A THESIS ENTITLED

"A STEREOCHEMICAL STUDY OF

THE S_E' REACTION"

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for the Degree of Doctor of Philosophy

in the Faculty of Science

by

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To my Mum and Dad

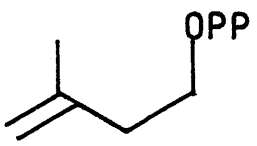
and my wife, Catherine.

CONTENTS

SUMMARY

Summary

The *in vivo* isomerisation of iso-pentenyl pyrophosphate (13) to dimethylallyl pyrophosphate (14) and the condensation of these two C-5 units to geranyl pyrophosphate (15), although formally recognisable as S_E2' processes[30] (Scheme 9) have been rationalised in a stepwise manner.[32] One reason for doing so is the uncertainty as to the stereochemical preference in the non-enzymic S_E' reaction and this is compounded by the fact that of the two biological reactions, one proceeds with overall *syn*- and the other with overall *anti*-stereochemistry.[31]



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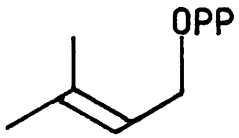

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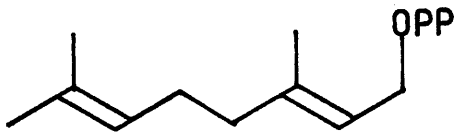

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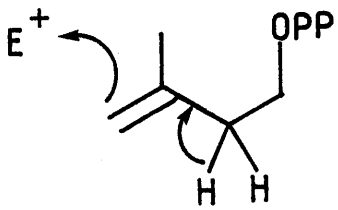
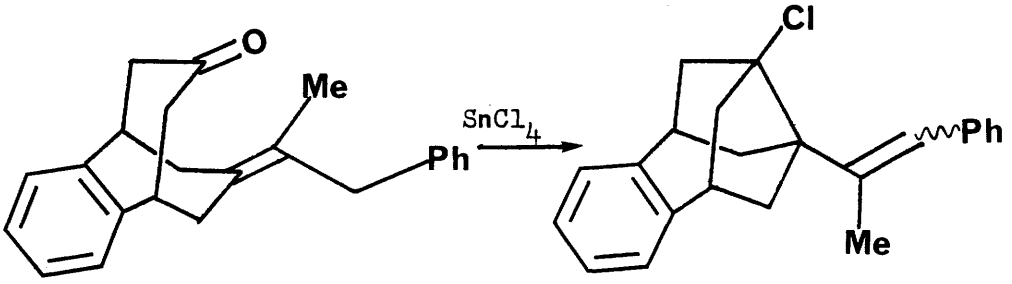


Scheme 9

Whereas stereochemical preference in the formally analogous S_N2' and S_N' reactions has recently received considerable attention,[10] only two published investigations deal with the S_E' reaction,[30,38] and both have limitations as models for the general reaction.

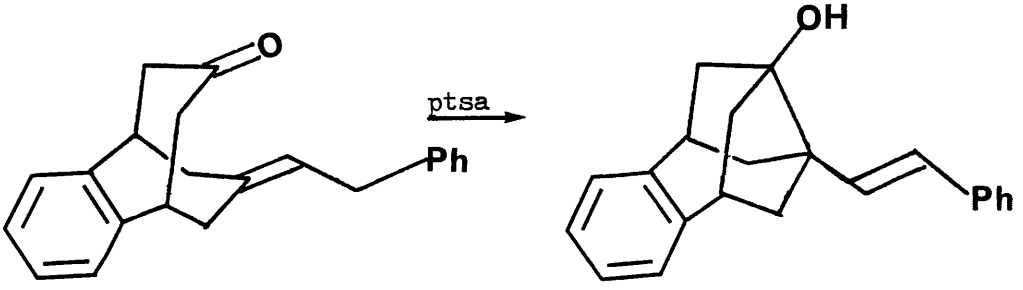
The aim of this thesis was to demonstrate stereochemical preference of an <u>in vitro</u> S_E' reaction in an appropriate laboratory model system.

The first part describes synthetic approaches to, and synthesis of, potential model systems. Conditions for an S_E' reaction were established for the model systems (140) and (99) as illustrated in Schemes 61 and 62. The model system (99), being more readily accessible than (140) was selected for this investigation.



(140)

Scheme 61

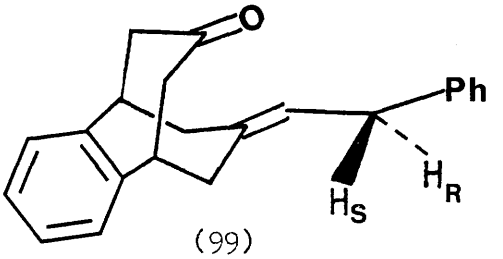


(99) (113)

Scheme 62

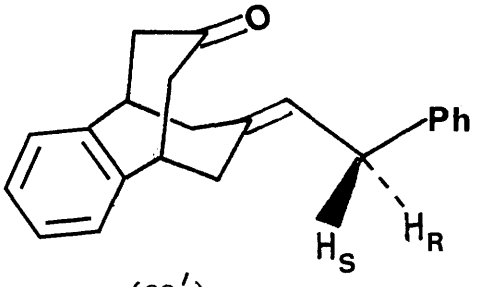
A stereochemical study of the S_E' reaction of (99) required:

(a) Stereospecific incorporation of a deuterium label in the side chain [i.e. (99) H_R or H_S=D].

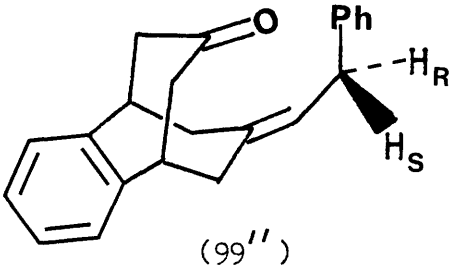


(99)

(b) Resolution of (99) (H_R or H_S=D) into (99′) and (99″) (H_R or H_S=D).

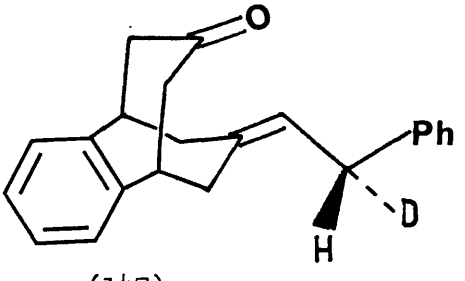


(99′)



(99″)

(c) The use of labelled, resolved material [e.g. (147) or (148)] in an S_E' reaction.



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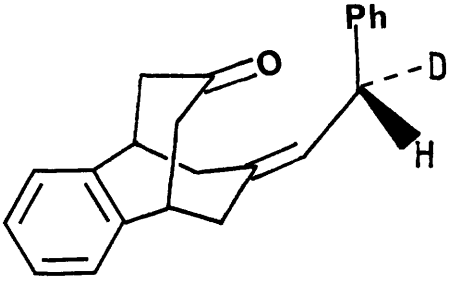


(148)

(d) Investigations of the deuterium content in the products by NMR and MS.

The synthesis of stereospecifically labelled model system (99) (H_R=D) has been completed but resolution, to give (147) and (148) although achieved on an analytical scale by chromatographic techniques, requires further development. The analysis of the possible products from S_E' reactions of (147) and (148) is discussed.

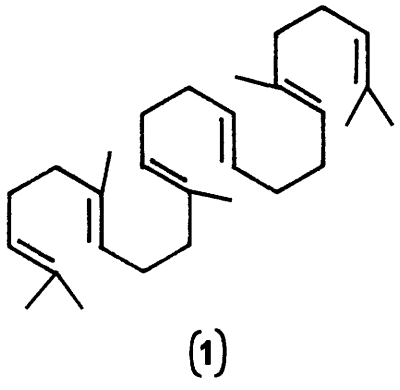
INTRODUCTION

Introduction

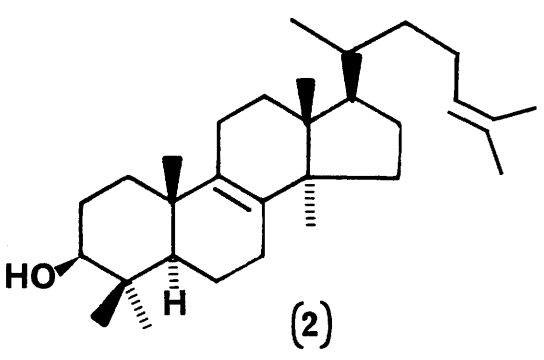
(i) Background

One of the most important achievements of modern organic chemistry has been the unravelling of the intricate details of terpenoid biosynthesis, particularly by Cornforth,[1] Popjak[2] and Arigoni.[3] Equally impressive are the more recent detailed investigations of Battersby[4] and others in the field of porphyrin biosynthesis.

Such investigations have revealed the remarkably high stereospecificity of biological transformations. This specificity is most often explained by the involvement of the enzyme catalysing the transformation but may sometimes be rationalised in other ways. In 1955 Stork[5] and Eschenmoser with Ruzicka and Arigoni[6] independently pointed out that the stereochemical course of the biological cyclisation of the open-chain polyolefin, squalene (1), to produce ultimately the tetracyclic substance, lanosterol (2), could be rationalised on stereo-electronic grounds. The enzyme-catalysed cyclisation is particularly striking in that squalene, which has no centres of chirality, is converted into a product with seven chiral centres and although the product is theoretically capable of existing in 128 different stereochemical forms, only a single isomer is produced.

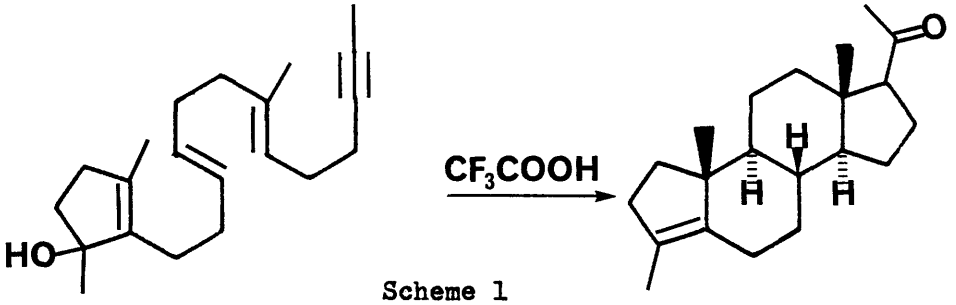


(1)



(2)

This very remarkable stereoselectivity may, at first sight, suggest a very intimate relationship of the enzyme with the substrate directing the course of the cyclisation, however, the Stork-Eschenmoser hypothesis proposes that squalene-like (all trans) polyolefins should have an intrinsic susceptibility to cyclise stereoselectively to give a product having the 'natural' configuration. This hypothesis, in due course, stimulated serious biomimetic studies particularly by the groups of van Tamelen[7] and Johnson,[8] both at Stanford, and the viability of this concept has been demonstrated in the laboratory. A recent example from Johnson's work,[9] Scheme 1, illustrates the point.



Scheme 1

The Stork-Eschenmoser hypothesis was important not only in stimulating research which has led to some elegant steroid syntheses,[9] but also because it demonstrated the value of comparing *in vivo* and *in vitro* reactions and of probing reaction stereochemistry in terms of intrinsic stereo-electronic and conformational preferences.

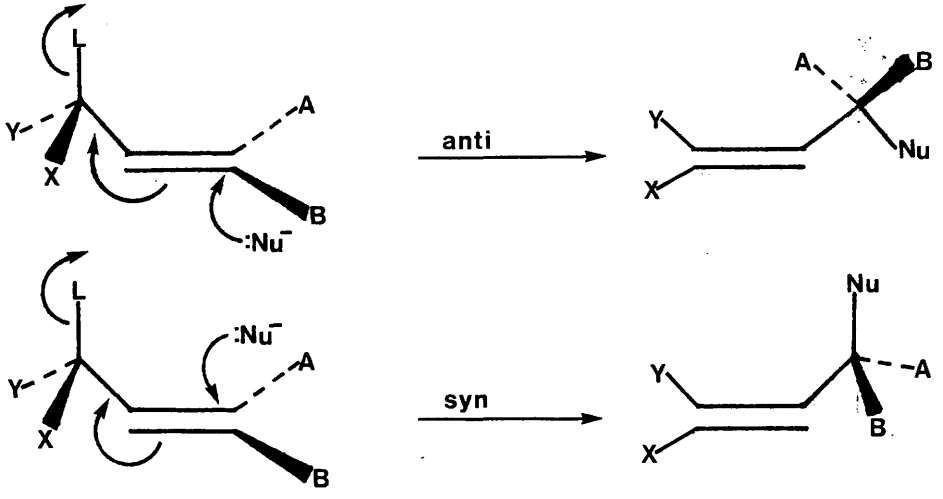
The question of what determines stereochemical choice in enzymic reactions has long intrigued organic chemists.[10] Clearly the interaction of the substrate with the chiral active site of the enzyme is crucial in determining the reaction stereochemistry. But this dependence on the

active site of the enzyme raises the question as to whether the reaction mechanism has played a role in the course of evolution in determining the relative geometry of the active sites on the enzyme.

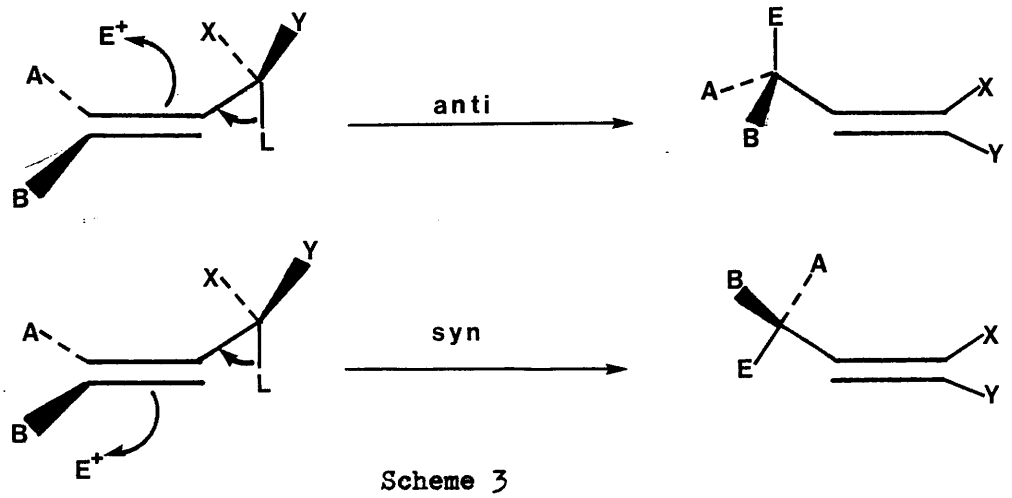
Consider two formally related reactions (Scheme 2 and Scheme 3) both of which involve allylic displacements. The first is a bimolecular nucleophilic substitution with allylic displacement, S_N2'; the second is a bimolecular electrophilic substitution with allylic displacement, S_E2'. As illustrated, each represents a simple choice of stereochemical modes (i.e. syn versus anti). In order to probe whether for enzymic reactions formally related to these reaction types, evolution has followed a stereo-electronically preferred pathway it would be necessary to determine whether:

(a) the same stereospecifity is manifested by different enzymes for the same reaction type

(b) non-enzymic model systems, in the absence of any constraints that might bias the stereochemical course of the reaction, exhibit the same preference.

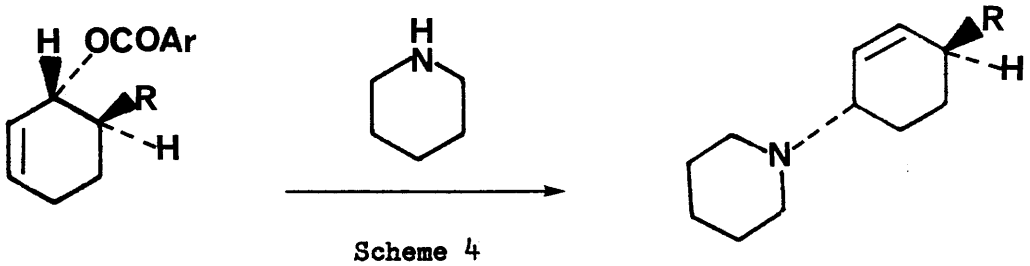


Scheme 2



Scheme 3

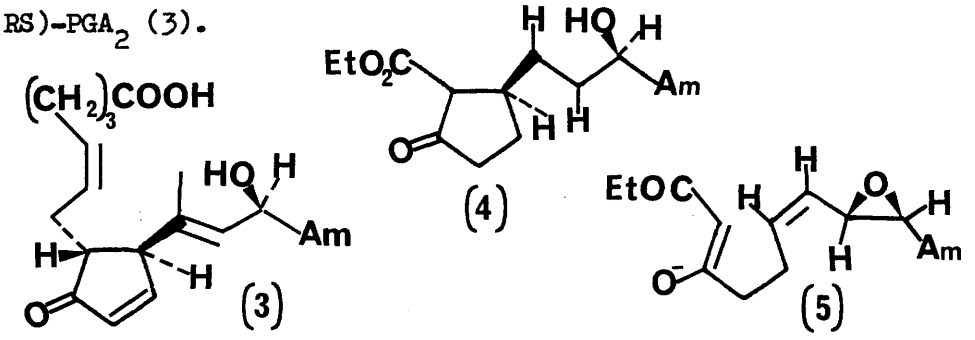
The S_N2' reaction has received a great deal of attention from organic chemists since the pioneering paper of Stork and White[11] was published in 1956, and until recently there has been a general acceptance[12] that the S_N2' reaction requires a <u>syn</u> relationship between entering and departing groups. Stork and White studied the piperidinolysis of <u>trans</u>-6-alkyl cyclohex-2-enyl 2,6 dichlorobenzoates (Scheme 4) and noted that in all cases in which an S_N2' reaction was observed the displacing group entered the molecule <u>syn</u> to the departing substituent.



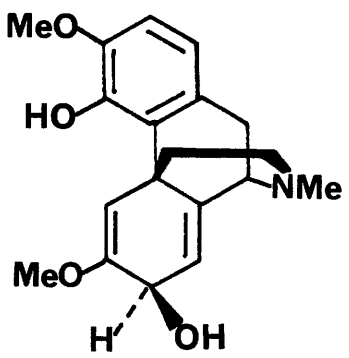
Scheme 4

The <u>syn</u> preference of this S_N2' reaction was in accord with most theoretical predictions[13-19] (however, see a recent theoretical analysis by Epiotis[20] in which both <u>syn</u> and <u>anti</u> modes are predicted) and has been

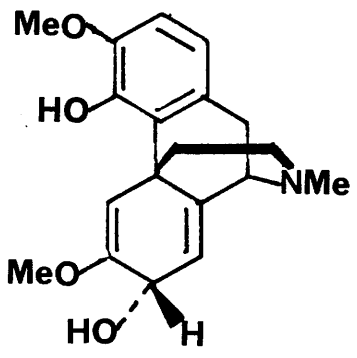
widely accepted by organic chemists. The Roussel-Uclaf group in 1972 incorporated this apparent syn preference of S_N2' reactions to plan a stereo-controlled prostaglandin synthesis.[21] In an attempt to synthesise the prostaglandin (RS)-PGA_2 (3) they planned to establish the correct configurations of C-12 and C-15 in the intermediate (4) by the opening of the epoxide in the precursor (5) by a syn S_N' mechanism. Treatment of the pyrrolidine enamine of the β-keto-ester (5) with sodium amide did, indeed, result in a single diastereomeric racemate that was converted into (RS)-PGA_2 (3).



The general acceptance of the syn preference of the S_N2' reaction can be further seen in its use to rationalise observed stereochemistry. Barton and Kirby[22] found that salutaridinol I (6), but not its epimer salutaridinol II (7), was a biological precursor of thebaine (8) in the opium poppy. An anti-S_N' displacement involving attack of the phenolic hydroxyl and allylic displacement of -OR, as shown in Scheme 5, would account for the observed stereochemistry of the biological conversion of salutaridinol I (6) into thebaine (8). Barton and Kirby, however, discount this one-step S_N' reaction and suggest two possible alternatives: either a direct displacement of the -OR group giving an intermediate (9) with the inverted configuration which can now undergo a syn S_N' reaction (Scheme 6), or a preliminary allylic rearrangement to give intermediate (10) followed by an S_N2 attack (Scheme 7).



(6)



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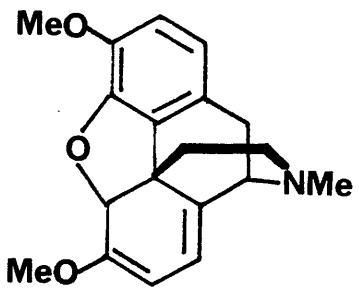

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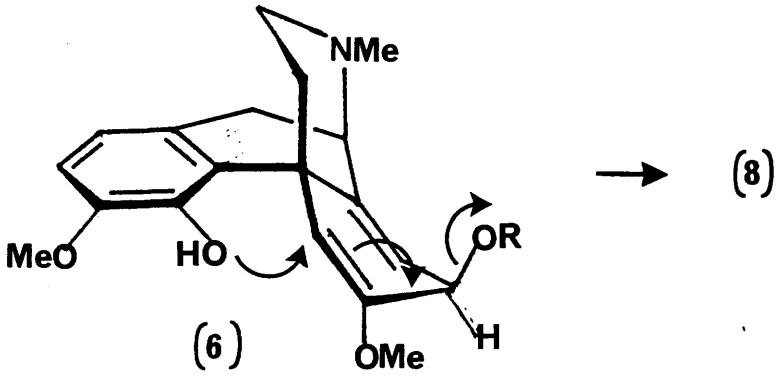
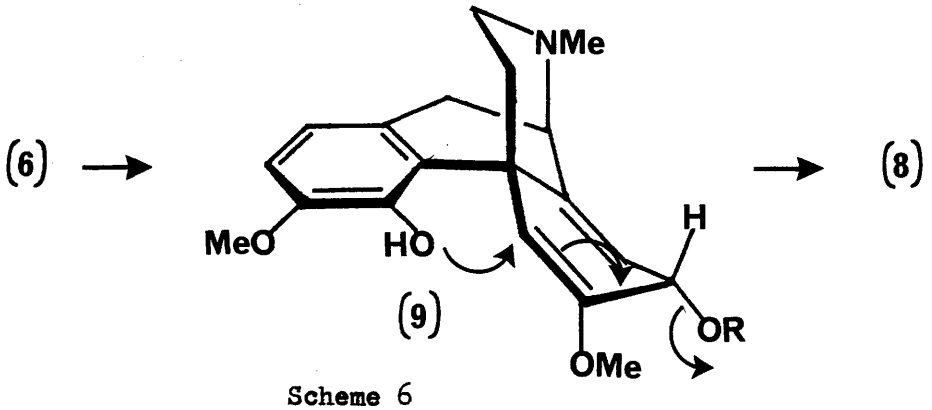
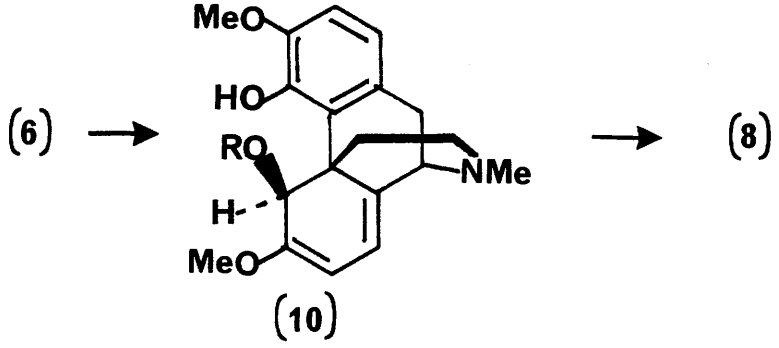


Scheme 5



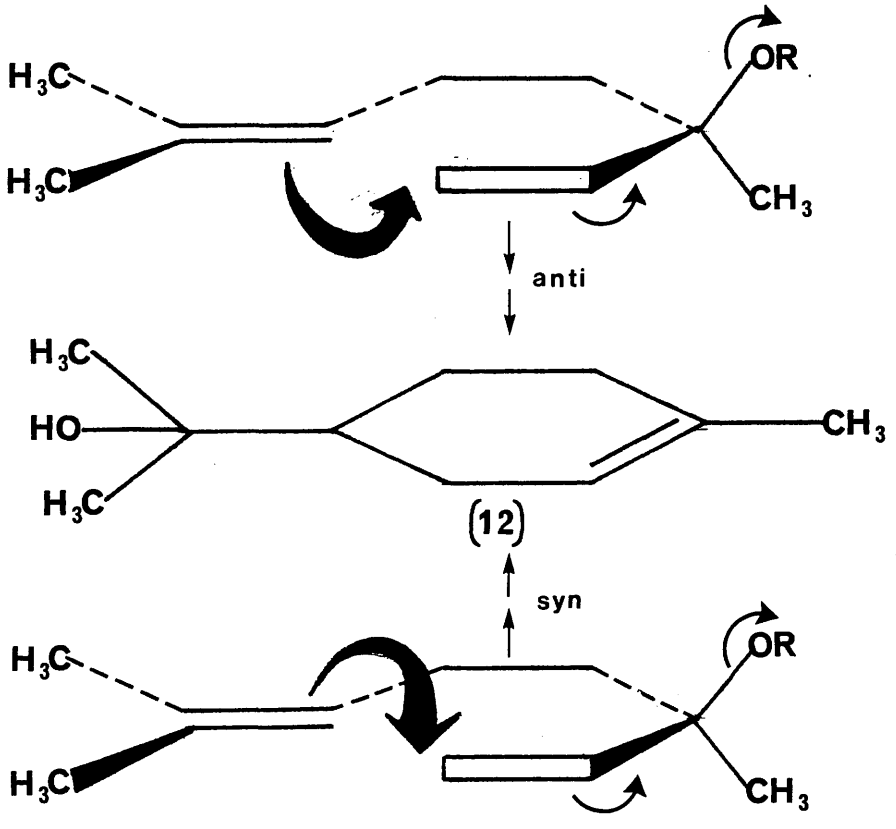
Scheme 6



Scheme 7

One biochemical reaction which, formally at least, is recognisable as an S_N' reaction is the conversion of (R)-linalool (11) into (R)-α-terpineol (12). Treatment of (R)-linalool (11) with aqueous acids or solvolysis of a variety of its esters has been shown[23,24] to lead to (R)-α-terpineol (12) in high enantiomeric excess.

(11) (12)



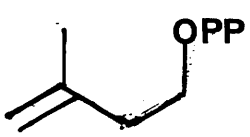
Scheme 8

The observed product can be explained equally well in terms of either an anti or a syn S_N' reaction (Scheme 8). Rittersdorf[23] and Winstein[24] both argued in favour of syn preference for the cyclisation, largely on the basis of Stork and White's results.[11] Recently Arigoni and his colleagues[25] have shown that the cyclisation, in fact, proceeds predominantly in an anti fashion. Similar anti S_N' reactions have also been found in other biosynthetic reactions.[10,26]

With the analytical tools now available Stork[27] and Overton,[28] independently, decided to re-investigate the piperidinolysis reaction (Scheme 4). Their results supported the earlier conclusions of syn preference for this particular S_N2' reaction although the course of the reaction was seen to be more complex than the original analysis had revealed.

However, by extending the enquiry to a variety of other situations,[29] including the study of acyclic systems, it became apparent that the whole spectrum of possible stereochemistries spanned by the syn and anti extremes was to be expected for the S_N' reaction.

Two processes of fundamental importance in terpenoid biosynthesis are the isomerisation of isopentenyl pyrophosphate (13) to dimethylallyl pyrophosphate (14) and the condensation of these two C-5 units to give geranyl pyrophosphate (15).



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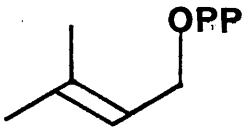

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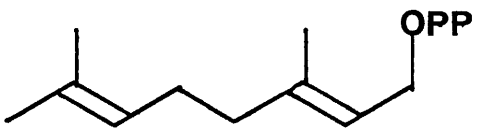
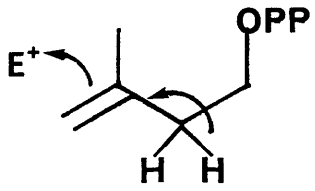


(15)

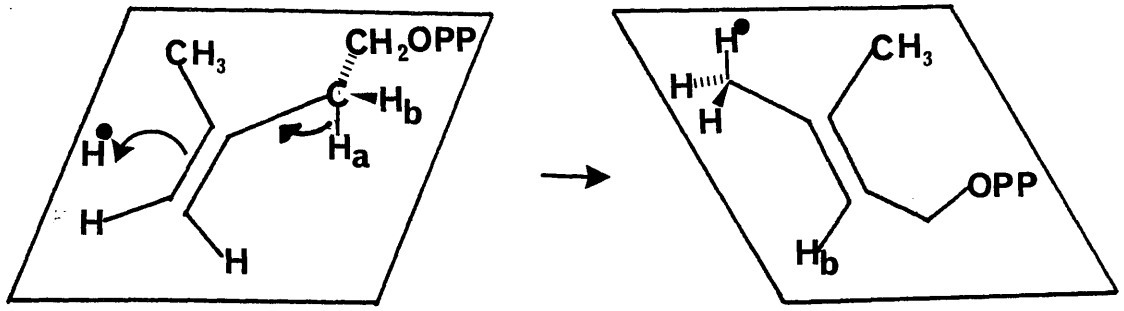
These processes are formally recognisable as bimolecular electrophilic substitutions with allylic displacement (S_E2')[30] as depicted in Scheme 9 where, for the isomerisation, the electrophile (E^+) is a proton, and for the condensation it is dimethylallyl pyrophosphate(14).



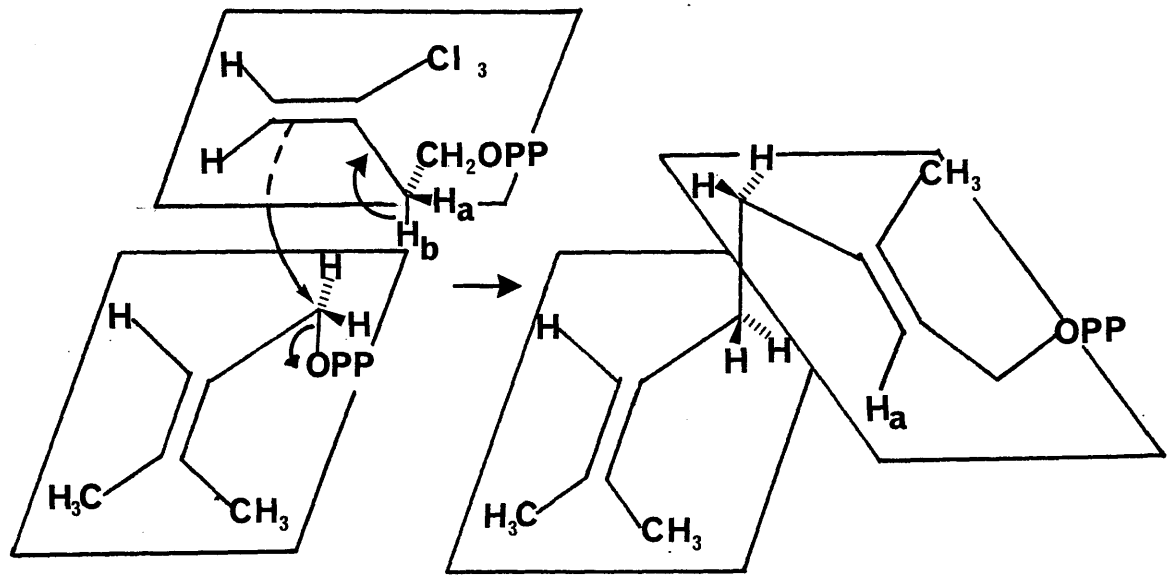
Scheme 9

The stereochemical details of these processes have been established by Cornforth and his colleagues[31] as being overall <u>anti</u> for the isomerisation (Scheme 10) and overall <u>syn</u> for the condensation (Scheme 11).

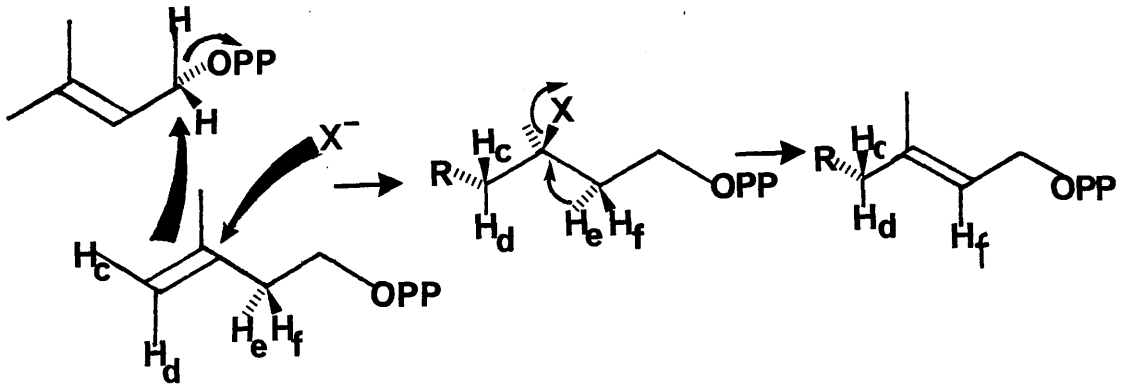
Qualitative theoretical interpretations of the S_E2' reaction predict <u>anti</u> stereochemistry.[13a,14] Also, intuitively one might expect the <u>anti</u> mode to be energetically preferable since it involves maximum separation of electronic charge during the reaction (cf. Scheme 3) - i.e. the electrons from the breaking bond approach from one face of the molecule, to form a new double bond, as the electrons from the old double bond are released from the opposite face of the molecule, to bond to the electrophile.



Scheme 10



Scheme 11



Scheme 12

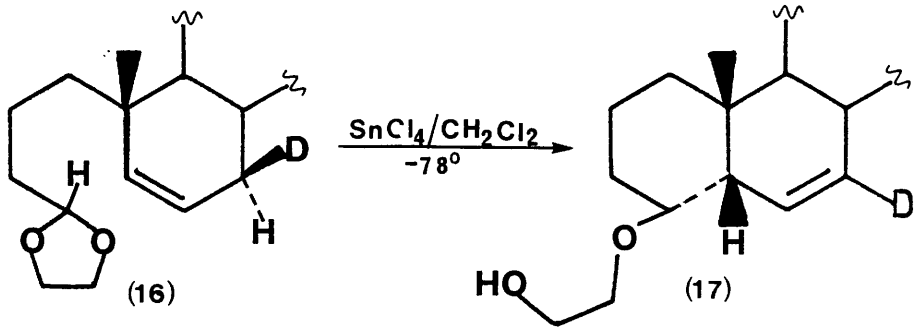
Cornforth employs this 'intuitive' argument to discount a concerted process for the coupling reaction (Scheme 11) comparing a <u>syn</u> S_E2' reaction to a "nucleophilic substitution with retention of configuration".[32] He explains the apparent <u>syn</u> stereochemistry by means of a two-step process (the X-group mechanism) shown in Scheme 12.

The first step involves addition of a nucleophilic group (X^-) (unspecified, but plausibly part of the enzyme or an enzyme-bound electron-donating group such as water) and dimethylallyl-pyrophosphate across the double bond of isopentenyl pyrophosphate in an <u>anti</u> fashion, followed by an <u>anti</u> - elimination of H_eX producing geranyl pyrophosphate.

The absence of concrete evidence for the participation of a group X makes this mechanism, although attractive on stereo-electronic grounds, purely speculative. In evolutionary terms one could argue that the one-step <u>syn</u> S_E2' mechanism is more economical and would be preferred over the two-step X-group mechanism. Moreover, the lessons learned from the investigations of the stereochemical preference of the analogous S_N' reaction make it clear that deductions concerning electron movement, made on purely intuitive grounds, may be unreliable.

There was clearly a need to devise a laboratory model system suitable for investigating the stereochemical preference of a non-enzymic S_E2' reaction both in its own right and also for the relevance it might have to notionally related enzymic reactions. By determining the stereochemistry of an <u>in vitro</u> S_E2' reaction, evidence for or against the necessity to invoke the X-group mechanism should be obtained.

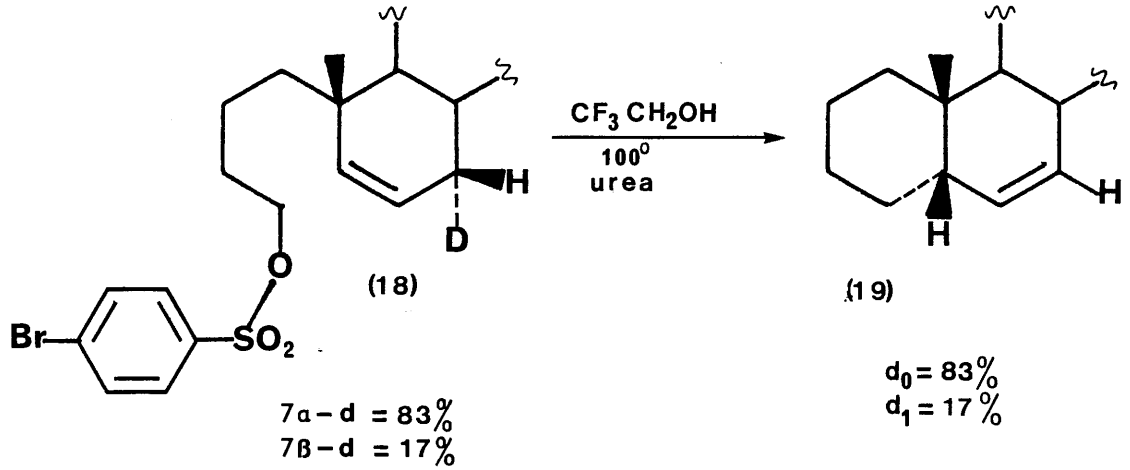
The first planned effort to investigate such a model system was published by Overton and Cunnigham[30] in 1975. Their model, using intramolecular electrophilic substitution at allylic carbon (S_E'), was based on the 4,5 seco-steroids (16) and (18). Conditions were established whereby S_E' cyclisations occurred readily to give the steroids (17) and (19). Schemes 13 and 14 show the stereochemical outcome of these cyclisations.



(16) (17)

7β-d = ≤ 95% d_1 = ≤ 95%

Scheme 13



(18) (19)

7α-d = 83%
7β-d = 17%

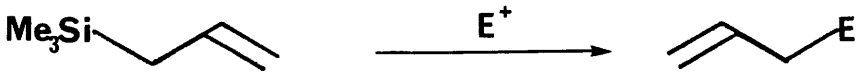
d_0 = 83%
d_1 = 17%

Scheme 14

Exclusive <u>syn</u> preference was observed in these reactions but, as pointed out by the authors, the system suffered from an intrinsic bias: the hydrogen (or deuterium) lost in these cyclisations is quasi-axial and as such is intrinsically labile, the quasi-axial bond being more nearly aligned with the π-orbital of the olefin. This is a well-documented

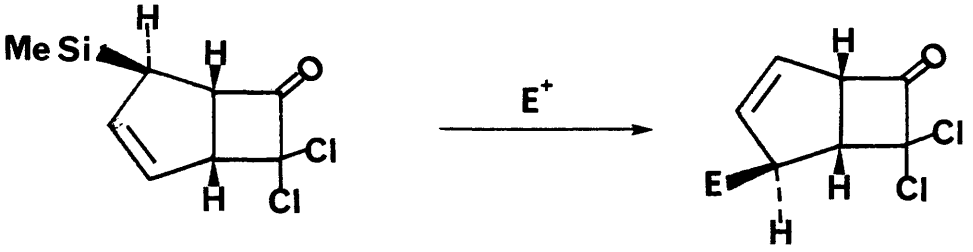
feature of allylic substituents in cyclohexenyl systems.[33] The observed syn stereochemistry, therefore, may simply be a reflection of this lability.

The reactivity of allylsilanes with electrophiles as illustrated in Scheme 15, first observed in 1948,[34] is now well documented.[35,36] Recent stereochemical studies of the S_E' reaction have come from this area.



Scheme 15

Fleming's group at Cambridge have used the allylsilane (20) as a key intermediate in a route to a prostaglandin synthon[36] and in the synthesis of loganin.[36] Treatment of the allylsilane (20) with a Lewis acid and an electrophile (E) results in the olefin (21) (Scheme 16).

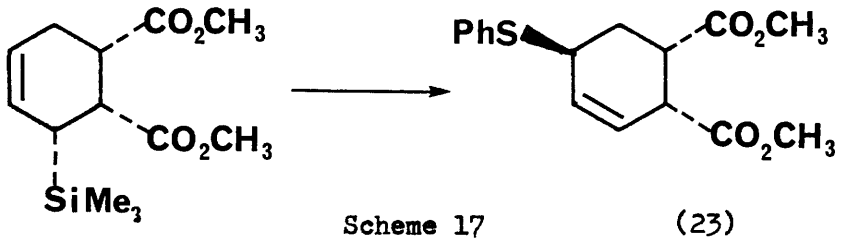


(20) Scheme 16 (21)

In order to study the stereochemistry of this reaction a deuteriodesilylation reaction was carried out.[36] Treatment with deuteriated toluene-p-sulphonic acid afforded the enone (21), (E=D). The entering deuterium was shown to be syn to the departing group as illustrated in Scheme 16. The authors observe, however, that this is the inherently preferred stereochemistry because of the preferred exo entry in this

bicyclic system.

Another example, again from Fleming's group,[37] dealing with a cyclohexenyl system [(22) ⟶ (23), Scheme 17] provides an example of anti stereochemistry. Treatment of the diester (22) with phenylsulphenyl tetrafluoroborate in nitromethane gave the allyl sulphide (23) with the stereochemistry as illustrated (Scheme 17).



(22) Scheme 17 (23)

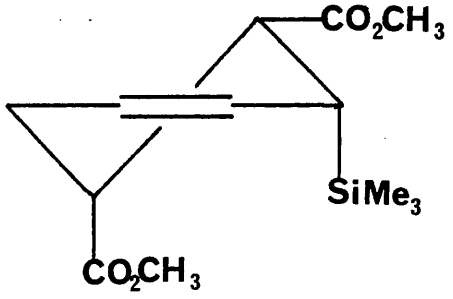
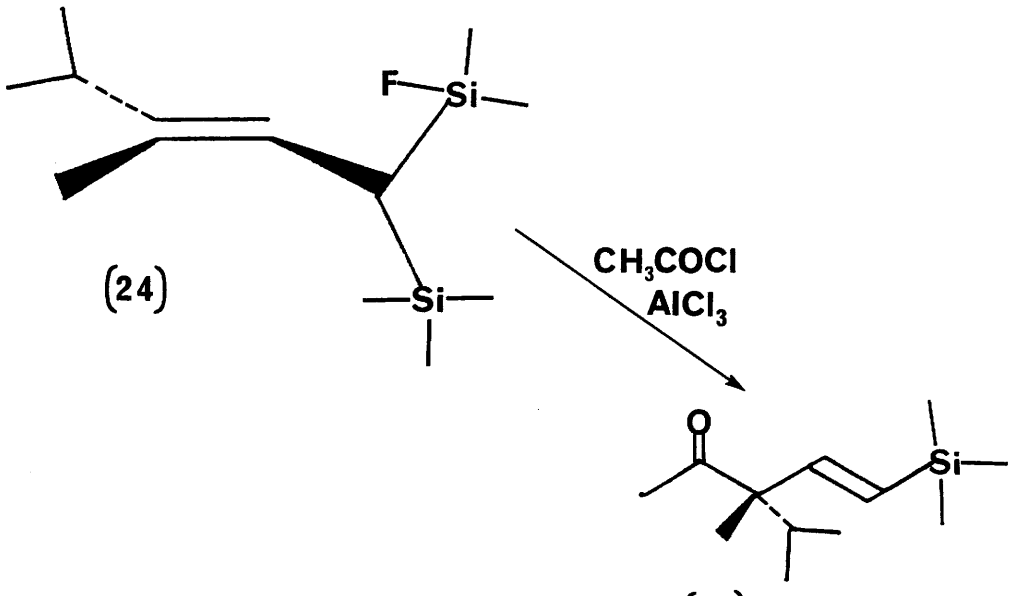


Figure 1

The reactive conformation of (22) is probably as shown in Figure 1 with the silyl group quasi-axial. Apparently the quasi-axial $-CO_2Me$ group hinders the approach of the electrophile (PhS^+) from the lower face of the olefin as shown; the electrophile approaches, therefore, from the less hindered face and thus leads to the observed stereochemistry.

The above examples of S_E' reactions are subject to the conformational restraints imposed by inclusion of the allylic moiety in a cyclic array. The first stereochemical study of an S_E' reaction in an acyclic model system has been provided by Wetter.[38] His results

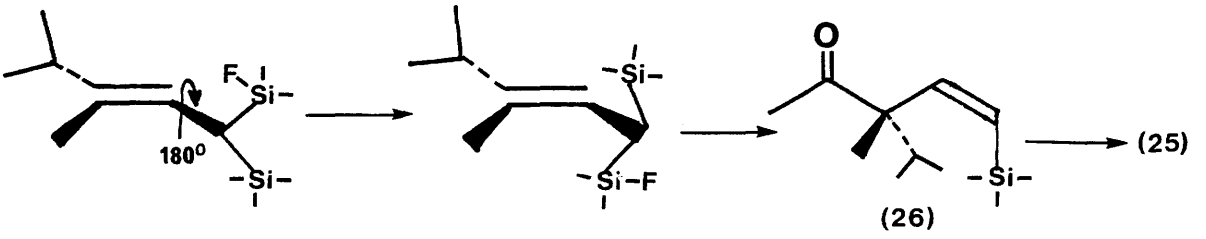
demonstrate that the acylative desilylation of the acyclic allylsilane [(24)⟶(25), Scheme 18] proceeds with high syn stereoselectivity (97% syn, 3% anti).



(24) (25)

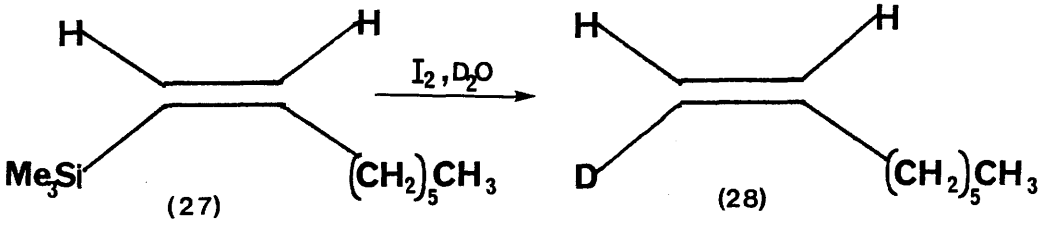
Scheme 18

The syn S_E' pathway assumes, reasonably, that the reactive conformation of the disilyl compound is that shown in (24). The authors draw attention to an alternative pathway for the formation of (25): this involves rotation of the disilylmethyl group through 180° with respect to the double bond, then an anti S_E' reaction giving (26), the cis isomer of (25), and finally isomerisation of the olefin (under the reaction conditions) to (25) (Scheme 19).



Scheme 19

The authors then observe that this is unlikely in view of the stereoselective nature of the substitution of Z -vinyl silanes with retention of configuration at the double bond,[39,40] for example, deuteriodesilylation of Z -1-trimethylsilyl-1-octene (27) gave Z -deuterio-1-octene (28) stereoselectively[39] (Scheme 20).



Scheme 20

There is, however, the possibility in the acylative desilylation reaction (Scheme 18) that the fluorine of the departing silyl group complexes with the acylating agent thereby delivering the acyl group to the same side and leading to syn selectivity. Clearly, then, an investigation of the effects of varying electrophiles and silylalkenes on the stereochemical outcome of the reaction would be most instructive.

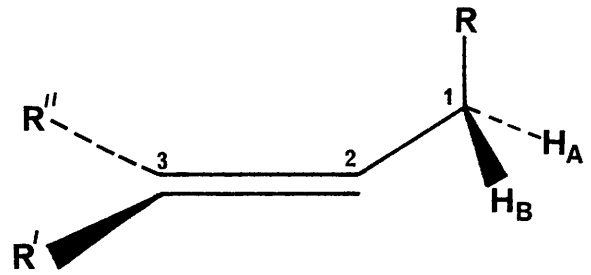
The known examples of S_E' reactions, although limited by certain constraints, are important in that in each case a vastly preferred and probably exclusive stereochemistry is observed and that in three out of the four examples the syn stereochemistry observed is contrary to

theoretical predictions.

Clearly it would be instructive to study stereochemical preference in a laboratory model system in which any constraints, conformational or otherwise, have been reduced to a minimum. The construction and examination of such a model system formed the basis of this thesis.

(ii) Design of a Model System

In order to define the stereochemisty of an S_E2' reaction it is necessary to determine certain factors. Consider the S_E2' reaction involving electrophilic attack at C-3 of (29) with concomitant loss of H_A or H_B from C-1.



(29)

The electrophile must approach the olefin in the plane of the π-orbital and the C-H bond to be cleaved must align itself in a plane parallel (syn- or anti-periplanar) to this π-orbital. Scheme 21 depicts a syn S_E2' process involving loss of H_B and addition of the electrophile (E^+) both from the lower face of the molecule (29) giving the E-olefin (30). Scheme 22 depicts the corresponding anti S_E2' process involving addition of E^+ to the upper face of (29) and loss of H_A from the lower face, giving the Z-olefin (31).

(30) and (31) are only two of eight possible products (see Scheme 23). It will be necessary, for the purposes of a stereochemical investigation, to distinguish between these eight possible products. This requires that the following three variables can be defined (see Scheme 23):

(a) the absolute configuration at C-3′.

(b) the geometry (Z or E) of the new olefinic linkage C-1′ — C-2′, and

(c) the identity of the proton (H_A or H_B) lost from C-1.

The necessary requirements are then (see Scheme 23):-

(i) Synthesis of olefin (29) with one of the allylic protons (H_A or H_B) stereospecifically replaced by deuterium (or tritium at a tracer level).

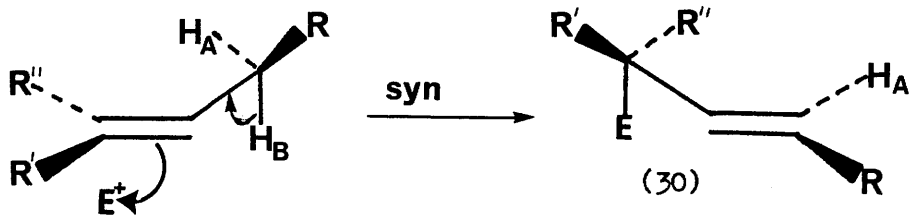
(ii) Reaction of this olefin (29) with an electrophile at C-3, forming a new chiral centre (C-3′), the absolute configuration of which must be determined.

(iii) As the electrophile begins to interact with the π-orbital concomitant weakening of C-H_A or C-H_B will neutralise the developing positive charge at C-2; the departing proton must be identified.

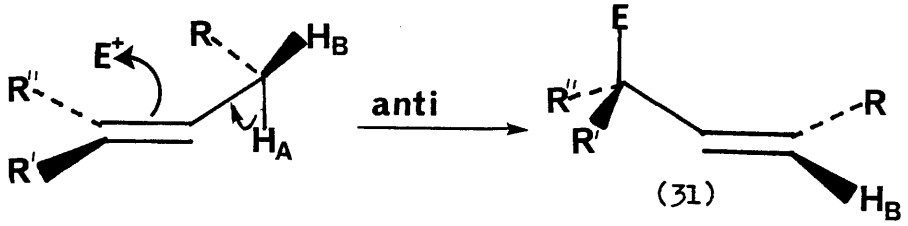
(iv) Resulting double bond isomers must be separated.

In summary, the S_E2' reaction of (29) with an electrophile will result in products of the type (30) and (31); these products will require separation, identification and analysis for label content.

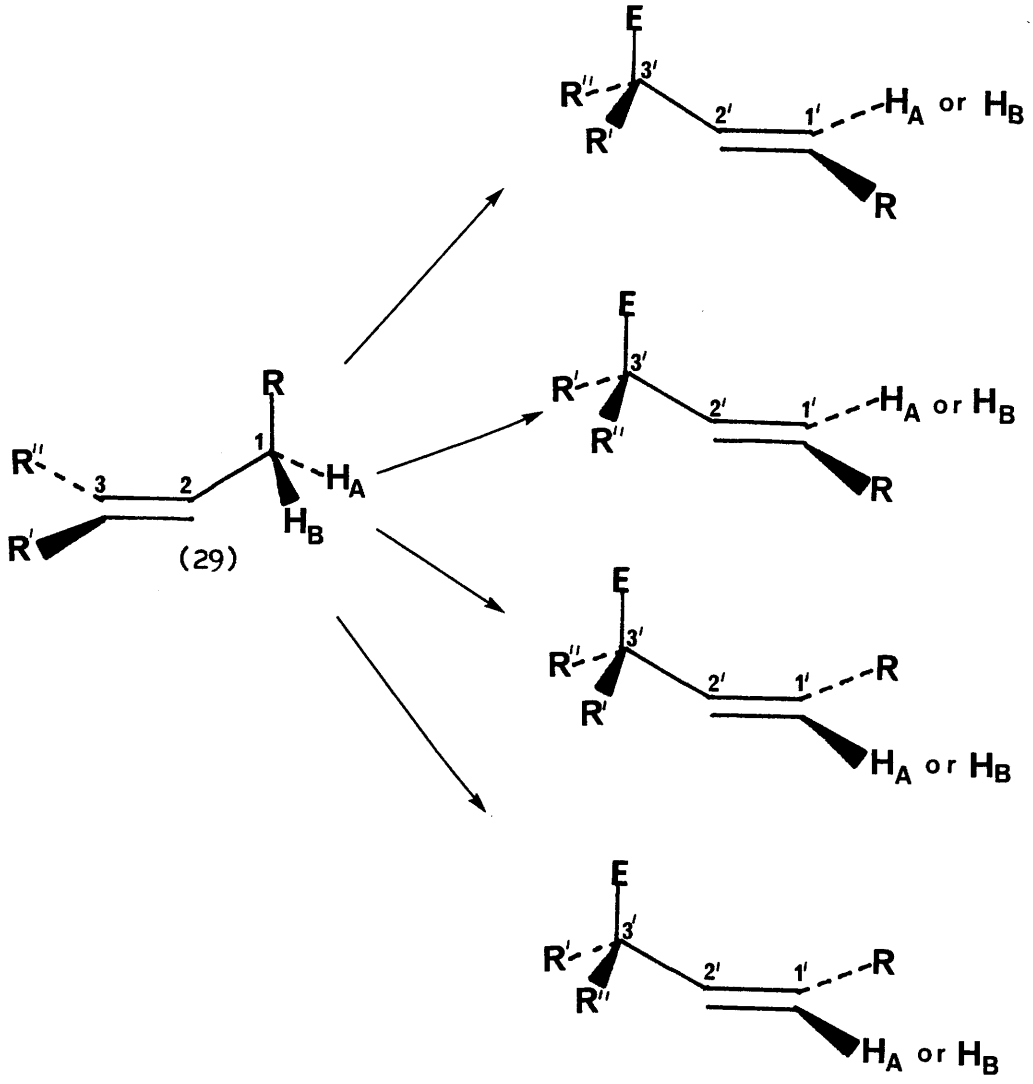
An important practical consideration in the selection of a model system is that it should be synthetically accessible in good yield.



Scheme 21



Scheme 22

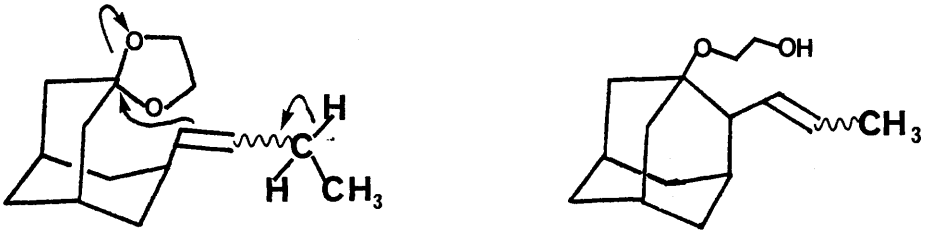


Scheme 23

(iii) Choice of a Model System

Unless otherwise stated, the structures of the bicyclo [3.3.1.] nonanes and the benz-bicyclo [3.3.2.] nonanes as drawn do not purport to show preferred conformations.

Synthetic approaches to a model system suitable for a stereochemical study of the S_E2' reaction have previously been investigated in this department.[41] The basic intention was to effect S_E' cyclisation of a suitably functionalised bicyclo [3.3.1.] nonane - a "seco-adamantane" - to an adamantane nucleus as, for example, in Scheme 24. In general the nucleophilicity of olefins is low unless activated in some way as in enamines and allylsilanes. For this reason the nucleophilic and electrophilic components required for an S_E2' reaction were incorporated into a single molecule, as in (32). This transforms the reaction into an S_E' reaction but does not affect the validity of any stereochemical deductions.

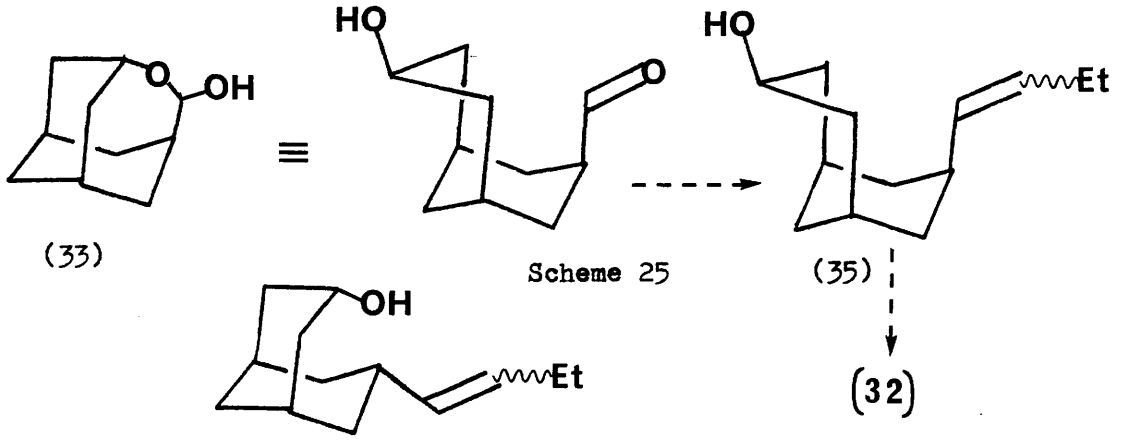


(32)

Scheme 24

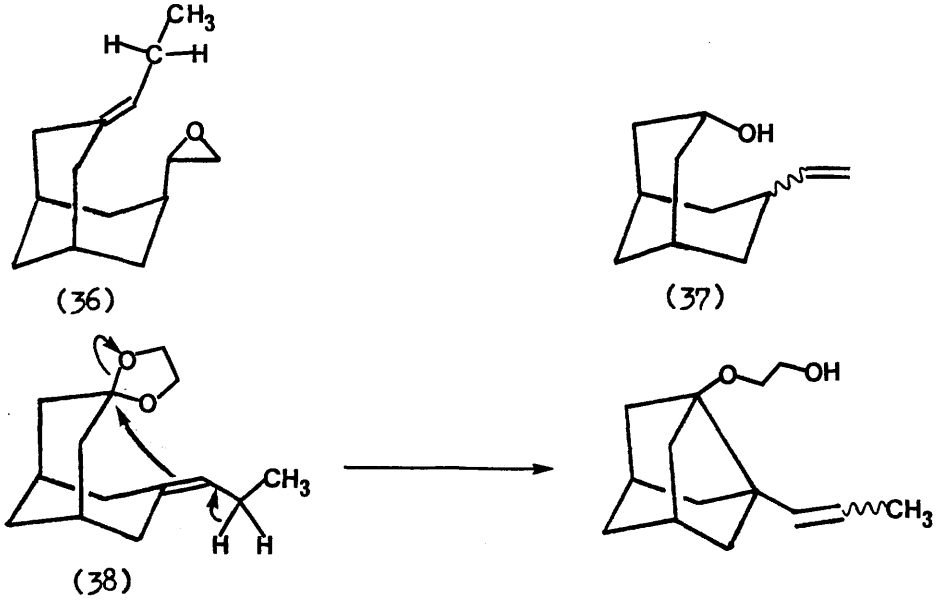
Several approaches to the first of such models (32) were probed and one, the strategy of which is illustrated in Scheme 25, seemed promising. However, after extensive experimentation, it was established

that aldehyde epimerisation had occurred during the Wittig reaction on lactol (33) giving the exo-alkenyl product (34) and not the required endo-alkenyl product (35).



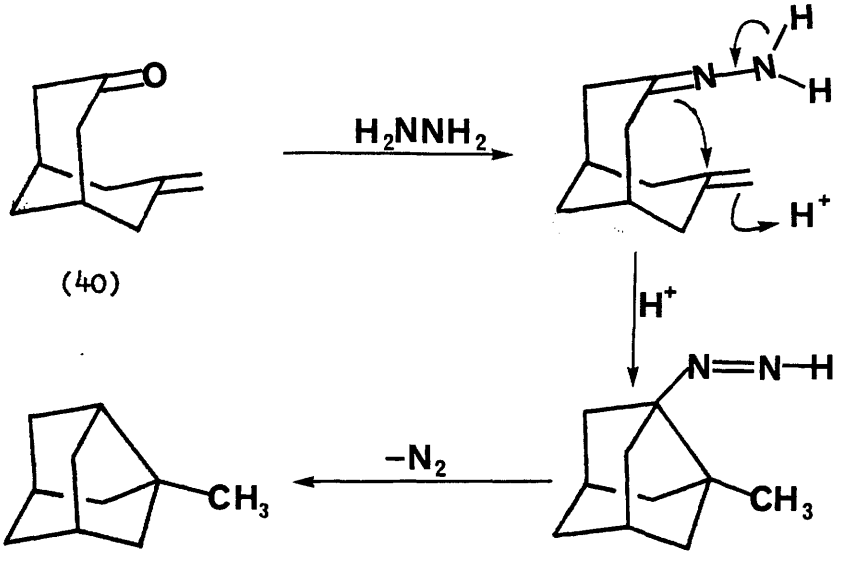
Scheme 25

A second model system (36) was investigated and considerable progress made towards it, but spectral data of the potential precursor (37) suggested than an epimerisation had occurred in this case also.



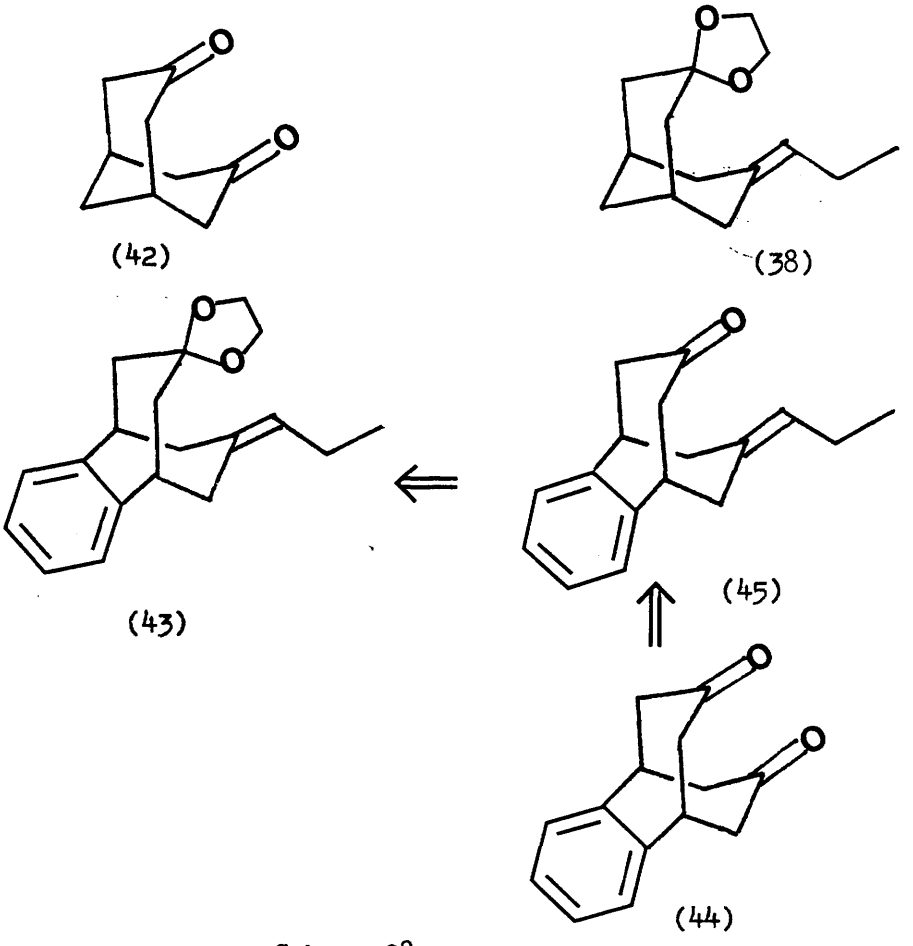
Scheme 26

In order to avoid this complication of epimerisation, a model system of the type (38) was next investigated. That such a system could undergo an S_E' reaction (as in Scheme 26) was suggested by the work of Momose and Muraoko.[42] These workers re-investigated a claim[43] that adamantane (39) was the sole product of an attempted Wolff-Kishner reduction of the enone (40). They showed that under Wolff-Kishner conditions methyl noradamantane (41) was the major product, with no adamantane (39) being observed. The mechanism proposed[42] for the formation of (41) involves the cyclisation illustrated in Scheme 27, formally an S_E' reaction.



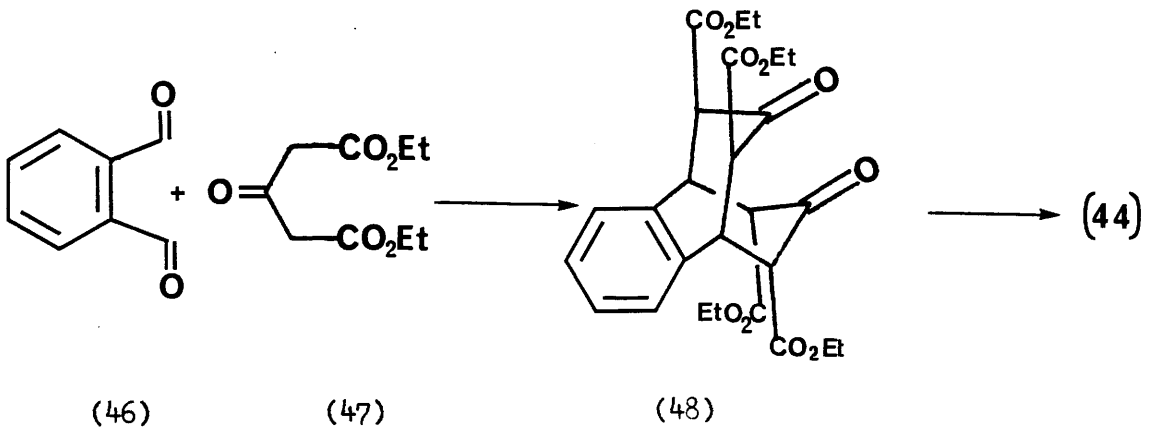
(40) (41) (39) Scheme 27

Experimental difficulties with the formation of the dione (42), a potential precursor of (38), resulted in a switch to the closely related system (43). This is potentially available from the known dione (44)[44] by a Wittig reaction to give the enone (45) followed by ketalisation to give (43) (Scheme 28).



Scheme 28

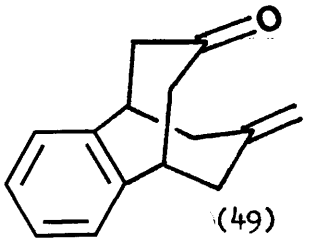
The crystalline dione (44) can be readily obtained[44] in good yield by a base-catalysed double Michael condensation of phthalaldehyde (46) and diethyl-3-ketoglutarate (47) followed by hydrolysis and decarboxylation of the intermediate tetra-ester (48) (Scheme 29).



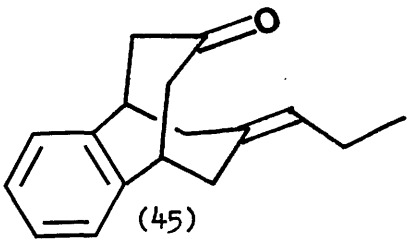
(46) (47) (48)

Scheme 29

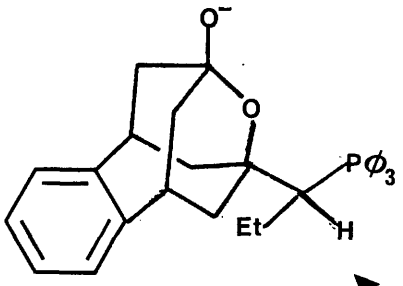
A trial Wittig reaction on the dione (44) using methylidenetriphenylphosphorane gave (49) in 60% yield.[41] However, when propylidenetriphenylphosphorane was used in the Wittig reaction under analogous conditions the yield of (45) was less than 10%. Assuming that ylid addition had taken place, then it was likely that difficulties were being encountered in the formation of the oxaphosphetane (50) which has the necessary geometry for elimination of triphenylphosphine oxide to give (45). Zwitterions (51) and (52) are likely to represent two canonical forms of the ylid addition product. The main problem may be that (51), which cannot fragment to (45), is the major contributor and that (50) is not readily available. A further problem is that (52) must approximate to the geometry of (50) for fragmentation and this may be disfavoured by steric factors; this was suggested by the fact that when the ethyl group was replaced by a proton in the Wittig reaction a considerably higher yield of olefinic product was achieved.



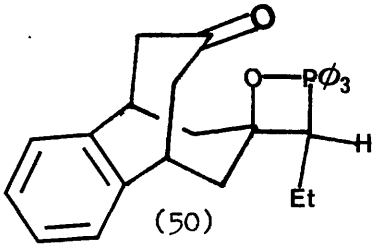
(49)



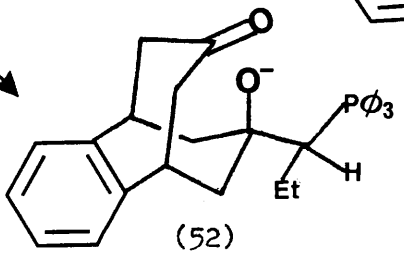
(45)



(51)

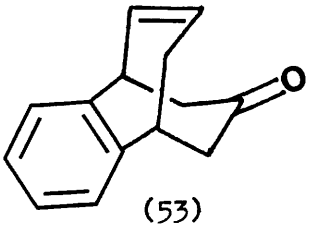


(50)

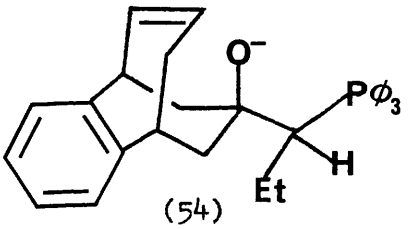


(52)

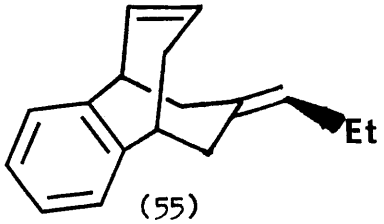
Using enone (53) instead of dione (44) in the Wittig reaction removes the first problem since ylid addition should result in formation of the zwitterion (54) with no cyclisation likely in this case. The products of this Wittig reaction with propylidenetriphenylphosphorane as the ylid should be the dienes(55) and (56).



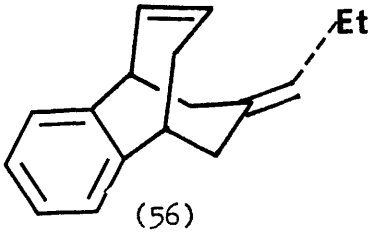
(53)



(54)

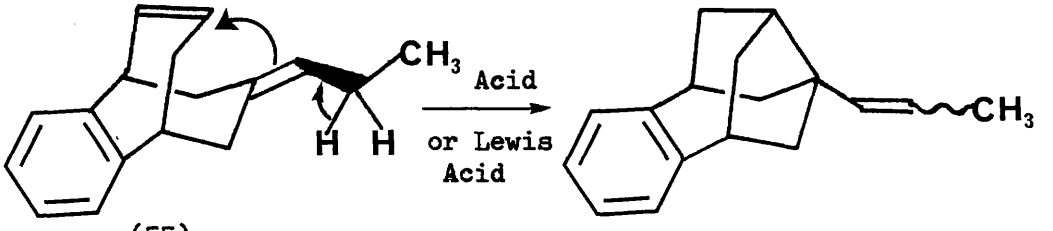


(55)



(56)

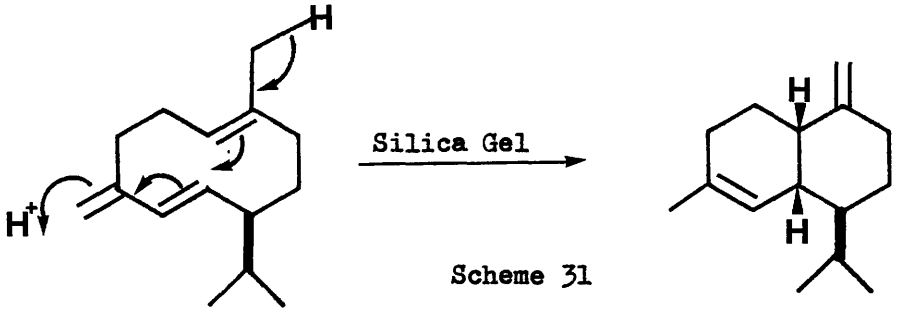
Separation of dienes (55) and (56) will provide two potential model systems. Scheme 30 illustrates a possible S_E' cyclisation of diene (55).



(55)

Scheme 30

This idea of diene cyclisation initiated by protonation or by interaction with Lewis acids clearly stems from the early work on polyene cyclisations in steroid synthesis.[8a,45] Initiation by other electrophiles has also been investigated[46] and may be worth considering. Diene and polyene cyclisations have also been noted in natural product chemistry,[47,48] for example, Hirose observed that Germacrene D (57), on treatment with silica gel, gave (58) as one of the main products,[48] arising, presumably, by the mechanism illustrated in Scheme 31.



Scheme 31

(57) (58)

The initial aim, then, was to synthesise the dienes (55) and (56) and to establish conditions whereby they will undergo an S_E' reaction, as illustrated in Scheme 30. The introduction of the necessary deuterium label and the study of the S_E' reaction of a model system to determine its stereochemical preference will be discussed in an appropriate section later in this thesis (p.76).

DISCUSSION

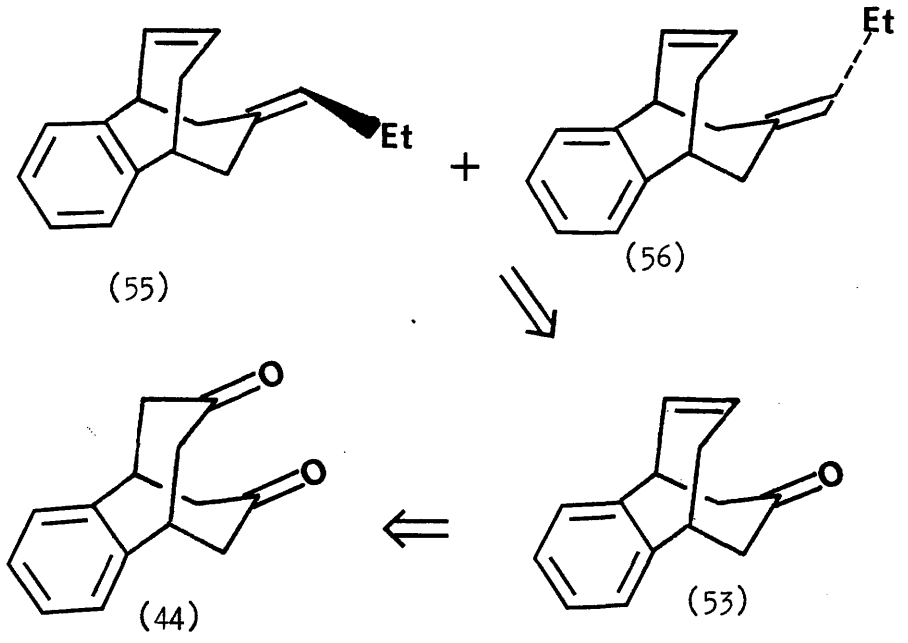
Discussion

This discussion falls into two main parts. The first part describes synthetic approaches to model systems suitable for using in a stereochemical study of the S_E' reaction and also describes attempts to find conditions whereby these model systems undergo S_E' cyclisation.

The second part is concerned with a stereochemical study of the S_E' reaction of a particular model system and describes the stereospecific introduction of a deuterium label and attempts at resolution of this system. The use of a labelled, resolved model system in an S_E' reaction and analysis of the possible products is discussed.

Part 1. Synthetic Approaches to a Model System

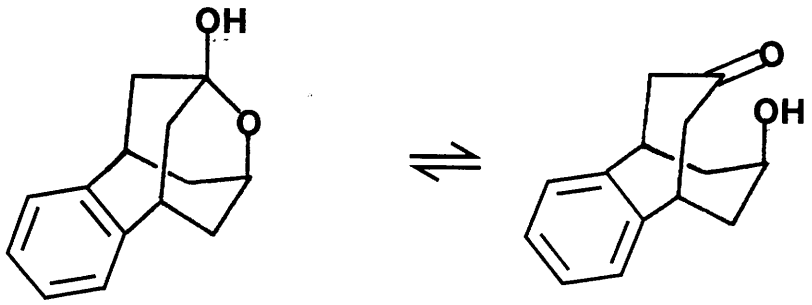
The first priority was to synthesise the dienes (55) and (56) and to investigate their potential as model systems in a stereochemical study of the S_E' reaction. It was envisaged that (55) and (56) could be formed from a Wittig reaction on the enone (53), which was potentially available from the known dione[44] (44) (Scheme 32).



Scheme 32

Sodium borohydride reduction of (44) was known[44] to give the hemiketal (59). Postulating an equilibrium between (59) and its open form (60) (Scheme 33), it was expected that treatment of (59) under conditions suitable for dehydration of an alcohol would afford the desired enone (53) by 1,2-elimination from (60), since 1,2-elimination from (59)

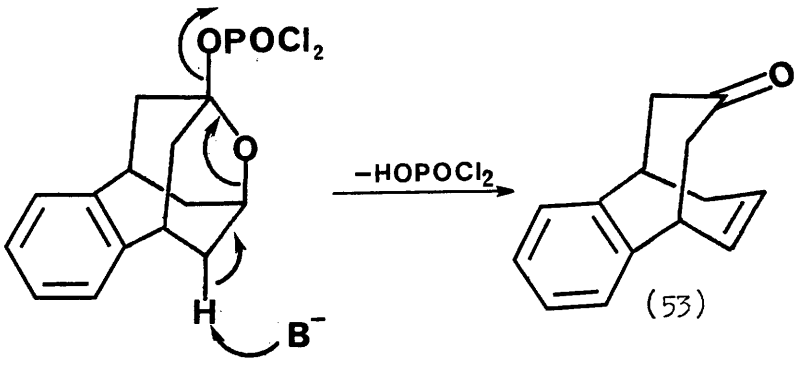
would result in an anti-Bredt double bond.



(59) (60)

Scheme 33

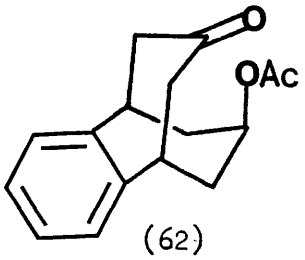
Treatment of (59), however, with phosphoryl chloride and pyridine gave the stable dichlorophosphate (61), m.p. 120-121°C, with no hydroxyl or carbonyl bands in the i.r. spectrum, the ^{1}H.nmr spectrum showed a multiplet centred at δ 4.70 (m, 1H, >CH-O-). This ester (61) was still potentially useful since it was ideally set up (anti-periplanar) for base-assisted fragmentation to (53) and dichlorophosphinic acid (Scheme 34), providing the proton H_A was sufficiently acidic to be extracted. Treatment of (61) with diazabicycloundecene (DBU) returned only the hemiketal (59).



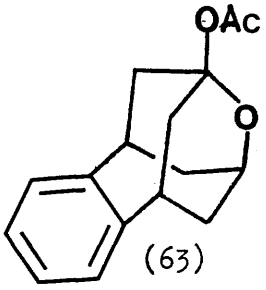
(61) (53)

Scheme 34

Still postulating the equilibrium between (59) and (60) (Scheme 33), acetylation might be expected to favour the formation of the secondary acetate (62) in preference to (63). Elimination of acetic acid from (62) would then afford the desired enone (53).



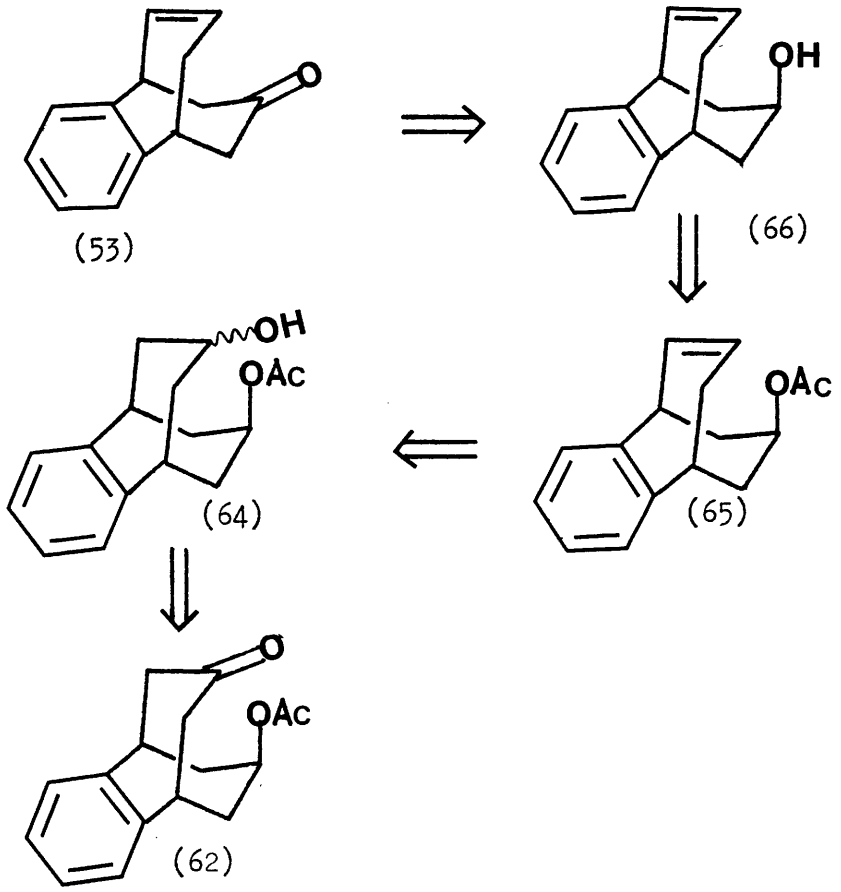
(62)



(63)

Treatment of (59) with sodium acetate and acetic anhydride under reflux gave the acetate (63); its i.r. spectrum showed an ester carbonyl band at 1730 cm^{-1} and no ketonic carbonyl band. However, acetylation of (59) under acidic conditions (a catalytic amount of conc. sulphuric acid and acetic anhydride in acetone) afforded the desired keto-acetate (62), m.p. 185-190°C, displaying in the i.r. spectrum ester carbonyl (1730 cm^{-1}) and ketonic carbonyl (1690 cm^{-1}) bands. T.l.c. and ^{1}H.nmr indicated that (63) had not been formed. The keto-acetate (62), however, resisted all attempts at conversion to the enone (53) by elimination of acetic acid (see experimental p.106).

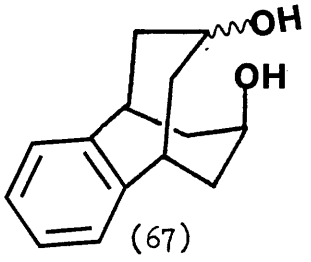
An alternative approach to (53) from the keto-acetate (62), outlined in Scheme 35, was now considered.



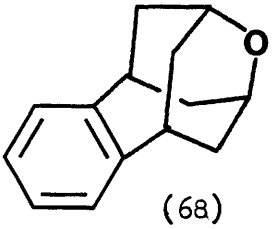
Scheme 35

An initial borohydride reduction of (62) gave the diol (67), m.p. 176-178°C, with no ester carbonyl band in the i.r. spectrum, but, under buffered conditions the desired hydroxy-acetate (64), m.p. 113-113.5°C, was obtained in high yield. This showed in the i.r. spectrum hydroxyl (3380 cm^{-1}) and ester carbonyl (1730 cm^{-1}) bands. Dehydration of (64) with phosphoryl chloride and pyridine gave the ene-acetate (65), m.p. 86-89°C, for which the i.r. spectrum indicated an ester carbonyl band (1730 cm^{-1}) and no hydroxyl band. The ^{1}H.nmr spectrum indicated complex olefinic absorption between δ 6.20 and 5.30 (m, 2H,-CH-CH=CH-CH_2-), a multiplet between δ 5.0 and 4.5 (m, 1H,-CH-OAc), and a singlet at δ 2.0 (s, 3H, -C-CH_3). Saponification of (65) provided the enol (66), m.p.

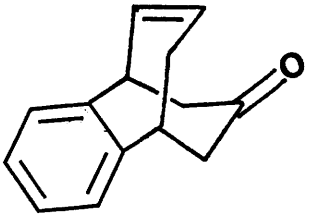
88-90°C, whose i.r. spectrum had a hydroxyl band (3570 cm^{-1}) and no ester carbonyl band. Treatment of (66) with Jones reagent gave two compounds which were separated by preparative t.l.c. The major product from this mixture had an intense i.r. absorption at 1690 cm^{-1}, its ^{1}H.nmr spectrum indicated two olefinic protons (δ 6.1-5.4), and was identified as the desired enone (53), m.p. 104-105°C. No olefinic signals were present in the ^{1}H.nmr spectrum of the minor product and there were no significant absorptions in the i.r. spectrum; it was therefore probably the cyclic ether (68). This was further verified by the facile conversion of the enol (66) into (68) on acid treatment (dilute hydrochloric acid in aqueous ethanol at reflux). Analogous ether formation had previously been observed with related bicyclo [3.3.1.] nonanes by Grob.[49] For example, (69) was converted to the cylic ether (70) under acid conditions.[49] It was not surprising, then, that under the acidic conditions of a Jones oxidation some (68) was formed. Collins oxidation of (66) circumvented this problem and afforded (53) in good yield.



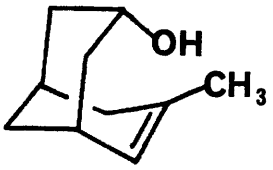
(67)



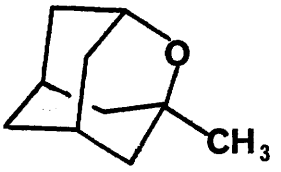
(68)



(53)

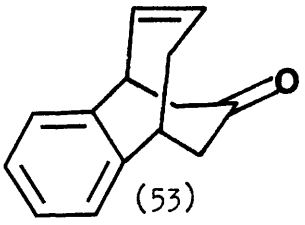


(69)

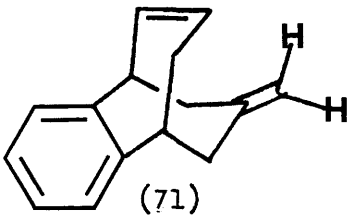


(70)

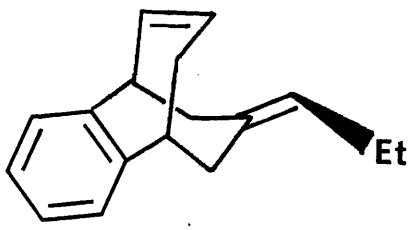
A trial Wittig reaction on the enone (53) using methylidenetriphenylphosphorane produced a non-polar product, assigned structure (71), which, from its ^{1}H.nmr spectrum still had the two endo-cyclic olefinic protons (δ 5.9-5.6) and also two broad singlets at δ 5.00 and δ 4.75 suggesting the presence of the exo-methylene moiety. Treatment of (53) with propylidenetriphenylphosphorane under analogous conditions failed to give any of the required dienes (55) and (56). When the reaction was repeated, at 100°C for 20 h, a complex mixture of products was obtained. The non-polar component of this mixture was isolated by preparative t.l.c. and the ^{1}H.nmr spectrum indicated, in addition to the characteristic -CH=CH- signals of the endo-cyclic double bond, new low-field signals at δ 5.2 and δ 4.9 consistent with dienes (55) and (56). This reaction was, however, irreproducible and subsequent attempts failed to furnish this non-polar material.



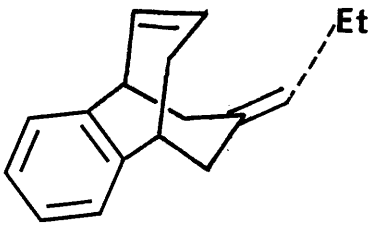
(53)



(71)

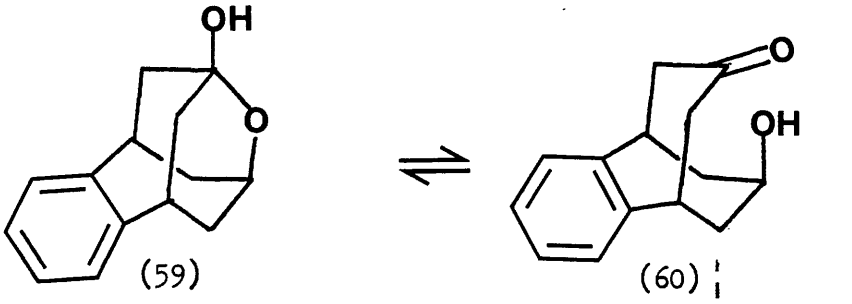


(55)



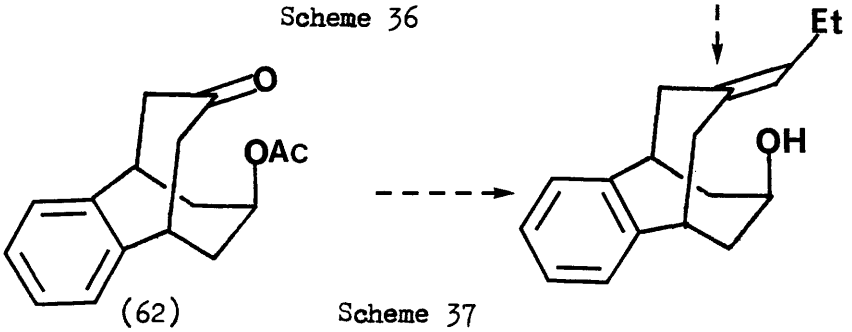
(56)

While attempts to effect a Wittig reaction on (53) were being investigated, Wittig reactions on the readily available hemiketal (59) (Scheme 36) and keto-acetate (62) (Scheme 37) were also explored. These attempted Wittig reactions were largely unsuccessful. However, on one occasion treatment of the hemiketal (59) with propylidenetriphenylphosphorane gave, as a minor product, non-polar material whose ^{1}H.nmr spectrum showed, promisingly, a broad signal at δ 5.3. Subsequent attempts to improve this reaction were unsuccessful.



(59) (60)

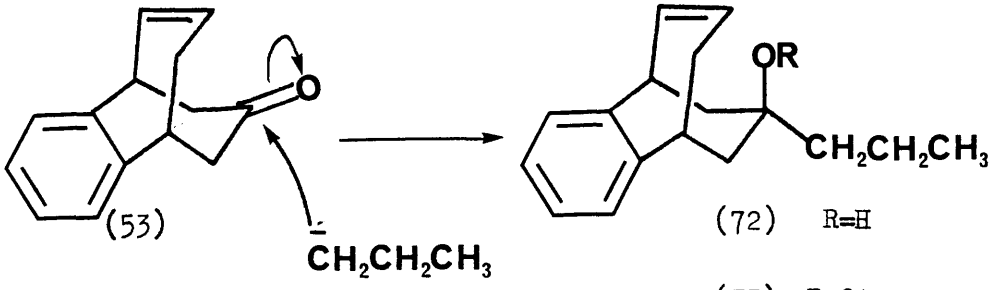
Scheme 36



(62)

Scheme 37

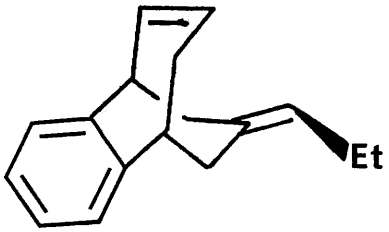
Such a lack of reactivity in these Wittig reactions can only be attributed to the steric hindrance discussed above (p. 25). An alternative method for the introduction of the alkenyl substituent was now considered. If the preferred conformation of (53) is as shown (Scheme 38), then addition of a carbanion to the ketone would be expected to take place at the less hindered exo-face providing the endo-ol (72), as illustrated in Scheme 38.



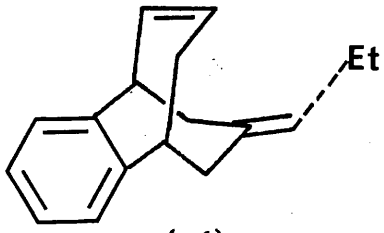
Scheme 38

A syn or anti-1,2 elimination from this alcohol (72), or an ester derivative (73), can give rise to four possible products: the required dienes (55) and (56) and two new dienes (74) and (75). It is not easy to predict which conformation of the alcohol (or ester) will eliminate. Space-filling (CPK) models suggest either the 'chair-chair' (A) or the 'chair-boat' (B) is possible. Assuming free rotation, the propyl side chain is equally well disposed to syn- and anti-elimination of H_aOR to give (55) and (56). Conformation (A) is ideally set up (anti-periplanar) for an anti-elimination of H_bOR to give the endo-cyclic double bond isomers (74) and (75) but is not so well set up (syn-periplanar) for syn-elimination of H_cOR (see Figure 2), although only a slight distortion

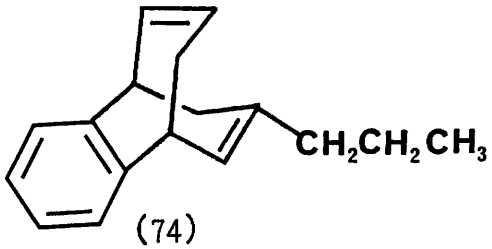
of the conformation is required for syn-periplanarity. Similarly with conformation (B) only slight conformational distortion is required for syn-elimination of H_dOR; however, anti-elimination from this conformation to give (74) and (75) is not possible (see Figure 3). If the endo-ol (72) or its ester (73) could be made to adopt conformation (B) then anti-elimination would favour formation of the exo-cyclic double bond. For example, treatment of (72) with phosphoryl chloride and pyridine should give the dichlorophosphate ester (76); this bulky ester group may compel the adoption of (B) as the reactive conformation and ionic (anti) elimination may give predominantly (55) and (56) as required.



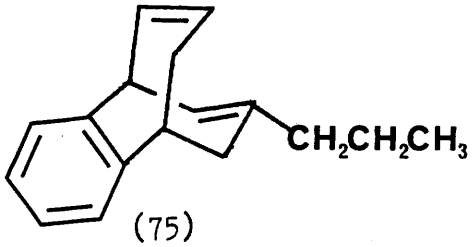
(55)



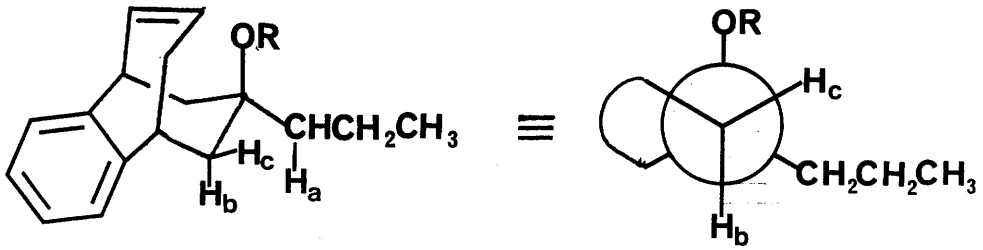
(56)



(74)

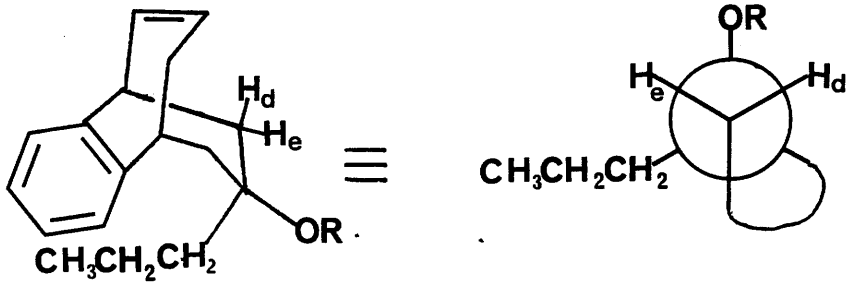


(75)



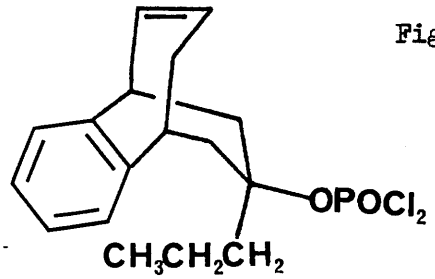
(A)

Figure 2



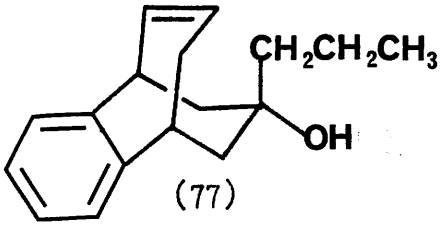
(B)

Figure 3



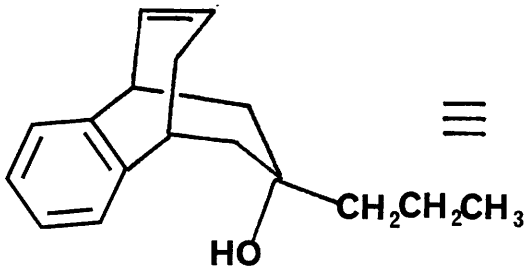
(76)

Inspection of molecular models of the alternative alcohol, the exo-ol (77), indicates the 'chair-chair' conformation (C) to be unlikely due to the steric bulk of the side chain. Conformation (D) is ideally set up for anti-elimination but would require some conformational distortion for syn-elimination (Figure 4).



(77)

(C)



(D)

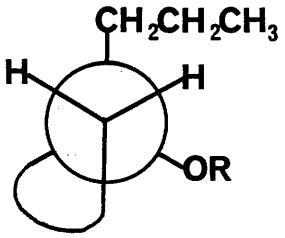
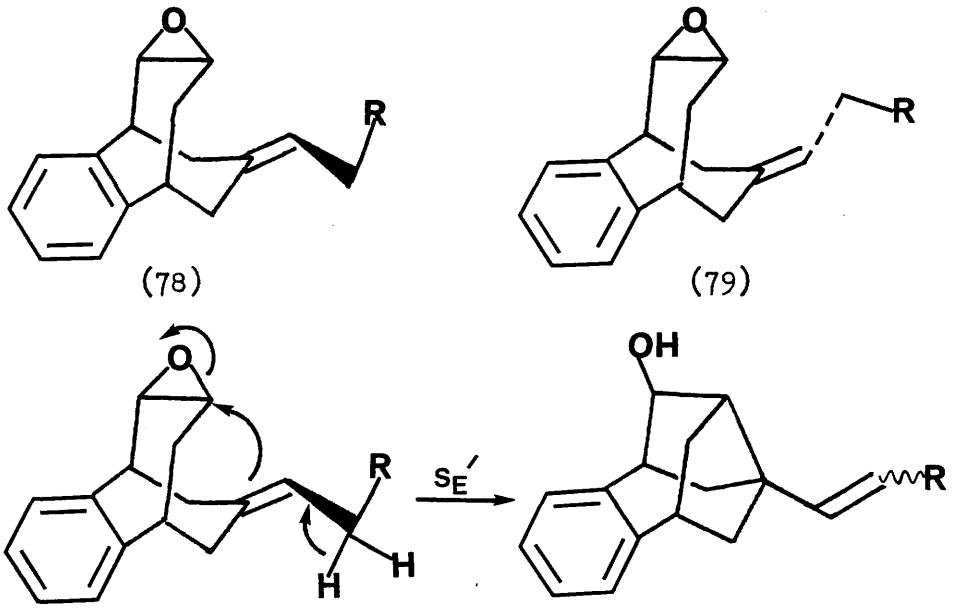


Figure 4

Because of the purely speculative nature of the above conformational analysis it was decided that experiments expected to produce both <u>syn</u>-and <u>anti</u>-eliminations should be investigated.

At the same time a modification of the target system was introduced for which the above conformational analysis still holds. The target model systems were modified to the epoxides (78) and (79); Scheme 39 illustrates an S_E' reaction on (78). This modification would provide in the products a convenient 'handle' (a hydroxyl group) for resolution, an essential step in the analysis of the products. An added advantage in this system is that the epoxide component being more electrophilic than the corresponding olefinic component in (55) and (56) would be expected to facilitate the

initiation of an S_E' reaction.



(78)

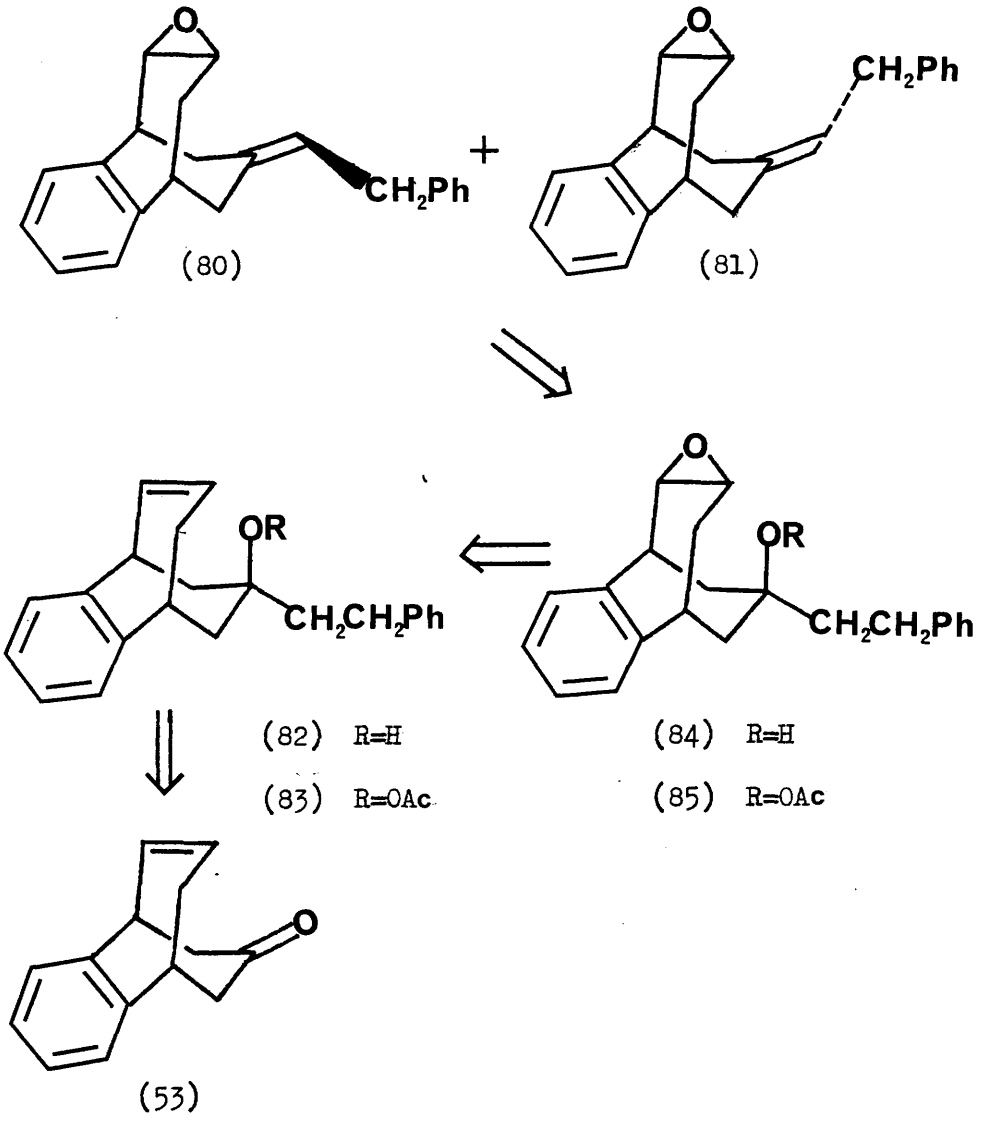
Scheme 39

Another modification of the target model system was also introduced. With a view to the stereospecific labelling of the side chain, it was decided to incorporate a phenethyl group into the model system in place of the propyl group. The reason for doing so was two-fold:

(i) stereospecifically labelled phenethyl-based compounds were potentially available from the readily accessible (R) and (S) - mandelic acids;[50-55] and

(ii) the less volatile intermediates would be easier to handle than those derived from lactic acid.

The strategy for the preparation of the modified model system (80) and (81) is outlined in Scheme 40.

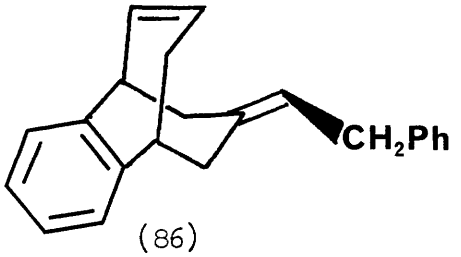


Scheme 40

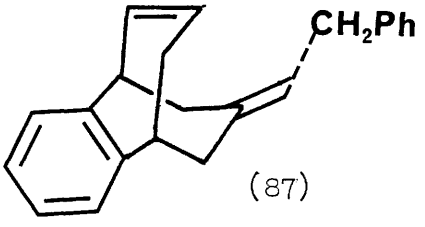
Treatment of enone (53) with ß-phenethyl magnesium bromide gave a compound, m.p. 76-77.5°C, formulated as the endo-ol (82) on the basis of the expected attack at the less-hindered exo-face of (53) (Scheme 38) [Later results prompted a reappraisal of this surmise and will be discussed later in the thesis (p. 62)]. The enol (82) displayed in the i.r.

spectrum the expected hydroxyl band (3520 cm^{-1}) and in the ^{1}H.nmr spectrum olefinic proton signals (δ 6.35-5.65). Attempted epoxidation of the enol (82), under conditions designed for the epoxidation of acid sensitive compounds,[56] gave a mixture of two compounds, whose separation proved troublesome and the reaction was not further pursued.

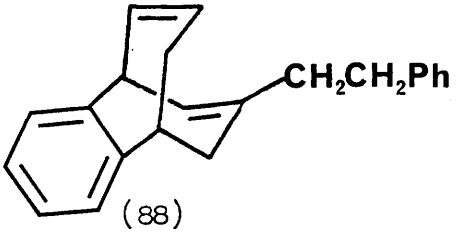
With a view to obtaining potential model systems (86) and (87), (82) was treated with phosphoryl chloride and pyridine and a non-polar material was produced. The ^{1}H.nmr spectrum of this material showed complex olefinic proton signals (δ 6.1-5.5) and integration of the spectrum indicated three olefinic protons were present. T.l.c., however, on silver nitrate-impregnated silica gel plates[57] indicated a mixture of four compounds, presumably (86), (87), (88) and (89).



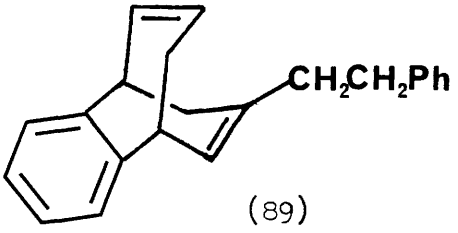
(86)



(87)



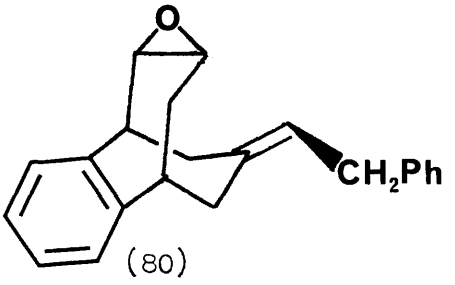
(88)



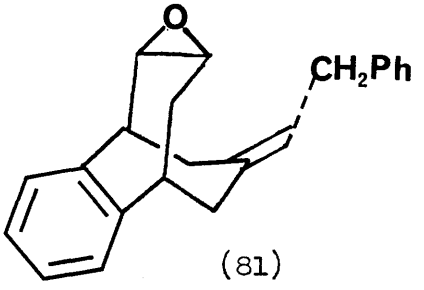
(89)

Attention was now turned to effecting a <u>syn</u>-elimination by pyrolysis of the oxido-acetate (85) (Scheme 40). Oxido-acetate (85), m.p. 138-142°C, was prepared from (82) via the acetate (83) by standard procedures. The i.r. spectrum of (85) had an ester carbonyl band at 1730 cm^{-1} and bands

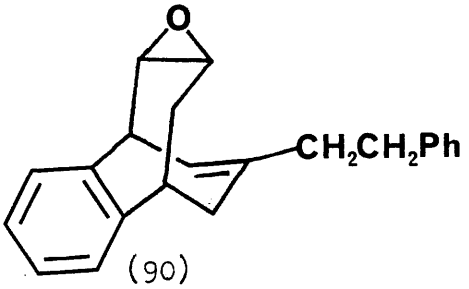
consistent with an epoxide moiety at 1260 and 920 cm^{-1}. The ^1H.nmr spectrum had no olefinic proton signals and showed signals between δ 4.00 and 3.10 (in addition to the bridgehead proton signals), consistent with the presence of an epoxide. An attempt at vapour phase pyrolysis of (85) at 450°C returned starting material and a non-polar product. The ^1H.nmr spectrum of this non-polar material displayed complex olefinic signals (δ 6.0-5.0). T.l.c. on silver nitrate-impregnated silica gel plates indicated four compounds presumed to be the oxido-olefins (80), (81), (90) and (91).



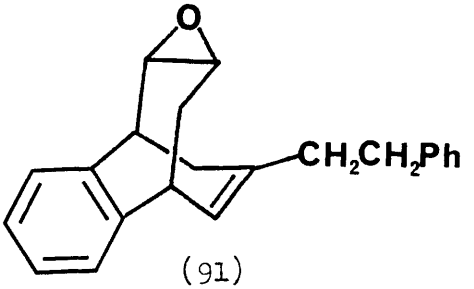
(80)



(81)



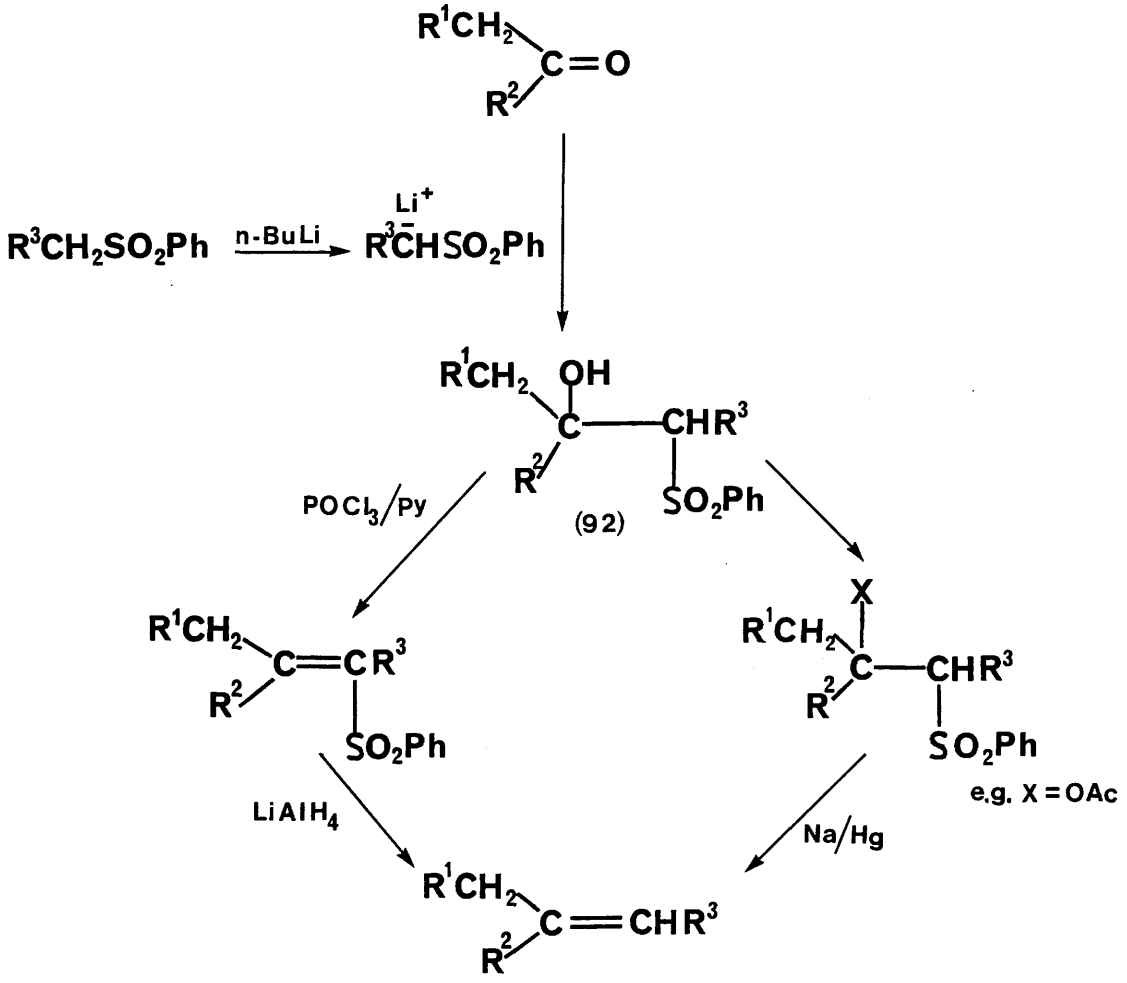
(90)



(91)

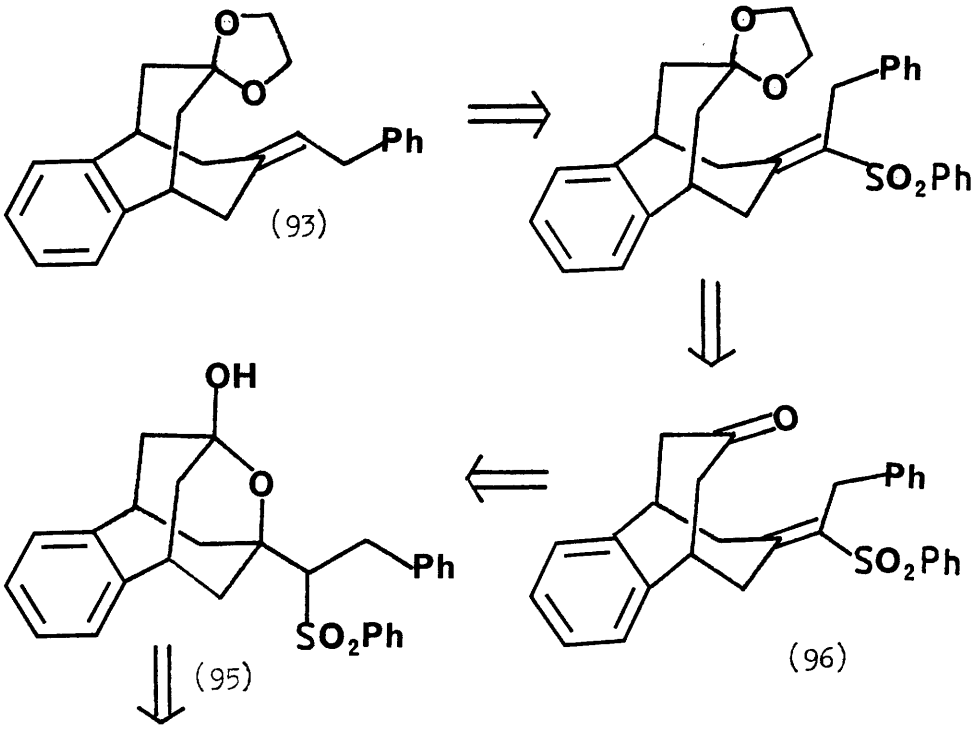
Although model systems (80), (81), (86) and (87) were thus potentially available by preparative t.l.c. on silver nitrate-impregnated silica gel, this route was kept in abeyance and a more selective method for the introduction of the exo-cyclic double bond was sought.

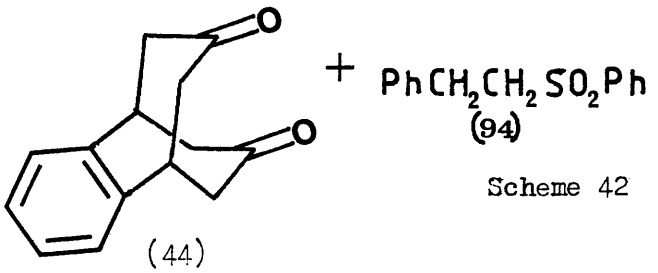
Two simple methods for the regiospecific synthesis of olefins from β-hydroxy-sulphones (92) were described by M. Julia in 1973[58] (Scheme 41), and the viability of these methods has been demonstrated by Julia and others.[58-62]



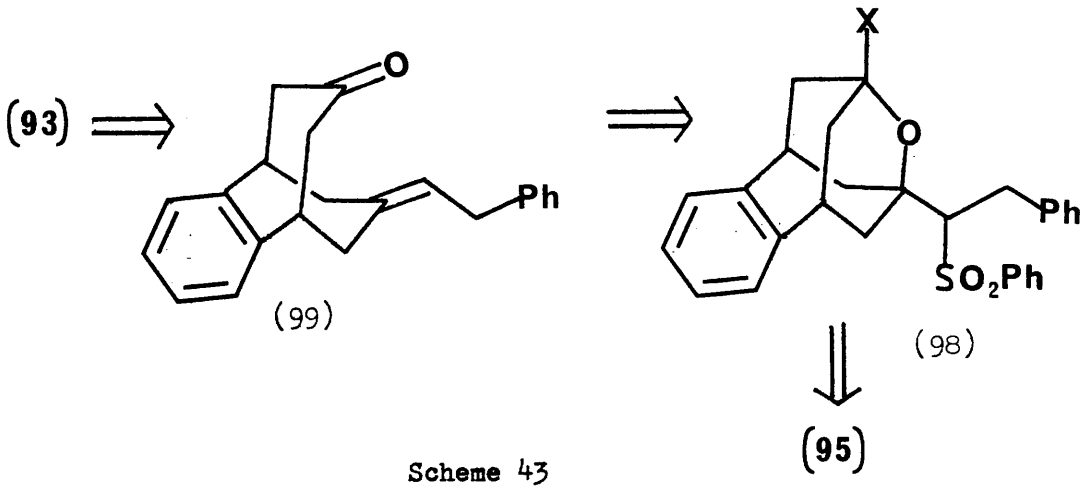
Scheme 41

Schemes 42 and 43 indicate how these methods might be exploited to provide the potential model system (93). [cf. model system (43), Scheme 28, p.24]





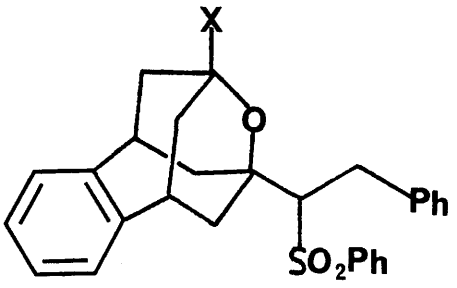
Scheme 42



Scheme 43

The dione (44) was reacted with the lithium salt of β-phenethyl phenyl sulphone (94) in THF at -78°C to furnish, virtually quantitatively, the hemiketal sulphone (95), m.p. 238.5-240°C. It was found that unless the reaction was quenched at low temperature (-40°C), the yield of (95) was poor. The i.r. spectrum of (95) indicated a hydroxyl group (3350 cm^{-1}) and also bands at 1300, 1160 and 1140 cm^{-1} indicative of a sulphone group. The presence of a phenyl sulphone group was further confirmed by the low-field aromatic proton signals in the ^{1}H.nmr spectrum between δ 7.80 and 7.30 and the multiplet at δ 3.59 corresponding to the proton ∝ to the sulphone group.

Treatment of (95) with phosphoryl chloride and pyridine did not furnish the desired keto-sulphone (96) but gave, instead, the stable dichlorophosphate ester (97), m.p. 168-170°C. The ^{1}H.nmr spectrum of (97) showed a clear similarity to that of (95), the i.r. spectrum indicated the absence of a hydroxyl group. Confirmation of the molecular formula of $C_{28}H_{27}O_5PSCl_2$ was obtained from microanalysis.



(98)

(97) x = $OPOCl_2$
(100) x = OTs
(101) x = OBz
(102) x = OAc
(103) x = $OPO(OMe)_2$
(104) x = $OC(O)CF_3$

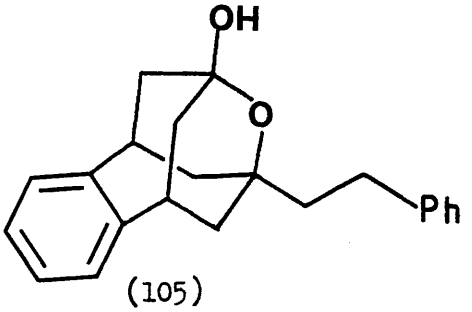
The alternative route, outlined in Scheme 43, was now pursued. The first step necessitated the formation of a derivative (98) from which the simultaneous elimination of X and SO_2Ph to give (99) might be achieved.

Difficulties were encountered in the formation of the toluene-p-sulphonate (100) and the benzoate (101). However, the crude toluene-p-sulphonate (100) on treatment with sodium amalgam in an ethyl acetate/methanol mixture gave a complex mixture of compounds from which the enone (99), m.p. 160-162°C, could be isolated. This showed in the i.r. spectrum intense carbonyl absorption at 1685 cm^{-1} and in the ^{1}H.nmr spectrum a triplet at δ 5.5 (t, J=8Hz, 1H, >C=CH-CH-Ph). The ^{13}C.nmr spectrum showed a signal at δ 210.75 (>C=O) and the rest of the spectrum was also consistent with structure (99). Microanalysis and accurate mass measurement confirmed the required molecular formula of $C_{22}H_{22}O$.

The acetate (102), m.p. 197.5-199°C, was readily accessible but treatment with sodium amalgam consistently returned the hemiketal (95) as the major product. Sodium amalgam treatment of the dichlorophosphate ester (97) in a methanol/ethyl acetate mixture at times provided the enone (99) in acceptable yield but, unfortunately, not reproducibly. On one occasion the major product was identified as the dimethoxyphosphate ester (103), m.p. 193-194°C. This compound showed in the ^{1}H.nmr spectrum a doublet at δ 3.65 (d, 6H, -P-OCH$_3$) and in the i.r. spectrum a strong band at 1045 cm^{-1} (P-O-Me) consistent with proposed structure.

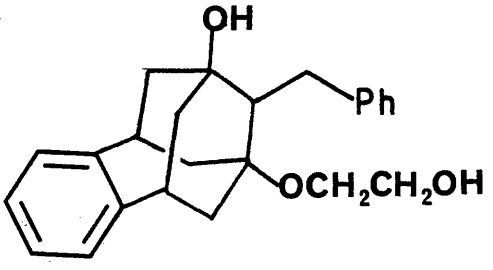
By far the best method for obtaining the enone (99) consistently in good yield was via the trifluoroacetate (104), which could be obtained quantitatively by treating the hemiketal sulphone (95) in THF with trifluoroacetic anhydride, and used without purification. In this way, yields in excess of 80% were routinely achieved.

One minor by-product detected in these reductive elimination reactions was the hemiketal (105), m.p. 218-220°C. The ^{1}H.nmr spectrum of this compound had no signals below δ 7.30 indicating the loss of the sulphone group. This was further suggested by the i.r. spectrum which also showed a hydroxyl band at 3330 cm^{-1}. Reductive removal of the sulphone group under these conditions is a well known event.[63]



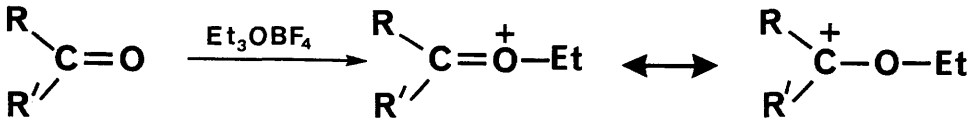
(105)

Attempts at ketalisation of (99) to give target compound (93) were unsuccessful giving complex mixtures; no olefinic proton signals were evident in the ^{1}H.nmr spectra of these crude mixtures. One polar compound isolated from the complex mixture had in the i.r. spectrum a hydroxyl band at 3570 cm^{-1} and its ^{1}H.nmr spectrum integrated for 19 high-field protons (δ 3.6-1.5). By analogy with later results, this product was tentatively assigned structure (106); the m/e value of 346.1931 suggested a molecular formula of $C_{24}H_{28}O_3$ and was consistent with a parent-H_2O m/e peak for structure (106).

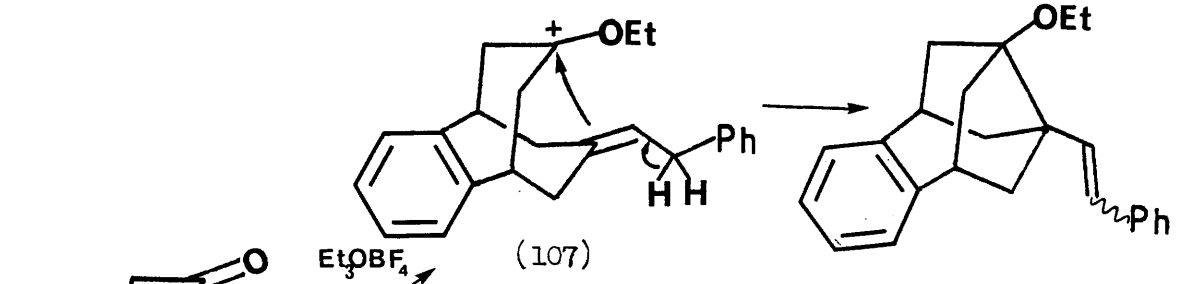


(106)

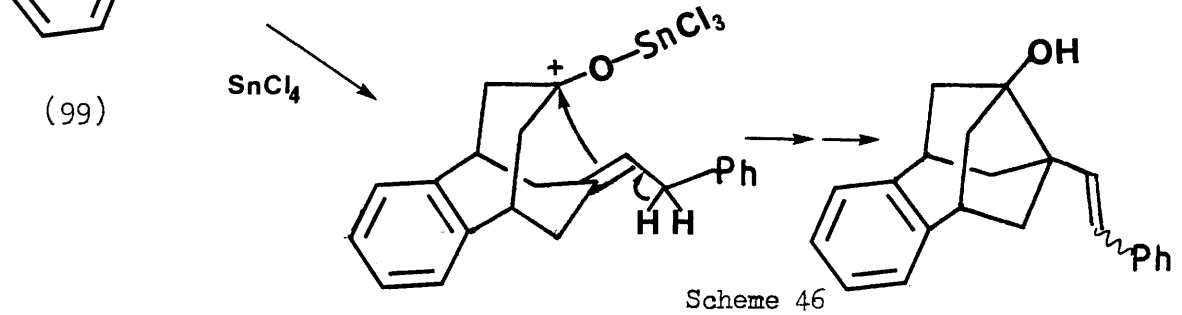
Meerwein salts such as triethyloxonium tetrafluoroborate are believed to react with ketones in the sense depicted in Scheme 44.[64,65] It is conceivable that the intermediate (107) formed from reaction of (99) with a Meerwein salt will either spontaneously, or when assisted by a non-nucleophilic base, undergo an S_E' reaction (Scheme 45). Alternatively reaction of (99) with a Lewis acid, such as stannic chloride, may result in an S_E' cyclisation as illustrated in Scheme 46.



Scheme 44



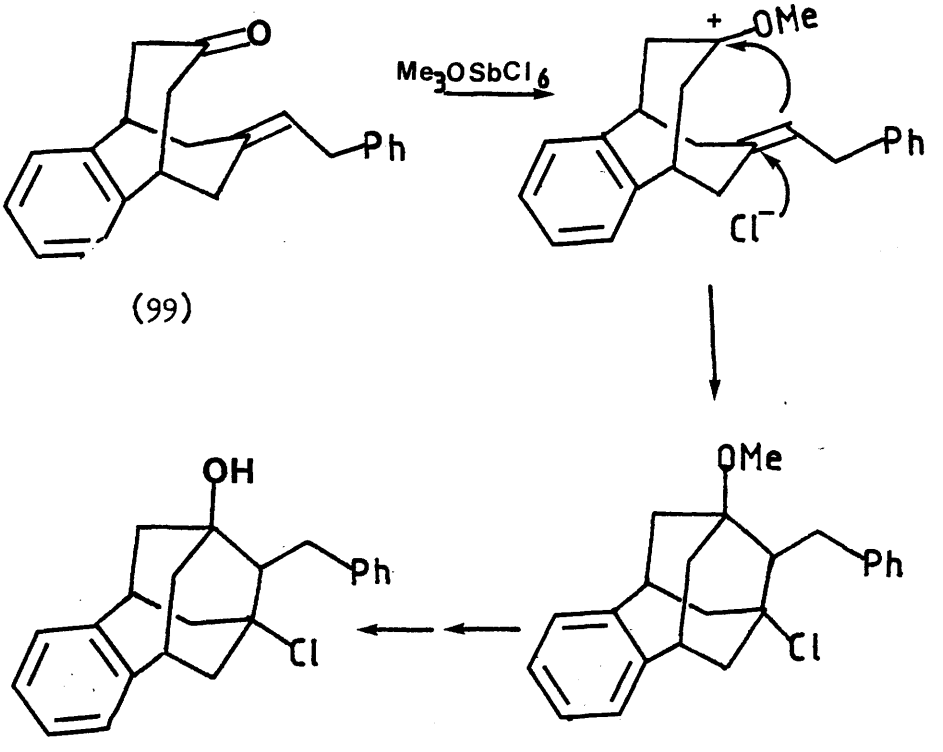
Scheme 45



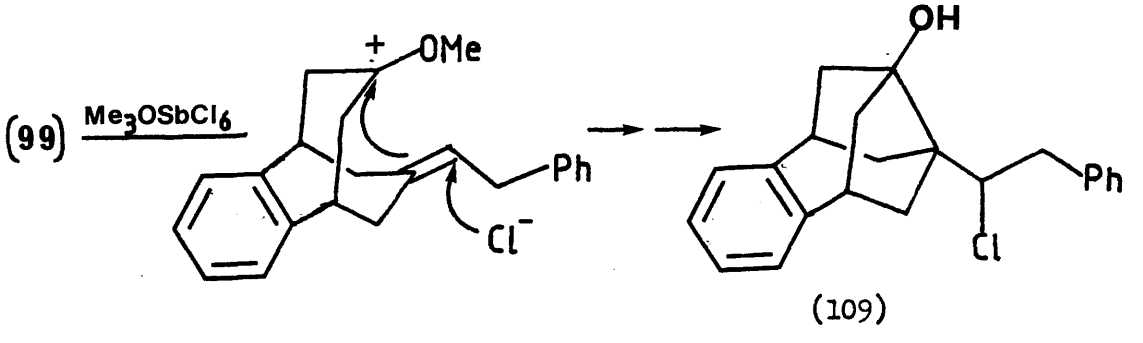
Scheme 46

Treatment of (99) with trimethyloxonium hexachloroantimonate gave a compound, m.p. 113-114°C, for which no olefinic proton signals were evident in the ^{1}H.nmr spectrum. In the mass spectrum the highest peaks (m/e 338.1439

and 340.1395) were in a ratio of 3:1, indicative of the presence of one chlorine atom; this mass spectral data was in agreement with a molecular formula (from microanalysis) of $C_{23}H_{23}OCl$. The i.r. spectrum indicated the presence of a hydroxyl function (3600 cm^{-1}). Two possible structures, (108) and (109) were initially proposed for this compound; Schemes 47 and 48 suggest a possible mechanism for the formation of each.

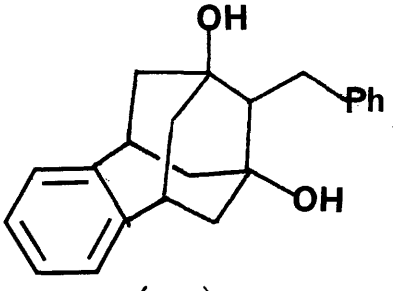


Scheme 47

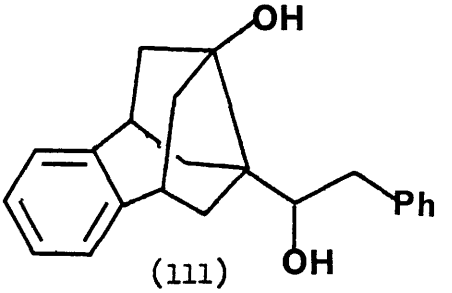


Scheme 48

To avoid this complication of nucleophilic attack by the chloride ion the reagent was changed to that of triethyloxonium tetrafluoroborate. The product from this reaction, m.p. 143-144°C, had a hydroxyl band (3600 cm^{-1}) in the i.r. spectrum, and two protons (exchangeable in D_2O) in the ^1H.nmr spectrum suggested two hydroxyl groups. The molecular formula $C_{22}H_{24}O_2$ was confirmed by microanalysis and mass spectroscopy and two possible structures (110) and (111) were proposed. Presumably water, available in the aqueous work-up, acted here as a nucleophile.



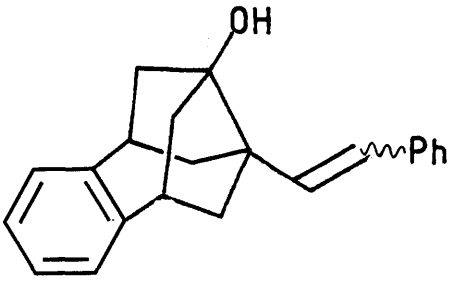
(110)



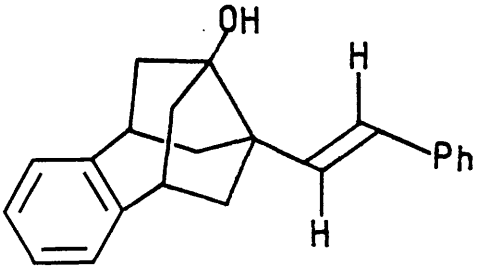
(111)

The crude product of the reaction of (99) with stannic chloride had a ^1H.nmr spectrum similar to that of the hydroxy-chloride, (108) or (109), obtained above. An indication that this hydroxy-chloride was (109) came from treatment of this crude product under dehydrohalogenation conditions (pyridine at reflux). Dehydrochlorination of (109) would be expected to be facile and afford the styryl product (112) whereas dehydrochlorination of (108) would result in an anti-Bredt double bond. The product isolated from the reaction, m.p. 169-171°C had a molecular formula of $C_{22}H_{22}O$ (from microanalysis and accurate mass measurement), a hydroxyl band (3590 cm^{-1}) in the i.r. spectrum, a u.v. absorption at 253 nm with an extinction coefficient of 17,600 and was clearly the styryl product (112). The ^1H.nmr spectrum of (112) was particularly revealing, showing a low-field AB quartet (δ 6.53 and 6.30) for the styryl protons with a coupling

constant of 16 Hz indicating the trans product (113). ^{13}C.nmr and t.l.c. indicated that this was a single compound with no cis isomer detectable.

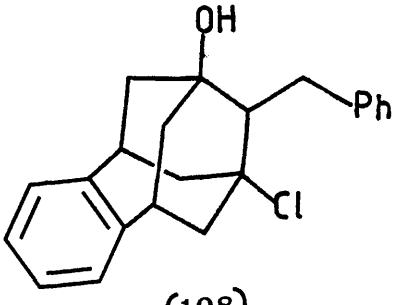


(112)

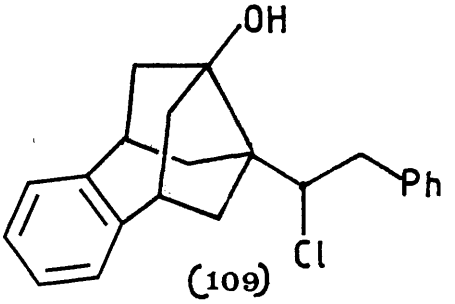


(113)

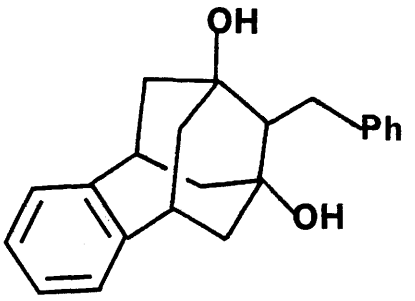
Conclusive evidence that the structure of the products obtained in the above S_E' reactions were, however, (108) and (110) and not (109) and (111) came from the ^{13}C.nmr spectra. The off-resonace ^{13}C.nmr spectra of (108) should show two low-field singlets (>C-OH and >C-Cl) whereas for (109) a low-field singlet (>C-OH) and a low-field doublet (>CH-Cl) would be expected. Two low-field singlets were observed (δ75.81 and 74.48) in accord with structure (108) and the rest of the spectrum was consistent with this structure. The off-resonance ^{13}C.nmr spectrum of (110) should show one low-field singlet (>C-OH) (the carbinol carbons are now equivalent due to a plane of symmetry) and (111) should reveal a low-field singlet (>C-OH), and a low-field doublet (>CH-OH). One low-field singlet was observed (δ74.62) indicating (111) and the rest of the spectrum was consistent with this structure.



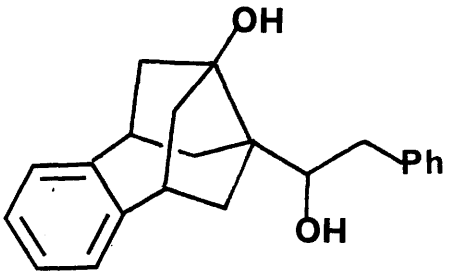
(108)



(109)



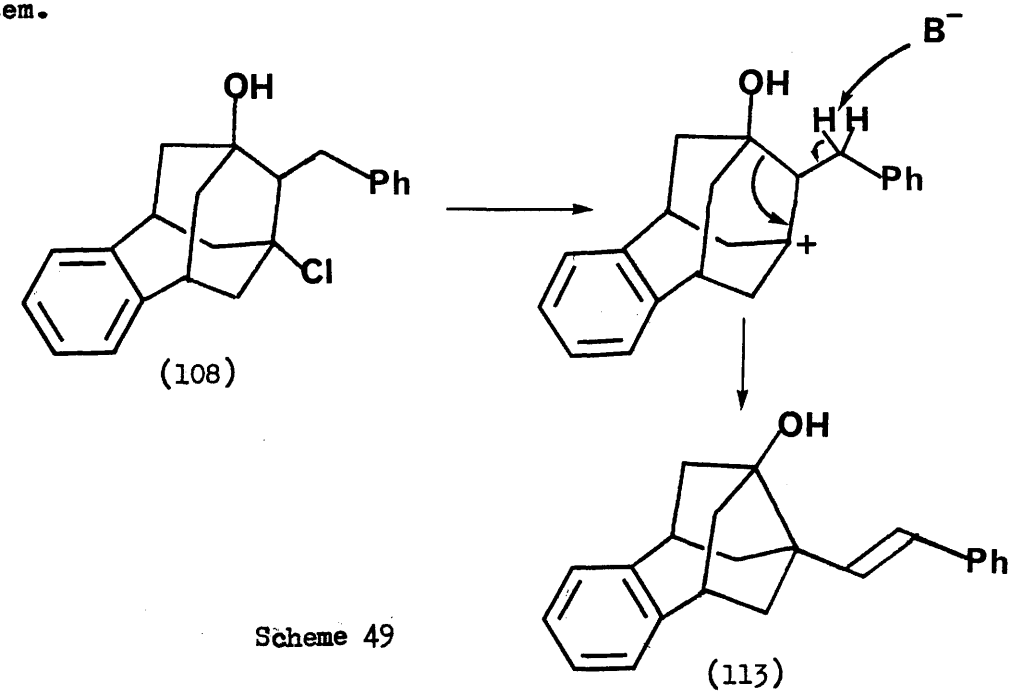
(110)



(111)

That the styryl product (113), prepared above, was formed from (108) was demonstrated by treating (108)[prepared from (99) by treatment with stannic chloride; its structure was confirmed by ^{13}C.nmr spectroscopy] with pyridine under reflux whereby (113) was formed.

Scheme 49 suggests a possible mechanism for this rearrangement, for which the driving force must surely be the formation of the stable styrene system.

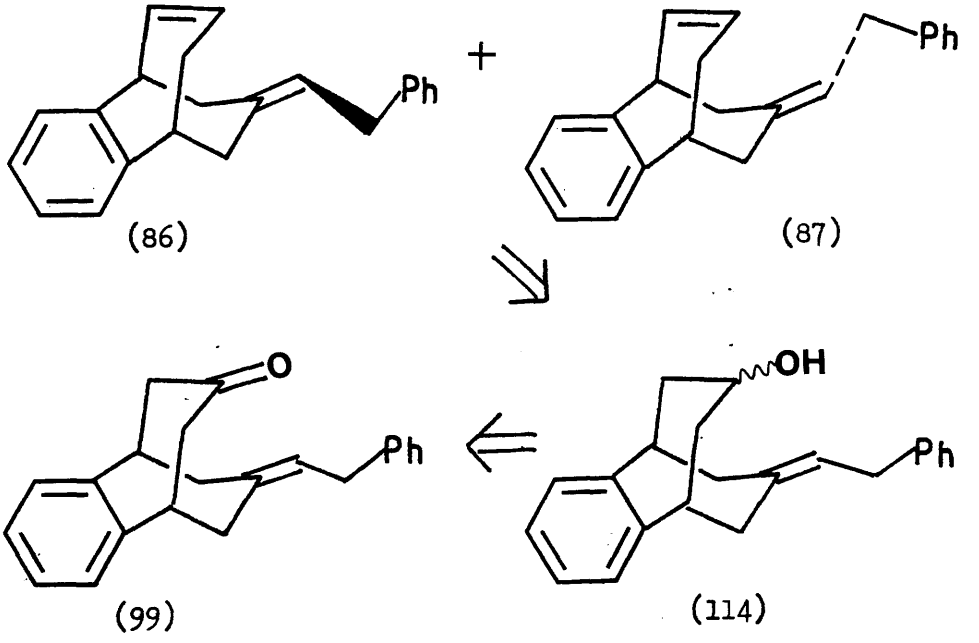


(108)

(113)

Scheme 49

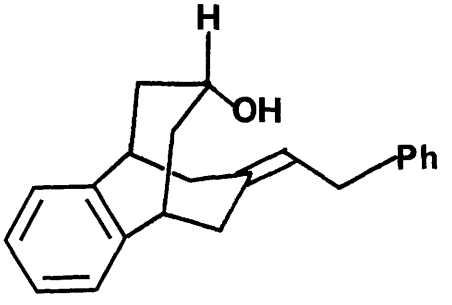
The alternative model systems dienes (86) and (87) were now sought. It was anticipated that these would be accessible by a borohydride reduction of (99) to give (114) followed by dehydration to (86) and (87) (Scheme 50).



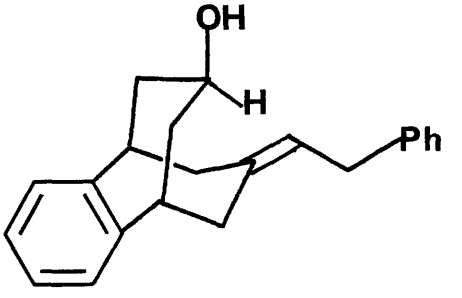
Scheme 50

Anticipating hydride attack from the less hindered face, it was expected that the predominant if not the exclusive product would be the endo-ol (115). Sodium borohydride reduction of (99) gave two products of very similar polarity which were separated by vacuum liquid chromatography (v.l.c.).[66] The less polar of the two compounds, m.p. 119-120.5°C, (60% of isolated product) had a hydroxyl band at 3620 cm^{-1} in the i.r. spectrum and a triplet at δ 5.55 (t, 1H, $\geq C=\underline{CH}-CH_2-Ph$) in the ^1H.nmr spectrum. A molecular formula of $C_{22}H_{24}O$ was indicated by microanalysis and accurate mass measurement. Collins oxidation of this compound reformed the enone (99) as the major product. The more polar of the two compounds m.p.

93.5-94.5°C (40% of isolated product) had in the i.r. spectrum a hydroxyl band (3610 cm^{-1}) and in the ^1H.nmr spectrum a triplet at δ 5.33 ($\geq C=C\underline{H}-CH_2-PH$) and a multiplet between δ 5.00 and 4.60 ($\geq C\underline{H}-OH$). Microanalysis and accurate mass measurement confirmed a molecular fomula of $C_{22}H_{24}O$ and Collins oxidation of the compound furnished the enone (99). The above data strongly indicated that these compounds were the <u>endo</u>-ol (115) and the <u>exo</u>-ol (116).



(115)

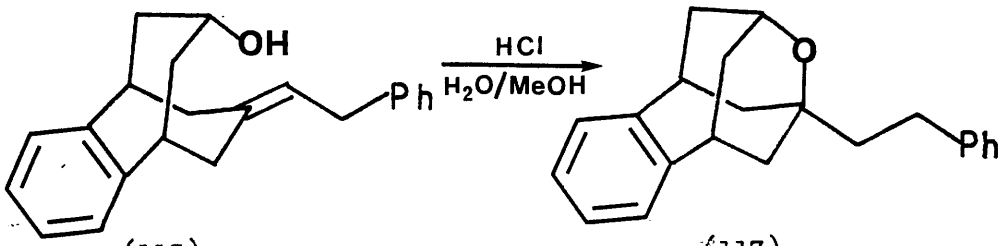


(116)

The chemical shift of a carbinol methine proton ($\geq C\underline{H}-OH$) is generally between δ 4.0 and 3.5. The signal for the carbinol proton of the less polar alcohol was hidden among the high-field proton signals (δ 3.30-1.50) suggesting some shielding of this proton. On the other hand, the signal for the carbinol proton of the other alcohol was at δ 5.00-4.60 suggesting deshielding. However, since the preferred conformations of these compounds are unknown, this anomaly cannot be used to formulate them.

The epimeric alcohols (115) and (116) were assigned unequivocally by chemical means. The alcohols were subjected to treatment with dilute hydrochloric acid in aqueous ethanol at reflux,[49] when the less polar alcohol cyclised to the ether (117) (Scheme 51) demonstrating that the less polar alcohol must be the <u>endo</u>-ol (115). This ether, m.p. 114-116°C, lacked

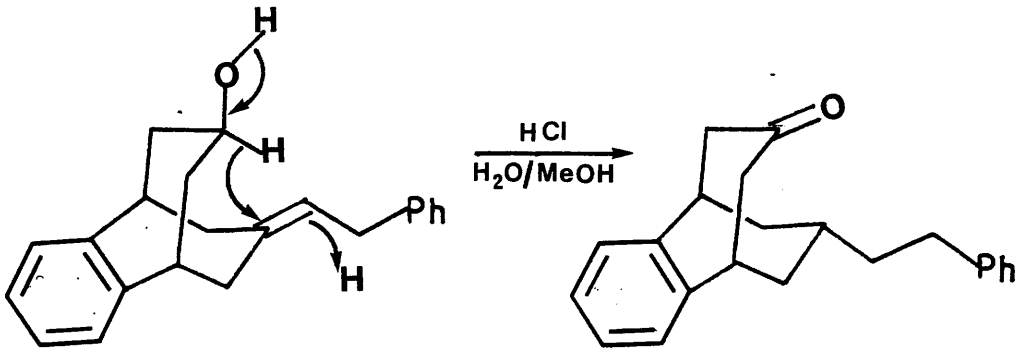
hydroxyl and carbonyl bands in the i.r. spectrum but had an ether band at 1040 cm^{-1}. The ^{1}H.nmr spectrum indicated the absence of olefinic protons but revealed one low-field signal between δ 4.40 and δ 4.20 (m, 1H, >CH-O-C).



(115) (117)

Scheme 51

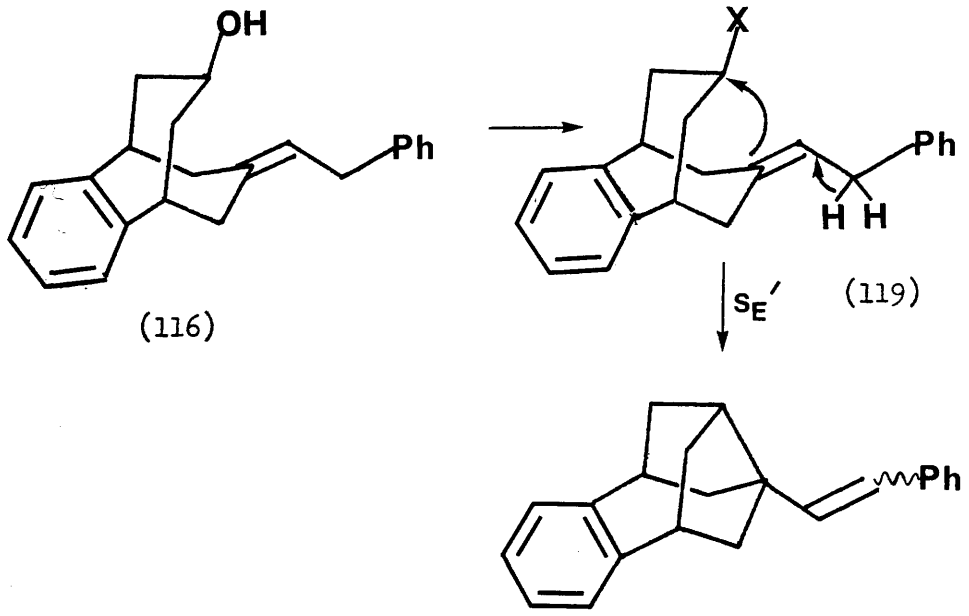
Interestingly the exo-ol (116) under these conditions furnished a compound which had an intense ketonic carbonyl band at 1690 cm^{-1} in the i.r. spectrum and no low-field signals in the ^{1}H.nmr spectrum. This product was tentatively assigned structure (118) and presumably arises by intramolecular hydride shift as illustrated in Scheme 52.



(116) (118)

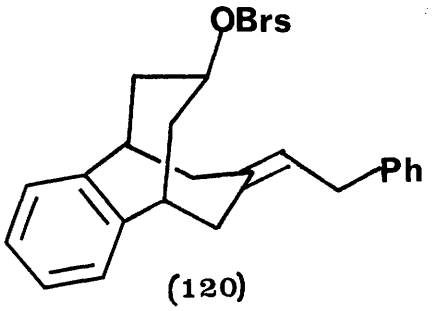
Scheme 52

This unexpected availability of the exo-ol (116) provided, by functionalisation, another potential model system (119) (Scheme 53) while the endo-ol (115) could still be used to prepare dienes (86) and (87).

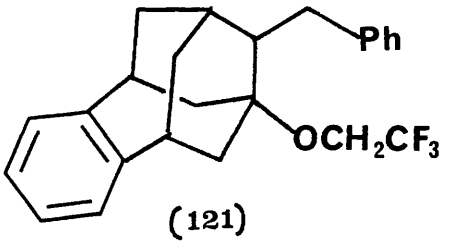


Scheme 53

Attempted formation of the p-bromobenzenesulphonate (120) by treatment of the exo-ol (116) with p-bromobenzenesulphonyl chloride and pyridine gave, at the first attempt, a mixture of starting exo-ol (116) and a less-polar product showing in the ^{1}H.nmr spectrum a singlet at δ 7.57 consistent with (120) (accidental equivalence of the two pairs of protons on the p-disubstituted aromatic ring). This crude product, in trifluoroethanol, was heated in a sealed tube at 100°C. The major product isolated from this reaction had no olefinic proton signals evident in the ^{1}H.nmr spectrum and was not further investigated, although, this ^{1}H.nmr spectrum was virtually identical to that of a product formed subsequently and identified as (121).

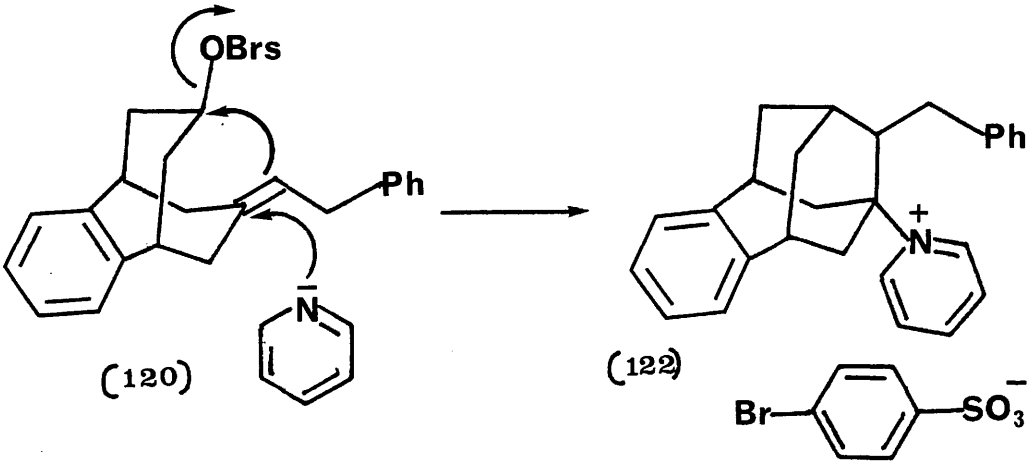


(120)



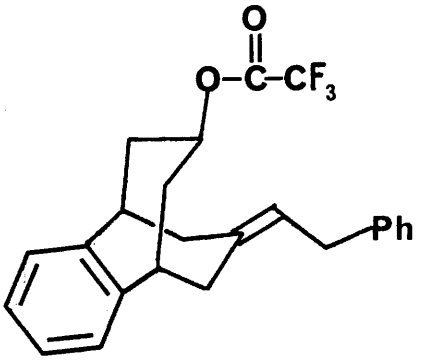
(121)

The major product isolated from a second attempt at formation of (120) was an extremely polar compound, m.p. 191.5-194 °C. There were no distinctive bands in the i.r. spectrum of this compound but the ^{1}H.nmr spectrum was particularly revealing with a two-proton multiplet between δ 9.50 and 9.35 and a three-proton multiplet between δ 8.20 and 8.00 suggestive of a pyridinium salt,[67] and a four-proton AB quartet (δ 7.80 and 7.40, J=8Hz) suggestive of a p-bromobenzenesulphonate residue. This product was formulated as the pyridinium salt (122) which was further confirmed by ^{13}C.nmr and microanalysis. This may have been formed via (120) by a nucleophilic attack of pyridine, illustrated in Scheme 54, in a manner analogous to the formation of (108) and (110) (cf. Scheme 47).

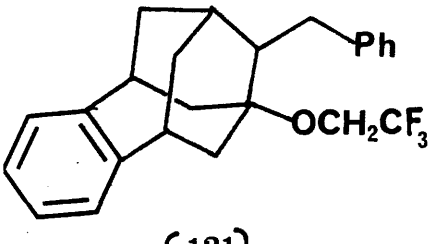


Scheme 54

The trifluoroacetate (123) was obtained virtually quantitatively from (116) and had in the i.r. spectrum a carbonyl band at 1780 cm^{-1}. The ^{1}H.nmr spectrum revealed a low-field multiplet at δ 6.45-6.15 ($>C\underline{H}-OC(O)-CF_3$) and a triplet at δ 5.58 ($>C=C\underline{H}-CH_2Ph$). Heating (123) in trifluoroethanol at 100°C in a sealed tube afforded the ether (121) as an oil. The i.r. spectrum of (121) displayed extensive absorption between 1300 and 1000 cm^{-1} consistent with the presence of a trifluoromethyl moiety. The ^{1}H.nmr spectrum showed a quartet at δ 3.75 ($\underline{q}$, 2H, $-O\underline{CH}_2-CF_3$) with a coupling constant, $^3J_{H-F}$ of 9Hz ($CF_3-\underline{CH}_2OH$ has $^3J_{H-F}$=9Hz). The quartet at δ 124.43 in the proton-decoupled ^{13}C.nmr spectrum with a coupling constant, $^1J_{C-F}$, of 279.9Hz was consistent with the presence of a trifluoromethyl moiety ($\underline{C}F_3CO_2H$ has $^1J_{C-F}$=294Hz) and the quartet at δ 58.89 ($^2J_{C-F}$=34Hz, $-O-\underline{CH}_2CF_3$) was also consistent with the proposed structure. The reaction was repeated using the bulkier hexafluoroisopropanol in place of trifluoroethanol but a complex mixture of products, as indicated by t.l.c., was formed. The ^{1}H.nmr spectrum of this complex mixture did not look promising (no olefinic proton signals) and the reaction was not further investigated.

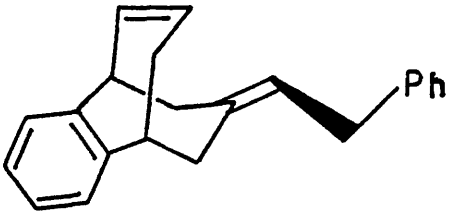


(123)

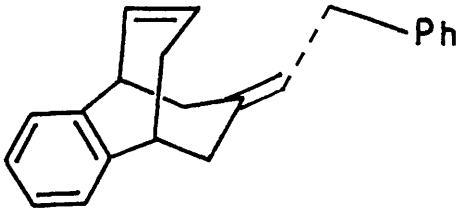


(121)

Attention was now turned to the formation of systems (86) and (87) (Scheme 50). Treatment of the endo-ol (115) with phosphoryl chloride and pyridine gave a non-polar product. T.l.c. of this product on silver nitrate-impregnated silica gel plates indicated two compounds. These were separated by vacuum liquid chromatography on a silver nitrate-impregnated silica gel column[68,69] and formulated as the dienes (86) and (87). The ^{1}H.nmr spectrum of both compounds revealed complex olefinic proton signals between δ 5.85 and 5.40 for one, and between δ 5.85 and 5.25 for the other, integrating for three protons in each case.

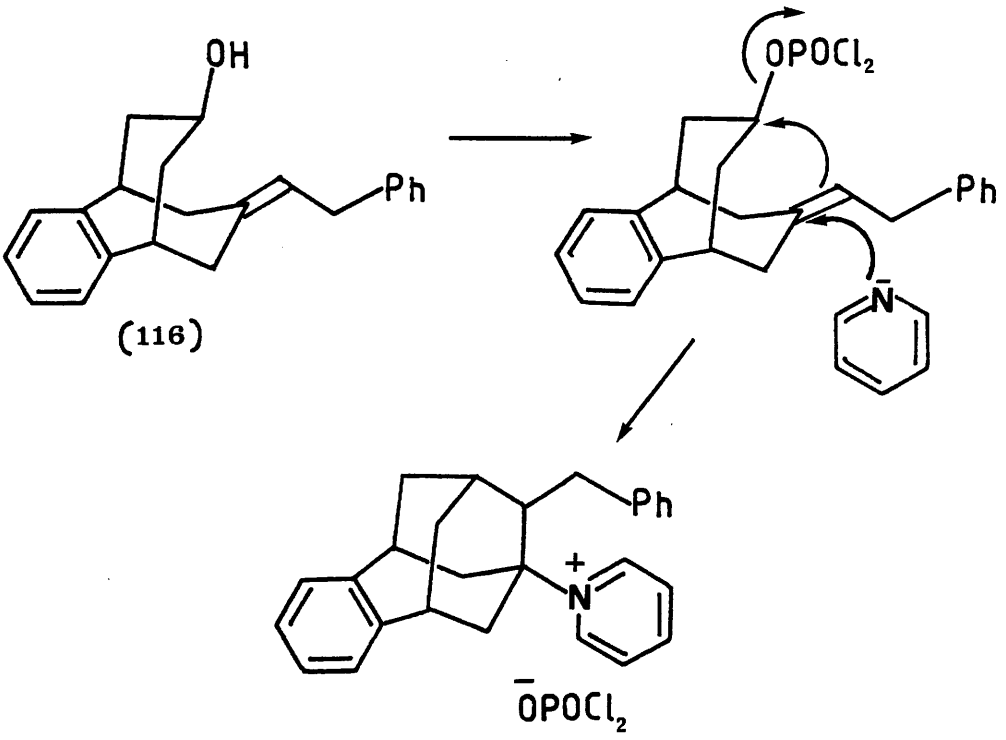


(86)



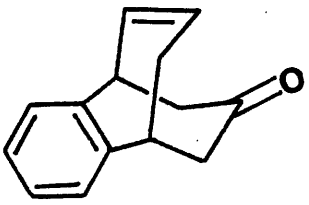
(87)

Treatment of the exo-ol (116) with phosphoryl chloride and pyridine gave a very polar compound for which the ^{1}H.nmr spectrum revealed two low-field multiplets at δ 9.6-9.4 (2 protons) and δ 8.4-7.9 (3 protons) suggestive of a pyridinium salt similar to (122). Scheme 55 suggests a possible mechanism for the formation of such a salt in this reaction. The reaction, however, was not further investigated.

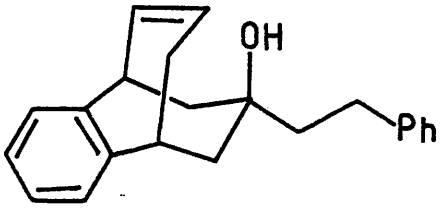


Scheme 55

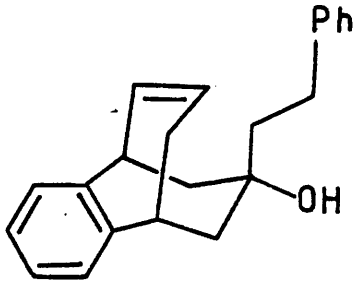
With a view to obtaining a higher proportion of endo-ol (115) in the reduction of (99), a bulky reducing agent, K-selectride, was tried but this gave the exo-ol (116) virtually exclusively. This unexpected result prompted a re-examination of an earlier experiment for which attack at the exo face of the carbonyl group in (53) was assumed (cf. Scheme 38, p. 37) to give endo-ol (82) (p. 42). Clearly the above result suggests that the product may, in fact, have been the exo-ol (82′) and not the endo-ol (82). Consideration of the spectral data did not allow a distinction between these possible products. Treatment of the product under Grob's conditions for ether formation[49] (cf. Scheme 50) caused dehydration giving a mixture of dienes [presumably (86), (87), (88) and (89)] which could arise from either (82) or (82′) and the problem remained unresolved.



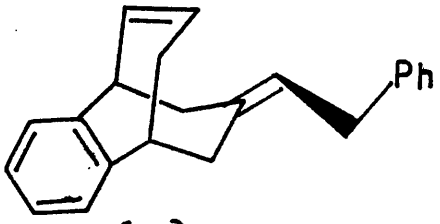
(53)



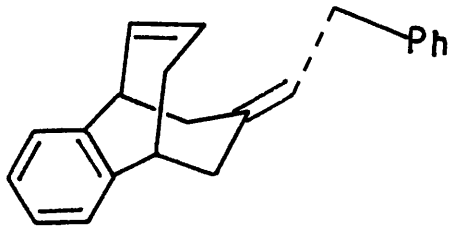
(82)



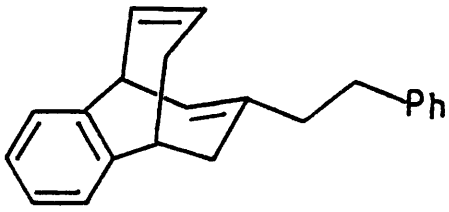
(82')



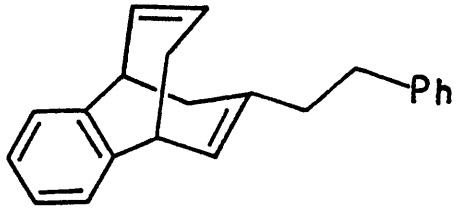
(86)



(87)



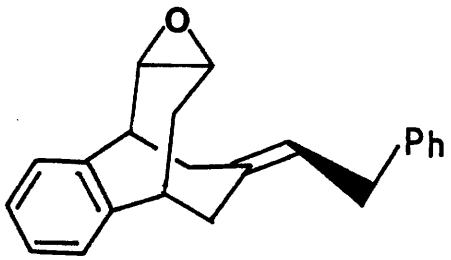
(88)



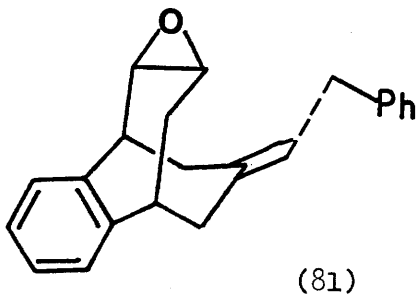
(89)

S_E' cyclisation attempts with (86) and (87), including heating in dioxan in the presence of amberlite I.R. 120 cation exchange resin[70,71] and the presence of dilute sulphuric acid[47] were unsuccessful, returning only starting material.

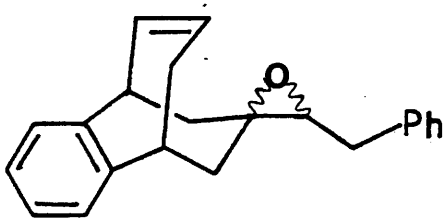
A speculative attempt at forming the epoxides (80) and (81) (cf. Scheme 39) gave, not unexpectedly, the epoxide (124), m.p. 143-146°C, by epoxidation of the more highly substituted double bond. The i.r. spectrum was consistent with this structure, displaying bands at 1270, 950 and 860 cm^{-1} characteristic of an epoxide. The ^1H.nmr spectrum indicated the presence of two olefinic protons ruling out (80) and (81) as possible structures.



(80)



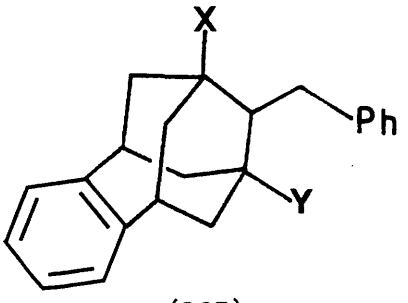
(81)



(124)

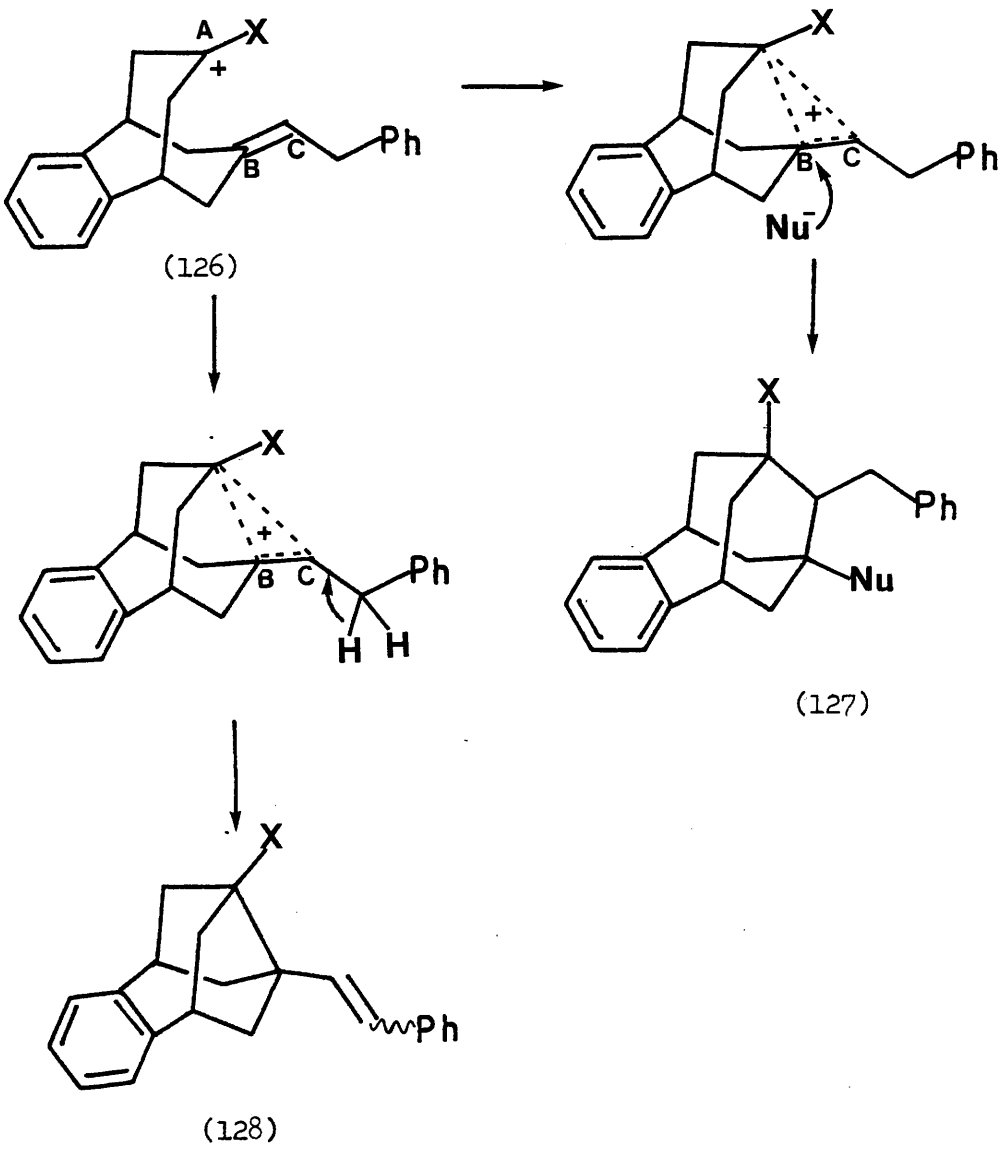
So far, then, synthesis of potential model systems had been achieved but attempts at S_E' cyclisation of these systems gave either no reaction or, in most cases, cyclisation to the 'adamantyl' type structure (125). It

was evident that a modification of the model system was required that might favour S_E' cyclisation over the formation of these 'adamantyl' type products.



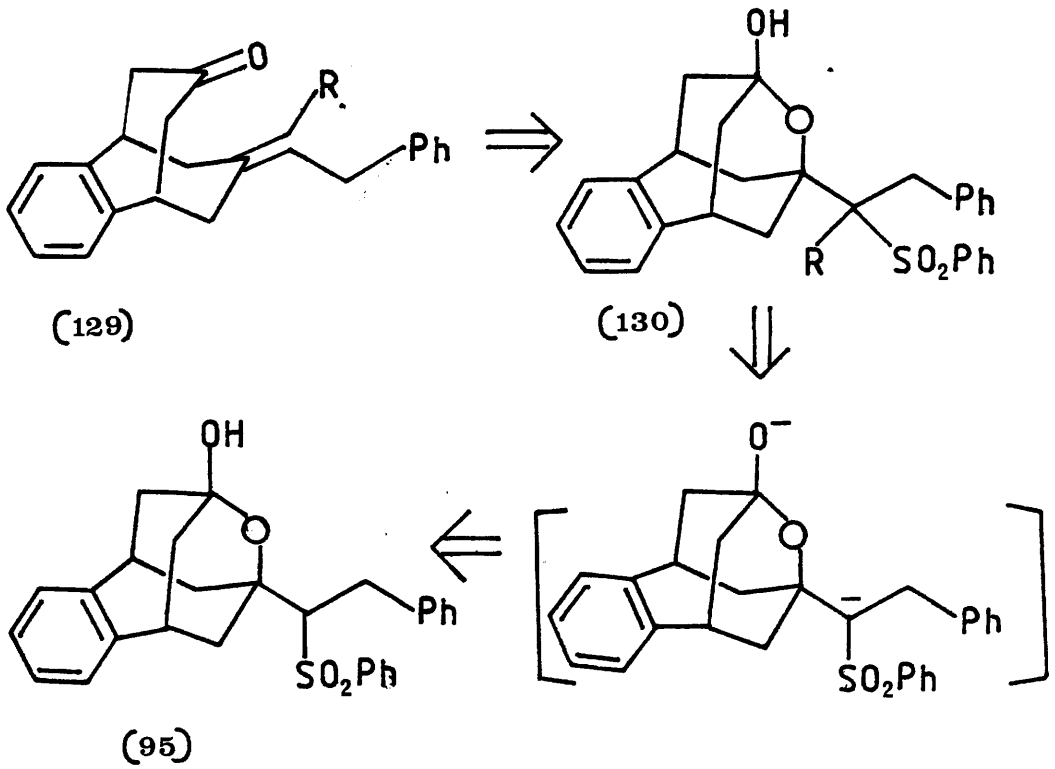
(125)

The mechanism for the formation of these cyclised products was postulated as follows [Scheme 56, (126)→(127)] : as the double bond interacts with the cationic centre A of (126) positive charge develops at either B or C. B, being tertiary, can better stabilise the positive charge; addition of an external nucleophile then neutralises the charge accounting for observed products. On this basis, if C were tertiary, then the alternative pathway [Scheme 56, (126)→(128)] would be as likely and in the absence of an external nucleophile should be preferred.



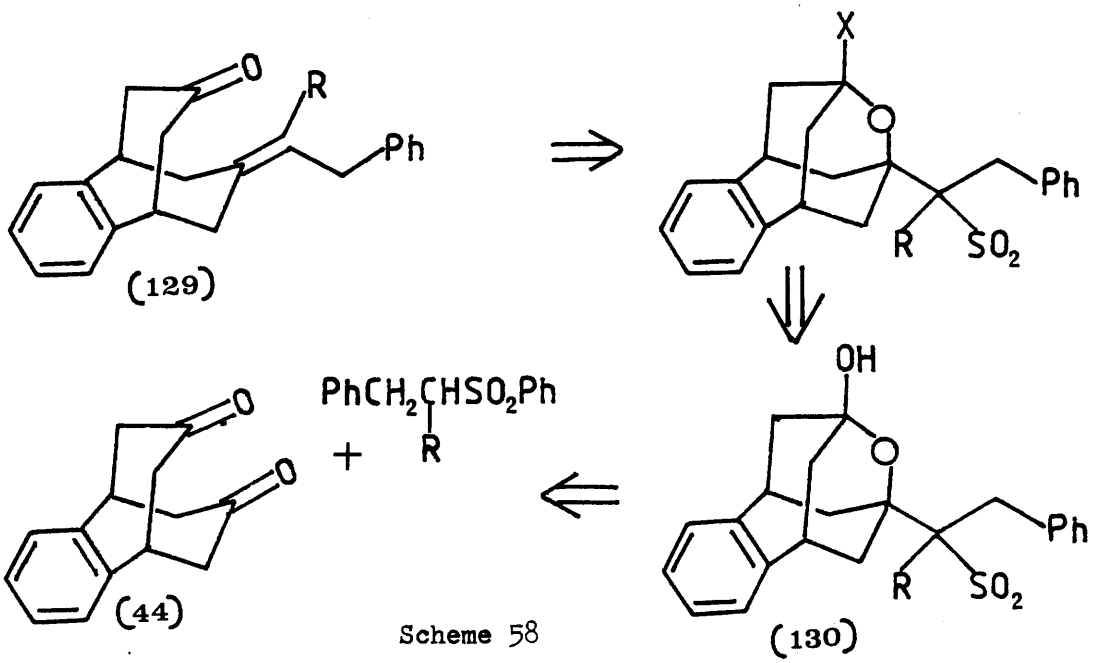
Scheme 56

Modification of the model system to that of (129) (R=CH_3 or Ph), potentially available via (130), was now considered. One direct method of forming (129) was by C-alkylation (or C-arylation) of the dianion of (95) as illustrated in Scheme 57. This approach was unfruitful, returning only starting material.



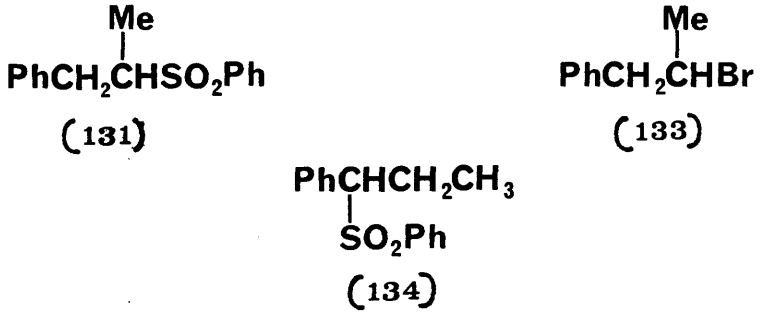
Scheme 57

Scheme 58 illustrates an alternative route to (129).



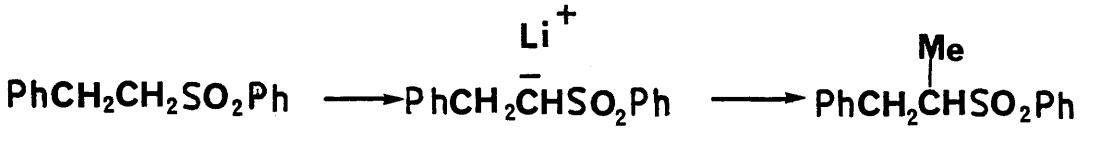
Scheme 58

In an attempt to form methyl sulphone (131), by a similar method to that used for the preparation of β-phenethyl phenyl sulphone (94), 2-bromopropylbenzene (133) was treated with the sodium salt of benzene sulphinic acid in dimethylformamide. After 4 days at room temperature, t.l.c. indicated that much starting material remained but that a minor product was forming. This minor product was isolated by column chromatography. Its ^{1}H.nmr spectrum showed a high-field three-proton triplet (δ 0.81, J=8Hz) inconsistent with the required methyl sulphone (131) which should show a high-field doublet. The ^{1}H.nmr spectrum strongly suggested that the product was, in fact, the rearranged sulphone (134): it showed, apart from the aromatic protons, a doublet of doublets at δ 3.95 (dd, 1H, $-C\underline{H}CH_2CH_3$), a multiplet between δ 2.65 and 1.90 (m, 2H, $-CHC\underline{H}_2CH_3$) and a triplet at δ 0.81 (t, 2H, $-CHCH_2C\underline{H}_3$). That the starting material was 2-bromopropylbenzene (133) was verified by ^{1}H.nmr.



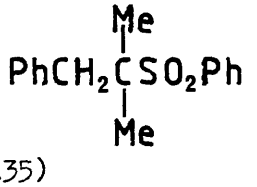
The required methyl sulphone (131) was prepared by methylation of β-phenethyl phenyl sulphone (94) as shown in Scheme 59. Using one equivalent of base and methyl iodide afforded three products of very similar polarity, one major and two minor. One of the minor products was starting sulphone (94), as determined by t.l.c. and the other was assumed to be the dimethyl sulphone (135) with the major product being

the required methyl sulphone (131). By using a slight excess of base and methyl iodide no starting sulphone (94) was recovered. The ^{1}H.nmr spectrum of this two-compound mixture confirmed that the major product was the methyl sulphone (131) with a multiplet between δ 3.50 and 3.12 (m, 2H, $-CH_2-CH-CH_3$), a multiplet between δ 2.65 and 2.30 (m, 1H, $-CH_2-CH-CH_3$) and a three-proton doublet at δ 1.07 ($-CH_2-CH-CH_3$). That the minor product was the dimethyl sulphone (135) was demonstrated by repeating the reaction using two equivalents of base and methyl iodide whereby the ^{1}H.nmr spectrum of the product had a two-proton singlet at δ 3.02 ($-CH_2-C(CH_3)_2$) and a six-proton singlet at δ 1.18 ($-CH_2-C(CH_3)_2$) which corresponded to the impurity signals in the ^{1}H.nmr spectrum of (131).



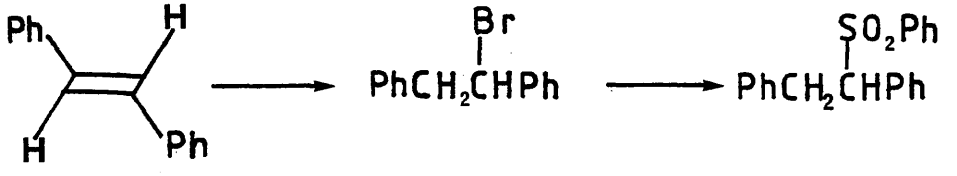
(94) (131)

Scheme 59



(135)

The phenyl sulphone (132) was prepared without incident from trans-stilbene (136) via the bromide (137) as shown in Scheme 60.

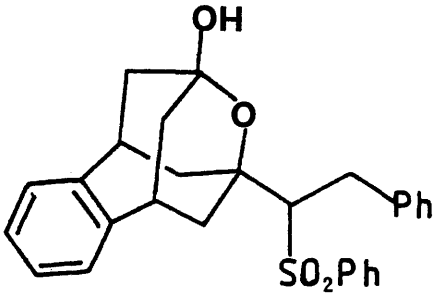


(136) (137) (132)

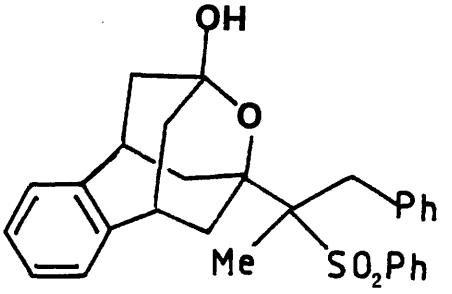
Scheme 60

The methyl hemiketal sulphone (138), m.p. 206-208°C, was prepared, in an analogous manner to the hemiketal sulphone (95), in 60% yield [cf.

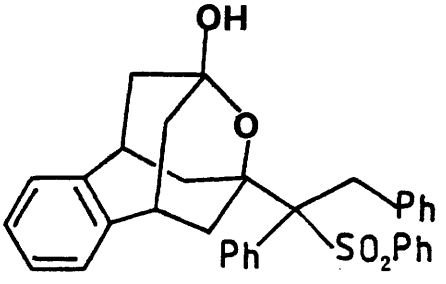
100% for (95)]. The phenyl hemiketal sulphone (139), m.p. 148-151°C could be prepared in only 10% yield and was not further pursued.



(95)



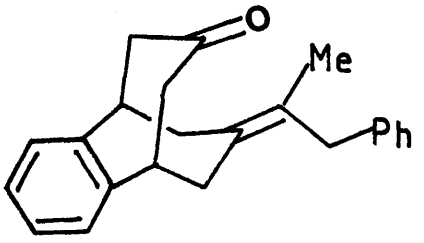
(138)



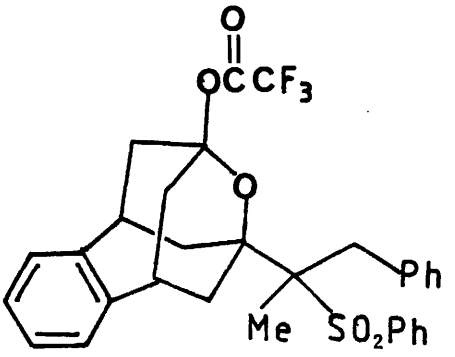
(139)

An attempt to produce the methyl enone (140) by treatment of the trifluoroacetate (141) with sodium amalgam in an analogous manner to that used for the preparation of enone (99) was disappointing, affording (140) in only 20% yield. This enone (140), m.p. 109-111°C, showed an intense carbonyl absorption at 1680 cm^{-1} in the i.r. spectrum and a vinylic methyl singlet at δ 1.58 in the ^{1}H.nmr spectrum. The major product, m.p. 151-155°C, isolated from this reaction displayed hydroxylic absorption at 3310 cm^{-1} in the i.r. spectrum. The ^{1}H.nmr spectrum clearly indicated the absence of the phenyl sulphone moiety (no aromatic signals between δ 7.80 and 7.30) and showed a three-proton doublet at δ 0.7 suggesting a methyl attached to a carbon bearing one proton. This product was formulated

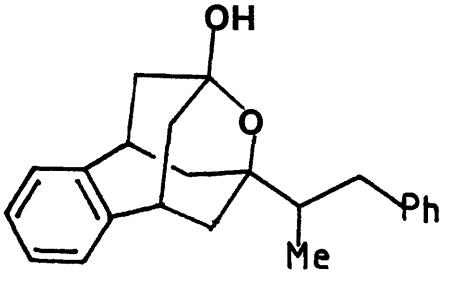
as the hemiketal (142) and this was further confirmed by microanalysis and mass spectroscopy.



(140)

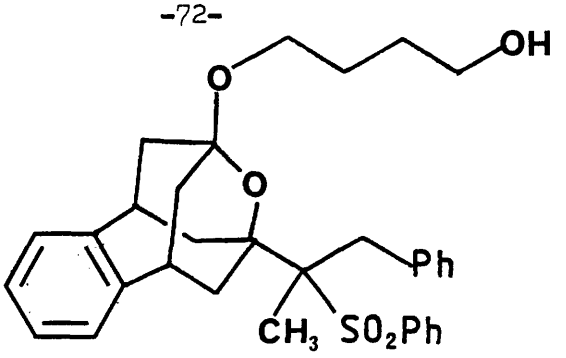


(141)



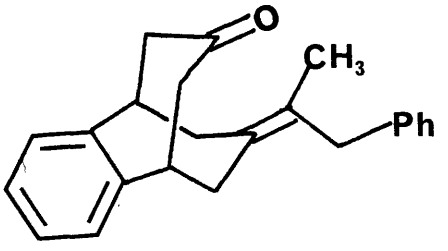
(142)

Hemiketal (142) was presumably formed by reductive removal of the sulphone group without elimination of the leaving group (as had been observed in the desmethyl series), and in an attempt to circumvent this problem, a less protic solvent was used in the reaction. Treatment of (141), in tetrahydrofuran with a small amount of methanol, with sodium amalgam gave very little hemiketal (142) but also very little methyl enone (140). The major product in this case still contained the sulphone moiety as indicated by the signals in the ^{1}H.nmr spectrum between δ 8,0 and 7.6. The ^{1}H.nmr spectrum also showed a singlet at δ 1.9 exchangeable in D_2O suggesting a hydroxyl proton, a singlet at δ 1.40 (3H) indicating an uncoupled methyl group, and integration of this spectrum indicated 24 high-field protons. The product was tentatively assigned structure (143) indicating reaction with tetrahydrofuran and was not further investigated.



(143)

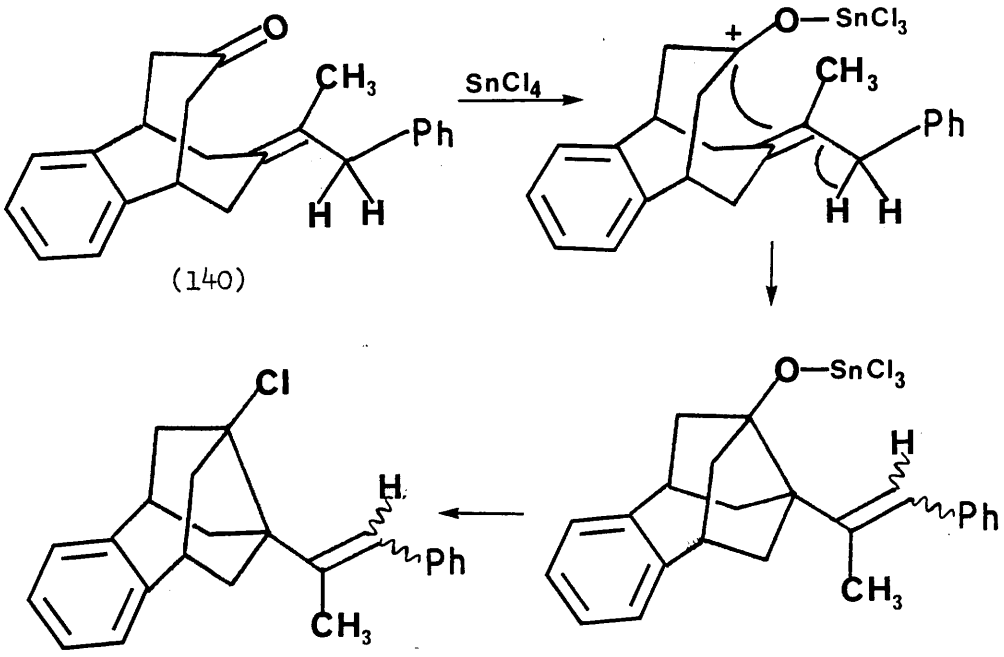
Extensive experimentation including varying solvents, co-solvents, leaving groups, and reaction temperature failed to provide suitable conditions for the preparation of the methyl enone (140) in good yield.



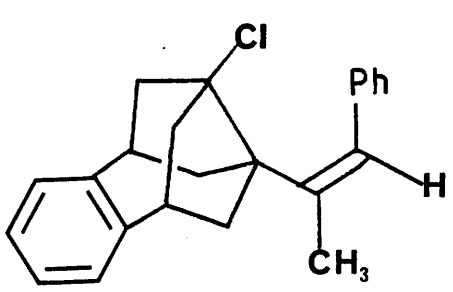
(140)

The methyl enone (140) that was isolated from the above attempts was used to explore conditions for S_E' cyclisation. Treatment of (140) with stannic chloride gave a mixture of products from which the non-polar component was isolated by preparative t.l.c. The spectral data of this material (homogeneous by t.l.c.) was consistent with its being the product of an S_E' cyclisation (Scheme 61). The ^{1}H.nmr spectrum showed a broad singlet at δ 6.01 (-CH=C$<^{CH_3}$) and a broad singlet at δ 1.90 (-CH=C$<^{CH_3}$); double irradiation ^{1}H.nmr experiments confirmed the presence of coupling between the vinylic proton and the allylic protons of the methyl group. The i.r. spectrum showed no significant bands (no O-H or C=O) although there was an intense band at 755 cm^{-1} (C-Cl). The

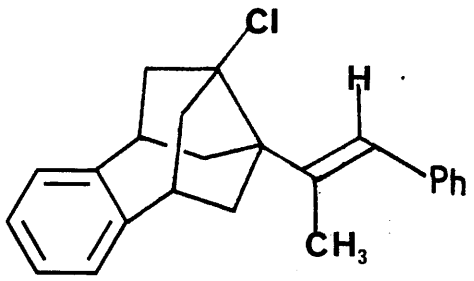
^{13}C.nmr spectrum indicated one major product with a quartet ($-\underline{C}H_3$) at δ 20.26 and a minor product with a quartet at δ 28.43 ($-\underline{C}H_3$) suggesting that both the Z (144) and E (145) isomers were present. That the minor product was the Z isomer (144) was suggested by its methyl signal being ca. 8 ppm upfield from the methyl signal of the major product, a known feature[72] of vinylic methyls attached to trisubstituted double bonds.



Scheme 61

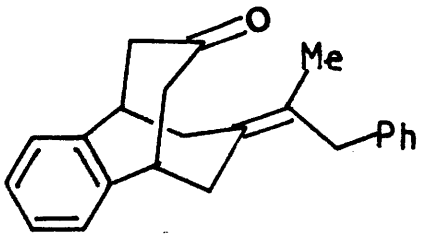


(144)

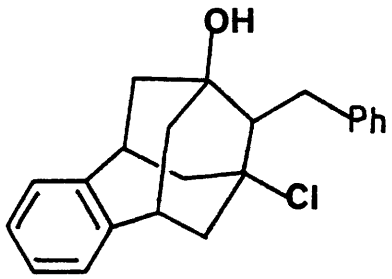


(145)

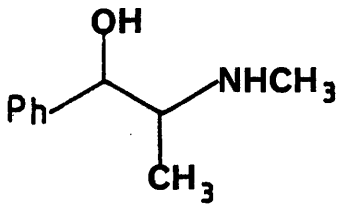
Further developments with this model system were postponed due to unexpected, but welcome, developments with a previous model system (99). While attempts were being made to establish an acceptable route to the methyl enone (140), investigations into possible methods for the resolution of (140) were initiated. One method employed successfully for the resolutuon of compounds whose only handle for resolution is a ketone functionality, involves formation of oxazolidine diastereomers with optically active ephedrine (146).[73] A preliminary attempt to exploit this method was carried out on the readily accessible enone (99). Treatment of (99) with l-ephedrine and toluene-p-sulphonic acid at reflux in benzene gave a single product quantitatively. This product was readily identified as the trans-styryl product (113), prepared previously by the dehydrochlorination of (108), and must surely have arisen by an S_E' mechanism (Scheme 62). Ephedrine was found to be unnecessary for this reaction.



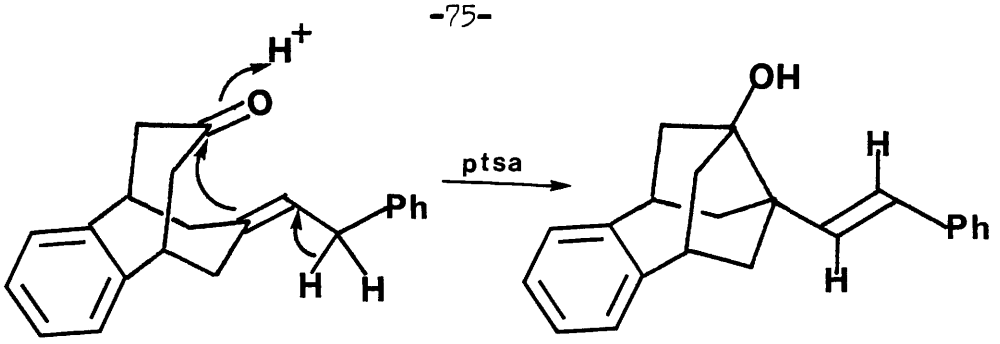
(140)



(108)



(146)



(99) (113)

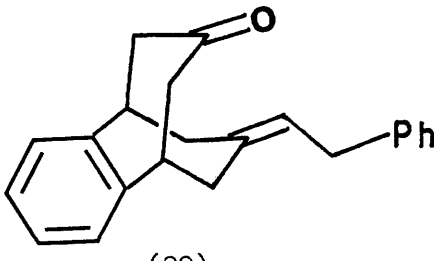
Scheme 62

Thus, somewhat fortuitously, conditions for the elusive S_E' reaction of (99) were established. This enone (99), being much more readily accessible than the methyl enone (140), was chosen as the model system for a stereochemical study of the S_E' reaction.

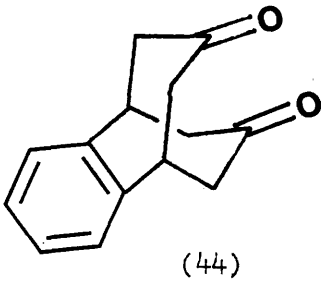
Part 2 A Stereochemical Study of the S_E' Reaction of the Enone (99)

(i) Introduction

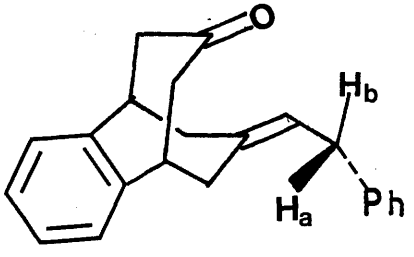
The enone (99), available from the known dione (44)[44] in an optimised overall yield of about 80%, undergoes S_E' cyclisation quantitatively and is therefore a convenient system for stereochemical study. Inspection of molecular models demonstratedthat the conformation required for a *syn* process (figure 5) and that required for an *anti*-process (figure 6) were comparable and, as such, it seemed unlikely that conformational restraints would bias the stereochemical course of this reaction. Consequently, it was felt that the stereochemistry observed in this reaction should closely reflect true stereo-electronic preference.



(99)

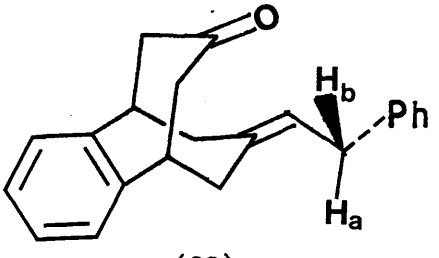


(44)



(99)

Figure 5



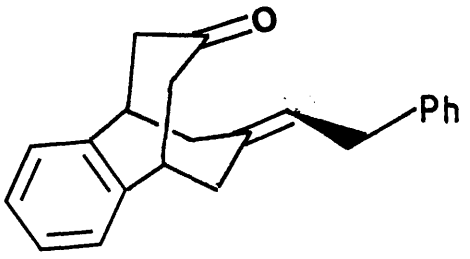
(99)

Figure 6

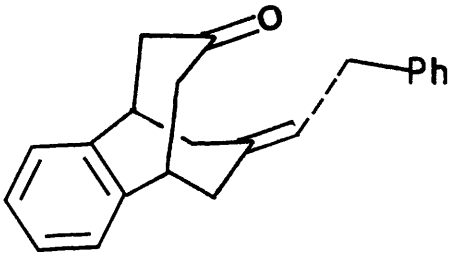
A stereochemical study of the S_E' reaction of (99) requires:

(a) the stereospecific replacement of one of the allylic protons with deuterium [i.e. H_a or H_b of (99) in figures 5 and 6 = D] such that the absolute configuration at this labelled carbon is known.

(b) the resolution of (99) into (99′) and (99″) and the determination of their absolute configuration by X-ray analysis.

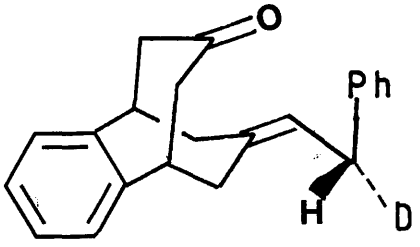


(99′)

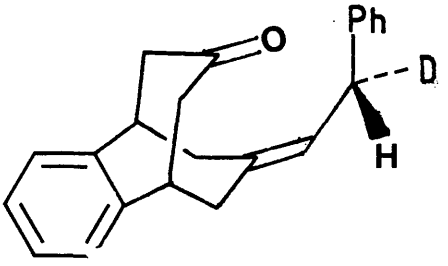


(99″)

(c) the use of labelled, resolved enone [e.g. (147) or (148)] in an S_E' reaction and analysis of the product for loss or retention of deuterium.



(147)



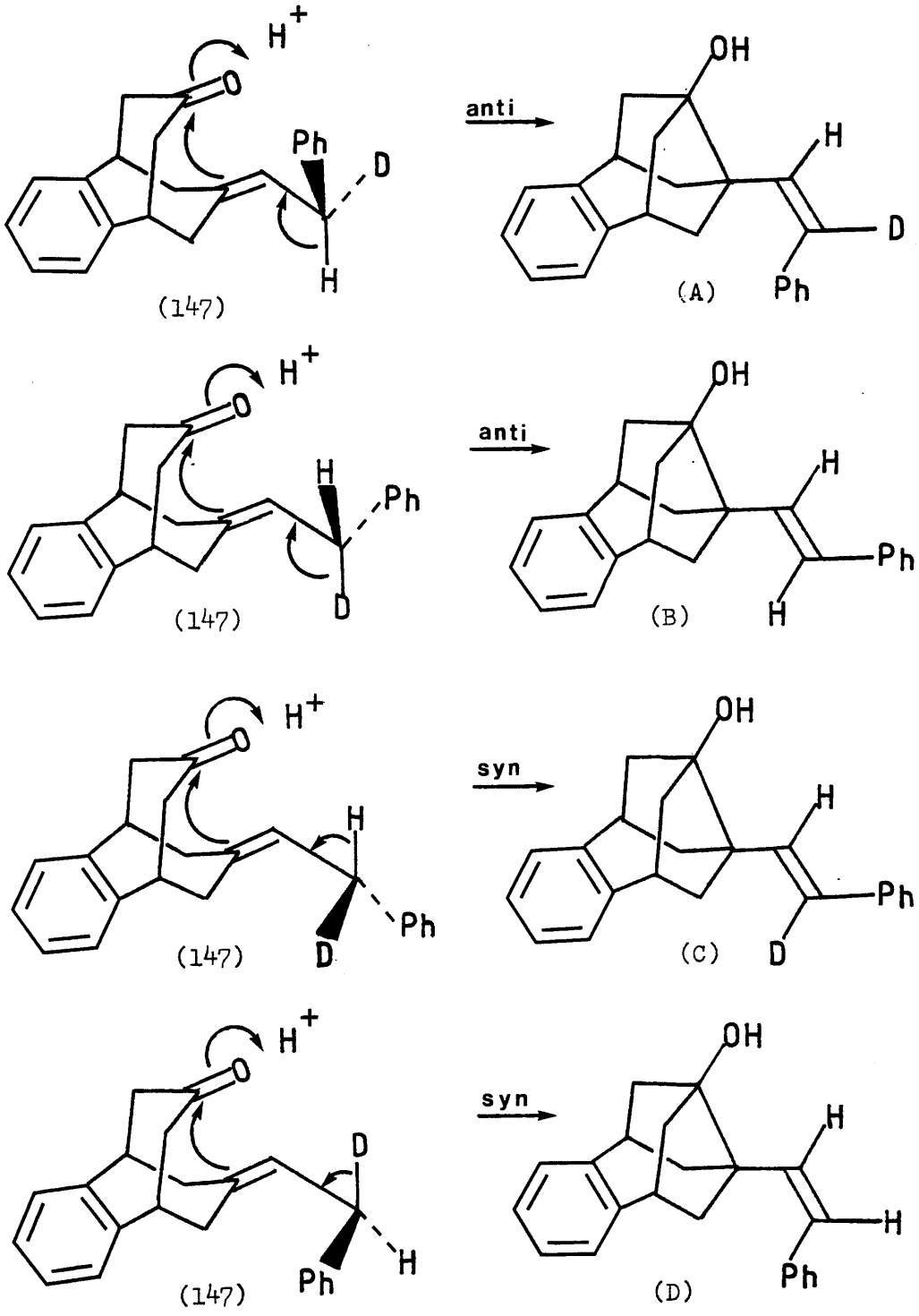
(148)

Either (147) or (148) is a suitable system for this study and comparison of the results from both provides a checking mechanism, rendering complementary labelling experiments unnecessary. Scheme 63 illustrates the theoretically possible products, and their formation, from an S_E' cyclisation of (147). The E-olefinic products (A) and (D) can be ruled out since only the Z-styryl product is formed in this reaction. The two possible products, then, are the undeuteriated Z-olefin (B) formed by an anti process and the deuteriated Z-olefin (C) formed by a

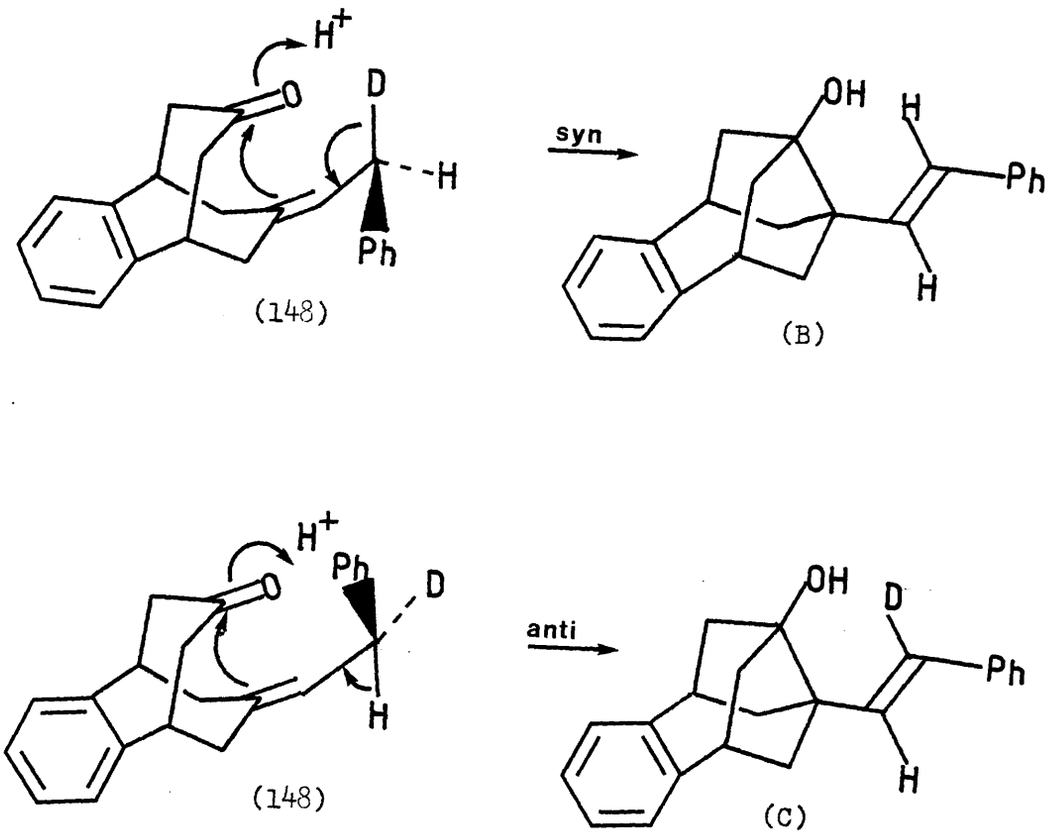
syn process.

The two possible products from (148) are the undeuteriated *Z*-olefin (B) formed this time by a *syn* process and the deuteriated *Z*-olefin (C) formed this time by an *anti* process (Scheme 64).

Analysis for the deuterium content, therefore, should provide a quantitative measure of stereochemical preference in these cyclisations. For example, in the S_E' reaction of (147) 80% retention of deuterium would indicate that the reaction had proceeded in an 80% *syn* mode. The results from (148) should substantiate this, that is, there should be 20% retention of deuterium. This analysis neglects the intervention of a deuterium isotope effect.


H+
O
Ph
D
H
(147)
anti
OH
H
D
Ph
(A)
H+
O
H
Ph
D
(147)
anti
OH
H
Ph
H
(B)
H+
O
H
Ph
D
(147)
syn
OH
H
Ph
D
(C)
H+
O
D
H
Ph
(147)
syn
OH
H
H
Ph
(D)

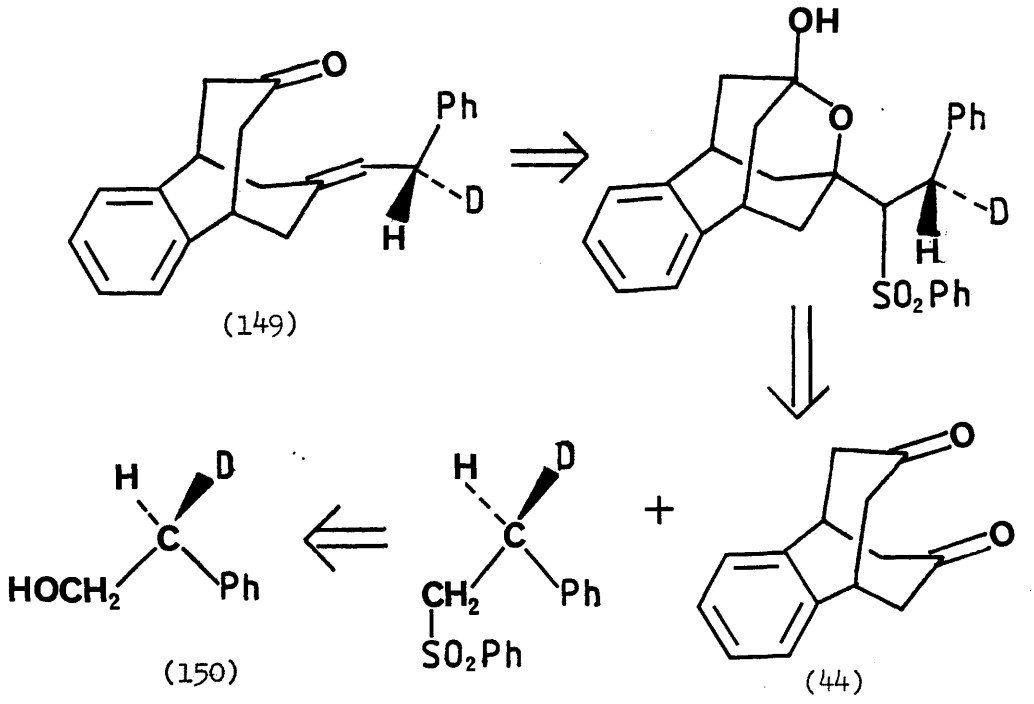
Scheme 63



Scheme 64

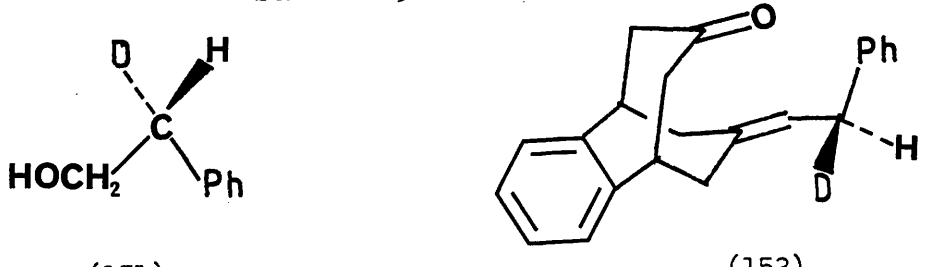
(ii) Incorporation of the Deuterium Label

The strategy for the stereospecific incorporation of a deuterium label into the side chain of the model system [e.g. to give (149)] starting from the known (S)-2-phenylethanol-2-d (150)[50] is outlined in Scheme 65. Similarly, starting with the known (R)-2-phenylethanol[51-55] -2-d (151), the alternative labelled system (152) should be obtainable.



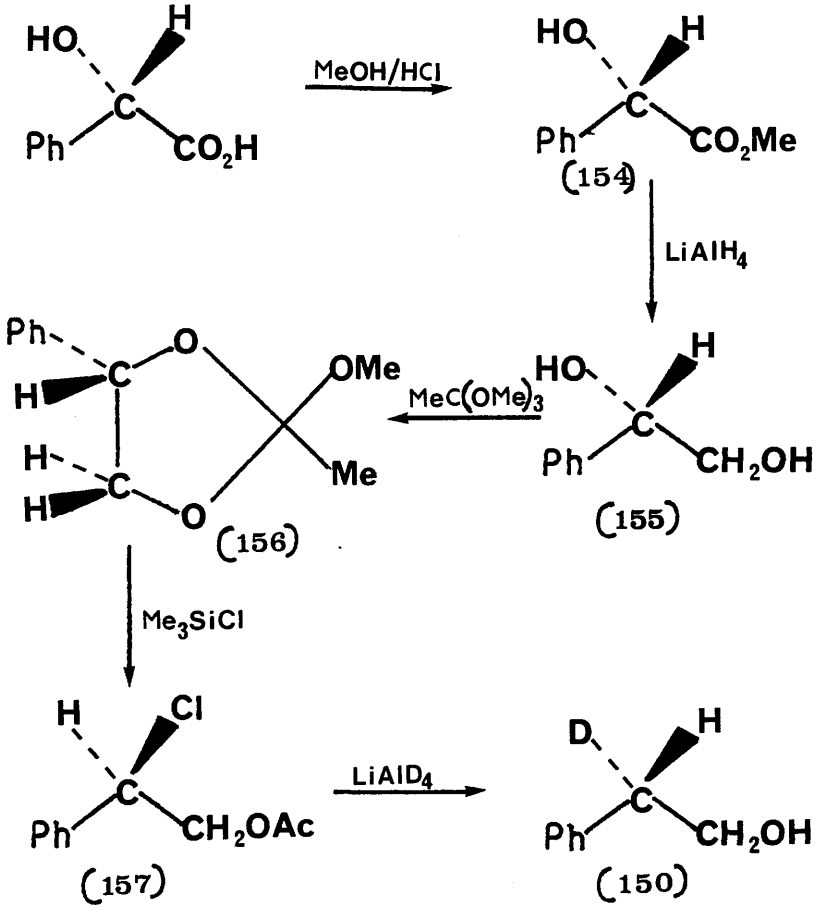
(149) (150) (161) (44)

Scheme 65



(151) (152)

Mosher has converted (R)-mandelic acid by stereospecific reactions into enantiomerically pure (R)-2-phenylethanol-2-d (151).[55] Following Mosher's procedure very closely, (S)-mandelic acid was converted to (S)-2-phenylethanol-2-d (150) by the route outlined in Scheme 66.

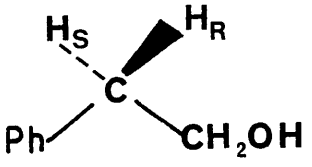


Scheme 66

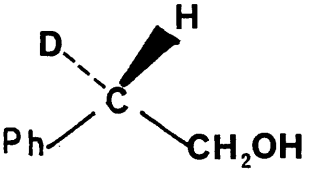
(S)-(+)-methyl mandelate (154), from (S)-(+)-mandelic acid, was reduced with lithium aluminium hydride to (S)-phenylethylene glycol (155). Reaction of (155) with trimethylorthoacetate by the method of Newman[74,75] afforded a mixture of (2R, 4S) and (2S, 4S) dioxolanes (156). Subsequent treatment of (156) with trimethylsilylchloride[74] afforded (R)-2-chloro-2-phenyl-

ethyl acetate (157). Newman[74,75] has shown that this reaction proceeds by a stereospecific S_N2 process. Direct reduction of (157) with lithium aluminium hydride afforded 2-phenylethanol. Mass spectral studies indicated a very high (>95%) deuterium incorporation. From the unambiguous nature of this mode of synthesis this phenylethanol must be the (S)-2-phenylethanol-2d (150).

Mosher has determined the enantiomeric purity of his (R)-2-phenylethanol-2d (151) by ^{1}H.nmr spectroscopy utilising Whitesides' chiral shift reagent Eu(dcm)$_3$.[76,77] This reagent was not commercially available and required synthesis.[77] The commercially available chiral shift reagent Eu(hfc)$_3$[78] was found, in our hands, to be ineffective for distinguishing between the enantiotopic protons H_R and H_S of phenylethanol (158). Since the labelled phenylethanol (150) had still to undergo several synthetic steps (Scheme 64) it seemed prudent to defer determination of enantiomeric purity to a later stage.

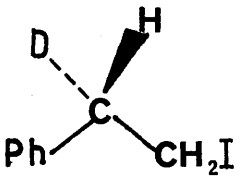


(158)

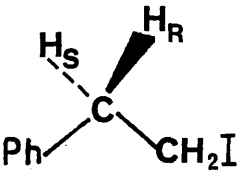


(150)

(S)-2-phenylethanol-2d (150) was converted to (S)-2-phenethyl iodide (159) under mild conditions using trimethylsilyliodide in carbon tetrachloride at 50°C.[79] ^{1}H.nmr studies of unlabelled phenethyl iodide (160) with chiral shift reagent did not permit a distinction between H_R and H_S.

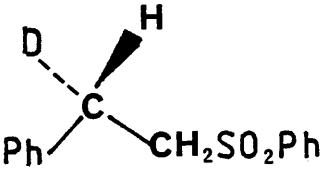


(159)

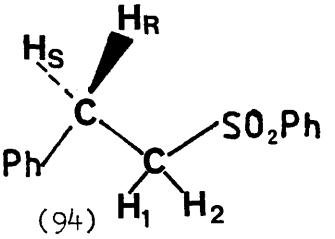


(160)

Treatment of (159) with the sodium salt of benzene sulphinic acid afforded the required labelled sulphone (161). ^{1}H.nmr studies at 360 MHz with Eu(hfc)$_3$ (2 equivalents) now allowed a distinction between the enantiotopic protons H_R and H_S of the unlabelled sulphone (94). Irradiating at a resonance frequency close to that of protons H_1 and H_2 of (94) caused the multiplet for H_R and H_S, in this shifted spectrum, to collapse to an AB quartet. The labelled sulphone under similar conditions displayed only a broad singlet indicating high enantiomeric purity of this labelled sulphone (161).

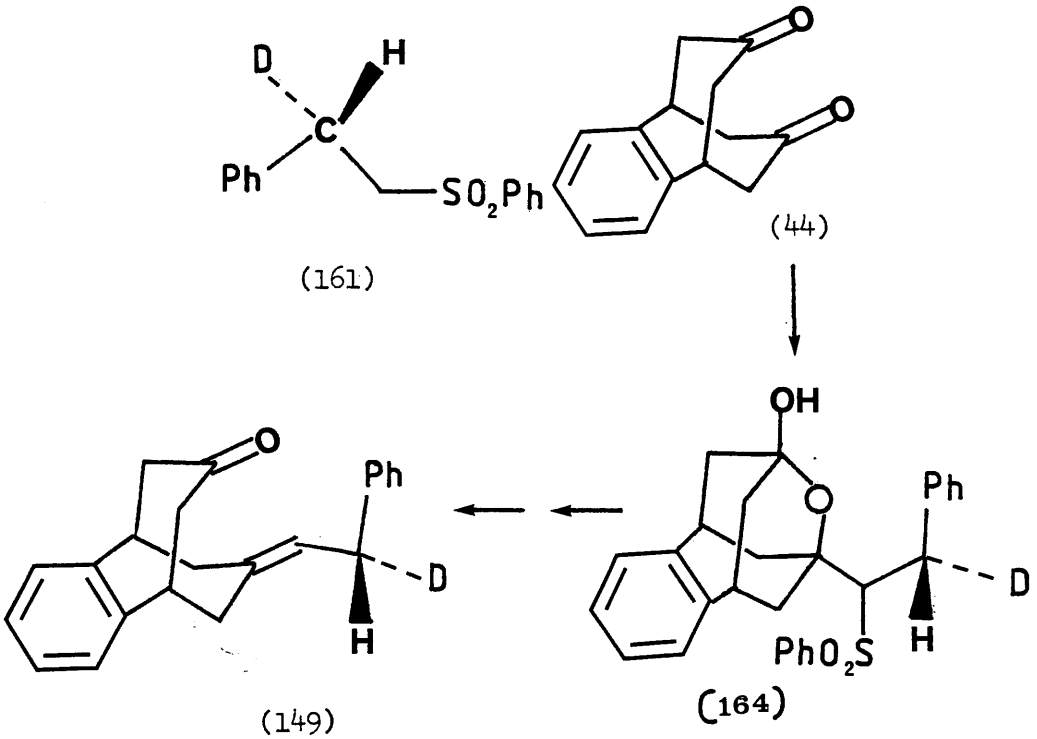


(161)



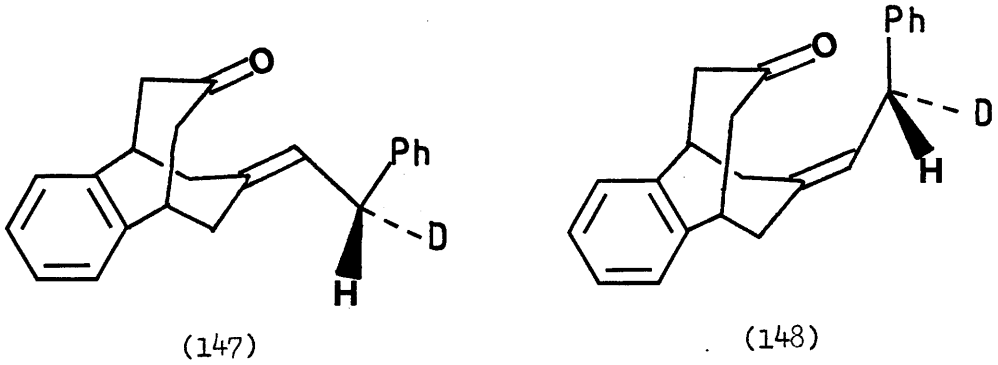
(94)

Using this labelled sulphone (161) the labelled enone (149) was prepared in an analogous manner to that for the preparation of the unlabelled enone (99) (Scheme 67). Mass spectral studies of this labelled enone (149) indicated a very high incorporation of deuterium (>95%). ^{1}H.nmr studies in the presence of a chiral shift reagent to determine enantiomeric purity at the labelled carbon requires prior resolution of (149) into (147) and (148).



(161) (44) (164) (149)

Scheme 67



(147) (148)

(iii) Resolution of the Enone (99)

Unlike many other chemical methods the carrying out of resolutions is still very much an art, in which trial and error is the principal experimental approach. The classical method of resolution involves fractional recrystallisation of diastereomeric salts and considerable success has been recorded by this approach.[80] However, this conventional method is often laborious, can involve high losses, is essentially restricted to carboxylic acids and amines, and often only provides one enantiomer. Consequently attempts have been made to develop other methods of resolution.

A potentially powerful technique for resolution by chromatography is under active development. Two general techniques for resolution are available via chromatography. The first involves chromatographic separation of a diastereomeric mixture and the other involves reversible adsorption of enantiomers on a chiral support. A chromatographic method of resolution is particularly expedient since it can potentially provide both enantiomers in high optical purity.

Implicit in any resolution is the determination of optical, or enantiomeric, purity. In classical methods a resolution is often deemed to be complete when the melting point and rotation of a diastereomeric salt is unchanged by further crystallisation. However, this criterion is not absolutely reliable. A better gauge of optical purity is obtained when the optical rotation of both enantiomers is equal but opposite. This method is often inconvenient since both enantiomers are required pure. The most powerful tool for the determination of optical purity has come

from N.M.R. spectroscopy. For example, the N.M.R. spectrum of a diastereomeric mixture consists in principle of two overlapping spectra. As resolution proceeds, the intensity of peaks due to one diastereomer will diminish and the ratio of integrated intensities provides a measure of optical purity. Resolution is complete when one set of signals has completely disappeared. In practice, this chemical shift non-equivalence is normally only detectable for nuclei or groups of nuclei which are close to one or both chiral centres.

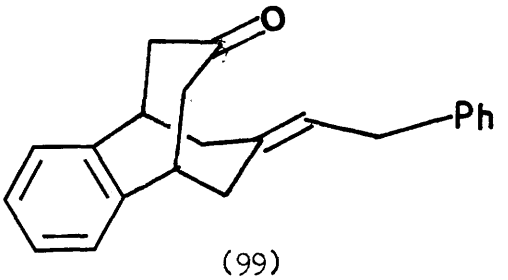
No standard procedures exist for the resolution of compounds whose only handle for resolution is a ketone function. Several approaches to the problem have been suggested[81,82,83] involving the use of optically active reagents such as hydrazines, semicarbazides, diols, dithiols, semioxamazides, acid hydrazides, carbamates, amine bisulphites, amino-alcohols, and second-order methods such as reduction to the alcohol followed by resolution and reoxidation. These methods at times require tedious preparation of optically active reagents and some require stringent conditions for the regeneration of the carbonyl component.

In particular, resolution of the enone (99) was expected to be difficult for two additional reasons:

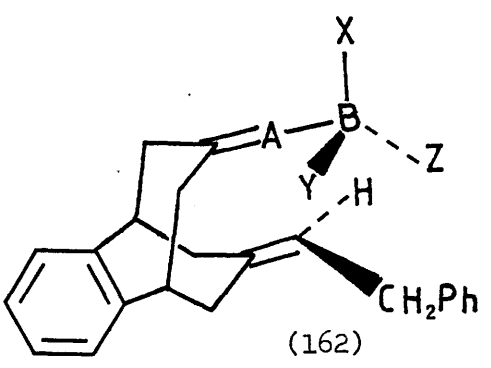
(a) The propensity for (99) to cyclise imposes problems since under conditions for diastereomer formation or for ketone regeneration a cyclisation reaction is conceivable;

(b) Any resolution method must exploit the steric difference at the double bond of the enone (99) (i.e. between the vinylic proton and the benzyl group). This requires that the chiral centre introduced by diastereomer

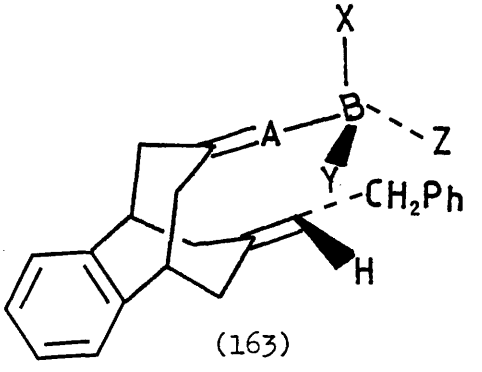
formation be close to the double bond. It is, however, difficult to predict the preferred conformations of potential diastereomers. If the conformation of the hypothetical diastereomers (162) and (163) are as shown in Figure 7, for example, then one would envisage that resolution was not out of the question, whereas if they were as shown in Figure 8 then a successful resolution would seem unlikely.



(99)

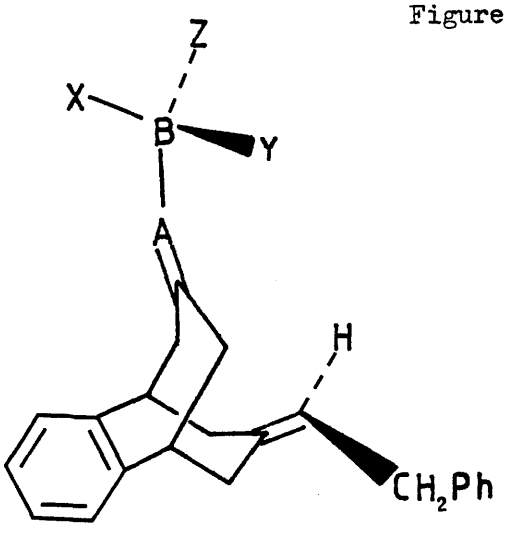


(162)

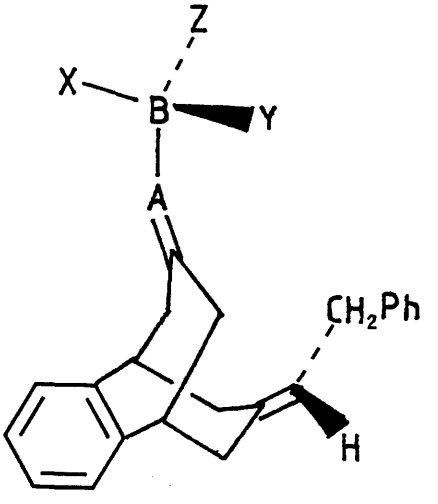


(163)

Figure 7



(162)



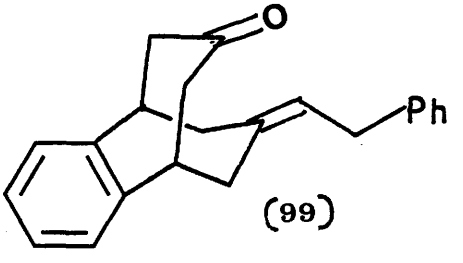
(163)

Figure 8

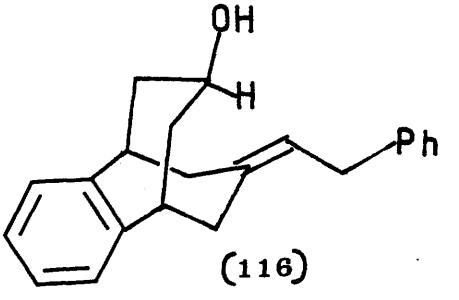
(a) Attempted Resolution of the Enone (99) by Classical Methods

One approach to the resolution of ketones involves reduction of the carbonyl group to a hydroxyl group, resolution of the resulting alcohol, and re-oxidation to the optically active enantiomers. The resolution of the alcohol normally involves conversion to the hydrogen phthalate ester followed by salt formation with an optically active base and then resolution by fractional recrystallisation.

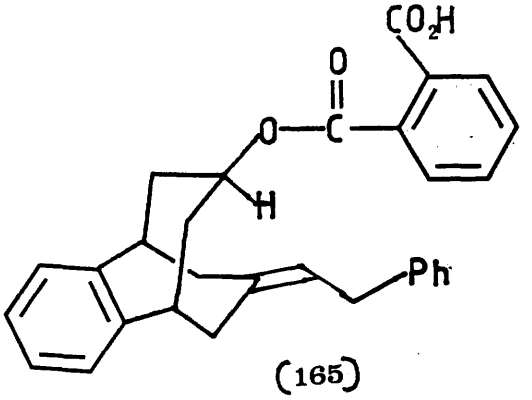
Thus the enone (99) was converted to the exo-ol (116) as previously described and this was, in turn, converted to the hydrogen phthalate ester (165), m.p. 160-163°C. The ^{1}H.nmr spectrum of (165) showed a signal between δ 7.65 and 7.40 (m, 4H, $-O_2C-C_6H_4-CO_2H$), a signal between δ 6.50 and 6.15 (m, 1H, $-CH-O_2-Ar$, $-O_2C-C_6H_4-CO_2H$) at δ 5.49 (t, J=6 Hz, 1H, $>C=CH-CH_2Ph$).



(99)



(116)



(165)

Diastereomer salt formation utilising optically active bases such as dehydroabietylamine, d and l-ephedrine, d-α-phenylethylamine, cinchonidine, and cinchonine were carried out by the addition of a solution of the acid in a minimum of solvent to a solution of the base in a minimum of solvent. In some cases crystallisation of the salt proved troublesome and in all cases where crystallisation was achieved the melting point range on successive recrystallisations failed to show any significant improvement.

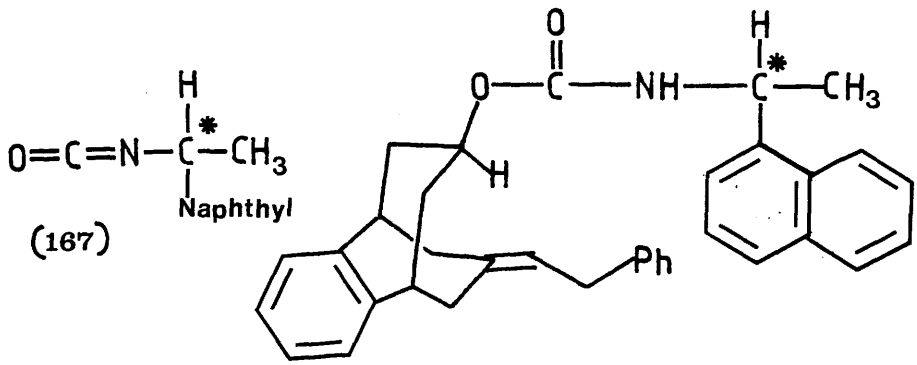
It is possible that a resolution might be achieved by this approach but with time now at a premium and with a surfeit of optically active bases, methods of recrystallisation, and solvents for recrystallisation available, this approach was abandoned and attention was concentrated on chromatographic methods of separation.

(b) Attempted Resolution of the Enone (99) by Chromatographic Separation of Diastereomeric Derivatives

Some measure of success has been recorded in the resolution of diastereomers by chromatography. Racemic alcohols have been converted with optically active isocyanates into diastereomeric carbamates[84,85] and racemic amines with optically active lactones into diastereomeric amides[86] and then separated on alumina or silica gel.

Following Pirkle's method[85,87] the carbamate diastereomers (166), m.p. 173-177°C, were prepared from the exo-ol (116) and (R)-(-)-1-(1-naphthyl) ethyl isocyanate (167). No chemical shift differences between these diastereomers could be detected in the ^{1}H.nmr spectrum or the ^{13}C.nmr spectrum. The ^{1}H.nmr spectrum showed a multiplet between δ 6.10 and 5.73

(1H, >C<u>H</u>-O-C(O)-), a multiplet between δ 5.70 and δ 5.30 (2H, >C=C<u>H</u>-CH_2-Ph and —NH-C<u>H</u>-(CH_3)-naphthyl), a signal at δ 4.82 exchangeable in D_2O (<u>d</u>, J=8 Hz, 1H, $-O_2C$-N<u>H</u>-CH-) and a signal at δ 1.53 (<u>d</u>, J=7 Hz, 3H, -NH-CH(CH_3)-naphthyl). These assignments were further confirmed by double irradiation experiments.

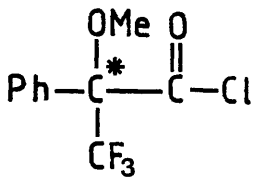


(166)

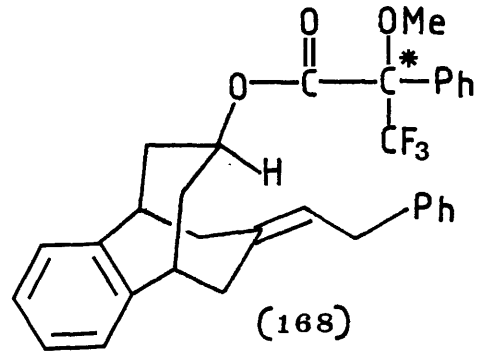
No separation of these diastereomers could be observed by analytical t.l.c. on alumina or silica gel with various solvent systems. Under conditions for analytical gas chromatography it appeared that decomposition of the carbamates (166) was occurring.

The next diastereomeric mixture to be investigated was that of the esters (168). Treatment of the <u>exo</u>-ol (116) with (-)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (169) in tetrahydrofuran with 4-dimethylaminopyridine gave the esters (168), m.p. 107-110°C. This reagent, (169), introduced by Mosher,[88] is particularly useful since large chemical shift differences between the trifluoromethyl signals in the ^{19}F.nmr spectra have been noted.[89] The ^{1}H.nmr spectrum of (168) looked encouragingly like two overlapping spectra with many of the signals very diffuse including a signal between δ 6.70 and δ 6.15 (<u>m</u>,

1H, -CH-OC(O)-) a broad signal at δ 5.55 (m, 1H, >C=CH-CH_2-Ph) and a broad singlet at δ 3.50 (s, 3H, -OMe). The proton-decoupled ^{19}F.nmr spectrum showed two distinct fluorine singlets at δ 72.07 and δ 72.13 corresponding to the trifluoromethyl group of each diastereomer thus providing a superb method for monitoring the progress of a resolution.



(169)



(168)

No separation of the diastereomers could be detected by analytical t.l.c. on silica gel but on alumina some separation, though incomplete, was evident. Attempts at separation by analytical h.p.l.c. on alumina were unsuccessful, (168) having a very short retention time even with hexane as eluting solvent. A measure of success was achieved, however, in the attempted preparative scale separation by vacuum liquid chromatography (v.l.c.)[66] on alumina. The ^{19}F.nmr spectra of the extreme head and tail fractions from this v.l.c. column showed significant enrichment in one or other diastereomer (see Figure 9). By continually rechromatographing middle fractions and collecting extreme head and tail fractions an appreciable amount (ca. 100 mg of each) of reasonably enriched material was procured. The combined head fractions and combined tail fractions were each chromatographed and extreme fractions showed considerable enrichment (see Figure 10). This method, however, was tedious, provided only small amounts (a few milligrams) of considerably enriched material, and

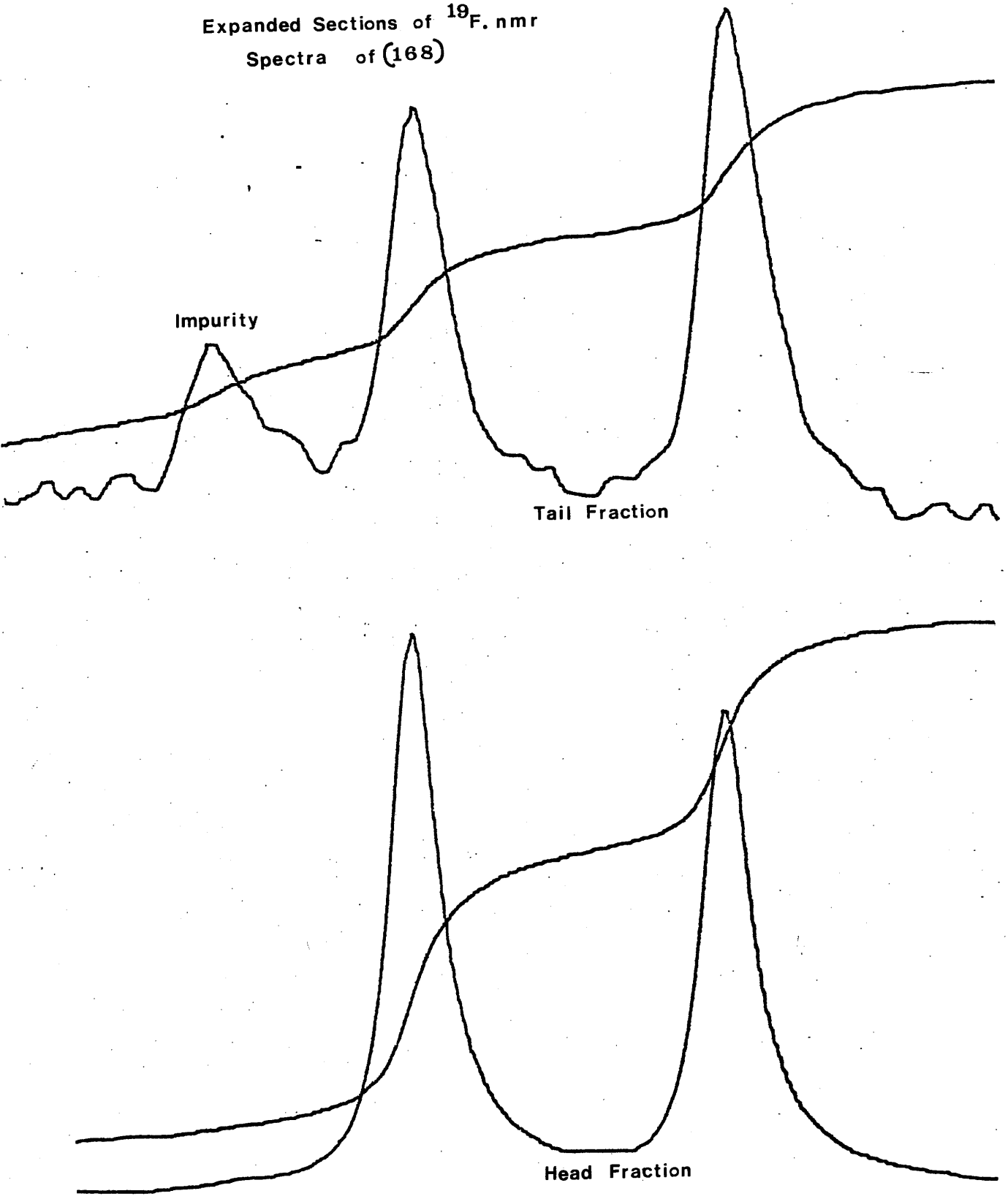

Expanded Sections of ^{19}F. nmr
Spectra of (168)
Impurity
Tail Fraction
Head Fraction

Figure 9

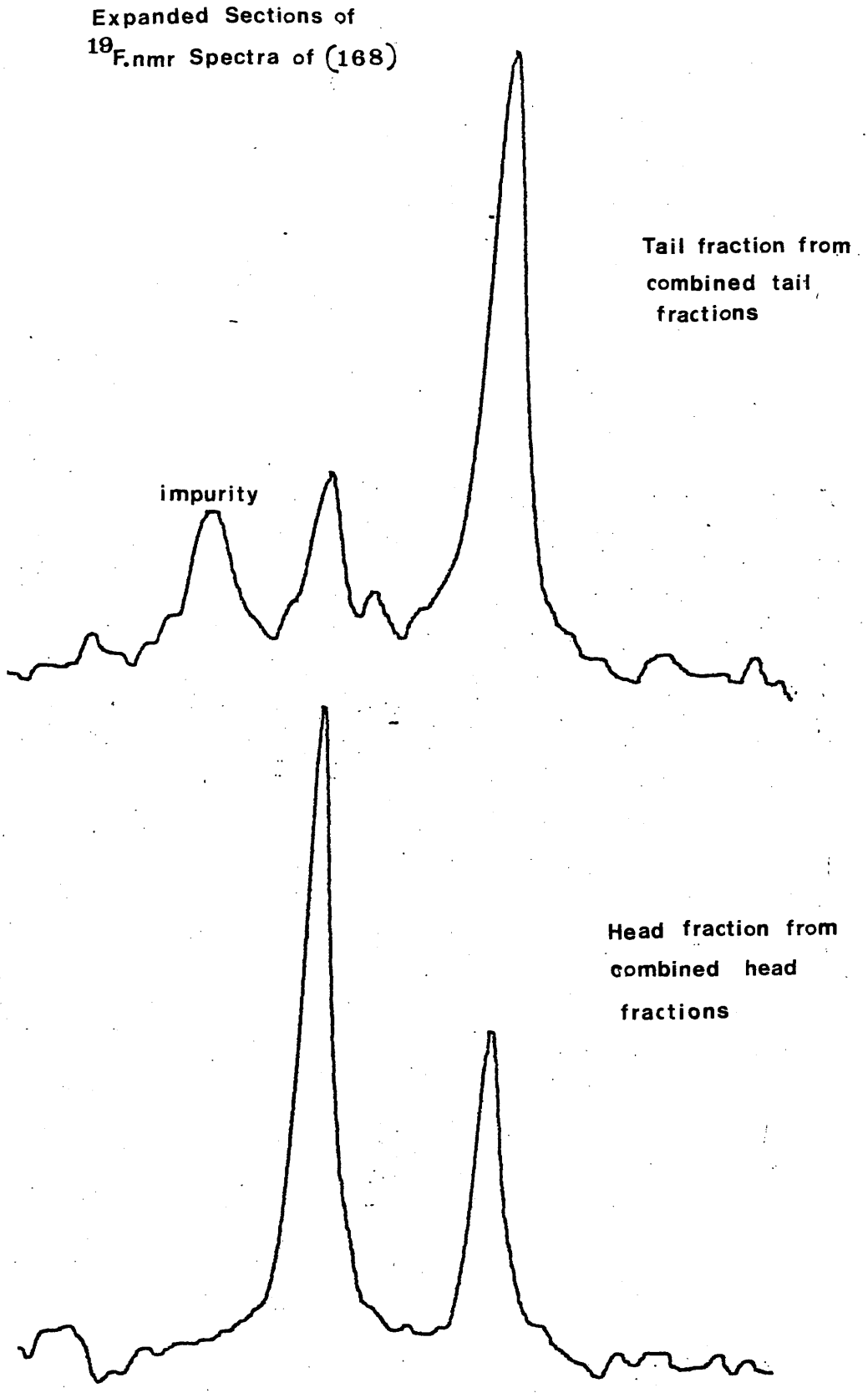

Expanded Sections of
^{19}F.nmr Spectra of (168)
Tail fraction from combined tail fractions
impurity
Head fraction from combined head fractions

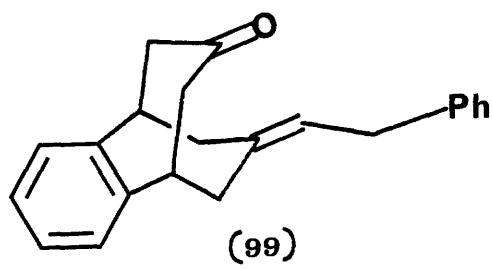
Figure 10

on no occasion was optical purity achieved. Attempted separation using a Chromatotron (a centrifugal t.l.c. device) did not lead to any improvement in the separation of these esters.

(c) Resolution of the Enone (99) by Chromatographic Separation on an Optically Active Support

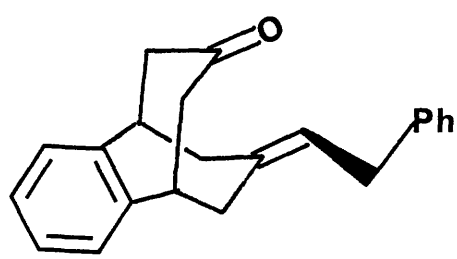
The direct chromatographic resolution of racemates on optically active adsorbents is one of the most potentially useful methods of resolution.[90-93] In this method diastereomeric complexes are formed by reversible adsorption, and their different stabilities result in different rates of elution of the two enantiomers thereby allowing separation. The methods available and their usefulness are discussed in a recent review by Blaschke.[90]

An attempt was made at a preparative scale separation of the enone (99) using the optically active adsorbent, cellulose triacetate. This cellulose triacetate was prepared by the method described by Hesse and Hagel.[94] The initial and final fraction from this chromatographic attempt using 95% ethanol as eluant had no enantiomeric enrichment detectable by circular dichroism (CD).

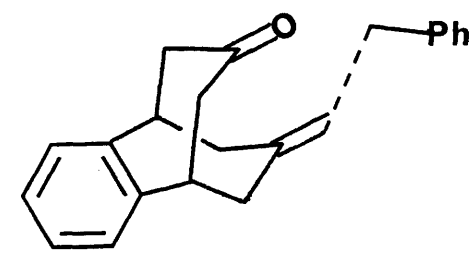


(99)

Professor M. Schneider (Hohenheim), who has had some success[95,96] with this method of resolution, succeeded (with Dr. Bippi) in resolving the enone (99)[97] on an analytical scale by h.p.l.c. using commercially available crosslinked cellulose triacetate. The product eluted from the h.p.l.c. column was detected by U.V. and C.D. Figure 11 shows the U.V. signals for multiple injections; each signal corresponds to both enantiomers and no separation of the enantiomers is evident. Figure 12, however, shows, the corresponding C.D. signals and clearly there is separation, though unresolved. Schneider, by collecting the extreme head and tail fractions, with repeated recycling of the rest of the material, managed to accumulate very small amounts of optically pure samples of (99′) and (99″); their C.D. spectra are shown in Figure 13.



(99′)



(99″)

This method was tedious, however, and only very small quantities of (99′) and (99″) could be obtained. Nevertheless it demonstrates the viability of this method and encourages further development in this approach.

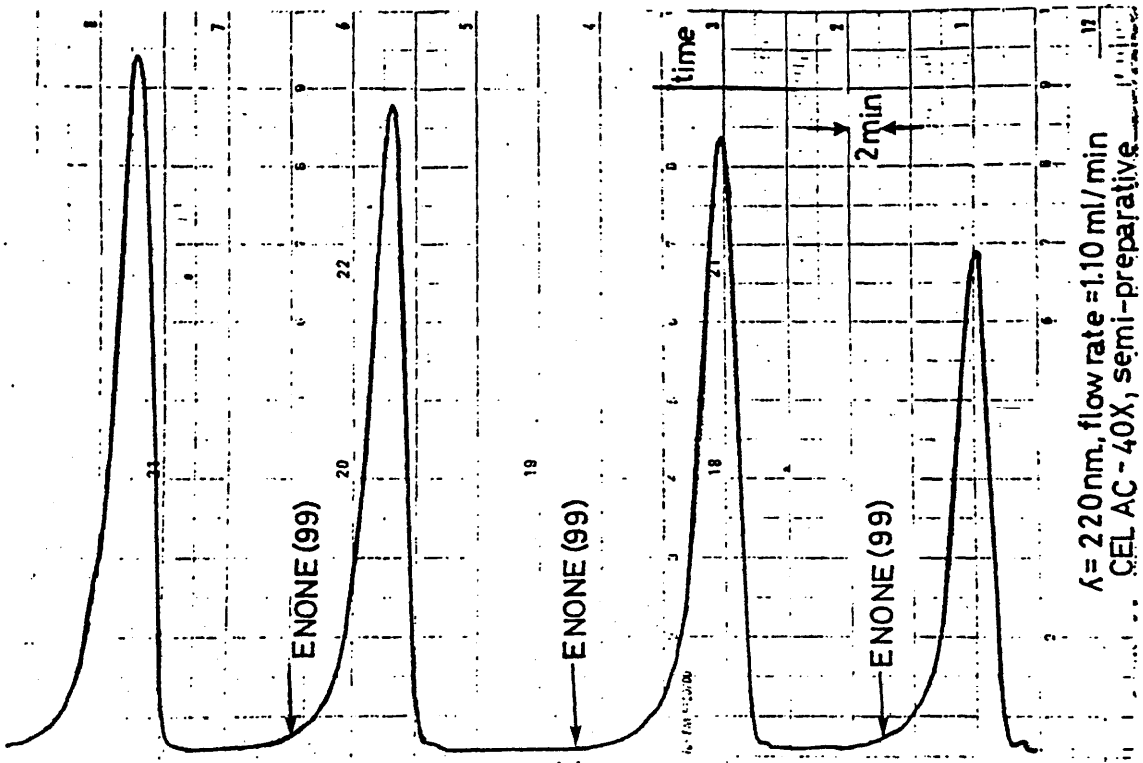


Figure 11

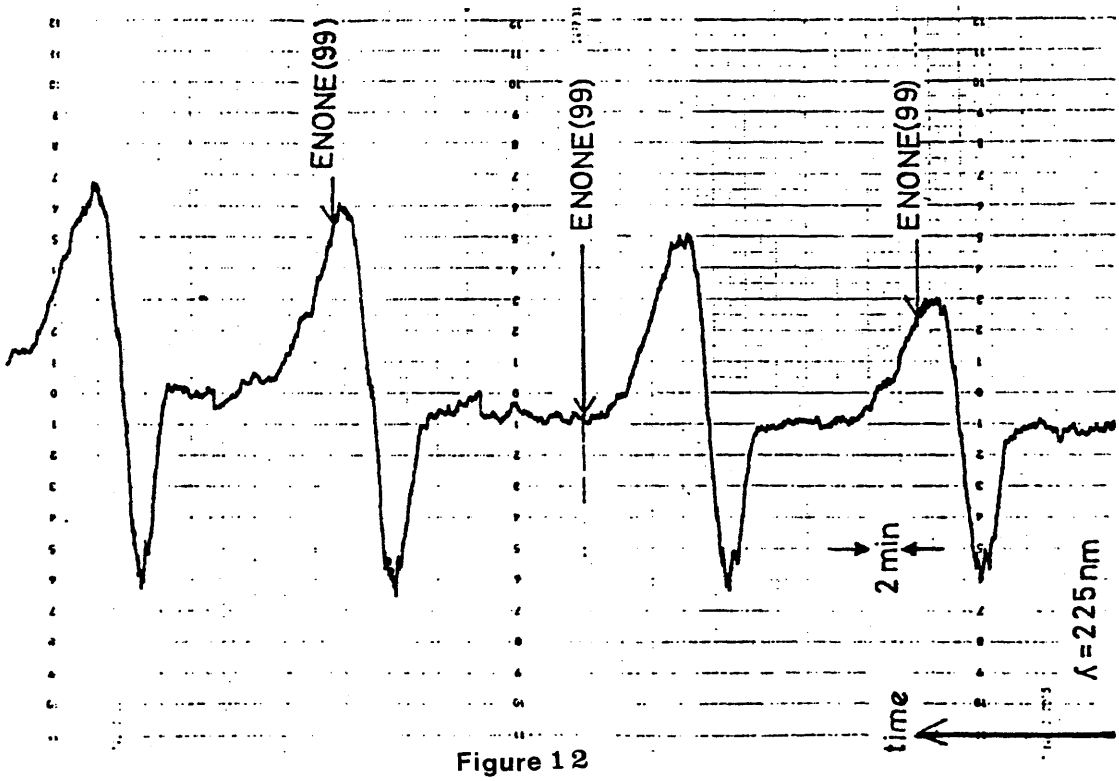
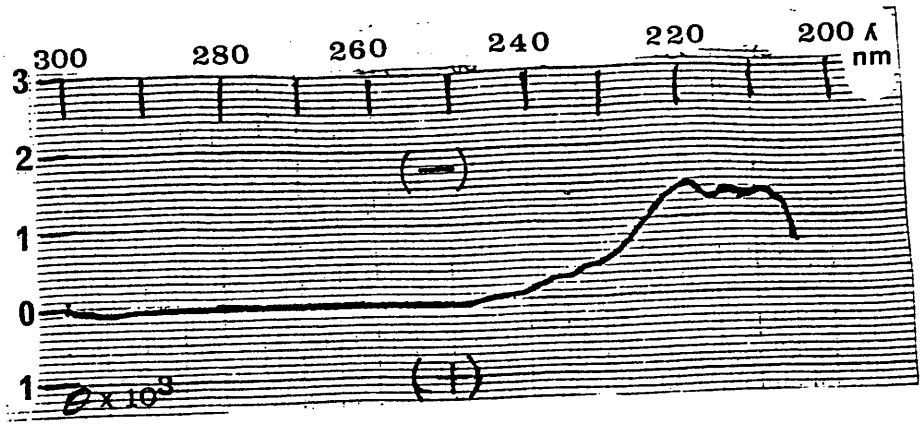
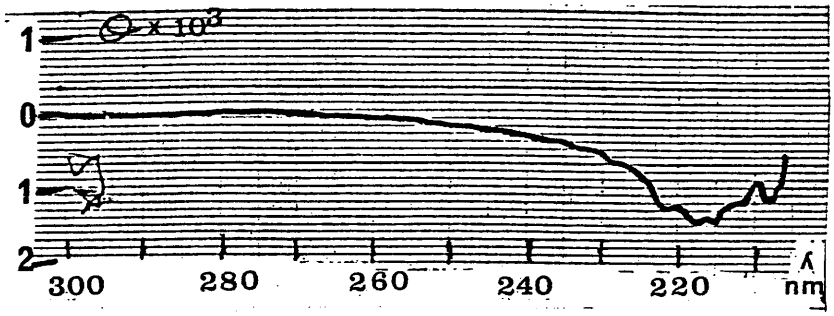


Figure 12

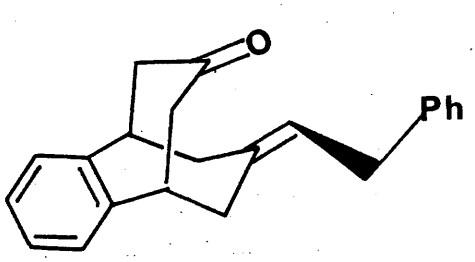


(−)-enantiomer

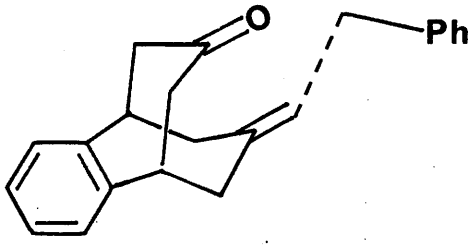


(+)-enantiomer

Figure 13

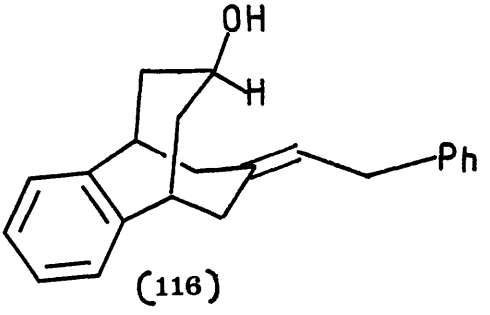


(99′)

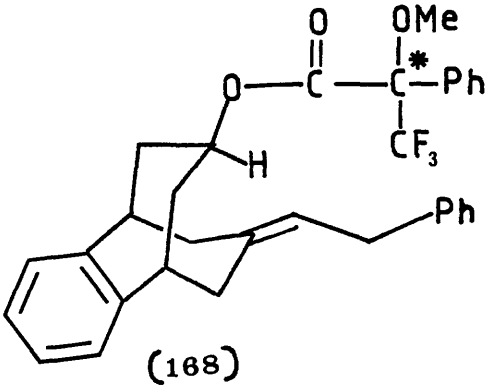


(99″)

One problem encountered by Schneider in this separation attempt was the insolubility of the enone (99) in ethanol (the solvent of choice in this form of chromatography). An attempt to circumvent this problem by using the more soluble exo-ol (116) under essentially the same conditions as used by Schneider and on commercially prepared cellulose triacetate, as prepared by Macherey-Nagel, in our hands, met with problems. A major difficulty in this attempt was that the separation of the alcohol (116) could not be monitored by C.D. The small amounts of head and tail fractions (ca. 3 mg in both cases) required conversion to the esters (168) and the recording of the ^{19}F.nmr spectrum. Unfortunately signals arising from impurities overlapped the signals of interest and the effectiveness of the separation could therefore not be reliably determined.



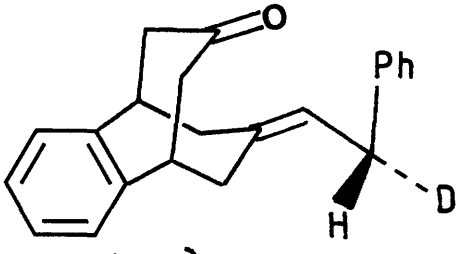
(116)



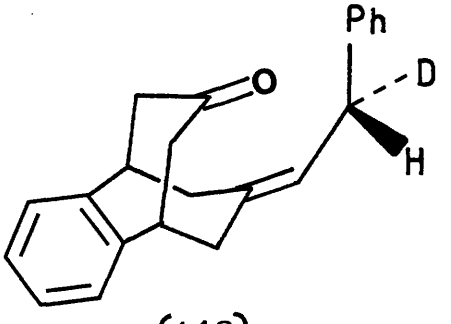
(168)

In summary, then, some success although limited, has been achieved in the chromatographic separation of the enone (99) (or its derivatives) but further investigations into these and related methods are required to allow a preparative scale resolution of enone (99) to be achieved.

The remaining objective will then be to use the labelled, resolved enones (147) and (148) (absolute configurations known) in a stereochemical study of the S_E' reaction (see page 77).



(147)



(148)

EXPERIMENTAL

General Experimental Procedure

All melting points (m.p.) were determined on a Kofler hot-stage apparatus, and are uncorrected. Routine infra-red spectra were recorded on a Perkin-Elmer 580 or a Perkin-Elmer 257 spectrophotometer. Ultra-violet spectra were recorded on a Pye-Unicam SP 800 spectrophotometer. ^{1}H.nmr spectra were recorded in deuteriochloroform (unless otherwise stated), using tetramethylsilane (TMS) as internal standard, on a Varian T.60 (60 MHz) or a Perkin-Elmer R.32 (90 MHz); ^{13}C.nmr and ^{19}F.nmr were recorded on a Varian XL100. Mass spectra were routinely recorded using a V.G./Kratos M.S.12 spectrometer; high resolution spectra were recorded on a V.G./Kratos M.S.902S spectrometer.

In all cases where product was isolated "by solvent extraction", the procedure followed was to extract the aqueous layer with several portions of the indicated solvent; then the organic layers were combined and washed with water, followed by saturated brine. The organic layer was dried over anhydrous sodium sulphate, then filtered, and the solvent evaporated from the filtrate under reduced pressure (water aspirator) using a Buchi rotary evaporator. The use of the terms "base wash" and "acid wash" indicate washing the combined organic layers with saturated aqueous sodium bicarbonate, or with dilute (6N) hydrochloric acid, respectively, prior to the aforementioned washing with water.

Preparative t.l.c. was run using the indicated percentages of ethyl acetate in light petroleum (60-80°) as developing solvent (d.s.); Merck Kieselgel G.F.$_{254}$ was used for analytical and preparative t.l.c.

plates. Column chromatography was run using increasing percentages of ethyl acetate in light petroleum (60-80°) as eluting solvent, and either I.C.N. silica gel Woelm, or aluminium oxide Woelm as adsorbent. V.l.c. refers to vacuum liquid chromatography[66] and was run using increasing percentages of ethyl acetate in light petroleum (60-80°); and Merck aluminium oxide PF_{254} or Kieselgel HF_{254} as adsorbent. H.p.l.c. was carried out on a Water Associates Liquid Chromatograph - 201 with H.p.l.c. - Sorb Cel AC-40X (cellulose triacetate, 8 μm Macherey-Nagel, Duren) and Merck Lichrosorb Aloxt (alumina, 5 μm). G.C. was carried out on a Perkin Elmer F33 or F11 Gas Chromatograph with OV-17 or 1% OV-1 column packing. Chromatography using a Chromatotron (supplied by Gelman Sciences Inc.) was carried out using Merck aluminium oxide GF_{254}.

All solvents were purified and dried using standard procedures.

Standard abbreviations are used when quoting spectral data; only significant spectral characteristics are quoted.

Benz-bicyclo [3.3.2.] decan-3,7-dione (44)

The procedure followed was similar to that of Fohlisch.[44] To a solution of ortho-phthalicdicarboxaldehyde (46) (8.0 g, 0.06 mol) and diethyl-1,3-acetonedicarboxylate (47) (24.24 g, 0.12 mol) in ethanol (120 ml), was added diethylamine (1 ml). The mixture was swirled, became slightly hot and was allowed to stand at 20°C for 6 h and then 0°C for 12 h. The separated crystals were filtered off and washed with ice-cold ethanol. Recrystallisation from ethanol gave colourless crystals of the tetraester (48) (19.6 g, 65%) having m.p. 138-141°C (lit.[44] 139-141°C). Concentration of mother liquors gave further crops of crystals, (4.8 g, 16%).

A solution of the tetraester (48) (20 g) in glacial acetic acid (110 ml) and concentrated hydrochloric acid (35.5 ml), was heated under reflux for 12 h. The solvents were then removed in vacuo and the residue triturated with ether. The crude dione was purified by fractional sublimation; the material which sublimed at 60-110°C/0.5 mmHg was pure dione (44) [6.5 g, 76% based on the tetraester (48)] having m.p. 196-198°C (lit.[44] 196-199°C).

I.R. ν_{max} ($CHCl_3$): 1705 cm^{-1}.

^{1}H.NMR δ($CDCl_3$): 7.18 (s, 4H), 3.22 (m, 2H), 2.85 (d, J=4Hz, 8H).

Hemiketal (59)

The procedure followed was similar to that of Fohlisch.[44] The dione (44) (1 g, 4.7 mmol) was dissolved in a mixture of water (25 ml) and ethanol (25 ml) containing potassium hydroxide (0.25 g), and sodium borohydride (0.1 g) added. The mixture was stirred at 70°C for 15 h.

Concentration in vacuo, filtration of the separated crystalline solid, and washing with ice-cold water afforded the hemiketal (59), (0.9 g, 89%) having m.p. 199-201°C (lit.[44] 200-202°C).

I.R. ν_{max} (KBr): 3300 br, 1010 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.18 (s, 4H), 4.50 (m, 1H), 3.22 (m, 2H), 3.03 (m, 2H), 2.81 (s, 1H, -OH), 2.5-1.5 (m, 8H).

Attempted Dehydration of the Hemiketal (59)

To the hemiketal (59) (100 mg, 0.5 mmol) in pyridine (5 ml) was added phosphoryl chloride (1 ml). The mixture was heated at 70°C for 30 mins and concentrated in vacuo. The product was extracted into ether and the combined ether extracts were washed with dilute hydrochloric acid (2x10 ml), water (2x10 ml), and brine (1x10 ml), dried, and the solvent evaporated to give a colourless solid product. This was recrystallised from ethyl acetate/light petroleum (60-80°) to give colourless prisms of the dichlorophosphate ester (61) (64 mg, 41%), m.p. 120-121°C.

I.R. ν_{max}(KBr): 1300, 1290, 1055, 1020, 980, 960, 950 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.1 (s, 4H), 4.7 (m, 1H), 3.25 (m, 2H), 2.7-1.45 (m, 8H).

^{13}C.NMR δ ($CDCl_3$): 144.44 (s), 128.62 (d), 127.17 (d), 110.11 (d, J_{C-O-P}=11Hz), 75.64 (d), 39.70 (d of t, $J_{C-C-O-P}$= 3.5Hz), 39.41 (d), 31.78 (t).

(Found: C, 50.53; H, 4.37%; M^+=332. $C_{14}H_{15}O_3PCl_2$ requires C, 50.31; H, 4.52%; M^+=332).

Attempted Formation of the Enone (53) from the Dichlorophosphate Ester (61)

The dichlorophosphate ester (61) (70 mg, 0.2 mmol) was dissolved in anhydrous ether (10 ml) and to this solution was added 1,5 diazabicyclo-[5.6.0.] -undecene (DBU) (40 mg) dissolved in anhydrous ether (10 ml). The reaction mixture was heated under reflux for 2 h. The cooled mixture was poured into cold, dilute sulphuric acid. Extraction into chloroform (3x10 ml) and normal work-up gave a solid product (30 mg). T.l.c. and ^{1}H.nmr indicated recovery of the hemiketal (59).

Attempted Formation of the Keto-acetate (62)

The hemiketal (59) (12 mg) and sodium acetate (6 mg) were heated under reflux in acetic anhydride (2 ml) for 5 h. The reaction mixture was cooled and saturated aqueous sodium bicarbonate (3 ml) was added and the mixture stirred for 1 h. The usual work-up, using methylene chloride as solvent, gave, after preparative t.l.c. (d.s. 30%), a solid product (9 mg). T.l.c. indicated conversion to one less polar compound, i.r. indicated ester carbonyl but no ketonic carbonyl bands. This compound was assigned structure (63).

I.R. ν_{max} (KBr): 1730, 1220 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.1 (s, 4H), 4.60 (m, 1H), 3.19 (m, 2H), 2.7-1.5 (m, 11H including s at 2.02).

^{13}C.NMR δ ($CDCl_3$): 168.30 (s), 145.20 (s), 128.49 (d), 126.83 (d), 102.00 (s), 73.52 (d), 39.04 (t), 37.17 (d). 32.53 (t), 22.25 (q).

(Found: M^+=258. $C_{16}H_{18}O_3$ requires M^+=258).

Keto-acetate (62)

The hemiketal (59) (330 mg, 1.65 mmol) and acetic anhydride (2 ml) were dissolved in acetone (30 ml), and conc. sulphuric acid (2 drops) was added. The reaction mixture was left to stand at room temperature for 12 h during which time it darkened. The acetone was evaporated in vacuo to give a dark yellow residue which was dissolved in methylene chloride (20 ml) and stirred with saturated aqueous sodium bicarbonate (10 ml) for 30 mins. Work-up as normal gave a colourless crystalline product, recrystallisation from ethyl acetate/light petroleum (60-80°) gave colourless plates of the keto-acetate (62) (280 mg, 70%) having m.p. 185-190°C.

I.R. ν_{max} (KBr): 1730, 1690, 1250, 1220, 1070, 1040 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.16 (s, 4H), 5.20 (m, 1H), 3.22 (m, 2H), 3.10-2.40 (m, 4H), 2.20-2.05 (m, 4H), 2.00 (s, 3H).

^{13}C.NMR δ ($CDCl_3$): 208.80 (s), 170.00 (s), 143.78 (s), 128.48 (d), 127.63 (d), 72.04 (d), 48.60 (t), 39.61 (d), 34.92 (t), 21.51 (q).

(Found: M^+=258.1259. $C_{16}H_{18}O_3$ requires M^+=258.1256).

Attempted Elimination of Acetic Acid from the Keto-acetate (62)

The conditions employed included heating the keto-acetate (62) at reflux in xylene with and without added base (pyridine and triton B), vapour phase pyrolysis at 320°C, 450°C and 520°C, and heating at 220°C for several hours in a sealed tube.

In all cases only starting material was recovered as shown by t.l.c. and ^{1}H.nmr.

Attempted Formation of the Hydroxy-acetate (64)

The keto-acetate (62) (6.1 g, 23 mmol) was dissolved in a mixture of ethanol (150 ml) and water (75 ml) and excess sodium borohydride (2.5 g) was added. The reaction mixture was heated at 60°C for 2 h and then concentrated in vacuo affording the crystalline diol (67). Recrystallised from ethanol, this had m.p. 176-178°C (4.9 g, 95%).

I.R. ν_{max} (KBr): 3300, 1040, 770 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.25-6.95 (m, 4H), 3.66-3.40 (m, 2H), 3.35-3.05 (m, 2H), 2.42-1.90 (m, 8H), 1.20 (s, 2H, exchangeable in D_2O).

(Found: C, 76.96; H, 8.25%; M^+=218. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31; M^+=218).

Hydroxy-acetate (64)

To the keto-acetate (62) (2.2 g, 8.5 mmol) dissolved in ethanol (300 ml) was added phosphate buffer (100 ml) [potassium dihydrogen orthophosphate (6.8 g) and sodium hydroxide (1.16 g) in water (1 litre)] . To the stirred solution was added sodium borohydride (1.1 g) and stirring was continued for 1 h. On concentration in vacuo the product crystallised out and the product was collected by filtration and washed well with cold water. Recrystallisation from ethanol gave the hydroxy-acetate (64) (1.9 g, 85%), m.p. 113-113.5°C.

I.R. ν_{max} (KBr): 3380, 1730, 1260, 1240, 1030, 780 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.25-7.00 (m, 4H), 5.05-4.75 (m, 1H), 3.60-3.35 (m, 1H), 3.35-3.05 (m, 2H), 2.27-2.10 (m, 8H), 2.00 (s, 3H), 1.60 (s, 1H).

^{13}C.NMR δ ($CDCl_3$): 170.24 (s), 141.74 (s), 128.56 (d), 127.18 (d), 73.12 (d), 69.65 (d), 38.44 (t), 37.91 (d), 36.61 (t), 21.60 (q).

(Found: C, 73.76; H, 7.74%; M^+=260.1404. $C_{16}H_{20}O_3$ requires C, 73.82; H, 7.74%; M^+=260.1412).

Ene-acetate (65)

Phosphoryl chloride (3 ml) was added to a stirred solution of hydroxy-acetate (64) (1.7 g, 6.5 mmol) in pyridine (20 ml). After stirring for 1 h at room temperature the solution was concentrated in vacuo. The residue was then dissolved in ethyl acetate (50 ml), washed with dilute hydrochloric acid (2x20ml), water (2x20 ml), and brine (1x20 ml), dried, and the solvent evaporated to give a solid product. Recrystallisation from ethyl acetate/light petroleum (60-80°) gave colourless crystals of the ene-acetate (65) (1.5 g, 95%) having m.p. 86-89°C.

I.R. ν_{max} (KBr): 1730, 1260, 1210, 1030, 1020 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.15 (s, 4H), 6.2-5.8 (m, 1H), 5.7-5.3 (m, 1H), 5.0-4.5 (m, 1H), 3.6-3.1 (m, 2H), 2.6-1.9 (m, 9H, including s at 2.00).

(Found: C, 79.47; H, 7.58%; M^+=242. $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49%; M^+=242).

Enol (66)

The ene-acetate (65) (1.55 g, 6.4 mmol) was dissolved in methanol (20 ml), and aqueous sodium hydroxide (50 ml, 5%) was added and the solution was heated at 60°C for 0.5 h. The reaction mixture was then concentrated in vacuo to ca. 20 ml. The product was isolated by ethyl acetate extraction, and recrystallisation from ethyl acetate/light petroleum (60-80°) gave colourless needles of the enol (66) (1.2 g, 94%) having m.p. 88-90°C.

I.R. ν_{max} (CCl_4): 3610, 3570, 1490, 1050, 1035, 730 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.15 (s, 4H), 6.4-6.0 (m, 1H), 5.8-5.4 (m, 1H), 4.0-3.6 (m, 1H), 3.6-3.0 (m, 3H, including s at 3.1 exchangeable in D_2O), 2.6-2.4 (m, 2H), 2.5-2.0 (m, 4H).

(Found: C, 83.72; H, 7.90%; M^+=200. $C_{14}H_{16}O$ requires C, 83.96; H, 8.05%; M^+=200).

Jones Oxidation of the Enol (66)

The enol (66) (100 mg, 0.5 mmol) in acetone (5 ml) at 0°, was treated with Jones reagent, dropwise with stirring, until the red colour persisted. Stirring was continued for a further 15 mins at 0°, then isopropanol (1 ml) added, followed by saturated aqueous sodium bicarbonate (5 ml), and the product was isolated by ethyl acetate

extraction (3x10 ml) giving a mixture of two compounds identified as the enone (53) and the ether (68). These were isolated by preparative t.l.c. (d.s. 15%) to give the enone (53) (57 mg, 57%) having m.p. 104-105°C and the oily ether (68) (21 mg, 21%).

Enone (53):-

I.R. ν_{max}(KBr): 1690, 1180, 730 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.2 (s, 4H), 6.1-5.4 (m, 2H), 3.8-3.4 (m, 1H), 3.4-3.2 (m, 1H), 2.7 (d, 4H, J=4Hz), 2.5 (m, 2H).

(Found: C, 85.01; H, 6.80%; M^+=198. $C_{14}H_{14}O$ requires C, 84.81; H, 7.12%; M^+=198).

Ether (68):-

^{1}H.M.R. δ ($CDCl_3$): 7.09 (s, 4H), 4.2 (m, 2H), 3.03 (m, 2H), 2.50-2.30 (m, 4H), 1.85-1.53 (m, 4H).

(Found: M^+=200. $C_{14}H_{16}O$ requires M^+=200).

Ether (68)

A solution of the enol (66) (30 mg, 0.15 mmol) in ethanol (4 ml) and hydrochloric acid (1 ml, 5M) was heated under reflux for 12 h and then concentrated in vacuo. The product was isolated by solvent extraction as usual, to give an oily product whose t.l.c. and ^{1}H.m.r. were identical with the ether (68) obtained above.

Collins Oxidation of the Enol (66)

Chromium trioxide (6 g) was added to a solution of dry pyridine (9.5 ml) in methylene chloride (150 ml) and the resulting burgundy solution was stirred at room temperature for 15 mins. The enol (66) (2 g, 10 mmol) in methylene chloride (10 ml) was then added in one portion and immediately a black, tarry substance precipitated. The solution was stirred for a further 30 mins; the supernatant liquid was then decanted and the residue was washed well with methylene chloride. The combined organic extracts were then washed with sodium hydroxide (5%, 4x10 ml), aqueous sodium bicarbonate (1x10 ml), dilute hydrochloric acid (2x 10 ml), and brine (3x10 ml). The solution was dried and the solvent evaporated to give a colourless crystalline solid. Recrystallisation from ethyl acetate/light petroleum (60-80°) gave colourless crystals (1.85 g, 93%), m.p. 102-105°C, identical by i.r. and ^{1}H.nmr with the enone (53) obtained above.

Diene (71)

To sodium hydride (0.5 g) was added dry dimethylsulphoxide (10 ml) and the mixture stirred at 65-70°C (bath temp.) until evolution of hydrogen had stopped (ca. 1 h). A portion of the cooled dimsyl anion solution (0.25 ml) was added to methyltriphenylphosphonium iodide (230 mg, 0.5 mmol) in dry dimethylsulphoxide (3 ml), when a deep red colour developed. Stirring was continued for a further 10 mins and then the enone (53) (100 mg, 0.5 mmol) in dimethylsulphoxide (3 ml) was added slowly over 10 mins. After 20 h at room temperature, the reaction mixture was poured onto ice and the product isolated by ether extraction.

Preparative t.l.c. (d.s. 10%) gave an oily product (58mg, 58%) which was formulated as the diene (71).

^{1}H.NMR δ ($CDCl_3$): 7.2 (s, 4H), 5.9-5.6 (m, 2H), 5.0 (br. s, 1H), 4.75 (br. s, 1H), 3.6-3.3 (m, 1H), 3.2-3.0 (m, 1H), 2.8-2.4 (m, 6H).

Dienes (55) and (56)

(a) Dimsyl sodium solution (0.25 ml) (prepared as above) was added to n-propyltriphenylphosphonium iodide (216 mg, 0.5 mmol) in dry dimethylsulphoxide (3 ml) and a deep red colour developed. After stirring for 10 mins, a solution of the enone (53) (100 mg, 0.5 mmol) in dry dimethylsulphoxide (3 ml) was added slowly over 10 mins. After 20 h at room temperature the yellow solution was poured onto ice and the product isolated by extraction with ethyl acetate. T.l.c. and ^{1}H.m.r. indicated that the major product was the starting enone (53).

The above reaction was repeated but this time the reaction mixture was heated at 100°C for 20 h. Product recovery with ethyl acetate gave an oil for which t.l.c. indicated a complex mixture. Preparative t.l.c. (d.s. 5%) gave a mixture of non-polar compounds (17 mg). The olefinic region of the ^{1}H.nmr spectrum showed δ ($CDCl_3$) 5.7-5.5 (m, 2H), 5.2 (m, 0.5H) 4.9 (m, 0.5H) consistent with formation of the dienes (55) and (56).

The above reaction was not always reproducible and variations of the procedure including heating at various temperatures, extending the reaction time, and adding crown ether, did not lead to the desired products.

(b) n-propyltriphenylphosphonium iodide (433 mg, 1 mmol) dissolved in dry THF (15 ml) was cooled to -78°C under an atmosphere of dry nitrogen. n-Butyl lithium (1.5 ml of a 1.6M solution in hexane, 2.4 mmol) was added slowly and the solution was stirred at -78°C for 30 mins. Enone (53) (100 mg, 0.5 mmol) dissolved in dry THF (5 ml) was then slowly added over 3 mins. The reaction mixture was allowed to warm slowly to room temperature and stirring was continued for a further 24 h. The reaction mixture was then heated under reflux for a further 24 h. Saturated aqueous ammonium chloride was added and the product isolated by ethyl acetate extraction. T.l.c. and ^{1}H.nmr indicated only starting enone (53).

Attempted Wittig Reaction with the Hemiketal (59)

(a) The procedure was identical to procedure (a) of the previous reaction. T.l.c. and ^{1}H.nmr indicated that the major product was starting hemiketal (59). The ^{1}H.nmr spectrum of the total product did not indicate olefinic signals.

(b) The procedure used was identical to procedure (b) of the previous reaction. T.l.c. and ^{1}H.nmr indicated that the major product was starting material (59). However, in this case, ^{1}H.nmr of the total product indicated that a minor product had olefinic protons with a broad signal at δ 5.3.

Variations in temperature and reaction time with this reaction failed to improve the yield of olefinic product.

Attempted Wittig Reaction with the Keto-acetate (62)

The procedures used were identical with procedures (a) and (b) used in the attempts to form the dienes (55) and (56). T.l.c. and spectroscopic examination of the product indicated the hemiketal (59) as the only product in both cases.

Enol (82)

To magnesium turnings (300 mg) in dry ether under an atmosphere of dry nitrogen was added a small portion of phenethyl bromide in dry ether. The reaction mixture was heated gently and the remainder of the phenethyl bromide [in all 2.2 g, 12 mmol in dry ether (50 ml)] added dropwise. After the addition was complete, the reaction mixture was heated at reflux for a further 10 mins, cooled to room temperature, and the enone (53) (500 mg, 2.5 mmol) in dry ether (20 ml) added slowly over a few minutes. The reaction mixture was then heated under reflux for 5 h and then saturated aqueous ammonium chloride (10 ml) was added cautiously to the cooled reaction mixture. The product was isolated by ether extraction and purified by column chromatography (grade III alumina) to furnish the crystalline enol (82) (530 mg, 69%). Recrystallisation from ethyl acetate/light petroleum 60-80° gave the enol (82) as colourless plates having m.p. 76-77°C.

I.R. ν_{max} (KBr): 3520, 1495, 1455, 740 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.3-7.05 (m, 9H), 6.35-6.05 (m, 1H), 5.9-5.65 (m, 1H), 4.1 (s, 1H, exchangeable in D_2O), 3.55-3.30 (m, 1H), 3.2-3.05 (m, 1H), 2.83-2.50 (m, 4H), 2.40-1.45 (m, 6H).

^{13}C.NMR δ ($CDCl_3$): 75.07 (s), 48.63 (t), 44.55 (t) 42.72 (d), 41.92 (d), 41.38 (t), 33.70 (t), 29.37 (t).

(Found: C, 87.10; H, 8.38%; M^+=304.1824. $C_{22}H_{24}O$ requires C, 86.80; H, 7.95%; M^+=304.1827).

Attempted Epoxidation of the Enol (82)

To the enol (82) (200 mg, 0.6 mmol) dissolved in methylene chloride (20 ml) was added, dropwise, m-chloroperbenzoic acid (85%, 120 mg, 0.7 mmol) in methylene chloride (10 ml); the temperature was kept below 25°C during the addition. The reaction mixture was stirred at room temperature for 12 h. Aqueous sodium bisulphite (10 ml of a 10% solution) was added and the two layers separated. The organic layer was washed thoroughly with saturated aqueous sodium bicarbonate solution, water (2x10 ml), dried, and the solvent evaporated to give an oily residue; t.l.c. of this residue indicated a complex mixture. Attempts to separate the products by preparative t.l.c. were unsuccessful and the reaction was not further investigated.

Ene-acetate (83)

A solution of toluene-p-sulphonic acid (10 mg) in acetic anhydride (1 ml) was added to a mixture of the enol (82) (360 mg, 1.2 mmol) and

acetic anhydride (20 ml) at room temperature. When the reaction was complete (ca. 3 h), as judged by t.l.c. (d.s. 20%), the mixture was quenched with water and neutralised with saturated aqueous sodium bicarbonate. The product was isolated by solvent extraction as usual to give a colourless solid. Recrystallisation from ethyl acetate/light petroleum (60-80°) gave colourless crystals of the ene-acetate (83) (390 mg, 95%) having m.p. 117-132°, pure by t.l.c. (pyrolytic elimination?).

I.R. ν_{max} (KBr): 1740, 1490, 1450, 1240 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.3-7.0 (m, 9H), 6.2-5.5 (m, 2H), 3.60-3.15 (m, 2H), 2.85-1.60 (m, 13H, including s at 2.00).

(Found: C, 83.20; H, 7.53%; M^+=346. $C_{24}H_{26}O_2$ requires C, 83.20; H, 7.56%; M^+=346).

Oxido-acetate (85)

The acetate (83) (400 mg, 1.15 mmol) was dissolved in methylene chloride (25 ml), and sodium bicarbonate (150 mg) was added. This was stirred at room temperature and m-chloroperbenzoic acid (85%, 250 mg, 1.2 mmol) dissolved in methylene chloride was added slowly. The reaction was complete within 12 h as indicated by t.l.c. Aqueous sodium bisulphite solution (10%) was added and the two layers separated. The organic layer was washed thoroughly with aqueous sodium bicarbonate, water, dried, and the solvent evaporated to give a solid product which was purified by column chromatography (grade III alumina). Recrystallisation from ethyl acetate/light petroleum (60-80°) gave colourless crystals of the oxido-acetate (85) (378 mg, 86%) having m.p. 138-142°C.

I.R. ν_{max} (KBr): 1730, 1260, 1230, 920 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.35-7.05 (m, 9H), 4.00-3.75 (m, 1H), 3.70-3.35 (m, 2H), 3.30-3.10 (m, 1H), 3.05-1.70 (m, 13H, including s at 2.00).

(Found: M^+=362.1881. $C_{24}H_{26}O_3$ requires M^+=362.1882).

Attempted Elimination of Acetic Acid from Acetate (85)

(a) The oxido-acetate (85) (40 mg) was dissolved in m-xylene (5 ml) and sodium bicarbonate (25 mg) added and the mixture heated under reflux for 3 h. T.l.c. of the isolated product indicated a complex mixture and the ^{1}H.nmr spectrum of this mixture indicated the absence of olefinic protons. T.l.c. and ^{1}H.nmr also indicated the presence of some starting material. This complex mixture was not further investigated.

(b) The oxido-acetate (85) (50 mg) was sealed in a tube under argon and heated at 250°C for 2 h. T.l.c. and ^{1}H.nmr of the product indicated mainly starting material and some less polar material displaying some olefinic absorption at δ 5.3.

Extending the reaction time and increasing the temperature of the above pyrolysis resulted in a complex mixture of products.

(c) Vapour phase pyrolysis of the oxido-acetate (85) (100 mg) at 450°C furnished starting oxido-acetate (50 mg) and a non-polar product (22 mg). The latter was isolated by preparative t.l.c. ^{1}H.nmr indicated complex olefinic absorption (δ 6.0-5.0). T.l.c. of this product on silver

nitrate-impregnated silica gel plates indicated a mixture of compounds, which was not further pursued.

Dehydration of Enol (82)

The enol (82) (100 mg, 0.3 mmol) was dissolved in pyridine (3 ml) and phosphoryl chloride (1 ml) was added. The reaction mixture was heated at 50°C for 1 h and then concentrated in vacuo. The product was isolated by ethyl acetate extraction including acid wash. The non-polar product was isolated by preparative t.l.c. (d.s. 5%), and the ^{1}H.nmr spectrum of this product indicated complex olefinic absorption between δ 6.1 and δ 5.5. T.l.c. on silver nitrate-impregnated silica gel plates indicated a mixture of four products, which was not further studied.

ß-Phenethyl Phenyl Sulphone (94)

This was prepared by the method of Julia.[98] ß-Phenethyl bromide (1.85 g, 10 mmol) and benzene sulphinic acid, sodium salt (2.0 g, 12 mmol) were dissolved in freshly distilled dimethylformamide (80 ml) and the reaction mixture was stirred for 24 h. The mixture was then poured into water (400 ml) and the product extracted with methylene chloride (3x150 ml). The combined methylene chloride extracts were washed thoroughly with water (5x200 ml), dried, and the solvent evaporated to give an oil. The product crystallised from ether/light petroleum (40-60°). Recrystallisation gave colourless crystals of the sulphone (94) (1.6 g, 67%) having m.p. 57-58°C (lit.[99] 58°C).

I. R. ν_{max} (KBr): 1310, 1145 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 8.0-7.85 (m, 2H), 7.7-7.4 (m, 3H), 7.3-7.0 (m, 5H), 4.5-4.2 (m, 2H), 4.13-3.87 (m, 2H).

(Found: M^+=246.0715 $C_{14}H_{14}SO_2$ requires M^+=246.07144.

Hemiketal Sulphone (95)

The sulphone (94) (1.9 g, 7.7 mmol) was dissolved in anhydrous THF (15 ml) under an atmoshpere of dry argon and the solution was stirred, and cooled to -70°C. n-Butyl lithium (5.2 ml of a 1.6M solution in hexane, 7.8 mmol) was added and the yellow solution was allowed to warm to 0°C and was then recooled to -70°C. The dione (44) (1.7 g, 7.9 mmol) dissolved in dry THF (35 ml) was added to the reaction mixture in one portion and stirring was continued for 2 h. Saturated aqueous ammonium chloride solution (25 ml) was then added to the reaction mixture at -70°C. The reaction was allowed to warm to room temperature and the product isolated by extraction into methylene chloride, giving a colourless solid (3.6 g, 100%). A portion of this was recrystallised from ethanol to give colourless crystals of the hemiketal sulphone (95), m.p. 238.5-240°C.

I.R. ν_{max}(KBr): 3350, 1495, 1300, 1160, 1140, 735 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.80-7.65 (m, 2H), 7.60-7.30 (m, 3H), 7.30-6.85 (m, 9H), 3.65-3.53 (m, 1H), 3.40-3.13 (m, 4H), 2.45-2.30 (m, 2H), 2.10-1.75 (m, 6H).

(Found: C, 72.81; H, 5.97; S, 6.76%; M^+=460. $C_{28}H_{28}SO_4$ requires C, 73.02; H, 6.13; S, 6.96%; M^+=460).

Dichlorophosphate Ester (97)

The hemiketal sulphone (95) (100 mg, 0.2 mmol) was dissolved in pyridine (5 ml) and phosphoryl chloride (2 ml) was added. The reaction mixture was heated at 70°C for 2 h and then concentrated in vacuo. The product was isolated by ethyl acetate extraction, including acid wash, giving the solid dichlorophosphate (97). Recrystallisation from methylene chloride/ethyl acetate gave colourless crystals (108 mg, 86%), m.p. 168-170°C.

I.R. ν_{max} (KBr): 1300, 1150, 980, 740, 580 cm^{-1}.

^{1}H.NMR δ (CDCl): 7.9-7.6 (m, 2H), 7.6-7.3 (m, 3H), 7.3-7.05 (m, 9H), 3.8-3.6 (m, 1H), 3.5-3.0 (m, 4H), 2.6-2.0 (m, 8H).

(Found: C, 58.15; H, 4.85; Cl, 12.21%; M^+=442 $C_{28}H_{27}O_5PSCl_2$ requires C, 58.24; H, 4.71; Cl, 12.28%; M^+-$HOPOCl_2$=442).

Attempted Formation of the Toluene-p-sulphonate (100)

The hemiketal sulphone (95) (200 mg, 0.4 mmol) was dissolved in dry pyridine (5 ml) and cooled to 0°C. To this was added toluene-p-sulphonyl chloride (200 mg, 1 mmol) dissolved in dry pyridine (5 ml) and the reaction mixture was kept at 0°C for 60 h. The reaction mixture was then poured into iced water, when crystals separated. The solid was filtered, washed well with water, and dried in vacuo. T.l.c. and ^{1}H.nmr indicated only starting material (95).

Toluene-p-sulphonate (100)

The hemiketal sulphone (95) (200 mg, 0.4 mmol) was dissolved in dry THF (10 ml) and phenanthroline (2 mg) was added. The solution was then cooled to -70°C and n-butyl lithium (1.6M solution in hexane) was added dropwise until the deep red colouration persisted. Toluene-p-sulphonyl chloride (200 mg, 1 mmol) dissolved in dry THF (5 ml) was then added and the solution was stirred at -70°C for 2 h. Water was then added and the product was isolated by ether extraction. T.l.c. indicated that the major product was a new non-polar product along with some starting material and some of the sulphone (95). ^{1}H.nmr was consistent with the major product being the toluene-p-sulphonate (100); δ ($CDCl_3$) 7.9 and 7.4 (AB quartet, J=8Hz) and 2.6 (s). Variations of this procedure failed to improve the yield of the toluene-p-solphonate (100). The crude material was used without further purification.

Sodium Amalgam

Sodium amalgam was prepared by the procedure described by Brasen and Hauser.[100] A filter flask (500 ml) was fitted with a two-hole rubber stopper carrying a dropping funnel and an outlet tube. The flask was then charged with sodium (32 g) and mineral oil (100 ml). With a stream of nitrogen passing through the side-arm of the flask, the flask was heated on a hot-plate until the sodium melted, the mercury (500 g) was added rapidly from the dropping funnel and a vigorous exothermic reaction took place. The partially solid material was heated strongly to produce a homogeneous melt. The mineral oil was decanted and the sodium amalgam was poured onto a metal pan and broken into small pieces as it solidified. The sodium amalgam was

then washed with petroleum ether and stored in a tightly stoppered bottle.

A portion of this amalgam was added to water and kept for 12 h. Titration of the resulting sodium hydroxide solution with standard hydrochloric acid showed the amalgam to contain approximately 5.5% sodium.

Enone (99) from the Toluene-p-sulphonate (100)

To the crude toluene-p-sulphonate (100) (0.5 g, 0.8 mmol) prepared as above, dissolved in ethyl acetate (10 ml) and methanol (20 ml), was added sodium dihydrogen orthophosphate (0.5 g) followed by sodium amalgam (5.5%, 1.3 g). The reaction mixture was stirred at room temperature for 2 h. The product was isolated by extraction into methylene chloride giving an oil (280 mg). T.l.c. of this oil indicated 2 major products. These products were isolated by preparative t.l.c. (d.s. 35%) and identified as the hemiketal sulphone (95) (193 mg, 51%) and the enone (99) (57mg, 23%). Recrystallisation from ethanol gave the enone (99) as colourless crystals having m.p. 160-162°C.

I.R. ν_{max} (KBr): 1685, 1600, 1580, 1495, 760 and 755 cm^{-1}.

$^{1}H.NMR$ δ ($CDCl_3$): 7.2 (s, 9H), 5.5 (t, J=8Hz, 1H), 3.7-2.9 (m, 4H), 2.8-2.0 (m, 8H).

$^{13}C.NMR$ δ ($CDCl_3$): 210.75 (s), 144.74 (s), 140.65 (s), 134.82 (s), 132.68 (d), 128.54 (d), 127.40 (d), 125.98 (d), 48.59 (2t), 44.08 (t), 42.29 (d), 40.85 (d), 34.65 (t), 33.89 (t).

(Found: C, 87.15; H, 7.47%; M^+=302.1671. $C_{22}H_{22}O$ requires C, 87.37; H, 7.33%; M^+=302.16705).

Attempted Benzoate (101) Formation

The procedure used was analogous to that for the preparation of the toluene-p-sulphonate (100). A complex mixture was obtained. One of the major products was isolated by preparative t.l.c. (d.s. 35%) and its ^{1}H.nmr spectrum was consistent with that of the benzoate (101), (12 mg, 16%), but the reaction was not further investigated.

^{1}H.NMR δ ($CDCl_3$): 8.2-7.0 (m, 19H), 3.8-3.6 (m, 1H), 3.5-3.2 (m, 4H), 2.6-2.2 (m, 8H).

Sulphone-acetate (102)

To the hemiketal sulphone (95) (100 mg, 0.2 mmol) in acetone (10 ml) was added concentrated sulphuric acid (2 drops) and acetic anhydride (2 ml). The mixture was allowed to stand at room temperature for 12 h and was then concentrated in vacuo and the product was isolated by ethyl acetate extraction, including base wash, giving a solid product. This solid product was triturated with ether and filtered, and the solid was recrystallised from ethyl acetate/light petroleum (60-80°) to give colourless crystals of the acetate (102) (83 mg, 76%), having m.p. 197.5-199°C.

I.R. ν_{max}(KBr): 1735, 1305, 1220, 1150, 1010, 760, 740, 690 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.8-7.65 (m, 2H), 7.5-7.3 (m, 3H), 7.2-6.9 (m, 9H),

3.7-3.5 (m, 1H), 3.4-3.15 (m, 4H), 2.5-2.1 (m, 8H), 1.9 (s, 3H).

^{13}C.NMR δ ($CDCl_3$): 168.07 (s), 80.52 (s), 76.70 (d), 22.33 (q).

(Found: C, 71.78; H, 6.09%; M^+=442. $C_{30}H_{30}O_5S$ requires C, 71.70; H, 6.02%; M-AcOH=442).

Attempted formation of the Enone (99) from the Acetate (102)

The procedure used was analogous to that for the preparation of the enone (99) from the toluene-p-sulphonate (100). T.l.c. and ^{1}H.nmr indicated that very little of the enone (99) had been formed and that the major product was the hemiketal sulphone (95). Variation of the reaction temperature did not improve the yield of the enone (99).

Formation of the Enone (99) from the Dichlorophosphate (97)

The procedure used was analogous to that for the preparation of the enone (99) from the toluene-p-sulphonate (100) except that the reaction was carried out at between -30°C and -20°C for 12 h. Purification of the total product by column chromatography on grade III alumina gave the enone (99) (0.89 g, 75%).

The above reaction was not consistently reproducible, sometimes the hemiketal sulphone (95) was a major product. On one occasion the major product was identified as the dimethoxyphosphate ester (103) having m.p. 193-194°C.

I.R. ν_{max} (KBr): 1460, 1450, 1305, 1280, 1150, 1045, 1005, 985 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.7-7.0 (m, 14H), 4.0-3.1 (m, 11H), 3.0-2.0 (m, 8H).

(Found: C, 63.18; H, 5.72%; M^+=568. $C_{30}H_{33}O_7PS$ requires C, 63.37; H, 5.85%; M^+=568.

Formation of the Enone (99) from the Trifluoroacetate (104)

The hemiketal sulphone (95) (0.5 g, 1.1 mmol) was dissolved in anhydrous THF (30 ml) and trifluoroacetic anhydride (5 ml) was added. The reaction mixture was stirred for 24 h under an inert atmosphere. The solvent and reagent were then removed in vacuo to give the trifluoroacetate (104) quantitatively (608 mg).

I.R. ν_{max} (thin film): 1785 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.80-7.67 (m, 2H), 7.55-7.35 (m, 3H), 7.20-7.00 (m, 9H), 3.65 (t, J=5Hz, 1H), 3.43-3.15 (m, 4H), 2.60-2.10 (m, 8H).

This trifluoroacetate was used without further purification, it was dissolved in anhydrous THF (30 ml), dry methanol (20 ml) and di-sodium hydrogen orthophosphate (200 mg) were added, and the stirred mixture was cooled to -70°C. Sodium amalgam (3 g) was added and the reaction mixture gradually allowed to warm to -20°C over several hours. The reaction mixture was kept at -20°C for 3 h and then allowed to warm to room temperature and stirring was continued for a further 8 h. Work-up as normal gave the enone (99) (273 mg, 83%) identical by t.l.c., i.r. and

^{1}H.nmr to that obtained above. A common by-product of this reaction was the hemiketal (105) having m.p. 218-220°C.

I.R. ν_{max} (KBr): 3330, 1170, 1115, 1000, 770, 700 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.30-7.10 (m, 9H), 3.35-3.10 (m, 2H), 2.93 (s, 1H), 2.80-2.57 (m, 2H), 2.10-1.50 (m, 10H).

(Found: C, 82.40; H, 7.53%; M^+=320.1781. $C_{22}H_{24}O_2$ requires C, 82.46; H, 7.55%; M^+=320.1776).

Attempted Ketalisation of the Enone (99)

A solution of the enone (99) (120 mg, 0.4 mmol) and ethylene glycol (300 mg) in benzene (10 ml) containing toluene-p-sulphonic acid (5 mg) was heated at reflux with azeotropic removal of water. After 24 h the reaction mixture was cooled and the product isolated by ethyl acetate extraction. T.l.c. indicated many products and ^{1}H.nmr of the total product indicated very little olefinic absorption.

The above reaction was repeated in the presence of triethylorthoformate and this time fewer compounds were apparent by t.l.c. Preparative t.l.c. gave one compound in reasonable purity, tentatively assigned structure (106).

I.R. ν_{max} (CCl_4): 3570 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.4-7.0 (m, 9H), 3.6-2.9 (m, 9H), 2.5-1.5 (m, 10H).

(Found: M^+=346.1931; $C_{24}H_{28}O_3$ requires $M^+(-H_2O)$=346.1933).

Attempted S_E' Cyclisation of the Enone (99)

(a) With Trimethyloxoniumhexachloroantimonate

To the enone (99) (120 mg, 0.4 mmol) dissolved in methylene chloride (2 ml) was added trimethyloxoniumhexachloroantimonate (300 mg, 0.8 mmol) in methylene chloride (5 ml). The resulting yellow cloudy suspension was stirred for 30 mins under argon at room temperature then diisopropylethylamine (300 mg) in methylene chloride (3 ml) was added. The solution became clear and stirring was continued for a further 2 h. The product was isolated by methylene chloride extraction and purified by preparative t.l.c. (d.s. 30%). Recrystallisation from ethyl acetate/light petroleum (60-80°) gave colourless crystals of the hydroxy-chloride (108) (93 mg, 69%), m.p. 113-114°C.

I.R. ν_{max}(KBr): 3600, 2940, 1610, 1590, 1495, 760, 725, 700 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.50-7.10 (m, 9H), 3.35-2.80 (m, 4H), 2.60-1.45 (m, 10H, including s at 1.48 exchangeable in D_2O).

^{13}C.NMR δ ($CDCl_3$): 145.01 (s), 144.32 (s), 143.71 (s), 129.32 (d), 128.36 (2d), 128.18 (d), 128.02 (d), 126.88 (d), 125.73 (d), 75.81 (s), 74.48 (s), 60.14 (d), 47.28 (t), 44.94 (t), 40.61 (d), 40.17 (d), 38.85 (t), 35.75 (t), 32.40 (t).

(Found: C, 77.80; H, 6.77%; M^+=338.1439 and 340.1395 (3:1). $C_{23}H_{23}OCl$ requires C, 77.98; H, 6.84%; M^+=338.1438 and 340.1408 (3:1)).

(b) With Triethyloxoniumtetrafluoroborate

The enone (99) (100 mg, 0.33 mmol) was treated with triethyloxonium-tetrafluoroborate (1 ml of a 1M solution in methylene chloride, 1 mmol) under conditions similar to those described in (a) above. The isolated product was recrystallised from ethyl acetate/light petroleum (60-80°) to give colourless crystals of the diol (110) (69 mg, 65%), m.p. 143-144°C.

I.R. ν_{max} (CCl_4): 3600, 1495, 1030, 755, 700 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.40-7.00 (m, 9H), 3.25-2.80 (m, 4H), 2.40-1.30 (m, 11H, including s, 2H, at 1.5 exchangeable in D_2O).

^{13}C.NMR δ ($CDCl_3$): 145.65 (s), 144.93 (s), 144.00 (s), 129.22 (d), 128.63 (d), 128.20 (d), 128.06 (d), 126.78 (d), 125.78 (d), 74.62 (s), 58.92 (d), 45.37 (2t), 39.34 (d), 38.82 (d), 36.61 (2t), 30.08 (t).

(Found: C, 82.3; H, 7.69%; M^+=320. $C_{22}H_{24}O_2$ requires C, 82.46; H, 7.55%; M^+=320).

The above reaction was repeated with trimethyloxoniumtetrafluoroborate and again with the exclusion of diisopropylethylamine. On both occasions similar results were obtained.

(c) With Stannic Chloride

The enone (99) (90 mg, 0.3 mmol) in methylene chloride (10 ml) was cooled to -78°C and to this stirred solution was added stannic chloride (10 ml of a 0.1M solution in methylene chloride, 1 mmol). Stirring was continued for a further 2 h at -78°C and then the solution was allowed to warm slowly to room temperature. The reaction mixture was then passed through a short column of grade III alumina and the product eluted with methylene chloride. Evaporation of the solvent in vacuo gave an oil whose ^{1}H.nmr was similar to that of the hydroxy-chloride obtained in (a) above.

The oil was dissolved in pyridine (5 ml) and heated under reflux for 2 h. The solvent was then removed in vacuo and the product isolated by methylene chloride extraction including acid wash. A colourless solid product was obtained which was recrystallised from ethyl acetate/light petroleum (60-80°) to give colourless prisms of the styrene (113) (52 mg, 58%) having m.p. 169-171°C.

I.R. ν_{max} (CCl_4): 3590, 2950, 1495, 1490, 1450, 1090 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.50-7.05 (m, 9H), 6.53 and 6.30 (AB quartet, J_{AB}= 16 Hz, 2H), 3.30-3.05 (t, J=7Hz, 2H), 2.75-1.63 (m, 9H).

^{13}C.NMR δ ($CDCl_3$): 144.71 (s), 137.47 (s), 136.21(d), 129.36 (d), 128.57 (d), 128.46 (d), 127.23 (d), 126.97 (d), 90.30 (s), 55.18 (s), 50.70 (t), 47.97 (t), 44.95 (d).

U.V. λ_{max} (EtOH): 253 nm (ϵ, 17600).

(Found: C, 87.52; H, 7.46%; M^+=302.168. $C_{22}H_{22}O$ requires C, 87.37; H, 7.33%; M^+=302.167).

Borohydride Reduction of the Enone (99)

To the enone (99) (1.5 g, 5 mmol) dissolved in THF (50 ml) and ethanol (150 ml) was added sodium borohydride (0.75 g) and the mixture was stirred for 16 h at room temperature. Isolation by ethyl acetate extraction as normal gave a colourless solid product (1.47 g, 97%). T.l.c. (d.s. 25%) indicated two products of very similar polarity. Separation by vacuum liquid chromatography on silica gel afforded the endo-ol (115) (631 mg, 42%) pure by t.l.c.; a mixture of the endo-ol (115) and the exo-ol (116) (162 mg, 11%), as determined by t.l.c.; and the exo-ol (116) (499 mg, 33%) pure by t.l.c.

A portion of the endo-ol (115) was recrystallised from ethyl acetate/light petroleum (60-80°) to give colourless needles having m.p. 119-120.5°C.

Endo-ol (115)

I.R. ν_{max} (CCl_4): 3620, 2930, 1495, 1490, 1455, 1030, 760 cm^{-1}.

^{1}H.NMR δ($CDCl_3$): 7.30-7.05 (m, 9H), 5.55 (t, J=7Hz, 1H) 3.45 (d, J=8Hz, 2H), 3.30-2.75 (m, 2H), 2.40-1.50 (m, 10H).

^{13}C.NMR δ ($CDCl_3$): 68.71 (d), 45.53 (t), 39.51 (d), 39.32 (d), 36.18 (t), 36.04 (t), 35.39 (t), 33.76 (t).

(Found: C, 86.78; H, 7.78%; M^+=304.1830. $C_{22}H_{24}O$ requires C, 86.80; 7.95%; M^+=304.1827).

A portion of the exo-ol (116) was recrystallised from ethyl acetate/light petroleum (60-80°) to give colourless prisms having m.p. 93.5-94.5°C.

Exo-ol (116):-

I.R. ν_{max} (CCl_4): 3610, 3600, 2910, 1490, 1450, 1030, 700 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.33-7.05 (m, 9H), 5.33 (t, J=8Hz, 1H), 5.00-4.60 (m, 1H), 3.35 (d, J=8Hz, 2H), 3.25-3.00 (m, 2H), 2.95-2.10 (m, 9H).

^{13}C.NMR δ ($CDCl_3$): 66.96 (d), 48.53 (t), 42.47 (d), 41.70 (d), 41.38 (t), 41.04 (t), 33.79 (t), 33.40 (t).

(Found: C, 86.79; H, 7.89%; M^+=304.1825. $C_{22}H_{24}O$ requires C, 86.80; H, 7.95%; M^+=304.1827).

Collins oxidation of the Endo-ol (115)

Chromium trioxide (100 mg) was added to a solution of dry pyridine (10 drops) in methylene chloride (5 ml) and the resulting deep burgundy solution was stirred at room temperature for 15 mins. The endo-ol (30 mg) in methylene chloride (2 ml) was then added in one portion and the mixture stirred for a further 30 mins. Isolation of the product by methylene chloride extraction including base and acid wash gave an oil. Preparative t.l.c. (d.s. 20%) gave the major product (18 mg) for which t.l.c., i.r. and ^{1}H.nmr were identical with that of the enone (99).

Collins Oxidation of the Exo-ol (116)

Collins oxidation of the exo-ol (116) (30 mg), as above, gave as the major product (21 mg) a compound identified by i.r., and ^{1}H.nmr as the enone (99).

Ether (117) Formation from the Endo-ol (115)

A solution of the endo-ol (115) (120 mg, 0.4 mmol) in ethanol (16 ml) and hydrochloric acid (4 ml, 5M) was heated at reflux for 12 h. Concentration in vacuo and ethyl acetate extraction, as normal, gave a colourless solid product (117 mg, 97%). Recrystallisation from ethyl acetate/light petroleum (60-80°) gave colourless crystals (103 mg, 86%) of the ether (117) m.p. 114-116°C.

I.R. ν_{max} (KBr): 2910, 1490, 1450, 1435, 1220, 1040, 760, 705 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$: 7.20-7.05 (m, 9H), 4.40-4.20 (m, 1H), 3.20-2.95 (m, 2H), 2.80-2.55 (m, 2H), 2.43-1.85 (m, 4H), 1.85-1.60 (m, 6H).

(Found: C, 86.61; H, 7.82%; M^+=304.1831. $C_{22}H_{24}O$ requires C, 86.80; H, 7.95%; M^+=304.1827).

Acid Treatment of the Exo-ol (116)

Treatment of the exo-ol (116) (60 mg, 0.2 mmol) under the conditions described above gave an oily product (35 mg) assigned structure (118).

I.R. ν_{max} (CCl_4): 1690 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.50-7.05 (m, 9H), 3.35-3.00 (m, 2H), 2.90-2.55 (m,

6H), 2.40-1.20 (m, 7H).

(Found: M^+=304.1825. $C_{22}H_{24}O$ requires M^+=304.1827).

Attempted Formation of the p-Bromobenzenesulphonate (120)

The exo-ol (116) (140 mg, 0.46 mmol) was dissolved in pyridine (5 ml) and cooled to 0°C. p-Bromobenzenesulphonyl chloride (250 mg, 1 mmol) in pyridine (2 ml) was added to the cooled solution and the reaction mixture was kept at room temperature for 24 h. The mixture was poured onto ice and the product (30 mg) isolated by ethyl acetate extraction, including washing with aqueous copper sulphate solution (10 ml). T.l.c. and ^{1}H.nmr indicated some starting material and a new product with a 'singlet' at δ 7.57 consistent with the p-bromobenzenesulphonate (120).

The above reaction was repeated under essentially the same conditions and this time the major product was an extremely polar compound assigned structure (122), m.p. 191.5-194°C.

I.R. ν_{max} (KBr): 1470, 1225, 1205, 1035, 1005, 830, 740 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 9.50-9.35 (m, 2H), 8.20-8.00 (m, 3H), 7.80 and 7.40 (AB quartet, J=8Hz, 4H), 7.15-7.00 (m, 9H), 3.55-1.60 (m, 14H).

^{13}C.NMR δ ($CDCl_3$): 75.51 (s), 47.14 (d), 44.92 (t), 41.05 (d), 40.26 (d), 35.34 (t), 34.54 (d), 33.54 (t), 33.12 (t), 27.15 (t).

(Found: C, 65.71; H, 5.47; N, 2.13%; $C_{33}H_{32}NSO_3Br$ requires C, 65.78; H, 5.35; N, 2.32%).

Attempted S_E' Cyclisation of p-Bromobenzenesulphonate (120)

The crude brosylate (30 mg), prepared above, was placed in a pressure-resistant flask, urea (10 mg) and trifluoroethanol (0.15 ml) were added and the flask sealed under argon. The sealed flask was heated at 100°C (±5°) for 24 h and the resulting solution was purified by preparative t.l.c. (d.s. 20%) and the major product (12 mg) isolated. This compound was identical by ^{1}H.nmr and i.r. with the ether (121) prepared subsequently (p134).

Trifluoroacetate (123)

The exo-ol (116) (130 mg, 0.43 mmol), dissolved in anhydrous ether (10ml), was cooled to 0°C and trifluoroacetic anhydride (200 mg, 1.1 mmol) in ether (2 ml) was added. The reaction was stirred at room temperature and then concentrated in vacuo to give the trifluoroacetate (123) as a solid (167 mg, 98%) which was used without further purification.

I.R. ν_{max} (KBr): 1780 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.35-7.10 (m, 9H), 6.45-6.15 (m, 1H), 5.58 (t, J=8Hz, 1H), 3.47 (d, J=8Hz, 2H), 3.37-3.00 (m, 2H), 2.80-2.60 (m, 2H), 2.55-2.22 (m, 4H), 2.10-1.70 (m, 2H).

Attempted Cyclisation of the Trifluoroacetate (123)

The trifluoroacetate (123) (160 mg, 0.42 mmol), urea (48 mg), and trifluoroethanol (2 ml) were placed in a pressure-resistant flask which was sealed under argon. The reaction mixture was heated at 100°C (±5°) for

24 h and the resulting clear brown solution was purified by preparative t.l.c. (d.s. 20%) to give the ether (121) as an oil (108 mg, 70%).

I.R. ν_{max} (CCl_4): 1280, 1160, 1120, 700 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.25-7.05 (m, 9H), 3.75 (q, J=9Hz, 2H), 3.45-3.00 (m, 2H), 2.78-2.45 (m, 1H), 2.40-1.35 (m, 11H).

^{13}C.NMR δ ($CDCl_3$): 124.43 (q, J_{CF}=277.9Hz), 76.51 (s), 58.89 (q of t, J_{C-C-F}=34Hz), 49.05 (d), 41.58 (d), 40.64 (d), 40.35 (t), 36.47 (t), 33.64 (t), 33.15 (d), 31.74 (t), 27.99 (t).

(Found: M^+=386. $C_{24}H_{25}OF_3$ requires M^+=386).

Repeating this reaction using hexafluoroisopropanol instead of trifluoroethanol afforded a complex mixture of products as revealed by t.l.c. The ^{1}H.nmr spectrum of this mixture did not indicate olefinic signals and the reaction was not further investigated.

Dehydration of the Endo-ol (115)

To the endo-ol (115) (300 mg, 1 mmol) in dry pyridine (10 ml) was added phosphoryl chloride (2 ml) and the reaction mixture was heated at 60°C for 2 h. Concentration in vacuo and isolation of the product by ethyl acetate extraction including an acid wash gave an oil (200 mg, 70%). T.l.c. on silver nitrate-impregnated silica gel indicated two compounds. These were separated using v.l.c. on silver nitrate-impregnated silica gel to give the dienes (86) and (87) as oils.

Less polar diene:-

I.R. ν_{max} (CCl_4): 1500, 1455, 730, 700 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.20-7.05 (m, 9H), 5.85-5.40 (m, 3H), 3.35 (d, J=7Hz, 2H), 3.10-2.80 (m, 2H), 2.58-2.03 (m, 6H).

^{13}C.NMR δ ($CDCl_3$): 45.39 (t), 44.22 (d), 43.24 (d), 33.88 (2t), 33.47 (t).

(Found: M^+=286.1715. $C_{22}H_{22}$ requires M^+=286.1721).

More polar diene:-

I.R. ν_{max} (CCl_4): 1500, 1460, 730, 700 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.20-7.05 (m, 9H), 5.85-5.25 (m, 3H), 3.50 (d, J=8Hz, 2H), 3.20-2.90 (m, 2H), 2.58-2.05 (m, 6H).

^{13}C.NMR δ ($CDCl_3$): 44.64 (d), 43.35 (t), 43.06 (d), 35.80 (t), 33.80 (2t).

(Found: M^+=286.1720. $C_{22}H_{22}$ requires M^+=286.1721).

Attempted Dehydration of the Exo-ol (116)

Treatment of the exo-ol (116) (50 mg) under conditions similar to above gave a very polar product. ^{1}H.nmr of the crude material suggested a compound similar to (122) δ 9.6-9.4 (m, 2H) and δ 8.4-7.9 (m, 3H). This product was not further investigated.

K.Selectride Reduction of the Enone (99)

To the enone (300 mg, 1mmol) in dry THF at -78°C was added K. Selectride (2.5 ml of a 0.5M solution in THF, 1.25 mmol). The stirred solution was allowed to warm to room temperature over 3 h, recooled to

-70°C, and aqueous sodium hydroxide solution (15 ml, 3M) then hydrogen peroxide (30%, 2.5 ml) were added. Isolation of the product by methylene chloride extraction, as normal, gave a solid (280 mg, 93%). T.l.c. and ^{1}H.nmr indicated that the product was almost exclusively the exo-ol (116) with very little of the endo-ol (115) present.

Acid Treatment of the Enol (82)

A solution of the enol (82) (100 mg, 0.33 mmol) in ethanol (16 ml) and dilute hydrochloric acid (4 ml, 5M) was heated at reflux for 12 h. Concentration in vacuo and ethyl acetate extraction gave an oil. The non-polar product was isolated by preparative t.l.c. (d.s. 5%) and ^{1}H.nmr of this product indicated complex olefinic absorption between δ 6.1 and 5.5. T.l.c. on silver nitrate-impregnated silica gel plates indicated a mixture of products, which was not further pursued.

Attempted Cyclisation of the Dienes (86) and (87)

(a) Amberlite 1R-120 cation exchange resin (500 mg, 14-52 mesh) was added to a solution of the diene mixture, (86) and (87), (50 mg) in dioxan (10 ml). The mixture was stirred in an atmosphere of dry nitrogen for 24 h, the resin was then filtered off and the solvent removed in vacuo. T.l.c. and ^{1}H.nmr indicated recovery of the diene mixture. Variations of the above procedure including longer reaction times and higher reaction temperatures were ineffective.

(b) The diene mixture, (86) and (87), (50 mg) was dissolved in sulphuric

acid (0.1N in 80% aqueous dioxan) and the mixture was stirred at room temperature for 24 h. The product (43 mg) was isolated by ethyl acetate extraction and ^{1}H.nmr and t.l.c. showed only starting material.

Extending the reaction time and increasing the temperature were ineffective

Epoxidation of the Diene Mixture (86) and (87)

To the diene mixture (86) and (87) (200 mg, 0.7 mmol) in chloroform (10 ml) was added m-chloroperbenzoic acid (85%; 145 mg, 0.7 mmol) in chloroform (5 ml), and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then washed with saturated aqueous sodium bicarbonate solution (5 ml) and brine (5 ml), dried and the solvent evaporated. Preparative t.l.c. (d.s. 5%) gave a solid product which was crystallised from ethyl acetate/light petroleum (60-80°) to give colourless crystals of the oxido-olefin (124), (100 mg, 52%), m.p. 143-146°C.

I.R. ν_{max}(KBr): 1500, 1460, 1450, 1270, 950, 860, 730 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.35-7.00 (m, 9H), 6.05-5.35 (m, 2H), 3.55-1.97 (m, 11H).

(Found: M^+=302.167. $C_{22}H_{22}O$ requires M^+=302.167).

Attempted Formation of the Methyl Hemiketal Sulphone (138)

To the hemiketal sulphone (95) (100 mg, 0.2 mmol) in dry THF (5 ml) at -78°C was added n-butyl lithium (0.3 ml of a 1.6M solution in hexane, 0.5 mmol) and the yellow solution was allowed to warm to room temperature

and was then recooled to -78°C. A solution of methyl iodide (75 mg, 0.5 mmol) in dry THF was added in one portion and the reaction mixture was stirred at -78°C for 1 h. Saturated aqueous ammonium chloride solution (5 ml) was added and the reaction mixture allowed to warm to room temperature. The product was isolated by extraction into methylene chloride. The ^{1}H.nmr spectrum of the isolated product indicated only starting material.

With variations in the above procedure including the use of lithium diisopropylamide instead of butyl lithium, longer reaction times, and higher reaction temperatures, only starting material was recovered.

Attempted Formation of Methyl Sulphone (131)

2-Bromopropylbenzene (133) (2.0 g, 10 mmol) and benzene sulphinic acid, sodium salt (1.8 g, 11 mmol) were dissolved in dimethylformamide and the reaction mixture was stirred for 4 days at room temperature. The reaction mixture was then poured into water (500 ml) and the product was extracted into ethyl acetate (3x200 ml), the combined ethyl acetate extracts were then washed thoroughly with water (6x100 ml), dried, and the solvent evaporated to give an oil. T.l.c. indicated mainly starting material and a new, more polar, product. This new product was isolated as an oil by column chromatography (grade III alumina d.s. 10%) and ^{1}H.nmr indicated the rearranged sulphone (134).

^{1}H.NMR δ ($CDCl_3$): 7.63-7.37 (m, 5H), 7.35-7.00 (m, 5H), 3.95 (dd, J_1=12Hz, J_2=5Hz, 1H), 2.65-1.90 (m, 2H), 0.81 (t, J=8Hz, 3H).

Methyl Sulphone (131)

To a stirred solution of β-phenethyl phenyl sulphone (94) (500 mg, 2 mmol) in dry THF (15 ml) at -70°C was added n-butyl lithium (1.3 ml of a 1.6M solution in hexane, 2.1 mmol). The solution was stirred for 5 min at -70°C and methyl iodide (300 mg, 2.05 mmol) in dry THF (3 ml) was added in one portion.

After 5 min the reaction was quenched with saturated aqueous ammonium chloride solution (5 ml) and the product was isolated by ether extraction. T.l.c. indicated one major and one minor product. The major product was identified as the methyl sulphone (131).

^{1}H.NMR δ ($CDCl_3$): 7.98-7.82 (m, 2H), 7.62-7.40 (m, 3H), 7.35-7.00 (m, 5H), 3.50-3.12 (m, 2H), 2.65-2.30 (m, 1H), 1.07 (d, J=8Hz, 3H).

The reaction was repeated using 2 equivalents of butyl lithium and 2 equivalents of methyl iodide and gave the dimethyl sulphone (135). T.l.c. and ^{1}H.nmr suggested that this was the minor product from the above reaction.

^{1}H.NMR δ ($CDCl_3$): 7.99-7.85 (m, 2H), 7.75-7.50 (m, 3H), 7.40-7.00 (m, 5H), 3.02 (s, 2H), 1.18 (s, 6H).

1-Bromo-1,2-diphenylethane (137)

t-Stilbene (5 g, 27 mmol) was dissolved in ethyl acetate (50 ml) and hydrobromic acid (in glacial acetic acid, 45% W/V of hydrobromic acid, 10 ml, 55 mmol). The reaction flask was tightly stoppered and allowed to stand at room temperature for 12 h. The reaction mixture was then poured into water (20 ml) and the product isolated by ethyl acetate extraction, including base wash, to give the bromide (137) (6.8 g, 93%) which was used without further purification.

^{1}H.NMR δ ($CDCl_3$): 7.3-7.0 (m, 10H), 5.0 (t, J=8Hz, 1H), 3.4 (d, J=8Hz, 2H).

Phenyl Sulphone (132)

The phenyl sulphone (132) was prepared by the procedure used for the preparation of β-phenethyl phenyl sulphone (94) (p. 118). In this way 1-bromo-1,2-diphenylethane (137) (1 g, 3.8 mmol) and benzene sulphinic acid (0.7 g, 4.2 mmol) reacted to give the phenyl sulphone (132). Recrystallised from ether/light petroleum (40-60°) this had m.p. 147.5-148.5°C, (690 mg, 56%).

I.R. ν_{max} (KBr): 1460, 1450, 1315, 1155, 1090, 760, 715, 700, 685, 620, 550, 515 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.62-7.27 (m, 5H), 7.25-6.90 (m, 10H), 4.26 (dd, J=12Hz and 4Hz, 1H), 3.83 (dd, J=14Hz and 4Hz, 1H), 3.36 (dd, J=14Hz and 12Hz, 1H).

(Found: C, 74.40; H, 5.60; S, 10.29%; M^+=322. $C_{20}H_{18}SO_2$ requires C, 74.52; H, 5.63; S, 9.93%; M^+=322).

Methyl Hemiketal Sulphone (138)

The methyl hemiketal sulphone (138) was prepared from the dione (44) and the methyl sulphone (131) by a procedure similar to that used for the preparation of the hemiketal sulphone (95). (p. 119). In this way the methyl sulphone (131) (500 mg, 1.9 mmol) in the presence of n-butyl lithium (1.3 ml of a 1.6M solution in hexane, 2 mmol) reacted with the dione (44) to give the methyl hemiketal sulphone (138) (550 mg, 60%). A portion of this was recrystallised from ethanol and had m.p. 206-208°C.

I.R. $\nu_{max}(CHCl_3)$: 3700, 1500, 1300, 1150, 1140 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.95-7.81 (m, 2H), 7.68-7.40 (m, 3H), 7.15-7.05 (m, 9H), 3.37 (s, 2H), 3.30-3.08 (m, 2H), 2.80-1.65 (m, 9H), 1.38 (s, 3H).

^{13}C.NMR δ ($CDCl_3$): 94.60 (s), 82.68 (s), 76.21 (s), 38.96 (4t), 35.96 (t), 32.72 (d), 32.10 (d), 17.38 (q).

(Found: C, 73.22; H, 6.35; S, 6.89%. $C_{29}H_{30}O_4S$ requires C, 73.40; H, 6.37; S, 6.74%).

Phenyl Hemiketal Sulphone (139)

This was prepared from the dione (44) and the phenyl sulphone (132) by a procedure similar to that used for the preparation of the hemiketal sulphone (95) (p.119). In this way the phenyl sulphone (132) (200 mg, 0.62 mmol) in the presence of n-butyl lithium (0.45 ml of a 1.6M solution

in hexane, 0.72 mmol) was reacted with the dione (44). The phenyl hemiketal sulphone (139) was isolated by preparative t.l.c. (d.s. 80%) (33 mg, 10%) and had m.p. 148-151°C. This reaction was not further pursued.

I.R. ν_{max} (KBr): 3450 (br), 1500, 1285, 1130 cm^{-1}.

^{1}H.NMR δ ($CDCL_3$): 8.17-8.00 (m, 2H), 7.50-6.70 (m, 17H), 4.62 and 3.66 (AB quartet, J=16Hz, 2H, confirmed by double irradiation experiment), 3.43-3.22 (m, 1H), 3.00-2.77 (m, 1H), 2.45-1.60 (m, 9H, including s at 2.07 exchangeable in D_2O.

Methyl Enone (140)

The methyl enone (140) was prepared from the methyl hemiketal sulphone (138) via the trifluoroacetate (141) by a procedure similar to that previously described for the preparation of the enone (99) via the trifluoroacetate (104) (p.125). By this method the methyl hemiketal sulphone (138) (300 mg, 0.64 mmol) afforded the methyl enone (140), m.p. 109-111°C, (40 mg, 20%) and the hemiketal (142) m.p. 151-155°C, (120 mg, 56%) as the major products. These were purified by column chromatography on silica gel.

The reaction was repeated using very little methanol (0.1 ml) and in this case the major product was tentatively formulated as (143).

Variations of the procedure including changing the solvents and co-solvents, the leaving group, and the reaction temperature failed to improve the yield of the methyl enone (140).

Methyl enone (140):-

I.R. ν_{max} (KBr): 1680, 1495, 1455, 710, 700 and 635 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.35-7.13 (m, 9H), 3.90 and 2.89 (AB quartet, J=16Hz, 2H, confirmed by double irradiation experiments) 3.40-2.03 (m, 10H), 1.57 (s, 3H).

^{13}C.NMR δ ($CDCl_3$): 209.85 (s), 145.34 (2s), 139.80 (s), 135.25 (s), 130.53 (s), 128.68 (2d), 128.37 (4d) 127.23 (2d), 125.98 (d), 48.10 (t), 47.96 (t), 43.08 (d), 39.45 (dd), 36.65 (2dd), 18.21 (q).

(Found: M^+=316.183. $C_{23}H_{24}O$ requires M^+=316.183).

Hemiketal (142):-

I.R. ν_{max} (KBr): 3310, 1170, 995, 985, 970 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.30-7.08 (m, 9H), 3.45-3.07 (m, 4H), 2.23-1.53 (m, 10H), 0.70 (d, J=7Hz, 3H).

(Found: C, 82.70; H, 7.70%. $C_{23}H_{26}O_2$ requires C, 82.59; H, 7.84%).

(143):-

^{1}H.NMR δ ($CDCl_3$): 8.00-7.83 (m, 2H), 7.71-7.40 (m, 3H), 7.11(s, 9H), 3.70-3.49 (m, 4H), 3.42-3.10 (m, 4H), 2.80-1.37 (m, 16H, including br s at 1.9 exchangeable in D_2O and s at 1.40).

S_E' Cyclisation of the Methyl Enone (140)

The methyl enone (140) (40 mg, 0.125 mmol) was dissolved in dry methylene chloride (3 ml) and cooled to -70°C. To this stirred solution was added stannic chloride (1 ml of a 0.5M solution in methylene chloride). The reaction mixture was allowed to warm to room temperature and stirring was continued for a further 24 h. The reaction was quenched by pouring it into dilute aqueous sodium hydrogen carbonate (10 ml) and the product isolated by methylene chloride extraction. T.l.c. showed a number of compounds. The non-polar fraction was isolated by preparative t.l.c. (d.s. 15%) and the resulting oil was identified as a mixture of Z- and E-methyl styrenes (144) and (145) (18 mg, 45%).

I.R. ν_{max} (KBr): 1490 and 755 cm^{-1}.

^{1}H.NMR δ ($CDCl_3$): 7.25 (m, 9H), 6.01 (br s, 1H), 2.99 (t, J=5Hz, 2H), 2.45-1.97 (m, 8H), 1.89 (s, 3H).

^{13}C.NMR δ ($CDCl_3$): 28.43 (q), and 20.25 (q).

S_E' Cyclisation of the Enone (99)

The enone (99) (100 mg, 0.33 mmol), l-ephedrine (55 mg, 0.33 mmol), and tolene-p-sulphonic acid (1 mg) in dry toluene (10 ml) were heated under reflux for 48 h. The cooled reaction mixture was washed with water (5 ml), dried, and the solvent evaporated to give a solid product (113). Crystallisation from ethyl acetate/light petroleum (60-80°) gave colourless crystals of the styrene (113) (93 mg, 93%) having m.p. 169-171°C. This was identical by t.l.c., i.r., ^{1}H.nmr and ^{13}C.nmr with

the styrene (113) prepared previously (p.129).

The reaction was repeated in the absence of l-ephedrine and a similar result was obtained.

(S)-Methyl Mandelate (154)

To (S)-(+)-mandelic acid (14 g, 0.09 mol)[$[\alpha]_D$+153.0°, (C. 2.913, 95%); lit. value[101] $[\alpha]_D$+155.4°] in dry methanol (200 ml) was added acetyl chloride (10 ml) and the reaction mixture was left to stand at room temperature for 12 h. Concentration of the mixture in vacuo gave a solid which was crystallised from ether/light petroleum (40-60°) to give colourless crystals of (S)-methyl mandelate (154) (14.2 g, 93%) having m.p. 55-56°C (lit. value[55] 55-56°C).

^{1}H.NMR δ ($CDCl_3$): 7.35 (s, 5H), 5.16 (s, 1H), 3.72 (s, 3H), 3.2-2.8 (br s, 1H exchangeable in D_2O).

(S)-Phenylethylene Glycol (155)

This was prepared by the method of Mosher.[55] A solution of (S)-methyl mandelate (154) (14 g, 0.084 mol) in dry THF (20 ml) was added slowly with stirring to a suspension of lithium aluminium hydride (4 g) in dry THF (200 ml). After stirring for 12 h at 20°C, the mixture was hydrolysed with saturated aqueous ammonium chloride (10 ml) followed by hydrochloric acid (3N, 10 ml). The product was isolated by extraction into ethyl acetate and was crystallised from ether/light petroleum (40-60°) to give colourless crystals of (S)-phenylethylene glycol (155)

(8.9 g, 76%) having m.p. 63-65.5°C (lit.[101] m.p. 63-65°C).

^{1}H.NMR δ ($CDCl_3$): 7.28 (s, 5H), (4.77 dd, J_1=7Hz, J_2=5Hz, 1H), 3.69 (d, J=5Hz, 1H), 3.63 (d, J=7Hz, 1H), 2.38 (s, 1H).

Dioxolanes (156)

(2RS, 4S)-2-Methoxy-2-methyl-4-phenyl-1,3-dioxolane (156) was prepared by the method described by Mosher[55]. A mixture of S-(+)-phenylethylene glycol (155) (8.8 g, 0.065 mol), trimethylorthoacetate (23 ml) and concentrated sulphuric acid (0.2 ml) was stirred at 20°C for 10 min followed by heating at 50°C under reduced pressure (5 mm Hg) for 2 h. The residual oil was distilled (b.p. 89-93°C, 0.3 mm Hg) to give the dioxolanes (156) (11.8 g, 95%).

^{1}H.NMR δ ($CDCl_3$): 7.35 (s, 5H), 5.25 (dd, 0.56H), 5.11 (dd, 0.44H), 4.36 (m, 1H), 3.81 (m, 1H), 3.41 (s, 1.32H), 3.38 (s, 1.68H), 1.72 (s, 1.68H), 1.63 (s, 1.32H).

(R)-2-Chloro-2-Phenethyl Acetate (157)

This was prepared by the method of Mosher[55]. To a solution of the dioxolanes (156) (11.5 g, 0.06 mol) in methylene chloride (50 ml) at 0°C was added chlorotrimethylsilane (23 ml). After 2 h at 0°C the mixture was concentrated under reduced pressure and the residual oil was distilled (85-88°C, 0.5 mm/Hg) to give the chloro-acetate (157) (10.8 g, 91%).

^{1}H.NMR δ ($CDCl_3$): 7.32 (s, 5H), 5.05 (t, J=8Hz, 1H), 4.40 (d, J=8Hz, 2H), 1.95 (s, 3H).

S-2-Phenylethanol-2-d_1 (150)

This was prepared by the procedure described by Mosher.[55] A suspension of lithium aluminium deuteride (3 g) in dry THF (150 ml) was stirred at 20°C for 0.5 h, after which was added a solution of the chloroacetate (157) (10.5 g, 0.053 mol) in dry THF (50 ml). After stirring for 7 h the mixture was hydrolysed by adding saturated aqueous ammonium chloride (10 ml) followed by dilute hydrochloric acid (3N, 20 ml). Isolation by ether extraction gave an oily residue which was distilled (95-100°C, 3 mm Hg) to give (S)-2-phenylethanol-2-d_1 (150) (4.5 g, 69%).

^{1}H.NMR δ ($CDCl_3$): 7.25 (s, 5H), 3.85 (d, J=7Hz, 2H), 2.81 (tt, J_{HH}=7Hz, J_{HD}=2Hz, 1H), 1.62 (br s, 1H).

(Found: M^+=123.0789. C_8H_9DO requires M^+=123.0794.

(S)-2-Phenethyl Iodide-2d_1 (159)

To S-2-phenylethanol -2d_1 (2.8 g, 0.023 mol) in carbon tetrachloride (50 ml) was added trimethylsilyliodide[79] (4.6 g, 0.023 mol). The stirred reaction was heated at 50°C for 48 h under an inert atmosphere and the reaction was monitored by ^{1}H.nmr. On completion the reaction mixture was washed well with saturated aqueous sodium thiosulphate (2x10 ml) and brine (10 ml), dried and the solvent evaporated to give the phenethyl iodide (159) as an oil (3.9 g, 74%).

^{1}H.NMR δ ($CDCl_3$): 7.35-6.95 (m, 5H), 3.23-3.00 (m, 3H).

S-2-Phenethyl-2-d_1 Phenyl Sulphone (161)

S-2-Phenethyl iodide-2-d_1 (159) (3.5 g, 0.015 mol) and benzene sulphinic acid, sodium salt (3 g, 0.018 mol) were dissolved in dimethylformamide and stirred at room temperature for 24 h. Work-up as for the unlabelled sulphone (94) (p.118) gave colourless crystals of the labelled sulphone (161) (3.0 g, 74%), m.p. 55-56°C.

^{1}H.NMR δ ($CDCl_3$): 8.00-7.85 (m, 2H), 7.68-7.42 (m, 3H), 7.35-7.01 (m, 5H), 3.44-3.26 (d, J=9Hz, 2H), 3.18 -2.85 (m, 1H).

(Found: M^+=247.0778. $C_{14}H_{13}DSO_2$ requires M^+=247.0777).

Labelled Hemiketal Sulphone (164)

This was prepared by the same procedure as that used for the preparation of the unlabelled hemiketal sulphone (95) (p. 120). In this way the labelled phenethyl phenyl sulphone (161) (1.5 g, 6 mmol) reacted with the dione (44) (1.34 g, 6.2 mmol) to give the labelled hemiketal sulphone (164) (2.8 g, 100%) as a colourless solid. A portion of this recrystallised from ethanol had m.p. 238-240°C. The remainder was used without further purification.

Labelled Enone (149)

This was prepared from the labelled hemiketal sulphone (**164**) by the same procedure as that used for the formation of the unlabelled enone (99) via the trifluoroacetate (104) (p. 126). The labelled hemiketal sulphone (**164**) (2.5 g, 5.5 mmol) in THF (100 ml) was treated with trifluoroacetic anhydride (15 ml) to give the labelled trifluoroacetate, quantitatively (3.4 g), which was used without further purification.

Treatment of this trifluoroacetate (3.4 g, 55 mmol) with 5.5% sodium amalgam (12 g) gave the labelled enone (149). This was purified by column chromatography on silica to give the pure labelled enone (149), (1.2 g, 73%), m.p. 160-162°C.

^{1}H.NMR δ ($CDCl_3$): 7.20 (s, 9H), 5.52 (d, J=8Hz, 1H), 3.60-2.92 (m, 3H), 2.80-1.80 (m, 8H).

(Found: M^+=303.1728. $C_{22}H_{21}DO$ requires M^+=303.1733).

Phthalate Ester (165)

To the exo-ol (200 mg, 0.66 mmol) and phthalic anhydride (110 mg, 0.74 mmol) in THF (3 ml) were added 4-dimethylaminopyridine (1 mg) and triethylamine (0.5 ml). The mixture was stirred at room temperature for 24 h and then poured onto a dilute hydrochloric acid/ice mixture and the product isolated by methylene chloride extraction. Crystallisation from ethyl acetate/light petroleum (60-80°) gave the phthalate (**165**) as colourless crystals (273 mg, 92%) having m.p. 160-163°C.

^{1}H.NMR δ ($CDCl_3$): 9.75-9.15 (br s, 1H, exchangeable in D_2O), 7.65-7.40 (m, 4H), 7.30-7.05 (m, 9H), 6.50-6.15 (m, 1H), 5.49 (t, J=8Hz, 1H), 3.44 (d, J=8Hz, 2H), 3.32-2.98 (m, 2H), 2.77-1.55 (m, 8H).

Diastereomeric Salt Formation of the Phthalate Ester (165) and Attempts at Fractional Recrystallisation.

The phthalate ester (165) in a minimum volume of solvent was added to the optically active base in a minimum volume of solvent. The resulting salt was then allowed to crystallise. The optically active bases used were cinchonidine, cinchonine, dehydroabietylamine, d and l-ephedrine, and d-(α)-phenylethylamine. Various solvents and solvent mixtures were used for attempts at fractional recrystallisation. For those salts where crystallisation occurred, fractional recrystallisation showed no significant improvement in the melting point range. This approach was not further pursued.

Carbamates (166)

A mixture of the exo-ol (116) (200 mg, 0.66 mmol), R-(-)-1-(1-naphthyl) ethyl isocyanate (167) (150 mg, 0.76 mmol) and N,N-dimethyl-ethanolamine (1wt %) in benzene (20 ml) was heated at reflux for 36 h. The solvent was removed in vacuo and the product isolated by passing it through a short column of grade III alumina using ether as the eluting solvent. The diastereomeric carbamates (166) were recrystallised from methylene chloride/benzene and had m.p. 173-177°C.

^{1}H.NMR δ ($CDCl_3$): 8.17-6.95 (m, 16H), 6.10-5.73 (m, 1H), 5.70-5.30 (m, 2H), 4.82 (d, J=8Hz, 1H, exchangeable in D_2O), 3.40 (d, J=7Hz, 2H), 3.20-1.35 (m, 14H including d at 1.53, J=7Hz).

^{13}C.NMR δ ($CDCl_3$): 70.55 (d), 46.56 (d), 42.13 (t), 41.59 (t), 41.24 (t), 37.83 (d), 37.49 (d), 33.72 (t), 33.06 (t), 21.87 (q).

α-Methoxy-α-trifluoromethylphenylacetic Acid Chloride (169)

α-Methoxy-α-trifluoromethylphenylacetic acid (MTPA) (250 mg, 1.07 mmol) was dissolved in excess oxalyl chloride (1 ml), dimethylformamide (1 drop) was added and the reaction mixture was stirred overnight at room temperature. The excess oxalyl chloride was removed under reduced pressure and the MTPA acid chloride (169) was purified by distillation (212 mg, 84.5%) and had b.p. 53-56°C (1mm. Hg).

MTPA-Esters (168)

The exo-ol (116) (200 mg, 0.66 mmol) and the (-)-α-methoxy-α-trifluoromethylphenylacetic acid chloride (169) (180 mg, 0.70 mmol) were dissoved in dry THF and 4-dimethylaminopyridine (1 mg) was added followed by triethylamine (1ml). Immediately a precipitate formed and t.l.c. indicated that the reaction was complete. The product was isolated by methylene chloride extraction, including acid wash. Crystallisation of the oily product from light petroleum (40-60°) gave colourless crystals of the diastereomeric MTPA-esters (168) having m.p. 108-111°C.

I.R. ν_{max} (KBr): 1740, 1295, 1260, 1195, 1170, 1020, 770 cm^{-1}.

$^{1}H.NMR$ δ ($CDCl_3$): 7.70-7.05 (m, 14H), 6.65-6.20 (m, 1H), 5.65-5.42 (m, 1H), 3.61-3.36 (m, 5H, including br s) 3.25-2.95 (m, 2H), 2.75-1.62 (m, 8H).

$^{19}F.NMR$ δ ($CDCl_3$): 72.13 (s), 72.07 (s).

(Found: M^+=520.2223. $C_{32}H_{31}O_3F_3$ requires M^+=520.2225).

Cellulose Triacetate

Cellulose triacetate was prepared by the method of Hesse.[94] Microcrystalline cellulose (100 g), benzene (2000 ml) acetic acid (400 ml), acetic anhydride (400 ml) and perchloric acid (60%, 3 ml) were stirred and heated at 35°C for 3 days. The resulting brown gel was centrifuged down and the supernatant liquid removed. The gel was then washed well with methanol and centrifuged down with removal of supernatant liquid; this process was repeated several times. The resulting buttery paste was spread out on glass to air-dry. The brown lumps were powdered in a mill, and the particle size separated by means of sieves. The fractions used were between 53μm and 120μm, about 50% of the product.

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