INTRAMOLECULAR RHODIUM CARBENOID
INSERTION REACTIONS

a thesis presented by

ROGER JOHN TAYLOR

in partial fulfilment of the
requirements of the University of
London for the degree of

DOCTOR OF PHILOSOPHY

Hofmann Laboratory,

Department of Chemistry,

Imperial College of Science,

Technology and Medicine,

London, SW7 2AY.

September, 1988.

Abstract

The intramolecular insertion reactions of rhodium carbenoids, derived from diazo compounds, into heteroatom-hydrogen bonds and C-H bonds are reviewed.

The work presented is based on the intramolecular reaction of transient rhodium carbenoid species with nucleophiles. A new method has been developed to synthesise α-diazo-β-ketoesters, the precursors of the carbenoid species, in an efficient manner. This involves the low temperature acylation reaction of ethyl lithiodiazoacetate with cyclic electrophiles, including lactones, thiolactones, lactams, anhydrides, and carbonates. The acylation of other α-lithiodiazo compounds with cyclic electrophiles has also been investigated, and ethyl lithiodiazomethylphosphonate, lithiodiazoacetone, *tert*-butyl lithiodiazoacetate, and lithiotrimethylsilyldiazomethane all gave the corresponding functionalised diazo compounds, in variable yield.

The diazo compounds, so prepared, were subjected to dirhodium tetraacetate mediated cyclisation, to give cyclic ethers (6, 7, and 8 membered rings), and thioethers (6 and 7 membered rings), from diazoalcohols and -mercaptans, respectively. However, the reaction of diazoamides gave cyclopentanones, derived from insertion of the carbenoid into a γ-C-H bond. Factors affecting the balance between competing intramolecular C–H bond insertion and formal O-H bond insertion, in the synthesis of oxecanes, have been explored. The synthesis of an ε-lactone from a diazoacid is also reported.

The intramolecular reactions of alkyl, allyl, and acyl sulphides with rhodium carbenoids, derived from α-diazo-β-ketoesters, gave 2-substituted thiane and thiepane derivatives, by rearrangement of cyclic sulphonium ylides, which were isolable in some cases. The corresponding reaction of α-diazo-β-ketones also gave thiepanes.

The analogous intramolecular reaction of γ- and δ-diazosulphoxides with rhodium carbenoids gave stable five and six membered cyclic sulphoxonium ylides, and the chemistry of these novel ylides was investigated. Deoxygenation of the sulphoxide was the sole product in the reaction of a β-diazosulphoxide.

Acknowledgements

I am indebted to my supervisor, Dr. C. J. Moody, for his patience, guidance and encouragement throughout the course of this project.

I would like to thank Mr. J. Bilton, Mr. K. I. Jones, and Mr. R. N. Sheppard for the excellent mass spectroscopic, microanalytical, and NMR services, and I would also like to thank to Dr. D. J. Williams and Miss A. M. Z. Slawin for the X-ray crystallographic service.

Thanks are also due to Mr. P. Sulsh and Mr. D. Everitt, the techical staff, for their unfailing assistance.

I extend warm thanks to my colleagues in the Hofmann Laboratory for their friendship and support throughout the past three years, especially Pritom Shah, and Graham Jones.

I would like to thank Dr. C. J. Moody and Professor C. W. Rees for the use of their Macintoshs'. Special thanks go to Graham Jones for proof reading the manuscript.

Finally, grateful acknowledgement is made of the Science and Engineering Research Council for financial support.

Abbreviations

Bn	Benzyl
Boc	*tert*-butoxycarbonyl
n-BuLi	*n*-butyllithium
t-BuOK	Potassium *tert*-butoxide
Cbz	Benzyloxycarbonyl
m-CPBA	3-Chloroperbenzoic acid
CSA	Camphorsulphonic acid
Cu(acac)$_2$	Copper (II) acetylacetonate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulphoxide
EDA	Ethyl diazoacetate
ELDA	Ethyl lithiodiazoacetate
IR	Infra red
LDA	Lithium diisopropylamide
NMR	Nuclear magnetic resonance
OTf	Trifluoromethanesulphonate (triflate)
PDC	Pyridinium dichromate
PhH	Benzene
Rh$_2$(OAc)$_4$	Dirhodium tetraacetate
TBDMS	*tert*-butyldimethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	4-Toluenesulphonate

Contents

Chapter Three: Synthesis and Dirhodium Tetraacetate Mediated Cyclisation of α-Diazocarbonyl Compounds

Chapter Four: Dirhodium Tetraacetate Catalysed Reaction of Diazosulphides: Preparation and Rearrangement of Cyclic Sulphonium Ylides

CHAPTER ONE

Intramolecular Reactions of Diazo Carbonyl Compounds Catalysed by Rhodium (II) Salts

1.1 Introduction

The reactions of diazoketones with transition metal catalysts have enjoyed continued attention since the initial discovery of the facility of copper and copper salts to promote decomposition of diazo compounds. The utility of copper catalysis has been demonstrated by its ability to harness the very high reactivity of carbenes in a broad range of transformations, to give good yields of products in synthetically useful reactions. Further work has led to the introduction of soluble copper catalysts, offering lower reaction temperatures, and finally to the development of optically active copper catalysts, which have opened the door to the chiral synthesis of cyclopropanes in both intermolecular and intramolecular reactions.[1,2]

The discovery of dirhodium tetraacetate as an efficient catalyst for the decomposition of diazo compounds by Teyssie and Hubert et al[3] in 1973 paved the way for their general acceptance as versatile synthetic tools, and the development of the diazo transfer reaction[4] for the mild synthesis of acid stable diazo compounds, spurred an interest in their reactions. Rhodium (II) salts catalyse the decomposition of diazoketones at room temperature, and this activity has been exploited largely in intramolecular insertion and cyclopropanation reactions.[5] Mechanistic work suggests the involvement of a metallo-carbenoid intermediate, which accounts for the mild, selective and predictable nature of rhodium catalysis. The catalyst also aids suppression of deleterious rearrangement and dimerisation reactions that are often the major products of thermally and photochemically generated carbenes.

Intramolecular reactions of diazoketones catalysed by rhodium (II) salts usually lead to one of four classes of product (Scheme 1); the reactions proceed along different mechanistic pathways in each case, the outcomes of which are listed below:

(1) Cyclopropanation (1,2-cycloaddition)

(2) Insertion into a C-H bond

(3) Reactions with nucleophiles (insertion into a Nu-R bond)

(4) Rearrangement (e.g. 1,2-H shift and the Wolff rearrangement)

The transient nature of the metallo-carbenoid complex has so far thwarted efforts to characterise its structure. However, several transition metals, including tungsten and molybdenum, form stable carbene complexes (not prepared from diazo compounds), and these act as cyclopropanation agents. Doyle has compared the stereo- and regio-selectivity of cyclopropanes formed from $(CO)_5W=CHPh$ with those formed in the

9

dirhodium tetraacetate catalysed decomposition of phenyldiazomethane, and his results suggest the presence of a rhodium carbenoid intermediate in the latter reaction.[6] Despite the lack of detailed mechanistic knowledge, however, the intramolecular insertion of rhodium-carbenoids into C-H bonds (selective insertion into the γ- C-H bond to give five membered rings), and the reaction of rhodium carbenoids with nucleophiles (novel heterocycle synthesis), are both areas of current interest.
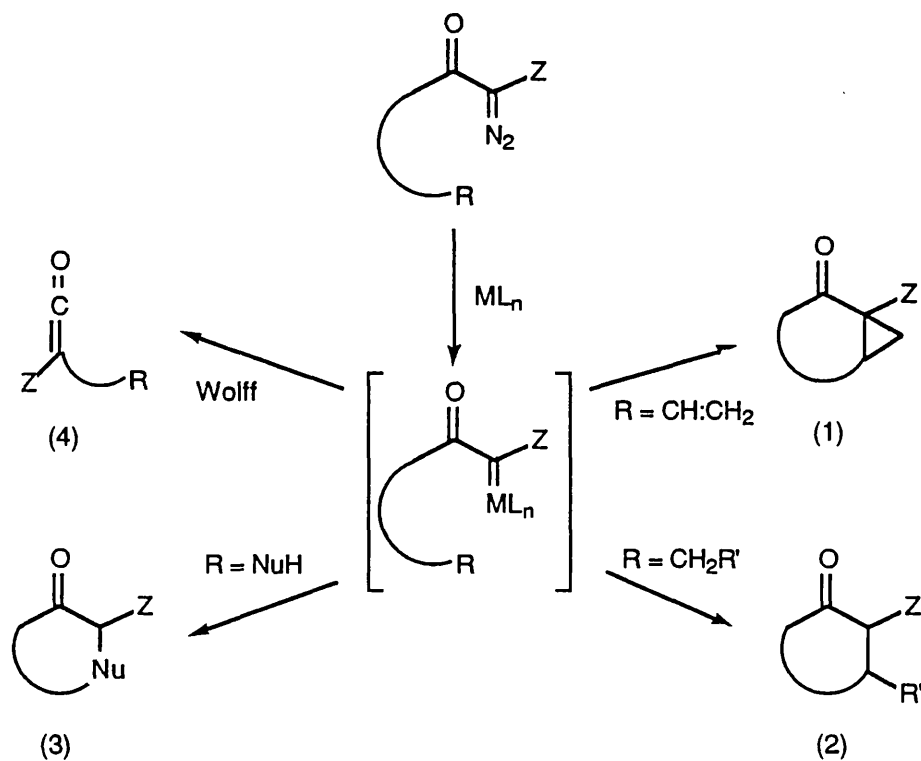
Scheme 1.

This chapter will outline the recent advances in dirhodium tetraacetate catalysed ring synthesis: the first part will cover reactions of diazoketones with nucleophiles, and the second part will deal with the synthesis of carbocycles by C-H bond insertion. Although the title suggests a review on the catalytic reactions of dirhodium tetraacetate, examples of copper catalysis will also be discussed to facilitate a comparison between their activity and reactivity. This work surveys the literature from 1985 to 1988, but in order that an accurate picture is painted of the range of reactions studied, earlier work will be referred to where appropriate. The review by Maas[5] which covers work up to 1985 is an excellent introduction to the subject.

1.2   Reactions with Nucleophiles

This section is organised according to the atom or group acting as the nucleophilic agent.

The inter- and intra-molecular reactions of diazo compounds with nucleophilic groups, catalysed by Lewis acids or protic acids, is well known, and proceeds by the trapping of a carbenium ion generated by loss of nitrogen from the diazo compound. Alternatively, a neutral, electron deficient intermediate- a carbene - can be generated by thermolysis or photolysis of diazo compounds. Rearrangement of these high energy carbenes occurs readily, usually faster than reaction with a nucleophile. In comparison, the mild generation of carbenoids with transition metal catalysts, and their inherent lower reactivity combine to make reaction with nucleophiles a synthetically valuable transformation.

The proposed mechanism for the catalytic cycle (Scheme 2) is initiated by transition metal catalysed loss of nitrogen from the diazo compound, to generate the metallo-carbenoid. This powerfully electrophilic species is rapidly quenched by a nucleophile to give a dipolar intermediate (5). The final steps in the catalytic cycle are the loss of the catalyst, and rearrangement of the resulting ylide (6). Although the order of the
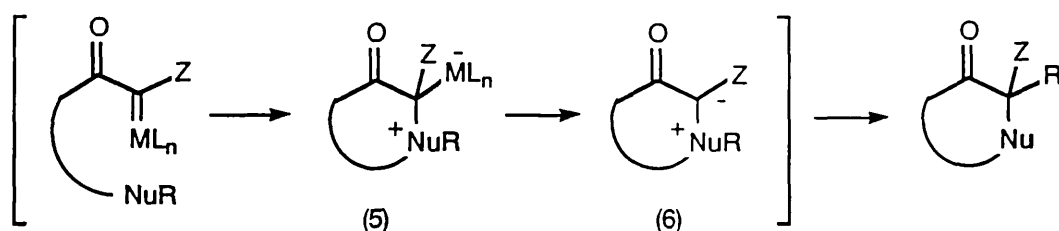
Scheme 2.

steps has not been determined, it is likely that loss of the metal precedes rearrangement, even when ti migration of the R group is facile (e.g.,the [2,3]-rearrangement of an allyl group). In cases where migration of the R group is not facile, the ylide (6) can be isolated. Subsequent reaction of the ylides can occur by a variety of pathways: [1,2]-and [2,3]- shifts, and β- eliminations are common.

1.2.1   Alcohols and Ethers

Alcohols

The intermolecular reaction of alcohols with α-diazoketones to give α-alkoxyketones is well documented for copper and rhodium catalysts. The first application of this process to ring synthesis is in the $Cu(acac)_2$ catalysed synthesis of macrocyclic oxa-crown ethers (9) from α,ω-diazoketones (8) and long chain polyethylene glycols (7).[7] The reaction proceeds in two steps, the first intermolecular, followed by the cyclisation step to give 22-26 membered rings in 7-26% yield. No C-H insertion derived products were reported, and this supports the idea of a template effect in the reaction. Indeed, a 52 membered ring product was prepared in 40% yield from the

(7)   (8)   (9)

n = 2 - 3 , m = 6 - 9
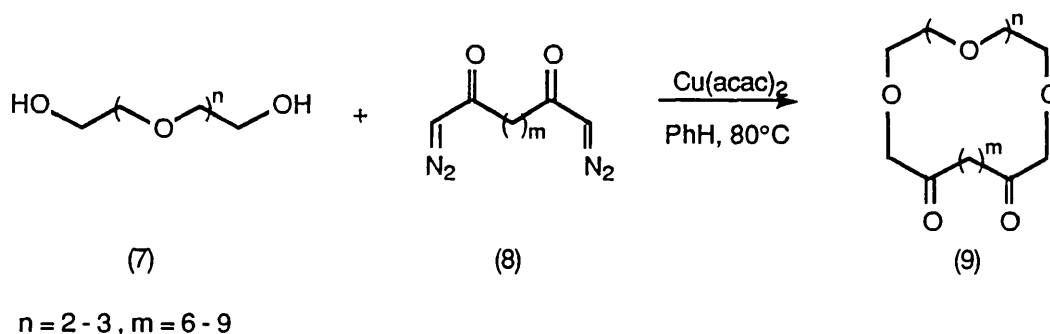
combination of two molecules of each reagent. The synthesis of small and medium rings by O-H insertion under rhodium catalysis has been developed by the groups of Rapoport[8] and Moody,[9] respectively. Both groups used α-diazo-β-ketoesters (11) as

P = protecting group, n = 1-6

(11)
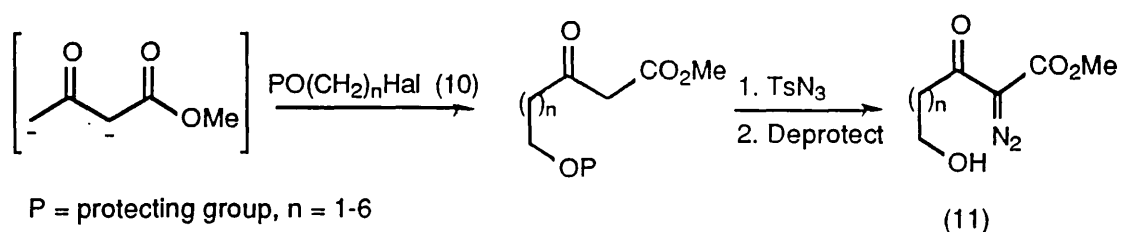
substrates for cyclisation. The compounds were readily prepared in three steps by alkylation of the dianion of methyl acetoacetate with the relevant protected α,ω–halogeno alcohols (10), followed by deprotection of the alcohol, and diazo transfer on the β-ketoester using tosyl azide. Cyclisation of the diazo- alcohols (11) was

accomplished in a dilute solution of boiling benzene with 1-2 mol% of dirhodium tetraacetate, to give: an oxotetrahydrofuran (12) in quantitative yield, an oxo-oxepane (14) (78%), and an oxo-oxecane (15) (24%). The 3-oxotetrahydropyran (13)

$$\text{HO} \underset{\text{N}_2}{\overset{\text{O}}{\diagup}}_{n} \text{CO}_2\text{Me} \xrightarrow[\text{PhH, 80°C}]{\text{Rh}_2(\text{OAc})_4} \text{O} \underset{\text{CO}_2\text{Me}}{\overset{\text{O}}{\diagup}}_{n}$$

(12) n = 1
(13) n = 2
(14) n = 3
(15) n = 4

(16)

(17)
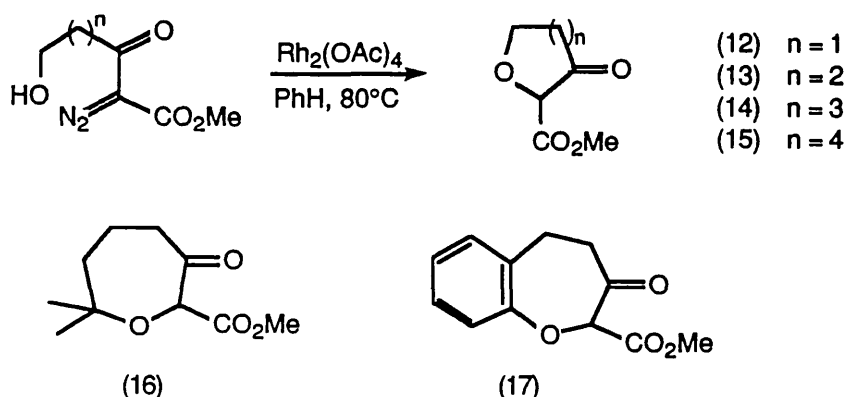
appeared to be unstable, and could not be isolated. Exclusive insertion into the O-H bond in the synthesis of oxepanes demonstrates the kinetic preference for reaction at the hydroxy group. Indeed, insertion into the O-H bonds of tertiary and primary alcohols occurred equally well, for example (16) was prepared in 72% yield, and insertion into a phenol also occurred readily, (17) being obtained in 71% yield.

Ethers

The intermolecular reactions of ethers with diazo compounds in the presence of dirhodium tetraacetate is also a known reaction, and the intermediate obtained is a non-isolable oxonium ylide, which can rearrange either by a symmetry forbidden [1,2]-Stevens shift or by an allowed [2,3]- shift, to the product of a formal C-O insertion. The reaction of allyl ethers with diazoketones is rare due to competing cyclopropanation of the alkene.

Extension of the reaction to intramolecular systems has been exploited separately by the groups of Pirrung and Johnson. Their results show that ethers are sufficiently strong nucleophiles to trap the intermediate rhodium carbenoid. The oxonium ylide can rearrange either by [1,2]- or [2,3]- shift of the exo group (18) or endo group (19), to give rise to compounds of totally dissimilar structure (Scheme 3). Johnson[10] has reported the cyclisation of several γ-alkoxy-α-diazoketones (20) (dirhodium tetraacetate/ benzene/ 25°C) to cyclobutanones (21) in 45-68% yield,

and this occurs by ring contraction of the oxonium ylide. The rearrangement of the oxonium ylide in an endo fashion is observed as the sole product; the geometry of the
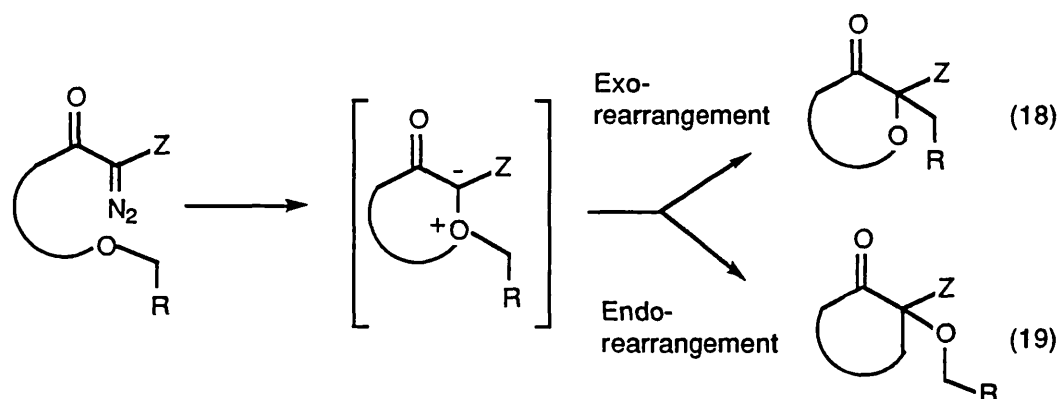
Scheme 3.

ylide favours internal [1,2]- shift over external [1,2]- shift. The oxonium ylides derived from ω-allyloxy-α-diazo-β-ketones and -ketoesters (22), however, rearrange exclusively in an exo manner by a [2,3]- sigmatropic shift, to 2-allylfuranones (23) and 2-allylpyranones (24), and this reaction is analogous to O-H insertion. The reaction was applied to the synthesis of a variety of furanones and pyran

R = Me, R' = Ph
R = CH:CH$_2$, R' = H
R = H, R' = CO$_2$Me

(20)   (21)

(22)   (23) n =1, (24) n = 2
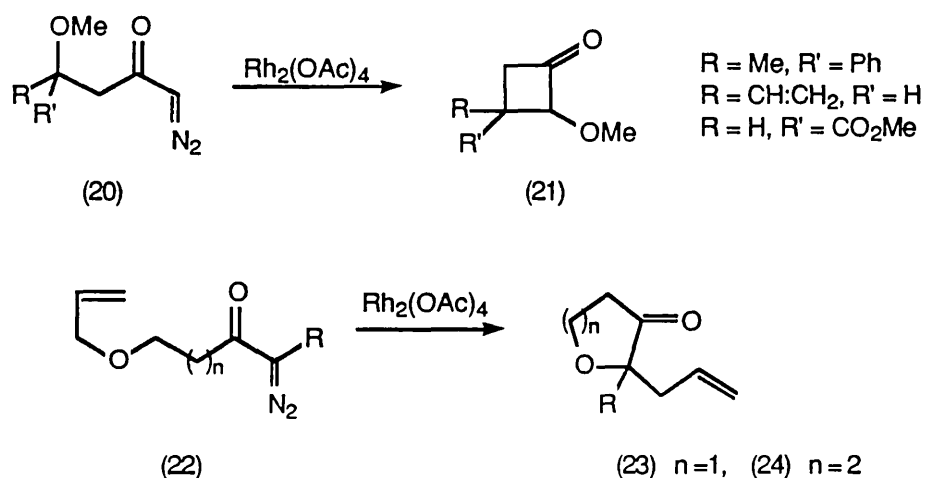
-ones in very good yield,[10,11] however, in the later system C-H insertion, to give cyclopentanones, was a competing reaction. The often strained nature of the transition states required for rearrangement is illustrated by the balance between [1,2]- and [2,3]- shifts: the synthesis of oxecane (26) from (25)[11] occurs by a [2,3]-rearrangement, whereas (28) is the product of Stevens rearrangement of the ylide derived from (27).

(25) Rh₂(OAc)₄ (26)

(27) Rh₂(OAc)₄ (28)
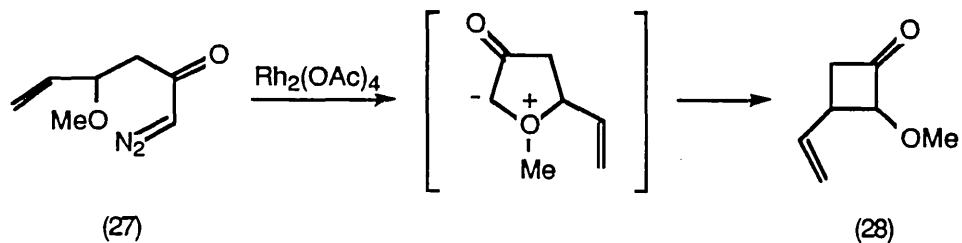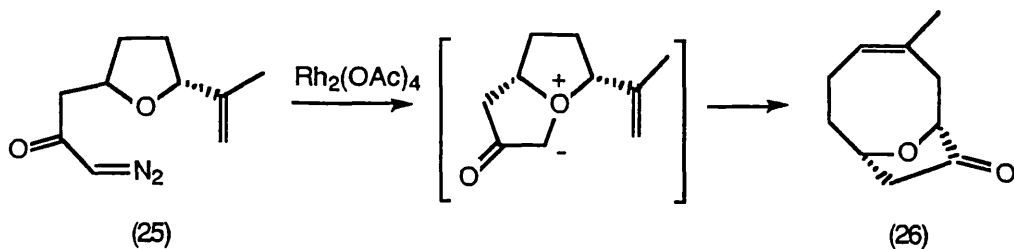
1.2.2 Amines and β-Lactams

Although the intermolecular insertion of copper-ketocarbenoids into the N-H bond of primary and secondary amines has been documented, the literature on intramolecular insertions into the N-H bond of amines is scant.

(29) Rh₂(OAc)₄ (30)
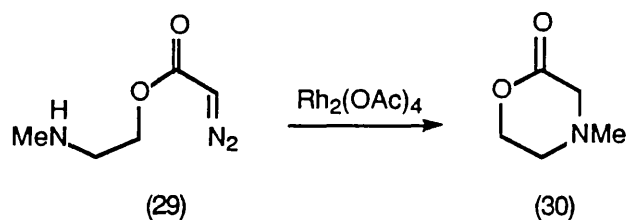
Treatment of diazoester (29) with dirhodium tetraacetate gave (30) in 18% yield.[12] The synthesis of 1,2-diazetidinones[13] (32) was achieved by treatment of diazo hydrazides (31) in boiling benzene with dirhodium tetraacetate. The N-H insertion

(31) Rh₂(OAc)₄ (32)

R	R'	Z
Bn	Ph	CO_2Et
$CO_2{}^tBu$	Bn	CO_2Et (COMe)
$CO_2{}^tBu$	CH_2CO_2Et	CO_2Et (COMe)
CO_2Bn	CH_2CO_2Et	CO_2Et (COMe)
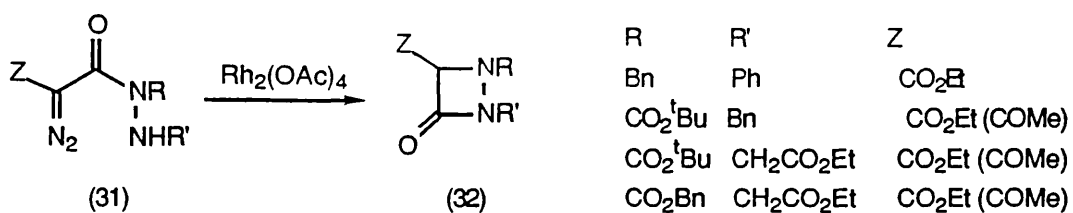
products were isolated in high yield. Treatment of diazo hydrazide (33) with dirhodium tetraacetate gave a high yield of the pyrrolidine[14] (34) by cyclisation onto the more nucleophilic nitrogen, to give an ylide which rearranges to (34).

(33)   (34)
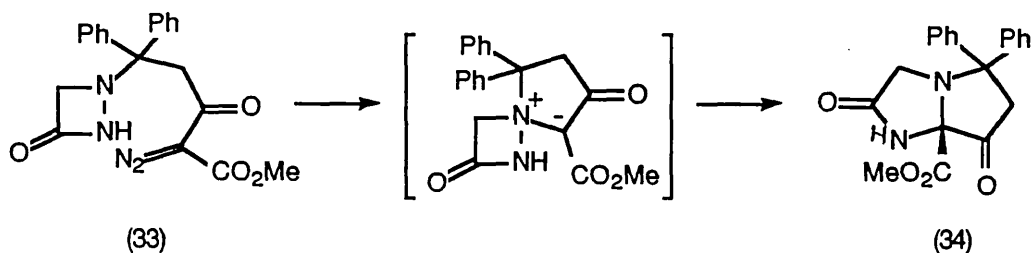
A study by Rapoport *et al*[8] into the intramolecular reactions of ω-benzylcarbamate α-diazo-β-ketoesters catalysed by dirhodium tetraacetate reports the synthesis of four, five and six membered N-Cbz cyclic amines. Synthesis of the diazo compounds (35) was achieved in two steps from N-protected ω-aminoacids, by chain extension on the acid imidazolide using the dianion of mono methyl malonate, followed by diazo transfer on the resulting β-ketoester. The insertion of the rhodium carbenoid, derived by treating (35) with dirhodium tetraacetate, into the N-H bond to form four and five membered amines, (36) and (37) respectively, in quantitative yield, is evidence of the facile nature of the reaction. Extension of the reaction to larger ring sizes resulted in a rapidly diminishing yield of the N-H insertion product. Attempted preparation of the azepine (39) resulted in C-H insertion to give cyclopentanone (40, n=1) in 39% yield as the only product of cyclisation. In the synthesis of the piperidine (38) (21–67%), the cyclopentanone (40, n=0) (5-10%) was also isolated. The reaction was investigated closely, and the product ratio was shown to have a marked dependence on the solvent employed, the reaction temperature, and the amount of catalyst used. Placing a heteroatom in the chain of the diazo compound reduced the yield of cyclised product dramatically.

(35)   (40)

(36) n=1
(37) n=2
(38) n=3
(39) n=4
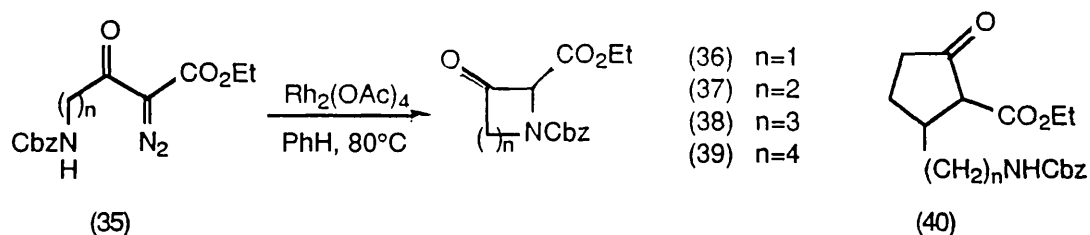
A great deal of work has been reported on the intramolecular reactions of β-lactams with rhodium carbenoids, and in general the insertion reaction into the lactam N-H bond is very facile. The reason for this may lie in the decreased conformational flexibility of the 4-(γ-diazo-β-carbonyl) substituted 2-azetidinones (41) over the alicyclic amines; thus, the lower entropy of the molecule favours cyclisation.

Initial work on the cyclisation was reported in 1976 by workers at Merck, and continued effort by many groups has produced structurally and pharmaceutically interesting compounds.[5] The synthesis of carba- and oxa- penams and cephams has been reported using this reaction (Scheme 4). Dirhodium tetraacetate was found to be a superior catalyst for these transformations. Many systems employed α-diazo-β-ketoester based substituents at the 4-position, but the efficacy of cyclisation onto the carbenoid opened the possibility of employing β-alkyl-α-diazoesters at the 4-position, without [1,2]-hydrogen shift reactions being problematic, for example (42) gives (43) in 55% yield.[5]

(41)   (42)

R, R' = amide or alkyl

Z = CO$_2$R   X = CH$_2$, O, (CH$_2$)$_2$, OCH$_2$
Z = PO(OMe)$_2$ X = CH$_2$

Scheme 4.

(42)   (43)
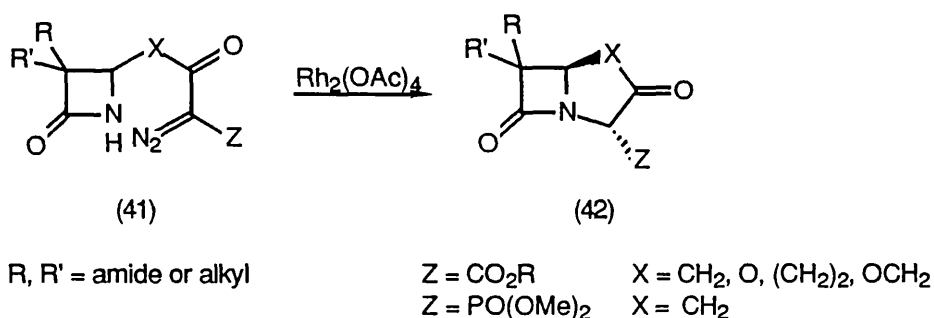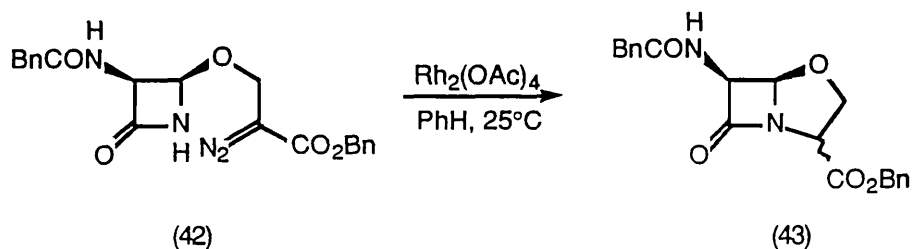
The novel azabicyclo[4.1.1]octane (45) was prepared from diazo azetidinone (44) by N-H insertion.[15] The seven membered ring was formed under dirhodium tetraacetate catalysis in 50% yield, and this contrasts with the results of Rapoport. However, this ambiguity can be explained by realisation of the rigidity imparted to the structure of the diazo compound by the β-lactam ring.

(44) (45)
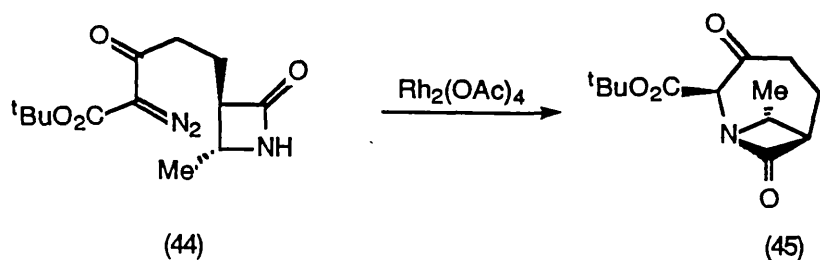
1.2.3 Mercaptans and Sulphides

Mercaptans

The insertion of carbenes into the S-H bond of mercaptans would be expected to be a facile process, on account of the nucleophilic nature of sulphur. Indeed, examples of the intermolecular reaction have been documented, and the extension to intramolecular systems has recently been reported by Rapoport.[8] Tetrahydrothiophene (46), was prepared in 73% yield by treatment of methyl 2-diazo-5-mercapto-3-oxopentanoate with dirhodium tetraacetate in benzene at 80°C.

(46)
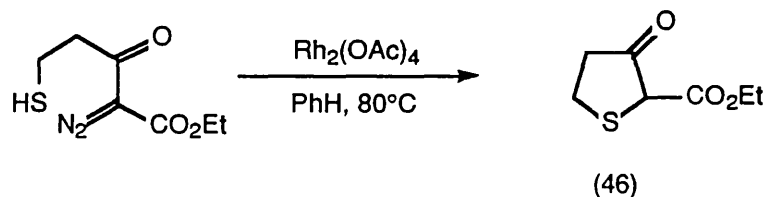
Sulphides

The intermolecular reactions of sulphides with diazocarbonyl compounds catalysed by copper and rhodium salts are well documented, especially in the case of allyl sulphides. The common intermediate in all reactions is a sulphonium ylide derived by attack of the sulphur atom on the carbenoid. Symmetry allowed [2,3]-shifts are facile, and with allyl sulphides rearrangement usually occurs under the reaction conditions. Intramolecular examples of the reaction have been studied with a broad range of ω-sulphide-α-diazoketones, although not allyl sulphides, and dirhodium tetraacetate has been the catalyst of choice in recent work. The work can be divided into two sections according to the mode of fragmentation of the sulphonium ylide: the first type is

18

characterised by the presence of a hetero atom β- to the ylide sulphur (Scheme 5). This controls the process by inducing fission of one of the two C-S bonds. It also removes the need for a "symmetry allowed" pathway or a migration labile group to be present for facile rearrangement, by facilitating a stepwise process. In the second group are cyclic sulphonium ylides which react by the classical routes, such as β-elimination, [1,2]- (Stevens) or [1,4]- shift. The role of the substituents on sulphur is pivotal to which C-S bond is cleaved.
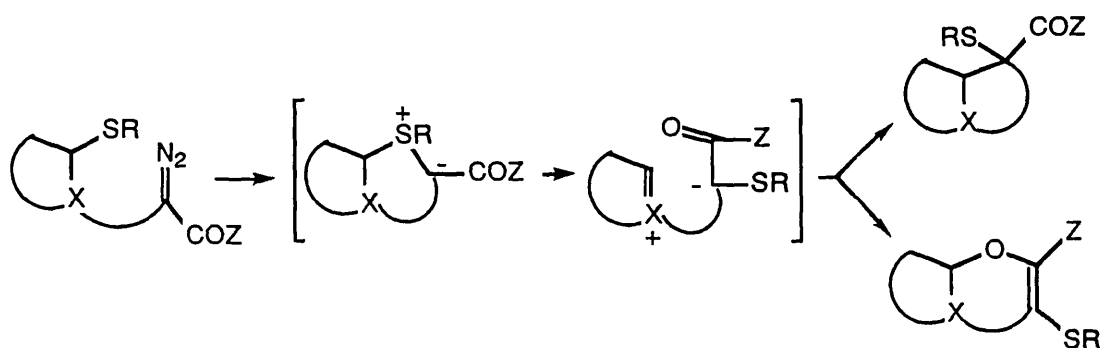
Scheme 5.

In the first type of rearrangement, nitrogen and oxygen systems have been studied: β–lactams and γ-lactams have been the focus of study in nitrogen systems, and Kametani[16] has reported the synthesis of pyrrolizidine alkaloids employing diazo-

X=S (55%), X=Se (36%)
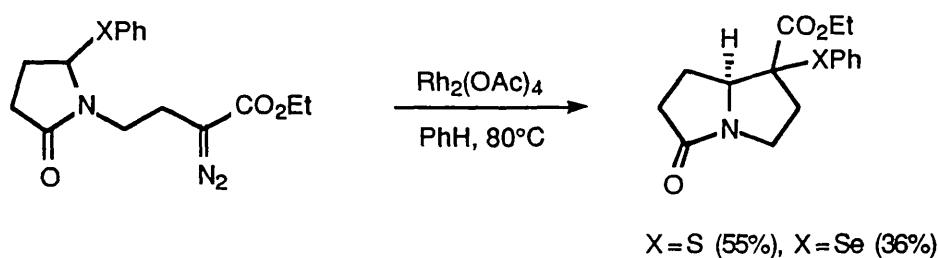
Scheme 6.

sulphides and diazo-selenides in a ring formation step, the intermediate sulphur and seleno-ylides rearrange to give the ring contracted azabicyclo[3.3.0]octan-2-ones in good yield via an iminium species (Scheme 6). Overall, the rearrangement is equivalent to a [1,2]-shift. Oxygen assisted ylide fragmentation has been applied to the synthesis of O-glycosides from S-glycosides[17] (Scheme 7), and this occurs by thermal cleavage of the isolable ylide to an oxonium ion, which reacts with the enol tautomer of the ester to give a bicyclic compound. The rearrangement is an overall

[1,4]-shift. The exocyclic sulphide substituent, in all ylides in this section, is either aryl or vinyl, the groups being chosen primarily for their low migratory aptitude. However, the secondary role they play in the rearrangement step, is often vital in the
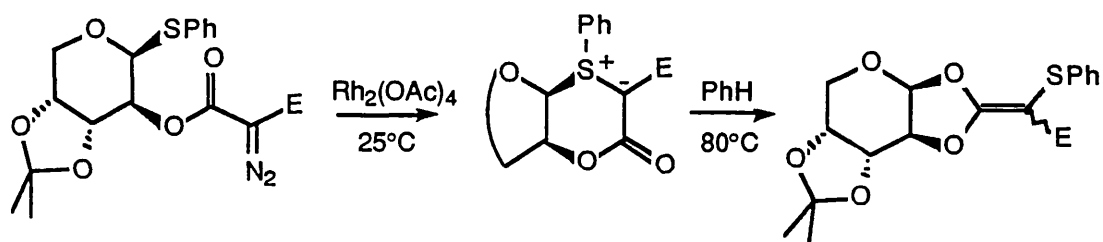
Scheme 7.   E = CO$_2$Me

outcome of the reaction. An illustration of this is in the synthesis of a carbapenam and oxapenam[18,19] from the diazosulphide (47, R'=H), where increasing steric interactions at the enolate carbon result in exclusive O-alkylation of the proposed iminium ion intermediate (Scheme 8), whereas the more highly substituted diazosulphide (47, R'=Me, R=Ph) gave products derived exclusively from attack at the

R = CH:CHCO$_2$CH$_2$Ph   33%   52%
R = Ph   -   27%
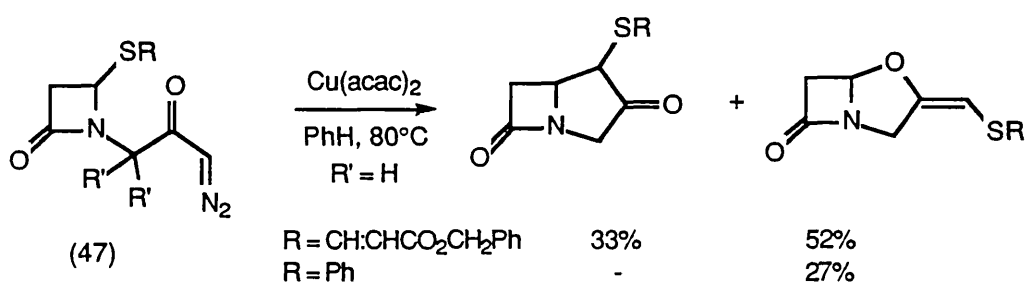
Scheme 8.

β-lactam oxygen. Tricycle (49) was the major product from the Cu(acac)$_2$ catalysed reaction of (48, n=1), formed by C-alkylation of the intermediate iminium species;

(48) R = NHC(O)CH$_2$OPh

20
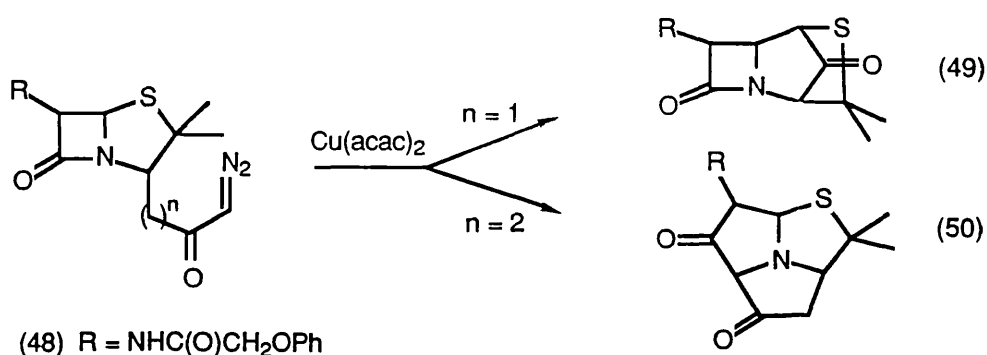
O-alkylation was only observed as a minor product, a consequence of the geometrical requirements for attack at the iminium ion. However, increasing the length of the alkyl chain (48, n=2) resulted in nitrogen ylide formation, followed by Stevens rearrangement to give (50).[20]

The second group of ylide rearrangements is characterised by a greater variety of ylide structure and ring size. The work of Davies[21] on phenyl sulphides (Scheme 9) has proven the versatility the cyclisation reaction by the isolation of five, six, and seven membered ylides (51), in 45-67% yield, although the C-H insertion competed with the formation of the seven membered cyclic ylide. The diazosulphides were prepared in five steps from chloroalcohols. The ylides were stable and isolable, although, rearrangement occurred on heating (160°C). Attempts to synthesise the four membered cyclic ylide (51, n=1) resulted in isolation of a compound (52) derived from the ylide by [1,4]-rearrangement involving the ester group, and similar results were obtained on heating the six membered cyclic ylide (51, n=3). In comparison, the ylide (53) rearranged *in situ* at 80°C by [1,2]-shift to give the cyclopentane (54) as the major product.[22] The more flexible cyclic ylide introduced by the extra sp^3 centre favours the Stevens reaction.

(51)   (52) R = Ph, Et
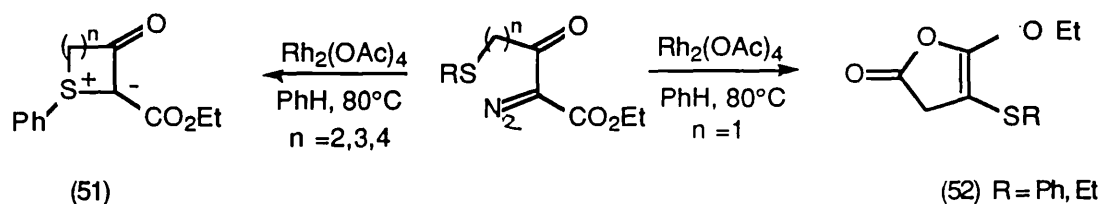
Scheme 9.

Reaction of the five and seven membered cyclic ylides (51, n=2,4) occurred by β-elimination, to give acyclic alkenes, presumably a reflection on ring conformation.

(53)   Ar = 4-methylphenyl   (54)
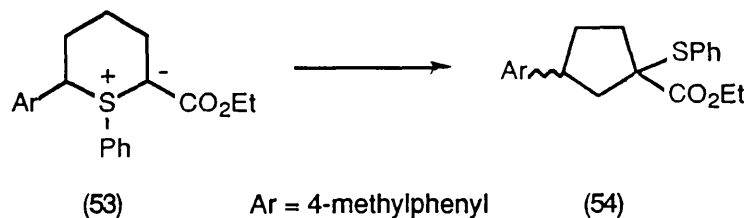
Although β-elimination is a common reaction in acyclic ylides, the ylides from ethyl sulphides can only lose ethene if a low energy transition state is geometrically

possible: rapid loss of ethene was found in the copper (II) or rhodium (II) acetate catalysed decomposition of (55, R=Et) to give the fused thiane system (56),[23] but [1,4]-shift occurred in the isolable ylide (51, R=Et) when heated ($80^{\circ}C$), to give dihydrofuran (52). Facile rearrangement of the benzyl group has also been observed, and 2-benzylthiotetrahydrofuran-3-one[24] was obtained by *in situ* Stevens rearrangement of the corresponding S-benzyl ylide. However, in the decomposition of (55, R=Bn) the product of [1,4]-rearrangement of the ylide was observed to give the fused thiane (57). Finally, the S-acetyl derivative of (55), upon copper acetate mediated decomposition, gave (57, R=Ac), again derived by a [1,4]-rearrangement of the ylide.[23]
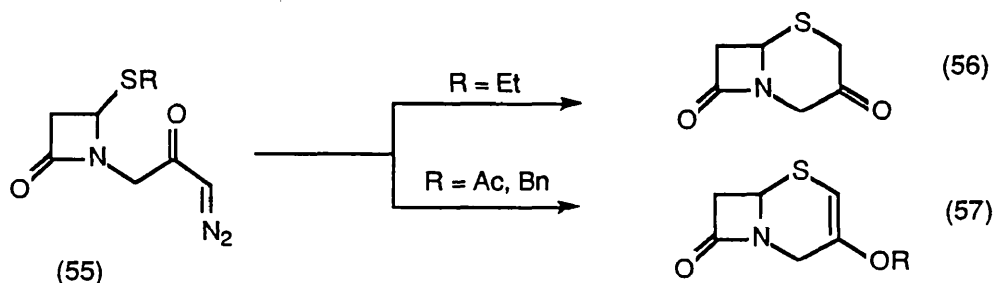
1.2.4   Reactions involving the Carbonyl Group

All the examples in this section proceed by nucleophilic attack of a carbonyl oxygen onto the metallocarbenoid, to generate a carbonyl ylide. The 1,3-dipolar nature of the ylide has been exploited by inter- and intramolecular trapping reactions with multiple bonds (carbon-carbon or carbon-hetero). An alternative fate for the ylide is proton transfer. This becomes the exclusive pathway in systems with α-protons, giving rise to enolates.

Treatment of 2,6-dioxo-1-diazophenylsulphone (58) with dirhodium tetraacetate gave tetrahydro-oxepane (59) (22%), the thermodynamic isomer, as the result of proton transfer in the intermediate carbonyl ylide.[25]
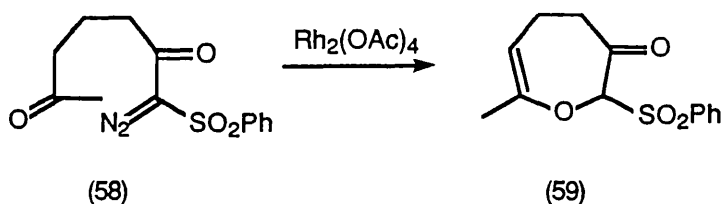
Dirhodium tetraacetate catalysed decomposition of o-methoxycarbonyl-α-diazoacetophenone (60) in boiling benzene at high dilution gave a dimer (61) (75%).[26] The complex structure was confirmed by X-ray, and the structure previously proposed by Ibata *et al* was shown to be incorrect.

(60)   Ar = 2-(methoxycarbonyl)phenyl   (61)
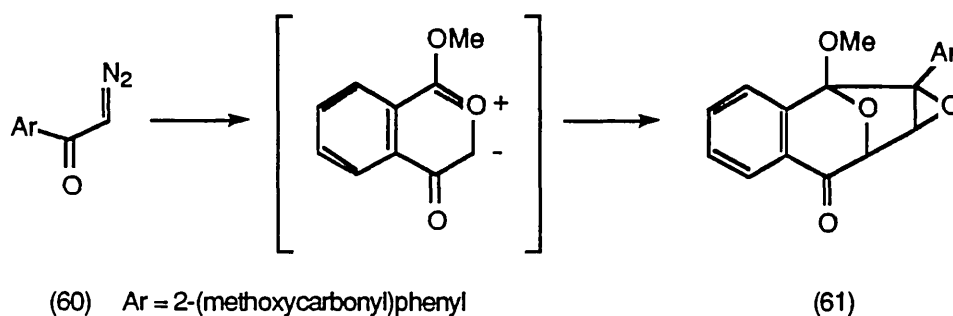
Intramolecular trapping of the carbonyl ylide has been reported by Padwa:[27] cyclisation of diazoketoester (62) in benzene with dirhodium tetraacetate gave cyclohepta[1,2-b]furanone in 87% yield, formed by intramolecular 1,3-cycloaddition of the ylide and the alkene. In a similar fashion, a diazoketoamide also gave a bridged tricycle.[27]

(62)
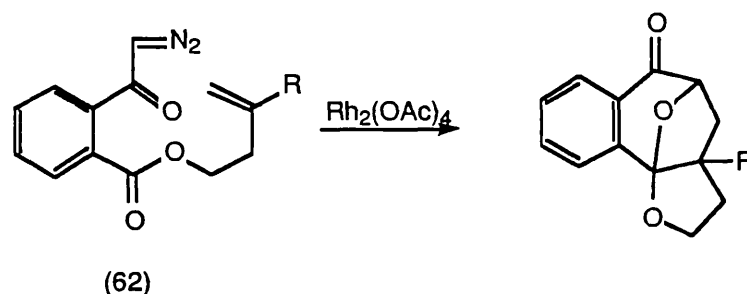
Finally, the mesoionic carbonyl ylides, the isomunchnones, have been generated from the diazo precursors (63, Z=Ac) by dirhodium tetraacetate catalysis. They are

(63)   Z = H, Ac; n = 1,2   (64)

23
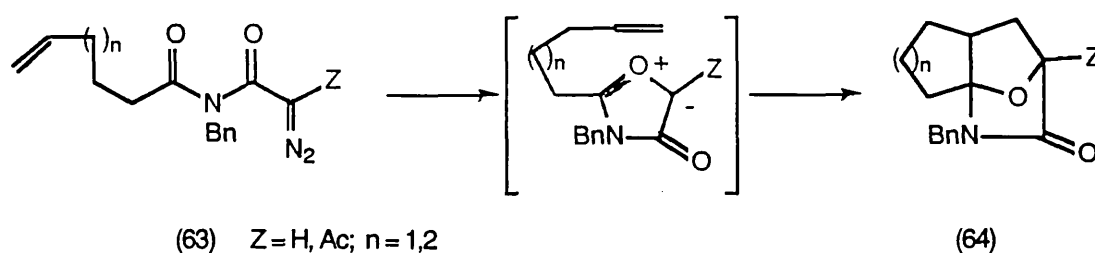
trapped intramolecularly by unactivated alkenes, to give tricyclic systems (64) in high yield (72-91%).[28] The diazoalkane analogues (63, Z=H) were found to give poor yields of adducts, due to the lower reactivity of the intermediate 1,3-dipole.

1.3   Insertion into C-H Bonds

The aim of this section is to cover intramolecular C-H insertion in aliphatic diazocarbonyl compounds, that is, direct insertion of a metallocarbenoid into an unactivated C-H bond. The work discussed in this section is easily summarized (Scheme 10).

Aromatic and heteroaromatic diazoketones undergo formal C-H insertion, but the mechanism can proceed by either cyclopropanation or electrophilic substitution. In the former pathway, the reaction of a benzene gives an intermediate benzocyclopropene, which can rearrange by electrocyclic reaction to a cycloheptatriene, or by acid catalysis, to the product of formal C-H insertion. Similarly, insertion into an allylic C-H bond can sometimes occur with the involvement of the double bond in an intermediate.
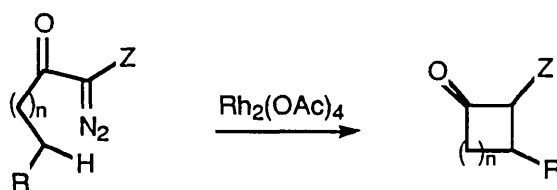
Scheme 10.   n = 1,2,3

The mechanism of the reaction (Scheme 10) is unknown, but fundamentally it is an insertion reaction into a C-H bond that is activated by a transition metal. Although 'naked' carbenes insert into unactivated C-H bonds, the reaction has low selectivity. Participation of the less reactive metallocarbenoid in the reaction leads to a selective C-H insertion and predictable products.

The intramolecular insertion of metallocarbenes (carbenoids) into C-H bonds was reported as long as 30 years ago.[2,5] Initial reports described the use of copper, copper oxide and copper sulphate catalysis, but silver salts, photolysis and thermolysis were shown to be effective in some examples. Yields were usually low and the reaction temperatures high (>100°C). C-H Insertion gave four or five membered

rings, with five membered rings the major product where competitive cyclisation was possible. The diazoketones were often bicyclic or fairly rigid structures, providing a significant bias towards insertion at a particular C-H bond, and this is clearly shown in the synthesis of (65) from diazocamphor.[29] Transannular reaction of α-diazocyclodecanone gave a decalin in poor yield by δ-C-H insertion.[30]

(65)
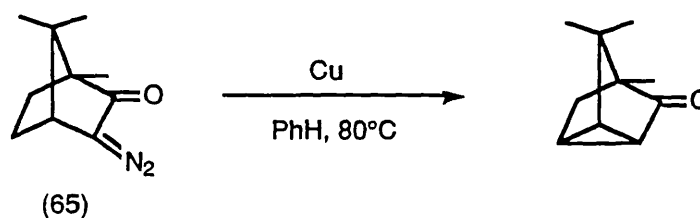
More recently, the development of more active copper salts, such as copper (II) triflate, has allowed lower reaction temperatures to be used. The combination of $Ni(acac)_2$ and a tungsten light has been reported as an efficient catalyst in the synthesis of fused cyclopentanones.[31]

The advent of dirhodium tetraacetate transformed inter- and intra-molecular C-H insertion reactions. As a result of the milder conditions required for catalysis (25–80°C), and the greater selectivity of the carbenoid, yields have become synthetically useful. The scope of the reaction was extended dramatically: cyclisation reactions could now be performed on acyclic, flexible systems, whilst retaining the selective C-H insertion observed with other catalysts in more rigid systems.

1.3.1 Cyclopentanone Synthesis

Initial reports of the efficacy of dirhodium tetraacetate for cyclopentanone synthesis were made by Taber[32] and Wenkert,[33] and the intramolecular reaction has been investigated thoroughly by Taber. Aliphatic diazo compounds underwent selective γ-C-H insertion reaction to give cyclopentanones in high yield (Scheme 11). Treatment
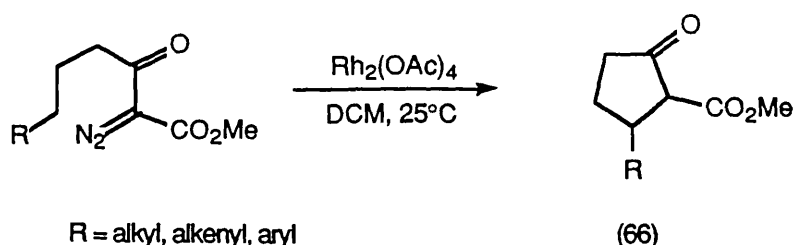
Scheme 11.   R = alkyl, alkenyl, aryl   (66)

of α-diazo-β-ketoesters, readily prepared from β-ketoesters by diazo transfer using tosyl azide, with dirhodium tetraacetate in dichloromethane at room temperature, generated the cyclopentanones (66) rapidly, in 48-77% yield.

Competition studies reported by Taber[34] have established the factors governing C-H insertion:

1. Electronic Effects

Taber synthesised diazo compounds with two competing sites for C-H insertion. The ratio of the two cyclopentanones, normalised for the number of equivalent C-H bonds, was used as a ratio of the rate of insertion into the two C-H bonds. The results are listed below, with examples:

- Methylene C-H more reactive than a methyl C-H

77% only product
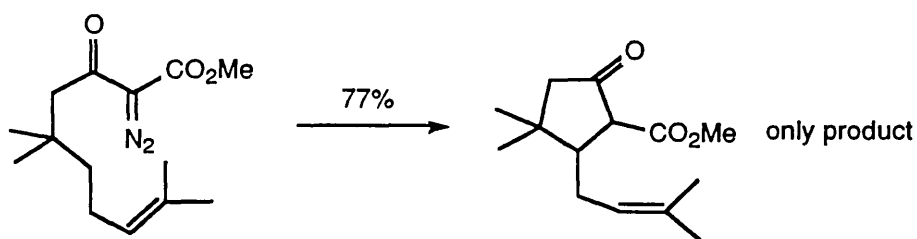
- Methine C-H more reactive than a methylene C-H

84%

4.6 : 1
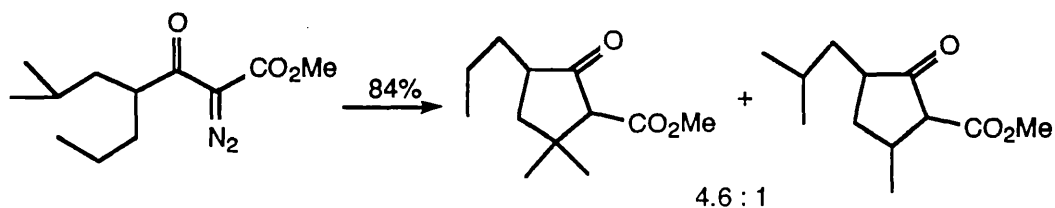
- Benzylic/ allylic C-H less reactive than a methylene C-H

R = Bn, CH:CH₂   75-88%   2.3-2.9 : 1
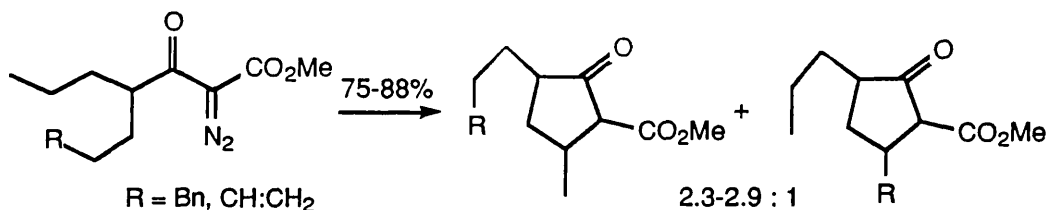
This trend in reactivity can be explained on inductive grounds. The rate of attack of the electrophilic carbenoid at the C-H bond is a function of electron density, therefore the inductively withdrawing benzyl group is expected to react more sluggishly. Stork has noted a similar result in the competitive cyclisation reactions of α-diazoketones.[35] It was found that the strongly electron withdrawing ester group had the effect of totally inhibiting insertion into C-H bonds α- and β- to the ester, resulting in a selective cyclopentanone synthesis (Scheme 12). Where a second site was not available for insertion, dimerisation became the major pathway.
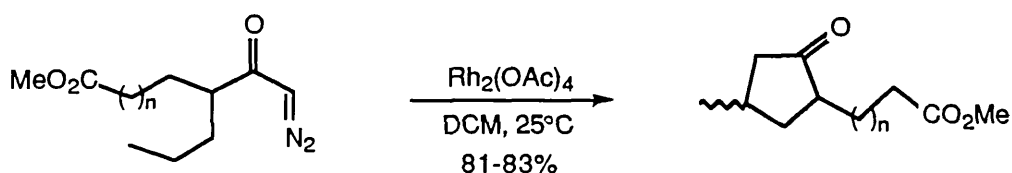
Scheme 12.   n = 1,2

- Aromatic C-H as reactive as a methylene C-H

1.2 : 1
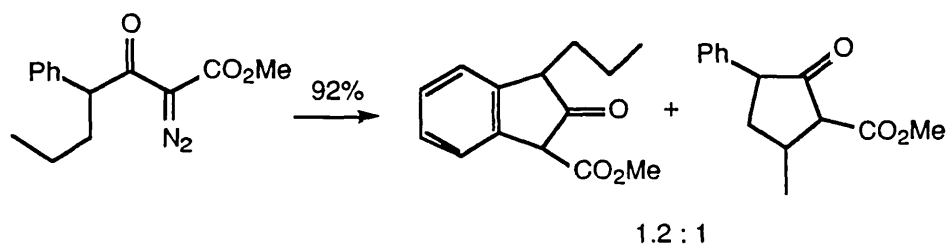
- Cyclopropanation as facile as methine C-H

1.1 : 1
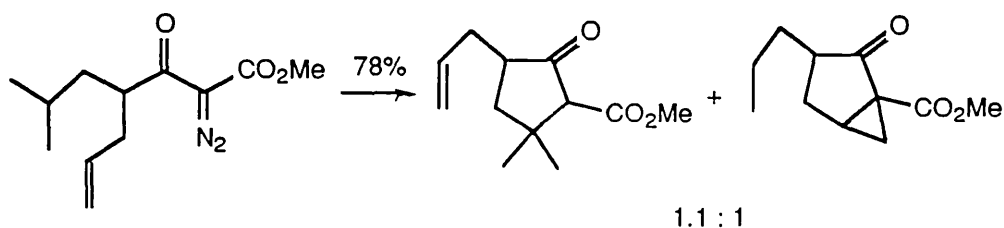
2. Steric Effects

The effect of a bulky group was investigated in the reaction of (67). Interaction between the metal complex and the large t-butyl group resulted in predominant

reaction at the less hindered site.

(67) →73%→ 3.4 : 1
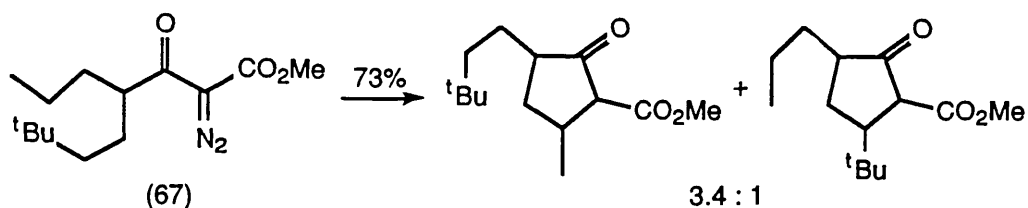
3. Diastereoselectivity

The C-H insertion reaction was found to show diastereoselectivity: the cyclisation of (68, R=H) gave the *cis* isomer as the only product. Similarly, cyclisation of (69) gave only the *cis* isomer of the cyclopentanone (70) (45%), together with a cyclobutanone (71), the product of β- C-H insertion (22%). Insertion into the cyclohexane ring of (68, R=Me) gave the *cis* isomer as the major product (3:1), but the ratio improved dramatically (15:1) with the sterically more demanding catalyst tetraphenylporphyrinrhodium (III) chloride. The *trans*-2,3 disubstituted cyclopentanone was formed as the only isomer in the cyclisation of (72).[36] Taber

(68) R = H, Me

(69)   (70)   (71)
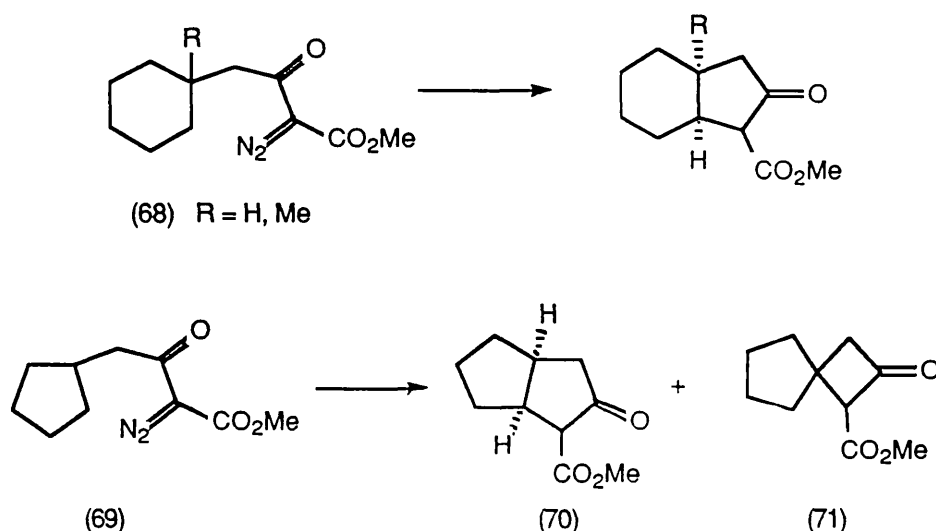
rationalised these observations by proposing a chair-like six membered transition state for the insertion reaction (Scheme 13). In this example, the phenyl and methyl groups both adopt equatorial positions, so that insertion occurs at one C-H bond only. Implicit in this model is the fact that the insertion reaction occurs with retention of

28

configuration.
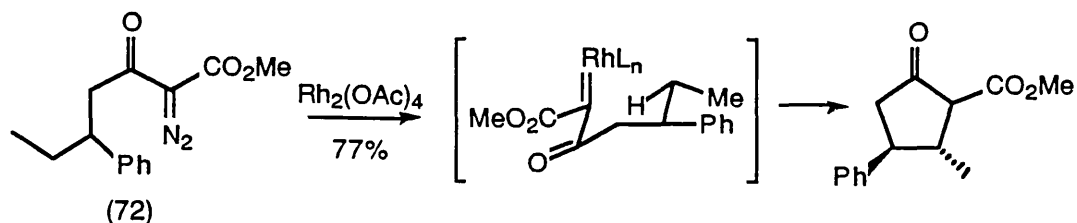
Scheme 13.

4. Enantioselective Synthesis

Taber approached this problem by preparing a chiral ester of the diazo-compound (Scheme 14). It was found that 2-naphthyl-3-hydroxybornane esters displayed good diastereoface-selectivity in the cyclisation reaction.[37] The chiral diazo esters underwent specific C-H insertion to give the diastereomeric cyclopentanones (73) and (74), in 6:1 - 12:1 ratio. The absolute configuration was confirmed. It was proposed that the transition state was a chair-like six membered ring, with the substituent sitting in an equatorial position. Chiral induction occurred by the γ-hydrogen approaching the prochiral carbenoid centre from the face least hindered by the naphthyl group of the ester. That is, the insertion reaction occurs significantly faster when the alkyl chain lies below the plane of the ketoester, as shown. The minor isomer (74) is formed by insertion on the more hindered face.
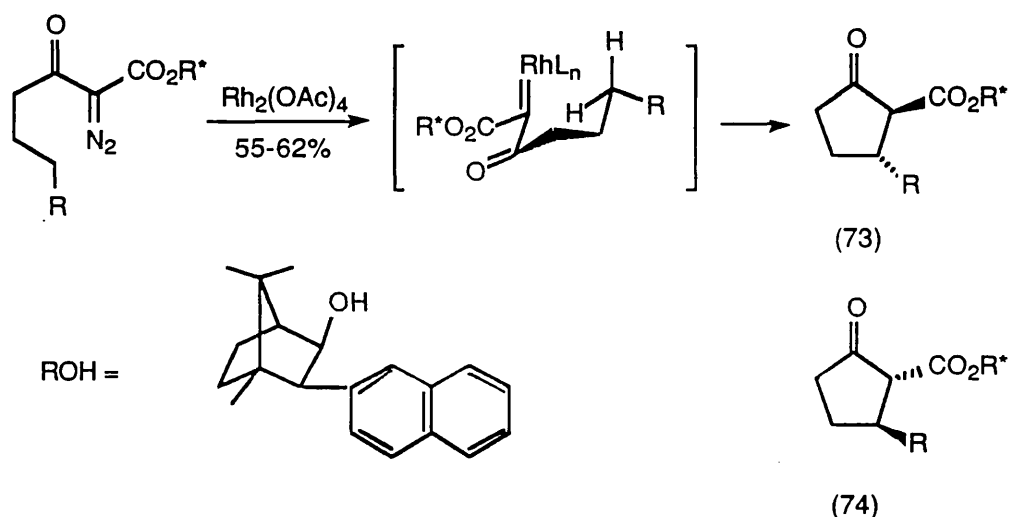
Scheme 14.   R = alkyl, alkenyl

29

Taber has applied the reaction to natural product synthesis: Vinyl cyclopentanone (73, R=vinyl) was used in the chiral synthesis of (+) estrone methyl ester. The reaction has also been applied to the synthesis of the highly functionalised sesquiterpene (rac)-pentalenolactone E methyl ester (77).[38] The diazoester (75), obtained in six steps from 4,4-dimethylcyclohexanone, was cyclised to give the tricycle (76) in 91% yield. This was converted into the natural product in two steps. In summary: cyclopentanone carboxylate esters have been synthesised in high yield from easily accessible starting materials. The regio- and stereo- selectivity of the reaction has been investigated in detail.
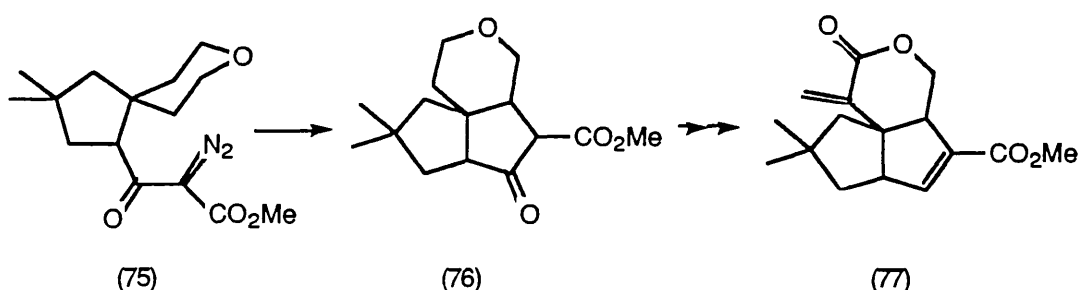
Although the majority of rhodium catalysed C-H insertion reactions have employed the α-diazo-β-ketoester unit, the reaction is tolerant of, groups other than carboxylate and protium. Work has recently appeared on studies of the cyclisation reactions of α–diazo-β-ketosulphones and α-diazo-β-keto-phosphonates and phosphine oxides.

The diazoketo-phosphonates and phosphine oxides (78, Z=PO(OEt)$_2$, POPh$_2$) were synthesised by standard diazo-transfer chemistry, and decomposed in boiling dichloromethane by dirhodium tetraacetate (Scheme 15),[39] to give cyclopentanones in good, but variable yield (33-70%). The yields are lower than the carbon esters, and this was explained on the grounds of the lower reactivity of the carbenoid, due to the lower electronegativity and the steric bulk of the phosphorus groups. The lower reactivity may also be due to poisoning of the catalyst by phosphorus. Indeed, an
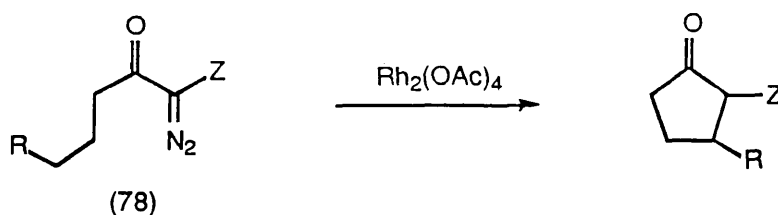
Scheme 15.   Z = PO(OEt)$_2$, POPh$_2$, SO$_2$Ph ; R = alkyl, alkenyl

observed side reaction is the Wolff rearrangement. α-Diazo-β-ketosulphones (78, Z=SO$_2$Ph) were prepared by diazo transfer using an azidinium salt. They underwent smooth cyclisation in dichloromethane, catalysed by dirhodium tetraacetate, to give cyclopentanones in very good yield (53-75%) (Scheme 15).[40] Competition between allylic C-H insertion and cyclopropanation was observed with 1-diazo-2-oxohept-6-enyl phenyl sulphone.

α-Diazo-β-ketosulphones (79) were synthesised by diazo transfer with tosyl azide, and cyclisation was carried out in boiling benzene with dirhodium tetraacetate catalysis, to give compounds of bicyclic structure (80) in poor yield (18-22%).[25] The observed regioselectivity is opposite to that expected, since the rate of insertion into a C-H bond adjacent to a carbonyl group is reported to be dramatically lower than an alkyl C-H.[35]

(79)   X = (CH$_2$)$_2$, CMe$_2$ (80)
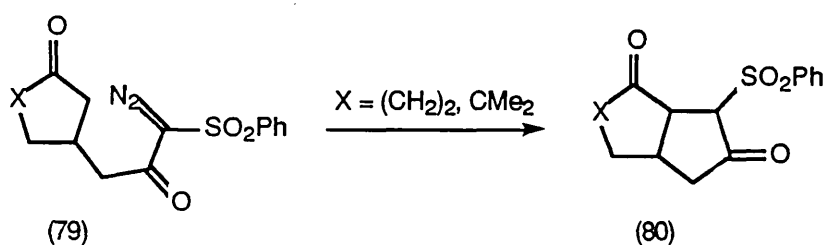
1.3.2   Synthesis of Four and Six Membered Rings

Rigid systems often display different regioselectivity in C-H insertion compared to the γ-C-H insertion observed in acyclic systems. Geometric or conformational constraints can lead to three (very unusual), four, or six (uncommon) membered rings; this effect has been found with copper and rhodium catalysts.

(81)   (82)
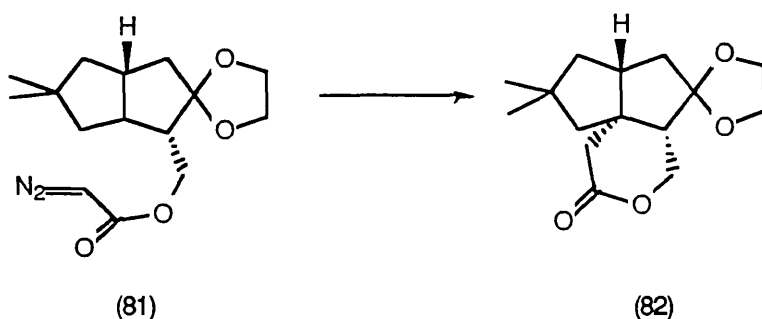
Dirhodium tetraacetate catalysed reaction of diazoalkane (81) in refluxing Freon TF

gave hexanolide (82), the product of δ-C-H insertion, in 43% yield.[41] No γ-C-H insertion was observed. The geometric constraint imposed by an amide bond has been used to advantage in the synthesis of four membered rings. Photochemically induced insertion into a C-H bond of an amide to give a β-lactam was reported by Corey in 1965. More recently, the α-diazoamide (83) was shown to give β-lactam (85) photolytically (55%) or by treatment with dirhodium tetraacetate in dichloromethane (75%),[42] and the reaction was also highly diastereoselective,[43] with the dirhodium tetraacetate mediated cyclisation of (84) giving (86) in 63% yield, together with 6.3% of an isomer in which the methyl group has the opposite configuration.

(83) R = H
(84) R = Me

(85) R = H
(86) R = Me
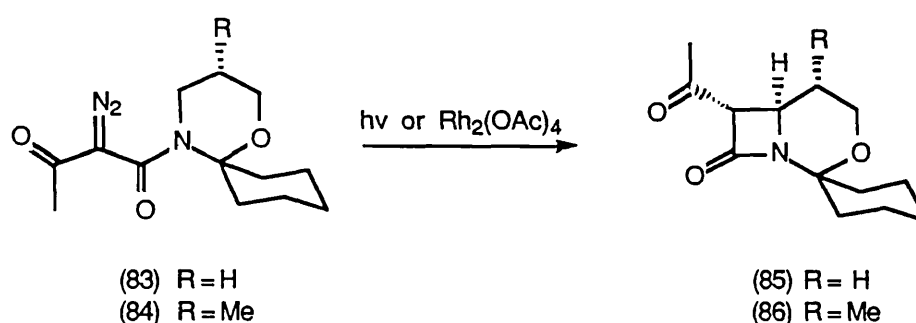
Doyle has investigated this reaction more closely, and concluded that the observed selectivity in favour of β- C-H insertion was due to the proximity of the β-hydrogen to the carbenoid complex, and not a function of electronic influence by the substituents.[44]

R = Ac   (87)
R = H   (89)

(88)

(90)

(91)
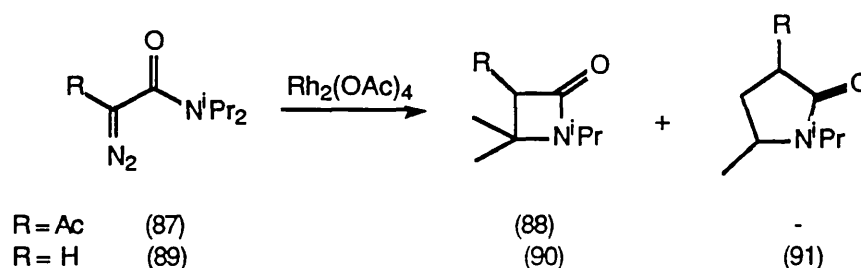
Several symmetrical diazoacetoacetamides, including diisopropylacetoacetamide (87) were treated with dirhodium tetraacetate in benzene at room temperature to give β–lactams, including (88), in 89-100% yield, the product of exclusive β-C-H insertion. Selectivity in the reaction of diisopropyl diazoacetamide (89) was poorer, affording a mixture of β-and γ-lactams (90) and (91) (4:1) in 95% combined yield. The ratio of β:γ insertion was found to be catalyst dependent. The sterically demanding

catalyst rhodium (II) 2-phenoxybenzoate favoured β C-H insertion (6:1), whereas rhodium (II) perfluorobutyrate showed lower selectivity (2:1).

The amide bond fixes the molecule into a conformation where the group held syn to the carbenoid rotates about the CH-N bond, away from the catalytic centre to reduce steric interaction. This places the β- proton proximal to the active centre, and favoured for insertion, and the electronic influence of the R group becomes a secondary factor in the reaction (Figure 1). Indeed, cyclisation of benzyl ethyl diazoacetoacetamide gave a mixture of three products: insertion into the β C-H bonds of the ethyl and benzyl groups was equally likely, but the major product was γ C-H insertion into the methyl group (55%), and in this case the distribution of products relies on rotation about the amide and CH-N bonds.
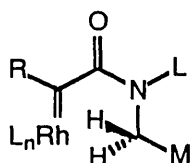
Figure 1.   R = Ac, H ; L, M = allkyl, or aryl, and L is sterically more demanding than CH₂M

Doyle studied the cyclisation of a series of benzyl t-butyldiazoacetamides (Scheme 16): treatment of diazoacetoacetamides (92) with dirhodium tetraacetate gave β-lactams (93) as the exclusive products in 90-98% yield. Doyle rationalised
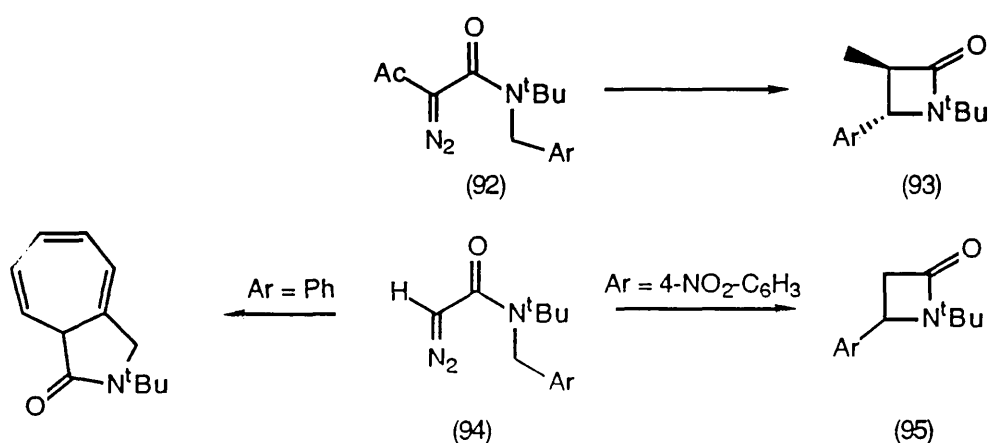
Scheme 16.   Ar = 4-NO₂-C₆H₄, 3-Br-C₆H₄, 3-MeO-C₆H₄, 3,4-(MeO)-C₆H₃

this by postulating a mechanism in which the amide bond was locked into a conformation where the larger (t-Bu) group is oriented towards the carbonyl group, away from the bulky carbenoid (Figure 1). For diazoacetamide (94) (Ar=Ph), the exclusive product is of aromatic addition, but in contrast, the only product observed in the treatment of diazoacetamide (94) (Ar=4-$NO_2C_6H_4$) with dirhodium tetraacetate is that of β C-H insertion (95).

Doyle notes that the t-butyl group is necessary for specific benzyl C-H insertion.

1.4 Conclusions

The intramolecular reactions of diazo compounds reported over the last decade have increasingly used rhodium salts as the catalytic agents, especially dirhodium tetraacetate, in preference to copper catalysts, because of the higher yields and milder conditions offered by this catalyst.

The synthesis of cyclopentanones from β–keto diazoesters by inserion into a γ-C-H bond has been explored extensively, and also exploited synthetically, by Taber and co-workers. The dirhodium tetraacetate catalysed synthesis is the first general route to cyclopentanones utilising carbenes, and is also high yielding and highly specific.

The electrophilic rhodium carbenoids generated in the decomposition of stabilised diazo compounds are also susceptible to reaction with nucleophiles, and this has led to the synthesis of five membered oxygen, nitrogen, and sulphur heterocycles by 'insertion' of the carbene into the X-H bond; the approach has also been applied to the synthesis of six and seven membered oxygen and nitrogen containing rings. The mechanism for this reaction, however, probably involves attack by the nucleophile at the carbenoid, unlike the C-H bond insertion. Overall, this method is a selective, neutral, and mild method for the synthesis of heterocycles.

CHAPTER TWO

Intramolecular Reactions of Rhodium Carbenoids with Oxygen, Nitrogen, and Sulphur Nucleophiles: Synthesis of Heterocycles

2.1 Introduction

2.1.1 Synthesis of Seven and Eight Membered Heterocycles

Traditionally, the synthesis of medium ring heterocycles has been regarded as difficult, since the enthalpic factors which, on the whole, favour cyclisation, are finely balanced by the entropy of the system, which prefers the 'freedom' of acyclic compounds.

This fundamental obstacle in the synthesis of seven, eight, and larger membered rings contrasts sharply with the wealth of facile, high yielding methods available for the synthesis of five and six membered heterocyclic rings, which possess significantly lower free energy relative to their acyclic precursors.

Many natural products contain seven and eight membered cyclic ethers, and this has provided an impetus for the development of new methods for the synthesis of oxygen heterocycles.[45]

Approaches to the synthesis of seven and eight membered rings which involve intramolecular cyclisation often suffer from low yields and competing reactions, however. An alternative strategy, which involves a ring expansion reaction, has not been widely exploited, even though it is often more selective.

A summary of the older[46] and newer methods available for the construction of seven and eight membered rings is presented below. The summary will be divided into two sections, according the method chosen to prepare the ring.

Cyclisations

There have been four general modes of cyclisation developed (Scheme 17), and two of these use the heteroatom (X) as the nucleophilic cyclisation agent (97, 98). In (96), however, the heteroatom is often placed adjacent to the Y group, to increase regiocontrol in the reaction, by directing cyclisation. Although the reaction types listed above are ionic, analogous radical cyclisations are possble, however, they are relatively rare.

The Dieckmann condensation is the most common reaction of type (96), and a pertinent example is seen in the synthesis of oxepane (100)[47] (Scheme 18), a compound which

we have also prepared using a dirhodium tetraacetate mediated cyclisation (Table 3).

(96) (97) (98) (99)
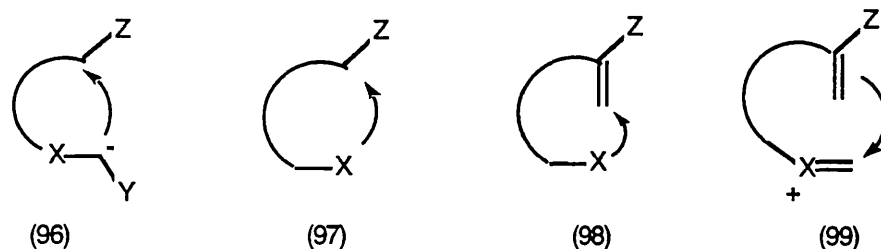
Scheme 17.   X= O, N, S

Unfortunately, the reaction requires strongly basic conditions, and often gives rise to isomeric and dimeric products, especially in the synthesis of eight membered rings.

(100)
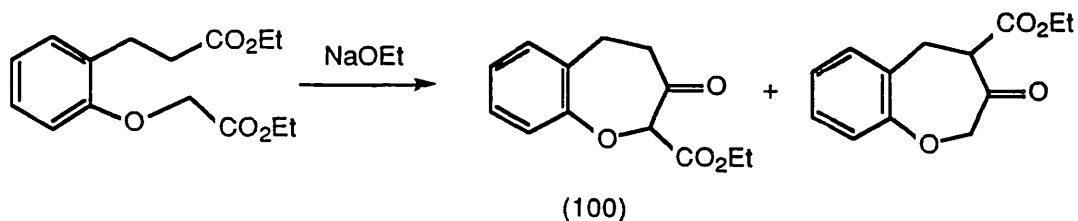
Scheme 18.

Included in this cyclisation mode are the intramolecular acylation and alkylation reactions of unsymmetrical sulphides, ethers, and amines (Scheme 19).[48]
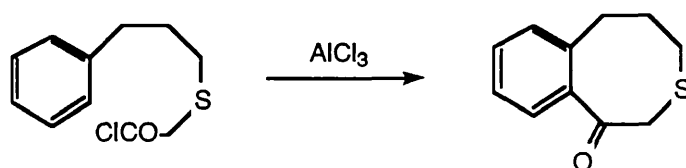
Scheme 19.

The most general and widely used mode of cyclisation is type (97). Indeed, the acid catalysed cyclodehydration of α,ω-diols, and the reaction of α,ω dibromides with sodium sulphide or with primary amines gives cyclic ethers, sulphides, and amines, respectively.[46] The reaction conditions are often harsh, and the yields low, although milder methods hve recently been developed, especially for the synthesis of cyclic ethers.   For example, treatment of dithioacetal (101) (Z= SEt) with

N–chlorosuccinimide, silver nitrate, and 2,6-lutidine at room temperature gave the oxecane (102) in 95% yield, by capture of an intermediate sulphonium species by the hydroxyl group.[49]

(101)   Z= SEt   (102)
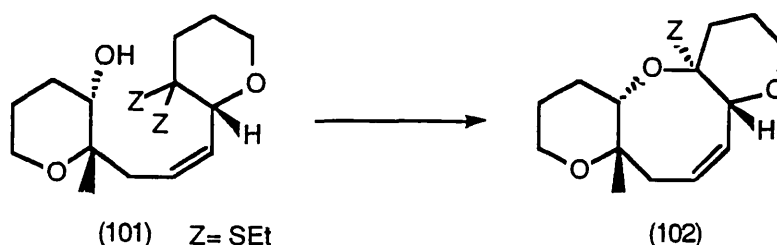
The intramolecular reaction of alcohols with epoxides has also been studied in the synthesis of oxepanes. Regiospecific reaction at the least hindered epoxide carbon atom of (103) catalysed by tin (IV) chloride gave the oxepane (104) as the major product (79%), together with a small amount of a pyran resulting from attack by the hydroxyl group at the more hindered epoxide carbon (Scheme 20).[50] An analogous reaction, which involves the intramolecular reaction of seleniranium ions, generated from the reaction of alkenes with selenating agents, with oxygen nucleophiles, has been used to synthesise oxecanes.[51] The dirhodium tetraacetate mediated cyclisation of diazo-alcohols, and -amines to cyclic ethers and amines (Section 1.2), respectively, conforms with the type (97) approach.

(103)   (104)
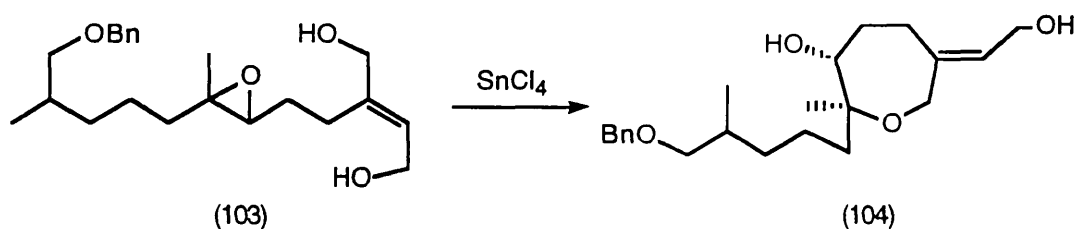
Scheme 20.

The third mode of reaction to be discussed is type (98), and although it is similar to type (97) it has received little attention because of the strained nature of the transition state. The cyclisation onto unactivated alkenes can be achieved with the use of palladium catalysts. Thus, *N*-allyl-*N'*-(3-iodo-4-oxopentyl)toluene-4-sulphonamide gave a mixture of a piperidine and an azepine on treatment with Pd(PPh$_3$)$_4$.[52]

Schreiber and co-workers have recently reported the reaction of alkyne lithiums with α-disubstituted δ-lactones to give oxecanes.[53] This is achieved by ring opening the lactone with the alkyne anion, followed by endocyclic conjugate addition of the lithium alkoxide to the acetylenic ketone (Scheme 21).
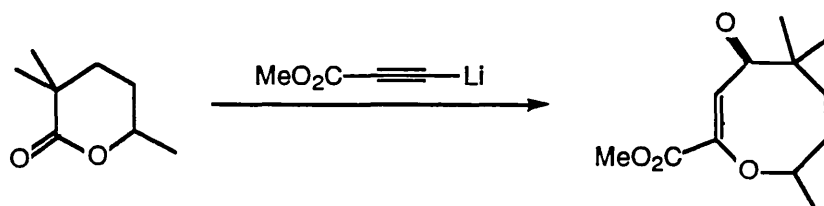
Scheme 21.

Finally, the most recently developed strategy for the cyclisation (99) involves the reaction of enol ethers and vinyl silanes: Kocienski and co-workers have exploited the intramolecular Mukaiyama directed-aldol condensation between enol ethers and cyclic acetals.[54] The reaction was applied to the synthesis of tetrahydropyran-4-ones, oxepan-4-ones, and oxecan-4-ones, although the cleavage of the acetal was often not regiospecific, and this led to a mixture of cyclic ethers of different ring size. Thus, treatment of dioxane (105) with titanium tetrachloride in dichloromethane at -78°C gave (106) as a mixture of diastereoisomers in 43% yield (Scheme 22).

(105)   (106)
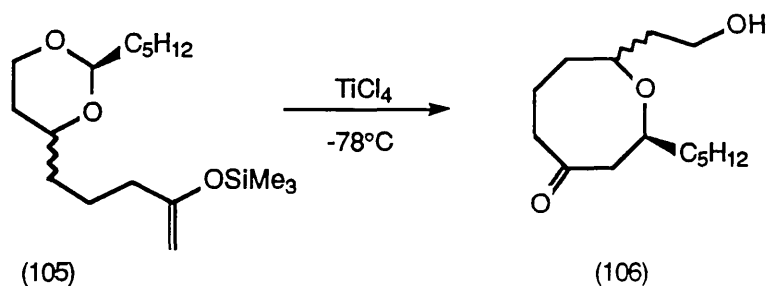
Scheme 22.

Overman and co-workers have reported a general approach to the synthesis of six, seven, eight, and nine membered cyclic ethers, and six and seven membered cyclic amines, that is based on the reaction of vinyl silanes with *in situ* generated oxonium and iminium, respectively. Oxepanes were prepared in very good yield, and oxecanes were prepared in moderate yield. For example, (108) was prepared in 37% yield, as

the only isomer, by treating vinyl silane (107) with tin (IV) chloride in dichloromethane at room temperature, followed by selective desilylation with tetrabutylammonium fluoride[55] (Scheme 23). The reaction proceeds by tin (IV) chloride mediated oxonium ion formation, then loss of ethanol from the mixed acetal, followed by cyclisation to give an α-silyl carbanion, which rapidly loses a proton to give (108).
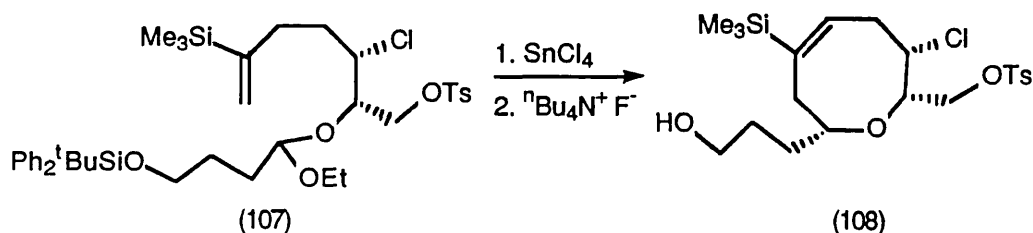
Scheme 23.

The reaction was extended to azepines;[56] treatment of amine (109) with formaldehyde, catalysed by camphorsulphonic acid, gave the azepine (110) together with the desilylated amine from (109) in a combined yield of 42%.
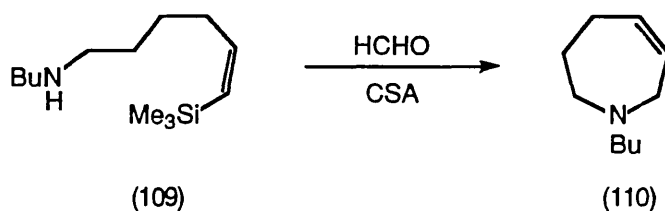
Ring Expansion

The second method for the synthesis of seven and eight membered rings employs a ring expansion step to generate the product, and this section can be sub-divided into rearrangements and migrations.

Rearrangements: the increase in ring size during the ring expansion is dependent upon the nature of the rearrangement. Thus, the thermal [2+2]-cycloaddition of dimethyl acetylenedicarboxylate and dihydropyran gives a cyclobutene, which could be induced to undergo electrocyclic ring opening, either thermally, or by treatment with

a Lewis acid, to give the oxecane[57] (111) (Scheme 24).

(111)
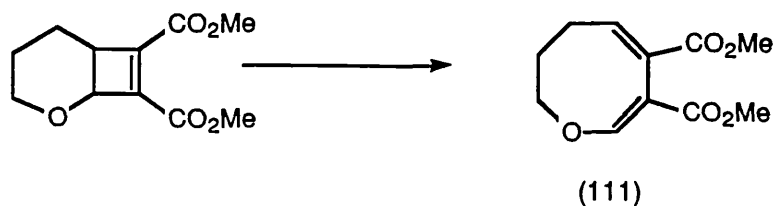
Scheme 24.

Holmes and co-workers have reported the synthesis of an oxecan-2-one from an ester enolate by a Claisen rearrangement.[58] The ester enolate was prepared *in situ* from a dioxane by elimination of phenylselenic acid (Scheme 25).
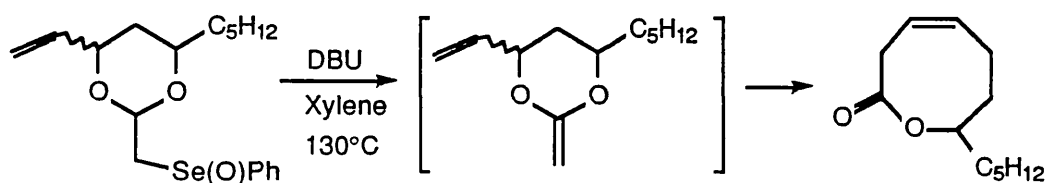
Scheme 25.

The above transformations have not been widely used in heterocyclic synthesis, but a more general approach to the synthesis of seven ring heterocycles involves the [3,3]-rearrangement of (112) to (113).

(112)   (113)

X = CH$_2$, Y = S, O   or   X = O , NH , Y = CH$_2$
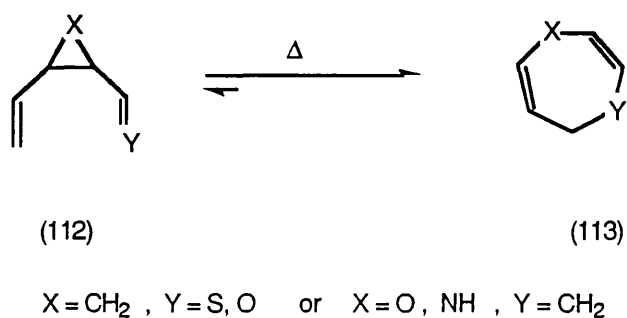
The rearrangement of allylsulphonium ylides has been widely explored,[59] and the reaction leads to cyclic sulphides in very good yield, although the reaction is most useful for large rings (Section 4.1.3).

Migrations: the Baeyer-Villiger reaction has been used to prepare oxecan-2-ones from cycloheptanones.[60] Thus, the migration of a group to an electron deficient centre expands the ring by one atom. The Beckmann reaction has also been used to convert cycloheptanone oximes into eight membered lactam rings.[46]

Finally, the aldol type addition of ethyl lithiodiazoacetate to ketone (114), followed by the acid catalysed loss of nitrogen and concomitant acid catalysed alkyl shift, gave the benzothiepane[61] (115) (Scheme 26). Other carbenium ion mediated migrations have been observed.[46]

1. LiC(N₂)CO₂Et
2. H⁺

(114)   (115)
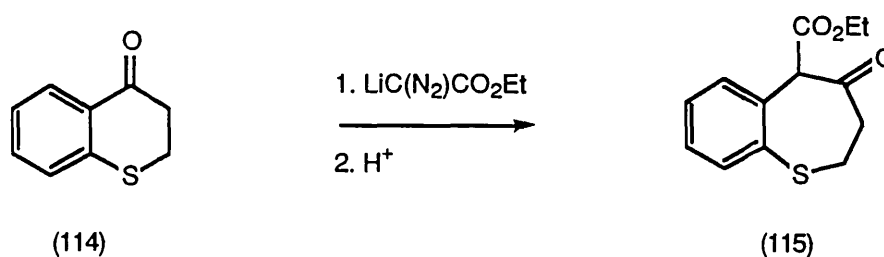
Scheme 26.

To summarise, recently there has been a great deal of effort directed towards the synthesis of oxepanes and oxecanes, although, there are relatively few mild methods available for the synthesis of seven and eight membered cyclic sulphides and amines.

2.1.2 Synthesis of Functionalised Diazo Compounds

A recent development in the synthesis of five and six membered heterocycles has focussed on the selective intramolecular insertion reaction of rhodium carbenoids, generated under mild and neutral conditions from α-diazo-β-ketoesters, into O-H, S–H, and N-H bonds. Extension of this methodology to the synthesis of larger rings has received little attention, although work by Moody and Heslin[9] has shown that seven and eight membered rings can be prepared.

Previous workers have synthesised α-diazo-β-ketoesters with pendant nucleophiles (11), the precursors of the heterocycles, in three steps (Scheme 27), by first introducing the protected nucleophilic group in an alkylation step, and then introducing the diazo group using the diazo transfer reaction. However, the strategy is inefficient because it requires the nucleophilic group to be protected during the

reaction sequence, and the diazo group to be introduced in a separate step.
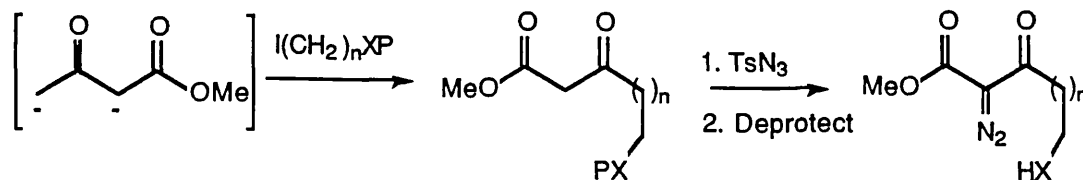
Scheme 27.   X = O, S, N R   P = protecting group

The aim of the project was therefore twofold: firstly, to develop a shorter synthesis of α-diazo-β-ketoesters with pendant functionality, and secondly, to investigate the scope of the dirhodium tetraacetate mediated cyclisation of these diazo compounds as a general route to seven and eight membered heterocylic rings.

Clearly, to develop a shorter route to the diazo compounds would require that the two deficiencies mentioned above be eliminated, and this would necessitate using a readily available diazo compound, in the chain extension step, together with an unprotected ω–functionalised alkyl halide.

The remainder of this section will discuss the possible approaches to solve this problem, that is, functionalisation of a simple diazo compound.

There are two logical approaches to the synthesis of α-diazo-β-ketoesters (116) (Scheme 28), and these involve disconnection at the bonds (a) or (b), to give two recognisable fragments that could be used in a short synthesis. Disconnection (a) is analogous to the approach employed in previous syntheses.
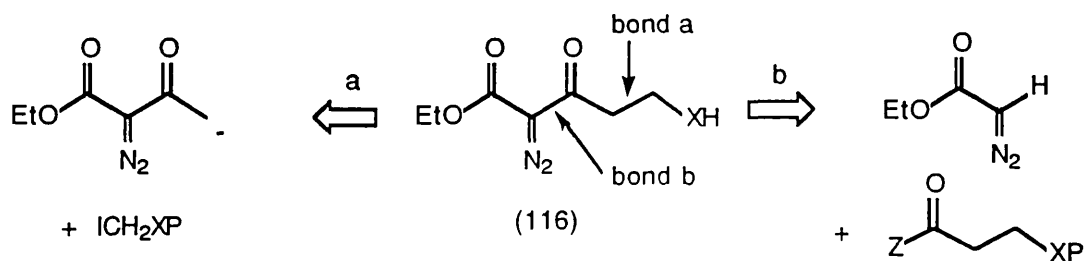
Scheme 28.   X = O, S, N   P = protecting group

Disconnection (a)

The synthesis of (116) would involve alkylation of the enolate of an α-diazo-β–ketoester. Although benzyl α-diazoacetoacetate was readily metallated with lithium hexamethyldisilazide at-78°C, the metallated compound (117, M=Li) only gave a low

43

yield (12%) of an adduct with an acetoxy β-lactam (Scheme 29.).[62] However, the silyl enol ether (117, M=*t*-BuMe$_2$Si) was alkylated by a similar acetoxy β-lactam in the presence of trimethylsilyl trifluoromethanesulphonate, in 85% yield (Scheme 29).[63]

(117)

R = CH(Me)OSi^{t}BuMe$_2$, R' = 4-NO$_2$-C$_6$H$_5$, R" = Me, M = Si^{t}BuMe$_2$
R = Et, R' = Bn, R" = H, M = Li
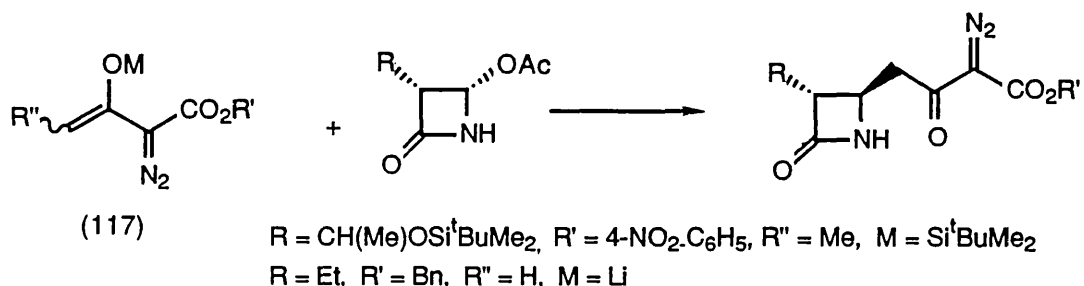
Scheme 29.

Disconnection (b)

The disconnection (b) appears more promising, since it gives a commercially available diazo compound, ethyl diazoacetate (EDA). The synthesis would therefore require acylation or an aldol type reaction of EDA, with an acid chloride (Z=Cl) or aldehyde (Z=H), respectively. The aldol reaction of EDA with an aldehyde forms an alcohol, however, and this would require oxidation to give the required compound (Scheme 30). Unfortunately, the ω-functionalised acid chlorides required for the acylation of EDA cannot be isolated, because they spontaneously cyclise to lactones, thiolactones, or lactams, unless the nucleophilic group is protected. These heterocycles are also electrophiles, but are significantly less reactive than the acid chlorides. However, they do have the advantage of liberating the nucleophilic group as an integral part of the acylation reaction, to give (116), obviating the use of protecting groups for the nucleophiles in the reaction.
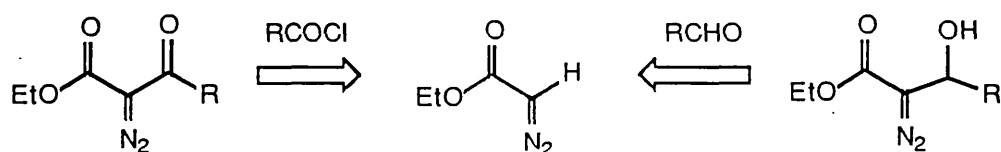
Scheme 30.

The reaction of EDA with lactones, and other cyclic electrophiles would satisfy the criteria for a short synthesis of α-diazo-β-ketoesters, because all the relevant functionality is introduced in one step (Scheme 31). Simple lactones, lactams, cyclic

anhydrides, and thiolactones are also commercially available, and the methodology to prepare more complex examples has been developed.
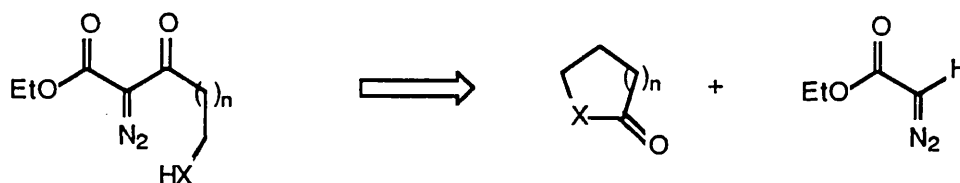
Scheme 31.   X= O, S, N

So far we have discussed the possible alternatives for the synthesis of (116) using disconnection (b), but is EDA a good nucleophile? Diazomethane is readily acylated by acid chlorides, the first step of the Arndt-Eistert reaction, and this demonstrates the ability of diazo compounds to act as carbon nucleophiles, by virtue of the charge separated canonical form (117) in which the negative charge resides on the carbon atom. The electron withdrawing ester group on EDA, however, reduces the reactivity of the diazo compound by delocalising the negative charge onto the carbonyl group.

(117)   (118)

E = CO₂Et
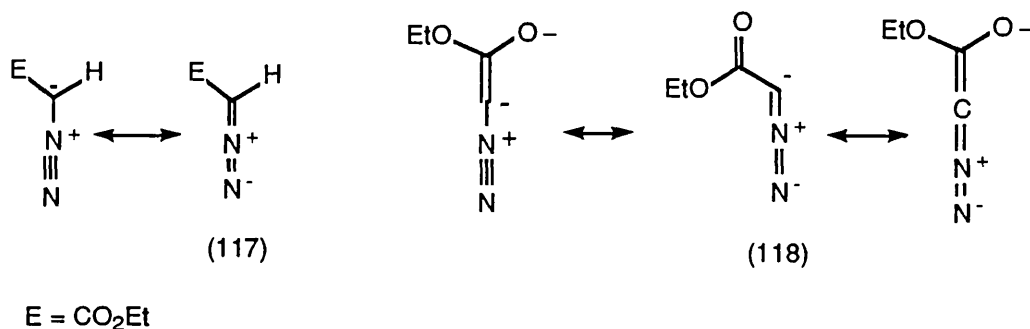
Indeed, diazomethane reacts readily, albeit reversibly, with aldehydes and ketones, but very slowly with acid anhydrides, and very rarely with unactivated esters, whereas EDA is a poor nucleophile and will only react with highly electrophilic carbonyl groups,[4] such as α-dicarbonyl compounds and small ring ketones, although the reaction often takes days or weeks to reach completion, r an equilibrium (Scheme 32).

The aldol adducts of EDA with aldehydes and ketones are stable compared to the diazomethane adducts, which rapidly lose nitrogen, initiating a molecular rearrangement. The aldol reactions of EDA often require a weak base as a catalyst, for

example, diethylamine (Scheme 32), which probably generates a small amount of the anion of EDA (118), and this is far more nucleophilic.
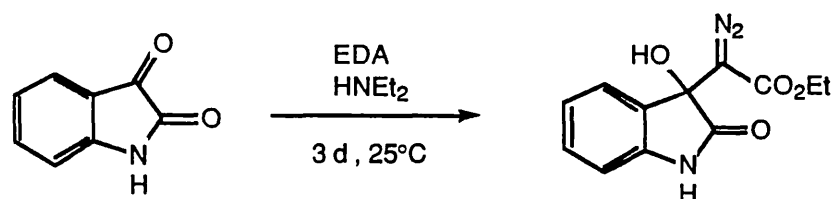
Scheme 32.   EDA = ethyl diazoacetate

Wenkert and co-workers[64] have extended this reaction to acyclic, and some aromatic, aldehydes by using ethanolic potassium hydroxide to catalyse the reaction (Scheme 33). The reaction was found to be reversible, and the yields of the adducts were reduced significantly when the R group was bulky, and the aryl group electron donating.
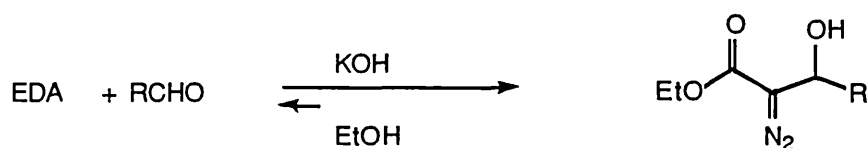
Scheme 33.   R = methyl, hexyl, iso-propyl, cyclohexyl, phenyl, 4-nitrophenyl

The potassium salt of (118) could also be generated by the potassium cyanide mediated desilylation or destannylation of (119),[65] and this reacted with primary alkyl, and some aryl aldehydes, to give β-siloxy or β-stannyloxy α-diazocompounds.
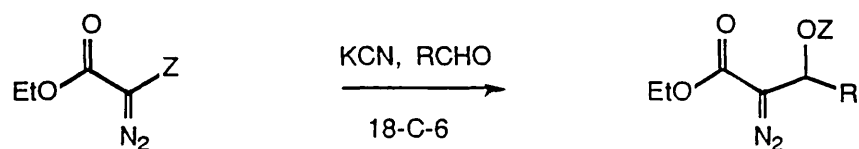
(119)   Z = SiMe₃, SnMe₃   R = primary alkyl, or aryl

In neither of the above examples could adducts with ketones be formed, because the reaction equilibrium strongly favoured the starting materials. However, treatment of a solution of EDA, in THF at low temperature, with either n-butyl lithium or LDA generated a solution of ethyl lithiodiazoacetate, and this α-metallated derivative of

EDA, although only stable below -50°C, was sufficiently nucleophilic to react at −78°C with alkyl halides, aryl acid chlorides, aryl aldehydes, and ketones to give alkylated or acylated diazoesters.[4,66] Superior yields were recorded for the aldol reaction when LDA was added to a mixture of EDA and the aldehyde (or ketone) at -78°C. This shows that the α-diazo proton of EDA has greater kinetic acidity than the α-protons of the ketones; presumably the diazo group is a net activating group, because of the high degree of charge delocalisation over the heteroatoms (118), even though contribution from the canonical form (117) increases the negative charge at the deprotonation site. The reaction of EDA with poor electrophiles, such as esters, appears very rare, and reaction of ethyl lithiodiazoacetate with esters has not been reported, however, we decided to investigate the reaction of the diazo anion with lactones and analogous compounds as a one step route to the α-diazo-β-ketoesters required for the cyclisation studies.

2.2   Reactions of Ethyl Lithiodiazoacetate with Acylating Agents

This section reports the results of the reactions of ethyl lithiodiazoacetate (ELDA) with lactones, cyclic carbonates, thiolactones, lactams, and cyclic acid anhydrides.

2.2.1   Lactones and Cyclic Carbonates

The reaction of ethyl lithiodiazoacetate (ELDA) in THF at low temperature with a variety of lactones and cyclic carbonates (Table 1) gave acylated diazoesters resulting from the ring-opening reaction, in variable yield (Scheme 34). Thus, ELDA is sufficiently reactive to displace an alkoxide group, in an irreversible manner.
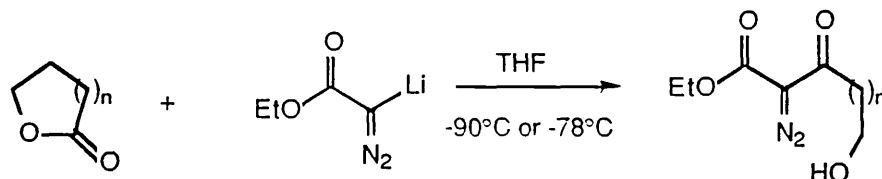
Scheme 34.

The ring opening reaction could be accomplished either by adding the lactone to a

solution of ELDA, or by generating ELDA in the presence of the lactone. EDA was metallated by adding it to a solution of LDA in THF at -90°C, and to the resulting orange solution of the anion (which was stable at this temperature), a lactone was added, and the reaction mixture was then warmed to -75°C. After two to four hours, acetic acid was added to the solution, which was then subjected to an aqueous work-up, and the residue purified by chromatography on silica gel, to give ω-hydroxy α-diazo-β—ketoesters, as pale yellow oils. Alternatively, LDA was added to a solution of EDA and the lactone in THF at -75°C, to generate the anion *in situ*, and the solution was maintained at this temperature for 2-4 hours, before work-up and purification to give the product.

The two methods are complementary, since in the former (the *normal* addition mode), the lactone is always present in far lower concentration than the anion, whereas in the latter (the *inverse* addition mode), the anion is often in low concentration, because it is consumed as it is formed, and thus the two methods are suited to different types of lactones. The inverse addition mode was effective for most of the lactones investigated, with the notable exception of γ-lactones (Table1, entries 1-2), where the yield of the adducts was ~20%, compared with 47-51% for the normal addition mode. The poorer yields are probably the result of the relatively high acidity of the protons α-to the carbonyl group compared to EDA, and therefore the presence of LDA emphasises this fact.

Six, seven and eight membered alicyclic lactones, without α,β-unsaturation were very good substrates for the reaction (Table 1, entries 3-4, 9-11), and the products were isolated in 58-99% yield, and the lactones often react well under both sets of conditions.

Five and six membered cyclic carbonates were also ring-opened: 1,3 dioxan-2-one gave the diazo compound (124) in 41% yield, using the inverse addition mode, however, when the normal addition mode was used, the diazoalkoxide formed in the reaction mixture reacted intermolecularly, at the ethyl ester of another molecule, displacing ethanol, to form a dimeric compound. The product and the dimer could not be separated by chromatography, and the dimer accounted for ~15% of the material. 4-Methyl-1,3-dioxolan-2-one reacted with ELDA, to give a mixture of inseparable regioisomeric diazoalcohols (Scheme 35).

α,β-Unsaturated δ-lactones were poor substrates: 5,6-dihydropyran-2-one gave a low yield of the adduct (125), and coumarin gave no adduct at all; this effect is

48

probably due to the lower electrophilicity of the carbonyl group in the unsaturated compounds.
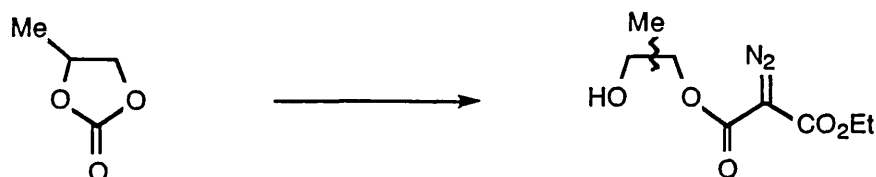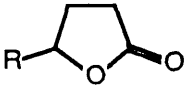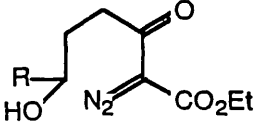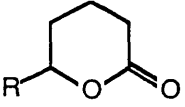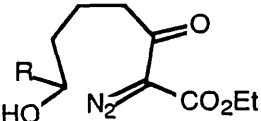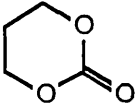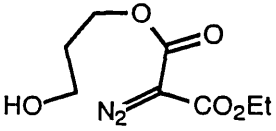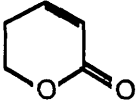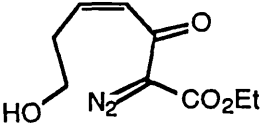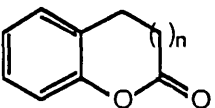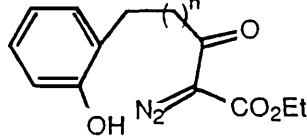
Scheme 35.

The base initiated polymerisation of lactones is well known, however, the success of the reaction with ELDA relies on the anion acting solely as a nucleophile, and rapidly reacting with the lactones at the carbonyl group. In the inverse addition mode, LDA is added to a solution of the lactone, so favouring the polymerisation process, which is suppressed only if the ELDA is rapidly formed and then quickly consumed by the lactone. Although the lower yields in the reaction of seven and eight membered lactones reflect a greater tendency to polymerise, this could be suppressed, in the inverse mode, by adding the LDA to the reaction mixture at -90°C, and then allowing the reaction mixture to warm to -75°C. Using this modification, the yield of (122) was increased from 76% to 81%.

If the lactone was a poorer electrophile, or possessed acidic α-protons, then base mediated polymerisation became a problem. An obvious solution was to use the normal addition mode, where the lactone concentration is kept low, and this was successful for γ-lactones. An alternative course of action was to increase the concentration of the anion. This was applied to the synthesis of (123) from undecanoic acid δ-lactone, which reacts far more sluggishly than δ-valerolactone, and the yield increased from 47% when 1.1 equivalents of EDA was used, to 88% with 1.3 equivalents, and finally to 99% with 1.5 equivalents. In the reaction of benzo-fused lactones (Table 1, entries 7-8, 12), the yield of the diazo alcohols was increased significantly when 1.5 equivalents of EDA was used instead of the usual 1.1 equivalents. The sluggish reaction of the benzo-fused and dibenzo-fused lactones reflects the bulky nature of the aromatic group and the lower reactivity of the carbonyl group, which outweighs the enhanced leaving group ability of the phenoxide relative to the alkoxide group. Unfortunately, the moderate rate of decomposition of ELDA at -75°C meant that 1.5 equivalents of EDA was required to effect completion of the reaction.

Table 1. Reaction of Ethyl Lithiodiazoacetate with Lactones and Cyclic Carbonates

Entry	Lactone	Diazo Alcohol	Addition[a]	Yield (%)
1	R=H	(120)	N	47
2	R=Me	(121)	N	51
3	R=H	(122)	I (N)	81 (32)
4	R=C_6H_{13}	(123)	I (N)	99 (95)
5		(124)	N	41
6		(125)	I	6
7	n=1	(126)	I	80
8	n=2[c]	(127)	I	56

9   (128)   I   58

10   n=1   (129)   I (N)   63 (65)

11   n=2[c]   (130)   I   65

12   (132)[c]   (131)   I   8[d]
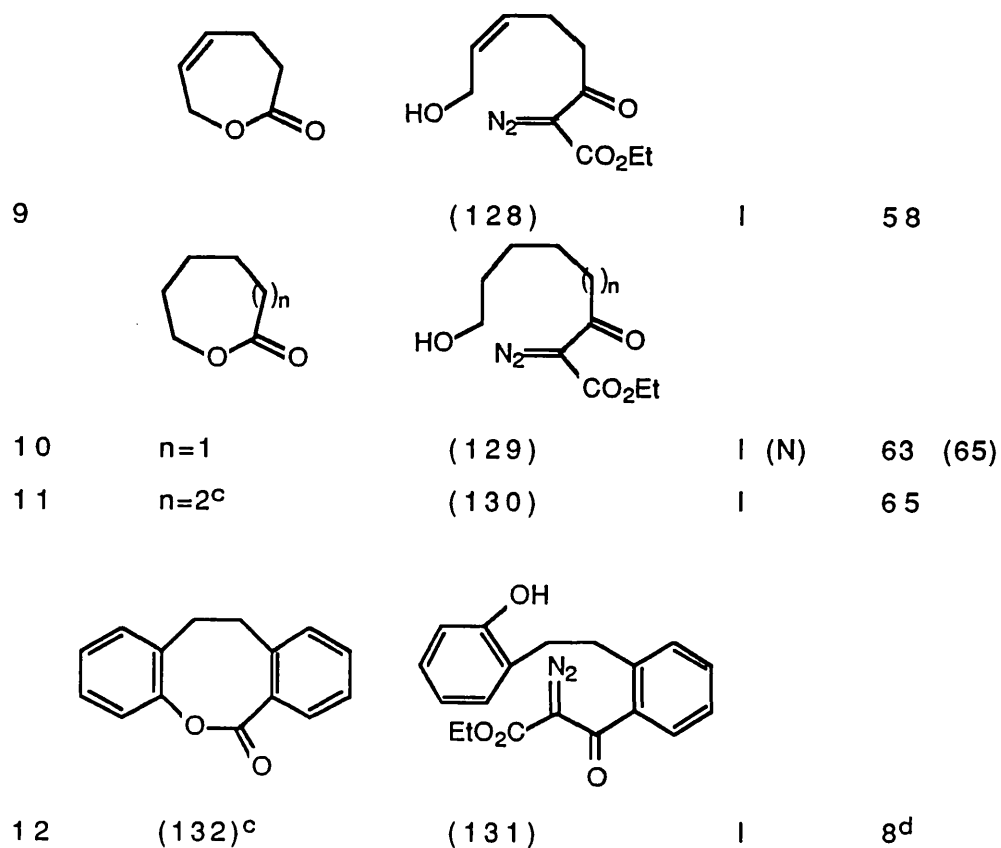
a, N= normal addition mode, I= inverse addition mode; b, prepared by the literature procedure, see Chapter Six; c, prepared from the corresponding ketones with m-CPBA, see Chapter Six; d, starting material recovered.

As a possible solution to the decomposition of ELDA at -75°C, LDA was added to the reaction mixture over 0.5-1 hour, to keep the anion in low concentration. However, this resulted in the isolation of a yellow oil, in addition to the product, in ~10% yield. The structure of the molecule was determined as diethyl diazomalonate (133), and confirmed by preparing the authentic material from diethyl malonate using the diazo transfer reaction.[67] The compound probably arises from the reaction of ELDA at the

(133)

Scheme 36.

51
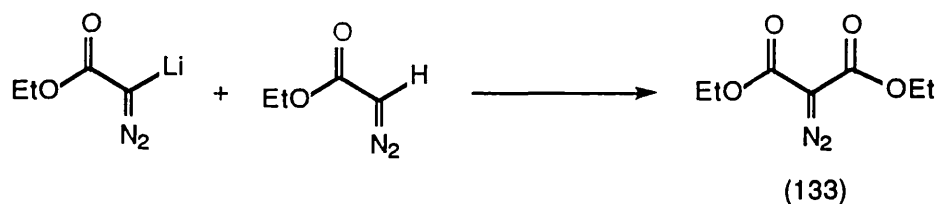
carbonyl group of EDA, resulting in displacement of diazomethyl lithium, and not the ethoxide anion (Scheme 36). The compound resulting from displacement of the ethoxide group was not isolated, presumably it is unstable.

Attempts to extend the reaction to β-lactones (β-butyrolactone and diketene) failed, as did the reaction with the highly oxygenated tetramethyl 1,5-gluconolactone. The reaction was also inhibited by the presence of a quaternary carbon adjacent to the carbonyl group, and (134) was recovered from the reaction mixture in 56% yield. Also, the α-carbonyl protons of isochroman-3-one (135) were sufficiently acidic for LDA to form the enolate of the lactone in preference to deprotonating EDA, and (135) was recovered in 66% yield from the reaction mixture. The reaction of δ–valerolactone with the Grignard of EDA[66] was also unsuccessful.

The reaction of ELDA with alicyclic lactones, cyclic carbonates, and certain benzo-fused lactones therefore provides an efficient route to ω-hydroxy α-diazo-β–ketoesters in one step.
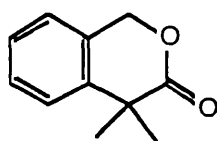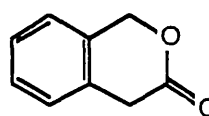
(134)   (135)

2.2.2 Thiolactones

The reaction of ELDA with γ- and δ-thiolactones to give diazomercaptans (Table 2, entries 1-2) was only successful when the normal addition procedure was used, since the thiolactones are very readily polymerised.

The diazomercaptans do not exist in the cyclic hemithioacetal form, probably due to the poor electrophilicity of the diazoketone, which is the result of delocalisation of charge from the diazo group into the ketone. Indeed, the carbonyl absorption in the IR spectrum occurs at 1650 cm^{-1}, and this also explains why the keto (and ester) groups in the product are resistant to further reaction with ELDA.

Table 2. Reaction of ELDA with thiolactones, lactams, and cyclic anhydrides

Entry	Starting Material	Diazo Compound	Addition[a]	Yield (%)
1	n=1	(136)	N	44
2	n=2	(137)	N	52
	Boc	Boc		
3	(144) n=1	(138)	I	60
4	(145) n=2	(139)	I (N)	73 (45)
	CO^tBu	CO^tBu		
5	(146)	(140)	N	18[b]
6	n = 1	(141)	I (N)	25 (43)
7	n = 2	(142)	I	36
8		(143)	I	26

a, N=normal addition, I= inverse addition; b, starting material recovered (25%)

2.2.3 Lactams

The reaction of *N*-methyl γ-, δ-, and ε-lactams with ELDA using the inverse addition mode was unsuccessful, indicating that the amide anion was too poor a leaving group. *N*-Methylphthalimide was also unreactive. Therefore, *N*-Boc derivatives of δ–valerolactam (144) and ε-caprolactam (145) were prepared, in high yield, by treating a solution of the corresponding lactams in acetonitrile, with Boc-anhydride and a catalytic amount of 4-dimethylaminopyridine. Treatment of the *N*-Boc lactams under the standard inverse addition conditions gave, after work-up and purification, the corresponding diazocarbamates (Table 2, entries 3-4) in very good yield.

N-*t*-Butylcarbonyl δ-valerolactam (146), prepared in 96% yield from a solution of δ-valerolactam in THF, by adding pivaloyl chloride and triethylamine, was a less satisfactory substrate for the anion reaction, since the bulky *t*-butyl group inhibits the approach of ELDA to the endocyclic carbonyl group (Table 2, entry 5).

2.2.4 Cyclic Carboxylic Acid Anhydrides

Succinic, glutaric, and phthalic anhydrides also underwent reaction with ELDA, to give ω-carboxy α-diazo-β-ketoesters in moderate yield (Table 2, entries 6-8). The normal mode of addition gave better results than the inverse mode for succinic anhydride.

The carboxylate anion is a very good leaving group compared to the substrates discussed so far, however, treating a solution of glutaric anhydride and EDA in THF with DBU or potassium *t*-butoxide gave no adduct.

The ω-carboxy α-diazo-β-ketoesters are stable yellow solids, in contrast to ω–carboxy α-diazo-β-ketones, which autocatalytically decompose by loss of nitrogen upon standing.

2.3 Rhodium Tetraacetate Mediated Cyclisation Reactions

In the work described in this section, the functionalised diazo compounds prepared in the previous section were subjected to dirhodium tetraacetate catalysed decomposition, to generate transient rhodium carbenoids which, under the reaction conditions react intramolecularly, either by inserting into heteroatom-hydrogen bonds, or into C-H bonds, to give heterocycles or cyclopentanones, respectively (Scheme 37). The influence of the ring size, the type of heteroatom, and the reaction conditions on the outcome of the reaction will be discussed, and also the dependence of the product(s) on the nature of the metallocarbenoid intermediate will be reported.
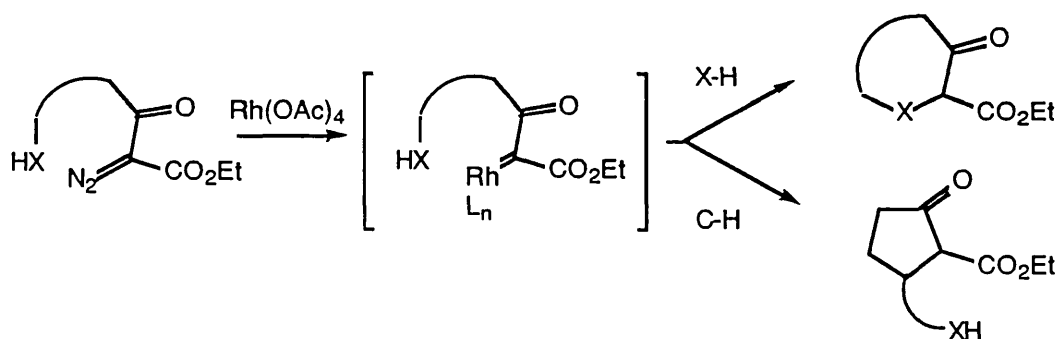
Scheme 37.
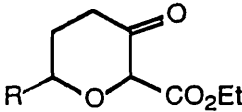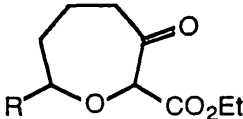
2.3.1 Cyclisation of the Diazoalcohols
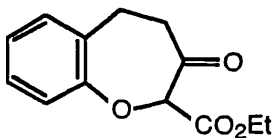
The cyclisations could be realised using two different methods: the addition of a catalytic amount of dirhodium tetraacetate to a dilute solution of the diazoalcohol in dichloromethane at room temperature, led to consumption of the starting material (<1 hour), to give the cyclised product; however, the reaction was found to work equally well when a solution of the diazoalcohol in benzene was added to a suspension of a catalytic amount of dirhodium tetraacetate in boiling benzene, and the reaction time was usually less than five minutes. After the reaction reached completion, the catalyst was removed and the solvent evaporated, and the residue was purified by distillation or chromatography.
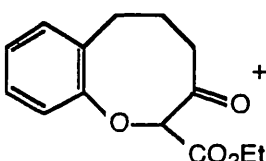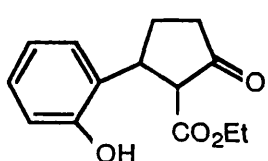
Thus, treatment of the diazo alcohols (Table 3) with a catalytic amount of dirhodium tetraacetate (0.2-2 mol%), using the methods described above, gave six and seven membered cyclic ethers, the products of insertion into the O-H bond, as the only products, in 57-80% yield. Pyrans have not been prepared by this route

55
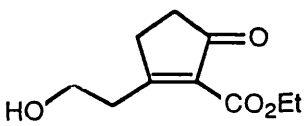
previously.[9] Structural assignments for the ethers were made with the aid of proton NMR, carbon-13 NMR, and IR spectroscopy. The structural assignments were confirmed by comparison with previously prepared cyclic ethers,[9] and by the preparation of derivatives (Section 2.3.4). The ethers prepared from secondary and benzylic alcohols were unstable to chromatography, on silica gel and Florisil, and in general the pyrans were less stable than the oxepanes.
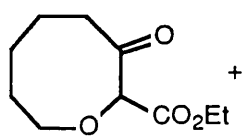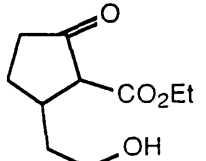
Table 3. Cyclisation Reactions of the Diazoalcohols
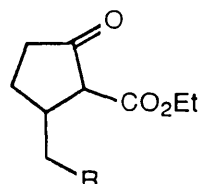
Diazo	Catalyst	Solvent[a]	Product	Yield (%)	
(120)	$Rh_2(OAc)_4$	B (D)	(147) R=H	57	(59)
(121)	$Rh_2(OAc)_4$	B (D)	(148) R=Me	80	(64)
(122)	$Rh_2(OAc)_4$	B (D)	(149) R=H	64	(58)
"	$Rh_2(OCOCF_3)_4$	B (D)	"	57	(45)
"	$Cu_2(OAc)_4$	B	"	28	
"	$Cu(OCOCF_3)_2$	B (T)	"	46	(51)
"	$Cu(acac)_2$	T	"	45	
"	$Cu(OSO_2CF_3)_2$	B	"	57	
"	$AgBF_4$	T	"	12	
"	$Pd(OAc)_2$	B	"	23[b]	
"	$Mo_2(OAc)_4$	T	"	19	
(123)	$Rh_2(OAc)_4$	B (D)	(150) R=C_6H_{13}	77	(68)

Structure (151): 4,5-dihydro-1-benzoxepin-3-one with CO_2Et

(126)	$Rh_2(OAc)_4$	B (D)	(151)	80 (59)
"	$Rh_2(OCOCF_3)_4$	B	"	6 3

Structures (152) and (153)

(127)	$Rh_2(OAc)_4$	B	(152)	(153)	1 2+6 9
"	$Rh_2(OAc)_4$	D	"		1 1+6 2
"	$Rh_2(OCOCF_3)_4$	D	"		3 2+3 4
"	$Cu(acac)_2$	B	"		0+5 4

Structure (154) with HO and CO_2Et

(128)	$Pd(OAc)_2$	T	(154)	2 1

Structures (155) and (156) with CO_2Et and OH

(129)	$Rh_2(OAc)_4$	B	(155)	(156)	3 1+5
"	$Rh_2(OAc)_4$	D	"		1 8+3 0

Structure (157)/(159) with CO_2Et and R

(130)	$Rh_2(OAc)_4$	D	(157) R=$(CH_2)_2$O H	4 1
"	$Rh_2(OCOCF_3)_4$	D	"	3 9
(158)	$Rh_2(OAc)_4$	D	(159) R=OSi^{t}BuMe$_2$	2 5

a, B = benzene, D = dichloromethane, T = toluene; b, + 26% Starting material

Treatment of the diazomalonate derivative (124) under either set of reaction conditions, on the other hand, gave a complex mixture of products, from which a dimeric compound was isolated in low yield. This was probably formed by intermolecular O-H insertion, followed by intramolecular O-H insertion of the carbenoid of one molecule onto the hydroxy of the other, and the oxepane was probably not formed because of restricted mobility of the alkyl chain imposed by the ester.

The yields recorded for the synthesis of oxepane (149) when the reaction was carried out in benzene at room temperature (5 h) and reflux (5 min), were 63% and 64%, respectively; this shows the tolerant nature of the rhodium carbenoid, and also suggests that it has a very short lifetime, and rapidly undergoes intramolecular attack by the hydroxy group, indeed, the independence of the yield upon the amount of catalyst used suggests a very high rate of catalytic turnover.

A study of the dirhodium tetraacetate mediated cyclisation of (122) using a variety of solvents and temperatures also confirmed the tolerant nature of the carbenoid: oxepane (149) was formed in 52-57% yield when the reaction was carried out in boiling hexane, carbon tetrachloride, or ethylene dichloride. However, the rate of reaction in dichloromethane lowered significantly as the temperaure was dropped to 0°C. The reaction was totally inhibited when strongly coordinating solvents (e.g. THF) were employed. As a measure of the power of dirhodium tetraacetate catalysis, the decomposition of (122) without a catalyst required prolonged reflux in toluene, but this gave polymeric material, and no oxepane. Also, the acid catalysed decompositions of ω-methoxy α-diazoketones is only useful for the synthesis of five and six membered rings.[68]

Next, we looked at the effect of altering the catalyst (ligand and metal): we postulated that increasing the electrophilicity of the carbene would favour the capture of nucleophiles. Thus, we prepared rhodium (II) trifluoroacetate, which is soluble in most organic solvents, and forms a deep blue solution. However, during the reaction with diazoalcohols, the solution turned green, suggesting that the alcohol coordinates to the active sites of the electrophilic catalyst. Indeed, the rate is slower than the dirhodium tetraacetate catalysed reaction, because of the lower free catalyst concentration.

The traditional catalysts for decomposition of diazo compounds are copper (II) salts, although the active catalysts are probably the copper (I) salts, formed *in situ* by oxidation of the diazo group. Copper (II) acetylacetonate and copper (II) acetate share

the same dimeric structure as dirhodium tetraacetate. A solution of (122) in boiling benzene or toluene was treated with copper (II) acetylacetonate (homogeneous catalyst) or copper (II) acetate, respectively, for 2-2.5 h, to give the oxepane (149) in moderate yields, and the more electrophilic copper (II) trifluoroacetate (homogeneous catalyst) and copper (II) trifluoromethanesulphonate, gave the oxepane in 46% and 59% yields, respectively, after 1-2 h in boiling benzene, although the reaction time for copper (II) trifluoroacetate could be reduced to 0.25 h in boiling toluene, with a small increase in yield. The reactions catalysed by copper salts are sluggish compared to dirhodium tetraacetate , and the yields depend markedly on the ligand, although the electrophilic catalysts give the best results.

Finally, we explored a broad range of transition metal salts as possible catalysts, but the only positive results were recorded for silver (I), palladium (II), and molybdenum (II) salts (Table 3): silver salts are known to be effective catalysts for the promotion of the Wolff rearrangement, but only the oxepane was isolated from the reaction of (122), however, the catalyst was reduced *in situ*, to silver metal. Palladium salts are usually regarded as cyclopropanation or C-H insertion catalysts, however, the oxepane (149) was formed in low yield, as the only product. Molybdenum diacetate, with a similar dimeric structure to dirhodium tetraacetate, was also a catalyst, but molybdenum (0) and (IV) complexes were inactive, although molybdenum complexes are known to decompose diazo compounds. Rhodium (I) catalysts were inactive for the reaction, whereas zinc (II) iodide, a strong Lewis acid, decomposed the diazo compound, but gave no cyclic ether.

The investigation of different catalysts, above, has shown the superiority of dirhodium tetraacetate as a catalyst for O-H bond insertion

Next, we investigated the synthesis of eight membered ethers: the dirhodium tetraacetate mediated cylisation of (127) in boiling benzene gave a mixture of two components (Table 3), the oxecane (152) (12%) derived from O-H bond insertion, and the cyclopentanone ester (153) (69%) from insertion into the γ-C-H bond of the alkyl chain. The major change in the site of insertion can be attributed to the relatively low rate of formation of eight membered rings. Indeed, the rate of formation of five membered rings is about 10^4-10^6 times faster than for the corresponding eight membered ring, and there is a 10-100 times difference between the rate of formation of seven and eight membered rings.[69] The ratio of the two products indicates that the mechanism for C-H and O-H bond insertions are different, and this is

generally accepted: the former probably involves oxidative addition across the C-H bond, whereas the hydroxy group attacks the electrophilic carbenoid centre, to give an intermediate complex (5, R=H), which undergoes proton transfer and loss of the catalyst to give the cyclic ether (Scheme 2). The initial nucleophilic addition is rapid because it does not involve breaking a bond, the O-H bond being stronger than the C-H bond. The rate of C-H bond insertion is diminished by an α- or β- electron withdrawing group[35], an effect which favours the formation of (149), but is lost in the reaction of (127).

In the rhodium (II) trifluoroacetate catalysed reaction of (127), the yield of the benzoxocin (152) was improved to 32%, at the expense of the cyclopentanone (153) (34%), and this is a reflection of the higher electrophilicity of the carbenoid. Copper (II) acetylacetonate, on the other hand, gave solely the cyclopentanone (153), in 54% yield; in general, copper catalysts are more effective in the promotion of C-H bond insertion.[5]

In an attempt to favour the formation of oxecanes by restricting the flexibility of the molecule, we prepared the diazoalcohol (128). However, when treated with dirhodium tetraacetate it gave no isolable products, although when (128) was treated with a catalytic amount of palladium (II) acetate in boiling toluene, the cyclopentanone (154) was isolated in 21% yield. The reaction is thought to proceed *via* a palladocyclobutane.[70]

The dirhodium tetraacetate mediated cyclisation of (129) in boiling benzene or dichloromethane gave the oxecane (155) in a fair yield (18-31%), and a cyclopentanone (156) in variable yield. The cyclisation of (129) gave a larger amount of the cyclic ether than did the phenol (127), and this is probably due to the greater nucleophilicity of the primary alcohol.

Rhodium trifluoroacetate or dirhodium tetraacetate mediated cyclisation of (130) (Table 3) gave a moderate yield of the cyclopentanone (157); the nine membered ether was not formed because the C-H insertion reaction was faster.

In summary, the nature of the metallocarbenoid appears to be critical for the synthesis of oxecanes. Where the rate of O-H and C-H insertion are comparable, however, for the synthesis of six and seven membered rings, cyclopentanone formation was not observed, and dirhodium tetraacetate was found to be the catalyst of choice.

The efficacy of the dirhodium tetraacetate mediated cyclopentanone synthesis[5] prompted us to extend the reaction of ELDA with lactones to prepare substrates for the synthesis of cyclopentanones. Thus, the substituted cyclopentanone (159) (Table 3) could be prepared from (122), in two steps, by silylation with TBDMSCl, followed by dirhodium tetraacetate mediated C-H insertion (25%). The poor yield is probably due to the bulky, electron withdrawing nature of the siloxy group. Alternatively, diazo alcohol (122) could be oxidised to the corresponding aldehyde (160) in good yield, by pyridinium dichromate (63%) (the transformation was also possible using pyridinium chlorochromate or Swern oxidation), which was then treated with (carboxymethylene)triphenylphosphorane, to give the diazoester (161) in 80% yield. This was cyclised by treatment with a catalytic amount of dirhodium tetraacetate , to give the cyclopentanone (162) in 58% yield (Scheme 38).
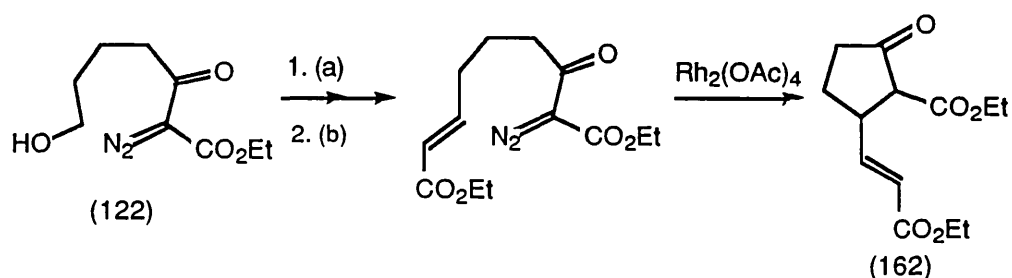
Scheme 38.   (a) PDC   (b)   Ph$_3$P=CHCO$_2$Et

The ω-hydroxy group in the α-diazo-β-ketoesters (Table 1) can therefore be used for further chain extension steps, to provide an alternative route to cyclopentanones.
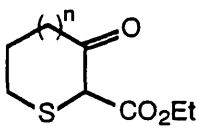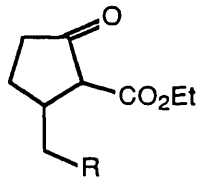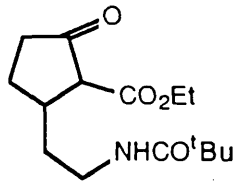
2.3.2 Cyclisation of Diazo-mercaptans and -amines

The intramolecular dirhodium tetraacetate catalysed cyclisation of diazosulphides has been extensively studied (Chapter 4) but, with the exception of Rapoport[8], the intramolecular reaction of mercaptans with diazo compounds has not been studied. The reaction can give either a thioether, the product of S-H bond insertion, or an alkane resulting from reduction of the carbene.

Diazomercaptans (136) and (137) were subjected to dirhodium tetraacetate mediated cyclisation in boiling benzene to give, after work-up and distillation, the cyclic thioethers (163) and (164), in 57% and 34% yield, respectively (Table 4). No C-H bond insertion products were isolated. The cyclic thioethers are highly enolised,

chromatographically stable odourless oils. Derivatives were prepared to confirm their structure (Section 2.3.4).

Table 4. Cyclisation Reactions of Diazo-mercaptans and -amines

Diazo	Catalyst	Solvent[a]	Product	Yield (%)

(136)	$Rh_2(OAc)_4$	B	(163) n=1	57
(137)	$Rh_2(OAc)_4$	B	(164) n=2	34

(138)	$Rh_2(OAc)_4$	D	(165) R=NHBoc	73
(139)	$Rh_2(OAc)_4$	D	(166) R=CH_2NHBoc	63
"	$Rh(OCOCF_3)$	D	"	76

(140)	$Rh_2(OAc)_4$	B	(167)	19

a, B = benzene, D = dichloromethane.

Unfortunately, the ability of sulphur to poison catalysts reduced the rate of reaction at room temperature significantly, and so cyclisation was performed in boiling benzene with ~2 mol% of dirhodium tetraacetate, and under these conditions the solution turned purple, indicating coordination of the mercaptan to the catalyst.

In comparison, the diazo-carbamates and -amides gave only the products of C-H insertion on treatment with a catalytic amount of dirhodium tetraacetate (Table 4): the cyclopentanones (165) and (166) were obtained in 73% and 63% yield, respectively, whereas (167) was only obtained in a poor yield, presumably because the pivaloyl group inhibits the reaction far more than the t-Boc group. Interception of the carbenoid by nitrogen was not observed, because it is hindered and relatively non-nucleophilic. However, insertion into N-H and N(CO)-H bonds to give four, five, and six membered rings has been reported,[8,13] although competing C-H bond insertion was noted in the synthesis of the six membered ring.

Attempts to remove the t-butoxycarbonyl group from (138) using trifluoroacetic acid in dichloromethane were unsuccessful.

2.3.3 Cyclisation of Diazoacids

Esterification of carboxylic acids under neutral conditions using diazoalkanes, such as diazomethane or diphenyldiazomethane, is a well known reaction and it can also be applied to the less reactive diazoketones, in the presence of an acid catalyst. The intramolecular acid catalysed reaction is particularly facile and can be used for the preparation of δ-lactones; thus, 1,4-dioxoisochroman[71] was prepared in high yield by the addition of dilute aqueous hydrochloric acid to the diazoketone carboxylate (Scheme 39). The reaction proceeds by loss of nitrogen, to generate a carbenium ion, followed by cyclisation of the carboxylic acid residue. The corresponding transition metal catalysed reaction, however, has been little studied[72].
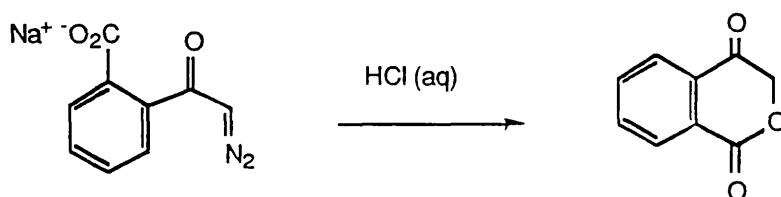
Scheme 39.

A solution of the diazoacids (141) or (142) were added to a suspension of dirhodium tetraacetate in boiling benzene, however, after work-up and distillation of the reaction mixture, no characterisable products were isolated. The reaction was repeated in the

presence of DBU, but no product was formed. Decomposition of (142) mediated by either copper (II) trifluoromethanesulphonate or boron trifluoride etherate also failed.

Therefore, we decided to prepare an ω- carboxy α-diazoketone, in order to generate a less electrophilic and less reactive carbenoid, which would be more selective in its reactions. Thus, diazodimedone, easily prepared from dimedone using the diazo transfer reaction, was dissolved in dichloromethane, and aqueous sodium hydroxide was added. The two phase mixture was stirred rapidly overnight, and then subjected to acidic aqueous work-up to give the crude diazoacid[73] (168), which was relatively stable in solution. Boron trifluoride etherate was added to a solution of the crude acid (168) in dichloromethane at room temperature, and after twelve hours, aqueous work-up and purification of the residue by chromatography, gave the ε-lactone (169) (30% from diazodimedone) (Scheme 40). Alternatively, the crude diazoacid was subjected to quick flash chromatography on silica gel, to give (168) in 52% yield. The acid was immediately treated with dirhodium tetraacetate in boiling benzene, to give the lactone (169) in 67% yield, as well as a symmetrical lactone dimer (4%).
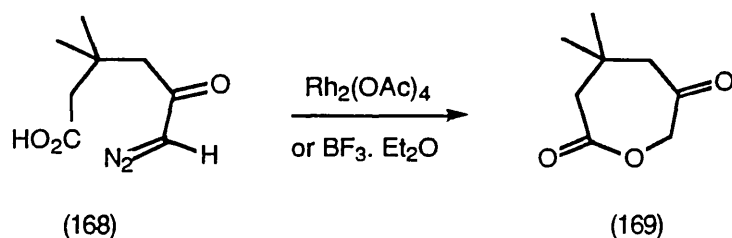
Scheme 40.
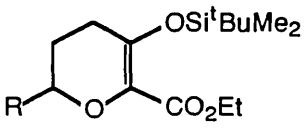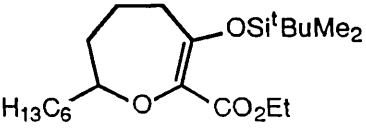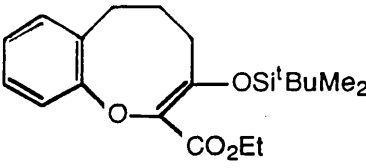
The successful cyclisation of (168) mediated by a Lewis acid or dirhodium tetraacetate may be due to the presence of the gem dimethyl group in the ring, since this group strongly favours cyclisation to medium sized rings, and the presence of the 14–membered ring dimer in the dirhodium tetraacetate mediated reaction suggests that the formation of the parent seven membered ring is disfavoured, so that dimerisation or polymerisation is facilitated. Thus, the role of the ester group α-to the carbenoid can be pivotal to the outcome of the reaction.
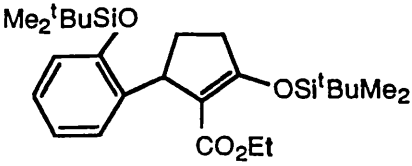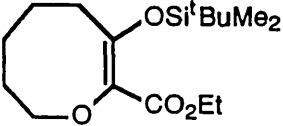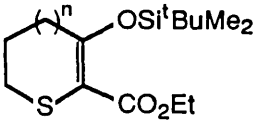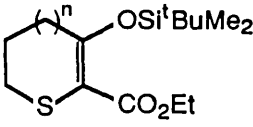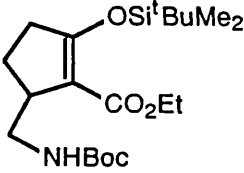
2.3.4 Derivatisation of the Heterocycles and Cyclopentanones

As observed previously,[9] the heterocycles exist as a mixture of keto and enol tautomers, and the ratio in a deuteriochloroform solution was dependent upon the ring size, the substituents around the ring, and on the heteroatom.

To simplify analysis of the spectra, the β-ketoesters were locked into the enol tautomer by preparing the *t*-butyldimethylsilyl enol ether derivatives, by treating a solution of the heterocycle in THF with *t*-butyldimethylsilyl trifluoromethanesulphonate (TBDMSOTf) and triethylamine (Table 5). The NMR and IR spectra of the silyl ethers, which were usually stable to distillation, were greatly simplified, and confirmation of the structures was facilitated. Derivatisation of the cyclopentanones (153) and (165) also supported the structural assignment (Table 5).

Table 5. *t*-Butyldimethylsilyl Enol Ethers

β-ketoester	Silyl Ether	Yield (%)
(147)	(170) R=H	69
(148)	(171) R=Me	57
(150)	(172)	86
(152)	(173)	46

Structure (153) → (174), yield 53

(155)   (175)   1 0 0

(163)   (176) n=1   1 0 0
(164)   (177) n=2   1 0 0

(165)   (178)   2 3

Finally, a solution of the cyclopentanone (153) in boiling benzene was treated with a catalytic amount of camphorsulphonic acid, and after three hours the reaction mixture was subjected to work-up and purification, to give the tricyclic lactone (179) (32%), as a single isomer.

$$\text{(153)} \xrightarrow[\text{PhH 80°C}]{\text{CSA}} \text{(179)}$$

(153)   (179)
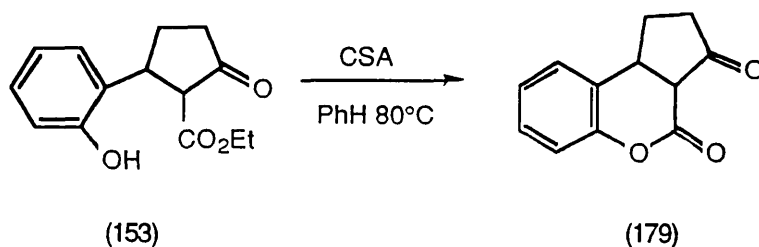
2.4   Conclusions

The methodology developed herein allows the preparation of a variety of ω–functionalised α-diazo-β-ketoesters in one step from ethyl diazoacetate, by the addition of cyclic electrophiles, such as lactones, to a solution of ethyl lithiodiazoacetate.   Thus, the diazo group is readily introduced into the molecules without recourse to the use of diazomethane or the diazo transfer reaction.

The dirhodium tetraacetate mediated cyclisation reaction of the diazo-alcohols and –mercaptans, prepared from lactones and thiolactones, respectively, gave six and seven membered cyclic ethers and thioethers.   Therefore overall, the reaction is a two step ring expansion of the lactone or thiolactone, by insertion of the $CHCO_2Et$ group into the (O)C-X bond.   Oxecanes could be prepared in low yield, reflecting the difficulty in preparing eight membered rings, but the reaction suffered from competing C-H insertion, leading to cyclopentanones. Cyclopentanones were the sole products from the reaction of N-Boc amino- and N-pivaloyl-diazoketoesters.

The nature of the metal and the ligands of the metallocarbenoid were found to alter the ratio of C-H to O-H insertion.   Also, the effect of the substituent at the carbenoid centre could also be profound, as shown in the cyclisations of ω-carboxy diazoacids.

CHAPTER THREE

Synthesis and Dirhodium Tetraacetate Mediated Cyclisation of α-Diazocarbonyl Compounds

3.1 Introduction

In the previous chapter we reported a two step procedure for the synthesis of heterocycles, which involved the reaction of ethyl lithiodiazoacetate with cyclic electrophiles, such as lactones, to give α-diazo-β-ketoesters with remote nucleophilic functionality, and these compounds were cyclised with the aid of dirhodium tetraacetate to six, seven, and eight membered heterocycles.

The reaction could be extended to α-metallated diazo compounds with different stabilising groups at the α- position, to prepare a variety of α-diazo-β-keto-compounds, which would be subjected to dirhodium tetraacetate mediated cyclisation, to give heterocycles with other synthetically useful substituents at the C-2 position (Scheme 41).
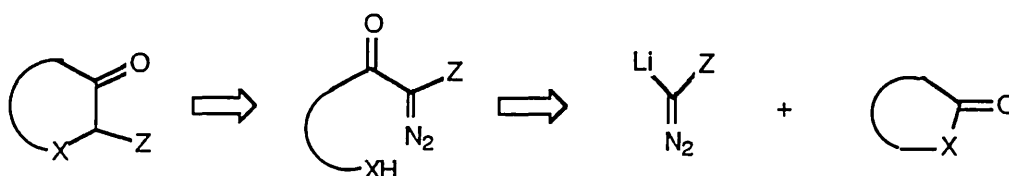
Scheme 41.   X = O, S, NBoc   Z = SO$_2$Ph, PO(OEt)$_2$, Me$_3$Si, CO$_2$^{t}Bu, COMe

Relatively few diazo compounds have been α-metallated,[74] but the most notable examples are α-diazo-esters and -methylphosphonates, which are readily metallated to give a variety of stable and isolable compounds with metals such as silver (I), tin (IV), silicon, lead (IV), and mercury (II), although the compounds appear to be of little synthetic interest. The more reactive and less stable metallo-derivative can be prepared at low temperature with strong bases, such as LDA, n-butyllithium, or potassium t-butoxide. The α-lithio derivatives of α-diazoketones and trimethylsilyldiazomethane have been prepared by the action of LDA at -78°C, and n-butyllithium at 0°C or -100°C, respectively. α-Lithiodiazoketones and -esters are less stable than the corresponding -methylphosphonyl and -silyl derivatives.

The most frequently used and the most readily accessible anion is ethyl lithiodiazoacetate, and its alkylation and acylation reactions have been discussed (Sections 2.1.2 and 2.2), although a few reactions of the methyl ester have also been reported.[74]

Several aryl- and alkyl-diazoketones undergo aldol-type addition to aryl aldehydes and ketones in the presence of LDA, to give β-hydroxy-α-diazoketones in high yield.[66]

Diethyl and dimethyl diazomethylphosphonate are poor carbon nucleophiles, and they slowly react with α-tricarbonyl compounds, or with benzaldehyde in the presence of triethylamine, to give aldol adducts.[63] However, the reaction of lithiodiazomethylphosphonates with ketones is facile and has been widely employed, especially for the synthesis of the very reactive vinyl carbenes, for example (Scheme 42).[75] The reaction proceeds by initial addition of the diazo anion to the ketone to form an aldol adduct, and this is followed by loss of nitrogen and the phosphate ester to generate the vinyl carbene, which rapidly inserts into a nearby C-H bond to give the product, a dihydrofuran.
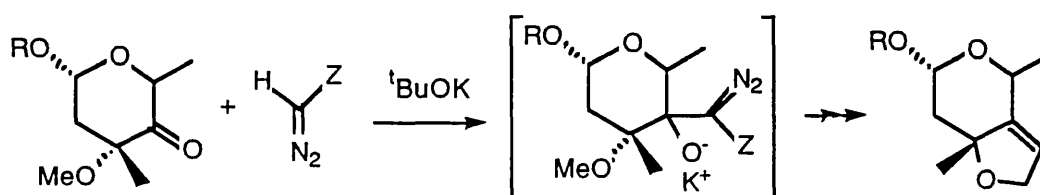
Scheme 42.   R = macrolide   Z = PO(OMe)₂

Diethyl lithiodiazomethylphosphonate reacts with diaryl ketones[74] or aryl aldehydes[76] to give acetylenes, in good yield, and the reaction of lithio trimethylsilyldiazomethane with diaryl ketones occurs in an analogous manner[76] (Scheme 43).
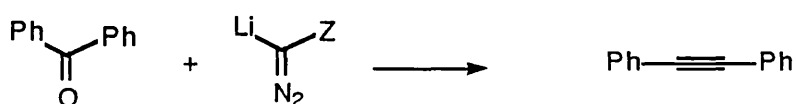
Scheme 43.   Z = PO(OEt)₂, Me₃Si

The reaction is thought to proceed by Wolff rearrangement of the initialy formed aldol adduct, to give an alkene, which then losses ‾OTMS or ‾OPO(OEt)₂, to give the alkyne, although the order of the steps is not known.

On the other hand, the reaction of lithio trimethylsilyldiazomethane with dialkyl ketones or aryl aldehydes gave β-hydroxy-α-diazosilanes, which decomposed at room

temperature, by loss of nitrogen, to give epoxides (180); the epoxides underwent further acid catalysed rearrangement to aldehydes (Scheme 44).[77]

(180)
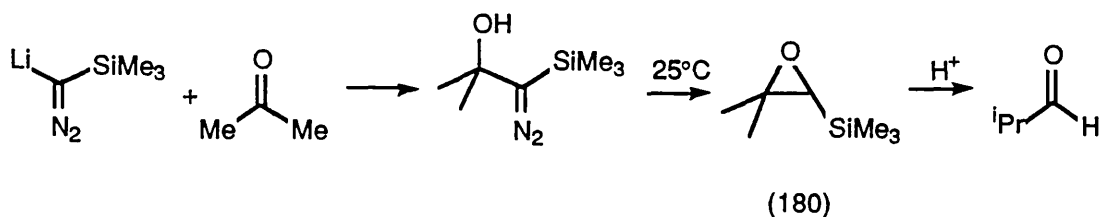
Scheme 44.

Finally, the reaction of lithio trimethylsilyldiazomethane with thioketones, dithioesters, and thiocarbonates has been investigated, but in all cases a mixture of products was isolated, including acetylenes derived from the aldol addition reaction, and also products from the cycloaddition reaction between the diazo group and the C=S bond.[78,79]

In summary, the reaction between α-lithio diazo compounds and aldehydes or ketones initially gives aldol-type addition products, which are often unstable and rearrange on loss of nitrogen.

3.2 Preparation and Reaction of α-Substituted Diazomethanes

We prepared several diazomethane derivatives (Section 3.2.1), and subjected these to the ring opening reaction with lactones, thiolactones, and N-Boc lactams using the methodology previously developed (Section 2.2).

3.2.1 Preparation of α-Substituted Diazomethanes

t-Butyl diazoacetate[80] (181) and diazoacetone[73] (182) were prepared from t-butyl acetoacetate and pentane-2,4-dione, respectively, in very good yield, by a diazo transfer reaction, followed by deacylation of the 1,3-dicarbonyl compound using aqueous sodium hydroxide or sodium methoxide in methanol, at or below $0°C$ (Scheme 45).

Diazomethylphenylsulphone[81] (183) could only be prepared by the deacylation route when the labile pyruvate group was used instead of the acetyl group, due to the poor base stability of the α-diazosulphone. Thus, treatment of methylphenylsulphone with
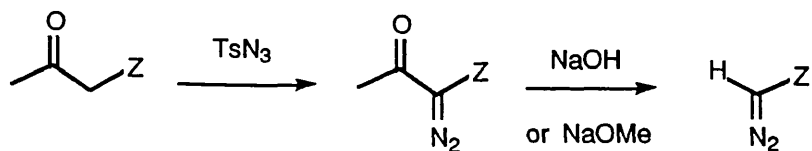
Scheme 45. Z = $CO_2{}^tBu$ (181), COMe (182)

diethyl oxalate gave the corresponding pyruvate[82] in very good yield, which underwent facile diazotisation under diazo transfer conditions, followed by *in situ* deacylation, to give (183) in moderate yield (Scheme 46).

(183)
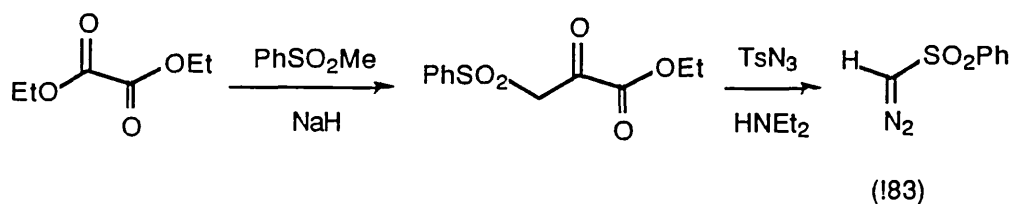
Scheme 46.

The analogous deacylation reaction of α-diazo-β-ketophosphonates is not known, therefore, diethyl diazomethylphosphonate (184) was prepared by the literature procedure,[83] which introduced the diazo group using nitrous acid, from the α-aminophosphonate precursor (Scheme 47).

(184)
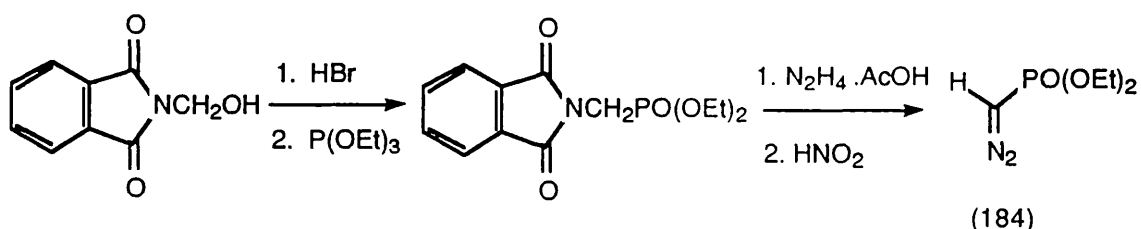
Scheme 47.

Finally, trimethylsilyldiazomethane[84] (185) was prepared in one step from diazomethane, as a solution in ether (standardised by NMR), by adding trimethylsilyl trifluoromethanesulphonate and diisopropylethylamine to a solution of diazomethane in ether at -78°C (Scheme 48).

Diazo-compounds (181)-(183) are stable at room temperature, but the silyl and sulphonyl substituted diazo compounds (184) and (185) decomposed slowly at -10°C,

and were therefore used immediately after purification.
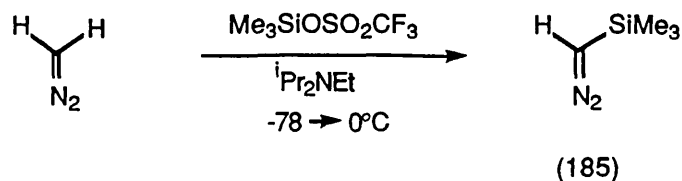
Scheme 48.

3.2.2 Acylation of α-Substituted Diazomethanes

t-Butyl lithiodiazoacetate was prepared by adding LDA to a solution of the diazoester (181) in THF at -90°C, and to the resulting orange solution either δ-valerolactone, δ-thiovalerolactone, or *N*-Boc-δ-valerolactam were added, and the solution was then warmed to -75°C. After three hours the reaction mixture was subjected to work-up and purification, to give the corresponding ring opened α-diazo-β-ketoesters in 87%, 0%, and 56% yield, respectively (Table 6, entries 1-3).

The yields compare favourably with the corresponding reactions of ethyl lithiodiazoacetate, although the bulkier nature of the nucleophile, thus the higher base character, resulted in preferential polymerisation of the thiolactone.
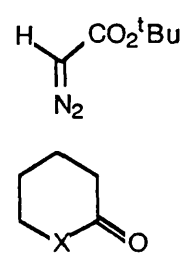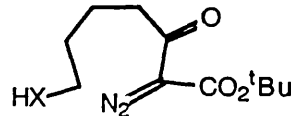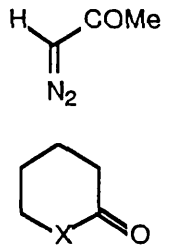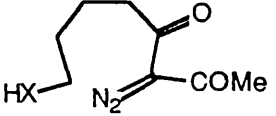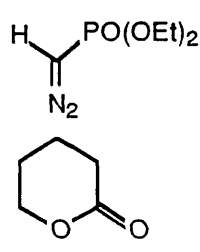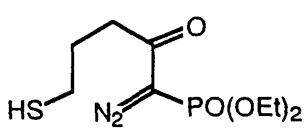
t-Butyl lithiodiazoacetate, which appears not to have been prepared before, is far more stable than the corresponding ethyl ester, and does not decompose at -75°C. With this in mind, we repeated the ring opening reaction using the inverse addition mode, by adding LDA to a solution of the diazoester (181) and δ-valerolactone in THF at -75°C. After work-up and purification of the reaction mixture, the diazoester (186) was isolated in 76% yield: identical to the yield of the ethyl ester (122).

Lithiodiazoacetone was prepared *in situ* with the acylating agents, thus, LDA was added to a solution of diazoacetone (182) and δ-valerolactone or δ-thiovalerolactone in THF at -90°C, and the solution was then allowed to warm to -75°C; after three hours the reaction mixture was subjected to work-up and purification, to give the ring opened products (188) and (189) in 26% and 20% yield, respectively. The yields of the products were significantly lower when the LDA was added at -75°C.

Although the diazoacetone is deprotonated specifically at the α-diazo position,[66] which reflects the activating nature of the diazo group, the reaction of the anion with lactones and thiolactones is slower than with ketones, and so self-condensation of the anion occurs in competition with the ring opening reaction. Indeed, the recovery of

73

δ–thiovalerolactone from the reaction mixture suggests that the anion is rapidly consumed during the reaction.

Table 6. Reaction of Lactones, Thiolactones, and N-Boc-Lactams with α-Lithiodiazomethanes (181)-(185)

Entry	Diazo compound	Adduct	Addition[a]	Yield(%)

1	X = O	(186)	I (N)	76 (87)
2	X = NBoc	(187)	N	56
3	X = S	-	N	-

4	X = O	(188)	I	26
5	X = S	(189)	I	20

6		-	N	-
7		(190)	N	18

74

8		**(191)**	**N** **32**
9		**(192)**c	**N** **-**

a, I = inverse mode of addition, N = normal mode of addition; b, δ-thiovalerolactone recovered (19%); c, unstable.

Diethyl lithiodiazomethylphosphonate was prepared by the addition of *n*-butyl lithium to a solution of the diazo compound (184) in THF at -75°C, and to the resulting orange solution was added either δ-valerolactone or γ-thiobutyrolactone; however, after work-up and purification of the reaction mixtures, the only adduct isolated was the diazo thiol (190). This suggests that lithiodiazomethylphosphonate is not sufficiently reactive to be acylated by the lactones, and raising the reaction temperature facilitated base catalysed polymerisation of the lactone or thiolactone. Therefore, it was decided to use a more reactive electrophile to prepare the ω–functionalised α-diazo-β-ketophosphonates, and so 5-benzylthiopentanoyl chloride was synthesised (Section 4.3, Scheme 64). Reaction of the lithiodiazomethylphosphonate anion with the acid chloride under the standard reaction conditions gave the β-ketodiazo phosphonate (193) in 30% yield, and the low yield is most likely due to the ready deprotonation of the acid chloride to form a ketene.

(193)
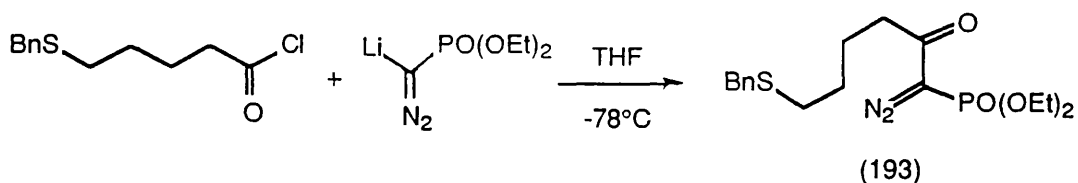
Next, we attempted to prepare lithiodiazomethylphenylsulphone. However, addition of

LDA, or n-butyl lithium to a solution of (183) in THF at -90°C led to decomposition of the substrate. Repeating the deprotonation in the presence of lactones, thiolactones, or more reactive electrophiles, such as allyl bromide and benzaldehyde, also led to decomposition of the diazosulphone. Weaker bases, such as potassium t-butoxide, also decomposed the diazosulphone (183).

Finally, we prepared lithiotrimethylsilyldiazomethane from (185) by the addition of a n-butyl lithium to a solution of (185) in THF/ether at -65°C. To this solution δ–valerolactone was added, followed after three hours by one equivalent of acetic acid; the reaction mixture was subjected to a neutral aqueous work-up, and chromatography on neutral alumina to give the diazoketone (191), the result of desilylation of the expected product. The facile desilylation is attributed to the effect of the β-keto-group, since the corresponding β-hydroxy-α-diazosilanes are stable to aqueous work-up.[84] The reaction was repeated, but the acetic acid (0.96 equivalent) was added slowly at -70°C, then the reaction mixture was warmed to room temperature, and all the solvent evaporated under vacuum. NMR and IR spectroscopy of the crude reaction mixture showed that partial desilylation (~40%) had occurred during the addition of acetic acid. The crude product was then subjected to chromatography, to give (191), showing the ease of hydrolysis of the silyl group.

Lithiotrimethylsilyldiazomethane was also treated with γ-thiobutyrolactone, but the compound isolated in poor yield was unstable, although IR and NMR evidence supported the structural assignment (192).

In order to prepare a more stable α-diazo-β-keto-'mercaptan', we treated the anion of (185) with 5-benzylthiopentanoyl chloride, however, no product was isolated from the reaction mixture. Therefore, a solution of 5-benzylthiopentanoyl chloride was added to an ethereal solution of trimethylsilyldiazomethane (185) (three equivalents) at room temperature. After 24 hours the solvent was evaporated and the residue purified by chromatography on Florisil, to give (194) in 58% yield, as the only product (Scheme 49). A closer investigation of the reaction, using NMR and IR spectroscopy, showed that (194) and its α-diazo-β-ketosilane precursor were formed in ~1:1 throughout the the course of the reaction; that is, the hydrogen chloride liberated in the condensation desilylated the α-diazo-β-ketosilane, as well as reacting with (185). The benzyl sulphide (194) was also prepared from diazomethane and the acid chloride in 66% yield (Section 4.3, Scheme 64).

The acylation of lithiotrimethylsilyldiazomethane offers a convenient alternative route

for the preparation of α-diazoketones, as a result of the facile desilylation reaction of α-diazo-β-ketosilanes.

$$PhCH_2S(CH_2)_4 \overset{O}{\underset{}{\text{—}}} Cl \quad + \quad \underset{N_2}{\overset{H\,\diagup\,SiMe_3}{\text{—}}} \quad \longrightarrow \quad PhCH_2S(CH_2)_4 \overset{O}{\underset{N_2}{\text{—}}} X$$

$$\xrightarrow{\text{Florisil}} \quad PhCH_2S(CH_2)_4 \overset{O}{\underset{N_2}{\text{—}}} H \qquad X = H:SiMe_3 \quad 1:1$$

(194)
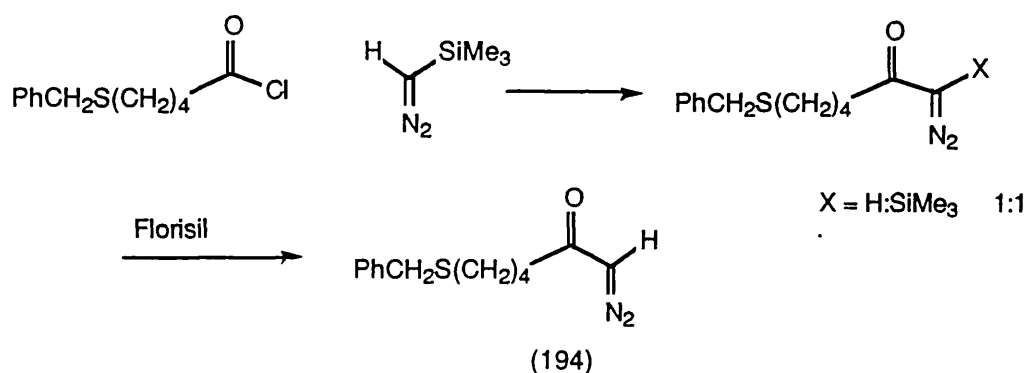
Scheme 49.

Unfortunately, using the methodology developed herein, we cannot prepare ω-hydroxy α-diazo-β-ketosulphones and -phosphonates for cyclisation studies, hence we needed to develop a new approach for their synthesis. The route we chose relied on a more traditional approach, and at its simplest it involves the ring-opening reaction of δ-lactones with the lithio anions of methylphenylsulphone or diethyl methylphosphonate, to give β-keto-sulphones and -phosphonates, respectively, which were diazotised, using the diazo transfer reaction reaction, to give the required compounds. However, there are problems with this approach: the β-keto- compounds formed in the reaction are more acidic than the anions they were derived from, and the yields can be reduced, therefore, by proton transfer reactions. Also, the isolated products can exist in the cyclic hemiacetal form, and this may interfere with the diazotisation step. Neither of these problems occur in the reactions of the α-diazo anions.

Ditrich and Hoffmann have published a one-pot procedure for ring-opening γ- and δ-lactones using diethyl lithiomethylphosphonate which avoids these complications:[85] the lactone is added to the phosphonate anion at -75°C, and then a second equivalent of base (LDA) is added to the reaction mixture, which is finally quenched with two equivalents of trimethylsilyl chloride, to give the adduct in the acyclic form, as a bis trimethylsilyl ether (of the alcohol and the ketone). Upon mild acidic work-up the silyl enol ether was selectively hydrolysed.

This method was applied to the reaction of undecanoic acid-δ-lactone using methylphenylsulphone and diethyl methylphosphonate, to give 6-trimethylsiloxy-2–keto-sulphones and -phosphonates, which were subjected to the diazo transfer

reaction using tosyl azide, without purification, to give the α-diazo-β-keto compounds (195) and (197) in 36% and 40% overall yield, respectively, after chromatographic purification. The trimethylsilyl ethers were readily cleaved using aqueous acetic acid in THF, to give (196) and (198), the substrates for cyclisation (Scheme 50). Although the overall yields for the syntheses are only moderate, the reaction warrants further investigation as a general route to such compounds.

Z = SO₂Ph   (195)
Z = PO(OEt)₂   (197)

(196)
(198)
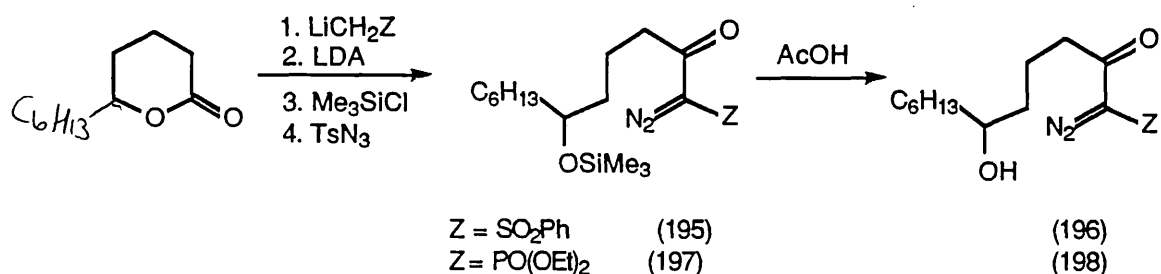
Scheme 50.

3.3   Dirhodium Tetraacetate Mediated Cyclisation Reactions

The second step in the synthetic sequence (Scheme 41) is the dirhodium tetraacetate mediated cyclisation of the ω-functionalised α-diazoketo compounds to heterocycles.

As a result of the ready synthesis of α-diazo-β-ketones, from acid chlorides and diazomethane, and of α-diazo-β-ketoesters, little work has been reported on the intramolecular reactions of other α-substituted diazo compounds until recently, and the cyclisation onto heteroatoms has been particularly poorly investigated: the acid catalysed cyclisation of an α-diazosulphone gives the product derived from the cyclic oxygen ylide, by loss of methanol, in very good yield (Scheme 51).[86]
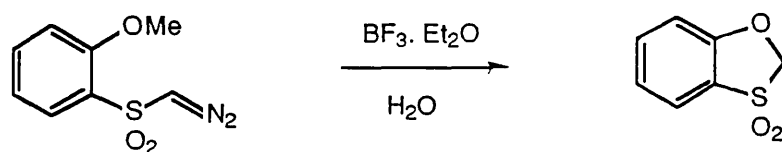
Scheme 51.

An example of a carbene inserting into an O-H bond was recorded in the decomposition of an unstable β-hydroxy-α-diazosilane which gives the epoxide (180) upon standing. The dirhodium tetraacetate catalysed reaction of α-diazo-β-ketophosphonates (Scheme

4) and α-diazo-β-sulphonylesters[87] (Scheme 52) has been used in the synthesis of nitrogen heterocycles, by insertion of the rhodium carbenoid into the β-lactam N-H bond.
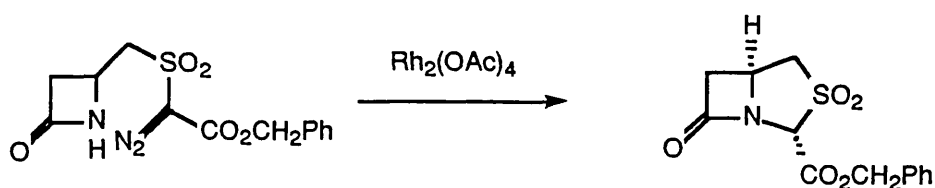
Scheme 52.

ω–Alkenyl α-diazo-β-ketophosphonates have been successfully used in copper catalysed intramolecular cyclopropanation reactions,[5] and recently the dirhodium tetraacetate mediated cyclisation of α-diazo-β-ketosulphones and -phosphonates, and phosphine oxides has been reported as a general route to cyclopentanones *via* γ-C-H bond insertion[25,39,40] (Scheme 15).
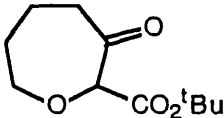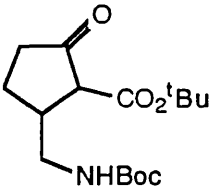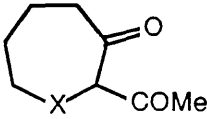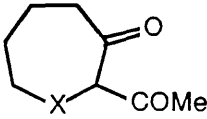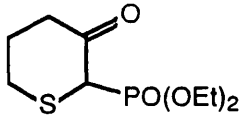
We have previously shown that the formal insertion of rhodium carbenoids into O-H and S-H bonds can be used to prepare six and seven membered heterocycles in good yield (Section 2.3), and therefore cyclisation of the diazo compounds (186)-(191) would show that the strategy developed herein is a general one for the synthesis of 3–oxo-2-substituted heterocycles.

Thus, a solution of the diazo alcohols (Table 7, entries 1,3,6-8) in benzene was added to a suspension of dirhodium tetraacetate in boiling benzene to give, after work-up and purification of the reaction mixture, by chromatography or distillation, the 2–substituted oxepanes (199), (201), and (204)-(206) in 46-73% yield. The reaction could also be carried out in dichloromethane at room temperature, to give the products in similar yield.

These results show that the insertion of rhodium carbenoids into O-H bonds does not have a strong dependence on the nature of the stabilising group, although this is at least partly due to the facile nature of the reaction. Similarly, the diazo mercaptans (Table 7, entries 4-5) gave the thiepane (202) and the thiane (203) in 41% and 44% yield, respectively. Again, the yields of cyclisation are not significantly different from the corresponding 2-ethoxycarbonyl substituted heterocycles, which shows that the reactivity profile of the rhodium carbenoid is determined primarily by the nature of the metal-carbene bond, and the electronic influences of the substituents

are therefore secondary. However, the phosphonate group partially deactivates the catalyst, and reduces the reaction rate, and this may be the reason for the lower than average yields for the heterocyclic phosphonates (190) and (198), although the reaction was complete within twenty minutes. Decomposition of the diazo sulphide (193), on the other hand, required several hours in boiling benzene, and neither the cyclic sulphonium ylide or its rearrangement product were isolated from the reaction mixture. In this example, the bulky sulphide group, which also poisons the catalyst, probably swings the balance against cyclisation.

Table 7. Dirhodium Tetraacetate Mediated Cyclisation of α-Substituted α-Diazo-β-Ketones

Entry	Diazo	Solvent[a]	Heterocycle	Yield(%)
1	(186)	B (D)	(199)[b]	46-56 (47)
2	(187)	D	(200)	31
3	(188)	B	X = O (201)	62
4	(189)	B	X = S (202)	41
5	(190)	B	(203)	44
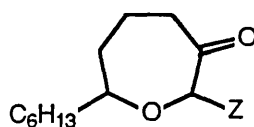
6	(191)	B (D)		Z= H	(204)	56	(64)
7	(196)	B (D)		Z= SO$_2$Ph	(205)	73	(31)
8	(198)	B		Z= PO(OEt)$_2$	(206)	54	

a, D = dichloromethane, B = benzene; b, rhodium (II) trifluoroacetate in dichloromethane gave 51% yield.

The cyclisation of (186) to give *t*-butoxycarbonyl oxepane (199) was studied more closely. The yield of the oxepane was found to be dependent on the scale of the reaction, but broadly independent on the amount of catalyst used: cyclisation of 1.0 g, 4.0 mmol of (186) using 0.45 mol% and 0.16 mol% of dirhodium tetraacetate gave the oxepane in 48% and 46% yield, respectively. However, the yield was increased to 56% when the reaction was performed on a 0.40 mmol scale.

The bulky *t*-butoxycarbonyl group, which is probably constrained in the plane of the diazo group during the reaction, because of charge delocalisation, was found to depress yields of the insertion products, and this resulted in a lower yield of the cyclopentanone (200) (31%), formed from the dirhodium tetraacetate mediated reaction of the *N*-Boc carbamate (187), compared to the ethyl ester, which gave (165) in 73% yield. The yield of 2-(*t*-butoxycarbonyl)oxepane (199) was ~10% lower than the corresponding ethyl ester (149), which was lower than the yield recorded for the 2-methoxycarbonyloxepane.[9] The reason for this effect is probably steric repulsion between the ester and the bulky metallocarbenoid complex, but there are examples of metallocarbenoids derived from α-diazoesters inserting into the β–C–H bond of the ester group to give γ-lactones.[2]

3.4   Conclusions

The reaction of various α-lithio diazo compounds with lactones and thiolactones provides a one step synthesis of a range of ω-hydroxy or ω-mercapto α-diazo-β–ketones substituted at the α-position by *t*-butoxycarbonyl, acyl, phosphonyl ester, or by trimethylsilyl groups.   *t*-Butyl lithiodiazoacetate, which is far more stable than the corresponding ethyl ester, gave good yields of adducts with lactams and lactones, whereas the reaction of lithiotrimethylsilyldiazomethane with lactones gave diazoketones, the result of facile desilylation of the initial adduct. Trimethylsilyldiazomethane therefore behaves as a diazomethane equivalent, and it is more versatile because it is easily handled, and because it reacts with poor electrophiles, such as lactones.

ω-Hydroxy α-diazo-β-keto-sulphones and -phosphonates were prepared more satisfactorily in a two step sequence, using the diazo transfer reaction to introduce the diazo group, because of the instability or unreactivity of the corresponding diazo anions.

Dirhodium tetraacetate mediated cyclisation of the diazo compounds gave seven membered oxygen and sulphur heterocycles in good yield.   The yield was not dependent on the α-substituent on the diazo compound.

Thus, the work reported herein offers two alternative routes to 2-substituted heterocycles.

CHAPTER FOUR

Dirhodium Tetraacetate Catalysed Reaction of Diazosulphides: Preparation and Rearrangement of Cyclic Sulphonium Ylides

4.1 Introduction

4.1.1 Reaction Between Carbenes and Sulphides

The reaction of electrophilic carbenes and carbenoids with sulphides has been extensively investigated. The reaction proceeds by initial attack of the nucleophilic sulphur atom on the electron deficient carbene centre, to generate a sulphonium ylide (Scheme 53). The ylide bond is dipolar, any covalent nature in the bond is the result of an empty d_π orbital on sulphur overlapping with the full p_π orbital on carbon. The d_π-p_π back bonding is the dominant form of bonding in systems where the 2p orbital on sulphur cannot achieve sufficient overlap for a covalent bond.

The fate of the ylide depends largely upon the type of substituents on the sulphur atom. Rearrangement of the ylide to a neutral species proceeds by either migration of the RCH_2CH_2 or R' group from from sulphur to carbon (207), or by a fragmentation pathway which involves β- elimination of an alkene and liberation of a new sulphide (208). The latter elimination pathway is a concerted process, and is competitive with the migration pathway, (207), in cases where the groups on sulphur are of low migratory aptitude. Often, one of the substituents on sulphur is allylic, and then the ylide rearranges rapidly by a low energy concerted [2,3]-sigmatropic shift, in preference to fragmentation. Stabilised ylides (Z= electron withdrawing group) are often isolable.
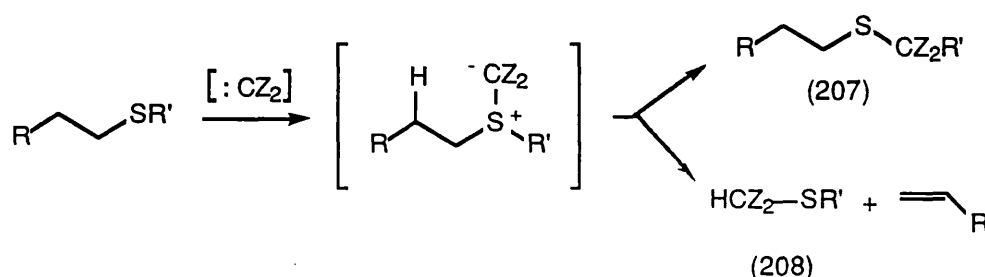
Scheme 53.

The reaction of diazo compounds with sulphides can be carried out under thermal or photochemical conditions, but a more selective and higher yielding route involves the participation of transition metal catalysts in the reaction. Recently, dirhodium tetraacetate has superceded copper salts as the catalyst of choice, because it is an

efficient catalyst even at room temperature.

A demonstration of the selectivity of the reaction is shown in competition reactions between sulphides, alkenes, and alkanes for carbenoids. Usually, the only process observed is that of ylide formation, and cyclopropanation of allylic sulphides is rare. The reaction is tolerant of other nucleophilic atoms. The potential of the method has been illustrated by a novel conversion of the cephalosporin nucleus into the penicillin nucleus.[88]

4.1.2 Cyclic Sulphonium Ylides from Carbenes

The synthesis and reactions of cyclic sulphonium ylides has been relatively poorly explored, compared to their acyclic counterparts. The majority of the cyclisation reactions of ω-diazosulphides catalysed by copper and rhodium salts that have been reported to date were discussed in Chapter 1, but the main points are summarised here: the dirhodium tetraacetate catalysed cyclisation of ω-diazophenylsulphides gave stable five-, six-, and seven-membered sulphonium ylides. Stabilised ylides could only be isolated when the carbanion centre was flanked by two powerfully electron withdrawing groups. The mode of rearrangement of the cyclic ylides was found to be acutely dependent upon the ring size as well as the nature of the exocyclic group. Groups with a high migratory aptitude were required as the exocyclic sulphur substituent, in order that the ring remained intact during rearrangement. In some systems, more than one method was used for the cyclisation reaction, and the metal catalysed route usually gave superior results to the photochemical reaction.

(209)   (210)
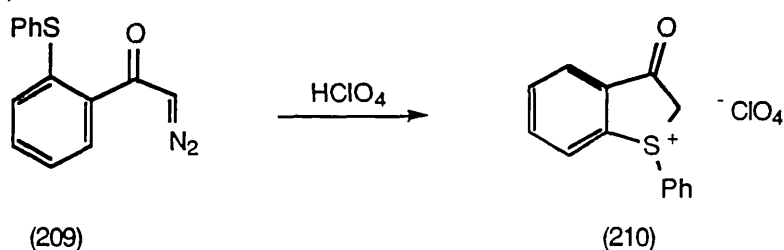
There are a few examples of acid catalysed and thermally mediated diazosulphide cyclisations in the literature,[89] for example, the diazoalkane (209) was decomposed on treatment with perchloric acid, to the sulphonium salt (210). The unstable ylide could be liberated on treating the salt with triethylamine. The reaction probably proceeds *via* a carbenium ion.

A three membered ylide has been postulated as an intermediate in the reaction of (211). Thermolysis of tosylhydrazone salt (211) probably generates a carbene directly, which is trapped by the proximal sulphide to give a thiiranium ylide.[89] The ylide undergoes a [2,3]-sigmatropic shift, followed by a further rearrangement, to (212).

(211)   (212)
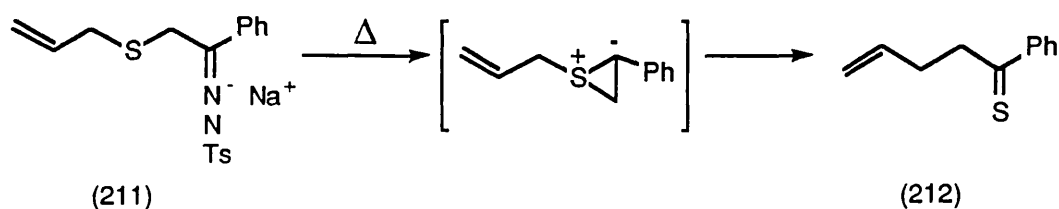
Although, the thermally generated carbene (213) rapidly cyclises to the thietanium ylide (214), the products isolated after rearrangement of the ylide suggest the co–intermediacy of ylide (215) (Scheme 54). The distribution of products can be accommodated if the two sulphonium ylides are interconvertable. The ylide (214) rapidly equilibrates with the thermodynamically more stable exocyclic ylide (215).[89]

(213)   (214)

(215)
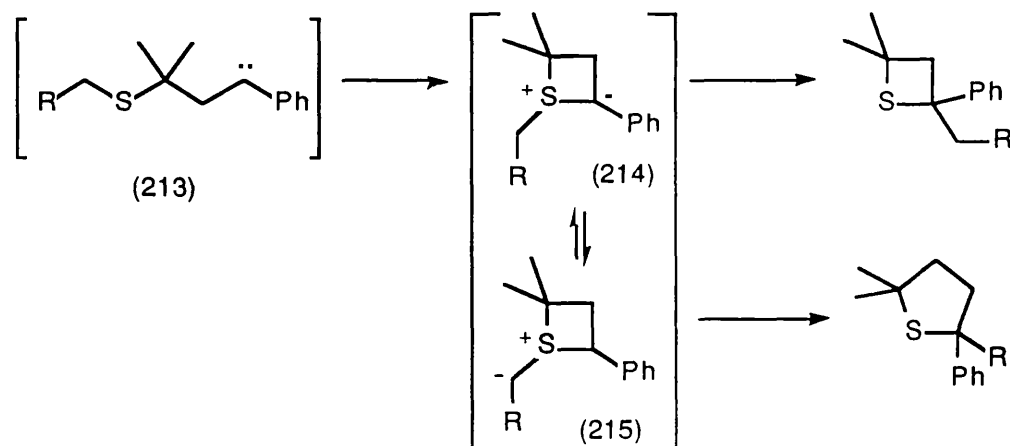
Scheme 54.   R=Ph, CH₂:CH

The reverse is true for the ylide (216), which was prepared from the corresponding sulphide and the carbenoid derived from ethyl diazoacetate. The exocyclic ylide is less stable than the cyclic ylide (217), which rearranges by a Stevens process to (218).[90]

(216)   (217)   (218)
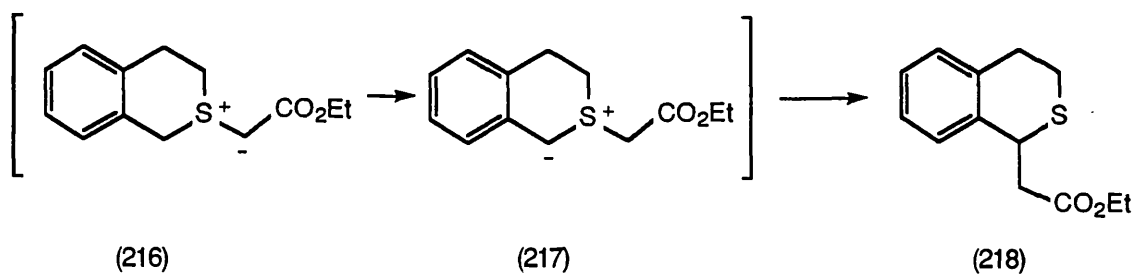
4.1.3 Cyclic Sulphonium Ylides from Sulphonium Salts

The classic alternate route to sulphonium ylides is that of deprotonation of sulphonium salts. The synthesis of cyclic sulphonium salts necessitates that the ring is synthesised before the deprotonation step, although the salts can be prepared by inter- or intramolecular alkylation reactions.

The regiochemistry of deprotonation, a factor which does not arise in the carbenoid/sulphide reaction, can be a problem with this approach. If there is no strong kinetic or thermodynamic bias for deprotonation at a specific site, then exocyclic deprotonation is usually observed. Thus, to prepare cyclic sulphonium ylides, a carbanion stabilising group is often placed adjacent to the site of charge development; for example, the ylide (219) is formed exclusively from the corresponding salt.[89]

(219)
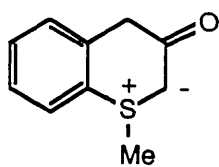
The α-deprotonation of sulphonium salts can be achieved with bases such as DBU, and potassium tert-butoxide, although very stabilised ylides can be prepared using potassium carbonate. Regioselective deprotonation of (220) was achieved (Scheme 55) by treatment with DBU, to give the exocyclic ylide, which rearranged spontaneously to the (E)-nine membered ring (221).[91] When a less hindered base was used, such as potassium hydroxide, the cyclic ylide was formed competitively, leading to 2-allyl-2-vinylthiane as a second product. This ring expansion reaction has been exploited by Vedejs and co-workers, in the synthesis of large ring sulphides

containing an *E*-alkene. The double bond is introduced stereospecifically by the [2,3]-rearrangement. The *E*-stereochemistry is a consequence of the *trans* relationship between the sulphonium substituent and the alkyl group on the ring. Kinetically controlled alkylation of the cyclic sulphide furnishes the *trans* salt, which is deprotonated without epimerisation to the *trans* ylide.

(220)   (221)
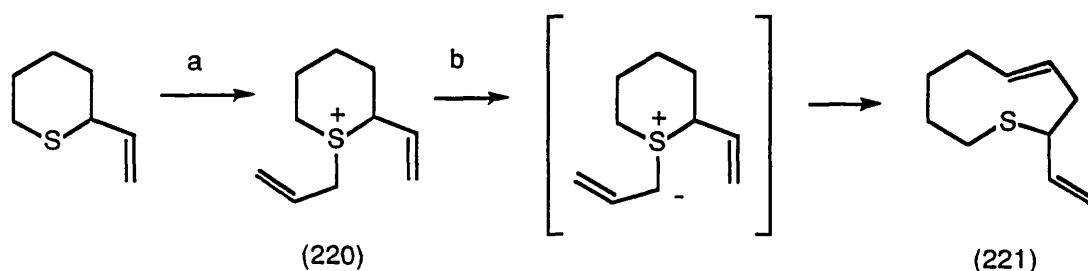
Scheme 55.   a CH$_2$:CHCH$_2$OTf, b DBU

Alkylation of (222) and treatment of the salt with potassium *tert*-butoxide, at room temperature, resulted in ring expansion to the *Z*-isomer (223) (Scheme 56). This appears to contradict the above rationale. If the geometry of the groups in the ylide are *trans*, then the orbital interactions required for a concerted rearrangement are not

(224a)   (224b)   (224c)

(222)   (223)
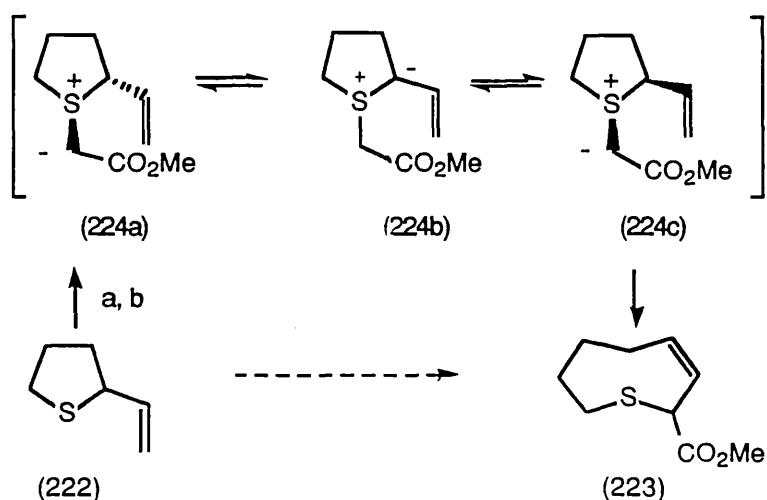
Scheme 56.   a MeO$_2$CCH$_2$OTf , b ^{t}BuO$^-$ K$^+$

possible. If the stereochemistry of the ylide was *cis*, then rearrangement could occur to the *cis* alkene. However, isomerisation of the pyramidal sulphur is slow at ambient temperature. Inversion of the ring substituent would require a planar intermediate. It was shown that the initially formed *trans* ylide (224a) was

converted into the *cis* exocyclic ylide (224c) *via* the less stable endocyclic ylide (224b), so providing a low energy pathway for rearrangement.[92]

4.2   Synthesis and Reactions of 1,5-and 1,6-Diazosulphides

We have previously reported the cyclisation of 1,5- and 1,6-diazomercaptans, (136) and (137), in the presence of dirhodium tetraacetate, as an efficient synthesis of substituted thianes and thiepanes, respectively (Section 2.3 2).   Extension of this approach to the study of the cyclisations of ω- diazosulphides would broaden the methodology, and could offer a convenient route for the synthesis of 2,3-substituted sulphur containing rings, from simple acyclic precursors, by rearrangement of the cyclic sulphonium ylides.   The goal was also a comparative study of the effects of substituents, on both the carbene and sulphur atom, on the course of the reaction.

The work is divided into two sections; the first deals with the synthesis of thiane- and thiepane-2-carboxylates from α-diazo-β-ketoesters, and the second is a study of the cyclisations of α-diazo-β-ketones to thiepanes.

4.2.1   Synthesis of Diazosulphides

All approaches to the preparation of non-symmetrical sulphides involve the alkylation of a mercaptan at some stage in the route.   The method most widely used to prepare diazosulphides involves alkylation of a simple thiolate anion with a functionalised alkyl iodide, followed by the introduction of the diazo group into the molecule.   We decided to tackle the synthesis by adopting the reverse strategy, of alkylating a mercaptan that already contained the prerequisite functionality, including the diazo group, with a simple alkylating agent.

We have already discussed a simple sequence for the preparation of diazomercaptans, (136) and (137) (Section 2.2.2).   The mercaptans were prepared by nucleophilic ring opening of γ–and δ–thiolactones, with ethyl lithiodiazoacetate, at low temperature. Extension of this work to the synthesis of sulphides requires an alkylation step.   There are two approaches to the alkylation (Scheme 57): the first involves *in situ* quenching of the lithium thiolate, with an alkylating agent, in a one-pot reaction.   The second approach requires the initial isolation of the mercaptan, followed by alkylation at ambient temperature.   We found both methods to be suitable for the synthesis of

diazosulphides.

n = 1, 2
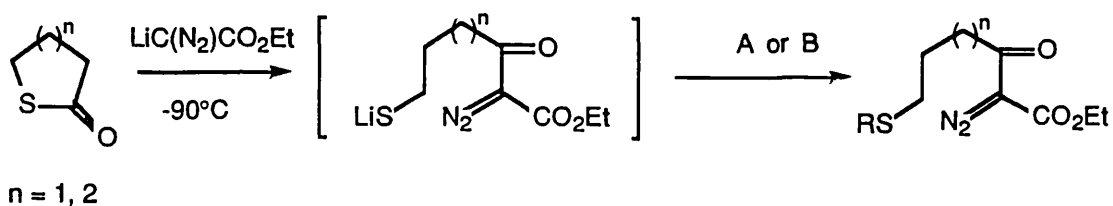
Scheme 57.   A = 1. RX, -75°C   B = 1. AcOH, 2. RX, NEt$_3$, DMF, 25°C

1,5-Diazosulphides

The reaction between γ-thiobutyrolactone and ethyl lithiodiazoacetate furnished the diazomercaptan (136), in 44% yield, after purification on acidic alumina. The yellow oil was dissolved in DMF under nitrogen, and triethylamine was added, followed by the alkylating agent. The reaction mixture was stirred at room temperature for 12-15 hours, before aqueous work-up and purification of the residue by chromatography on silica gel. The sulphides could therefore be obtained in two steps in moderate yield. An occasional problem in the synthesis of sulphides is over-alkylation to the sulphonium salt, and dealkylation of the salt, initiated by bromide or sulphide, to a different sulphide. This was not found to be a serious problem in our case.

A modification of the above method for preparing the sulphides was found to be equally successful: after work-up of the anion reaction, the crude diazomercaptan (136) was purified by flash chromatography on silica gel, to give partially purified (136). This material could then be used in the alkylation reaction, without any significant loss in yield of the sulphide (Table 8, entries 3 and 9)

We applied the above approach to the synthesis of several alkyl- and allyl-diazosulphides. We also found that acylation of the diazomercaptan was equally facile (Table 8, entries 1-9). The diazosulphides are non volatile yellow oils, with good acid and thermal stability, but are slowly oxidised in air.

The reaction of (136) with various allyl bromides was rapid (Table 8, entries 1-4), the triethylammonium salt being precipitated a few minutes after the addition of the allylating agent. The yields are lower for the more highly substituted allyl bromides. This probably reflects the greater S_N1 character of the substitution reaction. Indeed, prenyl bromide readily polymerises under the standard reaction conditions

90

(DMF/room temperature).

As a possible solution to this problem, we investigated the *in situ* alkylation reaction (Scheme 57). The lower reaction temperature would inhibit the polymerisation of prenyl bromide. The more potently nucleophilic lithium thiolate, in conjunction with the lower solvent polarity of THF, would combine to favour the S_N2 pathway over the dissociative mechanism. Prenyl bromide was added dropwise to a solution of the lithium thiolate in THF at -75°C. Standard work-up and purification of the residue gave the prenyl sulphide (228), in an improved yield of 54%.

Table 8. Preparation of Diazosulphides from the Diazomercaptan (136)

Entry	RX	Yield [a] (%)	Number
1	CH_2:$CHCH_2Br$	55	(225)
2	E-MeCH:$CHCH_2Br$	52 [20][b]	(226)
3	E-PhCH:$CHCH_2Br$	46 (62)[b]	(227)
4	Me_2C:$CHCH_2Br$	37 [54]	(228)
5	(MeCO)$_2$	50	(229)
6	MeO_2CCH_2COCl	47	(230)
7	BnBr	50	(231)
8	EtI	60	(232)
9	$ClCH_2COCH_2CO_2Et$	34 (60)	(233)
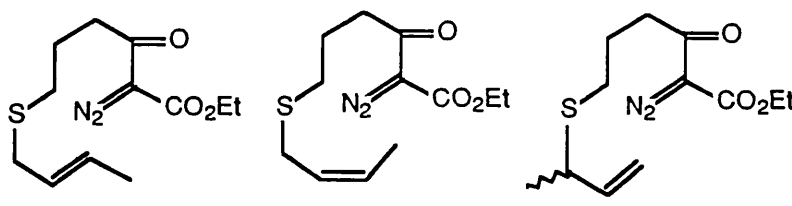
a, Yields refer to alkylation of partially purified (136), and were calculated from this material. Yields in parenthesis: () refers to alkylation of the pure mercaptan (136), and [] refers to the *in situ* procedure; b, mixture of isomers, see (Scheme 58) and text for details.

Allylation of mercaptan (136) by prenyl and cinnamyl bromides occurred regiospecifically by attack of sulphur at the bromine bearing carbon, probably by an S_N2 mechanism. Reaction at the allylic position is not observed, because of the steric bulk of the phenyl and dimethyl groups, and high selectivity in the reactions of 3–substituted allyl halides is well known.

The allylation of mercaptan (136) with *trans*-crotyl bromide, which contained

~20% 3-bromo-1-butene, gave (226), as a mixture of three isomers, which could not be separated by flash chromatography (Scheme 58). Structural assignments were made on the basis of NMR spectroscopy, the allylic and methyl protons were clearly defined. Repeating the reaction using the *in situ* procedure gave a mixture of two isomers. The major product was assigned as the *trans* isomer (226a), formed by attack of the sulphur nucleophile at the least hindered site in both bromides. Substitution at the more hindered site (in one or both of the isomeric) bromides, to give (226c), was not observed in the low temperature reaction (kinetic conditions), but (226c) was a minor product in the room temperature reaction. The *cis* isomer (26b) was formed from the reaction of 3-bromo-1-butene with the sulphur nucleophile at the allylic position: the reaction gives equal amounts of the *cis* and *trans* (26a) isomers. However, the preponderance of the *cis* isomer in the low temperature/lithium thiolate reaction suggests that an electron transfer process may be operating. Transfer of an electron from the thiolate to crotyl bromide would generate an allylic radical anion, which can equilibrate to a mixture of *cis* and *trans* isomers.

The distribution of products in the room temperature reaction was not significantly altered when the reaction was repeated in less polar solvents (THF and dichloromethane), although the reactions take longer.

Alkylation conditions	(226a)	(226b)	(226c)
THF, -75°C	6	4	-
NEt₃, DMF, 25°C	8	1	1

Scheme 58.

Diazomercaptan (136) could be readily acylated with acetic anhydride or methyl malonyl chloride, in the presence of pyridine and triethylamine, respectively, to give thioesters in good yield (Table 8, entries 5 and 6).

Alkylation of the diazomercaptan (136) was possible with a variety of alkylating

agents. Alkyl iodides, benzyl bromides, and α-chloroketones were all good alkylating agents (Table 8, entries 7-9), and the corresponding sulphides were obtained in good yield.

The yield of (233) was significantly lower when the reaction was performed at room temperature with the partially purified mercaptan (136), and this is probably because of the greater stability of the chloride to the reaction conditions at lower temperatures.

Attempts to extend the reaction to other reactive alkylating agents were unsuccessful. Michael acceptors, such as acrylonitrile and methyl propiolate, were polymerised under the reaction conditions. Attempted synthesis of the tetrahydropyranyl thioether of (136), using boron trifluoride etherate as a catalyst, was also unsuccessful. Tentative interpretation of the spectroscopic data suggested that the thiol was trapped by dihydropyran in the cyclic hemithioacetal form, to give the O-tetrahydropyranyl ether.

1,6-Diazosulphides

The reaction of δ-thiovalerolactone with ethyl lithiodiazoacetate, in an analogous manner to that discussed earlier, gave diazomercaptan (137).

The mercaptan was treated with cinnamyl and benzyl bromides, in DMF, to give the corresponding sulphides in fair to good yield (Table 9, entries 1,2). However, reaction of the mercaptan with ethyl iodide resulted in a mixture of compounds, from which the desired compound (236) could not be isolated in a pure form by chromatography.

Table 9. Preparation of Diazosulphides from the Diazomercaptan (137)

Entry	RX	Yield ^{a} (%)	Number^c
1	E-PhCH:CHCH$_2$Br	48	(234)
2	BnBr	31	(235)
3	EtI	b	(236)

a, As for Table 8; b, (236) could not be obtained pure; c, for structures see Table 11.

4.2.2 Dirhodium Tetraacetate Mediated Cyclisation Reactions

The dirhodium tetraacetate catalysed reactions of diazosulphides to give cyclic sulphonium ylides has been reported, and examples of the synthesis and rearrangement reactions of cyclic sulphonium ylides have been discussed (Sections 1.2.3. and 4.1). Our findings will be compared with literature reactions, in an attempt to determine the factors affecting the course of rearrangement.

The section will be subdivided into the synthesis of six and seven membered rings.

Thianes

This section deals with the dirhodium tetraacetate catalysed decomposition of 1,5–diazosulphides (Table 10, entries 1-8), to give six membered sulphonium ylides and their rearrangement products.

We employed the standard procedure for the cyclisation reaction, which involved the addition of a dilute solution of the diazo compound in benzene to a suspension of dirhodium tetraacetate (~2 mol%) in boiling benzene over two to five minutes. The reaction was usually complete within five to ten minutes. During the addition of the diazosulphide solution to the suspension of dirhodium tetraacetate in benzene the catalyst dissolved; this was accompanied by the development of a deep pink colouration in the solution. This suggests coordination at the active sites of the catalyst by the sulphides. It is known that a red colour develops in a solution of dirhodium tetraacetate when dimethyl sulphide or dimethyl sulphoxide is added. The coordination is most probably with the starting sulphide, and not with the cyclic sulphide product, because the colour also develops in the synthesis of stable sulphonium ylides, which lack the ability to coordinate. This coordination prevents catalytic activity and therefore retards the rate of reaction by lowering the effective catalytic turnover. Indeed, the reaction of sulphides is slow compared to the reaction of diazoalcohols and diazoamides, although the latter are able to form adducts with dirhodium tetraacetate, and this suggests that the sulphides are strongly bound to the metal, so a large proportion of the catalyst is present as its adduct during the reaction.

In some instances, more catalyst was added to the reaction mixture at five minute intervals, until the reaction was complete, in order to mitigate the effects of (irreversible) coordination.

The relatively high reaction temperature was chosen because the dirhodium tetraacetate catalysed reaction did not proceed at a significant rate in dichloromethane at room temperature or at reflux.

The reaction could be accurately followed by monitoring the disappearance of the diazo group absorption in the IR spectrum. After consumption of the starting material, the reaction mixture was cooled, evaporated, and the residue purified by chromatography. Alternatively, the catalyst could be recovered from the crude reaction mixture by trituration with hexane/ether mixtures, followed by filtration through a cotton wool plug.

The products obtained from the reactions could be categorised into three groups according to the nature of the diazosulphide. The cyclisation reactions will therefore be separately reported as the reactions of allyl, acyl and alkyl sulphides, respectively (Table 10).

Allyl Diazosulphides

These constitute the largest group of reactions, and the most profitable in terms of synthetic value. The clean and facile decomposition of the allyl sulphides under the standard conditions led not to cyclic sulphonium ylides, but directly to thiane derivatives, as a consequence of the spontaneous rearrangement of the ylides (Scheme 59). The reaction time increased from allyl- to prenyl-sulphides, and this suggests that the bulkier allylic groups slow down the rate of cyclisation and rearrangement.
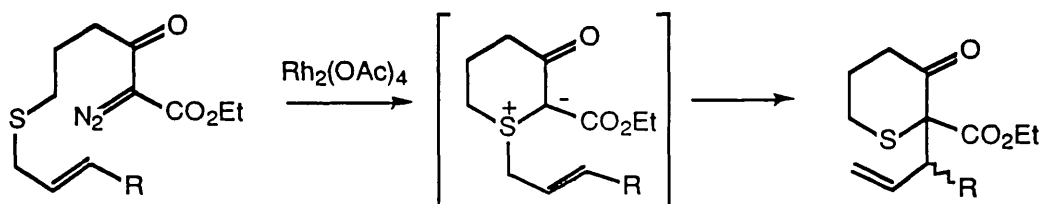
Scheme 59.

Although the rearrangement of allyl sulphonium ylides has been intensively studied in the alicyclic series, extension to the synthesis and rearrangement of cyclic ylides has been paid scant attention, and the dirhodium tetraacetate catalysed reaction has not been reported. Examples of the thermally-generated carbene mediated cyclisation

were discussed in the introduction, as well the alternative approach of deprotonating a sulphonium salt. Both methods have drawbacks. The harsh conditions in the former reaction have been overcome, herein, by generating a rhodium carbenoid from a diazo compound under less forcing conditions. In the latter reaction, the poor regioselectivity of deprotonation, does not allow cyclic ylides to be prepared cleanly, in most cases.

Cyclic sulphides have been used to synthesise six, eight, and larger membered sulphur rings by a ring expansion reaction. As an example, (Scheme 60), the copper carbenoid of ethyl diazomalonate reacts with a dihydrothiophene (237) to give a thiane derivative[88], via [2,3]-rearrangement of an allyl sulphonium ylide. To effect the ring expansion process, the ylide needs to be exocyclic, but the allylic group cannot be exocyclic, and must be partially embedded within the sulphide ring. In the reaction we have developed, however, the opposite criteria apply, so the integrity of the ring and the allylic group is retained upon rearrangement.[88]

(237)
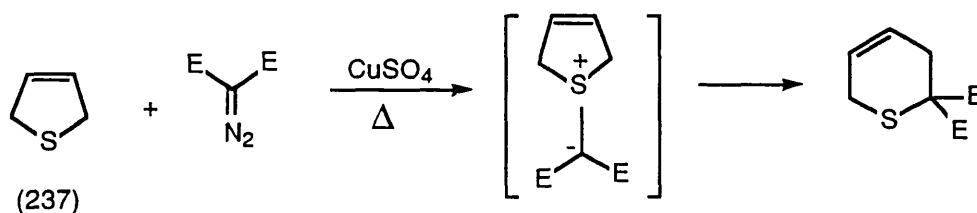
Scheme 60.   E = CO₂Et

The dirhodium tetraacetate catalysed cyclisation of allyl sulphide (Table 10, entry 1) gave the 2-allyl-3-oxothiane-2-carboxylate ester in good yield, 57-59%. The reaction was highly reproducible, even when the reaction variables were altered; that is, we found that the yield was insensitive to the amount of catalyst used, to the concentration of the diazo sulphide (the rate of addition and volume of solvent), and to the scale of the reaction. Assignment of the structure was made by NMR, IR, MS, and microanalysis, and all were consistent with a cyclic compound containing allyl and carbonyl functions.

As mentioned earlier, we postulated that the reaction proceeds via a cyclic allyl sulphonium ylide, which rearranges under the reaction conditions, but to prove that this was indeed the case, we needed to repeat the reaction on a substituted allyl group. This is because the [2,3]-sigmatropic shift of the allyl group involves the conversion

of a sp^2 hybridised carbon into a sp^3 hybridised carbon atom, and *vice versa*, and so placing a substituent at either of the terminal carbons of the allyl group in the diazo sulphide (Scheme 59) should elucidate the mechanism.

Decomposition of crotyl, cinnamyl, and prenyl diazo sulphides with a catalytic amount of dirhodium tetraacetate (Table 10, entries 2-4) resulted in the isolation of substituted thianes, in very good yield, which contained the inverted allyl group. This proves that the reaction occurs by a [2,3]-sigmatropic shift, and not by a direct [1,2]-rearrangement. This also suggests that the ylide is formed as the final intermediate in the reaction, that is, rearrangement only occurs after the rhodium complex is lost from the molecule, generating the ylide. It is well known that the rearrangement reaction of allylic ylides occurs readily without the ylide being complexed to a metal salt; the ylides formed in free-carbene reactions spontaneously rearrange, as do the ylides prepared from sulphonium salts. This is not, however, unambiguous proof that the rearrangement does not occur by initial [2,3]-shift of the allyl group to the metal atom, followed by reductive elimination of the metal salt to the product, although the final step would require a Stevens shift to give the product (Scheme 2).

The [2,3]-sigmatropic shift of prochiral allyl groups also implies that a chiral centre is generated in the process. The relative stereochemistry of this new chiral centre can be influenced by several factors, most notably by the presence of other asymmetric centres, either in the starting material (the sulphonium centre) or in the transition state (the developing chiral centre at C-2). The cyclisation of cinnamyl and crotyl sulphides (Table 10, enties 2-3) gives thianes containing two adjacent chiral centres, as a mixture of two racemic diastereoisomers. Unfortunately, the relative stereochemistry of the products could not be assigned by NMR.

The reaction showed low diastereoselectivity, with the thiane (240) being formed as a 3:2 ratio of isomers, which suggests that the transition states to the two products are very similar in energy. The stereoselectivity of the [2,3]-shift reaction is often low in comparison with the corresponding [3,3]-rearrangement, and this is explained on the grounds that the five membered ring transition state has greater conformational flexibility, and is therefore more susceptible to the effects of stereochemical control by the substituents.

The five membered transition state involved in the rearrangement probably adopts a folded envelope shape, with the substituents around the ring trying to adopt pseudo-

97

equatorial positions, for the lowest energy conformational arrangement. Of the two transition states shown (Scheme 61), the diequatorial arrangement of the ester and R group in (246) would give the *trans* product (240) *via* the lower energy transition state (assuming that the major steric interaction is between these two substituents). The transition state (245) leads to the *cis* relative stereochemistry. Of course, there are other steric interactions in the transition state, a significant one being with the axial C-6 proton on the thiane ring, and these may oppose the major interaction, lowering the selectivity of the reaction.

(245)

(246)
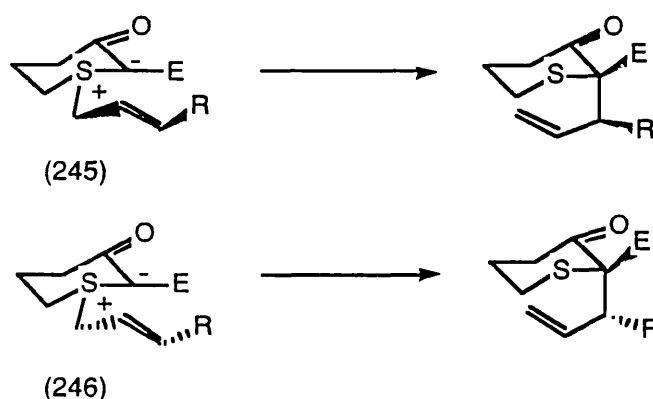
Scheme 61.   E = CO₂Et

Cyclisation of the crotyl diazosulphide (Table 10, entry 2), which consisted of a mixture of three isomers (8:1:1, Scheme 58), gave two regioisomeric rearrangement products in 9:1 ratio. The major isomer (239), a mixture of two diastereomers (2:1), was derived from the *cis* and *trans* isomers, (226a) and (226b), whilst the minor isomer (247) was the result of cyclisation of the sulphide (226c). This rearrangement was shown to proceed by a [2,3]-sigmatropic shift pathway for all isomers, by analysis of the NMR data. Indeed, cyclisation of the three isomers would be expected to give the observed ratio of products.

(247)
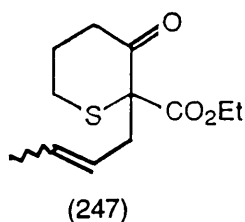
As means of a comparison, we investigated the efficiency of a copper catalyst in the

cyclisation reaction. A solution of prenyl sulphide (228) was added to a suspension of a catalytic amount of copper (II) triflate in boiling benzene. Copper (II) triflate is a recently developed (and cheap) catalyst , that catalyses cyclopropanation and C-H insertion reactions in good yield. The cupric salt is reduced to the cuprous salt *in situ*, by the diazo compound, and the copper (I) salt then acts as the catalytic species. Standard work-up and purification of the reaction mixture gave the expected product (241), in a low yield (26%). The copper (II) triflate catalysed synthesis of oxepane (149) from the diazo alcohol (122), on the other hand, occurred in good yield. These observations are consistent with the reaction involving a copper carbenoid, and the low yield of the thiane suggests that the catalyst may be more readily poisoned than rhodium. It appears unlikely that radical-cationic species are involved in the copper catalysed reaction.[5]

Table 10. Dirhodium Tetraacetate Mediated Synthesis of Thianes
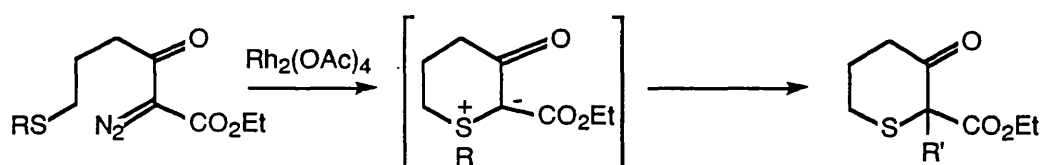
Entry	RS Group	Ylide (%)	-R' Group	Thiane (%)	Compound
1	CH_2:$CHCH_2S$	-	-CH_2CH:CH_2	57-59	(238)
2	E-MeCH:$CHCH_2S$	-	-CH(Me)CH:CH_2	71[a]	(239)
3	E-PhCH:$CHCH_2S$	-	-CH(Ph)CH:CH_2	78[a]	(240)
4	Me_2C:$CHCH_2S$	-	-C(Me_2)CH:CH_2	66 (26)[b]	(241)
5	MeCOS	-	-COMe	40	(242)
6	MeO_2CCH_2COS	-	- H	13	(163)
7	BnS	24 (12)[c]	-	-	(243)
8	EtS	62	-	-	(244)

a, Mixture of diastereomers; b, $Cu(OTf)_2$ catalysed reaction; c, reaction performed in boiling chloroform.

The results in this section indicate that the dirhodium tetraacetate mediated intramolecular reaction of sulphides to give 2,3-trisubstituted thianes is a general and synthetically useful reaction for allyl sulphides. The reaction also generates a tertiary carbon atom at C-2, and such highly substituted centres are usually difficult to prepare.

Acyl Diazosulphides

Acyl sulphides are thioesters, and are as such, less nucleophilic than sulphides. The application of acyl sulphides to the carbenoid mediated cyclisation reaction has been briefly looked at (Section 1.2.3). In the example quoted, the intermediate acylsulphonium ylide derived from (55, R=Ac) rearranged *in situ*, and the product isolated resulted from [1,4]-migration of the acyl group, to give an enol acetate. In contrast, the dirhodium tetraacetate catalysed decomposition of (229) in boiling benzene gave, after work-up and chromatographic purification of the residue, the thiane (242), in 40% yield, the result of [1,2]-rearrangement of the ylide. The difference in the mode of rearrangement of the two ylides is probably the result of the extra conformational freedom of the thiane ring (242), compared to (55, R=Ac), which is restricted by fusion of the thiane ring to a β–lactam ring; this could prevent attainment of a geometry suitable for [1,2]-migration of the acyl group. The ester group in (242) stabilises the ylide, and this may play a part in determining the mode of rearrangement.

The mechanism of [1,2]-rearrangement cannot be concerted, on stereochemical grounds, and must therefore involve homo- or heterolytic bond cleavage between the carbonyl and sulphur. The acyl sulphonium ylides undergo rapid rearrangement because of two contibutory factors: (1), the destabilising effect on the ylide of the electron withdrawing group on sulphur; and (2), the easy cleavage of the C(O)-S bond compared to a C-C bond. Both of these factors favour migration of the acyl group to a carbanionic centre by a stepwise process.

The product isolated in low yield from the dirhodium tetraacetate catalysed reaction of substituted thioester (Table 10, entry 6) is thiane (163). This degradation probably occured in the intermediate ylide (248), by loss of the malonyl group in a β-elimination reaction, which liberated the product and ethoxycarboylketene. This fragmentation reaction is facile because of activation of the proton by the ester group.

(248)
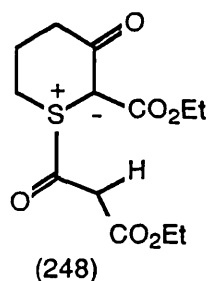
Alkyl Diazosulphides

In all the examples of dirhodium tetraacetate catalysed cyclisation of diazosulphides discussed so far, we have only isolated the product of rearrangement, and not the intermediate ylides, although we have strong evidence for their intermediacy from the reaction of allyl sulphides.

The dirhodium tetraacetate catalysed reaction of benzyl and ethyl diazosulphides (Table 10, entries 7-8), however, resulted in the isolation of purple solids, after removal of the catalyst and solvent from the reaction mixture (all the thiane derivatives prepared so far were liquids). The solids were purified by crystallisation, to give colourless crystalline compounds, with high melting points, and low wavenumber IR absorptions (1660 cm^{-1}). These facts, together with NMR evidence, which showed that the protons α-to the sulphur atom were considerably deshielded compared to the thianes prepared previously, are characteristic of stabilised sulphonium ylides. Additional proof for the assignments was obtained by heating the ylides in an inert solvent: thermolysis of benzyl sulphonium ylide (243) in boiling xylene for 2.5 hours led cleanly to the product of [1,2]-rearrangement, the thiane (249), in 55% yield.

The spectroscopic and physical properties of the thiane (249) were consistent with the previously prepared thianes (238)-(242), with the IR absorption of the keto and ester groups appearing at 1746 cm^{-1} and 1712 cm^{-1}, respectively.

There is evidence that a radical pair cage mechanism is operating in the Stevens rearrangement of stabilised sulphonium ylides. This is illustrated (Scheme 62). The stepwise mechanism involves initial cleavage of the bond between sulphur and the benzyl group, to generate two radical species, which can recombine to the product (249) by forming a bond with the radical at C-2. The driving force behind the reaction is the strength of the C-C bond in comparison with the C-S bond, which is

101

partly why the radicals form so readily in the first place.
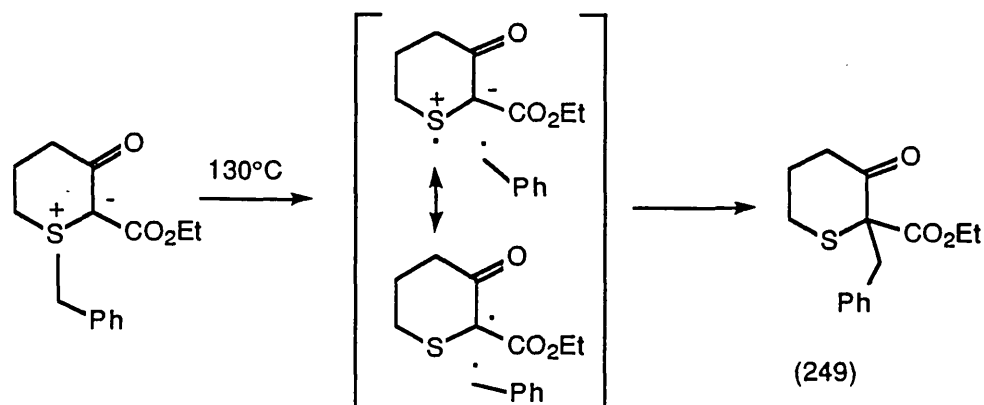
Scheme 62.

In comparison, the dirhodium tetraacetate catalysed decomposition of the diazoketone (55, R=Bn) leads directly to the thiane (57), which is the result of [1,4]-rearrangement of the benzyl group in the ylide. The reasons behind the contrasting behaviour are analogous to those discussed for the acyl sulphides. The [1,4]-rearrangement does not preclude migration of the group by an intramolecular radical pathway, because the two radicals are held together by the solvent cage surrounding them.

Smooth decomposition of the ethyl sulphonium ylide (244) was observed on rapidly heating a suspension of it in xylene to reflux, to give the thiane (163), by loss of ethene. No [1,2]-rearrangement of the ethyl group was observed because a lower energy concerted pathway can operate, that of β-elimination. This transformation provides an alternative route to (163). Indeed, decomposition of ethyl diazosulphide (232) under the standard dirhodium tetraacetate catalysed conditions, using refluxing toluene or xylene, instead of benzene, gave (163) directly in 92% and 83-84% yield, respectively (Scheme 63). The reaction in toluene required twenty minutes at reflux, whereas in xylene, the evolution of gas was over in about thirty seconds.
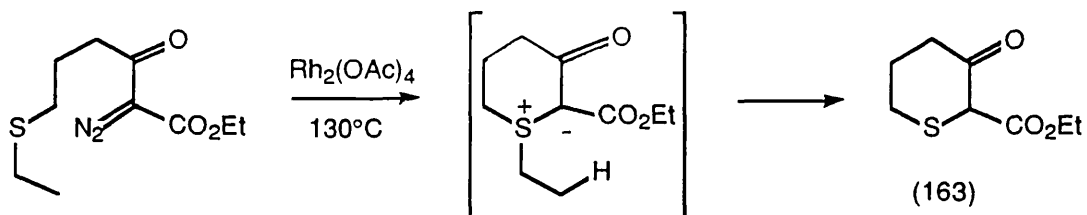
Scheme 63.

Elimination of ethene has been observed previously in the cyclisation of ethyl diazoketosulphide (55) to a thiane, but the ylide was not isolated. Rearrangement of the ethyl ylide (250), however, occurred at 80°C, to give (251), the result of a [1,4]-shift, involving the carbonyl group of the ester. The importance of the geometrical constraints imposed by the ring on the outcome of rearrangement is aptly illustrated in (250), where the required transition state for β-elimination cannot be attained.[21] Davies also reports that upon heating to 160°C, five and seven membered

<div align="center">

80°C

(250)   (251)

</div>
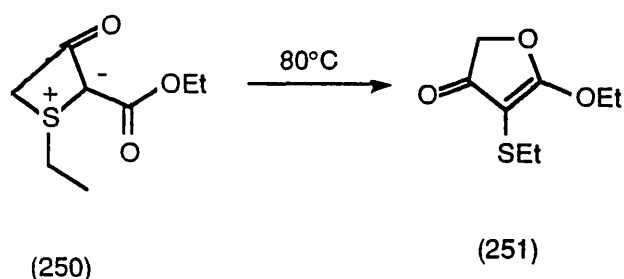
phenyl sulphonium ylides suffer endocyclic β-elimination, to give acyclic products, whereas the six ring ylide undergoes a [1,4]-rearrangement.[21] In none of the six ring sulphonium ylides prepared herein, was internal [1,4]-rearrangement observed, in contrast with the above observation. However, no evidence for endocyclic β-elimination was found either. In our case all rearrangements that did occur were exocyclic, i.e. the thiane ring remained intact. This is explained by the fact that in the literature examples, the strength of the sulphur bond to the phenyl ring, lowers its migratory aptitude.

Thiepanes

The dirhodium tetraacetate catalysed decomposition of the sulphides (234)-(236) was also investigated, and the results are illustrated in Table 11. We have previously found that the cyclisation of 1,6-diazomercaptan (137) gave thiepane (164), in ~30% yield, and extension of the reaction to the less nucleophilic sulphides would give the corresponding C-2-substituted thiepanes. Indeed, the dirhodium tetraacetate catalysed decomposition of cinnamyl diazosulphide (234), gave the expected thiepane (252) in 29% yield, as a mixture of two diastereoisomers (3:2), and so the extra conformational flexibility in the seven membered ring does not enhance the selectivity

in the rearrangement of the ylide.

The synthesis of seven membered cyclic sulphonium ylides has received little attention, and reports of their rearrangement reactions are equally rare. However, Davies has recently prepared a seven membered phenylsulphonium ylide, in good yield. The ylide ring was fragmented upon thermolysis by β-elimination.

The reaction of benzyl diazosulphide (Table 11) gave, after chromatography, a low yield of the debenzylated thiepane (164). The thiepane may have resulted from decomposition of the ylide on silica gel, or may be from the loss of a benzyl radical upon rearrangement of the ylide *in situ*. No ylide could be isolated from the complex crude reaction mixture by recrystallisation, and we could not isolate any products derived from the ylide by [1,2]-shift or β-elimination under the reaction conditions, either. Nor was any γ-C-H insertion product identified, or the fate of the benzyl group determined.

Finally, the reaction of the crude ethyl diazosulphide (Table 11) gave the ethyl sulphonium ylide (253), in a very poor yield (12%).

In summary, allyl thiepanes can be prepared in moderate yield using this procedure, but thiepane ylides could only be isolated in a very poor yield.

Table 11. Dirhodium Tetraacetate Mediated Synthesis of Thiepanes
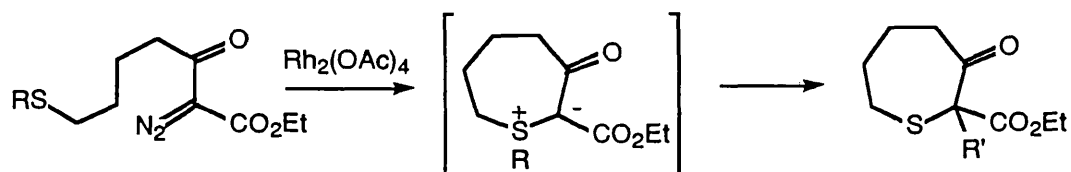
Diazo	RS Group	Ylide (%)	-R' Group	Thiepane (%)	Compound
(234)	E-PhCH:CHCH$_2$S	-	-CH(Ph)CH:CH$_2$	29	(252)
(235)	Bn	-	-H	7	(164)
(236)	Et	12	-	-	(253)

4.3   Synthesis and Reactions of α-Diazo-β-Ketosulphides

We have already shown that substituted thianes can be formed in very good yield by dirhodium tetraacetate mediated cyclisation of diazoketoesters, but the reaction was less successful when applied to the synthesis of thiepanes. In a similar manner, the corresponding diazoketones are also known to be good substrates for the synthesis of thianes. Therefore, in accordance with our aim of exploring the factors effecting the outcome of formation and rearrangement of cyclic sulphonium ylides, we prepared several ω-mercaptodiazoketones (Scheme 64).

The diazoketones were prepared using standard chemistry: alkylation of 5–mercaptopentanoic acid, to give (254a), was achieved in moderate yield, by treatment of the mercaptan with allyl bromide, and triethylamine, in DMF, although some of the mercaptan was recovered and the product of esterification, allyl 5–allylthiopentanoate, was also present, after work-up and purification. Alkylation of methyl 5-mercaptopentanoate, under the same conditions, with cinnamyl bromide, gave the sulphide ester (255b), in 37% yield, but some mercaptan was still recovered. Alkylation of methyl 5-mercaptopentanoate with benzyl bromide, and excess potassium carbonate, in acetone at reflux, gave the benzyl ester (255c), in 77% yield. The methyl esters (255b-c) could be hydrolysed in high yield, with aqueous methanolic potassium hydroxide, to give the acids (254b-c).
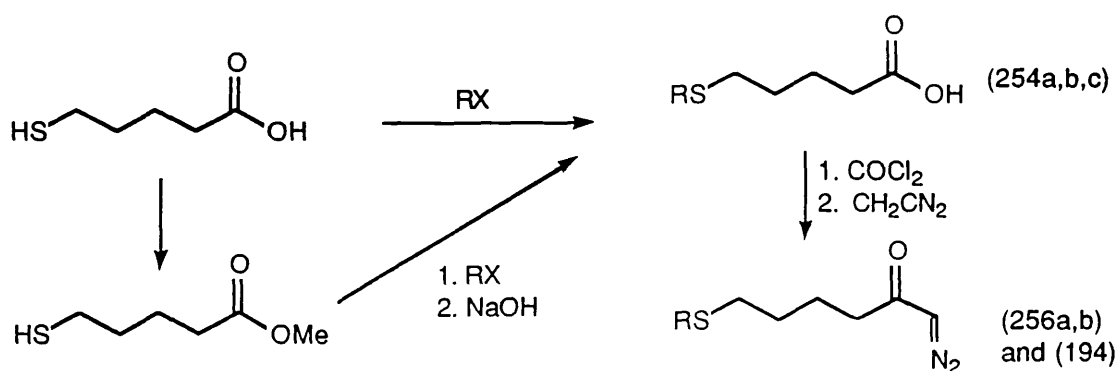
Scheme 64.   R =   allyl (a) , 3-phenylallyl (b) . benzyl (c)

The acids were converted into their acid chlorides with excess oxalyl chloride (15 h/ 25°C), and the :de acid chlorides could be purified by distillation under reduced pressure.

The diazoketones (256a-b) and (194), were prepared, in good yield (49-66%), by the addition of three molar equivalents of a solution of diazomethane in ether (ethanol free) to a solution of the acid chlorides in ether. After 12 h, the solvent was evaporated, and the residue subjected to chromatography on Florisil. The diazoketones are yellow oils, with lower thermal and acid stability than the corresponding diazoketoesters.

Next, our attention was turned to the cyclisation reaction (Table 12). The dirhodium tetraacetate catalysed decomposition of the allyl diazoketosulphide (256a) in boiling benzene led to rapid consumption of the starting material, and work-up and purification of the crude product by chromatography, gave the thiepane (257), in good yield. Dirhodium tetraacetate mediated cyclisation of (256b) gave (258), in 64% yield, as a mixture of diastereoisomers (4:1). The coupling constants between the benzylic protons and the proton at C-1 were recorded for the major and minor isomers as 9.9 Hz and 8.7 Hz, respectively. This suggests that the protons have adopted an anti geometry in both diastereomers. The increased selectivity observed in the reaction of the diazoketone (256b), compared to the diazoketoester (252), is a result of a reducion in the steric interaction between the substituent at C-2 on the thiepane ring, and the phenyl substituent on the allyl group, in the transition state for the rearrangement. With the diazoketoesters, steric repulsion between the ester and phenyl groups disfavours the transition state (246) (Scheme 61), in which both substituents adopt an equatorial configuration, relative to the transition state (245), where only one group is equatorial. With the diazoketones (a proton instead of the ester), this interaction is diminished significantly, and so the transition state with two equatorial substituents (cf. 245)is strongly favoured.

Benzyl sulphide (194) was decomposed under standard conditions to give, upon purification, the thiepane (259), in a moderate yield (26%). The ylide rearranged in situ at 80°C, because it is less stabilised without the ester group than (243). The reaction was repeated at room temperature, in dichloromethane, but under these conditions, neither the ylide nor the thiepane were isolated.

By comparing the yields obtained from the dirhodium tetraacetate catalysed reactions of the diazoketo- and diazoketoester- sulphides, (Table 12) and (Table 11), respectively, it can be seen that the former are superior substrates for the cyclisation reaction; for both sets of substrates, the allyl sulphides give the best results.

Table 12. Dirhodium Tetraacetate Mediated Cyclisation of Diazoketosulphides
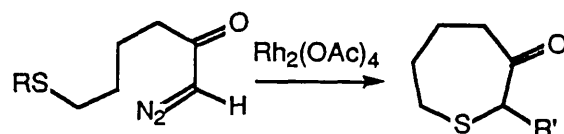
Diazo	RS Group	-R' Group	Yield(%)	Compound
(256a)	$CH_2CH:CH_2S$	$-CH_2CH:CH_2$	42	(257)
(256b)	E-PhCHCH:CH$_2$S	$-CH(Ph)CH:CH_2$	64[a]	(258)
(194)	Bn	-Bn	26 (0)[b]	(259)

a, Mixture of diastereomers; b, yield in dichloromethane at 25°C.

The superior yields recorded may be due to the more facile rearrangement of the ylides; due to their lower stability, however, an alternative explanation is that of the steric hindrance of the ester group, which would inhibit the cyclisation and rearrangement reactions. Indeed, benzyl sulphide (194) gave the thiepane (259), whereas the more bulky ester benzyl sulphide (235) gave no adducts.

Finally, the difference in the spectrum of reactivity may be due to the electronics of the rhodium carbenoid. The ketoester carbenoid should be more electrophilic compared to the diazoketone derived carbenoid, and therefore more susceptible to attack by nucleophiles. Infact, the latter carbenoid appears a more efficient trap for the sulphides. Indeed, the reaction of the carbenoids with the reaction solvent (benzene) was only observed, in low yield, in the reactions of the diazoketo sulphides, which would give the less electrophilic carbenoid (Scheme 65).

The reaction with benzene involves initial cyclopropanation of the aromatic ring, followed by a rapid electrocyclic ring expansion to a cycloheptatriene (260, 261). No further rearrangement, to the conjugated isomers by sigmatropic hydrogen shifts, was observed, even after chromatography on silica gel. The reaction of ketocarbenoids with benzene is well known, although the corresponding reaction of ketoestercarbenoids is relatively rare.[5]

The apparently anomalous difference in reactivity between the carbenoids is a reminder that their structure remains unknown.
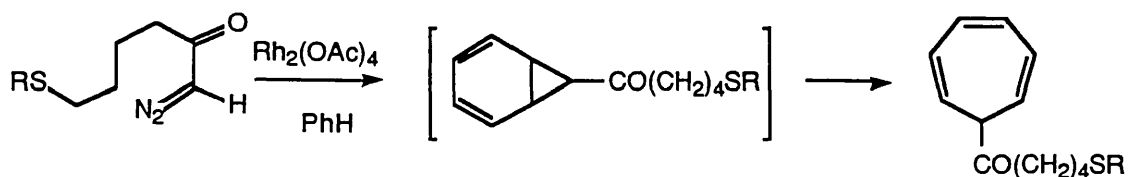
Scheme 65. R = CH₂CH:CHPh (260), CH₂Ph (261)

4.4 Conclusions

The dirhodium tetraacetate catalysed cyclisation reaction of 1,5- and 1,6–diazosulphides has been explored. The transformation provides access to substituted thianes and thiepanes, in very good and poor yields, respectively. The cyclisation involves an intramolecular reaction between a rhodium carbenoid and the sulphide, to give a cyclic sulphonium ylide. The intermediacy of this species was confirmed by the isolation of stable ylides in the reactions of benzyl and ethyl sulphides. In allyl sulphonium ylides the presence of a low energy rearrangement pathway, the [2,3]-sigmatropic shift, resulted in the spontaneous rearrangement of these ylides.

The propensity of the ylide to rearrange is also a function of the stability of the ylide bond. Destabilising the ylide by removing the ester group, from the carbanion centre, encourages rearrangement to occur at a lower temperature. In an analogous manner, the presence of an electron withdrawing group at sulphur allows Stevens rearrangement to occur below 80°C.

CHAPTER FIVE

Dirhodium Tetracetate Catalysed Reaction of Diazosulphoxides: Preparation and Reactions of Cyclic Sulphoxonium Ylides

5.1 Introduction

The reaction of sulphides with metallo-carbenoids has been well documented, and an application of the intramolecular reaction to the synthesis of 2-substituted thianes and thiepanes was discussed in the previous Chapter.

In contrast, increasing the oxidation state of sulphur from sulphide to sulphoxide might be expected to decrease the electron density on sulphur, and so destabilise the ylide. Infact, sulphoxonium ylides are more stable than sulphonium ylides. This point can be illustrated by comparing the stability of dimethylsulphoxonium methylide and dimethylsulphonium methylide: the former is stable at room temperature, and the latter is only stable below 0°C. The reason behind this behaviour lies in the ability of oxygen to stabilise the carbanion portion of the ylide, either by delocalisation of the charge onto the oxygen atom, or by facilitating d_π-p_π bonding between the carbon and the sulphur atoms.

The chemistry of substituted sulphoxonium methylides is broad, as a result of their powerful nucleophilicity; they are readily prepared by deprotonation of the corresponding sulphoxonium salt. In comparison with sulphides, the reaction of sulphoxides with carbenes and carbenoids to generate ylides is little studied.

The dipolar nature of the sulphoxide bond imparts the ability to act as either an oxygen or a sulphur nucleophileor as a sulphur electrophile, and this feature is found in all sulphoxide chemistry. The reaction with carbenes does not lead to [1,2]-cycloaddition products, but to two discrete products resulting from attack at different heteroatoms (Scheme 66).
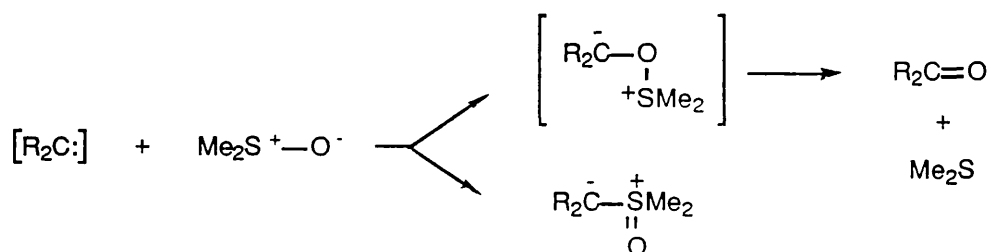
Scheme 66.

Carbenes can attack at the oxygen atom to furnish a dipolar intermediate, which fragments into a ketone and a sulphide, therefore overall, a reduction of the sulphoxide

and oxygenation of the carbene is accomplished. This pathway has been observed in the reaction of dichlorocarbene with sulphoxides, and under phase transfer catalysis conditions , the sulphides were formed in good to very good yield, as the only reported product.[93]

Exclusive attack at sulphur has been reported for the copper (II) sulphate catalysed reaction of dimethyl- and diphenylsulphoxide with ethyl diazoacetate, and also in the photochemical reaction between diethyl diazomalonate and sulphoxides (Scheme 67).[94] The yields are moderate for the copper catalysed reaction, but poor for the photochemical reaction. Various aryl substituted ethyl diazoacetates have been thermolysed in the presence of dimethyl sulphoxide (DMSO) and catalytic amounts of copper (I) cyanide, to give very high yields of sulphoxonium ylides (63-94%).[95] This route to sulphoxonium ylides is the only alternative to deprotonation of the sulphoxonium salt, and the ester substituted ylides were found to be thermally stable, showing that the substituents on the carbene/carbenoid and the method of generation have significant control on the course of the reaction.

$$ \underset{N_2}{\overset{R}{\diagdown}}\!\!-\!\!CO_2Et \quad \xrightarrow[\text{hv or copper salts}]{Me_2SO} \quad R\diagdown\!\!\overset{-}{C}(CO_2Et)\!\!-\!\!\overset{+}{S}Me_2(=O) $$
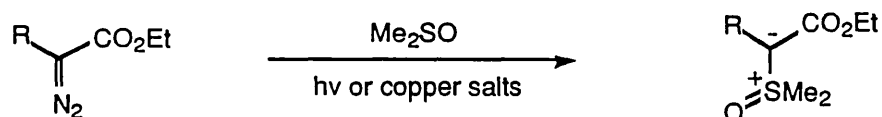
Scheme 67.   R = aryl (CuCN), H (CuSO$_4$), or CO$_2$Et (hv)

The factors affecting the regioselectivity of the reaction have not been explored, and application of this reaction to intramolecular systems has not been investigated. The aim of this Chapter, therefore, is to explore the cyclisation reactions of 1,3 - 1,6- diazosulphinyl compounds catalysed by dirhodium tetraacetate, with special reference to the synthesis of cyclic sulphoxonium ylides.

5.2   Synthesis and Reactions of 1.5- and 1.6-Diazosulphoxides

This section details our approach to six and seven membered cyclic sulphoxonium ylides.

5.2.1   Synthesis of Ethyl 2-Diazo-3-Oxo-6- and 7-Sulphinyl Carboxylates

The methodology developed for the synthesis of 2-diazo-3-oxo-6- and 7–thioalkylcarboxylates (Chapters 2 and 4), was applied to the synthesis of sulphoxides. The reaction of ethyl lithiodiazoacetate with γ– and δ–thiolactones, and subsequent alkylation of the mercaptan, provided a simple two step synthesis of the precursors for oxidation. Treatment of the sulphides, in a dichloromethane solution at -10°C, with m-CPBA gave the sulphoxides (262a-266a) in good yield (53-61%), after reductive work-up (10% sodium metabisulphite) and chromatography on silica gel (Scheme 68). Over-oxidation to the sulphones (263b-265b) occurred as a competing, but minor reaction. Suppression of this side reaction could not be achieved by lowering the reaction temperature or by adding the peracid more slowly.

The sulphoxides are often low melting solids, with greater longevity than the corresponding sulphides.

n = 0	Bn	(262a)	-
	Et	(263a)	(263b)
	CH_2:$CHCH_2$	(264a)	(264b)
	PhCH:$CHCH_2$	(265a)	(265b)
n = 1	PhCH:$CHCH_2$	(266a)	-
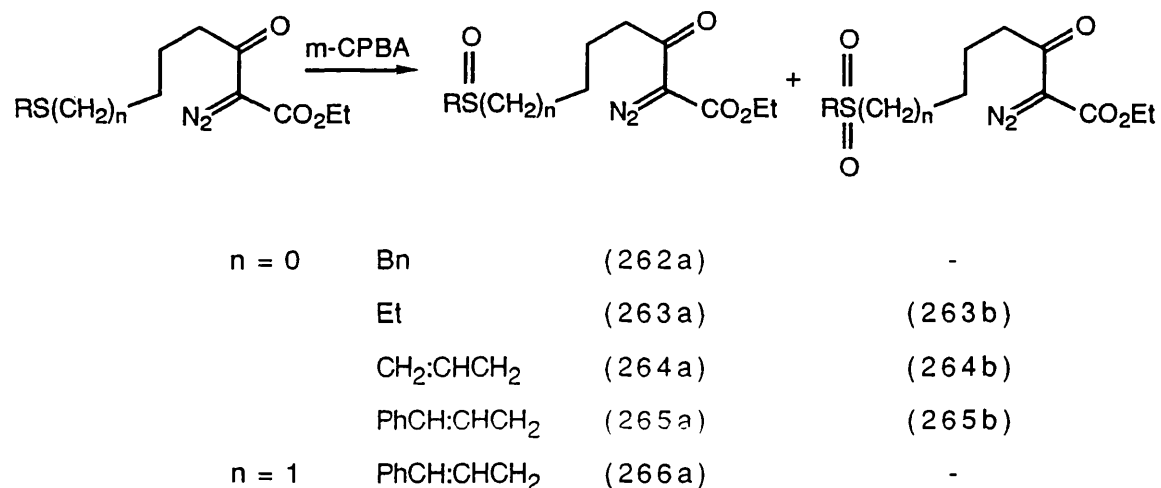
Scheme 68.

5.2.2 Dirhodium Tetraacetate Mediated Cyclisation of Sulphoxides

The lower nucleophilicity of the sulphoxide group compared to the sulphide would be expected to compromise its reactivity. However, the sulphoxides (262a-266a) favour the participation of sulphur over oxygen as nucleophile, because the ring size of the transition state is smaller. Trapping of the carbenoid by the nucleophile needs to be rapid in order that competing reactions, such as C-H insertion, rearrangement, dimerisation, are suppressed. Treatment of a solution of the sulphoxides (262a–265a) in boiling benzene with a catalytic amount of dirhodium tetraacetate, rapidly led to consumption of the starting materials (<2 min). The catalyst did not dissolve, and no colour change was observed in the solution, suggesting that complexation of the sulphoxide to the catalyst was not a serious problem. After removal of the catalyst, and evaporation of the solvent, the polar residues were recrystallised from benzene/ethyl acetate or benzene/dichloromethane, to give colourless crystals of the sulphoxonium ylides (268-271) as the only products, in 54-84% yield (Scheme 69).

R	
Bn	(268)
Et	(269)
CH_2:$CHCH_2$	(270)
PhCH:$CHCH_2$	(271)
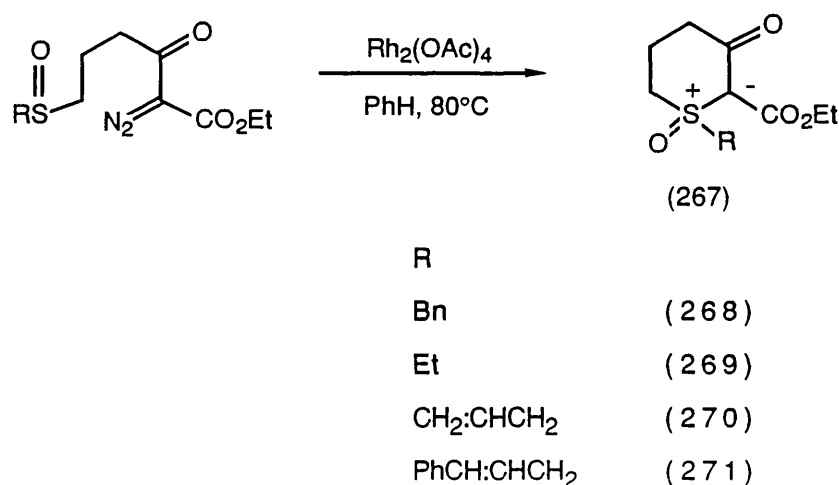
Scheme 69.

Evidence for the general structure (267) of the ylides is outlined below:

The high melting points recorded for (268-271), in the range 130-175°C, broadly agree with examples in the literature; the values suggest a structure with strong intermolecular forces, a criterion satisfied by a highly polar compound. The polarity of the structure was confirmed by TLC. (R_f ~0.1, ethyl acetate); (267) is far more polar than the diazosulphoxide precursors. The fact that the compound runs on TLC

indicates stability towards mild acid hydrolysis.

High-field NMR indicates the presence of chiral centres; protons α- to the sulphur are diastereotopic, and the methylene protons of the ethyl ester are not a simple quartet. The ring α-sulphinyl protons ($\sim$3.4-3.6 ppm) are also deshielded relative to the sulphoxide precursors ($\sim$2.6-2.8 ppm). The protons on the R group are also deshielded, and this supports the ylide (267), rather than a rearranged structure, with the R group at C-2; the complexity of the NMR also suggests a cyclic structure, although unambiguous proof of the structure by NMR was not possible. The IR spectra of (268-271) showed the presence of two bands, centred at 1690 and 1630 cm^{-1}; the absorptions were assigned to the ester and keto groups, respectively. This is a strong indication of the presence of an ylide moiety in the molecule. Cyclic sulphonium ylides (Section 4.2.2), have carbonyl absorptions centred at 1675 and 1610 cm^{-1}. Comparing the two ylides, the sulphoxonium ylides absorb at higher frequencies, and this suggested a smaller degree of delocalisation of charge into the keto-ester system (less enolate character). This is in accord with the greater stability of the sulphoxonium ylides being derived in part from delocalisation of the negative charge onto the sulphoxide unit.

To confirm the assignment, the three dimensional structure of (270) was obtained by X-ray crystallography (Figure 2) (see Appendix).

The crystal structure of (270), ethyl 1-allyl-3-oxo-3,4,5,6-tetrahydrothiabenzene-1-oxide-2-carboxylate, confirms the proposed general structure (267). Furthermore, the X-ray data shows that: a), the molecule adopts a half-chair conformation, with the sulphoxide oxygen axial, and the more bulky allyl group in the equatorial position. In cyclic sulphoxides, there is an observed preference for the oxygen to adopt an axial configuration, based on steric considerations. The reduced steric interactions in the ring (270), together with the observed coplanarity of the p-orbital on the carbanion and the oxygen-sulphur bond, suggests that the configuration is electronically controlled; b), lengthening of the carbonyl bonds, and shortening of the C2-3 bond, compared to average values. This indicates some delocalisation of electron density into the keto- and ester groups.

Cyclic sulphoxonium ylides are a rare class of compound. The only literature examples are those prepared by Corey and Chaykovsky,[96,97] although other workers have prepared the ylides by a similar route.[98] The ylides (272) were synthesised from α,β-unsaturated esters and dimethylsulphoxonium methylide in THF

(Scheme 70).

$$Me_2\overset{+}{S}\underset{CH_2}{\overset{O}{\overset{\|}{}}}^{-} \quad + \quad \overset{R}{\underset{R'}{}}\diagup CO_2Et \quad \xrightarrow{\text{THF, 65°C}} \quad (272)$$
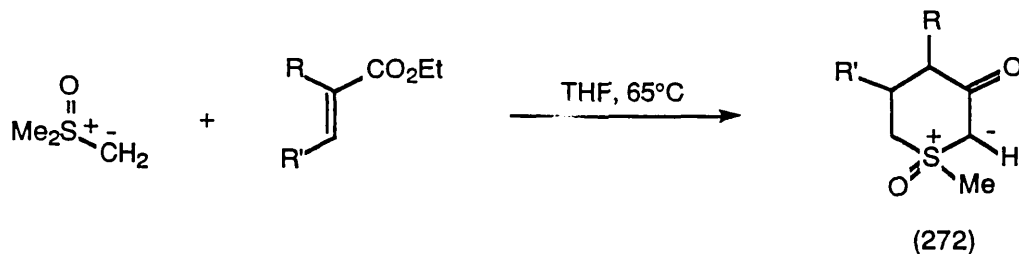
Scheme 70.   R, R' = H, H; H, Ph; (CH₂)₄;

The cyclic ylides (272), although less stabilised than (267), exhibit similarly high melting points, and low IR absorption frequencies.

Our attention was next turned from the synthesis of six membered ring sulphoxonium ylides to larger rings. We have shown that the synthesis of 1-substituted thiepane ylides by intramolecular trapping of a carbenoid by a sulphide was possible in poor to moderate yield (Section 4.2.2). Results in this section show that the lower nucleophilicity of the sulphoxide is not reflected in lower yields of the sulphoxonium ylides, at least in the six membered ring series. Infact, the recorded yields of (267) are higher than for the corresponding sulphonium ylides, and this is probably a consequence of the greater stability of the sulphoxonium ylides.

Treatment of a solution of diazosulphoxide (266a) in boiling benzene with a catalytic amount of dirhodium tetraacetate, followed by the usual work-up after two minutes, gave a multicomponent mixture, from which no solid could be isolated by recrystallisation. IR spectroscopy on the crude reaction mixture did not indicate the presence of either an ylide or a cyclopentanone, from C-H insertion. To determine whether the failure to cyclise was the result of the sulphoxide group, or the electronics of the carbene, we prepared sulphoxide (273), the sole product of oxidation of (194) with mCPBA at-20°C, in 84% yield.

$$\text{BnS}\diagdown\diagup\diagdown\underset{N_2}{\diagup}\overset{O}{\diagdown}_H \qquad \xrightarrow[\substack{-20°C \\ Na_2HPO_4}]{\text{m-CPBA}} \qquad \text{BnS}\underset{\|}{\overset{O}{\|}}\diagdown\diagup\diagdown\underset{N_2}{\diagup}\overset{O}{\diagdown}_H$$

(194)   (273)
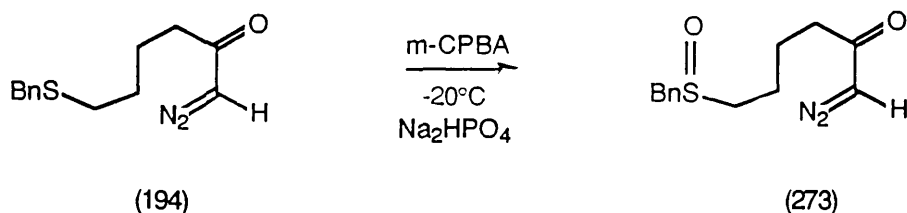
Dirhodium tetraacetate catalysed decomposition of (273) in boiling benzene also gave a

115

multicomponent mixture, from which no products could be isolated. Decomposition of (273) by boron trifluoride etherate in dichloromethane led to a complex mixture. Presumably, the failure to cyclise is due to the inability of the sulphoxide to react with the carbene or carbonium ion fast enough to prevent the destructive side reactions taking place.

5.3   Synthesis and Reactions of 1,4-Diazosulphoxides

This section details the synthesis of five membered ring sulphoxonium ylides.

5.3.1   Synthesis of Ethyl 2-Diazo-3-Oxo-[(2-Sulphinyl)phenyl] propanoates

An alternative strategy was developed for the synthesis of 1,4-diazosulphoxides, based on the reaction of ethyl lithiodiazoacetate with aromatic aldehydes (Scheme 71).
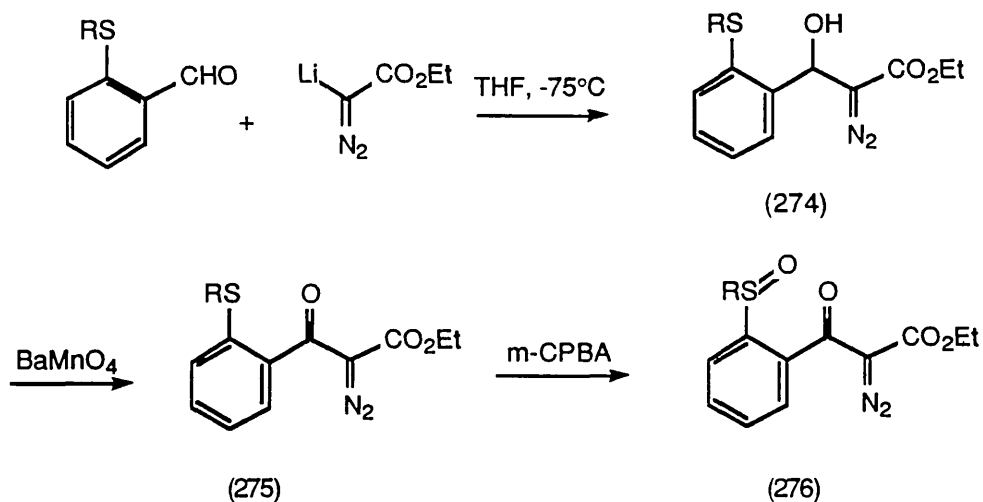
Scheme 71.   R = Ph (a), Bn (b)

The reaction of benzaldehyde with ethyl lithiodiazoacetate has been reported to be facile and high yielding.[66] We observed an analogous ease of reactivity in the condensation of *ortho-* substituted benzaldehydes with ethyl lithiodiazoacetate; the bulky nature of the *ortho* groups were not detrimental to the reaction.   Thus, 2-(benzylthio)benzaldehyde and 2-(phenylthio)benzaldehyde reacted at -75°C with ethyl lithiodiazoacetate generated *in situ*, to give the diazo-alcohols (274), in

excellent yield. The alcohols (274) could be oxidised by treatment with 2-3 equivalents of barium manganate in dichloromethane, to give (275) in high yield. Competing oxidation of the sulphides by barium manganate was not observed, even in dichloromethane at reflux. Further oxidation of the diazoketo-sulphides to the sulphoxides (276) was successfully achieved using m-CPBA as the oxidant, and the products were isolated in high yield. No sulphone was formed in the reaction, even when it was conducted at 25°C.

5.3.2 Dirhodium Tetraacetate Catalysed Reaction of 1,4-Diazosulphoxides

Rapidly heating a benzene solution of (276) to reflux, followed by the addition of a catalytic amount of dirhodium tetraacetate, resulted in the rapid evolution of a gas, for about one minute, together with the development of a yellow colour in the solution. After removal of the catalyst, and evaporation of the solvent, the residue was recrystallised to give the ylides (277a) and (278a), as crystalline solids in 70% and 58% yields, respectively. The mother liquors were subjected to flash chromatography on silica gel, to furnish the tricarbonyl compounds (277b) and (278b) as minor products, in 19% and 6% yields, respectively (Scheme 72).

Ph	(277a)	(277b)
Bn	(278a)	(278b)
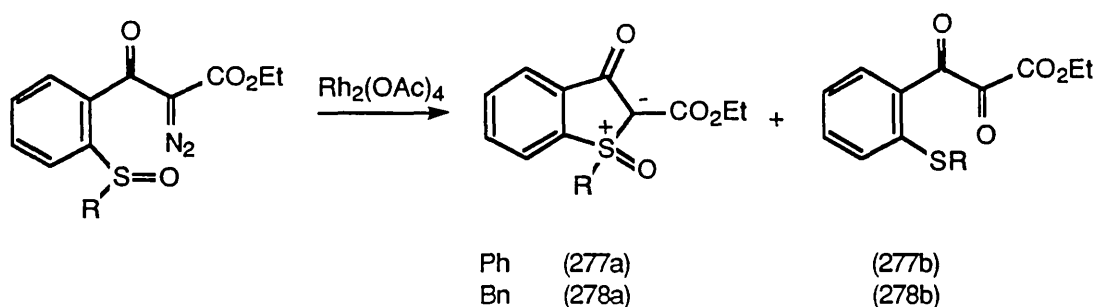
Scheme 72.

The physical and analytical data for the sulphoxonium ylides (277a and 278a) was consistent with those observed for the six membered ring ylides (267). The carbonyl absorptions in the IR spectrum ,~1720 cm^{-1}(ester), and 1630-1655 cm^{-1} (keto) reflect the additional strain present in a five membered ring. There has been no reported synthesis of this ring system before, therefore, the absolute structure.of the ring system was confirmed by X-ray crystallography on (278a)

(Figure 3).(Appendix).

The tricarbonyl compounds (277b and 278b) are yellow and readily hydrated oils. Proton and carbon-13 NMR spectroscopy showed the presence of the keto- and hydrate forms, in varying ratio. Dehydration of the hydrate could be achieved *in vacuo* over phosphorus pentoxide, resulting in considerable simplification of the NMR spectrum. The IR spectrum also indicated the presence of a hydrate; the carbonyl region was complex, absorptions centred at 1745, 1710, and 1675 cm^{-1} were recorded. Further evidence for the structure of (277b) was obtained by treating it with tosylhydrazide. The expected tosylhydrazone was not isolated; chromatography of the crude reaction mixture on Florisil gave the diazosulphide (276a), in 58% yield. Tosylhydrazones of di- and tri-carbonyl compounds are labile, and decomposition can be effected by treatment with a weak base, resulting in the elimination of toluenesulphinic acid, to give diazo compounds. The isolation of (276a) is consistent with decomposition of the tosylhydrazone of (277b) on Florisil. Furthermore, TLC (on silica gel) of the reaction mixture before and after chromatography showed two compounds of widely differing R_f values, the latter was far less polar.

The power of the intramolecular reaction between nucleophiles and rhodium carbenoids has been aptly demonstrated in the high yielding syntheses of five and six membered cyclic sulphoxonium ylides reported herein. The dirhodium tetraacetate catalysed reaction of sulphoxides (276) to give (277) and (278) occurs in overall high yield. The sulphoxonium ylides, (277a) and (278a), are the result of sulphur attacking the carbenoid carbon, *via* a five membered transition state, whereas the tricarbonyl products, (277b) and (278b), are the result of a six membered ring transition state, in which the oxygen atom is transferred from sulphur to the carbene centre (Scheme 66). The fact that there is a kinetic preference for the involvement of a five membered transition state over a six membered transition state,[69] indicates that the intrinsic reactivity (nucleophilicity) of the oxygen is at least equal to the sulphur atom, a reflection on the dipolarity of the sulphoxide bond.

The ratio between the two products varies from 10:3 for (277), to 10:1 for (278), and this is in accord with steric and inductive effects lowering the nucleophilicity of the diarylsulphoxide (276a), favouring participation of oxygen as the nucleophile.

The dirhodium tetraacetate catalysed reaction of (276b) ı dichloromethane (room temperature/15h) gave a mixture of both possible products, (278a/278b), in 72% overall yield, and 11:2 ratio, which indicates the product ratio is both solvent and

temperature dependent.

5.4   Synthesis and Reaction of Ethyl 4-[(2-Carboxymethyl)-phenylsulphinyl]-2-Diazo-3-Oxobutanoate

Finally, our attention was turned to the chemistry of 1,3-diazosulphoxides.

Sulphoxide (281) was prepared in three steps, using the more conventional diazo transfer reaction to introduce the diazo group (Scheme 73). Alkylation of methyl 2-mercaptobenzoate with ethyl 4-chloroacetoacetate in DMF gave β-ketoester (279) in 96% yield. Diazo transfer on (279) with tosyl azide gave the diazoester (280) in 44% yield, which was oxidised selectively to the sulphoxide (281), by m-CPBA, in 93% yield.
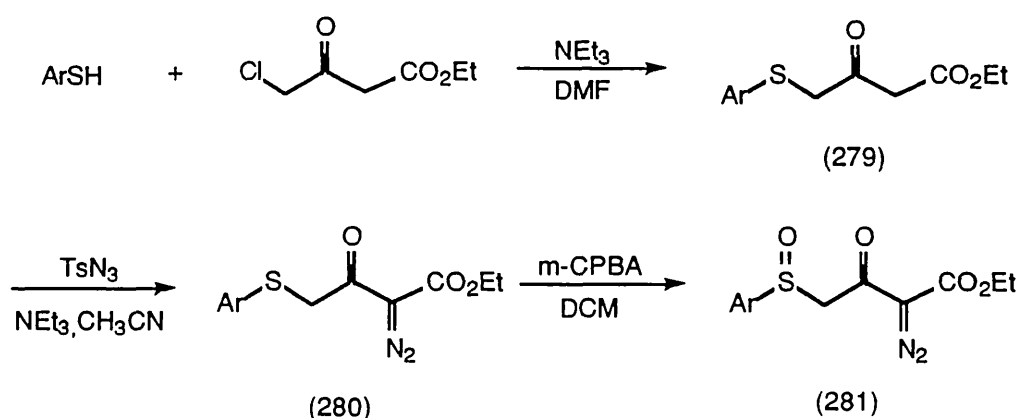
Scheme 73.   Ar = 2-(ethoxycarbonyl)phenyl

By analogy with the previous examples, dirhodium tetraacetate catalysed decomposition of (281) could either lead to a four membered sulphoxonium ylide, or to a tricarbonyl compound, by oxygen transfer, through a five membered transition state.

Addition of a catalytic amount of dirhodium tetraacetate to a solution of (281) in boiling benzene, led to a rapid evolution of nitrogen and the development of a yellow colour in the solution. Removal of the catalyst, evaporation of the solvent, and crystallisation of the residue gave a yellow solid, (282), in 51% yield, as the only product.

The spectroscopic data fitted neither the ylide, nor the tricarbonyl compound or its

hydrate. The structure was determined by X-ray crystallography (Figure 4) (Appendix), as the compound derived by oxygen transfer from the sulphoxide. The solid state structure shows the molecule to exist solely in the Z-enolic form, with the proton $(H_{(3)})$ hydrogen bonded to the ketone $(C_{(3)}O_{(4)})$.There are two conformationally identical, crystallographically independent molecules in the crystal. The O-H bond lengths indicate a large asymmetry in the intramolecular H-bond: $O_{(3)}$–$H_{(3)}$ 0.97-0.98 Å, and $O_{(4)}$-$H_{(3)}$ 1.88-1.94 Å; and this is probably because the molecule cannot adopt the correct geometry for a five membered H-bonded ring containing two sp^2 centres. Hydrogen bonding is observed exclusively at the ketone, $(O_{(3)})$, and not at the ester carbonyl, $(O_{(4)})$, which would form a six membered ring. The shorter than expected C_3-C_4 bond (1.45 Å) suggests the double bond is partly delocalised into the ketone, by virtue of the vinylogous thioester character of the molecule, and this explains the enhanced donor ability of the ketone relative to the ester.

The IR spectrum of (282) shows a sharp hydroxy stretch, indicative of a strong intramolecular H-bond, and two carbonyl absorptions, at 1715 cm^{-1} (esters) and 1646 cm^{-1} (ketone). Only one tautomer was present in the high field NMR spectrum of (282) in $CDCl_3$: the molecule contained five protons in the aromatic region, a doublet at 6.50 ppm (1 H, J 2.0 Hz) and the two esters. Decoupling experiments and analysis of coupling constants suggested that the solution structure was the enol tautomer. The alkene proton appears at 7.62 ppm (1 H, J 1.7 Hz), and the enol at 6.50 ppm. Additional proof for the assignment of these protons was obtained by preparing the $tert$-butyldimethylsilyl enol ether derivative (283), also a yellow oil, by treating (282) with $tert$-butyldimethylsilyl triflate The doublet at 6.50 ppm vanished (283), whilst the aromatic region remained largely unaltered.

(281)   Rh$_2$(OAc)$_4$

R = H   (282)

^{t}BuMe$_2$Si   (283)
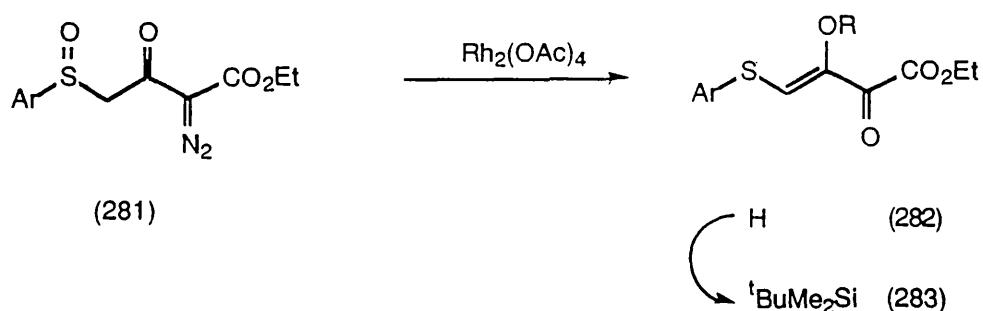
Ar = 2-(carboxyethyl)phenyl

The dramatic change in regioselectivity in the reaction of 1,3-diazosulphoxide (281) can be ascribed to the lower rate of the formation of the four membered product, compared to the five membered transition state for deoxygenation. Therefore, the molecule is biased towards oxygen transfer, a reversal of the situation in the previous sections, where five and six ring sulphoxonium ylides were formed in very good yield.

5.5   Reactivity of Sulphones

The analogous reactions of carbenes with sulphones have not been explored. The formation of a sulphone-ylide is impossible because all the valence electrons are already used in bonding. However, carbene mediated deoxygenation is possible, and the transformation would be a synthetically useful selective reduction of a sulphone to a sulphoxide.

We have previously prepared some diazosulphones by oxidation of the sulphides with m-CPBA (Section 5.2.1). Treatment of a solution of allylsulphone (264b) in dichloromethane with a catalytic amount of dirhodium tetraacetate led to rapid consumption of the starting material, and TLC showed the formation of baseline material only. This result could be due to the low reactivity of the sulphone group. Also, the transition state for the oxygen-transfer reaction would require the formation of a seven membered ring, and therefore would be relatively unfavourable. To increase the rate of formation of a cyclic transition state, we prepared a molecule which could adopt a five membered transition state (Scheme 74). The hydroxyl group was introduced at the ε-carbon atom to trap the carbene, in the event that the sulphone oxygen being insufficiently nucleophilic to complete the task. The rate difference between the formation of five and seven membered rings is large enough to favour significantly the deoxygenation route.

The synthesis of (286) was straightforward. Diazotransfer reaction on ethyl 4–chloroacetoacetate gave a stable yellow oil (284), in 92% yield. Alkylation of 2–mercaptoethanol with chloride (284) in DMF occurred exclusively on sulphur, in 93% yield. Conversion of sulphide (285) into sulphone (286) was achieved by oxidation with m-CPBA at room temperature, in moderate yield. Although a deficiency of the oxidant was used, no diazosulphoxide was isolated: treatment of (285) with one equivalent of m-CPBA, at -10°C, led to rapid consumption of starting material. The crude reaction mixture was subjected to a reductive and basic work-up (10% sodium

metabisulphite, and 50% sodium bicarbonate), which led to decomposition of the sulphoxide.
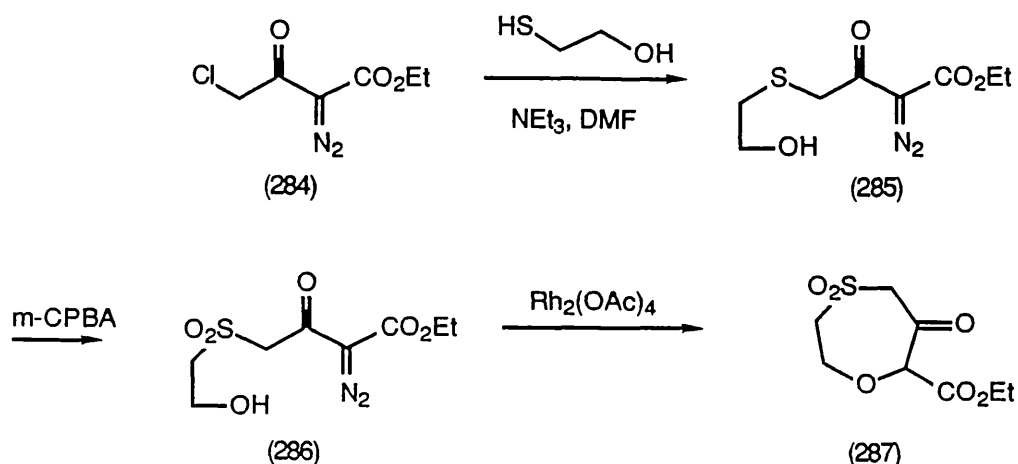
Scheme 74.

The standard dirhodium tetraacetate catalysed reaction of sulphone (286) led to rapid consumption of the starting material. After work-up, the cru. e reaction mixture was purified by flash chromatography on silica gel, to give (287), as the only isolated product, in 19% yield. The thiaoxepane was a viscous oil that slowly solidified, and it was shown to exist almost totally as the enol form of the β-ketoester by NMR (CDCl₃). The observed mode of reaction is a good indication of the poor affinity of the sulphone group for carbenoids. This contrasts markedly with the facile reaction of sulphoxides, observed earlier. Both groups possess dipolar sulphur-oxygen bonds, however, it appears that with the sulphone the negative charge on oxygen is more associated with bonding to sulphur.

The alkylation/oxidation/cyclisation procedure (Scheme 74) allows a rapid entry into the functionalised thiaoxepane ring system (287). This approach could well be applied to the synthesis of other heterocycles, containing a powerful nucleophile (e.g. sulphur) and a weak nucleophile (e.g. phosphate, ether). This type of competitive cyclisation has not been well documented.

5.6 Reactivity of the Sulphoxonium Ylides

This section is divided into two parts, the first covers rearrangement reactions of the ylides, and the second, their chemical reactivity.

5.6.1 Thermal and Photochemical Reactions

Thermal Reactions

The cyclic sulphoxonium ylides prepared herein are high melting solids, stable at their melting points, and this is reflected in their high thermal stability, and low aptitude for rearrangement to non-ylidic species. This is in stark contrast to the sulphonium ylides, and is directly attributable to the ability of the sulphoxide oxygen to stabilise the carbanion portion of the ylide.

The five membered cyclic ylides (277a) and (278a) were both stable in mesitylene at reflux (160°C) for prolonged periods. Suprisingly, the ethylthiabenzene derivative (268) was also stable at 160°C, and did not lose ethene, but the benzylthiabenzene ylide (269) was slowly decomposed at this temperature, to a complex set of products. The corresponding allyl and 3-phenylallyl ylides, (270) and (271) respectively, were decomposed at 130°C, in refluxing xylene, to mixtures containing several components. Close examination of the reaction mixture from (270) showed that the expected product (288), derived from [2,3]-sigmatropic rearrangement of the allyl group to C-2, was not present. Of the two major components isolated in the reaction, only one could be identified. The structure of the relatively non-polar fraction, isolated in 19% yield, was assigned on the basis of spectroscopic data as (163), derived from the ylide by loss of the allyl group and oxygen. A possible mechanism for this transformation is discussed later (Scheme 76). The structure of the polar component could not be assigned, although analysis of the spectroscopic data suggested that the compound was cyclic sulphoxide, which retained the allyl group, and was probably a mixture of stereoisomers. To determine whether this was indeed the rearrangement product (288), the sulphoxide (288) was independently prepared by m-CPBA oxidation of sulphide (238), in 62% yield. The sulphoxide (288) is probably diastereomerically pure, but the stereochemistry is unknown. The two compounds' data are broadly similar; however, if the thermally derived product is a

mixture of diastereomers of (288), then the required overlap of peaks with the spectrum of (288) is not observed. This suggests that the compound isolated from the rearrangement of (270) is probably not (288), but both compounds are structurally related.

(238)   (288)
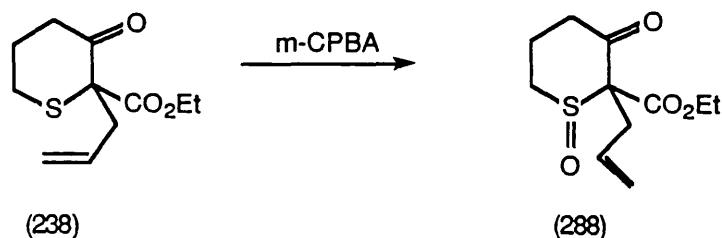
Photochemical Reactions

In the previous section we found that the energy required to disrupt the ylide bond was sufficient for processes other than the simple, *i.e.* Stevens, rearrangement to supervene. An alternative to thermally promoted rearrangements would be a photochemically assisted process. Under photochemical conditions, the [1,2]-rearrangement is allowed, and the [2,3]-process disallowed, the reverse of the thermal reaction. However, the photolysis of ylides can also result in a retro-addition reaction, where the ylide bond is broken heterolytically, to regenerate the nucleophile and the carbene. A carbene so generated is highly energetic and usually undergoes rapid Wolff rearrangment to a ketene. If the photolysis is carried out in an alcoholic solvent, then esters, the result of trapping the ketene with the alcohol, can be isolated. Corey and workers have demonstrated that this reaction occurs in the photochemical reaction of sulphoxonium ylide (272) (Scheme 75).[97]

(272)
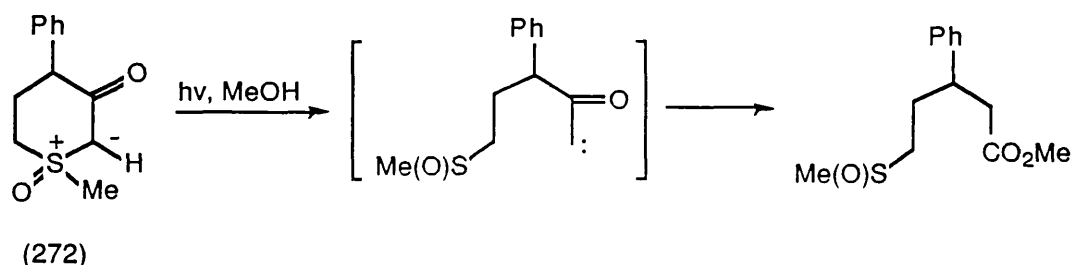
Scheme 75.   R' = H, R = Ph

We chose to investigate the photochemistry of 3-phenylallyl ylide (271), phenyl

ylide (277a), and benzyl ylide (278a). The reactions were carried out in ethanol, to intercept any ketenes or unsaturated species generated.

Irradiation of (271), at 254 nm for two hours, totally decomposed the molecule. On the other hand, (277a) was recovered unchanged after three hours irradiation. Benzyl ylide (278a) underwent smooth photolytic decomposition over two hours, to give two components which were separated by chromatography on silica gel. Analysis of spectroscopic data showed that neither component had incorporated ethanol, suggesting that the ylide bond was not being cleaved. However, it is possible that the carbene was formed, but spontaneouly reformed the ylide. The result is a reflection on the greater stability of the ylides (267) over (272), imparted by the ester group.

The first, relatively non polar, low melting component, isolated in 31% yield, was assigned the structure (289) on the basis of spectroscopic data.[99] To confirm the assignment, the alcohol was acetylated to give (290); the melting point was in agreement with the literature value.[100]

The structure of the second component, a polar yellow oil, could not be assigned. NMR and mass spectrometry (M^+=238) suggested that the compound was derived from (278a) by loss of the benzyl group. The NMR was complex, but suggested the presence of the ester group. There were two IR carbonyl absorbtions, at 1740 and 1713 cm^{-1}, as well as a broad stretch in the hydroxyl region.

The mechanism for this unususal photochemical reaction appears analogous to the thermal decomposition of the allyl ylide (270), in that both involve loss of the R-group and reduction of the sulphoxide. The reaction probably involves initial cleavage of the sulphur-allyl and sulphur-benzyl bonds, by rearrangement of the groups in a [2,3]-and [1,2]-fashion, onto the oxygen of the sulphoxide, to give the sulphonium intermediates (291) and (292), respectively (Scheme 76). The analogous thermal/photochemical rearrangement is known for sulphoxides, which rearrange to sulphenates, and vice versa. The former are thermodynamically more stable.

Involvement of this allowed rearrangement step is supported by the fact that no rearrangement products are observed when the thermal/photochemical conditions are reversed: i.e. the benzyl ylide (277a) is stable to thermolysis, and the 3-phenylallyl ylide (271) is totally decomposed by photolysis.

The elimination of the OR group would complete the reaction. It could be achieved by either homolytic or heterolytic bond cleavage. The ylide (291) is set up for a β–elimination. This fragmentation would directly liberate (163) and but-3-enone.

125

Alternatively, in the photochemical reaction, (292) could fragment by hydrogen abstraction at the benzylic site. This abstraction is possible intramolecularly (293), by the delocalised radical generated in the excited state of the ketone. This route also generates (289) directly with the concomitant loss of benzaldehyde.
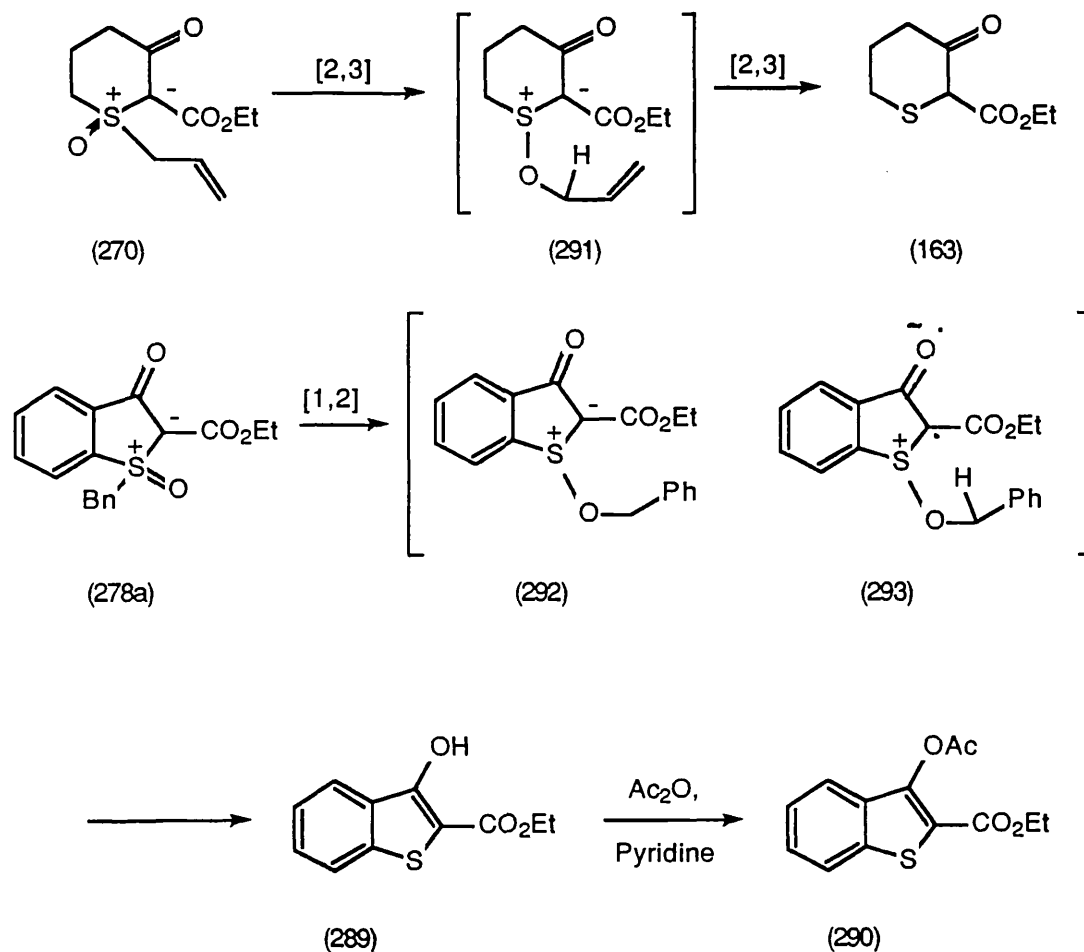
Scheme 76.

Further mechanistic studies need to be undertaken to determine the pathway(s) involved in the fragmentation. The reductive-dealkylation reaction has not been observed before in sulphoxonium ylide chemistry, and it represents a novel transformation.

5.6.2 Chemical Reactivity

The resistance of the ylides towards simple rearrangement would be expected to be parallelled in their chemical reactivity; the thermodynamic stability of the ylide bond imparts a robust quality to the compounds.

Reduction

Corey and co-workers have reported reduction of the ylide bond with zinc in acetic acid at $0^{\circ}C$ (Scheme 77).[97]
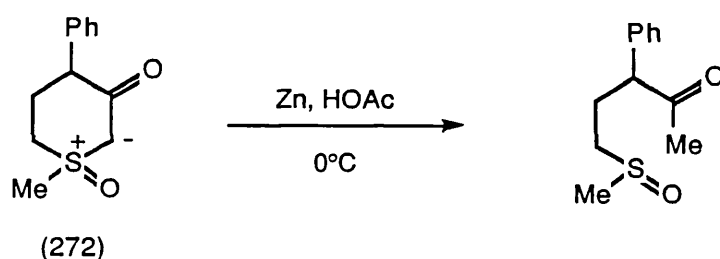
Scheme 77.   R' = H, R = Ph

Attempts to effect the analogous reaction with (277a) were unsuccessful. The ylide was stable for prolonged periods at room temperature. The stabilising effect of the ester group probably has a major contribution in the lowering of reactivity of the ylide.

Hydrolytic Reactivity

The ylide (277a) was stable to acetic acid. The sulphoxonium ylide bond is reported as being stable towards strong mineral acids.[95]

The reactivity of the ylides to nucleophiles was tested by treating (277a) and (278a) with ethanolic sodium ethoxide. No reaction was observed at room temperature or at reflux. However, under aqueous hydrolytic conditions (sodium hydroxide/ water/ethanol), a reaction was observed. Hydrolysis of (277a) gave the very polar acid (294), in 58% yield, the result of selective hydrolysis of the ester. This reaction again reflects the robust nature of the sulphoxonium ylide. The acid

spontaneously lost carbon dioxide at its melting point (174-178°C). The inability of the β-ketoester to decarboxylation under mild conditions is a result of the difficulty in effectively delocalising the negative charge generated at the carbanionic centre during the reaction (Scheme 78).

O
NaOH
Xylene
130°C
AcOH

Ph′ —CO₂Et   Ph′ —CO₂H   Ph′

(277a)   (294)   (295)
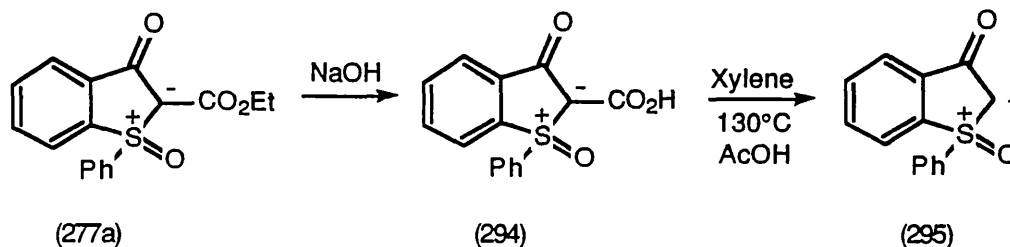
Scheme 78.

A suspension of the acid in xylene was heated to reflux, but no decarboxylation occurred, however, on addition of acetic acid to the refluxing reaction solution, gas evolution occurred readily. Ylide (295) was isolated as a yellow solid (m.p. 165-167°C), after chromatography on silica gel, in an excellent yield of 88%. It is assumed that the ylide carbanion is protonated by acetic acid before loss of carbon dioxide can occur.

The sulphuric acid mediated hydrolysis and decarboxylation of an ester stabilised sulphoxonium ylide has been reported, but the resulting decarboxylated compound existed as the hydrogen sulphate sulphoxonium salt, and not as a ylide.[95]

The NMR spectrum of sulphoxonium ylide (295) indicates that the ylidic proton is considerably deshielded, appearing at 4.77 ppm. The IR carbonyl absorption of the ylide occurs at 1631 cm⁻¹, reflecting the considerable delocalisation of charge into the ketone.

5.7 Conclusions

The cyclisation reaction of rhodium carbenoids with sulphoxides has been studied. We exploited the reaction in the high yielding synthesis of five and six membered sulphoxonium ylides, the first such intramolecular reactions to be reported. The cyclic sulphoxonium ylides are thermally very stable, and were found to be resistant to the [1,2]- and [2,3]-rearrangements as observed in the corresponding sulphonium ylides, even at elevated temperatures. However, an unusual fragmentation reaction was found in certain ylides, resulting in reductive-dealkylation of the molecule. This reaction could be promoted thermally or photochemically, dependng on the nature of the exocyclic substituent on the ylide. Attempted extension of the reaction to the synthesis of four and seven membered sulphoxonium ylides was not successful.

The dirhodium tetraacetate catalysed intramolecular reaction of 1,3-diazosulphoxides resulted in attack of the carbenoid on the oxygen atom of the sulphoxide, and transfer of the oxygen atom to the carbene centre. This was also a minor, but competing pathway in the synthesis of the five membered ring ylides. The distribution of the products appears to be largely dependent on the proximity of the nucleophile to the carbene centre. This means that there is a strong preference for products which form *via* a five membered transition state, where the alternative is a six or four membered ring.

CHAPTER SIX

EXPERIMENTAL

6.1 General Information

Solvents

Petroleum ether refers to the fraction boiling in the range 40-60°C, and was distilled before use. Diethyl ether and THF were dried by distillation from potassium-benzophenone ketyl. Benzene, toluene, and xylene were dried by distillation from calcium hydride. Acetonitrile and dichloromethane were dried by distillation from phosphorus pentoxide. DMF was dried by stirring over barium oxide for 12 h at room temperature, followed by distillation at reduced pressure. All dried solvents were stored over 4 Å molecular sieves under nitrogen.

Chromatography

TLC was carried out using aluminium plates coated with Merck Kieselgel 60 GF_{254}. For column chromatography, Merck Kieselgel 60 H silica was used, unless otherwise stated, and the products were eluted by petrol/ether or petrol/ethyl acetate.

Spectroscopy

IR spectra were recorded using a Perkin-Elmer 298 or 1710 spectrophotometer, calibrated against polystyrene. Proton NMR spectra were recorded on a Jeol GSX270 (270 MHz), a Bruker WM250 (250 MHz), a Perkin-Elmer R32 (90 MHz), or on a Varian EM360 (60 MHz) spectrometer. Carbon-13 NMR. spectra were recorded on a Bruker AM500 (125 MHz), or on a Bruker WM250 (63 MHz). High and low resolution mass spectra were recorded on a VG Micromass 7070B instrument, in the electron ionisation mode , at 70 eV, unless otherwise specified.

Other Information

Melting points were determined on a Reichert Kofler hot stage apparatus and are uncorrected. Distillations were carried out in a Kugelrohr apparatus. Internal reaction temperatures were measured with a Comark digital temperature probe. In quoting ^{1}H NMR data for compounds that exist as keto/enol mixtures, the "theoretical" integral is given for signals corresponding to the individual keto and enol forms; the observed integral is the theoretical value multiplied by the percentage of keto or enol form present. Ethyl diazoacetate (Aldrich) was distilled under reduced pressure before use. Unless otherwise stated, all chemicals used are commercially available.

6.2   Experimental for Chapter Two

Preparation of Starting Materials

Lactones

5,6-Dihydropyran-2-one[101] and 2,3,4,7-tetrahydrooxepin-2-one[102] were prepared by the literature methods.   Heptanolactone[103] and 2,3,4,5-tetrahydrobenz[b]oxepin-2-one[104] were prepared by Baeyer Villiger oxidation of the corresponding ketones with 3-chloroperbenzoic acid.

5,6-Dihydrobenz[b,f]oxecin-2-one (132).

A mixture of dibenzosuberone (5.0 g, 0.024 mol) and 3-chloroperbenzoic acid (6.2 g, 1.5 eq) was heated at reflux in chloroform (45 ml) for 48 h.   The organic phase was washed successively with sodium metabisulphite (10%) and saturated sodium hydrogen carbonate, dried, and evaporated. Chromatography of the residue gave the title compound (132) (1.90 g, 35%), m.p. 112.5-114.5°C.   (Found: C, 80.2; H, 5.2. $C_{15}H_{12}O_2$ requires C, 80.3; H, 5.4%); $v_{max.}$ (Nujol) 1734 and 1066 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 3.10-3.26 (4 H, m), 6.96-7.15 (6 H, m), and 7.19-7.34 (2 H, m); m/z (120°C) 224 (M$^+$, 100%), 206 (52), 118 (66), and 90 (32).

Lactams

N-Boc Lactams were prepared according to the following general procedure:

Di-t-butyldicarbonate (Boc$_2$O) (11 mmol) was added to a solution of the lactam (10 mmol) in acetonitrile (6 ml).   4-Dimethylaminopyridine (DMAP) (1 mmol) was added and the reaction mixture was stirred at room temperature overnight (ca. 18 h).   The acetonitrile was evaporated and the residue purified by filtration through a pad of silica, eluting with ether-petroleum, to give the product as a clear oil. The product could be further purified by distillation.

N-tert-Butoxycarbonyl-δ-valerolactam (144).

DMAP (140 mg) was added to a solution of δ-valerolactam (1.00 g, 10.2 mmol) and Boc$_2$O (2.45 g, 11.2 mmol) in acetonitrile (10 ml). After 24 h, the reaction mixture was concentrated and the residue purified by chromatography and distillation to give the title compound (144) (1.49 g, 74%) as a low melting solid, b.p. 110°C at 0.1 mmHg. (Found: C, 60.5; H, 8.7; N, 7.0. C$_{10}$H$_{17}$NO$_3$ requires C, 60.3; H, 8.6; N, 7.0%); $\nu_{max.}$ (film) 1718 (br), 1288, 1249, 1158, and 1138 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.47 (9 H, s, t-Bu), 1.68-1.84 (4 H, m, CH$_2$CH$_2$), 2.44 (2 H, t, J 7.5 Hz, CH$_2$CO), and 3.59 (2 H, t, J 7.5 Hz, CH$_2$N); m/z (150°C) 199 (M$^+$, 1%), 184 (1), 144 (39), 126 (16), 99 (36), and 57 (100).

N-tert-Butoxycarbonyl-ε-caprolactam (145).

DMAP (120 mg) was added to a solution of ε-caprolactam (1.00 g, 8.8 mmol) and Boc$_2$O (2.12 g, 9.7 mmol) in acetonitrile (6 ml). After 18 h, the solvent was evaporated and the residue chromatographed to give the title compound (145) (1.27 g, 67%) as a clear oil, b.p. 120°C at 0.03 mmHg. (Found: C, 61.9; H, 9.2; N, 6.3. C$_{11}$H$_{19}$NO$_3$ requires C, 61.9; H, 9.0; N, 6.6%); $\nu_{max.}$ (film) 1769, 1714, and 1153 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.51 (9H, s, t-Bu), 1.60-1.83 (6 H, m, CH$_2$CH$_2$CH$_2$), 2.63 (2 H, m, CH$_2$CO), and 3.74 (2 H, m, CH$_2$N); m/z (170°C) 213 (M$^+$, 1%), 198 (1), 158 (36), 140 (16), 114 (24), 85 (41), and 57 (100).

N-tert-Butylcarbonyl-δ-valerolactam (146).

A solution of δ-valerolactam (0.90 g, 9.08 mmol) and triethylamine (1.6 ml, 11 mmol) in THF (10 ml) was cooled to 0°C, and pivaloyl chloride (1.3 ml, 10.5 mmol) added dropwise; a white solid immediately precipitated. The suspension was stirred for 18 h at room temperature, filtered through Celite, and the Celite washed with cold ether. The filtrate and washings were evaporated to give crude product which was purified by chromatography to give the title compound (146) (1.595 g, 96%) as a low melting solid, b.p. 90°C at 0.2 mmHg: (Found: C, 65.5; H, 9.5; N, 7.8. C$_{10}$H$_{17}$NO$_2$ requires C, 65.5; H, 9.4; N, 7.6 %); $\nu_{max.}$ (film) 1685 (br), 1290, and 1167 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.19 (9 H, s, t-Bu), 1.69-1.83 (4 H, m, CH$_2$CH$_2$), 2.37 (2 H, m, CH$_2$CO), and 3.41 (2 H, m, CH$_2$N); m/z (100°C) 183 (M$^+$, 6%), 168 (4), 128 (29), 99 (92), and 57 (100).

General Procedures for the Preparation of the Diazo Compounds.

Normal addition.

Ethyl diazoacetate (EDA) (3.3 mmol) was added dropwise over approximately 5 min to a cold solution of LDA (3.3 mmol) in THF (20 ml), under an atmosphere of nitrogen, maintaining the temperature at $-90^{\circ}C$. The orange-brown solution was stirred at $-90^{\circ}C$ for 10-15 min followed by dropwise addition of a lactone (3.0 mmol) at $-90^{\circ}C$. The solution was stirred for 1 h at $-90^{\circ}C$, allowed to warm to $-75^{\circ}C$, and finally stirred for 1 h at $-75^{\circ}C$ before dropwise addition of acetic acid (10 mmol). The reaction mixture was allowed to warm to $0^{\circ}C$, water (10 ml) was added and the contents transferred to a separating funnel. The solution was acidified to pH5 with dilute hydrochloric acid, if required, and then extracted three times with dichloromethane. The combined organic extracts were washed successively with water, then brine, and finally dried over $MgSO_4$. The solvent was evaporated and the crude product purified by flash chromatography on silica gel.

Inverse addition.

A solution of LDA (3.3 mmol) in THF (10 ml) (see below) was added dropwise to a solution of ethyl diazoacetate (3.3 mmol) and a lactone (3.0 mmol) in THF (15 ml) over a period of 10-60 min maintaining the temperature below $-72^{\circ}C$. The solution was stirred for 3 h at $-75^{\circ}C$ and the acetic acid (6 mmol) added dropwise. The product was extracted and purified as described as above.

Lithium Diisopropylamide (LDA).

Solutions of LDA in THF were prepared by the addition of n-butyllithium (in hexanes) to a stirred solution of dry diisopropylamine in dry THF at 0°C. All LDA solutions were used within 30 min of their preparation.

Ethyl 2-Diazo-6-hydroxy-3-oxohexanoate (120).

EDA (0.67 ml, 6.39 mmol) was added dropwise to a solution of LDA (6.39 mmol) in THF (25 ml) at $-91^{\circ}C$. The solution was stirred for 15 min, and then γ-butyrolactone (0.45 ml, 5.81 mmol) was added dropwise over 8 min. The temperature was maintained at $-90^{\circ}C$ for 0.5 h, and then warmed to $-75^{\circ}C$ for 1.5 h before dropwise

addition of acetic acid (0.44 ml). Work-up and chromatography gave the title compound (120) (544 mg, 47%) as a pale yellow oil; (Found: C, 48.1; H, 6.2; N, 13.9. $C_8H_{12}N_2O_4$ requires C, 48.0; H, 6.0; N, 14.0%); $\nu_{max.}$ (film) 3425, 2137, 1718, 1655, and 1304 cm^{-1}; δ_H (90 MHz; $CDCl_3$) 1.35 (3 H, t, J 7 Hz, CH_2Me), 1.92 (2 H, quin, J 6.5 Hz, CH_2CH_2OH), 2.65 (1 H, br, OH), 2.99 (2 H, t, J 6.5 Hz, CH_2CO), 3.70 (2 H, t, J 6.5 Hz, CH_2OH), and 4.34 (2 H, q, J 7 Hz, CH_2Me); m/z (FAB; $CHCl_3$/glycerol) 201 (MH^+, 100%), 183 (49), 127 (67); m/z (60°C) 172 (M^+ - N_2, 1%).

Ethyl 2-Diazo-6- hydroxy-3-oxoheptanoate (121).

EDA (0.87 ml, 8.24 mmol) was added dropwise to a solution of LDA (8.24 mmol) in THF (40 ml) at -91°C. The solution was stirred for 10 min and then γ-valerolactone (0.71 ml, 7.49 mmol) was added dropwise over 10 min. The temperature was maintained at -90°C for 1 h and then kept at -75°C for 3 h before the addition of acetic acid (0.65 ml). Work-up and chromatography gave the title compound (121) (811 mg, 51%) as a pale yellow oil, that solidified at 4°C; (Found: C, 50.4; H, 6.8; N, 13.2. $C_9H_{14}N_2O_4$ requires C, 50.5; H, 6.6; N, 13.1%); $\nu_{max.}$ (film) 3426, 2137, 1719, 1656, and 1305 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.19 (3 H, d, J 6.1 Hz, $CHMe$), 1.32 (3 H, t, J 6.9 Hz, CH_2Me), 1.77 (2 H, m, $CHCH_2$), 2.40 (1 H, br, OH), 2.96 (2 H, t, J 7.2 Hz, CH_2CO), 3.78 (1 H, sextet, J 6.1 Hz, $CHOH$), and 4.30 (2 H, q, J 6.9 Hz, CH_2Me); m/z (FAB; thiodiethanol) 215 (MH^+, 100%), 197 (69), 127 (96), and 99 (68); m/z (60°C) 197 (M^+ - OH, 4%), and 186 (M^+-N_2, 3%).

Ethyl 2-Diazo-7-hydroxy-3-oxoheptanoate (122).

A solution of LDA (7.34 mmol) in THF (10 ml) was added dropwise to a solution of EDA (838 mg, 7.34 mmol) and δ-valerolactone (700 mg, 6.99 mmol) in THF (35 ml) over 0.75 h at -90°C. The solution was allowed to warm to -75°C over 1h, stirred for 1.25 h, before acetic acid (0.46 ml) was added. Work-up and chromatography gave the title compound (122) (1.18 g, 81%) as a pale yellow oil, b.p. 110°C at 0.2 mmHg (decomposes); (Found: C, 50.6; H. 6.8; N, 13.0. $C_9H_{14}N_2O_4$ requires C, 50.5; H, 6.6; N, 13.1%. Found: M^+, 196.0844; requires M-H_2O, 196.0848); $\nu_{max.}$ (film) 3426, 2136, 1718, 1656, and 1305 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.30 (3 H, t, J 7.0 Hz, CH_2Me), 1.41-1.78 (4 H, m, CH_2CH_2), 2.05 (1 H, br, OH), 2.86 (2 H, t, J 6.7 Hz, CH_2CO), 3.61 (2 H, t, J 6.7 Hz, CH_2OH), and 4.28 (2 H, q, J 7.0 Hz,

C$\underline{H}_2$Me); δ_C (62.9 MHz; CDCl$_3$) 192.1, 160.9, 75.3, 61.5, 60.9, 39.2, 31.7, 20.3, and 13.7; m/z (90°C) 215 ($\underline{M}$H$^+$, 2%), 196 (5), 184 (1), 169 (1), 156 (15), 130 (27), and 101 (31).

Ethyl 2-Diazo-7-hydroxy-3-oxotridecanoate (123).

A solution of LDA (1.50 mmol) in THF (5 ml) was added dropwise to a solution of EDA (171 mg, 1.50 mmol) and undecanoic δ-lactone (184 mg, 1.00 mmol) in THF (7.5 ml) over a period of 15 min at -75°C. The solution was stirred for 4 h, and acetic acid (0.1 ml) added. Work-up and chromatography gave the title compound (123) (295 mg, 99%) as a pale yellow oil which solidified at 4°C; (Found: C, 60.4; H, 8.9; N, 9.2. C$_{15}$H$_{26}$N$_2$O$_4$ requires C, 60.4; H, 8.8; N, 9.4%. Found: $\underline{M}^+$, 270.1831; requires $\underline{M}$-N$_2$, 270.1831); ν$_{max.}$ (film) 3449, 2134, 1720, 1657, and 1303 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.87 (3 H, m, CH$_2$CH$_2$$\underline{Me}$), 1.32 (3 H, t, $\underline{J}$ 7.1 Hz, CH$_2$$\underline{M}$e), 1.20-1.54 (12 H, m), 1.63-1.84 (2 H, m), 1.87 (1 H, br, OH), 2.73-2.97 (2 H, m, C$\underline{H}_2$CO), 3.52-3.63 (1 H, m, C$\underline{H}$OH), and 4.27 (2 H, q, $\underline{J}$ 7.1 Hz, C$\underline{H}_2$Me); δ_C (62.9 MHz; CDCl$_3$) 192.5, 161.1, 75.5, 70.9, 61.1, 39.8, 37.3, 36.6, 31.6, 29.1, 25.4, 22.3, 20.2, 14.0, and 13.7; m/z (FAB; glycerol) 299 ($\underline{M}$H$^+$, 100%), 281 (75); m/z (90°C) 280 ($\underline{M}^+$ - H$_2$O, 2%), 270 ($\underline{M}^+$ - N$_2$, 21), 252 (11), 224 (3), 213 (13), 185 (33), 166 (29), and 99 (100).

Ethyl 3-Hydroxypropyl Diazomalonate (124).

EDA (472 mg, 4.14 mmol) was added dropwise to a solution of LDA (4.14 mmol) in THF (20 ml) at -93°C over 10 min. After stirring for 15 min, a solution of 1,3-dioxan-2-one (422 mg, 4.14 mmol) in THF (14 ml) was added over 10 min. The solution was stirred at -90°C for 1 h, and then -75°C for 2 h, before the addition of acetic acid (0.24 ml). Work-up and extraction gave the title compound (124) (364 mg, 41%) as a yellow oil; (Found: $\underline{M}^+$, 186.0652. C$_8$H$_{12}$N$_2$O$_5$-CH$_2$O requires $\underline{M}$, 186.0641); ν$_{max.}$ (film) 3510, 2144, 1740, 1697, and 1323 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.26 (3 H, t, $\underline{J}$ 7.0 Hz, CH$_2$$\underline{Me}$), 1.90 (2 H, quin, $\underline{J}$ 5.9 Hz, CH$_2$C$\underline{H}_2$OH), 2.80 (1 H, br, OH), 3.70 (2 H, t, $\underline{J}$ 5.3 Hz, C$\underline{H}_2$OH), 4.25 (2 H, q, $\underline{J}$ 7.0 Hz, C$\underline{H}_2$Me), and 4.36 (2 H, t, $\underline{J}$ 6.1 Hz, C$\underline{H}_2$OCO); m/z (FAB; glycerol) 217 ($\underline{M}$H$^+$); m/z (120°C) 216 (M$^+$, 1%), 186 (22), 159 (32), and 59 (18).

(Z)-Ethyl 2-Diazo-7-hydroxy-3-oxohept-4-enoate (125).

A solution of LDA (5.33 mmol) in THF (7.5 ml) was added dropwise to a solution of EDA (608 mg, 5.33 mmol) and 5,6-dihydropyran-2-one (350 mg, 3.55 mmol) in THF (10 ml) over 25 min at -74°C. The solution was stirred for 3.25 h and acetic acid (0.45 ml) was added. Work-up and chromatography gave the title compound (125) (66 mg, 6%) as a yellow oil; (Found: M^+, 212.0793. $C_9H_{12}N_2O_4$ requires M, 212.0797); $v_{max.}$ (film) 3443, 2138, 1718, 1653, 1611, and 1303 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.33 (3 H, t, J 7.1 Hz, CH$_2$Me), 1.69 (1 H, br, OH), 2.81 (2 H, dq, J 6.2, 1.3 Hz,=CHCH$_2$), 3.80 (2 H, t, J 5.9 Hz, CH$_2$OH), 4.30 (2 H, q, J 7.1 Hz, CH$_2$Me), 6.31 (1 H, dt, J 11.9, 8.1 Hz, =CH), and 7.19 (1 H, dt, J 11.7, 1.3 Hz, =CH); m/z (90°C) 212 (M^+, 22%), 182 (65), 125 (21), 108 (58), and 99 (74).

Ethyl 2-Diazo-5-(2-hydroxyphenyl)-3-oxopentanoate (126).

A solution of LDA (5.25 mmol) in THF (15 ml) was added dropwise to a solution of EDA (608 mg, 5.25 mmol) and dihydrocoumarin (520 mg, 3.50 mmol) in THF (10 ml) at -72°C over 8 min. The solution was stirred at -75°C for 5 h, before adding a solution of acetic acid (1.0 ml) in ether (4 ml). Work-up and chromatography gave the title compound (126) (740 mg, 80%) as a pale yellow solid, m.p. 85-87°C (from ether); (Found: C, 59.7; H, 5.4; N, 10.6. $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.4; N, 10.7%); $v_{max.}$ (Nujol) 3200, 2140, 1712, and 1627 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.33 (3 H, t, J 7.1 Hz, CH$_2$Me), 2.92 (2 H, t, J 6.4 Hz, CH$_2$CO), 3.22 (2 H, t, J 6.4 Hz, CH$_2$Ar), 4.30 (2 H, q, J 7.1 Hz, CH$_2$Me), 6.81-6.92 (2 H, m, ArH), 7.06-7.16 (2H, m, ArH), and 7.80 (1 H, br, OH); m/z (130°C) 262 (M^+, 28%), 234 (3), 177 (16), 160 (14), 120 (45), and 107 (100).

Ethyl 2-Diazo-6-(2-hydroxyphenyl)-3-oxohexanoate (127).

A solution of LDA (3.99 mmol) in THF (10 ml) was added dropwise to a solution of EDA (455 mg, 3.99 mmol) and 2,3,4,5-tetrahydrobenz[b]oxepin-2-one (432 mg, 2.66 mmol) in THF (10 ml) at -70°C over 8 min. The solution was stirred for 3 h at -75°C and water (1.0 ml) added. Work-up and chromatography gave the title compound (127) (414 mg, 56%) as a cream solid, m.p. 94-95°C (from ether); (Found: C, 61.1; H, 6.0; N, 9.9. $C_{14}H_{16}N_2O_4$ requires C, 60.9; H, 5.8; N, 10.1%) $v_{max.}$ (Nujol) 3380, 2142, 1680, and 1650 cm^{-1}; δ_H (250 MHz;CDCl$_3$) 1.32 (3 H, t, J 7.1 Hz, CH$_2$Me), 1.82-1.96 (2 H, m, CH$_2$CH$_2$Ar), 2.58 (2 H, t, J 7.9 Hz, CH$_2$Ar),

2.94 (2 H, t, J 6.2 Hz, C$\underline{H}_2$CO), 4.29 (2 H, q, J 7.1 Hz, C$\underline{H}_2$Me), 6.80 (1 H, dt, J 7.1, 1.1 Hz), 6.86 (1 H, dd, J 8.3, 0.9 Hz), 7.03-7.14 (2 H, m), and 7.18 (1 H, s, OH); m/z (100°C) 276 ($\underline{M}^+$, 50%), 248 (6), 203 (6), 174 (22), 169 (62), 147 (34), 120 (52), and 107 (100).

(Z)-Ethyl 2-Diazo-8-hydroxy-3-oxooct-6-enoate (128).

A solution of LDA (4.91 mmol) in THF (15 ml) was added dropwise to a solution of EDA (560 mg, 4.91 mmol) and 2,3,4,7-tetrahydrooxepin-2-one (500 mg, 4.46 mmol) in THF (15 ml) over a period of 25 min at -73°C. The solution was stirred at -75°C for 4 h, and then saturated ammonium chloride (4 ml) was added. Work-up and chromatography gave the title compound (128) (588 mg, 58%) as a pale yellow oil; (Found: C, 53.0; H, 6.4; N, 12.3. $C_{10}H_{14}N_2O_4$ requires C, 53.1; H, 6.2; N, 12.4%); $\nu_{max.}$ (film) 3420, 2140, 1720, 1655, and 1303 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.31 (3 H, t, J 7.3 Hz, CH$_2$$\underline{Me}$), 2.29 (1 H, br, OH), 2.42 (2 H, m, =CHC$\underline{H}_2$), 2.93 (2 H, t, J 6.6 Hz, C$\underline{H}_2$CO), 4.17 (2 H, dd, J 6.8, 0.8 Hz, C$\underline{H}_2$OH), 4.27 (2 H, q, J 7.3 Hz, C$\underline{H}_2$Me), 5.46 (1 H, dtt, J 10.6, 7.6, 1.0 Hz, CH$_2$CH$_2$C$\underline{H}$=), and 5.66 (1 H, dtt, J 10.9, 6.8, 1.3 Hz, =C$\underline{H}$CH$_2$OH); m/z (FAB; glycerol) 227 ($\underline{M}$H$^+$).

Ethyl 2-Diazo-8-hydroxy-3-oxooctanoate (129).

A solution of LDA (1.20 mmol) in THF (5 ml) was added dropwise to a solution of EDA (171 mg, 1.20 mmol) and ε-caprolactone (114 mg, 1.00 mmol) in THF (5 ml) over a period of 0.5 h at -67°C. The solution was stirred for 3.5 h and water (1.5 ml) added. Work-up and chromatography gave the title compound (129) (143 mg, 63%) as a pale yellow oil; (Found: C, 52.8; H, 7.4; N, 12.3. $C_{10}H_{16}N_2O_4$ requires C, 52.6; H, 7.1; N, 12.3%. Found: $\underline{M}^+$, 228.1114; requires $\underline{M}$, 228.1110); $\nu_{max.}$ (film) 3423, 2136, 1718, 1655, and 1304 cm^{-1}; δ_H (90 MHz; CDCl$_3$) 1.32 (3 H, t, J 7 Hz, CH$_2$$\underline{Me}$), 1.20-1.90 (6 H, m), 2.70 (1 H, br, OH), 2.85 (2 H, t, J 6.5 Hz, C$\underline{H}_2$CO), 3.62 (2 H, t, J 6.5 Hz, C$\underline{H}_2$OH), and 4.34 (2 H, q, J 7 Hz, C$\underline{H}_2$Me); m/z (80°C) 228 ($\underline{M}^+$, 1%), 200 (2), 183 (1), 156 (100), 115 (21), and 99 (40).

Ethyl 2-Diazo-9-hydroxy-3-oxononanoate (130).

A solution of LDA (3.58 mmol) in THF (20 ml) was added dropwise to a solution of EDA (449 mg, 3.94 mmol) and heptanolactone (459 mg, 3.58 mmol) in THF (30 ml) over

a period of 10 min. The solution was stirred for 3 h at -75°C, and acetic acid (0.35 ml) added. Work-up and chromatography gave the title compound (130) (563 mg, 65%) as a pale yellow oil; (Found: C, 54.4; H, 7.7; N, 11.6. $C_{11}H_{18}N_2O_4$ requires C, 54.5; H, 7.5; N, 11.6%); $\nu_{max.}$ (film) 3423, 2136, 1718, 1656, and 1304 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.28 (3 H, t, J 7.1 Hz, CH$_2$Me), 1.20-1.67 (8 H, m), 1.78 (1 H, br, OH), 2.80 (2 H, t, J 7.4 Hz, CH$_2$CO), 3.58 (2 H, t, J 6.4 Hz, CH$_2$OH), and 4.24 (2 H, q, J 7.1 Hz, CH$_2$Me); m/z (FAB; neat) 243 (MH$^+$).

Ethyl 2-Diazo-3-[(2-hydroxyphenyl)ethyl]phenyl-3-oxopropanoate (131).

A solution of LDA (3.23 mmol) in THF (10 ml) was added to a solution of EDA (0.34 ml, 3.23 mmol) and 5,6-dihydrodibenzo[b,f]oxecin-2-one (132) (482 mg, 2.15 mmol) over a period of 35 min at -75°C. The solution was stirred for 3 h before acetic acid (0.2 ml) was added. Work-up and chromatography gave (i) the lactone substrate (132) (68mg, 14%) and (ii) the title compound (131) (60 mg, 8%) as a viscous yellow oil; (Found: M$^+$, 338.1267. $C_{19}H_{18}N_2O_4$ requires M, 338.1267); $\nu_{max.}$ (film) 3427, 2147, 1727, 1709, 1631, 1610, and 1314 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.20 (3 H, t, J 7.0 Hz, CH$_2$Me), 2.75-2.97 (4 H, m), 4.20 (2 H, q, J 7.0 Hz, CH$_2$Me), and 6.95-7.55 (9 H, m, ArH and OH); m/z (150°C) 338 (M$^+$, 12%), 310 (16), 294 (10), 264 (28), 220 (46), and 107 (100).

Ethyl 2-Diazo-6-mercapto-3-oxohexanoate (136).

EDA (2.34 ml, 22.3 mmol) was added dropwise to a solution of LDA (21.6 mmol) in THF (40 ml) over 10 min at -90°C. The orange solution was stirred for 10 min, and γ-thiobutyrolactone (1.77 ml, 20.6 mmol) added over a period of 15 min. The solution was stirred for 0.5 h at -90°C, and then 0.5 h at -75°C before the addition of acetic acid (1.8 ml). Work-up and chromatography on acidic alumina gave the title compound (136) (1.97g, 44%) as a yellow oil. (Found: C, 44.4; H, 5.6. $C_8H_{12}N_2O_3S$ requires C, 44.4; H, 5.6%; $\nu_{max.}$ (film) 2572, 2137, 1717, 1655, and 1306 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.30 (3 H, t, J 7.2 Hz, CH$_2$Me), 1.33 (1 H, t, J 8.1 Hz, SH), 1.92 (2 H, quin, J 7.1 Hz. CH$_2$CH$_2$CH$_2$), 2.56 (2 H, q, J 7.4 Hz, CH$_2$SH), 2.95 (2 H, t, 7.2 Hz, CH$_2$CO), and 4.27 (2 H, q, J 7.1 Hz, CH$_2$Me); m/z (FAB) 217 (MH$^+$); m/z (140°C) 188 (M$^+$ - N$_2$, 4%), 171 (2), 169 (3), 156 (29), and 142 (100).

Ethyl 2-Diazo-7-mercapto-3-oxoheptanoate (137).

EDA (0.43 ml, 4.1 mmol) was added dropwise to a solution of LDA (4.1 mmol) in THF (20ml) at -92°C over a period of 12 min. After 15 min the solution was cooled to -95°C and δ-thiovalerolactone (453 mg, 3.90 mmol) in THF (2 ml) added dropwise over 12 min. The solution was stirred at -92°C for 0.5 h, and then at -75°C for 3 h before the addition of acetic acid (0.66 ml). Work-up and chromatography gave the title compound (137) (522 mg, 58%) as a yellow oil; (Found: C, 47.2; H, 6.2; N, 12.3; S, 13.5. $C_9H_{14}N_2O_3S$ requires C, 46.9; H, 6.1; N, 12.2; S, 13.9%); $\nu_{max.}$ (film) 2572, 2136, 1718, 1656, and 1306 cm^{-1}; δ_H (90 MHz; CDCl$_3$) 1.1-1.4 (4 H, m, CH$_2$Me and SH), 1.40-2.05 (4 H, m), 2.52 (2 H, q, J 6.6 Hz, CH$_2$SH), 2.83 (2 H, t, J 6.5 Hz, CH$_2$CO), and 4.28 (2 H, q, J 6.9 Hz, CH$_2$Me); m/z (FAB; glycerol) 231 (MH$^+$, 7%), 197 (18), and 169 (21).

Ethyl 7-(tert-Butoxycarbonyl)amino-2-diazo-3-heptanoate (138).

A solution of LDA (2.45 mmol) in THF (10 ml) was added dropwise to a solution of EDA (284 mg, 2.45 mmol) and N-tert-butoxycarbonyl-δ-valerolactam (144) (450 mg, 2.26 mmol) in THF (10 ml) at -71°C over a period of 26 min. The solution was stirred for 3 h at -70°C and saturated aqueous ammonium chloride solution (3.5 ml) added. Work-up and chromatography gave the title compound (138) (425 mg, 60%) as a low melting yellow solid, m.p. 33-36°C (from hexane/ether); (Found: C, 54.0; H, 7.4; N, 13.3. $C_{14}H_{23}N_3O_5$ requires C, 53.7; H, 7.4; N, 13.4%); $\nu_{max.}$ (melt) 3351, 2150, 1713, 1683, 1659, and 1171 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.27 (3 H, t, J 7.1 Hz, CH$_2$Me), 1.39 (9 H, s, t-Bu), 1.30-1.70 (4 H, m), 2.80 (2 H, t, J 7.3 Hz, CH$_2$CO), 3.08 (2 H, q, J 6.4 Hz, CH$_2$N), 4.24 (2 H, q, J 7.1 Hz, CH$_2$Me), and 4.65 (1 H, br, NH); m/z (FAB; glycerol) 314 (MH$^+$), 258 (29), 214 (12), 140 (37), and 57 (100).

Ethyl 8-(tert-Butoxycarbonyl)amino-2-diazo-3-oxooctanoate (139).

A solution of LDA (2.49 mmol) in THF (10 ml) was added dropwise to a solution of EDA (284 mg, 2.49 mmol) and N-tert-butoxycarbonyl-ε-caprolactam (145)(482 mg, 2.26 mmol) over a period of 20 min at -72°C. The solution was stirred for 3 h at -75°C and then acetic acid (0.2 ml) added. Work-up and chromatography gave the title compound (139) (543 mg, 73%) as a viscous yellow oil; (Found: M$^+$, 254.1140. $C_{15}H_{25}N_3O_5$-C_4H_9O requires M, 254.1141); $\nu_{max.}$ (film) 3388, 2135, 1717,

1655, and 1175 cm^{-1}; δ_H(250 MHz; CDCl$_3$) 1.30 (3 H, t, J 7.1 Hz, CH$_2$Me), 1.40 (9 H, s, t-Bu), 1.20-1.52 (4 H, m), 1.61 (2 H, quin, J 7.3 Hz, CH$_2$CH$_2$N), 2.81 (2 H, t, J 7.1 Hz, CH$_2$CO), 3.08 (2 H, t, J 6.5 Hz, CH$_2$N), 4.26 (2 H, q, J 7.1 Hz, CH$_2$Me), and 4.52 (1 H, br, NH); m/z (70°C) 271 (M^+ - t-Bu, 1%), 254 (7), 243 (2), 226 (6), 158 (11), 140 (12), and 57 (100).

Ethyl 7-(tert-Butylcarbonyl)amino-2-diazo-3-oxoheptanoate (140).

EDA (0.37 ml, 3.51 mmol) was added dropwise to a solution of LDA (3.51 mmol) in THF (25 ml) over 2 min at -92°C. The solution was stirred for 15 min and a solution of N-tert-butylcarbonyl-δ-valerolactam (146)(585 mg, 3.19 mmol) in THF (3 ml) was added over 8 min. The temperature was maintained at -90°C for 1 h, then increased to -75°C for 2 h, and finally was warmed to -25°C over 5 min, before the addition of acetic acid (0.25 ml). Work-up and chromatography gave (i) the δ-lactam substrate (146) (145 mg, 25%) and (ii) the title compound (140) (174 mg, 18%) as a yellow oil; (Found: M^+, 297.1691. C$_{14}$H$_{23}$N$_3$O$_4$ requires M, 297.1689); $\nu_{max.}$ (film) 3351, 2134, 1719, 1646, 1531, and 1303 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.16 (9 H, s, t-Bu), 1.30 (3 H, t, J 6.7 Hz, CH$_2$Me), 1.42-1.70 (4 H, m), 2.83 (2 H, t, J 7.0 Hz, CH$_2$CO), 3.22 (2 H, q, J 6.1 Hz, CH$_2$N), 4.25 (2 H, q, J 6.7 Hz, CH$_2$Me), and 5.93 (1 H, br, NH); m/z (FAB; glycerol) 298 (MH$^+$), 270 (16), 140 (18), 100 (14), and 57 (100).

Ethyl 5-Carboxy-2-diazo-3-oxohexanoate (141).

EDA (0.58 ml, 5.50 mmol) was added dropwise to a solution of LDA (5.50 mmol) in THF (20 ml) at -95°C. After 15 min a solution of succinic anhydride (500 mg, 5.00 mmol) in a mixture of THF (4 ml) and 1,3-dimethylpropyleneurea (1 ml) was added over a period of 10 min at -90°C. The solution was stirred for 1 h at -90°C, then 0.5 h at -75°C, before water was added. The aqueous phase was saturated with sodium bicarbonate and extracted with dichloromethane. The aqueous phase was acidified with hydrochloric acid (2M) and extracted with dichloromethane (x 3). The organic phase was washed with water and brine, dried over MgSO$_4$, and evaporated. Chromatography of the residue gave the title compound (141) (459 mg, 43%) as a pale yellow solid, m.p. 71-74°C (from hexane/ether); (Found: C, 45.1; H, 4.7; N, 12.8. C$_8$H$_{10}$N$_2$O$_5$ requires C, 44.9; H, 4.7; N, 13.1%); $\nu_{max.}$ (melt) 3100 (br.), 2141, 1718 (br), 1656, and 1310 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.34 (3 H, t, J 7.0 Hz, CH$_2$Me), 2.70

(2 H, t, J 6.5 Hz, C$\underline{H}_2$CO), 3.17 (2 H, t, J 6.5 Hz, C$\underline{H}_2$COOH), and 4.30 (2 H, q, J 7.0 Hz, C$\underline{H}_2$Me); COOH not observed; m/z (90°C) 214 (M$^+$, 7%), 197 (5), 187 (17), 169 (3), 112 (32), and 101 (100); $\underline{m/z}$ (FAB; glycerol) 215 ($\underline{M}$H$^+$, 100%).

Ethyl 6-Carboxy-2-diazo-3-oxoheptanoate (142).

A solution of LDA (3.30 mmol) in THF (10 ml) was added dropwise to a solution of EDA (0.35 ml, 3.30 mmol) and glutaric anhydride (342 mg, 3.00 mmol) at -75°C over a period of 25 min. The solution was stirred for 2 h and acetic acid (0.21 ml) added. Work-up and chromatography gave the title compound (142) (244 mg, 36%) as a yellow solid, m.p. 48-50°C (from hexane/ether); (Found: C, 47.3; H, 5.3; N, 12.1. $C_9H_{12}N_2O_5$ requires C, 47.4; H, 5.3; N, 12.3%); $\nu_{max.}$ (melt) 3000 (br), 2144, 1707, 1659, and 1313 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.26 (3 H, t, J 7.0 Hz, CH$_2$$\underline{Me}$), 1.90 (2 H, quin, J 7.2 Hz, C$\underline{H}_2$CH$_2$CO), 2.36 (2 H, t, J 7.2 Hz, C$\underline{H}_2$CO), 2.86 (2 H, t, J 7.2 Hz, C$\underline{H}_2$COOH), 4.23 (2 H, q, J 7.0 Hz, C$\underline{H}_2$Me), and 11.10 (1 H, br, COOH); m/z (80°C) 228 ($\underline{M}^+$, 14%), 200 (1), 183 (1), 156 (58), 115 (100), and 87 (56).

Ethyl 3-(2-Carboxyphenyl)-2-diazo-3-oxopropanoate (143).

A solution of LDA (4.10 mmol) in THF (12 ml) was added dropwise to a solution of EDA (470 mg, 4.10 mmol) and phthalic anhydride (551 mg, 3.72 mmol) in THF (15 ml) at -75°C over 15 min. After 2 h at -75°C, acetic acid (0.26 ml) was added. Work-up and chromatography gave the title compound (143) (251 mg, 26%) as a viscous oil; (Found: $\underline{M}^+$, 234.0531. $C_{12}H_{10}N_2O_5$-N$_2$ requires $\underline{M}$, 234.0528); $\nu_{max.}$ (film) 3300, 2147, 1725, 1640, and 1305 cm^{-1}; δ_H (60 MHz; CDCl$_3$) 1.10 (3 H, t, J 7 Hz, CH$_2$$\underline{Me}$), 4.10 (2 H, q, J 7 Hz, C$\underline{H}_2$Me), 7.2-8.3 (4 H, m, ArH), and 10.2 (1 H, br, COOH); $\underline{m/z}$ (70°C) 234 ($\underline{M}^+$ - N$_2$, 2%), 228 (22), and 149 (100).

General Procedures for the Dirhodium Tetraacetate Catalysed Decomposition of the Diazo Compounds

(a) A solution of the diazo compound (0.6 mmol) in benzene (10 ml) was added dropwise to a rapidly stirred suspension of dirhodium tetraacetate (2 mg) in benzene (15 ml) at reflux, over a period of 5-60 min, under a nitrogen atmosphere The suspension was maintained at reflux for a period of 5-30 min, allowed to cool and filtered through a pad of Celite. Evaporation of the solvent, and distillation or flash chromatography of the residue gave the product.

(b) Dirhodium tetraacetate (2 mg) was added in one portion to a solution of the diazo compound (0.6 mmol) in dichloromethane (25 ml) at room temperature and the mixture stirred for 0.5-3 h, to give a green solution. The solvent was evaporated and the residue either directly purified by chromatography or triturated with light petroleum-ether, filtered through Celite, evaporated, and then distilled.

Ethyl 3-Oxotetrahydropyran-2-carboxylate (147).

A solution of the diazo compound (120) (185 mg, 0.924 mmol) in benzene (10 ml) was added to a suspension of dirhodium tetraacetate (3.8 mg, 0.9 mol%) in benzene (12 ml) at reflux over 35 min and the mixture maintained at reflux for 1 h. Work-up and distillation gave the title compound (147) (91 mg, 57%) as a pale oil, b.p. 90-95°C at 0.3 mmHg; (Found: M^+ 172.0737. $C_8H_{12}O_4$ requires 172.0736), ν_{max}. (film) 3440, 1749, 1733, 1665, 1626, 1467, 1418, 1309, 1235, 1207, and 1089 cm^{-1}; δ_H (270 MHz; CDCl$_3$) 1.29 (3 H, t, CH$_2$Me, keto), 1.35 (3 H, t, CH$_2$Me, enol), 1.94 (2 H, m, CH$_2$CH$_2$O, enol), 2.07-2.20 (2 H, m, CH$_2$CH$_2$O, keto), 2.36 (2 H, t, J 6.2 Hz, CH$_2$CO, enol), 2.58 (2 H, t, J 6.2 Hz, CH$_2$CO, keto), 3.88 (1 H, m, CHHO, keto), 3.93 (2 H, t, J 4.8 Hz, CH$_2$O, enol), 4.14 (1 H, ddd, J 11.0, 6.0, 4.0 Hz, CHHO, keto), 4.26 (2 H, q, CH$_2$Me, keto), 4.30 (2 H, q, CH$_2$Me, enol), 4.54 (1 H, s, CHCOOEt, keto), and 10.30 (1 H. s. OH. enol); ca. 75% enol form; m/z (120°C) 172 (M^+, 6%), 144 (3), 126 (14), 115 (31), 91 (28), 87 (90), and 42 (100).

Ethyl 6-Methyl-3-oxotetrahydropyran-2-carboxylate (148).

A solution of the diazo compound (121) (200 mg, 0.934 mmol) in benzene (9 ml) was added to a suspension of dirhodium tetraacetate (4 mg) in benzene (10 ml) at reflux over 12 min. Reflux was continued for 5 min. Work-up and distillation gave the title compound (148) (139 mg, 80%) as a clear oil, b.p. 90-100°C at 0.25 mmHg; (Found C, 58.0; H, 7.8. $C_9H_{14}O_4$ requires C, 58.1; H, 7.6%); $\nu_{max.}$ (film) 3428, 1741, 1664, 1626, 1312, 1239, 1208, and 1052 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.27 (3 H, t, J 7.1, CH$_2$Me, keto), 1.30 (3 H, d, J 5.8 Hz, Me, keto/enol), 1.33 (3 H, t, J 7.1, CH$_2$Me, enol), 1.58-1.74 (1 H, m, CHHCH$_2$O, enol), 1.88 (ddt, J 13.2, 7.1, 2.6 Hz, CHHCH$_2$O, enol), 1.95-2.10 (2 H, m, CH$_2$CH$_2$O, keto), 2.29 (1 H, ddd, J 18.4, 6.6, 2.9 Hz, CHHCO, enol), 2.43 (1 H, ddd, J 17.6, 10.3, 7.1 Hz, CHHCO, enol), 2.54 (2 H, m, CH$_2$CO, keto), 3.77-3.91 (1 H, m, CHMe, enol), 4.15-4.25 (1 H, m, CHMe, keto), 4.28 (2 H, q, J 7.1, CH$_2$Me, keto/enol), 4.56 (1 H, s, CHCOOEt, keto), and 10.39 (1 H, s, OH, enol); ca. 80% enol form; m/z (140°C) 186 (M$^+$, 1%), 158 (4), 140 (2), 129 (26), 101 (57), 83 (27), and 56 (100).

Ethyl 3-Oxo-oxepane-2-carboxylate (149).

A solution of the diazo compound (122) (103 mg, 0.481 mmol) in benzene (13 ml) was added to a suspension of dirhodium tetraacetate (4.9 mg) in benzene (14 ml) at room temperature over 20 min. After 5 h the mixture was filtered, concentrated, and distilled to give the title compound (149) (57 mg, 64%) as a clear oil, b.p. 90°C at 0.2 mmHg; (Found: C, 57.9; H, 7.8. $C_9H_{14}O_4$ requires C, 58.1; H, 7.6%) $\nu_{max.}$ (film) 3475, 1748, 1718, 1654, 1618, 1320, 1272, 1182, and 1132 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.24 (3 H, t, J 7.1 Hz, CH$_2$Me, keto), 1.27 (3 H, t, J 7.1 Hz, CH$_2$Me, enol), 1.40-2.00 (4 H, m, CH$_2$CH$_2$, keto/enol), 2.42-2.52 (2 + 1 H, m, CH$_2$CO, enol and CHHCO, keto), 2.84 (1 H, dt, J 11.9. 2.8 Hz, CHHCO keto), 3.42 (1 H, ddd, J 12.8, 10.0, 2.3 Hz, CHHO, keto), 3.73 (2 H, t, J 5.0 Hz, CH$_2$O, enol), 4.10-4.32 (2 + 1 H, m, CH$_2$Me, keto/enol+ CHHO, keto), 4.42 (1 H, CHCOOEt, keto), and 10.87 (1 H, s, OH, enol); ca. 20% enol form; δ_C (62.9 MHz; $CDCl_3$) 207.9, 166.3, 86.3, 73.3, 72.8, 61.6. 60.6, 41.7, 33.2, 31.9, 30.8, 23.6, 22.7, 13.9, and 13.7; m/z (100°C) 186 (M$^+$, 66%), 158 (17), 140 (66), 129 (77), 113 (31), 101 (47), 84 (42), 55 (100), and 41 (71).

Ethyl 7-Hexyl-3-oxo-oxepane-2-carboxylate (150).

A solution of diazo compound (123) (163 mg, 0.547 mmol) in benzene (5 ml) was added dropwise to a suspension of dirhodium tetraacetate (2.8 mg, 1.2 mol%) in benzene (15 ml) at reflux over 4 min. After 3 min at reflux the suspension was cooled, filtered, concentrated, and distilled to give the title compound (150) (113 mg, 76.5%) as a viscous oil, b.p. 170-180°C at 0.02 mmHg; (Found: C, 66.7; H, 9.8. $C_{15}H_{26}O_4$ requires C, 66.6; H, 9.7%); $\nu_{max.}$ (film) 1753, 1720, 1690, 1657, 1619, 1319, 1276, 1247, and 1184 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.76-0.90 (3 H, m, (CH$_2$)$_5$Me, keto/enol), 1.29 (3 H, t, J 7.1 Hz, CH$_2$Me, keto/enol), 1.15-2.02 (14 H, m, keto/enol), 2.28 (1 H, dd, J 14.3, 6.2 Hz, CHHCO, enol), 2.46 (1 H, dd, J 12.4, 5.7 Hz, CHHCO, keto), 2.71 (1 H, ddd, J 14.7, 11.4, 1.4 Hz, CHHCO, enol), 2.97 (1 H, dt, J 12.3, 2.4 Hz, CHHCO, keto), 3.27 (1 H, dt, J 9.5, 1.9 Hz, CHO, enol), 3.78-3.95 (1 H, m, CHO, keto), 4.13-4.36 (2 H, m, CH$_2$Me, keto/enol), 4.42 and 4.69 (1 H, s, CHCOOEt, keto), and 10.92 (1 H, s, OH, enol); ca. 75% enol form; m/z (100°C) 270 (M$^+$, 100%), 224 (7), 213 (30), 197 (14), 167 (46), 149 (52), 104 (35), 84 (69), and 55 (54).

Decomposition of the Diazo Compound (124).

A solution of the diazo compound (124) (150 mg, 0.694 mmol) in benzene (7 ml) was added to a suspension of dirhodium tetraacetate (3 mg) in benzene (7 ml) at reflux over 10 min. The mixture was stirred for a further 5 min, cooled, and filtered. Evaporation of the filtrate and distillation of the residue gave a liquid (27 mg, 21%) b.p. 170°C at 0.35 mmHg, which consisted of several components, and a solid (6 mg), an unknown dimer, m.p. 105-110°C, (Found: C, 50.8; H, 6.4. $C_{16}H_{24}O_{10}$ requires C, 51.1; H, 6.4%), $\nu_{max.}$ (Nujol) 1761, 1733, 1462, 1377, 1300, 1256, 1219, and 1149 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.29 (3 H, t, J 7.1 Hz), 1.30 (3 H, t, J 7.1 Hz), 1.90-2.20 (4 H, m), 3.60-3.90 (4 H, m), 4.25 (2 H, q, J 7.1 Hz), 4.27 (2 H, q, J 7.1 Hz), 4.34-4.45 (4 H, m), 4.55 (1 H, s), and 4.58 (1 H, s); m/z (140°C) 376 (M$^+$, 47%), 348 (6), 332 (7), 330 (11), 303 (27), 276 (64), 189 (23), 173 (100), 115 (37), and 87 (49).

Ethyl 3-Oxo-2,3,4,5-tetrahydrobenzoxepin-2-carboxylate (151).

A solution of diazo compound (126) (69.5 mg, 0.265 mmol) in benzene (7.5 ml) was added dropwise to a suspension of dirhodium tetraacetate (2.3 mg) in benzene (7.5

ml) over 45 min. The mixture was heated under reflux for 1 h. Work-up and distillation gave the title compound (151) as a clear oil (49.5 mg, 80%) b.p. 135°C at 0.1 mmHg (lit.,[47]123°C at 0.1 mmHg); $\nu_{max.}$(film) 3440, 1740, 1722, and 1442 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.27 (3 H, t, J 7.1 Hz, CH$_2$Me, keto), 1.39 (3 H, t, J 7.1 Hz, CH$_2$Me, enol), 2.71 (2 H, q, J 6.9 Hz, CH$_2$CO, enol), 2.73 (1 H, dd, J 14.4, 7.0 Hz, HCHCO, keto), 2.93-3.34 (2 +1 H, m, ArCH$_2$, keto/enol and HCHCO, keto), 4.27 (2 H, q, J 7.1 Hz, CH$_2$Me, keto), 4.31 (2 H, q, J 7.1 Hz, CH$_2$Me, enol), 4.95 (1 H, s, CHCOOEt, keto), 6.97-7.25 (4 H, m, ArH), and 11.02 (1 H, s, OH, enol); ca. 35% enol form; m/z (170°C) 234 (M$^+$, 10%), 188 (3), 161 (9), 149 (17), 133 (8), and 120 (20).

Ethyl 3-Oxo-3,4,5,6-tetrahydrobenzoxocin-2-carboxylate (152) and Ethyl 5-(2-Hydroxyphenyl)-2-oxocyclopentanecarboxylate (153).

(a) A solution of diazo compound (127) (121 mg, 0.438 mmol) in benzene. (7.5 ml) was added dropwise to a suspension of dirhodium tetraacetate (1.0 mg) in benzene (7.5 ml) at reflux over 35 min. After 2 h at reflux the suspension was cooled, filtered, concentrated, and the residue and chromatographed to give (i) the benzoxocin (152) (13 mg, 12%) as a clear oil, b.p. 150°C at 0.1 mmHg, and m.p. 37-40°C; (Found: C, 67.6; H, 6.8. C$_{14}$H$_{16}$O$_4$ requires C, 67.7; H, 6.5%); $\nu_{max.}$(film) 1760, 1740, 1724, 1656, 1491, 1223, 1186, and 1097 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.32 (3 H, t, J 7.0 Hz, CH$_2$Me), 1.60 (1 H, m, CHHCH$_2$CO), 2.11-2.25 (1 H, m, CHHCH$_2$CO), 2.38 (1 H, ddd, J 10.5, 6.8, 3.8, CHHCO), 2.62 (1 H, ddd, J 13.5, 6.0, 2.4 Hz, CHHAr), 3.00 (1 H, ddd, J 11.6, 10.4, 3.9 Hz, CHHCO), 3.17 (1 H, ddd, J 13.5, 12.0, 3.7 Hz, CHHAr), 4.31 (2 H, q, J 7.0 Hz, CH$_2$Me), and 7.00-7.26 (4 H, m, ArH); ca. 100% keto form; m/z (100°C) 248 (M$^+$, 71%), 202 (27), 193 (19), 174 (17), 160 (46), 147 (24), 133 (30), 107 (86), and 91 (47); and (ii) the cyclopentanone (153) (75 mg, 69%), b.p. 145°C at 0.02 mmHg; (Found: C, 67.5; H, 6.8. C$_{14}$H$_{16}$O$_4$ requires C, 67.7; H, 6.5%); $\nu_{max.}$(film) 3418, 1751, 1723, 1457, 1232, 1118 and 756 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.22 (3 H, t, J 7.1 Hz, CH$_2$Me), 2.10-2.40 (2 H, m, CH$_2$CH$_2$CO), 2.40-2.78 (2 H, m, CH$_2$CO), 3.56 (1 H, d, J 11.4 Hz, CHCOOEt), 3.93 (1 H, dt, J 11.6, 6.0 Hz, CHAr), 4.06-4.25 (2 H, m, CH$_2$Me), 6.78-6.96 (3 H, m, ArH and OH), 7.11 (1 H, dt, J 7.5, 1.5 Hz, ArH), and 7.17 (1 H, dd, J 7.5, 1.5 Hz, ArH); m/z (100°C) 248 (M$^+$, 28%), 202 (47), 173 (25), 147 (40), 107 (20), 84 (60), and 43 (73).

(b).-Addition of a solution of (127) (91.4 mg, 0.330 mmol) in dichloromethane (2.5 ml) to a solution of dirhodium tetrakis(trifluoroaacetate) (1.0 mg) in dichloromethane (7.5 ml) at reflux over 35 min, followed by 1 h at reflux gave, upon purification, (152) (26 mg, 32%) and (153) (28 mg, 34%).

(c).-Addition of a solution of (127) (103 mg, 0.375 mmol) in benzene (9 ml) to a solution of copper (II) acetonylacetate (5.3 mg) in benzene (10 ml) at reflux over 30 min, followed by 3.5 h at reflux gave, upon purification, solely (153) (50 mg, 54%).

Ethyl 2-(2-Hydroxyethyl)-5-oxocyclopentenecarboxylate (154).

A solution of diazo-compound (128) (122 mg, 0.539 mmol) in toluene (6.5 ml) was added to a solution of palladium (II) acetate (8 mg) in toluene (6.5 ml) at reflux over 7 min. After a further 5 min, the mixture was cooled, filtered, concentrated, and distilled (ca. 220°C at 0.1 mmHg; partial decomposition). Chromatographic purification of the distillate gave the title compound (154) (22 mg, 21%) as a viscous oil; (Found: $\underline{M}^+$, 198.0895. $C_{10}H_{14}O_4$ requires $\underline{M}$, 198.0892); $\nu_{max.}$(film) 3451, 1738, 1710, 1621, 1375, 1299, and 1034 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.30 (3 H, t, $\underline{J}$ 7.0 Hz, CH$_2$Me), 2.41-2.49 (2 H, m, C$\underline{H}_2$CO), 2.52 (1 H, br, OH), 2.67-2.77 (2 H, m, C$\underline{H}_2$C=), 2.95 (2 H, t, $\underline{J}$ 6.0 Hz, C$\underline{H}_2$CH$_2$OH), 3.87 (2 H, t, $\underline{J}$ 6.0 Hz, C$\underline{H}_2$OH), and 4.26 (2 H, q, $\underline{J}$ 7.0 Hz, C$\underline{H}_2$Me); δ_C (62.9 MHz; CDCl$_3$) 202.6, 183.6, 163.9, 134.7, 61.0, 60.5, 35.8, 35.1, 31.0, 14.1; m/z (190°C) 198 ($\underline{M}^+$, 2%), 180 (3), 168 (45), 153 (31), 152 (34), 122 (100), and 94 (18).

Ethyl 3-Oxo-oxecane-2-carboxylate (155) and Ethyl 5-(2-hydroxyethyl)-2-oxocyclopentanecarboxylate (156).

A solution of diazo compound (129) (200 mg, 1.00 mmol) in benzene (10 ml) was added dropwise to a suspension of dirhodium tetraacetate (3 mg) in benzene (10 ml) at reflux over 5 min. After a further 5 min, the mixture was cooled, filtered, concentrated, and distilled to give the oxecane (155) (54 mg, 31%) as a clear oil, b.p. 100°C at 0.4 mmHg; (Found: C, 59.7; H, 8.2. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.1%); $\nu_{max.}$(film) 1738 (br), 1659, 1621, 1324, 1238, and 1186 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.23 (3 H, t, $\underline{J}$ 7.0 Hz, CH$_2$Me, keto), 1.29 (3 H, t, $\underline{J}$ 7.1 Hz,

CH$_2$Me, enol), 1.50-2.26 (6 H, m, (CH$_2$)$_3$CH$_2$O, keto/enol), 2.41 (2 H, t, J 5.6 Hz, CH$_2$CO, enol), 2.54-2.65 (1 H, m, CHHCO, keto), 2.99 (1 H, dt, J 11.4, 3.1, CHHCO, keto), 3.67 (1 H, ddd, J 12.0, 4.5, 1.9 Hz, CHHO, keto), 3.84 (2 H, t, J 4.8 Hz, CH$_2$O, enol), 3.99 (1 H, dt, J 12.3, 3.7 Hz, CHHO, keto), 4.10 (1 H, s, CHCOOEt, keto), 4.13-4.26 (2 H, m, CH$_2$Me, keto), 4.24 (2 H, q, J 7.0 Hz, CH$_2$Me, enol), and 10.92 (1 H, s, OH, enol); ca. 55% enol form; m/z (170°C) 200 (M$^+$, 100%), 154 (38), 143 (66), 126 (22), 115 (29), 97 (48), 69 (97), and 55 (88).

Purification of the distillation residue by chromatography gave the cyclopentanone (156) (9 mg, 5%) as a viscous oil, b.p. 120°C at 0.002 mmHg, (Found: C, 60.0; H, 8.4. C$_{10}$H$_{16}$O$_4$ requires C, 60.0; H, 8.1%); $\nu_{max.}$(film) 3450, 1752, 1724, 1655, 1193 and 1127 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.28 (3 H, t, J 7.0 Hz, CH$_2$Me), 1.41-1.90 (4 H, m, CH$_2$CH$_2$), 2.15-2.50 (2 H, m, CH$_2$), 2.63-2.82 (1 H, m, CHCHCOOEt), 2.86 (1 H, d, J 11.3 Hz, CHCOOEt), 3.57-3.74 (2 H, m, CH$_2$OH), and 4.21 (2 H, q, J 7.0 Hz, CH$_2$Me); m/z (120°C) 200 (M$^+$, 11%), 182 (2), 171 (18), 155 (73), 127 (72), 109 (55), and 99 (100).

Ethyl 5-(3-Hydroxypropyl)-2-oxocyclopentanecarboxylate (157).

Dirhodium tetraacetate (2 mg) was added to a solution of the diazo compound (130) (138 mg, 0.570 mmol) in dichloromethane (20 ml). After 3 h, the catalyst was filtered off, the filtrate evaporated, and the residue chromatographed to give the title compound (157) (26 mg, 32%) as a viscous oil (50 mg, 41%), b.p. 140-150°C at 0.0005 mmHg; (Found: C, 61.6; H, 8.6. C$_{11}$H$_{18}$O$_4$ requires C, 61.7; H, 8.5%); $\nu_{max.}$(film) 3437, 1758, 1724, 1278, 1192, and 1127 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.23 (3 H, t, J 7.0 Hz, CH$_2$Me), 1.35-1.67 (5 H, m), 1.82 (1 H, br, OH), 2.12-2.45 (3 H, m), 2.47-2.63 (1 H, m, CHCHCOOEt), 2.78 (1 H, d, J 11.1 Hz, CHCOOEt), 3.52-3.65 (2 H, m, CH$_2$OH), and 4.16 (2 H, q, J 7.3 Hz, CH$_2$Me); δ_C (62.9 MHz; CDCl$_3$) 211.1, 169.4, 65.0, 62.7, 61.3, 41.2, 38.3, 31.4, 30.4, 27.4, and 14.2; m/z (130°C) 214 (M$^+$, 4%), 186 (7), 168 (12), 155 (53), 113 (35), 109 (46), and 29 (100).

Ethyl 7-t-Butyldimethylsiloxy-2-diazo-3-oxoheptanoate (158).

Imidazole (77 mg, 1.3 mmol) was added to a solution of (122) (110 mg, 0.514 mmol) and t-butyldimethylsilyl chloride (85 mg, 0.56 mmol) in DMF (1.5 ml). After 12 h at room temperature, work-up and purification gave the title compound

(158) (143 mg, 85%) as an oil; (Found: C, 55.1; H, 8.7; N, 8.6. $C_{15}H_{28}N_2O_4Si$

requires C, 54.9; H, 8.6; N, 8.5%); $\nu_{max.}$ (film) 2134, 1722, 1660, 1304. and

1103 cm^{-1}; δ_H (90 MHz; CDCl$_3$) 0.06 (6 H, s), 0.90 (9 H, s), 1.34 (3 H, t, J 7.0

Hz, CH$_2$C$\underline{H}_3$), 1.33-1.93 (4 H, m), 2.90 (2 H, t, J 7.0 Hz, C$\underline{H}_2$CO), 3.66 (2 H, t, J

5.5 Hz, C$\underline{H}_2$O), and 4.33 (2 H, q, J 6.4 Hz, CO$_2$C$\underline{H}_2$); m/z (FAB; glycerol) 329

($\underline{M}^+$, 1%), 313 (1), 285 (1), 271 (5), 243 (5), 215 (4), 197 (2), 99 (10),

and 73 (100).

Ethyl 2-(t-Butyldimethylsiloxy)methyl-5-oxocyclopentanecarboxylate (159).

Dirhodium tetraacetate (3 mg) was added to a solution of (158) (150 mg, 0.455

mol) in dichloromethane (25 ml) and the mixture stirred for 12 h at room

temperature, after which time the solvent was evaporated and the residue

chromatographed to give the title compound (159) (34 mg, 25%) as a viscous oil; (

Found: $\underline{M}^+$, 301.1835. $C_{15}H_{28}N_2O_4Si$ requires $\underline{M}H^+$, 301.1835); $\nu_{max.}$ (film)

1759, 1730, 1660, 1255, 1099, and 838 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.04 (6 H,

s), 0.88 (9 H, s), 1.29 (3 H, t, J 7.2 Hz, CH$_2$C$\underline{H}_3$), 1.47-1.84 (1 H, m,

C$\underline{H}_2$CH$_2$CO), 2.00-2.14 (1 H, m, C$\underline{H}_2$CH$_2$CO), 2.24-2.53 (2 H, m, C$\underline{H}_2$CO), 2.67-

2.85 (1 H, m, C$\underline{H}$CHCO$_2$), 3.12 (1 H, d, J 11.5 Hz, C$\underline{H}$CO$_2$), 3.56-3.78 (2 H, m,

C$\underline{H}_2$O), and 4.20 (2 H, dq, J 7.2, 0.7 Hz); m/z (130°C) 301 ($\underline{M}H^+$, 2%), 285

(3), 255 (11), 243 (100), 215 (30), 197 (24), 155 (35), 123 (68), and 75

(66).

Ethyl 2-Diazo-3,7-dioxoheptanoate (160).

Pyridinium chlorochromate (0.45 g, 2.2 mmol) was added to a solution of (122)

(160 mg, 0.75 mmol) in dichloromethane (5 ml), and the suspension rapidly stirred

at room temperaturefor 1.25 h. After filtration through Celite, the residue was

purified by chromatography, to give the title compound (160) (99 mg, 63%) as a

pale yelow oil; (Found: $\underline{M}^+$, 212.0794. $C_9H_{12}N_2O_4$ requires $\underline{M}$, 212.0797);

$\nu_{max.}$ (film) 2137, 1718, 1655, and 1304 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.30 (3

H, t, J 7.1 Hz), 1.95 (2 H, quin, J 7.2 Hz), 2.50 (2 H, dt, J 7.2, 1.3 Hz,

CH$_2$C(O)H), 2.88 (2 H, t, J 7.2 Hz, C$\underline{H}_2$CO), 4.27 (2 H, q, J 7.1 Hz, C$\underline{H}_2$CO$_2$), and

9.73 (1 H, t, J 1.3 Hz, CH$_2$CHO); m/z (100°C) 212 (M$^+$, 1%), 184 (4), 167 (3), 156 (66), 99 (51), and 29 (100).

(E)-Diethyl 7-Diazo-8-oxonon-2-ene-1,9-dicarboxylate (161).

(Carbethoxymethylene)triphenylphosphorane (163 mg, 0.468 mmol) was added to a solution of (160) (90 mg, 0.425 mmol) in THF (3 ml). The reaction was stirred for 2 h, then subjected to aqueous work-up and the residue purified, to give the title compound (161) (96 mg, 80%) as an oil; (Found: C, 55.4; H, 6.6; N, 9.8. C$_{13}$H$_{18}$N$_2$O$_5$ requires C, 55.3; H, 6.4; N, 9.9%); $v_{max.}$ (film) 2136, 1719, 1656, and 1305 cm^{-1}; δH (250 MHz; CDCl$_3$) 1.24 (3 H, t, J 7.1 Hz), 1.29 (3 H, t, J 6.9 Hz), 1.78 (2 H, quin, J 7.5 Hz, CH$_2$CH$_2$CO), 2.22 (2 H, q, J 7.1 Hz, CH$_2$CH), 2.84 (2 H, t, J 7.0 Hz, CH$_2$CO), 4.14 (2 H, q, J 7.1 Hz, CHCO$_2$CH$_2$), 4.26 (2 H, q, J 6.9 Hz, CNCO$_2$CH$_2$), 5.80 (1 H, approx d, J 15.8 Hz, CHCO), and 6.90 (1 H, dt, J 15.8, 7.8 Hz, CHCH$_2$); m/z (100°C) 282 (M$^+$, 1%), 254 (4), 237 (8), 208 (12),180 (28), 162 (37), 153 (46), :d 29 (100).

Ethyl 2-[2-(Ethoxycarbonyl)ethenyl]-5-oxocyclopentanecarboxylate (162).

Dirhodium tetraacetate (1.5 mg) was added to a solution of (161) (82 mg, 0.291 mmol) in dichloromethane (10 ml). After 1 h. the green solution was evaporated and the residue purified by chromatography to give the title compound (162) (43 mg, 58%) as a colourless oil; (Found: M$^+$, 254.1148. C$_{13}$H$_{18}$O$_5$ requires M, 254.1154); $v_{max.}$ (film) 1760, 1723, 1657, 1313, 1269, and 1190 cm^{-1}; δH (250 MHz; CDCl$_3$) 1.27 (3 H, t, J 6.9 Hz, CH$_2$CH$_3$), 1.28 (3 H, t, J 6.9 Hz, CH$_2$CH$_3$), 1.65-1.90 (1 H, m, CH$_2$CH$_2$CO), 2.18-2.62 (3 H, m, CH$_2$CH$_2$CO), 3.05 (1 H, d, J 10.9 Hz, CHCHCO$_2$), 3.37 (1 H, hept, J ~6 Hz, CHCHCO$_2$), 4.10-4.28 (4 H, m, CO$_2$CH$_2$), 5.92 (1 H, dd, J 15.2, 1.5 Hz, CH:CHCO$_2$), and 6.90 (1 H, dd, J 15.2, 7.0 Hz, CH:CHCO$_2$); m/z (100°C) 254 (M$^+$. 15%), 225 (4), 208 (67), 181 (21), 162 (100), 153 (20), 135 (40), and 107 (19).

Ethyl 3-Oxothiane-2-carboxylate (163).

A solution of (136) (120 mg, 0.556 mmol) in benzene (5 ml) was added to a suspension of dirhodium tetraacetate (4 mg) in benzene (15 ml) at reflux over 5 minutes. After 10 minutes at reflux the pale purple solution was cooled, evaporated, and the residue subject subjected to chromatography.to give the title compound (163) (59 mg, 57%) as a clear oil; b.p. 130-140°C at 0.4 mmHg; (Found: C, 51.1; H, 6.7. $C_8H_{12}O_3S$ requires C, 51.0; H, 6.4%); $v_{max.}$ (film) 1745, 1719, 1651, 1603, 1380, 1297 and 1219 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.29 (3 H, t, J 7.0 Hz, CH_2CH_3, keto), 1.32 (3 H, t, J 7.0 Hz, CH_2CH_3, enol), 2.10 (2 H, m, $CH_2CH_2CH_2$, keto/enol), 2.40 (2 H, approx t, J 6.5 Hz, CH_2S, enol), 2.40-2.64 (2 H, m, CH_2S, keto), 2.78 (2 H, approx t, J 5.6 Hz, CH_2CO, enol), 2.80-3.14 (2 H, m, CH_2CO, keto), 3.95 (1 H, s, $COCHS$, keto), 4.23 (2 H, q, J 7.0 Hz, CO_2CH_2, keto), 4.24 (2 H, q, J 7.0 Hz, CO_2CH_2, enol), and 10.48 (1 H, s, OH, enol); ca. 75% enol form; m/z (110°C) 188 (M^+, 56%), 142 (100), 115 (18), 86 (41), and 69 (21).

Ethyl 3-Oxothiepane-2-carboxylate (164).

A solution of (137) (462 mg, 2.01 mmol) in benzene (10 ml) was added over 1 h to a stirred suspension of dirhodium tetraacetate (2.9 mg) in benzene (40 ml) at reflux. After 0.5 h, extra catalyst (3 mg) was added. Reflux was continued for 2 h, before the mixture was cooled, evaporated and the residue purified by chromatography to give the title compound (164) (138 mg, 34%) as a clear oil; (Found: C, 53.7; H, 7.2. $C_9H_{14}O_3S$ requires C, 53.4; H, 7.0%. Found: M^+, 202.0663; requires M, 202.0664); $v_{max.}$ (film) 1742, 1707, 1632, 1595, 1377, 1308, and 1242 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.24 (3 H, t, J 7.0 Hz, CH_2CH_3, keto), 1.29 (3 H, t, J 7.0 Hz, CH_2CH_3, enol), 1.56-2.05 (4 H, m, $CH_2CH_2CH_2S$, keto/enol), 2.54 (2 H, approx t, J 5.5 Hz, CH_2S, enol), 2.68 (2+2 H, m, CH_2S keto, and CH_2CO keto/enol), 4.22 (1 H, s, $COCHS$, keto), 4.23 (2 H, q, J 7.1 Hz, CO_2CH_2, keto), 4.26 (2 H, q, J 7.1 Hz, CO_2CH_2, enol), and 9.63 (1 H, s, OH, enol); ca. 65% enol; m/z (180°C) 202 (M^+, 61%), 169 (6), 156 (80), 128 (33), 100 (13), 87 (100).

Ethyl 5-(N-tert-Butoxycarbonyl)aminomethyl-2-oxocyclopentanecarboxylate (165).

To a rapidly stirred solution of the diazo compound (138) (247 mg, 0.788 mmol) in dichloromethane (35 ml), dirhodium tetraacetate (2 mg) was added. After 1.5 h the

solvent was evaporated and the residue chromatographed to give the title compound (165) (164 mg, 73%) as a low melting solid, m.p. 50-55°C (from ether); (Found: C, 58.8; H, 8.3; N, 5.0. $C_{14}H_{23}NO_5$ requires C, 58.9; H, 8.1; N, 4.9%); $v_{max.}$ (film) 3383, 1757, 1719 (br.), 1520, 1368, 1250 and 1172 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.23 (3 H, t, J 7.0 Hz, CH$_2$Me), 1.40 (9 H, s, t-Bu), 1.50-1.85 (1 H, m), 2.08-2.23 (1 H, m), 2.25-2.50 (2 H, m), 2.74 (1 H, CHCHCO), 2.90 (1 H, d, J 11.5 Hz, CHCOOEt), 3.19 (1 H, dt, J 13.9, 6.7 Hz, CHHN), 3.31 (1 H, dt, J 13.8, 5.6 Hz, CHHN), 4.19 (2 H, q, J 7.0 Hz, CH$_2$Me), 4.70 (1 H, br, NH), and 10.68 (s, OH, enol); ca. 10% enol form; δ_C (125.8 MHz; CDCl$_3$) 210.5, 169.0, 155.8, 79.3, 61.3, 59.4, 43.8, 41.7, 38.0, 28.24, 28.18, 27.8, 24.6, and 14.0; m/z (140°C) 285 (M$^+$, 0.1%), 228 (1), 212 (2), 199 (1), 184 (3), 168 (6), 144 (24), and 31 (100); m/z (CI; NH$_3$) 303 (M$^+$+NH$_3$, 100%), 286 (75), 247 (40), 230 (17), and 186 (32).

Ethyl 5-(2-N-tert-Butoxycarbonyl)aminoethyl-2-oxocyclopentanecarboxylate (166).

A solution of the diazo compound (139) (97.3 mg, 0.298 mmol) in dichloromethane (20 ml) was added to a blue solution of dirhodium tetrakis(trifluoroacetate) (2 mg) in dichloromethane (20 ml) over a period of 2.2 h to give a green solution. After 1 h the solvent was evaporated, and the residue chromatographed to give the title compound (166) (68 mg, 76%) as a viscous oil; b.p. 130°C at 0.003 mmHg; (Found: C, 60.2; H, 8.6; N, 4.7. $C_{15}H_{25}NO_5$ requires C, 60.2; H, 8.4; N, 4.7%); $v_{max.}$(film) 3380, 1757, 1710 (br), 1515, 1250, and 1172 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.28 (3 H, t, J 7.0 Hz, CH$_2$Me), 1.42 (9 H, s, t-Bu), 1.45-1.65 (1 H, m), 1.68 (2 H, q, J 6.9 Hz, CH$_2$CH$_2$N), 2.14-2.49 (3 H, m), 2.60 (1 H, m, CHCHCO), 2.81 (1 H, d, J 11.3 Hz, CHCOOEt), 2.98-3.30 (2 H, m, CH$_2$N), 4.20 (2 H, q, J 7.0 Hz, CH$_2$Me), and 4.64 (1 H, br, NH); m/z (120°C) 299 (M$^+$, 3%), 243 (33), 226 (27), 199 (9), 182 (50), 170 (15), 155 (81), 136 (64), and 57 (100).

Ethyl 5-(N-tert-Butylcarbonyl)aminomethyl-2-oxocyclopentanecarboxylate (167).

A solution of diazo compound (140) (170 mg, 0.572 mmol) in benzene (5 ml) was added dropwise to a suspension of dirhodium tetraacetate (4.9 mg) in benzene (15 ml) at reflux over 5 min. After 5 min at reflux the suspension was cooled, filtered,

concentrated, and the residue chromatographed to give the title compound (167) (30 mg, 19%), m.p. 85-86°C, (Found: C, 62.5; H, 8.7; N, 5.2. $C_{14}H_{23}NO_4$ requires C, 62.4; H, 8.6; N, 5.2%); $v_{max.}$ (film) 3358, 1755, 1724, 1646, 1530, 1206, and 1127 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.18 (9 H, d, J 2.2 Hz, t-Bu), 1.30 (3 H, t, J 7.0 Hz, CH$_2$Me), 1.45-1.68 (1 H, m, CHHCH$_2$CO), 2.12-2.26 (1 H, m, CHHCH$_2$CO), 2.28-2.53 (2 H, m, CH$_2$CO), 2.70-2.88 (1 H, m, CHCHCOOEt), 2.92 (1 H, d, J 11.0 Hz, CHCOOEt), 3.32 (1 H, ddd, J 13.8, 7.5, 5.6 Hz, CHHN), 3.50 (1 H, dt, J 13.1, 5.1 Hz, CHHN), 4.12-4.31 (2 H, m, CH$_2$Me), and 5.95 (1 H, br, NH); m/z (140°C) 269 (M$^+$, 6%), 224 (11), 212 (12), 196 (5), 184 (10), 168 (89), 155 (43), 115 (40), and 57 (100).

4,4-Dimethyl-2,6-dioxo-oxepane (169).

6-Diazo-3,3-dimethyl-5-oxohexanoic acid (168) was prepared by a modification of the literature procedure;[73] diazodimedone (0.50 g, 3.0 mmol) was dissolved in dichloromethane (10 ml), sodium hydroxide solution (1 M; 7.5-10 ml) was added, and the two phase mixture rapidly stirred (16-18 h). The two layers were separated, the aqueous phase acidified to pH4 with hydrochloric acid (2 M), and quickly extracted with dichloromethane. The organic phase was washed with water, brine and finally dried over MgSO$_4$, to give a crude solution of the diazo acid (168).

(a).-Boron trifluoride diethyl ether (0.85 ml, 3 mmol) was added dropwise to a stirred solution of crude diazoacid (168) in dichloromethane (100 ml) (see above), and the mixture stirred for 12 h. Aqueous work-up and chromatography gave the title compound (169) (140 mg, 30% from diazodimedone) as a low melting solid, m.p. 52-56°C; (Found: C, 61.3; H, 7.9. $C_8H_{12}O_3$ requires C, 61.5; H, 7.8%); $v_{max.}$(film) 1754, 1720, 1486, 1432, 1308, 1283, and 1077 cm^{-1}; δ_H (270 MHz; CDCl$_3$) 1.17 (6 H, s, Me), 2.47 (2 H, s, CH$_2$CO), 2.59 (2 H, s, CH$_2$CO), and 4.50 (2 H, s, CH$_2$O); m/z (100°C) 156 (M$^+$, 21%), 126 (29), 98 (7), 83 (16), 70 (61), and 56 (100).

(b).-Alternatively, evaporation of the dichloromethane solution of (168) prepared from diazodimedone (803 mg, 4.8 mmol), gave a viscous unstable oil which was immediately subjected to partial purification by filtration through a pad of silica with ether as eluant. The diazo acid (168) (462 mg, 52%) was immediately dissolved in benzene (10 ml) and added dropwise to a suspension of dirhodium tetraacetate (5 mg)

in benzene (100 ml) at reflux over a period of 10 min. After a further 15 min, the mixture was cooled and filtered through a pad of Celite. The filtrate was evaporated and the residue purified by chromatography to give (i) the title compound (169) (263 mg, 67%), and (ii) a second component (15 mg, 4%), a symmetrical dimer, m.p. 121-122°C (hexane/ether); (Found: C, 61.6; H, 7.8. $C_{16}H_{24}O_6$ requires C, 61.5; H, 7.8%); $\nu_{max.}$ (Nujol) 1726, 1426, 1378, 1250, and 1093 cm^{-1}; δ_H (270 MHz; CDCl$_3$) 1.23 (12 H, s), 2.47 (4 H, s), 2.62 (4 H, s), and 4.43 (4 H, s); m/z (180°C) 312 (M$^+$, 7%), 254 (3), 239 (2), 212 (1), 198 (57), 183 (4), 170 (6), 156 (37), 140 (30), 115 (12), 97 (8), and 83 (100).

Preparation of Derivatives

General Procedure for Preparation of tert-Butyldimethylsilyl Enol Ethers.

Triethylamine (1.25-2.5 eq) and tert-butyldimethylsilyl trifluoromethane-sulphonate (TBDMSOTf) (1.2-2.0 eq) were added in succession to a solution of the β-ketoester (0.1 - 0.5 mmol) in ether or THF (1 ml). The resulting suspension was stirred for 12 h at room temperature before all the volatile material was removed under high vacuum, and the residue subjected to a neutral aqueous work-up. The crude product was distilled to give the enol silyl ether.

Ethyl 3-tert-Butyldimethylsiloxy-4,5-dihydropyran-2-carboxylate (170).
Triethylamine (0.12 ml, 0.85 mmol) and TBDMSOTf (0.19 ml, 0.85 mmol) were added simultaneously to a solution of ethyl 3-oxotetrahydropyran-2-carboxylate (147) (120 mg, 0.70 mmol) in THF (1 ml) at -70°C. The solution was allowed to warm to room temperature and stirred for 1.5 h before work-up. Rapid distillation of the residue gave the title compound (170) (137 mg, 69%), b.p. 160°C at 0.3 mmHg; (Found: C, 58.6; H, 9.3. $C_{14}H_{26}O_4Si$ requires C, 58.9; H, 9.2%); $\nu_{max.}$ (film) 1719, 1628, 1297, 1255, 1223, 1164, 1078, 842, and 782 cm^{-1}; δ_H (270 MHz; CDCl$_3$) 0.18 (6 H, s, SiMe), 0.95 (9 H, s, t-Bu), 1.31 (3 H, t, J 7.1 Hz, CH$_2$Me), 1.93 (2 H, quin, J 5.9 Hz, CH$_2$CH$_2$O), 2.29 (2 H, t, J 6.7 Hz, CH$_2$CO),

3.95 (2 H, t, J 5.1 Hz, CH_2O), and 4.25 (2 H, q, J 7.1 Hz, CH_2Me); m/z (140°C) 286 (M$^+$, 1%), 271 (1), 241 (9), 229 (53), 201 (100), 189 (17), 173 (12), 147 (54), and 75 (40).

Ethyl 3-tert-Butyldimethylsiloxy-4,5-dihydro-6-methylpyran-2-carboxylate (171).

Triethylamine (96 µl, 0.69 mmol) and TBDMSOTf (151 µl, 0.66 mmol) were added to a solution of ethyl 6-methyl-3-oxotetrahydropyran-2-carboxylate (148) (102 mg, 0.548 mmol) in ether (4 ml) at 0°C. The solution was allowed to warm to room temperature and stirred for 10 h before work-up. Rapid distillation of the residue gave the title compound (171) (95 mg, 57%) as a clear oil, b.p. 135°C at 0.5 mmHg; (Found: M$^+$, 300.1751. $C_{15}H_{28}O_4Si$ requires M, 300.1757); $\nu_{max.}$ (film) 1719, 1630, 1224, and 1178 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.33 (6 H, s, SiMe), 0.91 (9 H, s, t-Bu), 1.27 (3 H, t, J 7.1 Hz, CH$_2$Me), 1.30 (3 H, d, J 6.0 Hz, CHMe), 1.57-1.69 (1 H, m, CHHCHO), 1.83 (1 H, dddd, J 13.5, 7.0, 2.9, 2.6 Hz, CHHCHO), 2.18 (1 H, ddd, J 3.0, 6.4, 2.9 Hz, CHHC=), 2.34 (1 H, ddd, J 18.0, 10.5, 7.1 Hz, CHHC=), 3.83 (1 H, ddq, J 9.8, 6.0, 2.3 Hz, MeCHO), and 4.10-4.32 (2 H, m, CH$_2$Me); m/z (140°C) 300 (M$^+$, 2%), 285 (1), 259 (53), 243 (57), 215 (89), and 75 (100).

Ethyl 3-tert-Butyldimethylsiloxy-7-hexyloxepane-2-carboxylate (172).

Triethylamine (42 µl, 0.29 mmol) and TBDMSOTf (51 µl, 0.22mmol) were added to a solution of ethyl 7-hexyl-3-oxo-oxepane-2-carboxylate (150) (39.8 mg, 0.147 mmol) in THF (1 ml). After 12 h work-up and distillation of the residue gave the title compound (172) (49 mg, 86%) as a clear oil, b.p. 130-140°C at 0.0005 mmHg; (Found: C, 65.4; H, 10.5. $C_{21}H_{40}O_4Si$ requires C, 65.6; H, 10.5%); $\nu_{max.}$ (film) 1714, 1621, 1235, 1177, and 833 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.15 (6 H, s, SiMe), 0.81-0.93 (3 H, m, Me), 0.93 (9 H, s, t-Bu), 1.27 (3 H, t, J 6.9 Hz, CH$_2$Me), 1.18-1.88 (14 H, m), 2.11 (1 H, dd, J 13.5, 6.0 Hz, CHHC=), 2.80 (1 H, ddd, J 14.3, 11.3, 1.7 Hz, CHHC=), 3.28-3.39 (1 H, m, CHRO), and 4.08-4.27 (2 H, m, CH$_2$Me); m/z (170°C) 384 (M$^+$, 1%), 369 (2), 339 (3), 327 (100), 299 (6), and 73 (47).

Ethyl 3-tert-Butyldimethylsiloxy-5,6-dihydrobenzoxocin-2-carboxylate (173).

Triethylamine (22.5 μl, 0.16 mmol) and TBDMSOTf (30 μl, 0.13 mmol) were added to a solution of ethyl 3-oxo-3,4,5,6-tetrahydrobenzoxocin-2-carboxylate (152) (16.1 mg, 64.4 μmol) in ether (1 ml). The mixture was stirred for 24 h, evaporated, and the residue chromatographed to give the title compound (173) (9.6 mg, 41%) as an oil; (Found $\underline{M}^+$, 362.1913. $C_{20}H_{30}O_4Si$ requires $\underline{M}$, 362.1913); ν_{max}.(film) 1718, 1625, 1594, 1249, and 839 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.18 (6 H, s, SiMe), 0.93 (9 H, s, t-Bu), 1.28 (3 H, t, $\underline{J}$ 7.0 Hz, CH$_2$Me), 1.95-2.15 (2 H, m, C$\underline{H}_2$ CH$_2$Ar), 2.61 (2 H, t, $\underline{J}$ 6.4 Hz, C$\underline{H}_2$Ar), 2.85 (2 H, t, $\underline{J}$ 5.8 Hz, C$\underline{H}_2$CO), 4.22 (2 H, q, $\underline{J}$ 7.0 Hz, C$\underline{H}_2$Me), 6.95 (1 H, dt, $\underline{J}$ 7.1, 1.1 Hz), 7.03 (1 H, dd, $\underline{J}$ 8.0, 1.8 Hz), 7.12 (1 H, dt, $\underline{J}$ 7.5 , 1.8 Hz), and 7.26 (1 H, dd, 8.0, 1.0 Hz); m/z (160°C) 362 ($\underline{M}^+$, 1%), 347 (2), 317 (6), 305 (100), 277 (78), and 75 (56).

Ethyl 2-tert-Butyldimethylsiloxy-5-(2-tert-butyldimethylsiloxyphenyl)cyclo-pentenoate (174).

Triethylamine (0.13 ml, 0.94 mmol) and TBDMSOTf (0.18 ml, 0.78 mmol) were added to a solution of ethyl 5-(2-hydroxyphenyl)-2-oxocyclopentane-2-carboxylate (153) (78 mg, 0.313 mmol) in DMF (2.5 ml). After 12 h, work-up and chromatography gave the title compound (174) (80 mg, 53%), m.p. 57-60°C; (Found: C, 65.6; H, 9.4. $C_{26}H_{44}O_4Si_2$ requires C, 65.5; H, 9.3%); ν_{max}.(film) 1713, 1629, 1487, 1254, 1226, and 840 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.25-0.28 (12 H, 4 x s, SiMe), 1.00 (9 H, s, t-Bu), 1.01 (9H, s, t-Bu), 1.05 (3 H, t, $\underline{J}$ 7.0 Hz, CH$_2$Me), 1.52-1.67 (1 H, m, HC$\underline{H}$CH$_2$), 2.22-2.60 (3 H, m, HC$\underline{H}$C$\underline{H}_2$), 4.02 (2 H, q, $\underline{J}$ 7.0 Hz, C$\underline{H}_2$Me), 4.45 (1 H, d, $\underline{J}$ 7.9 Hz, C$\underline{H}$Ar), 6.72-6.88 (2 H, m, ArH), and 6.95-7.09 (2 H, m, ArH); m/z (130°C) 461 ($\underline{M}^+$ - Me, 2%), 431 (4), 419 (100), 183 (32), and 73 (40).

Ethyl 3-tert-Butyldimethylsiloxyoxecane-2-carboxylate (175).

Triethylamine (42 μl, 0.30 mmol) and TBDMSOTf (52 μl, 0.23 mmol) were added to a solution of ethyl 3-oxo-oxecane-2-carboxylate (155) (30.0 mg, 0.150 mmol) in THF (2 ml). After 12 h, work-up with 5% aqueous sodium carbonate and distillation of the residue gave the title compound (175) (47.1 mg, 100%) as a clear oil, b.p. 150-160°C at 0.25 mmHg; (Found: $\underline{M}^+$, 257.1204. $C_{16}H_{30}O_4Si$ - C_4H_9 requires $\underline{M}$, 257.1209); ν_{max}..(film) 1717, 1623, 1226, and 841 cm^{-1}; δ_H (250 MHz;

CDCl$_3$) 0.18 (6 H, s, SiMe), 0.94 (9 H, s, t-Bu), 1.24 (3 H, t, J 7.0 Hz, CH$_2$Me),
1.55-1.77 (4 H, m, CH$_2$ CH$_2$), 2.30-2.40 (2 H, m, C=), 3.83-3.95 (2 H, m,
CH$_2$O), and 4.20 (2 H, q, J 7.0 Hz, CH$_2$Me); m/z (170°C) 314 (M$^+$, 1%), 299
(3), 269 (6), 257 (100), 229 (13), 173 (16), and 75 (97).

Ethyl 3-t-Butyldimethylsiloxy-4,5-dihydrothiin-2-carboxylate (176).

Triethylamine (48 μl, 0.346 mmol) and t-butyldimethylsilyl triflate (64 μl, 0.277
mmol) were added to a solution of (163) (26 mg, 0.138 mmol) in THF (1 ml) and
the mixture stirred overnight. Aqueous work-up with 5% sodium bicarbonate
solution and distillation of the crude product gave the title compound (176) (42 mg,
100%) as a clear oil, b.p. 150-160°C at 0.2 mm Hg; (Found: C, 55.4; H, 8.7.
C$_{14}$H$_{26}$O$_3$SSi requires C, 55.6; H, 8.7%); ν$_{max.}$ (film) 1720, 1688, 1591,
1262, 1200 and 831 cm^{-1}; δ$_H$ (250 MHz; CDCl$_3$) 0.16 (6 H, s), 0.93 (9 H, s),
1.28 (3 H, t, J 7.1 Hz, CH$_2$CH$_3$), 2.02-2.15 (2 H, m, CH$_2$CH$_2$S), 2.27 (2 H, t, J
6.0 Hz, CH$_2$COSi), 2.78-2.70 (2 H, m, CH$_2$S), and 4.18 (2 H, q, J 7.1 Hz, CO$_2$CH$_2$);
m/z (170°C) 302 (M$^+$, 5%), 257 (12), 245 (66), 217 (100), and 75 (38).

Ethyl 3-t-Butyldimethylsiloxy-4,5,6,7-tetrahydrothiepin-2-carboxylate (177).

Triethylamine (33 μl, 0.232 mmol) and t-butyldimethylsilyl triflate (43 μl, 0.186
mmol) were added to a solution of (164) (18.8 mg, 93 μmol) in ether (1 ml) and the
mixture stirred overnight. Aqueous work-up with 5% sodium bicarbonate solution
and distillation of the crude product gave the title compound (177) (29.6 mg, 100%)
as a clear oil, b.p. 160°C at 0.25 mm Hg; (Found: C, 57.0; H, 9.0. C$_{15}$H$_{28}$O$_3$SSi
requires C, 56.9; H, 8.9%); ν$_{max.}$ (film) 1714, 1573, 1283, 1207 and 831 cm^{-1}; δ$_H$ (250 MHz; CDCl$_3$) 0.08 (6 H,s), 0.93 (9 H, s), 1.27 (3 H, t, J 7.1 Hz,
CH$_2$CH$_3$), 1.51-1.63 (2 H, m, (CH$_2$)$_2$CH$_2$S), 1.91-2.02 (2 H, m, (CH$_2$)$_2$CH$_2$S),
2.58-2.66 (2 H, m, CH$_2$COSi), 2.73-2.81 (2 H, m, CH$_2$S), and 4.16 (2 H, q, J 7.1
Hz, CO$_2$CH$_2$); m/z (170°C) 316 (M$^+$, 2%). 301 (2), 271 (11), 259 (79), 231
(100), 145 (9), and 75 (43).

Ethyl 5-(N-tert-Butoxycarbonyl)aminomethyl-2-tert-butyldimethylsiloxy-cyclopentenoate (178).

Triethylamine (26 μl, 0.19 mmol) and TBDMSOTf (40 μl, 0.17 mmol) were added to a solution of ethyl 5-(N-t-butoxycarbonyl)aminomethyl-2-oxocyclopentane-2-carboxylate (165) (41 mg, 0.14 mmol) in ether (1 ml). After 12 h, work-up and chromatography gave the title compound (178) (13 mg, 23%) as a low melting solid, m.p. 64-66°C; (Found: C, 60.0; H, 9.3; N, 3.4. $C_{20}H_{37}NO_5Si$ requires C, 60.1; H, 9.3; N, 3.5%); $\nu_{max.}$(film) 3373, 1714 (br), 1622, 1253, 1173, and 843 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.19 (6 H, s, SiMe), 0.95 (9 H, s, t-BuSi), 1.26 (3 H, t, J 7.1 Hz, CH$_2$Me), 1.41 (9 H, s, t-BuO), 1.59-1.73 (1 H, m, HCHCH$_2$), 1.88-2.06 (1 H, m, HCHCH$_2$), 2.28 (1 H, ddd, J 16.8, 9.6, 3.2 Hz, CHHC=), 2.52 (1 H, ddt, J 16.8, 8.4, 1.8 Hz, CHHC=), 2.91-3.03 (1 H, m, CH CH$_2$N), 3.24 (2 H, t, J 5.7 Hz, CH$_2$N), 4.16 (2 H, m, CH$_2$Me), and 4.97 (1 H, br, NH); m/z (130°C) 342 (M$^+$- t-Bu, 0.1%), 326 (0.1), 297 (0.2), 285 (1), 269 (1), 212 (16), 168 (60), 155 (100), 109 (53), and 57 (89).

Lactone (179).

A solution of ethyl 5-(2-hydroxyphenyl)-2-oxocyclopentanecarboxylate (153) (29.6 mg, 0.119 mmol) and camphorsulphonic acid (CSA) (3 mg) in benzene (5 ml) was heated to reflux. After 1 h, an extra portion of CSA (3 mg) was added to the reaction mixture and heating continued for 2 h. After cooling, the benzene was washed with water, dried over MgSO$_4$, evaporated and the residue chromatographed to give the title compound (179) (7.4 mg, 32%) as a viscous oil; (Found: M$^+$, 202.0629. $C_{12}H_{10}O_3$ requires M, 202.0630); $\nu_{max.}$ (film) 1784, 1737, 1613, 1489, 1454, 1218, and 760 cm^{-1}; δ_H (270 MHz; CDCl$_3$) 2.07-2.27 (1 H, m, HCHCH$_2$CO), 2.31-2.58 (3 H, m, HCHCH$_2$CO), 3.58 (1 H, d, J 7.0 Hz, CHCO), 3.90 (1 H, dd, J 7.0, 4.5 Hz, CHCHCO), and 7.05-7.37 (4 H, m, ArH); m/z (150°C) 202 (M$^+$, 100%), 173 (33), 158 (6), 147 (57), 118 (16), 103 (24), and 91 (14).

6.3   Experimental for Chapter Three

Preparation of the Diazo Compounds

t-Butyl 2-Diazo-7-hydroxy-3-oxoheptanoate (186).

t-Butyl diazoacetate (0.750 g, 5.25 mmol) was added dropwise to a solution of LDA (5.25 mmol) in THF (30 ml) at -90°C. After fifteen minutes at -90°C, δ–valerolactone (5.00 mmol, 0.501g) was added dropwise over 5 minutes. After fifteen minutes at -90°C, the solution was warmed to -77°C for 4.5 h. Acetic acid (0.3ml) was added , and the mixture allowed to warm to 0°C before the addition of water and extraction into dichloromethane. The crude product was purified by chromatography to give the title compound (186) (1.06g, 87%) as a pale yellow oil; (Found: C, 54.6; H, 7.7; N, 11.4. $C_{11}H_{18}N_2O_4$ requires C, 54.5; H, 7.5; N, 11.6%); $\nu_{max.}$ (film) 3421, 2133, 1713, 1655, 1315, and 1135 cm^{-1} ; δ_H (250 MHz; CDCl$_3$) 1.52 (9 H, s, t-Bu), 1.50-1.80 (4 H, m,), 1.90 (1 H, s, OH.), 2.84 (2 H, t, J 7.1 Hz, CH$_2$CO), and 3.64 (2 H, t, J 6.4 Hz, CH$_2$O); m/z (FAB; glycerol) 243 (MH$^+$, 51%), 225 (10), 187 (39), 169 (31), 141 (26), 99 (31), and 57 (100).

t-Butyl 7-(t-Butoxycarbonyl)amino-2-diazo-3-oxoheptanoate (187).

t-Butyl diazoacetate (0.373 g, 2.63 mmol) was added dropwise to a solution of LDA (2.63 mmol) in THF (22 ml) at -90°C. After 15 minutes N-t-butoxycarbonyl-δ–valerolactam (0.498 g, 2.50 mmol) was added dropwise over three minutes, and after fifteen minutes the reaction mixture was allowed to warm to -78°C and stirred for 3.5 h. Acetic acid (0.3 ml) was added and the mixture warmed to 0°C before aqueous work-up. The crude product was purified by chromatography to give the title compound (187) (481 mg, 56%) as a yellow solid, m.p. 72-75°C; (Found: M$^+$, 268.1290. $C_{16}H_{27}N_3O_5$ - t-BuO requires M, 268.1297) ; $\nu_{max.}$ (melt) 3376, 2133, 1713, 1654, 1314, and 1174 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.37 (9 H, s), 1.47 (9 H, s), 1.40-1.70 (4 H, m), 2.77 (2 H, t , J 7.2Hz, CH$_2$CO), 3.08 (2 H, q, J 6.1 Hz, CH$_2$N), and 4.67 (1 H, s, NH); m/z (100°C) 268 (M$^+$-t-BuO, 2%), 212 (8), 200 (4), 156 (9), 140 (13), 128 (8), 112 (4), 100 (5), and 57 (100).

3-Diazo-8-hydroxyoctane-2,4-dione (188).

A solution of LDA (2.38 mmol) in THF (5 ml) was added dropwise to a solution of diazoacetone (200 mg, 2.38 mmol) and δ-valerolactone (238 mg, 2.38 mmol) in THF (10 ml) at -92°C. The solution was stirred at -90°C for 0.5 h followed by 4.5 h at -75°C, before the addition of acetic acid (0.15 ml). Aqueous work-up and purification of the residue by chromatography gave the title compound (188) (114 mg, 26%) as a yellow oil; (Found: $\underline{M}^+$, 184.0844. $C_8H_{12}N_2O_3$ requires $\underline{M}$, 184.0848); $\nu_{max.}$ (film) 3419, 2130, 1662, 1367, and 1299 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.43-1.56 (2 H, m), 1.56-1.70 (2 H, m), 2.33 (3 H, s, CO$\underline{Me}$), 2.66 (2 H, t, $\underline{J}$ 6.9 Hz, C$\underline{H}_2$CO), 2.66 (1 H, br, OH), and 3.53 (2 H, t, $\underline{J}$ 5.8 Hz, C$\underline{H}_2$O); $\underline{m/z}$ (80°C) 184 ($\underline{M}^+$, 1%), 166 (5), 156 (7), 138 (4), 126 (7), 100 (16), 85 (18), 55 (31), and 43 (100).

3-Diazo-8-mercapto-octane-2,4-dione (189).

Diazoacetone (177 mg, 2.10 mmol) was added dropwise to a solution of LDA (2.10 mmol) in THF (6 ml) at -90°C. After five minutes δ-thiovalerolactone (232 mg, 2.00 mmol) was added dropwise, and after five more minutes the reaction was warmed to −75°C, and the temperature maintained for 2 h. Acetic acid (0.3 ml) was added , and the mixture warmed to -20°C, then water was added, followed by work-up and purification by chromatography to give δ-thiovalerolactone (44 mg,19%) and the title compound (189) (78 mg, 20%) as a yellow oil; (Found: $\underline{M}^+$,172.0555. $C_8H_{12}N_2O_2S-N_2$ requires $\underline{M}$, 172.0558); $\nu_{max.}$ (film) 2570, 2123, 1666, 1365, 1298, and 1224 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.31 (1 H, t, $\underline{J}$ 7.8 Hz, SH), 1.51-1.77 (4 H, m, C$\underline{H}_2$C$\underline{H}_2$CH$_2$), 2.37 (3 H, s, CO$\underline{Me}$), 2.48 (2 H, q, $\underline{J}$ 7.1 Hz, C$\underline{H}_2$S), and 2.69 (2 H, t, $\underline{J}$ 6.9 Hz, C$\underline{H}_2$CO); $\underline{m/z}$ (90°C) 172 ($\underline{M}^+$-N$_2$, 5%), 167 (3), 154 (7), 139 (5), 85 (46), and 43 (100).

<u>Diethyl</u> (1-<u>Diazo</u>-5-<u>mercapto</u>-2-<u>oxopentyl</u>)<u>phosphonate</u> (190).

<u>n</u>-Butyllithium (0.47 ml, 0.73 mmol) was added dropwise to a solution of diethyl diazomethylphosphonate (130 mg, 0.73 mmol) in THF (5 ml) at -75°C. After fifteen minutes γ–thiobutyrolactone (74 mg, 0.73 mmol) was added dropwise. The reaction mixture was stirred for 3 h and allowed to warm to -30°C over 1 h before the addition of acetic acid (0.1 ml). Aqueous work-up and chromatography gave the <u>title compound</u> (190) (36 mg, 18%) as a yellow oil; (Found: $\underline{M}^+$, 252.0592. $C_9H_{17}N_2O_4PS$ - N_2 requires $\underline{M}$, 252.0585); $\nu_{max.}$ (film) 2547, 2122, 1656, 1262, and 1018 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.27 (1 H, t, $\underline{J}$ 7.1 Hz, SH), 1.33 (6 H, dt, $\underline{J}$ 7.0, 0.9 Hz, CH$_2$C$\underline{H}_3$), 1.89 (2 H, quin, $\underline{J}$ 7.1 Hz, C$\underline{H}_2$CH$_2$S), 2.52 (2 H, q, $\underline{J}$ 7.2 Hz, C$\underline{H}_2$S), 2.65 (2 H, t, $\underline{J}$ 6.8 Hz, C$\underline{H}_2$CO), and 4.04-4.26 (4 H, m, OC$\underline{H}_2$); $\underline{m/z}$ (120°C) 252 ($\underline{M}^+$-N$_2$, 100%), 234 (5), 224 (35), 219 (27), 196 (60), 178 (57), and 98 (92).

1-<u>Diazo</u>-6-<u>hydroxydodecan</u>-2-<u>one</u> (191).

<u>n</u>-Butyl lithium (1.9 ml, 3.00 mmol) was added dropwise to a standardized solution of trimethylsilyldiazomethane in ether (1.50 ml, 3.0 mmol), diluted with THF (15 ml) at -65°C. The solution was stirred for twenty minutes before the dropwise addition of undecanoic acid δ-lactone (498 mg, 2.70 mmol). After 3 h at -70°C, acetic acid (0.17 ml, 3.0 mmol) was added. The reaction mixture was warmed to 0°C, water added and the mixture rapidly extracted with ether. The crude product was purified by chromatography on neutral alumina, to give the <u>title compound</u> (191) (198 mg, 32%) as a low melting yellow solid, m.p. 30-33°C; (Found: $\underline{M}^+$, 198.1625. $C_{12}H_{22}N_2O_2$-N$_2$ requires $\underline{M}$,198.1620); $\nu_{max.}$ (film) 3319, 3083, 2105, 1634, 1377, 1130, and 1087 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.88 (3 H, t, $\underline{J}$ 7 Hz, C$\underline{H}_3$), 1.15-1.60 (12 H, m), 1.62-1.85 (3 H, m), 2.36 (2 H, approx. t , $\underline{J}$ 7 Hz, C$\underline{H}_2$CO), 3.58 (1 H, m, C$\underline{H}$O), and 5.26 (1 H, br, C$\underline{H}$N); $\underline{m/z}$ (100°C) 198 ($\underline{M}^+$–N$_2$, 6%), 185 (8), 167 (8), 156 (4), 141 (35), 113 (34), 84 (74), 55 (100).

Diethyl (6-Benzylthio-1-diazo-2-oxohexyl)phosphonate (193).

n-Butyl lithium (0.46 ml, 0.730 mmol) was added dropwise to a solution of diethyl diazomethylphosphonate (129 mg, 0.730 mmol) in THF (3 ml) at -70°C. After twelve minutes a solution of 5-(benzylthio)pentanoyl chloride (176 mg, 0.725 mmol) in THF (3 ml) was added dropwise . After 1 h the reaction mixture was quenched with excess water. Work-up and chromatography gave the title compound (193) (84 mg, 30%) as a yellow oil; (Found: M^+, 356.1205. $C_{17}H_{25}N_2O_4PS$ - N_2 requires $\underline{M}$, 356.1211); ν_{max}. (film) 2119, 1657, 1264, 1206, 1164, 1018, 975, and 703 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.37 (6 H, t, J 7.2 Hz, CH$_2$CH$_3$), 1.50-1.78 (4 H, m), 2.41 (2 H, t, J 7.1 Hz, CH$_2$S), 2.54 (2 H, quin., J 8.0 Hz, CH$_2$CO), 3.70 (2 H, s, CH$_2$Ph), 4.05-4.30 (4H, m, OCH$_2$), and 7.15-7.36 (5H, m, ArH); m/z (100°C) 356 ($\underline{M}^+$-N$_2$, 4%), 338 (3), 323 (1), 294 (1), 265 (17), 249 (12), 234 (15), 177 (13), 123 (14), 91 (100).

1-Diazo-1-phenylsulphonyl-6-trimethylsiloxydodecan-2-one (195).

n-Butyl lithium (4.2 ml, 6.57 mmol) was added to a solution of methyl phenylsulphone (1.03 g, 6.57 mmol) in THF (5 ml) at -78°C. After fifteen minutes undecanoic acid δ-lactone (1.26 g, 6.57 mmol) was added over a five minute period, and the reaction stirred for 1.5 h. LDA [prepared from n-butyl lithium (4.2 ml, 6.57 mmol) and diisopropylamine (0.92 ml, 6.57 mmol) in THF (6 ml)] was added over 5 minutes and after 1 h trimethylsilyl chloride (1.44 g, 13.2 mmol) was added, and the reaction mixture warmed to room temperature overnight. Saturated ammonium chloride (5 ml) was added and the mixture extracted with ether. The ether phase was washed successively with saturated sodium bicarbonate, water then brine, and finally evaporated to give crude 1-phenylsulphonyl-6-trimethylsiloxydodecan-2-one, which was dissolved in ethanol (30 ml). Triethylamine (0.92 ml, 6.50 mmol) and then tosyl azide (1.28 g, 6.50 mmol) were added and the reaction stirred at room temperature for 6 h. The solvent was removed and petrol/ether added to precipitate tosyl amide. The mixture was filtered and the filtrate subject to chromatography to give the title compound (195) (1.04 g, 36%) as a clear oil; ν_{max}. (film) 2112, 1668, 1448, 1344, 1250, 1178, 1157, 1086, 841, and 724 cm^{-1}; δ_H (60 MHz; CDCl$_3$) 0.08 (9 H, s), 0.50-1.65 (17 H, m), 2.38 (2 H, t, J 6 Hz,CH$_2$CO) 3.10-3.50 (1 H, m, CHO), 7.03-7.98 (5 H, m, ArH); m/z (130°C) 423 ($\underline{M}^+$-Me, 1%), 397 (7), 395 (7), 379 (1), 351 (1), 327 (8), 297 (6),

281 (9), 273 (9), 187 (33), and 73 (100).

1-Diazo-6-hydroxy-1-phenylsulphonyldodecan-2-one (196).

Acetic acid (2 ml) and water (4 ml) were added to a solution of (195) (0.86 g, 1.96 mmol) in THF (15 ml). The solution was stirred at room temperature for twenty minutes, then subjected to work-up and chromatography to give the title compound (196) (0.584 g, 81%) as white needle crystals, m.p. 77-78°C, dec. 130°C; (Found: C, 59.0; H, 7.1; N, 7.7. $C_{18}H_{12}N_2O_4S$ requires C, 59.0; H, 7.2; N, 7.7%); $\nu_{max.}$ (melt) 3436, 2114, 1667, 1448, 1337, 1155, and 725 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.88 (3 H, t, J 6.7 Hz, Me), 1.16-1.57 (13 H m), 1.57-1.83 (2 H, m), 2.60 (2 H, t, J 7.1 Hz, CH$_2$CO), 3.43-3.57 (1 H, m, CHOH), 7.54-7.73 (3 H, m, ArH), and 7.98 (2 H, approx dd, J 6.7, 1.Hz, ArH); m/z (150°C) 320 (M$^+$-N$_2$, 1%), 281 (1), 274 (3), 253 (3), 211 (3), 197 (6), 125 (21), 99 (100), and 77 (64).

Diethyl (1-diazo-2-oxo-6-trimethylsiloxydodecyl) phosphonate (197).

n-Butyllithium (4.2 ml, 6.57 mmol) was added dropwise to a solution of diethyl methylphosphonate (1.00 g, 6.57 mmol) in THF (5 ml) at -78°C over two minutes. After stirring for 0.25 h a solution of undecanoic acid δ-lactone (1.26 g, 6.57 mmol) in THF (1.5 ml) was added dropwise over three minutes. After 0.5 h a solution of LDA [for preparation see (195); (6.57 mmol) in THF (6 ml)] was added by catheter over two minutes. After 0.5 h trimethylsilyl chloride (1.44 g,13.2 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature overnight. Work-up as for (195) gave crude diethyl (2-oxo-6-trimethylsiloxydodecyl) phosphonate. The product was dissolved in acetonitrile (15 ml), cooled to 0°C, and triethylamine (0.921 ml, 6.50 mmol) added, followed by tosyl azide (1.28 g, 6.50 mmol). The solution was warmed to room temperature and stirred for 36 h. The solvent was evaporated and petrol/ether added to precipitate tosyl amide. The mixture was filtered and the filtrate purified by chromatography to give the title compound (197) (1.15 g, 40%) as a clear oil; $\nu_{max.}$ (film) 2121, 1661, 1370, 1250, 1022, 973, and 841 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.08 (9 H, s), 0.85 (3 H, t, J 6.7 Hz, Me), 1.04-1.80 (20 H, m), 2.53 (2 H, t, J 7.1 Hz, CH$_2$CO), 3.58 (1 H, quin, J 5.5 Hz, CHO), and 3.96-4.27 (4 H, m, POCH$_2$); m/z (100°C) 419 (M$^+$-Me,

1%), 408 (2), 393 (17), 318 (8), 269 (100), 179 (21), 73 (33).

Diethyl (1-diazo-6-hydroxy-3-oxododecyl) phosphonate (198).

Acetic acid (1 ml) and water (2 ml) were added to a solution of (197) (325 mg, 0.749 mmol) in THF (10 ml). The solution was stirred at room temperature for 0.5 h. Work-up and purification by chromatography gave the title compound (198) (164 mg, 61%) as a clear oil; (Found: M^+, 334.1907. $C_{16}H_{31}N_2O_5P$ - N_2 requires M, 334.1909); $\nu_{max.}$ (film) 3487, 2121, 1658, 1369, 1262, 1018, and 975 cm^{-1}; δ_H (250 MHz; CDCl$_3$).. 0.88 (3 H, t, J 6.7 Hz, Me), 1.19-1.57 (18 H, m), 1.76 (2 H, quin, J 7.2 Hz), 1.95 (1 H, br, OH), 2.46-2.72 (2 H, m, CH_2CO), 3.57 (1 H, m, CHOH), and 4.10-4.31 (4 H, m, CH_2O); m/z (100°C) 334 (M^+-N_2, 3%), 318 (4), 316 (8), 277 (44), 220 (100), 194 (75), 179 (71), and 65 (69).

Dirhodium Tetraacetate Catalysed Decomposition of the Diazo Compounds

t-Butyl 3-oxo-oxepane-2-carboxylate (199).

A solution of (186) (979 mg, 4.04 mmol) in benzene (9 ml) was added dropwise to a suspension of dirhodium tetraacetate (8.1 mg, 0.45 mol%) in benzene (51 ml) at reflux, over thirteen minutes. After three minutes at reflux the reaction mixture was cooled, filtered , evaporated, and the residue distilled to give the title compound (199) (420 mg, 48%) as a clear oil, b.p. 90-95°C at 0.03 mmHg; (Found: C, 61.5; H, 8.6. $C_{11}H_{18}O_4$ requires C, 61.7; H, 8.5%); $\nu_{max.}$ (film) 3475, 1746, 1718, 1652, 1621, 1370, 1326, 1275, 1248, and 1153 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.42 (9 H, s, t-Bu, keto), 1.48 (9 H, s, t-Bu, enol), 1.50-1.98 (4 H, m, keto/enol), 2.40-2.54 (2+1 H, m, CH_2CO enol, and HCHCO keto), 2.85 (1 H, dt, J 11.7, 2.5 Hz, HCHCO, keto), 3.42 (1 H, ddd, J 12.0, 9.7, 2.4 Hz, CHO, keto), 3.71 (2 H, t, J 5.1 Hz, CH_2O, enol), 4.22 (1H. ddt, J 13.0 ,3.8, 1.4 Hz, CHO, keto), 4.31 (1H, s, CHCO, keto), and 10.97 (1 H, s, OH); ca. 10% enol form; δ_C (62.9 MHz, CDCl$_3$) 22.6 (enol), 23.5, 27.7, 28.2 (enol). 30.7, 31.80 (enol), 33.1 (enol), 41.5, 72.3, 72.9 (enol), 81.6 (enol), 82.4, 86.8, 165.4, and 208.1; m/z (110°C) 214 (M^+, 3%), 158 (43), 140 (30), 113 (33), 101 (59), 57 (100).

t-Butyl 5-[(N-t-Butoxycarbonyl)amino]methyl-2-oxocyclopentanecarboxylate (200).

Dirhodium tetraacetate (2.8 mg) was added to a stirred solution of (187) (160 mg, 0.47 mmol) in dichloromethane (25 ml). After 2 h the solvent was evaporated and the residue subject to chromatography, to give the title compound (200) (45 mg, 31%) as a solid, m.p. 75-80°C; (Found: C, 61.1; H, 8.8; N, 4.6. $C_{16}H_{27}NO_5$ requires C, 61.3; H, 8.7; N, 4.5%); $\nu_{max.}$ (melt) 3384, 1756, 1716, 1520, 1368, 1252, and 1170 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.43 (9 H, s) 1.48 (9 H, s), 2.08-2.53 (4 H, m, CH$_2$CH$_2$CO), 2.62-2.83 (1 H, m, CHCH$_2$N), 2.91 (1 H, d, J 18 Hz, CHCO$_2$), 3.07-3.27 (1 H, m, CHN), 3.30-3.48 (1 H, m, CHN), and 4.72 (1 H, br, NH); m/z (130°C) 313 (M$^+$,1%), 257 (3), 240 (1), 224 (1), 215 (1), 201 (15), 184 (28), 166 (11), 140 (44), 127 (44), 57 (100).

2-Acetyloxepan-3-one [enol form] (201).

A solution of (188) (87.9 mg, 0.477 mmol) in benzene (7 ml) was added dropwise to a suspension of dirhodium tetraacetate (3 mg) in benzene (15 ml) at reflux over five minutes. After two minutes at reflux the suspension was cooled, filtered and evaporated, and the residue purified by chromatography to give the title compound (201) (46.4 mg, 62%) as a clear oil, b.p. 130°C at 0.25 mmHg; (Found: M$^+$, 156.0783. $C_8H_{12}O_3$ requires M, 156.0786); $\nu_{max.}$ (film) 2700, 1736 (weak), 1711 (weak), 1596, 1435, 1300, and 873 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.70 (2 H, quin, J 5.5 Hz, CH$_2$CH$_2$CO), 1.87 (2 H, quin, J 5.4 Hz, CH$_2$CH$_2$O), 2.10 (3 H, s, COMe), 2.59 (2 H, approx. t, J 6.2 Hz, CH$_2$CO), 3.81 (2 H, t, J 7.1 Hz, CH$_2$O), and 13.97 (1 H, s , OH); m/z (120°C) 156 (M$^+$, 9%), 155 (18), 129 (12), 101 (93), 83 (30), 55 (75), and 43 (100).

2-Acetylthiepan-3-one [enol form] (202).

As solution of (189) (56.8 mg, 0.285 mmol) in benzene (5 ml) was added dropwise to a suspension of dirhodium tetraacetate (3 mg) in benzene (15 ml) at reflux over three minutes. After two minutes at reflux , the reaction mixture was cooled, filtered and evaporated. The residue was subject to chromatography , to give the title compound (202) (20 mg, 41%) as a low melting solid , m.p. 38-40°C, b.p. 120-130°C at 0.25 mmHg; (Found: C, 56.0; H, 7.0. $C_8H_{12}O_2S$ requires C, 55.8; H, 7.0%); $\nu_{max.}$ (film) 2750, 1592, 1435, 1293, 983, and 904 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.53-1.87 (2 H, m,), 2.02 (2 H, approx. quin, J 5.6 Hz), 2.36 (3 H, s, COMe), 2.60 (2 H, dd, J 5.4, 4.5 Hz, CH$_2$CO), 2.92 (2 H, d, J 10.3 Hz, CH$_2$S), and 14.21 (1 H, s, OH); m/z (130°C) 172 (M$^+$, 11%), 57 (100), and 41 (66).

Diethyl 3-oxothiane-2-phosphonate (203).

A solution of (190) (34.5 mg, 0.123 mmol) in benzene (6 ml) was rapidly heated to reflux. Dirhodium tetraacetate (1 mg) was added and reflux continued for five minutes. Extra catalyst (2 mg) was added, and reflux maintained for fifteen minutes. The reaction mixture was cooled, evaporated, and the residue purified by chromatography to give the title compound (203) (13.7 mg, 44%) as a clear oil; (Found: C, 43.0; H, 6.9. $C_9H_{17}O_4PS$ requires C, 42.9; H 6.8%); $\nu_{max.}$ (film) 3484, 1712, 1601, 1250, 1048, 1022, and 973 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.30 (3 H, t, J 7.1 Hz , CH$_2$CH$_3$), 1.36 (3 H, t, J 7.1Hz, CH$_2$CH$_3$), 2.10-2.60 (4H, m), 2.73-2.95 (2+1 H, m, CH$_2$S enol, and HCHS keto), 3.41 (1 H, d, J 20.7 Hz, CHP, keto), 3.65 (1 H, t, J 10.3 Hz, CHS, keto), 4.11 (2 H, dq , J 7.8, 7.0 Hz, OCH$_2$), 4.30 (2 H, dq , J 7.8, 7.0 Hz, OCH$_2$), and 10.98 (1H, br, OH, enol); ca. 18% enol form; m/z (100°C) 252 (M$^+$, 100%), 224 (18), 219 (35), 207 (7), 196 (32), 178 (25), 163 (14), 139 (18), 115 (20), 98 (43), and 86 (47).

7-Hexyloxepan-3-one (204).

A solution of (191) (99 mg, 0.44 mmol) in benzene (5 ml) was added dropwise to a suspension of dirhodium tetraacetate (3 mg) in benzene (20 ml) at reflux over three minutes. After one minute at reflux, the reaction mixture was cooled, filtered, evaporated and the residue purified by chromatography on Florisil to give the title compound (204) (49 mg, 56%) as a clear oil , b.p. 150°C at 0.2 mmHg; (Found: C, 72.9; H, 11.4. $C_{12}H_{22}O_2$ requires C, 72.7; H, 11.2%); $\nu_{max.}$ (film) 1714, 1456, 1332, 1127, and 1110 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.83 (3 H, t, J 6.7 Hz, C$\underline{H}_3$), 1.13-1.70 (12 H, m), 1.77-2.00 (2 H, m), 2.43 (1 H, approx dd, J 12.5, 5.8 Hz, C$\underline{H}_2$CO), 2.86 (1 H , dt, J 12.2, 2.5 Hz, C$\underline{H}_2$CO), 3.17 (1 H, approx t, J 8.9 Hz, CH$_2$C$\underline{H}$O), 3.88 (1 H, d, J 18.3 Hz, OC$\underline{H}_2$CO), and 4.23 (1 H, d, J 18.3 Hz, OC$\underline{H}_2$CO); m/z (150°C) 198 ($\underline{M}^+$, 13%), 166 (3), 124 (8), 113 (15), 98 (28), 84 (100), 55 (32), 41 (34).

7-Hexyl-2-phenylsulphonyloxepan-3-one (205).

A solution of (196) (270 mg, 0.794 mmol) in benzene (7 ml) was added to a suspension of dirhodium tetraacetate (4 mg) in benzene (30 ml) at reflux over seven minutes. After five minutes at reflux, the suspension was cooled, filtered , evaporated and the residue subjected to chromatography to give the title compound (205) (182 mg,73%) as white needles, m.p. 60-62°C (ether/hexane); (Found: $\underline{M}^+$, 338.1558. $C_{18}H_{26}O_4S$ requires $\underline{M}$, 338.1552); $\nu_{max.}$ (melt) 1722, 1449, 1131, 1083, 758, 721, and 688 cm^{-1}; δ_H (250 MHz; CDCl$_3$). 0.83 (3 H, t, J 6.7 Hz, Me), 0.90-1.85 (12 H, m), 1.85-2.04 (2 H, m), 2.49 (1 H, dd, J 11.1, 5.4 Hz, C$\underline{H}_2$CO), 2.86 (1 H, ddd, J 13.4, 8.9, 2.2 Hz, C$\underline{H}_2$CO), 3.12-3.25 (1 H, m, CH$_2$C$\underline{H}$O), 4.67 (1 H, s, C$\underline{H}$S), 7.48-7.62 (2 H, m, ArH), 7.62-7.71 (1 H, m, ArH), and 7.93 (2 H, approx dd, J 6.7, 1 Hz, ArH); m/z (150°C) 338 ($\underline{M}^+$, 2%), 197 (87), 143 (85), 125 (41), 95 (71), 69 (79), 55 (99), and 41 (100).

Diethyl 7-Hexyl-3-oxo-oxepane-2-phosphonate (206).

A solution of (198) (140 mg, 0.417 mmol) in benzene (7 ml) was added to a suspension of dirhodium tetraacetate (4 mg) in benzene (15 ml) at reflux over five minutes. After twenty minutes at reflux, the reaction mixture was cooled, filtered and evaporated and the residue purified by chromatography to give the title compound (206) (70 mg, 54%) as a clear oil, b.p.160-165°C at 0.25 mmHg; (Found: C, 57.6; H, 9.6. $C_{16}H_{31}O_5P$ requires C, 57.5; H, 9.4%); $\nu_{max.}$ (film) 3473, 1715, 1632, 1259, 1118, 1055, and 1025 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 0.85 (3 H, t, J 6.7 Hz, Me), 1.18-1.84 (18 H, m), 1.89-2.04 (2 H, m), 2.44 (1 H, dd, J 15.0, 6.2 Hz, HCHCO), 3.02-3.20 (2 H, m, HCHCO and CH$_2$CHO), and 4.09-4.28 (5 H, m, CH$_2$CH$_3$ and CHP); $\delta_{P\{H\}}$ (36.2 MHz, CDCl$_3$) 15.65 (enol) and 13.16 (keto); m/z (150°C) 334 (M$^+$, 14%), 167 (100), 139 (45), 111 (38), 84 (32), and 41 (27).

6.4   Experimental for Chapter Four

General Procedure for the Alkylation of Ethyl 2-Diazo-6-Mercapto-3-Oxohexanoate (136) and Ethyl 2-Diazo-7-Mercapto-3-Oxoheptanoate (137)

Crude ethyl 2-diazo-6-mercapto-3-oxohexanoate (136) or ethyl 2-diazo-7-mercapto-3-oxoheptanoate (137) (0.5-1 mmol) in DMF (1-2 ml), under an atmosphere of nitrogen, was treated with triethylamine (1.3-1.5 eq) and alkylating agent (1.1-1.3 eq) in succession. After stirring for 12 h at room temperature, the reaction mixture was extracted into dichloromethane and the organic phase was washed with water. The dichloromethane solution was dried over $MgSO_4$, evaporated, and the residue subjected to chromatography to give the title compounds in moderate yield.

Ethyl 6-Allylthio-2-diazo-3-oxohexanoate (225).

A solution of crude (136) (117 mg, 0.541 mmol) in THF (1.5 ml) was treated with triethylamine (0.10 ml, 0.76 mmol) and allyl bromide (100 mg, 1 mmol). After 12 h, work-up and purification gave the title compound (225) (76 mg, 55%) as a pale yellow liquid; (Found: C, 51.4; H, 6.3; N, 11.0; S, 12.7. $C_{11}H_{16}N_2O_3S$ requires C, 51.4; H, 6.3; N, 10.9; S, 12.5%); $v_{max.}$ (film) 2136, 1718, 1657, and 1303 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.27 (3 H, t, J 7.2 Hz, CH$_2$C$\underline{H}_3$), 1.85 (2 H, quin, J 7.2 Hz, C$\underline{H}_2$CH$_2$S), 2.45 (2 H, t, J 7.2 Hz, CH$_2$C$\underline{H}_2$S), 2.90 (2 H, t, J 7.2 Hz, C$\underline{H}_2$CO), 3.07 (2 H, d, J 7.0 Hz, CHC$\underline{H}_2$S), 4.24 (2 H, q, J 7.2 Hz, CO$_2$C$\underline{H}_2$), 4.98-5.09 (2 H, m, CH:C$\underline{H}_2$), and 5.71 (1 H, ddt, J 16.5, 10.0, 7.1 Hz, CH$_2$:C$\underline{H}$); m/z (80°C) 256 (M$^+$, 12%), 228 (6), 211 (4), 187 (49), 169 (9), 155 (12), 113 (23), 109 (71), 41 (100).

Ethyl 6-[(E)-But-2-enyl]thio-2-diazo-3-oxohexanoate (226).

A solution of crude (136) (250 mg, 1.16 mmol) in DMF (2 ml) was treated with triethylamine (0.20 ml, 1.4 mmol) and crotyl bromide (0.14 ml, 1.4 mmol), to give the title compound (226a) (163 mg, 52%) as the major isomer (~80%); together with two minor isomers: ethyl 6-[(Z)-But-2-enyl]thio-2-diazo-3-oxohexanoate (226b) (~10%) and ethyl 6-[(1-methylprop-2-enyl)thio]-2-diazo-3-

oxohexanoate (.226c) (~10%); (Found: $\underline{M}^+$, 270.1046. $C_{12}H_{18}N_2O_3S$ requires $\underline{M}$, 270.1038); $\nu_{max.}$ (film) 2135, 1717, 1655, 1374, 1302, and 1221 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.27 (3 H, d, $\underline{J}$ 6.5 Hz, M$\underline{e}$, isomer c), 1.31 (3 H, t, $\underline{J}$ 7.0 Hz, CH$_2$C$\underline{H}_3$), 1.63 (3 H, d, $\underline{J}$ 6.4 Hz, M$\underline{e}$, isomer b), 1.67 (3 H, dd, $\underline{J}$ 6.0, 0.5 Hz, M$\underline{e}$, isomer a), 1.88 (2 H, quin, $\underline{J}$ 7.2 Hz, CH$_2$C$\underline{H}_2$CH$_2$), 2.49 (2 H, t, $\underline{J}$ 7.2 Hz, SC$\underline{H}_2$), 2.94 (2 H, approx t, $\underline{J}$ 7.2 Hz, C$\underline{H}_2$CO), 3.05 (2 H, approx d, $\underline{J}$ 7.0 Hz, CHC$\underline{H}_2$S, isomer a), 3.15 (2 H, d, $\underline{J}$ 7.5 Hz, CHC$\underline{H}_2$S, isomer b), 3.29 (1 H, quin, $\underline{J}$ 7.2 Hz, SC$\underline{H}$(Me), isomer c), 4.27 (2 H, q, $\underline{J}$ 7.0 Hz, CO$_2$C$\underline{H}_2$), 4.92-5.03 (2 H, m, CH:C$\underline{H}_2$, isomer c) and 5.31-5.70 (2+2+1 H, m, C$\underline{H}$:C$\underline{H}$ isomers a and b, and C$\underline{H}$:CH$_2$ isomer c); $\underline{m/z}$ (80°C) 270 ($\underline{M}^+$, 3%), 242 (12), 196 (11), 188 (22), 142 (43), 109 (49), and 55 (100).

Ethyl 2-Diazo-3-oxo-6-[(3-phenylprop-2-enyl)thio]hexanoate (227).

Treatment of a solution of (136) (355 mg, 1.64 mmol) in DMF (6 ml) with triethylamine (0.25 ml, 1.80 mmol) and cinnamyl bromide (356 mg, 1.80 mmol) gave the title compound (227) (337 mg, 62%) as a low melting solid; (Found: C, 61.5; H, 6.4; N, 8.2; S, 9.9. $C_{17}H_{20}N_2O_3S$ requires C, 61.4; H, 6.1; N, 8.4; S, 9.7%); $\nu_{max.}$.(film) 2135, 1714, 1654, 1374, 1303, and 1221 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.32 (3 H, t, $\underline{J}$ 7.1 Hz, CH$_2$C$\underline{H}_3$), 1.91 (2 H, quin, $\underline{J}$ 6.9 Hz , CH$_2$C$\underline{H}_2$CH$_2$), 2.55 (2 H, t, $\underline{J}$ 6.9 Hz, CH$_2$C$\underline{H}_2$S), 2.95 (2 H, t, $\underline{J}$ 7.3 Hz, C$\underline{H}_2$CO), 3.28 (2 H, d, $\underline{J}$ 7.9 Hz, CHC$\underline{H}_2$S), 4.26 (2 H, q, $\underline{J}$ 7.1 Hz, CO$_2$C$\underline{H}_2$), 6.15 (1 H, dt, $\underline{J}$ 15.2, 7.2 Hz, C$\underline{H}$CH$_2$S), 6.42 (1 H, d, $\underline{J}$ 15.2 Hz, PhC$\underline{H}$), and 7.17-7.40 (5 H, m, ArH); $\underline{m/z}$ (130°C) 304 ($\underline{M}^+$, 11%), 258 (3), 225 (3), 202 (4), 117 (100).

Ethyl 2-Diazo-6-(3-methylbut-2-enyl)thio-3-oxohexanoate (228).

A solution of crude (136) (500 mg, 3.32 mmol) in DMF (4 ml) was treated with triethylamine (0.50 ml, 5.0 mmol) and prenyl bromide (0.346 g, 4.00 mmol), to give the title compound (228) (246 mg, 37%) as a yellow oil; (Found: C, 55.1; H, 7.5; N, 10.1. $C_{13}H_{20}N_2O_3S$ requires C. 54.9; H, 7.1; N, 9.9%. Found: $\underline{M}^+$, 256.1132; requires $\underline{M}$-N$_2$, 256.1133); $\nu_{max.}$ (film) 2135, 1718, 1657, 1375, 1303, and 1221 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.26 (3 H, t, $\underline{J}$ 7.0 Hz, CH$_2$C$\underline{H}_3$), 1.58 (3 H, s, M$\underline{e}$), 1.66 (3 H, s, M$\underline{e}$), 1.85 (2 H, quin, $\underline{J}$ 7.0 Hz, CH$_2$C$\underline{H}_2$CH$_2$), 2.45 (2 H, t, $\underline{J}$ 7.0 Hz, C$\underline{H}_2$S), 2.90 (2 H, t , $\underline{J}$ 7.0 Hz, C$\underline{H}_2$CO), 3.06 (2 H, d , $\underline{J}$ 7.6 Hz,

CHC$\underline{H}_2$S), 4.23 (2 H, q, $\underline{J}$ 6.9 Hz, CO$_2$C$\underline{H}_2$), and 5.25 (1 H, t quin, $\underline{J}$ 7.6, 1.4 Hz, C$\underline{H}$CMe); m/z (100°C) 284 ($\underline{M}^+$, 1%), 256 (9), 210 (6), 195 (5), 188 (13), 155 (5), 142 (34), 69 (100), and 41 (73).

Ethyl 6-Acetylthio-2-diazo-3-oxohexanoate (229).

Acetic anhydride (65 μl, 0.68 mmol) was added to a solution of crude (136) (118 mg, 0.546 mmol) in pyridine (0.55 ml, 6 mmol) and the mixture stirred for 5 h. Aqueous work-up, washing the ether phase with copper (II) sulphate solution, and chromatographic purification of the residue gave the title compound (229) (70.0 mg, 50%) as a yellow oil, (Found: C, 46.8; H, 5.5; N, 10.6; S, 12.9. C$_{10}$H$_{14}$N$_2$O$_4$S requires C, 46.5; H, 5.5; N, 10.9; S, 12.4%); $v_{max.}$.(film) 2136, 1718, 1694, 1656, 1375, and 1132cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.29 (3 H, t, $\underline{J}$ 7.0 Hz, CH$_2$C$\underline{H}_3$), 1.89 (2 H, quin, $\underline{J}$ 7.1 Hz), 2.29 (3 H, s, CO$\underline{Me}$), 2.89 (4 H, t, $\underline{J}$ 7.1 Hz, C$\underline{H}_2$CO and C$\underline{H}_2$S), and 4.26 (2 H, q, $\underline{J}$ 7.0 Hz, C$\underline{H}_2$CH$_3$); m/z (80°C) 258 ($\underline{M}^+$, 3%), 226 (2), 215 (2), 188 (35), 156 (29), 142 (38), and 43 (100).

Ethyl 2-Diazo-6-[(methoxycarbonyl)acetyl]thio-3-oxohexanoate (230).

Treatment of a solution of crude (136) (445 mg, 2.06 mmol) in DMF (5 ml) with triethylamine (0.32 ml, 2.27 mmol) and methyl malonylchloride (281 mg, 2.06 mmol) resulted in an exothermic reaction. After 18 h, work-up and purification gave the title compound (230) (305 mg, 47%) as a viscous oil; (Found: C, 45.7; H, 5.3; N, 8.8; S, 10.4. C$_{12}$H$_{16}$N$_2$O$_6$S requires C, 45.6; H, 5.1; N, 8.9; S, 10.1%); $v_{max.}$.(film) 2138, 1748, 1717, 1691, 1654, 1376, and 1304 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.30 (3 H, t, $\underline{J}$ 7.2 Hz, CH$_2$C$\underline{H}_3$), 1.92 (2 H, quin, $\underline{J}$ 7.2 Hz), 2.90 (2 H, t, $\underline{J}$ 7.1 Hz, C$\underline{H}_2$S), 2.95 (2 H, t, $\underline{J}$ 7.1 Hz, CH$_2$C$\underline{H}_2$CO), 3.28 (2 H, s, C$\underline{H}_2$CO$_2$Me), 3.70 (3 H, s, CO$_2$C$\underline{H}_3$), and 4.26 (2 H, q, $\underline{J}$ 7.2 Hz, CO$_2$C$\underline{H}_2$); m/z (100°C) 316 ($\underline{M}^+$, 1%), 285 (1), 274 (1), 256 (1), 242 (1), 228 (1), 215 (2), 188 (13), 142 (54), 101 (100), and 59 (61).

Ethyl 6-Benzylthio-2-diazo-3-oxohexanoate (231).

Treatment of a solution of crude (136) (250 mg, 1.16 mmol) in DMF (2 ml) with triethylamine (0.20 ml, 1.50 mmol) and benzyl bromide (0.146 ml, 1.22 mmol) gave the title compound (231) (179 mg, 50%) as a yellow oil; (Found: C, 59.1; H, 6.3; N, 9.0; S, 10.6. C$_{15}$H$_{18}$N$_2$O$_3$S requires C, 58.8; H, 5.9; N, 9.2; S, 10.5%);

ν_{max}. .(film) 2135, 1718, 1655, 1374, 1303, and 1222 cm^{-1}; δ_H (90 MHz; CDCl$_3$) 1.31 (3 H, t, J 7 Hz, CH$_2$CH$_3$), 1.90 (2 H, quin, J 7 Hz), 2.48 (2 H, t, J 7 Hz, CH$_2$S), 2.95 (2 H, t, J 7 Hz, CH$_2$CO), 3.70 (2 H, s, CH$_2$Ph), 4.30 (2 H, q, J 7 Hz, CO$_2$CH$_2$), and 7.30 (5 H, m, ArH); m/z (80°) 306 (M$^+$, 1%), 278 (4), 232 (7), 204 (5), 187 (7), and 91 (100).

Ethyl 2-Diazo-6-ethylthio-3-oxohexanoate (232).

Treatment of a solution of crude (136) (250 mg, 1.16 mmol) in DMF (2 ml) with triethylamine (0.21 ml, 1.50 mmol) and ethyl iodide (0.10 ml, 1.28 mmol) gave the title compound (232) (169 mg, 60%) as a yellow oil; (Found: M$^+$, 216.0815. C$_{10}$H$_{16}$N$_2$O$_3$S requires M, 216.0820); ν_{max}. (film) 2135, 1718, 1656, and 1303 cm^{-1}; δ_H (270 MHz; CDCl$_3$). 1.23 (3 H, t, J 6.6 Hz, SCH$_2$CH$_3$), 1.31 (3 H, t, J 6.4 Hz, CO$_2$CH$_2$CH$_3$), 1.93 (2 H, quin, J 6.3 Hz, CH$_2$CH$_2$), 2.52 (2 H, q, J 6.8 Hz, SCH$_2$Me), 2.56 (2 H, q, J 6.5 Hz, CH$_2$CH$_2$S), 2.97 (2 H, m, COCH$_2$), and 4.29 (2 H, q, J 6.5 Hz, CO$_2$CH$_2$); m/z (130°C) 244 (M$^+$, 1%), 216 (31), 187 (33), 170 (3), 156 (18), 142 (23), and 109 (100).

Ethyl 2-diazo-6-[(3-methoxycarbonyl-2-oxopropyl)thio]-3-oxohexanoate (233).

Ethyl 4-chloroacetoacetate (0.24 ml, 1.80 mmol) was added to a solution of the pure diazomercaptan (136) (355 mg, 1.64 mmol) and triethylamine (0.25 ml, 1.80 mmol) in DMF at 0°C. After 12 h at -5°C, the reaction mixture was subjected to aqueous work-up, and the residue was purified by chromatography, to give the title compound (233) (339 mg, 60%), as an oil; (Found: C, 49.1; H, 6.0; N, 8.0. C$_{14}$H$_{20}$N$_2$O$_6$S requires C, 48.8; H, 5.9; N, 8.1%); ν_{max}. (film) 2137, 1744, 1718, 1655, and 1304 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.25 (3 H, t, J 7.0 Hz, CH$_2$Me), 1.30 (3 H, t, J 7.1 Hz, CH$_2$Me), 1.90 (2 H, quin, J 6.9 Hz, CH$_2$CH$_2$S), 2.51 (2 H, t, J 7.1 Hz, CH$_2$COCN), 2.92 (2 H, t, J 7.2 Hz, CH$_2$S), 3.34 (2 H, s, COCH$_2$S), 3.64 (2 H, s, COCH$_2$CO), 4.18 (2 H, q, J 7.0 Hz, CH$_2$Me), and 4.27 (2 H, q, J 6.9 Hz, CH$_2$Me); m/z (100°C) 344 (M$^+$, 1%), 306 (1), 292 (1), 278 (2), 205 (6), 159 (9), 57 (25), 43 (35) and 28 (100).

Ethyl 2-Diazo-3-oxo-7-[(3-phenylprop-2-enyl)thio]heptanoate (234).

Treatment of a solution of (137) (415 mg, 1.80 mmol) in DMF (4 ml) with triethylamine (0.38 ml, 2.70 mmol), and cinnamyl bromide (391 mg, 1.98 mmol) gave , after work-up and chromatography, the title compound (234) (298 mg, 48%), as a yellow oil; (Found: C, 62.4; H, 7.7; N, 9.7. $C_{18}H_{22}N_2O_3S$ requires C, 62.4; H, 7.7; N, 9.7%); $\nu_{max.}$ (film) 2135, 1718, 1656, 1372, 1305, and 1218 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.33 (3 H, t, J 7.1 Hz, CH$_2$C$\underline{H}_3$), 1.56-1.84 (4 H, m), 2.52 (2 H, t, J 7.1 Hz, C$\underline{H}_2$S), 2.87 (2 H, t, J 7.1 Hz, C$\underline{H}_2$CO), 3.31 (2 H, dd, J 7.6, 0.7 Hz, CHC$\underline{H}_2$S), 4.30 (2 H, q, J 7.1 Hz, CO$_2$C$\underline{H}_2$), 6.18 (1 H, dt, J 15.3, 7.5 Hz, C$\underline{H}$CHPh), 6.44 (1 H, d, J 15.6 Hz, C$\underline{H}$Ph), and 7.20-7.43 (5 H, m, ArH); m/z (FAB; glycerol) 347 ($\underline{M}$H$^+$, 4%), 318 (1), 117 (100), and 91 (15).

Ethyl 7-Benzylthio-2-diazo-3-oxoheptanoate (235).

To a solution of (137) (155 mg, 0.673 mmol) in DMF (2 ml) triethylamine (0.14 ml, 1.00 mmol), and benzyl bromide (84 µl, 0.71 mmol) were added. After 12 h, work-up and chromatography on neutral alumina gave the title compound (235) (66 mg, 31%), as a yellow oil; (Found: C, 60.0; H, 6.5; N, 8.7. $C_{16}H_{20}N_2O_3S$ requires C, 60.0; H, 6.3; N, 8.8%); $\nu_{max.}$ (film) 2135, 1717, 1656, 1372, 1304, and 1218 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.33 (3 H, t, J 7.1 Hz, CH$_2$C$\underline{H}_3$), 1.53-1.82 (4 H, m), 2.42 (2 H, t, J 7.1 Hz, C$\underline{H}_2$S), 2.82 (2 H, t, J 7.1 Hz, C$\underline{H}_2$CO), 3.70 (2 H, s, C$\underline{H}_2$Ph), 4.29 (2 H, q, J 7.1 Hz, CO$_2$C$\underline{H}_2$), and 7.15-7.44 (5 H, m, ArH); m/z (120°C) 292 ($\underline{M}^+$, 1%), 274 (1), 246 (3), 218 (1), 169 (16), 123 (48), and 91(100).

Ethyl 2-Diazo-7-ethylthio-3-oxoheptanoate (236).

Treatment of a solution of (137) (155 mg, 0.673 mmol) in DMF (2 ml) with triethylamine (0.14 ml, 1.00 mmol), and ethyl iodide (80 µl, 1.00 mmol) gave , after work-up and chromatography, the title compound (236), as an impure oil which was used directly in the next step; $\nu_{max.}$ (film) 2135, 1718, 1657, and 1305 cm^{-1}; m/z (100°C) 258 ($\underline{M}^+$, 1%).

Ethyl 2-Allyl-3-oxothiane-2-carboxylate (238).

A solution of (225) (400 mg, 1.56 mmol) in benzene (10 ml) was added to a suspension of dirhodium tetraacetate (9 mg) in benzene (30 ml) at reflux over 10

min. After 5 min at reflux the green mixture was cooled, filtered, evaporated and the residue subjected to chromatography to give the title compound (238) (210 mg, 59%) as an oil; (Found: C, 57.9; H, 7.3; S, 14.1. $C_{11}H_{16}O_3S$ requires C, 57.9; H, 7.1; S, 14.0%); $\nu_{max.}$ (film) 1746, 1714, 1641, 1220, and 1189 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.29 (3 H, t, J 7.2 Hz, CH_2CH_3), 2.24-2.62 (6 H, m), 2.82 (1 H, ddt, J 14.5, 7.2, 1.2 Hz, $CH_2CH:CH_2$), 3.03 (1 H, ddd, J 13.2, 11.5, 3.4 Hz, CH_2CO), 4.26 (2 H, dq, J 7.2, 1.0 Hz, CH_2CH_3), 5.05-5.15 (2 H, m, $CH_2:CH$), and 5.74 (1 H, dddd, J 17.3, 9.5, 7.4, 6.6 Hz, $CH_2:CH$); m/z (140°C) 228 (M^+, 99%), 200 (11), 187 (32), 155 (63), 127 (50), 113 (22), 85 (100), and 41 (61).

Ethyl 2-(1-Methylprop-2-enyl)-3-oxothiane-2-carboxylate (239).

A solution of (226) (83 mg, 0.307 mmol) in benzene (5 ml) was added to a suspension of dirhodium tetraacetate (2.3 mg) in benzene (10 ml) at reflux over 9 min. After 5 min at reflux the suspension was cooled, filtered, evaporated, and the residue subjected to chromatography to give the title compound (239) (52.6 mg, 71%) an oil, as a mixture of three isomers: two diastereomers (239a) (2:1, ~86%), together with ethyl 2-(but-2-enyl)-3-oxothiane-2-carboxylate (247, b) (~14%), b.p. 175°C at 1.8 mmHg; (Found: C, 59.4; H, 7.6. $C_{12}H_{18}O_3S$ requires C, 59.5; H, 7.5%); $\nu_{max.}$ (film) 1743, 1713, 1639, 1447, 1221, and 1192 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.05 (3 H, d, J 6.9 Hz, Me, minor isomer a), 1.12 (3 H, d , J 6.9 Hz, Me, major isomer a), 1.26 (3 H, t, J 7.1 Hz, CH_2CH_3, major isomer a, and isomer b), 1.30 (3 H, t, J 7.1 Hz, CH_2CH_3, minor isomer a), 1.61 (3 H, dd, J 6.9, 0.5 Hz, Me, isomer b), 2.17-2.65 (~5 H, m), 2.68-3.15 (~2 H, m), 4.20 (2 H, q, J 6.7 Hz, $COCH_2$, major isomer a), 4.26 (2 H, q, J 6.7 Hz, $COCH_2$, isomer b), 4.28 (2 H, dq, J 6.7, 0.7 Hz, $COCH_2$, minor isomer a), 4.94-5.10 (2 H, m, $CH:CH_2$, isomer a), 5.25-5.47 (2 H, m, $CH:CH$, isomer b), and 5.72-5.92 (1 H, m, $CH:CH_2$, isomer a); m/z (130°C) 242 (M^+, 38%), 196 (3), 188 (64), 142 (100), and 99 (15).

Ethyl 3-Oxo-2-(1-phenylprop-2-enyl)thiane-2-carboxylate (240).

A solution of (227) (121 mg, 0.364 mmol) in benzene (6 ml) was added to a suspension of dirhodium tetraacetate (1.9 mg) in benzene (10 ml) at reflux over 7 min and reflux of the mauve solution continued for 20 min. Evaporation of solvent and

chromatography of the residue gave the title compound (240) (86 mg, 78%), a low melting solid, as a mixture of two diastereomers (7:3), m.p. 58-63°C, b.p. 130-140°C at 0.0005 mmHg; (Found: C, 66.8; H, 6.6; S, 10.5. $C_{17}H_{20}O_3S$ requires C, 67.1; H, 6.6; S, 10.5%); $\nu_{max.}$ (film) 1742, 1713, 1635, 1453, 1219, 1189, 1028 and 703 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.00 (3 H, t, J 6.9 Hz, CH$_2$C$\underline{H}_3$, minor isomer), 1.21 (3 H, t, J 6.9 Hz, CH$_2$C$\underline{H}_3$, major isomer), 2.20-2.45 (2 H, m), 2.45-2.64 (3 H, m), 2.87 (1 H, ddd, J 14.6, 10.2, 4.0 Hz, HC$\underline{H}$S, major isomer), 2.97-3.13 (1 H, m, HC$\underline{H}$S, minor isomer), 3.80-4.01 (2 H, m, CO$_2$C$\underline{H}_2$, minor isomer), 4.18 (3H, dq, J 6.6, 2.2 Hz, CO$_2$C$\underline{H}_2$ and C$\underline{H}$Ph, major isomer), 4.49 (1 H, d, J 6.3 Hz, C$\underline{H}$Ph, minor isomer), 4.87-5.20 (2 H, m, CH:C$\underline{H}_2$), 6.10-6.40 (1 H, m, C$\underline{H}$:CH$_2$), and 7.15-7.40 (5 H, m, ArH); m/z (160°C) 304 ($\underline{M}^+$, 6%), 286 (2), 258 (3), 229 (1), 213 (1), 188 (2), 161 (1), 142 (4), 129 (6), and 117 (100).

Ethyl 2-(1,1-Dimethylprop-2-enyl)-3-oxothiane-2-carboxylate (241).

A solution of (228) (148 mg, 0.521 mmol) in benzene (6 ml) was added to a suspension ofdirhodium tetracetate (4.3 mg) in benzene (20 ml) at reflux over 5 min. Reflux was continued for 25 min. Evaporation of solvent and chromatography of the residue gave the title compound (241) (88 mg, 66%) as a clear oil, b.p. 130°C at 0.5 mmHg; (Found: $\underline{M}^+$, 256.1132. $C_{17}H_{20}O_3S$ requires $\underline{M}$, 256.1133); $\nu_{max.}$ (film) 1741, 1713, 1635 and 1219 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.24 (3 H, s, M$\underline{e}$), 1.27 (3 H, s, M$\underline{e}$), 1.29 (3 H, q, J 7.0 Hz, CH$_2$C$\underline{H}_3$), 2.23-2.37 (2 H, m, C$\underline{H}_2$CH$_2$S), 2.38-2.53 (2 H, m, C$\underline{H}_2$S), 2.58 (1 H, ddd, J 14.0, 3.7, 1.1 Hz, C$\underline{H}_2$CO), 2.77-2.90 (1 H, m, C$\underline{H}_2$CO), 4.27 (2 H, dq, J 7.5, 0.6 Hz, CO$_2$C$\underline{H}_2$), 4.98 (1 H, dd, J 5.9, 1.1 Hz, CH:C$\underline{H}_2$), 5.05 (1 H, s, CH:C$\underline{H}_2$), and 6.26 (1 H, approx dd, J 15.6, 10.8 Hz, C$\underline{H}$:CH$_2$); m/z (100°C) 256 ($\underline{M}^+$,19%), 188 (60), 183 (4), 142 (100), 69 (30), and 41 (26).

Ethyl 2-Acetyl-3-oxothiane-2-carboxylate (242).

A solution of (229) (44.9 mg, 0.174 mmol) in benzene (15 ml) was rapidly heated to reflux and dirhodium tetraacetate (1.5 mg) added. Reflux was continued for 10 min. After cooling the mixture was filtered, evaporated, and the residue subjected to chromatography to give the title compound (242) (16 mg, 40%) as an oil; (Found: $\underline{M}^+$, 188.0505. $C_{10}H_{14}O_4S$ requires $\underline{M}$, 188.0507); $\nu_{max.}$ (film) 1746, 1734,

1712, 1241, and 1181 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.20 (3 H, t, J 7.1 Hz, CH$_2$C$\underline{H}_3$), 2.26 (3 H, s, COM$\underline{e}$), 2.18-2.45 (2 H, m, C$\underline{H}_2$CH$_2$S), 2.48-2.80 (4 H, m), and 4.23 (2 H, q, J 7.1 Hz, CO$_2$C$\underline{H}_2$); m/z (100°C) 230 ($\underline{M}^+$, 1%), 202 (2), 188 (14), 160 (3), 142 (27), 116 (5), 103 (13), and 83 (100).

Ethyl 3-Oxothiane-2-carboxylate (163).

A solution of (230) (210 mg, 0.665 mmol) in benzene (8 ml) was added to a suspension of dirhodium tetraacetate (4.9 mg) in benzene (22 ml) at reflux over 5 minutes. After 5 minutes at reflux the reaction mixture was cooled, the solvent evaporated, and the residue was subjected to filtration then purification to give the title compound (163) (16 mg, 13%), identical to the previously prepared sample.

Ethyl 1-Benzyl-3-oxo-3,4,5,6-tetrahydrothiabenzene-2-carboxylate (243).

A solution of (231) (120 mg, 0.392 mmol) in benzene (5 ml) was added to a suspension of dirhodium tetraacetate (5 mg) in boiling benzene (10 ml) over 8 min and reflux was continued for a further 5 min. after addition. The solvent was evaporated to give a solid, which was purified by crystallization to give the title compound (243) (26 mg, 24%) as colourless crystals, m.p. 134-135°C (benzene/hexane); (Found: C, 64.6; H, 6.5; S, 11.4. C$_{15}$H$_{18}$O$_3$S requires C, 64.7; H, 6.5; S, 11.5%); $v_{max.}$ (Nujol) 1681, 1606, 1577, 1374, 1250, 1056, and 710 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.36 (3 H, t, J 7.0 Hz, CH$_2$C$\underline{H}_3$), 2.10-2.40 (4 H, m, C$\underline{H}_2$C$\underline{H}_2$CO), 2.78-3.05 (2 H, m, C$\underline{H}_2$S), 3.97 (1 H, d, J 13.1 Hz, C$\underline{H}_2$Ph), 4.19-4.39 (2 H, m, CO$_2$C$\underline{H}_2$), 4.60 (1 H, d, J 13.1 Hz, C$\underline{H}_2$Ph), and 7.30-7.48 (5 H, m, ArH), m/z (150°C) 262 ($\underline{M}^+$, 8%), 232 (2), 188 (3), 142 (15), 115 (6), and 91 (100).

Ethyl 1-Ethyl-3-oxo-3,4,5,6-tetrahydrothiabenzene-2-carboxylate (244).

A solution of (232) (20.0 mg, 0.082 mmol) in benzene (8 ml) was rapidly heated to reflux and dirhodium tetraacetate (1.3 mg) added. Reflux was continued for 5 min. After cooling the mixture was filtered through cotton wool, evaporated, and the residue recrystallized to give the title compound (244) (11 mg, 62%), m.p. 116-118°C; (Found: $\underline{M}^+$, 216.0815. C$_{10}$H$_{16}$O$_3$S requires $\underline{M}$, 216.0820); v_{max} (Nujol) 1674, 1543, 1370, 1204, and 1051 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.32 (3 H, t, J 7.0 Hz,

CH_2CH_3), 1.36 (3 H, t, J 7.4 Hz, CH_2CH_3), 2.13-2.48 (4 H, m, CH_2CH_2CO), 2.90-3.31 (4 H, m, CH_2SCH_2), and 4.16-4.32 (2 H, m, CO_2CH_2); m/z (140°C) 216 (M^+, 100%), 188 (71), 171 (24), 159 (26 (68), 113 (59), and 85 (54).

Ethyl 2-Benzyl-3-oxothiane-2-carboxylate (249).

A suspension of (243) (11.4 mg, 41 μmol) in xylene (4 ml) was quickly brought to reflux and maintained at reflux for 2.5 h. The solvent was evaporated and the residue purified by chromatography to give the title compound (249) (6.3 mg, 55%) as a low melting solid, m.p. 45-48°C; (Found: M^+, 278.0974. $C_{15}H_{18}O_3S$ requires M, 278.0977); $\nu_{max.}$ (melt) 1746, 1712, 1670, 1242, and 1181 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.19 (3 H, t, J 7.0 Hz, CH_2CH_3), 2.26-2.66 (6 H, m, $(CH_2)_3$), 2.97 (1 H, d, J 14.3 Hz, CH_2Ph), 3.52 (1 H, d, J 14.3 Hz, CH_2Ph), 4.13 (2 H, dq, J 7.0, 0.7 Hz, CO_2CH_2), and 7.05-7.38 (5 H, m, ArH); m/z (120°C) 278 (M^+, 28%), 232 (2), 218 (2), 205 (10), 187 (6), 177 (3), 172 (6), 159 (7), 116 (14), and 91 (73).

Ethyl 3-Oxothiane-2-carboxylate (163).

A solution of (244) (52.5 mg, 0.215 mmol) in xylene (5 ml) was added to a suspension of dirhodium tetraacetate (1.5 mg) in xylene (5 ml) at reflux over 8 minutes. After 20 minutes at reflux, evaporation of solvent and chromatography of the residue gave the title compound (163) (34 mg, 84%), identical to the previously prepared sample.

Ethyl 3-Oxo-2-(1-phenylprop-2-enyl)thiepane-2-carboxylate (252).

A solution of (234) (100 mg, 0.289 mmol) in benzene (5 ml) was added over 5 minutes to a suspension of dirhodium tetraacetate (2 mg) in benzene (15 ml) at reflux. After 2 minutes at reflux, extra catalyst (2 mg) was added and reflux continued for 12 minutes. The reaction mixture was allowed to cool, evaporated and the residue purified by chromatography to give the title compound (252) (27 mg, 26%), an oil, as a mixture of diastereomers (3:2); (Found: C, 67.7; H, 7.2. $C_{18}H_{22}O_3S$ requires C, 67.9; H, 7.0%); $\nu_{max.}$ (film) 1735, 1713, 1636, 1453, 1224, 1189, 1150, 1103, and 703 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.12 (3 H, J 7.1 Hz, CH_2CH_3, minor isomer), 1.21 (3 H, J 7.0 Hz, CH_2CH_3, major isomer), 1.53-1.90 (4H, m), 2.02-2.20 (1 H, m), 2.52-2.91 (3 H, m), 3.94-4.09 (2 H, m,

$CO_2C\underline{H}_2$, minor isomer), 4.16 (2 H, dq, J 6.9, 1.0 Hz, $CO_2C\underline{H}_2$, major isomer), 4.28 (1 H, t, J 8.6 Hz, C$\underline{H}$Ph), 5.08-5.24 (2 H, m, C$\underline{H}_2$:CH), 6.36-6.50 (1 H, m, C$\underline{H}$CHPh), 7.16-7.32 (3 H, m, ArH), and 7.41-7.54 (2 H, m, ArH); $\underline{m/z}$ (120°C) 318 ($\underline{M}^+$, 4%), 300 (11), 272 (3), 243 (4), 214 (3), 156 (3), 129 (11), and 117 (100).

<u>Ethyl</u> 7-<u>Benzylthio</u>-2-<u>diazo</u>-3-<u>oxoheptanoate</u> (164).

A solution of (235) (51 mg, 0.16 mmol) in benzene (4 ml) was added over 5 minutes to a suspension of dirhodium tetraacetate (2 mg) in benzene (10 ml) at reflux. After 5 minutes at reflux, extra catalyst (2 mg) was added. After 0.25 h at reflux the reaction mixture was cooled, evaporated, and the residue chromatographed to give ethyl 3-oxothiepane-2-carboxylate (164) (2.1 mg, 7%), identical to the previously prepared material.

<u>Ethyl</u> 1-<u>Ethyl</u>-3-<u>oxothiepane</u>-2-<u>carboxylate</u>, <u>inner salt</u> (253).

A solution of crude (236) (71 mg, 0.28 mmol) in benzene (4 ml) was added over 7 minutes to a suspension of dirhodium tetraacetate (3 mg) in benzene (10 ml) at reflux. After 10 minutes at reflux, the reaction mixture was cooled and evaporated. Dichloromethane was added to the residue, and the solution filtered through cotton wool. The filtrate was recrystallized to give the <u>title compound</u> (253) (7.5 mg, 12%), as a fawn solid, m.p. 157-160°C (ethyl acetate/benzene); (Found: $\underline{M}^+$,230.0975. $C_{11}H_{18}O_3S$ requires $\underline{M}$, 230.0943); v_{max}. (Nujol) 1672, 1558, 1456, 1336, 1238, 1165, and 1049 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.28 (3 H, t, J 7.5 Hz, $CO_2CH_2C\underline{H}_3$), 1.38 (3 H, t, J 7.8 Hz, SCH$_2$C$\underline{H}_3$), 1.72-1.87 (2 H, m), 2.00-2.15 (2 H, m), 2.47-2.56 (2 H, m, C$\underline{H}_2$CO), 2.89-3.11 (2 H, m, C$\underline{H}_2$S), 3.18-3.34 (2 H, m, C$\underline{H}_2$S), and 4.11-4.25 (2 H, m. $CO_2C\underline{H}_2$); $\underline{m/z}$ (130°C) 230 ($\underline{M}^+$, 44%), 201 (48), 185 (23), 156 (24), 148 (29), 127 (54), 99 (100), and 55 (40)

5-Allylthiopentanoic acid (254a).

A solution of 5-mercaptopentanoic acid (402 mg, 3.00 mmol) in dichloromethane (5 ml) at 0°C was degassed and placed under an atmosphere of nitrogen; triethylamine (0.44 ml, 3.15 mmol) and allyl bromide (0.30 ml, 3.3 mmol) were then added dropwise, in succession, and the resulting suspension was stirred for 0.75 h at 0°C and then 12 h at room temperature. Aqueous work-up and chromatographic purification gave the title compound (254a) (242 mg, 47%), the second of three components, as an oil; (Found: C, 54.9; H, 8.3; S, 18.1. $C_8H_{14}O_2S$ requires C, 55.1; H, 8.1; S, 18.4%); $\nu_{max.}$ (film) 3600-2400, 1709, 1635, 1229, and 918 cm^{-1}; δ_H (90 MHz; CDCl$_3$) 1.50-1.90 (4 H, m), 2.30-2.54 (4 H, m, C$\underline{H}_2$CO and C$\underline{H}_2$S), 3.10 (2 H, d, J 7 Hz, CHC$\underline{H}_2$S), 4.92-5.05 (1 H, m, CH:C$\underline{H}_2$), 5.13 (1 H, d, J 2 Hz, CH:C$\underline{H}_2$), 5.50-6.00 (1 H, m, CH$_2$:C$\underline{H}$), and 11.50 (1 H, br, CO$_2$H); m/z (110°C) 174 ($\underline{M}^+$, 61%), 133 (7), 114 (55), 101 (46), 73 (66), and 41 (100).

Methyl 5-(3-Phenylprop-2-enyl)pentanoate (255b).

Cinnamyl bromide (3.31 g, 17.0 mmol) was added to a solution of methyl 5-mercaptopentanoate (2.37 g, 16.0 mmol) and triethylamine (2.46 ml, 18.0 mmol) in DMF (20 ml), and a solid was immediately precipitated exothermically. The reaction was stirred at room temperature for 24 h before aqueous work-up .The crude product was purified by chromatography and distillation to give the title compound (255b) (1.56 g, 37%) as an oil, b.p. 190-200°C at 0.3 mmHg; (Found: $\underline{M}^+$, 264.1176. $C_{15}H_{20}O_2S$ requires $\underline{M}$, 264.1184); $\nu_{max.}$ (film) 1738, 1436, 1206, 1174, and 754 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.53-1.80 (4 H, m), 2.33 (2 H, t, J 7.0 Hz, C$\underline{H}_2$CO), 2.50 (2 H, t, J 7.0 Hz, C$\underline{H}_2$S), 3.30 (2 H, dd, J 7.3, 1.0 Hz, CHC$\underline{H}_2$S), 3.65 (3 H, s, O$\underline{Me}$), 6.18 (1 H, dt, J 15.5, 7.3 Hz, C$\underline{H}$CHPh), 6.43 (1 H, d, J 15.5, 7.3 Hz, CHC$\underline{H}$Ph), and 7.19-7.42 (5 H, m, ArH); m/z (150°C) 264 ($\underline{M}^+$, 8%), 234 (2), 134 (14), 117 (100), and 91 (30).

5-(3-Phenylprop-2-enyl)pentanoic acid (254b).

A solution of potassium hydroxide (2.0 g) in water (10 ml) was added to a solution of (255b) (1.00 g, 3.79 mmol) in methanol. The reaction was stirred at room temperature for 24 h. Work-up gave the title compound (254b) (0.97 g, 100%) as a pale solid, which was used in the next step without further purification. A small sample was recrystallised, m.p. 79-80°C (ether/petrol); (Found: C, 67.1; H, 7.3.

$C_{14}H_{18}O_2S$ requires C, 67.2; H, 7.3%); $\nu_{max.}$ (film) 3500-2500, 1698, 1040, 1286, 1228, 969, and 750 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.50-1.83 (4 H, m), 2.38 (2 H, t, J 6.9 Hz, $C\underline{H}_2CO$), 2.51 (2 H, t, J 6.9 Hz, $C\underline{H}_2S$), 3.30 (2 H, dd, J 7.2, 1.0 Hz, $CHC\underline{H}_2S$), 6.18 (1 H, dt, J 15.6, 7.2 Hz, $C\underline{H}CHPh$), 6.42 (1 H, d, J 15.6, $CHC\underline{H}Ph$), 7.15-7.42 (5 H, m, ArH), and 9.70 (1 H, br, CO_2H); m/z (100°C) 250 ($\underline{M}^+$, 17%), 149 (6), 134 (1), 117 (100), and 91 (8).

Methyl 5-Benzylthiopentanoate (255c).

Benzyl bromide (0.39 ml, 3.29 mmol) and methyl 5-mercaptopentanoate (0.42 g, 3.13 mmol) were added to a suspension of potassium carbonate (10 g) in acetone under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 24 h and then heated at reflux for 4 h. Aqueous work-up and purification of the residue by chromatography gave the title compound (255c) (0.540g, 77%) as an oil; (Found: $\underline{M}^+$,.238.1024. $C_{15}H_{20}O_2S$ requires $\underline{M}$, 238.1027); $\nu_{max.}$ (film) 1738, 1454, 1204, 1174, and 700 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.50-1.80 (4 H, m), 2.29 (2 H, t, J 7.0 Hz, $C\underline{H}_2CO$), 2.38 (2 H, t, J 7.0 Hz, $C\underline{H}_2S$), 3.66 (3 H, s, O$\underline{Me}$), 3.70 (2 H, s, $C\underline{H}_2Ph$), and 7.12-7.43 (5 H, m, ArH); m/z (200°C) 237 ($\underline{M}^+$, 55%), 181 (28), 115 (90), 91 (100), and 55 (33).

5-(Benzylthio)pentanoic acid (254c).

A solution of potassium hydroxide (1.5g) in water (8 ml) was added to a solution of (255c) (490 mg, 2.06 mmol) in methanol.(8 ml) The reaction mixture was stirred at room temperature for 12 h. Work-up and chromatography of the residue gave the title compound (254c) (379 mg, 82%) as a low melting solid, lit.[105] m.p. 31°C; $\nu_{max.}$ (film) 3400-2400, 1708, 1454, 1235, and 702 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.45-1.80 (4 H, m), 2.31 (2 H, t, J 7.0 Hz, $C\underline{H}_2CO$), 2.42 (2 H, t, J 7.0 Hz, $C\underline{H}_2S$), 3.71 (2 H, s, $C\underline{H}_2Ph$), and 7.15-7.40 (5 H, m, ArH), acid proton not observed; m/z (100°C) 224 ($\underline{M}^+$, 16%), 207 (1), 190 (1), 161 (1), 123 (19), and 91 (100)

6-Allylthio-1-diazohexan-2-one (256a).

A solution of (254a) (173 mg, 0.993 mmol) and oxalyl chloride (0.15 ml, 1.8 mmol) in ether (5 ml) was stirred for 12 h at room temperature. All volatile material was evaporated under high vacuum to give the crude acid chloride as a

viscous oil; $\nu_{max.}$ (film) 1800 cm^{-1}.

The crude acid chloride was dissolved in ether (5 ml) and an ethereal solution of diazomethane (12 ml, 4.5 mmol) added dropwise. After 18 h at room temperature the ether was slowly evaporated under a stream of nitrogen. Chromatographic purification of the residue on Florisil gave the title compound (256a) (109 mg, 55%) as an unstable yellow oil; (Found: $\underline{M}^+$,170.0766. $C_9H_{14}N_2OS$ - N_2 requires $\underline{M}$, 170.0765); $\nu_{max.}$ (film) 2104, 1641, and 1376 cm^{-1}; δ_H (90 MHz; CDCl$_3$) 1.45-2.05 (4 H, m), 2.34 (2 H, t, $\underline{J}$ 7.0 Hz, C$\underline{H}_2$S), 2.46 (2 H, t, $\underline{J}$ 6.5 Hz, C$\underline{H}_2$CO), 3.11 (2 H, d, $\underline{J}$ 7. Hz, CHC$\underline{H}_2$S), 4.95-5.05 (1 H, m, C$\underline{H}$CH$_2$S), 5.14 (1 H, approx d, $\underline{J}$ 2 Hz, CH:C$\underline{H}_2$), 5.27 (1 H, s, C$\underline{H}$CN$_2$), and 5.55-6.00 (1 H, m, CH:C$\underline{H}_2$), $\underline{m/z}$ (100°C) 202 ($\underline{M}^+$, 1%), 170 (3), 157 (2), 142 (4), 137 (1), 129 (30), 101 (27), 67 (38), and 41 (100).

1-Diazo-6-(3-phenylprop-2-enyl)thiohexan-2-one (256b).

A solution of (254b) (0.909 g, 3.63 mmol) and oxalyl chloride (0.34 ml, 1.80 mmol) in benzene (50 ml) was stirred for 18 h at room temperature. All volatile material was evaporated under high vacuum and the residue distilled to give 5-(3-phenylprop-2-enyl)pentanoyl chloride (0.529 g, 52%), as a viscous oil; b.p. 165°C at 2 mmHg; $\nu_{max.}$ (film) 1800 cm^{-1}.

The acid chloride (490 mg, 1.82 mmol) was dissolved in ether (10 ml) and an ethereal solution of diazomethane (20 ml, 6.0 mmol) added dropwise. After 14 h at room temperature the ether was slowly evaporated under a stream of nitrogen. Chromatographic purification of the residue on Florisil gave the title compound (256b) (245 mg, 49%) as an unstable yellow oil; (Found: $\underline{M}^+$, 246.1080. $C_{15}H_{18}N_2OS$ requires $\underline{M}$, 246.1078); $\nu_{max.}$ (film) 2103, 1641, 1379, 1323, 965, and 754 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.45-1.72 (4 H, m), 2.23 (2 H, approx t, $\underline{J}$ 6.0 Hz, C$\underline{H}_2$CO), 2.40 (2 H, t, $\underline{J}$ 7.1 Hz, C$\underline{H}_2$S), 3.20 (2 H, dd, $\underline{J}$ 7.1, 1.0 Hz, CHC$\underline{H}_2$S), 5.20 (1 H, br, C$\underline{H}$N$_2$), 6.19 (1 H, dt, $\underline{J}$ 15.4, 7.1 Hz, C$\underline{H}$CHPh), 6.44 (1 H, d, $\underline{J}$ 15.4, CHC$\underline{H}$Ph), 7.20-7.42 (5 H, m, ArH); $\underline{m/z}$ (FAB; glycerol) 275 ($\underline{M}$H$^+$, 1%), and 117 (100).

6-Benzylthio-1-diazo-hexan-2-one (194).

A solution of (254c) (340 mg, 1.56 mmol) and oxalyl chloride (0.27 ml, 3.1 mmol) in benzene (40 ml) was stirred for 18 h at room temperature. All volatile material

was evaporated under high vacuum and the residue distilled to give 5-benzylpentanoyl chloride (352 mg, 96%) as a viscous oil, b.p. 160°C at 0.5 mmHg; $\nu_{max.}$ (film) 1800 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.52-1.68 (2 H, m), 1.68-1.86 (2 H, m), 2.42 (2 H, t, J 7.0 Hz, C$\underline{H}_2$S), 2.86 (2 H, t, J 7.0 Hz, C$\underline{H}_2$CO), 3.71 (2 H, s, C$\underline{H}_2$Ph), 7.20-7.40 (5 H, m, ArH).

The acid chloride (350 mg, 1.44 mmol) was dissolved in ether (10 ml) and an ethereal solution of diazomethane (18 ml, 5.0 mmol) added dropwise. After 15 h at room temperature the ether was slowly evaporated under a stream of nitrogen. Chromatographic purification of the residue on Florisil gave the title compound (194) (236 mg, 66%) as an unstable yellow oil; $\nu_{max.}$ (film) 2102, 1641, 1375, 1322, and 1099 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.50-1.73 (4 H, m), 2.25 (2 H, t, J 6.2 Hz, C$\underline{H}_2$CO), 2.38 (2 H, t, J 6.9 Hz, C$\underline{H}_2$S), 3.68 (2 H, s, C$\underline{H}_2$Ph), 5.18 (1 H, br, C$\underline{H}$N$_2$), 7.17-7.31 (5 H, m, ArH); m/z (FAB; glycerol) 249 ($\underline{M}$H$^+$, 4%), 247 (2), 221 (2), 207 (2), 191 (1), 179 (1), 129 (3), 101 (3), and 91 (100).

2-Allylthiepan-2-one (257).

A solution of (256a) (82 mg, 0.414 mmol) in benzene (8 ml) was added dropwise to a suspension of dirhodium tetraacetate (3 mg) in benzene (10 ml) at reflux. After 1 h the pink solution was cooled, evaporated, and the residue subject to chromatography to give the title compound (257) (30 mg, 42%) as an oil, b.p. 100°C at 0.8 mmHg (Found: $\underline{M}^+$, 170.0768. C$_9$H$_{14}$OS requires $\underline{M}$, 170.0765); $\nu_{max.}$ (film) 1699, 1641, and 918 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.60-1.95 (3 H, m), 2.00-2.17 (1 H, m), 2.34 (1 H, ddt, J 14.7, 7.4, 1.3 Hz), 2.58-2.73 (4 H, m), 2.80 (1 H, ddd, J 14.2, 10.6, 3.2 Hz, SCHC$\underline{H}_2$), 3.57 (1 H, dd, J 7.9, 6.6 Hz, SC$\underline{H}$CH$_2$), 5.00-5.16 (2 H, m, CH:C$\underline{H}_2$), and 5.82 (1 H, ddt, J 17.4, 10.2, 7.0 Hz, C$\underline{H}$:CH$_2$); m/z (140°C) 170 ($\underline{M}^+$, 22%), 129 (12), 105 (31), 101 (30), and 41 (100).

2-(1-Phenylprop-2-enyl)thiepan-3-one (258).

A solution of (256b) (153 mg, 0.558 mmol) in benzene (7.5 ml) was added over 5.5 minutes to a suspension of dirhodium tetraacetate (4 mg) in benzene (20 ml) at reflux. After 3 minutes at reflux, the reaction mixture was cooled, evaporated and the residue purified by chromatography on silica gel to give the title compound (258) (87 mg, 64%), a low melting solid, as a mixture of two diastereomers, m.p. 35-38°C, b.p. 145-155°C at 0.25 mmHg; (Found: C, 73.1; H, 7.4. C$_{15}$H$_{18}$OS requires

C, 73.1; H, 7.4%); $\nu_{max.}$ (film) 1699, 1637, 1453, 1200, 922, and 701 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.54-1.80 (2H, m), 1.80-2.15 (2 H, m), 2.30-2.43 (1 H, m, CH$_2$CO), 2.49 (1 H, ddd, J 12.4, 6.6, 2.3 Hz, CH$_2$CO), 2.63 (1 H, approx dd, J 14.9, 7.4 Hz, CH$_2$S), 2.72-2.85 (2 H, m, CH$_2$S, minor isomer), 2.92 (1 H, approx ddd, J 13.2, 10.7, 2.7 Hz, CH$_2$S, major isomer), 3.78 (1 H, approx t, J 8.7 Hz, CHPh, major isomer), 3.86 (1 H, t, J 8.3 Hz, CHPh, minor isomer), 3.98 (1 H, d, J 8.7 Hz, CHS, minor isomer), 4.01 (1 H, d, J 9.9 Hz, CHS, major isomer), 4.98-5.20 (2 H, m, CH:CH$_2$), 5.92-6.18 (1 H, m, CH:CH$_2$), and 7.17-7.32 (5 H, m, ArH); m/z (120°C) 246 ($\underline{M}^+$, 16%), 157 (3), 129 (12), and 117 (100); together with a second compound: 1-[5-(3-phenylprop-2-enyl)thio]pentanoylcyclohepta-2,4,6-triene (260) (21 mg, 12%), an oil; (Found: $\underline{M}^+$, 324.1543. C$_{21}$H$_{24}$OS requires $\underline{M}$, 324.1548); ν_{max} (film) 1717, 1600, 1450, 1288, 965, 751, and 703 cm^{-1}; δ_H (270 MHz; CDCl$_3$) 1.45-1.78 (4 H, m), 2.37 (1 H, t, J 5.6 Hz, CHCO), 2.48 (2 H, t, J 6.8 Hz, CH$_2$CO), 2.55 (2 H, t, J 6.8 Hz, CH$_2$S), 3.31 (2 H, d, J 7.3 Hz, SCH$_2$CH), 5.02 (2 H, dd, J 7.6, 5.6 Hz, CHCHCO), 6.17 (1 H, dt, J 15.6, 7.5 Hz, CHCHPh), 6.26-6.31 (2 H, m, CHCHCHCO), 6.43 (1 H, d, J 15.8 Hz, CHPh), 6.57 (2 H, dd, J 3.1, 2.8 Hz, CH:CHCH), and 7.08-7.25 (5 H, m, ArH); m/z (120°C) 324 ($\underline{M}^+$, 1%), 246 (9), 203 (10), 129 (30), 117 (100), and 91 (54).

2-Benzyloxothiepan-3-one (259).

A solution of (194) (107 mg, 0.431 mmol) in benzene (5 ml) was added over 5 minutes to a suspension of dirhodium tetraacetate (4 mg) in benzene (15 ml) at reflux. After five minutes at reflux, the reaction mixture was cooled, evaporated and the residue purified by chromatography on silica gel to give the title compound (259) (25 mg, 26%), as an oil, b.p. 145°C at 0.25 mmHg; (Found: $\underline{M}^+$, 220.0922. C$_{13}$H$_{16}$OS requires $\underline{M}$, 220.0928); $\nu_{max.}$ (film) 1699, 1604, 1496, 1453, 1436, 752, and 700 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.56-1.94 (3 H, m), 1.95-2.18 (1 H, m), 2.45-2.80 (3 H, m, CH$_2$S and CHPh), 2.81 (2 H, dd, J 14.3, 8.0 Hz, CH$_2$CO), 3.29 (1 H, dd, J 14.3, 5.4 Hz, CH$_2$Ph), 3.80 (1 H, dd, J 7.6, 5.4 Hz, SCHCO), and 7.12-7.40 (5 H, m, ArH); m/z (160°C) 220 ($\underline{M}^+$, 66%), 187 (8), 131 (18), 101 (100), 91 (64), and 87 (27); together with a second compound: 1-(5-benzylthio)pentanoylcyclohepta-2,4,6-triene (261) (8 mg, 6%) as an oil; (Found: $\underline{M}^+$, 298.1391. C$_{19}$H$_{22}$OS requires $\underline{M}$, 298.1383); $\nu_{max.}$ (film) 1717, 1689 (wk), 1602, 1494, 1454, 749, and 703 cm^{-1}; δ_H (270 MHz; CDCl$_3$) 1.45-1.75

(4 H, m, CH$_2$CH$_2$CH$_2$S), 2.37 (1 H, t, J 5.4 Hz, CHCO), 2.41 (2 H, t. J 6.8 Hz, CH$_2$CO), 2.53 (2 H, t, J 6.8 Hz, CH$_2$S), 3.69 (2 H, s, CH$_2$Ph), 5.03 (2 H, dd, J 7.6, 5.5 Hz, CHCHCO), 6.25-6.36 (2 H, m, CHCHCHCO), 6.57 (2 H, dd, J 3.1, 2.6 Hz), and 7.20-7.46 (5 H, m, ArH); m/z (170°C) 298 (M$^+$, 1%), 224 (6), 207 (4), 193 (24), and 91 (100).

6.5 Experimental for Chapter Five

General procedure for m-CPBA oxidations

A solution of the sulphide substrate (0.2-1 mmol) in dichloromethane (~10 ml) was cooled to -10°C and m-CPBA (85% tech., 1.1-1.3 eq.) added batchwise over 10-30 minutes. After a further 10 minutes, the suspension was quenched with 10% aqueous sodium metabisulphite at -10°C. The dichloromethane phase was separated and washed with saturated sodium bicarbonate, water and brine. The crude product was subjected to chromatography on silica gel to give the sulphoxide as the major product, together with some sulphone.

Ethyl 6-Benzylsulphinyl-2-diazo-3-oxohexanoate (262a).

m-CPBA (57 mg, 0.33 mmol) was added over 10 minutes to a solution of ethyl 6-benzylthio-2-diazo-3-oxohexanoate (231) (92 mg, 0.30 mmol) in dichloromethane (10 ml) at -10°C. After 0.2 h, sodium metabisulphite (2 ml, 10%) was added. Work-up and purification gave the title compound (262a) (53 mg, 55%) as a low melting solid, m.p. 52-54°C; (Found: C, 56.0; H, 5.7; N, 8.7. $C_{15}H_{18}N_2O_4S$ requires C, 55.9; H, 5.6; N, 8.7%); $\nu_{max.}$ (melt) 2136, 1714, 1654, 1304, 1224, 1045, and 701 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.36 (3 H, t, J 7.1 Hz), 2.08-2.22 (2 H, m, SCH_2CH_2), 2.59-2.78 (2 H, m, CH_2CO), 3.03 (2 H, dt, J 6.9, 1.4 Hz, SCH_2),.4.02 (2 H, s, $PhCH_2$), 4.32 (2 H, q, J 7.1 Hz, OCH_2), 7.27-7.48 (5 H, m, ArH); m/z (C.I.; NH_3) 323 (MH^+, 67%), 295 (36), 91 (100);

Ethyl 2-Diazo-6-ethylsulphinyl-3-oxohexanoate (263a).

m-CPBA (110 mg, 0.64 mmol) was added over 0.75 h to a solution of ethyl 2-diazo-6-ethylthio-3-oxohexanoate (232)(131 mg, 0.536 mmol) in dichloromethane (12 ml) at -10°C. After 0.2 h, sodium metabisulphite (2 ml, 10%) was added. Work-up and purification gave the title compound (263a) (74 mg, 53%) as a low melting solid, m.p. 35-38°C; (Found: M^+, 260.0823. $C_{10}H_{16}N_2O_4S$ requires M, 260.0831); $\nu_{max.}$ (film) 2136, 1718, 1654, 1305, and 1020 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.31 (3 H, t, J 7.0 Hz), 1.32 (3 H, t, J 7.4 Hz), 2.11 (2 H, quin, J

7.1 Hz, SCH$_2$CH$_2$), 2.62-2.79 (4 H, m, CH$_2$SCH$_2$), 3.03 (2 H, dt, J 6.7, 1.9 Hz, CH$_2$CO), and 4.28 (2 H, q, J 6.9 Hz, OCH$_2$); m/z (140°C) 260 (M$^+$, 1%), 243 (1), 231 (8), 183 (26), 131 (10), 127 (39), 109 (57), 99 (33), 69 (41), and 29 (100); and a less polar component ethyl 2-diazo-6-ethylsulphonyl-3-oxohexanoate (263b) (10 mg, 7%) as an oil; (Found: M$^+$, 276.0771. C$_{10}$H$_{16}$N$_2$O$_5$S requires M, 276.0780); ν $_{max.}$ (film) 2139, 1717, 1653, 1379, 1305, and 1131 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.32 (3 H, t, J 7.1 Hz), 1.40 (2 H, t, J 7.4 Hz, SCH$_2$CH$_3$), 2.07-2.24 (2 H, m, SCH$_2$CH$_2$), 2.94-3.10 (6 H, m), and 4.29 (2 H, q, J 7.4 Hz, CO$_2$CH$_2$); m/z (80°C) 276 (M$^+$, 7%), 183 (3), 163 (49), 156 (21), 147 (64), 135 (21), 109 (19), and 69 (100).

Ethyl 6-Allylsulphinyl-2-Diazo-3-oxohexanoate (264a).

A solution of ethyl 6-allylthio-2-diazo-3-oxohexanoate (225) (196 mg, 0.765 mmol) in dichloromethane (7 ml) at 0°C was buffered with anhydrous disodium hydrogen phosphate (0.9 g) and then treated with m-CPBA (0.21 g, 1.15 mmol) over 0.25 h. After a further 0.25 h , work-up and purification gave the title compound (264a) (112 mg, 54%) as a viscous polar oil; (Found: C, 48.5; H, 6.1; N, 10.2. C$_{11}$H$_{16}$N$_2$O$_4$S requires C, 48.5; H, 5.9; N, 10.3%); ν $_{max.}$ (film) 2136, 1717, 1654, 1377, 1305, and 1041 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.25 (3 H, t, J 7.1 Hz), 2.06 (2 H, quin, J 7.2 Hz, CH$_2$CH$_2$S), 2.62-2.75 (2 H, m, CH$_2$S), 2.97 (2 H, dt, J 6.9, 1.5 Hz, CH$_2$CO), 3.34 (1 H, ddt, J 12.5, 6.8, 0.6 Hz, SCH$_2$CH), 3.46 (1 H, ddt, J 12.5, 6.8, 0.6 Hz, SCH$_2$CH), 4.23 (2 H, q, J 7.1 Hz, CO$_2$CH$_2$), 5.26-5.43 (2 H, m, CH$_2$:CH), and 5.83 (1 H, ddt, J 16.5, 10.2, 7.4 Hz, CHCH$_2$S); m/z (120°C) 272 (M$^+$, 1%), 256 (1), 231 (100), 227 (3), 203 (2), 159 (10), 127 (21), 109 (19), and 41 (86); and a less polar product, ethyl 6-allylsulphonyl-2-diazo-3-oxohexanoate (264b) (43 mg, 20%) as an oil; (Found: M$^+$, 260.0718. C$_{11}$H$_{16}$N$_2$O$_5$S -N$_2$ requires M, 260.0660); ν $_{max.}$ (film) 2138, 1714, 1652, 1380, 1306, and 1132 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.27 (3 H, t, J 7.1 Hz), 2.12 (2 H, quin, J 7.3 Hz, SCH$_2$CH$_2$), 2.92-3.07 (4 H, m, SCH$_2$CH$_2$CH$_2$CO), 3.68 (2 H, d, J 7.0 Hz, CHCH$_2$S), 4.25 (2 H, q, J 7.1 Hz, OCH$_2$), 5.36-5.50 (2 H, m), and 5.89 (1 H, ddt, J 16.9, 10.6, 7.2 Hz); m/z (160°C) 288 (M$^+$, 1%), 260 (1), 247 (1), 243 (1), 224 (1), 196 (5), 159 (14), 109 (16), 41 (100).

<u>Ethyl</u> 2-<u>Diazo</u>-3-<u>oxo</u>-6-(3-<u>phenylprop</u>-2-<u>enyl</u>)<u>sulphinylhexanoate</u> (265a).

m-CPBA (210 mg, 1.2 mmol) was added over 1 h to a solution of ethyl 2-diazo-3-oxo-6-(3-phenylprop-2-enyl)thiohexanoate (227) (335 mg, 1.01 mmol) in dichloromethane (30 ml). After 5 minutes, 10% sodium metabisulphite was added, and the product extracted and purified, to give the <u>title compound</u> (265a) (212 mg, 61%) as a solid, m. p. 81-83°C; (Found: C, 58.5; H, 5.8; N, 7.8. $C_{17}H_{20}N_2O_4S$ requires C, 58.6; H, 5.8; N, 8.0%); $\nu_{max.}$ (melt) 2136, 1714, 1651, 1376, 1304, 1224, and 1039 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.29 (3 H, t, J 7.0 Hz, CH$_2$C$\underline{H}_3$), 2.12 (2 H, m, SCH$_2$C$\underline{H}_2$), 2.70-2.82 (2 H, m, CH$_2$C$\underline{H}_2$S), 3.01 (2 H, dt, J 7.0, 1.0 Hz, C$\underline{H}_2$CO), 3.56 (1 H, ddd, J 12.5, 7.5 ,0.8 Hz, CHC$\underline{H}_2$S), 3.67 (1 H, ddd, J 12.5, 7.5, 0.8 Hz, CHC$\underline{H}_2$S), 4.26 (2 H, q, J 7.0 Hz, CO$_2$C$\underline{H}_2$), 6.24 (1 H, dt, J 15.5, 7.2 Hz, C$\underline{H}$CHPh), 6.65 (1 H, d, J 15.5 Hz, C$\underline{H}$Ph), and 7.20-7.43 (5 H, m, ArH); <u>m/z</u> (FAB; glycerol) 349 ($\underline{M}$H$^+$, 4%), 155 (2), 117 (100), and 91 (7); and a less polar product <u>ethyl</u> 2-<u>diazo</u>-3-<u>oxo</u>-6-(3-<u>phenylprop</u>-2-<u>enyl</u>)<u>sulphonylhexanoate</u> (265b) (28 mg, 8%) as an oil; (Found: C, 56.1; H, 5.7; N, 7.6. $C_{17}H_{20}N_2O_5S$ requires C, 56.0; H, 5.5; N, 7.7%); $\nu_{max.}$ (film) 2138, 1714, 1652, 1379, 1304, 1225, 1122, 971, and 745 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.30 (3 H, t, J 7.0 Hz, CH$_2$C$\underline{H}_3$), 2.10-2.24 (2 H, m, CH$_2$C$\underline{H}_2$S), 2.95-3.09 (4 H, m, SC$\underline{H}_2$CH$_2$C$\underline{H}_2$CO), 3.85 (2 H, d, J 7.3 Hz, CHC$\underline{H}_2$S), 4.26 (2 H, q, J 7.0 Hz, CO$_2$C$\underline{H}_2$), 6.24 (1 H, dt, J 15.5, 7.2 Hz, PhCHC$\underline{H}$), 6.72 (1 H, d, J 15.5 Hz, PhC$\underline{H}$), 7.21-7.47 (5 H,m, ArH); <u>m/z</u> (FAB; glycerol) 365 ($\underline{M}$H$^+$, 1%), 215 (1), 203 (2), 185 (3), 117 (100), and 91 (16).

<u>Ethyl</u> 2-<u>Diazo</u>-3-<u>oxo</u>-7-(3-<u>phenylprop</u>-2-<u>enyl</u>)<u>sulphinylheptanoate</u> (266a).

m-CPBA (108 mg, 0.62 mmol) was added over 20 minutes to a solution of ethyl 2-diazo-3-oxo-7-(3-phenylprop-2-enyl)thioheptanoate (234) (180 mg, 0.52 mmol) in dichloromethane (10 ml) at -11°C. After 0.3 h, sodium metabisulphite (2 ml, 20%) was added. Work-up and purification gave the <u>title compound</u> (266a) (113 mg, 60%) as a low melting solid, m.p. 48-50°C; (Found: C, 59.7; H, 6.2; N, 7.7. $C_{18}H_{22}N_2O_4S$ requires C, 59.7; H. 6.1; N, 7.7%); $\nu_{max.}$(melt) 2135, 1714, 1652, 1450, 1372, 1305, 1218, 1025, and 748 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.32 (3 H, t, J 7.0 Hz, CH$_2$C$\underline{H}_3$), 1.70-1.94 (4 H, m), 2.75 (2 H, approx t, J 7.1 Hz, CH$_2$C$\underline{H}_2$S), 2.90 (2 H, approx t, J 6.7 Hz, C$\underline{H}_2$CO), 3.53-3.73 (2 H, m, CHC$\underline{H}_2$S), 4.28 (2 H, q, J 7.0 Hz, CO$_2$C$\underline{H}_2$), 6.25 (1 H, dt, J 15.6, 7.8 Hz, PhCHC$\underline{H}$),

6.68 (1 H, d, J 15.8 Hz, PhC$\underline{H}$), and 7.22-7.44 (5 H, m, ArH); m/z (FAB; glycerol) 363 ($\underline{M}^+$, 4%), 337 (1), 165 (1), 147 (1), 129 (2), 117 (100), 91 (14).

Ethyl 1-Benzyl-3-oxothiane-1-oxide-2-carboxylate, inner salt (268).

A solution of (262a) (62 mg, 0.194 mmol) in benzene (5 ml) was added to a suspension of dirhodium tetraacetate (1 mg) in benzene (10 ml) at reflux over 0.2 h. After 5 minutes at reflux, the suspension was cooled, filtered, evaporated, and the residue recrystallized to give the title compound (268) (43mg, 76%) as colourless crystals, m.p. 175-177°C (benzene/dichloromethane); (Found: C, 61.0; H, 6.0. $C_{15}H_{18}O_4S$ requires C, 61.2; H, 6.2%); $\nu_{max.}$ (Nujol) 1633, 1611, 1319, 1250, 1208, and 1126 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.39 (3 H, t, J 6.8 Hz, CH$_2$C$\underline{H}_3$), 1.86-2.00 (1 H, m), 2.08-2.55 (3 H, m), 3.04 (1 H, dd, J 13.1, 5.6 Hz, CH$_2$C$\underline{H}_2$S), 3.30 (1 H, dt, J 12.5, 2.8 Hz, CH$_2$C$\underline{H}_2$S), 4.26-4.44 (2 H, m, CO$_2$C$\underline{H}_2$), 5.23 (1 H, d, J 13.5 Hz, PhC$\underline{H}_2$), 5.32 (1 H, d, J 13.5 Hz, PhC$\underline{H}_2$S), and 7.45 (5 H, m, ArH); m/z (190°C) 294 ($\underline{M}^+$, 2%), 248 (3), 204 (3), 187 (12), 142 (13), 103 (9), 91 (100).

Ethyl 1-Ethyl-3-oxothiane-1-oxide-2-carboxylate, inner salt (269).

A solution of (263a) (60 mg, 0.23 mmol) in benzene (5 ml) was added to a suspension of dirhodium tetraacetate (1.1 mg) in benzene (7.5 ml) over 7 minutes. After 1 minute at reflux the suspension was cooled, filtered, evaporated, and the residue recrystallized to give the title compound (269) (42 mg, 78 %) as colourless crystals, m.p. 174-177°C (benzene/ether); (Found: $\underline{M}^+$, 232.0773. $C_{10}H_{16}O_4S$ requires $\underline{M}$, 232.0769); $\nu_{max.}$ (Nujol) 1723, 1655, 1373, 1207, 1054, and 756 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.30 (3 H, t, J 7.0 Hz. OCH$_2$C$\underline{H}_3$), 1.40 (3 H, J 7.3 Hz, SCH$_2$C$\underline{H}_3$), 2.12-2.60 (4 H, m, C$\underline{H}_2$C$\underline{H}_2$CO), 3.27-3.54 (2 H, m, CH$_2$C$\underline{H}_2$S), 3.97 (2 H, approx. q, J 7.5 Hz, CH$_3$C$\underline{H}_2$S), and 4.13-4.34 (2 H, m, CO$_2$C$\underline{H}_2$); m/z (180°C) 232 ($\underline{M}^+$, 100%), 187 (41), 162 (40), 159 (23), 134 (31), 116 (23), 111(15).

Ethyl 1-Allyl-3-oxothiane-1-oxide-2-carboxylate, inner salt (270).

A solution of (264a) (114 mg, 0.419 mmol) in benzene (6 ml) was added dropwise to a suspension of dirhodium tetraacetate (5 mg) in benzene (10 ml) at reflux over 6

minutes. After 0.2 h, at reflux the suspension was cooled, filtered, evaporated, and the residue recrystallized to give the title compound (270) (81 mg, 84%) as colourless crystals, m.p. 128-130°C (benzene/ethyl acetate); (Found: C, 53.8; H, 6.6; S, 13.1. $C_{11}H_{16}O_4$ S requires C, 54.1; H, 6.6; S, 13.1%); $\nu_{max.}$ (Nujol) 1697, 1574, 1370, 1336, and 1190 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.33 (3 H, t, $\underline{J}$ 6.9 Hz, CH$_2$C$\underline{H}_3$), 2.10-2.63 (4 H, m, C$\underline{H}_2$C$\underline{H}_2$CO), 3.21-3.47 (2 H, m, SC$\underline{H}_2$), 4.21-4.37 (2 H, m, CO$_2$C$\underline{H}_2$), 4.53 (1 H, dd, $\underline{J}$ 10.1, 7.5 Hz, CHC$\underline{H}_2$), 4.78 (1 H, dd, $\underline{J}$ 10.1, 6.6 Hz, CHC$\underline{H}_2$), 5.50-5.62 (2 H, m, CHC$\underline{H}_2$), and 5.71-5.80 (1 H, m, CHC$\underline{H}$); m/z (FAB; glycerol/ CHCl$_3$) 245 ($\underline{M}$H$^+$, 100%), 205, (36), 199 (33), 185 (21), and 159 (15).

Ethyl 3-oxo-1-(3-Phenylprop-2-enyl)thiane-1-oxide-2-carboxylate, inner salt (271).

A solution of (265a) (200 mg, 0.574 mmol) in benzene (7 ml) was added to a suspension of dirhodium tetraacetate (4 mg) in benzene (20 ml) over 1 minute. After 1 minute at reflux, the suspension was cooled, filtered, evaporated, and the residue recrystallized to give the title compound (271) (100 mg, 54%) as a colourless solid, m.p. 143-144°C (benzene); (Found: C, 63.5; H, 61.9; S, 9.7. $C_{17}H_{20}O_4$S requires C, 63.7; H, 6.3; S, 10.0%); $\nu_{max.}$ (Nujol) 1692, 1576, 1462, 1374, 1202, and 756 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.37 (3 H, t, $\underline{J}$ 7.1Hz, CH$_2$C$\underline{H}_3$), 2.10-2.63 (4 H, m, C$\underline{H}_2$C$\underline{H}_2$CO), 3.26-3.39 (1 H, m, CH$_2$C$\underline{H}_2$S), 3.40-3.56 (1 H, m, CH$_2$C$\underline{H}_2$S), 4.21-4.44 (2 H, m, CO$_2$C$\underline{H}_2$), 5.85 (1 H, dd, $\underline{J}$ 14.5, 8.0 Hz, CHC$\underline{H}_2$S), 5.94 (1 H, dd, $\underline{J}$ 14.5, 8.0 Hz , CHC$\underline{H}_2$S), 6.12 (1 H, d t, $\underline{J}$ 15.5, 7.0 Hz, PhCHC$\underline{H}$), 6.83 (1 H, d, $\underline{J}$ 15.5 Hz, PhC$\underline{H}$), and 7.21-7.53 (5 H, m, ArH); m/z (130°C) 320 ($\underline{M}^+$, 4%), 304 (1), 286 (1), 274 (25), 188 (30), 142 (46), 129 (45), 117 (100), 105 (87), and 77 (64).

6-Benzylsulphinyl-1-diazohexan-2-one (273).

A solution of 6-benzylthio-1-diazohexan-2-one (194) (57 mg, 0.23 mmol) in dichloromethane (10 ml) at -20°C was buffered with anhydrous disodium hydrogen phosphate (0.2 g) and then treated with m-CPBA (43 mg, 0.25 mmol) over 0.2 h. After a further 5 minutes, water was added to the reaction mixture. The two phases were separated, the organic phase washed with 5% sodium bicarbonate solution and

brine, dried over magnesium sulphate and then evaporated. Purification of the residue by chromatography on Florisil gave the title compound (273) (51 mg, 84%) as a solid, m.p. 71-74°C; $\nu_{max.}$ (melt) 3080, 2119, 1623, 1387, 1022, 699 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.64-1.89 (4 H, m), 2.27-2.42 (2 H, m, C$\underline{H}_2$CO), 2.57 (2 H, approx t, $\underline{J}$ 7.1 Hz, C$\underline{H}_2$S), 3.93 (1 H, d, $\underline{J}$ 12.9 Hz, C$\underline{H}_2$Ph), 4.05 (1 H, d, $\underline{J}$ 12.9 Hz, C$\underline{H}_2$Ph), 5.23 (1 H, br, C$\underline{H}$N$_2$), and 7.23-7.43 (5 H, m, ArH).

Ethyl 2-Diazo-3-hydroxy-3-(2-phenylthio)phenylpropanoate (274a).

A solution of LDA (6.68 mmol) in THF (10 ml) , prepared by the addition of n-butyl lithium in hexane (4.03 ml, 6.68 mmol) to diisopropylamine (0.94 ml, 6.68 mmol) in THF (10 ml) at 0°C, was added dropwise by catheter to a solution of ethyl diazoacetate (0.87 g, 7.59 mmol) and 2-(phenylthio)benzaldehyde (1.30 g, 6.07 mmol) in THF (30 ml) at -75°C over 0.25 h. After stirring for 1.5 h, acetic acid (0.5 ml) was added and the solution allowed to warm to 0°C, before the addition of water. Work-up and purification of the residue by chromatography on silica gel gave the title compound (274a) (1.93 g, 97%) as a yellow solid, m.p. 69-70°C (dec.); (Found: C, 62.4; H, 4.9; N, 8.4. C$_{17}$H$_{16}$N$_2$O$_3$S requires C, 62.2; H, 4.9; N, 8.5%); $\nu_{max.}$ (melt) 3439, 2097, 1674, 1295, 1108, and 741 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.23 (3 H, t, $\underline{J}$ 7.1 Hz, CH$_2$C$\underline{H}_3$), 3.44 (1 H, br, O$\underline{H}$), 4.07-4.29 (2 H, m, COC$\underline{H}_2$), 6.32 (1 H, d, $\underline{J}$ 3.1 Hz, C$\underline{H}$OH), 7.10-7.47 (8 H, m), and 7.74 (1 H, d, $\underline{J}$ 6.7 Hz); m/z (100°C) 300 ($\underline{M}^+$-N$_2$, 77%), 283 (100), 254 (24), 226 (48), 213 (69), 197 (75), 184 (46), 137 (41)

Ethyl 3-(2-Benzylthio)phenyl-2-diazo-3-hydroxypropanoate (274b).

A solution of LDA (4.62 mmol) in THF (10 ml) , prepared by the addition of n-butyl lithium in hexane (2.93 ml, 4.62 mmol) to diisopropylamine (0.68 ml, 4.84 mmol) in THF (10 ml) at 0°C, was added dropwise by catheter to a solution of ethyl diazoacetate (0.553 g, 4.84 mmol) and 2-(benzylthio)benzaldehyde (1.01 g, 4.40 mmol) in THF (25 ml) at -75°C over 0.25 h. After stirring for 1.5 h, acetic acid (0.4 ml) was added and the solution allowed to warm to 0°C, before the addition of water and subsequent extraction of organic material into dichloromethane. The dichloromethanephase was washed with water, then brine and finally dried over magnesium sulphate. After evaporation, the residue was purified by chromatography

on silica gel to give the title compound (274b) (1.38 g, 92%) as a yellow oil which solidified at 0°C; (Found: C, 63.2; H, 5.3; N, 8.0. $C_{18}H_{18}N_2O_3S$ requires C, 63.1; H, 5.3; N, 8.2%); $\nu_{max.}$ (film) 3441, 2097, 1675, 1373, 1294, 1107, and 749 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.28 (3 H, t, J 7.0 Hz, CH$_2$CH$_3$), 3.00 (1 H, br, OH), 4.05 (1 H, d, J 12.3 Hz, CH$_2$Ph), 4.12 (1 H, d, J 12.3 Hz, CH$_2$Ph), 4.26 (2 H, dq, J 7.0, 2.0 Hz, CO$_2$CH$_2$), 6.11 (1 H, d, J 3.2 Hz, CHOH), and 7.11-7.65 (9 H, m, ArH); m/z (150°C) 314 (M$^+$-N$_2$, 4%), 296 (7), 228 (14), 223 (34), 206 (21), 161 (22),137 (21), and 91 (100).

Ethyl 2-Diazo-3-oxo-3-(2-phenylthio)phenylpropanoate (275a).

Barium manganate (2.5 g, 9.8 mmol) was added to a solution of (274a) (1.55g, 4.71 mmol) in dichloromethane (50 ml) and the suspension stirred rapidly for 15 h at room temperature, and then heated at reflux for 3 h. The reaction mixture was filtered through Celite, evaporated, and the residue subjected to chromatography to give the title compound (275a) (1.06 g, 91%) as a yellow oil; (Found: M$^+$, 326.0717. $C_{17}H_{14}N_2O_3S$ requires M, 326.0725); $\nu_{max.}$ (film) 2143, 1724, 1635, 1317, and 750 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.18 (3 H, t, J 7.1 Hz, CO$_2$CH$_2$CH$_3$), 4.18 (2 H, q, J 7.1 Hz, CO$_2$CH$_2$CH$_3$), and 7.16-7.46 (9 H, m, ArH); m/z (100°C) 326 (M$^+$, 1%), 300 (1), 253 (5), 225 (100), 197 (50), and 176 (27).

Ethyl 3-(2-Benzylthio)phenyl-2-diazo-3-oxopropanoate (275b).

Barium manganate (1.8 g, 6.9 mmol) was added to a solution of (274b) (1.18g, 3.44 mmol) in dichloromethane (50 ml) and the suspension stirred rapidly for 12 h at room temperature. More barium manganate (0.88 g, 3.44 mmol) was added and the suspension heated at reflux for 6 h. The reaction mixture was filtered through Celite, evaoorated and the residue subjected to chromatography to give the title compound (275b) (1.35 g, 88%) as a yellow oil; (Found: C, 63. 4; H, 4.7; N, 8.4. $C_{18}H_{16}N_2O_3S$ requires C, 63.5; H, 4.7; N, 8.2%); $\nu_{max.}$ (film) 2142, 1724, 1694, 1634, 1370, 1304, 1118, and 752 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.16 (3 H, t, J 6.8 Hz, CO$_2$CH$_2$CH$_3$), 4.06 (2 H, s, CH$_2$Ph), 4.16 (2 H, q, J 6.8 Hz, CO$_2$CH$_2$), and 7.22-7.35 (9 H, m, ArH); m/z (FAB; glycerol) 341 (MH$^+$, 1%), 313 (1), 277 (2), 239 (4), 227 (4), 211 (3), 185 (26), and 91 (100).

Ethyl 2-Diazo-3-oxo-3-(2-phenylsulphinyl)phenylpropanoate (276a).

m-CPBA (0.82 g, 4.8 mmol) was added over 0.5 h to a solution of (275a) (1.30 g, 4.00 mmol) in dichloromethane (25 ml) at -15°C. After 0.2 h, 20% sodium metabisulphite was added. Basic work-up and purification gave the title compound (276a) (1.16 mg, 85%) as a yellow solid, m.p. 94-95°C; (Found: C, 59.4; H, 4.0; N, 8.0. $C_{17}H_{14}N_2O_4S$ requires C, 59.6; H, 4.1; N, 8.2%); $v_{max.}$ (melt) 2147, 1724, 1625, 1304, 1041, and 751 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.16 (3 H, t, J 7.1 Hz, CO$_2$CH$_2$C$\underline{H}_3$), 4.15 (2 H, q, J 7.1 Hz, CO$_2$C$\underline{H}_2$CH$_3$), 7.12-7.78 (8 H, m, ArH), and 8.08 (1 H, d, J 7.6 Hz, ArH); m/z (FAB; glycerol) 343 ($\underline{M}$H$^+$, 3%), 315 (19), 299 (6), 269 (25), 229 (23), 213 (23), 185 (43), and 93 (100).

Ethyl 3-(2-Benzylsulphinyl)phenyl-2-diazo-3-oxopropanoate (276b).

m-CPBA (0.58 g, 3.4 mmol) was added over 0.5 h to a solution of (275b) (0.960 g, 2.82 mmol) in dichloromethane (25 ml) at -13°C. After 0.25 h, 20% sodium metabisulphite was added. Basic work-up and purification gave the title compound (276b) (868 mg, 86%) as a viscous oil; (Found: C, 61.0; H, 4.7; N, 7.9. $C_{18}H_{16}N_2O_4S$ requires C, 60.7; H, 4.5; N, 7.9%); $v_{max.}$ (film) 2148, 1724, 1619, 1321, 1271, and 752 cm^{-1}; δ_H (60 MHz; CDCl$_3$) 1.22 (3 H, t, J 6.4 Hz, CO$_2$CH$_2$C$\underline{H}_3$), 4.02 (1 H, d, J 11.0 Hz, C$\underline{H}_2$Ph), 4.19 (2 H, q, J 6.4 Hz, CO$_2$C$\underline{H}_2$CH$_3$), 4.40 (1 H, d, J 11.0 Hz,C$\underline{H}_2$Ph), and 6.95-7.88 (9 H, m, ArH); m/z (FAB; glycerol) 357 ($\underline{M}$H$^+$, 6%), 331 (12), 277 (4), 223 (7), 185 (48), and 93 (100).

Ethyl 2,3-Dihydro-3-oxo-1-phenylbenzo[b]thiophene-1-oxide-2-carboxylate, inner salt (277a)

Dirhodium tetraacetate (4 mg) was added to a solution of (276a) (1.13 g, 3.29 mmol) in benzene (30 ml) which had been rapidly heated to reflux. After 2 minutes at reflux , the yellow coloured solution was cooled, evaporated, dichloromethane (5 ml) added and the catalyst removed by filtration through Celite. The filtrate was evaporated, and the residue recrystallized to give the title compound (277a) as colourless crystals, m.p. 175-176°C (benzene); (Found: C, 65.0; H, 4.4. $C_{17}H_{14}O_4S$ requires C, 65.0; H, 4.5%); $v_{max.}$ (Nujol) 1719, 1656, 1606, 1370, 1196, 1040 and 771 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.17 (3 H, t, J 6.9 Hz, CO$_2$CH$_2$C$\underline{H}_3$), 4.00-4.29 (2 H, m, CO$_2$C$\underline{H}_2$), 7.54-7.74 (5 H, m, P$\underline{h}$H), 7.80 (1 H,

dt, J 7.4, 0.8 Hz), 7.90 (2 H, m), and 8.02 (1 H, d, J 7.5 Hz); δ_C (62.9 MHz; $CDCl_3$) 13.8, 59.2, 85.0, 122.9, 123.0, 124.0, 127.6, 129.8, 133.2, 134.1, 134.2, 135.4, 136.3, 161, and 175.0; m/z (190°C) 314 ($\underline{M}^+$, 54%), 269 (97), 213 (100), 197 (18), 177 (30), 136 (62), 118 (78), and 77 (60). The mother liquor from the recrystallization was subjected to chromatography and gave a second component ethyl 2,3-dioxo-3-(2-phenylthio)phenylpropanoate (277b) (194 mg, 19%) as a yellow and readily hydrated oil; (Found: C, 64.8; H, 4.8; S, 10.5. $C_{18}H_{16}O_4S$ requires C, 65.0; H, 4.5; S, 10.2%); $\nu_{max.}$ (film) 3423, 1747, 1720, 1675, 1585, 1463, 1300, 1233, 1100, 1069, 1047, 1016, and 743 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.11 (3 H, t, J 7.0 Hz, $CO_2CH_2CH_3$ hydrate), 1.26 (3 H, t, J 7.0 Hz, $CO_2CH_2CH_3$ keto), 4.23 (2 H, q, J 6.9Hz, CO_2CH_2 hydrate), 4.29 (2 H, q, J 6.9 Hz, CO_2CH_2 keto), 5.36 (2 H, br, OH hydrate), 6.86 (1 H, dd, J 7.8, 1.0 Hz, ArH hydrate), 7.05-7.60 (~7 H, m, ArH), 7.98 (1 H, dd, J 7.8, 1.9 Hz, ArH keto), and 8.00 (1 H, dd, J 7.8, 1.6 Hz, ArH hydrate); δ_C (62.9 MHz; $CDCl_3$) 13.0, 13.2, 62.4, 62.6, 92.3, 124.0, 127.9, 128.1, 128.3, 128.7, 129.1, 129.3, 129.6, 130.0,131.3, 131.6, 132.5, 133.0, 133.8, 134.4, 134.6, 135.0, 135.5, 137.2, 145.5, 159.3, 169.8, 180.7, 191.6, and 192.2; m/z (150°C) 314 ($\underline{M}^+$, 5%), 227 (1), 213 (100), 184 (19), 152 (3), and 139 (2).

Ethyl 1-Benzyl-2,3-dihydro-3-oxobenzo[b]thiophene-1-oxide-2-carboxylate, inner salt (278a)

Dirhodium tetraacetate (4 mg) was added to a solution of (276b) (554 mg, 1.56 mmol) in benzene (30 ml) which had been rapidly heated to reflux. After 2 minutes at reflux, the yellow coloured solution was cooled, evaporated, dichloromethane (5 ml) added and the catalyst removed by filtration through Celite. The filtrate was evaporated, and the residue recrystallized to give the title compound (278a) as colourless crystals, m.p. 168-172°C (benzene); (Found: C, 65.8; H, 4.8. $C_{18}H_{16}O_4S$ requires C, 65.8; H, 4.9%); $\nu_{max.}$ (Nujol) 1714, 1630, 1374, 1345, 1211, 1075, and 762 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.45 (3 H, t, J 7.1 Hz, $CO_2CH_2CH_3$), 4.38 (2 H, m, CO_2CH_2), 5.16 (1 H, d, J 13.5 Hz, CH_2Ph), 5.36 (1 H, d, J 13.5 Hz, CH_2Ph), 7.05-7.12 (2 H, m, CH_2Ph), 7.19-7.36 (3 H, m, CH_2Ph), 7.61 (1 H, approx d, J 7.1 Hz), 7.69 (1 H, dt, J 7.3, 1.5 Hz), 7.77 (1 H, dt, J 7.3, 1.5 Hz), and 7.83 (1 H, approx d, J 7.7 Hz); m/z (160°C) 328 ($\underline{M}^+$, 1%), 312 (1), 282 (1), 255 (1), 227 (53), 176 (5), 136 (5), and 91(100). The mother

liquor from the recrystallization was subjected to chromatography and gave a second component ethyl 3-(2-benzylthio)phenyl-2,3-dioxopropanoate (278b) (30 mg, 6%) as a yellow and readily hydrated oil; (Found: C, 65.8; H, 5.2. $C_{18}H_{16}O_4S$ requires C, 65.8; H, 4.9%); $\nu_{max.}$ (film) 3438, 1747, 1705, 1673, 1311, 1231, 1100, and 698 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.07 (3 H, t, J 7.2 Hz, CO$_2$CH$_2$C$\underline{H}_3$ hydrate), 1.32 (3 H, t, J 7.2 Hz, CO$_2$CH$_2$C$\underline{H}_3$ keto), 3.78 (2 H, s, C$\underline{H}_2$Ph keto), 4.19 (2 H, s, C$\underline{H}_2$Ph hydrate), 4.20 (2 H, q, J 7.2 Hz, CO$_2$C$\underline{H}_2$ hydrate), 4.39 (2 H, q, J 7.2 Hz, CO$_2$C$\underline{H}_2$ keto), 5.29 (2 H, br, O$\underline{H}$ hydrate), 7.12-7.37 (5 H, m, CH$_2$P$\underline{h}$), 7.38-7.57 (3 H, m), and 7.95-8.06 (1 H, m); m/z (150°C) 328 ($\underline{M}^+$, 1%), 282 (1), 255 (1), 237 (1), 227 (58), and 91 (100).

Ethyl 4-[(2-Methoxycarbonylphenyl)thio]-3-oxobutanoate (279).

Triethylamine (0.18 ml, 1.30 mmol) was added dropwise to a stirred solution of ethyl 2-mercaptobenzoate (182 mg, 1.08 mmol) and ethyl 4-chloroacetoacetate (0.155 ml, 1.14 ml) in DMF (3 ml), to give an immediate exothermic reaction and precipitation of a white solid. After 1 h, the reaction mixture was subjected to aqueous work-up and chromatography to give the title compound (279) (308 mg, 96%) as colourless crystals, m.p. 52-53°C; (Found: C, 56.4; H, 5.4. $C_{14}H_{16}O_5S$ requires C, 56.7; H, 5.4%); $\nu_{max.}$ (melt) 1744, 1713, 1280, 1255, 1029, and 745 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.24 (3 H, t, J 6.9 Hz, CH$_2$C$\underline{H}_3$), 3.66 (2 H, s, SC$\underline{H}_2$), 3.88 (2 H, s, O$_2$CC$\underline{H}_2$), 3.92 (3 H, s, CO$_2$C$\underline{H}_3$), 4.16 (2 H, q, J 6.9 Hz, CO$_2$C$\underline{H}_2$), 7.21 (1 H, dt, J 7.5, 0.5 Hz), 7.29 (1 H, dd, J 7.7, 0.5 Hz), 7.41-7.51 (1 H, m), 8.00 (1 H, dd, J 8.0, 1.5 Hz); m/z (150°C) 296 ($\underline{M}^+$, 10%), 224 (33), 181 (47), 150 (42), 45 (100).

Ethyl 2-Diazo-4-[(2-methoxycarbonylphenyl)thio]-3-oxobutanoate (280).

Triethylamine (0.154 ml, 1.10 mmol) was added dropwise to a solution of tosyl azide (216 mg, 1.10 mmol) and (279) (295 mg, 0.997 mmol) in acetonitrile (3 ml) at -10°C, to give an immediate precipitate. After 0.25 h, the reaction mixture was allowed to warm to 4°C and stirred for 12 h. The solvent was evaporated, dichloromethane added and the organic phase washed with saturated sodium bicarbonate solution and brine. The dichloromethane was evaporated and the crude product purified by chromatography to give the title compound (280) (142 mg, 44%) as colourless

crystals, m.p. 105-110°C (dec.); (Found: $\underline{M}^+$, 322.0622. $C_{14}H_{14}N_2O_5S$ requires $\underline{M}$, 322.0623); $\nu_{max.}$ (Nujol) 2138, 1712, 1651, 1328, 1283, 1252, and 744 cm^{-1}; δ_H (270 MHz; CDCl$_3$) 1.33 (3 H,t, J 7.1 Hz, CH$_2$C$\underline{H}_3$), 3.91 (3 H, s, CO$_2$C$\underline{H}_3$), 4.25 (2 H, s, SC$\underline{H}_2$), 4.35 (2 H, q, J 7.1 Hz, CO$_2$C$\underline{H}_2$), 7.20 (1 H, dt, J 7.0, 1 Hz), 7.45 (1 H, dt, J 7.0, 1 Hz), 7.55 (1 H, dd, J 7.0, 1 Hz), and 7.95 (1 H, dd, J 7.3 Hz); m/z (100°C) 322 ($\underline{M}^+$, 29%), 294 (22), 265 (12), 235 (14), 219 (16), 181 (31), 168 (32), 136 (74), and 45 (100).

Ethyl 2-Diazo-4-[(2-methoxycarbonylphenyl)sulphinyl]-3-oxobutanoate (281).
m-CPBA (61 mg, 0.35 mmol) was added to a solution of (280) (95 mg, 0.295 mmol) in dichloromethane (10 ml) at -10°C over 0.5 h. After 0.2 h, 10% sodium metabisulphite was added. Work-up and purification gave the title compound (281) (93 mg, 93%) as a viscous oil; (Found: C, 49.5; H, 4.1; N, 8.4. $C_{14}H_{14}N_2O_6S$ requires C, 49.7; H, 4.2; N, 8.3%); $\nu_{max.}$ (film) 2139, 1713, 1651, 1396, 1328, 1289, and 1027 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.27 (3 H, t, J 7.0 Hz, CH$_2$C$\underline{H}_3$), 3.92 (3 H, s, CO$_2$C$\underline{H}_3$), 4.23 (2 H, q, J 7.0 Hz, CO$_2$C$\underline{H}_2$), 4.35 (1 H, d, J 14.3 Hz, SC$\underline{H}_2$), 4.62 (1 H, d, J 14.6 Hz, SC$\underline{H}_2$), 7.58 (1 H, dt, J 7.5, 1.3 Hz), 7.81 (1 H, dt, J 7.8, 1.3 Hz), 8.07 (1 H, dd, J 7.5, 1.1 Hz), and 8.27 (1 H, dd, J 8.0, 1.1 Hz); m/z (100°C) 338 ($\underline{M}^+$, 1%), 310 (3), 293 (3), 262 (2), 209 (15), 183 (100), 167 (36), 152 (81), 139 (56).

Ethyl 4-[(2-Methoxycarbonylphenyl)thio]-2,3-dioxobutanoate [enol form] (282).
Dirhodium tetraacetate (2 mg) was added to a solution of (281) (68 mg, 0.20 mmol) in benzene (30 ml) which had been rapidly heated to reflux. After 5 minutes at reflux, the yellow coloured solution was cooled, evaporated, dichloromethane (5 ml) added and the catalyst removed by filtration through Celite. The filtrate was evaporated, and the residue recrystallized to give the title compound (282) (32 mg, 51%) as yellow crystals, m.p. 113-117°C (benzene/hexane); (Found: $\underline{M}^+$, 310.0506. $C_{14}H_{14}O_6S$ requires $\underline{M}$, 310.0511); $\nu_{max.}$ (Nujol) 3387, 1715, 1646, 1578, 1562, 1280, 1258, 1167. and 1048 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.39 (3 H, J 7.1 Hz, CH$_2$C$\underline{H}_3$), 3.95 (3 H, s, CO$_2$C$\underline{H}_3$), 4.37 (2 H, q, J 7.1 Hz, CO$_2$C$\underline{H}_2$), 6.50 (1 H, d, J 2.0 Hz, SCHCO$\underline{H}$ enol), 7.37 (1 H, ddd, J 7.8, 5.2, 2.0 Hz, ArH), 7.56 (1 H, dt, J 8.0, 1.5 Hz, ArH), 7.59 (1 H, dd, J 7.8, 1.7 Hz, ArH), 7.62 (1 H, d, J 1.7 Hz, C$\underline{H}$SAr enol), and 7.97 (1 H, dd, J 7.0, 1.5 Hz, ArH); m/z

(150°C) 310 ($\underline{M}^+$, 54%), 279 (4), 209 (24), 181 (100), 167 (45), 136 (26),and 45 (86).

Ethyl 3-(t-Butyldimethylsiloxy)-4-[(2-methoxycarbonylphenyl)thio]-2-oxobut-3-enoate (283).

Triethylamine (10 μl, 71 μmol) and t butyldimethylsilyl trifluoromethanesulphonate (15.1 μl, 66μmol) were added to a solution of (282) (17.0 mg, 55 μmol) in THF (1ml) and the solution stirred for 6 h at room temperature, before evaporation of the solvent, and rapid chromatography of the residue on Florisil to give the title compound (283) (16 mg, 69%) as a yellow oil; (Found: $\underline{M}^+$, 409.1141. $C_{20}H_{28}O_6SSi$ - CH_3 requires $\underline{M}$, 409.1141); $\nu_{max.}$(film) 1724, 1666, 1557, 1354, 1288, 1256, and, 1061 cm^{-1}; δ_H ¸70 MHz; $CDCl_3$) 0.25 (6 H,s), 1.03 (9 H,. s), 1.36 (3 H, t, $\underline{J}$ 7.0 Hz, $CH_2C\underline{H}_3$), 3.93 (3 H, s, $CO_2C\underline{H}_3$), 4.33 (2 H, q, $\underline{J}$ 7.0 Hz, $CO_2C\underline{H}_2$), 7.30-7.40 (1 H, m), 7.48-7.63 (3 H, m), and 7.94 (1 H, d, $\underline{J}$ 7.0 Hz); m/z (130°C) 424 ($\underline{M}^+$, 1%), 409 (3), 393 (1), 367 (100), 235 (30), 167 (46), 136 (45), 73 (44).

Ethyl 4-Chloro-2-diazo-3-oxobutanoate (284).

Triethylamine (1.02 ml, 7.61 mmol) was added dropwise over 0.2 h to a solution of tosyl azide (1.50 g, 7.61 mmol) and 4-chloroacetoacetate (1.20 g, 7.25 mmol) in acetonitrile at -10°C. The reaction mixture was stirred at -10°C for 12 h and then water was added. The aqueous solution was extracted with dichloromethane, and the organic phase was dried over magnesium sulphate and ₂vaporated. The residue was purified by chromatography on silica gel to give the title compound (284) (1.27 g, 92%) as a yellow oil; (Found: $\underline{M}^+$, 190.0141. $C_6H_7ClN_2O_3$ $\underline{M}$, requires 190.0145); $\nu_{max.}$ (film) 2142, 1714, 1671, 1337, 1293, 1216, 1029, and 745 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.32 (3 H, t, $\underline{J}$ 7.0 Hz, $CH_2C\underline{H}_3$), 4.30 (2 H, q, $CO_2C\underline{H}_2$), and 4.60 (2 H, s, $C\underline{H}_2Cl$); m/z (150°C) 190 (M^+, 13%), 155 (12), 141 (26), 134 (11), and 91 (20).

Ethyl 2-Diazo-4-(2-hydroxyethyl)thio-3-oxobutanoate (285).

2-Mercaptoethanol (0.142 ml, 2.02 mmol) was added dropwise to a solution of triethylamine (0.280 ml, 2.02 mmol) and (284) (350 mg, 1.84 mmol) in DMF (5

ml) at room temperature . A precipitate rapidly formed. After 2 h work-up, and chromatography of the residue gave the title compound (285) (395 mg, 93%) as an oil; (Found: $\underline{M}^+$, 232.0519. $C_8H_{12}N_2O_4S$ requires $\underline{M}$, 232.0518); $v_{max.}$ (film) 3417, 2137, 1714, 1646, 1327, 1178, and 1046 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.32 (3 H, t, $\underline{J}$ 7.0 Hz, CH$_2$C$\underline{H}_3$), 2.28 (1H, br, O$\underline{H}$), 2.76 (2 H, t $\underline{J}$ 6.9 Hz, C$\underline{H}_2$S), 3.75 (2 H, t $\underline{J}$ 6.9 Hz, C$\underline{H}_2$O), 3.76 (2 H, s, C$\underline{H}_2$CO), and 4.29 (2 H, q, $\underline{J}$ 7.0 Hz, CO$_2$C$\underline{H}_2$); m/z (100°C) 232 ($\underline{M}^+$, 33%), 214 (26), 187 (5), 159 (15), 127 (37), 99 (37), 86 (49), and 61 (100).

Ethyl 2-Diazo-4-(2-hydroxyethyl)sulphonyl-3-oxobutanoate (286).

m-CPBA (0.31 g, 1.80 mmol) was added over 5 minutes to a solution of (285) (380 mg, 1.64 mmol) in dichloromethane (10 ml) at-20°C. The reaction mixture was allowed to warm to 25°C over 0.5 h. TLC showed a very polar component. More m-CPBA (0.17 g, 1.0 mmol) was added over 1 minute at 25°C and the reaction mixture stirred for 0.25 h. Water was added and the mixture extracted with dichloromethane (x3). The combined organic phase was washed with 5% sodium bicarbonate (x3), dried, evaporated, and the residue purified by chromatography on silica gel to give the title compound (286) (122 mg, 28%) as a viscous oil; (Found: $\underline{M}^+$, 236.0357. $C_8H_{12}N_2O_6S$ - N$_2$ requires $\underline{M}$, 236.0355); $v_{max.}$ (film) 3524, 2147, 1714, 1651, 1375, 1320, 1121, and 1034 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.35 (3 H, t, $\underline{J}$ 7.1 Hz, CH$_2$C$\underline{H}_3$), 1.80 (1H, br, OH), 3.48 (2 H, t, $\underline{J}$ 5.2 Hz, CH$_2$C$\underline{H}_2$S), 4.15 (2 H, t, $\underline{J}$ 5.1 Hz, C$\underline{H}_2$O), 4.35 (2 H, q, $\underline{J}$ 7.1 Hz, CO$_2$C$\underline{H}_2$), and 4.84 (2 H, s, COC$\underline{H}_2$S); m/z (120°C) 236 ($\underline{M}^+$-N$_2$, 27%), 226 (2), 208 (3), 190 (20), 144 (15), 117 (46), 84 (75), and 49 (100). No sulphoxide was isolated.

Ethyl 6-Oxo-[1,4]thiaoxepan-1,1-dioxide-5-carboxylate (287).

A solution of (286) (110 mg, 0.417 mmol) in benzene (9 ml) and dichloromethane (2 ml) was rapidly heated to reflux. After 2 minutes at reflux the reaction mixture was cooled, evaporated and the residue purified by chromatography to give the title compound (287) (19 mg, 19%) as a solid, m.p. 73-77°C; (Found: $\underline{M}^+$, 236.0357. $C_8H_{12}O_6S$ requires $\underline{M}$, 236.0355); $v_{max.}$ (melt) 3400, 1752, 1732, 1667, 1628, 1329, 1303, 1271, 1198, and 1129 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.30 (3 H, t, $\underline{J}$ 6.9 Hz, CH$_2$C$\underline{H}_3$, keto), 1.36 (3 H, t, $\underline{J}$ 6.9 Hz, CH$_2$C$\underline{H}_3$, enol), 3.30 (1 H,

approx d, J 14.5 Hz, CH$_2$CH$_2$S, keto), 3.53 (2 H, approx t, J 5.1 Hz, CH$_2$CH$_2$S, enol), 3.79 (1 H, ddd, J 14.5, 10.4, 3.5 Hz, CH$_2$CH$_2$S, keto), 3.98 (1 H, dd, J 13.1, 2.9 Hz, CH$_2$O, keto), 4.10 (1 H, ddd, J 13.1, 10.9, 1.5 Hz, CH$_2$O, keto), 4.17 (2 H, s, SCH$_2$CO, enol), 4.21-4.39 (2+2 H, m, CO$_2$CH$_2$ keto/enol, and CH$_2$O enol), 4.63 (1 H, dt, J 13.2, 3.3 Hz, SCH$_2$CO, keto), 4.73 (1 H, s, CHCO$_2$, keto), 4.78 (1 H, d, J 13.2 Hz, SCH$_2$CO, keto), and 10.73 (1 H, s, OH, enol); ca. 90% enol; m/z (100°C) 236 (M^+, 16%), 208 (2), 190 (12), 166 (11), 144 (9), 135 (16), 122 (16), 107 (12), 99 (19), 84 (79), and 49 (100).

Ethyl 3-oxo-2-allylthiane-1-oxide-2-carboxylate (288).

A solution of (238) (57.5 mg, 0.225 mmol) in dichloromethane (2 ml) was treated with mCPBA (58 mg) at 15°C. The reaction mixture was subjected to reductive work-up and chromatographic purification, to give the title compound (288) as a viscous oil (38 mg, 62%), b.p. 130°C at 0.4 mmHg; (Found: C, 54.1; H, 6.7. C$_{11}$H$_{16}$O$_4$S requires C, 54.1; H, 6.6%); $v_{max.}$ (film) 1728, 1713, 1641, 1299, 1219, and 1054 cm^{-1}; δ_H (270 MHz; CDCl$_3$) 1.25 (3 H, t, J 6.0 Hz), 2.20-2.34 (1 H, m), 2.46-2.66 (2 H, m), 2.70-3.00 (3 H, m), 3.05-3.29 (2 H, m), 4.23 (2 H, dq, J 6.0, 2.0 Hz), 5.12-5.29 (2 H, m), and 5.65-5.85 (1 H, m); m/z (140°C) 244 (M^+, 74%), 228 (2), 216 (6), 198 (25), 187 (7), 181 (57), 176 (34), 171 (7), 118 (54), 90 (92), and 41 (100).

Ethyl 3-Hydroxybenzo[b]thiophene-2-carboxylate (289).

A solution of (278a) (150 mg, 0.45 mmol) in ethanol (100 ml) under nitrogen was irradiated (254 nm) for 1.25 h. The solvent was evaporated and the residue purified by chromatography to give the title compound (289) (31 mg, 31%) as low melting crystals, m.p. 52-55°C, lit.[99] m.p. 74°C; $v_{max.}$ (melt) 3113, 1715, 1658, 1577, 1536, 1401, 1378, 1342, 1307, 1237, 1148, 758, and 733 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.42 (3 H, t, J 7.0 Hz, CH$_2$CH$_3$), 4.43 (2 H, q, J 7.0 Hz. CH$_2$CH$_3$), 7.40 (1 H, dt, J 7.1, 1.5 Hz). 7.50 (1 H. dt. J 7.3. 1.5 Hz), 7.74 (1 H, approx d, J 8.1 Hz), 7.94 (1 H, approx d, J 6.8 Hz), and 10.20 (1 H, br, OH); m/z (100°C) 222 (M^+, 33), 176 (100), 148 (2), 120 (25), 104 (6), and 77 (7).

Ethyl 3-Acetoxybenzo[b]thiophene-2-carboxylate (290).

Acetic anhydride (7.4 µl, 78 µmol) and pyridine (26 µl, 0.30 mmol) were added to a solution of (289) (14.5 mg, 65 µmol) in dichloromethane (0.5 ml). The solution was stirred for 12 h and evaporated under high vacuum. The crude product was recrystallized to give the title compound (290) as colourless crystals, m.p. 104-105°C, lit.[100] m.p. 105°C; $\nu_{max.}$ (Nujol) 1706, 1535, 1280, 1249, 1186, 1061, and 737 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 1.38 (3 H, t, J 7.0 Hz, CH$_2$CH$_3$), 2.47 (3 H, s, COMe), 4.36 (2 H, q, J 7.0 Hz, CH$_2$CH$_3$), 7.42 (1 H, m), 7.50 (1 H, dt, J 7.5, 1.5 Hz), 7.71 (1 H, dt, J 8.5, 1.1 Hz), and 7.80 (1 H, m); m/z (100°C) 264 (M$^+$, 6%), 222 (51), 176 (100), 120 (16), 104 (5), 76 (5), and 43 (13).

2,3-Dihydro-3-oxo-1-phenylbenzo[b]thiophene-1-oxide-2-carboxylic acid , inner salt (294).

A solution of potassium hydroxide (0.38 g, 6.8 mmol) in water (5 ml) was added to a solution of (277a) (215 mg, 0.684 mmol) in ethanol (8 ml) and the solution stirred at room temperature for 15 h, and then heated at reflux for 1 h. Work-up and recrystallization of the crude product gave the title compound (294) (114 mg, 58%) as colourless crystals, m.p. 174-178°C (dec.), (ethyl acetate/ methanol); (Found: C, 62.7; H, 3.6. C$_{15}$H$_{10}$O$_4$S requires C, 62.9; H, 3.5%); $\nu_{max.}$ (Nujol) 3400-2200, 1720, 1689, 1619, 1448, 1382, 1219, and 1110 cm^{-1}; δ_H (250MHz; d^6 DMSO) 7.67-7.76 (2 H, m), 7.77-7.88 (2 H, m), 7.90-7.97 (2 H, m), 7.97-8.05 (3 H, m), and 10.92 (1 H, br, CO$_2$H); m/z (150°C) 286 (M$^+$, 16%), 242 (33), 213 (8), 197 (19), 184 (9), 165 (28), 136 (100), 108 (22), 77 (32), and 44 (58).

2,3-Dihydro-3-oxo-1-phenylbenzo[b]thiophene-1-oxide, inner salt (295).

A solution of (294) (114 mg, 0.40 mmol) and acetic acid (0.2 ml) in xylene (7 ml) was heated at reflux for 1.25 h. The solvent was evaporated, and the residue subjected to chromatography on silica gel to give the title compound (295) (85 mg, 88%) as yellow crystals, m.p. 165-167°C (ether/hexane); (Found: C, 69.2; H, 4.1. C$_{14}$H$_{10}$O$_2$S requires C, 69.4; H, 4.1%); $\nu_{max.}$ (Nujol) 1631, 1605, 1510, 1277, and 1224 cm^{-1}; δ_H (250 MHz; CDCl$_3$) 4.77 (1 H, br, SCH), 7.50-7.75 (6 H, m), 7.87-7.94 (1 H, m), and 8.00-8.08 (2 H, m); m/z (100°C) 242 (M$^+$, 41%), 213 (47), 184 (20), 165 (19), 136 (100), 108 (21), and 77 (22).
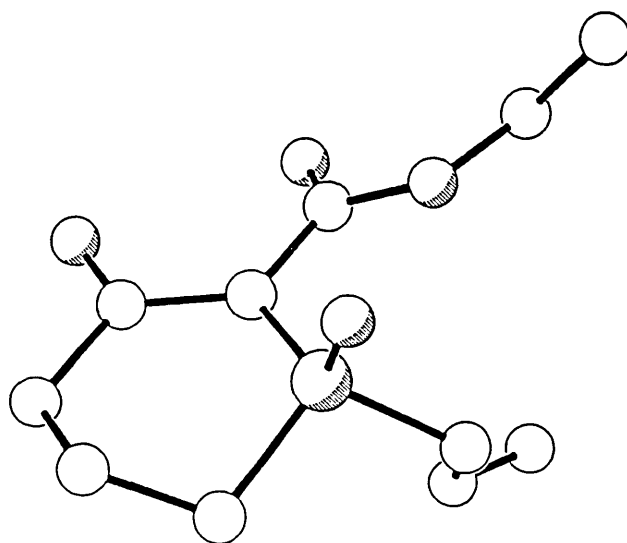
Appendix

Figure 2.   X-ray crystal structure of compound (270)
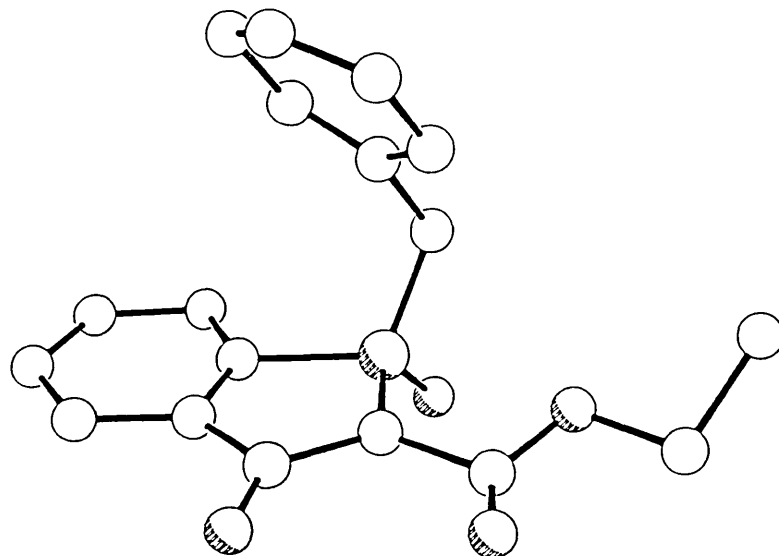

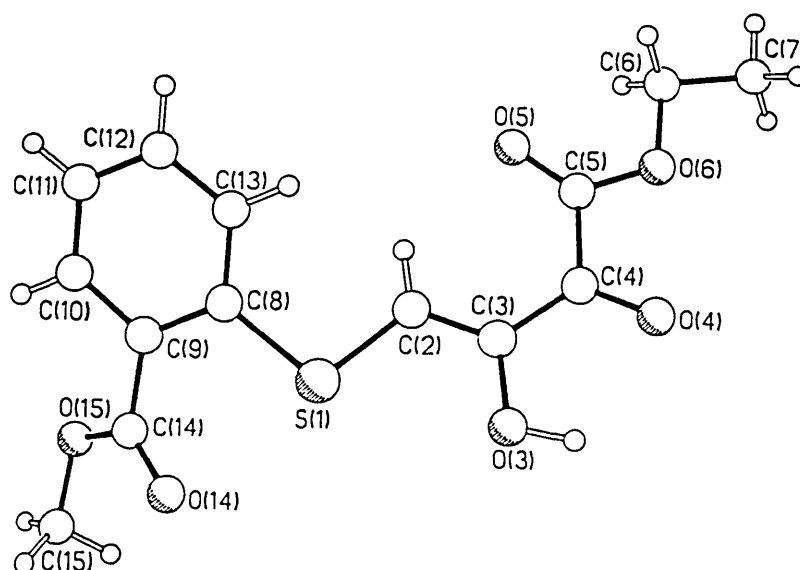Figure 3.   X-ray crystal structure of compound (278a)

<u>Figure 4.   X-ray crystal structure of compound (282)</u>

<u>Crystal Data for Figures (2), (3), and (4),</u>

Compound (270): crystal data: $C_{11}H_{16}O_4S$, $\underline{M}$ = 244.3, monoclinic, $\underline{a}$ = 7.334 (3), $\underline{b}$ = 7.770 (3), $\underline{c}$ = 20.298 (5) Å, β = 94.19 (3)$^{\circ}$, $\underline{U}$ = 1154 Å^3, space group $\underline{P}2_1/\underline{n}$, $\underline{Z}$ = 4, $\underline{D}_c$ = 1.41 gcm^{-3}, Cu radiation, λ = 1.54178 Å , μ(Cu-K$_{\alpha}$) = 24 cm^{-1}, $\underline{F}$(000) = 520. Compound (278a): crystal data: $C_{18}H_{16}O_4S$, $\underline{M}$ = 328.4, triclinic, $\underline{a}$ = 7.359 (3), $\underline{b}$ = 8.617 (4), $\underline{c}$ = 13.445 (6) Å, α = 97.90 (4), β = 95.97 (4), γ = 105.36 (3)$^{\circ}$, $\underline{U}$ = 806 Å^3, space group $\underline{P}1$, $\underline{Z}$ = 2, $\underline{D}_c$ = 1.35 gcm^{-3}, Cu radiation, λ = 1.54178 Å , μ(Cu-K$_{\alpha}$) = 19 cm^{-1}, $\underline{F}$(000) = 344. Compound (282): crystal data: $C_{14}H_{14}O_6S$, $\underline{M}$ = 310.3, monoclinic, $\underline{a}$ = 15.906 (3), $\underline{b}$ = 11.106 (2), $\underline{c}$ = 16.514 (2) Å, β = 96.76 (2)$^{\circ}$, $\underline{U}$ = 2897 Å^3, space group $\underline{P}2_1/\underline{a}$, $\underline{Z}$ = 8 (two crystallographically independent molecules), $\underline{D}_c$ = 1.42 gcm^{-3}, Cu radiation, λ = 1.54178 Å , μ(Cu-K$_{\alpha}$) = 22 cm^{-1}, $\underline{F}$(000) = 1296. All three structures were solved by direct methods and refined anisotropically to give for (270) R = 0.044, R_w = 0.054, for (278a) R = 0.050, R_w = 0.062, and for (282) R = 0.040, R_w = 0.042 for respectively 1500, 2084, and 2540 independent observed reflections [$|F_o| \geq 3\sigma$ ($|F_o|$), $\theta \leq$ 58, 58, and 50°]. Data were measured on a Nicolet R3m diffractometer with Cu-K_{α} radiation (graphite monochromator) using ω-scans. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.

References

1. D. S. Wulfman, G. Linstrumelle, and C. F. Cooper, "The Chemistry of Diazonium and Diazo Groups", S. Patai (Ed.), Vol. 2, Chap. 18, Wiley, New York, 1978.

2. S. D. Burke and P. A. Grieco, *Org. React.* 1979, 26, 361.

3. R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert, P. Teyssie, *Tetrahedron Lett.*, 1973, 14, 2233.

4. M. Regitz, *Synthesis*, 1972, 351.

5. G. Maas, *Top. Curr. Chem.*, 1987, 137, 75.

6. M. P. Doyle, *Chem. Rev.*, 1986, 86, 919.

7. S. Kulkowit and A. McKervey, *J. Chem. Soc., Chem. Commun.*, 1979, 616.

8. M. P. Moyer, P. L. Feldman, and H. Rapoport, *J. Org. Chem.*, 1985, 50, 5223.

9. J. C. Heslin and C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1417.

10. E. J. Roskamp and C. R. Johnson, *J. Am. Chem. Soc.*, 1986, 108, 6062.

11. M. C. Pirrung and J. A. Werner, *J. Am. Chem. Soc.*, 1986, 108, 6060.

12. E. A. Shapiro, T. N. Romanova, I. E. Dolgii, O. M. Nevedov, *Akad. Nauk SSSR, Ser . Khim.*, 1983, 1933.

13. G. Lawton, C. J. Moody, and C. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1987, 899.

14. E. C. Taylor and H. M. L. Davies, *J. Org. Chem.*, 1984, 49, 113.

15. R. M. Williams and B. H. Lee, *J. Am. Chem. Soc*, 1986, 108, 6431.

16. T. Kametani, H. Yukawa, and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1988, 833.

17. T. Kametani, K. Kawamura, and T. Honda, *J. Am. Chem. Soc*, 1987, 109, 3010.

18. K. Prassad, G. Schulz, C. P. Mak, H. Hamberger, and P. Stutz, *Heterocycles*, 1981, 16, 1305.

19. S. Oida, A. Yoshida, and E. Ohki, *Heterocycles*, 1980, 14, 1999.

20. C. P. Mak, K. Baumann, F. Mayerl, C. Mayerl, and H. Fliri, *Heterocycles*, 1982, 19, 1647.

21. H.M. L. Davies and L. V. T. Cristo, *Tetrahredron Lett.*, 1987, 28, 371.

22. T. Kametani, K. Kawamura, M. Tsubuki, and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1988, 193.

23. H. Fliri, C. P. Mak, K. Prassad, G. Schulz, and P. Stutz, *Heterocycles*, 1983, **20**, 205.

24. K. Konda and I. Ojima, *J. Chem. Soc., Chem. Commun.*, 1972, 860.

25. V. Barre and D. Ugen, *Tetrahredron Lett.*, 1987, **28**, 6045.

26. T. Ibata, J. Toyoda, M. Sawada, Y. Takai, and T. Tanaka, *Tetrahredron Lett.*, 1988, **29**, 317.

27. A. Padwa, S. P. Carter, and H. Nimmesgern, *J. Org. Chem.*, 1986, **51**, 1157.

28. M. Maier and K. Evertz, *Tetrahredron Lett.*, 1988, **29**, 1677.

29. P. Yates and S. Danishefsky, *J. Am. Chem. Soc*, 1962, **84**, 879.

30. M. Regitz and J. Ruter, *Chem. Ber.*, 1969, **102**, 3877.

31. A. K. Chakraborti, J. K. Ray, K. K. Kundu, S. Chakrabarty, D. Mukherjee, and U. R. Ghatak, *J. Chem. Soc., Perkin Trans. 1*, 1984, 261.

32. D. F. Taber and E. H. Petty, *J. Org. Chem.*, 1982, **47**, 4808.

33. E. Wenkert, L. L. Davis, B. L. Mylari, M. F. Solomon, R. R. da Silva, S. Shulman, R. J. Warnet, P. Ceccherelli, M. Curini, and R. Pellicciari, *J. Org. Chem*, 1982, **47**, 3242.

34. D. F. Taber and R. E. Ruckle, *J. Am. Chem. Soc*, 1986, **108**, 7686.

35. G. Stork and K. Nakatani, *Tetrahedron Lett.*, 1988, **29**, 2283.

36. D. F. Taber and R. E. Ruckle, *Tetrahedron Lett.*, 1985, **26**, 3059.

37. D. F. Taber, K. Raman, and M. D. Gaul, *J. Org. Chem.*, 1987, **52**, 28.

38. D. F. Taber and J. L. Schuchardt, *J. Am. Chem. Soc*, 1985, **107**, 5289.

39. B. Corbel, D. Hernot, J. P. Haelters, and G. Sturtz, *Tetrahedron Lett.*, 1987, **28**, 6605.

40. H. J. Monteiro, *Tetrahedron Lett.*, 1987, **28**, 3459.

41. D. E. Cane and P. J. Thomas, *J. Am. Chem. Soc*, 1984, **106**, 5295.

42. R. J. Ponsford and R. Southgate, *J. Chem. Soc.. Chem. Commun.*, 1979, 846.

43. P. Brown and R. Southgate, *Tetrahedron Lett..* 1986, **27**, 247.

44. M. P. Doyle, M. S. Shanklin, S. M. Oon, H. Q. Pho, F. R. van der Heide, and W. R. Veal, *J. Org. Chem.*, 1988, **53**, 3384.

45. J. C. Heslin, Ph. D., University of London. 1987.

46. "Comprehensive Heterocyclic Chemistry", Vol. 7, W. Lwowski (Ed.), Pergamon Press, 1984.

47. D. Huckle, I. M. Lockhart, and M. Wright, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2425.

48. P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.*, 1959, 1998.

49. K. C. Nicolaou, M. E. Duggan, and C. K. Hwang, *J. Am. Chem. Soc*, 1986, 108, 2468.

50. R. C. Cookson and N. J. Liverton, *J. Chem. Soc., Perkin Trans. 1*, 1985, 1589.

51. W. P. Jackson, S. V. Ley, and J. A. Morton, *Tetrahedron Lett.*, 1981, 22, 2601.

52. M. Mori, N. Kanda, Y. Ban, and K. Aoe, *J. Chem. Soc., Chem. Commun.*, 1988, 12.

53. S. L. Schreiber and S. E. Kelly, *Tetrahedron Lett.*, 1984, 25, 1757.

54. G. S. Cockerill and P. Kocienski, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2093.

55. L. E. Overman and A. S. Thomas, *J. Am. Chem. Soc*, 1988, 110, 2248.

56. C. Flann, T. C. Malone, and L. E. Overman, *J. Am. Chem. Soc.*, 1987, 109, 6097.

57. K. C.Nicolaou, C. K. Hwang, M. E. Duggan, and K. Bal Reddy, *Tetrahedron Lett.*, 1987, 28, 1501.

58. R. W. Carling and A. B. Holmes, *J. Chem. Soc., Chem. Commun.*, 1986, 325.

59. E. Vedejs, *Acc. Chem. Res.*, 1984, 17, 358.

60. R. W. Carling and A. B. Holmes, *J. Chem. Soc., Chem. Commun.*, 1986, 6133.

61. R. Pelliciari and B. Natalini, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1822.

62. T. Kametani, T. Honda, A. Nakayama, Y. Sasakai, T. Mochizuki, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2228.

63. C. U. Kim, B. Luh, and R. A. Partyka, *Tetrahedron Lett.*, 1987, 28, 507.

64. E. Wenkert and C. A. McPherson, *J. Am. Chem. Soc*, 1972, 94, 8084.

65. D. A. Evans, L. K. Truesdale, and K. G. Grimm, *J. Org. Chem.*, 1976, 41, 3335.

66a. R. Pellicciari, B. Natalini, S. Cecchetti, and R. Fringuelli, *J. Chem. Soc., Perkin Trans. 1*, 1985, 493.

66b. U. Schollkopf, B. Banhidai, H. Frasnelli, R. Meyer, and H. Beckhaus, *Liebigs. Ann. Chem.*, 1974, 1767.

67. M. Regitz and A. Liedhegener, *Chem. Ber.*. 1966,99, 3128.

68. H. E. Sheffer and J. A. Moore, *J. Org. Chem.*, 1963, 28, 129.

69. G. Illuminati and L. Mandolini, *Acc.Chem. Res.*, 1981, 14, 95.

70. D. F. Taber, J. C. Almedio, and R. G. Sherill, *J. Org. Chem.*, 1986, 51, 3382.

71. G. Holt and D. K. Wall, *J. Chem. Soc. [C]*, 1966, 857.

72   M. Regitz and G. Maas, "Diazo Compounds; Properties and Synthesis", Chap.3, Academic Press, New York, 1986.

73.   J. B. Hendrickson and W. A. Wolf, *J. Org. Chem.*, 1968, 33, 3610.

74.   O. A. Kruglaya and N. S. Vyazankin, *Russ. Chem. Rev.*, 1980, 49, 357.

75.   J. R. Hawke, M. Guadliana, and K. Desai, *J. Org. Chem.*, 1982, 47, 5019.

76.   E. W. Colvin and B. J. Hamill, *J. Chem. Soc., Perkin Trans. 1*, 1977, 869.

77.   U. Schollkopf and H. U. Scholz, *Synthesis*, 1976, 271.

78.   T. Aoyama, Y. Iwamoto, and T. Shioiri,*Heterocycles*, 1987, 25, 1467.

79.   T. Aoyama, Y. Iwamoto, and T. Shioiri, *Heterocycles*, 1986, 24, 589.

80.   M. Regitz, J. Hocker, and A. Liedhegener, *Org. Synth. Coll. Vol. 5*, 179.

81.   A. L. Fridman, Y. S. Andreichikov, L. F. Gein, and V. L. Gein, *J. Org. Chem. (USSR)*, 1977, 12, 457.

82.   A. L. Fridman, Y. S. Andreichikov, L. F. Gein, and V. L. Gein, *J. Org. Chem. (USSR)*, 1978, 13, 1925.

83.   M. Regitz, A. Liedhegener, U. Eckstein, M. Martin, and W. Anschutz, *Ann.*, 1971, 748, 207.

84.   M. Martin, *Synth. Commun.*, 1983, 13, 809.

85.   K. Dietrich and R. W. Hoffmann, *Tetrahedron Lett.*, 1985, 26, 6325.

86.   A. M. van Leusen, P. Richters, and J. Strating, *Rec. Trav. Chim.*, 1966, 85, 323.

87.   J. Brennan, and I. L. Pinto, *Tetrahedron Lett.*, 1983, 24, 4731.

88.   W. Ando, *Acc. Chem. Res.*, 1977, 10, 179.

89.   "The Chemistry of the Sulphonium Group", Part 2, C. J. M. Stirling (Ed.), Chaps. 13 and 16, Wiley, New York, 1981.

90.   R. Pellicciari, M. Curini, and P. Ceccherelli, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1155.

91.   E. Vedejs, M. J. Mulins, J. M. Renga, and S. P. Singer, *Tetrahedron Lett.*, 1978, 19, 519.

92.   E. Vedejs, J. P. Hagen, B. L. Roach. and K. L. Spear, *J. Org. Chem.*, 1978, 43, 1185.

93.   J. C. Dyer and S. A. Evans, *J. Org. Chem.*, 1980, 45, 5350.

94.   W. Ando, T. Yagihara, S. Tozune, S. Nakaido, and T. Migita, *Tetrahedron Lett.*, 1969, 1979.

95.   F. Dost and J. Gosselck, *Chem. Ber.*,1972, 105, 948.

96.   E J. Corey and M. Chaykovsky, *Tetrahedron Lett.*, 1963, 169.

97.   E J. Corey and M. Chaykovsky, *J. Am. Chem. Soc*, 1964, **86**, 1640.

98.   A. Burger, M. Bernabe, P. W. Collins, *J. Med. Chem.*, 1970, **13**, 33.

99.   F. Arndt and P. Nachtwey, *Chem. Ber.*, **59**, 1073.

100. E. W. McClelland, M. J. Rose, and D. W. Stammers, *J. Chem. Soc.*, 1948, 81.

101. M. Nakagawa, J. Saegusa, M. Tonozuka, M. Obi, M.Kiuchi, T. Hino, and Y. Ban, *Org. Synth.*, 1977, **56**, 49.

102. T. Fujisawa, K. Umezu, and M. Kawashima, *Chem. Lett.*, 1984, 1795.

103. R. Huisgen and H. Ott, *Angew. Chem.*, 1958, **70**, 312.

104. J. P. Nicolle, J. F. Haman, and M. Wakselman, *Bull. Soc. Chim. Fr.*, 1977, 83.

105. W. Fraefel and V. du Vigneaud, *J. Am. Chem. Soc*, 1970, **92**, 1030.

106. "RNA Protein Synthesis", K. Moldave (Ed.), p. 627, Academic Press, New York, 1981.