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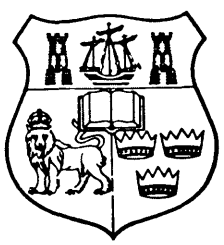
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SYNTHETIC AND STEREOCHEMICAL ASPECTS OF INTRAMOLECULAR REACTIONS OF α-DIAZOKETONES CATALYSED BY RHODIUM(II) CARBOXYLATES

by

ANITA R. MAGUIRE, B.Sc.



Being a Thesis submitted for the degree of

DOCTOR OF PHILOSOPHY

to

THE NATIONAL UNIVERSITY OF IRELAND

Based on research carried out under the direction of

Professor M.A. McKervey,
Department of Chemistry,
University College
Cork

February, 1989

To my parents

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Once a thing is known it can never be unknown.

A. Brookner

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Anita R. Maguire

ABSTRACT

Chapter 1 of this thesis is a brief introduction to the preparation and reactions of α-diazocarbonyl compounds, with particular emphasis on the areas relating to the research undertaken: C-H insertion, addition to aromatics, and oxonium ylide generation and rearrangement. A short summary of catalyst development illustrates the importance of rhodium(II) carboxylates for α-diazocarbonyl decomposition.

Chapter 2 describes intramolecular C-H insertion reactions of α-diazo-β-keto sulphones to form substituted cyclopentanones. Rhodium(II) carboxylates derived from homochiral carboxylic acids were used as catalysts in these reactions and enantioselection achieved through their use is discussed.

Chapter 3 describes intramolecular Buchner cyclisation of aryl diazoketones with emphasis on the stereochemical aspects of the cyclisation and subsequent reaction of the bicyclo[5.3.0]decatrienones produced. The partial asymmetric synthesis achieved through use of chiral rhodium(II) carboxylates as catalysts is discussed. The application of the intramolecular Buchner reaction to the synthesis of hydroazulene lactones is illustrated.

Chapter 4 demonstrates oxonium ylide formation and rearrangement in the decomposition of an α-diazoketone. The consequences of the use of chiral rhodium(II) carboxylates as catalysts are described.

Particularly significant was the discovery that rhodium(II) (S)-mandelate acts as a very efficient catalyst for α-diazoketone decompositions, in general. Moderate asymmetric induction was possible in the decomposition of α-diazoketones with chiral rhodium(II) carboxylates, with rhodium(II) (S)-mandelate being one of the more enantioselective catalysts investigated. However, the asymmetric induction obtained was very dependent on the exact structure of the α-diazoketone, the catalyst, and the nature of the reaction.

Chapter 5 contains the experimental details, and the spectral and analytical data for all new compounds reported.

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CHAPTER 1

INTRODUCTION TO α-DIAZOCARBONYL COMPOUNDS

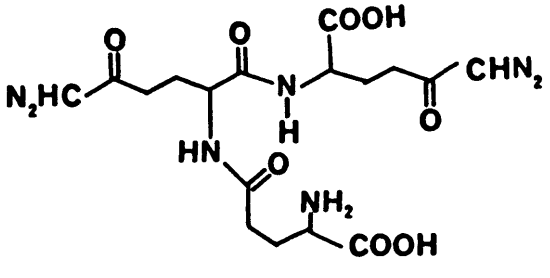
α-Diazocarbonyl compounds[1] have been used extensively in organic synthesis; their preparation from readily available starting materials is well characterised and a wide variety of chemical transformations can be achieved under mild conditions.

1.1 Synthesis of α-Diazocarbonyl Compounds

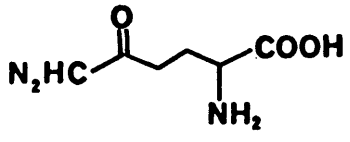
Although Curtius[2] first reported the synthesis of an α-diazocarbonyl compound in 1883 by diazotisation of glycine esters, simple diazocarbonyl compounds could not be readily prepared until the successful acylation of diazomethane with acid chlorides was reported in the late 1920s by Arndt and Eistert,[3] and by Bradley and Robinson.[4]

1.1.1. *Acylation of diazomethane*

Diazomethane acylation constitutes the most important route to acyclic terminal α-diazoketones. To ensure successful acylation a sufficient excess of diazomethane must be used to trap the hydrogen chloride liberated thus preventing chloroketone formation. A new apparatus designed for diazomethane acylation has been developed by Pettit and Nelson[5] for the synthesis of azotomycin (1), an anticancer *bis*-diazoketone.



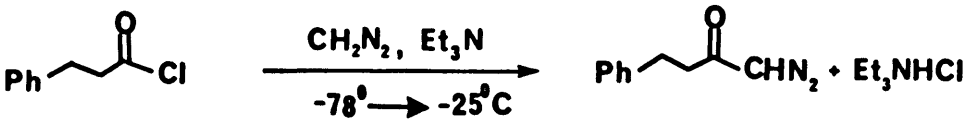
(1)



(2)

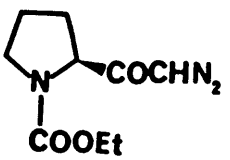
The antibiotic 6-diazo-5-oxo-L-norleucine (2) (DON)[6] has been synthesised by diazomethane acylation in very low yields (0.5-1.0% overall). The inefficiency is associated with acid chloride formation.

In the case of non-enolisable acid chlorides,[7,8] addition of 1 equivalent of triethylamine obviates the necessity for using excess diazomethane. For enolisable diazoketones, this approach is occasionally successful at low temperatures (equation 1)[9] but, in general, competitive ketene formation reduces both the yield and purity of the diazoketone.

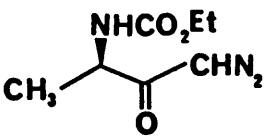


(1)

Anhydrides[10] may also be used in diazomethane acylation but result in formation of equimolar mixtures of α-diazoketone and methyl ester. In unsymmetrical anhydrides, diazomethane attack normally occurs at the more electrophilic acyl group. Consequently, treatment of the carboxylic acid with dicyclohexylcarbodiimide followed by treatment with ethereal diazomethane is a convenient route to α-diazoketones.[11] The homochiral α-diazoketones (3) and (4) derived from N-protected amino acids have been prepared in this manner.[12]



(3)

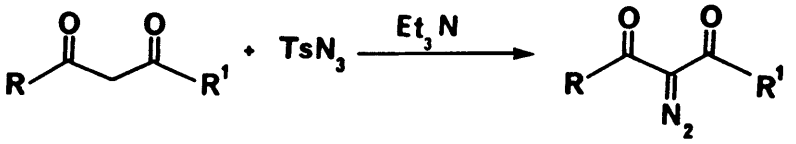


(4)

Acylation of higher diazoalkanes[13] is possible though less efficiently than of diazomethane and at least in the case of diazoethane, precise experimental conditions must be maintained for optimum yields.[14,15,16]

1.1.2. *Diazo transfer reactions*

The diazo transfer technique, developed in the late 1960s by Regitz and co-workers[17] for the preparation of cyclic α-diazoketones, has become a standard method of preparation not only of cyclic α-diazoketones but also of many acyclic systems which are difficult to prepare by alternative routes. The standard procedure involves treatment of an ester or ketone substrate bearing an α-activated methylene group with a sulphonyl azide (usually tosyl) in the presence of a base strong enough to deprotonate the substrate. Since the presence of very strong bases reduces the yield of α-diazocarbonyl product, simple carbonyl compounds are generally activated prior to diazo transfer. However, compounds such as β-diketones, malonic esters, acetoacetic esters, and β-keto sulphones have sufficiently active α-methylene protons to ensure smooth diazo transfer in the presence of a mild base such as triethylamine (equation 2).



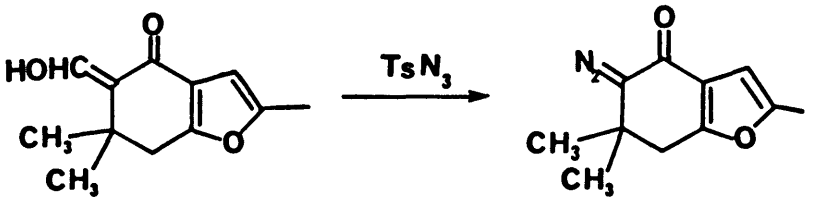
(2)

R,R^1 = alkoxy

R,R^1 = alkyl

R = alkyl, R^1 = alkoxy

Diazo transfer to some less active compounds such as benzyl ketones may be effective provided a potassium alkoxide is used as the base.[18] Recently, Rao and Nagarajan[19] have reported the successful use of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) for smooth diazo transfer, notably in the case of hindered compounds where the standard diazo transfer conditions were inefficient (equation 3).

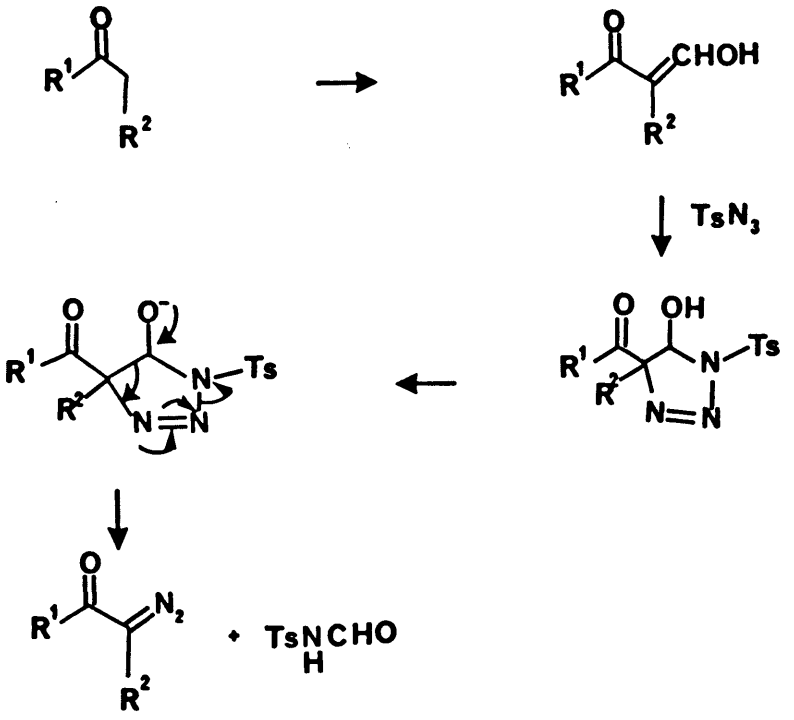


(3)

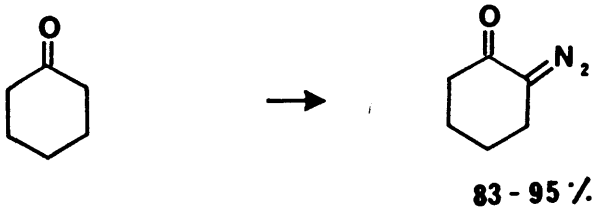
Base	
DBU	100%
Et_3N	very slow reaction

Mander and Lombardo[20] have reported diazo transfer to some unactivated cyclic ketones by replacement of tosyl azide with the more active 2,4,6-triisopropylbenzenesulphonyl azide and use of phase transfer conditions. However, in general, diazo transfer to simple ketones is carried out by a technique known as deformylating diazo transfer,[17,21] in which a strongly activating formyl group is introduced at the methylene position prior to diazo transfer and is subsequently released in the course of the transfer reaction as tosyl formamide (Scheme 1).

Equations 4[22] and 5[19] illustrate the applicability of tosyl azide diazo transfer in the synthesis of both cyclic and acyclic α-diazocarbonyl compounds.



Scheme I



83 - 95 %

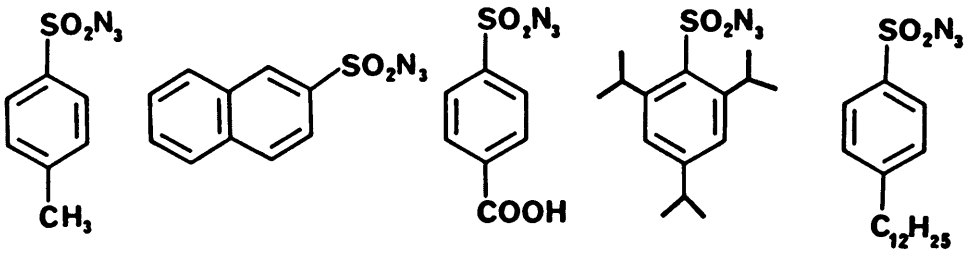
(4)[22]

$CH_2(CO_2Me)_2 \longrightarrow N_2C(CO_2Me)_2$

81 %

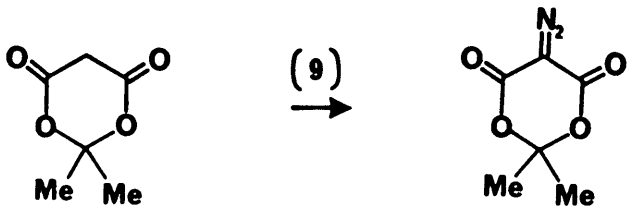
(5)[19]

Despite the widespread use of tosyl azide as a diazo donor, doubts have been raised about its safety[23] and Curphey[24] has emphasised the importance of replacement of ethanol in the preparation[25] of tosyl azide by acetone thus ensuring the isolation of a more pure product.



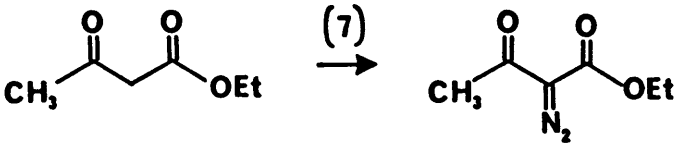
(5) (6) (7) (8) (9)

In a study[23] of various sulphonyl azides (5-9), tosyl azide (5) was found to be the most dangerous whereas *p*-dodecylbenzenesulphonyl azide (9) was the safest of the group, with a much lower risk of explosion. Equations (6) and (7) illustrate the use of some of these reagents.



63·4 %

(6)



67·4 %

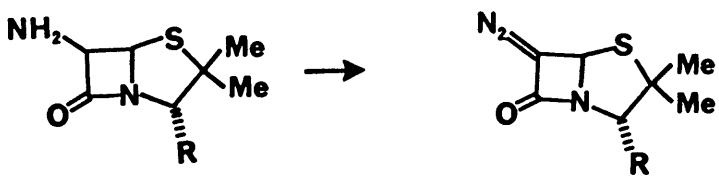
(7)

More recently, mesyl azide[26] has been reported to be a superior reagent to tosyl azide for diazo transfer. Interestingly, a polymer bound sulphonyl azide[27] has been used for diazo transfer with the advantages of easier workup and greater safety.

1.1.3. *Other routes to α-diazocarbonyl compounds*

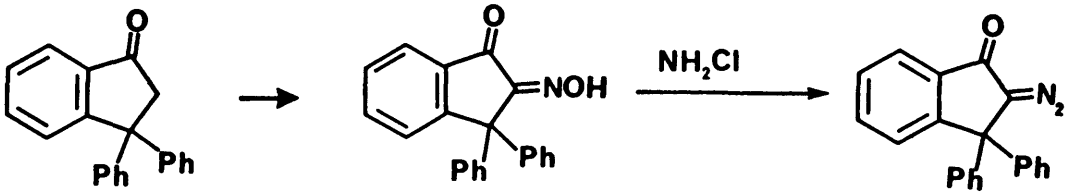
Another important method of preparation of α-diazocarbonyl compounds is diazotisation, as, for example, in the synthesis of ethyl diazoacetate (EDA)[28] and of 6-diazopenicillanates[29] from the corresponding amino compounds (equations 8 and 9 respectively).

$$NH_2CH_2CO_2Et \longrightarrow N_2CHCO_2Et \qquad (8)$$

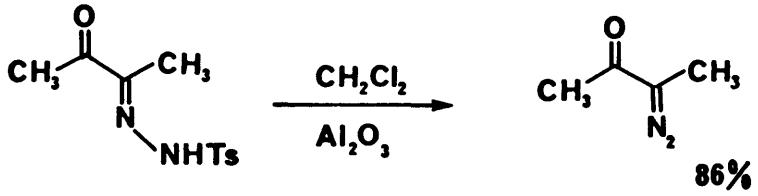


(9)

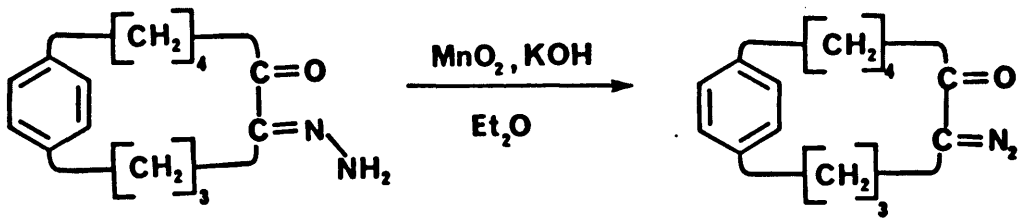
Other routes to α-diazocarbonyl compounds include the Forster reaction, which proceeds *via* initial oxime formation at the α-methylene group of a ketone followed by treatment with chloramine (equation 10);[30] the Bamford-Stevens tosylhydrazone decomposition (equation 11);[31] and dehydrogenation of hydrazones (equation 12).[32] However, the importance of these methods has diminished following the introduction of diazo-transfer methods. These reactions have been described in detail by Regitz.[33]



(10)

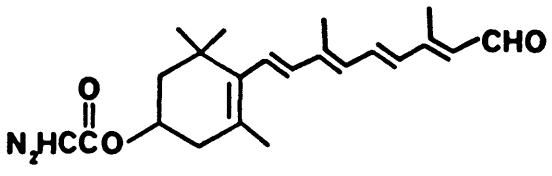


(11)

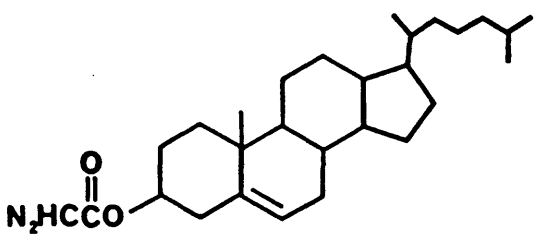


(12)

An interesting method of preparation of α-diazoesters developed by House[34] has been used in the synthesis of photoaffinity diazo esters (10)[35] and (11)[36].

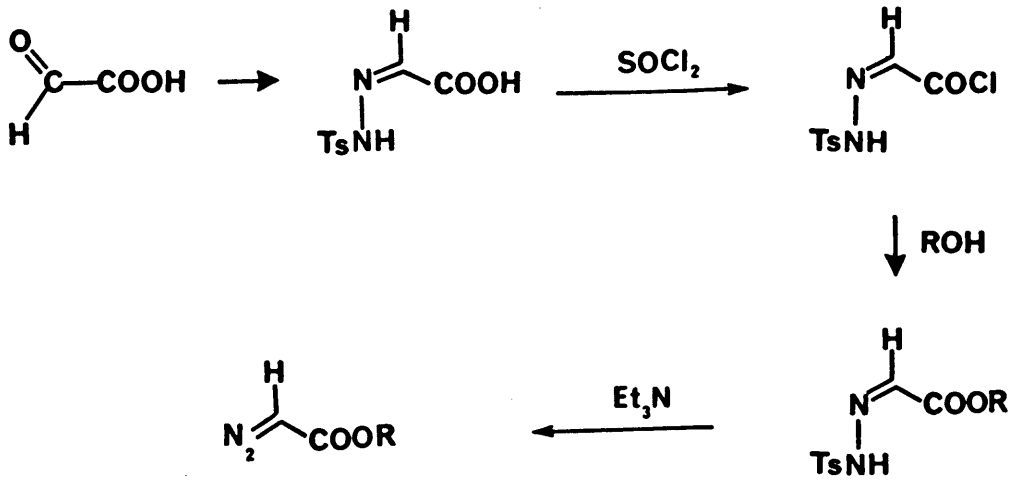


(10)



(11)

This process involves conversion of glyoxylic acid to its tosylhydrazone followed by treatment with thionyl chloride to form the acyl chloride which is then reacted with the appropriate alcohol to give the ester hydrazone. Finally the hydrazone is decomposed by treatment with triethylamine (Scheme 2).



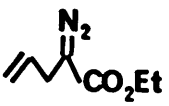
Scheme 2

1.1.4. *Substitution reactions of α-diazocarbonyl compounds*

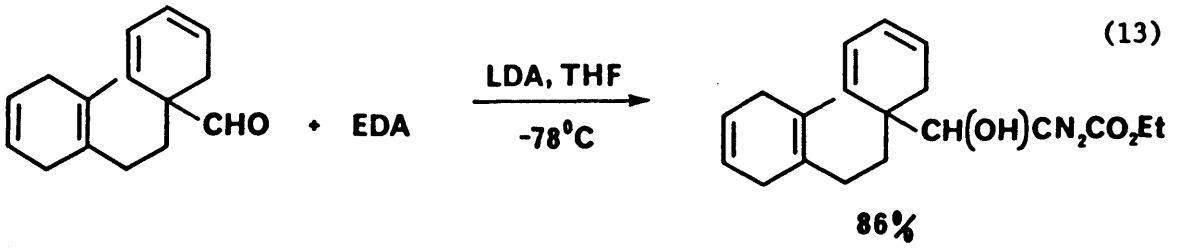
Chemical modification of the α-position of a diazocarbonyl compound[37] without loss of the diazo group can be considered an extension of the synthesis of α-diazocarbonyl compounds. In general the hydrogen atom of a terminal acyclic α-diazocarbonyl compound can be substituted by electrophilic reagents, demonstrating the stability of the diazo group under such conditions. Metallation, halogenation, nitration, and alkylation

TABLE 1

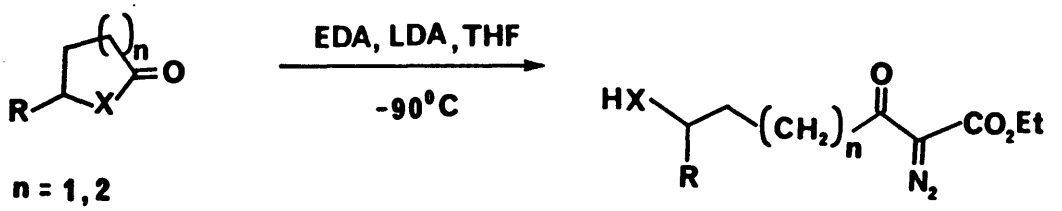
Substitution reactions of α-diazocarbonyl compounds

	Substrate	Conditions	Product	Yield %	Ref
Metallation	$PhCOCHN_2$	HgO, 20°C	$Hg(CN_2COPh)_2$	97	38
	$N_2HCCOOEt$	nBuLi, -100°C	$LiCN_2COOEt$	-	39
	$N_2HCCOOEt$	Ag_2O, ≤ 0°C	$AgCN_2COOEt$	-	40
Halogenation	$Hg(CN_2COOEt)_2$	$SOCl_2$	$ClCN_2CO_2Et$	30	41
		Br_2	$BrCN_2CO_2Et$	80-90	
		I_2	ICN_2CO_2Et	70-90	
Nitration	N_2CHCO_2Et	N_2O_5, CCl_4, -30°C	$O_2NCN_2CO_2Et$	-	42
Alkylation	$AgCN_2CO_2Et$	$H_2C{=}CH_2{-}CH_2{-}I$, Et_2O, 0°C		66	40

have been developed by Regitz:[1(c)] a few examples of these processes will suffice to demonstrate the utility of these reactions (Table 1). Reaction of metallated α-diazocarbonyl derivatives with carbonyl compounds is very useful synthetically forming α-diazo-β-hydroxycarbonyl compounds (see for example equation 13),[43] useful substrates for the preparation of 1,3-dicarbonyl compounds *via* hydride shifts, or in the case of lactones giving hydroxy-α-diazo-β-keto esters as shown in equation 14.[44]



(13)



n = 1,2
R = H,Me
X = O,S

(14)

1.2 Reactions of α-Diazocarbonyl Compounds

α-Diazocarbonyl compounds are extremely flexible in organic synthesis, their reactions generally proceeding with loss of nitrogen. The reaction pathway depends on the nature of the diazo substrate, the catalyst used (if any), the coreactants, and the reaction conditions. Reactive intermediates

include carbenes, carbenoids, ylides, and diazonium cations. The reactions of α-diazocarbonyl compounds are best classified in terms of product type, as this illustrates clearly their versatility in organic synthesis. Their most important uses are:

(i) cyclopropanation;

(ii) Wolff rearrangement;

(iii) α,α-substitution;

(iv) ylide formation;

(v) C-H insertion;

(vi) addition to aromatics;

(vii) acid catalysed cyclisations;

(viii) 1,3-dipolar cycloadditions;

(ix) 1,2-hydride and alkyl shifts;

(x) dimerisation.

The subsequent discussion will concentrate mainly on the areas of ylide formation, C-H insertion, and addition to aromatics as these are the areas investigated in the course of this work.

Generally both inter- and intramolecular processes are possible with each reaction mode. The intramolecular reactions, which are very successful in most cases, are frequently the more important processes for synthesis and, as a result, are largely responsible for the ongoing high level of interest in diazocarbonyl chemistry.

Although α-diazocarbonyl compounds may be decomposed thermally, photochemically, or by acid catalysis, decomposition using transition metals and their salts as catalysts is by far more useful and widely employed in synthesis.

1.2.1. *Catalyst development*

Metal catalysed decomposition of α-diazocarbonyl compounds has been known for over 80 years[45] and has been dominated by use of copper and its salts, notably copper bronze and copper(II) sulphate.[46] Improvements were obtained with the introduction of homogeneous copper catalysts such as $Cu(acac)_2$,[47] $CuCl.P(OR)_3$,[48] and $Cu(OTf)_2$[49] (acac = acetylacetonate, OTf = triflate), followed by other transition metals such as $Pd(OAc)_2$[50] and $Rh_6(CO)_{16}$[51] which were reported to be cyclopropanation catalysts. However, the major development in catalysis was the introduction by Teyssie[52] in the early 1970s of rhodium(II) acetate as an extremely effective catalyst for a wide variety of useful synthetic transformations involving diazocarbonyl compounds. Since their introduction, rhodium(II) carboxylates have dominated the use of catalytic decomposition of α-diazocarbonyl compounds in organic synthesis.

Metal catalysed decomposition of α-diazocarbonyl compounds is believed to proceed *via* a carbenoid intermediate.[53] Rhodium(II) carboxylates have the binuclear structure[54] shown (Fig. 1) with one vacant coordination site per metal atom (indicated in the diagram by arrows).

Complexes are readily formed with donor ligands such as nitriles and amines,[55] and it is thought that the carbene derived from the α-diazocarbonyl compound coordinates axially to the catalyst to form a carbenoid intermediate.

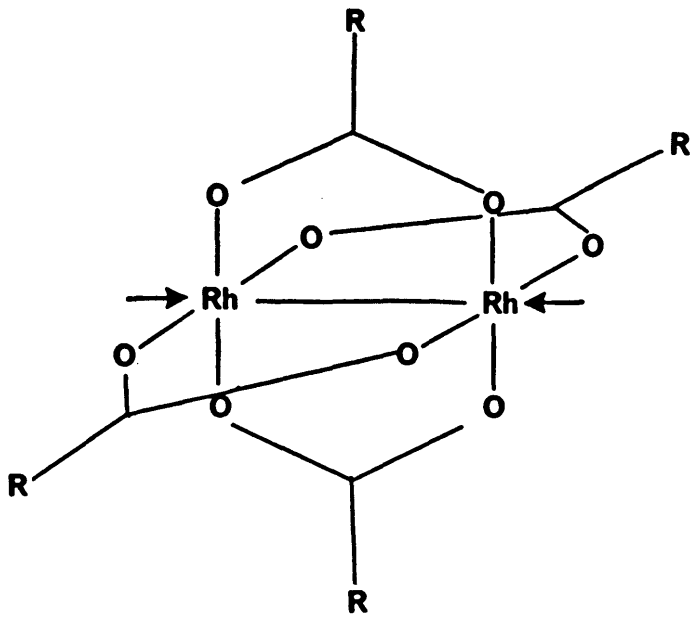
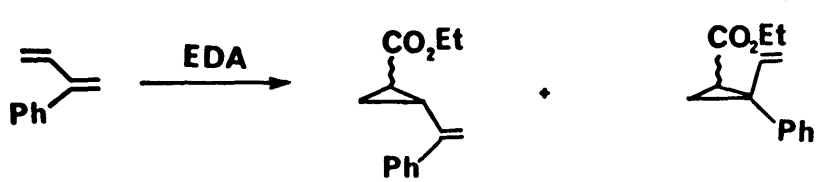


Fig. 1

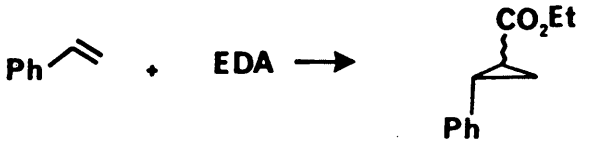
Control of regio- and stereoselectivity of catalysed decomposition, notably in cyclopropanation and C-H insertion, can be achieved by careful catalyst selection.[56,57,58] For example in the cyclopropanation of the diene in equation 15[56] rhodium(II) acetate resulted in higher regioselection in favour of the less substituted double bond than did a palladium catalyst which favoured the more sterically hindered double bond.



(15)

	a	b
	Yield (%)	a/b
$Rh_2(OAc)_4$	81	2.27
$PdCl_2.2PhCN$	<10	0.9

Doyle and co-workers[57(b)] have introduced rhodium(II) acetamide as an efficient cyclopropanation catalyst. Higher *trans* stereoselectivity was observed in its use in cyclopropanation of styrene as shown in equation 16 as compared with that observed with rhodium(II) acetate.



(16)

	Yield (%)	*trans/cis*
$Rh_2(OAc)_4$	95	1.6
$Rh_2(NHCOCH_3)_4$	89	2.1

Rhodium(III) porphyrins (Fig. 2) have recently been introduced as catalysts. These bulky ligands result in enhanced *syn* cyclopropanation of Z-olefins and enhanced C-H insertion at primary C-H bonds, while still giving predominantly insertion at secondary C-H bonds, compared to rhodium(II) carboxylates.[59]

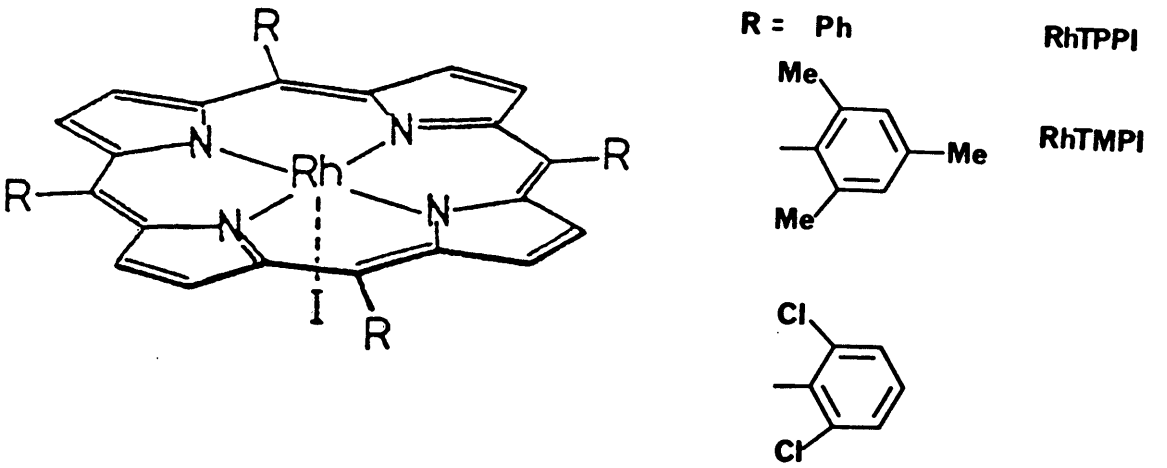
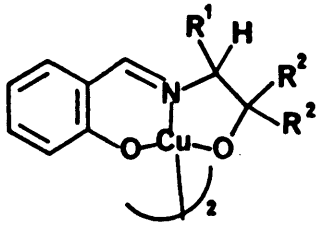


Fig. 2

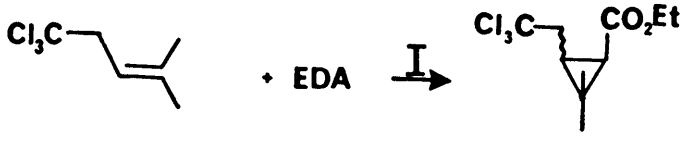
To date there have been no reports of enantioselection in diazocarbonyl decomposition through the use of chiral rhodium complexes, despite the moderate success achieved in this area with chiral copper complexes.[60,61] Among the most successful to date have been Schiff base derived complexes[62,63] (Fig. 3) which have been used for the cyclopropanation of the alkene shown in equation 17.[62] The product was predominantly the *cis* cyclopropanecarboxylate in which the degree of enantioselection (91% e.e.) was higher than in the *trans* product (11% e.e.).



I R^1 = methyl
R^2 = 2-octyloxy-5-t-butylphenyl

II R^1 = CH_2Ph
R^2 = Ph

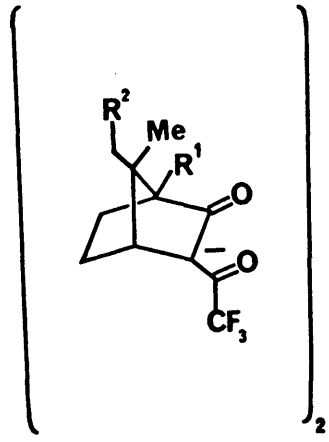
Fig. 3



(17)

Yield 59%
cis/trans 85/15
% e.e. *cis* 91
trans 11

Copper catalysts derived from chiral β-diketones have also been used in the enantioselective cyclopropanation e.g. Fig. 4 and equation 18;[64] in one case a total asymmetric synthesis was achieved.

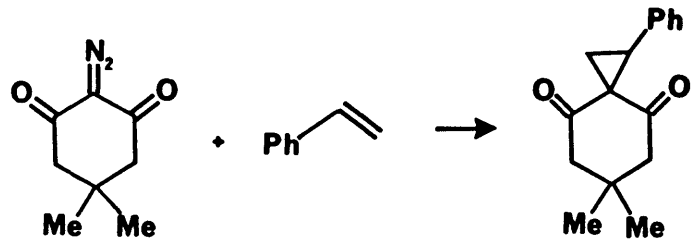


I R^1 = Me, R^2 = H

II R^1 = Me, R^2 = I

III R^1 = $CH{=}CH_2$, R^2 = H

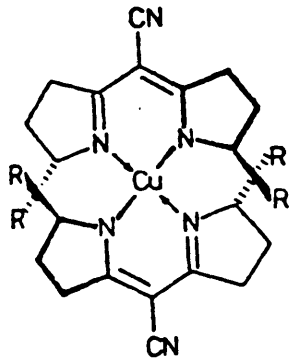
Fig. 4



(18)

	Yield (%)	% e.e.
I	36	91.7
II	21	73.3
III	48	100

Chiral copper-semicorrin complexes[65] (Fig. 5) have also been applied in enantioselective cyclopropanation of styrene with diazoesters (equation 19).



I R = CO_2Me

II R = $CH_2OSiMe_2{}^tBu$

III R = CMe_2OH

Fig. 5



(19)

		R = *L*-menthyl	R = ethyl
Yield (%)		65-75	65
a/b		85/15	78/22
% e.e.	a	91	85
	b	90	68

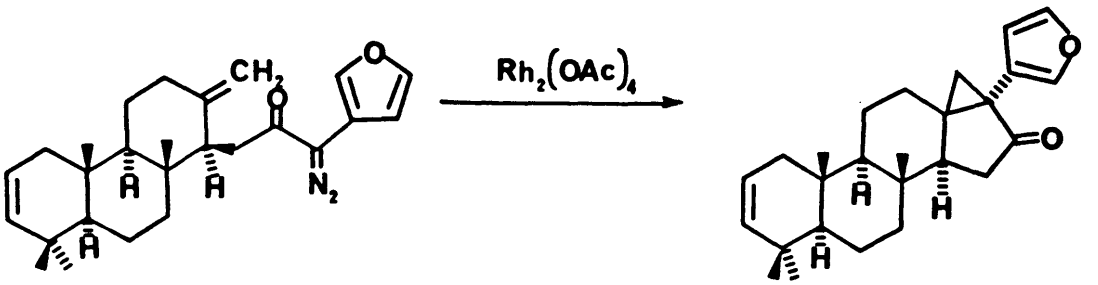
When the chiral catalyst was used in combination with a chiral diazoester the asymmetric induction in the cyclopropanation was considerably enhanced compared to reaction with EDA. Clearly, modern catalyst development has significantly increased the utility of α-diazocarbonyl compounds in organic synthesis.

1.2.2. *Cyclopropanation reactions*

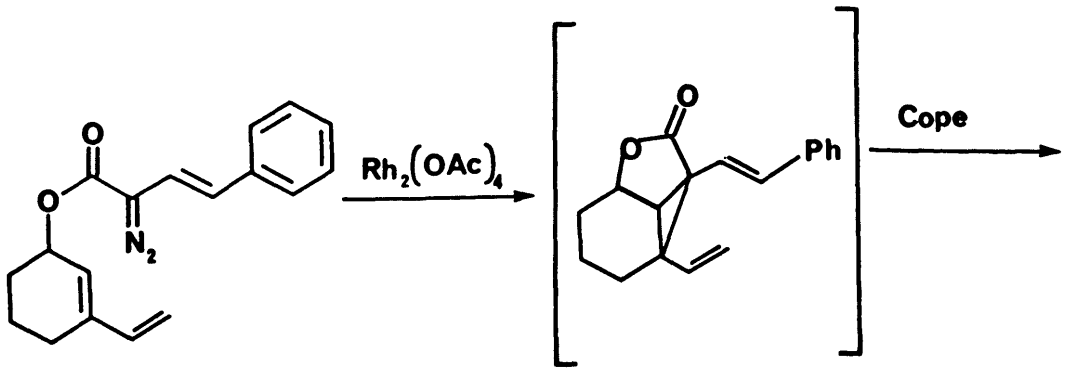
Cyclopropanation of an olefin with an α-diazocarbonyl compound is usually promoted catalytically. Maas[1(f)] has recently discussed in detail the effect of various transition metal salts and complexes on the cyclopropanation reaction. In general, rhodium(II) carboxylates are the most efficient catalysts giving higher yields[66] and obviating the necessity of using excess alkene as is often the case with copper catalysts.[67] A notable exception to the efficiency of rhodium catalysts in cyclopropanation is with electron poor olefins such as methyl maleate.[66] However, palladium catalysts[50,68] such as $Pd(OAc)_2$ are complementary to rhodium catalysts[69] in that they show high efficiency for electron poor olefins[70,71] such as α,β-unsaturated esters and ketones and a high affinity for terminal and strained alkenes.[52,66]

The major application of cyclopropanation in organic synthesis is intramolecularly. Since Stork and Ficini[72] first reported an intramolecular cyclopropanation in 1961, numerous examples have been reported, testifying to its immense synthetic utility. A few recent examples are shown in equations 20-23.

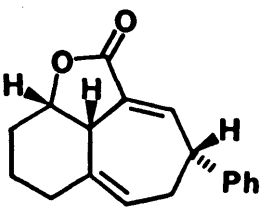
These equations demonstrate the ease with which sterically strained structures are formed under mild conditions. Equation 21 is an example of the tandem cyclopropanation/Cope rearrangement sequence which has been wildly applied in organic synthesis. Equation 22 is an example of cyclopropanation of a vinyl ether, made possible only with the introduction of rhodium(II) carboxylates as catalysts. Application of intramolecular cyclopropanation in the synthesis of the limonoid system is illustrated in equation 20 while equation 23 illustrates its use in pseudoguaianolide synthesis.



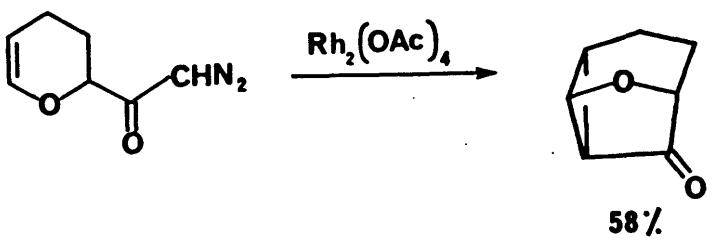
(20)[73]



(21)[74]

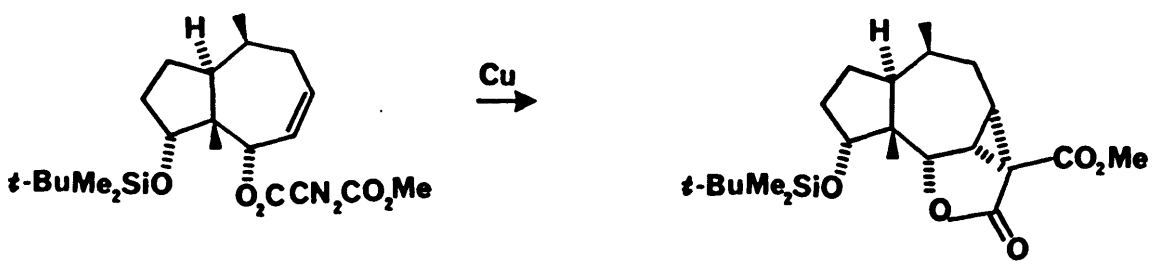


61%



(22)[75]

58%

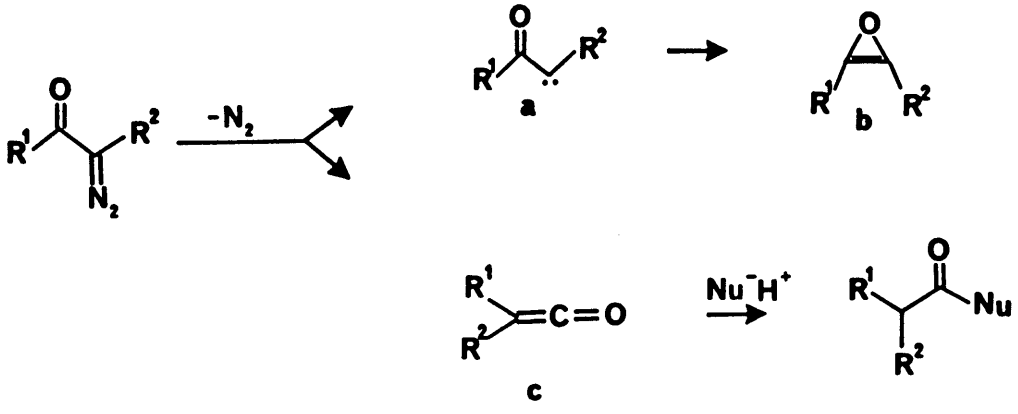


(23)[76]

40%

1.2.3. *Wolff rearrangement*

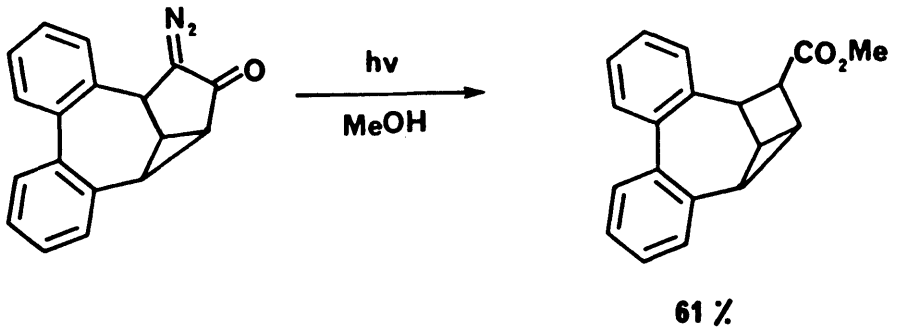
Since its discovery over seventy years ago[77] this rearrangement has been widely used as a means of forcing angle strain on cyclic systems through ring contraction. This 1,2-rearrangement with loss of nitrogen forms a ketene which then further reacts to give the rearranged products e.g. with nucleophiles such as H_2O, ROH, R_3N (Scheme 3). The rearrangement may be initiated thermally, catalytically[78] (Ag_2O), and photochemically.



Scheme 3

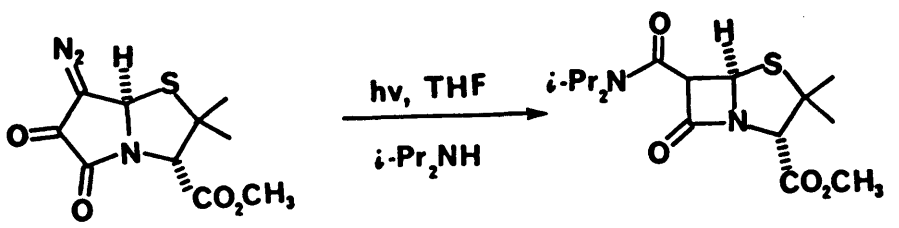
Photodecomposition is by far the most widely employed method. There has been much investigation as to the nature of the intermediates,[79-81] involving low temperature matrix isolation and spectroscopic techniques.[82-84] The existence of ketene (c) as an intermediate has been confirmed but although ketocarbene[85] (a) and oxirene[86] (b) have been detected recently, it is not fully decided[87,88] whether the rearrangement to ketene proceeds

in a concerted manner[89] or *via* these distinct intermediates.[90] Two recent examples of the Wolff rearrangement in organic synthesis are shown in equations 24[91] and 25[92] illustrating the utility of this rearrangement for generating strained products.



61 %

(24)

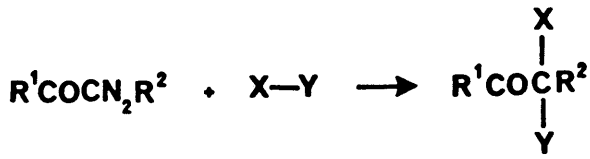


72 %

(25)

1.2.4. α,α-*Substitution of* α-*diazocarbonyl compounds*

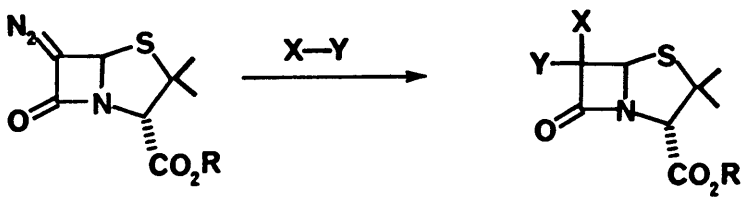
Reaction of α-diazocarbonyl compounds with a wide variety of compounds (X-Y) can result in replacement of the diazo group by two new substituents, a process formally corresponding to carbene insertion into the X-Y bond (equation 26).



(26)

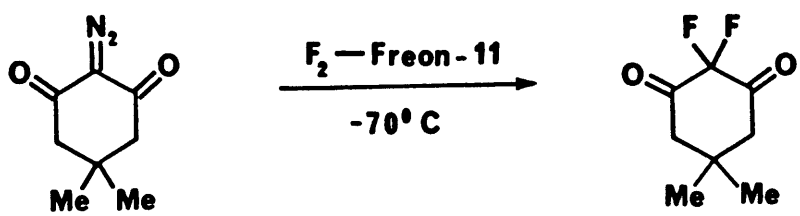
It is likely that a range of mechanisms may apply depending on the nature of the substrate X-Y. α,α-Substitution of α-diazocarbonyls offers a convenient route to regiodefined α-substituted carbonyls under mild conditions. Suitable reagents X-Y are the halogens, hydrogen halides, and compounds containing O-H, S-H, N-H, Si-H, Se-H, Se-Se, S-S, S-X, and Se-X bonds.

Reaction of a 6-diazopenicillanate derivative with chlorine, bromine, iodine, or with the mixed halides[96] ICl and IBr gives the α,α-bishalogenated products[93-97] (equation 27) while successful substitution with fluorine can be obtained by dilution with an inert gas (equation 28).[98]



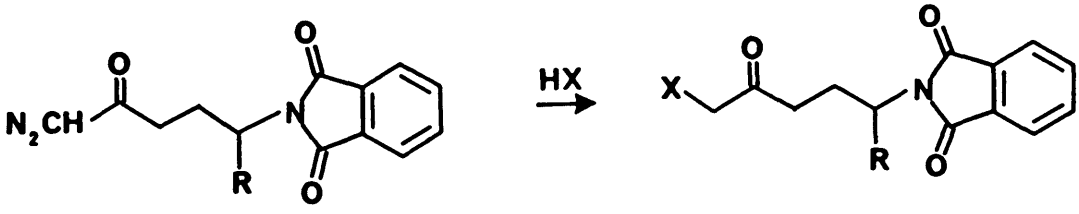
(27)

X,Y = Cl, Br, I



(28)

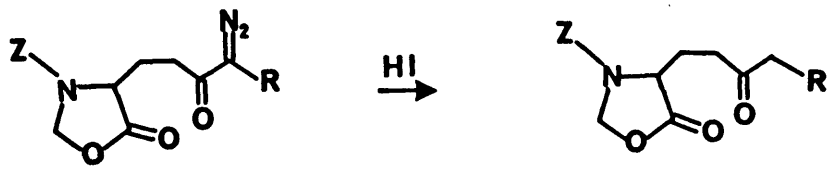
α-Halogenoketones are easily produced by reaction of α-diazoketones with the hydrogen halides (for example equation 29).[99]



(29)

R = H, CH_3, X = Br, Cl

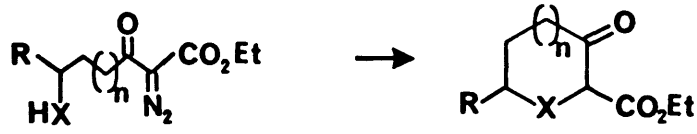
However, hydriodic acid, due to its reducing nature, gives instead a ketone (equation 30).[100]



(30)

Z = Benzyloxycarbonyl R = H, Me, Pr, Ph

Insertion of α-diazocarbonyl derived carbenoids into O-H,[101] N-H,[52(a)] and Si-H[102] bonds is efficiently catalysed by rhodium(II) acetate while rhodium(II) trifluoroacetate is a more efficient catalyst for S-H insertion reactions.[12,103] Rapoport[104] and Moody[44] have studied intramolecular insertions into O-H, S-H, and N-H bonds as a route to 5, 6 and 7-membered heterocycles of the type shown in equation 31.

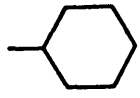


(31)

n = 0, 1, 2

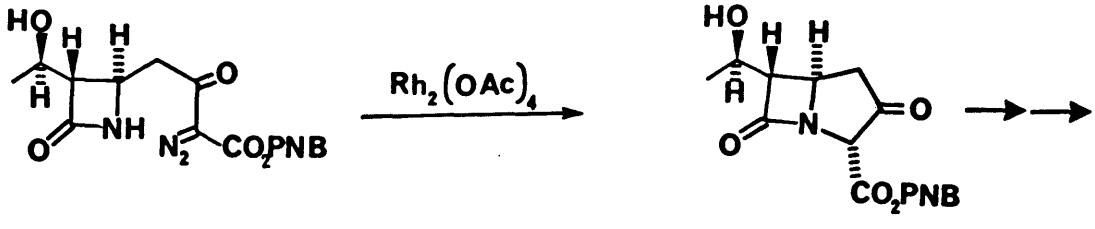
X = O, S, NBoc

R = H, Me,



Rhodium acetate catalysed intramolecular insertions were efficient for 5 and 6-membered ring formation (70-100% yield for O-H and N-H insertion but 35-73% yield for S-H insertion) but for larger ring sizes yields were reduced because of competing cyclopentanone formation by C-H insertion reactions. However, cyclic ethers of up to 8-membered rings have been formed although in low yields (12-24%) using rhodium acetate but more efficiently with rhodium trifluoroacetate (32%).

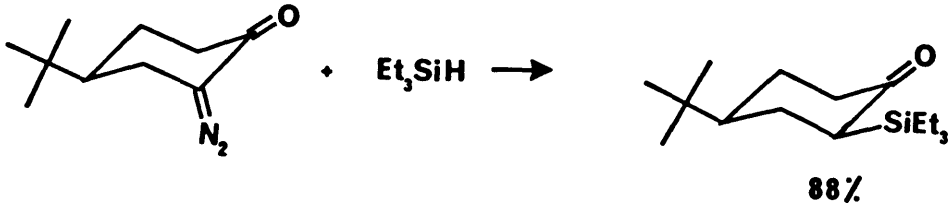
Intramolecular N-H insertion reactions are widely used in small ring heterocycle synthesis. Since the Merck synthesis of thienamycin, which utilises N-H insertion to construct a 5-membered ring fused to a β-lactam, was published (equation 32)[105,106] numerous examples of its application to the construction of bicyclic β-lactams have appeared.[107]



(32)

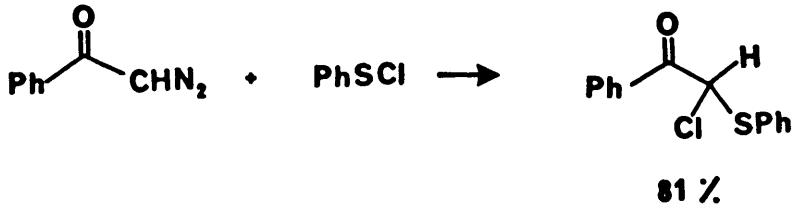
thienamycin

Doyle and co-workers[102] have recently carried out Si-H insertions with diazocyclohexanones using rhodium(II) acetate or copper(II) acac as catalyst (equation 33).



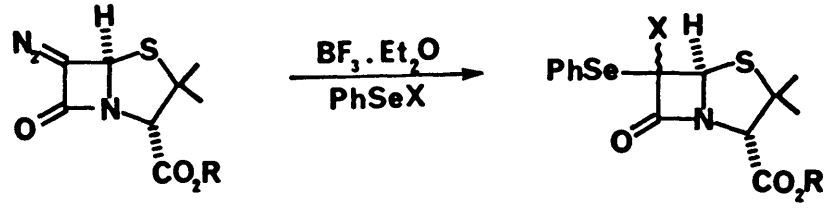
(33)

In general Se-X[108] and S-X[109-111] insertions can be achieved readily without catalysis (e.g. equation 34).



(34)

Lewis acid catalysis gives successful insertion of 6-diazopenicillanate esters into allyl phenyl selenide,[112,113] diphenyl selenide,[109,114] and benzeneselenol[109] (equation 35).

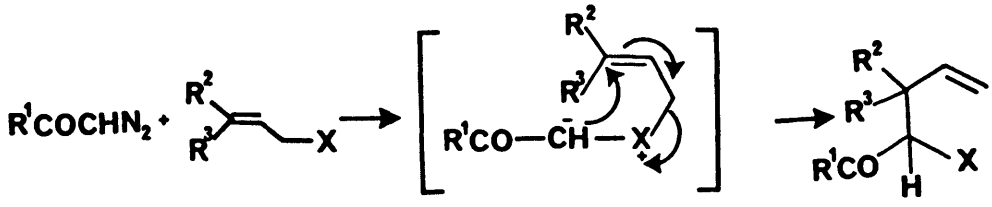


(35)

X = H, , SePh

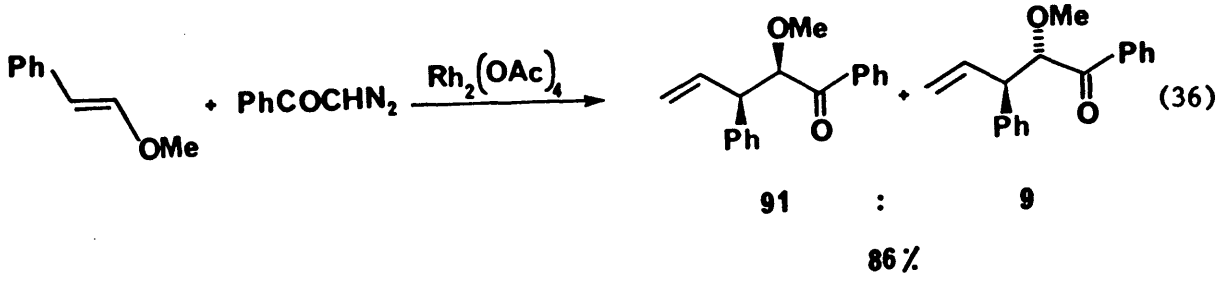
1.2.5. *Ylide formation*

Decomposition of α-diazocarbonyl compounds in the presence of molecules containing heteroatoms, e.g. S, O, Se, N, or halogen, may result in ylide formation (Scheme 4) with the resulting products derived from subsequent reaction or rearrangement of the intermediate ylide. One reaction pathway, that of [2,3]-sigmatropic rearrangement, is illustrated in Scheme 4.



Scheme 4

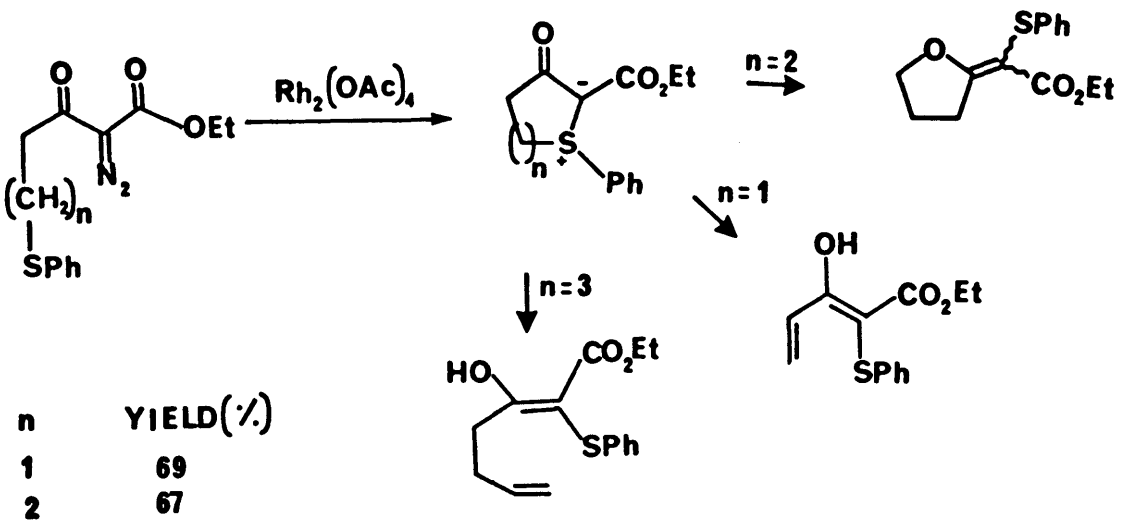
For example, treatment of an α-diazoketone with an allyl ether gave products derived from ylide formation and subsequent [2,3]- sigmatropic rearrangement, with only small yields (6%) of cyclopropanation products (equation 36).[115]



(36)

The erythro isomer was largely favoured over the threo isomer; this diastereoselectivity was rationalised as being due to steric and/or electronic effects in the transition state for the rearrangement.

Stable cyclic sulphonium ylides[116] have been isolated by intramolecular trapping of a carbenoid generated by rhodium(II) acetate decomposition of an α-diazo-β-keto-ester. Subsequent rearrangement of the ylide was strongly dependent on ring size as shown in Scheme 5.

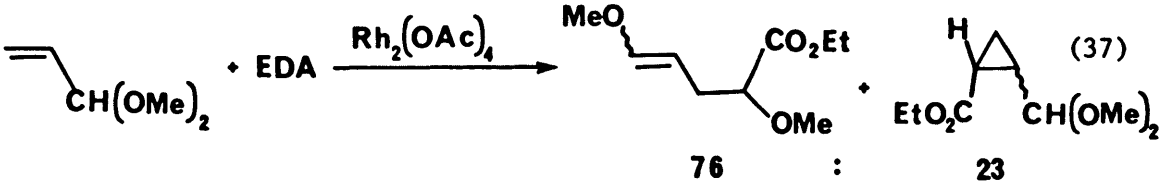


n	YIELD(%)
1	69
2	67
3	45

Scheme 5

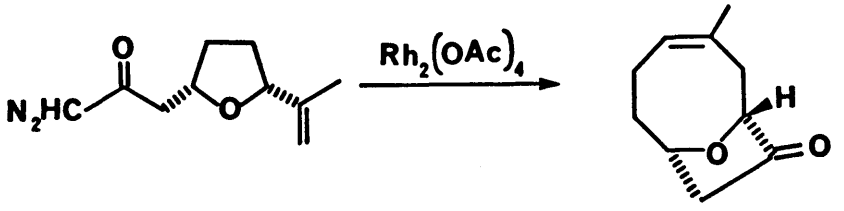
The 6-membered ring ylide rearranged to an E/Z mixture of olefins as shown, the product of an overall 1,4-rearrangement. In contrast the 5- and 7- membered ring ylides underwent fragmentation.

Until Doyle's[115] recent success (equation 36), oxonium ylide generation has proved more elusive than its sulphonium counterpart, mainly due to greater competition from cyclopropanation; even with allyl acetals, ylide generation is favoured by only a factor of three over cyclopropanation, a typical comparison being that shown in equation 37.[117]

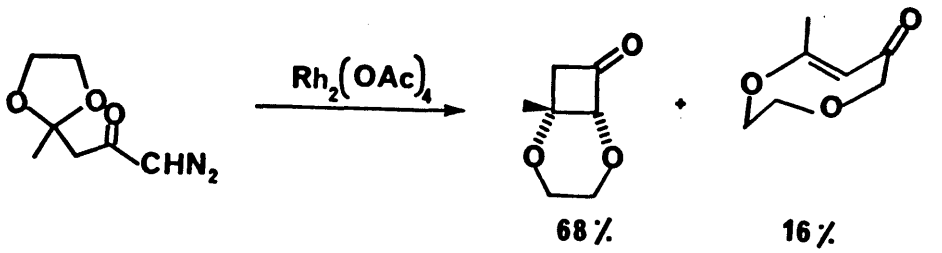


(37)

Pirrung and Werner[118] and Roskamp and Johnson[119] have independently demonstrated successful intramolecular oxonium ylide generation using rhodium(II) acetate catalysis; the former leading to oxygen heterocycles (equation 38) while the latter furnished cyclobutanones (equation 39).



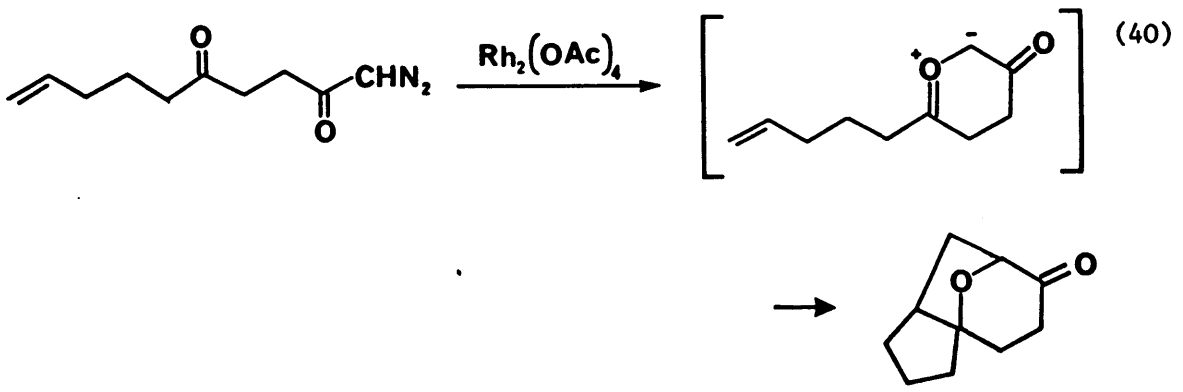
(38)



(39)

Carbonyl ylides, which can act as 1,3-dipoles in cycloadditions, can be generated by reaction of a carbenoid with a carbonyl group. Equation 40[120] is an example of an intramolecularly generated carbonyl

ylide which is subsequently trapped intramolecularly by a C-C double bond in a 1,3-dipolar cycloaddition.

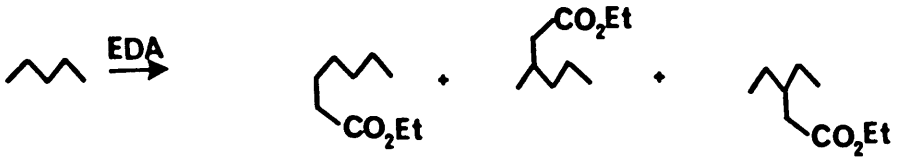


(40)

1.2.6. *C-H insertion*

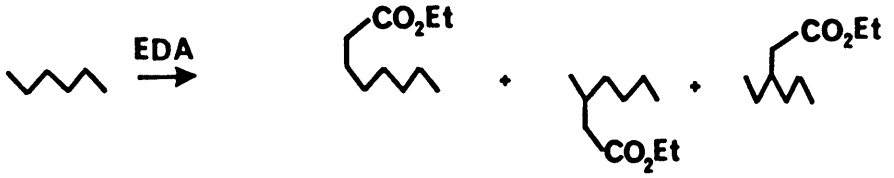
C-H insertion reactions of carbenes or carbenoids derived from α-diazocarbonyl compounds became synthetically useful with the introduction of rhodium catalysts. Significantly improved yields and selectivities as compared to copper catalysts[121] resulted. In C-H insertions of carbenoids with alkanes the order of reactivity is tertiary > secondary > primary. This preference for the more substituted positions is illustrated in equations 41[58,112] and 42[59] for the rhodium catalysed decomposition of EDA in n-pentane and n-hexane.

As illustrated in equation 41, use of rhodium(II) trifluoroacetate[122] as the decomposition catalyst of EDA gave very little insertion into the primary C-H bonds, while decomposition with the bulky rhodium(II) 9-triptycenecarboxylate,[58] although still resulting predominantly in substitution at the secondary position, gave more insertion into the primary C-H bonds. Similarly, the bulky rhodium porphyrin RhTMPI[59] (see Fig. 2, 1.2.1.) resulted predominantly in secondary substitution but gave enhanced attack at the primary position compared to less sterically hindered catalysts.



(41)

				Yield (%)
$Rh_2(OCOCF_3)_4$	7	66	27	66
$Rh_2(TC)_4$	30	61	9	86

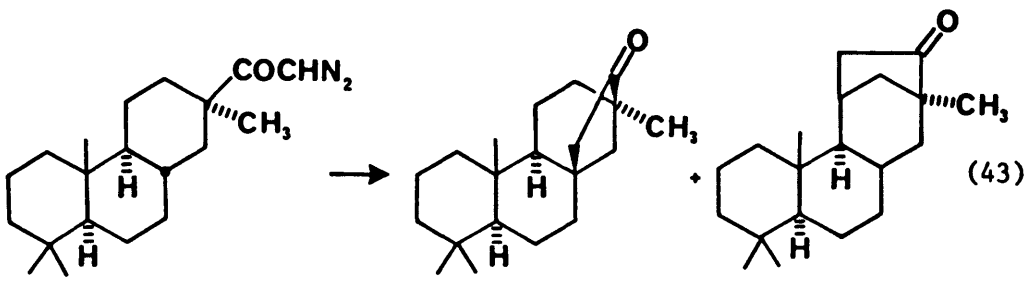


(42)

				Yield (%)
$Rh_2(pivalate)_4$	5	62	33	50
Rh TPPI	8	71	21	46
Rh TMPI	25	61	14	36

Since steric effects affect the regioselectivities obtained in C-H insertion reactions, it appears that strong catalyst-substrate interactions exist in the transition state for the insertion process.

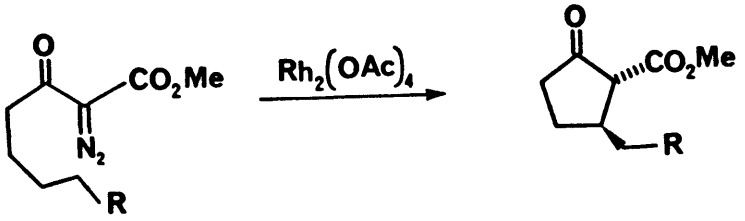
Intramolecular C-H insertion reactions of α-diazocarbonyl compounds show in general a strong preference for cyclopentanone formation thought to be due to a preference for a highly ordered 6-membered transition state (e.g. equation 43).[123] The preference for tertiary C-H bonds rather than secondary is also illustrated in this cyclisation with the regioselectivity depending on the ligand present in the copper catalyst.



(43)

$CuSO_4$	1.5	:	1
$Cu(acac)_2$	4.3	:	1
$Cu(OAc)_2$	7.4	:	1

Since Taber and Petty[124] showed that intramolecular C-H insertion reactions of α-diazocarbonyl compounds can be efficiently catalysed by rhodium(II) acetate even in an acyclic freely rotating system, as in equation 44, this remarkably regioselective method of remote functionalisation has become increasingly important in cyclopentanone synthesis.



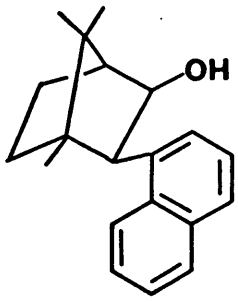
(44)

R = C_7H_{15} , i-Pr , $=CH_2$, $CH=C(CH_3)_2$, H

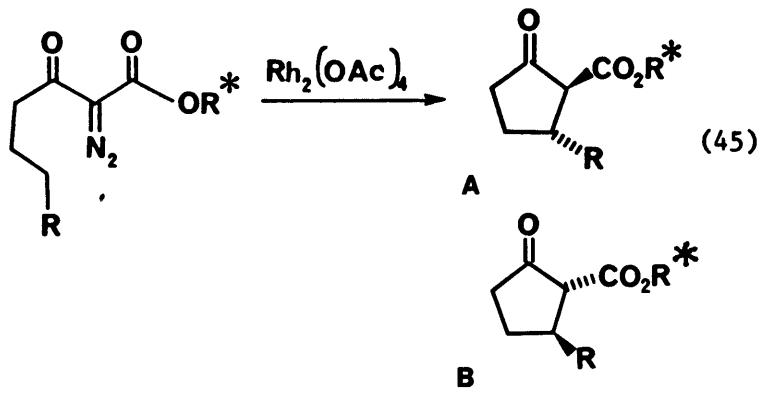
a b c d e

Under rhodium acetate catalysis allylic C-H insertion competes favourably with the normally efficient intramolecular cyclopropanation giving 48% of cyclopentanone in cyclisation c(R, = CH_2) of equation 44.

By use of diazoesters derived from chiral alcohols, notably alcohol (12), Taber and Raman[125] were able to achieve asymmetric induction in the carbocyclisation shown in equation 45.



(12)

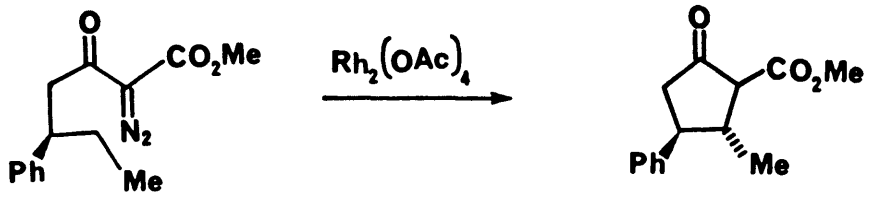


(45)

R	Diastereoselectivity A : B
C_5H_9	87 : 13
$CH{=}CH_2$	92 : 8
Pr^i	83 : 17
Bu^t	83 : 17
Ph	85 : 15

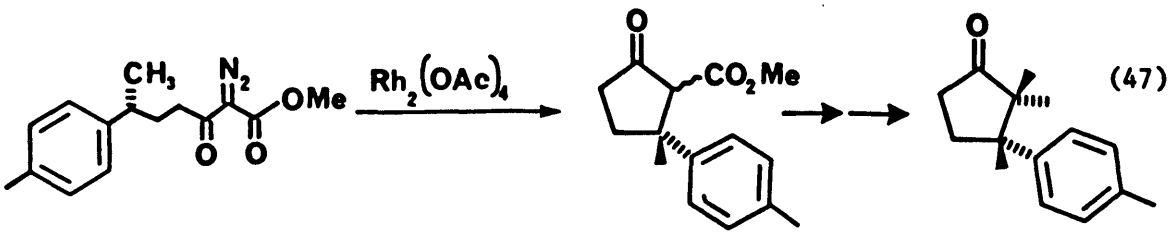
The asymmetric induction is quoted as a diastereoselectivity because even though the cyclopentanone rings formed are *trans*-disubstituted, both enantiomers are formed at the ring which, because of the chiral auxiliary, are diastereoisomeric in nature.

Diastereoselection in an intramolecular C-H insertion reaction of a racemic α-diazo-β-keto ester is illustrated in equation 46,[126] with exclusive formation of the product in which the methyl and phenyl groups are *trans* to one another.



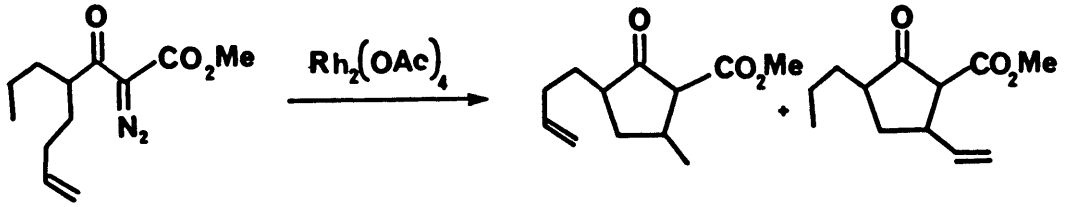
(46)

Taber's synthesis of (+)-α-cuparenone,[127] the key step of which is shown in equation 47, demonstrates that the intramolecular C-H insertion of a homochiral α-diazo-β-keto ester proceeds with retention of configuration at the position undergoing C-H insertion.



(47)

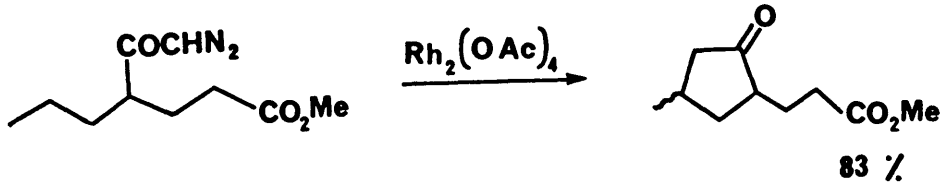
In an investigation of steric and electronic effects of intramolecular C-H insertion of α-diazocarbonyl compounds, Taber and Ruckle[128] found that allylic and benzylic C-H bonds are less reactive than aliphatic C-H bonds (as illustrated in equation 48).



(48)

2.9 : 1 88%

This was thought to be due to decreased electron density in the bond when adjacent to electron-withdrawing groups such as vinyl or phenyl. Similarly, Stork and Nakatani[129] achieved regiocontrol in cyclopentanone formation *via* intramolecular C-H insertion of α-diazoketones, by use of the electron-withdrawing 2-carboxyethyl group to steer insertion away from its α and β methylene groups (equations 49 and 50) while offering no protection to the γ-position (equation 51). This may be a particularly useful strategy synthetically since the ester group can be used first to direct the cyclisation and then be transformed into a variety of other substituents.



83 %

(49)



81 %

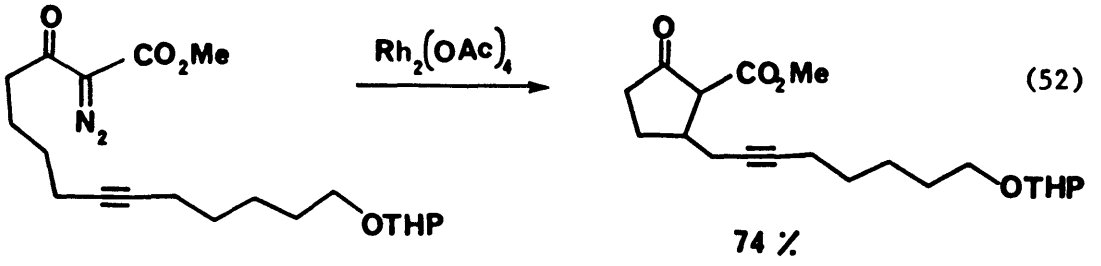
(50)



64 %

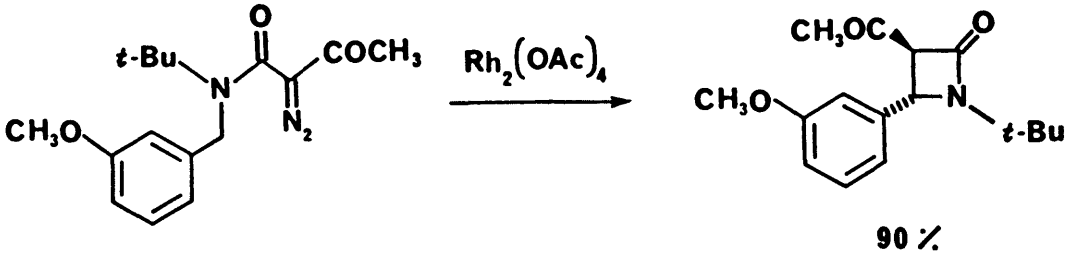
(51)

An example of the application of cyclopentanone formation in organic synthesis by means of an intramolecular C-H insertion is shown in equation 52[130] illustrating the remarkable regioselection possible in such reactions.

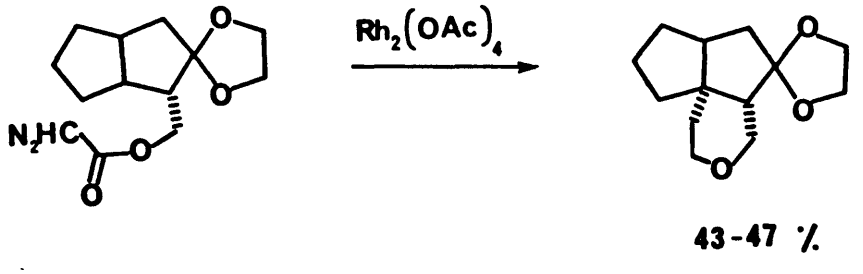


(52)

4-Membered[131] and 6-membered[132] rings have also been formed by intramolecular C-H insertion of ketocarbenoids as shown in equations 53[131] and 54,[132] respectively, although fewer such examples are known than for 5-membered rings.



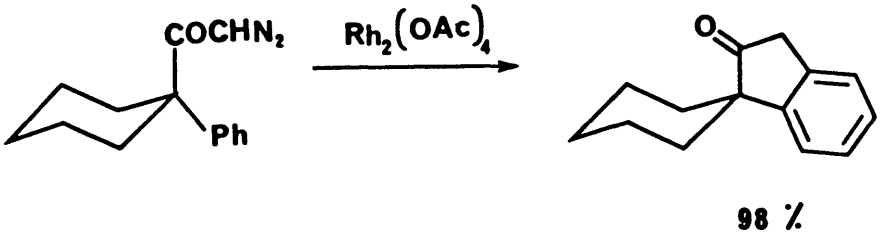
(53)



(54)

Of particular interest synthetically is the application of intramolecular C-H insertion to the preparation of β-lactams, as illustrated by the recent work of Doyle and co-workers[131] in equation 53.

Reactions corresponding formally to C-H insertion into an aromatic C-H bond have been reported, for example, equation 55 shows Nakatani's[133] preparation of 2-indanones by α-diazoketone decomposition.



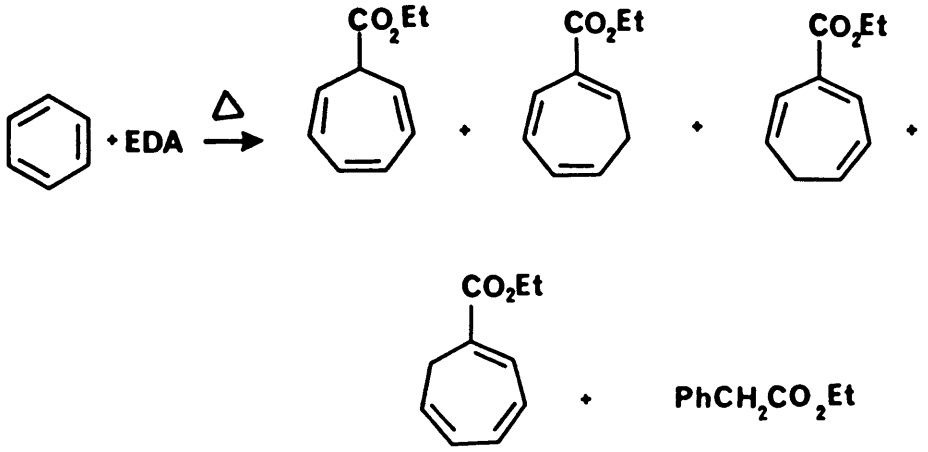
98 %

(55)

However, this is probably more correctly described as either the cycloaddition of a carbenoid to an aromatic ring or rhodium catalysed electrophilic aromatic substitution.

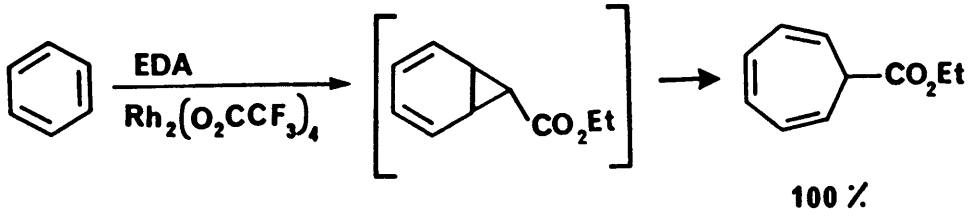
1.2.7. *Addition to aromatics*

Although Buchner[134] reported the thermal reaction of EDA with benzene over 100 years ago, its applicability in cycloheptatriene synthesis was limited because of the complex product mixtures obtained (equation 56).[135] As well as the initially formed unconjugated cycloheptatrienyl ester, its conjugated isomers were obtained, formed by sigmatropic shifts in the initially formed ester. Ethyl 2-phenylacetate was also formed, probably by rearomatisation of the cycloheptatrienyl ester.



(56)

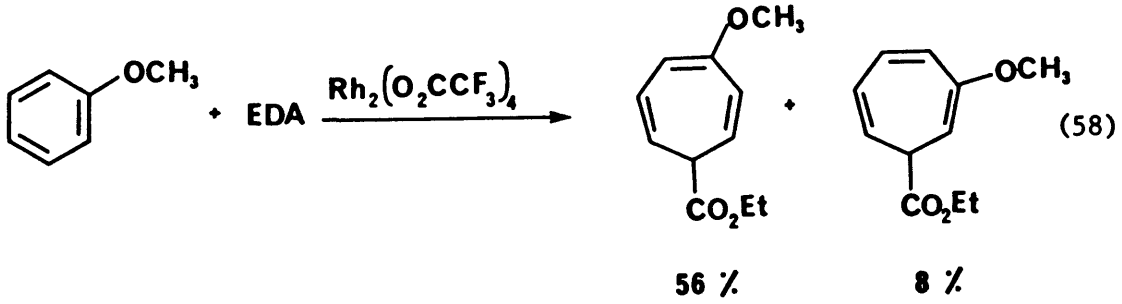
However, rhodium(II) trifluoroacetate[136] is efficient in catalysing the ring expansion of benzene with EDA under mild conditions, resulting in isolation of the kinetic isomer of the cycloheptatrienyl ester (equation 57) rather than its conjugated isomers.



(57)

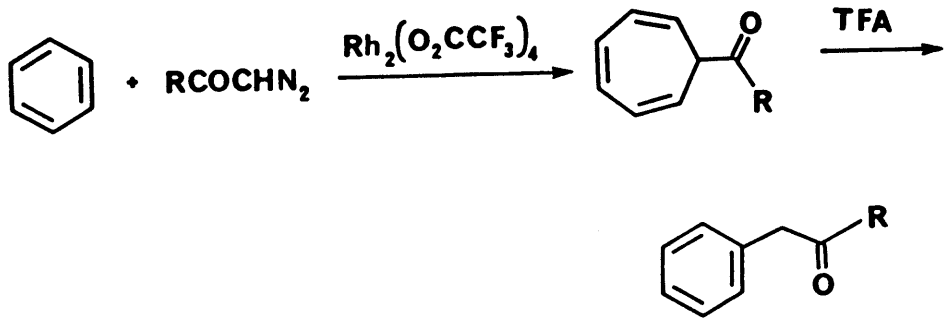
The reaction mechanism is thought to involve carbenoid attack to give initially a norcaradiene intermediate which is in mobile equilibrium with the much more stable cycloheptatrienyl tautomer. The effect of substituents on the benzene ring on the regioselectivity of the EDA

addition has been investigated.[136] For example, reaction of EDA and anisole gave predominantly the 4-methoxy-substituted product with some of the 3-methoxy-substituted product also present.



(58)

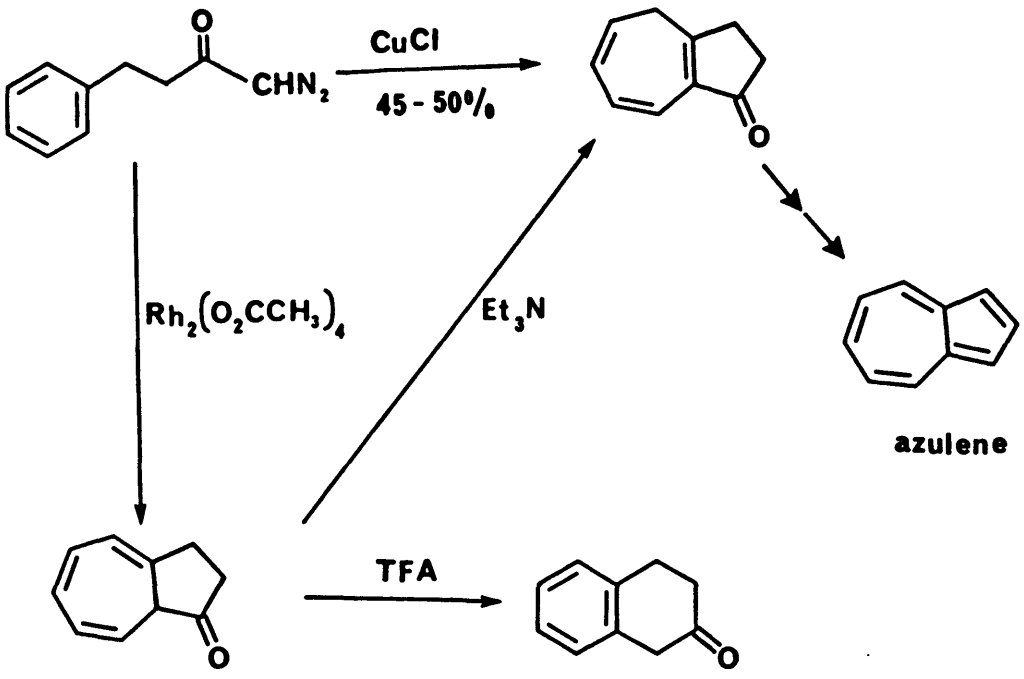
As with α-diazoesters treatment of benzene with α-diazoketones[137] under rhodium trifluoroacetate catalysis gives ring expansion to cycloheptatrienyl ketones (equation 59). Rearomatisation occurs readily on treatment with trifluoroacetic acid to give benzyl ketones.



(59)

R = CH_3, CH_3OCH_2, CH_3CHBr, $ClCH_2$

Intramolecular Buchner additions to benzene provide a mild route to fused cycloheptatrienes[138] which are useful synthetic intermediates (Scheme 6). Early investigations of intramolecular Buchner reactions involved copper catalysis and suffered from poor yields.[139]

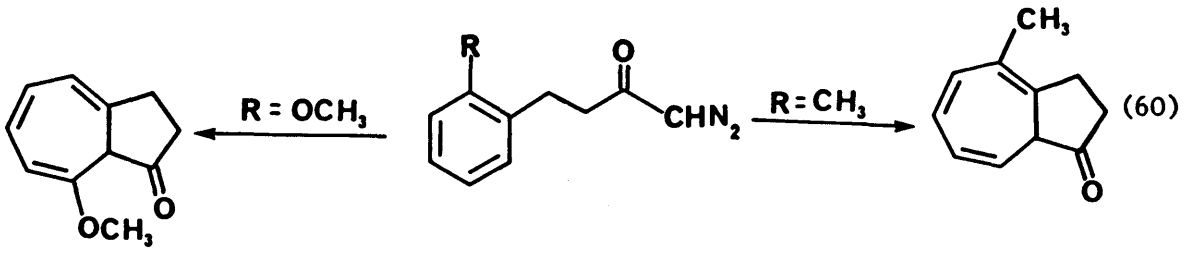


Scheme 6

Most significant was Scott's synthesis of azulene,[140,141] the key step of which involved cuprous chloride catalysed cyclisation as shown in Scheme 6. The product isolated from this cycloaddition was the conjugated cycloheptatrienyl ketone, but, as shown in scheme 6, the kinetic unconjugated cycloheptatrienone can be readily obtained using rhodium(II) acetate as catalyst.[138] This kinetic isomer is readily transformed into Scott's conjugated isomer on treatment with triethylamine, while 2-tetralone is obtained by TFA catalysis.[138]

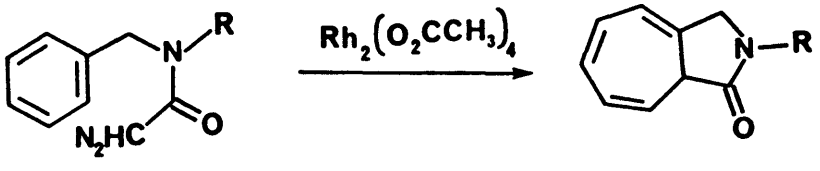
A study[138] of substituent effects on the directionality of the intramolecular Buchner reaction of substituted 4-phenyl-1-diazobutan-2-ones has shown, for example, that an *ortho*-methyl group has a repulsive

effect on the ketocarbenoid addition while an *ortho*-methoxy group favours cyclisation towards the substituted position (equation 60).[138]



(60)

Doyle *et al.*[142] have recently investigated the rhodium(II) acetate catalysed cyclisation of *N*-benzyldiazoacetamides to azabicyclo[5.3.0] decatrienones (equation 61) and found these products to be insensitive to TFA unlike the carbon analogue. Yields are higher with the t-butyl and benzyl protecting groups on nitrogen because the most stable conformer of the intermediate carbenoid in these cases has the benzyl and carbenoid groups close to one another.

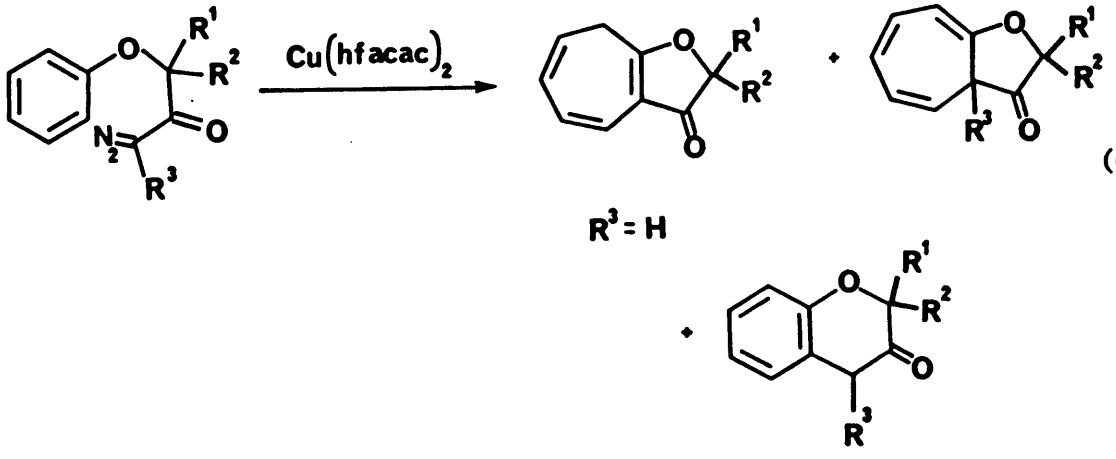


(61)

R	Yield (%)
Bu^t	100
CH_2Ph	93
Me	37

It is interesting to compare this reaction to equation 53[131] where an α-diazo-β-ketoamide undergoes C-H insertion to form a β-lactam, rather than addition to the aromatic ring.

In a study of the cyclisation of α[1]-phenoxy-α-diazoketones to furanones and chromanones the product ratio was found to be dependent on the substituents (equation 62).[143]

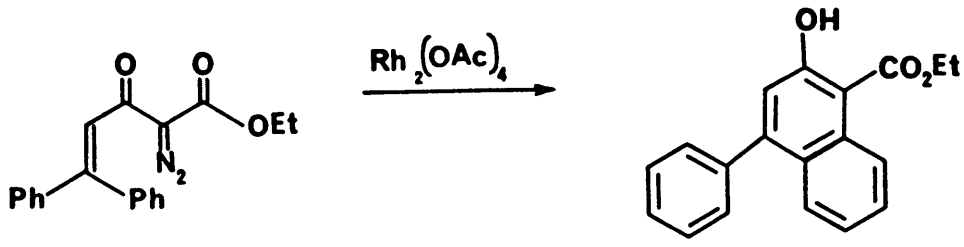


(62)

R^1, R^2 = H, CH_3, Ph

R^3 = H, CH_3

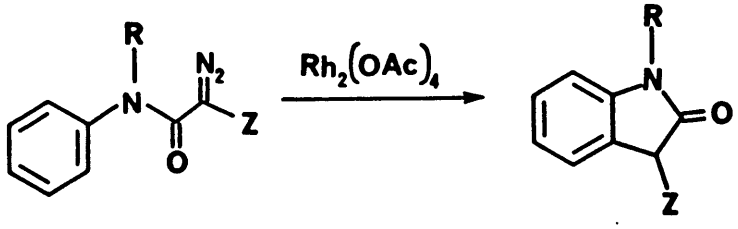
The question of whether the intramolecular Buchner cyclisation gives trienones or tetralones depends on individual structural considerations and reaction conditions. For example, in equation 63, although the mild rhodium(II) acetate catalyst is used, only the aromatised product is obtained[144] without isolation of a cycloheptatrienyl intermediate. In this case the driving force for the rearomatisation of the cycloheptatriene intermediate is the formation of two aromatic rings on enolisation of the ketone.



(63)

90%

In Doyle's[145] rhodium acetate catalysed decomposition of *N*-aryldiazoamides to give 2(3*H*)-indolinones (equation 64) an electrophilic aromatic substitution mechanism is more likely than cycloaddition to the aromatic ring, due to the steric strain which would be involved in such a cycloaddition.



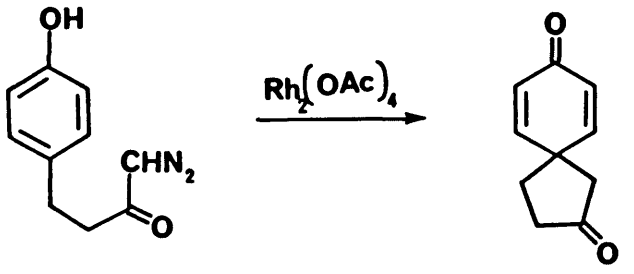
(64)

70-90%

R = CH_3, Et, $PhCH_2$

Z = H, CH_3CO

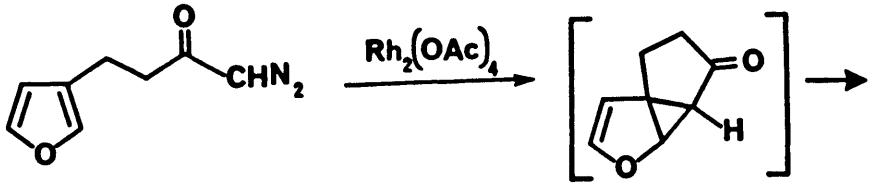
The cyclisation of *para* phenolic diazobutanones to spirodienones has been studied by Iwata[146] (equation 65). This alternative mode of addition of a carbenoid derived from an α-diazoketone to an aromatic ring has been applied in synthetic studies directed towards the aphidicolane and stemodane diterpenes.[146]



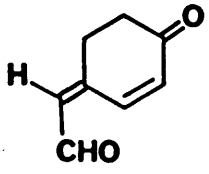
70 %

(65)

α-Diazocarbonyl compounds also react with Π-excessive heteroaromatics. A recent example involves the intramolecular cyclopropanation of furan followed by electrocyclic ring opening to give a cyclohexenone in 88% yield (equation 66).[147]



(66)

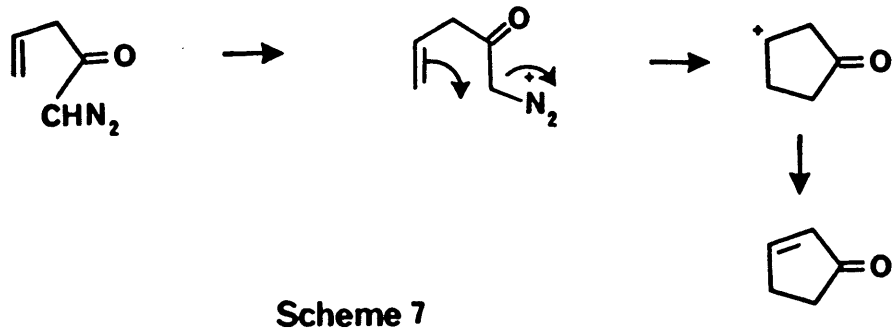


88 %

1.2.8. *Acid catalysed cyclisations of unsaturated α-diazocarbonyl compounds*[148]

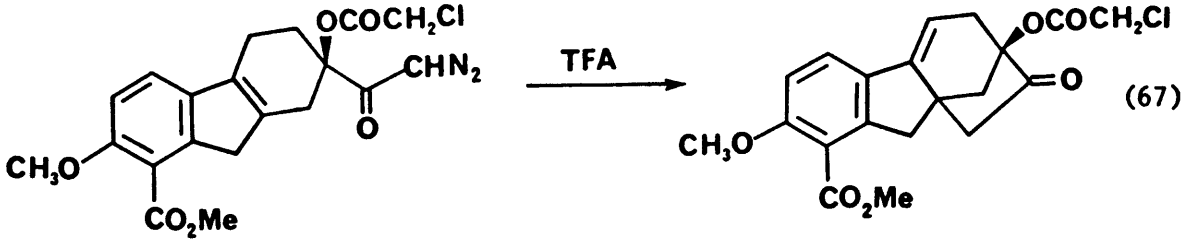
These cyclisations probably proceed by protonation (in the case of Bronsted acids) or complexation (for Lewis acids) of the diazocarbonyl with Π-electron participation in the electrophilic diazonium species. Loss of

nitrogen gives a cyclised cation which is stabilised by proton loss (Scheme 7). They may thus be referred to as Π-route cyclisations. Boron trifluoride-etherate is normally the catalyst of choice.



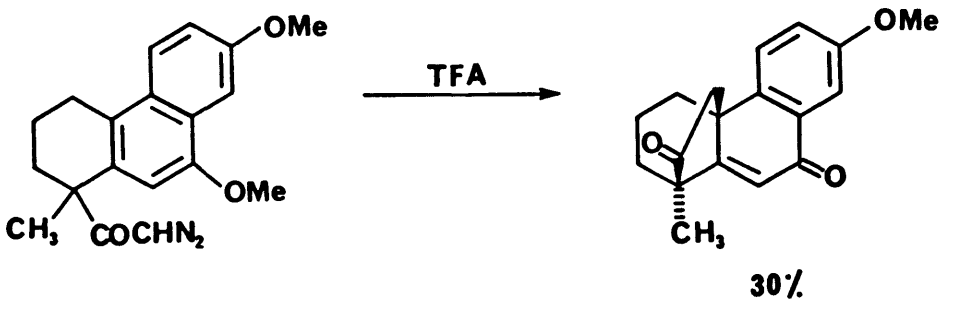
Scheme 7

Cyclopentane annulation *via* acid catalysed intramolecular diazoketone cyclisation has been used extensively in synthesis. The key step of Mander's total synthesis of gibberellic acid[149] (equation 67) is an outstanding example of its application to the preparation of fused polycyclic compounds with angular substituents.



(67)

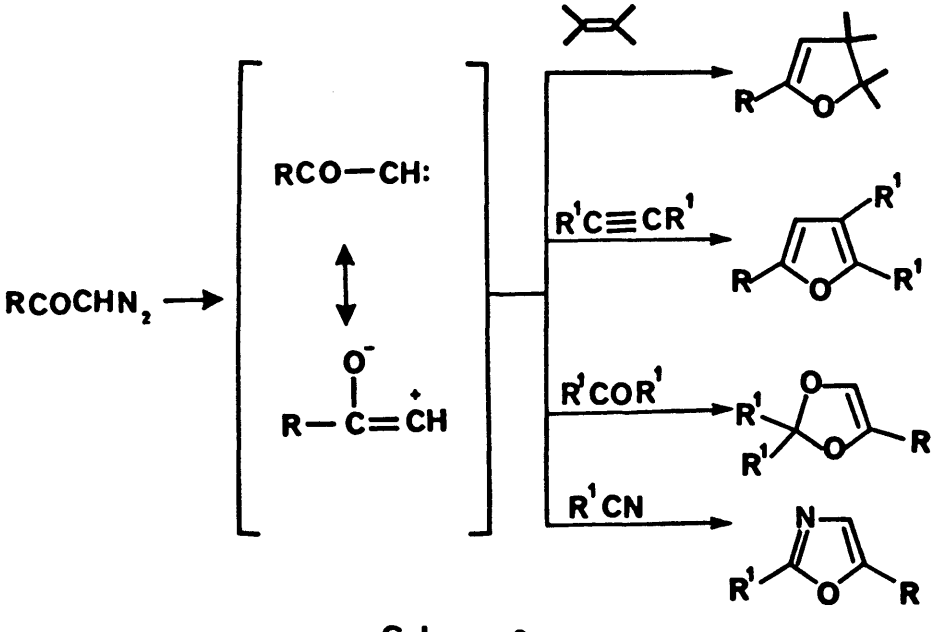
Aromatic participation in acid catalysed cyclisation of an α-diazoketone is illustrated in equation 68[150] as an example of a stereocontrolled route to bridged tetracyclic ketones which are particularly useful in diterpenoid synthesis.



(68)

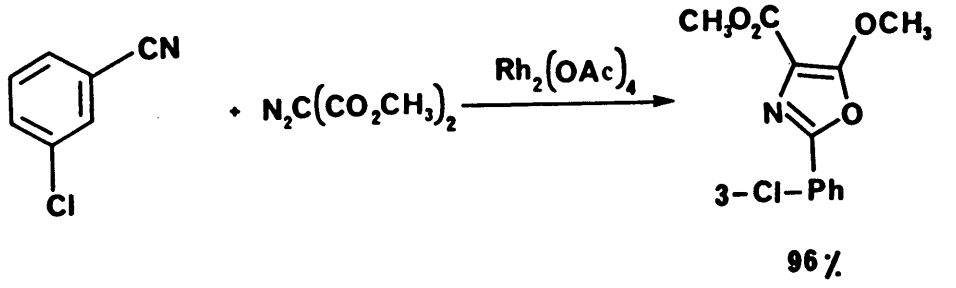
1.2.9. *1,3-Dipolar cycloaddition*

Carbenes or carbenoids derived from α-diazocarbonyl compounds can add to multiple bonds with participation of both the carbenic carbon and the carbonyl oxygen in the form of a 1,3-dipole; suitable dipolarophiles include olefins,[151] acetylenes,[152] carbonyls,[153] and nitriles[154] (Scheme 8).



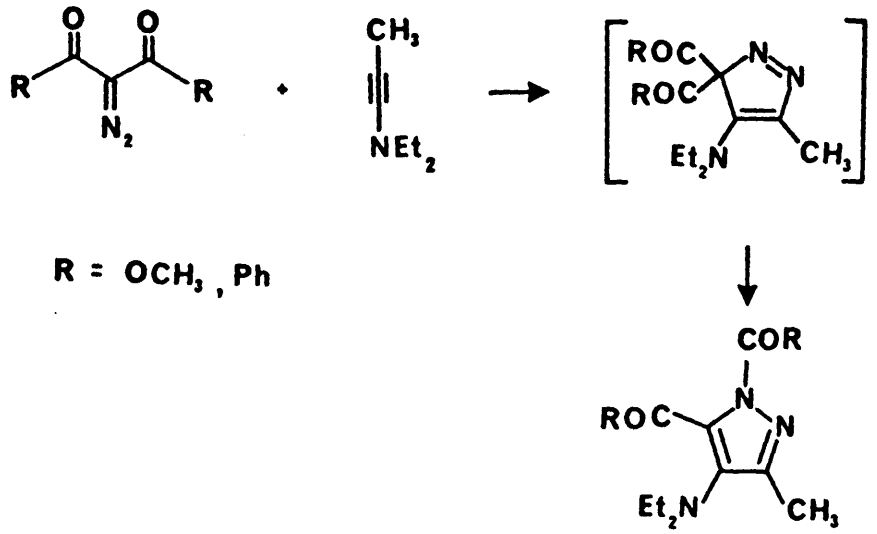
Scheme 8

A recent example of oxazole formation by 1,3-dipolar cycloaddition of a nitrile with a carbenoid generated by rhodium(II) acetate catalysed decomposition of dimethyldiazomalonate is shown in equation 69.[155]



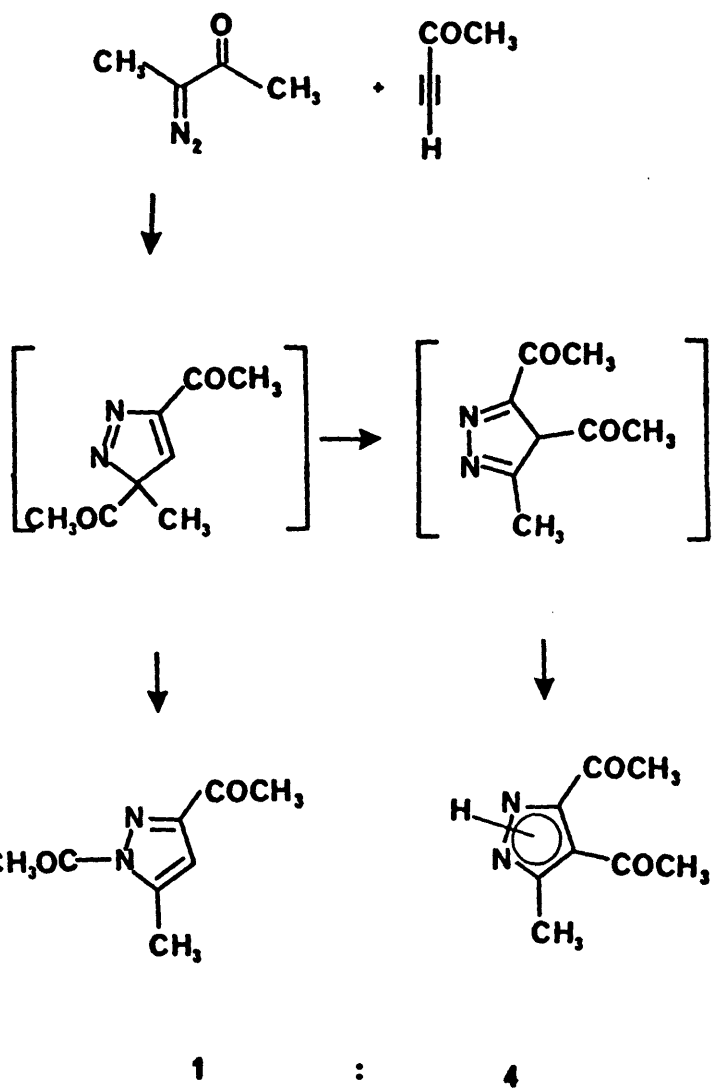
(69)

1,3-Dipolar cycloaddition of a diazocarbonyl without loss of nitrogen is also possible. For example, when disubstituted α-diazocarbonyl compounds react with disubstituted alkynes, pyrazolenines are formed initially which rearrange to N(2)substituted pyrazoles by a [1,5]migration of the acyl or carbalkoxy group (equation 70).[156] However, with monosubstituted alkynes, competitive [1,5]migration of the acyl or carbalkoxy group to N(2) and C(4) takes place (equation 71).[157]



R = OCH_3 , Ph

(70)

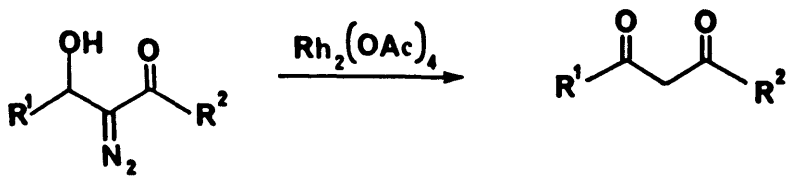


(71)

1 : 4

1.2.10. *1,2-Hydride and alkyl shifts*

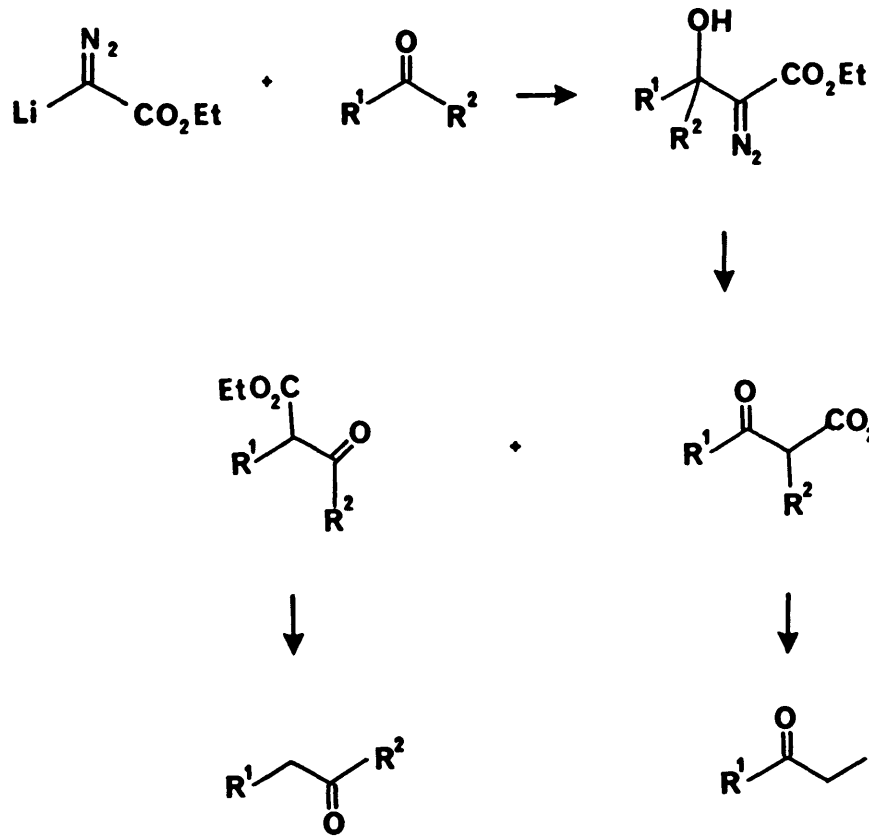
1,2-Hydride shift in α-diazo-β-hydroxy-carbonyl compounds to give β-dicarbonyl compounds is a useful process synthetically and is readily catalysed by rhodium(II) acetate (equation 72).[158]



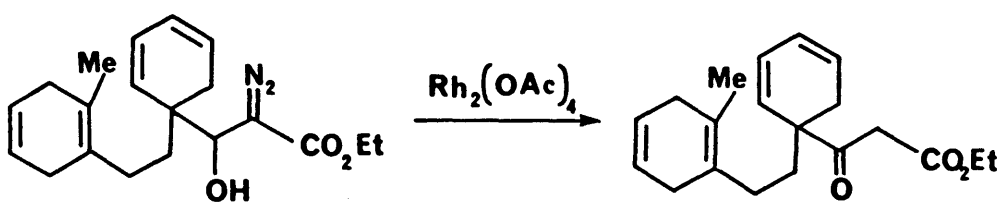
(72)

Since α-diazo-β-hydroxy-carbonyl compounds are easily prepared by reaction of lithiated diazocarbonyl compounds with aldehydes and ketones, e.g. equation 13, this rearrangement is part of a three step ketone homologation (Scheme 9)[159] which is highly regioselective, with the smaller group migrating preferentially in the rearrangement step.

A recent example of such a rhodium(II) acetate catalysed 1,2-hydride shift in synthesis is in Corey's[43] synthesis of atractyligenin; the rearrangement step is illustrated in equation 73. 1,2-Alkyl shifts have been used in thiepin and oxepin preparation,[160,161] e.g. as in equation 74. Interestingly, the C-4 methyl group of the diazo precursor is necessary for thiepin formation, replacement by hydrogen gives 4-methylene-4*H*-thiopyrans *via* 1,2-hydride shifts.[161]

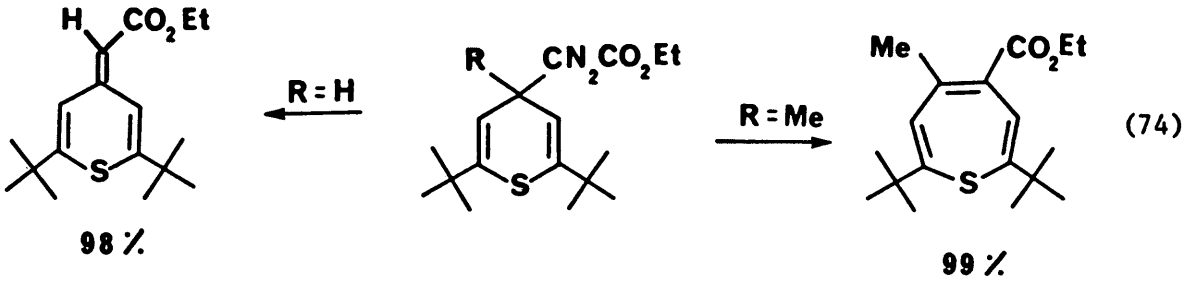


Scheme 9



(73)

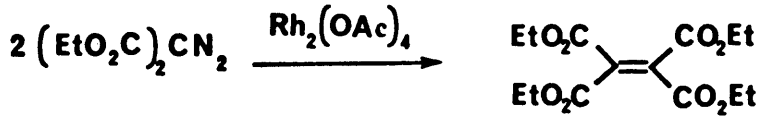
72 %



(74)

1.2.11. *Formation of carbene dimers*

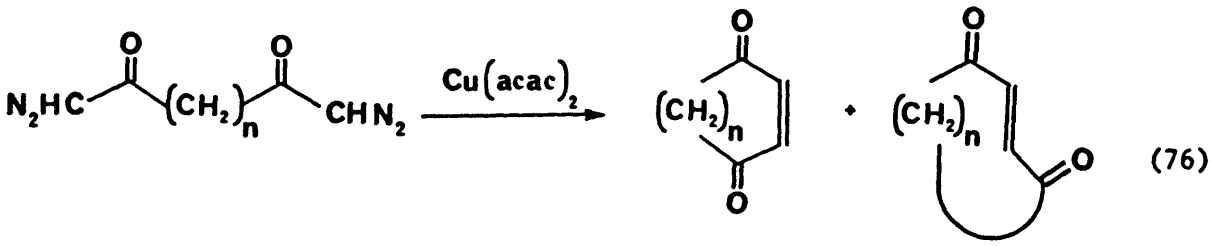
In many metal catalysed decompositions of α-diazocarbonyl compounds, notably EDA which forms diethyl fumarate and maleate,[162] carbene dimers are obtained as sideproducts. However, in inert solvents, the coupling process can predominate and the dimeric products can be isolated, often in good yield, e.g. equation 75.[163]



(75)

Intramolecular coupling of *bis* diazoketones under $Cu(acac)_2$ catalysis formed cycloalk-2-ene-1,4-diones[164] in 25-80% yield; 8-, 11-, 12-, 13-, 14-, 16-, and 20- membered rings are accessible (equation 76) in this way, and mixtures of *cis* and *trans* isomers are possible.

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(76)

n = 4, 7, 8, 9, 10, 12, 16

n = 7, 8, 9, 10, 12, 16

1.3 References

1. For comprehensive descriptions of diazo compounds see:
   (a) 'The Chemistry of Diazonium and Diazo Groups', ed. S. Patai, Wiley, New York, 1978, Vol. 1 and 2;
   (b) 'Carbene Chemistry', W. Kirmse, Academic Press, New York, 1971, 2nd ed.;
   (c) 'Diazo Compounds - Properties and Synthesis', M. Regitz and G. Maas, Academic Press, 1986;
   (d) 'Diazoalkanes', M. Regitz, G. Thieme, Verlag, Stuttgart, 1977;
   (e) 'Newer Methods of Preparative Organic Chemistry', F. Weygand and H.J. Bestmann, 1964, 3, 451;
   (f) 'Transition - metal Catalysed Decomposition of Aliphatic Diazo Compounds - New Results and Applications in Organic Synthesis', G. Maas, *Top. Curr. Chem.*, 1987, 137, 75.
2. T. Curtius, *Ber.*, 1883, 16, 2230.
3. F. Arndt, B. Eistert, and W. Partale, *Ber*, 1927, 60B, 1364;
   F. Arndt and J. Amende, *Ber.*, 1928, 61B, 1122;
   F. Arndt, B. Eistert, and J. Amende, *Ber.*, 1928, 61B, 1949.
4. W. Bradley and R. Robinson, *J. Chem. Soc.*, 1928, 1310.
5. G.R. Pettit and P.S. Nelson, *J. Org. Chem.*, 1986, 51, 1282.
6. H.A. DeWald and A.M. Moore, *J. Am. Chem. Soc.*, 1958, 80, 3941;
   F. Weygand, H.J. Bestmann and E. Klieger, *Chem. Ber.*, 1958, 91, 1037.
7. M.S. Newman and P. Beal, *J. Am. Chem. Soc.*, 1949, 71, 1506.
8. M. Berenbom and W.S. Fones, *J. Am. Chem. Soc.*, 1949, 71, 1629.

9. L.T. Scott and M.A. Minton, *J. Org. Chem.*, 1977, 42, 3757.

10. W. Bradley and R. Robinson, *J. Am. Chem. Soc.*, 1930, 52, 1558.

11. D. Hodson, G. Holt, and D.K. Wall, *J. Chem. Soc.*, 1970, 971.

12. B.M. Dilworth and M.A. McKervey, unpublished results.

13. A.L. Wilds and A.L. Meader, *J. Org. Chem.*, 1948, 13, 763.

14. T. Hudlicky, F.J. Koszyk, T.M. Kutchen, and J.P. Sheth, *J. Org. Chem.*, 1980, 45, 5020.

15. P. Yates, D.G. Farnum, and D.W. Wiley, *Chem. and Ind.*, 1958, 69.

16. R.P. Short, J.-M. Revol, B.C. Ranu, and T. Hudlicky, *J. Org. Chem.*, 1983, 48, 4453.

17. M. Regitz, *Angew. Chem. Int. Ed. Engl.*, 1967, 6, 733; *Synthesis*, 1972, 351.

18. M. Regitz, *Tetrahedron Lett.*, 1964, 1403; *Chem. Ber.*, 1965, 98, 1210.

19. Y.K. Rao and M. Nagarajan, *Indian J. Chem., Sect. B.*, 1986, 25, 735.

20. L. Lombardo and L.N. Mander, *Synthesis*, 1980, 368.

21. M. Regitz, F. Menz, and J. Rüter, *Tetrahedron Lett.*, 1967, 739.

22. M. Regitz, J. Rüter, and A. Liedhegener, *Org. Synth.*, 1971, 51, 86.

23. G.G. Hazen, L.M. Weinstock, R. Connell and F.W. Bollinger, *Synth. Commun.*, 1981, 11, 947.

24. T.J. Curphey, *Org. Prep. Proced. Int.*, 1981, 13, 112.

25. M. Regitz, J. Hocker, and A. Liedhegener, *Org. Synth.*, Coll. Vol. V, 1973, 179.

26. D.F. Taber, R.E. Ruckle, Jr., and M.J. Hennessy, *J. Org. Chem.*, 1986, 51, 4077.

27. W.R. Roush, D. Feitler, and J. Rebek, *Tetrahedron Lett.*, 1974, 1391; H. Dürr, G. Hauck, W. Brück, and H. Kober, *Z. Naturforsch*, 1981, 86B, 1149.

28. N.E. Searle, *Org. Synth.*, Coll. Vol. IV, 1963, 424.

29. D. Hauser and H.P. Sigg, *Helv. Chim. Acta.*, 1967, 50, 1327.

30. M.P. Cava, R.L. Little, and D.R. Napier, *J. Am. Chem. Soc.*, 1958, 80, 2257.

31. J.M. Muchowski, *Tetrahedron Lett.*, 1966, 1773.

32. N.L. Allinger and L.A. Freiberg, *J. Org. Chem.*, 1962, 27, 1490.

33. M. Regitz, in ref. 1(c).

34. H.O. House and C.J. Blankley, *J. Org. Chem.*, 1968, 33, 53; C.J. Blankley, F.J. Sauter, and H.O. House, *Org. Synth.*, 1969, 49, 22.

35. R. Sen, T.S. Widlanski, V. Balogh-Nair, and K. Nakanishi, *J. Am. Chem. Soc.*, 1983, 105, 5160; R. Sen, J.D. Carriker, V. Balogh-Nair, and K. Nakanishi, *J. Am. Chem. Soc.*, 1982, 104, 3214.

36. S.A. Keilbaugh and E.R. Thornton, *J. Am. Chem. Soc.*, 1983, 105, 3283.

37. J. Fink and M. Regitz, *Synthesis*, 1985, 569.

38. P. Yates, F.X. Garneau, and J.P. Lokensgard, *Tetrahedron*, 1975, 31, 1979.

39. U. Schollkopf, B. Banhidai, H. Frasnelli, R. Meyer, and H. Beckhaus, *Liebegs Ann. Chem.*, 1974, 1767.

40. U. Schollkopf and N. Rieber, *Chem. Ber.*, 1969, 102, 488.

41. U. Schollkopf, F. Gerhart, M. Reetz, H. Frasnelli, and H. Schumacher, *Justus Liebegs Ann. Chem.*, 1968, 716, 204; F. Gerhart, U. Schollkopf, and H. Schumacher, *Angew. Chem.*, 1967, 79, 50; *Angew. Chem. Int. Ed. Engl.*, 1967, 6, 74.

42. U. Schollkopf, P. Tonne, H. Schafer, and P. Markusch, *Justus Liebegs Ann. Chem.*, 1969, 722, 45.

43. A.K. Singh, R.K. Bakshi, and E.J. Corey, *J. Am. Chem. Soc.*, 1987, 109, 6187.

44. C.J. Moody and R.J. Taylor, *Tetrahedron Lett.*, 1987, 28, 5351; J.C. Heslin and C.J. Moody, *J. Chem. Soc., Perkin Trans 1*, 1988, 1417.

45. O. Silberrad and C.S. Roy, *J. Chem. Soc.*, 1906, 89, 179.

46. V. Dave and E. Warnhoff, *Org. React.*, 1970, 18, 217.

47. H. Nozaki, S. Moriuti, M. Yamabe, and R. Noyori, *Tetrahedron Lett.*, 1966, 59.

48. W.R. Moser, *J. Am. Chem. Soc.*, 1969, 91, 1135; 1141.

49. R.G. Salomon and J.K. Kochi, *J. Am. Chem. Soc.*, 1973, 95, 3300.

50. R. Paulissen, A.J. Hubert, and P. Teyssie, *Tetrahedron Lett.*, 1972, 1465.

51. M.P. Doyle, W.H. Tamblyn, W.E. Buhro, and R.L. Dorow, *Tetrahedron Lett.*, 1981, 22, 1783.

52. (a) R. Paulissen, H. Reimlinger, E. Hayez, A.J. Hubert, and P. Teyssie, *Tetrahedron Lett.*, 1973, 2233;
(b) A.J. Hubert, A.F. Noels, A.J. Anciaiux, and P. Teyssie, *Synthesis*, 1976, 600.

53. M.P. Doyle, *Chem. Rev.*, 1986, 86, 919; *Acc. Chem. Res.*, 1986, 19, 348.

54. F.A. Cotton, and R.A. Walton, 'Multiple Bonds Between Metal Atoms', Wiley, New York, 1982, p.311.

55. R.S. Drago, J.R. Long, and R. Cosmano, *Inorg. Chem.*, 1982, 21, 2196.

56. M.P. Doyle, R.L. Dorow, W.H. Tamblyn, and W.E. Buhro, *Tetrahedron Lett.*, 1982, 23, 2261.

57. (a) M.P. Doyle, R.L. Dorow, W.E. Buhro, J.H. Griffin, W.H. Tamblyn, and M.L. Trudell, *Organometallics*, 1984, 3, 44;
(b) M.P. Doyle, K.-L. Loh, K.M. DeVries, and M.S. Chinn, *Tetrahedron Lett.*, 1987, 28, 833.

58. A. Demonceau, A.F. Noels, A.J. Hubert, and P. Teyssie, *Bull. Soc. Chim. Belg.*, 1984, 93, 945.

59. (a) H.J. Callot and F. Metz, *Tetrahedron Lett.*, 1982, 23, 4321;
(b) H.J. Callot, F. Metz, and C. Piechocki, *Tetrahedron*, 1982, 38, 2365.

60. H. Nozaki, H. Takaya, S. Moriuti, and R. Noyori, *Tetrahedron*, 1968, 24, 3655.

61. T. Aratani, Y. Yoneyoshi, and T. Nagase, *Tetrahedron Lett.*, 1975, 1707.

62. T. Aratani, Y. Yoneyoshi, and T. Nagase, *Tetrahedron Lett.*, 1982, 23, 685.

63. H. Brunner and W. Miehling, *Monatsh. Chem.*, 1984, 115, 1237.

64. S.A. Matlin, W.J. Lough, L. Chan, D.M.H. Abram, and Z. Zhou, *J. Chem. Soc., Chem. Commun.*, 1984, 1038.

65. H. Fritschi, U. Leutenegger, and A. Pfaltz, *Angew. Chem. Int. Ed. Engl.*, 1986, 25, 1005.

66. A.J. Anciaux, A.J. Hubert, A.F. Noels, N. Petiniot, and P. Teyssie, *J. Org. Chem.*, 1980, 45, 695.

67. M.P. Doyle, D. Van Leusen, and W.H. Tamblyn, *Synthesis*, 1981, 787.

68. A. Nakamura, T. Koyama, and S. Otsuka, *Bull. Chem. Soc. Jpn.*, 1978, 51, 593.

69. A.J. Anciaux, A. Demonceau, A.F. Noels, R. Warin, A.J. Hubert, and P. Teyssie, *Tetrahedron*, 1983, 39, 2169.

70. U. Mende, B. Raduchel, W. Skuballa, and H. Vorbruggen, *Tetrahedron Lett.*, 1975, 629.

71. M.W. Majchrzak and A. Kotelko, *Synthesis*, 1983, 469.

72. G. Stork and J. Ficini, *J. Am. Chem. Soc.*, 1961, 83, 4678.

73. E.J. Corey, G. Wess, Y.B. Xiang, and A.K. Singh, *J. Am. Chem. Soc.*, 1987, 109, 4717; E.J. Corey, J.G. Reid, A.G. Myers, and R.W. Hahl, *J. Am. Chem. Soc.*, 1987, 109, 918; see also ref. 43.

74. H.M.L. Davies, C.E.M. Oldenburg, M.J. McAfee, J.G. Nordahl, J.P. Henretta, and K.R. Romines, *Tetrahedron Lett.*, 1988, 29, 975.

75. J. Adams, R. Frenette, M. Belley, F. Chibante, and J.P. Springer, *J. Am. Chem. Soc.*, 1987, 109, 5432; J. Adams and M. Belley, *Tetrahedron Lett.*, 1986, 27, 2075.

76. B. Tinant, J.P. Declercq, M. Van Meerssche, P. Kok, G. Rozing, F. Scott, M. Demuynck, N.D. Sinha, P. De Clercq, and M. Vandewalle, *Bull. Soc. Chim. Belg.*, 1987, 96, 81.

77. L. Wolff, *Justus Liebegs Ann. Chem.*, 1912, 394, 23.

78. A.B. Smith, B.H. Toder, and S.J. Branca, *J. Am. Chem. Soc.*, 1984, 106, 3995; A.B. Smith, B.H. Toder, R.E. Richmond, and S.J. Branca, *J. Am. Chem. Soc.*, 1984, 106, 4001.

79. G. Maier, H.P. Reisenauer, and T. Sayrac, *Chem. Ber.*, 1982, 115, 2192.

80. Y. Ogata, Y. Sawaki, and T. Ohno, *J. Am. Chem. Soc.*, 1982, 104, 216.

81. W. Ruhl, F. Bolsing, E. Hofer, D. Speer, and M. Jansen, *Z. Naturforsch*, 1986, 41B, 772.

82. O.L. Chapman, J. Gano, P.R. West, M. Regitz, and G. Maas, *J. Am. Chem. Soc.*, 1981, 103, 7033.

83. N.P. Hacker and N.J. Turro, *Tetrahedron Lett.*, 1982, 23, 1771.

84. M. Torres, J.L. Bourdelande, A. Clement, and O.P. Strausz, *J. Am. Chem. Soc.*, 1983, 105, 1698.

85. R.J. McMahon, O.L. Chapman, R.A. Hayes, T.C. Hess, and H.-P. Krimmer, *J. Am. Chem. Soc.*, 1985, 107, 7597.

86. K. Tanigaki and T.W. Ebbesen, *J. Am. Chem. Soc.*, 1987, 109, 5883.

87. M.A. Blaustein and J.A. Berson, *Tetrahedron Lett.*, 1981, 22, 1081.

88. M. Torres, J. Ribo, A. Clement, and O.P. Strausz, *Can. J. Chem.*, 1983, 61, 996.

89. F. Kaplan and M.L. Mitchell, *Tetrahedron Lett.*, 1979, 759.

90. R.A. Cormier, *Tetrahedron Lett.*, 1980, 21, 2021.

91. M. Banciu, *Rev. Roum. Chim.*, 1982, 27, 769; M. Banciu, M. Elian, A. Banciu, C. Draghici, and E. Cioranescu, *Rev. Roum. Chim.*, 1986, 31, 1019.

92. H.W. Moore and M.J. Arnold, *J. Org. Chem.*, 1983, 48, 3365.

93. R.G. Micetich, S.N. Maiti, M. Tanaka, T. Yamazaki, and K. Ogawa, *J. Org. Chem.*, 1986, 51, 853.

94. W.J. Leanza, F. DiNinno, D.A. Muthard, R.R. Wilkening, K.J. Wildonger, R.W. Ratcliffe, and B.G. Christensen, *Tetrahedron*, 1983, 39, 2505.

95. D.D. Keith, J. Tengi, P. Rossman, L. Todaro, and M. Wiegele, *Tetrahedron*, 1983, 39, 2445.

96. R.A. Volkmann, R.D. Carroll, R.B. Drolet, M.L. Elliott, and B.S. Moore, *J. Org. Chem.*, 1982, 47, 3344.

97. J.C. Kapur and H.P. Fasel, *Tetrahedron Lett.*, 1985, 26, 3875.

98. T.B. Patrick, J.J. Scheibel, and G.L. Cantrell, *J. Org. Chem.*, 1981, 46, 3917.

99. S. Elz and W. Schunack, *Z. Naturforsch*, 1987, 42B, 238.

100. T.L. Ho, B. Gopalan, and J.J. Nestor, Jr., *J. Org. Chem.*, 1986, 51, 2405.

101. A.F. Noels, A. Demonceau, N. Petiniot, A.J. Hubert, and P. Teyssie, *Tetrahedron*, 1982, 38, 2733.

102. V. Bagheri, M.P. Doyle, J. Taunton, and E.E. Claxton, *J. Org. Chem.*, 1988, 53, 6158.

103. M.A. McKervey and P. Ratananukul, *Tetrahedron Lett.*, 1982, 23, 2509.

104. M.P. Moyer, P.L. Feldman, and H. Rapoport, *J. Org. Chem.*, 1985, 50, 5223.

105. L.D. Cama and B.G. Christensen, *Tetrahedron Lett.*, 1978, 4233.

106. T.N. Salzmann, R.W. Ratcliffe, B.G. Christensen, and F.A. Bouffard, *J. Am. Chem. Soc.*, 1980, 102, 6161.

107. For example, D. Habich and W. Hartwig, *Tetrahedron Lett.*, 1987, 28, 781; D.A. Evans and E.B. Sjogren, *Tetrahedron Lett.*, 1986, 27, 3119.

108. M.A. McKervey and P. Ratananukul, *Tetrahedron Lett.*, 1983, 24, 117.

109. P.J. Giddings, D.I. John, and E.J. Thomas, *Tetrahedron Lett.*, 1980, 21, 399.

110. D.J. Buckley and M.A. McKervey, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2193.

111. T.G. Back and R.G. Kerr, *J. Organomet. Chem.*, 1985, 286, 171.

112. P.J. Giddings, D.I. John, and E.J. Thomas, *Tetrahedron Lett.*, 1980, 21, 395.

113. C.D. Foulds, A.A. Jaxa-Chamiec, A.C. O'Sullivan, and P.G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1984, 21.

114. K. Hirai, Y. Iwano, and K. Fujimoto, *Tetrahedron Lett.*, 1982, 23, 4021.

115. M.P. Doyle, V. Bagheri, and N.K. Harn, *Tetrahedron Lett.*, 1988, 29, 5119.

116. H.M.L. Davies and L.V.T. Crisco, *Tetrahedron Lett.*, 1987, 28, 371.

117. M.P. Doyle, J.H. Griffin, M.S. Chinn, and D. Van Leusen, *J. Org. Chem.*, 1984, 49, 1917.

118. M.C. Pirrung and J.A. Werner, *J. Am. Chem. Soc.*, 1986, 108, 6060.

119. E.J. Roskamp and C.R. Johnson, *J. Am. Chem. Soc.*, 1986, 108, 6062.

120. A. Padwa, G.E. Fryxell, and Lin Zhi, *J. Org. Chem.*, 1988, 53, 2875.

121. A.P. Marchand and N. MacBrockway, *Chem. Rev.*, 1974, 74, 431.

122. A. Demonceau, A.F. Noels, A.J. Hubert, and P. Teyssie, *J. Chem. Soc., Chem. Commun.*, 1981, 688.

123. B.L. Buckwalter, I.R. Burfitt, H. Felkin, M. Joly-Goudket, K. Naemura, M.F. Salomon, E. Wenkert, and P.M. Wovkulich, *J. Am. Chem. Soc.*, 1978, 100, 6445.

124. D.F. Taber and E.H. Petty, *J. Org. Chem.*, 1982, 47, 4808.

125. D.F. Taber and K. Raman, *J. Am. Chem. Soc.*, 1983, 105, 5935.

126. D.F. Taber and R.E. Ruckle, *Tetrahedron Lett.*, 1985, 26, 3059.

127. (a) D.F. Taber, E.H. Petty, and K. Raman, *J. Am. Chem. Soc.*, 1985, 107, 196;

(b) H. Ledon, G. Linstrumelle, and S. Julia, *Tetrahedron Lett.*, 1973, 25.

128. D.F. Taber and R.E. Ruckle, *J. Am. Chem. Soc.*, 1986, 108, 7686.

129. G. Stork and K. Nakatani, *Tetrahedron Lett.*, 1988, 29, 2283.

130. K. Sakai, T. Fujimoto, M. Yamashita, and K. Kondo, *Tetrahedron Lett.*, 1985, 26, 2089.

131. M.P. Doyle, M.S. Shanklin, S.-M. Oon, H.Q. Pho, F.R. van der Heide, W.R. Veal, *J. Org. Chem.*, 1988, 53, 3384.

132. D.E. Cane and P.J. Thomas, *J. Am. Chem. Soc.*, 1984, 106, 5295.

133. K. Nakatani, *Tetrahedron Lett.*, 1987, 28, 165.

134. E. Buchner and T. Curtius, *Ber.*, 1885, 18, 2377; E. Buchner, *Ber.*, 1896, 29, 106.

135. G. Linstrumelle, *Bull. Soc. Chim. Fr.*, 1970, 920.

136. (a) A.J. Anciaux, A. Demonceau, A.J. Hubert, A.F. Noels, N. Petiniot, and P. Teyssie, *J. Chem. Soc., Chem. Commun.*, 1980, 765; (b) A.J. Anciaux, A. Demonceau, A.F. Noels, A.J. Hubert, R. Warin, and P. Teyssie, *J. Org. Chem.*, 1981, 46, 873.

137. M.A. McKervey, D.N. Russell, and M.F. Twohig, *J. Chem. Soc., Chem. Commun.*, 1985, 491.

138. M.A. McKervey, S.M. Tuladhar, and M.F. Twohig, *J. Chem. Soc., Chem. Commun.*, 1984, 129.

139. A. Costantino, G. Linstrumelle, and S. Julia, *Bull. Soc. Chim. Fr.*, 1970, 907; 912.

140. L.T. Scott, M.A. Minton, and M.A. Kirms, *J. Am. Chem. Soc.*, 1980, 102, 6311.

141. H. Gugel, K.-P. Zeller, and C. Wentrup, *Chem. Ber.*, 1983, 116, 2775.

142. M.P. Doyle, M.S. Shanklin, and H.Q. Pho, *Tetrahedron Lett.*, 1988, 29, 2639.

143. A. Pusino, A. Saba, and V. Rosnati, *Tetrahedron*, 1986, 42, 4319.

144. E.C. Taylor and H.M.L. Davies, *Tetrahedron Lett.*, 1983, 24, 5453.

145. M.P. Doyle, M.S. Shanklin, H.Q. Pho, and S.N. Mahapatro, *J. Org. Chem.*, 1988, 53, 1017.

146. (a) C. Iwata, M. Yamada, Y. Shinoo, K. Kobayashi, and H. Okada, *Chem. Pharm. Bull.*, 1980, 28, 1932; (b) C. Iwata, K. Miyashita, Y. Koga, Y. Shinoo, M. Yamada, and T. Tanaka, *Chem. Pharm. Bull.*, 1983, 31, 2308;

(c) C. Iwata, T. Morie, N. Maezaki, H. Shimamura, T. Tanaka, and T. Imanishi, *J. Chem. Soc., Chem. Commun.*, 1984, 930;

(d) C. Iwata, K. Miyashita, T. Imao, K. Masuda, N. Kondo, and S. Uchida, *Chem. Pharm. Bull.*, 1985, 33, 853.

147. A. Padwa, T.J. Wisnieff, and E.J. Walsh, *J. Org. Chem.*, 1986, 51, 5036.

148. (a) S.D. Burke and P.A. Grieco, *Org. React.*, W.G. Dauben, ed., Wiley, 1979, 26, 361.

(b) A.B. Smith, *Tetrahedron*, 1981, 37, 2407; A.B. Smith, B.H. Toder, S.J. Branca, and R.K. Dieter, *J. Am. Chem. Soc.*, 1981, 103, 1996; A.B. Smith and R.K. Dieter, *J. Am. Chem. Soc.*, 1981, 103, 2009; 2017.

149. J.M. Hook, L.N. Mander, and R. Urech, *J. Org. Chem.*, 1984, 49, 3250; L. Lombardo, L.N. Mander, and J.V. Turner, *J. Am. Chem. Soc.*, 1980, 102, 6626; J.M. Hook, L.N. Mander, and R. Urech, *J. Am. Chem. Soc.*, 1980, 102, 6628.

150. S.K. Maity, S. Bhattacharyya, and D. Mukherjee, *J. Chem. Soc., Chem. Commun.*, 1986, 481.

151. G. Binsch, R. Huisgen, and H. Konig, *Chem. Ber.*, 1964, 97, 2893.

152. R. Huisgen, G. Binsch, and H. Konig, *Chem. Ber.*, 1964, 97, 2884.

153. H. Dworschak and F. Weygand, *Chem. Ber.*, 1968, 101, 289.

154. R. Huisgen, H.J. Sturm, and G. Binsch, *Chem. Ber.*, 1964, 97, 2864.

155. R. Connell, F. Scavo, P. Helquist, and B. Akermark, *Tetrahedron Lett.*, 1986, 27, 5559.

156. R. Huisgen, M.P.B. Verderol, A. Gieren, and V. Lamm, *Angew. Chem. Int. Ed. Engl.*, 1981, 20, 694.

157. M. Franck-Newmann and C. Dietrich-Buchecker, *Tetrahedron Lett.*, 1976, 2069.

158. R. Pellicciari, R. Fringuelli, P. Ceccherelli, and E. Sisani *J. Chem. Soc., Chem. Commun.*, 1979, 959; R. Pellicciari, E. Sisani, and R. Fringuelli, *Tetrahedron Lett.*, 1980, 21, 4039; R. Pellicciari, R. Fringuelli, E. Sisani, and M. Curini, *J. Chem. Soc. Perkin Trans 1*, 1981, 2566; R. Pellicciari, E. Castagnino, and S. Corsano, *J. Chem. Research (S)*, 1979, 76; R. Pellicciari, B. Natalini, S. Cecchetti, and R. Fringuelli, *J. Chem. Soc., Perkin Trans 1*, 1985, 493.

159. K. Nagao, M. Chiba, and S.-W. Kim, *Synthesis*, 1983, 197.

160. K.L. Hoffmann and M. Regitz, *Tetrahedron Lett.*, 1983, 24, 5355; K.L. Hoffmann, G. Maas, and M. Regitz, *Chem. Ber.*, 1985, 118, 3700.

161. K. Nishino, S. Yano, Y. Kohashi, K. Yamamoto, and I. Murata, *J. Am. Chem. Soc.*, 1979, 101, 5059; K. Yamamoto, S. Yamazaki, Y. Kohashi, A. Matsukawa, and I. Murata, *Chem. Lett.*, 1982, 1843; I. Murata and K. Nakasuji, *Top. Curr. Chem.*, 1981, 97, 33.

162. D.S. Wulfman, B.W. Peace, and R.S. McDaniel, Jr., *Tetrahedron*, 1976, 32, 1251.

163. R.J. Gillespie and A.E.A. Porter, *J. Chem. Soc., Perkin Trans 1*, 1979, 2624.

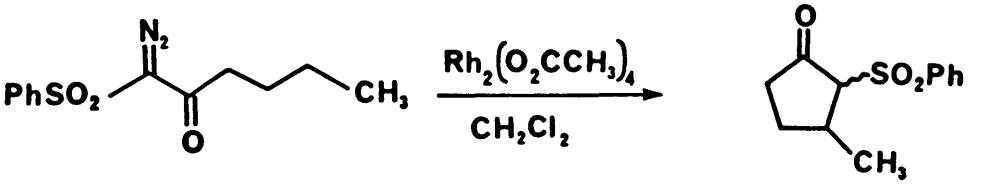
164. S. Kulkowit and M.A. McKervey, *J. Chem. Soc., Chem. Commun.*, 1978, 1069.

CHAPTER 2

INTRAMOLECULAR C-H INSERTION REACTIONS OF α-DIAZO-β-KETO SULPHONES

2.1 Intramolecular C-H Insertion

Monteiro[1] has recently reported intramolecular C-H insertion on decomposition of α-diazo-β-keto sulphones catalysed by rhodium(II) acetate as illustrated by equation 1.

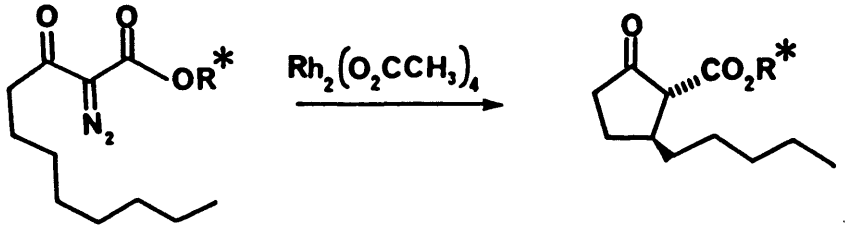


(1)

An earlier study[2] of thermal and copper catalysed decomposition of acyclic unsaturated α-diazo-β-keto phenylsulphones resulted only in poor yields of cyclopentanones from C-H insertion and addition reactions of the intermediate carbenes.

A preference for cyclopentanone formation is observed in intramolecular C-H insertion reactions of α-diazocarbonyl compounds and is believed to be due to a preference for a highly ordered six-membered transition state.[3] When rhodium catalysts with bulky ligands[4,5] were employed as decomposition catalysts in intermolecular C-H insertions of alkanes with EDA, changes in product ratios were observed as compared to less hindered catalysts, with enhanced substitution at primary C-H bonds, although substitution at secondary positions predominated. Thus it appears that catalyst-substrate interactions in the transition state for the C-H insertion reaction are significant and it was thought that replacement of rhodium(II) acetate by rhodium(II) carboxylates derived from chiral carboxylic acids would result in asymmetric induction in the C-H insertion step.

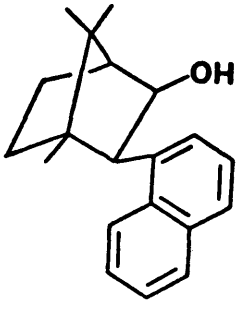
To date there has been no report of asymmetric induction in C-H insertion reactions of α-diazocarbonyl compounds by use of a chiral catalyst. However, some success in asymmetric cyclopropanation has been achieved through use of chiral copper catalysts (Section 1.2.1). The only report of asymmetric induction in C-H insertion reactions is by Taber and Raman,[6] who have cyclised an α-diazo-β-keto ester using an optically active alcohol as a chiral auxiliary resulting in good diastereoselection in the C-H insertion step (equation 2). The asymmetric induction in this case results in formation of diastereoisomers because of the presence of the chiral auxiliary.



(2)

Diastereoselectivity 87:13

R*OH =



However, only the *trans*-substituted cyclopentanone is formed. This diastereoselectivity is also indicative of a highly ordered transition state, thus offering promise to our hope of asymmetric induction by use of chiral rhodium(II) carboxylates. This catalytic route, if successful,

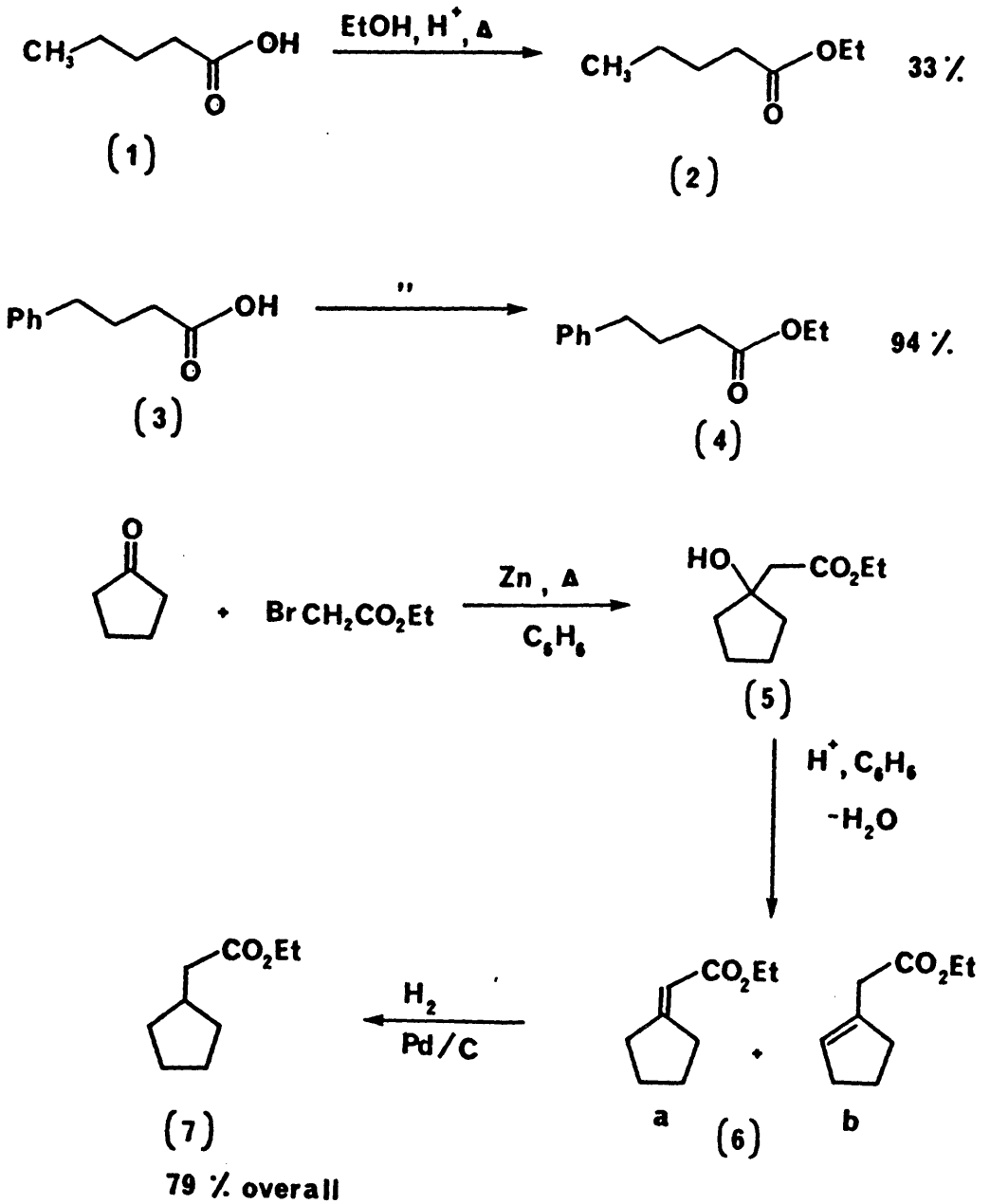
would be preferable to use of a chiral auxiliary, as it would obviate the necessity for 1 equivalent of a homochiral compound as starting material using instead a catalytic amount of a chiral rhodium(II) carboxylate.

Thus it was decided to firstly investigate the application of intramolecular C-H insertion reactions of α-diazo-β-keto sulphones in cyclopentanone synthesis, and secondly, to see if asymmetric induction was possible in such reactions through use of chiral rhodium(II) carboxylates.

2.1.1. *Preparation of the β-keto sulphones*

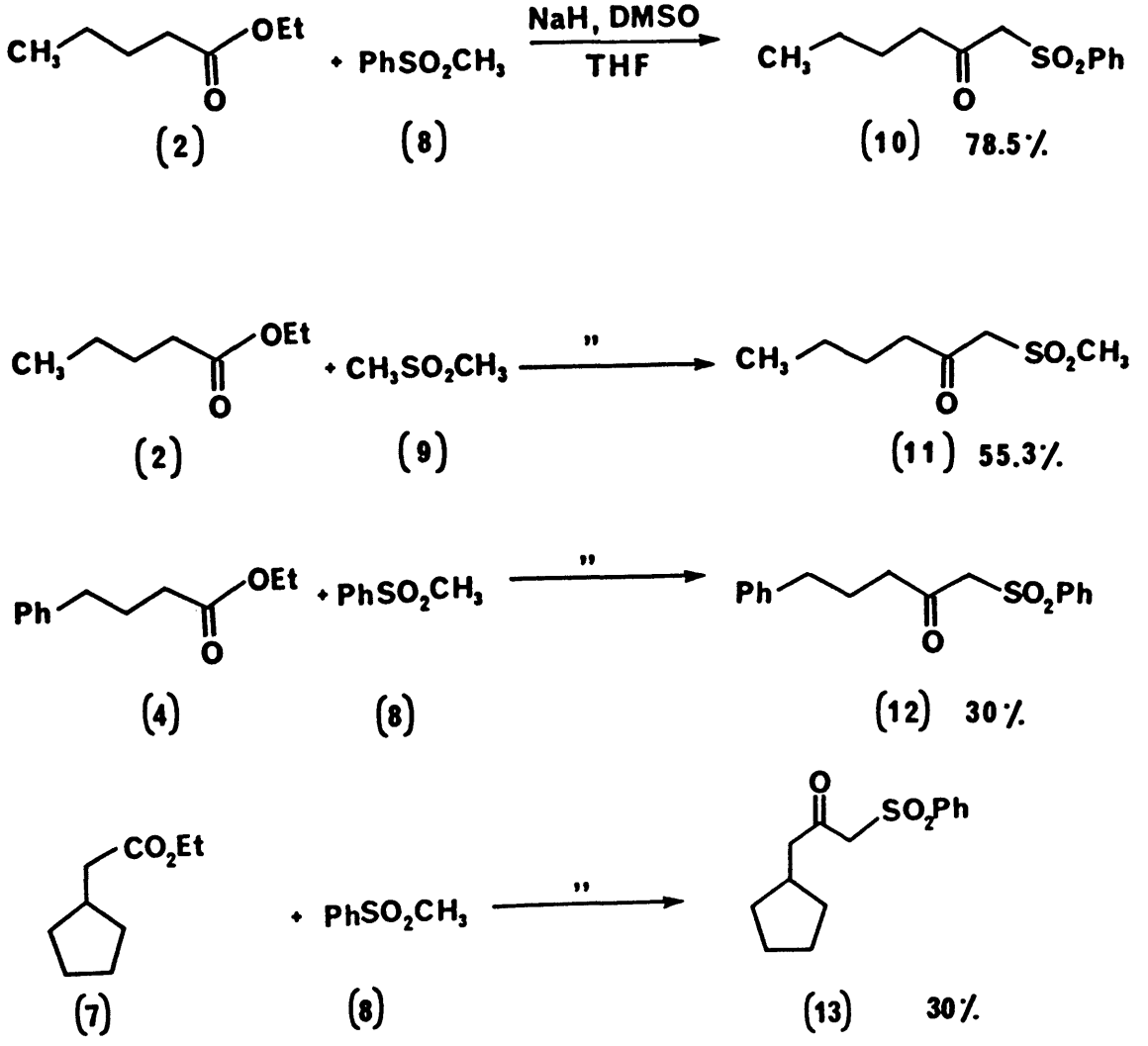
The general procedure used for the preparation of the β-keto sulphones involved condensation of the appropriate ester with the sulphonyl anion following Corey's method.[7] Scheme 1 shows the ester preparations.

Ethyl valerate (2) was prepared from commercially available valeric acid (1). Ethyl 3-phenylbutanoate (4)[8] was prepared by esterification of 3-phenylbutanoic acid (3). Ethyl cyclopentylacetate (7) was prepared by a Reformatsky reaction of ethyl bromoacetate and cyclopentanone to give the alcohol (5), dehydrated to a mixture of the regioisomeric unsaturated esters (6), followed by hydrogenation. Methyl phenyl sulphone (8) and dimethyl sulphone (9) were prepared by oxidation of thioanisole and dimethylsulphoxide respectively.


EtOH, H+, Δ
33 %
(1)
(2)
"
94 %
(3)
(4)
Br CH2CO2Et
Zn , Δ
C6H6
(5)
H+, C6H6
-H2O
H2
Pd/C
(7)
79 % overall
a
(6)
b

Scheme 1

Scheme 2 summarises the conversion of the esters to β-keto sulphones. Due to the acidity of β-keto sulphones, two equivalents of sulphonyl anion were required in each case. As a result the crude product contained equimolar mixtures of β-keto sulphone and sulphone.

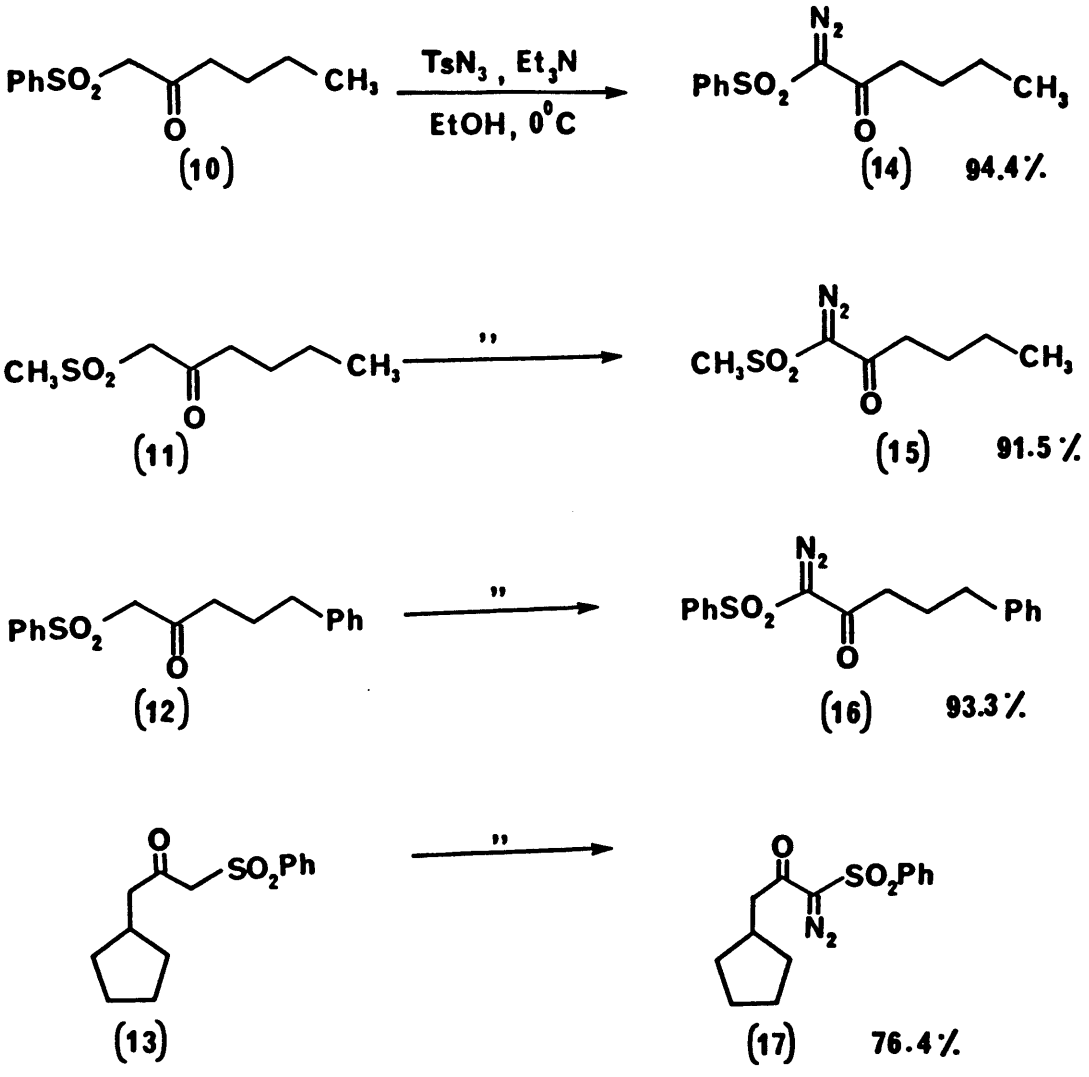


Scheme 2

In the case of dimethyl sulphone (9), this was easily removed by aqueous washing but for the methyl phenyl sulphone chromatographic separation was required (for 10 and 13) whereas β-keto sulphone (12) was obtained pure by recrystallisation.

2.1.2. *Diazo transfer to β-keto sulphones*

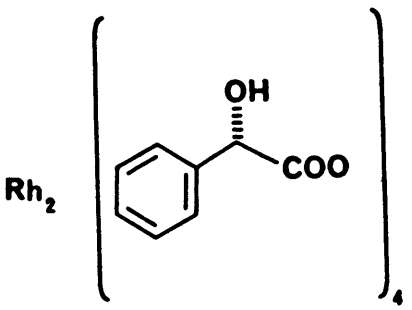
Monteiro[9] carried out diazo transfer to β-keto sulphones by use of an azidinium salt generated *in situ*. However, we found tosyl azide to be a satisfactory diazo transfer reagent giving excellent yields of the α-diazo-β-keto sulphones following the procedure of Regitz and co-workers.[10] Tosyl azide was prepared by Curphey's procedure[11] and stored at 0°C. The possibility of deacylation in the diazo transfer mentioned by Monteiro[9] did not cause any problems and although a small amount of an impurity, thought to be *p*-toluenesulphonamide, was present in the α-diazo-β-keto sulphones, this could be removed either by chromatography or after diazoketone decomposition, in the cyclopentanone purification. Its presence in the α-diazo-β-keto sulphones did not affect the C-H insertion reactions and it was easily removed from the cyclopentanones. Analytically pure samples of the α-diazo-β-keto sulphones were easily obtained by chromatography. In practice, however, it was found that passage of the crude product through a short column of silica to remove the baseline impurities gave the diazo substrates in sufficient purity for further reaction. Removal of the highly-coloured baseline impurities was essential, however, as these poisoned the rhodium(II) carboxylate catalysts if decomposition was attempted without purification. Scheme 3 summarises the preparation of the α-diazo-β-keto sulphones which were quite stable and could be stored at 0°C for several months without decomposition.



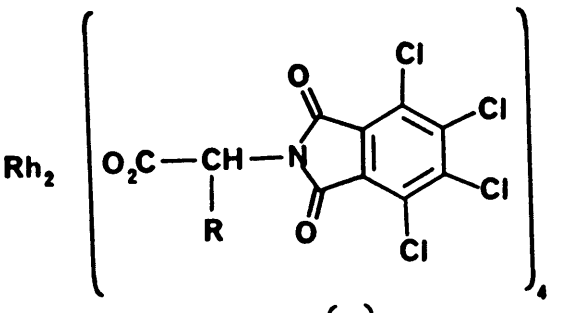
Scheme 3

2.1.3. *Preparation of chiral rhodium(II) carboxylates*

Our interest in this area began with rhodium(II) (S)-mandelate (18) [$Rh_2(mand)_4$], the preparation of which was reported by Cotton.[12] Although rhodium(II) carboxylates (19) derived from homochiral carboxylic acids were reported as catalysts for diazo ester decomposition in intermolecular C-H insertions,[5] no mention was made of the possibility of asymmetric induction in these reactions.



(18)



(19) R = CH_3, CH_2Ph

Preliminary results of asymmetric induction in α-diazoketone decomposition using $Rh_2(mand)_4$ as catalyst were encouraging. Therefore a series of homochiral rhodium(II) carboxylates were prepared for investigation.[13] Amino acids were chosen for initial studies as they are a ready source of homochiral carboxylic acids and because the α-nitrogen substituent is reminiscent of the α-hydroxy group of mandelic acid, with which catalyst some success had been achieved. Examination of the X-ray crystal structure of rhodium(II) mandelate[12] showed that the hydroxy group is not coordinated to rhodium,[14] and it is thought that this hydroxy group may play a part in the asymmetric induction obtained with this catalyst. When a catalyst was prepared using α-methoxy-α-phenylacetic acid,[15] i.e. mandelic acid where the hydroxy group was methylated, asymmetric induction in α-diazoketone decomposition with this catalyst was much lower than with rhodium(II) mandelate. Examination of the crystal structures of the two catalysts[12] shows that in rhodium(II) mandelate, an intramolecular hydrogen bond between the hydroxy group and a carboxylate oxygen limits rotation in the ligand thus giving a more rigid structure, whereas no hydrogen bond exists in the structure of rhodium(II) α-methoxy-α-phenylacetate and the phenyl groups of the ligands are arranged so as to minimise steric repulsions. Thus,

due to the α-hydroxy group of rhodium(II) mandelate a more rigid structure is present in the catalyst and this may be responsible for the enhanced asymmetric induction obtained with rhodium(II) mandelate compared to rhodium(II) α-methoxy-α-phenylacetate.

N-Protected L-amino acids were prepared by standard procedures.[16] The sulphonyl derivatives of L-proline and L-phenylalanine were generally prepared by treatment of a basic solution of the amino acid with the appropriate sulphonyl chloride. The compounds were characterised spectroscopically and were analytically pure when used in the catalyst preparations. In *N*-protected derivatives of L-proline, there are no N-H substituents for hydrogen bonding as in rhodium(II) mandelate but in the *N*-protected derivatives of L-phenylalanine a N-H bond is present in each. However, the effect observed due to the O-H bond in rhodium(II) mandelate compared to rhodium(II) α-methoxy-α-phenylacetate was not observed by comparison of catalysts derived from L-proline and L-phenylalanine derivatives. This indicates that the factors controlling asymmetric induction in rhodium(II) carboxylate derived α-diazocarbonyl decomposition are extremely sensitive to structural changes and cannot be generalised.

Rhodium(II) carboxylates were generally prepared from the sodium salt of rhodium(II) carbonate (20) and the appropriate carboxylic acid by a displacement reaction[17] (Table 2.1). The carbonate was in turn available in >90% yield[18] from rhodium(II) acetate.[19] Scheme 4 illustrates this reaction sequence.

Table 2.1 : Preparation of rhodium(II) carboxylates from rhodium carbonate.

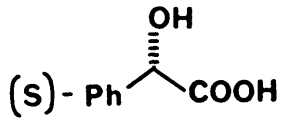
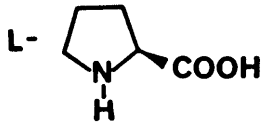
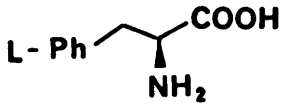
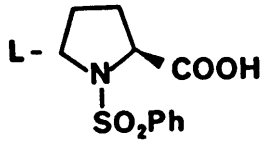
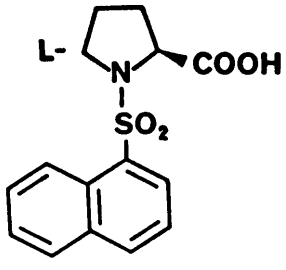
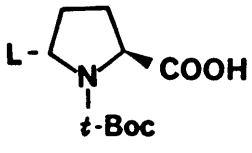
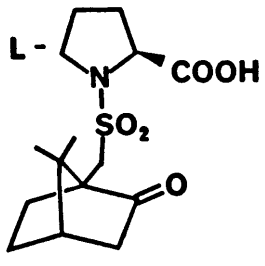
RCOOH	Catalyst	Yield %
	1	90
	2	Pale green powder only
	3	Pale green powder only
	4	90
	5	85
	6	77
	7	87

Table 2.1 contd.

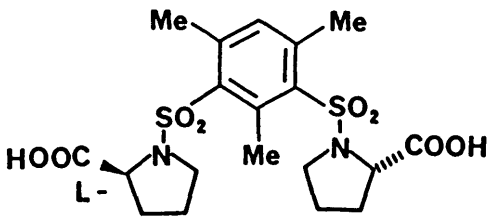
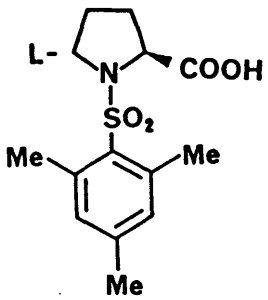
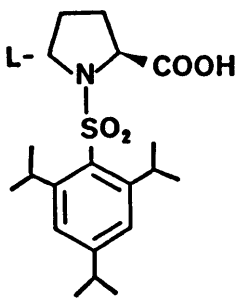
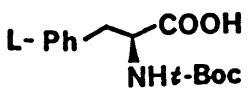
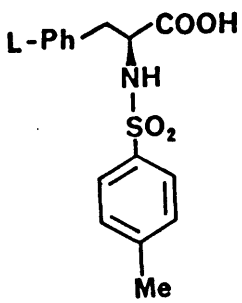
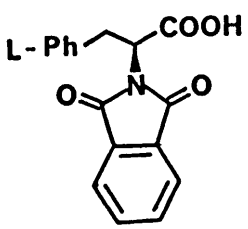
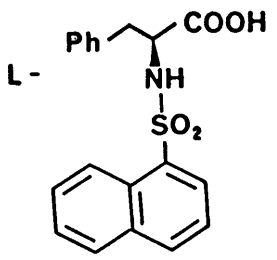
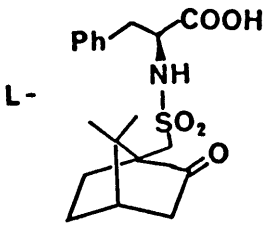
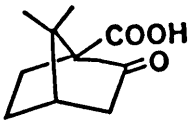
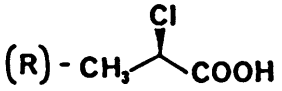
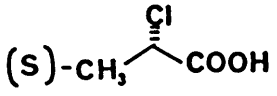
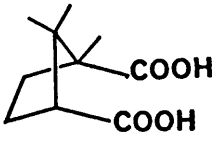
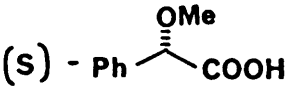
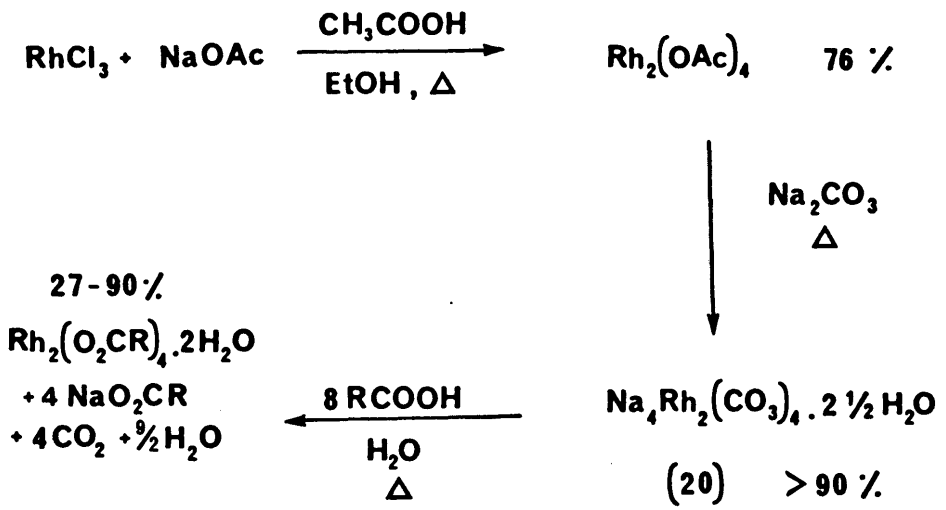
	8	69
	9	-
	10	pale green solid
	11	80
	12	62
	13	92

Table 2.1 contd.

	14	65
	15	27
	16	85
	17	52
	18	63
Tartaric Acid	19	Concentrated reaction mixture was a blue-green solid.
Lactic acid	20	"
	21	80
	22	-



Scheme 4

This displacement was very convenient; the catalysts formed as green or blue-green crystalline solids which could be collected by filtration while any excess carbonate and the sodium carboxylate were washed away in the aqueous filtrate. The rhodium(II) carboxylates were generally analytically pure and used without purification. However, chromatography on silica is possible with these complexes. The rhodium(II) mandelate prepared by this procedure was found to be more efficient catalytically and to result in higher asymmetric inductions than that prepared following Cotton's procedure.[12]

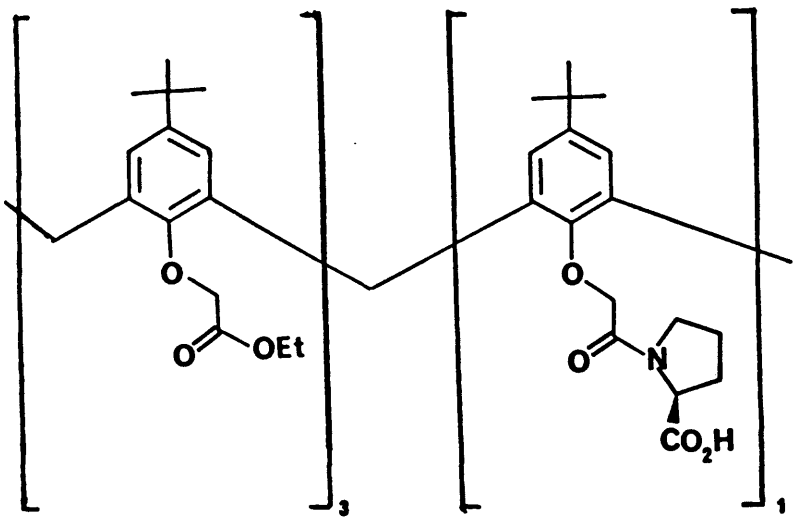
In the cases of the unprotected amino acids (entries 2 and 3) only a light green powder was formed, in agreement with the literature[20] which reports very low yields of rhodium(II) carboxylates with free amino acids. Studies of axial ligand substitution[14] show that colour changes occur in rhodium(II) carboxylates on changing the axial ligand. Thus a simple explanation for the poor yields is that instead of two axial water molecules, coordination by an amino group occurs to give more complex products. An alternative possibility is that the free NH or NH_2 group may change the pH of the solution. In reactions where the ratio of carbonate to carboxylic acid was 1:4 instead of 1:8, light green powders were obtained even with *N*-protected amino acids. It is unlikely that these green powders are dimeric rhodium species and it is thought that when the pH of the solution is not controlled (in this case excess carbonate was present) substitution to form rhodium(II) carboxylates is unsuccessful.

When the acid system became extremely sterically demanding as in 2,4,6-triisopropylbenzenesulphonyl-L-proline (entry 10), formation of the dirhodium species was difficult. A similar problem was encountered by Callot and Metz[21] in their preparation of sterically crowded complexes.

Other homochiral carboxylic acids which were treated with rhodium carbonate (20) to give rhodium(II) carboxylates were ketopinic acid,[22] (entry 16), (R) and (S)-2-chloropropanoic acid (entries 17 and 18 respectively), tartaric acid (entry 19), lactic acid (entry 20), (S)-mandelic acid (entry 1), and camphoric acid (entry 21). These

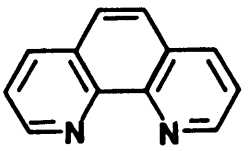
rhodium(II) carboxylates formed as blue-green crystals whereas those derived from *N*-protected amino acids were generally green in colour. In the cases of dibasic acids (entries 8, 19, 20, and 21), the complexes form with only one coordinating carboxylate per molecule.[20] Even when reaction was carried out with only 4 equivalents of acid, carbonate persisted in the reaction mixture until a further 4 equivalents were added. For tartaric and lactic acids, no precipitate formed as the complexes are water soluble. Instead the reaction mixture was concentrated at reduced pressure and the crude isolated mixture of sodium carboxylate and rhodium(II) carboxylate was tested for catalytic activity.

Catalyst 22, rhodium(II) α-methoxy-α-phenylacetate was prepared by Cotton's procedure,[12] not by displacement with rhodium carbonate. When catalyst preparation was attempted with a proline-calixarene derivative (21),[23] reaction was unsuccessful presumably due to steric hindrance to dimer formation.

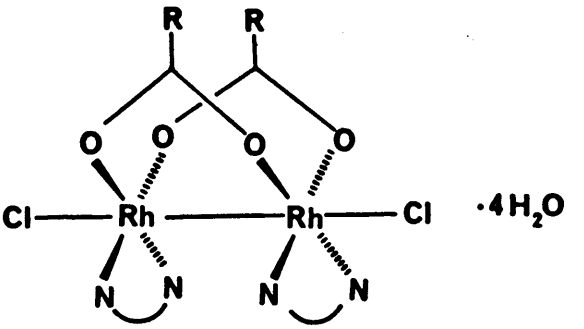


(21)

Many rhodium(II) carboxylates where some of the carboxylate ligands are replaced by nitrogen or phosphorus donors are known. It was decided to prepare some of these complexes, preferably with chiral ligands, and test their catalytic activity with α-diazoketones. Catalyst (23)[17] was prepared by displacement of two mandelate ligands by phenanthroline (22).



(22)

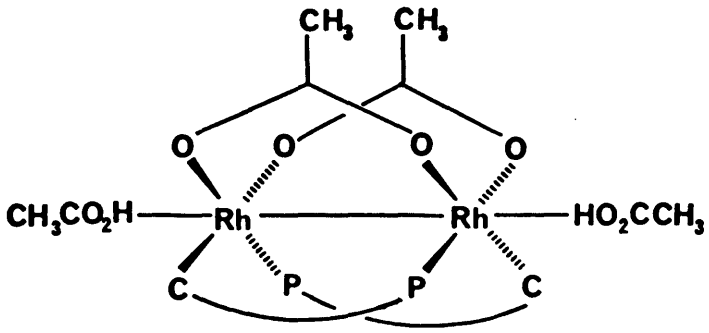


(23) R = (S)-PhCHOH

$Rh_2(mand)_2(phen)_2Cl_2.4H_2O$

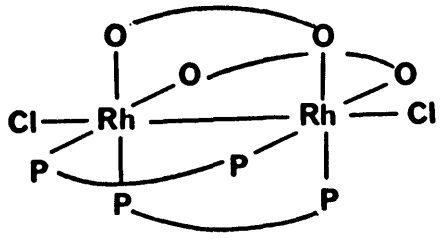
Catalyst (24)[24] where two acetate ligands were replaced by a phosphorus and a carbon donor to give an achiral compound was also prepared.

Catalyst (25) where two acetate ligands were replaced by *bis*-diphenylphosphinoethane (dppe), analogous to the literature preparation[25] with *bis*-diphenylphosphinomethane, was also prepared for testing.



(24)

$Rh_2(OAc)_2(Ph_2PC_6H_4)_2 . 2\,CH_3COOH$

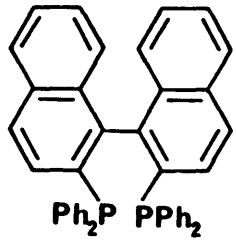


(25) $Rh_2(OAc)_2(dppe)_2Cl_2$

dppe = $Ph_2PCH_2CH_2PPh_2$

(26) $Rh_2(OAc)_2[(R)-(+)-BINAP]_2 Cl_2$

BINAP =



Catalyst (26), where two acetate ligands were displaced by (R)-(+)-2,2^{1}-*bis*(diphenylphosphino)-1,1^{1}-binaphthyl (BINAP) was similarly prepared.

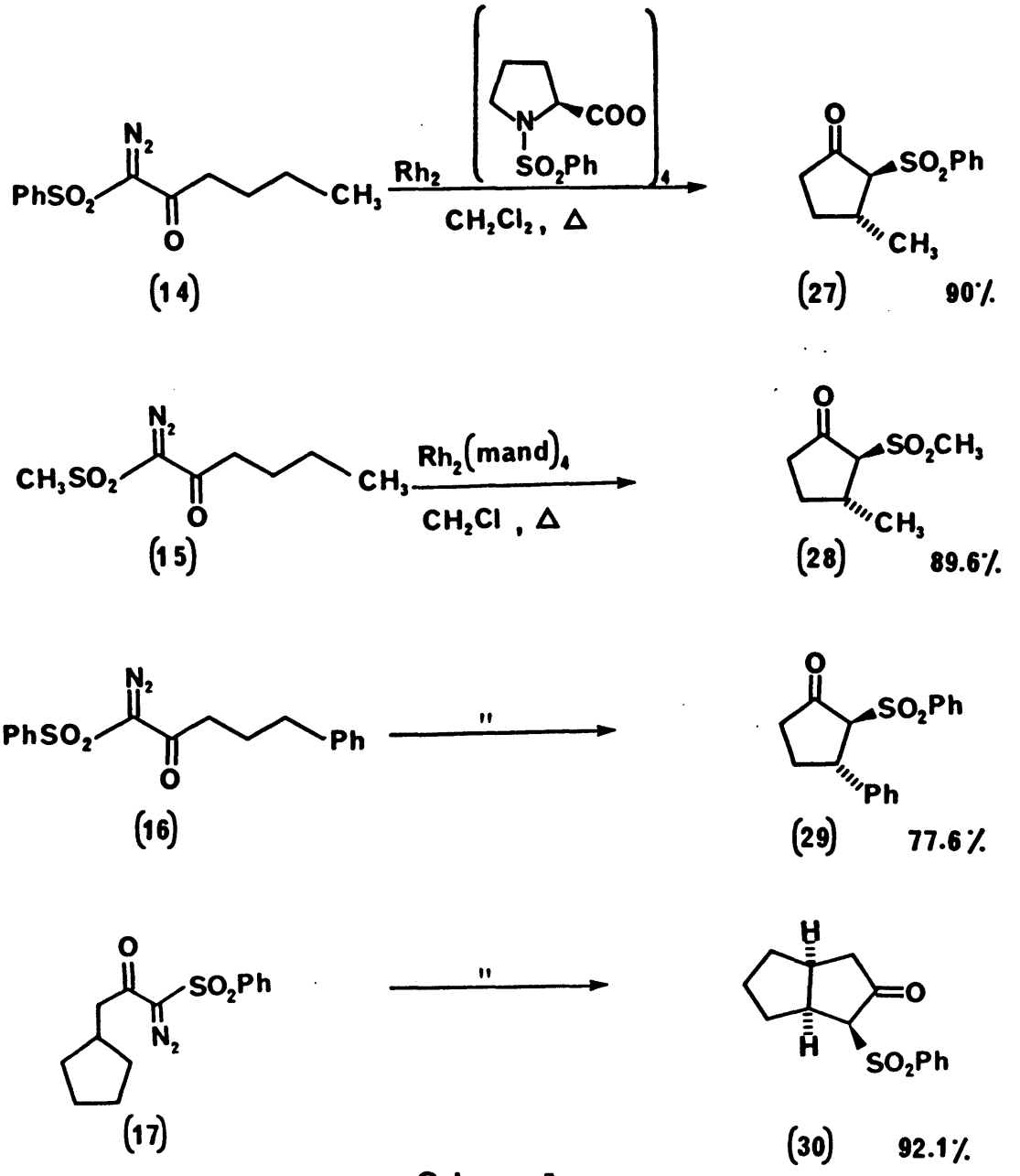
It was hoped that these complexes would have retained some catalytic activity and if so a series of complexes involving chiral phosphines or amines could be tested as asymmetric induction catalysts in α-diazoketone decomposition.

Optical rotations could not be obtained for the chiral rhodium(II) carboxylates as the catalysts in solution were too strongly coloured to allow passage of light. The rhodium(II) carboxylates were characterised by ir spectroscopy and elemental analysis.

2.1.4. *Intramolecular C-H insertion reactions of α-diazo-β-keto sulphones*

All four intramolecular C-H insertions of the α-diazo-β-keto sulphones summarised in Scheme 5 gave 2-sulphonylcyclopentanones[1] using as catalysts the various rhodium(II) carboxylates. The results shown were the optimum yields obtained using the catalysts indicated. Rhodium(II) acetate was unique in giving rapid reaction in dichloromethane at room temperature. With the other catalysts reaction was very slow at room temperature but was rapid, generally being complete within 2 hours, at reflux in the same solvent. The standard conditions used were high dilution (100 mg diazoketone in 20 ml dichloromethane added to 200 ml refluxing dichloromethane) and slow addition (20 min) with two catalyst additions (2 x 0.5 mg), one before diazoketone addition and the other halfway through the addition. These conditions were used throughout this

work for intramolecular reactions of α-diazoketones; they are designed to minimise dimer formation by maintaining a low concentration of α-diazoketone in the solution at all times.

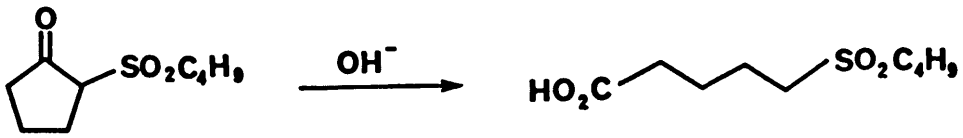


Scheme 5

In the case of α-diazo-β-keto sulphones, dimer formation was not a problem, and in fact these reactions could be carried out under much more concentrated conditions. However, to maintain uniformity with the

α-diazoketone decompositions of Chapter 3, in which dimer formation occurs as a side reaction, these standard conditions were employed.

The products of the α-diazoketone decompositions had no detectable impurities due to side reactions. Exclusive cyclopentanone formation occurred in agreement with Taber's[3] work with similar reactions. Pure cyclopentanones were easily obtained by dissolving the crude product in dichloromethane, extracting the product into aqueous sodium hydroxide, followed by rapid neutralisation with saturated ammonium chloride, and finally extraction into dichloromethane. The exposure time of the 2-sulphonylcyclopentanones to base had to be minimised as slow decomposition occurs to carboxylate in basic solution as shown in equation 3[26] and in fact serious losses in yield did result from this extraction technique.



(3)

However, it is an extremely convenient method of isolating the pure product. Particularly important for this study was that the trace of catalyst present in the reaction product was removed in this purification step.

The products obtained by this base extraction were all white crystalline solids which were analytically pure and could be characterised spectroscopically by the distinctive carbonyl stretch in the ir spectrum

at approx. 1740 cm^{-1}. ^1H n.m.r. showed that the products after base extraction consisted exclusively of one isomer, which by comparison with Taber's[3] work was presumed to be *trans*-disubstituted, or in the case of (30) the benzenesulphonyl group was *trans* to the bridgehead hydrogens.

When rhodium(II) acetate was employed as the decomposition catalyst of α-diazo-β-keto sulphone (15) at room temperature, the crude product of the reaction consisted exclusively of the *trans* isomer (see Table 2.3). However, when the other rhodium(II) carboxylates were employed as catalysts at reflux both *cis* and *trans* isomers were present in the crude product in a ratio dependent on the catalyst employed. After base extraction the mixture returned exclusively to the *trans* isomer. When rhodium(II) trifluoroacetate[27] and rhodium(II) (S)-mandelate were employed as catalysts at room temperature, reaction was incomplete after 24h but ^1H n.m.r. showed that only the *trans* isomer was formed. Thus the *cis* isomer is formed only when the reaction is carried out at reflux and the ratio of *cis:trans* isomers depends on the catalyst employed. This effect was also observed with the other α-diazo-β-keto sulphones but was most easily observed with (14) and (15) (Tables 2.3 and 2.6) as the ^1H n.m.r. spectra of (27) and (28) showed clearly distinct doublets for the C(2)*H* and the C(3)CH_3 protons for the *cis* and *trans* isomers. The ^1H n.m.r. spectra of (29) and (30) were less amenable to estimation of the *cis:trans* ratio due to overlapping signals.

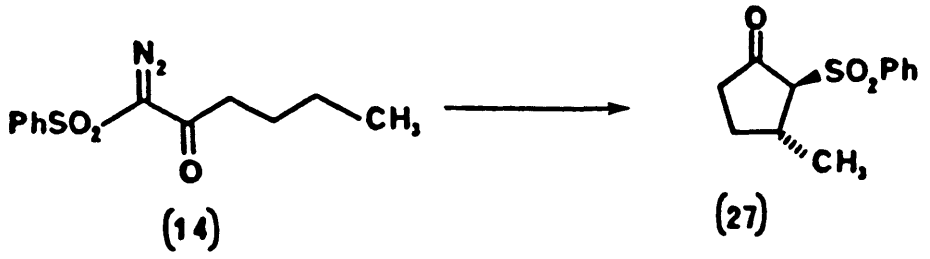
(i) *Catalyst considerations*

Catalyst efficiency in the intramolecular C-H insertion reactions of α-diazo-β-keto sulphones was best measured by the reaction time rather than by the overall yield; as already mentioned the reaction yield was normally quantitative for the crude product but the overall yield was determined by the loss in the base extraction step. Tables 2.2-2.5 show the effect of various catalysts on the decomposition of α-diazo-β-keto sulphones (14)-(17) respectively.

α-Diazo-β-keto sulphone (14) was the most studied compound as its ^{1}H n.m.r. spectrum showed clearly distinctive signals for the methyl groups and the C(2)*H* protons for the two isomers. In the *trans* isomer the methyl group doublet was at δ1.27 and the C(2)*H* doublet at δ3.32 whereas the *cis* isomer had doublets at δ1.52 and δ3.80. Table 2.2 shows that most of the rhodium(II) carboxylates were active catalysts for the transformation in just a few hours at reflux. However, the green powders obtained from attempted catalyst preparation with L-proline, L-phenylalanine, and *N*-2,4,6-triisopropylbenzenesulphonyl-L-proline (2,3,10) were not catalytically active suggesting that these are not dimeric rhodium species. Catalysts derived from lactic and tartaric acids (19,20) were very inefficient; with the tartarate no decomposition was observed while lactate gave very slow reaction. On the other hand catalysts 17 and 18 derived from α-chloropropanoic acid were extremely efficient for diazoketone decomposition. With sterically hindered catalysts, e.g.9, derived from *N*-2,4,6-trimethylbenzenesulphonyl-L-proline, reaction was very slow, and a yellow colour developed in solution. This effect was also observed by Callot and Metz[21] with sterically hindered

Table 2.2

Decomposition of 1-benzenesulphonyl-1-diazohexan-2-one (14) with rhodium(II) carboxylates at reflux in dichloromethane



(14) (27)

Catalyst	Yield / %	Reaction time / h	*trans:cis* (crude)	$[\alpha]_D^{20}$ / °(c, CH_2Cl_2)
1	70-80	2	40:60	-16.1 (2.2)
2	-	-	-	-
3	-	-	-	-
4	90.0	2	30:70	-19.1 (20.8)
5	88.2	3	-	-4.6 (7.9)
6	57.5	2	80:20	-8.5 (5.2)
7	39.1	3	30:70	-6.9 (3.5)
8	86.8	1	50:50	+10.0 (7.8)
9	55.3	20	100:0	-0.7 (4.9)
10	-	-	-	-
11	66.5	3	40:60	-6.9 (5.0)
12	67.8	3	50:50	+0.2 (6.1)
13	57.0	2	15:85	-0.6 (5.1)

Table 2.2 contd.

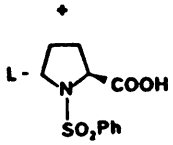
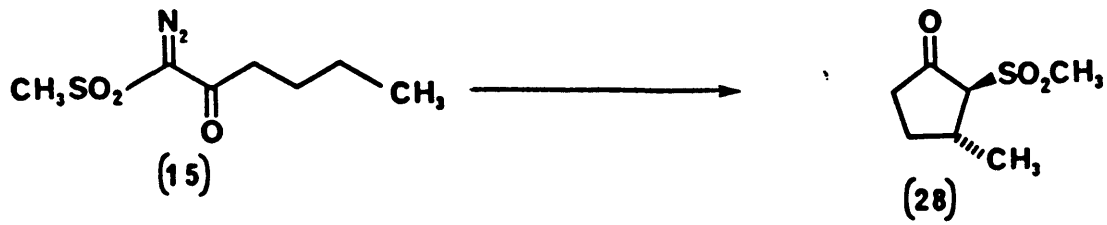
14	59.7	4	100:0	-0.7 (5.3)
15	44.5	3	-	+1.2 (4.0)
16	53.7	2	90:10	-4.5 (4.8)
17	65.6	2	-	-3.0 (5.9)
18	50.3	2	-	+3.3 (4.5)
19	-	-	-	-
20	74.5	10	70:30	+3.3 (6.7)
21	65.0	3	80:20	+0.1 (5.8)
22	22.6	2	40:60	-2.7 (3.0)
23	-	-	-	-
24	only partial decomposition	-	-	-
25	61.6	3	-	-
26	57.3	8	100:0	-0.2 (5.2)
$Rh_2(OAc)_4$ (1 mg) +  (25mg)	43.8	1.5	80:20	Racemic

Table 2.3 : Decomposition of 1-methanesulphonyl-1-diazohexan-2-one (15) with rhodium(II) carboxylates



Catalyst	Temperature °C	Yield %	Reaction time h	*trans:cis* (crude)	$[\alpha]_D^{20}$ °(c, CH_2Cl_2)
$Rh_2(OAc)_4$	20	58.0	0.3	100:0	0
$Rh_2(O_2CCF_3)_4$	20	78.1	18	100:0	0
1	20	Only partial decomposition	26	100:0	-
1	40	89.6	2	70:30	+3.8 (8.1)

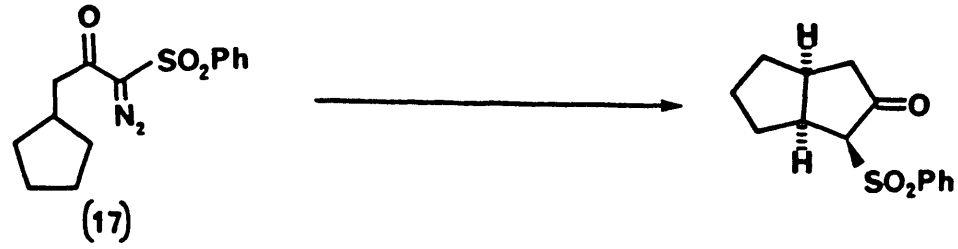
Table 2.4 : Decomposition of 1-benzenesulphonyl-1-diazo-5-phenylpentan-2-one (16) with rhodium(II) carboxylates at reflux in dichloromethane.



(16) (29)

Catalyst	Yield / %	Reaction time / h	*trans:cis* (crude)	$[\alpha]_D^{20}$ / °(c, CH_2Cl_2)
1	77.6	1	Not resolved on ^1H n.m.r.	-0.9 (7.1)
4	45.2	1	"	-3.1 (4.1)
5	49.0	2	"	-1.6 (4.5)

Table 2.5 : Decomposition of 1-benzenesulphonyl-1-diazo-3-cyclopentylpropan-2-one (17) with rhodium(II) carboxylates at reflux in dichloromethane.



(17) (30)

Catalyst	Yield / %	Reaction time / h	*trans:cis* (crude)	$[\alpha]_D^{20}$ / °(c, CH_2Cl_2)
1	80.9	0.6	70:30	+7.4 (4.4)
4	51.6	2.5	80:20	+0.4 (2.8)

Table 2.6 : Effect of temperature on the decomposition of 1-benzenesulphonyl-1-diazohexan-2-one (14)



Temperature °C	Yield %	Extent of reaction[a] %	Reaction time h	*trans:cis* (crude)	$[\alpha]_D^{20}$ °(c,CH_2Cl_2)
20	26.9	60	36	100:0	-8.6 (4.8)
40	53.1	100	1.5	40:60	-10.2 (4.0)

[a] Estimated from ^1H n.m.r. spectrum of crude product.

Identical samples of $Rh_2(mand)_4.2EtOH$ were used in each reaction.

catalysts. They described the yellow form as a 'deactivated' catalyst but from the evidence obtained from enantioselections (see later) it is likely that the rhodium(II) dimer containing such bulky ligands breaks up in solution to monomeric species which are likely to be yellow rhodium(III) complexes.[28] These monomeric species appear to be much less active catalytically than the rhodium(II) dimer and result in longer reaction times. As can be seen in Table 2.2, changing the catalyst ligand from *N*-benzenesulphonyl-L-proline (4) to *N*-naphthalenesulphonyl-L-proline (5) results in a longer reaction time due to steric hindrance. This steric hindrance to reaction is also seen in Tables 2.4 and 2.5. With α-diazo-β-keto sulphone (16) changing from catalyst 4 to 5 significantly reduces the rate of reaction, whereas with α-diazo-β-keto sulphone (17) even catalyst 4 appears to offer steric hindrance to the reaction showing much longer reaction time than rhodium(II) mandelate. Of course this is consistent with the structure of (17) as the cyclopentyl ring is more sterically demanding than the *n*-butyl group of α-diazoketones (14-16).

The rhodium complexes containing nitrogen and phosphorus donors were much less efficient in α-diazoketone decomposition than rhodium(II) carboxylates, e.g. catalyst 26 required 8h for complete decomposition of (14). When cobalt and copper catalysts were tested no decomposition of (14) was observed.

The ratio of *cis:trans* isomers obtained in the crude product of the decomposition of α-diazoketone (14) was dependent on the catalyst employed as shown in Table 2.2. This ratio was not simply due to a thermal equilibration of isomers: when a mixture of the *cis* and *trans*

isomers was refluxed in dichloromethane for several hours no change in the ratio was observed. This implies that the isomer ratio must be a genuine catalyst effect, and further suggests that strong catalyst-substrate interactions are present in the transition state for the insertion.

The catalysts were also found to decrease in activity which may have been due to poisoning of the catalyst by electron donor impurities. To test this theory a diazoketone decomposition was carried out in the presence of triphenylphosphine (1 equivalent with catalyst 4) and the result was a considerable decrease in activity. Thus fresh batches of catalysts were prepared regularly and stored under nitrogen in the dark. Sometimes reduced activity catalysts could be reactivated by heating *in vacuo* for a few hours, but this was not always successful. A decrease in asymmetric induction was also observed accompanying the catalyst deactivation. Therefore, freshly prepared catalyst samples were always used in catalyst trials. Interestingly, if for example rhodium(II) mandelate was recrystallised from ethanol the second crop catalyst, while being extremely active catalytically, resulted in reduced asymmetric induction.

Most of the catalysts used for α-diazoketone decomposition contained two water molecules as axial ligands since the catalysts were isolated from aqueous solution. These were easily replaced by ethanol by recrystallisation or simply by dissolving the aqueous adduct in ethanol and then evaporating off the solvent at reduced pressure to give the *bis*-ethanol adduct. The axial ligands could be removed completely by heating the complex at 60-80°C at 10 mmHg for 2h. However, it was found

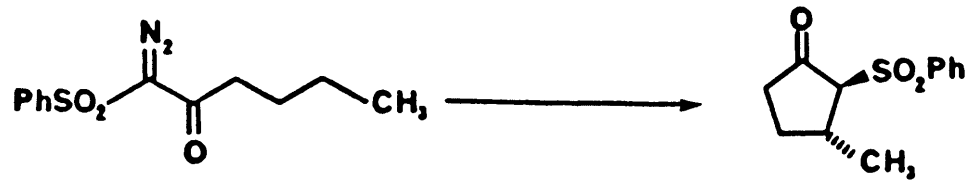
that the presence of water or ethanol in the complex had no effect on the catalyst activity or on the asymmetric induction obtained, giving exactly the same results as dehydrated catalysts. In fact when the rhodium(II) carboxylates contain axial ligands they are crystalline and they may be more stable in this form than if the crystals are broken by dehydration leaving an amorphous powder in which the rhodium atoms each have a vacant coordination site, which is readily poisoned by an electron donor. In the case of catalysts 23-26 the axial chloride and acetic acid ligands may be more strongly bound to the rhodium atom and therefore be detrimental to carbenoid formation.

Solvent effect on the cyclisation of α-diazo-β-keto sulphone (14) was investigated as shown in Table 2.7. Reaction was slowest in hexane and ether. In hexane, the rhodium(II) mandelate catalyst was completely insoluble explaining the slow reaction, while in ether, coordination of the solvent to the catalyst may have been responsible for slowing the reaction or the decrease in rate may have been simply due to the decrease in reflux temperature compared to the other solvents. A similar study carried out by Rapoport and co-workers[29] showed that α-diazoketone decomposition was solvent dependent.

(ii) *Enantioselection*

A certain degree of asymmetric induction was obtained in the intramolecular C-H insertions of α-diazo-β-keto sulphones (14-17) by use of chiral rhodium(II) carboxylates. The majority of the studies were carried out on diazoketone (14), but some investigation of asymmetric synthesis with (15-17) was also carried out; the results are displayed

Table 2.7 : Effect of solvent on the decomposition of 1-benzenesulphonyl-1-diazohexan-2-one (14)



(14) (27)

Solvent	b.p. °C	Yield %	Reaction time h	*trans:cis* (crude)	$[\alpha]_D^{20}$ °(c, CH_2Cl_2)
Hexane	69	32.4	3	-	-7.1 (2.9)
Ether	34	24.0	4	-	-5.6 (2.2)
Carbon tetrachloride	77	36.8	1	50:50	-5.1 (3.3)
Dichloromethane	40	41.7	1	40:60	-10.4 (3.7)
Benzene	80	45.6	1.5	50:50	-5.9 (4.1)
1,2-Dichloroethane	84	58.9	2	60:40	-5.8 (5.3)

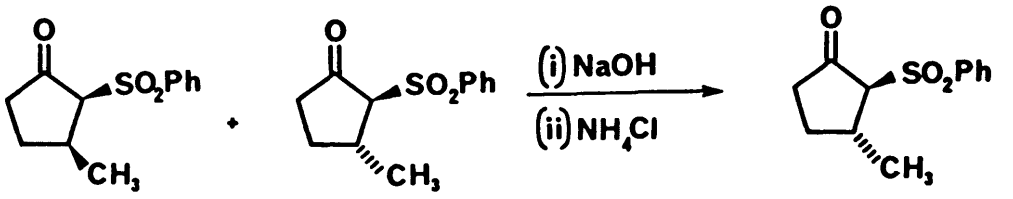
Identical samples of $Rh_2(mand)_4.2EtOH$ were used in each reaction.

in Tables 2.2-2.7. Optical rotation data were used for comparison of relative efficiencies of the various rhodium(II) carboxylates for asymmetric induction. The extent of the asymmetric induction in absolute terms is small; with α-diazo-β-keto sulphone (14) the maximum asymmetric induction was obtained with catalyst 4, rhodium(II) *N*-benzenesulphonyl-L-prolinate, and corresponds to 12% e.e. The determination of this enantiomeric excess is discussed in later sections. Chiral shift ^{1}H n.m.r. studies on the cyclopentanone (27) did not give any indication of the asymmetric induction obtained in the cyclisations. Although the doublet for the C(2)*H* proton split into two doublets on addition of Eu(tfc)$_3$ {Tris[3(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) derivative}, accurate integration was impossible. Coordination of the carbonyl group to the europium complex appeared not to be sufficiently strong to resolve the doublets due to the methyl groups of the two enantiomers.

Optical rotation was a very convenient method of establishing relative optical purity of the cyclopentanones, chemically pure samples of which were easily obtained by base extraction as described earlier (albeit with yield loss). Most importantly this extraction gave the product free of any trace of catalyst which could have interfered with optical rotation data. A further advantage of the base extraction was that it converted the crude product mixture of isomers into the *trans* isomer exclusively, with the result that specific rotations could be compared directly. If chromatographic purification had been employed, varying *cis:trans* isomer ratios would probably have resulted depending on the catalyst employed and comparison of specific rotations would not

be possible. Thus the extraction and optical rotation method provided a rapid indication that asymmetric induction had occurred.

The base extraction simplified the problem from dealing with two pairs of enantiomers to one of simply two enantiomers. Only asymmetric induction at C(3) was observed since after extraction the stereochemistry at C(2) was controlled completely by that at C(3) (equation 4).



(4)

As can be seen from Table 2.2, enantioselection in the formation of (27) is greatest with catalyst 4 (rhodium(II) *N*-benzenesulphonyl-L-prolinate), with the rhodium(II) (S)-mandelate catalyst (1) offering the next highest asymmetric induction. The remaining rhodium(II) carboxylates gave lower asymmetric inductions, some of which were in the opposite direction. The sensitivity of the enantioselection to change in the ligand structure of the catalyst shows that catalyst-substrate interactions are significant and that by further changing the catalyst structure, greater enantioselection may be achieved. Catalyst 26, derived from the chiral BINAP ligand, gave an essentially racemic product indicating that this series of complexes is unlikely to result in high asymmetric inductions.

The final entry in Table 2.2 where rhodium(II) acetate was employed as decomposition catalyst in the presence of *N*-benzenesulphonyl-L-proline

was carried out to check whether coordination in solution would be sufficient for enantioselection in α-diazoketone decomposition. However, this gave a racemic product indicating that prior complexation of the homochiral ligand is required for asymmetric induction. This result implies that the rhodium(II) carboxylate complexes remain intact in solution, a promising fact in terms of asymmetric induction. This contrasts with the result of Brunner and Miehling[30] where chiral copper catalysts used in enantioselective cyclopropanation of 1,1-diphenylethylene with EDA were generated *in situ* from copper(II) acetate and Schiff base ligands.

Further evidence that catalysts which gave good asymmetric inductions remain intact in solution is by the reaction colour. With catalysts 1 and 4, the reaction mixture which was initially the characteristic yellow colour of an α-diazoketone decolourised to an essentially colourless solution as reaction proceeded. However, with the sterically hindered catalysts, e.g. 9, as described earlier a deep yellow colour developed in the reaction mixture and reaction was slow with low asymmetric induction resulting. As discussed earlier with these sterically hindered catalysts cleavage of the rhodium-rhodium bond to form Rh(III) species appears to be occurring with a resulting decrease in reaction rate because these species are less active catalytically and with decrease in asymmetric induction because of either a less rigid structure in the monomeric species or because of complete loss of the homochiral ligands on the bond cleavage. As can be seen in Table 2.2, increasing the steric bulk of the ligand on the catalyst from *N*-benzenesulphonyl-L-proline to *N*-naphthalenesulphonyl-L-

proline or *N*-2,4,6-trimethylbenzenesulphonyl-L-proline had a detrimental effect on the asymmetric induction obtained with diazoketone (14) with an associated slowing of reaction rate. This can be explained as cleavage of the rhodium-rhodium bond in the sterically hindered catalysts to form rhodium(III) species with lower catalytic activity and low asymmetric induction due to the loss of the rigid rhodium(II) carboxylate structure. Callot and Metz[21] in their report of sterically hindered catalysts ascribed the deactivation to formation of a species which retains some catalytic activity, but with low selectivities in the cyclopropanations they were studying - in agreement with the observations in this study.

Clearly, improvements in asymmetric induction in the C-H insertion of α-diazo-β-keto sulphone (14) would not be made by simply increasing the steric bulk of the catalyst ligand. Instead modification of the ligand structure within the estimated steric limitations would probably give more successful results. For example, comparison of the asymmetric inductions obtained from rhodium(II)(S)-mandelate (1) and rhodium(II)(S)-α-methoxy-α-phenylacetate (22) indicated that the α-hydroxy group in mandelic acid, which has been shown in the X-ray crystal structure[12] of rhodium(II) (S)-mandelate to hold the ligand in a fixed conformation because of a hydrogen bond to a carboxylate oxygen, may be a determining factor in the stereochemistry of the carbenoid intermediate resulting in significantly increased asymmetric induction in this case.

The α-chloropropanoic acid derived catalysts 17 and 18 gave essentially the same magnitude of asymmetric induction, but in opposite directions (Table 2.2), verifying that the ligands maintain their

asymmetric centre on the catalyst. This had been proven for rhodium(II) (S)-mandelate and rhodium(II) (R)-α-methoxy-α-phenylacetate by crystal structure.[12] The catalysts 17 and 18 were found to be extremely active in α-diazoketone decomposition in general, but resulted in poor enantioselectivity with α-diazo-β-keto sulphone (14). Further structural modifications of these ligands, by perhaps increasing their steric bulk or forcing a more rigid structure, may enhance their enantioselectivity considerably.

This 'tailoring' of the catalyst ligand would involve careful study of crystal structures of both efficient and inefficient asymmetric induction catalysts to see if any indications of factors which might improve enantioselectivity are present. Of course, the structures of the complexes in solution might not be the same as the solid state structures, but since there is evidence that the complexes remain intact in solution, the solid and solution states may not be that unalike. The intermolecular interactions described by Cotton and co-workers[31] for molybdenum(II) mandelate.2THF where an oxygen of one complex is coordinated axially to a molybdenum of another, are not present in the structure of rhodium(II) mandelate.2EtOH because the ethanol molecules block the axial sites for intermolecular coordination.[12] Therefore, dissolution of this complex at least should result in very little structural change.

Table 2.6 shows that in the rhodium(II) (S)-mandelate-catalysed decomposition of α-diazo-β-keto sulphone (14), asymmetric induction is higher at reflux than at room temperature. The effect of increased asymmetric induction at higher temperature was observed also with the

α-diazoketone cyclisations discussed in Chapter 3. This effect was more dramatic with rhodium(II) *N*-benzenesulphonyl-L-prolinate than with rhodium(II) (S)-mandelate. This temperature dependence of the asymmetric induction illustrates once more the complexity of the complex-substrate pair.

Table 2.7 illustrates the effect of solvent on the asymmetric induction obtained in the same reaction. In the cyclisation of α-diazo-β-keto sulphone (14) the highest specific rotation in the cyclopentanone product (27) was obtained when the reaction was carried out in dichloromethane. No possible explanation can be offered for this observation, except perhaps that dichloromethane is the most acidic of the group. It is reminiscent of Rapoport's[29] solvent investigation however.

As already mentioned, rhodium(II) carboxylates decrease in catalytic efficiency with age; their enantioselectivities in cyclisation also drop rapidly, freshly prepared catalysts being more enantioselective than aged catalysts. For example, the sample of rhodium(II) (S)-mandelate (which when freshly prepared and used for cyclising (14) gave a specific rotation in the cyclopentanone product (27) of -19.1°) which was used to produce the results in Table 2.7 gave a product (cyclisation having been performed in dichloromethane) of specific rotation -10.4°. This sample was approximately 6 months old and the results give an indication of the rate at which catalyst deactivation occurs. To prolong their activity, the catalysts were stored in the dark under nitrogen. Interestingly when rhodium(II) (S)-mandelate was recrystallised from

ethanol, following Cotton's preparation,[12] second crop material while possessing high catalytic activity resulted in a decreased asymmetric induction compared to first crop material. Because of this catalyst deterioration all the catalysts tested for asymmetric induction were used immediately after preparation.

Asymmetric inductions were also observed in the decompositions of α-diazo-β-keto sulphones (15-17) by use of chiral rhodium(II) carboxylates (Tables 2.3-2.5). Interestingly, while compound (16) cyclised with highest asymmetric induction through use of rhodium(II) *N*-benzenesulphonyl-L-prolinate [as for (14)], α-diazo-β-keto sulphone (17) resulted in higher asymmetric induction from a rhodium(II) mandelate catalysed cyclisation and the rhodium(II) *N*-benzenesulphonyl-L-prolinate catalysed reaction was considerably slower and resulted in a low asymmetric induction. This suggests that for α-diazo-β-keto sulphone (17), even rhodium(II) *N*-benzenesulphonyl-L-prolinate is probably too sterically hindered for efficient reaction. This reflects the increased steric demand of the cyclopentyl ring compared to the *n*-butyl group of the other α-diazo-β-keto sulphones.

Thus, even within the same reaction type, i.e. intramolecular C-H insertion reactions of α-diazo-β-keto sulphones, the catalyst giving optimum asymmetric induction depended strongly on the exact structure of the diazo substrate, making catalyst 'design' even more important. This extreme sensitivity is a measure of the significance of the catalyst-substrate interactions, and if just the right catalyst-substrate combination was attained, high enantioselection could result.

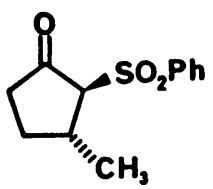
In conclusion, the absolute asymmetric inductions were low; the cyclisation of α-diazo-β-keto sulphone (14) with rhodium(II) *N*-benzenesulphonyl-L-prolinate, which gave a specific rotation of -19.1° in cyclopentanone (27), corresponded to approximately 12% e.e. (estimated by desulphonylation to 3-methylcyclopentanone as described later in section 2.1.6.). However, the extreme sensitivity of asymmetric induction to change in the ligand structure of the catalyst offers promise of higher asymmetric induction if the correct catalyst-substrate combination could be found. This means that it is unlikely that a catalyst can be found to give high asymmetric inductions with many α-diazoketones and in many different reaction types. To date, rhodium(II) (S)-mandelate is the most successful general catalyst studied in terms of both catalyst activity and enantioselectivity, probably due to the rigid ligand structure because of the intramolecular hydrogen bond, and it is in fact the catalyst of choice for many α-diazoketone transformations studied by this research group. To improve on rhodium(II) mandelate as a general catalyst, a carboxylate with a rigid ligand structure while retaining high catalytic activity and without steric hindrance due to catalyst bulk would have to be designed and prepared. The degree of enantioselection obtained with α-diazoketones (15-17) was not estimated.

2.1.5. *Enhancement of the optical purity of 2-benzenesulphonyl-3-methylcyclopentanone (27)*

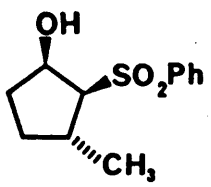
In the original purification of 2-benzenesulphonyl-3-methylcyclopentanone (27) by recrystallisation from ether it was observed that when an optically active sample was employed, the less soluble crystals produced were racemic, while the mother liquor, when concentrated, gave material

with enhanced optical rotation. Thus cyclopentanone (27) is a racemic compound, i.e. opposite enantiomers pair up in the unit cell of the crystal.

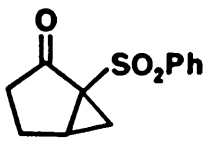
This phenomenon[32] was found to be more general than would be expected. Not only did cyclopentanone (27) tend to crystallise racemically, but a similar observation was made with compounds (31) and (32), and to a lesser extent with the tosylate derivative (33).



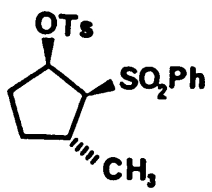
(27)



(31)



(32)

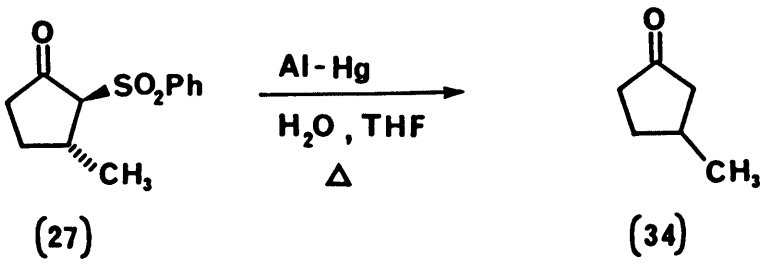


(33)

The racemic crystals (m.p. 124-126°C; lit.,[1] 124-125°C) obtained by recrystallisation of (27) from ether were chunky and uniform in both shape and size. However, as the optical purity of the more soluble material increased, further recrystallisation gave crystals which were no longer totally racemic, but had a lower specific rotation than the material before recrystallisation, while the specific rotation of the material obtained by concentration of the mother liquor was enhanced accordingly. Also as the optical purity of (27) increased, the more soluble sample became less crystalline and in fact towards the end of the recrystallisation sequence was quite gummy and difficult to solidify. These two combined factors meant that it was difficult to enhance the optical purity of the compound above 36% e.e., corresponding to a specific

rotation of -62.0° (c 10.4 in CH_2Cl_2). Enantiomeric excess was determined by desulphonylation of a sample of (27) to 3-methylcyclopentanone as described in the next section (2.1.6.).

2.1.6. *Desulphonylation of 2-benzenesulphonyl-3-methylcyclopentanone (27)*



(27) (34) (5)

36.0%

Successful desulphonylation of (27) to 3-methylcyclopentanone (34) was obtained using aluminium amalgam[33] following Corey's procedure.[7] The recovery of 3-methylcyclopentanone (34) was poor due to difficulty in its isolation as it is partially water soluble. 3-Methylcyclopentanone (34) was purified by distillation and identified by its ir and ^1H n.m.r. spectra and by refractive index.

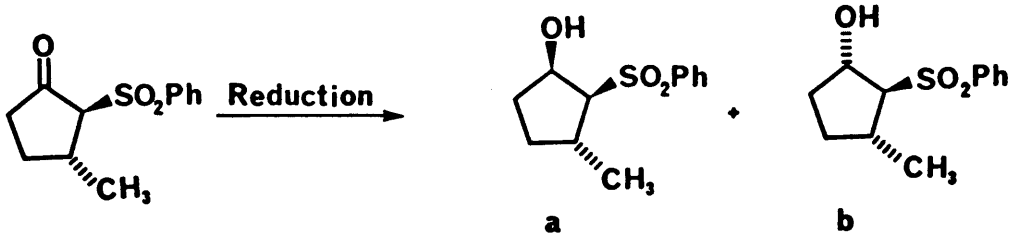
The sample of (27) which was desulphonylated had a specific rotation of -49.9° (c 7.1 in CH_2Cl_2). The resulting 3-methylcyclopentanone (34) had $[\alpha]_D^{20}$ -43.4° (c 6.7 in MeOH). The literature values for 3-methylcyclopentanone are $+143.7^{\circ}$ (undiluted),[34] $+154.8^{\circ}$ (c 0.6 in MeOH),[35] $+148^{\circ}$ (c 4.5 in MeOH).[36] Thus this sample corresponds to 29.3% e.e. and by comparison of values, the maximum asymmetric induction obtained in a cyclisation of α-diazo-β-keto sulphone (14) to (27) was 12% e.e. corresponding to $[\alpha]_D^{20}$ -19.1°, and the enantiomeric excess in

the sample of (27) enantiomerically enriched by recrystallisation ($[\alpha]_D^{20}$ -62.0°) was 36%, i.e. of 68% optical purity. Since the predominant enantiomer has a (-) rotation it follows that it has the (S)-configuration.[37]

Desulphonylation of (27) with zinc in acetic acid was unsuccessful, and although use of sodium amalgam resulted successfully in formation of 3-methylcyclopentanone (34), this was not reproducible, and therefore was less satisfactory than use of aluminium amalgam.

2.1.7. *Reductions of 2-benzenesulphonyl-3-methylcyclopentanone (27)*

Since direct chiral shift ^{1}H n.m.r. studies on (27) did not give information on the optical purity, it was decided to reduce the keto group to the corresponding alcohol and then see if this derivative responded well to chiral shift reagents. From the previous experience with the compounds described in Chapter 3, it seemed that coordination of alcohols in the europium complex is stronger than with ketones resulting in better resolution of the signals for the enantiomers in the ^{1}H n.m.r. spectra. With cyclopentanone (27) there was the possibility of formation of two diastereoisomeric alcohols by reduction as shown in equation 6.



(27) (31) (6)

However, sodium borohydride reduction of (27) in benzene-methanol at 0°C successfully gave the alcohol (31) in quantitative yield as a white crystalline solid, m.p. 82-83°C, following chromatographic purification on silica, with only one isomer detected in the 60 MHz ^{1}H n.m.r. spectrum and in the ^{13}C n.m.r. spectrum. However, at 270 MHz the ^{1}H n.m.r. spectrum showed that a minor trace of a second isomer was visible (< 5%). The doublet for the methyl group of the alcohol (31) was seen at δ1.12 (J = 8.1Hz) while the proton geminal to the hydroxy group appeared as a pair of doublets at δ2.97. The stereochemistry was assumed to be that shown in (a) above, because the sulphonyl group should hinder approach of the reducing agent from the α-face of the molecule. However, we were unable to assign the stereochemistry from the n.m.r. spectrum.

Alcohol (31) tended to recrystallise racemically from ether in the same way as did cyclopentanone (27), giving an enhanced optical purity of the material in the mother liquor. Thus when a sample of cyclopentanone (27) of 36% e.e. was reduced, the alcohol (31) obtained had $[\alpha]_D^{20}$ +16.0° (c 19.6 in CH_2Cl_2). By careful repeated recrystallisation and collection of the mother liquor, a sample of the alcohol (31) with a specific rotation of +22.4° (c 25.5 in CH_2Cl_2) was obtained, which was estimated by chiral shift studies to have 60% e.e., and which by extrapolation to the desulphonylation studies would be expected to have 50% e.e. Therefore, the maximum optical purity of the alcohol (31) obtained was 75-80% based on both the chiral shift ^{1}H n.m.r. and desulphonylation studies. Of course at such high optical purities the crystals of (31) obtained were not actually racemic but showed decreased

specific rotation compared to the material before recrystallisation, while the concentrated mother liquor showed enhanced specific rotation.

Alcohol (31) was very amenable to chiral shift ^1H n.m.r. studies with $Eu(tfc)_3$ with better results at 270 MHz than 60 MHz. Figure 1 shows the 270 MHz ^1H n.m.r. spectrum of alcohol (31) prior to addition of $Eu(tfc)_3$. The proton geminal to the hydroxy group was shifted to lower field (δ4.7-5.0) on addition of $Eu(tfc)_3$ and most significantly the doublet for the methyl group split in two for the two enantiomers (see figure 2). By comparison of the chiral shift spectra of the racemate (figure 3) with those of the alcohol with maximum specific rotation, $[\alpha]_D^{20}$ +22.4° (c 25.5 in CH_2Cl_2) (figure 2), an estimation of 60% e.e. was made. At 60 MHz accurate integration of the two doublets for the methyl groups of the enantiomers was impossible, as they overlapped with the multiplet for the cyclopentyl protons. However, at 270 MHz the signal resolution was much more satisfactory, rendering accurate integration possible.

When lithium aluminium hydride reduction of cyclopentanone (27) was attempted at 0°C in an ether-THF mixture, slow disappearance of the starting material was observed by t.l.c. However, on addition of saturated aqueous ammonium chloride the starting material was recovered quantitatively. Thus it appeared that deprotonation rather than reduction occurred in the reaction mixture. When (27) was refluxed in THF with lithium aluminium hydride, the anion of (27) was formed in the reaction mixture which then reacted within 3h to give a new product (35). If the reaction was quenched by addition of saturated aqeuous ammonium chloride as soon as the yellow cloudy solution, characteristic of the anion, formed,

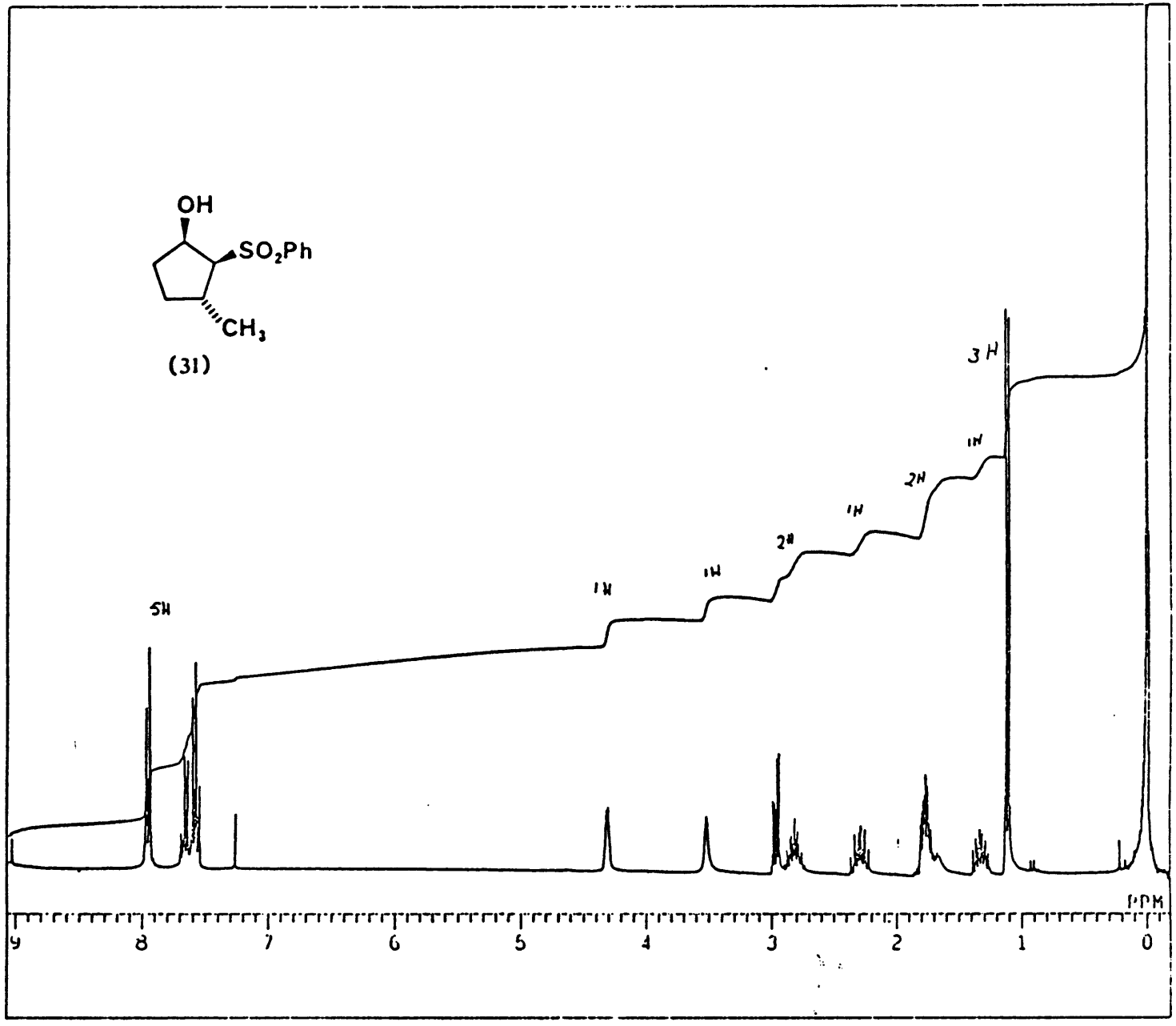
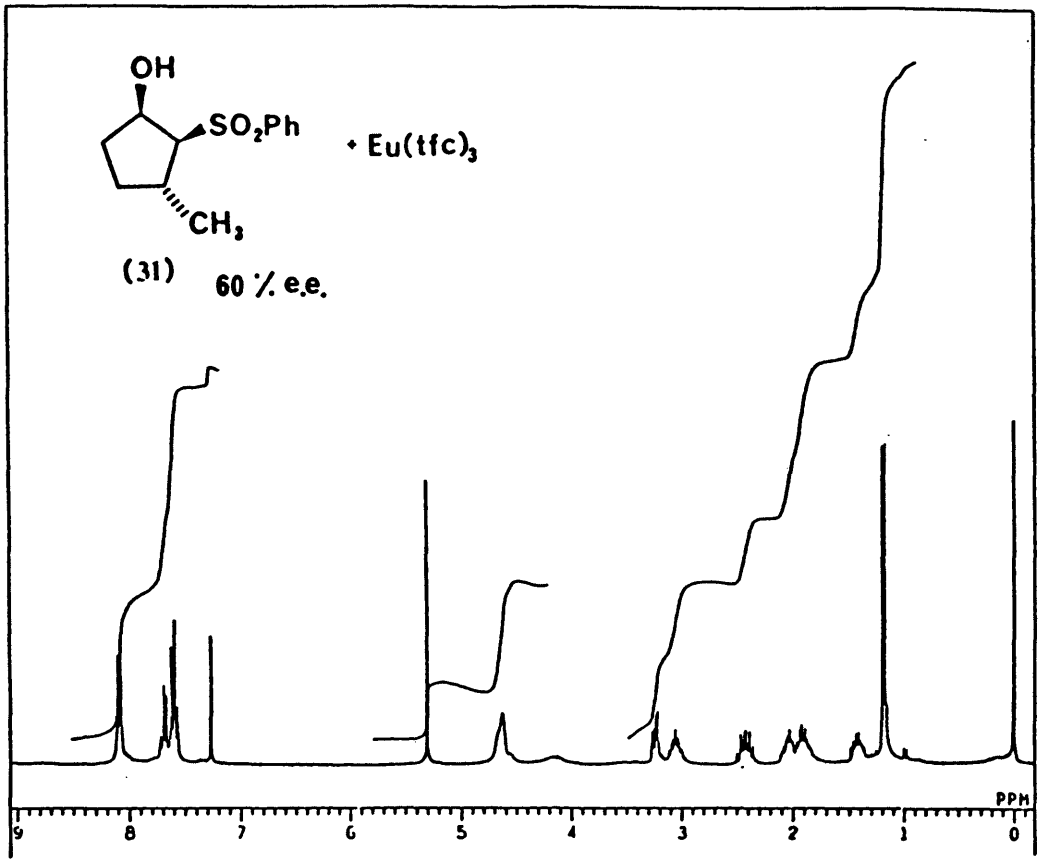


Figure 1 : 270MHz ^{1}H n.m.r. spectrum of cyclopentanol (31)



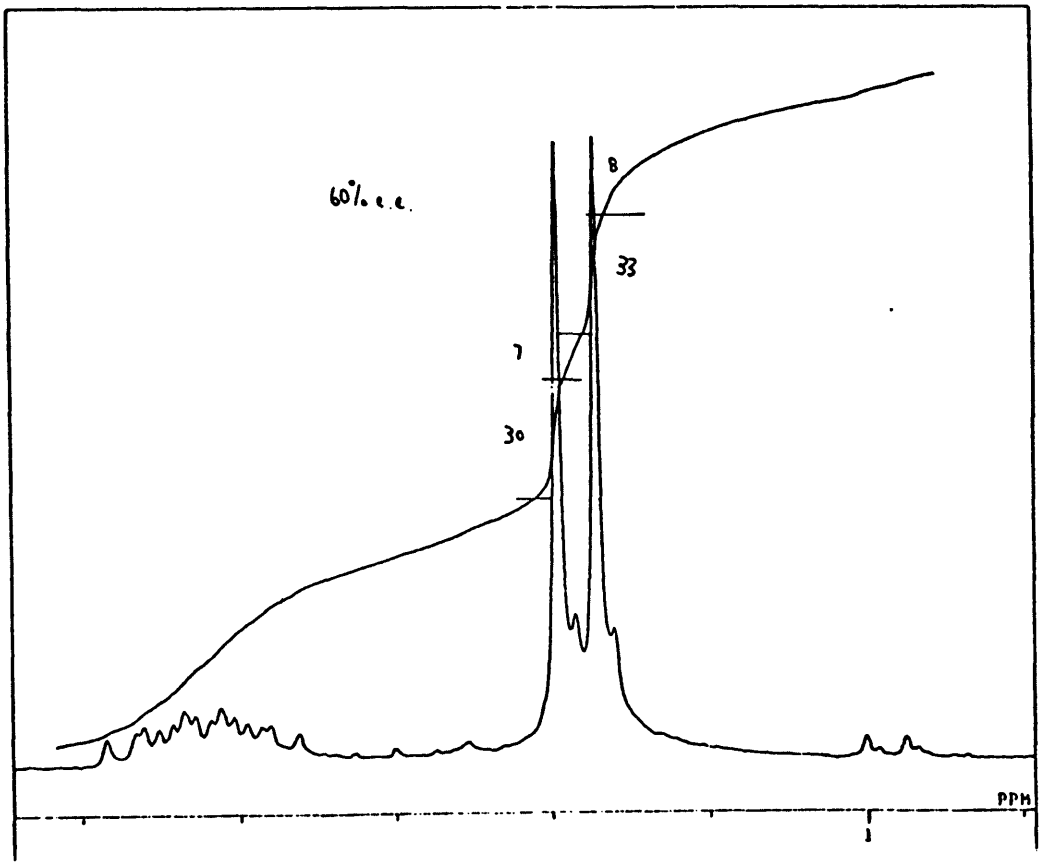


Figure 2 : ^{1}H n.m.r. spectrum of cyclopentanol (31), $[\alpha]_D^{20} = +22.4^{\circ}$ (c 25.5 in CH_2Cl_2), with $Eu(tfc)_3$, with an expansion of the region δ0.90-1.50, indicating the presence of 60% e.e.

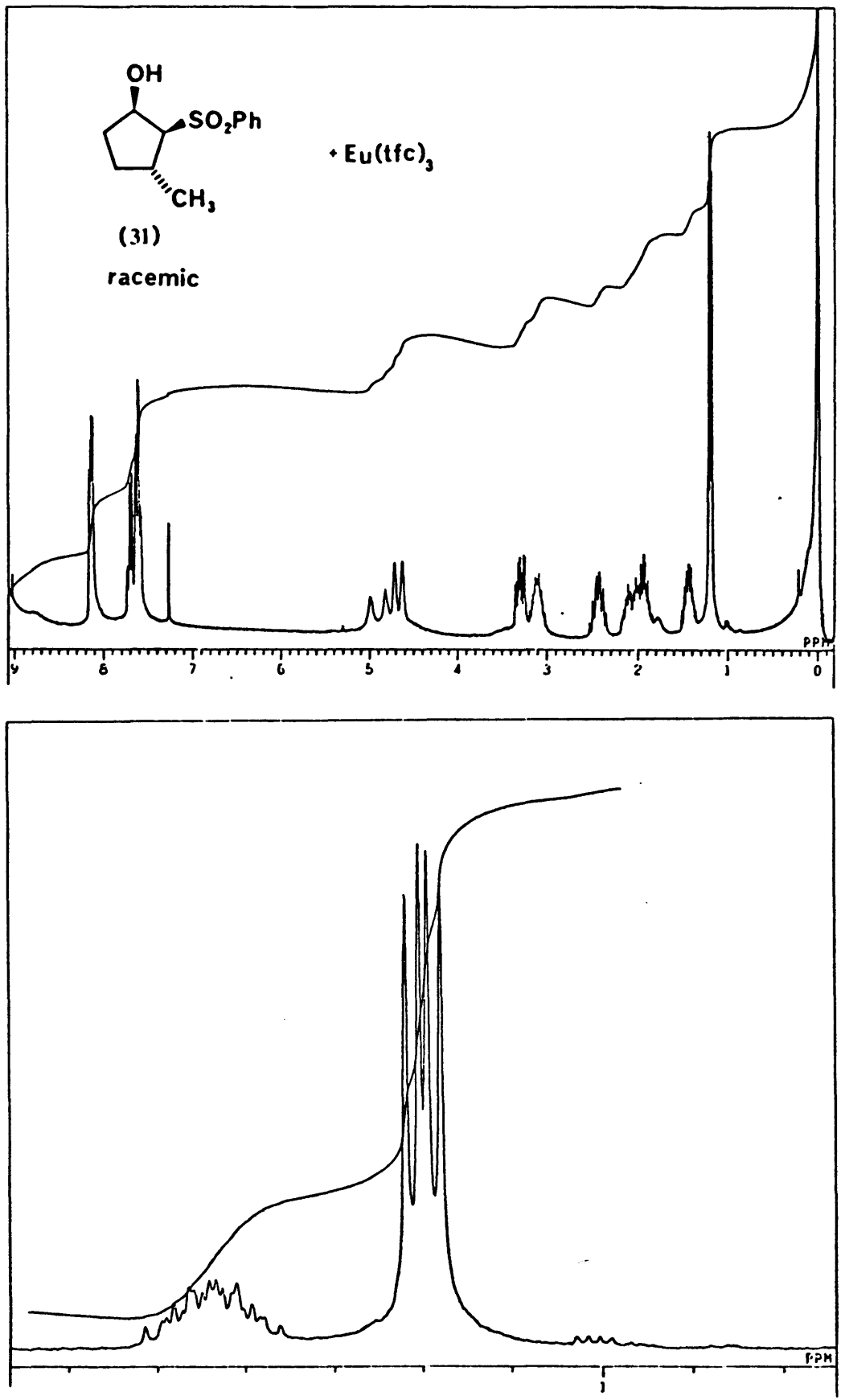
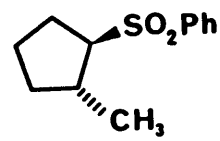


Figure 3 : ^{1}H n.m.r. spectrum of racemic cyclopentanol (31) with $Eu(tfc)_3$, with an expansion of the region δ0.80-1.60.

the material recovered was predominantly starting material. Thus, it seems likely that deprotonation of (27) to the anion, a cloudy yellow solution in THF, occurred first and that this subsequently reacted to form a new compound believed to be sulphone (35), i.e. complete removal of the carbonyl oxygen had occurred.

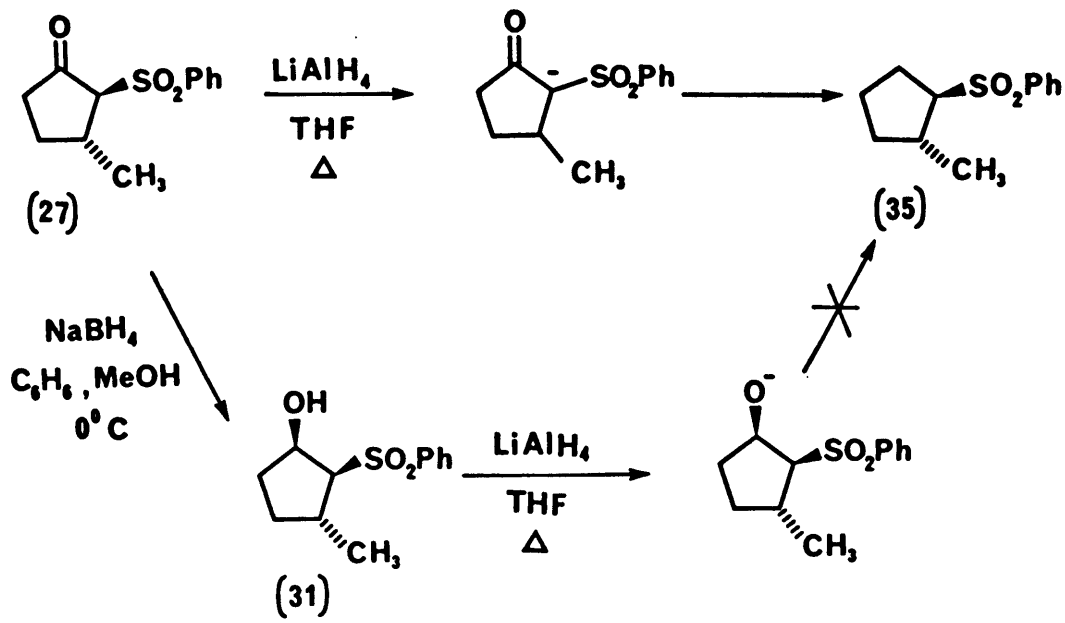


(35)

Sulphone (35) was obtained from cyclopentanone (27) in 77% yield as a low melting solid after purification by p.l.c. on silica. The sulphone was identified spectroscopically and by elemental analysis. Its ir spectrum contained strong bands at 1450, 1300, and 1150 cm^{-1}, characteristic stretching vibrations of the $-SO_2-$ group, while the ^1H n.m.r. spectrum had a doublet at δ0.96 (J = 7.2Hz) for the methyl group with the proton geminal to the sulphonyl group appearing as a multiplet at δ2.85-3.20. Only one isomer was visible in the ^1H and ^{13}C n.m.r. spectra and it was presumed to have *trans* stereochemistry as in cyclopentanone (27). When derived from a cyclopentanone (27) sample with $[\alpha]_D^{20}$ -10.5 (c 33.0 in CH_2Cl_2) the sulphone (35) was optically active with $[\alpha]_D^{20}$ +2.5° (c 18.6 in CH_2Cl_2), which by extrapolation to the desulphonylation data should correspond to 6.1% e.e.

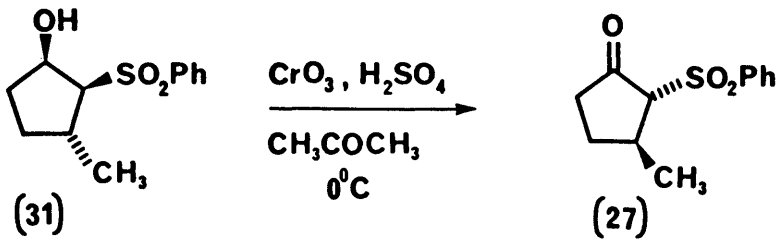
The mechanism of formation of sulphone (35) is unclear, but it does not appear to be formed *via* the alcohol (31). When a sample of the alcohol was refluxed with lithium aluminium hydride in THF, the alkoxide

was formed and on aqueous work-up the alcohol (31) was recovered unchanged. The evidence points towards a sulphonyl anion intermediate as shown in Scheme 6. The chiral integrity of the C-3 position of (27) appears to be retained in the transformation indicated by the fact that the reduction product (35) is optically active though its enantiomeric excess was not determined and therefore any racemization that may have occurred remained undetected.



Scheme 6

2.1.8. *Oxidation of 2-benzenesulphonyl-3-methylcyclopentanol (31)*

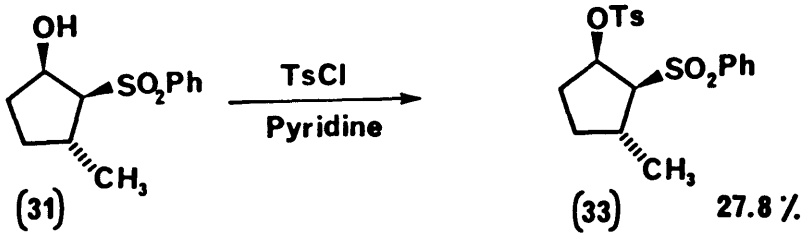


(7)

34.5%

Oxidation of the alcohol (31), whose optical purity had been enhanced by successive recrystallisation and evaporation of the mother liquor, to the cyclopentanone (27) was achieved by use of Jones' reagent. Reaction did not go to completion despite the presence of a large excess of oxidising agent, and on each of two occasions the crude product contained approximately 30% alcohol (31). However, the cyclopentanone (27) was easily recovered pure from the mixture by the base extraction described earlier. When the sample of alcohol of $[\alpha]_D^{20}$ +22.4° (c 25.5 in CH_2Cl_2), 60% e.e. from chiral shift ^1H n.m.r. studies, was oxidised the specific rotation of the cyclopentanone (27) was -81.3° (c 14.2 in CH_2Cl_2). This corresponds to 50% e.e. by extrapolation to the desulphonylation data. Thus the maximum enantiomerically enhanced sample of (27) had 50-60% e.e.

2.1.9. *Tosylate preparation*



(31) (33) 27.8 %

(8)

The tosylate derivative of the alcohol (31) was prepared by treatment of a pyridine solution of (31) at 0°C with tosyl chloride. The tosylate was purified by chromatography on silica and recrystallised from ether as white needles, m.p. 159-161°C, in 27.8% yield from the alcohol (31). Only one diastereoisomer was evident by spectroscopic analysis and again was assumed to have the indicated stereochemistry though this was not proven. The ^{1}H n.m.r. spectrum contained a doublet at δ1.05 (J = 6Hz) for the methyl group on the cyclopentyl ring while the aryl methyl group appeared as a singlet at δ2.43. The ir spectrum had strong bands at 1308 and 1151 cm^{-1} characteristic of the tosylate and sulphone groups.

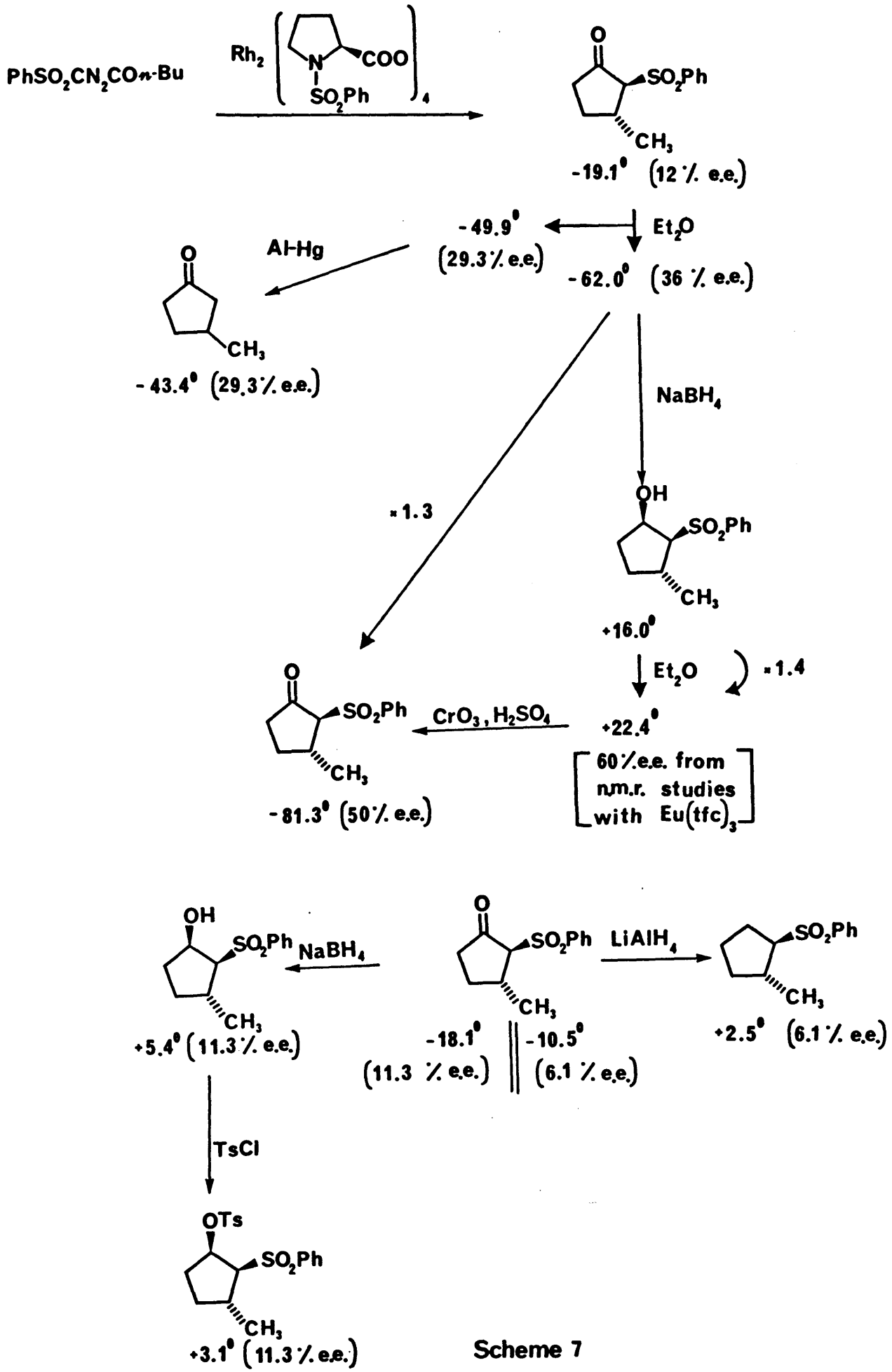
The tosylate (33) had a specific rotation of +3.1° (c 3.6 in CH_2Cl_2) when prepared from alcohol (31) of $[\alpha]_D^{20}$ +5.4 (c 10.3 in CH_2Cl_2) which was in turn prepared from cyclopentanone (27) of $[\alpha]_D^{20}$ -18.1 (c 9.6 in CH_2Cl_2), i.e. 11.3% e.e. approximately.

2.1.10 *Asymmetric synthesis*

Scheme 7 illustrates the development of the asymmetric synthesis with α-diazo-β-keto sulphone (14) and rhodium(II) *N*-benzenesulphonyl-L-prolinate. The initial asymmetric induction was low (12% e.e.) but was enhanced by careful repeated recrystallisation and recovery of the mother liquor of each recrystallisation. Estimation of optical purity was by desulphonylation to (S)-3-methylcyclopentanone for which specific rotation values are known. Estimation of the optical purity of the alcohol by chiral shift ^{1}H n.m.r. studies gave similar results to those obtained by extrapolation of the desulphonylation data. While the desulphonylation method gave an estimate of 75% optical purity for the sample of (27) with maximum enhanced optical rotation, chiral shift ^{1}H n.m.r. studies on the corresponding alcohol gave an estimate of 80% optical purity. Thus the maximum enantiomeric excess was 50-60%.

Notably the proportional enhancement of the specific rotation values of the alcohol on recrystallisation (1.3 enhancement) was very close to that of the cyclopentanones before reduction and after oxidation (1.4 enhancement) showing the accuracy of the specific rotation data.

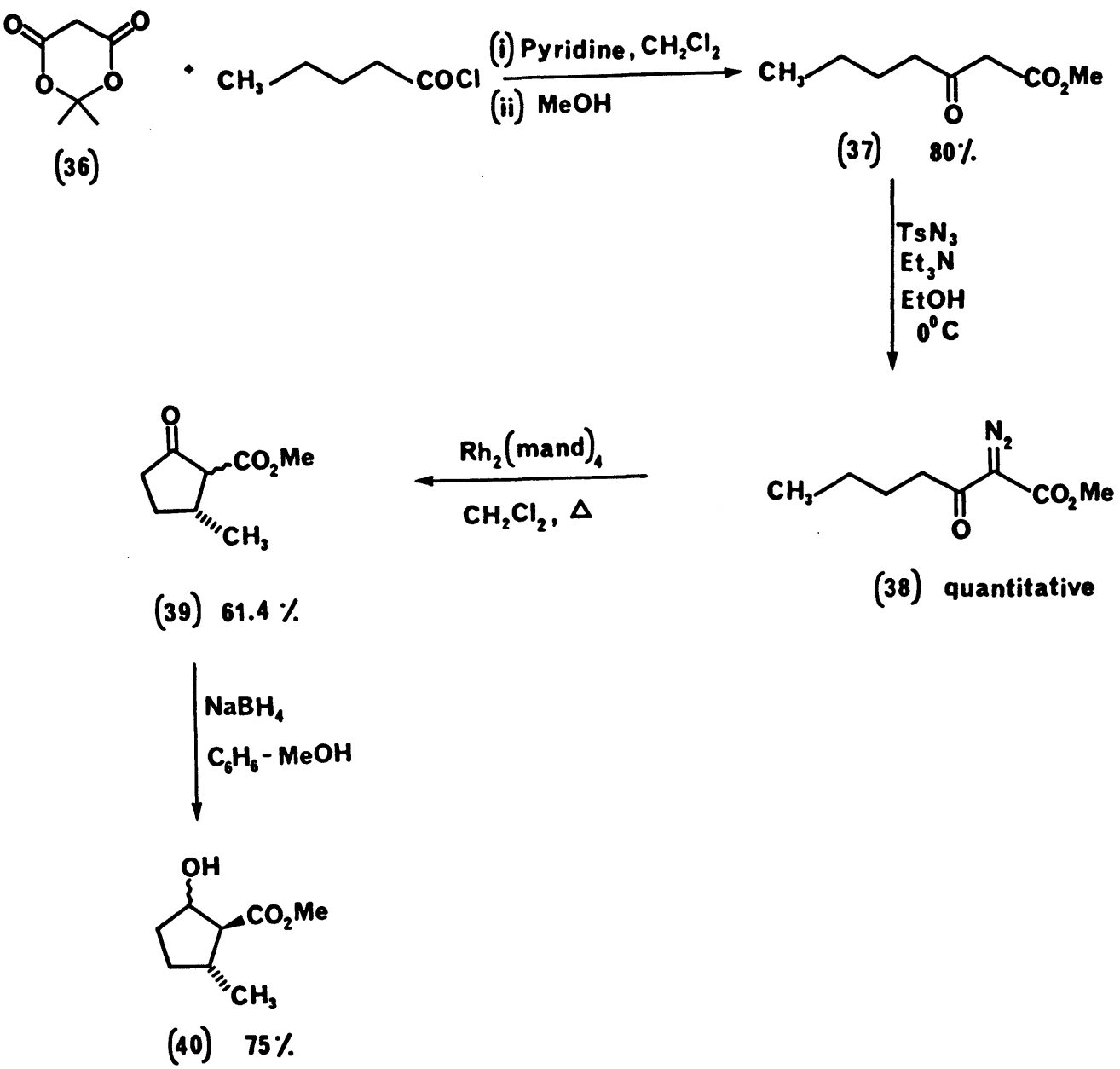
Thus enantiomeric excess of 50-60% was obtained by this route, with the advantage that a chiral auxiliary was not required, and in fact 1 mg of the chiral rhodium(II) *N*-benzenesulphonyl-L-prolinate catalyst resulted eventually in this degree of asymmetric induction, with the aid of recrystallisation enhancement.


PhSO2CN2CO-n-Bu
Rh2
COO
N
SO2Ph
4
SO2Ph
CH3
-19.1° (12 % e.e.)
-49.9°
(29.3 % e.e.)
Et2O
-62.0° (36 % e.e.)
Al-Hg
CH3
-43.4° (29.3 % e.e.)
NaBH4
×1.3
OH
SO2Ph
CH3
+16.0°
Et2O
×1.4
+22.4°
60 % e.e. from n.m.r. studies with Eu(tfc)3
CrO3, H2SO4
SO2Ph
CH3
-81.3° (50 % e.e.)
OH
SO2Ph
NaBH4
CH3
+5.4° (11.3 % e.e.)
SO2Ph
LiAlH4
CH3
-18.1°
(11.3 % e.e.)
-10.5°
(6.1 % e.e.)
SO2Ph
CH3
+2.5° (6.1 % e.e.)
TsCl
OTs
SO2Ph
CH3
+3.1° (11.3 % e.e.)

Scheme 7

If a more efficient catalyst for asymmetric induction could be obtained, then the efficiency of this route in going from an achiral α-diazoketone to a chiral cyclopentanone, with induction by just 1 mg of a chiral catalyst, would be preferable to Taber's method[3] where a chiral auxiliary was required.

2.1.11. *Intramolecular C-H insertion of an α-diazo-β-keto ester.*



Scheme 8

Scheme 8 summarises the preparation and intramolecular C-H insertion under rhodium(II) (S)-mandelate catalysis of α-diazo-β-keto ester (38). This work is more closely related to Taber's[3] work in the area of asymmetric induction by use of α-diazo-β-keto esters containing a homochiral alcohol as the chiral auxiliary.

The β-keto ester (37) was prepared by acylation of Meldrum's acid (36) with subsequent methanolysis in 80% yield.[38] Diazo transfer with tosyl azide and triethylamine in ethanol at 0°C gave the α-diazo-β-keto ester (38) in quantitative yield as a yellow oil which was purified by passage through a short column of silica to remove highly coloured baseline impurities. The diazo stretch in the ir spectrum of (38) was at 2125 cm^{-1} while the carbonyl stretches were at 1718 and 1650 cm^{-1} for the ester and ketone groups respectively. The ester methyl group protons were seen in the ^1H n.m.r. as a sharp singlet at δ3.84.

Cyclisation to (39) was carried out under rhodium(II) (S)-mandelate catalysis at reflux in dichloromethane, as described for the α-diazo-β-keto sulphone cyclisations. Removal of the solvent gave the crude product as an oil. Both the *cis* and *trans* isomers of (39) were visible in the ^1H n.m.r. spectrum, appearing as two singlets for the ester methyl groups at δ3.74 and 3.76. Accurate integration to give an isomeric ratio was not possible but an estimate of 60-70% *cis* isomer was made. Extraction into base followed by acidification in the usual manner described earlier for the 2-sulphonylcyclopentanones, gave the *trans* isomer of (39) exclusively as an oil in 61% yield from the α-diazo-β-keto ester (38). Two carbonyl stretches were visible in the ir spectrum of (39) at 1749 and 1718 cm^{-1}. The ester methyl group appeared in the ^1H n.m.r. spectrum at δ3.76 as a

sharp singlet while the cyclopentyl methyl group was seen as a doublet at δ1.17 (J = 7.8Hz).

The optical rotation of the cyclopentanone (39) after extraction was low, $[\alpha]_D^{20}$ -0.70° (c 10.4 in CH_2Cl_2). It was hoped that coordination of the two carbonyl oxygens of the β-keto ester (39) with $Eu(tfc)_3$ would result in splitting of the sharp singlet in the ^1H n.m.r. spectrum for the ester methyl group. However, resolution of enantiomers was not observed in the ^1H n.m.r. spectrum of (39) on addition of $Eu(tfc)_3$.

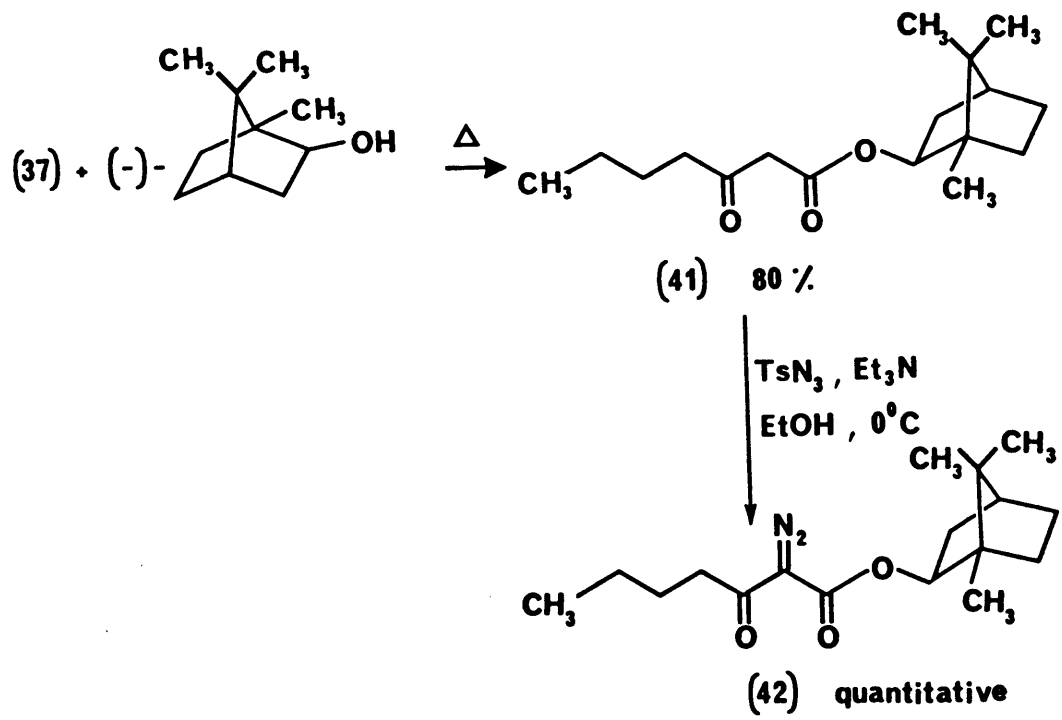
Instead the β-keto ester was selectively reduced to the alcohol mixture (40). The reduction was carried out by addition of sodium borohydride to the β-keto ester (39) in a benzene–methanol mixture at 0°C. The alcohol mixture (40) was obtained in 75% yield as an oil. In the 60MHz ^1H n.m.r. spectrum of (40) the signal for the ester methyl group was a broad singlet at δ3.74, which did not resolve for the two diastereoisomers. Addition of chiral shift reagent $Eu(tfc)_3$ split this signal in two for the two diastereoisomers and then split one of the signals in two for the enantiomeric pair indicating that approximately equal amounts of the two diastereoisomers were present and that the enantiomeric excess was very low (< 10%). The specific rotation of the alcohol mixture was also very low, +0.20° (c 7.6 in CH_2Cl_2), in agreement with this observation.

Thus, use of rhodium(II) (S)-mandelate as the decomposition catalyst of α-diazo-β-keto ester (38) did not result in high asymmetric induction and could not be compared with Taber's results with α-diazo-β-keto esters using a homochiral alcohol as a chiral auxiliary.[3] In that study the

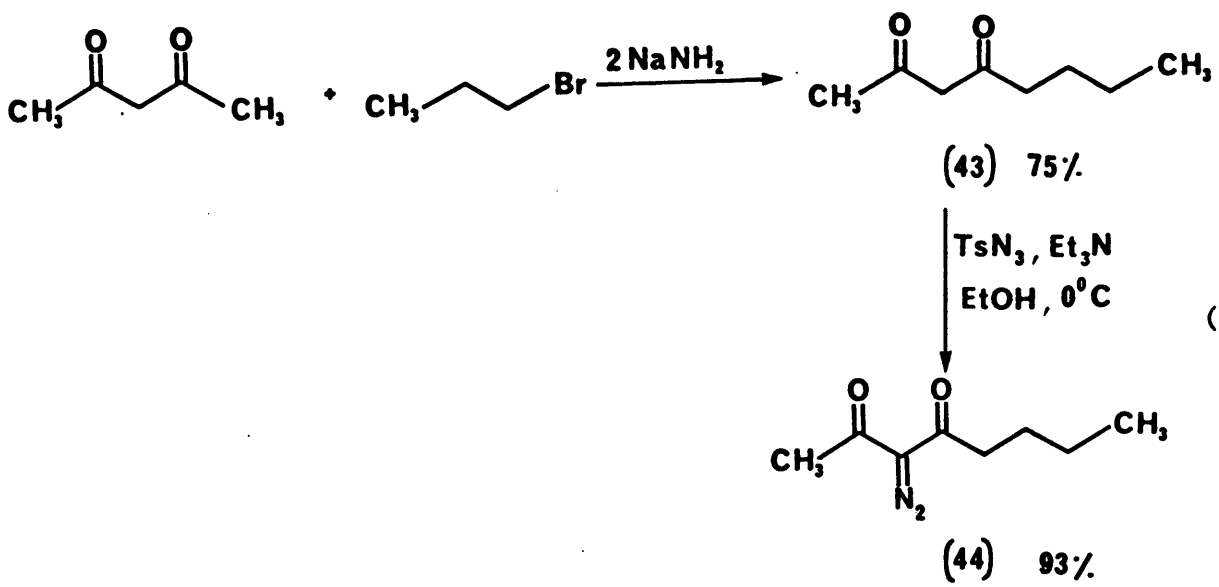
α-diazo-β-keto esters had much more bulky substituents, and the decreased steric constraints in α-diazo-β-keto ester (38) may be partially responsible for the poor enantioselection.

An α-diazo-β-keto ester derived from (-)-borneol was prepared as shown in equation 9 while equation 10 shows the preparation of an α-diazo-β-diketone. Ester exchange of the β-keto ester (37) with (-)-borneol gave the bornyl ester (42)[39] in 80% yield with purification by chromatography on silica. The ester (42) had a specific rotation of -15.7^{o} (c 2.6 in CH_2Cl_2). Diazo transfer with tosyl azide and triethylamine in ethanol at $0^{o}C$ gave the α-diazo-β-keto ester (42) as a yellow oil in quantitative yield with purification by passage through a short column of silica to remove highly coloured baseline impurities. The α-diazo-β-keto ester had a specific rotation of -14.7^{o} (c 11.3 in CH_2Cl_2) and was characterised spectroscopically. The ir spectrum contained the distinctive diazo band at 2124 cm^{-1} and carbonyl stretches at 1710 and 1657 cm^{-1} for the ester and ketone carbonyl groups respectively.

2,4-Octanedione (43)[40] was prepared by alkylation of the disodium salt of 2,4-pentanedione with propyl bromide in 75% yield as an oil. Diazo transfer with tosyl azide and triethylamine in ethanol at $0^{o}C$ gave the α-diazo-β-diketone (44) as a yellow oil in 93% yield following removal of baseline impurities by passage through a short column of silica. The diazo band in the ir spectrum of (44) was seen at 2111 cm^{-1} while the carbonyl stretch was seen at 1758 cm^{-1}. The C-1 methyl group protons appeared as a sharp singlet at δ2.40 in the ^{1}H n.m.r. spectrum.


(37) + (-)-
Δ
(41) 80 %
TsN3 , Et3N
EtOH , 0°C
(42) quantitative

(9)


2 NaNH2
(43) 75%
TsN3 , Et3N
EtOH , 0°C
(44) 93%

(10)

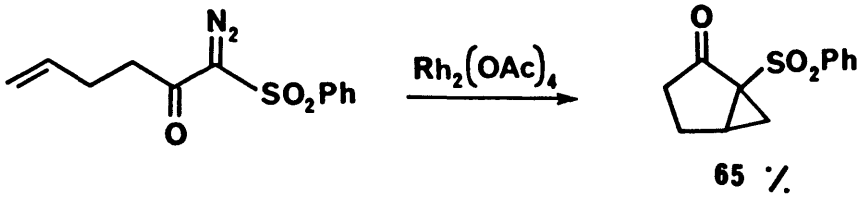
Preliminary investigations of the cyclisation of the diazo compounds (42) and (44) under rhodium(II) carboxylate catalysis indicated that cyclopentanone products were obtained, and when chiral rhodium(II) carboxylate catalysts were employed the products of the cyclisation of (44) were optically active indicating that at least some degree of asymmetric induction was obtained. Of course, the decomposition products of (42) were optically active due to the presence of (-)-borneol, so this could not be taken as an indication of asymmetric induction in the diazoketone decomposition.

The chiral auxiliary, (-)-borneol, in α-diazo-β-keto ester (42) was much less sterically demanding than that used by Taber,[3] so a much lower diastereoselectivity would be expected in its intramolecular C-H insertion when rhodium(II) acetate is employed as catalyst. However, it was hoped that with chiral rhodium(II) carboxylates, the interaction of the chiral substrate with the chiral catalyst would result in a 'double diastereoselection', significantly affecting the diastereoselectivity of the C-H insertion reaction. Further investigation of the cyclisation of α-diazo-β-keto ester (42) is currently being undertaken.

Similarly, cyclisation of α-diazo-β-diketone (44) is currently undergoing further investigation. To our knowledge there have been no previous reports of intramolecular C-H insertion with α-diazo-β-diketones.

2.2 Intramolecular Cyclopropanation of an α-Diazo-β-keto Sulphone

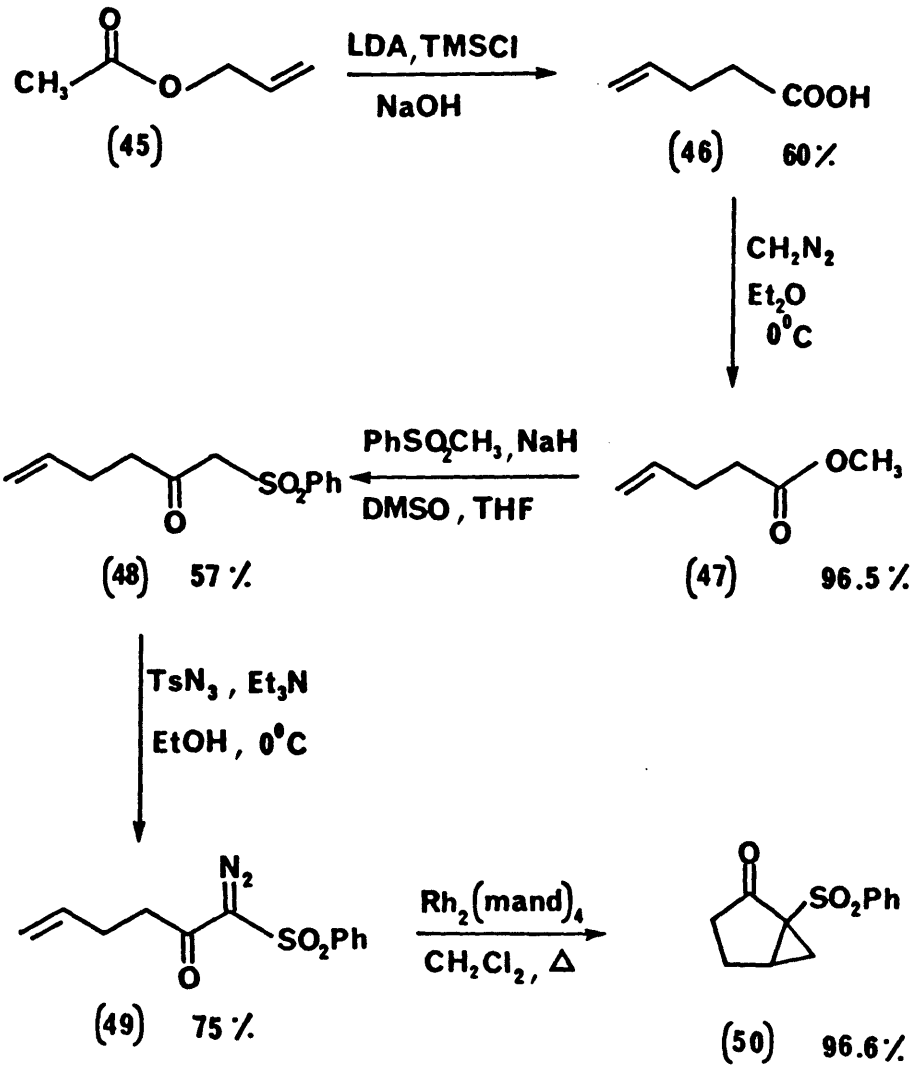
Monteiro[1] reported the use of rhodium(II) acetate as decomposition catalyst for the intramolecular alkene cyclopropanation shown in equation 11.



65 %

(11)

It was decided to attempt this reaction with chiral rhodium(II) carboxylates in an attempt to achieve asymmetric induction in the carbocyclisation. Scheme 9 summarises the preparation of α-diazo-β-keto sulphone (49) and its intramolecular cyclopropanation to form the bicyclo[3.1.0]hexanone (50) under rhodium(II) carboxylate catalysis. Pent-4-enoic acid (46) was obtained in 60% yield as an oil by ester enolate Claisen rearrangement from allyl acetate. The ester (47) was obtained in 96.5% yield by treatment of the acid (46) with ethereal diazomethane at $0^{o}C$. The ester (47) was obtained as an oil which was sufficiently pure to use without purification. Treatment of the ester (47) with methyl phenyl sulphonyl anion in a mixture of DMSO and THF following the procedure described earlier for the preparation of β-keto sulphones[7] (section 2.1.1.) gave the crude product containing equimolar amounts of β-keto sulphone (48) and methyl phenyl sulphone which were separated chromatographically to give the β-keto sulphone (48) as an oil in 57% yield which solidified on cooling. The β-keto sulphone (48) was characterised spectroscopically with a carbonyl stretch in the ir spectrum at 1719 cm^{-1} while the C=C double bond was visible at 1640 cm^{-1}. The methylene protons adjacent to the sulphonyl group appeared as a sharp singlet in the ^{1}H n.m.r. spectrum at δ4.14. Diazo transfer


LDA, TMSCl
NaOH
(45)
(46) 60%
COOH
CH_2N_2
Et_2O
0^0C
$PhSO_2CH_3$, NaH
DMSO, THF
OCH_3
(48) 57 %
(47) 96.5 %
TsN_3, Et_3N
EtOH, 0^0C
N_2
SO_2Ph
$Rh_2(mand)_4$
CH_2Cl_2, Δ
(49) 75 %
(50) 96.6%

Scheme 9

to β-keto sulphone (48) was carried out with tosyl azide and triethylamine in ethanol at 0°C to give the α-diazo-β-keto sulphone (49) as a yellow oil in 75% yield following chromatographic purification on silica. The methylene group singlet at δ4.14 in the ^{1}H n.m.r. spectrum of (48) disappeared on diazo transfer to form (49). The ir spectrum of (49) had a band at 2108 cm^{-1} for the diazo group and a carbonyl stretch at 1663 cm^{-1}.

The standard decomposition conditions described earlier for the α-diazo-β-keto sulphone C-H insertion reactions, were employed for the intramolecular cyclopropanation of (49), i.e. the decomposition was carried out at reflux in dichloromethane at high dilution with slow addition of the α-diazo-β-keto sulphone. Reaction was facile under rhodium(II) (S)-mandelate (1) catalysis and gave the fused cyclopropane (50) in essentially quantitative yield. Isomer formation was not possible with this system due to the steric constraints of the cyclopropane. Purification by base extraction was not possible with this compound so chromatographic purification was employed to remove the catalyst residue. The bicycle (50) was obtained as a stable white crystalline solid, m.p. 96-98°C (lit.,[1] 96-97°C), in 96.6% yield. The ^{1}H n.m.r. spectrum of (50) was complex. However a distinctive triplet was visible at δ1.56 (J = 5.4Hz) which was assigned to one of the cyclopropyl protons which are in distinctly different environments as shown in Figure 4. The multiplicity of the signal for this proton was explained by coupling to the bridgehead proton and geminal coupling, resulting in a pair of doublets which appeared as a triplet due to overlap.

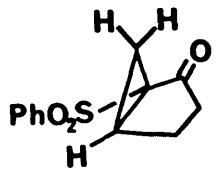


Figure 4

The bridgehead proton was seen as a multiplet at δ2.90-3.10 and the remaining five protons appeared as a multiplet at δ1.90-2.30, while the aromatic protons were seen at δ7.50-8.20.

Table 2.8 shows the effect of catalyst variation on the reaction. As the steric bulk of the ligand in the catalyst increased, catalyst efficiency, as shown by reaction time, decreased as observed with α-diazo-β-keto sulphone (14), and product yield also decreased. Highest asymmetric induction was observed when rhodium(II) *N*-naphthalenesulphonyl-L-prolinate (5) was used as catalyst. As observed with α-diazo-β-keto sulphone (14), the specific rotation obtained depended strongly on the catalyst employed, and the most efficient catalyst in terms of enantioselection was different to that in the earlier studies, i.e. with compound (14) the highest asymmetric induction was obtained with catalyst (4), rhodium(II) *N*-benzenesulphonyl-L-prolinate.

The bicycle (50) was found to crystallise racemically from ether as mentioned earlier, with enhancement of optical rotation of the material present in the mother liquor. A sample with a specific rotation

Table 2.8 : Decomposition of 1-benzenesulphonyl-1-diazohex-5-en-2-one (49) under rhodium(II) carboxylate catalysis at reflux in dichloromethane.



(49) (50)

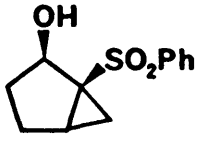
Catalyst	Reaction Time / h	Yield / %	$[\alpha]_D^{20}$ / °(c, CH_2Cl_2)
1	0.5	96.6	+1.5 (8.6)
4	1.5	79.0	+0.5 (5.7)
5	2.0	68.5	+1.8 (5.8)

Catalyst 1 Rh_2((S)-mandelate)$_4$; 4 Rh_2(*N*-benzenesulphonyl-L-prolinate)$_4$;

5 Rh_2(*N*-naphthalenesulphonyl-L-prolinate)$_4$.

of $[\alpha]_D^{20}$ +5.9° (c 5.0 in CH_2Cl_2) was obtained by two recrystallisations and repurification by p.l.c. on silica, from a sample with an initial specific rotation of +1.8° (c 5.8 in CH_2Cl_2), constituting a threefold increase in the initial asymmetric induction.

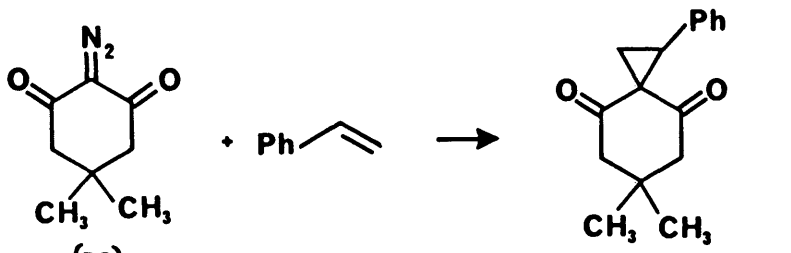
Preliminary investigation[42] of the reduction of cyclopentanone (50) with sodium borohydride to give the alcohol (51) as a crystalline solid, m.p. 121-123°C, has shown by Eu(tfc)$_3$-shifted ^{1}H n.m.r. studies of (51), that the sample of (50) with $[\alpha]_D^{20}$ +5.9° contains at least 12% e.e. Further investigation is currently being undertaken.



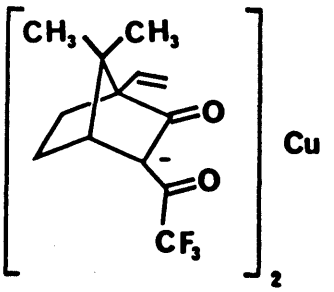
(51)

2.3 Intermolecular Cyclopropanation with Rhodium(II) (S)-Mandelate

In an attempt to compare chiral rhodium(II) carboxylates with chiral copper catalysts, the cyclopropanation[43] of styrene with diazodimedone was carried out with rhodium(II) (S)-mandelate as catalyst. This reaction was reported to result in optically pure cyclopropane using copper(II) 10-methylenefacam as catalyst as shown in equation 12.



(12)



2-Diazodimedone (52) was prepared quantitatively by treatment of dimedone with tosyl azide and triethylamine in ethanol at $0^{o}C$, and was purified by chromatography on silica to give the product as a very pale yellow crystalline solid, m.p. 99-101°C (106°C, decomp.). Decomposition of 2-diazodimedone (52) in styrene using rhodium(II) (S)-mandelate as catalyst gave the cyclopropane (53) in 40% yield following chromatographic purification on silica, as an oil. The product had a specific rotation of -1.6^{o} (c 5.7 in CH_2Cl_2) indicating that some degree of asymmetric induction had occurred. Addition of $Eu(tfc)_3$ did not result in resolution of the signals for the enantiomers in the ^{1}H n.m.r. spectrum. Furthermore a specific rotation for enantiomerically pure cyclopropane (53) was not available. Therefore, estimation of the asymmetric induction obtained in the cyclopropanation through use of

rhodium(II) mandelate was not possible and its efficiency as an asymmetric induction catalyst could not be compared to that of the chiral copper catalyst.

2.4 References

1. H.J. Monteiro, *Tetrahedron Lett.*, 1987, 28, 3459.
2. I. Kuwajima, Y. Highuchi, H. Iwasawa, and T. Sato, *Chem. Lett.*, 1976, 1271.
3. D.F. Taber and E.H. Petty, *J. Org. Chem.*, 1982, 47, 4808.
4. H.J. Callot and F. Metz, *Tetrahedron Lett.*, 1982, 23, 4321.
5. A. Demonceau, A.F. Noels, A.J. Hubert, and P. Teyssie, *Bull. Soc. Chim. Belg.*, 1984, 93, 945.
6. D.F. Taber and K. Raman, *J. Am. Chem. Soc.*, 1983, 105, 5935.
7. E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, 87, 1345.
8. P. Hetherington, 4th year project.
9. H.J. Monteiro, *Synth. Commun.*, 1987, 17, 983.
10. W. Illger, A. Liedhegener, and M. Regitz, *Justus Liebegs Ann. Chem.*, 1972, 760, 1.
11. T.J. Curphey, *Org. Prep. Proced. Int.*, 1981, 13, 112.
12. P.A. Agaskar, F.A. Cotton, L.R. Falvello, and S. Han, *J. Am. Chem. Soc.*, 1986, 108, 1214.
13. Catalyst preparation was carried out by G. Roos.
14. R.N. Shchelokov, A.G. Maiorova, S.S. Abdullaev, O.N. Evstaf'eva, I.F. Golovaneva, and G.N. Emel'yanova, *Russ. J. Inorg. Chem.*, 1981, 26, 1774.
15. Prepared by N. Garvey following Cotton's procedure in ref. 12.
16. B.M. Dilworth, Ph.D. thesis, N.U.I., 1987.
17. F. Pruchnik, B.R. James, and P. Kvintovics, *Can. J. Chem.*, 1986, 64, 936, and references therein.

18. C.R. Wilson and H. Taube, *Inorg. Chem.*, 1975, 14, 405.

19. G.A. Rempel, P. Legzdins, H. Smith, and G. Wilkinson, *Inorg. Synth.*, 1972, 90; S.A. Johnson, H.R. Hunt, and H.M. Neumann, *Inorg. Chem.*, 1963, 2, 960.

20. M.A. Golubnichaya, I.B. Baranovskii, G. Ya. Mazo, and R.N. Shchelokov, *Russ. J. Inorg. Chem.*, 1981, 26, 1534.

21. H.J. Callot and F. Metz, *Tetrahedron*, 1985, 41, 4495.

22. Ketopinic acid (1-apocamphanecarboxylic acid, 2-oxo) was prepared from camphorsulphonyl chloride by the procedure of P.D. Bartlett and L.H. Knox, *Org. Synth.*, Coll. Vol. V, 1973, p.689.

23. Prepared by M. Owens.

24. A.R. Chakravarty, F.A. Cotton, D.A. Tocher, and J.H. Tocher, *Organometallics*, 1985, 4, 8.

25. F.A. Cotton, K.R. Dunbar, and M.G. Verbruggen, *J. Am. Chem. Soc.*, 1987, 109, 5498.

26. J. Ficini and G. Stork, *Bull. Soc. Chim. Fr.*, 1964, 723.

27. P. Legzdins, R.W. Mitchell, G.L. Rempel, J.D. Ruddick, and G. Wilkinson, *J. Chem. Soc. (A)*, 1970, 3322.

28. 'Basic Inorganic Chemistry', F.A. Cotton and G. Wilkinson, Wiley, New York, 1976, p.434.

29. M.P. Moyer, P.L. Feldman, and H. Rapoport, *J. Org. Chem.*, 1985, 50, 5223.

30. H. Brunner and W. Miehling, *Monatsh. Chem.*, 1984, 115, 1237.

31. F.A. Cotton, L.R. Falvello, and C.A. Murillo, *Inorg. Chem.*, 1983, 22, 382.

32. 'Stereochemistry of Carbon Compounds', E.L. Eliel, McGraw-Hill, 1962, p.44.

33. 'Reagents for Organic Synthesis', Fieser and Fieser, 1967, Vol. 1, Wiley, p.20.

34. 'Handbook of Chemistry and Physics', 67th ed., CRC press.

35. W.C.M.C. Kokke and F.A. Varkevisser, *J. Org. Chem.*, 1974, 39, 1535.

36. Commercially available sample of (R)-(+)-3-methylcyclopentanone from Aldrich Chemical Company.

37. Ref. 32, p.419.

38. Preparation of β-keto ester was carried out by G. Roos following the procedure in Y. Oikawa, T. Yoshioka, K. Sugano, and O. Yonemitsu, *Org. Synth.*, 1985, 63, 198. Meldrum's acid was prepared as described by D. Davidson and S.A. Bernhard, *J. Am. Chem. Soc.*, 1948, 70, 3426.

39. The bornyl ester (41) was prepared by G. Roos following the ester exchange procedure in D.F. Taber, J.C. Amedio, and K. Raman, *J. Org. Chem.*, 1988, 53, 2984.

40. The β-diketone (43) was prepared by G. Roos following the procedure in K.G. Hampton, T.M. Harris, and C.R. Hauser, *Org. Synth.*, Coll. Vol. V, 1973, 848.

41. The acid (46) was prepared by G. Roos by a modification of the procedure in R.E. Ireland, R.H. Mueller, and A.K. Willard, *J. Am. Chem. Soc.*, 1976, 98, 2868, where isopropylcyclohexamine was replaced by diisopropylamine.

42. Reduction of (50) and chiral shift ^{1}H n.m.r. studies of (51) with $Eu(tfc)_3$ were carried out by M. Kennedy.

43. S.A. Matlin, W.J. Lough, L. Chan, D.M.H. Abram, and Z. Zhou, *J. Chem. Soc., Chem. Commun.*, 1984, 1038.

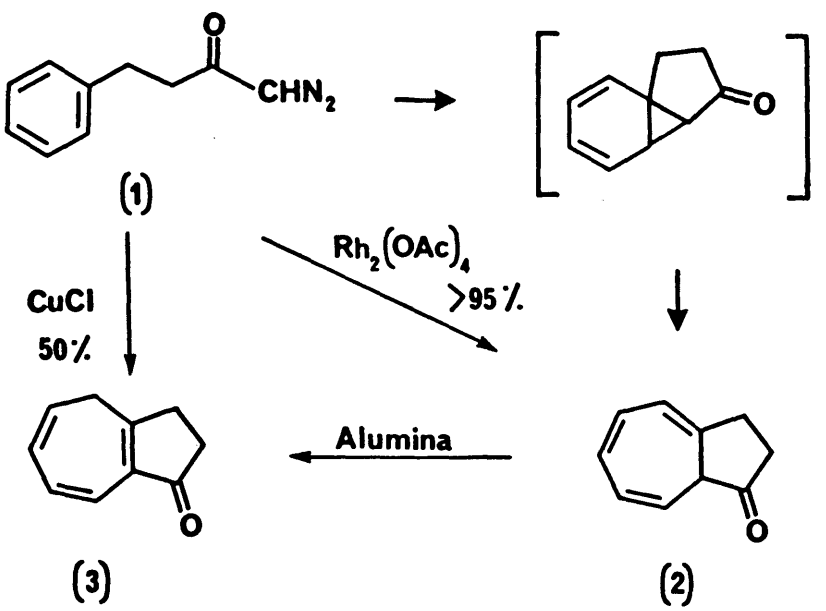
CHAPTER 3

THE INTRAMOLECULAR BUCHNER REACTION OF ARYL DIAZOKETONES

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3.1 Introduction

α-Diazoketones derived from dihydrocinnamic acids cyclise to bicyclo[5.3.0]decatrienones[1-4] very efficiently in the presence of certain rhodium(II) carboxylates, (1) the parent member of the series cyclising in > 95% yield with rhodium(II) acetate as shown in Scheme 1.



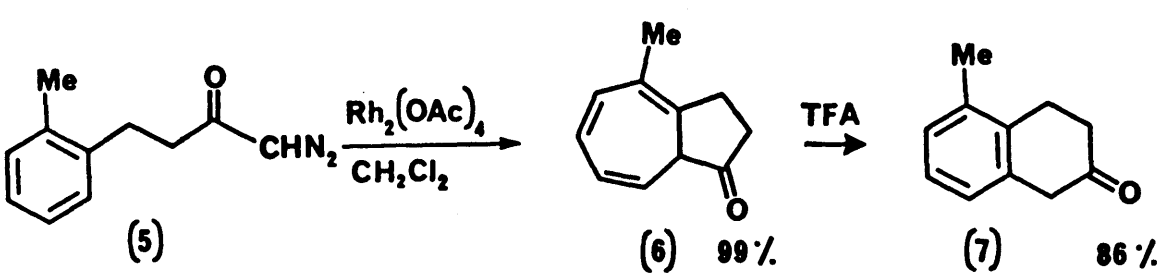
Scheme 1

This reaction is often referred to as the intramolecular Buchner reaction and is a relatively recent discovery.[5] In 1973 Scott[6] found that treatment of 1-diazo-4-phenylbutan-2-one (1) with cuprous chloride in bromobenzene furnished 3,4-dihydro-1(2*H*)-azulenone (3) in 50% yield after chromatography on alumina, as shown in Scheme 1. Evidence was obtained from n.m.r. analysis that the conjugated trienone (3) was not the primary cyclisation product, but that the less conjugated trienone (2) was formed initially which then isomerised on contact with alumina.

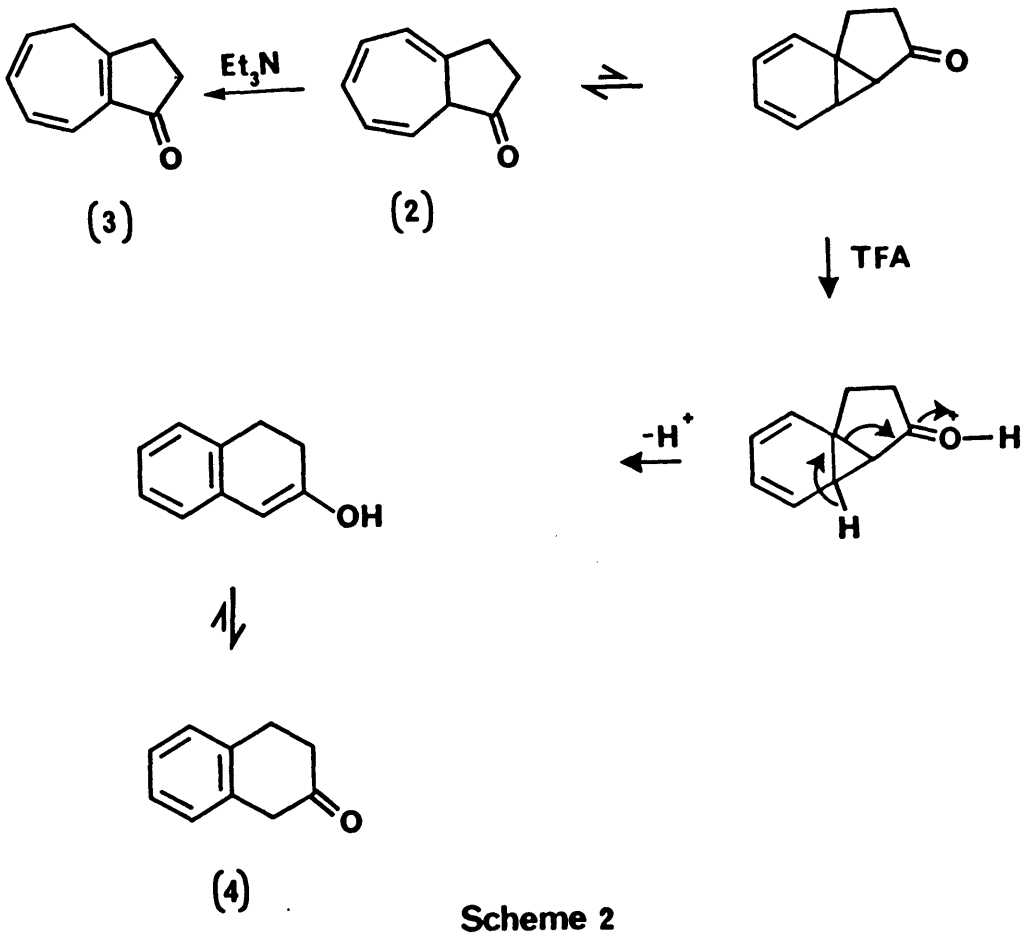
The reaction pathway is believed to involve addition of a carbenoid to the benzene ring forming a norcaradiene-like intermediate followed by electrocyclic ring opening to form trienone (2) as shown in Scheme 1. Bond isomerisation on alumina then resulted in formation of the conjugated trienone (3).

However, the milder conditions associated with rhodium(II) carboxylate catalysts meant that the kinetic isomer (2) could be isolated from a rhodium(II) acetate catalysed decomposition of α-diazoketone (1),[1] as shown in Scheme 1. The product (2) could be easily converted[1] into the conjugated trienone (3) on treatment with triethylamine or into the tetralone (4) on treatment with trifluoroacetic acid as shown in Scheme 2. This rearrangement of the trienone (2) to tetralone (4) on TFA treatment implies the existence of a trienone-norcaradienone equilibrium with acid promoted cyclopropane ring opening in the norcaradieneone resulting in tetralone formation.

The effect of substituents on the aromatic ring of the α-diazoketone on the directionality of the Buchner cyclisation has been investigated.[1,3] For example, the *o*-methyl substituted α-diazoketone (5) cyclised to give trienone (6) which on TFA treatment gave tetralone (7) as shown in equation 1 indicating that an *ortho*-methyl group has a repulsive effect on the direction of the carbenoid cycloaddition.

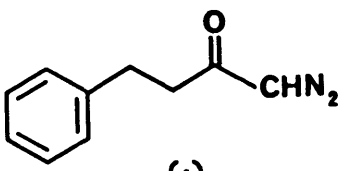


(1)

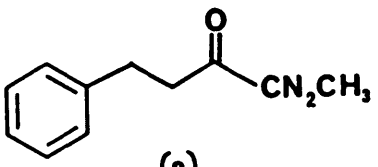


Scheme 2

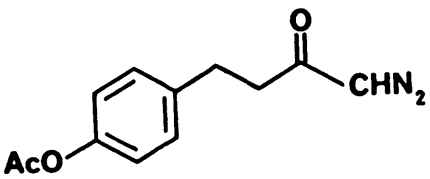
The aim of this study was to investigate the preparation of substituted bicyclo[5.3.0]decatrienones by the Buchner cyclisation of appropriately substituted α-diazoketones. Those chosen for study were the α-diazoketones (1), (8), (9), and (10).



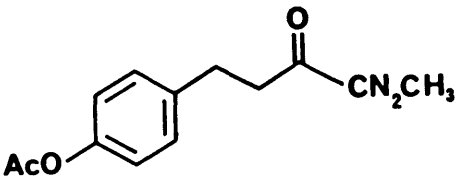
(1)



(8)

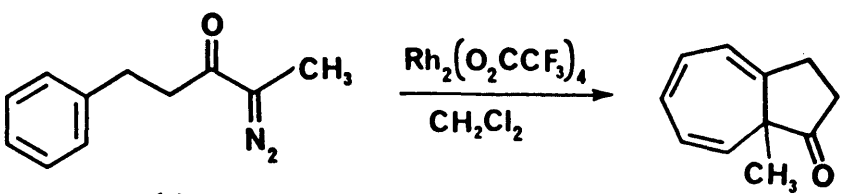


(9)



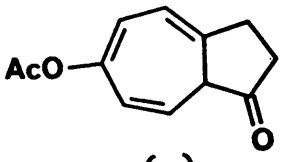
(10)

An earlier study[7] had shown that α-diazoketone (8) cyclised successfully with rhodium(II) trifluoroacetate to give trienone (11) with a bridgehead methyl group, as shown in equation (2). Therefore, the α-diazoketones (8), (9), and (10) on cyclisation could give a series of bicyclo[5.3.0]decatrienones (11), (12), and (13), respectively, in which bridgehead methyl substitution and acetoxy functionality on the cycloheptatriene ring could be investigated.

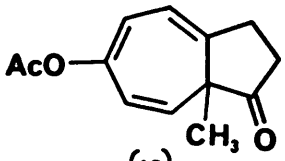


(8) (11) (2)

It was decided to also investigate further synthetic transformations of these trienones to determine their utility in the preparation of compounds containing the bicyclo[5.3.0]decane skeleton.



(12)



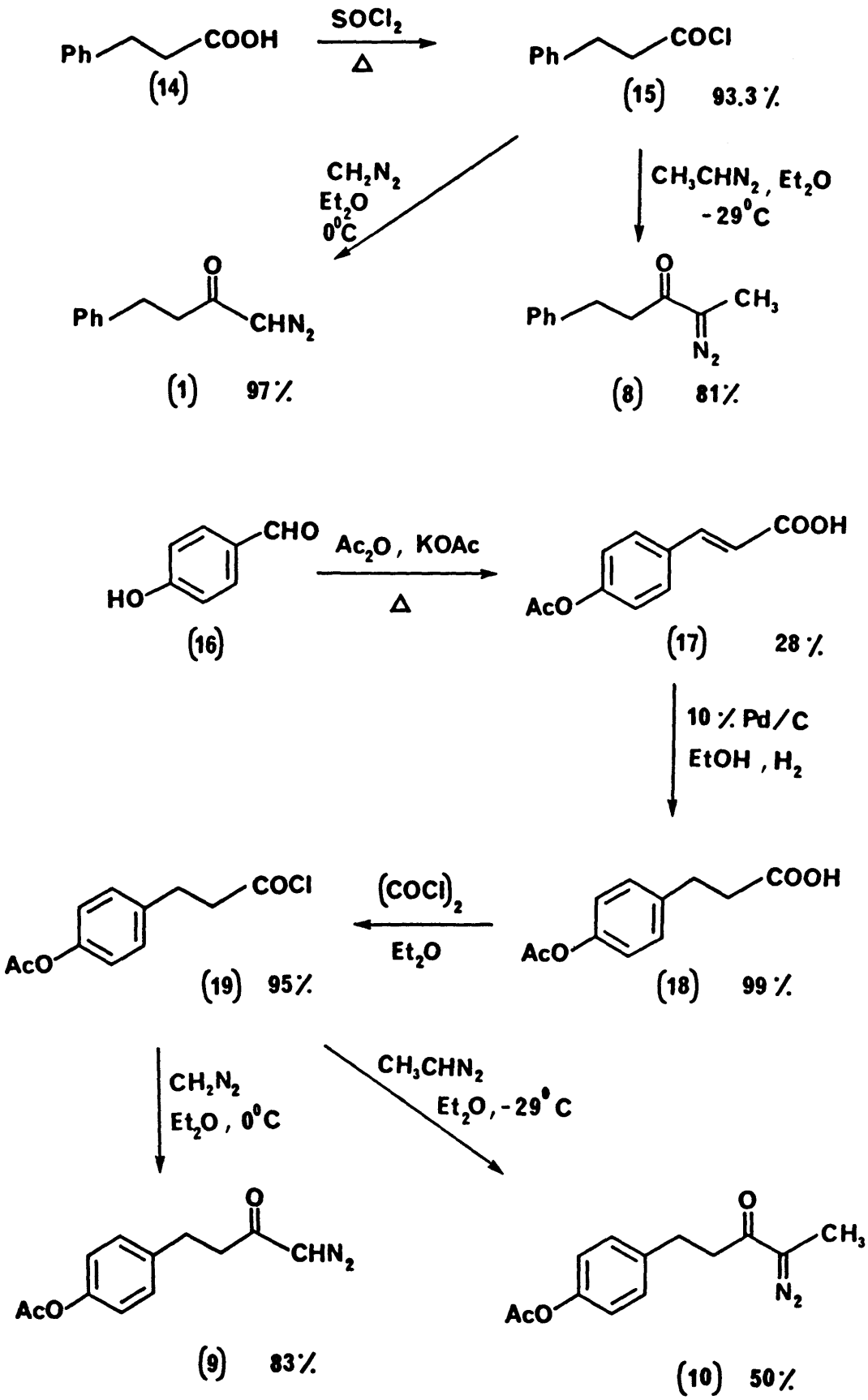
(13)

Furthermore, it was decided to investigate the possibility of asymmetric synthesis in these cyclisations by use of the chiral rhodium(II) carboxylate catalysts discussed in Chapter 2, as an asymmetric centre at the bridgehead position adjacent to the carbonyl group is created in the cyclisation.

3.2. Preparation of the α-Diazoketones

All the α-diazoketones used in this work were prepared by treatment of the appropriate acid chloride with either ethereal diazomethane or diazoethane furnishing the terminal and non-terminal α-diazoketones, respectively. Scheme 3 summarises the preparation of the α-diazoketones.

3-Phenylpropanoyl chloride (15) was prepared by treatment of the carboxylic acid (14) with thionyl chloride. *p*-Acetoxycinnamic acid (17) was prepared in low yield by Perkin condensation of *p*-hydroxybenzaldehyde (16), potassium acetate, and acetic anhydride. Hydrogenation to 3-(*p*-acetoxyphenyl)propanoic acid (18) was facile but attempts at purification of the product (18) by crystallisation were unsuccessful. Oxalyl chloride was employed to convert the crude (18) into the acid chloride (19) which was sufficiently pure to use directly in the diazoalkane acylation.


Ph
COOH
(14)
SOCl2
Δ
Ph
COCl
(15) 93.3 %
CH2N2
Et2O
0°C
CH3CHN2, Et2O
-29°C
Ph
O
CHN2
(1) 97 %
Ph
O
CH3
N2
(8) 81 %
HO
CHO
(16)
Ac2O, KOAc
Δ
AcO
COOH
(17) 28 %
10 % Pd/C
EtOH, H2
AcO
COOH
(18) 99 %
(COCl)2
Et2O
AcO
COCl
(19) 95 %
CH2N2
Et2O, 0°C
CH3CHN2
Et2O, -29°C
AcO
O
CHN2
(9) 83 %
AcO
O
CH3
N2
(10) 50 %

Scheme 3

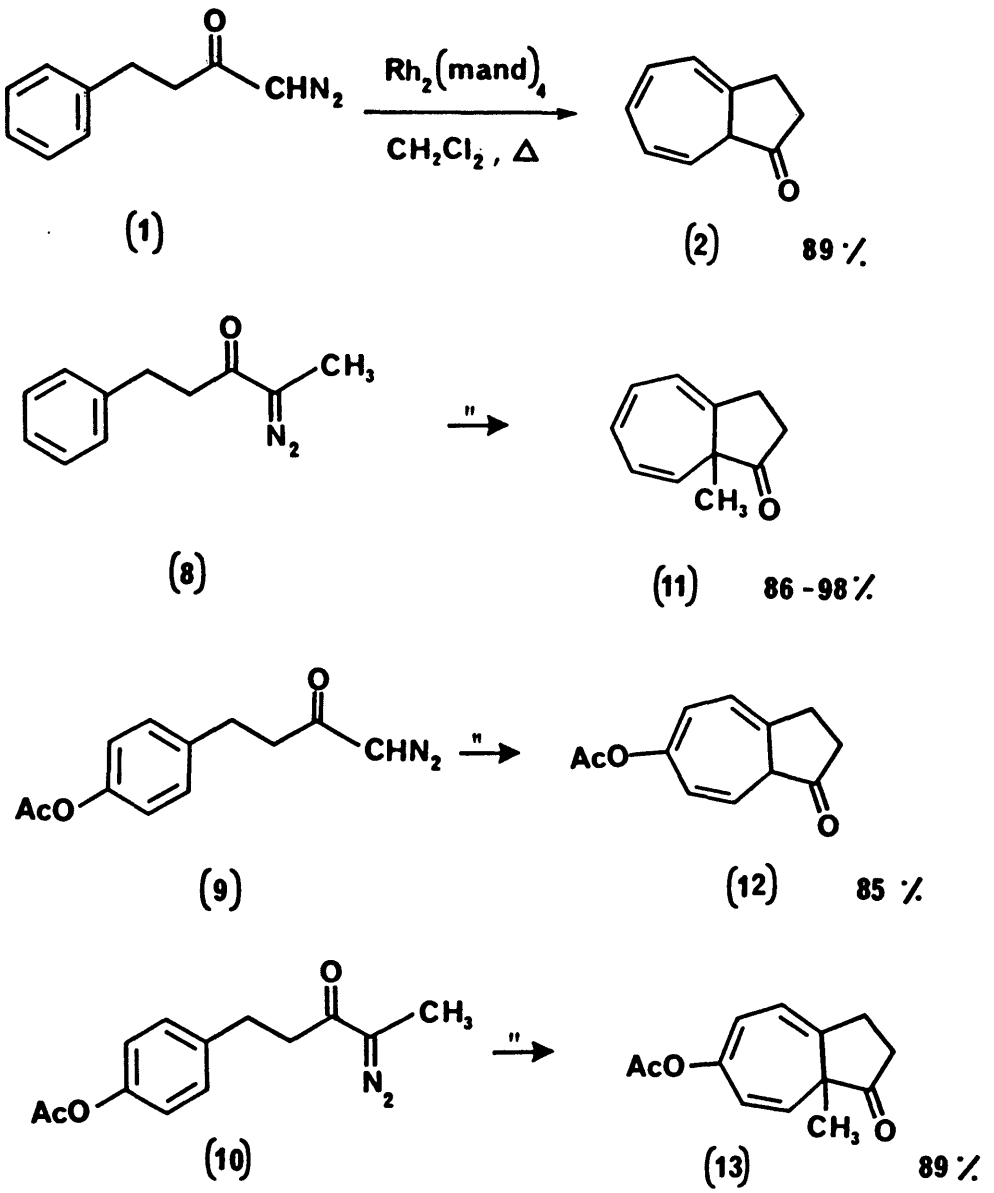
Ethereal solutions of diazomethane[8] and diazoethane[9] were prepared from Diazald and *N*-ethyl-*N*-nitrosourea, respectively, by standard procedures. The diazoalkane solutions were freshly prepared and distilled before use. The terminal α-diazoketones (1) and (9) were obtained in good purity by treatment of the corresponding acid chloride with 4-5 equivalents of ethereal diazomethane at 0°C. However, with diazoethane the reaction conditions had to be much more carefully controlled to obtain α-diazoketones (8) and (10) in pure form. A byproduct, thought to be due to reaction of the α-diazoketone with a second molecule of diazoethane, was formed in these reactions. This had earlier been observed by Wilds and Meader.[10] To minimise formation of the byproduct the reaction was carried out at -29°C (using a nitromethane-liquid nitrogen slush bath), which was found to be the optimum reaction temperature. Use of 4.5 equivalents of ethereal diazoethane was found to be most satisfactory; if less than this was used the crude product contained unreacted acid chloride, whereas if a larger excess was used increasing amounts of the byproduct were formed. The concentration of the solution also had to be strictly controlled; when the diazoethane solution was too dilute the amount of byproduct formed was greatly increased. A 1M solution of diazoethane in ether was found most satisfactory. Hudlicky and co-workers[11] have also observed the significance of concentration control in reactions of acid chlorides with diazoethane, reporting that a 0.1M ethereal solution of diazoethane gave best results with their compounds. By careful control of these factors α-diazoketones (8) and (10) were obtained with less than 10% of the impurity present. Any deviation from the optimum conditions gave the α-diazoketones containing up to 50% of the byproduct.

Although the α-diazoketones (1), (8), (9), and (10) were sensitive to silica, chromatographic purification was necessary to remove the impurities which poisoned the rhodium(II) carboxylate catalysts if decomposition of the crude α-diazoketones was attempted. The contact time of the α-diazoketones with silica was kept as brief as possible to minimise losses due to decomposition. It was essential to avoid the use of hydroxylic solvents in the chromatographic purification of the α-diazoketones as their presence resulted in greater losses of α-diazoketones, presumably due to O-H insertion reactions on the silica surface.

The α-diazoketones were very sensitive and were stored in a freezer under nitrogen. Even under these conditions slow decomposition of α-diazoketone (12) was observed and repurification was often necessary after 2-3 months storage.

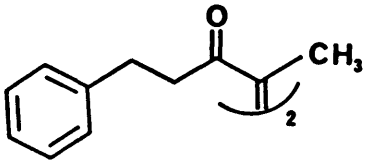
3.3. Cyclisation of Diazoketones

α-Diazoketones (1), (8), (9), and (10) were decomposed by rhodium(II) carboxylate catalysis in dichloromethane, and the structures of the products were determined by spectral methods. The standard conditions employed for the cyclisations were high dilution (100 mg of α-diazoketone in 20 ml dichloromethane added to 200 ml refluxing dichloromethane), slow addition (30 min), with two additions of catalyst (2 x 0.5 mg), one before and one halfway through the α-diazoketone addition. The optimum results and the products obtained are summarised in Scheme 4 using rhodium(II) mandelate as decomposition catalyst in each case.



Scheme 4

Each of the cycloheptatrienone products was accompanied by an aromatic impurity which was assumed to be the carbene dimer in each case although only that which corresponded to α-diazoketone (8), i.e. dimer (20), was isolated.

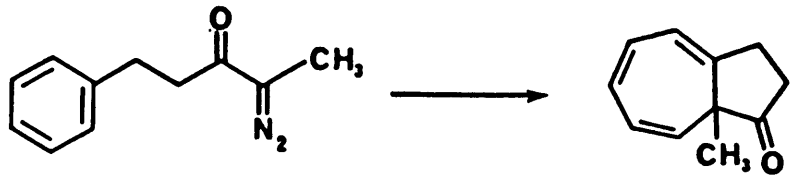


(20)

The ^{1}H n.m.r. spectrum of (20) contained only one singlet at δ2.28 (6H) for the methyl groups of the dimer suggesting that only one isomer of the dimer had formed, but giving no indication of its stereochemistry. The aromatic protons also appeared as a singlet at δ7.19 (10H), and an estimate of the amount of dimer impurity present was obtained by comparison of the integration of the aromatic protons of the dimer with the signal for the cycloheptatrienyl protons.

The standard cyclisation conditions of high dilution and slow addition were designed to minimise the concentration of α-diazoketone in the solution at any time thereby reducing dimer formation. In order to isolate dimer (20), decomposition of α-diazoketone (8) was deliberately carried out at high concentration giving the product containing 62% trienone (11) and 38% dimer (20), from which (20) was isolated by chromatographic separation on silica. Tables 3.1 and 3.2 show the effect of concentration and addition time on the cyclisation of α-diazoketone (12) demonstrating that dimer formation was minimised by high dilution and slow addition.

Table 3.1 : Effect of concentration on $Rh_2(mand)_4$ catalysed cyclisation of 2-diazo-5-phenylpentan-2-one (8)

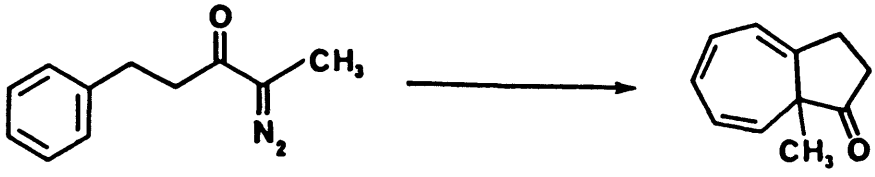


(8) (11)

Concentration mg/ml	Trienone:dimer %
100/50	82:18
100/100	87:13
100/150	90:10

Reactions were carried out at reflux in dichloromethane.

Table 3.2 : Effect of addition time on rhodium(II) *N*-benzenesulphonyl-L-prolinate catalysed cyclisation of 2-diazo-5-phenylpentan-2-one (8).



(8) (11)

Addition time h	Trienone:dimer %
0.17	60:40
1.00	75:25

Reactions were carried out at room temperature in dichloromethane.

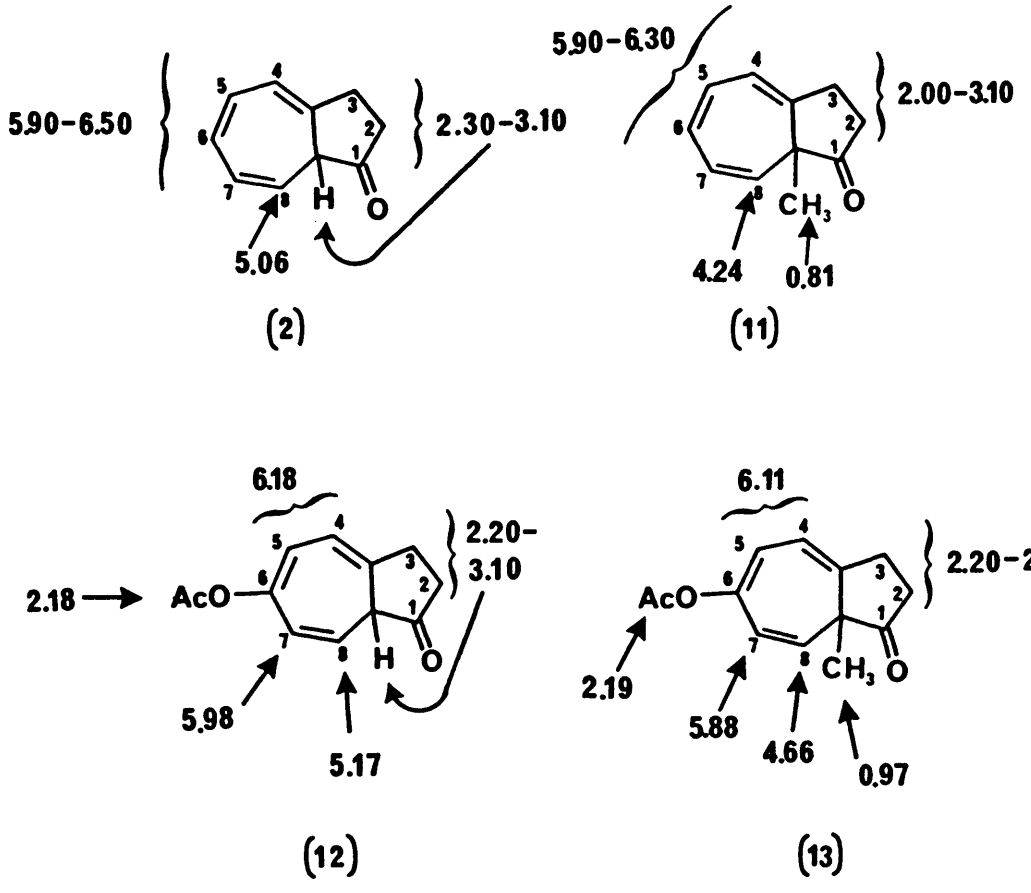
The cycloheptatrienone products (2), (11), (12), and (13), which were all coloured viscous oils, were characterised spectroscopically and were generally used without purification as they are extremely reactive compounds. Trienones (11) and (13) containing the bridgehead methyl substituents were more stable than (2) and (12), in which bond isomerisation to form conjugated trienones was possible.[1] Analytical samples of (11) and (13) were isolated by p.l.c. on silica, but contact time had to be minimised to prevent serious losses due to decomposition.

3.3.1. *Spectroscopic characterisation and cycloheptatrienone-norcaradiene equilibrium*

The ^{1}H n.m.r. features of trienones (2), (11), (12), and (13) are shown over.

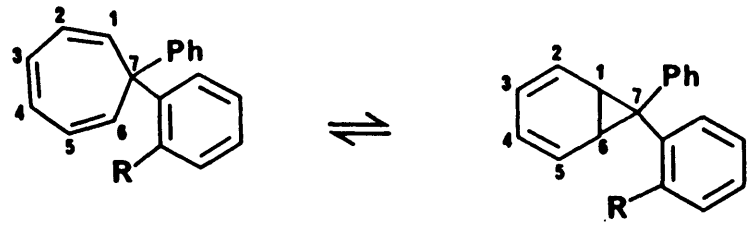
All four of the cyclisation products showed carbonyl stretches for the cyclopentanone at approximately 1740 cm^{-1} in their ir spectra, while the acetoxy-substituted compounds showed a carbonyl stretch at 1755 cm^{-1} also. However, compounds (11) and (13), i.e. those containing the bridgehead methyl group, contained an additional unexpected carbonyl stretch at 1708 cm^{-1}, which was equal in intensity to the cyclopentanone band for compound (11) but weaker in the case of (13).

These two compounds also had anomalous features in their ^{1}H n.m.r. spectra. While the cycloheptatrienyl protons of trienone (2) were all in the region δ5.00-6.50, the C(8)*H* of compound (11) appeared as a doublet at δ4.24 (J = 7.2Hz). Similarly for trienone (12) all the cycloheptatrienyl protons appeared at lower field than δ5.00, but for compound (13), the C(8)*H* appeared at δ4.66 (J = 9.6Hz).



The bridgehead methyl groups of (11) and (13) appeared as distinctive singlets in the ^{1}H n.m.r. spectra at δ0.81 and 0.97, respectively.

The atypical positions of the vinylic C(8)*H* protons in the ^{1}H n.m.r. spectra of (11) and (13) were explicable following the recent publication of Hannemann's[12] analysis of the n.m.r. spectra of several cycloheptatrienes in equilibrium with their norcaradiene counterparts.



(21a) (21b) (3)

	$\delta_{1,6H}$	$\delta_{1,6C}$
R = H	4.54 (m)	96.20 (d)
R = CH_3	2.87 (m)	42.27 (d)

Equation (3) illustrates one example of the equilibria between cycloheptatriene and norcaradiene forms studied by Hannemann. When the aromatic rings of (21) were unsubstituted (R = H) the signal for the 1,6-*H*s appeared at δ4.54 in the ^{1}H n.m.r. spectrum but the introduction of an *ortho*-methyl group in one of the aromatic rings resulted in a corresponding signal at δ2.87 for the 1,6-*H*s. Similarly the 1,6-*C*s of the unsubstituted compound appeared at δ96.20 in the ^{13}C n.m.r. spectrum while the compound containing the *ortho*-methyl group had a signal for the 1,6-*C*s at δ42.27.

The chemical shifts of 1,6-*H* and *C* atoms of pure cycloheptatrienes normally appear in the region δ_H5.2-5.3 and δ_C120-130, respectively, whereas those for norcaradienes are at δ_H2.8-3.5 and δ_C35-45 as shown in Table 3.3. For equilibrating systems the resonances for these atoms usually lie between these values and the position of the norcaradiene-cycloheptatriene equilibrium can be estimated from the chemical shift observed. For example, compound (21) (R = CH_3) exists entirely in the norcaradiene form whereas for R = H approx. 35% of the norcaradiene is present in the equilibrium at room temperature, based on the position of the n.m.r. resonances.

Table 3.3 : NMR data of some cycloheptatrienes (CHT) and norcaradienes (NCD)

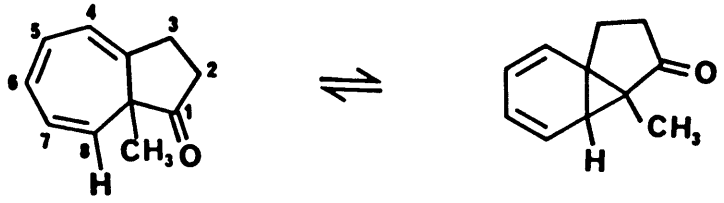
Substitution pattern	Isomer	^{1}H NMR[a] 1,6-H	2,5-H	3,4-H	^{13}C NMR[a] 1,6-C	7-C
7-*tert*-Butyl[b,f]	CHT	5.21	6.09	6.57	126.0	50.6
7-Phenyl[b]	CHT	5.31	6.14	6.63	-	-
7-Spirofluorenylidene[c]	CHT/NCD	4.74	6.16		-	-
7,7-Diphenyl[d]	CHT/NCD	4.54	6.36	6.02	96.20	43.76
7-Phenyl-7-*o*-tolyl[d]	NCD	2.87	6.25	5.71	42.27	26.06
7,7-Dicyano[e]	NCD	3.47	6.2-6.8		-	-
1,6-(1,3-Propanediyl)[f]	NCD	-	-	-	38.6	20.2

(a) Chemical shift δ relative to TMS. (b) H. Gunther, M. Gorlitz, H.-H. Hinrichs, *Tetrahedron*, 1968, 24, 5665.
(c) H. Durr, H. Kober, *Angew. Chem.*, 1971, 83, 362; *Angew. Chem. Int. Ed. Engl.*, 1971, 10, 342.
(d) ^{1}H-NMR in acetone-d_6, ^{13}C-NMR in $CDCl_3$. (e) C. Ganter, J.D. Roberts, *J. Am. Chem. Soc.*, 1966, 88, 741.
(f) H. Gunther, T. Keller, *Chem. Ber.*, 1970, 103, 3231.

Table reproduced from reference 12.

Thus, the position of the phenyl norcaradiene-phenyl cycloheptatrienyl equilibrium is strongly influenced by an *ortho*-methyl substituent, a fact which Hannemann concluded was due to steric interactions, while electronic effects also affect the equilibrium position, e.g. in the case of the 7,7-dicyano derivative in Table 3.3 where the norcaradiene form is present exclusively. This indicates that the equilibrium position is very sensitive to the precise nature of the compound in question.

Returning to the trienones of this study (2), (11), (12), and (13), it seems that the cycloheptatrienone structure is an inadequate representation of the product (11), and to a lesser extent (13), while it is satisfactory for trienones (2) and (12).



(11a) (11b) (4)

It appears that there exists a rapid equilibrium between the two forms (11a) and (11b) as shown in equation 4, with the norcaradiene-like tricyclic tautomer (11b) present as a significant partner at room temperature. From the position of the C(8)*H* resonance in the ^{1}H n.m.r. spectrum, δ4.24, lying halfway between the values for pure cycloheptatriene and norcaradiene forms at δ5.2-5.3 and δ2.8-3.5, respectively, it was

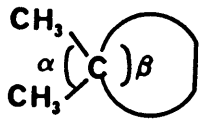
estimated that approximately equal amounts of (11a) and (11b) are present in the equilibrium at room temperature. This dynamic equilibrium is rapid on the ^{1}H n.m.r. timescale, therefore an average signal was seen for the C(8)*H*, and indeed for all of the protons in the molecule.

In the case of the acetoxy-substituted trienone (13), the equilibrium was much more in favour of the bicyclic tautomer as evidenced by the lesser shift to high field of the C(8)*H* signal in the ^{1}H n.m.r. spectrum, compared to that in trienone (11).

Thus, the stretch at 1708 cm^{-1} in the ir spectra of the trienones (11) and (13) was explained by the presence of the norcaradiene tautomer, with much less of it present in the case of the acetoxy-substituted trienone (13) than (11). Non-averaged signals were observed in the ir spectra because the timescale of ir spectroscopy is much more rapid than that of ^{1}H n.m.r. spectroscopy and is evidently faster than the dynamic equilibrium between the tautomers.

Further evidence for the norcaradiene tautomer was obtained in the ^{13}C n.m.r. spectra of (11) and (13). The *C*-8 signal for the trienone (11) appeared at $\delta_C 94.99$ whereas for trienone (18) the signal was at $\delta_C 106.17$. This corroborated the evidence for a norcaradiene-cycloheptatriene equilibrium observed in the ^{1}H n.m.r. spectra.

No evidence for a norcaradiene form was seen for trienones (2) and (12). Therefore the norcaradiene tautomer is stabilised by a bridgehead methyl group and destabilised by a 6-acetoxy substituent. The stabilising effect of the bridgehead methyl group may be explained by the Thorpe-Ingold effect.[13]

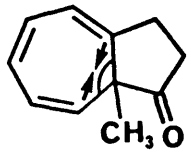


$\alpha > 109.5^{o}$

$\beta < 109.5^{o}$

Figure 1

Thorpe and Ingold suggested that small ring formation is aided by the presence of geminal substituents on a carbon atom in the ring, as the small internal angle leads to a spreading apart of the substituents thereby relieving steric compression, as shown in Figure 1. In the case of trienone (11), the steric effect of the bridgehead methyl group could narrow the angle shown thereby bringing the indicated atoms closer together aiding formation of the cyclopropane ring. This would explain the increased amount of the norcaradiene tautomer present compared to trienone (2) in which there is no bridgehead substituent.



(11)

In subsequent discussion compounds (11) and (13) will be described as 'trienones' (11) and (13) but their existence as an equilibrium between the two forms is implicit in this description.

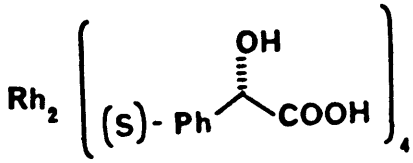
3.3.2. *Catalyst considerations*

Table 3.4 shows the effect of catalyst variation on cyclisation of α-diazoketone (1) while Table 3.5 shows the effect of catalyst and temperature variation on the cyclisation of α-diazoketone (8). The catalysts used were those described in Chapter 2 whose structures are shown again over, numbered as in Table 2.1.

Decomposition of α-diazoketones (1) and (8) was facile and catalyst efficiency was best measured in terms of reaction time and the percentage of dimer in the product when the standard conditions, which minimise dimer formation, were employed. For example, with α-diazoketone (1), changing the catalyst used from rhodium(II) (S)-mandelate(1) to rhodium(II) *N*-naphthalenesulphonyl-L-prolinate (5) slowed down the reaction considerably and increased the amount of carbene dimer present in the product (estimated by integration of the ^{1}H n.m.r. spectrum). This can be explained due to increasing steric hindrance in the catalyst making approach of the carbenoid to the aromatic ring more difficult, thereby giving less efficient reaction with increased dimer formation.

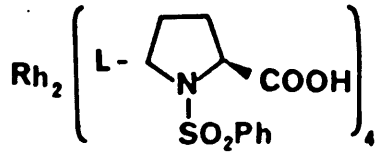
A more comprehensive investigation of the cyclisation of α-diazoketone (8) was carried out. Rhodium(II) acetate has already been shown to be an ineffectual catalyst for aromatic cycloadditions with disubstituted α-diazoketones.[3] However, rhodium(II) trifluoroacetate and rhodium(II) (S)-mandelate (1) were extremely efficient in the cyclisation of α-diazoketone (8). The trienone:dimer ratios given in Table 3.5 are average values for the rhodium(II) (S)-mandelate (1) catalysed reaction, but in fact the cyclisation can be practically quantitative (98%) with a

freshly prepared batch of (1) with only a trace of aromatic impurity (2%). Rhodium(II) (S)-mandelate (1) is in fact the catalyst of choice for these cycloadditions.

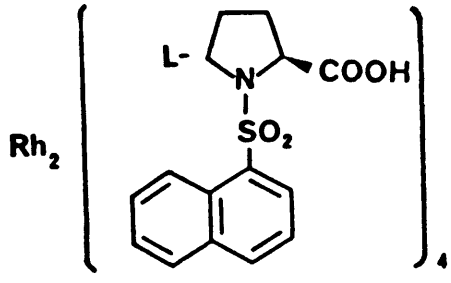


$[Rh_2((S)\text{-mand})_4]$

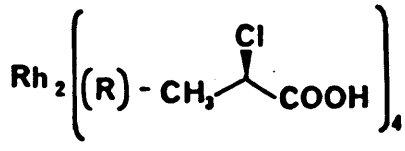
Catalyst 1



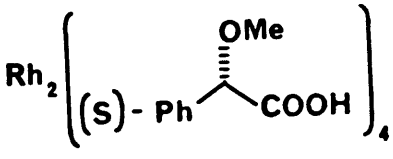
4



5



17



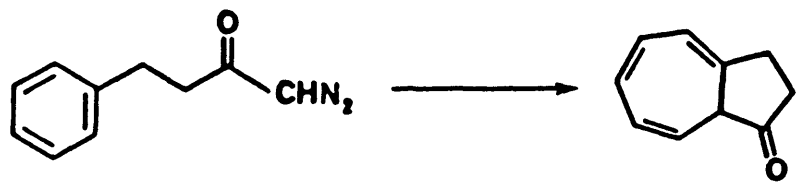
22

$Rh_2(OAc)_2(dppe)_2Cl_2$

$(dppe = Ph_2PCH_2CH_2PPh_2)$

25

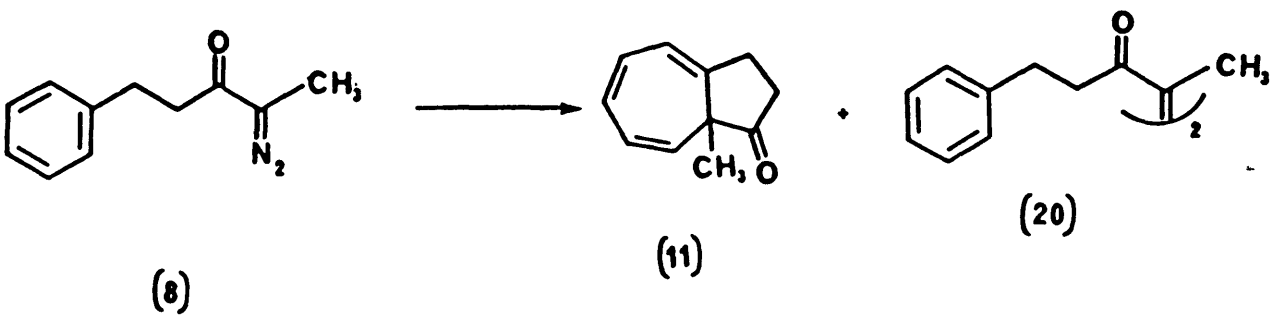
Table 3.4 : Effect of catalyst on cyclisation of 1-diazo-4-phenylbutan-2-one (1)



(1) (2)

Catalyst	Ratio of trienone:dimer %	Reaction time h
1	89:11	0.6
5	80:20	3.0

Table 3.5 : Effect of catalyst and temperature on cyclisation of 2-diazo-5-phenylpentan-2-one (8)



(8) (11) (20)

Catalyst	Reaction Temperature °C	Trienone:dimer %	Reaction Time h	$[\alpha]_D^{20}$ °(c, CH_2Cl_2)	%e.e.[a]
$Rh_2(O_2CCF_3)_4$	40	95:5	0.5	0	0
1	40	86:14-98:2	0.3	+17.7 (9.4)	25
1	20	84:16	0.25	-	-
1	0	88:12	0.2	-	20
1	-20	85:15	0.25	-	-
22	0	50:50	1.0	-	0
4	40	82:18	0.5	+16.9 (10.0)	25
4	20	75:25	0.5	-	20
4	0	70:30	1.0	-	10
4 + PPh_3	20	60:40	0.5	-	15
5	40	80:20	1.0	-	33
17	40	85:15	1.0	-	10
25	40	50:50	2.0	-	-

[a] Enantiomeric excess was estimated by chiral shift ^1H n.m.r. studies of the alcohol (22) obtained by $LiAlH(OBu^t)_3$ reduction of the azulenone (11). The chiral shift reagent employed was $Eu(tfc)_3$.

As the steric bulk of the ligand on the catalyst increased, e.g. to rhodium(II) *N*-naphthalenesulphonyl-L-prolinate (5), the catalyst efficiency decreased with a longer reaction time and higher dimer ratio than for rhodium(II) (S)-mandelate (1). This slowing of reaction with increasing steric bulk of the ligand on the catalyst has been observed previously with the α-diazo-β-keto sulphones in Chapter 2.

The high dimer ratio observed with catalyst (22), rhodium(II) (S)-α-methoxy-α-phenylacetate, was not due to low catalyst efficiency, but rather because the catalyst used was impure. This indicates the ease with which rhodium(II) carboxylates are poisoned. Similarly when triphenylphosphine (1 equivalent to the catalyst) was added to a decomposition catalysed by rhodium(II) *N*-benzenesulphonyl-L-prolinate (4), the amount of dimer formed increased greatly showing that coordination of the phosphine to the catalyst blocked one of the axial sites thus slowing the α-diazoketone decomposition with a resulting increase in carbene dimer formation. $Rh_2(O_2CCH_3)_2$ $(dppe)_2$ Cl_2 (25) was very inefficient for this transformation resulting in a slow reaction and 50% dimerisation. This may have been due to the presence of the axially-coordinated chloride anions blocking the catalyst sites or it may be caused by a fundamental electronic change in the complex by the change in the ligand.

The catalyst derived from (R)-α-chloropropanoic acid (17) was extremely efficient in the decomposition of α-diazoketone (8), resulting in a low dimer ratio in the product, and has been found to be an efficient catalyst for α-diazoketone decomposition in general. This reaction was a good test of its catalytic efficiency, however, as α-diazoketone (8) is a

very sensitive compound and the amount of dimer formed acts as an indication of the efficiency of the catalyst employed. The high activity of the rhodium(II) α-chloropropanoate catalysts (17) and (18) may be due to the electronegative α-chlorine atom in the same way that rhodium(II) trifluoroacetate is in general a more efficient catalyst than rhodium(II) acetate. (However the α-diazo-β-keto sulphones, whose decomposition was discussed in Chapter 2, were an exception to this generalisation.)

The catalyst deactivation discussed in Chapter 2 was also observed in the addition of α-diazoketones to aromatics. With fresh batches of rhodium(II) (S)-mandelate (1), trienone (11) formed with very little dimeric impurity. However, as the catalyst aged its activity gradually decreased and more and more dimerisation was observed in the reactions. Similar deactivation was observed with the other catalysts.

Table 3.5 shows that rhodium(II) (S)-mandelate (1) efficiently catalysed the decomposition of α-diazoketone (8) at temperatures as low as $-20^{o}C$, with $0^{o}C$ resulting in the least amount of dimerisation. Rhodium(II) *N*-benzenesulphonyl-L-prolinate (4) was also shown to be catalytically active at $0^{o}C$ but when it was established that higher asymmetric inductions resulted at reflux than at lower temperatures all subsequent α-diazoketone decompositions were carried out at reflux in dichloromethane.

The *p*-acetoxy-substituted α-diazoketones (9) and (10) were cyclised only with rhodium(II) (S)-mandelate (1) which gave good yields of the trienone products (12) and (13) with only 15% and 11% dimer present,

respectively. In the case of α-diazoketone (9) reaction was very inefficient at 0°C presumably reflecting the decreased activity of the acetoxy-substituted ring to cycloaddition compared to the unsubstituted benzene ring in α-diazoketone (8). α-Diazoketone (10) was decomposed at reflux only. Its behaviour at lower temperatures is unknown.

3.3.3. *Enantioselection*

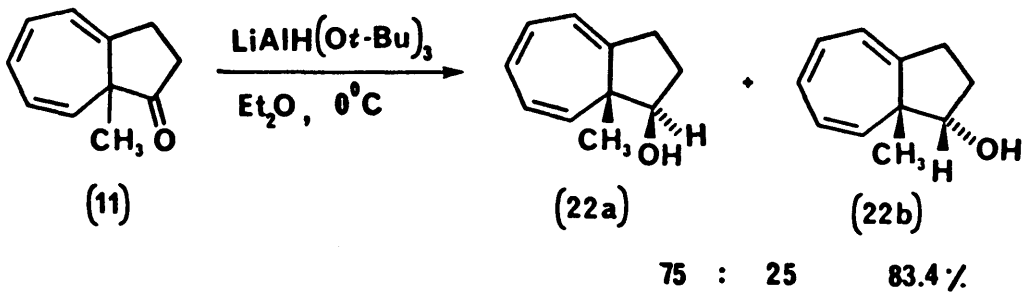
Determination of asymmetric induction in the reactions leading to the trienones (2), (11), (12), and (13) proved difficult. Extensive purification of these sensitive compounds was not possible, and in general the crude products were too highly coloured for accurate determination of optical rotation. At any rate the crude products contained chiral catalyst residues and varying amounts of dimer impurity with the result that specific rotations could not be reliably compared. However, two samples of trienone (11) which had been purified by p.l.c. showed significant optical rotations at the sodium D line (shown in Table 3.5) indicating that some extent of asymmetric induction had occurred in these cyclisations of α-diazoketone (8) brought about by the use of chiral rhodium(II) carboxylate catalysts. The first of these samples of trienone (11) was obtained from a rhodium(II) (S)-mandelate (1) catalysed reaction and had a specific rotation of $[\alpha]_D^{20}$ +17.7 (c 9.4 in CH_2Cl_2) while the other was obtained from a decomposition catalysed by rhodium(II) *N*-benzenesulphonyl-L-prolinate (4) and had $[\alpha]_D^{20}$ +16.9 (c 10.0 in CH_2Cl_2). Both reactions had been carried out at reflux. The fact that the two samples had similar specific rotations indicated that they had comparable enantiomeric excesses, which is later demonstrated.

A crude sample of trienone (2) from a reaction catalysed by rhodium(II) *N*-naphthalenesulphonyl-L-prolinate (5) was measurably optically active with a specific rotation of $[\alpha]_D^{20}$ -4.02° (c 13.2 in CH_2Cl_2), indicating that enantioselection probably occurred in the cyclisation of α-diazoketone (1) also. However, this crude product contained chiral catalyst residues, and as a result, a measurable optical rotation cannot be taken as absolute proof of an enantiomeric excess in trienone (2).

The trienones (2), (11), (12), and (13) were not amenable to ^1H n.m.r. studies with chiral shift reagents. Although the bridgehead methyl group in compound (11) appears as a sharp singlet in the ^1H n.m.r. spectrum at δ0.81, and might be expected to appear as two signals for the enantiomers on addition of $Eu(tfc)_3$, this proved not to be so. It appears that coordination of the carbonyl oxygen atom to the europium of the chiral shift reagent was not sufficiently strong to result in resolution of the signals for the enantiomers in the ^1H n.m.r. spectrum. (This was already observed with the chiral cyclopentanones synthesised in Chapter 2.)

3.4 Reduction of the Azulenones and Estimation of Asymmetric Induction

Reduction of the azulenone or trienone (11) was successful with lithium tri-*tert*-butoxyaluminohydride in ether at 0°C as shown in equation 5 to give a mixture of the diastereoisomeric azulenols (22) which were not easily separable. The reaction was generally stirred overnight at room temperature at which stage completion of reduction was indicated by t.l.c.



(11) (22a) (22b) (5)

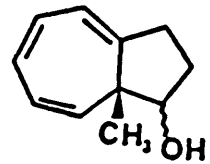
75 : 25 83.4%

Purification by p.l.c. on silica gave the azulenols (22) as a colourless oil which were characterised spectroscopically as a mixture, and were considerably more stable than their azulenone precursor (11) and could be stored in a freezer for several days without apparent decomposition. Particularly distinctive in the ^{1}H n.m.r. spectrum were the signals for the bridgehead methyl groups which were resolved at 270MHz at δ0.68 (*cis*, 22a) and 0.70(*trans*, 22b) but appeared as one singlet at 60MHz. Because of this, routine estimation of the diastereoisomeric ratio of the alcohols (22) by 60MHz ^{1}H n.m.r. was difficult. The cycloheptatrienyl protons of the azulenols (22) were in the region δ5.00-6.50 with the C(8)*H* protons appearing as doublets at δ5.20 (*cis*, 22a, J = 10.0Hz) and 5.61 (*trans*, 22b, J = 10.1Hz). The diastereoisomeric ratio could be estimated by integration of these doublets, but as they were broad signals integration was not very accurate rendering this an unsuitable method of determination of the diastereoisomeric ratio. The proton geminal to the hydroxy group of the azulenols appeared as a triplet at δ4.10.

Tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(tfc)$_3$]-shifted ^{1}H n.m.r. analysis[14] of the azulenol mixture showed a clear separation of the signals for the methyl groups of the diastereoisomers, and a further resolution of the enantiomeric forms of the *cis*-alcohol (22a) allowed assignment of the enantiomeric excess present in the trienol mixture. Thus both the diastereoisomeric and enantiomeric ratios in the azulenol mixture (22) were estimated by ^{1}H n.m.r. analysis with Eu(tfc)$_3$. Figure 2 shows the ^{1}H n.m.r. spectrum of the trienol mixture (22) prior to addition of the chiral shift reagent. Figures 3 and 4 show spectra of optically active and racemic samples, respectively, of the trienols containing Eu(tfc)$_3$. As can be seen in the spectra, the singlet for the bridgehead methyl groups at δ0.70 was shifted to lower field on addition of the chiral shift reagent with a larger shift for the *cis*-isomer than for the *trans*. This was as predicted because coordination of the hydroxy group to the europium would be expected to affect the environment of the *cis*-methyl group more than that of the *trans*-methyl group. Similarly, resolution of the enantiomeric signals was seen only for the *cis*-isomer. These observations confirmed the assignment of *cis*-stereochemistry to the major isomer of the azulenol.

The other major change in the ^{1}H n.m.r. spectrum on addition of Eu(tfc)$_3$ was the large downfield shift of the signal for the proton geminal to the hydroxy group, presumably due to its proximity to the coordinated europium complex.

Best results were obtained in the chiral shift studies when the concentration of the trienol (22) was kept as low as possible (typically 30-50 mg in 0.5 ml $CDCl_3$) with two additions of the chiral shift reagent,



(22)

0·08H
3·68H
1·41
0·39H
0·70H
0·94H
1·88H
3·52H
7·82H
36
45
47
6·77
5·10
4·11
4·14
5·45
5·14
1·90
1·77
1·10
1·14
1·24
1·41
1·71
1·97
1·93
1·97
1·97
1·97

33% e.e.

Figure 3 : ^{1}H n.m.r. spectrum of trienol mixture (22) derived from α-diazoketone (8) by rhodium(II) *N*-naphthalenesulphonyl-L-prolinate catalysis, with $Eu(tfc)_3$, indicating the presence of 33% e.e.

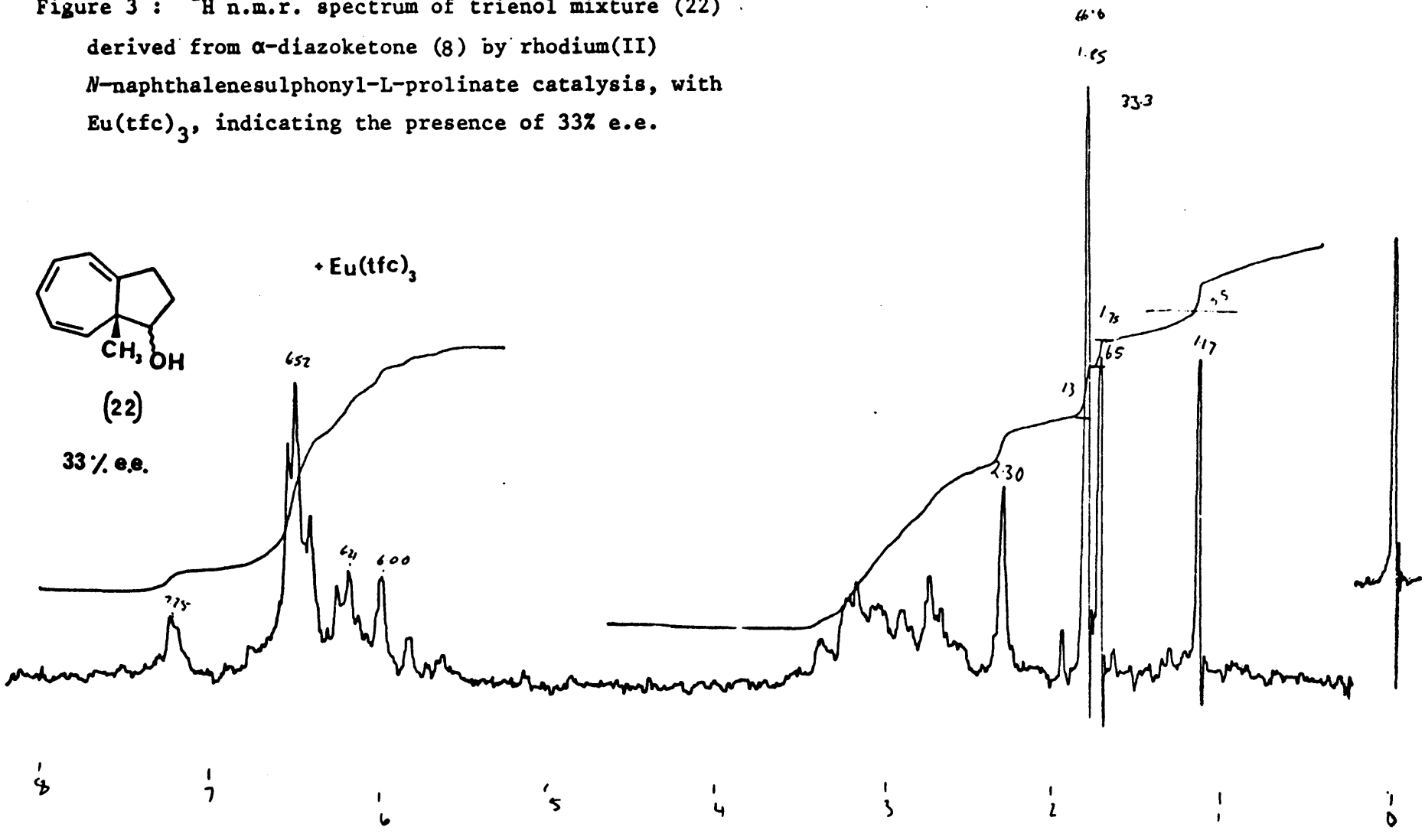
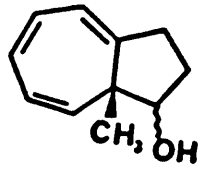


Figure 4 : ^{1}H n.m.r. spectrum of a racemic sample of the trienol mixture (22) with $Eu(tfc)_3$



(22)

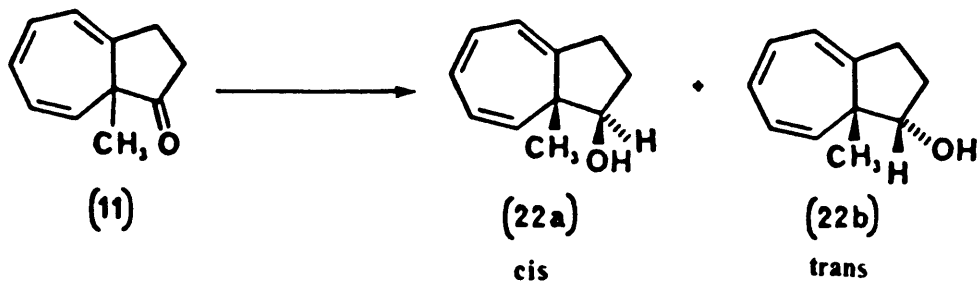
racemic

• $Eu(tfc)_3$

each of which was 10% mole equivalent. Generally the first addition gave resolution of the diastereoisomeric signals while the second addition was required to observe splitting for the enantiomers. Further addition of the shift reagent did not give any further information, as the resolution in the spectrum deteriorated rapidly as the europium concentration increased. The solution was filtered after each addition of $Eu(tfc)_3$ to maximise resolution in the spectra.

By $Eu(tfc)_3$-shifted n.m.r. analysis of the trienol mixture (22) as described above the diastereoisomeric ratio obtained by lithium tri-*tert*-butoxyaluminohydride reduction of the trienone (11) was estimated as 75:25 *cis:trans*. The major isomer was assumed to have *cis*-stereochemistry, as the bridgehead methyl group would be expected to hinder attack from the β-face of the molecule. This assignment was confirmed when the signals in the ^1H n.m.r. spectrum corresponding to the major isomer were affected more than those for the minor isomer on addition of $Eu(tfc)_3$. The diastereoisomeric ratio in the azulenol mixture was altered by varying the reducing agent employed as shown in Table 3.6. The highest diastereoselectivity was observed with lithium tri-*tert*-butoxyaluminohydride as reducing agent, with no change in the ratio on changing the solvent from ether to THF. The less sterically demanding lithium aluminium hydride resulted in a lower diastereoselectivity giving the epimeric alcohols (22) in a 70:30 ratio. Interestingly DIBAL-H resulted in the opposite diastereoselectivity to the other reducing agents, giving 55% *trans*-isomer.

Table 3.6 : Stereoselection in the reduction of 2,3-dihydro-1(8a-methyl)-azulenone (11)



(11) (22a) cis (22b) trans

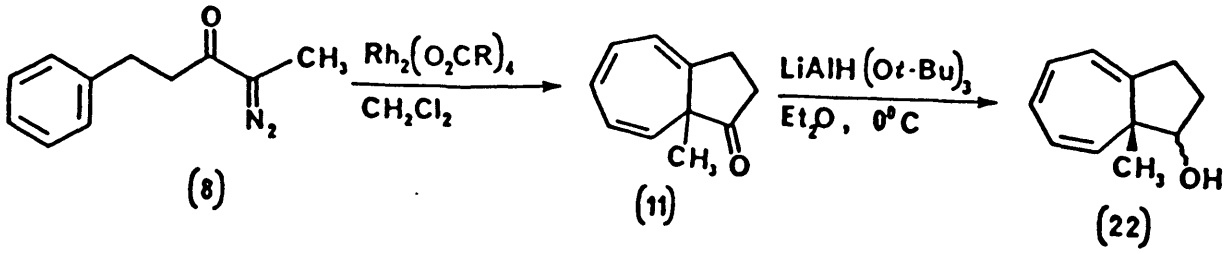
Reducing agent	Yield %	*cis:trans* %
$LiAlH(OBu^t)_3$-Et_2O	83.4	75:25
$LiAlH(OBu^t)_3$-THF	81.2	75:25
$LiAlH_4$-Et_2O-THF	89.4	70:30
$NaBH_4$-EtOH	86.0	65:35
DIBAL-H-toluene	85.0	45:55
K-Selectride-THF	68.6	70:30

No evidence for a tricyclic form of the trienols (22) was observed. On reduction the norcaradiene equilibrium disappeared completely and the C(8)*H* signals in the ^{1}H n.m.r. spectrum of the trienols (22) shifted to δ5.20 *(cis)* and 5.61 *(trans)*, compared to the higher field position of the C(8)*H* signal for the trienone (11) at δ4.24.

Since stereospecific reduction was not achieved with trienone (11), the problem of detecting asymmetric induction became more complex in the trienols (22) due to the presence of diastereoisomers formed from the original enantiomeric pair. However, the Eu(tfc)$_3$-shifted ^{1}H n.m.r. analysis overcame this problem and provided estimations for both the diastereoisomeric and enantiomeric ratios present as illustrated earlier. When the trienol mixture (22) was prepared to test the asymmetric induction obtained in a cyclisation involving a chiral rhodium(II) carboxylate catalyst, lithium tri-*tert*-butoxyaluminohydride was the reducing agent of choice as it gave the highest diastereoselection thereby maximising the amount of *cis*-isomer present in the mixture and simplifying the ^{1}H n.m.r. analysis with Eu(tfc)$_3$, since enantiomeric resolution was observed only for the *cis*-isomer. Furthermore, as the same isomer ratio was present in each of the trienol samples, specific rotation data could be at least qualitatively compared to corroborate the evidence for asymmetric induction obtained from the ^{1}H n.m.r. analysis. Also, as the trienol samples had been purified by p.l.c. on silica any chiral catalyst residues had been removed, making the optical rotation data more reliable.

Table 3.7 illustrates the results obtained by ^{1}H n.m.r. analysis with Eu(tfc)$_3$ on trienol samples derived from rhodium(II) carboxylate catalysed

Table 3.7 : Enantioselection in the cyclisation of 2-diazo-5-phenyl-pentan-2-one using rhodium(II) carboxylates as catalyst. Enantiomeric ratios were estimated by reduction of 2,3-dihydro-1(8a-methyl)-azulenone formed in the cyclisation to 2,3-dihydro-1(8a-methyl)-azulenol on which chiral shift ^1H n.m.r. studies were carried out.



(8) (11) (22)

Catalyst	Temperature of diazoketone decomposition °C	% e.e. in alcohols[a]	$[\alpha]_D^{20}$ of alcohols[b] °(c, CH_2Cl_2)
$Rh_2(O_2CCF_3)_4$	40	0	0
1	0	20	-
1	40	25	-7.73 (5.73)
22	0	0	-
4	0	10	-1.26 (4.62)
4	20	20	-3.28 (5.06)
4	40	25	-7.21 (5.81)
4 + PPh_3	20	15	-5.27 (5.20)
5	40	33	-9.44 (8.81)
17	40	10	+0.67 (6.43)

[a] % e.e. estimated from ^1H n.m.r. to ±8% accuracy using $Eu(tfc)_3$.

[b] all reductions were carried out using lithium tri-*tert*-butoxy-aluminohydride giving the same isomer ratio in each product. Therefore specific rotation data can be at least qualitatively compared as an indication of asymmetric induction.

decomposition of α-diazoketone (8). Enantioselection as high as 33% e.e. was obtained by use of rhodium(II) *N*-naphthalenesulphonyl-L-prolinate (5) as the decomposition catalyst. Rhodium(II) (S)-mandelate (1) proved to be quite efficient in terms of asymmetric induction also, giving 25% e.e. from a reaction carried out at reflux, thus confirming its position as the most successful general catalyst to date. The extremely efficient rhodium(II) (R)-α-chloropropanoate catalyst (17) resulted in disappointingly low enantioselection, while rhodium(II) *N*-benzenesulphonyl-L-prolinate (4) gave the same asymmetric induction as the rhodium(II) (S)-mandelate (1) when the decompositions were carried out at reflux.

An interesting observation from Table 3.7 is that the enantioselection was higher from decompositions carried out at reflux than at lower temperatures (as observed with the α-diazo-β-keto sulphones discussed in Chapter 2). The effect was less with rhodium(II) (S)-mandelate (1), which gave 25% e.e. at reflux and 20% e.e. at 0°C, than with rhodium(II) *N*-benzenesulphonyl-L-prolinate (4) which also gave 25% e.e. at reflux but only 10% e.e. at 0°C. This strange temperature effect, i.e. higher selectivity at higher temperature, indicates the complexity of the catalyst-substrate interactions.

The most efficient catalyst in terms of enantioselection in the cyclisation of α-diazoketone (8), rhodium(II) *N*-naphthalenesulphonyl-L-prolinate (5), was surprisingly one of the less catalytically active catalysts tested resulting in 20% dimer formation in the transformation. Furthermore, this catalyst was different from that which gave the highest enantioselection in the C-H insertions discussed in Chapter 2, showing that the enantioselection obtained depends on the precise structure of the substrate and the catalyst and the nature of the reaction.

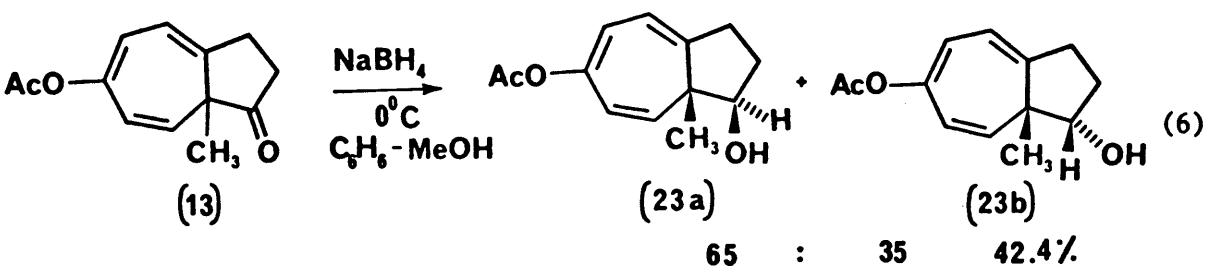
The high asymmetric induction observed with the rhodium(II) *N*-naphthalenesulphonyl-L-prolinate catalyst (5) in the cyclisation of α-diazoketone (8), despite the bulky ligand which slows the reaction appreciably, may be due to interaction between the naphthalene ring system and the benzene ring to which cycloaddition takes place. Such interaction could hold the catalyst substrate pair in a rigid conformation resulting in good enantioselection.

Evidence in support of this theory is that the other two catalysts which gave moderate enantioselection in this reaction (25% e.e.), rhodium(II) (S)-mandelate (1) and rhodium(II) *N*-benzenesulphonyl-L-prolinate (4), each contain an aromatic ring which could have the same effect but to a lesser extent than the naphthalene ring system. However, there is no direct evidence for this. Examination of the crystal structures of the catalysts to determine the orientation of the aromatic rings may be helpful in proving or disproving this theory.

Catalyst (22), derived from (S)-α-methoxy-α-phenylacetate, resulted in very little asymmetric induction, confirming the observation made in Chapter 2, that the rigid structure imposed on the rhodium(II) (S)-mandelate catalyst due to a hydrogen bond between the hydroxy-group and a carboxylate oxygen, is significant in its success as an enantioselective catalyst.

The variation in asymmetric induction obtained by changing the catalyst ligand indicates that further change in the ligand structure may result in higher enantioselection in the cyclisation of α-diazoketone (8), thereby improving the asymmetric synthesis possible by this route.

The observation of similar enantiomeric excess (25% e.e.) from reactions catalysed by rhodium(II) (S)-mandelate (1) and rhodium(II) *N*-benzenesulphonyl-L-prolinate (4) was in agreement with the earlier observation (Section 3.3.3) that trienone (11) samples derived from reactions catalysed by these catalysts carried out at reflux and purified by p.l.c., had very similar specific rotations (Table 3.5). Furthermore, specific rotations obtained for the trienol samples (22) and shown in Table 3.7 are in agreement with the enantioselections estimated by ^{1}H n.m.r. analysis, with the highest observed rotation for the trienol (22) sample derived from a decomposition catalysed by rhodium(II) *N*-naphthalenesulphonyl-L-prolinate (5). Interestingly, all the asymmetric inductions observed, with the exception of that obtained by catalysis with rhodium(II) (R)-α-chloropropanoate (17), were in the same direction (i.e. same sign in $[\alpha]_D^{20}$ value). This was also observed in the chiral shifted ^{1}H n.m.r. spectra with the predominant enantiomer experiencing a larger chemical shift downfield than the minor isomer.



(13) (23a) (23b)

65 : 35 42.4%

Having established a method of determining the asymmetric induction in the cyclisation of α-diazoketone (8) to trienone (11) by reduction to the trienol mixture (22) and $Eu(tfc)_3$-shifted ^1H n.m.r. analysis, reduction of the acetoxy-substituted azulenone (13) to the corresponding azulenol pair (23) was carried out also. Successful reduction of (13) was achieved with sodium borohydride in a 3:1 benzene-methanol mixture. The azulenone (13) was stirred in the benzene-methanol mixture in an ice-bath until the reaction mixture became semi-solid, then the reducing agent was added in portions and the reaction mixture was allowed to return slowly to room temperature. Complete reduction was shown by t.l.c. within two hours. Purification of the crude product by p.l.c. gave the trienol mixture (23) as an oil in 42.4% yield.

The ^1H n.m.r. spectrum of the azulenol mixture (23) showed only one singlet for the bridgehead methyl groups at δ0.83 and one singlet for the acetoxy protons at δ2.19, without resolution of the signals for the diastereoisomers. The C(8)*H* protons were resolved, as observed for trienol mixture (22), giving two doublets at δ5.26 (J = 10.8Hz, major isomer, *cis*) and 5.58 (J = 8.4Hz, minor isomer, *trans*) but these were too broad for accurate determination of the diastereoisomeric ratio. The assignment of *cis*-stereochemistry to the major isomer was made by comparison of the spectra for the trienol mixture (23) with those of trienol mixture (22).

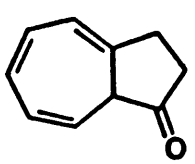
As before with trienol mixture (22), $Eu(tfc)_3$-shifted ^1H n.m.r. analysis of the trienols (23) resulted in resolution of the bridgehead methyl group signals for the diastereoisomers, and further resolution of the signal for the *cis*-isomer for the enantiomeric pair was observed. Thus

both the diastereoisomeric and enantiomeric ratios in the trienol mixture were calculated, showing that 65:35 *cis:trans* isomers were present with 10% e.e. from decomposition of α-diazoketone (10) by rhodium(II) (S)-mandelate (1) at reflux.

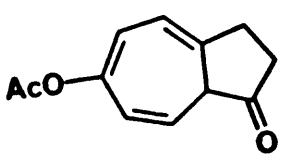
Although sodium borohydride had been shown to be a relatively unselective reagent in the reduction of trienone (11), it was chosen for the reduction of trienone (13) to ensure selective reduction of the cyclopentanone with retention of the acetoxy group. The resulting diastereoselection was poor as expected (65:35, *cis:trans*).

Thus a lower enantioselection was obtained in the rhodium(II) (S)-mandelate catalysed decomposition of α-diazoketone (10) than in a similarly catalysed decomposition of α-diazoketone (8), again illustrating the dependency of the asymmetric induction on the exact structure of the diazo-substrate.

Reduction of the more sensitive trienones (2) and (12) was less successful.



(2)



(12)

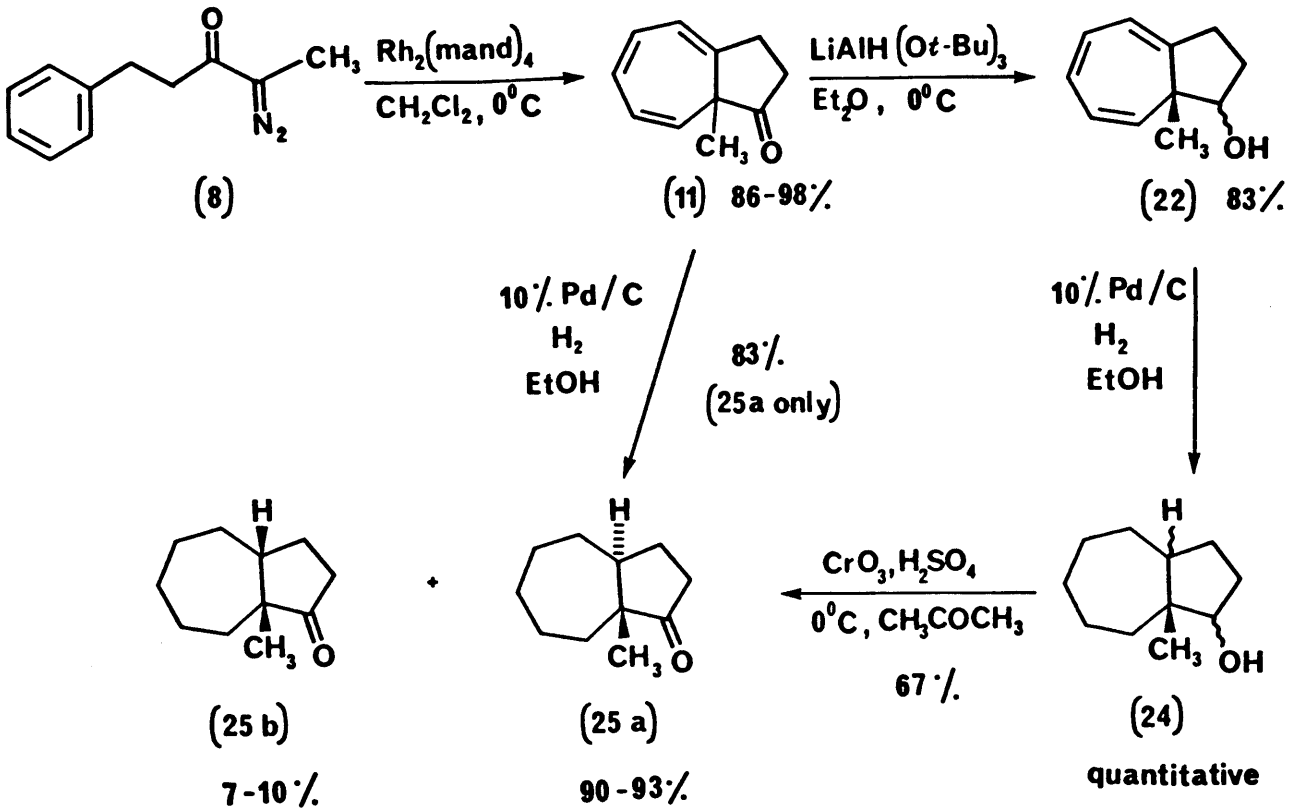
In the case of (12) no recognisable material was recovered from attempted reduction with sodium borohydride or lithium aluminium hydride. With trienone (2) the product of reduction with lithium tri-*tert*-butoxyalumino-

hydride appeared to be cycloheptatrienyl in nature, but seemed to contain a complex mixture of isomers and was not fully characterised. Therefore, no estimation of asymmetric induction was made for the α-diazoketone decompositions leading to trienones (2) and (12), although a crude sample of trienone (2) from a decomposition catalysed by rhodium(II) *N*-naphthalenesulphonyl-L-prolinate (5) was optically active as discussed earlier (Section 3.3.3).

3.5 Hydrogenation of Azulenols (22) and Oxidation to Perhydro-1(8a-methyl)-azulenone (25)

Having established that cyclisation to substituted trienones was possible and that their subsequent reduction to trienols could be brought about, the next phase was to determine if they could be hydrogenated and thus provide a new route to bicyclo[5.3.0]decane derivatives along the lines summarised in Scheme 5.

The azulenol (22), derived from lithium tri-*tert*-butoxyaluminohydride reduction of azulenone (11), the product of rhodium(II) (S)-mandelate (1) catalysed decomposition of α-diazoketone (8), which had been shown by $Eu(tfc)_3$-shifted ^1H n.m.r. analysis to contain 20% e.e., was hydrogenated in ethanol over 10% palladium on charcoal at 40 p.s.i. at room temperature. The perhydroazulenol (24) was obtained in quantitative yield following purification by p.l.c. on silica as an oil which crystallised on refrigeration, as an inseparable mixture of isomers. The stereochemistry of the hydrogenation product was not determined at this stage, as in the ^1H n.m.r. spectrum the signal for the bridgehead methyl group appeared as a broad singlet.



Scheme 5

However, addition of $Eu(tfc)_3$ had an effect similar to that observed with the trienols (22), resulting in significant changes in the ^1H n.m.r. spectrum. The singlet for the bridgehead methyl group, originally at δ0.74, shifted considerably downfield with a resolution of the signals for the enantiomers of the predominant isomer. As for trienol (22), the major enantiomer experienced a larger downfield shift. The enantiomeric excess was estimated by integration of the two singlets as 20% e.e., in agreement with that observed in the trienols (22) prior to hydrogenation. The $Eu(tfc)_3$-shifted ^1H n.m.r. spectra of (24) indicated that the compound was largely one diastereoisomer, with smaller amounts of the other

diastereoisomers present. This suggested that the bridgehead methyl group had a significant influence in directing the hydrogenation to the α-face of the molecule. As observed in the ^{1}H n.m.r. studies of trienols (22) with $Eu(tfc)_3$ when the shift reagent was added to the alcohol (24) the signal for the proton geminal to the hydroxy group (δ3.60) experienced large downfield shifts confirming that strong coordination of the hydroxy group to the europium complex occurred.

Oxidation of the perhydroazulenol mixture (24), derived from a rhodium(II) (S)-mandelate (1) catalysed cyclisation at reflux, followed by the sequence of reduction with lithium tri-*tert*-butoxyaluminohydride and hydrogenation discussed above, to perhydro-1(8a-methyl)-azulenone (25) was successfully achieved using Jones' reagent. The perhydroazulenol (24) was stirred at 0°C in acetone while the reagent was added dropwise. The crude product was purified by distillation to give the bicyclo[5.3.0]-decanone (25) as an oil in 67% yield. The ^{1}H n.m.r. spectrum of (25) showed singlets at δ0.92 and 1.15 for the bridgehead methyl groups of the two isomers, which by comparison with the values reported[15] for the *cis*- and *trans*-fused isomers of (25), δ0.88, *trans*, and δ1.03, *cis*, showed that 7-10% of the *cis*-fused isomer (25b) was present in the product.

In contrast when the trienone (11) was hydrogenated directly in ethanol over 10% palladium on charcoal catalyst at 40 p.s.i. hydrogen at room temperature, the perhydroazulenone (25) was obtained as an oil after distillation in 83% yield with only the *trans*-fused isomer (25a) visible in the ^{1}H n.m.r. spectrum.[16] Thus the bridgehead methyl group directed hydrogenation to the α-face of the molecule. However, on introduction of a hydroxy group, i.e. in the hydrogenation of the azulenol

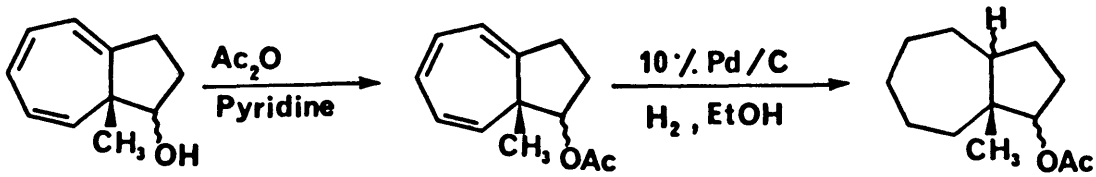
mixture (22), hydrogenation no longer proceeded exclusively from the α-face of the molecule, indicating that the hydroxy group also had a directive effect on the hydrogenation.

Addition of $Eu(tfc)_3$ to the perhydroazulenone (25) resulted in a slight downfield shift of the signal in the ^1H n.m.r. for the bridgehead methyl group. However, as observed with the trienone (11), coordination of the carbonyl oxygen to the europium complex was not sufficiently strong to result in resolution of the enantiomeric signals in the ^1H n.m.r. spectrum.

The trienone sample (11) which was hydrogenated directly as described above was derived from α-diazoketone (8) by decomposition with rhodium(II) *N*-naphthalenesulphonyl-L-prolinate (5) and was shown to contain 33% e.e. by $Eu(tfc)_3$-shifted ^1H n.m.r. spectra on a corresponding trienol sample (22). This hydrogenation gave the perhydroazulenone (25a) in 83% yield after distillation with a specific rotation $[\alpha]_D^{20}$ $+18.7^\circ$ (c 2.6 in CH_2Cl_2), constituting a partial asymmetric synthesis of *trans*-1-methylbicyclo[5.3.0]decan-10-one (25a) in two steps from α-diazoketone (8) in 66.4% overall yield with 33% e.e. in the product.

3.6 Acetylation of *cis* and *trans* 2,3-Dihydro-1(8a-methyl)-azulenols (22)

Among other reactions examined in this series was derivatization of the bicyclic trienols derived from the original trienones. One such reaction was acetylation.



(22) (26) 79% (27) 99%

Scheme 6

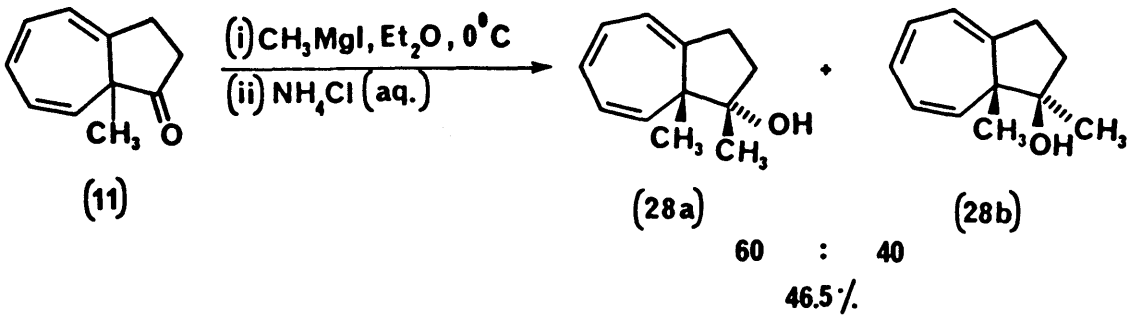
Acetylation of the trienol mixture (22) was achieved by addition of acetic anhydride to a pyridine solution of the alcohol at room temperature. Purification by chromatography on silica gave the acetate (26) as an oil as an inseparable mixture of isomers, in 79% yield. In the ^{1}H n.m.r. spectrum of the acetate mixture, the signals for the acetoxy methyl groups overlapped at δ2.08 and 2.09, but the bridgehead methyl groups appeared as well resolved singlets; the signal for the *cis*-isomer was at δ0.63 while that for the *trans* was at δ0.72. Thus the diastereoselectivity of the reduction of the azulenone (11) to the azulenol mixture (22) could be easily estimated after acetylation by integration of these well resolved singlets. When lithium aluminium hydride was employed as the reducing agent in the preparation of the azulenol (22), the corresponding acetate mixture (26) was shown by ^{1}H n.m.r. to contain 70% *cis* and 30% *trans*-isomers in agreement with the ^{1}H n.m.r. studies of (22) with $Eu(tfc)_3$ as the chiral shift reagent. The proton geminal to the acetoxy group overlapped with the C(8)*H* signal in the region δ5.00-5.40.

Hydrogenation of the acetate mixture (26) in ethanol over 10% palladium on charcoal catalyst at 40 p.s.i. at room temperature gave the saturated acetate (27) in 99% yield as an oil as an inseparable mixture of isomers, which appeared as a single component on t.l.c. analysis. 1-Methylbicyclo[5.3.0]dec-10-yl acetate (27) was identified spectroscopically with a carbonyl stretch at 1731 cm^{-1} in the ir spectrum. It had been thought that since the isomer ratio in the acetate (26) was clearly visible in the ^{1}H n.m.r. spectrum, that the stereochemistry of the hydrogenation could be investigated. However, in the ^{1}H n.m.r. spectrum of the hydrogenated acetate (27), the bridge-head methyl groups showed only one signal in the ^{1}H n.m.r. spectrum at δ0.82, so estimation of the diastereoisomeric ratios was not possible. The acetoxy protons also appeared as a singlet at δ2.00. Therefore, the degree of hydrogenation from the α- and β-faces of the molecule could not be determined.

Treatment of the acetate (26) with Wilkinson's catalyst under an atmosphere of hydrogen, in the hope of selective hydrogenation of the disubstituted double bonds, returned the unreacted acetate (26).

3.7 Grignard Addition to Azulenone (11)

A further reaction investigated in this series was the addition of Grignard reagents to the trienone (11) to prepare functionalised bicyclo[5.3.0]decanes.



(11) (28a) (28b) (7)

60 : 40

46.5%

When the trienone (11) was added to an ethereal solution of methylmagnesium iodide at 0°C, followed by an aqueous ammonium chloride work-up, a mixture of epimeric tertiary alcohols (28) (equation 7) was isolated as an oil in 46.5% yield following purification by p.l.c. on silica. The isomer ratio was found to be 60:40 by comparison of the ^{1}H n.m.r. spectrum of the alcohol mixture (28) with that of the secondary trienol mixture (22). In particular the doublets for the C(8)*H* at δ5.50 (*J* = 11.4Hz, major) and δ4.68 (*J* = 10.2Hz, minor) indicated that the major isomer corresponded to attack from the β-face of the molecule, showing that the increase in steric hindrance on going from a hydride reducing agent to a Grignard reagent did not result in exclusive attack from the α-face of the molecule as might have been expected, and in fact resulted in a poor stereoselectivity of addition to the cyclopentanone carbonyl.

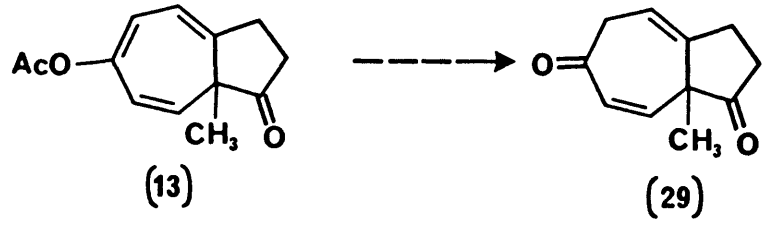
The product mixture had four singlets in the ^{1}H n.m.r. spectrum: δ0.73 and 1.31 for the major isomer (28a) and δ0.58 and 1.37 for the minor isomer (28b), with the higher field signal in each case corresponding to the bridgehead methyl group. Addition of Eu(tfc)$_3$ resulted in a shift of the signals for the bridgehead methyl groups downfield with that of the

minor isomer shifted to lower field than that of the major isomer suggesting that the minor isomer had the hydroxy group and the bridgehead methyl group *cis*, thereby confirming the assignment of isomers. No resolution of the signals for the enantiomers was observed in the $Eu(tfc)_3$-shifted ^1H n.m.r. studies.

The alcohols (28) were not stable; after only two days at 0^oC two new singlets had appeared in the ^1H n.m.r. spectrum and the two singlets corresponding to (28a) had decreased considerably. It was thought that dehydration of the tertiary alcohol may have occurred, but this was not confirmed.

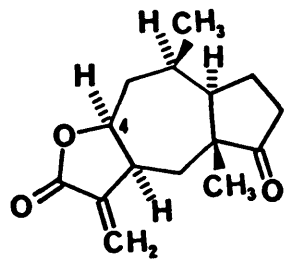
3.8 Hydrolysis of 6-Acetoxy-2,3-dihydro-1(8a-methyl)-azulenone (13)

One of the reasons for studying the *p*-acetoxy series was to investigate the possibility of using the acetoxy group to introduce other substituents after the original cyclisation had been successfully carried out. One obvious possibility was to hydrolyse the enol acetate to the cycloheptenone as shown in equation 8.



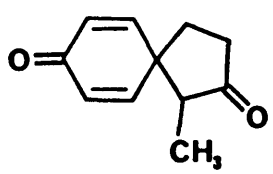
(13) (29) (8)

This possibility was particularly interesting as pseudoguaianolides such as confertin (30) contain the bicyclo[5.3.0]decane skeleton with the bridgehead methyl group and oxygenated functionality at the C-4 position, and cycloheptanone (29) could prove useful as an intermediate in synthetic approaches to such pseudoguaianolide structures. Accordingly, an attempt was made to hydrolyse the enol acetate in (13).



(30)

When a dioxan solution of azulenone (13) was treated with aqueous sodium hydroxide at 0°C the mixture immediately became deep red and t.l.c. indicated rapid disappearance of the starting material. The product, obtained in 51% yield, following purification by p.l.c. on silica, was a white crystalline solid (m.p. 93-95°C) which was identified as the spirodienedione (31).

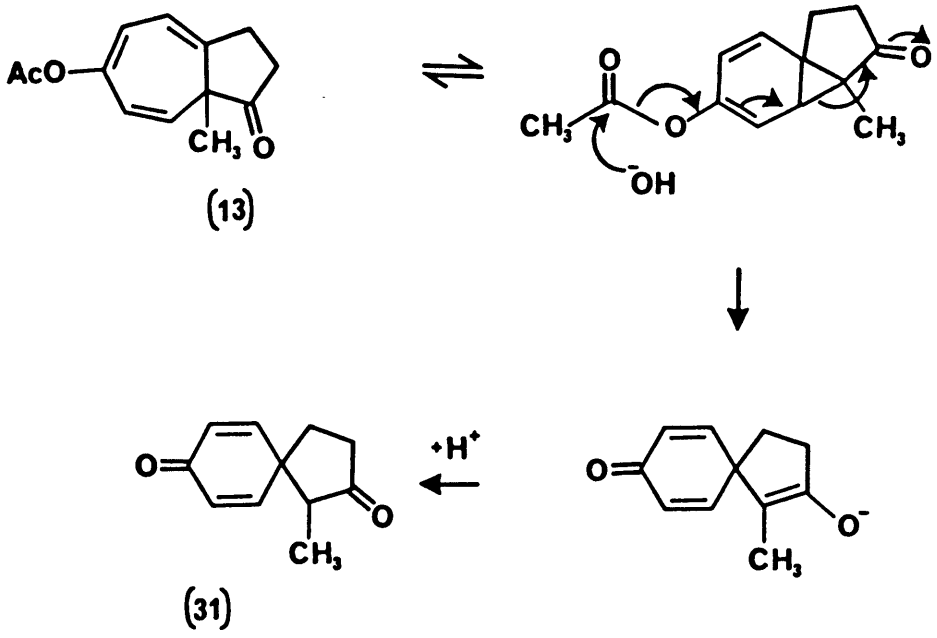


(31)

It was characterised spectroscopically and identified by comparison of the spectral details and melting point with those reported by Iwata and co-workers,[17] who recorded a melting point of 93-94°C for this compound. The carbonyl stretches in the ir spectra at 1742 (cyclopentanone) and 1660 cm^{-1} (conjugated) were in good agreement with the reported values of 1738 and 1660 cm^{-1}, while the C=C stretch appeared at 1623 cm^{-1} in agreement with Iwata's value of 1625 cm^{-1}. Similarly the ^{1}H n.m.r. data were in agreement with the reported values, with the methyl group appearing as a doublet at δ0.86 (J = 7.2Hz) compared to Iwata's value of δ0.84 (J = 7Hz).

Thus instead of the predicted dione (29), the spirodienedione (31) was isolated unexpectedly. The spirodienedione may be formed by initial hydroxide attack on the acetoxy carbonyl in the norcaradiene form followed by a fragmentation which cleaves the cyclopropyl ring as shown in Scheme 7. This fragmentation reaction also supports the existence of a norcaradiene form of the trienone (13) which was earlier shown to be present at a low equilibrium concentration, by ^{1}H and ^{13}C n.m.r. and ir spectroscopy.

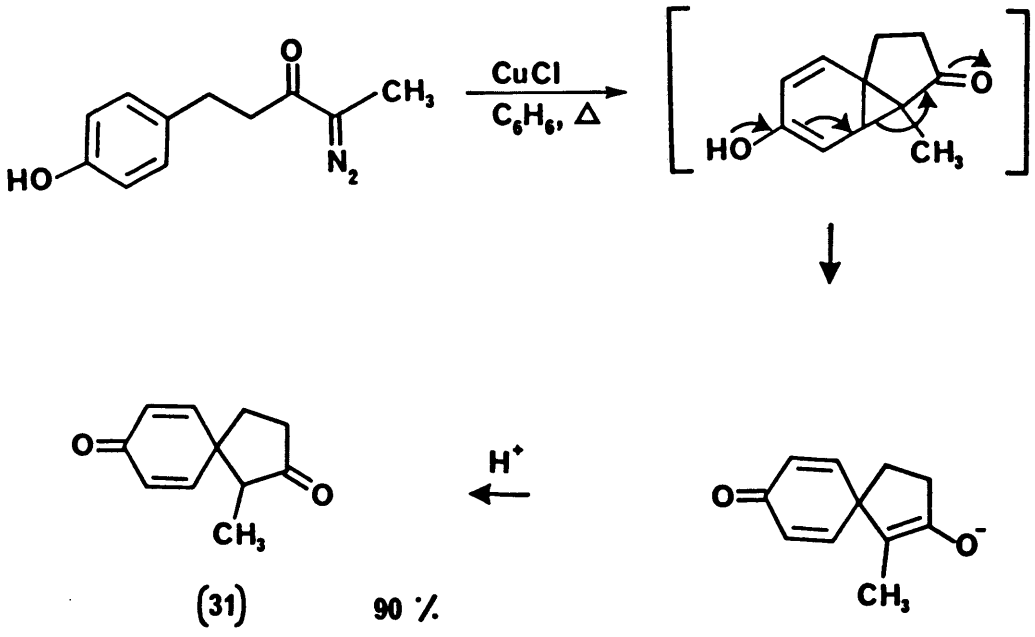
In an attempt to improve the yield of the rearrangement to (31), the hydrolysis was carried out in a two phase ether-water system. However, this resulted only in slow decomposition of the starting material (13) and although traces of (31) were detected by t.l.c., no recognisable product was isolated.



Scheme 7

In the hydrolysis of (13) with concomitant rearrangement to (31) any asymmetry present in the azulenone was expected to be lost due to enolisation at the α-position to the carbonyl as shown in Scheme 7.

Iwata and co-workers[17] prepared the spirodienedione (31) by decomposition of a *p*-hydroxy-α-diazoketone with cuprous chloride in refluxing benzene as shown in equation 9. The *p*-hydroxy group resulted in spontaneous fragmentation of the cyclopropane ring in the norcaradiene intermediate to give the product (31) in 90% yield.

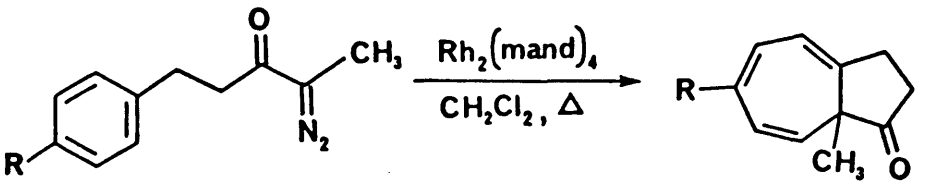


(9)

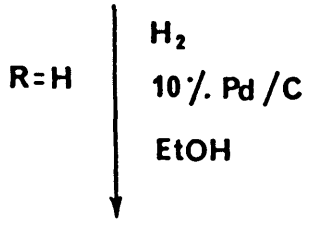
(31) 90 %

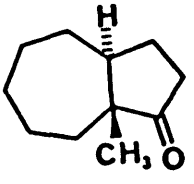
3.9 Application of Intramolecular Buchner Reactions to the Synthesis of Perhydroazulene Lactones[4]

As indicated above, part of our objective was to explore the application of the intramolecular Buchner reaction to the synthesis of perhydroazulene lactones, e.g. confertin. The intramolecular α-diazoketone cyclisation to bicyclo[5.3.0]decatrienones suggested a possible effective approach to the synthesis of structures containing the azulene skeleton, particularly the construction of highly functionalised hydroazulenes found in many natural products of the guaianolide and pseudoguaianolide families. With regard to the pseudoguaianolides, cyclisation of α-diazoketones (8) and (10) to azulenones (11) and (13) demonstrated that the bridgehead substituent could be positioned in this cyclisation, as illustrated in Scheme 8.



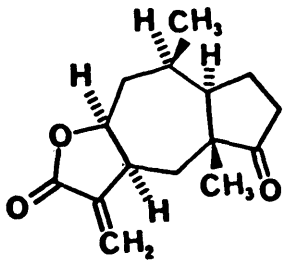
R = H (8) (11) 86 - 98 %.
= OAc (10) (13) 89 %.



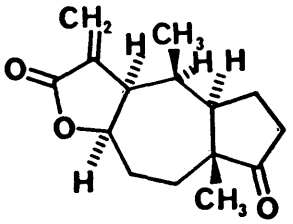


Scheme 8 (25a) 83%

Furthermore, hydrogenation of azulenone (11) was highly stereoselective with respect to formation of the *trans*-perhydroazulenone (25a). This *trans*-geometry is characteristic of many pseudoguaianolides e.g. confertin (30). Interest in the chemistry of the pseudoguaianolides has been strong because of the biological activity of many members of the series. In this work the intention was to prepare a tricyclic lactone to which the highly reactive α-methylene group could be attached at the end of the synthetic sequence by use of established procedures. The synthetic target therefore to produce the unnatural isomer of confertin (32) was the tricyclic lactone (33) which could be prepared by hydrogenation of (34), a

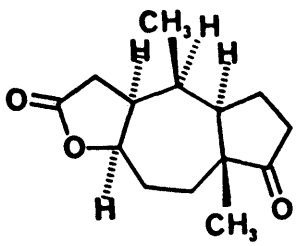


(30)

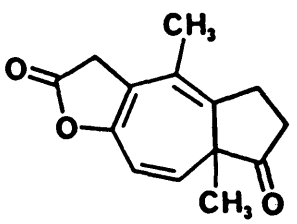


(32)

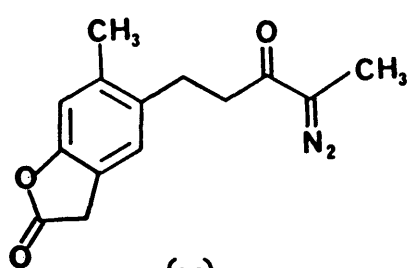
potential cyclisation product of α-diazoketone (35) as summarised in Scheme 9. In a parallel study, Dr M. Kennedy of this laboratory has carried out a synthesis of a confertin intermediate using the isomeric diazoketone (36).



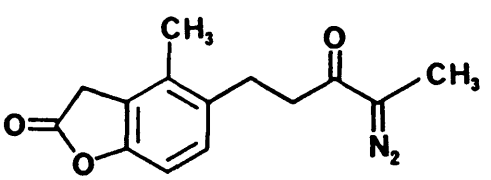
(33)



(34)



(36)



(35)

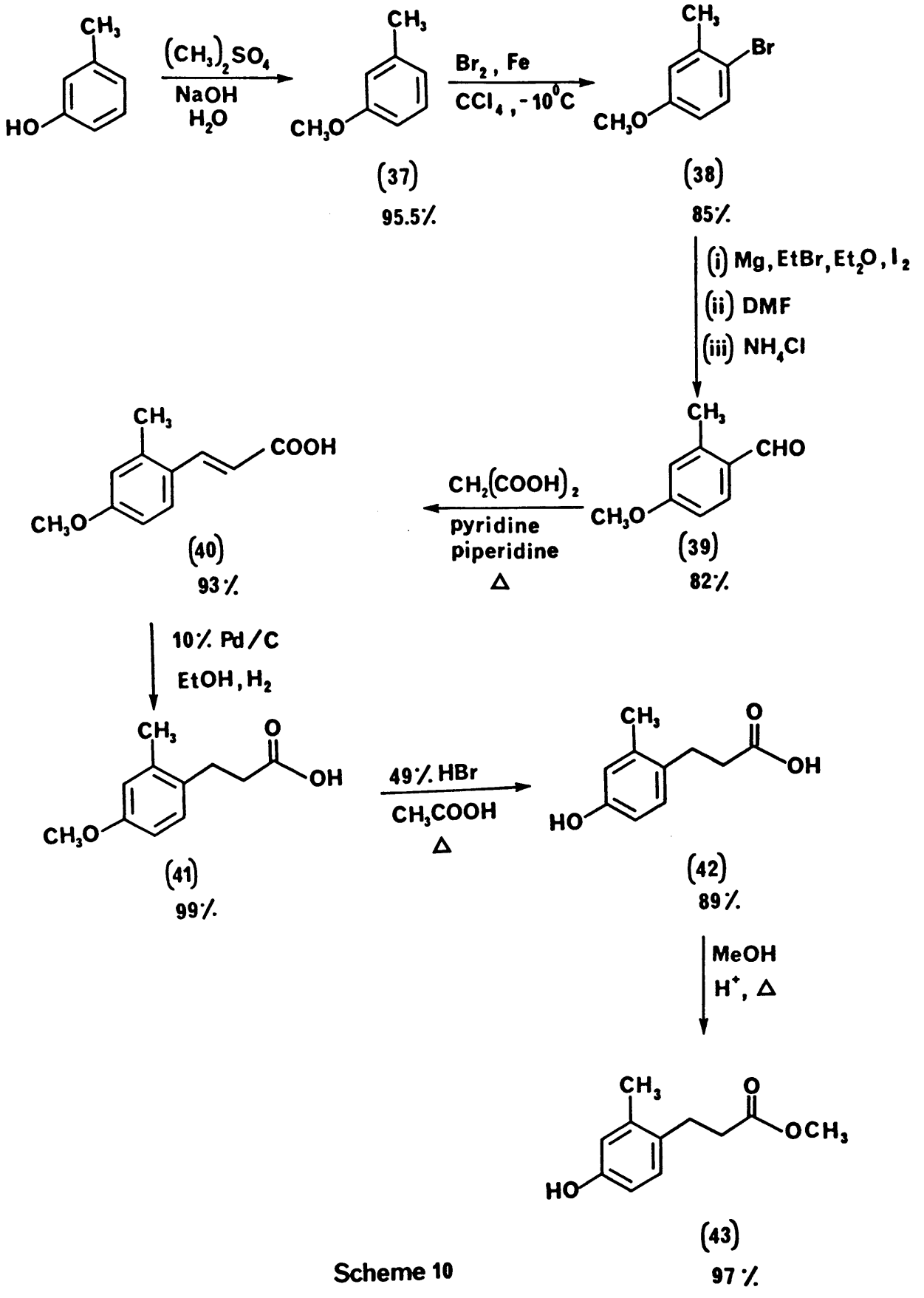
Scheme 9

Earlier investigations of the cyclisation of a mixture of α-diazoketones (35) and (36) had shown that the required functionalised azulenone (34) could be detected among the decomposition products. Therefore the lactone diazoketone (35) became the initial synthetic target.

3.9.1. *Preparation of the phenol ester (43)*[7,18,19]

The phenol ester (43), whose preparation is summarised in Scheme 10, was required for the preparation of the lactone diazoketone (35). The synthetic sequence to the cinnamic acid (40) was well established.[18,19] *m*-Methylanisole was prepared by methylation of commercially available *m*-cresol with dimethyl sulphate in aqueous sodium hydroxide to give the product in 95.5% yield as an oil. This product was selectively brominated using a catalytic amount of iron filings and bromine in carbon tetrachloride solution. After 3h excess bromine was destroyed by addition of aqueous sodium bisulphite and the bromide was isolated in 85% yield after purification by distillation, b.p. 60°C at 0.6 mmHg (lit.,[18] b.p. 72°C at 1.2 mmHg).

Conversion of the bromide (38) to the corresponding Grignard reagent in ether required the presence of bromoethane, as the bromide (38) was itself relatively unreactive. Treatment of the Grignard reagent thus prepared with *N,N*-dimethylformamide, followed by hydrolysis with saturated ammonium chloride solution gave the crude product containing both unreacted bromide (38) and the aldehyde (39) which were separated by fractional distillation. The bromide (38) was collected at 60°C at 0.6 mmHg, while the aldehyde (39) distilled at 80°C at 0.6 mmHg (lit.,[19] 106°C at 1.2 mmHg). The aldehyde (39) was obtained in 82% yield, as an oil, based on the bromide (38) consumed.


CH3
HO
(CH3)2SO4
NaOH
H2O
CH3O
(37)
95.5%
Br2, Fe
CCl4, -10°C
Br
(38)
85%
(i) Mg, EtBr, Et2O, I2
(ii) DMF
(iii) NH4Cl
CHO
(39)
82%
CH2(COOH)2
pyridine
piperidine
Δ
COOH
(40)
93%
10% Pd/C
EtOH, H2
OH
(41)
99%
49% HBr
CH3COOH
Δ
(42)
89%
MeOH
H+, Δ
OCH3
(43)
97%

Scheme 10

Condensation of the aldehyde (39) with malonic acid by heating in pyridine containing a catalytic amount of piperidine gave the cinnamic acid derivative (40) in 93% yield as white needles, m.p. 191-193°C lit.,[19] 187°C), after crystallisation from an acetone/ethanol mixture. The coupling constant observed in the ^{1}H n.m.r. spectrum of (40) for the vinylic protons J = 15.6Hz indicated that the cinnamic acid was formed with *trans*-stereochemistry.

Hydrogenation of the cinnamic acid (40) in ethanol over 10% palladium on charcoal at 40 p.s.i. gave the phenylpropanoic acid derivative (41) in 99% yield as a white solid which was used in the next reaction without purification. The cinnamic acid (40) was not completely soluble in the ethanol used as the hydrogenation solvent, but as reaction proceeded the starting material dissolved.

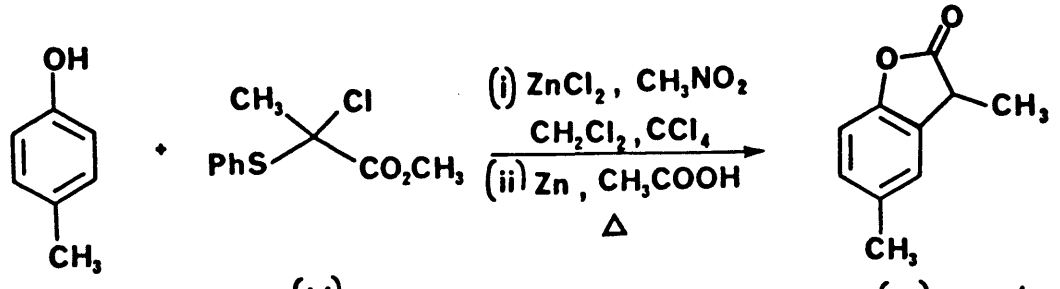
Demethylation was achieved by refluxing a solution of (41) in acetic acid with 49% hydrobromic acid for 24h. The phenolic acid (42) was isolated in 89% yield as white crystals by crystallisation from chloroform, m.p. 98.5-99.5°C.

The phenol ester (43) was prepared by esterification of the acid (42) and was purified by passage through a short column of silica to give the ester (43) as a gold-coloured oil in 97% yield from the acid (42). The spectral characteristics of the phenol ester (43) were in agreement with those reported previously.[7] The ester carbonyl stretch appeared at 1712 cm^{-1} in the ir spectrum. The aryl methyl group protons appeared in the ^{1}H n.m.r. spectrum at δ2.13 while the ester methyl group was visible at δ3.57. A distinctive aromatic pattern was visible with an AB quartet for

the C(5)*H* and C(6)*H* at δ6.60-7.10 and a broad singlet at δ6.76 for the C(3)*H*, confirming the substitution pattern on the aromatic ring.

3.9.2. *Lactonisation of phenol ester (43)*

The next stage was to attach the γ-lactone ring through the phenolic group of (43). γ-Lactone groups have been successfully attached to phenols in this laboratory, using α-chlorosulphide esters as electrophiles[20,21] as shown for example in equation 10.



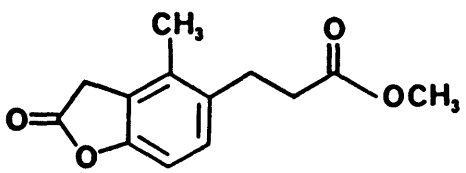
(44) (45) 72%. (10)

Therefore, this route was chosen to attach the lactone ring to phenol ester (43). This process involves a Friedel-Crafts alkylation *ortho* to the hydroxy group of the phenol followed by intramolecular condensation of the phenol with the ester portion of the electrophile to produce the lactone ring. The sulphide substituent is required for the alkylation reaction as its presence imparts greater electrophilicity to the α-chloro ester. α-Halogenated acetates are not good electrophiles for aromatic alkylation but they are conveniently activated by the presence of an alkylthio or arylthio group at the position geminal to the halogen atom, presumably because the sulphur substituent promotes ionisation of

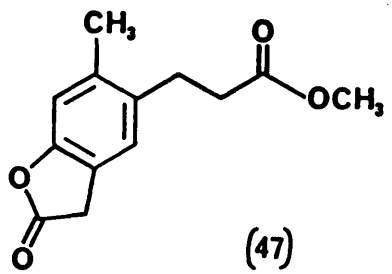
the C-halogen bond.[20] A phenylthio substituent is sufficiently activating with tertiary α-chlorosulphide esters, e.g. (44), but for successful alkylation with secondary α-chlorosulphide esters the more activating butylthio group is preferred.

The Friedel-Crafts alkylation of phenols with α-chlorosulphides is promoted by mild Lewis acid catalysts such as zinc chloride. The crude product of the alkylation can be desulphurised to give the lactone. This two step process has been found very convenient in the preparation of γ-lactones from phenols.

As there existed the possibility of the formation of two regioisomeric lactone esters from (43), i.e. (46) and (47), a range of α-chlorosulphides were prepared in order to study the regioselectivity of alkylation.

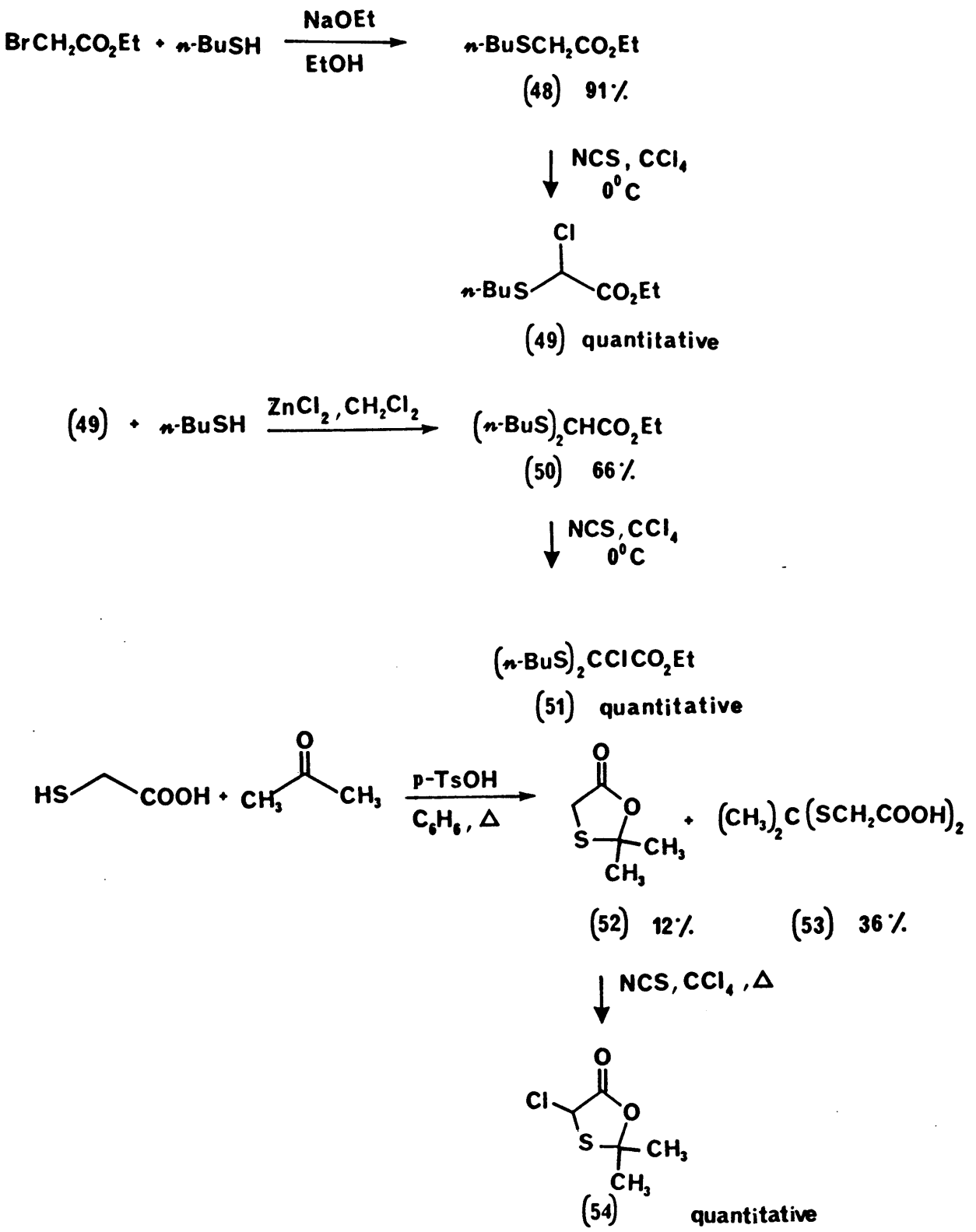


(46)



(47)

Scheme 11 summarises the preparation of the α-chlorosulphides used in this study from the corresponding sulphides by the procedure of Arai and co-workers.[22]


BrCH2CO2Et + n-BuSH
NaOEt
EtOH
n-BuSCH2CO2Et
(48) 91%
NCS, CCl4
0°C
Cl
n-BuS
CO2Et
(49) quantitative
(49) + n-BuSH
ZnCl2, CH2Cl2
(n-BuS)2CHCO2Et
(50) 66%
NCS, CCl4
0°C
(n-BuS)2CClCO2Et
(51) quantitative
HS
COOH + CH3
CH3
p-TsOH
C6H6, Δ
S
CH3
CH3
+ (CH3)2C(SCH2COOH)2
(52) 12%
(53) 36%
NCS, CCl4, Δ
Cl
S
CH3
CH3
(54) quantitative
Me
PhS
CO2Me
(55)
NCS, CCl4
0°C
Me
Cl
PhS
CO2Me
(44)
"
NCS, 0°C
CCl4, CH2Cl2
S
Cl
(56)
(57)
"

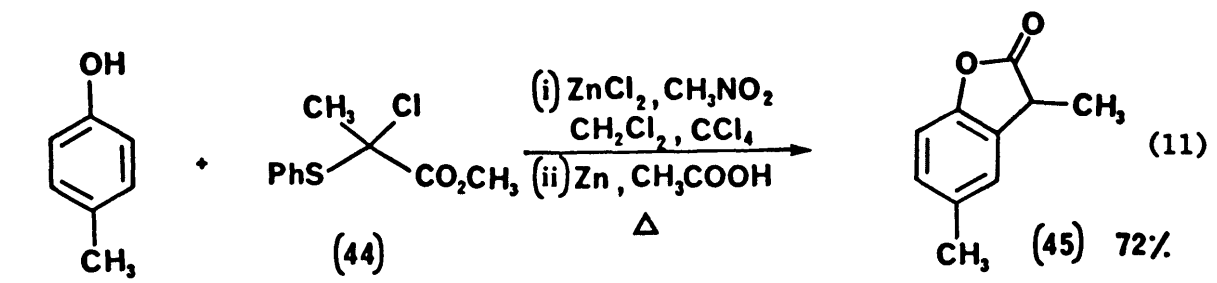
Scheme 11

Sulphide ester (48) was prepared in high yield by thiolate displacement on ethyl bromoacetate. The *bis* sulphide ester (50) was prepared from α-chlorosulphide (49) by Lewis acid catalysed addition of butanethiol following the procedure[23] developed in this laboratory for such transformations. The *bis* sulphide (50) was purified by chromatography on silica and was obtained as an oil and characterised spectroscopically. The α-*H* appeared in the ^{1}H n.m.r. spectrum as a distinctive singlet at δ4.24. The oxathiolanone (52)[24] was prepared in low yield by condensation of mercaptoacetic acid and acetone, the main product being the diacid (53). However, isolation of the oxathiolanone (45) in pure form was easily achieved as the diacid could be removed by washing with aqueous sodium bicarbonate. The oxathiolanone (45) was purified by distillation, b.p. 44°C at 10 mmHg, and characterised spectroscopically with a carbonyl stretch at 1769 cm^{-1} in the ir spectrum and two singlets in the ^{1}H n.m.r. spectrum at δ1.71 (6H, 2 x C*H*$_3$) and 3.69 (2H, C*H*$_2$). The sulphides (55)[25] and (56)[26] were already available.

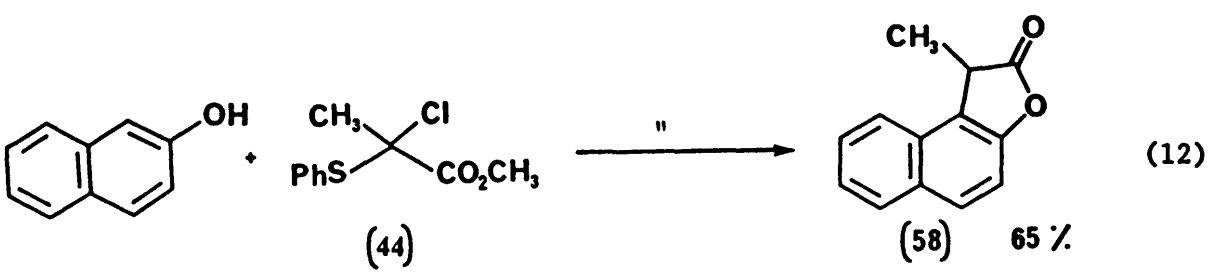
Transformation to the α-chlorosulphides was carried out with *N*-chlorosuccinimide in carbon tetrachloride at 0°C except in the case of oxathiolanone (52) where heating was required to complete the reaction. In the case of sulphide (56) addition of dichloromethane was necessary for dissolution of the starting material. The succinimide formed in the reactions was removed by filtration giving the α-chlorosulphide product as a solution in carbon tetrachloride. In general α-chlorosulphides are very sensitive species. The examples used in this work were stored as carbon tetrachloride solutions in a freezer and their purity was checked

by ^{1}H n.m.r. before use. Exceptionally, α-chlorosulphide (54) was remarkably stable and was recovered unchanged from an unsuccessful attempt to alkylate benzene, despite the use of an aqueous work-up. Similarly, α-chlorosulphide (57) seemed to be less sensitive than (44) and (49).

As a preliminary investigation of γ-lactone formation from phenols, *p*-cresol and β-naphthol were chosen as simple model compounds for alkylation with α-chlorosulphide (44) as shown in equations 11 and 12.



(11)



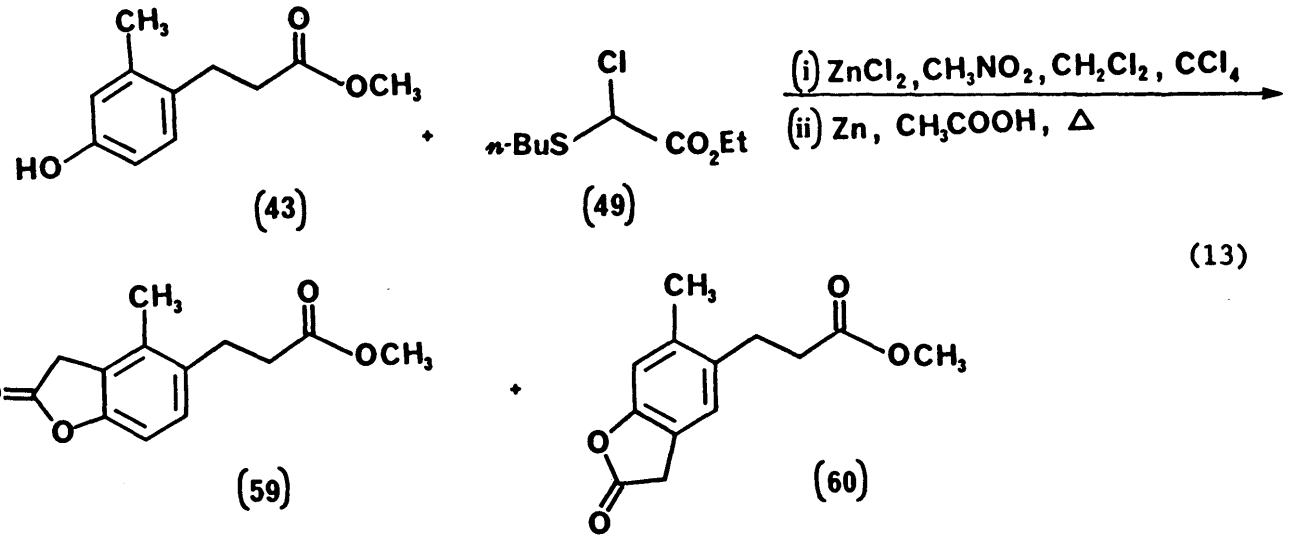
(12)

The alkylations were carried out at room temperature by stirring the phenol and zinc chloride in a dichloromethane–nitromethane mixture while a solution of the α-chlorosulphide in carbon tetrachloride was added dropwise. T.l.c. monitoring showed that reactions in general were

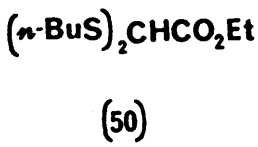
complete within 1h. Following an aqueous work-up, the crude alkylation product was desulphurised by refluxing in acetic acid with zinc dust, which had been freshly activated with dilute aqueous HCl. Purification of the product by chromatography on silica gave the lactones (45) and (58) from alkylations of *p*-cresol and β-naphthol, respectively, in 72% and 65% yield. Both the lactones were known compounds and their spectral characteristics agreed with reported values. Lactone (45)[27] was isolated as a viscous oil with a carbonyl stretch in the ir spectrum at 1797 cm^{-1} for the γ-lactone and signals in the ^1H n.m.r. spectrum at δ1.52 (J = 6.6Hz), a doublet for the α-methyl group protons, and δ2.36, a singlet for the aryl methyl group protons, in agreement with the reported values[27] of δ1.52 and 2.33 for these signals. Lactone (58)[28] was obtained as a white crystalline solid, m.p. 125-127°C (lit.,[28] 121-124°C), with a carbonyl stretch in the ir spectrum at 1783 cm^{-1}, in good agreement with the reported value[28] of 1790 cm^{-1}, and a doublet in the ^1H n.m.r. spectrum for the methyl group protons at δ1.69 (J = 7.2Hz).

Having established the optimum conditions for the alkylation reactions with the model compounds, alkylation of the phenol ester (43) with α-chlorosulphide (49) was carried out as shown in equation 13.

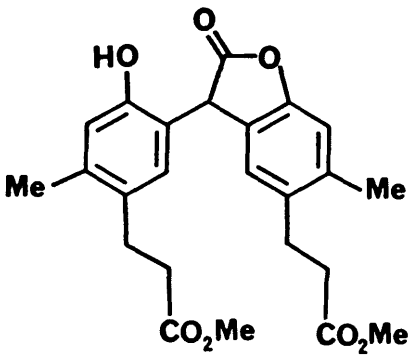
Alkylation of (43) with the secondary α-chlorosulphide (49) was less efficient than those in the model studies using the tertiary α-chlorosulphide. The alkylation was carried out as described for *p*-cresol and β-naphthol and the crude product of the alkylation was desulphurised directly. Chromatographic separation of the desulphurisation product gave an inseparable mixture of lactones (59) and (60) in 30% yield, and the two major byproducts, the *bis* sulphide ester (50) and a compound tentatively assigned as the dimer (61).



Fleming and Iqbal[29] have reported dimers very similar to (61) in their phenylthioalkylation of phenols.



(50)



(61)

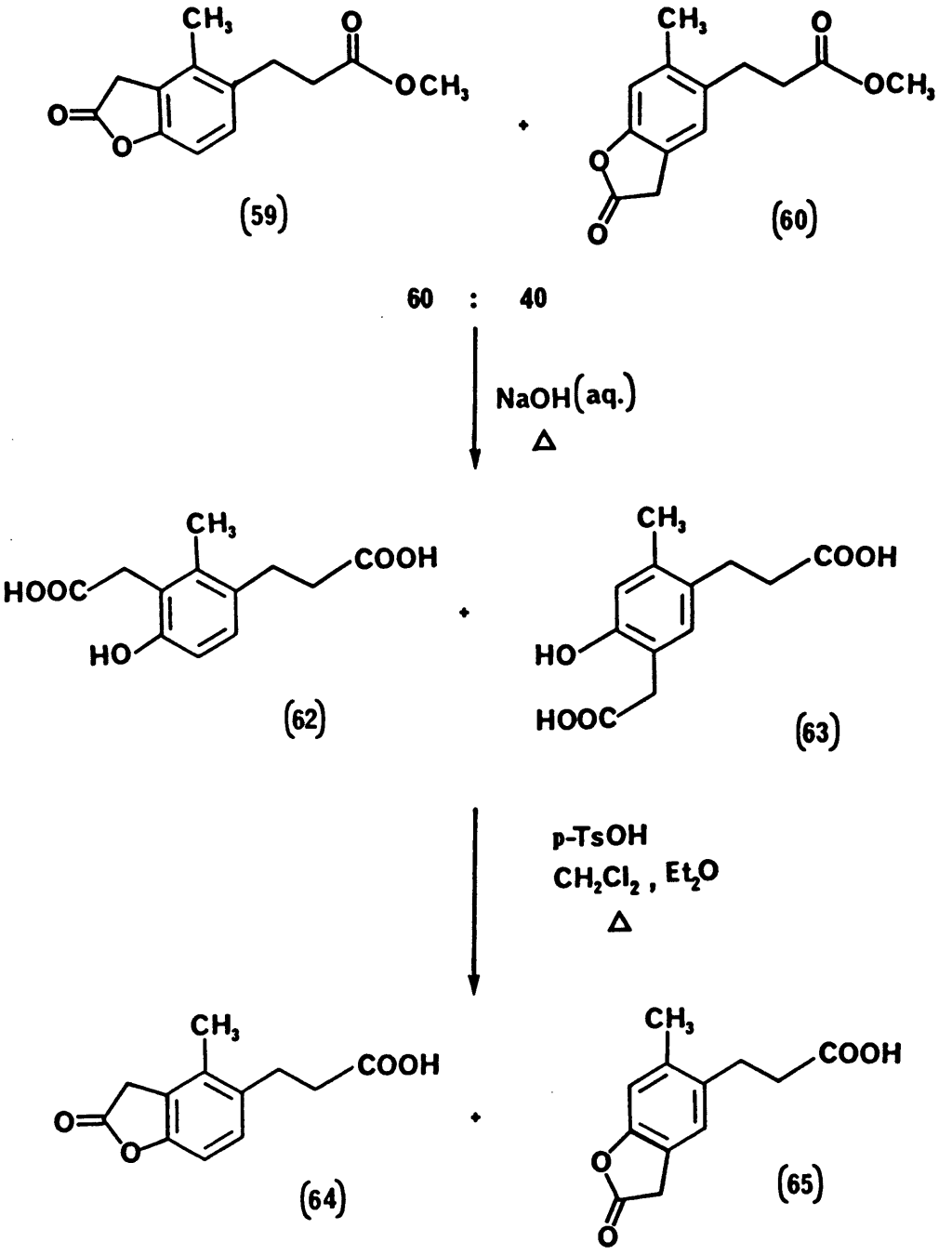
The mixture of lactones (59) and (60) were obtained as a yellow solid with a broad melting range, presumably due to the isomer mixture (55-70°C). All attempts to separate the lactones at this stage were

unsuccessful. The carbonyl stretch for the lactone was at 1800 cm^{-1} in the ir spectrum while the ester carbonyl stretch was seen at 1727 cm^{-1}. The isomer ratio was determined by integration of the singlets in the ^{1}H n.m.r. spectrum for the aryl methyl groups which appeared at δ2.20 (major) and 2.33 (minor), showing a 60:40 ratio. The assignment of the major isomer as (59) was made by examination of the pattern in the aromatic region of the spectrum: (59) had an AB quartet for the two aromatic protons while (60) showed two singlets which overlapped with the AB quartet at δ6.80-7.30. The pattern of signals showed clearly that the major isomer of the alkylation was (59). Thus the regioselectivity of the alkylation was disappointingly low with α-chlorosulphide (49).

As the lactone esters (59) and (60) could not be separated, the mixture was subjected to the reaction sequence shown in Scheme 12.

The lactone esters (59) and (60) were refluxed for 1 minute in aqueous sodium hydroxide and then the mixture was stirred for 20h at room temperature. The hydroxy acids were isolated as a mixture by careful acidification of the reaction mixture and ether extraction. The hydroxy acids (62) and (63) were obtained in 98% yield as a yellow solid and were not purified before relactonisation. ^{1}H n.m.r. spectroscopy was employed to ensure complete disappearance of the ester methyl group in the saponification.

Relactonisation, catalysed by *p*-toluenesulphonic acid, was carried out in refluxing ether/dichloromethane. The lactone acids (64) and (65)


CH3
O
OCH3
O
O
(59)
(60)
60 : 40
NaOH(aq.)
Δ
HOOC
COOH
HO
(62)
(63)
p-TsOH
CH2Cl2 , Et2O
Δ
(64)
(65)
60 : 40
96%.

Scheme 12

were obtained in 96% yield as a yellow solid. Relactonisation was indicated by the reappearance of the lactone carbonyl stretch in the ir spectrum at 1801 cm^{-1} while the acid carbonyl stretch was at 1705 cm^{-1}. In the ^1H n.m.r. spectrum the signals for the aryl methyl groups overlapped at δ2.15 but the signals for the lactone methylene groups were resolved at δ3.58 (minor) and 3.78 (major) showing the 60:40 ratio of isomers (64) and (65), respectively.

Trituration of the mixture with ether gave a pure sample of the less soluble major isomer (64), but the minor isomer (65) was not obtained in pure form. On recrystallisation from methanol, lactone acid (64) formed yellow plates, m.p. 188-191°C. This compound was quite insoluble dissolving only in highly polar solvents such as methanol and DMSO. The regiochemistry of the lactone acid (64) was established with certainty by the AB quartet in the ^1H n.m.r. spectrum at δ6.80-7.30 for the aromatic protons.

Returning to the alkylation of phenol ester (43), attempts to modify the regioselectivity of the alkylation of (43) were made using the alternate α-chlorosulphide reagents shown in Scheme 11. The chloro *bis* sulphide (51) gave very little lactonisation with phenol ester (43). The chlorooxathiolanone (54) gave the lactone esters (59) and (60) in a 60:40 ratio as before but in only 16% yield, lower than with α-chlorosulphide (49), probably due to the low reactivity of α-chlorosulphide (54). However, when the bicyclic α-chlorosulphide lactone (57) was employed as the electrophile in the alkylation of phenol ester (43), a notable change in the regiochemistry was observed with a 90:10 preference for isomer (59). The overall yield for the

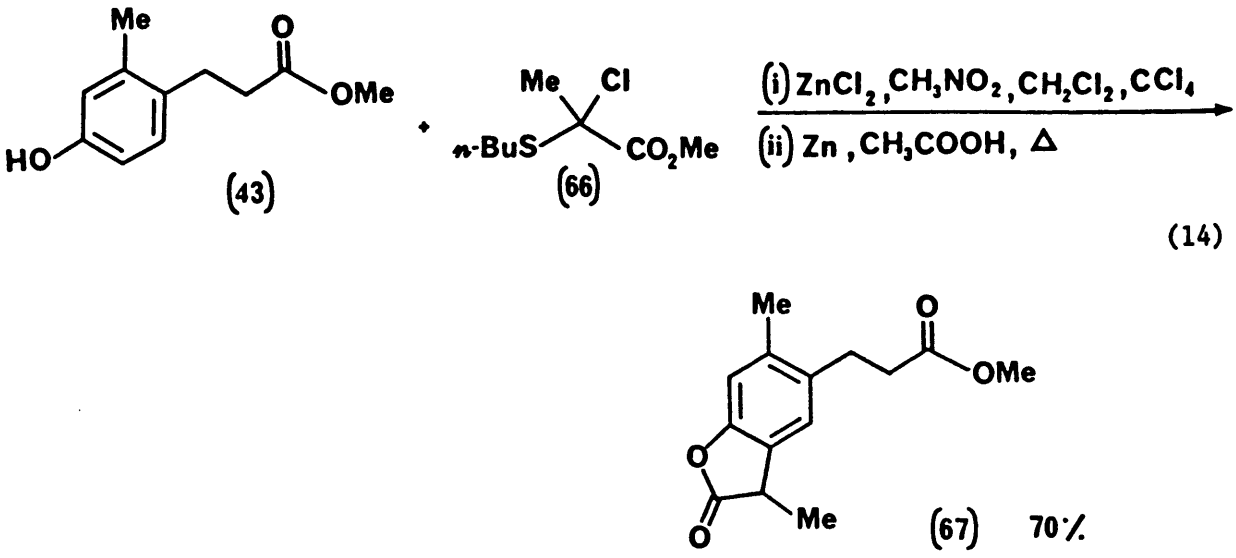
alkylation and desulphurisation process was higher than that obtained using α-chlorosulphide (49), giving a 39% yield of the lactone ester mixture. Alkylation of phenol ester (43) with α-chlorosulphide (57) was carried out by adding a solution of (57) in dichloromethane to the substrate (43) and zinc chloride, in a nitromethane-dichloromethane mixture. Reaction was slower than with α-chlorosulphide (49), requiring 10h for complete reaction compared to 1h for (49). Product isolation and desulphurisation were carried out as discussed before.

Thus, although a 60:40 mixture of the lactone esters (59):(60) was used in the sequence to isolate lactone acid (64), a higher yield of this product could be obtained by carrying out the alkylation with α-chlorosulphide (57) instead, as this would have resulted in a 90:10 mixture of (64):(65), from which a greater yield of (64) could have been isolated, thereby improving the yield of the overall synthetic sequence.

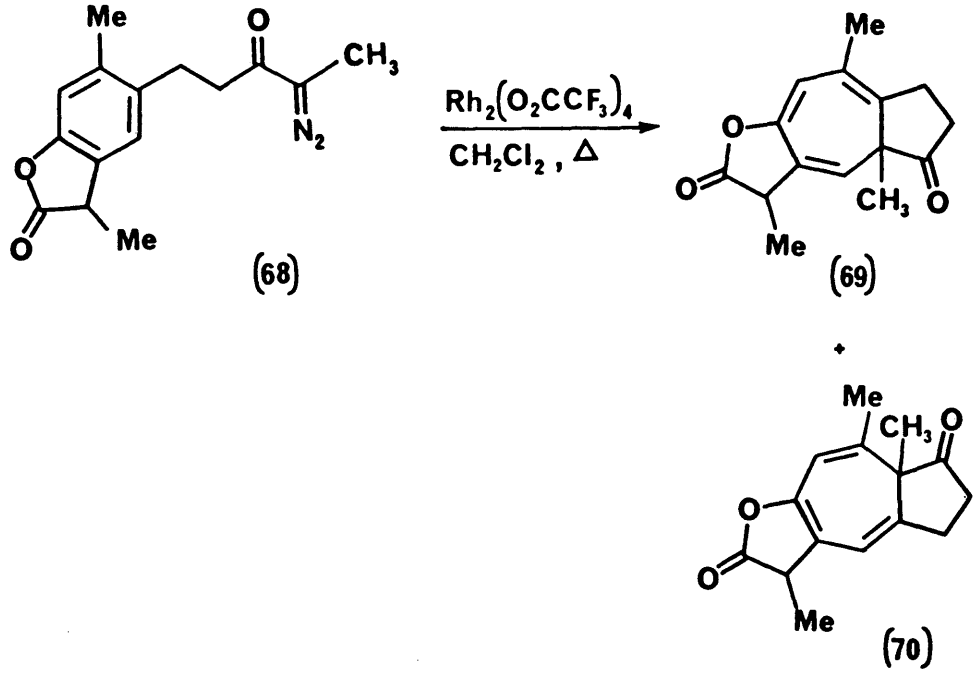
The problem of regioselectivity of alkylation of phenol ester (43) was a complex one. Strangely, the predominant isomer of the alkylation, (59), corresponded to alkylation in the more sterically hindered position, suggesting that reaction at this position was favoured electronically. However, it should be recalled that the dimer (61), which constituted 30% of the reaction product, corresponded to alkylation at the less hindered position as in the minor isomer (60). Essentially, therefore, reaction at the less hindered position was actually predominant but much of the alkylation at the less hindered position resulted in dimer formation. Thus in order to maximise isolation of lactone ester (60), i.e. the isomer required for synthesis

of confertin, not only would alkylation at the less hindered position have to be promoted, but dimer formation would have to be minimised. However, an alternative route, involving an intramolecular Buchner cyclisation of an α-diazoketone, to confertin was developed,[2] with the result that isomer (60) was no longer required. Following the fortuitous discovery of alkylation of (43) with α-chlorosulphide (57) to give a 90:10 ratio of (59):(60), further attempts to alter the regioselectivity of the alkylation were therefore unnecessary.

An earlier study in this laboratory[4,7,21] in which phenol ester (43) was alkylated with a tertiary α-chlorosulphide (66) had resulted in regiospecific formation of lactone ester (67) in 70% yield after desulphurisation (equation 14).



Alkylation with the tertiary α-chlorosulphide was clearly more successful than with the secondary α-chlorosulphides, which are less electrophilic, resulting in a higher yield of lactone and with regiospecific product formation, albeit in the unwanted position to the isomer required for this study.

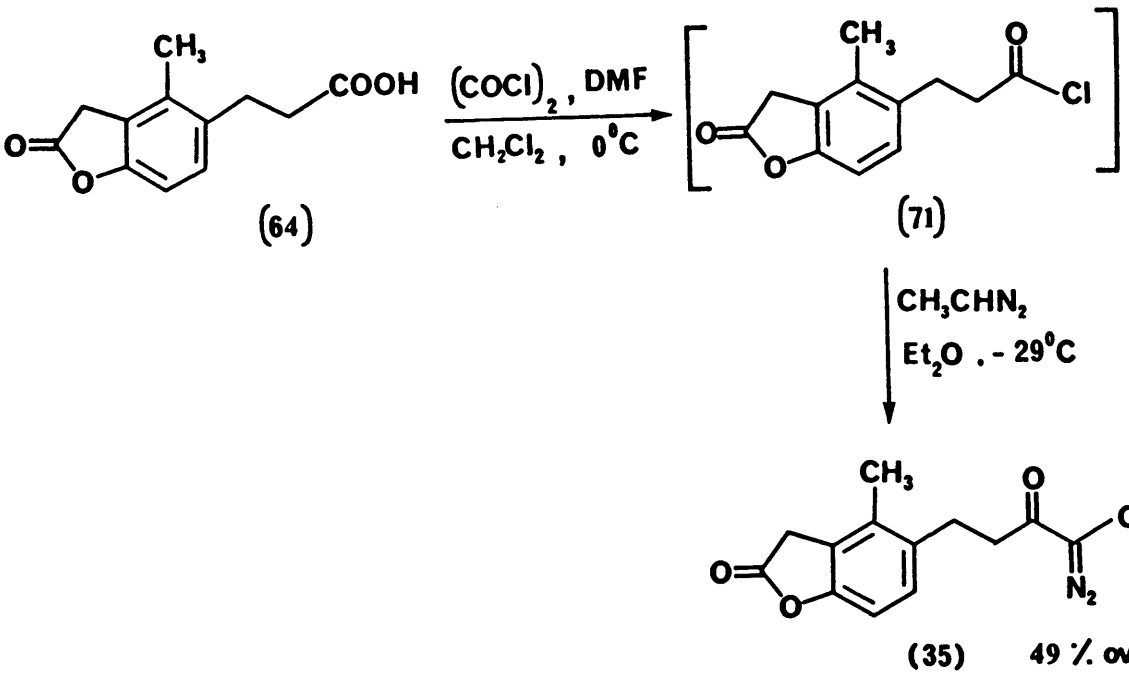


(15)

However, when lactone (67) was eventually transformed into α-diazoketone (68) and decomposed with rhodium(II) trifluoroacetate, both cyclisation products (69) and (70) were formed in approximately equal amounts as shown in equation 15. Therefore, although the methyl group had a beneficial effect on the alkylation reaction, it was detrimental to the regioselectivity of the intramolecular α-diazoketone cyclisation in the key step of the sequence.

3.9.3. *Preparation of α-diazoketone (35)*

Having obtained lactone acid (64) free from its isomer, the next stage was to transform it to the α-diazoketone (35) as shown in equation 16.



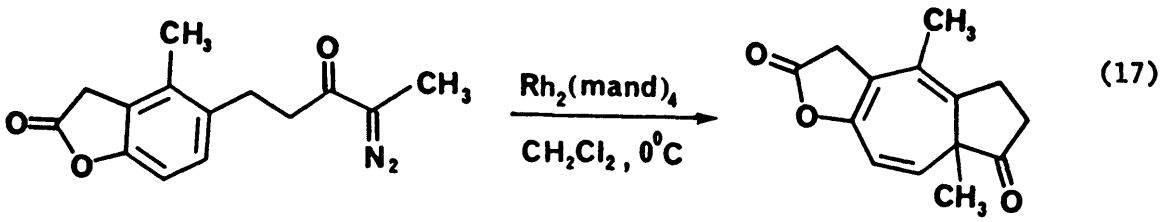
(64) (71) (35) 49 % overall (16)

The acid chloride (71) was prepared by stirring the acid in dichloromethane at 0°C with a catalytic amount of *N,N*-dimethylformamide while oxalyl chloride (1.05 equivalent) was added. The initially insoluble acid dissolved as reaction proceeded and the transformation was generally complete within 90 minutes. The acid chloride (71) proved very sensitive and all attempts to isolate it resulted in hydrolysis. It was found most satisfactory to add the acid chloride in the solution in which it was prepared into a freshly prepared and distilled solution of diazoethane in ether while stirring at -29°C. The reaction conditions had to be strictly controlled to obtain the α-diazoketone in good yields. 4.5-5.0 Equivalents of diazoethane gave the best results. The concentration of the ethereal diazoethane was maintained at 1M approximately; at lower concentrations the purity of the α-diazoketone

obtained decreased considerably. The volume of dichloromethane present had to be minimised also, as its presence appeared to be detrimental to diazoketone formation. Generally 0.20g lactone acid (64) in 2 mls dichloromethane gave satisfactory results. The catalytic amount of DMF present in the acid chloride solution did not appear to have a detrimental effect on the diazoethane acylation.

α-Diazoketone (35) was purified by chromatography on silica, with some loss due to decomposition, and was obtained as a yellow crystalline solid, m.p. 93-95°C, in 49% overall yield from the acid (64). It was reasonably stable when stored at 0°C with no apparent decomposition in 3 days. The α-diazoketone was characterised spectroscopically by the diazo absorption in the ir spectrum at 2070 cm^{-1} while the absorptions at 1794 and 1628 cm^{-1} were assigned to the lactone and diazoketone carbonyls, respectively. The ^{1}H n.m.r. spectrum showed a singlet at δ1.93 assigned to the diazoketone methyl group and a singlet at δ2.19 for the aryl methyl group. A broad singlet was seen at δ3.53 for the lactone methylene protons. A distinctive AB quartet was visible at δ6.80-7.30 for the aromatic protons. The ^{13}C n.m.r. also confirmed the identity of the α-diazoketone; even the singlet for the diazo-carbon, which is frequently too weak to detect in ^{13}C n.m.r. spectra of non-terminal α-diazoketones, was visible at δ_C 62.44.

3.9.4. *Cyclisation of α-diazoketone (35)*



(35) (34) >90%

(17)

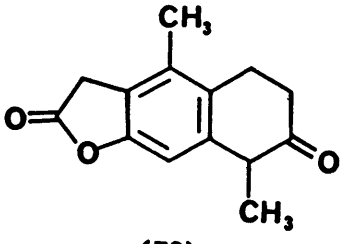
Rhodium(II) (S)-mandelate (1) was found to be an extremely efficient catalyst for the decomposition of α-diazoketone (35) at 0°C in dichloromethane to give the cycloheptatrienone (34) as a single isomer as shown in equation 17. With a freshly prepared batch of rhodium(II) (S)-mandelate less than 10% of an aromatic impurity was seen in the reaction product, which was tentatively assigned as the carbene dimer from the ^{1}H n.m.r. spectrum. The cyclisation was carried out at high dilution to minimise dimer formation, with slow addition of the α-diazoketone to the reaction mixture to keep the diazoketone concentration as low as possible throughout the decomposition. T.l.c. monitoring showed complete disappearance of the α-diazoketone within 1h and removal of the solvent gave the reaction product, which was a pale yellow flocculent solid and was characterised spectroscopically.

The ir spectrum of the reaction product had carbonyl stretches at 1803 cm^{-1} for the lactone, 1743 cm^{-1} for the cyclopentanone, and 1711 cm^{-1}, a very weak band presumably due to the presence of a small

concentration of the norcaradiene form of (34). The ^{1}H n.m.r. spectrum contained a singlet at δ0.89 for the bridgehead methyl group, a singlet at δ1.93 for the second methyl group, a broad singlet at δ3.49 for the lactone methylene group, and a multiplet at δ2.10-3.00 for the four cyclopentanone methylene protons. An AB pattern (J = 10.2Hz) for the vinylic protons at δ5.14 for the C(8)*H* and δ6.22 for the C(7)*H*, confirmed that cyclisation had occurred in the required direction to give exclusive formation of (34). The position of the C(8)*H* signal at δ5.14 indicated that very little of the norcaradiene tautomer was present at room temperature.

With samples of rhodium(II) (S)-mandelate which had been prepared several months previously approximately 10% aromatic impurity was detectable in the cycloheptatrienone product. Similarly when rhodium(II) trifluoroacetate was employed as the decomposition catalyst at reflux in dichloromethane, the cycloheptatrienone product contained 10% aromatic impurity.

Asymmetric induction in the cyclisation of (35) to (34) was not investigated, although by comparison with the studies on trienone (11) it is likely that some degree of enantioselection was present in the cyclisation. However, the rhodium(II) (S)-mandelate catalysed cyclisation had been carried out at 0°C, therefore the asymmetric induction obtained may have been lower than that possible in the system with reaction at reflux. Attempted reduction of (34) with lithium tri-*tert*-butoxyaluminohydride resulted only in formation of the tetralone (72) with the result that the asymmetric induction could not be investigated by Eu(tfc)$_3$-shifted ^{1}H n.m.r. analysis as with earlier studies.



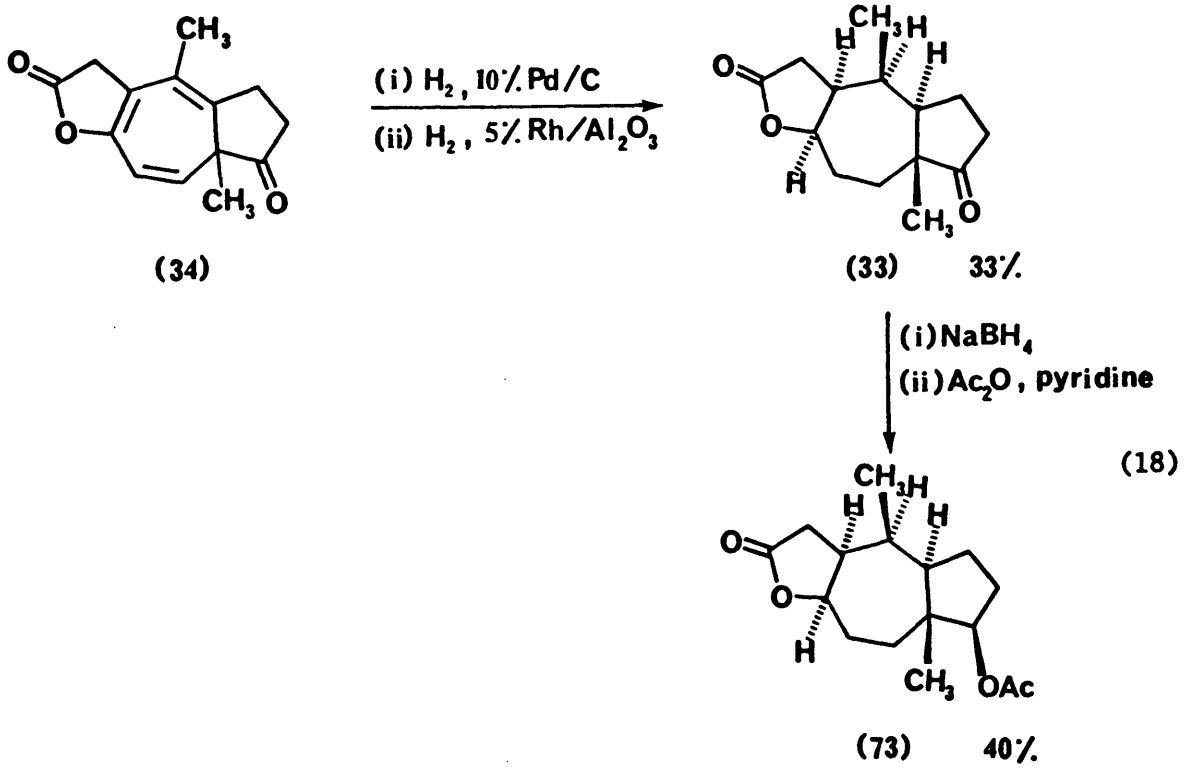
(72)

The tetralone (72) was characterised spectroscopically and the spectral details were in agreement with an earlier study.[7] The tetralone was obtained as a yellow solid in 56.3% yield. Carbonyl stretches were detected in the ir spectrum at 1800 cm^{-1} for the lactone and 1711 cm^{-1} for the tetralone. In the ^{1}H n.m.r. spectrum the aryl methyl group appeared as a singlet at δ2.29 while the second methyl group resulted in a doublet at δ1.46 (J = 7.8Hz). The lactone methylene protons were seen as a broad singlet at δ3.63 and the aromatic proton was seen as a distinctive singlet at δ6.93, confirming the identity of the tetralone.

3.9.5. *Hydrogenation, reduction, and acetylation of the trienone (34)*[30]

Exhaustive hydrogenation of the crude cycloheptatrienone (34) gave a single fully saturated isomer (33) as shown in equation 18, thus completing the synthetic sequence. The cyclopentanone (33) was reduced and acetylated to give lactone acetate (73) whose structure and relative stereochemistry were elucidated by ^{1}H n.m.r. analysis and by X-ray crystal structure.[4] Transformation of (33) to an unnatural isomer of

confertin could be achieved by attachment of an α-methylene group by well established procedures. Thus this constitutes the synthesis of an unnatural pseudoguaianolide structure.



(34)

(33) 33%

(18)

(73) 40%

3.10 References

1. M.A. McKervey, S.M. Tuladhar, and M.F. Twohig, *J. Chem. Soc., Chem. Commun.*, 1984, 129.
2. M. Kennedy and M.A. McKervey, *J. Chem. Soc., Chem. Commun.*, 1988, 1028.
3. M. Kennedy, M.A. McKervey, A.R. Maguire, S.M. Tuladhar, and M.F. Twohig, in preparation.
4. H. Duddeck, G. Ferguson, M. Kennedy, M.A. McKervey, and A.R. Maguire, in preparation.
5. A. Costantino, G. Linstrumelle, and S. Julia, *Bull. Soc. Chim. Fr.*, 1970, 907; 912.
6. L.T. Scott, *J. Chem. Soc., Chem. Commun.*, 1973, 882; L.T. Scott, M.A. Minton, and M.A. Kirms, *J. Am. Chem. Soc.*, 1980, 102, 6311.
7. M. Kennedy, Ph.D. thesis, N.U.I., 1986.
8. 'Textbook of Practical Organic Chemistry', Vogel, 4th ed., Longmans, 1978, p.291.
9. J.A. Marshall and J.J. Partridge, *J. Org. Chem.*, 1968, 33, 4090 for the preparation of diazoethane from *N*-ethyl-*N*-nitrosourea; the reagent was prepared following the procedure given by F. Arndt, *Org. Synth.*, Coll. Vol. II, 1943, 461.
10. A.L. Wilds and A.L. Meader, *J. Org. Chem.*, 1948, 13, 763.
11. T. Hudlicky, F.J. Koszyk, T.M. Kutchan, and J.P. Sheth, *J. Org. Chem.*, 1980, 45, 5020.
12. K. Hannemann, *Angew. Chem. Int. Ed. Engl.*, 1988, 27, 284.
13. 'Stereochemistry of Carbon Compounds', E.L. Eliel, McGraw-Hill, Tokyo, 1962, p.197-202; R.M. Beesley, C.K. Ingold, and J.F. Thorpe, *J. Chem. Soc.*, 1915, 107, 1080; C.K. Ingold, *J. Chem. Soc.*, 1921, 119, 305.

14. For discussion of the use of $Eu(tfc)_3$ as a chiral shift reagent in ^1H n.m.r. studies see V. Schurig, Kontakte (Darmstadt), 1985, 22.

15. B.B. Snider and C.P. Cartaya-Marin, *J. Org. Chem.*, 1984, 49, 153.

16. This was also observed by S.M. Tuladhar, Ph.D. thesis, N.U.I., 1984.

17. C. Iwata, M. Yamada, Y. Shinoo, K. Kobayashi, and H. Okada, *Chem. Pharm. Bull.*, 1980, 28, 1932.

18. D.J. Nelson and E.A. Uschak, *J. Org. Chem.*, 1977, 42, 3308.

19. A.J. Pearson, T.R. Perrior, and D.A. Griffin, *J. Chem. Soc., Perkin Trans. 1*, 1983, 625.

20. M. Kennedy, A.R. Maguire, and M.A. McKervey, *Tetrahedron Lett.*, 1986, 27, 761.

21. M. Kennedy, M.A. McKervey, A.R. Maguire, and S. Naughton, in preparation.

22. K. Arai, Y. Ohara, T. Iizumi, and Y. Takakuwa, *Tetrahedron Lett.*, 1983, 24, 1531.

23. J.P. Cronin, B.M. Dilworth, and M.A. McKervey, *Tetrahedron Lett.*, 1986, 27, 757.

24. (a) S. Satsumabayashi, S. Irioka, H. Kudo, K. Tsujimoto, and S. Motoki, *Bull. Chem. Soc.,Jpn.*, 1972, 45, 913;
(b) K. Pihlaja, A. Nikkila, K. Neuvonen, and R. Keskinen, *Acta. Chem. Scand., Part A*, 1976, 30, 457.
(c) J. Butera, J. Rini, and P. Helquist, *J. Org. Chem.*, 1985, 50, 3676.

25. Prepared by M. Kennedy following the procedure in reference 7.

26. Prepared by S. Naughton following the procedure given in J.K. Koskimies, *Acta. Chem. Scand., Part B*, 1984, 38, 101.

27. O. Piccolo, L. Filippini, L. Tinucci, E. Valoti, and A. Citterio, *J. Chem. Res. (S)*, 1985, 258.

28. R.A. Clement and T.-C. Shieh, *J. Org. Chem.*, 1960, 25, 1850.

29. I. Fleming and J. Iqbal, *Synthesis*, 1982, 11, 937.

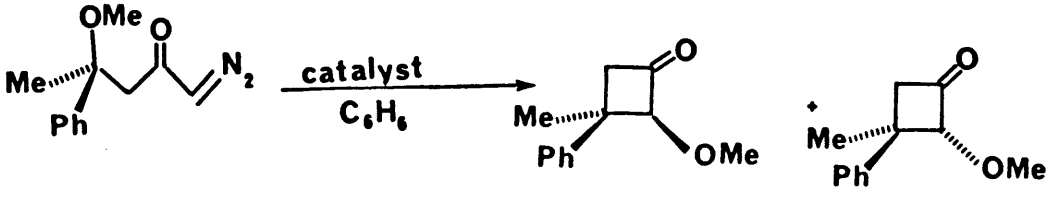
30. The sequence of hydrogenation, reduction, and acetylation was completed by M. Kennedy as described in reference 4.

CHAPTER 4

OXONIUM YLIDE FORMATION AND REARRANGEMENT

INTRODUCTION

Following the discovery of Roskamp and Johnson[1] that in the diazoketone decomposition illustrated in equation 1, which is believed to proceed *via* formation and subsequent rearrangement of an oxonium ylide (Scheme 1), the diastereoisomeric ratio of the product mixture depended strongly on the catalyst employed, it was decided to investigate oxonium ylide generation with some of the chiral rhodium(II) carboxylate catalysts.

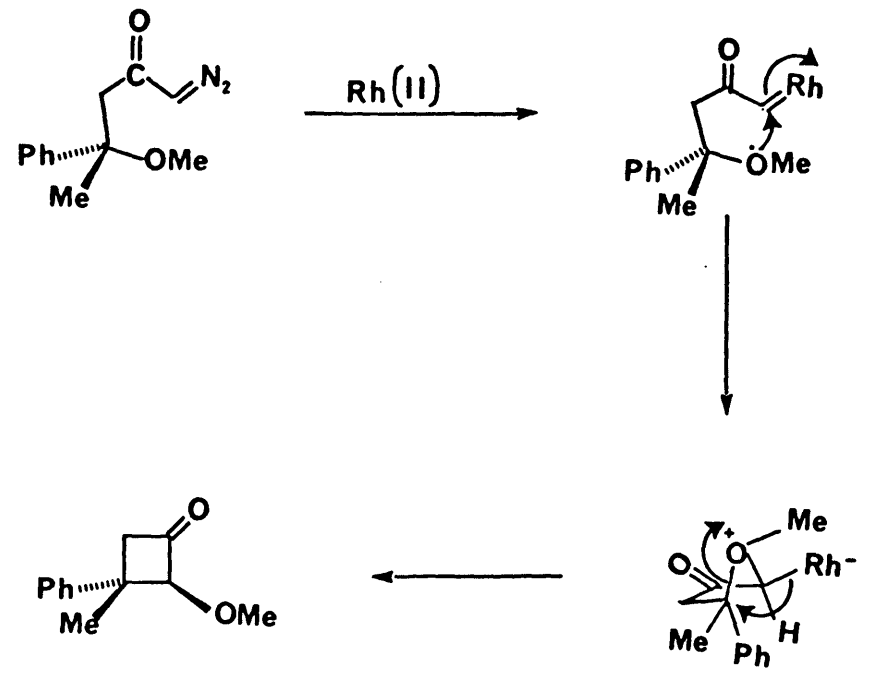


(1)

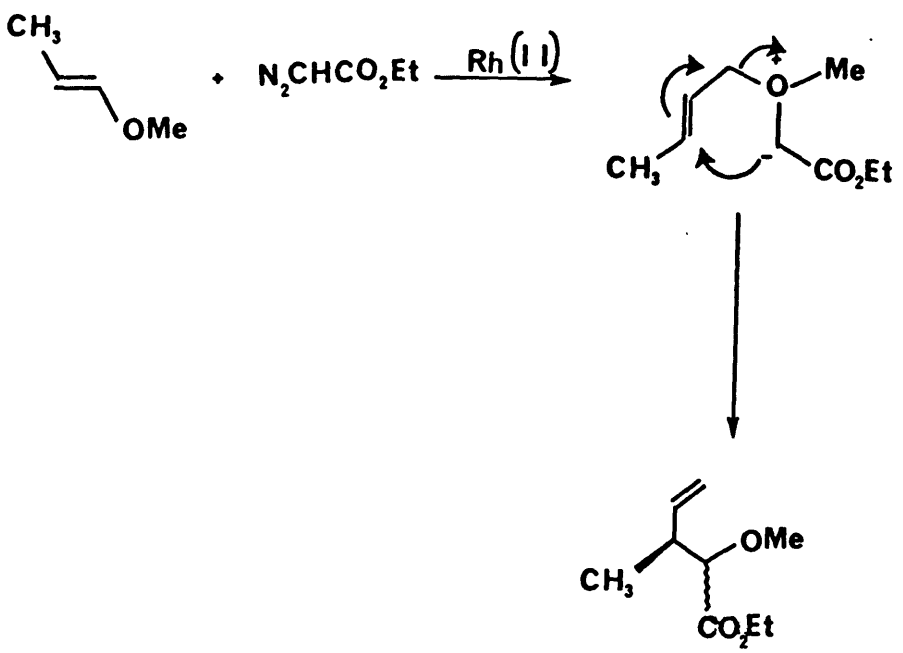
$Rh_2(OAc)_4$	3	:	1
$Cu(acac)_2$	1	:	6
$RhCl(Ph_3P)_3$	1	:	10

The strong stereochemical dependence on the catalyst used suggested that strong catalyst-substrate interactions are present in the transition state, and thus it was hoped that in a reaction of this nature, use of a chiral rhodium(II) carboxylate catalyst would result in significant asymmetric induction.

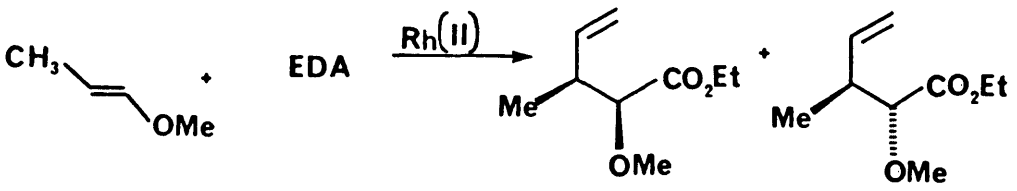
In contrast, since this work was undertaken, Doyle *et al.*[2] have reported no change in the diastereoisomeric ratio obtained in the reaction illustrated in equation 2 on changing the catalyst from rhodium(II) acetate to rhodium(II) perfluorobutyrate, $Rh_2(pfb)_4$. This reaction is believed to proceed *via* oxonium ylide generation and [2,3]-sigmatropic rearrangement as shown in Scheme 2.



Scheme I



Scheme 2



(2)

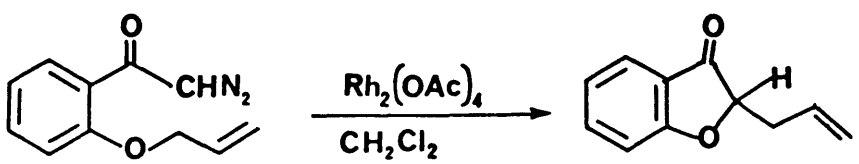
79 : 21 (92%)

+ cyclopropane products (8%)

(86% yield overall)

Doyle interpreted this result as indicating that the [2,3]-sigmatropic rearrangement occurs from the free ylide rather than a metal-associated ylide. If this is the case, asymmetric induction through the use of a chiral catalyst would be expected to be poor.

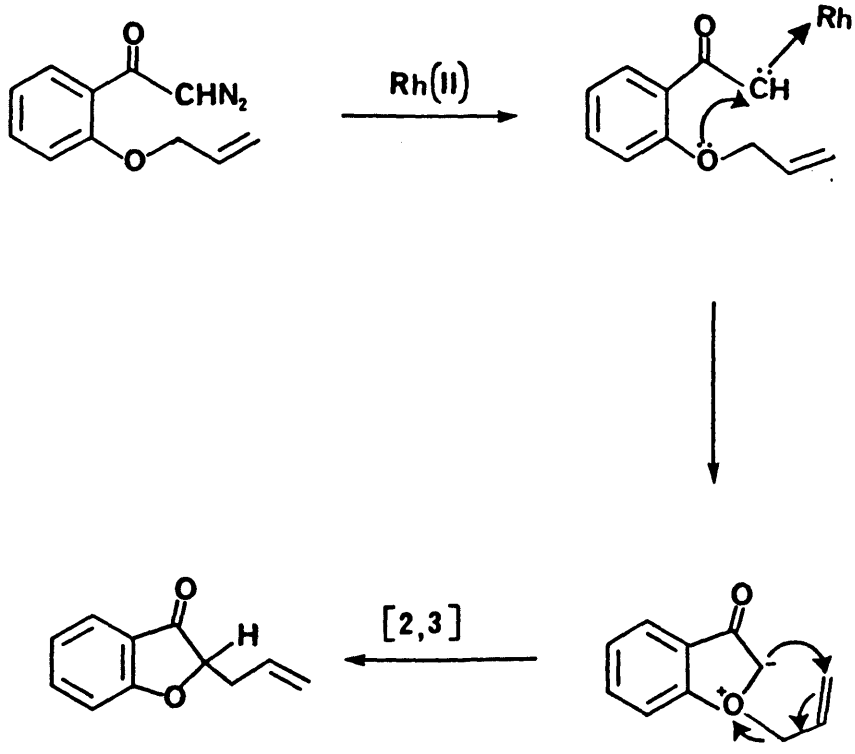
The reaction chosen for study was the diazoketone decomposition reported by Pirrung and Werner[3] shown in equation 3.



(3)

71%

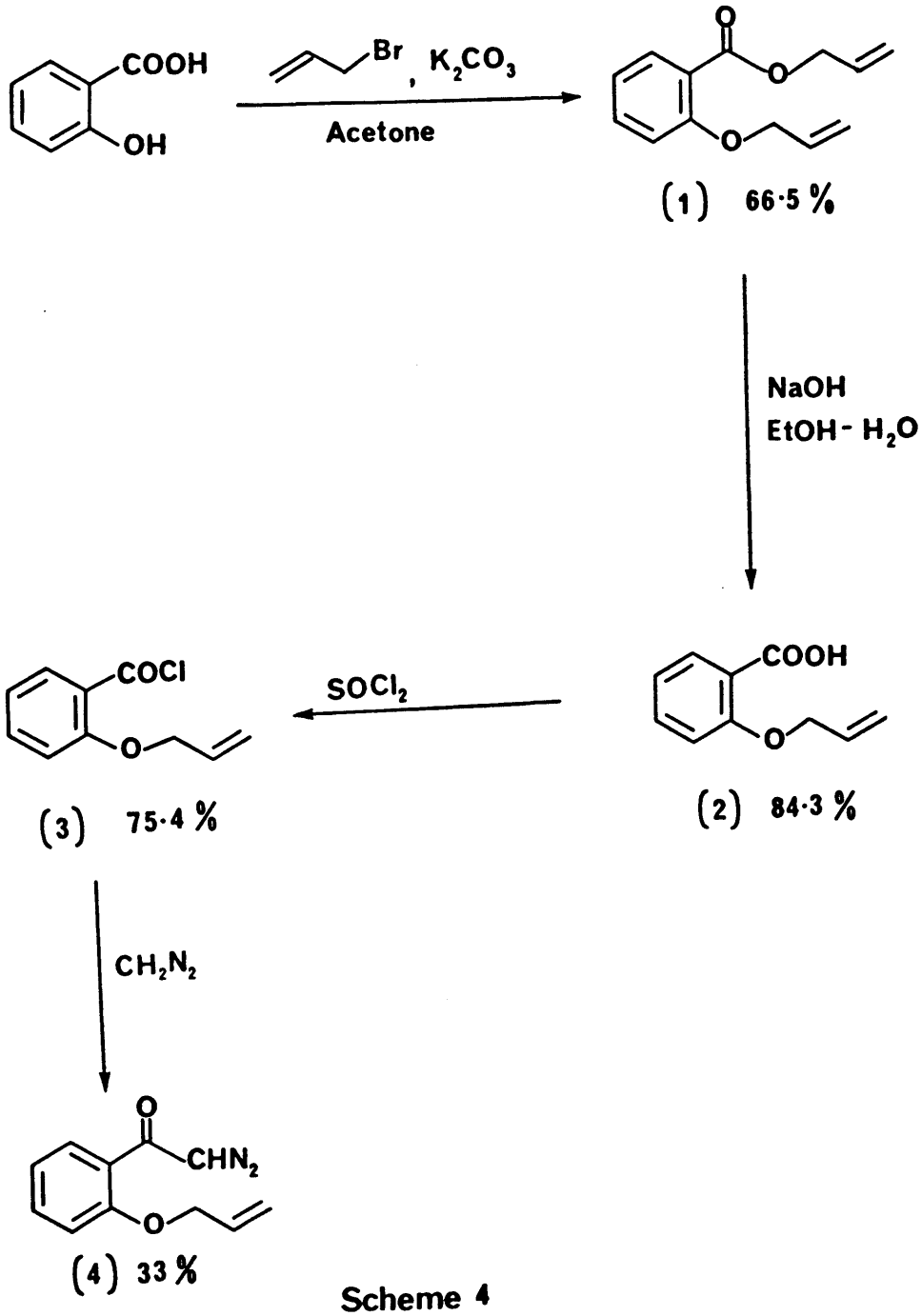
This reaction is believed to proceed *via* oxonium ylide generation and subsequent [2,3]-sigmatropic rearrangement as illustrated in Scheme 3.



Scheme 3

4.1 Preparation of *o*-allyloxy-(diazoacetyl)benzene (4)[3]

The α-diazoketone (4) was prepared as illustrated in Scheme 4. Salicylic acid was allylated to give the *bis*-allylated ester (1) which was hydrolysed to the allyl ether acid (2).

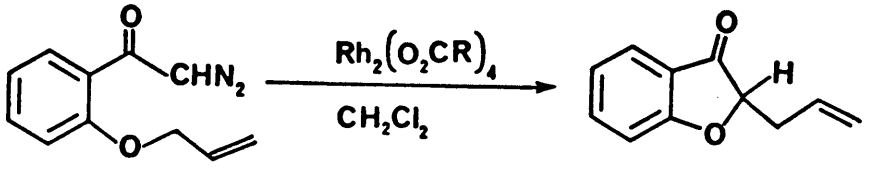


Scheme 4

Conversion of the acid (2) to the α-diazoketone (4) was by the standard route of acid chloride formation and treatment with excess diazomethane. The yield of the pure α-diazoketone (4) was low due to decomposition on silica during purification. Although the crude α-diazoketone was satisfactory by ir and ^{1}H n.m.r. spectroscopy, it did contain some highly coloured baseline impurities which poisoned the rhodium(II) carboxylate catalysts when decomposition was attempted without purification. Thus despite the tendency of the α-diazoketone to decompose on silica, purification was necessary.

4.2 Decomposition of α-diazoketone (4)

α-Diazoketone (4) was readily decomposed by rhodium(II) carboxylate catalysis as a dilute solution in dichloromethane to give 2-allyl-(2*H*)-benzofuran-3-one (5) (equation 4). Reaction was rapid even at room temperature; with each of the catalysts, reaction was complete within 10 minutes.



(4) (4)

(4) (5) 73.5%

RCOOH = CH_3COOH, (S)-mandelic acid, *N*-benzenesulphonyl-L-proline

However, to maintain uniformity with the earlier diazoketone decompositions, and since higher asymmetric inductions were obtained at reflux in the earlier studies, the decomposition of α-diazoketone (4) was carried out at reflux. Similarly to enable comparison of these studies with earlier

studies, the decomposition was carried out by slow addition of the α-diazoketone (100 mg) as a solution in dichloromethane (10 ml) to refluxing dichloromethane (100 ml) containing the catalyst (0.5 mg), although such precautions (i.e. slow addition and high dilution) were not strictly necessary with this α-diazoketone as neither dimer formation nor any other side-reactions were significant.

The product was readily purified by chromatography on silica and identified by spectroscopy. Its ir spectrum showed bands at 1710 and 1608 cm^{-1} for the carbonyl group and double bond respectively. The most characteristic feature of the ^{1}H n.m.r. spectrum was a pair of doublets at δ 4.57 (J_1= 4.2Hz, J_2= 7.2Hz) assigned to the C(2)*H*. However, despite many attempts accurate elemental analysis was not obtained though the compound was believed to be pure.

4.3 Asymmetric induction in decomposition of α-diazoketone (4)

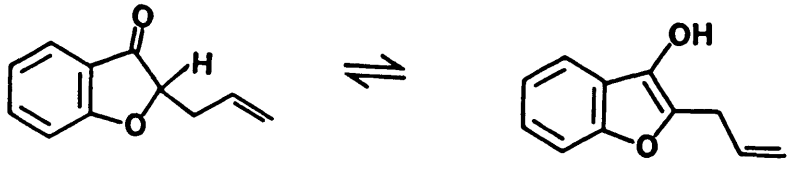
This investigation proved difficult due to the sensitivity of the benzofuranone (5). As expected, the product obtained by rhodium(II) acetate catalysed decomposition was optically inactive. However, when the chiral catalysts, i.e. those derived from (S)-mandelic acid (1) and *N*-benzenesulphonyl-L-proline (4), were used, the crude product of the reaction displayed considerable optical activity, while after purification by chromatography on silica the benzofuranone (5) was essentially optically inactive in each case (Table 4.1).

This observation is believed to be the result of racemisation on silica due to a keto-enol equilibrium on the surface of the silica (equation 5).

Table 4.1 : Effect of catalyst on the decomposition of *o*-allyloxy-(α-diazoacetyl)-benzene (4)

Catalyst	$[\alpha]_D^{20}$ (crude)* ^{o}(c, CH_2Cl_2)	$[\alpha]_D^{20}$ (after chromatography) ^{o}(c, CH_2Cl_2)
$Rh_2(OAc)_4$	-	-
1	+3.1 (8-9)	<1 (6.3)
4	-14.2 (10-12)	<1 (8.0)

* Average of several reactions



(5)

Because of this racemisation process on silica, purification on neutral alumina was attempted but resulted in complete decomposition to give a strongly coloured yellow product which could not be eluted from alumina even with methanol. Attempts at crystallisation were also unsuccessful.

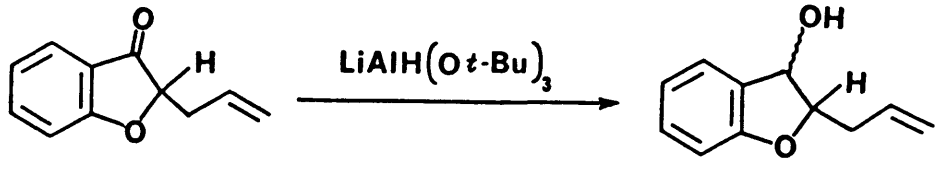
Thus since pure samples of benzofuranone (5) could not be obtained without racemisation, optical rotation data could not be strictly compared for the different catalysts, as the crude products contained optically active catalyst residues. However, there did appear to be a significant difference in the asymmetric induction obtained depending on the catalyst employed (Table 4.1). The specific rotations reported are the average of a number of reactions. Rhodium(II) mandelate catalysis gave a specific rotation for the crude product of $[\alpha]_D^{20}$ +3.1 (c 8-9 in CH_2Cl_2) while rhodium(II) *N*-benzenesulphonyl-L-prolinate gave $[\alpha]_D^{20}$ -14.2 (c 10-12 in CH_2Cl_2). Unfortunately the specific rotations of the catalysts themselves could not be measured as in solution they are too strongly coloured to allow passage of light. Thus an estimation of the contribution of the catalyst residue to the optical rotation measured could not be made.

The prolinate catalyst (4) appears to be much more efficient in inducing asymmetry in the decomposition than the mandelate (1). Interestingly, the direction of the asymmetry is opposite for the two catalysts. These features indicate that the catalyst-substrate interactions are significant in the transition state and that even though α-diazoketone (4) does not appear to be suitable for an asymmetric induction study, further investigation of asymmetric induction in oxonium ylide type decomposition of α-diazoketones may prove successful.

Attempts to discover the enantiomeric excess present in the benzofuranone (5) were unsuccessful. Addition of $Eu(tfc)_3$ as a chiral shift reagent resulted in a downfield shift of the signal at δ 4.57 into the broad signal for the allyl group protons. Since this pair of doublets

was the only characteristic signal in the spectrum which could be expected to give information on the % e.e. present, chiral shift ^{1}H n.m.r. investigation was not suitable with this compound.

4.4 Reduction of benzofuranone (5)



(6)

(5) (6)

Successful reduction was carried out with lithium tri-*tert*-butoxyaluminohydride as reducing agent (equation 6). The ^{13}C n.m.r. spectrum of the alcohol produced showed it to be a pair of diastereoisomers in an approximately 60:40 ratio, as indicated by the pairs of signals observed in the n.m.r. spectrum. The ^{1}H n.m.r. of the alcohol mixture was complex and not suitable for chiral shift study as each of the protons appeared as a multiplet. Thus the enantiomeric excess could not be estimated in the alcohol either.

However, the racemisation route on silica was now no longer possible as enolisation was not possible in (6). Thus when an optically active sample of the benzofuranone (5), $[\alpha]_{20}^{D}$ -10.5 (c 12.9 in CH_2Cl_2), (derived from a reaction catalysed by rhodium(II) *N*-benzenesulphonyl-L-prolinate) was reduced, chromatography on silica gave a pure sample of the alcohol mixture (6) which was measurably optically active with

$[\alpha]_D^{20}$ -3.5 (c 3.6 in CH_2Cl_2), confirming that asymmetric induction had occurred in the diazoketone decomposition although still giving no indication of the degree of induction obtained.

4.5 Conclusion

There appears to be asymmetric induction in the diazoketone decomposition *via* oxonium ylide formation and rearrangement catalysed by chiral rhodium(II) carboxylates, and this induction appears to be strongly dependent on the catalyst employed. However, the system studied does not appear to have been a suitable choice. Despite this the results obtained are sufficiently promising to indicate that another study should be undertaken.



4.6 References

1. E.J. Roskamp and C.R. Johnson, *J. Am. Chem. Soc.*, 1986, 108, 6062.
2. M.P. Doyle, V. Bagheri, and N.K. Harn, *Tetrahedron Lett.*, 1988, 29, 5119.
3. M.C. Pirrung and J.A. Werner, *J. Am. Chem. Soc.*, 1986, 108, 6060.

CHAPTER 5

EXPERIMENTAL

General Experimental

Solvents were dried by standard procedures according to A.I. Vogel, 'A Textbook of Practical Organic Chemistry', Pergamon Press, 1966. The drying agent used throughout this work was anhydrous sodium sulphate.

Silica gel PF_{254} was used in both column chromatography and preparative thin layer chromatography. Radial chromatography was performed on a chromatotron (model 7924, Harrison Research) on silica gel PF_{254} (with $CaSO_4.\frac{1}{2}H_2O$, type 60 t.l.c. grade). Thin layer chromatography (t.l.c.) was carried out on Riedel-de-Haën DC cards SiF.

Melting points were determined on a Reichert microscope hot stage melting point apparatus and are uncorrected. Elemental analyses were performed by the Microanalysis Laboratory, University College Cork using a Perkin-Elmer 240 elemental analyser. Infrared (ir) spectra were recorded, as KBr discs (solids) or thin films (liquids) on sodium chloride windows, on a Perkin-Elmer 682 infra-red spectrometer.

^1H n.m.r. spectra were recorded on a Hitachi Perkin-Elmer R-20A 60MHz n.m.r. spectrometer and a Jeol PMX-60-SI n.m.r. spectrometer in deuteriochloroform ($CDCl_3$) as solvent, unless otherwise stated, and tetramethylsilane (TMS) as internal standard. Chemical shifts are expressed in parts per million (ppm), positive shifts being downfield from TMS. 270MHz ^1H n.m.r. spectra were recorded in University College Cork on a Jeol JNM-GSX-270 n.m.r. spectrometer and by the University

College Galway N.M.R. service on a Jeol GX n.m.r. spectrometer. ^{13}C n.m.r. spectra were recorded at 15 MHz on a Jeol JNM-FX60 Fourier transform spectrometer at 24°C. The chiral shift reagent used was tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III) derivative, $Eu(tfc)_3$.

Optical rotations were obtained on a Perkin-Elmer 141 polarimeter in a 10 cm cell at 589 nm.

The experimental procedures for Chapter 2 are given in 5.1, Chapter 3 in 5.2, and Chapter 4 in 5.3.

5.1 C-H INSERTION REACTIONS

1(1-Hydroxycyclopentyl)acetic acid ethyl ester (5)[1]

Zinc dust was freshly activated by stirring in 5% hydrochloric acid for 5 min, filtered, washed copiously with water, alcohol, and ether, and dried. Zinc dust (15.6g, 0.239 mol) in benzene (20 ml) was stirred under nitrogen while a portion (10%) of a solution of cyclopentanone (20g, 0.238 mol) and ethyl bromoacetate (42.16g, 0.252 mol) in benzene (150 ml) was added. A crystal of iodine was added and the reaction mixture was heated to reflux giving a sudden exotherm. External heat was removed and the remaining solution was added dropwise, after which the mixture was refluxed for 2h, then cooled. Dilute sulphuric acid (250 ml) was added cautiously. The layers were separated and the aqueous phase was washed with ether (2 x 50 ml). The combined organic extracts were dried and evaporated at reduced pressure to yield the alcohol (5) (41.41g, quantitative crude yield) as a red-brown oil which was dehydrated without purification; ν_{max} (film) 3505(OH) and 1734 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.26(3H, t, J = 7.2Hz, CH_3), 1.30-2.50(8H, m, 4 x CH_2), 2.58(2H, s, CH_2CO_2Et), 4.11(2H, q, J = 7.2Hz, OCH_2), and 4.46(1H, brs, OH).

Dehydration of 1(1-hydroxycyclopentyl)acetic acid ethyl ester (5)

Cyclopentanol (5) (3g, 0.017 mol) in benzene (100 ml) containing a few drops of conc. sulphuric acid was refluxed for 7h while stirring under nitrogen. Water was removed from the reaction by azeotropic distillation using a Dean-Stark apparatus. The cooled solution was washed with water (2 x 50 ml), dried, and evaporated at reduced pressure to yield the

unsaturated esters (6a) and (6b) (2.60g, 97.0% crude yield) as a brown oil which was hydrogenated without purification; ν_{max}(film) 1731(β,γ-unsaturated ester), 1709(α,β-unsaturated ester), and 1636 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 1.00-1.40(3H, 2 overlapping t, OCH_2CH_3), 1.30-3.00(8H, m, 4 x CH_2), 3.06(1H, brs, CH_2CO of β,γ-unsaturated ester), 3.73(0.5H, s, α-*H* of α,β-unsaturated ester), 3.90-4.40(2H, 2 overlapping q, OCH_2CH_3), and 5.50-5.70(0.5H, m, γ-*H* of β,γ-unsaturated ester).

Ethyl cyclopentylacetate (7)[2]

The regioisomeric ester mixture (6a) and (6b) (2.0g, 0.013 mol) in ethanol (100 ml) was hydrogenated over palladium on charcoal (10%; 0.10g) under hydrogen (32 p.s.i.) for 15h. A second catalyst addition (0.10g) was made and hydrogenation (40 p.s.i.) was continued for 7h. The reaction mixture was filtered through celite and evaporated at reduced pressure to yield an oil which was purified by Kugelrohr distillation (oven temp. 85°C @ 10 mmHg) to give the ester (7) (1.63g, 80.5% yield) as a colourless oil; ν_{max}(film) 1732 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.80-2.10(12H, m, 4 x CH_2 and *CH* of ring, OCH_2CH_3 t visible at 1.25 with J = 7.2Hz), 2.28(2H, brs, CH_2CO), and 4.09(2H, q, J = 7.2Hz, OCH_2CH_3).

Ethyl valerate (2)[3]

The ester was prepared by esterification of commercially available valeric acid and purified by distillation at 144-145°C (lit.,[3] b.p. 143-146° C).

Methyl pent-4-enoate (47)[4]

Pent-4-enoic acid (46)[5] (1.70g, 0.017 mol) in ether (10 ml) was added dropwise over 10 min to a stirred solution of freshly prepared diazomethane[6] (2.14g, 0.051 mol) in ether (100 ml) at 0°C under nitrogen. Stirring was continued for 19h while the reaction mixture was allowed to return slowly to room temperature. Evaporation of the solvent at reduced pressure furnished the ester (47) (1.87g, 96.5% yield) as an oil; ν_{max}(film) 1732 (CO) and 1637 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 2.36,2.41(4H, 2 x brs, 2 x CH_2), 3.66(3H, s, CH_3), and 4.90-6.10(3H, m, $CH{=}CH_2$). The spectral data are in agreement with literature values.[4]

Methyl phenyl sulphone (8)

Methyl phenyl sulphone[7] was prepared by oxidation of thioanisole with H_2O_2 in acetic acid. The product was isolated as a white crystalline solid m.p. 85-88°C (lit.,[7] m.p. 86-88°C).

Dimethyl sulphone (9)

Dimethyl sulphone[8] was prepared by oxidation of dimethyl sulphoxide with potassium permanganate. Crystallisation of the crude product gave a white crystalline solid m.p. 110-111°C (lit.,[8] 102-109°C).

Preparation of β-keto sulphones[9]

1-Benzenesulphonylhexan-2-one (10)[10]

Sodium hydride (7.325g, 0.305 mol) was washed clean of mineral oil with hexane (4 x 50 ml) under nitrogen. A solution of methyl phenyl sulphone (45.439g, 0.291 mol) in dry DMSO (135 ml) was added slowly while stirring under nitrogen. The reaction mixture was heated to 70-75°C until all the sodium hydride had dissolved and hydrogen evolution had ceased, giving a cloudy yellow solution of the sulphonyl anion (approx. 30 min). The reaction mixture was cooled to room temperature, dry THF (135 ml) was added, then cooled to 0°C and a solution of ethyl valerate (18.93g, 0.145 mol) in THF (20 ml) was added dropwise over 10 min. Stirring was continued for 90 min at room temperature, then the reaction mixture was poured on to ice-water (400 ml), acidified to pH 1 with dilute hydrochloric acid, extracted with dichloromethane (4 x 100 ml), and dried. Evaporation at reduced pressure gave the crude product containing equimolar quantities of 1-benzenesulphonylhexan-2-one and methyl phenyl sulphone. Purification by chromatography on silica using gradient ethyl acetate-hexane as eluant gave 1-benzenesulphonylhexan-2-one (10) (27.43g, 78.5%) as a clear colourless oil (Found: C, 60.35; H, 6.95; S, 13.50. $C_{12}H_{16}O_3S$ requires C, 59.97; H, 6.71; S, 13.34%); ν_{max}(film) 1717 (CO), 1320, and 1160 cm^{-1} ($-SO_2-$); $\delta_H(CDCl_3)$ 0.60-1.70 (7H, m, $CH_3CH_2CH_2$), 2.64(2H, brt, CH_2CO), 4.16(2H, s, CH_2SO_2), and 7.30-8.00(5H, m, Ar-*H*); $\delta_C(CDCl_3)$ 13.77(q, CH_3), 21.90(t, CH_3CH_2), 25.14(t, $CH_3CH_2CH_2$), 44.12(t, CH_2CO), 66.66(t, CH_2SO_2), 128.26(d), 129.36(d), 134.30(d), 138.91(s), (Ar), and 198.36(s, *C*O).

1-Methanesulphonylhexan-2-one (11)

This was obtained using the procedure described for 1-benzenesulphonylhexan-2-one from sodium hydride (1.08g, 0.045 mol), dimethyl sulphone (4.23g, 0.045 mol) in DMSO (25 ml), THF (25 ml), and ethyl valerate (2.93g, 0.023 mol) in THF (10 ml). Purification by chromatography on silica with gradient ethyl acetate-hexane as eluant gave 1-methanesulphonylhexan-2-one (11) (2.22g, 55.3% yield) as a clear colourless oil (Found: C, 47.23; H, 7.75; S, 18.55. $C_7H_{14}O_3S$ requires C, 47.17; H, 7.92; S, 17.99%); ν_{max}(film) 1715 (CO), 1305, and 1143 cm^{-1} ($-SO_2-$); $\delta_H(CDCl_3)$ 0.70-1.80 (7H, m, $CH_3CH_2CH_2$), 2.48(2H, brt, CH_2CO), 2.89(3H, s, CH_3SO_2), and 3.91(2H, s, CH_2SO_2); $\delta_C(CDCl_3)$ 13.77(q, CH_3), 21.96(t, CH_3CH_2), 25.01(t, $CH_3CH_2CH_2$), 41.58(q, CH_3SO_2), 44.51(t, CH_2CO), 64.39(t, CH_2SO_2), and 199.92(s, CO).

1-Benzenesulphonyl-5-phenylpentan-2-one (12)

This was obtained using the procedure described for 1-benzenesulphonylhexan-2-one from sodium hydride (3.92g, 0.163 mol), methyl phenyl sulphone (25.50g, 0.163 mol) in DMSO (150 ml), THF (70 ml), and ethyl 4-phenylbutanoate (4)[11] (15.00g, 0.080 mol) in THF (70 ml). Recrystallisation from ethanol gave 1-benzenesulphonyl-5-phenylpentan-2-one (12) (7.23g, 30% yield) as a white crystalline solid, m.p. 80-83°C (Found: C, 67.62; H, 6.23; S, 10.69. $C_{17}H_{18}O_3S$ requires C, 67.52; H, 6.00; S, 10.62%); ν_{max}(KBr) 1709 (CO), 1313, 1303, and 1144 cm^{-1} ($-SO_2-$); $\delta_H(CDCl_3)$ 1.70-2.00(2H, sym m, $-CH_2CH_2CH_2$), 2.30-2.80(4H, 2 overlapping t, $-CH_2CH_2CH_2$), 4.09(2H, s, CH_2SO_2), and 7.00-8.00(10H, m, 2 x Ph); $\delta_C(CDCl_3)$ 24.50(t), 34.50(t), 43.47(t), (3 x CH_2), 66.47(t, CH_2SO_2), 125.98(d), 128.13(d), 128.39(d), 129.30(d), 134.17(d), 138.78(s), 141.19(s), (2 x Ph), and 197.97(s, CO).

1-Benzenesulphonyl-3-cyclopentylpropan-2-one (13)

This was obtained using the procedure described for 1-benzenesulphonylhexan-2-one from sodium hydride (0.33 g, 0.014 mol), methyl phenyl sulphone (2.00g, 0.013 mol) in DMSO (10 ml), THF (10 ml), and ethyl cyclopentylacetate (7) (1.00g, 0.006 mol) in THF (3 ml). Purification by chromatography on silica with gradient ethyl acetate-hexane as eluant gave 1-benzenesulphonyl-3-cyclopentylpropan-2-one (13) (0.51g, 30% yield) as a white crystalline solid, m.p. 65-69°C (Found: C, 63.49; H, 7.09; S, 12.28. $C_{14}H_{18}O_3S$ requires C, 63.13; H, 6.81; S, 12.04%); ν_{max}(KBr) 1709 (CO), 1303, and 1140 cm^{-1} ($-SO_2-$); δ_H($CDCl_3$) 1.00-2.30(9H, brm, cyclopentyl), 2.62(2H, d, J = 6Hz, CH_2CO), 4.15(2H, s, CH_2SO_2), and 7.40-8.00(5H, m, Ar-*H*); δ_C($CDCl_3$) 24.88(t), 32.36(t), (2 x CH_2 of cyclopentyl ring), 34.83(d, *C*H), 50.68(t, CH_2CO), 66.86(t, CH_2SO_2), 128.32(d), 129.36(d), 134.30(d), 138.78(s), (Ar), and 198.04(s, *C*O).

1-Benzenesulphonylhex-5-en-2-one (48)

This was obtained using the procedure described for 1-benzenesulphonylhexan-2-one from sodium hydride (0.77g, 0.032 mol), methyl phenyl sulphone (5.00g, 0.032 mol), in DMSO (30 ml), THF (30 ml), and methyl pent-4-enoate (47) (1.50g, 0.013 mol) in THF (10 ml). Purification by chromatography on silica with gradient ethyl acetate-hexane as eluant gave 1-benzenesulphonylhex-5-en-2-one (48) (1.75g, 57.0% yield) as a clear oil (Found: C, 60.28; H, 5.94; S, 13.73. $C_{12}H_{14}O_3S$ requires C, 60.48; H, 5.92; S, 13.45%); ν_{max}(film) 1719 (CO), 1640 (C=C), 1323, and 1147 cm^{-1} ($-SO_2-$); δ_H($CDCl_3$) 2.00-2.50(2H, m, $CH_2CH=CH_2$), 2.60-3.10(2H, m, CH_2CO), 4.14(2H, s, CH_2SO_2), 4.70-5.20(2H, m, $CH_2=$), 5.40-6.10(1H, m, *C*H=), and 7.20-8.00(5H, m, Ar-*H*); δ_C($CDCl_3$) 27.03(t), 43.34(t), (CH_2CH_2), 66.60(t, CH_2SO_2), 115.72(t, $CH_2=$), 127.41(d), 129.36(d), 134.30(d), 136.25(d), 138.85(s), (Ar and *C*H=), and 197.45(s, *C*O).

Diazo Transfer[12]

1-Benzenesulphonyl-1-diazohexan-2-one (14)[10]

1-Benzenesulphonylhexan-2-one (10) (2.00g, 0.08 mol) in ethanol (10 ml) was stirred at 0°C under nitrogen while triethylamine (0.84g, 0.008 mol) followed by tosyl azide[13] (1.64g, 0.008 mol) were added. The reaction mixture was stirred for 2h and then concentrated at reduced pressure. The residue was dissolved in dichloromethane (10 ml) and washed with aqueous potassium hydroxide (0.51g, 0.009 mol, in 10 ml water). The organic layer was dried, filtered, and evaporated at reduced pressure to give the crude product. Purification by flash chromatography on silica with dichloromethane as eluant gave 1-benzenesulphonyl-1-diazohexan-2-one (14) (2.09g, 94.4% yield) as a yellow crystalline solid, m.p. 26-29°C (lit.,[10] 35-37°C) (Found: C, 54.28; H, 5.50; N, 9.52; S, 11.75. $C_{12}H_{14}N_2O_3S$ requires C, 54.12; H, 5.59; N, 10.52; S, 12.04%); ν_{max}(film) 2119(CN_2), 1666(CO), 1309, and 1162 cm^{-1} ($-SO_2-$); δ_H($CDCl_3$) 0.50-1.70(7H, m, $CH_3CH_2CH_2$), 2.40-2.70(2H, m, CH_2CO), and 7.20-8.00(5H, m, ArH); δ_C($CDCl_3$) 13.71(q, CH_3), 22.03(t, CH_3CH_2), 25.73(t, $CH_3CH_2CH_2$), 38.85(t, CH_2CO), 84.79(s, CN_2), 127.48(d), 129.56(d), 134.30(d), 142.03(s), (Ar), and 188.35(s, CO).

1-Methanesulphonyl-1-diazohexan-2-one (15)

This was obtained using the procedure described for 1-benzenesulphonyl-1-diazohexan-2-one from 1-methanesulphonylhexan-2-one (11) (2.02g, 0.011 mol), triethylamine (1.15g, 0.011 mol), and tosyl azide (2.23g, 0.011 mol) in ethanol (10 ml), as a pale yellow oil (2.12g, 91.5% yield)

(Found: C, 41.34; H, 5.95; N, 13.47; S, 16.13. $C_7H_{12}N_2O_3S$ requires C, 41.16; H, 5.92; N, 13.72; S, 15.70%); ν_{max}(film) 2110(CN_2), 1658(CO), 1325, 1177, and 1140 cm^{-1}(-SO_2-); δ_H($CDCl_3$) 0.80-1.90(7H, m, $CH_3CH_2CH_2$), 2.62(2H, t, CH_2CO), and 3.31(3H, s, CH_3SO_2); δ_C($CDCl_3$) 13.77(q, CH_3CH_2), 22.09(t, CH_3CH_2), 25.79(t, $CH_3CH_2CH_2$), 38.98(t, CH_2CO), 45.29(q, CH_3SO_2), and 188.94(s, CO). Diazo carbon not seen.

1-Benzenesulphonyl-1-diazo-5-phenylpentan-2-one (16)

This was obtained using the procedure described for 1-benzenesulphonyl-1-diazohexan-2-one from 1-benzenesulphonyl-5-phenylpentan-2-one (12) (0.99g, 0.003 mol), triethylamine (0.33g, 0.003 mol), and tosyl azide (0.645g, 0.003 mol) in ethanol (15 ml), as a yellow crystalline solid (1.00g, 93.3% yield), m.p. 75-83°C (decomp.) (Found: C, 61.91; H, 5.14; N, 8.36; S, 10.04. $C_{17}H_{16}N_2O_3S$ requires C, 62.17; H, 4.91; N, 8.53; S, 9.77%); ν_{max}(KBr) 2115(CN_2), 1673(CO), 1323, and 1153 cm^{-1} (-SO_2-); δ_H($CDCl_3$) 1.50-2.00(2H, m, $CH_2CH_2CH_2$), 2.20-2.70(4H, m, $CH_2CH_2CH_2$), and 6.90-8.00(10H, m, 2 x Ph); δ_C($CDCl_3$) 25.01(t), 34.70(t), 38.27(t), (3 x CH_2), 126.11, 127.28, 128.45, 129.49, 134.17 (5 x d, Ar), 140.93(s), 142.03(s), (Ar), and 188.17(s, CO). Diazo carbon not seen.

1-Benzenesulphonyl-1-diazo-3-cyclopentylpropan-2-one (17)[10]

This was obtained using the procedure described for 1-benzenesulphonyl-1-diazohexan-2-one from 1-benzenesulphonyl-3-cyclopentylpropan-2-one (13) (0.47g, 0.002 mol), triethylamine (0.18g, 0.002 mol), and tosyl azide (0.348g, 0.002 mol) in ethanol (30 ml), as a yellow oil (0.394g, 76.4% yield) (Found: C, 57.91; H, 5.49; N, 9.30; S, 11.33. $C_{14}H_{16}N_2O_3S$ requires C, 57.52; H, 5.52; N, 9.58; S, 10.97%);

ν_{max}(film) 2105(CN_2), 1658(CO), 1335, and 1150 cm^{-1} ($-SO_2-$); δ_H($CDCl_3$) 0.80-2.20(9H, m, cyclopentyl), 2.45-2.55(2H, brd, CH_2CO), and 7.50-8.10 (5H, m, Ar-*H*); δ_C($CDCl_3$) 24.88(t), 32.42(t), 35.61(d), (cyclopentyl), 45.16(t, CH_2CO), 127.41(d), 129.49(d), 134.17(d), 142.33(s), (Ar), and 188.29(s, *C*O). Diazo carbon not seen.

1-Benzenesulphonyl-1-diazohex-5-en-2-one (49)[10]

This was obtained using the procedure described for 1-benzenesulphonyl-1-diazohexan-2-one from 1-benzenesulphonylhex-5-en-2-one (48) (1.44g, 0.006 mol), triethylamine (0.611g, 0.006 mol), and tosyl azide (1.19g, 0.006 mol) in ethanol (10 ml), as a yellow oil (1.20g, 75.0% yield) (Found: C, 54.48; H, 4.85; N, 10.40; S, 12.44. $C_{12}H_{12}N_2O_3S$ requires C, 54.53; H, 4.58; N, 10.60; S, 12.13%); ν_{max}(film) 2108(CN_2), 1663(CO and C=C), 1333, and 1152 cm^{-1} ($-SO_2-$); δ_H($CDCl_3$) 2.20-3.00(4H, m, 2 x CH_2), 4.80-5.30(2H, m, CH_2=), 5.50-6.30(1H, m, =C*H*), and 7.40-8.30(5H, m, Ar-*H*); δ_C($CDCl_3$) 27.55(t), 38.27(t), (2 x CH_2), 115.91(t, CH_2=), 127.35(d), 129.56(d), 134.24(d), 136.06(d), 142.10(s), (Ar and *C*H=), and 187.65(s, *C*O). Diazo carbon not seen.

Methyl 2-diazo-3-oxoheptanoate (38)

This was obtained using the procedure described for 1-benzenesulphonyl-1-diazohexan-2-one from methyl 3-oxoheptanoate (37)[14] (1.00g, 0.006 mol), triethylamine (0.64g, 0.006 mol), and tosyl azide (1.25g, 0.006 mol) in ethanol (10 ml), as a yellow oil (1.16g, quantitative yield) (Found: C, 52.62; H, 6.56; N, 14.72. $C_8H_{12}N_2O_3$ requires C, 52.17; H, 6.57; N, 15.20%); ν_{max}(film) 2125(CN_2), 1718(CO ester), and 1650 cm^{-1} (CO ketone); δ_H($CDCl_3$) 0.80-1.80(7H, m, $CH_3CH_2CH_2$), 2.82(2H, t, CH_2CO), and

3.84(3H, s, OCH_3); $\delta_C(CDCl_3)$ 13.90(q, CH_3CH_2), 22.42(t, CH_3CH_2), 26.57(t, $CH_3CH_2CH_2$), 40.02(t, CH_2CO), 52.24(q, OCH_3), 167.57(s, CO ester), and 198.75(s, CO ketone). Diazo carbon not seen.

Bornyl 2-diazo-3-oxoheptanoate (42)

This was obtained using the procedure described for 1-benzenesulphonyl-1-diazohexan-2-one from bornyl 3-oxoheptanoate (41)[15] (1.68g, 0.006 mol), triethylamine (0.67g, 0.007 mol), and tosyl azide (1.31g, 0.007 mol) in ethanol (10 ml), as a yellow oil (1.84g, quantitative yield), $[\alpha]_D^{20}$ -14.73° (c 11.3 in CH_2Cl_2); (Found: C, 66.80; H, 8.65; N, 8.69. $C_{17}H_{26}N_2O_3$ requires C, 66.34; H, 8.55; N, 9.14%); ν_{max}(film) 2124(CN_2), 1710(CO ester), and 1657 cm^{-1} (CO ketone); $\delta_H(CDCl_3)$ 0.80-2.60(23H, m, contains singlets at 0.87 and 0.91 for bornyl CH_3 groups), 2.84(2H, t, J = 8Hz, CH_2CO), and 4.80-5.20(1H, m, CHOCO); $\delta_C(CDCl_3)$ 13.58, 13.90, 18.84, 19.75, 22.42, 26.51, 27.22, 28.07, 36.97, 40.02, 44.96, 47.95, 48.99, 81.48(d, CHOCO), 161.66(s, CO ester), and 192.84(s, CO ketone). Diazo carbon not seen.

3-Diazo-2,4-octanedione (44)

This was obtained using the procedure described for 1-benzenesulphonyl-1-diazohexan-2-one from 2,4-octanedione[16] (2.00g, 0.014 mol), triethylamine (1.42g, 0.014 mol), and tosyl azide (2.77g , 0.014 mol) in ethanol (8 ml) as a yellow oil (2.37g, quantitative yield) (Found: C, 57.20; H, 7.11; N, 16.47. $C_8H_{12}N_2O_2$ requires C, 57.14; H, 7.14; N, 16.67%); ν_{max}(film) 2111 (CN_2) and 1758 cm^{-1}(CO); $\delta_H(CDCl_3)$ 0.80-1.90(7H, m, $CH_2CH_2CH_3$), 2.40(3H, s, CH_3CO), and 2.73(2H, t, J = 7.2Hz, CH_2CH_2CO); δ_C ($CDCl_3$) 13.90(q, CH_3CH_2), 22.35(t, CH_3CH_2), 26.25(t, $CH_3CH_2CH_2$), 28.59(q,CH_3CO), 40.35(t, CH_2CO), 188.49, and 191.09(2 x s, 2 x CO). Diazo carbon not seen.

2-Benzenesulphonyl-3-methylcyclopentanone (27)[17]

1-Benzenesulphonyl-1-diazohexan-2-one (14) (0.10g, 3.76×10^{-4} mol) in dichloromethane (20 ml) was added dropwise over 20 min to refluxing dichloromethane (200 ml) containing the catalyst (0.5 mg approx.) while stirring under nitrogen. A second catalyst addition was made halfway through the diazoketone addition. Diazoketone decomposition was monitored by t.l.c. and was usually complete within 2h at reflux. Evaporation of the solvent at reduced pressure gave the crude product in quantitative yield. ^{1}H n.m.r. spectra were obtained at this stage to determine the diastereoisomeric ratio, which depended on the catalyst and reaction conditions. The crude product was dissolved in dichloromethane (20 ml), extracted rapidly into sodium hydroxide (1N; 3 x 10 ml), followed by immediate neutralisation with saturated ammonium chloride. The product was extracted into dichloromethane and dried. Evaporation of the solvent at reduced pressure gave the cyclopentanone (27) (0.078g, 87% yield) as a white crystalline solid, m.p. 124-126°C (from ether) (lit.,[17] 124-125°C) (Found: C, 60.78; H, 5.87; S, 13.05. $C_{12}H_{14}O_3S$ requires C, 60.48; H, 5.92; S, 13.46%); ν_{max}(KBr) 1738 (CO), 1297, and 1140 cm^{-1} ($-SO_2-$); δ_H($CDCl_3$) 1.27(3H, d, J = 7.2Hz, CH_3), 1.00-1.90(1H, m, one of CH_2CH_2CO), 2.00-2.60(3H, m, CH_2CO) and one of CH_2CH_2CO), 2.60-3.20(1H, m, $CHCH_3$), 3.32(1H, d, J = 7.8Hz, $CHSO_2$), and 7.40-8.00(5H, m, Ar-*H*). The crude product gave signals at δ_H($CDCl_3$) 1.52(d, J = 6.6Hz, CH_3) and 3.80(d, J = 8.4Hz, $CHSO_2$) indicating the presence of the second diastereoisomer. The ratio

was dependent on catalyst and reaction conditions; $\delta_C(CDCl_3)$ 20.73(q, CH_3), 28.78(t, CH_2CH_2CO), 33.53(d, $CHCH_3$), 38.98(t, CH_2CO), 75.89(d, $CHSO_2$), 129.17(d), 134.17(d), 138.26(s), (Ar), and 206.94(s, CO). Effects of catalyst, temperature, and solvent on the diastereoisomeric ratio of the crude product and the specific rotation of the pure material are shown in Tables 5.2, 5.6, and 5.7. A list of the catalysts used is given in Table 5.1.

Loss of cyclopentanone was observed due to decomposition in base; therefore the extraction time was minimised. The overall reaction yield was therefore more dependent on the extraction conditions than on the catalyst efficiency.

The optical activity of 2-benzenesulphonyl-3-methyl-cyclopentanone (27) was enhanced by careful recrystallisation from ether to give racemic crystals while the mother liquor when concentrated gave (27) with increased specific rotation compared to the material before recrystallisation. By repeated recrystallisation the specific rotation of a sample of (27) was increased from $[\alpha]_D^{20}$ -13.0° (c 16.9 in CH_2Cl_2) to -62.0° (c 10.4 in CH_2Cl_2). As the optical purity of the sample increased, the crystals obtained were no longer racemic but had diminished optical activity while the specific rotation of the mother liquor was enhanced accordingly. Also at high optical purities (27) was sticky and difficult to crystallise. These factors made further enhancement of optical activity very difficult.

2-Methanesulphonyl-3-methylcyclopentanone (28)

The procedure described for 2-benzenesulphonyl-3-methyl-cyclopentanone (27) was used with 1-methanesulphonyl-1-diazohexan-2-one (15) (0.10g, 4.90×10^{-4} mol) to give cyclopentanone (28) (0.056g, 65.4% yield) as a white crystalline solid, m.p. 52-54°C (Found: C, 48.27; H, 6.88; S, 17.83. $C_7H_{12}O_3S$ requires C, 47.71; H, 6.86; S, 18.19%); ν_{max}(KBr) 1738 (CO), 1293, and 1120 cm^{-1} ($-SO_2-$); $\delta_H(CDCl_3)$ 1.34(3H, d, J = 6.6Hz, CH_3CH), 1.20-1.80(1H, m, 1 of CH_2CH_2CO), 2.00-2.70(3H, m, CH_2CO and 1 of CH_2CH_2CO), 3.12(3H, s, SO_2CH_3), and 3.19(1H, d, J = 6.0Hz, $CHSO_2CH_3$). The crude product gave signals at $\delta_H(CDCl_3)$ 1.41(d, J = 6.6Hz, CH_3CH), 3.04(s, CH_3SO_2), and 3.70(d, J = 8.3Hz, $CHSO_2$) indicating the presence of the second diastereoisomer; $\delta_C(CDCl_3)$ 20.92(q, $CHCH_3$), 29.04(t, CH_2CH_2), 32.03(q, SO_2CH_3), 39.04(t, CH_2CO), 40.87(d, $CHCH_3$), 74.20(d, $CHSO_2$), and 208.50(s, CO). Table 5.3 shows the effects of catalyst and temperature on the reaction.

2-Benzenesulphonyl-3-phenylcyclopentanone (29)

The procedure described for 2-benzenesulphonyl-3-methyl-cyclopentanone (27) was used with 1-benzenesulphonyl-1-diazo-5-phenyl-pentan-2-one (16) (0.10g, 3.05×10^{-4} mol) to give cyclopentanone (29) (0.071g, 77.6% yield) as a white crystalline solid, m.p. 91-95°C (from ether) (Found: C, 67.85; H, 5.22; S, 10.63. $C_{17}H_{16}O_3S$ requires C, 67.98; H, 5.37; S, 10.67%); ν_{max}(KBr) 1743 (CO), 1305, and 1148 cm^{-1} ($-SO_2-$); $\delta_H(CDCl_3)$ 2.10-2.70(4H, m, 2 x CH_2), 3.80-4.20(2H, m, $CHPh$ and $CHSO_2$), and 6.90-8.00(10H, m, 2 x Ph); $\delta_C(CDCl_3)$ 29.56(t,

CH_2CH_2CO), 39.24(t, CH_2CO), 43.73(d, $CHPh$), 75.43(d, $CHSO_2$), 126.89(d), 127.28(d), 129.97(d), 134.11(d), 137.94(s), 141.64(s), (Ar), and 206.22(CO). Table 5.4 shows the effect of catalyst on the reaction.

2-Benzenesulphonylbicyclo[3.3.0]octan-3-one (30)[17]

The procedure described for 2-benzenesulphonyl-3-methyl-cyclopentanone (27) was used with 1-benzenesulphonyl-1-diazo-3-cyclopentylpropan-2-one (17) (0.10g, 3.42×10^{-4} mol) to give cyclopentanone (30) (0.083g, 92.1% yield) as a white crystalline solid, m.p. 100-103°C (from ether; lit.,[17] 104-105°C) (Found: C, 63.47; H, 6.26; S, 12.13. $C_{14}H_{16}O_3S$ requires C, 63.61; H, 6.10; S, 11.71%); ν_{max}(KBr) 1737 (CO), 1303, and 1144 cm^{-1} ($-SO_2-$); δ_H ($CDCl_3$, 270MHz) 1.29, 1.48(2 x 1H, 2 x m, C(7)H_2), 1.65(2H, m, C(6)H_2), 2.17(3H, m, C(8)H_2 and C(5)H), 2.84(2H, m, C(4)H_2), 3.39(1H, m, C(1)H), 3.49(1H, d, J = 5.4Hz, $CHSO_2$), and 7.50-8.00(5H, m, Ar-H). The crude product showed a signal at δ_H($CDCl_3$) 4.19(d, J = 10.2Hz, $CHSO_2$) indicating the presence of the second diastereoisomer; δ_C($CDCl_3$) 25.27(t), 33.46(t), ($C(6)H_2$, $C(7)H_2$, and $C(8)H_2$), 37.55(d, $C(5)H$), 41.71(d, $C(1)H$), 45.16(t, CH_2CO), 76.73(d, $CHSO_2$), 128.97(d), 129.17(d), 134.17(d), 137.81(s), (Ar), and 207.98(CO). Table 5.5 shows the effect of catalyst on the reaction.

2-Methylcarboxy-3-methylcyclopentanone (39)

The procedure described for 2-benzenesulphonyl-3-methyl-cyclopentanone was used with methyl 2-diazo-3-oxoheptanoate (38) (0.10g, 5.43×10^{-4} mol) to give cyclopentanone (39) (0.051g, 61.4%

yield) as a colourless oil (Found: C, 61.44; H, 7.80. $C_8H_{12}O_3$ requires C, 61.52; H, 7.75%); ν_{max}(film) 1749(CO ester) and 1718 cm^{-1} (CO ketone); $\delta_H(CDCl_3)$ 1.17(3H, d, J = 7.8Hz, CH_3CH), 1.00-1.70(1H, brm, 1 of CH_2CH_2CO), 2.10-2.80(5H, m, remaining cyclopentyl H's), and 3.76(3H, s, OCH_3). The crude product gave a signal at $\delta_H(CDCl_3)$ 3.74(s, OCH_3) indicating the presence of the second diastereoisomer; $\delta_C(CDCl_3)$ 19.23(q, CH_3), 29.37(t, CH_2CH_2CO), 36.39(d, $CHCH_3$), 38.72(t, CH_2CO), 52.30(d, $CHCO_2$), 62.96(q, OCH_3), 169.64(s, CO ester), and 211.74(CO, ketone).

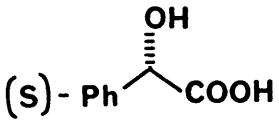
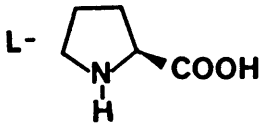
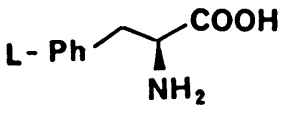
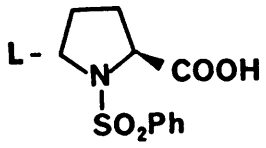
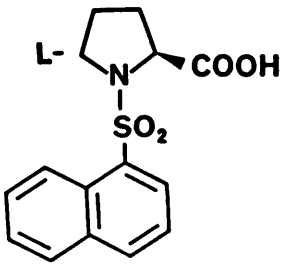
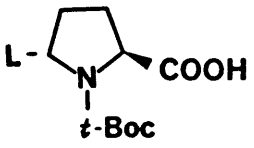
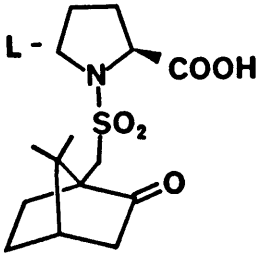
Only rhodium(II) mandelate was used as decomposition catalyst in this reaction resulting in a specific rotation for (39) of $[\alpha]_D^{20}$ -0.70° (c 10.4 in CH_2Cl_2).

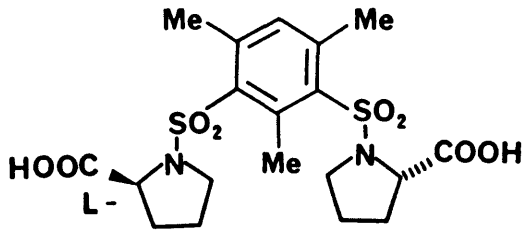
1-Benzenesulphonylbicyclo[3.1.0]hexan-2-one (50)[17]

The procedure described for 2-benzenesulphonyl-3-methyl-cyclopentanone (27) was used with 1-benzenesulphonyl-1-diazohex-5-en-2-one (49) (0.10g, 3.78 x 10^{-4} mol) with purification by p.l.c. on silica using 50% ethyl acetate, 50% hexane as eluant to give cyclopentanone (50) (0.086g, 96.6% yield) as a white crystalline solid, m.p. 96-98°C (from ether; lit.,[17] 96-97°C) (Found: C, 61.44; H, 5.28; S, 13.89. $C_{12}H_{12}O_3S$ requires C, 61.00; H, 5.12; S, 13.57%); ν_{max}(KBr) 1727(CO), 1319, 1308, and 1149 cm^{-1} ($-SO_2-$); $\delta_H(CDCl_3)$ 1.56(1H, t, J = 5.4Hz, one of C(6)H_2), 1.90-2.30(5H, m, one of C(6)H_2, C(3)H_2, and C(4)H_2), 2.90-3.10(1H, m, C(5)H), and 7.50-8.20(5H, m, Ar-H); $\delta_C(CDCl_3)$ 20.40(t, C(6)H_2 and C(4)H_2), 31.12(d, C(5)H), 33.66(t, C(3)H_2), 53.08(s, CSO_2Ph), 128.71(d), 128.91(d), 133.78(d), 139.43(s), (Ar), and

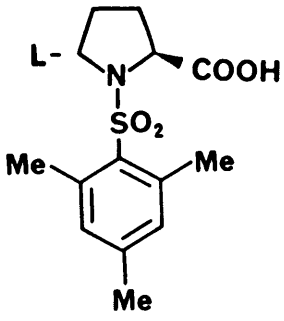
203.43(s, *C*O). Table 5.8 shows the effect of catalyst on the reaction. As reported for 2-benzenesulphonyl-3-methylcyclopentanone (27), this product (50) recrystallised racemically from ether. By repeated recrystallisation and concentration of the mother liquor the specific rotation of a sample of (50) was increased from $[\alpha]_D^{20}$ +1.8° (c 5.8 in CH_2Cl_2) to $[\alpha]_D^{20}$ +5.9° (c 5.0 in CH_2Cl_2). As with compound (27), as the optical purity increased (50) became less crystalline.

Table 5.1 : Rhodium(II) carboxylate catalysts employed in the intramolecular α-diazoketone cyclisations

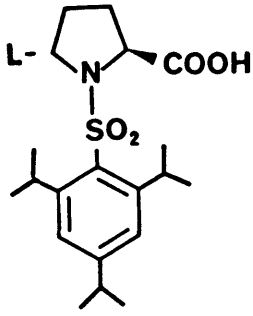
RCOOH	Catalyst
	1
	2
	3
	4
	5
	6
	7


Me
Me
SO2
SO2
HOOC
N
Me
N
COOH
L-

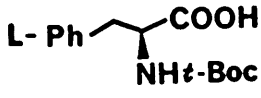
8


L-
N
COOH
SO2
Me
Me
Me

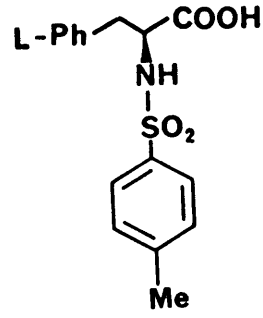
9


L-
N
COOH
SO2

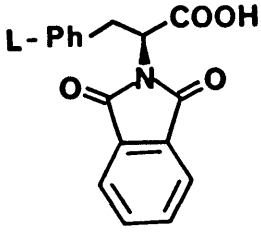
10


L-Ph
COOH
NHt-Boc

11


L-Ph
COOH
NH
SO2
Me

12


L-Ph
COOH
O
N
O

13

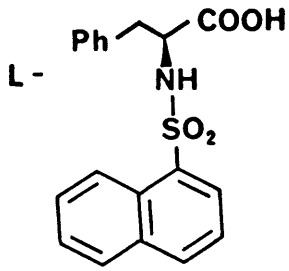
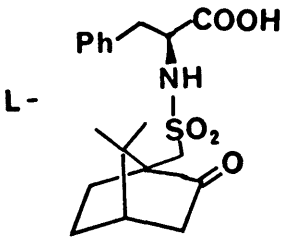
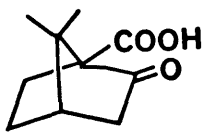
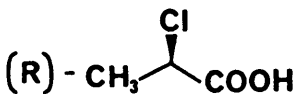
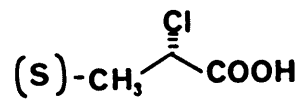
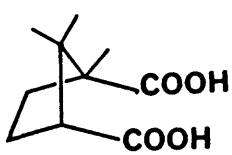
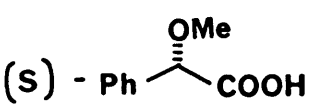
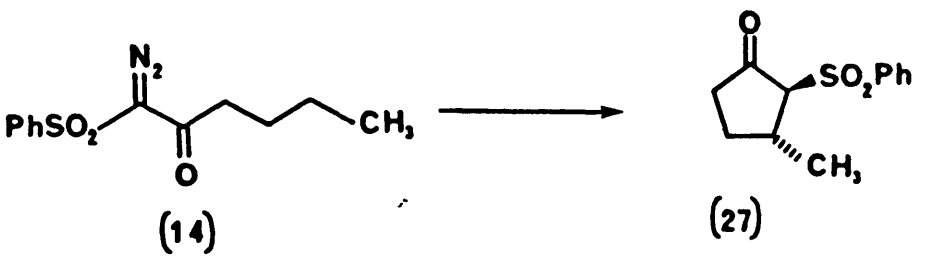
	14
	15
	16
	17
	18
Tartaric Acid	19
Lactic Acid	20
	21
	22
$Rh_2(mand)_2(phen)_2Cl_2.2H_2O$	23
$Rh_2(OAc)_2\ (Ph_2PC_6H_4)_2.2AcOH$	24
$Rh_2(OAc)_2\ (dppe)_2\ Cl_2$	25
$Rh_2(OAc)_2[(R)-(+)-BINAP]_2Cl_2$	26

Table 5.2

Decomposition of 1-benzenesulphonyl-1-diazohexan-2-one (14) with rhodium(II) carboxylates at reflux in dichloromethane



(14) (27)

Catalyst	Yield / %	Reaction time / h	*trans:cis* (crude)	$[\alpha]_D^{20}$ / °(c, CH_2Cl_2)
1	70-80	2	40:60	-16.1 (2.2)
2	-	-	-	-
3	-	-	-	-
4	90.0	2	30:70	-19.1 (20.8)
5	88.2	3	-	-4.6 (7.9)
6	57.5	2	80:20	-8.5 (5.2)
7	39.1	3	30:70	-6.9 (3.5)
8	86.8	1	50:50	+10.0 (7.8)
9	55.3	20	100:0	-0.7 (4.9)
10	-	-	-	-
11	66.5	3	40:60	-6.9 (5.0)
12	67.8	3	50:50	+0.2 (6.1)
13	57.0	2	15:85	-0.6 (5.1)

Table 5.2 contd.

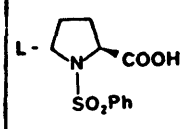
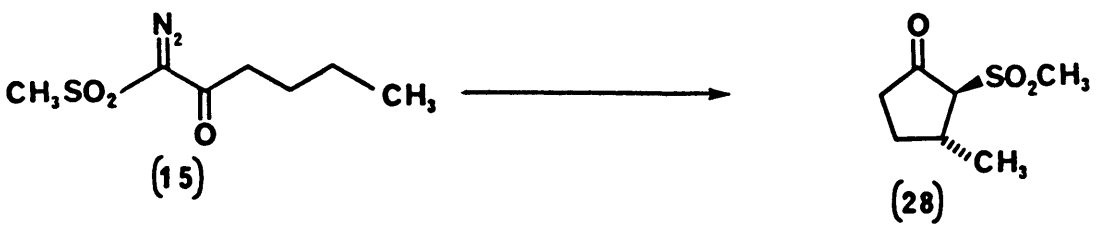
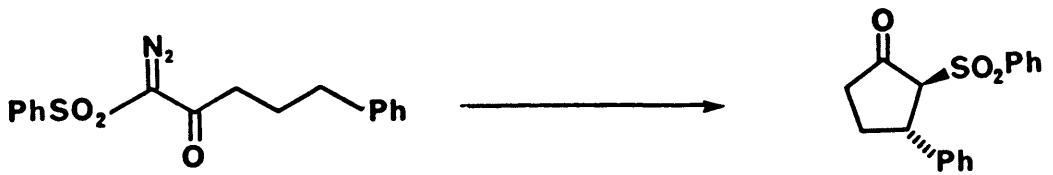
14	59.7	4	100:0	-0.7 (5.3)
15	44.5	3	-	+1.2 (4.0)
16	53.7	2	90:10	-4.5 (4.8)
17	65.6	2	-	-3.0 (5.9)
18	50.3	2	-	+3.3 (4.5)
19	-	-	-	-
20	74.5	10	70:30	+3.3 (6.7)
21	65.0	3	80:20	+0.1 (5.8)
22	22.6	2	40:60	-2.7 (3.0)
23	-	-	-	-
24	only partial decomposition	-	-	-
25	61.6	3	-	-
26	57.3	8	100:0	-0.2 (5.2)
$Rh_2(OAc)_4$ (1 mg) +  (25mg)	43.8	1.5	80:20	Racemic

Table 5.3 : Decomposition of 1-methanesulphonyl-1-diazohexan-2-one (15) with rhodium(II) carboxylates



Catalyst	Temperature / °C	Yield / %	Reaction time / h	*trans:cis* (crude)	$[\alpha]_D^{20}$ / °(c, CH_2Cl_2)
$Rh_2(OAc)_4$	20	58.0	0.3	100:0	0
$Rh_2(O_2CCF_3)_4$	20	78.1	18	100:0	0
1	20	Only partial decomposition	26	100:0	-
1	40	89.6	2	70:30	+3.8 (8.1)

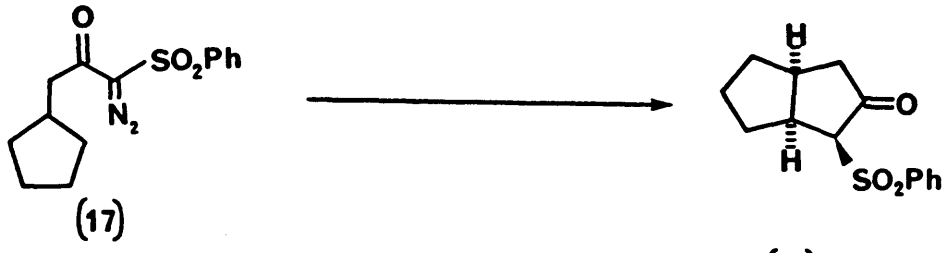
Table 5.4 : Decomposition of 1-benzenesulphonyl-1-diazo-5-phenylpentan-2-one (16) with rhodium(II) carboxylates at reflux in dichloromethane.



(16) (29)

Catalyst	Yield / %	Reaction time / h	*trans:cis* (crude)	$[\alpha]_D^{20}$ / ^{o}(c, CH_2Cl_2)
1	77.6	1	Not resolved on ^1H n.m.r.	-0.9 (7.1)
4	45.2	1	"	-3.1 (4.1)
5	49.0	2	"	-1.6 (4.5)

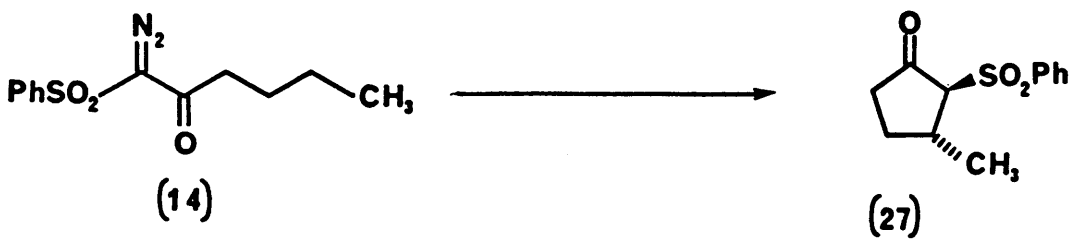
Table 5.5 : Decomposition of 1-benzenesulphonyl-1-diazo-3-cyclopentylpropan-2-one (17) with rhodium(II) carboxylates at reflux in dichloromethane.



(17) (30)

Catalyst	Yield / %	Reaction time / h	*trans:cis* (crude)	$[\alpha]_D^{20}$ / °(c, CH_2Cl_2)
1	80.9	0.6	70:30	+7.4 (4.4)
4	51.6	2.5	80:20	+0.4 (2.8)

Table 5.6 : Effect of temperature on the decomposition of 1-benzenesulphonyl-1-diazohexan-2-one (14)



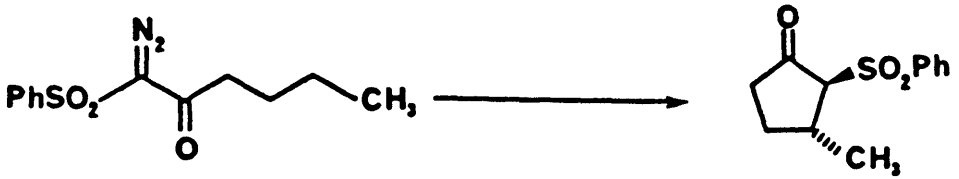
(14) (27)

Temperature / °C	Yield / %	Extent of reaction[a] / %	Reaction time / h	*trans:cis* (crude)	$[\alpha]_D^{20}$ / °(c, CH_2Cl_2)
20	26.9	60	36	100:0	-8.6 (4.8)
40	53.1	100	1.5	40:60	-10.2 (4.0)

[a] Estimated from ^1H n.m.r. spectrum of crude product.

Identical samples of $Rh_2(mand)_4.2EtOH$ were used in each reaction.

Table 5.7 : Effect of solvent on the decomposition of 1-benzenesulphonyl-1-diazohexan-2-one (14)



(14) (27)

Solvent	b.p. °C	Yield %	Reaction time h	*trans:cis* (crude)	$[\alpha]_D^{20}$ °(c, CH_2Cl_2)
Hexane	69	32.4	3	-	-7.1 (2.9)
Ether	34	24.0	4	-	-5.6 (2.2)
Carbon tetrachloride	77	36.8	1	50:50	-5.1 (3.3)
Dichloromethane	40	41.7	1	40:60	-10.4 (3.7)
Benzene	80	45.6	1.5	50:50	-5.9 (4.1)
1,2-Dichloroethane	84	58.9	2	60:40	-5.8 (5.3)

Identical samples of $Rh_2(mand)_4.2EtOH$ were used in each reaction.

Table 5.8 : Decomposition of 1-benzenesulphonyl-1-diazohex-5-en-2-one (49) under rhodium(II) carboxylate catalysis at reflux in dichloromethane.



(49) (50)

Catalyst	Reaction Time / h	Yield / %	$[\alpha]_D^{20}$ / °(c, CH_2Cl_2)
1	0.5	96.6	+1.5 (8.6)
4	1.5	79.0	+0.5 (5.7)
5	2.0	68.5	+1.8 (5.8)

3-Methylcyclopentanone (34)[18,19]

2-Benzenesulphonyl-3-methylcyclopentanone (27), $[\alpha]_D^{20}$ -49.9° (c 7.1 in CH_2Cl_2), (1.00g, 4.20 mmol) in THF and water (6 ml and 53 ml respectively) was stirred under nitrogen while aluminium amalgam,[20] freshly prepared from aluminium foil (3.40g, 0.126 mol), was added. The reaction mixture was stirred under nitrogen at 65°C for 2h, cooled, and filtered through celite which was washed thoroughly with ether. The layers were separated and the aqueous layer washed with ether (2 x 20 ml). The combined organic extracts were dried and the solvent evaporated. Distillation in a Kugelrohr apparatus [oven temperature 140-150°C (lit.,[20a] b.p. 144°C)] gave 3-methylcyclopentanone (34) (0.148g, 36.0% yield) as an oil, $[\alpha]_D^{20}$ -43.4° (c 6.7 in MeOH) {lit.,[18,20] $[\alpha]_D^{20}$ +148° (c 4.5 in MeOH); $[\alpha]_D^{20}$ +154.8° (c 0.6 in MeOH), $[\alpha]_D^{20}$ +143.7° (undil.)}, 29.3% e.e.; n_D^{20} = 1.4331 [lit.,[20a] 1.4340(d), 1.4329(dl)]; ν_{max}(film) 1745 cm^{-1} (lit.,[18c] 1750 cm^{-1}); $\delta_H(CDCl_3)$ 1.12(3H, d, *J* = 5.4Hz, CH_3) and 0.80-2.60(7H, m, cyclopentyl *H*'s), [lit.,[18] 1.13 (d, *J* = 6Hz)].

2-Benzenesulphonyl-3-methylcyclopentanol (31)

2-Benzenesulphonyl-3-methylcyclopentanone (27) (1.74g, 7.30 mmol) in methanol (30 ml) and benzene (90 ml) was stirred at 0°C under nitrogen while sodium borohydride (0.522g, 13.80 mmol) was added portionwise over 20 min. The reaction mixture, which was semisolid at 0°C, was allowed to return slowly to room temperature and was stirred for 12h. The mixture was poured onto saturated aqueous ammonium chloride (50 ml), extracted with ethyl acetate (3 x 70 ml), dried, filtered, and concentrated

at reduced pressure. Purification by passage through a short column of silica using 50% ethyl acetate, 50% hexane as eluant gave the alcohol (31) (1.77g, quantitative yield) as a white crystalline solid, m.p. 82-83°C (from ether) (Found: C, 60.30; H, 6.47; S, 13.62. $C_{12}H_{16}O_3S$ requires C, 59.97; H, 6.71; S, 13.34%); ν_{max}(KBr) 3520 (OH), 1320, and 1148 cm^{-1} ($-SO_2-$); δ_H($CDCl_3$, 270MHz) 1.12(3H, d, J = 8.1Hz, CH_3), 1.35(1H, m, one of C(4)H_2), 1.77(2H, m, C(5)H_2), 2.30(1H, m, one of C(4)H_2), 2.97(1H, dd, J_1= 10.8Hz, J_2= 4.5Hz, $CHSO_2$), 3.50(1H, brs, OH), 4.32(1H, dd, J_1= 7.5Hz, J_2= 4.5Hz, $CHOH$), and 7.40-8.00(5H, m, Ar-H); δ_C($CDCl_3$) 21.18(q, CH_3), 31.51, 32.75, 33.14, ($CHCH_3$ and CH_2CH_2), 73.81(d), 74.27(d), ($CHOH$ and $CHSO_2$), 128.26(d), 129.36(d), 133.91(d), and 139.89(s) (Ar). Both the ^1H and ^{13}C n.m.r. spectra indicated the presence of only one stereoisomer of the alcohol although a minor signal at δ_H ($CDCl_3$) 0.92(d) was visible in the 270MHz ^1H n.m.r. which may have been due to the second diastereoisomer present at < 5% by integration.

The alcohol (31) prepared from cyclopentanone (27) with a specific rotation of $[\alpha]_D^{20}$ -62.0° (c 10.4 in CH_2Cl_2), 36% e.e., had a specific rotation of $[\alpha]_D^{20}$ +16.0° (c 19.6 in CH_2Cl_2). Its specific rotation was enhanced by recrystallisation as described for compounds (27) and (50), i.e. the alcohol crystallised from ether as racemic crystals with enhancement of the optical activity of the material in the mother liquor. By repeated careful recrystallisation a sample of the alcohol (31) was obtained with a specific rotation of $[\alpha]_D^{20}$ +22.4° (c 25.5 in CH_2Cl_2). Chiral shift ^1H n.m.r. studies at 270MHz with Eu(tfc)$_3$ as chiral shift reagent showed 60% e.e., i.e. 80:20 enantiomeric ratio, in this alcohol sample.

Oxidation of 2-benzenesulphonyl-3-methylcyclopentanol (31) to 2-benzenesulphonyl-3-methylcyclopentanone (27)

Jones' reagent[21] was prepared using chromium(VI) oxide (5.34g, 0.053 mol) and conc. sulphuric acid (4.6 ml) in aqueous solution (50 ml). Alcohol (31) (0.416g, 1.73 mmol) in acetone (20 ml) was stirred at 0°C under nitrogen while Jones' reagent (5 ml) was added dropwise. Stirring was continued for 20 min, then sodium carbonate (2g) was added. The mixture was stirred for 30 min, filtered through celite and the solvent evaporated at reduced pressure. The crude product was dissolved in dichloromethane (20 ml), extracted with aqueous sodium hydroxide (1N; 3 x 10 ml), acidified with saturated aqueous ammonium chloride, and extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried and concentrated at reduced pressure to give the cyclopentanone (27) (0.142g, 34.5% yield) as a white crystalline solid as before.

The specific rotation of the alcohol (31) prior to oxidation was $[\alpha]_D^{20}$ +22.4° (c 25.5 in CH_2Cl_2). The specific rotation of the cyclopentanone (27) was $[\alpha]_D^{20}$ -81.3° (c 14.2 in CH_2Cl_2). Comparison with the desulphonylation data estimated 50% e.e. for this sample.

1-Benzenesulphonyl-2-methylcyclopentane (35)

2-Benzenesulphonyl-3-methylcyclopentanone (27) (0.60g, 2.52 mmol) in THF (20 ml) was stirred under nitrogen while lithium aluminium hydride (0.30g, 7.91 mmol) was added giving vigorous hydrogen evolution. The reaction mixture was refluxed for 3h, then cooled, and saturated ammonium chloride (20 ml) was added. The reaction mixture was filtered

through celite and the solvent was evaporated at reduced pressure. The residue was shaken in dichloromethane (20 ml) and water (20 ml), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 20 ml) and the combined organic extracts were dried, filtered, and concentrated at reduced pressure. P.l.c. on silica with 20% ethyl acetate 80% hexane as eluant gave the sulphone (35) (0.435g, 77.0% yield) as a waxy solid, m.p. 25°C approx. (Found: C, 64.55; H, 7.31; S, 14.69. $C_{12}H_{16}O_2S$ requires C, 64.25; H, 7.19; S, 14.29%); ν_{max}(film) 1450, 1300, and 1150 cm^{-1} ($-SO_2-$); $\delta_H(CDCl_3)$ 0.96(3H, d, J = 7.2Hz, CH_3), 1.00-2.00(6H, m, 3 x CH_2), 2.00-2.70(1H, m, $CHCH_3$), 2.85-3.20(1H, m, $CHSO_2$), and 7.20-8.00(5H, m, Ar-H). $\delta_C(CDCl_3)$ 20.66(q, CH_3), 24.82(t, $C(3)H_2$ and $C(4)H_2$), 35.48, 35.94(t and d, $C(5)H_2$ and $CHCH_3$), 70.76(d, $CHSO_2$), 128.52(d), 129.23(d), 133.52(d), and 138.98(s), (Ar). Both the ^1H and ^{13}C n.m.r. spectra indicated the presence of only one stereoisomer.

The sample of 2-benzenesulphonyl-3-methylcyclopentanone (27) used had a specific rotation of $[\alpha]_D^{20}$ -10.5° (c 33.0 in CH_2Cl_2). This gave the cyclopentane (35) with a specific rotation of $[\alpha]_D^{20}$ +2.5° (c 18.6 in CH_2Cl_2).

2-Methylcarboxy-3-methylcyclopentanol (40)

β-Keto ester (39) (0.10g, 0.64 mmol) in methanol (3 ml) and benzene (9 ml) was stirred at 0°C under nitrogen giving a semisolid reaction mixture. Sodium borohydride (0.025g, 0.66 mmol) was added portionwise over 5 min, then the reaction mixture was stirred at 0°C for 50 min. Water (10 ml) was added, followed by hydrochloric acid (5%; 10 ml) to

adjust the pH to 1. The layers were separated and the aqueous layer extracted with ether (3 x 15 ml). The combined organic extracts were washed with water (15 ml), dried, and concentrated at reduced pressure to give the alcohol (40) (0.076g, 75% yield) as an oil; ν_{max}(film), 3420 (OH) and 1722 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.08(3H, d, J = 6Hz, CH_3CH), 1.10-2.40(7H, m, 2 x CH_2, $CHCH_3$, CHCO, and OH), 3.74(3H, s, OCH_3), and 4.10-4.40(1H, m, CHOH). $Eu(tfc)_3$ chiral shift ^1H n.m.r. spectra gave splitting of the singlet at δ 3.74 which showed an approximately 1:1 ratio of diastereoisomers at C-1 and very low % e.e. (<10%). The β-keto ester (39) prior to reduction had a specific rotation of $[\alpha]_D^{20}$ -0.70° (c 10.4 in CH_2Cl_2); the alcohol (40) had a specific rotation of $[\alpha]_D^{20}$ +0.20° (c 7.6 in CH_2Cl_2).

2-Benzenesulphonyl-3-methylcyclopentyl tosylate (33)

2-Benzenesulphonyl-3-methylcyclopentanol (31) $[\alpha]_D^{20}$ +5.4° (c 10.3 in CH_2Cl_2), (0.079g, 0.33 mmol) in pyridine (5 ml) at 0°C was treated with tosyl chloride (0.50g, 2.60 mmol), then refrigerated for 72h, poured onto ice (30g), and extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and concentrated at reduced pressure to a white solid. P.l.c. on silica with 40% ethyl acetate, 60% hexane as eluant gave the tosylate (33) (0.036g, 27.8% yield) as white needles, m.p. 159-161°C (from ether); $[\alpha]_D^{20}$ +3.1° (c 3.6 in CH_2Cl_2) (before recrystallisation); (Found: C, 57.03; H, 5.65; S, 16.19. $C_{19}H_{22}O_5S_2$ requires C, 57.84; H, 5.62; S, 16.25%); ν_{max}(KBr) 1308 and 1151 cm^{-1} ($-SO_2-$ and $-SO_3-$); $\delta_H(CDCl_3)$ 1.05(3H, d, J = 6Hz, CH_3CH), 1.00-2.30(4H, brm, CH_2CH_2), 2.43(3H, s, CH_3-Ar), 2.50-3.00(1H, m, $CHCH_3$), 3.17(1H, dd, J_1= 8.1Hz, J_2= 5.1Hz, $CHSO_2$),

5.11(1H, m, C*H*OTs), and 7.20-8.00(9H, m, Ar-*H*); $\delta_C(CDCl_3)$ 20.99(q), 21.70(q), (2 x CH_3), 30.47, 30.99, 33.20(2 x t for CH_2CH_2 and d for $CHCH_3$), 73.10(d, $CHSO_2$), 81.74(d, *C*HOTs), 128.06(d), 129.04(d and s), 129.75(d), 133.65(d), 139.56(s), and 144.95(s), (Ar). Both the ^1H and ^{13}C n.m.r. spectra indicated the presence of only one stereoisomer of the tosylate. Recrystallisation of the tosylate (33) from ether gave crystals with reduced optical rotation compared to the material before recrystallisation while the material in the mother liquor had enhanced specific rotation. However, the effect was much smaller with this compound than with compounds (27), (31), and (50).

2-Diazodimedone (52)[22]

Dimedone (1g, 7.13 x 10^{-3} mol) was stirred in ethanol (15 ml) at 0°C under nitrogen while triethylamine (0.722g, 0.99 ml, 7.13 x 10^{-3} mol) was added followed by tosyl azide (1.41g, 7.14 x 10^{-3} mol). Stirring was continued for 2h while returning slowly to room temperature. The ethanol was removed at reduced pressure and the residue was dissolved in dichloromethane (30 ml), washed with aqueous potassium hydroxide (0.40g, 7.13 x 10^{-3} mol, in 20 ml water), dried, and concentrated at reduced pressure, then purified by passage through a short column of silica with dichloromethane as eluant to give diazoketone (52) (1.25g, quantitative yield) as a very pale yellow crystalline solid, m.p. 99-101°C (106° C decomp.) (Found: C, 57.59; H, 6.05; N, 16.45. $C_8H_{10}N_2O_2$ requires C, 57.82; H, 6.07; N, 16.93%); ν_{max}(KBr) 2180, 2138 (C=N_2), and 1628 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.09(6H, s, 2 x C*H*$_3$) and 2.43(4H, s, 2 x C*H*$_2$); $\delta_C(CDCl_3)$ 28.26(q, 2 x CH_3), 31.06(s, CMe_2), 50.42(t, 2 x CH_2), 83.43(s, CN_2), and 189.85(s, *C*O).

Cyclopropanation of 2-diazodimedone with styrene[22]

2-Diazodimedone (0.10g, 6.02×10^{-4} mol) in styrene (3 ml) with rhodium mandelate (0.5 mg) was heated at 64°C for 2h while stirring under nitrogen. The product was applied to a short column of silica and eluted with hexane until all the styrene had been collected. The remaining material was washed from the silica using ethyl acetate as eluant. Concentration at reduced pressure gave the crude product which was purified by p.l.c. on silica with dichloromethane as eluant to give the cyclopropane (53) (0.058g, 40% yield) as a solid; $[\alpha]_D^{20}$ -1.6° (c 5.7 in CH_2Cl_2); ν_{max}(KBr) 1669 and 1694 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.00, 1.11(6H, 2 x s, 2 x CH_3), 2.21,2.53(4H, 2 x brs, 2 x CH_2), 2.35, 3.20, 4.02(3H, 3 x m, cyclopropyl-*H*'s), and 7.20(5H, s, Ar-*H*).

5.2 INTRAMOLECULAR ADDITION TO AROMATICS

3-Phenylpropanoyl chloride (15)[23]

3-Phenylpropanoic acid (30g, 0.20 mol) in freshly distilled thionyl chloride (27 ml) was refluxed for 3h while stirring under nitrogen. Excess thionyl chloride was evaporated at reduced pressure. Distillation gave the acid chloride (15) (31.42g, 93.3% yield) as an oil, b.p. 60-62°C at 0.05 mmHg (Found: C, 64.35; H, 5.36; Cl, 20.79. C_9H_9OCl requires C, 64.10; H, 5.38; Cl, 21.03%); ν_{max}(film) 1794 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.60-2.90(4H, sym m, CH_2CH_2) and 6.90-7.20(5H, m, Ar-*H*); $\delta_C(CDCl_3)$ 30.99(t), 48.47(t), (2 x CH_2), 126.89(d), 128.39(d), 128.78(d), 138.72(s), (Ar), and 173.02(s, *C*O). The spectral characteristics were in agreement with the reported values.[23]

P-Acetoxycinnamic acid (17)[23,24]

p-Hydroxybenzaldehyde (9.58g, 0.078 mol), potassium acetate (18.19g, 0.185 mol; freshly fused) and acetic anhydride (23 ml; freshly distilled) were refluxed while stirring under nitrogen for 8h. The hot reaction mixture was poured into hot water (200 ml) and the crude product was collected by filtration. Recrystallisation from ethanol with charcoal treatment gave *p*-acetoxycinnamic acid (4.50g, 28% yield) as pale yellow crystals, m.p. 192-195°C (lit.,[23,24] 195°C) (Found: C, 64.22; H, 4.93; $C_{11}H_{10}O_4$ requires C, 64.07; H, 4.89%); ν_{max}(KBr) 3280-2200 (2955 max., COOH), 1744 (CO ester), 1674 (α,β-unsaturated, COOH), and 1628 cm^{-1} (C=C of α,β-unsaturated acid); $\delta_H(CDCl_3$ and DMSO-d_6) 2.27(3H, s, CH_3), 6.35(1H, d, *J* = 15.6Hz, C=C*H*COOH), 7.58(1H, d, *J* = 15.6Hz, Ar-C*H*=C), and 7.00-7.60(4H, ABq, Ar-*H*). The spectral characteristics were in agreement with the reported values.[23]

3-(p-Acetoxyphenyl)propanoic acid (18)[23]

p-Acetoxycinnamic acid (17) (9.03g, 0.049 mol) in ethanol (150 ml) with 10% palladium on charcoal catalyst (0.50g) was hydrogenated at 40 p.s.i. hydrogen for 16h, filtered through celite, and concentrated at reduced pressure to give the acid (18) (9.03g, 99% yield) as a pale yellow crystalline solid which resisted all attempts at recrystallisation, m.p. 75-85°C (lit.,[23] 85-87°C) (Found: C, 64.07; H, 5.72. $C_{11}H_{12}O_4$ requires C, 63.45; H, 5.81%); ν_{max}(KBr) 3500-2300 (max. 2930, COOH) and 1700 cm^{-1} (br, CO ester and acid); $\delta_H(CDCl_3)$ 2.23(3H, s, CH_3), 2.50-3.00(4H, sym m, CH_2CH_2), 6.80-7.30(4H, ABq, Ar-*H*), and 9.58(1H, brs, COO*H*). The spectral characteristics were in agreement with the reported values.[23]

3-(p-Acetoxyphenyl)propanoyl chloride (19)[23]

3-(*p*-Acetoxyphenyl)propanoic acid (18) (2.10g, 0.010 mol) in ether (40 ml) was stirred under nitrogen while oxalyl chloride (1.31g, 0.0102 mol) was added. Stirring was continued for 17h giving complete dissolution of the initially insoluble acid. Concentration at reduced pressure gave the acid chloride (19) (2.17g, 95% yield) as an oil which was used without purification; ν_{max}(film) 1790(CO acid chloride) and 1752 cm^{-1} (CO ester); $\delta_H(CDCl_3)$ 2.22(3H, s, CH_3), 2.70-3.20(4H, sym m, CH_2CH_2), and 6.80-7.20(4H, ABq, Ar-*H*). The spectral characteristics were in agreement with the reported values.[23]

Preparation of α-diazoketones

1-Diazo-4-phenylbutan-2-one (1)[23]

3-Phenylpropanoyl chloride (1.50g, 8.90 mmol) in ether (20 ml) was added dropwise over 20 min to a freshly prepared and distilled solution of diazomethane[6] (1.50g, 35.70 mmol) in ether (70 ml) while stirring at 0°C under nitrogen. Stirring was continued for 18h allowing the reaction mixture to return slowly to room temperature. Excess diazomethane and ether were evaporated at reduced pressure. Purification by chromatography on silica using 30% ethyl acetate, 70% hexane as eluant gave the α-diazoketone (1) (1.51g, 97.4% yield) as a yellow oil (Found: C, 69.59; H, 6.03; N, 16.25. $C_{10}H_{10}N_2O$ requires C, 68.95; H, 5.79; N, 16.08%); ν_{max}(film) 2088(CN_2) and 1634 cm^{-1} (CO); δ_H($CDCl_3$) 2.40-3.10(4H, sym m, CH_2CH_2), 5.13(1H, s, CHN_2), and 7.16(5H, s, Ar-*H*); δ_C($CDCl_3$) 30.93(t), 42.04(t), (CH_2CH_2), 54.77(d, CHN_2), 126.31(d), 128.39(d), 128.58(d), 140.67(s), (Ar), and 194.01(s, *C*O). The spectral characteristics were in agreement with the reported values.[23]

1-Diazo-4-(p-acetoxyphenyl)butan-2-one (9)[23]

The procedure described for 1-diazo-4-phenylbutan-2-one (1) was used with 3-(*p*-acetoxyphenyl)propanoyl chloride (1.50g, 6.62 mmol) in ether (30 ml) and diazomethane (1.50g, 35.70 mmol) in ether (70 ml). Purification by chromatography on silica with gradient ethyl acetate-hexane as eluant gave the α-diazoketone (9) (1.28g, 83% yield) as a yellow crystalline solid, m.p. 95-101°C (decomp.) (Found: C, 62.11; H, 5.20; N, 11.84. $C_{12}H_{12}N_2O_3$ requires C, 62.06; H, 5.21; N, 12.07%);

ν_{max}(KBr) 2055 (CN_2), 1749 (CO ester), and 1632 cm^{-1} (CO diazoketone); δ_H($CDCl_3$) 2.24(3H, s, CH_3), 2.30-3.00(4H, sym m, CH_2CH_2), 5.18(1H, s, CHN_2), and 6.80-7.20(4H, ABq, Ar-*H*); δ_C($CDCl_3$) 21.12(q, CH_3), 30.21(t), 41.91(t), (2 x CH_2), 54.77(d, CHN_2), 121.63(d), 129.36(d), 138.33(s), 149.18(s), (Ar), 169.58(s, *C*O ester) and 193.75(s, *C*O diazoketone). The spectral characteristics were in agreement with the reported values.[23]

2-Diazo-5-phenylpentan-3-one (8)[25]

3-Phenylpropanoyl chloride (3.124g, 0.019 mol) in ether (15 ml) was added dropwise over 20 min to a freshly prepared and distilled solution of diazoethane[26] (4.65g, 0.083 mol) in ether (80 ml) while stirring at -29°C (nitromethane- liquid nitrogen slush bath) under nitrogen. Stirring was continued for 16h allowing the reaction mixture to return slowly to room temperature. Excess diazoethane and ether were evaporated at reduced pressure. Purification by chromatography on silica using gradient ethyl acetate-hexane as eluant gave the α-diazoketone (8) (2.82g, 81% yield) as a yellow oil (Found: C, 70.49; H, 6.60. $C_{11}H_{12}N_2O$ requires C, 70.19; H, 6.43%); ν_{max}(film) 2065 (CN_2) and 1642 cm^{-1} (CO); δ_H($CDCl_3$) 1.79(3H, s, CH_3CN_2), 2.50-3.00(4H, sym m, CH_2CH_2), and 7.31(5H, s, Ar-*H*); δ_C($CDCl_3$) 8.06(q, CH_3), 30.67(t), 39.49(t), (CH_2CH_2), 62.18(s, CN_2), 126.18(d), 128.39(d), 140.86(s), (Ar), and 193.36(s, *C*O). The spectral characteristics were in agreement with the reported values.[25]

2-Diazo-5-(p-acetoxyphenyl)pentan-3-one (10)

The procedure described for 2-diazo-5-phenylpentan-3-one (8) was used with 3-(*p*-acetoxyphenyl)propanoyl chloride (3.26g, 0.014 mol) in ether (20 ml) and diazoethane (3.63g, 0.065 mol) in ether (70 ml). Purification by chromatography on silica using gradient ethyl acetate-hexane as eluant gave the α-diazoketone (10) (1.77g, 50% yield) as an orange oil; ν_{max}(film) 2038 (CN_2), 1735 (CO ester) and 1612 cm^{-1} (CO diazoketone); $\delta_H(CDCl_3)$ 1.92(3H, s, CN_2CH_3), 3.19(3H, s, CH_3CO), 2.60-3.10(4H, sym m, CH_2CH_2), and 6.80-7.30(4H, ABq, Ar-*H*); $\delta_C(CDCl_3)$ 8.19(q, CH_3CN_2), 21.12(q, CH_3CO), 30.08(t), 39.44(t), (CH_2CH_2), 53.09(s, CN_2), 121.63(d), 129.43(d), 138.46(s), 149.18(s), (Ar), 169.51(s, *C*O ester) and 196.93(s, *C*O diazoketone).

Intramolecular addition to aromatics

2,3 -Dihydro-1(8aH)-azulenone (2)

1-Diazo-4-phenylbutan-2-one (1) (0.10g, 5.74×10^{-4} mol) in dichloromethane (20 ml) was added dropwise over 30 min to a refluxing solution of the catalyst (0.5mg) in dichloromethane (200 ml) while stirring under nitrogen. A second catalyst addition (0.5mg) was made halfway through the α-diazoketone addition. Reflux was continued for 1h then the solvent was evaporated at reduced pressure to give 2,3-dihydro-1(8a*H*)-azulenone (2) (0.084g, quantitative yield) as an oil; ν_{max}(film) 1742 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.30-3.10(5H, m, CH_2CH_2, and C(8a)H), 5.06(1H, dd, J_1 = 8.4Hz, J_2 = 3.4Hz, C(8)*H*), 5.90-6.50(4H, m, C(4)*H*, C(5)*H*, C(6)*H*, and C(7)*H*, and 7.20(s, dimer impurity).

The spectral characteristics were in agreement with the reported values.[23,27] Table 5.9 shows the effect of catalyst on the reaction.

2,3-Dihydro-1(8a-methyl)-azulenone (11)[25]

The procedure described for 2,3-dihydro-1(8a*H*)-azulenone (2) was used with 2-diazo-5-phenylpentan-3-one (8) (0.10g, 5.31×10^{-4} mol) to give 2,3-dihydro-1(8a-methyl)-azulenone (11) (0.085g, quantitative yield) as an oil. An analytical sample was isolated by p.l.c. on silica using dichloromethane as eluant. (Found: C, 82.35; H, 7.86. $C_{11}H_{12}O$ requires C, 82.46; H, 7.55%); ν_{max}(film) 1741 and 1708 cm^{-1} (CO of trienone and norcaradiene forms respectively); $\delta_H(CDCl_3)$ 0.81(3H, s, CH_3), 2.00-3.10(4H, m, CH_2CH_2), 4.24(1H, d, J = 7.2Hz, C(8)*H*), 5.90-6.30(4H, m, C(4)*H*, C(5)*H*, C(6)*H*, and C(7)*H*), and 7.16(s, dimer impurity); $\delta_C(CDCl_3)$ 12.28(q, CH_3), 27.22(t, *C*(3)H_2), 34.83(t, *C*(2)H_2), 42.04(s, CCH_3), 94.99(d, *C*(8)H), 123.14(d), 125.46(d), 126.89(d), 127.15(d), (*C*(4)H, *C*(5)H, *C*(6)H, and *C*(7)H), 128.45(s, bridgehead *C*), and 219.80(s, *C*O). The spectral characteristics were in agreement with the reported values.[25] Catalyst and temperature effects on the reaction are shown in Table 5.10. Concentration effects are shown in Table 5.11. Effect of addition time is shown in Table 5.12.

6-Acetoxy-2,3-dihydro-1(8aH)-azulenone (12)[23]

The procedure described for 2,3-dihydro-1(8a*H*)-azulenone (2) was used with 1-diazo-4-(*p*-acetoxyphenyl)butan-2-one (9) (0.10g, 4.31×10^{-4} mol) to give 6-acetoxy-2,3-dihydro-1(8a*H*)-azulenone (12) (0.088g, quantitative yield) as an oil; ν_{max}(film) 1755 (CO ester) and 1742 cm^{-1}

(CO cyclopentanone); $\delta_H(CDCl_3)$ 2.18(3H, s, CH_3CO), 2.20-3.10(5H, m, CH_2CH_2 and C(8a)*H*), 5.17(1H, dd, J_1= 9.9Hz, J_2= 3.9Hz, C(8)*H*), 5.98(1H, brd, J = 10.0Hz, C(7)*H*), 6.18(2H, brs, C(4)*H* and C(5)*H*), and 7.00(m, dimer impurity). The spectral characteristics were in agreement with the reported values.[23] The catalyst used was rhodium(II) mandelate. The ^1H n.m.r. spectrum indicated the presence of 15% dimer impurity.

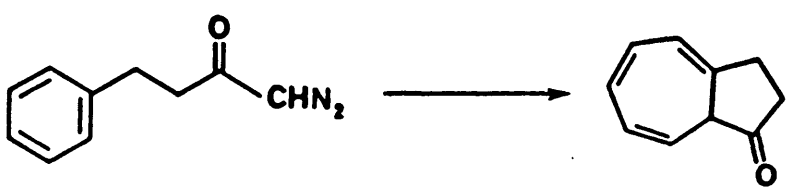
6-Acetoxy-2,3-dihydro-1(8a-methyl)-azulenone (13)

The procedure described for 2,3-dihydro-1(8a*H*)-azulenone (2) was used with 2-diazo-5-(*p*-acetoxyphenyl)pentan-2-one (10) (0.10g, 4.06×10^{-4} mol) to give 6-acetoxy-2,3-dihydro-1(8a-methyl)-azulenone (13) (0.089g, quantitative yield) as an oil. Purification by radial chromatography on silica using gradient ethyl acetate-hexane as eluant gave an analytical sample. (Found: C, 71.64; H, 6.64. $C_{13}H_{14}O_3$ requires C, 71.54; H, 6.47%); ν_{max}(film) 1755 (CO ester), 1743 (CO trienone), and 1708 cm^{-1} (CO norcaradiene); $\delta_H(CDCl_3)$ 0.97(3H, s, 8a-CH_3), 2.19(3H, s, CH_3CO_2), 2.20-2.80(4H, m, CH_2CH_2), 4.66(1H, d, J = 9.6Hz, C(8)*H*), 5.88(1H, brd, J = 9.6Hz, C(7)*H*), and 6.11(2H, brs, C(4)*H* and C(5)*H*); $\delta_C(CDCl_3)$ 14.03(q, 8a-CH_3), 20.99(q, CH_3CO_2), 27.09(t, $C(3)H_2$), 35.22(t, $C(2)H_2$), 45.61(s, CCH_3), 106.17(d, $C(8)H$), 119.61(s), 120.72(d), 121.11(d), 148.59(s), (cycloheptatrienyl carbons), 169.77(s, *C*O ester), and 219.35(s, *C*O cyclopentanone). The catalyst used was rhodium(II) mandelate. The ^1H n.m.r. spectrum indicated the presence of 11% dimer impurity in the crude product.

1,8-Diphenyl-4,5-dimethyloct-4-ene-3,6-dione (20)

2-Diazo-5-phenylpentan-3-one (8) (0.10g, 5.31×10^{-4} mol) was stirred in dichloromethane (12 ml) at room temperature. Rhodium(II) mandelate (0.5 mg) was added giving vigorous nitrogen evolution. Stirring was continued for 12h, then the solvent was evaporated at reduced pressure to give an oil (0.085g, quantitative yield) which was shown by ^{1}H n.m.r. to contain 38% dimer: 62% azulenone. Separation by p.l.c. on silica using dichloromethane as eluant gave the dimer (20) (0.014g, 16% yield) as an oil; ν_{max}(film) 1708 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.28(6H, s, 2 x CH_3), 2.80-3.10(8H, sym m, 4 x CH_2), and 7.19(10H, s, Ar-*H*). The presence of only one stereoisomer was indicated in the ^{1}H n.m.r. spectrum.

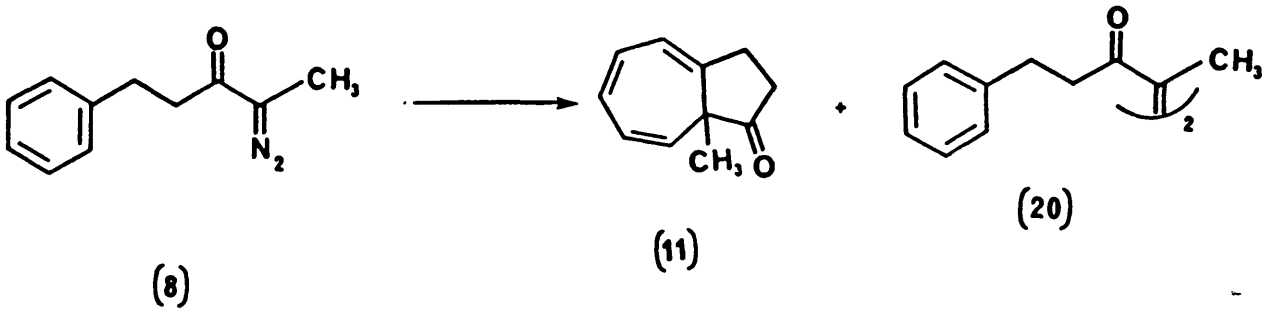
Table 5.9 : Effect of catalyst on cyclisation of 1-diazo-4-phenylbutan-2-one (1)



(1) (2)

Catalyst	Ratio of trienone:dimer %	Reaction time h
1	89:11	0.6
5	80:20	3.0

Table 5.10 : Effect of catalyst and temperature on cyclisation of 2-diazo-5-phenylpentan-2-one (8)

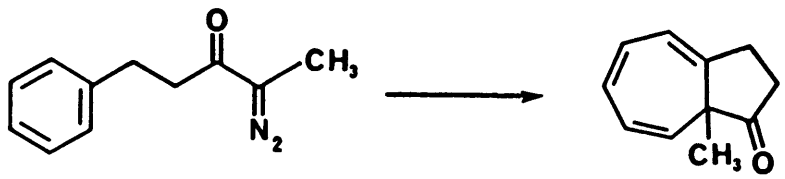


(8) (11) (20)

Catalyst	Reaction Temperature °C	Trienone:dimer %	Reaction Time h	$[\alpha]_D^{20}$ °(c, CH_2Cl_2)	%e.e.[a]
$Rh_2(O_2CCF_3)_4$	40	95:5	0.5	0	0
1	40	86:14-98:2	0.3	+17.7 (9.4)	25
1	20	84:16	0.25	-	-
1	0	88:12	0.2	-	20
1	-20	85:15	0.25	-	-
22	0	50:50	1.0	-	0
4	40	82:18	0.5	+16.9 (10.0)	25
4	20	75:25	0.5	-	20
4	0	70:30	1.0	-	10
4 + PPh_3	20	60:40	0.5	-	15
5	40	80:20	1.0	-	33
17	40	85:15	1.0	-	10
25	40	50:50	2.0	-	-

[a] Enantiomeric excess was estimated by chiral shift ^1H n.m.r. studies of the alcohol (22) obtained by $LiAlH(OBu^t)_3$ reduction of the azulenone (11). The chiral shift reagent employed was $Eu(tfc)_3$.

Table 5.11 : Effect of concentration on $Rh_2(mand)_4$ catalysed cyclisation of 2-diazo-5-phenylpentan-2-one (8)

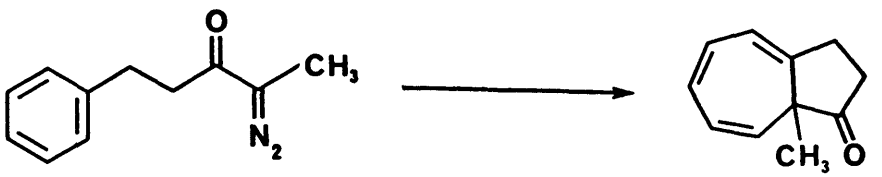


(8) (11)

Concentration mg/ml	Trienone:dimer %
100/50	82:18
100/100	87:13
100/150	90:10

Reactions were carried out at reflux in dichloromethane.

Table 5.12 : Effect of addition time on rhodium(II) *N*-benzenesulphonyl-L-prolinate catalysed cyclisation of 2-diazo-5-phenylpentan-2-one (8).



(8) (11)

Addition time h	Trienone:dimer %
0.17	60:40
1.00	75:25

Reactions were carried out at room temperature in dichloromethane.

2,3-Dihydro-1(8a-methyl)-azulenol (22)[25]

(a) Reduction with lithium tri-tert-butoxyaluminohydride.

2,3-Dihydro-1(8a-methyl)-azulenone (11) (0.27g, 1.685 mmol) in ether (15 ml) was added dropwise over 5 min to lithium tri-*tert*-butoxyaluminohydride (1.76g, 6.921 mmol) in ether (20 ml) while stirring at 0°C under nitrogen. Stirring was continued for 17h allowing the reaction mixture to return slowly to room temperature. The reaction

mixture was cooled in an ice-bath while water (5 ml) was added. The layers were separated and the aqueous layer was washed with ether (3 x 10 ml). The combined organic extracts were washed with brine (20 ml), dried, and concentrated at reduced pressure. Purification by p.l.c. on silica using dichloromethane as eluant gave the trienol mixture (22) (0.228g, 83.4% yield) as a colourless oil. Attempts to separate the isomers were unsuccessful. (Found: C, 81.75; H, 8.93. $C_{11}H_{14}O$ requires C, 81.44; H, 8.70%); ν_{max}(film) 3358 (OH) and 1631 cm^{-1} (C=C); δ_H($CDCl_3$, 270 MHz) 0.68(2.2H, s, CH_3 of major *cis*-isomer), 0.70(0.8H, s, CH_3 of minor *trans*-isomer), 1.80-2.10(2H, sym m, C(3)H_2), 2.40-2.80(2H, m, C(2)H_2), 1.99(1H, brs, OH), 4.10(1H, t, J = 6.6Hz, CHOH), 5.20(0.75H, d, J = 10.0Hz, C(8)H of major *cis*-isomer), 5.61(0.25H, d, J = 10.1Hz, C(8)H of minor *trans*-isomer), and 6.00-6.50 (4H, m, C(4)H , C(5)H, C(6)H, and C(7)H); δ_C($CDCl_3$) 11.70/17.74(q, CH_3), 30.28(t, C(3)H_2), 33.20(t, C(2)H_2), 48.28/47.95(s, CCH_3), 82.58/82.06(d, CHOH), 118.38(d), 124.81/123.95(d), 127.61(d), 128.65/128.17(d), 130.47(d), (C(4)H, C(5)H, C(6)H, and C(7)H), and 146.12/144.69(s, C(4a)). Where ^{13}C n.m.r. signals were visible for both isomers the peak corresponding to the major isomer is quoted first. From the ^1H n.m.r. spectrum the diastereoisomer ratio (*cis:trans*) was 75:25.

Chiral shift ^1H n.m.r. spectra with Eu(tfc)$_3$ as chiral shift reagent showed a splitting of the methyl group signal at δ_H 0.70 ppm firstly for the two diastereoisomers (enabling calculation of the diastereoisomeric ratio) and secondly a split in the peak for the major *cis*-isomer for the enantiomeric pair (enabling calculation of the enantiomeric ratio).

(b) Reduction with lithium aluminium hydride

2,3-Dihydro-1(8a-methyl)-azulenone (11) (0.80g, 4.99 mmol) in ether (10 ml) and THF (3 ml) was added dropwise over 10 min to lithium aluminium hydride (0.57g, 15 mmol) in ether (10 ml) while stirring at $0^{o}C$ under nitrogen. Stirring was continued at $0^{o}C$ for 30 min, then water (5 ml) was added cautiously. The layers were separated and the aqueous layer was washed with ether (3 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried, and concentrated at reduced pressure. Purification by p.l.c. on silica with dichloromethane as eluant gave the trienol mixture (22) (0.724g, 89.4% yield) with spectral characteristics as before. The diastereoisomeric ratio was estimated as 70:30 (*cis:trans*).

(c) Reduction with sodium borohydride

2,3-Dihydro-1(8a-methyl)-azulenone (11) (0.10g, 6.24×10^{-4} mol) in ethanol (5 ml) was added dropwise over 5 min to sodium borohydride (0.025g, 6.61×10^{-4} mol) in ethanol (15 ml) while stirring at $0^{o}C$ under nitrogen. Stirring was continued for 5 min then water (10 ml) was added. Ether (40 ml) was added and the layers separated. The aqueous layer was washed with ether (3 x 20 ml) and the combined organic extracts were washed with brine (20 ml), dried, and concentrated at reduced pressure. Purification by p.l.c. on silica with dichloromethane as eluant gave the trienol mixture (22) (0.087g, 86% yield). The spectral characteristics were as before. The diastereoisomeric ratio was estimated as 65:35 (*cis:trans*).

(d) Reduction with diisobutylaluminium hydride (DIBAL-H)

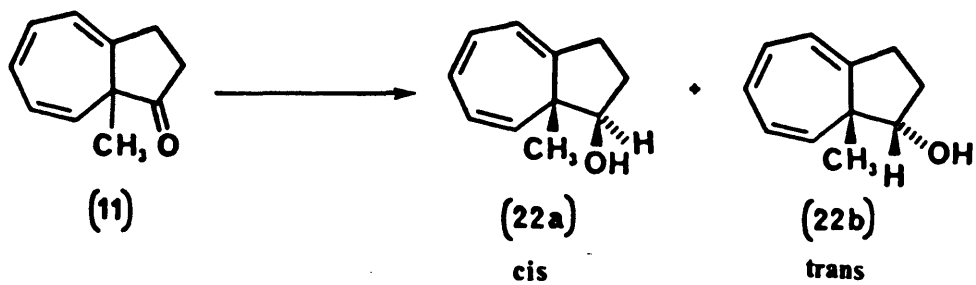
2,3-Dihydro-1(8a-methyl)-azulenone (11) (0.10g, 6.24 x 10^{-4} mol) in toluene (10 ml) was stirred at 0°C under nitrogen while DIBAL-H (0.355g, 2.50 mmol) in toluene (1 ml) was added over 5 min. Stirring was continued at room temperature for 15h then methanol (10 ml) and water (10 ml) were added, and the product extracted with ether (3 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried, and concentrated at reduced pressure. Purification by p.l.c. on silica with 20% ethyl acetate, 80% hexane as eluant gave the trienol mixture (22) (0.086g, 85% yield) with spectral characteristics as before. The diastereoisomeric ratio was estimated as 45:55 (*cis: trans*).

(e) Reduction with potassium tri-sec-butylborohydride (K-Selectride)[28]

2,3-Dihydro-1(8a-methyl)-azulenone (11) (0.069g, 4.28 x 10^{-4} mol) in THF (15 ml) was stirred at 0°C under nitrogen while K-Selectride (0.111g, 5 x 10^{-4} mol) in THF (0.5 ml) was added. Stirring was continued for 1h then water (3 ml) was added. The pH was adjusted to 5 by addition of aqueous ammonium chloride. The product was extracted with ether (3 x 15 ml). The combined organic extracts were dried and concentrated at reduced pressure. Purification by p.l.c. on silica with dichloromethane as eluant gave the trienol mixture (22) (0.048g, 68.6% yield) with spectral characteristics as before. The diastereoisomeric ratio was estimated as 70:30 (*cis:trans*).

Table 5.13 shows the stereoselection in the reduction of 2,3-dihydro-1(8a-methyl)-azulenone (11) with the various reducing agents. Table 5.14 shows the enantiomeric excess obtained from chiral shift ^{1}H n.m.r. spectra of azulenol samples obtained by $LiAlH(OBu^{t})_3$ reduction of azulenone samples from rhodium(II) carboxylate catalysed cyclisations.

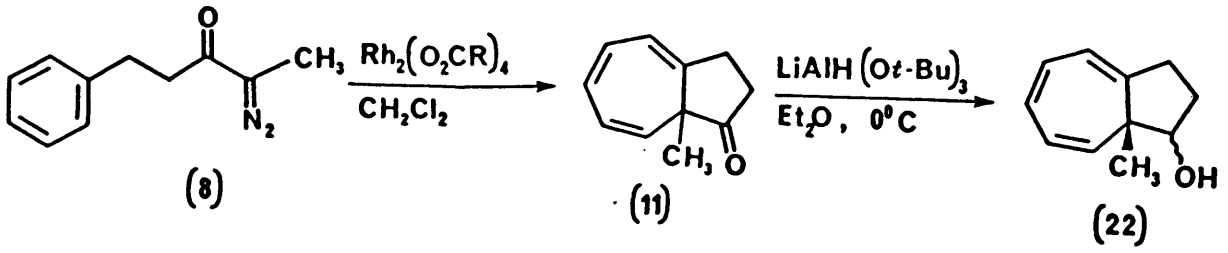
Table 5.13: Stereoselection in the reduction of 2,3-dihydro-1(8a-methyl)-azulenone (11)



(11) (22a) cis (22b) trans

Reducing agent	Yield / %	*cis:trans* / %
$LiAlH(OBu^{t})_3$-Et_2O	83.4	75:25
$LiAlH(OBu^{t})_3$-THF	81.2	75:25
$LiAlH_4$-Et_2O-THF	89.4	70:30
$NaBH_4$-EtOH	86.0	65:35
DIBAL-H-toluene	85.0	45:55
K-Selectride-THF	68.6	70:30

Table 5.14: Enantioselection in the cyclisation of 2-diazo-5-phenyl-pentan-2-one using rhodium(II) carboxylates as catalyst. Enantiomeric ratios were estimated by reduction of 2,3-dihydro-1(8a-methyl)-azulenone formed in the cyclisation to 2,3-dihydro-1(8a-methyl)-azulenol on which chiral shift ^1H n.m.r. studies were carried out.



(8) (11) (22)

Catalyst	Temperature of diazoketone decomposition °C	% e.e. in alcohols[a]	$[\alpha]_D^{20}$ of alcohols[b] °(c, CH_2Cl_2)
$Rh_2(O_2CCF_3)_4$	40	0	0
1	0	20	-
1	40	25	-7.73 (5.73)
22	0	0	-
4	0	10	-1.26 (4.62)
4	20	20	-3.28 (5.06)
4	40	25	-7.21 (5.81)
4 + PPh_3	20	15	-5.27 (5.20)
5	40	33	-9.44 (8.81)
17	40	10	+0.67 (6.43)

[a] % e.e. estimated from ^1H n.m.r. to ±8% accuracy using Eu(tfc)$_3$.

[b] all reductions were carried out using lithium tri-*tert*-butoxy-aluminohydride giving the same isomer ratio in each product. Therefore specific rotation data can be at least qualitatively compared as an indication of asymmetric induction.

6-Acetoxy-2,3-dihydro-1(8a-methyl)-azulenol (23)

6-Acetoxy-2,3-dihydro-1(8a-methyl)-azulenone (13) (0.25g, 1.15 mmol; from a rhodium(II) mandelate catalysed cyclisation) in in benzene (15 ml) and methanol (5 ml) was stirred at 0°C under nitrogen forming a semi-solid reaction mixture. Sodium borohydride (0.115g, 3.04 mmol) was added in portions over 10 min then the reaction mixture was stirred for 2h while returning slowly to room temperature, was poured onto saturated ammonium chloride solution (20 ml), and was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine (20 ml), dried, and concentrated at reduced pressure. Purification by p.l.c. on silica using 10% methanol 90% dichloromethane as eluant gave the alcohol mixture (23) (0.107g, 42.4% yield) as an oil; ν_{max}(film) 3430 (OH) and 1739 cm^{-1} (CO ester); $\delta_H(CDCl_3)$ 0.83(3H, s, CCH_3), 1.60-2.00(2H, m, C(3)H_2), 2.19(3H, s, CH_3CO_2), 2.10-2.80(2H, m, C(2)H_2), 2.68(1H, brs, O*H*), 4.06(1H, t, *J* = 6.0Hz, C*H*OH), 5.26(0.7H, d, *J* = 10.8Hz, C(8)*H* of major isomer), 5.58(0.3H, d, *J* = 8.4Hz, C(8)*H* of minor isomer), 5.90(1H, d, *J* = 10.8Hz, C(7)*H*), and 6.08(2H, brs, C(4)*H* and C(5)*H*). Chiral shift ^1H n.m.r. spectra using Eu(tfc)$_3$ showed 10% e.e. in the alcohols. The chiral shift spectra also enabled calculation of the diastereoisomeric ratio in the alcohols as 65:35 (*cis:trans*).

1-Methylspiro[4.5]deca-6,9-diene-2,8-dione (31)[29]

6-Acetoxy-2,3-dihydro-1(8a-methyl)-azulenone (13) (0.12g, 0.55 mmol) in 1,4-dioxan (2 ml) was stirred at 0°C under nitrogen. Sodium hydroxide (0.074g, 1.85 mmol) in water (5 ml) was added. The reaction mixture

immediately became deep red and t.l.c. indicated complete disappearance of starting material. The mixture was diluted with water (20 ml) and extracted with ether (3 x 20 ml). The combined ether extracts were dried and concentrated at reduced pressure. Purification by p.l.c. on silica with 60% ethyl acetate 40% hexane as eluant gave the spirodione (31) (0.049g, 51% yield) as a white crystalline solid, m.p. 93-95°C (from ether-hexane; lit.,[29] 93-94°C) (Found: C, 75.16; H, 7.04. $C_{11}H_{12}O_2$ requires C, 74.97; H, 6.86%); ν_{max}(KBr) 1742 (CO, cyclopentanone), 1660 (CO conjugated), and 1623 cm^{-1} (C=C) (lit.,[29] 1738, 1660, and 1625 cm^{-1}); $\delta_H(CDCl_3)$ 0.86(3H, d, J = 7.2Hz, CH_3), 2.00-2.80(5H, m, $CHCH_3$ and CH_2CH_2), and 6.20-7.00(4H, m, vinylic-H); $\delta_C(CDCl_3)$ 8.64(q, CH_3), 31.19(t, $C(3)H_2$), 34.37(t, $C(4)H_2$), 49.83(s, $C(5)$), 54.06(d, $CHCH_3$), 130.66(d), 147.81(d), 153.14(d), (vinylic-C), 185.63(s, CO conjugated), and 215.45(s, CO cyclopentanone). The spectral characteristics were in agreement with the reported values.[29]

Perhydro-1(8a-methyl)-azulenol (24)[25]

2,3-Dihydro-1(8a-methyl)-azulenol (22) (0.087g, 0.54 mmol) in ethanol (5 ml) with 10% palladium on charcoal (0.02g) was hydrogenated with 40 p.s.i. hydrogen at room temperature for 24h. Filtration and concentration at reduced pressure gave the crude product which was purified by p.l.c. on silica with dichloromethane as eluant to give the perhydroazulenol (24) as an inseparable mixture of isomers (0.091g, quantitative yield) as an oil which solidified on refrigeration (Found: C, 78.17; H, 12.13. $C_{11}H_{20}O$ requires C, 78.51; H, 11.98%); ν_{max}(film) 3366 cm^{-1} (OH); $\delta_H(CDCl_3)$ 0.74(3H, s, CH_3), 0.20-2.00(15H, brm, contained a distinctive pair of peaks at δ_H 0.91 and 0.96), 3.24(1H, brs, OH), and

3.60(1H, t, J = 7.2Hz, C*H*OH); $\delta_C(CDCl_3)$ 10.98(q, *C*H_3), 26.12, 26.64, 27.22, 29.17(t), 30.15(t), 40.48, 44.25, 46.26, and 83.23(d, *C*HOH). Minor signals were visible at 18.32 (q, *C*H_3) and 84.14(d, *C*HOH) for an isomer.

This sample was derived from α-diazoketone (8) by a rhodium(II) mandelate catalysed cyclisation at 0°C followed by reduction with lithium tri-*tert*-butoxyaluminohydride. Chiral shift ^{1}H n.m.r. spectra of the perhydroazulenol mixture (24) with Eu(tfc)$_3$ indicated 20% e.e. by splitting of the singlet for the methyl group. This was in agreement with the chiral shift spectra of the 2,3-dihydro-1(8a-methyl)-azulenol (22), and was further evidence that cyclisation of α-diazoketone (8) with rhodium(II) mandelate as catalyst at 0°C proceeded with an asymmetric induction of 20% e.e.

Perhydro-1(8a-methyl)-azulenone (25)[25,30]

Jones' reagent was freshly prepared using chromium(VI) oxide (5.34g) and conc. sulphuric acid (4.6 ml) in 50 ml aqueous solution.

Perhydro-1(8a-methyl)-azulenol (24) (0.091g, 0.54 mmol) in acetone (20 ml) was stirred at 0°C while Jones' reagent (0.5 ml) was added dropwise. Anhydrous sodium carbonate (0.50g) was added and stirring was continued for 1.5h. The reaction mixture was filtered through celite, concentrated at reduced pressure, redissolved in dichloromethane (20 ml), dried, and concentrated at reduced pressure to give the crude product which was purified by distillation in a Kugelrohr apparatus (oven-temperature 75-90°C at 0.03 mmHg) to give the perhydroazulenone (25) (0.06g, 67% yield) as an oil (Found: C, 79.63; H, 10.72.

$C_{11}H_{18}O$ requires C, 79.46; H, 10.91%); ν_{max}(film) 1736 cm^{-1} (CO, cyclopentanone); $\delta_H(CDCl_3)$ 0.92(2.8H, s, CH_3, *trans*), 1.15(0.2H, s, CH_3, *cis*), 1.20-2.40(15H, m). From the integration 7-10% of the *cis*-fused isomer was present. The spectral data were in agreement with the reported values.[25,30]

Hydrogenation of 2,3-dihydro-1(8a-methyl)-azulenone (11)[23]

2,3-Dihydro-1(8a-methyl)-azulenone (11) (0.102g, 0.64 mmol) in ethanol (20 ml) with 10% palladium on charcoal (0.02g) was hydrogenated at 40 p.s.i. hydrogen for 24h. Filtration through celite and concentration at reduced pressure gave the perhydroazulenone (25) which was purified by distillation as before (0.088g, 83% yield). The spectral characteristics were as before except that the signal at δ_H 1.15 ppm for the CH_3 of the *cis*-fused isomer was not present indicating exclusive hydrogenation to the *trans*-isomer had occurred.

The azulenone sample used in the hydrogenation was from a rhodium(II) *N*-naphthalenesulphonyl-L-prolinate catalysed reaction (i.e. 33% e.e.). The perhydroazulenone had a specific rotation of $[\alpha]_D^{20}$ +18.7° (c 2.6 in CH_2Cl_2).

Acetylation of 2,3-dihydro-1(8a-methyl)-azulenol (22)

2,3-Dihydro-1(8a-methyl)-azulenol (0.679g, 4.19 mmol) in pyridine (25 ml) was stirred under nitrogen while acetic anhydride (25 ml) was added. The reaction mixture was stirred for 17h, then poured onto ice (200g), and extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were washed with brine (50 ml), dried, and concentrated at reduced pressure. Purification by passage through a short column of

silica using dichloromethane as eluant gave 2,3-dihydro-1(8a-methyl)-azulenyl acetate (26) as an inseparable mixture of isomers (0.675g, 79% yield) as a colourless oil (Found: C, 76.17; H, 7.66. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%); ν_{max}(film) 1732 cm^{-1} (CO ester); $\delta_H(CDCl_3)$ 0.63(2H, s, CH_3,, *cis*-isomer), 0.72(1H, s, CH_3, *trans*-isomer), 1.80-2.20(2H, m, C(3)H_2), 2.08, 2.09(3H, 2 overlapping s, CH_3CO_2), 2.50-2.90(2H, m, C(2)H_2), 5.00-5.40(2H, m, C(8)*H* and C*H*OAc), and 5.80-6.30(4H, m, C(4)*H*, C(5)*H*, C(6)*H*, and C(7)*H*); $\delta_C(CDCl_3)$ 12.09(q, CH_3, finely split for 2 isomers), 17.61(t, *C*(3)H_2), 21.12(t, *C*(2)H_2), 30.86/30.80(q, CH_3CO_2), 47.76/47.24(s, CCH_3), 83.62/83.36(d, *C*HOAc), 118.06/118.38(d), 124.68/124.36(d), 127.80(d), 128.58/128.32 (d), 128.97(d), 144.50/143.85(s), (vinylic-*C*), and 170.81(s, *C*O, finely split for 2 isomers). Where pairs of signals were visible that which corresponded to the major *cis*-isomer is quoted first.

This sample was derived from a lithium aluminium hydride reduction of the azulenone (11). Estimation of the isomer ratio was possible by integration of the well resolved singlets in the ^1H n.m.r. spectrum for the C(8a)-methyl groups of the two isomers giving a 70:30 *cis:trans* ratio, in agreement with that obtained from the chiral shift ^1H n.m.r. spectra of the azulenol (22).

1-Methylbicyclo[5.3.0]dec-10-yl acetate (27)

The acetate mixture (26) (0.09g, 0.44 mmol) in ethanol (10 ml) with 10% palladium on charcoal (0.05g) was hydrogenated at room temperature at 40 p.s.i. hydrogen for 20h. Filtration and concentration at reduced pressure gave the acetate (27) as a mixture of isomers (0.092g, 99% yield)

as a clear colourless oil (Found: C, 74.69; H, 10.42. $C_{13}H_{22}O$ requires C, 74.24; H, 10.54%); ν_{max}(film) 1731 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.82(3H, s, CC*H*$_3$), 1.00-2.10(15H, m), 2.00(3H, s, C*H*$_3$CO$_2$), and 4.40-4.80(1H, m, C*H*OAc). The singlets for the methyl groups at δ_H 0.82 and 2.00 did not resolve for the isomers.

Reaction of methylmagnesium iodide and 2,3-dihydro-1(8a-methyl)-azulenone (11)

Magnesium turnings (1.252g, 0.052 mol) in ether (40 ml) was stirred under nitrogen while a solution of iodomethane (7.30g, 0.051 mol) in ether (15 ml) was added over 5 min giving a vigorous exothermic reaction. The reaction mixture was refluxed for 1h, then cooled to 0°C, and 2,3-dihydro-1(8a-methyl)-azulenone (11) (0.32g, 1.997 mmol) in ether (10 ml) was added dropwise over 5 min. Stirring was continued for 14h at room temperature, then the reaction mixture was cooled to 0°C and saturated aqueous ammonium chloride (10 ml) was added cautiously. The layers were separated and the aqueous layer washed with ether (3 x 10 ml). The combined organic extracts were dried and concentrated at reduced pressure. Purification by p.l.c. using dichloromethane as eluant gave the alcohol mixture (28) (0.164g, 46.5% yield) as a colourless oil; ν_{max}(film) 3415 (OH) and 1639 cm^{-1} (w, C=C); $\delta_H(CDCl_3)$ 0.58(1.2H, s, 8a-CH_3 of minor isomer), 0.73(1.8H, s, 8a-C*H*$_3$ of major isomer), 1.31(1.8H, s, C*H*$_3$COH of major isomer), 1.37(1.2H, s, C*H*$_3$COH of minor isomer), 1.50-2.70(4H, m, C*H*$_2$C*H*$_2$), 4.68(0.40H, d, J = 10.2Hz, C(8)*H* of minor isomer), 5.50(0.60H, d, J = 11.4Hz, C(8)*H* of major isomer), and 6.00-6.60(4H, m, C(4)*H*, C(5)*H*,

C(6)*H*, and C(7)*H*). By comparison with the spectra for the azulenol mixture (22), the major isomer (60%) of Grignard addition product had the methyl groups *cis* corresponding to attack from the β-face of the molecule. Enantiomeric resolution was not seen on the ^{1}H n.m.r. spectrum on addition of $Eu(tfc)_3$.

Preparation of the phenol ester (43)

m-Methylanisole (37)[23,31]

Dimethyl sulphate (315g, 2.5 mol) was added dropwise to a cold solution of *m*-cresol (216g, 2 mol) in aqueous sodium hydroxide (88g, 2.2 mol in 150 ml). The solution clouded immediately and was refluxed for 1h. The upper light yellow oil was separated and dissolved in ether (1*l*), washed with brine (300 ml), dried over anhydrous sodium carbonate, filtered, and concentrated at reduced pressure to give *m*-methylanisole (37) (233.2g, 95.5% yield) as an oil; ν_{max}(film) 1257 and 1151 cm^{-1} (C-O); $\delta_H(CDCl_3)$ 2.25(3H, s, Ar-C*H*$_3$), 3.58(3H, s, OC*H*$_3$), and 6.60-7.20(4H, m, Ar-*H*); $\delta_C(CDCl_3)$ 21.51(q, *C*H$_3$-Ar), 55.03(q, O*C*H$_3$), 110.85(d), 114.81(d), 121.56(d), 129.23(d), 139.50(s), and 159.64(s), (Ar). The spectral characteristics were in agreement with the reported values.[23]

4-Bromo-3-methylanisole (38)[25,31,32]

Bromine (62.04g, 0.39 mol) in carbon tetrachloride (120 ml) was added dropwise over 3h to a stirred suspension of iron filings (0.80g) in *m*-methylanisole (39.90g, 0.33 mol) and carbon tetrachloride (320 ml) at -10°C. The reaction mixture was stirred for 3h, water (200 ml) was

added followed by 45% sodium bisulphite solution (300 ml) giving slow decolourisation of the mixture. The layers were separated and the aqueous layer washed with carbon tetrachloride (50 ml). The combined organic extracts were concentrated at reduced pressure then shaken in ether and water (200 ml of each). The layers were separated and the organic layer washed with water (3 x 50 ml) and brine (50 ml), dried, and concentrated at reduced pressure. Distillation gave 4-bromo-3-methylanisole (38) (56g, 85% yield) as an oil, b.p. 60°C at 0.6 mmHg (lit.,[32] 72°C at 1.2 mmHg) (Found: C, 47.24; H, 4.08; Br, 39.41. C_8H_9BrO requires C, 47.79; H, 4.51; Br 39.75%); ν_{max}(film) 1605, 1580, and 1485 cm^{-1} (aromatic); $\delta_H(CDCl_3)$ 2.30(3H, s, CH_3-Ar), 3.64(3H, s, OCH_3), 6.30-6.70(2H, m, C(2)*H* and C(6)*H*), and 7.40(1H, d, J = 9.0Hz, C(5)*H*). The spectral characteristics were in agreement with the reported values.[25]

4-Methoxy-2-methylbenzaldehyde (39)[25,31,32]

4-Bromo-3-methylanisole (48g, 0.24 mol) and bromoethane (56.06g, 0.51 mol) in ether (280 ml) were added dropwise over 1.5h to a mechanically stirred suspension of magnesium turnings (21.6g, 0.89 mol) in ether (320 ml) under nitrogen, maintaining gentle reflux by adjusting the rate of addition. The reaction mixture was refluxed for 1h, cooled to -20°C, and a solution of *N*,*N*-dimethylformamide (58.9g, 0.81 mol) in ether (200 ml) was added slowly with vigorous stirring. The suspension was stirred for 1h then poured onto ice and saturated ammonium chloride solution (500 ml of each). The layers were separated and the aqueous layer was washed with ether (3 x 100 ml). The combined organic extracts

were washed with brine (100 ml), dried, and concentrated at reduced pressure. Fractional distillation gave unreacted bromide (b.p. 60°C at 0.6 mmHg), and the aldehyde (39) (b.p. 80°C at 0.6 mmHg) (29.6g, 82% yield based on bromide consumed); ν_{max}(film) 1690 cm^{-1} (CO); $\delta_H(CDCl_3)$ 2.59(3H, s, CH_3-Ar), 3.78(3H, s, OCH_3), 6.70-7.20(2H, m, C(3)*H* and C(5)*H*), 7.72(1H, d, *J* = 9Hz, C(6)*H*), and 10.03(1H, s, *CH*O). The spectral characteristics were in agreement with the reported values.[25]

4-Methoxy-2-methylcinnamic acid (40)[25,32]

4-Methoxy-2-methylbenzaldehyde (16g, 0.11 mol) was stirred with malonic acid (22.2g, 0.21 mol) in pyridine (50 ml) at 50°C until all the malonic acid had dissolved. The mixture was cooled and piperidine (1.39g, 0.016 mol) was added. The solution was heated at 80°C for 1h, then refluxed for 3h, poured into water (425 ml), and acidified to pH 1 with conc. hydrochloric acid (61 ml). The precipitate was collected by filtration and washed with cold water (73 ml). The crude product was dissolved in aqueous sodium hydroxide (8.80g, 0.22 mol in 300 ml water), heated to 65°C, and filtered. The filtrate was diluted with water (120 ml) and reacidified to pH 1 with 1:1 conc. hydrochloric acid and water (66 ml). The precipitate was collected by filtration, washed with cold water (110 ml), and dried at 65°C for 3 days. Recrystallisation from acetone/ethanol gave the acid (40) (19.05g, 93% yield) as white needles, m.p. 191-193°C (lit.,[32] 187°C) (Found: C, 68.30; H, 6.24. $C_{11}H_{12}O_3$ requires C, 68.73; H, 6.29%); ν_{max}(KBr) 3600-2000 (max. 2590, COOH), 1682 (CO), and 1597 cm^{-1} (C=C); δ_H(DMSO-d_6/acetone-d_6) 2.37(3H, s, CH_3-Ar), 3.77(3H, s, OCH_3), 6.26(1H, d, *J* = 15.6Hz, =*CH*CO_2H), 6.90(2H, m,

C(3)*H* and C(5)*H*), 7.70(1H, d, *J* = 9Hz, C(6)*H*), and 7.90(1H, d, *J* = 15.6Hz, =C*H*-Ar). The spectral characteristics were in agreement with the reported values.[32]

3-(4-Methoxy-2-methylphenyl)propanoic acid (41)[25]

4-Methoxy-2-methylcinnamic acid (40) (5.80g, 0.034 mol) was dissolved in hot ethanol (200 ml) and 10% palladium on charcoal was added (0.089g). Hydrogenation at 40 p.s.i. hydrogen was carried out for 16h, then the reaction mixture was filtered and concentrated at reduced pressure to give the acid (41) (5.80g, 99% yield) as a white crystalline solid; ν_{max}(KBr) 3200-2200 (max. 2910, COOH) and 1705 cm^{-1} (CO); δ_H($CDCl_3$/DMSO-d_6) 2.27(3H, s, CH_3-Ar), 2.50-3.00(4H, sym m, CH_2CH_2), 3.68(3H, s, OCH_3), 6.70-7.20(3H, ABq and s overlapping, Ar-*H*), and 11.00(1H, brs, COO*H*). The spectral characteristics were in agreement with the reported values.[25]

3-(4-Hydroxy-2-methylphenyl)propanoic acid (42)[25]

3-(4-Methoxy-2-methylphenyl)propanoic acid (41) (16.43g, 0.085 mol) in acetic acid (200 ml) was stirred under nitrogen while hydrobromic acid (49%; 125 ml) was added. The solution was refluxed for 24h, then the acetic acid was evaporated at reduced pressure. The residue was shaken in ether and water (200 ml of each). The layers were separated and the aqueous layer washed with ether (2 x 50 ml). The combined organic extracts were washed with water (2 x 50 ml), dried, and concentrated at reduced pressure. Recrystallisation from chloroform gave the acid (42) (13.57g, 89% yield) as white crystals, m.p. 98.5-99.5°C; ν_{max}(KBr) 3367 (OH), 3500-2400 (max. 3100, COOH), 1720, and 1679 cm^{-1} (CO);

δ_H($CDCl_3$/DMSO-d_6) 2.19(3H, s, CH_3), 2.30-3.00(4H, sym m, CH_2CH_2), 6.50-7.10(3H, ABq and s overlapping, Ar-*H*), and 7.70(2H, brs, COO*H* and O*H*). The spectral characteristics were in agreement with the reported values.[25]

Methyl 3-(4-hydroxy-2-methylphenyl)propanoate (43)[25]

3-(4-Hydroxy-2-methylphenyl)propanoic acid (42) (7.27g, 0.040 mol) in methanol (70 ml) with a few drops of conc. sulphuric acid was refluxed for 12h while stirring under nitrogen. The methanol was evaporated at reduced pressure and the residue was dissolved in dichloromethane (50 ml), stirred with anhydrous sodium carbonate (2g) for 1h, filtered, and concentrated at reduced pressure. Passage through a short column of silica with dichloromethane as eluant gave the ester (43) (7.60g, 97% yield) as a gold-coloured oil; ν_{max}(film) 3395(OH) and 1712 cm^{-1} (CO); δ_H($CDCl_3$) 2.13(3H, s, CH_3-Ar), 2.40-2.90(4H, sym m, 2 x CH_2), 3.57(3H, s, OCH_3), 6.15(1H, brs, O*H*), 6.76(1H, brs, C(3)*H*), and 6.60-7.10(2H, ABq, C(5)*H* and C(6)*H*). The spectral characteristics were in agreement with the reported values.[25]

Preparation of sulphide esters

Ethyl 2-(n-butylthio)acetate (48)[25]

Sodium (2.04g, 0.089 mol) was added over 45 min to ethanol (150 ml) while stirring under nitrogen. When all the sodium had dissolved, 1-butanethiol (8.00g, 0.089 mol) was added and the reaction mixture was stirred for 30 min. Ethyl bromoacetate (14.808g, 0.089 mol) was added dropwise over 1h and stirring was continued for 16h. The reaction mixture was filtered and concentrated at reduced pressure. The residue

was shaken in ether and water (100 ml of each) and the layers were separated. The aqueous phase was washed with ether (3 x 20 ml). The combined organic extracts were dried and concentrated at reduced pressure to give ethyl 2-(*n*-butylthio)acetate (48) (14.22g, 91.0% yield) as a colourless oil; ν_{max}(film) 1728 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.80-1.80(10H, m, $CH_3CH_2CH_2$ and OCH_2CH_3, triplet visible at 1.25), 2.69(2H, brt, J = 7.2Hz, CH_2CH_2S), 3.14(2H, s, SCH_2CO), and 4.10(2H, q, OCH_2CH_3). The spectral characteristics were in agreement with the reported values.[25]

Ethyl 2,2-bis(n-butylthio)acetate (50)[33]

Ethyl 2-chloro-2-(*n*-butylthio)acetate (49) (0.50g, 2.37 mmol) in dichloromethane (10 ml) was stirred under nitrogen. *n*-Butanethiol (0.214g, 2.37 mmol) was added, followed by freshly fused zinc chloride (0.65g, 4.77 mmol). Stirring was continued for 18h then the reaction mixture was washed with water (10 ml), dried, and concentrated at reduced pressure. Purification by radial chromatography on silica with 2% ethyl acetate, 98% hexane as eluant gave ethyl 2,2-*bis*(*n*-butylthio)-acetate (50) (0.412g, 66% yield) as an oil (Found: C, 54.62; H, 8.96. $C_{12}H_{24}O_2S_2$ requires C, 54.50; H, 9.15%); ν_{max}(film) 1726 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.80-1.90(17H, brm, OCH_2CH_3 and 2 x $CH_3CH_2CH_2$, t visible at 1.30), 2.63(4H, brt, J = 6.6Hz, 2 x CH_2S), 4.13(2H, q, J = 6.6Hz, OCH_2CH_3), and 4.24(1H, s, $CH(SBu)_2$).

2,2-Dimethyl-1,3-oxathiolan-5-one (52)[34]

Mercaptoacetic acid (36.85g, 0.40 mol), acetone (46.50g, 0.80 mol), and *p*-toluenesulphonic acid (0.30g, 1.58 mmol) in benzene (400 ml) was refluxed for 1h. A Dean-Stark apparatus was inserted and reflux was

continued for 3h while the water formed in the reaction was removed by azeotropic distillation. The reaction mixture was stirred at room temperature for 15h while a precipitate of the diacid (53) formed. The solution was decanted, washed with saturated sodium bicarbonate solution (3 x 250 ml) and brine (250 ml), dried, and concentrated at reduced pressure. Distillation gave 2,2-dimethyl-1,3-oxathiolan-5-one (52) (6.0g, 12% yield) as a clear colourless oil, b.p. 44°C at 10 mmHg; ν_{max}(film) 1769 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.71(6H, s, 2 x CH_3) and 3.69(2H, s, CH_2); $\delta_C(CDCl_3)$ 30.60(q, 2 x CH_3), 33.33(t, CH_2), 89.08(s, $C(CH_3)_2$), and 172.18(s, CO). The spectral characteristics were in agreement with the reported values.[34b]

The major product of the condensation was the diacid (53) (16.0g, 35.6% yield) as a white crystalline solid, m.p. 121-127°C (Found: C, 37.79; H, 5.28; S, 28.67. $C_7H_{12}O_4S_2$ requires C, 37.48; H, 5.39; S, 28.59%); ν_{max}(KBr) 3600-2500 (max. 3080, COOH) and 1702 cm^{-1} (CO); δ_H 1.61(6H, s, 2 x CH_3), 3.32(4H, s, 2 x CH_2), and 9.70(2H, brs, 2 x COOH).

Preparation of α-chlorosulphides[35]

Ethyl 2-chloro-2-(n-butylthio)acetate (49)[25]

Ethyl 2-(*n*-butylthio)acetate (48) (13.83g, 0.078 mol) in carbon tetrachloride (55 ml) was stirred at 0°C under nitrogen while *N*-chlorosuccinimide (11.06g, 0.082 mol) was added. Stirring was continued for 16.5 h allowing the reaction mixture to return slowly to room temperature. The suspension was cooled to 0°C and filtered to remove the succinimide which was washed with ice-cold carbon tetrachloride (42 ml).

Because of the sensitivity of the reagent it was refrigerated and handled in the solution in which it was prepared. The yield was assumed to be quantitative and the α-chlorosulphide solution was used on a 'by-weight' basis. Analysis was by ^{1}H n.m.r. only and before use the reagent was checked by ^{1}H n.m.r.; $\delta_H(CCl_4)$ 0.80-1.90(10H, m, $CH_3CH_2CH_2$ and OCH_2CH_3, t visible at 1.33), 2.76(2H, brt, J = 6.0Hz CH_2S), 4.17(2H, q, J = 7.2Hz, OCH_2), and 5.30(1H, s, CHCl). The ^{1}H n.m.r. characteristics were in agreement with the reported values.[25]

Ethyl 2-chloro-2,2-bis(n-butylthio)acetate (51)

The procedure described for ethyl 2-chloro-2-(*n*-butylthio)acetate (49) was used with ethyl 2,2-*bis*(*n*-butylthio)acetate (50) (0.363g, 1.37 mmol) in carbon tetrachloride (2 ml) and *N*-chlorosuccinimide (0.193g, 1.45 mmol) with a carbon tetrachloride (1 ml) wash of the solids to give a quantitative yield of the α-chlorosulphide (51) as a solution in carbon tetrachloride; $\delta_H(CCl_4)$ 0.90-1.90(17H, m, 2 x $CH_3CH_2CH_2$ and OCH_2CH_3, t visible at 1.40), 2.50-2.90(4H, m, 2 x CH_2S), and 4.29(2H, q, J = 6.9Hz, OCH_2CH_3).

Methyl 2-chloro 2-(phenylthio)propionate (44)[25]

The procedure described for ethyl 2-chloro-2-(*n*-butylthio)acetate (49) was used with methyl 2-(phenylthio)propionate (55)[36] (8.00g, 0.041 mol) in carbon tetrachloride (32 ml) and *N*-chlorosuccinimide (5.72g, 0.043 mol) with a carbon tetrachloride (24 ml) wash of the solids to give a quantitative yield of the α-chlorosulphide (44) as a solution in carbon tetrachloride; $\delta_H(CCl_4)$ 1.96(3H, s, CH_3C), 3.65(3H, s, CH_3O_2C), and 7.10-7.70(5H, m, Ar-*H*). The ^{1}H n.m.r. characteristics were in agreement with the reported values.[25]

4-Chloro-2,2-dimethyl-1,3-oxathiolan-5-one (54)

The procedure described for ethyl 2-chloro-2-(*n*-butylthio)-acetate (49) was used with 2,2-dimethyl-1,3-oxathiolan-5-one (52) (3.00g, 0.022 mol) in carbon tetrachloride (30 ml) and *N*-chlorosuccinimide (3.10g, 0.023 mol) with a carbon tetrachloride (10 ml) wash of the solids. It was necessary to heat the reaction mixture to 45°C for 2h for complete reaction. A quantitative yield of the α-chlorosulphide (54) as a solution in carbon tetrachloride was obtained; $\delta_H(CCl_4)$ 1.81, 1.97(6H, 2 x s, 2 x CH_3) and 5.82(1H, s, C*H*Cl).

3-Chloro-trans-hexahydro-1,4-benzoxathiin-2(3H)-one (57)

The procedure described for ethyl 2-chloro-2-(*n*-butylthio)-acetate (49) was used with *trans*-hexahydro-1,4-benzoxathiin-2(3*H*)-one (56)[37] (0.50g, 2.90 mmol) in carbon tetrachloride (10 ml) and dichloromethane (1 ml) and *N*-chlorosuccinimide (0.41g, 3.07 mmol) with a carbon tetrachloride (1 ml) wash to give a quantitative yield of the α-chlorosulphide (57) in solution; $\delta_H(CCl_4)$ 1.10-2.60(8H, m, 4 x CH_2), 3.00-3.60(1H, m, C*H*S), 5.00-5.50(1H, m, C*H*O), and 5.86, 5.89(1H, 2 x s, C*H*Cl, two isomers in 3:1 ratio).

Alkylation with α-chlorosulphides

5-Benzofuranpropanoic acid, 2,3-dihydro-4-methyl-2-oxo-methyl ester (59) and 5-benzofuranpropanoic acid, 2,3-dihydro-6-methyl-2-oxo-methyl ester (60)[38]

A solution of ethyl 2-chloro-2-(*n*-butylthio)acetate (49) (11.93g, 0.056 mol) in carbon tetrachloride (60 ml) was added dropwise over 1h to a stirred mixture of phenol ester (43) (10.00g, 0.051 mol) and freshly

fused zinc chloride (10.53g, 0.077 mol) in nitromethane (40 ml) and dichloromethane (40 ml) under nitrogen. Stirring was continued for 1h then the reaction mixture was poured into ice-water (200 ml) and stirred for 1h. The layers were separated and the aqueous layer was washed with dichloromethane (30 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (3 x 50 ml) and brine (50 ml), dried, and concentrated at reduced pressure. The crude product was dissolved in glacial acetic acid (100 ml), freshly activated zinc powder (40g, 0.61 mol) was added, and the reaction mixture was refluxed while stirring under nitrogen for 16h. The cooled mixture was filtered and the solids were washed thoroughly with dichloromethane. Evaporation of the solvent at reduced pressure gave a yellow oil which was dissolved in dichloromethane (150 ml), washed with water (100 ml), saturated aqueous sodium bicarbonate (3 x 100 ml), and brine (100 ml), dried, and concentrated at reduced pressure. Chromatography on silica with gradient dichloromethane-hexane as eluant gave the lactone esters (59) and (60) (3.58g, 30% yield) as a yellow solid, m.p. 55-70°C (Found: C, 66.67; H, 5.87. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.02%); ν_{max}(melt) 1800 (CO lactone) and 1727 cm^{-1} (CO ester); $\delta_H(CDCl_3)$ 2.20(1.8H, s, CH_3-Ar of major isomer), 2.33(1.2H, s, CH_3-Ar of minor isomer), 2.50-3.00(4H, sym m, CH_2CH_2), 3.55, 3.59(2H, 2 x s, CH_2 of lactones), 3.61(3H, s, OCH_3), and 6.80-7.30 (2H, ABq for major isomer and 2 x s for minor isomer overlapping, Ar-*H*). From the ^1H n.m.r. spectrum the ratio of isomers was 60:40 (59):(60).

Alkylation with 4-chloro-2,2-dimethyl-1,3-oxathiolan-5-one (54)

4-Chloro-2,2-dimethyl-1,3-oxathiolan-5-one (54) (0.47g, 2.83 mmol) in dichloromethane (5 ml) was added dropwise over 20 min to a stirred suspension of phenol ester (43) (0.50g, 2.57 mmol) and zinc chloride (0.526g, 3.86 mmol) in nitromethane (5 ml) and dichloromethane (5 ml) under nitrogen. After 1h the reaction mixture was processed exactly as described above. The crude product was dissolved in glacial acetic acid (15 ml), activated zinc powder was added (0.80g, 0.012 mol), and the reaction mixture was refluxed for 12h while stirring under nitrogen. The lactone esters (59) and (60) were isolated as before (0.09g, 16% yield). Isomer ratio was 60:40 (59):(60) as before.

Alkylation with 3-chloro-trans-hexahydro-1,4-benzoxathiin-2(3H)-one (57)

A solution of α-chlorosulphide (57) (0.30g, 1.45 mmol) in dichloromethane (5 ml) was added dropwise over 20 min to a stirred mixture of phenol ester (43) (0.268g, 1.38 mmol) and zinc chloride (0.283g, 2.08 mmol) in nitromethane (2 ml) and dichloromethane (2 ml). After 10h the mixture was processed as before. The crude product was dissolved in glacial acetic acid (30 ml), activated zinc powder (0.32g, 4.89 mmol) was added, and the reaction mixture was refluxed for 12h while stirring under nitrogen. The lactone esters (59) and (60) were isolated as before (0.126g, 39% yield). From the ^{1}H n.m.r. spectrum the isomer ratio was 90:10 (59):(60).

Alkylation with ethyl 2-chloro-2,2-bis(n-butylthio)acetate (51)

Ethyl 2-chloro-2,2-*bis*(*n*-butylthio)acetate (51) (0.72g, 2.41 mmol) in carbon tetrachloride (5 ml) was added dropwise over 20 min to a stirred mixture of the phenol ester (43) (0.427g, 2.20 mmol) and zinc chloride (0.45g, 3.30 mmol) in nitromethane (3 ml) and dichloromethane (3 ml) under nitrogen. After 1h the reaction mixture was processed as before to give the crude product (1.11g) as a yellow oil. The ir spectrum indicated that very little lactonisation had occurred and t.l.c. showed that the major component was unreacted phenol ester (43).

3,5-Dimethyl-2(3H)-benzofuranone (45)[38,39]

A solution of methyl 2-chloro-2-(phenylthio)propionate (44) (2.35g) 0.010 mol) in carbon tetrachloride (12 ml) was added dropwise over 15 min to a stirred mixture of *p*-cresol (1g, 0.009 mol) and zinc chloride (1.90g, 0.014 mol) in nitromethane (15 ml) and dichloromethane (10 ml) under nitrogen. After 1h the reaction mixture was poured into ice-water (100 ml) and processed as before. The product (2.76g) was dissolved in glacial acetic acid (70 ml), activated zinc powder (6.7g, 0.049 mol) was added, and the reaction mixture was refluxed for 8h while stirring under nitrogen. The product was isolated as before with purification by radial chromatography on silica with gradient ethyl acetate-hexane as eluant to give the lactone (45) (1.08g, 72% yield) as a colourless viscous oil (Found: C, 73.80; H, 6.10. $C_{10}H_{10}O_2$ requires C, 74.05; H, 6.22%); ν_{max}(film) 1797 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.52(3H, d, J = 6.6Hz, CH_3CH), 2.36(3H, s, CH_3-Ar), 3.60(1H, q, J = 6.6Hz, $CHCH_3$), and 6.80-7.20(3H, m, Ar-*H*); $\delta_C(CDCl_3)$ 15.92(q, $CHCH_3$), 21.05(q, CH_3Ar), 38.46(d, *C*H), 110.26(d), 124.62(d), 128.71(s), 129.17(d), 133.85(s), 151.52(s), (Ar), and 178.35(s, *C*O). The spectral characteristics were in agreement with the reported values.[39]

1-Methylnaphtho[2,1-b]furan-2(1H)-one (58)[40]

A solution of methyl 2-chloro 2-(phenylthio)propionate (44) 0.007 mol) in carbon tetrachloride (9 ml) was added dropwise over 20 min to a stirred mixture of β-naphthol (1g, 0.007 mol) and zinc chloride (1.42g, 0.010 mol) in nitromethane (10 ml) and dichloromethane (15 ml) under nitrogen. After 1h the product was isolated as before (2.76g), and was dissolved in glacial acetic acid (30 ml). Activated zinc powder was added (6.58g, 0.10 mol) and the mixture was refluxed for 4h while stirring under nitrogen. The product was isolated as before. Purification by radial chromatography on silica with gradient ethyl acetate-hexane as eluant gave the lactone (58) (0.89g, 65% yield) as a white crystalline solid, m.p. 125-127°C (lit.,[40] 121-124°C) (Found: C, 78.78; H, 5.16. $C_{13}H_{10}O_2$ requires C, 78.77; H, 5.09%); ν_{max}(KBr) 1783 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.69(3H, d, J = 7.2Hz, CH_3), 3.91(1H, q, CH), and 7.10-7.90(6H, m, Ar-H); $\delta_C(CDCl_3)$ 16.70(q, CH_3), 38.53(d, CH), 111.50(d), 121.50(s), 122.47, 124.68, 127.48, 129.43, 129.82, 130.86(s), 150.93(s), (Ar), and 178.55 (s, CO).

Hydrolysis of lactone esters (59) and (60)[25]

The lactone mixture (8.00g, 0.034 mol; 60:40 ratio of (59):(60)) and sodium hydroxide (6.94g, 0.174 mol) in water (200 ml) was refluxed for 1 min while stirring under nitrogen, then was stirred for 20h at room temperature. The solution was washed with ether (2 x 40 ml) and was

cautiously acidified with conc. hydrochloric acid. The product was extracted with ether (3 x 60 ml). The combined organic extracts were washed with brine (50 ml), dried, and concentrated at reduced pressure to give the hydroxy acids (62) and (63) (7.96g, 98% yield) as a yellow solid which was relactonised without purification; ν_{max}(KBr) 3600-2200 (max. 3190, COOH and OH) and 1704 cm^{-1} (br, CO); δ_H(acetone-d_6) 2.22(3H, s, Ar-C*H*$_3$), 2.30-3.00(4H, sym m, C*H*$_2$C*H*$_2$), 3.52, 3.70(2H, 2 x s, C*H*$_2$COOH of minor and major isomers respectively), 6.60-7.10(2H, m, Ar-*H*), and 9.20(3H, brs, 2 x COO*H* and O*H*).

Regeneration of lactone ring[25]

The mixture of hydroxy acids (62) and (63) (10.71g, 0.045 mol) was dissolved in dichloromethane (150 ml) and ether (20 ml) containing p-toluenesulphonic acid (0.10g). The solution was refluxed for 22h while stirring under nitrogen, then washed with water (2 x 100 ml) and brine (100 ml), dried, and concentrated at reduced pressure to afford the lactone acids (64) and (65) (9.50g, 95.9% yield) as a yellow solid; ν_{max}(KBr) 3600-2400(max. 2945, COOH), 1801 (CO, lactone) and 1705 cm^{-1} (CO, carboxylic acid); δ_H($CDCl_3$/DMSO-d_6) 2.15(3H, s, Ar-C*H*$_3$), 2.30-3.00 (4H, sym m, C*H*$_2$C*H*$_2$), 3.58, 3.75(2H, 2 x brs, C*H*$_2$ of lactone of minor and major isomers respectively), and 6.90-7.20(2H, m, Ar-*H*).

Trituration of the mixture with ether gave the less soluble major isomer (4.32g), with no detectable trace of the minor isomer, as yellow plate-like crystals, m.p. 188-191°C (from methanol) (Found: C, 65.33; H, 5.47. $C_{12}H_{12}O_4$ requires C, 65.44; H, 5.47%); ν_{max}(KBr) 3600-2400 (max. 2930, COOH), 1800 (CO, lactone), and 1704 cm^{-1} (CO, carboxylic acid);

δ_H($CDCl_3$/DMSO-d_6) 2.19(3H, s, CH_3-Ar), 2.40-3.00(4H, sym m, CH_2CH_2), 3.81(2H, brs, CH_2 in lactone), and 6.80-7.30(2H, ABq, Ar-*H*); δ_C(DMSO-d_6) 15.46, 27.42, 32.22, 34.57, 107.27, 123.51, 128.26, 132.61, 134.50, 152.17, 173.67, and 174.32.

Acid chloride (71)

Lactone acid (64) (0.20g, 0.91 mmol) was stirred under nitrogen at 0°C in dichloromethane (1.5 ml). *N*,*N*-Dimethylformamide (1 drop) was added followed by oxalyl chloride[41] (0.128g, 1.0 mmol). The mixture was stirred for 90 min while the insoluble acid slowly dissolved. Attempts to isolate or characterise the acid chloride (71) resulted in its immediate hydrolysis. Therefore the acid chloride was treated with diazoethane without isolation.

Diazoketone (35)

A freshly prepared and distilled solution of diazoethane[26] (0.25g, 4.55 mmol) in ether (6 ml) was stirred under nitrogen at -29°C (nitromethane-liquid nitrogen slush) while the freshly prepared solution of the acid chloride in dichloromethane was added dropwise over 5 min. The residual acid chloride solution was rinsed through with ether (1 ml). The reaction mixture was stirred for 3h while slowly returning to room temperature. Excess diazoethane and ether were evaporated at reduced pressure. Chromatography of the residue on silica with 50% ethyl acetate, 50% hexane as eluant gave the diazoketone (35) (0.115g, 49% yield from the acid (64) as a yellow crystalline solid, m.p. 93-95°C (Found: C, 64.82; H, 4.93; N, 10.62. $C_{14}H_{14}N_2O_3$ requires C, 65.10; H, 5.46; N, 10.85%); ν_{max}(KBr) 2070 (CN_2), 1794 (CO, lactone), and

1628 cm^{-1} (CO, diazoketone); $\delta_H(CDCl_3)$ 1.93(3H, s, CH_3CN_2), 2.19(3H, s, CH_3Ar), 2.50-3.10(4H, sym m, CH_2CH_2), 3.53(2H, brs, CH_2 of lactone), and 6.80-7.30(2H, ABq, Ar-*H*); $\delta_C(CDCl_3)$ 8.06(q, CH_3CN_2), 15.85(q, CH_3-Ar), 27.48(t), 32.42(t), (CH_2CH_2), 38.27(t, CH_2 of lactone), 62.44(s, CN_2), 107.99(d), 122.99(s), 129.04(d), 132.87(s), 134.82(s), 152.69(s), (Ar), 174.26(s, *C*O lactone), and 193.36(s, *C*O diazoketone).

Cyclisation of α-diazoketone (35)

α-Diazoketone (35) (0.15g, 0.58 mmol) in dichloromethane (20 ml) was added dropwise over 20 min to dichloromethane (200 ml) containing the catalyst (0.5mg) while stirring under nitrogen (at 0°C with rhodium(II) mandelate, at reflux with rhodium(II) trifluoroacetate). Stirring was continued for 1h after which concentration at reduced pressure gave the cycloheptatrienone (34) (0.138g, quantitative yield) as a pale yellow flocculent solid; ν_{max}(film) 1803 (CO, lactone), 1743 (CO, cyclopentanone), and 1711 cm^{-1} (w, CO, norcaradiene); $\delta_H(CDCl_3)$ 0.89(3H, s, CH_3 bridgehead), 1.93(3H, s, CH_3-C=), 2.10-3.00(4H, m, CH_2CH_2), 3.49(2H, brs, CH_2 of lactone), 5.14(1H, d, J = 10.2Hz, C(8)*H*), and 6.22(1H, d, J = 10.2Hz, C(7)*H*). An impurity, tentatively identified as dimer, was responsible for the signal at δ_H 7.02. By integration, the trienone was approx. 90% pure. Product quality was similar with each catalyst.

Attempted reduction of trienone (34)

Trienone (72) (0.142g, 0.62 mmol) in ether (5 ml) and THF (1 ml) was added dropwise over 10 min to lithium tri-*tert*-butoxyaluminohydride (0.157g, 0.62 mmol) while stirring in ether (10 ml) at 0°C under nitrogen.

Stirring was continued for 1h, then water (5 ml) was added and the layers were separated. The aqueous layer was washed several times with dichloromethane and ether. The combined organic extracts were dried and concentrated at reduced pressure to afford tetralone (72)[25] (0.08g, 56.3% yield) as a yellow crystalline solid; ν_{max}(melt) 1800 (CO, lactone) and 1711 cm^{-1} (CO, ketone); $\delta_H(CDCl_3)$ 1.46(3H, d, J = 7.8Hz, CH_3CH), 2.29(3H, s, Ar-CH_3), 2.50-3.10(5H, m, CH_2CH_2 and $CHCH_3$), 3.63(2H, s, CH_2 of lactone), and 6.93(1H, s, Ar-H). These spectral data were in agreement with the reported values.[25]

5.3 OXONIUM YLIDE FORMATION AND REARRANGEMENT

Allyl o-allyloxybenzoate (1)

A mixture of salicyclic acid (20g, 0.145 mol) and potassium carbonate (50g, 0.362 mol) in acetone (300 ml) was refluxed while stirring under nitrogen for 45 min then cooled to room temperature. A solution of allyl bromide (43.80g, 0.362 mol) in acetone (250 ml) was added over 10 min and heating was continued for 37h. The cooled mixture was filtered and concentrated at reduced pressure to an oil which was shaken in dichloromethane and water (200 ml of each). The organic layer was separated, dried, and concentrated at reduced pressure to give the ester (1) (21g, 66.5% yield) as a clear, pale yellow oil which was used in the next experiment without purification; ν_{max}(film) 1721 (CO), 1672 (C=C), and 1643 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 4.53(2H, d, J = 4.8Hz, CH_2O), 4.75(2H, d, J = 6Hz, CH_2OCO), 5.00-5.70 (4H, m, 2 x CH_2=), 5.80-6.30(2H, m, 2 x OC*H*=), and 6.80-8.00(4H, m, Ar-*H*).

o-Allyloxybenzoic acid (2)

Allyl *o*-allyloxybenzoate (1) (17.89g, 0.082 mol) and sodium hydroxide (10.02g, 0.251 mol) in ethanol (100 ml) and water (50 ml) were refluxed for 5h while stirring under nitrogen, then concentrated at reduced pressure. The residue was shaken in dichloromethane and water (100 ml of each) and the layers separated. The aqueous layer was acidified cautiously with conc. sulphuric acid at 0°C then extracted with dichloromethane (4 x 50 ml). The combined organic extracts were

dried and concentrated at reduced pressure to furnish a yellow solid which was recrystallised from ether-hexane to give the acid (2) (12.316g, 84.3% yield) as pale yellow crystals, m.p. 62-65°C (lit.,[42] 64-65°C) (Found: C, 67.90; H, 5.61. $C_{10}H_{10}O_3$ requires C, 67.40; H, 5.66%); ν_{max}(KBr) 3500-2120 (COOH), 1689 (CO), and 1661 cm^{-1} (C=C); δ_H($CDCl_3$) 4.77(2H, d, *J* = 7.8Hz, CH_2), 5.20-5.80(2H, m, =CH_2), 5.80-6.50 (1H, m, =C*H*), 6.90-8.20(4H, m, Ar-*H*), and 10.50(1H, brs, CO_2H); δ_C($CDCl_3$) 70.50(t, CH_2), 113.31(d), 117.99(s), 119.74(d), 121.89(d), 131.31(t, =CH_2), 133.33(d), 135.02(d), 157.56(s), and 166.72(s, *C*O).

o-Allyloxybenzoyl chloride (3)[42]

o-Allyloxybenzoic acid (5.0g, 0.028 mol) in thionyl chloride (20 mls, 0.27 mol) was heated at 74°C for 2h while stirring under nitrogen, then concentrated at reduced pressure to a brown oil which was purified by distillation in a Kugelrohr apparatus (oven temp. 94-95°C at 0.05 mmHg) to afford acid chloride (3) (4.16g, 75.4% yield) as a white crystalline solid, m.p. 15°C approx. (Found: C, 60.74; H, 4.36. $C_{10}H_9O_2Cl$ requires C, 61.08; H, 4.61%); ν_{max}(film) 1775 (CO) and 1646 cm^{-1} (C=C); δ_H($CDCl_3$) 4.62(2H, d, *J* = 4.8Hz, CH_2), 5.10-6.40(3H, m, C*H*=CH_2), and 6.90-8.10(4H, m, Ar-*H*).

o-Allyloxy-(diazoacetyl)benzene (4)[43]

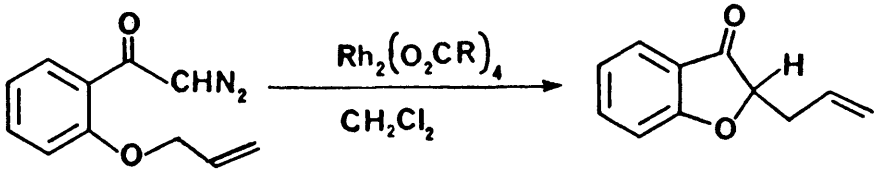
o-Allyloxybenzoyl chloride (3.50g, 0.018 mol) in ether (20 ml) was added dropwise over 15 min to a freshly prepared and distilled solution of diazomethane[6] (3.0g, 0.071 mol) in ether (200 ml) while stirring at 0°C under nitrogen. Stirring was continued for 16h allowing the reaction mixture to return slowly to room temperature. Evaporation of excess

diazomethane and ether at reduced pressure gave a yellow oil which was purified by chromatography on silica with dichloromethane-hexane as eluant to give diazoketone (4) (1.179g, 33% yield, major loss due to decomposition on silica) as a yellow crystalline solid, m.p. 56-57°C (Found: C, 64.87; H, 4.99; N, 13.58. $C_{11}H_{10}N_2O_2$ requires C, 65.34; H, 4.99; N, 13.85%); ν_{max}(KBr) 2095 (CN_2) and 1590 cm^{-1} (CO); $\delta_H(CDCl_3)$ 4.62(2H, d, J = 5.4Hz, CH_2), 5.00-6.50(3H, m, $CH{=}CH_2$), 6.34(1H, s, CHN_2), and 6.90-8.00(4H, m, Ar-*H*); $\delta_C(CDCl_3)$ 57.96(d, CHN_2), 69.59(t, CH_2), 112.08, 118.57, 120.98, 136.31(s), 130.34, 132.42, 133.33, 157.24(s), 185.31(s, *C*O).

2-Allyl-(2H)-benzofuran-3-one (5)[43]

Diazoketone (4) (0.10g, 0.495 mmol) in dichloromethane (10 ml) was added dropwise over 10 min to dichloromethane (100 ml) containing a rhodium(II) carboxylate catalyst (0.5 mg) (see Table 5.15 for list of catalysts used) at reflux while stirring under nitrogen. Within 10 min t.l.c. showed complete decomposition of the diazoketone. Evaporation of the solvent at reduced pressure gave an oil which was purified by p.l.c. on silica with dichloromethane as eluant to give the benzofuranone (5) (0.063g, 73.5% yield) as a clear colourless oil; ν_{max}(film) 1710 (CO) and 1608 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 2.40-2.80(2H, m, CH_2), 4.57(1H, dd, J_1= 4.2Hz, J_2= 7.2Hz, C(2)*H*), 5.00-6.20(3H, m, $CH{=}CH_2$), and 6.90-7.80 (4H, m, Ar-*H*); $\delta_C(CDCl_3)$ 35.48(t, CH_2), 84.60(d, *C*H), 113.57(d), 118.96(t), 121.04(s), 121.95(d), 124.29(d), 131.77(d), 138.07(d), 172.76(s), and 201.28(s, *C*O). Table 5.15 shows the catalyst dependency of the asymmetric induction observed in the rearrangement leading to (5). Attempted purification of the crude product on alumina gave almost total decomposition.

Table 5.15: Effect of catalyst on the decomposition of *o*-allyloxy-(diazoacetyl)benzene (4)



(4) (5)

Catalyst	$[\alpha]_D^{20}$ (crude)[a] / °(c, CH_2Cl_2)	$[\alpha]_D^{20}$ (after chromatography) / °(c, CH_2Cl_2)
$Rh_2(OAc)_4$	0	0
1	+3.1 (8-9)	<1 (6.3)
4	-14.2 (10-12)	<1 (8.0)

[a] The specific rotation reported was the average obtained in several reactions.

2-Allyl-2,3-dihydrobenzofuran-3-ol (6)

The benzofuranone (5) (0.130g, 0.746 mmol) in ether (10 ml) was added dropwise over 30 min to lithium tri-*tert*-butoxyaluminohydride (0.59g, 2.32 mmol) in ether (10 ml) while stirring at 0°C under nitrogen. Stirring was continued for 20h at room temperature, then the reaction mixture was cooled to 0°C and water (5 ml) was added cautiously. The layers were separated and the aqueous layer was extracted with ether (3 x 10 ml). The combined organic extracts were dried and concentrated at reduced pressure to an oil which was purified by p.l.c. on silica with 60% ethyl acetate, 40% hexane as eluant to give the alcohol mixture (6) (0.036g, 27.4% yield) as an oil; ν_{max}(film) 3370 (OH) and 1610 cm^{-1} (C=C); $\delta_H(CDCl_3)$ 1.90(1H, brs, O*H*), 2.20-2.80(2H, m, CH_2), 4.30-4.70(1H, m, C(2)*H*), 4.90-6.30(4H, m, C*H*OH and C*H*=CH_2), and 6.70-7.30(4H, m, Ar-*H*); $\delta_C(CDCl_3)$ 32.81/37.68(t, *C*H_2), 72.45/76.54(d, *C*(2)H), 86.22/89.99(d, *C*HOH), 110.59(d), 117.73/118.38, 121.04, 125.85/125.59, 128.97/127.93, 130.79, 134.24/132.81, and 159.77(s). The pairs of peaks indicated in the ^{13}C n.m.r. spectrum suggested the formation of a 60:40 pair of diastereoisomeric alcohols. ^1H n.m.r. studies with chiral shift reagents did not provide any further information on the composition of the mixture.

The benzofuranone (5), derived from diazoketone (4) by a rhodium(II) *N*-benzenesulphonyl-*L*-prolinate catalysed decomposition, had a specific rotation $[\alpha]_D^{20}$ -10.5° (c 12.9 in CH_2Cl_2). The benzofuranol mixture produced on reduction had $[\alpha]_D^{20}$ -2.1° (c 9.3 in CH_2Cl_2) (crude), $[\alpha]_D^{20}$ -3.5° (c 3.6 in CH_2Cl_2) (after p.l.c.).

5.4 References

1. M.W. Rathke and A. Lindert, *J. Org. Chem.*, 1970, 35, 3966.
2. 'Dictionary of Organic Compounds', 4th ed., Vol. 2, Eyre and Spottiswode, p.802.
3. 'Textbook of Practical Organic Chemistry', Vogel, 4th ed., Longmans, 1978, p.513.
4. W.G. Taylor, *J. Org. Chem.*, 1981, 46, 4290.
5. Prepared by G. Roos in 60% yield from allyl acetate *via* the TMS enolate rearrangement (modified Claisen) by a modification of the literature procedure in R.E. Ireland, R.H. Mueller, and A.K. Willard, *J. Am. Chem. Soc.*, 1976, 98, 2868. Isopropylcyclohexylamine was replaced by diisopropylamine.
6. Ref. 3, p.291, for the preparation of diazomethane from Diazald.
7. L. Field and R.D. Clark, *Org. Synth.*, Coll. Vol. IV, 1963, 674.
8. 'Reagents for Organic Synthesis', Fieser and Fieser, 1967, Vol. 1, p.296.
9. E.J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, 87, 1345.
10. H.J. Monteiro, *Synth. Commun.*, 1987, 17, 983.
11. Prepared by P. Hetherington, 4th year project, in 94% yield from phenylbutyric acid.
12. W. Illger, A. Liedhegener, and M. Regitz, *Justus Liebegs Ann. Chem.*, 1972, 760, 1.
13. For the preparation of tosyl azide see T.J. Curphey, *Org. Prep. Proced. Int.*, 1981, 13, 112.

14. Preparation by G. Roos in 80% yield by acylation of Meldrum's acid with pentanoyl chloride and subsequent methanolysis according to Y. Oikawa, T. Yoshioka, K. Sugano, and O. Yonemitsu, *Org. Synth.*, 1985, 63, 198. Meldrum's acid was prepared as described by D. Davidson and S.A. Bernhard, *J. Am. Chem. Soc.*, 1948, 70, 3426.

15. Preparation by G. Roos by ester exchange of methyl 3-oxoheptanoate[14] and borneol (80% yield) using the procedure in D.F. Taber, J.C. Amedio, and K. Raman, *J. Org. Chem.*, 1988, 53, 2984. $[\alpha]_D^{20}$ -15.7° (c 2.6 in CH_2Cl_2).

16. Preparation by G. Roos by alkylation of the disodium salt of pentan-2,4-dione with propyl bromide (75% yield) using the procedure in K.G. Hampton, T.M. Harris, and C.R. Hauser, *Org. Synth.*, Coll. Vol. V, 1973, 848; 'Dictionary of Organic Compounds', 5th ed., Chapman and Hall, Vol. 4, 1982, 4380.

17. H.J. Monteiro, *Tetrahedron Lett.*, 1987, 28, 3459.

18 (a) 'Dictionary of Organic Compounds', Chapman and Hall, 5th ed., 1982, Vol. 4, p. 3816;

(b) W.C.M.C. Kokke and F.A. Varkevisser, *J. Org. Chem.*, 1974, 39, 1535;

(c) W.G. Dauben, L. Schutte, R.E. Wolf, and E.J. Deviny, *J. Org. Chem.*, 1969, 34, 2512.

19. See ref. 9 for the desulphonylation procedure; for the preparation of aluminium amalgam see 'Reagents for Organic Synthesis', Fieser and Fieser, 1967, Vol. 1, Wiley, p.20.

20. (a) 'Handbook of Chemistry and Physics', 67th ed., CRC press;

(b) Commercially available sample of (R)-(+)-3-methylcyclopentanone from Aldrich Chemical Co. Ltd.

21. 'Reagents for Organic Synthesis', Fieser and Fieser, 1967, Vol. 1, Wiley, p. 142.

22. S.A. Matlin, W.J. Lough, L. Chan, D.M.H. Abram, and Z. Zhou, *J. Chem. Soc., Chem. Commun.*, 1984, 1038.

23. S.M. Tuladhar, Ph.D. thesis, N.U.I., 1984.

24. J.R. Johnson, *Org. React.*, 1942, 1, 210.

25. M. Kennedy, Ph.D. thesis, N.U.I., 1986.

26. J.A. Marshall and J.J. Partridge, *J. Org. Chem.*, 1968, 33, 4090, for the preparation of diazoethane from *N*-ethyl-*N*-nitrosourea; the reagent was prepared following the procedure given by F. Arndt, *Org. Synth.*, Coll. Vol. II, 1943, 461.

27. L.T. Scott, M.A. Minton, and M.A. Kirms, *J. Am. Chem. Soc.*, 1980, 102, 6311.

28. For use of K-Selectride see B. Ganem, *J. Org. Chem.*, 1975, 40, 146.

29. C. Iwata, M. Yamada, Y. Shinoo, K. Kobayashi, and H. Okada, *Chem. Pharm. Bull.*, 1980, 28, 1932.

30. B.B. Snider and C.P. Cartaya-Marin, *J. Org. Chem.*, 1984, 49, 153.

31. D.J. Nelson and E.A. Uschak, *J. Org. Chem.*, 1977, 42, 3308.

32. A.J. Pearson and T.R. Perrior, and D.A. Griffin, *J. Chem. Soc., Perkin Trans I*, 1983, 625.

33. J.P. Cronin, B.M. Dilworth, and M.A. McKervey, *Tetrahedron Lett.*, 1986, 27, 757.

34. (a) S. Satsumabayashi, S. Irioka, H. Kudo, K. Tsujimoto, and S. Motoki, *Bull. Chem. Soc. Jpn.*, 1972, 45, 913;
(b) K. Pihlaja, A. Nikkila, K. Neuvonen, and R. Keskinen, *Acta Chem. Scand., Part A*, 1976, 30, 457.
(c) J. Butera, J. Rini, and P. Helquist, *J. Org. Chem.*, 1985, 50, 3676.

35. K. Arai, Y. Ohara, T. Iizumi, and Y. Takakuwa, *Tetrahedron Lett.*, 1983, 24, 1531.

36. Prepared by M. Kennedy by the procedure in ref. 25.

37. Prepared by S. Naughton by the procedure in J.K. Koskimies, *Acta Chem. Scand., Part B*, 1984, 38, 101.

38. M. Kennedy, A.R. Maguire, and M.A. McKervey, *Tetrahedron Lett.*, 1986, 27, 761.

39. O. Piccolo, L. Filippini, L. Tinucci, E. Valoti, and A. Citterio, *J. Chem. Res. (S)*, 1985, 258.

40. R.A. Clement and T.-C. Shieh, *J. Org. Chem.*, 1960, 25, 1850.

41. T.F. Buckley and H. Rapoport, *J. Am. Chem. Soc.*, 1981, 103, 6157.

42. T. Shimizu, Y. Hayashi, Y. Nagano, and K. Teramura, *Bull. Chem. Soc. Jpn.*, 1980, 53, 429.

43. M.C. Pirrung and J.A. Werner, *J. Am. Chem. Soc.*, 1986, 108, 6060.

APPENDIX

Preparation of Rhodium(II) Carboxylates

The rhodium(II) carboxylate catalysts were prepared[1] from the sodium salt of rhodium carbonate and the appropriate acid by a simple displacement reaction.[2] The carbonate, $Na_4Rh_2(CO_3)_4.2\frac{1}{2}H_2O_2$, was prepared from rhodium(II) acetate in >90% yield,[3] which was in turn prepared from rhodium(III) chloride.[4]

The *N*-protected L-amino acids were prepared by standard procedures.[5] The sulphonyl derivatives of L-proline and L-phenylalanine were generally prepared by treatment of a basic solution of the amino acid with the appropriate sulphonyl chloride. The carboxylic acids were characterised spectroscopically and were analytically pure when used in the catalyst preparation.

Rhodium(II) (S)-mandelate.$2H_2O$

Rhodium carbonate (25 mg, 4.29×10^{-5} mol) and (S)-mandelic acid (52 mg, 3.43×10^{-4} mol) in water (2 ml) was heated at 80-100°C while stirring for 30 min. The precipitate was collected by filtration and washed with water to give rhodium(II) (S)-mandelate.$2H_2O$ (31 mg, 90% yield) as blue-green crystals. (Found: C, 45.22; H, 3.87. $C_{32}H_{28}O_{12}Rh_2.2H_2O$ requires C, 45.39; H, 3.78%); ν_{max}(KBr) 1601 cm^{-1} (CO).

The rhodium(II) mandelate obtained was identical to that obtained following Cotton's procedure,[6] except that the ethanol ligands were replaced by water ligands.

The rhodium(II) carboxylates in Table 5.16 were prepared following the procedure given for rhodium(II) mandelate from rhodium carbonate (25 mg) and the appropriate carboxylic acid (8 equivalents). The carboxylates were obtained as green or blue-green precipitates except for those derived from lactic acid and tartaric acid, which were water soluble and were isolated in crude form by concentration of the reaction mixture. Several of the rhodium(II) carboxylates gave very poor microanalyses, possibly due to uncertainty about solvent of crystallisation.

Catalyst (22), rhodium(II) α-methoxy-α-phenylacetate, was prepared following Cotton's procedure.[6,7] Catalysts (23), $Rh_2(mand)_2(phen)_2Cl_2.4H_2O$[2], and (24), $Rh_2(OAc)_2(Ph_2PC_6H_4)_2.2AcOH$[8], were prepared by literature procedures. Catalysts (25), $Rh_2(OAc)_2(dppe)_2Cl_2$, and (26), $Rh_2(OAc)_2[(R)-(+)-BINAP]_2Cl_2$, were prepared as orange solids by a modification of the literature procedure[9] in which diphenylphosphinomethane was replaced by diphenylphosphinoethane and (R)-(+)-BINAP to give (25) and (26), respectively.

Rhodium(II) trifluoroacetate was prepared from rhodium(II) acetate following the literature procedure.[10]

Table 5.16 : Preparation of rhodium(II) carboxylates from $Na_4Rh_2(CO_3)_4.2\frac{1}{2}H_2O$

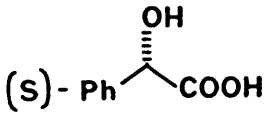
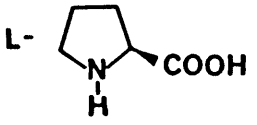
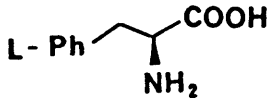
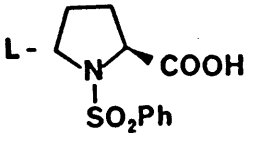
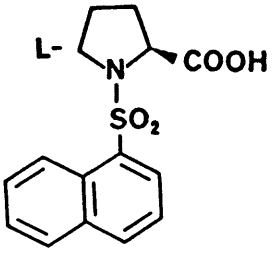
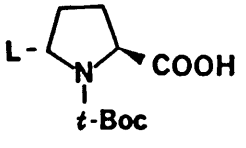
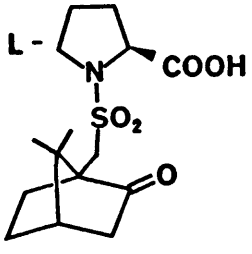
RCOOH	Catalyst	Yield	ν_{max} cm^{-1}	Elemental Analysis
	1	90	1601	Found: C, 45.22; H, 3.87. $C_{32}H_{28}O_{12}Rh_2.2H_2O$ requires C, 45.39; H, 3.78%
	2	-	-	- Pale green powders only
	3	-	-	-
	4	90	1601	Found: C, 43.40; H, 4.39; N, 4.25. $C_{44}H_{48}O_{16}N_4S_4Rh_2$. 2EtOH requires C, 43.84; H, 4.60; N, 4.26%.
	5	85	1596	Found: C, 49.07; H, 4.18; N, 3.81. $C_{60}H_{56}N_4S_4O_{16}Rh_2.2H_2O$ requires C, 49.39; H, 4.12; N, 3.84.
	6	77	1687, 1593	Found: C, 43.44; H, 6.03; N, 5.05. $C_{40}H_{64}N_4O_{16}Rh_2$. $2H_2O$ requires C, 43.88; H, 6.22; N, 5.12.
	7	87	1738, 1598	Found: C, 45.49; H, 5.85; N, 3.50. $C_{60}H_{88}N_4S_4O_{20}Rh_2.2H_2O$ requires C, 46.33; H, 5.66; N, 3.60%.

Table 5.16 contd.

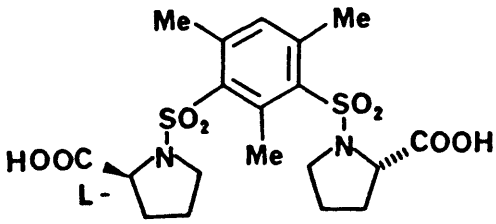
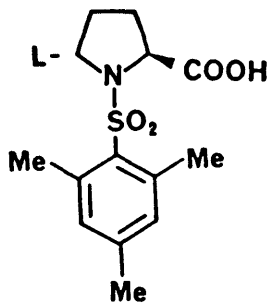
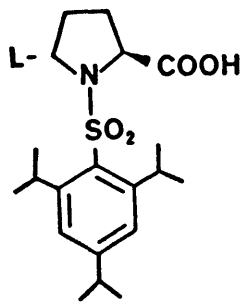
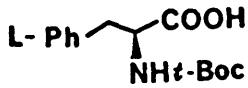
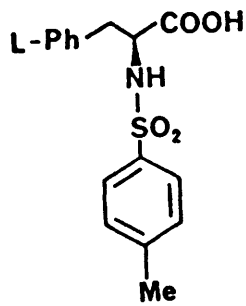
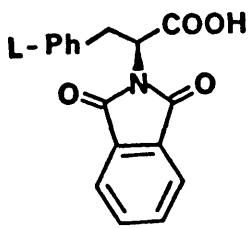
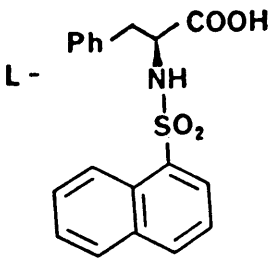
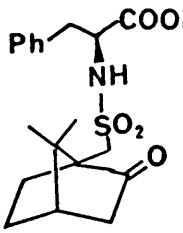
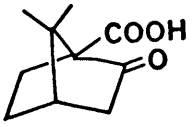
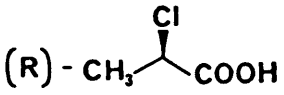
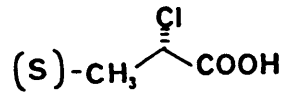
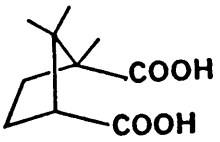
	8	69	1599, 1726	Found: C, 40.48; H, 4.84; N, 4.62. $C_{76}H_{96}N_8S_8O_{32}Rh_2 \cdot 2H_2O$ requires C, 42.82; H, 4.51; N, 5.26%.
	9	-	-	-
	10	-	-	-
	11	80	1593, 1686	Found: C, 53.99; H, 6.08; N, 4.46. $C_{56}H_{72}N_4O_{16}Rh_2$ requires C, 53.26; H, 5.71; N, 4.44%.
	12	62	1591	Found: C, 48.70; H, 4.20; N, 3.57; S, 8.46. $C_{64}H_{64}N_4S_4O_{16}Rh_2 \cdot 2H_2O$ requires C, 50.70; H, 4.49; N, 3.70; S, 8.46%.
	13	92	1708, 1598	Found: C, 55.97; H, 3.67; N, 4.01. $C_{68}H_{48}N_4O_{16}Rh_2 \cdot 2H_2O$ requires C, 57.70; H, 3.68; N, 3.96%.

Table 5.16 contd.

L- 	14	65	1588	-
L- 	15	27	-	Found: C, 52.93; H, 6.18; N, 2.87. $C_{26}H_{96}N_4S_4O_{20}Rh_2.2H_2O$ requires C, 52.00; H, 5.47; N, 3.19%.
	16	85	1572, 1739	Found: C, 47.58; H, 5.55. $C_{40}H_{52}O_{12}Rh_2.2H_2O$ requires C, 49.69; H, 5.79%.
(R)- 	17	52	1588	Found: C, 23.03; H, 2.52; Cl, 22.02. $C_{12}H_{16}Cl_4O_8Rh_2.2H_2O$ requires C, 22.65; H, 2.52; Cl, 22.33%.
(S)- 	18	63		
Tartaric acid	19	-	-	-
Lactic acid	20	-	-	-
	21	80	1688, 1566	-

1. Catalyst preparation was carried out by G. Roos.

2. F. Pruchnik, B.R. James, and P. Kvintovics, *Can. J. Chem.*, 1986, 64, 936.

3. C.R. Wilson and H. Taube, *Inorg. Chem.*, 1975, 14, 405.

4. G.A. Rempel, P. Legzdins, H. Smith, and G. Wilkinson, *Inorg. Synth.*, 1972, 90.

5. B.M. Dilworth, Ph.D. thesis, N.U.I., 1987.

6. P.A. Agaskar, F.A. Cotton, L.R. Falvello, and S. Han, *J. Am. Chem. Soc.*, 1986, 108, 1214.

7. Catalyst (22) prepared by N. Garvey.

8. A.R. Chakravarty, F.A. Cotton, D.A. Tocher, and J.H. Tocher, *Organometallics*, 1985, 4, 8.

9. F.A. Cotton, K.R. Dunbar, and M.G. Verbruggen, *J. Am. Chem. Soc.*, 1987, 109, 5498.

10. P. Legzdins, R.W. Mitchell, G.L. Rempel, J.D. Ruddick, and G. Wilkinson, *J. Chem. Soc. (A)*, 1970, 3322.

Abbreviations

The following are a list of abbreviations used in this thesis.

^{1}H n.m.r.

s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
dd	doublet of doublets

Prefix br broad

ir

br	broad
w	weak

t.l.c.	thin layer chromatography
p.l.c.	preparative thin layer chromatography
EDA	ethyl diazoacetate
THF	tetrahydrofuran
DMSO	dimethylsulphoxide
acac	acetylacetonato
hfacac	hexafluoroacetylacetonato
TFA	trifluoroacetic acid
$Eu(tfc)_3$	tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium(III) derivative.

Publications

1. Organic Synthesis with α-Chlorosulphides. Conversion of Phenols into γ-Lactones using Methyl-2-chloro-2-(alkyl or arylthio)carboxylates , M. Kennedy, A.R. Maguire, and M.A. McKervey, *Tetrahedron Lett.*, 1986, 27, 761.
2. Organic Synthesis with α-Chlorosulphides. Preparation of Aromatic γ-Lactones from Phenols and α-Chlorosulphide Carboxylates, M. Kennedy, M.A. McKervey, A.R. Maguire, and S. Naughton, in preparation.
3. The Intramolecular Buchner Reaction of Aryl Diazoketones. Substituent Effects and Scope in Synthesis, M. Kennedy, M.A. McKervey, A.R. Maguire, S.M. Tuladhar, and M.F. Twohig, in preparation.
4. The Intramolecular Buchner Reaction of Aryl Diazoketones. Synthesis of Polyfunctional Hydroazulene Lactones, H. Duddeck, G. Ferguson, M. Kennedy, M.A. McKervey, and A.R. Maguire, in preparation.
5. Organic Synthesis with α-Diazocarbonyl Compounds, A.R. Maguire and M.A. McKervey, in preparation.

Tetrahedron Letters, Vol.27, No.6, pp 761-764, 1986 0040-4039/86 $3.00 + .00
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ORGANIC SYNTHESIS WITH α-CHLOROSULPHIDES. CONVERSION OF PHENOLS INTO γ-LACTONES USING METHYL-2-CHLORO-2-(ALKYL OR ARYLTHIO)CARBOXYLATES

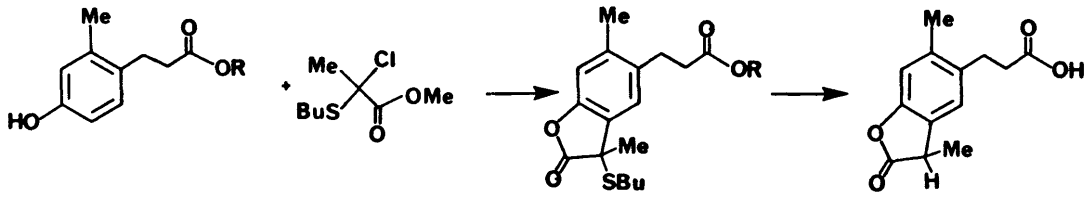
Michael Kennedy, Anita R. Maguire, and M. Anthony McKervey

Department of Chemistry, University College, Cork. Ireland.

Summary Aromatic γ-lactones can be synthesised from 4-substituted phenols in a single step by zinc chloride-catalysed alkylation with methyl-2-chloro-2-(butylthio or phenylthio)propionate or acetate.

Recent work has established that α-chloroalkyl sulphides are useful electrophiles for alkylation of aromatics[1,2], alkenes[3], alkynes[4], silyl enol ethers[5] and ketene (bis-trimethylsilyl)acetals[6], and in the preceding paper we have shown that they are also readily transformed into a wide variety of (phenylthio)acetals[7,8]. In connection with a problem in sesquiterpene synthesis we required a method of transforming phenolic acid (1) into the γ-lactone (4). A quick solution to the problem was forthcoming when we examined the reaction of (1) with methyl-2-chloro-(butylthio)-propionate (2)[2] in the presence of Lewis acids. The reaction has proved to be quite general for phenols bearing para substitution, offering a convenient route to aromatic γ-lactones. Although zinc chloride and stannic chloride were both efficacious catalysts, the latter was less satisfactory in practice due to its tendency to promote side reactions.

Addition of (2) (.017 mol) to a 1:1 dichloromethane:nitromethane solution of (1) (.016 mol) and anhydrous zinc chloride (.032 mol) at room temperature (reaction time ca. 1 h) gave the sulphenylated lactone (3) in 44% yield[9]. Desulphurisation of (3) with zinc dust in glacial acetic acid furnished the desired lactone (4)[9], m.p. 150-152°C, in essentially quantitative yield. The lactonisation step was much more efficient with the methyl ester rather than the free carboxylic acid, (5) furnishing (6) in 70% yield. Whilst examining the scope of the reaction we found that



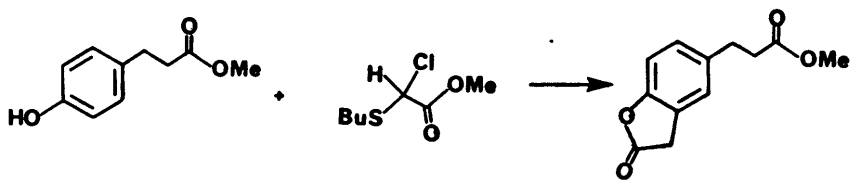
(1) R = H
(5) R = Me

(2)

(3) R = H
(6) R = Me

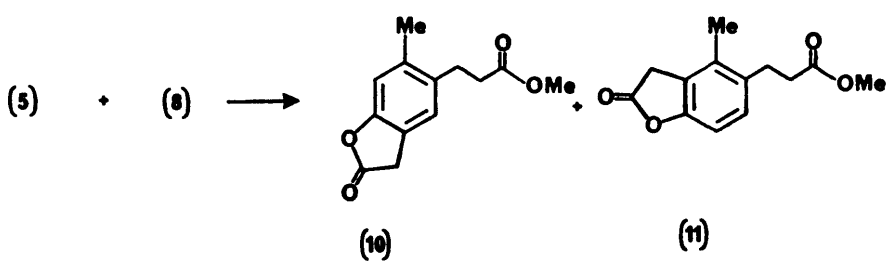
(4)

the α-(butylthio) substituent was sufficiently activating to permit alkylation of phenols with sulphenylated electrophiles derived from α-chloroacetate also. Thus treatment of phenolic cinnamate (7) with methyl-2-chloro-2-(butylthio)acetate (8) in the presence of zinc chloride, followed by desulphurisation with zinc-acetic acid, furnished lactone (9)[9], m.p. 67-68°C, in



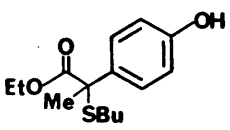
(7) (8) (9)

58% overall yield. However, in terms of regioselectivity the sulphenylated α-chloroacetate is less discriminating than the corresponding α-chloropropionate. Thus whereas (5) gave a single alkylated product (6) with chlorosulphide (2), a similar reaction with chlorosulphide (8) gave, after desulphurisation, a 40:60 mixture[10] of lactones (10) and (11) in 35% yield.

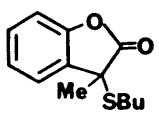


(10) (11)

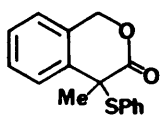
This aromatic lactonisation is most successful with phenols in which the para position is blocked. When we applied the procedure to phenol itself and the ethyl ester of chlorosulphide (2), the phenolic ester (12) was the major product (60%)[11] with less than 10% of lactone (13) which was not isolated. p-Cresol and 2-naphthol, on the other hand, underwent smooth lactonisation with chloro-(phenylthio)propionate (14) giving, after reductive desulphurisation, lactone (15)[9] (80%) and (16)[12] (82%), respectively. An attempt was made to extend the process



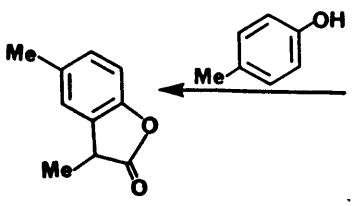
(12)



(13)



(17)



(15) (14) (16)

to the synthesis of δ-lactones using benzyl alcohols as substrates. However, p-methylbenzyl alcohol produced less than 15% of a lactone presumed from n.m.r. and i.r. data to be (17),though it was not isolated in a pure state. In summary, this aromatic lactonisation is most successful with p-substituted phenols. Furthermore, the thioether substituent in the product is nicely placed for other functional group manipulations, e.g. production of α-methylene lactones via sulphoxide elimination.

References and Footnotes

1. H. Gross and G. Matthey, Chem.Ber., 1964, 97, 2606; K. Arai and M. Oko, Bull.Chem.Soc., Jap., 1976, 49, 553; M.A. McKervey and P. Ratananukul, Tetrahedron Lett., 1983, 24, 117.
2. Y. Tamura, H. Shindo, J. Uenishi, and H. Ishibashi, Tetrahedron Lett., 1980, 21, 2547.
3. M. Wada, T. Shigehisa, H. Kitani and K. Akiba, Tetrahedron Lett., 1983, 24, 1715.
4. H. Ishibashi, S. Akai, H.D. Choi, H. Nakagawa, and Y. Tamura, Tetrahedron Lett., 1983,24, 3877.
5. I. Paterson and I. Fleming, Tetrahedron Lett., 1979, 993, 995, 2179; I. Fleming, Chem.Soc. Rev., 1981, 10, 83; P. Brownbridge, Synthesis, 1983, 1, 85.
6. H.A. Khan and I. Paterson, Tetrahedron Lett., 1982, 23, 5083.
7. J.P. Cronin, B.M. Dilworth, and M.A. McKervey, Tetrahedron Lett., 1985, preceding paper.
8. For a recent review of organic synthesis with α-chlorosulphides see B.M. Dilworth and M.A. McKervey, Tetrahedron Reports, in the press.
9. All new compounds gave spectroscopic data consistent with the assigned structures and satisfactory analytical data.
10. The isomer ratio was determined by n.m.r.; the compounds were not separated.
11. This reaction has also been reported by Tamura et al. (ref. 2) who record compound(12) as the sole product. We obtained (12) (60%) with about 30% of a dimeric by-product.
12. R.A. Clement and T-C. Shieh, J.Org.Chem., 1960, 25, 1850.

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