:1)): found *M*⁺ 268.1685, C₁₅H₂₄O₄ requires 268.1675; λ_{max} (ε) (*n*-hexane) 251 sh. (13800), 261 (21800), 269 (27000), 279 (21500) nm; IR ν_{max} 3422, 2926, 1612, 1459, 1366, 1167, 1091, 986, 966 cm⁻¹; ¹H NMR (270 MHz, CDCl₃)

[(**1.11a**) major diastereoisomer] δ 7.74 (1H, s, -OOH), 6.58 (1H, dd, $J = 15.7, 11.0$ Hz, -CH=CH-CH=C(CH₃)-), 6.40 (1H, dd, $J = 17.4, 10.5$ Hz, -CH=CH₂), 6.09 (1H, d, $J = 11.2$ Hz, =CH-CH=C(CH₃)-), 5.93 (1H, d, $J = 15.6$ Hz, -C(CH₃)(OO)-CH=CH-), 5.23 (1H, d, $J = 17.4$ Hz, -CH=C(H)H), 5.06 (1H, d, $J = 10.5$ Hz, -CH=C(H)H), 4.25 (1H, m, (-CH₂)CH(-OO-)), 2.08-1.63 (4H, br.m, -CH₂-CH₂-), 1.89 (3H, s, =C(CH₃)-CH=CH₂), 1.30 (3H, s, (-CH₂)C(CH₃)(-OO-)), 1.26 (3H, s, -C(OOH)(CH₃)(CH₃)), 1.22 (3H, s, -C(OOH)(CH₃)(CH₃)) ppm; ¹³C NMR[†] (67.8 MHz, CDCl₃) δ 141.0 (C2), 136.8 (C6), 136.7 (C3), 130.7 (C4), 126.1 (C5), 112.8 (C1), 84.5 (C10), 83.2 (C11), 81.0 (C7), 33.6 (C8), 21.5 (C7-CH₃), 21.1 (C9), 21.0 (C12), 20.9 (C11-CH₃), 12.2 (C3-CH₃) ppm; ¹H NMR (270 MHz, CDCl₃) [(**1.11a**) minor diastereoisomer] δ 7.83 (1H, s, -OOH), 6.60 (1H, dd, $J = 15.6, 11.0$ Hz, -CH=CH-CH=C(CH₃)-), 6.42 (1H, dd, $J = 17.4, 10.5$ Hz, -CH=CH₂), 6.03 (1H, d, $J = 11.2$ Hz, =CH-CH=C(CH₃)-), 5.69 (1H, d, $J = 15.4$ Hz, -C(CH₃)(OO)-CH=CH-), 5.25 (1H, [partly obscured] d, $J = 17.4$ Hz, -CH=C(H)H), 5.08 (1H, [partly obscured] d, $J = 10.8$ Hz, -CH=C(H)H), 4.27 (1H, [partly obscured] m, (-CH₂)CH(-OO-)), 2.08-1.63 (4H, br.m, -CH₂-CH₂-), 1.88 (3H, s, =C(CH₃)-CH=CH₂), 1.50 (3H, s, (-CH₂)C(CH₃)(-OO-)), 1.25 (3H, [partly obscured], s, -C(OOH)(CH₃)(CH₃)), 1.22 (3H, s, -C(OOH)(CH₃)(CH₃)) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 140.9 (C2), 136.3 (C6), 135.3 (C3), 130.4 (C4), 126.4 (C5), 113.2 (C1), 84.6 (C10), 83.2 (C11), 80.0 (C7), 32.8 (C8), 26.8 (C7-CH₃), 21.0 (C12), 20.9 (C11-CH₃), 20.4 (C9), 12.2 (C3-CH₃) ppm; ¹H NMR (270 MHz, CDCl₃) [(**1.11b**) major diastereoisomer] δ 9.00 (1H, s, -OOH), 6.95 (1H, dd, $J = 17.1, 11.0$ Hz, -CH=CH₂), 6.72 (1H, dd, $J = 15.4, 11.4$ Hz, -CH=CH-CH=C(CH₃)-), remainder obscured; ¹H NMR (270 MHz, CDCl₃) [(**1.11b**) minor diastereoisomer] δ 8.92 (1H, s, -OOH), 6.94 (1H, dd, $J = 17.1, 11.0$ Hz, -CH=CH₂), 6.69 (1H, dd, $J = 15.4, 11.4$ Hz, -CH=CH-CH=C(CH₃)-), remainder obscured; MS m/z (rel. int. %) 268(1.3), 236(1), 220(1), 205(2), 193(5), 176(3), 149(4), 133(6), 119(10), 105(9), 93(18), 91(18), 86(30), 84(45), 77(17), 58(25), 43(100).

[†] Atom numbering as for hydroperoxide (**1.7a**).

1-Methyl-1-(6'-methyl-6'-(4''-methyl-1''*E*, 3''*E*, 5''-hexatrien-1''-yl)-1',2'-dioxan-3'-yl) ethan-1-ol (1.12a) and 1-methyl-1-(6'-methyl-6'-(4''-methyl-1''*E*, 3''*Z*, 5''-hexatrien-1''-yl)-1',2'-dioxan-3'-yl) ethan-1-ol (1.12b). (Scheme 1.13)

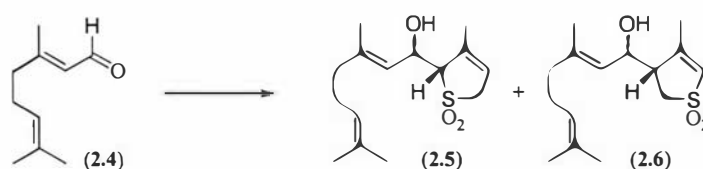


Triphenylphosphine (54.0 mg, 0.2 mmol) was added to a solution of the hydroperoxides (**1.11a**) and (**1.11b**) (49.0 mg, 0.2 mmol, 3*E*:3*Z* = 85:15, [each as a 1.2:1 mixture of diastereoisomers]) in benzene (10 ml) at rt under N₂. The reaction mixture was stirred for 5 min and the solvent removed under reduced pressure. The residue was purified immediately by preparative centrifugal chromatography on a silica rotor under an argon atmosphere, eluting with cold (0°C) hexane-ethyl acetate (4:1) to yield the *title compounds* (**1.12a**) and (**1.12b**) (85:15, 45 mg, 98%, 3*E*:3*Z* = 85:15) each as an inseparable *ca.* 1.2:1 mixture of diastereoisomers (R_f = 0.12; hexane-ethyl acetate (4:1)): found M⁺ 252.1724, C₁₅H₂₄O₃ requires 252.1725; λ_{max} (ε) (*n*-hexane) 250 sh. (9300), 260 (15400), 269 (19300), 279 (15400) nm; IR ν_{max} 3424, 2925, 1614, 1451, 1378, 1169, 1089, 985, 965 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) [(**1.12a**) major diastereoisomer] δ 6.55 (1H, dd, J = 15.8, 11.2 Hz, -CH=CH-CH=C(CH₃-), 6.42 (1H, dd, J = 17.4, 10.6 Hz, -CH=CH₂), 6.09 (1H, d, J = 11.2 Hz, =CH-CH=C(CH₃-), 5.94 (1H, d, J = 15.8 Hz, -C(CH₃)(OO)-CH=CH-), 5.23 (1H, d, J = 17.4 Hz, -CH=C(H)H), 5.06 (1H, d, J = 10.7 Hz, -CH=C(H)H), 3.95-3.86 (1H, m, (-CH₂-)CH(-OO-), 2.07-1.61 (4H, br.m, -CH₂-CH₂-), 1.89 (3H, s, =C(CH₃)-CH=CH₂), 1.26 (4H, [partly obscured], br.s, (-CH₂-)C(CH₃)(-OO-), -OH), 1.21 (3H, s, -C(OH)(CH₃)CH₃) 1.16 (3H, s, -C(OH)(CH₃)CH₃) ppm; ¹³C NMR[†] (67.8 MHz, CDCl₃) δ 141 (C2), 137.0 (C6), 136.6 (C3), 130.8 (C4), 126.0 (C5), 112.7 (C1), 86.8 (C10), 80.9 (C7), 71.8 (C11), 33.6 (C8), 26.1 (C12), 24.9 (C11-CH₃), 21.6 (C7-CH₃), 20.2 (C9), 12.2 (C3-CH₃) ppm; ¹H NMR (270 MHz, CDCl₃) [(**1.12a**) minor diastereoisomer] δ 6.60 (1H, dd, J = 15.6, 11.2 Hz, -CH=CH-CH=C(CH₃-), 6.41 (1H, dd, J = 17.4, 10.6 Hz, -CH=CH₂), 6.04 (1H, d, J = 11.2 Hz, =CH-CH=C(CH₃-), 5.69 (1H, d, J = 15.2 Hz, -C(CH₃)(OO)-CH=CH-), 5.25

[†] Atom numbering as for hydroperoxide (**1.7a**).

8.1 Hz, =CH-CHO), 5.05-5.00 (1H, m, =CH-CH₂-), 2.18-2.12 (4H, m, -CH₂-CH₂-), 2.12 (3H, s, -C(CH₃)=CH-CHO), 1.64 (3H, s, =C(CH₃)CH₃), 1.56 (3H, s, =C(CH₃)CH₃) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 191.0, 168.6, 132.8, 127.3, 122.4, 40.6, 25.8, 25.7, 17.8, 17.7 ppm; MS *m/z* (rel. int. %) 152(4), 137(5), 123(5), 109(6), 94(12), 84(21), 69(100), 53(8), 41(91).

2-(1'-Hydroxy-3',7'-dimethylocta-2'E,6'-dien-1'-yl)-3-methyl-2,5-dihydrothiophene-1,1-dioxide (2.5) and 3-(1'-hydroxy-3',7'-dimethylocta-2'E,6'-dien-1'-yl)-4-methyl-2,3-dihydrothiophene-1,1-dioxide (2.6). (Scheme 2.3)



A solution of lithium hexamethyldisilazide (1.3 mmol) in THF-hexanes [prepared by the dropwise addition of BuLi (1.59 M [hexanes], 0.79 ml, 1.3 mmol) to a solution of hexamethyldisilazane (0.20 g, 1.3 mmol) in THF (3.0 ml) at 0°C under N₂] was added dropwise to a stirred solution of 3-methyl-2,5-dihydrothiophene-1,1-dioxide (**1.23**)⁹⁹ (0.150 g, 1.13 mmol) and geranial (**2.4**) (0.173 g, 1.13 mmol) in THF (7.0 ml) at -90°C under N₂. The reaction was quenched after 15 min at -90°C by the addition of saturated NH₄Cl solution (2 ml) and warmed to rt, whereupon water (10 ml) was added the mixture extracted with ether (3x20 ml). The combined ethereal extracts were washed with sat. brine (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (2:1) to yield recovered geranial (**2.4**) (30.2 mg, 18%) followed by 2-(1'-hydroxy-3',7'-dimethylocta-2'E,6'-dien-1'-yl)-3-methyl-2,5-dihydrothiophene-1,1-dioxide (**2.5**) (0.119 g, 37%) as a pale yellow viscous oil as an inseparable *ca.* 2:1 mixture of diastereoisomers (R_f = 0.20; hexane-ethyl acetate (2:1)): found M⁺ 284.1446, C₁₅H₂₄O₃S requires 284.1446; IR ν_{max} (thin film) 3500, 2921, 1666, 1444, 1306, 1113 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) [major diastereoisomer] δ 5.78 (1H, br.s, =CHCH₂SO₂-), 5.50 (1H, d, J = 9.0 Hz, =CH-CH(OH)-), 5.06 (1H [partly obscured], m, (CH₃)₂C=CH-), 4.74 (1H, m, =CH-CH(OH)-CH), 3.80-3.70 (2H [partly obscured], m, =CHCH₂SO₂-), 3.57 (1H, m, -CH(OH)-CH(SO₂R)-C(CH₃)=), 2.15-2.03 (4H [partly

obscured], m, $-\text{CH}_2\text{-CH}_2\text{-}$), 1.92 (3H [partly obscured], s, $-\text{C}(\text{CH}_3)=\text{CH-}$), 1.71 (3H [partly obscured], s, $-\text{C}(\text{CH}_3)=\text{CH-}$), 1.68 (3H [partly obscured], s, $=\text{C}(\text{CH}_3)\text{CH}_3$), 1.60 (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) [major diastereoisomer] δ 141.4, 136.8, 131.8, 123.5, 122.6, 118.9, 72.3, 66.8, 56.1, 39.6, 26.2, 25.7, 19.1, 17.8, 16.9 ppm; MS m/z (rel. int. %) 284(0.2), 266(0.3), 220(0.6), 219(1), 202(6), 159(5), 153(15), 134(9), 119(11), 95(13), 69(100), 59(9), 41(49). Further elution gave 3-(1'-hydroxy-3',7'-dimethylocta-2'E,6'-dien-1'-yl)-4-methyl-2,3-dihydro-thiophene-1,1-dioxide (**2.6**) (0.112 g, 35%) as a pale yellow viscous oil as an inseparable *ca.* 1:1 mixture of diastereoisomers ($R_f = 0.15$; hexane-ethyl acetate (2:1)): found $M+H^+$ 285.1563, $\text{C}_{15}\text{H}_{25}\text{O}_3\text{S}$ requires 285.1524; IR ν_{max} (thin film) 3479, 2967, 2919, 2855, 1665, 1630, 1439, 1291, 1146, 912, 733 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.38 and 6.31 [each one diastereoisomer] (1H, m, $=\text{CHSO}_2\text{-}$), 5.22 and 5.14 [each one diastereoisomer] (1H, br.d, $J = 9.2$ Hz, $-\text{CH}(\text{OH})\text{CH}=\text{C}$), 5.02 [both diastereoisomers] (1H, m, $(\text{CH}_3)_2\text{C}=\text{CH-}$), 4.76 (1H, dd, $J = 8.3, 3.3$ Hz, $-\text{CH}(\text{OH})\text{-}$), 4.67 (1H, dd, $J = 9.2, 6.8$ Hz, $-\text{CH}(\text{OH})\text{-}$) 3.45-3.03 [each one diastereoisomer] (4H, br.m, $-\text{SO}_2\text{CH}_2\text{CHR}$, $-\text{OH}$), 2.05 [each one diastereoisomer] (4H, m, $-\text{CH}_2\text{-CH}_2\text{-}$), 2.01 [both diastereoisomers] (3H [partly obscured], s, $\text{C}(\text{CH}_3)=\text{CH-}$) 1.73 and 1.71 [each one diastereoisomer] (3H, d, $J = 1.3$ Hz, $-(\text{CH}_3)\text{C}=\text{CHSO}_2\text{-}$), 1.59 [both diastereoisomers] (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$), 1.56 [both diastereoisomers] (3H, s, $=\text{C}(\text{CH}_3)\text{CH}_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) [both diastereoisomers] δ 153.2, 152.3, 142.6, 141.0, 131.9, 131.8, 128.3, 127.4, 124.1, 123.3, 123.1, 69.1, 66.2, 52.3, 50.2, 49.0, 48.5, 39.6, 39.5, 26.2, 26.1, 25.6, 18.5, 17.8, 17.1, 16.9, 16.9 ppm; MS m/z (rel. int. %) 284(3), 266(2), 210(6), 199(7), 153(9), 135(27), 95(10), 69(100), 41(55).

3,7,11-Trimethyldodeca-1,3E,6E,10-tetraen-5-ol (**2.1**). (Scheme 2.5)



This is a modification of the procedure by Brimble *et al.*⁵⁶ A solution of 2-(1'-hydroxy-3',7'-dimethylocta-2'E,6'-dien-1'-yl)-3-methyl-2,5-dihydro thiophene-1,1-dioxide (**2.5**) [as a *ca.* 2:1 mixture of diastereoisomers] (117 mg, 0.41 mmol) and DBU (62 mg, 0.41

mmol) in xylene (5.0 ml) was heated to reflux for 15 min under N₂. The reaction mixture was cooled to rt and sat. aq. KH₂PO₄ (5 ml) and water (5 ml) were added. The two phase system was extracted with ether (3x20 ml) and the combined ethereal extracts were washed with sat. brine (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (5:1)-triethylamine (0.1%), to yield the *title compound* (**2.1**) (45 mg, 50%) as a colourless oil (R_f = 0.30; hexane-ethyl acetate (5:1)-triethylamine (0.1%)): found M⁺ 220.1833, C₁₅H₂₄O requires 220.1827; IR ν_{max} (thin film) 3333, 2923, 1666, 1606, 1444, 1377, 989 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 6.37 (1H, dd, J = 17.4, 10.8 Hz, -CH=CH₂), 5.53 (1H, m, -CH(OH)-), 5.25 (2H, d, J = 5.3 Hz, =CH-CH(OH)-CH=), 5.21 (1H, d, J = 17.4 Hz, -CH=C(H)H), 5.08 (1H, m, (CH₃)₂C=CH-), 5.06 (1H, d, J = 10.8 Hz, -CH=C(H)H), 2.15-2.00 (4H, m, -CH₂-CH₂-), 1.83 (3H, s, -C(CH₃)=CH-), 1.74 (3H, s, -C(CH₃)=CH-), 1.68 (3H, s, =C(CH₃)CH₃), 1.60 (3H, s, =C(CH₃)CH₃) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 140.9, 140.7, 138.5, 134.6, 133.6, 125.9, 123.7, 112.9, 65.6, 39.6, 26.4, 25.9, 25.5, 17.0, 16.6 ppm; MS *m/z* (rel. int. %) 220(2), 202(12), 159(35), 133(24), 119(22), 105(40), 91(37), 81(33), 69(100), 55(30), 41(80).

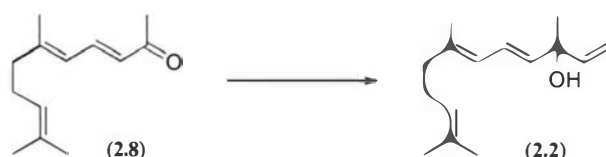
6,10-Dimethylundeca-3*E*,5*E*,9-trien-2-one (*pseudoionone*) (**17**).¹⁰⁶ (Scheme 2.7)



Geranial (**2.4**) (17.76 g, 0.117 mol) was added to a slurry of Ba(OH)₂·8H₂O (1.0 g, 3.2 mmol) in acetone (150 ml) and the resulting mixture was heated to reflux for 2 hrs through a soxhlet extractor containing freshly activated 4Å molecular sieves under an atmosphere of dry N₂. The pale yellow reaction mixture was cooled to rt, diluted with ether (100 ml), washed with dilute HCl (2% v/v, 50 ml) then water (3x50 ml) and sat. brine (50 ml), dried over MgSO₄, filtered under reduced pressure and concentrated *in vacuo* to give an oil that was purified by short path distillation (Kugelrohr) to yield the *title compound* (**2.8**) (18.34 g, 82%) as a pale yellow oil (R_f = 0.13 in hexane-dichloromethane-ethyl acetate (40:20:1)), b.p. 110-111°C/1.5 mmHg (lit. b.p.¹⁰⁶ 114-

116/2.0 mmHg): Found 192.1516, $C_{13}H_{20}O$ requires 192.1514; IR ν_{\max} (thin film) 2916, 1666, 1631, 1588, 1440, 1361, 1254, 977 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 7.43 (1H, dd, $J = 15.4, 11.4$ Hz, =CH-CH=CH-C=O), 6.08 (1H, d, $J = 15.4$ Hz, -CH=CH-C=O), 6.01 (1H, d, $J = 11.4$ Hz, =CH-CH=CH-C=O), 5.08 (1H, m, $(CH_3)_2C=CH-$), 2.28 (3H, s, -C(O)- CH_3), 2.17 (4H, m, - CH_2-CH_2-), 1.92 (3H, s, - $CH_2-C(CH_3)=CH-$), 1.70 (3H s, =C(CH_3) CH_3), 1.61 (3H, s, =C(CH_3) CH_3) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 198.6, 151.0, 139.5, 132.2, 128.3, 123.6, 123.1, 40.5, 27.6, 26.4, 25.8, 17.8, 17.6 ppm; MS m/z (rel. int. %) 192(4), 177(1), 149(4), 124(27), 109(30), 81(47), 69(100), 53(7), 43(44), 41(87).

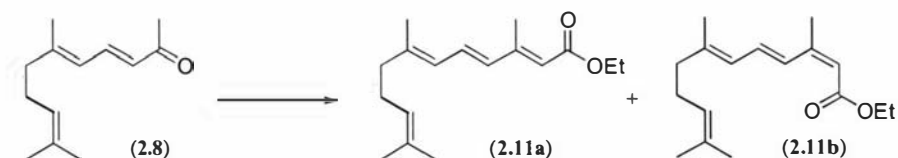
3,7,11-Trimethyldodeca-1,4E,6E,10-tetraen-3-ol (2.2). (Scheme 2.7)



A solution of vinyl magnesium bromide (10.1 mmol) in THF was added dropwise to a stirred solution of pseudoionone (**2.8**) (1.3 g, 6.7 mmol) in THF (40 ml) at $0^\circ C$ under N_2 . The reaction was quenched after 30 min by the addition of sat. aq. KH_2PO_4 solution (30 ml) and extracted with ether (3x30 ml). The combined ethereal extracts were washed with water (50 ml), sat. brine (50 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (6:1) to yield the *title compound* (**2.2**) (1.05 g, 71%) as a viscous, colourless oil ($R_f = 0.27$; hexane-ethyl acetate (6:1)): found M^+ 220.1824, $C_{15}H_{24}O$ requires 220.1827; IR ν_{\max} (thin film) 3387, 2924, 1654, 1424 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 6.47 (1H, dd, $J=15.4, 10.8$ Hz, =CH-CH=CH-), 6.00 (1H, dd, $J = 17.4, 10.6$ Hz, -CH=CH $_2$), 5.84 (1H, br.d, $J = 10.8$ Hz, -C(CH_3)=CH-CH=), 5.69 (1H, d, $J = 15.4$ Hz, =C-CH=CH-C(OH)), 5.27 (1H, d, $J = 17.4$ Hz, -CH=C(H)H), 5.10 (1H, m, $(CH_3)_2C=CH-$), 5.09 (1H, d, $J = 10.8$ Hz, -CH=C(H)H), 2.17-2.05 (4H, m, - CH_2-CH_2-), 1.78 (3H, s, - $CH_2-C(CH_3)=CH-$), 1.70 (3H s, =C(CH_3) CH_3), 1.62 (3H, s, =C(CH_3) CH_3), 1.42 (3H, s, -C(CH_3)OH) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 143.8, 139.5, 136.1, 131.6, 124.5, 123.8(x2), 112.0, 73.3, 40.0, 28.2, 26.6, 25.8, 17.8,

16.9 ppm; MS m/z (rel. int. %) 220(10), 202(10), 177(7), 159(13), 137(7), 133(17), 119(10), 109(18), 107(18), 105(22), 93(36), 81(24), 69(72), 55(20), 43(100).

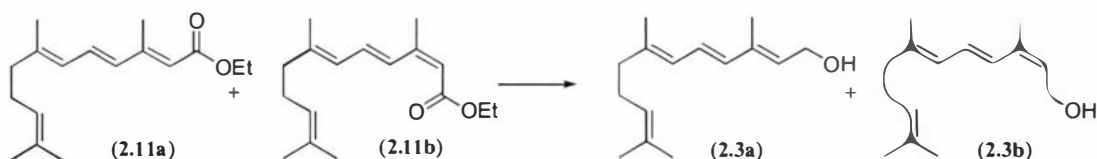
Ethyl-3,7,11-trimethyldodeca-2*E*,4*E*,6*E*,10-tetraenoate (2.11a) and ethyl-3,7,11-trimethyldodeca-2*Z*,4*E*,6*E*,10-tetraenoate (2.11b). (Scheme 2.8)



Triethylphosphonoacetate (**2.12**) (0.87 g, 3.9 mmol) was added dropwise to a stirred suspension of hexane-washed sodium hydride (94 mg, 3.9 mmol) in toluene (10 ml) under N_2 at $0^\circ C$. Pseudoionone (**2.8**) (0.5 g, 2.6 mmol) was added and the mixture was heated to reflux. After 5 hrs the reaction was quenched by the addition of water (20 ml) and the resulting yellow emulsion was extracted with ether (3x30 ml). The combined ethereal extracts were washed with sat. brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-dichloromethane-ethyl acetate (40:20:1) to yield recovered pseudoionone (**2.8**) (0.2 g, 40%) and the *title compounds* (**2.11a**) and (**2.11b**) (0.336 g, 49%) as a *ca.* 4:1 mixture of 2*E*:2*Z* isomers. The *title compounds* (**2.11a**) and (**2.11b**) were separated by preparative centrifugal chromatography on silica rotors, eluting with hexane-dichloromethane-ethyl acetate (40:20:1) to give, firstly, (**2.11b**) as a colourless oil ($R_f = 0.33$; hexane-dichloromethane-ethyl acetate (40:20:1)): found M^+ 262.1925, $C_{17}H_{26}O_2$ requires 262.1933; IR ν_{max} (thin film) 2925, 1710, 1604, 1238, 1150, 1044, 960 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 7.65 (1H, d, $J = 15.4$, =CH-CH=CH-C(CH₃)=), 6.85 (1H, dd, $J = 15.4, 11.2$ Hz, =CH-CH=CH-C(CH₃)=), 6.07 (1H, d, $J = 11.2$ Hz, -C(CH₃)=CH-CH=CH-), 5.62 (1H, s, =CH-CO₂R), 5.11-5.08 (1H, m, (CH₃)₂C=CH-), 4.17 (2H, q, $J = 7.0$ Hz, -CO₂CH₂CH₃), 2.14 (4H, br.s, -CH₂-CH₂-), 2.05 (3H, s, -C(CH₃)=CH-CO₂R), 1.85 (3H, s, -C(CH₃)=CH-), 1.70 (3H, s, =C(CH₃)CH₃), 1.62 (3H, s, =C(CH₃)CH₃), 1.30 (3H, t, $J = 7.0$ Hz, -CO₂CH₂CH₃) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 166.3, 151.3, 144.0, 132.2, 131.9, 127.4, 125.5, 123.6, 116.0, 59.6, 40.3, 26.6, 25.8, 21.1, 17.8, 17.3, 14.5 ppm; MS m/z (rel. int. %) 262(22), 217(8), 193(29), 169(9), 147(100), 121(27), 119(58), 105(26), 91(16), 69(44), 41(37). Further elution gave (**2.11a**), also as a colourless oil ($R_f = 0.29$; hexane-

dichloromethane-ethyl acetate (40:20:1)): found M^+ 262.1924, $C_{17}H_{26}O_2$ requires 262.1933; IR ν_{\max} (thin film) 2925, 1710, 1607, 1235, 1152, 1053, 975 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 6.85 (1H, dd, $J = 15.2, 11.0$ Hz, $=CH-CH=CH-C(CH_3)=$), 6.18 (1H, d, $J = 15.2$, $=CH-CH=CH-C(CH_3)=$), 5.97 (1H, d, $J = 11.0$ Hz, $-C(CH_3)=CH-CH=CH-$), 5.75 (1H, s, $=CH-CO_2R$), 5.14-5.07 (1H, m, $(CH_3)_2C=CH-$), 4.17 (2H, q, $J = 7.0$ Hz, $-CO_2CH_2CH_3$), 2.34 (3H, s, $-C(CH_3)=CH-CO_2R$), 2.14 (4H, br.s, $-CH_2-CH_2-$), 1.85 (3H, s, $-C(CH_3)=CH-$), 1.70 (3H, s, $=C(CH_3)CH_3$), 1.62 (3H, s, $=C(CH_3)CH_3$), 1.30 (3H, t, $J = 7.0$ Hz, $-CO_2CH_2CH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 167.1, 152.8, 143.7, 133.3, 131.9, 131.0, 124.8, 123.5, 117.9, 59.6, 40.3, 26.6, 25.8, 17.8, 17.3, 14.5, 13.9 ppm; MS m/z (rel. int. %) 262(25), 217(9), 193(32), 169(11), 147(100), 121(30), 119(65), 105(28), 91(18), 69(57), 41(52).

3,7,11-Trimethyldodeca-2E,4E,6E,10-tetraen-1-ol (2.3a) and 3,7,11-trimethyldodeca-2Z,4E,6E,10-tetraen-1-ol (2.3b). (Scheme 2.9)



Diisobutylaluminium hydride (1.5 M [toluene], 1.26 ml, 1.9 mmol) was added dropwise to a stirred solution of the isomeric ethyl esters (2.3a) and (2.3b) (0.226 g, 0.86 mmol) in CH_2Cl_2 (5.0 ml) at $-78^\circ C$ under N_2 . The reaction mixture was warmed to $-50^\circ C$ over 15 mins and quenched by the addition of 2% NaOH (1.0 ml). After warming to rt, sat. aq. Rochelle's salt [potassium sodium tartrate] (5.0 ml) was added and the reaction mixture was extracted with CH_2Cl_2 (3x10 ml). The combined organic extracts were washed with water (20 ml), sat. brine (20 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (3:1) to yield 3,7,11-trimethyldodeca-2Z,4E,6E,10-tetraen-1-ol (2.3b) (45.9mg 24%) as a colourless oil ($R_f = 0.38$; hexane-ethyl acetate (3:1)): found M^+ 220.1825, $C_{15}H_{24}O$ requires 220.1827; IR ν_{\max} (thin film) 3354, 2920, 1626, 1484, 1424, 1378, 1000, 957 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 6.52 (2H, m, $=CH-CH=CH-C(CH_3)=$), 5.96 (1H, m, $=CH-CH=CH-C(CH_3)=$), 5.54 (1H, t, $J = 7.0$ Hz, $=CH-CH_2OH$), 5.14-5.08 (1H, m, $(CH_3)_2C=CH-$), 4.31 (2H, d, $J = 7.0$ Hz,

-CH₂OH), 2.12 (4H, br.s, -CH₂-CH₂-), 1.92 (3H, s, -C(CH₃)=CH-), 1.82 (3H, s, -C(CH₃)=CH-), 1.70 (3H, s, =C(CH₃)CH₃), 1.63 (3H, s, =C(CH₃)CH₃), 1.32 (1H, s, -OH) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 140.6, 135.9, 131.7, 127.2, 127.1, 126.3, 125.1, 123.7, 58.5, 40.2, 26.7, 25.8, 20.5, 17.8, 17.0 ppm; MS *m/z* (rel. int. %) 220(62), 202(22), 189(6), 159(27), 151(49), 145(9), 133(72), 123(34), 121(43), 107(76), 105(76), 95(18), 93(55), 91(59), 79(28), 69(70), 55(35), 41(100). Further elution gave 3,7,11-trimethyldodeca-2*E*,4*E*,6*E*,10-tetraen-1-ol (**2.3a**) (0.138 g, 73%) as a colourless oil (*R_f* = 0.33; hexane-ethyl acetate (3:1)): found *M*⁺ 220.1829, C₁₅H₂₄O requires 220.1827; IR *v*_{max} (thin film) 3288, 2924, 1624, 1483, 1449, 1390, 1000, 955 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 6.47 (1H, dd, *J* = 15.2, 10.8 Hz, =CH-CH=CH-C(CH₃)=), 6.17 (1H, d, *J* = 15.2 Hz, -CH=CH-C(CH₃)=), 5.91 (1H, d, *J* = 10.8 Hz, -C(CH₃)=CH-CH=CH-), 5.65 (1H, t, *J* = 7.0 Hz, =CH-CH₂OH), 5.13-5.08 (1H, m, (CH₃)₂C=CH-), 4.28 (2H, d, *J* = 7.0 Hz, -CH₂OH), 2.11 (4H, br.s, -CH₂-CH₂-), 1.85 (3H, s, -C(CH₃)=CH-), 1.81 (3H, s, -C(CH₃)=CH-), 1.70 (3H, s, =C(CH₃)CH₃), 1.62 (3H, s, =C(CH₃)CH₃), 1.47 (1H, s, -OH) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 139.6, 136.9, 134.2, 131.6, 128.9, 125.1, 125.0, 123.8, 59.5, 40.2, 26.7, 25.8, 17.8, 17.0, 12.7 ppm; MS *m/z* (rel. int. %) 220(61), 202(16), 189(4), 159(18), 151(45), 145(5), 133(60), 123(42), 121(44), 107(79), 105(66), 95(22), 93(47), 91(56), 79(26), 69(60), 55(32), 41(100).

6.3.2 Transposition Reactions.

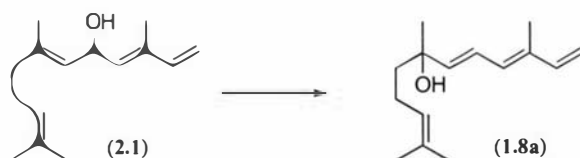
7-Hydroperoxy-3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraene (1.7a) from 3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraen-5-ol (2.1). (Table 2.1, entry 2)



p-Toluenesulfonic acid monohydrate (0.5 mg, 2.6×10⁻⁶ mol, 4 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraen-5-ol (**2.1**) (12.9 mg, 5.9×10⁻⁵ mol) in anhydrous H₂O₂/THF (0.89 M, 5.0 ml, 4.5 mmol, 76 equiv.) under an atmosphere of dry N₂ at rt. The solution was stirred for 5 min, diluted with water (10

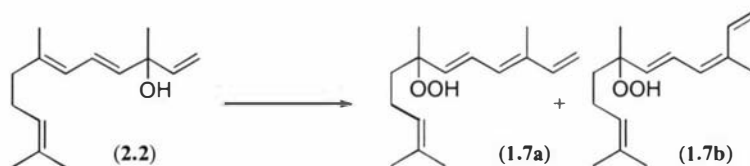
ml) and extracted with ether (2x10 ml). The combined ethereal extracts were washed with water (2x10 ml) then sat. brine (10 ml), dried over MgSO₄, filtered and concentrated *in vacuo* to give the *title compound* (1.7a) (13.8 mg, 100%; 3*E*:3*Z* = > 99:1) as a colourless oil.

3,7,11-Trimethyldodeca-1,3*E*,5*E*,10-tetraen-7-ol (1.8a) from 3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraen-5-ol (2.1). (Table 2.1, entry 3)



p-Toluenesulfonic acid monohydrate (0.5 mg, 2.6x10⁻⁶ mol, 6 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraen-5-ol (2.1) (9.8 mg, 4.4x10⁻⁵ mol) and water (60 mg, 3.3 mmol, 75 equiv.) in THF (5.0 ml) at rt under N₂. The solution was stirred for 5 min, diluted with water (10 ml) and extracted with ether (2x10 ml). The combined ethereal extracts were washed with sat. brine (10 ml), dried over MgSO₄, filtered and concentrated *in vacuo* to give the *title compound* (1.8a) (9.8 mg, 100%; 3*E*:3*Z* = > 99:1) as a colourless oil.

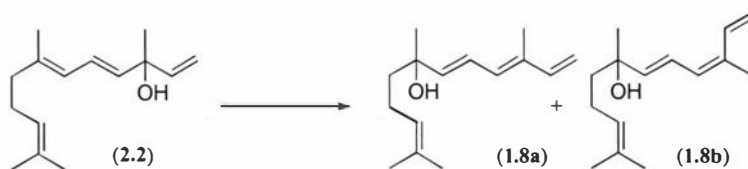
7-Hydroperoxy-3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraene (1.7a) and 7-hydroperoxy-3,7,11-trimethyldodeca - 1,3*Z*,5*E*,10-tetraene (1.7b) from 3,7,11-trimethyldodeca-1,4*E*,6*E*,10-tetraen-3-ol (2.2). (Table 2.1, entry 4)



p-Toluenesulfonic acid monohydrate (11.0 mg, 5.8x10⁻⁵ mol, 5 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,4*E*,6*E*,10-tetraen-3-ol (2.2) (0.250 g, 1.13 mmol) in anhydrous H₂O₂/THF (0.89 M, 95 ml, 85 mmol, 75 equiv.) under an atmosphere of dry N₂ at rt. The solution was stirred for 6 hrs, diluted with water (50 ml), worked up as described above and purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (10:1) to yield the *title compounds* (1.7a) and (1.7b) (0.254 g, 95%, 3*E*:3*Z*

= 73:27) as an inseparable mixture of isomers. NMR data for the 3*Z*-isomer (**1.7b**): ¹H NMR (270 MHz, CDCl₃) δ 7.53 (1H, s, OOH), 6.96 (1H, dd, J = 17.1, 10.8 Hz, -CH=CH₂), 6.71 (1H, dd, J = 15.6, 11.2 Hz, -CH=CH-CH=C(CH₃-), 6.01 (1H, d, J = 11.2 Hz, =CH-CH=C(CH₃-), 5.70 (1H, d, J = 15.6 Hz, -C(OOH)-CH=CH-), 5.28 (1H, d, J = 17.1 Hz, -CH=C(H)H), 5.18 (1H, d, J = 10.8 Hz, -CH=C(H)H), 5.17-5.06 (1H, m, (CH₃)₂C=CH-), 2.04-1.98 (2H, m, (CH₃)₂C=CH-CH₂-), 1.91 (3H, s, =C(CH₃)-CH=CH₂), 1.77-1.66 (2H, m, -CH₂-C(OOH)), 1.69 (3H s, =C(CH₃)CH₃), 1.62 (3H, s, =C(CH₃)CH₃), 1.39 (3H, s, -C(CH₃)(OOH)-) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 135.5 (C6), 134.6 (C3), 133.0 (C2), 132.0 (C11), 129.0 (C4), 125.8 (C5), 124.0 (C10), 114.7 (C1), 84.6 (C7), 37.7 (C8), 25.7 (C12), 22.5 (C9), 21.8 (C7-CH₃), 19.9 (C3-CH₃), 17.7 (C11-CH₃) ppm.

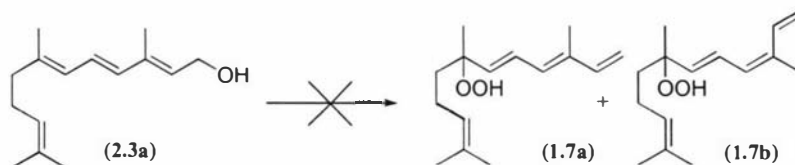
3,7,11-Trimethyldodeca-1,3*E*,5*E*,10-tetraen-7-ol (1.8a) and 3,7,11-trimethyldodeca-1,3*Z*,5*E*,10-tetraen-7-ol (1.8b) from 3,7,11-trimethyldodeca-1,4*E*,6*E*,10-tetraen-3-ol (2.2). (Table 2.1, entry 5)



p-Toluenesulfonic acid monohydrate (11 mg, 5.8x10⁻⁵ mol, 5 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,4*E*,6*E*,10-tetraen-3-ol (**2.2**) (0.257 g, 1.17 mmol) and water (1.58 g, 87 mmol, 74 equiv.) in THF (130 ml) at rt under N₂. The solution was stirred for 6 hrs, diluted with water (50 ml), worked up as described above and purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) to yield the *title compounds* (**1.8a**) and (**1.8b**) (0.246 g, 96%, 3*E*:3*Z* = 72:28) as an inseparable mixture of isomers. NMR data for the 3*Z*-isomer (**1.8b**): ¹H NMR (270 MHz, CDCl₃) δ 6.99 (1H, dd, J = 17.4, 10.8 Hz, -CH=CH₂), 6.72 (1H, dd, J = 15.2, 11.2 Hz, -CH=CH-CH=C(CH₃-), 6.01 (1H, d, J = 11.2 Hz, =CH-CH=C(CH₃-), 5.74 (1H, d, J = 15.2 Hz, -C(OH)-CH=CH-), 5.26(1H, d, J = 17.4 Hz, -CH=C(H)H), 5.15-5.09 (2H, m, (CH₃)₂C=CH- and -CH=C(H)H), 2.08-1.98 (2H, m, (CH₃)₂C=CH-CH₂-), 2.00 (1H, s, -OH), 1.88 (3H, s, =C(CH₃)-CH=CH₂), 1.68 (3H s, =C(CH₃)CH₃), 1.66-1.54 (2H, m, -CH₂-C(OH)), 1.60 (3H, s, =C(CH₃)CH₃), 1.31 (3H, s, -C(CH₃)(OH)) ppm; ¹³C NMR

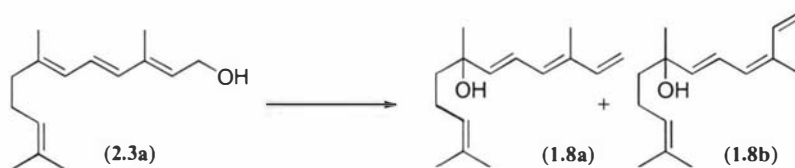
(67.8 MHz, CDCl_3) δ 140.1 (C6), 133.3 (C3), 133.1 (C2), 131.6 (C11), 129.1 (C4), 124.2 (C10), 122.3 (C5), 114.0 (C1), 73.2 (C7), 42.4 (C8), 28.2 (C7- CH_3), 25.6 (C12), 22.9 (C9), 19.8 (C3- CH_3), 17.7 (C11- CH_3).

Attempted hydroperoxidation of 3,7,11-trimethyldodeca-2*E*,4*E*,6*E*,10-tetraen-1-ol (2.3a). (Table 2.1, entry 6)



p-Toluenesulfonic acid monohydrate (26.6 mg, 1.4×10^{-4} mol, 2.0 equiv.) was added to a solution of 3,7,11-trimethyldodeca-2*E*,4*E*,6*E*,10-tetraen-1-ol (**2.3a**) (15.4 mg, 7.0×10^{-5} mol) in anhydrous $\text{H}_2\text{O}_2/\text{THF}$ (0.89 M, 6.0 ml, 5.3 mmol, 75 equiv.) under an atmosphere of dry N_2 at rt. The reaction was monitored by tlc. Trace quantities of 7-hydroperoxy-3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraene (**1.7a**) and 7-hydroperoxy-3,7,11-trimethyl-dodeca-1,3*Z*,5*E*,10-tetraene (**1.7b**) could be detected by comparison with authentic material. The solution was stirred for 6 hrs, diluted with water (10 ml), worked up as described above and purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (10:1) to yield a colourless mobile oil, identified as 6-methyl-5-hepten-2-one (**1.27**) (2 mg, 23%) by comparison with authentic material (Aldrich).

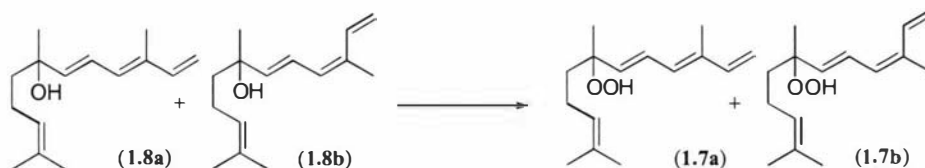
3,7,11-Trimethyldodeca-1,3*E*,5*E*,10-tetraen-7-ol (1.8a) and 3,7,11-trimethyldodeca-1,3*Z*,5*E*,10-tetraen-7-ol (1.8b) from 3,7,11-trimethyldodeca-2*E*,4*E*,6*E*,10-tetraen-1-ol (2.3a). (Table 2.1, entry 7)



p-Toluenesulfonic acid monohydrate (0.122 g, 0.64 mol, 2.0 equiv.) was added to a solution of 3,7,11-trimethyldodeca-2*E*,4*E*,6*E*,10-tetraen-1-ol (**2.3a**) (70.6 mg, 0.32 mmol) and water (0.58 g, 32 mmol, 100 equiv.) in THF (25 ml) at rt under N_2 . The solution was stirred for 6 hrs, diluted with water (25 ml) and extracted with ether (2x25 ml). The combined ethereal extracts were washed with sat. brine (30 ml), dried over

MgSO₄, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) to give, firstly, 3 elimination products, tentatively assigned as (2.12a), (2.12b) and (2.13) (5mg, 8%) (Scheme 2.10) as a colourless oil: found (GCMS) M⁺ 202.1720; M⁺ 202.1718; M⁺ 202.1720, C₁₅H₂₂ requires 202.1722); ¹H NMR (270 MHz, CDCl₃) [as mixture] δ 7.08-6.94 (m), 6.82-5.89 (br.m), 5.57-4.91 (br.m), 2.86 (br.q, J = 7.4 Hz), 2.35-2.12 (br.m), 1.91 (br.s), 1.83 (m), 1.72 (br.s), 1.66 (br.s), 1.64 (br.s), 1.45 (s), 1.27 (s) ppm; ¹³C NMR (67.8 MHz, CDCl₃) [as mixture] δ 141.3, 141.2, 141.1, 138.6, 135.6, 135.5, 134.6, 134.3, 132.8, 132.4, 132.2, 132.1, 132.0, 131.7, 130.6, 130.5, 130.3, 125.4, 125.0, 124.9, 124.6, 124.0, 122.5, 122.4, 122.0, 115.9, 112.4, 112.3, 111.7, 32.3, 30.4, 27.7, 27.2, 26.8, 26.8, 25.8, 25.8, 20.6, 18.7, 17.9, 17.9, 12.6, 12.3, 12.2 ppm. Further elution gave the *title compounds* (1.8a) and (1.8b) (5.0 mg, 15%, 3*E*:3*Z* = 87:13) as a colourless oil as an inseparable mixture of isomers. Further elution gave recovered starting material (2.3a) (40.0 mg, 56%).

7-Hydroperoxy-3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraene (1.7a) and 7-hydroperoxy-3,7,11-trimethyldodeca-1,3*Z*,5*E*,10-tetraene (1.7b) from 3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraen-7-ol (1.8a) and 3,7,11-trimethyldodeca-1,3*Z*,5*E*,10-tetraen-7-ol (1.8b). (Table 2.1, entry 8)



p-Toluenesulfonic acid monohydrate (2.3 mg, 1.2x10⁻⁵ mol, 5 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraen-7-ol (1.8a) and 3,7,11-trimethyldodeca-1,3*Z*,5*E*,10-tetraen-7-ol (1.8b) (53.7 mg, 0.24 mmol; 3*E*:3*Z* = 72:28) in anhydrous H₂O₂/THF (0.89 M, 20.5 ml, 18.2 mmol, 75 equiv.) under an atmosphere of dry N₂ at rt. The solution was stirred for 48 hrs, diluted with water (40 ml) and extracted with ether (2x30 ml). The combined ethereal extracts were washed with water (2x30 ml) then sat. brine (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo* to give an oil that was purified by preparative centrifugal chromatography on a silica gel rotor eluting with hexane-ethyl acetate (6:1) to yield recovered 3,7,11-trimethyldodeca-1,3,5*E*,10-tetraen-7-ol (1.8a) and 3,7,11-trimethyldodeca-1,3*Z*,5*E*,10-tetraen-7-ol (1.8b)

(15.0 mg, 26%, 3*E*:3*Z* = 73:27) and the *title compounds* (1.7a) and (1.7b) (30.5 mg, 53%, 3*E*:3*Z* = 69:31) as a colourless oil.

7-Methoxy-3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraene (2.17a) from 3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraen-5-ol (2.1). (Table 2.3, entry 1)



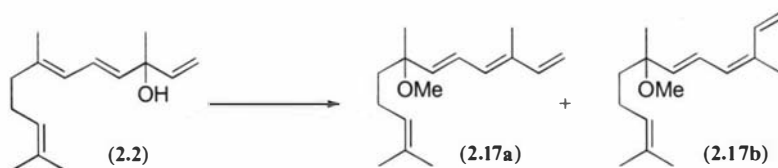
p-Toluenesulfonic acid monohydrate (1.0 mg, 5×10^{-6} mol, 5 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraen-5-ol (2.1) (22 mg, 9.9×10^{-5} mol) and methanol (0.237 g, 7.41 mmol, 75 equiv.) in anhydrous THF (4.7 ml) under an atmosphere of dry N_2 at rt. The solution was stirred for 5 min, diluted with water (10 ml) and extracted with ether (2x10 ml). The combined ethereal extracts were washed with sat. brine (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (6:1) to yield the *title compound* (2.17a) (19 mg, 82%, 3*E*:3*Z* = > 99:1) as a colourless oil (R_f = 0.60; hexane-ethyl acetate (6:1)): found M^+ 234.1987, $C_{16}H_{26}O$ requires 234.1983; λ_{max} (ϵ) (*n*-hexane) 251 sh. (20100), 261 (34200), 270 (45500), 281 (36000) nm; IR ν_{max} (thin film) 2928, 1614, 1450, 1375, 1085 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 6.48 (1H, dd, J = 15.6, 11.0 Hz, $-CH=CH-CH=C(CH_3)-$), 6.42 (1H, dd, J = 17.2, 10.8 Hz, $-CH=CH_2$), 6.10 (1H, d, J = 11.0 Hz, $=CH-CH=C(CH_3)-$), 5.67 (1H, d, J = 15.6 Hz, $C(OCH_3)-CH=CH-$), 5.23 (1H, d, J = 17.2 Hz, $CH=C(H)H$), 5.13-5.08 (1H, m, $(CH_3)_2C=CH-$), 5.05 (1H, d, J = 10.8 Hz, $-CH=C(H)H$), 3.17 (3H, s, $-OCH_3$), 2.03-1.94 (2H, m, $(CH_3)_2C=CH-CH_2-$), 1.89 (3H, s, $=C(CH_3)-CH=CH_2$), 1.68 (3H s, $=C(CH_3)CH_3$), 1.62-1.56 (2H, m, $-CH_2-C(OCH_3)-$), 1.60 (3H, s, $=C(CH_3)CH_3$), 1.29 (3H, s, $-C(CH_3)(OCH_3)-$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 141.0 (C6), 139.3 (C2), 135.0 (C3), 131.3 (C11), 130.9 (C4), 126.0 (C10), 124.3 (C5), 112.5 (C1), 77.2 (C7), 50.1 (C1'), 39.8 (C8), 25.8 (C12), 22.6 (C7- CH_3), 22.5 (C9), 17.8 (C11- CH_3), 12.2 (C3- CH_3) ppm; MS m/z (rel. int. %) 234(2), 202(14), 187(7), 159(24), 151(100), 133(32), 119(69), 105(37), 91(41), 73(74), 69(63), 59(63), 41(82).

7-*tert*-Butylperoxy-3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraene (**2.18a**) from 3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraen-5-ol (**2.1**). (Table 2.3, entry 2)



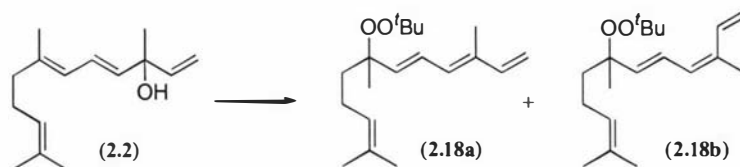
p-Toluenesulfonic acid monohydrate (1.0 mg, 5×10^{-6} mol, 5 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,3*E*,6*E*,10-tetraen-5-ol (**2.1**) (22 mg, 9.9×10^{-5} mol) and anhydrous *tert*-butylhydroperoxide (0.67 g, 7.48 mmol, 75 equiv.) in anhydrous THF (4.4 ml) under an atmosphere of dry N_2 at rt. The solution was stirred for 5 min, diluted with water (10 ml) and extracted with ether (2x10 ml). The combined ethereal extracts were washed with water (2x10 ml) then sat. brine (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (6:1) to yield the *title compound* (**2.18a**) (25 mg, 85%, 3*E*:3*Z* = > 99:1) as a pale yellow oil (R_f = 0.61; hexane-ethyl acetate (6:1)): found M^+ 292.2422, $C_{19}H_{32}O_2$ requires 292.2402; λ_{max} (ϵ) (*n*-hexane) 252 sh. (17500), 261 (22000), 270 (27000), 281 (22500) nm; IR ν_{max} (thin film) 2975, 1616, 1448, 1384, 1362, 1197 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 6.48 (1H, dd, $J = 15.4, 11.0$ Hz, $-CH=CH-CH=C(CH_3)-$), 6.42 (1H, dd, $J = 17.4, 10.7$ Hz, $-CH=CH_2$), 6.09 (1H, d, $J = 11.0$ Hz, $=CH-CH=C(CH_3)-$), 5.85 (1H, d, $J = 15.4$ Hz, $C(OOR)-CH=CH-$), 5.21 (1H, d, $J = 17.4$ Hz, $CH=C(H)H$), 5.15-5.08 (1H, m, $(CH_3)_2C=CH-$), 5.04 (1H, d, $J = 10.7$ Hz, $-CH=C(H)H$), 2.05-1.96 (2H, m, $(CH_3)_2C=CH-CH_2-$), 1.88 (3H, s, $=C(CH_3)-CH=CH_2$), 1.68 (3H, s, $=C(CH_3)CH_3$), 1.66-1.56 (2H, m, $-CH_2-C(OOR)$), 1.60 (3H, s, $=C(CH_3)CH_3$), 1.36 (3H, s, $-C(CH_3)(OOC(CH_3)_3)$), 1.23 (9H, s, $OOC(CH_3)_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 141.2 (C2), 138.9 (C6), 134.7 (C3), 131.3 (x2) (C11 and C4), 125.3 (C5), 124.5 (C10), 112.2 (C1), 82.0 (C7), 78.6 (C1'), 38.8 (C8), 26.8 (C2'), 25.8 (C12), 22.7 (C9), 22.6 (C7- CH_3), 17.7 (C11- CH_3), 12.2 (C3- CH_3) ppm; MS m/z (rel. int. %) 292(0.1), 219(2), 203(32), 161(6), 147(10), 133(9), 123(9), 121(11), 119(12), 109(18), 103(15), 81(17), 69(100), 55(13), 41(29).

7-Methoxy-3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraene (2.17a) and 7-methoxy-3,7,11-trimethyldodeca-1,3*Z*,5*E*,10-tetraene (2.17b) from 3,7,11-trimethyldodeca-1,4*E*,6*E*,10-tetraen-3-ol (2.2). (Table 2.3, entry 3)



p-Toluenesulfonic acid monohydrate (2.5 mg, 1.3×10^{-5} mol, 5 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,4*E*,6*E*,10-tetraen-3-ol (**2.2**) (57.0 mg, 2.59×10^{-4} mol) and methanol (0.623 g, 19.4 mmol, 75 equiv.) in anhydrous THF (5.0 ml) under an atmosphere of dry N_2 at rt. The solution was stirred for 1 hr, diluted with water (30 ml) and extracted with ether (2x30 ml). The combined ethereal extracts were washed with sat. brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (6:1) to yield the *title compounds* (**2.17a**) and (**2.17b**) (56.3 mg, 93%, 3*E*:3*Z* = 71:29) as a colourless oil (R_f = 0.60; hexane-ethyl acetate (6:1)). NMR data for the 3*Z*-isomer (**2.17b**); 1H NMR (270 MHz, $CDCl_3$) δ 6.98 (1H, dd, J = 17.1, 10.8 Hz, $-CH=CH_2$), 6.61 (1H, dd, J = 15.4, 11.2 Hz, $-CH=CH-CH=C(CH_3)-$), 6.02 (1H, d, J = 11.2 Hz, $=CH-CH=C(CH_3)-$), 5.60 (1H, d, J = 15.4 Hz, $-C(OCH_3)-CH=CH-$), 5.27 (1H, d, J = 17.1 Hz, $-CH=C(H)H$), 5.12 (1H [partly obscured], $-CH=C(H)H$), 5.16-5.09 (1H [obscured], m, $(CH_3)_2C=CH-$), 3.16 (3H, s, $-OCH_3$), 2.04-1.94 (2H [obscured], m, $(CH_3)_2C=CH-CH_2-$), 1.91 (3H, s, $=C(CH_3)-CH=CH_2$), 1.63-1.55 (2H, m, $-CH_2-C(OCH_3)$), 1.68 (3H [obscured], s, $=C(CH_3)CH_3$), 1.62 (3H, s, $=C(CH_3)CH_3$), 1.26 (3H, s, $-C(CH_3)(OCH_3)-$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.1, 133.5, 133.1, 131.3, 129.3, 126.0, 124.8, 114.3, 77.1, 50.1, 39.9, 25.7, 22.3, 19.9, 17.7, 12.2 ppm.

7-*tert*-Butylperoxy-3,7,11-trimethyldodeca-1,3*E*,5*E*,10-tetraene (2.18a) and 7-*tert*-Butylperoxy-3,7,11-trimethyldodeca-1,3*Z*,5*E*,10-tetraene (2.18b) from 3,7,11-trimethyldodeca-1,4*E*,6*E*,10-tetraen-3-ol (2.2). (Table 2.3, entry 4)



p-Toluenesulfonic acid monohydrate (3.0 mg, 1.5×10^{-5} mol, 5 mol%) was added to a solution of 3,7,11-trimethyldodeca-1,4*E*,6*E*,10-tetraen-3-ol (2.2) (66.2 mg, 3.0×10^{-4} mol) and anhydrous *tert*-butylhydroperoxide (2.03 g, 22.5 mmol, 75 equiv.) in anhydrous THF (15.0 ml) under an atmosphere of dry N_2 at rt. The solution was stirred for 1 hr, diluted with water (30 ml) and extracted with ether (2x30 ml). The combined ethereal extracts were washed with water (2x30 ml) then sat. brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (6:1) to yield the *title compounds* (2.18a) and (2.18b) (83.9 mg, 96%, 3*E*:3*Z* = 71:29) as a pale yellow oil (R_f = 0.66; hexane-ethyl acetate (6:1)). NMR data for the 3*Z*-isomer (2.18b); 1H NMR (270 MHz, $CDCl_3$) δ 6.97 (1H, dd, $J = 17.1, 10.8$ Hz, $-CH=CH_2$), 6.61 (1H, dd, $J = 15.6, 11.2$ Hz, $-CH=CH-CH=C(CH_3)-$), 6.00 (1H, d, $J = 11.2$ Hz, $=CH-CH=C(CH_3)-$), 5.78 (1H, d, $J = 15.6$ Hz, $-C(OCH_3)-CH=CH-$), 5.25 (1H, d, $J = 17.1$ Hz, $-CH=C(H)H$), 5.11 (1H [obscured], m, $(CH_3)_2C=CH-$), 5.06 (1H [obscured], $-CH=C(H)H$), 2.07-1.94 (2H [obscured], m, $(CH_3)_2C=CH-CH_2-$), 1.91 (3H, s, $=C(CH_3)-CH=CH_2$), 1.68 (3H [partly obscured], s, $=C(CH_3)CH_3$), 1.66-1.56 (2H, m, $-CH_2-C(OOR)$), 1.58 (3H [partly obscured], s, $=C(CH_3)CH_3$), 1.36 (3H, s, $-C(CH_3)(OOC(CH_3)_3)$), 1.23 (9H, s, $OOC(CH_3)_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 137.8, 133.3, 131.3, 131.2, 129.7, 124.5, 124.0, 114.1, 81.9, 78.6, 38.8, 26.8, 25.7, 22.5, 22.5, 19.9, 17.7 ppm.

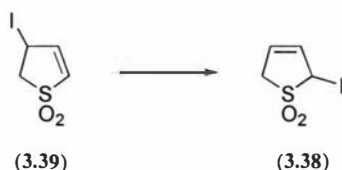
6.4 Experimental for Chapter 3.

6.4.1 Synthesis of Coupling Partners.

3-Iodo-2,3-dihydrothiophene-1,1-dioxide (3.39).¹³⁹ (Table 3.1, entry 1)

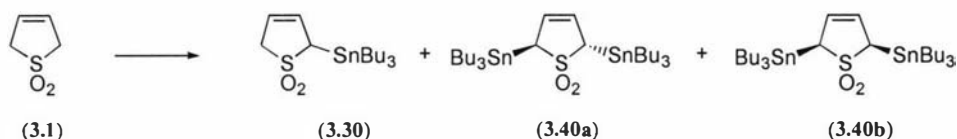
This is a modification of the procedure by Chou and Tseng.¹³⁹ BuLi (1.5 M [hexanes], 3.1 ml, 4.65 mmol) was added dropwise to a stirred solution of 2,5-dihydrothiophene-1,1-dioxide (**3.1**) (0.5 g, 4.23 mmol) in THF (30 ml) and HMPA (3.6 ml) at -105°C (liquid N_2 /ethanol) and the resultant deep red solution was stirred for 5 mins at this temperature. Anhydrous ZnCl_2 (0.577 g, 4.23 mmol) was fused under vacuum, cooled under argon and dissolved in THF (10 ml). This solution was added to the lithium sulfolenylate solution prepared above and stirred at -78°C for 5 mins prior to the addition of iodine (1.047 g, 4.23 mmol) in THF (10 ml). The purple reaction mixture was warmed to rt over 30 mins, diluted with hexane (50 ml) and passed through a plug of silica gel (40 mm x 25 mm) to give a brown solution that was concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (2:1) to yield the *title compound* (**3.39**) (0.292 g, 28%) as a pale yellow oil, ($R_f = 0.19$; hexane-ethyl acetate (2:1)) that rapidly discoloured on exposure to light and air: found M^+ 243.9051, $\text{C}_4\text{H}_5\text{IO}_2\text{S}$ requires 243.9055; IR ν_{max} (thin film) 3080, 3006, 2974, 1591, 1402, 1305, 1250, 1216, 1142, 1096, 918, 900, 870 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.91 (1H, dd, $J = 6.6, 3.3$ Hz, $-\text{SO}_2\text{CH}=\text{CHCHI}-$), 6.62 (1H, dd, $J = 6.6, 1.3$ Hz, $-\text{SO}_2\text{CH}=\text{CH}-$), 5.21 (1H, m, $-\text{CHI}-$), 3.77 (1H, dd, $J = 15.0, 7.7$ Hz, $-\text{SO}_2\text{CH}(\text{H})\text{CHI}-$), 3.53 (1H, dd, $J = 15.0, 2.9$ Hz, $-\text{SO}_2\text{CH}(\text{H})\text{CHI}-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 141.6, 131.0, 58.0, 8.3 ppm; MS m/z (rel. int. %) 244(31), 180(59), 127(16), 117(59), 89(20), 53(100).

2-Iodo-2,5-dihydrothiophene-1,1-dioxide (3.38): Attempted isomerisation of 3-iodo-2,3-dihydrothiophene-1,1-dioxide (3.39). (Scheme 3.21)



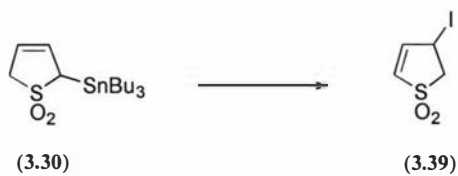
Iodine (21 mg, 8.2×10^{-5} mol) was added to a solution of 3-iodo-2,3-dihydrothiophene-1,1-dioxide (3.39) (20 mg, 8.2×10^{-5} mol) in CDCl_3 (0.6 ml) in the dark. ^1H NMR spectra were recorded after 1 and 24 hrs. The solvent was removed *in vacuo* and purification of the residue was attempted by repeated chromatography on silica gel eluting with hexane-ethyl acetate- CH_2Cl_2 (2:1:1). 2-Iodo-2,5-dihydrothiophene-1,1-dioxide (3.38) could not be isolated as a pure compound. ^1H NMR (270 MHz, CDCl_3) [(3.38) from the mixture] δ 6.35 (1H, br.d, $J = 8.6$ Hz, $-\text{CH}=\text{CH}-$), 6.08 (1H, m, $-\text{CH}=\text{CH}-$), 5.61 (1H, m, $-\text{SO}_2\text{C}(\text{I})\text{H}-$), 3.96 (2H, m, $-\text{CH}_2\text{SO}_2-$) ppm.

2-Tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.30),¹⁸² *trans*-2,5-bis-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.40a) and *cis*-2,5-bis-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.40b). (Table 3.2, entry 1)

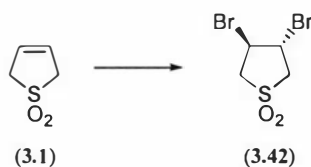


This is a modification of the procedure by Gomez, Lopez and Fraser-Reid.¹⁸² A solution of lithium hexamethyldisilazide (5.33 mmol) [prepared from hexamethyldisilazane (0.861 g, 5.33 mmol) and BuLi (1.6 M [hexane], 3.4 ml, 5.33 mmol) in THF (15 ml) at 0°C] was added to a stirred solution of 2,5-dihydrothiophene-1,1-dioxide (3.1) (0.90 g, 7.167 mmol) and tributyltin iodide (1.59 g, 3.81 mmol) in THF (30 ml) at -78°C under argon. The reaction mixture was stirred for 10 min, sat. NH_4Cl (15 ml) and ether (50 ml) were added, the cooling bath removed and the reaction mixture warmed to rt. The organic phase was removed and the aqueous residue extracted with ether (2x50 ml). The combined extracts were washed with water (50 ml), sat. brine (50 ml), dried over MgSO_4 , filtered and concentrated *in vacuo* to give a

crude oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (19:1) through to hexane-ethyl acetate (2:1) to yield *trans*-2,5-bis-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.40a**) (0.25 g, 19%) as a clear viscous oil, as a single diastereoisomer ($R_f = 0.56$; hexane-ethyl acetate (19:1)): found (FAB, +ve ion) M^+ 698.2207, $C_{28}H_{58}O_2SSn_2$ requires 698.2212; IR ν_{max} (thin film) 2956, 2921, 2852, 1463, 1376, 1283, 1197, 1106, 1074, 986, 890, 651 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 5.75 (2H, br.s, $J_{Sn-H} = 5.9$ Hz, $-CH=CH-$), 3.67 (2H, br.s, $J_{Sn-H} = 37.8$ Hz, $-CH(SnR_3)SO_2-$), 1.53 (12H, m, $-CH_2CH_2CH_2-$), 1.33 (12H, sext, $J = 7.3$ Hz, $-CH_2CH_3$), 1.10 (12H, m, $SnCH_2-$), 0.91 (18H, t, $J = 7.3$ Hz, $-CH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 122.1 ($J_{Sn-C} = 30.0, 21.0$ Hz), 57.5 ($J_{Sn-C} = 153.0, 7.5$ Hz), 28.9 ($J_{Sn-C} = 19.5$ Hz), 27.3 ($J_{Sn-C} = 61.5$ Hz), 13.7, 10.7 ($J_{Sn-C} = 377.7$ Hz) ppm; MS m/z (rel. int. %) 696(11), 639(37), 525(6), 425(7), 369(10), 291(77), 235(79), 179(100), 121(12). Further elution gave *trans*-2,5-bis-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.40a**) and *cis*-2,5-bis-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.40b**) (0.55 g, 41%) as a clear viscous oil, as a mixture of diastereoisomers, ($R_f = 0.56$; hexane-ethyl acetate (19:1)): 1H NMR (270 MHz, $CDCl_3$) [(**3.40b**) from mixture] δ 5.78 (2H, d, $J = 1.3$ Hz, $J_{Sn-H} = 5.9$ Hz, $-CH=CH-$), 3.67 (2H, d, $J = 1.3$ Hz, $J_{Sn-H} = 37.4$ Hz, $-CH(SnR_3)SO_2-$), 1.53 (12H, m, $-CH_2CH_2CH_2-$), 1.33 (12H, sext, $J = 7.3$ Hz, $-CH_2CH_3$), 1.10 (12H, m, $SnCH_2-$), 0.91 (18H, t, $J = 7.3$ Hz, $-CH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) [(**3.40b**) from mixture] δ 123.6, 56.2, 28.9 ($J_{Sn-C} = 19.5$ Hz), 27.3 ($J_{Sn-C} = 61.5$ Hz), 13.7, 10.7 ($J_{Sn-C} = 377.7$ Hz) ppm. Further elution gave 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.30**) (1.189 g, 38%) as a viscous, colourless oil ($R_f = 0.20$; hexane-ethyl acetate (8:1)): found M^+ 408.1154, $C_{16}H_{32}O_2Sn$ requires 408.1145; IR ν_{max} (thin film) 2957, 2923, 2871, 2853, 1598, 1463, 1298, 1236, 1132, 1109 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 6.04 (1H, m, $-CH=CH-$), 5.85 (1H, m, $-CH=CH-$), 3.75-3.57 (3H, m, $-CH_2SO_2CH(SnR_3)-$), 1.52 (6H, m, $-CH_2CH_2CH_2-$), 1.30 (6H, sext, $J = 7.5$ Hz, $-CH_2CH_3$), 1.09 (6H, m, $SnCH_2-$), 0.88 (9H, t, $J = 7.5$ Hz, $-CH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 129.1 ($J_{Sn-C} = 19.0$ Hz), 117.2 ($J_{Sn-C} = 28.0$ Hz), 56.8 ($J_{Sn-C} = 141.0$ Hz), 56.0, 28.8 ($J_{Sn-C} = 21.0$ Hz), 27.2 ($J_{Sn-C} = 62.0$ Hz), 13.6, 10.7 ($J_{Sn-C} = 340.2$ Hz) ppm; MS m/z (rel. int. %) 408(3), 351(100), 287(33), 231(73), 177(63), 121(35).

3-Iodo-2,3-dihydrothiophene-1,1-dioxide (3.39). (Scheme 3.22)

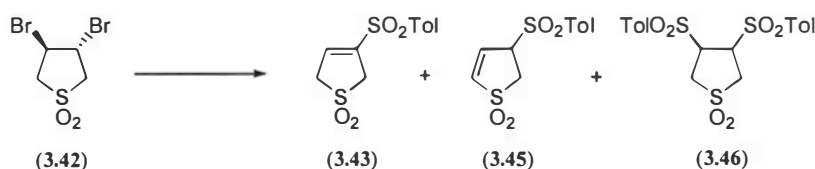
Iodine (15.6 mg, 6.1×10^{-5} mol) was added to a stirred solution of 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.30**) (25.0 mg, 6.1×10^{-5} mol) in CH_2Cl_2 (2.0 ml) at rt under argon in the dark. The disappearance of starting material was monitored by tlc. When the last traces of (**3.30**) were consumed (*ca.* 1.5 hrs), the solvent was removed under a stream of dry N_2 , and the residue flashed through a short plug of silica gel (25 mm x 5 mm) with hexane-ethyl acetate (2:1, 40 ml) and purified further by trituration with hexane (2x10 ml) to yield the *title compound* (**3.39**) (9.4 mg, 63%) as a pale yellow oil.

***Trans*-3,4-dibromotetrahydrothiophene-1,1-dioxide (3.42).¹⁴⁹ (Scheme 3.23)**

This is a modification of the procedure reported by Bailey and Cummins.¹⁴⁹ A solution of bromine (20.29 g, 0.127 mol) in CHCl_3 (10 ml) was added dropwise over 6 hrs to a refluxing, stirred solution of 2,5-dihydrothiophene-1,1-dioxide (**3.1**) (15.0 g, 0.127 mol) in CHCl_3 (30 ml) under argon. The reaction mixture was cooled to rt and the solvent removed *in vacuo*. The resultant pale orange solid was recrystallised from water-ethanol (2:1, 250 ml) to give the *title compound* (**3.42**) as white needles (28.25 g, 80%, m.p. 144-146°C (lit. m.p.¹⁴⁹ 141.0-141.8°C)) that were dried over P_2O_5 : Found C 17.4%, H 2.3%, Br 57.6%, S 11.6%, $\text{C}_4\text{H}_6\text{Br}_2\text{O}_2\text{S}$ requires C 17.3%, H 2.2%, Br 57.5%, S 11.5%; found M^+ 278.8529, $\text{C}_4\text{H}_6\text{Br}_2\text{O}_2\text{S}$ requires 278.8513; IR ν_{max} (KBr disc) 3016, 2984, 2939, 1406, 1325, 1314, 1291, 1263, 1237, 1143, 1116, 1097, 907, 837 701, 564, 461, 431 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 4.79 (2H, m, $-\text{CHBr}-$), 4.03 (2H, m, $-\text{CH}(\text{H})\text{SO}_2-$), 3.54 (2H, m, $-\text{CH}(\text{H})\text{SO}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 58.3,

45.6 ppm; MS m/z (rel. int. %) 279(1), 213(2), 135(62), 133(64), 108(8), 106(8), 53(100), 39(39).

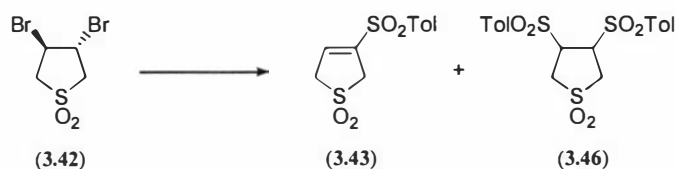
3-(4'-Tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (3.43),¹⁸⁴ 3-(4'-tolylsulfonyl)-2,3-dihydrothiophene-1,1-dioxide (3.45) and 3,4-bis-(4'-tolylsulfonyl) tetrahydrothiophene-1,1-dioxide (3.46). (Table 3.3, entry 2)



This is a modification to the procedure by Inomata *et al.*¹⁸⁴ To a methanolic solution (190 ml) of sodium hydroxide (1.1 g, 27.7 mmol) was added sodium 4-toluenesulfinate tetrahydrate (18.9 g, 75.6 mmol) and *trans*-3,4-dibromotetrahydrothiophene-1,1-dioxide (**(3.42)**) (7.0 g, 25.2 mmol). The solution was refluxed for 2 hrs and poured onto crushed ice (*ca.* 200 g). The crude product was filtered on a Büchner funnel and dried under vacuum. Hot filtration from ethanol (100 ml), yielded a colourless supernatant and an insoluble white solid ($R_f = 0.01$; hexane-ethyl acetate (2:1)). The solid was recrystallised from boiling water (80 ml) to give 3,4-bis-(4'-tolylsulfonyl) tetrahydrothiophene-1,1-dioxide (**(3.46)**) (1.352 g, 13%; m.p. 263-264°C) as a white crystals: found C 50.6%, H 4.3%, S 22.2%, $C_{18}H_{20}O_6S_3$ requires C 50.5%, H 4.7%, S 22.4%; found M^+ 428.0446, $C_{18}H_{20}O_6S_3$ requires 428.0422; IR ν_{max} (KBr disc) 3066, 3017, 2948, 1596, 1339, 1321, 1304, 1156, 1119, 1084 cm^{-1} ; 1H NMR (270 MHz, d_6 -DMSO) δ 7.60 (4H, d, $J = 8.4$ Hz, ArH), 7.29 (4H, d, $J = 8.4$ Hz, ArH), 4.51 (2H, m, -CH(SO₂Ar)-), 3.79 (4H, m, -CH₂SO₂CH₂-), 2.42 (6H, s, ArCH₃) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 145.7, 132.1, 130.0, 128.7, 59.2, 49.4, 21.4 ppm; MS m/z (rel. int. %) 428(0.4), 273(3), 209(1), 156(3), 139(11), 129(2), 107(3), 91(100), 65(11), 53(9). Concentration of the mother liquor (65 ml) and cooling (0°C), gave 3-(4'-tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (**(3.43)**) and 3-(4'-tolylsulfonyl)-2,3-dihydrothiophene-1,1-dioxide (**(3.45)**) (4.236 g 62%; m.p. 117-120°C (lit. m.p.¹⁸⁴ 125-126°C)) as an inseparable 72:28 mixture of regioisomers as a white crystalline solid, ($R_f = 0.16$; hexane-ethyl acetate (2:1)): found C 48.5%, H 4.1%, S 23.5%, $C_{11}H_{12}O_4S_2$ requires C 48.5%, H 4.4%, S 23.5%; found M^+ 272.0171, $C_{11}H_{12}O_4S_2$ requires 272.0177; IR ν_{max} (KBr disc) 3058, 3017, 2979, 1619, 1596, 1315, 1306, 1152, 1134 cm^{-1} ; 1H NMR (270

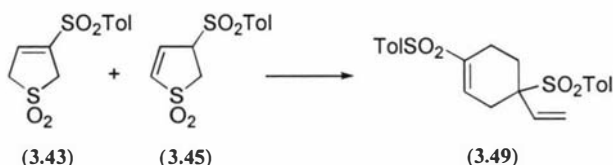
MHz, CDCl₃) [(3.43) from mixture] δ 7.76 (2H, d, $J = 8.4$ Hz, ArH), 7.41 (2H, d, $J = 8.4$ Hz, ArH), 7.02 (1H, m -CH=C(SO₂Ar), 4.05 (2H, m, -CH₂SO₂CH₂-), 3.87 (2H, m, -CH₂SO₂CH₂-), 2.48 (3H, s, ArCH₃); [(3.45) from mixture] δ 7.76 (2H [partly obscured], ArH), 7.41 (2H [partly obscured], ArH), 6.84 (2H, qd, $J = 8.7, 2.4$ Hz, -CH=CH-), 4.63 (1H, tt, $J = 7.0, 2.3$ Hz, =CH-CH(SO₂Ar-), 3.47 (2H, d, $J = 7.0$ Hz, -SO₂CH₂-), 2.49 (3H s, ArCH₃) ppm; ¹³C NMR (67.8 MHz, CDCl₃) [(3.43) from mixture] δ 146.1 (s), 139.3 (s), 133.9 (s), 131.1 (d), 130.4 (d), 128.3 (d), 57.9 (t), 53.8 (t), 21.8 (q); [(3.45) from mixture] δ 146.7 (s), 136.7 (d), 131.8 (s), 131.5 (d), 130.2 (d), 129.1 (d), 63.9 (d), 48.2 (t), 21.8 (q) ppm; MS m/z (rel. int. %) 272(14), 208(10), 156(100, 144(21), 139(91), 129(27), 92(56), 91(96), 65(48), 53(100), 39(28).

3-(4'-Tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (3.43) and 3,4-bis-(4'-tolylsulfonyl) tetrahydrothiophene-1,1-dioxide (3.46). (Table 3.3, entry 4)



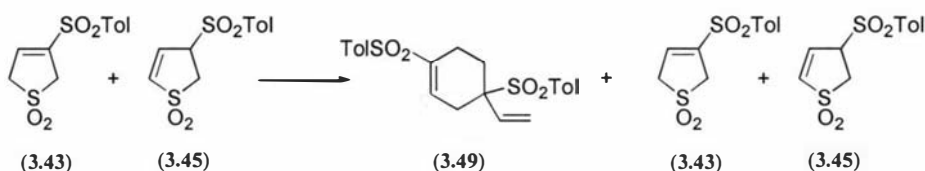
This is a modification to the procedure by Inomata *et al.*¹⁸⁴ To a methanolic solution (150 ml) of potassium hydroxide (2.619 g, 46.7 mmol) was added sodium 4-toluenesulfinate tetrahydrate (25.0 g, 0.117 mol) and *trans*-3,4-dibromotetrahydrothiophene-1,1-dioxide (**3.42**) (6.487 g, 23.3 mmol). The solution was refluxed for 3 hrs and poured onto crushed ice (*ca.* 100 g). The crude product was filtered on a Büchner funnel and dried under vacuum. Hot filtration from ethanol (60 ml), yielded 3,4-bis-(4'-tolylsulfonyl) tetrahydrothiophene-1,1-dioxide (**3.46**) as an insoluble white solid (4.1 g, 42%) and a colourless supernatant which yielded 3-(4'-tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (**3.43**) (0.40 g 6%).

Isomerisation of 3-(4'-tolylsulfonyl)-2,3-dihydrothiophene-1,1-dioxide (3.45) to 3-(4'-tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (3.43) and formation of 1,4-bis-(4'-tolylsulfonyl)-4-vinyl-1-cyclohexene (3.49). (Scheme 3.26)



This is a modification to the procedure by Inomata *et al.*¹⁸⁴ A solution of 3-(4'-tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (3.43) and 3-(4'-tolylsulfonyl)-2,3-dihydrothiophene-1,1-dioxide (3.45) (0.50 g, 1.83 mmol, (73:27)), pyridine (0.145 g, 1.83 mmol) and hydroquinone (*ca.* 5 mg) in xylene (10.0 ml) was refluxed for 90 mins. Volatiles were removed *in vacuo* and the residue recrystallised from ethanol (12 ml) to give 1,4-bis-(4'-tolylsulfonyl)-4-vinyl-1-cyclohexene (3.49) (0.369 g, 96%, m.p. 163-164°C (lit. m.p.¹⁸⁴ 166-170°C)): found M^+ 416.1124, $C_{22}H_{24}O_4S_2$ requires 416.1116; IR ν_{max} (KBr disc) 3061, 2937, 2869, 1653, 1596, 1286, 1152, 1092, 1012, 933, 810, 708, 665, 599, cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 7.66 (2H, d, $J = 8.3$ Hz, ArH), 7.65 (2H, d, $J = 8.3$ Hz, ArH), 7.32 (2H, d, $J = 8.3$ Hz, ArH), 7.30 (2H, d, $J = 8.3$ Hz, ArH), 6.95 (1H, m, $-CH=C(R)_2$) 5.69 (1H, dd, $J = 17.4, 10.8$ Hz, $CH_2=CH-$), 5.29 (1H, d, $J = 10.8$ Hz, $CH(H)=CH-$), 4.95 (1H, d, $J = 17.4$ Hz, $CH(H)=CH-$), 2.91 (1H, br.d, $J = 18.7$ Hz, $=CHCH(H)C(R)(SO_2Ar)$), 2.45 (3H, s, $ArCH_3$), 2.43 (3H, s, $ArCH_3$), 2.41-1.95 (5H, br.m, $-CH_2CH_2-$, $CHCH(H)C(R)(SO_2Ar)$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 145.1 (s), 144.4 (s), 139.3 (s), 135.4 (s), 133.3 (d), 131.4 (d), 130.5 (d), 129.7 (d), 129.2 (d), 127.8 (d), 121.6 (t), 109.7 (s), 65.6 (s), 28.0 (t), 24.6 (t), 21.7 (q), 21.6 (q), 20.4 (t) ppm; MS m/z (rel. int. %) 416(1), 261(37), 155(5), 139(100), 121(15), 105(27), 91(65), 79(25), 91(65), 79(25), 65(26), 51(6), 39(13).

Attempted isolation of 3-(4'-tolylsulfonyl)-2,3-dihydrothiophene-1,1-dioxide (3.45). (Scheme 3.26)



This is a modification to the procedure by Inomata *et al.*¹⁸⁴ A solution of 3-(4'-tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (**3.43**) and 3-(4'-tolylsulfonyl)-2,3-dihydrothiophene-1,1-dioxide (**3.45**) (0.50 g, 1.83 mmol, (73:27)) in xylene (10.0 ml) was refluxed for 2.5 hrs. Volatiles were removed *in vacuo* and the residue taken up in CH₂Cl₂ (10 ml), absorbed onto silica gel and purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (2:1) through to hexane-ethyl acetate (1:1) to yield 1,4-bis-(4'-tolylsulfonyl)-4-vinyl-1-cyclohexene (**3.49**) (0.249 g, 65%) and a mixture of 3-(4'-tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (**3.43**) and 3-(4'-tolylsulfonyl)-2,3-dihydrothiophene-1,1-dioxide (**3.45**) (0.128 g, 26%, (86:14)).

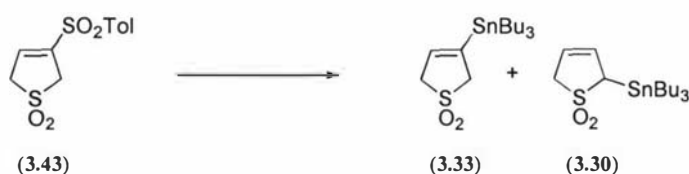
**3-Tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.33)¹⁸¹ and
2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.30). (Scheme 3.29)**



This is a modification of the procedure by Bew and Sweeney.¹⁸¹ A solution of 3-(4'-tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (**3.43**) and 3-(4'-tolylsulfonyl)-2,3-dihydrothiophene-1,1-dioxide (**3.45**) (1.0 g, 3.67 mmol, (73:27)), 2,2'-azo-bis-isobutyronitrile (AIBN) (30 mg, 0.19 mmol, 5 mol%) and tributyltin hydride¹⁸⁵ (2.14 g, 7.34 mmol) in benzene (15 ml) was heated to reflux. After 2 hrs, additional AIBN (30 mg, 0.19 mmol, 5 mol%) was added and the disappearance of starting material monitored by tlc for a further 2 hrs. The reaction mixture was cooled and concentrated *in vacuo*, hexane (50 ml) was added and the resulting white solid removed by filtration. The solid was washed with hexane (2x25 ml) and the combined hexane fractions were concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) to yield the *title compounds* (**3.33**) and (**3.30**) (1.265 g, 85%, (64:36)) as a mixture of regioisomers. Repeated chromatography on silica gel eluting with hexane-ethyl acetate (8:1), gave 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) as a viscous, colourless oil ($R_f = 0.22$; hexane-ethyl acetate (8:1)): found M^+ 408.1151, C₁₆H₃₂O₂Sn requires 408.1145; IR ν_{max} (thin film) 2956, 2925, 2871, 2853, 1578, 1463, 1311, 1228, 1123 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 6.06 (1H, m, $J_{Sn-H} = 42.2$ Hz, -CH=C(SnR₃-), 3.75 (2H, br.s, -CH₂SO₂CH₂-),

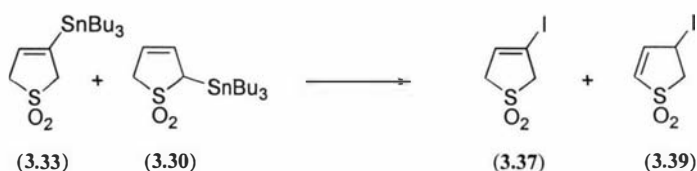
3.72 (2H, br.s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 1.50 (6H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.30 (6H, sext, $J = 7.5$ Hz, $-\text{CH}_2\text{CH}_3$), 0.98 (6H, m, SnCH_2-), 0.89 (9H, t, $J = 7.5$ Hz, $-\text{CH}_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 141.3, 132.0 ($J_{\text{Sn-C}} = 22.0$ Hz), 61.3 ($J_{\text{Sn-C}} = 29.0$ Hz), 56.2 ($J_{\text{Sn-C}} = 28.0$ Hz), 28.9 ($J_{\text{Sn-C}} = 22.0$ Hz), 27.2 ($J_{\text{Sn-C}} = 57.0$ Hz), 13.6, 9.6 ($J_{\text{Sn-C}} = 351.2$ Hz) ppm; MS m/z (rel. int. %) 408(1), 351(20), 287(93), 231(17), 177(100), 145(8), 121(37). Further elution gave 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.30**) as a viscous, colourless oil ($R_f = 0.20$; hexane-ethyl acetate (8:1)).

3-Tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.33) and 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.30) from 3-(4'-tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (3.43).



This is a modification of the procedure by Bew and Sweeney.¹⁸¹ A solution of 3-(4'-tolylsulfonyl)-2,5-dihydrothiophene-1,1-dioxide (**3.43**) (0.112 g, 0.41 mmol), 2,2'-azobis-isobutyronitrile (AIBN) (3.4 mg, 2.07×10^{-5} mol, 5 mol%) and tributyltin hydride¹⁸⁵ (0.24 g, 0.825 mmol) in benzene (3.0 ml) was heated to reflux. After 1 hr, additional AIBN (3.4 mg, 2.07×10^{-5} mol, 5 mol) was added and the disappearance of starting material monitored by tlc for a further 2 hrs. The reaction mixture was worked-up as described above to give the *title compounds* (**3.33**) and (**3.30**) (0.123 g, 73%, (73:27)) as a mixture of regioisomers.

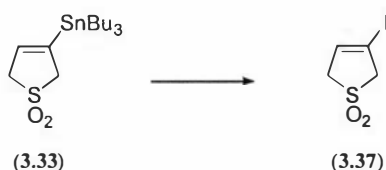
3-Iodo-2,5-dihydrothiophene-1,1-dioxide (3.37) and 3-iodo-2,3-dihydrothiophene-1,1-dioxide (3.39). (Scheme 3.30)



Iodine (0.234 g, 0.92 mmol) was added to a stirred solution of 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) and 2-tributylstannyl-2,5-dihydrothiophene-1,1-

dioxide (**3.30**) (0.376 g, 0.92 mmol, (64:36)) in CH_2Cl_2 (10 ml) at 0°C under argon in the dark. The reaction mixture was warmed to rt and the disappearance of starting material (typically 1 hr) was monitored by tlc. The reaction mixture was transferred to a separating funnel, washed with sat. $\text{Na}_2\text{S}_2\text{O}_3$ (5 ml), water (20 ml) and sat. brine (20ml), dried over MgSO_4 , filtered and concentrated *in vacuo* to give an orange solid that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) through to hexane-ethyl acetate (2:1) to give tributyltin iodide (0.296 g, 76%) as a pink oil ($R_f = 0.56$; hexane-ethyl acetate (2:1)) that rapidly discoloured on exposure to light: found $M^+ - \text{C}_4\text{H}_9$ 360.9480, $\text{C}_8\text{H}_{18}\text{ISn}$ requires 360.9477; IR ν_{max} (thin film) 2956, 2922, 2870, 2853, 1463, 1377, 1074, 876 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.64 (6H, m, $\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.35 (12H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.93 (9H, t, $J = 7.3$ Hz, $-\text{CH}_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 27.9 ($J_{\text{Sn-C}} = 23.0$ Hz), 26.9 ($J_{\text{Sn-C}} = 64.0$ Hz), 17.6 ($J_{\text{Sn-C}} = 337.2$ Hz), 13.7 ppm; MS m/z (rel. int. %) 361(16), 267(71), 247(7), 213(20), 176(29), 167(29), 149(100), 121(15), 91(16), 71(27), 57(90), 41(69). Further elution gave a white solid that was recrystallised from ether/ CH_2Cl_2 to yield 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (0.108 g, 48%) as a white, crystalline solid ($R_f = 0.26$; hexane-ethyl acetate (2:1), m.p. $159-160^\circ\text{C}$): found C 19.8%, H 2.0%, I 52.1%, S 12.9%, $\text{C}_4\text{H}_5\text{IO}_2\text{S}$ requires C 19.7%, H 2.1%, I 52.0%, S 13.1%; found M^+ 243.9056, $\text{C}_4\text{H}_5\text{IO}_2\text{S}$ requires 243.9055; IR ν_{max} (KBr disc) 3074, 2970, 2920, 1613, 1404, 1290, 1230, 1213, 1014, 976, 883, 794, 961, 599, 454, 417 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.59 (1H, m, $-\text{CH}=\text{Cl}-$), 3.95 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.79 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 132.8 (d), 83.1 (s), 63.7 (t), 58.7 (t) ppm; MS m/z (rel. int. %) 244(24), 180(37), 127(5), 53(100). Further elution yielded 3-iodo-2,3-dihydrothiophene-1,1-dioxide (**3.39**) (55 mg, 24.5%) as a pale yellow oil.

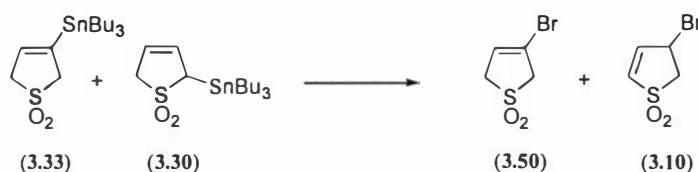
3-Iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**). (Scheme 3.30)



Iodine (0.184 g, 0.73 mmol) was added to a stirred solution of 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) (0.295 g, 0.73 mmol) in CH_2Cl_2 (10 ml) at rt under argon in the dark and the disappearance of starting material (typically *ca.* 1 hr) was

monitored by tlc. The reaction mixture was worked-up as described above to give an orange solid that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) through to hexane-ethyl acetate (2:1) to give a white solid that was recrystallised from ether/ CH_2Cl_2 to yield 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (0.142 g, 80%).

3-Bromo-2,5-dihydrothiophene-1,1-dioxide (**3.50**) and 3-bromo-2,3-dihydrothiophene-1,1-dioxide (**3.10**).¹⁴⁹ (Scheme 3.30)

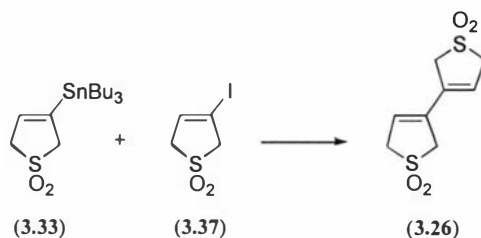


A solution of bromine in CH_2Cl_2 (1.94 M, 1.89 ml, 3.67 mmol) was added to a stirred solution of 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) and 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.30**) (1.259 g, 3.67 mmol, (49:51)) in CH_2Cl_2 (10 ml) at rt under argon in the dark. The reaction mixture was worked-up as described above to give a brown solid that was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) through to hexane-ethyl acetate (2:1) to yield tributyltin bromide (0.528 g, 40%) as a colourless oil ($R_f = 0.56$; hexane-ethyl acetate (2:1)): found $M^+ - \text{C}_4\text{H}_9$ 312.9612, $\text{C}_8\text{H}_{18}\text{BrSn}$ requires 312.9604; IR ν_{max} (thin film) 2956, 2921, 2852, 1463, 1376, 1075, 875 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.64 (6H, m, $\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.33 (12H, m, $\text{SnCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.92 (9H, t, $J = 7.3$ Hz, $-\text{CH}_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 27.9 ($J_{\text{Sn-C}} = 22.0$ Hz), 26.9 ($J_{\text{Sn-C}} = 63.0$ Hz), 17.6 ($J_{\text{Sn-C}} = 337.2$ Hz), 13.7 ppm; MS m/z (rel. int. %) 313(12), 291(12), 169(100), 235(5), 213(16), 177(31), 155(25), 121(14), 57(46), 41(41). Further elution gave a white solid that was recrystallised from ether/ CH_2Cl_2 to yield 3-bromo-2,5-dihydrothiophene-1,1-dioxide (**3.50**) (0.289 g, 40%) as a white crystalline solid ($R_f = 0.37$; hexane-ethyl acetate (2:1), m.p. 131-132.5°C): found C 24.6%, H 2.5%, Br 40.8%, S 16.3%, $\text{C}_4\text{H}_5\text{BrO}_2\text{S}$ requires C 24.4%, H 2.6%, Br 40.6%, S 16.3%; found M^+ 195.9206, $\text{C}_4\text{H}_5\text{BrO}_2\text{S}$ requires 195.9194; IR ν_{max} (KBr disc) 3078, 2975, 2927, 1628, 1407, 1294, 1247, 1232, 1134, 1027, 985, 882, 799, 715, 603, 456, 430 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.30 (1H, m, $-\text{CH}=\text{CBr}-$), 3.97 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.85 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 124.7 (d), 113.0 (s), 60.6 (t),

58.5 (t) ppm; MS m/z (rel. int. %) 198(1), 196(1), 134(14), 132(14), 81(2), 79(2), 64(15), 53(100). Further elution gave 3-bromo-2,3-dihydrothiophene-1,1-dioxide (**3.10**) (0.314 g, 43%) as a pale yellow oil ($R_f = 0.24$; hexane-ethyl acetate (2:1)): found M^+ 195.9199, $C_4H_5BrO_2S$ requires 195.9194; IR ν_{max} (thin film) 3079, 3012, 2956, 1570, 1403, 1301, 1221, 1184, 1145, 1074, 922, 875, 758, 656 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 6.83 (1H, dd, $J = 6.6, 3.3$ Hz, $-SO_2CH=CHCHBr-$), 6.73 (1H, dd, $J = 6.6, 1.3$ Hz, $-SO_2CH=CH-$), 5.14 (1H, m, $-CHBr-$), 3.77 (1H, dd, $J = 14.7, 7.7$ Hz, $-SO_2CH(H)CHBr-$), 3.52 (1H, dd, $J = 14.7, 3.1$ Hz, $-SO_2CH(H)CHBr-$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 139.2, 132.7, 56.6, 37.3 ppm; MS m/z (rel. int. %) 198(3), 196(3), 134(20), 132(20), 117(56), 99(7), 89(20), 78(20), 53(100), 45(11), 39(13).

6.4.2 Coupling Reactions.

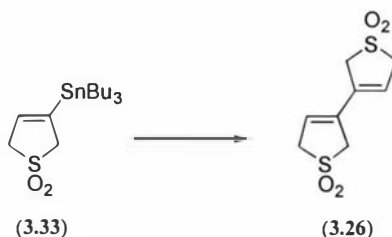
3,3'-Bi-2,5-dihydrothiophene-1,1-dioxide (**3.26**). (Scheme 3.31)



A solution of 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) (0.535 g, 1.313 mmol) and 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (0.321 g, 1.313 mmol) in freshly distilled DMF (6.0 ml) was twice freeze-thaw degassed under argon. *Bis*-(acetonitrile) palladium (II) dichloride (17.0 mg, 6.6×10^{-5} mol, 5 mol%) was added, whereupon the colourless solution rapidly darkened. The reaction mixture was degassed once more and stirred at rt for 18 hrs. Ether (10 ml) was added and the supernatant decanted from the precipitate. The precipitate was triturated successively with ether (2x10 ml), hexane (2x10 ml) and refluxing acetone (2x5 ml) to give the *title compound* (**3.26**) (0.292 g, 95%) as an amorphous white solid (m.p. $> 300^\circ C$): found C 40.6%, H 4.1%, S 27.0%, $C_8H_{10}O_4S_2$ requires C 41.0%, H 4.3%, S 27.4%: found M^+ 234.0021, $C_8H_{10}O_4S_2$ requires 234.0020; IR ν_{max} (KBr disc) 3071, 2975, 2929, 1663, 1409, 1384, 1308, 1281, 1276, 1245, 1234, 1133, 1118, 1002, 954, 917, 899, 865, 769, 671, 590, 460, 452, 407 cm^{-1} ; 1H NMR (270 MHz, d_6 -DMSO) δ 6.15 (2H, m, $-CH=CR-$), 4.11 (4H, m, $-SO_2CH_2C(R)=$), 4.04 (4H, m, $=CHCH_2SO_2-$) ppm; ^{13}C NMR (67.8

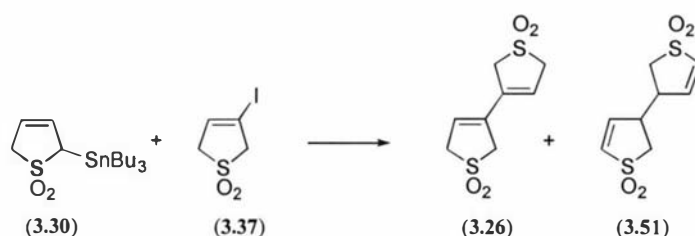
MHz, CDCl_3) δ 132.8 (s), 123.9 (d), 57.7 (t), 55.3 (t) ppm; MS m/z (rel. int. %) 234(5), 170(5), 106(20), 105(77), 104(87), 91(100), 78(39), 64(37), 51(18), 39(18).

3,3'-Bi-2,5-dihydrothiophene-1,1-dioxide (3.26) from 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.33) directly. (Scheme 3.31)



Iodine (46.0 mg, 0.182 mmol) was added to a stirred solution of 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.33) (0.148 g, 0.363 mmol) in DMF (2.0 ml) under argon at rt. The reaction mixture was stirred for a further 2 hrs then twice freeze-thaw degassed. *Bis*-(acetonitrile) palladium (II) dichloride (2.3 mg, 8.8×10^{-6} mol, 5 mol%) was added, whereupon the pale yellow solution rapidly darkened. The reaction mixture was degassed once more and stirred at rt for 18 hrs. The reaction was treated as described above to give the *title compound* (3.26) (36.1 mg 85%) as an amorphous white solid.

3,3'-Bi-2,5-dihydrothiophene-1,1-dioxide (2.26) and 3,3'-bi-2,3-dihydrothiophene-1,1-dioxide (3.51). (Scheme 3.32)



Under the conditions described above, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (3.37) (17.9 mg, 7.32×10^{-5} mol), 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.30) (29.8 mg, 7.32×10^{-5} mol) and *bis*-(acetonitrile) palladium (II) dichloride (0.9 mg, 3.6×10^{-6} mol, 5 mol%) in DMF (0.5 ml) at rt over 18 hrs gave the *title compounds* (3.26) and (3.51) (16.6 mg, 97%, (64:36)) as an amorphous off white solid. Attempts to recrystallise the mixture were unsuccessful. Data for (3.51) from the mixture: ¹H NMR

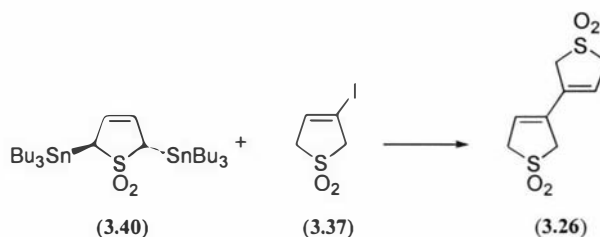
(270 MHz, CDCl₃) δ 7.21 (2H, d, $J = 6.8$ Hz, $-CH=CH-$), 6.97 (2H, d, $J = 6.8$ Hz, $-CH=CH-$), 3.53 (2H [partly obscured], m, $-CH(R)-$), 3.53 (2H, br.s, $-SO_2CH(H)-$), 3.02 (2H, d, 10.1 Hz, $-SO_2CH(H)-$) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 140.8 (d), 133.6 (d), 50.5 (t), 42.1 (d) ppm.

2,3-Dihydrothiophene-1,1-dioxide (3.54).¹⁴⁹ (Table 3.5)



This is a modification of the procedure reported by Bailey and Cummins.¹⁴⁹ A solution of 2,5-dihydrothiophene-1,1-dioxide (3.1) (25.0 g, 0.212 mol) in dilute KOH (0.5 M, 50 ml) was stirred at rt for 48 hrs. The reaction mixture was acidified with conc. HCl (25 ml), extracted with CH₂Cl₂ (6x100 ml) and the combined organic extracts dried over MgSO₄, filtered and concentrated *in vacuo* to give a yellow oil. The oil was heated at 150°C under reduced pressure (15 mmHg) for 1 hr and the residue was recrystallised from ethanol (20 ml) to give the *title compound* (3.54) (8.2 g, 33%, m.p. 47-48.5°C (lit. m.p.¹⁴⁹ 48-49°C)) as white needles ($R_f = 0.19$; hexane-ethyl acetate (2:1)): ¹H NMR (270 MHz, CDCl₃) δ 6.76 (1H, dt, $J = 6.6, 3.3$ Hz, $-CH=CHSO_2-$), 6.66 (1H, dt, $J = 6.6, 2.2$ Hz, $-CH=CHSO_2-$), 3.23 (2H, m, $-SO_2CH_2-$), 2.95 (2H, m, $-SO_2CH_2CH_2-$) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 138.8 (d), 131.9 (d), 47.5 (t), 26.5 (t) ppm.

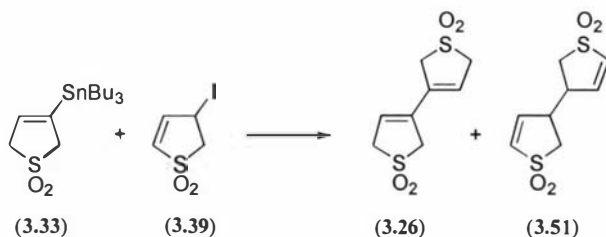
3,3'-Bi-2,5-dihydrothiophene-1,1-dioxide (3.26). (Scheme 3.33)



Under the conditions described above, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (3.37) (41.3 mg, 0.17 mmol), 2,5-bis-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.40) (58.9 mg, 8.46×10^{-5} mol, (*cis:trans* unspecified)) and *bis*-(acetonitrile) palladium (II)

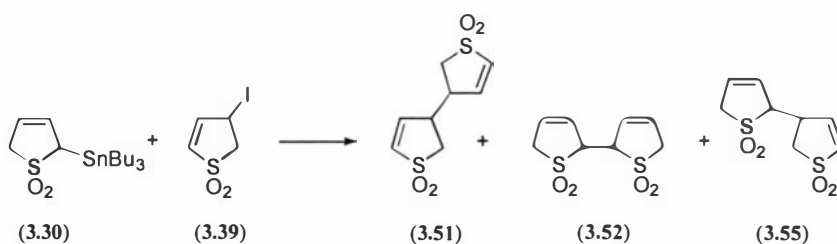
dichloride (1.1 mg, 4.2×10^{-6} mol, 5 mol%) in DMF (0.8 ml) at rt over 24 hrs gave the *title compound* (**3.26**) (18.1 mg, 91%) as an amorphous white solid.

3,3'-Bi-2,5-dihydrothiophene-1,1-dioxide (3.26) and 3,3'-bi-2,3-dihydrothiophene-1,1-dioxide (3.51). (Scheme 3.34)



Under the conditions described above, 3-iodo-2,3-dihydrothiophene-1,1-dioxide (**3.39**) (30.5 mg, 0.125 mmol), 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) (50.8 mg, 0.125 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (1.6 mg, 6.24×10^{-6} mol, 5 mol%) in DMF (0.7 ml) at rt over 18 hrs gave the *title compounds* (**3.26**) and (**3.51**) (17.0 mg, 58%, (79:21)) as an amorphous brown solid. Attempts to recrystallise the mixture were unsuccessful.

Coupling of 3-iodo-2,3-dihydrothiophene-1,1-dioxide (3.39) and 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.30). (Scheme 3.35)



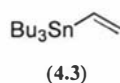
Under the conditions described above, 3-iodo-2,3-dihydrothiophene-1,1-dioxide (**3.39**) (33.6 mg, 0.137 mmol), 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.30**) (56.0 mg, 0.137 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (1.8 mg, 6.88×10^{-6} mol, 5 mol%) in DMF (0.8 ml) at rt over 18 hrs gave a mixture of 3 compounds (*ca.* 2:1:1) as an amorphous dark brown solid (8.2 mg, 26%). The mixture contained 3,3'-bi-2,3-dihydrothiophene-1,1-dioxide (**3.51**) as the major component. Data is given for the other components from the mixture: ^1H NMR (270 MHz, d_6 -DMSO) δ 7.21 (1H [partly obscured], d, $J = 2.4$ Hz), 7.06 (1H, d, $J = 6.6$ Hz), 6.94 (1H, dd, $J = 7.5, 2.6$ Hz), 6.82 (1H, ddd, $J = 6.8, 2.6, 0.7$ Hz), 6.24 (1H, br.s), 6.02 (1H, br.d, $J = 5.9$ Hz), 4.98

(1H, br.s), 3.94 (2H, br.s), 3.67 (2H, ddd, $J = 13.6, 7.5, 0.7$ Hz), 2.93 (1H [partly obscured], dd, $J = 13.6, 3.5$ Hz) ppm; ^{13}C NMR (67.8 MHz, $\text{d}_6\text{-DMSO}$) δ 142.7 (d), 139.6 (d), 134.0 (d), 132.6 (d), 126.3 (d), 126.1 (d), 67.3 (d), 65.5 (d), 56.7 (t), 55.5 (t), 51.2 (t) 38.9 (d) ppm. (Table 3.6)

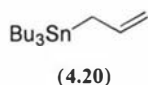
6.5 Experimental for Chapter 4.

6.5.1 Stannane Synthesis.

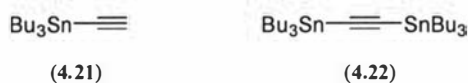
Tributylvinyl tin (4.3).²⁰¹ (Figure 4.2)



This is a modification of the procedure by Seyferth and Stone.²⁰¹ A solution of vinyl magnesium bromide (1.0 M, 100 ml, 0.1 mol) [prepared in the usual manner from magnesium turnings (2.55 g, 0.105 mol) and vinyl bromide (7.05 g, 0.1 mol) in THF (100 ml) with catalytic iodine (*ca.* 5 mg)] was added to a stirred solution of tributyltin chloride (32.55 g, 0.1 mol) in THF (100 ml) at 0°C over 30 mins. The reaction mixture was warmed to rt and stirred for an additional 30 mins. Water (50 ml) was added and the reaction mixture extracted with ether (3x50 ml). The combined ethereal extracts were washed with water (50 ml), sat. brine (50 ml), dried over MgSO_4 , filtered and concentrated *in vacuo* to give a crude oil that was purified by short path Kugelrohr distillation under reduced pressure to give the *title compound* (4.3) (24.73 g, 78%, 100–110 °C, 3.5 mmHg) as a colourless oil ($R_f = 0.75$; hexane-ethyl acetate (2:1)): found $\text{M}^+ \text{-C}_4\text{H}_9$ 261.0652, $\text{C}_{10}\text{H}_{21}\text{Sn}$ requires 261.0667; IR ν_{max} (thin film) 3033, 2958, 2927, 2853, 1464, 1376, 1072, 1006, 941, 662 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.49 (1H, dd, $J = 20.7, 14.1$ Hz, $J_{\text{Sn-H}} = 81.5$ Hz, $\text{CH}_2=\text{CH-}$), 6.17 (1H, dd, $J = 14.1, 3.7$ Hz, $J_{\text{Sn-H}} = 148.6$ Hz, CH(H)=CH-), 5.68 (1H, dd, $J = 20.7, 3.7$ Hz, $J_{\text{Sn-H}} = 74.2$ Hz, CH(H)=CH-), 1.52 (6H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.34 (6H, sext, $J = 7.3$ Hz, $-\text{CH}_2\text{CH}_3$), 0.92 (6H, t, $J = 8.0$ Hz, $J_{\text{Sn-H}} = 51.4$ Hz, SnCH_2-), 0.91 (9H, t, $J = 7.3$ Hz, $-\text{CH}_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 139.1 ($J_{\text{Sn-C}} = 375.2$ Hz), 133.5, 29.2 ($J_{\text{Sn-C}} = 21.0$ Hz), 27.4 ($J_{\text{Sn-C}} = 56.0$ Hz), 13.8, 9.4 ($J_{\text{Sn-C}} = 341.2$ Hz) ppm; MS m/z (rel. int. %) 261(100), 203(97), 177(15), 147(70), 121(22).

Tributylallyl tin (4.20).²⁰² (Figure 4.2)

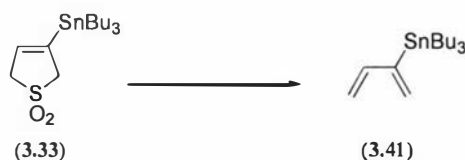
This is a modification of the procedure by Seyferth and Weiner.²⁰² A solution of allyl magnesium bromide (1.0 M, 100 ml, 0.1 mol) [prepared in the usual manner from magnesium turnings (2.55 g, 0.105 mol) and allyl bromide (12.1 g, 0.1 mol) in THF (100 ml) with catalytic iodine (*ca.* 5 mg)] was added to a stirred solution of tributyltin chloride (32.55 g, 0.1 mol) in THF (100 ml) at 0°C and the reaction mixture was worked up in the manner described for tributylvinyl tin (4.3) (*vide supra*) to give the *title compound* (4.20) (20.86 g, 63%, 80-90 °C, 0.15 mmHg) as a colourless oil ($R_f = 0.62$; hexane): found $M^+ - C_3H_5$ 291.1137, $C_{12}H_{27}Sn$ requires 291.1137; IR ν_{max} (thin film) 3077, 2957, 2925, 2853, 1623, 1464, 1376, 1072, 879, 727, 669 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 5.94 (1H, m, $CH_2=CH-$), 4.80 (1H, br.d, $J = 16.7$ Hz, $J_{Sn-H} = 20.6$ Hz, $CH(H)=CH-$), 4.80 (1H, br.d, $J = 10.1$ Hz, $J_{Sn-H} = 19.4$ Hz, $CH(H)=CH-$), 1.79 (2H, d, $J = 8.6$ Hz, $J_{Sn-H} = 61.0$ Hz, $=CHCH_2Sn$), 1.50 (6H, m, $-CH_2CH_2CH_2-$), 1.32 (6H, sext, $J = 7.3$ Hz, $-CH_2CH_3$), 0.91 (9H, t, $J = 7.3$ Hz, $-CH_3$), 0.89 (6H, t, $J = 8.0$ Hz, $J_{Sn-H} = 50.3$ Hz, $SnCH_2-$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 138.0 ($J_{Sn-C} = 43.0$ Hz), 109.1 ($J_{Sn-C} = 44.0$ Hz), 29.2 ($J_{Sn-C} = 21.0$ Hz), 27.4 ($J_{Sn-C} = 53.0$ Hz), 16.2 ($J_{Sn-C} = 245.1$ Hz), 13.8, 9.2 ($J_{Sn-C} = 318.2$ Hz) ppm; MS m/z (rel. int. %) 291(37), 275(10), 251(7), 235(40), 177(100), 149(7), 131(9), 121(38), 69(27), 57(14), 41(29).

Tributylethynyl tin (4.21)²⁰³ and bis-tributylstannylethyne (4.22). (Figure 4.2)

This is a modification of the procedure by Renaldo *et al.*²⁰³ A solution of tributyltin chloride (20.0 g, 61.4 mmol) in THF (30 ml) was added to a stirred slurry of lithium acetylide ethylenediamine complex (6.79 g, 73.7 mmol) in THF (200 ml) at 0°C under argon. The reaction was warmed to rt and stirred for 18 hrs. Water (5.5 ml) was added cautiously to the brown slurry and the solvent removed under reduced pressure. The residue was triturated with hexane (100 ml) and passed through a silica gel plug (50 mm x 25 mm diameter). Additional hexane (3x50 ml) was used to flush the column. The

combined hexane extracts were concentrated *in vacuo* to give a colourless oil that was purified by short path Kugelrohr distillation under vacuum (120-125°C, 0.7 mmHg, (lit. b.p.²⁰³ 90-94°C, 0.5 mmHg)) to give tributylethynyl tin (**4.21**) (12.09 g, 63%) as a colourless oil ($R_f = 0.79$; hexane-ethyl acetate (2:1)): found $M^+ - C_4H_9$ 259.0505, $C_{10}H_{19}Sn$ requires 259.0509; IR ν_{max} (thin film) 3286, 2957, 2923, 2853, 2006, 1464, 1377, 1074, 876 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 2.19 (1H, s, $J_{Sn-H} = 25.3$ Hz, $\equiv CH$), 1.56 (6H, m, $-CH_2CH_2CH_2-$), 1.34 (6H, sext, $J = 7.0$ Hz, $-CH_2CH_3$), 1.01 (6H, m, $SnCH_2-$), 0.90 (9H, t, $J = 7.0$ Hz, $-CH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 96.7 (d, $J_{Sn-C} = 55.0$ Hz), 88.7 (s), 28.8 (t, $J_{Sn-C} = 23.0$ Hz), 27.0 (t, $J_{Sn-C} = 60.0$ Hz), 13.7 (q), 11.0 (t, $J_{Sn-C} = 381.2$ Hz) ppm; MS m/z (rel. int. %) 259(100), 203(63), 177(33), 145(54), 121(23). The distillation residue was dissolved in hexane (20 ml) and passed through a short silica gel plug (10 mm x 25 mm diameter) and rinsed with additional hexane (3x30 ml). The combined hexane extracts were concentrated *in vacuo* to give *bis*-tributylstannylethyne (**4.22**) (1.07 g, 5.8%) as a colourless oil ($R_f = 0.50$; hexane) that was used without further purification: found $M^+ - C_4H_9$ 549.1598, $C_{22}H_{45}Sn_2$ requires 549.1576; IR ν_{max} (thin film) 2957, 2926, 2832, 1463, 1376, 1073, 875, 668 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 1.56 (12H, m, $-CH_2CH_2CH_2-$), 1.34 (12H, sext, $J = 7.3$ Hz, $-CH_2CH_3$), 0.97 (12H, m, $SnCH_2-$), 0.90 (18H, t, $J = 7.3$ Hz, $-CH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 116.3 (s), 28.9 (t, $J_{Sn-C} = 23.0$ Hz), 27.0 (t, $J_{Sn-C} = 60.0$ Hz), 13.7 (q), 11.3 (t, $J_{Sn-C} = 379.2$ Hz) ppm; MS m/z (rel. int. %) 547(100), 490(5), 433(2), 376(3), 322(3), 295(5), 263(18), 293(12), 177(9), 145(5), 121(5), 57(18), 41(22).

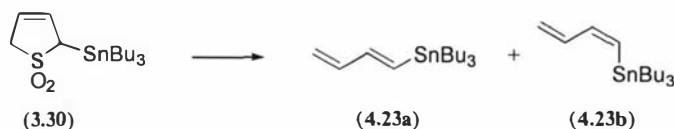
2-Tributylstannyl-1,3-butadiene (**3.41**).¹⁸¹ (Scheme 4.8)



This is a modification of the procedure by Bew and Sweeney.¹⁸¹ 2-(tributylstannyl)-2,5-dihydrothiophene-1,1-dioxide (**3.33**) (0.360 g, 0.88 mmol) was subjected to short path Kugelrohr distillation under vacuum (200°C, 0.5 mmHg) through a coiled glass column to give the *title compound* (**3.41**) (0.305 g, quant.) as a viscous, colourless oil ($R_f = 0.77$; hexane-ethyl acetate (2:1)): found M^+ 343.1455, $C_{16}H_{32}Sn$ requires 343.1451; IR ν_{max} (thin film) 3083, 3044, 2956, 2927, 2871, 2854, 1611, 1464, 984,

912, 896 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.61 (1H, dd, $J = 17.4, 9.9$ Hz, $J_{\text{Sn-H}} = 74.5$ Hz, $\text{CH}_2=\text{CH-}$), 5.91 (1H, d, $J = 2.9$ Hz, $J_{\text{Sn-H}} = 127.0$ Hz, $-\text{C}(\text{SnR}_3)=\text{CH}(\text{H})$), 5.36 (1H, d, $J = 2.9$ Hz, $J_{\text{Sn-H}} = 58.0$ Hz, $-\text{C}(\text{SnR}_3)=\text{CH}(\text{H})$), 5.09 (1H, d, $J = 16.0$ Hz, $\text{C}(\text{H})\text{H}=\text{CH-}$), 5.08 (1H, d, $J = 10.1$ Hz, $\text{C}(\text{H})\text{H}=\text{CH-}$), 1.54 (6H, m, $\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.36 (6H, sext, $J = 7.0$ Hz, $-\text{CH}_2\text{CH}_3$), 1.00 (6H, m, SnCH_2-), 0.92 (9H, t, $J = 7.0$ Hz, $-\text{CH}_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 152.4 (s), 144.3 (d, $J_{\text{Sn-C}} = 37.0$ Hz), 129.2 (t, $J_{\text{Sn-C}} = 24.0$ Hz), 116.7 (t, $J_{\text{Sn-C}} = 21.0$ Hz), 29.2 (t, $J_{\text{Sn-C}} = 20.0$ Hz), 27.4 (t, $J_{\text{Sn-C}} = 57.0$ Hz), 13.8 (q), 9.9 (t, $J_{\text{Sn-C}} = 338.2$ Hz) ppm; MS m/z (rel. int. %) 343(14), 287(74), 231(49), 177(100), 145(9), 121(32), 69(7), 57(11), 41(14).

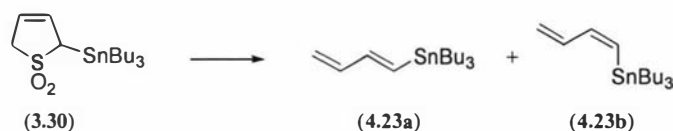
1-Tributylstannyl-1*E*,3-butadiene (4.23a) and 1-tributylstannyl-1*Z*,3-butadiene (4.23b).¹⁸² (Scheme 4.8)



This is a modification of the procedure by Gomez *et al.*¹⁸² A solution of 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.30**) (0.797 g, 1.96 mmol), pyridine (1.8 ml) and hydroquinone (*ca.* 5 mg) in xylene (40 ml) was refluxed under argon for 5 hrs. The reaction mixture was cooled, volatiles removed under reduced pressure and the residue was passed through a plug of deactivated silica gel (hexane- Et_3N 5%, 20 ml) with hexane as eluent (80 ml) to give the *title compounds* (**4.23a**) and (**4.23b**) (0.121 g, 18%, 1*E*:1*Z* = 87:13), a colourless mobile oil ($R_f = 0.65$; hexane), as an inseparable mixture of isomers: found $\text{M}^+-\text{C}_4\text{H}_9$ 287.0817, $\text{C}_{12}\text{H}_{23}\text{Sn}$ requires 287.0824; IR ν_{max} (thin film) 3084, 2957, 2926, 2883, 1807, 1559, 1464, 1376, 1071, 1009, 902, 665 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) [*E*-isomer (**4.23a**) from mixture] δ 6.56 (1H, dd, $J = 18.9, 10.0$ Hz, $-\text{CH}=\text{CHSn}$), 6.34 (1H, dt, $J = 16.9, 9.9$ Hz, $\text{CH}_2=\text{CHCH}=\text{}$), 6.27 (1H, d, $J = 18.9$ Hz, $-\text{CH}=\text{CHSn}$), 5.17 (1H, dd, $J = 16.9, 1.5$ Hz, $\text{CH}(\text{H})=\text{CH-}$), 5.06 (1H, dd, $J = 9.9, 1.5$ Hz, $\text{CH}(\text{H})=\text{CH-}$), 1.53 (6H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.34 (6H, sext, $J = 7.2$ Hz, $-\text{CH}_2\text{CH}_3$), 0.93 (6H, t, $J = 8.0$ Hz, $J_{\text{Sn-H}} = 51.6$ Hz, SnCH_2-), 0.92 (9H, t, $J = 7.2$ Hz, $-\text{CH}_3$) ppm; ^1H NMR (270 MHz, CDCl_3) [*Z*-isomer (**4.23b**) from mixture] δ 7.08 (1H, dd, $J = 12.7, 10.5$ Hz, $-\text{CH}=\text{CHSn}$), 6.47-6.11 (2H [partly obscured], br.m, $\text{CH}_2=\text{CHCH}=\text{}$), 5.25 (1H, d, $J = 16.9$ Hz, $\text{CH}(\text{H})=\text{CH-}$), 5.22 (1H [partly obscured], d, $\text{CH}(\text{H})=\text{CH-}$), 1.53 (6H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.34 (6H, sext, $J = 7.2$ Hz, $-\text{CH}_2\text{CH}_3$), 0.93

(6H, t, $J = 8.0$ Hz, $J_{\text{Sn-H}} = 51.6$ Hz, SnCH_2 -), 0.92 (9H, t, $J = 7.2$ Hz, $-\text{CH}_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) [*E*-isomer (**4.23a**) from mixture] δ 147.3, 140.1, 134.5, 115.7, 29.2 ($J_{\text{Sn-C}} = 20.0$ Hz), 27.4 ($J_{\text{Sn-C}} = 54.0$ Hz), 13.8, 9.6 ($J_{\text{Sn-C}} = 347.2$ Hz) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) [*Z*-isomer (**4.23b**) from mixture] δ 146.9, 139.5, 134.9, 118.4, 29.2 ($J_{\text{Sn-C}} = 20.0$ Hz), 27.4 ($J_{\text{Sn-C}} = 54.0$ Hz), 13.8, 9.6 ($J_{\text{Sn-C}} = 347.2$ Hz) ppm; MS m/z (rel. int. %) 287(100), 231(61), 175(58), 145(10), 121(19), 41(10).

1-Tributylstannyl-1*E*,3-butadiene (4.23a) and 1-tributylstannyl-1*Z*,3-butadiene (4.23b). (Scheme 4.8)



2-Tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.30**) (0.331 g, 0.81 mmol) was subjected to short path Kugelrohr distillation through a coiled glass column under vacuum (230°C, 0.1 mmHg) to give a pale yellow oil that was dissolved in hexane (10 ml) and passed through a plug of deactivated silica gel (hexane-Et₃N 5%, 20 ml) with hexane (50 ml) as eluent to give the *title compounds* (**4.23a**) and (**4.23b**) (99.0 mg, 36%, 1*E*:1*Z* = 87:13), a colourless mobile oil ($R_f = 0.65$; hexane), as an inseparable mixture of isomers. Further elution with ether (50 ml) gave recovered 2-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.30**) (83.5 mg, 25%).

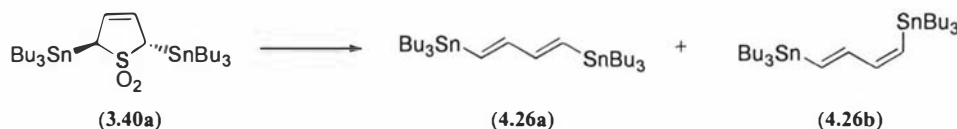
(*E*)-1,2-Bis-tributylstannylethene (4.24).²⁰³ (Scheme 4.9)



This is a modification of the procedure by Renaldo *et al.*²⁰³ Tributylethynyl tin (**4.21**) (5.45 g, 17.3 mmol), freshly distilled tributyltin hydride¹⁸⁵ (6.04 g, 20.7 mmol) and 1,1'-azo-bis-(cyclohexanecarbonitrile) (**4.25**) (106 mg, 0.432 mmol) were heated to 90°C under argon and the disappearance of the alkyne was monitored by ¹H NMR. After 5 hrs the reaction mixture was cooled and purified by short path Kugelrohr distillation under reduced pressure to give recovered tributyltin hydride (1.42 g, 24%, rt-150 °C, 0.05 mmHg), followed by the *title compound* (**4.24**) (9.51 g, 91%, 150-180

$^{\circ}\text{C}$, 0.05 mmHg (lit. b.p.²⁰³ 170-186 $^{\circ}\text{C}$, 0.3 mmHg)) as a colourless oil ($R_f = 0.60$; hexane): found M^+ 606.2427, $\text{C}_{26}\text{H}_{56}\text{Sn}_2$ requires 606.2431; IR ν_{max} (thin film) 2956, 2925, 2853, 1463, 1376, 1142, 1070, 1008, 873 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.91 (2H, s, $J_{\text{Sn-H}} = 109.6$ Hz, $-\text{CH}=\text{CH}-$), 1.52 (6H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.33 (6H, sext, $J = 7.3$ Hz, $-\text{CH}_2\text{CH}_3$), 0.91 (9H, t, $J = 7.3$ Hz, $-\text{CH}_3$), 0.90 (6H [partly obscured], t, $J = 7.6$ Hz, $J_{\text{Sn-H}} = 50.5$ Hz, SnCH_2-) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 152.9 (d, $J_{\text{Sn-C}} = 343.2$, 37.0 Hz), 29.3 (t, $J_{\text{Sn-C}} = 20.0$ Hz), 27.4 (t, $J_{\text{Sn-C}} = 52.0$ Hz), 13.8 (q), 9.7 (t, $J_{\text{Sn-C}} = 326.2$ Hz) ppm; MS m/z (rel. int. %) 604(1), 549(36), 492(4), 439(3), 354(4), 291(63), 261(61), 235(43), 203(44), 177(90), 147(59), 121(53), 56(27), 41(100).

1,4-Bis-tributylstannyl-1E,3E-butadiene (4.26a) and 1,4-bis-tributylstannyl-1E,3Z-butadiene (4.26b). (Scheme 4.10)



A solution of *trans*-2,5-bis-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.40a**) (0.249 g, 0.36 mmol), pyridine (0.5 ml) and hydroquinone (5 mg) in xylene (10 ml) was refluxed under argon for 5 hrs. The reaction mixture was cooled, volatiles removed under reduced pressure and the residue was passed through a plug of deactivated silica gel (hexane- Et_3N 5%, 40 ml) with hexane as eluent (50 ml) to give the *title compounds* (**4.26a**) and (**4.26b**) (0.153 g, 67%, *E:Z* 57:43) as an inseparable mixture of isomers as a colourless oil ($R_f = 0.65$; hexane): found M^+ - C_4H_9 577.1891, $\text{C}_{24}\text{H}_{49}\text{Sn}_2$ requires 577.1889; IR ν_{max} (thin film) 2957, 2925, 2853, 1531, 1463, 1376, 1072, 1007, 874, 664 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 7.04 [*E,Z*-isomer (**4.26b**)] (1H, dd, $J = 11.6$, 9.7 Hz, $-\text{CH}=\text{}$), 6.60-6.05 [both isomers] (7H, br.m, $-\text{CH}=\text{}$), 1.53 [both isomers] (6H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 1.34 [both isomers] (6H, sext, $J = 7.3$ Hz, $-\text{CH}_2\text{CH}_3$), 0.93 [both isomers] (6H [partly obscured], t, $J = 8.0$ Hz, $J_{\text{Sn-H}} = 51.0$ Hz, SnCH_2-) 0.92 [both isomers] (9H, t, $J = 7.3$ Hz, $-\text{CH}_3$), ppm; ^{13}C NMR (67.8 MHz, CDCl_3) [*E,E*-isomer (**4.26a**)] δ 149.8, 132.6, 29.2 ($J_{\text{Sn-C}} = 20.0$ Hz), 27.4 ($J_{\text{Sn-C}} = 55.0$ Hz), 13.8, 9.6 ($J_{\text{Sn-C}} = 344.2$ Hz) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) [*E,Z*-isomer (**4.26b**)] δ 149.6, 149.3, 135.6, 133.0, 29.2 ($J_{\text{Sn-C}} = 20.0$ Hz), 27.4 ($J_{\text{Sn-C}} = 55.0$ Hz), 13.8, 9.6 ($J_{\text{Sn-C}} = 344.2$ Hz) ppm; MS m/z (rel. int. %) 575(44), 518(5), 337 (31), 287(100), 229(48), 175(84), 121(39), 56(29), 41(88).

1,4-Dichloro-2-butyne (4.29).²⁰⁹ (Scheme 4.14)

This is a modification of the procedure by Montijon *et al.*²⁰⁹ 2-Butyne-1,4-diol (1.00 g, 11.6 mmol) was placed in a 3 neck flask fitted with a CaCl₂ guard tube, an N₂ inlet and a rubber septum. The vessel was swept with dry N₂, cooled to 0°C in an ice bath and the diol wetted with DMF (0.121 g, 1.7 mmol). Thionyl chloride (1.86 ml, 25.6 mmol) was added dropwise and the reaction mixture stirred at 0°C for 10 min and then warmed to rt over 1 hr. Volatiles were removed under reduced pressure (15 mmHg, 50°C) and the residue taken up in ether (10 ml), washed with sat. NaHCO₃ (10 ml), water (2x10 ml) and sat. brine (10 ml), dried over MgSO₄, filtered and concentrated *in vacuo* to give a yellow oil. The crude product was purified by short path distillation (Kugelrohr) at reduced pressure (65-68°C, 20 mmHg) to give the *title compound* (4.29) (1.342 g, 94%) as a colourless, mobile oil (R_f = 0.67; hexane-ethyl acetate (2:1)): found M⁺ 121.9687, C₄H₄Cl₂ requires 121.9690; IR ν_{max} (thin film) 2995, 2954, 1686, 1428, 1263, 1162, 703 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 4.19 (4H, s, ClCH₂C≡) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 81.0, 30.1 ppm; GCMS *m/z* (rel. int. %) 124(13), 122(20), 87(100), 51(27).

Trimethyltin bromide.²¹¹

This is a modification of the procedure by Eaborn and Waters.²¹¹ Bromine (12.62 g, 0.079 mol) was added dropwise to stirred tetramethyl tin (14.12 g, 0.079 mol) at 0°C under argon over a 2 hr period. The resulting yellow oil was purified by short path distillation (Kugelrohr) at reduced pressure to give the *title compound* (16.73 g, 87%, 75-80°C, 30 mmHg (lit. b.p.²¹¹ 159°C)) as a colourless oil that solidified on cooling (m.p. 27°C): found M⁺-CH₃ 228.8664, C₂H₆BrSn requires 228.8663; IR ν_{max} (thin film) 2994, 2917, 1736, 1702, 1396, 1191, 783 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 0.77 (9H, s, J_{Sn-H} = 57.4 Hz, -CH₃) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ -0.91 (J_{Sn-C} = 357.2 Hz, -

CH₃) ppm; MS *m/z* (rel. int. %) 229(78), 195(68), 165(100), 151(40), 135(51), 120(20), 84(10), 44(6).

Trimethyltin lithium (solution in THF).²¹⁰



This is a modification of the procedure by Tamborski *et al.*²¹⁰ A solution of trimethyltin bromide (14.621 g, 0.06 mol) in THF (30 ml) was added dropwise to lithium wire (0.85 g, 0.122 mol) in THF (25 ml) at 0°C under argon. The green reaction mixture was warmed to rt and stirred for 2 hrs. Aliquots (0.5 ml) were removed and standardised against dilute HCl [BDH] (0.100 M) with phenolphthalein as indicator. This gave trimethyltin lithium as a solution in THF (0.98 M, 55 ml, 0.054 mol, 90%). This solution could be stored under argon in the freezer for several weeks without significant loss of activity.

1,4-Bis-trimethylstannyl-2-butyne (4.30).²⁰⁸ (Scheme 4.14)



This is a modification of the procedure by Reich *et al.*²⁰⁸ A solution of trimethyltin lithium in THF (0.98 M, 25.0 ml, 24.5 mmol) was added dropwise to a solution of 1,4-dichloro-2-butyne (4.29) (1.51 g, 12.25 mmol) in THF (25 ml) at -78°C under argon. The reaction mixture was stirred for 10 min, water (20 ml) and hexane (50 ml) were added and the cooling bath removed. The aqueous phase was extracted with hexane (2x50 ml) and the combined organic extracts were washed with water (2x50 ml) and sat. brine (50 ml), dried over MgSO₄, and concentrated *in vacuo* to give an orange oil that was purified by short path distillation (Kugelrohr) at reduced pressure to give recovered starting material (4.29) (0.199 g, 13%, 20-75°C, 0.1 mmHg) and followed by the *title compound* (4.30) (3.118 g, 77%, 75-115 °C, 0.1 mmHg) as a colourless oil (*R_f* = 0.18; hexane): found M⁺-CH₂Sn(CH₃)₃ 202.9892, C₆H₁₁Sn requires 202.9883; IR *v*_{max} (thin film) 2980, 2904, 2203, 1419, 1187, 1171, 769 cm⁻¹; ¹H NMR (270 MHz, CDCl₃)

δ 1.56 (4H, s, $J_{\text{Sn-H}} = 61.3, 24.6$ Hz, $\text{R}_3\text{SnCH}_2\text{C}\equiv$), 0.16 (18H, s, $J_{\text{Sn-H}} = 54.5$ Hz, $(\text{CH}_3)_3\text{Sn-}$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 77.1 ($J_{\text{Sn-C}} = 17.1$ Hz), -1.5 ($J_{\text{Sn-C}} = 294.2, 12.2$ Hz), -9.5 ($J_{\text{Sn-C}} = 335.7$ Hz) ppm; MS m/z (rel. int. %) 203(100), 165(81), 135(42), 120(12), 53(35).

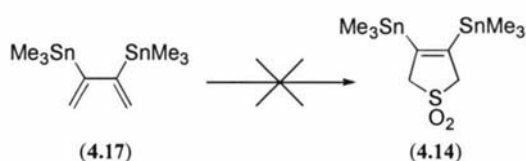
2,3-Bis-trimethylstannyl-1,3-butadiene (4.17).²⁰⁸ (Scheme 4.14)



This is a modification of the procedure by Reich *et al.*²⁰⁸ A solution of trimethyltin lithium in THF (0.98 M, 28.0 ml, 27.44 mmol) was added to a stirred solution of HMPA (4.92 g, 27.44 mmol) in THF (28.0 ml) at 0°C under argon. 1,4-Dichloro-2-butyne (4.29) (1.52 g, 12.36 mmol) was added dropwise, the cooling bath removed after 10 min and the reaction mixture warmed to rt over 2 hrs. Water (20 ml) and hexane (50 ml) were added and the aqueous phase was extracted with hexane (2x50 ml). The combined organic extracts were washed with water (2x50 ml) and sat. brine (50 ml), dried over MgSO_4 , and concentrated *in vacuo* to give a brown oil that was purified by flash chromatography on silica gel eluting with hexane through to hexane-ethyl acetate (6:1) to yield the *title compound* (4.17) (2.860 g, 61%) as a colourless, viscous oil ($R_f = 0.56$; hexane) which solidified on storage in the freezer: found M^+ 381.9759, $\text{C}_{10}\text{H}_{22}\text{Sn}_2$ requires 381.9765; IR ν_{max} (thin film) 3044, 2982, 2936, 2913, 1812, 1696, 1568, 1567, 1382, 1188, 904, 767 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.69 (2H, d, $J = 2.3$ Hz, $J_{\text{Sn-H}} = 149.7$ Hz, $\text{CH}(\text{H})=\text{CSn-}$), 5.33 (2H, d, $J = 2.3$ Hz, $J_{\text{Sn-H}} = 68.9$ Hz, $\text{CH}(\text{H})=\text{CSn-}$), 0.20 (18H, s, $J_{\text{Sn-H}} = 53.9$ Hz, $-\text{Sn}(\text{CH}_3)_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 158.4, 126.7 ($J_{\text{Sn-C}} = 40.6$ Hz), -8.2 ($J_{\text{Sn-C}} = 334.0$ Hz) ppm; MS m/z (rel. int. %) 380(16), 365(9), 311(5), 202(33), 165(100), 150(19), 135(23). Further elution gave 1,4-bis-tributylstannyl-2-butyne (4.30) (0.757 g, 16%).

2-Trimethylstannyl-1,3-butadiene (4.32).²⁰⁸ (Scheme 4.17)

This is a modification of the procedure by Reich *et al.*²⁰⁸ Trifluoroacetic acid (0.26 g, 2.28 mmol) was added to a stirred solution of 1,4-*bis*-trimethylstannyl-2-butyne (4.30) (0.865 g, 2.28 mmol) in CH₂Cl₂ (20 ml) at rt under argon. The reaction mixture was stirred for 18 hrs and the volatiles removed under reduced pressure. The residue was triturated with hexane (50 ml) and filtered through a short plug of silica gel eluting with hexane (50 ml) to give the *title compound* (4.32) (0.210 g, 43%) as a colourless oil (*R_f* = 0.56; hexane) that was used without further purification: found *M*⁺-CH₄ 201.9803, C₆H₁₀Sn requires 201.9804; IR *v*_{max} (thin film) 3084, 3045, 2984, 2952, 2915, 1612, 1568, 1387, 1190, 985, 899, 769 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 6.59 (1H, ddt, *J* = 17.4, 9.9, 0.9 Hz, *J*_{Sn-H} = 81.5 Hz, CH₂=CH-), 5.88 (1H, br.d, *J* = 2.6 Hz, *J*_{Sn-H} = 139.7 Hz, -C(SnR₃)=CH(H)), 5.38 (1H, br.d, *J* = 2.6 Hz, *J*_{Sn-H} = 66.6 Hz, -C(SnR₃)=CH(H)), 5.12 (1H, br.d, *J* = 10.5 Hz, C(H)H=CH-), 5.11 (1H, br.d, *J* = 16.0 Hz, C(H)H=CH-), 0.23 (9H, s, *J*_{Sn-H} = 54.9 Hz, -Sn(CH₃)₃) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 143.4, 128.9, 126.7, 117.2, -9.0 ppm; MS *m/z* (rel. int. %) 202(22), 165(100), 135(28), 95(10), 85(12), 71(18), 57(30), 43(21).

Attempted synthesis of 3,4-*bis*-trimethylstannyl-2,5-dihydrothiophene-1,1-dioxide (4.14). (Scheme 4.15)

A thick walled glass test tube (12 mm I.D. x 100 mm) fitted with a resealable Young's stopcock was charged with a solution of 2,3-*bis*-trimethylstannyl-1,3-butadiene (4.17) (0.20 g, 0.527 mmol) in ether-methanol (1.5 ml, 1:1), hydroquinone (*ca.* 1 mg) and a small magnetic stirrer. SO₂ (2.0 ml) was distilled into the vessel at -78°C, the headspace swept with argon and the stopcock firmly sealed. The tube was warmed to rt behind a secure blast shield where a heavy white precipitate formed. The reaction

mixture was stirred for an additional 18 hrs, cooled to 0°C and the SO₂ vented off. The solid (0.1847 g) was filtered and rinsed with ether (2x10 ml). Attempts to recrystallise this material proved unsuccessful: found C 22.9%, H 4.8%, S 12.8%, Sn 45.8%; IR ν_{\max} (KBr disc) 3417, 2995, 2915, 1717, 1637, 1400, 1325, 1012, 965, 782, 548 cm⁻¹; ¹H NMR (270 MHz, d₆-DMSO) δ 2.97 (2H, s), 0.48 (9H, s, $J_{\text{Sn-H}} = 70.5$ Hz, -Sn(CH₃)₃) ppm; ¹³C NMR (67.8 MHz, d₆-DMSO) δ 78.1, 53.0, 1.2 ppm; MS m/z (rel. int. %) 429(1), 392(5), 165(100), 150(15), 135(30), 120(8), 64(48); (FAB +ve ion) MS m/z (rel. int. %) 671(10), 165(100).

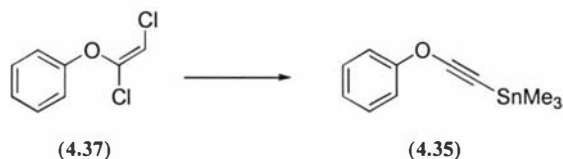
3-Trimethylstannyl-2,5-dihydrothiophene-1,1-dioxide (4.33). (Scheme 4.17)



A thick walled glass test tube (12 mm I.D. x 100 mm) fitted with a resealable Young's stopcock was charged with a solution of 2-trimethylstannyl-1,3-butadiene (4.32) (0.20 g, 0.92 mmol) in ether (1.5 ml), hydroquinone (*ca.* 1 mg) and a small magnetic stirrer. SO₂ (2.0 ml) was distilled into the vessel at -78°C, the headspace swept with argon and the stopcock firmly sealed. The tube was warmed to rt behind a secure blast shield where after 20 mins a heavy white precipitate began to form. The reaction mixture was stirred for an additional 2 hrs, cooled to 0 °C and the SO₂ vented off. The solid (90.4 mg) was filtered, and rinsed with ether (2x10 ml): found C 22.0%, H 4.4%, S 11.7%, Sn 45.7%. The combined supernatant and washings were concentrated under reduced pressure and the residue purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (2:1) to give the *title compound* (4.33) (20.0 mg, 8%) as a clear viscous oil ($R_f = 0.25$; hexane-ethyl acetate (2:1)): found M^+ 281.9740, C₇H₁₄O₂SSn requires 281.9737; IR ν_{\max} (thin film) 2978, 2919, 1580, 1305, 1229, 1120, 1007, 776, 693 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 6.11 (1H, quint., $J = 2.4$ Hz, $J_{\text{Sn-H}} = 48.8$ Hz, -CH=C(R)-), 3.79 (2H, m, -CH₂SO₂CH₂-), 3.75 (2H, m, -CH₂SO₂CH₂-), 0.25 (9H, s, $J_{\text{Sn-H}} = 56.7$ Hz, -Sn(CH₃)₃) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 141.4, 131.9 ($J_{\text{Sn-C}} = 28.1$ Hz), 60.8 ($J_{\text{Sn-C}} = 39.1$ Hz), 56.5, -9.7 ($J_{\text{Sn-C}} = 379.6$ Hz) ppm; MS m/z (rel. int. %) 282(<1), 267(3), 229(10), 218(5), 203(100), 165(75), 135(30), 120(7), 53(26).

E-1,2-Dichloro-1-phenoxyethene (4.37). (Scheme 4.20)

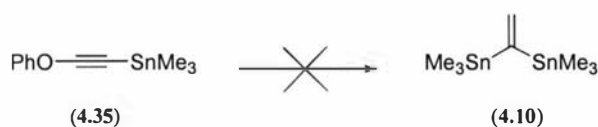
This is a modification of a procedure by Moyano *et al.*²¹⁷ A solution of phenol (5.88 g, 0.063 mol) in THF (100 ml) was added to an oil free slurry of potassium hydride (5.09 g, 0.127 mol) in THF (125 ml) at 0°C under argon over 15 min. The reaction was stirred for an additional 15 min, cooled to -50°C and freshly distilled 1,1,2-trichloroethene (8.212 g, 0.063 mol) was added dropwise over 15 min. The cooling bath was removed and the reaction mixture refluxed for 3 hrs. On cooling, sat. K₂HPO₄ (50 ml) and water (50 ml) were added, the organic phase isolated and the aqueous phase extracted with ether (2x50 ml). The combined organic layers were washed with water (2x50 ml), and sat. brine (50 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by short path Kugelrohr distillation under reduced pressure (55-60°C, 0.1 mmHg) to give the *title compound* (4.37) (11.03 g, 93%) as a pale yellow oil (*R_f* = 0.57; hexane-ethyl acetate (8:1)): found *M*⁺ 187.9792, C₈H₆Cl₂O requires 187.9796; IR *v*_{max} (thin film) 3103, 1631, 1592, 1489, 1272, 1195, 1164, 1079, 830, 745, 688 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 7.43-7.08 (5H, m, C₆H₅-), 5.99 (1H, s, =CHCl) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 153.6 (s), 139.9 (s), 129.7 (d), 124.4 (d), 116.9 (d), 103.7 (d) ppm; MS *m/z* (rel. int. %) 190(18), 188(31), 152(6), 125(32), 114(10), 94(12), 77(100), 65(11), 51(32), 39(15).

1-Phenoxy-2-trimethylstannylethyne (4.35). (Scheme 4.20)

This is a modification of a procedure by Moyano *et al.*²¹⁷ BuLi (1.46 M [hexanes], 9.46 ml, 13.82 mmol) was added dropwise to a stirred solution of 1,2-dichloro-1-phenoxyethene (4.37) (1.244 g, 6.58 mmol) in THF (30 ml) at -50°C under argon. The reaction mixture was warmed to -10 °C over 20 mins and a solution of trimethyltin

chloride (1.442 g, 7.24 mmol) in THF (10 ml) was added as a single aliquot. The cooling bath was removed and the reaction mixture stirred at rt for 1 hr. Water (10 ml) and ether (30 ml) were added, the organic phase isolated and the aqueous phase extracted with ether (2x20 ml). The combined organic layers were washed with water (2x30 ml), and sat. brine (30 ml), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by short path Kugelrohr distillation under reduced pressure (85-95°C, 0.15 mmHg) to give the *title compound* (4.35) (1.048 g, 57%) as a viscous, colourless oil ($R_f = 0.52$; hexane-ethyl acetate (8:1)): IR ν_{\max} (thin film) 2987, 2919, 2158, 1591, 1488, 1207, 1162, 779, 751, 686 cm⁻¹; ¹H NMR (270 MHz, CDCl₃) δ 7.40-7.12 (5H, m, C₆H₅-), 0.36 (9H, s, $J_{\text{Sn-H}} = 59.1$ Hz, -Sn(CH₃)₃) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 155.6, 129.4, 124.1, 114.8, 104.8, 41.7, -7.4 ($J_{\text{Sn-C}} = 208.5$ Hz) ppm.

Attempted synthesis of 1,1-bis-trimethylstannylethene (4.10).



1,1-Bis-trimethylstannylethene (4.10) has been prepared by Mitchell.²¹⁵ A solution of 1-phenoxy-2-trimethylstannylethyne (4.35) (0.145 g, 0.517 mmol), freshly prepared trimethyltin hydride²¹⁸ (0.256 g, 1.55 mmol) and AIBN (5.17×10^{-5} mol, 10 mol%) in benzene (10 ml) was heated to reflux while the disappearance of the stannane was monitored by tlc. After 5 hrs the reaction mixture was cooled and the volatiles removed under reduced pressure. The residue was subjected to destructive short path Kugelrohr distillation under reduced pressure (20-200°C, 0.1 mmHg). No volatiles were collected and considerable charring of the residue occurred.

1,1-Dibromo-2-methyl-1-propene (4.42).²²² (Scheme 4.21)



This is a modification of the procedure by Corey and Fuchs.²²² Triphenylphosphine (18.78 g, 0.072 mol) was added in three portions to a stirred solution of freshly

sublimed carbontetrabromide (11.87 g, 0.036 mol) in benzene (80 ml) under argon. The reaction mixture was stirred for an additional 30 mins and acetone (1.04 g, 0.18 mol) was added dropwise over 10 mins. The slurry was refluxed for 18hrs, cooled and filtered. The residue was extracted with hexane (2x50 ml) and the combined filtrate and extracts were concentrated *in vacuo*. MgSO_4 (ca. 10 g) was added and the residue stirred vigorously with hexane (100 ml) for 2 hrs. The solid material was removed by filtration and the hexane fraction concentrated *in vacuo* and purified by short path Kugelrohr distillation under reduced pressure (35-40°C, 15 mmHg) to give the *title compound* (4.42) (2.07 g, 54%) as a colourless mobile oil ($R_f = 0.62$; hexane): found M^+ 211.8833, $\text{C}_4\text{H}_6\text{Br}_2$ requires 211.8836; IR ν_{max} (thin film) 3002, 2916, 2851, 1600, 1443, 1368, 1211, 1079, 853, 813 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.92 (6H, s, - CH_3) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 138.2 (s), 84.3 (s), 24.6 (q) ppm; MS m/z (rel. int. %) 216(4), 214(8), 135(6), 133(7), 119(9), 8(37), 86(52), 84(52), 49(100), 47(89), 35(23).

1-Bromo-1-trimethylstannyl-2-methyl-1-propene (4.43).²¹⁴ (Scheme 4.21)



This is a modification of the procedure by Mitchell and Reimann.²¹⁴ Trimethyltin lithium (0.98 M [THF], 15.0 ml 14.7 mmol) was added dropwise to a stirred solution of 1,1-dibromo-2-methyl-1-propene (4.42) (1.52 g, 7.11 mmol) in THF (10 ml) at -78°C under argon. The reaction mixture was warmed to rt and water (20 ml) was added. The organic phase was isolated and the aqueous phase extracted with ether (2x30 ml). The combined organic layers were washed with water (50 ml), and sat. brine (50 ml), dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by short path Kugelrohr distillation under reduced pressure (115-135°C, 15 mmHg) to give the *title compound* (4.43) (1.626 g, 77%) as a colourless mobile oil ($R_f = 0.67$; hexane): found M^+ 297.9359, $\text{C}_7\text{H}_{15}\text{BrSn}$ requires 297.9379; IR ν_{max} (thin film) 2981, 2913, 1611, 1444, 1365, 1191, 1069, 773 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.97 (3H, s, $J_{\text{Sn-H}} = 6.4$ Hz, - CH_3), 1.85 (3H, s, $J_{\text{Sn-H}} = 8.8$ Hz, - CH_3), 0.31 (9H, s, $J_{\text{Sn-H}} = 56.0$ Hz, - $\text{Sn}(\text{CH}_3)_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 146.2, 121.1, 25.4 ($J_{\text{Sn-C}} = 28.0$ Hz),

24.7 ($J_{\text{Sn-C}} = 29.0$ Hz), -6.6 ($J_{\text{Sn-C}} = 367.2$ Hz) ppm; MS m/z (rel. int. %) 298(8), 283(15), 229(100), 199(18), 165(12), 135(17), 53(12).

1,1-Bis-trimethylstannyl-2-methyl-1-propene (4.41).²¹⁴ (Scheme 4.21)



This is a modification of the procedure by Mitchell and Reimann.²¹⁴ Trimethyltin lithium (0.98 M [THF], 5.7 ml 5.6 mmol) was added dropwise to a stirred solution of 1-bromo-1-trimethylstannyl-2-methyl-1-propene (4.43) (1.12 g, 3.76 mmol) in THF (15 ml) at -78°C under argon. The reaction mixture was maintained at -78°C for 1 hr then warmed to rt and stirred for an additional hour. The reaction mixture was worked-up as described above to give a residue that was purified by flash chromatography on silica gel eluting with hexane. This gave recovered starting material (4.43) (0.150 g, 13%) and a colourless oil ($R_f = 0.76$; hexane) that was further purified by short path Kugelrohr distillation under reduced pressure (120°C , 15 mmHg) to give the *title compound* (4.41) (0.171 g, 12%): found M^+ 383.9938, $\text{C}_{10}\text{H}_{24}\text{Sn}_2$ requires 383.9928; IR ν_{max} (thin film) 2978, 2910, 1692, 1580, 1440, 1181, 909, 761 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 1.98 (6H, s, $J_{\text{Sn-H}} = 11.2, 4.0$ Hz, $-\text{CH}_3$), 0.21 (18H, s, $J_{\text{Sn-H}} = 48.8$ Hz, $-\text{Sn}(\text{CH}_3)_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 158.9, 136.2, 30.7 ($J_{\text{Sn-C}} = 93.1, 71.0$ Hz), -10.1 ($J_{\text{Sn-C}} = 244.2$ Hz) ppm; MS m/z (rel. int. %) 381(11), 367(29), 313(23), 165(100), 135(61), 47(25).

6.5.2 Standard Cross-coupling Conditions.

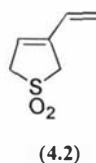
A solution of stannane and iodide (3.37), or diiodide (4.15), in freshly distilled DMF was twice freeze-thaw degassed under argon and catalyst was added. Typically the colourless solution darkened rapidly, becoming black over time. The reaction mixture was degassed once more and stirred under argon. The temperature and duration of the reaction conditions varied from substrate to substrate and progress of the reaction was followed by tlc. After tlc analysis the reaction mixture was again degassed. Two standard work up procedures were employed.

- A. For insoluble products. Ether was added to the reaction mixture and the supernatant decanted from the precipitate. The precipitate was triturated successively with ether, CH_2Cl_2 and finally hexane to give the coupled product as an amorphous solid. (Recovery by centrifugation was performed where necessary.) Recrystallisation from an appropriate solvent system was then attempted. Where a soluble product was also present the combined supernatant and trituration washings were subjected to work-up protocol B.
- B. For soluble products. Volatiles were removed under reduced pressure (typically 45°C , 0.1 mmHg) and the residue purified by flash chromatography on silica gel eluting with an appropriate solvent system. Recrystallisation was then attempted.

Generally no effort was made to recover any trialkyltin halide by-products with either work-up protocol. *Bis*-(acetonitrile) palladium (II) dichloride was prepared according to the method of Brandsma.¹⁹⁵ *Tris*-(dibenzylideneacetone) dipalladium (0).chloroform was prepared according to the method of Ukai *et al.*^{195,226}

6.5.2.1 Coupling Reactions with *Mono*-stannanes.

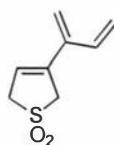
3-Vinyl-2,5-dihydrothiophene-1,1-dioxide (4.2).¹⁹⁸ (Scheme 4.22)



3-Vinyl-2,5-dihydrothiophene-1,1-dioxide (4.2) has been prepared by other means by Cadogan *et al.*¹⁹⁸ Under standard cross-coupling conditions (type B) at rt over 2 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (3.37) (0.105 g, 0.429 mmol), tributylvinyl tin (4.3) (0.164 g, 0.515 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (5.6 mg, 2.15×10^{-5} mol, 5 mol%) in DMF (4.0 ml) gave the *title compound* (4.2) (57.1 mg, 92%) as a white solid ($R_f = 0.20$; hexane-ethyl acetate (2:1) that was recrystallised from CH_2Cl_2 -ether (m.p. $88.5\text{-}90^\circ\text{C}$ (lit. m.p.¹⁹⁸ $75\text{-}76^\circ\text{C}$)): found M^+ 144.0242, $\text{C}_6\text{H}_8\text{O}_2\text{S}$ requires 144.0245; IR ν_{max} (KBr disc) 3060, 2964, 2937, 1634, 1586, 1399, 1302, 1239, 1125, 996, 923, 819, 564 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.45 (1H, dd, $J = 17.4$, 10.8 Hz, $\text{CH}_2=\text{CH}-$), 5.95 (1H, m, $-\text{CH}=\text{CR}-$), 5.34 (1H, d, $J = 10.8$ Hz, $\text{CH}(\text{H})=\text{CH}-$),

5.16 (1H, d, $J = 17.4$ Hz, $CH(H)=CH-$), 3.94 (2H, m, $-CH_2SO_2CH_2-$), 3.89 (2H, m, $-CH_2SO_2CH_2-$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 136.1 (s), 132.4 (d), 121.1 (d), 118.4 (t), 57.4 (t), 54.9 (t) ppm; MS m/z (rel. int. %) 144(18), 80(93), 79(100), 65(7), 52(17), 39(19).

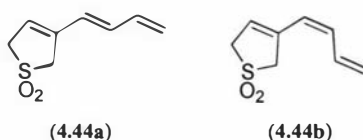
2-(1',1'-Dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (4.5).¹⁹⁹ (Scheme 4.23)



(4.5)

Sulfolene (4.5) has been prepared previously by Roth *et al.*¹⁹⁹ in an undisclosed yield by the addition of sulfur dioxide to [4]-dendralene (4.4). Under standard cross-coupling conditions (type B) at rt over 72 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (3.37) (0.103 g, 0.42 mmol), 2-tributylstannyl-1,3-butadiene (3.41) (0.145 g, 0.42 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (5.5 mg, 2.1×10^{-5} mol, 5 mol%) in DMF (4.0 ml) gave the *title compound* (4.5) (53.7 mg, 75%) after trituration with hexane (2x2 ml) as a yellow solid ($R_f = 0.30$; hexane-ethyl acetate (2:1)) that underwent extensive polymerisation upon recrystallisation from ether (m.p. 161-162°C): found M^+ 170.0399, $C_8H_{10}O_2S$ requires 170.0402; 1H NMR (270 MHz, $CDCl_3$) δ 6.43 (1H, dd, $J = 17.4$, 10.8, Hz, $CH_2=CH-$), 6.04 (1H, m, $-CH=C(R)-$), 5.46 (1H, dd, $J = 17.4$, 1.3 Hz, $CH(H)=CH-$), 5.38 (1H, s, $CH(H)=(R)R$), 5.27 (1H, dd, $J = 10.8$, 1.3 Hz, $CH(H)=CH-$), 5.00 (1H, s, $CH(H)=(R)R$) 3.95 (2H, br.s, $-CH_2SO_2CH_2-$), 3.92 (2H, br.s, $-CH_2SO_2CH_2-$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 141.6 (s), 135.9 (s), 133.9 (d), 119.8 (d), 118.3 (t), 116.4 (t), 57.5 (t), 56.3 (t) ppm; MS m/z (rel. int. %) 170(1), 106(10), 105(40), 104(37), 91(46), 78(18), 64(7), 53(100), 41(15), 39(16).

1-(1',1'-Dioxo-2'5'-dihydrothien-3'-yl)-1*E*,3-butadiene (4.44a) and 1-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1*Z*,3-butadiene (4.44b). (Table 4.1, entry 1)

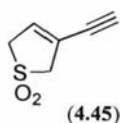


(4.44a)

(4.44b)

Under standard cross-coupling conditions (type B) at rt over 2 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (98 mg, 0.401 mmol), 1-tributylstannyl-1,3-butadienes (**4.23a**) and (**4.23b**) (0.151 g, 0.442 mmol, 1*E*:1*Z* = 87:13) and *bis*-(acetonitrile) palladium (II) dichloride (5.2 mg, 2.01×10^{-5} mol, 5 mol%) in DMF (4.0 ml) gave the *title compounds* (**4.44a**) and (**4.44b**) (62.7 mg, 92%, 1*E*:1*Z* = 85:15) as a pale yellow solid ($R_f = 0.29$; hexane-ethyl acetate (2:1)) that was recrystallised from CH_2Cl_2 -hexane to give the 1*E*-isomer (**4.44a**) as yellow needles (50.1 mg, 74%, m.p. 79-81°C): found M^+ 170.0401, $\text{C}_8\text{H}_{10}\text{O}_2\text{S}$ requires 170.0402; IR ν_{max} (KBr disc) 3095, 3025, 2966, 2916, 1618, 1296, 1125, 1005, 911, 788, 589, 446 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) [1*E*-isomer (**4.44a**)] δ 6.38 (1H, ddd, $J = 16.9, 10.1, 10.1$ Hz, $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}$ =), 6.29 (1H, d, $J = 15.6$ Hz, $-\text{CH}=\text{CH}-\text{C}(\text{R})=\text{CH}$ =), 6.12 (1H, dd, $J = 10.1, 15.6$ Hz, $=\text{CH}-\text{CH}=\text{CH}-$), 5.93 (1H, br.s, $-\text{CH}=\text{C}(\text{R})-$), 5.36 (1H, d, $J = 16.9$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.25 (1H, d, $J = 10.1$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 3.92 (2H, br.s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.88 (2H, br.s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^1H NMR (270 MHz, CDCl_3) [1*Z*-isomer (**4.44b**) from mixture] δ 6.63 (1H, ddd, $J = 16.7, 11.9, 10.1$ Hz, $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}$ =), 6.17 (1H, br.t, $J = 11.9$ Hz, $=\text{CH}-\text{CH}=\text{CH}-$), 5.97 (1H, m, $-\text{CH}=\text{C}(\text{R})-$), 5.89 (1H, br.d, $J = 11.9$ Hz, $-\text{CH}=\text{CH}-\text{C}(\text{R})=\text{CH}$ =), 5.39 (1H, d, $J = 16.7$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.32 (1H, d, $J = 10.1$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 4.01 (2H, br.s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.89 (2H, br.s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) [1*E*-isomer (**4.44a**)] δ 135.7 (d), 135.5 (s), 133.6 (d), 127.8 (d), 120.8 (d), 120.4 (t), 57.3 (t), 55.0 (t) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) [1*Z*-isomer (**4.44b**) from mixture] δ 134.6 (s), 132.8 (d), 131.8 (d), 124.2 (d), 122.5 (d), 122.2 (t), 57.8 (t), 56.2 (t) ppm; MS m/z (rel. int. %) 170(24), 106(41), 91(100), 78(33), 65(10), 51(14), 39(17).

3-Ethynyl-2,5-dihydrothiophene-1,1-dioxide (**4.45**). (Table 4.1, entry 2)



Under standard cross-coupling conditions (type B) at rt over 2 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (0.113 g, 0.461 mmol), tributylethynyl tin (**4.21**) (0.153 g, 0.484 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (6.0 mg, 2.31×10^{-5} mol, 5 mol%) in DMF (4.0 ml) gave the *title compound* (**4.45**) (62.1 mg, 95%) as a white solid ($R_f = 0.29$; hexane-ethyl acetate (2:1)) that was recrystallised from CH_2Cl_2 -hexane (m.p. 137-138°C): found M^+ 142.0083, $\text{C}_6\text{H}_6\text{O}_2\text{S}$ requires 142.0088; IR ν_{max}

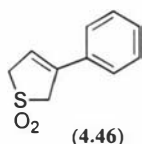
(KBr disc) 3254, 3070, 2980, 2936, 2099, 1602, 1396, 1309, 1248, 1150, 1130, 1110, 718, 679, 514, 425 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.35 (1H, m, $-\text{CH}=\text{CR}-$), 3.89 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.83 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.17 (1H, s, $\equiv\text{CH}$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 129.9 (d), 118.4 (s), 81.9 (d), 77.2 (s), 57.3 (t), 56.7 (t) ppm; MS m/z (rel. int. %) 142(7), 78(100), 63(7), 52(29), 39(14).

Attempted synthesis of 3-ethynyl-2,5-dihydrothiophene-1,1-dioxide (4.45) from 3-bromo-2,5-dihydrothiophene-1,1-dioxide (3.50).



Under standard cross-coupling conditions (type B) at 80°C over 24 hrs, 3-bromo-2,5-dihydrothiophene-1,1-dioxide (**3.50**) (0.105 g, 0.531 mmol), tributylethynyl tin (**4.21**) (0.167 g, 0.531 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (6.9 mg, 2.65×10^{-5} mol, 5 mol%) in DMF (4.0 ml) gave recovered starting materials: (**3.50**) (0.099 g, 94%) and (**4.21**) (0.146 g, 87%).

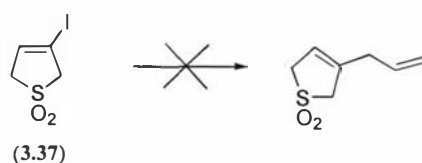
3-Phenyl-2,5-dihydrothiophene-1,1-dioxide (4.46). (Table 4.1, entry 3)



3-Phenyl-2,5-dihydrothiophene-1,1-dioxide (**4.46**) has been prepared previously by the Heck arylation of 3-sulfolene (**3.1**).^{170,171} Under standard cross-coupling conditions (type B) at rt over 18 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (0.102 g, 0.417 mmol), trimethylphenyl tin (0.105 g, 0.437 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (5.4 mg, 2.08×10^{-5} mol, 5 mol%) in DMF (2.0 ml) gave the *title compound* (**4.46**) (54.8 mg, 68%) as a white solid ($R_f = 0.27$; hexane-ethyl acetate (2:1)) that was recrystallised from CH_2Cl_2 -ether (m.p. $134\text{--}136^\circ\text{C}$ (lit. m.p.¹⁷⁰ $131.3\text{--}131.8^\circ\text{C}$)): found C 61.9%, H 5.2%, S 16.7%, $\text{C}_{10}\text{H}_{10}\text{O}_2\text{S}$ requires C 61.8%, H 5.2%, S 16.5%; found M^+ 194.0407, $\text{C}_{10}\text{H}_{10}\text{O}_2\text{S}$ requires 194.0402; IR ν_{max} (KBr disc) 3087,

2970, 2925, 1451, 1299, 1237, 1129, 1105, 754, 690, 590 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 7.39 (5H, m, C_6H_5^-), 6.36 (1H, m, $-\text{CH}=\text{CPh}-$), 4.16 (2H, q, $J = 1.8$ Hz, $-\text{CH}_2\text{SO}_2\text{CH}_2^-$), 4.07 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2^-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 136.2 (s), 133.8 (s), 129.2 (d), 128.9 (d), 125.4 (d), 117.1 (d), 57.7 (t), 56.7 (t) ppm; MS m/z (rel. int. %) 194(14), 130(100), 115(39), 102(12), 94(27), 77(12), 64(10), 57(5), 39(7).

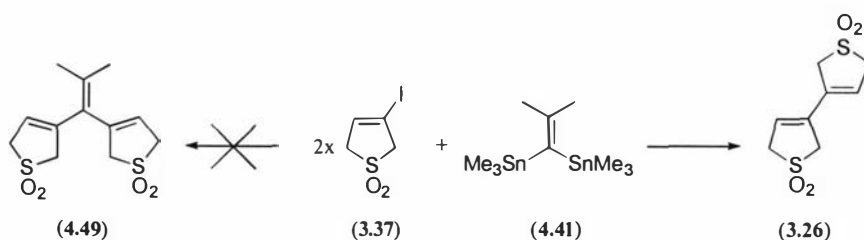
Attempted coupling of tributylallyl tin (4.20) with 3-iodo-2,5-dihydrothiophene-1,1-dioxide (3.37). (Table 4.1, entry 4)



Under standard cross-coupling conditions (type B) at rt over 24 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (3.37) (0.126 g, 0.52 mmol), tributylallyl tin (4.20) (0.189 g, 0.57 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (6.7 mg, 2.59×10^{-5} mol, 5 mol%) in DMF (4.0 ml) gave recovered iodide (3.37) (43.3 mg, 34%) as the only isolable product.

6.5.2.2 Coupling Reactions with *Bis*-stannanes.

Attempted synthesis of 1,1-*bis*-(1',1'-dioxo-2',5'-dihydrothien-3'-yl)-2-methyl-1-propene (4.49). (Scheme 4.26)



Under standard cross-coupling conditions (type A) at rt over 72 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (3.37) (0.220 g, 0.897 mmol), 1,1-*bis*-trimethylstannyl-2-methyl-1-propene (4.41) (0.171 g, 0.448 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (6.0 mg, 2.24×10^{-5} mol, 5 mol%) in DMF (4.0 ml) gave trimethyltin iodide

(34.6 mg, 13%), recovered 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (62.3 mg, 28%) and 3,3'-bi-2,5-dihydrothiophene-1,1-dioxide (**3.26**) (44.3 mg, 39%).

1,1,2-Tribromoethane (**4.51**).²²³ (Scheme 4.27)



This is a modification of the procedure by Furukawa *et al.*²²³ A solution of vinyl bromide (10.0 g, 0.093 mol) in CHCl_3 (20 ml) was added to a stirred solution of bromine (14.19 g, 0.089 mol) in CHCl_3 (25 ml) at 0°C under argon. The cooling bath was removed and the reaction mixture warmed to rt over 1 hr. Volatiles were removed under reduced pressure and the residual orange oil was purified by short path Kugelrohr distillation *in vacuo* (85°C , 18 mmHg) to give the *title compound* (**4.51**) (21.26 g, 90%), a colourless mobile oil: found M^+ 263.7793, $\text{C}_2\text{H}_3\text{Br}_3$ requires 263.7785; IR ν_{max} (thin film) 3022, 3002, 2960, 1418, 1218, 1147, 880, 688, 610 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.68 (1H, t, $J = 6.6$ Hz, $\text{Br}_2\text{HC-}$), 4.11 (2H, d, $J = 6.6$ Hz, $-\text{CH}_2\text{Br}$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 40.3, 38.9 ppm; MS m/z (rel. int. %) 268(12), 266(8), 264(4), 189(48), 187(100), 185(54), 107(20), 105(23), 79(5).

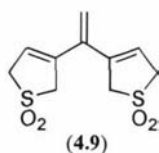
1,1-Dibromoethene (**4.50**).²²⁴ (Scheme 4.27)



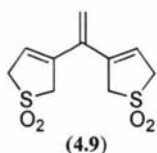
This is a modification of the procedure by Jacobsen and Berman.²²⁴ Potassium acetate (7.38 g, 0.075 mol) and potassium carbonate (10.39 g, 0.075 mol) were placed in a 3 neck 250 ml flask fitted with a dropping funnel, a Dean-Stark distillation apparatus and a rubber septum. The contents of the flask were slurried with dry ethanol (60 ml), purged thoroughly with argon and heated to reflux. Once the ethanol began to collect in the Dean-Stark apparatus, 1,1,2-tribromoethane (**4.51**) (20 g, 0.075 mol) was added rapidly as a single aliquot through the dropping funnel. With the use of a hot air gun the distillation was continued until only a solid cake remained in the flask. The

distillate was added to a separating funnel containing argon degassed water (100 ml) under a stream of argon. The organic layer was run off under a stream of argon and dried over CaCl_2 to give the *title compound* (**4.50**) (11.91 g, 86%) as a dense colourless oil. Exposure to air at any time resulted in significant decomposition and the attempted purification of a small aliquot (1.15 g) by short path Kugelrohr distillation *in vacuo* (60–65°C, 180 mmHg) gave the *title compound* (**4.50**) (0.63 g, 55%) in no greater purity than the initial isolate. Hence, the bulk of the material was used without further purification: found $\text{M}+\text{H}^+$ 184.8605, $\text{C}_2\text{H}_3\text{Br}_2$ requires 184.8601; IR ν_{max} (thin film) 3174, 3108, 3021, 1740, 1593, 1078, 1046, 881, 696 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.28 (2H, s, $=\text{CH}_2$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 125.7, 95.1 ppm; MS m/z (rel. int. %) 189(50), 187(100), 185(51), 107(26), 105(24).

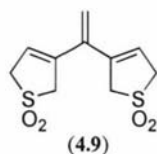
1,1-Bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-ethene (4.9). (Table 4.2, entry 1)



Under standard cross-coupling conditions (type B) at 40°C over 36 hrs, 1,1-dibromoethene (**4.50**) (0.116 g, 0.626 mmol), 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) (0.510 g, 1.252 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (8.1 mg, 3.13×10^{-5} mol, 5 mol%) in DMF (4.0 ml) gave 2,5-dihydrothiophene-1,1-dioxide (**3.1**) (28.1 mg, 19%) as a white solid ($R_f = 0.65$; hexane-ethyl acetate (1:3)) and the *title compound* (**4.9**) (18.6 mg, 11%) as an off white solid ($R_f = 0.19$; hexane-ethyl acetate (1:3)). This material was recrystallised from acetone- d_6 -DMSO (m.p. > 300°C): found $\text{M}^+ - \text{SO}_2$ 195.0477, $\text{C}_{10}\text{H}_{12}\text{O}_2\text{S}$ requires 195.0479; IR ν_{max} (KBr disc) 2984, 2939, 1638, 1400, 1307, 1233, 1129, 921, 795 cm^{-1} ; ^1H NMR (270 MHz, d_6 -DMSO) δ 6.10 (2H, m, $-\text{CH}=\text{C}(\text{R})-$), 5.34 (2H, s, $=\text{CH}_2$), 4.05 (4H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 4.01 (4H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 138.9, 134.1, 122.8, 118.8, 56.8, 56.1 ppm; MS m/z (rel. int. %) 195(13), 131(100), 117(88), 104(32), 91(54), 77(16), 63(24), 53(15), 39(15).

1,1-Bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-ethene (4.9). (Table 4.2, entry 2)

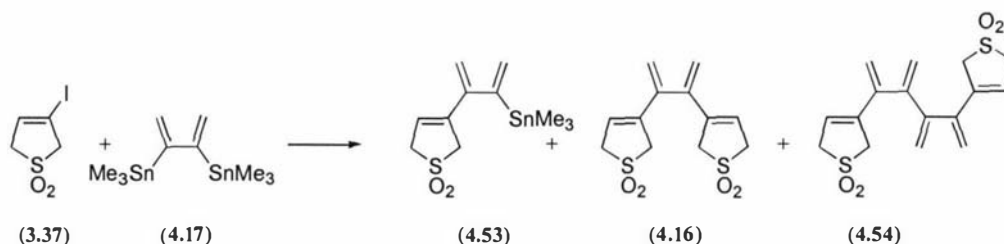
This procedure uses the general reaction conditions developed by Farina.¹⁷⁷ Triphenylarsine (18.7 mg, 6.11×10^{-5} mol, 8 mol%) and *tris*-(dibenzylideneacetone) dipalladium. CHCl_3 (15.8 mg, 1.53×10^{-5} mol, 2 mol%) were added to a stirred solution of 1,1-dibromoethene (**4.50**) (70.9 mg, 0.382 mmol) and 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) (0.311 g, 0.763 mmol) in NMP (3.8 ml) under argon. The reaction mixture slowly darkened and was stirred for 18 hrs at rt in the dark. Volatiles were removed under reduced pressure (65°C, 0.1 mmHg), the residue adsorbed onto silica gel (3 g) in acetone (10 ml) and purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) through to hexane-ethyl acetate (1:3). This gave recovered stannane (**3.33**) (0.118 g, 38%), 2,5-dihydrothiophene-1,1-dioxide (**3.1**) (22.4 mg, 25%) and the *title compound* (**4.9**) (3.2 mg, 3%) contaminated with traces of tributyltin bromide.

1,1-Bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-ethene (4.9). (Table 4.2, entry 3)

This procedure uses the reaction conditions developed by Torii *et al.*²²⁷ Triphenylphosphine (10.9 mg, 4.13×10^{-5} mol, 10 mol%) and palladium acetate (4.6 mg, 2.07×10^{-5} mol, 5 mol%) were added to a stirred solution of 1,1-dibromoethene (**4.50**) (76.9 mg, 0.413 mmol) and 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) (0.337 g, 0.827 mmol) in acetonitrile (2.0 ml) under argon. The reaction mixture slowly darkened and was stirred for 18 hrs at 60°C in the dark. Volatiles were removed under reduced pressure (40°C, 0.1 mmHg), the residue was adsorbed onto silica gel (3 g) in acetone (10 ml) and purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) through to hexane-ethyl acetate (1:3). This gave recovered stannane

(**3.33**) (0.153 g, 45%), 2,5-dihydrothiophene-1,1-dioxide (**3.1**) (11.3 mg, 25%) and the *title compound* (**4.9**) (6.3 mg, 6%).

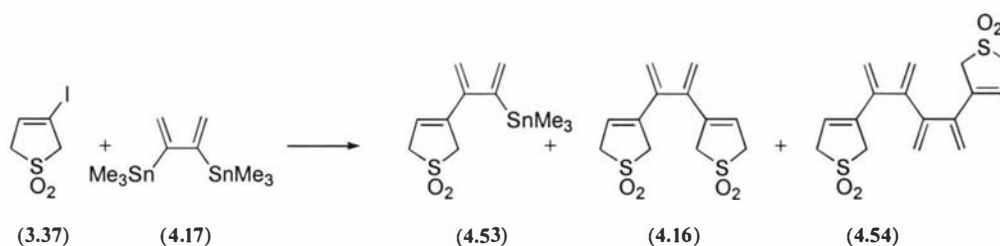
2-Trimethylstannyl-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (4.53),
2,3-bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (4.16) and
3,4-dimethylene-2,5-bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,5-hexadiene (4.54).
(Table 4.3, entry 1)



A solution of 2,3-bis-trimethylstannyl-1,3-butadiene (**4.17**) (0.150 g, 0.376 mmol) and 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (91.8 mg, 0.376 mmol) in freshly distilled DMF (5.0 ml) was twice freeze-thaw degassed under argon. *Bis*-(acetonitrile) palladium (II) dichloride (9.8 mg, 3.76×10^{-5} mol, 10 mol%) was added, the reaction mixture was degassed once more and stirred at 60°C for 72 hrs. The reaction mixture was cooled and concentrated *in vacuo* (45°C, 0.1 mmHg). The residue was dissolved in acetone (5 ml), adsorbed onto silica (0.5 g) and purified by flash column chromatography on silica gel eluting with hexane-ethyl acetate (10:1) through to ethyl acetate to give 2-trimethylstannyl-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.53**) (23.2 mg, 19%) as a white solid ($R_f = 0.29$; hexane-ethyl acetate (5:1)) that was recrystallised from ether- CH_2Cl_2 (m.p. 85-86.5°C): found M^+ 334.0051, $\text{C}_{11}\text{H}_{18}\text{O}_2\text{SSn}$ requires 334.0050; UV λ_{max} (ϵ) (EtOH) 227.6 (11500), 203.8 (13000) nm; IR ν_{max} (KBr disc) 3038, 2972, 2923, 1580, 1403, 1295, 1141, 924, 884, 774, 531 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.87 (1H, br.s, $-\text{CH}=\text{C}(\text{R})_2$), 5.79 (1H, d, $J = 2.9$ Hz, $J_{\text{Sn-H}} = 134.9$ Hz, $\text{CH}(\text{H})=\text{C}(\text{R})\text{Sn}$), 5.48 (1H, d, $J = 2.9$ Hz, $J_{\text{Sn-H}} = 65.5$ Hz, $\text{CH}(\text{H})=\text{C}(\text{R})\text{Sn}-$), 4.95 (1H, br.s, $J_{\text{Sn-H}} = 9.7$ Hz, $\text{CH}(\text{H})=\text{C}(\text{R})_2$), 4.83 (1H, br.s, $\text{CH}(\text{H})=\text{C}(\text{R})_2$), 3.93 (4H, br.s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 0.16 (9H, s, $J_{\text{Sn-H}} = 54.9$ Hz, $\text{Sn}(\text{CH}_3)_3$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 152.5 (s), 148.7 (s), 136.3 (s), 128.8 (t), 120.8 (d), 112.7 (t), 57.8 (t), 55.9 (t), -8.9 (q) ppm; MS m/z (rel. int. %) 334(10), 319(3), 255(29), 225(9), 165(100), 150(9), 135(17), 105(70), 77(10). Further elution gave 3,4-dimethylene-2,5-bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,5-hexadiene (**4.54**) (18.7 mg, 30%) as an amorphous, off white solid ($R_f = 0.11$; hexane-ethyl acetate (2:1)) that could not be recrystallised (m.p.

> 350°C): found M^+ 338.0657, $C_{16}H_{18}O_4S_2$ requires 338.0647; UV λ_{max} (ϵ) (EtOH) 219.8 (14800) nm; IR ν_{max} (KBr disc) 3073, 2970, 2926, 1614, 1583, 1404, 1289, 1129, 909, 882, 600, 452 cm^{-1} ; 1H NMR (270 MHz, d_6 -DMSO) δ 6.02 (2H, br.s, $-CH=C(R)_2$), 5.37 (2H, m, $CH(H)=C(R)_2$), 5.31 (2H, br.s, $CH(H)=C(R)_2$), 5.22 (2H, br.s, $CH(H)=C(R)_2$), 5.13 (2H, m, $CH(H)=C(R)_2$), 3.96 (4H, m, $-CH_2SO_2CH_2-$), 3.89 (4H, m, $-CH_2SO_2CH_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 145.6 (s), 142.9 (s), 135.7 (s), 121.6 (d), 118.9 (t), 118.6 (t), 57.4 (t), 55.3 (t) ppm; MS m/z (rel. int. %) 338(<1), 274(1), 210(64), 195(100), 181(62), 167(67), 153(36), 141(43), 128(44), 115(49), 103(11), 91(38), 77(40), 64(91), 48(28), 39(25). Further elution gave 2,3-*bis*-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.16**) (23.3 mg, 43%) as an amorphous, white solid (R_f = 0.40; ethyl acetate) that could not be recrystallised (m.p. > 350°C): found M^+ 286.0321, $C_{12}H_{14}O_4S_2$ requires 286.0333; UV λ_{max} (ϵ) (EtOH) 223.2 (22100) nm; IR ν_{max} (KBr disc) 3096, 3055, 2987, 2958, 2920, 1624, 1583, 1300, 1231, 1137, 920, 787, 605, 467, 447, 427 cm^{-1} ; 1H NMR (270 MHz, d_6 -DMSO) δ 5.88 (2H, br.s, $-CH=C(R)_2$), 5.38 (2H, br.s, $CH(H)=C(R)_2$), 5.22 (2H, br.s, $CH(H)=C(R)_2$), 4.12 (4H, m, $-CH_2SO_2CH_2-$), 3.98 (4H, m, $-CH_2SO_2CH_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 141.8 (s), 135.3 (s), 121.9 (d), 119.3 (t), 57.4 (t), 55.2 (t) ppm; MS m/z (rel. int. %) 286(<1), 221(3), 157(29), 143(41), 129(39), 115(24), 105(8), 91(23), 77(16), 64(100), 42(48).

2-Trimethylstannyl-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (4.53), 2,3-*bis*-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (4.16) and 3,4-dimethylene-2,5-*bis*-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,5-hexadiene (4.54).
(Table 4.3, entry 2)

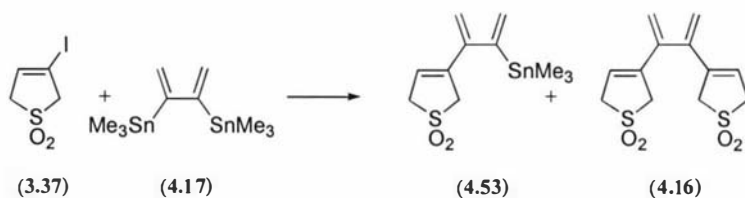


Under the conditions described above, 2,3-*bis*-trimethylstannyl-1,3-butadiene (**4.17**) (50.0 mg, 0.132 mmol,) and 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (64.3 mg, 0.263 mmol) in DMF (2.0 ml) with *bis*-(acetonitrile) palladium (II) dichloride (3.4 mg, 1.32×10^{-5} mol, 5 mol%) gave recovered 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (10.1 mg, 16%); 2-trimethylstannyl-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-

butadiene (**4.53**) (24.2 mg, 55%), 2,3-*bis*-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.16**) (4.5 mg, 12%) and 3,4-dimethylene-2,5-*bis*-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,5-hexadiene (**4.54**) (1.1 mg, 5%).

2-Trimethylstannyl-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (4.53**) and 2,3-*bis*-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.16**).**

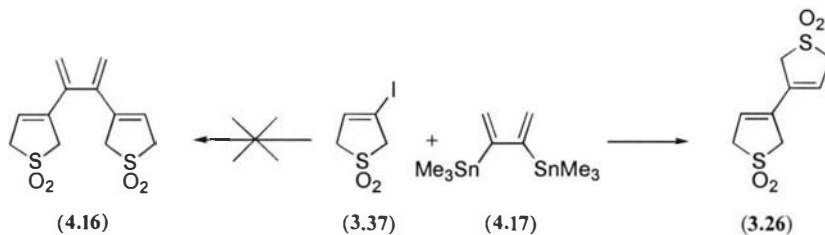
(Table 4.3, entry 3)



This procedure uses the general reaction conditions developed by Farina.¹⁷⁷ Triphenylarsine (16.3 mg, 5.32×10^{-5} mol, 10 mol%) and *tris*-(dibenzylideneacetone) dipalladium. CHCl_3 (13.8 mg, 1.33×10^{-5} mol, 2.5 mol%) were added to a stirred solution of 2,3-*bis*-trimethylstannyl-1,3-butadiene (**4.17**) (0.213 g, 0.532 mmol) and 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (0.130 g, 0.532 mmol) in NMP (5.0 ml) under argon. The reaction mixture slowly darkened and was stirred for 72 hrs at rt in the dark. Volatiles were removed under reduced pressure (65°C, 0.1 mmHg), the residue adsorbed onto silica gel (3 g) in acetone (10 ml) and purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (6:1) through to hexane-ethyl acetate (1:3) to give 2-trimethylstannyl-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.53**) (17.8 mg, 10%) and 2,3-*bis*-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.16**) (14.2 mg, 19%).

Attempted synthesis of 2,3-*bis*-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (4.16**), formation of 3,3'-bi-2,5-dihydrothiophene-1,1-dioxide (**2.26**).**

(Table 4.3, entry 4)



This procedure uses the general reaction conditions developed by Farina.¹⁷⁷ Under the conditions described above, triphenylarsine (32.6 mg, 1.06×10^{-4} mol, 20 mol%) and *tris*-(dibenzylideneacetone) dipalladium. CHCl_3 (27.5 mg, 2.66×10^{-5} mol, 5 mol%) were added to a stirred solution of 2,3-*bis*-trimethylstannyl-1,3-butadiene (**4.17**) (0.213 g, 0.532 mmol) and 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (0.259 g, 1.063 mmol) in NMP (5.0 ml). The reaction mixture slowly darkened and was stirred for 72 hrs at rt in the dark. The reaction mixture was diluted with ether (10 ml) and the supernatant decanted from the precipitate. The precipitate was triturated successively with ether (2x10 ml) and hexane (2x10 ml) to give (**3.26**) (0.104 g, 83%) as an amorphous off white solid. The combined supernatant and washings were concentrated under reduced pressure (65°C, 0.1 mmHg) and the residue adsorbed onto silica gel (3 g) in acetone (10 ml). The attempted isolation of additional products by flash chromatography on silica gel eluting with hexane-ethyl acetate (6:1) through to hexane-ethyl acetate (1:3) was unsuccessful.

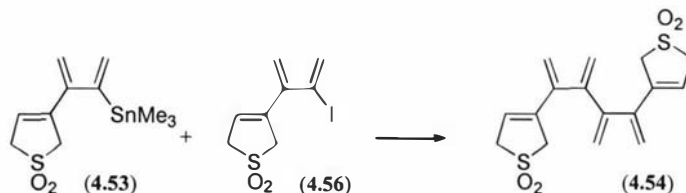
2-Iodo-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (4.56). (Scheme 4.30)



Iodine (18.7 mg, 7.4×10^{-5} mol) was added to a solution of 2-trimethylstannyl-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.53**) (21.1 mg, 6.3×10^{-5} mol) in CH_2Cl_2 (2 ml) at rt under argon. The reaction mixture was stirred for 1 hr, ether (25 ml) was added and the brown solution washed with sat. $\text{Na}_2\text{S}_2\text{O}_3$ (5 ml), water (2x10 ml) and sat. brine (10 ml), dried over MgSO_4 , and concentrated *in vacuo* to give the *title compound* (**4.56**) (19.0 mg, quant.) as a white solid ($R_f = 0.32$; hexane-ethyl acetate (1:1)) that was recrystallised from hexane-ether (m.p. 120.5-122°C): found M^+ 295.9387, $\text{C}_8\text{H}_9\text{IO}_2\text{S}$ requires 295.9368; UV λ_{max} (ϵ) (EtOH) 225.2 (13500), 210.2 sh. (12000) nm; IR ν_{max} (KBr disc) 3089, 3071, 2979, 2937, 1860, 1819, 1612, 1580, 1575, 1388, 1306, 1262, 1132, 905, 760, 450 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.26 (1H, d, $J = 1.3$ Hz, $\text{CH}(\text{H})=\text{C}(\text{R})\text{I}$), 6.16 (1H, m, $-\text{CH}=\text{C}(\text{R})_2$), 6.07 (1H, d, $J = 1.3$ Hz, $\text{CH}(\text{H})=\text{C}(\text{R})\text{I}$ -), 5.48 (1H, br.s, $\text{CH}(\text{H})=\text{C}(\text{R})_2$), 5.08 (1H, br.s, $\text{CH}(\text{H})=\text{C}(\text{R})_2$), 3.99 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.92 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ

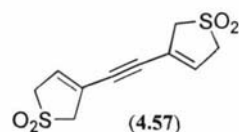
146.4 (s), 133.3 (s), 131.0 (t), 122.4 (d), 118.2 (t), 100.5 (s), 57.7 (t), 55.9 (t) ppm; MS m/z (rel. int. %) 296(<1), 230(44), 127(6), 105(100), 77(45), 65(10), 52(24).

3,4-Dimethylene-2,5-bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,5-hexadiene (4.54).
(Scheme 4.30)



A solution of 2-trimethylstannyl-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.53**) (17.3 mg, 5.2×10^{-5} mol) and 2-iodo-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.56**) (15.4 mg, 5.2×10^{-5} mol) in freshly distilled DMF (1.0 ml) was twice freeze-thaw degassed under argon. *Bis*-(acetonitrile) palladium (II) dichloride (0.7 mg, 2.6×10^{-6} mol, 5 mol%) was added, the reaction mixture was degassed once more and stirred at 60°C for 48 hrs. The reaction mixture was cooled and concentrated *in vacuo* (45°C, 0.1 mmHg). The residue was dissolved in acetone (5 ml), adsorbed onto silica (0.5 g) and purified by flash column chromatography on silica gel eluting with hexane-ethyl acetate (4:1) through to ethyl acetate to give recovered iodide (**4.56**) (5.2 mg, 34%) followed by the *title compound* (**4.54**) (2.7 mg, 15%) as a white solid.

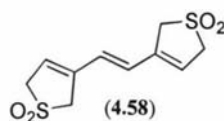
***Bis*-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-ethyne (4.57).** (Table 4.4, entry 1)



Under standard cross-coupling conditions (type A) at rt over 2 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (51.6 mg, 0.21 mmol), *bis*-tributylstannylethyne (**4.22**) (63.4 mg, 0.105 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (2.7 mg, 1.05×10^{-5} mol, 5 mol%) in DMF (2.0 ml) gave the *title compound* (**4.57**) (25.3 mg, 93%) as an amorphous white solid ($R_f = 0.45$; hexane-ethyl acetate (1:3)) that was recrystallised from acetone (m.p. > 300°C): found C 43.4%, H 3.6%, S 24.2%, $C_{10}H_{10}O_4S_2$ requires C 46.5%, H 3.9%, S 24.8%; found M^+ 258.0035, $C_{10}H_{10}O_4S_2$ requires 258.0021; IR ν_{max} (KBr disc) 3071, 2975, 2929, 1304, 1244, 1124, 802, 620,

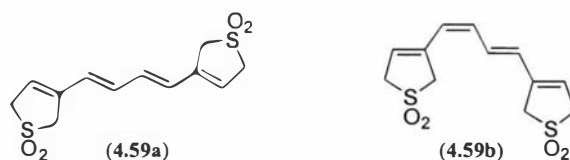
568, 495, 405 cm^{-1} ; ^1H NMR (270 MHz, d_6 -DMSO) δ 6.54 (2H, br.s, $-\text{CH}=\text{C}(\text{R})-$), 4.03 (4H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 4.00 (4H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 132.3 (d), 117.4 (s), 86.9 (s), 56.4 (t), 56.3 (t) ppm; MS m/z (rel. int. %) 258(3), 194(22), 130(100), 115(44), 102(20), 91(11), 77(18), 64(37), 48(23), 39(21).

***E*-1,2-Bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-ethene (4.58). (Table 4.4, entry 2)**



Under standard cross-coupling conditions (type A) at rt over 3 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (55.1 mg, 0.23 mmol), (*E*)-1,2-bis-tributylstannylethene (**4.24**) (75.2 mg, 0.12 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (3.0 mg, 1.15×10^{-5} mol, 5 mol%) in DMF (2.0 ml) gave the *title compound* (**4.58**) (27.9 mg, 95%) as an off white amorphous solid that could not be recrystallised (m.p. $> 300^\circ\text{C}$): found M^+ 260.0175, $\text{C}_{10}\text{H}_{12}\text{O}_4\text{S}_2$ requires 260.0178; IR ν_{max} (KBr disc) 3058, 2981, 2939, 1665, 1314, 1243, 1130, 1102, 970, 792, 502 cm^{-1} ; ^1H NMR (270 MHz, d_6 -DMSO) δ 6.40 (2H, s, $-\text{CH}=\text{CH}-$), 6.15 (2H, br.s, $-\text{CH}=\text{C}(\text{R})-$), 4.02 (8H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 135.3, 128.3, 124.1, 57.1, 54.5 ppm; MS m/z (rel. int. %) 260(2), 196(29), 132(56), 117(100), 104(31), 91(61), 79(42), 64(63), 53(19), 48(26), 39(22).

1,4-Bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1*E*,3*E*-butadiene (4.59a) and 1,4-bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1*E*,3*Z*-butadiene (4.59b). (Table 4.4, entry 3)

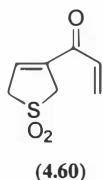


Under standard cross-coupling conditions (type A) at rt over 18 hrs, 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (29.6 mg, 0.123 mmol), 1,4-bis-tributylstannyl-1*E*,3*E*-butadiene (**4.26a**) and 1,4-bis-tributylstannyl-1*E*,3*Z*-butadiene (**4.26b**) (38.4 mg, 6.07×10^{-5} mol, *E,E:E,Z* = 57:43) and *bis*-(acetonitrile) palladium (II) dichloride (1.6 mg, 6.15×10^{-6} mol, 5 mol%) in DMF (1.0 ml) gave an inseparable mixture of the *title*

compounds (**4.59a**) and (**4.59b**) (12.3 mg, 74%, *E,E:E,Z* = *ca.* 1:1) as an off white amorphous solid that could not be recrystallised (m.p. > 300°C): found M^+ 286.0297, $C_{12}H_{14}O_4S_2$ requires 286.0333; IR ν_{max} (KBr disc) 3066, 2981, 2937, 1666, 1295, 1244, 1133, 1117, 988, 598, 455 cm^{-1} ; 1H NMR (270 MHz, d_6 -DMSO) [*E,E*-isomer (**4.59a**)] δ 6.42 (4H, m, =CH-), 6.17 (2H, br.s, -CH=C(R)-), 4.04 (4H, m, -CH₂SO₂CH₂-), 4.00 (4H, m, -CH₂SO₂CH₂-) ppm; 1H NMR (270 MHz, d_6 -DMSO) [*E,Z*-isomer (**4.59b**)] δ 6.52-6.11 (4H [partly obscured], m, =CH-), 6.13 (2H, br.s, -CH=C(R)-), 4.31 (2H, m, -CH₂SO₂CH₂-), 4.23 (2H, m, -CH₂SO₂CH₂-), 4.00 (2H [partly obscured], m, -CH₂SO₂CH₂-), 3.95 (2H, m, -CH₂SO₂CH₂-) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) [*E,E*-isomer (**4.59a**)] δ 135.5 (s), 132.2 (d), 129.8 (d), 123.1 (d), 57.0 (t), 54.5 (t) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) [*E,Z*-isomer (**4.59b**)] δ 135.9 (s), 134.5 (s), 131.3 (d), 130.0 (d), 128.8 (d), 126.7 (d), 125.3 (d), 123.2 (d), 57.2 (t), 56.7 (t), 55.7 (t), 54.7 (t) ppm; MS *m/z* (rel. int. %) 286(2), 222(29), 158(54), 143(63), 128(62), 115(42), 105(82), 91(66), 77(39), 64(100), 48(44), 39(34).

6.5.3 Carbonylative Cross-coupling Reactions.

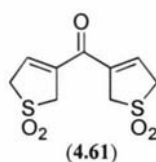
Vinyl-(1,1-dioxo-2,5-dihydrothien-3-yl) ketone (**4.60**). (Scheme 4.31)



A stirred solution of 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (50.0 mg, 0.205 mmol) in DMF (2.0 ml) was twice freeze-thaw degassed under an atmosphere of carbon monoxide. *Bis*-(acetonitrile) palladium (II) dichloride (2.6 mg, 1.024×10^{-5} mol, 5 mol%) was added and the yellow solution was degassed once more under an atmosphere of carbon monoxide. Tributylvinyl tin (**4.3**) (71.5 mg, 0.225 mmol) was added and the black solution was stirred under an atmosphere of carbon monoxide at rt for 18 hrs. Volatiles were removed under reduced pressure (45°C, 0.1 mmHg) and the residue purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (10:1) through to hexane-ethyl acetate (1:1) to give the *title compound* (**4.60**) (25.4 mg, 72%) as a white solid (R_f = 0.18; hexane-ethyl acetate (1:1)) that was recrystallised from CH₂Cl₂-hexane (m.p. 85.5-90°C): found C 48.2%, H 4.5%, S 18.5%, C₇H₈O₃S

requires C 48.8%, H 4.7%, S 18.6%; found M^+ 172.0195, $C_7H_8O_3S$ requires 172.0194; IR ν_{\max} (KBr disc) 3078, 2989, 2972, 2925, 1661, 1607, 1412, 1395, 1230, 1189, 985, 749, 678 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.96 (1H, m, $-\text{CH}=\text{C}(\text{R})-$), 6.89 (1H, dd, $J = 16.9, 10.5$ Hz, $\text{CH}_2=\text{CH}-$), 6.45 (1H, dd, $J = 16.9, 1.5$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.94 (1H, dd, $J = 10.5, 1.5$ Hz, $\text{CH}(\text{H})=\text{CH}$), 4.12 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 4.09 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 185.2, 138.5, 132.3, 131.0, 129.4, 58.2, 54.9 ppm; MS m/z (rel. int. %) 172(2), 108(29), 79(20), 80(19), 55(100), 53(20).

Di-(1,1-dioxo-2,5-dihydrothien-3-yl) ketone (4.61). (Scheme 4.31)



A stirred solution of 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (0.120 g, 0.493 mmol) in DMF (2.0 ml) was twice freeze-thaw degassed under an atmosphere of carbon monoxide. *Bis*-(acetonitrile) palladium (II) dichloride (6.4 mg, 2.47×10^{-5} mol, 5 mol%) was added and the yellow solution was degassed once more under an atmosphere of carbon monoxide. A solution of 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) (0.169 g, 0.493 mmol) in DMF (1.0 ml) was twice freeze-thaw degassed under argon and added to the iodide (**3.37**) and catalyst. The green solution was stirred under an atmosphere of carbon monoxide at rt for 18 hrs. Volatiles were removed under reduced pressure (45°C, 0.1 mmHg) and the residue purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (10:1) through to hexane-ethyl acetate (1:1) to give the *title compound* (**4.61**) (0.101 g, 82%) as a white solid ($R_f = 0.20$; hexane-ethyl acetate (1:1)) that was recrystallised from CH_2Cl_2 -acetone (m.p. $> 300^\circ\text{C}$): found C 41.2%, H 3.7%, S 24.7%, $\text{C}_9\text{H}_{10}\text{O}_5\text{S}_2$ requires C 41.2%, H 3.8%, S 24.4%; found $M+H^+$ 263.0053, $\text{C}_9\text{H}_{11}\text{O}_5\text{S}_2$ requires 263.0048; IR ν_{\max} (KBr disc) 3007, 2950, 2935, 1642, 1610, 1389, 1334, 1251, 1219, 1197, 1130, 1002, 913, 741, 664 585 cm^{-1} ; ^1H NMR (270 MHz, d_6 -DMSO) δ 7.02 (2H, m, $-\text{CH}=\text{C}(\text{R})-$), 4.24 (4H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 4.09 (4H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 185.9, 136.4, 134.6, 57.8, 54.7 ppm; MS m/z (rel. int. %) 263(<1), 198(1), 134(56), 105(10), 91(24), 81(34), 64(40), 53(100), 48(18), 39(6).

6.5.4 Cross-coupling Reactions of 3,4-Diiodo-2,5-dihydrothiophene-1,1-dioxide.

2,3-Diiodo-1,3-butadiene (4.64).²⁰⁸ (Scheme 4.32)



This is a modification of the procedure by Reich *et al.*²⁰⁸ Iodine (1.066 g, 4.2 mmol) was added portion-wise to a solution of 1,4-bis-trimethylstannyl-2-butyne (4.30) (0.757 g, 2.0 mmol) in CH_2Cl_2 (10 ml) at -78°C under argon. The reaction mixture was stirred for 10 min and the cooling bath removed. Hexane (50 ml) was added and the brown solution washed with sat. $\text{Na}_2\text{S}_2\text{O}_3$ (25 ml), water (2x50 ml) and sat. brine (50 ml), dried over MgSO_4 , and concentrated *in vacuo* to give the *title compound* (4.64) (0.609 g, quant) as a pink oil ($R_f = 0.52$; hexane) that rapidly discoloured and polymerised on exposure to light. The freshly prepared diiodide was used immediately without further purification: found M^+ 305.8430, $\text{C}_4\text{H}_4\text{I}_2$ requires 305.8403; IR ν_{max} (thin film) 2920, 1563, 1382, 1343, 1139, 1050, 901 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.78 (2H, d, $J = 1.5\text{Hz}$, $\text{CH}(\text{H})=\text{CI}$ -), 6.21 (2H, d, $J = 1.5\text{Hz}$, $\text{CH}(\text{H})=\text{CI}$ -) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 137.1, 103.9 ppm; MS m/z (rel. int. %) 306(100), 181(37), 179(87), 128(20), 127(38), 52(80).

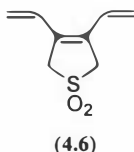
3,4-Diiodo-2,5-dihydrothiophene-1,1-dioxide (4.15). (Scheme 4.32)



A thick walled glass test tube (12 mm I.D. x 100 mm) fitted with a Young's stopcock was charged with a solution of freshly prepared 2,3-diiodo-1,3-butadiene (4.64) (1.398 g, 4.57 mmol) in ether-methanol (1.5 ml, 1:1), hydroquinone (2 mg) and a small magnetic stirrer. SO_2 (7.5 ml) was distilled into the vessel at -78°C , the headspace swept with argon and the stopcock firmly sealed. The tube was heated to 90°C behind a secure blast shield for 48 hrs then cooled to 0°C . The SO_2 was vented off and the

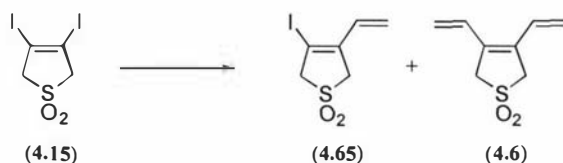
solvent removed under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (4:1) to give recovered diiodide (**4.64**) (0.573 g, 41%) and the *title compound* (**4.15**) (0.875 g, 50%) as a white solid ($R_f = 0.50$; hexane-ethyl acetate (2:1)) that was recrystallised from CH_2Cl_2 -ether (m.p. 188-190 °C): found C 13.1%, H 0.9%, I, 68.8%, S 8.9%, $\text{C}_4\text{H}_4\text{I}_2\text{O}_4\text{S}$ requires C 13.0%, H 1.1%, I, 68.6%, S 8.7%; found M^+ 369.8008, $\text{C}_4\text{H}_4\text{I}_2\text{O}_4\text{S}$ requires 369.8021; IR ν_{max} (KBr disc) 2960, 2913, 1582, 1411, 1394, 1300, 1249, 1222, 1124, 1005, 891, 875, 465, 454 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 4.03 (4H, s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 97.9 (s), 66.1 (t) ppm; MS m/z (rel. int. %) 370(88), 306(65), 179(100), 127(7), 52(69).

3,4-Divinyl-2,5-dihydrothiophene-1,1-dioxide (**4.6**). (Scheme 4.33)



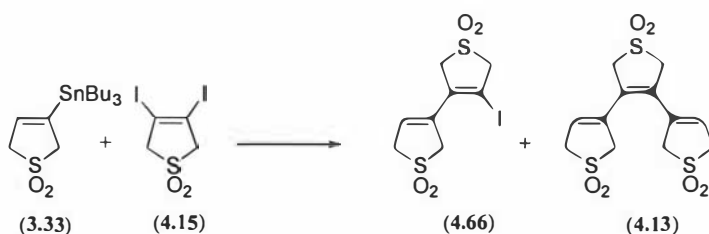
Sulfolene (**4.6**) has been prepared previously by Roth *et al.*¹⁹⁹ in an undisclosed yield by the addition of sulfur dioxide to [4]-dendralene (**4.4**). Under standard cross-coupling conditions (type B) at rt over 2 hrs, 3,4-diiodo-2,5-dihydrothiophene-1,1-dioxide (**4.15**) (0.129 g, 0.349 mmol), tributylvinyl tin (**4.3**) (0.276 g, 0.869 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (4.5 mg, 1.74×10^{-5} mol, 5 mol%) in DMF (3.0 ml) gave the *title compound* (**4.6**) (54.2 mg, 91%) as a white solid ($R_f = 0.33$; hexane-ethyl acetate (2:1)) that was recrystallised from CH_2Cl_2 -ether (m.p. 115-117 °C, (lit. m.p.¹⁹⁹ 113°C)): found M^+ 170.0397, $\text{C}_8\text{H}_{10}\text{O}_2\text{S}$ requires 170.0402; IR ν_{max} (KBr disc) 2961, 2927, 1718, 1637, 1400, 1307, 1254, 1116, 983, 923, 898. 571, 447 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.90 (2H, dd, $J = 17.1, 10.8$ Hz, $\text{CH}_2=\text{CH}-$), 5.41 (2H, d, $J = 10.8$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.20 (2H, $J = 17.1$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 4.07 (4H, s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 130.2 (s), 128.1 (d), 119.3 (t), 57.0 (t) ppm; MS m/z (rel. int. %) 170(42), 106(29), 105(37), 103(6), 91(100), 78(46), 65(12), 53(12), 51(20), 41(7), 39(21).

3-Iodo-4-vinyl-2,5-dihydrothiophene-1,1-dioxide (4.65) and 3,4-divinyl-2,5-dihydrothiophene-1,1-dioxide (4.6). (Scheme 4.33)



A solution of 3,4-diiodo-2,5-dihydrothiophene-1,1-dioxide (**4.15**) (51.4 mg, 0.139 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (1.8 mg, 7.0×10^{-6} mol, 5 mol%) in DMF (2.0 ml) was twice freeze-thaw degassed under argon. Tributylvinyl tin (**4.3**) (48.5 mg, 0.153 mmol) was added to the reaction mixture over the course of 2 hrs with a syringe pump. The reaction was stirred for a further 30 min and the volatiles removed under reduced pressure (45°C, 0.1 mmHg). The residue was shown by ¹H NMR to contain 3 components: 3,4-diiodo-2,5-dihydrothiophene-1,1-dioxide (**4.15**); 3,4-divinyl-2,5-dihydrothiophene-1,1-dioxide (**4.6**) and 3-iodo-4-vinyl-2,5-dihydrothiophene-1,1-dioxide (**4.65**), ((**4.15**):(**4.6**):(**4.65**)) 47:43:10). Tlc indicated the diiodide (**4.15**) and 3-iodo-4-vinyl-2,5-dihydrothiophene-1,1-dioxide (**4.65**) co-spotted with a variety of solvent systems ($R_f = 0.5$; hexane-ethyl acetate (2:1)) and further separation was not attempted. For 3-iodo-4-vinyl-2,5-dihydrothiophene-1,1-dioxide (**4.65**) from the mixture: ¹H NMR (270 MHz, CDCl₃) δ 6.57 (1H, dd, $J = 17.4, 10.8$ Hz, CH₂=CH-), 5.51 (1H, d, $J = 10.8$ Hz, CH(H)=CH-), 5.20 (1H, $J = 17.4$ Hz, CH(H)=CH-), 4.18 (2H, br.s, -CH₂SO₂CH₂-), 3.87 (2H, br.s, -CH₂SO₂CH₂-) ppm; ¹³C NMR (67.8 MHz, CDCl₃) δ 137.6, 134.0, 121.9, 85.4, 66.6, 55.6 ppm.

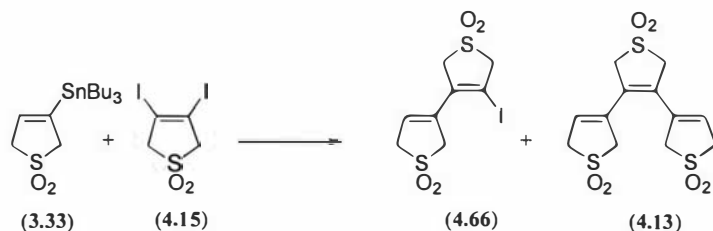
4-Iodo-3,3'-bi-2,5-dihydrothiophene-1,1-dioxide (4.66) and 3,3':4',3''-ter-2,5-dihydrothiophene-1,1-dioxide (4.13). (Table 4.5, entry 1)



A solution of 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (**3.33**) (0.239 g, 0.588 mmol) and 3,4-diiodo-2,5-dihydrothiophene-1,1-dioxide (**4.15**) (0.218 g, 0.588 mmol)

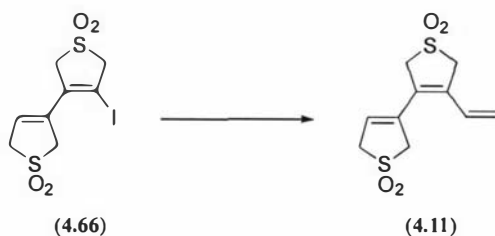
in DMF (5.0 ml) was twice freeze-thaw degassed under argon. *Bis*-(acetonitrile) palladium (II) dichloride (7.6 mg, 2.94×10^{-5} mol, 5 mol%) was added, the reaction mixture was degassed once more and stirred at rt for 96 hrs. The reaction mixture was diluted with ether (25 ml) and the precipitate removed by centrifugation. The precipitate was triturated successively with acetone (2x20 ml), ether (2x20 ml) and hexane (2x20 ml), being recovered after each treatment by centrifugation, to yield 3,3':4',3''-ter-2,5-dihydrothiophene-1,1-dioxide (**4.13**) (20.2 mg, 20%) as an amorphous white solid (m.p. $> 300^\circ\text{C}$): found M^+ 350.0005, $\text{C}_{12}\text{H}_{14}\text{O}_6\text{S}_3$ requires 349.9952; IR ν_{max} (KBr disc) 3081, 2975, 2934, 1670, 1630, 1395, 1380, 1256, 1234, 1131, 1106, 906, 595, 460 cm^{-1} ; ^1H NMR (270 MHz, d_6 -DMSO) δ 6.21 (2H, br.s, $-\text{CH}=\text{CR}_2$), 4.24 (4H, s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 4.04, (4H, br.s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.99 (4H, br.d, $J = 2.4\text{ Hz}$, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 131.3 (s), 128.9 (s), 126.7 (d), 58.1 (t), 55.9 (t), 55.8 (t) ppm; MS m/z (rel. int. %) 350(2), 286(7), 222(7), 157(18), 143(20), 129(27), 115(19), 105(20), 91(32), 84(100), 64(16). The supernatant and trituration residues were combined and concentrated *in vacuo* (45°C , 0.1 mmHg) to give a dark oil (0.48 g) that was dissolved in acetone- CH_2Cl_2 (2:1, 25 ml), adsorbed onto silica (4 g) and purified by flash column chromatography on silica gel eluting with hexane-ethyl acetate (8:1) through to ethyl acetate to give recovered diiodide (**4.15**) (0.135 g, 62%) and 4-iodo-3,3'-bi-2,5-dihydrothiophene-1,1-dioxide (**4.66**) (28.6 mg, 14%) as a white solid ($R_f = 0.19$; hexane-ethyl acetate (1:1)) that was recrystallised from CHCl_3 -acetone (m.p. $182\text{-}183^\circ\text{C}$): found M^+ 359.8990, $\text{C}_8\text{H}_9\text{IO}_4\text{S}_2$ requires 359.8987; IR ν_{max} (KBr disc) 3065, 2987, 2967, 2922, 1350, 1304, 1259, 1240, 1129, 879, 795, 594, 477, 459 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3 - d_6 acetone (1:1)) δ 6.10 (1H, br.s, $-\text{CH}=\text{CR}_2$), 3.99 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.95 (2H, br.s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.75 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 3.65 (2H, m, $-\text{CH}_2\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3 - d_6 acetone (1:1)) δ 134.7, 131.6, 126.4, 83.1, 66.9, 57.3, 55.6, 55.6 ppm; MS m/z (rel. int. %) 360(6), 296(18), 232(5), 127(3), 105(100), 77(32), 64(16), 60(12), 53(10), 39(13).

4-Iodo-3,3'-bi-2,5-dihydrothiophene-1,1-dioxide (4.66) and 3,3':4',3''-ter-2,5-dihydrothiophene-1,1-dioxide (4.13). (Table 4.5, entry 2)



Under the conditions described above 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.33) (0.200 g, 0.497 mmol) and 3,4-diiodo-2,5-dihydrothiophene-1,1-dioxide (4.15) (91.3 mg, 0.247 mmol) in DMF (3.0 ml) with *bis*-(acetonitrile) palladium (II) dichloride (3.2 mg, 1.23×10^{-5} mol, 5 mol%) gave recovered 3-tributylstannyl-2,5-dihydrothiophene-1,1-dioxide (3.33) (28.6 mg, 14%); recovered 3,4-diiodo-2,5-dihydrothiophene-1,1-dioxide (4.15) (20.3 mg, 22%); 3,3':4',3''-ter-2,5-dihydrothiophene-1,1-dioxide (4.13) (36.7 mg, 43%); and 4-iodo-3,3'-bi-2,5-dihydrothiophene-1,1-dioxide (4.66) (12.6 mg, 14%).

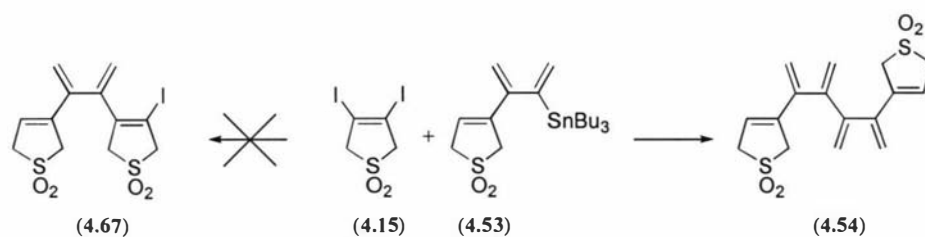
4-Vinyl-3,3'-bi-2,5-dihydrothiophene-1,1-dioxide (4.11). (Scheme 4.34)



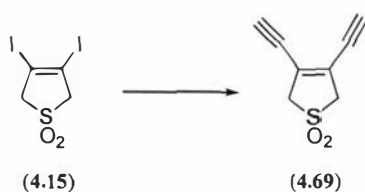
A solution of tributylvinyl tin (4.3) (30.2 mg , $9.5 \times 10^{-5} \text{ mol}$) and 4-iodo-3,3'-bi-2,5-dihydrothiophene-1,1-dioxide (4.66) (22.9 mg , $6.4 \times 10^{-5} \text{ mol}$) in DMF (1.0 ml) was twice freeze-thaw degassed under argon. *Bis*-(acetonitrile) palladium (II) dichloride (0.8 mg , $3.2 \times 10^{-6} \text{ mol}$, 5 mol%) was added, the reaction mixture was degassed once more and stirred at rt for 2 hrs. The reaction mixture was concentrated *in vacuo* (45°C , 0.1 mmHg) dissolved in acetone (5 ml), adsorbed onto silica (0.5 g) and purified by flash column chromatography on silica gel eluting with hexane-ethyl acetate (10:1) through to hexane-ethyl acetate (1:2) to give a white solid ($R_f = 27$; hexane-ethyl acetate (1:2)) that was triturated with hexane (2 ml) to yield the *title compound* (4.11) (14.7 mg , 90%). Recrystallisation from CH_2Cl_2 -acetone gave white needles (m.p. $157\text{-}158^\circ\text{C}$):

found M^+ 260.0178, $C_{10}H_{12}O_4S_2$ requires 260.0178; UV λ_{\max} (ϵ) (EtOH) 282.2 (6700), 270.4 (10320), 262.0 (11020) nm; IR ν_{\max} (KBr disc) 3067, 1690, 1398, 1306, 1254, 1236, 1195, 1132, 1104, 936, 802, 594, 556, 459 cm^{-1} ; 1H NMR (270 MHz, d_6 -acetone) δ 6.92 (1H, dd, $J = 17.1, 10.8$, $CH_2=CH-$), 6.27 (1H, m, $-CH=C(R)_2$), 5.45 (1H, d, $J = 17.1$ Hz, $CH(H)=CH-$), 5.44 (1H, d, $J = 10.8$ Hz, $CH(H)=CH-$), 4.18 (2H, br.s, $-CH_2SO_2CH_2-$), 4.13 (2H, br.s, $-CH_2SO_2CH_2-$), 4.07 (2H, m, $-CH_2SO_2CH_2-$), 3.97 (2H, m, $-CH_2SO_2CH_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -acetone) δ 130.1 (s), 132.0 (s), 130.7 (d), 128.7 (s), 126.7 (d), 120.8 (t), 58.9 (t), 57.4 (t), 57.0 (t), 56.8 (t) ppm; MS m/z (rel. int. %) 260(4), 196(3), 132(27), 131(37), 117(100), 104(39), 91(48), 77(21), 64(24), 51(17), 44(12), 41(16).

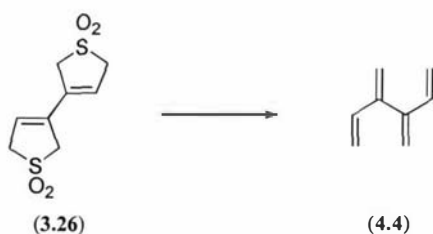
Attempted synthesis of 2-(4'-iodo-1',1'-dioxo-2'5'-dihydrothien-3'-yl)-3-(1'',1''-dioxo-2'',5''-dihydrothien-3''-yl)-1,3-butadiene (4.67). (Scheme 4.35)



A solution of 2-trimethylstannyl-3-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (4.53) (27.6 mg, 8.3×10^{-5} mol) and 3,4-diiodo-2,5-dihydrothiophene-1,1-dioxide (4.15) (22.9 mg, 6.4×10^{-5} mol) in DMF (1.0 ml) was twice freeze-thaw degassed under argon. *Bis*-(acetonitrile) palladium (II) dichloride (2.0 mg, 8.2×10^{-6} mol, 10 mol%) was added, the reaction mixture was degassed once more and stirred at 60°C for 48 hrs. The reaction mixture was cooled and concentrated *in vacuo* (45°C, 0.1 mmHg). The residue was dissolved in acetone (5 ml), adsorbed onto silica (0.5 g) and purified by flash column chromatography on silica gel eluting with hexane-ethyl acetate (4:1) through to hexane-ethyl acetate (1:2) to give recovered diiodide (4.15) (16.3 mg, 48%) and a white solid that was triturated with hexane (2x1 ml) to yield 3,4-dimethylene-2,5-bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,5-hexadiene (4.54) (2.2 mg, 16%).

3,4-Diethynyl-2,5-dihydrothiophene-1,1-dioxide (4.69). (Scheme 4.36)

Under standard cross-coupling conditions (type B) at rt over 2 hrs, 3,4-diiodo-2,5-dihydrothiophene-1,1-dioxide (**4.15**) (0.106 g, 0.29 mmol), tributylethynyl tin (**4.21**) (0.226 g, 0.72 mmol) and *bis*-(acetonitrile) palladium (II) dichloride (3.7 mg, 1.43×10^{-5} mol, 5 mol%) in DMF (3.0 ml) gave the *title compound* (**4.69**) (19.0 mg, 40%) as a white solid ($R_f = 0.26$; hexane-ethyl acetate (2:1)) that was recrystallised from ether-hexane (m.p. 101-102°C, decomp.): found M^+ 166.0090, $C_8H_6O_2S$ requires 166.0089; IR ν_{max} (KBr disc) 3279, 3252, 2093, 1396, 1316, 1256, 1168, 1111, 688, 644, 554 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 3.95 (4H, s, $-CH_2SO_2CH_2-$), 3.55 (2H, s, $\equiv CH$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 122.8 (s), 87.5 (d), 76.6 (s), 58.2 (t) ppm; MS m/z (rel. int. %) 166(39), 102(100), 76(31), 74(19), 63(17), 51(29), 50(26), 39(7).

6.6 Experimental for Chapter 5.**6.6.1 Solution State Thermolysis.****3,4-Dimethylene-1,5-hexadiene ([4]-dendralene) (4.4). (Scheme 5.7 and Figure 5.2)**

A solution of 3,3'-bi-2,5-dihydrothiophene-1,1-dioxide (**3.26**) (2.2 mg, 9.4×10^{-6} mol) in d_6 -DMSO (0.6 ml) was sealed in an NMR tube (septum), twice freeze-thaw degassed under argon and heated at 130°C in the probe of an NMR spectrometer while 1H NMR spectra were recorded every 2 mins. After 50 min the *title compound* (**4.4**) was formed as a single product that was not isolated: 1H NMR (270 MHz, d_6 -DMSO) δ 6.44 (2H, dd, $J = 17.6, 10.5$ Hz, $CH_2=CH-$), 5.29 (2H, br.s, $R_2C=CH(H)$), 5.21 (2H, br.d, $J = 17.1$

Hz, CH(H)=CH-), 5.12 (2H, br.d, $J = 10.5$ Hz, CH(H)=CH-), 5.03 (2H, m, R₂C=CH(H)) ppm.

6.6.2 Capillary Pyrolysis (CP).

6.6.2.1 Standard Capillary Pyrolysis (CP) Method. (Figure 5.3)

A long form glass Pasteur pipette was sealed at the tip with a Bunsen burner, shortened in the body to *ca.* 25 mm and tarred on an accurate balance. A localised area of the pipette body was heated (Bunsen burner) and a shallow indent pushed into the softened glass wall. With the aid of a stainless steel wire, the polyene precursor was tamped into the sealed end of the modified pipette followed by a short plug of glass wool (*ca.* 10 mm). The pipette was clamped horizontally, connected to a vacuum/argon manifold and purged three times with argon. Around the body of the pipette a small cotton wool jacket was secured with a twist of thin wire. The jacket was doused with liquid nitrogen while the solid was heated by the blast of a hot air gun (*ca.* 450°C). During this process the contents of the pipette were maintained at either an ambient pressure of argon or under a vacuum as necessary. Typically, a bright yellow/green band of material was seen at the edge of the cooling zone as the volatile products distilled across. Once the solid had sublimed (typically *ca.* 1 min) the heating and cooling zones were removed and the stem of the pipette scored with a glass knife. The manifold hose was removed, the glass stem cracked and its contents rinsed rapidly into an argon flushed NMR tube with CDCl₃ (0.6 ml). Yields were calculated by comparison of the integrational intensity of the pyrolysate signals with the residual chloroform peak of the NMR solvent normalised against a standard solution of *t*-butyl methyl ether (1 µl/0.6 ml) in a sample of the *same* CDCl₃ (see **Appendix 5.1**).

6.6.2.2. [n]-Dendralene Synthesis.

1,3-Butadiene (5.17). (Scheme 5.15)



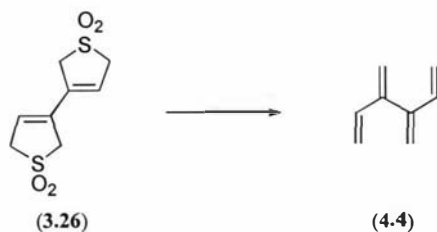
2,5-Dihydrothiophene-1,1-dioxide (**3.1**) (6.8 mg, 5.76×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (**5.17**) (4.23×10^{-5} mol, 74%) as a colourless solution in CDCl_3 : found M^+ 54.0468, C_4H_6 requires 54.0469; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 226.4 (6450) nm; IR ν_{max} (CDCl_3 , sol. cell) 3091, 3045, 2974, 1590, 1016 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.36 (2H, m, $\text{CH}_2=\text{CH}-$), 5.24 (2H, dm, $J = 16.3$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.12 (2H, dm, $J = 9.9$ Hz, $\text{CH}(\text{H})=\text{CH}-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 137.5 (d), 117.6 (t) ppm; GCMS m/z (rel. int. %) 54(100), 39(96).

3-Methylene-1,4-pentadiene ([3]-Dendralene) (4.1). (Scheme 5.8)



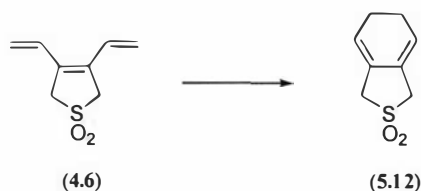
3-Vinyl-2,5-dihydrothiophene-1,1-dioxide (**4.2**) (6.6 mg, 4.58×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (**4.1**) (4.09×10^{-5} mol, 89%) as a colourless solution in CDCl_3 ($R_f = 0.60$; hexane): found M^+ 80.0630, C_6H_8 requires 80.0626; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 232.2 (8150), 216.6 sh. (4690), (EtOH) 231.2 (10120), 206.6 (15860) nm; IR ν_{max} (CDCl_3 , sol. cell) 3092, 3009, 2978, 1601, 1585, 990 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.47 (2H, dd, $J = 17.6, 11.2$ Hz, $\text{CH}_2=\text{CH}-$), 5.42 (2H, dd, $J = 17.6, 1.5$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.17 (2H, br.d $J = 11.2$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.17 (2H, br.s, $\text{CH}_2=\text{C}(\text{R})_2$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 144.5 (s), 135.7 (d), 115.6 (t), 115.4 (t) ppm; GCMS m/z (rel. int. %) 80(71), 79(100), 77(64), 65(11), 52(29), 39(30).

3,4-Dimethylene-1,5-hexadiene ([4]-dendralene) (4.4). (Scheme 5.9)



3,3'-Bi-2,5-dihydrothiophene-1,1-dioxide (**3.26**) (6.2 mg, 2.65×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (**4.4**) (2.24×10^{-5} mol, 85%) as a colourless solution in CDCl_3 ($R_f = 0.60$; hexane): found M^+ 106.0779, C_8H_{10} requires 106.0782; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 222.6 (13500), (EtOH) 216.2 (27000) nm; IR ν_{max} (CDCl_3 , sol. cell) 3092, 3009, 2974, 1583, 990 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.44 (2H, dd, $J = 17.4, 10.6$ Hz, $\text{CH}_2=\text{CH}-$), 5.25 (2H, m, $\text{R}_2\text{C}=\text{CH}(\text{H})$), 5.19 (2H, br.d, $J = 17.4$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.11 (2H, br.d, $J = 10.6$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.07 (2H, m, $\text{R}_2\text{C}=\text{CH}(\text{H})$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 146.4 (s), 137.4 (d), 117.7 (t), 116.5 (t) ppm; GCMS m/z (rel. int. %) 106(35), 105(45), 103(10), 91(100), 78(43), 65(16), 51(19), 39(18).

1,3,5,6-Tetrahydroisobenzothiophene-2,2-dioxide (5.12). (Table 5.1, entry 1)



A solution of 3,4-divinyl-2,5-dihydrothiophene-1,1-dioxide (**4.6**) (11.2 mg, 6.58×10^{-5} mol) in xylene (1.0 ml) was refluxed under argon and the disappearance of starting material monitored by tlc. After 2.5 hrs the solvent was removed *in vacuo* and the residue recrystallised from ether- CH_2Cl_2 to give the *title compound* (**5.12**) (10.2 mg, 91%) as white needles (m.p. 95-98°C), ($R_f = 0.26$; hexane-ethyl acetate (2:1)): found M^+ 170.0401, $\text{C}_8\text{H}_{10}\text{O}_2\text{S}$ requires 170.0402; IR ν_{max} (KBr disc) 2989, 2931, 2883, 2827, 1624, 1298, 1224, 1150, 1099, 968, 862, 669, 590, 527, 489, 456 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 5.82 (2H, br.s, $-\text{CH}_2\text{CH}=\text{}$), 3.81 (4H, br.s, $-\text{CH}_2\text{SO}_2\text{CH}_2-$), 2.29 (4H,

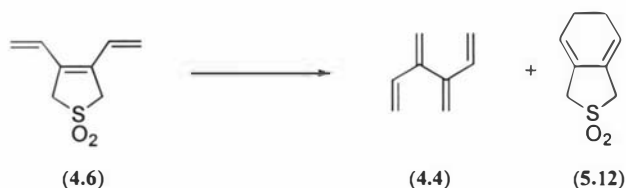
br.s, $-CH_2CH=$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 127.2 (s), 123.5 (d), 55.2 (t), 22.2 (t) ppm; MS m/z (rel. int. %) 170(46), 106(53), 105(27), 91(100), 78(40), 65(10), 53(9), 51(16), 39(15).

3,4-Dimethylene-1,5-hexadiene ([4]-dendralene) (4.4). (Table 5.1, entry 2)



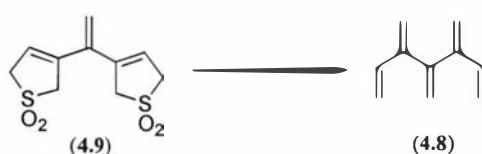
3,4-Divinyl-2,5-dihydrothiophene-1,1-dioxide (4.6) (4.0 mg, 2.35×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (4.4) (1.89×10^{-6} mol, 8%) as a colourless solution in $CDCl_3$.

3,4-Dimethylene-1,5-hexadiene ([4]-dendralene) (4.4) and 1,3,5,6-tetrahydroisobenzothiophene-2,2-dioxide (5.12). (Table 5.1, entry 3)



3,4-Divinyl-2,5-dihydrothiophene-1,1-dioxide (4.6) (4.2 mg, 2.47×10^{-5} mol) was subjected to CP under reduced pressure (0.8 mmHg) to give a mixture of 3,4-dimethylene-1,5-hexadiene (4.4) (3.76×10^{-6} mol, 15%), 1,3,5,6-tetrahydroisobenzothiophene-2,2-dioxide (5.12) (6.86×10^{-6} mol, 27%) and recovered 3,4-divinyl-2,5-dihydrothiophene-1,1-dioxide (4.6) (1.55×10^{-5} mol, 63%) as a colourless solution in $CDCl_3$.

3,4,5-Trimethylene-1,6-heptadiene ([5]-dendralene) (4.8). (Scheme 5.11)

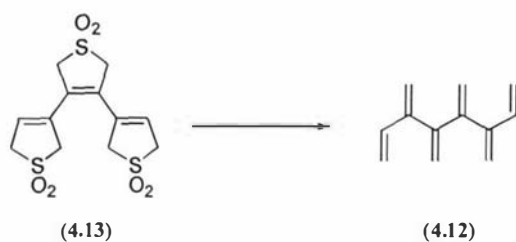


1,1-Bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-ethene (**4.9**) (2.3 mg, 8.83×10^{-6} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (**4.8**) (5.66×10^{-6} mol, 64%) as a colourless solution in CDCl_3 ($R_f = 0.48$; hexane): found M^+ 132.0914, $\text{C}_{10}\text{H}_{12}$ requires 132.0939; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 219.8 (22200) nm; IR ν_{max} (CDCl_3 , sol. cell) 3092, 1580, 1131, 991 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.44 (2H, dd, $J = 17.4, 10.6$ Hz, $\text{CH}_2=\text{CH}-$), 5.34 (2H, dd, $J = 17.4, 1.5$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.26 (2H, s, $\text{CH}_2=\text{C}(\text{R})_2$), 5.23 (2H, m, $\text{CH}(\text{H})=\text{C}(\text{R})\text{R}$), 5.14 (2H, br.d, $J = 10.6$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.12 (2H, m, $\text{CH}(\text{H})=\text{C}(\text{R})\text{R}$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 146.9 (s), 146.5 (s), 136.9 (d), 116.8 (t), 116.4 (t), 116.2 (t) ppm; GCMS m/z (rel. int. %) 132(13), 131(48), 130(9), 117(100), 103(11), 91(57), 86(8), 78(16), 69(13), 63(12), 50(6).

3,4,5,6-Tetramethylene-1,7-octadiene ([6]-dendralene) (**4.12**). (Scheme 5.12)



2,3-Bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,3-butadiene (**4.16**) (3.9 mg, 1.36×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (**4.12**) (7.05×10^{-6} mol, 52%) as a colourless solution in CDCl_3 ($R_f = 0.49$; hexane): found M^+ 158.1090, $\text{C}_{12}\text{H}_{14}$ requires 158.1095; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 220.0 (25050) nm; IR ν_{max} (CDCl_3 , sol. cell) 3092, 2978, 2875, 1581, 1113, 989 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.46 (2H, dd, $J = 17.4, 10.5$ Hz, $\text{CH}_2=\text{CH}-$), 5.29 (2H, dm, $J = 17.4$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.28 (2H, m, $\text{CH}(\text{H})=\text{C}(\text{R})\text{R}$), 5.26 (2H, m, $\text{CH}(\text{H})=\text{C}(\text{R})\text{R}$), 5.13 (2H, dm, $J = 10.5$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.09 (4H, m, $\text{CH}_2=\text{C}(\text{R})\text{R}$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 147.3 (s), 146.4 (s), 137.8 (d), 117.7 (t), 117.4 (t), 116.2 (t) ppm; GCMS m/z (rel. int. %) 158(16), 157(53), 143(56), 129(100), 128(99), 115(75), 105(17), 103(17), 91(62), 84(44), 77(44), 65(29), 51(39), 39(36).

3,4,5,6-Tetramethylene-1,7-octadiene ([6]-dendralene) (4.12). (Scheme 5.12)

3,3':4',3''-Ter-2,5-dihydrothiophene-1,1-dioxide (4.13) (4.4 mg, 1.25×10^{-5} mol) was subjected to CP under reduced pressure (0.1 mmHg) to give the *title compound* (4.12) (2.35×10^{-6} mol, 19%) as a colourless solution in CDCl_3 .

3,4,5,6,7,8-Hexamethylene-1,9-decadiene ([8]-dendralene) (5.16). (Scheme 5.14)

3,4-Dimethylene-2,5-bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-1,5-hexadiene (4.54) (4.2 mg, 1.24×10^{-5} mol) was subjected to CP under reduced pressure (0.1 mmHg) to give the *title compound* (5.16) (7.93×10^{-6} mol, 64%) as a colourless solution in CDCl_3 ($R_f = 0.40$; hexane): found M^+ 210.1405, $\text{C}_{16}\text{H}_{18}$ requires 210.1409; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 220.6 (25160) nm; IR ν_{max} (CDCl_3 , sol. cell) 3093, 3008, 2930, 1577, 1319, 1131, 990 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.46 (2H, dd, $J = 17.4, 10.5$, Hz, $\text{CH}_2=\text{CH}-$), 5.36-5.25 (8H, m, $\text{CH}_2=$), 5.12 (8H, m, $\text{CH}_2=$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 147.5 (s), 147.3 (s), 146.9 (s), 137.7 (d), 117.8 (t), 117.5 (t), 117.2 (t), 116.2 (t) ppm; GCMS m/z (rel. int. %) 210(10), 209(31), 195(100), 181(41), 179(43), 167(78), 165(87), 155(39), 153(52), 141(46), 128(48), 115(52), 103(10), 91(33), 77(30), 65(13), 51(18), 39(13).

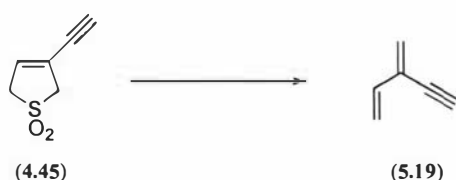
6.6.2.3 Other Polyene Synthesis.

2-Phenyl-1,3-butadiene (5.18). (Table 5.3, entry 1)



2-Phenyl-1,3-butadiene (5.18) has been prepared previously by the Li_2CuCl_4 catalysed coupling of 1,3-butadien-2-yl magnesium bromide with iodobenzene.²⁵² 3-Phenyl-2,5-dihydrothiophene-1,1-dioxide (4.46) (3.3 mg, 1.70×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (5.18) (1.34×10^{-5} mol, 79%) as a colourless solution in CDCl_3 ($R_f = 0.40$; hexane): found M^+ 130.0777, $\text{C}_{10}\text{H}_{10}$ requires 130.0782; IR ν_{max} (CDCl_3 , sol. cell) 3092, 3059, 3033, 1604, 1590, 1492, 1445, 1074, 1030, 993 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 7.34 (5H, m, C_6H_5 -), 6.63 (1H, dd, $J = 17.6, 10.8$ Hz, $\text{CH}_2=\text{CH}$ -), 5.31 (1H, m, $\text{CH}(\text{H})=\text{CPh}$ -), 5.22 (1H, d, $J = 10.8$ Hz, $\text{CH}(\text{H})=\text{CH}$ -), 5.21 (1H, m, $\text{CH}(\text{H})=\text{CPh}$ -), 5.20 (1H, d, $J = 17.6$ Hz, $\text{CH}(\text{H})=\text{CH}$ -) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 148.1 (s), 139.6 (s), 138.0 (d), 128.2 (d), 128.0 (d), 127.4 (d), 117.1 (t), 116.8 (t) ppm; MS m/z (rel. int. %) 130(100), 115(40), 102(11), 91(12), 77(12), 64(9), 51(11).

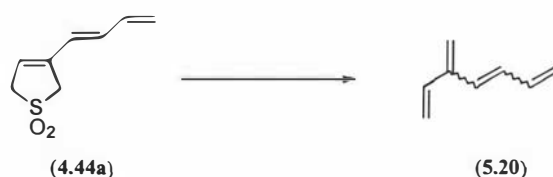
2-Ethynyl-1,3-butadiene (5.19). (Table 5.3, entry 2)



2-Ethynyl-1,3-butadiene (5.19) has been prepared previously by the rearrangement of propargylallene.²⁵³ 3-Ethynyl-2,5-dihydrothiophene-1,1-dioxide (4.45) (4.9 mg, 3.43×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (5.19) (2.16×10^{-5} mol, 63%) as a colourless solution in CDCl_3 : found M^+ 78.0467, C_6H_6 requires 78.0469; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 232.0 (13550) nm; IR ν_{max} (CDCl_3 , sol. cell) 3305, 3098, 3029, 2252, 1573, 1297, 1216, 984 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.37 (1H, dd, $J = 17.1, 10.3$ Hz, $\text{CH}_2=\text{CH}$ -), 5.68 (1H, d, $J =$

17.1 Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.62 (1H, br.s, $\text{CH}(\text{H})=\text{C}(\text{C}\equiv\text{C})-$), 5.51 (1H, m, $\text{CH}(\text{H})=\text{C}(\text{C}\equiv\text{C})-$), 5.29 (1H, d, $J = 10.3$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 3.07 (1H, s, $-\text{C}\equiv\text{CH}$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 135.5 (d), 129.1 (s), 125.1 (t), 118.0 (t), 80.1 (s), 79.4 (d) ppm; GCMS m/z (rel. int. %) 78(100), 63(7), 52(38), 39(12).

3-Methylene-1,4,6-heptatriene (5.20). (Table 5.3, entry 3)



3-Methylene-1,4,6-heptatriene (5.20) has been prepared previously from 7-methylenebicyclo-[4.1.0]-hept-2-ene by FVP.²⁵⁴ 1-(1',1'-Dioxo-2'5'-dihydrothien-3'-yl)-1*E*,3-butadiene (4.44a) (4.3 mg, 2.53×10^{-5} mol) was subjected to CP under argon at ambient pressure to give a mixture of 3 isomeric tetraenes and one dimeric product (1.47×10^{-5} mol, 58%) as a pale yellow solution in CDCl_3 : found (GCMS [each one isomer]) M^+ 106.0782, M^+ 106.0782, M^+ 106.0788, C_8H_{10} requires 106.0783, M^+ 212.1555, $\text{C}_{16}\text{H}_{20}$ requires 212.1565; ^1H NMR (270 MHz, CDCl_3) δ 6.53-4.97 (br.m), 2.41-2.12 (br.m).

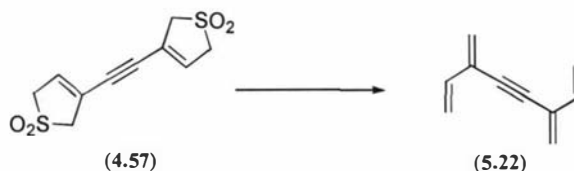
3,6-Dimethylene-1,4*E*, 7-octatriene (5.21). (Table 5.3, entry 4)



E-1,2-Bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-ethene (4.58) (6.2 mg, 2.38×10^{-6} mol) was subjected to CP under reduced pressure (0.1 mmHg) to give the *title compound* (5.21) (7.58×10^{-6} mol, 32%) as a pale yellow solution in CDCl_3 ($R_f = 0.40$; hexane): found M^+ 132.0932, $\text{C}_{10}\text{H}_{12}$ requires 132.0939; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 344.4 (2160), 313.6 sh. (3760), 268.0 (13210), 211.4 (28480) nm; IR ν_{max} (CDCl_3 , sol. cell) 3092, 2932, 1671, 1265, 991, 966 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.51 (2H, s, $-\text{HC}=\text{CH}-$), 6.49 (2H, dd, $J = 17.4, 10.8$ Hz, $\text{CH}_2=\text{CH}-$), 5.44 (2H, dd, $J = 17.4, 1.3$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.20 (4H, br.s, $\text{CH}_2=\text{C}(\text{R})_2$), 5.19 (2H, dd, $J = 10.8, 1.3$ Hz, $\text{CH}(\text{H})=\text{CH}-$)

ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 144.1 (s), 135.9 (d), 129.3 (d), 115.9 (t), 115.8 (t) ppm; GCMS m/z (rel. int. %) 132(69), 117(100), 104(39), 91(85), 79(50), 65(18), 51(20), 39(20).

3,6-Dimethylene-1,7-octadien-4-yne (5.22). (Table 5.3, entry 5)



Bis-(1',1'-dioxo-2'5'-dihydrothien-3'-yl)-ethyne (**4.57**) (2.6 mg, 1.01×10^{-5} mol) was subjected to CP under reduced pressure (0.1 mmHg) to give the *title compound* (**5.22**) (2.5×10^{-6} mol, 25%) as a colourless solution in CDCl_3 ($R_f = 0.38$; hexane): found M^+ 130.0781, $\text{C}_{10}\text{H}_{10}$ requires 130.0783; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 271.8 (7740), 257.8 (8280), 232.2 sh. (12960), 205.6 sh. (22080) nm; IR ν_{max} (CDCl_3 , sol. cell) 3152, 1601, 1224, 984 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.41 (2H, dd, $J = 16.9, 10.3$ Hz, $\text{CH}_2=\text{CH}-$), 5.70 (2H, d, $J = 16.9$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.60 (2H, br.s, $\text{CH}(\text{H})=\text{C}(\text{C}\equiv)-$), 5.50 (2H, br.s, $\text{CH}(\text{H})=\text{C}(\text{C}\equiv)-$), 5.30 (2H, d, $J = 10.3$ Hz, $\text{CH}(\text{H})=\text{CH}-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 135.9 (d), 129.8 (s), 124.1 (t), 117.8 (t), 88.0 (s), ppm; GCMS m/z (rel. int. %) 130(100), 128(78), 115(65), 102(18), 91(11), 77(18), 74(10), 65(14), 63(17), 51(29), 39(14).

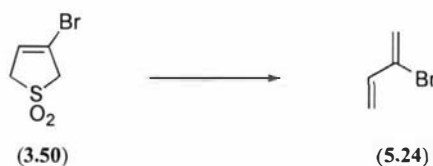
2,3-Diethynyl-1,3-Butadiene (5.23). (Table 5.3, entry 6)



3,4-Diethynyl-2,5-dihydrothiophene-1,1-dioxide (**4.69**) (2.5 mg, 1.50×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (**5.23**) (1.81×10^{-6} mol, 12%) as a colourless solution in CDCl_3 ($R_f = 0.33$; hexane): found M^+ 102.0469, C_8H_6 requires 102.0469; UV λ_{max} (ϵ) (EtOH- CDCl_3 0.4%) 268.8 sh. (3150), 242.4 sh. (12430), 236.6 (14170), 206.6 sh. (26190) nm; IR ν_{max} (CDCl_3 , sol. cell)

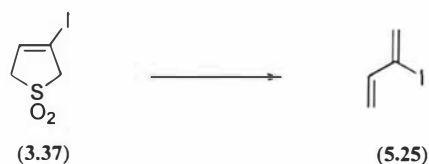
3305, 1558, 1253, 1056 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.12 (2H, br.t, $J = 0.9$ Hz, $\text{CH}(\text{H})=$), 5.80 (2H, br.t, $J = 0.9$ Hz, $\text{CH}(\text{H})=$), 3.14 (2H, s, $\equiv\text{CH}$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 126.0, 80.6 (2x quat. C not observed) ppm; GCMS m/z (rel. int. %) 102(100), 76(39), 74(16), 63(12), 50(24), 39(3).

2-Bromo-1,3-butadiene (5.24). (Table 5.3, entry 7)



2-Bromo-1,3-butadiene (**5.24**) has been prepared previously from vinylacetylene.¹⁹⁵ 3-Bromo-2,5-dihydrothiophene-1,1-dioxide (**3.50**) (5.9 mg, 2.99×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (**5.24**) (1.75×10^{-5} mol, 59%) as a colourless solution in CDCl_3 : found M^+ 131.9572, $\text{C}_4\text{H}_5\text{Br}$ requires 131.9575; IR ν_{max} (CDCl_3 , sol. cell) 3104, 3014, 1628, 1602, 1582, 1202, 972 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.32 (1H, dd, $J = 16.3, 10.3$ Hz, $\text{CH}_2=\text{CH}-$), 5.84 (1H, m, $\text{CH}(\text{H})=\text{CBr}-$), 5.69 (1H, m, $\text{CH}(\text{H})=\text{CBr}-$), 5.62 (1H, d, $J = 16.3$ Hz, $\text{CH}(\text{H})=\text{CH}-$), 5.34 (1H, d, $J = 10.3$ Hz, $\text{CH}(\text{H})=\text{CH}-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 134.9 (d), 130.4 (s), 120.7 (t), 120.4 (t) ppm; GCMS m/z (rel. int. %) 134(60), 132 (65), 53(100).

2-Iodo-1,3-butadiene (5.25). (Table 5.3, entry 8)



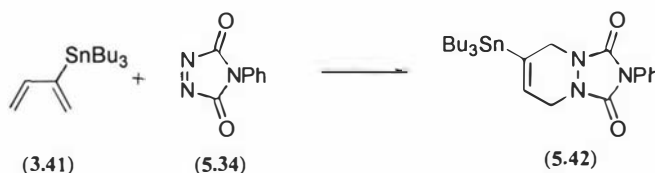
2-Iodo-1,3-butadiene (**5.25**) has been prepared previously from but-2,3-dien-1-ylethylcarbonate.²⁶⁶ 3-Iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (7.6 mg, 3.11×10^{-5} mol) was subjected to CP under argon at ambient pressure to give the *title compound* (**5.25**) (1.59×10^{-5} mol, 51%) as a colourless solution in CDCl_3 that rapidly became pink on exposure to light: found M^+ 179.9420, $\text{C}_4\text{H}_5\text{I}$ requires 179.9436; IR ν_{max} (CDCl_3 , sol. cell) 3099, 3004, 1620, 1602, 1574, 1192, 969 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 6.37

(1H, m, $CH(H)=C-$), 6.04 (1H, m, $CH(H)=C-$), 5.86 (1H, dd, $J = 16.0, 10.0$ Hz, $CH_2=CH-$), 5.41 (1H, d, $J = 16.0$ Hz, $CH(H)=CH-$), 5.35 (1H, d, $J = 10.0$ Hz, $CH(H)=CH-$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 137.9 (d), 129.2 (t), 124.1 (t), 109.1 (s) ppm; GCMS m/z (rel. int. %) 180(24), 127(4), 53(100).

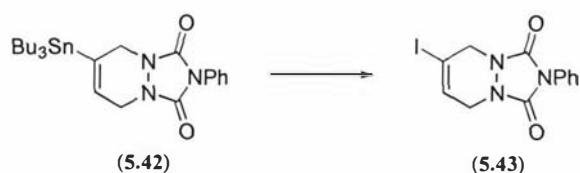
6.6.3 Diene-Transmissive Diels-Alder (DTDA) Reactions.

2-Phenyl-5-tributylstannyl-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione (5.42).

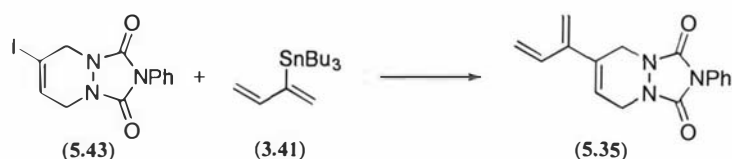
(Scheme 5.20)



4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD) (5.35) (0.229 g, 1.31 mmol) was added to a solution of 2-tributylstannyl-1,3-butadiene (3.41) (0.449 g, 1.31 mmol) in ether (10 ml) at rt under argon. The reaction was stirred for 30 min, the solvent removed *in vacuo* and the crude oil purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) to give a colourless oil ($R_f = 0.35$; hexane-ethyl acetate (5:1)) which solidified on storage at $-18^\circ C$. Recrystallisation from ether gave the *title compound* (5.42) (0.649 g, 96%) as a white crystalline solid (m.p. $38-39^\circ C$): found C 55.6%, H 7.4%, N 8.3% Sn 22.7%, $C_{24}H_{37}N_3O_2Sn$ requires C 55.6%, H 7.2%, N 8.1% Sn 22.9%; found M^+ 519.1894, $C_{24}H_{37}N_3O_2Sn$ requires 519.1908; IR ν_{max} (thin film) 2956, 2926, 2851, 1772, 1714, 1504, 1416, 1244, 1132, 966 cm^{-1} ; 1H NMR (270 MHz, $CDCl_3$) δ 7.57-7.32 (5H, m, C_6H_5-), 5.94 (1H, m, $J_{Sn-H} = 55.4$ Hz, $-(SnR_3)C=CH-$), 4.30 (2H, m, $-CH_2N-$), 4.21 (2H, m, $-NCH_2-$), 1.53 (6H, m, $-CH_2CH_2CH_2-$), 1.35 (6H, sext, $J = 7.0$ Hz, $-CH_2CH_3$), 1.01 (6H, m, $SnCH_2-$), 0.92 (9H, t, $J = 7.0$ Hz, $-CH_3$) ppm; ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 152.2 (s x2, inverse gated), 134.5 (s), 131.2 (s), 128.9 (d), 127.8 (d), 127.6 (d, $J_{Sn-C} = 19.0$ Hz), 125.3 (d), 48.3 (t, $J_{Sn-C} = 56.0$ Hz), 44.8 (t, $J_{Sn-C} = 43.0$ Hz), 29.0 (t, $J_{Sn-C} = 21.0$ Hz), 27.3 (t, $J_{Sn-C} = 58.0$ Hz), 13.7 (q), 9.4 (t, $J_{Sn-C} = 346.2$ Hz) ppm; MS m/z (rel. int. %) 518(2), 462(100), 406(12), 348(23), 296(20), 203(7), 175(12), 151(5).

2-Phenyl-5-iodo-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione (5.43). (Scheme 5.20)

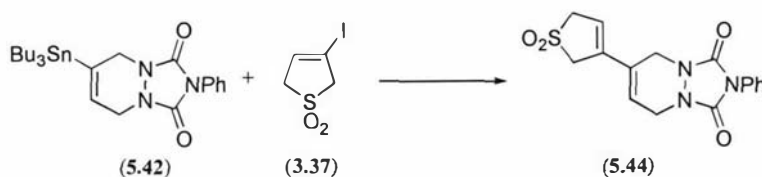
Iodine (0.984 g, 0.39 mmol) was added to a solution of 2-phenyl-5-tributylstannyl-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione (**5.42**) (0.201 g, 0.39 mmol) in CH_2Cl_2 (5.0 ml) at rt under argon. The reaction was stirred for 1 hr, whereupon the solvent was removed *in vacuo* and the crude oil purified by flash chromatography on silica gel eluting with hexane-ethyl acetate (8:1) through to hexane-ethyl acetate (2:1) to give a white solid (0.138 g, quant., $R_f = 0.28$; hexane-ethyl acetate (2:1)). Recrystallisation from ether- CH_2Cl_2 gave the *title compound* (**5.43**) as a white crystalline solid (m.p. 156-157 °C): found C 40.6%, H 2.5%, I 36.0%, N 12.0%, $\text{C}_{12}\text{H}_{10}\text{IN}_3\text{O}_2$ requires C 40.6%, H 2.8%, I 35.7%, N 11.8%; found M^+ 354.9819, $\text{C}_{12}\text{H}_{10}\text{IN}_3\text{O}_2$ requires 354.9818; IR ν_{max} (KBr disc) 3066, 2886, 2846, 1774, 1715, 1505, 1494, 1431, 1302, 1238, 764 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 7.54-7.36 (5H, m, C_6H_5 -), 6.53 (1H, m, $-\text{IC}=\text{CH}-$), 4.35 (2H, q, $J = 2.4$ Hz, $-\text{CH}_2\text{N}-$), 4.21 (2H, q, $J = 2.9$ Hz, $-\text{NCH}_2-$) ppm; ^{13}C NMR (67.8 MHz, CDCl_3) δ 152.4 (s), 151.5 (s), 130.7 (s), 129.9 (d), 129.1 (d), 128.2 (d), 125.3 (d), 84.9 (s), 53.0 (t), 46.7 (t) ppm; MS m/z (rel. int. %) 355(100), 180(3), 119(44), 109(59), 91(14), 66(9), 53(4), 39(7).

2-(2'-Phenyl-4',7'-dihydro-2',3a',7a'-triazaindan-5'-yl-1',3'-dione)-1,3-butadiene (5.35). (Scheme 5.20)

A solution of 2-tributylstannyl-1,3-butadiene (**3.41**) (0.133 g, 0.39 mmol) and 2-phenyl-5-iodo-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione (**5.43**) (0.125 g, 0.35 mmol) in DMF (2.0 ml) was twice freeze-thaw degassed under argon. *Bis*-(acetonitrile) palladium (II) dichloride (4.6 mg, 1.7×10^{-5} mol, 5 mol%) was added whereupon the colourless solution rapidly darkened. The reaction mixture was degassed once more and stirred at rt for 24

hrs. The solvent was removed under reduced and the residue taken up in CH_2Cl_2 (10 ml), adsorbed onto silica gel (*ca.* 2 g) and purified by flash chromatography on silica gel, eluting with hexane-ethyl acetate (8:1) through to hexane-ethyl acetate (2:1) to yield recovered stannane (**3.41**) (79.6 mg, 60%), recovered iodide (**5.43**) (82.0 mg, 66%) and the *title compound* (**5.35**) (18.0 mg, 18%) as a colourless oil. ($R_f = 0.32$; hexane-ethyl acetate (2:1)): found M^+ 281.1158, $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$ requires 281.1164; IR ν_{max} (thin film) 3065, 2956, 2922, 2852, 1778, 1714, 1504, 1418, 1306, 1249, 1137, 766 cm^{-1} ; ^1H NMR (270 MHz, d_6 -DMSO) δ 7.57-7.37 (5H, m, C_6H_5 -), 6.54 (1H, dd, $J = 17.5, 10.5$ Hz, $\text{CH}_2=\text{CH}(\text{R})$ -), 6.05 (1H, br.s, $-\text{CH}_2\text{CH}=\text{C}(\text{R})$ -), 5.44 (1H, dd, $J = 17.5, 1.4$ Hz, $\text{CH}(\text{H})=\text{CH}(\text{R})$ -), 5.32 (1H, s, $\text{CH}(\text{H})=\text{CR}_2$), 5.26 (1H, dd, $J = 10.5, 1.4$ Hz, $\text{CH}(\text{H})=\text{CH}(\text{R})$ -), 5.21 (1H, s, $\text{CH}(\text{H})=\text{CR}_2$), 4.26 (4H, br.s, $-\text{CH}_2\text{NNCH}_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 152.3 (s), 152.1 (s), 143.4 (s), 136.0 (d), 131.5 (s), 130.1 (s), 129.0 (d), 128.1 (d), 126.2 (d), 119.8 (d), 117.5 (t), 114.3 (t), 44.2 (t), 43.5 (t) ppm; MS m/z (rel. int. %) 281(100), 263(18), 149(19), 134(11), 119(24), 105(23), 91(53), 79(14), 48(8).

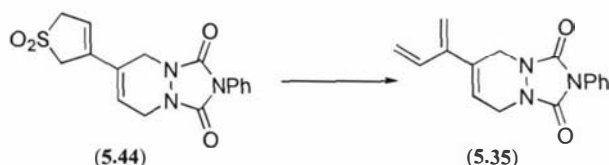
3-(2'-Phenyl-4',7'-dihydro-2',3a',7a'-triazaindan-5'-yl-1',3'-dione)-2,5-dihydrothiophene-1,1-dioxide (5.44). (Scheme 5.20)



A solution of 3-iodo-2,5-dihydrothiophene-1,1-dioxide (**3.37**) (47.1 mg, 0.193 mmol) and 2-phenyl-5-tributylstannyl-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione (**5.42**) (106 mg, 0.193 mmol) in DMF (2.0 ml) was twice freeze-thaw degassed under argon. Bis(acetonitrile) palladium (II) dichloride (2.5 mg, 9.6×10^{-6} mol, 5 mol%) was added, whereupon the colourless solution rapidly darkened. The reaction mixture was degassed once more and stirred at 60°C for 72 hrs. Ether (10 ml) was added and the supernatant decanted from the precipitate. The precipitate was triturated successively with ether (2x10 ml), hexane (2x10 ml) and acetone (2x5 ml), being recovered after each treatment by centrifugation, to give the *title compound* (**5.44**) (39.7 mg, 60%) as an amorphous white solid (m.p. $> 300^\circ\text{C}$): found M^+ 345.0783, $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_4\text{S}$ requires 345.0783; IR ν_{max} (KBr disc) 3083, 2976, 2936, 2851, 1771, 1698, 1491, 1433, 1299,

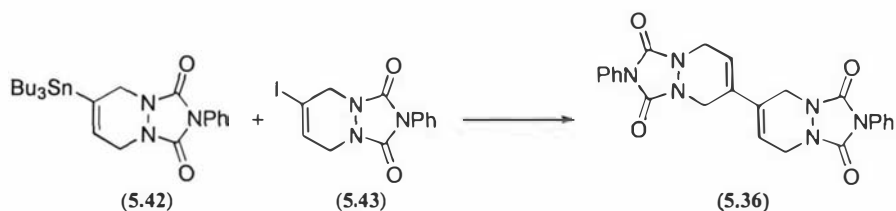
1254, 1122, 766 cm^{-1} ; ^1H NMR (270 MHz, d_6 -DMSO) δ 7.57-7.38 (5H, m, C_6H_5 -), 6.26 (1H, br.s, $-\text{CH}=\text{C}(\text{R})-$), 6.06 (1H, br.s, $-\text{CH}=\text{C}(\text{R})-$), 4.37 (2H, br.s, $-\text{CH}_2\text{N}-$), 4.28 (2H, br.s, $-\text{NCH}_2-$), 4.13 (2H, br.s, $-\text{CH}_2\text{SO}_2-$), 4.03 (2H, br.s, $-\text{SO}_2\text{CH}_2-$) ppm; ^{13}C NMR (67.8 MHz, d_6 -DMSO) δ 152.3(s), 152.0 (s), 133.0 (s), 131.4 (s), 128.9 (d), 128.0 (d), 127.0 (s), 126.1 (d), 121.7 (d), 119.3 (d), 56.9 (t), 55.0 (t), 43.6 (t), 42.8 (t) ppm; MS m/z (rel. int. %) 345(10), 281(100), 134(55), 119(18), 106(15), 91(33), 79(12), 64(7), 52(6), 39(6).

2-(2'-Phenyl-4',7'-dihydro-2',3a',7a'-triazaindan-5'-yl-1',3'-dione)-1,3-butadiene (5.35). (Scheme 5.20)



A solution of 3-(2'-phenyl-4',7'-dihydro-2',3a',7a'-triazaindan-5'-yl-1',3'-dione)-2,5-dihydrothiophene-1,1-dioxide (**5.44**) (4.0 mg, 1.16×10^{-5} mol) in d_6 -DMSO (0.6 ml), was heated to 130°C in the probe of a NMR spectrometer and the disappearance of starting material monitored by observing the ^1H NMR. After 2 hrs integration of the spectra indicated that 65% of the starting material had been converted to the *title compound* (**5.35**) giving ^1H NMR data consistent with that observed previously. Attempts to isolate the *title compound* using an aqueous work up were unsuccessful.

5,5'-Bi-(2-phenyl-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione) (5.36). (Scheme 5.20)



A solution of 2-phenyl-5-tributylstannyl-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione (**5.42**) (57.5 mg, 0.11 mmol) and 2-phenyl-5-iodo-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione (**5.43**) (39.4 mg, 0.11 mmol) in DMF (2.0 ml) was twice freeze-thaw degassed under argon. *Bis*-(acetonitrile) palladium (II) dichloride (1.4 mg, 5.5×10^{-6} mol, 5

mol%) was added whereupon the colourless solution rapidly darkened. The reaction mixture was degassed once more and stirred at rt for 24 hrs. Ether (10 ml) was added and the supernatant decanted from the precipitate which was triturated successively with ether (2x10 ml) and hexane (2x10 ml), being recovered after each treatment by centrifugation, to give the *title compound* (**5.36**) (27.3 mg, 54%) as an insoluble, amorphous white solid (m.p. > 300°C): found M^+ 456.1554, $C_{24}H_{20}N_6O_4$ requires 456.1546; IR ν_{\max} (KBr disc) 3073, 2941, 2863, 1765, 1694, 1506, 1439, 1285, 1141, 768, 710 cm^{-1} ; 1H NMR (270 MHz, d_6 -DMSO) δ 7.56-7.40 (10H, m, C_6H_5 -), 6.17 (2H, br.s, -CR=CH-), 4.38 (4H, br.s, -CH₂N-), 4.26 (4H, br.s, -NCH₂-) ppm; MS m/z (rel. int. %) 456(16), 279(9), 149(10), 119(100), 91(50), 64(27), 44(58).

DTDA reactions of [4]-dendralene (4.4) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (5.34). (Scheme 5.19)

Reaction with one molar equivalent of PTAD. A solution of 4-phenyl-1,2,4-triazoline-3,5-dione (**5.34**) in $CDCl_3$ (0.066 M, 0.36 ml, 2.3×10^{-5} mol) was added at rt under argon to a vigorously stirred solution of [4]-dendralene (**4.4**) in $CDCl_3$ (0.046 M, 0.5 ml, 2.3×10^{-5} mol). The reaction was stirred for 24 hrs whereupon the solvent was removed *in vacuo* and the residue taken up in d_6 -DMSO (2.0 ml): Found M^+ 281.1164, $C_{16}H_{15}N_3O_2$ requires 281.1164. 1H NMR showed the presence of 2 components in the ratio 2:1. The major component, 2-(2'-phenyl-4',7'-dihydro-2',3a',7a'-triazaindan-5'-yl-1',3'-dione)-1,3-butadiene (**5.35**), showed spectral characteristics identical to those reported, *vide supra*. The minor component, 2-phenyl-5,6-divinyl-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione (**5.40**) was assigned on the basis of NMR data; 1H NMR (270 MHz, d_6 -DMSO) δ 7.56-7.39 (5H [obscured], m, C_6H_5 -), 7.09 (2H, dd, $J = 17.4, 11.0$ Hz, $CH_2=CH(R)$ -), 5.45 (2H, d, 17.4 Hz, $CH(H)=CH(R)$ -), 5.33 (d, $J = 11.0$ Hz, $CH(H)=CH(R)$ -), 4.36 (4H, br.s, -CH₂NNCH₂-).

Reaction with two molar equivalents of PTAD. A solution of 4-phenyl-1,2,4-triazoline-3,5-dione (**5.34**) in $CDCl_3$ (0.066 M, 0.71 ml, 4.6×10^{-5} mol) was added at rt under argon to a vigorously stirred solution of [4]-dendralene (**4.4**) in $CDCl_3$ (0.046 M, 0.5 ml, 2.3×10^{-5} mol). The reaction was stirred for 24 hrs whereupon the solvent was removed *in vacuo* and the residue taken up in d_6 -DMSO (2.0 ml): Found M^+ 456.1554, $C_{24}H_{20}N_6O_4$ requires 456.1546; M^+ 281.1151, $C_{16}H_{15}N_3O_2$ requires 281.1164. 1H NMR showed the presence of 3 major components; 2-phenyl-5,6-divinyl-4,7-dihydro-2,3a,7a-

triazaindane-1,3-dione (**5.40**), 2-(2'-phenyl-4',7'-dihydro-2',3a',7a'-triazaindan-5'-yl-1',3'-dione)-1,3-butadiene (**5.35**) and an unknown in the ratio of 2:1:1. Vinylic signals consistent with an ABX spin system characterised the unknown component. ^1H NMR (270 MHz, d_6 -DMSO) δ 7.01 (2H, dd, $J = 17.6, 11.6$ Hz, $\text{CH}_2=\text{CH}(\text{R})-$), 5.61 (2H, d, 17.6 Hz, $\text{CH}(\text{H})=\text{CH}(\text{R})-$), 5.12 (d, $J = 11.6$ Hz, $\text{CH}(\text{H})=\text{CH}(\text{R})-$). 5,5'-Bi-(2-phenyl-4,7-dihydro-2,3a,7a-triazaindane-1,3-dione) (**5.36**) constituted $< 5\%$ of the d_6 -DMSO soluble component.

Reaction with three molar equivalents of PTAD. A solution of 4-phenyl-1,2,4-triazoline-3,5-dione (**5.34**) in CDCl_3 (0.066 M, 1.07 ml, 6.9×10^{-5} mol) was added at rt under an atmosphere of argon to a vigorously stirred solution of [4]-dendralene (**4.4**) in CDCl_3 (0.046 M, 0.5 ml, 2.3×10^{-5} mol). The reaction was stirred for 24 hrs whereupon the solvent was removed *in vacuo* and the residue taken up in d_6 -DMSO (2.0 ml): Found M^+ 631.1973, $\text{C}_{32}\text{H}_{25}\text{N}_9\text{O}_6$ requires 631.1928; M^+ 456.1582, $\text{C}_{24}\text{H}_{20}\text{N}_6\text{O}_4$ requires 456.1546; M^+ 281.1171, $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_2$ requires 281.1164.

Appendices

Appendix 5.1

Calculation of Yield by Capillary Pyrolysis.

Solutions of polyenes in a fixed volume of CDCl_3 (0.6 ml) were prepared by CP as outlined in the experimental section. Yields were calculated by comparison of the integrational intensity of the polyene with the integrational intensity of the residual chloroform peak of the NMR solvent. The intensity of the residual chloroform peak was in turn calibrated against a standard solution of *t*-butyl methyl ether (*t*BME) (1.0 μl /0.6 ml) in a sample of the same CDCl_3 . Peak areas for the analyte and *t*BME were normalised against the area of their respective residual chloroform peaks. Hence

$$I_A = An_A R \quad \text{eq. 1}$$

$$I_B = Bn_B R \quad \text{eq. 2}$$

Where:

- I_A = integrational intensity of analyte ([*n*]-dendralene).
- I_B = integrational intensity of *t*BME (1.0 μl /0.6 ml).
- A = number of moles of A ([*n*]-dendralene).
- B = number of moles of B (*t*BME).
- n_A = number of integrated protons in A ([*n*]-dendralene).
- n_B = number of integrated protons in B (*t*BME).
- R = response factor of the spectrometer.

Combining equations 1 and 2 gives equation 3.

$$R = \frac{I_A}{An_A} = \frac{I_B}{Bn_B} \quad \text{eq. 3}$$

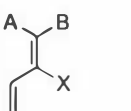
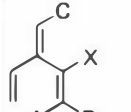
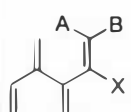
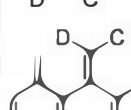
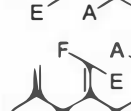
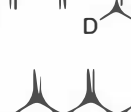
Rearrangement of equation 3 gives equation 4.

$$A = \frac{I_A B n_B}{I_B n_A} \quad \text{eq. 4}$$

Hence, knowing the theoretical maximum yield based on the mass of dendralene precursor, the number of moles of *t*BME, the number of integrated protons in the sample and analyte and the integrational intensities of both, it is possible to calculate the number of moles of [*n*]-dendralene (A).







Appendix 5.2

¹H NMR Data for [n]-Dendralenes.

n	[n]-dendralene	δ / ppm, J / Hz							
		H _A	H _B	H _C	H _D	H _E	H _F	H _G	H _X
2	 (5.17)	5.24 br.d 16.3	5.12 br.d 9.9						6.36 m
3	 (4.1)	5.42 dd 17.6 1.5	5.17 d 11.2	5.17 s					6.47 dd 17.6 11.2
4	 (4.4)	5.19 br.d 17.4	5.11 br.d 10.6	5.25 m	5.07 m				6.44 dd 17.4 10.6
5	 (4.8)	5.34 dd 17.4 1.5	5.14 br.d 10.6	5.26 m	5.23 m	5.12 m			6.44 dd 17.4 10.6
6	 (4.12)	5.29 br.d 17.4	5.13 br.d 10.5	5.28 m	5.26 m	5.09 m	5.09 m		6.46 dd 17.4 10.5
8	 (5.16)	5.36-5.25 br.m			5.12 m				6.46 dd 17.4 10.5

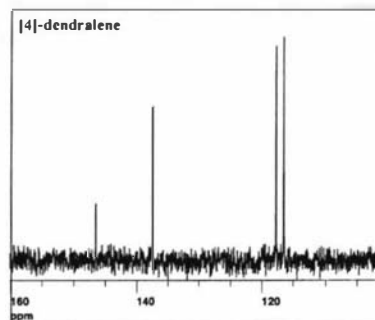
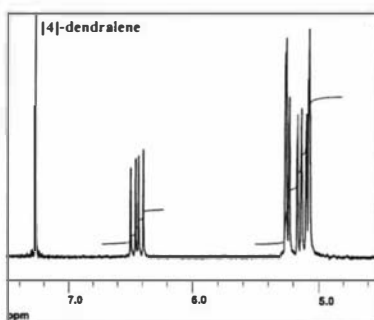
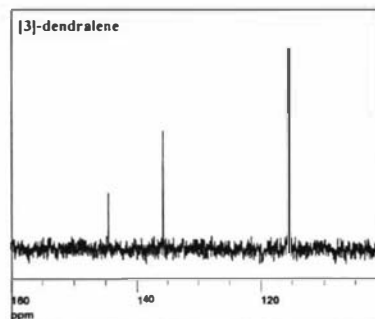
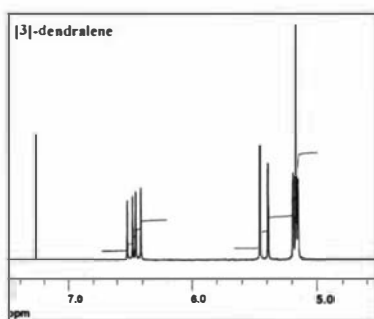
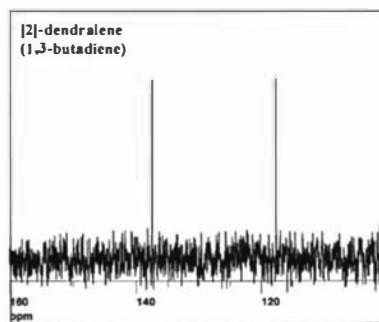
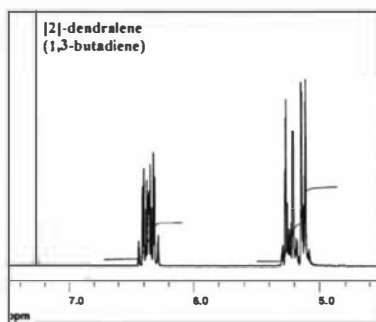
Appendix 5.3

¹³C NMR Data for [n]-Dendralenes.

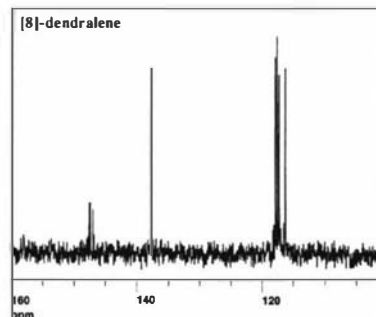
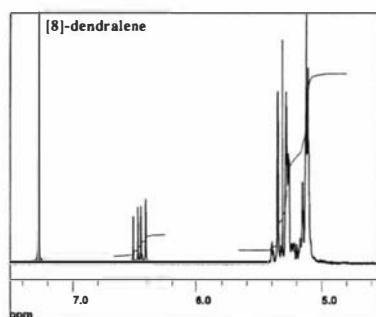
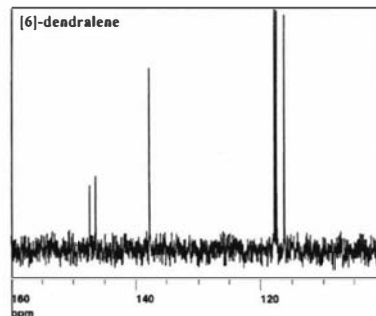
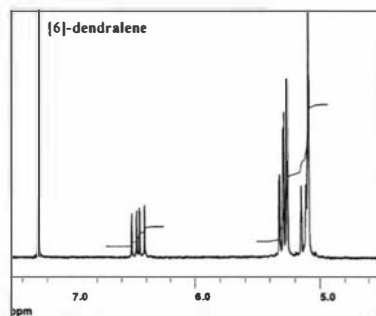
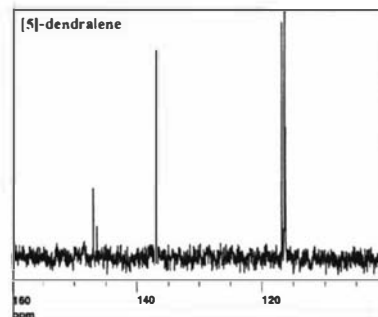
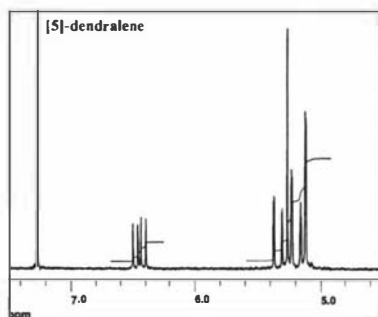
n	[n]-dendralene	δ / ppm (multiplicity)							
		C ₁	C ₂	C ₃	C ₄	C ₅	C _{3'}	C _{4'}	C _{5'}
2	 (5.17)	117.6 (t)	137.5 (d)						
3	 (4.1)	115.6 (t)	135.7 (d)	144.5* (s)			115.4* (t)		
4	 (4.4)	117.7 (t)	137.4 (d)	146.4 (s)			116.5 (t)		
5	 (4.8)	116.8 (t)	136.9 (d)	146.9 (s)	146.5* (s)		116.4 (t)	116.2* (t)	
6	 (4.12)	117.7 (t)	137.8 (d)	147.3 (s)	146.4 (s)		117.4 (t)	116.2 (t)	
8	 (5.16)	117.8 (t)	137.7 (d)	147.5 (s)	147.3 (s)	146.9 (s)	117.5 (t)	117.2 (t)	116.2 (t)

* Signals observed with half intensity relative to signals of similar multiplicity.

Appendix 5.4

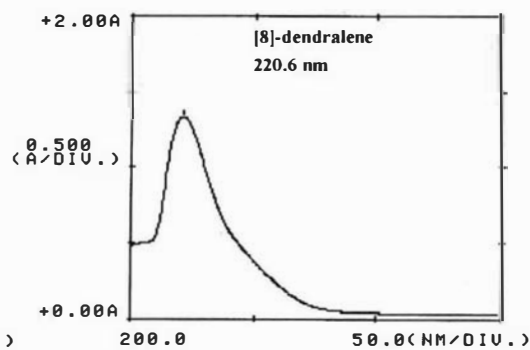
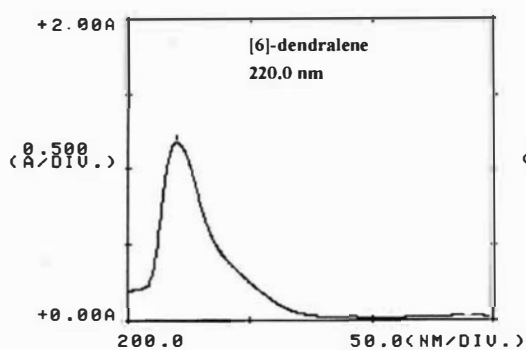
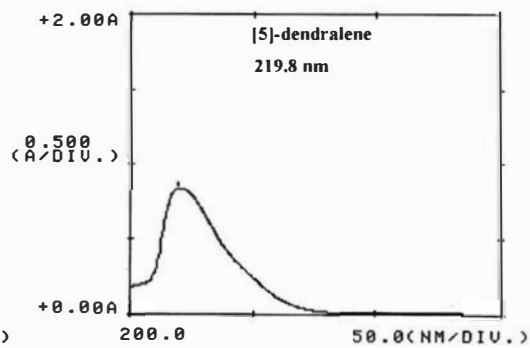
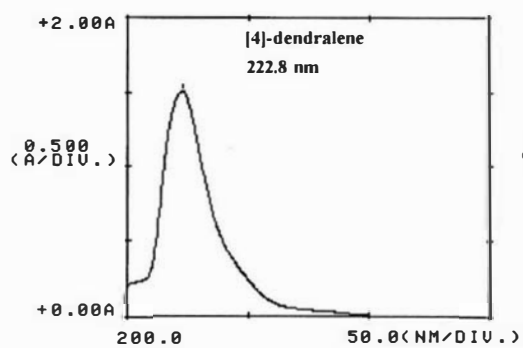
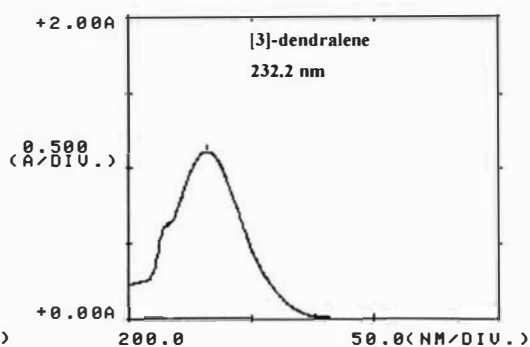
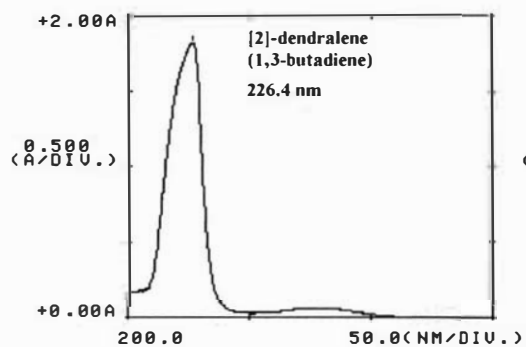
 ^1H and ^{13}C NMR Spectra of the [n]-Dendralenes

Appendix 5.4 cont.

 ^1H and ^{13}C NMR Spectra of the [n]-Dendralenes

Appendix 5.5

UV Spectra of the [n]-Dendralenes



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