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THE SYNTHESIS, STRUCTURE AND CHEMICAL REACTIVITY OF CYCLIC AND BRIDGED BICYCLIC SULFUR-CONTAINING HETEROCYCLES

A Thesis

by

Patricia L. Folkins

Submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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To Mom and Dad

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ABSTRACT

A general synthesis for bridged bicyclic disulfide compounds was refined and expanded from [3.2.1] to [4.2.1] and [2.2.1] systems. Various derivatives were synthesized through modification of the hydroxyl functionality in these molecules. The oxidation of all bridged bicyclic disulfide compounds to their corresponding bridged bicyclic thiosulfinate esters (a previously unknown class of compounds) was performed. Three crystal structures were obtained and selected bond lengths, bond angles and torsion angles were compared with the calculated values obtained using MMX molecular mechanics *via* the PCMODEL program.

The *m*-CPBA oxidation of the above bridged bicyclic thiosulfinate esters was followed at low temperature using ^{1}H and ^{13}C NMR spectroscopy. α-Disulfoxides were detected as the first intermediates in this oxidation process and were seen at temperatures and concentrations greater than any previously reported. Strong evidence was also found to suggest the intermediacy of *O,S*-sulfenyl sulfinates. A clear mechanistic proposal for the rearrangement of bridged bicyclic α-disulfoxides to their corresponding thiosulfonate esters was presented based on experimental results.

Attempts towards the synthesis of the bridged bicyclic disulfide analogue of ergosterol peroxide using diatomic sulfur methodologies were reported. These attempts were not successful.

The generation of the pseudo-diatomic species, R-P=S (thioxophosphanes), using a methodology previously developed in our laboratory was examined. The thioxophosphanes (R = C_6H_5, C_2H_5 and p-Cl-C_6H_4) were trapped with 1,3-dienes to give cyclic and bridged bicyclic thiophosphoranes.

SYNTHESE, STRUCTURE ET REACTIVITE d'HETEROCYCLES CYCLIQUES ET BICYCLIQUES PONTES CONTENANT DES ATOMES DE SOUFRE

par Patricia L. Folkins

RESUME

Une méthodologie générale pour la synthèse de bisulfures bicycliques pontés a été raffinée et appliquée à la préparation des systèmes bicycliques [3.2.1], [4.2.1] et [2.2.1]. De ces molécules, différents dérivés ont été préparés par dérivations synthétiques du groupement hydroxyle. De l'oxydation des bisulfures bicycliques pontés résulte une nouvelle classe de composés, les esters thionosulfinates bicycliques pontés. Trois structures cristallines ont été obtenues par rayons X; la longueur des liens, les angles de liaison et les angles de torsion ont été comparés avec les valeurs calculées par la methode MMX, mécanique moleculaire, par l'intermédiaire du programme PCMODEL.

L'oxydation au *m*-CPBA des esters thionosulfinates bicycliques pontée, mentionnés ci-haut, a été suivie à basse température utilisant les méthodes spectroscopiques ^{1}H-RMN et ^{13}C-RMN. Les α-disulfoxydes ont été détectés comme étant les premiers intermédiaires de ce processus d'oxydation, et ce, à des températures et des concentrations supérieures à ce que la littérature soutient jusqu'à maintenant. Les résultats obtenus suggèrent aussi des structures du type *O,S*-sulfényl sulfinates comme intermédiaires. Un mécanisme pour le réarrangement des α-disulfoxydes bicycliques pontés aux esters thionosulfonates est proposé à partir des résultats expérimentaux observés.

La synthèse de l'analogue bisulfure bicyclique pontés du péroxyde d'ergostérol en utilisant la méthode du soufre diatomique s'est révélée sans succès.

La génération d'espèces pseudo-diatomiques, R-P=S (thioxophosphanes), à partir d'une méthodologie développée antérieurement dans notre laboratoire, à été examinée. Le piégeage des thioxophosphanes (R = C_6H_5, C_2H_5 et *p*-Cl-C_6H_4) en présence de diènes-1,3 donne des thiophosphoranes cycliques et bicycliques pontés.

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I would like to first thank the Department of Chemistry for the opportunity of pursuing a doctorate in an environment that fosters excellent research through encouragement and by providing all students with an equal and fair chance for success.

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Finally, a very special thanks to Bill Power. Your friendship and support from so far away have been my ultimate inspiration. Thank you for being there when the phone rang or the computer "beeped". I know this is the beginning of something wonderful...

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ABBREVIATIONS

Anal	Analysis
APT	Attached Proton Test
br s	broad singlet
Calc'd	Calculated
°C	Degrees Celsius
cm	centimetre
COSY	Correlation Spectroscopy
d	doublet
D_c	Calculated Density
dd	doublet of doublets
DEPT	Distortionless Enhancement by Polarization Transfer
d-H_2O	distilled water
dm	doublet of multiplets
EI	Electron Impact
Et	Ethyl
EtOAc	Ethyl Acetate
EtOH	Ethanol
g	gram
hr	hour
HETCOR	Heteronuclear Correlation Spectroscopy
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
IR	Infrared
L	Litre
lit	literature
M	Molecular Weight
m	multiplet
m-CBA	*meta*-Chlorobenzoic Acid
m-CPBA	*meta*-Chloroperbenzoic Acid
Me	Methyl
mg	milligram
MHz	Megahertz
min	minutes
ml	millilitre

mm	millimetre
mmol	millimole
mol	mole
M.p.	Melting Point
MS	Mass Spectrometry
n	normal
nm	nanometres
NMR	Nuclear Magnetic Resonance
o	ortho
p	para
Ph	Phenyl
ppm	parts per million
q	quartet
Rf	relative mobility
s	singlet
t	triplet
t	tertiary
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
UV	Ultraviolet
V	Volume

CHAPTER 1: INTRODUCTION

1.1 Cyclic Disulfides

There are endless examples in the literature of both synthetic and naturally occurring cyclic disulfides. Several reviews have been published indicating their importance from both a chemical and biological perspective.[1] In this introduction, a general overview of structural classes of cyclic disulfides including 5-membered rings (1,2-dithiolanes), 6-membered rings (1,2-dithianes and 1,2 dithiins) and bridged bicyclic disulfides will be discussed mainly in terms of their biological importance. Also, a special reference to cyclic thiosulfinate esters will be made. Synthetic methodologies towards bridged bicyclic disulfides will be discussed in the introduction to Chapter 2.

Perhaps the most important characteristic about a disulfide is the dihedral angle about the S-S bond (θ). Much of the chemical behavior for a disulfide is determined by this value. For unstrained disulfides, the value of θ is normally in the range of 80-90° in order to minimize the interaction between the two pairs of 3p, nonbonding electrons on the sulfur atoms (Figure 1). When the disulfide moiety is placed in a cyclic system, the value of θ becomes smaller and movement is restricted due to the constraints of the ring system. The extreme situation occurs when the disulfide is incorporated into a bridged bicyclic system. In this example, the relatively rigid framework of the bicyclo-backbone forces the dihedral angle about the S-S bond to become, of necessity, close to 0°.

Figure 1: Dihedral Angle About the Sulfur-Sulfur Bond in a Disulfide (θ)

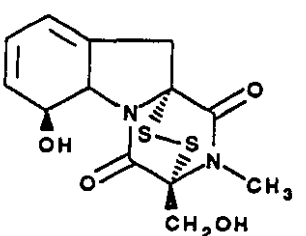
---

1. a) O. Foss, in *Organic Sulfur Compounds*, N. Kharasch, Ed., New York: Pergamon Press, Vol. 1, 79-80 (1966); b) F. Freeman, D. S. H. L. Kim and E. Rodriguez, *Sulfur Reports*, **9**, 153-256 (1989); c) L. Teuber and C. Christophersen, *Acta Chem. Scand.*, **B42**, 629 (1988); d) L. Teuber, *Sulfur Reports*, **9**, 257 (1990).

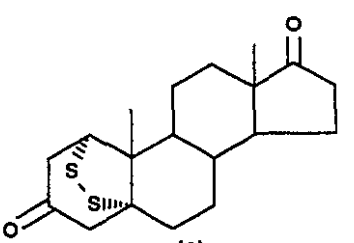
One particular characteristic of a disulfide that is greatly affected by the value of θ is the position of the lowest energy transition in the UV spectrum. As θ decreases from 90° to 0°, the lowest energy transition in the UV is shifted to longer wavelengths (lower energy) and the extinction coefficient decreases. This is well illustrated in Table 1 where several examples of disulfides along with their corresponding dihedral angles and UV absorptions are listed.

Table 1: Dihedral Angle and Lowest Energy UV absorption for Various Disulfides

Compound	Dehedral Angle (°)	λ (nm)
open chain	~90	~250[2]
1,2-dithiane	~60	286[3]
1,2-dithiolane	~27	330[3]
(1)	14	340[3]
(2)	~0	370[4]
(3)	~0	367[5] 369[6]



(1)



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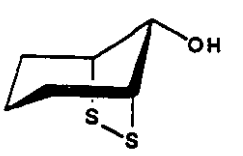

(3)

A correlation also exists between θ and the energy difference between the first and second

2. J. A. Barltrop, P. M. Hayes and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4384 (1954).

3. A. F. Beecham and A. McL. Mathieson, *Tetrahedron Lett.*, 3130 (1966).

4. G. Bergson, B. Sjöberg, R. C. Tweit, R. M. Dodson, *Acta. Chem. Scand.*, **1960**, *14*, 222.

5. P. L. Folkins, D. N. Harpp and B. R. Vincent, *J. Org. Chem.*, **56**, 904 (1991).

6. R. M. Wilson, D. N. Buchanan and J. E. Davis, *Tetrahedron Lett.*, 3919 (1971).

ionization levels ($\Delta\epsilon$) for a disulfide, which can be measured by photoelectron spectroscopy (PES).[7] A graph of $\Delta\epsilon$ versus θ is shown in Figure 2 which illustrates this point. Jorgensen and McCabe[8] have performed a semi-emperical, CNDO/S molecular orbital calculation based on the fully optimized MM1 conformation for bridged bicyclic disulfide **4** and have determined the highest occupied orbital to be the out-of-phase combination of the sulfur lone pairs (n_{SS}^-) and that it is completely localized on the sulfur atoms (97%). The next occupied orbital was found to be the n_{SS}^+ combination which is diluted by mixing with the σ orbitals of the carbon framework (78% localized on the sulfur atoms). The energy difference ($\Delta\epsilon$) between these two energy levels for **4** was calculated to be 2.43 eV. From their data, Jorgensen and McCabe[8] concluded that the value of $\Delta\epsilon$ will be primarily dependent on the dihedal angle about the S-S bond, but also on the interaction with the lower lying σ-orbitals. In this same paper, the photoelectron spectrum for bicyclic disulfide **5** was reported and found to show the largest energy difference between the first two ionization levels ever observed for a simple, non-aromatic disulfide. This confirmed that the dihedral angle about the S-S bond in **5** was near 0°.

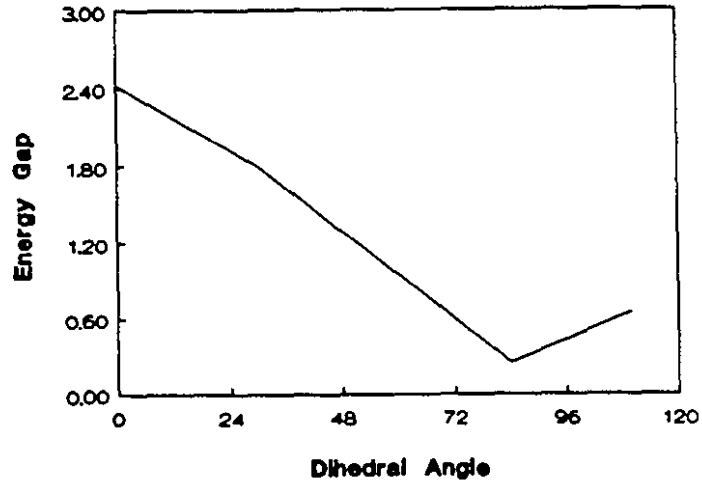

Figure 2: Experimental Values for $\Delta\epsilon$ vs θ for Dialkyl Disulfides

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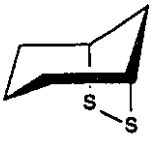
7. a) H. Bock and G. Wagner, *Angew. Chem.*, **84**, 119 (1972); b) H. Bock and B. G. Ramsey, *Angew. Chem. Int. Ed. Engl.*, **12**, 734 (1973); c) G. Wagner and H. Bock, *Chem. Ber.*, **107**, 68 (1974); d) M. F. Guimon, C. Guimon and G. Pfister-Guillouzo, *Tetrahedron Lett.*, 441 (1975); e) M. F. Guimon, C. Guimon, F. Metras and G. Pfister-Guillouzo, *Can. J. Chem.*, **54**, 146 (1976); f) M. F. Guimon, C. Guimon, F. Metras and G. Pfister-Guillouzo, *J. Amer. Chem. Soc.*, **98**, 2078 (1976); g) G. Rindorf, F. S. Jorgensen and J. P. Snyder, *J. Org. Chem.*, **45**, 5343 (1980); h) H. G. Guttenberger, H. J. Bestmann, F. L. Dickert, F. S. Jorgensen and J. P. Snyder, *J. Amer. Chem. Soc.*, **103**, 159 (1981).

8. F. S. Jorgensen and P. H. McCabe, *Tetrahedron Lett.*, **24**, 319 (1983).



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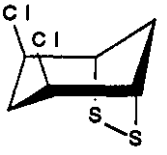


(5)

There is also a relationship between the value of the sulfur-sulfur stretching frequency (ν_{S-S}) in Raman spectroscopy and θ.[9]

In the biological sense, the disulfide bond is found in cystinyl residues thus making it one of nature's most widely used functional moieties for temporarily or permanently controlling the conformation or folding of proteins.[10] The rate of the disulfide exchange reaction (Eq 1), which is universal in biology,[11b] is profoundly affected by the strength of the disulfide bond. It has been shown to occur over one thousand times faster when the disulfide bond is part of a strained small ring, as compared to geometrically unconstrained disulfides.[11]

$$R'S^- + RSSR \longrightarrow RS^- + RSSR' \qquad \text{(Eq 1)}$$

1.2 1,2-Dithiolanes

There are numerous natural and synthetic 1,2-dithiolanes that possess biological activity. These compounds are known to be rather unstable and most cannot be isolated in pure form without some degree of polymerization. The increased reactivity and lower stability of these compounds is due, at least in part, to the strain invoked by the 5-membered ring.

A recent study by Teuber and Christophersen[1c] on the stability of 4-substituted 1,2-dithiolanes reports a discrepancy between the relative stability of these compounds and the energy

---

9. H. E. Van Wart and H. A. Scheraga, *J. Chem. Phys.*, **80**, 1823 (1976).

10. a) C. C. Malbon, S. T. George and C. P. Moxham, *TIBS*, **1**, 72 (1987); b) I. L. Karle, R. Kishore, S. Raghothama and P. Balciram, *J. Amer. Chem. Soc.*, **110**, 1958 (1988); c) A. Holtzer, M. Holtzer and J. Skolnick, in *Protein Folding: Deciphering the Second Half of the Genetic Code*, L. M. Gierasch and J. King, Eds., Washington: AAAS, Ch. 18 (1990).

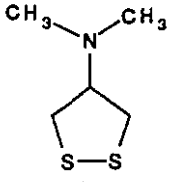
11. a) R. Singh and G. M. Whitesides, *J. Amer. Chem. Soc.*, **112**, 6304 (1990) and references cited therein; b) T. M. Kitson, *J. Chem. Ed.*, **65**, 829 (1988); c) M. Prorok and D. S. Lawrence, *J. Amer. Chem. Soc.*, **112**, 8626 (1990); d) J. Houk and G. M. Whitesides, *J. Amer. Chem. Soc.*, **109**, 6825 (1987); e) J. C. Pleasants, W. Guo and D. L. Rabenstein, *J. Amer. Chem. Soc.*, **111**, 6553 (1989).

difference between the first and second ionization levels ($\Delta\epsilon$) as measured by ultraviolet photoelectron spectroscopy. The most stable dithiolane had the largest value for $\Delta\epsilon$ and thus it was concluded that other factors besides ring strain must play a role in governing the stability of these compounds; substituent effects were suggested. It was also noted that spontaneous sulfur loss was another pathway for the degradation available to at least some 1,2-dithiolanes. A recent review by Williams and Harpp[12] documents the many examples where sulfur loss is reported in a chemical procedure.

1.2.1. Naturally Occurring 1,2-Dithiolanes

This class of compounds has recently been extensively reviewed by Teuber,[1d] thus only some of the highlights and the very recent developments will be covered here.

The first naturally occurring 1,2-dithiolane to be isolated was nereistoxin **(6)** (4-(N,N-dimethylamino)-1,2-dithiolane). In 1934 it was found in marine annelids of the genera *Lumbriconereis* and *Lumbrenereis*,[13] but the structure was not elucidated until 1960.[14] It was observed that insects which came in contact with these worms became paralyzed and died; as a result many studies into the use of nereistoxin as an insecticide have been reported.[15]



(6)

One of the the main initiatives for enhanced interests in 1,2-dithiolanes was the discovery that lipoic acid **(7)** (5-(1,2-dithiolan-3-yl)pentanoic acid) acts as a coenzyme in the transfer of acetyl groups from pyruvic acid to coenzyme A in the tricarboxylic acid cycle of oxidative

---

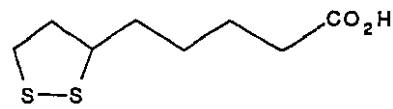
12. C. R. Williams and D. N. Harpp, *Sulfur Reports*, **10**, 103 (1990).

13. S. Nitta, *J. Pharm. Soc. Jpn.*, **54**, 648 (1934).

14. a) Y. Hashimoto and T. Okaichi, *Ann. N. Y. Acad. Sci.*, **90**, 607 (1960); b) T. Okaichi and Y. Hashimoto, *Agric. Biol. Chem.*, **26**, 224 (1962).

15. a) K. Konishi, *Agr. Biol. Chem. (Tokyo)*, **32**, 1199 (1968); b) M. Injac and K. Dulic, *Proc. - Br. Crop Prot. Conf. --Pests Dis.*, **3**, 1117 (1984); c) G. C. Scott, J. A. Pickett, M. C. Smith, C. M. Woodstock, P. G. W. Harris, R. P. Harman and H. D. Koetecha, *Proc. -Br. Crop Prot. Conf. --Pests Dis.*, **1**, 133 (1984).

phosphorylation.[16] Since then, lipoic acid has also been shown to be involved in oxidative decarboxylation[17] and photosynthesis.[18] The list of other areas where lipoic acid has been implicated and also the many biological applications of lipoic acid are recorded in the review by Teuber.[1d]



(7)

Of the remaining naturally occurring 1,2-dithiolanes, four may be grouped together under the heading of "alkyl substituted". They include 3,3-dimethyl- **(8)**, 3-ethyl- **(9)**, 3-propyl- **(10)** and 3,4-dimethyl- **(11)** 1,2-dithiolane. They have all been isolated in the anal secretions of small carnivores belonging to the genus *Mustela*,[19] their main use by these animals being chemical

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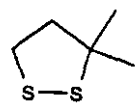
16. a) L. J. Reed, B. G. Bebusk, I. C. Gunsalus and C. S. Hornberger, Jr., *Science*, **114**, 93 (1951); b) M. W. Bullock, J. A. Brockman, Jr., E. L. Patterson, J. V. Pierce and E. L. R. Stokstad, *J. Amer. Chem. Soc.*, **74**, 3455 (1952); c) L. J. Reed, I. C. Gunsalus, G. H. F. Schakenberg, Q. F. Soper, H. E. Boaz, S. F. Kern and T. V. Parke, *J. Amer. Chem. Soc.*, **75**, 1267 (1953); d) I. C. Gunsalus, L. Struglia and D. J. O'Kane, *J. Biol. Chem.*, **194**, 859 (1952).

17. a) D. E. Griffiths, in *Genet. Biog. Chloroplasts Mitochondria, Interdiscip. Conf.*, Th. Buecher, W. Neupert and W. Sebald, Eds., Amsterdam: North-Holland, 175 (1976); *Chem. Abstr.*, **87**, 97500 (1976); b) D. E. Griffiths, *Biochem. J.*, **160**, 809 (1976); c) M. D. Partis, R. L. Hyams and D. E. Griffiths, *FEBS Lett.*, **75**, 47 (1977); d) D. E. Griffiths, R. L. Hyams and M. D. Partis, *FEBS Lett.*, **78**, 155 (1977); e) D. E. Griffiths, K. Cain and R. L. Hyams, *Biochem. Soc. Trans.*, **5**, 205 (1977); f) D. E. Griffiths and R. L. Hyams, *Biochem. Soc. Trans.*, **5**, 207 (1977), g) D. E. Griffiths, *Biochem. Soc. Trans.*, **5**, 1283 (1977); h) D. E. Griffiths, *Mol. Biol. Memb., (Proc. Symp.), 1977*, S. Fleisher, Y. Hatefi and D. H. Maclennan, Eds., New York: Plenum, 275 (1978); *Chem. Abstr.*, **90**, 67803 (1978); i) R. Johnston, S. Sharf and R. S. Criddle, *Biochem. Biophys. Res. Commun.*, **77**, 1361 (1977).

18. a) M. Calvin, *Proc. Int. Symp. Thioctic Acid 1955*, Naples, 17 (1956); b) M. Calvin and J. A. Barltrop, *J. Amer. Chem. Soc.*, **74**, 6153 (1952); c) M. Calvin and P. Massini, *Experimentia*, **8**, 445 (1952); d) D. F. Bradley and M. Calvin, *Proc. Natl. Acad. Sci.*, **41**, 563 (1955); e) M. Calvin, *J. Chem. Soc.*, 1895 (1956); f) M. Calvin, *Angew. Chem.*, **68**, 253 (1956); g) D. F. Bradley and M. Calvin, *Arch. Biochem. Biophys.*, **53**, 99 (1954).

19. a) D. R. Crump, *J. Chem. Ecol.*, **6**, 341 (1980); b) D. R. Crump, *J. Chem. Ecol.*, **6**, 837 (1980); c) V. E. Sokolov, E. S. Albone, P. F. Flood, P. F. Heap. M. Z. Kagan, V. S. Vasilieva, V. V. Roznov and E. P. Zinkevich., *J. Chem. Ecol.*, **6**, 805 (1980); d) H. Schildknecht, C. Birkner and D. Krausz, *Chem.-Ztg.*, **105**, 273 (1981); e) C. Brinck, R. Gerell and G. Odham, *Oikos*, **30**, 68 (1978); f) H. Schildknecht, I. Wilz, F. Enzmann, N. Grund and M. Ziegler, *Angew. Chem.*, **88**, 228 (1976); g) H. Schildknecht, C. Birkner, *Chem.-Ztg.*, **107**, 267 (1983).

communication.[19c,20] These compounds have been further investigated for their potential use as area repellents to protect crops and livestock from predators such as rats,[21] hares,[22] gophers[23,24] and voles.[25] The repellent characteristics of **8-11** are a result of fear responses produced when these animals detect the odor of one of their predators.



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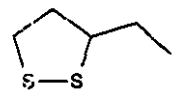

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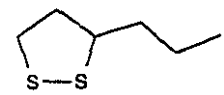

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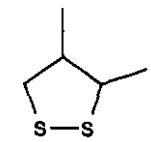


(11)

Asparagusic acid **(12)** or 1,2-dithiolane-4-carboxylic acid has been isolated from etiolated and green asparagus shoots and its use as a plant growth inhibitor has been actively investigated.[26] Due to their similarity in structure, the ability of asparagusic acid to mimic the biological action of lipoic acid has been examined.[27] Asparagusic acid also had a cytotoxic effect on Strain L mouse fibroblasts *in vitro*.[28] Finally, an aqueous solution of asparagusic acid (50 ppm) totally inhibited the hatching of second stage larvae of *Heterodera rostochiensis* and *H. glycines* and exerted a nematocidal effect (% mortality in brackets) on second stage larvae of *H. rostochiensis* (99), *Meloidogyne hapla* (92) as well as the larvae and adults of *Pratylenchus*

20. B. K. Clapperton, E. O. Minot and D. R. Crump, *Anim. Behav.*, **36**, 541 (1988).

21. E. Vernet-Maury, E. H. Polak and A. Damael, *J. Chem. Ecol.*, **10**, 1007 (1984).

22. T. P. Sullivan and D. R. Crump, *J. Chem. Ecol.*, **10**, 1809 (1984).

23. T. P. Sullivan and D. R. Crump, *Chem. Signals Vertebr. 4 [Proc. Int. Conf.] 4th*, D. Duvall, D. Mueller-Schwarze and R. M. Silverstein, Eds., New York: Plenum, 519 (1986).

24. T. P. Sullivan, D. R. Crump and D. S. Sullivan, *J. Chem. Ecol.*, **14**, 379 (1988).

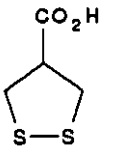
25. T. P. Sullivan, D. R. Crump and D. S. Sullivan, *J. Chem. Ecol.*, **14**, 363 (1988).

26. a) Y. Kitahara, H. Yanagawa, T. Kato and N. Takahashi, *Plant and Cell Physiol.*, **13**, 923 (1972); b) H. Yanagawa, T. Kato, Y. Kitahara and Y. Kato, *Tetrahedron Lett.*, 2549 (1972); c) H. Yanagawa, *Plant and Cell Physiol.*, **17**, 931 (1976); d) Y. Kitahara, T. Kato, H. Yanagawa, H. Aizawa and T. Watanabe, **Jpn. Pat. 74,117,616** (1974); *Chem. Abstr.*, **82**, 134039 (1974).

27. H. Yanagawa, T. Kato, Y. Kitahara and N. Takahashi, *Plant and Cell Physiol.*, **14**, 791 (1973).

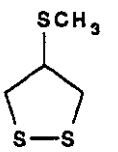
28. J. Kieler, *Biochem. Pharm.*, **11**, 453 (1962).

penetrana (82) and *P. curvitatus* (82).[29]



(12)

Charatoxin **(13)** or 4-(methylthio)-1,2-dithiolane is another naturally occurring 1,2-dithiolane with characteristics similar to those of nereistoxin **(6)**. Compound **13** was first isolated from the green algae *Chary globularis*[30] and later in other *Chary* species.[31] These algae are characterized by strong pungent smells and are usually the dominant species in the areas where they grow. The pungent smell is due to the presence of sulfur compounds (like **13**) that are produced by the algae. These compounds have a strong inhibitory effect on photosynthesis, suppressing the growth of phytoplankton in their area. Like nereistoxin, the use of charatoxin as an insecticide has been investigated.[32] Studies concerning the action of **13** as a nerve poison are also reported.[33]



(13)

The last of the known 4-substitued naturally occurring 1,2-dithiolanes is 4-hydroxy-1,2-dithiolane **(14)**. It was isolated in 1959 from the stem and bark of *Bruguiera cylindrica*, a member of the Mangrove family.[34] No known biological testing has been reported on the parent hydroxy

29. M. Takasugi, Y. Yachida, M. Anetai, T. Masamune and T. Watanabe, *Chem. Lett.*, 42 (1975).

30. U. Anthoni, C. Christophersen, J. O. Madsen, S. Wium-Anderson and N. Jacobson, *Phytochemistry*, **19**, 1228 (1980).

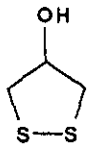
31. S. Wium-Anderson, U. Anthoni, C. Christophersen and G. Houen, *Oikos*, **39**, 187 (1982).

32. a) N. Jacobson and L.-E. K. Pederson, *Pestic. Sci.*, **14**, 90 (1983); b) L.-E. Nielsen and L.-E. K. Pederson, *Experimentia*, **40**, 186 (1984).

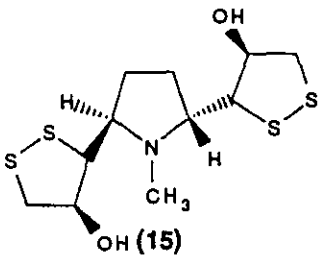
33. S. M. Sherby, A. T. Eldefrawi, J. A. David, D. B. Satelle and M. E. Eldefrawi, *Arch. Insect Biochem. Physiol.*, **3**, 431 (1986).

34. a) G. Claeson, *Acta. Chem. Scand.*, **13**, 1709 (1959); b) A. Kato and J. Takahashi, *Phytochemistry*, **15**, 220 (1976).

compound, however, synthetic analogs have been prepared and tested. This will be discussed further in the next section on synthetic 1,2-dithiolanes.



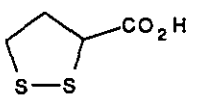
(14)



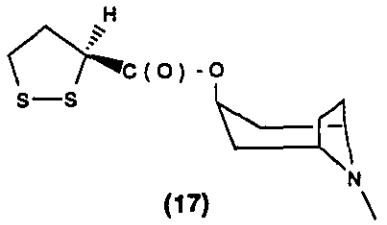
(15)

Gerrardine or 1-methyl-2,5-bis(4-hydroxy-1,2-dithiolan-3-yl)pyrrol **(15)**, a structural analog of 4-hydroxy-1,2-dithiolane, was isolated from an extract of the leaves and twigs of *Cassipourea gerrardii*[35] and the bark of *C. guianensis*.[36] Along with the isolation, the bactericidal effects of **15** on *Salmonella* and *Sitgella* strains,[36] *Candida albicans* TA., *E. coli* NIHJ JC-2, *E. coli* 0-111 and *Klebsiella pneumoniae*[37] were also reported.

The last two of the known naturally occurring 1,2-dithiolanes are closely related. 1,2-Dithiolane-3-carboxylic acid **(16)** occurs naturally as a metabolite of lipoic acid[37] and when **16** is esterified with the amino alcohol tropine, the resulting alkaloid is the naturally occurring brugine **(17)**. Brugine was the major alkaloid isolated from *Bruguiera sexangula*,[38,39] *B. exaristata*[39] and *B. cylindrica*,[40] all members of the family Rhizophoraceae. Biological testing was reported only for the extracts of *B. sexangula*.[39] Antitumor activity was found with two types of tumors, sarcoma 180 and Lewis Lung carcinoma, but the active ingredient was not absolutely determined; the alkaloids are known to be toxic.



(16)



(17)

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35. a) W. G. Wright and F. L. Warren, *J. Chem. Soc. (C)*, 283 (1967); b) W. G. Wright and F. L. Warren, J. *Chem. Soc. (C)*, 284 (1967).

36. A. Kato, M. Okada and Y. Hashimoto, *J. Nat. Prod.*, **47**, 706 (1984).

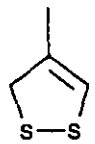
37. H. C. Furr, H.-H. Chang and D. B. McCormick, *Arch. Biochem. Biophys.*, **185**, 576 (1978).

38. J. W. Loder and G. B. Russell, *Tetrahedron Lett.*, 6327 (1966).

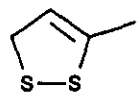
39. J. W. Loder and G. B. Russell, *Aust. J. Chem.*, **22**, 1271 (1969).

40. A. Kato, *Phytochemistry*, **14**, 1458 (1975).

Very recently, two new 5-membered ring disulfide compounds, **18** and **19**, were isolated from garlic oil.[41] Unlike the other naturally occurring 1,2-dithiolanes described here, the ring contains one double bond.



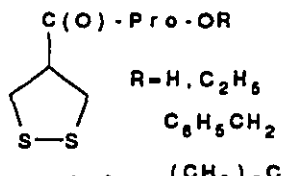
(18)



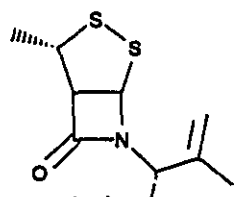
(19)

1.2.2 Synthetic 1,2-Dithiolanes

Many of the 1,2-dithiolanes that have been synthesized and tested for biological activity are analogs of known naturally occurring compounds. Among such examples are the analogues of asparagusic acid. *N*-(1,2-Dithiolane-4-carbonyl)*L*-proline and its esters **(20)** were prepared as inhibitors of hypertension induced by angiotensin I.[42] The synthesis of compounds **21** and **22** as immunomodulating analogs of asparagusic acid has also been reported.[43]



(20)



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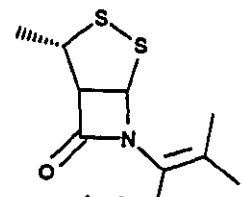

(22)

Synthetic analogs of charatoxin have been reported. Compounds of the general formula **23** were prepared and used as constituents of an ascaricide.[44] As an example, a mixture containing 20% **23** (R = $C(CH_3)_3$), 75% xylene and 5% poly(oxyethylene)glycol ether exhibited 70% ascaricidal activity at 500 ppm against *Tetranychus urticae*. Under the same conditions, charatoxin showed only 30% activity.[44]

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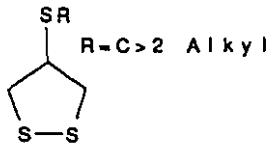
41. Z. Ding, J. Ding, C. Yang and Y. Saruwatari, *Yunnan Zhiwu Yanjiu*, **10**, 223 (1988); *Chem. Abstr.*, **110**, 22443 (1989).

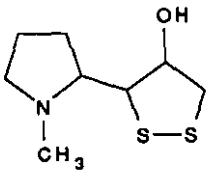
42. Y. Oka, T. Aono and K. Amura, **Jpn. Kokai Tokkyo Koho 79,125,669** (1979); *Chem. Abstr.*, **92**, 215770 (1980).

43. C.-P. Mak and G. Schulz, *Heterocycles*, **27**, 331 (1988).

44. H. Koji, T. Uekado and H. Uneme, **Jpn. Kokai Tokkyo Koho JP, 63,196,578** (1988); *Chem. Abstr.*, **110**, 19874 (1989).

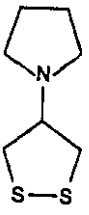


(23)

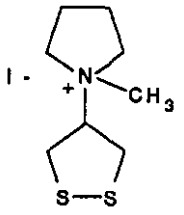


(24)

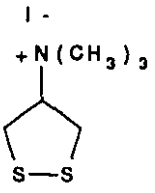
As mentioned in the previous section, synthetic analogs of 4-hydroxy-1,2-dithiolane (**14**) have been prepared and tested for their insecticidal activity. The *N*-methyl and *N*-ethyl carbamates of **14**, when exposed to house mosquitoes, gave 90% and 80% mortality rates respectively.[45] Another analog of **14** that has been prepared as an agrochemical insecticide and microbicide is 2-(4-hydroxy-1,2-dithiolan-3-yl)-1-methylpyrrolidine (**24**).[46] The salts of **24** have also been prepared; however, no biological data was provided for either.



(25)



(26)



(27)

Several synthetic anologs of nereistoxin have been prepared mainly for use as insecticides. Compounds **25-27** were tested along with nereistoxin for neuromuscular blocking effects and a comparison in reactivity was made.[47] All of the 1,2 dithiolanes tested showed activity similar to nereistoxin. Analogues of nereistoxin with the general structure of **28** were synthesized as insecticides.[48] The oxalic and hydrochloric salts of nereistoxin have also been tested as

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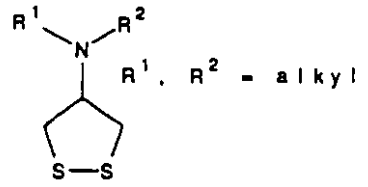
45. A. Kato and Y. Hashimoto, in *Nat. Sulfur Compd., [Proc. Int. Meet.], 3rd. 1979*, D. Cavillini, G. E. Gaull and V. Zappia, Eds., New York: Plenum Press, 361 (1980).

46. H. Mitsudera, Y. Okada and H. Uneme, **Jpn. Kokai Tokkyo Koho JP, 01,34,981** (1989); *Chem. Abstr.*, **111**, 57716 (1989).

47. a) S. Chiba and Y. Nagawa, *Jap. J. Pharmacol.*, **21**, 175 (1971); b) Y. Nagawa, Y. Saji. S. Chiba and T. Yui, *Jap. J. Pharmacol.*, **21**, 185 (1971).

48. W. Guo, H. Peng, D. Liu and X. Zhou, **Faming Zhuanli Shenqing Gongkai Shuomingshu CN 85,102,251**; *Chem. Abstr.*, **108**, 186779 (1988).

insectici[illegible].[49] Finally, analogs with the general structure **29** have been prepared and at 500 ppm gave a 100% fatality rate against *Chilo suppressalis* 5th stage larvae.[50]



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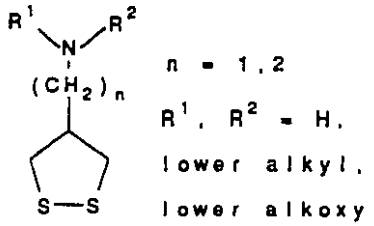
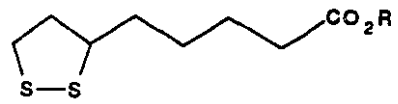


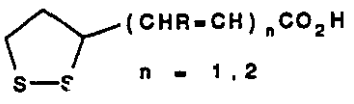
(29)

Among the recent examples of lipoic acid analogs are several used in hair preparations and skin lotions. For example, there have been references to the use of compounds with the general structure **30** in skin ointments, lotions and creams[51] and also as part of a hair preparation which controls dandruff and stimulates hair growth.[52] Compounds of the general formula **31** were prepared and tested along with their physiologically acceptable salts as immunoregulators.[53] They were found to be more effective than lipoic acid as immunostimulants in BALB/C mouse spleen cells stimulated by the T-cell mitogen, concanavalin A.



R = OH, OM, NH_2, OC_nH_{2n+1}
M = alkali metal

(30)



(31)

A study into the cytostatic effects of a number of 1,2-dithiolanes on strain L mouse

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49. Y. Wei and Y. Wang, **Faming Zhuanli Shenqing Gongkai Shuomingshu CN 86,103,012**; *Chem. Abstr.*, **110**, 7955 (1989).

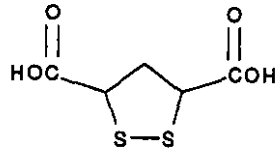
50. H. Uneme, H. Mitsudera, J. Yamada and Y. Kone, **Jpn. Kokai Tokkyo Koho JP 01 45,380** (1987); *Chem. Abstr.* **111**, 134205 (1989).

51. a) K. Hasunuma, **Jpn Kokai Tokkyo Koho JP 62,175,417** (1987); *Chem Abstr.*, **108**, 62465 (1988); b) Y. Ojama, **Jpn Kokai Tokkyo Koho JP 63 08,316** (1988); *Chem Abstr.*, **109**, 196908 (1988).

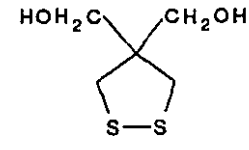
52. K. Hasunuma, **Jpn Kokai Tokkyo Koho JP 62,175,415** (1987); *Chem Abstr.*, **108**, 26828 (1988).

53. I. Yamamoto, A. Matsubara, H. Yamashita, O. Mizuno, M. Sakaguchi and M. Kumakura, **Jpn Kokai Tokkyo Koho JP 62 22,779** (1987); *Chem. Abstr.*, **106**, 176369 (1987).

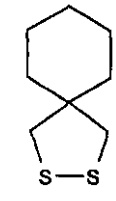
fibroblasts *in vitro* has been reported.[28] The compounds tested were **32-37** along with the naturally occurring 1,2-dithiolanes lipoic acid (**7**) and asparagusic acid (**12**). The strain L. fibroblasts were particularly sensitive to compounds **12**, **32**, **34**, **36** and **37**. The growth inhibiting effect of these compounds against Ehrlich's ascites tumor *in vivo* was also tested but only **32** had significant positive results at a dose of 1.5 mmole/kg. The rate of respiration of Ehrlich's tumor cells did show an inhibitory effect to compound **36** and, to a lesser degree, **34**. The apparent *in vivo* resistance of Ehrlich's tumor cells towards the cytotoxic effects of 1,2-dithiolane derivatives was suggested to be due to their rapid elimination from the body.



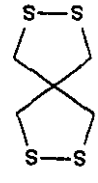
(32)



(33)



(34)



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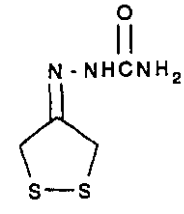

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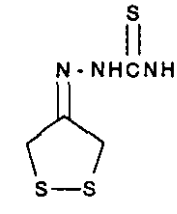
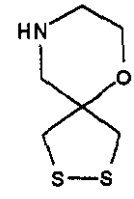


(37)

The spirocyclic 1,2-dithiolanes **38** and **39** were prepared as insecticides and nematocides.[54] No data on their activity was reported. The amino acid 1,2-dithiolanes **40** were synthesized and used in mixtures as artificial sweeteners.[55]



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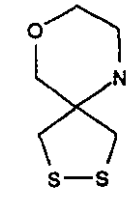

(39)

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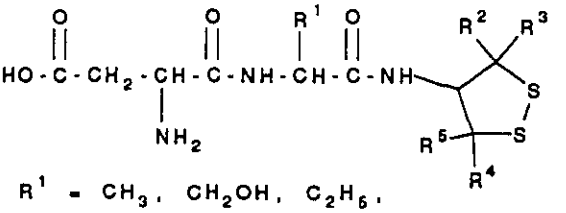
54. M. D. Turnball and I. T. Kay, **Eur. Pat. Appl. EP 227, 338** (1987), *Chem. Abstr.*, **108**, 6033 (1988).

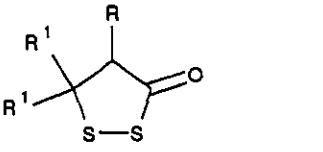
55. T. M. Brennan and M. E. Hendrick, **U. S. Pat. 4,797,298** (1989); *Chem. Abstr.*, **111**, 97732 (1989).



R^1 = CH_3, CH_2OH, C_2H_5, C_3H_7, $i\text{-}C_3H_7$

R^2-R^5 = alkyl

(40)



R = NHAc, NHBz, CH_3

R^1 = H, CH_3

(41)

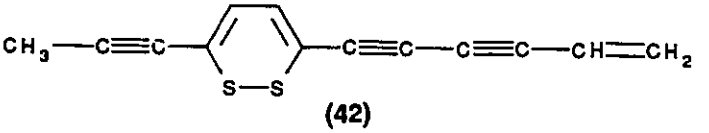
Several 1,2-dithiolane-3-ones **(41)** were recently prepared as radioprotective agents.[56] They had activity after both i.v. and oral administration at does ranging from 1.4-300 mg/kg.

1.3 1,2-Dithiins

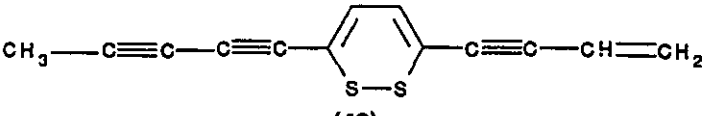
1.3.1 Naturally Occurring 1,2-Dithiins

(i) Polyacetylenic 1,2-Dithiins

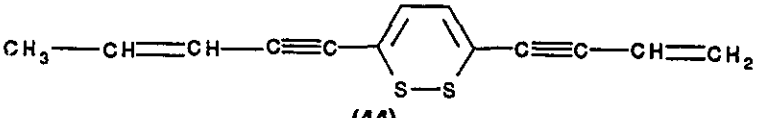
Perhaps one of the best studied class of naturally occuring 1,2-dithiins are the dithiacyclohexadiene polyines of which compounds **42-45** are the four most common examples. Compounds **42** and **43** are better known as thiarubrines A and B respectively.



(42)



(43)



(44)

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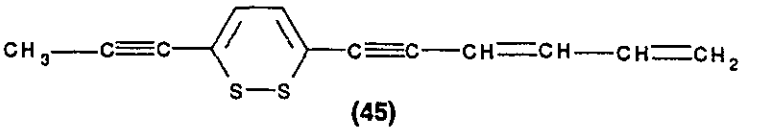
56. N. I. Lisina, T. P. Vasil'evea, V. M. Bystrova, O. V. Kil'disheva and G. A. Chernov, *Khim.-Farm. Zh.*, **21**, 177 (1987).



(45)

Polyacetylenes are very common naturally occuring compounds and a review by Bohlmann and coworkers[57] published in 1973 presents an extensive list of such compounds and their origins. The formation of sulfur compounds in the field of natural acetylenes is also very common and is believed to proceed by the formal addition of H_2S to a double or triple bond.[57] The addition of one molecule of H_2S provides the thiophene analogues, whereas double addition, followed by oxidation leads to 1,2-dithiins (Figure 3). Recently, ^{35}S labelling studies concerning the incorporation of sulfur into 1,2-dithiins and thiophenes in hairy root cultures (described later) of *Chaenactis douglasii* showed that sulfur was incorporated simultaneously and at the same rate for both compounds.[58] The conclusion was that these compounds are not synthesized sequentially in *C. douglasii*.

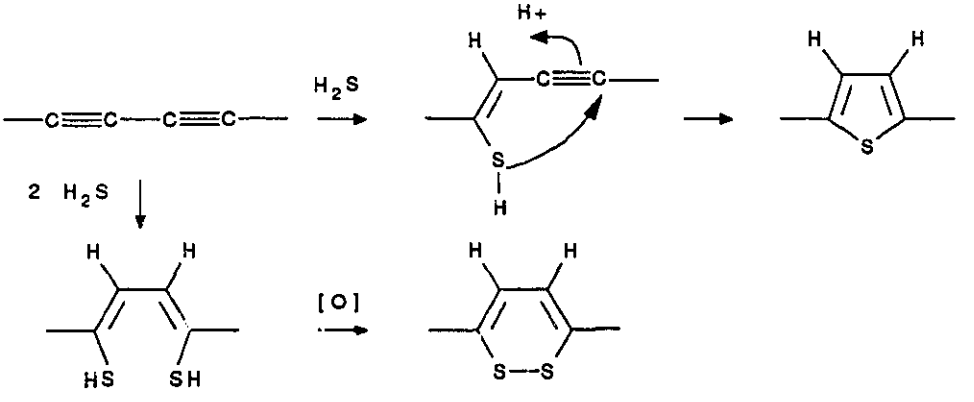


Figure 3: Proposed Biosynthetic Origin of Natural Polyactylenic 1,2-Dithiins

Plants from the family Compositae, one of the most thoroughly investigated of all plant families, are the only known source of naturally occurring 1,2-dithiins.[57] Particular interest in the biological activity of these compounds was initiated by an anthropological study into the feeding behavior of chimpanzees in Tanzania.[59] In this study it was reported that wild chimps would eat the leaves from the genus *Aspilia* (family Compositae) slowly and individually, rolling and pressing them around in their mouths but not chewing them. In one area (Gombe National Park), the chimps would only eat these leaves early in the morning. These unusual eating patterns suggested

57. F. Bohlmann, T. Burkhardt and C. Zdero, *Naturally Occurring Acetlyenes*, New York: Academic Press (1973).

58. C. P. Constabel and G. H. N. Towers, *Phytochemistry*, **28**, 109 (1988).

59. R. W. Wrangham and T. Nishida, *Primates*, **24**, 276 (1983).

that the chimps swallowed the leaves of these plants for therapeutic reasons. Also, the use of the leaves and roots of *Aspilia* by African natives for the treatment of abdominal pains, convulsions, intestinal worms, skin infections and as a stimulator for milk production in both cattle and humans has been reported.[60] *Chenactis douglasii*, another member of the family Compositae which is known to contain compounds **42** and **43**, has been used to treat stomach disorders, swellings, colds and as a snakebite remedy by native Americans.[61]

Normally the configuration about all double bonds in these naturally occurring polyacetylenes is *trans*, yet, recently the *cis*-isomer of **45** has been isolated from root cultures of *Rubreckia hirta*.[62]

Of these acetylenic 1,2-dithiins, only **42** has been subjected to a wide array of biological testing. One of the first such investigations was reported by Towers and coworkers.[63] Here, thiarubrine A (**42**) was shown to have strong antifungal activity against *Candida albicans* and *Aspergillus fumigatus*. The level of activity was comparable to that of the known antifungal agent, Amphotericin B. Also, **42** behaved as an antibiotic towards *E. coli*, *Bacillus subtilis*, *Saccharomyces cerviseae* and *Mycobacterium phlei*.[63] Although the nematode, *Coenorhabditis elegans*, is not known as a human parasite, the toxicity of **42** towards it suggests a basis for its use as a stomachic.[63] In other investigations reported by Towers and coworkers, **42** had antiviral activity against murine cytomegalovirus and Sinbis virus,[64] both of which possess membranes. In these examples, **42** acted only as a phototoxic agent, meaning it required the presence of UV-A light for activity. The known phototoxic agent, α-terthienyl (α-T), was used as a comparative standard in all investigations.[63,64] Thiarubrine A (**42**) was found to be less toxic than α-T in the presence of UV-A light, however it did show activity in the dark against some microorganisms[63]

60. a) J. M. Daziel, *The Useful Plants of West Tropical Africa*, London: The Crown Agents for the Colonies, (1937); b) J. M. Watt and M. G. Breyer-Brandwijk, *The Medicinal and Poisonous Plants of Southern and Eastern Africa*, 2nd Ed, Edinburgh: E. & S.Livingstone Ltd. (1962); C) P. J. Greenway, *E. Afr. Med. J.*, **13**, 346 (1936).

61. D. E. Moerman, *American Medical Ethnobotany. A Reference Dictionary*, New York: Garland Publ. Inc. (1977).

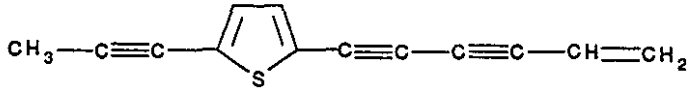
62. C. P. Constabel, F. Balza and G. H. N. Towers, *Phytochemistry*, **27**, 3533 (1988).

63. G. H. N. Towers, Z. Abramowski, A. J. Finlayson and A. Zucconi, *Planta Medica*, **3**, 225 (1985).

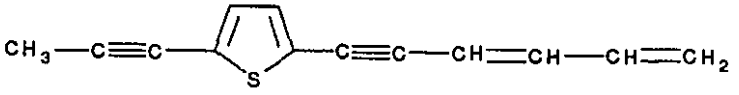
64. a) J. B. Hudson, E. A. Graham, R. Fong, A. J. Finlayson and G. H. N. Towers, *Planta Medica*, **4**, 51 (1986); b) J. B. Hudson, E. A. Graham, G. Chan, A. J. Finlayson and G. H. N. Towers, *Planta Medica*, **4**, 453 (1986); c) Y. Y. Marchant and G. H. N. Towers, *Biochem. Syst. Ecol.*, **14**, 565 (1986); *Chem. Abstr.*, **106**, 46508 (1987).

whereas α-T did not.

In a recent study,[65] Towers and co-workers proposed a complex mechanism concerning the toxicity of dithiacyclohexadiene polyines **42** and **45**. These disulfides are unique in that they possess some activity in the dark whereas their corresponding thiophenes, **46** and **47**, do not. Other important characteristics about **42** and **45** include their greater activity in UV-A than in the dark, and greater activity than their corresponding thiophenes in UV-A. Since **42** is converted to its corresponding thiophene **(46)** in UV-A light, it was difficult to separate the activity of the two species in biological testings. Towers was able to show that **42** could be converted to **46** by incandescent light without photoactivating **46** (it was only active in the presence of UV-A). This provided a means to probe the process of light-induced ring conversion for antibiotic effects without interference from the activity of **46**. Under these conditions (incandescent light only), the growth inhibition of **42** against *E. coli* and *Saccharomyces cervisiae* was enhanced over the toxicity of **42** in the dark. These results suggested that, since the products of this conversion are not active under these conditions, the antibiotic mode of action of **42** must involve some form of energy release to one of products formed during the ring contraction, which in turn interacts with living cells. A possible species suggested was singlet sulfur ($^1S_2$) although this was in no way demonstrated. The activity of disulfide **45** was comparable to that of **42** suggesting that an increase in the saturation of the chain does not lower the light independent toxicity of these compounds; this was also suggested in an earlier report.[66]



(46)



(47)

Two recent reviews of the antiviral and nematicidal activity of thiorubrine A **(42)** and other dithiapolyacetylenes have been published.[67]

Attempts to develop a culture of crown gall tumor cells of *Chaenactis douglasii* that would

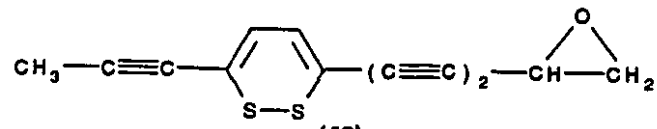
65. C. P. Constable and G. H. N. Towers, *Planta Medica*, **55**, 35 (1989).

66. J. Reisch, W. Spitzner and K. E. Schulte, *Arzneim. -Forsch.*, **17**, 816 (1967).

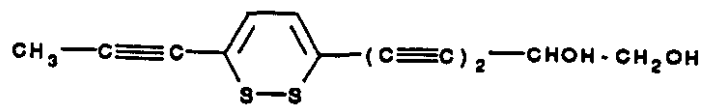
67. a) J. B. Hudson and G. H. N. Towers, *Bioact. Mol.*, **7**, 315 (1988); b) E. Rodriguez, *ACS Symp. Ser.*, **380**, 432 (1988).

accumulate thiarubrine A (42) have been reported and have had moderate success.[68] A new approach for obtaining high yields of secondary metabolites from tissue cultures has been applied to the production of thiarubrine A from hairy root cultures of *Chaenactis douglasii*.[69] These types of cultures were established by infecting the tissue with a causative bacterial agent of hairy root disease, in this case, *Agrobacterium rhizogenes*. The bacterium was able to transfer a segment of its DNA to the host's genome and conferred the ability of autonomous and high root growth at the site of infection. The hairy root culture of *C. douglassi* accumulated twice the levels of 42 compared to nontransformed controls, which were the best results recorded to date.

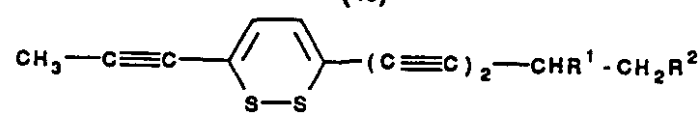
Further investigations into this area has uncovered several novel derivatives of thiarubrine A (42) from the roots of *Ambrosia chamissonis*. These include epoxide 48,[70] diol 49,[70] isomeric chloroalcohols **50a** and **50b** and alcohol **51**.[71] The thiosulfinate of 42 was also isolated along with all the corresponding thiophenes.



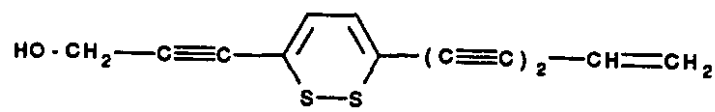
(48)



(49)



(50) a R^1 = OH R^2 = Cl
b R^1 = Cl R^2 = OH



(51)

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68. a) E. A. Cosio, R. A. Norton, E. Towers, R. J. Finlayson, E. Rodriguez and G. H. N. Towers, *J. Plant Physiol.*, **124**, 155 (1986); b) E. G. Cosio, G. H. N. Towers and J. McPherson, *J. Plant Physiol.*, **129**, 1 (1987).

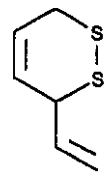
69. C. P. Constabel and G. H. N. Towers, *J. Plant Physiol.*, **133**, 67 (1988).

70. F. Balza, I. Lopaz, E. Rodriguez and G. H. N. Towers, *Phytochemistry*, **28**, 3523 (1989).

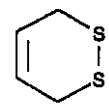
71. F. Balza and G. H. N. Towers, *Phytochemistry*, **29**, 2901 (1990).

(ii) Dihydro 1,2-Dithiins

All the remaining naturally occurring 1,2-dithiins have only one double bond in the ring containing the disulfide bond. Dithiin **52** has been shown to be a component in the flavor of cooked asparagus[72] and it has been isolated in garlic.[73] It has also been isolated from caucus and shown to have antithrombotic activity.[74] 1,2-Dithiin **53** has also been isolated from garlic[73,75] and shown to be a component of the aroma of cooked asparagus.[72]



(52)



(53)

The last of the known naturally occurring 1,2-dithiins, **54**, (myrcene disulfide) was isolated from steamed distilled hops.[76] In biological testing it has been proven active against Gram positive bacteria and the HIV virus; however, its platelet aggregating properties prevented its clinical use.[77] Dithiin **54** has also been identified as a component of the Bulgarian rose oil by gas

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72. R. Tressl, D. Bahri, M. Holzer and T. Kossa, *J. Agric. Food Chem.*, **25**, 459 (1977).

73. a)E. Block, S. Ahmad, J. L. Catalfamo, M. K. Jain and R. Apitz-Castro, *J. Amer. Chem. Soc.*, **108**, 7045 (1986); b) M. H. Brodnitz, J. V. Pascale and L. Van Derslice, *J. Agric. Food Chem.*, **19**, 273 (1971); c) M. S. Legendre, H. P. Dupuy, E. T. Rayner and W. H. Schuller, *J. Amer. Oil Chem. Soc.*, **57**, 361 (1980); d) B. Tokarska and K. Karwowski, *Nahrung*, **27**, 443 (1983); *Chem. Abstr.*, **99**, 69118 (1983); e) M. G. B. Zoghbi, L. S. Ramos, J. G. S. Maia, M. L. Da Silva and A. I. R. Luz, *J. Agric. Food Chem.*, **32**, 1009 (1984); f) M. E. Voight, *Dtsch. Apoth.-Ztg.*, **126**, 591 (1986); *Chem. Abstr.*, **104**, 193276 (1986).

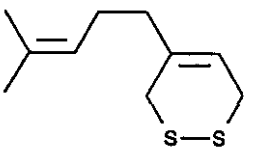
74. H. H. Nishimura, C. H. Wijaya and J. Mizutani, *J. Agric. Food Chem.*, **36**, 563 (1988); *Chem. Abstr.*, **108**, 203507 (1988).

75. a) C. S. Marvel and D. T.-M. Wong, **U. S. Pat. 4,069,205** (1978); *Chem Abstr.*, **88**, 170766 (1978); b) J. Riga and J. J. Verbist, *J. Chem. Soc., Perkin Trans. 2*, 1545 (1983).

76. a) T. L. Peppard and J. A. Eldridge, *Chem. Ind. (London)*, 552 (1979); b) J. A. Elvidge, S. P. Jones and T. L. Peppard, *J. Chem. Soc., Perkin Trans. 1*, 1089 (1982); c) T. Uyehara, T. Ohnuma, T. Suzuki, T. Kato, T. Yoshida and K. Takahashi, *Tennen Yuki Kagobutsu Tornkai Koen Yoshishu, 22nd*, 235 (1979); *Chem. Abstr.*, **93**, 168433 (1980).

77. K. Steliou. Y. Gareau, G. Milot and P. Salama, *Developments in the Organic Chemistry of Sulfur [Proc. XIII Int. Symp. Org. Chem. Sulfur, 1988]*, C. Th. Pedersen and J. Becher, Eds., New York: Gordon and Breach Science Publishers, 209 (1989).

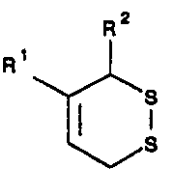
chromatography[78] and has been used as an odor enhancing agent in odorous preparations due to its property of enhancing the dispersion of odors.[79]



(54)

1.3.2 Synthetic Dihydro 1,2-Dithiins

The synthetic dihydro 1,2-dithiins that have been tested for biological activity are compounds **55-60**. They were synthesized by Steliou and co-workers *via* Diels-Alder addition of diatomic sulfur precursors to the appropiate diene.[77] These compounds did not show any activity against Gram negative bacteria (*E. coli* and *Ps. aerugunosa*), fungi (*C. albicans*) or mycobacteria (BCG strain of *M. bovis*). Dithiins **59** and **60** did show activity against Gram positive bacteria (Oxford strain of *Staph. aureus*, *Staph. epidermis*, *Strep. pyogenes* and *Strep. faecalis*) and **59** had some activity against HIV.[77]



(55)	$R^1 = CH_2CO_2H$	$R^2 = H$
(56)	$R^1 = CH_2CO_2CH_3$	$R^2 = H$
(57)	$R^1 = CH_2CH_2OH$	$R^2 = H$
(58)	$R^1 = CH_2CH_2OAc$	$R^2 = H$
(59)	$R^1 = H$	$R^2 = CH_2CH_2OH$
(60)	$R^1 = H$	$R^2 = CH_2CH_2OAc$

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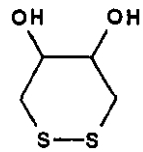
78. A. Omata, K. Yomogida, Y. Ohta, S. Nakamura, T. Toyoda, A. Amano and S. Muraki, *Dev. Food Sci.*, **18**, 707 (1988).

79. A. Komata, K. Yomogida, T. Ota, Y. Morikawa, S. Nakamura, T. Toyoda, A. Akira and S. Muraki, **Jpn. Kokai Tokkyo Koho JP 62,120,314** (1987); *Chem. Abstr.*, **107**, 204955 (1987).

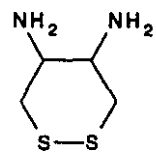
1.4 1,2-Dithianes

Although not as prevalent as their five-membered ring counterparts, 1,2-dithianes have been reported to show some biological activity.

The cyclic disulfide derivative of dithiothreitol, 1,2-dithiane-1,2-diol **(61)**, is one such example. A recent report[80] analysed the use of **61** as a radioprotector for DNA and it was proposed to act as an efficient chemical repair agent of aqueous DNA solutions irradiated under gamma radiation. Dithiane **61** was also used to quantify free diazonium groups in insoluble proteins through a microanalytical method which was based on the oxidation of dithiothreitol to **61** by the diazonium groups.[81] The amount of **61** present could be quantitified by spectrophotometric means. 4,5-Diamino-1,2-dithiane **(62)** and *N*-acyl and *N*-alkyl derivatives thereof were prepared as antihypertensive agents;[82] however, no data for their activity was presented.

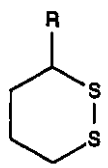


(61)



(62)

1,2-Dithianes **63-68** were also synthesized and tested for biological activity. These compounds were reported by Stellou and co-workers and were synthesized by a Diels-Alder addition of diatomic sulfur precursors to the appropiate diene followed by diimide reduction of the double bond.[77] Compounds **63** and **68** showed significant antiviral activity against HIV and, unlike the disulfide adduct of myrcene **(54)**, they did not express any toxic behavior towards normal cells.[77]



(63) R = CH_2CO_2H

(64) R = $CH_2CO_2CH_3$

(65) R = CH_2CH_2OH

(66) R = CH_2CH_2OAc

(67) R = $CH_2CONHCH_2CO_2H$

(68) R = $CH_2CONHCH_2CO_2CH_3$

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80. W. A. Pruetz, *Int. J. Radiat. Biol.*, **56**, 21 (1989).

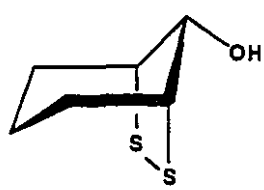
81. D. Cordier, L. Grasset and A. Ville, *Process Biochem.*, **23**, 82 (1988).

82. M. T. Dupriest and B.M. York, Jr., **U. S. Pat. 4,659,733** (1987).

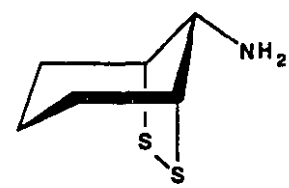
1.5 Bridged Bicyclic Disulfides

As stated in Section 1.1, incorporation of a disulfide moiety into the relatively rigid structure of a bridged bicyclic system forces the dihedral angle about the sulfur-sulfur bond to decrease to about 0°. The many examples of biologically important cyclic disulfides discussed above along with the expected enhanced reactivity of bridged bicyclic disulfides due to the increased strain of the bicyclic structure suggests that their biological activity and chemistry may also prove to be worth investigating.

Along with the expected lower stability and thus higher reactivity of these compounds, there is also the benefit of having a particular reactive functionality held in a rigid conformation. This idea was the stimulus for the design of analogs of cystamine derivatives that may be more effective as radioprotection agents than freely rotating cystamine.[83] It was thought that cystamine is active in only one conformation and it was hoped that this conformation could be obtained and held in a bridged bicyclic system. Bridged bicyclic disulfides that could be converted into cystamine derivates were prepared, including **3** and the corresponding amino derivative **69**.[6,83]



(3)



(69)

1.5.1 Epidithiadioxopiperazine Compounds

Perhaps the best known examples of bridged bicyclic disulfides with biological importance come from the family of fungal toxins characterized by an epidithiadioxopiperazine system (**70**). Some representative examples include gliotoxin (**1**), sirodesmin (**71**) and sporidesmin (**72**). This family of compounds, their fungal sources, biological mode of action and biosynthesis have been

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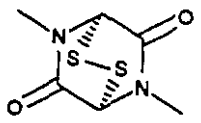
83. W. R. Marshall and D. N. Buchanan, *U.S.N.T.I.S., AD/A Rep.*, No. 002587 (1975); *Chem. Abstr.*, **83**, 97093 (1975).

well reviewed in the past,[84] thus, once again, only the recent developments will be described here.



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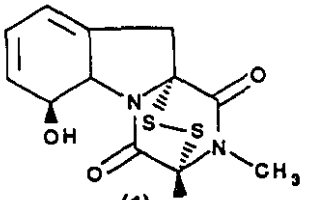
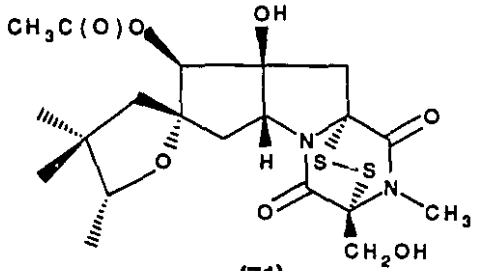


(1)



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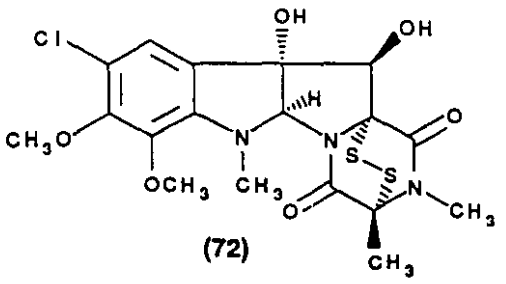

(72)

Epidithiadioxopiperazine (ETP) compounds possess antiviral, antibacterial and antifungal activity; however, their extreme toxicity to mammalian cells has prevented therapeutic applications. The activity of all ETP compounds has been associated with the bridged bicyclic disulfide moiety as activity is lost upon reduction of the disulfide to the dithiol.[85]

There have been many recent studies reporting new biological actions for ETP compounds. One such example is the recent discovery by Eichner and Müllbacher of their immunosuppressive properties.[86] Gliotoxin **(1)** is a toxic fungal metabolite produced by *Aspergillus fumigatus*, a fungus that has been associated with a large number of lung diseases in vertebrates, including man.[87] Eichner and Müllbacher proposed that once *A. fumigatus* infects its

84. a) D. Brewer, D. E. Hannah and A. Taylor, *Can. J. Microbiol.*, **12**, 1187 (1966); b) A. Taylor, in *Biochemistry of Some Foodborne Microbial Toxins*, R. I. Mateles and G. N. Wogan, Eds., Cambridge, Mass.: M.I.T. Press, 69 (1967); c) A. Taylor, *Microbial Toxins Vol. VII*, A. Ciegler and S. J. Ajl, Eds., New York: Academic Press, 337 (1971); d) G. W. Kirby and D. J. Robins, *The Biosynthesis of Mycotoxins*, P. S. Stein, Ed., New York: Academic Press, 301 (1980); e) W. B. Turner and D. C. Aldridge, *Fungal Metabolites II*, New York: Academic Press, 417 (1983).

85. a) C. J. Cavillito, J. H. Bailey and W. F. Warner, *J. Amer. Chem. Soc.*, **68**, 715 (1967); b) P. W. Trown and J. A. Bilello, *Antimicrobial Agents in Chemotherapy*, **2**, 261 (1972); c) C. M. Middleton, *Biochem. Pharm.*, **23**, 811 (1974).

86. a) R. D. Eichner and A. Müllbacher, *Aust. J. Exp. Biol. Med. Sci.*, **62**, 479 (1984); b) A. Müllbacher and R. D. Eichner, *Proc. Natl. Acad. Sci. USA*, **81**, 3835 (1984).

87. a) J. Pepys, in *Immunologic Diseases*, M. Santer, Ed., Boston: Little Brown, 692 (1978); b) M. Turner-Warwick, *Postgrad. Med. J.*, **55**, 642, (1979); c) P. B. Marsh, P. D. Miller and J. M. Kla, *Mycopathologia*, **69**, 67 (1979).

host, it produces gliotoxin which causes inhibition of phagocytosis by the host's macrophages and also halts the T-cell-mediated immune mechanisms. This process insures the survival of the fungus in its host organism. Due to the similarity of the symptoms of infection by *A. fumigatus* and those of AIDS, many implications concerning the involvement of ETP compounds in this disease have been made.

Gliotoxin (**1**) has also been used to prevent graft-*vs*-host disease in fully allogenic bone marrow graphs.[88] Bone marrow contains a subpopulation of cells that are resistant to the toxic effects of gliotoxin and these cells are capable of allowing the recolonization of lethally irradiated patients with new bone marrow. Successful experiments were performed on mice and the authors suggested that "gliotoxin treatment offers a fast and convenient alternative to existing T-cell depletion methods for the establishment of allogenic bone marrow chimeras and the prevention of graft-*vs*-host disease".[88] The immunomodulating characteristic of gliotoxin in human fetal cells has also been investigated.[89]

Another new biological function for ETP compounds is their ability to inhibit blood platelet aggregation.[90] In Japan, a pharmaceutical containing gliotoxin produced by fermentation with *Aspergillus fumigatus* has recently been patented.[90b]

The use of gliotoxin as a biological control of fungal plant pathogens has been investigated.[91] In this study the resistance to gliotoxin of two phytopathogens, *Pythium ultimum* and *Rhizoctonia solani* and also a mutant of *Salmonella tryphimurium* that is deficient in outer membrane polysaccharide, was reported. The results indicated that the primary mode of action of gliotoxin toxicity involves selective binding to cytoplasmic membrane thiol groups (involving the disulfide exchange reaction).

The mode of action of gliotoxin has been the subject of many recent investigations. Gliotoxin has been shown to cause apparently random double stranded fragmentation of genomic

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88. A. Müllbacher, D. Hume, A. W. Braithwaite, P. Waring and R. D, Eichner, *Proc. Natl. Acad. Sci. USA*, **84**, 3822 (1987).

89. B. E. Tuch, J. R. Lissing and M. G. Suranyi, *Immunol. Cell. Biol.*, **66**, 307 (1988).

90. a) M. Sakai and M. Watanuki, *Agric. Biol. Chem.*, **51**, 2167 (1987); b) M. Sakai, M. Watanuki and M. Mutai, **Jpn. Kokai, Tokkyo Koho JP 61,277,617** (1985); *Chem. Abstr.*, **106**, 162584 (1987).

91. R. W. Jones and J. G. Hancock, *J. Gen. Microbiol.*, **134**, 2067 (1988).

DNA in a variety of cell types[92] and single-stranded scission in isolated plasmid DNA.[93] Another study reports the effect of gliotoxin treatment on macrophages.[94] These studies suggested that gliotoxin is only active in the presence of reducing agents, such as glutathione and dithiothreitol, and that an intracellular redox cycling reaction generates an active oxygen species, which may be the proximate agent responsible for the toxic effects. This has also been suggested in a recent investigation into the toxicity of sporidesmin.[95]

Recently, several new members of this class of compounds have been isolated. Emestrin[96] **(73)** was isolated from several species of the fungal genus *Emericella* and was shown to have strong antifungal activity against *Microsporum* and *Trichophyton* species. Phomalirazine **(74)** was isolated from *Phoma lingam*,[97] a pathogenic fungus infecting rapeseed and canola causing "blackleg disease". A unique ETP compound was recently isolated from *Aspergillus silaticus* and given the name dithiosilvatin **(75)**.[98] The unusual characteristic of **75** is that it appears to be a rare example of a naturally occurring ETP compound that is biosynthesized from glycine and tyrosine or phenylalanine. Emethallicin A **(76)** was isolated as the major metabolite from the mycelial extracts of *Emericella heterothallica*.[99] Compound **76** had potent inhibitory activity against induced histamine release from mast cells and was also a 5-lipoxygenase inhibitor.

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92. A. W. Braithwaite, R. D. Eichner, P. Waring and A. Müllbacher, *Mol. Immunol.*, **24**, 47 (1987).

93. R. D. Eichner, P. Waring, A. Geue, A. W. Braithwaite and A. Müllbacher, *J. Biol. Chem.*, **41**, 361 (1988).

94. P. Waring, R. D. Eichner, A. Müllbacher and A. Sjaarda, *J. Biol. Chem.*, **263**, 18493 (1988).

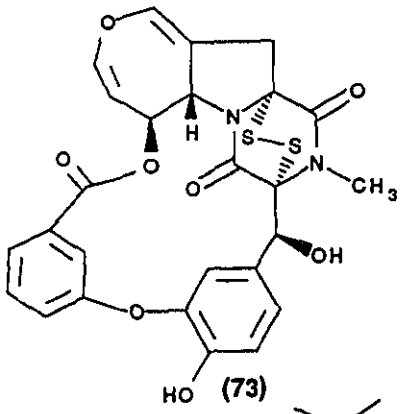
95 R. Munday, *J. Appl. Toxicol.*, **7**, 17 (1987).

96. K. Norizuki, H. Seya, S. Nakajima, K. Kawai, K. Norizuki, S. Udagawa and M. Yamazaki, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, **28**, 41 (1986); *Chem. Abstr.*, **106**, 134811 (1987).

97. M. Soledade, C. Padras, S. R. Abrams, G. Séguin-Swartz, J. W. Quail and Z. Jia, *J. Amer. Chem. Soc.*, **111**, 1904 (1989).

98. N. Kawahara, K. Nozawa, S. Nakajima and K. Kawai, *J. Chem. Soc., Perkin Trans. I*, 2099 (1987).

99. N. Kawahra, K. Nozawa, S. Nakajima, K. Kawai, T. Sato, M. Chin, H. Mitsuhashi and M. Yamazaki, *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu*, **31**, 260 (1989); *Chem. Abstr.*, **112**, 175313 (1990).



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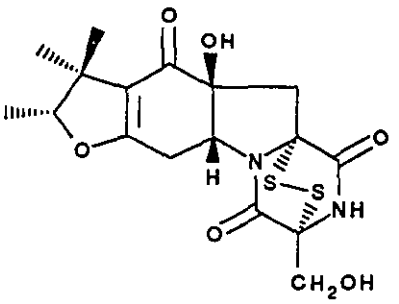

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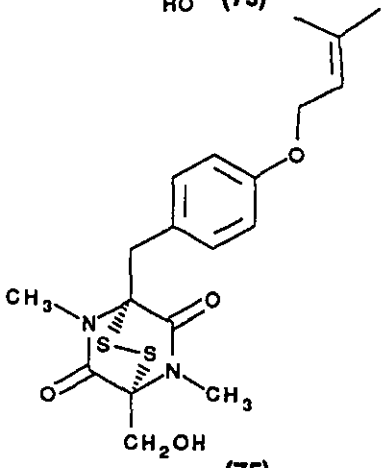

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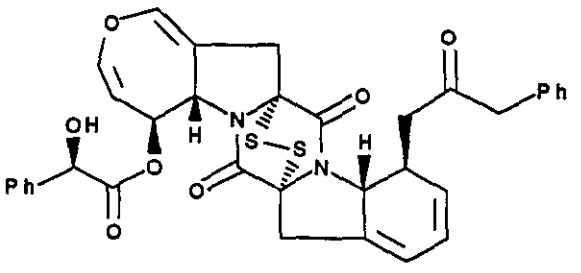
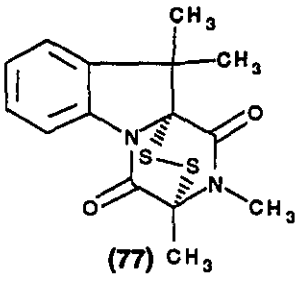


(76)

A synthetic analogue of dehydrogliotoxin (77) has been reported by Ottenheijm and co-workers.[100] Compound 77 was found to inhibit the enzyme reverse transcriptase, the RNA-dependent DNA polymerase of RNA tumor virus, at approximately the same activity levels as gliotoxin.



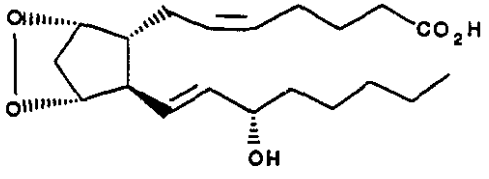
(77)

1.5.2 Prostaglandin Bridged Bicyclic Disulfides

The bridged bicyclic endoperoxide PGH_2 (78) is an important intermediate in the

100. H. C. J. Ottenheijm, J. D. M. Herscheid, G. P. C. Kerkhoff and T. F. Spande, *J. Org. Chem.*, **41**, 3433 (1976).

biosynthesis of prostaglandins, prostacyclin and thromboxanes and it possesses some interesting biological properties.[101] Efforts to study the biological action and the biosynthesis of prostaglandins have been hampered due to the low stability of **78** in aqueous buffer solution. The synthesis (disussed in detail in the Introduction to Chapter 2) of a bridged bicyclic disulfide methyl ester analog **(79)** has thus been carried out by several groups in hope of obtaining a substitute for use in these types of investigations.[102] Compound **79** was also found to cause a rapid irreversible aggregation of platelets, thus acting as a strong mimic of thromboxane A_2.[102a,c]



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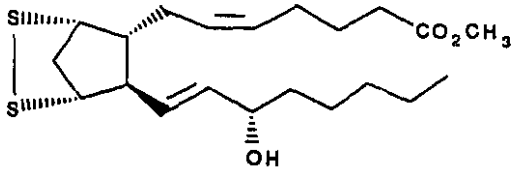

(79)

1.6 Cyclic Thiosulfinate Esters

The chemistry of organic thiosulfinate esters has received a greater amount of attention since the discovery of allicin **(80)**, a natural product isolated from garlic[103] that has a wide range of biological activity.[104] The mode of action of allicin most often has been ascribed to the formation of mixed disulfides with protein sulfhydryl groups;[104a,b,c] however, a recent study suggested that its antibacterial characteristics at least are a result of a specific but reversible inhibition of RNA synthesis in cells.[104d]

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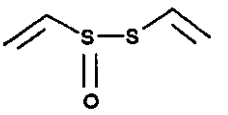
101. a) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. USA*, **70**, 899 (1973); b) M. Hamburg, B. Samuelsson, T. Wakabayashi and B. Samuelsson, *Proc. Natl. Acad. Sci. USA*, **71**, 345 (1974); c) M. Hamburg and B. Samuelsson, *Proc. Natl. Acad. Sci. USA*, **71**, 3400 (1974).

102. a) H. Miyake, S. Iguchi, H. Itoh and M. Hayashi, *J. Amer. Chem. Soc.*, **99**, 3536 (1977); b) A. E. Greene, A. Padilla and P. Crabbe, *J. Org. Chem.*, **43**, 4377 (1978); c) S.S. Ghosh, J. C. Martin and J. Fried, *J. Org. Chem.*, **52**, 862 (1987).

103. C. J. Cavallito, J. S. Buck and C. M. Suter, *J. Amer. Chem. Soc.*, **66**, 1950 (1944).

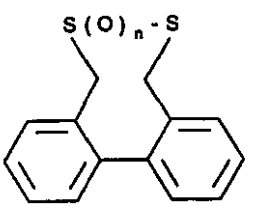
104. a) N. Isenberg and M. Grdinic, *Int. J. Sulfur Chem.*, **8**, 307 (1973), and references therein; b) E. Block, *Sci. Amer.*, **252**, 114 (1985); c) E. Block, S, Ahmad, J. L. Catalfamo, M. K. Jain and R. Apitz-Castro, *J. Amer. Chem. Soc.*, **106**, 7045 (1986); d) R. S. Feldberg, S. C. Chang, A. N. Kotik, M. Nadler, Z. Neuwirth, D. C. Sundstrom and H. H. Thompson, *Antimicrob. Agts. Chemo.*, **32**, 1763 (1988).



(80)

Molecules containing the S(O)-S linkage (especially dialkyl thiosulfinates) have been shown to have unusual reactivity and low stability and are often associated with strong, unpleasant odors[105] (in fact this was what prevented the use of allicin as a therapeutic agent).

Block and O'Connor have determined the S-S bond energy in methyl methanethiosulfinate to be 46 kcal/mol and that of its corresponding disulfide to be 74.5 kcal/mol.[105] Fava and co-workers measured the S-S bond energy in aryl arenethiosulfinates and found it to be 35.4 kcal/mol.[106] Kice[107] suggested that the weakness in this bond may lie in the considerable stability of the sulfinyl radical derived from the homoloysis of the thiosulfinate S-S bond. An X-ray crystallographic investigation into *5H,8H*-dibenzo[*d,f*][1,2]-dithiocin **(81a)** and its *S*-oxide **(81b)** and *S,S*-dioxide **(81c)** has shown that the thiosulfinate **(81b)** has the longest S-S bond of the three at 2.098(2)Å.[108] The S-S bond length of **81a** was 2.035(2)Å and that of **81c**, 2.048(2)Å.



(81) a n=0, **b** n=1, **c** n=2

Cyclic thiosulfinate esters have been shown to have a greater stability than their straight-chained counterparts. Padwa and co-workers[109] were the first to report that the cyclic

105. E. Block and J. O'Connor, *J. Amer. Chem. Soc.*, **96**, 3921, 3929, (1974).

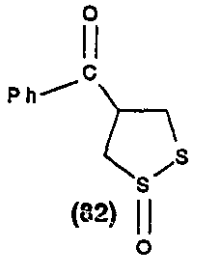
106. P. Koch, E. Cluffarin and A. Fava, *J. Amer. Chem. Soc.*, **92**, 5971 (1970), and references therein.

107. J. L. Kice, in *Sulfur in Organic and Inorganic Chemistry*, A. Senning, Ed., New York: Marcel Dekker, Vol. 1, Chapt. 6 (1971).

108. a) G. H. Wahl, Jr., J. Bordner, D. N. Harpp and J. G. Gleason, *J. Chem. Soc., Chem. Comm.*, 985 (1972); b) G. H. Wahl, Jr., J. Bordner, D. N. Harpp and J. G. Gleason, *Acta Cryst., Sect. B*, **28**, 2272 (1973).

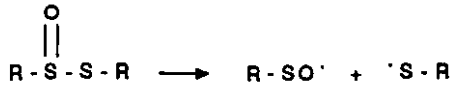
109. F. Wudl, R. Gruber and A. Padwa, *Tetrahedron Lett.*, 2133 (1969).

thiosulfinate **82** was configurationally stable up to 166°C whereas open chain dialkyl[105] and aryl arene[106] thiosulfinates will undergo facile thermal racemization and disproportionation (to give mainly thiosulfonate and disulfide) at temperatures ranging from 25-90°C.

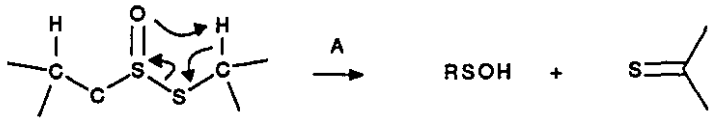


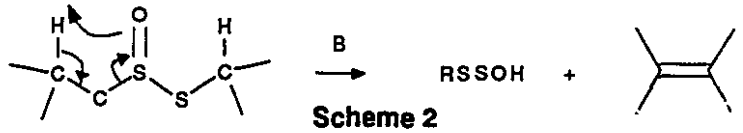
(82)

Fava[106] proposed a radical mechanism for the thermal disproportionation of aryl thiosulfinates in which the first step is the homolytic cleavage of the S-S bond to give a sulfinyl and sulfenyl radical (Scheme 1). Detailed kinetic and radioactive labelling experiments were presented that supported this mechanism. Block,[105] however, proposed complex mechanisms for both the scrambling and disproportionation reactions that began with one of two possible cycloelimination pathways shown in Scheme 2. Pathway A is expected to be favoured due to the weakness of the S-S bond and enhanced acidity of the α-sulfenyl protons and was shown to occur by trapping the sulfenic acid generated with acetylenes to produce α,β-unsaturated sulfoxides. If the thiosulfinate had no α-sulfenyl protons it underwent cycloelimination of type B to give alkanethiosulfoxylic acids and isobutylene. The generated RSSOH compounds were trapped with acetylenes to give α,β-unsaturated thiosulfinates. Block's proposed mechanism explained the thermal stability of compound **82**; a coplanar cycloelimination is not possible in this structure. The racemization of aryl arenethiosulfinates was explained through a reaction of arenesulfenic acid (perhaps generated from the thiosulfinate through reaction with traces of water) with optically active thiosulfinate as an alternative to Fava's radical mechanism. Block could not detect radicals under conditions of pyrolysis, both neat and in solution at temperatures up to 140°C, in an ESR spectrometer, using a spin trap or using CIDNP techniques.[105]



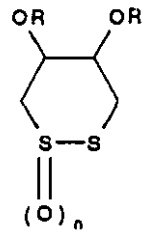
Scheme 1



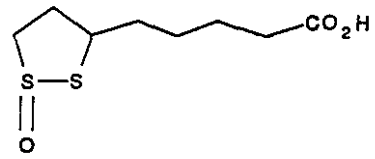


Scheme 2

The first cyclic thiosulfinates to be described in the literature were 1,2-dithiane *S*-oxide[110] **(83a)** and the *S*-oxide of lipoic acid **(84)**, often called *β*-lipoic acid or protogen-B.[111] Other naturally occuring cyclic thiosulfinates include the *S*-oxide **(85)** of 4-hydroxy-1,2-dithiolane **(14)**, isolated as both the *cis* and *trans* isomer from *Brugiera conjugata*,[112] and asparagusic acid *S*-oxide **(86)** isolated from etiolated young asparagus shoots.[113]



(83a) R=H n=1
(83b) R=Ac n=1
(83c) R=Ac n=0
(83d) R=Ac n=2



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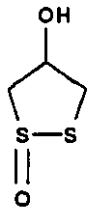

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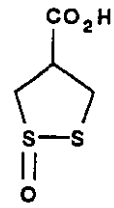


(86)

Field and Khim[114] investigated the diacetate of 1,2-dithiane-4,5-diol *S*-oxide **(83b)** as an antiradiation drug. It had an LD_{50} in mice of 120 mg/kg at doses of 25-50 mg/kg and 7-13% of the mice irradiated survived after 30 days. These results were better than those of the corresponding disulfide **(83c)** which had an LD_{50} of 750 mg/kg at doses of 200 mg/kg and only 13% of the mice survived past 17 days. The oxidation of **83b** to **83d** was also investigated in this report and it was found to proceed with great difficulty. Under most oxidizing conditions, cleavage to sulfonic acids

110. C. J. Cavillito and L. D. Small, **U. S. Patent 2,508,745** (1950).

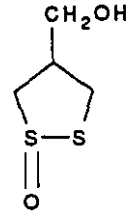
111. a) E. L. Patterson, J. A. Brockman, Jr., F. P. Day, J. V. Pierce, M. E. Macchi, C. E. Hoffman, C. T. O. Fong, E. L. R. Stokstad and T. H. Jukes, *J. Amer. Chem. Soc.*, **73**, 5919 (1951); b) J. A. Brockman, Jr., E. L. R. Stokstad, E. L. Patterson, J. V. Pierce and M. E. Macchi, *J. Amer. Chem. Soc.*, **76**, 1827 (1954).

112. A. Kato and M. Numata, *Tetrahedron Lett.*, 203 (1972).

113. H. Yanagawa, T. Kato and Y. Kitahara, *Tetrahedron Lett.*, 1073 (1973).

114. L. Field and Y. H. Khim, *J. Org. Chem.*, **37**, 2710 (1972).

occurred. It was also found that attempted oxidation of **87** usually led to cleavage and polymerization. Direct oxidation of the disulfides **88**[114] and **33**[115] to the *S,S*-dioxide with hydrogen peroxide has been achieved. It is interesting to note that Field reports the monoxides **83b** (both *cis* and *trans*) to be remarkably stable compounds;[114] the melting point of *trans*-**83b** was unchanged after 20 months. This, along with its apparent resistance to oxidation was explained in terms of conformational or steric factors.



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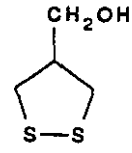
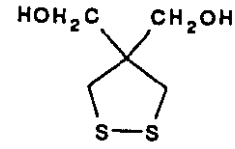


(88)



(33)

It has been noticed by several groups that disulfides with a smaller dihedral angle about the S-S bond are more easily oxidized to thiosulfinates by electrophilic reagents than disulfides with a larger dihedral angle.[3,116] Frisell and Bergson[116] proposed that the electron transfer from the disulfide to the oxidizing reagent was the rate determining step and thus rationalized that a decrease in the value of θ would increase the reaction rate by relieving some of the interaction between the nonbonding pairs of electrons. This may also be part of the reason for the enhanced stablility of cyclic thiosulfinate compounds. There are no known examples of bridged bicyclic thiosulfinate compounds. Following the trends established here, they are expected to be relatively stable compounds and may provide further unique examples (like compound **82**) in thiosulfinate chemistry. The synthesis and chemistry of bridged bicycic thiosulfinates has been investigated in this work and is reported in Chapters 2 and 3.

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115. B. Lindberg and G. Bergson, *Ark. Kemi.*, **23**, 319 (1965).

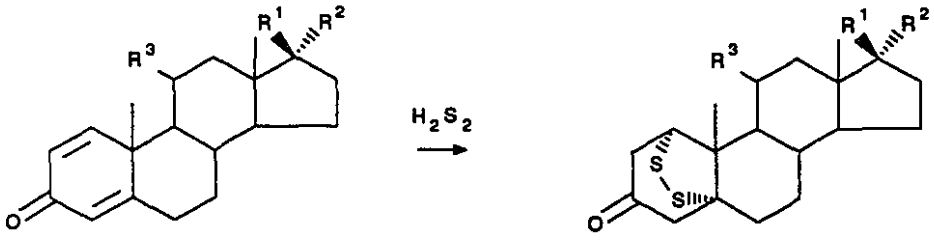
116. C. Frisell and G. Bergson, *Ark. Kemi*, **25**, 263 (1966).

CHAPTER 2: BRIDGED BICYCLIC DISULFIDES: SYNTHESIS AND STRUCTURE

2.1 Introduction

There are a vast number of acyclic and cyclic disulfides known (both natural and synthetic); the knowledge about bridged bicyclic disulfides, however, is quite limited. A systematic study into the synthesis and chemical reactivity of bridged bicyclic disulfides has never been reported. The unique characteristic of a near zero dihedral angle about the S-S bond along with the fact that the majority of known bridged bicyclic disulfides have interesting biological activity warrants a closer look at this class of compounds.

The first synthesis of a bridged bicyclic disulfide was reported in 1959. Tweit and Dodson[117] synthesized an unusual 1α,5α-epidithia-3-oxosteroid *via* transannular addition of hydrogen disulfide to the double bonds in the A-ring of various steroids (**89a-f**). Although no NMR data was available at the time, exhaustive reactivity investigations along with combustion analysis, UV and IR data all supported the structural assignment as shown in Scheme 3 (**2** and **90b-f**). The yields, however, were only in the range of 5-10%.



(89) **(2)**

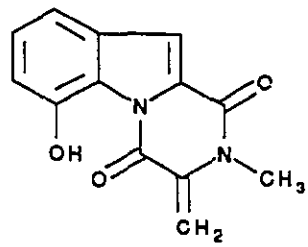
(a) $R^1 = R^2 = O$	$R^3 = H$		**(90b-f)**
(b) $R^1 = Ac$	$R^2 = R^3 = H$		
(c) $R^1 = C(O)CH_2OAc$	$R^2 = R^3 = H$		
(d) $R^1 = C(O)CH_2OAc$	$R^2 = OH$	$R^3 = H$	
(e) $R^1 = C(O)CH_2OAc$	$R^2 = OH$	$R^3 = =O$	
(f) $R^1 = C(O)CH_2OAc$	$R^2 = OH$	$R^3 = \beta$-OH	

Scheme 3

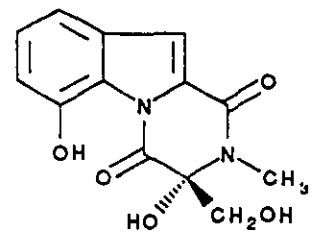
The biosynthesis of the disulfide moiety in epidithiadioxopiperazine compounds is also believed to involve the addition of hydrogen disulfide to intermediates such as **91**.[118] Intermediates with a similiar structure have been isolated from the culture media of *Penicillium*

117. R. C. Tweit and R. M. Dodson, *J. Amer. Chem. Soc.*, **81**, 4409 (1959).

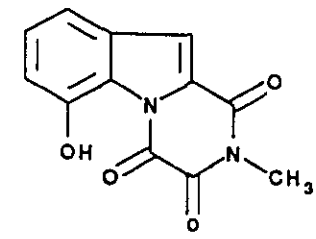
terlikowskii; for example, compound **92** (proposed as the true metabolite but isolated as **93** due to the acidic conditions used).



(91)



(92)



(93)

In 1973, Kishi and co-workers reported a general method for the synthesis of epidithiadioxopiperazines.[119] The key step in their procedure involved protection of the disulfide linkage as a thioacetal derived from anisaldehyde, which was prepared by reacting *cis* or *trans* dithiol **94** with anisaldehyde in methylene chloride containing $BF_3{\cdot}OEt_2$ (Scheme 4). The use of anisaldehyde was essential because the deprotection of thioacetal **95** required the formation of a carbonium ion which was stabilized by the electron-donating methoxy group. Cleavage of the thioacetal was accomplished in a two step procedure which involved *m*-CPBA oxidation to give the sulfoxide followed by treatment with acid (such as BCl_3, $BF_3{\cdot}OEt_2$, H_2SO_4 or $HClO_4$) in order to cleave the S(O)-C bond and form the carbonium ion which rearranged to give disulfide **96**. The protection of the sensitive disulfide group in this way allowed for manipulations in other regions of the molecule required for the total synthesis of the desired epidithladioxopiperazines.

Kishi and co-workers used this methodology to synthesize compounds **97**,[119] **98**,[119] dehydrogliotoxin **(99)**,[120] sporidesmin A **(72)**[121] and *d,l*-sporidesmin B **(100)**.[122]

An efficient route to dehydrogliotoxin analogues **(77)** was reported by Ottenheijm and co-workers.[100] The synthesis was performed in three steps with an overall yield of 81%. Ottenheijm speculated that since this synthetic scheme proceeded with high stereoselectivity, high yields and was performed at room temperature and neutral pH, it may be biomimetic.

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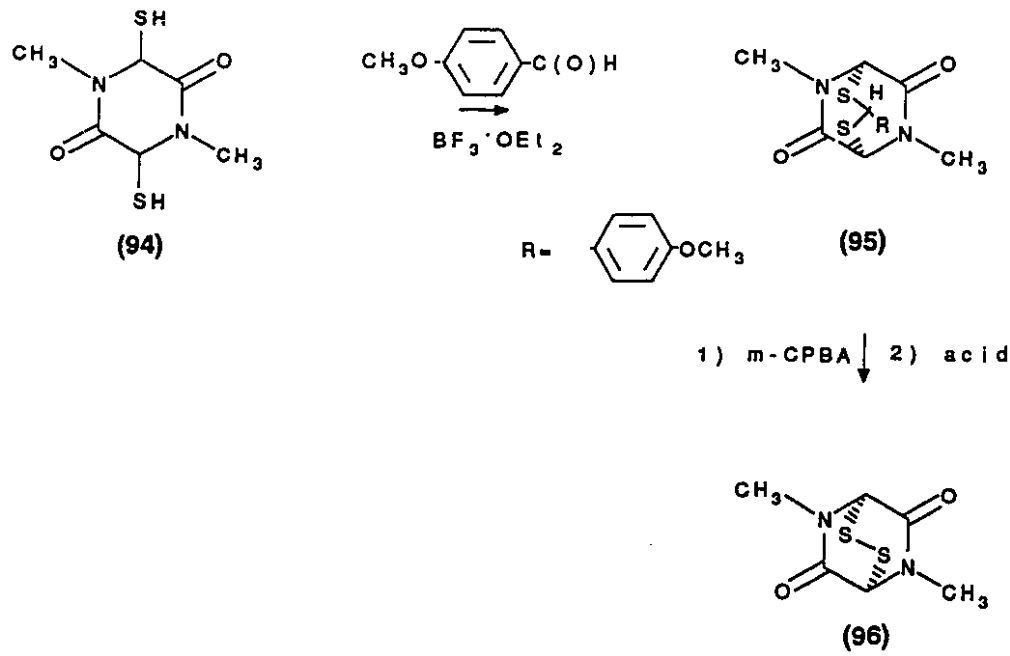
118. M. Ali, J. Shannon and A. Taylor, *J. Chem. Soc. (C)*, 2044 (1968).

119. Y. Kishi, T. Fukuyama and S. Nakatsuka, *J. Amer. Chem. Soc.*, **95**, 6490 (1973).

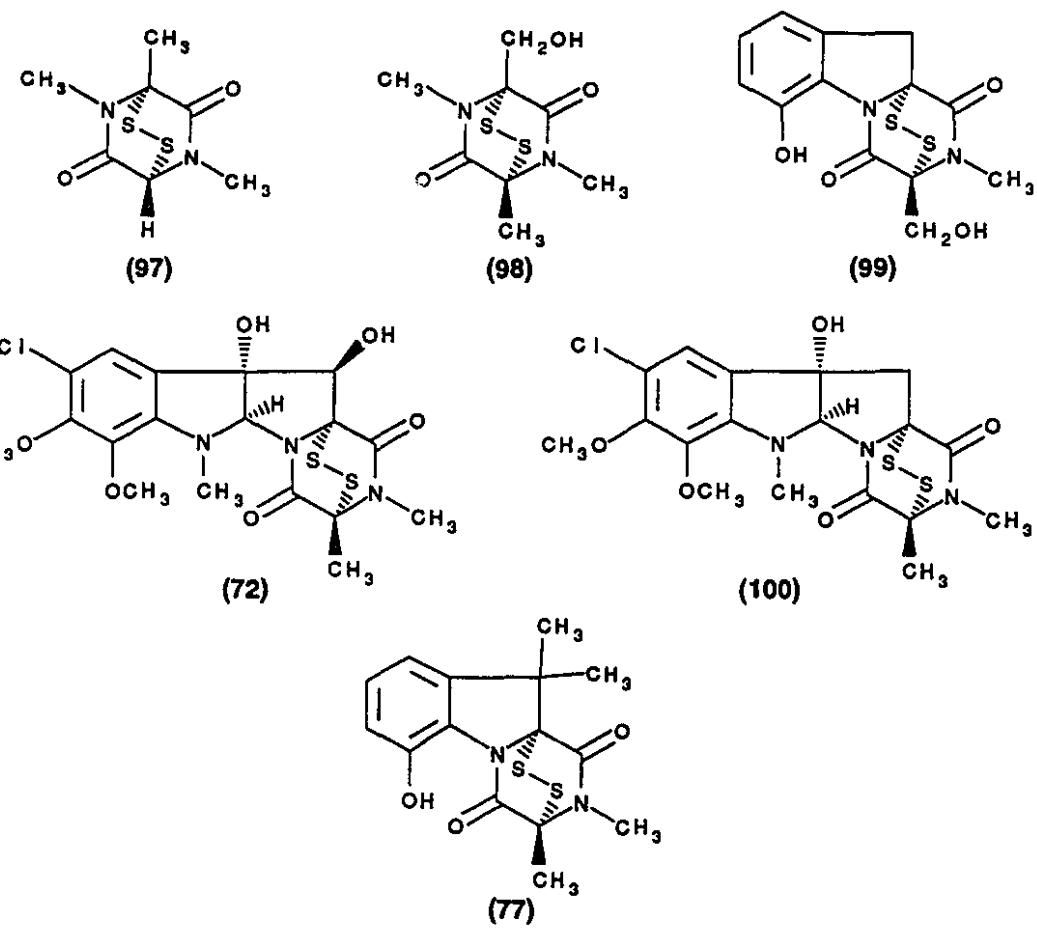
120. Y. Kishi, T. Fukuyama and S. Nakatsuka, *J. Amer. Chem. Soc.*, **95**, 6492 (1973)

121. Y. Kishi, S. Nakatsuka, T. Fukuyama and M. Havel, *J. Amer. Chem. Soc.*, **95**, 6493 (1973).

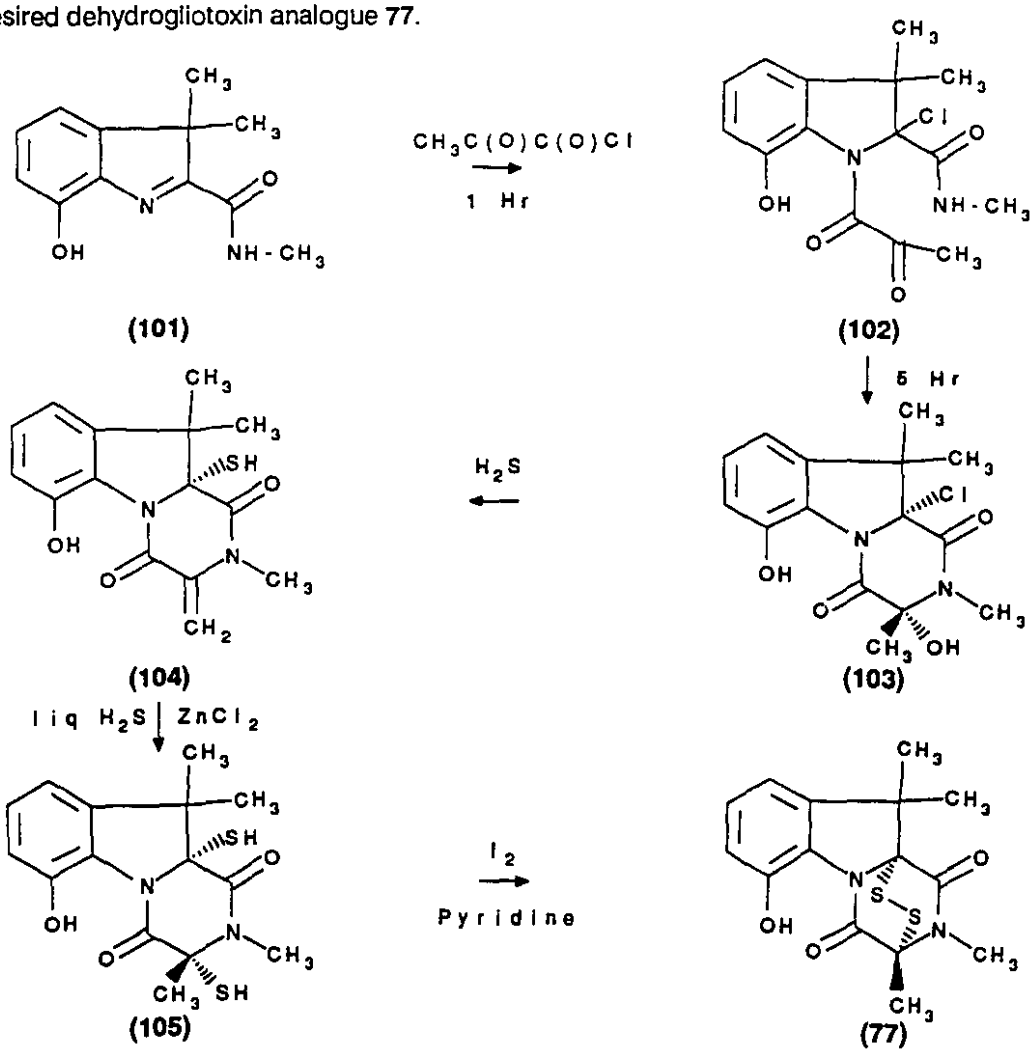
122. S. Nakatsuka, T. Fukuyama and Y. Kishi, *Tetrahedron Lett.*, 1549 (1974).


SH
CH3
N
O
CH3
SH
(94)
CH3O
C(O)H
BF3·OEt2
CH3
N
S
H
S
R
O
O
N
CH3
R=
OCH3
(95)
1) m-CPBA
2) acid
CH3
N
S
S
O
O
N
CH3
(96)

Scheme 4


CH3
CH3
N
S
S
O
O
N
CH3
H
(97)
CH2OH
CH3
N
S
S
O
O
N
CH3
CH3
(98)
OH
N
S
S
O
O
N
CH3
CH2OH
(99)
Cl
OH
OH
CH3O
H
N
N
S
S
O
O
N
CH3
OCH3
CH3
CH3
(72)
Cl
OH
CH3O
H
N
N
S
S
O
O
N
CH3
OCH3
CH3
CH3
(100)
CH3
CH3
OH
N
S
S
O
O
N
CH3
CH3
(77)

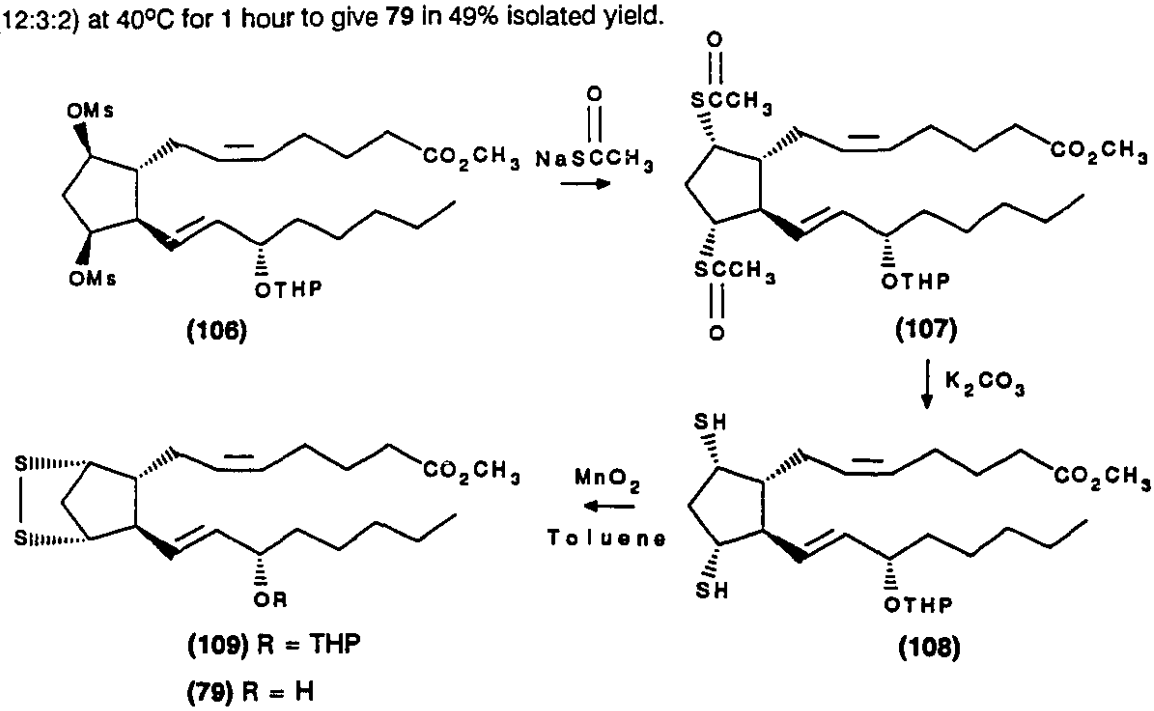
The synthesis (Scheme 5) began with the reaction of the indolenine carboxamide **101** with pyruvoyl chloride in carbon tetrachloride.[100] After 1 hour at room temperature, adduct **102** was formed, however, if the reaction time was extended to 5 hours, **102** was completely converted into the cyclized product **103** as only one stereoisomer. Bubbling H_2S through a methylene chloride solution of **103** for 1 hour resulted in the formation of mercapto alkene **104**. Treatment of **104** with liquid H_2S in the presence of $ZnCl_2$ yielded the *cis*-dithiol **105** quantitatively. Oxidation to the bicyclic disulfide was found to proceed most efficiently using I_2 in the presence of pyridine to give the desired dehydrogliotoxin analogue **77**.



Scheme 5

The synthesis of bridged bicyclic disulfide analogues of prostaglandin endoperoxide PGH_2 (**78**) has also been reported. Again it was the construction of the disulfide linkage that was the critical and most difficult step. Two groups successfully synthesized compound **79** and reported their results almost simultaneously.[102a,b]

Hayashi and co-workers[102a] began their synthesis (Scheme 6) with dimeslyate monotetrahydropyranyl ether **(106)** which was obtained from the corresponding 9β,11β-diol[123] by reaction with mesyl chloride and triethylamine. The mesylates were displaced with excess sodium thioacetate in DMSO/DMF (1:1) *via* a S_n2 reaction to give inversion of stereochemistry at C9 and C11 **(107)**. Saponification of the thioacetates was performed using potassium carbonate in methanol to give dithiol **108**. The oxidation of **108** to endodisulfide **109** required very specific conditions in order to minimize side products. Treatment of **108** with 1.5 equivalents of active manganese dioxide in degassed toluene at -20°C for 40 minutes under argon gave **109** in 86% yield. The THP protecting group was removed using a mixture of acetic acid, water and THF (12:3:2) at 40°C for 1 hour to give **79** in 49% isolated yield.

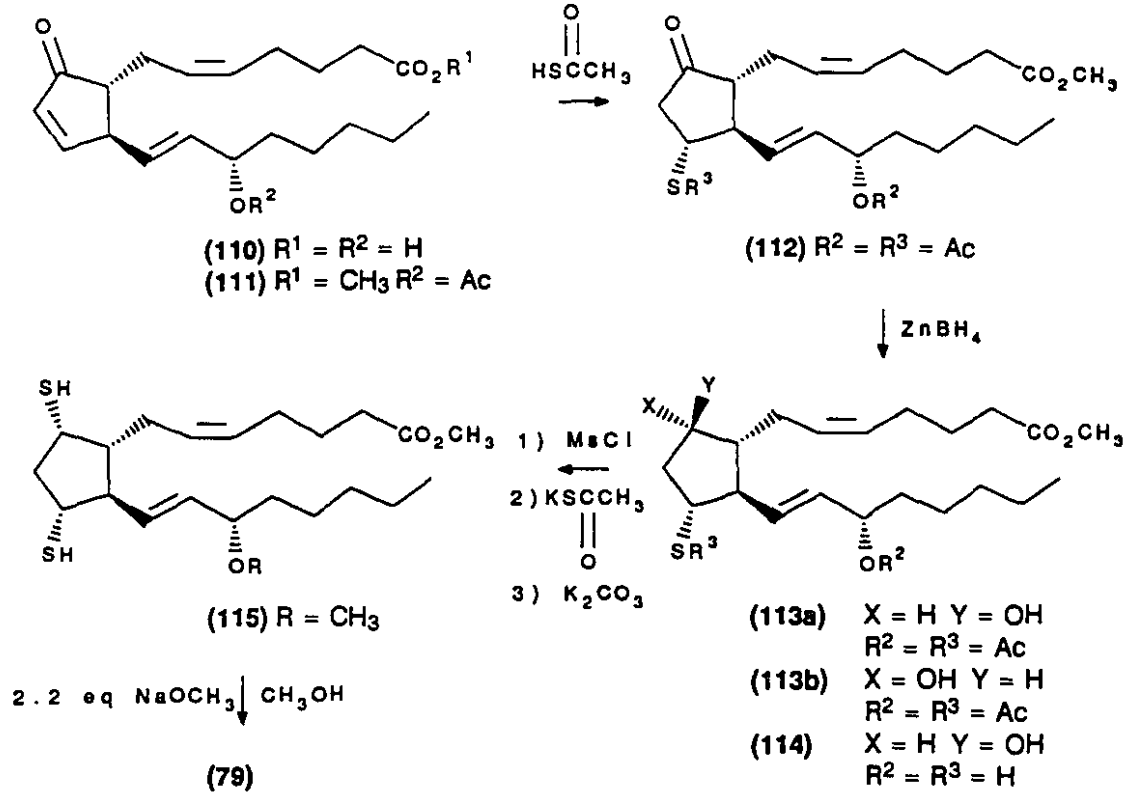


Scheme 6

The second reported synthesis of **79** was by Crabbe and co-workers (Scheme 7).[102b] Their starting material was (+)-PGA_2 **(110)**, readily obtained in large quantities by enzymatic hydrolysis of the lipophilic extracts of *Plexaura homomalla*. Compound **110** was converted to the diester **(111)** using diazomethane followed by acetic anhydride in pyridine and then reacted with thioacetic acid in a kinetically controlled conjugate addition in order to place a mercapto-functionality at the 11α position **(112)**. Compound **112** was reduced with zinc borohydride to

123. Previously synthesized from methyl(5*Z*,11β,13*E*,15*S*)-9-oxo-11,15-bis(2-tetrahydropyranyloxy)prosta-5,13-dienoate [D. M. Floyd, *et al.*, *Tetrahedron Lett.*, 3269 (1972)] in 6 steps.

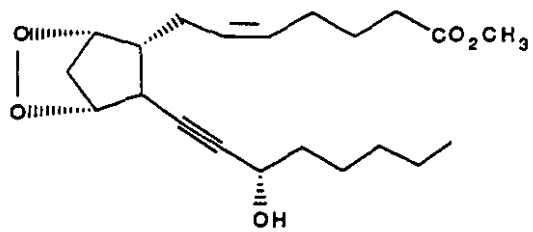
afford a 4:1 mixture of the 9β (**113a**) and 9α (**113b**) alcohols which could be separated by column chromatography. Removal of the acetates on the hydroxy group at C15 and the sulfur at C11 was achieved using methanolysis to give compound **114**. The hydroxy group at C9 was converted to the required mercapto-functionality using the same procedure employed by Hayashi.[102a] Mesylation followed by a S_n2 displacement with potassium thioacetate, saponificaton and esterification gave dithiol **115**. This group found that cyclization was best achieved by passing oxygen through a dilute methanolic solution of **115** and 2.2 equivalents of sodium methoxide to give the desired endodisulfide **79**.



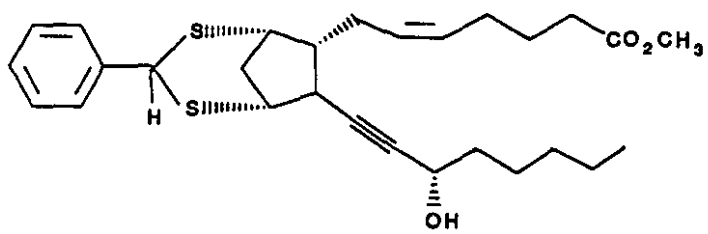
Scheme 7

Finally, in 1987, Fried and co-workers[102c] attempted the total synthesis of the bridged bicyclic disulfide analogue of 13,14-dehydro-PGH_2 (**116**). Their strategy was to employ Kishi's method (see above) for protection of the disulfide functionality as the thioacetal derived from *p*-anisaldehyde.[119] It was found that the anisaldehyde protecting group was incompatable with the procedures for the attachment of the chain at C6, thus an unsubstituted benzylidene protecting group was employed. They were able to obtain the required precursor (**117**) after several steps in modest yields but were unable to convert **117** to the final product. In order to complete their

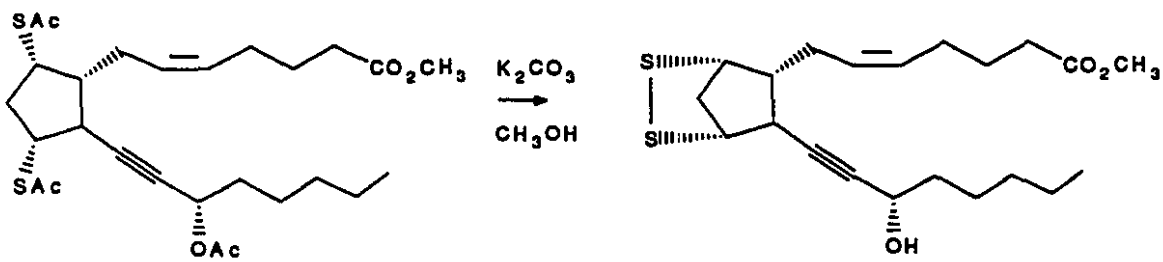
synthesis, **117** was converted to the triacetate **118** *via* a trans-acetylation procedure using 1,3-propanedithiol in the presence of $BF_3{\cdot}OEt_2$ followed by acetic anhydride. It was found that under hydrolysis conditions (potassium carbonate, methanol) **118** cyclized to the final product **119** (Scheme 8). Their explanation for the facile cyclization of **118** to **119** was based on the presence of the bulky side groups on C6 and C7 which favoured intramolecular rather than intermolecular disulfide formation.



(116)



(117)



(118) **(119)**

Scheme 8

In 1980, McCabe and Stewart[124] reported the synthesis of bridged bicyclic disulfide **5** which was the subject of a photoelectron spectroscopic investigation described in the Introduction (Chapter 1). The electrophilic cleavage of unsaturated thiirans with SCl_2 was under investigation and it was found that **5** could be isolated from the the reaction of thiiran **120** with SCl_2 in 42% yield (Scheme 9).

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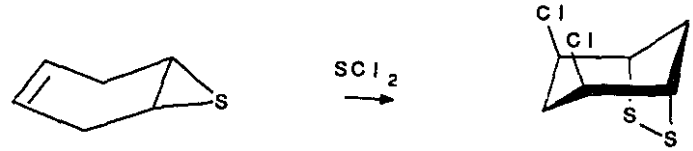
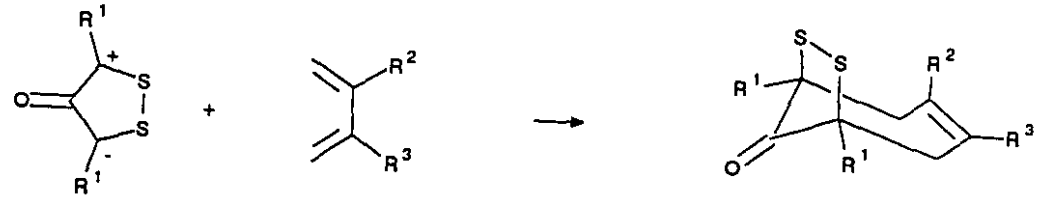
124. P. H. McCabe and A. Stewart, *J. Chem Soc., Chem. Comm.*, 100 (1980).



(120) (5)

Scheme 9

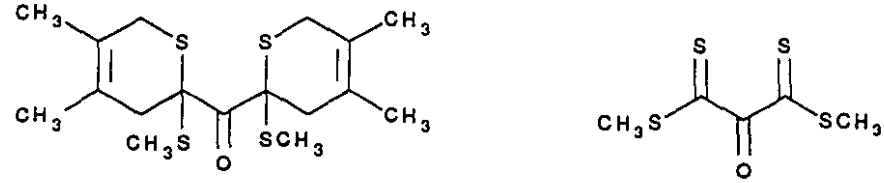
The reaction of mesoionic 1,2-dithiolylium-4-olates **(121a-h)** with 1,3-dienes gave several novel 7,8-dithiabicyclo[4.2.1]non-3-en-9-ones **(122a-h)** *via* a thermal 1,3-dipolar [4+3] cycloaddition reaction (Scheme 10).[125] Bulky groups at the bridgehead positions (R^1) seems to be a requirement for this reaction to produce bridged bicyclic disulfides. When R^1 = SMe **(121i)**, reaction with 2,3-dimethyl-1,3-butadiene gave only a mixture of the stereoisomeric 1:2 adducts **(123)**, explained by a [4+2] cycloaddition reaction of the diene with a valence tautomer **(124)** of **121i**.



(122a-h)

(121a) R^1=Ph R^2=Me R^3=Me
(b) R^1=Ph R^2=Me R^3=H
(c) R^1=Ph R^2=R^3=-$[CH_2]_4$-
(d) R^1=*t*-Bu R^2=Me R^3=Me
(e) R^1=*t*-Bu R^2=Ph R^3=H
(f) R^1=*t*-Bu R^2=R^3=-$[CH_2]_4$-
(g) R^1=PhNHCO R^2=Me R^3=Me
(h) R^1=PhNCO R^2=R^3=-$[CH_2]_4$-
(i) R^1=SMe R^2=Me R^3=Me

Scheme 10



(123) **(124)**

Unusual tetracyclic epidithio compounds were isolated in 13-45% yields from the

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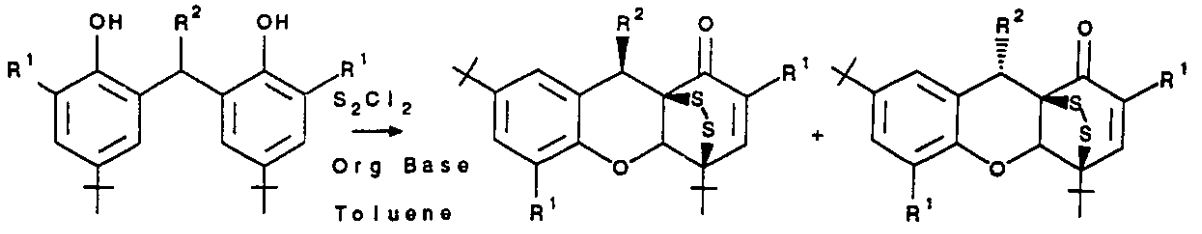
125. N. Jubran, H. Cohen, Y. Koresh and D. Meyerstein, *J. Chem. Soc., Chem. Comm.*, 1683 (1984).

condensation reaction between bisphenols **125a-e** and S_2Cl_2 (Scheme 11).[126] The structure of one of the products, **126a**, was confirmed by X-ray crystallography. The S-S bond length was found to be 2.07Å and θ, 18.9°. Disulfide **127a**, an epimer of **125a**, was isolated as a minor side product in this example only.



(125a) $R^1 = (CH_3)_3C$ R^2 = Me
(125b) $R^1 = (CH_3)_3C$ R^2 = Et
(125c) $R^1 = R^2$ = Me
(125d) $R^1 = (CH_3)_3C$ R^2 = H
(125e) $R^1 = (CH_3)_3C$ $R^2 = (CH_3)_2CH$

(126a-e) **(127a)**

Scheme 11

In summary, the syntheses of bridged bicyclic disulfides reported in the literature involve: (a) addition of H_2S_2 or S_2Cl_2 across a suitably placed diene; (b) placement of thiol groups *via* substitution of mesylates by potassium thioacetate, followed by hydrolysis and oxidation and (c) Diels-Alder addition of disulfide mesoionic compounds with 1,3-dienes. The last methodology requires the presence of bulky groups at the bridgehead positions and would be difficult to apply to the synthesis of simple molecules and to extend to other systems. The first method requires the suitable placement of double bonds which is not always possible. The second method has been applied most frequently and does appear to be fairly general. It requires the placement of two hydroxyl groups in the bridgehead positions for subsitution with thioacetates. There remains another synthesis of this class of compounds which, like the second method, involves substitution reactions in order to place the thiol groups. This synthesis will be discussed and expanded in this thesis.

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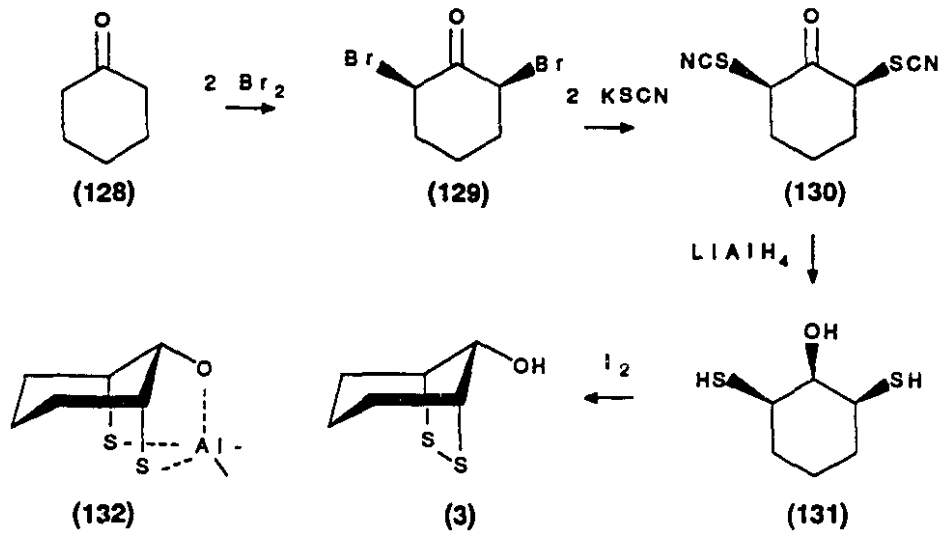
126. S. Kolly, H. Meier, G. Rihs and T. Winkler, *Helv. Chem. Acta*, **71**, 1101 (1988).

2.2 Results and Discussion

2.2.1 Synthetic Methodology and Structure

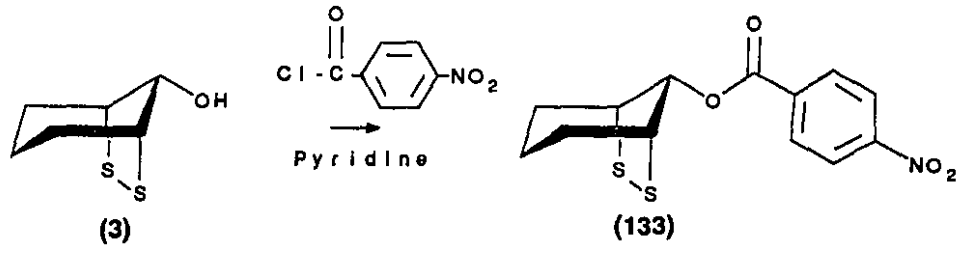
One of the simplest methods for the synthesis of bridged bicyclic disulfides begins with readily available compounds, involves only 4 steps and allows for modifications in the bicyclic structure.[6] The synthesis of bridged bicyclic disulfide **3** (Scheme 12) was the first reported using this procedure. The starting material, cyclohexanone **(128)** was dibrominated to give *cis*-2,6-dibromocyclohexanone **(129)** which was converted to the dithiocyanato compound **(130)** by a nucleophilic displacement with two equivalents of potassium thiocyanate. This species was fully reduced to disulfide alcohol **131** with excess $LiAlH_4$ and immediately oxidized (without workup) to disulfide **3** with I_2 under high dilution conditions. A chelated imtermediate, like **132**, formed during the reduction step was proposed in order to predict the stereochemistry of **3** to be as shown.[6] This was not, however, unambigously determined, nor was the possibility of extending this reaction to further bicyclic systems. Given the potential of this methodolgy to produce bridged bicyclic disulfides in a relatively simple way it seemed appropriate to further explore its use for a thorough investigation into this unique class of compounds.



Scheme 12

The first objective was to determine, with certainty, the stereochemistry at C8 and also to confirm the monomeric nature of **3**. An X-ray crystallographic investigation was thus initiated. Crystals of **3** that were suitable for X-ray analysis could not be obtained, thus derivatization of the hydroxy group was performed in hopes of enhancing the crystallinity of this compound.

Esterification of **3** with *p*-nitrobenzoyl chloride in pyridine provided ester **133** as a bright yellow solid (Scheme 13). Recrystallization from ethanol gave clear yellow prisms which were suitable for X-ray analysis. The ORTEP diagram of **133** is shown in Figure 4. The *p*-nitrobenzoyl ester is clearly in the equatorial position, *syn* to the disulfide linkage. This supports the existence of the proposed chelated intermediate **(132)** in the reduction of **129**.



Scheme 13

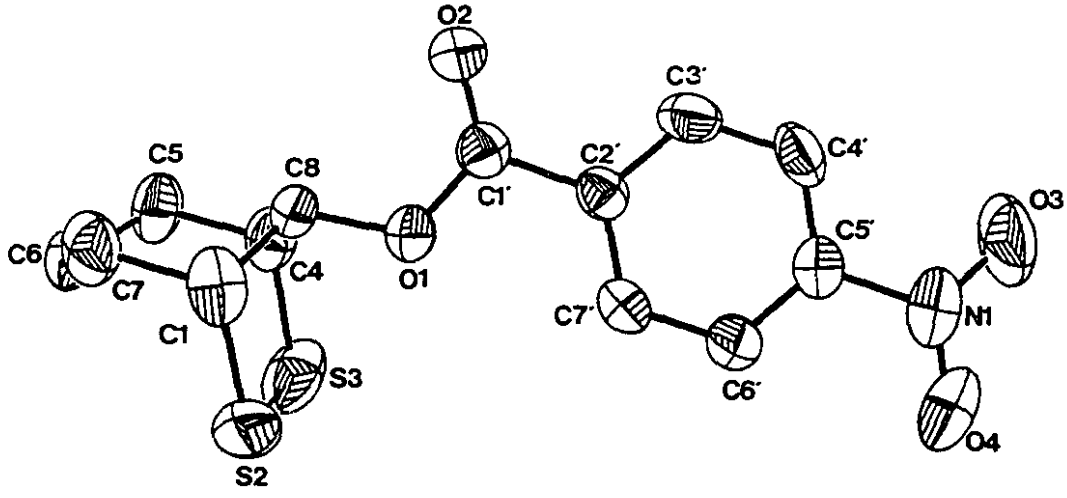


Figure 4: ORTEP Drawing of 133

The dihedral angle about the S-S bond in **133** was 1.3°; as expected, near 0°. The S-S bond length was normal for cyclic disulfides at 2.08Å. The UV absorption for the disulfide group could not be determined due to the broadness of the *p*-nitrobenzoate absorption. Molecular

modelling *via* MMX calculations using the PCMODEL program[127] was also performed on compound **133**. A comparison between some values obtained from the X-ray structure and the calculated structure is given in Table 2. The agreement is remarkably good.

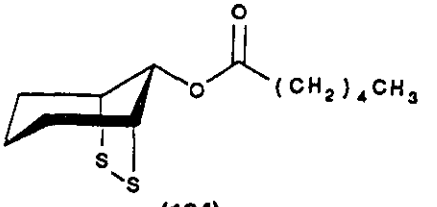
Table 2: Experimental *vs* Calculated Values for Bond Lengths, Bond Angles and Torsion Angles in 133

	Expt'l	Calc'd
Bond Lengths (Å)		
S2-S3	2.081(2)	2.07
C1-S2	1.807(4)	1.83
C4-S3	1.796(4)	1.83
C8-C1	1.511(6)	1.54
C8-C4	1.489(6)	1.54
C8-O1	1.432(5)	1.42
Bond Angles (°)		
C1-S2-S3	95.5(1)	96.74
C4-S3-S2	94.8(1)	96.71
S2-C1-C8	106.5(3)	105.09
S2-C1-C7	113.4(3)	110.46
S3-C4-C5	112.1(3)	110.22
S3-C4-C8	107.2(3)	105.15
C1-C8-C4	106.5(3)	108.04
Torsion Angles (°)		
C1-S2-S3-C4	-1.3(2)	0.29
S3-S2-C1-C8	-28.2(3)	-29.12
S3-S2-C1-C7	89.5(3)	88.51
S2-S3-C4-C8	31.3(3)	28.58
S2-S3-C4-C5	-90.1(3)	-88.99

One other analogue of bicyclic disulfide **3** was synthesized *via* derivatization of the hydroxy group. This was the *n*-hexanoyl ester **134**, prepared following the same procedure as for ester **133**. Compounds **3**, **134** and the thiosulfinate ester of **134** (discussed in greater detail later) were all subjected to a wide range of biological testing. The microorganisms these compounds were tested against are listed in Table 3. It was hoped that the presence of the long hydrocarbon

127. This program was obtained from Dr. K. Steliou (University of Montreal) and is generally available from Serena Software, P. O. Box 3076, Bloomington, Indiana, USA 47402-3076.

chain on **134** would increase its likelihood of mimicking the action of prostaglandin endoperoxides (like **78**). Unfortunately, no significant activity was found against any of the organisms in Table 3 (See General Methods, Section 6.1, for details on the biological testing).



(134)

Table 3: Microorganisms for Biological Testing[a]

Gram Positive Bacteria	**Gram Negative Bacteria**
Staphylococcus aureus	*Escherichia coli*
Staph. epidermis	*Pseudomonas aeruginosa*
Strepococcus pyogenes	
Strep. Faecalis	
Fungi	**Virus**
Candida albicans	Polio
	HIV
Mycobacteria	
Mycobacterium Bovis (BCG Strain)	

[a]See Section 6.1 for details

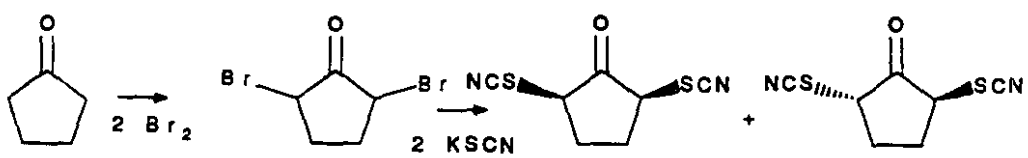
2.2.2 [2.2.1] and [4.2.1] Bridged Bicyclic Disulfides

The extension of this methodology to the synthesis of the [2.2.1] and [4.2.1] bicyclic systems was the next goal. This required making *cis*-2,5-dibromocyclopentanone **(135)** and *cis*-2,7-dibromocycloheptanone **(136)**. The preparation of α,α'-dibromocycloalkanones was reported

by Hoffmann in 1974.[128] Specifically, stereoisomeric α,α'-dibromocycloalkanones from C_6 to C_{12} were synthesized and their physical and spectroscopic properties investigated. In general, it was found that the *cis* isomers had higher melting points and higher IR stretching frequencies and were more polar as well as less soluble than the *trans* isomers which were considered to be conformationally more mobile. The syntheses were performed in anhydrous ether at temperatures ranging from 0-5°C with two equivalents of bromine being added to the appropiate cycloalkanone very slowly and dropwise. The synthesis of **135** was the only one carried out in glacial acetic acid. High dilution conditions had to be maintained for the synthesis of **129**. Only one isomer was isolated from the synthesis of **135** and **136**. Although the assigments were not absolute, it was suggested that both products were in the *trans* configuration based on their melting points, solubility and IR absorptions. An earlier report[129] had implied the existence of the *cis* isomers of **135** and **136**, however, no experimental details were provided.

In this work, the synthesis for compound **129** was found to proceed best using water as the solvent. All attempts using anhydrous ether resulted in the formation of a wine-red solution that would yield no crystals. The *cis* isomer crystallized out of a solution of ether:petroleum ether (6:1) upon sitting at -10°C. The *trans* isomer could not be induced to crystallize. These results were consistent with those of Hoffmann.[128]

The synthesis of **135** was performed following the procedure of Hoffman;[128] the synthesis of **136** was executed using the same procedure as for **135** instead of that suggested by Hoffmann (glacial acetic acid was used as the solvent instead of ether). Only one isomer was isolated from the synthesis of **135** from cyclopentanone **(137)** (Scheme 14). This product had the same melting point as that recorded in the literature which had been assigned as the *trans* isomer.[128,130]



(137) **(135)** **(138a)** **(138b)**

4 1

Scheme 14

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128. H. M. R. Hoffmann and J. G. Vinter, *J. Org. Chem.*, **39**, 3921 (1974).

129. R. H. Prager and J. M. Tippett, *Tetrahedron Lett.*, 5199 (1973).

130. PCMODEL (Ref 127) predicts the *trans* isomer to be more stable than the *cis* isomer by 0.7 kcal/mol.

Compound **135** was reacted with two equivalents of potassium thiocyanate in dry acetone at room temperature to provide a mixture of two isomeric 2,5-dithiocyanatocyclopentanones (**138a** and **138b**) in quantitative yields (Scheme 14). This crude product was analyzed by ^{1}H NMR spectroscopy and was found to contain a ratio of 4:1 of **138a** and **138b**. The multiplet for H2 and H5 of **138a** was centered at 3.99 ppm and that of **138b** was centered at 3.74 ppm. Recrystallization of the crude solid from pentane:$CHCl_3$ (10:1) resulted in the isolation of fine yellow crystals of **138a**. The mother liquor was evaporated to yield a yellow gum that was found to contain mainly **138b**. Since the *cis* isomer was required for the synthesis of the bridged bicyclic disulfide, it was necessary to absolutely determine the configuration of the two thiocyanato groups in this molecule; **138a** was thus subjected to an X-ray crystallographic investigation. The ORTEP drawing for **138a** is shown in Figure 5 and it is very clear that the thiocyanato groups were indeed *cis* to each other. The pure cystals of **138a** were thus used to carry out the synthesis of [2.2.1] bridged bicyclic disulfides.

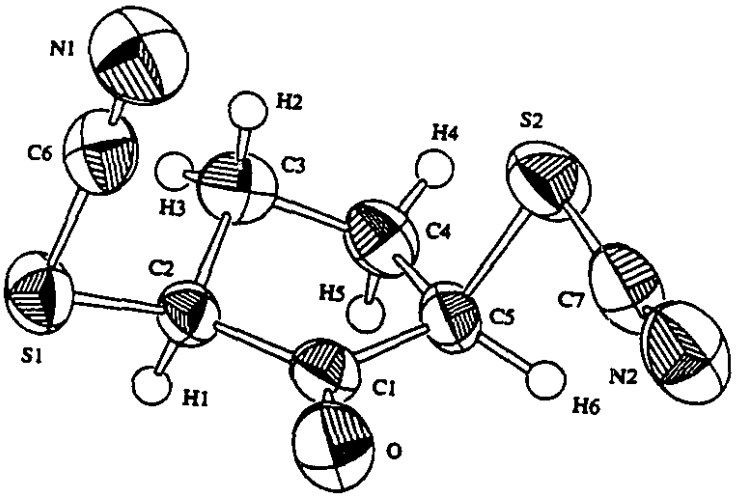
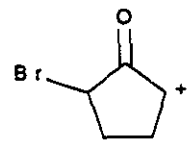


Figure 5: ORTEP Drawing of 138a

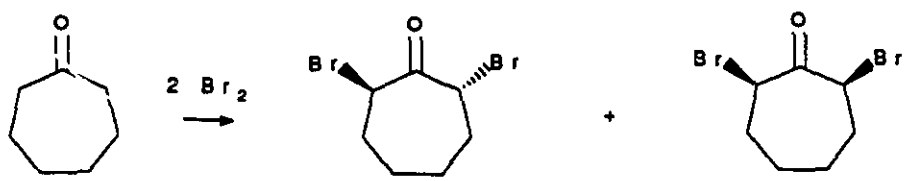
It is interesting to note that both the *cis* and *trans* isomers of **138** were isolated from one isomer of **135**. Although this may suggest a small amount of S_n1 substitution occurring *via* cation **139**, more likely a second substitution of a thiocyanato group by another thiocyanate nucleophile through a S_n2 mechanism is the explanation for the formation of a small amount of the *trans* isomer. This proposal was confirmed by a simple experiment. The addition of KSCN to **138a** under the same conditions used for the inital substitution reaction caused isomerization and resulted in the isolation of a mixture containing both **138a** and **138b**. This implies that the ease for S_n2 subtitution at the α-position from a ring carbonyl increases as ring size decreases, a proposal that is supported by the fact that the substitution reaction involving 2,7-dibromocycloheptanone required refluxing temperatures to force it to proceed to completion. The formation of the *cis*

isomer as the major species in the synthesis of **138** confirms that the configuration of the bromine atoms in **135** was also *cis*.



(139)

Contrary to the results of Hoffmann,[128] the bromination of cycloheptanone (**140**) in glacial acetic acid provided two isomeric 2,7-dibromocycloheptanones, (**136a**) and (**136b**), in a ratio of 2:1 (Scheme 15). The quartet for H2 and H7 of **136a** was at a higher frequency (4.71 ppm) than that of **136b** (4.61 ppm). Recrystallization from petroleum ether:ethyl acetate (1:1) provided fine white crystals of **136a**. Although crystals of **136a** that were suitable for X-ray crystallography could not be obtained, the identity of each isomer may be deduced from further experimental work. The melting point, ^{1}H NMR spectrum and IR data for **136a** all match the literature values reported by Hoffmann[128] who had assigned this compound as the *trans* isomer. Although a sample of **136b** that was not contaminated with **136a** could not be obtained, its carbonyl stretching frequency in the IR was found to be at a smaller wavenumber that that of **136a**.[131] Following the trends reported by Hoffmann, this would suggest that **136a** was the *trans* isomer and **136b**, the *cis* isomer. This was also supported by the fact that using only pure **136a** to continue on with the synthesis of a [4.2.1] bridged bicyclic disulfide did not produce any of the desired compound whereas using the crude mixture containing **136a** and **136b** was successful in this goal.[132]



(140) **(136a)** **(136b)**

2 **1**

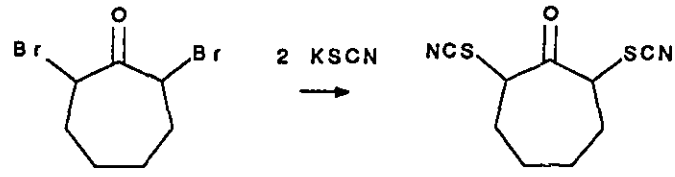
Scheme 15

Reaction of the mixture of **136a** and **136b** with two equivalents of potassium thiocyanate in dry acetone at refluxing temperatures provided a isomeric mixture of 2,7-dithiocyanatocycloheptanones (**141a** and **141b**) (Scheme 16). The ratio of *cis* to *trans*

131. Carbonyl stretching frequency for **136a**: 1728 cm^{-1}; **136b**: 1701 cm^{-1}.

132. PCMODEL (Ref 127) predicts the *trans* isomer to be more stable by 12.9 kcal/mol.

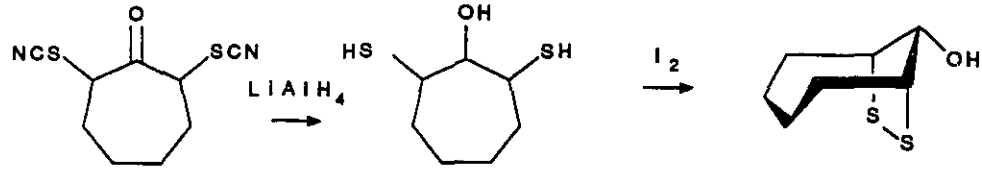
(**141a**:**141b**) remained the same as in the crude mixture of **136a** and **136b**.



(136a and b) **(141a and b)**

Scheme 16

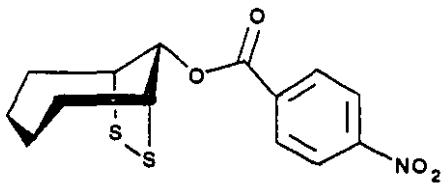
The synthesis of the desired [4.2.1] bridged bicyclic disulfide was relatively straightforward once identification of the isomers was made. Thus, a mixture containing both **141a** and **141b** was reduced with excess $LiAlH_4$ to obtain dithiol alcohol **142** which was oxidized without workup to *syn*-2,3-dithiabicyclo[4.2.1]nonan-9-ol **(143)** (Scheme 17). Based on the amount of **141b** that was present in the initial reaction mixture, the yields of **143** ranged from 60-70%. This was much better than the yields of **3** which rarely were above 50%. The major sideproduct in the oxidation reaction was a polymeric material formed by intermolecular rather than intramolecular oxidation of the thiol groups. High dilution conditions were used in order to minimize intermolecular reactions. The larger size of disulfide **143** over **3** helped to favour intramolecular oxidation and thus increased the yield of the desired product. The UV absorption for the disulfide group in **143** was at 357 nm, confirming the presense of a small dihedral angle in this molecule (See Table 1).



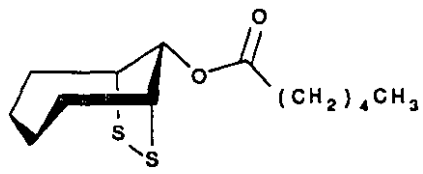
(141a and b) **(142)** **(143)**

Scheme 17

The *p*-nitrobenzoyl **(144)** and *n*-hexanoyl **(145)** esters of **143** were also synthesized to be used in a comparative study on their reactivity with their [3.2.1] bridged bicyclic disulfide analogues (to be described later). These derivatizations were again performed by reaction of the alcohol with the acid chloride in pyridine.

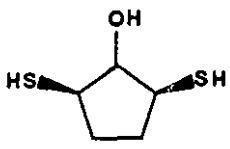


(144)

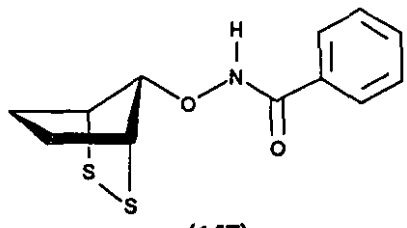


(145)

The synthesis of the [2.2.1] bridged bicyclic disulfide was not as straightforward as the previous two analogues. Reduction of **138a** was easily performed using an excess of $LiAlH_4$ to give the foul-smelling dithiol alcohol **146**. All attempts to oxidize **146** even under very dilute conditions (1.6 mM) only led to the isolation of polymeric products. This polymerization took place once the product was concentrated to dryness and is a common problem in many examples of the isolation of 1,2-dithiolanes (see Introduction). An attempt at making the phenyl aminocarbonyl ester **(147)** of the product following a procedure used for the isolation of 4-hydroxy-1,2-dithiolane **(14)**[34b] was made before concentration in hopes of preventing polymerization; however, this synthesis was not successful.

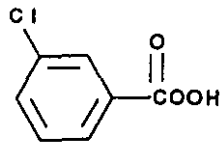


(146)

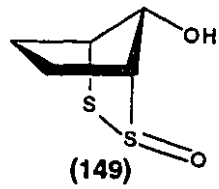


(147)

It was hoped that the trend for cyclic thiosulfinate esters of disulfides to be more stable than their corresponding disulfides might provide a means for the isolation of a [2.2.1] bridged bicyclic species. The reactions were repeated starting from the dithiocyanato compound **(138a)** following identical procedures to those used in the other systems; however, once the iodine oxidation was complete, the product was never allowed to sit in a concentrated solution. The solvent for oxidation was ether and this was removed under reduced pressure at room temperature until about 100 millilitres remained. Methylene chloride was then added and the remaining ether carefully removed. Oxidation of the disulfide to thiosulfinate was performed immediately using one equivalent of *m*-CPBA **(148)** at 0°C leading to the isolation of *syn*-2,3-dithiabicyclo[2.2.1]heptan-7-ol *S*-oxide **(149)**. This compound was a white solid and was able to be chromatographed on silica gel; further details concerning the reactivity and stability of **149** are reported in the next section.



(148)



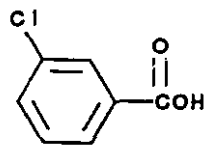
(149)

2.2.3 Bridged Bicyclic Thiosulfinate Esters

(I) Synthesis and Structure

Electrophilic oxidation using *m*-CPBA **(148)** was used as a means to probe the reactivity of the bridged bicyclic disulfides prepared in this work. To the best of our knowledge, there have been no previous reports of bridged bicyclic thiosulfinate compounds, thus we had at hand an opportunity to explore the chemistry of an entire new class of compounds.

All oxidations of bridged bicyclic disulfide compounds were performed in methylene chloride at 0°C under a nitrogen atmosphere, with the addition of one equivalent of *m*-CPBA **(148)**. The *m*-CBA **(149)** formed as a side product was separated by washing with dilute sodium bicarbonate or by column chromatography. All reactions of bicyclic disulfides with *m*-CPBA proceded with excellent yields (>90%).



(149)

Thiosulfinate esters are chiral at the sulfinyl sulfur atom, thus there was the possibility of obtaining four different stereoisomers during the oxidation of bridged bicyclic disulfides (Figure 6). Attack of the oxidizing agent could occur from two possible directions to give two diastereomers. The side nearest the hydroxy functionality has been labelled as the *exo* face and that nearest the carbon ring, the *endo* face. The two diastereomers, *exo* and *endo*, will each have two enantiomers. The enantiomers will have identical NMR spectra, whereas those of the diastereomers will be significantly different.

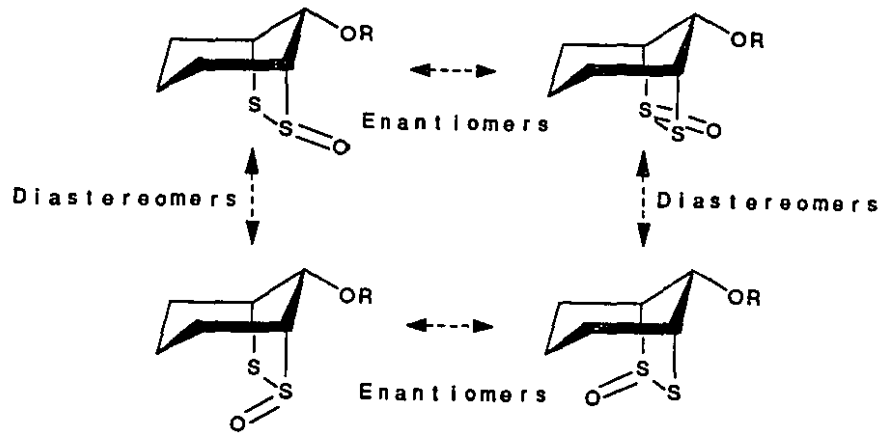
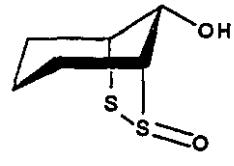
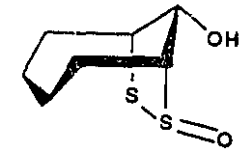


Figure 6: Isomers of Bridged Bicyclic Thiosulfinates

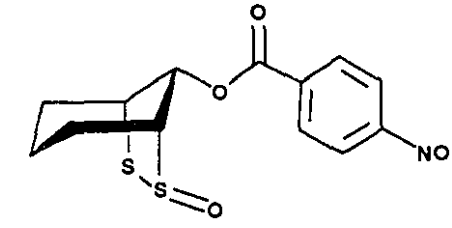
The oxidation of [3.2.1] and [4.2.1] underivatized bridged bicyclic disulfides, **3** and **142**, proceeded with the formation of only one diastereomer, thiosulfinates **150** and **151**, respectively. The exact orientation of the oxygen on the sulfinyl sulfur could not be easily established from spectroscopic data. The oxidation of **133** also produced only one diastereomeric thiosulfinate (**152**) which was shown (through comparisons of the spectroscopic data) to be identical to that synthesized *via* derivatization of **150** with *p*-nitrobenzoyl chloride; thus oxidation of **3** and **133** occurred on the same face of the disulfide. In order to establish the preferred direction for oxidation, the crystalline thiosulfinate **152** was subjected to X-ray crystallographic analysis. The ORTEP drawing of this compound is shown in Figure 7. Some of the important bond lengths, bond angles and torsion angles are presented in Table 4 along with the corresponding calculated values obtained from the PCMODEL program.[127] The agreement is again seen to be exceptionally good.



(150)



(151)



(152)

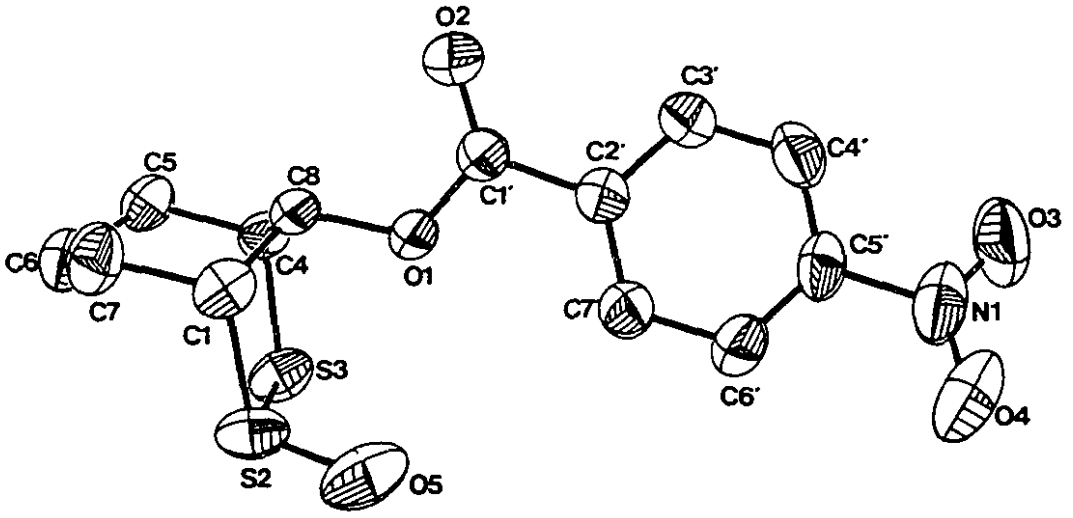
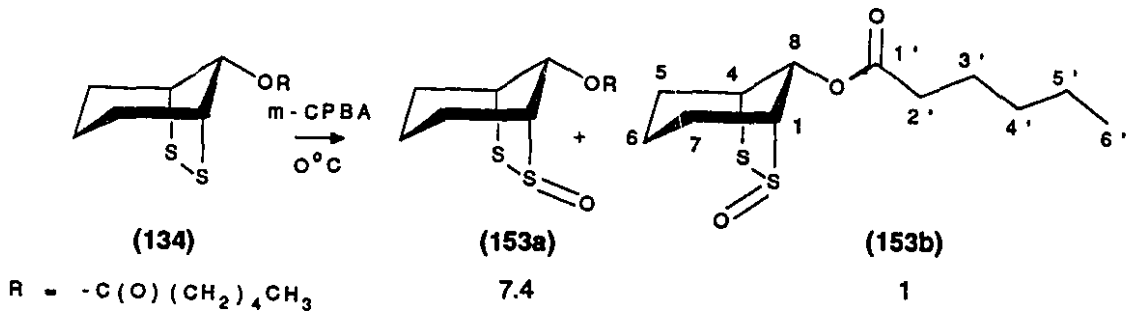


Figure 7: ORTEP Drawing of 152

The isomer that was obtained in the oxidation of **3** and **133** was the *exo* diastereomer (Figure 7). It appears that attack from the *endo* face was blocked by the ring hydrogens. The only example of a [3.2.1] bicyclic thiosulfinate where a small amount of the *endo* isomer was obtained was in the oxidation of the *n*-hexanoyl ester **(134)** (Scheme 18). Here, the *exo* isomer **(153a)** was the major species by a ratio of 7.4:1. The presence of the long hydrocarbon chain caused some blockage of the *exo* face, thus allowing some attack to occur from the *endo* face to give diastereomer **153b**.



(134) **(153a)** **(153b)**

R = $-C(O)(CH_2)_4CH_3$ 7.4 1

Scheme 18

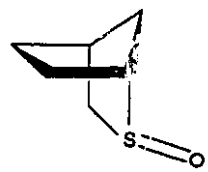
Table 4: Experimental and Calculated Values for Bond Lengths, Bond Angles and Torsion Angles in 152

	Expt'l	Calc'd
Bond Lengths (Å)		
S2-S3	2.100(2)	2.06
C1-S2	1.847(5)	1.83
C4-S3	1.835(5)	1.85
C8-C1	1.503(6)	1.54
C8-C4	1.499(6)	1.54
C8-O1	1.445(4)	1.42
S2-O5	1.494(3)	1.45
Bond Angles (°)		
C1-S2-S3	93.4(1)	96.83
C4-S2-S3	96.4(1)	95.71
S2-C1-C8	108.0(3)	105.90
S2-C1-C7	110.5(3)	112.27
S3-C4-C5	110.8(3)	109.96
S3-C4-C8	106.9(3)	106.78
C1-C8-C4	107.2(3)	106.19
O5-S2-S3	108.9(2)	108.14
Torsion Angles (°)		
C1-S2-S3-C4	1.5(2)	1.82
S3-S2-C1-C8	-30.5(2)	-31.11
S3-S2-C1-C7	89.1(3)	87.91
S2-S3-C4-C8	27.6(2)	27.84
S2-S3-C4-C5	-91.2(3)	-91.02
O5-S2-S3-C4	-109.2(6)	-107.96
O5-S2-C1-C8	80.7(3)	80.11
O5-S2-C1-C7	-159.6(3)	-160.87

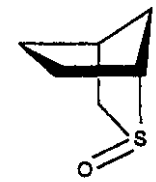
Diastereomers **153a** and **153b** were separated using column chromatography. The assignment of *exo* and *endo* to these compounds was done by comparing their NMR data with those previously synthesized (**150** and **152**) and was supported by their chromatographic retention times. One method used for the assignment of the *exo* and *endo* isomers of 2-thiabicyclo[2.2.1]heptane (**154a** and **154b**) was based on their chromatographic behavior.[133] Retention times for chromatography were correlated with the accessibility of the oxygen on the

133. C. R. Johnson, H. Diefenbach, J. E. Keiser and J. C. Sharp, *Tetrahedron*, **25**, 5649 (1969).

sulfoxide for interaction with the stationary phase. The *endo* oxygen **(154b)** was less accessible than the *exo* **(154a)** and it eluted first. In this work, the *endo* isomer **(153b)** clearly has the less accessible oxygen and accordingly, it eluted from the column first.



(154a)



(154b)

Isomerization of **153a** to **153b** could also be achieved by heating a neat sample of **153a**. When this was done at 130°C for 30 minutes a mixture containing roughly 2:1 **153a**:**153b** was obtained. Further equilibrium studies will be discussed in the next section on the stability of these compounds.

The ^{1}H, ^{13}C and IR spectra were clearly different for isomers **153a** and **153b**. Table 5 lists the relevant spectral data for these two compounds. The MS data were virtually identical with only a few minor differences in the fragmentation pattern.

The [4.2.1] bridged bicyclic thiosulfinate **(151)** was a crystalline compound, thus an X-ray structure was used to determine the preferred orientation for the sulfinyl oxygen in these compounds. This molecule had a large amount of packing disorder in the region from C5-C8 which was only partially resolved by the structure refinement program (See Experimental, Chapter 6). This resulted in high agreement factors; $R = 0.079$, $R_w = 0.083$. The important region about the sulfur-sulfur bond and the bridgehead areas were all well-resolved and thus provided an accurate representation of the positioning of these atoms. There were two independent molecules of **151** in the unit cell, both with the same stereochemistry about the sulfinyl sulfur atom. The ORTEP drawing for molecule B of **151** is shown in Figure 8. Once again, the *exo* isomer was the only diastereomer formed. This was also true for the oxidation of disulfides **144** and **145**, from which thiosulfinates **154** and **155** were isolated respectively.

Table 5: Spectral Data for Thiosulfinates 153a and 153b

	153a	153b
^{1}H NMR[a] ($CDCl_3$, 200 MHz)δ:		
H1	4.62 (s)	4.18 (s)
H4	4.11 (s)	3.94 (s)
H8	5.51 (t)	5.47 (t)
^{13}C NMR ($CDCl_3$, 300 MHz)δ:		
C1	74.9	67.2
C4	59.5	58.1
C5	30.2	30.7
C6	17.5	16.7
C7	34.1	34.1
C8	83.0	82.0
C1'	173.5	172.7
C2'	31.2	31.1
C3'	24.8	24.4
C4'	24.2	22.6
C5'	22.2	22.2
C6'	13.9	13.8
IR (Neat, NaCl) cm^{-1}:		
C=O stretch	1743	1734
S=O stretch	1084	1088

[a] Only bridgehead and C8 protons are given due to complexity of the alkyl region; bridgehead proton signals were broad.

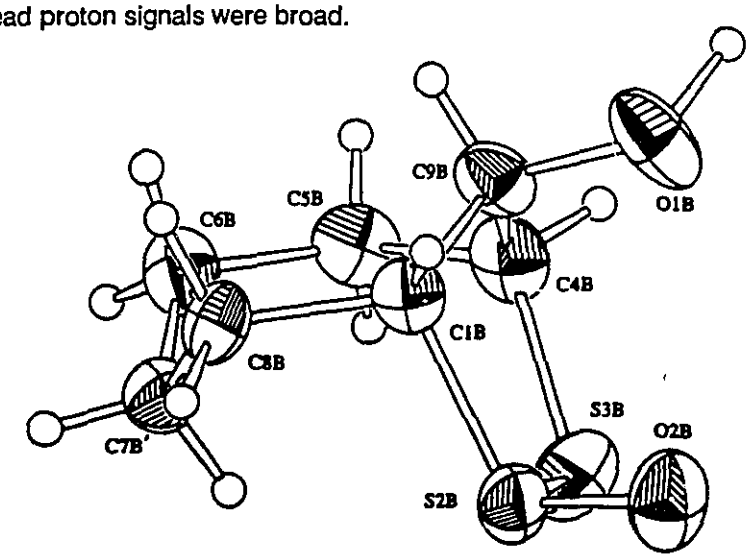
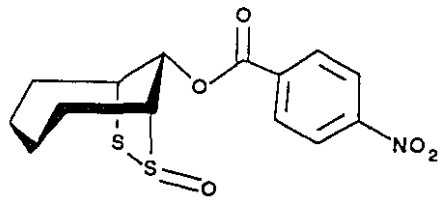
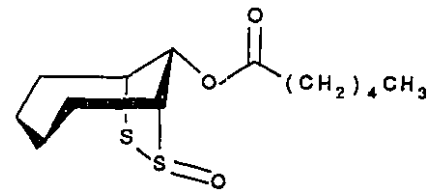


Figure 8: ORTEP Drawing of Molecule B of 151



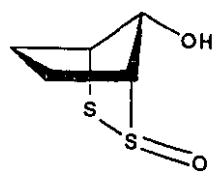
(154)



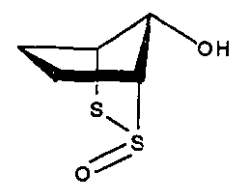
(155)

Some of the important bond lengths, bond angles and torsion angles for compound **151** are listed in Table 6. The molecular modelling results using PCMODEL[127] were in good agreement for the values of the bond lengths and the bond angles. The calculated torsion angles closely matched those of molecule B, however they were of the opposite sign, indicating they were opposite enantiomers.

As mentioned at the end of the last section, the [2.2.1] bridged bicyclic thiosulfinate ester **149** was synthesized successfully. The formation of both the *exo* **(149a)** and *endo* **(149b)** isomers was confirmed in the ^{1}H NMR and ^{13}C spectra. These two isomers could not be separated but the *exo* isomer was the major species by a ratio of 4:1 based on the integration of the ^{1}H spectrum. The smaller carbon ring in these species does not hinder the *endo* face as much as in the [3.2.1] and [4.2.1] examples, thus allowing for the formation of a significant amount of the *endo* thiosulfinate.



(149a)



(149b)

Table 6: Selected Bond Lengths, Bond Angles and Torsion Angles for the Two Crystallographically Independent Molecules of 151

	A	B	Calc'd
Bond Lengths (Å):			
S2-S3	2.070(4)	2.079(4)	2.04
C1-S2	1.847(9)	1.856(9)	1.83
C4-S3	1.84(1)	1.82(1)	1.85
C9-C1	1.51(1)	1.52(1)	1.54
C9-C4	1.50(1)	1.52(1)	1.54
C9-O1	1.43(1)	1.41(1)	1.42
S2-O2	1.465(6)	1.477(6)	1.45
Bond Angles (°):			
C1-S2-S3	93.0(3)	93.7(3)	97.42
C4-S3-S2	99.3(3)	100.0(3)	98.59
S2-C1-C9	107.6(7)	107.6(6)	108.21
S2-C1-C8	108.8(7)	106.7(6)	111.09
S3-C4-C5	109.6(9)	112.1(7)	110.62
S3-C4-C9	107.4(7)	106.5(6)	107.95
C1-C9-C4	112.0(9)	112.3(9)	111.88
S3-S2-O2	109.8(3)	110.3(3)	109.38
Torsion Angles (°):			
C1-S2-S3-C4	-13.1(5)	6.4	-4.57
S3-S2-C1-C9	35.5(7)	-29.9(6)	26.32
S3-S2-C1-C8	-91.0(7)	96.8(5)	-99.30
S2-S3-C4-C9	-11.3(7)	17.9(7)	-17.94
S2-S3-C4-C5	117.2(7)	-110.8(7)	108.50
O2-S2-S3-C4	100.9(5)	-104.6(5)	107.57
O2-S2-C1-C9	-77.1(7)	82.9(7)	-86.85
O2-S2-C1-C8	156.4(7)	-150.4(6)	147.53

(ii) Stability

The enhanced stability of cyclic over acyclic thiosulfinate esters discussed in the Introduction (Chapter 1) brings about the question of the stability of bridged bicyclic thiosulfinate esters. It has already been noted in this work that the bridged bicyclic disulfides were readily oxidized under electrophilic oxidizing conditions to their corresponding thiosulfinate esters. This may suggest that replacing a lone pair of electrons with an oxygen atom decreases the repulsion between the nonbonding pairs of electrons that are forced to be parallel to each other due to the

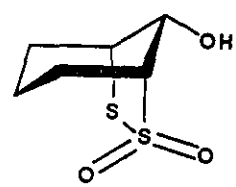
dihedral angle of 0° about the sulfur-sulfur bond imposed by the bicyclic structure. This proposal has been made previously and was discussed in the Introduction.

The thiosulfinates synthesized in this work (except **149**) were all very stable compounds that could be left at room temperature in the light for several weeks without any sign of decompostion. They had no odor and were easily purified by column chromatography on silica gel.

Isomerization between the *exo* and the *endo* isomers of these bridged bicyclic thiosulfinates occured under certain circumstances. One of the most readily isomerized thiosulfinates was **153a**. As mentioned previously, heating of this compound (neat) caused isomerization to occur. A solution of **153a** in $CDCl_3$ left on the bench for several months was shown to contain an equal mixture of **153a** and **153b**. This suggests that the energy difference between the two isomers is not great and that the product of *m*-CPBA oxidation was most certainly the kinetic product. Thiosulfinate **150** could also be induced to isomerize. Refluxing a solution of **150** at 80°C for 24 hours gave a mixture containing about 1.2:1 *exo*:*endo* isomers (**150a**:**150b**, Scheme 19), along with a small amount (8%) of the thiosulfonate **156**[134] as determined from the ^1H NMR spectrum. Again, the two isomers appear to be of approximately the same energy, with the *exo* being slightly more favoured. These two isomers could not be separated using column chromatography.

(150a) ⇌ **(150b)**

Scheme 19



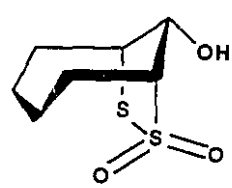
(156)

134. Thiosulfinates are known to disproportionate into thiosulfonates and disulfides (ref. 105). Any disulfide formed in this experiment likely polymerized due to the high temperatures used. A small amount of dark gum along the bottom of the flask provided support for this proposal.

Thermal isomerization of [4.2.1] bridged bicyclic thiosulfinate **151** produced very different results from the isomerization of the corresponding [3.2.1] species (**150**). After refluxing in toluene (110°C) for 24 hours,[135] ^{1}H NMR evidence indicated that the ratio of *exo*:*endo* (**151a**:**151b**) was 6:1 (Scheme 20). Again, a small amount (8%) of thiosulfonate **157** was also seen. It was thought that isomerization of **151** might be induced photochemically so a solution in toluene was stirred under a UV lamp for 8 hours. ^{1}H NMR analysis of the resulting mixture, however, indicated that ratio of **151a**:**151b** had not changed.

(151a) **(151b)**

Scheme 20



(157)

Heating a sample of the [2.2.1] bridged bicyclic thiosulfinate caused decomposition, thus isomerization studies could not be performed.

The most likely mechanism for this isomerization would involve homolysis (induced either thermally or photochemically) of the S-S bond with the formation of a stable sulfinyl radical and a sulfenyl radical which, in a solvent cage, could recombine in give the mixture of isomers (Scheme 21). This mechanism has been previously proposed by Fava[106] to explain the isomerization of diaryl thiosulfinates (Scheme 1, Chapter 1). The co-planar rearrangement proposed by Block[105] (Scheme 2, Chapter 1) is not possible for bridged bicyclic thiosulfinates. The isomerization of the [3.2.1] thiosulfinates to provide roughly an equal amount of each isomer suggests that the energy difference between the two is not great. The resistance to isomerization displayed by the [4.2.1] thiosulfinates suggests that the *exo* isomer is energetically more favoured.

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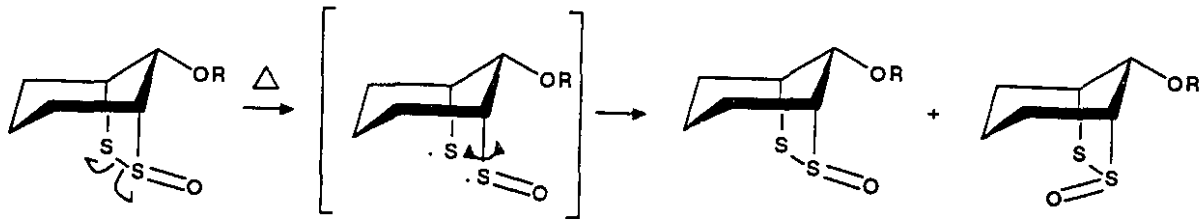
135. Refluxing at 80°C (benzene) produced no change.



Scheme 21

Molecular modelling using PCMODEL[127] was also been performed on these compounds to see if it could predict the correct energetics for each isomer and to examine the possibility that the lack of isomerization of compound **151** could be explained by a large energy difference between the *exo* and *endo* isomers of this compound. Table 7 lists the calculated energy differences ($\Delta\Delta H_f$) between the *exo* and *endo* isomers of various bridged bicyclic thiosulfinates. Within the experimental error of these calculations it is not possible to predict which of the two isomers would be the more stable for the [3.2.1] and [4.2.1] examples, however these results do imply that the *endo* isomer is more stable than the *exo* isomer in the [2.2.1] bridged bicyclic thiosulfinates.

Table 7: Calculated $\Delta\Delta H_f$ for Bridged Bicyclic Thiosulfinates ($\Delta H_{f(exo)}$ - $\Delta H_{f(endo)}$, kcal/mol)

149 [2.2.1]	14.2
150 [3.2.1]	1.2
151 [4.2.1]	0.3

A detailed thermodynamic study into the stability of these compounds is beyond the scope of this thesis. It can be stated, however, that the bridged bicylcic thiosulfinate esters are very stable compounds especially when compared with their acyclic counterparts. Their ability to isomerize seems to increase from [4.2.1] to [3.2.1] species. A further look into the chemical reactivity of these compounds is described in the next chapter where their electrophilic oxidation to bridged bicyclic thiosulfonate esters is described.

2.3 Conclusion

The synthesis of bridged bicyclic disulfides using the procedure of Wilson[6] has been

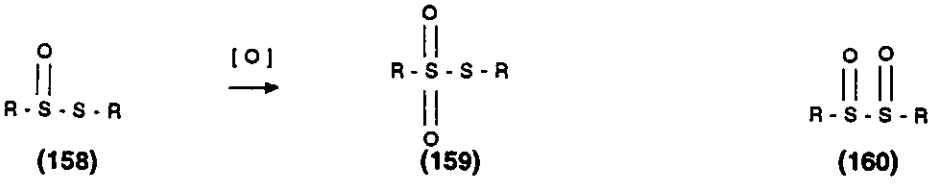
successfully applied to [2.2.1], [3.2.1] and [4.2.1] species. Further derivatives of [3.2.1] and [4.2.1] bicyclic disulfides have been synthesized *via* derivatization of the hydroxy group. All of the disulfides synthesized have been oxidized to their corresponding thiosulfinate esters using *m*-CPBA; a reaction that proceeds with high yields. The thiosulfinate esters were shown to be very stable compounds especially compared to their acyclic counterparts. Preliminary isomerization experiments have been performed.

CHAPTER 3: LOW TEMPERATURE *m*-CPBA OXIDATION OF BRIDGED BICYCLIC THIOSULFINATES

3.1 Introduction

3.1.1 α-Disulfoxides

The electrophilic oxidation of thiosulfinates **(158)** to thiosulfonates **(159)** using peracids has been well investigated (Scheme 22).[136] Early structural assignments for the product of thiosulfinate oxidation had the second oxygen entering on the sulfenyl sulfur atom to give a *S,S'*-dioxide or α-disulfoxide **(160)**.[137] Later work using dipole moments and Raman spectroscopy[138] and also from NMR spectra[139] fully confirmed that the actual oxidation product was the *S,S*-dioxide or thiosulfonate **(159)**. The thiosulfonate structure has been shown to be the more stable of the two by theoretical calculations,[140] infrared and Raman studies[141] and through X-ray crystallography.[142] This does not, however, rule out the possibility of the existence of α-disulfoxides as reaction intermediates.



(158) **(159)** **(160)**

Scheme 22

136. a) P. Allen and J. W. Brook, *J. Org. Chem.*, **27**, 1019 (1962); b) W. E. Savige and J. A. MacLaren, in *The Chemistry of Organic Sulfur Compounds*, Vol. 2, N. Kharasch and C. Y. Meyers, Eds., Toronto: Pergamon Press, Chapt. 15 (1966), and references therein; c) J. Hoyle, in *The Chemistry of Sulfinic Esters and their Derivatives*, S. Patai, Ed., New York: John Wiley and Sons Ltd., Chapt. 4 (1990).

137. a) G. Toennies and T. F. Lavine, *J. Biol. Chem.*, **113**, 571 (1936); b) T. F. Lavine, *J. Biol. Chem.*, **113**, 583 (1936); c) R. Emilozzi and L. Pichat, *Bull. Soc. Chim. Fr.*, 1887 (1959); d) G. E. Utzinger, *Experientia*, **17**, 374 (1961).

138. M. I. Grishko and E. N. Gur'yanova, *Chem. Abstr.*, **52**, 17917 (1958).

139. a) P. Allen, P. J. Berner and E. R. Malinowski, *Chem. and Ind.*, 1164 (1961); b) *Ibid.*, 208 (1963).

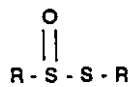
140. F. Freeman, C. N. Angeletakis, W. J. Pietro and W. J. Hehre, *J. Amer. Chem. Soc.*, **104**, 1161 (1982).

141. S. S. Block and J. P. Weidner, *Appl. Spectrosc.*, **20**, 736 (1966), and references therein.

142. J. H. Noordik and A. Vos, *Recl. Trav. Chim. Pays. Bas*, **86**, 156 (1967).

The existence of α-disulfoxides has been a point of much controversy. A review by Freeman[143] presents a thorough account of the evidence published concerning this matter prior to 1984. Freeman concludes from this survey that transient α-disulfoxides are reasonable intermediates in a wide variety of complex reactions involving organosulfur compounds.[143]

Freeman[144] has found direct evidence for the existence of α-disulfoxides in the electrophilic oxidation of symmetrical dialkyl thiosulfinates. In low temperature NMR experiments, signals indicating the presence of diastereotopic α-disulfoxides in the *m*-CPBA **(148)** oxidation of thiosulfinates **161-167** were seen at temperatures below -30°C. An α-disulfoxide would be expected as the first intermediate in these oxidations based on the theory of hard and soft acids and bases (HSAB).[145] The sulfenyl sulfur is expected to be "softer" (*i.e.* more electron rich) than the sulfinyl sulfur, therefore electrophilic oxidation should preferentially occur at this location. The absence of any thiosulfonate in the initial product mixture suggests that the oxidation of thiosulfinate initially occurred exclusively on the sulfinyl sulfur in these examples. The exact pathway for rearrangement and/or disproportionation of α-disulfoxides is still in question.



(161) R = *neo*-C_5H_{11}
(162) R = CH_3
(163) R = *t*-C_4H_9
(164) R = *n*-C_3H_7
(165) R = $C_6H_5CH_2$
(166) R = *i*-C_3H_7
(167) R = *n*-C_4H_9

More recently, Harpp[146] reported strong evidence for the intermediacy of α-disulfoxides in a non-oxidative preparation of thiosulfonates using sulfinyl chlorides and lithium tri-*n*-butyltin (Scheme 23). The tributyl tin anion **168** initially reacted with sulfinyl chloride **169** to give intermediate **170** which reacted with another molecule of sulfinyl chloride, possibly through a four-membered transition state, to give an α-disulfoxide. Peaks were present in the ^{13}C NMR spectrum of the reaction mixture at -55°C that were assigned to the diastereotopic α-disulfoxides. Signals were also found to strongly suggest the intermediacy of a rearrangement species **(171)** formed by

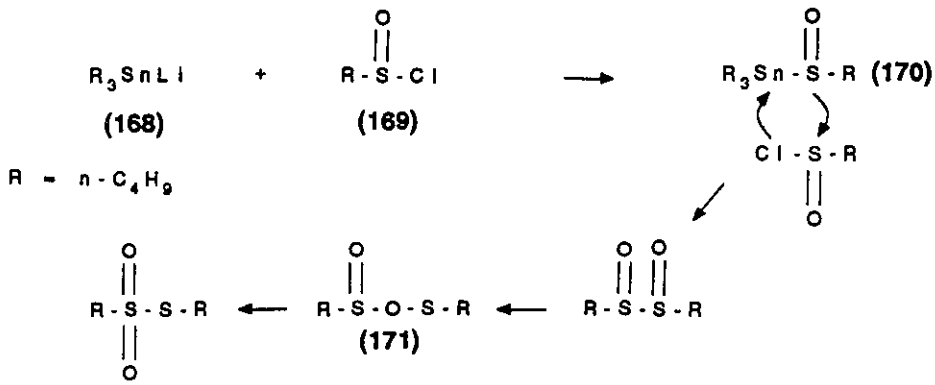
143. F. Freeman, *Chem. Rev.*, **64**, 117 (1984).

144. a) F. Freeman and C. N. Angeletakis, *J. Amer. Chem. Soc.*, **103**, 6232 (1981); b) F. Freeman and C. N. Angeletakis, *J. Amer. Chem. Soc.*, **104**, 5766 (1982); c) F. Freeman and C. N. Angeletakis, *J. Amer. Chem. Soc.*, **105**, 4039 (1983); d) F. Freeman and C. N. Angeletakis, *J. Amer. Chem. Soc.*,**105**, 6232 (1983); e) F. Freeman and C. Lee, *J. Org. Chem.*, **53**, 1263 (1988).

145. R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

146. D. N. Harpp and S. J. Bodzay, *Sulfur Letters*, **7**, 73 (1988).

the attack of either sulfinyl oxygen on the adjacent sulfinyl sulfur atom. This type of species is known as an *O,S*-sulfenyl sulfinate and was also proposed by Freeman[143] as being a viable intermediate. The *O,S*-sulfenyl sulfinate can rearrange to the thiosulfonate product as shown in Scheme 23. This will be discussed in greater detail below.



Scheme 23

3.1.2 Mechanisms for α-Disulfoxide Rearrangement

There have been four mechanisms proposed for the formation of rearrangement or disproportionation products from α-disulfoxides. These include: 1) rapid isomerization *via* *O,S*-sulfenyl sulfinates in a concerted fashion;[147] 2) homolytic cleavage of the S-S bond of the α-disulfoxide to give sulfinyl radicals which can serve as initiators in the disproportionation of thiosulfinate to disulfide and thiosulfonate;[148] 3) homolytic cleavage of the S-S bond of the α-disulfoxide to give sulfinyl radicals which recombine randomly with each other in a head-to-tail fashion to give all possible *O,S*-sulfenyl sulfinates which rearrange to the more stable thiosulfonate[149] and 4) ionic mechanisms involving the hydrolysis of the S-S bond in either the α-disulfoxides or *O,S*-sulfenyl sulfinates leading to sulfinic and sulfenic acids.[143,144]

Mechanism 1 (Scheme 24) was first proposed by Modena and co-workers[147] in 1960. If it were to be operative in any given example, the only possible products of thiosulfinate oxidation would be thiosulfonate; one if the original thiosulfinate was symmetric and two if it were

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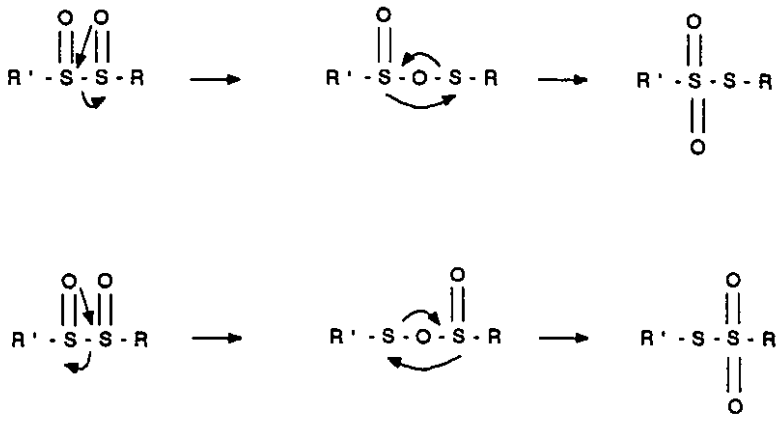
147. U. Marangelli, G. Modena and P. E. Todesco, *Gazz. Chim. Ital.*, **90**, 1 (1960).

148. D. Barnard and E. J. Percy, *Chem. Ind.*, 1332 (1960).

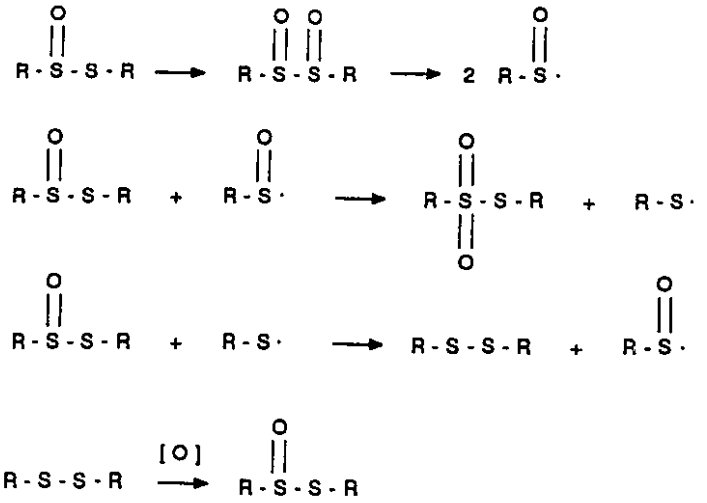
149. M. M. Chau and J. L. Kice, *J. Amer. Chem. Soc.*, **98**, 7711 (1976).

unsymmetric. In many examples including those of Freeman,[143] Barnard and Percy[146] and Chau and Kice,[149] other side products have been identified, thus this mechanism cannot be the only one in operation in any given reaction; however, the possibility of its partial participation in the overall reaction cannot be ruled out completely.



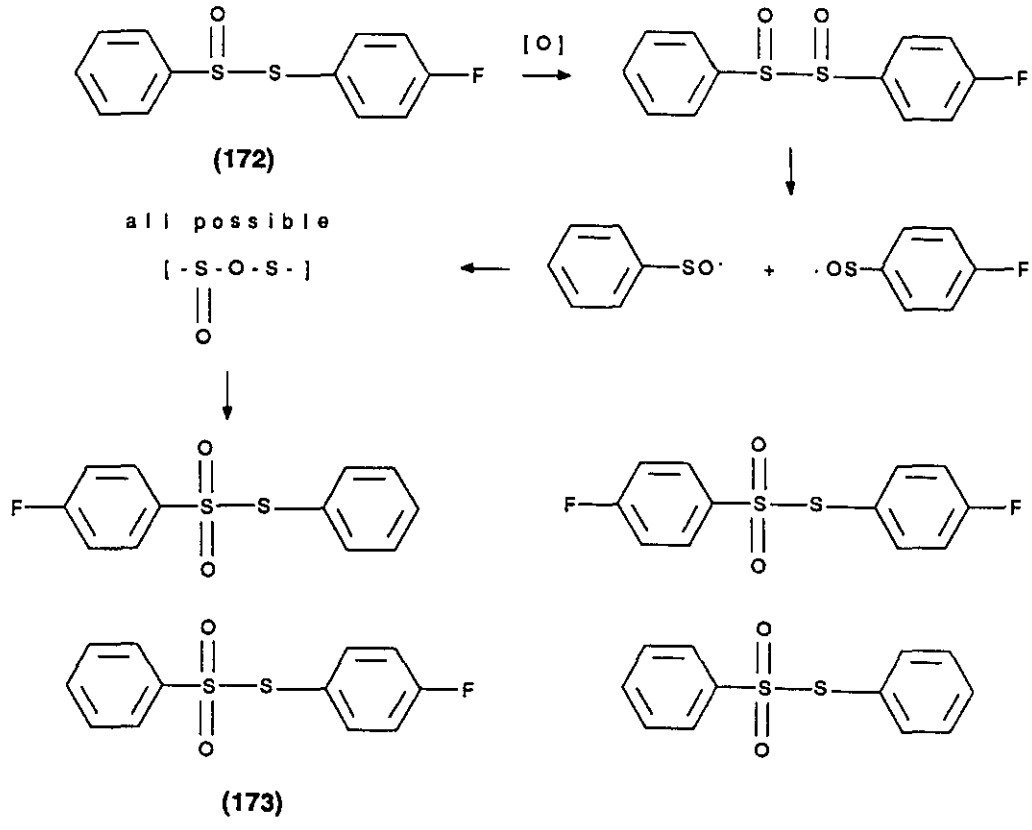
Scheme 24

Much conflicting evidence has been presented for the support of radical mechanisms. As seen in Scheme 25, this particular radical mechanism (#2), which was first reported by Barnard and Percy,[148] requires that transient amounts of disulfide exist during the course of the reaction. The disulfide formed is expected to be oxidized to thiosulfinate by the oxidizing agent (Scheme 25) thus leaving some of the original thiosulfinate unoxidized. In many examples, thiosulfinate has been present in the final product mixture.[143] Barnard and Percy[148] looked at the oxidation of *S*-phenyl benzenethiosulfinate with hydrogen peroxide, organic hydroperoxides and peroxyacids and detected phenyl disulfide as a transient product in amounts up to 30% of the original concentration of thiosulfinate. They obtained as a product mixture, all four of the possible thiosulfonates which is a requirement if a radical mechanism is to be considered. Other data presented in support of their proposed mechanism included the fact that thiosulfinate was found to be consumed more rapidly than oxidant and that one equivalent of oxidant caused the disappearance of several equivalents of thiosulfinate to give thiosulfonate and disulfide in equal amounts. Contrary to the results of Barnard and Percy, Modena and Todesco[147] did not see any disulfide formation in their study of the oxidation of *S*-aryl arenethiosulfinates by *m*-CPBA in dioxane solution.



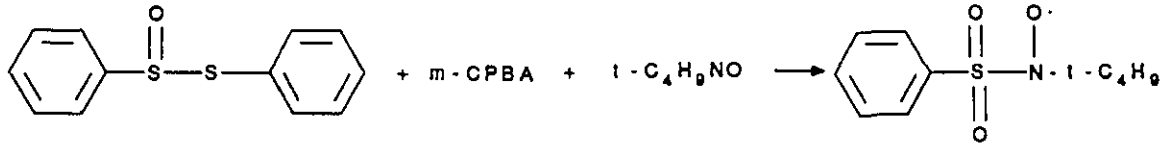
Scheme 25

Chau and Kice[149] reported the oxidation of *p*-fluorophenylthiosulfinates. Like Modena and co-workers,[147] no evidence was found for the formation of disulfide during the oxidation, even at temperatures of -20°C, as followed by ^{19}F NMR. However, all four possible thiosulfonate products were obtained when unsymmetrical thiosulfinate, *S*-(*p*-fluorophenyl) benzenethiosulfinate **(172)** was oxidized. The mechanism proposed by Chau and Kice (#3) is shown in Scheme 26 and involves the initial formation of an α-disulfoxide followed by homolytic cleavage of the S-S bond to give two sulfinyl radicals. These recombine randomly, in a head-to-tail fashion, to give *O,S*-sulfenyl sulfinates which rearrange to thiosulfonate. This mechanism predicts that the product ratio for the four possible thiosulfonates be roughly equal, however, this was not the case. Thiosulfonate **173** was formed in amounts that were 2.5 times larger than the other three. It was suggested that this was due to a small amount of direct oxidation on the sulfinyl sulfur of the thiosulfinate and this pathway was calculated to account for about 25% of the final product. No direct evidence for α-disulfoxides was seen and it was concluded that this was because of their very low stability. In this report, Chau and Kice suggested that the formation of disulfide in the experiments reported by Barnard and Percy[148] may have been cause by a disproportionation of thiosulfinate in the acidic oxidizing conditions used, thus explaining the discrepancy with their results and the results obtained by the Italian workers.[147]



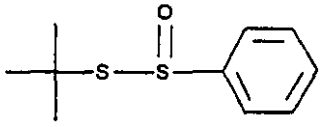
Scheme 26

The only other evidence for the involvement of radical mechanisms in the peroxidation of thiosulfinates was obtained from radical scavenging experiments.[150] The *m*-CPBA oxidation of **174** in the presence of *t*-butyl nitroxide **(175)** gave an ESR signal for the sulfonyl adduct **176** (Scheme 27). This type of adduct was also seen in the peroxidation of *S*-(2-methyl-2-propyl) benzenethiosulfinate **(177)** and *S*-(2-methyl-2-propyl) 2-methyl-2-propylthiosulfinate **(163)**.



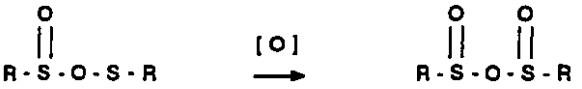
Scheme 27

150. B. C. Gilbert, B. Gill and M. J. Ramsden, *Chem. Ind. (London)*, 283 (1979).



(177)

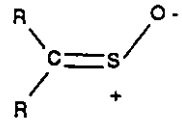
Freeman[143] thoroughly investigated the oxidation of several structural types of thiosulfinates and reported evidence for intermediates supporting mechanism number 4. As mentioned earlier, direct evidence for α-disulfoxide formation was seen in the oxidation of symmetrical dialkyl thiosulfinates. α-Disulfoxides may rearrange to *O,S*-sulfenyl sulfinates (Scheme 24). Competing oxidation of this species to sulfinic anhydrides **178** (Scheme 28) was proposed as an explanation for the incomplete oxidation of the starting thiosulfinate. In the oxidation of thiosulfinates **162**,[144c] **163**,[144a] **166**[143] and **167**[143] there were peaks in the low temperature ^{13}C NMR spectra assigned to the corresponding sulfinic anhydrides at temperatures less that -20°C.



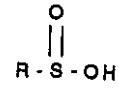
(178)

Scheme 28

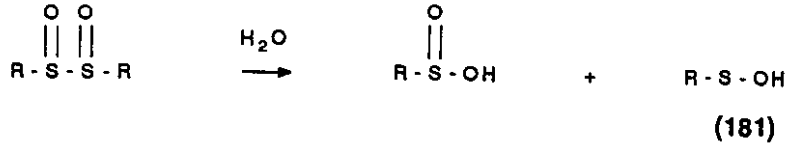
Other intermediates seen directly after the formation of α-disulfoxide in the oxidation of symmetrical dialkyl thiosulfinates included sulfines **(179)**, sulfinic acids **(180)** and thiosulfinates **(158)**. Freeman[143,144] proposed that the hydrolysis of α-disulfoxides and/or *O,S*-sulfenyl sulfinates leads to sulfenic **(181)** and sulfinic **(180)** acids (Scheme 29). Reaction of sulfinic acid with starting thiosulfinate lead to the formation of thiosulfonate and sulfenic acid (Scheme 30). The sulfenic acids **(181)** are expected to dimerize *via* intermediate **182** to give thiosulfinates (Scheme 31) which, again, is another possible explanation for the presence of thiosulfinates in the final product mixture. With all of this evidence at hand, Freeman[143] concluded that sulfinyl radicals do not play a major role in the peroxidation of symmetrical dialkyl thiosulfinates.



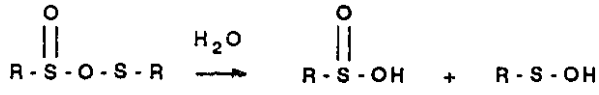
(179)



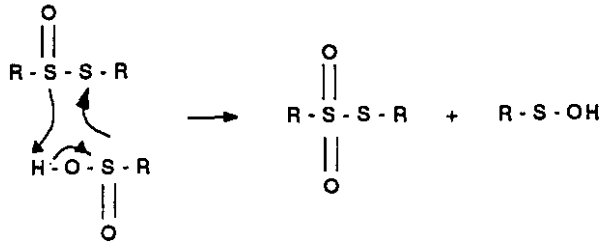
(180)



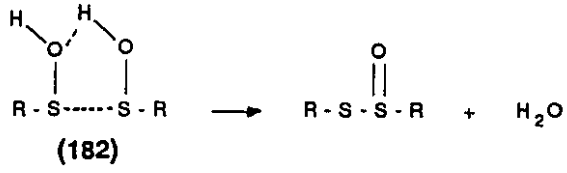
(181)



Scheme 29



Scheme 30



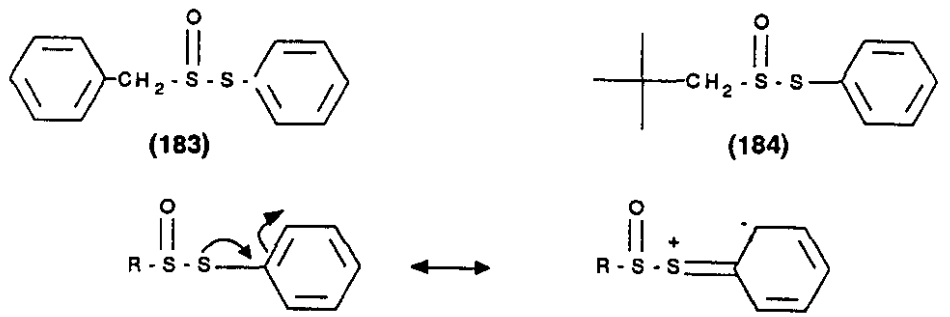
(182)

Scheme 31

Freeman also looked at the *m*-CPBA oxidation *S*-aryl alkylthiosulfinates, in particular *S*-phenyl phenylmethylthiosulfinate **(183)**[151] and *S*-phenyl 2,2-dimethylpropanethiosulfinate

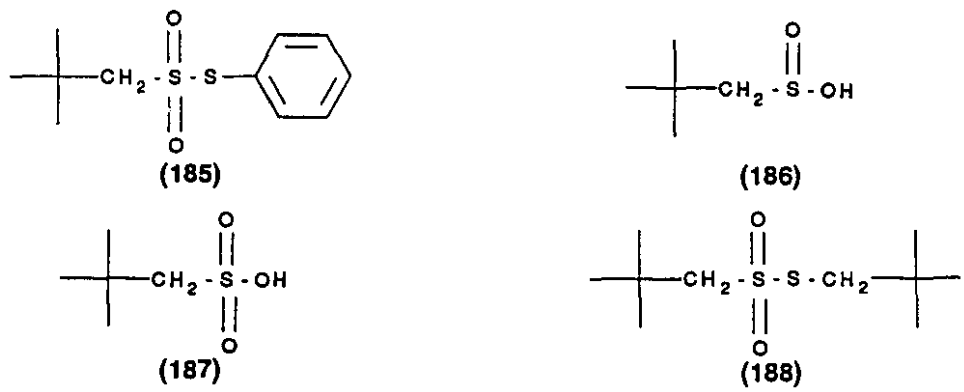
151. F. Freeman and C. N. Angeletakis, *J. Org. Chem.*, **46**, 3991 (1981).

(184).[152] In this situation, one cannot assume that oxidation will occur exclusively on the sulfenyl sulfur atom due to possible conjugation with the phenyl group that removes some of the electron density at this location (Scheme 32). The alkyl group on the sulfinyl sulfur is electron releasing and could also enhance the possibility of oxidation occurring at this location first. The results were similar for both cases, thus only the more recent results for the oxidation of **184** will be discussed here. The initial product mixture (-30°C, 105 min) for the oxidation of **184** contained thiosulfonate **185** (32%), **184** (28%), sulfinic acid **186** (18%), sulfonic acid **187** (12%) and thiosulfonate **188** (7%). As the temperature and time were increased, the concentration of **184** decreased, the concentration of **185** increased and the remaining concentrations remained essentially the same. The presence of **188**, **186** and **187** in the initial reaction mixture indicated that oxidation did not exclusively occur on the sulfinyl sulfur atom of **184**, thus some α-disulfoxide must have been formed; however, oxidation at the sulfinyl sulfur was certainly more prevalent here than in the dialkyl examples. Freeman[143,151,152] proposed several possible mechanisms for the observed products, including homolytic cleavage of the S-S bond of the α-disulfoxide to give sulfinyl radicals followed by rapid radical recombination in a solvent cage to explain the presence of symmetric thiosulfonate **188**.



(183) **(184)**

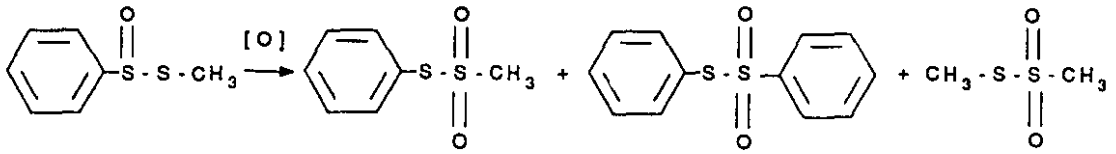
Scheme 32



(185) **(186)** **(187)** **(188)**

152. F. Freeman, C. N. Angeletakis and T. J. Maricich, *J. Org. Chem.*, **47**, 3403 (1982).

Another group of investigators[153] looked at the peroxidation of *S*-methyl phenylthiosulfinate **(189)** using ^{18}O-labelling experiments. This provided an example for the structural class involving *S*-alkyl arylthiosulfinates where oxidation is largely expected to occur on the sulfenyl sulfur due to the added electron releasing effect of the methyl group. The main products obtained from the oxidation of **189** were *S*-phenyl methylthiosulfonate **190** (25%), *S*-phenyl phenylthiosulfonate **191** (25%), *S*-methyl methylthiosulfonate **192** (13%) and **189** (19%) (Scheme 33). It is important to observe that there was no product resulting from direct oxidation on the sulfinyl sulfur. The formation of all of these products indirectly supports the initial step in this reaction to have been oxidation at the sulfenyl sulfur to give an α-disulfoxide. The experimenters proposed that the mechanisms in operation included initial hydrolysis of the S-S bond of the α-disulfoxide to give sulfenic acids which recombined (Scheme 31) to give thiosulfinates which were in turn oxidized to the products identified.



(189) **(190)** **(191)** **(192)**

Scheme 33

The conclusions that may be made about the mechanism for the peroxidation of thiosulfinates from all of this evidence are not definite. The mechanism in operation seems to be dependent on the structure and reaction conditions. There is a greater tendency for diaryl thiosulfinates to form sulfinyl radicals possibly because of a weaker S-S bond;[154] if this is also true for the corresponding α-disulfoxides, then a radical mechanism would be favored for these species. With a stronger S-S bond, an ionic mechanism may be able to compete more favorably with the radical mechanism in the case of dialkyl thiosulfinates. As for *S*-aryl alkylthiosulfinates, oxidation will occur directly on the sulfinyl sulfur with evidence for some α-disulfoxide formation.

Regardless of which mechanism is in operation, the initial formation of an α-disulfoxide species has been directly confirmed in at least some instances. It would seem safe to assume that these are legitimate intermediates in the peroxidation of all thiosulfinates and that the product mixture can be expected to contain some of the starting thiosulfinate and a mixture of the possible

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153. S. Oae, Y. H. Kim, T. Takata and D. Fukushima, *Tetrahedron Lett.* 1195 (1977).

154. E. Block and J. O'Connor, *J. Amer. Chem. Soc.*, **96**, 3921 (1974).

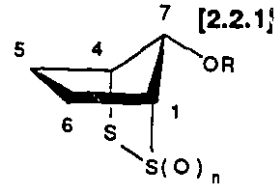
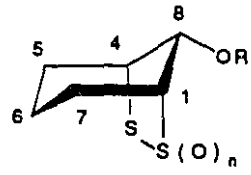
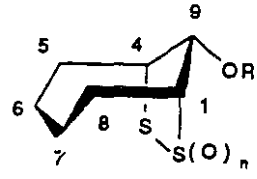
thiosulfonates (depending on the structure) along with products of disproportionation.

The readily accessible bridged bicyclic thiosulfinates synthesized in this work provided an opportunity to further investigate the peroxidation of thiosulfinates. The characteristic of a small C-S-S-C dihedral angle makes these compounds unique from all the examples mentioned above and it was thought that some additional information about the stereochemistry of this oxidation could be determined. Thus the low temperature *m*-CPBA oxidation of all of the bridged bicyclic thiosulfinates at hand was carried out. The analysis provided unique insights into the detailed steps of this oxidation process.

3.2 Results and Discussion

The general procedure for the *m*-CPBA oxidation of bridged bicyclic thiosulfinates utilized in this study closely resembles that used by Freeman.[144c] The details are found in the experimental section. All efforts were made to keep the conditions anhydrous and the oxidation of most thiosulfinates was followed by both ^{1}H and ^{13}C NMR spectroscopy at temperatures ranging from -40°C to +30°C. Peak assignments were made by following the rate of appearance of the signals. Those that showed a common abundance throughout the experiment and contained the required number of peaks in the different regions of the spectrum were considered to be the same compound. In the case of [3.2.1] bridged bicyclic thiosulfinates, if a compound contained six signals in the ^{13}C spectrum for the ring carbons, it was considered to be unsymmetric about the C8-C6 axis. If there were only four signals in the ^{13}C spectrum, the species was considered to be symmetric about the C6-C8 axis. In the ^{1}H NMR spectra of these compounds, the peaks of interest were H1, H4 and H8. The remaining protons gave complex and overlapping signals that made assignments difficult. If the compound was unsymmetric there were three separate signals for H1, H4 and H8, with identical integration values. If the compound was symmetric, there were only two signals in this region, one for H8 and one for H1 and H4 with an integration ratio of 1:2. The same was true for the [4.2.1] thiosulfinates. If the intermediate was symmetric then there were only four signals in the carbon spectra for the ring carbons. Likewise, there was only one peak in the region of the bridgehead protons for H1 and H4 with an integration value twice that of H8. The unsymmetrical [4.2.1] species gave seven peaks in the carbon spectra and the signals for H1 and H4 were separated by about 0.5 ppm. The ^{13}C spectra of symmetric [2.2.1] species contained three signals whereas that of the unsymmetric species had five. Table 8 summarizes the above information.

Table 8: NMR Characteristics for Bridged Bicyclic Oxidation Intermediates

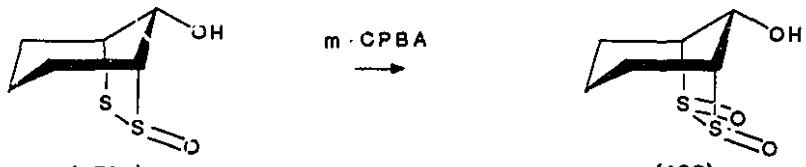
		Symmetric	Unsymmetric
[2.2.1] 	^{13}C	3 signals C1 and C4, C5 and C6 equivalent	5 signals
[3.2.1] 	^{13}C	4 signals C1 and C4, C5 and C7 equivalent	6 signals
	^{1}H	H1 and H4 equivalent	H1 and H4 nonequivalent
[4.2.1] 	^{13}C	4 signals C1 and C4, C5 and C8, C6 and C7 equivalent	7 signals
	^{1}H	H1 and H4 equivalent	H1 and H4 nonequivalent

3.2.1 Oxidation of Bridged Bicyclic [3.2.1] Thiosulfinates

(i) syn-2,3-Dithiabicyclo[3.2.1]octan-8-ol S-oxide **(150a)**

The first product of the *m*-CPBA oxidation of *syn*-2,3-dithiabicyclo[3.2.1]octan-8-ol *S*-oxide **(150a)** was *NOT* the thiosulfonate, but a symmetrical intermediate **(193)** (Scheme 34) that first appeared at the lowest temperature recorded (-30°C) in both the ^{13}C and ^{1}H NMR spectra (Figure 9 and Figure 10, respectively). This clearly indicates that oxidation occurred at the sulfenyl sulfur atom of **150a** first to give an α-disulfoxide intermediate **(193)**. It has already been shown (Chapter 2) that the preferred direction of attack by the oxidizing agent, *m*-CPBA **(148)**, is from the front or *exo* face due to the steric hindrance of the six-membered ring. Therefore, it was not surprising that the oxygen in this step once again, preferred to enter from the *exo* face to give a symmetrical α-disulfoxide intermediate **(193)**. The mutual dipolar repulsion of the adjacent sulfur-oxygen bonds must not be strong enough to inhibit the attack of oxygen parallel to it; clearly the *endo* face must

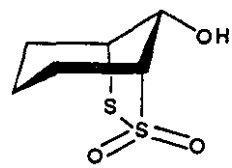
be highly hindered!



(150a) (193)

Scheme 34

The next question of importance is what possible routes may α-disulfoxide **193** take in order to get to the final product(s). As seen in Figures 9 and 10, the final product mixture of this oxidation contained mainly thiosulfonate **156** and some of the starting material **(150a)**. In the ^{13}C NMR experiment (Figure 9), there were clearly two other intermediates formed during the course of the oxidation, **194** and **195**. These species were also seen in the ^{1}H NMR spectra; however, their concentrations did not reach the amounts attained in the ^{13}C experiment. This is believed to be due to the difference in experimental acquisition time required for the ^{13}C and ^{1}H NMR spectra. The longer experimental times to acquire the ^{13}C spectra allowed more time for the concentration of these intermediates to build up. Species **194** was unsymmetric whereas **195** was symmetric. Table 9 lists the chemical shifts for all of the compounds seen during the ^{13}C NMR oxidation experiment. The final products isolated from a chromatographic workup of the reaction mixture were thiosulfinate **150a** (10%) and thiosulfonate **156** (60%).



(156)

Table 9: ^{13}C Chemical Shifts for the *m*-CPBA Oxidation of 150a (ppm)

Cpd	C8	C1	C7	C6	C5	C4
150a	83.4	76.8	29.3	16.8	24.1	63.5
193	91.9	68.2	25.3	19.3	25.3	68.2
194	81.4	71.9	24.4	18.2	21.0	70.1
195	75.0	64.2	21.7	17.6	21.7	64.2
156	75.5	69.7	31.4	15.8	26.5	62.9

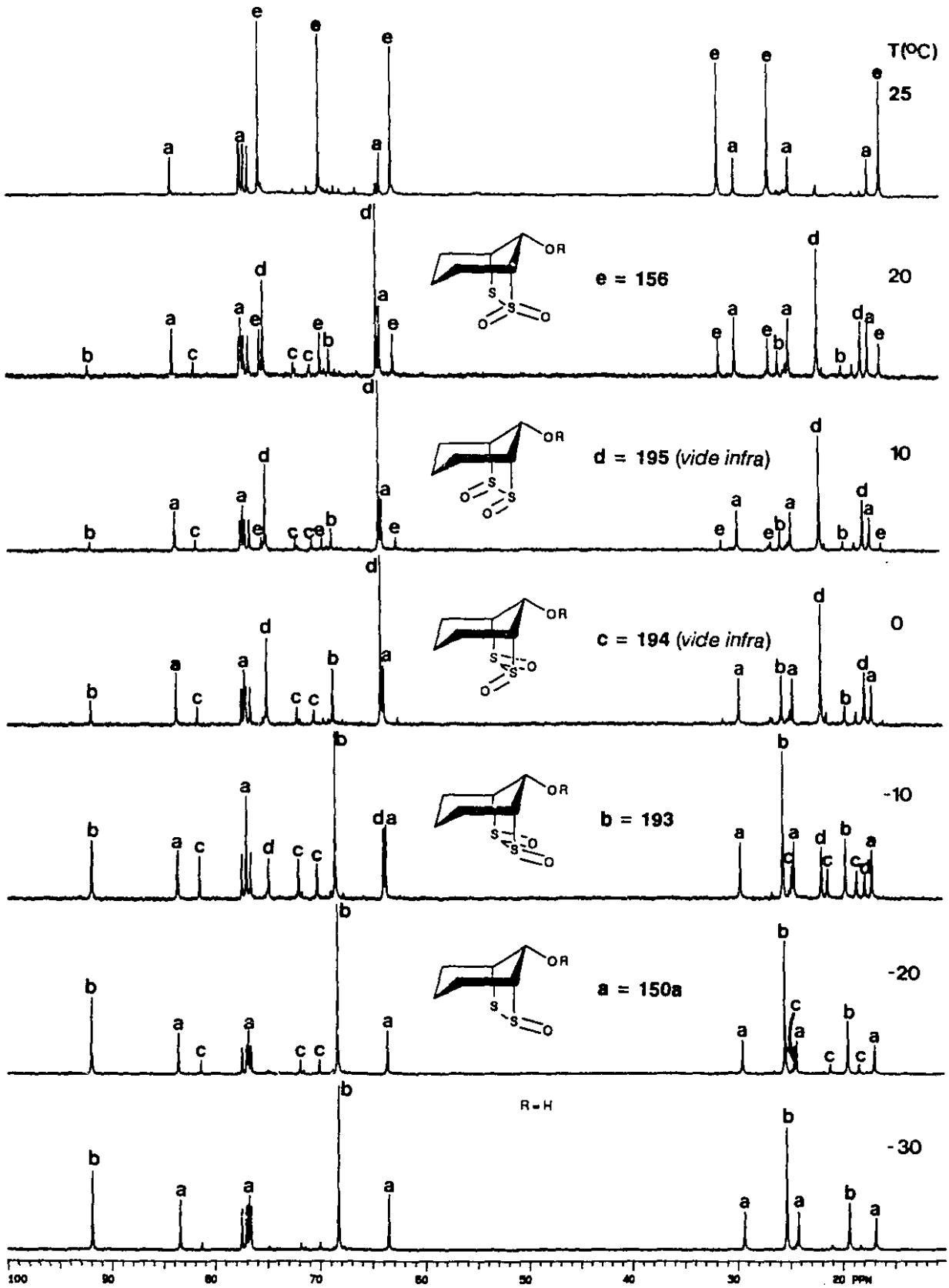
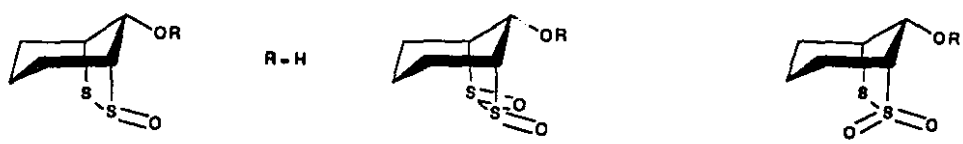


Figure 9: Low Temperature *m*-CPBA Oxidation of 150a; ^{13}C Spectra



a = 150a **b = 193** **e = 156**

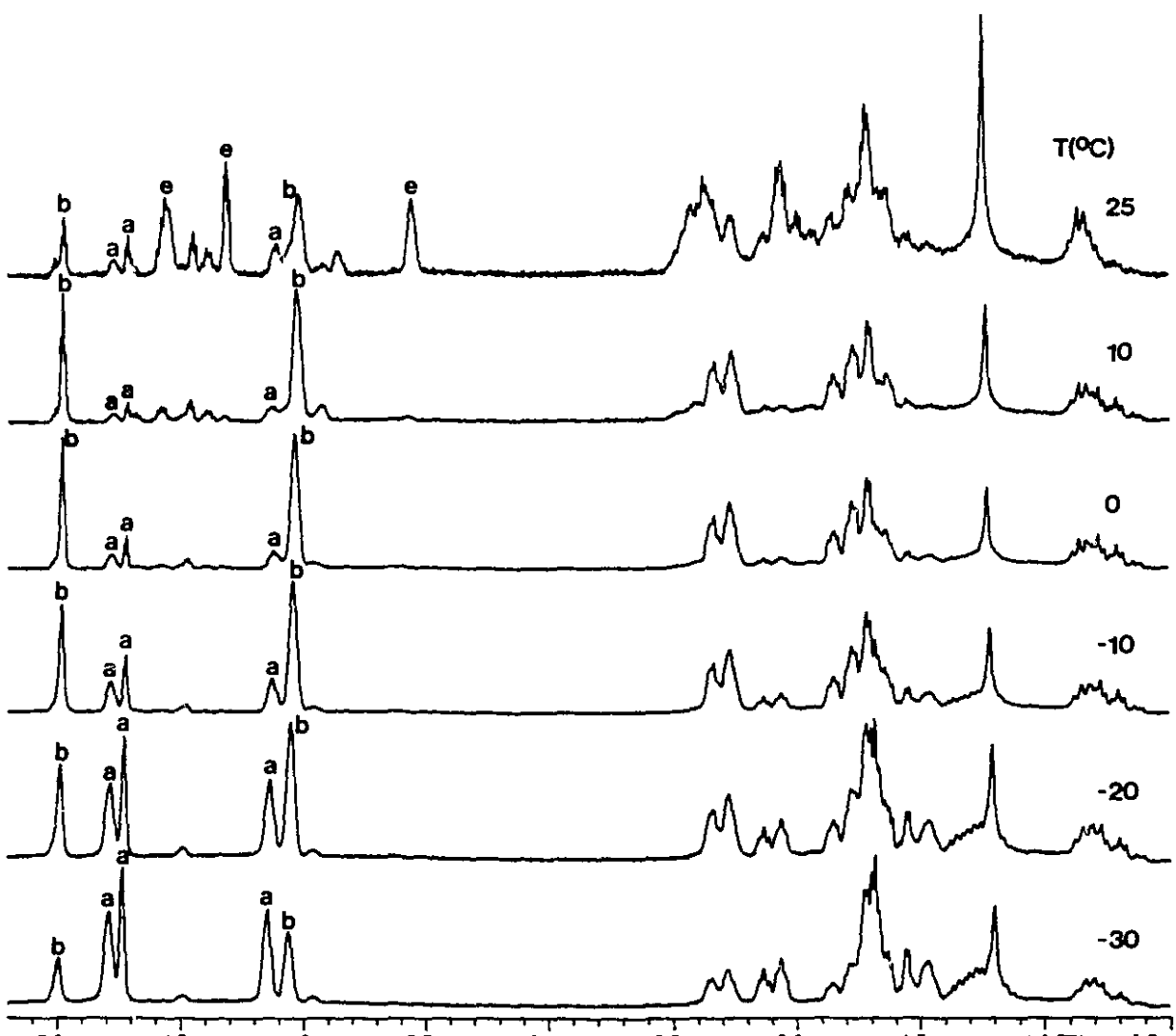


Figure 10: Low Temperature *m*-CPBA Oxidation of 150a; ^{1}H Spectra

To aid in the visualization of the transformations occurring in this experiment, Table 10 lists the percent composition of the reaction mixture at each temperature based on the integration of the ^1H NMR spectra and a graph of this data is presented in Figure 11.

Table 10: Percent Composition of Reaction Mixtures During the Oxidation of 150a[a]

Temp (°C)	150a	193	194	195	156
-30	69	25	6	0	0
-20	49	43	8	0	0
-10	32	60	8	0	0
0	23	65	12	0	0
10	19	48	7	15	11
25	19	21	5	15	30

[a]Based on integration of the ^1H spectra

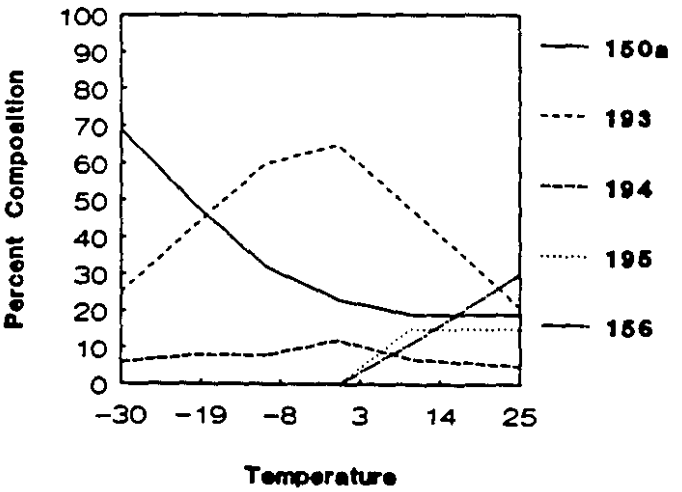


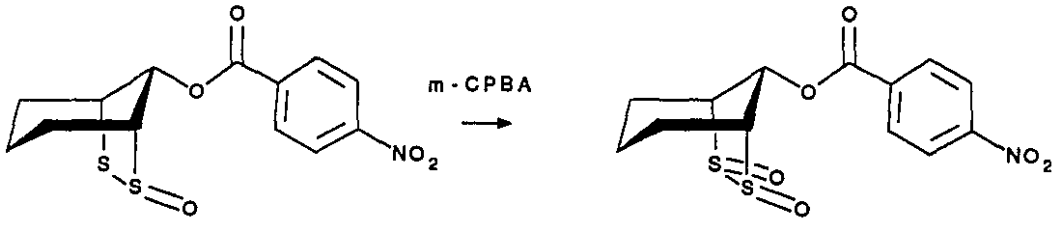
Figure 11: Graph of Percent Composition *vs* Temperature During the Oxidation of 150a (^1H NMR Experiment)

Before a final conclusion about the identity of intermediates **194** and **195** can be made, further evidence from the oxidation of the other bridged bicyclic thiosulfinates must be presented and analyzed.

(ii) syn-2,3-Dithia-[8-p-(nitrobenzoyl)oxy]bicyclo[3.2.1]octane S-Oxide **(152)**

In the oxidation of thiosulfinate **152**, once again, the first product formed was not the

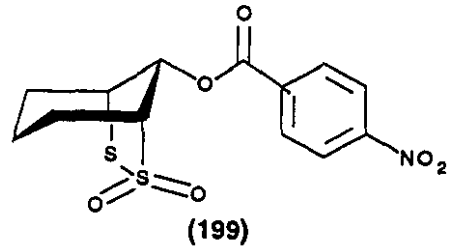
thiosulfonate, but a symmetrical intermediate to which the α-disulfoxide **(196)** structure has been assigned (Scheme 35). Compound **196** was first seen at -40°C in both the ^{13}C (Figure 12) and ^{1}H (Figure 13) spectra and its abundance was consistent in both experiments; **196** was not present in the room temperature spectra. A second species **(197)** was first seen at -20°C in the ^{13}C spectra and its peak locations (Table 11) and abundance closely resembled those of intermediate **194** (Table 9) in the oxidation of **150a**. Due to broadness of the ^{1}H NMR signals in the region where the bridgehead protons appear, assignments for these peaks were difficult. The signals for H8 were well resolved, thus were used to determine the number and type of species present. The similarity in the abundance of the species with H8 appearing at 5.83 ppm with the signals for **197** in the ^{13}C NMR spectra would indicate that this was the signal for H8 of **197**. Compound **197** was not present in the room temperature ^{13}C and ^{1}H NMR spectra.



(152) **(196)**

Scheme 35

The spectra recorded at temperatures greater than +10°C, began to get very complicated. A third intermediate **(198)** first appeared at 20°C. It was unsymmetric and was the second most abundant species in the final product mixture of the ^{13}C NMR experiment (the most abundant species in this experiment was the final product, thiosulfonate **199**). A ^{1}H NMR spectrum of the final product mixture from the ^{13}C NMR experiment showed that compound **198** was the same species that was the most abundant in the final ^{1}H NMR mixture (H8 at 5.55 ppm). The thiosulfonate **(199)** was visible at 20°C and became the major species in the room temperature ^{13}C NMR spectrum but was barely visible in the ^{1}H NMR spectrum. The reason for this was, again, the longer amount of time required to collect the ^{13}C NMR spectra which would allow more time for intermediates to rearrange to final products. In both experiments, there was a small amount of starting material remaining at the end of the run.



(199)

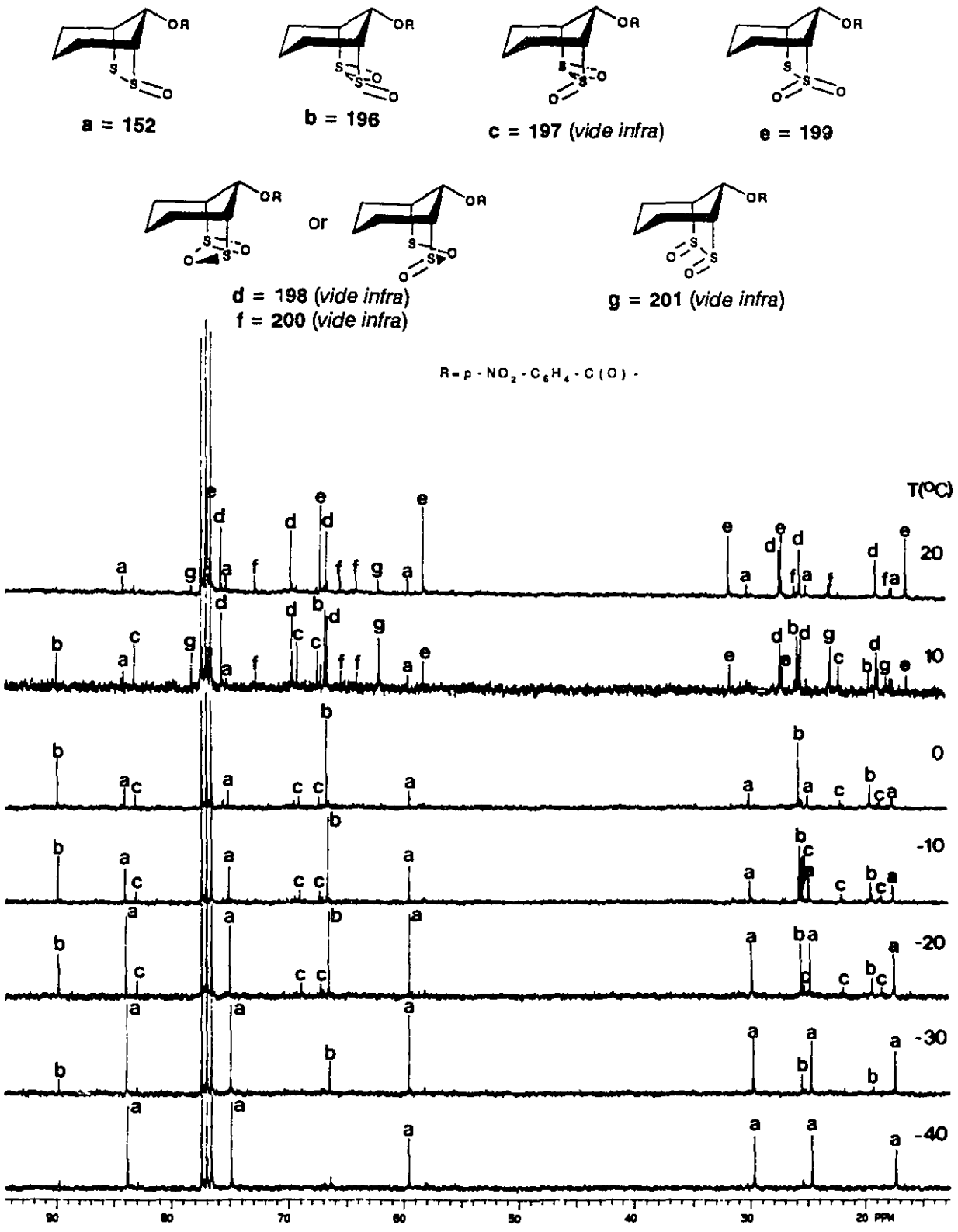
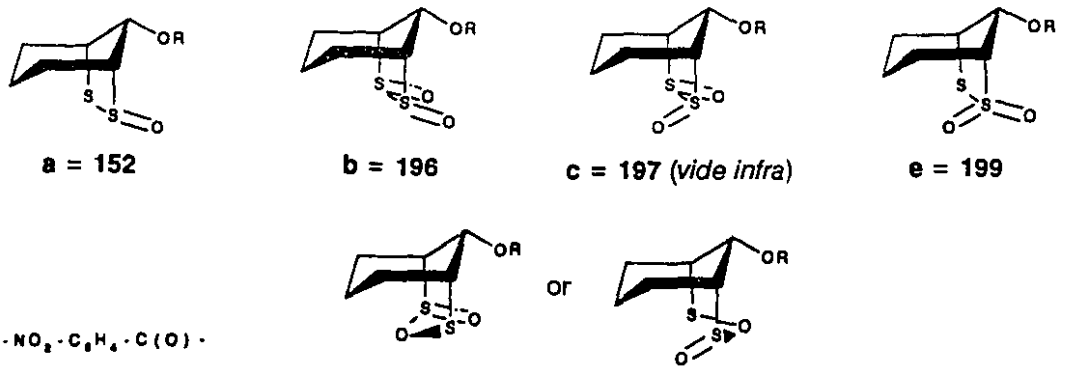


Figure 12: Low Temperature *m*-CPBA Oxidation of 152; ^{13}C Spectra



a = 152 **b = 196** **c = 197** (*vide infra*) **e = 199**

R = p-NO_2-C_6H_4-C(O)-

d = 198 (*vide infra*)
f = 200 (*vide infra*)

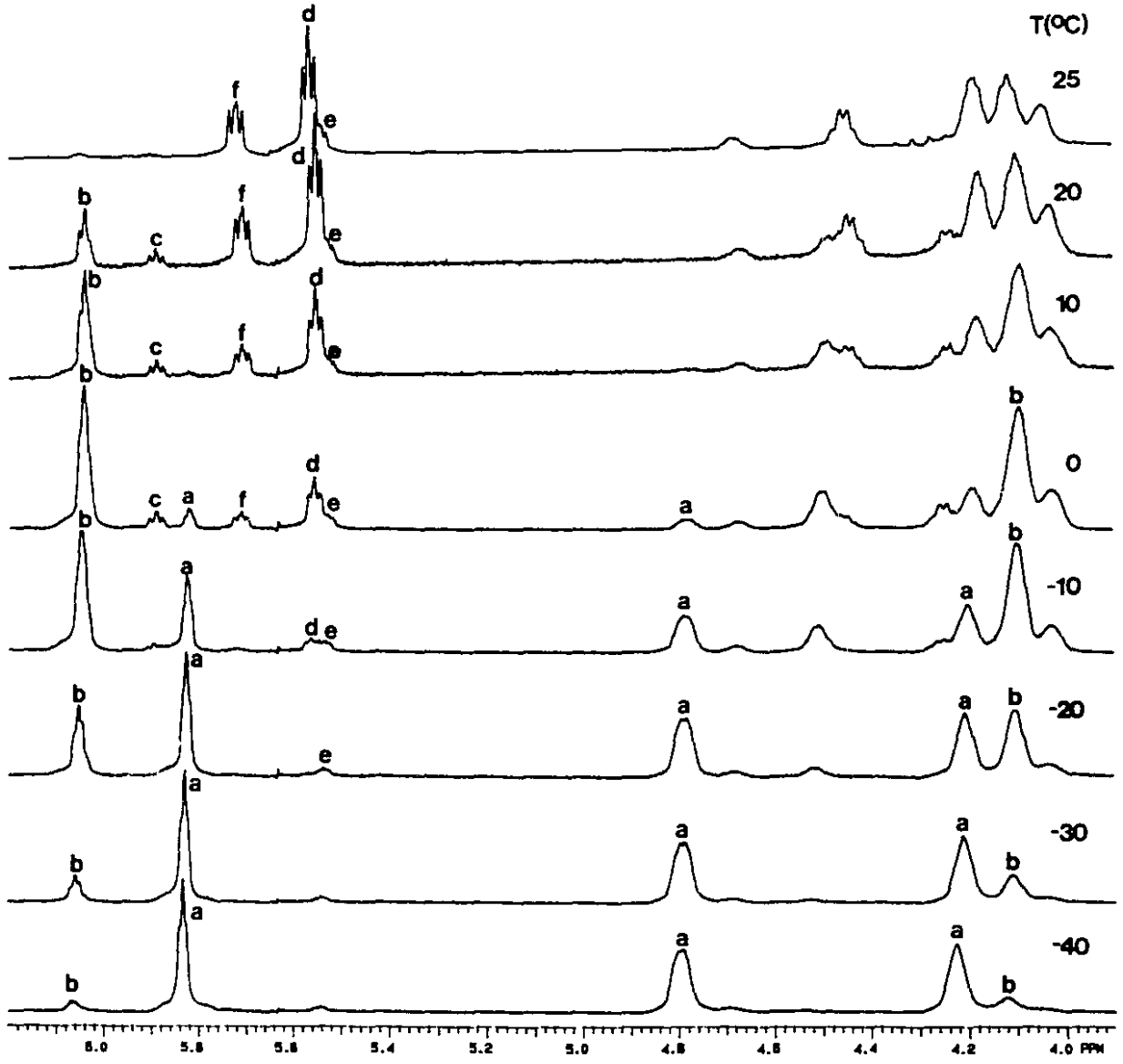


Figure 13: Low Temperature *m*-CPBA Oxidation of 152; ^{1}H Spectra

Two other minor species were seen in the final two spectra, one unsymmetric (**200**) and one symmetric (**201**). Using the ^{1}H NMR spectrum of the final product mixture from the ^{13}C NMR experiment, the H8 proton of **200** was found to correspond to the signal centered at 5.71 ppm. The peak locations for **201** in the ^{13}C NMR spectra were similar to those of intermediate **195**, seen in the oxidation of **150a**. This species was not visible in the ^{1}H NMR spectra and was only a very minor component of the ^{13}C spectra. A chromatographic workup of the final reaction mixture lead to the isolation of only thiosulfonate **199**, but in very low yield (18%). The low yield of final product can be rationalized by the relatively large concentration of compounds **199** and **200** present at the end of the experiment. These compounds were not able to be purified by column chromatography on silica or alumina. It is likely that they became attached to the solid support through an esterification reaction.

The ^{13}C chemical shifts of the intermediates and products of the oxidation of **152** are given in Table 11 whereas the behavior of the intermediates in the ^{1}H NMR experiment is displayed in Table 12 and Figure 14.

Table 11: ^{13}C Chemical Shifts for the *m*-CPBA Oxidation of 152 (ppm)

Cpd	C8	C1	C7	C6	C5	C4
152	83.8	74.9	29.6	24.0	32.5	59.5
196	89.9	66.5	25.4	19.2	25.4	66.5
197	83.2	69.2	25.3	17.7	21.9	67.4
198	75.7	69.7	27.1	18.6	25.3	66.5
199	76.9	67.1	31.5	16.0	26.9	58.1
200	72.8	65.4	24.8	17.4	22.6	64.0
201	78.2	62.0	22.7	18.4	22.7	62.0

Table 12: Percent Composition of the Reaction Mixtures in the Oxidation of 152[a]

Temp (°C)	152	196	197	198	199	200
-40	88	8	0	0	4	0
-30	79	17	0	0	4	0
-20	55	39	0	2	4	0
-10	27	61	3	4	4	1
0	6	58	5	20	4	7
10	1	40	5	36	4	14
20	0	18	5	49	5	23
25	0	0	0	62	7	31

[a]Based on integration of the ^{1}H spectra

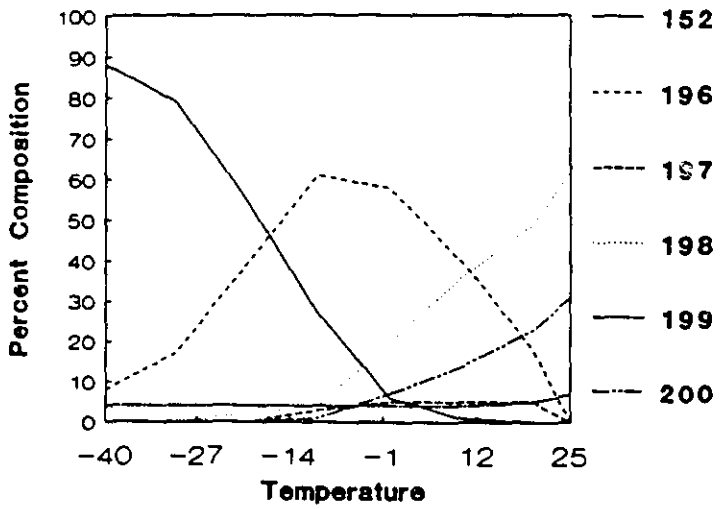


Figure 14: Graph of Percent Composition *vs* Temperature During the Oxidation of 152 (^{1}H NMR Experiment)

(iii) syn-2,3-Dithia-[(8-n-hexanoyl)oxy]bicyclo[3.2.1]octane S-oxide (**153a** and **153b**)

The oxidation of the *exo* and *endo* isomers of *syn*-2,3-dithia-8-*n*-hexanoyloxybicyclo[3.2.1]octane *S*-oxide (**153a** and **153b**, respectively) provided even more information about the mechanism for the peroxidation of bridged bicyclic thiosulfinates. The oxidation of each isomer was followed by both ^{1}H and ^{13}C NMR; these spectra are displayed in Figures 15-18.

(153a) **(153b)**

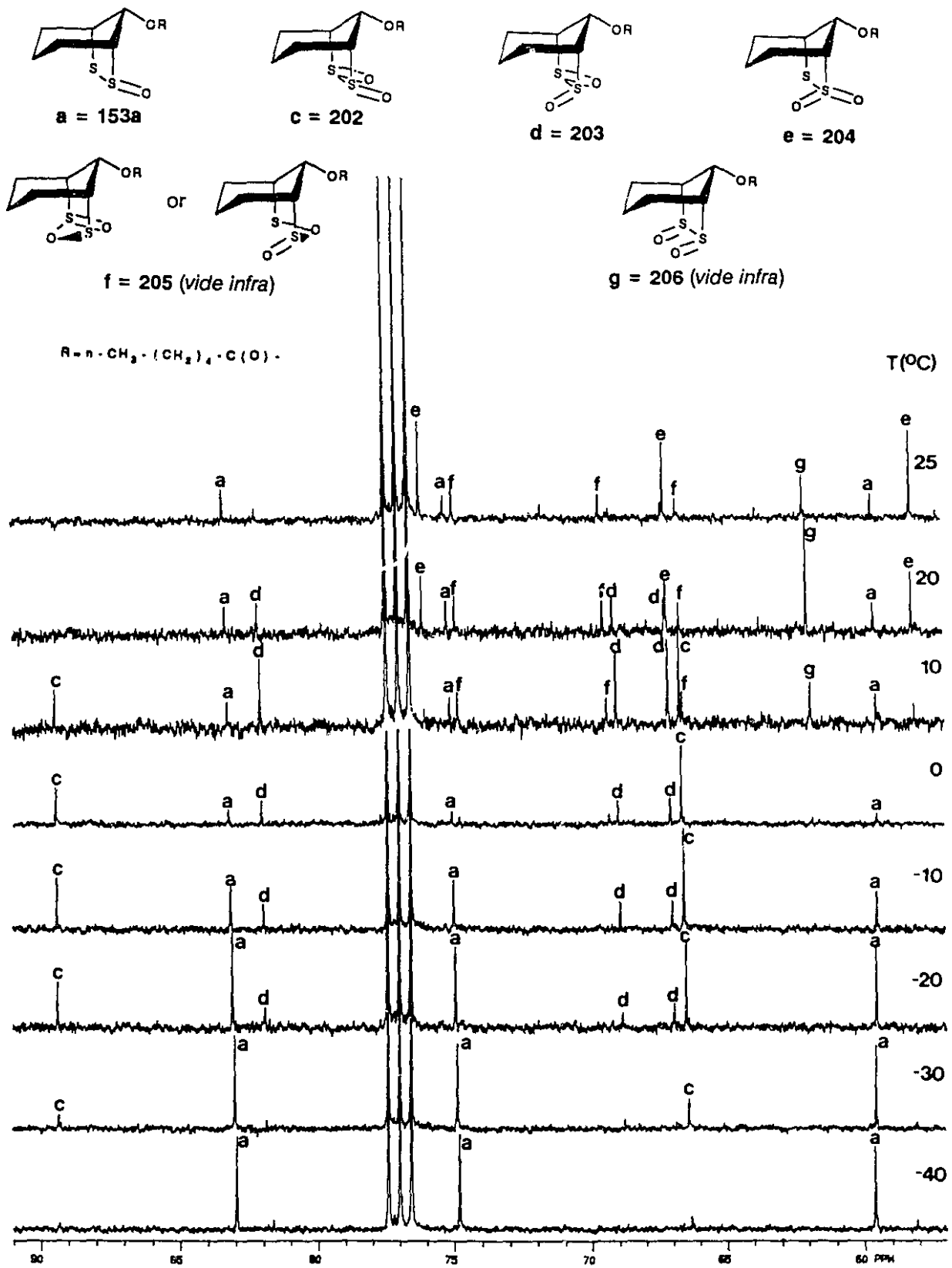
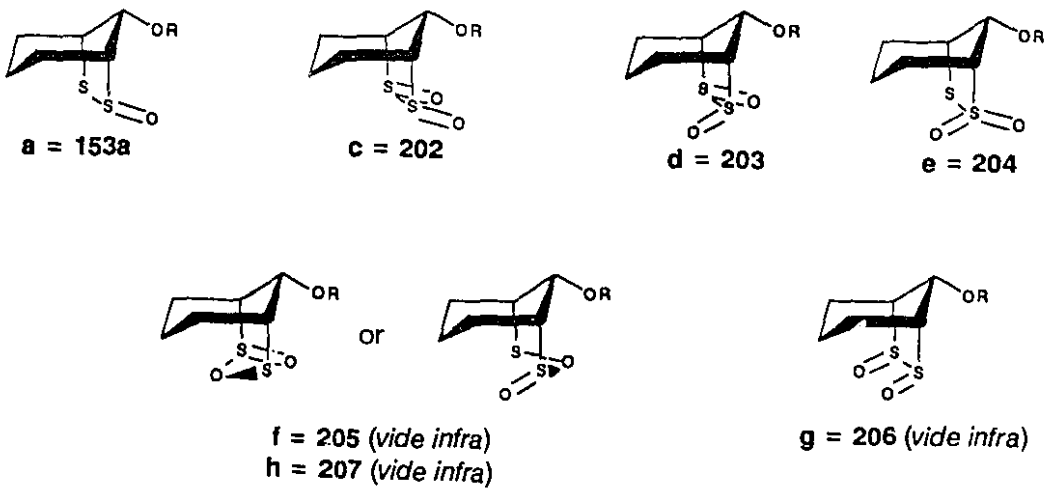


Figure 15: Low Temperature *m*-CPBA Oxidation of 153a; ^{13}C Spectra



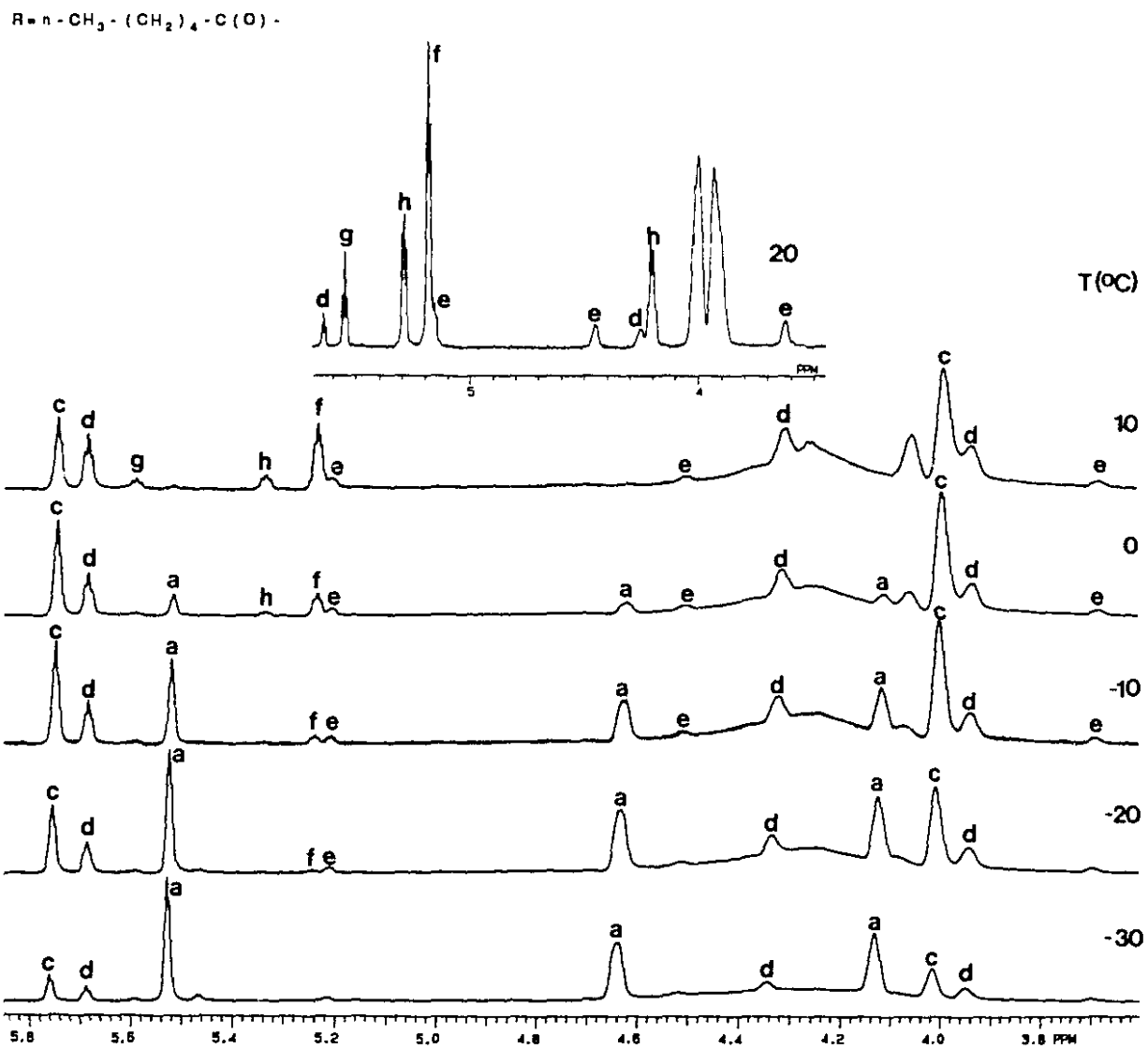


Figure 16: Low Temperature *m*-CPBA Oxidation of 153a; ^{1}H Spectra

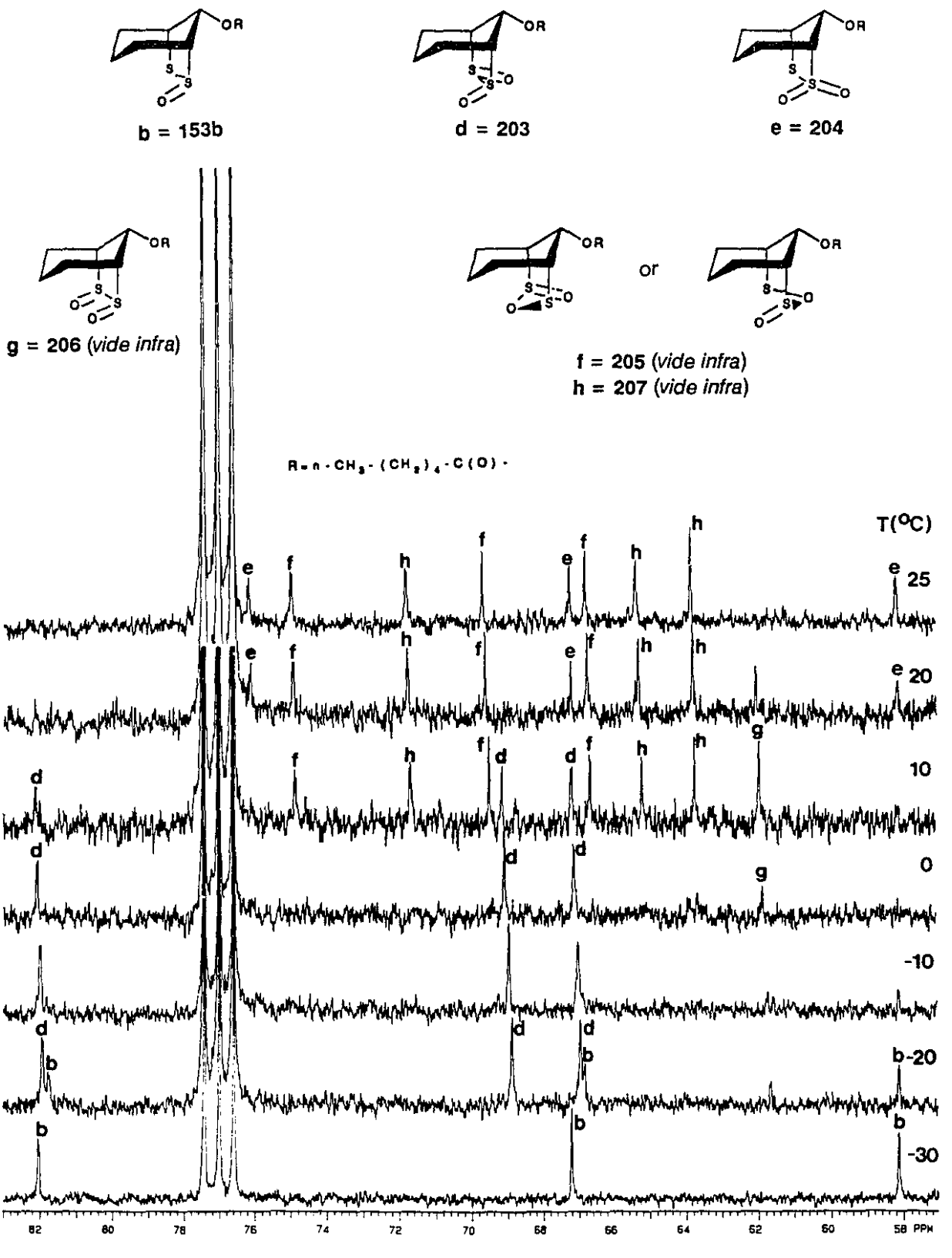


Figure 17: Low Temperature *m*-CPBA Oxidation of 153b; ^{13}C Spectra

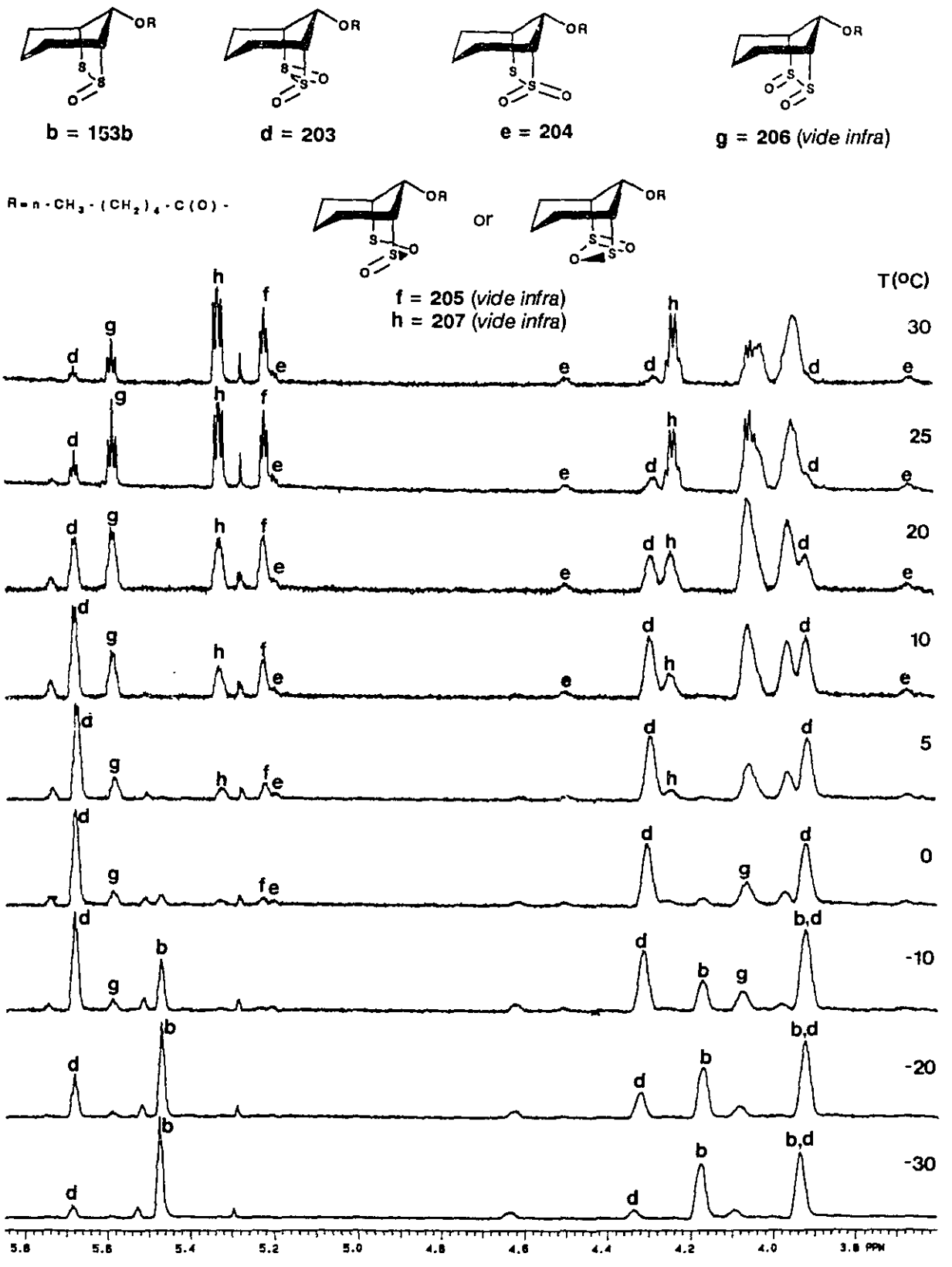
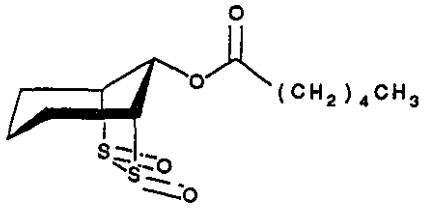
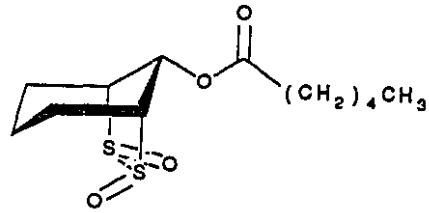


Figure 18: Low Temperature *m*-CPBA Oxidation of 153b; ^{1}H Spectra

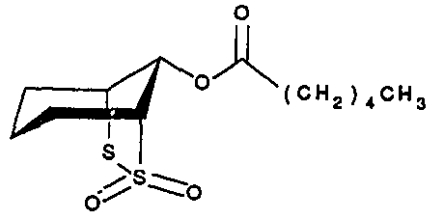
The first species (**202**) formed in the oxidation of **153a** was a symmetrical compound and it was the only one not present in the oxidation of **153b**. Once again, the thiosulfonate was not seen in the initial product mixture, thus oxidation initially occurred at the sulfenyl sulfur so that compound **202** was the symmetrical α-disulfoxide. It is very important to note that if oxidation of **153b** were to occur at the sulfenyl sulfur and from the expected direction (*exo*), the resulting α-disulfoxide would be unsymmetric. This was indeed the case, as seen in the NMR spectra of the oxidation of **153b** (Figures 17 and 18). The initial intermediate (**203**) was not the thiosulfonate and it was unsymmetric. *This confirmed a mechanism where the oxygen enters from the exo face.* Compound **203** was also seen in the oxidation of **153a** as the second intermediate formed; this is another important clue for the elucidation of the mechanism of this oxidation process and will be expanded below.



(202)



(203)



(204)

All of the remaining intermediates were found in both oxidations with slight variations in their rate of appearance and abundance at each temperature. Thiosulfonate **204** was consistently not a major part of the reaction mixture, even at room temperature and above. There were three other intermediates formed during the oxidation of **153a** and **153b**: **205**, **206** and **207**. Compounds **205** and **207** were unsymmetric; **206** was symmetric. The ^{13}C chemical shifts are presented in Table 13 and the ^{1}H NMR experiment is described in Tables 14 and 15 and Figures 19 and 20. The isolated yield of thiosulfonate **204** ranged from 15-40%; once again, the stablity of intermediates **205**, **206** and **207** resulted in a low yield of final product. Compounds **205**, **206** and **207** could not be isolated by column chromatography.

Table 13: ^{13}C Chemical Shifts for the *m*-CPBA Oxidation of 153a and 153b[a]

Cpd	C8	C1	C4
153a	83.0	74.9	59.5
153b	82.0	67.2	58.1
202	89.4	66.6	66.6
203	82.0	69.0	67.0
204	76.1	67.2	58.1
205	74.9	69.5	66.7
206	77.0	62.0	62.0
207	71.7	65.3	63.7

[a]Only C8, C1 and C7 could be identified due to the complexity of the alkyl region

Table 14: Percent Composition of Reaction Mixtures During Oxidation of 153a[a]

Temp (^{O}C)	153a	202	203	204	205	206	207
-30	71	16	8	3	1	1	0
-20	50	29	15	3	2	1	0
-10	32	41	18	4	4	1	0
0	9	47	22	4	13	2	3
10	1	28	23	5	30	5	8
25	0	1	6	6	48	13	26

[a]Based on integration of the ^{1}H spectra

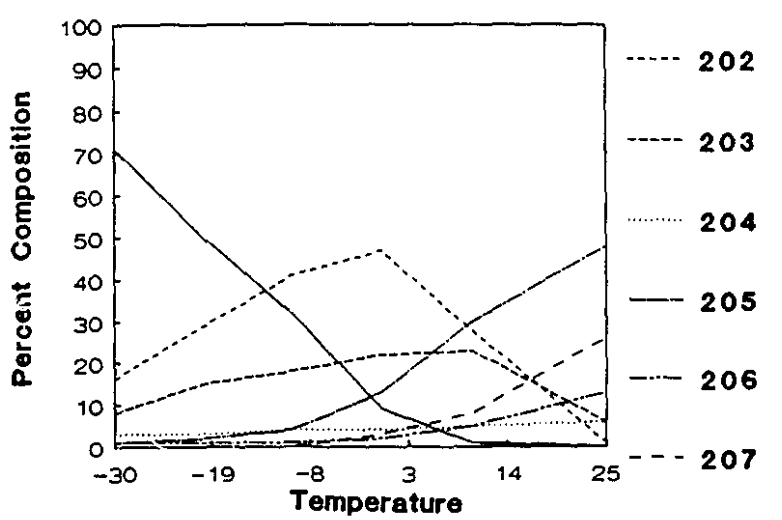


Figure 19: Graph of Percent Composition *vs* Temperature During the Oxidation of 153a (^{1}H NMR Experiment)

Table 15: Percent Composition of Reaction Mixtures During Oxidation of 153b[a]

Temp (°C)	153b	203	204	205	206	207
-30	83	17	0	0	<1	0
-20	65	31	0	0	4	0
-10	28	60	2	2	8	0
0	7	69	3	5	13	4
10	<1	61	3	12	14	10
15	0	40	4	18	23	15
20	0	22	4	22	28	24
25	0	12	4	24	24	36
35	0	7	5	27	15	46

[a]Based on integration of the ^{1}H spectra

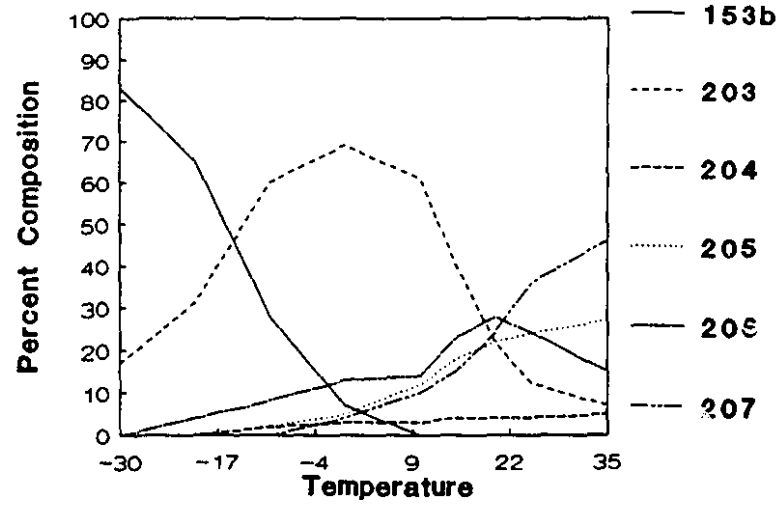


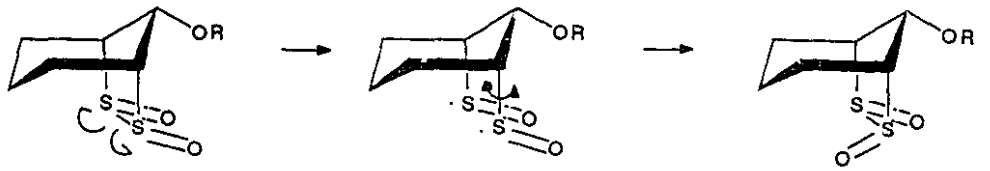
Figure 20: Graph of Percent Composition *vs* Temperature During the Oxidation of 153b (^{1}H NMR Experiment)

3.2.2 Proposed Mechanism for the Electrophilic Oxidation of Bridged Bicyclic Thiosulfinates

From a careful analysis of the data presented above on the *m*-CPBA oxidation of [3.2.1] thiosulfinates, it is possible to propose a detailed mechanism for the transformation of α-disulfoxide to final product(s) and to propose structures for the other intermediates seen during this process.

It is expected that the S-S bond in a bridged bicyclic α-disulfoxide, like **193**, **196**, **202** and **203**, would be very weak due to the strain of the bicyclic system and the repulsion between the two parallel sulfur-oxygen bonds. A concerted-type rearrangement, like that depicted in Scheme 24, is

not likely for these species as the sulfinyl oxygen is not able to reach an empty orbital on the adjacent sulfur atom due to the rigidity of the bicyclic system. It is expected, then, that homolysis of the S-S bond would readily occur to give two sulfinyl radicals (**208-210**, Scheme 36) which can recombine by several possible routes. There is evidence from the oxidation of the two isomers of thiosulfinate **153** that one of these routes involves rotation about one C-S bond followed by a head-to-head recombination of the sulfinyl radicals to give an unsymmetrical α-disulfoxide (Scheme 36). The evidence for this mechanism is the formation of compound **203** (previously identified as the unsymmetrical α-disulfoxide in the oxidation of the *endo* isomer, **153b**) as the second intermediate in the oxidation of **153a**.[155] The similarity in the ^{13}C chemical shifts (Table 16) and abundance of **203** with **194** and **197**, seen as the second intermediates in the oxidation of **150a** and **152**, respectively, supports an assignment of the unsymmetrical α-disulfoxide structure to these species.



(193) **(208)** **(194)** R = H
(196) **(209)** **(197)** R = *p*-NO_2-C_6H_5-C(O)-
(202) **(210)** **(203)** R = CH_3-$(CH_2)_4$-C(O)-

Scheme 36

Table 16: ^{13}C Chemical Shifts for [3.2.1] Unsymmetric α-Disulfoxides (ppm)

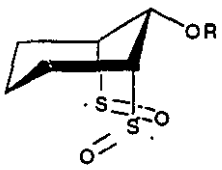
Cpd	C8	C1	C4
194	81.4	71.9	70.1
197	83.2	69.2	67.4
203	82.0	69.0	67.0

From this point, there are several possible pathways for intermediates **208-210** and **194**, **197** and **203** to follow. Although some may be more favoured than others, all cannot not be ruled out completely and the structure assignments for the remaining intermediates may only be proposed as there is no direct evidence for their identity. From a careful analysis of the NMR

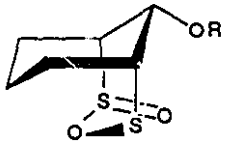
155. Unsymmetric α-disulfoxides could also be formed by a direct attack on the oxidizing agent from the *endo* side of the sulfur-sulfur bond; however, reactions on this side of these molecules has been shown to be unfavourable. Thus this mechanism should not account for the formation of a significant amount of unsymmetrical α-disulfoxide from thiosulfinate.

chemical shifts, the most likely structural assignment for each intermediate has been made. In all oxidations, the final product isolated after column chromatography, was the thiosulfonate and, in some cases, thiosulfinate.

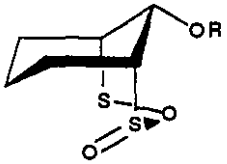
The next intermediate expected in this oxidation process, based on the literature examples (see Section 3.1.2), is an *O,S*-sulfenyl sulfinate. There are two possible *O,S*-sulfenyl sulfinates (plus their enantiomers) that could be formed by either a head-to-tail recombination (Scheme 37) of the sulfinyl radicals (**208-210**) or a concerted-type rearrangement (Scheme 38) of the unsymmetrical α-disulfoxides (**194, 197** and **203**). These species are unsymmetric, thus intermediates **198** and **200**, from the oxidation of the *p*-nitrobenzoyl thiosulfinate (**152**), and **200** and **207**, from the oxidation of the *n*-hexanoyl thiosulfinates (**153a** and **153b**), have been assigned to this structure.



(209) R = *p*-NO_2-C_6H_4-C(O)-
(210) R = CH_3-$(CH_2)_4$-C(O)-

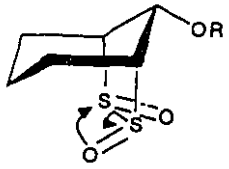


(198) or **(200)** R = *p*-NO_2-C_6H_4-C(O)-
(205) or **(207)** R = CH_3-$(CH_2)_4$-C(O)-

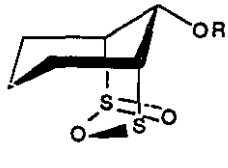


(198) or **(200)** R = *p*-NO_2-C_6H_4-C(O)-
(205) or **(207)** R = CH_3-$(CH_2)_4$-C(O)-

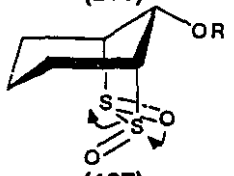
Scheme 37



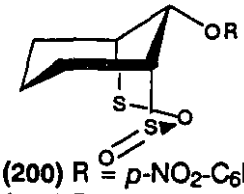
(197)
(203)



(198) or **(200)** R = *p*-NO_2-C_6H_4-C(O)-
(205) or **(207)** R = CH_3-$(CH_2)_4$-C(O)-



(197)
(203)



(198) or **(200)** R = *p*-NO_2-C_6H_4-C(O)-
(205) or **(207)** R = CH_3-$(CH_2)_4$-C(O)-

Scheme 38

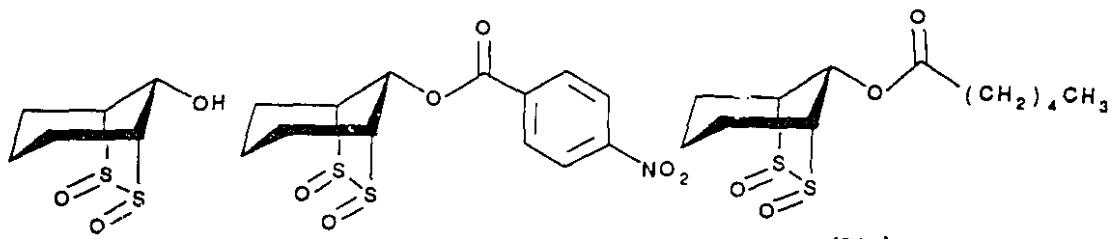
The similarity in their rate of appearance and the ^{13}C chemical shifts of intermediates **198** and **205** and those of **200** and **207** (Table 17) confirms that they are indeed the same species. It is difficult to determine the identity of each isomeric *O,S*-sulfenyl sulfinate, therefore the distinction between the two has not been made. There was no evidence for the formation of an *O,S*-sulfenyl sulfinate in the oxidation of **150a**; once formed, rapid conversion to the thiosulfonate product must have occurred. The conversion of *O,S*-sulfenyl sulfinate to thiosulfonate is depicted in Scheme 39.

Table 17: ^{13}C Chemical Shifts for [3.2.1] *O,S*-Sulfenyl Sulfinates (ppm)

Cpd	C8	C1	C4
198	75.7	69.7	66.5
205	74.9	69.5	66.7
200	72.8	65.4	64.0
207	71.7	65.3	63.7

Scheme 39

The remaining species to be identified are all symmetric. Although it would seem logical to assume that these species are sulfinic anhydrides (like **178**), the oxidation products of the above *O,S*-sulfenyl sulfinates, their disappearance from the reaction mixture without any sign of decomposition products precludes this possibility. The only other structure possible for these species is a symmetrical *endo* α-disulfoxide formed from a head-to-head recombination of the sulfinyl radicals **208-210** after appropiate rotations about the C-S bonds. Intermediate **195** from the oxidation of thiosulfinate **150a**; **201**, from the oxidation of **152** and **206**, from the oxidation of **153a** and **153b** have all been assigned to this structure. Table 18 shows the similarity in the ^{13}C chemical shifts of these species. Intermediate **195** was much more abundant than the other two *endo* α-disulfoxides. This fact, along with the absence of an *O,S*-sulfenyl sultinate in this reaction, suggests that **195** was more stable than **201** or **206**.



(195) (201) (206)

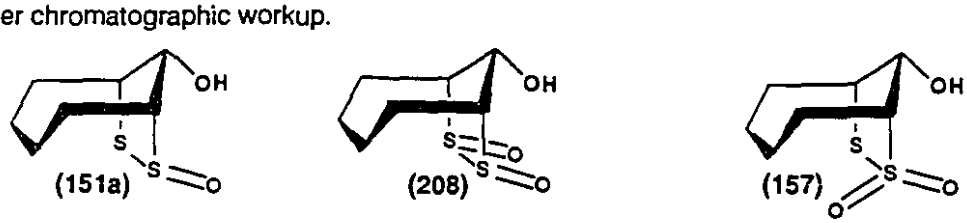
Table 18: ^{13}C Chemical Shifts for [3.2.1] *endo* α-Disulfoxides (ppm)

Cpd	C8	C1	C4
195	75.0	64.2	64.2
201	78.2	62.0	62.0
206	77.0	62.0	62.0

3.2.3 Oxidation of Bridged Bicyclic [4.2.1] Thiosulfinates

(i) syn-2,3-Dithia[4.2.1]bicyclononan-9-ol S-oxide **(151a)**

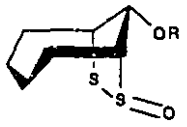
Oxidations involving a [4.2.1] bridged bicyclic thiosulfinates were not as complex as the [3.2.1] species. The first intermediate formed was always a symmetrical species to which an α-disulfoxide structure has been assigned. Oxidation of thiosulfinate **151a** produced α-disulfoxide **208** which became clearly visible at -30°C in both the ^{13}C (Figure 21) and ^{1}H (Figure 22) NMR spectra. Compound **208** was not present in the ^{13}C NMR spectra acquired at temperatures greater than 0°C, but was visible in the ^{1}H NMR spectrum acquired at 30°C. This, again, was most likely due to the longer amount of time required to collect the ^{13}C NMR spectra allowing more time for the intermediates to rearrange to more stable species. α-Disulfoxide **208** appeared to convert cleanly into thiosulfonate **157**, although a large peak at 68.9 ppm and two smaller peaks at 75.7 and 75.8 ppm in the ^{13}C NMR spectra was evidence for the formation of a small amount of other intermediates. The concentration of these species was never enough to allow structure assignment. The peak listings for the ^{13}C chemical shifts of compounds involved in this oxidation are given in Table 19. Thiosulfonate **157** was isolated in 70% yield (based on recovered starting material) after chromatographic workup.



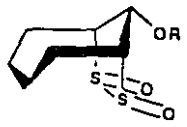
(151a) (208) (157)

Table 19: ^{13}C Chemical Shifts for the *m*-CPBA Oxidation of 151a (ppm)

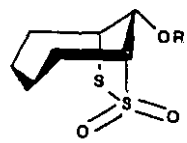
Cpd	C9	C1	C8	C7	C6	C5	C4
151a	86.8	78.0	30.9	23.7	23.3	24.2	68.1
208	91.1	76.0	25.6	24.9	24.9	25.6	76.0
157	75.1	74.2	33.9	24.7	22.9	23.9	64.3



a = 151a
R = H



b = 208



c = 157

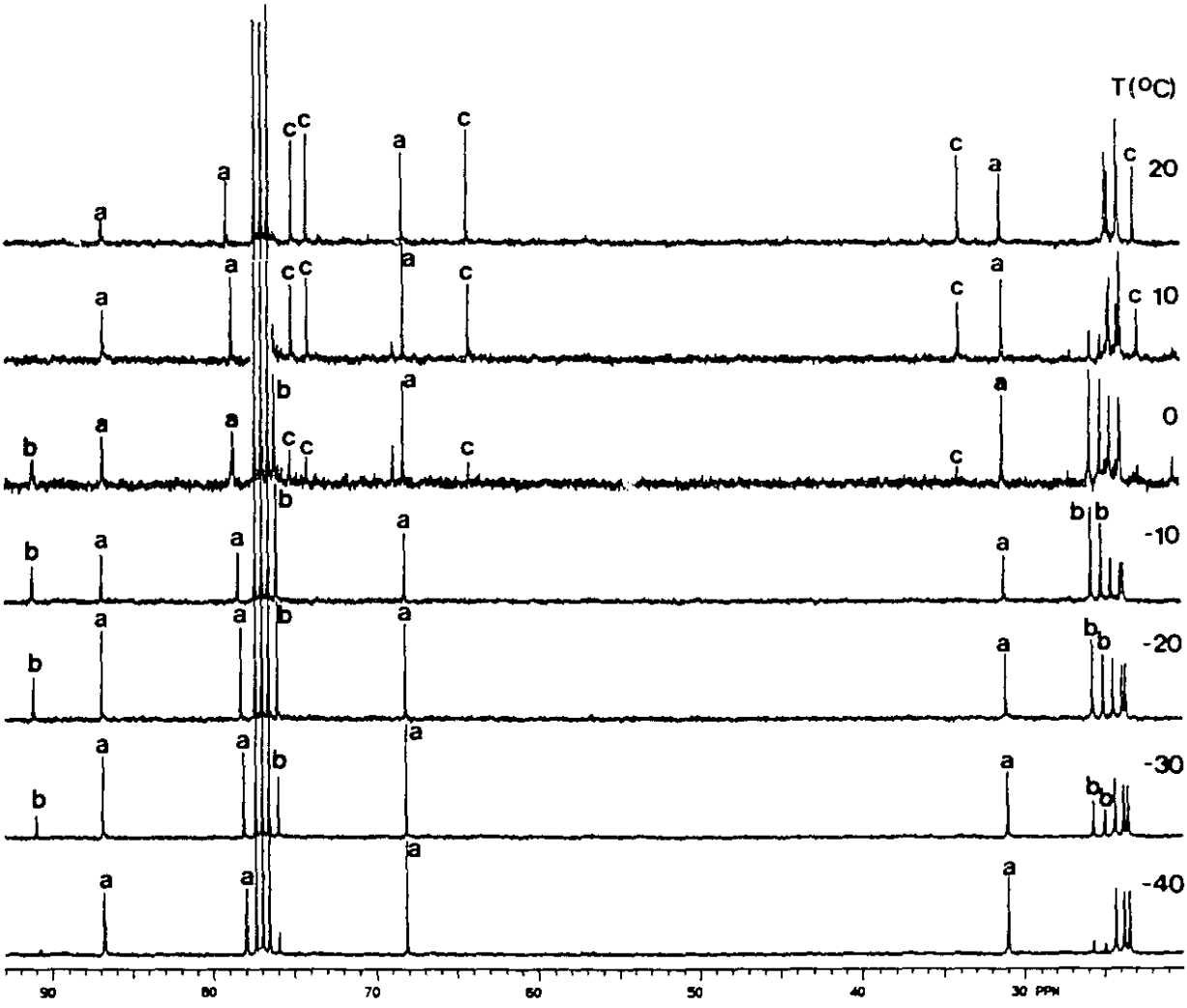
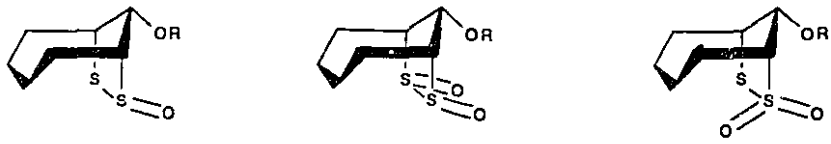


Figure 21: Low Temperature *m*-CPBA Oxidation of 151a; ^{13}C Spectra



a = 151a **b = 208** **c = 157**

R = H

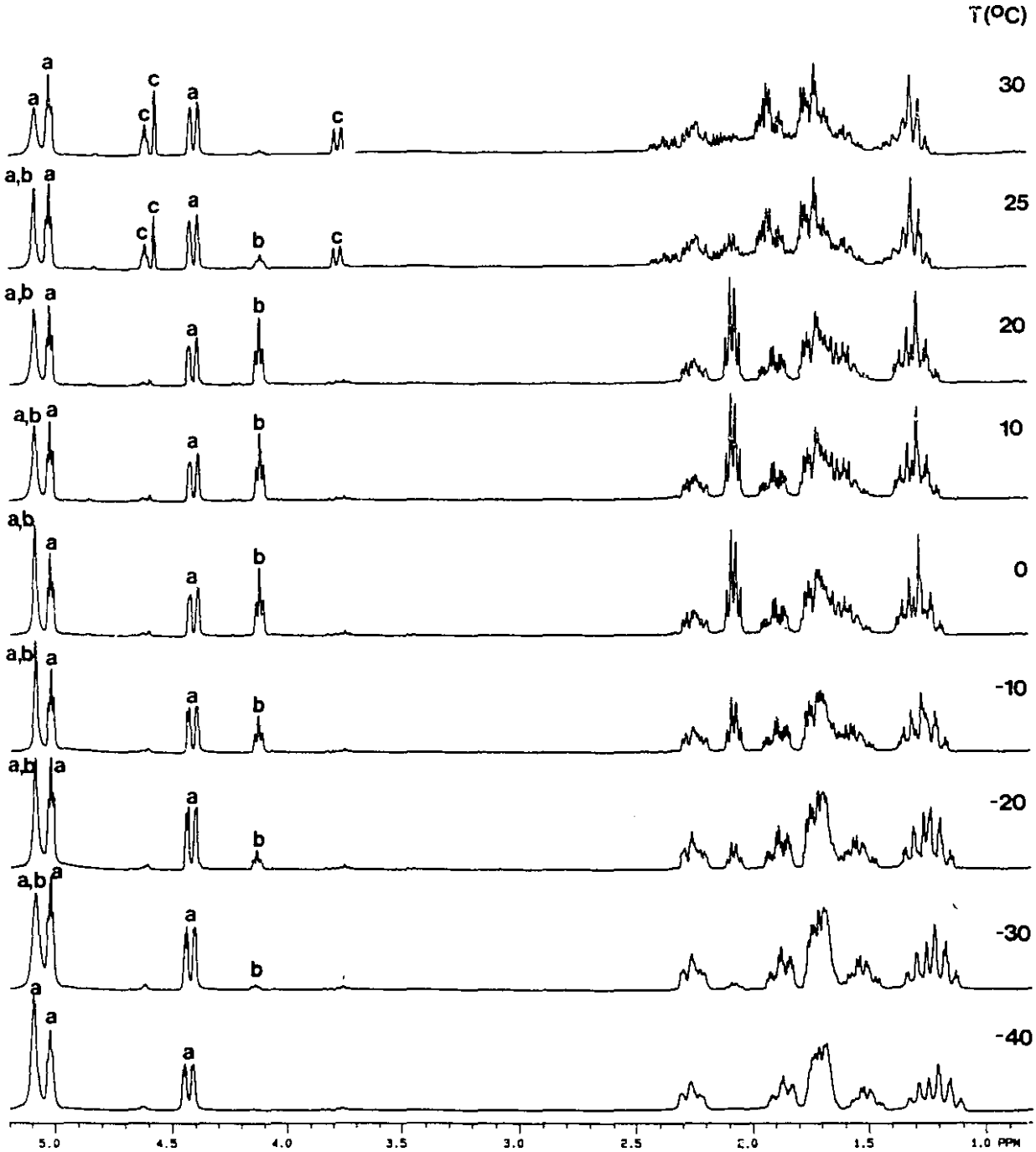


Figure 22: Low Temperature *m*-CPBA Oxidation of 151a; ^{1}H Spectra

In the ^{1}H NMR (Figure 22), the signal for H1 and H4 of **208** was a triplet centered at 4.14 ppm and that of H9 was buried under the H1 peak of compound **151a**. The percent compositions of the reaction mixtures during the oxidation of **151a** based on the integration of the ^{1}H NMR spectra are listed in Table 20 and a graph of this data is shown in Figure 23. In this experiment there was a large amount of thiosulfinate remaining at the end of the experiment. This was most likely due to an error in the addition of the correct amount of *m*-CPBA. Although less than in the ^{1}H experiment, there was also a significant amount of thiosulfinate remaining after the ^{13}C NMR experiment, thus the oxidation of this species does not proceed to completion with the addition of only one equivalent of oxidizing agent.

Table 20: Percent Composition of the Reaction Mixtures in the Oxidation of 151a[a]

Temp (°C)	151a	208	157
-30	94	4	2
-20	87	10	3
-10	76	21	3
0	65	32	3
10	65	31	4
20	64	32	4
25	64	8	28
30	65	3	32

[a]Based on integration of the ^{1}H spectra

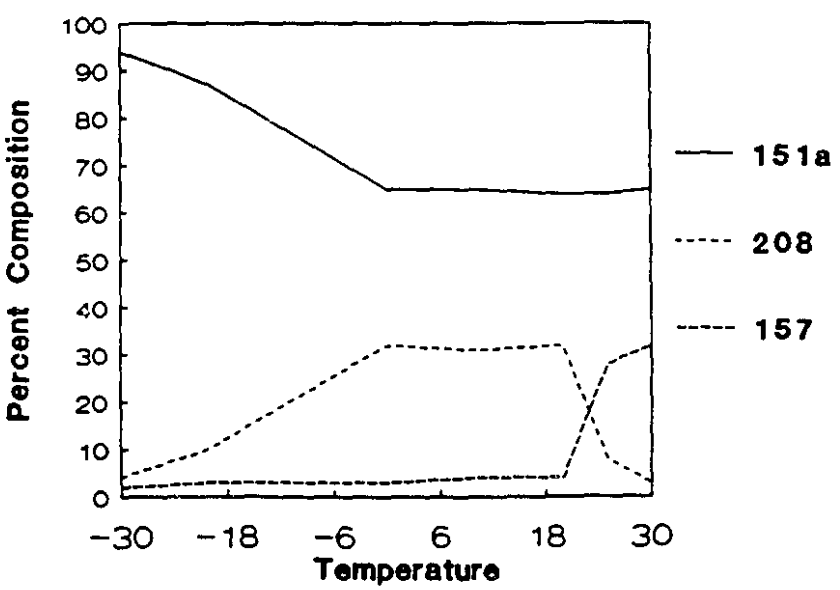
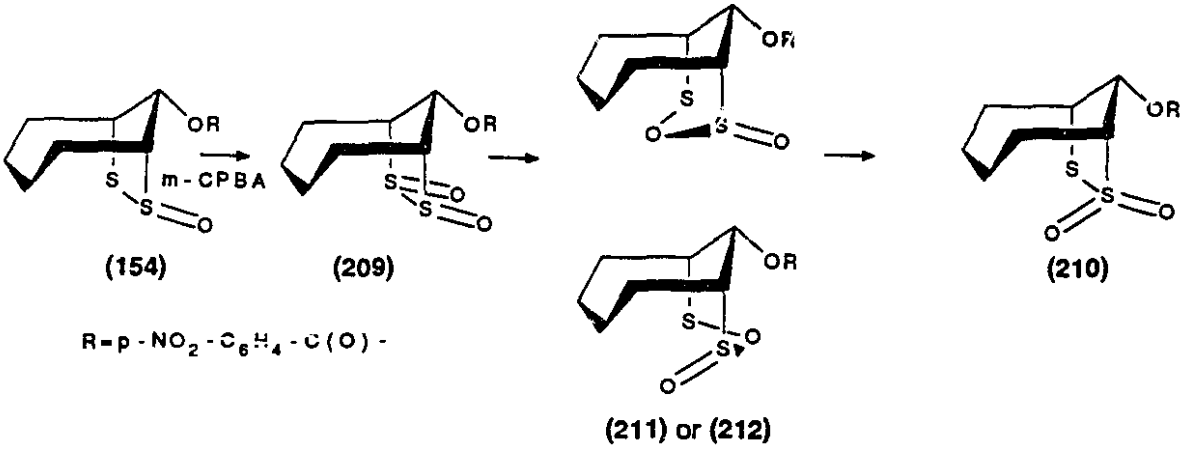


Figure 23: Graph of Percent Composition *vs* Temperature During the Oxidation of 151a (^{1}H NMR Experiment)

(ii) syn-2,3-Dithia-[(9-p-nitrobenzoyl)oxy]bicyclo[4.2.1]nonane S-oxide **(154)**

The first compound formed in the oxidation of thiosulfinate **154** was α-disulfoxide **209** (Scheme 40). This species did not become clearly visible until -20°C in both the ^{13}C (Figure 24) and ^{1}H (Figure 25) NMR experiments, but was present in every spectrum up to room temperature, where it was completely gone.

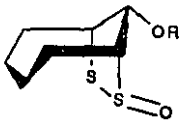
In the ^{13}C NMR experiment, the only species present at room temperature was thiosulfonate **210** and there was no evidence for the formation of other intermediates. This was most likely because of the low concentration of **154** used in this experiment and the lower sensivity of the ^{13}C NMR experiment. There were signals in the ^{1}H NMR spectra assignable to two other intermediates in the oxidation of **154**. Table 23 lists the percent compositions of the reaction mixtures during this experiment and this data is depicted by the graph in Figure 26. After the initial formation of α-disulfoxide **209**, an intermediate **(211)** with H9 appearing at 5.89 ppm became visible at 0°C. It was an unsymmetrical intermediate with H1 and H4 signals at 4.15 and 4.08 ppm, respectively. The concentration of **211** continued to grow and it was present in the spectrum acquired at 30°C. Another intermediate **(212)** was only a minor species first appearing at +10°C. It was another unsymmetrical intermediate with H8 appearing at 6.05 ppm. The position of the peaks for intermediates **211** and **212** suggest that they were *O,S*-sulfenyl sulfinates (Scheme 40) following the pattern that has been established in the *m*-CPBA of [3.2.1] thiosulfinates. The presence of a symmetrical intermediate assignable to an *endo* α-disulfoxide was not detected. This was also true in the ^{1}H NMR experiment for the oxidation of the [3.2.1] *p*-nitrobenzoyl thiosulfinate **(152)**. Thiosulfonate **210** was isolated in 60% yield by column chromatography.



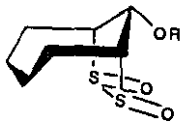
Scheme 40

Table 21: ^{13}C Chemical Shifts for the *m*-CPBA Oxidation of 154 (ppm)

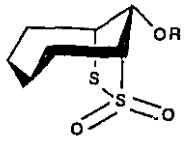
Cpd	C9	C1	C8	C7	C6	C5	C4
154	85.8	79.6	31.9	24.2	23.9	24.3	64.4
209	89.3	74.3	25.9	24.9	24.9	25.9	74.3
210	75.0	73.6	34.5	24.3	22.2	24.8	59.6



a = 154



b = 209



c = 210

R = p - NO_2 - C_6H_4 - C(O) -

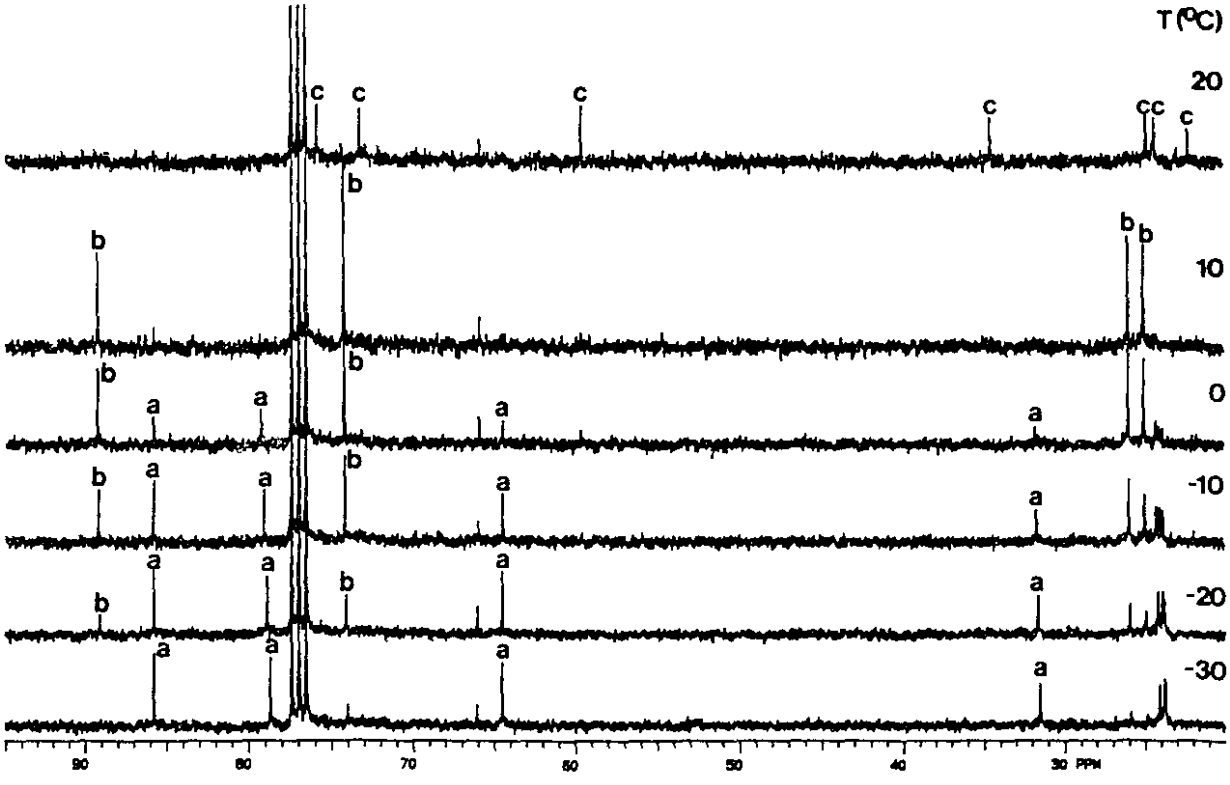


Figure 24: Low Temperature *m*-CPBA Oxidation of 154; ^{13}C Spectra

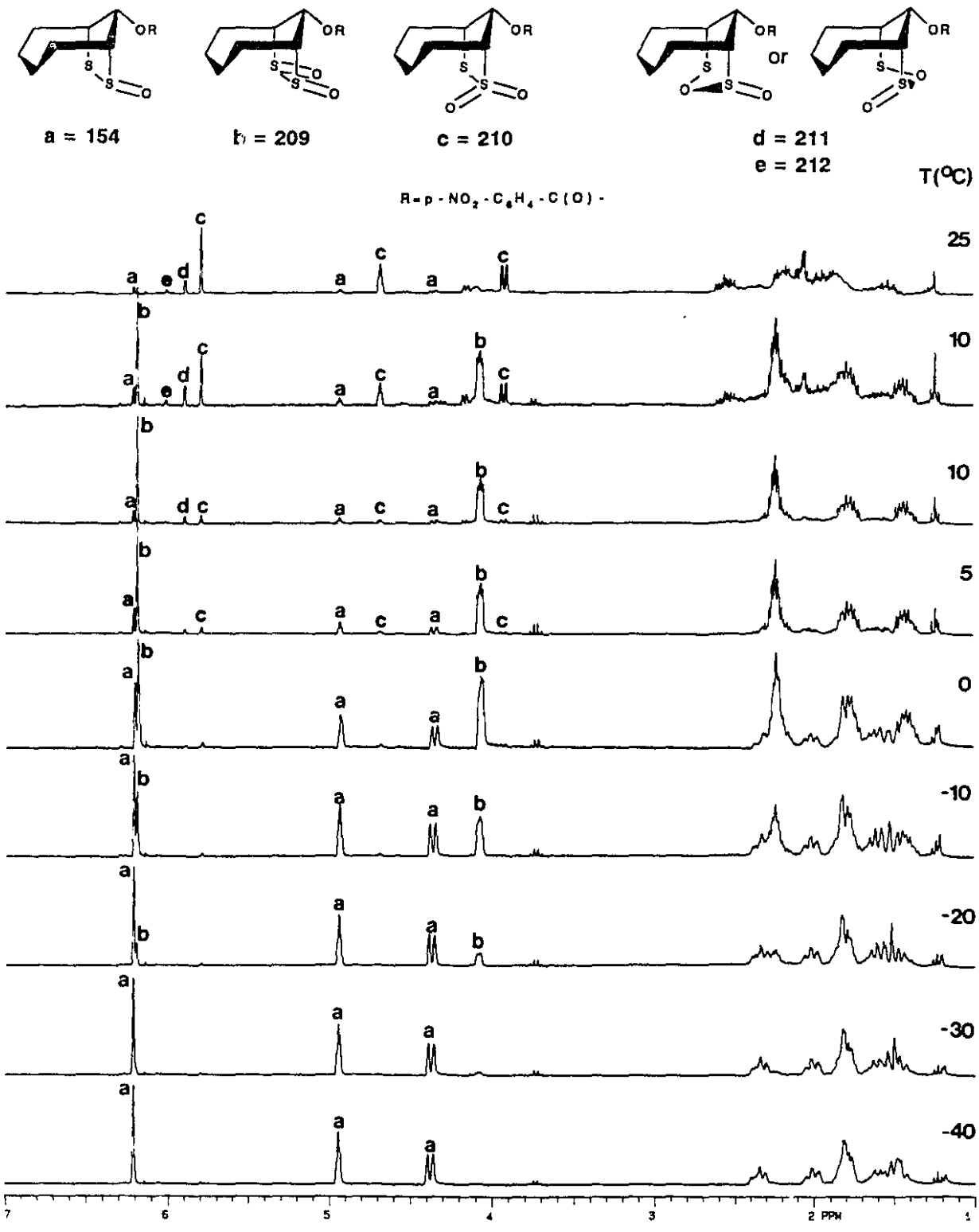


Figure 25: Low Temperature *m*-CPBA Oxidation of 154; ^{1}H Spectra

Table 22: ^{1}H Chemical Shifts for the *m*-CPBA Oxidation of 154 (ppm)

Cpd	H9	H1	H4
154	6.21 (s)	4.93 (t)	4.36 (d)
209	6.19 (t)	4.06 (m)	4.06 (m)
210	5.80 (t)	4.68 (t)	3.91 (d)
211	5.89 (m)	4.15 (d)	4.08 (m)
212	6.05 (m)	4.53 (d)	4.20 (d)

Table 23: Percent Composition of the Reaction Mixtures in the Oxidation of 154[a]

Temp (°C)	154	209	210	211	212
-30	91	7	2	0	0
-20	79	19	2	0	0
-10	59	39	2	0	0
0	35	60	3	2	0
5	19	71	5	5	0
10	12	70	8	8	2
20	10	47	26	14	3
25	6	0	65	17	4

[a]Based on integration of the ^{1}H spectra

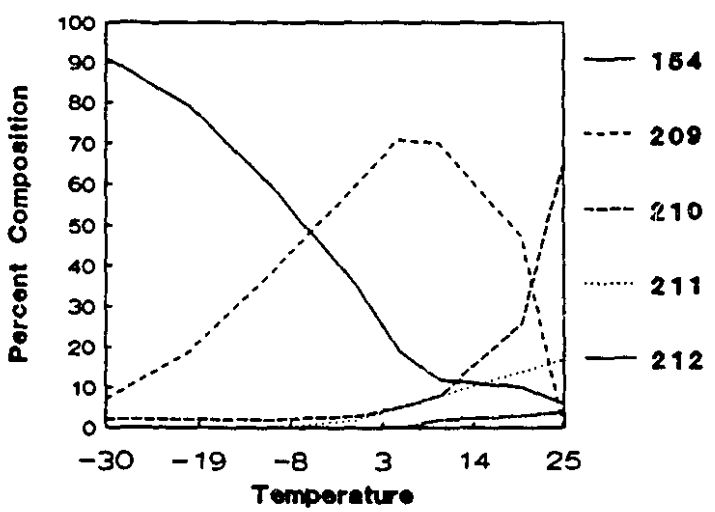
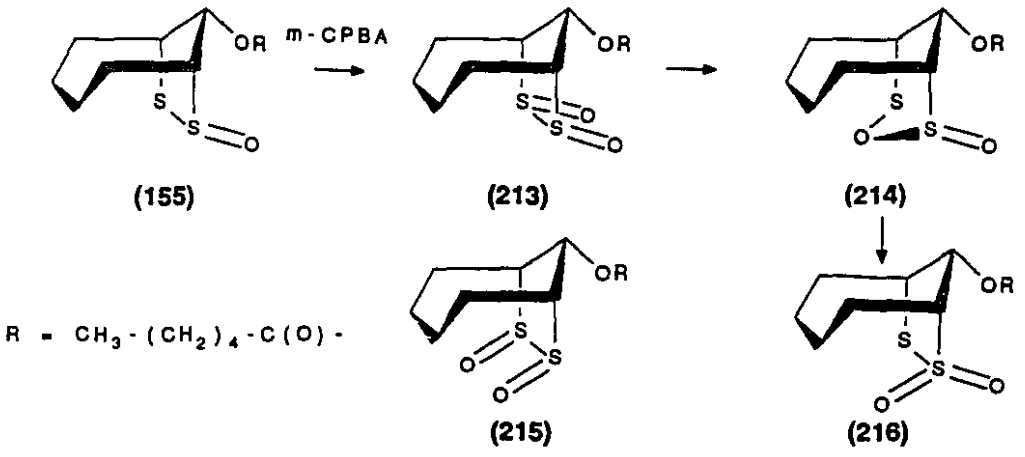


Figure 26: Graph of Percent Composition *vs* Temperature During the Oxidation of 154 (^{1}H NMR Experiment)

(iii) syn-2,3-Dithia-[(9-n-hexanoyl)oxy]bicyclo[4.2.1]nonane S-oxide **(155)**

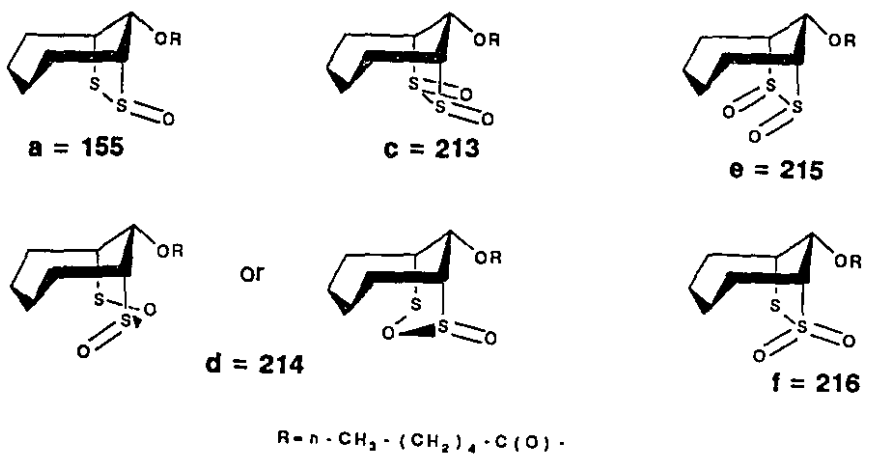
The *m*-CPBA oxidation of **155** was followed by ^{13}C NMR spectroscopy only (Figure 27). The α-disulfoxide **(213)** was already present at -30°C and it reached a maximum concentration at 0°C. In this example, there was evidence for the formation of the other intermediates in the rearrangement of α-disulfoxide to thiosulfonate (Scheme 41), although they were not as abundant as those seen in the oxidations of [3.2.1] thiosulfinates. The second intermediate, **214**, first appeared at 0°C and its peak positions (Table 24) suggest that is was an *O,S*-sulfenyl sulfinate (only one of the two possible isomers is drawn below). The next species **(215)** was symmetric and it appeared first at 5°C. Its peak locations are consistent with a symmetrical *endo* α-disulfoxide structure. The final reaction mixture contained mainly thiosulfonate **216** which was isolated in 55% yield by column chromatography.



Scheme 41

Table 24: ^{13}C Chemical Shifts for the *m*-CPBA Oxidation of 155 (ppm)

Cpd	C9	C1	C4
155	84.3	79.9	64.8
213	88.2	74.2	74.2
214	74.6	72.8	71.9
215	80.0	66.8	66.8
216	74.8	73.5	59.5



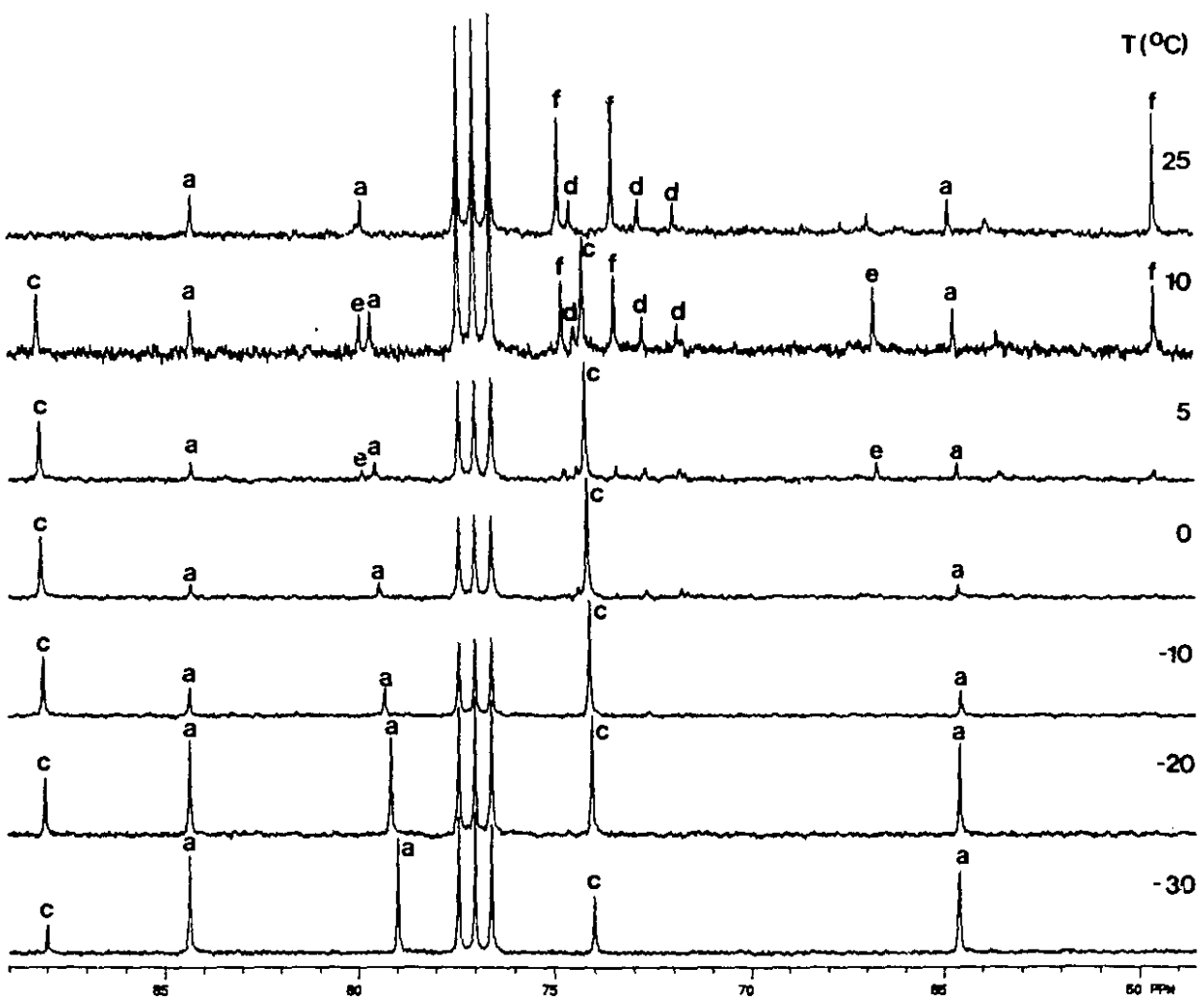
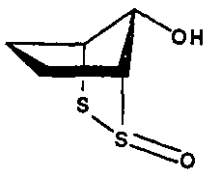


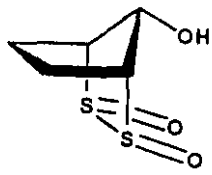
Figure 27: Low Temperature *m*-CPBA Oxidation of 155; ^{13}C Spectra

3.2.4 Oxidation of Bridged Bicyclic [2.2.1] Thiosulfinates

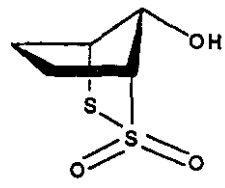
Low temperature oxidation experiments were also attempted on the [2.2.1] thiosulfinates; however, they were not as informative as the above examples with the [3.2.1] and [4.2.1] thiosulfinates. The oxidation of thiosulfinate **149a** was followed by ^{13}C NMR spectroscopy. A symmetrical intermediate **(217)** was detected at -35°C and it was the main species in the spectrum at -25°C. Upon further warming of this reaction mixture, no signals were observed corresponding to any species even after an hour of experimental time. The number of species formed must have been too great and thus each was too dilute to be detected. The spectrum of the final reaction mixture, warmed to room temperature, contained several peaks that could not be identified. Chromatography of this mixture resulted in the isolation of thiosulfonate **218**, however in only 5% yield. The peak positions of thiosulfinate **149a**, α-disulfoxide **217** and thiosulfonate **218** are given in Table 25.



(149a)



(217)



(218)

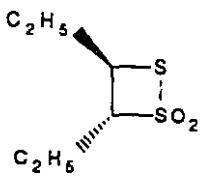
Table 25: ^{13}C Chemical Shifts for the *m*-CPBA Oxidation of 149a (ppm)

Cpd	C7	C1	C6	C5	C4
149a	86.2	64.3	27.5	17.0	57.1
217	95.8	59.7	16.7	16.7	59.7
218	67.2	61.9	28.3	20.5	29.7

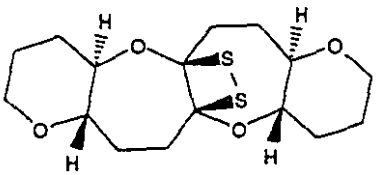
The [2.2.1] thiosulfonate **(218)** was a very stable compound. It could be left at room temperature in ambient light for a period of over a month without any evidence of decomposition. This contrasts with the stability of thiosulfinate **149a**, which had to be stored in the freezer in order to prevent decomposition. The stability of **218** is not surprising as the first example of an isolable 1,2-dithietane derivative was 3,4-diethyl-1,2-dithietane 1,1-dioxide **(219)**.[156] The explanation offered for the stability of **219** was the removal of the destabilizing effect of the repulsion between

156. E. Block, A.A. Bazzi and L. K. Revelle, *J. Amer. Chem. Soc.*, **102**, 2490 (1980).

the neighbouring lone pair of electrons on the sulfur atoms. This theory has been mentioned previously to explain the stabilitity of 1,2-dithiolane-*S*-oxides (Chapter 1) and earlier in this chapter to explain the stability of bridged bicyclic thiosulfinates over their corresponding disulfides. The [4.2.1] and [3.2.1] thiosulfonates are also very stable compounds. The only known 1,2-dithietane stable enough to be isolated thus far is dithiatopazine (220).[157]



(219)



(220)

3.3 Conclusion

Oxidation of bridged bicyclic thiosulfinates using *m*-CPBA at low temperatures (-30 to -40°C) produced a species that was not the corresponding thiosulfonate but was converted, through a series of intermediates, to this expected product. There is no doubt that oxidation occurred at the "softer" sulfenyl sulfur atom to give an α-disulfoxide intermediate. The quantity of α-disulfoxide formed and the temperatures at which signals were observed for its presence (25°C in some examples) were higher than any previous direct evidence reported for α-disulfoxide formation by both Freeman[143] and Harpp.[146] The results reported in this work have provided the most conclusive evidence to date for α-disulfoxide formation and have given many insights into the mechanism for α-disulfoxide rearrangement or disproportionation into final product(s).

The α-disulfoxides initially formed in the oxidation of the *exo* diastereomers of bridged bicyclic thiosulfinates were symmetrical compounds. This resulted because the preferred direction for *m*-CPBA to enter was from the *exo* face due to steric hindrance of the six-membered ring. This preference for *"exo"* attack was first noticed in the peroxidation of bridged bicyclic disulfide to thiosulfinate.

The existence and isolation of an *endo* bridged bicyclic thiosulfinate **(153b)** provided further insight into the mechanism for the peroxidation of thiosulfinates. Oxidation of **153b** from the *exo* face produced the only unsymmetrical α-disulfoxide **(203)** seen as the first intermediate in

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157. K. C. Nicolaou, C.-K. Hwang, M. E. Duggan and P. J. Caroll, *J. Amer. Chem. Soc.*, **102**, 3801 (1987).

these reactions. It turned out that intermediate **203** was also the second intermediate seen in the oxidation of the *exo* thiosulfinate (**153a**). This discovery provided evidence for one pathway in the mechanism of α-disulfoxide rearrangement/disproportionation; that is, after the initial oxidation to symmetrical α-disulfoxide, homolysis of the S-S bond occurred followed by rotation about one C-S bond and radical recombination in a head-to-head fashion to give an unsymmetrical α-disulfoxide (Scheme 36). The peak positions and time of appearance for intermediates **194** and **197** were similar to those of **203**, thus these species were assigned the unsymmetrical α-disulfoxide structure. There was evidence that rotation about both C-S bonds also occurred followed by radical recombination in a head-to-head fashion to provide another symmetrical α-disulfoxide, with both sulfinyl oxygens in the *endo* conformation. Symmetrical intermediates **195**, **201**, **206** and **215** have been assigned this structure.

It is interesting to note that no evidence was found for the formation of unsymmetrical α-disulfoxides in the oxidation of [4.2.1] thiosulfinates. Formation of *O,S*-sulfenyl sulfinates was observed, thus recombination of the sulfinyl radicals in these examples must favour a head-to-tail pathway. This most likely reflects the lower stability of the unsymmetrical [4.2.1] α-disulfoxides which may be due to steric factors. A small amount of head-to-head recombination of the sulfinyl radicals occurred during the oxidation of **155** to give the symmetrical *endo* α-disulfoxide.

Strong evidence was also found for the formation of *O,S*-sulfenyl sulfinates. The peak positions and time of appearance for intermediates **198**, **205**, **209** and **207** in the oxidation of [3.2.1] thiosulfinates and intermediates **210**, **211** and **214** in the oxidation of [4.2.1] thiosulfinates provides powerful support for the existence of these species, the best reported to date.

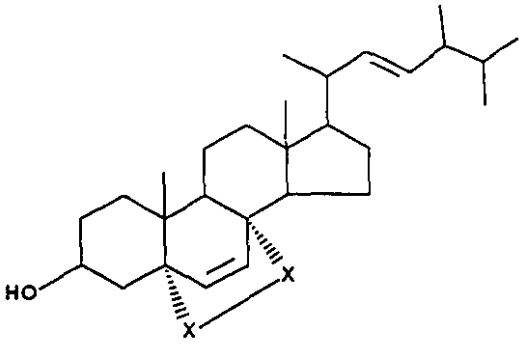
The isolation of final product, the corresponding thiosulfonate ester, was performed by column chromatography. The yields were good in examples where the intermediates had all converted to final product by the end of the experiment. This occurred in all reactions except the oxidation of substituted [3.2.1] bridged bicyclic thiosulfinates. The final reaction mixture from the oxidation of thiosulfinates **152**, **153a** and **153b** contained significant amounts of intermediate species. These compounds were not stable enough to be isolated by column chromatography on silica or alumina likely due to an esterification reaction with the hydroxyl groups on the solid support. This resulted in low yields of thiosulfonates **199** and **204**. It also provides an explanation for the reported difficulty in oxidizing cyclic thiosulfinates **83b** and **87**[114] (Chapter 1). The mechanism described in this work is mostly likely also in operation during the attempted oxidation of **83b** and **87**. The possibility for the formation of even more products *via* dimerization would be greater with these smaller molecules than with the bicyclic compounds, thus it is not surprising that the isolation of thiosulfonates was not successful.

It is evident that further investigations into the peroxidation of bridged bicyclic thiosulfinates should provide more information about the mechanism of this reaction. There is also a potential for investigating the chemical behavior of an unstudied class of compounds, α-disulfoxides, *via* low temperature reactions. The work reported here has already produced α-disulfoxides in amounts and at temperatures greater than any previously reported, thus providing a prime target for further studies into these species.

Chapter 4: Attempts Towards the Synthesis of Ergosta-6,22-dien-5α,8α-epidithia-3-ol: The Bridged Bicyclic Disulfide Analogue of Ergosterol Peroxide

4.1 Introduction

Ergosterol peroxide (**221a**, ergosta-6,22-5α,8α-epidioxy-3-ol) is a well known natural product which was first isolated in 1947 from the mycelium of *Aspergillus fumigatus*.[158] Since then it has been isolated from a number of other fungi,[159] lichens[160] and marine organisms.[161]



(**221**) **a** X = O, **b** X = S

The biological activity of compound **221a** has been well documented and includes platelet aggregating properties[159e] and phytotoxic activity against a variety of plant tissues.[162] With regard to this latter property, ergosterol peroxide has been recently investigated as a potential

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158. P. Wieland and V. Prelog, *Helv. Chim. Acta.*, **30**, 1028 (1947).

159. a) G. Bauslaugh, G. Just and F. Blank, *Nature*, **202**, 1218 (1964); b) H. K. Adam, I. M. Campbell and N. J. McCorkin, *Nature*, **216**, 397 (1967); c) E. P. Serebryakov, A. V. Simolin, V. F. Kucherov and B. V. Rosynov, *Tetrahedron*, **26**, 5215 (1970); d) J. Arditti, R. Ernst, M. H. Fisch and B. H. Flick, *J. Chem. Soc. Chem. Comm.*, 1217 (1972); e) J. D. Weete, *Phytochemistry*, **12**, 1843 (1973); f) L. C. Brown and J. J. Jacobs, *Aust. J. Chem.*, **28**, 2317 (1975); g) W. Lu, I. Adachi, K. Kano, A. Yasuta, K. Toriizuka, M. Ueno and I. Horikoshi, *Chem. Pharm. Bull.*, **33**, 5083 (1985); g) G. Kusano, H. Ogawa, A. Takahashi, S. Nozoe and K. Yokoyama, *Chem. Pharm. Bull.*, **35**, 3482 (1987).

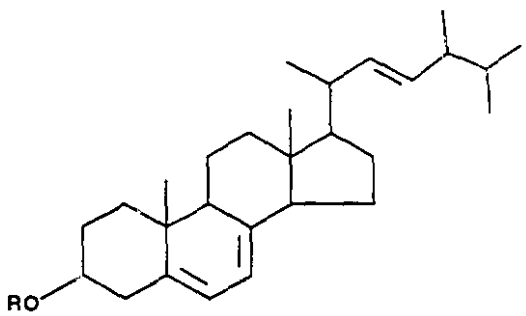
160. T. Hirayama, F. Fujikawa, I. Yosioka and I. Kitagawa, *Chem. Pharm. Bull.*, **23**, 693 (1975).

161. a) A. A. L. Gunatilata, Y. Gopichand, F. J. Schmitz and C. Djerassi, *J. Org. Chem.*, **46**, 3860 (1981) and references therein; b) M. Guyot and M. Durgeat, *Tetrahedron Lett.*, **22**, 1391 (1981).

162. a) N. Otomo, H. Sato and S. Sakamura, *Agric. Biol. Chem.*, **47**, 1115 (1983); b) Y. S. Tsantrizos, Ph. D. Thesis, McGill University, Montreal, Quebec, Canada (1988).

herbicide for the perennial weed, *Convolvulus arvensis*, better known as field bindweed.[162b,163] In fact, research into *P. convolvulus* was initiated in hope of developing means for the effective control of field bindweed which has developed resistance to the presently available synthetic herbicides and has been classified as one of the most serious agricultural pests worldwide.[164]

Ergosterol **(222a)**, the biosynthetic precursor of metabolite **221a**, was also isolated from the growth medium of *P. convolvulus*.[162b] This compound did not show any activity against field bindweed. Since the only structural difference between compounds **221a** and **222a** is the epidioxy bridge, it is tempting to conclude that this moiety is responsible for the phytotoxicity of **221a**. It was proposed that if the activity of **221a** was to be increased, analogues should possess a bridged bicyclic structure with variations in the atomic composition. This provided a prime target for the synthesis of another bridged bicyclic disulfide **(221b)** and an opportunity to further extend the usefulness of this class of compounds as biologically important molecules.



(222) a R = H, **b** R = TBDPS, **c** R = OAc

The synthesis of sulfur analogues of natural products for the purpose of imitating or even increasing the biological activity of the parent compounds is not unprecedented. Perhaps one of the best examples may be found in the prostaglandin area. The bridged bicyclic endoperoxides PGG_2 **(223)** and PGH_2 **(78)** (mentioned in Chapter 1 and 2) are important intermediates in the biosynthesis of prostaglandins, prostacyclin and thromboxanes.[101] Efforts to study the biological mode of action and the biosynthesis of these compounds have been hampered by their low

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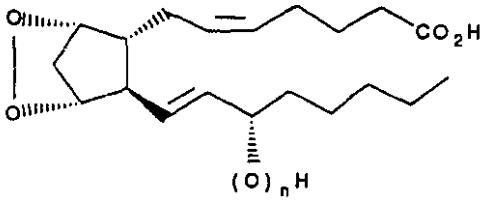
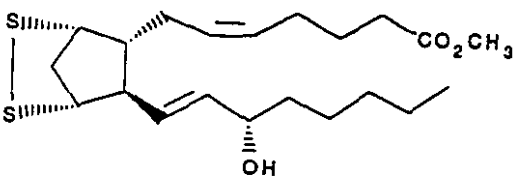
163. Ergosterol peroxide **(221a)** caused slight browning on the leaves of field bindweed at a concentration of 0.2 mg/ml in a 5% ethanol solution (ref. 162b). Biological testing was limited by the poor solubility of **221a** in aqueous media. This same solution also showed 10% inhibition of growth of the aquatic small plant, *Lemna*.

164. a) J. F. Alex, in *Biology and Ecology of Weeds*, W. Holzner and M. Numata, Eds., The Hagues. 309 (1982); b) L. G. Holm, D. L. Plunknett, J. V. Pancho and J. P. Herberger, in *The World's Worst Weeds*, Hawaii: University Press of Hawaii, Chapt. 12 (1977); c) S. S. Rosenthal, *Calif. Agric.*, **37**, 16 (1983).

stability in aqueous buffer solutions; this stimulated synthetic investigations into their sulfur analogues.[102] It was believed that the bridged bicyclic disulfide system would be more stable than the oxygen analogue. This has been proven correct and a sulfur analogue (**79**) has been shown to act as an irreversible aggregator of platelets and as a strong mimic of thromboxane A_2 in contracting rabbit aorta strips.[102a,c]



(223) n = 2
(78) n=1



(79)

Several other sulfur analogues of biologically important molecules also have been reported. These include analogues of clavulanic acid,[165] leukotriene B_4,[166] monoamine oxidase inhibitors[167] and vitamin B_6 derivatives.[168]

4.2 Results and Discussion

Ergosterol peroxide (**221a**) has been synthesized from ergosterol (**222a**) both enzymatically[169] and chemically.[170] Many of the chemical syntheses involve a photochemical generation of singlet oxygen which reacts with the diene of **222a** *via* a Diels-Alder addition. Following this strategy, the synthesis of a sulfur analog of ergosterol peroxide was attempted *via* the Diels-Alder addition of diatomic sulfur to ergosterol.

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165. J. L. Douglas, A. Martel, G. Caron, M. Menard, L. Silveira and J. Clardy, *Can. J. Chem.*, **62**, 3382 (1984).

166. Y. Guindon and D. Delorme, *Can. J. Chem.*, **65**, 1438 (1987).

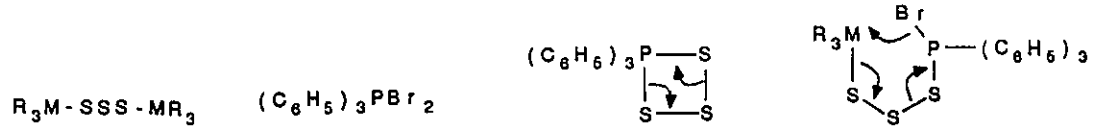
167. T. R. Bosin, R. P. Maickel, A. Dinner, A. Snell and E. Campaigne, *J. Heterocyclic Chem.*, **9**, 1265 (1972).

168. M. Iwata and H. Kuzuhara, *Bull. Chem. Soc. Jpn.*, **58**, 2502 (1985).

169. M. L. Bates and W. W. Reid, *J. Chem. Soc., Chem. Comm.*, 44 (1976).

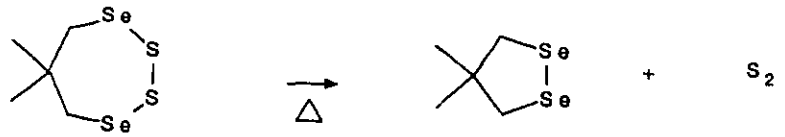
170. a) V. A. Windaus and J. Brunken, *Justus Liebigs Ann. Chem.*, **465**, 225 (1928); b) L. F. Fieser and M. Fieser, in *Steroids*, New York: Reinhold Publishing Corporation, (1959) and references therein; c) D. H. R. Barton, G. Leclerc, P. D. Magnus and I. D. Menzies, *J. Chem. Soc. Chem. Comm.*, 447 (1972); d) D. H. R. Barton, R. K. Haynes, P. D. Magnus and I. D. Menzies, *J. Chem. Soc., Chem. Comm.*, 511 (1974).

There have been several methods reported for the generation of diatomic sulfur and their reactions with dienes to give cyclic disulfides as products. The first synthetically useful procedure to appear in the literature involved the reaction of organometallic trisulfides of general structure **224** with triphenyldibromophosphorane **(225)**.[171] This same procedure was used to generate the pseudo-diatomic species, R-P=S (commonly known as thiophosphanes, phenyl thioxophosphanes and phosphinothioylidenes) which is the subject of Chapter 5. In the published examples, the reaction generated and delivered diatomic sulfur to a diene by one of two possible mechanisms. A four-membered ring intermediate **(226)** may have been involved, which is analogous to that proposed in the generation of singlet oxygen *via* thermal decomposition of a phosphine or phosphite ozone adduct;[172] or the intermediate may have been an open chain species such as **227**.



(224) **(225)** **(226)** **(227)**

In 1987, two methods appeared in the literature for the generation of diatomic sulfur. Schmidt and Görl[173] reported that the cyclic species, 5,5-dimethyl-1,2-dithia-3,7-diselenacycloheptane **(228)** will undergo ring contraction with the formation of 4,4-dimethyl-1,2-diselenacyclopentane **(229)** and S_2 under thermolytic conditions (Scheme 42). The S_2 generated was trapped as a cyclic disulfide when dienes were present.



(228) **(229)**

Scheme 42

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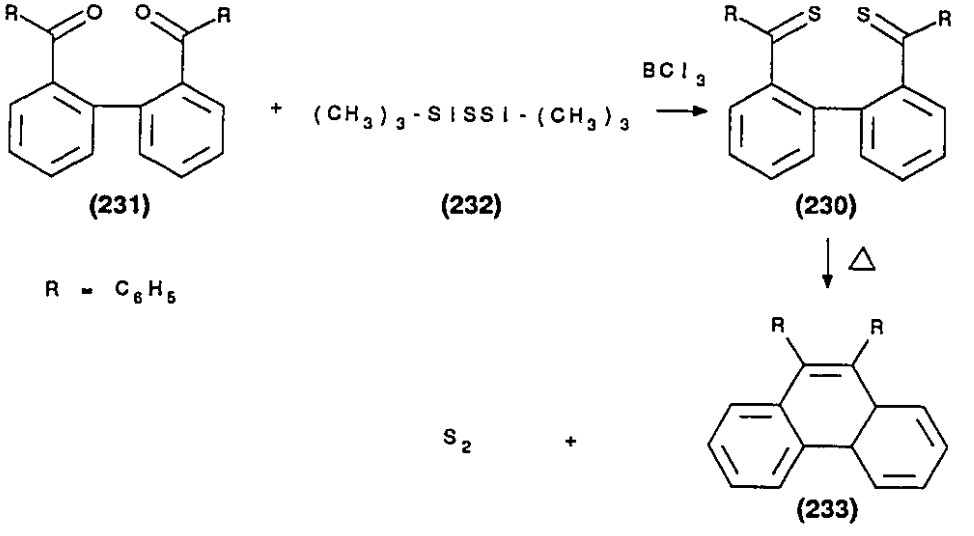
171. K. Steliou, Y. Gareau and D. N. Harpp, *J. Amer. Chem. Soc.*, **106**, 799 (1984).

172. P. D. Bartlett and C. M. Lonzetta, *J. Amer. Chem. Soc.*, **105**, 1984 (1983) and references therein.

173. M. Schmidt and U. Görl, *Angew. Chem. Int. Ed. Engl.*, **26**, 887 (1987).

Alternatively, Steliou and co-workers[77,174] investigated the thermal rearrangement of aromatic thioketones of general structure **230** for the release of diatomic sulfur (Scheme 43). The aromatic thioketones were prepared *in situ* by reaction of the corresponding diones **(231)** with BCl_3 and thiane **232**.[175] Heating **230** in the presence of a diene resulted in the isolation of cyclic disulfides in good yields, along with the energetically favoured phenanthrene side product **(233)**. Steliou has applied this method to the synthesis of several sulfur-containing compounds.[77,176] This method was selected as an approach to the synthesis of **221b**.



Scheme 43

In order to initially establish that the proper procedure for this synthesis was being followed, the reaction was performed in the presence of 2,3-diphenylbutadiene **(234)**. The product of this reaction was the known dihydro 1,2-dithiin **235** and it was isolated in 65% yield (based on recovered starting material).

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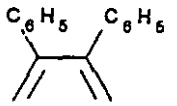
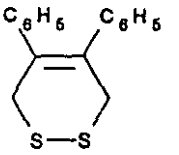
174. a) K. Steliou, P. Salama, D. Brodeur and Y. Gareau, *J. Amer. Chem. Soc.*, **109**, 926 (1987).

175. K. Steliou and M. Mrani, *J. Amer. Chem. Soc.*, **104**, 3104 (1982).

176. a) K. Steliou, Y. Gareau, G. Milot and P. Salama, *Phosphorus, Sulfur and Silica*, **43**, 209 (1989).

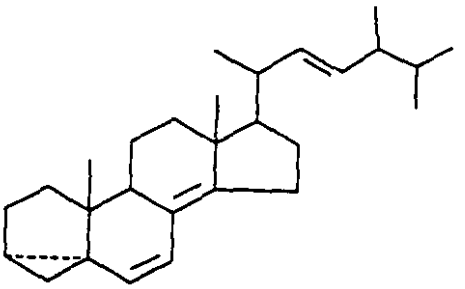


(234)



(235)

The synthesis of thioketone **231** in the presence of ergosterol (**222a**) led to the formation of two major steroidal products. The major species turned out to be the known compound, 3,5-cyclo-6,8(14),22-ergostatriene (**236**), previously isolated as the dehydration product of ergosterol with either phosphorus oxychloride or *p*-toluenesulfonylchloride in pyridine.[177] Although the complete NMR data for **236** were not available in the literature, its UV and melting point were in complete agreement with those previously reported.



(236)

The second species isolated (**237**) had ^{1}H and ^{13}C NMR data very similar to those of ergosterol (**222a**). In the ^{1}H NMR spectrum, the signal for H3 was shifted downfield by 0.2 ppm from that of ergosterol and the signal for the H4 protons was shifted by approximately the same amount. In the ^{13}C NMR spectrum, the signals that were shifted by the greatest amount from those in ergosterol were those for the carbons of the A ring. The C3 carbon showed the largest shift; in **237**, this signal appeared 31 ppm upfield from its location in the ^{13}C spectrum of **222a**. This type of shift would be expected if the OH group had been replaced by an SH group. Other examples of the chemical shift difference between the α-carbons of alcohols and thiols are given in Table 26.

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177. M. Fieser, W. E. Rosen and L. F. Fieser, *J. Amer. Chem. Soc.*, **74**, 5397 (1952).

Table 26: ^{13}C Chemical Shifts of the α-Carbon of Alcohols and Their Sulfur Analogues (ppm)[178]

Cpd	Alcohol (X = O)	Thiol (X = S)
CH_3XH	50.2	6.5
CH_3CH_2XH	57.8	19.1
$CH_3CH_2CH_2XH$	64.2	26.4
$(CH_3)_2CHXH$	64.0	29.9
$(CH_3)_3CXH$	68.9	41.12
cyclohexane-XH	69.5[179]	38.5

The UV spectrum of compound **237** and ergosterol **(222a)** were virtually identical, but the IR spectrum of **237** did not have the characteristic OH stretch at 3650 cm^{-1}. All of the spectral data suggested that compound **237** is the mercapto-analog of ergosterol, which was confirmed by an X-ray structure. The ORTEP drawing of **237** is shown in Figure 28.

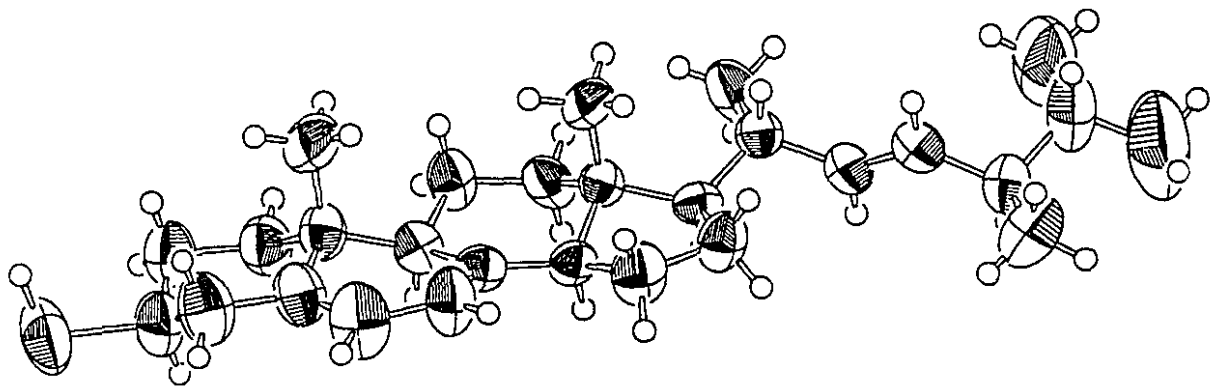


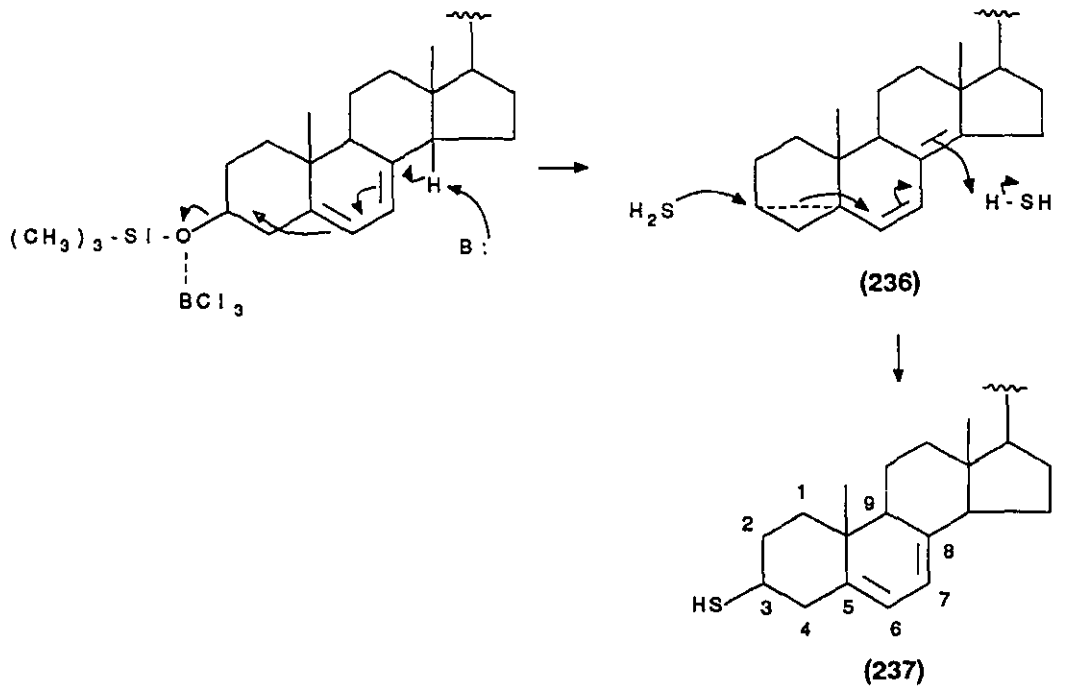
Figure 28: ORTEP Drawing of 237

The mechanism for the formation of both compounds **236** and **237** clearly involved Lewis

178. *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd Ed., W. Fresenius, J. F. K. Huber, E. Pungor, G. A. Rechnitz, W. Simon and Th. S. West, Eds., New York: Springer-Verlag (1989).

179. R. M. Silverstein, G. C. Bassler and T. C. Morrill, *Spectrometric Identification of Organic Compounds*, 4th Ed., Toronto: John Wiley & Sons, p. 268 (1981).

acid-assisted, OH elimination (Scheme 44). Silylation of the alcohol functionality is likely to occur first which, in the presence of BCl_3, can be eliminated to give compound **236**.[180] Since the SH group of compound **237** has the same stereochemistry as the OH functionality of ergosterol, formation of this compound likely occurred *via* the attack of H_2S on the β face of the A ring of **236**. These results, along with the fact that the same two products were isolated when **231** was omitted from the reaction mixture, add support to the proposed mechanism.



Scheme 44

In order to avoid the problem of OH elimination in the presence of BCl_3, ergosterol was protected with *t*-butyldiphenylsilyl chloride **(222b)** and the reaction was repeated. Unfortunately no major steroidal products were isolated. The isolation of 21% of 9,10-diphenylphenanthrene **(233)** provided proof that the diatomic sulfur precursor had been formed, but had failed to cause the addition of S_2 to the ergosterol diene.

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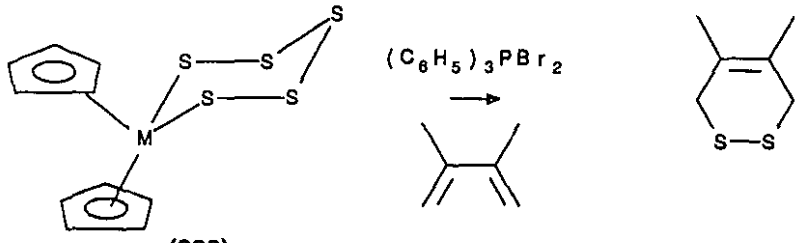
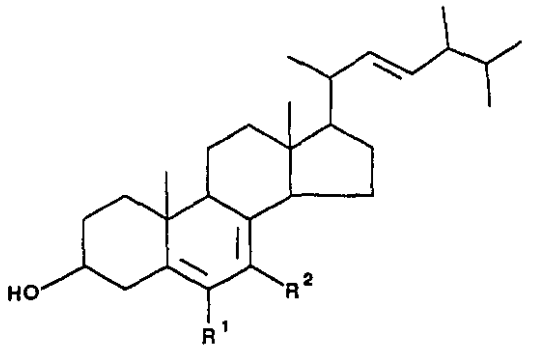
180. This mechanism was verified by repeating the procedure on isopropanol. Upon the addition of thiane **232** to isopropanol, immediate silylation occurred (^1H NMR). When BCl_3 was added, the corresponding thiol was one of the products identified in the ^1H NMR spectrum.

More recently, Harpp[181] reported the generation and trapping of diatomic sulfur from different titanium and zirconium pentasulfides **(238)** (Scheme 45). Once again, the reagent used to initiate the reaction was triphenyldibromophosphorane **(225)**. In a collaboratory effort, the synthesis of **221b** was attempted using this method; however, only modest yields of mercaptans **239a** and **239b** (along with elemental sulfur) were isolated.[162b]



(238)

Scheme 45



(239) **a** R^1 = SH, **b** R^2 = H
a R^1 = H, **b** R^2 = SH

It was thought at this point that the absence of any detectable amounts of Diels-Alder products from this reaction might indicate that an alternate mechanism was in operation. The products obtained may have been formed by the action of elemental sulfur on the diene of ergosterol through a radical or ionic mechanism.[182] In order to confirm this, ergosterol was refluxed in the presence of S_8 using toluene as the solvent. When no reaction occurred after several hours, the possibility that "activated sulfur" was the true reagent responsible for the formation of **239a** and **239b** was investigated. Liquid ammonia and triethylamine are widely used

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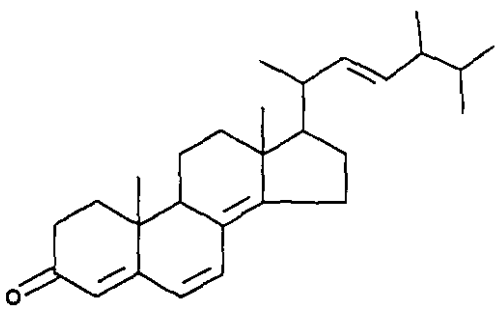
181. D. N. Harpp and J. G. MacDonald, *J. Org. Chem.*, **53**, 3812 (1988).

182. M. G. Voronkov, N. S. Vyazankin, E. N. Deryagine, A. S. Nakhmanovich and V. A. Usov, in *Reactions of Sulfur with Organic Compounds*, J. S. Pizey, Ed., New York: Plenum Publishing Corporation (1987).

as activating agents in the reactions of elemental sulfur with organic compounds.[183] Thus, ergosterol, triethylamine and sulfur were refluxed in toluene for several hours; however, the major compound isolated from this reaction was compound **240**, a compound previously characterized as a derivative of a steroid metabolite from *Aspergillus niger*.[184] This reaction was also repeated on the acetate of ergosterol (**222c**), but once again, no major steroidal products were isolated. Since compounds **239a** and **239b** were not among the products, it was concluded that they were formed by diatomic insertion into the double bonds of ergosterol.



(240)

4.3 Conclusion

The synthesis of the sulfur analogue of ergosterol peroxide, while a compelling target for increasing the biological activity of this compound, appears to be unaccessible *via* diatomic sulfur methodology.

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183. a) Chapter 2, in *Reactions of Sulfur with Organic Compounds* (previous reference) and references therein; b) R. Mayer, *Z. Chem.*, **13**, 321 (1973).

184. D. H. R. Barton and T. Bruun, *J. Chem. Soc.*, 2728 (1951).

CHAPTER 5: GENERATION AND TRAPPING OF THIOXOPHOSPHANES: SYNTHESIS OF CYCLIC THIOPHOSPHORANES

5.1 Introduction

The various methods for the generation and trapping of diatomic sulfur with 1,3-dienes as a means for the preparation of cyclic disulfides were discussed in Chapter 4. One of these methods was developed in our laboratory[171] and has the potential for extension to the generation of other diatomic or "pseudo-diatomic" species. This is illustrated in the equation shown in Scheme 46. The potential for this reaction to generate species such as "S=O", "Se_2", "S=Se" or "R-P=S" has yet to be examined. It is the purpose of this Chapter to explore the possibility of extending this methodology to the generation and trapping of the pseudo-diatomic species "R-P=S" (thioxophosphanes).

$$R_3MXYXMR_3 + (C_6H_5)_3PBr_2 \longrightarrow 2R_3MBr + (C_6H_5)_3P{=}X + \text{"XY"}$$

X = O, Se, S
Y = O, S, S_2, S(O), Se, S_2, Se(O), P-R
M = Si, Ge, C
R = C_6H_5, cyclo-C_6H_{11}, *p*-CH_3-C_6H_4

Scheme 46

The pseudo-diatomic species "R-P=S" **(241)** has been proposed as a reaction intermediate in a number chemical transformations. Japanese researchers were the first to report reactions which suggested the intermediacy of species they refer to as phosphinothioylidenes.[185] The reactions that generated the intermediate "R-P=S" species involved the dechlorination of dichlorothioxophosphoranes (**242a** and **242b**) with an equimolar amount of magnesium (Scheme 47). This reaction was carried out in the presence of several trapping reagents.

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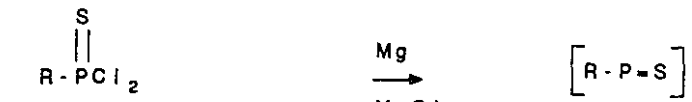
185. a) S. Nakayama, M. Yoshifuji, R. Okazaki and N. Inamoto, *J. Chem. Soc., Chem. Comm.*, 1186 (1971); b) M. Yoshifuji, S. Nakayama, R. Okazaki and N. Inamoto, *J. Chem. Soc., Perkin Trans. I*, 2065 (1973); c) S. Nakayama. M. Yoshifuji, R. Okazaki and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **48**, 546 (1975); d)S. Nakayama, M. Yoshifuji, R. Okazaki and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **48**, 3733 (1975).

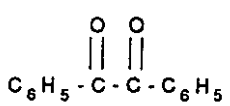


(242a) R = C_6H_5
(242b) R = cyclo-C_6H_{11}

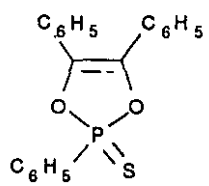
(241a)
(241b)

Scheme 47

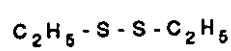
The first trapping reagent employed was benzil **(243)**, which provided **244**, the product of 1,4-cycloaddition to both oxygen atoms, in quantitative yields.[185a,b] The reaction was also carried out in the presence of diethyl disulfide **(245)**[185a,b] to give the product formed by insertion into the S-S bond **(246)** in 41% yield. Also reported was the same reaction with R = cyclo-C_6H_{11} **(242b)** to provide **246b** in 69% yield.[185b]



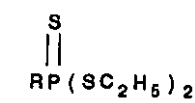
(243)



(244)

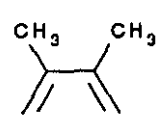


(245)

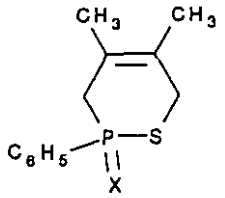


(246a) R = C_6H_5
(246b) R = cyclo-C_6H_{11}

A third trapping procedure employed during the generation of "C_6H_5-P=S" **(241a)** involved the use of 1,3-dienes.[185a,c] With 2,3-dimethyl-1,3-butadiene **(247)** in THF, the products isolated were 4,5-dimethyl-2-phenyl-3*H*,6*H*-1,2-thiaphosphorin 2-oxide **(248a)** and 2-sulfide **(248b)** in 21% and 44% yields respectively. These products were proposed to be formed by a Diels-Alder addition of **241** with the 1,3-diene followed by oxidation during isolation and sulfurization with unreacted dichloride during the reaction to give **248a** and **248b** respectively. In the presence of 1,3-cyclohexadiene **(249)**, the bridged bicyclic compound **250** was isolated in 21% yield.[185c] Once again, sulfuration was proposed to occur by reaction with unreacted dichloride during the reaction.

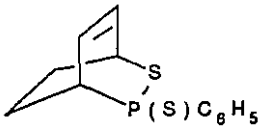


(247)



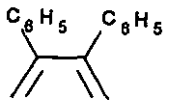
(248a) X = O
(248b) X = S

(249)

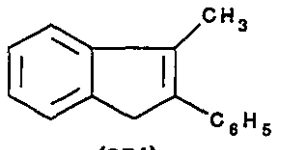


(250)

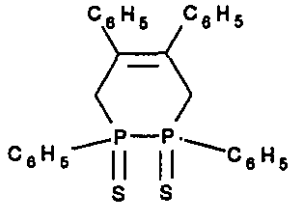
When 2,3-diphenyl-1,3-butadiene **(234)** was used as the trapping reagent, the products isolated were **251** and **252** in 52.5% and 13.5% yields respectively.[185c] Compound **251** was shown by a separate experiment to be a product obtained from the cyclization of diene **234** on silica gel. The formation of **252** was explained by the preference for diene **234** to adopt the *trans* conformation. This made the Diels-Alder reaction less favourable and allowed **241** to dimerize to the more reactive intermediate **(253)** which cyclized with diene **234** to give the observed product.



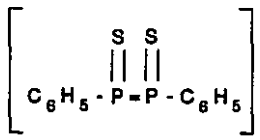
(234)



(251)

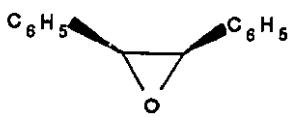


(252)

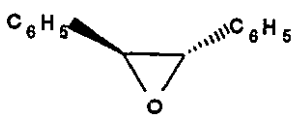


(253)

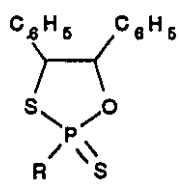
Finally, the reaction of **241a** and **241b** with *cis* and *trans* stilbene oxides **254a** and **245b** were reported to give, *via* insertion into the C-O bond of **254**, 1,3,2-oxathiaphospholane 2-sulfide derivatives **255** stereospecifically but in low yields (6-32%).[185d] The major species isolated from these reactions were *cis* and *trans* stilbene **(256)** formed by deoxygenation of the stilbene oxides by **241a** or **241b** *via* intermediate **257** (Scheme 48). The isolation of the expected phosphonothioic acid was not attempted.



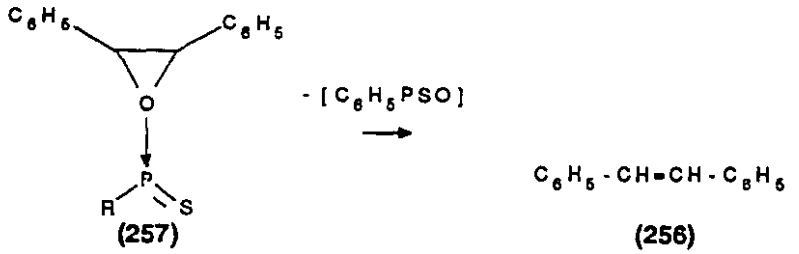
(254a)



(254b)



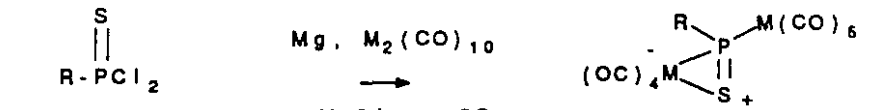
(255)



(257) (256)

Scheme 48

Thioxophosphanes generated by dechlorination of dichlorothioxophosphoranes (**242a, c-g**) have also been trapped in the protecting coordination sphere of carbonylmolybdenum and -manganese complexes (**258**) as shown in Scheme 49.[186] The yields ranged from 3-44%.



(242a) R = C_6H_5
(242c) R = CH_3
(242d) R = C_2H_5
(242e) R = *p*-CH_3O-C_6H_4
(242f) R = *p*-CH_3-C_6H_4
(242g) R - *p*-F-C_6H_4

(258)

M = Mn, Mo

Scheme 49

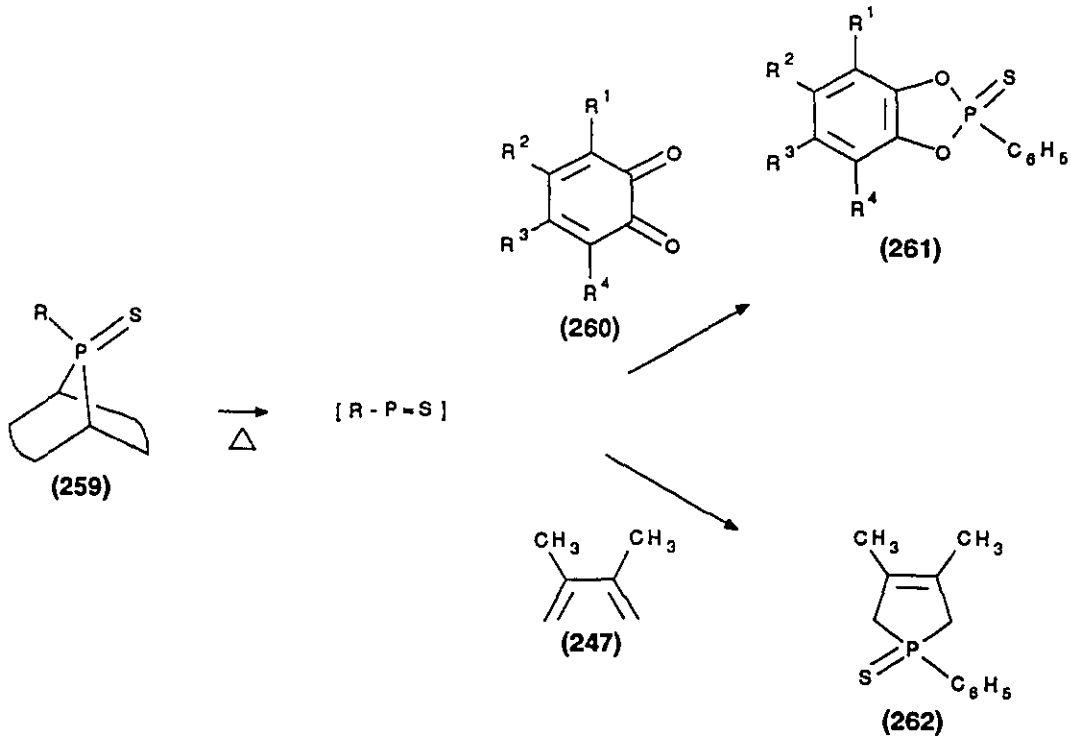
Another general route to the generation of the "R-P=S" unit involves cycloelimination from bicyclic systems **259** (Scheme 50) induced either thermally[187] or photochemically.[188] In the examples involving thermal generation, the thioxophosphanes have been trapped *via* [4 + 1] cycloaddition with various *o*-quinones (**260**) to give dioxaphospholsulfides (**261**)[187c] and also with 2,3-dimethyl-1,3-butadiene (**247**).[187a] The product isolated in this latter example was 1-phenyl-3,4-dimethylphosphol-3-en sulfide (**262**) in 50% yield (Scheme 50).

---

186. a) E. Lindner, K. Auch, W. Hiller and R. Fawzi, *Angew Chem. Int. Ed. Engl.*, **23**, 320 (1984); b) E. Lindner, K. Auch, G. A. Weib, W. Hiller and R. Fawzi, *Chem. Ber.*, **119**, 3076 (1986).

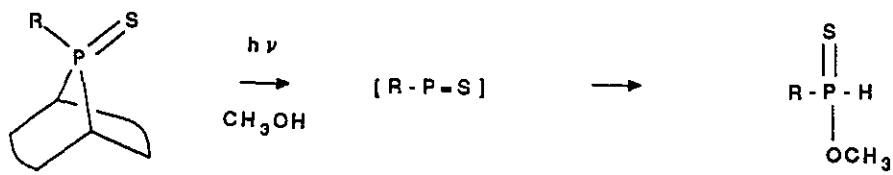
187. a) C. C. Santini, J. Fischer, F. Mathey and A Mitschler, *J. Amer. Chem. Soc.*, **102**, 5809 (1980); b) R. Hussong, H. Heydt and M. Regitz, *Phosphorus Sulfur*, **25**, 210 (1985); c) R. Hussong, H. Heydt and M. Regitz, *Z. Naturforsch*, **41b**, 915 (1986).

188. a) H. Tomioka, S. Takata, Y. Kato and Y. Izawa, *J. Chem. Soc., Perkin Trans. II*, 1017 (1980); b) S. Holland and F. Mathey, *J. Org. Chem.*, **46**, 4386 (1981).



Scheme 50

The photochemical reactions (Scheme 51) were all carried out in methanol, thus the isolated products were a result of the addition of methanol to the generated "R-P=S" to give phosphinothioates **(263)** in yields ranging from 65-80%.[188a,b] These compounds were used to build a new route to carbon-phosphorus heterocycles.[188b]



R = C_6H_5
R = C_4H_9
R = $Br(CH_2)_4$
R = $Br(CH_2)_5$
R = $Br(CH_2)_6$

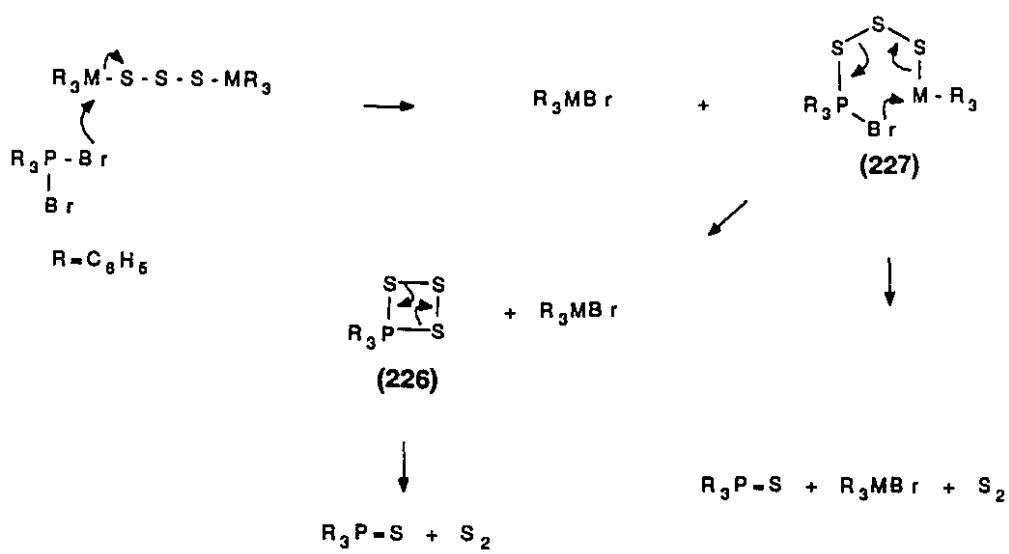
Scheme 51

5.2 Results and Discussion

5.2.1 Proposed Mechanism for the Generation of Diatomic Species

Although the thioxophosphorane intermediates proposed in the above examples had short lifetimes, their existence as transient intermediates was well established. Thus, it would seem highly possible that the generation of such a species from the reaction presented in Scheme 46 would be successful.

The mechanism of this reaction was alluded to in Chapter 5. Using the organometallic trisulfide as the example, the proposed pathway for this reaction is shown in Scheme 52. It is not known whether the S_2 was generated from a four-membered ring intermediate (**226**) or an open chained species like **227**. It is also not known whether the S_2 existed as a discrete species or was transferred from intermediate **226** or **227** directly to the diene. The driving force for this reaction is the formation of the energetically favourable[189] phosphine sulfide.



Scheme 52

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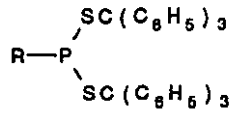
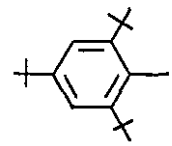
189. D. N. Harpp and R. A. Smith, *J. Amer. Chem. Soc.*, **104**, 6045 (1982) and references cited therein.

5.2.2 Synthesis of Precursor Molecules

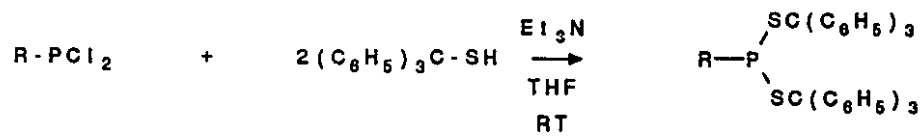
For the generation of a thioxophosphane species *via* the mechanism shown in Scheme 52 a precursor molecule analogous to the trisulfide had to be developed. In order to simplify procedures, the replacement of the metal atom with carbon was desired and the necessary replacement of the central sulfur atom with a "P-R" group also had to be achieved. The required precursor molecule thus has the general structure **264**.



(264a) R = C_6H_5
(264b) R = C_2H_5
(264c) R = *p*-Cl-C_6H_4

(264d) R = 

The synthesis of compounds **264a** and **264b** was performed by a simple substitution reaction involving two equivalents of the thiolate anion of triphenylmethyl (trityl) thiol **(265)** and dichlorophenyl- **(266a)** and ethylphosphines **(266b)** (Scheme 53). The reaction proceeded with quantitative yields under anhydrous conditions in THF at room temperature and the products could be purified by flash chromatography on neutral alumina.[190] The structure of **264a** was confirmed *via* X-ray crystallography. The ORTEP drawing is shown in Figure 29. The structure has no unusual bond lengths or bond angles and the experimental details are found in Chapter 6.



(266a) R = C_6H_5
(266b) R = C_2H_5

(265)

(264a)
(264b)

Scheme 53

190. Chromatography on silica gel resulted in hydroylsis of the P-S bonds to give trityl mercaptan and uncharacterized phosphorus compounds.

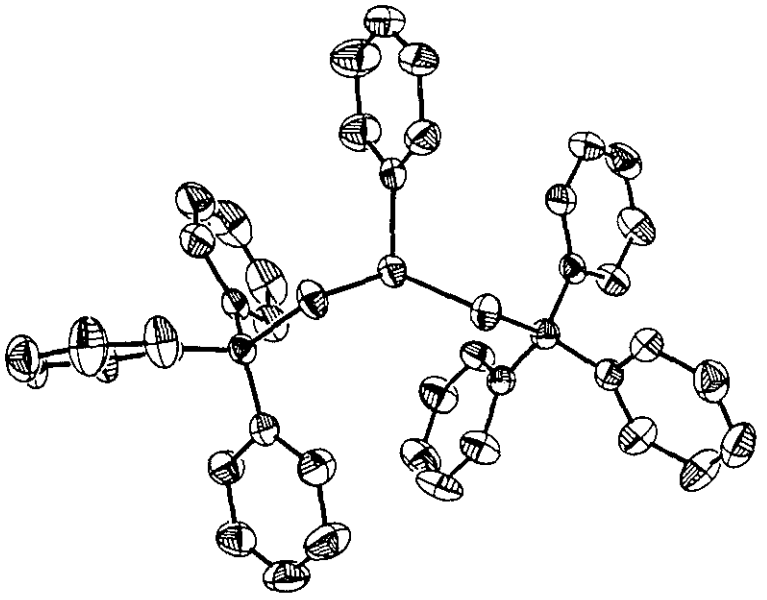
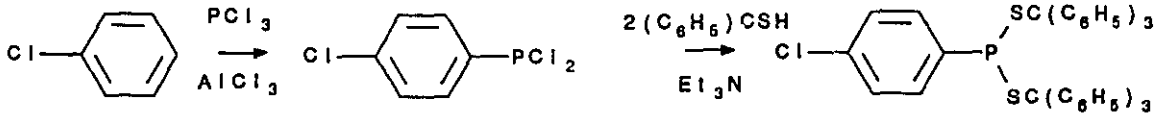


Figure 29: ORTEP Drawing of 264a

The corresponding dichlorophosphines for the synthesis of **264c** and **264d** using the above procedure had to be prepared. Both were literature compounds and, although the procedures were not straightforward, they were successfully synthesized. Compound **267** was prepared from chlorobenzene **(268)** *via* a Friedel-Crafts-type reaction with phosphorus trichloride using aluminum trichloride as the catalyst (Scheme 54).[191] Reaction of **267** with the anion of trityl thiol following the procedure described above provided **264c** quantitatively. Compound **264c** was purified by column chromatography on alumina.



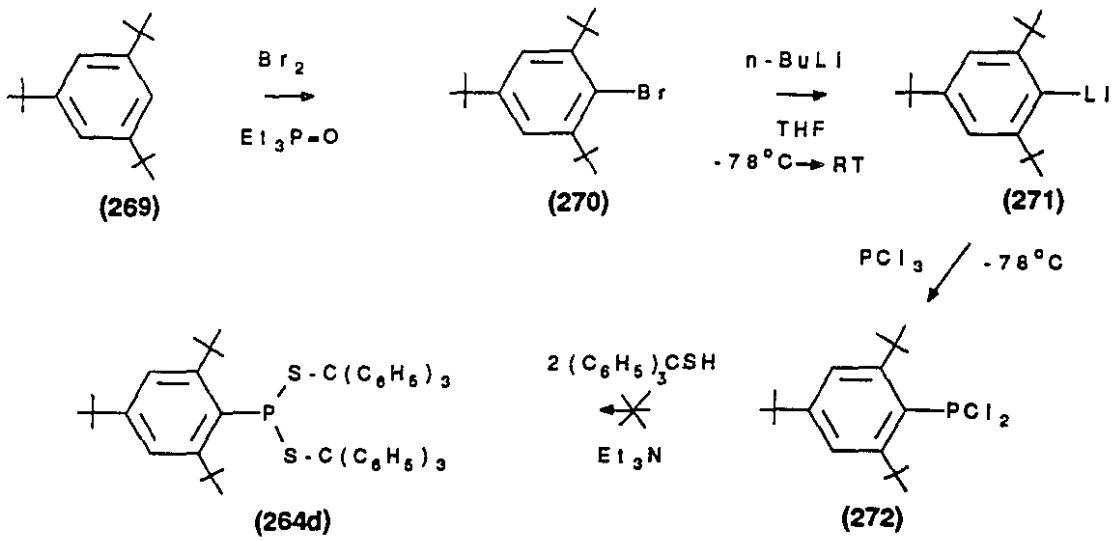
(268) **(267)** **(264c)**

Scheme 54

The dichlorophosphine required for the synthesis of compound **264d** was prepared from 2,4,6-tri-*t*-butylbenzene **(269)** (Scheme 55). Bromination of **269** was carried out in triethyl phosphate following the procedure of Pearson and co-workers[192] to give **270**. The reaction never proceeded to completion; however, the product could be separated from the starting material by careful chromatography on silica gel using hexanes as the eluent. (2,4,6-Tri-*t*-butylphenyl)lithium

191. E. L. Gefter, *J. Gen. Chem. USSR (Engl. Trans.)*, **32**, 3336 (1962).

(271) was prepared by the addition of *n*-butylithium to **270** in THF at -78°C.[193] The greatest yields of **272** were obtained by allowing the reaction mixture containing **271** to warm to room temperature and stir for two hours before cooling back to -78°C for the addition of phosphorus trichloride. Dichlorophosphine **272** was isolated from this reaction mixture in 30% yield.



Scheme 55

Unfortunately, after all of this effort, the next step to precursor molecule **264d** did not bear fruit. Indeed, the molecule of interest would be highly crowded, thus this result is not all that surprising. It was hoped that **264d** might have offered the opportunity of isolating the corresponding thioxophosphane as a discrete species given the stabilizing factor of a bulky R group; however, this possibility will not be confirmed using this methodology.

5.2.3 Trapping Results

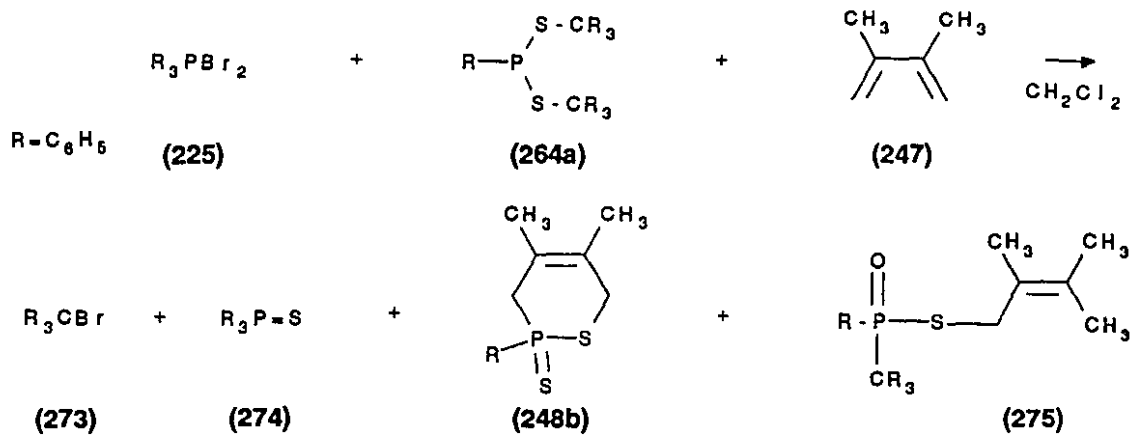
The general procedure used for the trapping reactions is described in the Experimental Section (Section 6.5). Conditions had to be strictly anhydrous and the synthesis of the triphenyldibromophosphorane **(225)** carried out in the absence of light and at 0°C. The trapping procedure employed in this work involved the Diels-Alder addition of the generated thioxophosphorane to 1,3-dienes. The dienes used were 2,3-dimethyl-1,3-butadiene **(247)**, 2,3-

192. D. E. Pearson, M. G. Frazer, V. S. Frazer and L. C. Washburn, *Synthesis*, 621 (1976).

193. M. Yoshifuji, I. Shima and N. Inamoto, *Tetrahedron Lett.*, 3963 (1979).

diphenyl-1,3-butadiene (**234**) and 1,3-cyclohexadiene (**249**). All reactions were carried out in freshly distilled methylene chloride.

The crude reaction mixture for the addition of triphenyldibromophosphorane (**225**) to **264a** in the presence of diene **247** was shown (^{1}H NMR) to contain triphenylmethyl bromide (**273**), triphenylphosphine sulfide (**274**), and a compound that was consistent with a trapped product (**248b**) (Scheme 56).[194] Separation of these compounds turned out to be a difficult task due to the similarities in the Rf values for **273**, **274** and **248b** and often required two chromatographies; the trapped compound always remained contaminated with a small (<1%) amount of bromide **273** and sulfide **274**.



Scheme 56

Initial separation of the above crude mixture resulted in the isolation of a inseparable mixture of bromide **273** and sulfide **274**, both in 80% yield. Along with the trapped product (**248b**), another compound with a higher Rf and with NMR data suggesting an open chain structure like **275** (Scheme 56) was also obtained in 17% yield; the yield of **248b** was 26%. Structure determination for the initial trapped product was confirmed by a comparison with the literature values. The ^{1}H NMR data (Table 27) closely resembled that reported by the Japanese workers.[185a,c] It was certainly not the symmetrical compound isolated by Santini and co-workers (**262**).[187a,195] Sulfuration of the phosphorus atom, once again, occurred during the reaction. The source of sulfur was likely the precursor molecule itself (**264a**), thus partially explaining the low

194. Occasionally, small amounts of trityl thiol and trityl methane were also detected.

195. NMR data for **262**: ^{1}H: 1.78 (s, 2x CH_3) and 6.36 (s, 2x CH_2) ppm; ^{31}P: -67.4 ppm. F. Mathey and R. Mankowski, *Bull. Chem. Soc. Fr.*, 4433 (1970).

yields of isolated product.[196]

Table 27: Spectral Data for 248b

	This Work	Literature[185a,c]	Assignment
^{1}H NMR (ppm)	200 MHz, $CDCl_3$	100 MHz, CCl_4	
	1.61 (s)	1.68 (s)	5-CH_3
	1.86 (d $^4J_{HP}$ = 5 Hz)	1.93 (d $^4J_{HP}$ = 5 Hz)	4-CH_3
	2.9-3.6 (m)	2.7-3.9 (m)	2x CH_2
	7.4-8.0 (m)	7.4-8.0 (m)	5x aromatic H
IR (cm^{-1})	$CDCl_3$	KBr	
	1436		CH_3-C=C
		1650	C=C
	1098	1100	P-Ph
^{13}C NMR[197] (ppm)	300 MHz, $CDCl_3$	not reported	
	19.5 (d $^4J_{CP}$ = 3.5 Hz)		5-$\underline{C}H_3$
	21.2 (d $^3J_{CP}$ = 5.8 Hz)		4-$\underline{C}H_3$
	35.0 (d $^2J_{CP}$ = 6.2 Hz)		$\underline{C}H_2$-S
	45.2 (d $^1J_{CP}$ = 45 Hz)		$\underline{C}H_2$-P
	127.0 (d $^3J_{CP}$ = 12.4 Hz)		=$\underline{C}$-
	127.9 (s)		Ph C_{meta}
	128.3 (d $^2J_{CP}$ = 12.9 Hz)		Ph C_{ortho}
	130.6 (d $^2J_{CP}$ = 13 Hz)		-$\underline{C}$=
	131.4 (d $^2J_{CP}$ = 11 Hz)		Ph C_{ortho}
	131.8 (d $^3J_{CP}$ = 3.1 Hz)		Ph C_{meta}
	134.5 (d $^1J_{CP}$ = 78.6 Hz)		Ph C1
	146.7 (s)		Ph C_{para}
^{31}P NMR (ppm)	300 MHz, $CDCl_3$	not reported	
	63.9		
MS	254	254	$M^{+\cdot}$

The structure for the other trapped product **(275)** was assigned based on its spectral data. Although it did not give a molecular ion in the mass spectrum, the fragmentation pattern did support the assigned structure. The trityl cation was detected along with the ion resulting from

196. Desulfurization of the precursor molecule was achieved using the known desulfurization reagent, triphenylphosphine (see D. N. Harpp, D. K. Ash and R. A. Smith, *J. Org. Chem.*, **45**, 5135 (1980) and references therein).

197. APT and proton-coupled ^{13}C NMR spectra were used to confirm assignments.

cleavage of the S-C bond (m/z = 83, base peak). The remaining spectral data for this compound is given in Table 28.

Table 28: Spectral Data for 275

^{1}H NMR (200 MHz, $CDCl_3$) δ:

1.54-1.66 (m, 3x CH_3, 9H)
2.70 (dd J_{Ha-Hb} = 11.4 J_{Ha-P} = 6.04 Hz, CH_{2a}, 1H)
3.57 (dd J_{Hb-Ha} = 11.4 J_{Hb-P} = 8.3 Hz, CH_{2b}, 1H)
7.12-7.68 (m, aromatics, 20H)

^{13}C NMR[197] (300 MHz, $CDCl_3$) δ:

18.2 (s, CH_3)
20.5 (s, CH_3)
20.9 (s, CH_3)
37.8 (s, CH_2-S)
69.6 (d $^{1}J_{CP}$ = 42.2 Hz, P-C-Ph_3)
122.2 (d $^{2}J_{CP}$ = 6.9 Hz, -C=)
127.1-127.5 (trityl C-H)
130.9 (d $^{4}J_{CP}$ = 3.1 Hz, Ph C_{para})
131.3 (s, =C-$(CH_3)_2$)
131.8 (d $^{3}J_{CP}$ = 5.9 Hz, Ph C_{meta})
134.0 (d $^{2}J_{CP}$ = 9.8 Hz, Ph C_{ortho})
134.0 (d $^{1}J_{CP}$ = 69.5 Hz, Ph C1)
143.0 (s, trityl C1)

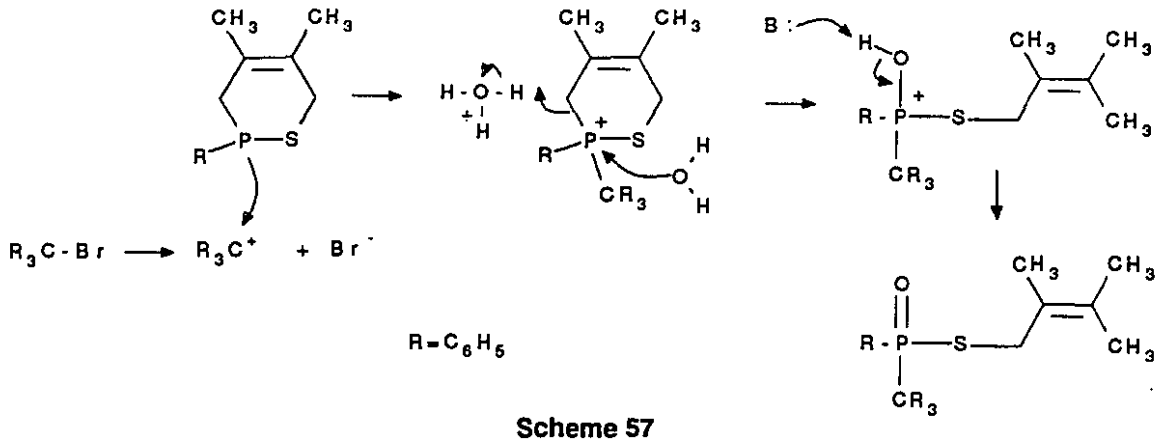
^{31}P NMR (300 MHz, $CDCl_3$) δ:

4.15

IR (KBr, cm^{-1})

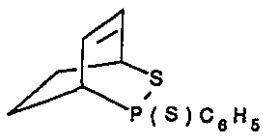
1084 (P-Ph), 1200 (P=O), 1436, 1492

The formation of compound **275** can be rationalized by an acid-catalyzed opening of the ring in the unsulfurized trapped adduct **276** upon the addition of silica gel to the crude mixture for column chromatography (Scheme 57). The abundance of trityl compounds in this mixture provided the source of this moiety. Prior to the addition of silica, there was no evidence for the formation of **275**.



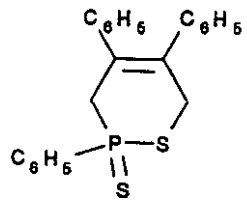
Scheme 57

The generation of phenylthioxophosphane **(241a)** in the presence of 1,3-cyclohexadiene **(249)** also provided a product that had spectral data consistent with a trapped adduct **(250)**. The yield of this compound was only 21% and separation from the side products was, once again, very difficult. There was no evidence for the formation of a compound derived from C-P bond breakage, analogous to **275**. The data for compound **250** is presented in Table 29 along with the literature values obtained by the Japanese workers.[185c] Sulfuration of the phosphorus atom once again occurred during the reaction so that the isolated product was sulfide **250**.



(250)

The trapped adduct isolated from the generation of phenylthioxophosphane **(241a)** in the presence of 2,3-diphenyl-1,3-butadiene **(234)** was not the same as that reported in the literature **(252)**. Compound **277** was an unsymmetrical compound that was analogous to the products isolated in first two trapping experiments. The yield was only 21% and complete separation from side products could not be achieved.



(277)

Table 29: Spectral Data for 250

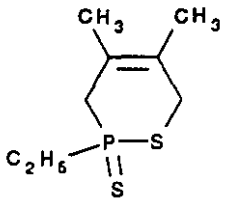
	This Work	Literature[185c]
^{1}H NMR[198] (ppm)	200 MHz, $CDCl_3$	100 MHz, CCl_4
	1.5-2.0 (m, 2x H7)	1.0-2.9 (m, 2x H7 + 2x H8)
	2.46 (m, H8a)	2.9-3.4 (m, H3)
	2.9-3.25 (m, 1x H8b + H3)	3.8-4.4 (m, H6)
	4.07-4.19 (dm, H6)	5.98 (q J = 8 Hz, H4)
	6.00 (q J = 8 Hz, H4)	6.60 (q J = 8 Hz, H5)
	6.60 (q J = 8 Hz, H5)	7.2-7.6(m, 2x H_{meta} + H_{para})
	7.35-7.5 (m, 2x H_{meta} + H_{para})	7.65-8.1 (m, 2x H_{ortho})
	7.8-8.0 (m, 2x H_{ortho})	
IR (cm^{-1})	$CDCl_3$	KBr
	1097 (P-Ph)	1100 (P-Ph)
	1200 (P=O)	
	1439 (C=C)	
^{13}C NMR[199] (ppm)	300 MHz, $CDCl_3$	not reported
	18.1 (d $^3J_{CP}$ = 3.1 Hz, C7)	
	29.5 (d $^2J_{CP}$ = 10.1 Hz, C8)	
	41.9 (d $^1J_{CP}$ = 34.7 Hz, C3)	
	(42.2, s, C6)	
	127.0 (d $^2J_{CP}$ = 29.9 Hz, Ph C_{ortho})	
	128.1 (d $^2J_{CP}$ = 12.7 Hz, C4)	
	129.3 (s, Ph C_{para})	
	130.5 (d $^3J_{CP}$ = 9.8 Hz, Ph C_{ortho})	
	131.4 (d $^3J_{CP}$ = 3.1 Hz, Ph C_{meta})	
	132.4 (d $^2J_{CP}$ = 10.2 Hz, C5)	
	134.2 (d $^1J_{CP}$ = 77.8 Hz, Ph C1)	
	135.5 (d, $^3J_{CP}$ = 14.2 Hz, Ph C_{meta})	
^{31}P NMR (ppm)	300 MHz, $CDCl_3$	not reported
	75.6	
MS	252 ($M^{+\cdot}$)	252 ($M^{+\cdot}$)

The trapping experiments performed on **264b** were not as successful as those reported above for **264a**. The only example where products could be isolated in form pure enough to allow characterization was the experiment performed using the dimethyl-diene **(247)** as the trapping reagent. A compound with NMR peaks suggesting a trapped adduct like **278** could be seen in initial crude NMR spectrum. Upon purification, however, the only product that could be isolated

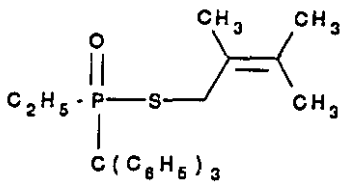
198. Assignments confirmed by decoupling experiments.

199. APT and proton-coupled ^{13}C NMR spectra were used to confirm assignments.

was a species formed by ring opening **(279)**. Yields of this compound were around 30%. The ease with which ring-opening occurred was greater for the ethyl-substituted product. This was likely due to the smaller size of the ethyl group allowing more space for the trityl group to enter on the phosphorus atom.

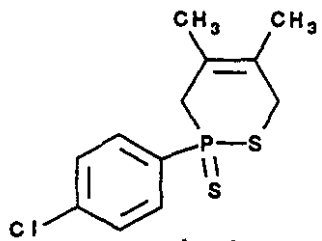


(278)



(279)

A trapped product **(280)** was also isolated from the generation of the thioxophosphane from **264c**. The yield of **280** was only 10% and its spectral data were similar to that of **248b**. The alkyl regions of the ^1H NMR spectra of compounds **248b** and **280** are shown in Figure 30.



(280)

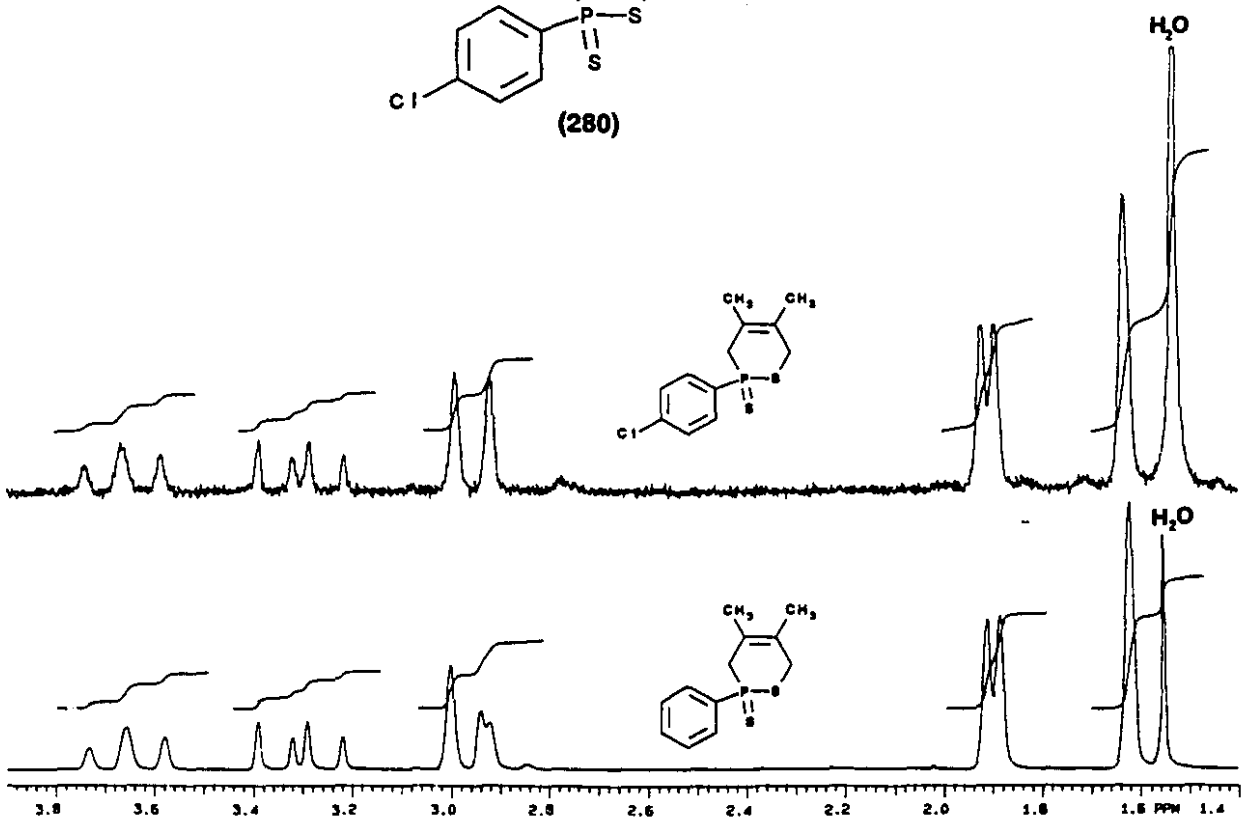


Figure 30: ^1H NMR Spectra of Compounds 248b and 280; Alkyl Region Only

5.3 Conclusion

The generation of thiooxophosphoranes using the methodology previously developed in our laboratory for the generation of diatomic sulfur was possible. The trapped adducts were identified based on the ^{1}H, ^{13}C and ^{31}P NMR and IR and mass spectra. The P-S moiety was very sensitive in the trapped adducts. Sulfuration of the phosphorus atom usually occurred to give the more stable phosphine sulfide product. When sulfuration did not occur, ring opening and oxidation of the phosphorus atom was the alternate pathway to the isolated products.

The methodology described above was not an efficient route to the synthesis of cyclic thiophosphoranes. The results indicate that it was indeed general and can likely be extended to other systems. The major difficulty with this work was the separation of the desired product from side products. The yields of cyclic products were comparable to those reported in the literature. Perhaps another cyclic species would be easier to purify, thus the generation of another diatomic species should be examined in order to determine the viability of this methodology for the synthesis of heterocycles.

CONTRIBUTIONS TO ORIGINAL KNOWLEDGE

The synthesis and chemical reactivity of bridged bicyclic disulfides and their derivatives has been investigated. A general synthesis of the bridged bicyclic system has been refined and expanded to the synthesis of [2.2.1] and [4.2.1] bridged bicyclic disulfides. Various derivatives of these compounds have been prepared including thiosulfinate (*S*-oxides) and thiosulfonate (*S,S*-dioxides) esters along with derivatization of the hydroxyl group to provide various *O*-esters. The oxidation of the bridged bicyclic disulfides using *m*-CPBA provided the *exo* diastereomer as the major isomer in all examples. This was shown to be the kinetic product by a brief study into the stability of these compounds. The structure of these compounds was also examined *via* three X-ray structures and the experimental values of the bond lengths, bond angles and torsion angles were all compared with the calculated structures obtained using PCMODEL. This was performed only to study the applicability of PCMODEL to this class of compounds.

The *m*-CPBA oxidation of bridged bicyclic thiosulfinates was followed using low temperature ^{13}C and ^{1}H NMR spectroscopy. Clear evidence was found to suggest that oxidation occurred first on the electron-rich sulfenyl sulfur atom to give an α-disulfoxide intermediate. The α-disulfoxide structure has been proposed as an intermediate in the low temperature *m*-CPBA oxidation of acyclic thiosulfinate esters and in the preparation of thiosulfonates using tri-*n*-butyl tin and sulfinyl chlorides; however, these species were never present in large amounts or at temperatures greater that -20°C. The α-disulfoxides were detected in this work at temperatures up to 25°C and were often the only bicyclic species present at temperatures near 0°C. The mechanism for the rearrangement of α-disulfoxides to thiosulfonates was examined. The initial α-disulfoxide was a symmetrical species which meant that the second oxygen entered on the less hindered *exo* face of these molecules. When the *endo* thiosulfinate was oxidized, the resulting α-disulfoxide was an unsymmetrical molecule. This unsymmetrical α-disulfoxide was also seen as the second intermediate in the oxidation of the *exo* thiosulfinates, suggesting that homolysis of the S-S bond of the symmetrical α-disulfoxide occured followed by rotation about a C-S bond and radical recombination. Evidence was also provided for the existence of α-disulfoxides formed by rotation about both C-S bonds followed by radical recombination to give the symmetric *endo* α-disulfoxides. The strongest evidence to date was also found for the existence of *O,S*-sulfenyl sulfinates, species formed by the attack of a sulfinyl oxygen on an adjacent sulfinyl sulfur atom in the unsymmetric α-disulfoxides. These species can rearrange to the thiosulfonate product.

An attempt was made to synthesize a bridged bicyclic disulfide analogue of ergosterol peroxide using diatomic sulfur methodology. It was hoped that the sulfur analogue would have

enhanced herbicidal activity over the peroxide. The addition of diatomic sulfur to the diene of ergosterol *via* a Diels-Alder reaction was attempted following literature procedures; however, none of the reagents employed led to the formation of the desired product. Three steroidal compounds were isolated and fully characterized. These included the new compound, ergosta-5,7,22-trien-3-thiol **(237)**, along with the known compounds, 3,5-cyclo-6,8(14),22-ergostatriene **(236)** and ergosta-4,6,8(14),22-tetraen-3-one **(240)**.

The expansion of a new general methodology for the generation of diatomic species developed in our laboratory for the synthesis of cyclic heterocycles *via* trapping with 1,3-dienes was initiated. The generated species was a thioxophosphane (R-P=S), previously identified as a transient reaction intermediate in other reactions. The required precursor molecules were synthesized and trapping reactions performed using 2,3-dimethyl-1,3-butadiene, 1,3-cyclohexadiene and 2,3-diphenyl-1,3-butadiene. When R = C_6H_5, a cyclic product was isolated with all three dienes; sulfuration of the phosphorus atom occurred during the reaction. A small amount of ring opening occurred with the dimethyl-diene to give an open-chained species. When R = C_2H_5, only an open-chained species was isolated. When R = *p*-Cl-C_6H_5, a cyclic product was isolated with the dimethyl-diene in low yields. The main difficulty with this reaction was the separation of the product from the side products (triphenylmethyl bromide and triphenylphosphine sulfide). Yields were comparable to those reported in the literature for the preparation of these compounds using different synthetic procedures.

CHAPTER 6: EXPERIMENTAL

6.1 General Methods

Commercially available reagents were obtained from Aldrich Chemical Company (Milwaukee, Wisc.) and used directly except as indicated. Solid reagents were recrystallized when their melting points indicated insufficient purity. The *m*-CPBA used was a mixture containing 20% *m*-CBA. Potassium thiocyanate was dried under vacuum over P_2O_5 for several days prior to use. Phosphorus trichloride and chlorobenzene were distilled prior to use and stored over 3Å molecular sieves that were activated at 400°C overnight and cooled in a desiccator.

Methylene chloride was distilled from anhydrous P_2O_5 and used directly. THF was distilled from the blue sodium-benzophenone ketyl and also used directly. Hexanes were distilled from concentrated H_2SO_4 and passed through an alumina column prior to use. Benzene and toluene were stored over metallic sodium. Ether refers to diethyl ether in all cases. Petroleum ether was low boiling (35-60°C). Pyridine and triethylamine were distilled from KOH and used directly.

Melting points were obtained on a Gallenkamp capillary meting point apparatus and are uncorrected. Silica gel chromatography was performed on Merck Kieselgel 60 (230-400 mesh, #9385) using flash chromatography.[200] Alumina chromatography was performed using flash column procedures[200] on Fisher Scientific Neutral Alumina (80-200 mesh, # A540) that had been dried at 150°C for several days and cooled in a desiccator. All reactions were monitored by thin-layer chromatography performed on 0.25 mm Merck silica gel plates (60F-254) using UV light and a 10% sulfuric acid ethanolic-solution of ammonium molybdate-cerium sulfate developing dip.

Ultraviolet spectra were recorded on a Hewlett Packard 8451A DIODE ARRAY spectrophotometer. Nuclear magnetic resonance spectra were obtained at 20-22°C (unless otherwise indicated) using Varian XL-200 and XL-300 MHz instruments. ^1H and ^{13}C NMR chemical shifts are quoted in ppm and are referenced to the internal deuterated solvent to high frequency from TMS. ^{31}P NMR chemical shifts are quoted in ppm relative to 85% H_3PO_4 as an external standard. Infrared spectra were recorded on an Analect ASQ-18 FTIR Spectrophotometer calibrated to the 1602 cm^{-1} line of polystyrene and equipped with an Analect Instruments MAP-67

200. W. C. Still, M. Khan and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).

Data System and an Analect Instruments RAM-56 Color Display. All low-resolution electron Impact mass spectra were obtained on a Dupont Instruments 21-492B or Kratos MS25RFA Mass Spectrometer. High-resolution and chemical-ionization mass spectra were performed at the Biomedical Mass Spectrometry Unit, McGill University. Elemental analysis were obtained from the laboratory of Dr. Charles Larsen at Kemisk Laboratorium, University of Copenhagen, Denmark.

Sulfur analysis was performed on an Antek Model 714 Sulfur Detector coupled with an Antek Model 771 Pyroreactor. Sulfur percentages were determined from a calibration curve of total counts *vs* percent sulfur (w/v) of standard solutions of benzyl disulfide. Total counts refers to the intensity of the signal that results from the fluorescence of SO_2 emitted from the pyrolysis of the sample.

X-ray crystallography on compounds **133**, **152** and **264a** was performed by Dr. Beverly Vincent at Organisch-chemisches Institut der Universität Zürich, Zürich, Switzerland; X-ray crystallography on compounds **138a**, **151a** and **237** was performed by Dr. James Britten at the Department of Chemistry, McGill University, Montreal, Quebec, Canada. ORTEP drawings were obtained using the ORTEPII program.[201]

Antimicrobial testing on compounds **3**, **134** and **153a** was performed by Dr. David Thomson and Dr. Geoffrey K. Richards at the Montreal General Hospital, Montreal, Quebec. Antifungal testing was carried out by Dr. Zev Lidert at Rohm & Haas (USA). Antiviral testing was performed by Dr. Mark Winberg at the Lady Davis Institute of Medical Research at the Jewish General Hospital, Montreal, Quebec.

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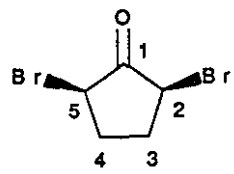
201. C. K. Johnson, *ORTEPII. Report ORNL-5138*, Oak Ridge National Laboratory, Oak Ridge, Tennessee (1976).

6.2 Chapter 2

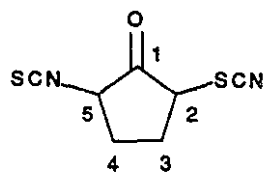
6.2.1 [2.2.1] Bridged Bicyclic Compounds

Preparation of *cis*-2,5-Dibromocyclopentanone (135):



Cyclopentanone **(137)** (9.51 g, 0.113 mol) was dissolved in glacial acetic acid (50 ml), cooled to 3°C and bromine (36.14 g, 0.226 mol) was added (dropwise). A stream of nitrogen was blown over the reaction and bubbled through a NaOH solution to neutralize the HBr formed. The reaction mixture was then poured onto ice and neutralized to pH 5. The product was extracted into $CHCl_3$ and the organic layer washed several times with d-H_2O and 5% $NaHCO_3$, dried over $MgSO_4$ and evaporated to a yellow oil. This oil was redissolved in *n*-pentane:$CHCl_3$, and allowed to crystallize at 0°C to give fine, off-white crystals (4.9 g, 18%) of **135**. M.p. = 64-65.5°C (lit[128] 67°C); Rf ($CHCl_3$): 0.50; ^1H NMR (200 MHz, $CDCl_3$)δ: 2.47 (m, 2x H3 and H4, 4H) and 4.26 (m, H2 and H5, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 31.4 (C3 and C4), 43.4 (C2 and C5) and 204.6 (C1) ppm; IR ($CHCl_3$): 1759 (C=O) cm^{-1}; MS [EI, direct inlet, 30°C], m/z (% relative intensity, assignment): 244 (21.9, $C_5H_6{}^{81}Br_2O^{+}\cdot$), 242 (47.8, $C_5H_6{}^{79}Br^{81}BrO^{+}\cdot$), 240 (28.9, $C_5H_6{}^{79}Br_2O^{+}\cdot$).

Preparation of *cis* and *trans*-2,5-Dithiocyanatocyclopentanone (138a and 138b):



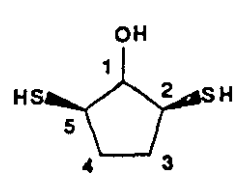
2,5-Dibromocyclopentanone **(135)** (1.32 g, 5.46 mmol) was dissolved in dry acetone (75 ml) under a nitrogen atmosphere and KSCN (1.06 g, 10.92 mmol) in dry acetone (75 ml) was added all at once. The solution was allowed to stir for 1 hr then the white precipitate (KBr) was filtered and the acetone removed under reduced pressure. The resulting yellow solid was partitioned between d-H_2O and $CHCl_3$ and the organic layer dried over $MgSO_4$ and evaporated to give a yellow solid (0.90 g, 90%). Recrystallization from hexanes:CH_2Cl_2 provided off-white crystals shown to contain **138a** and **138b** (0.80 g, 80%) in ~4:1 ratio (^1H NMR) respectively. A second, slower recrystallization from pentane:$CHCl_3$ (10:1) gave yellow needles which contained only one isomer **(138a)**, confirmed to be in the *cis* conformation by X-ray crystallography (see Figure 5, Chapter 2). M.p. 92-93°C; Rf ($CHCl_3$): 0.10;

138a: ^{1}H NMR (200 MHz, $CDCl_3$)δ: 2.30-2.77 (m, 2x H3 and H4, 4H) and 3.94-4.02 (m, H2 and H5, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 28.1 (C3 and C4), 48.5 (C2 and C5), 109.00 (SCN) and 201.9 (C1) ppm; IR (KBr): 1761 (C=O) and 2154 (SCN) cm^{-1}; MS [EI, direct inlet, 120 °C], m/z (% relative intensity, assignment): 198 (6.9, $M^{+}\cdot$), 140 (31.6, $M^{+}\cdot$ - SCN), 139 (29.9, $M^{+}\cdot$ - HSCN).
138b: ^{1}H NMR (200 MHz, $CDCl_3$)δ: 2.05-2.95 (m, 2x H3 and H4, 4H) and 3.68-3.79 (m, H2 and H5, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 28.4 (C3 and C4), 48.9 (C2 and C5), 108.96 (SCN) and 202.0 (C1) ppm; IR (KBr): 1750 (C=O) and 2154 (S-C N) cm^{-1}; MS: Same as **138a**.

X-Ray Data for 138a:

Empirical Formula: $C_7H_6N_2OS_2$, M = 198.26, monoclinic, space group $P2_1/n$ (#14), a = 9.242(2), b = 8.964(3), c = 14.032(2) Å, β = 91.48(1)°, V = 902.8(3) Å^3, Z = 4, D_c = 1.458 gcm^{-3}, $\mu_{(CuK\alpha)}$ = 49.04 cm^{-1}, F_{000} = 408. Data were collected at room temperature on a Rigaku AFC6S diffractometer with graphite-monochromated CuK_α (λ = 1.54178 Å) radiation at 1.75 kW using the ω-2θ scan technique to a maximum 2θ value of 109.8°. An extinction correction was applied and the structure solved by direct methods[202] and refined by full-matrix least squares to residuals of R = 0.036 and R_w = 0.028 for 874 observed reflections with $I > 3\sigma(I)$ and with 134 variables.

Preparation of *cis*-2,5-Dimercaptocyclopentanol (146):



A slurry of lithium aluminum hydride (0.56 g, 14.8 mmol) in THF (50 ml) was cooled to 0°C under an atmosphere of nitrogen and a solution of *cis*-2,5-dithiocyanatocyclopentanone **(138a)** (0.50 g, 2.53 mmol) was added dropwise. After the addition was complete, the solution was allowed to warm to room temperature and stirred overnight. The excess $LiAlH_4$ was then quenched with EtOAc (20 ml) and allowed to stir for another 4 hr. A TLC ($CHCl_3$) indicated that all the starting material had been consumed. The characteristic foul smell of a dithiol was also noted. This reaction mixture was used without further workup for the following oxidation step.

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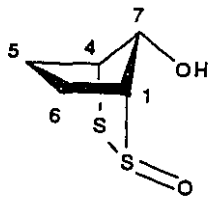
202. a) C. J. Mithril, *MITHRIL- An Integrated Direct MethodsComputer Program, J. Appl. Cryst.*, **17**, 42-46, University of Glasgow, Scotland (1984); b) P. T. Beurskens, *DIRDIF: Direct Methods for Difference Structures- An Automated Procedure for Phase Extension and Refinement of Difference Structure Factors*, Technical Report 1984/1, Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.

Isomerization of 2,5-Dithiocyanatocyclopentanone (136):

A sample containing *cis*-**138** was dissolved in dry acetone and a solution containing 1 equivalent of KSCN in acetone was added and the mixture allowed to stir under nitrogen for 4 hr. The solvent was the removed under reduced pressure and the crude material was partitioned between $CHCl_3$ and d-H_2O. The organic layer was dried over $MgSO_4$ and evaporated to dryness to yield a yellow oil. This material was dried under vacuum for 24 hr and a ^1H NMR spectrum revealed that the ratio of *cis*:*trans* (**138a**:**138b**) was 1:2.4.

Preparation of *syn*-2,3-Dithiabicyclo[2.2.1]heptan-7-ol *S*-Oxide (149a and 149b):



The quenched reaction mixture containing *cis*-2,3-dimercaptocyclopentanol (**146**) (0.415 g, 2.53 mmol) was added simultaneously with a solution of I_2 (0.642 g, 2.53 mmol) in anhydrous ether (30 ml) to 2 L of refluxing anhydrous ether under an atmosphere of nitrogen. After the addition was complete, the solution was cooled to room temperature and a 2.5% aqueous NaOAc/HOAc buffer solution (200 ml) was added and the ether layer separated, washed with H_20 (4x) and dried over $CaCl_2$. The solvent was evaporated to a volume of ~100 ml under reduced pressure at room temperature.[203] Freshly distilled CH_2Cl_2 (20 ml) was added and the remaining ether was carefully removed under reduced pressure at room temperature. This solution was then cooled to 0°C and a solution of *m*-CPBA (0.55 g, 2.53 mmol) was added dropwise. The product was purified by flash chromatography using 9:1 CH_2Cl_2:EtOAc as the eluent. The two isomers (0.0516 g, 12%) of **149** were found in fractions 20-45 in a ratio of 4:1 for **149a**:**149b**. Rf (9:1 CH_2Cl_2: EtOAc) = 0.20.

149a: ^1H NMR (200 MHz, $CDCl_3$)δ: 0.95-2.0 (m, 2x H5 and H6, 4H), 3.86 (dd J_1 = 5.94 J_2 = 2.45 Hz, H4, 1H), 4.21 (s, H1, 1H), 4.61 (d J_{OH-H7} = 10.0 Hz, O<u>H</u>, 1H) and 5.05 (d J_{H7-OH} = 10.0 Hz, H7, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 17.2 (C5), 27.8 (C6), 57.2 (C4), 64.6 (C1) and 86.6 (C7) ppm; IR ($CDCl_3$): 882, 900 and 929 cm^{-1}; MS [EI, direct inlet, 70°C], m/z (% relative intensity, assignment): 164 (22.8, $M^+\cdot$).

149b[204]: ^1H NMR (200 MHz, $CDCl_3$)δ: 1.8-2.3 (m, 2x H5 and H6, 4H), 2.7-2.9 (m, H4, 1H), 3.8 (dd,

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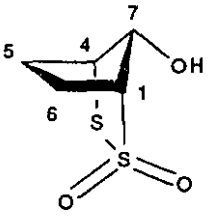
203. Removal of all of the ether under vacuum at 0°C gave a yellow oil which was shown by ^1H NMR spectroscopy to contain a species that may have been the disulfide, however all attempts to purify this mixture resulted in polymerization. Polymerization also occurred during the isolation of 1,2-dithiolane from the oxidation of 1,3-propanedithiol using I_2/Et_3N (J. G. Gleason, Ph. D. Thesis, McGill University, Montreal, Quebec, Canada (1970)).

204. NMR data was difficult to resolve from the peaks of **149a**. Only positions for H1, H4 and H7 along with C1, C4 and C7 could be assigned with certainty.

H1, 1H) and (4.92, t, H7, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 60.5 (C4), 66.8 (C1) and 83.5 (C7) ppm; MS: Same as **149a**.

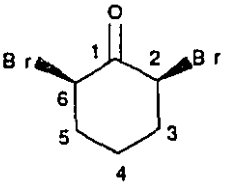
syn-2,3-Dithiabicyclo[2.2.1]heptan-7-ol _S,S_-Dioxide (218):



Compound **218** was isolated from the reaction mixture of the low temperature NMR *m*-CPBA oxidation experiment on **149a** (See Section 6.2). Purification was performed by column chromatography using 9:1 CH_2Cl_2:EtOAc as the eluent. The product (**218**, 5%) was found in fractions 20-26. M.p. 131-132°C; Rf (9:1 CH_2Cl_2:EtOAc): 0.19; ^1H NMR (200 MHz, $CDCl_3$)δ: 2.14-2.29 (m, 3H), 2.50-2.57 (m, 1H), 3.56-3.58 (m, H4, 1H), 3.68 (d $J_{OH\text{-}H7}$ = 11.5 Hz, OH, 1H), 4.20 (m, H1, 1H) and 4.56 (dm $J_{H7\text{-}OH}$ = 11.5 Hz, H7, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 20.5 (C5), 28.3 (C6), 29.7 (C4), 61.9 (C1) and 67.2 (C7) ppm; IR ($CDCl_3$): 881, 924 and 1137 (SO_2) cm^{-1}; HRMS [EI, direct inlet, 240°C]: m/z for $M^{+\cdot}$ ion: Calc'd for $C_5H_8O_3S_2$ 179.99149, Found 179.99148.

6.2.2 [3.2.1] Bridged Bicyclic Compounds

Preparartion of _cis_-2,6-Dibromocyclohexanone (129):



Bromine (319.1 g, 2.0 mol) was added dropwise to a stirred solution of cyclohexanone (**128**) (98.15 g, 1.0 mol) in water (350 ml). The addition was carried out so that the bromine color was allowed to dissipate after each drop and took approximately five hr. The resulting mixture was neutralized with $NaHCO_3$. The lower organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure to yield a tan oil. This was redissolved in a mixture of ether (300 ml) and petroleum ether (50 ml) and allowed to stand in the freezer overnight in order to allow the more stable *cis* isomer to crystallize. The first crop that was collected provided 23.9 g (10%) of white crystals, which were recrystallized from ether/$CHCl_3$ to give pure **129**. M.p. 109-110°C (lit[205] 109.5-110.5°C); ^1H NMR (200 MHz, $CDCl_3$)δ: 1.7-2.25 (m, 4H), 2.59-1.65 (m, 2H) and 4.64 (dd J_1 = 12.2 J_2 = 5.8 Hz, H2 and H6, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 26.0 (C4), 38.9 (C3 and C5), 52.8 (C2 and C6) and 193.2 (C1); IR

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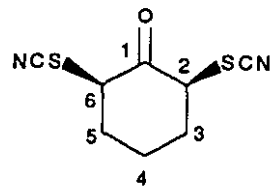
205. E.J. Corey, *J. Amer. Chem. Soc.* **75**, 3297 (1953).

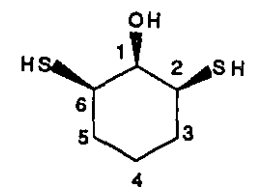
($CDCl_3$): 1753 (C=O) cm^{-1}.

Preparation of *cis*-2,6-Dithiocyanatocyclohexanone (130):



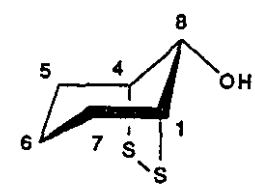
A solution of KSCN (6.2 g, 0.64 mol) in dry acetone (60 ml) was added very quickly to a solution of **129** (8.16 g, 0.032 mol) in dry acetone (60 ml). A fine white precipitate formed and the solution turned yellow. The solution was allowed to stir at room temperature for 30 min, then it was set in the freezer for a further 30 min. The white precipitate (KBr) was then filtered off and the acetone evaporated under reduced pressure. The resulting yellow solid was partitioned between d-H_2O and chloroform and the chloroform layer was dried over $MgSO_4$. This was evaporated under reduced pressure to yield 6.35 g (94%) of crude **130**. This material was recrystallized from hexane/EtOAc; final yield was 5.75 g (85%). M.p. 103.5-105.5°C (lit[6] 103-105°C); ^1H NMR (200 MHz, $CDCl_3$)δ: 1.95-2.26 (m, 4H), 2.79-2.84 (m, 2H) and 4.26-4.35 (m, H2 and H6, 2H); ^{13}C NMR (300 MHz, $CDCl_3$)δ: 24.9 (C4), 36.0 (C3 and C5), 56.9 (C2 and C6), 110.2 (2x SCN) and 196.9 (C1) ppm; IR (KBr): 1725 (C=O) and 2265 (SCN) cm^{-1}.

Preparation of *cis*-2,6-Dimercaptocyclohexanol (131):



To a solution of $LiAlH_4$ (1.63 g, 0.0430 mol) in freshly distilled THF (100 ml) at 0°C under an atmosphere of nitrogen was slowly added a solution of **130** (1.56 g, 0.0073 mol) in THF (50 ml). After the addition, the solution was allowed to warm to room temperature and stirred overnight. The unreacted $LiAlH_4$ was quenched with EtOAc (30 ml) and this solution was used for the next reaction without any further workup. TLC ($CHCl_3$) indicated that all starting material had been consumed.

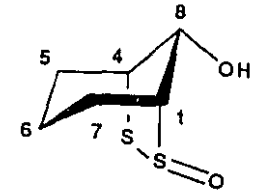
Preparation of *syn*-2,3-Dithiabicyclo[3.2.1]octan-8-ol (3):



To 2.0 L of refluxing anhydrous ethyl ether were added, simultaneously, a solution of iodine (1.85 g, 0.0073 mol) in ether and the previous reaction mixture containing **131** under an atmosphere of nitrogen. The addition took approximately 2 hr. The resulting solution was treated with 200 ml of a 5% NaOAc/HOAc buffer solution. The ether layer was separated, washed with d-H_2O (4x), dried over calcium chloride and the solvent removed under reduced pressure. The resulting yellow oil was chromatographed on silica gel with

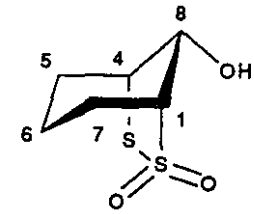
chloroform as the eluent. The desired product (Rf = 0.21) was collected to give a yellow solid which was sublimed to give pure **3**, 0.614 g (52%).[206] M.p. 233-234°C, sealed tube, rapid sublimation (lit[6] 235-236°C); ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.73-2.15 (m, 2x H5, H6 and H7, 6H), 2.63 (dm J_{OH-H8} = 11.8 Hz, OH, 1H), 3.86 (br s, H1 and H4, 2H) and 4.35 (dm J_{H8-OH} = 11.8 Hz, H8, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 16.6 (C6), 33.4 (C5 and C7), 58.7 (C1 and C4) and 80.7 (C8) ppm; UV ($CHCl_3$, nm): 367 (ϵ = 76).

Preparation of 2,3-Dithiabicyclo[3.2.1]Octan-8-ol *S*-Oxide (150a):



2,3-Dithiabicyclo[3.2.1]octan-8-ol **(3)** (0.219 g, 1.35 mmol) was dissolved in chloroform (10 ml) and this solution was cooled to 0°C. To this was added *m*-CPBA (0.291 g, 1.35 mmol) slowly over a period of 15 min. The resulting solution was then stirred for a further 30 min at room temperature. The product was purified directly by column chromatography using 1:1 Hexanes:EtOAc as the eluent. Compound **150a** was found in fractions 38-80 and was isolated as a white solid (0.211 g, 88%). NMR spectroscopy indicated the presence of only one isomer. Derivatization of this compound with *p*-nitrobenzoyl chloride and comparison of the spectral data with those of compound **152** (below) indicated that the sulfinyl oxygen in **150a** was in the *exo* configuration. M.p. 181-182 °C, sealed tube; Rf (1:1 hexanes:EtOAc): 0.10; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.2-1.7 (m, 2x H5 and H6, 4H), 2.01-2.14 (m, 2x H7, 2H), 4.07 (br s, H4, 1H), 4.14 (br s, OH, 1H), 4.68 (br s, H8, 1H) and 4.75 (br s, H1, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 17.0 (C6), 24.7 (C5), 29.9 (C7), 64.2 (C4), 77.2 (C1) and 84.7 (C8) ppm; IR ($CDCl_3$): 1038, 1061 (S=O) and 3450 (OH) cm^{-1}; MS [EI, direct inlet, 30°C], m/z (% relative intensity, assignment): 178 (40, $M^{+\cdot}$), 98 (100, $M^{+\cdot} - S_2O$).

Preparation of *syn*-2,3-Dithiabicyclo[3.2.1]octan-8-ol *S,S*-Dioxide (156):

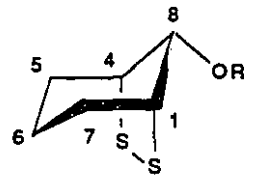


2,3-Dithiabicyclo[3.2.1]octan-8-ol *S*-oxide **(150a)** was oxidized using 1 equivalent of *m*-CPBA following the same procedure used for the oxidation of 2,3-dithiabicyclo[3.2.1]octan-8-ol **(3)** described above. Purification was performed by column chromatography using 3:1 CH_2Cl_2:EtOAc as the eluent. Compound **156** was in fractions 10-15 and was isolated as a white solid (yield 60%). Rf (3:1 CH_2Cl_2:EtOAc): 0.39; ^{1}H NMR (200 MHz,

206. This was the best yield obtained from the many times this reaction was repeated. Yields ranged from 20-52%.

$CDCl_3$)δ: 1.6-2.5 (m, 2x H5, H6 and H7, 6H), 3.43 (d J_{OH-H8} = 10.5 Hz, OH, 1H), 3.54 (br s, H4, 1H), 4.30 (dm J_{H8-OH} = 10.5 Hz, H8, 1H) and 4.55 (br s, H1, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 15.8 (C6), 26.5 (C5), 31.4 (C7) 62.9 (C4), 69.7 (C1) and 75.5 (C8) ppm; IR ($CDCl_3$): 753, 909, 1134 (SO_2), 1283 and 1315 (SO_2) cm^{-1}; HRMS [EI, direct inlet, 70°C], m/z for $M^{+\cdot}$ ion: Calc'd for $C_6H_{10}O_3S_2$ 194.0071, Found 194.0074.

Preparation of *syn*-2,3-Dithia-[(8-*p*-nitrobenzoyl)oxy]bicyclo[3.2.1]octane (133):



R = -C(O)-C_6H_4-NO_2

2,3-Dithiabicyclo[3.2.1]octan-8-ol **(3)** (0.169 g, 1.04 mmol) was dissolved in pyridine (2 ml) and a solution of *p*-nitrobenzoylchloride (0.193 g, 1.04 mmol) in pyridine (0.5 ml) was added dropwise. The resulting solution was heated over a steam bath for 0.5 hr and d-H_2O (~5 ml) was added and the solution extracted with ether. The ether layer was washed with water (3x), 5% Na_2CO_3 (3x), dried over $MgSO_4$ and evaporated to dryness to yield an orange/yellow solid. This was recrystallized from ethanol to give orange crystals of **133** (0.150 g, 47%). The structure was confirmed by X-ray crystallography (see Figure 4, Chapter 2). M.p. 143-144°C; ^1H NMR (200 MHz, $CDCl_3$)δ: 1.5-2.26 ppm (m, 2x H5, H6 and H7, 6H), 4.1 ppm (br s, H1 and H4, 2H), 5.6 (br s, H8, 1H) and 8.2 (q, aromatics, 4H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 16.5 (C6), 33.3. (C5 and C7), 54.4 (C1 and C4), 83.2 (C8), 123.6 (C3' and C7'), 131.0 (C4' and C6'). 135.2 (C2'), 150.7 (C5') and 165.0 (C=O) ppm; Anal. Calc'd for $C_{13}H_{13}NO_4S_2$: C 50.14; H 4.20; N 4.50; S 20.60; Found: C 49.94; H 4.05; N 4.60; S 20.77.

X-Ray Data for 133:

Empirical Formula: $C_{13}H_{13}NO_4S_2$, M = 311.36, orthorhombic, space group $Pbn2_1$ (#33), a = 7.215(2), b = 10.654(4), c = 18.076(5) Å, V = 1388.8(7) $Å^3$, Z = 4, D_c = 1.489 Mgm^{-3}, μ = 3.78 cm^{-1}, F_{000} = 648. Data were collected at room temperature on a Nicolet R3 four-circle diffractometer with graphite-monochromated MoK_α radiation (λ = 0.70926 Å) using ω scans ($2\theta_{max}60°$). An extinction correction was applied and the structure solved by direct methods[207] and refined by full-matrix least squares to residuals of R = 0.057 and R_w = 0.038 for 1375 observed reflections with $I > 3\sigma(I)$ and with 181 variables.

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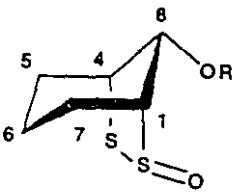
207. G. M. Sheldrick, *SHELXTL. An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data*, Revision 5.1, Federal Republic of Germany: University of Gottingen (1985).

Preparation of *syn*-2,3-Dithia-[(8-*p*-nitrobenzoyl)oxy]bicyclo[3.2.1]octane *S*-Oxide (152):



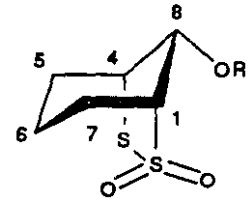
R = -C(O)-C_6H_4-NO_2

2,3-Dithia-[(8-*p*-nitrobenzoyl)oxy]bicyclo[3.2.1]octane **(133)** (0.100 g, 0.321 mmol) was dissolved in CH_2Cl_2 (5 mls) and cooled to 0°C. A solution of *m*-CPBA (0.069 g, 0.321 mmol) was added dropwise with stirring. After the addition was complete, the ice bath was removed and the solution allowed to stir overnight. To this solution was added $NaHSO_3$ (25 mg) in water (20 ml) and the organic layer was washed with 10% $NaHCO_3$ (3x), dried over $MgSO_4$ and concentrated to yield 93mg (90%) of a white solid **(152)**. This material was recrystallized from ethanol subjected, to X-ray crystallography and the oxygen on the sulfur atom was shown to be in the *exo* configuration (see Figure 7, Chapter 2). M.p. 166-168°C; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.35-2.25 (m, 2x H5, H6 and H7, 6H), 4.13 (br s, H4, 1H), 4.78 (br s, H1, 1H), 5.81 (t $J_{H8\text{-}H1} = J_{H8\text{-}H4}$ = 1.6 Hz, H8, 1H) and 8.27 (q, aromatics, 8H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 17.4 (C6), 24.8 (C5), 30.0 (C7), 59.4 (C4), 75.3 (C1), 84.2 (C8), 123.6 (C3' and C7'), 131.5 (C4' and C6'), 134.8 (C2'), 150.8 (C5') and 164.0 (C=O) ppm; IR: 722, 1069 (S=O), 1104 (NO_2), 1122, 1242, 1270 (NO_2), 1336 (NO_2), 1530 (NO_2) and 1725 (C=O) cm^{-1}; MS [EI, direct inlet, 125 °C], m/z (% relative intensity, assignment): 327 (13, $M^{+}\cdot$).

X-Ray Data for 152:

Empirical Formula: $C_{13}H_{13}NO_5S_2$, M = 327.37, monoclinic, space group $P2_1/c$ (#14), a = 10.753(3), b = 10.811(3), c = 13.396(3) Å, b = 112.67(2), V = 1436.9(6) Å^3, Z = 4, D_c = 1.513 Mgm^{-3}, μ = 3.74 cm^{-1}, F_{000} = 680. Data were collected on a Nicolet R3 four-circle diffractometer with graphite-monochromated MoK_α (λ = 0.70926 Å) using ω scans ($2\theta_{max}60°$). The structure was solved by direct methods[207] and refined by blocked cascade least squares to residuals of R = 0.059, R_w = 0.059 for 2268 observed reflections with $I > 2.5\sigma(I)$ and with 203 variables.

Isolation of *syn*-2,3-Dithia-[(8-*p*-nitrobenzoyl)oxy]bicyclo[3.2.1]octane *S,S*-Dioxide (199):

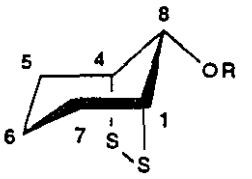


R = -C(O)-C_6H_4-NO_2

Compound **199** was isolated from the product mixture of the low temperature NMR *m*-CPBA oxidation experiments on **152** (See Section 6.3). Purification was performed by column chromatography using 3:2 hexanes:EtOAc as the eluent. Compound **199** was isolated from fractions 19-41 in 18% yield. M.p. 157-159°C; Rf (3:2 hexanes:EtOAc): 0.20; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.6-2.6 (m, 2x H5, H6 and H7, 6H), 3.78 (br s, H4, 1H), 4.67 (br s, H1, 1H), 5.54 (m, H8, 1H) and 8.3 (q, aromatics, 4H); ^{13}C NMR (300 MHz,

$CDCl_3$)δ: 16.0 (C6), 26.9 (C5), 31.5 (C7), 58.1 (C4), 67.1 (C1), 76.9 (C8), 123.7 (C3' and C7'), 131.7 (C4' and C6'), 134.2 (C2'), 151.0 (C5') and 163.6 (C1', C=O) ppm; IR ($CDCl_3$): 1105 (NO_2), 1118 (SO_2), 1268 (NO_2), 1530 (NO_2) and 1730 (C=O); MS [EI, direct inlet, 180°C], m/z (% relative intensity, assignment): 150 (100, $M^{+\cdot}$ - $C(O)C_6H_4NO_2$. Confirmation of this structure was obtained by derivation of compound **156** with *p*-nitrobenzoyl chloride and a comparison of the spectral data with that of **199**; the two compounds were found to be identical.

Preparation of *syn*-2,3-Dithia-[(8-*n*-hexanoyl)oxy]bicyclo[3.2.1]octane (134):

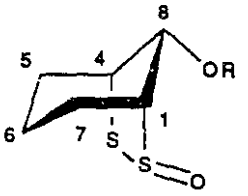


R = -C(O)-$(CH_2)_4$-CH_3

2,3-Dithiabicyclo[3.2.1]octan-8-ol **(3)** (0.178 g, 1.10 mmol) was dissolved in freshly distilled pyridine (2 ml) and cooled to 0°C under nitrogen. To this was added *n*-hexanoyl chloride (0.150 g, 1.10 mmol) *via* syringe. This was allowed to stir overnight at room temperature. Ether (5 ml) was then added and the resulting solution was washed several times with 5% $NaHCO_3$ and d-H_2O, dried over $MgSO_4$ and evaporated to dryness. The resulting oil was pumped under high vacuum to remove residual pyridine and unreacted disulfide. This was then subjected to flash column chromatography for further purification using chloroform as the eluent. The first fraction was collected to give a yellow oil (0.204 g, 84%). Rf ($CHCl_3$): 0.53; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 0.88 (t J = 5 Hz, 3x H6', 3H), 1.26-1.34 (m, 2x H3', H4' and H5' and 2x H5, H6 and H7, 12H), 2.36 (t $J_{H2'-H3'}$= 7.4 Hz, 2x H2', 2H) 3.97 (br s, H1 and H4, 2H) and 5.39 (t J_{H8-H1} = J_{H8-H4} = 1.7 Hz, H8, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 13.8 (C6'), 16.5 (C6) 22.2 (C5'), 24.5 (C4'), 31.1 (C3'), 33.3 (C5 and C7), 34.3 (C2'), 54.4 (C1 and C4), 82.2 (C8) and 173.3 (C=O) ppm; IR (neat): 1730 (C=O) cm^{-1}; MS [EI, direct inlet, 40°C], m/z (% relative intensity, assignment): 260 (34, $M^{+\cdot}$), 28 (100, $CO_2^{+\cdot}$ or $C_2H_4^{+\cdot}$).

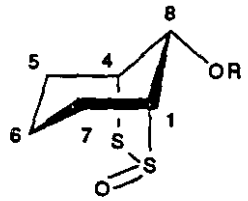
Preparation of *syn*-2,3-Dithia-[(8-*n*-hexanoyl)oxy]bicyclo[3.2.1]octane *S*-Oxides (153a and 153b):

To a solution of 2,3-dithia-[(8-*n*-hexanoyl)oxy]bicyclo[3.2.1]octane **(134)** (0.0248 g, 0.254 mmol) in CH_2Cl_2 (5 ml) was added *m*-CPBA (0.027 g, 0.254 mmol) in CH_2Cl_2 (5 ml) at 0°C. After the addition was complete, the solution was allowed to warm to room temperature and was stirred for a further 30 min. The product was purified by column chromatography using 3:1 hexanes:EtOAc as the eluent. Fractions 7-12 were shown to contain the *endo* isomer **(153b)** and fractions 15-27 contained the *exo* isomer **(153a)**. The overall yield of *S*-oxide was 90%.



R = -C(O)-$(CH_2)_4$-CH_3

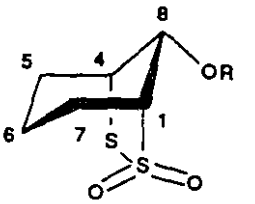
Exo S-Oxide **153a** (0.028 g, 79%): Rf (3:1 hexanes:EtOAc) = 0.13; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 0.85 (t $J_{H6'\text{-}H5'}$ = 6.5 Hz, 3x H6', 3H), 1.2-2.2 (m, 2x H3', H4' and H5' and 2x H5, H6 and H7, 12H), 2.35 (t $J_{H2'\text{-}H3'}$ = 7.6 Hz, 2x H2', 2H), 4.1 (br s, H4, 1H), 4.6 (br s, H1, 1H) and 5.5 (t $J_{H8\text{-}H1}$ = $J_{H8\text{-}H4}$ = 1.5 Hz, H8, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 13.9 (C6'), 17.5 (C6), 22.2 (C5'), 24.2 (C4'), 24.8 (C3') 30.2 (C5), 31.2 (C2'), 34.1 (C7), 59.4 (C4), 75.3 (C1), 83.4 (C8) and 173.5 (C=O) ppm; IR (neat): 1084 (S=O) and 1743 (C=O) cm^{-1}; HRMS [EI, direct inlet, 40°C], m/z for $M^+\cdot$ ion: Calc'd for $C_{12}H_{20}O_3S_2$ 276.08539, Found 276.08551.



R = -C(O)-$(CH_2)_4$-CH_3

Endo S-Oxide **153b** (0.0028 g, 11%): Rf (3:1 hexanes:EtOAc) = 0.21; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 0.85 (t $J_{H6'\text{-}H5'}$ = 6.5 Hz, 3x H6', 3H), 1.2-2.2 (m, 2x H3', H4' and H5' and 2x H5, H6 and H7, 12H), 2.35 (t $J_{H2'\text{-}H3'}$ = 7.6 Hz, 2x H2', 2H), 3.94 (br s, H4, 1H), 4.18 (br s, H1, 1H) and 5.47 (t $J_{H8\text{-}H1}$ = $J_{H8\text{-}H4}$ = 1.5 Hz, H8, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 13.8 (C6'), 16.7 (C6), 22.2 (C5'), 22.6 (C4'), 24.4 (C3'), 30.7 (C5), 31.1 (C2'), 34.1 (C7), 58.1 (C4), 67.2 (C1), 82.1 (C8) and 172.7 (C=O) ppm; IR (neat): 1088 (S=O) and 1734 (C=O) cm^{-1}; HRMS [EI, direct inlet, 40°C], m/z for $M^+\cdot$ ion: Calc'd for $C_{12}H_{20}O_3S_2$ 276.08539, Found 276.08551.

Preparation of *syn*-2,3-Dithia-[(8-*n*-hexanoyl)oxy]bicyclo[3.2.1]octane *S,S*-Dioxide (204):



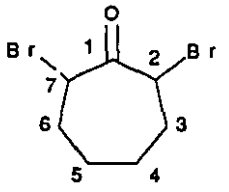
R = -C(O)-$(CH_2)_4$-CH_3

2,3-Dithia-[(8-*n*-hexanoyl)oxy]bicyclo[3.2.1]octane *S*-oxide **(153a)** (23.2 mg, 0.084 mmol) was dissolved in dry CH_2Cl_2 (2 ml) and cooled to 0°C. *m*-CPBA (18.1 mg, 0.084 mmol) was then added as a solution in CH_2Cl_2 and the reaction mixture was allowed to warm to room temperature and stirred for 1 hr. The product mixture was absorbed onto silica gel and flash column chromatography performed using $CHCl_3$ as the eluent. The product, a clear oil (15 mg, 61%), was found in fractions 3-11. Rf (3:1 hexanes:EtOAc): 0.14; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 0.87 (t $J_{H6'\text{-}H5'}$ = 6.3 Hz, 3x H6', 3H), 1.2-2.2 (m, 2x H3', H4' and H5' and 2x H5, H6 and H7, 12H), 2.41 (t $J_{H2'\text{-}H3'}$ = 7.5 Hz, 2x H2', 2H), 3.65 (br s, H4, 1H), 4.5 (br s, H1, 1H) and

173.1 (C=O) ppm; IR (neat): 1137 (SO_2), 1308 (SO_2) and 1735 (C=O) cm^{-1}. Confirmation of this structure was obtained by derivation of compound **156** with *n*-hexanoyl chloride and a comparison of the spectral data with that of **204**; the two compounds were found to be identical.

6.2.3 [4.2.1] Bridged Bicyclic Compounds

Preparation of *trans* and *cis*-2,7-Dibromocycloheptanone (136a and 136b):



Cycloheptanone **(140)** (4.75 g, 0.0424 mol) was dissolved in glacial acetic acid (150 ml), along with 2 drops of HBr (50%) to initiate the reaction, and bromine (13.55 g, 0.0848 mol) was added (dropwise) at 10°C. The solution was then allowed to warm to room temperature and stirred for a further 2 hr, at which time it was neutralized to pH 6 with $NaHCO_3$. The product was then extracted into ether and the ether layer washed with d-H_2O (3x) and 5% $NaHCO_3$ (3x), then dried over $MgSO_4$ and evaporated under reduced pressure to a yellow oil. This oil was redissolved in petroleum ether:EtOAc (1:1) and allowed to crystallize at -15°C for 24 hr. The white crystals formed were collected to yield 5.32 g (46%) of a crude mixture containing the *trans* and *cis* isomers of **136** in a ratio of 2:1 respectively. Recrystallization from petroleum ether:EtOAc (1:1) resulted in the isolation of the *trans* isomer **(136a)** only. M.p 70-71°C (lit[128] 70°C); Rf (CH_2Cl_2): 0.68; ^1H NMR (200 MHz, $CDCl_3$)δ: 1.40-2.55 (m, 2x H3-H6 for **136a** and **136b**, 16H), 4.61 (dd J_1 = 8.52 J_2 = 4.29 Hz, H2 and H7 for **136b**, 2H) and 4.71 (dd J_1 = 10.34 J_2 = 4.86 Hz, H2 and H7 for **136a**, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 26.4 (C4 and C5, **136b**), 27.0 (C4 and C5, **136a**), 33.8 (C3 and C6, **136b**), 35.0 (C3 and C6, **136a**), 49.7 (C2 and C7, **136a**), 51.7 (C2 and C7, **136b**) and 198.5 (C1, **136a**) ppm; IR ($CHCl_3$): 1728 (C=O, **136a**) and 1701 (C=O, **136b**) cm^{-1}. The crude mixture containing both isomers was used for the next step of the reaction sequence.[208]

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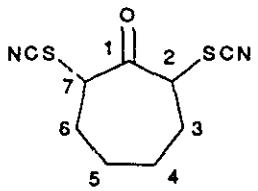
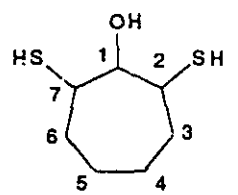
208. Using the pure sample of **136a** did not lead to the successful preparation of a [4.2.1] bridged bicyclic disulfide.

Preparation of 2,7-Dithiocyanatocycloheptanone (141a and 141b):



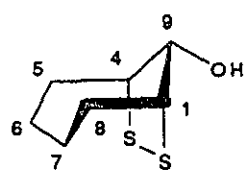
2,7-Dibromocycloheptanone **(136a and 136b)** (2.09 g, 7.73 mmol) was dissolved in dry acetone (100 ml) and a solution of KSCN (1.520 g, 15.4 mmol) in dry acetone (50 ml) was added all at once under an atmosphere of nitrogen. The solution was refluxed for 4 hr, cooled and the precipitated KBr filtered. The acetone was evaporated under reduced pressure and the resulting solid partitioned between d-H_2O and $CHCl_3$. The organic layer was washed, dried over $MgSO_4$ and evaporated to a yellow oil (1.38 g, 80%) containing a 2:1 mixture of two isomers (a,b). Rf (CH_2Cl_2): 0.20; ^1H NMR (200 MHz, $CDCl_3$)δ: 1.42-2.60 (m, 2x H3-H6 for isomer a and b, 16H), 4.21 (dd J_1 = 11.97 J_2 = 4.36 Hz, H2 and H7 for isomer b, 2H) and 4.59 (dd J_1 = 7.68 J_2 4.48 Hz, H2 and H7 for isomer a, 2H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 25.5 (C4 and C5, isomer a), 27.7 (C4 and C5, isomer b), 31.9 (C3 and C6, isomer a), 32.0 (C3 and C6, isomer b), 54.7 (C2 and C7, isomer b), 57.6 (C2 and C7, isomer a), 110.0 (SCN, isomer b), 111.1 (SCN, isomer a), 200.2 (C1, isomer b) and 201.2 (C1, isomer a) ppm; IR ($CHCl_3$): 1712 (C=O) and 2159 (S=C=N) cm^{-1}; MS [EI, direct inlet, 30 °C], m/z (% relative intensity, assignment): 226 (11.3, $M^{+\cdot}$).

Preparation of 2,7-Dimercaptocycloheptanol (142):



2,7-Dithiocyanatocycloheptanone (**141a** and **141b**) (1.30 g, 5.78 mmol) was dissolved in dry THF (20 ml) and added to a slurry of $LiAlH_4$ in dry THF (100 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was then allowed to warm to room temperature and stirred overnight. The unreacted $LiAlH_4$ was quenched with EtOAc (50 ml) at 0°C and the solution was once again stirred overnight. No further workup procedures were carried out and the mixture was used directly for the proceding oxidation step.

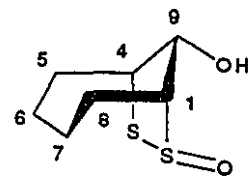
Preparation of *syn*-2,3-Dithiabicyclo[4.2.1]nonan-9-ol (143):



The quenched reaction mixture containing 2,7-dimercaptocycloheptanol **(142)** was added simultaneously with a solution of I_2 (1.46 g, 5.8 mmol) in anhydrous ether (50 ml) to 2 L of refluxing anhydrous ether under an atmosphere of nitrogen. The addition of iodine normally lagged behind that of the dithiol alcohol and was continued until the yellow color of iodine persisted, at which time the mixture was cooled to room temperature and a 5% aqueous HOAc/NaOAc buffer solution (200 ml) was added. The organic layer was

separated, washed with d-H_2O (4x 200 ml), dried over $MgSO_4$ and evaporated to dryness to give a yellow solid. The product was purified *via* flash column chromatography using $CHCl_3$ as the eluent. Fractions 6-11 were combined to yield (after recrystallization from hexane:CH_2Cl_2) 0.212 g (63%)[209] of **143** as yellow crystals. M.p. 120-122°C (sealed tube); Rf ($CHCl_3$): 0.20; ^1H NMR (200 MHz, $CDCl_3$)δ: 1.35-1.50 (m, 2H), 1.68-1.92 (m, 4H), 1.93-2.09 (m, 2H), 2.76 (d J_{OH-H9} = 11.5 Hz, OH, 1H), 3.88-3.92 (m, H1 and H4, 2H) and 4.55 (d J_{H9-OH} = 11.6 Hz, H9, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 24.0 (C6 and C7), 33.4 (C5 and C8), 61.93 (C1 and C4), and 82.31 (C9) ppm; IR (KBr): 939, 1049 and 3300 (OH) cm^{-1}; UV ($CHCl_3$): μ_{max} 357 nm (ϵ = 131); MS [EI, direct inlet, 30°C] m/z (% relative intensity, assignment): 176 (95, $M^{+\cdot}$), 112 (100, $M^{+\cdot}$ - S_2); Anal. Calc'd for $C_7H_{12}OS_2$: C 47.69; H 6.86; S 36.37; Found: C 47.51; H 6.84; S 36.02.

Preparation of *syn*-2,3-Dithiabicyclo[4.2.1]nonan-9-ol *S*-Oxide (151a):



2,3-Dithiabicyclo[4.2.1]nonan-9-ol **(143)** (30.9 mg, 0.175 mmol) was dissolved in dry CH_2Cl_2 (25 ml) and cooled to 0°C under an atmosphere of nitrogen. To this was added (dropwise) a solution of *m*-CPBA (30.2 mg, 0.175 mmol) in dry CH_2Cl_2 and the solution allowed to warm and stirred for 1 hr. An aqueous solution of $NaHSO_3$ (25 mg in 25 ml) was added and the organic layer was separated, washed with 5% $NaHCO_3$ (3x), H_2O, dried over $MgSO_4$ and evaporated to dryness under reduced pressure to give 31.5 mg (90%) of **151a** as a white solid. Recrystallization from ethanol gave clear prism of **151a** and the structure was confirmed by X-ray crystallography (see Figure 8, Chapter 2). M.p. = 130-131°C; Rf ($CHCl_3$): 0.10; ^1H NMR (200 MHz, $CDCl_3$)δ: 1.24-1.40 (m, 2H), 1.50-1.99 (m, 4H), 2.15-2.30 (m, 2H), 4.38 (dd J_1 = 10.75 and J_2 = 2.50 Hz, H4, 1H), 4.85 (br s, OH, 1H), 5.02 (t J = 3.49, H9, 1H) and 5.07 (br s, H1, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 23.3 (C6), 23.7 (C7), 24.2 (C5), 30.9 (C8), 68.1 (C4), 78.0 (C1) and 86.8 (C9) ppm; IR ($CDCl_3$): 1056 (S=O) and 3450 (OH) cm^{-1}; Anal Calc'd for $C_7H_{12}O_2S_2$: C 43.72; H 6.29; Found: C 43.55; H 6.24.

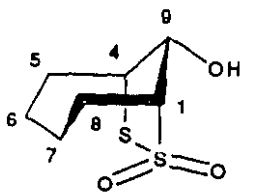
X-Ray Data for 151a:

Empirical Formula: $C_7H_{13}O_2S_2$, M = 193.30, triclinic, space group P1 (#2), a = 11.205(4), b = 11.482(2), c = 7.2117(8) Å, α = 92.87, β = 91.48(1), γ = 107.39°, V = 884.7(4) $Å^3$, Z = 4, D_c = 1.451 gcm^{-3}, $\mu_{(CuK_\alpha)}$ = 49.89 cm^{-1}, F_{000} = 412. Data were collected at room temperature on a Rigaku AFC6S diffractometer with graphite-monochromated CuK_α (λ = 1.54178 Å) radiation at

209. Based on the amount of *cis*-**141** present in the starting material.

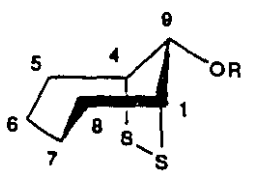
1.75 kW using the ω-2θ scan technique to a maximum 2θ value of 120.0°. An empirical absorption correction was applied using the program DIFABS[210] and the structure solved by direct methods[202] and refined by full-matrix least squares to residuals of R = 0.079 and R_w = 0.083 for 1878 observed reflections with $I > 3\sigma(I)$ and with 197 variables.

Isolation of *syn*-2,3-Dithiabicyclo[4.2.1]nonan-9-ol *S,S*-Dioxide (157):



Compound **157** was isolated from the product mixture of the low temperature NMR *m*-CPBA oxidation experiments on **151a** (See Section 6.3). Purification of **157** was performed using column chromatography with 4:1 $CHCl_3$:EtOAc as the eluent. Compound **157** was found in fractions 5-11 and was isolated in 40% yield (70% based on recovered starting material). Rf (4:1 $CHCl_3$:EtOAc): 0.10; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.7-2.45 (m, 2x H5, H6, H7 and H8, 8H), 3.60 (d $J_{OH\text{-}H9}$ = 11 Hz, OH, 1H), 3.75 (d J = 9 Hz, H4, 1H), 4.55 (d $J_{H9\text{-}OH}$ = 11 Hz, H9, 1H) and 4.62 (br s, H1, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 22.9 (C6), 23.9 (C5), 24.7 (C7), 33.9 (C8), 64.3 (C4), 74.2 (C1) and 75.1 (C9) ppm; IR ($CDCl_3$): 909, 1127 (SO_2) and 1292 (SO_2); HRMS [EI, direct inlet, 80°C]: m/z for $M^{+\cdot}$ ion: Calc'd for $C_7H_{12}O_3S_2$ 208.02279, Found 208.02285.

Preparation of *syn*-2,3-Dithia-[(9-*p*-nitrobenzoyl)oxy]bicyclo[4.2.1]nonane (144):



2,3-Dithiabicyclo[4.2.1]nonan-9-ol **(143)** (0.135 g, 0.768 mmol) was dissolved in freshly distilled pyridine (10 ml) and a solution of *p*-nitrobenzoyl chloride in pyridine (5 ml) was added (dropwise). The resulting solution was heated over a steam bath for 10 min and then d-H_2O (10 ml) was added. A yellow precipitate formed immediately and this was collected, washed with 5% $NaHCO_3$ and d-H_2O to give 0.160 g (60%) of pure **144.** M.p. 114-116°C; Rf ($CHCl_3$): 0.60; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.55-2.19 (m, 2x H5, H6, H7 and H8, 8H), 4.17 (m, H1 and H4, 2H), 5.85 (t $J_{H9\text{-}H1}$ = $J_{H9\text{-}H4}$ = 1.06 Hz, 1H) and 8.24 (q, aromatic protons, 4H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 23.9 (C6 and C7), 34.0 (C5 and C8), 58.5 (C1 and C4), 85.3 (C9), 123.6 (C3' and C7'), 131.0 (C4' and C6'), 135.1 (C2'), 150.8 (C5') and 163.8 (C1', C=O) ppm; IR ($CDCl_3$): 1102 (NO_2), 1275 (NO_2), 1349, 1530 (NO_2) and 1723 (C=O) cm^{-1}; MS [EI, direct inlet, 30°C] m/z (% relative intensity, assignment): 325 (11.6 $M^{+\cdot}$), 150 (100, $M^{+\cdot}$ - -C(O)-Ph-NO_2).

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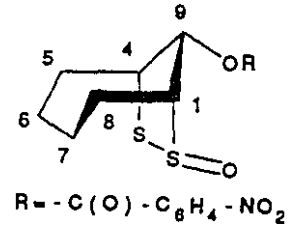
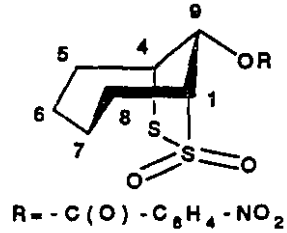
210. N. Walker and D. Stuart, *Acta Cryst.*, **A39**, 158 (1983).

Preparation of *syn*-2,3-Dithia-[(9-*p*-nitrobenzoyl)oxy]bicyclo[4.2.1]nonane *S*-Oxide (154):



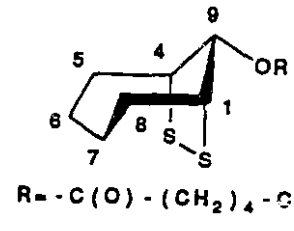
Compound **144** (70.0 mg, 0.215 mmol) was dissolved in CH_2Cl_2 (10 ml) and cooled to 0°C under an atmosphere of nitrogen and a solution of *m*-CPBA (37.1 mg, 0.215 mmol) in CH_2Cl_2 was added (dropwise). The solution was allowed to warm to room temperature and stirring was continued for 1 hr, after which the solution was absorbed onto silica and the product purified by column chromatography using 7:3 hexanes:EtOAc as the eluent. Compound **154** was obtained as a white solid (68.3 mg, 93%). M.p. 138-139°C; Rf ($CHCl_3$): 0.13; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.46-2.29 (m, 2x H5, H6, H7 and H8, 8H), 4.30 (dt J_1 = 10.4 Hz J_2 1.23 Hz, H4, 1H), 4.91 (t J = 3.17 Hz, H1, 1H), 6.19 (s, H9, 1H) and 8.25 (q, aromatic protons, 4H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 22.2 (C6), 24.3 (C7), 24.8 (C5), 34.5 (C8), 59.6 (C4), 73.6 (C1), 75.0 (C9), 123.6 (C3' and C7'), 131.5 (C4' and C6'), 134.7 (C2'), 150.8 (C5') and 164.0 (C1', C=O) ppm; IR (KBr): 722 (NO_2), 1076 (S=O), 1105 (NO_2), 1271 (NO_2), 1524 (NO_2) and 1721 (C=O) cm^{-1}; MS [EI, direct inlet, 200°C] m/z (% relative intensity, assignment): 341 (1.3, $M^{+}\cdot$), 150 (100, $M^{+}\cdot$ - ·C(O)-Ph-NO_2).

Isolation of *syn*-2,3-Dithia-[(9-*p*-nitrobenzoyl)oxy]bicyclo[4.2.1]nonane *S,S*-Dioxide (210)



Compound **210** was isolated from the product mixture of the low temperature NMR *m*-CPBA oxidation experiments on **154** (See Section 6.3). Purification of **210** was performed using column chromatography with 4:1 $CHCl_3$:EtOAc as the eluent. ^{1}H NMR (300 MHz, $CDCl_3$)δ: 1.5-2.6 (m, 2x H5, H6, H7 and H8, 8H), 3.91 (d J = 8.42 Hz, H4, 1H), 4.68 (s, H1, 1H), 5.80 (t, H9, 1H), and 8.25 (q, aromatic protons, 4H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 22.2 (C6), 24.3 (C7), 24.8 (C5), 34.5 (C8), 59.6 (C4), 73.6 (C1), 75.0 (C9), 123.8 (C3' and C7'), 130.9 (C4' and C6'), 134.1 (C2'), 151.0 (C5') and 164.0 (C1', C=O) ppm.

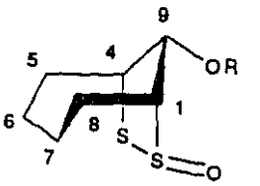
Preparation of *syn*-2,3-Dithia-[(9-*n*-hexanoyl)oxy]bicyclo[4.2.1]nonane (145):



2,3-Dithiabicyclo[4.2.1]nonan-9-ol **(143)** (0.115 g, 0.653 mmol) was disolved in freshly distilled pyridine (5 ml) and cooled to 0°C under an atmosphere of nitrogen. *n*-Hexanoyl chloride (0.088 g, 0.653 mmol) was added *via* syringe and the solution allowed to warm to room temperature. After the addition of d-H_2O (10 ml) the product was extracted into $CHCl_3$ and washed with 5% $NaHCO_3$ (3x), d-H_2O (3x), dried over $MgSO_4$ and evaporated to dryness. Purification was performed by column chromatography using 1:1

CH_2Cl_2:Hexanes as the eluent. The product (92.6 mg, 52%) was found in fractions 15-35. Rf (1:1 CH_2Cl_2:Hexanes): 0.17; ^1H NMR (200 MHz, $CDCl_3$)δ: 0.86 (t $J_{H6'\text{-}H5'}$ = 6.5 Hz, 3x H6', 3H), 1.23-2.12 (m, 2x H3', H4' and H5' and 2x H5, H6, H7 and H8, 14H), 2.31 (t $J_{H2'\text{-}H3'}$ = 7.5 Hz, 2x H2', 2H), 4.00 (br s, H4 and H1, 2H) and 5.58 (br s, H9, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 13.9 (C6'), 22.3 (C5'), 23.9 (C6 and C7), 24.5 (C4'), 31.2 (C3'), 34.1 (C5 and C8), 58.6 (C1 and C4), 83.9 (C9) and 173.2 (C1', C=O) ppm; IR (neat): 1164 and 1735 (C=O) cm^{-1}; HRMS [EI, direct inlet, 30°C]: m/z for $M^{+\cdot}$ ion: Calc'd for $C_{13}H_{22}O_2S_2$ 274.10612, Found 274.10601.

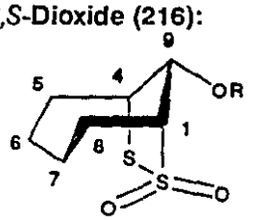
Preparation of *syn*-2,3-Dithia-[(9-*n*-hexanoyl)oxy]bicyclo[4.2.1]nonane *S*-Oxide (155):



R = -C(O)-$(CH_2)_4$-CH_3

Compound **155** was prepared following standard *m*-CPBA oxidation procedures on **145**. The product was purified by column chromatography using 3:1 hexanes:EtOAc as the eluent. The product was found in fractions 13-25 and was isolated as a clear oil in 91.5% yield. Rf (3:1 hexanes:EtOAc): 0.16; ^1H NMR (200 MHz, $CDCl_3$)δ: 0.86 (t $J_{H6'\text{-}H5'}$ = 6.5 Hz, 3x H6', 3H), 1.15-2.00 (m, 2x H3', H4' and H5' and 2x H5, H6, H7 and H8, 14H), 2.33 (t $J_{H2'\text{-}H3'}$ = 7.5 Hz, 2x H2', 2H), 4.17 (d J = 11.2 Hz, H4, 1H), 4.77 (t J = 3 Hz, H1, 1H) and 5.88 (s, H9, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 13.8 (C6'), 22.2 (C5'), 23.7 (C6), 24.2 (C4'), 24.2 (C7), 24.3 (C3'), 31.1 (C2'), 32.0 (C5), 34.1 (C8), 64.3 (C4), 79.9 (C1), 84.5 (C9) and 173.4 (C1', C=O) ppm; IR ($CDCl_3$)): 1098 (S=O), 1164, 1380, 1470 and 1733 (C=O) cm^{-1}; MS [EI, direct inlet, 100°C], m/z (% relative intensity, assignment): 290 (13.8, $M^{+\cdot}$), 99 (100, $^+C(O)(CH_2)_4CH_3$).

Isolation of *syn*-2,3-Dithia-[(9-*n*-hexanoyl)oxy]bicyclo[4.2.1]nonane *S,S*-Dioxide (216):



R = -C(O)-$(CH_2)_4$-CH_3

Compound **216** was isolated from the product mixture of the low temperature NMR *m*-CPBA oxidation experiments on **155** (See Section 6.3). Purification of **210** was performed using column chromatography with 3:1 hexanes:EtOAc as the eluent. Compound **216** was isolated as a clear oil in 55% yield. Rf (3:1 hexanes:EtOAc): 0.30; ^1H NMR (200 MHz, $CDCl_3$)δ: 0.87 (t $J_{H6'\text{-}H5'}$ = 6.5 Hz, 3x H6', 3H), 1.23-2.17 (m, 2x H3', H4' and H5' and 2x H5, H6, H7 and H8, 14H), 2.39 (t $J_{H2'\text{-}H3'}$ = 7.5 Hz, 2x H2', 2H), 3.76 (d J = 8.2 Hz, H4, 1H), 4.51 (br s, H1, 1H) and 5.48 (s, H9, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 13.9 (C6'), 22.0 (C6), 22.2 (C5'), 24.27 (C4'), 24.32 (C7), 24.6 (C3'), 31.1 (C2'), 34.1 (C2'), 34.1 (C5), 34.7 (C8), 59.5 (C4), 73.5 (C1), 74.9 (C9) and 173.1 (C1', C=O) ppm; IR ($CDCl_3$): 902, 1109, 1131 (SO_2), 1158, 1169, 1310 (SO_2) and 1737 (C=O) cm^{-1}.

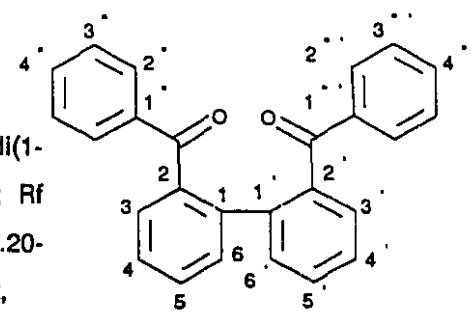
6.3 Chapter 3:

General Procedure

The bicyclic thiosulfinate was dissolved in 2 ml of $CDCl_3$ and cooled to -40°C in a dry ice/isopropanol bath under an atmosphere of nitrogen. *m*-CPBA (1 equivalent) was then added as a solid to the cooled solution and this mixture was stirred for a further 15 minutes at this temperature. The solution was then filtered as quickly as possible into an NMR tube previously cooled to -40°C. The sample was then placed into the spectrometer probe that had been precooled to -40°C and acquisition was initiated. At least 15 min was allowed prior to spectral acquisition at each temperature in order for the sample to equilibriate at the desired temperature. An increment of 10°C was used until the sample was brought to room temperature. Occasionally the sample was heated slightly above room temperature.

6.4 Chapter 4

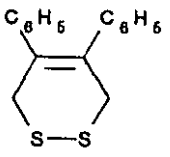
Preparation of 2,2'-Dibenzoylbiphenyl (231)[211]:



Prepared *via* oxidation of 2,2'-di(1-phenylmethanol)biphenyl.[211] M.p. 150°C (decomposition); Rf (9:1 hexanes/EtOAc): 0.21; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 7.20-7.40 (m, 14H) and 7.67-7.71 (m, 4H) ppm; ^{13}C NMR (300, MHz, $CDCl_3$)δ: 126.7 (C4 and C4'), 127.9 (C6 and C6'), 129.3 (C3", C3"'), 130.1 (C3 and C3'), 130.3 (C1", C1"'), 131.4 (C4" and C4"'), 132.7 (C5 and C5'), 137.3 (C2 and C2'), 138.2 (C8 and C8'), 140.2 (C1 and C1') and 197.5 (<u>C</u>=O) ppm. IR (KBr): 1654 (C=O) cm^{-1}.

211. D. Mullins, Ph. D. Thesis, McGill University, Montreal, Quebec, Canada (1981).

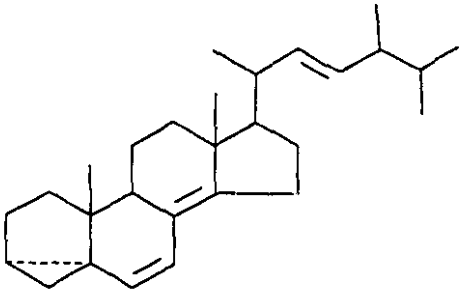
Preparation of 3-dehydro-4,5-Diphenyl-1,2-dithiin (235):



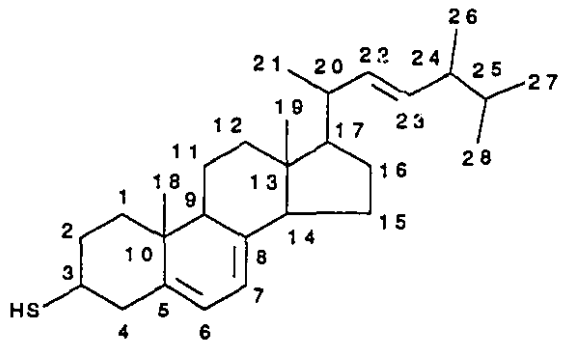
2,2'-Dibenzoylbiphenyl **(231)** (77.7 mg, 0.215 mmol) and 2,3-diphenyl-1,3-butadiene **(234)** (0.200 mg, 0.97 mmol) were dissolved in dry toluene (12 ml) under a nitrogen atmosphere. To this was added 1,1,1,3,3,3-hexamethyldisilylathiane **(232)** (76.6 mg, 0.09 mmol) and boron trichloride (0.286 ml of a 1 M solution in CH_2Cl_2, 0.286 mmol) consecutively *via* syringe. After approximately 1 min the solution began to turn blue and then the solution was allowed to reflux for 8 hrs or until the blue color dissipated. Once cooled to room temperature, the product was absorbed onto silica and purified using flash column chromatography. The eluents employed were hexanes and, from fractions 50 onward, 9:1 hexanes:EtOAc. Fractions 7-24 contained recovered diene (100 mg, 50%); fractions 29-55, the trapped product and the phenanthrecene side product (60 mg) and fractions 67-74 contained recovered 2,2'-dibenzoylbiphenyl (15 mg, 19%). The trapped product was recovered by fractional crystallization and the total yield was 29.4 mg (51%; 65%, based on recovered starting material). M.p. 100-101°C (lit[174] 101-102°C); ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.67 (s, 2x H3 and H6, 4H) and 7.0-7.25 (m, aromatics, 10H) ppm.

Preparation of 3,5-Cyclo-6,8(14),22-ergostatriene (236) and Ergosta-5,7,22-trien-3-thiol (237):

1,1,1,3,3,3-Hexamethyldisilylathiane **(232)** (0.166 g, 0.933 mmol) was added *via* syringe under an atmosphere of nitrogen to a solution of 2,2'-dibenzoylbiphenyl **(231)** (0.169 g, 0.467 mmol) and ergosterol **(222a)** (0.185 g, 0.467 mmol) in dry toluene (30 ml). The resulting mixture was cooled to 0°C and boron trichloride (0.623 ml of a 1M solution in CH_2Cl_2, 0.623 mmol) was added slowly *via* syringe. The reaction was warmed to room temperature and then allowed to reflux for 9.5 hr. Evaporation of the solvent, followed by flash column chromatography of the resulting crude mixture with petroleum ether, led to the isolation of two compounds, 3,5-cyclo-6,8(14),22-ergostatriene **(236)** (fractions 3-6, 72.3 mg, 41%) and the ergosterol thiol (237) (fractions 8-13, 36.8 mg, 19%). Further elution with petroleum ether/EtOAc (3:1) led to the recovery of unreacted 2,2'dibenzoylbiphenyl (140 mg, 83%).



3,5-Cyclo-6,8(14),22-ergostatriene (236): M.p. 98.5-100°C (lit[177] 102-102.5°C); Rf (petroleum ether): 0.57; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 0.46 (dd J_1 = 8.2 J_2 = 5.0 Hz, H3, 1H), 0.76 (s, 18-CH_3, 3H), 0.79-0.84 (2d J = 6.8 Hz, 26-CH_3 and 27-CH_3, 6H), 0.90 (s, 19-CH_3, 3H), 0.91 (d J = 6.8 Hz, 28-CH_3, 3H), 1.02 (d J = 6.7 Hz, 21-CH_3, 3H), 1.2-2.4 (m, steroid skeleton, 19H), 5.2 (m, H6, H22 and H23, 3H) and 6.19 (d J = 9.5 Hz, H7, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 15.6 (C4), 17.0 (C18), 17.6 (C28), 19.3 (C19), 19.6 (C28), 19.65 (C26), 20.0 (C27), 20.4 (C11), 21.2 (C21), 25.2 (C2), 25.3 (C15), 26.5 (C3), 28.0 (C16), 30.8 (C1), 33.1 (C25), 37.4 (C12), 37.6 (C10), 39.4 (C9), 40.8 (C20), 42.9 (C24), 43.5 (C5), 43.9 (C13), 56.1 (C17), 124.1 (C7), 124.6 (C14), 130.6 (C6), 132.0 (C23), 135.5 (C22) and 147.0 (C8) ppm; Chemical shift assignments were consistent with DEPT, APT and COSY NMR experiments; IR ($CDCl_3$): 1458, 1600 (C=C), 2869 and 2961 (C-C) cm^{-1}; UV (EtOH): μ_{max} 262 nm; MS [E.I., direct inlet, 65°C], m/z (% relative intensity, assignment): 378 (16, $M^{+\cdot}$).



Ergosta-5,7,22-trien-3-thiol (237): M.p. 121.5-123°C; Rf (petroleum ether): 0.42; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 0.61 (s, 18-CH_3, 3H), 0.79-0.83 (2d J = 6.8 Hz, 26-CH_3 and 27-CH_3, 6H), 0.90 (d J = 6.8 Hz, 28-CH_3, 3H), 0.94 (s, 19-CH_3, 3H), 1.02 (d J = 6.6 Hz, 21-CH_3, 3H), 1.22-2.08 (m, steroid skeleton, 19H), 2.59-2.63 (m, 2x H4, 2H), 3.80-3.86 (m, H3, 1H), 5.15-5.20 (m, H22 and H23, 2H), 5.37 (dd, H7, 1H) and 5.55 (bd J = 5.62 Hz, H6, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 12.1 (C18), 16.1 (C19), 17.6 (C28), 19.6 (C26), 20.0 (C27), 21.0 (C11), 21.1 (C21), 23.0 (C15), 28.3 (C16), 33.1 (C25), 33.6 (C2), 36.8 (C10), 39.0 (C12), 40.0 (C1), 40.4 (C20), 41.9 (C4), 42.8 (C13 and C24), 46.2 (C9), 54.6 (C14), 55.7 (C17), 59.1 (C3), 116.1 (C7), 119.8 (C6), 132.0 (C23), 135.5 (C22), 139.2 (C5) and 141.9 (C8) ppm; Chemical shift assignments were consistent with DEPT, APT and COSY NMR experiments; IR ($CDCl_3$): 1458 (C=C), 2873 and 2960 (C-C) cm^{-1}; UV (EtOH): μ_{max} 274, 284, μ_{min} 296 nm; M.S. [E.I., direct inlet, 95°C] m/z (% relative intensity, assignment): 378 ($M^{+\cdot}$ - H_2S). Sample analysis using the Antek analyzer confirmed the presence of sulfur in this compound. In addition, a nitroprusside[212] test for thiol was positive. Structure confirmed by X-ray crystallography (See Figure 28, Chapter 4).

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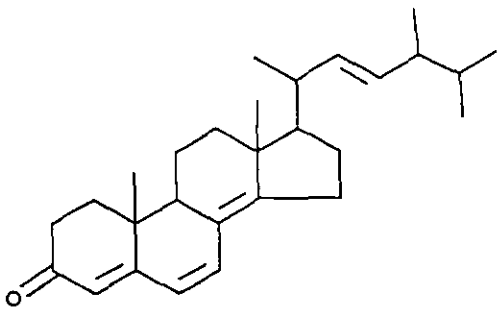
212. K. G. Krebs, D. Heusser and H, Wimmer, in *Thin Layer Chromatography, A Laboratory Handbook*, E. Stahl, Ed., New York: Springer Verlag, p. 890 (1969).

X-Ray Data for 237:

Empirical Formula: $C_{28}H_{44}S$, M = 412.72, monoclinic, space group $P2_1$ (#4), a = 10.984(2), b = 7.599(1), c = 15.6594(3) Å, β = 102.691(8), V = 1275.1(3) $Å^3$, Z = 2, D_c = 1.075 gcm^{-3}, $\mu_{(CuK_\alpha)}$ = 11.47 cm^{-1}, F_{000} = 456. Data were collected at room temperature on a Rigaku AFC6S diffractometer with graphite-monochromated CuK_α (λ = 1.54178 Å) radiation at 1.75 kW using the ω-2θ scan technique to a maximum 2θ value of 120.2°. The structure solved by direct methods[202] and refined by full-matrix least squares to residuals of R = 0.057 and R_w = 0.047 for 2067 observed reflections with $I > 2.5\sigma(I)$ and with 261 variables.

Isolation of Ergosta-4,6,8(14),22-tetraen-3-one (240):

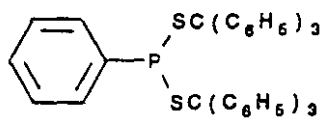


Ergosterol **(222a)** (5.0 g, 12.6 mmol) and S_8 (3.00 g, 11.7 mmol = ~4 eq. of S_2) were refluxed in dry toluene (~200 ml) in the presence of one equivalent of triethylamine (1.5 ml, ~12 mmol). After a period of 24 hr the crude mixture was filtered, washed with d-H_2O (3x 100 ml) and evaporated to dryness. Flash column chromatography (2x) of the product mixture with petroleum ether/EtOAc (4:1), (2nd chromatography was performed on fractions 13-17 of the 1st column) led to the isolation of compound **240** as an orange-yellow solid. Preparative thin layer chromatography on silica gel plates, developed twice with hexane/EtOAc (9:1), followed by recrystallization from ethanol gave crystalline compound **240** in approximately 5% yield (30 mg). M.p. 112.5-113°C (lit 114-115°C[184]) Rf (petroleum ether/EtOAc 3:1): 0.45 (fluorescent spot under uv); ^{1}H NMR (200 MHz, $CDCl_3$)δ: 0.78-0.83 (2d J = 6.7 Hz, 26-CH_3 and 27-CH_3, 6H), 0.90 (d J = 6.8 Hz, 28-CH_3, 3H), 0.93 and 0.96 (2s, 18-CH_3 and 19-CH_3, 6H), 1.03 (d J = 6.7 Hz, 21-CH_3, 3H), 1.15-2.55 (m, steroid skeleton, 18H), 5.17-5.22 (m, H22 and H23, 2H), 5.70 (s, H2, 1H), 6.00 (d J = 9.5 Hz, H6, 1H) and 6.57 (d J = 9.5 Hz, H7, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ: 16.6 (C18), 17.6 (C28), 2x 18.9 (C19 and C2), 19.6 (C26), 20.0 (C27), 21.2 (C21), 25.3 (C11), 27.7 (C16), 33.0 (C25), 2x 34.1 (C1 and C12), 35.6 (C15), 36.7 (C10), 39.2 (C20), 42.8 (C24), 44.0 (C13), 44.3 (C9), 55.7 (C17), 123.0 (C4), 124.4 (C6), 124.4 (C8), 132.5 (C23), 134.0 (C7), 135.0 (C22), 156.0 (C14), 164.3 (C5) and 199.4 (C3) ppm; Chemical shift assignments were consistent with DEPT, APT and

COSY NMR experiments; IR ($CDCl_3$): 1584 (C=C), 1636 and 1646 (C=O) cm^{-1}; UV (CH_3CH_2OH): μ_{max} 350; MS [C.I. (NH_3), direct inlet, 150°C], m/z (% relative intensity, assignment): 394 (31, $M^{+\cdot}$ + 1), 393 (100, $M^{+\cdot}$).

6.5 Chapter 5

Preparation of Ditritylphenylphosphine (264a):

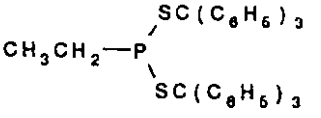


Trityl thiol **(265)** (15.04 g, 0.0545 mol) was dissolved in dry THF (150 ml) and kept under an atmosphere of nitrogen. Triethylamine (5.515 g, 0.0545 mol) was then added *via* a syringe. Dichlorophenylphosphine **(266a)** (4.89 g, 0.0272 mol) in dry THF (100 ml) was added dropwise to the above solution with stirring. A white precipitate formed immediately (Et_3NHCl). Once the addition was complete (15 mins) the solution was allowed to stir for a further hr. The white solid (0.255 g) was then filtered and the THF evaporated under reduced pressure to give a pure white solid (16.72 g, 94%). Recrystallization from acetone gave white hexagons and the structure was confirmed by X-Ray crystallography (See Figure 29, Chapter 5). M.p. decomposes at 129°C; Rf (4:1 hexanes:CH_2Cl_2): 0.24; ^1H NMR (200 MHz, $CDCl_3$)δ: 7.03-7.26 (m, 35H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 70.5 (d $^2J_{CP}$ = 15.5 Hz, 2x $\underline{C}$-Ph_3), 126.6 (trityl C_{para}), 127.3 (Ph-P C_{para}), 127.5 (trityl C_{meta}), 127.7 (d $^3J_{CP}$ = 8 Hz, Ph-P C_{meta}), 129.1 (d $^2J_{CP}$ = 28.5 Hz, Ph-P C_{ortho}), 130.2 (trityl C_{ortho}), 132.2 (d $^1J_{CP}$ = 26.8 Hz, $\underline{C}$-P) and 145.2 (trityl C1) ppm; ^{31}P NMR (300 MHz, $CDCl_3$)δ: 40.8 ppm.

Crystal Data for 264a:

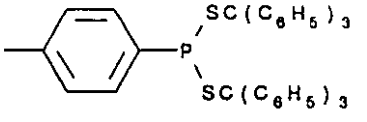
Empirical Formula: $C_{44}H_{35}PS_2$, M = 658.85, monoclinic, space group $P2_1/c$ (#14), a = 18.439(5), b = 10.489(3), c = 17.731(9), Å, β = 91.00(3)°, V = 3429(2) $Å^3$, Z = 4, D_c = 1.276 Mgm^{-3}, $\mu_{(MoK_\alpha)}$ = 2.24 cm^{-1}. Data were collected at room temperature on a Nicolet R3 four-circle diffractometer with graphite-monochromated MoK_α radiation (λ = 0.70926 Å) using ω scans ($2\theta_{max}46°$). An extinction correction was applied and the structure solved by direct methods[207] and refined by full-matrix least squares to residuals of R = 0.038 and R_w = 0.035 for 3211 observed reflections with $I > 2.5\sigma(I)$ and with 460 variables.

Preparation of Ditritylethylphosphine (264b):



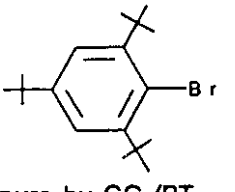
Compound **264b** was prepared from **266b** following the same procedure used for the preparation of **264a**. The product was obtained as a white solid that foams easily under vacuum in 94%. If needed, the product was purified by flash column chromatography on neutral alumina using 4:1 hexanes:CH_2Cl_2 as the eluent. Compound **264b** was found in fractions 14-37. M.p. decomposes at 117°C; Rf (4:1 hexanes:CH_2Cl_2): 0.27; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 0.68 (d J = 12.8 Hz, CH_2 + CH_3, 5H) and 7.14-7.42 (m, aromatics, 30H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 9.0 (d $^2J_{CP}$ = 11.5 Hz, $\underline{C}H_3$), 25.9 (d $^1J_{CP}$ = 33.6 Hz, $\underline{C}H_2$), 69.6 (d $^1J_{CP}$ = 15.9 Hz, 2x $\underline{C}$-Ph_3), 126.5 (trityl C_{para}), 127.6 (trityl C_{meta}), 130.0 (trityl C_{ortho}) and 145.5 (trityl C1) ppm; ^{31}P NMR (300 MHz, $CDCl_3$)δ: 40.7 ppm.

Preparation of Dityryl-*p*-chlorophenylphosphine (264c):



Compound **264c** was prepared from **267**[191] following the same procedure used for the preparation of **264a**. The product was obtained as a white solid that foams easily under vacuum in quantitative yield and was purified (to remove any remaining thiol) by flash column chromatography on neutral alumina using 19:1 hexanes:CH_2Cl_2 as the eluent. The product was found in fractions 43-45 and was isolated as a white solid in 74% yield. M.p. decomposes at 123°C; Rf (4:1 hexanes:CH_2Cl_2): 0.27; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 6.83-7.02 (m, *p*-Cl-$C_6\underline{H}_4$, 4H) and 7.08-7.29, (m, trityl protons, 30H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 70.7 (d J_{CP} = 15.3 Hz, 2x $\underline{C}(C_6H_5)_3$), 126.7 (trityl C_{para}), 127.5 (trityl C_{meta}), 127.8 (d $^3J_{CP}$ = 8.3, *p*-Cl-Ph-P C_{meta}), 128.3 (Cl-$\underline{C}$), 129.4 (d $^2J_{CP}$ = 9.1 Hz, *p*-Cl-Ph-P C_{ortho}), 130.0 (trityl C_{ortho}), 133.5 (d $^1J_{CP}$ = 27.3 Hz. $\underline{C}$-P) and 144.0 (trityl C1) ppm; ^{31}P NMR (300 MHz, $CDCl_3$)δ: 38.1 ppm.

Preparation of 2,4,6-Tri-t-butylbromobenzene (270):

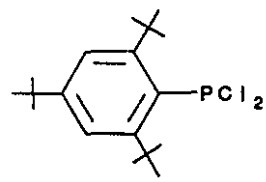


Compound **270** was prepared from tri-*t*-butylbenzene **(269)** following the procedure of Pearson and co-workers.[192] The crude product containing both **269** and **270** was purified by column chromatography on silica using hexanes as the eluent. The product was isolated from fractions 8-13 and shown to be 99.6% pure by GC (RT = 14.21 min). Total yield of **270** was 70%, however the starting material could be recovered as the remaining 30%. M.p. 164-167 (lit[192] 171.5-173.5); Rf (hexanes): 0.60; ^{1}H NMR (200 MHz, $CDCl_3$)δ:

1.29 (s, 9H), 1.56 (s, 18H) and 7.39 (s, 2H) ppm.

Preparation of 2,4,6-Tri-t-butyldichlorophenylphosphine (272):

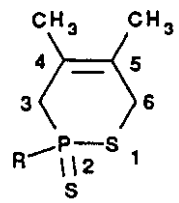
Compound **272** was prepared from 2,4,6-tri-*t*-butylbromobenzene **(270)** following the procedure of Inamoto and co-workers.[193] ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.29 (s, 9H), 1.58 (s 18H) and 7.40 (d $^4J_{HP}$ = 2.9 Hz, 2H) ppm.

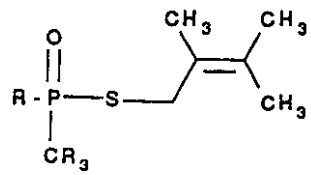


General Procedure for Trapping of "R-P=S":

Triphenylphosphine was dissolved in freshly distilled, dry CH_2Cl_2 and cooled to 0°C under N_2. The flask was wrapped in aluminum foil to keep the reaction in the dark and Br_2 (mole ratio of triphenylphosphine to bromine was 1:1) was added very slowly with a syringe. This mixture was stirred in the dark, under N_2 and at 0°C for 15 minutes. It was then transferred directly into a dropping funnel (wrapped with foil) and added very slowly, to a solution containing $(Ph_3CS)_2PR$ (equimolar to previous two reagents) and diene (excess) in dry CH_2Cl_2. After the addition the mixture was stirred for a further 2 hr after which the product was absorbed onto silica[213] and flash column chromatography performed. Yields were based on the amount of $(Ph_3CS)_2PR$ used.

Trapping of "Ph-P=S" with 2,3-Dimethyl-1,3-butadiene; Isolation of 248b and 275:





R = C_6H_5

Purification of the trapped adducts was performed using a range of solvents: fractions 1-19: hexanes; fractions 20-40 17:3 hexanes:CH_2Cl_2; fractions 40-80 3:1 hexanes:CH_2Cl_2; fractions 80-120 1:1 hexanes:CH_2Cl_2; fractions 120-140 2:3 hexanes:CH_2Cl_2 and fractions 140-170 CH_2Cl_2. The product distribution was as follows:

Fractions 96-116: Compound **275** (17%)

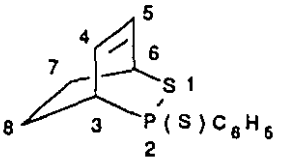
Fractions 131-162: $(C_6H_5)_3CBr$ **(273)** (80%) and $(C_6H_5)_3P=S$ **(274)** (80%)[214]

Fractions 163-166: Compound **248b** (26%) and **273** and **274**

213. Chromatography on neutral alumina did not provide adequate separation.

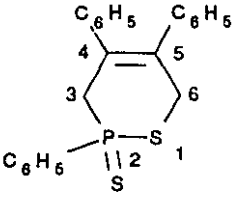
Spectral Data for **248b**: See Table 27; Clear oil; Rf (9:1 hexanes:EtOAc): 0.44.
Spectral Data for **275**: See Table 28; White solid; M.p. 43-45°C; Rf (9:1 hexanes:EtOAc):0.20.

Trapping of "Ph-P=S" with 1,3-Cyclohexadiene; Isolation of 250:



Flash column chromatography (2x) was required for purification of **250**. The initial separation was performed using 9:1 hexanes:EtOAc as the eluent. The trapped product **(250)** had an Rf of 0.18 in this eluent system and was found in fractions 13-15. It was further purified using 46:1 petroleum ether:EtOAc as the eluent. Compound **250** was found in fractions 20-26 as a clear oil; the total isolated yield was 21%. The other products included triphenylphosphine sulfide **(274)** and triphenylmethyl bromide **(273)** (combined yield ~80%). Spectral Data for **250**: See Table 29.

Trapping of "Ph-P=S" with 2,3-Diphenyl-1,3-butadiene; Isolation of 277:



Initial separation of the products from this reaction was performed by column chromatogrpahy using 9:1 hexanes:EtOAc as the eluent. Compound **277** was found in fractions 18-26. A second column using 3:2 hexanes CH_2Cl_2 as the eluent was used in an attempt to remove bromide **273** and sulfide **274** that remained as impurities. Compound **277** was isolated from fractions 9-23, however the sample still contained a small amount the two side products. The best yield of **277** obtained was 21% and due to impurities, it was isolated as a white semi-solid; compounds **274** amd **273** were each isolated in ~80%. Rf (9:1 hexanes:EtOAc): 0.15; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 3.48 (dd $^2J_{H3a-P}$ = 19.4 Hz $J_{H3a-H3b}$ = 15.1 Hz, H3a, 1H), 3.55 (dd $^2J_{H3b-P}$ = 24.8 Hz $J_{H3b-H3a}$ = 15.1 Hz, H3b, 1H), 3.91 (dd $^3J_{H6a-P}$ = 17.2 Hz $J_{H6a-H6b}$ = 14 Hz, H6a, 1H), 4.14 (dd $^3J_{H6b-P}$ = 21.1 Hz $J_{H6b-H6a}$ = 14 Hz, H6b, 1H) and 6.6-8.2 (m, aromatic protons, 15H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 35.9 (d $^2J_{CP}$ = 6.1 Hz, C6) and 46.8 (d $^1J_{CP}$ = 42.3 Hz, C3) ppm; ^{31}P NMR (300 MHz, $CDCl_3$)δ: 65.5 ppm; IR ($CDCl_3$): 1098 (P-Ph), 1437 (C=C) cm^{-1}.

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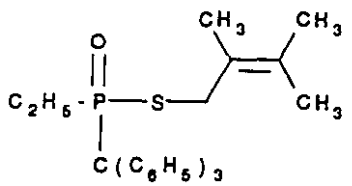
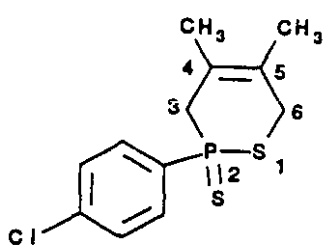
214. Identity of **273** and **274** was confirmed by comparison to known materials.

Trapping of "Et-P=S" with 2,3-Dimethyl-1,3-butadiene; Isolation of 279:



Purification of the crude reaction mixture obtained in this reaction was performed by column chromatography using 17:3 hexanes:EtOAc as the eluent. Triphenylphosphine sulfide **(274)** and trityl bromide **(273)** were isolated from fractions 4-12, each in 80% yield. Compound **279** was found in fractions 16-31 and was obtained in 37% yield as a clear oil. Rf (17:3 hexanes:EtOAc): 0.12; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.0-1.5 (m, CH_2-C$\underline{H}_3$ + 1x C$\underline{H}_2$, 4H), 1.60 (s, 3x CH_3, 9H), 1.9-2.1 (m, 1x CH_2, 1H) and 7.2-7.6 (m, aromatic protons, 15H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$)δ: 6.2 (s, =C-$\underline{C}H_3$), 6.3 (s, =C-$\underline{C}H_3$), 17.8 (s, $\underline{C}H_3$-C=), 20.6 (d $^{2}J_{CP}$ = 40.1 Hz, $\underline{C}H_3$-CH_2), 28.3 (d $^{1}J_{CP}$ = 66 Hz, CH_3-$\underline{C}H_2$), 34.6 (d $^{2}J_{CP}$ = 2.3 Hz, $\underline{C}H_2$-C=), 66.5 (d $^{1}J_{CP}$ = 56.1 Hz, $\underline{C}$-Ph_3), 123.4 (d $^{3}J_{CP}$ = 5.2 Hz, -$\underline{C}$=), 127.1, 128.0, 130.6 (s, =$\underline{C}$-) and 131.0 ppm; ^{31}P NMR (300 MHz, $CDCl_3$)δ: -12.4 ppm; IR ($CDCl_3$): 1033, 1096, 1169 (P=O), 1380, 1470 (CH_3-C=C); MS [EI, direct inlet, 200°C] m/z (% relative intensity, assignment): 243 (100, Ph_3-C^+), 191 ($M^{+\cdot}$ - Ph_3C^+).

Trapping of "*p*-Cl-Ph-P=S" with 2,3-Dimethyl-1,3-butadiene; Isolation of 280:



Compound **280** was separated from side products by column chromatography using 19:1 hexanes:EtOAc as the eluent. Fractions 34-41 were combined and evaporated to give **280** in 10% yield as a clear oil (contaminated with **273** and **274**). Rf (19:1 hexanes:EtOAc): 0.11; ^{1}H NMR (200 MHz, $CDCl_3$)δ: 1.63 (s, 5-CH_3, 3H), 1.90 (d $^{4}J_{HP}$ = 4.8 Hz, 4-CH_3, 3H), 2.95 (d $^{3}J_{HP}$ = 14.5 Hz, 2x H6, 2H), 3.31 (dd $^{2}J_{H3a\text{-}P}$ = 21.0 Hz $^{1}J_{H3a\text{-}H3b}$ = 15 Hz, H3a, 1H); 3.67 (t $^{2}J_{H3b\text{-}P}$ = $^{1}J_{H3b\text{-}H3a}$ = 15 Hz H3b, 1H), 7.4-7.5 (m, 2x H_{meta}, 2H) and 7.8-8.0 (m, 2x H_{ortho}, 2H) ppm; ^{31}P (300 MHz, $CDCL_3$)δ: 41.8 ppm; IR ($CDCl_3$): 1100 (P-Ph) cm^{-1}; MS [EI, direct inlet, 100°C], m/z (% relative intensity, assignment): 288 (13.6, $M^{+\cdot}$).

APPENDIX

Atomic Coordinates (a,b,c) and Temperature Factors (U_{eq}, $Å^2$) for Compound 133

	a	b	c	Ueq
S1	0.9551(2)	0.4276(1)	0.7186	0.088(1)
S2	0.8323(2)	0.2917(2)	0.6520(1)	0.086(1)
C1	1.0610(5)	0.1947(4)	0.7515(2)	0.046(2)
C2	1.1369(5)	0.3268(4)	0.7532(2)	0.062(2)
C3	1.3120(5)	0.3280(4)	0.7051(2)	0.066(2)
C4	1.2698(5)	0.2911(4)	0.6253(2)	0.060(2)
C5	1.1624(5)	0.1712(4)	0.6211(2)	0.062(2)
C6	0.9975(5)	0.1714(4)	0.6743(2)	0.056(2)
O1	0.9107(4)	0.1857(3)	0.8030(2)	0.062(1)
C7	0.8906(5)	0.0828(4)	0.8432(2)	0.044(1)
O2	0.9991(4)	-0.0028(3)	0.8446(2)	0.060(1)
C8	0.7112(5)	0.0861(4)	0.8855(2)	0.040(1)
C9	0.5897(5)	0.1850(4)	0.8776(2)	0.048(1)
C10	0.4244(5)	0.1827(4)	0.9151(2)	0.053(1)
C11	0.3805(5)	0.0834(4)	0.9576(2)	0.046(1)
C12	0.4987(6)	-0.0164(4)	0.9674(2)	0.058(2)
C13	0.6673(6)	-0.0132(4)	0.9310(2)	0.056(1)
N1	0.1962(5)	0.0781(4)	0.9942(2)	0.064(2)
O3	0.0931(4)	0.1680(4)	0.9850(2)	0.083(1)
O4	0.1580(5)	-0.0134(4)	1.0308(2)	0.103(2)

Atomic Coordinates (x,y,z) and Temperature Factors (B_{eq}, $Å^2$) for Compound 138a

atom	x	y	z	B(eq)
S(1)	0.4109(1)	0.2058(2)	0.56591(7)	4.25(5)
S(2)	0.5470(1)	0.1999(2)	0.90232(8)	5.00(6)
O	0.2587(3)	0.1908(4)	0.7612(2)	5.1(2)
N(1)	0.5799(4)	0.5170(5)	0.6327(3)	6.2(2)
N(2)	0.3155(4)	0.3845(6)	0.9927(3)	6.5(2)
C(1)	0.3652(4)	0.0949(5)	0.7548(3)	3.4(2)
C(2)	0.4391(4)	0.0385(6)	0.6630(3)	3.1(2)
C(3)	0.5919(4)	-0.0161(7)	0.6943(3)	3.8(2)
C(4)	0.5687(5)	-0.1117(7)	0.7900(3)	4.0(2)
C(5)	0.4527(4)	0.0069(6)	0.8374(3)	3.5(2)
C(6)	0.5119(5)	0.3898(6)	0.6075(3)	4.2(2)
C(7)	0.4034(5)	0.3084(7)	0.9539(3)	4.9(2)
H(1)	0.391(3)	-0.071(4)	0.639(2)	2.3(8)
H(2)	0.645(3)	0.089(5)	0.702(2)	2.6(9)
H(3)	0.632(4)	-0.102(5)	0.652(2)	4(1)
H(4)	0.647(3)	-0.118(5)	0.825(2)	4(1)
H(5)	0.525(4)	-0.243(5)	0.779(3)	6(1)
H(6)	0.397(3)	-0.026(5)	0.900(2)	3.2(8)

Atomic Coordinates (a,b,c) and Temperature Factors (U_{eq}, Å^2) for Compound 151a

atom	x	y	z	B(eq)
S(2A)	0.9475(2)	0.3116(3)	0.4411(3)	5.6(1)
S(3A)	0.8247(3)	0.1442(3)	0.3520(4)	7.8(2)
O(1A)	0.7446(7)	0.3759(8)	0.213(1)	9.5(5)
O(2A)	0.8853(6)	0.3751(6)	0.5714(9)	6.5(3)
C(1A)	0.9551(9)	0.3724(8)	0.208(1)	5.0(4)
C(4A)	0.7792(9)	0.184(1)	0.123(1)	6.8(5)
C(5A)	0.820(1)	0.108(1)	-0.029(1)	7.6(6)
C(6A)	0.954(1)	0.152(1)	-0.083(2)	8.7(7)
C(7A)	1.042(2)	0.265(3)	-0.041(4)	5.7(3)
C(7A')	1.055(2)	0.204(2)	0.049(2)	5.7
C(8A)	1.063(1)	0.345(1)	0.105(1)	7.5(6)
C(9A)	0.827(1)	0.321(1)	0.117(1)	6.0(5)
H(1)	0.9759	0.4586	0.2217	6.3
H(2)	0.6916	0.1601	0.1139	8.1
H(3)	0.8107	0.0292	0.0111	9.4
H(4)	0.7770	0.1075	-0.1383	9.4
H(11)	0.8328	0.3423	-0.0089	7.4
S(2B)	0.4248(2)	0.2914(3)	0.9336(3)	5.6(1)
S(3B)	0.4693(3)	0.1409(3)	0.8166(4)	6.5(1)
O(1B)	0.6633(6)	0.3946(6)	0.700(1)	7.0(3)
O(2B)	0.5229(6)	0.3595(7)	1.0701(8)	7.1(4)
C(1B)	0.4491(8)	0.3734(8)	0.715(1)	4.6(4)
C(4B)	0.5199(9)	0.196(1)	0.590(1)	5.6(4)
C(5B)	0.430(1)	0.1298(9)	0.437(1)	5.5(4)
C(6B)	0.312(1)	0.1689(9)	0.406(1)	6.1(5)
C(7B)	0.312(2)	0.298(2)	0.434(4)	4.7(3)
C(7B')	0.250(1)	0.209(1)	0.552(2)	4.7
C(8B)	0.319(1)	0.3475(8)	0.621(1)	5.1(4)
C(9B)	0.5478(9)	0.335(1)	0.607(1)	5.1(4)
H(12)	0.4792	0.4584	0.7467	5.4
H(13)	0.5958	0.1794	0.5662	6.7
H(14)	0.4720	0.1380	0.3246	6.7
H(15)	0.3992	0.0459	0.4645	6.7
H(22)	0.5493	0.3643	0.4862	6.2
H(24)	0.7464	0.3851	0.6274	8.4
H(25)	0.9969	0.0946	-0.0360	9.9
H(26)	0.9578	0.1424	-0.2170	9.9
H(27)	1.1220	0.2526	-0.0607	6.8
H(28)	1.0262	0.3133	-0.1359	6.8
H(29)	1.1198	0.4217	0.0674	8.5
H(30)	1.1124	0.3158	0.1966	8.5
H(31)	0.3324	0.2353	0.3210	6.9
H(32)	0.2493	0.1016	0.3381	6.9
H(33)	0.1637	0.1986	0.5181	5.8
H(34)	0.2490	0.1572	0.6541	5.8
H(35)	0.2638	0.3739	0.7049	5.8
H(36)	0.3261	0.3957	0.5133	5.8

Atomic Coordinates (a,b,c) and Temperature Factors (U_{eq}, Å^2) for Compound 152

atom	x	y	z	U_{eq}
S(1)	0.0707(1)	0.3468(1)	0.0196(1)	0.058(1)
S(2)	0.1460(1)	0.1653(1)	0.0410(1)	0.055(1)
C(1)	-0.0522(4)	0.1936(4)	0.1143(3)	0.046(2)
C(6)	0.0721(4)	0.1172(4)	0.1375(3)	0.045(2)
C(5)	0.1705(4)	0.1411(4)	0.2545(3)	0.052(2)
C(4)	0.2079(5)	0.2765(4)	0.2735(4)	0.058(2)
C(3)	0.0859(5)	0.3606(4)	0.2312(4)	0.061(2)
C(2)	-0.0114(4)	0.3269(4)	0.1169(3)	0.047(2)
O(1)	-0.1500(3)	0.1638(3)	0.0078(2)	0.056(1)
O(2)	-0.3030(3)	0.1069(4)	0.0723(3)	0.079(2)
O(5)	-0.0367(4)	0.3585(4)	-0.0912(3)	0.083(2)
C(7)	-0.2701(4)	0.1241(4)	-0.0023(3)	0.043(1)
C(8)	-0.3579(4)	0.1018(4)	-0.1178(3)	0.041(1)
C(9)	-0.3324(4)	0.1614(4)	-0.2001(3)	0.050(2)
C(10)	-0.4166(4)	0.1390(4)	-0.3068(3)	0.055(2)
C(11)	-0.5188(4)	0.0555(4)	-0.3271(3)	0.053(2)
C(12)	-0.5445(4)	-0.0052(5)	-0.2471(4)	0.058(2)
C(13)	-0.4638(4)	0.0199(4)	-0.1414(4)	0.053(2)
N(1)	-0.6065(4)	0.0284(5)	-0.4403(4)	0.074(2)
O(3)	-0.6072(4)	0.1034(5)	-0.5066(3)	0.102(2)
O(4)	-0.6728(4)	-0.0662(5)	-0.4592(3)	0.106(2)

Atomic Coordinates (x,y,z) and Temperature Factors (B_{eq}, Å^2) for Compound 237

	x	y	z	Beq
S	0.82854(22)	0.71270	0.98184(14)	9.44(16)
C1	0.9621 (7)	0.9329 (11)	0.7801 (5)	6.8 (5)
C2	0.9233 (8)	0.9135 (12)	0.8714 (5)	7.4 (5)
C3	0.8809 (8)	0.7273 (16)	0.8795 (5)	7.7 (6)
C4	0.9857 (8)	0.6032 (12)	0.8808 (5)	8.0 (6)
C5	1.0350 (8)	0.6174 (14)	0.7986 (5)	6.6 (5)
C6	1.0753 (9)	0.4797 (11)	0.7617 (5)	8.0 (6)
C7	1.1338 (8)	0.4847 (10)	0.6884 (5)	7.5 (6)
C8	1.1288 (6)	0.6372 (10)	0.6414 (5)	4.9 (4)
C9	1.0674 (6)	0.8031 (11)	0.6711 (4)	4.3 (4)
C10	1.0639 (7)	0.8031 (13)	0.7704 (5)	5.0 (4)
C11	1.1183 (7)	0.9740 (10)	0.6422 (5)	6.0 (5)
C12	1.1491 (6)	0.9712 (10)	0.5506 (4)	5.4 (4)
C13	1.2355 (5)	0.8230 (10)	0.5398 (4)	3.2 (4)
C14	1.1682 (6)	0.6536 (10)	0.5554 (4)	4.2 (4)
C15	1.2383 (7)	0.5096 (10)	0.5240 (5)	6.4 (5)
C16	1.2873 (7)	0.5885 (9)	0.4477 (5)	6.0 (5)
C17	1.2524 (5)	0.7846 (9)	0.4468 (4)	3.7 (4)
C18	1.3607 (6)	0.8383 (11)	0.6026 (4)	6.3 (4)
C19	1.1876 (7)	0.8570 (11)	0.8271 (4)	8.4 (5)
C20	1.3387 (6)	0.9002 (10)	0.4049 (4)	4.4 (4)
C21	1.3121 (6)	1.0949 (9)	0.4068 (5)	7.0 (5)
C22	1.3354 (6)	0.8406 (10)	0.3137 (4)	4.8 (4)
C23	1.4273 (6)	0.7776 (10)	0.2828 (5)	5.2 (4)
C24	1.4182 (7)	0.7237 (11)	0.1888 (4)	5.8 (4)
C25	1.5206 (10)	0.8181 (14)	0.1519 (6)	9.8 (7)
C26	1.5152 (12)	0.7771 (16)	0.0602 (7)	17.7 (10)
C27	1.5077 (11)	1.0088 (15)	0.1601 (6)	13.6 (8)
C28	1.4352 (8)	0.5282 (12)	0.1853 (5)	8.6 (3)

Atomic Coordinates (x,y,z, x 10^4) and Temperature Factors (U_{eq}, $Å^2$ x 10^3) for Compound 264a

atom	x	y	z	U_{eq}
S(1)	3578(1)	4497(1)	6637(1)	36(1)
S(2)	2754(1)	7010(1)	7185(1)	40(1)
P(1)	2807(1)	5833(1)	6215(1)	34(1)
C(1)	3351(1)	2989(3)	6097(1)	31(1)
C(2)	1756(1)	7137(3)	7371(2)	31(1)
C(11)	3839(1)	1983(3)	6480(1)	33(1)
C(12)	3593(2)	776(3)	6664(2)	48(1)
C(13)	4055(2)	-114(3)	6984(2)	61(1)
C(14)	4771(2)	167(4)	7127(2)	58(1)
C(15)	5028(2)	1352(3)	6939(2)	50(1)
C(16)	4571(2)	2245(3)	6607(2)	40(1)
C(21)	2535(1)	2762(3)	6198(2)	33(1)
C(22)	2264(2)	2480(3)	6904(2)	50(1)
C(23)	1529(2)	2326(4)	7012(2)	65(1)
C(24)	1049(2)	2465(4)	6419(2)	59(1)
C(25)	1301(2)	2769(3)	5727(2)	56(1)
C(26)	2039(1)	2917(3)	5616(2)	44(1)
C(31)	3562(1)	3053(3)	5260(1)	31(1)
C(32)	3412(2)	1995(3)	4811(2)	43(1)
C(33)	3578(2)	1994(4)	4053(2)	51(1)
C(34)	3899(2)	3031(3)	3731(2)	54(1)
C(35)	4070(2)	4064(3)	4174(2)	55(1)
C(36)	3904(2)	4073(3)	4933(2)	42(1)
C(41)	1667(1)	8306(3)	7887(1)	33(1)
C(42)	993(2)	8878(3)	7940(2)	45(1)
C(43)	876(2)	9878(3)	8417(2)	53(1)
C(44)	1430(2)	10360(3)	8855(2)	55(1)
C(45)	2103(2)	9814(3)	8815(2)	65(1)
C(46)	2213(2)	8795(3)	8338(2)	52(1)
C(51)	1387(1)	7351(3)	6599(2)	34(1)
C(52)	1434(2)	8528(3)	6248(2)	49(1)
C(53)	1144(2)	8716(4)	5533(2)	67(2)
C(54)	813(2)	7739(4)	5150(2)	76(2)
C(55)	768(2)	6566(4)	5483(2)	66(2)
C(56)	1059(2)	6367(4)	6205(2)	47(1)
C(61)	1470(1)	5982(3)	7810(2)	32(1)
C(62)	1913(2)	5130(3)	8184(2)	48(1)
C(63)	1640(2)	4203(4)	8651(2)	66(1)
C(64)	902(2)	4099(3)	8743(2)	62(1)
C(65)	450(2)	4921(3)	8370(2)	55(1)
C(66)	729(2)	5841(3)	7906(2)	46(1)
C(71)	3352(1)	6931(3)	5659(2)	34(1)
C(72)	4078(2)	7215(3)	5779(2)	49(1)
C(73)	4433(2)	8094(3)	5334(2)	57(1)
C(74)	4067(2)	8693(4)	4768(2)	65(1)
C(75)	3349(2)	8437(4)	4639(2)	75(2)
C(76)	2992(2)	7552(3)	5077(2)	56(1)