

A)  $\pi$ -FACIAL DIASTEREOSELECTIVITY IN DIELS-  
ALDER REACTIONS OF 2,5-DIMETHYLTHIOPHENE  
OXIDE AND RELATED COMPOUNDS

B) A SYNTHETIC APPROACH TO A CHIRAL  
KETENE EQUIVALENT

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ARVIN MARK NAPERSTKOW, B.Sc.







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**B) A SYNTHETIC APPROACH TO A CHIRAL KETENE EQUIVALENT**

by

**Arvin Mark Naperstkow, B. Sc.**

**A Thesis submitted in partial fulfillment  
of the requirements for the degree of  
Master's of Science**

**Department of Chemistry  
Memorial University of Newfoundland**

**August 1990**

**St. John's, Newfoundland**



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## Abstract

The reactivity and diastereofacial selectivity of some thiophene oxides particularly 2,5-dimethylthiophene oxide in Diels-Alder reactions are reported. The sulfoxides were generated "*in situ*" by peracid oxidation (*m*-chloroperoxybenzoic acid). In all successful cases of cycloaddition, the dienophiles benzoquinone, naphthoquinone, tetracyanoethylene, *N*-phenylmaleimide and 2-chloroacrylonitrile afforded exclusively the *syn* adduct with respect to the sulfoxide oxygen. The structures were confirmed by X-ray crystallographic analysis.

This facial preference is consistent with the relative donor ability of the lone pair versus the sulfoxide oxygen. In accord with the concept of transition state stabilization by  $\sigma$  electron donation into the vacant  $\sigma^*$  orbital, associated with the incipient bond, addition should occur *anti* to the better donor, (i.e.) the lone pair, as observed. Thiophene oxides thus represent latent butadiene equivalents that react with complete facial control.

The second and third parts of this thesis describe unsuccessful synthetic studies directed toward intramolecular thiophene oxide cycloadditions and the preparation of a sulfoxide based ketene equivalent.

## Abbreviations Table

### 1. Chemical Abbreviations:

2,5-BCT	<i>bis</i> -2,5-chloromethylthiophene
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
2,5-DMT	2,5-dimethylthiophene
HMPA	Hexamethylphosphoramide
LDA	Lithium diisopropylamide
TMEDA	Tetramethylethylenediamine

### 2. Instrumental Abbreviations:

GC/MS	Gas Chromatograph coupled to a Mass Selective Detector
IR	Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance Spectroscopy
TLC	Thin Layer Chromatography

### **Acknowledgements**

I would like to acknowledge the guidance and patience given by Prof. Alex G. Fallis throughout this work. I would like to express my appreciation and respect to Prof. D.J. Burnell for the support given during the completion of this thesis. I would like to thank Prof. M.J. Newlands and the National Research Council of Canada for the many X-ray crystallographic determinations.

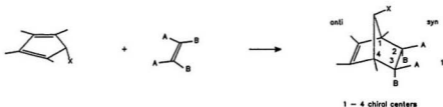
Furthermore, I would like to express my gratitude to Dr. Ken Michalko, Chief, Division of Biopharmaceutics Evaluation, Bureau of Pharmaceutical Surveillance (Health and Welfare Canada) for providing assistance in the completion of this thesis through the procurement of computer hardware and software as well as time.

Lastly, I would like to express my deepest appreciation to my wife, Andrea for the support that has been given for the duration of this thesis.

## CHAPTER ONE

### Introduction:

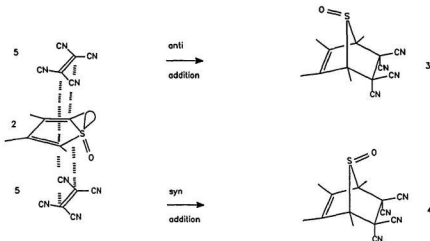
The Diels-Alder reaction has become a powerful synthetic tool since its discovery in 1928.<sup>1</sup> The reaction has been studied extensively in a variety of applications yet all facets are still imperfectly understood.<sup>2-4</sup> One such feature is the facial diastereoselectivity created when a diene or dienophile contains a stereogenic centre (see illustration below). The Diels-Alder reaction is a  $[4+2]$  cycloaddition derived from the union of the  $4\pi$  electrons of the diene with  $2\pi$  electrons of the dienophile. The theoretical aspects of this reaction have not been fully resolved but several hypotheses have been advanced to accommodate the mechanism.<sup>5-8</sup> Frontier-Molecular Orbital (FMO) theory successfully predicted the regiochemistry and stereochemistry of the Diels-Alder reaction.<sup>5a</sup> More recently, a series of papers have suggested other methods (e.g. electrostatic modelling) to predict the facial selectivity of the cycloaddition.<sup>8a-d</sup> This thesis focuses on an aspect of facial stereoselectivity which involves a combination of electronic and steric effects upon the  $[4+2]$  cycloaddition. There are several recent literature examples of facial stereoselectivity, primarily involving systems which incorporate heteroatoms into the structure of the diene or dienophile. The electronic effects are often due to the presence of a lone pair of electrons in the heteroatom, although in some instances steric interactions contribute.



Sulfoxides are tetrahedral and thus present two different faces which differ in electron density and reactivity, since in symmetrical systems one face contains oxygen while the opposite face is occupied by a lone pair of electrons. *A priori*, it has proved difficult to decide which face is more

electron dense and consequently arguments have been made to support both views.<sup>6,7</sup> Figure 1 illustrates the "*syn*" and "*anti*" adducts that may arise from a symmetrical sulphoxide diene in which only the lone pair or the sulphoxide oxygen can influence the facial selectivity of the cycloaddition.\*

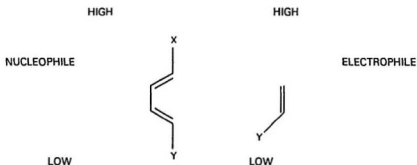
FIGURE 1



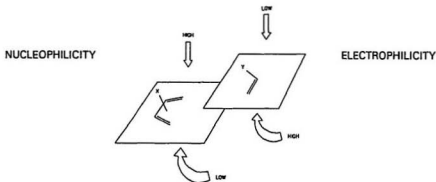
If, the dienophile 5 approached the diene 2 from above (lone pair side) the resulting adduct 3 would be "*anti*" with respect to the sulphoxide oxygen. The other possibility will result in adduct 4, the "*syn*" addition product. The factors which govern the facial preference, if any, are clearly of interest and potential synthetic utility.

\*The nomenclature used to describe the relative stereochemistry of C-7 substituted norbornenes employs the prefix *anti* when the substituent is on the side of the bridge remote from the double bond. However, this is the adduct which arises from *syn* attack of the dienophile on a substituted cyclopentadiene. Thus to avoid confusion the use of the terms *syn* and *anti* are restricted to descriptors for the facial approach of the addends, so that the *syn* adducts result from the *syn* approach of the reactants. This is standard usage, however an alternative nomenclature is possible, such as like and unlike or distal and proximal. Based on the Seebach-Prelog convention<sup>8</sup> the relative topicities of the approach to the face of an enantiomer are unlike (*anti*) when the addition occurs on the *si* face of a double bond possessing an adjacent R allylic center. However for consistency, a predetermined priority order must be followed, that may differ from the standard sequence rules. Similarly the terms distal and proximal are more useful to describe conformational geometries.

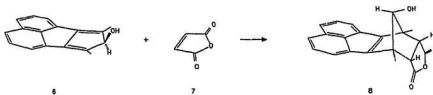
Recently, a series of papers by Hehre *et al* have appeared, based on electrostatic modelling.<sup>64</sup> They attempted to predict the regiochemistry of the adduct through the electronic effects of the diene and dienophile.<sup>64</sup> In Hehre's approach, the diene and dienophile components are viewed as nucleophilic and electrophilic partners. In the [4+2] cycloaddition, there is a matching of nucleophilicity (of the diene) as a function of position with the electrophilicity (of the dienophile) which will allow the prediction of the regiochemistry with greater accuracy than the related FMO theory. It can be illustrated in the following manner.<sup>64</sup>



The results from electrostatic modelling of the [4+2] cycloaddition imply that with chiral dienes and electron poor dienophiles addition should occur preferentially onto the diene face which is more nucleophilic. In addition, this should result in binding onto the face of the dienophile which exhibits greater electrophilicity.<sup>64</sup>



Hehre concluded that the Diels-Alder reaction involving allylic substituents has an inherent preference for the addition of electrophiles "*syn*" to a lone pair contained in these substituents particularly alcohols, amines and their derivatives. Several studies support this conclusion. For example, Jones examined the cycloaddition of diene **6** with maleic anhydride (**7**) and found the single "*syn*" adduct **8**.<sup>9</sup>



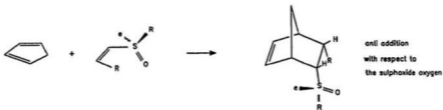
The facial stereoselectivity of the dienophile will also be influenced by heteroatom functionality. The electron rich face of the diene will prefer the more electron poor face of the dienophile.

Hehre has also argued that the preferred geometry of vinyl sulfoxides is the *s-cis* conformation as illustrated.



If the sulfoxide oxygen in **9** is in the same plane as the double bond, the competition for an approaching diene is between the R-group and the lone pair of electrons on the other face of the sulphur atom. Based upon electrostatic considerations the electron rich face of the diene should approach the electrophilic face (R-group) of the dienophile preferentially. This can be illustrated with the example by DeLucchi *et al.*<sup>10</sup> (See Scheme A).

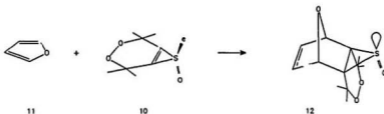
# SCHEME A



Note:  $e^-$  = pair of electrons

The results are consistent with Hehre's prediction but a better example may be 10, since the conformational ambiguity is removed.<sup>11</sup>

## SCHEME B

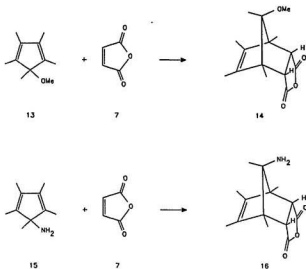


Note:  $e^-$  = pair of electrons

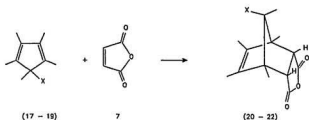
Based on Hehre's conclusions, the diene 11 should approach the more electrophilic face of the thioether-S-oxide (10), but which is it? Is the S=O oxygen more electron rich than the lone pair of electrons or vice versa? Experimentally, the adduct 12 was obtained in 86% yield and the structure was established by X-ray crystallography. Clearly, the addition of furan (11) was "anti" with respect to the sulfoxide oxygen. A result consistent with Hehre's theory is that the oxygen bearing face will be the more electron rich face.

Recent studies on facial stereoselectivity suggest a possible inconsistency with Hehre's proposals, particularly with regard to sulphur groups. Macaulay and Fallis examined heteroatom directed syn/anti stereoselection in Diels-Alder cycloadditions of plane nonsymmetric cyclopentadienes and found that "syn" addition occurred when C(5) was substituted with either oxygen or nitrogen functionality.<sup>12</sup> These results were consistent with those of Jones' adduct 8 above and the previous

example of Woodward.<sup>13</sup>



The "syn" addition was expected as the electron rich faces of dienes 13 and 15 contain the heteroatoms. When sulphur was used as the heteroatom at C(5) for 17, 18 and 19, there was a reversal of facial selectivity and the "anti" adducts 20, 21 and 22 predominated.



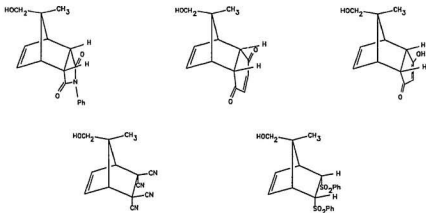
X = SMe (17)  
X = SOMe (18)  
X = SO<sub>2</sub>Me (19)

9:1 *anti* addition (20) X = SMe  
100% *anti* addition (21) X = SOMe  
100% *anti* addition (22) X = SO<sub>2</sub>Me

The result with SMe did not fit the electrostatic modelling concept since "syn" addition to the sulphur face was expected. This may indicate that the thioether face was less electron rich than the

methyl face or steric interactions were more important than in the oxygen analogues. For the sulphoxide and sulfone cases, the dienophile approached the less sterically hindered face of the diene. The thiomethyl group was larger<sup>14ac</sup> than the oxymethyl but this was not the entire explanation. Due to the difference in relative rates and the fact that the mercaptan (SH) gave a significant amount of "anti" adduct, there was an important electronic component.

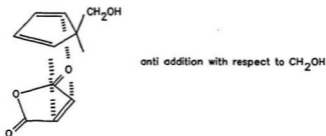
Recently, Paquette reported findings<sup>16</sup> differing from the work of Macaulay and Fallis<sup>12,33</sup> involving the "syn" addition of 5-oxygenated-1,3-cyclopentadienes and the example reported by Jones.<sup>9</sup> Paquette used 5-hydroxymethyl-5-methyl-1,3-cyclopentadiene as a benchmark diene in cycloaddition reactions with the dienophiles of *N*-phenylmaleimide, benzoquinone, 4-cyclopentene-1,3-dione, tetracyanoethylene and (Z)-1,2-bis(phenylsulfonyl)ethylene. In all cases the facial stereoselectivity was largely "anti" with respect to the oxygen functional group, in a ratio greater than 4:1 (*anti*:*syn*). (Only *syn*-CH<sub>3</sub> is shown.)



Dienophile	Solvent	Conditions	<i>syn</i> -CH <sub>3</sub>	<i>syn</i> -CH <sub>3</sub> OH
<i>N</i> -phenylmaleimide	C <sub>6</sub> H <sub>6</sub>	rt, 5 days	87%	13%
benzoquinone	C <sub>6</sub> H <sub>6</sub>	rt, 5 days	84%	16%
4-cyclopentene-1,3-dione	C <sub>6</sub> H <sub>6</sub>	85°C, 5 days	85%	15%
tetracyanoethylene	C <sub>6</sub> H <sub>6</sub>	rt, 20 h	87%	13%
(Z)-1,2-bis(phenylsulfonyl)ethylene	CH <sub>2</sub> Cl <sub>2</sub>	rt, 90000 psi	82%	18%

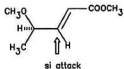
Note: rt = room temperature

Paquette's examples of "*anti*" addition required partitioning on the basis of steric interactions in the transition state between the hydroxymethyl and methyl groups of the diene. The hydroxymethyl group was considered bulkier than the methyl groups.<sup>16a,b</sup> The more favourable transition state (lowest energy) yielded the "*anti*" facial selectivity.

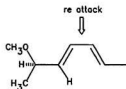


Although the Paquette examples were convincing, a simple model (i.e. electrostatic modelling) may not work when steric contributions outweigh the electronic contributions. It is still essential to determine if the electronic demands are the same once the steric factors are removed. Paquette could also have considered the consequences if the hydroxymethyl group was substituted for a smaller or equal size group (with respect to methyl). Therefore, Paquette's steric argument is probably valid but the difficult question is to what extent do steric and/or electronic contributions affect the Diels-Alder reaction?

Franck *et al.*, recently published a paper on facial selectivity involving acyclic dienes which have a stereogenic allylic carbon.<sup>17</sup> In part, their findings were also at variance with Hehre's electrostatic modelling theory<sup>2a,d</sup> and their own earlier results.<sup>18</sup> Initially, Franck *et al.* proposed that dienophile **23**, which had an allylic R chiral center, would undergo "*si*" attack while a diene **24**, which had a R chiral center, would undergo "*re*" attack.



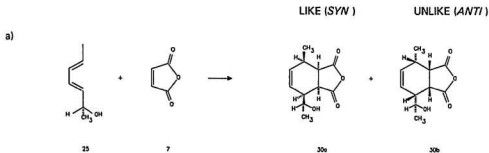
23



24

This concept was remarkably similar to Hehre's theory. In both, the diene would approach the dienophile from the "si" face which also was the more electrophilic face according to Hehre. The situation was reversed in the diene. But, predicting the facial preference depends upon the rotamer population and the relative reactivity of the diene and/or dienophile, thus the facial selectivity could be radically changed if one considers the eclipsed form of equal importance since a mixture of adducts would result.

Subsequently, Franck *et al* found that the diene with the stereogenic allylic carbon gave one set of results with maleic anhydride (7) and *N*-phenylmaleimide (27), and a different set of results with tetracyanoethylene (5), dimethylacetylene dicarboxylate (28) and 4-phenyl-1,2,4-triazoline-3,5-dione (29).<sup>17</sup> (Franck now believes that steric effects are the dominant influence.<sup>17a</sup>) The following examples are illustrative.



LIKE (*SYN*)

UNLIKE (*ANTI*)

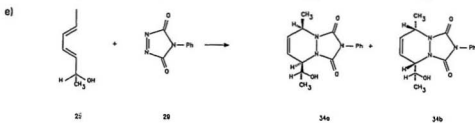
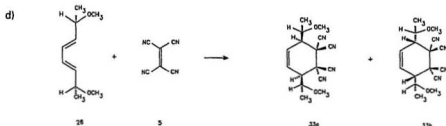
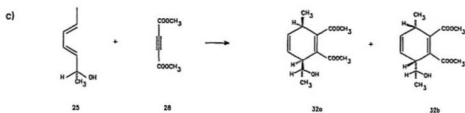
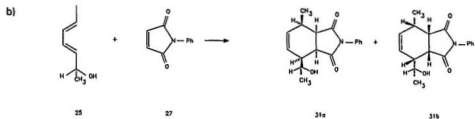
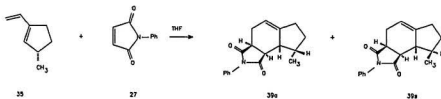


Table of Results (Syn : Anti Ratios)

Compounds	Syn	Anti
30a / 30b	2.5	1
31a / 31b	1.7	1
32a / 32b	1	2.7
33a / 33b	1	5.7
34a / 34b	1	2.8

These results of Franck's indicated that the facial stereoselectivity was not entirely "*syn*" or "*anti*".<sup>17</sup> The free rotation of the chiral center was probably responsible for the lack of discrimination between the faces. This result was dependent upon the different rates of reaction for the rotamers. It is possible that certain orientations of the allylic chiral center created repulsive electronic interactions in the transition state. It is not certain why there was a pronounced "*anti*" addition when strongly activated dienophiles were used, but it could have resulted from a change of mechanism.<sup>18a,b</sup> In the fourth case, **26** and **5** exhibited a preference for the unlike ("*anti*") addition, but this diene had two stereogenic allylic carbons. Franck did not mention this, but it is possible that the diene had several orientations which it can adopt allowing the unlike addition to be preferred.

Recent contributions by Overman *et al*,<sup>20,21</sup> and Hehre,<sup>21</sup> have further eroded the confidence of Hehre's electrostatic models from the study of 1(E)-substituted-1,3-dienes with *N*-phenylmaleimide (**27**) and tetracyanoethylene (**5**). Their findings were inconsistent with the earlier reported results for 5-substituted-1,3-cyclopentadienes. The dienes **35** - **38** with *N*-phenylmaleimide (**27**) and tetracyanoethylene (**5**) provided adducts as illustrated.<sup>12</sup> (a = "*anti*" and s = "*syn*")



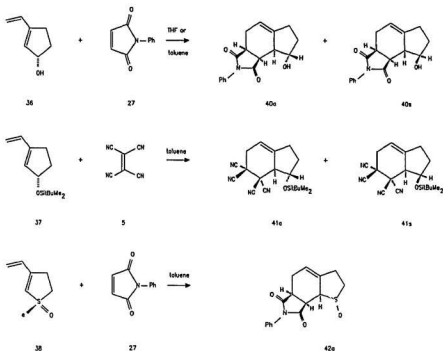
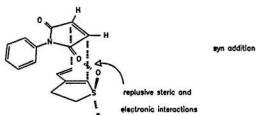


Table of Results (Syn : Anti Ratios)

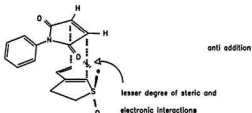
Compounds	Solvent	Anti	Syn
39s / 39s	THF	82%	18%
40s / 40s	Toluene	36%	64%
40s / 40s	THF	64%	36%
41a / 41s	Toluene	69%	31%
42a / 42s	Toluene	100%	0%

Overman *et al* stated that the lack of facial stereoselectivity originated from a destabilizing steric interaction and a repulsive electrostatic interaction between the proximal oxygen of the imide dienophile **27** and the allylic oxygen of the diene **36** during the "syn" approach in the transition state. The sulfoxide case was similar but had a more pronounced "anti" addition due to the repulsive

interactions between diene and dienophile.

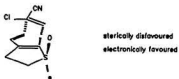


hence,



Note:  $\bullet$  = pair of electrons

The "syn" oxygen addition in both the methyl diene 35 and the sulfoxide cases should have been favoured on electronic grounds. To control this situation, the allylic substituent could be changed or dienophiles substituted at one terminus of the olefin. This would eliminate the offending steric and electronic interactions. Consequently, if Overman *et al* had used 2-chloroacrylonitrile (43) as a dienophile instead of *N*-phenylmaleimide (27) and tetracyanoethylene (5), they might have observed results that fit with Hehre's conclusions in the case of the minor meta adduct.



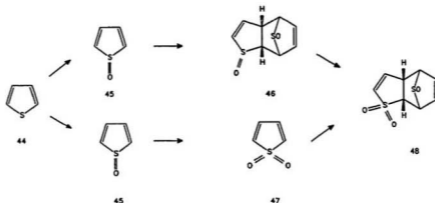
Note: • = pair of electrons

Of the four possible approaches, two would be disfavoured. The competition would be between "*syn*" and "*anti*" and the results would reflect an electronic competition.

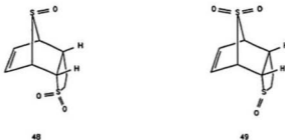
The facial diastereoselectivity of the Diels-Alder reaction can be assessed without any bias, if the molecule employed has the sulfoxide group locked into the structure. Planar molecules are ideal, possessing two distinct faces, free of any extraneous steric or electronic interactions. Thiophene oxides are well suited for the investigation of these electronic effects as the sulfoxide has a locked configuration.

Thiophene and related oxidized species have only been examined intermittently and few aspects of their reactivity in the [4 + 2] cycloaddition have been thoroughly investigated. To engage thiophene as a reactant, the aromaticity must be disrupted and this can be accomplished by oxidation of the allylic sulphide to either the sulfoxide or sulphone.

In 1952, Davies *et al* reported the peracid oxidation of thiophene (44) to thiophene oxide (45) which resulted in a Diels-Alder dimerization.<sup>22a,b</sup> An adduct was isolated with the molecular formula of  $C_8H_8O_3S_2$ , subsequently referred to as thiophene sesquioxide (48). Davies suggested two possible routes for the mixed oxidation state [4 + 2] cycloaddition.



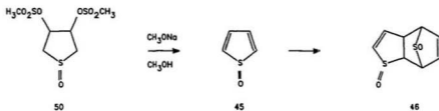
Davies presumed that thiophene oxide (45) behaved as the diene and that the fully oxidized sulphone 47 reacted as the dienophile. However, the molecular formula  $C_8H_8O_3S_2$  satisfied two different adducts 48 and 49.



The structure of the thiophene sesquioxide was assigned by Merrill and Sherwood in 1977 employing NMR techniques.<sup>23</sup> Merrill and Sherwood repeated the Davies experiment and subjected the adduct to a series of spin-decoupling experiments ( $^1H$  NMR, 300 MHz). They concluded that the structure was *syn-endo*-3a,4,7,7a-tetrahydro-4,7-epithiobenzo[b]thiophene-1,1,8-trioxide (48). Preparation of the sesquioxide required concentrated solutions of thiophene and hydrogen peroxide in glacial acetic acid and stirring for 7 days to achieve a 15% yield.

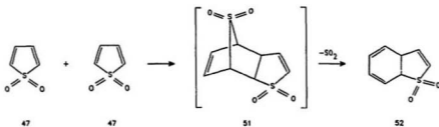
Prochaska has also studied the [4 + 2] cycloaddition of thiophene oxide (45) as both diene and

dienophile.<sup>24</sup> Adduct **46** was accomplished through the elimination of methanesulfonic acid of tetrahydro-3,4-bis(methylsulfonyloxy)thiophene-1-oxide (**50**).

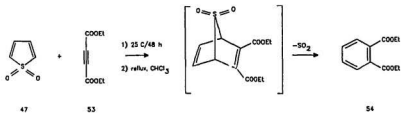


The adduct **46** was not properly characterized as only the UV spectrum was recorded, and the chemistry was confirmed by the sodium borohydride reduction which yielded thiophene (**44**).

Thiophene dioxide has been studied more extensively. Bailey and Cummings synthesized thiophene dioxide (**47**) *in situ* and found that thiophene dioxide acted as both diene and dienophile.<sup>26</sup>

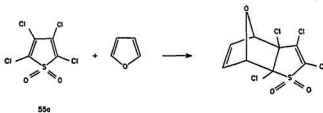


The adduct **51** was very unstable losing the  $\text{SO}_2$  bridge to form the product **52**. Thiophene dioxide (**47**) preferred to react as a diene and was trapped with diethylacetylene dicarboxylate (**53**).

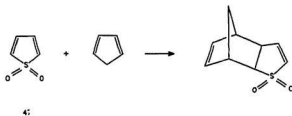


Here also, the  $\text{SO}_2$  bridge was lost easily to form the aromatic product 54. Thiophene-1,1-dioxide (47), and related species 55a, 55b have been investigated previously. The following reactions provide a brief overview of these thiophene dioxide studies.<sup>28-29b</sup>

a)

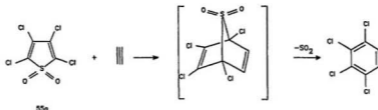


b)

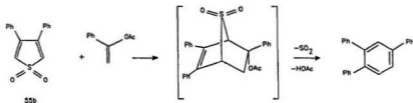


**Note:** The stereochemistry was not determined for examples a and b.

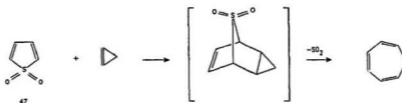
c)



d)



e)




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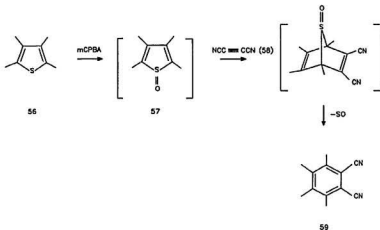
Reaction References:

- a) See reference 26.
  - b) See reference 27.
  - c) See reference 26.
  - d) See reference 28.
  - e) See reference 29a,b.
- 

The thiophene dioxide was employed primarily as a diene to form aromatic products.

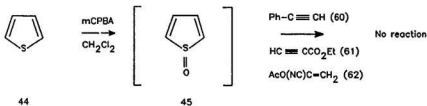
Mock successfully synthesized thiophene oxides which were stable at 25°C.<sup>30</sup> This was accomplished by incorporating bulky R-groups (t-butyl or t-octyl) at positions 2 and 5 of the thiophene molecule. The procedure was straightforward as it employed 1.1 equivalents of *m*-chloroperoxybenzoic acid as an oxidant. More importantly, it provided evidence that it was possible to isolate a substituted thiophene oxide. Helder adapted Mock's procedure to generate thiophene oxide

(57) "in situ" in his reaction scheme.<sup>31</sup>

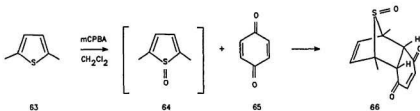


The oxidation of tetramethylthiophene (56) with *m*-chloroperoxybenzoic acid in the presence of dicyanoacetylene (58) yielded tetramethyl-1,2-benzenedicarbonitrile (59) (70%) directly.

Torsell adapted Mock's procedure to generate thiophene oxide "in situ" for his examination of [4 + 2] cycloadditions.<sup>32</sup> The objective was purely synthetic as it provided a potential pathway into a series of aromatic compounds. These initial Diels-Alder reactions were conducted to explore the reactivity of thiophene oxide (45). Torsell established that thiophene oxide was an electron deficient diene as it failed to react with phenyl acetylene (60), ethyl propiolate (61) and  $\alpha$ -acetoxyacrylonitrile (62).



Next, Torssell examined 2,5-dimethylthiophene (**63**). Compound **63** was not as electron deficient due to the electron density donated by the methyl groups. The diene was generated "*in situ*" and it reacted with benzoquinone (**65**).



The reaction conditions consisted of adding *m*-chloroperoxybenzoic acid to a stirred solution of 2,5-dimethylthiophene (**63**) and benzoquinone (**65**) in dichloromethane. The reaction mixture was stirred for 36 h. The product **66** was purified and recrystallized (33% yield). Torssell intended to employ the adduct **66** as an intermediate in a juglone synthesis. This did not require a knowledge of the facial selectivity, hence, no determination of stereochemistry was attempted. It was important to determine the level of diastereoselectivity experienced in thiophene oxide cycloadditions.

Macaulay and Fallis,<sup>33</sup> re-examined some of Torssell's work to determine if the facial diastereoselectivity was consistent with their findings that used C(5) substituted cyclopentadienes.<sup>12</sup> The Torssell reaction was repeated and the product was isolated, recrystallized and examined by X-ray crystallography. X-ray crystallography confirmed that the addition was "*syn*", so the addition had occurred in a contrasteric fashion but in agreement with Hehre's concept of electrostatic modelling.

## AIM OF RESEARCH

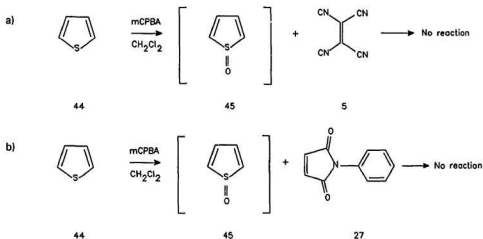
It was not clear if the reaction of **64** and **65** represented a general phenomenon or a special situation. For example, would different dienophiles reflect a different facial preference as found in some other systems?<sup>17,20</sup> Perhaps, dienophiles which were electron deficient would produce the "*syn*" addition while dienophiles which were electron rich would permit "*anti*" addition. The research in this thesis is directed towards increasing the understanding of the behaviour of allylic sulphoxides in Diels-Alder reactions. Examination of plane nonsymmetric sulphoxides in which the facial selectivity will be determined by a competition between the lone pair and oxygen faces is particularly attractive. Thus, symmetrical thiophene oxides coupled with symmetrical dienophiles removes the problem of regiochemistry and allows an easier investigation of facial preference. If successful, this would allow the use of thiophene oxides as latent butadiene equivalents with complete facial control.

## RESULTS

### a) Summary:

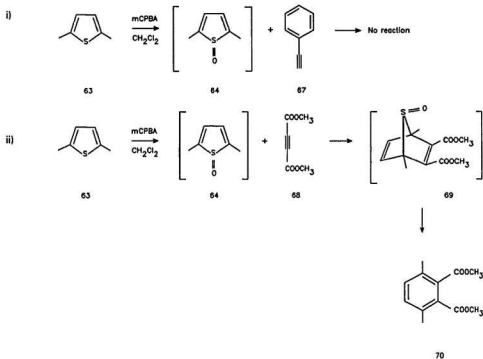
In order to ascertain if the Diels-Alder cycloadditions consistently added "*syn*" to thiophene oxides as the Macaulay and Fallis<sup>33</sup> result implied and to learn more about their general behaviour, the following series of experiments were conducted.<sup>34</sup> The reactions were conducted using a modification of the Torsell procedure. This consisted of slow addition of *m*-chloroperoxybenzoic acid in dichloromethane to a stirred solution of either thiophene or 2,5-dimethylthiophene and the dienophile in dichloromethane. The reaction was stirred between 5 - 60 h (in most cases) at 21°C to permit formation of the adduct. The reactions attempted are categorized by diene and dienophile type.

### Thiophene Reactions:

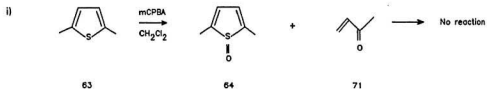


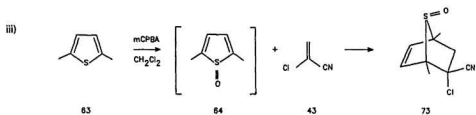
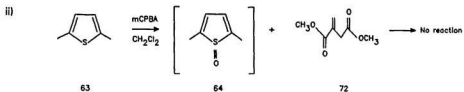
## 2,5-Dimethylthiophene oxide Reactions:

### a) Acetylene Series:



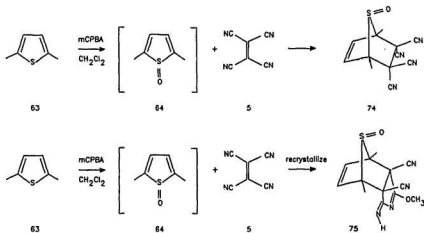
### b) Ethylene Series:





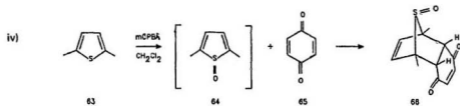
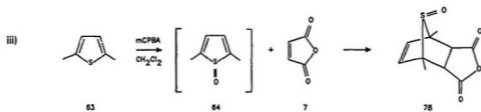
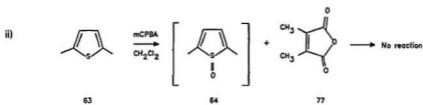
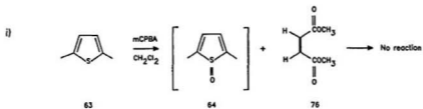
c) Tetracyanoethylene Series:

1)

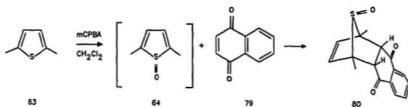


Note: Recrystallization of Adduct 74 from  $\text{CH}_3\text{CN}/\text{CH}_3\text{OH}/\text{Et}_2\text{O}$  (8:1:1) afforded Adduct 75.

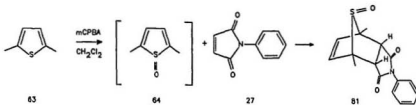
d) Dicarbonyl Activated Series:



v)

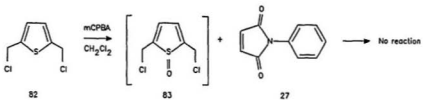


vi)

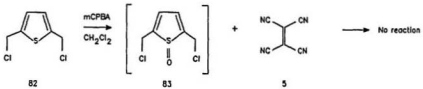


e) *bis*-2,5-Chloromethylthiophene Series:

i)



ii)



## RESULTS

### b) Discussion:

#### Thiophene Series:

Thiophene (44) was investigated first. Unfortunately, the individual reactions between thiophene oxide (45) and *N*-phenylmaleimide (27) and tetracyanoethylene (5) failed to produce any adduct at room temperature. The reactions were closely monitored by GC/MS but after 168 h at 21°C, there was no indication of any adduct. Similarly, *N*-phenylmaleimide (27) gave no product in spite of refluxing in toluene for 168 h. In both cases, after the work up, GC/MS indicated the presence of dienophile but not the desired adduct or sesquioxide adduct (48). To generate the sesquioxide adduct, a concentrated reaction mixture was employed. In Merrill's case a 0.932 M solution of thiophene in glacial acetic acid afforded a 15% yield.<sup>23</sup> In contrast, the concentration of thiophene in our studies was only 0.040M, too dilute to facilitate the dimerization. The concentrations for the successful 2,5-dimethylthiophene cases ranged from 0.040 - 0.050 M. These [4 + 2] cycloadditions were not as dependent on concentration as the formation of the sesquioxide adduct. An NMR study, (stack plot <sup>1</sup>H, 300 MHz) using 2,5-dimethylthiophene (63) and *m*-chloroperoxybenzoic acid (0.12 M 2,5-dimethylthiophene in deuterated dichloromethane), established that after 19 h, the sesquioxide reaction had not occurred. Clearly the dimerization reaction was not of major consequence.

#### Acetylene Series:

Subsequent reactions employed a more electron rich "*in situ*" diene 64 (2,5-dimethylthiophene oxide). Phenyl acetylene (67) failed to produce an adduct, probably a consequence of the relatively high electronic density of the acetylene bond. The dimethyl acetylene dicarboxylate (68) reacted slowly (168 h, GC/MS), and it was extremely difficult to isolate the adduct 69. The mass spectrum displayed a peak at *m/z* = 222 (M-48 peak) representing the adduct with the loss of the labile sulphoxide bridge. The signals (60 MHz, CDCl<sub>3</sub> δ: 2.11 (s,6H), 3.85 (s,6H), 6.28 (s,2H)) in the NMR spectrum of the crude product confirmed the presence of the adduct. However, purification through

flash chromatography (20% EtOAc/80% pet. ether) provided aromatic material ( $^1\text{H}$  60 MHz NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.35 (s,6H), 3.85 (s,6H), 7.4 (s,2H)). This result was similar to Helder's case with tetramethylthiophene (56) and dicyanoacetylene (58) which gave tetramethyl-1,2-benzene dicarbonitrile (59).<sup>31</sup> Direct recrystallization also proved fruitless and the investigation was terminated.

#### Ethylene Series:

2,5-Dimethylthiophene oxide (64) was also investigated with dienophiles in which one terminal of the double bond was unsubstituted. Methyl vinyl ketone (71), dimethyl itaconate (72) and  $\alpha$ -chloroacrylonitrile (73) were used as dienophiles. The first reaction between methyl vinyl ketone (71) and 2,5-dimethylthiophene oxide (64) failed to produce an adduct, which was not entirely unexpected as 71 was not sufficiently reactive to facilitate the cycloaddition.

The reaction between 2,5-dimethylthiophene oxide (64) and dimethyl itaconate (72) also failed to produce an adduct even though this dienophile was considered to be more reactive. The reaction followed the modified Torssell procedure (168 h at 21 °C, monitored by GC/MS). Therefore, a very electron deficient dienophile of this series structure must be employed to facilitate the [4+2] cycloaddition.

The final reaction within this class involved 2-chloroacrylonitrile (43) which has a two electron withdrawing groups, therefore, it should be a better dienophile. The standard reaction conditions were used (21 °C, 60 h, monitored by GC/MS). The presence of the desired adduct 73 was confirmed by the molecular ion of  $m/z = 167$ , (M-48 peak). The crude adduct could not be identified by NMR as the signals were quite different from the known symmetrical adducts. The adduct 73 NMR signals (60 MHz) were obscured by the side products of the reaction (2,5-dimethylthiophene dioxide and thiophene coupled product). The adduct was purified via flash chromatography (30% EtOAc/70% pet. ether) and recrystallized from  $\text{CH}_2\text{Cl}_2$ /hexane. The  $^1\text{H}$  300 MHz NMR proton spectrum displayed 2 AB multiplets for the 2 vinyl protons ( $\text{CDCl}_3$   $\delta$ : 6.07 (d, 1H,  $J = 6.9$  Hz), 6.34 (d, 1H,  $J = 6.9$  Hz)) and the C(3) exo/endo protons ( $\delta$ : 2.56 (d, 1H,  $J = 14.5$  Hz), 3.46 (d, 1H,  $J = 14.5$  Hz)), and two singlets for the methyl groups attached to C(1) ( $\delta$ : 1.82) and C(4) ( $\delta$ : 1.55). The NMR indicated that only one adduct

was formed but uncertainty existed, regarding the stereochemistry at C(2). X-ray crystallography established that the nitrile group was exo and the chlorine group was endo, and the cycloaddition had followed a "syn" pathway with respect to the sulphoxide oxygen. This appeared to agree with Hehre's concept of electrostatic modelling as the electron deficient dienophile had added preferentially to the electron rich oxygen face.

#### Tetracyanoethylene Series:

Tetracyanoethylene (5) is a highly electron deficient dienophile due to the four electron withdrawing groups. Hence, this will be well matched with the "in situ" diene. The addition of a dichloromethane solution of 2,5-dimethylthiophene (63) to tetracyanoethylene (5) dissolved in dichloromethane produced an intense purple colour, possibly the result of a charge transfer complex. The reaction mixture was stirred with *m*-chloroperoxybenzoic acid for 24 h at 21 °C and the GC/MS indicated the presence of the desired adduct 74. The reaction was worked up in the normal manner to yield a colourless crystalline material. The mass spectrum of 74 yielded a strong signal at  $m/z$  = 208 and a base peak of  $m/z$  = 193. This spectrum indicated that several routes of fragmentation were possible. The following table was construct to illustrate some of the routes.

Route 1	Route 2	Route 3	Route 4
$m/z$ = 208, loss of SO	$m/z$ = 208, loss of SO	$m/z$ = 208, loss of SO	$m/z$ = 208, loss of SO
$m/z$ = 193, loss of CH <sub>3</sub>	$m/z$ = 182, loss of CN	$m/z$ = 182, loss of CN	$m/z$ = 182, loss of CN
$m/z$ = 167, loss of CN	$m/z$ = 167, loss of CH <sub>3</sub>	$m/z$ = 156, loss of CN	$m/z$ = 156, loss of CN
$m/z$ = 141, loss of CN	$m/z$ = 141, loss of CN	$m/z$ = 141, loss of CH <sub>3</sub>	$m/z$ = 130, loss of CN
$m/z$ = 126, loss of CH <sub>3</sub>	$m/z$ = 126, loss of CH <sub>3</sub>	$m/z$ = 126, loss of CH <sub>3</sub>	$m/z$ = 104, loss of CN
$m/z$ = 100, loss of CN	$m/z$ = 100, loss of CN	$m/z$ = 100, loss of CN	$m/z$ = 89, loss of CH <sub>3</sub>
$m/z$ = 74, loss of CN	$m/z$ = 74, loss of CN	$m/z$ = 74, loss of CN	$m/z$ = 74, loss of CH <sub>3</sub>

The NMR spectrum of 74 (<sup>1</sup>H, 300 MHz, CD<sub>3</sub>CN)

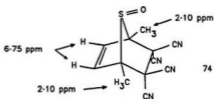
displayed the expected singlet signal at  $\delta$ : 2.10 (s,6H)

for the two methyl groups and singlet signal at  $\delta$ :

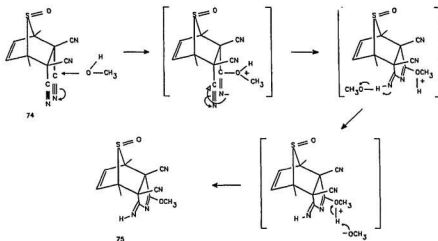
6.75 (s,2H) for the two vinyl protons. The spectrum

also indicated that residual CH<sub>3</sub>CN was trapped from

the recrystallization. The adduct 74 upon further recrystallization (CH<sub>3</sub>CN/CH<sub>3</sub>OH/Et<sub>2</sub>O;8:1:1) afforded



fine monoclinic crystals in a low yield (10%) and the X-ray analysis revealed the empirical formula was  $C_{13}H_{12}N_4O_2S$  **75** instead of  $C_{12}H_8N_4OS$  **74** indicating that the adduct **74** has undergone a transformation. The ORTEP structure differed from the expected tetracyanoethylene adduct **74** due to the condensation of methanol across two of the nitrile groups to form an unique endo cyclic system **75**. This could have arisen as illustrated.



The NMR contained no additional multiplicity of signals and confirmed a single adduct had been isolated. The  $^{13}C$  NMR spectrum contained resonances for every carbon atom (75 MHz, DMSO  $d_6$   $\delta$ : 11.86, 12.38, 60.44, 61.96, 62.96, 73.72, 74.47, 111.50, 113.57, 132.05, 134.01, 164.42, 173.65). The two adducts of **74** and **75**, were further characterized by X-ray crystallography demonstrating unequivocally that the preferred face of attack bore the sulphoxide oxygen.

#### Dicarbonyl Series:

The last class of dienophiles investigated with 2,5-dimethylthiophene oxide (**64**) was activated by a dual carbonyl functionality, and adducts **66**, **78**, **80** and **81** have been either identified or isolated. The first reaction between dimethyl maleate (**76**) and 2,5-dimethylthiophene (**64**) was stopped after 168 h as the reaction failed to produce any adduct, although 2,5-dimethylthiophene-1,1-dioxide had

formed (GC/MS and  $^1\text{H}$  NMR). A similar result was obtained with 2,3-dimethylmaleic anhydride (77) as only 2,5-dimethylthiophene-1,1-dioxide was identified. The reaction between maleic anhydride (7) and 2,5-dimethylthiophene oxide (64) presented a different case. The reactivity of the dienophile was greatly enhanced compared to 2,3-dimethyl maleic anhydride (77) due to the absence of the vinyl methyl groups. It has been reported by Sauer that maleic anhydride reacts  $10^3$  times faster than 2,3-dimethyl maleic anhydride with respect to cyclopentadiene.<sup>36a,b</sup> The adduct formation with 2,5-dimethylthiophene oxide (64) was complete after 5 h at  $21^\circ\text{C}$ . The reaction mixture was worked up in the normal manner and the NMR ( $^1\text{H}$ , 200 MHz) of the crude product revealed adduct and 2,5-dimethylthiophene-1,1-dioxide. The isolation of the adduct 78 proved to be difficult as it decomposed in the flash chromatography column. The polarity of the adduct 78 enabled washing with highly non-polar solvents (i.e. hexanes, pet. ether) to remove the side products. The NMR ( $^1\text{H}$ , 200 MHz) indicated that this technique was effective as the spectra displayed only residual amounts of the undesired products. Recrystallization was unsuccessful, although the NMR data suggested that there was one adduct present. The facial stereoselectivity was not established but based on the previous results, it was likely "*syn*".

The reaction between 2,5-dimethylthiophene oxide (64) and benzoquinone (65) was initially reported by Torssell<sup>32</sup> and re-examined by Macaulay and Fallis.<sup>32</sup> Macaulay and Fallis modified Torssell's procedure and purified the adduct 66 by flash chromatography followed by recrystallization from  $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$  to produce orthorhombic crystals in a 27% yield. The NMR ( $^1\text{H}$ , 300 MHz) data were consistent with a single adduct 66. The X-ray analysis determined that the addition was "*syn*" and the stereochemistry at C(2) and C(3) was *endo* (quinone cyclic system).

Thus, 2,5-dimethylthiophene oxide (64) and naphthoquinone (79) were reacted under analogous conditions and afforded a Diels-Alder adduct 80. The adduct 80 was isolated by flash chromatography (30% EtOAc/70% pet.ether) and recrystallized sequentially from  $\text{CCl}_4/\text{EtOH}$ ; 2/1 and  $\text{CH}_3\text{CN}/\text{Et}_2\text{O}$ ; 1:2 to afford a product in an 18% yield. The NMR ( $^1\text{H}$ , 300 MHz,  $\text{CDCl}_3$ ) spectrum was consistent with a symmetrical adduct as 3 singlet signals (6 methyl protons,  $\delta$ : 1.74 (s, 6H); 2 *exo* protons,  $\delta$ : 3.83

(s, 2H); 2 vinyl protons,  $\delta$ : 5.88 (s, 2H)) and 2 aromatic signals ( $\delta$ : 7.71 - 7.75 (m, 2H), 7.96 - 8.00 (m, 2H)) were displayed. The X-ray data indicated that the cycloaddition was "syn" and the naphthoquinone system was endo.

The last reaction in this class was between 2,5-dimethylthiophene oxide (**64**) and *N*-phenylmaleimide (**27**). The standard conditions (48 h, 21 °C, monitored by GC/MS) followed by normal work up provided crude product, which according to the NMR (<sup>1</sup>H, 60 MHz), was a mixture that contained adduct **81**. Adduct **81** was purified by flash chromatography (CH<sub>3</sub>CN/CCl<sub>4</sub>;1:8.5) and recrystallized (EtOAc/hexane) to afford monoclinic crystals (yield 13.6%). The NMR (<sup>1</sup>H, 300 MHz) data indicated that only one type of adduct was present. X-ray crystallography established that the stereochemistry at C(2) and C(3) was endo (*N*-phenylmaleimide system) and that the stereoselectivity had followed the expected pattern with addition to the "syn" face.

## CONCLUSIONS

The X-ray crystallographic studies have provided overwhelming evidence that when employed as a diene, 2,5-dimethylthiophene oxide reacted with exclusive "*syn*" selectivity. These compounds possess unrecognized potential as latent butadienes that react with complete  $\pi$ -facial control. The cycloaddition required a deactivated dienophile. The "*syn*" facial diastereoselectivity may be explained on the basis of the relative donor ability of the adjacent functionalities and their interaction with the developing incipient bonds. Thus, in these cases where the competition is between a lone pair and a sulfoxide oxygen, cycloaddition should be *anti* to the lone pair as observed in all the cases above. To be truly useful, the yields from the thiophene oxide cycloadditions must be raised and the range of dienes increased. This should be possible as thiophene possesses a rich chemistry and by choosing compounds with increased electron density (masked enol ethers, etc.), the formation of new and useful synthetic intermediates will become available.

In particular other pericyclic reactions, enolate alkylations and carbonium ion quenches may display a preference for addition *anti* to the adjacent antiperiplanar  $\sigma$  bond that is the better electron donor. Recent unpublished extensions of this work to related 1,3-oxathiolanes have encountered a high level of stereocontrol in nucleophilic additions and alkylations.

## EXPERIMENTAL

### GENERAL:

Melting points were determined in capillary tubes with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 783 infrared Spectrophotometer and were calibrated with the 2850 and 1601  $\text{cm}^{-1}$  bands of polystyrene film. Proton magnetic resonance spectra ( $^1\text{H}$  NMR) were measured at 60 MHz with a Varian EM 360 spectrometer or at 300 MHz with a General Electric GN 300 or at 200 MHz on a Varian Gemini 200 spectrometer. Carbon magnetic resonance spectra ( $^{13}\text{C}$  NMR) were measured at 75 or 50 MHz. The spectra were recorded in deuteriochloroform and signal positions are reported in ppm downfield from tetramethylsilane ( $\delta$  scale) as an internal standard: the multiplicity, number of protons, coupling constants and assignments are indicated in parentheses. Mass spectra were determined on a V.G. Micromass 7070HS instrument using an ionization energy of 70 eV or on a Hewlett Packard 5890A gas chromatograph with a 5970B mass selective detector equipped with a 12.5 m capillary column (0.2 mm ID) coated with crosslinked dimethyl silicone (0.33  $\mu\text{m}$ ). A Picker or Nonius four circle diffractometer was used for crystallographic measurements conducted at the National Research Council of Canada at Ottawa, Ontario. Flash chromatography using E. Merck silica gel 60 (230 - 400 mesh) was employed for all column chromatography. Analytical thin layer chromatography (TLC) was carried out on aluminium sheets precoated (0.2 mm layer thickness) with silica gel 60 F<sub>254</sub> (E. Merck).

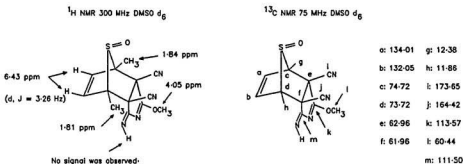
Petroleum ether refers to a fraction with the boiling range of 30 - 60°C. Dichloromethane, acetonitrile, carbon tetrachloride, chloroform, diethyl ether and hexane were ACS grade or better. Ethyl acetate, methanol, chloroform and petroleum ether were redistilled in glass. Solutions in organic solvents were dried over anhydrous magnesium sulphate and stripped of solvent with a Büchi rotary evaporator connected to a water aspirator.

**1,4-Dimethyl-2,2,3,3-tetracyano-7-thiabicyclo[2.2.1]hept-5-ene anti-7-oxide (74):**

*m*-Chloroperoxybenzoic acid (0.906 g, 0.42 mmol, 80% purity Aldrich) in dichloromethane (15 mL) was added dropwise over 30 minutes to a stirred dichloromethane solution (15 mL) containing 2,5-dimethylthiophene (63) (0.370 g, 3.3 mmol, Aldrich) and tetracyanoethylene (5) (0.320 g, 2.5 mmol). The reaction was stirred for 36 h at 21 °C and neutralized with saturated aqueous sodium bicarbonate (2 X 40 mL), dried, filtered and concentrated to yield **74** as orange-white crystals. Recrystallization from diethyl ether / acetonitrile afforded **74**, 0.075 g (11.7%), mp 220 °C (dec.). <sup>1</sup>H NMR 300 MHz, (CD<sub>3</sub>CN) δ: 2.10 (s, 6H), 6.75 (s, 2H). Exact mass calculated for C<sub>12</sub>H<sub>8</sub>N<sub>4</sub> (m/z -SO): 208.0756; found 208.0749. See Table 4 (p. 39) for the summary of X-ray crystallography data.

**1,4-Dimethyl-5,9-exo-dicyano-6-immino-7-aza-8-methoxy-10-thia-tricyclo[5.2.1.0<sup>8,9</sup>]deca-2,7-diene anti-10-oxide (75):**

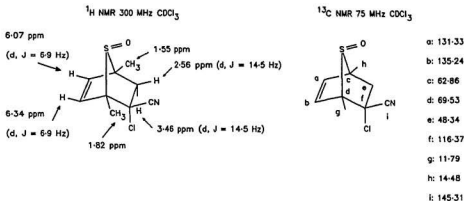
The standard reaction with *m*-chloroperoxybenzoic acid (0.539 g, 2.5 mmol), 2,5-dimethylthiophene (63) (0.224 g, 2.0 mmol) and tetracyanoethylene (5) (0.197 g, 1.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL), was stirred for 24 h at 21 °C and worked up as above to yield **74** as yellowish-white crystals. Recrystallization from 10% Et<sub>2</sub>O / 10% CH<sub>3</sub>OH / 80% CH<sub>3</sub>CN afforded **75**, 0.041 g (9.6%), mp 162 °C (darkens), 182 °C (dec.). <sup>1</sup>H NMR 300 MHz (DMSO d<sub>6</sub>) δ: 1.81 (s, 3H), 1.84 (s, 3H), 4.05 (s, 3H), 6.43 (d, 2H, J = 3.26 Hz). <sup>13</sup>C NMR 75 MHz (DMSO d<sub>6</sub>) δ: 11.86, 12.38, 60.44, 61.96, 62.96, 73.72, 74.47, 111.50, 113.57, 132.05, 134.01, 164.42, 173.65. The following signal assignments have been proposed.



Exact mass calculated for C<sub>13</sub>H<sub>12</sub>N<sub>4</sub>O (m/z -S=O): 240.1011; found 240.1012. See Table 4 (p. 39) for the summary of X-ray crystallography data.

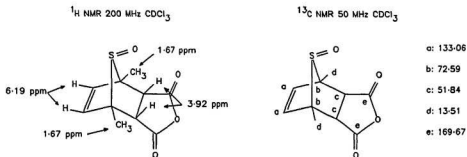
**1,4-Dimethyl-2-exo-cyano-2-endo-chloro-7-thiabicyclo[2.2.1]hept-5-ene anti-7-oxide (73):**

The standard reaction with *m*-chloroperoxybenzoic acid (2.21 g, 10.2 mmol), 2,5-dimethylthiophene (63) (1.02 g, 9.1 mmol) and 2-chloroacrylonitrile (43) (0.586 g, 6.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (240 mL), was stirred for 60 h at 21 °C and worked up as above to give a dark yellow oil which was purified by chromatography (30% EtOAc / 70% pet. ether) and recrystallized from CH<sub>2</sub>Cl<sub>2</sub> / hexane to yield adduct **73**, 0.110 g (7.6%), mp 108 - 109 °C. <sup>1</sup>H NMR 300 MHz (CDCl<sub>3</sub>) δ: 1.55 (s, 3H), 1.82 (s, 3H), 2.56 (d, 1H, J = 14.5 Hz), 3.46 (d, 1H, J = 14.5 Hz), 6.07 (d, 1H, J = 6.9 Hz), 6.34 (d, 1H, J = 6.9 Hz). <sup>13</sup>C NMR 75 MHz (CDCl<sub>3</sub>) δ: 11.79, 14.48, 48.34, 62.86, 69.53, 116.37, 131.33, 135.24, 145.31. The following signal assignments have been proposed (evidence supported by <sup>1</sup>H/<sup>13</sup>C HETCOR NMR experiment).



See Table 4 (p. 39) for the summary of X-ray crystallography data.

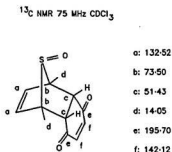
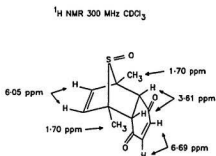
**1,4-Dimethyl-2,3-(furan-1,3(2H)-dione)-7-thiabicyclo[2.2.1]hept-5-ene anti-7-oxide (78).**  
The standard reaction with *m*-chloroperoxybenzoic acid (2.21 g, 10.2 mmol), 2,5-dimethylthiophene (63) (1.02 g, 9.1 mmol) and maleic anhydride (7) (0.657 g, 6.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (160 mL), was stirred for 36 h at 21 °C and worked up as above to give a dark orange oil, which was purified by repeated pet. ether (50 mL) and hexane (50 mL) washings to yield 78, 0.250 g (~16%). <sup>1</sup>H NMR 200 MHz (CDCl<sub>3</sub>) δ: 1.67 (s,6H), 3.92 (s,2H), 6.19 (s,2H). <sup>13</sup>C NMR 50 MHz (CDCl<sub>3</sub>) δ: 13.51, 51.84, 72.59, 133.06, 169.67. The following signal assignments have been proposed.



**1,4-Dimethyl-2-endo-3-endo-(cyclohex-2-ene-1,4-dione)-7-thiabicyclo[2.2.1]hept-5-ene anti-7-oxide (66).**

The standard reaction with *m*-chloroperoxybenzoic acid (3.26 g, 15.1 mmol), 2,5-dimethylthiophene (63) (1.08 g, 9.6 mmol) and benzoquinone (65) (1.03 g, 9.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 mL), was stirred for 48 h at 5 °C and worked up as above to give a yellow oil which was recrystallized from CH<sub>3</sub>CN / Et<sub>2</sub>O to yield 66, 0.610 g (27%), mp 144 - 146 °C. IR (CHCl<sub>3</sub>): 3018 cm<sup>-1</sup> (C=H), 1676 cm<sup>-1</sup> (C=O). <sup>1</sup>H NMR 300 MHz (CDCl<sub>3</sub>) δ: 1.70 (s,6H), 3.61 (s,2H), 6.05 (s,2H), 6.69 (s,2H). <sup>13</sup>C NMR 75 MHz

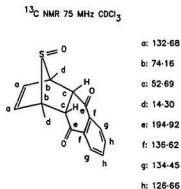
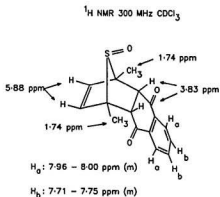
(CDCl<sub>3</sub>)  $\delta$ : 14.05, 51.43, 73.50, 132.52, 142.12, 195.70. The following signal assignments have been proposed.



X-ray crystallography data was recorded at the NRC laboratories in Ottawa, Ontario but the interpretation of the data was not completed. Preliminary findings indicated clearly that the sulphoxide oxygen was "syn" and the structure was very similar to other adducts examined by X-ray crystallography.

**1,4-Dimethyl-2-endo-3-endo-(2,3-naphthoquin-1,4-dione)-7-thiabicyclo[2.2.1]hept-5-ene anti-7-oxide (80).**

The standard reaction with *m*-chloroperoxybenzoic acid (2.21 g, 10.2 mmol), 2,5-dimethylthiophene (63) (1.02 g, 9.1 mmol) and 1,4-naphthoquinone (79) (1.06 g, 6.7 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (240 mL), was stirred for 36 h at 21°C and worked up as above to give a dark brown oil, which was purified by chromatography (30% EtOAc / 70% pet. ether) and recrystallized from 33% CH<sub>3</sub>CN / 67% Et<sub>2</sub>O to yield 80, 0.352 g (18.4%), mp 164 - 166°C. <sup>1</sup>H NMR 300 MHz (CDCl<sub>3</sub>)  $\delta$ : 1.74 (s, 6H), 3.83 (s, 2H), 5.88 (s, 2H), 7.71 - 7.75 (m, 2H), 7.96 - 8.00 (m, 2H). <sup>13</sup>C NMR 75 MHz (CDCl<sub>3</sub>)  $\delta$ : 14.30, 52.69, 74.19, 126.66, 134.45, 136.62, 194.92. The following signal assignments have been proposed (evidence supported by <sup>1</sup>H/<sup>13</sup>C HETCOR NMR experiment).

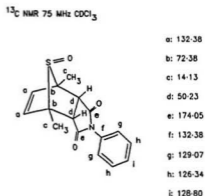
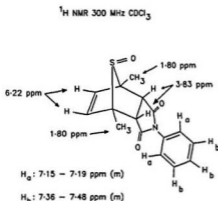


Exact mass calculated for C<sub>18</sub>H<sub>14</sub>O<sub>2</sub> (m/z-SO): 238.0982; found: 238.1006. See Table 5 (p. 40) for

the summary of X-ray crystallography data.

**1,4-Dimethyl-2-endo-3-endo-(2-phenylpyrrole-1,3-(2H)-dione)-7-thiabicyclo[2.2.1]hept-5-ene anti-7-oxide (81).**

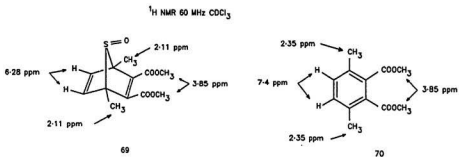
The standard reaction with *m*-chloroperoxybenzoic acid (2.21 g, 10.2 mmol), dimethylthiophene (63) (1.02 g, 9.1 mmol) and *N*-phenylmaleimide (27) (1.16 g, 6.7 mmol) in  $\text{CH}_2\text{Cl}_2$  (190 mL), was stirred for 48 h at 21°C and worked up as above to give a dark yellow oil which was purified by chromatography (15%  $\text{CH}_3\text{CN}$  / 85%  $\text{CCl}_4$ ) and recrystallized from EtOAc / hexane to yield **81**, 0.275 g (13.6%), mp 169 - 170°C.  $^1\text{H}$  NMR 300 MHz ( $\text{CDCl}_3$ )  $\delta$ : 1.80 (s, 6H), 3.83 (s, 2H), 6.22 (s, 2H), 7.15 - 7.19 (m, 2H), 7.36 - 7.48 (m, 3H).  $^{13}\text{C}$  NMR 75 MHz ( $\text{CDCl}_3$ )  $\delta$ : 14.13, 50.23, 72.38, 126.34, 128.80, 132.38, 174.05. The following signal assignments have been proposed (evidence supported by  $^1\text{H}/^{13}\text{C}$  HETCOR NMR experiment).



Exact mass calculated for  $\text{C}_{18}\text{H}_{18}\text{NO}_2$  (m/z-SO): 253.1137; found: 253.1103. See Table 5 (p. 40) for the summary of X-ray crystallography data.

**1,4-Dimethyl-2,3-dimethyldicarboxylate-7-thiabicyclo[2.2.1]hept-5-ene anti-7-oxide (69).**

The standard reaction with *m*-chloroperoxybenzoic acid (3.00 g, 17.4 mmol), 2,5-dimethylthiophene (63) (1.00 g, 8.9 mmol) and dimethyl acetylenedicarboxylate (68) (1.26 g, 8.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (60 mL), was stirred for 96 h at 5°C and worked up as above to yield yellow-white crystalline material (0.55 g, 22.8%).  $^1\text{H}$  NMR 60 MHz ( $\text{CDCl}_3$ )  $\delta$ : 2.11 (s, 6H), 3.85 (s, 6H), 6.28 (s, 2H). Low resolution mass spectra: m/z = 222, 207, 191, 173, 148, 134, 90, 78, 59, 44. Purification through flash chromatography (20% EtOAc/80% pet. ether) provided aromatic compound **70** in a yield of 0.105 g. ( $^1\text{H}$  60 MHz NMR ( $\text{CDCl}_3$ )  $\delta$ : 2.35 (s, 6H), 3.85 (s, 6H), 7.4 (s, 2H)). Low resolution mass spectra: m/z = 222, 207, 192, 161, 147, 124, 91, 77, 59, 45. The following signal assignments have been proposed.



The same procedure was employed in the following cases where the cycloadditions were unsuccessful. Tables on the next page illustrate the reaction conditions.

Table 1

Dienophile	mass and molar equivalent of dienophile	mass and molar equivalent of <i>m</i> -CPBA	mass and molar equivalent of 2,5-DMT	Time and temperature
phenyl acetylene (67)	0.92 g, 8.9 mmol	2.15 g, 10.0 mmol	1.02 g, 9.1 mmol	16 h @ 21°C
dimethyl acetylene dicarboxylate (68)	0.950 g, 6.7 mmol	2.21 g, 10.2 mmol	1.02 g, 9.1 mmol	96 h @ 5°C
dimethyl itaconate (72)	1.06 g, 6.7 mmol	2.21 g, 10.2 mmol	1.02 g, 9.1 mmol	168 h @ 21°C
dimethyl maleate (76)	0.966 g, 6.7 mmol	2.21 g, 10.2 mmol	1.02 g, 9.1 mmol	168 h @ 21°C
2,3-dimethyl anhydride (77)	0.530 g, 6.7 mmol	2.21 g, 10.2 mmol	1.02 g, 9.1 mmol	168 h @ 21°C
methyl vinyl ketone (71)	0.624 g, 8.9 mmol	2.15 g, 10.0 mmol	1.02 g, 9.1 mmol	120 h @ 21°C

Table 2

Dienophile	mass and molar equivalent of dienophile	mass and molar equivalent of <i>m</i> -CPBA	mass and molar equivalent of thiophene	Time and temperature
tetracyano ethylene (5)	0.600 g, 4.3 mmol	1.62 g, 7.5 mmol	0.505 g, 6.0 mmol	144 h @ 21°C
<i>N</i> -phenylmaleimide (27)	0.600 g, 3.4 mmol	1.10 g, 5.1 mmol	0.362 g, 4.3 mmol	120 h @ 110°C toluene reflux

Table 3

Dienophile	mass and molar equivalent of dienophile	mass and molar equivalent of <i>m</i> -CPBA	mass and molar equivalent of 2,5-BCT	Time and temperature
tetracyano ethylene (5)	0.630 g, 4.9 mmol	1.62 g, 7.5 mmol	1.09 g, 6.0 mmol	144 h @ 21°C
<i>N</i> -phenylmaleimide (27)	0.690 g, 4.0 mmol	1.29 g, 6.0 mmol	0.910 g, 5.0 mmol	120 h @ 110°C toluene reflux

## Legend:

*m*-CPBA: *m*-Chloroperoxybenzoic acid  
 2,5-DMT: 2,5-Dimethylthiophene  
 2,5-BCT: *bis*-2,5-Chlorometh, thiophene

Table 4

## Crystal Data and Summary of Intensity Data Collection and Structure Refinement

Compound	66	73	74	75
Empirical Formula	C <sub>12</sub> H <sub>12</sub> O <sub>2</sub> S	C <sub>9</sub> H <sub>12</sub> NO <sub>2</sub> Cl	C <sub>12</sub> H <sub>8</sub> N <sub>4</sub> O <sub>2</sub> S	C <sub>12</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> S
crystal class	n/a	monoclinic	orthorhombic	monoclinic
formula wt	236.15	215.70	256.08	288.19
space group	n/a	P 2 <sub>1</sub> /n	P bcn	P 2 <sub>1</sub>
temp., °C	n/a	20°C	20°C	20°C
cell constants <sup>a</sup>				
a, Å	n/a	6.2793 (13)	7.8049 (5)	9.2702 (4)
b, Å	n/a	6.557 (3)	10.6998 (6)	11.2355 (3)
c, Å	n/a	24.210 (7)	14.9437 (8)	13.1967 (4)
α, deg	*****	*****	*****	*****
β, deg	n/a	96.580 (20)	112.270 (10)	90.482 (3)
γ, deg	*****	*****	*****	*****
cell vol., Å <sup>3</sup>	n/a	990.24	1246.80	1374.46
formula units/unit cell	n/a	4	4	4
D <sub>calc</sub> , Mg m <sup>-3</sup>	n/a	1.447	2.731	1.393
μ <sub>calc</sub> , mm <sup>-1</sup>	n/a	0.54	4.43	2.01
diffractometer scen	n/a	Nonius/B-2θ	Picker/B-2θ	Picker/B-2θ
radiation, graphite monochromator (CuK <sub>α</sub> )	n/a	λ = 0.70930 Å	λ = 1.54056 Å	λ = 1.54056 Å
max. crystal dimens., mm	n/a	0.10 X 0.15 X 0.20	0.15 X 0.20 X 0.30	0.30 X 0.30 X 0.40
2θ range, deg	n/a	2 ≤ 2θ ≤ 39.9	2 ≤ 2θ ≤ 119.9	2 ≤ 2θ ≤ 119.9
no. of measured reflections	n/a	1226	1535	3173
no. of unique reflections	n/a	471	968	2045
range of hkl				
h	n/a	-5 to 5	0 to 8	-10 to 10
k	n/a	0 to 6	0 to 12	0 to 10
l	n/a	0 to 23	0 to 16	0 to 11
no. of obsd. reflections [F <sub>o</sub> > 2.5σ(F <sub>o</sub> )] <sup>b</sup>	n/a	471	968	2045
computer programs	NRC VAX	NRC VAX	NRC VAX	NRC VAX
structure solution	MULTAN	MULTAN	MULTAN	MULTAN
no. of params. varied	n/a	118	101	230
weights	n/a	unit	unit	counting statistics
GOF	n/a	0.504	1.908	6.086
R <sub>1</sub> = Σ    F <sub>o</sub>   -   F <sub>c</sub>    / Σ   F <sub>o</sub>   (sig)	n/a	0.078	0.044	0.033
R <sub>w</sub> (sig)	n/a	0.087	0.053	0.033
R <sub>1</sub> (all reflections)	n/a	0.159	0.060	0.035
R <sub>w</sub> (all reflections)	n/a	0.153	0.062	0.033
largest feature	n/a	0.400e <sup>-3</sup> Å <sup>-3</sup>	0.270e <sup>-3</sup> Å <sup>-3</sup>	0.220e <sup>-3</sup> Å <sup>-3</sup>
final diff. map				

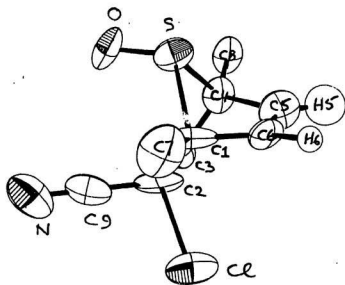
Note: \* = MoK<sub>α</sub> n/a = not available\* = Least squares refinement of ((sinθ/λ)<sup>2</sup>)<sup>b</sup> = Corrections: Lorenz-polarization

**Table 5**  
Crystal Data and Summary of Intensity Data Collection and Structure Refinement

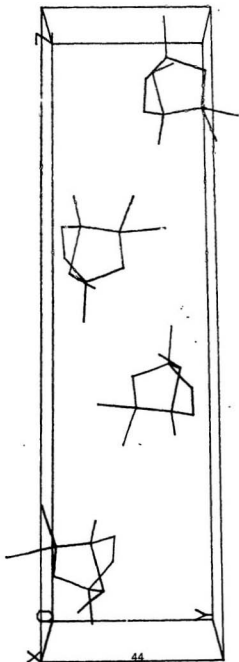
Compound	80	81
Empirical Formula	C <sub>18</sub> H <sub>14</sub> O <sub>2</sub> S	C <sub>18</sub> H <sub>14</sub> NO <sub>2</sub> S
crystal class	monoclinic	monoclinic
formula wt	286.33	301.19
space group	P2 <sub>1</sub> /n	P 2 <sub>1</sub>
temp., °C	20°C	20°C
cell constants*		
a, Å	7.8016 (3)	11.0920 (5)
b, Å	19.3897 (7)	6.5804 (4)
c, Å	9.8235 (4)	20.2788 (10)
α, deg	*****	*****
β, deg	112.270 (10)	101.000 (10)
γ, deg	*****	*****
cell vol., Å <sup>3</sup>	1375.16	1452.95
formula units/unit cell	4	4
D <sub>calc</sub> , M gm <sup>-3</sup>	1.373	0.689
μ <sub>calc</sub> , mm <sup>-1</sup>	2.08	1.01
diffractometer scan	Pickering-2θ	Nonius-θ-2θ
radiation, graphite monochromator (CuK <sub>α</sub> )	λ = 1.54056 Å	λ = 1.54058 Å
max. crystal dimens., mm	0.30 X 0.40 X 0.50	0.15 X 0.25 X 0.30
2θ range, deg	2 ≤ 2θ ≤ 119.9	2 ≤ 2θ ≤ 119.9
no. of measured reflections	3155	2813
no. of unique reflections	2040	2742
range of hkl		
h	-7 to 7	0 to 12
k	0 to 19	0 to 7
l	0 to 10	0 to 22
no. of obsd. reflections [F <sub>o</sub> > 2.5σ(F <sub>o</sub> )] <sup>b</sup>	1771	2198
computer programs	NRC VAX	NRC VAX
structure solution	MULTAN	MULTAN
no. of params. varied	237	379
weights	counting statistics	counting statistics
GOF	6.935	2.404
R = Σ   F <sub>o</sub>    -   F <sub>c</sub>    / Σ   F <sub>o</sub>    (sig)	0.053	0.047
R <sub>w</sub> (sig)	0.054	0.030
R <sub>i</sub> (all reflections)	0.059	0.065
R <sub>w</sub> (all reflections)	0.054	0.031
largest feature final diff. map	0.190e Å <sup>-3</sup>	0.360e Å <sup>-3</sup>

Note: \* = MoK<sub>α</sub> n/a = not available    \* = Least squares refinement of ((sinθ)/λ)<sup>2</sup>    <sup>b</sup> = Corrections: Lorenz-polarization

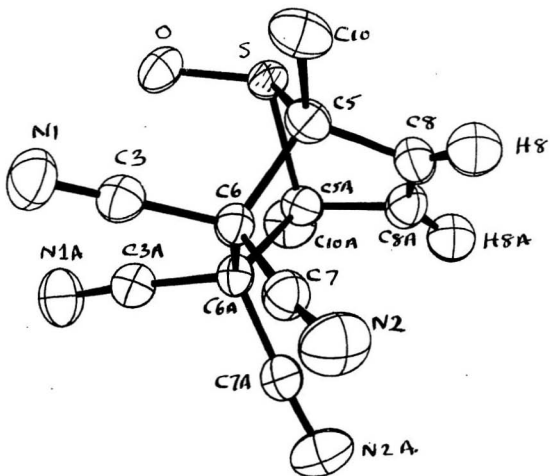
Ortep Diagram for Compound 73



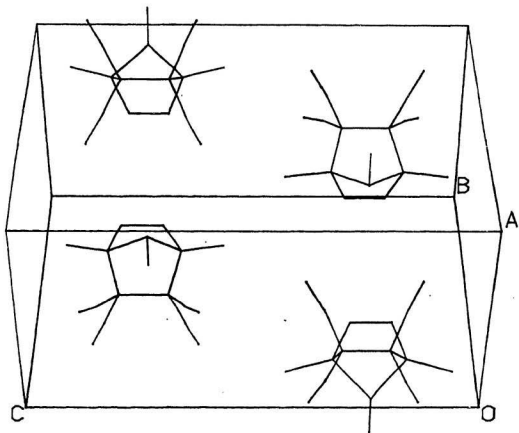
Unit Cell Diagram for Compound 73



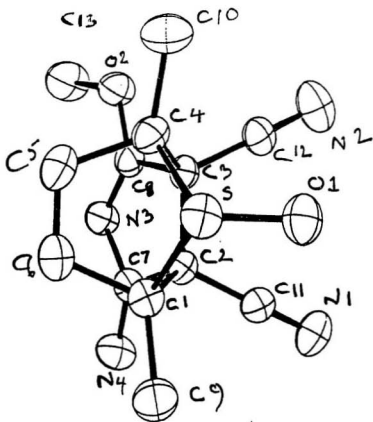
Ortep Diagram for Compound 74



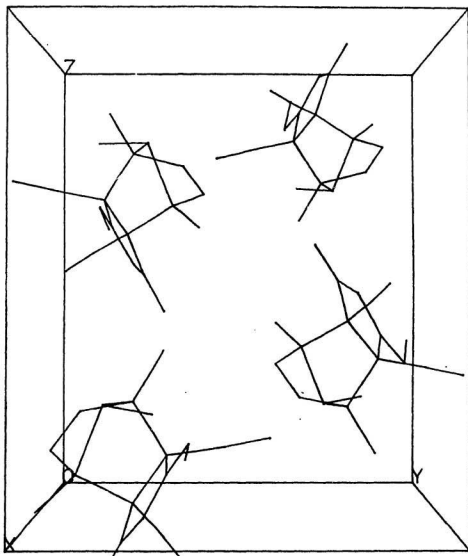
Unit Cell Diagram for Compound 74



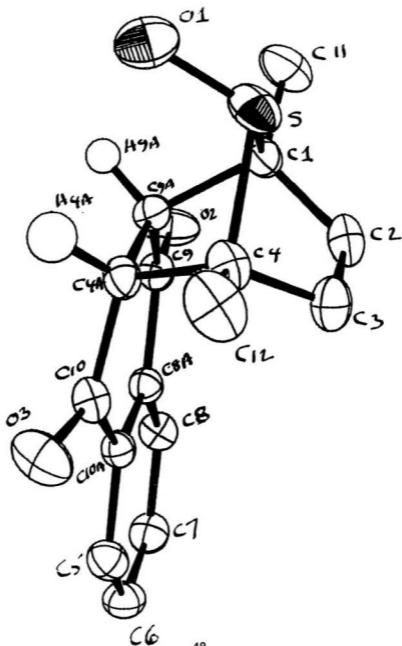
Ortep Diagram for Compound 75



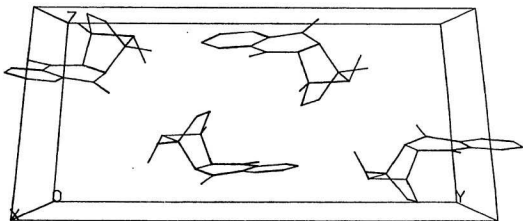
Unit Cell Diagram for Compound 75



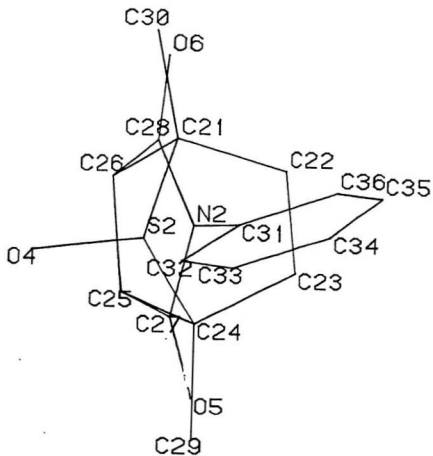
Ortep Diagram for Compound 80



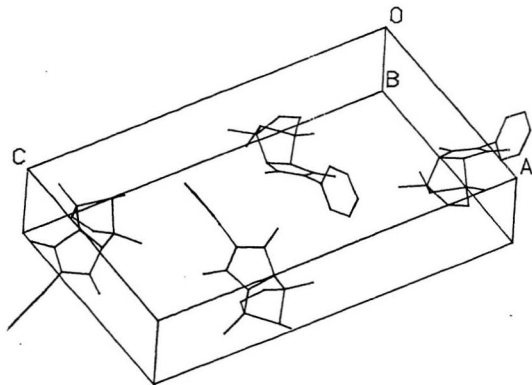
Unit Cell Diagram for Compound 80



Ortep Diagram for Compound 81



Unit Cell Diagram for Compound 81

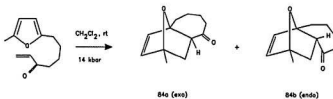


## CHAPTER TWO

The intermolecular Diels-Alder reaction between the sulfoxide diene and various dienophiles provided results which were consistent with Hehre's concept of electrostatic modelling. However, a more satisfactory explanation is based on the relative  $\sigma$  donor ability of the adjacent bonds and their interaction with the developing incipient bonds. An attempt was made to establish if the intramolecular reaction would behave in a similar manner particularly if a less electrophilic dienophile were employed. Intramolecular cycloadditions provide an efficient route to complex structures (e.g. terpenes, steroids, 11-keto steroids, gibbane skeletons, etc).<sup>36b,38a-f</sup> The same intermolecular reaction [4 + 2] rules apply to the intramolecular reaction but there is an additional constraint. The molecule must have a skeleton that is sufficiently flexible to permit the overlapping of the orbitals between the diene and dienophile segments. If this is achieved, the reaction should be governed more by electronic rather than steric factors.

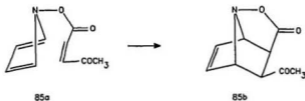
The intramolecular Diels-Alder reaction of thiophene has yet to be reported. Furan and pyrrole are electronically similar to thiophene, but they are more reactive as dienes due to a lower degree of aromaticity (resonance energies: pyrrole (21 kcal/m), furan (16 kcal/m) and thiophene (29 kcal/m)<sup>37,38</sup>). It is not surprising that furan has been studied the most with respect to inter and intra cycloadditions.

There are a number of furan examples, but the following example (see Scheme) was chosen as it most closely resembled the attempted thiophene case. The furan reaction was the first example of a 7-membered carbocycle fused to a [2.2.1] skeleton. This reaction was generally considered to be unfavourable as indicated through the number of unsuccessful Lewis acid and thermal attempts.<sup>39</sup>



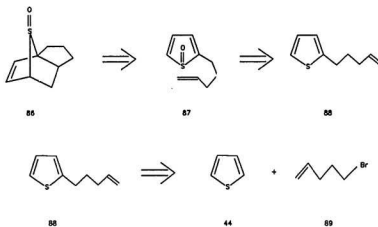
This fused ring system could be used to generate the daphnane diterpenes. It was observed that both the exo **84a** and the endo **84b** products were unstable as they reverted to the starting material through the retro Diels-Alder route. The exo **84a** and endo **84b** had half-lives of  $t_{1/2} = 90$  min. at 40°C and  $t_{1/2} = 1100$  min. at 40°C, respectively. This was also contrary to earlier reports that *intermolecular* reactions which used high pressure were irreversible. This may be a result of intramolecularity or entropic factors such as the ring size and/or relative volumes of activation of the transition state involved.<sup>40</sup>

The first example of an intramolecular [4+2] cycloaddition involving pyrrole was recently published. The reaction consisted of an acylated 1-hydroxypyrrole (**85a**) stirred at a temperature of 39°C for 21 h to afford adduct **85b** in a 68% yield.<sup>41</sup>

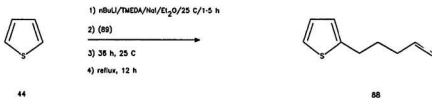


The adduct **85b** upon further transformations provided an entry into the norcocaine structure. The success of the intramolecular Diels-Alder reaction involving **85a** and our findings with the *"in situ"* 2,5-dimethylthiophene oxide (**64**), suggested that a derivatized thiophene oxide with a sufficiently deactivated and flexible alkene side chain may facilitate such an event.

To accomplish the desired intramolecular Diels-Alder reaction, a retrosynthetic approach was used to determine the simplest route. The ideal adduct **86** would have the [2.2.1] skeleton with an adjacent 5-membered alkyl ring fused to position C(1) and C(2).



Hence, the precursor molecules would be thiophene (**44**) and 5-bromopentene (**89**). The second compound **89** was not commercially available but it was synthesized from commercially prepared 4-penten-1-ol.<sup>42</sup> The first step was the generation of the thiophene carbanion followed by the subsequential alkylation with 5-bromopentene (**89**). The formation of the carbanion proved to be troublesome as initially *n*-BuLi in THF at  $-78^{\circ}\text{C}$  was not strong enough to abstract the proton from thiophene. After a number of attempts were made to optimize the reaction conditions, it was found that TMEDA/NaI was required to assist the formation of the anion. The alkylation proceeded without difficulties under the following conditions:



The crude material was purified by flash chromatography (100% pet. ether) to provide a 70% yield of the alkylated product **88**. The  $^1\text{H}$  300 MHz NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.69-1.83 (m, 2H), 2.08-2.17

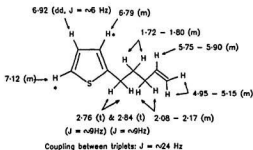
(m,2H), 2.76 (t,1H), 2.84 (t,1H), 4.95-5.05 (m,2H), 5.75-5.90 (m,1H) and 6.79-7.12 (m,3H),  $^{13}\text{C}$  NMR 75 MHz ( $\text{CDCl}_3$ )  $\delta$ : 29.19, 30.85, 33.04, 114.96, 122.82, 123.50, 124.04, 126.62, 138.14 and low resolution mass spectra ( $m/z$  = 152, 138, 125, 111 and 97) confirmed the structure but there was a contaminant (<5%) that was difficult to remove. The by-product was dialkylated thiophene product **90** identified by the mass spectrum ( $m/z$  = 222) and by NMR ( $^1\text{H}$ , 60 MHz). The two thiophene protons produced a single peak at  $\delta$  6.50 ppm.



90

The following diagrams are the proposed assignments of  $^1\text{H}$  and  $^{13}\text{C}$  NMR signals for **88**.

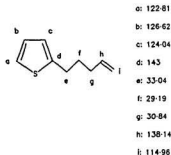
300 MHz NMR



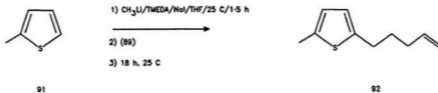
Note: All values are reported in ppm.

• Chemical shifts for these protons may be interchanged.

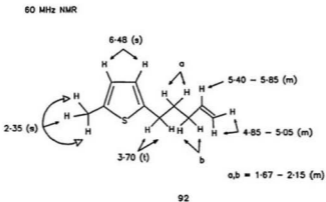
$^{13}\text{C}$  NMR 75 MHz



The contamination of the desired product **88** by the dialkyl thiophene compound **90** forced reconsideration of the synthetic strategy. The contamination could be eliminated if 2-methylthiophene (**91**) was substituted forcing the alkylation to occur at one site. The optimum conditions for the generation of the 2-methylthiophene carbanion and the ensuing alkylation are described below.

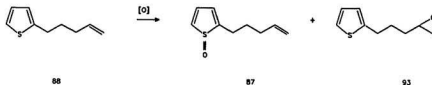


The crude material was purified by flash chromatography (100% pet. ether) to provide a 24% yield of the alkylated product **92**. The NMR ( $^1\text{H}$ , 60 MHz,  $\text{CDCl}_3$ ,  $\delta$ : 6.48 (s, 2H), 5.85-5.40 (m, 1H), 3.70 (t, 2H) and 2.15-1.67 (m, 4H)) and low resolution mass spectrum ( $m/z$  = 166, 151, 137, 124, 111 and 97) confirmed the structure of the molecule **92**. The following diagram is the proposed assignment of  $^1\text{H}$  NMR signals for **92**.



Note: All values are reported in ppm.

The next phase of the synthetic strategy involved the oxidation of the allylic sulphide **88** to the sulfoxide **87** but this proved to be extremely difficult.



[O] = *m*-CPBA, MnO<sub>2</sub>, SeO<sub>2</sub>/H<sub>2</sub>O<sub>2</sub>, KHSO<sub>5</sub>, NaIO<sub>4</sub>, NaClO<sub>2</sub> and NaOCl.

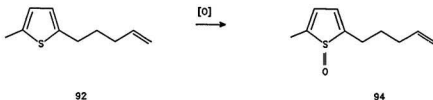
Initially, *m*-CPBA was tried (Torsell reported success with the *m*-CPBA in the intermolecular cycloaddition)<sup>32</sup> under various reaction conditions (variable temperature and solvent conditions) and all attempts were unsuccessful. In the first attempt, *m*-CPBA was employed (0°C for 30 minutes then 25°C for 19 h) and it failed to react (confirmed by <sup>1</sup>H, NMR, 60 MHz). The next approach utilized the *m*-CPBA addition at 25°C, then a 2 h stirring at ambient temperature followed by refluxing in chloroform for 18 h. The result was negative as epoxide **93** was slowly formed as indicated by <sup>1</sup>H NMR (60 MHz). The final attempt consisted of a stirred solution at -20°C for 240 h and the same result was obtained. Epoxide **93** formed slowly as indicated by the NMR (<sup>1</sup>H, 60 MHz). The heteroatom should have been more readily oxidized, but it is conceivable that the alkyl side chain folded in front of the sulphur atom thus blocking the oxidation.

Weaker oxidants (MnO<sub>2</sub>, NaClO<sub>2</sub>) failed to react while stronger oxidants provided either epoxidation or degradation products.<sup>43a</sup> The oxidation with SeO<sub>2</sub>/H<sub>2</sub>O<sub>2</sub> in CH<sub>3</sub>OH was a slow epoxidation reaction which was evident from the NMR (<sup>1</sup>H, 60 MHz).<sup>43b,c</sup> The NaIO<sub>4</sub> oxidation (based on a Russell and Ochrymoygez procedure)<sup>43d</sup> was tried under cold (-20°C/15 h) and refluxing (85°C/18 h) temperatures and neither was successful. NaIO<sub>4</sub> failed to react at -20°C and formed unidentified degradation products (isolated by flash chromatography, 20% EtOAc/80% pet. ether) at refluxing temperatures. The periodate oxidation was repeated (40°C/144 h) and only degradation products were observed (<sup>1</sup>H NMR, 60 MHz).

The oxone oxidation (KHSO<sub>5</sub>) of the thiophene compound **88** was similar to the NaIO<sub>4</sub> case.

The NMR ( $^1\text{H}$ , 60 MHz) of the crude product was recorded and epoxidation was indicated. This approach had to be abandoned.

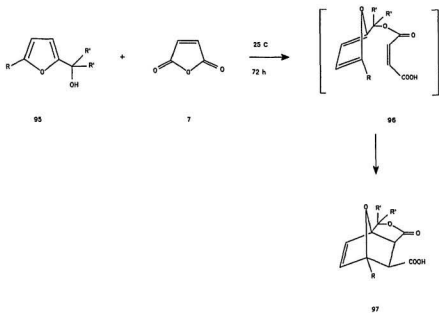
Based on an epoxidation procedure by Fava *et al*, NaOCl was used as an oxidant with **88**.<sup>44</sup> This reaction was promising as the TLC indicated a transformation different from previous results. The reaction mixture was analyzed for products by flash chromatography (100% pet. ether) and the products were examined by  $^1\text{H}$  NMR (60 MHz) and IR and suggested that the elusive sulfoxide **87** was obtained in a low yield as well as various unidentifiable products.



The oxidation of thiophene compound **92** proceeded poorly as the oxidation failed with *m*-CPBA ( $-20^\circ\text{C}/\text{CH}_2\text{Cl}_2$ ) and NaOCl (dioxane/ $5^\circ\text{C}/216\text{ h}$ ) as the starting material was recovered. The oxidation with *m*-CPBA was tried again under refluxing conditions ( $\text{CHCl}_3/336\text{ h}$ ) and the GC/MS indicated 3 components, none of which corresponded to the desired sulfoxide **94**.

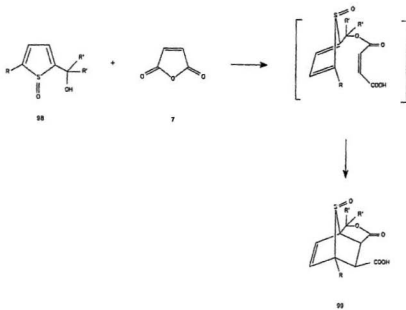
To overcome the difficulties of the synthesis and oxidation steps, the following synthetic scheme (see Scheme C) from Imagawa *et al* might be considered. They prepared adduct **97** via condensation of the substituted furan **95** and maleic anhydride (**7**) through alcoholysis.<sup>45</sup>

### Scheme C



Substitution of the analogous thiophene oxide compound **98** should afford similar reactions. This would eliminate the unwanted dialkylation and oxidation of the terminal double bond in the thiophene synthesis of **87** from **88**. The synthetic scheme is illustrated on the next page (Scheme D). In other projects in our laboratory, we have utilized dioxirane for both epoxidation and sulfoxide synthesis. In view of its high reactivity, it should also be examined for the oxidation of thiophenes.

Scheme D



## EXPERIMENTAL

**GENERAL:** See Chapter 1 Experimental for details.

### 2-(4-Pentenyl)thiophene (88).

A THF solution (10 mL) of thiophene (3.00g, 0.036 m) was added to a cooled and stirred THF solution (50 mL) (-78°C; solid CO<sub>2</sub> / acetone) of tetramethylethylenediamine (4.18 g, 0.036 m), sodium iodide (5.40 g, 0.036 m) and 2.3 M *n*-butyllithium (19.55 mL, 0.045 m) under a nitrogen atmosphere. The reactants were warmed to 21°C and stirred for 3 h thereafter. A THF solution (10 mL) of 5-bromopentene (89) (5.32 g, 0.036 m) was added dropwise and the resulting solution was stirred for 12 h at 21°C and then refluxed for 120 h. The reaction mixture was quenched with saturated ammonium chloride (2 X 75 mL), washed with water (1 X 75 mL), dried, filtered and concentrated to reveal a dark red oil. The oil was purified by flash chromatography (100 % pet. ether) to afford a colourless oil **88** in a yield of 3.31 g (60.4%). <sup>1</sup>H 300 MHz NMR (CDCl<sub>3</sub>) δ: 1.69-1.83 (m,2H), 2.08-2.17 (m,2H), 2.76 (t,1H), 2.84 (t,1H), 4.96-5.08 (m,2H), 5.76-5.90 (m,1H), 6.78-7.12 (m,3H). <sup>13</sup>C NMR 75 MHz (CDCl<sub>3</sub>) δ: 29.19, 30.85, 33.04, 114.96, 122.82, 123.50, 124.04, 126.62, 138.14. Low resolution mass spectra: *m/z* = 152, 138, 125, 111, 97.

### 2-(4-Pentenyl)-5-methylthiophene (92).

A THF solution (10 mL) of methylthiophene (1.00 g, 0.010 m) was added to a stirred THF solution (70 mL) of tetramethylethylenediamine (0.64 g, 0.010 m), sodium iodide (1.50 g, 0.010 m) and 1.4 M methylolithium (7.86 mL, 0.011 m) under a nitrogen atmosphere. The reactants were stirred at 21°C for 1.5 h. A THF solution (10 mL) of 5-bromopentene (89) (1.48 g, 0.010 m) was added dropwise and the resulting solution was stirred for 18 h at 21°C. The reaction mixture was quenched with saturated ammonium chloride (3 X 75 mL) and water (1 X 75 mL), dried, filtered and concentrated to reveal a yellow oil. The oil was purified by flash chromatography (100 % pet. ether) to afford a

colourless oil **92** in a yield of 0.39 g (23.5%).  $^1\text{H}$  60 MHz NMR, ( $\text{CDCl}_3$ )  $\delta$ : 6.48 (s, 2H), 5.85-5.40 (m, 1H), 3.70 (t, 2H), 2.35 (s, 3H) and 2.15-1.67 (m, 4H). Low resolution mass spectrometry ( $m/z$  = 166, 151, 137, 124, 111 and 97).

#### 5-Bromopentene (**89**).

To a solution of triphenylphosphine (57.6 g, 0.22m) in dry benzene (150 mL), mechanically stirred and cooled in an ice bath, bromine (35.2 g, 0.22 m) was added dropwise. The resulting suspension of  $\text{PPh}_3\text{Br}_2$  was stirred at 22°C for 1 h, pyridine (17.4 g, 0.22 m) added, the stirred mixture was recooled to 0°C and 4-penten-1-ol (18.1 g, 0.21 m) in dry benzene (10 mL) added dropwise. After addition was complete, the ice bath was removed and stirring was continued for a further 18 h at 22°C. Petroleum ether (400 mL) was added, the flask cooled in the freezer to precipitate triphenylphosphine oxide, the mixture was filtered, concentrated, and the bromide purified by distillation, bp 74°-76°C/160 Torr (bp 127°-129°C/770 Torr)<sup>48</sup> to give the bromide **89** 20.2 g (65%).  $^1\text{H}$  60 MHz ( $\text{CDCl}_3$ )  $\delta$ : 1.75-2.30 (m,4H), 3.33 (t,2H), 4.85-5.05 (m,2H), 5.50-6.10 (m,1H).

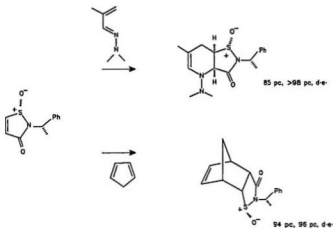
### CHAPTER THREE

The facial diastereoselectivity of the locked sulphoxide diene has been established to be "syn" with respect to oxygen in additions to the dienophile. This raises a question about the behaviour of the facial diastereoselectivity when the sulphoxide is locked into the dienophile structure. The only evidence presented thus far, was the thiirene-S-oxide example by Ando *et al* (see Scheme B; Chapter 1, pg. 5) where the facial stereoselectivity agreed with Hehre's concept of electrostatic modelling<sup>40,41</sup> and the opposing view of Koizumi that [4 + 2] cycloadditions were primarily influenced by the steric factors of the ground state conformers.<sup>7</sup>

Very recently (while this thesis was being written), Waldner published results on the synthesis and application of a highly efficient, homochiral dienophile (2((S)-1-phenylethyl)-1,2-thiazolin-3-on-(S)-1-oxide) which paralleled our intended strategy with dienophile 101 (see later text).<sup>47</sup> Waldner accurately stated that there was a need for diastereoselective [4 + 2] cycloadditions for the synthesis of biologically active compounds. Lewis acids often promote the enantio- or diastereoselective cycloadditions of non-chiral auxiliary compounds (acrylates) but the catalyst cannot be used here due to its behaviour toward the ester functionality as reported by Koizumi<sup>48</sup> and Maignan.<sup>49</sup> Waldner has shown that an  $\alpha$ -position chiral auxiliary such as sulphoxide could accomplish the desired diastereoselective cycloaddition without the need of Lewis acids. Afterwards, the sulphoxide functionality of the adduct could be reduced or eliminated to afford the desired biologically active compound.

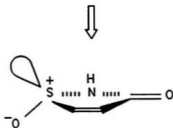
Waldner observed this effect by re-examining work published by Weiler and Brennan which showed that racemic 4-isothiazolin-3-on-(S)-1-oxide adds cleanly to cyclopentadiene and 2,3-dimethylbutadiene.<sup>50</sup> (See Scheme E on the next page.)

# Scheme E



Note: pc = per cent; d.e. = diastereomeric excess

One of Waldner's conclusions stated; "The steric discrimination occurs between the oxygen and the lone pair on the sulphur atom and is sufficient for excellent diastereoselectivity with dienes like cyclopentadiene."<sup>47</sup>



Waldner supported his conclusions by citing examples by Koizumi,<sup>48,51</sup> where furan and 2-methoxyfuran provided similar results. Outwardly, Waldner's conclusions paralleled Hehre's concept of electrostatic modelling in which the electron rich face of the diene approached the electron poor face of the dienophile as supported by our own locked sulfoxide diene cases<sup>34</sup> and the work of Macaulay and Fallis.<sup>12,23</sup> Waldner's other conclusions deviated from Hehre's concept and suggested

that other cycloadditions were influenced by a mixture of electronic and steric interactions such as the work published by Overman.<sup>20</sup> In view of Waldner's work, two other papers have appeared which clearly indicated that diastereoselective Diels-Alder research is under active investigation.<sup>52,53</sup> Ruano has reported that optically active 2-*p*-tolylsulphinyl-2-cycloalkenones add to cyclopentadiene with complete facial diastereoselectivity in the presence of Lewis acids (yields: 73 - 92%). In this case, there were no labile groups in the structure of the adduct which could have been degraded by the Lewis acid.<sup>52</sup> The only disadvantage of this reaction was the lack of control over the *exo/endo* stereochemistry. The second report used (S)-2-*p*-Tolylsulfinyl-1,4-benzoquinone as the dienophile in the presence of cyclopentadiene and Lewis acid (Eu(fod)<sub>3</sub>). It afforded almost exclusively one *endo* product (yield of 58% in CH<sub>2</sub>Cl<sub>2</sub>; 62% in CH<sub>3</sub>CN) while in the absence of Lewis acid, a mixture of *endo* products was obtained.<sup>53</sup>

To further the understanding of facial stereoselectivity, an attempt was made to synthesize a planar and locked sulfoxide dienophile, free from steric effects which may provide more accurate results than the examples cited earlier. The prime motivation was to synthesize a system which could serve as a dienophile and more importantly as a chiral ketene equivalent. In recent years, sulfoxides have gained much attention due to their inherent chirality. Sulfoxides have been utilized in asymmetric synthesis<sup>54a,b,c</sup> and more recently as a chiral ketene equivalent in cycloaddition reactions. (For general reviews on ketene equivalents see Ranganthan<sup>54a</sup> or Brady.<sup>54b</sup>)



101

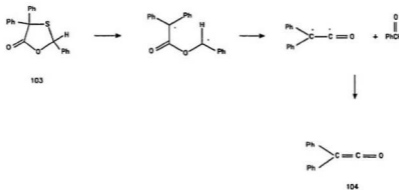


102

The model dienophile **101** could in principle be derived from the unoxidized class of compounds known as 1,3-oxathiolan-5-ones (**102**) which are relatively unstudied. This class was first reported in 1914 when diphenyl substituted oxathiolanones were conveniently prepared by the condensation

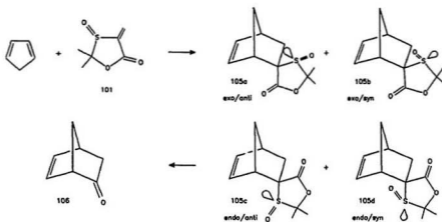
of mercaptodiphenylacetic acid with carbonyl compounds.<sup>66</sup> A number of literature examples have now appeared for the synthesis of various 2,4 or 2,4,4 di- or tri-substituted 1,3-oxathiolan-5-ones via the basic condensation between mercapto-substituted acetic acids with either ketones or aldehydes and subsequent oxidation to the corresponding sulfoxide.<sup>66,68,67\*\*</sup> This type of compound was selected to provide definitive answers concerning facial diastereoselectivity and the second objective was to employ it as a latent chiral ketene equivalent.

The previously reported research was centered on desulphuration experiments with 1,3-oxathiolan-5-ones to achieve other synthetic goals, but as early as 1959 oxathiolanones have been proposed as a potential ketene source.<sup>68</sup> Romo *et al* employed desulphuration of 2,4,4,-triphenyl-1,3-oxathiolan-5-one (103) with Raney nickel. This proceeded via a 1,4 to 1,2 biradical to give diphenylketene (104).<sup>68</sup> The *in situ* diphenylketene (104) was trapped with aniline to produce diphenylacetanilide.



The synthetic strategy is outlined in the following scheme. (Chirality is dependent on the chiral sulfoxide and only one configuration is illustrated.) (See Scheme F on the next page.)

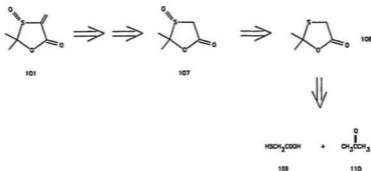
Scheme F



The Diels-Alder reaction could yield four isomers of 105 but one should be dominant if past results are indicative. The facial diastereoselectivity in all probability should be "*anti*" with respect to the sulfoxide oxygen (syn to the lone pair) and the stereochemistry will likely prefer the lactone endo (i.e. 105a). Nevertheless, the stereochemistry will be lost if the adducts are oxidized to norbornenone (106) but the chirality would be retained.

A suitable compound for the cycloaddition was 4-methylene-2,2-dimethyl-1,3-oxasulfinylan-5-one-(S)-3-oxide (101). The synthetic challenge in the strategy was the  $\alpha$ -methylenation within this heterocyclic skeleton. The retrosynthetic approach is outlined in Scheme G.

Scheme G

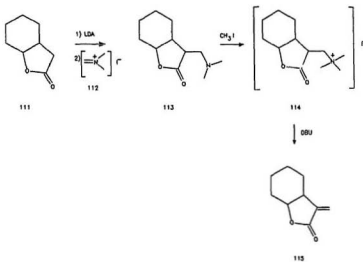


The basic synthetic feature was adapted from a procedure of Tsujimoto *et al.*<sup>89</sup> Mercaptoacetic acid (109) was refluxed in acetone (110) for 18 h then vacuum distilled to yield 108. The distillation of 108 did not behave properly as an azeotrope formed. The NMR spectrum of the distillate indicated the presence of 108 and an unidentified product. The NMR spectra of 108 should display two singlet signals, one signal for the 6 protons from two methyl groups and one signal for 2  $\alpha$ -protons. The recorded spectrum for 108 displayed two signals at (<sup>1</sup>H 60 MHz, CDCl<sub>3</sub>) at  $\delta$ : 1.75 (s, 6H) and at  $\delta$ : 3.75 (s, 2H) with an extraneous singlet signal at  $\delta$ : 2.15. It is likely that acetone was trapped with compound 108 to form the azeotrope.

The distilled compound 108 was unstable at room temperature and had a shelf life of approximately 48 h at -20°C. Thus, it was promptly oxidized to the sulphoxide 107 by *m*-CPBA in CH<sub>2</sub>Cl<sub>2</sub> (buffered by NaOAc) at -22.5°C (solid CO<sub>2</sub> / CCl<sub>4</sub> bath). The reactants were stirred for 4 h (It was observed that if the oxidation reaction was stirred past 5 h, the desired sulphoxide 107 decomposed.). The reaction mixture was filtered to remove precipitated *m*-chlorobenzoic acid and the dissolved acid was neutralized with one washing of saturated sodium bicarbonate solution. The sulphoxide 107 was water soluble, and it was easily lost if washed repeatedly with aqueous media. The product 107 was recrystallized (hexane / acetone) in an overall yield of 15%. The structure was confirmed by GC/MS and NMR (<sup>1</sup>H, 300 MHz, CDCl<sub>3</sub>;  $\delta$ : 1.59 (s, 3H), 1.74 (s, 3H), 3.66 (d, 1H, *J* = 17.8

Hz), 4.03 (d, 1H,  $J = 17.8$  Hz)]. The 2  $\alpha$ -protons resonate at  $\delta$  3.85 as a 4 line AB multiplet at 300 MHz but the outer lines are not visible at 60 MHz and the signal resembles a doublet.

In principal, several methods are available for  $\alpha$ -methylenation of the oxasulfinylidene system 107. The Danishefsky approach form the synthesis of *d,l*-vernolepin and *d,l*-vernomenin was attempted first,<sup>80a,b</sup> as outlined using Eschenmoser's salt (112). This strategy was dependent on a variation of the Mannich reaction where the lactone system 111 would react with the Eschenmoser's salt (112) to form a new carbon - carbon bond at the  $\alpha$ -position.



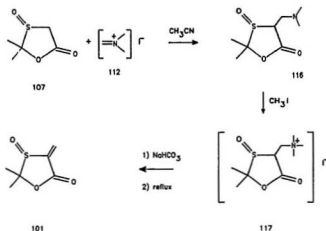
The new carbon - carbon bond was generated by the formation of the lactone enolate which reacted with the Eschenmoser's salt 112 to form the Mannich base 113. The Mannich base 113 was converted to methiodide 114 with  $\text{CH}_3\text{I}$ . DBU was used to eliminate the amine to yield 115 (65%) (in the full publication, Danishefsky used potassium carbonate to eliminate the amine<sup>80c</sup>).

This approach was applied to the 2,2-dimethyl-1,3-oxasulfinylan-5-one (107) but, in this case the  $\alpha$ -position was between two electron withdrawing centers. This should increase the acidity of the  $\alpha$ -protons and possibly permit the Mannich-type reaction to proceed without the use of base.<sup>80c</sup> The

overall strategy was simpler and would allow a one-pot transformation to the  $\alpha$ -methyleneated product

118. The synthetic route is outlined in Scheme H.

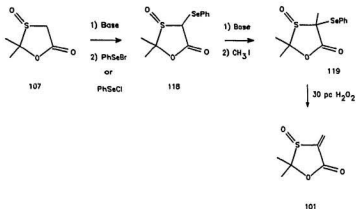
Scheme H



The reaction scheme was attempted by partially dissolving the Eschenmoser's salt 112 and the sulfoxide 107 in dry  $\text{CH}_3\text{CN}$  under a nitrogen atmosphere. The reaction was stirred (at  $21^\circ\text{C}$ ) until a precipitate formed. Methyl iodide was added and stirred (18 h) to promote the formation of the methiodide 117. The reaction mixture was washed with  $\text{NaHCO}_3$  (5% w/v) to eliminate the methiodide 117 to the  $\alpha$ -methyleneated product 118. This was not successful as indicated by NMR and GC/MS spectra. This reaction scheme was repeated with minor variations such as the addition of base ( $\text{Et}_3\text{N}$ , DBU or KH) in the alkylation step between the Eschenmoser's salt 112 and the sulfoxide 107 and prolonged refluxing periods during the elimination step. None of these modifications produced the desired reaction. The problem was identified at the initial step between 107 and 112. The quality of the Eschenmoser's salt 112 was questionable. New salt 112 was obtained and the old salt 112 was recrystallized according to the original Eschenmoser paper.<sup>81</sup> In both cases, the major problem was the limited solubility of the salt in organic solvents. (Danishefsky used a slurry in THF with HMPA to accomplish the synthetic transformation in *dl*-vernolepin and *dl*-vernolemin.<sup>80a</sup>) Eschenmoser

synthesized and recrystallized his salt **112** from protic solvents 'synthesis: dioxane / ethanol; recrystallization: ethylene glycol).<sup>81</sup> Therefore, solubility was a problem as the synthesis was dependent on aprotic solvent. In the final attempts with this strategy, HMPA and HMPA with KH were used as base, respectively. Neither produced satisfactory results. Scheme I outlines a different synthetic strategy based on Sharpless chemistry.<sup>82,83a</sup>

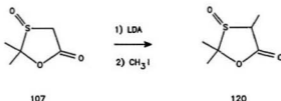
Scheme I



The scheme was initially attempted without base (selenenylation step) as it was believed that the oxasulfinylanone system would enolize readily. The electrophile and sulfoxide **107** were dissolved in dry EtOAc and stirred at 25°C under a nitrogen atmosphere until the initial solution colour changed from a deep red to yellow (36 h reaction time). TLC confirmed a transformation did occur. An  $\alpha$ -alkylation with LDA/ $\text{CH}_3\text{I}$  did not give **119**, molecular weight 318.09. Instead, the GC/MS indicated a molecular ion of  $m/z = 314$  (peaks ranged from  $m/z-8$  to  $m/z+4$ ), which suggested the formation of  $\text{PhSeSePh}$  ( $m/z = 314, 234, 156, 80$  and  $77$ ). The fragmentation pattern was unique as each major isotope of selenium could be observed (CRC Handbook: natural abundances of major isotopes;  $^{76}\text{Se} \approx 10\%$ ,  $^{77}\text{Se} \approx 10\%$ ,  $^{78}\text{Se} \approx 10\%$ ,  $^{80}\text{Se} \approx 49\%$  and  $^{82}\text{Se} \approx 10\%$ ).<sup>83</sup> The base molecular ion represented  $\text{Ph}^{80}\text{Se}^{80}\text{SePh}$  and the remaining peaks represented a mixture of homo or heteroisotopic molecules. (The formation of this compound probably resulted by the base abstracting the halogen

from PhSeCl to form a nucleophile ( $\text{PhSe}^-$ ) that readily attacked its electrophilic counterpart to create the diselenide.

A series of  $\alpha$ -selenenylation reactions employed a base (LDA or KH) to enolize the oxasulfinylanone system in the hopes of preventing the diselenide formation. The same results were obtained as the diselenide was the major product. By altering the reaction order, it was hoped that this would facilitate the formation of **120**.



The  $\alpha$ -alkylation was considered to be straightforward and initially the reactants, **107** and methyl iodide were placed in a flask without the presence of base to determine if the reaction would proceed.<sup>64</sup> The result was unsuccessful. Then, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was used as a base (25°C, dry THF) with **107** and methyl iodide, but it was observed to be ineffective as starting material and various unidentified degradation products were recovered. The result was similar when KH was used (0°C, dry THF) as the GC/MS spectra identified the starting material **107** and the same byproducts or degradation species. A stronger base (LDA) was used under a number of conditions as listed in Table 6.

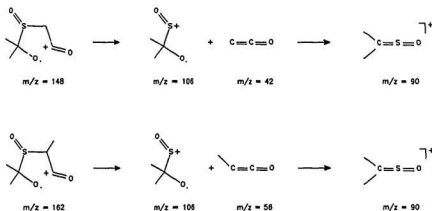
Table 6

Trial 1:	<i>"in situ"</i> generation of LDA at -78°C, sulfoxide / methyl iodide was added, stirred for 75 minutes at -78°C.
Trial 2:	<i>"in situ"</i> generation of LDA at -78°C, sulfoxide / methyl iodide was added, warmed to 0°C and stirred for 3 hours.
Trial 3:	<i>"in situ"</i> generation of LDA at -78°C, sulfoxide / methyl iodide was added, stirred at -78°C for 5 hours.

**Trial 4:**      *"in situ"* generation of LDA at -78°C, sulfoxide / methyl iodide was added, warmed to -50°C, stirred for 20 minutes.

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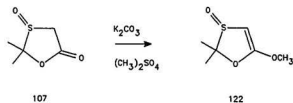
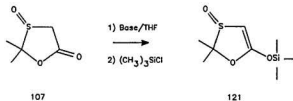
The last attempt with LDA yielded a crude product whose  $^1\text{H}$  NMR, 60 MHz, ( $\text{CDCl}_3$ ) suggested the possible presence of **120**. A new doublet signal was observed even though a quartet was expected for the  $\alpha$ -proton ( $\delta$ : 3.90,  $J$  = 8 Hz) (sulfoxide  $\alpha$ -protons **107**, 60 MHz, ( $\text{CDCl}_3$ )  $\delta$ : 3.85 (d, 2H,  $J$  = 7 Hz)). The GC/MS spectra indicated a fragmentation pattern that was inconclusive. The apparent molecular ion peak was  $m/z$  = 132 which would not satisfy the expected fragmentation pattern for both **107** and desired product **120**. In the cases of **107** and **120**, the expected fragmentation pattern would be the loss of ketene ( $m/z$  = 42) and methyl ketene ( $m/z$  = 56) respectively, to yield a common fragment of  $\text{C}_3\text{H}_6\text{SO}_2^+$  ( $m/z$  = 106), thereafter, this common fragment would yield smaller fragments of  $m/z$  = 90 and 59.



Pihlaja *et al* has published the EI induced fragmentation pattern for 2,2-dimethyl-1,3-oxathiolan-5-one and 2,2-dimethyl-4-methyl-1,3-oxathiolan-5-one, the unoxidized versions of **107** and **120**, respectively.<sup>85</sup> Pihlaja used a GC/MS system (Jeol DX-300) which provided reference to the expected fragmentation pattern of **107** and **120** but suggested that other pathways were possible for the

sulphide systems.

An attempt was made to trap the enolate to clarify the enolate formation. Furthermore, a successful reaction with the trapping agent would provide a planar dienophile which could be substituted for **101**. The sulphoxide **107** was treated with (LDA or KH) in dry THF ( $-78^{\circ}\text{C}$ ) and then trimethylsilylchloride. Unfortunately, this was unsuccessful as were experiments with KH and  $\text{K}_2\text{CO}_3$  /  $(\text{CH}_3)_2\text{SO}$ .<sup>68</sup> Consequently deuteration was examined to establish the intermediary of the enolate.



The reaction conditions are summarized in Table 7.

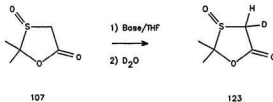


Table 7

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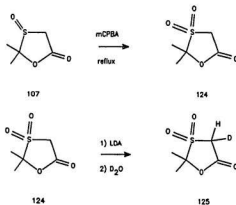
<b>Trial 1:</b>	KH, sulfoxide was added, stirred for 40 minutes at 0°C, then quenched with D <sub>2</sub> O.
<b>Trial 2:</b>	" <i>in situ</i> " generation of LDA at -78°C, sulfoxide was added, stirred for 10 minutes at -78°C, then quenched with D <sub>2</sub> O.
<b>Trial 3:</b>	<i>t</i> -Butyllithium, sulfoxide was added, stirred for 30 minutes at -78°C, then quenched with D <sub>2</sub> O.
<b>Trial 4:</b>	Methylolithium, sulfoxide was added, stirred for 30 minutes at -78°C, then quenched with D <sub>2</sub> O.
<b>Trial 5:</b>	" <i>in situ</i> " generation of LDA at -78°C, sulfoxide was added, stirred for 10 minutes at -78°C, then warmed to 25°C over 30 minutes, stirred for 30 minutes at 25°C, cooled to -78°C, D <sub>2</sub> O was added, stirred for 10 minutes at -78°C and warmed to room temperature before quenching.
<b>Trial 6:</b>	Trial 5 was repeated but warmed to 0°C instead of 25°C after the addition of the sulfoxide, cooled to -78°C, D <sub>2</sub> O was added, warmed to 25°C and stirred for 30 minutes before quenching.
<b>Trial 7:</b>	" <i>in situ</i> " generation of LDA at -40°C, sulfoxide was added, stirred for 45 minutes at -40°C, then quenched with D <sub>2</sub> O.
<b>Trial 8:</b>	" <i>in situ</i> " generation of LDA at -60°C, sulfoxide was added, stirred for 75 minutes at -60°C, then quenched with D <sub>2</sub> O.
<b>Trial 9:</b>	" <i>in situ</i> " generation of LDA at -78°C, sulfoxide was added, stirred for 75 minutes at -78°C, then quenched with D <sub>2</sub> O.
<b>Trial 10:</b>	" <i>in situ</i> " generation of LDA at -78°C, sulfoxide was added, stirred for 20 minutes at -78°C, then quenched with D <sub>2</sub> O.

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The first 9 reactions failed and in many cases with longer reaction times, the sulfoxide decomposed. Therefore, the last trial utilized a shorter enolization time at the same temperature (-78°C). This reaction proved to be successful as material was recovered. The  $^1\text{H}$  NMR (60 MHz) indicated a sulfoxide, but the integration for the  $\alpha$ -proton was different as the value was approximately 1/2. This would suggest incorporation of the deuterium atom, but the multiplicity of the signal was incorrect ( $\alpha$ -proton,  $\text{CDCl}_3$ :  $\delta$  = 3.75 - 3.85(d)). A doublet appeared even though a singlet was the expected signal. The GC/MS spectra indicated the presence of the sulfoxide, but it was difficult to ascertain if the deuterium was incorporated as the fragmentation pattern and values were identical to 107. Thus, it was difficult to assign an unambiguous structure to the isolated compound.

In view of this lack of success, the sulphone was examined since anion formation should occur more readily.

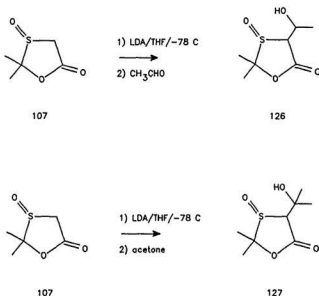
The formation of the sulphone 124 was accomplished through a direct oxidation of the sulfoxide 107 with *m*-CPBA in refluxing  $\text{CH}_2\text{Cl}_2$ . The product 124 was isolated in a yield of 53%. The structure assignment was confirmed by the fragmentation pattern of the GC/MS and NMR spectroscopy ( $^1\text{H}$ , 60 MHz,  $\text{CDCl}_3$ ,  $\delta$ : s, 6H, 1.80 ppm; s, 2H, 3.95 ppm).

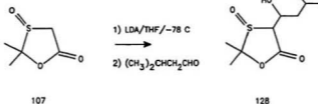


The same approach was used to generate the carbanion of the sulphone 124. The LDA was

generated *in situ* and stirred with the sulphone **124** for 10 minutes at  $-78^{\circ}\text{C}$ . At this point,  $\text{D}_2\text{O}$  was added and the reaction was worked up under standard conditions. The NMR ( $^1\text{H}$ , 60 MHz,  $\text{CDCl}_3$ ) revealed a transformation had occurred. The spectrum of **125** was different to the spectrum of the sulphone **124**, as the signal of the **125**  $\alpha$ -proton ( $\delta$ : 3.95 ppm) was slightly diminished and the integration suggested only one proton. The "proton" to methyl group "proton" ratio decreased from 6:2 to 6:1. The GC/MS was inconclusive as there was difficulty in obtaining a spectrum. This strongly suggested that the sulphone **124** would undergo alkylation.

Once the conditions which favoured carbanion formation for the sulphoxide **107** or sulphone **124** were established, a series of condensation reactions was attempted with several carbonyl compounds. The purpose of these reactions was to eliminate the OH group and create reactive dienophiles which could be employed in the Diels-Alder study. The following condensation reactions were attempted with the sulphoxide **107**.

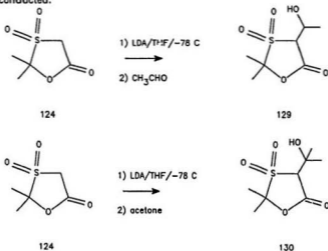


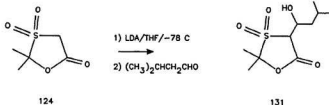


In the first case, the sulfoxide enolate was generated as in the  $D_2O$  studies and the reaction vessel was charged with acetaldehyde. The reactants were stirred in THF at  $-78^\circ\text{C}$  for 3 minutes before quenching with saturated aqueous  $NH_4Cl$ . The crude product was isolated and examined by NMR. The spectrum had changed but resembled more of the degradation product(s) as observed earlier in the  $D_2O$  studies.

The reaction was repeated using acetone and then isovaleraldehyde in the place of acetaldehyde. The crude product examined by GC/MS clearly indicated the absence of the desired compounds indicating that the condensation had not occurred.

A parallel study was conducted with the sulphone 124 using similar conditions. The following reactions were conducted.



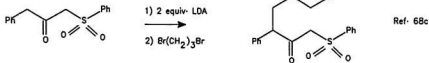
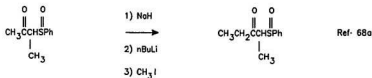


The same procedure was performed for the generation of the sulphone enolate as in the  $D_2O$  studies. Again, these series of sulphone reactions were unsuccessful.

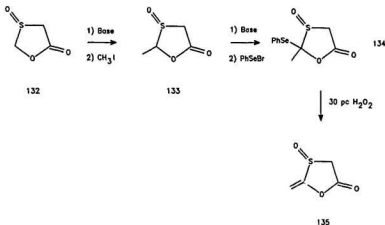
Considering the lack of success with the enolization, alkylation and condensation with either the sulfoxide **107** or sulphone **124**, two possible factors may have influenced these reactions. The structure of the sulfoxide **107** was unambiguously established by X-ray crystallography after some doubts were raised with many unsuccessful reactions. X-ray analysis revealed that one molecule of water was associated with each molecule of **107**. This would explain the limited shelf life of the molecule and the difficulties in the formation of the carbanion. It was interesting to note that the water molecule was never detected by NMR ( $^1H$ , 60 or 300 MHz) spectroscopy. If one used 1.5 equivalents of LDA in the enolization, the effective amount of LDA was only 0.5 molar equivalents. This should have yielded some carbanion but in a majority of cases only degradation products were isolated. This raised a second question about the solubility of the sulfoxide **107**. It was possible the condensation or deuterated product was obtained but lost in the work up with saturated aqueous  $NH_4Cl$ . Therefore, a non-aqueous work up should have been used for these reactions. This workup could have isolated the desired deuterated product.

If the reactions were not water sensitive, the following phenomenon may have contributed to their lack of success. After a literature search on  $\beta$ -ketosulfoxides or  $\beta$ -ketosulphones, the following was concluded.<sup>87</sup> The acidity of  $\alpha$ -protons is enhanced in the  $\beta$ -ketosulfoxide or  $\beta$ -ketosulphone systems by the increased electronegativity of the sulphur atom. Therefore, weaker bases could be employed to abstract the  $\alpha$ -proton. The resulting carbanion is more resonance stabilized than the

analogous  $\beta$ -diketo or  $\beta$ -ketoester systems. Highly reactive alkylating agents are required to permit the formation of the carbon-carbon bond at the  $\alpha$ -center. Published examples have demonstrated that dianions can be generated in the  $\beta$ -ketosulphoxide or  $\beta$ -ketosulphone systems.<sup>68a-c</sup> The initial alkylation occurs at the  $\gamma$ -position as the  $\alpha$ -position is too heavily resonance stabilized. The following examples illustrate this aspect.

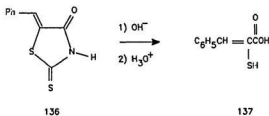


Once the  $\gamma$ -alkylation has occurred, the  $\alpha$ -alkylation would proceed, but it is not as facile. The structure of 107 would not permit  $\gamma$ -alkylation as this position was fully occupied by two methyl groups. An alternative molecule, in retrospect, would have been the unsubstituted oxathiosulfinylanone 132 which might have permitted  $\gamma$ -substitution of 133 via the dianion.



The synthesis of **135** would not affect the Diels-Alder facial stereoselectivity study as the sulfoxide would remain locked in a planar position and it could still be used as a chiral ketene equivalent, although less reactive.

The  $\alpha$ -alkylation of sulfoxide **107** was unsuccessful as the chemical behaviour could not be controlled. A review of the literature suggested an alternative means of synthesis of the desired molecule **101** (or yielding analogous compound thus eliminating the  $\alpha$ -alkylation step). Jensen *et al* examined the synthesis and esterification (or acylation of amines) of 2-mercaptocinnamic acid (**137**).<sup>68</sup> The 2-mercaptocinnamic acids are not commercially available but can be derived by base hydrolysis of 5-benzylidenerhodanine (**136**).



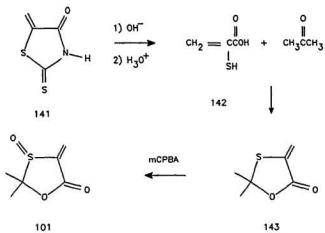
The 2-mercaptocinnamic acid was isolated by column chromatography (Et<sub>2</sub>O / pet. ether; 20/80) but no yield was mentioned as Jensen immediately converted the acid to various types of cinnamates. Jensen adopted a procedure by Ito *et al* to produce 4-benzylidene-1,3-oxathiolan-5-one (**139**) from 2-mercaptocinnamic acid (**137**) and formaldehyde.<sup>70a,b</sup> (Ito *et al* reported a yield of 70% for **139**.)<sup>70a</sup>



This would provide an analogous unoxidized compound **139**, which would suit the needs of our project and could be used for both studies (facial stereoselectivity and chiral ketene equivalent). The above molecule **139** could be oxidized to the oxasulfinylanone **140** by *m*-CPBA/NaOAc.



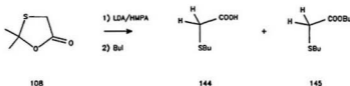
In view of this strategy, it should be possible to construct the desired molecule **101** through the condensation of the modified unsaturated mercaptoacetic acid **142** with acetone. Thus, the precursor molecule **141** must be adjusted to allow this transformation.



This concept might allow the synthesis of **101** via alternative means but the precursor rhodanine molecule **141** is required.

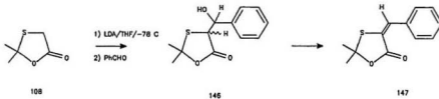
## Addendum

A series of papers published by McIntosh dealt with the synthetic usefulness of the 1,3-oxathiolan-5-one systems.<sup>67a-c</sup> McIntosh encountered the same difficulties with **108** when attempting alkylations at the 4 position with the heterocycle.<sup>67c</sup> Similar reaction conditions were employed by McIntosh to facilitate the alkylation with simple alkyl halides as in the thesis. The "*in situ*" formation of LDA was used as well as HMPA to facilitate the generation of the anion. McIntosh reported that the alkylation was unsuccessful. The alkylation reaction of **108** proceeded in the following manner:

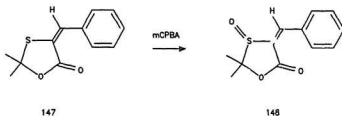


The two by-products of **144** and **145** were identified by comparison with authentic samples using GC and <sup>1</sup>H NMR. It should be noted that 2,2,4-trimethyl-1,3-oxathiolan-5-one was alkylated successfully with a number of alkyl halides and condensed with several carbonyl compounds. McIntosh also reported that a number of successful condensation reactions did occur with **108** (acetone, benzaldehyde and cyclohexenone), but he concluded that this ring system had a very limited synthetic utility.<sup>67a</sup>

Helquist utilized McIntosh's work and reported a successful condensation reaction between **108** and benzaldehyde.<sup>71</sup>



The same conditions were employed as reported by McIntosh<sup>57c</sup> to afford **146** and the subsequent transformation to **147** in an overall yield of 72%.



Therefore, product **147** could have been oxidized with a peracid to achieve **148**, which could have been employed for the facial diastereoselectivity studies with appropriate dienes.

## EXPERIMENTAL

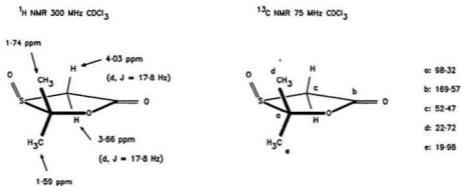
**GENERAL:** See Chapter 1 Experimental for details.

### 2,2-Dimethyl-1,3-oxathiolan-5-one (108).

Mercaptoacetic acid (109) (41.46 g, 0.45 m) was added to a stirred solution of acetone (ACS grade - redistilled in glass) (110) (30.84 g, 0.54 m). The resulting solution was refluxed for 18 h under nitrogen atmosphere. Upon cooling to 20°C, the crude product was fractionally distilled *in vacuo* (56° - 60°C, 0.3 mm Hg) to afford 108 in a 58% yield. (Note: 108 has a shelf life of 48 h at 5°C). <sup>1</sup>H NMR 60 MHz (CDCl<sub>3</sub>) δ: 1.75 (s,6H), 3.75 (s,2H). Mass spectrometry was not possible due to its labile nature.

### 2,2-Dimethyl-1,3-oxasulfinylan-5-one-(S)-3-oxide (107).

*m*-Chloroperoxybenzoic acid (23.73 g, 0.110 m, 80% purity Aldrich) in dichloromethane (300 mL) was added to a chilled (-22.5°C; solid CO<sub>2</sub> / CCl<sub>4</sub>) and stirred dichloromethane solution (250 mL) containing 2,2-dimethyl-1,3-oxathiolan-5-one (108) (13.23 g, 0.100 m) and sodium acetate (9.02 g, 0.110 m). The reaction mixture was stirred for 1 h at -22.5°C and filtered to remove the resulting precipitate. The filtrate was neutralized with saturated aqueous sodium bicarbonate (250 mL), dried, filtered and concentrated to yield a colourless crystalline product. The product was recrystallized from hexane / acetone to yield sulfoxide 107, 4.71 g (31.8%), mp 84° - 86°C. <sup>1</sup>H NMR 300 MHz (CDCl<sub>3</sub>) δ: 1.59 (s,3H), 1.74 (s,3H), 3.66 (d,1H, J = 17.8 Hz), 4.03 (d,1H, J = 17.8 Hz). <sup>13</sup>C NMR 75 MHz (CDCl<sub>3</sub>) δ: 19.98, 22.72, 52.47, 98.32, 169.51. The following signal assignments have been proposed (evidence supported by <sup>1</sup>H/<sup>13</sup>C HETCOR NMR experiment).



See Table 8 (p. 83) for the summary of X-ray crystallography data.

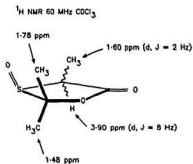
### 2,2-Dimethyl-1,3-oxasulfinylan-5-one-(S)-3-dioxide (124).

*m*-Chloroperoxybenzoic acid (3.00 g, 0.139 m, 80% purity Aldrich) in dichloromethane (30 mL) was added dropwise to a stirred dichloromethane solution (20 mL) containing 2,2-dimethyl-1,3-oxasulfinylan-5-one-(S)-oxide (107) (1.00 g, 0.0066m). The resulting solution was refluxed for 36 h under a nitrogen atmosphere and neutralized with saturated aqueous sodium bicarbonate (100 mL), dried, filtered and concentrated to yield an off-white crystalline product. The product was recrystallized from EtOAc/ hexane to afford sulphone 124, 0.550 g (51.5%), mp 82° - 84°C, dec. 90°C. <sup>1</sup>H 60 MHz NMR (CDCl<sub>3</sub>) δ: 1.80 (s,6H), 3.95 (s,2H).

**Attempted Eschenmoser Reaction for the synthesis of 4-methylene-2,2-dimethyl-1,3-oxasulfinyl-5-one-(S)-3-oxide (101).**

Potassium hydride (0.054 g, 0.0013 m) was purified and suspended in THF (8 mL) under a nitrogen atmosphere. A THF solution (3 mL) of sulphoxide **107** was added to the chilled (0°C; ice water) KH / THF suspension and stirred thereafter for 40 minutes. A THF (3.0 mL) and HMPA (3.0 mL) solution of Eschenmoser's salt **112** was added via syringe to the sulphoxide solution. The reactants were stirred at 0°C for 3 h and then at 21°C for 48 h. Dilute HCl (10% w/v) was added until the solution was acidic. Solid NaHCO<sub>3</sub> was added until the solution was slightly basic. The mixture was diluted with water (1 mL) and extracted with ethyl acetate (3 X 15 mL), dried, filtered and concentrated to afford a light red crystalline residue.\* The crude product was redissolved in dioxane (10 mL) and methyl iodide (2.00 mL, 4.56 g, 0.032 m). The resulting solution was refluxed for 24 h under a nitrogen atmosphere. The resulting solution was concentrated to afford a light red crystalline residue. The residue was washed with diethyl ether (5 X 10 mL) to afford a pale yellow solid. The washings were retained. The residue was treated with water containing sodium bicarbonate (1.6 g in 20 mL) and 50 mL of ethyl acetate. The solution was stirred for 60 minutes and the organic layer was separated, dried, filtered and concentrated to afford none of the desired product.

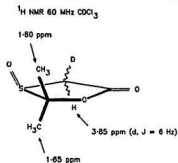
**Attempted synthesis of 2,2-dimethyl-4-methyl-1,3-oxasulfinylan-5-one-(S)-3-oxide (120) (Trial 4).** Diisopropylamine (0.22 mL, 1.6 mmol) was dissolved in anhydrous THF (7 mL) under nitrogen, cooled to -78°C, and treated dropwise with *n*-butyllithium in hexane (0.76 mL of 1.6 M, 1.5 mmol). After 45 minutes of stirring, the temperature was warmed to -35°C, then cooled again to -78°C before the dropwise addition of a THF solution (3 mL) of sulphoxide **107** (0.207 g, 1.4 mmol). The reaction mixture was stirred for 20 minutes and warmed to -50°C. Methyl iodide (2.28 g, 16.0 mmol) was introduced and the reaction was stirred at -50°C for a further 20 minutes. Saturated ammonium chloride (2 mL) was introduced and the reaction mixture was warmed to room temperature. The organic phase was diluted with diethyl ether (25 mL) and washed with saturated ammonium chloride (1 X 40 mL), dried, filtered and concentrated to afford a pale yellow oil (0.120 g). <sup>1</sup>H 60 MHz NMR (CDCl<sub>3</sub>) δ: 1.48 (s,3H), 1.60 (d,3H, J = 2 Hz), 1.78 (s,3H), 3.90 (d, = 1H, J = 8 Hz). The following signal assignments have been proposed.



**Attempted generation and trapping of the 2,2-dimethyl-1,3-oxasulfinylan-5-one-(S)-3-oxide onolate (123) with deuterium oxide.**

Diisopropylamine (0.22 mL, 1.6 mmol) was dissolved in anhydrous THF (7 mL) under nitrogen, cooled to -78°C, and treated dropwise with *n*-butyllithium in hexane (0.76 mL of 1.6 M, 1.5 mmol). After 30 minutes of stirring at -78°C, sulphoxide **107** (0.207 g, 1.4 mmol) dissolved in THF (3 mL) was introduced dropwise and the reaction mixture was stirred for 20 minutes at -78°C. Deuterium oxide (0.55 g, 28.0 mmol) was introduced, and the reaction was stirred at -78°C for a further 10 minutes and warmed to room temperature. The reaction mixture was extracted with diethyl ether (25 mL).

The organic phase was washed with saturated ammonium chloride (1 X 40 mL), dried, filtered and concentrated to afford a pale yellow oil.  $^1\text{H}$  60 MHz NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.65 (s,3H), 1.80 (s,3H), 3.85 (d,  $\approx$  1H,  $J$  = 6 Hz). The following signal assignments have been proposed.



**Generation and trapping of the 2,2-dimethyl-1,3-oxasulfinylan-5-one-(S)-3-dioxide enolate (125) with deuterium oxide.**

Diisopropylamine (0.11 mL, 0.8 mmol) was dissolved in anhydrous THF (5 mL) under nitrogen, cooled to  $-78^\circ\text{C}$ , and treated dropwise with *n*-butyllithium in hexane (0.38 mL of 1.6 M, 0.8 mmol). After 30 minutes of stirring at  $-78^\circ\text{C}$ , sulphone **124** (0.096 g, 0.6 mmol) dissolved in THF (3 mL) was introduced dropwise and the reaction mixture was stirred for 10 minutes at  $-78^\circ\text{C}$ . Deuterium oxide (0.55 g, 28.0 mmol) was introduced and the reaction was stirred at  $-78^\circ\text{C}$  for a further 10 minutes and then warmed to room temperature. The reaction mixture was extracted with diethyl ether (25 mL). The organic phase was washed with saturated ammonium chloride (2 X 40 mL), dried, filtered and concentrated to afford a pale yellow oil.  $^1\text{H}$  60 MHz NMR ( $\text{CDCl}_3$ )  $\delta$ : 1.80 (s,6H), 3.90 (s,1H). The following signal assignments have been proposed.

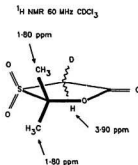


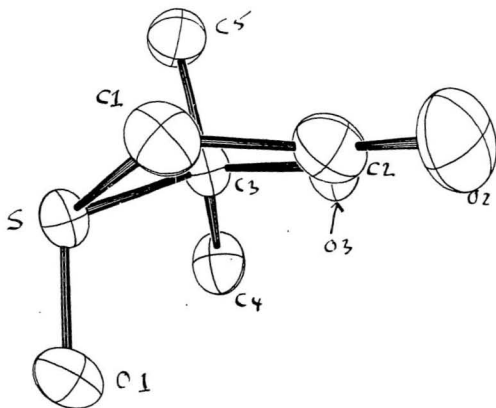
Table 8

Crystal Data and Summary of Intensity Data Collection and Structure Refinement

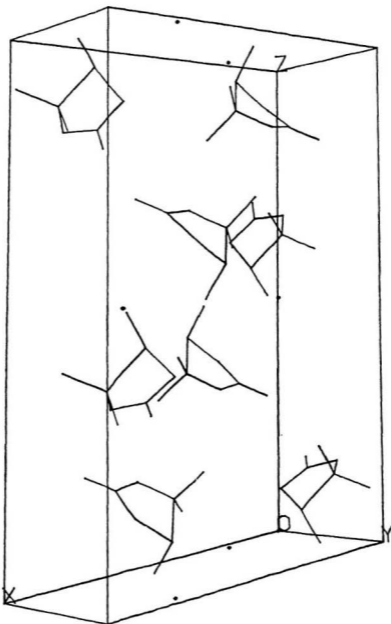
Compound	107
Empirical Formula	C <sub>2</sub> H <sub>4</sub> O <sub>2</sub> S
crystal class	monoclinic
formula wt	148.18
space group	A 2/a
temp., C	20°C
cell constants <sup>a</sup>	
a, Å	13.9154 (13)
b, Å	5.2961 (4)
c, Å	19.1265 (13)
α, deg	.....
β, deg	95.650 (10)
γ, deg	.....
cell vol., Å <sup>3</sup>	1402.65
formula units/cell	8
D <sub>calc</sub> , M gm <sup>-3</sup>	1.403
μ <sub>MoKα</sub> , mm <sup>-1</sup>	3.55
diffractometer scan	Pickering-2θ
radiation, graphite monochromator (CuKα)	λ = 1.54056 Å
max. crystal dimens., mm	0.10 X 0.10 X 0.20
2θ range, deg	2 ≤ 2θ ≤ 119.9
no. of measured reflections	1035
no. of unique reflections	1035
range of hkl	
h	-15 to 15
k	0 to 5
l	0 to 21
no. of obsd. reflections ( F <sub>o</sub>   > 2.5σ(F <sub>o</sub> )) <sup>b</sup>	832
computer programs	NRC VAX
structure solution	MULTAN
no. of params. varied	115
weights	unit
GOF	1.600
R = Σ   F <sub>o</sub>   -  F <sub>c</sub>    / Σ  F <sub>o</sub>   (sig)	0.034
R <sub>w</sub> (sig)	0.035
R <sub>i</sub> (all reflections)	0.046
R <sub>w</sub> (all reflections)	0.043
largest feature	0.250e <sup>-3</sup> Å <sup>-3</sup>
final diff. map	

Note: <sup>a</sup> = MoK<sub>α</sub> n/a = not available <sup>b</sup> = Least squares refinement of (|sinθ|/λ)<sup>2</sup> <sup>c</sup> = Corrections: Lorenz-polarization

Ortep Diagram for Compound 107



Unit Cell Diagram for Compound 107



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